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Orientation reactions of phenoxathiin and its derivatives

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ORIENTATION REACTIONS OF PHENOXATHIIN AND ITS DERIVATIVES

by

Scott H. Eidt

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major Subject: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College
1955

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INTRODUCTION

Phenoxathiin (I) is a compound which has been the subject of considerable investigation by various workers who have not been concerned primarily with its chemical properties. As an anti-bacterial agent phenoxathiin has been tested for its action upon *Mycobacterium tuberculosis*[1,2], *Escherichia coli*[2], *Streptococcus hemolyticus* (oyler strain)[3], *S. h. epidemicus*[3] and *S. viridans*.[3] The compound was shown to have slight anthelmintic activity against *Haemonchus contortus*.[4] The insecticidal properties of phenoxathiin have attracted the greatest attention. In one series of tests[5] phenoxathiin gave high kills of American cockroach, cabbage aphid, diamond-back moth, European corn borer, Hawaiian beet webworm and termite. Other insects upon which phenoxathiin

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[1] M. Tomita and W. Watanabe, *J. Pharm. Soc. Japan*, *71*, 2104 (1951) [*C. A.*, *46*, 7618 (1952)].

[2] M. Tomita and W. Watanabe, *ibid.*, *72*, 478 (1952) [*C. A.*, *47*, 7028 (1953)].

[3] E. L. Everitt and M. X. Sullivan, *J. Wash. Acad. Sci.*, *30*, 457 (1940).

[4] H. McL. Gordon and M. Lipson, *J. Council Sci. Ind. Research*, *13*, 173 (1940).

[5] L. E. Smith, *U. S. Dept. Agr., Bur. Entomol. and Plant Quarantine*, *E-580* (1942).

has been tested are cattle lice[6], chicken lice[7], sheep ticks[8], caterpillars[9] and chiggers.[10-13] Phenoxathiin has been shown to have larvacidal activity upon the larvae of the mosquito[14], greenhouse leaf tyer[15], fleeceworm[16], screw worm[17], fly[18] and the codling moth.[19] Other uses for which

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[6]J. G. Matthysse, New York (Ithaca) Agr. Expt. Sta., Bull. 832 (1946).

[7]H. S. Telford, J. Econ. Entomol., 38, 573 (1945).

[8]H. H. Schwardt and J. G. Matthysee, New York (Ithaca) Agr. Expt. Sta., Bull. 844 (1948).

[9]W. J. Reid, Jr., and F. P. Cuthbert, Jr., U. S. Dept. Agr., Bur. Entomol. and Plant Quarantine, E-787 (1949).

[10]F. M. Snyder and F. A. Morton, J. Econ. Entomol., 39, 385 (1946).

[11]J. P. Linduska, F. A. Morton and W. C. McDuffie, ibid., 41, 43 (1948).

[12]H. F. Cross and F. M. Snyder, Soap Sanit. Chemicals, 25, No. 2, 135 (1949).

[13]C. N. Smith, Proc. Chem. Specialties Mfgrs. Assoc., Dec., 79 (1950) [Original not available for inspection; abstracted in C. A., 45, 5871 (1951)].

[14]D. E. Fink and L. E. Smith, J. Econ. Entomol., 29, 804 (1936).

[15]R. L. Metcalf and C. W. Kearns, ibid., 34, 306 (1941)

[16]E. F. Knipling, ibid., 34, 314 (1941).

[17]L. E. Smith and R. Melvin, ibid., 36, 475 (1943).

[18]E. S. Loeffler and W. M. Hoskins, ibid., 39, 589 (1946).

[19]E. H. Siegler, F. Munger and L. E. Smith, U. S. Dept. Agr., Circ. 523 (1939).

phenoxathiin has been tested are odor inhibitor[20], vinyl heat stabilizer[21], starting material for synthesis of vinyl polymers[22-25] and as an analytical reagent for palladium.[26]

As a result of the interest shown in phenoxathiin by industrial organizations, the compound has been made commercially available at a price much less than those of the related heterocycles, dibenzothiophene and thianthrene. Even though phenoxathiin is much less expensive than dibenzothiophene, the chemistry of the latter heterocycle has been investigated more completely than that of phenoxathiin. Derivatives of phenoxathiin have been tested for practical application rather infrequently considering the amount of interest in the parent compound. This lack of investigation

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[20] L. H. Flett, U. S. Patent 2,469,378 (1949) [C. A., 43, 6846 (1949)].

[21] R. F. Boyer, U. S. Patent 2,462,352 (1949) [C. A., 43, 4520 (1949)].

[22] R. G. Flowers and L. W. Flowers, J. Am. Chem. Soc., 71, 3102 (1949).

[23] R. G. Flowers and L. W. Flowers, U. S. Patent 2,449,527 (1948) [C. A., 43, 904 (1949)].

[24] R. G. Flowers and L. W. Flowers, U. S. Patent 2,449,528 (1948) [C. A., 43, 1223 (1949)].

[25] R. G. Flowers and L. W. Flowers, U. S. Patent 2,451,818 (1948) [C. A., 43, 1814 (1949)].

[26] O. Kőnig and W. R. Crowell, Mikrochemie ver. Mikrochim. Acta, 33, 298 (1948).

may be due to the absence of convenient methods of preparing pure derivatives of known structure.

The need for a comprehensive compilation of the existing knowledge of the chemistry of phenoxathiin prompted a review by Deasy[27] in 1943. This work has remained as the sole survey of this field. Phenoxathiin, unlike dibenzothiophene, has not been included in the popular books dealing with heterocycles. However, a forthcoming volume of the series by Elderfield[28a] will contain part of a chapter devoted to phenoxathiin.[28b]

It is the purpose of this investigation to make a systematic study of the chemistry of phenoxathiin and its derivatives. This study includes a collection and correlation of the data in the literature and the performance of those selected chemical reactions which will integrate the existing data and extend the knowledge of orientation in the phenoxathiin nucleus. An integral accompanying phase of the investigation is the comparison of the relative orienting influences of the two hetero atoms, oxygen and sulfur.

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[27] C. L. Deasy, Chem. Revs., 32, 173 (1943).

[28a] R. C. Elderfield, "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, N. Y.

[28b] R. C. Elderfield, University of Michigan, Ann Arbor, Michigan, Private communication, May 30, 1955.

Though phenoxathiin has been studied from this viewpoint on earlier occasions and valuable predictions were made, the meager data available may have led to premature conclusions. Due to the structural similarities of phenoxathiin to the oxygen and sulfur heterocycles, dibenzofuran and dibenzothiophene, respectively, and since the chemistry of these compounds having only one hetero atom has been more thoroughly investigated, frequent recourse was made to the literature concerning these heterocycles. A large part of the investigation is concerned with the chemical properties of the two oxidation products of phenoxathiin, i.e., phenoxathiin-10-oxide and phenoxathiin-10-dioxide. The 10-oxide and the 10-dioxide present sites where the orienting influences of the sulfoxide and sulfone groups can be compared. It will be shown that, with appropriate utilization of the directive influences of these two groups, the most convenient routes to many derivatives of phenoxathiin will be by way of substitution reactions of the 10-oxide and the 10-dioxide.

HISTORICAL

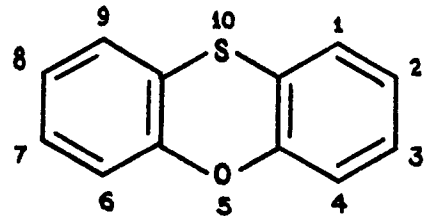
The Historical section of this thesis includes a survey of the methods of preparation of, and the physical and chemical properties of phenoxathiin and its known derivatives. Particular emphasis is placed upon those reactions which are involved in the determination of the location of a substituent in the phenoxathiin nucleus. Supplementing the text are tables of those derivatives of phenoxathiin, phenoxathiin-10-oxide and phenoxathiin-10-dioxide which have been described in the literature and those prepared in the course of this investigation. At the end of this section is a bibliography of phenoxathiin itself. Coverage of the literature on phenoxathiin is complete through 1954. The period between 1954 and June, 1955 was covered as completely as possible by a survey of the Heterocyclic section of Current Chemical Papers. This publication contains a classified world list of the new papers in pure chemistry. Each entry in the list consists of the title of the article, the name(s) of the author(s) and the journal reference.

Nomenclature

Phenoxathiin has been identified by several names. The name used in this thesis is that preferred by Patterson and

Capell[29] and employed by Chemical Abstracts since 1937. Other names which have appeared in the literature are dibenzothioxin, dibenzothioxine, dibenzo-1,4-oxthiin, phenoxthionine, phenthioxine, phenoxthin, phenoxthine and phenothioxin. The last name is used currently by Matheson, Coleman and Bell, Inc. and by the Dow Chemical Company.

Several systems of numbering the ring positions have been used and no universally accepted system exists. Employed herein and illustrated below (I) is the system preferred by Patterson and Capell[29] and adopted by Chemical Abstracts. Mauthner[30], the initial worker in the field of



I

phenoxathiin chemistry, proposed the name "phenoxthin" and the system illustrated by formula Ia. This numbering system

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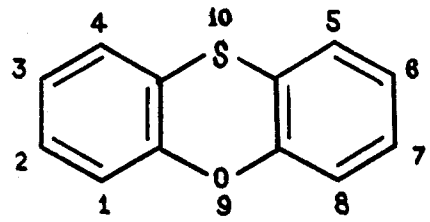
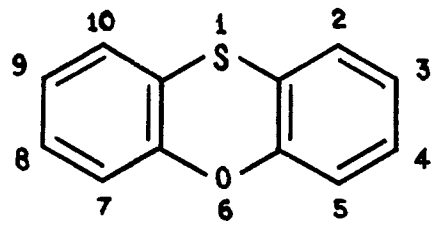
[29] A. M. Patterson and L. T. Capell, "The Ring Index", Reinhold Publishing Corp., New York, N. Y., 1940, p. 259.

[30] F. Mauthner, Ber., 38, 1411 (1905).



Ia



Ib

is frequently encountered in the German and Japanese literature. The system Ib was used by Pollack, Riesz and Riesz.[31]

Physical Properties of Phenoxathiin

Phenoxathiin is a white solid having a density of 1.38 g./ml.[32] At 60° the specific gravity of liquid phenoxathiin is 1.226.[33] The compound can be distilled at atmospheric pressure as the boiling point at 745 mm. is 311°.[34] However,

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[31] R. Pollack, E. Riesz and J. Riesz, Monatsh., 58, 129 (1931).

[32] R. G. Wood, C. H. McCale and G. Williams, Phil. Mag., 31, 71 (1941).

[33] The Dow Chemical Company, "Dow Special Chemicals", Midland, Michigan, 1950.

[34] C. M. Suter and F. O. Green, J. Am. Chem. Soc., 59, 2578 (1937).

there is slight decomposition at this temperature and most distillations have been performed at reduced pressure. The following boiling points and pressures have been recorded: 185-187°/23 mm.[35], 180-183°/15 mm.[36], 183-184°/12 mm.[37], 180°/10 mm.[33], 150-152°/5 mm.[36] and 120-121°/1 mm.[38] Due to its low vapor pressure phenoxathiin is not appreciably volatile with steam.[39]

Melting points for phenoxathiin have been reported in the range 53-61°. The commercially available material, for which the quantitative solubility data are available, melts at 53-55°.[33] The melting point of 55.3-55.5° was recorded for a sample which had been purified by vacuum distillation followed by crystallization from ethanol.[40] Mauthner, who performed the original synthesis of phenoxathiin, recorded the highest melting point. The sample melted at 60-61° after several recrystallizations from ethanol.[39] A sample

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[35] C. M. Suter, J. P. McKenzie and C. E. Maxwell, ibid., 58, 717 (1936).

[36] C. M. Suter and C. E. Maxwell, "Organic Syntheses", Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 485.

[37] G. M. Bennett, M. S. Leslie and E. E. Turner, J. Chem. Soc., 444 (1937).

[38] This thesis.

[39] F. Mauthner, Ber., 39, 1340 (1906).

[40] O. A. Nelson and L. E. Smith, J. Am. Chem. Soc., 64, 1057 (1942).

recrystallized from methanol "until pure" melted at 57.5-58° when the melting point was observed with a polarizing microscope.[35] After an extensive purification process which consisted of extraction with 30% aqueous sodium hydroxide solution, washing with water, recrystallization from ethanol, sublimation and again recrystallization from ethanol, the resulting white needles of phenoxathiin melted at 55.7°.[41]

The crystals of phenoxathiin appear to belong, as far as the external symmetry is concerned, to the orthorhombic holohedral class, but X-ray results show that the crystals are enantiomorphic.[32] The crystal lattice is Γ_o and the space group $P2_12_12_1(D^4_2)$.[32] Phenoxathiin was shown to be isomorphous with phenothiazine on the basis of the similarity of the axial ratios. This similarity exists even though the crystals appear quite different externally.[32]

The stereochemistry of phenoxathiin has been investigated by consideration of bond angles and atomic radii, crystal structure, dipole moment and by chemical methods. If the molecule were not planar it would have no center of symmetry and could possibly give rise to optically active derivatives. Bennett, Leslie and Turner[37] had no success in resolving either 3-nitro-8-methyl-1-phenoxathiincarboxylic

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[41] N. M. Cullinane and W. T. Rees, Trans. Faraday Soc., 36, 507 (1940).

acid or _-phenoxathiincarboxylic acid. The former acid was converted to the brucine salt but no diastereoisomers were separated. Similarly, the latter was non-resolvable by way of the strychnine salt or the α-phenylethylamine salt. The finding that the acids did not exist in two separable forms was not proof that the molecule was planar, however.

Cullinane and Rees[41], using valence angles and atomic radii of carbon, oxygen and sulfur, made calculations of the angle of fold about the O-S axis and concluded that phenoxathiin was folded. These same workers attempted to show that phenoxathiin possessed a folded structure by a comparative study of binary mixtures of phenoxathiin, phenothiazine, thianthrene, phenoxazine and dibenzo-p-dioxin. They assumed that binary mixtures of isomorphous compounds formed solid solutions and that isomorphism existed when two compounds of analogous constitution had like spatial structures. Reference compounds in the study were dibenzo-p-dioxin, which has a zero dipole moment and a planar structure, and thianthrene, which has a dipole of approximately 1.5 D[42-45] and

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[42]E. Bergmann and M. Tschudnowsky, Ber., 65, 457 (1932).

[43]W. S. Walls and C. P. Smyth, J. Chem. Physics, 1, 337 (1934).

[44]G. M. Bennett and S. Glasstone, J. Chem. Soc., 128 (1934).

[45]I. G. M. Campbell, C. G. LeFèvre, R. J. W. LeFèvre and E. E. Turner, ibid., 404 (1938).

a folded structure. It was expected that phenoxathiin would form a solid solution with thianthrene. The pertinent experimental results[41] are listed in Table 1.

By application of the rule that binary mixtures of isomorphous compounds form solid solutions it was concluded

Table 1. Type of solution formed by binary mixtures of related heterocycles

Components of mixture	Type of solution
Dibenzo-p-dioxin and phenoxathiin	eutectic
Dibenzo-p-dioxin and phenothiazine	eutectic
Dibenzo-p-dioxin and thianthrene	eutectic
Phenothiazine and phenoxathiin	solid
Phenothiazine and thianthrene	solid
Thianthrene and phenoxathiin	eutectic

that phenoxathiin and phenothiazine were isomorphous and that both have folded structures. Logically it would follow that phenoxathiin and thianthrene were isomorphous, but the data revealed otherwise. Due to this apparent anomaly the binary mixture studies yielded no conclusive evidence for folding.

Wood, McCale and Williams[32] compared the axial ratios and the results of X-ray measurements of phenoxathiin, phenothiazine, phenoxaselenin and phenoxatellurin and concluded that the four are isomorphous. Also, each compound contained four molecules per unit cell as indicated by the similarity in the observed and calculated densities. These workers state that the four isomorphous compounds possessed structures in which the molecules were folded along the line joining the two hetero atoms. The suggested angles of fold for these molecules and for thianthrene are phenothiazine, 160-170°; phenoxathiin, 150-160°; phenoxaselenin, 140-150°; phenoxatellurin, 135-145°; and thianthrene, 140°.

A reason suggested[32] for the absence of solid solutions in the phenoxathiin-thianthrene mixtures was the appreciable difference between the angles of fold of the two compounds. This reasoning does not take into account that phenothiazine and thianthrene form solid solutions even though the difference in suggested angles of fold is greater than in the case of phenoxathiin-thianthrene.

The most conclusive evidence for the folded structure is based upon the dipole moment. Higasi and Uyeo[46] determined the moment in benzene and hexane solutions to be

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[46] K. Higasi and S. Uyeo, J. Chem. Soc. Japan, 62, 400 (1941) [C. A., 35, 6167 (1941)].

1.09 D. They concluded that the molecule was folded. Higasi[47] predicted that no optical isomerism would be expected in derivatives of phenoxathiin since the activation energy for racemization would be too small, no more than a few kilocalories. The angle of fold of $155\pm5^{\circ}$ was suggested by Leonard and Sutton who found the dipole moment in benzene to be 0.92 D.[48]

Phenoxathiin is soluble in all the common organic solvents. The approximate solubility in some common solvents is listed in Table 2.[33]

The usual solvents for recrystallization are methanol and ethanol, though crystallization can be effected from acetic acid and low boiling petroleum ethers. Suter and Maxwell[36] have recommended that, when recrystallizing from hot methanol, the solution be chilled rapidly and stirred vigorously to prevent the formation of an oil.

Physical Properties of Phenoxathiin-10-oxide

The recorded melting points of phenoxathiin-10-oxide

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[47] K. Higasi, Sci. Papers Inst. Phys. Chem. Research (Tokyo), 38, 331 (1941) [C. A., 35, 6167 (1941)].

[48] N. J. Leonard and L. E. Sutton, J. Am. Chem. Soc., 70, 1564 (1948).

Table 2. Approximate solubility of phenoxathiin

(Grams per 100 grams of solvent at 25°)

Solvent	Solubility
Acetone	200
Benzene	165
Carbon tetrachloride	100
Ether	165
Methanol	7
VMP Naphtha	33
Water (at 80°)	Practically insoluble

lie in the range 151-159°.[33,38,49-53] Tomita and Ikeda[48] observed the melting point of 151-154° for phenoxathiin-10-oxide

[49] M. Tomita and T. Ikeda, J. Pharm. Soc. Japan, 58, 780 (in German, 231) (1938) [C. A., 33, 2526 (1939)].

[50] T. Irie, Bull. Inst. Phys. Chem. Research (Tokyo), 20, 150 (1941) [C. A., 36, 2881 (1942)].
T. Irie, J. Faculty Sci., Hokkaido Univ., Ser. 3, 4, No. 2, 70 (1951) (in English) [C. A., 47, 6949 (1953)]. This article is a translation of the preceding article in Bull. Inst. Phys. Chem. Research (Tokyo), 20, 150 (1941).

[51] H. Gilman and D. L. Esmay, J. Am. Chem. Soc., 74, 2021 (1952).

[52] J. F. Nobis, A. J. Blardinelli and D. J. Blaney, ibid., 75, 3384 (1953).

[53] H. D. K. Drew, J. Chem. Soc., 511 (1928).

obtained by oxidation of phenoxathiin with dilute nitric acid. Melting points of 151-153° and 153.5°, the latter being of a sample recrystallized from methanol, were recorded by Irie.[50] In the same range is the melting point of 152-153° reported by Gilman and Esmay.[51] The pure grade of commercial phenoxathiin-10-oxide obtained for this study melted at 154-155.5°. Benzene was the recrystallization solvent used by Nobis, Blardinelli and Blaney[52], who reported the melting point of 154-156°. Drew[53] observed that phenoxathiin-10-oxide melted at 158-159° after recrystallization from benzene or acetic acid.

Table 3 contains the approximate solubility of phenoxathiin-10-oxide in some common solvents.[33]

Phenoxathiin-10-oxide crystallizes in the form of massive needles or prisms from glacial acetic acid or benzene. Other commonly employed recrystallization solvents are methanol, ethanol and dilute acetic acid.

Physical Properties of Phenoxathiin-10-dioxide

Melting points reported for phenoxathiin-10-dioxide have been in the range 140-148°.[39,49-51] The melting point encountered most frequently is 147-148°. Mauthner's product melting at 140-141° may have contained a small amount of

Table 3. Approximate solubility of phenoxathiin-10-oxide (Grams per 100 grams of solvent at 25°)

Solvent	Solubility
Acetone	3.0
Benzene	0.2
Carbon tetrachloride	0.4
Ether	0.5
Methanol	5.0
VMP Naphtha	0.1
Water	0.1

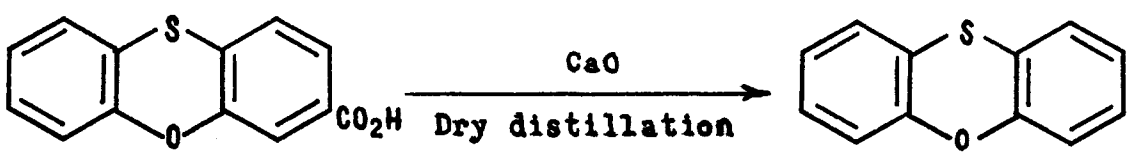
phenoxathiin or phenoxathiin-10-oxide as it gave a blue color in concentrated sulfuric acid.[39] This supposition is based upon the observation that phenoxathiin and phenoxathiin-10-oxide yield purple to violet solutions in concentrated sulfuric acid, whereas phenoxathiin-10-dioxide forms a colorless solution.[53] The pure grade of the commercially available material melting at 147-148° gives no color in concentrated sulfuric acid solution.

Phenoxathiin-10-dioxide is insoluble in petroleum ether and ligroin.[39] Though slightly soluble in hot carbon

tetrachloride, the compound is very soluble in chloroform. Mauthner[39] reported that the product melting at 140-141° was soluble in ether, ethanol and benzene. The present writer observed that only a small amount of pure phenoxathiin-10-dioxide was soluble in a large volume of ether. Ether and benzene were concluded to be in different solvent categories as far as the ability to dissolve phenoxathiin-10-dioxide was concerned. The solvents normally employed for recrystallization are dilute acetic acid, glacial acetic acid and ethanol.

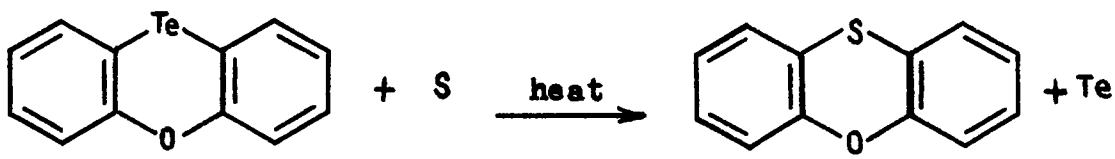
Methods of Preparation of Phenoxathiin

In 1906 Mauthner[39] reported the first preparation of phenoxathiin. The compound was prepared from 3-phenoxathiincarboxylic acid which was decarboxylated by heating with calcium oxide.



The decarboxylation reaction was used for a different purpose by Gilman, Van Ess, Willis and Stuckwisch.[54] These investigators had carried out the reaction between phenoxathiin and n-butyllithium, followed by carbonation and acidification. The resulting 4-phenoxathiincarboxylic acid was proved to contain the phenoxathiin ring system by decarboxylation to yield phenoxathiin. In this case decarboxylation was effected when a mixture consisting of the acid, copper bronze and quinoline was heated at 200° for 30 minutes.

The method of preparation of phenoxathiin which was reported by Drew[53] is interesting in that it involved replacement of tellurium by sulfur. Phenoxathiin was formed in over 90% yield when phenoxatellurin was heated with sulfur.



Following removal of the tellurium, the organic product was recrystallized from acetic acid. Even though the melting

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[54] H. Gilman, Marian W. Van Ess, H. B. Willis and C. G. Stuckwisch, J. Am. Chem. Soc., 62, 2606 (1940).

point was 58°, the crystallized phenoxathiin yet contained 6-7% phenoxatellurin. The two isomorphous compounds were inseparable by crystallization. Since only phenoxatellurin formed an insoluble 10,10-dibromide, a solution of the mixture was treated with bromine and phenoxatellurin was removed as the 10,10-dibromide. The pure phenoxathiin melted at 58°. The identity of the product was established on the basis of the preparation process, analysis and proximity of the melting point to that of Mauthner's[39] phenoxathiin. Repeated recrystallization failed to raise the melting point to the 60-61° reported by Mauthner. Drew did not mention the two other reports of the preparation of phenoxathiin. The omission is surprising since the close agreement between the melting point of Drew's phenoxathiin and the 59° reported earlier by Ferrario[55] would have constituted additional evidence for the assignment of structure.

The route from a readily available starting material to phenoxathiin is a long one if phenoxatellurin is an intermediate. Involved is the reaction between diphenyl ether and tellurium tetrachloride and subsequent reduction of the resulting 10,10-dichlorophenoxatellurin to phenoxatellurin.[56] Attempts to extend the "phenoxatellurin to phenoxathiin

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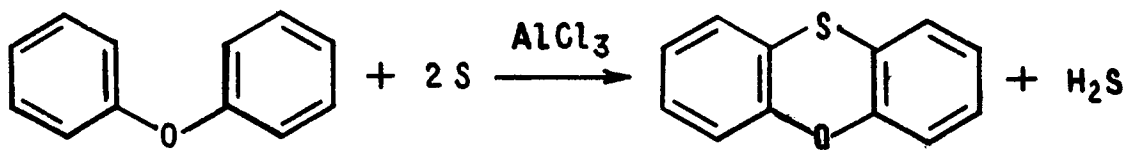
[55]E. Ferrario, Bull. soc. chim., France, 9, 536 (1911).

[56]H. D. K. Drew, J. Chem. Soc., 223 (1926).

synthesis" to include the preparation of phenoxathiin derivatives were mentioned by Drew[53], but no experimental details were published. 2-Chloro-8-methylphenoxatellurin was reported to behave towards sulfur in a manner similar to that of phenoxatellurin. Explosions resulted when nitrophenoxatellurins were heated with sulfur.

The principal method used for the preparation of phenoxathiin is based upon the reaction of diphenyl ether with sulfur in the presence of aluminum chloride.



In 1911 descriptions of the above reaction were published almost simultaneously by Ferrario[55] and Ackermann.[57] The latter worker had described the reaction in 1910 in a patent application. It was evident that Ackermann recognized that the reaction was not limited to the preparation of the parent compound since he reported also the preparation of a chloro-

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[57]F. Ackermann, German Patent 234,743 (1911) [C. A., 5, 2912 (1911); Chem. Zentr., 82, I, 1768 (1911)].

and a methylphenoxathiin from the appropriately substituted diphenyl ethers. However, for the purpose of convenience the reaction was called the "Ferrario reaction".[34] This name will be used in this thesis.

In the experimental procedure described by Ferrario the reactants were mixed in approximately the stoichiometric ratio, i.e., 0.5 mole each of diphenyl ether and aluminum chloride and 1.0 gram atom of sulfur. The time and temperature of reaction, work-up procedure, melting point and analysis of the product were described.

Suter, McKenzie and Maxwell[35] stated that, "Ferrario claimed practically quantitative yields for his last method . . . .". The first of the two methods by Ferrario was an unsuccessful attempt to prepare phenoxathiin by the reaction between diphenyl ether and sulfur. The only reference which Ferrario made as to the success of the second method, other than the experimental procedure mentioned above, occurs in the following sentence:

> If one effects the reaction in presence of a catalyst (anhydrous magnesium chloride or aluminum chloride) one obtains a very good result, especially if the temperature is not too high.[35]

Suter and coworkers[35] obtained mostly tarry products when they carried out the reaction according to the procedure of Ferrario. After considerable research, these workers found that, when excess of diphenyl ether was employed, pure

phenoxathiin in yields of 67-72% was obtained. The use of solvents other than the excess of diphenyl ether failed to improve the yield. Little, if any, reaction occurred in refluxing carbon disulfide. The reaction in sym-tetrachloroethane at steam bath temperature produced a 48% yield of phenoxathiin. Bennett, Leslie and Turner[37], using the best method of Suter, McKenzie and Maxwell[35], prepared phenoxathiin in 88% crude yield. The yield of pure product, obtained after two recrystallizations from ethanol, was 59.5%.

The most detailed experimental procedure for the preparation of phenoxathiin is that by Suter and Maxwell.[36] Crude yields in the vicinity of 87% are obtained by this procedure. The loss on one recrystallization from methanol is about 3%. In the course of preparing phenoxathiin for use in metalation reactions, Gilman, Van Ess, Willis and Stuckwisch[54] confirmed the yields reported by Suter and Maxwell.

Preparation of Phenoxathiin-10-oxide

Derivatives of phenoxathiin-10-oxide have been synthesized by ring closure methods but the parent heterocycle has been prepared only by oxidation of phenoxathiin and by hydrolysis of 10,10-dichlorophenoxathiin. The reduction of phenoxathiin-10-dioxide to phenoxathiin-10-oxide has not

been reported. Despite the fact that it has been prepared by principally one method, there has been general agreement as to the structure of phenoxathiin-10-oxide. Yet no large scale preparation has been described, probably because there are so few preparations in which phenoxathiin-10-oxide is known to be a good starting material.

From the standpoint of its preparation, phenoxathiin-10-oxide enjoys an unenviable position between its reduction product, phenoxathiin, and its oxidation product, phenoxathiin-10-dioxide. It is shown below that if too mild oxidizing conditions are employed the 10-oxide will contain unreacted phenoxathiin. On the other hand, under slightly more vigorous oxidizing conditions a mixture of the 10-oxide and 10-dioxide may be formed. The separation problem in this latter case is more difficult than in the case of a mixture of phenoxathiin and one of the oxidation products.

Gilman and Esmay[51] compiled an extensive table of data in the course of study of the peroxide oxidation of phenoxathiin. Upon examination of this table it is evident that the course of the oxidation in glacial acetic acid is extremely dependent upon such factors as ratio of moles of peroxide to moles of phenoxathiin, amount of acetic acid, temperature of reaction and time of reaction. Though these workers did not carry it out with this purpose in mind, one

of the experiments is quite similar to that procedure of Drew.[53] Thus, when a 10% excess of 30% aqueous hydrogen peroxide was added to a 20% solution of phenoxathiin in glacial acetic acid, the mixture heated at 90-98° for 20 minutes and then diluted with water, there resulted a 40% yield of phenoxathiin-10-oxide and a 49% recovery of starting material. In other experiments the yields of the 10-oxide ranged from zero, in which case a 97% yield of the 10-dioxide was obtained, to 90%.

As a part of the above mentioned investigation Gilman and Esmay[51] found that ethanol was superior to glacial acetic acid as a solvent for the preparation of phenoxathiin-10-oxide. There was no appreciable oxidation to the dioxide even when an eightfold excess of hydrogen peroxide was employed. Yields of 96% and 98% of pure phenoxathiin-10-oxide were obtained in the 0.05-mole runs.

Phenoxathiin-10-oxide has been prepared in yields of 91-95% by nitric acid oxidation of phenoxathiin in glacial acetic acid solution. Tomita and Ikeda[49] prepared phenoxathiin-10-oxide, m.p. 151-154°, in 92% yield by adding a multifold excess of fuming nitric acid (sp. gr. 1.45) to a dilute solution of phenoxathiin at 30-40°. Similar conditions were employed by Nobis, Blardinelli and Blaney[52] in an unsuccessful attempt to prepare 2-nitrophenoxathiin.

Thus, fuming nitric acid (sp. gr. 1.5) at 30° effected no nitration, but afforded a 91% yield of phenoxathiin-10-oxide.

In the course of this work phenoxathiin-10-oxide was prepared in yields of 93% and 95% by oxidation with dilute nitric acid (sp. gr. 1.2). This oxidizing agent had been used by Mauthner for the preparation of 10-oxides of 1,3-dinitrophenoxathiin[30] and 1-nitro-3-phenoxathiincarboxylic acid.[39]

In an unsuccessful attempt to nitrate phenoxathiin Irie[50] added acetyl nitrate to a cold solution of phenoxathiin in carbon tetrachloride. Phenoxathiin-10-oxide was the only product isolated.

Irie[50] isolated 10,10-dichlorophenoxathiin and observed that this orange, crystalline compound was easily hydrolyzed to phenoxathiin-10-oxide. Hydrolysis was accomplished when the crystals were poured upon ice or left exposed to the atmosphere. Nobis, Blardinelli and Blaney[52] prepared phenoxathiin-10-oxide in 81% yield by pouring upon ice that 10,10-dichlorophenoxathiin mixture formed by passing chlorine into a solution of phenoxathiin in glacial acetic acid.

Drew[53] found that phenoxathiin-10-oxide was formed by hydrolysis of a solution of phenoxathiin in cold, concentrated sulfuric acid. The reaction was not intended as one

of preparative value, but was carried out as part of an investigation of the action of sulfuric acid upon phenoxathiin.

Preparation of Phenoxathiin-10-dioxide

Phenoxathiin-10-dioxide has been prepared only by oxidation of phenoxathiin and phenoxathiin-10-oxide. Since the product is not in an intermediate oxidation state, the conditions for carrying out the oxidation are not so limited as in the case of the preparation of phenoxathiin-10-oxide. There has been no report of cleavage of the ring system by an oxidizing agent.

The initial preparation of phenoxathiin-10-dioxide was reported by Mauthner[39], who oxidized phenoxathiin with a solution of chromic acid in acetic acid. The preparation has been repeated by Drew[53] and by Irie.[50] That the 10-oxide was the probable intermediate oxidation product in the oxidation of phenoxathiin to the 10-dioxide was shown by Tomita and Ikeda[49] when they carried out the chromic acid oxidation of phenoxathiin-10-oxide to phenoxathiin-10-dioxide.

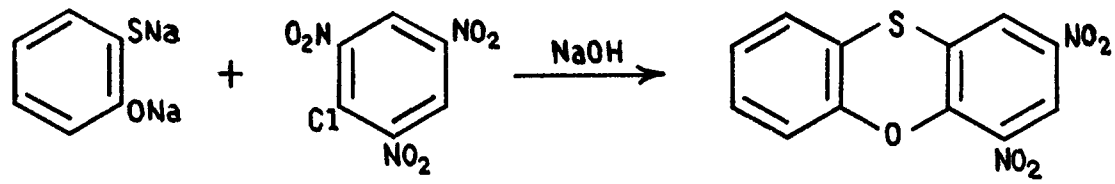
Irie[50] prepared phenoxathiin-10-dioxide by oxidizing phenoxathiin in glacial acetic acid with excess fuming nitric acid (sp. gr. 1.45). With two exceptions these conditions are very similar to those described by Tomita and Ikeda[49]

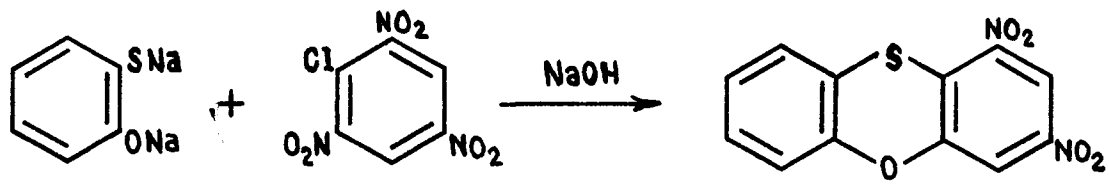
for the preparation of the 10-oxide. The actual amount of oxidizing agent employed by Irie was only 60% of that amount used when the oxide was the desired product. The temperature was the important factor, however. Irie carried out the reaction at 80° as compared to 30-40° used by Tomita and Ikeda.

