# THE CHEMISTRY OF PHENOXATHIIN AND ITS DERIVATIVES

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CONTENTS



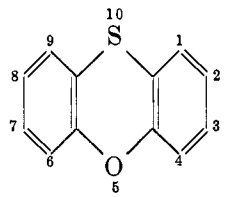
## I. Introduction

A search of the literature reveals that no general survey of the chemistry of phenoxathiin and its derivatives has ever been published. It is believed that the increasing interest in this compound and its recent commercial availability warrant a review at the present time.

## II. Nomenclature

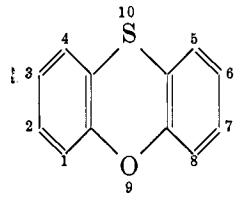
Several names have been applied to the parent heterocyclic compound. Phenoxathiin is given as the preferred name by Patterson and Capell (25), and will be used in this paper. Other names often encountered in the literature are phenoxthin, phenothioxin, dibenzothioxin, and dibenzo-1,4-oxthiin.[1]

No generally accepted method of numbering exists, so that care must be taken to observe the notation used in any particular paper. The numbering given as preferred by Patterson and Capell (25) and used here is indicated in the following formula:

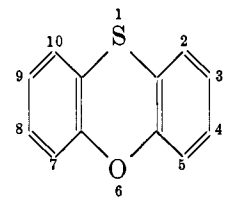



[1] The numbering used in this name is not compatible with the preferred numbering of Patterson and Capell.

More frequently encountered is the numbering originally proposed by Mauthner (21):

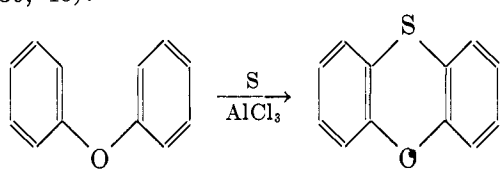


Also in use is the numbering proposed by Pollak, Riesz, and Riesz (28):



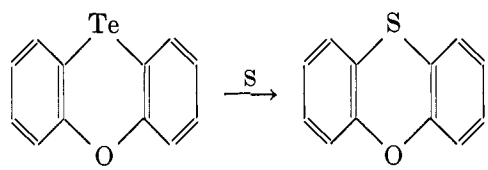
## III. Phenoxathiin and its Oxides

Phenoxathiin is a white crystalline compound, the pale yellow color sometimes observed (7) probably being due to impurities. Three methods of preparation of phenoxathiin have been used. Most widely encountered is the reaction between diphenyl ether and sulfur in the presence of anhydrous aluminum chloride (1, 2, 9, 11, 38, 39, 40):

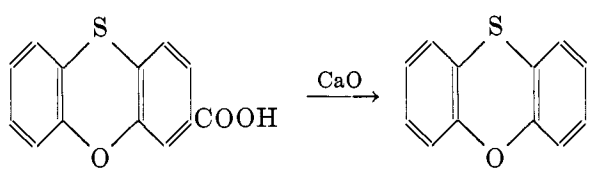


This has been called the Ferrario reaction. Greater than 80 per cent yields of purified product have been obtained in this way (39).

When phenoxatellurin is heated with sulfur, phenoxathiin is formed in over 90 per cent yield (7):



A third method is decarboxylation of phenoxathiin-3-carboxylic acid by heating with calcium oxide (22):



Hinsberg (17) in 1929 reported the preparation of an isophenoxathiin-10-dioxide in 0.5 per cent yield by the action of 70 per cent perchloric acid on commercial phenyl sulfide or by the action of hydrogen peroxide on "isophenyl sulfide." The substance has 0.5 molecule of water of crystallization and melts at 225°C. Phenoxathiin-10-dioxide melts at 147–148°C. The isomerism is explained on the basis of two centers of valency for the sulfur atom. This explanation does not agree with present theory and the experimental work seems questionable.

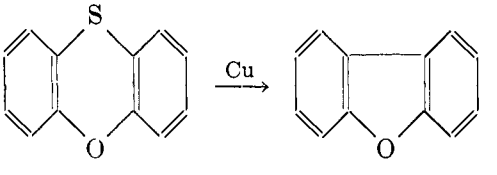
The melting point of phenoxathiin is variously given as from 56° to 61°C. (2, 7, 22, 39, 40); Suter, McKenzie, and Maxwell (40) report the melting point of a sample, recrystallized until pure when examined with a polarizing microscope, as 57.5–58°C. Phenoxathiin boils at 311°C. at 745 mm. pressure, with slight decomposition (38); at 23 mm. the boiling point is 185–187°C. (40), and at 15 mm. it is 180–183°C. (39). Phenoxathiin is, therefore, only difficultly volatile with steam (22). It is readily soluble in all the usual organic solvents.

Wood, McCale, and Williams (44) report that x-ray measurements show that the crystal lattice is $\Gamma_0$ and the space group $P2_12_12_1(D_2^4)$. This is enantiomorphic, and the crystals are not holohedral as indicated by external symmetry measurements.

Drew (6) discusses a formulation of the electronic structure of phenoxathiin.

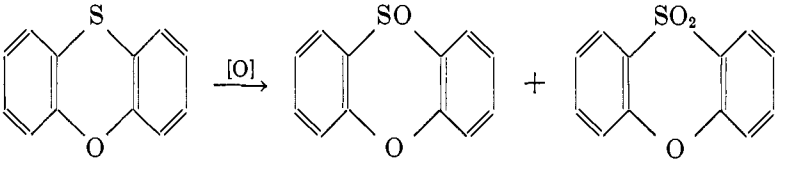
The reactions of phenoxathiin are given for the most part in the section on phenoxathiin derivatives in Part IV, but a few not included there will be mentioned here.

Ferrario (9) states that phenoxathiin can be converted to dibenzofuran by heating with metallic copper at 250°C.:




However, Gilman, Van Ess, Willis, and Stuckwisch (11) and Suter, McKenzie, and Maxwell (40) could not duplicate his results.

When treated with oxidizing agents, phenoxathiin can form either the 10-oxide or the 10-dioxide:

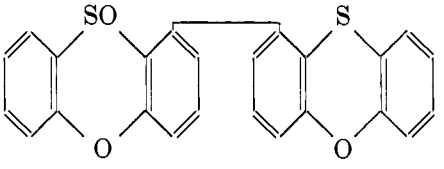



With a mixture of concentrated nitric and acetic acids, the 10-oxide is formed in 93 per cent yield (43). The oxide is also obtained by the action of hydrogen peroxide on an acetic acid solution of phenoxathiin. When phenoxathiin is dissolved in cold concentrated sulfuric acid and allowed to stand for 3 hr., one-half of it is converted into the oxide (7).

Phenoxathiin-10-oxide forms colorless crystals, m.p. 158–159°C., when crystallized from acetic acid or from benzene. It is rather sparingly soluble in hot water and does not form an hydroxide (7).

When it is heated with zinc dust and acetic acid, phenoxathiin-10-oxide is reduced to phenoxathiin. This reduction also takes place when it is heated with acetic and hydrochloric acids, the chlorine evolved partly chlorinating the resulting phenoxathiin.

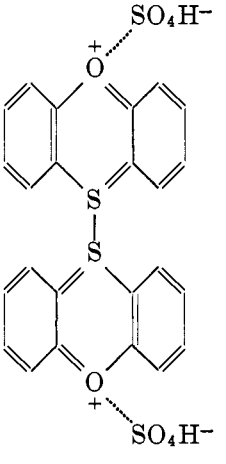
If phenoxathiin-10-oxide is treated with cold concentrated sulfuric acid for 2 hr., a 35 per cent yield of phenoxathiin and larger amounts of a brown amorphous substance are obtained. This compound is considered to have the following structure:



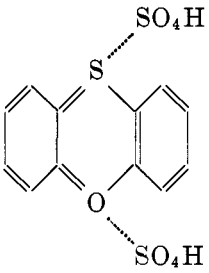

With a 30-min. treatment with concentrated sulfuric acid on the water bath, a 29 per cent yield of phenoxathiin is formed; and if the time is limited to 5 min., both phenoxathiin and unchanged 10-oxide are recovered (7). In the two latter cases the brown amorphous substance is also obtained.

Phenoxathiin-10-dioxide is formed when phenoxathiin is oxidized by chromic acid (22, 43), by potassium permanganate, or by prolonged treatment with hydrogen peroxide (7). It is obtained as colorless needles, m.p. 147–148°C., after recrystallization from dilute acetic acid.

Phenoxathiin gives a violet color when dissolved in cold concentrated sulfuric acid. The 10-oxide also forms a violet solution, which turns blue irreversibly on warming; the 10-dioxide does not give a color. The violet color has been attributed by Drew (7) to the formation of thionylium compounds of the following type:



Hilditch and Smiles (15, 16) postulated an explanation on the basis of the formation of thionium salts, such as:




Moir (24) examined a series of sulfuric acid solutions of compounds in which two benzene rings are connected, in *o*-positions, by two identical or different elements, including phenoxathiin, its oxide, and dioxide. He found that the wave numbers of the strongest lines of most of the substances examined can, by certain divisions, be made to yield the same quotient.

