The Preparation and Properties of Arylglyoxylic Acids.

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THE PREPARATION AND PROPERTIES OF ARYLGLYOXYLIC ACIDS

by

Alexander Bold Neill, Jr.

A DISSERTATION

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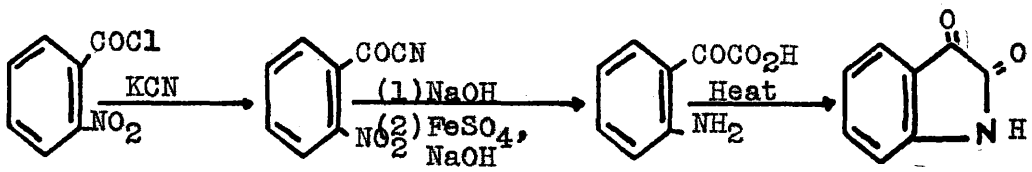
Part I

Introduction

Introduction

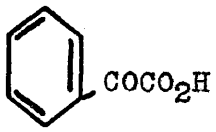
The earliest mention of a phenylglyoxylic acid was made some eighty years ago when Kekulé (55) postulated that isatin had a benzene nucleus with a $-CO-CO_2H$ group, as well as, an amino group, $-NH_2$. He also postulated that isatin was the lactam of isatic acid which he thought was o-aminobenzoylformic acid or o-aminophenylglyoxylic acid.

It was not untill879, some ten years later, that Claisen and Shadwell (28) proved that Kekulé was right by preparing isatic acid and isatin from o-nitrobenzoyl chloride according to the following scheme:



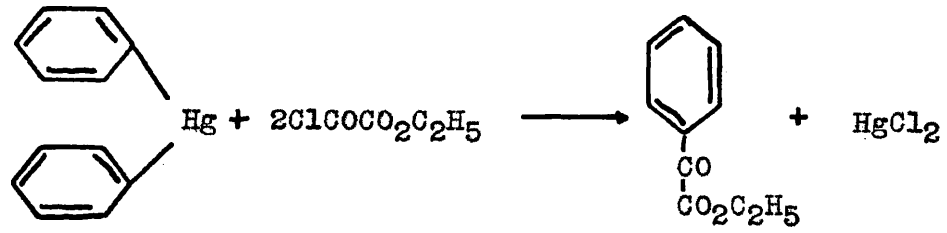
o-Nitrobenzoyl Chloride | o-Nitrobenzoyl Cyanide | Isatic Acid | Isatin

Previous to this work, Claisen (22,23,24,25) in the years 1877-79 had characterized unsubstituted phenylglyoxylic acid through its amide, esters and various metallic



Phenylglyoxylic Acid

salts. Alongwith this work, Claisen proposed the two following general methods for preparing phenylglyoxylic acids or their esters: a. hydroxylsis of benzoyl cyanide (22,23,24,25), and b. condensation of diphenyl mercury with ethyl chlorooxalate (26,27):

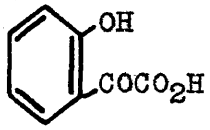


Mercury Diphenyl — Ethyl Chlorooxalate — Ethyl Phenylglyoxylate

In this same manner, Claisen and Morley (27) prepared α-naphthylglyoxylic acid.

In 1881, Roser (71,72) used ethyl chlorooxalate, benzene, aluminum chloride and carbon disulfide to prepare the ethyl ester of phenylglyoxylic acid and used toluene in place of benzene to form the 4-methyl phenylglyoxylic acid. This method and that of Claisen's, using benzoyl cyanide, were two of the most generally accepted methods for the preparation of phenylglyoxylic acids.

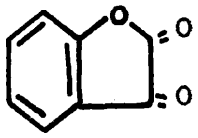
In 1884 Baeyer and Fritsch (6) prepared o-hydroxyphenylglyoxylic acid by heating diazotized isatin and characterized the acid through the phenylhydrazone and oxime.



o-Hydroxyphenylglyoxylic Acid

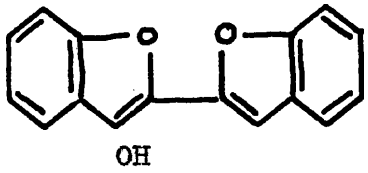
In 1902, Stoermer and Kahlert (79) prepared o-hydroxyphenylglyoxylic acid from 2-nitrobenzofuran. These men discovered that the oxime formed from their acid was the same as that obtained by Baeyer and Fritsch (6) for o-hydroxyphenylglyoxylic acid.

Shad (75) in 1893 attempted to prepare the lactone of o-hydroxyphenylglyoxylic acid by using various ring-closing agents, acetyl chloride, phosphorous pentachloride, acetic anhydride and concentrated sulfuric acid but without success. He then tried to form the lactone by condensing sodium phenoxide with ethyl chlorooxalate but failed in this attempt, also. Shad did succeed in forming a phenylhydrazone of o-hydroxyphenylglyoxylic acid.



o-Hydroxyphenylglyoxylic Acid Lactone

The lactone of o-hydroxyphenylglyoxylic acid was not prepared until 1909 when Stoermer (78) oxidized leucooxindigo with chromic acid. The yellow lactone was

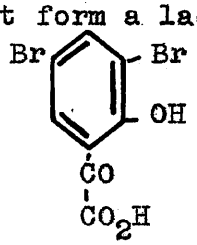


Leucooxindigo

found to contain one molecule of water. The coumarandione or lactone of o-hydroxyphenylglyoxylic acid gave no reaction with sodium bicarbonate but did dissolve in base, giving a yellow solution. The lactone was not split by long heating with water; however, dilute hydrochloric acid converted it into the free acid.

Also, in 1909, Fries (36) succeeded in preparing the lactone of o-hydroxyphenylglyoxylic acid by heating the acid with phosphorous pentoxide and benzene. Later Fries and Pfaffendorf (40) found that the lactone could be formed by vacuum distillation. As can be easily observed, these methods are rather general ones for the conversion of an o-hydroxyphenylglyoxylic acid to its lactone.

By bromination of the lactone of o-hydroxyphenylglyoxylic acid, Fries and Pfaffendorf (40) formed the 2-hydroxy-3,5-dibromophenylglyoxylic acid. They discovered that this acid would not form a lactone by using a benzene-



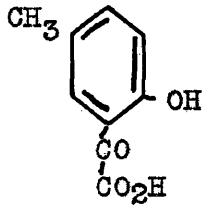
2-Hydroxy-3,5-dibromophenylglyoxylic Acid

phosphorous pentoxide mixture.

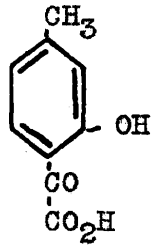
Fries and Pfaffendorf (40) prepared the phenylhydrazone of the lactone of o-hydroxyphenylglyoxylic acid either by treating the lactone directly or by ring

closure of the hydrazone of the free acid. The anil of the lactone was prepared by treating the lactone with p-amino dimethyl aniline. This anil, however, did undergo ring closure to form the lactone. Upon heating the lactone for a short while with absolute alcohol, the o-hydroxyphenylglyoxylic acid ethyl ester was formed.

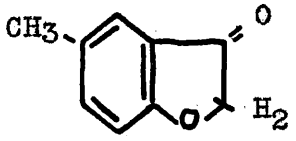
Fries and Finck (38) in 1908 prepared 5-methyl-2-hydroxyphenylglyoxylic acid from 4-methyl coumaranone. This method consisted of converting the coumaranone by treatment with sodium nitrite and hydrochloric acid to form the 4-methyl-1-isonitroso-2-coumaranone.



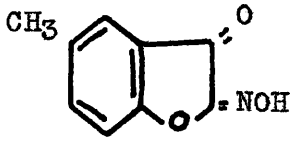
5-Methyl-2-hydroxyphenylglyoxylic Acid



4-Methyl-2-hydroxyphenylglyoxylic Acid



4-Methyl-2-coumaranone

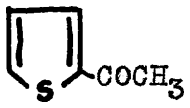


4-Methyl-1-isonitroso-2-coumaranone

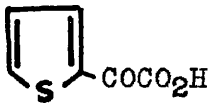
The isonitroso compound, on heating with concentrated hydrochloric acid, yielded the 5-methyl-2-hydroxyphenylglyoxylic acid. The 4-methyl-2-hydroxyphenylglyoxylic acid was prepared in a similar manner to the 5-methyl acid. The starting material was 5-methyl-2-coumaranone.

Both the 4-methyl and the 5-methyl-2-hydroxyphenylglyoxylic acids formed lactones, according to the procedure given by Fries (36). These acids also formed anils with aniline and quinoxaline derivatives with o-phenylene diamine (38).

In 1884 Peter (68) and in 1885 Beidermann (8) and Bradley (17) prepared α-thienylglyoxylic acid by the oxidation of α-acetylthiophene with alkaline potassium permanganate. Beidermann found that heat caused the α-thienylglyoxylic acid to decompose, forming carbon dioxide and α-thiophenealdehyde. Egli (30) found that α-thiophenecarboxylic acid, as well as, some α-thienylglyoxylic acid is formed on oxidation of α-ethylthiophene by alkaline potas-



α-Acetylthiophenene



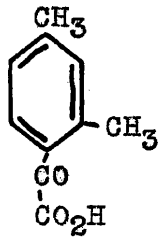
α-Thienylglyoxylic Acid

sium permanganate.

From 1896 to 1898, Bouveault (10,11,12,13,14,15,16) published a series of papers dealing with various substituted phenyl glyoxylic acids. He prepared these various acids by condensing the appropriate aromatic hydrocarbon or phenol ether with ethyl chlorooxalate and aluminum chloride in a carbon disulfide and nitrobenzene mixture.

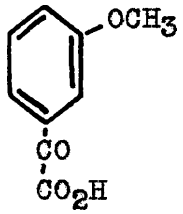
The ester formed in the reaction was then hydrolyzed to form the free acid by using dilute base. By this

method, the following compounds were prepared: 2,4-dimethylphenylglyoxylic acid from m-xylene; p-methoxy and m-methoxyphenylglyoxylic acid from anisole; 3,4-dimethoxyphenylglyoxylic acid and veratrole; 2,4-dimethoxyglyoxylic acid from resorcinol dimethyl ether and 2,5-dimethoxyphenylglyoxylic acid from hydroquinone dimethyl ether.

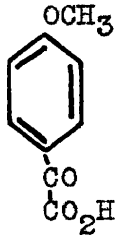


2,4-Dimethylphenylglyoxylic acid

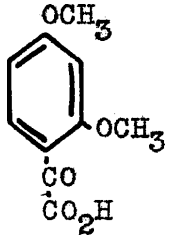
p-Methoxyphenylglyoxylic acid



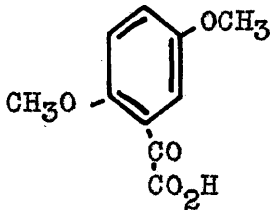
m-Methoxyphenylglyoxylic acid



3,4-Dimethoxyphenylglyoxylic acid



2,4-Dimethoxyphenylglyoxylic acid

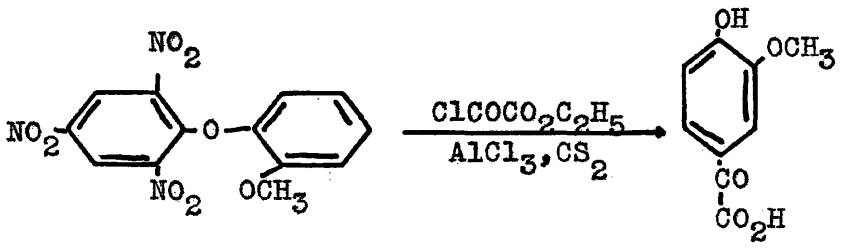


2,5-Dimethoxyphenylglyoxylic acid

This method, using phenol ethers, is an extension of Roser's work (71,72) (p. 3), using aromatic hydrocarbons, to form ethers of hydroxyphenylglyoxylic acids.

The above reaction could not be extended to free phenols; however, Bouveault (15) found that, by using

the picryl derivative, the free phenol could be recovered from the reaction after the removal of the picryl group.



Guiacol picrate

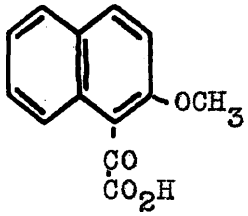
3-Methyl-4-hydroxyphenyl-glyoxylic acid

Bouveault (16) discovered that p-methoxyphenyl-glyoxylic acid could be demethylated by heating the acid to 170°C. under pressure. An attempt to extend this method to the demethylation of 3,4-dimethoxy-phenylglyoxylic acid in order to produce 3-methoxy-4-hydroxyphenylglyoxylic acid proved unsuccessful.

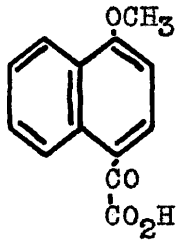
In his work on glyoxylic acids, Bouveault (11) found that the aryglyoxylic acids were stronger than the corresponding acids in the benzoic acid series. He also found that the glyoxylic acids when distilled decomposed to form carbon monoxide, carbon dioxide and a mixture of the corresponding benzoic acid and benzaldehyde derivative in almost a quantitative yield for the two latter compounds. On heating the arylglyoxylic acid in concentrated sulfuric acid, benzoic acid derivatives were obtained. Bouveault (12,13,14) found that the oximes and hydrazones could be prepared; the oximes

readily underwent decarboxylation and dehydration to form the corresponding benzonitriles which, on hydrolysis, formed benzoic acid; the hydrazones decomposed with loss of nitrogen to form symmetrical stilbenes.

Rousset (73,74) in 1897 extended Roser's work (71,72) into the naphthalene series by preparing the ethers of hydroxynaphthylglyoxylic acids. He prepared the 2- and 4-methoxynaphthylglyoxylic acids by using aluminum chloride,



2-Methoxynaphthylglyoxylic acid



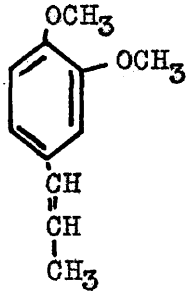
4-Methoxynaphthylglyoxylic acid

ethyl chlorooxalate and α-methoxy or β-methoxynaphthalene. Rousset also prepared various esters of both the ethoxy and methoxynaphthylglyoxylic acids.

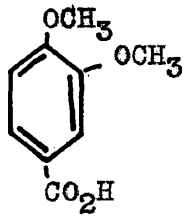
Some twenty years later, Kamm, McClugage, and Landstrom (53) obtained the 4-ethoxynaphthylglyoxylic acid by oxidizing 4-acetylethoxynaphthalene with alkaline potassium permanganate.

The use of alkaline permanganate is another general method of preparing arylglyoxylic acids, first used by Peter (68) (p. 7) in preparing α-thienylglyoxylic acid. Again, this method was not applicable to the free phenols or compounds with an oxidizable side chain. In 1890 Ciamician

and Silber (21) prepared 3,4-dimethoxyphenylglyoxylic acid alongwith some veratric acid by the oxidation of the methyl ether of isoeugenol with potassium permanganate.

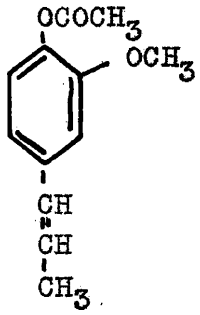


Methyl ether of isoeugenol

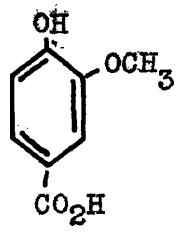


Veratric acid

Tiemann (80), a year later, oxidized acetylated isoeugenol with potassium permanganate to form 3-methoxy-4-hydroxyphenylglyoxylic acid and vanillic acid. In 1909, Barger and Ewins (7) oxidized 3,4-methylenedioxymandelic acid with



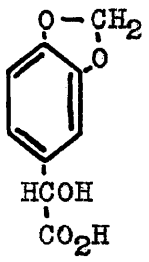
Acetylated isoeugenol



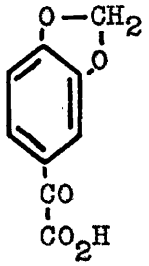
Vanillic acid

alkaline potassium permanganate and obtained the 3,4-methylenedioxyphenylglyoxylic acid. An attempt to oxidize the same acid, using potassium dichromate and sulfuric acid, was un-

successful.

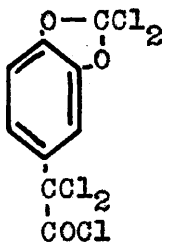


3,4-Methylenedioxy-mandelic acid

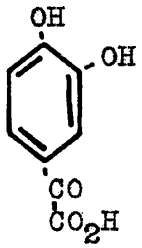


3,4-Methylenedioxyphenyl-glyoxylic acid

The 3,4-methylenedioxyphenylglyoxylic acid on treatment with phosphorous pentachloride gave 3,4-dichloro-methylenedioxyphenyldichloracetyl chloride and this compound on treatment with formic acid followed by boiling water formed the 3,4-dihydroxyphenylglyoxylic acid.



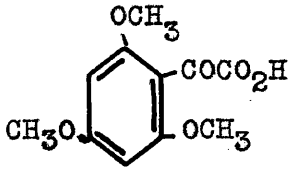
3,4-Dichloromethylenedichloro-phenyldichloroacetyl chloride



3,4-Dihydroxyphenyl-glyoxylic Acid

In 1909 Jonas (51) reported that on oxidation of phloracetophenone trimethyl ether with 3% potassium permanganate, the phloroglucinolglyoxylic acid trimethyl ether

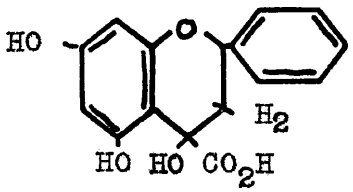
was formed.



Phloroglucinolglyoxylic acid trimethyl ether

Some twenty years later, Popavici (69) used this same method to prepare β -naphthylglyoxylic acid from β -acetylnaphthalene. Again in 1932 Kurodo and Nakamura (57) prepared 2,4,5-trimethoxy and 2,3,4,6-tetramethoxy-phenylglyoxylic acids by oxidation of the corresponding acetophenones.

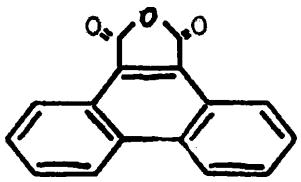
Bulow and Wagner (19) obtained 2,4-dihydroxy-phenylglyoxylic acid by the alkali splitting of 2-phenyl-7-hydroxy-(1,4-benzopyranol)-4-carboxylic acid.



2-Phenyl-7-hydroxy-(1,4-benzopyranol)-4-carboxylic acid

In 1905 Meyer and Spengler (63) reported the preparation of the lactone of 9-hydroxy-phenanthrene-10-glyoxylic acid by the treatment of phenanthraquinone and

glycolic acid with methyl alcoholic potassium hydroxide.



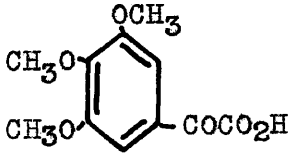
9-Hydroxyphenanthrene-10-glyoxylic acid lactone

About twenty-five years later, Fieser (31) found that on treatment of 3-hydroxy-1,4-phenanthroquinone with alkali 2-acetonaphthylglyoxylic acid was obtained.