Drew[53] obtained phenoxathiin-10-dioxide by long heating of a glacial acetic acid solution of phenoxathiin and hydrogen peroxide. A similar but much more detailed procedure, one which afforded a 97% yield of the 10-dioxide, was described by Gilman and Esmay.[51] Drew[53] also mentioned the preparation of phenoxathiin-10-dioxide by oxidation with potassium permanganate, but he provided no details.

Ring Closure Methods of Preparation of Phenoxathiin Derivatives

The first compound containing the phenoxathiin ring system was prepared by the condensation of picryl chloride with the disodium salt of o-thiolphenol. Mauthner[30] believed that the reaction occurred as shown below and that the product melting at 187° was 2,4-dinitrophenoxathiin. However, it will be shown subsequently that the compound was 1,3-dinitrophenoxathiin.





Stevenson and Smiles[58] encountered the same problem in that the reaction between 2-hydroxy-1-thiolnaphthalene and picryl chloride would yield the dinitro derivative (II) or (III) depending upon whether sodium nitrite was eliminated through the salt of the thiol or the phenol. It was proved that the reaction occurred by the latter mechanism when the dinitro compound, III, was found to be identical with the product from the action of sodium hydroxide upon the S-picryl derivative of 2-acetyloxy-1-thiolnaphthalene.

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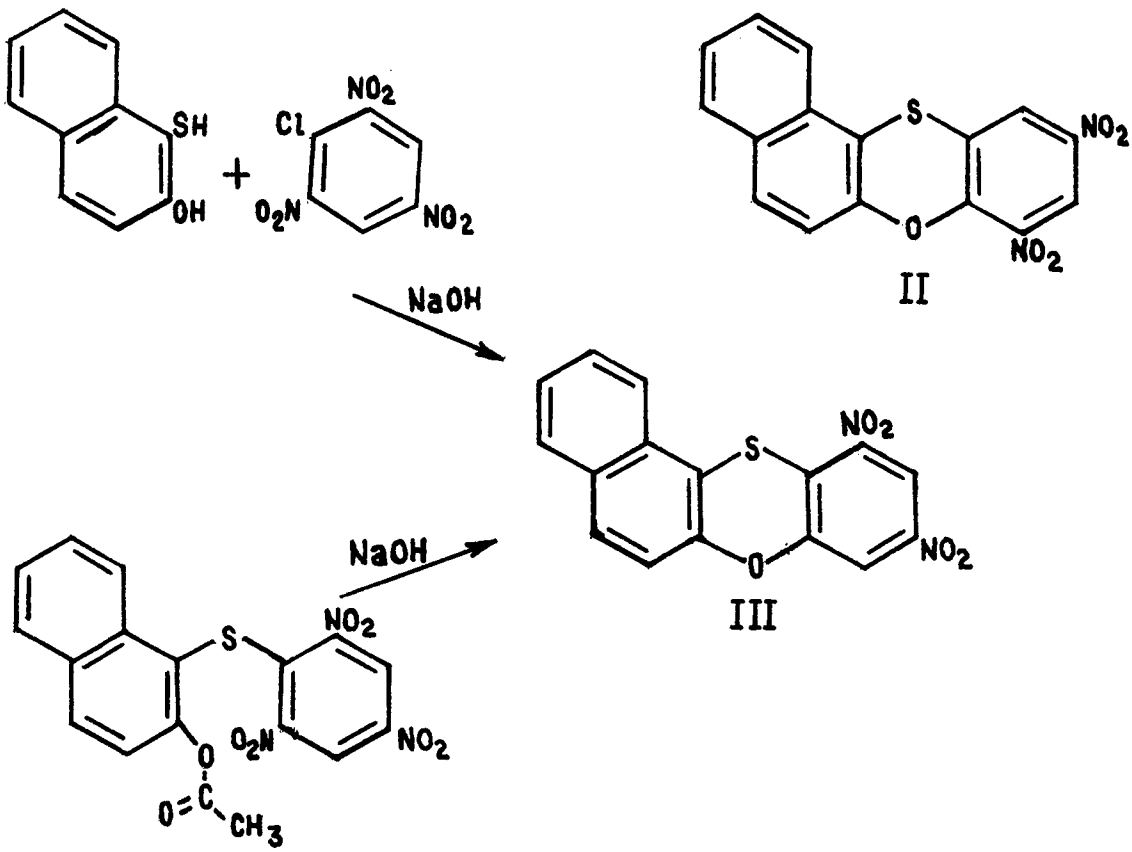
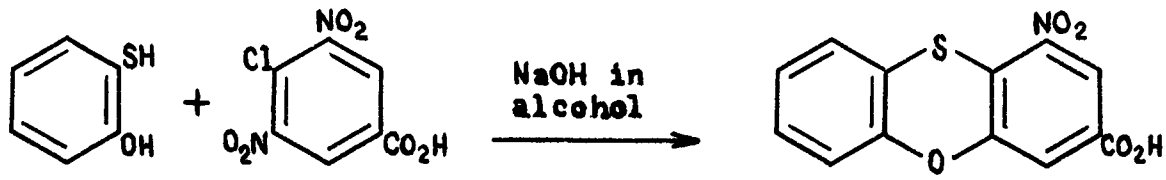
[58]H. A. Stevenson and S. Smiles, J. Chem. Soc., 718 (1931).



Additional evidence for the formation of 1,3-dinitrophenoxathiin and not the 2,4-isomer was provided by Mauthner[39] when he carried out the base-catalyzed reaction between o-thiolphenol and 3,5-dinitro-4-chlorobenzoic acid. This reaction, illustrated below, is very similar to the one used in the preparation of 1,3-dinitrophenoxathiin; the only difference between the 3,5-dinitro-4-chlorobenzoic acid and picryl chloride being a carboxyl group in the former and a nitro group in the latter compound.



It is somewhat surprising that this product which melted at 262° was designated 1-nitro-3-phenoxathiincarboxylic acid by Mauthner.[39] This designation was shown to be correct when a later worker proved that the nitro group was in the 1-position.[50] Thus, there is little doubt that the dinitro compound, prepared by the same type of reaction, was 1,3-dinitrophenoxathiin.

The preparation of 1-nitro-3-phenoxathiincarboxylic acid according to Mauthner's method has been repeated by Irie[50] and by Shirley and Lehto[59], who reported melting points of 259° and 260-262°, respectively. All three groups of workers prepared 1-amino-3-phenoxathiincarboxylic acid by reduction of the nitro compound.[39,50,59]

Mauthner[39] and Shirley and Lehto[59] carried out the diazotization of 1-amino-3-phenoxathiincarboxylic acid and subsequent removal of the diazo group. The resulting 3-phenoxathiincarboxylic acid, m.p. 223°, was the first

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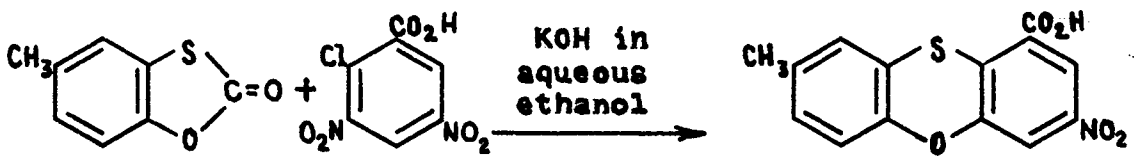
[59]D. A. Shirley and E. A. Lehto, J. Am. Chem. Soc., 77, 1841 (1955).

phenoxathiin derivative containing only a carboxyl group. Shirley and Lehto[59] showed by a mixed melting point determination that the 3-acid was different from the 1-phenoxathiincarboxylic acid, m.p. 221-222°, which they prepared by metalation of phenoxathiin-10-oxide with n-butyllithium.

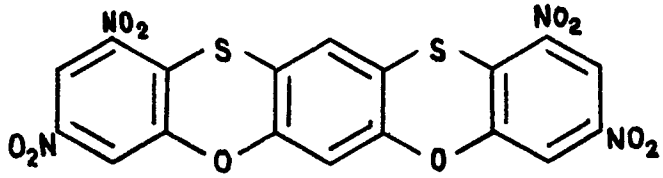
Irie[50] converted 1-amino-3-phenoxathiincarboxylic acid to 1-chloro-3-phenoxathiincarboxylic acid by diazotization followed by the Sandmeyer reaction. Subsequent decarboxylation by dry distillation from calcium oxide yielded 1-chlorophenoxathiin, m.p. 78-80°. That the chlorophenoxathiin was neither the 2-isomer, m.p. 88-89°, nor the chlorophenoxathiin, m.p. 78-79°, obtained by chlorination of phenoxathiin, was shown by depressions in melting points of the mixtures. 4-Chlorophenoxathiin is a liquid.

Several polysubstituted derivatives of phenoxathiin were prepared by ring closure syntheses which were modifications of Mauthner's picryl chloride method. Bennett, Leslie and Turner[37] prepared 3-nitro-8-methyl-1-phenoxathiincarboxylic acid by condensing 3-thiol-p-tolyl carbonate with 2-chloro-3,5-dinitrobenzoic acid in an aqueous ethanol solution of potassium hydroxide. The structure of the product was assigned on the basis of the reaction by which it was prepared and the analytical data.



Pollack and Riesz[60,61] prepared a tetranitrodiphenoxathiin and two polynitrophenoxathiin disulfides by heating dipicryl derivatives of dithiolphenols in ethanolic potassium hydroxide. The identity of each of the products was based on the analytical data.

The compound prepared from the dipicryl derivative of 4,6-dithiolresorcinol was assigned the structure illustrated below.[60]



1,3,1',3'-Tetranitrophenoxathiin-8,8'-disulfide, a compound which decomposes explosively on heating, was prepared from the dipicryl derivative of 2,4-dithiolphenol.[61]

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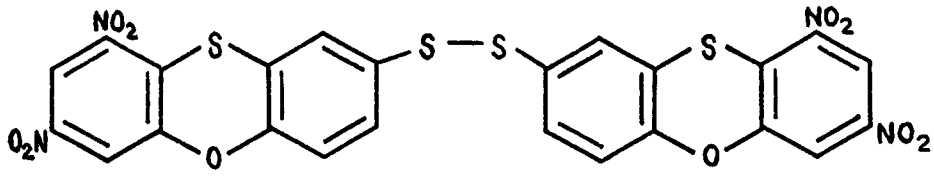
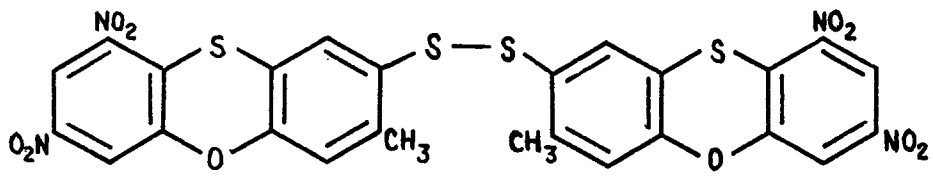
[60] J. Pollack and E. Riesz, Monatsh., 50, 251 (1928).

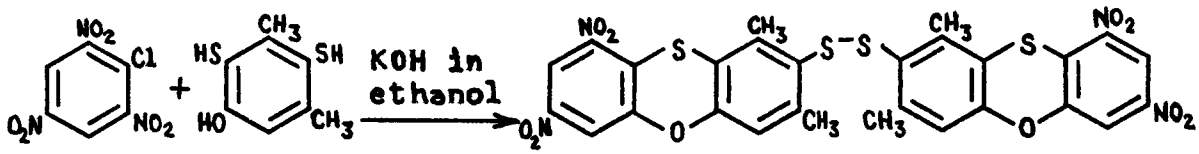
[61] J. Pollack and E. Riesz, ibid., 53 & 54, 90 (1929).



A dark red compound, 1,3,1',3'-tetranitro-7,7'-dimethylphenoxathiin-8,8'-disulfide, was obtained from the dipicryl derivative of 2,4-dithiol-5-methylphenol.[60]



Katscher and Lehr[62] prepared 1,3,1',3'-tetranitro-7,9,7',9'-tetramethylphenoxathiin-8,8'-disulfide, m.p. 255-257°, by heating picryl chloride with 2,4-dithiol-3,5-dimethylphenol in ethanolic potassium hydroxide solution.



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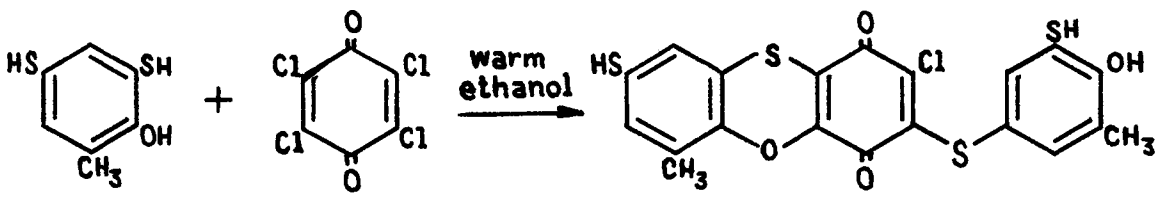
[62] E. Katscher and H. Lehr, ibid., 64, 236 (1934).

When Pollack, Riesz and Riesz[31] carried out the condensation of 2,4-dithiol-6-methylphenol with chloranil there resulted a brown solid which decomposed at 250° without melting. This material, the constitution of which was based only upon the analytical data, was called 1,4-diketo-2-chloro-3-(3'-methyl-4'-hydroxy-5'-thiolphenyl)thiol-6-methyl-8-thiolphenoxathiin.



Several phenoxathiin derivatives have been prepared from 2-hydroxydiphenyl sulfides or sulfoxides by intramolecular ring closure reactions. Hilditch and Smiles[63] prepared 2,8-dimethylphenoxathiin (IV) by allowing 2,2'-dihydroxy-5,5'-dimethyldiphenyl sulfoxide to stand in contact with cold, concentrated sulfuric acid for several hours. The mixture containing 2,8-dimethylphenoxathiin and the 10-oxide yielded pure 2,8-dimethylphenoxathiin, m.p. 74°, after reduction with zinc in glacial acetic acid. In a subsequent

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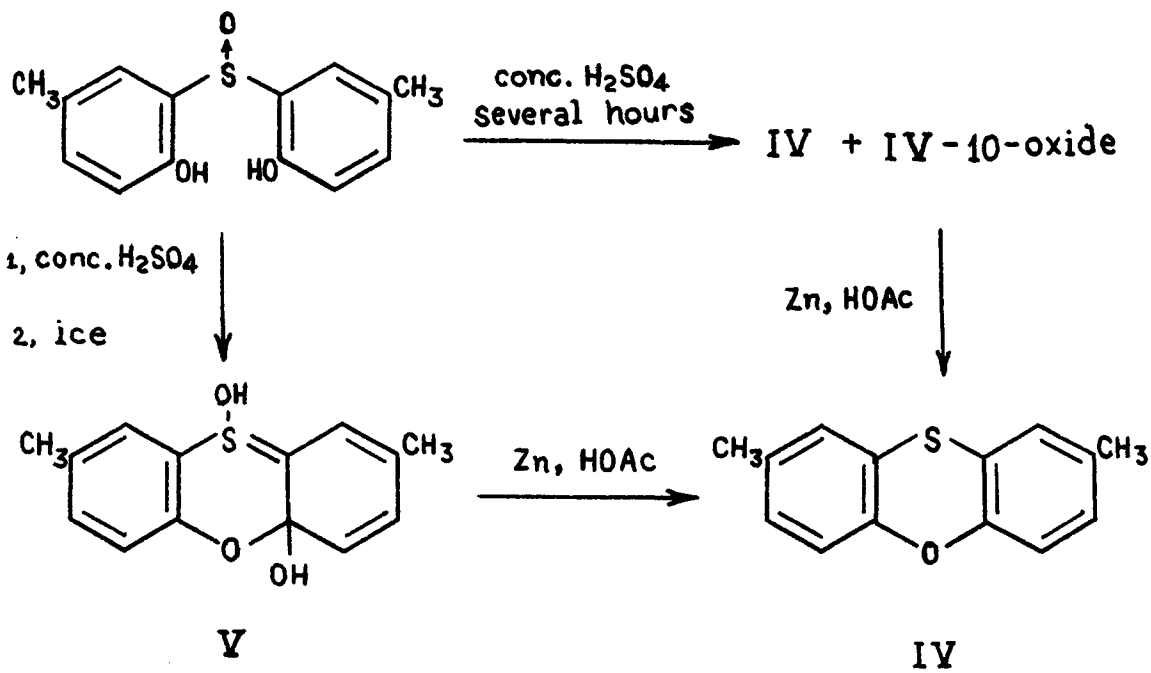
[63]T. P. Hilditch and S. Smiles, J. Chem. Soc., 408 (1911).

paper[64] these workers showed that the ring closure reaction was not a simple dehydration. When the cold reaction mixture consisting of the sulfoxide and sulfuric acid was allowed to stand only a few minutes, and then poured into ice, there were obtained orange leaflets, m.p. 105-110°. This rather unstable compound, isomeric with the starting material, was called 2,8-dimethylphenothioxonium hydroxide. The structure which has been proposed is shown by compound V. 2,8-Dimethylphenothioxonium hydroxide was reduced to 2,8-dimethylphenoxathiin by treatment with zinc in cold glacial acetic acid.



[64] T. P. Hilditch and S. Smiles, ibid., 973 (1911).

Tomita[65] prepared 2,8-dimethylphenoxathiin from 4,4'-dimethyldiphenyl ether by the Ferrario reaction. This later worker reported the melting point as 73-74°.

Hilditch and Smiles[63] obtained pure 2,8-dichlorophenoxathiin-10-oxide, m.p. 168°, by treating 2,2'-dihydroxy-5,5'-dichlorodiphenyl sulfoxide with cold, concentrated sulfuric acid. As in the case of the dimethyl derivative, an orange phenothioxonium hydroxide was isolated.[64] The 2,8-dichlorophenothioxonium hydroxide melted at 142-145°. When a cold solution of this hydroxide was poured into water, the 10-oxide, m.p. 166°, was formed. However, when the isolated hydroxide was dissolved in glacial acetic acid and the solution refluxed one-half hour, 2,8-dichlorophenoxathiin, m.p. 135°, was the product. This last compound was also prepared by reduction of 2,8-dichlorophenoxathiin-10-oxide with zinc and acetic acid. The method of Hilditch and Smiles[63] was used by Irie[50] who reported that 2,8-dichlorophenoxathiin melted at 137°.

Stevenson and Smiles[58] prepared one of the most important of the phenoxathiin derivatives when they carried out the ring closure of 2,5,5'-tribromo-2'-hydroxydiphenyl sulfide.

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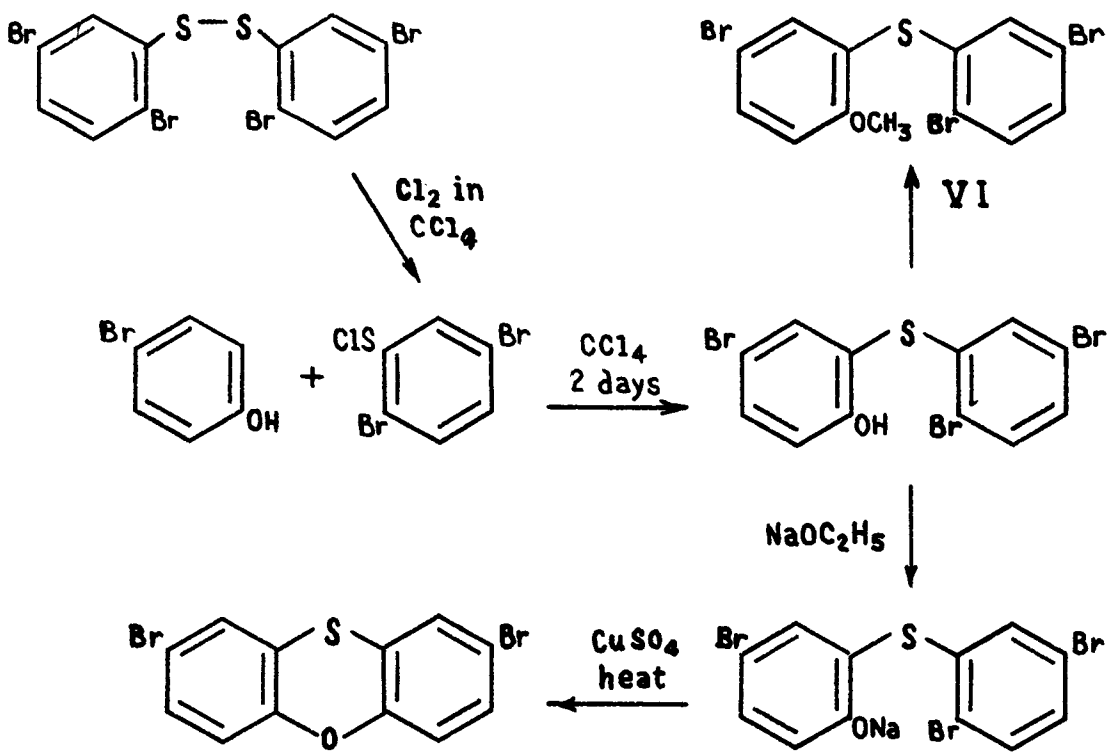
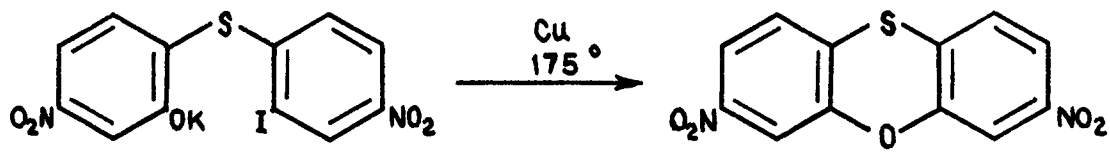
[65] M. Tomita, J. Pharm. Soc. Japan, 58, 510 (in German, 136) (1938) [C. A., 32, 7467 (1938); Chem. Zentr., 110, 1, 3892 (1938)].



The product, 2,8-dibromophenoxathiin, is the reference compound upon which are based the structural assignments of many substitution products of phenoxathiin. The synthesis of the diphenyl sulfide began, for all practical purposes, with the preparation of 2,5-dibromobenzenesulfenyl chloride from bis-(2,5-dibromophenyl)disulfide and chlorine. The sulfenyl chloride was not isolated, but was allowed to react with p-bromophenol in carbon tetrachloride solution for 2 days. From the mixture there was obtained 2,5,5'-tribromo-2'-hydroxydiphenyl sulfide as a viscous oil which was characterized by conversion to the methyl ether (VI), m.p.

142°. The structure of the methyl ether was not proved. An ethanolic solution containing the impure 2,5,5'-tribromo-2'-hydroxydiphenyl sulfide and one equivalent of sodium ethoxide was allowed to evaporate and the resulting sodium salt was dried under reduced pressure. Cyclization was effected when the salt was heated with cupric sulfate. Following crystallization of the sublimate from alcohol pure 2,8-dibromophenoxathiin, m.p. 92°, was obtained.

3,7-Dinitrophenoxathiin, m.p. 204-205°, was prepared in 81% yield when the potassium salt of 2-hydroxy-2'-iodo-4,4'-dinitrodiphenyl sulfide was heated with copper powder.[66] It is unfortunate that Amstutz[66] did not reduce the 3,7-dinitro-



phenoxathiin to 3,7-diaminophenoxathiin since this latter compound had been prepared by Irie.[50] There should be little doubt as to the identity of Amstutz's product, though the possibility exists that Irie's diamine, prepared by the

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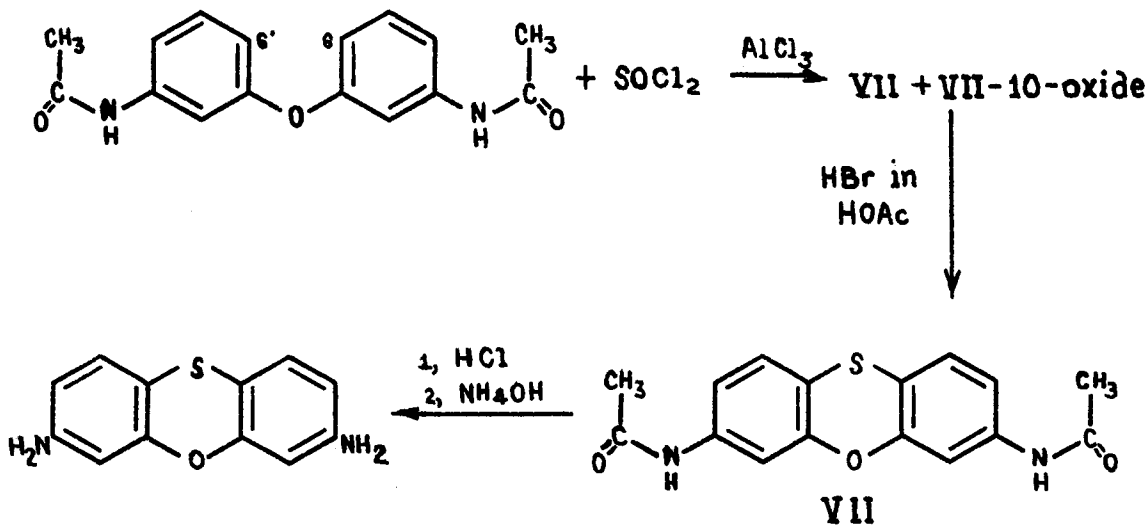
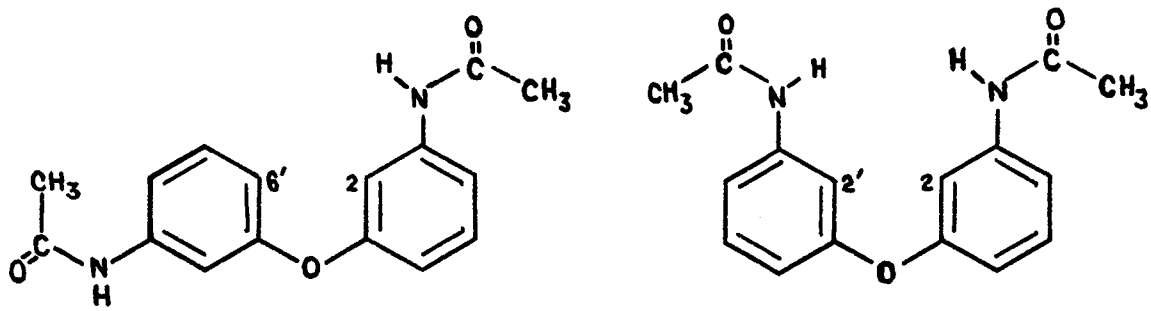
[66]E. D. Amstutz, J. Am. Chem. Soc., 72, 3420 (1950).

reactions illustrated below, may have been the 1,7- or 1,9-derivative.

The ring closure reaction which Irie used to obtain the precursor to 3,7-diaminophenoxathiin belongs, as far as type of reaction is concerned, in the class with the Ferrario reaction. However, it is described here since it was the only reaction reported, other than that of Amstutz, which yielded a 3,7-phenoxathiin derivative. The aluminum chloride-catalyzed reaction between 3,3'-diacetamidodiphenyl ether and thionyl chloride yielded a mixture of 3,7-diacetamidophenoxathiin and its 10-oxide. After the mixture was treated with hydrogen bromide in glacial acetic acid, the pure 3,7-diacetamidophenoxathiin, m.p. 289-290°, was obtained. The corresponding diamine melted at 167-168°.[50]



Irie[50] believed that ring closure occurred through the 6,6'-positions, para to the acetamido groups. Ring closure through the 2,6'- or the 2,2'-positions in 3,3'-diacetamidodiphenyl ether would yield 1,7- or 1,9-diacetamidophenoxathiin, respectively. These last two possibilities cannot be completely disregarded.



Several substituted diphenyl ethers containing the sulfinic acid group in the 2-position have been converted to phenoxathiin derivatives upon treatment with dehydrating agents. The method was first applied when Krishna[67] added concentrated sulfuric acid to a suspension of 2-sulfino-4-nitrodiphenyl ether in acetic anhydride and obtained a mixture of 2-nitrophenoxathiin (VIII) and its 10-oxide. Following treatment of the mixture with hydrobromic acid there was

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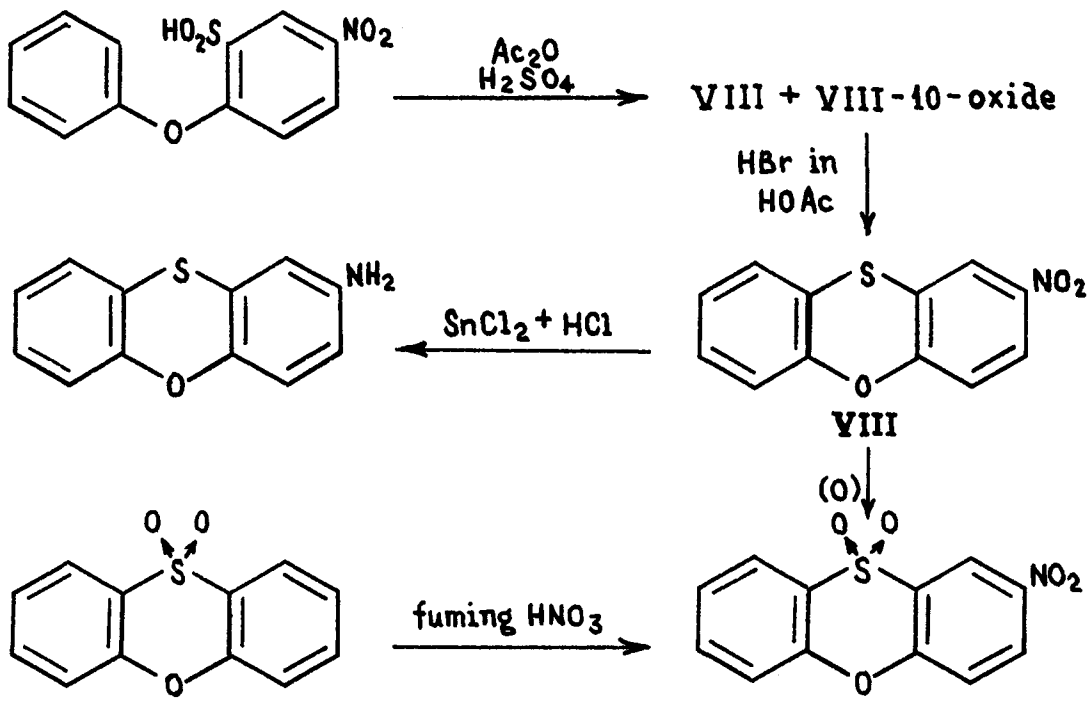
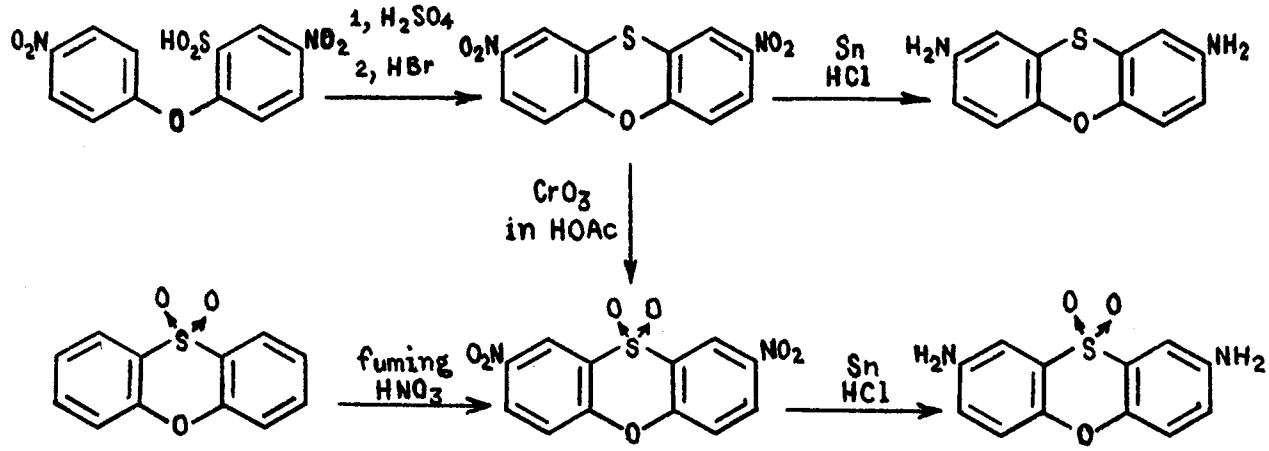
[67]S. Krishna, J. Chem. Soc., 2782 (1923).

isolated a product, m.p. 140°, which was reported as 2-nitrophenoxathiin. Irie[50] repeated the preparation and observed that the compound melted at 160°. After oxidation to the 10-dioxide, Krishna's compound melted at 205-206°[67], while that of Irie melted at 196.5.[50] The lower melting point is closer to the 192-194° which Nobis, Blardinelli and Blaney[52] reported for 2-nitrophenoxathiin-10-dioxide prepared by nitration of phenoxathiin-10-dioxide with fuming nitric acid. Irie carried out the reduction of 2-nitrophenoxathiin to 2-aminophenoxathiin, m.p. 98°.[50] Nobis and co-workers[52], who prepared the amine by the Beckmann rearrangement of 2-acetylphenoxathiin oxime, reported the melting point as 93-95°.



Irie[50] prepared 2,8-dinitrophenoxathiin, m.p. 143°, from 2-sulfino-4,4'-dinitrodiphenyl ether (see equations below) by employing the procedure described above for the preparation of the mononitro compound. When 2,8-dinitrophenoxathiin was reduced there resulted an amine, m.p. 118°, which was expected to be 2,8-diaminophenoxathiin. Nobis and co-workers[52] reported that this amine melted at 171-173°. Irie carried out the oxidation of 2,8-dinitrophenoxathiin and showed that the 10-dioxide was identical with 2,8-dinitrophenoxathiin-10-dioxide, m.p. 276-278°, obtained by nitration of phenoxathiin-10-dioxide. Nobis and co-workers[52] repeated this last reaction and observed that 2,8-dinitrophenoxathiin-10-dioxide melted at 283-286°. The melting points of 239-240° and 244-247.5° were reported by Irie[50] and by Nobis and co-workers[52], respectively, for 2,8-diaminophenoxathiin-10-dioxide.



It is evident that one of the two diamines designated as 2,8-diaminophenoxathiin, either the one melting at 118° or that melting at 171-173°, is another compound. The latter melting point appears more logical upon consideration that the structurally similar 3,7-diaminophenoxathiin[66] melts at 167-168°. The possibility that the dinitro compound, m.p. 143°, of Irie[50] could be reduced to the diamine, m.p. 171-173°, of Nobis[52] is quite remote in view of the fact that the melting point of each of the other mono- and dinitrophenoxathiins was higher than that of the corresponding mono- and diamines. It appears strange that 2,8-dinitrophenoxathiin should melt at 143°, whereas 2-nitrophenoxathiin melts at 160° and 1,3-[30] and 3,7-dinitrophenoxathiin[66] melt at 187° and 204-205°, respectively. However, it is unlikely that any compound other than 2,8-dinitrophenoxathiin or its 10-oxide could be oxidized to 2,8-dinitrophenoxathiin-10-dioxide, a derivative with a well-established structure. Further discussion of this controversy occurs in the section dealing with the Friedel-Crafts acetylation of phenoxathiin. In this section is described the preparation of 2,8-diacetylphenoxathiin, a compound which is a precursor for the amine melting at 171-173°.