## IV. Derivatives of Phenoxathiin and its Oxides

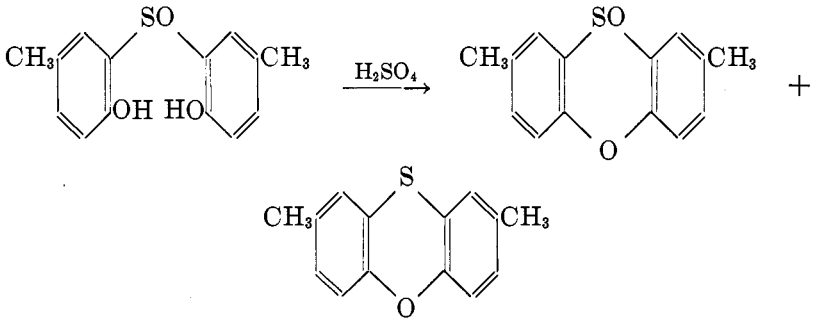
### A. Derivatives with one type of functional group

#### *1. Alkyl derivatives*

Three monomethylphenoxathiins have been prepared according to the Ferrario reaction by condensation of the three tolyl phenyl ethers with sulfur in the presence of aluminum chloride (38). *o*-Tolyl phenyl ether yields the 4-methyl derivative, and the para compound yields the 2-methyl derivative. With *m*-tolyl phenyl ether either 1- or 3-methylphenoxathiin may be formed. Suter and Green assume that the 3-methyl compound is the more probable.

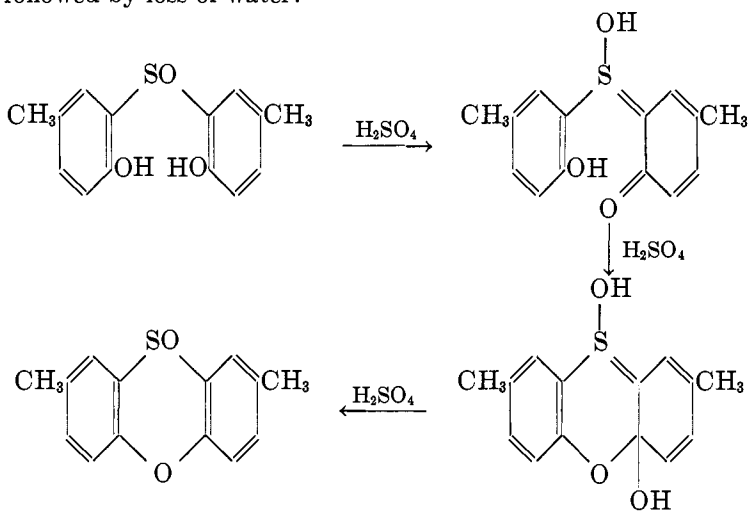
The corresponding 10-dioxides are prepared by oxidation of the phenoxathiins with hydrogen peroxide. Data of Suter and Green are given in table 1.

One dimethyl derivative, 2,8-dimethylphenoxathiin, has been prepared. Hilditch and Smiles (15, 16) obtained it by treatment of 3,3′-dimethyl-6,6′-dihydroxydiphenyl sulfoxide with cold sulfuric acid for several hours:



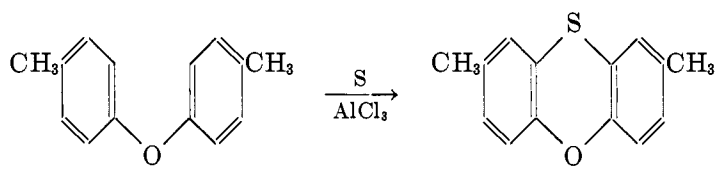

A mixture of 2,8-dimethylphenoxathiin and the 10-oxide is formed. The reaction is not a simple dehydration, but probably involves the formation of a sul-

fonium quinone and a phenothioxonium hydroxide by intramolecular rearrangements, followed by loss of water:




If the treatment with sulfuric acid is for 7 or 8 min. only, 2,8-dimethylphenothioxonium hydroxide can be isolated as orange leaflets, m.p. 105–110°C. This substance forms a buff-colored platinichloride and a greenish brown picrate. Reduction with zinc dust and acetic acid yields 2,8-dimethylphenoxathiin. With aqueous alkali, 2,8-dimethylphenoxathiin is also formed, together with other unidentified compounds (16).

Tomita (42) obtained 2,8-dimethylphenoxathiin, m.p. 73–74°C., from di-*p*-tolyl ether by the Ferrario reaction:




Oxidation of 2,8-dimethylphenoxathiin gives a variety of products. With cold hydrogen peroxide, 2,8-dimethylphenoxathiin-10-oxide, m.p. 132–133°C., is produced. The oxide can be reduced to the original compound with zinc dust and glacial acetic acid. When a solution of the oxide in cold acetic acid is treated with the calculated quantity of potassium permanganate, the 10-dioxide is formed as colorless prisms, m.p. 172°C. (15). Tomita (42) reported that 2,8-dimethylphenoxathiin can be oxidized to give phenoxathiin-10-dioxide-2,8-dicarboxylic acid. The methyl ester melts at 204–208°C.

2,8-Diethylphenoxathiin was prepared by reduction of 2,8-diacetylphenoxathiin or of 2,8-di-(β-chloroacetyl)phenoxathiin with zinc amalgam (42). On oxidation, 2,8-diethylphenoxathiin-10-dioxide is formed.

Smith and Moll (31, 32, 35) state that alkyl groups may be introduced by treating phenoxathiin or halophenoxathiins with an alcohol or an olefin in the presence of an acid-activated bleaching earth as a catalyst. Cycloalkyl groups

are introduced by treating phenoxathiin, or a halogen-, alkyl-, or phenyl-substituted phenoxathiin, with a cycloalkylating agent. When cycloalkyl or substituted cycloalkyl halides are employed as cycloalkylating agents, aluminum bromide or aluminum chloride is suitable as a catalyst. With cycloalkenes or hydroxycycloalkanes, an acid-activated bleaching earth serves as a catalyst. Phenoxathiins substituted with a cycloalkyl group may be oxidized to the corresponding 10-oxides and 10-dioxides with nitric acid (34).

TABLE 1

*Methylphenoxathiins*

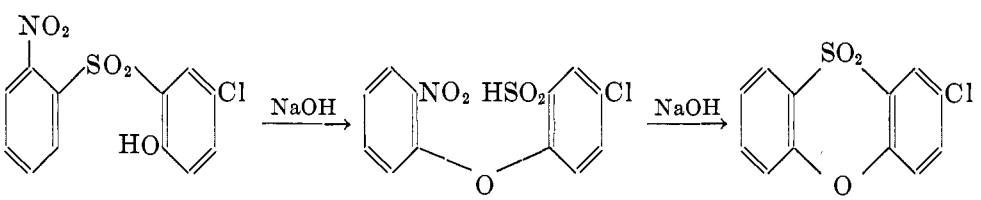
| COMPOUND | MELTING POINT | PERCENTAGE YIELD | MELTING POINT OF 10-DIOXIDE |
|---|---|---|---|
| | °C. | | °C. |
| 2-Methylphenoxathiin | 38–39 | 49 | 134–135 |
| 3(?)-Methylphenoxathiin | 83–84 | 77 | 138–139 |
| 4-Methylphenoxathiin | b.p. 186–187 (14 mm.) | 46 | 141–142 |

### *2. Halogen derivatives*

Only chloro and bromo derivatives of phenoxathiin have been prepared.

Direct chlorination of phenoxathiin was studied by Suter and Green (38). A compound was isolated from the monochlorinated fraction, b.p. 212°C. at 28 mm., which was not thought to be identical with any of the three monochloro compounds prepared by the Ferrario reaction. It was therefore assumed to be 1-chlorophenoxathiin. Substitution in the 1-position on chlorination is unexpected, since bromination is known to give 2-bromophenoxathiin (40). The compound melts at 81–82°C., and forms a 10-dioxide, m.p. 178–179°C., on oxidation with hydrogen peroxide.