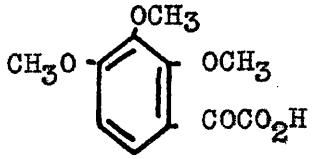
3-Hydroxy-1,4 phenanthroquinone

2-Acetonaphthylglyoxylic acid

Mauthner (61,62) prepared 3,4,5-trimethoxyphenylglyoxylic acid by saponification of the benzoyl nitrile formed from the acid chloride and hydrogen cyanide. He also



3,4,5-Trimethoxyphenylglyoxylic acid



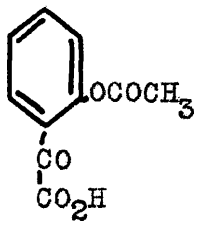
2,3,4-Trimethoxyphenylglyoxylic acid

prepared several dimethoxy acids by this method: 3,4-dimethoxyphenylglyoxylic acid, 2,5-dimethoxyphenylglyoxylic acid and 2,3,4-trimethoxyphenylglyoxylic acid. Mauthner also prepared the glyoxylic acid amides from the free acids or the benzoyl cyanides.

It has been shown by previous investigators, as well as Mauthner, that glyoxylic acids could be converted to aldehydes. Mauthner pointed out how one could start with benzonitriles and convert them into aldehydes by using the following procedure:

$$RCOCl \longrightarrow RCOCN \longrightarrow RCOCO_2H \longrightarrow RCONR \longrightarrow RCHO$$

Anschutz and Claus (4) prepared o-acetoxyphenylglyoxylic acid from salicylic acid by preparing the intermediate salicylyl chloride and salicylonitrile; the nitrile was hydrolyzed first to form the acid amide and then to form

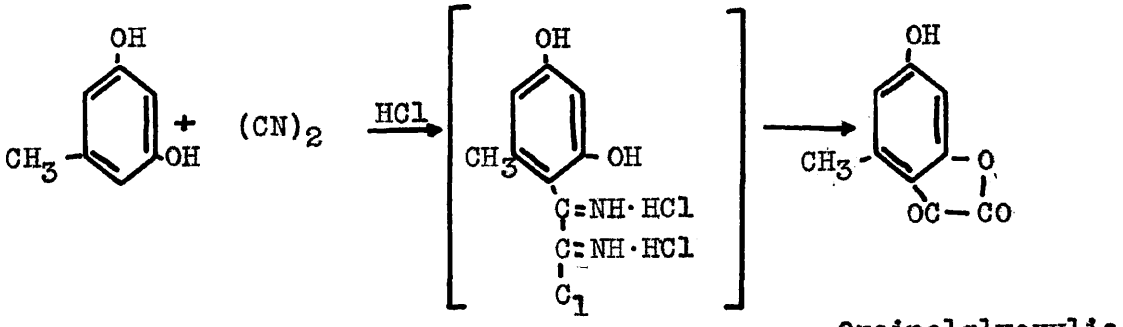


o-Acetoxyphenylglyoxylic acid

the free acid. The o-acetoxyphenylglyoxylic acid could not be transformed into the free phenolic compound nor could the free phenolic compound be acetylated.

In 1911 Vorlander (81,82,83) prepared glyoxylic acids by an entirely new method. He condensed the aromatic hydrocarbon or phenol ether with cyanogen in the presence of aluminum chloride. By this method p-methylbenzoyl cyanide, p-ethoxybenzoyl cyanide and p-methoxybenzoyl cyanide were prepared. The ethoxy compound was the only compound hydrolyzed to form the glyoxylic acid.

Some ten years later Karrer and Ferla (54) extended Vorlander's work (81,82,83) to form free phenolic acids by the use of dry hydrogen chloride gas in place of aluminum chloride. This method is the first really general one for preparing the free phenolic glyoxylic acids. Orcinolglyoxylic acid lactone and resorcinolglyoxylic acid were prepared by this method from orcinol and resorcinol respectively. The preparation of orcinolglyoxylic acid illustrates this method.



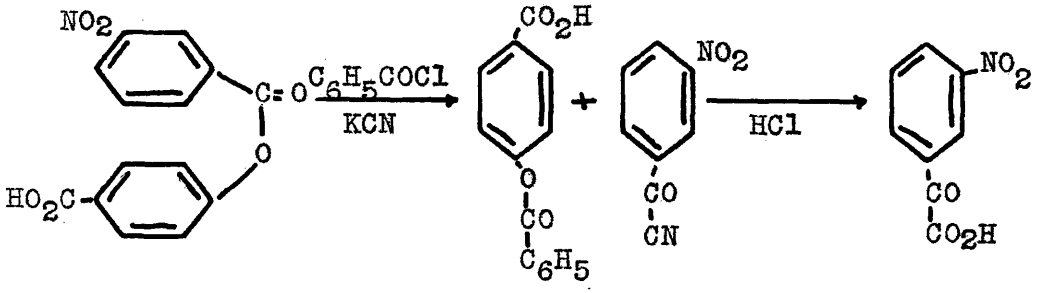
Orcinol — A Ketimine Hydrochloride — Orcinolglyoxylic acid lactone

Karrer and Ferla postulated the formation of an imino chloride as an intermediate and this chloride on hydrolysis gave the glyoxylic acid. These investigators also found that orcinol-

glyoxylic acid lactone was formed instead of the free acid.

In 1948 Knobloch and Schraufstatter (56) prepared 1-hydroxynaphthyl-2-glyoxylic acid lactone by the reaction of cyanogen on ∝-naphthol. These chemists also reacted cyanogen with 1,5-dihydroxynaphthalene but they were not sure whether they had obtained the 1,5-dihydroxynaphthyl-2 or 4-glyoxylic acid.

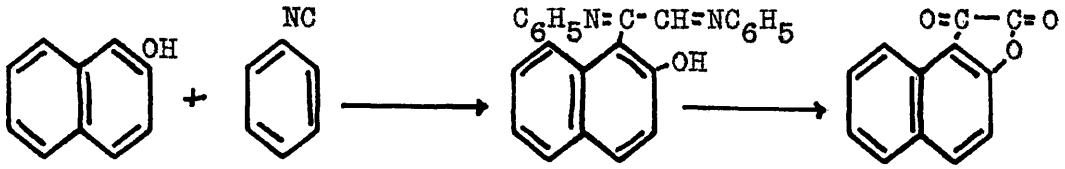
Francis and Nierenstein (35) in 1914 discovered a general method for preparing substituted phenylglyoxylic acids which consisted of treating the properly substituted benzoyloxybenzoic acid with unsubstituted benzoyl chloride and potassium cyanide. The preparation is illustrated by the following equations:



3-Nitrophenylglyoxylic acid

If a free phenolic glyoxylic acid was desired, the phenolic group was protected by an easily removed group, such as, CH_3COO-, or $-OCO_2C_2H_5$ until the final hydrolysis. Francis and Nierenstein prepared 3,4,5-trihydroxyphenylglyoxylic acid and 3-nitro-4-hydroxyphenylglyoxylic acid by this method.

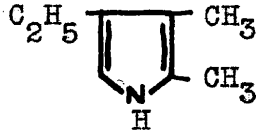
Passerini (64,66) reported in a series of papers the preparation of 2-hydroxynaphthylglyoxylic acid lactone by the action of two moles of phenyl isonitrile on β-naphthol. The dianil was first formed and then hydrolyzed to form the glyoxylic acid lactone.



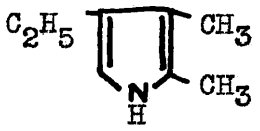
Phenyl isonitrile — A Dianil — 2-Hydroxynaphthyl-glyoxylic acid lactone

If α-naphthol is used in this reaction, then hydroxynaphthyl-2-glyoxylic acid is formed.

Fisher and Stangler (34) in 1927 prepared 2,3-dimethyl-4-ethyl-pyrrole-glyoxylic acid from hemopyrrole by using ethyl cyanoformate and dry hydrogen chloride. An imino



Hemopyrrole



2,3-Dimethyl-4-ethylpyrrole-glyocylic acid

hydrochloride was postulated as being the intermediate in this reaction. This reaction is somewhat similar to that of Vorlander's (81,82,83) and Karrer and Ferla (54) in that an

active nitrile group is the basis of the reaction. These reactions have all been discussed.

Apparently, Fisher and Stangler (34) did not realize the potentialities of this reaction, for they only prepared this one glyoxylic acid. In 1948, Hunsberger and Amstutz (50) published a paper showing how the reaction of Fisher and Stangler, using ethyl cyanoformate in the preparation of the pyrroleglyoxylic acid, could be extended to the preparation of phenylglyoxylic acids containing free phenolic groups by using zinc chloride as a catalyst. Various 2,4-dihydroxyphenylglyoxylic acids, thus, were prepared by this method, some of which are 5-ethyl-2,4-dihydroxyphenylglyoxylic acid and 3-ethyl-5-methyl, 2,4-dihydroxyphenylglyoxylic acids. This reaction is a general method for preparing glyoxylic acids containing free phenolic groups. The subject of this dissertation is the extension of this reaction to hydroxy-naphthalenes.

Part II

Discussion of Results

Discussion of Results

The investigations described in this dissertation were concerned with the syntheses of certain arylglyoxylic acids by using ethyl cyanoformate. These syntheses are based on the discovery of Fisher and Stangler (34) that ethyl cyanoformate could be used to prepare hemopyrrolglyoxylic acid from hemopyrrole. Hunsberger and Amstutz (50) extended the reaction and showed how ethyl cyanoformate could be used to prepare dihydroxyphenylglyoxylic acids. In this dissertation the use of ethyl cyanoformate to introduce the $-CO-CO_2H$ group into the ring is extended to the hydroxy and dihydroxynaphthalenes and some trihydroxybenzenes.

The method of Hunsberger and Amstutz (50) for preparing the glyoxylic acids was modified slightly. Their method consisted of passing dry hydrogen chloride gas into the reaction mixture which consisted of ethyl cyanoformate, zinc chloride, absolute ether, and the hydroxy aromatic hydrocarbon for two to eight hours depending on the individual reaction.

The method used in this dissertation consisted of passing dry hydrogen chloride into the same reaction mixture as above (cooled with an ice-bath) for two hours. The reaction mixture was then sealed from moisture and placed in the refrigerator for twenty-four hours. After this time, dry hydrogen chloride gas was again passed into the cooled

solution for two hours. The reaction mixture was sealed from moisture again and placed in the refrigerator for three days.

After the three-day refrigeration period, the reaction was worked up; the acid, collected and purified.

In all cases, the intermediate compound in the above reaction was postulated as an arylketimine, having the general formula, $R\text{-}C(NH\cdot HCl)CO_2C_2H_5$. Similar compounds have been postulated for the intermediate in the Gattermann aldehyde synthesis (43,44,45), in Vorlander's (82,83) and Karrer and Ferla's (54) glyoxylic acid syntheses and in other reactions involving a nitrile group and an activated position in an aromatic ring.

On hydrolysis of the ketimine hydrochloride, the free arylglyoxylic acid was formed.

α-Naphthol Series

The previously unknown 4-hydroxynaphthylglyoxylic acid monohydrate (I) was obtained from the reaction of α-naphthol and ethyl cyanoformate. This acid which was yellow melted at 188.4-189.4°C. with decomposition. The anhydrous acid (II) which was also yellow melted at 191.2-191.8°C. with decomposition, and was prepared from the monohydrate (I) by drying over phosphorous pentoxide at 80°C. for two days. Several investigators (4,36) have reported a 30-40°C. difference in the melting point between the anhydrous acid and the monohydrate; however, in this series there

was only a 3° difference.

Several attempts were made to prepare the 2,4-dinitrophenylhydrazone of 4-hydroxynaphthylglyoxylic acid monohydrate (I) but without success.

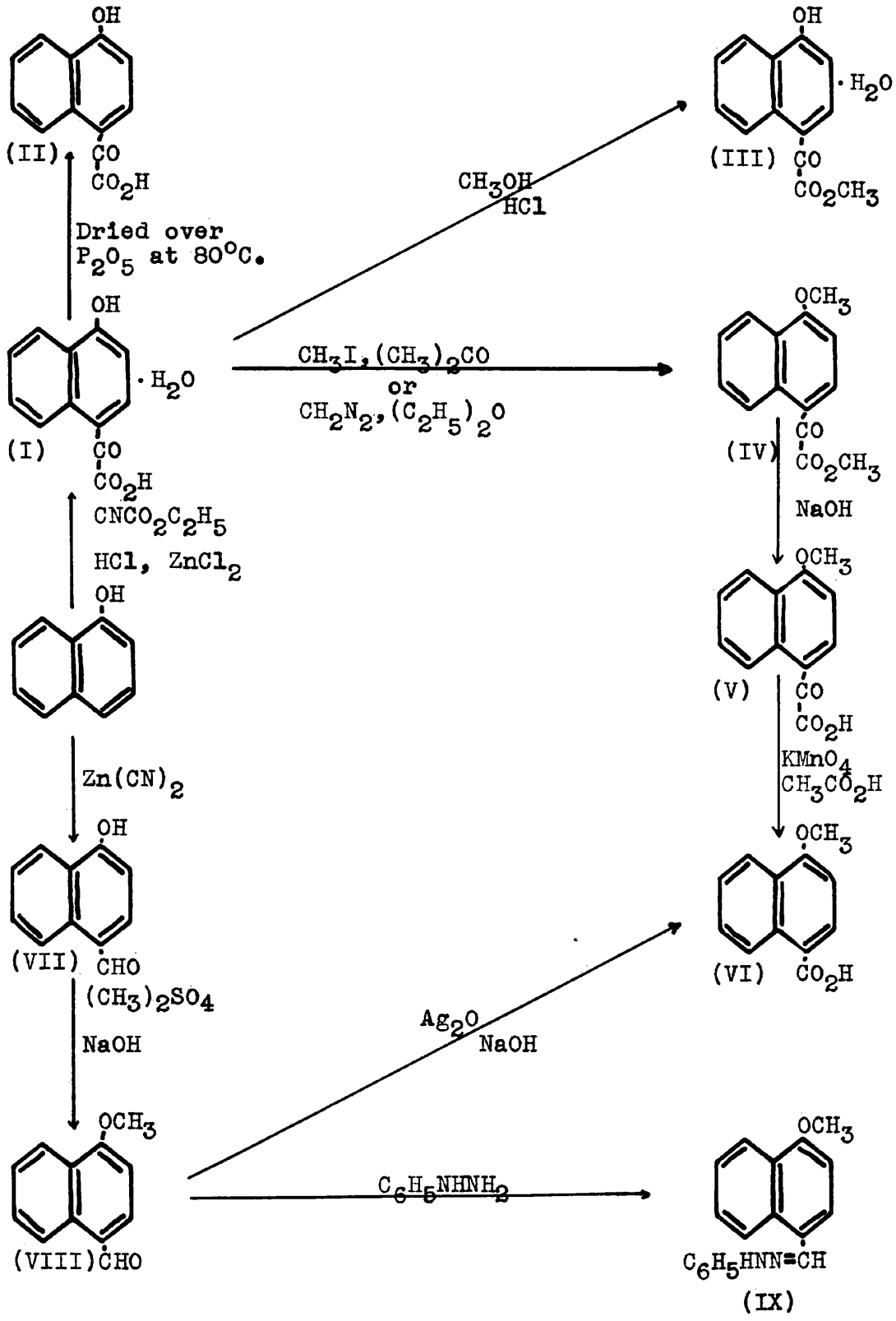
The reactions involved in this part of the work are outlined in the accompanying diagram (p. 24).

It is interesting to note that in the formation of methyl 4-hydroxynaphthylglyoxylate monohydrate (III) from the corresponding acid monohydrate by passing dry hydrogen chloride into absolute methanol solution of the acid, the molecule of water attached to the acid was retained by the ester. The ester, like the acid, has a light yellow color.

In preparation of methyl 4-methoxynaphthylglyoxylate (IV), two methods were used, both giving almost the same yield. The method using methyl iodide and acetone gave a 74.9% yield of the methoxy ester while the other method using diazomethane gave a 72.9% yield. On hydrolysis of this ester 4-methoxynaphthylglyoxylic acid (V) was formed.

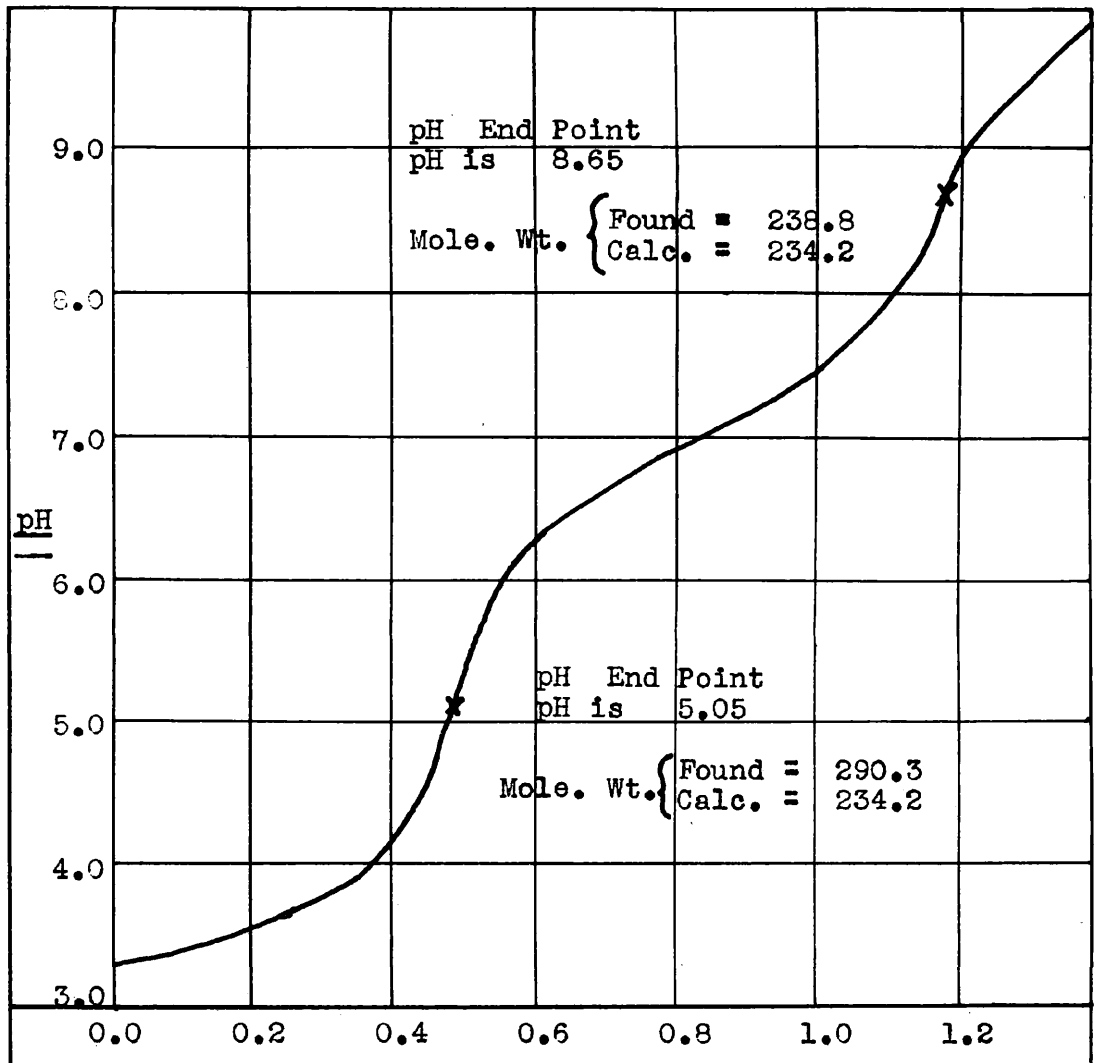
Satisfactory neutral equivalents were obtained for both 4-hydroxynaphthylglyoxylic acid monohydrate (I) (two acid hydrogens titrated per mole) and 4-methoxynaphthylglyoxylic acid (V) by visual titration in water using phenolphthalein as an indicator. If the titrations were performed with a Beckmann pH meter, however, the curves produced had well defined equivalence points which corresponded to the titration of one acid hydrogen ion. The hydroxy acid had a

α-Naphthol Series



pH of 5.05 at the equivalence point, indicating that the acid was strongly acidic while the methoxy acid had a pH of 6.85 at the equivalence point, indicating that the acid was very weak. The neutral equivalents calculated from these results were 74 units too high in the case of the hydroxy acid and 32 units too high in the case of the methoxy acid. These results substantiated what Hunsberger and Amstutz (50) had found in the dihydroxyphenylglyoxylic acid series.