Two workers, Krishna[67] and then Irie[50], reported the preparation of 2-chloro-8-nitrophenoxathiin from

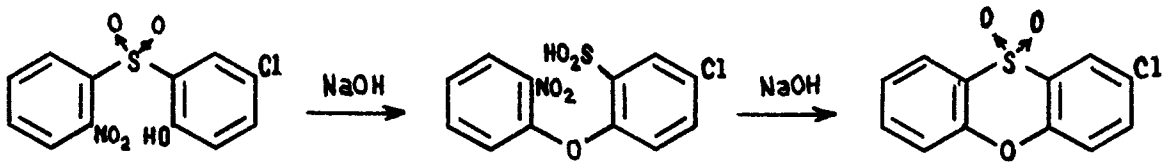
2-sulfino-4-nitro-4'-chlorodiphenyl ether and acetic anhydride. Krishna's product melted at 128-129° while that of Irie, prepared according to the method of Krishna, melted at 195°. The compound melting at 128-129° was oxidized to the 10-dioxide, m.p. 183-185°.

2-Methyl-8-nitrophenoxathiin was prepared from 2-sulfino-4-nitro-4'-methyldiphenyl ether by Krishna[67], who reported that the product melted at 156°, and by Irie[50], who reported the melting point as 160°. Of the several preparations of phenoxathiin derivatives from sulfinodiphenyl ethers, this is the only one which has yielded apparently the same product to two different workers.

Irie[50] prepared 2-methoxy-8-nitrophenoxathiin, m.p. ca. 300°, by the ring closure reaction of 2-sulfino-4-nitro-4'-methoxydiphenyl ether with acetic anhydride and concentrated sulfuric acid. 2-Amino-8-methoxyphenoxathiin, prepared by reduction of the nitro compound, melted at 277°.[50] These two melting points appear extremely high. It is strange that the introduction of a methoxy group into a nitro- or an amino-phenoxathiin should have such an effect upon the melting point.

Two phenoxathiin-10-dioxide derivatives were obtained as side products from rearrangement reactions of hydroxysulfones. Kent and Smiles[68] reported that 2-chlorophenoxa-

thiin-10-dioxide was formed along with the expected product, 2-sulfino-4-chloro-2'-nitrodiphenyl ether, when 2-hydroxy-5-chloro-2'-nitrodiphenyl sulfone was warmed with aqueous sodium hydroxide. Neither the melting point nor the analysis of the 10-dioxide was reported.



When Kent and Smiles[68] carried out the rearrangement of 2-hydroxy-5-methyl-2'-nitro-4'-chlorodiphenyl sulfone they obtained 2-sulfino-4-methyl-2'-nitro-4'-chlorodiphenyl ether, the formula of which was shown incorrectly as IX in the article, and a phenoxathiin derivative which melted at 173°. The compound was named 3-chloro-8-methoxyphenoxathiin-10-dioxide and the structure illustrated by X was shown. The "methoxy" was undoubtedly a typographical error and the placement of the chlorine in the 3-position was a continuation of the error in IX. The phenoxathiin derivative was

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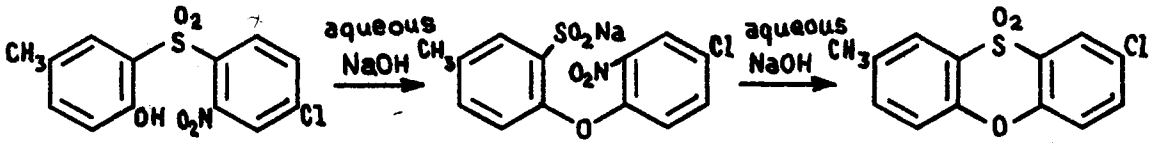
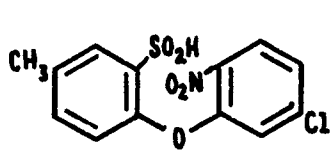
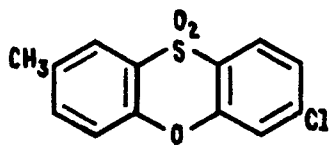
[68] B. A. Kent and S. Smiles, J. Chem. Soc., 422 (1934).

obtained when the solution of the sodium sulfinate was heated longer than necessary to cause rearrangement of the sulfone to take place. It was believed to have formed as a result of an intramolecular reaction between the nitro and the sodium sulfinate groups. Though not so named, the compound which melted at 173° was probably 2-chloro-8-methylphenoxathiin-10-dioxide.





IX

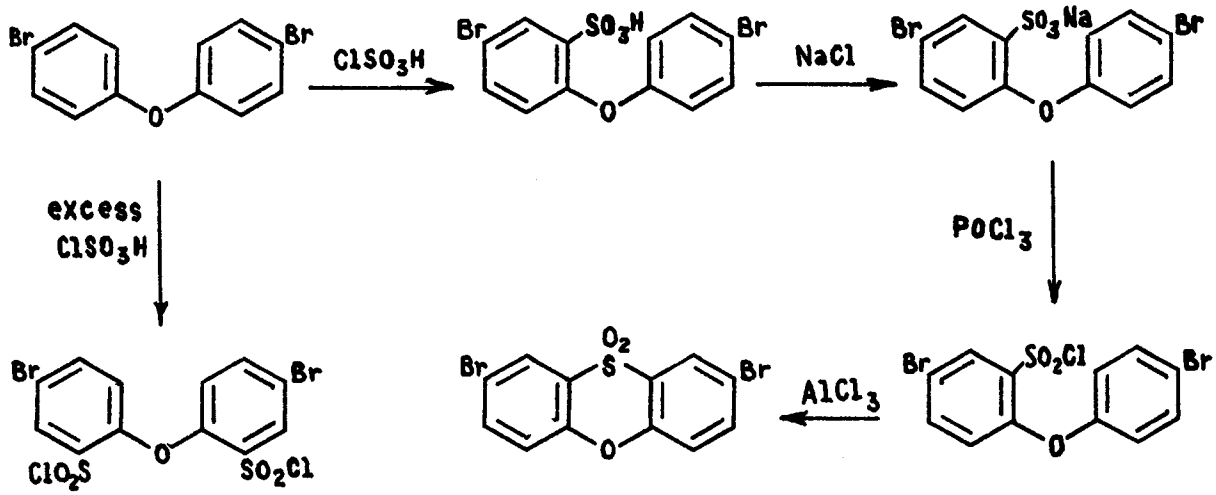


X

There was no indication that Kent and Smiles[68] believed that X was formed directly from 2-hydroxy-5-methyl-2'-nitro-4'-chlorodiphenyl sulfone. The ring closure would involve elimination of sodium nitrite between the nitro group and the sodium salt of the phenol. A similar reaction was described

earlier in connection with the proof of the structure of 1,3-dinitrophenoxathiin and with Stevenson and Smiles[58] work with the S-picryl derivative of 2-acetyloxy-1-thiol-naphthalene.

Suter, McKenzie and Maxwell[35] prepared 2,8-dibromophenoxathiin-10-dioxide, m.p. 183-186°, by treatment of a solution of 2-(4-bromophenoxy)-5-bromobenzesulfonyl chloride (XI) in sym.-tetrachloroethane with aluminum chloride. Since the structure of XI was based upon the reactions by which XI was prepared, those reactions are described below. An attempt to prepare XI by the reaction of 4,4'-dibromodiphenyl ether with excess chlorosulfonic acid was unsuccessful. The product was a disulfonyl chloride which probably had the structure illustrated by XII. The reaction of 4,4'-dibromodiphenyl ether with one equivalent of chlorosulfonic acid yielded a benzenesulfonic acid which was not isolated, but was converted to the sodium salt. A quantitative analysis for sodium was performed on the salt. 2-(4-Bromophenoxy)-5-bromobenzenesulfonyl chloride was formed when the salt was refluxed with excess phosphorus oxychloride.



XII XI

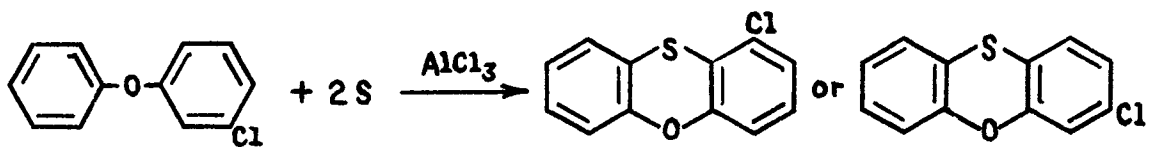
The reaction between substituted diphenyl ethers, sulfur and aluminum chloride, called the Ferrario reaction, has been employed for the preparation of chloro- and alkyl-substituted phenoxathiins. The first compound of this type was prepared when Ackermann[57] obtained 2-methylphenoxathiin from the reaction of 4-methyldiphenyl ether with sulfur and aluminum chloride. The melting point of the product, 36°, is in agreement with the 38-39° which Suter and Green[34] observed after repeating the preparation. Suter and Green[34] prepared 4-methylphenoxathiin, a liquid, and a methyl derivative which melted at 83-84° from 2- and from 3-methyldiphenyl ether, respectively. There was the possibility that the meta-

substituted ether yielded either 1- or 3-methylphenoxathiin, depending upon whether ring closure occurred ortho or para, respectively, to the methyl group. The investigators believed that the latter possibility was the more likely and suggested that the compound which melted at 83-84° was 3-methylphenoxathiin.

Mentioned earlier was the preparation of 2,8-dimethylphenoxathiin by the Ferrario reaction[65] and by the ring closure of 2,2'-dihydroxy-5,5'-dimethyldiphenyl sulfone.[63] Tomita prepared 2,8-diethylphenoxathiin, a liquid, from 4,4'-diethyldiphenyl ether.[65]

Ackermann[57] carried out the Ferrario reaction on 4-chlorodiphenyl ether and reported that the product, m.p. 37°, was 2-chlorophenoxathiin. However, when Suter and Green[34] repeated the reaction, these workers obtained a compound which, according to later work by Irie[50], is 2-chlorophenoxathiin. The melting point, 88-89°, of the product of Suter and Green was also observed by Irie[50], who prepared 2-chlorophenoxathiin from 2-aminophenoxathiin.

The product from the Ferrario reaction of 3-chlorodiphenyl ether was designated as 3-chlorophenoxathiin by Suter and Green.[34] However, the same situation exists as in the case of the reaction of 3-methyldiphenyl ether. If a chlorophenoxathiin was the product, it may have been either the



1- or the 3- derivative. The question as to whether a chlorophenoxathiin was isolated has arisen for two reasons. First, there was no rigorous evidence that the compound melting at 59-60° was a pure chlorophenoxathiin. Second, there have been reported, in addition to the chlorophenoxathiin, m.p. 37°, of Ackermann[57], five compounds designated as chlorophenoxathiins. Since there are only four different positions in phenoxathiin, it is logical that one of the five compounds is not a chlorophenoxathiin. The 1-, m.p. 78-80°[50], the 2-, m.p. 88-89°[34,50], and the 4-chlorophenoxathiin, a liquid[34], have been prepared by unambiguous syntheses. A fourth chlorophenoxathiin, m.p. 78-79°[50], 81-82°[34], the product of chlorination, has been obtained by two workers and shown to be different from the 1-[50], 2-[34,50] and 4-[34,50] isomers. Either this chlorination product or the material, m.p. 59-60°, which has been prepared only one time and then by an ambiguous reaction, is 3-chlorophenoxathiin.

Suter and coworkers[34,35] made numerous attempts to prepare 2-bromophenoxathiin from 4-bromodiphenyl ether, sulfur and aluminum chloride. The reaction was violent at 100° and the product was a mixture with an indefinite melting point from which no pure compound was isolated.[34] Suter and Green[34] reported that 2-methoxydiphenyl ether gave no evidence of undergoing the Ferrario reaction at 100°, but suggested that 3-methoxydiphenyl ether would probably react. The Ferrario reaction did not take place when Gilman, Van Ess, Willis and Stuckwisch[54] heated a mixture of 2-carboxydiphenyl ether, sulfur and aluminum chloride for 4 hours at 120-140°.

Oxidation Reactions

The oxidations of phenoxathiin to phenoxathiin-10-oxide and to phenoxathiin-10-dioxide were discussed in the sections dealing with the preparation of these two oxidation products.

In several cases the reagent which effected the oxidation of phenoxathiin to the 10-dioxide was also used to prepare the 10-oxide. This latter compound was the principal product when the same oxidizing agent was employed either in smaller amounts, at a lower temperature, or in a different solvent.

Several oxidizing agents convert derivatives of phenoxathiin to the corresponding 10-oxides. However, since relatively few 10-oxides have been prepared, no one of the reagents has been used extensively. The 10-oxides of _-cyclohexylphenoxathiin[69], 1,3-dinitrophenoxathiin[30], and 1-nitro-3-phenoxathiincarboxylic acid[39] were prepared by oxidation with dilute nitric acid. Hydrogen peroxide in glacial acetic acid oxidized 1,3-diacetamidophenoxathiin[50] and 2,8-dimethylphenoxathiin[63] to the respective 10-oxides.

Nobis, Blardinelli and Blaney[52] added an aqueous solution of sodium hypochlorite to 2-acetamidophenoxathiin in glacial acetic acid and obtained a mixture of 2-acetamidophenoxathiin-10-oxide and 10-dioxide. Though only the 10-oxide derivative was isolated, the workers[52] had expected the 10-dioxide to be the major product since the reaction was carried out under the conditions which Gilman and Nobis[70] had employed to oxidize 2,8-diacetamidodibenzothiophene to the 5-dioxide. However, it cannot be concluded from this one reaction that dibenzothiophene is more readily oxidized to the dioxide than is phenoxathiin. This one experiment is certainly not the

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[69]F. B. Smith and H. W. Moll, U. S. Patent 2,273,905 (1942) [C. A., 36, 3807 (1942)].

[70]H. Gilman and J. F. Nobis, J. Am. Chem. Soc., 71, 274 (1949).

basis of a general comparison of the relative ease of oxidation of the two heterocycles. After an extensive study of the oxidation of dibenzothiophene and phenoxathiin by hydrogen peroxide, Gilman and Esmay[51] stated that "the oxidation of phenoxathiin to either the monoxide or the dioxide proceeds more readily than does the corresponding oxidation of dibenzothiophene."

The conversion of phenoxathiin derivatives to the 10-oxides is often a side reaction which must be considered when carrying out reactions involving the use of halogens or mild oxidizing agents. Mentioned earlier was the observation that 10,10-dichlorophenoxathiin, formed by the action of chlorine on phenoxathiin in benzene, was hydrolyzed to phenoxathiin-10-oxide upon exposure to the atmosphere.[50]

Sodium hypohalite, a reagent which is used in the Hofmann reaction and in the oxidation of methyl ketones to carboxylic acids, has been shown to oxidize various sulfides to sulfoxides and sulfones.[71] However, 4-aminodibenzothiophene was prepared in 48% yield from 4-acetamidodibenzothiophene by way of the Hofmann reaction.[51] Thus some sulfides are not oxidized to a great extent under the conditions of the Hofmann reaction. The relatively high concentration of

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[71] A. E. Wood and E. G. Travis, J. Am. Chem. Soc., 50, 1226 (1928).

alkali used in this reaction may inhibit oxidation of some sulfides. Wood and Travis[71] showed that oxidation of diphenyl sulfide in aqueous media occurred more rapidly at low sodium hydroxide concentrations. These reactions were carried out at temperatures less than 27° however, whereas higher temperatures are employed in the rearrangement reaction.

The Hofmann reaction carried out on 4-phenoxathiincarboxylic acid amide yielded a product, m.p. 223-225°, with decomposition, which was designated as 4-aminophenoxathiin hydrochloride.[54] It was shown later by Gilman and Esmay[51], after a recalculation of the theoretical percentage of nitrogen, that the percentage nitrogen found by analysis agreed more closely with that for 4-aminophenoxathiin-10-oxide hydrochloride. This analysis cannot be accepted as conclusive proof that the 10-oxide was formed, however. Apparently the same amine hydrochloride was obtained from the reaction of 4-phenoxathiinyllithium with O-methylhydroxylamine.[54] The conditions in this reaction are not usually considered as oxidizing. The amine was a liquid which was distilled at 209°/5 mm. It is the belief of this writer that 4-aminophenoxathiin-10-oxide would be a solid which could be distilled only with great difficulty. The hydrochloride of the liquid amine melted at 223-224°, with decomposition.

The melting point of a mixture of the amine hydrochlorides prepared by the two methods was not taken.

A large excess of hydrogen peroxide in hot glacial acetic acid oxidizes phenoxathiin and its derivatives to the corresponding 10-dioxides.[34,35,51-54,59,66] Mauthner[39], Krishna[67] and Irie[50] carried out the preparation of several 10-dioxides by employing chromic acid in acetic acid as the oxidizing agent. Krishna[67] employed concentrated nitric acid in acetic acid to oxidize 2-nitrophenoxathiin, m.p. 140°, to the 10-dioxide, m.p. 205-206°. Irie's 2-nitrophenoxathiin, m.p. 160°, yielded 2-nitrophenoxathiin-10-dioxide, m.p. 196°, upon oxidation with chromic acid.[50]

Hilditch and Smiles[63] added the theoretical quantity of potassium permanganate to a cold acetic acid solution of 2,8-dichlorophenoxathiin-10-oxide, m.p. 168°, and obtained the 10-dioxide, m.p. 196°. The same reagent was used to oxidize 2,8-dimethylphenoxathiin to the 10-dioxide.[59]

The oxidation of 2,8-dimethylphenoxathiin by alkaline potassium permanganate yielded 2,8-phenoxathiindicarboxylic acid-10-dioxide, m.p. greater than 300°, and a material, m.p. 270°, which may have been 2,8-phenoxathiindicarboxylic acid-10-oxide.[65] This latter compound may have contained some unoxidized material since the percentages of carbon and hydrogen found by analysis were greater than the theoretical

values for 2,8-phenoxathiindicarboxylic acid-10-oxide. The higher melting acid was also obtained by the haloform oxidation of 2,8-diacetyl- and 2,8-bis-(α-chloroacetyl)phenoxathiin.[65] Gilman, Van Ess, Willis and Stuckwisch[54] heated an aqueous mixture consisting of 4-methylphenoxathiin-10-dioxide and alkaline potassium permanganate for 48 hours, but obtained no acid.

Suter, McKenzie and Maxwell[35] carried out the haloform oxidation of 2-acetylphenoxathiin according to the following procedure. "Five grams of 2-acetylphenoxathiin and 25 grams of bleaching powder were mixed with 200 cc. of dilute sodium hydroxide and the whole heated on the steam bath for 5 hours."[35] The authors designated the product, m.p. 259-260°, as 2-phenoxathiincarboxylic acid. The only analytical datum reported was a neutralization equivalent of 239 as compared with the theoretical value of 244. In view of the extreme ease of conversion of phenoxathiin to the oxide by either chlorination followed by hydrolysis or by hypohalite oxidation, it appears strange that neither the 10-oxide or 10-dioxide was isolated. When Irie[50] repeated the reaction using the procedure as stated above the product was 2-phenoxathiincarboxylic acid 10-dioxide, m.p. 268-269°. The following analytical data were reported for the compound. Calcd. for $C_{13}H_8O_5S$: C, 56.50; H, 2.92. Found: C, 56.32;

H, 3.11. The theoretical percentages of carbon and hydrogen for the unoxidized acid are 63.92 and 3.30, respectively.

The above experimental procedure of Suter, McKenzie and Maxwell[35] was employed by Tomita[65] in the previously mentioned oxidation of 2,8-diacetylphenoxathiin to 2,8-phenoxathiindicarboxylic acid 10-dioxide.

Reduction Reactions

In Ferrario's only article concerned with phenoxathiin there is the statement that phenoxathiin adds two atoms of hydrogen upon reduction.[55] No details of the reaction were provided, however. There has been no report of an attempt to reduce phenoxathiin to a derivative such as 1,4-dihydrophenoxathiin in which the tricyclic ring system remains intact.

The sulfoxide group in phenoxathiin-10-oxide and its derivatives is reduced by mild reducing agents. This conversion was first reported by Hilditch and Smiles[63] who employed zinc and acetic acid to reduce 2,8-dimethyl- and 2,8-dichlorophenoxathiin-10-oxide to the corresponding phenoxathiin derivatives. Drew[53] later reported the reduction of phenoxathiin-10-oxide by zinc and acetic acid and by a mixture of hydrochloric and acetic acids. Partial

chlorination was said to have occurred in this latter reaction. Krishna[67] and Irie[50] carried out the reduction of several derivatives of phenoxathiin-10-oxide with hydrobromic acid in acetic acid, but reported no bromination products. Chlorination accompanied reduction when Irie[50] added concentrated hydrochloric acid to a solution of phenoxathiin-10-oxide in concentrated sulfuric acid. The chlorophenoxathiin was the same one obtained by direct chlorination in benzene. Drew[53] showed that the reaction of phenoxathiin-10-oxide with concentrated sulfuric acid produced phenoxathiin as one of the products.

Reduction of the sulfoxide group accompanies metalation when dibenzothiophene-5-oxide[72], thianthrene-5-oxide[73] and phenoxathiin-10-oxide[59] are treated with n-butyllithium at low temperatures. It has been postulated that metalation precedes reduction or that both processes occur almost simultaneously.[59,72]

Irie[50] reported that phenoxathiin-10-dioxide was very resistant to reducing agents and that unsuccessful attempts were made to reduce it to phenoxathiin or to the 10-oxide.

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[72]H. Gilman and D. L. Esmay, J. Am. Chem. Soc., 74, 266 (1952).

[73]H. Gilman and D. R. Swayampati, ibid., 77, 3387 (1955).

The 10-dioxide was not affected when heated with sulfur, and ring scission occurred when it was heated with hydrazine hydrate.

There may be several reasons why the above article[50] contains the only mention of the reduction of the 10-dioxide. It may be that workers have attempted the reduction and observed either no reaction or cleavage of the heterocycle. Too, the reduction would be of no great preparative value unless a useful derivative of the 10-dioxide were much more available than the corresponding reduction product. The related heterocycle, dibenzothiophene-5-dioxide, was reduced to dibenzothiophene in 74% yield by lithium aluminum hydride.[74] However, the results of reductions of other heterocyclic sulfones[74] suggested that the reduction of dibenzothiophene-5-dioxide may not be a model reaction for phenoxathiin-10-dioxide. Thiacyclohexane-1-dioxide and 2,3-dihydro-1,4-benzothiapyran-1-dioxide were not reduced when treated with lithium aluminum hydride under the conditions used for reduction of dibenzothiophene-5-dioxide. Bordwell and McKellin[74] stated that the reduction of six-membered ring sulfones appeared to be roughly one hundred times slower than that of five-membered ring sulfones.

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[74] F. G. Bordwell and W. H. McKellin, ibid., 73, 2251 (1951).

Substitution Reactions

Halogenation reactions

The first successful halogenation of phenoxathiin was reported by Suter, McKenzie and Maxwell[35], who prepared a mono- and a dibromophenoxathiin by direct bromination. The reaction was carried out by adding bromine to a stirred solution of phenoxathiin in carbon tetrachloride. When one molar equivalent of bromine was employed a monobromophenoxathiin, m.p. 59-60°, was obtained in 83% yield. A dibromophenoxathiin, m.p. 92-93°, was prepared in 75% yield when two molar equivalents of bromine were used. Both bromination products were crystallized from methanol. No experimental details such as the use of a bromination catalyst, time and temperature of reaction or any precautions to exclude moisture were provided. The dibromophenoxathiin was oxidized to the 10-dioxide, m.p. 185-186°, which showed no depression in melting point when mixed with a sample of 2,8-dibromophenoxathiin-10-dioxide, m.p. 183-186°, prepared by the ring closure* of 2-(4-bromophenoxy)-5-bromobenzenesulfonyl chloride.

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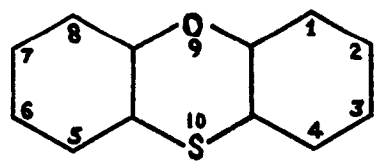
*See the equations and description of the synthesis in the latter part of the section on Ring closure reactions.

An alternative proof of the structure of the dibromination product would have involved a mixed melting point determination with a sample of 2,8-dibromophenoxathiin, m.p. 92°, which Stevenson and Smiles[58] had prepared by ring closure only 5 years earlier. However, the reader is given the impression that Suter, McKenzie and Maxwell[35] became aware of the other preparation only after proving the structure of 2,8-dibromophenoxathiin by way of the 10-dioxide. The following is the only reference to the work of the other authors.[35]

> It has just recently come to our attention that this substance has also been prepared by Stevenson and Smiles, J. Chem. Soc., 718 (1931), who obtained it from 2,5,5'-tribromo-2'-hydroxydiphenyl sulfide. In their system of nomenclature it is designated as 2,8-dibromodibenzothioxine.

Suter and coworkers[35] used the name 3,6-dibromophenoxthin. The compound of Stevenson and Smiles[58] was listed as shown below in the Chemical Abstracts Subject Index for the year 1931. It is surprising that Suter and coworkers[35] did not

Phenothioxin (dibenzothioxine, phenoxthine)



3,6-dibromo-3338[8]

call attention to the fact that the dibromination product melted at the same temperature as the 2,8-dibromophenoxathiin of Stevenson and Smiles.[58]

The position of the bromine in the bromophenoxathiin, m.p. 59-60°, was designated as 2-, *para* to the oxygen, due to the fact that the dibromination product was 2,8-dibromophenoxathiin. The conversion of 2-bromophenoxathiin to 2,8-dibromophenoxathiin by bromination with one equivalent of bromine was not carried out.

The bromination of phenoxathiin was repeated by Gilman, Van Ess, Willis and Stuckwisch[54], who obtained an 88% yield of 2-bromophenoxathiin, m.p. 58-59°. The experimental procedure employed was that of Suter and coworkers[35] and no additional details were provided.

The product isolated from the first reported chlorination of phenoxathiin was a monochlorophenoxathiin, m.p. 81-82°, which was subsequently oxidized to the 10-dioxide, m.p. 178-179°.[34] Neither experimental details nor analytical results were reported. The product was presumed to be 1-chlorophenoxathiin since it was different from each of the three compounds designated as 2-, 3- and 4-chlorophenoxathiin. 2-Chloro-, m.p. 88-89°, and 4-chlorophenoxathiin, a liquid, were prepared from 4-chloro- and 2-chlorodiphenyl ether, respectively.[34] The material, m.p. 59-60°, which was

obtained from the Ferrario reaction on 3-chlorodiphenyl ether, was assumed to be 3-chlorophenoxathiin.

The melting point of the 2-isomer has since been confirmed by Irie[50], who prepared 2-chlorophenoxathiin from 3-aminophenoxathiin.[50] This worker also prepared 1-chlorophenoxathiin, m.p. 78-80°, by decarboxylation of 1-chloro-3-phenoxathiincarboxylic acid. Thus far it would appear that the chlorophenoxathiin, m.p. 81-82°, of Suter and Green was the 1-derivative. However, Irie[50] chlorinated phenoxathiin in cold, dry benzene and obtained a chlorophenoxathiin, m.p. 78-79°, and a dichlorophenoxathiin, m.p. 166-167°, which were subsequently oxidized to the 10-dioxides, m.p. 172-174° and 208-210°, respectively. The chlorophenoxathiin obtained by chlorination was shown to be different from 1- and 2-chlorophenoxathiin by mixed melting point determinations. Since the chlorination product is not the 1-, 2-, or 4-chloro-phenoxathiin, (the last named is a liquid) it is logically concluded by this writer to be 3-chlorophenoxathiin. Though Suter and Green[34] had assumed that the compound which melted at 59-60° was 3-chlorophenoxathiin, the available evidence favors the compound melting at 78-79° (Irie[50]) or 81-82° (Suter and Green[34]). Irie[50] prepared 2,8-dichlorophenoxathiin, m.p. 137°, according to the method of Hilditch and Smiles[63] in order to prove that the

dichlorophenoxathiin, m.p. 166-167°, was not the 2,8-isomer. Irie did not report a mixed melting point determination involving 2,8-dichlorophenoxathiin-10-oxide, m.p. 168°[63], and the dichlorophenoxathiin. However, the analytical data found for the dichlorination product agrees well with the theoretical values for the unoxidized dichloro compound.

There has been no report of an attempted iodination of phenoxathiin. However, three iodophenoxathiins have been synthesized by Nobis and Burske.[75] 4-Iodophenoxathiin, m.p. 42.5-43°, was prepared by adding iodine to 4-phenoxathiinyllithium, whereas 2-iodophenoxathiin, m.p. 92-94°, and 3-iodophenoxathiin, m.p. 70-72°, were obtained in yields of 10% and 15%, respectively, from the reaction of potassium iodide with the corresponding diazotized aminophenoxathiin. The workers reported that the diazotization reactions were attended by considerable difficulty.

No direct halogenation of either phenoxathiin-10-oxide or 10-dioxide has been reported. The reaction of phenoxathiin-10-oxide in sulfuric acid with hydrochloric acid[50] probably involved chlorination of the reduction product, phenoxathiin. Halogenation of the 10-oxide or 10-dioxide

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[75] J. F. Nobis and N. W. Burske, J. Am. Chem. Soc., 76, 3034 (1954).

would be expected to proceed quite slowly due to the deactivating influences of the sulfoxide and sulfone groups.

Friedel-Crafts reactions

Of the substitution reactions of phenoxathiin, the Friedel-Crafts acetylation has been utilized the most extensively. The reaction was first described by Suter, McKenzie and Maxwell[35], who prepared 2-acetylphenoxathiin, m.p. 111-112°, in 58% yield by the reaction of equimolar amounts of phenoxathiin, acetyl chloride and aluminum chloride. When Flowers and Flowers[22] repeated the reaction there was obtained a 31% yield of product having the same melting point as that reported by Suter and coworkers. Nobis, Blardinelli and Blaney[52] made numerous unsuccessful attempts to duplicate the above yields. These workers reported a 26% yield of 2-acetylphenoxathiin melting at 117.5-118°. This difference in melting points suggests that the lower melting material was less pure. The oxime which Suter and coworkers[35] prepared from the acetyl compound, m.p. 111-112°, melted at 142-144°, whereas the 2-acetylphenoxathiin oxime of Nobis and coworkers melted at 158-159.5°. This great difference in melting points is significant. If the lower melting compound was pure, then it was probably the

oxime of the other configuration (*cis*- or *trans*-) or an oxime of a different ketone.

2-Phenoxathiincarboxylic acid was the key compound in the proof of the structure of 2-acetylphenoxathiin, m.p. 111-112°. As mentioned in the section on oxidation reactions, Suter, McKenzie and Maxwell[35] carried out the haloform oxidation of the acetyl compound and obtained an acid which melted at 259-260°. These workers then prepared the same acid from 2-bromophenoxathiin, m.p. 59-60°, by way of carbonation of the Grignard reagent.[35] The only successful preparation of the Grignard reagent was accomplished by adding an ether solution of 0.078 mole of the bromo compound to a mixture of ether, 0.10 gram atom of magnesium and approximately 0.04 mole of ethyl iodide. One of the products of the reaction consisted of "about 8% of the theoretical amount of material soluble in alkali".[35] There was no indication as to whether this material was pure 2-phenoxathiincarboxylic acid or whether a purification by crystallization was necessary in order to obtain the acid which melted at 260-262°. This acid was shown by a mixed melting point determination to be identical with the acid obtained by the haloform oxidation of the acetylphenoxathiin. No quantitative elemental analysis was reported for the acid.

The proof of the structure of the 2-acetylphenoxathiin of Nobis and coworkers[52] was based upon the conversion of 2-acetylphenoxathiin oxime to 2-aminophenoxathiin, m.p. 93-95°, by the Beckmann rearrangement. Irie[50] prepared 2-aminophenoxathiin, m.p. 98°, by reduction of 2-nitrophenoxathiin.

The preparation of 2,8-diacetylphenoxathiin by the Friedel-Crafts reaction was first carried out by Tomita[65], who reported the melting point of the product as 175°. Nobis, Blardinelli and Blaney[52] repeated the reaction and observed the melting point of 184-186°. The question arises as to whether both products are 2,8-diacetylphenoxathiin. Oxidation of the diacetyl compound, m.p. 175°, was carried out under the conditions which Suter, McKenzie and Maxwell[35] had employed for the oxidation of 2-acetylphenoxathiin. The product was 2,8-phenoxathiindicarboxylic acid 10-dioxide, m.p. over 300°.[65] The same acid was obtained by the alkaline permanganate oxidation of 2,8-dimethylphenoxathiin, a compound with a well-proven structure. The acids were not compared, but were converted to the dimethyl esters, m.p. 204-208°, which were shown to be identical by a mixed melting point determination.[65] The diacetylphenoxathiin, m.p. 184-186°, was converted to the dioxime and then by way of the Beckmann rearrangement, to the diaminophenoxathiin, m.p.

171-173°.* Nobis and coworkers[52] cited as evidence for the structure of 2,8-diaminophenoxathiin the fact that Todd observed a melting point of 166-168° for 2,8-diaminophenoxathiin which was prepared by the Hofmann reaction from 2,8-dicarboxamidophenoxathiin.[76] This work of Todd has not been published. It has not been proven conclusively that phenoxathiin derivatives are not oxidized to the sulfoxides under the conditions of this reaction. The possibility of oxidation as a side reaction in the Hofmann reaction has been discussed. Acetylation of the diaminophenoxathiin, m.p. 171-173°, with acetic anhydride produced the diacetamidophenoxathiin which was subsequently oxidized to the 10-dioxide, m.p. 349-353°. The other route to the diacetamidophenoxathiin-10-dioxide was by way of acetylation of 2,8-diaminophenoxathiin-10-dioxide, m.p. 244-247.5°. (Irie[50] reported 239-240°.) The diacetamido-10-dioxide melted at 338-341°. A mixture of this material and the compound, m.p. 349-353°, melted at 345-350°. The absence of depression in melting point was assumed to be evidence that each product was 2,8-diacetamidophenoxathiin-10-dioxide.

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[76] D. Todd, Private communication to J. F. Nobis, Research Division, National Distillers Chemical Co., Cincinnati, Ohio. [Cited in J. F. Nobis, A. J. Blardinelli and D. J. Blaney, J. Am. Chem. Soc., 75, 3384 (1953).]

*Irie[50] reported 2,8-diaminophenoxathiin to melt at 118°.

Tomita[65] carried out the reaction of phenoxathiin with chloroacetyl chloride in the presence of aluminum chloride and obtained a 98% yield of 2,8-bis-(β-chloroacetyl)phenoxathiin. The product was oxidized to 2,8-phenoxathiindicarboxylic acid 10-dioxide which was subsequently converted to the dimethyl ester. This ester was identical with that obtained from 2,8-diacetylphenoxathiin by the same two reactions. Both the 2,8-diacetyl- and the 2,8-bis-(β-chloroacetyl)phenoxathiin yielded 2,8-diethylphenoxathiin upon reduction.[65]

The reaction of molar equivalent amounts of phenoxathiin, benzoyl chloride and aluminum chloride produced a mixture from which were obtained a 33% yield of benzoylphenoxathiin, m.p. 96-97°, and an 11% yield of dibenzoylphenoxathiin, m.p. 197°.[35] Suter, McKenzie, and Maxwell[35] assumed that the benzoylation reaction was strictly analogous to the acetylation reaction which had yielded 2-acetylphenoxathiin. On this basis the two products, m.p. 96-97° and 197°, were designated as 2-benzoyl- and 2,8-dibenzoylphenoxathiin, respectively.

Two monoacylation products, γ-oxo-2- and γ-oxo-3-phenoxathiinbutyric acid were obtained from the reaction of phenoxathiin with succinic anhydride and aluminum

chloride.[77] The two acids were separated by crystallization from acetic acid, the less soluble 2-acid crystallizing first. No proof of the structures of the two isomers was described.