2-Chlorophenoxathiin, m.p. 88–89°C., was prepared in 65 per cent yield by the Ferrario reaction by heating *p*-chlorophenyl phenyl ether with sulfur and aluminum chloride (1, 38). Kent and Smiles (19) obtained the corresponding 10-dioxide by the action of aqueous alkali on 5-chloro-2-hydroxy-2′-nitrodiphenyl sulfone. 4-Chloro-2-sulfino-2′-nitrodiphenyl ether, the primary product, loses nitrous acid and forms 2-chlorophenoxathiin-10-dioxide:

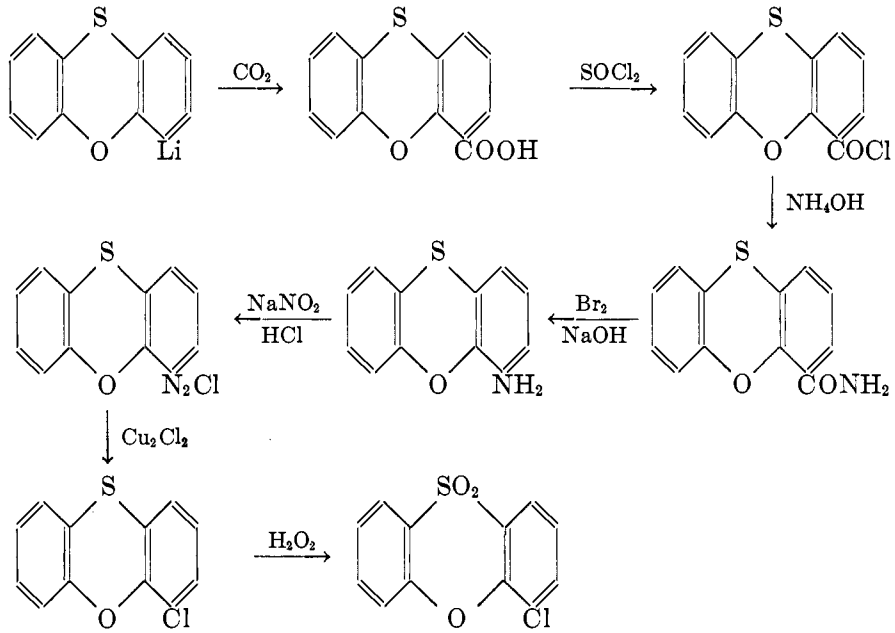



This reaction was noted as a side reaction in a study of the rearrangement of *o*-hydroxysulfones to *o*-sulfinodiphenyl ethers in alkaline solution and was not studied extensively. Suter and Green (38) prepared the 10-dioxide, m.p. 158–159°C., by oxidation of 2-chlorophenoxathiin with hydrogen peroxide.

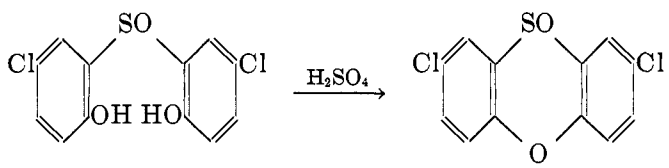
By heating *m*-chlorophenyl phenyl ether with sulfur and aluminum chloride, Suter and Green (38) obtained a monochlorophenoxathiin, m.p. 59–60°C., in 71

per cent yield. This was assumed to be 3-chlorophenoxathiin, although it could also be the 1-chloro compound. The corresponding 10-dioxide, m.p. 152–153°C., was prepared by oxidation with hydrogen peroxide.

4-Chlorophenoxathiin was prepared from *o*-chlorophenyl phenyl ether in 50 per cent yield by the Ferrario reaction (38). It is an oil, b.p. 192–193°C. at 7 mm. On oxidation with hydrogen peroxide, it is converted into the 10-dioxide, m.p. 148–149°C. Gilman, Van Ess, Willis, and Stuckwisch (11) showed that phenoxathiin undergoes metalation with *n*-butyllithium in the 4-position by conversion of the organometallic compound so formed into 4-chlorophenoxathiin-10-dioxide according to the following scheme:




One dichlorophenoxathiin has been prepared. Its 10-oxide was obtained in 25 per cent yield by treating "*p*-chlorophenol-*o*-sulfoxide" with cold concentrated sulfuric acid. Recrystallization from ethyl alcohol gave shiny crystals, m.p. 168°C.




Hilditch and Smiles (15) regard the compound as being probably 2,8-dichlorophenoxathiin-10-oxide, as shown in the equation, although the structure of the "*p*-chlorophenol-*o*-sulfoxide" is not definitely established. If the treatment with sulfuric acid is limited to 15 min., an unstable compound, probably 2,8-dichlorophenothioxonium hydroxide, is formed as pale orange plates, m.p. 142–145°C. (16). On treatment of the oxide or the thioxonium hydroxide with

zinc dust and glacial acetic acid, or of the thioxonium hydroxide with cold aqueous alkali, 2,8-dichlorophenoxathiin, m.p. 135°C., is obtained. 2,8-Dichlorophenoxathiin-10-dioxide, m.p. 196°C., is prepared by oxidation of the monoxide with cold potassium permanganate solution. Suter, McKenzie, and Maxwell (40) obtained the same dichlorophenoxathiin by heating with phosphorus pentachloride the dichloride of the disulfonic acid obtained by sulfonation of phenoxathiin with chlorosulfonic acid.

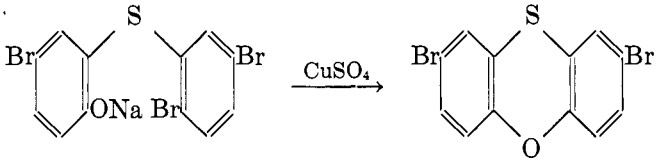
Drew (7) reports that, in the reduction of phenoxathiin-10-oxide with acetic and hydrochloric acids, the resulting phenoxathiin is partly chlorinated by the chlorine which is evolved.

Pützer and Muth (29) state that halogen derivatives of phenoxathiin can be converted to the corresponding hydroxy derivatives by heating them with aqueous caustic alkalies or alkaline earths under pressure.

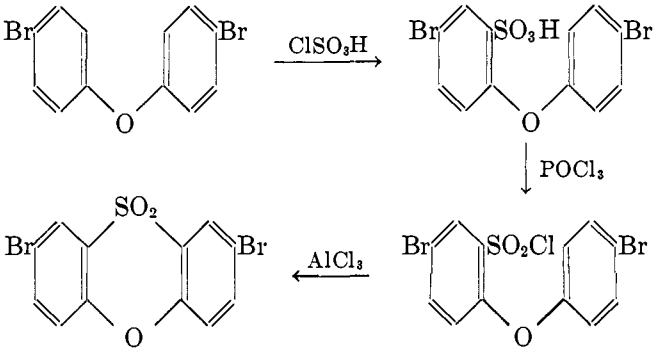
The only monobrominated phenoxathiin of definitely known structure is the 2-bromo compound. This was obtained in yields of over 80 per cent as crystals, m.p. 59–60°C., by treatment of phenoxathiin with an equimolar quantity of bromine (11, 40). It is difficult to form a Grignard reagent of 2-bromophenoxathiin directly (40).

The Ferrario reaction cannot be used in the preparation of bromo compounds, as only tars are obtained (1, 38, 40).

The only known dibromo compound is the 2,8-dibromo derivative. This was first prepared as crystals, m.p. 92°C., by heating the sodium derivative of 2,5,5′-tribromo-2′-hydroxydiphenyl sulfide with copper sulfate (37):

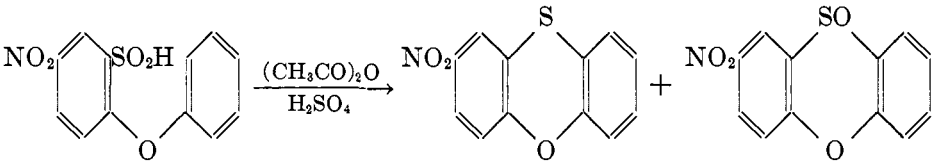



It was also obtained by Suter, McKenzie, and Maxwell (40) in 75 per cent yield by bromination of phenoxathiin with a slight excess of bromine. Oxidation with hydrogen peroxide gave 2,8-dibromophenoxathiin-10-dioxide, m.p. 185–186°C., in 92 per cent yield. They established the positions at which the bromine entered by determining that the 10-dioxide of the dibromocompound so prepared was identical with the compound synthesized in the following way:



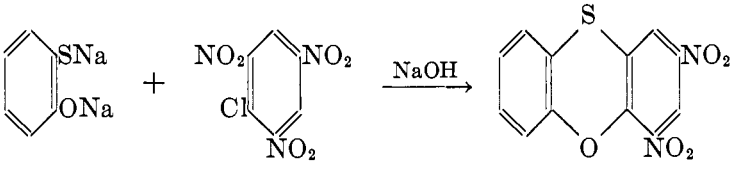
*3. Nitro derivatives*

2-Nitrophenoxathiin is the only mononitro derivative known. A mixture of this compound, m.p. 140°C., and its 10-oxide was obtained by treating 4-nitro-2-sulfinodiphenyl ether with acetic anhydride and concentrated sulfuric acid (20):

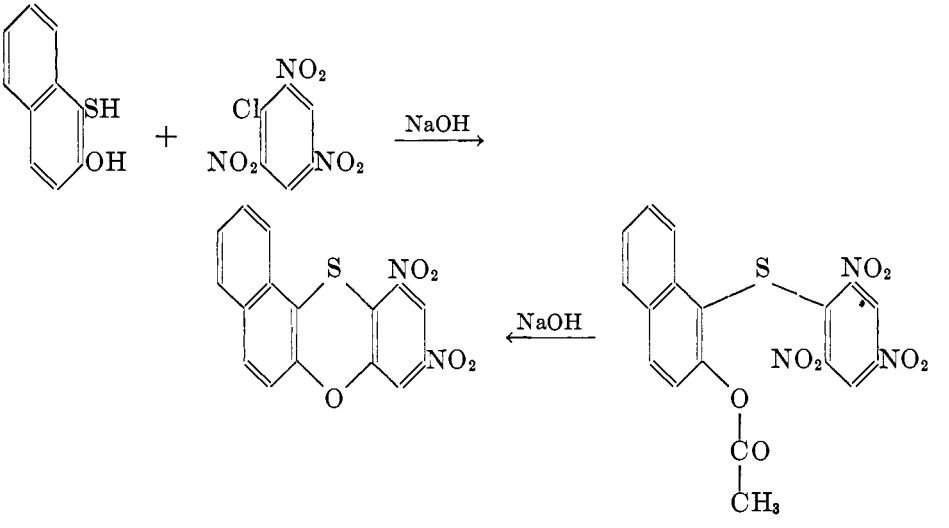



On heating with nitric acid, 3-nitrophenoxathiin is converted to the 10-dioxide, m.p. 205–206°C.