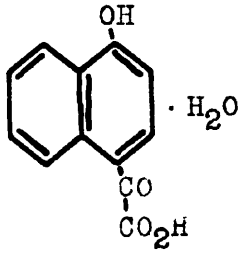
Both the methyl 4-methoxynaphthylglyoxylate and the 4-methoxynaphthylglyoxylic acid had been prepared previously (73) but the position of the entering glyoxylic acid group was not definitely proven. This investigation has indicated that the glyoxylic acid group went into position four in the hydroxynaphthalene nucleus. To prove that the glyoxylic acid group went into position four, 4-methoxynaphthylglyoxylic acid was oxidized with potassium permanganate in 50% acetic acid to form the known 4-methoxynaphthoic acid (V). The melting point for this acid was 241.8-242.8°C. while the melting point as reported by Gattermann (42) was 232°C. In order to be sure that this acid was the correct one, the acid was synthesized by another method. This synthesis consisted of preparing the 4-hydroxynaphthaldehyde (VII) by Adams and Levine's (1) modification of Gattermann's method (42,43,44,45) using α-naphthol, zinc cyanide, and dry hydrogen chloride gas. The resulting hydroxyaldehyde (VII) was methylated using dimethyl sulfate; the 4-methoxynaphthaldehyde (VIII) formed was then oxidized by silver oxide, Pearl's

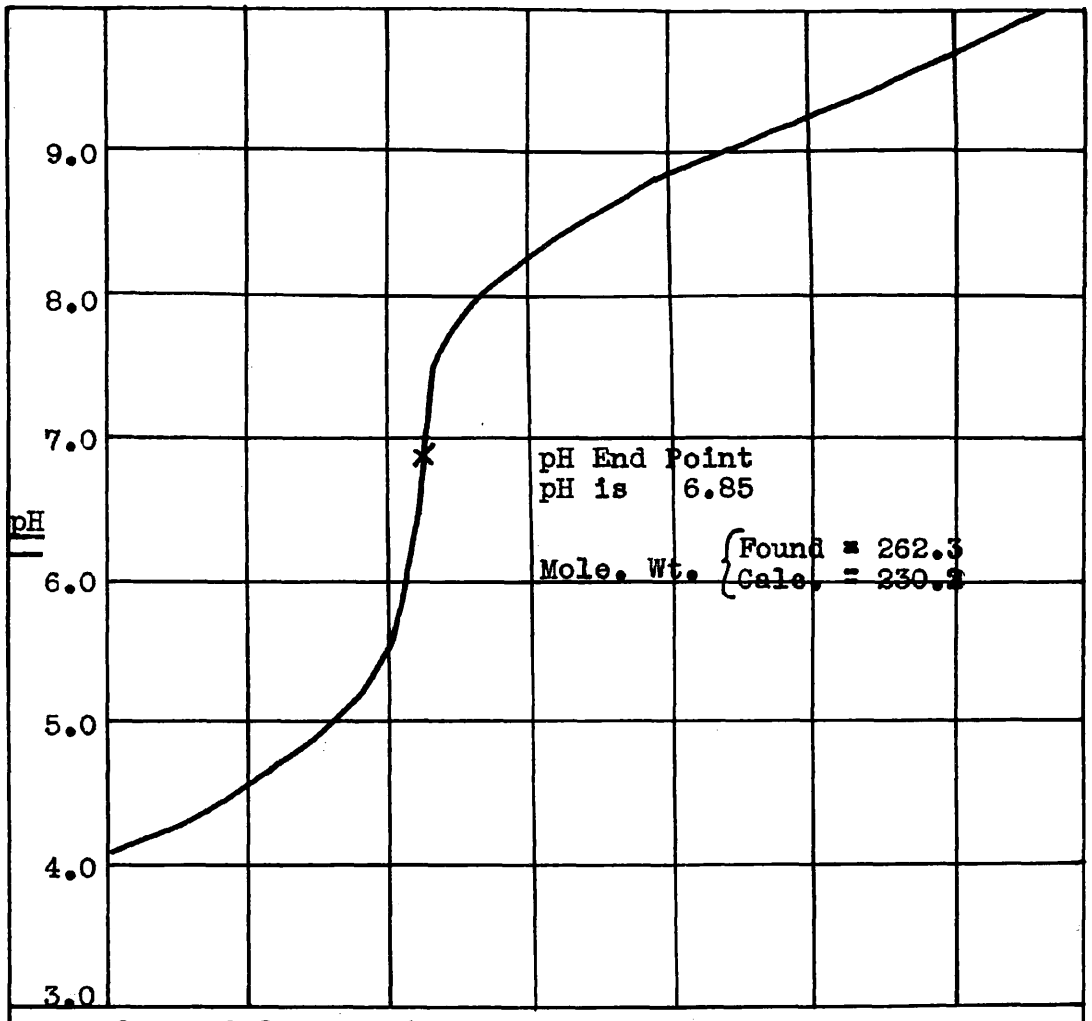


Neutral Equivalent

of

4-Hydroxynaphthylglyoxylic Acid Monohydrate (I)

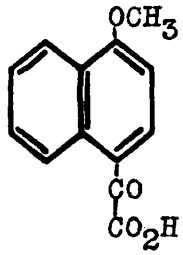




Neutral Equivalent

of

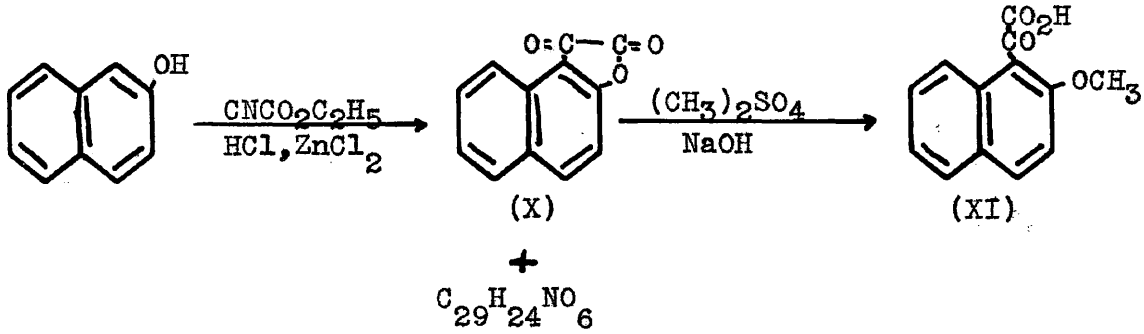
4-Methoxynaphthylglyoxylic Acid (V)



method (67), to form the 4-methoxynaphthoic acid (VI). This acid was, in every respect, the same as that acid prepared from the oxidation of 4-methoxynaphthylglyoxylic acid (V). Thus, the position of the entering glyoxylic acid group was established.

β-Naphthol Series

The action of ethyl cyanoformate on β-naphthol yielded the lactone of 2-hydroxynaphthylglyoxylic acid (X). This acid had been previously prepared by a number of investigators (39,41,47,48,64,77). The position of the glyoxylic acid group had been determined by Passerini (64) by oxidation of the lactone (X) to form the known 2-hydroxynaphthoic acid.



(X) + $C_{29}H_{24}NO_6$

(XI)

It is interesting to note that the free acid could not be prepared; only the lactone was obtained. This tendency to form lactones in compounds containing a hydroxy group ortho to a glyoxylic acid has been found in other compounds in the naphthalene series, not only in the work reported here, but also in that reported by other investigators (39,40, 41,47,48,54,56,64,66). In all the various hydroxynaphthylgly-

oxylic acids which have a hydroxy group ortho to the glyoxylic acid group, a lactone was formed except in the case of the 1-hydroxy-naphthyl 2-glyoxylic acid. In these cases, the free acid was formed and the lactone was not produced at all. This same tendency to form the free acid and not the lactone has been observed in the hydroxyphenylglyoxylic acid series. Fries and Pfaffendorf (40) have shown, as mentioned before, that o-hydroxyphenylglyoxylic acid formed a lactone with difficulty; phosphorous pentoxide and benzene were needed to form the lactone. These investigators found that the lactone of 2-hydroxy-3,5-dibromophenylglyoxylic acid was not formed even on treatment of the acid with benzene and phosphorous pentoxide. Karrer and Ferla (54) found that the reaction of cyanogen and orcinol gave the lactone of 2,4-dihydroxy-6-methylphenylglyoxylic acid instead of the free acid. When resorcinol was used, however, then the free acid, 2,-4 dihydroxyphenylglyoxylic acid was formed. Hunsberger and Amstutz (50) found that in condensing various alkylresorcinols with ethyl cyanoformate, 2,4-dihydroxy-5-alkylphenylglyoxylic acids were formed instead of the lactones.

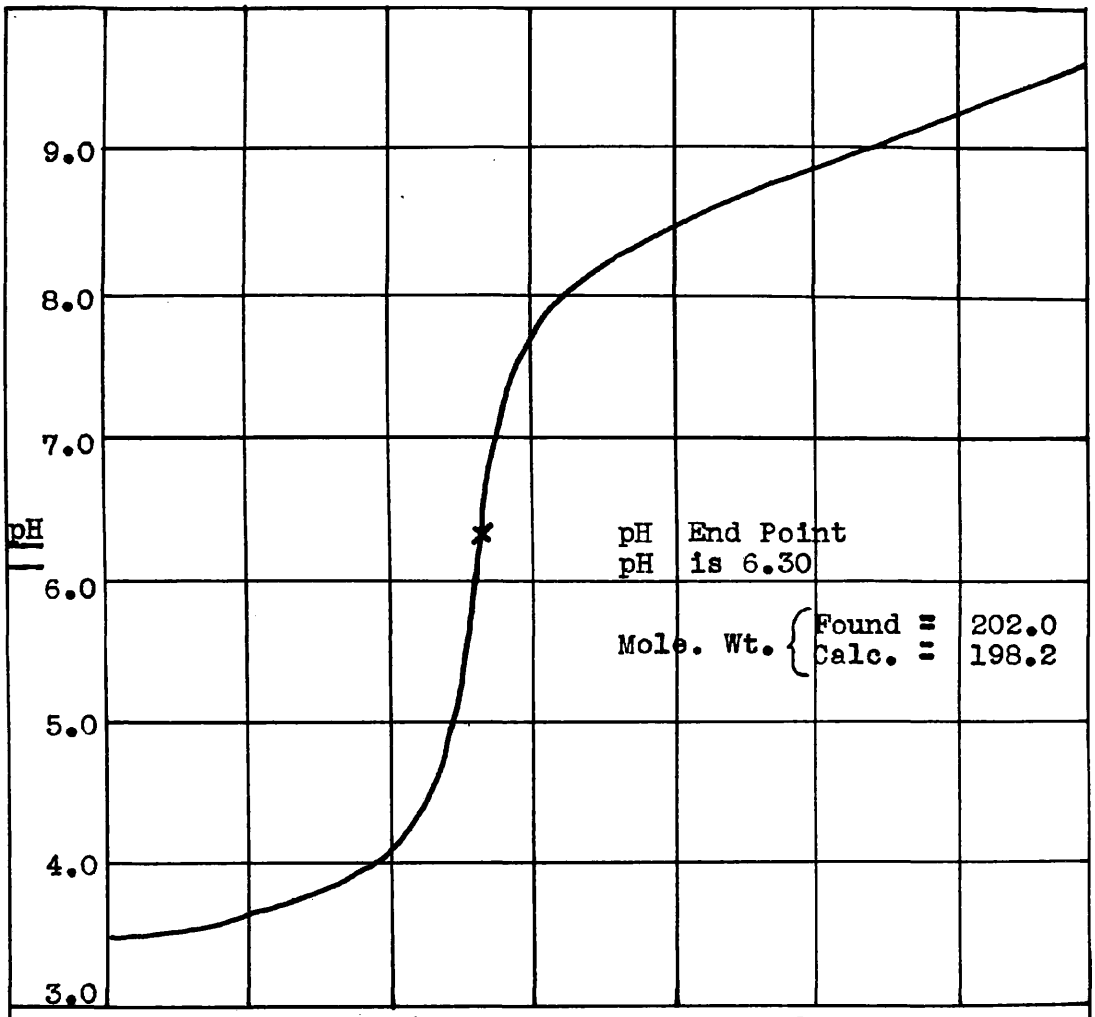
No explanation has been offered as to why some of the hydroxyarylglyoxylic acids formed lactones instead of the free acids while other hydroxyarylglyoxylic acids form lactones with difficulty or not at all.

Alongwith the formation of 2-hydroxynaphthylglyoxylic acid (X), an unknown compound which was insoluble

in base was formed. This compound appeared to have the empirical formula, $C_{29}H_{24}NO_6$. All attempts to find functional groups on this compound failed. No further work was attempted on this compound.

On methylation of the 2-hydroxynaphthylglyoxylic acid lactone (X) with dimethyl sulfate, the 2-methoxynaphthylglyoxylic acid (XI) was formed. Staudinger, Schlenker and Goldstein (77) reported that this methoxy compound (XI) could not be obtained by the action of dimethyl sulfate or methyl iodide on the lactone (X). Rousset (73,74) had previously prepared the methoxy acid by condensing ethyl chlorooxalate with β-methoxynaphthalene in the presence of aluminum chloride. No difficulties were experienced in this investigation on methylation of 2-hydroxynaphthylglyoxylic acid lactone (X).

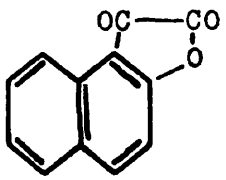
Neutral equivalents of both the lactone of 2-hydroxynaphthylglyoxylic acid (X) and the 2-methoxynaphthylglyoxylic acid (XI) were obtained by using a Beckman pH meter. (pp. 31,32) Visual titration in water using phenolphthalein as an indicator were unsuccessful since the end points were obscured by the yellow color of the solution. The equivalence points on both acids were well defined and the pH at these points were 6.5 for the lactone (X) and 6.3 for the methoxy acid (XI). This indicated that the acids were weak, as would be expected. Neutral equivalents calculated for the equivalence points were 202.0 in stead of 198.2 for the

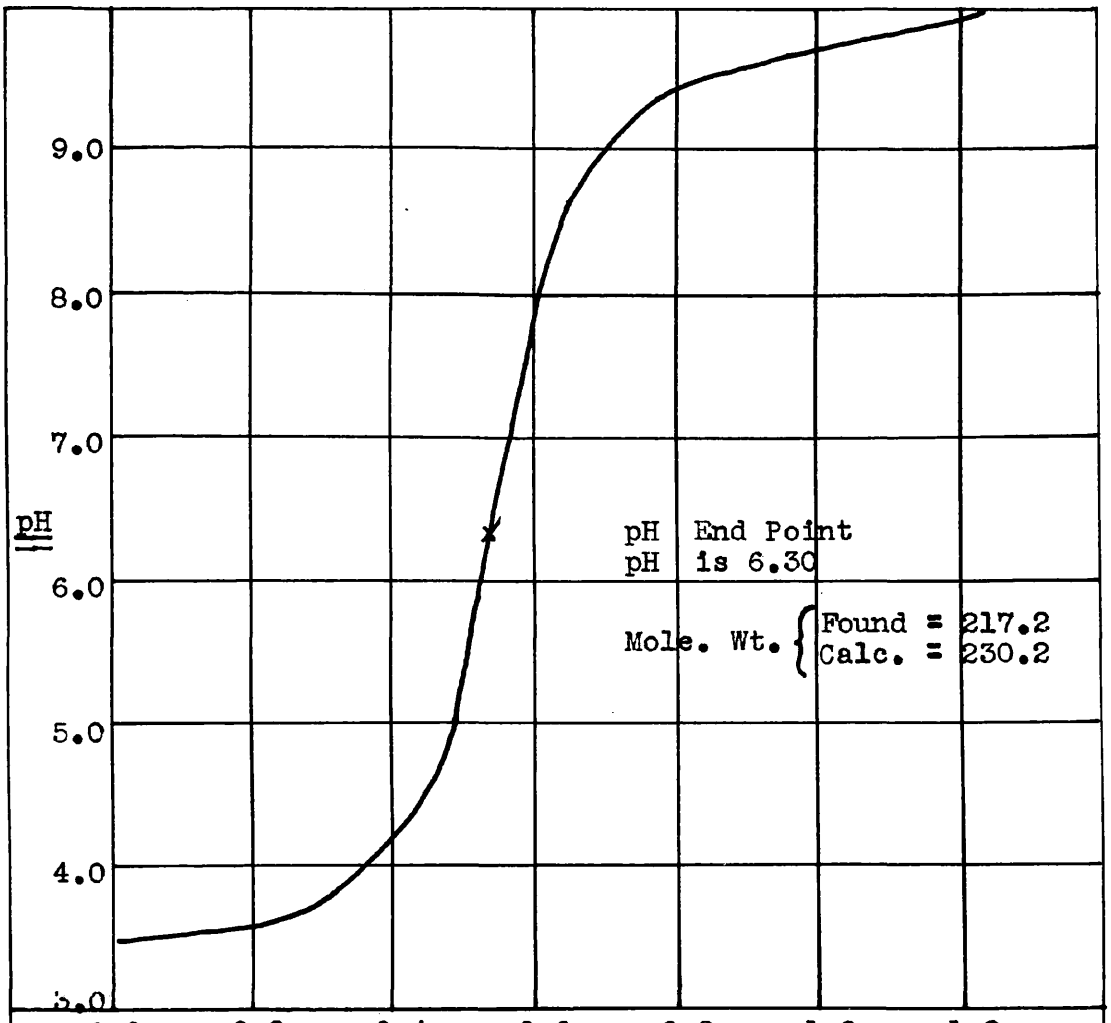


Neutral Equivalent

of

2-Hydroxynaphthylglyoxylic Acid Lactone (X)

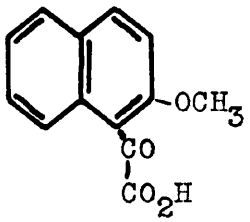




Neutral Equivalent

of

2-Methoxynaphthylglyoxylic Acid (XI)



lactone (X) and 217.2 instead of 230.2 for the methoxy acid (XI).