It has been shown that upon bromination and upon acetylation in the presence of aluminum chloride substitution occurred in the 2-position, whereas a product which is probably 3-chlorophenoxathiin was obtained upon chlorination of phenoxathiin. The isolation of both the 2- and the 3-acids from the acylation with succinic anhydride precipitates the question as to whether bromination, chlorination and acetylation actually yield only a 2- or a 3- derivative and not both. In the case of bromination it was unlikely that a second bromophenoxathiin could have formed in any appreciable amount considering the reported yields of 83%[35] and 88%[54] for 2-bromophenoxathiin. An isomer of 2-bromophenoxathiin would probably have very similar solubility properties and thus make it quite difficult to obtain one pure monobromophenoxathiin in such high yields. Since neither Suter and Green[34] nor Irie[50] reported the yield of the chlorination product, little is known about the possibility of there having been two monochlorophenoxathiins formed. It is significant that Irie obtained both a mono- and a dichloro-

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[77] R. R. Burtner and J. M. Brown, U. S. Patent 2,480,220 (1949) [C. A., 44, 1143 (1950)].

phenoxathiin from the same reaction, whereas Suter, McKenzie and Maxwell[35] reported only a monobromo- and a monoacetylphenoxathiin from the reactions in which one equivalent of the substitution reagent was employed. Also, the report that both the 2- and the 3-isomers were isolated from one Friedel-Crafts reaction[77] should cause the worker to view with caution the designation of the dibenzoylphenoxathiin as the 2,8-derivative[35] until the structure of this compound has been proved.

Nitration

The primary amino group probably imparts greater synthetic potential to an aromatic molecule than any other functional group. This group can be acylated and used for activation of the molecule towards subsequent substitution reactions, and then can be readily removed. It can be converted to the diazonium salt which can be replaced easily and unambiguously by other functional groups. Generally the most convenient method of introduction of the amino group into a molecule is by way of reduction of the nitro group. Therefore, the nitration reaction is a common but very valuable tool in the synthesis of derivatives of aromatic compounds. This reaction is particularly convenient in the

dibenzofuran series since the nitro group enters the 3-position, whereas other substitution reactions (except metalation) take place at the 2-position.* Dibenzothiophene is nitrated in the 2-position while dibenzothiophene-5-oxide and 5-dioxide are nitrated in the 3-position, making available convenient routes to various derivatives in both positions.

No nitrophenoxathiin has been prepared by direct nitration of the parent heterocycle. Oxidation was always the principal reaction which occurred when phenoxathiin and its unoxidized derivatives were treated with nitrating agents. The use of nitric acid for the preparation of phenoxathiin-10-oxide and 10-dioxide and for the oxidation of derivatives of phenoxathiin to the 10-oxide and 10-dioxide was discussed earlier in this thesis.

All nitrations of phenoxathiin, phenoxathiin-10-oxide and phenoxathiin-10-dioxide yield nitro derivatives of phenoxathiin-10-dioxide. These reactions were first described by Irie[50], who obtained both 2-nitrophenoxathiin-10-dioxide, m.p. 196.5°, and 2,8-dinitrophenoxathiin-10-dioxide, m.p. 276-278°, by treatment of phenoxathiin with fuming nitric

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*For a review of the nitration reactions of dibenzofuran, dibenzothiophene, diphenylene dioxide, phenoxathiin and thianthrene see D. L. Esmay, Unpublished Ph.D. Thesis, Iowa State College Library, 1951, p. 29.

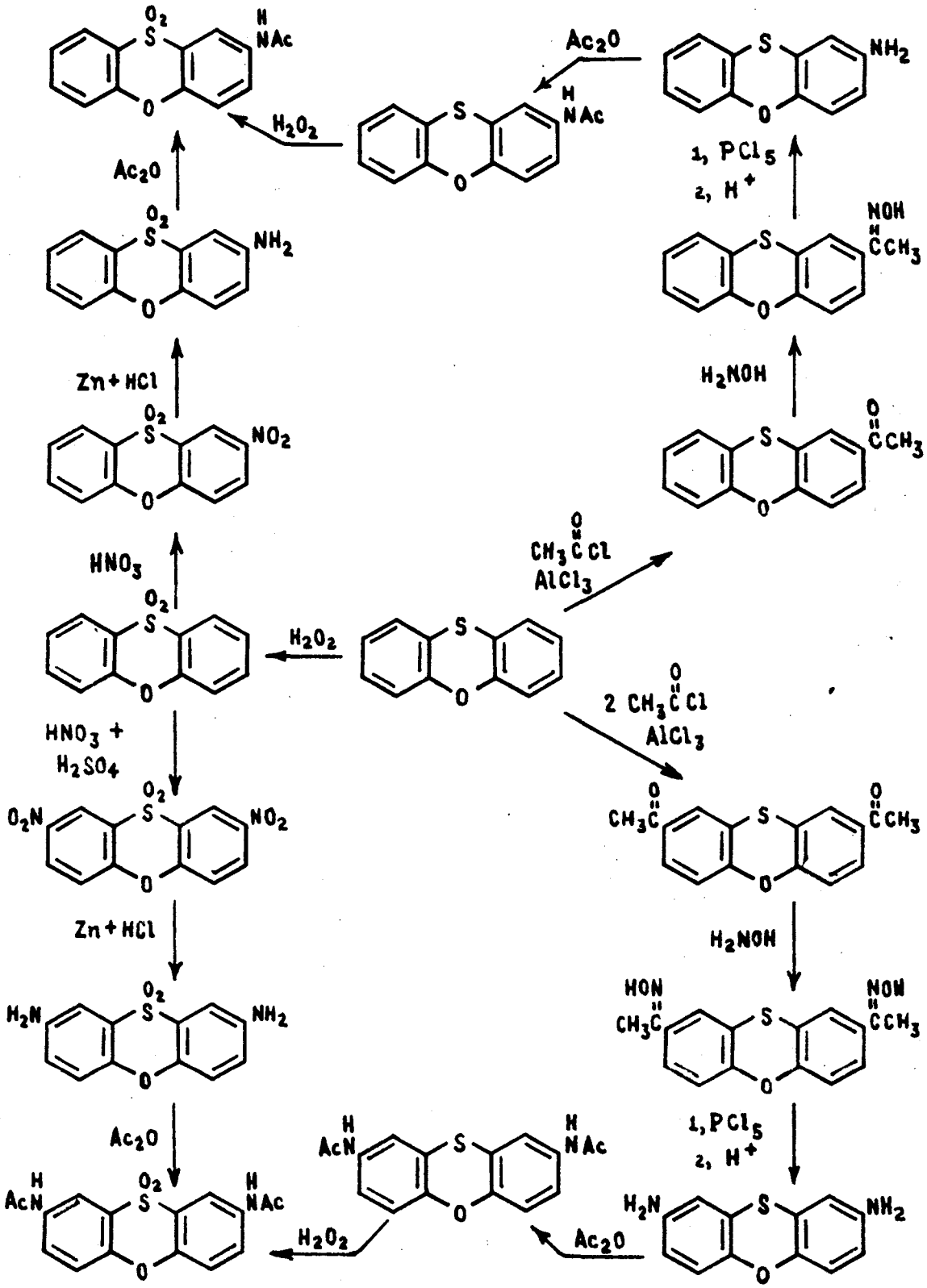
acid (sp. gr. 1.45) at steam bath temperature. Nitration of phenoxathiin-10-dioxide under similar conditions yielded the same two products. In order to prove the structures of the nitration products Irie[50] prepared the two compounds by oxidizing 2-nitro- and 2,8-dinitrophenoxathiin to the 10-dioxides. The synthesis of each of the unoxidized compounds was described in the section dealing with ring closure reactions.

Nobis, Blardinelli and Blaney[52] obtained a 30% yield of 2-nitrophenoxathiin-10-dioxide, m.p. 187-188°, from the reaction of phenoxathiin-10-oxide in glacial acetic acid with a mixture of fuming nitric acid and concentrated sulfuric acid. Nitration did not take place in the absence of concentrated sulfuric acid. 2-Nitrophenoxathiin-10-dioxide, m.p. 192-194°, was prepared in a yield of 43% when fuming nitric acid was heated with phenoxathiin-10-dioxide in glacial acetic acid.[52] Nobis and coworkers[52] gave no explanation for the difference in melting points, 187-188° and 192-194°, for 2-nitrophenoxathiin-10-dioxide prepared from phenoxathiin-10-oxide and phenoxathiin-10-dioxide, respectively. A mixed melting point determination was not reported. It is interesting that the lower-melting material melted over the narrower range.

The use of glacial acetic acid as a solvent appeared to inhibit nitration of phenoxathiin. Nobis, Blardinelli and Blaney[52] isolated only phenoxathiin-10-oxide from the reaction of phenoxathiin in glacial acetic acid with fuming nitric acid. However, when the nitration mixture consisting of fuming nitric acid and concentrated sulfuric acid was added to phenoxathiin in glacial acetic acid, 2,8-dinitrophenoxathiin-10-dioxide, m.p. 283-286°, was produced in 30% yield. A 41% yield of 2,8-dinitrophenoxathiin-10-dioxide, m.p. 277-280°, was obtained when fuming nitric acid was added to a mixture of phenoxathiin-10-dioxide and concentrated sulfuric acid.

The reactions employed by Nobis, Blardinelli and Blaney[52] in proving the structures of 2-nitro- and 2,8-dinitrophenoxathiin-10-dioxide are illustrated in the equations on the following page. Most of the reactions were discussed in connection with the proof of the structure of 2,8-diacetylphenoxathiin. Though Nobis and coworkers[52] had assumed that this compound, m.p. 184-186°, was the 2,8-derivative, the proof of its structure seemed as necessary as those of the nitration products since Tomita[65] had reported the melting point as 175°.

Due to the fact that the melting point of Nobis and coworkers' dinitration product agreed with that reported by


Ac2O
H2O2
1, PCl5
2, H+
H2NOH
Zn + HCl
Ac2O
HNO3
CH3COCl
AlCl3
H2O2
2 CH3COCl
AlCl3
HNO3 +
H2SO4
Zn + HCl
H2NOH
Ac2O
1, PCl5
2, H+
H2O2
Ac2O

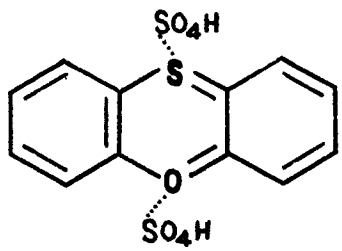
Irie[50], who had obtained the compound both by dinitration and by ring closure followed by oxidation, 2,8-dinitrophenoxathiin-10-dioxide was used as the key 2,8-derivative in the structure proof of 2,8-diacetylphenoxathiin described earlier.

Nobis and Burske[75] carried out a low temperature nitration of 2-acetamidophenoxathiin in expectation of obtaining 2-acetamido-3-nitrophenoxathiin. The only product isolated from the mixture was a small amount of material which melted at 174-176.5°. Analytical results for the compound indicated that it may have been 2-acetamido-3,8-dinitrophenoxathiin. Various conditions were employed in unsuccessful attempts to nitrate 2-acetamidophenoxathiin-10-dioxide.[75] There resulted only mixtures of products from which no pure compound was isolated.

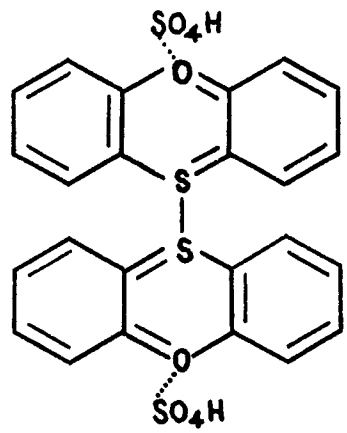
Sulfonation reactions

The action of sulfuric acid on phenoxathiin and phenoxathiin-10-oxide was a subject of considerable investigation by Drew[53] and by Hilditch and Smiles.[63] The violet color of the cold, concentrated sulfuric acid solutions was the center of the interest. Hilditch and Smiles[63] attributed

the color to the presence of a thionium salt such as that shown by formula XIII. Drew[53] provided experimental data



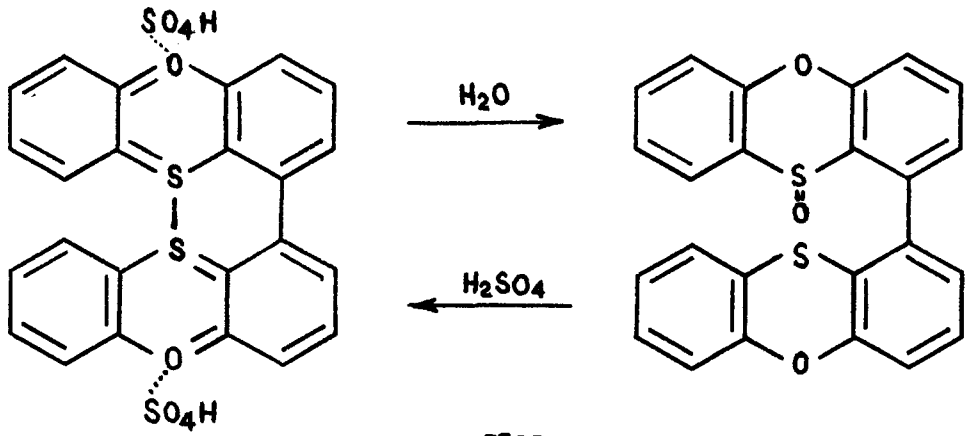
XIII



XIV

which he believed to support his theory that thionylium compounds of the type represented by XIV were responsible for the color. This worker dissolved phenoxathiin in cold, concentrated sulfuric acid, removed the sulfur dioxide that was evolved, and then hydrolyzed the mixture. The two products, phenoxathiin and phenoxathiin-10-oxide, were isolated quantitatively in molar equivalent amounts. When phenoxathiin-10-oxide was dissolved in sulfuric acid the violet solution did not evolve sulfur dioxide, but yielded the same two products and a yellow, amorphous solid upon

hydrolysis. Drew believed that sulfur dioxide would have been evolved had phenoxathiin been present as such in the sulfuric acid solution. The yellow, amorphous product, m.p. 215-220°, which was not a sulfonic acid, gave an intensely blue color in sulfuric acid. According to Drew, the yellow solid was "probably a nuclear-oxidation product of a thionylium compound, e.g., (XV)".[53]

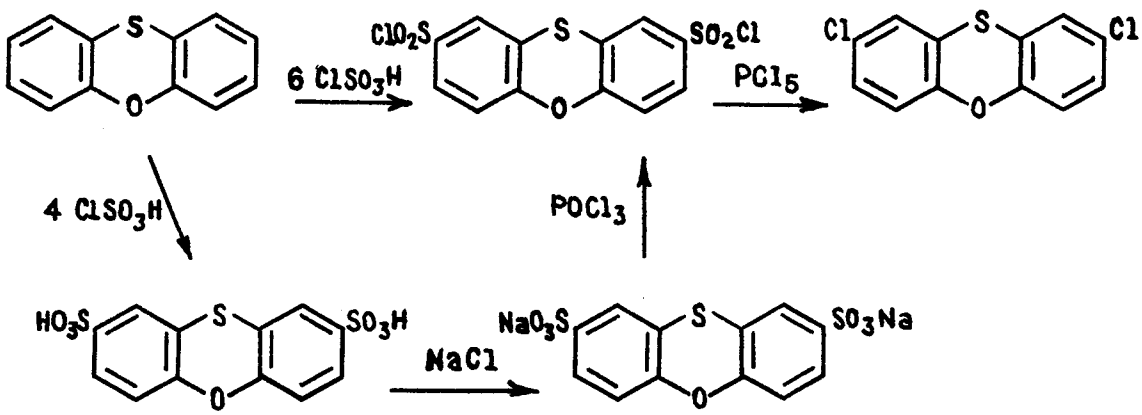


XV

Suter, McKenzie and Maxwell[35] carried out the first reaction which yielded a phenoxathiinsulfonic acid. The product from the reaction of molar equivalents of phenoxathiin and chlorosulfonic acid was not isolated, but was converted to the sodium salt. When the sodium salt was refluxed with excess phosphorus oxychloride the corresponding

phenoxathiinsulfonyl chloride, m.p. 127-128°, was formed. The product was designated as 2-phenoxathiinsulfonyl chloride, but the structure was not proved.

A disulfonic acid, also isolated as the salt, was prepared from phenoxathiin and 4 molar equivalents of chlorosulfonic acid. The disulfonyl chloride, m.p. 142-143°, was prepared by treatment of the disodium salt with phosphorus oxychloride and by the reaction of phenoxathiin with 6 molar equivalents of chlorosulfonic acid. Suter, McKenzie and Maxwell[35] designated the product as 2,8-phenoxathiindisulfonyl chloride and attempted to prove the structure by conversion to 2,8-dichlorophenoxathiin, m.p. 135[63], 137°.[50] Thus, from the reaction of the disulfonyl chloride and phosphorus pentachloride there was obtained a small amount of product which melted at 134-135°. However, neither a mixed melting point nor analytical datum was reported for the compound.



Tomita and Yamada[78] carried out the sulfonation of phenoxathiin by heating the heterocycle with concentrated sulfuric acid. After the reaction mixture was poured into water, this mixture was added to a saturated sodium chloride solution and the disodium salt was isolated. The 2,8-phenoxathiindisulfonyl chloride, obtained by heating the disodium salt with phosphorus trichloride, melted at 149°, 6° higher than the melting point reported by Suter, McKenzie and Maxwell.[35]

As a derivative of 2-phenoxathiinsulfonyl chloride, Suter and coworkers[35] prepared 2-phenoxathiinsulfonamide, m.p. 177-178°. 2,8-Phenoxathiindisulfonamide, m.p. 192°, was prepared by Irie[50], who reported the same melting point for 2,8-phenoxathiindisulfonyl chloride as did the original workers. The disulfonyl chloride of Tomita and Tamada[78] was reduced to the dithiol, an unstable compound from which was prepared 2,8-dimercaptophenoxathiin dimethyl ether, m.p. 68-69°, and 2,8-dimercaptophenoxathiin diacetate, m.p. 108-109°.

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[78] M. Tomita and H. Yamada, J. Pharm. Soc. Japan, 71, 451 (1951) [C. A., 46, 992 (1952)].

Metalation reactions

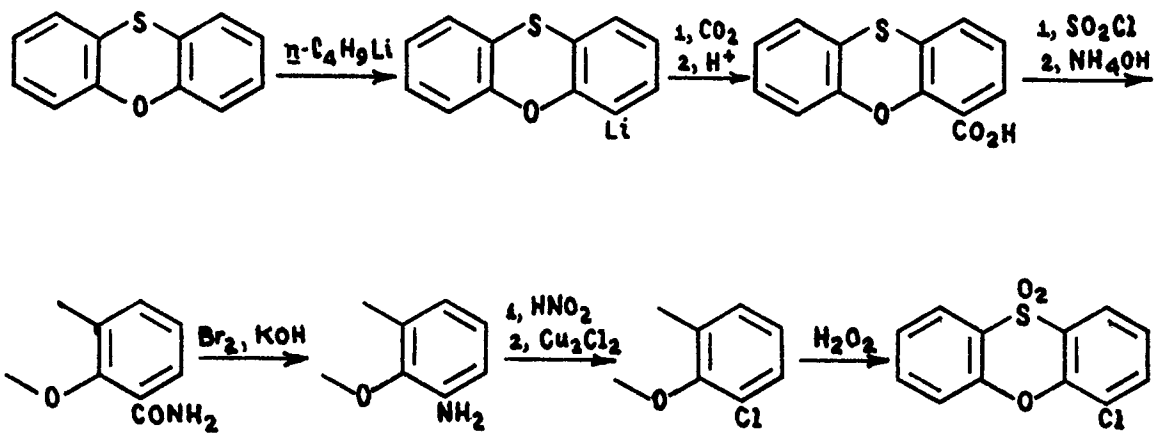
Metalation* of phenoxathiin was first reported by Gilman, Van Ess, Willis and Stuckwisch.[54] The reaction was carried out by refluxing for 24 hours an ether solution containing equimolar amounts of phenoxathiin and n-butyllithium. Subsequent to carbonation of the metalation product there was obtained a 61% yield of acid which melted between 157 and 160°. The pure 4-phenoxathiincarboxylic acid, m.p. 168-169°, was obtained after three recrystallizations from glacial acetic acid.

Oxidation of 4-phenoxathiincarboxylic acid with hydrogen peroxide in glacial acetic acid yielded a product, m.p. 183-184°, designated as 4-phenoxathiincarboxylic acid 10-dioxide. The following analytical datum was reported[54] for the compound. Anal. Calcd. for $C_{13}H_8O_5S$: neut. equiv., 256. Found: neut. equiv., 261. The theoretical neutralization equivalent is 276, making the experimental value 15 units low. The value of 261 agrees well with the theoretical value of 260 for 4-phenoxathiincarboxylic acid 10-oxide. Esterification of the acid which melted at 183-184° yielded methyl

*A comprehensive description of the metalation reaction with organolithium compounds appears in the chapter by H. Gilman and J. W. Morton, Jr., in R. Adams, "Organic Reactions", John Wiley and Sons, Inc., New York, N. Y., 1955, Vol. 8, p. 258.

4-phenoxathiincarboxylate 10-dioxide, m.p. 124°.[54] Shirley and Lehto[59] reported the melting point of 123-124° for the methyl ester prepared from 4-phenoxathiincarboxylic acid 10-dioxide, m.p. 189-190°.

Metalation was proved to have occurred ortho to oxygen in phenoxathiin when the acid was converted to the known 4-chlorophenoxathiin-10-dioxide by the sequence of reactions illustrated below.[54] The product was shown by a mixed



melting point determination to be identical with an authentic specimen of 4-chlorophenoxathiin-10-dioxide[34] prepared by oxidation of the product from the Ferrario reaction of 2-chlorodiphenyl ether.

Several 4-substituted phenoxathiin derivatives have been prepared by way of 4-phenoxathiinyllithium. 4-Amino-phenoxathiin was obtained in 59% yield from the reaction

of O-methylhydroxylamine with this lithium compound.[54] The reaction of 4-phenoxathiinyllithium with oxygen in the presence of n-butylmagnesium bromide afforded a 47% crude and a 16% pure yield of 4-hydroxyphenoxathiin.[79] This is the only hydroxyphenoxathiin which has been described in detail in the literature. In the abstract of a patent[80] there is a brief mention of the preparation of hydroxyphenoxathiins by heating the halogen derivatives under pressure with aqueous caustic alkalies or alkaline earths. When iodine was added to the metalated phenoxathiin there was obtained a 21% yield of 4-iodophenoxathiin.[75] Produced in the same process was a considerable amount of material thought to have been 4,6-diiodophenoxathiin which resulted from the reaction of iodine with dimetalated phenoxathiin. The compound was not isolated, however.

The reaction of phenoxathiin with phenylcalcium iodide, followed by carbonation, yielded a very small amount of a yellow acid which melted at 260-262°.[54] Neither a neutralization equivalent nor a quantitative elemental analysis was reported for the compound. A mixed melting point with a

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[79] H. Gilman and D. L. Esmay, J. Am. Chem. Soc., 76, 5787 (1954).

[80] B. Pützer and F. Muth, German Patent 606,350 (1934) [C. A., 29, 1434 (1935)]; British Patent 427,816 [C. A., 29, 6608 (1935)].

sample of 2-phenoxathiincarboxylic acid[35], m.p. 260-262°, was depressed, showing that metalation had not occurred in the 2-position. Since the product was not the known 2-, 3-, or 4-acid, the orientation in metalation was considered as anomalous and was suggestive of another interesting metalation by phenylcalcium iodide. Metalation in the position meta to the sulfur had been observed in the reaction of phenylcalcium iodide with dibenzothiophene.[81] Carbonation of the metalation product had yielded 3-dibenzothiophenecarboxylic acid in contrast to the 4-acid which was the product when metalation had been effected by organolithium compounds.

Avakian[82] carried out the metalation of 0.08 mole of phenoxathiin with 0.11 mole of n-butyllithium and obtained two acids, one of which, m.p. 258-260°, did not depress the melting point of the acid from the phenylcalcium iodide metalation.[54] It is stated in the doctoral dissertation of F. J. Webb[83] that the acid, m.p. 258-260°, was a dibasic acid. However, the experimental procedure provided by Avakian[82] contained no data which indicated that the compound was a

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[81] H. Gilman, A. L. Jacoby and H. A. Pacevitz, J. Org. Chem., 3, 120 (1938).

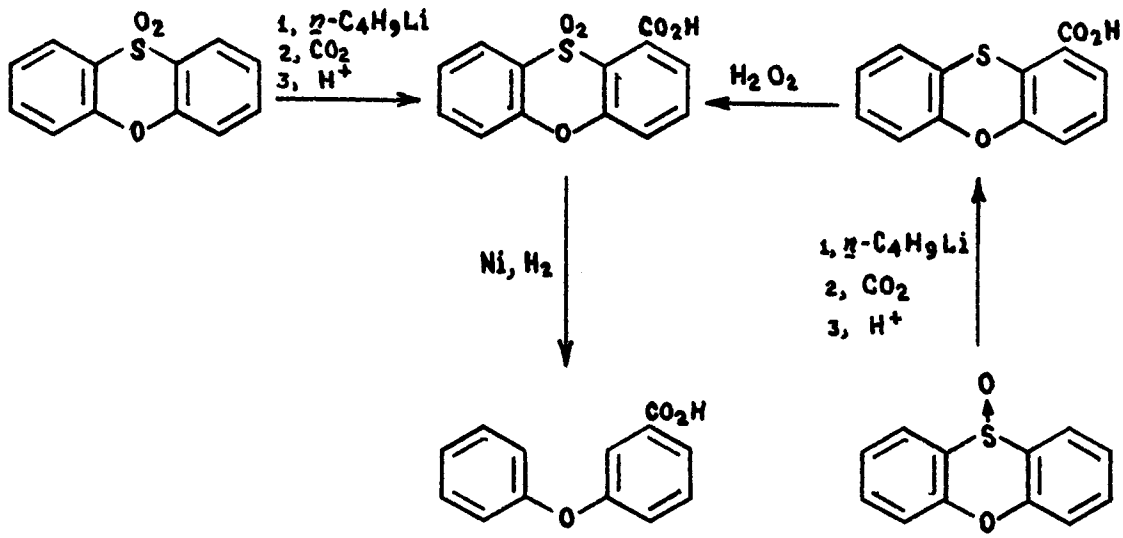
[82] S. Avakian, Private communication to Prof. H. Gilman, Iowa State College, Aug. 10, 1953.

[83] F. J. Webb, Unpublished Ph.D. Thesis, Iowa State College Library, 1941, p. 36.

dibasic acid. The other acid obtained from the reaction was "a dibasic acid which did not melt at 285°".[82] Analytical data in the form of a quantitative sulfur analysis of this acid and its dimethyl ester, m.p. 149-150°, were reported.[82]

The reaction of phenoxathiin-10-dioxide with one molar equivalent of n-butyllithium produced, subsequent to carbonation, a 46% yield of 1-phenoxathiincarboxylic acid 10-dioxide, m.p. 228-229°.[59] Metalation of phenoxathiin-10-oxide[59] occurred under low temperature conditions similar to those employed by Gilman and Esmay[72] for metalation of dibenzothiophene-5-oxide. Three molar equivalents of n-butyllithium were stirred with suspension of the 10-oxide for 5 hours at -20° and then the mixture was allowed to warm to room temperature. Following carbonation there was isolated a 22% yield of 1-phenoxathiincarboxylic acid, m.p. 221-222°.[59] The analytical data indicated that the acid was a phenoxathiincarboxylic acid rather than an acid 10-oxide. It was confirmed that reduction had occurred when the acid was unaffected upon treatment with zinc dust in glacial acetic acid. That metalation occurred in the same position in phenoxathiin-10-oxide and 10-dioxide was proved when oxidation of 1-phenoxathiincarboxylic acid with hydrogen peroxide in glacial acetic acid yielded the same acid as that obtained by metalation of phenoxathiin-10-dioxide. The cleavage of

1-phenoxathiincarboxylic acid 10-dioxide by Raney nickel yielded 3-carboxydiphenyl ether, a product which would arise upon desulfurization of either 1- or 3-phenoxathiincarboxylic acid 10-dioxide. That the carboxyl group was not in the 3-position of phenoxathiin was shown by a mixed melting point determination involving 3-phenoxathiincarboxylic acid, m.p. 223-224°, and the acid obtained by metalation of phenoxathiin-10-oxide.



Reduction had accompanied metalation in the reaction of dibenzothiophene-5-oxide with n-butyllithium.[72] Since dibenzothiophene was not metalated at -10°[72] under the low temperature conditions employed for metalation of the 5-oxide

Gilman and Esmay[72] postulated that, in the case of the 5-oxide, metalation either preceded or occurred simultaneously with reduction. The same sequence of reactions was believed to have occurred when phenoxathiin-10-oxide was treated with n-butyllithium.[59] Had reduction occurred first, any metalation would have taken place in the 4-position, since phenoxathiin had been metalated in this position in earlier experiments.[54]

One reaction between a substituted phenoxathiin and n-butyllithium has been reported. Gilman, Van Ess, Willis and Stuckwisch[54] carried out a halogen-metal interconversion* reaction by allowing a 1:1 ether-benzene solution containing 2-bromophenoxathiin and excess n-butyllithium to reflux for 15 minutes. Subsequent to carbonation there was obtained a 64% yield of "pure" 2-phenoxathiincarboxylic acid melting between 260 and 265°. The product was converted to the ethyl ester which gave no depression in a mixed melting point determination with an authentic specimen of ethyl 2-phenoxathiincarboxylate. This melting point was not indicated. No other report of the preparation of this ethyl ester has been published.

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*For a recent review of the halogen-metal interconversion reaction with organolithium compounds, see the chapter by R. G. Jones and H. Gilman, in R. Adams, "Organic Reactions", John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. 6, p. 339.

Cleavage reactions

Three cleavage reactions of phenoxathiin and its derivatives have been described in the literature. The first of these was the cleavage which occurred during the previously mentioned attempted reduction of phenoxathiin-10-dioxide by hydrazine hydrate.[50] The products of the reaction were not reported. The cleavage reaction employed in the proof of the position of metalation of phenoxathiin-10-dioxide[59], i.e., the reaction of 1-phenoxathiincarboxylic acid 10-dioxide with Raney nickel to produce 3-carboxydiphenyl ether, involved desulfurization and hydrogenolysis. The hydrogen adsorbed on Raney nickel during the preparation[84] of the catalyst has been shown to effect hydrogenolysis of a number of sulfur-containing compounds, the sulfur being removed as nickel sulfide.* The hydrogenolysis procedure employed in the desulfurization of 1-phenoxathiincarboxylic acid 10-dioxide was modeled after the work of Mozingo and coworkers[85], who isolated benzene in yields of 65 to 75%

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[84] R. Mozingo, Org. Syntheses, 21, 15 (1941).

[85] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, J. Am. Chem. Soc., 65, 1013 (1943).

*A review of Raney nickel desulfurizations was provided by J. F. W. McOmie, Ann. Reports on Progress Chem. (Chem. Soc. London), 45, 198 (1948).

from the Raney nickel cleavage of diphenyl sulfide, diphenyl sulfoxide and diphenyl sulfone. A method employing dilute sodium carbonate as the reaction solvent gave excellent yields of cleavage products from sulfur heterocycles containing carboxyl groups.[86-89] Dibenzothiophene was converted successfully to biphenyl by Raney nickel[86], but dibenzothiophene-5-oxide and 5-dioxide yielded products which were not identified.[89] The isolation of biphenyl in 31% yield from the cleavage of 2-bromodibenzothiophene revealed that debromination had accompanied desulfurization.[89]

The reaction of phenoxathiin with sodium in liquid ammonia probably involved cleavage of a carbon-sulfur bond since the product was considered to be 2-thioldiphenyl ether.[90] Assignment of the structure was based upon analytical data and upon the observation that the compound reacted with salts of heavy metals to form mercaptides. No cleavage

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[86]S. A. Harris, R. Mozingo, D. E. Wolf, A. N. Wilson and K. Folkers, ibid., 67, 2102 (1945).

[87]F. F. Blicke and D. G. Sheets, ibid., 70, 3768 (1948).

[88]F. F. Blicke and D. G. Sheets, ibid., 71, 4010 (1949).

[89]H. Gilman and D. L. Esmay, ibid., 75, 2947 (1953).

[90]M. Tomita, Y. Inubushi and H. Niwa, J. Pharm. Soc. Japan, 72, 206 (1952) [C. A., 47, 6428 (1953)].

of a carbon-oxygen bond in 2-thioldiphenyl ether occurred when excess sodium was employed.

The above cleavage reaction of phenoxathiin illustrates another difference in the chemical properties of phenoxathiin and dibenzothiophene. Reduction of a benzenoid ring occurred when the latter heterocycle was treated with sodium in liquid ammonia.[91]

Both dibenzofuran and dibenzothiophene were cleaved by lithium in refluxing dioxane.[89] Irrespective of whether the cleavage of dibenzofuran was followed by hydrolysis or by carbonation, the product was 2-hydroxybiphenyl. However, the analogous product, 2-thiolbiphenyl, was obtained only when the dibenzothiophene cleavage was followed by carbonation; only biphenyl having been isolated when hydrolysis was subsequent to cleavage. When each of the heterocycles was treated with lithium in refluxing diethyl ether, reaction occurred only with dibenzofuran. Carbonation of this cleavage product produced 3,4-benzocoumarin in 47% yield. The results of the experiments in diethyl ether[89] would indicate that in this solvent lithium cleaves the carbon-oxygen bond more readily than the carbon-sulfur bond. Phenoxathiin, which has both the ether and sulfide linkages in the same

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[91]H. Gilman and A. L. Jacoby, J. Org. Chem., 3, 108 (1938).

molecule, was cleaved by lithium in diethyl ether, but the product was not identified.[92]

Derivatives of Phenoxathiin

In Tables 4-8 are included those derivatives of phenoxathiin which have been described in the literature and those prepared during the course of this investigation. The coverage of the literature on phenoxathiin was thorough through 1954. The period between 1954 and June, 1955 was covered as completely as possible by a survey of the Heterocycle section of Current Chemical Papers. This publication contains a classified world list of the papers in pure chemistry. Each entry in the list consists of the title of the article, the name(s) of the author(s) and the journal reference.

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[92] T. L. Reid, Unpublished Studies.

Table 4. Derivatives of phenoxathiin

Name of compound	M.p., °C	Reference
Monosubstituted phenoxathiins		
2-Acetamidophenoxathiin*	129-30	(52)
3-Acetamidophenoxathiin*	181-2.5	(75)
2-(p-Acetamidophenylsulfonamido)-phenoxathiin	195-6	(93)
4-(p-Acetamidophenylsulfonamido)-phenoxathiin	192	(94)
2-Acetylphenoxathiin	111-2	(22,25,35)
	116.5-8.5	(38)
	117.5-8	(52)
2-Acetylphenoxathiin oxime	142-4	(35)
	156-8	(38)
	158-9.5	(52)
2-Acetylphenoxathiin phenylhydrazone	93.5-4.5	(35)
2-Aminophenoxathiin*	93-5	(38,52)
	98	(50)

[93]M. Tomita and S. Fukunaga, J. Pharm. Soc. Japan, 65, No. 7/8A, 11 (1945) [C. A., 45, 5649 (1951)].

[94]H. Gilman and C. G. Stuckwisch, J. Am. Chem. Soc., 65, 1461 (1943).

*Compound is included in a treatment of melting points in the Discussion section of this thesis.