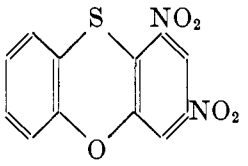
The first compound containing the phenoxathiin nucleus to be prepared was the dinitro derivative of Mauthner (21). It was obtained by reduction with sodium amalgam of the monosodium salt of *o,o'*-dihydroxydiphenyl disulfide to the disodium salt of 2-mercaptophenol, which was condensed with picryl chloride in the presence of sodium hydroxide. Orange-red leaflets, m.p. 187°C., were formed in 80 per cent yield. Mauthner represented the reaction by the following equation:




Stevenson and Smiles (37), however, in studying the reaction between 2-hydroxy-1-naphthyl mercaptan and picryl chloride, observed that the dinitro compound so obtained was identical with that formed by the action of alkali on the *S*-picryl derivative of 2-acetoxy-1-naphthyl mercaptan:



This would indicate that the elimination of nitrous acid involves the hydroxyl and not the thiol group. Mauthner's dinitro compound would therefore be the 1,3-dinitro compound:




Oxidation of the dinitrophenoxathiin with nitric acid gives a 73 per cent yield of the 10-oxide, yellow needles melting at 202–203°C. With chromic acid, the 10-dioxide is formed as light yellow crystals, m.p. 256.5–257°C., in 86 per cent yield.

Nitrophenoxathiins cannot be prepared from the corresponding nitrophenoxatellurins, for they decompose explosively when heated with sulfur (7).

### *4. Amino derivatives*

4-Aminophenoxathiin hydrochloride, m.p. 223–225°C. with decomposition, was prepared by Gilman, Van Ess, Willis, and Stuckwisch (11), as shown in section 2. It was also obtained by them in 70 per cent yield by the action of α-methylhydroxylamine on 4-phenoxathiinyllithium.

One diamino compound is known. This compound has the same orientation as Mauthner's dinitro compound, and is therefore either the 1,3- or the 2,4-dinitro derivative. It was obtained as colorless needles, m.p. 158°C., by reduction of Mauthner's dinitro compound with tin and hydrochloric acid or of the corresponding 10-oxide with zinc dust and glacial acetic acid (21). A solution of the hydrochloride changes to a color similar to Bismarck brown on the addition of nitrite. The sulfate was obtained by treating an ether–alcohol solution of the amine with dilute sulfuric acid.

The diacetyl derivative was obtained in 65 per cent yield as colorless needles, m.p. 224–225°C., by heating the diamine with acetic anhydride. With benzoyl chloride, the diamine gave the dibenzoyl derivative, m.p. 257°C., in 72 per cent yield.

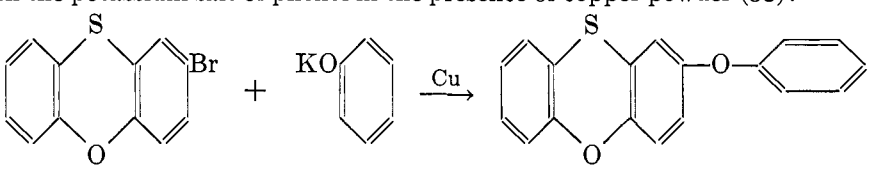
When the 10-dioxide of Mauthner's dinitro compound was reduced with stannous chloride, the 10-dioxide of the diamino compound was obtained in 85 per cent yield as colorless needles, m.p. 228°C.

### *5. Hydroxy derivatives*

Pützer and Muth (29) state that hydroxy derivatives of phenoxathiin may be prepared by treating the corresponding halogen derivatives with aqueous alkalies or alkaline earths under pressure.

### *6. Phenoxy derivatives*

2-Phenoxyphenoxathiin can be prepared by condensing 2-bromophenoxathiin with the potassium salt of phenol in the presence of copper powder (38):



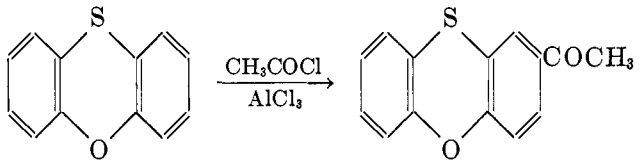
The crude product was formed in 58 per cent yield and, after recrystallization from ethyl alcohol, melted at 81–82°C.

When heated with excess hydrogen peroxide, 2-phenoxyphenoxathiin is converted into the 10-dioxide, m.p. 112–113°C. 2-Phenoxyphenoxathiin evolves hydrogen sulfide slowly when heated at 40°C. with sulfur and aluminum chloride. At higher temperatures decomposition sets in with the evolution of hydrogen chloride, but no diphenoxathiin was isolated.

*o*-Methoxyphenyl phenyl ether gave no evidence of undergoing the Ferrario reaction at 100°C.

### *7. Acetyl derivatives*

2-Acetylphenoxathiin is obtained in 58 per cent yield by a Friedel–Crafts reaction between phenoxathiin and acetyl chloride (40):

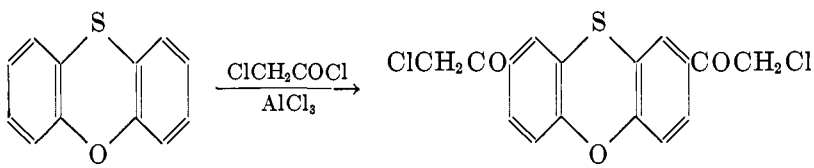



It is a light yellow powder melting at 111–112°C. The phenylhydrazone melts at 93.5–94.5°C.; the oxime melts at 142–143°C.

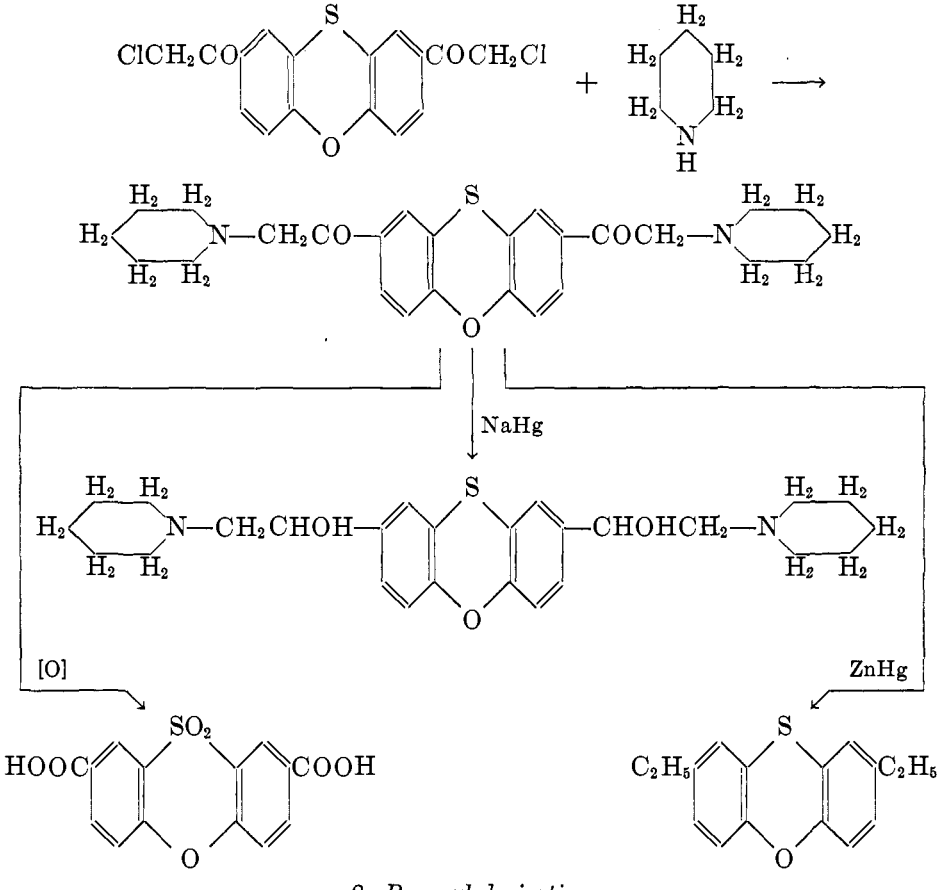
That the acetyl group has entered in the 2-position is shown by oxidation of the compound to the corresponding acid with bleaching powder. The phenoxathiin-2-carboxylic acid, m.p. 259–260°C., thus obtained in 60 per cent yield, is identical with the acid obtained by the action of carbon dioxide on the Grignard reagent from 2-bromophenoxathiin.