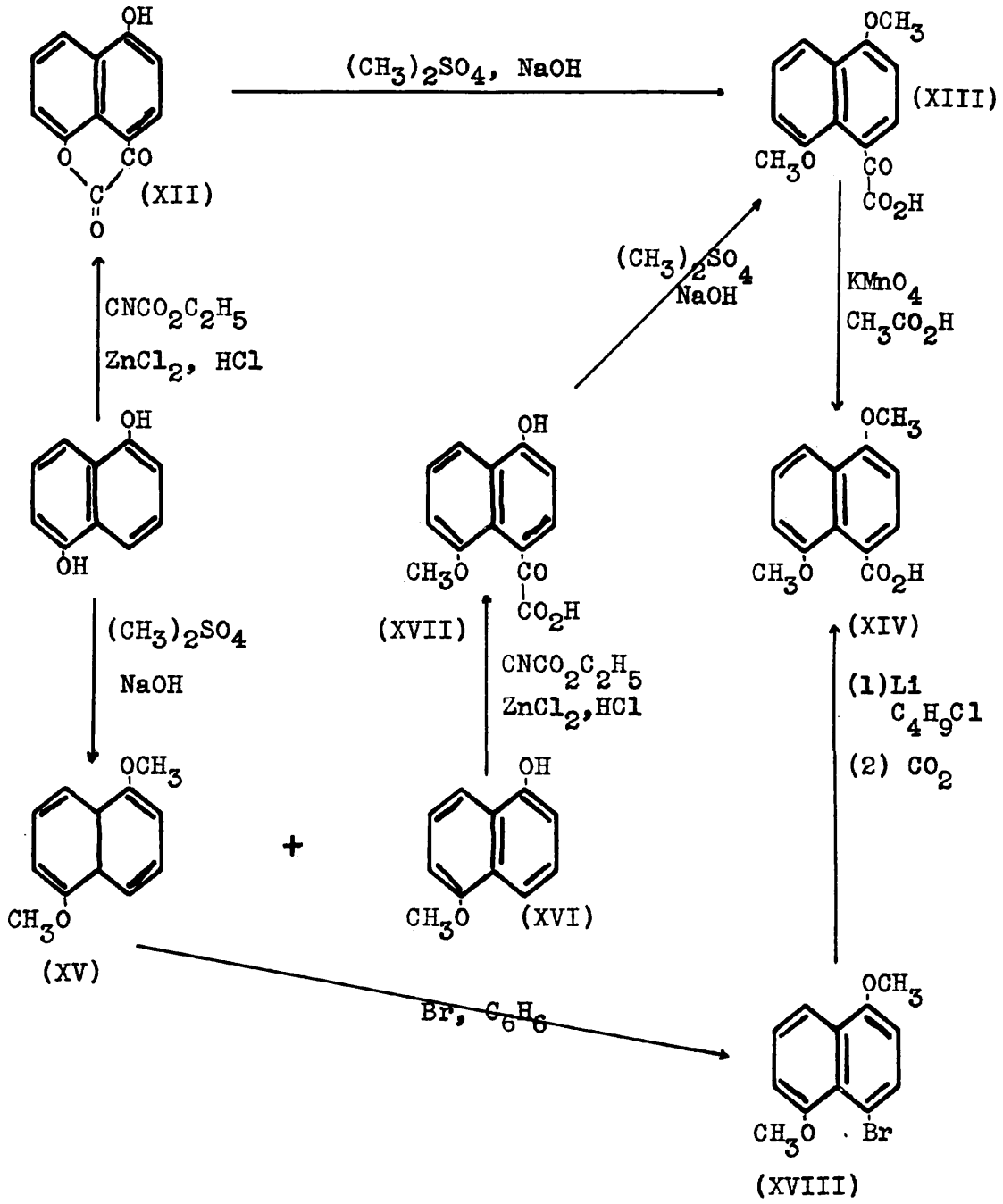
1,5-Dihydroxynaphthalene Series

The reactions involved in this part of the work are outlined in the accompanying diagram (p. 34).

On reacting ethyl cyanoformate with 1,5-dihydroxynaphthalene, an impure brick-red compound was obtained. After many fractional crystallizations, a small amount of a pure brick-red compound was obtained. This compound was later identified as the 4,8-dihydroxynaphthylglyoxylic acid lactone (XII). Here again the lactone was readily formed instead of the free acid. Apparently, there was a small amount of the other isomer, 1,5,-dihydroxynaphthyl-2-glyoxylic acid lactone formed, for the impure red compound remaining after the pure lactone (XII) was obtained analyzed correctly for the lactone even though the melting point was over a range, 284-295°C. with decomposition. The pure lactone (XII) melted at 294-296°C. with decomposition.

Knobloch and Schraufstatter (56) reported a melting point of 272°C. for a brick-red compound which they obtained from the reaction of cyanogen on 1,5-dihydroxynaphthalene. They were not sure whether they had the 1,5-dihydroxynaphthyl-2 or 4-glyoxylic acid lactone. From the work reported in this dissertation, it appears as though they had the 1,5-dihydroxynaphthyl-2-glyoxylic acid lactone since

1,5-Dihydroxynaphthalene Series



in this investigation, the lactone obtained was shown to be the 4,8-dihydroxynaphthylglyoxylic acid lactone (XII).

On methylation of the 4,8-dihydroxynaphthylglyoxylic acid lactone (XII) with dimethyl sulfate in the usual manner, 4,8-dimethoxynaphthylglyoxylic acid (XIII) was obtained. This acid (XIII) was pale yellow and melted at 190.8-191.6°C. with decomposition.

Methylation of 1,5-dihydroxynaphthalene with dimethyl sulfate yielded two products; 1,5-dimethoxynaphthalene (XV) and 1,5-methoxynaphthol (XVI). Both of these compounds were of use for later synthetic work in this series.

The 1,5-methoxynaphthol was treated with ethyl cyanoformate and a yellow acid, 4-hydroxy-8-methoxy naphthylglyoxylic acid (XVII) was obtained. The position of the glyoxylic acid group on the ring was determined by methylation to form the same dimethoxy acid (XIII) as that obtained from the lactone (XII).

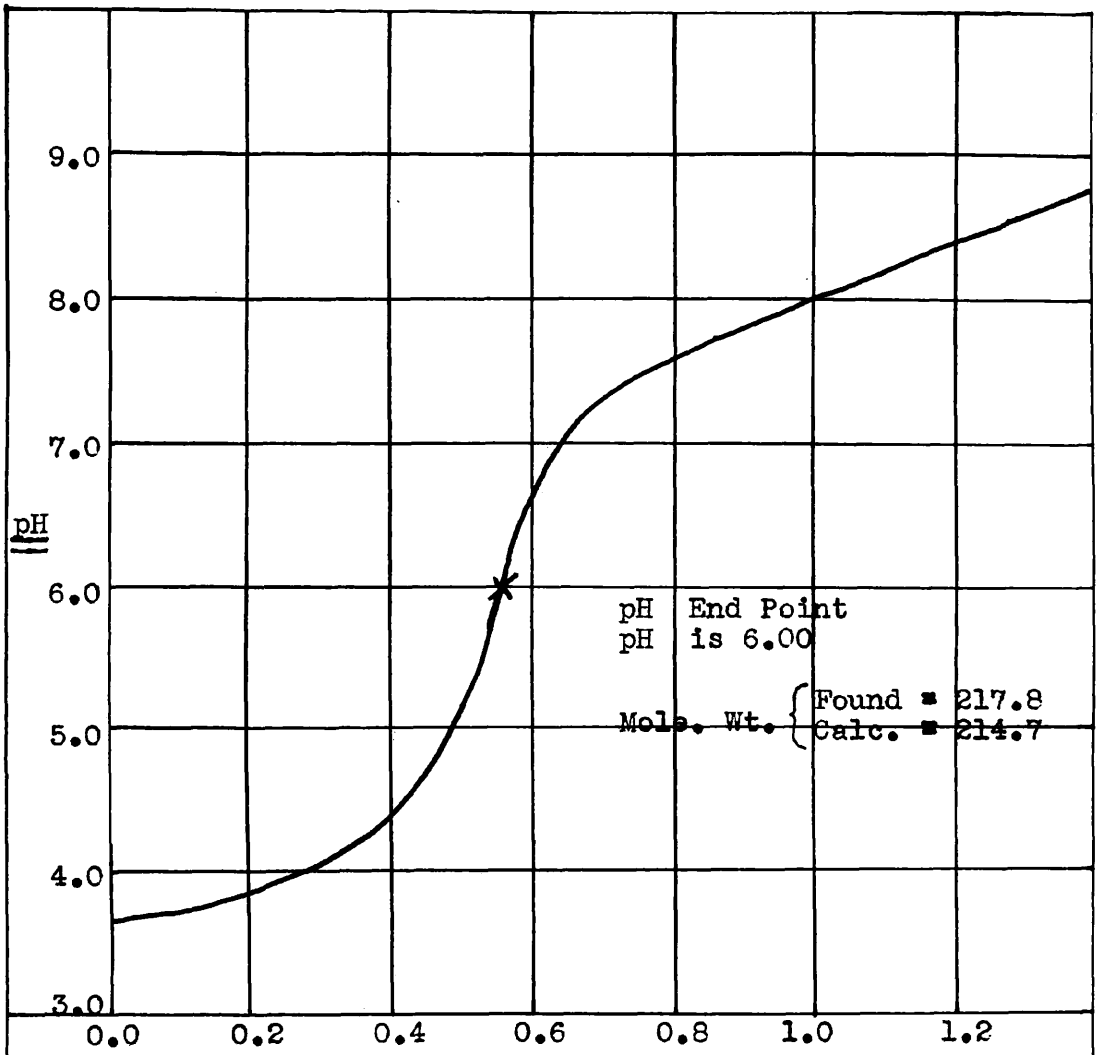
The position of the glyoxylic acid group on the ring of the dimethoxy acid (XIII) was determined by the oxidation of the dimethoxy acid (XIII) by potassium permanganate. The acid obtained, 4,8-dimethoxynaphthoic acid, was a known acid. A sample of this known acid was prepared from 1,5-dimethoxynaphthalene (XV) by bromination to the 4,8-dimethoxybromonaphthalene (XVIII), conversion to a lithium Grignard compound and finally formation of the naphthoic acid (XIV) by treating the lithium complex with carbon dioxide.

A mixed melting point of this acid with that obtained from the 4,8-dimethoxynaphthoic acid (XIII) showed no depression. As the position of the carboxyl group in the 4,8-dimethoxynaphthoic acid (XIV) was known (49), then the position of the glyoxylic acid group in all the compounds prepared was also known. This fact then proves that the acids obtained were as named.

Neutral equivalents of the acids, 4,8-dihydroxynaphthylglyoxylic acid lactone (XII), 4-hydroxy-8-methoxynaphthylglyoxylic acid (XVII) and 4,8-dimethoxynaphthylglyoxylic acid (XIII) were all determined using a Beckmann pH meter. Visual titrations in water using phenolphthalein as an indicator were unsuccessful since the endpoints were obscured by the yellow color of the solution. The equivalence points on the acids were as in the previous series well-defined and the pH at these points were 6.0 for the lactone (XII), 6.2 for the methoxyhydroxy acid (XVII) and 6.8 for the dimethoxy acid (XIII). This indicated that the acids were weak acids as would be expected. Neutral equivalents calculated for the equivalence points were 217.8 instead of 214.7 for the lactone (XII), 233.4 instead of 246.2 for the methoxy hydroxy acid (XVII) and 251.8 instead of 260.2 for the dimethoxy acid (XIII).

2,7-Dihydroxynaphthalene Series

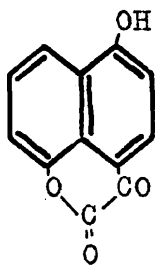
This series of reactions using 2,7-dihydroxynaphthalene as shown in the accompanying diagram (p. 40)

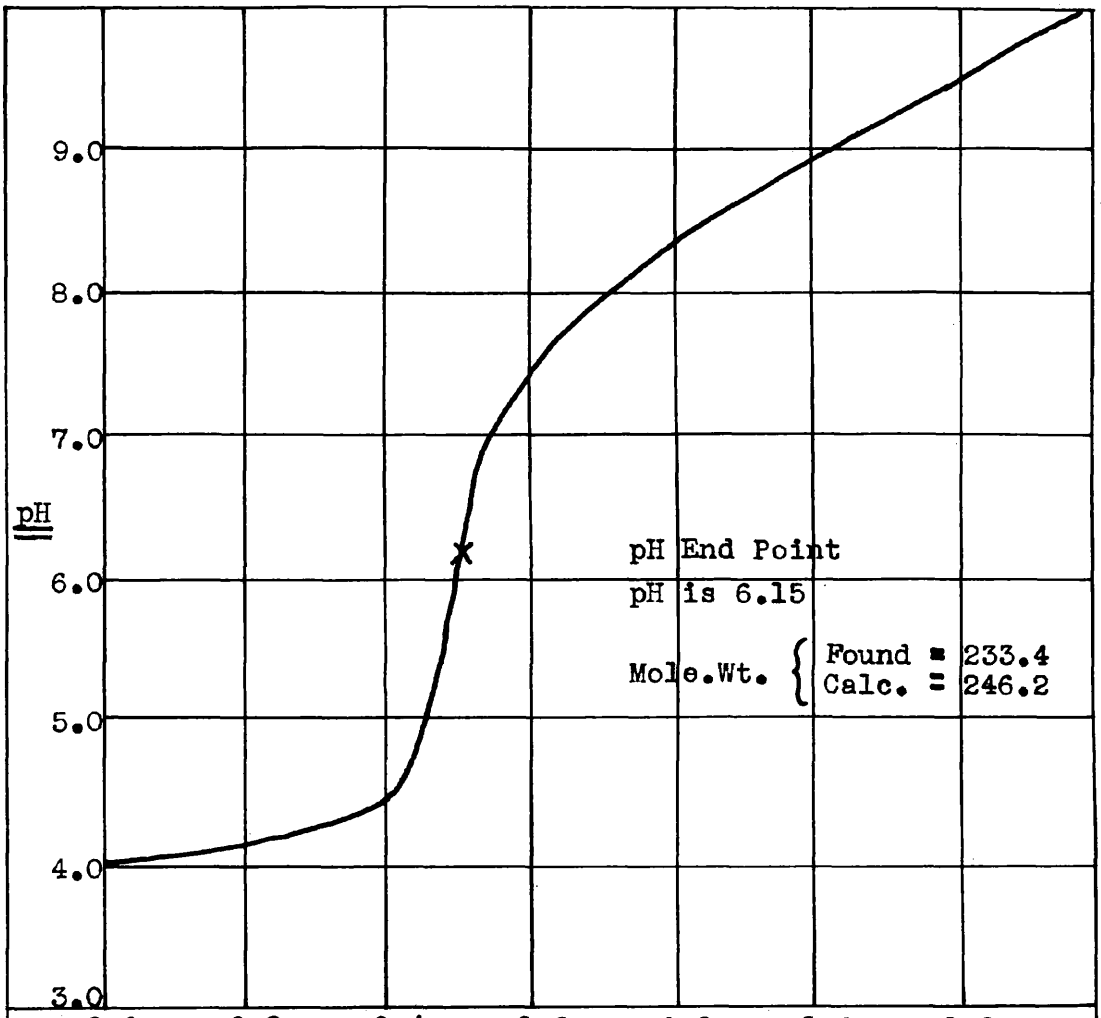


Neutral Equivalent

of

1,5-Dihydroxynaphthylglyoxylic Acid Lactone (XII)

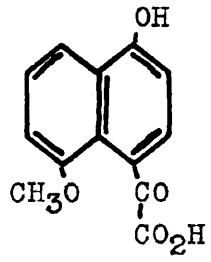


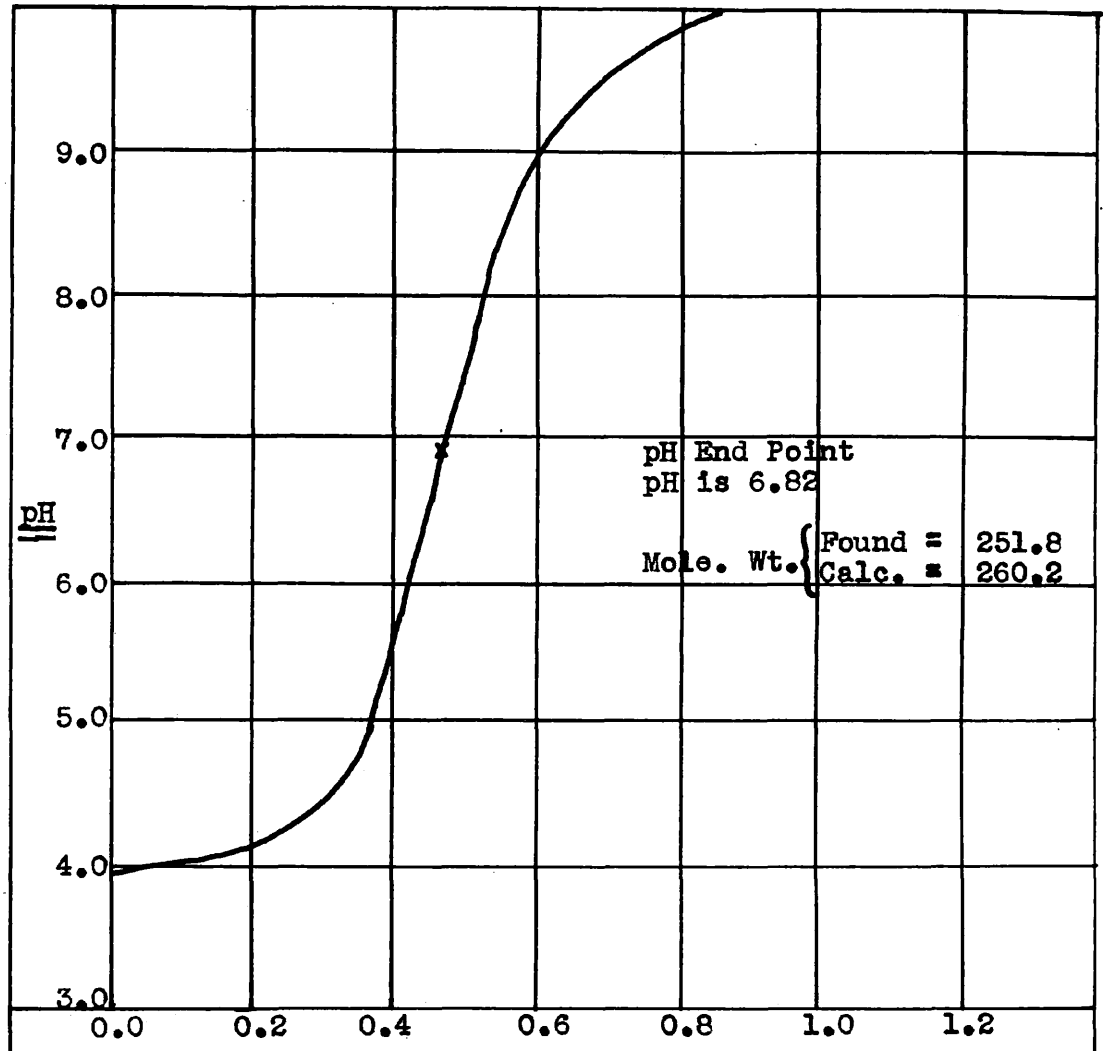


Neutral Equivalent

of

4-Hydroxy-8-Methoxynaphthylglyoxylic Acid (XVII)