Table 4. (Continued)

Name of compound	M.p., °C	Reference
3-Aminophenoxathiin*	81.5-3	(75)
4-Aminophenoxathiin*	b.p. 209/5 mm.	(54)
4-Aminophenoxathiin hydrochloride (?)	223-4, 223-5	(54)
2-(p-Aminophenylsulfonamido)-phenoxathiin	186-7	(93)
4-(p-Aminophenylsulfonamido)-phenoxathiin	168	(94)
2-Benzoylphenoxathiin	96-7	(35)
2-Bromophenoxathiin*	59-60	(35)
	90-1	(38)
	58-9	(54)
β-Bromo-β-(2-phenoxathiinoyl)-propionic acid	173	(95)
_-Butylphenoxathiin	b.p. 245-264/20 mm.	(96)
1-Chlorophenoxathiin*	78-80	(50)
2-Chlorophenoxathiin*	88-9	(35,38,50)

[95]R. R. Burtner, U. S. Patent 2,604,478 (1952) [C. A., 48, 12813 (1954)].

[96]F. B. Smith and H. W. Moll, U. S. Patent 2,221,819 (1940) [C. A., 35, 1803 (1941); Chem. Zentr., 112, I, 3131 (1941)].

Table 4. (Continued)

Name of compound	M.p., °C	Reference
3-Chlorophenoxathiin*	81-2[a]	(34)
	79-81	(38)
	78-9[b]	(50)
4-Chlorophenoxathiin*	b.p. 192-3/7 mm.	(34)
_-Chlorophenoxathiin (?)	37[c]	(57)
_-Chlorophenoxathiin (?)	59-60[d]	(34)
2-Cyanomethylphenoxathiin	85-8	
_-Cyclohexylphenoxathiin	b.p. 190-205/10 mm.	(97)
	b.p. 232-8/20 mm.	(98)
_-Decylphenoxathiin	---	(99)

[97] W. Wenner, U. S. Patent 2,489,348 (1940) [C. A., 44, 2559 (1950)].

[98] F. B. Smith and H. W. Moll, U. S. Patent 2,221,820 (1940) [C. A., 35, 1803 (1941), Chem. Zentr., 112, I, 3131 (1941)].

[99] F. B. Smith and H. W. Moll, U. S. Patent 2,277,833 (1942) [C. A., 36, 4832 (1942)].

[a] Designated as 1-chlorophenoxathiin by Suter and Green.

[b] Position not designated by Irie.

[c] Designated as 2-chlorophenoxathiin by Ackermann.

[d] Designated as 3-chlorophenoxathiin by Suter and Green.

Table 4. (Continued)

Name of compound	M.p., °C	Reference
_-Dodecylphenoxathiin	---	(99)
Ethyl 2-phenoxathiincarboxylate	---	(54)
_-Heptadecylphenoxathiin	---	(99)
2-(α-Hydroxyethyl)phenoxathiin	65-7	(22,25)
4-Hydroxyphenoxathiin	98-9	(79)
_-Hydroxyphenoxathiin	---	(80)
2-Iodophenoxathiin*	92-4	(75)
3-Iodophenoxathiin*	70-2	(75)
4-Iodophenoxathiin*	42.5-3	(75)
Methyl γ-oxo-3-phenoxathiinbutyrate	60-2	
	b.p. 214-222/0.5 mm.	(77)
2-Methylphenoxathiin*	38-9	(34)
	37	(57)
4-Methylphenoxathiin*	b.p. 186-7/14 mm.	(34)
_-Methylphenoxathiin*	83-4[e]	(34)
Methyl 1-phenoxathiincarboxylate*	95-6	(59)
Methyl 4-phenoxathiincarboxylate*	b.p. 183-7/1 mm.	(59)

[e]Designated as 3-methylphenoxathiin by Suter and Green.

Table 4. (Continued)

Name of compound	M.p., °C	Reference
2-Nitrophenoxathiin*	140	(67)
	160	(50)
γ-Oxo-2-phenoxathiinbutyric acid*	191-2	(77)
γ-Oxo-3-phenoxathiinbutyric acid*	159-161	(77)
2-Phenoxathiinacetamide	200-2	(97)
	202-3	(100)
2-Phenoxathiinacetic acid*	193-4	(97)
	136-7	(100)
2-Phenoxathiinacetonitrile (2-Cyanomethylphenoxathiin)	85-8	(97)
1-Phenoxathiincarboxylic acid*	221-2	(59)
	223-4	(38)
2-Phenoxathiincarboxylic acid*	259-60, 260-2	(35)
	260-5	(54)
3-Phenoxathiincarboxylic acid*	223-4	(39,59)
4-Phenoxathiincarboxylic acid*	169-71	(38)
	168-9	(54)
_-Phenoxathiincarboxylic acid (?)	230-8	(37)

[100]H. Gilman and S. Avakian, J. Am. Chem. Soc., 68, 2104 (1946).

Table 4. (Continued)

Name of compound	M.p., °C	Reference
4-Phenoxathiincarboxylic acid amide	185-6	(54)
1-Phenoxathiincarboxylic acid hydrazide*	197-8	(59)
4-Phenoxathiincarboxylic acid hydrazide*	127-8	(59)
β-(2-Phenoxathiinoyl)acrylic acid	190	(95)
β-(2-Phenoxathiinoyl)propionic acid* (γ-Oxo-2-phenoxathiinbutyric acid)	191-2	(77)
β-(3-Phenoxathiinoyl)propionic acid* (γ-Oxo-3-phenoxathiinbutyric acid)	159-61	(77)
2-Phenoxathiinsulfonamide	177-8	(35)
2-Phenoxathiinsulfonic acid, sodium salt	---	(35)
2-Phenoxathiinsulfonyl chloride	127-8	(35)
2-Phenoxyphenoxathiin	81-2	(34)
1-Phenylphenoxathiin (?)	70.5-1.5	(96)
_-Propylphenoxathiin	b.p. 200-16/20 mm.	(96)
2-Vinylphenoxathiin	39.5-41	(22,25)
Disubstituted phenoxathiins		
1-Acetamido-3-phenoxathiincarboxylic acid	294-5	(39)
2-Amino-8-chlorophenoxathiin hydrochloride	220-1	(50)
2-Amino-8-methoxyphenoxathiin	277	(50)
2-Amino-8-methylphenoxathiin*	97	(50)

Table 4. (Continued)

Name of compound	M.p., °	Reference
1-Amino-3-phenoxathiincarboxylic acid	250	(39)
	259	(50)
	248-9	(59)
2,8-Bis-(β-chloroacetyl)phenoxathiin	193	(65)
2,8-Bis-(α-hydroxy-β-piperidylethyl)-phenoxathiin	133	(65)
2,8-Bis-(β-piperidylacetyl)phenoxathiin	105	(65)
3-Chloro-_-cyclohexylphenoxathiin (?)	b.p. 215-31/4 mm.	(98)
2-Chloro-8-nitrophenoxathiin*	195	(50)
	128-9	(67)
1-Chloro-3-phenoxathiincarboxylic acid	249-50	(50)
_-Cyclohexyl-1-phenylphenoxathiin (?)	b.p. 215-70/3.5 mm.	(98)
1,3-Diacetamidophenoxathiin	224-5	(30)
	242	(50)
2,8-Diacetamidophenoxathiin	253-4	(52)
3,7-Diacetamidophenoxathiin	289-90	(50)
2,8-Diacetylphenoxathiin	186-7	(38)
	184-6	(52)
	175	(65)
2,8-Diacetylphenoxathiin dioxime	220-1	(52)

Table 4. (Continued)

Name of compound	M.p., °C	Reference
1,3-Diaminophenoxathiin*	158	(30)
2,8-Diaminophenoxathiin*	118	(50)
	171-3	(52)
	166-8	(76)
3,7-Diaminophenoxathiin*	167-8	(50)
1,3-Dibenzamidophenoxathiin	257	(30)
2,8-Dibenzoylphenoxathiin	197	(35)
2,8-Dibromophenoxathiin*	92-3	(35,58)
2,8-Dichlorophenoxathiin*	134-5	(35,63,64)
	137	(50)
_,_-Dichlorophenoxathiin	168-9	(38)
	166-7	(50)
_,_-Dicyclohexylphenoxathiin (?)	b.p. 300-60/3.5 mm.	(98)
_,_-Didecylphenoxathiin (?)	---	(99)
_,_-Didodecylphenoxathiin (?)	---	(99)
2,8-Diethylphenoxathiin	b.p. 203-4/4 mm. 205-6/5 mm.	(65)
_,_-Diethylphenoxathiin	b.p. 200-15, 215-26/20 mm.	(96)
2,8-Dimercaptophenoxathiin	unstable	(78)

Table 4. (Continued)

Name of compound	M.p., °C	Reference
2,8-Dimercaptophenoxathiin diacetate	108-9	(78)
2,8-Dimercaptophenoxathiin dimethyl ether	68-9	(78)
2,8-Dimethylphenoxathiin*	74	(63,65)
	71	(64)
Dimethyl 1,6-phenoxathiindicarboxylate	150.5-1.5	(38)
	149-50	(78)
Dimethyl 4,6-phenoxathiindicarboxylate	82.5-3	(38)
1,3-Dinitrophenoxathiin*	187	(30)
2,8-Dinitrophenoxathiin*	143	(50)
3,7-Dinitrophenoxathiin*	204-5	(66)
_,_-Dipropylphenoxathiin (?)	b.p. 216-27, 226-44/20 mm.	(94)
2-Methoxy-8-nitrophenoxathiin*	ca. 300	(50)
2-Methyl-8-nitrophenoxathiin*	160	(50)
	156	(67)
1-Nitro-3-phenoxathiincarboxylic acid*	262	(39)
	259	(50)
	260-2	(59)
1,6-Phenoxathiindicarboxylic acid	354-6	(38)

Table 4. (Continued)

Name of compound	M.p., °C	Reference
4,6-Phenoxathiindicarboxylic acid	266-7	(38)
2,8-Phenoxathiindisulfonamide	192	(50)
2,8-Phenoxathiindisulfonic acid, disodium salt	---	(35)
2,8-Phenoxathiindisulfonic acid, disilver salt	---	(35)
2,8-Phenoxathiinsulfonyl chloride	142-3	(35)
	149	(78)
2,8-Phenoxathiindithiol (2,8-Dimercaptophenoxathiin)	unstable	(78)
Trisubstituted phenoxathiins		
2-Acetamido-3,8-dinitrophenoxathiin (?)	174-6.5	(75)
3-Chloro-_,_-dicyclohexylphenoxathiin (?)	b.p. 235-60/5 mm.	
	b.p. 260/5 mm. to 270/3 mm.	(98)
_,_-Dicyclohexyl-1-phenylphenoxathiin (?)	b.p. 270-330/3.5 mm.	(98)
3-Nitro-8-methyl-1-phenoxathiincarboxylic acid	253-4	(37)

Table 5. Derivatives of phenoxathiin-10-oxide

Name of compound	M.p., °C	Reference
Monosubstituted phenoxathiin-10-oxides		
2-Acetamidophenoxathiin-10-oxide	234-5	(52)
_-Cyclohexylphenoxathiin-10-oxide	---	(69)
1-Phenoxathiincarboxylic acid 10-oxide*	262	(38)
4-Phenoxathiincarboxylic acid 10-oxide	171-3	(38)
Disubstituted phenoxathiin-10-oxides		
_-Cyclohexyl-1-phenylphenoxathiin-10-oxide (?)	---	(69)
1,3-Diacetamidophenoxathiin-10-oxide	286	(50)
1,3-Diaminophenoxathiin-10-oxide*	262-3	(50)
2,8-Dichlorophenoxathiin-10-oxide	168	(63)
2,8-Dimethylphenoxathiin-10-oxide	132-3	(63)
1,3-Dinitrophenoxathiin-10-oxide	202-3	(30)
1-Nitro-3-phenoxathiincarboxylic acid 10-oxide*	251-2	(39)
2,8-Phenoxathiindicarboxylic acid 10-oxide (?)	270	(65)

*Compound is included in a treatment of melting points in the Discussion section of this thesis.

Table 6. Derivatives of phenoxathiin-10-dioxide

Name of compound	M.p., °C	Reference
Monosubstituted phenoxathiin-10-dioxides		
2-Acetamidophenoxathiin-10-dioxide	280-2	(52)
2-Aminophenoxathiin-10-dioxide*	169-176, 175.5-6	(38)
	164-5	(52)
2-Bromophenoxathiin-10-dioxide*	177-8	(38)
4-Bromophenoxathiin-10-dioxide	157.5-8	(38)
2-Chlorophenoxathiin-10-dioxide*	158-9	(34,38)
	---	(68)
3-Chlorophenoxathiin-10-dioxide	178-9[a]	(34)
	172-4[b]	(50)
4-Chlorophenoxathiin-10-dioxide	148-9	(34,54)
_-Chlorophenoxathiin-10-dioxide (?)	152-3[c]	(34)
_-Cyclohexylphenoxathiin-10-dioxide	---	(69)

*Compound is included in a treatment of melting points in the Discussion section of this thesis.

[a]Designated as 1-chlorophenoxathiin-10-dioxide by Suter and Green.

[b]Position not designated by Irie.

[c]Designated as 3-chlorophenoxathiin-10-dioxide by Suter and Green. Compound is the oxidation product of _-chlorophenoxathiin, m.p. 59-60°.

Table 6. (Continued)

Name of compound	M.p., °C	Reference
2-Iodophenoxathiin-10-dioxide*	171-2	(38)
2-Methylphenoxathiin-10-dioxide*	134-5	(34)
4-Methylphenoxathiin-10-dioxide*	141-2	(34)
_-Methylphenoxathiin-10-dioxide*	138-9[d]	(34)
Methyl 1-phenoxathiincarboxylate 10-dioxide	144-5	(59)
Methyl 4-phenoxathiincarboxylate 10-dioxide	124	(54)
	123-4	(59)
2-Nitrophenoxathiin-10-dioxide*	187-90	(38)
	196.5	(50)
	187-8, 192-4	(52)
	205-6	(67)
1-Phenoxathiincarboxylic acid 10-dioxide	229-31	(38)
	228-9	(59)
1-Phenoxathiincarboxylic acid 10-dioxide hydrazide	240	(59)
2-Phenoxathiincarboxylic acid 10-dioxide	268-9	(50)
4-Phenoxathiincarboxylic acid 10-dioxide	183-4	(54)
	189-190	(59)

[d]Designated as 3-methylphenoxathiin-10-dioxide by Suter and Green. Obtained by oxidation of _-methylphenoxathiin, m.p. 83-84°.

Table 6. (Continued)

Name of compound	M.p., °C	Reference
4-Phenoxathiincarboxylic acid 10-dioxide hydrazide	260	(59)
2-Phenoxyphenoxathiin-10-dioxide	112-3	(34)
Disubstituted phenoxathiin-10-dioxides		
2,8-Bis-(α-chloroacetyl)phenoxathiin-10-dioxide	224-9	(65)
2-Chloro-8-methylphenoxathiin-10-dioxide*	173	(68)
2-Chloro-8-nitrophenoxathiin-10-dioxide	183-5	(67)
_-Cyclohexyl-3(?)-chlorophenoxathiin-10-dioxide (?)	195-6	(69)
_-Cyclohexyl-1(?)-phenylphenoxathiin-10-dioxide (?)	82-4.5	(69)
2,8-Diacetamidophenoxathiin-10-dioxide	338-41, 349-353	(52)
3,7-Diacetamidophenoxathiin-10-dioxide	359-62	(66)
1,3-Diaminophenoxathiin-10-dioxide*	228	(30)
2,8-Diaminophenoxathiin-10-dioxide	239-40	(50)
	244-7.5	(52)
3,7-Diaminophenoxathiin-10-dioxide	224-5.5	(66)
2,8-Dibromophenoxathiin-10-dioxide	183-6, 185-6	(35)
2,8-Dichlorophenoxathiin-10-dioxide	196	(63)
_,_-Dichlorophenoxathiin-10-dioxide	208-10	(50)

Table 6. (Continued)

Name of compound	M.p., °C	Reference
2,8-Diethylphenoxathiin-10-dioxide	oil	(65)
Diethyl 1,9-phenoxathiindicarboxylate 10-dioxide	143-3.5	(38)
2,8-Dimethylphenoxathiin-10-dioxide*	172	(63)
Dimethyl 1,9-phenoxathiindicarboxylate 10-dioxide	170-1	(38)
Dimethyl 2,8-phenoxathiindicarboxylate 10-dioxide	204-8	(65)
1,3-Dinitrophenoxathiin-10-dioxide	256.5-7	(30)
2,8-Dinitrophenoxathiin-10-dioxide	276-8, ca. 280	(50)
	283-6	(52)
3,7-Dinitrophenoxathiin-10-dioxide	246-7	(66)
2-Methoxy-8-nitrophenoxathiin-10-dioxide	300	(50)
2-Methyl-8-nitrophenoxathiin-10-dioxide*	196-7	(50)
1-Nitro-3-phenoxathiincarboxylic acid 10-dioxide	296-7	(39)
1,6-Phenoxathiindicarboxylic acid 10-dioxide	351-3	(38)
1,9-Phenoxathiindicarboxylic acid 10-dioxide	356-8	(38)
2,8-Phenoxathiindicarboxylic acid 10-dioxide	392-4	(38)
	300	(65)
4,6-Phenoxathiindicarboxylic acid 10-dioxide	329-31	(38)

Table 7. Phenothioxonium derivatives

Name of compound	M.p., °C	Reference
Chlorophenothioxonium chloride (10,10-Dichlorophenoxathiin)	71	(50)
	---	(52)
2,8-Dichlorophenothioxonium hydroxide	142-5	(64)
2,8-Dimethylphenothioxonium hydroxide	105-10	(64)
2-Nitro-8-chlorophenothioxonium hydroxide	135	(50)

Table 8. Miscellaneous derivatives of phenoxathiin, phenoxathiin-10-oxide and phenoxathiin-10-dioxide

Name of compound	M.p., °C	Reference
1,4-Diketo-2-chloro-3-(3'-methyl-4'-hydroxy-5'-thiolphenyl)thiol-6-methyl-8-thiolphenoxathiin (?)	250, decomp.	(31)
3,7-Diphenyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophenoxathiin-10-oxide (?)	216	(101)
Isophenoxathiin-10-dioxide (?)	225	(102)
3,3,7,7-Tetramethyl-1,9-diketo-1,2,3,4,6,7,8,9-octahydrophenoxathiin-10-oxide (?)	181-2	(101)
1,3,1',3'-Tetranitro-7,7'-dimethyl-phenoxathiin-8,8'-disulfide (?)	---	(60)
Tetranitrodiphenoxathiin (?)	280, decomp.	(60)
1,3,1',3'-Tetranitrophenoxathiin-8,8'-disulfide (?)	decomp.	(61)
1,3,1',3'-Tetranitro-7,9,7',9'-tetramethylphenoxathiin-8,8'-disulfide (?)	255-7	(62)

[101] R. D. Desai and M. A. Wali, J. Indian Chem. Soc., 13, 735 (1936).

[102] O. Hinsberg, Ber., 62 B, 127 (1929).

Bibliography of Phenoxathiin

Ackermann, F., German Patent 234,743 (1911) [C. A., 5, 2912 (1911); Chem. Zentr., 82, I, 1768 (1911)].

Amstutz, E. D., J. Am. Chem. Soc., 72, 3420 (1950).

Avakian, S., Private communication to Prof. H. Gilman, Iowa State College, Aug. 10, 1953.

Bennett, G. M., M. S. Leslie and E. E. Turner, J. Chem. Soc., 444 (1937).

Boyer, R. F., U. S. Patent 2,462,352 (1949) [C. A., 43 4520 (1949)].

Burtner, R. R., U. S. Patent 2,604,478 (1952) [C. A., 48, 12813 (1954)].

Burtner, R. R., and J. M. Brown, U. S. Patent 2,480,220 (1949) [C. A., 44, 1143 (1950)].

Bushland, R. C., J. Econ. Entomol., 33, 666 (1940).

Ciba Ltd., Swiss Patent 238,633 (1945) [C. A., 43, 4484 (1949)].

Cross, H. F., and F. M. Snyder, Soap Sanit. Chemicals, 25, No. 2, 135 (1949).

Cullinane, N. M., and W. T. Rees, Trans. Faraday Soc., 36, 507 (1940).

Deasy, C. L., Chem. Revs., 32, 173 (1943).

Desai, R. D., and M. A. Wali, J. Indian Chem. Soc., 13, 735 (1936).

Dow Chemical Company, "Dow Special Chemicals", Midland, Michigan, 1950.

Drew, H. K. D., J. Chem. Soc., 223 (1926).

Drew, H. K. D., ibid., 511 (1928).

Drew, H. K. D., Chemistry and Industry, 47, 949 (1928).

Elderfield, R. C., University of Michigan, Ann Arbor, Michigan, Private communication, May 30, 1955.

Esmay, D. L., Unpublished Ph.D. Thesis, Iowa State College Library, 1951.

Everitt, E. L., and M. X. Sullivan, J. Wash. Acad. Sci., 30, 457 (1940).

Ferrario, E., Bull. soc. chim. France, 9, 536 (1911).

Fink, D. E., and L. E. Smith, J. Econ. Entomol., 29, 804 (1936).

Flett, L. H., U. S. Patent 2,469,378 (1949) [C. A., 43, 6846 (1949)].

Flowers, R. G., and L. W. Flowers, J. Am. Chem. Soc., 71, 3102 (1949).

Flowers, R. G., and L. W. Flowers, U. S. Patent 2,449,527 (1948) [C. A., 43, 904 (1949)].

Flowers, R. G., and L. W. Flowers, U. S. Patent 2,449,528 (1948) [C. A., 43, 1223 (1949)].

Flowers, R. G., and L. W. Flowers, U. S. Patent 2,551,818 (1948) [C. A., 43, 1814 (1949)].

Geigy, J. R., British Patent 536,011 (1941) [C. A., 36, 1617 (1942)].

Geigy, J. R., British Patent 536,047 (1941) [C. A., 36, 1617 (1942)].

Gilman, H., and S. Avakian, J. Am. Chem. Soc., 68, 2104 (1946).

Gilman, H., and D. L. Esmay, ibid., 74, 2021 (1952).

Gilman, H., and D. L. Esmay, ibid., 76, 5787 (1954).

Gilman, H., and C. G. Stuckwisch, ibid., 65, 1461 (1943).

Gilman, H., Marian W. Van Ess, H. B. Willis and C. G. Stuckwisch, ibid., 62, 2606 (1940).

Goodhue, L. D., Compressed Gas Manuf.'s Assoc., Annual Rept., 31, 67 (1943) [Original not available for inspection; abstracted in C. A., 41, 2526 (1947)].

Gordon, H. McL., and M. Lipson, J. Council Sci. Ind. Research, 13, 173 (1940).

Graham, O. W., and G. W. Eddy, J. Econ. Entomol., 41, 521 (1948).

Gunter, M. J., K. S. Kim, D. F. Magee, H. Ralston and A. C. Ivy, J. Pharmacol. Exptl. Therap., 99, No. 4, Pt. 1, 465 (1950).

Higasi, K., Sci. Papers Inst. Phys. Chem. Research (Tokyo), 38, 331 (1941) [C. A., 35, 6167 (1941)].

Higasi, K., and S. Uyeo, J. Chem. Soc. Japan, 62, 400 (1941) [C. A., 35, 6167 (1941)].

Hilditch, T. P., and S. Smiles, J. Chem. Soc., 408 (1911).

Hilditch, T. P., and S. Smiles, ibid., 973 (1911).

Hinsberg, O., Ber., 62 B, 127 (1929).

Hughes, M. B., Unpublished studies.

Irie, T., Bull. Inst. Phys. Chem. Research (Tokyo), 20, 150 (1941) [C. A., 36, 2881 (1941)].

Irie, T., J. Faculty Sci., Hokkaido Univ., Ser. 3, 4, No. 2, 70 (1951) (in English) [C. A., 47, 6949 (1953)]. This article is a translation of the preceding article in Bull. Inst. Phys. Chem. Research (Tokyo), 20, 150 (1941).

Katscher, E., and H. Lehr., Monatsh., 64, 236 (1934).

Kent, B. A., and S. Smiles, J. Chem. Soc., 422 (1934).

Knipling, E. F., J. Econ. Entomol., 34, 314 (1941).

Kønig, O., and W. R. Crowell, Mikrochemie ver. Mikrochim. Acta, 33, 298 (1948).

Krishna, S., J. Chem. Soc., 2782 (1923).

Leonard, N. J., and L. E. Sutton, J. Am. Chem. Soc., 70, 1564 (1948).

Levine, N. D., and V. Ivens, Am. J. Vet. Research, 15, 349 (1954).

Linduska, J. P., F. A. Morton and W. C. McDuffie, J. Econ. Entomol., 41, 43 (1948).

Loeffler, E. S., and W. M. Hoskins, ibid., 39, 589 (1946).

Matthysse, J. G., New York (Ithaca) Agr. Expt. Sta., Bull. 832 (1946).

Mauthner, F., Ber., 38, 1411 (1905).

Mauthner, F., Ber., 39, 1340 (1906).

Metcalf, R. L., and C. W. Kearns, J. Econ. Entomol., 34, 306 (1941).

Moir, J., Trans. Roy. Soc. S. Africa, 18, Pt. 2, 137 (1929) [Original not available for inspection; abstracted in C. A., 23, 4468 (1929)].

Nelson, O. A., and L. E. Smith, J. Am. Chem. Soc., 64, 1057 (1952).

Nobis, J. F., A. J. Blardinelli and D. J. Blaney, ibid., 75, 3394 (1953).

Nobis, J. F., and N. W. Burske, ibid., 76, 3034 (1954).

Patterson, A. M., and L. T. Capell, "The Ring Index", Reinhold Publishing Corp., New York, N. Y., 1940, p. 259.

Pfaff, K., Reichsamt Wirtschaftsausbau Chem. Ber., PB 52021, 1183 (1942). [Original not available for inspection; abstracted in C. A., 42, 9045 (1948)].

Pollack, J., and E. Riesz, Monatsh., 50, 251 (1928).

Pollack, J., and E. Riesz, ibid., 53 & 54, 90 (1929).

Pollack, R., E. Riesz and J. Riesz, ibid., 58, 129 (1931).

Pützer, B., and F. Muth, German Patent 606,350 (1934) [C. A., 29, 1434 (1935)].

Pützer, B., and F. Muth, British Patent 427,816 (1935) [C. A., 29, 6608 (1935)].

Reid, T. L., Unpublished Studies.

Reid, W. J., Jr., and F. P. Cuthbert, Jr., U. S. Dept. Agr., Bur. Entomol. and Plant Quarantine, E-787 (1949).

Schwardt, H. H., and J. G. Matthysse, New York (Ithaca) Agr. Expt. Sta., Bull. 844 (1948).

Shirley, D. A., and E. A. Lehto, J. Am. Chem. Soc., 77, 1841 (1945).

Siegler, E. H., F. Munger and L. E. Smith, U. S. Dept. Agr. Circ. 523 (1939).

Smith, C. N., Proc. Chem. Specialties Mfgrs. Assoc., Dec., 79 (1950) [Original not available for inspection; abstracted in C. A., 45, 5871 (1951)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,221,819 (1940) [C. A., 35, 1803 (1941); Chem. Zentr., 112, I, 3131 (1941)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,221,820 (1940) [C. A., 35, 1803 (1941); Chem. Zentr., 112, I, 3131 (1941)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,265,204 (1942) [C. A., 36, 2078 (1942)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,265,205 (1942) [C. A., 36, 2078 (1942)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,273,905 (1942) [C. A., 36, 3807 (1942)].

Smith, F. B., and H. W. Moll, U. S. Patent 2,277,833 (1942) [C. A., 36, 4832 (1942)].

Smith, L. E., U. S. Dept. Agr., Bur. Entomol. and Plant Quarantine, E-580 (1942).

Smith, L. E., and R. Melvin, J. Econ. Entomol., 36, 475 (1943).

Smith, L. E., E. H. Siegler and F. Munger, ibid., 29, 1027 (1936).

Snyder, F. M., and F. A. Morton, ibid., 39, 385 (1946).

Stevenson, H. A., and S. Smiles, J. Chem. Soc., 718 (1931).

Suter, C. M., and F. O. Green, J. Am. Chem. Soc., 59, 2578 (1937).

Suter, C. M., J. P. McKenzie and C. E. Maxwell, ibid., 58, 717 (1936).

Suter, C. M., and C. E. Maxwell, "Organic Syntheses", Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 485.

Telford, H. S., J. Econ. Entomol., 38, 573 (1945).

Thomson, M. C., and E. E. Turner, J. Chem. Soc., 29 (1938).

Todd, D., Private communication to J. F. Nobis, Research Division, National Distillers Chemical Co., Cincinnati, Ohio. [Cited in Nobis, J. F., A. J. Blardinelli and D. J. Blaney, J. Am. Chem. Soc., 75, 3384 (1953)].

Tomita, M., J. Pharm. Soc. Japan, 58, 510 (in German, 136) (1938) [C. A., 32, 7467 (1938); Chem. Zentr., 110, I, 3892 (1938)].

Tomita, M., and S. Fukunga, ibid., 65, No. 7/8 A, 11 (1945) [C. A., 45, 5649 (1951)].

Tomita, M., and T. Ikeda, ibid., 58, 780 (in German, 231) (1938) [C. A., 33, 2526 (1939)].

Tomita, M., Y. Inubushi and H. Niwa, ibid., 72, 206 (1952) [C. A., 47, 6428 (1953)].

Tomita, M., and W. Watanabe, ibid., 71, 2104 (1951) [C. A., 46, 7618 (1952)].

Tomita, M., and W. Watanabe, ibid., 72, 478 (1952) [C. A., 47, 7028 (1953)].

Tomita, M., and H. Yamada, ibid., 71, 451 (1951) C. A., 46, 992 (1952)].

Webb, F. J., Unpublished Ph.D. Thesis, Iowa State College Library, 1941, p. 36.

Wenner, W., U. S. Patent 2,489,348 (1949) [C. A., 44, 2559 (1950)].

Wood, R. G., C. H. McCale and G. Williams, Phil. Mag., 31, 71 (1941).

EXPERIMENTAL[103,104]

Reactions Involving Metalation and Subsequent Carbonation

General procedure

All preparations of organometallic compounds were carried out in an atmosphere of dry, oxygen-free nitrogen. The solvent employed in the reactions, anhydrous diethyl ether, was stored over sodium wire before usage. The metalation reaction was carried out in a three-necked, round-bottomed flask of proper size to allow efficient stirring. The flask was fitted with a stirrer, a graduated separatory funnel and either a reflux condenser or a thermometer. When the reaction was carried out at temperatures below 25°, a gas inlet tube fitted with a low temperature thermometer was employed in place of the condenser.

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[103] All melting points reported herein are uncorrected. The determinations were made in a silicone oil-bath when the compound melted below 250° and in an electrically-heated copper block when the melting point was above 250°. The bath and the block were heated at the rate of approximately 1°/min. at the melting point of the compound.

[104] All infrared spectra were obtained by use of the Baird double beam infrared spectrophotometer of the Institute for Atomic Research, Iowa State College. The writer expresses his appreciation to Robert McCord, Robert Cross, Richard Hedges and Dr. Velmer A. Fassel for the determination of the spectra.

The general method of Gilman and coworkers[105], with minor modifications, was employed for the preparation of n-butyllithium. Oil-covered lithium wire was cut into 3 mm. pieces which fell directly into the flask containing ether. The oil was removed by several decantations of ether from the flask. During the 45 to 60-minute period required for the addition of n-butyl bromide, the reaction temperature was maintained between -20° and -30°. The yields, as determined by double titration[106], of the sixteen one mole-scale preparations ranged from 86 to 93%, with an average yield of 89.5%.

Immediately prior to carbonation the metalation mixture was transferred to a dry separatory funnel which had been swept out with nitrogen. A nitrogen atmosphere was maintained above the metalation mixture during the transfer to the funnel and during the period in which the mixture was allowed to run into a very large beaker containing a stirred slurry of ether and powdered Dry Ice. The rate of addition, which sometimes was necessarily slow due to a vigorous carbonation reaction, was more easily controlled from a

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[105] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, J. Am. Chem. Soc., 71, 1449 (1949).

[106] H. Gilman and A. H. Haubein, ibid., 66, 1515 (1944).

separatory funnel than from a reaction flask. Subsequent to carbonation the mixture was allowed to stand until the ether had evaporated. The dry solid was pulverized and extracted with petroleum ether (b.p. 60-70°) in a Soxhlet extractor. The extract contained materials such as phenoxathiin, diphenyl ether and minor side reaction products. Following removal of the residual solvent, the salt mixture was dissolved in water. If a considerable amount of solid insoluble in petroleum ether and water were present, it was collected by filtration. The salt solution was stirred with Norit-A and filtered. Acidification was carried out by the dropwise addition of dilute (1:10) hydrochloric acid to the clear, stirred filtrate.

Reaction of phenoxathiin with one equivalent of n-butyllithium at low temperature

To a solution of 30.0 g. (0.15 mole) of phenoxathiin in 100 ml. of ether at -20° was added 112 ml. of a 1.34 M solution (0.15 mole) of n-butyllithium over a period of 30 minutes. After 6 hours at -20° the cooling bath was removed. The mixture was allowed to warm to room temperature over a period of 1.5 hours and was carbonated. Color Test II[107] was

[107] H. Gilman and J. Swiss, ibid., 62, 1847 (1940).

positive at the time of carbonation. After the mixture had been worked up as in the "General procedure" section, there was obtained 18.4 g. of yellow acid melting over the range 145-159°. The material was recrystallized from glacial acetic acid to yield 16.4 g., melting range 164-234°. Subsequent to additional recrystallizations, one from 50% acetic acid and two from glacial acetic acid, there was obtained 7.9 g. (21.6%) of 4-phenoxathiincarboxylic acid, m.p. and mixed m.p. 171-173°. Also obtained was 4.0 g. of a yellow acid mixture, melting range 167-240°. The range was not altered by a subsequent recrystallization from glacial acetic acid.

Reaction of phenoxathiin with one equivalent of n-butyllithium at 35°

To a stirred solution of 20.0 g. (0.10 mole) of phenoxathiin in 300 ml. of ether at 35° was added 50 ml. of a 1.06 M solution (0.05 mole) of n-butyllithium over a period of 45 minutes. Color Test II was negative 45 minutes after the addition of this first half-molar equivalent. The second half-molar equivalent (0.05 mole) of n-butyllithium was added over a 30-minute period. Color Test II was negative 30 minutes after the completion of the addition, at which time the

mixture was carbonated and worked up as in the "General procedure" section.

Filtered from the petroleum ether extract was a small amount of yellow crystals which melted at 166-167°, leaving a residue. A mixture of this unknown material and a sample of 4-phenoxathiincarboxylic acid (m.p. 171-173°) melted over the range 142-150°, leaving a residue. Unsuccessful attempts were made to purify the yellow crystals. Upon concentration of the petroleum ether filtrate there was recovered 0.7 g. (3.8%) of phenoxathiin, m.p. and mixed m.p. 53-55°.