2,8-Diacetylphenoxathiin was prepared from phenoxathiin by Tomita (42). When reduced with zinc amalgam, it gave 2,8-diethylphenoxathiin. Oxidation of 2,8-diacetylphenoxathiin gave phenoxathiin-10-dioxide-2,8-dicarboxylic acid, m.p. > 300°C.

When phenoxathiin is condensed with chloroacetyl chloride using aluminum chloride, 2,8-di-(β-chloroacetyl)phenoxathiin, m.p. 193°C., is obtained (42):

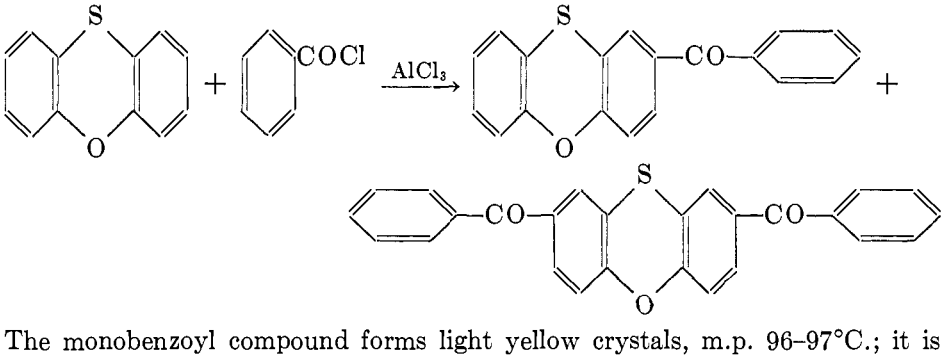



With piperidine, 2,8-di(β-chloroacetyl)phenoxathiin gives 2,8-di(β-piperidylacetyl)phenoxathiin, m.p. 105°C., which on reduction with sodium amalgam forms 2,8-di(α-hydroxypiperidylethyl)phenoxathiin, m.p. 133°C. When the reduction is carried out with zinc amalgam, 2,8-diethylphenoxathiin is formed. Oxidation of 2,8-di-(β-chloroacetyl)phenoxathiin with hydrogen peroxide gives 2,8-di(β-chloroacetyl)phenoxathiin-10-dioxide, m.p. 224–229°C. (43); further oxidation gives phenoxathiin-10-dioxide-2,8-dicarboxylic acid (42). These reactions are shown in the following equations:




*8. Benzoyl derivatives*

A monobenzoyl derivative and a dibenzoyl derivative are known. By analogy with the corresponding acetyl compounds, Suter, McKenzie, and Maxwell (40) consider that they are probably the 2-benzoyl and the 2,8-dibenzoyl compounds. They are formed as a mixture when equimolar amounts of phenoxathiin and benzoyl chloride are refluxed in carbon disulfide with aluminum chloride:




The monobenzoyl compound forms light yellow crystals, m.p. 96–97°C.; it is soluble in hot ethyl alcohol. The dibenzoyl compound, insoluble in ethyl alcohol, forms leaflets melting at 197°C.

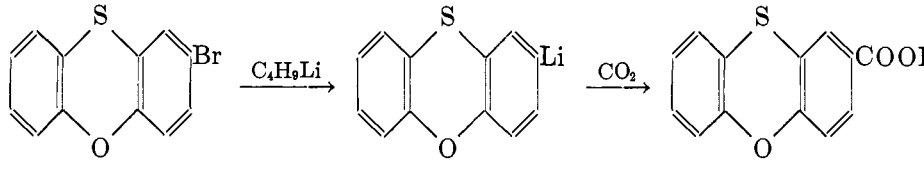
*9. Carboxylic acid derivatives*

Bennett, Lesslie, and Turner (2) prepared a monocarboxylic acid derivative for use in a study of the configuration of the phenoxathiin nucleus. The acid was obtained by heating phenoxathiin with phenylethylcarbamyl chloride and anhydrous zinc chloride. It melted at 230–238°C., even after repeated recrystallization from aqueous alcohol or xylene. It was presumed to be either the 1-carboxylic or the 2-carboxylic acid, although the position of the carboxyl group was not determined.

The strychnine salt, with half a molecule of ethyl alcohol of crystallization, melts at 178–179°C.; the *l*-$\alpha$-phenylethylamine salt melts at 188–189°C. Neither of these salts could be resolved into optical isomers.

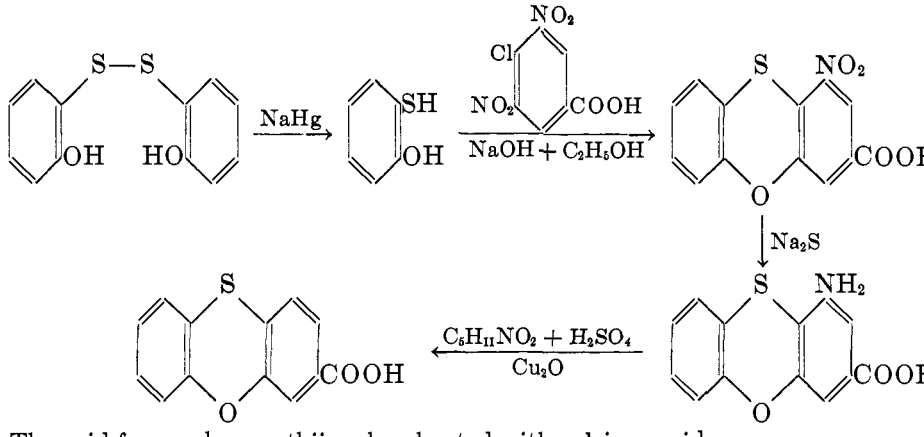
Phenoxathiin-2-carboxylic acid, m.p. 260–262°C., was prepared by Suter, McKenzie, and Maxwell (40) in 8 per cent yield by treatment of the Grignard reagent from 2-bromophenoxathiin with carbon dioxide. They also obtained the crude 2-carboxylic acid in 60 per cent yield by oxidation of the 2-acetyl compound with bleaching powder.

Gilman, Van Ess, Willis, and Stuckwisch (11) obtained a yield of over 50 per cent of purified phenoxathiin-2-carboxylic acid (m.p. 260–265°C.) by the action of *n*-butyllithium on 2-bromophenoxathiin and treatment of the resulting 2-lithium compound with carbon dioxide:




When metalation of phenoxathiin was carried out with phenylcalcium iodide, followed by carbonation, a compound melting at 260–262°C. was obtained. A mixed melting-point determination with an authentic specimen of phenoxathiin-2-carboxylic acid showed a depression, indicating that the metalation did not occur in the 2-position.

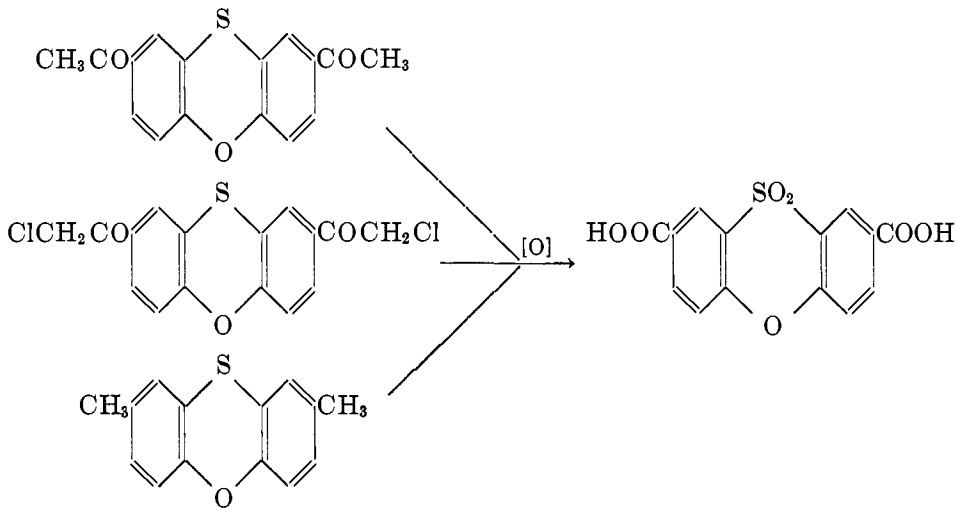
Mauthner (22) prepared phenoxathiin-3-carboxylic acid, m.p. 223°C., by the reduction of *o*,*o*′-dihydroxydiphenyl disulfide, followed by condensation with 4-chloro-3,5-dinitrobenzoic acid to form 1-nitrophenoxathiin-3-carboxylic acid. The nitro group was removed by reduction to the amino group, diazotization of the amino acid, and treatment of the diazonium compound with cuprous oxide.