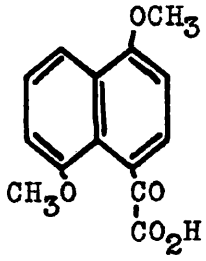




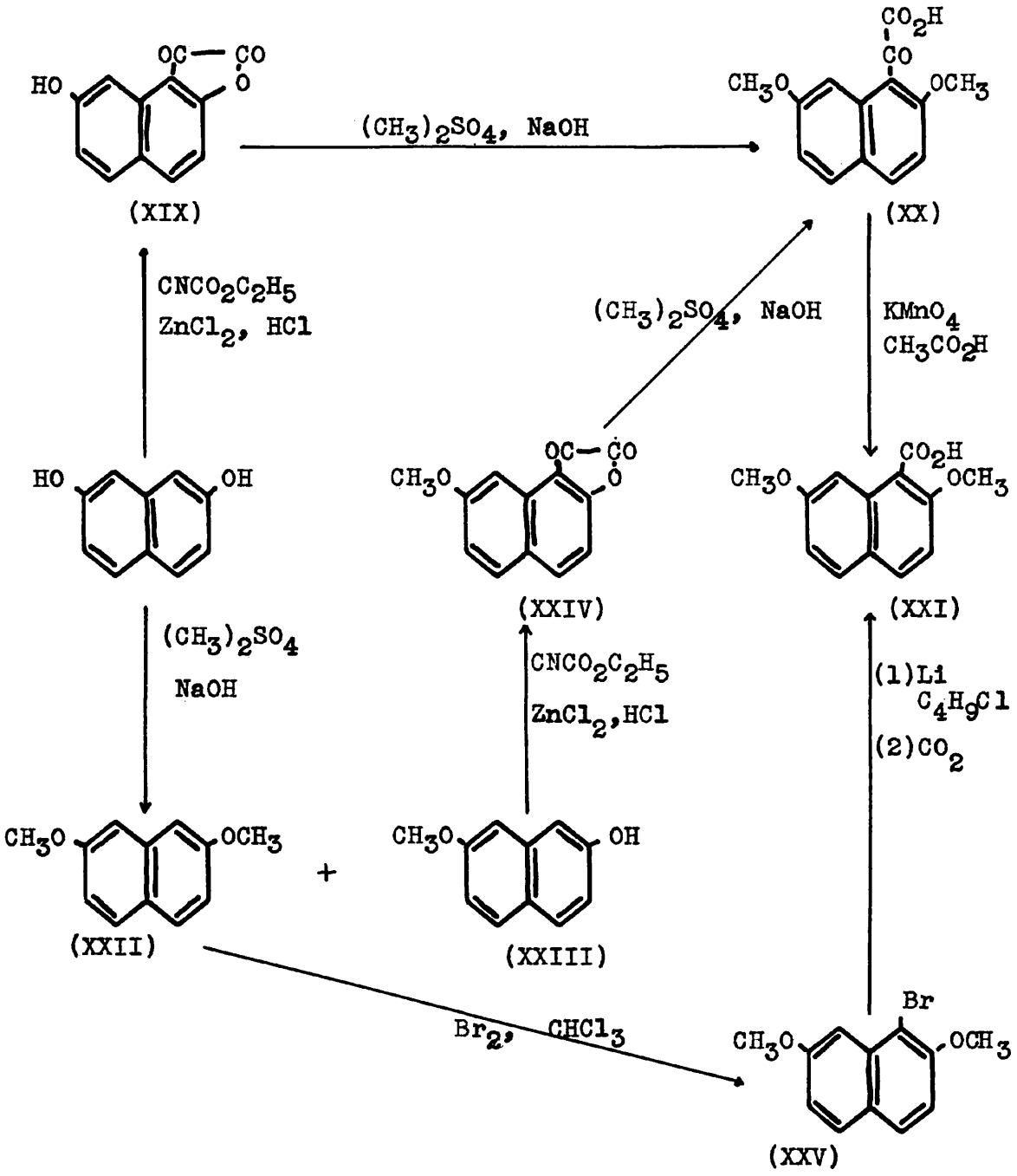
Neutral Equivalent

of

1,5-Dimethoxynaphthylglyoxylic Acid (XIII)



2,7-Dihydroxynaphthylene Series



followed that of the 1,5-dihydroxynaphthalene series.

On condensing ethyl cyanoformate with 2,7-dihydroxynaphthalene, a red compound was formed. This compound was later shown to be the 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX). Here again the lactone was formed instead of the free acid. This lactone, which melted at 280-282°C. with decomposition, had the same melting point as the lactone prepared by Passerini (64,66) from the reaction of phenyl isonitrile on 2,7-dihydroxynaphthalene.

Passerini (64,66) did not definitely prove the position of the glyoxylic acid group in the lactone (XIX) but he did oxidize the lactone (XIX), using 30% hydrogen peroxide in glacial acetic acid to form the 2,7-dihydroxynaphthoic acid. An attempt was made to repeat this work but nothing was obtained from the reaction.

Therefore, in order to prove the position of the glyoxylic acid group in the lactone (XIX), the lactone was methylated, using dimethyl sulfate to form the 2,7-dimethoxynaphthylglyoxylic acid (XX). This acid was then oxidized, using potassium permanganate and 50% acetic acid to form the 2,7-dimethoxynaphthoic acid (XXI). The position of the carboxyl group in this acid (XXI) was definitely proven by Adams, Miller, McGrew and Anderson (2). A sample of this acid was prepared by the same method used by Adams and his associates (2) and it proved to be the same as that obtained from the dimethoxy acid (XX).

The preparation of the 2,7-dimethoxynaphthoic acid consisted of methylation of the 2,7-dihydroxynaphthalene, using dimethyl sulfate, conversion of the 2,7-dimethoxynaphthalene (XXII) obtained to form the 2,7-dimethoxybromonaphthalene, using bromine in chloroform and finally carbonation of the lithium Grignard compound formed from the bromo compound (XXII) to form the acid. The yields on the 2,7-dimethoxybromonaphthalene and the 2,7-dimethoxynaphthoic acid were considerably lower than those reported in the literature (2).

Alongwith the 2,7-dimethoxynaphthalene (XXII), 2,7-methoxynaphthol (XXIII) was formed. The methoxynaphthol (XXIII) was used in preparing 2-hydroxy-7-methoxynaphthylglyoxylic acid (XXIV) by condensing ethyl cyanoformate with the naphthol (XXIII). The position of the glyoxylic acid was determined by methylation using dimethyl sulfate to form the same dimethoxy acid as that obtained by methylation of the 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX). A mixed melting of these two acids showed no depression.

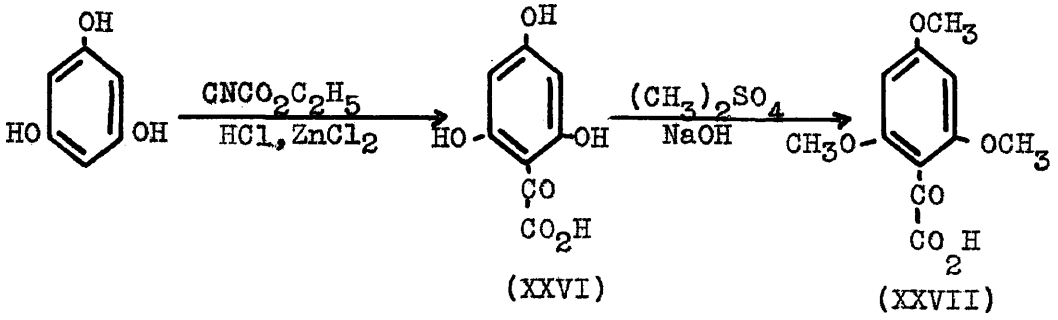
Staudinger, Schlenker and Goldstein (77) reported that they prepared the 2-hydroxy-7-methoxynaphthylglyoxylic (XXIV) acid by condensing oxalyl chloride with 2,7-dimethoxy naphthalene (XXII). The acid that they made has a melting point of 184°C. with decomposition, and its color was yellow-brown. These physical characteristics are different from those of the acid obtained in this investigation. The melting points of the acid which was proven to be the 2-hydroxy-7-methoxy-naphthylglyoxylic acid lactone (XXIV),

obtained in this investigation, was 199.6-200.6°C. with decomposition and its color is a bright orange. It appears that Staudinger, Schlenker and Goldstein did not have the acid which they reported.

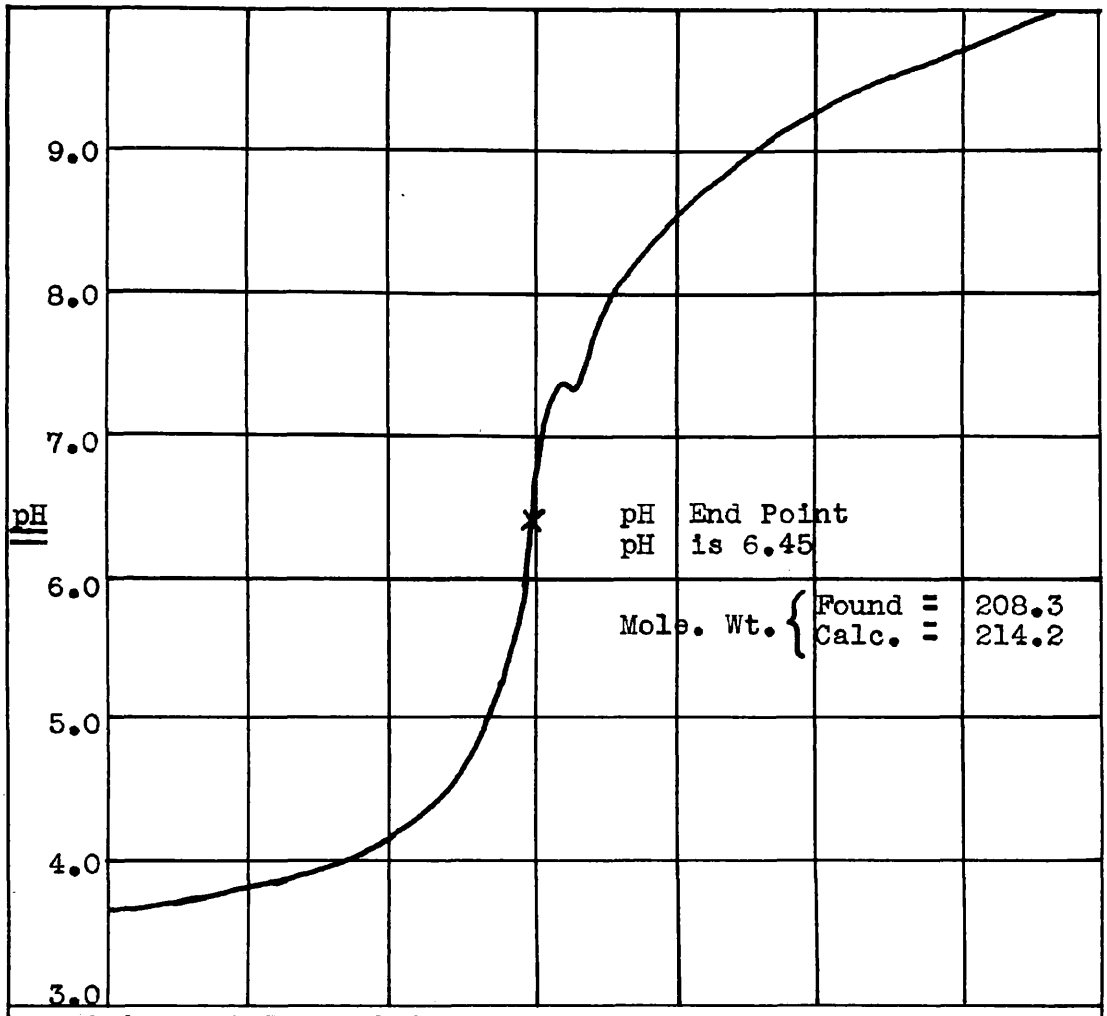
Neutral equivalents were obtained on the acids using a Beckman pH meter. The endpoint of visual titrations, using phenolphthalein as an indicator, were obscured by the yellow color of the solution. The neutral equivalents of the acids are 208.3 instead of 214.2 for 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX), 255.6 instead of 260.2 for 2,7-dimethoxynaphthylglyoxylic acid (XX), and 221.8 instead of 228.2 for 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIV). The curves for these acids are on the pages following.

Phloroglucinol Series

Several attempts were made to prepare the phloroglucinolglyoxylic acid (XXVI) by condensing ethyl cyanoformate and phloroglucinol; however, all that was obtained was a yellow compound which did not melt but turned black at 192°C. The empirical formula as obtained from the analytical



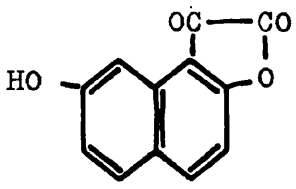
(XXVI) (XXVII)

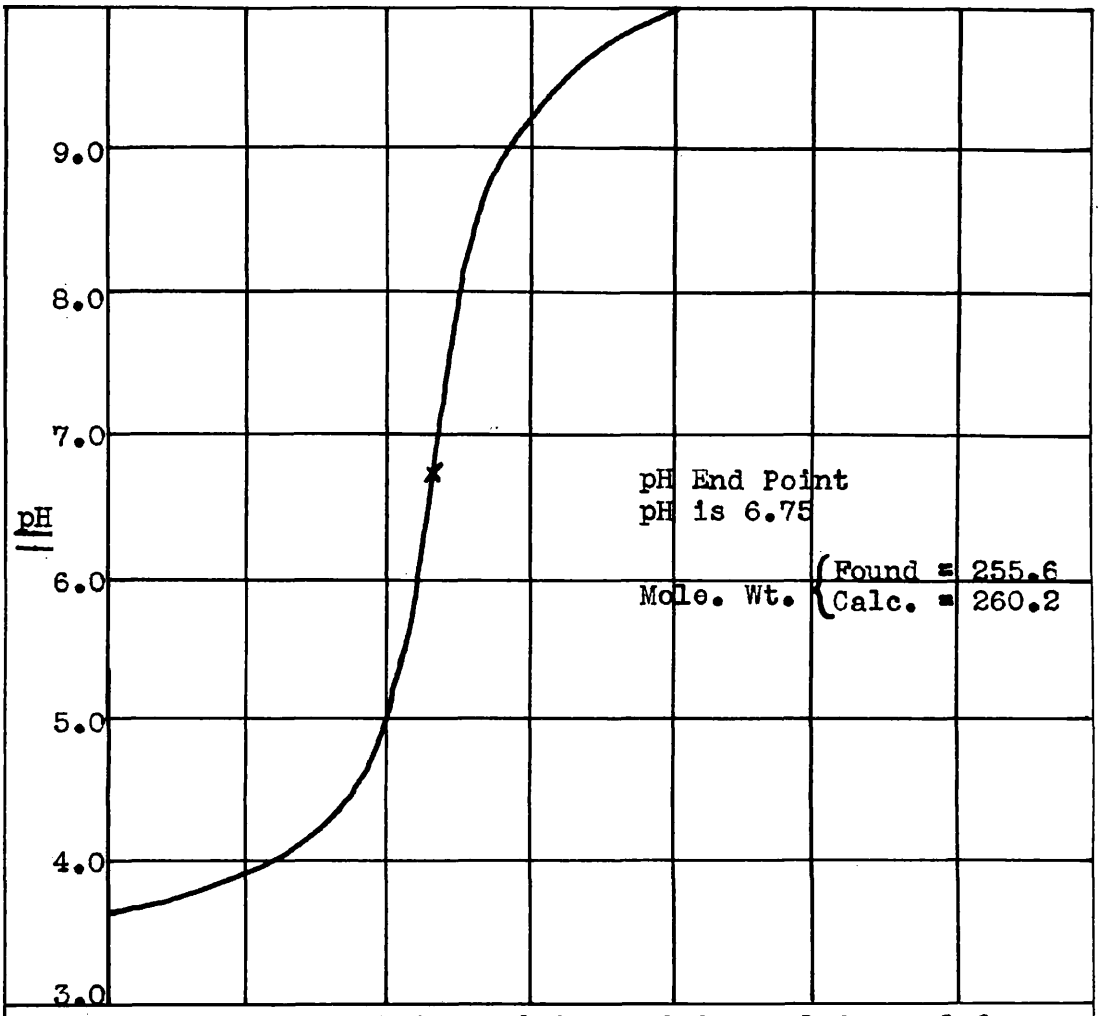


Neutral Equivalent

of

2,7-Dihydroxynaphthylglyoxylic Acid Lactone (XIX)

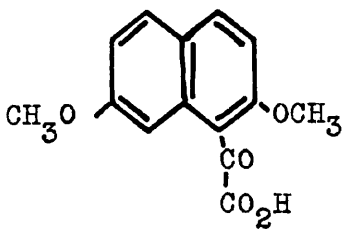


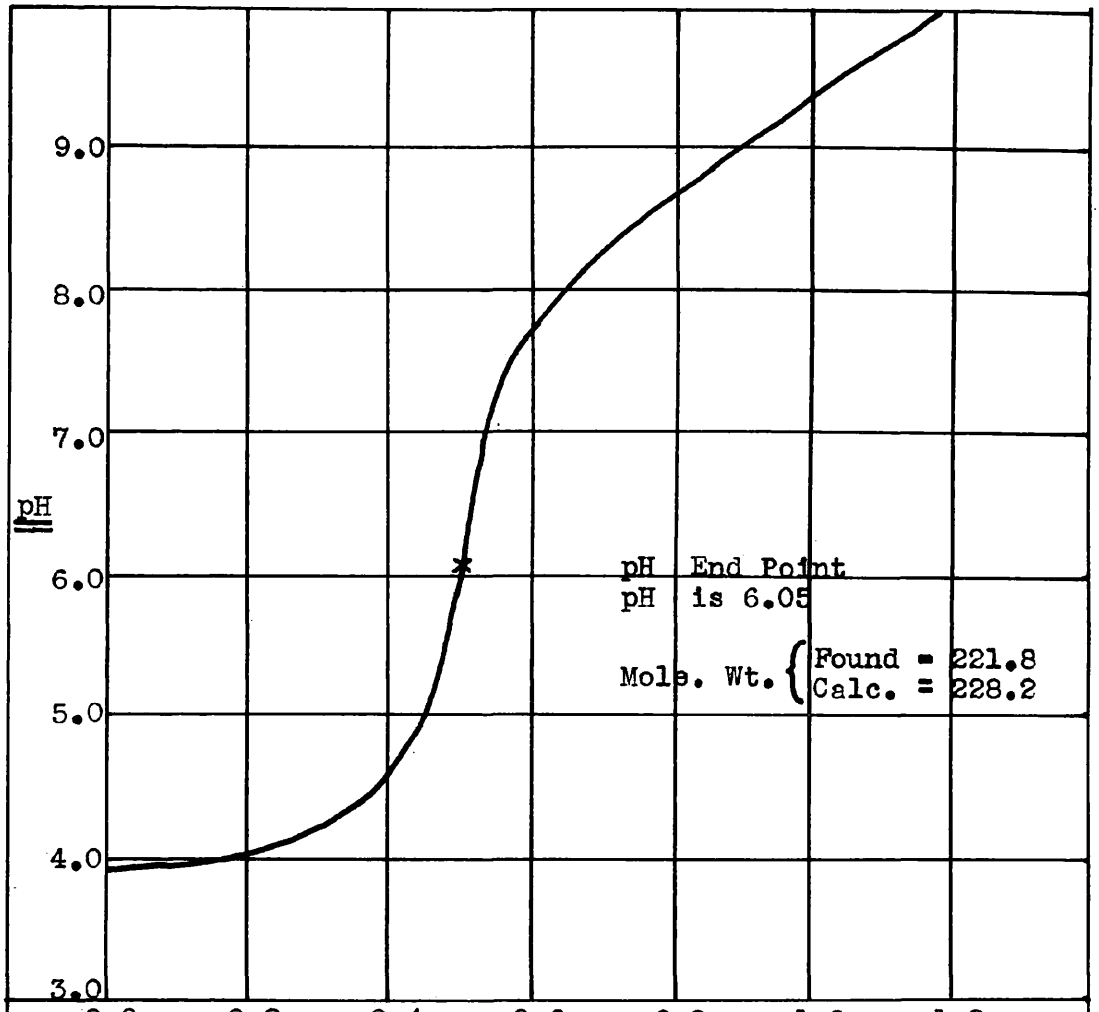


Neutral Equivalent

of

2,7-Dimethoxynaphthylglyoxylic Acid (XX)

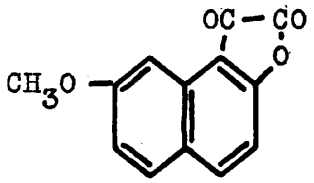




Neutral Equivalent

of

2-Hydroxy-7-Methoxynaphthylglyoxylic Acid Lactone (XXIV)



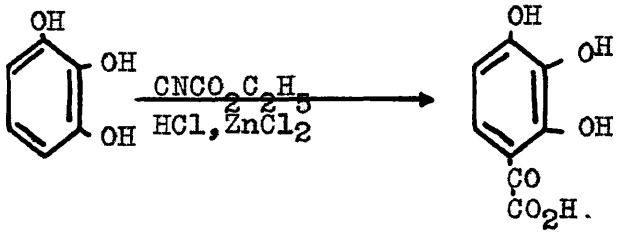
results was $C_{16}H_{19}O_5$.