The crude, yellow acid mixture weighed 18.6 g. and melted over the range 151-165°. An attempt was made to separate the acids by extraction with ether, followed by recrystallization from glacial acetic acid. No separation was effected. The resultant mixture which weighed 14.4 g. was digested with benzene, a solvent which dissolved the monocarboxylic acid and left the dicarboxylic acid as a residue. Recrystallization of the dicarboxylic acid from methanol yielded 0.4 g. (1.4%) of 1,6-phenoxathiindicarboxylic acid, m.p. 348-350°, with decomposition. The identity of the compound was established by a mixed melting point determination with an authentic specimen. (See "Reaction of phenoxathiin with two equivalents of n-butyllithium" and "Hydrogenolysis of 1,6-phenoxathiindicarboxylic acid".) Upon

concentration of the benzene solution there was obtained 11.5 g. of yellow crystals, melting range 156-172°. Following two recrystallizations from benzene there was collected 9.8 g. of yellow crystals, m.p. 170-172°. A final recrystallization from glacial acetic acid yielded 9.1 g. (36.9%) of 4-phenoxathiincarboxylic acid, m.p. and mixed m.p. 171-173°.

It is probable that higher yields of both acids could have been obtained had some of the numerous purification steps been omitted. A significant amount of product was lost during the attempt to separate the acids by selective solubility in ether. The second of the two recrystallizations from benzene could have been omitted since it effected little purification.

Reaction of phenoxathiin with two equivalents of n-butyllithium

Run I. To a stirred solution of 50.0 g. (0.25 mole) of phenoxathiin in 50 ml. of ether was added 427 ml. of a 1.23 M solution (0.53 mole) of n-butyllithium. After a 40-hour period of refluxing, at which time Color Test II was faintly positive, the mixture was carbonated and worked up by the method described in the "General procedure" section.

The yellow acid mixture which was filtered from the acidified salt solution weighed 64.3 g. (89% of the

theoretical yield of phenoxathiindicarboxylic acid) and melted over the range 240-295°. In a previous run the yield of crude product was 98%. Unsuccessful attempts were made to purify the product by crystallization from glacial acetic acid and from a mixture of ethanol and benzene.

A portion of the above crude mixture was esterified by reaction with absolute ethanol which had been saturated with hydrogen chloride. Following distillation of the excess alcohol the reaction mixture was dissolved in ether, the ether extract was washed with water and extracted with 5% potassium carbonate solution. The ether solution was dried over Drierite and the ether was removed by distillation. Crystallization of the residue first from ethanol and then from petroleum ether (b.p. 60-70°) yielded fractions which melted over the ranges 65-85° and 102-105°. The higher-melting fraction was recrystallized from a variety of solvents and the melting point was raised as high as 108-111°, but very little product was obtained. An attempt to separate the esters by chromatography on a silicic acid-Celite column was unsuccessful. None of four chromatographic fractions melted over a range less than 11°.

When the potassium carbonate extract of the ether solution was acidified there was recovered an amount of yellow acid equivalent to 28% of the starting material. (In a

previous esterification attempt a 35% recovery of unreacted acids was made.) The acid mixture was dissolved in dilute potassium carbonate solution and the solution was partially acidified with dilute hydrochloric acid. The acid which separated was collected by filtration and the filtrate was further acidified. This fractional acidification process was repeated two additional times. The first acid fraction gave yellow needles, m.p. 264-267°, upon recrystallization from glacial acetic acid. After each of two subsequent recrystallizations from glacial acetic acid the product melted at 266-267°. This acid, 4,6-phenoxathiindicarboxylic acid, was isolated in significant yields in a subsequent experiment. Difficulty was encountered in the process of dissolving in glacial acetic acid the last crude fraction obtained by the partial acidification procedure. From the cooled solution there was collected as the first fraction a bright, yellow powder which melted over the range 329-333°, with decomposition. The mother liquor gave crystalline material melting over the range 249-269°. Another recrystallization changed the melting range to 252-272°. The melting range suggested that both acids were being concentrated in material which crystallized. Therefore, it was believed that the acids in a mixture of such a composition could not be readily separated by an ordinary recrystallization procedure.

Run II. To a stirred solution of 40.0 g. (0.20 mole) of phenoxathiin in 100 ml. of ether was added 350 ml. of a 1.20 M solution (0.42 mole) of n-butyllithium and the mixture was heated at the reflux temperature for 46 hours. Following carbonation and work up as in the "General procedure" section there was collected 55.4 g. (91% of the theoretical yield of phenoxathiindicarboxylic acid) of yellow product melting over the range 250-295°.

The crude product was digested with refluxing glacial acetic acid, a solvent which dissolved most of the material. Subsequent to hot filtration there was removed from the filter paper a bright, canary-yellow powder which melted at 352-354°, with decomposition. The melting point of the yellow product, later shown to be that of 1,6-phenoxathiin-dicarboxylic acid, was not changed by a recrystallization from methyl cellosolve. The material which was soluble in the acetic acid was purified little by one crystallization from this solvent. The melting range of 263-293° indicated that also some of the higher melting (354°) acid had dissolved in the acetic acid. After many recrystallizations from methyl ethyl ketone and from dilute acetic acid, there was obtained a small amount of the pure acid melting at 266-267°. Since the purification process was very long and of an exploratory nature, the yield was not significant.

Run III. To a refluxing, stirred solution of 40.0 g. (0.20 mole) of phenoxathiin in 100 ml. of ether was added 375 ml. of a 1.17 M solution (0.44 mole) of n-butyllithium and the mixture was stirred at the reflux temperature for 40 hours. The mixture was carbonated and worked up according to the method described in the "General procedure" section.

The crude, yellow acid mixture, 54.5 g., (95%) melting range 221-275°, was extracted with benzene in a Soxhlet extractor in order to remove the more soluble 4-phenoxathiincarboxylic acid. None of the monocarboxylic acid was isolated from the benzene extract. Removed from the Soxhlet thimble was 46.0 g. of benzene-insoluble solid which melted over the range 240-267°. The solid was dissolved in 10% potassium hydroxide solution and to the vigorously stirred, pale orange solution was added slowly enough dilute acetic acid to precipitate most of the dull yellow acid. Following collection of the product, which weighed 33.0 g. and melted over the range 260-283°, the filtrate was further acidified with dilute hydrochloric acid. The bright canary yellow product weighed 16.0 g. and melted over the range 295-316°. (Since a total weight of 49.0 g. was obtained, there may have been approximately 3 g. of occluded salts.) The material melting over the range 260-283° was redissolved in dilute potassium hydroxide solution and the partial acidification process

was repeated. There was collected 24.6 g. of dull yellow material, melting range 256-266°, and 4.4 g. of bright yellow solid melting over the range 267-318°. The last batch was combined with the 16-g. fraction and the mixture was digested with 60% acetic acid. Upon filtration of the acetic acid suspension there was collected 9.6 g. of yellow solid which melted over the range 318-332°. The acetic acid filtrate was cooled and there was obtained 2.9 g. of yellow crystals melting over the range 246-267°.

Crystallization from 60% acetic acid of the material melting over the range 256-267° gave three fractions having the following weights and melting ranges: 5.1 g., 264-268°; 14.9 g., 267-270°, and 2.1 g., 253-260°. The first two fractions, 20.0 g., represented a 34.7% yield of relatively pure 4,6-phenoxathiindicarboxylic acid. An analytical sample, one which had been successively recrystallized from glacial acetic acid and methyl ethyl ketone with no change in melting point, melted at 266-267°.

Anal. Calcd. for $C_{14}H_8O_5S$: C, 58.33; H, 2.80; S, 11.12; neut. equiv., 144. Found: C, 58.31, 58.52; H, 2.99, 2.90; S, 11.01, 11.08; neut. equiv., 144, 146.

The material which melted over a range at temperatures above 300° was recrystallized from a large volume of aqueous acetone. There were obtained fractions with the following

weights and melting ranges: 5.1 g., 340-346°; 0.9 g., 334-339°; and 3.9 g., 318-324°. Decomposition accompanied melting in all three cases. The weight of 5.1 g. represents an 8.9% yield of relatively pure 1,6-phenoxathiindicarboxylic acid. This material did not depress the melting point of a sample (m.p. 351-353°, with decomposition) which was obtained by subsequent recrystallization from methyl cellosolve. Difficulty was encountered in reproducing the melting points of 1,6-phenoxathiindicarboxylic acid due to the high melting point and the accompanying decomposition of the sample at this temperature. For this reason the dimethyl ester, a compound which melted at a convenient temperature, was prepared. (See "Preparation of dimethyl 1,6-phenoxathiindicarboxylate".) The analytical data for 1,6-phenoxathiindicarboxylic acid are given below.

Anal. Calcd. for $C_{14}H_8O_5S$: S, 11.12; neut. equiv., 144. Found: S, 11.04, 10.97; neut. equiv., 144.5, 141.5.

The stepwise acidification method for the separation of the two acids was crude and highly empirical. However, being a method utilizing a chemical rather than physical properties, it was believed to be more efficient than fractional recrystallization, a procedure which was either ineffective or was accompanied by loss of large quantities of products. There were discernible, though slight,

differences in the colors and the apparent acid strengths of the two isomeric products. The bright canary yellow acid appeared to precipitate only after a considerable amount of the dilute hydrochloric (or acetic) acid was added to the salt solution. Though these differences in properties were not sufficient to facilitate a quantitative separation of the two acids, it is probable that, with the proper utilization of these properties, a more efficient separation than the one described can be effected. This improvement may entail the use of sodium or potassium bicarbonate as the base in which the acid mixture is dissolved. Such a buffered mixture may allow the more complete precipitation of the first acid before the acidity of the mixture is increased anough to cause precipitation of the second acid. Also, by filtering more fractions of acid during the stepwise acidification, one may be able to effect a sharper separation and obtain more of the relatively pure acids before resorting to recrystallization.

Reaction of phenoxathiin with methyllithium

Methyllithium was employed as a metalating agent in the course of attempts to limit the metalation of phenoxathiin to formation of the monolithium derivative.

To a stirred solution of 30.0 g. (0.15 mole) of phenoxathiin in 150 ml. of ether was added 138 ml. of a 1.31 M ether solution (0.18 mole) of methyllithium.[108] After a 20-hour reflux period the mixture was carbonated and worked up by the method described in the "General procedure" section. There was obtained from the petroleum ether extract 26.3 g. (87.7% recovery) of phenoxathiin. The yield of crude 4-phenoxathiincarboxylic acid melting at 169-172° was 3.4 g. (9.3%). After one recrystallization from glacial acetic acid there was collected 2.7 g. of pure 4-phenoxathiincarboxylic acid, m.p. and mixed m.p. 171-173°.

When two molar equivalents of methyllithium were employed in the reaction, the yield of crude product, m.p. 169-172°, was 11.6%. No interfering quantity of dicarboxylic acid was formed. This crude product was much more readily purified than was the crude acid mixture which was produced upon metalation with one equivalent of n-butyllithium.

Reaction of phenoxathiin with four equivalents of n-butyllithium

This experiment was carried out under the conditions employed in the halogen-metal interconversion reaction

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[108] H. Gilman, E. A. Zoellner and W. M. Selby, J. Am. Chem. Soc., 55, 1252 (1933).

between 2-bromophenoxathiin (m.p. 58-59°) and four equivalents of n-butyllithium.[54] Phenoxathiin was substituted for 2-bromophenoxathiin to determine whether extensive metalation would occur under these conditions.

To a stirred solution of 3.6 g. (0.018 mole) of phenoxathiin in 50 ml. of dry benzene was added 58.5 ml. of a 1.28 M solution (0.072 mole) of n-butyllithium over a period of 5 minutes. The mixture was refluxed for 15 minutes and then carbonated. After the carbonation mixture had warmed to room temperature, 200 ml. of water was added and the mixture was stirred and filtered. The layers were separated and the aqueous layer was extracted with ether. Following removal of the dissolved ether, the aqueous solution was treated with Norit-A, filtered and acidified. The dry, yellow solid weighed 2.83 g. (64.3% of theoretical if only phenoxathiincarboxylic acid) and melted over the range 155-240°. The neutralization equivalent of the mixture, determined by two titrations with standard base, was found to be 219-219.5. It was assumed that the mixture consisted of 4-phenoxathiindicarboxylic acids, neut. equiv. 244, and phenoxathiindicarboxylic acids, neut. equiv. 144. Calculations based upon the three neutralizations equivalents revealed that the mixture consisted of 84% mono- and 16% dicarboxylic acid.

Thus, it is probable that an attempted halogen-metal interconversion reaction carried out under the above conditions would be accompanied by both mono- and dimetalation as side reactions.

Reaction of phenoxathiin with phenylcalcium iodide

To a stirred solution of 32.0 g. (0.16 mole) of phenoxathiin in 150 ml. of ether was added 360 ml. of a 0.46 M ethereal solution (0.16 mole) of phenylcalcium iodide.[109] After a 38-hour reflux period the mixture was carbonated. When the dry carbonation mixture had been extracted with petroleum ether, the brown solid was removed from the Soxhlet thimble, the solvent was evaporated, the solid was stirred with water and the mixture was filtered. A water-insoluble brown solid was collected and the filtrate was acidified. There was obtained 0.5 g. of pale yellow acid which melted over the range 160-165°. After recrystallization from 50% ethanol and then from 50% acetic acid there was isolated 0.10 g. of 4-phenoxathiincarboxylic acid, m.p. and mixed m.p. 169.5-171.5°.

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[109] D. L. Esmay, Unpublished Ph.D. Thesis, Iowa State College Library, 1951.

The water-insoluble brown solid was stirred with water and the mixture was acidified. Upon filtration there was obtained 2.8 g. of a sticky, brown material which was subsequently dissolved in hot ethanol, the solution treated with Norit-A and filtered. Crystallization did not take place in absolute ethanol. When the solution was diluted with water a black oil and yellow-brown crystals separated. The crystals were decanted from the oil, collected, and recrystallized from 50% acetic acid. There was obtained 0.1 g. of yellowish-brown crystals, m.p. 253-256°. A mixture of this material and 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°) melted at 259-261°. The infrared spectra, determined on Nujol mulls of the two samples, contained no significant differences.

From the sample tray of Van Ess[54] there was procured a small amount of grey-brown needles which had been prepared by metalation of phenoxathiin with phenylcalcium iodide. A mixture of this acid (m.p. reported 260-262°, found 258-259°, with decomposition) and 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°) melted at 258-260°, with decomposition.

Preparation of dimethyl 4,6-phenoxathiindicarboxylate

To a cold, swirled, ethereal solution of approximately

0.084 mole of diazomethane[110] was added portion-wise 4.03 g. (0.014 mole) of 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°). Following evaporation of the ether, the crude product, m.p. 81-83°, was recrystallized from 10-15 ml. of methanol to yield 3.70 g. (83.5%) of pale yellow crystals, m.p. 81.5-82.5°. From a subsequent recrystallization there was obtained 3.52 g. (79.5%) of pure dimethyl 4,6-phenoxathiindicarboxylate, m.p. 82.5-83°.

Anal. Calcd. for $C_{16}H_{12}O_5S$: S, 10.13. Found: S, 9.72, 9.82.

Preparation of dimethyl 1,6-phenoxathiindicarboxylate

The reaction was carried out according to the procedure employed in the preceding preparation. There was obtained 4.45 g. of yellow solid, melting range 136-140°, which was recrystallized three times from large volumes of methanol to yield 2.65 g. of glistening, yellow plates, m.p. 150-151.5°. After a final recrystallization from 75 ml. of absolute ethanol there was obtained 2.55 g. (57.5%) of dimethyl 1,6-phenoxathiindicarboxylate, m.p. 150.5-151.5°.

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[110] F. Arndt, in "Organic Syntheses", Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

Anal. Calcd. for $C_{16}H_{12}O_5S$: S, 10.13. Found: S, 10.11, 10.08.

The low yield may be attributed either to incomplete esterification due to the insolubility of both the acid and the ester in ether or to loss during the several recrystallizations from large volumes of methanol.

Esterification of a mixture of phenoxathiindicarboxylic acids

An attempt was made to separate 1,6- and 4,6-phenoxathiindicarboxylic acid by way of the dimethyl esters. Crystallization from methanol appeared to be the ideal method of separation since the pure 4,6-ester, m.p. 82.5-83°, was fifty to one-hundred times more soluble than was the pure 1,6-ester, m.p. 150.5-151.5°.

To an ethereal solution of approximately 0.34 mole of diazomethane was added 8.06 g. (0.06 mole) of the powdered mixture of acids melting over the range 230-265°. After the ether had evaporated an attempt was made to recrystallize the residue from methanol. Oiling occurred even when crystallization was attempted from a dilute solution. No success was had when a crystal of the less soluble ester was added to induce crystallization of this product. Further attempts

to separate the esters by use of petroleum ether (b.p. 60-70°) as a solvent were unsuccessful.

Reaction of phenoxathiin-10-oxide with n-butyllithium

The results of nine runs of the reaction of phenoxathiin-10-oxide with n-butyllithium are summarized in Table 9 on the following page. Descriptions of four representative experimental procedures appear immediately after the table. The reaction, which in several cases yielded at least six products, is illustrated by the equation below.

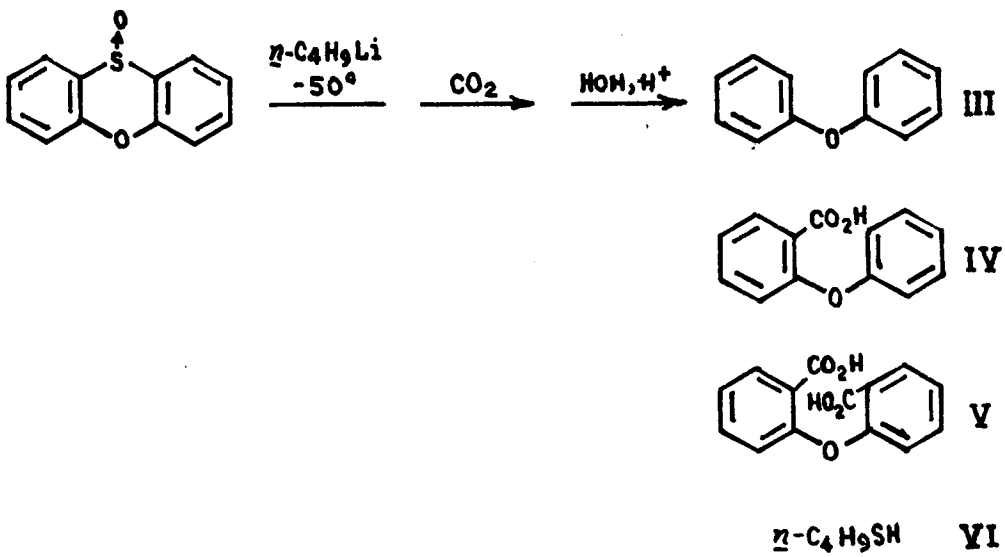

Table 9. Reaction of phenoxathiin-10-oxide with n-butyllithium

Equivalents of n-C_4H_9Li	Temp., °C.	Products, %					
		I	II	III	IV	V	VI
1	-50	37	4	18	8	---	[a]
2	-50	14[b]	2	a	a	37[c]	d
2	-50	19[b]	2	a	15	13	a
3	-50	17[b]	1	a	a	36[c]	13
3	-50	25	6	14	12	17	7
3	-50	12[b]	a	a	a	31[c]	a
1	-20,20	49[b]	-	a	-	---	-
2	-20,20	14	16	42	-	---	-
3	-20,20	[e]	21	[e]	-	---	-

[a]No isolation attempt made.

[b]Separated from III by crystallization.

[c]High yields believed due to rapid addition of n-C_4H_9Li to a concentrated mixture.

[d]Distilled as an azeotrope; derivatized, but not isolated quantitatively.

[e]A large amount of oil remained after removal of the extraction solvent. Separation into I and III by vacuum distillation not attempted.

Reaction of phenoxathiin-10-oxide with three equivalents of n-butyllithium at -50°

To a stirred suspension of 43.3 g. (0.20 mole) of phenoxathiin-10-oxide in 350 ml. of ether at -50° was added 543 ml. of a 1.18 M solution (0.64 mole) of n-butyllithium over a period of 45 minutes. All the solid had dissolved after the second equivalent had been added. Color Test I[111] was positive throughout, but Color Test II became positive only after the addition of the third equivalent and remained positive after 45 minutes at -50 ± 5°. The mixture was poured into a stirred slurry of ether-Dry Ice. After the ether had evaporated the solid carbonation mixture was extracted for 24 hours in a Soxhlet extractor with petroleum ether (b.p. 60-70°). The extract was dried and the solvent was distilled. The residue was distilled at 1.0 mm. to yield 4.6 g. (13.5%) of diphenyl ether, b.p. 78-80°, and 9.8 g. (24.5%) of phenoxathiin, b.p. 120-121°, m.p. and mixed m.p. with an authentic sample 56-57°. The identity of the diphenyl ether was proven by conversion to 4,4'-dibromodiphenyl ether. This bromination product showed no depression in m.p. (59-60°) with an authentic specimen. The solid from

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[111]H. Gilman and F. Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

the Soxhlet thimble was stirred with water, the mixture filtered and the yellow aqueous solution was extracted with ether to remove oily material. Following removal of dissolved ether from the salt solution, the latter was stirred with Norit-A, filtered and acidified with dilute hydrochloric acid. The sticky acid was collected and the filtrate saturated with sodium chloride and extracted with pentane. The acid was dissolved in dilute alkali and reprecipitated twice, the aqueous filtrate being extracted with pentane both times. The solid acid was stirred with 150 ml. of warm benzene, the mixture was allowed to cool and then filtered to yield 9.8 g. of white solid, melting range 220-227°. After crystallization from methyl ethyl ketone there was obtained 8.6 g. (16.7%) of 2,2'-dicarboxydiphenyl ether, m.p. and mixed m.p. with an authentic specimen,[112] 229-230°. The benzene solution was extracted with four 75-ml. portions of 5% sodium hydroxide solution and the warm extract was acidified. The acidic mixture was boiled and the supernatant liquid was filtered. Extraction was repeated 5 times with 200-ml. portions of hot water. Subsequent to cooling and filtration there was obtained 6.4 g. of solid melting over the range 98-103°. The product was recrystallized from hot water to

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[112]Kindly provided by Dr. R. H. F. Manske.

yield 4.9 g. (11.5%) of 2-carboxydiphenyl ether, m.p. and mixed m.p. 113-114°. The residue from the hot water extraction was washed with petroleum ether (b.p. 60-70°) and then crystallized twice from dilute acetic acid to yield 2.7 g. (5.5%) of 1-phenoxathiincarboxylic acid[113], m.p. and mixed m.p. 223-224.5°.

Distillation of the pentane extract of the acidic, aqueous filtrate yielded 1.2 g. (6.7%) of n-butyl mercaptan (b.p. 82-86°), characterized as the mercury salt which did not depress the melting point of an authentic specimen of mercury di-n-butyl mercaptide.[114]

Reaction of phenoxathiin-10-oxide with two equivalents of n-butyllithium at -50°

To a stirred suspension of 32.4 g. (0.15 mole) of phenoxathiin-10-oxide in 300 ml. of ether at -50° was added 288 ml. of a 1.10 M solution (0.32 mole) of n-butyllithium over a period of 1 hour. The mixture was stirred at -50° for 20 minutes and then carbonated. By working up the carbonation mixture as described in the preceding experiment,

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[113]An authentic specimen was kindly provided by Dr. D. A. Shirley.

[114]E. Wertheim, J. Am. Chem. Soc., 51, 3661 (1929).

except that phenoxathiin was isolated by crystallization and no attempt was made to isolate the diphenyl ether or the mercaptan, there were obtained 5.8 g. (19.3%) of phenoxathiin, 5.1 g. (13.2%) of 2,2'-dicarboxydiphenyl ether, 3.7 g. (15.1%) of 2-carboxydiphenyl ether and 0.7 g. (1.9%) of 1-phenoxathiincarboxylic acid.

Reaction of phenoxathiin-10-oxide with one equivalent of n-butyllithium at -50°

To a stirred suspension of 21.6 g. (0.10 mole) of phenoxathiin-10-oxide in 200 ml. of ether at -50° was added 81 ml. of a 1.35 M solution (0.11 mole) of n-butyllithium over a period of 15 minutes. After 1 hour of stirring at -50° ± 5° the mixture was carbonated. The procedure described for the reaction involving three equivalents was followed in the isolation of 3.0 g. (17.6%) of diphenyl ether, 7.4 g. (37.0%) of phenoxathiin, 1.7 g. (8.0%) of 2-carboxydiphenyl ether and 1.0 g. (4.1%) of 1-phenoxathiincarboxylic acid.

Reaction of phenoxathiin-10-oxide with two equivalents of n-butyllithium at -20°, room temperature

The same procedure was used as in the reaction carried

out at -50° (see p. 140) except that the neutral compounds were isolated by vacuum distillation. The n-butyllithium solution was added at -20° and the mixture was kept at this temperature for 5 hours; then it was allowed to warm to room temperature prior to carbonation. There were obtained 4.2 g. (14.0%) of phenoxathiin, 10.8 g. (42.4%) of diphenyl ether and 5.8 g. (15.8%) of 1-phenoxathiincarboxylic acid. The presence of n-butylmercaptan was not apparent, and therefore no attempt was made to isolate it.

Reaction of phenoxathiin-10-oxide with three equivalents of n-butyllithium at room temperature

To a stirred suspension of 21.6 g. (0.10 mole) of phenoxathiin-10-oxide in 200 ml. of ether was added 240 ml. of a 1.33 M solution (0.32 mole) of n-butyllithium over a period of 1.25 hours. The heat of the reaction maintained a very gentle reflux during the addition of the first two equivalents. During the course of the addition the suspension changed in color from yellow to brown. After 5 hours of stirring the mixture was carbonated and worked up as in the "General procedure" section.

The petroleum ether extract was dried and concentrated by distillation. There remained a yellow-orange oil which failed to crystallize.

The salt solution yielded a yellow acid which was collected, dissolved in dilute potassium hydroxide solution and reprecipitated by dilute hydrochloric acid. The product was contaminated by oily impurities which were subsequently removed by digestion with petroleum ether (b.p. 60-70°). The greenish-yellow solid was digested with refluxing glacial acetic acid and the suspension was filtered while hot. The acetic acid-insoluble solid was removed from the filter paper and recrystallized from methyl cellosolve to yield 2.3 g. (8.0%) of 1,6-phenoxathiindicarboxylic acid, m.p. and mixed m.p. 348-350°, with decomposition.

When the acetic acid filtrate was cooled there separated 4.0 g. of a sticky, yellow solid which was subsequently recrystallized from glacial acetic acid to yield a solid and a yellowish-brown oil. The solid, which weighed 1.2 g. and melted over the range 200-over 250°, probably consisted of a mixture of several acids.

Reaction of phenoxathiin-10-oxide with three equivalents of methyllithium at -20°, 0°

To a stirred suspension of 30.2 g. (0.14 mole) of phenoxathiin-10-oxide in 250 ml. of ether at -20° was added 565 ml. of a 0.815 M solution (0.46 mole) of methyllithium.[108]

The mixture became light orange in color during the addition of the first molar equivalent, but little change was observed during the addition of the last two equivalents. The addition was carried out over a 1.5-hour period, after which the mixture was allowed to warm to 0° over a period of 1 hour. No color change was apparent during this time. Color Test I was positive at the time of carbonation.

The pale pink carbonation mixture was allowed to stand until most of the ether had evaporated. There remained a sticky, reddish-brown mixture which was digested with petroleum ether (b.p. 60-70°) until the solid was dry enough to be placed in a Soxhlet extractor where it was extracted with petroleum ether. The red, petroleum ether extract was concentrated and allowed to cool. There was collected 16.3 g. (58.2%) of phenoxathiin which was identified by a mixed melting point determination.

The reddish-brown solid from the Soxhlet thimble was stirred with water and the aqueous mixture was filtered. Collected on the filter paper was a solid which was recrystallized from benzene (with Norit-A treatment) to yield 4.9 g. (16.2% recovery) of phenoxathiin-10-oxide, m.p. and mixed m.p. 153-155°.

The cloudy, aqueous extract was subjected to an ether extraction which removed a small amount of colored impurities.

Following the removal of dissolved ether, the aqueous solution was acidified and a small amount of gummy, rust-colored material was collected, redissolved in potassium hydroxide solution and the resulting mixture was slowly acidified. A granular, white solid first appeared, but, upon addition of more acid, a sticky, yellow material separated. The product was collected and crystallized from benzene, but was again contaminated by oily impurities. The amount of acid present was considered too small to warrant further separation attempts.

The aqueous mother liquor from the first precipitation of the acid by dilute hydrochloric acid was red-colored and was believed to contain additional product. An ether extraction was made and, following drying, the extract was concentrated. The residual red oil was not investigated.

Reaction of phenoxathiin-10-oxide with three equivalents of methyllithium at 35°

To a stirred suspension of 27.0 g. (0.125 mole) of phenoxathiin-10-oxide in 250 ml. of ether was added 425 ml. of a 0.97 M solution (0.41 mole) of methyllithium over a period of 2 hours. The reaction mixture was refluxed for 30 minutes and poured into a Dry Ice-ether slurry. The

carbonation mixture was allowed to stand overnight, was stirred with water and filtered to remove 10.6 g. (39.7% recovery) of phenoxathiin-10-oxide, m.p. and mixed m.p. 155-156.5°. The layers were separated and the ethereal layer was dried and concentrated by distillation. There remained as a residue several grams of a sticky, foul-smelling, yellow-orange solid. The material was believed to be principally phenoxathiin, contaminated by methyl mercaptan and other sulfur-containing by-products.

Following the removal of the dissolved ether, the aqueous layer was stirred with Norit-A, filtered and acidified. The yellow product was collected, redissolved in dilute alkali and reprecipitated. After the 3.6 g. of yellow solid was collected and recrystallized from methanol, there was obtained 1.9 g. of 1-phenoxathiincarboxylic acid, m.p. and mixed m.p. 222-223°.

Reaction of phenoxathiin-10-dioxide with two equivalents of n-butyllithium

To a stirred suspension of 46.4 g. (0.20 mole) of phenoxathiin-10-dioxide in 250 ml. of ether at -45° was added 320 ml. of a 1.33 M solution (0.43 mole) of n-butyllithium. After 3 hours at -45 ± 5° the mixture was allowed to warm

to -10° over a period of 1 hour. The yellow-orange suspension was poured into a stirred slurry of ether and Dry Ice. The mixture was allowed to warm to room temperature and the ether was removed by decantation. The white solid was dissolved in water and the filtered solution was acidified to yield 55.1 g. of finely divided, white solid which melted over the range 336-342°. Concentration of the aqueous filtrate yielded an additional crop of 4.1 g. of product. The total weight of acid, 59.2 g., represented a 92.5% yield of crude 1,9-phenoxathiindicarboxylic acid 10-dioxide. After two recrystallizations from large volumes of methanol there was obtained 33.4 g. (52.2%) of 1,9-phenoxathiindicarboxylic acid 10-dioxide, m.p. 354-357°, with decomposition. Another recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{14}H_8O_7S$: S, 10.01; neut. equiv., 160. Found: S, 9.82, 10.12; neut. equiv., 159, 159.

One of the small crops, 10.5 g., melting range 255-330°, obtained in the fractional recrystallization process, yielded 9.8 g. of white crystals, melting range 332-342°, after another recrystallization from methanol. In a subsequent experiment it was found that ethyl acetate was a good solvent for the separation of 1-phenoxathiincarboxylic acid 10-dioxide and 1,9-phenoxathiindicarboxylic acid 10-dioxide.

Reaction of phenoxathiin-10-dioxide with one and one-half equivalents of n-butyllithium

Shirley and Lehto[59], who obtained 1-phenoxathiincarboxylic acid 10-dioxide in yields ranging from 40 to 46% from the reaction of 0.10 mole of phenoxathiin-10-dioxide with 0.10 mole of n-butyllithium, stated that "Increasing the amount of n-butyllithium to 0.15 in the above procedure did not increase the amount of metalation acid." Since 1,9-phenoxathiindicarboxylic acid 10-dioxide is somewhat soluble in water, it is believed that the above workers missed this product. No details were provided for the reaction employing 0.15 mole of n-butyllithium.

To a stirred suspension of 23.2 g. (0.10 mole) of phenoxathiin-10-dioxide in 200 ml. of ether was added 155 ml. of a 0.97 M solution (0.15 mole) of n-butyllithium over a period of 30 minutes. The orange suspension was kept at ice-bath temperature during the addition and for a subsequent 4-hour period of stirring. (Shirley and Lehto[59] employed a 2-hour period of stirring.) The ice-bath was removed and stirring was continued for a 30-minute period, after which the mixture was allowed to run slowly into a stirred slurry of ether and Dry Ice. Following evaporation of the ether, the white solid was stirred with 1500 ml. of water and the

mixture was filtered. (Shirley and Lehto added 500 ml. of water to the mixture and separated the ether and aqueous layers. This step was not believed to be necessary since none of the expected products is soluble in ether.) When the filtered salt solution was acidified there was obtained 17.7 g. of product melting over the range 290-330°. The aqueous filtrate was made alkaline, concentrated to 400 ml., treated with Norit-A and filtered. Upon acidification there formed 9.4 g. of product melting over the range 335-341°.

The mixture of 27.1 g. of white solid, melting range 290-341°, was digested with 400 ml. of refluxing ethyl acetate and the hot mixture was filtered. Retained on the filter paper was 19.9 g. of slightly impure 1,9-phenoxathiindicarboxylic acid 10-dioxide, melting range 344-348°. Upon concentration of the ethyl acetate solution there was obtained 5.8 g. of impure product melting over the range 212-222°. The higher-melting fraction was recrystallized twice from methanol to yield 15.4 g. (48.1%) of 1,9-phenoxathiindicarboxylic acid 10-dioxide, m.p. 350-352°, with decomposition. A mixed melting point with a sample of 1,9-phenoxathiindicarboxylic acid 10-dioxide, obtained in the preceding preparation was not depressed.

After the low-melting fraction was recrystallized twice from 70% ethanol there was obtained 4.1 g. (14.9%) of 1-phenoxathiincarboxylic acid 10-dioxide, m.p. 230-232°.

The overall yield of pure products was higher in this experiment than in the preceding one in which two equivalents of n-butyllithium were employed. This higher yield is probably due to the use of ethyl acetate as the solvent for the separation of the two acids.

Reaction of phenoxathiin-10-dioxide with one equivalent of methyllithium

This experiment was conducted in an attempt to find a metalating agent which would effect only monometalation of phenoxathiin-10-dioxide.

To a stirred suspension of 23.2 g. (0.10 mole) of phenoxathiin-10-dioxide in 200 ml. of ether at 0-5° was added 84 ml. of a 1.31 M solution (0.10 mole) of methyllithium[108] over a period of 40 minutes. The pale orange suspension was stirred at ice-bath temperature for 2 hours and then allowed to warm to room temperature over a period of 1 hour. Following carbonation and evaporation of the ether, the white solid was stirred with 500 ml. of water and the mixture was filtered. There was collected 16.5 g. (77.1% recovery) of crude phenoxathiin-10-dioxide, m.p. and mixed m.p. 142-146°. The aqueous filtrate was acidified to yield 8.6 g. of white solid melting over the range 217-240°. After one

recrystallization from glacial acetic acid there was obtained 6.8 g. of white crystals, melting range 220-240°. Recrystallization from 95% ethanol yielded 5.0 g. (18.1%) of 1-phenoxathiincarboxylic acid 10-dioxide, m.p. and mixed m.p. 228-231°. The aqueous solution was concentrated and there was collected 0.9 g. (2.8%) of crude 1,9-phenoxathiindicarboxylic acid 10-dioxide, melting range 338-342°, with decomposition.