The acid forms phenoxathiin when heated with calcium oxide.

Phenoxathiin-4-carboxylic acid was prepared by Gilman, Van Ess, Willis, and Stuckwisch (11) by treatment of the 4-lithium derivative with carbon dioxide, as previously discussed in section 2. The crude acid, obtained in greater than 50 per cent yield, gave a melting point of 168–169°C. after three recrystallizations from acetic acid.

Phenoxathiin-10-dioxide-2,8-dicarboxylic acid, m.p. > 300°C., has been prepared by the oxidation of 2,8-diacetylphenoxathiin, 2,8-di(β-chloroacetyl)-phenoxathiin, and 2,8-dimethylphenoxathiin (42):

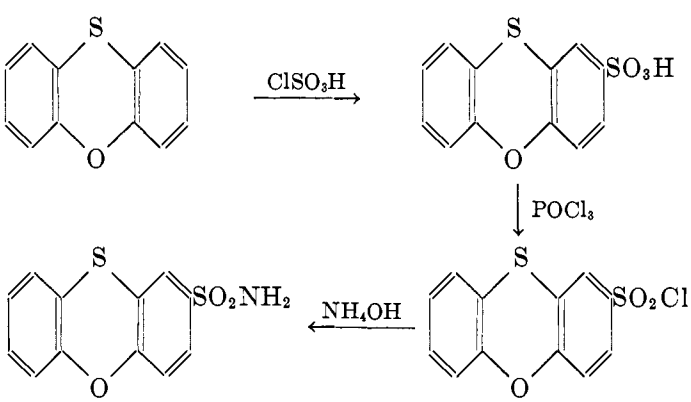



The methyl ester melts at 204–208°C.

### *10. Sulfonic acid derivatives*

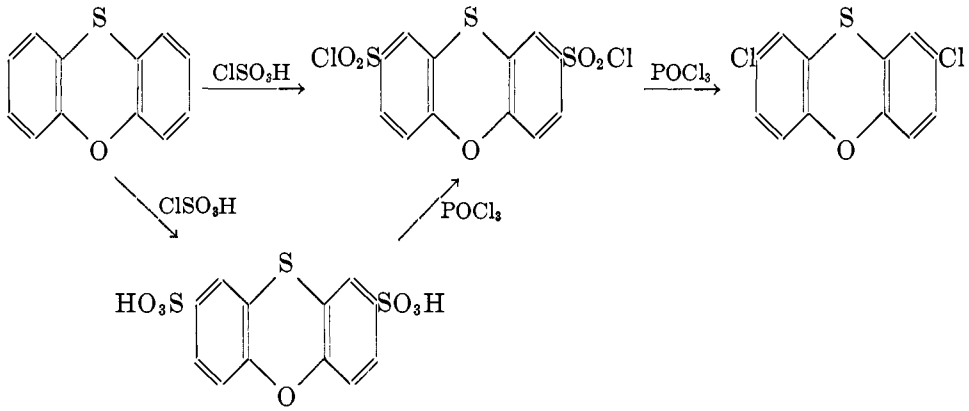
Only one monosulfonic acid derivative is known. Suter, McKenzie, and Maxwell (40) prepared phenoxathiin-2-sulfonic acid by the action of chlorosulfonic acid on an equimolar amount of phenoxathiin. It was isolated in 78 per cent yield as the crude sodium salt.

On refluxing the sodium salt with excess phosphorus oxychloride, the corresponding sulfonyl chloride was formed as a light yellow solid, m.p. 127–128°C. When warmed with concentrated ammonium hydroxide, the sulfonyl chloride was converted to colorless crystals of the amide, m.p. 177–178°C.



When phenoxathiin was heated with chlorosulfonic acid in a 1:4 molar ratio, phenoxathiin-2,8-disulfonic acid was isolated as the sodium salt. The silver salt was also prepared.

When the sodium salt was refluxed with phosphorus oxychloride, the disulfonyl chloride was formed as light yellow crystals, m.p. 142–143°C. This can also be prepared directly in 23 per cent yield by using phenoxathiin and chlorosulfonic acid in a 1:6 ratio. The positions in the phenoxathiin nucleus of the sulfonic acid groups in both the mono- and the di-sulfonic acids are established with a good degree of certainty, since the disulfonic acid can be transformed to the dichlorophenoxathiin of Hilditch and Smiles (15), which is probably the 2,8-dichloro compound.

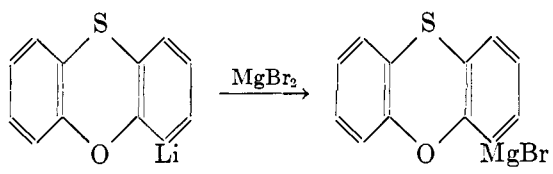



*11. Organometallic derivatives*

Gilman, Van Ess, Willis, and Stuckwisch (11) prepared the 4-lithium derivative by the action of *n*-butyllithium on phenoxathiin. The method of determination of the position of the entering lithium atom has already been discussed in section 2. The lithium compound is of particular importance because it gives a means of introduction of other substituents into the 4-position, which is otherwise inaccessible by direct nuclear substitution reactions.

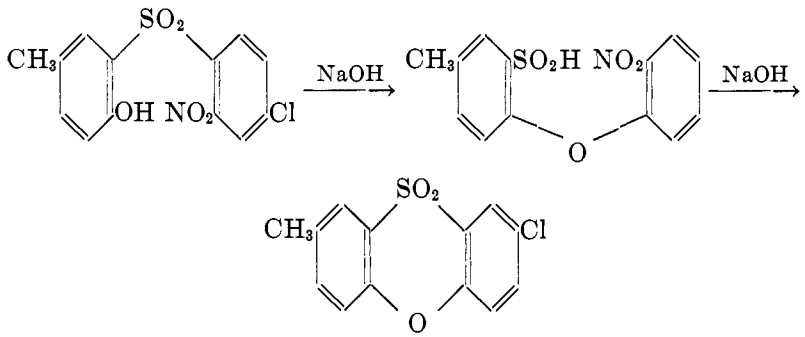
Gilman, Van Ess, Willis, and Stuckwisch (11) also showed that phenoxathiin undergoes metalation with phenylcalcium iodide, but did not determine the position of the entering group.

Suter, McKenzie, and Maxwell (40) state that the Grignard derivative can be prepared directly from 2-bromophenoxathiin only slowly and with difficulty. Gilman, Van Ess, Willis, and Stuckwisch (11) report that the Grignard reagent can be readily prepared by the following reaction:



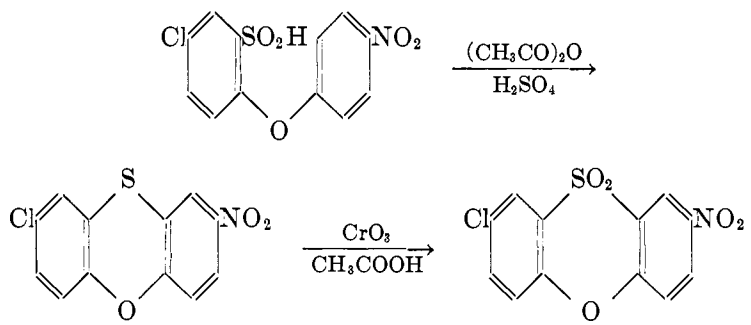
B. DERIVATIVES WITH MORE THAN ONE TYPE OF FUNCTIONAL GROUP

Several alkyl- and halogen-substituted phenoxathiins have been prepared. Drew (7) reports that 2-chloro-8-methylphenoxatellurin gives the corresponding phenoxathiin compound when heated with sulfur. Kent and Smiles (19) state that when 4-chloro-2-nitrophenyl 4′-hydroxy-*m*-tolyl sulfone is heated in alkaline solution longer than is necessary for rearrangement to 4-chloro-2-nitrophenyl-3′-sulfino-*p*-tolyl ether, the solution becomes turbid, owing to the separation of 2-chloro-8-methylphenoxathiin-10-dioxide,[2] m.p. 173°C.




Methods of introducing alkyl and cycloalkyl groups into halogen-substituted phenoxathiins have already been discussed in section 1.

2-Nitro-8-chlorophenoxathiin was prepared as orange-yellow needles, m.p. 128–129°C., by treating 2-sulfino-4-nitro-4′-chlorodiphenyl ether with acetic anhydride and sulfuric acid. 2-Nitro-8-methylphenoxathiin, yellow needles, m.p. 156°C., was similarly prepared. Oxidation of 2-nitro-8-chlorophenoxathiin with chromic acid gave the 10-dioxide as colorless plates, m.p. 183–185°C. (20).