Methylation of the yellow powder using dimethyl sulfate, methyl iodide or diazomethane produced no identifiable compound. Jonas (51) reported preparing this trimethoxyphloroglucinol glyoxylic acid (XXVII) by oxidation of the phloroacetophenone by potassium permanganate.

No further work was done with the compounds in this series.

Pyrogallol Series

An attempt was made to purify the yellow-orange compound (made by Dr. E. D. Amstutz), which was thought to be the pyrogallolglyoxylic acid (XXXVIII), by condensing ethyl cyanoformate with pyrogallol. After several recrystallizations from water, the yellow-orange acidic compound melted at 162.4-164.4°C. with decomposition.



(XXVIII)

No definite empirical formula could be assigned to this compound and no further work was done with this compound.

Phenol Series

Two attempts were made to prepare the p-hydroxy-

phenylglyoxylic acid (XXX); one, using phenol and the other, phenylacetate (XXXI). (See p. 49) The results in both cases were the same. Only phenol and oxalic acid were obtained from the reaction. The phenol itself was not obtained but the odor was quite discernable. The oxalic acid was obtained as a dihydrate and a mixed melting point with a known sample of oxalic acid dihydrate showed no depression.

No further work was done with this reaction.

Ethyl Cyanoformate Reaction

It was considered to be of interest to determine what would occur when a "dry-run" was made, using just ethyl cyanoformate, zinc chloride, absolute ether and dry hydrogen chloride without any aromatic hydrocarbon. From this reaction, oxalic acid dihydrate was recovered and was confirmed by a mixed melting point with a known sample of

$$CNCO_2C_2H_5 \xrightarrow[HCl]{ZnCl_2} ClH\cdot HN = C\text{-}CO_2C_2H_5 \xrightarrow{NaOH} (CO_2H)\cdot 2H_2O$$

(XXXIII)

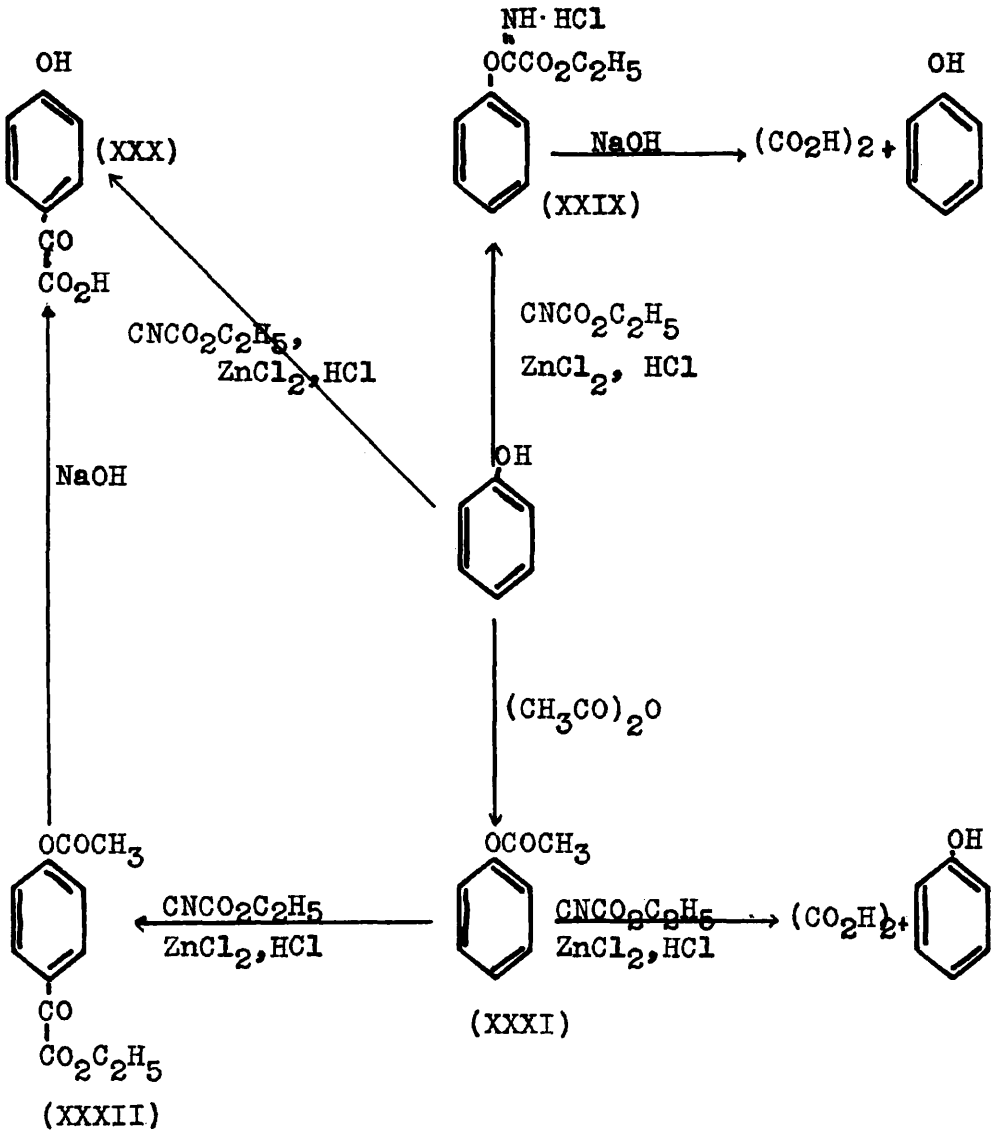
oxalic acid dihydrate.

This result showed how the oxalic acid was being formed in the reactions in the phenol series and thiophene series.

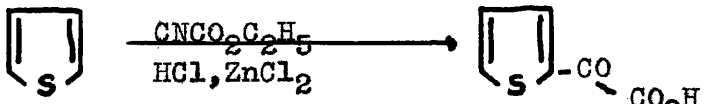
Thiophene Series

Attempts to prepare α-thienylglyoxylic acid

Phenol Series



(XXXIV) by condensing ethyl cyanoformate and thiophene were without success. All that could be recovered from the reaction mixture were thiophene, oxalic acid and some unidentifiable material.

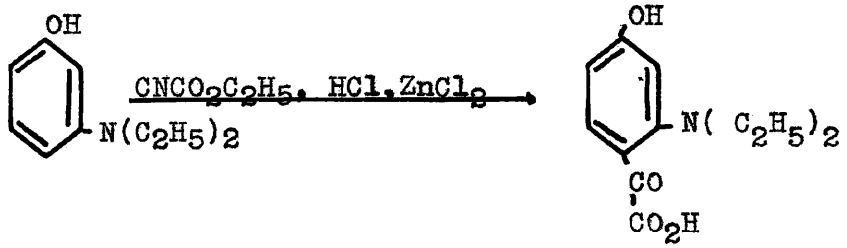


(XXXIV)

Peter (68) had previously prepared α-thienylglyoxylic acid by oxidation of α-acetylthiophene with potassium permanganate.

m-Diethylaminophenol Reaction

Several attempts were also made to prepare the 2-diethylamino-4-hydroxyphenylglyoxylic acid by condensing ethyl cyanoformate with m-diethylaminophenol without success.



(XXXV)

All that could be recovered from the reaction was an unidentifiable black tar. No further work was done with this reaction.

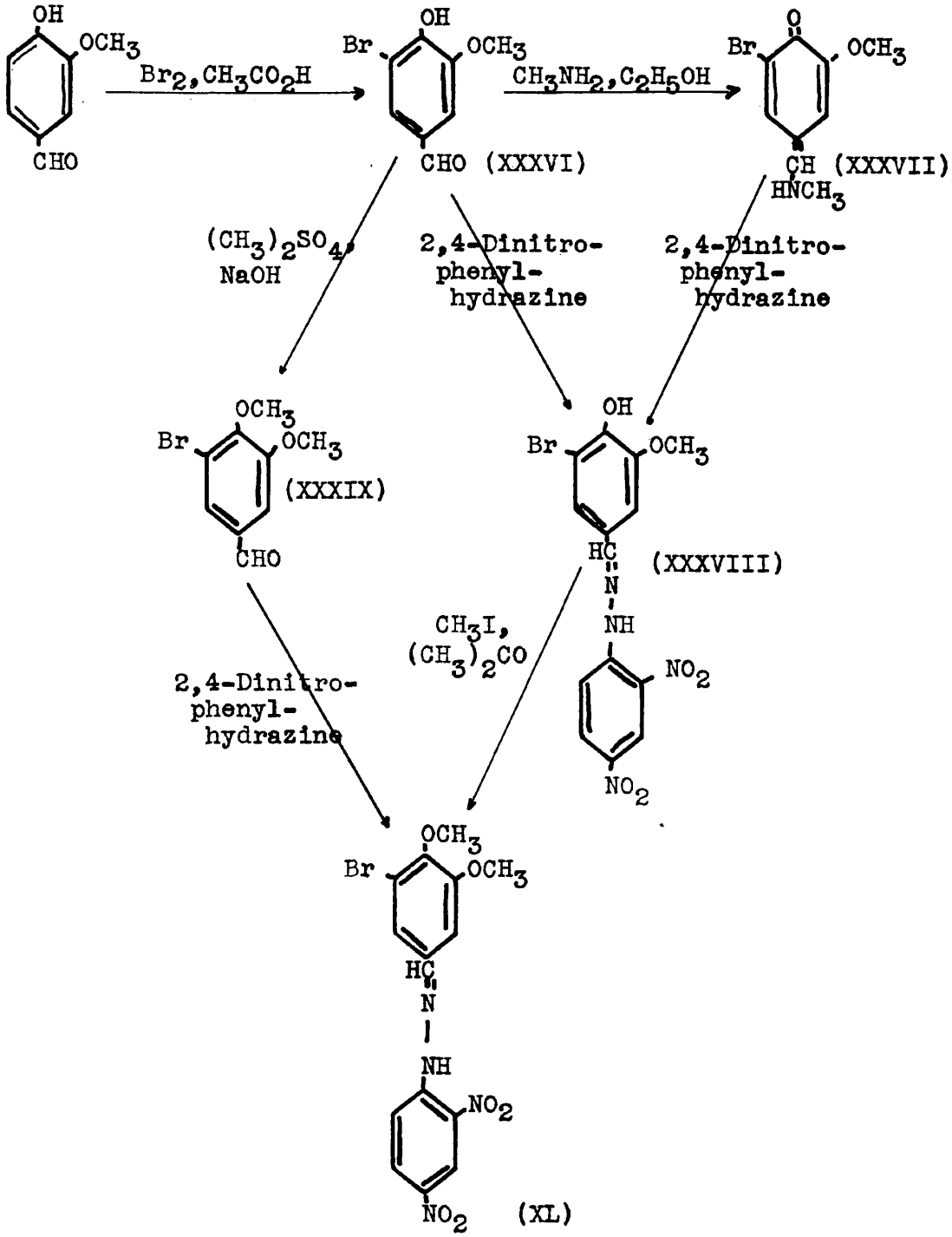
Methylenequinone Series

It was hoped that 3-methoxy-5-bromomethylaminomethylenequinone (XXXVII) could be used in an ultraviolet spectrometric investigation of the properties of the glyoxylic acids prepared in this investigation and in the one made by Hunsberger and Amstutz (50). It was thought that a comparison of the ultraviolet curves between a compound with a known methylenequinone structure, such as, compound XXXVII and some hydroxyarylglyoxylic acids would show whether these acids existed as methylenequinones; however, time would not permit this investigation.

In order to prepare the methylenequinone (XXXVII), vanillin was brominated and the 5-bromovanillin (XXXVI) obtained dissolved in alcohol and methylamine passed into it. The yellow compound which separated was the 3-methoxy-5-bromomethylaminomethylenequinone (XXXVII). The melting point obtained was 229.4-230.4°C. which was different from that obtained by Makarow (60), 211°C. with decomposition at 214-215°C.

An attempt to prepare the 2,4-dinitrophenylhydrazone of 3-methoxy-5-bromomethylaminomethylenequinone (XXXVIII) resulted in the formation of the same 2,4-dinitrophenylhydrazone as that obtained from 5-bromovanillin. (The following sheet outlines the reactions in this series.) Apparently, the conditions used in the formation of hydrazones were too strenuous and the methylamino group was

Methylenequinone Series



removed as methylamine. The methylenequinone (XXXVII) was then changed to the 5-bromovanillin (XXXVI) and it was this compound which reacted with the 2,4-dinitrophenylhydrazine.

Methylation of the hydrazone formed above (XXXVIII) with methyl iodide (methyl sulfate and diazomethane were unsuccessful) yielded the same hydrazone (XL) as that obtained from 5-bromoveratraldehyde. The 5-bromoveratraldehyde was obtained by methylation of 5-bromovanillin (XXXVI) with dimethyl sulfate.

Part III

Experimental

α-Naphthol Series*

Ethyl Cyanoformate - In a one-liter, three-necked flask, equipped with a thermometer and a stirrer was placed 160.6 g. (1.48 mole) of ethyl chloroformate (Eastman Kodak Company). To the chloroformate were added gradually over a one-hour period 121 g. (1.86 mole) of dried and powdered potassium cyanide containing 1,5% water, in accordance with the directions of Glund, Nüsseler and Keller (46). The temperature of the reaction gradually rose to 70°C. during the addition. Stirring was continued until it returned to room temperature. Distillation at dimished pressure (water-pump) yielded a clear distillate which was redistilled at atmospheric pressure (Widmer Column), producing 84.3 g. (57.5%) of ethyl cyanoformate boiling at 113-117°C.

4-Hydroxynaphthylglyoxylic Acid Monohydrate (I)** - To a 200 ml. three-necked flask fitted with a condenser, a large diameter gas inlet tube and a stirrer were added 14.4 g. (0.1 mole) of α-naphthol (Eastman Kodak Company), 11.0 g. (0.11 mole) of ethyl cyanoformate, 0.9 g. of freshly fused zinc chloride and 100 ml. of absolute ether. The solu-

* All melting points are corrected.
** The method used for preparing the glyoxylic acid is, with slight modifications, that of Hunsberger and Amstutz (50).

tion was stirred until all the solids had dissolved and then it was cooled with an ice-bath. Dry hydrogen chloride gas was passed into the reaction mixture for two hours, with the excess going out the condenser and through a gas trap. The flask was then sealed from moisture and placed overnight in the refrigerator. The next day, dry hydrogen chloride was again passed into the cold solution for two hours. The flask was then placed in the refrigerator for three days.

After three days a red, oily precipitate had separated out on the sides of the flask. This precipitate was filtered off from the ether. More oily precipitate was obtained from the ether by addition of fresh absolute ether. These precipitates were added to a 2.5% sodium hydroxide solution and heated for fifteen minutes. On acidification with concentrated hydrochloric acid, after cooling, a yellow-orange precipitate separated out alongwith some tarry material. After repeated treatments with Darco and recrystallizations from boiling water, the tarry material was removed and 8.8 g. (40.7%) of a fine crystalline yellow compound settled out. The glyoxylic acid melted at 188.4-189.4°C. with decomposition.

On analysis this compound was found to contain one molecule of water.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Neut. Eq., 234.2. Found: C, 61.33; H, 4.19. Neut. Eq., 290. 3.

Drying the above glyoxylic acid over P_2O_5 at

80°C. for two days yielded the yellow anhydrous 4-hydroxynaphthylglyoxylic acid (II) which melted at 191.2-191.8°C. with decomposition. Analysis showed that the acid had lost a molecule of water.

Anal. Calcd. for $C_{12}H_8O_4$: C, 66.66; H, 3.73. Found: C, 66.54; H, 3.98.

Repeated attempts to prepare the 2,4-dinitrophenylhydrazone of 4-hydroxynaphthylglyoxylic acid failed. The method used was that given by Shriner and Fuson (76).

Methyl 4-hydroxynaphthylglyoxylate monohydrate (III) - For thirty minutes dry hydrogen chloride was passed into a cooled solution containing 0.5 g. (0.00213 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I) in 20 ml. of absolute methanol. The solution was then refluxed for thirty minutes and evaporated almost to dryness on the steam bath. The yellow solid obtained was treated with 10% sodium bicarbonate and filtered. The precipitate remaining was treated with Darco and recrystallized several times from boiling aqueous alcohol. Yellow crystals amounting to 0.44 g. (83.5%) and melting at 142.8 - 143.5°C. were obtained.

On analysis this compound was found to contain one molecule of water.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.91; H, 4.88. Found: C, 62.98; H, 5.08.

Methyl 4-methoxynaphthylglyoxylate (IV)

A. Methyl iodide method. - In a 25 ml.

flask were placed 0.32 g. (0.00137 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I), 10 ml. of acetone dried over anhydrous sodium sulfate, 1.95 g. (0.0137 mole) of methyl iodide and 0.9 g. of potassium carbonate. This mixture was refluxed for eight hours, the potassium carbonate filtered off, and the acetone evaporated. The mustard colored oil, thus obtained, was treated with Darco and recrystallized several times from aqueous methanol. A light yellow crystalline ester separated yielding 0.25 g. (74.9%) of pure compound, melting at 84.8-85.6°C.*

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.69; H, 4.98.

B. Diazomethane method. - To 1.08 g. (0.005 mole) of 4-hydroxynaphthylglyoxylic acid monohydrate (I) in 20 ml. of ether was added slowly a solution containing 0.62 g. (0.015 mole) of diazomethane**. The ether solution stood for twenty-four hours and was then evaporated. The tan residue was then treated with Darco and recrystallized from methanol. The light yellow crystalline ester weighed 0.89 g. (72.9%) melted at 84.8-85.8°C. and was identical to that prepared by the methyl iodide method.

4-Methoxynaphthylglyoxylic acid (V) - A solution consisting of 0.39 g. (0.0016 mole) of methyl 4-methoxynaphthylglyoxylate (IV) was refluxed for ten minutes with

*Rousset (73) reported a melting point of 87°C.
**The diazomethane was made according to the directions given by Amstutz and Meyers (3) and Arndt (5).

0.1 g. (0.0025 mole) of sodium hydroxide in 10 ml. of water. Acidification with dilute hydrochloric acid and subsequent recrystallization from water yielded 0.33 g. (89.4%) of a yellow crystalline glyoxylic acid melting at 163.6-164.6°C. with decomposition*.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.83; H, 4.38. Neut. Eq., 230.2. Found: C, 67.92; H, 4.33. Neut. Eq., 262.3.

4-Methoxynaphthoic acid (VI) - In 15 ml. of 50% glacial acetic acid was dissolved 0.1279 g. (0.000555) of 4-methoxynaphthylglyoxylic acid (V). To this gently refluxing solution was slowly added a hot solution of 0.0374 g. (0.000236 mole) of potassium permanganate (5% more than needed for the oxidation) in 10 ml. of 50% acetic acid. Carbon dioxide was given off readily during the oxidation. The mixture was refluxed for thirty minutes. The solution was then poured into 25 ml. of water and the precipitate filtered and redissolved in 1% sodium hydroxide and filtered again to remove the manganese dioxide. The solution was acidified, the precipitate filtered and recrystallized from 95% alcohol. The acid, 0.0484 g. (43.1%), was obtained as fine white crystals melting at 241.8-242.8°C.**

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* Rousset (73) reported 164-165°C. with decomposition.
**Gattermann (42) reported m.p. 232°C.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.40; H, 4.96.