Reaction of phenoxathiin-10-dioxide with phenylcalcium iodide in tetrahydrofuran

To a stirred mixture of 46.4 g. (0.20 mole) of phenoxathiin-10-dioxide and 200 ml. of anhydrous tetrahydrofuran at 0° was added 255 ml. of a 0.86 M tetrahydrofuran solution (0.22 mole) of phenylcalcium iodide. After the half-hour addition period, followed by 2 hours at 0° and 2.5 hours at room temperature, the mixture was carbonated. The solvent was evaporated from the carbonation mixture, leaving a brownish-red, sticky mass which was digested with petroleum ether (b.p. 28-38°) until most of the oily material was removed. The resulting solid was stirred with 1 liter of water and the insoluble material was removed by filtration. The colored, aqueous filtrate was concentrated to 600 ml.,

cooled and acidified to yield 10.9 g. of pale brown product melting over the range 205-211°. After two recrystallizations from 60% ethanol there was obtained 5.1 g. (9.3%) of 1-phenoxathiincarboxylic acid 10-dioxide, m.p. and mixed m.p. 230-232°.

Preparation of dimethyl 1,9-phenoxathiindicarboxylate 10-dioxide

To a cold, vigorously swirled, ethereal solution of approximately 0.06 mole of diazomethane was added portionwise 3.2 g. (0.01 mole) of 1,9-phenoxathiindicarboxylic acid 10-dioxide (m.p. 350-352°, with decomposition). The mixture was allowed to stand for approximately 30 hours. Additional ether was added and the mixture was filtered. Upon evaporation of the ether there was collected 0.4 g. of white crystals, melting range 160-167°. After one recrystallization from methanol there was obtained 0.3 g. of slightly impure dimethyl 1,9-phenoxathiindicarboxylate 10-dioxide, m.p. 165.5-168°.

The dry, white, ether-insoluble solid was stirred with 5% sodium carbonate solution and the insoluble solid was collected by filtration and washed with water. The sodium carbonate filtrate was acidified and there was collected

0.80 g. (25.0% recovery) of 1,9-phenoxathiindicarboxylic acid 10-dioxide, identified by a mixed melting point determination.

The solid which was insoluble in sodium carbonate weighed 2.4 g. and melted over the range 167-225°. It was digested with 30 ml. of methanol and the hot mixture was filtered. Following crystallization there was collected 1.6 g. (46.0%) of dimethyl 1,9-phenoxathiindicarboxylate 10-dioxide, m.p. 170-171°. An additional recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_{16}H_{12}O_7S$: S, 9.20. Found: S, 9.07, 9.08.

Preparation of diethyl 1,9-phenoxathiindicarboxylate 10-dioxide

Into a 500-ml., three-necked flask fitted with a stopper, a stirrer and a reflux condenser equipped with a drying tube were placed 16.01 g. (0.05 mole) of 1,9-phenoxathiindicarboxylic acid 10-dioxide (m.p. 350-352°, with decomposition) and a solution of 100 g. of hydrogen chloride in 200 g. of absolute ethanol. The acid dissolved after the mixture had been stirred for 3 hours at the reflux temperature. After a 16-hour period of refluxing most of the ethanol was

distilled from the flask. The residual white solid was stirred with sodium bicarbonate solution and the mixture was filtered. Acidification of the filtrate yielded 1.0 g. of crystals, m.p. 206-207°. This material was not identified.

There was collected, following the sodium bicarbonate extraction, 16.4 g. of crude ester, melting range 138-142°, which was recrystallized from 50% ethanol to yield 14.2 g., m.p. 140-141.5°. A recrystallization from 80% ethanol yielded 12.8 g. (68.1%) of diethyl 1,9-phenoxathiindicarboxylate 10-dioxide, m.p. 143-143.5°. The melting point was not altered by another recrystallization from 80% ethanol.

Anal. Calcd. for $C_{18}H_{16}O_7S$: S, 8.52. Found: S, 8.52, 8.42.

Reaction of diphenyl ether with two equivalents of n-butyllithium

It was believed that n-butyllithium cleaved phenoxathiin-10-oxide at -50° to give 2,2'-dilithiodiphenyl ether, which subsequently metalated phenoxathiin-10-oxide when the reaction was carried out at -20° to 20°. To test the postulate, the reaction between preformed 2,2'-dilithiodiphenyl ether and phenoxathiin-10-oxide was investigated. On the basis of the metalation studies of K. Oita it was assumed that

2,2'-dilithiodiphenyl ether was formed from diphenyl ether in approximately 60% yield.

To a stirred solution of 28.7 g. (0.166 mole) of diphenyl ether in 200 ml. of ether was added 235 ml. of a 1.42 M solution (0.333 mole) of n-butyllithium and the mixture was refluxed for 130 hours. Color Test II was faintly positive after 114 hours of refluxing. A 5-ml. aliquot of the mixture was withdrawn, carbonated and worked up to yield 0.54 g., melting range 115-170° and 0.16 g., melting range 168-202°. The melting range suggests a mixture of 2-carboxy- and 2,2'-dicarboxydiphenyl ether. (A neutralization equivalent performed on the crude mixture of acids would have given a very good indication of the relative amounts of mono- and dicarboxylic acid present. Unfortunately, this operation was omitted.) The suspension of 2,2'-dilithiodiphenyl ether was used in the following experiment.

Reaction of phenoxathiin-10-oxide with 2,2'-dilithiodiphenyl ether

To a stirred suspension of 21.6 g. (0.10 mole) of phenoxathiin-10-oxide in 200 ml. of ether at -20° was added the suspension of 2,2'-dilithiodiphenyl ether (theoretical-0.10 mole) over a period of 1 hour. After 5 hours at

-20 ± 5° the orange-pink mixture was allowed to warm to 20° over a period of 1 hour and then carbonated.

When all the ether had evaporated from the carbonation mixture the dry solid was extracted overnight in a Soxhlet extractor with petroleum ether (b.p. 60-70°). The solvent-free solid from the Soxhlet thimble was stirred with water. The sticky material did not dissolve in water or in ether or in a mixture of the two solvents. After long heating in a mixture of water and acetone, most of the material dissolved and the mixture was filtered. When the filtrate was boiled to remove the acetone, a sticky, reddish-brown material separated. The supernatant salt solution was decanted from the resinous material. The latter subsequently came down as an oil after attempted crystallization from ethanol and from benzene.

The salt solution, following treatment with Norit-A and filtration, was acidified to yield an oily material. The aqueous solution was decanted from the product and the latter was dissolved in dilute sodium hydroxide solution. Into the alkaline solution was bubbled carbon dioxide, causing the precipitation of a sticky, tan-colored, semi-solid material. The phenolic material was removed from the mixture by extraction first with benzene and then with ether. Concentration of the extracts yielded a reddish-brown oil and 0.1 g.

of white crystals, m.p. 149-152°. Unsuccessful attempts were made to crystallize the reddish-brown phenolic material.

The salt solution, from which phenolic materials had been removed, was heated to expel dissolved solvents and was acidified. There was collected 19.0 g. of product, melting range 100-169°, which was digested with benzene and the mixture was filtered. The insoluble residue weighed 1.5 g. and melted over the range 231-236°, with decomposition. The benzene filtrate was extracted with dilute sodium hydroxide solution and the extract was acidified to yield 17.0 g. of white solid melting over the range 104-120°. The white solid was extracted with petroleum ether (b.p. 60-70°) in a Soxhlet extractor. After three extractions over an extended period of time, there was obtained from the extract a total of 13.2 g. (61.7% based upon 0.10 mole of 2-lithiodiphenyl ether) of 2-carboxydiphenyl ether, m.p. and mixed m.p. 112-113.5°.

The benzene-insoluble solid which weighed 1.5 g. (melting range 231-236°) was recrystallized from methanol-water (2:1) to yield 0.75 g. of white crystals of 1-phenoxathiincarboxylic acid 10-oxide, m.p. 262°, with decomposition. A mixed melting point with an authentic sample prepared by oxidation of 1-phenoxathiincarboxylic acid was not depressed.

Reactions Involving 2-Substituted Phenoxathiins

Friedel-Crafts acetylation of phenoxathiin[22,25,35,52,65]

Run I. Into a one-liter, four-necked flask fitted with a stirrer, a reflux condenser, a thermometer and a graduated separatory funnel containing a solution of 40.0 g. (0.51 mole) of acetyl chloride in 200 ml. of dry carbon disulfide were placed 100.0 g. (0.50 mole) of phenoxathiin, 80.0 g. (0.60 mole) of anhydrous aluminum chloride and 300 ml. of dry carbon disulfide. The acetyl chloride solution was added to the stirred mixture at 30° over a period of 5 hours. Immediately following the addition the tarry mixture became so viscous that it could not be stirred. The reaction mixture was allowed to stand overnight and was poured into a stirred mixture of ice and hydrochloric acid. After filtration had removed a small amount of sticky material, the layers were separated and the carbon disulfide layer was washed with dilute sodium bicarbonate solution and with water. The carbon disulfide solution was dried over Drierite and transferred to a distillation flask from which were distilled the carbon disulfide at atmospheric pressure, followed by the principal fraction at a pressure of 0.6 mm. There was collected 69.1 g. of distillate which boiled over

the range 116-130°. The residue which remained in the distillation flask would not distill at a pressure of 0.01 mm. and a bath temperature of 230°.

A solution of the distillate in petroleum ether (b.p. 60-70°) was allowed to percolate through a chromatography column packed with anhydrous alumina. After elution with petroleum ether there was collected 58.7 g. (58.7% recovery) of phenoxathiin, m.p. and mixed m.p. 56-57°. Elution with a mixture of ethanol and petroleum ether yielded a sticky, yellow material which was crystallized from ethanol. The yellow crystals weighed 1.6 g. and melted over the range 100-110°. No pure product was obtained.

Run II. In a one-liter, four-necked flask fitted with a stirrer, a reflux condenser, a thermometer and a separatory funnel containing a solution of 100.0 g. (0.50 mole) of phenoxathiin and 41.0 g. (0.52 mole) of acetyl chloride in 350 ml. of dry carbon disulfide was placed a suspension of 69.5 g. (0.52 mole) of anhydrous aluminum chloride in 150 ml. of dry carbon disulfide. The solution was added to the stirred mixture at 30° over a period of 4 hours. After an additional 4-hour period of stirring at the reflux temperature, the mixture was allowed to stand overnight and poured into a slurry of ice and hydrochloric acid. Upon filtration there was collected 9.8 g. of tan solid, melting range

180-184°, which was recrystallized twice from chloroform to yield 6.8 g. (4.8%) of pure 2,8-diacetylphenoxathiin, m.p. 186-187°. (The melting point has been reported as 175° by Tomita[65] and 184-186° by Nobis and coworkers.[52]) A mixture of the product and an authentic specimen[115] (m.p. found 174-179°) of 2,8-diacetylphenoxathiin melted over the range 175-182°. The infrared spectra of the authentic specimen and the product were superimposable.

The layers of the filtrate were separated. After having been washed with 10% sodium carbonate solution and with water, the carbon disulfide solution was dried over Drierite. Following the removal of the carbon disulfide, the products were distilled at 0.2 mm. There were collected 38.2 g., boiling range 103-113° and 37.3 g., boiling range 130-163°. The residue was recrystallized (with Norit-A treatment) from chloroform to yield 6.7 g. of crude 2,8-diacetylphenoxathiin, melting range 171-176°.

All the first distillation fraction and approximately one-half the second fraction were soluble in petroleum ether (b.p. 60-70°). The insoluble material weighed 16.7 g. and melted over the range 98-106°. The petroleum ether solution was allowed to percolate through a chromatography column

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[115]Kindly provided by Dr. M. Tomita.

packed with anhydrous alumina and the mixture was eluted with petroleum ether (b.p. 60-70°). The solution obtained from the column yielded 39.5 g. (39.5% recovery of phenoxathiin) m.p. and mixed m.p. 56-57°. The alumina from which the phenoxathiin had been removed was extracted with ethanol. The pale yellow extract was employed as the recrystallization solvent for the 16.7 g. of material, melting range 98-106°. Following recrystallization there were obtained 20.0 g. of yellow solid, melting range 104-108° and 5.8 g., melting range 86-91°. The larger fraction was recrystallized four times from methanol. The weights and melting ranges of the fractions after the successive recrystallizations were 16.8 g., 107-112.5°; 12.8 g., 111-115.5°; 8.1 g., 114-119.5° and 4.3 g., 115.5-119°. The last crop was recrystallized from petroleum ether (b.p. 60-70°) to yield 3.0 g. (2.5%) of 2-acetylphenoxathiin, m.p. 116.5-118.5°. The melting point of 2-acetylphenoxathiin has been reported as 111-112°[35] and 117.5-118°.[52] From the mother liquors there was recovered in three crops a total of 14.7 g. of yellow solid which melted over the range 106-118.5°.

The crude mixture which was obtained following the chromatographic procedure probably contained, in addition to 2-acetylphenoxathiin, small amounts of phenoxathiin, another acetylphenoxathiin and diacetylphenoxathiin. The

results of the following experiment revealed that 2-acetylphenoxathiin oxime was more readily purified than was the corresponding ketone.

Preparation of 2-acetylphenoxathiin oxime

In a 250-ml., three-necked flask fitted with a stopper, a stirrer and a reflux condenser were placed 12.11 g. (0.05 mole) of crude 2-acetylphenoxathiin (melting range 106-118.5°), 9.73 g. (0.14 mole) of hydroxylamine hydrochloride, 30 ml. of absolute ethanol and 45 ml. of dry pyridine. After the yellow mixture had been stirred at the reflux temperature for 3 hours, 40 ml. of the solvent was removed by distillation and the mixture was poured into water. Upon filtration there was collected 13.0 g. (100%) of crude, white product which melted over the range 140-150°. Upon recrystallization from ethanol (with Norit-A treatment) there was obtained 6.3 g. of 2-acetylphenoxathiin oxime, m.p. 156-158°. The mother liquor yielded 3.2 g., m.p. 154-156°. The combined material represents a 73.8% yield of slightly impure 2-acetylphenoxathiin oxime. The melting points reported for 2-acetylphenoxathiin oxime are 142-143°[35] and 158-159.5°.[52]

Preparation of 2-aminophenoxathiin by the Beckmann rearrangement of 2-acetylphenoxathiin oxime

In a 500-ml., four-necked flask fitted with a stirrer, a reflux condenser, a thermometer and a rubber tube with an attached flask containing 9.0 g. (0.043 mole) of phosphorus pentachloride were placed 9.0 g. (0.035 mole) of 2-acetylphenoxathiin oxime (m.p. 154-158°) and 150 ml. of sodium-dried benzene. The stirred suspension was warmed to 40° and the phosphorus pentachloride was added over a period of 30 minutes. After the apparent reaction had ceased the orange solution was stirred for 2 hours.

The reaction mixture was poured in water, neutralized with sodium carbonate and the benzene was removed by steam distillation. After the residue had been refluxed for 4 hours with 20% hydrochloric acid, the hot mixture was filtered. The insoluble residue was washed several times with hot water and the washings were combined with the original filtrate. After the filtrate had been made alkaline with ammonium hydroxide there was collected 6.1 g. (81.1%) of 2-aminophenoxathiin, m.p. 93-95°. The compound has been reported to melt at 93-95°[52] and 98°.[50]

Preparation of 2-bromophenoxathiin by the Sandmeyer reaction

Run I. To a cold solution of 0.024 mole of nitrosylsulfuric acid[116] was added a solution of 4.3 g. (0.020 mole) of 2-aminophenoxathiin (m.p. 93-95°) in 50 ml. of glacial acetic acid. The diazotization mixture was first purple, then brown in color. The mixture was allowed to warm to 12° over a period of 45 minutes and added to a hot solution of 0.015 mole of freshly prepared cuprous bromide[117] in 75 ml. of 48% hydrobromic acid. After the 15-minute addition period the stirred mixture was heated on a water bath for 1 hour, poured into an ice-water slurry and a sticky, brown solid was collected. After the solid had been dissolved in hot methanol, the solution was treated with Norit-A and filtered. The semi-solid, yellow material which separated was collected and crystallized from methanol-water. The resulting crystals weighed 0.4 g. and melted over the range 78-84°. Further attempts to isolate pure material were unsuccessful.

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[116] H. H. Hodgson and J. Walker, J. Chem. Soc., 1620 (1933).

[117] A. I. Vogel, "A Textbook of Practical Organic Chemistry", Longmans, Green and Company, New York, N. Y., 1948, p. 187.

Run II. A suspension of 1.75 g. (0.006 mole) of 2-aminophenoxathiin hydrobromide in 50 ml. of dilute hydrobromic acid was heated to 90-95° and then cooled rapidly. To the stirred suspension at 0° was added over a period of 20 minutes a solution of 0.49 g. (0.007 mole) of sodium nitrite in 2.5 ml. of water. The orange diazotization mixture was stirred at 0-5° for 1 hour.

A solution of cuprous bromide was prepared by dissolving approximately 0.004 mole of freshly prepared cuprous bromide[117] in 8.5 ml. of 48% hydrobromic acid. The purple bromide solution was diluted with 10 ml. of water. (This dilution step may have been unnecessary.) To the stirred cuprous bromide solution at room temperature was added the cold, orange-colored diazotization mixture. After a 15-minute period of stirring at room temperature, followed by an equal period at approximately 100°, the mixture consisted of a dark brown oil and a green aqueous solution. The contents of the flask were cooled and the aqueous solution was decanted. The residue was digested three times with dilute methanol and the methanol extracts were combined, treated with Norit-A and filtered. Following crystallization there was obtained 0.64 g. (39.5%) of white crystals of 2-bromophenoxathiin, m.p. 89-90°. There was no depression in the melting point of the mixture consisting of the above product

and a sample of the 2-bromophenoxathiin (m.p. 90-91°) which was prepared by reduction of 2-bromophenoxathiin-10-dioxide. (See "Preparation of 2-bromophenoxathiin".)

Reactions Involving 2-Substituted Phenoxathiin-10-dioxides

Preparation of 2-nitrophenoxathiin-10-dioxide

This reaction was carried out according to the procedure of Nobis, Blardinelli and Blaney[52], who reported a 43% yield of 2-nitrophenoxathiin-10-dioxide, m.p. 192-194°.

To a stirred solution of 232 g. (1.0 mole) of phenoxathiin-10-dioxide (m.p. 147-148°) in 900 ml. of glacial acetic acid was added 720 ml. (17.3 moles) of nitric acid (sp. gr. 1.5) over a period of 1.5 hours. The solution was stirred at the reflux temperature for 4 hours and then allowed to stand overnight in the refrigerator. Subsequent to filtration, washing and drying, the crystals weighed 218 g. and melted over the range 181-186°. After two recrystallizations from large volumes of acetone there was obtained 140 g. (50.5%) of 2-nitrophenoxathiin-10-dioxide, m.p. 187-190°.

Preparation of 2-aminophenoxathiin-10-dioxide by reduction of 2-nitrophenoxathiin-10-dioxide

This reaction was carried out according to the procedure of Nobis and coworkers[52], who obtained a 60% yield of 2-aminophenoxathiin-10-dioxide melting at 163-164.5°. Two modifications of the work-up procedure are mentioned in the description of the experiment.

In a two-liter, three-necked flask fitted with a stirrer, a reflux condenser and a thermometer were placed 90.0 g. (0.325 mole) of 2-nitrophenoxathiin-10-dioxide (m.p. 187-190°), 296 g. (1.32 moles) of stannous chloride dihydrate and 850 ml. of glacial acetic acid which had been saturated with hydrogen chloride. The solid dissolved upon stirring and the temperature rose spontaneously to 100°. After the mixture was stirred at 110-115° for 7 hours, it was allowed to cool and the crystalline product was collected by filtration. (Nobis and coworkers did not isolate the amine salt.) An aqueous suspension of the salt was made alkaline with dilute potassium hydroxide solution and the solid was collected. This crude amine was dissolved in hot, dilute hydrochloric acid, the solution was filtered while hot and the filtrate was made alkaline with potassium hydroxide solution. The product, 32.1 g., melting range 164-173°, was recrystallized twice

from methanol-water (1:1) to yield 27.1 g. of white crystals melting over the range 164-176°. The first recrystallization from acetone-water (1:1) yielded 22.0 g. (27.4%), melting range 169-176.5°. From a subsequent recrystallization using this solvent there was obtained 20.0 g. of product melting over the range 169-176°. Recrystallization from chloroform did not alter the melting range. The melting point was taken at various rates of heating and the sample was placed in the melting point bath at several temperatures with no effect upon the melting range. A sample was placed in a test tube, melted at 176°, allowed to cool, removed and pulverized. The melting point of this material was 175.5-176.0°, with no change at 169°. The infrared spectra of the two samples (in potassium bromide pellets) melting at 169-176° and 175.5-176.0° were almost identical. The results indicate that there may be two crystalline forms of 2-aminophenoxathiin-10-dioxide.

Anal. Calcd. for $C_{12}H_9NO_3S$: S, 12.95. Found: S, 12.83, 12.88.

The original acetic acid mother liquor which remained following the removal of the crystalline amine salt was treated with sodium hydroxide until the mixture was alkaline. The voluminous solid mixture, which probably consisted of sodium acetate, tin salts, unreacted nitro compound and the

amine, was collected by filtration and digested several times with hot methanol. Concentration of the methanol extracts yielded a solid which was stirred with hot, dilute hydrochloric acid and the hot mixture was filtered. (Nobis and coworkers did not carry out this procedure involving treatment of the mixture with acid, followed by reprecipitation of the amine.) After the filtrate was made alkaline with ammonium hydroxide there was collected 24.4 g. of solid melting over the range 148-160°. Successive recrystallizations from acetone-water (1:1) and methanol-water (2:1) did not alter the melting range significantly. The white crystals melted over the range 164-172° after recrystallization from chloroform.

Preparation of 2-chlorophenoxathiin-10-dioxide by the Sandmeyer reaction

To a stirred solution of 0.022 mole of nitrosylsulfuric acid[116] at 5° was added a solution of 4.94 g. (0.20 mole) of 2-aminophenoxathiin-10-dioxide (melting range 169-176°) in 60 ml. of glacial acetic acid. The temperature of the diazotization mixture was maintained at 5-10° during the 15-minute addition period and for an additional period of 30 minutes. The mixture was allowed to warm to 15° over an interval of 45 minutes.

Into a 250-ml. flask fitted with a stirrer was placed a solution of 0.012 mole of freshly prepared cuprous chloride[118] in 10 ml. of concentrated hydrochloric acid. To the stirred solution which was heated by a water-bath was added the diazotization mixture described above. After the 15-minute addition period the dark green solution was stirred for 1 hour and then poured upon crushed ice. Following filtration, washing with water and drying there was obtained 5.05 g. (95%) of crude 2-chlorophenoxathiin-10-dioxide melting over the range 153-158°. Successive recrystallizations from ethanol and aqueous acetic acid yielded 4.00 g., m.p. 157-159° (sintering at 153°) and 3.85 g. (72.2%) of 2-chlorophenoxathiin-10-dioxide, m.p. 158-159°. A mixed melting point with an authentic sample[119] was not depressed.

Preparation of 2-bromophenoxathiin-10-dioxide by the Sandmeyer reaction

To a stirred solution of 0.46 mole of nitrosylsulfuric acid at 5° was added a solution of 9.89 g. (0.040 mole) of 2-aminophenoxathiin-10-dioxide (melting range 169-176°) in

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[118] L. F. Fieser, "Experiments in Organic Chemistry", D. C. Heath and Company, New York, N. Y., 1941, p. 215.

[119] Kindly provided by Dr. C. M. Suter.

110 ml. of glacial acetic acid. The addition required a period of 20 minutes. After an additional 1-hour period at 5-10° the mixture was allowed to warm to 15° and was transferred to a separatory funnel.

In a 500-ml. flask fitted with a stirrer was placed a solution of 0.023 mole of freshly prepared cuprous bromide[117] in 125 ml. of 48% hydrobromic acid. To the purple solution which was heated by a water-bath was added the diazotization mixture described above. After 1.5 hours of stirring the purple mixture was poured upon crushed ice. There was obtained 11.2 g. (90%) of crude 2-bromophenoxathiin-10-dioxide melting over the range 170-176°. The material was recrystallized from ethanol to yield 9.6 g. of white crystals, m.p. 175.5-177°. Subsequent to recrystallization from glacial acetic acid there was obtained 7.1 g. (57.0%) of 2-bromophenoxathiin-10-dioxide, m.p. 177-178°. Another recrystallization from glacial acetic acid produced no change in the melting point.

Anal. Calcd. for $C_{12}H_7BrO_3S$: S, 10.30. Found: S, 10.23, 10.12.

Preparation of 2-iodophenoxathiin-10-dioxide from 2-aminophenoxathiin-10-dioxide

To a stirred solution of 0.022 mole of nitrosylsulfuric

acid[116] at 4-8° was added a solution of 4.94 g. (0.020 mole) of 2-aminophenoxathiin-10-dioxide (melting range 169-176°) in 60 ml. of glacial acetic acid. After the yellow mixture had been stirred for approximately 1 hour there was added 0.2 g. of urea (to remove excess nitrous acid) followed by a solution of 3.65 g. (0.022 mole) of potassium iodide in 40 ml. of water. When the dark brown mixture had warmed to 60-70° the excess iodine was removed by the addition of 5% sodium bisulfite solution. The mixture was stirred for 30 minutes, poured upon ice and the tan solid was collected by filtration. Upon recrystallization from aqueous acetic acid there resulted a red oil and a white solid which were separated manually. The white solid was digested five times with 75-ml. portions of hot petroleum ether (b.p. 60-70°). The pink material which did not dissolve melted over the range 120-160°. From the petroleum ether solution there was obtained 1.84 g. of product, m.p. 167-169°, which was recrystallized from aqueous acetic acid to yield 1.43 g. (20.0%) of 2-iodophenoxathiin-10-dioxide, m.p. 171-172°. A subsequent recrystallization from acetic acid-ethyl acetate did not change the melting point. (For the analysis see "Preparation of 2-iodophenoxathiin-10-dioxide by iodination of phenoxathiin-10-dioxide".)

Reduction of the Sulfone Group by Lithium Aluminum Hydride[74]

Preparation of phenoxathiin

In a 250-ml., three-necked flask fitted with a stirrer, two nitrogen inlet tubes and a reflux condenser were placed 5.80 g. (0.025 mole) of phenoxathiin-10-dioxide, 125 ml. of anhydrous ether and 1.42 g. (0.038 mole) of powdered lithium aluminum hydride. The ether began to reflux immediately upon the addition of the hydride. When the refluxing subsided heat was applied to the stirred mixture. After 18 hours of refluxing* the suspension was allowed to cool and the excess hydride was decomposed by the cautious addition of ethyl acetate, followed by wet ether, water and dilute hydrochloric acid. An emulsion was broken by the addition of approximately 30 ml. of 10% hydrochloric acid. The layers were separated and the aqueous layer was extracted with ether. After the ethereal extract had been dried over Drierite, the ether was removed by distillation. The residual oil was cooled and the resulting crystals were collected, washed with cold methanol and dried under reduced pressure. There was

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*A much shorter reaction period may have been sufficient.

obtained 2.64 g. (52.8%) of phenoxathiin, m.p. and mixed m.p. 53-55°.

Preparation of 2-chlorophenoxathiin

In a 250-ml., three-necked flask fitted with a stirrer, two nitrogen inlet tubes and a separatory funnel containing a suspension of 0.61 g. (0.016 mole) of powdered lithium aluminum hydride in 75 ml. of anhydrous ether was placed a suspension of 3.20 g. (0.012 mole) of 2-chlorophenoxathiin-10-dioxide (m.p. 158-159°) in 50 ml. of anhydrous ether. The hydride-suspension was added to the stirred mixture, causing very mild refluxing and the appearance of a yellow-grey color. After 22 hours of refluxing, the mixture was worked up as in the preceding experiment. The ether solution yielded an oil which consisted of 2-chlorophenoxathiin and unreacted 2-chlorophenoxathiin-10-dioxide. A 6% recovery of the latter compound was made. The 10-dioxide, being less soluble than 2-chlorophenoxathiin, prevented the isolation of the product by a conventional recrystallization procedure. Separation was accomplished by digestion of the mixture with petroleum ether (b.p. 28-38°), which dissolved only the un-oxidized compound. From the petroleum ether extracts there was obtained 0.61 g. (21.5%) of 2-chlorophenoxathiin, m.p.

88-89°. A mixed melting point with an authentic specimen[119] was not depressed.

Preparation of 2-bromophenoxathiin

In a 250-ml., three-necked flask fitted with a stirrer, two nitrogen inlet tubes and a reflux condenser was placed a suspension of 6.23 g. (0.02 mole) of 2-bromophenoxathiin-10-dioxide (m.p. 177-178°) in 125 ml. of anhydrous ether. To the cold suspension was added in one portion 1.14 g. (0.03 mole) of powdered lithium aluminum hydride. The mixture was stirred at room temperature for 45 minutes, then at the reflux temperature for 20 hours. Following decomposition of the excess hydride the layers were separated and the ethereal layer was dried. After distillation of the ether there was obtained a white solid which was recrystallized twice from ethanol. The resulting 1.25 g. of white needles, m.p. 89-90.5°, was recrystallized again from ethanol to yield 1.10 g. (19.7%) of 2-bromophenoxathiin, m.p. 90-90.5°. A final recrystallization from methanol did not alter the melting point.

Anal. Calcd. for $C_{12}H_7BrOS$: Br, 28.63; S, 11.49. Found: Br, 28.81, 28.65; S, 11.53, 11.55.

The infrared spectrum of 2-bromophenoxathiin was compared with that of 2-chlorophenoxathiin, both samples having been run as Nujol mulls and in carbon disulfide solutions. In the region 2-16μ there was no significant difference in the spectra of the two compounds. The spectrum of each of the two samples run in carbon disulfide contained 15 distinct absorption bands between 7.3 and 14.7μ.

Halogenation Reactions

Reaction of phenoxathiin with sulfuryl chloride in pentane

In a 250-ml., three-necked flask fitted with a stirrer, a reflux condenser and a separatory funnel containing a solution of 28.4 g. (0.21 mole) of sulfuryl chloride in 50 ml. of dry pentane was placed a solution of 40.0 g. (0.20 mole) of phenoxathiin in 100 ml. of pentane. The sulfuryl chloride was added to the yellow-orange refluxing mixture over a period of 2 hours. The yellow color disappeared during the subsequent 15-hour reflux period. After the mixture had been cooled and filtered there was collected 9.0 g. of white solid melting over the range 103-124°. The solid was recrystallized from a large volume of methanol to yield 3.0 g. of white crystals, melting range 146-168°.

Concentration of the mother liquor gave 2.5 g. of white solid, melting range 64-70°, 0.6 g., melting range 38-49° and an oil. The pentane mother liquor from the first crop of solid yielded 20.5 g. of white product melting over the range 38-55°.

The material melting over the range 146-168° was recrystallized from approximately 200 ml. of petroleum ether (b.p. 60-70°) to yield 2.1 g. of glistening, white plates, m.p. 168-169°. This compound is believed to be the same as the _,_-dichlorophenoxathiin, m.p. 166-167°, which Irie[50] obtained by direct chlorination of phenoxathiin. Irie[50] proved that the compound was not 2,8-dichlorophenoxathiin.

Five fractions of solid having melting ranges from 38 to 80° were combined into one batch weighing 29.4 grams. The material was dissolved in methanol and the following fractions were obtained upon recrystallization: 6.3 g., melting range 57-87°; 8.0 g., melting range 64-73°; 10.1 g., melting range 35-48° and an oil. The material melting over the range 64-73° was recrystallized from methanol to yield 4.5 g. of white crystals, melting range 72-78°. Another recrystallization yielded 3.3 g. of product, m.p. 77-80°. The melting point was raised to 79-81° by a recrystallization from petroleum ether (b.p. 60-70°). Another recrystallization from the same solvent did not alter the melting point

of the 1.8 g. of white crystals. The compound is believed to be 3-chlorophenoxathiin.

Anal. Calcd. for $C_{12}H_7ClOS$: S, 13.66. Found: S, 13.53, 13.43.

A sample of the material melting over the range 57-87° was analyzed and the percentages of sulfur were found to be 12.87 and 13.04. The values suggest that the mixture consisted of a chlorophenoxathiin contaminated by a _,_-dichlorophenoxathiin.

Among the many samples which were kindly provided by Dr. C. M. Suter was one designated as 3-chlorophenoxathiin (m.p. reported[34] 59-60°). The melting point on the label of the sample bottle was 58-59°, but the material was found to melt over the range 61-67°. An unsuccessful attempt was made to purify the solid by a conventional recrystallization from methanol. However, using tweezers and a small spatula there were separated diamond-shaped (m.p. 93-96°) and needle-like (m.p. 80-82°) crystals. The latter melting point is the same as that reported by Suter and Green[34] for the product of chlorination of phenoxathiin.

The infrared spectra were determined on carbon disulfide solutions of the samples. The spectrum of the original material (melting range 61-67°) contained twelve bands in the region 9.2-14.7μ. In this same region the spectrum of the

material melting at 80-82° contained eight bands, while that of the material melting at 93-96° contained seven bands. There were three bands, those at 9.7, 10.9 and 13.3μ, which were common to all three spectra.

A mixture of the crystals melting at 80-82° and those (m.p. 79-81°) obtained by chlorination of phenoxathiin with sulfuryl chloride showed no depression in melting point. The infrared spectra of the samples were superimposable, leaving no doubt that only one compound was involved.

There was much similarity in the infrared spectra of 2- (m.p. 88-89°) and 3-chlorophenoxathiin (m.p. ca. 80°), as would be expected since both compounds contain 1,2,4-trisubstituted benzene ring systems. The most notable difference was the presence in the spectrum of the 2-derivative of sharp bands at 12.1 and 12.4μ, whereas the 3-derivative exhibited one band at 12.5μ. The spectrum of the unknown material (m.p. 93-96°) contained no band between 12.0 and 12.9μ.

Preparation of 2-bromophenoxathiin and 2,8-dibromophenoxathiin by direct bromination (attempted)

The first run was carried out according to the procedure of Suter, McKenzie and Maxwell.[35] These workers obtained

2-bromophenoxathiin, m.p. 59-60°, and 2,8-dibromophenoxathiin, m.p. 92-93°, in yields of 83 and 75%, respectively by the direct bromination of phenoxathiin. All the bromination reactions were carried out before two unambiguous syntheses (see "Preparation of 2-bromophenoxathiin by the Sandmeyer reaction" and "Preparation of 2-bromophenoxathiin") revealed that 2-bromophenoxathiin melted at 90-91°.

Run I. In a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a separatory funnel containing 83.2 g. (0.52 mole) of bromine were placed 100 g. (0.50 mole) of phenoxathiin and 500 ml. of carbon tetrachloride. The bromine was added to the refluxing solution over a period of 2.5 hours. After the mixture was refluxed for 15 hours it was allowed to cool, treated with Norit-A and filtered. The volume of the mixture was reduced to approximately 100 ml. The residue solidified to give 135 g. of an oily product.

A 10-g. sample of the product was recrystallized from approximately 500 ml. of methanol. A total of 7.1 g. of white solid was obtained from three batches, each of which had an approximate melting range of 64-75°. The material was recrystallized from ca. 400 ml. of methanol to yield 5.2 g. of amorphous, white solid, melting range 66-76°.

An attempt was made to purify the material by distillation of a 10-g. sample which had been crystallized from methanol. The only distillate was 2.2 g. of white product, melting range 75-80°, which was collected at 180°/0.08 mm. After two recrystallizations from methanol there was obtained a small amount of needles melting over the range 78-83°.

Run II. In this experiment a solution of bromine in carbon tetrachloride was added to the refluxing, stirred solution of phenoxathiin. The mixture was worked up as before. Successive recrystallizations from methanol gave white, amorphous solids having melting ranges of 56-66°, 63-69° and 69-78°. Following a recrystallization from methanol-benzene (10:1) there was obtained a small amount of white solid melting over the range 95-113°.