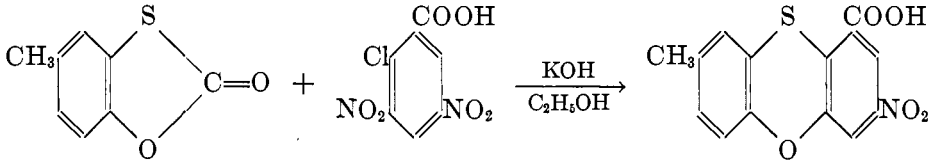



Mauthner (22) prepared orange-red crystals of 1-nitrophenoxathiin-3-carboxylic acid, m.p. 262°C., by reduction of *o*,*o*′-dihydroxydiphenyl disulfide, followed by condensation with 4-chloro-3,5-dinitrobenzoic acid (see section 9). Oxidation

[2] The statement of Kent and Smiles that 3-chloro-8-methoxyphenoxathiin-10-dioxide is formed is obviously incorrect.

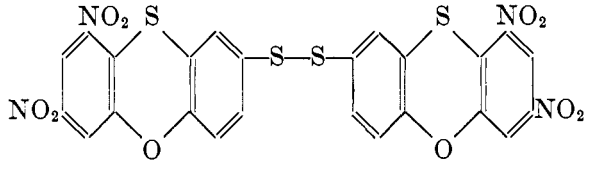
of 1-nitrophenoxathiin-3-carboxylic acid with chromic acid gives the 10-dioxide, m.p. 296–297°C.; with dilute nitric acid, the 10-oxide, m.p. 251–252°C., is obtained as light yellow needles. When 1-nitrophenoxathiin-3-carboxylic acid is reduced with sodium sulfide in aqueous alcohol, 1-amino-phenoxathiin-3-carboxylic acid is formed as colorless needles, melting at 250°C. with decomposition. The acetyl derivative, m.p. 294–295°C., is obtained by the action of acetyl chloride on the amino acid.

Bennett, Lesslie, and Turner (2) prepared 3-nitro-8-methylphenoxathiin-1-carboxylic acid by condensing 2-chloro-3,5-dinitrobenzoic acid and 3-thiol-*p*-tolyl carbonate in an aqueous alcohol solution of potassium hydroxide:



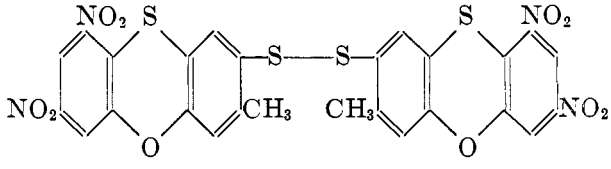

The crude acid was obtained in 40 per cent yield, and after crystallization from ethyl alcohol separated as orange clusters of slender needles, m.p. 253–254°C.

Several substituted phenoxathiin disulfides have been reported. Pollak and Riesz (27) state that 2,4-dithiolphenol forms an orange dipicryl derivative, m.p. 155°C., which, with alcoholic potassium hydroxide, forms 1,3,1′,3′-tetranitrodiphenoxathiin-8,8′-disulfide:



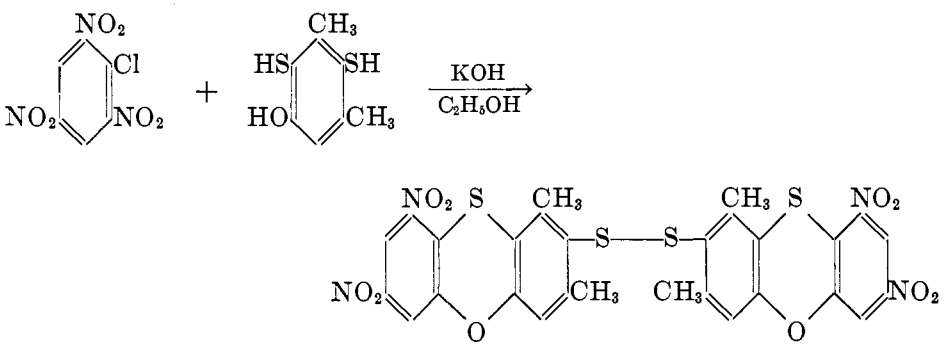

This compound decomposes explosively on heating, and is reduced by sodium sulfide to a dye which is light reddish brown on cotton.

Pollak and Riesz (26) also prepared what is probably 1,3,1′,3′-tetranitro-7,7′-dimethylphenoxathiin-8,8′-disulfide by heating with potassium hydroxide the orange-yellow dipicryl derivative of 4,6-dithiol-*m*-cresol:



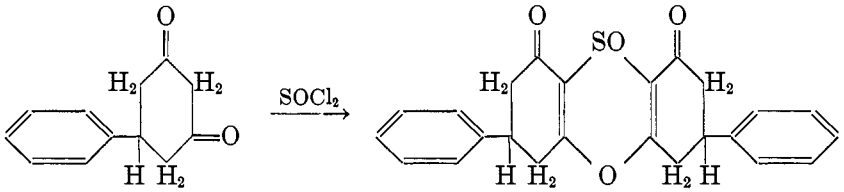

This dark red compound is reduced by sodium sulfide to a vat which dyes cotton a reddish brown.

Katscher and Lehr (18) prepared 1,3,1′,3′-tetranitro-7,9,7′,9′-tetramethylphenoxathiin-8,8′-disulfide by the action of picryl chloride in alcoholic potassium hydroxide solution on 2,4-dithiol-1,3,5-xylenol:

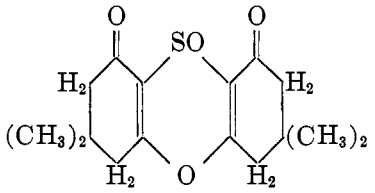


It forms dark red crystals, melting at 255–257°C.

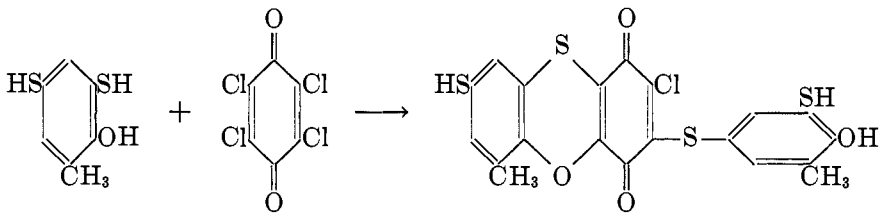
The structure of 3,7-diphenyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophenoxathiin-10-oxide has been provisionally assumed by Desai and Wali (5) for the product, $C_{24}H_{20}SO_4$, m.p. 216°C., obtained by the condensation of phenyldihydroresorcinol with thionyl chloride:



Similarly, the condensation of dimethyldihydroresorcinol and thionyl chloride is assumed to yield the corresponding 3,3,7,7-tetramethyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophenoxathiin-10-oxide, $C_{16}H_{20}SO_4$, m.p. 181–182°C.

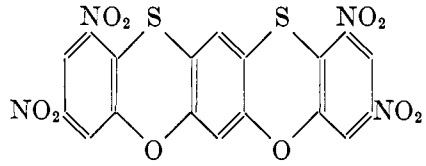


Pollak, Riesz, and Riesz (28) prepared 1,4-diketo-2-chloro-3-(3′-methyl-4′-hydroxy-5′-thiolphenyl)thiol-6-methyl-8-thiolphenoxathiin by warming 3,5-dithiol-*o*-cresol with chloranil in alcoholic solution:



It is a brown solid, decomposing at 250°C. without melting.

4,6-Dithiolresorcinol gives a yellow dipicryl derivative, which yields with potassium hydroxide a tetranitrodiphenoxathiin derivative (26):



This substance is dark red and decomposes above 280°C.

Pollak and Riesz (26) report that dimercapto-*o*-cresol forms an orange-red dipicryl derivative, which, when treated with alcoholic potassium hydroxide, yields a phenoxathiin derivative.

It is reported (3) that phosgene reacts with phenoxathiin compounds containing amino, halogen, and sulfonic acid groups, substituted ureas being formed. A similar reaction occurs with the halide or anhydride of carbamic acid.

## V. Stereochemistry

Higasi and Uyeo (13, 14) determined the dipole moment of phenoxathiin in benzene and in cyclohexane solutions to be 1.09 Debyes. They concluded that the phenoxathiin molecule is folded about the line joining the heterocyclic atoms. They predicted, however, that, since the activation energy of racemization would be at most a few kilogram-calories, no optical isomerism is to be expected in phenoxathiin derivatives.

This prediction was verified by Bennett, Lesslie, and Turner (2), who failed to resolve either 3-nitro-8-methylphenoxathiin-1-carboxylic acid or phenoxathiin-2(or 1)-carboxylic acid. The non-resolvability of phenoxathiin derivatives has also been attributed to the fact that there is only a slight tendency to stable folding, owing to the insufficient dissimilarity in size of sulfur and oxygen (41).