4-Hydroxynaphthaldehyde (VII) - A 200 ml., three-necked flask was fitted with a gas inlet tube, a stirrer, and a condenser leading to a hydrogen cyanide gas trap. This trap consisted of a bottle containing sulfuric acid, an empty bottle, and a bottle containing 10% sodium hydroxide solution. The inlet tube into the sodium hydroxide bottle was placed just above the surface of the solution.

Into the flask were added 30.0 g. (0.208 mole) of α-naphthol (Eastman Kodak Company), 200 ml. of absolute ether, and 36.6 g. (0.312 mole) of dry zinc cyanide. Dry hydrogen chloride was introduced for two hours. During this time the solution became yellow and very paste-like. The introduction of gas was stopped, the ether poured off, and the solid paste remaining poured into 700 ml. of 30% alcohol and allowed to stand overnight. The alcoholic solution was then filtered and the precipitate treated with Darco and recrystallized several times from 30% alcohol. A yellow crystalline compound, 22.3 g. (62.3%), was obtained which had a melting point of 179.0-180.0°C.*

4-Methoxynaphthaldehyde (VIII) - A hot solution consisting of 5.0 g. (0.029 mole) of 4-hydroxynaphthaldehyde (VII) dissolved in just enough 5% sodium hydroxide

* The method of preparation of the 4-hydroxynaphthaldehyde is that of Adams and Levine (1). They reported a m.p. 178°C. Gattermann (44) reported a m.p. 181°C.

solution to make it slightly basic was stirred vigorously while the solution was made alternately basic and acidic with dimethyl sulfate and sodium hydroxide solution. The additions were continued until a total of 8.3 g. (0.0658 mole) of dimethyl sulfate had been added. The solution was then made very basic to destroy the excess dimethyl sulfate and stirred for fifteen minutes longer.

The basic solution was extracted with ether several times. The ether extracts were dried over anhydrous sodium sulfate and distilled from a Claisen Flask. On distillation, 3.0 g. (55.6%) of a yellow oil was obtained which boiled at 120-160°C. at 7 mm.* The oil did not completely crystallize after standing for several weeks.

1.6 g. of 4-hydroxynaphthaldehyde (VII) was recovered from the basic solution on acidification.

The phenylhydrazone of 4-methoxynaphthaldehyde, a slightly pink powder, melted at 104.6-105.6°C.**

4-Methoxynaphthoic acid (VI) - The silver oxide used in the oxidation of 4-methoxynaphthaldehyde (VIII) was prepared according to the directions given by Pearl (67). The oxide was made as follows: 0.91 g. (0.00537 mole) of

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* Madinavertia and Puyal (59) reported the aldehyde as distilling at 210°C./25 mm. and it did not crystallize. Gattermann (44) reported 212°C./40 mm. and 200°C./11 mm. He found that the oil gave on crystallizing white crystals which melted at 34°C.

** Madinavertia and Puyal(59) reported m.p. of 111°C. and 113°C. and Gattermann (44), a m.p. of 119°C. for the phenylhydrazone.

silver nitrate was dissolved in 4 ml. of water and to this was added a solution consisting of 0.215 g. (0.00537 mole) of sodium hydroxide in 2 ml. of water. The precipitate was filtered and washed with water. The oxide obtained was used without drying.

A solution consisting of 11 ml. of water and 1.08 g. of sodium hydroxide in a three-necked flask fitted with a stirrer and thermometer was heated to 55°C. and then 1.0 g. (0.00537 mole) of 4-methoxynaphthaldehyde (VIII) and the silver oxide prepared above were added. The solution was heated for forty-five minutes at 75°C., cooled and extracted with ether. The basic solution was acidified and the white precipitate filtered off. After several recrystallizations from aqueous alcohol, a white acid melting at 241.0-242.0°C. was obtained. The yield was very poor; however, 4-methoxynaphthaldehyde (VIII) could be recovered from the ether and used over again.

A mixed melting point of this acid and that obtained from 4-methoxynaphthylglyoxylic acid (V) (p. 58) showed no depression.

β-Naphthol Series*

2-Hydroxynaphthylglyoxylic acid lactone (X) - Twenty-two grams (0.153 mole) of β-naphthol, 15.7 g. (0.159 mole) of ethyl cyanoformate (p. 55), 4.0 g. of freshly fused zinc chloride and 120 ml. of absolute ether were placed in a 300 ml. three-necked flask. The reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55).

After the three-day refrigeration period, the ether was filtered from the oily precipitate. Fresh ether was added to the filtrate and more oil separated. The oily precipitates were combined and dissolved in 3% base. The white material, insoluble in base, was filtered off. The basic solution was treated with Darco and then acidified. Some tarry material separated alongwith a yellow-orange precipitate. By repeatedly extracting the yellow-orange precipitate from the tarry material with hot water, all the acid was finally obtained. On recrystallization of the precipitate from acetone or benzene, 15.1 g. (50.0%) of a bright orange crystalline compound which had a m.p. of 182.0-183.0°C. with decomposition** was obtained.

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* All melting points are corrected.
** Fries and Frellstedt (39) reported a m.p. 182°C. with decomposition. Guia and de Franciscia (47) reported a m.p. 178°C. with decomposition.

Anal. Calcd. for $C_{12}H_6O_3$: C, 72.71; H, 3.05. Neut. Eq., 198.2. Found: C, 72.59; H, 3.12. Neut. Eq., 202.2.

The white material which was insoluble in base was treated with Darco and recrystallized several times from acetone. On final recrystallization 2.2 g. of white crystals were obtained which melted at 212.0-214.0°C. with decomposition. From the analytical results obtained, the empirical formula appeared to be $C_{29}H_{24}NO_6$. All tests for functional groups failed. No further work was done on this compound.

Anal. Calcd. for $C_{29}H_{24}NO_6$: C, 71.48; H, 5.14; N, 2.98; Mole. Wt., 470.5. Found: C, 71.48; H, 4.78; N, 2.79; Mole. Wt., 435.3*.

2-Methoxynaphthylglyoxylic acid (XI)** - Methylated 1.0 g. (0.00505 mole) of 2-hydroxynaphthylglyoxylic acid (X) by using 2.2 g. (0.0174 mole) of dimethyl sulfate in a similar manner to that used in the methylation of 4-hydroxynaphthaldehyde (VII) (p.60), although heating was not necessary.

On acidification of the basic solution, a yellow precipitate was obtained which was treated with Darco

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* The molecular weight was determined by the freezing point lowering method, using benzene as the liquid.
** Staudinger, Schlenker and Goldstein (77) reported that this compound could not be prepared by the action of dimethyl sulfate or methyl iodide on 2-hydroxynaphthylglyoxylic acid lactone.

and recrystallized several times from water. The bright yellow crystalline compound on drying at 100°C. over phosphorous pentoxide yielded 0.73 g. (62.8%) which melted at 153.8-154.6°C. with decomposition*.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.82; H, 4.37. Neut. Eq., 230.2. Found: C, 68.01; H, 4.60; Neut. Eq., 217.2.

* Rousset (73) reported a m.p. of 151°C.

1,5-Dihydroxynaphthalene Series*

4,8-Dihydroxynaphthylglyoxylic acid lactone

(XII) - For the preparation of this acid, pure 1,5-dihydroxynaphthalene was needed. Since technical 1,5-dihydroxynaphthalene was used in this work, further purification was necessary. The purification method used was that of Wheeler and Ergle (84) and was as follows: Forty grams of Eastman Kodak technical 1,5-dihydroxynaphthalene was made into a paste with water. This paste was suspended in 3 liters of water, containing 200 ml. of methyl alcohol and then boiled under reflux for 2½ hours. After cooling to 80°C. and saturating the solution with sulfur dioxide, the solution was heated almost to the boiling point for one hour. The solution was filtered on a steam-Buchner through a very fast filter paper. The yield on this purification is 10.8-12.7 g. (27-31.8%).

In a 200 ml. three-necked flask were placed 6.82 g. (0.0426 mole) of 1,5-dihydroxynaphthalene, 4.64 g. (0.0469 mole) of ethyl cyanoformate (p. 55), 1.09 g. of freshly fused zinc chloride and 80 ml. of absolute ether. The reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55).

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* All melting points are corrected.

After the three-day refrigeration period, the ether was filtered from the black oily precipitate. Fresh absolute ether was added to the filtrate, and the black oil which separated was filtered. The black oily precipitates were combined, added to 50 ml. of water and heated on the steam bath for fifteen minutes. The red precipitate which settled out was filtered, dissolved in alcohol and treated with Darco. By repeated fractional crystallizations from aqueous alcohol, a very small amount of a brick-red crystalline compound was obtained which gave a melting point of 294.0-296.0°C. with decomposition.*

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.83. Neut. Eq., 214.2. Found: C, 67.11; H, 2.79. Neut. Eq., 217.8.

All the other fractions of acid were combined and recrystallized again from aqueous alcohol. A brick-red compound was obtained which melted from 284.0-295.0°C. with decomposition. Apparently, a small amount of the 1,5-dihydroxynaphthalene-2-glyoxylic acid lactone is present, which could not be separated by fractional crystallization.

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.83. Found: C, 67.41; H, 2.99.

* Knobloch and Schraufstatter (56) reported a melting point of 272°C. for a brick-red compound which they obtained from the reaction of cyanogen on 1,5-dihydroxynaphthalene. They were not sure whether they had 1,5-dihydroxynaphthyl-2 or 4-glyoxylic acid lactone. From the work reported in this dissertation, it appears that they had the 1,5-dihydroxynaphthyl-2-glyoxylic acid lactone.

An attempt was made to make the 1,5-dihydroxy-naphthyl-4,8-diglyoxylic acid lactone by using twice as much ethyl cyanoformate as in the above reaction. The results, however, were the same as when equal molar quantities were used.

4,8-Dimethoxynaphthylglyoxylic acid (XIII) - To a solution containing 0.9 g. of sodium hydroxide in 10 ml. of water were added 1.5 g. (0.00698 mole) of 4,8-dihydroxy-naphthylglyoxylic acid lactone (XII). This solution was made alternately acidic and basic by the addition of small quantities of dimethyl sulfate and then 5% sodium hydroxide. During this addition, the solution was stirred vigorously. After a total of 12.6 g. (0.105 mole) of dimethyl sulfate had been added, enough 5% sodium hydroxide was included to make the solution basic. The stirring was continued for fifteen minutes longer.

The red basic solution was acidified with concentrated hydrochloric acid and a brown precipitate separated and was filtered. After treatment of this precipitate with Darco and recrystallization several times from Benzene, 1.09 g. (60.0%) of a yellow crystalline compound melting at 190.8-191.6°C. with decomposition was obtained.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Neut. Eq., 260.2. Found: C, 64.63; H, 4.80. Neut. Eq., 251.8.

4,8-Dimethoxynaphthoic acid (XIV) - In 4 ml. of 50% glacial acetic acid was dissolved 0.2 g. (0.000768 mole) of 4,8-dimethoxynaphthylglyoxylic acid (XIII). To this solution was added slowly a hot solution consisting of 0.051 g. (0.000322 mole) of potassium permanganate dissolved in 5 ml. of 50% acetic acid. The solution was refluxed gently during the addition and CO_2 was evolved vigorously. After thirty minutes the solution was poured into water. The tan precipitate obtained was dissolved in 2% sodium hydroxide, filtered to remove any manganese dioxide and acidified. The solution was filtered and the precipitate obtained recrystallized several times from aqueous alcohol. White crystals were obtained with a m.p. of 221.4-222.4°C.*

4,8-Dihydroxynaphthoic acid - An attempt was made to prepare this acid according to the direction given by Passerini (65). To 0.30 g. (0.0014 mole) of 4,8-dihydroxynaphthylglyoxylic acid lactone (XII) dissolved in 3 ml. of glacial acetic acid was added 10 drops of superoxol (30% hydrogen peroxide). The solution was heated on a water bath for two hours while CO_2 was evolved. The solution was then cooled and poured into 20 ml. of water. No precipitate was obtained and nothing could be obtained by ether extraction. Nothing further was done with this reaction.

* Hill, Short and Stromberg (49) reported a m.p. of 222.5°C.

1,5-Dimethoxynaphthalene (XV) and 1,5-hydroxynaphthol (XVI)* - To 13.41 g. (0.0838 mole) of 1,5-dihydroxynaphthalene in a three-necked flask fitted with a stirrer was added a solution containing 8.31 g. (0.148 mole) of potassium hydroxide in 50 ml. of water. The solution was cooled with an ice-bath and stirred vigorously while 15.75 g. (0.125 mole) of dimethyl sulfate was added. The solution was stirred for thirty minutes longer and then made very basic. The grey precipitate which settled out was 1,5-dimethoxynaphthalene. This precipitate was washed well with 2% sodium hydroxide and dried for twenty-four hours over potassium hydroxide. When dry, the grey precipitate was distilled at atmospheric pressure through a wide-side arm flask. The distillate came over as a clear liquid which soon solidified to a white solid. Recrystallization from alcohol yielded 5.13 g. (32.5%) of the white crystalline dimethoxynaphthalene which melted at 181.5-182.5°C.**

On acidification of the basic solution from the above reaction, a grey precipitate separated which was filtered, washed with water, dried, and distilled as was done with dimethoxynaphthalene. The white 1,5-hydroxynaphthol was recrystallized from glacial acetic acid. There was obtained 6.15 g. of the compound which melted at 136.6-137.2°C.***

* Followed the methods given by Bentley, Robinson and Weizmann (9) and Fisher and Bauer (32).
** Fisher and Bauer (32) reported 183°C.
***Fisher and Bauer (32) reported 140°C.

4-Hydroxy-8-methoxynaphthylglyoxylic acid (XVII) - This compound was prepared in a manner similar to that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55). The following quantities of reagents were used: 5.22 g. (0.03 mole) of 1,5-hydroxynaphthol (XVI), 3.27 g. (0.033 mole) ethyl cyanoformate (p. 55), 0.8 g. of freshly fused zinc chloride, and 125 ml. of absolute ether.

After the three-day refrigeration period, the ether was filtered from the dark red oily precipitate. Fresh absolute ether was added to the filtrate and the dark red oil which separated was filtered. The precipitates were combined, added to 100 ml. of water, and heated for ten minutes. A yellow precipitate alongwith some tarry material came out of the solution. By repeated extraction of the tar with boiling water, a yellow compound was obtained. On recrystallization from aqueous alcohol, 2.0 g. (36.9%) of the yellow 4-hydroxy-8-methoxynaphthylglyoxylic acid which melted at 188.2-190.2°C. with decomposition was obtained.

Anal. Calcd. for $C_{13}H_{10}O_5$: C, 63.40; H, 4.10. Neut. Eq., 246.2. Found: C, 63.57; H, 4.30. Neut. Eq., 233.4.

4,8-Dimethoxynaphthylglyoxylic acid (XIII) - Methylated 4-hydroxy-8-methoxynaphthylglyoxylic acid (XVII) in a similar manner to that used in the methylation of 4,8-dihydroxynaphthylglyoxylic acid lactone (XII) (p. 68). The

following quantities of material were used: 0.5 g. (0.00219 mole) of 4-hydroxy-8-methoxynaphthylglyoxylic acid (XVII) and 2.76 g. (0.0219 mole) of dimethyl sulfate.

On acidification of the basic solution, the yellow acid was obtained. Recrystallization from benzene gave 0.38 g. (66.9%) of the yellow acid melting at 190.8-191.8°C. with decomposition.

A mixed melting point with the acid prepared from 4,8-dihydroxynaphthylglyoxylic acid lactone (XII) showed no depression.

4,8-Dimethoxybromonaphthalene - Into 40 ml. of benzene were added 1.51 g. (0.008 mole) of dimethoxynaphthalene (XV) and then a solution of 1.28 g. (0.008 mole) bromine and 10 ml. of benzene was dropped in slowly. The solution became red and hydrogen bromide was evolved. After standing for thirty minutes, almost all the benzene was distilled off. Petroleum ether was added to the benzene to precipitate out the bromo compound. The crystalline mass was dissolved in aqueous alcohol and treated with Darco. After several recrystallizations, 0.9 g. (42.2%) of the white bromo compound which had a m.p. of 106.2-107.2°C.* was obtained.

4,8-Dimethoxynaphthoic acid (XIV) - To 0.026 g. (0.0038 mole) of lithium in 15 ml. of absolute ether was added

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* Fisher and Bauer (32) reported 115°C.

0.43 g. (0.0054 mole) of butyl chloride and the reaction mixture stirred for one hour. A solution of 0.8 g. (0.003 mole) of 4,8-dimethoxybromonaphthalene (XVIII) in 5 ml. of absolute ether was then added to the butyl lithium and the solution stirred for thirty minutes. The solution was then cooled to 0° and carbonated with dry ice chips and then allowed to warm to room temperature. The lithium complex formed was decomposed with iced hydrochloric acid and the resulting solution extracted with ether. The ether layer was extracted with 2% sodium hydroxide solution. The alkaline layer was acidified with concentrated hydrochloric acid and the product filtered. On recrystallization from aqueous alcohol, 0.1 g. (28.8%) of the white dimethoxy acid was obtained which had a m.p. of 221.5-222.5°C.

A mixed melting point of this acid with that prepared from 4,8-dimethoxynaphthylglyoxylic acid (XIII) (p. 68) gave no depression.

2,7-Dihydroxynaphthalene Series*

2,7-Dihydroxynaphthylglyoxylic acid lactone (XIX) - In a 100 ml. three-necked flask were placed 3.41 g. (0.0213 mole) of 2,7-dihydroxynaphthalene (Eastman Kodak Company), 3.2 g. (0.0319 mole) of ethyl cyanoformate (p. 55), 0.7 g. (0.0053 mole) of freshly fused zinc chloride and 30 ml. of absolute ether. The reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55).

After the three-day refrigeration period, the ether was filtered from the black oily precipitate. Fresh absolute ether was added to the filtrate and the black oil which separated was filtered. The black oily precipitates were combined, added to 50 ml. of water and heated on the steam-bath for fifteen minutes. The red precipitate which settled out was filtered, dissolved in alcohol and treated with Darco. After several recrystallizations from aqueous alcohol, 3.68 g. (80.5%) of the red acid was obtained which melted at 280.0-282.0°C. with decompositions.**

Anal. Calcd. for $C_{12}H_6O_4$: C, 67.27; H, 2.83. Neut. Eq., 214.2. Found: C, 67.32; H, 3.05. Neut. Eq., 208.3.

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* All melting points are corrected.
** Passerini (65) reported 282.0°C. with decomposition.

2,7-Dimethoxynaphthylglyoxylic acid (XX) - The methylation of 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX) was carried out in the same manner as that of 4,8-dihydroxynaphthylglyoxylic acid lactone (XII) (p. 68). The following amounts of material were used: 1.0 g. (0.0047 mole) of 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX) and 7.0 g. (0.056 mole) of dimethyl sulfate.

The yellow compound obtained from the reaction was recrystallized several times from benzene. A light yellow compound weighing 2.2 g. (45.2%) which had a m.p. of 150.6-151.4°C. with decomposition was obtained.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65. Neut. Eq., 260.2. Found: C, 64.82; H, 4.81. Neut. Eq., 254.3.