Cullinane and Rees (4) studied isomorphous relationships between phenoxathiin, phenothiazine, phenoxazine, and diphenylene dioxide. Assuming that the ability of binary mixtures of substances to form solid solutions is the criterion of isomorphism, and that similarity in molecular configuration is the reason for isomorphism, they conclude that phenoxathiin has a folded structure. This conclusion was also based on a calculation using the valence angles and atomic radii of the atoms in the phenoxathiin molecule. From measurements of the axial ratios and from x-ray observations, Wood, McCale, and Williams (44) showed that phenoxathiin, phenothiazine, phenoxaselenin, and phenoxatellurin are isomorphous. They concluded that the phenoxathiin molecule is folded, and tabulated suggested angles of fold. Magnetic measurements were consistent with the structure proposed.

## VI. Uses

A rather large number of uses have been proposed for phenoxathiin and some of its derivatives.

Many of these uses are due to the harmful action of phenoxathiin on some of the lower forms of life. It was found, for example, to show marked bacteriostatic

action on *Streptococcus hemolyticus* (oyler strain) and on *Streptococcus hemolyticus epidemicus* and considerable inhibition of *Streptococcus viridans* at a level of 100 parts per million of peptone broth (8). Halogen-substituted phenoxathiinureasulfonic acids have been recommended as bactericides and fungicides (3).

A slight anthelmintic effect against *Haemonchus contortus* was shown by phenoxathiin in 0.25 g. doses per kilogram of body weight of sheep, and larval development in fecal cultures was prevented. Doses of 0.5 g. per kilogram were fatal, and doses of 0.15 g. per kilogram were ineffective (12).

Fink and Vivian (10) have shown that phenoxathiin kills 50 per cent of mosquito larvae in 16 hr. at a concentration of 2 parts per million.

Phenoxathiin has been tested as a stomach poison against larvae of *Phlyctaenia rubigalis* and found to be more toxic than lead arsenate (23). Smith, Siegler, and Munger (30, 36) found that phenoxathiin was outstanding in initial toxicity against codling-moth larvae, but that it loses much of its effectiveness when exposed as a spray deposit for a week or more. Halogen-substituted phenoxathiinureasulfonic acids, which are fast to washing and fulling, have been recommended to protect wool against moths (3).

Various alkyl- or cycloalkyl-phenoxathiins, their oxides and dioxides, and their halogen derivatives are recommended for use as insecticides in dusts or sprays (31, 32, 33, 34).

The oxides and dioxides of cycloalkylphenoxathiins and their halogen derivatives have also been recommended as modifiers in plastic materials or as intermediates (34). Smith and Moll state that alkylphenoxathiins and their halogen derivatives can be used as modifiers in plastic compositions, as intermediates, as antioxidants, and as rubber and gum inhibitors (31, 35).

Pollak and Riesz (26, 27) state that the products obtained by the reduction with sodium sulfide of 1,3,1′,3′-tetranitrodiphenoxathiin-8,8′-disulfide and 1,3,1′,3′-tetranitro-7,7′-dimethylphenoxathiin-8,8′-disulfide are reddish brown dyes on cotton.

## REFERENCES

(1) ACKERMANN, F.: German patent 234,743; Chem. Abstracts **5,** 2912 (1911).
(2) BENNETT, G. M., LESSLIE, M. S., AND TURNER, E. E.: J. Chem. Soc. **1937,** 444.
(3) British patent 536,011; Chem. Abstracts **36,** 1617 (1942).
British patent 536,047; Chem. Abstracts **36,** 1618 (1942).
(4) CULLINANE, N. M., AND REES, W. T.: Trans. Faraday Soc. **36,** 507 (1940).
(5) DESAI, R. D., AND WALI, M. A.: J. Indian Chem. Soc. **13,** 735 (1936); Chem. Abstracts **31,** 4317 (1937).
(6) DREW, H. D. K.: Chemistry & Industry **47,** 949 (1928).
(7) DREW, H. D. K.: J. Chem. Soc. **1928,** 511.
(8) EVERITT, E. L., AND SULLIVAN, M. X.: J. Wash. Acad. Sci. **30,** 457 (1940); Chem. Abstracts **35,** 1088 (1941).
(9) FERRARIO, E.: Bull soc. chim. **9,** 536 (1911).
(10) FINK, D. E., AND VIVIAN, D. L.: J. Econ. Entomol. **29,** 804 (1936); Chem. Abstracts **30,** 7722 (1936).
(11) GILMAN, H., VAN ESS, MARIAN W., WILLIS, H. B., AND STUCKWISCH, C. G.: J. Am. Chem. Soc. **62,** 2606 (1940).
(12) GORDON, H. MCL., AND LIPSON, M.: J. Council Sci. Ind. Research **13,** 173 (1940); Chem. Abstracts **34,** 8049 (1940).

(13) HIGASI, K.: Sci. Papers Inst. Phys. Chem. Research (Tokyo) **38**, 331 (1941); Chem. Abstracts **35**, 6167 (1941).
(14) HIGASI, K., AND UYEO, S.: J. Chem. Soc. Japan **62**, 400 (1941).
(15) HILDITCH, T. P., AND SMILES, S.: J. Chem Soc. **1911**, 408.
(16) HILDITCH, T. P., AND SMILES: S.: J. Chem. Soc. **1911**, 973.
(17) HINSBERG, O.: Ber. **62**, 127 (1929).
(18) KATSCHER, E., AND LEHR, H.: Monatsh. **64**, 236 (1934).
(19) KENT, B. A., AND SMILES, S.: J. Chem. Soc. **1934**, 422.
(20) KRISHNA, S.: J. Chem. Soc. **1923**, 2782.
(21) MAUTHNER, F.: Ber. **38**, 1411 (1905).
(22) MAUTHNER, F.: Ber. **39**, 1340 (1906).
(23) METCALF, R. L., AND KEARNS, C. W.: J. Econ. Entomol. **34**, 306 (1941); Chem. Abstracts **35**, 6726 (1941).
(24) MOIR, J.: Trans. Roy. Soc. S. Africa **18**, Pt. 2, 137 (1929); Chem. Abstracts **23**, 4467 (1929).
(25) PATTERSON, A. M., AND CAPELL, L.: *The Ring Index*, No. 1914. Reinhold Publishing Corporation, New York (1940).
(26) POLLAK, J., AND RIESZ, E.: Monatsh. **50**, 251 (1928).
(27) POLLAK, J., AND RIESZ, E.: Monatsh. **53 & 54**, 90 (1929).
(28) POLLAK, J., RIESZ, E., AND RIESZ, J.: Montash. **58**, 129 (1931).
(29) PÜTZER, B., AND MUTH, F.: German patent 606,350 (Chem. Abstracts **29**, P1434 (1935)); British patent 427,816 (Chem. Abstracts **29**, P6608 (1935)).
(30) SIEGLER, E. H., MUNGER, F., AND SMITH, L. E.: U. S. Dept. Agr., Circ. 523 (1939).
(31) SMITH, F. B., AND MOLL, H. W.: U. S. patent 2,221,819; Chem. Abstracts **35**, 1803 (1941).
(32) SMITH, F. B., AND MOLL, H. W.: U. S. patent 2,221,820; Chem. Abstracts **35**, 1803 (1941).
(33) SMITH, F. B., AND MOLL, H. W.: U. S. patent 2,265,204 (Chem. Abstracts **36**, 2078 (1942)); U. S. patent 2,265,205 (Chem. Abstracts **36**, 2078 (1942)).
(34) SMITH, F. B., AND MOLL, H. W.: U. S. patent 2,273,905; Chem. Abstracts **36**, 3807 (1942).
(35) SMITH, F. B., AND MOLL, H. W.: U. S. patent 2,277,833; Chem. Abstracts **36**, 4832 (1942).
(36) SMITH, L. E., SIEGLER, E. H., AND MUNGER, F.: J. Econ. Entomol. **29**, 1027 (1936); Chem. Abstracts **31**, 1147 (1937).
(37) STEVENSON, H. A., AND SMILES, S.: J. Chem. Soc. **1931**, 718.
(38) SUTER, C. M., AND GREEN, F. O.: J. Am. Chem. Soc. **59**, 2578 (1937).
(39) SUTER, C. M., AND MAXWELL, C. E.: *Organic Syntheses*, Vol. 18 (R. C. Fuson, Editor), p. 64. John Wiley and Sons, Inc., New York (1938).
(40) SUTER, C. M., MCKENZIE, J. P., AND MAXWELL, C. E.: J. Am. Chem. Soc. **58**, 717 (1936).
(41) THOMPSON, M. C., AND TURNER, E. E.: J. Chem. Soc. **1938**, 29.
(42) TOMITA, M.: J. Pharm. Soc. Japan **58**, 510 (in German, 136) (1938); Chem. Abstracts **32**, 7467 (1938).
(43) TOMITA, M., AND IKEDA, T.: J. Pharm. Soc. Japan **58**, 780 (in German, 231) (1938); Chem. Abstracts **33**, 2526 (1939).
(44) WOOD, R. G., MCCALE, C. H., AND WILLIAMS, G.: Phil. Mag. **31**, 71 (1941).