2,7-Dimethoxynaphthoic acid (XXI) - The oxidation of 2,7-dimethoxynaphthylglyoxylic acid (XX) was carried out in the same manner as that of 4,8-dimethoxynaphthylglyoxylic acid (XIII) (p. 69). The following amounts of material were used: 0.1 g. (0.00038 mole) 2,7-dimethoxynaphthylglyoxylic acid (XX), 0.0239 g. (0.000151 mole) of potassium permanganate and 10 ml. of 50% acetic acid.

From the reaction some white crystals were obtained which, after several recrystallizations from alcohol, melted at 112.2-113.2°C.* The yield was very poor.

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* Adams, Miller, McGrew and Anderson (2) reported a m.p. of 112-113°C.

2,7-Dihydroxynaphthoic acid - An attempt was made to prepare this acid according to the directions given by Passerini (65). The reaction was carried out in the same manner as that used for the oxidation of 4,8-dihydroxynaphthylglyoxylic acid lactone (XII). The following amounts of material were used: 0.3 g. (0.00115 mole) of 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX), 2 ml. of glacial acetic acid and 10 drops of superoxol (30% hydrogen peroxide).

No dihydroxynaphthoic acid was obtained when the reaction was worked up.*

2,7-Dimethoxynaphthalene (XXII) and 2,7-Methoxynaphthol (XXIII)** - To 10.79 g. (0.0674 mole) of 2,7-dihydroxynaphthalene (Eastman Kodak Company) were added 50 ml. of water. This mixture was stirred until a suspension was formed. Then 8.83 g. (0.07 mole) of dimethyl sulfate were added and thoroughly mixed. A solution of 3.92 g. (0.07 mole) of potassium hydroxide in 15 ml. of water was added rapidly through a separatory funnel. Vigorous stirring was continued for thirty minutes. Then 15 ml. of a 2% potassium hydroxide solution was added and the solution stirred for five minutes. The grey precipitate which had settled was filtered; the solution was filtered into hydrochloric acid

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* Passerini (65) reported that he obtained the 2,7-dihydroxynaphthoic acid from the 2,7-dihydroxynaphthylglyoxylic acid lactone, m.p. 275°C.

** Methods of Fisher and Hammerschmidt (33), and Bunzley and Decker (20) were combined and used.

and immediately a precipitate, 2 hydroxy-7-methoxynaphthalene, was formed. The grey precipitate, 2,7-dimethoxynaphthalene, was recrystallized several times from alcohol. From this reaction 0.93 g. (7.3%) of 2,7-dimethoxynaphthalene was obtained which melted at 136.5-137.5°C.*

The acidified filtrate from above was filtered and washed several times with water. On recrystallization from ligroin (90-120°C.), 4.51 g. (39.5%) of white crystalline 2,7-dimethoxynaphthol, melting at 113.8-114.8°C.** was obtained.

2-Hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIV) - In a 100 ml. three-necked flask were placed 3.66 g. (0.021 mole) of 2,7-methoxynaphthol (XXIII), 2.28 g. (0.023 mole) of ethyl cyanoformate (p. 55), 0.5 g. of freshly fused zinc chloride and 50 ml. of absolute ether. The reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55).

After the three-day refrigeration period, the ether was filtered from the black oily precipitate. Fresh absolute ether was added to the filtrate and the black oil which separated was filtered. The black oily precipitates were combined, added to 50 ml. of water and heated on the steam-bath for fifteen minutes. The orange precipitate which

* Fisher and Hammerschmidt (33) reported 138°C.
** Fisher and Hammerschmidt (33) reported 113-114°C.

settled out was filtered, dissolved in hot water, and treated with Darco. After several recrystallizations from acetone, 2.42 g. (50.5%) of the bright orange colored acid with a m.p. 199.6-200.6°C. with decomposition* were obtained.

Anal. Calcd. for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Neut. Eq., 228.2. Found: C, 68.23; H, 3.76. Neut. Eq., 221.8.

2,7-Dimethoxynaphthylglyoxylic acid (XX) - Methylated 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIV) in a similar manner to that used in the methylation of 4,8 dihydroxynaphthylglyoxylic acid lactone (XII) (p.68). The following quantities of material were used: 0.5 g. (0.00219 mole) of 2-hydroxy-7-methoxynaphthylglyoxylic acid lactone (XXIV) and 2.76 g. (0.0219 mole) of dimethyl sulfate.

On acidification of the basic solution, a yellow precipitate was obtained. Recrystallization from benzene yielded 0.32 g. (56.2%) of the yellow acid with a m.p. 150.0-151.0°C. with decomposition.

A mixed melting point with the methylated acid prepared from 2,7-dihydroxynaphthylglyoxylic acid lactone (XIX) showed no depression.

* Staudinger, Schlenker and Goldstein (77) reported a m.p. 184°C. with decomposition and the color as brownish-yellow for the lactone.

2,7-Dimethoxybromonaphthalene (XXV)*- This compound was prepared in a similar manner to that of 4,8-dimethoxybromonaphthalene (XVIII) (p. 72). The following quantities of material were used: 0.753 g. (0.004 mole) of 2,7-dimethoxynaphthalene (XXII), 0.639 g. (0.004 mole) of bromine in chloroform in place of benzene.

After the reaction the chloroform solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated to dryness. The slightly yellow crystalline compound which was obtained gave on recrystallization from methanol 0.95 g. (60.8%) of the white bromo compound melting at 87.5-88.5°C.*

2,7-Dimethoxynaphthoic acid (XXI) - This acid was prepared in a similar manner to that of the 4,8-dimethoxynaphthoic acid (XIV) (p.72). The following quantities of material were used: 0.013 g. (0.00191 mole) of lithium, 0.216 g. (0.00272 mole) of butyl chloride, and 0.40 g. (0.0015 mole) of 2,7-dimethoxybromonaphthalene (XXV).

After decomposing the lithium complex with concentrated hydrochloric acid, the resulting solution was extracted with ether and the ether layer extracted with 2% sodium hydroxide solution. The alkaline solution was acidified with concentrated hydrochloric acid and the resulting

* Method of Adams, Miller, McGrew and Anderson (2) was used; they reported a m.p. of 88-89°C.

precipitate filtered. On recrystallization of the precipitate from dilute ethanol, 0.1 g. (28.8%) of the dimethoxy acid was obtained as a white crystalline compound melting at 111.8-112.8°C.

A mixed melting point with the acid prepared from the oxidation of 2,7-dimethoxynaphthylglyoxylic acid (XX) showed no depression.

Phloroglucinol Series*

Phloroglucinolglyoxylic acid (XXVI) - In a 100 ml. three-necked flask were placed 5.0 g. (0.0308 mole) of phloroglucinol (Eastman Kodak Company), 4.6 g. (0.0462 mole) of ethyl cyanoformate (p.55), 1.0 g. of freshly fused zinc chloride and 50 ml. of absolute ether. The reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I)(p.55).

After the three-day refrigeration period, the ether was filtered from the red, oily precipitate. Fresh absolute ether was added to the filtrate and more red oil collected. The red, oily precipitates were combined, added to 75 ml. of water and heated on the steam bath for fifteen minutes. The yellow precipitate which was obtained was dissolved in dilute sodium bicarbonate and extracted with ether. On acidification of the bicarbonate solution, a yellow precipitate was obtained which, when recrystallized from water containing hydrochloric acid, yielded 5.7 g. of a yellow powder. This compound did not give a definite melting point but turned dark orange at 163°C., brown at 170°C. and finally black at 192°C. The empirical formula, as obtained from the

* All melting points are corrected.

analytical results, was $C_{16}H_{19}O_{15}$. No further work was done with this compound.

Anal. Calcd. for $C_{16}H_{19}O_{15}$: C, 42.58; H, 4.24. Found: C, 42.75; H, 4.18.

Trimethoxyphoroglucinolglyoxylic acid (XXVII)*

An attempt was made to prepare this compound by the action of diazomethane on phloroglucinolglyoxylic acid (XXVI) by the same method as that used in preparing methyl 4-methoxynaphthylglyoxylate (IV) (p. 57). A red, oily compound was obtained from which nothing could be separated.

Another attempt was made to prepare this compound by methylation of phloroglucinolglyoxylic acid (XXVI) with dimethyl sulfate by the same method as that used in preparing 4-methoxynaphthaldehyde (VIII) (p. 60). A red oil was obtained from which nothing could be separated.

Still another attempt was made to prepare this compound by methylation of phloroglucinolglyoxylic acid (XXVI) with methyl iodide by the same method as used in preparing methyl 4-methoxynaphthylglyoxylate (IV) (p. 57). Again a red, oily compound was obtained from which nothing could be separated.

No further work was done on the preparation of this compound.

* Jonas (52) reported the preparation of this compound from 2,4,6-trimethoxyacetophenone by oxidation with potassium permanganate. The compound melted at 155.5°C.

Pyrogallol Series*

Pyrogallolglyoxylic acid (XXVIII) - This compound was prepared by Dr. E. D. Amstutz in a similar manner to that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55).

The resulting impure acid was recrystallized from water several times. A yellow-orange acid resulted which had a m.p. 162.4-164.4°C. with decomposition. From the analytical results, no definite empirical formula could be assigned. No further work was done with this compound.

Anal. Calcd. for $C_8H_6O_6$: C, 48.50; H, 3.10. Found: C, 40.44; H, 4.30.

* All melting points are corrected.

Phenol Series*

Attempted preparation of 4-Hydroxyphenylglyoxylic acid (XXX) -

A. Using Phenol. - This reaction was carried out in the same manner as that used in the preparation of 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55). 21.8 g. (0.22 mole) of ethyl cyanoformate (p. 55) and 100 ml. of absolute ether. The hydrogen chloride was passed into this reaction for only 2½ hours. The white ketimine hydrochloride formed was filtered off, dissolved in 5% sodium hydroxide and heated for thirty minutes on the steam bath. The solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was then extracted with dilute sodium bicarbonate and then the bicarbonate solution was extracted several times with fresh ether to remove any remaining trace of phenol. The bicarbonate solution was then acidified with dilute hydrochloric acid and extracted with ether. The ether was dried over anhydrous sodium sulfate and evaporated to dryness. The white, crystalline material, on recrystallization from water, yielded 8.9 g. (45%) of oxalic acid dihydrate which had a melting point of 99-100°C. A mixed melting point with a pure sample of oxalic acid dihydrate showed no depression of the melting point.

* All melting points are corrected.

Phenol was not recovered from the reaction, although the odor of phenol and some oily material were quite noticeable on acidification of the above solution obtained from the ketimine hydrolysis.

B. Using phenyl acetate (XXXI). - The reaction was carried out in a similar manner to that using phenol. The quantities of material used were as follows: 4.5 g. (0.033 mole) of phenyl acetate, 4.0 g. (0.040 mole) of ethyl cyanoformate (p. 55), 0.2 g. of freshly fused zinc chloride.

Phenol again was not recovered from the reaction but the odor was quite discernable. Oxalic acid dihydrate was recovered from the reaction in a 51.2% (1.84 g.) yield, and identified as in the above case.

Ethyl Cyanoformate Reaction*

Reaction of ethyl cyanoformate and hydrogen chloride - To a 100 ml. three-necked flask fitted with a condenser with a gas trap attached, a stirrer and large diameter gas inlet tube was added 6.0 g. (0.0605 mole) of ethyl cyanoformate (p. 55), 0.4 g. of freshly fused zinc chloride and 50 ml. of absolute ether. Dry hydrogen chloride was passed into the solution for 3½ hours. The white precipitate which had settled was filtered, dissolved in 50 ml. of 5% sodium hydroxide, and heated on the steam-bath for 20 minutes. The solution was then acidified with concentrated hydrochloric acid and extracted with ether. The ether solution was dried with anhydrous sodium sulfate and then evaporated on the steam-bath. On crystallization of the white precipitate from water, 2.97 g. (54.5%) of oxalic acid dihydrate were obtained, which melted at 99-100°C. A mixed melting point with pure oxalic acid dihydrate showed no depression.

* All melting points are corrected.

Thiophene Series

Attempted preparation of 2-thienylglyoxylic acid (XXXIV) - Several attempts were made to prepare this acid from thiophene in a manner similar to that used in preparing 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55). From the reaction were recovered thiophene, oxalic acid and some unidentifiable material.

No further work was done on this reaction.

m-Diethylaminophenol Series

Attempted preparation of 2-diethylamino-4-hydroxyphenylglyoxylic acid (XXXV) - Several attempts were made to prepare this acid from m-diethylaminophenol in a manner similar to that used in preparing 4-hydroxynaphthylglyoxylic acid monohydrate (I) (p. 55). An unidentifiable purplish-black tar was all that could be obtained from the reaction. All attempts to obtain some identifiable material were of no avail.

No further work was done with this reaction.

Methylenequinone Series*

5-Bromovanillin**(XXXVI) - Into a 100 ml. three-necked flask, fitted with a stirrer and a dropping funnel, were placed 15.2 g. (0.1 mole) of vanillin dissolved in glacial acetic acid. To this solution was added rapidly a solution consisting of 16.8 g. (0.105 mole) of bromine in 20 ml. of glacial acetic acid. Stirring was continued for ten minutes longer. The solution was diluted with water, the precipitate filtered off and then washed free of acid. On recrystallization from alcohol, 17.2 g. (74.7%) of the white crystalline 5-bromovanillin (XXXVI) was obtained. The pure compound had a m.p. of 163.0-164.0°C.**

The 2,4-dinitrophenylhydrazone of 5-bromovanillin (XXXVIII) had a m.p. of 293.4-294.0°C.

3-Methoxy-5-bromomethylaminomethylenequinone (XXXVII)*** - An alcoholic methylamine solution was made by passing in gaseous methylamine (prepared by gently heating methylamine hydrochloride and 40% sodium hydroxide) into alcohol until 1.25 g. (0.0216 mole) of methylamine had been absorbed. This amine solution was added to 5.0 g. (0.0216

* All melting points are corrected.
** Method of Dakin (29) was used. He reported a m.p. 163-164°C.
***Method of Makarow (60). He reported a m.p. of 211°C. with decomposition at 214-215°C.

mole) of 5-bromovanillin (XXXVI) and immediately a yellow precipitate formed. On recrystallization from alcohol, 4.47 g. (84.8%) of the yellow methylenequinone were obtained which had a m.p. of 229.4-230.2°C.*

The 2,4-dinitrophenylhydrazone of 3-methoxy-5-bromomethylaminomethylenequinone (XXXVIII) had a m.p. of 293.8-294.6°C.

Anal. Calcd. for $C_{14}H_{11}NO_6Br$: C, 40.88; H, 2.70. Found: C, 40.82; H, 2.54.

A mixed melting point of this hydrazone with that obtained from 5-bromovanillin (XXXVI) showed no melting point depression.

5-Bromoveratraldehyde (XXXIX)** To a hot solution of 2.77 g. (0.012 mole) of 5-bromovanillin (XXXVI), 0.5 g. (0.012 mole) of sodium hydroxide and 15 ml. of water were added alternately dimethyl sulfate and 5% sodium hydroxide. The solution was made alternately basic and then acidic with sodium hydroxide and dimethyl sulfate until 6.8 g. (0.054 mole) of dimethyl sulfate had been added. On cooling the solution, the oil, which soon crystallized, was filtered and recrystallized from petroleum ether. The white crystals which were obtained weighed 2.2 g. (75.8%) and melted at 63.0-

* Method of Makarow (60). Reported a m.p. of 211°C. with decomposition at 214-215°C.
** Buck's procedure was used (18).

64.0°C.*

The light orange-red 2,4-dinitrophenylhydrazone of 5-bromoveratraldehyde had a m.p. of 258.8-259.6°C.

The 2,4-dinitrophenylhydrazone of 5-bromoveratraldehyde was also prepared by methylation of the 2,4-dinitrophenylhydrazone of 5-bromovanillin (XXXVIII) with methyl iodide. The method was as follows: To 150 ml. of acetone, dried over anhydrous magnesium sulfate, was added 0.88 g. (0.00214 mole) of the 2,4-dinitrophenylhydrazone of 5-bromovanillin (XXXVI) and 1.0 g. of methyl iodide and refluxed for six hours. On cooling, a red-orange precipitate settled out. This precipitate was filtered. After several recrystallizations from acetone, the red-orange compound gave a m.p. 257.8-258.8°C.

Anal. Calcd. for $C_{15}H_{13}N_4BrO_6$: C, 42.37; H, 3.08. Found: C, 42.50; H, 2.92.

A mixed melting point of this hydrazone with that prepared from the 2,4-dinitrophenylhydrazone of 5-bromovanillin showed no depression.

An attempt was made to prepare the 2,4-dinitrophenylhydrazone of 5-bromoveratraldehyde (XL) by methylation of the 2,4-dinitrophenylhydrazone of 5-bromovanillin (XXXVIII) with dimethyl sulfate but, as the sodium salt was so insoluble,

* Dakin (29) reported a m.p. of 65-66°C. Bentley, Robinson and Weizmann (9) reported a m.p. of 62°C. and Pshorr (70), 62.0-64.0°C.

the reaction would not proceed. Another attempt was made to methylate the hydrazone by use of diazomethane but only an oil was obtained from which nothing could be separated. Nothing further was done with these reactions.

Summary

Summary

A brief review of the work done an arylglyoxylic acids has been presented in this dissertation.

The new synthetic approach to hydroxyarylglyoxylic acids, involving the use of ethyl cyanoformate, has been extended to the preparation of several new hydroxyarylglyoxylic acids. These acids were derived from α-naphthol, β-naphthol, 1,5-dihydroxynaphthalene and 2,7-dihydroxynaphthalene. In all cases except in that of β-naphthol series, where it had already been proven, the position of the entering glyoxylic acid group was determined.

Attempts to extend the use of ethyl cyanoformate to prepare α-thienylglyoxylic acid, pyrogallolglyoxylic acid, phloroglucinolglyoxylic acid and 2-diethylamino-4-hydroxyphenylglyoxylic acid were unsuccessful.

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Vita

Vita

Alexander Bold Neill, Jr., son of Alexander Bold Neill and Ida Hunter Neill, was born on September 27, 1919 in Jersey City, New Jersey. At the age of three, he moved with his family to Upper Montclair, New Jersey, where he later attended public school for eight years. He completed the college preparatory course at the Montclair High School and was graduated in June, 1937. In the fall of the same year, he began his college course at Lehigh University, where he majored in Chemistry. During the four years, he was on the Dean's List in 1939-1940 and 1940-1941; he was graduated in June, 1941, receiving the degree of Bachelor of Science.

After graduation from college, Mr. Neill began work for Hercules Powder Company in Wilmington, Delaware. His work involved investigation of methods to increase the effectiveness of "Thanite", a Hercules insecticide. Due to the increasing need for chemists in their powder plants, Mr. Neill was transferred to the single-base explosives plant at Belvidere, New Jersey in February, 1942. While there, he was promoted from a chemist in the analytical laboratory to safety shift supervisor and then to shift supervisor in the production of powder. When the Belvidere Plant was closed in January, 1944, Mr. Neill was transferred to the Radford,

Virginia explosives plant as a shift supervisor in the analytical laboratory. After a short time, he was transferred to the Rocket Testing Laboratory as a shift supervisor, the position which he held until the plant was closed in September, 1945.

After leaving the Hercules Powder Company, Mr. Neill returned to Lehigh University in October, 1945 and, with the help of a Devoe-Raynolds Fellowship, completed the requirements for the degree of Master of Science in Chemistry in February, 1947.

Mr. Neill continued his graduate studies at Lehigh University under the Student Chemistry Foundation Fellowship investigating the preparation and properties of arylglyoxylic acids, the results of which are embodied in the foregoing dissertation.

Mr. Neill is a member of the American Chemical Society and an associate member of Sigma Xi. He was married to the former Alice Louise Mathews of Sharon, Connecticut on August 9, 1947.