Run III. A solution of bromine in carbon tetrachloride was added to a refluxing, stirred solution of phenoxathiin in carbon tetrachloride. The product distilled at 122-123°/0.014 mm. The distillate, a white, oily solid, was recrystallized from methanol-benzene (10:1) to yield white solid which melted over the range 51-66°. Following chromatography of a petroleum ether (b.p. 60-70°) solution of the distillate there were collected fractions of white solid having melting ranges of 49-56°, 63-76° and 67-88°. The melting ranges were

not narrowed significantly by subsequent recrystallizations from methanol.

Run IV. In this run a carbon tetrachloride solution of two molar equivalents of bromine was added to a refluxing, stirred solution of phenoxathiin in carbon tetrachloride. The crude product, which melted over the range 80-100°, was recrystallized from methanol-isopropyl alcohol to yield white solid, melting range 119-126°. Further purification was not achieved by chromatography or by recrystallization. When a sample of the crude product was recrystallized from benzene, vacuum distilled and recrystallized from methanol, there was obtained a white solid melting over the range 115-122°. No pure product was obtained.

Run V. This and the following run were carried out in an attempt to determine whether the presence of water had an effect on the reaction.

A solution of bromine in 93% aqueous acetic acid was added to a warm, stirred solution of phenoxathiin in glacial acetic acid. Upon completion of the reaction the mixture was poured into an ice-water mixture. A sample of the product was recrystallized from methanol, vacuum-distilled, recrystallized from ethanol-water and petroleum ether (b.p. 60-70°). There were isolated white solids melting over the ranges 50-62° and 79-84°. Subsequent recrystallizations of

the higher-melting fraction raised the melting range to 81.5-85.5°. No pure product was isolated.

Run VI. In a 500-ml., three-necked flask fitted with a stirrer, a reflux condenser and a graduated separatory funnel containing 50 ml. of dry pentane was placed a solution of 40.0 g. (0.20 mole) of phenoxathiin in 100 ml. of dry pentane. Approximately 34 g. of bromine was distilled from phosphorus pentoxide into the separatory funnel. The bromine solution was added to the refluxing mixture over a period of 2 hours. A red-brown solid formed during the addition. The solid, believed to be the thionium bromide, was not observed in any of the previous bromination reactions. Dissolution of the solid occurred after a 12-hour reflux period. After 40 hours of refluxing the pale orange solution had ceased to evolve a significant amount of hydrogen bromide. Precautions were taken to avoid moisture during the distillation of 250 ml. of the solvent from the reaction flask. The residue was transferred to a distillation flask from which the product was distilled at 1.0 mm. There were collected 7.1 g. of first fraction, boiling range 100-135° and 16.4 g., boiling point 135-136°. After collection of the second fraction the distillation ceased even though the bath temperature was increased to 250°.

No pure product was isolated when the two fractions were recrystallized from methanol or from mixtures of methanol and petroleum ether (b.p. 60-70°). The residue which did not distill was recrystallized from methanol to yield 6.1 g. of white solid, melting range 74-99°. From the mother liquor there was obtained 3.1 g. of white material, melting range 64-73°.

The percentages of sulfur found by analysis of the samples melting at 74-99° and 64-73° were 9.59 and 9.92, respectively. The calculated percentages of sulfur in bromo- and dibromophenoxathiin are 11.48 and 8.95, respectively. The analytical data indicate that the mixture probably contained a considerable amount of dibromophenoxathiin. If this were the case it is likely that a significant quantity of unreacted phenoxathiin was also present in the crude mixture.

Preparation of 2-bromophenoxathiin-10-dioxide by bromination of phenoxathiin-10-dioxide (attempted)

To a stirred, refluxing solution of 11.6 g. (0.05 mole) of phenoxathiin-10-dioxide in 50 ml. of glacial acetic acid was added a solution of 9.3 g. (0.06 mole) of bromine in 50 ml. of glacial acetic acid. After 3 hours of refluxing, at

which time the solution was pale red in color, the initial evolution of hydrogen bromide was observed. An additional 2-g. portion of bromine was added to the mixture. After 18 hours of refluxing the dark-colored solution was concentrated by distillation of 65 ml. of the solvent. Norit-A was added to the solution in the reaction flask and, after the warm mixture was stirred, it was filtered. The filtrate was cooled and there was collected 8.3 g. (71.5% recovery) of starting material, m.p. and mixed m.p. with an authentic sample of phenoxathiin-10-dioxide 147-148.5°. The mother liquor was concentrated and, after the addition of water, there was obtained 2.3 g. of phenoxathiin-10-dioxide, m.p. and mixed m.p. 147-148°. The total recovery of starting material was 91.3%.

Preparation of 2-iodophenoxathiin-10-dioxide by iodination of phenoxathiin-10-dioxide

To a stirred mixture consisting of 23.2 g. (0.10 mole) of phenoxathiin-10-dioxide, 25.4 g. (0.10 mole) of iodine and 125 ml. of chloroform was added slowly 7.0 ml. of concentrated nitric acid. After 18 hours of refluxing another 7.0-ml. portion of nitric acid was added and the mixture was refluxed for an additional 20-hour period. The reaction

flask was cooled in an ice-bath and the chloroform solution was decanted from the large amount of crystalline iodine. The chloroform solution was washed successively with 5% sodium hydroxide solution, 5% sodium bisulfite solution and with water and dried. The solvent was distilled and there was collected 27.1 g. of yellow solid melting over the range 120-150°. The product was recrystallized (with Norit-A treatment) from a mixture of ethyl acetate and acetic acid to yield 12.3 g. of white solid, melting range 150-165°. After three recrystallizations from ethyl acetate- acetic acid there was isolated 4.3 g. (12.0%) of 2-iodophenoxathiin-10-dioxide, m.p. 171-172°. A mixed melting point with a sample of 2-iodophenoxathiin-10-dioxide which was prepared from 2-aminophenoxathiin-10-dioxide was not depressed.

Anal. Calcd. for $C_{12}H_7IO_3S$: I, 35.44; S, 8.95. Found: I, 35.59, 35.32; S, 9.17, 9.02.

Oxidation Reactions

Preparation of phenoxathiin-10-oxide by oxidation of phenoxathiin in ethanol with hydrogen peroxide (attempted)

Gilman and Esmay[51] prepared phenoxathiin-10-oxide in yields of 96 and 98% by oxidation of phenoxathiin in ethanol

with hydrogen peroxide. Though the preparation was successfully repeated on the 0.05-mole scale described in the literature, the reaction yielded no pure product in an attempt on a 0.60-mole scale.[120] The second attempt is described below.

To a stirred, refluxing solution of 80.0 g. (0.40 mole) of phenoxathiin in 1500 ml. of absolute ethanol was added dropwise 240 ml. (2.48 moles) of 30% aqueous hydrogen peroxide over a period of 1 hour. After 4 hours of refluxing an additional 160 ml.-portion of the peroxide was added over a period of 1 hour. The reaction mixture was refluxed for 16 hours, concentrated to 500 ml. and diluted to turbidity with hot water. Following filtration and drying, the material weighed 84.0 g. and melted over the range 110-132°. Recrystallization from benzene yielded 38.8 g. (41.8%) of slightly impure phenoxathiin-10-dioxide, m.p. 143-147°, mixed m.p. 146-148°. The mother liquor yielded 34.0 g. of material melting over the range 110-135°.

Preparation of phenoxathiin-10-oxide by oxidation of phenoxathiin with dilute nitric acid

To a stirred, refluxing solution of 200 g. (1.0 mole)

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[120] M. B. Hughes, Unpublished Studies.

of phenoxathiin in 2400 ml. of glacial acetic was added 325 ml. (2.0 moles) of dilute nitric acid (sp. gr. 1.2) over a period of 4 hours. The solution was refluxed for an additional hour and poured into 8 liters of an ice-water mixture. The white solid was collected by filtration, washed with cold water and dried. There was obtained 205 g. (94.8%) of phenoxathiin-10-oxide, m.p. 156-156.5°. A mixed melting point with an authentic sample of phenoxathiin-10-oxide was not depressed.

A 93% yield was obtained in a preparation employing 0.20 mole of phenoxathiin in 600 ml. of glacial acetic acid.

Sodium hypochlorite oxidation of 2,8-diacetylphenoxathiin to 2,8-phenoxathiindicarboxylic acid 10-dioxide

The reaction was carried out under the conditions employed by Suter, McKenzie and Maxwell[35] and by Irie[50] for the oxidation of 2-acetylphenoxathiin and by Tomita[65] for the oxidation of 2,8-diacetylphenoxathiin (m.p. 175°). There was on hand a sample[119] of the product, 2-phenoxathiincarboxylic acid (m.p. reported 259-260°), which Suter and coworkers had obtained from the reaction. The compound melted over the range 265-274° and gave an infrared spectrum containing a band at 8.6μ, characteristic of the sulfone

group. Also available was a sample[119] of 2-phenoxathiin-carboxylic acid (m.p. reported 260-262°) which the same workers[35] had prepared from the Grignard reagent of 2-bromophenoxathiin (m.p. 59-60°). The material melted over the range 188-260° and gave a poor infrared spectrum.

In a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a stopper were placed a suspension of 5.00 g. (0.018 mole) of 2,8-diacetylphenoxathiin (m.p. 186-187°, see "Friedel-Crafts acetylation of phenoxathiin") in 200 ml. of 1 N sodium hydroxide solution and 25 g. of bleaching powder (High Test Hypochlorite). The stirred mixture was heated by a water bath for 5 hours. Considerable foaming of the mixture occurred during this period. After the hot reaction mixture was filtered, the solid was washed with hot water and the filtrates were combined. Acidification of the cold filtrate yielded a negligible amount of acid which was discarded. The insoluble solid from the filter paper was dried and extracted with benzene in a Soxhlet extractor. Concentration of the benzene extract yielded 0.44 g. (8.8%) of 2,8-diacetylphenoxathiin, m.p. and mixed m.p. 185-187°.

Subsequent to the evaporation of the benzene from the calcium salt mixture, the solid was stirred with dilute hydrochloric acid. The resulting impure acid was collected, digested with 150 ml. of 2% sodium hydroxide solution and

the mixture was filtered while hot. Upon acidification of the cool filtrate there was obtained 4.70 g. (83.3%) of product melting over the range 384-387°, with decomposition. The acid was recrystallized from a large volume of 50% ethanol to yield 3.87 g. (68.7%) of 2,8-phenoxathiindicarboxylic acid 10-dioxide, m.p. 392-394°, with decomposition. (Tomita[65] reported the melting point as over 300°.)

Anal. Calcd. for $C_{14}H_8O_7S$: S, 10.01; neut. equiv., 160. Found: S, 10.07, 10.01; neut. equiv., 156.5, 157.

Preparation of 1-phenoxathiincarboxylic acid 10-oxide

To a yellow, refluxing solution of 2.44 g. (0.01 mole) of 1-phenoxathiincarboxylic acid (m.p. 223-224°) in 50 ml. of absolute ethanol was added dropwise 6 ml. (0.06 mole) of 30% aqueous hydrogen peroxide. After 3 hours of refluxing an additional 4 ml. of the peroxide was added and the mixture was refluxed for a period of 9 hours. The solvent was distilled until the volume of the residue was 15 ml. and the solution was allowed to cool. The white crystals of 1-phenoxathiincarboxylic acid 10-oxide weighed 2.38 g. (91.5%) and melted at 262°, with decomposition. A mixture of this material and a sample of the acid obtained by metalation of

phenoxathiin-10-oxide with 2,2'-dilithiodiphenyl ether melted at 262°, with decomposition.

Anal. Calcd. for $C_{13}H_8O_4S$: S, 12.32; neut. equiv. 260. Found: S, 12.20, 12.24; neut. equiv., 260, 262.

Preparation of 4-phenoxathiincarboxylic acid 10-oxide

When the hydrogen peroxide oxidation of 4-phenoxathiincarboxylic acid in glacial acetic acid was first carried out[54], there was obtained a product, m.p. 183-184° and neut. equiv. 261, designated as 4-phenoxathiincarboxylic acid 10-dioxide. The reported calculated value of 256 for the neutralization equivalent is obviously in error since this figure should be 276. The experimental neutralization equivalent agreed closely with the theoretical value of 260 for 4-phenoxathiincarboxylic acid 10-oxide. In order to determine whether the material which melted at 183-184° was 4-phenoxathiincarboxylic acid 10-oxide or an impure sample of 4-phenoxathiincarboxylic acid 10-dioxide (m.p. 189-190°[59]), it was deemed advisable to prepare the former compound.

Run I. To a yellow, refluxing solution of 2.44 g. (0.01 mole) of 4-phenoxathiincarboxylic acid (m.p. 169-171°) in 50 ml. of absolute ethanol was added dropwise 6 ml. (0.06 mole) of 30% aqueous hydrogen peroxide. The solution was refluxed

for 3 hours and a 4-ml. portion of the peroxide was added. After an additional 9-hour period of refluxing, the solution was reduced in volume to 15 ml. and allowed to cool. Since no crystals separated, the solution was concentrated and water was added until the hot solution became turbid. Following crystallization there was collected 2.53 g. of white crystals which melted over the range 174-183°. Recrystallization from hot water did not alter the melting range. Upon recrystallization from benzene there was collected 1.9 g. of crystals, melting range 179-186°. The mixture was believed to consist of 4-phenoxathiincarboxylic acid 10-oxide and 10-dioxide. Further purification was not attempted.

Run II. To a yellow, refluxing, stirred solution of 2.44 g. (0.01 mole) of 4-phenoxathiincarboxylic acid (m.p. 169-171°) in 25 ml. of glacial acetic acid was added dropwise 5 ml. (0.03 mole) of dilute nitric acid (sp. gr. 1.2). After 2 hours of refluxing the solution was poured into 80 ml. of an ice-water mixture. A finely divided white solid was collected, washed with cold water and dried. The 2.1 g. of product melted over the range 135-145°, but the melting range was indefinite and dependent upon the temperature of the bath when the sample was inserted and upon the rate of heating. After the product was recrystallized from approximately 100 ml. of benzene there was collected 1.6 g. (61.5%)

of 4-phenoxathiincarboxylic acid 10-oxide, m.p. 171-173°. Following a recrystallization from hot water the melting point of the crystals was again dependent upon the rate of heating of the bath. Samples melted immediately when placed in the bath at temperatures above 120°. After another recrystallization from benzene the white 4-phenoxathiincarboxylic 10-oxide melted sharply at 171-173°. The peculiar behavior suggested that the product contained water of crystallization when recrystallized from aqueous solvents. A mixture of the product and the starting material melted over the range 128-137°.

Anal. Calcd. for $C_{13}H_8O_4S$: neut. equiv., 260. Found: neut. equiv., 261, 264.

Preparation of 1,6-phenoxathiindicarboxylic acid 10-dioxide

A mixture consisting of 2.88 g. (0.01 mole) of 1,6-phenoxathiindicarboxylic acid (m.p. ca. 350°, with decomposition), 20 ml. of glacial acetic acid and 6 ml. (0.06 mole) of 30% aqueous hydrogen peroxide was stirred at 106° for 1 hour, during which time the mixture changed in color from yellow to white. A 40-ml. portion of glacial acetic acid was added in an unsuccessful attempt to dissolve the white solid. The mixture was stirred for an additional hour and

allowed to stand overnight. There was collected 2.8 g. of white solid melting over the range 351-354°, with decomposition. Recrystallization from a large volume of methanol yielded 2.6 g. (80.5%) of fine, white needles of 1,6-phenoxathiindicarboxylic acid 10-dioxide, m.p. 351-353°, with decomposition. A mixture of the white needles and the dense, blunt, white crystals of 1.9-phenoxathiindicarboxylic acid 10-dioxide (m.p. ca. 350°) melted over the range 324-334°.

Anal. Calcd. for $C_{14}H_8O_7S$: S, 10.01; neut. equiv., 160. Found: S, 9.86, 9.91; neut. equiv., 158, 161.

Preparation of 4,6-phenoxathiindicarboxylic acid 10-dioxide

A mixture consisting of 2.88 g. (0.01 mole) of 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°), 30 ml. of glacial acetic acid and 6 ml. (0.06 mole) of 30% aqueous hydrogen peroxide was stirred at 106-108° for 2 hours. The suspension changed from yellow to colorless after 15 minutes of stirring. After the mixture had cooled, it was filtered. The product was washed with acetic acid and with petroleum ether (b.p. 60-70°). There was collected 3.03 g. of white needles, m.p. 327-330°, with decomposition. After one recrystallization from a large volume of acetone-water there

was obtained 2.63 g. (82.2%) of 4,6-phenoxathiindicarboxylic 10-dioxide, m.p. 329-331°, with decomposition.

Anal. Calcd. for $C_{14}H_8O_7S$: S, 10.01; neut. equiv., 160. Found: S, 9.95, 9.94; neut. equiv., 161, 161.

Preparation of 2-bromophenoxathiin-10-dioxide by oxidation of crude 2-bromophenoxathiin

A mixture consisting of 27.9 g. (0.10 mole) of crude 2-bromophenoxathiin (melting range 63-72°), 85 ml. of glacial acetic acid and 62 ml. (0.60 mole) of 30% aqueous hydrogen peroxide was heated at the reflux temperature for 1 hour and allowed to stand overnight. Subsequent to filtration and drying there was obtained 29.3 g. of white solid, melting range 147-160°. The solid was recrystallized from methyl ethyl ketone to yield 20.0 g., melting range 152-165° and 3.2 g., melting range 130-155°. When the 20.0 g. of white solid was digested with refluxing isopropyl alcohol there remained 3.5 g. which did not dissolve. The material which was insoluble in isopropyl alcohol was repeatedly recrystallized from glacial acetic acid. The weights and melting points of the product after successive recrystallizations were: 3.3 g., 173-177°; 2.7 g., 175-177.5° and 2.4 g., 175.5-178°. After a recrystallization from ethanol there

was obtained 2.1 g. of 2-bromophenoxathiin-10-dioxide, m.p. 176.5-178°. A mixed melting point with a sample of 2-bromophenoxathiin-10-dioxide which was prepared from 2-aminophenoxathiin-10-dioxide was not depressed.

The material which was soluble in isopropyl alcohol crystallized when the solution was cooled. Fractions with melting ranges of 147-157° and 165-170° were collected. There was little change in the melting range of the lower-melting fraction subsequent to another recrystallization from isopropyl alcohol. Attempts were made to obtain pure material by chromatography followed by recrystallization from glacial acetic acid. Small amounts of fractions which melted over the ranges 186-206° and 166-172° were separated. However, subsequent recrystallizations did not alter the melting range.

Preparation of 4-bromophenoxathiin-10-dioxide by oxidation of crude 4-bromophenoxathiin

From the reaction of bromine with the metalation products which had been produced by treating phenoxathiin with one equivalent of n-butyllithium there resulted a liquid, boiling range 123-147° at 0.005 mm. Attempts to purify the material by crystallization were unsuccessful. Due to the fact that considerable dimetalation of phenoxathiin occurs

when one equivalent of n-butyllithium is employed as the metalating agent, the above crude product probably consisted of 4-bromophenoxathiin and dibromophenoxathiins. It was believed that the 10-dioxides could be crystallized and separated.

To a stirred, refluxing solution of 11.2 g. (0.04 mole) of the crude 4-bromophenoxathiin in 35 ml. of glacial acetic acid was added 31 ml. of a 30% aqueous solution (0.30 mole) of hydrogen peroxide. The mixture was stirred at the reflux temperature for 80 minutes and allowed to cool. Following crystallization there was collected 8.6 g. of white solid which melted over the range 136-144°. The product was recrystallized from ethanol to yield 6.3 g. of white solid, m.p. 147-150°. During the second recrystallization from ethanol the flask was broken and approximately one-half the product was lost. There was collected 2.3 g. of white crystals, m.p. 153-155°, which, upon recrystallization, yielded 1.4 g. (11.3%) of pure 4-bromophenoxathiin-10-dioxide, m.p. 157.5-158°. A subsequent recrystallization did not alter the melting point. The infrared spectrum of the product was almost superimposable on the spectrum of an authentic specimen of 4-chlorophenoxathiin-10-dioxide.[54] The most significant absorption bands were those at 8.65, 12.90 and 13.15μ,

characteristic of the sulfone group, 1,2,3-trisubstituted and 1,2-disubstituted benzene rings, respectively.

Anal. Calcd. for $C_{12}H_7BrO_3S$: S, 10.30. Found: S, 10.37, 10.39.

Cleavage Reactions

Hydrogenolysis of 1,9-phenoxathiindicarboxylic acid 10-dioxide

Run I. In a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a thermometer were placed 25-30 g. of Raney nickel[84] and a solution of 2.0 g. (0.006 mole) of 1,9-phenoxathiindicarboxylic acid 10-dioxide (m.p. 350-352°, with decomposition) in 600 ml. of 0.5% sodium carbonate. The stirred mixture was heated at 75-85° for 45 minutes and allowed to cool. The nickel was removed by filtration, washed with four 50-ml. portions of 0.5% sodium carbonate solution and with two 50-ml. portions of water. The filtrate was acidified to pH 7 and filtered through Celite to remove aluminum hydroxide. After the filtrate had been concentrated to 30 ml., it was acidified to pH 2 and there was collected 0.9 g. of white solid melting over the range 100-240°. Concentration of the aqueous filtrate produced

0.6 g. of white acid melting over the range 184-245°. The combined material was digested with hot benzene and the mixture was filtered. From the benzene extract there was obtained 0.35 g. of benzoic acid, m.p. and mixed m.p. 120-122°. The benzene-insoluble fraction weighed 1.0 g. and melted over the range 180-235°. Upon recrystallization from acetone-water there were obtained two fractions of white solid: 0.4 g., m.p. 247-249° and 0.4 g., melting range 194-260°. A portion of the second fraction was soluble in hot water and was recrystallized from this solvent to yield a material melting over the range 196-252°. The part which was insoluble in water was recrystallized from acetone-water to yield crystals which melted over the range 310-325°. The latter material was probably impure starting acid.

The 0.4 g. of material melting at 247-249° represented a 25.8% yield of 3,3'-dicarboxydiphenyl ether. A mixture of this product and an authentic specimen[115] of 3,3'-dicarboxydiphenyl ether (m.p. reported[121] 243-245°, found 247-251°) melted at 247-250°. The infrared spectra of the two samples are superimposable.

Run II. In a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a thermometer was placed

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[121] M. Tomita, J. Pharm. Soc. Japan, 57, 391 (in German, 76) (1937) [C. A., 33, 2117 (1939)].

a solution of 3.20 g. (0.01 mole) of 1,9-phenoxathiindicarboxylic acid 10-dioxide in 750 ml. of 0.5% sodium carbonate solution. The solution was heated to 70° and approximately 40 g. of freshly prepared Raney nickel catalyst was added. Also added was the amount of ethanol necessary to effect the transfer of the catalyst to the reaction flask. The mixture was stirred at 75° for 30 minutes and cooled. The nickel was removed by filtration, washed with four 50-ml. portions of 0.5% sodium carbonate solution and two 50-ml. portions of water. The filtrate was acidified to pH 7 and the aluminum hydroxide was separated by filtration. After the filtrate had been concentrated to approximately 200 ml. and acidified to pH 1-2, there was collected 2.03 g. of white product melting over the range 103-237°. Further concentration of the mother liquor yielded 0.34 g., melting range 108-289°.

The larger fraction was digested with hot water and the hot suspension was filtered. The material which had dissolved was believed to be a mixture of benzoic acid and m-hydroxybenzoic acid. Collected from the filter paper was 0.72 g. of crude product, m.p. 244-247°, which was recrystallized from acetone-water to yield 0.56 g. of white crystals, m.p. 247-249°. A subsequent recrystallization yielded 0.43 g. (16.7%) of 3,3'-dicarboxydiphenyl ether,

m.p. 249-250°. The infrared spectrum of this sample was identical with that of the product obtained in the preceding run.

The low yield of the desired acid was due to the difficulty in separating this material from a mixture which probably consisted of 1,9-phenoxathiindicarboxylic acid 10-dioxide, 3,3'-dicarboxydiphenyl ether and m-hydroxybenzoic acid. The last acid was believed to have accompanied benzoic acid as an ether-cleavage product since a purple color was obtained when a sample of the crude mixture was tested with ferric chloride.

Hydrogenolysis of 4,6-phenoxathiindicarboxylic acid

Run I. This reaction was carried out according to the procedure employed by Mozingo and coworkers[85] for the cleavage of diphenyl sulfide and by Shirley and Lehto[59] for the cleavage of 1-phenoxathiincarboxylic acid 10-dioxide.

In a 250-ml., three-necked flask fitted with a stirrer, a reflux condenser and a stopper were placed 2.0 g. (0.007 mole) of 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°), 25-30 g. of Raney nickel and 150 ml. of 75% ethanol. The mixture was stirred at the reflux temperature for 18 hours and allowed to cool. Following removal of the nickel by

filtration, the solution was concentrated to 20 ml., made alkaline, filtered and concentrated to a volume of 10 ml. No acid separated upon acidification.

The Raney nickel was then extracted several times with dilute sodium hydroxide solution and with ethanol-water mixtures. Following concentration, filtration and acidification of these extracts there was obtained 0.5 g. of white solid, melting range 208-214° and 0.2 g., melting range 214-219°. The first batch was recrystallized from ethanol-water to yield 0.25 g. of white crystals, melting range 214-222° and 0.15 g., melting range 208-212°. Due to the small amount and the state of purity of the mixture, no further attempts were made to isolate a pure product.

Run II. In a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a thermometer was placed 25-30 g. of Raney nickel catalyst. The ethanol accompanying the nickel was washed out of the flask by decantation with two 100-ml. portions of 0.5% sodium carbonate solution. A solution of 2.0 g. (0.007 mole) of 4,6-phenoxathiindicarboxylic acid (m.p. 266-267°) in 600 ml. of 0.5% sodium carbonate was added to the flask and the stirred mixture was heated to 75° over a period of 45 minutes. After an additional 30-minute period at 75° the mixture was cooled. The nickel was removed by filtration, washed with 300 ml.

of 0.5% sodium carbonate solution and with 150 ml. of water. The filtrate was acidified to pH 7, filtered through Celite, concentrated to 130 ml. and acidified to pH 1-2. There was collected 1.05 g. of white acid melting over the range 109-140°. The mother liquor was made alkaline, concentrated to 40 ml. and acidified to yield 0.45 g. of white product melting over the range 109-230°.

A small amount of the solid melting over the range 109-140° was tested for the presence of a phenol. Upon the addition of a solution of ferric chloride to the sample there resulted a purple color which was of the same hue as that given by a salicylic acid blank. Authentic samples of benzoic acid and 2,2'-dicarboxydiphenyl ether gave negative ferric chloride tests. It was believed that the reaction mixture contained benzoic acid, salicylic acid and 2,2'-dicarboxydiphenyl ether, the first two acids having been produced by cleavage of the diphenyl ether linkage.

The 1.5 g. of white solid, believed to be a mixture of three acids, was subjected to vacuum sublimation. The process was carried out over a temperature range of 100-120° at 0.01 mm. The sublimate weighed 1.12 g. and melted over the range 112-129°. The residue, which weighed 0.35 g. and melted over the range 219-223°, was recrystallized from water to yield 0.28 g., melting range 224-228°. After a

recrystallization from a mixture of benzene and methyl ethyl ketone there was obtained 0.20 g. (11.2%) of 2,2'-dicarboxydiphenyl ether, m.p. and mixed m.p. 227-229°. The infrared spectrum of the product was identical with that of an authentic sample of 2,2'-dicarboxydiphenyl ether.[112]

Hydrogenolysis of 1,6-phenoxathiindicarboxylic acid

Into a one-liter, three-necked flask fitted with a stirrer, a reflux condenser and a thermometer was placed a solution of 2.88 g. (0.01 mole) of the yellow 1,6-phenoxathiindicarboxylic acid (m.p. 347-350°, with decomposition) in 750 ml. of 0.5% sodium carbonate. The solution was warmed to 70° and there were added 30-35 g. of Raney nickel and the accompanying ethanol which was used in the transfer of the catalyst to the flask. The mixture was stirred at 70° for 30 minutes and then filtered. After the nickel had been washed with four 50-ml. portions of 0.5% sodium carbonate solution and with three 50-ml. portions of water, the aluminum hydroxide was precipitated and removed by filtration. Upon acidification of the filtrate there was obtained 1.40 g. of white solid melting over the range 218-229°. The mother liquor was extracted with three 75-ml. portions of ether. Concentration of the ethereal extract

yielded 1.05 g. of pale yellow solid. The material was subjected to vacuum sublimation and there was obtained a white sublimate melting over the range 108-112°. The yellow color and the high melting range of the residue indicated that it was principally unreacted starting material.

The 1.40 g. of white solid melting over the range 218-229° was recrystallized from acetone-water to yield 1.10 g. of white crystals, melting range 220-226°, with softening at 217°. The crystals were dissolved in hot acetone-benzene and the mixture was filtered and allowed to cool. The first fraction, a very small amount, melted over the range 240-300°. When the mother liquor was progressively concentrated, allowed to cool and filtered there were collected 0.38 g., melting range 220-228° and 0.32 g., m.p. 219-220°. When the first fraction was recrystallized from ethanol-water there was obtained 0.22 g. of white solid, melting range 220-228°, with most of the sample melting at 220-221°. Recrystallization of the second fraction from ethanol-water yielded 0.24 g. of 2,3'-dicarboxydiphenyl ether, m.p. 220-221°. The melting points reported for 2,3'-dicarboxydiphenyl ether are 202°[121] and 215°[122]. A mixture of the product and an authentic specimen[115] of 2,3'-dicarboxydiphenyl ether (m.p.

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[122] R. Anschutz, W. Stoltenhoff and F. Voeller, Ber., 58B, 1736 (1925).

found 205-210°) melted over the range 208-215°. The infrared spectra of the two samples are superimposable.

Cleavage of phenoxathiin by lithium, followed by hydrolysis

A stirred mixture consisting of 20.0 g. (0.10 mole) of phenoxathiin, 1.53 g. (0.22 g. atom) of finely cut lithium wire and 350 ml. of ether was heated at the reflux temperature for 16 hours. The pale pink suspension gave a positive Color Test I. The mixture was filtered through a tube filled with glass wool and the filtered suspension was run into a beaker of cold water. Following separation of the layers, the ether layer was extracted with three 100-ml. portions of dilute sodium hydroxide solution. The dissolved ether was expelled from the cloudy, aqueous solution which was subsequently stirred with Norit-A and filtered. Following acidification of the cloudy filtrate there was collected 16.3 g. of white solid, m.p. 64-67°. The product was recrystallized once from petroleum ether (b.p. 60-70°) and twice from methanol to yield 12.5 g. (61.9%) of 2-thioldiphenyl ether, m.p. 67.5-68.5°. (The product obtained by the cleavage of phenoxathiin with sodium in liquid ammonia was reported to melt at 65-67°.[90]) A mixed melting point with a sample of 2-thioldiphenyl ether, one which had been

prepared by the reaction of sulfur with 2-lithiodiphenyl ether, was not depressed.

Preparation of 2-thioldiphenyl ether by the reaction of sulfur with 2-lithiodiphenyl ether

To a stirred solution of 34.0 g. (0.20 mole) of diphenyl ether in 300 ml. of ether was added 154 ml. of a 1.36 M solution (0.21 mole) of n-butyllithium. After a 48-hour reflux period Color Test II was faintly positive.

To the cool, stirred solution of 2-lithiodiphenyl ether was added slowly 6.56 g. (0.20 g. atom) of powdered sulfur. Following the addition Color Test I was negative. To the stirred, white suspension was added 300 ml. of water. The layers were separated and the ether layer was extracted with 100 ml. of water. The dissolved ether was expelled from the aqueous solution by employing reduced pressure from a water aspirator. Subsequent to treatment with Norit-A, filtration and acidification there was collected 30.1 g. of vacuum-dried, white solid, m.p. 62-65°. After two recrystallizations from petroleum ether (b.p. 60-70°) and two recrystallizations from methanol, there was obtained 16.8 g. (40.5%) of 2-thioldiphenyl ether, m.p. 67.5-68.5°.

Anal. Calcd. for $C_{12}H_{10}OS$: S, 15.85. Found: S, 15.80, 15.90.

Oxidation of 2-thioldiphenyl ether to bis-(2-phenoxyphenyl)-disulfide

In a 250-ml., three-necked flask fitted with a stirrer, a reflux condenser and a separatory funnel containing 2.92 g. (0.01 mole) of iodine and a small amount of potassium iodide in 115 ml. of absolute ethanol was placed a solution of 4.04 g. (0.02 mole) of 2-thioldiphenyl ether in 50 ml. of absolute ethanol. The stirred mixture was warmed and the iodine solution was added over a period of 2 hours. After a 1-hour period of refluxing the iodine color was removed by the addition of sodium bisulfite. The reaction mixture was stirred with Norit-A, filtered, concentrated to half the original volume and filtered to remove inorganic salts. After several hours there formed 3.07 g. of colorless crystals, m.p. 74.5-75.5°. One recrystallization from absolute ethanol yielded 2.90 g. (72.2%) of bis-(2-phenoxyphenyl)disulfide, m.p. 75-76°.

Anal. Calcd. for $C_{24}H_{18}O_2S_2$: S, 15.93. Found: S, 15.85, 15.87.

There was very little difference in the infrared spectra of 2-thioldiphenyl ether and its disulfide, with the exception of the presence in the spectrum of the former compound of a weak band at 3.9μ which may be characteristic of the thiol group.

Preparation of 2-phenoxyphenylmercaptoacetic acid from 2-thioldiphenyl ether and chloroacetic acid

A mixture consisting of 6.06 g. (0.030 mole) of 2-thioldiphenyl ether, 2.84 g. (0.030 mole) of chloroacetic acid and a solution of 2.80 g. (0.07 mole) of sodium hydroxide in 75 ml. of water was stirred at the reflux temperature for 4 hours. A nitrogen atmosphere was maintained above the mixture to prevent oxidation of the thiol to the disulfide. After the mixture was concentrated by distillation of 60 ml. of the water, it was heated for an additional 6-hour period.

The reaction mixture was dissolved in 125 ml. of water, the solution was filtered and the filtrate was extracted with two 50-ml. portions of ether. Following removal of the dissolved ether, the salt solution was acidified to yield 7.15 g. of white solid melting over the range 120-124°. An attempt to purify the product by recrystallization from petroleum ether (b.p. 78-115°) resulted in the loss of 2.1 g. of the product. No change in the melting range was effected. After a digestion with hot water, the residue was dissolved in 5% sodium carbonate solution, the solution was treated with Norit-A, filtered and acidified. There was collected 3.4 g. of white crystals, m.p. 125.5-126.5°. The process was repeated to yield 3.2 g. (40.2%) of 2-phenoxyphenylmercaptoacetic acid, m.p. 126.5-127°.

Anal. Calcd. for $C_{14}H_{12}O_2S$: S, 12.32; neut. equiv., 260. Found: S, 12.38, 12.32; neut. equiv., 260.5, 260.

Cleavage of phenoxathiin by lithium, followed by carbonation

In a 500-ml., three-necked flask fitted with a stirrer, a reflux condenser and two nitrogen inlet tubes were placed 2.5 g. (0.36 g. atom) of finely cut lithium wire and a solution of 30.0 g. (0.15 mole) of phenoxathiin in 350 ml. of ether. After a 20-hour reflux period the suspension was filtered through glass wool into a stirred slurry of ether and Dry Ice.

When the carbonation mixture had warmed to room temperature water was added and the mixture was filtered to remove a small amount of resinous material. The layers were separated and the ether layer was extracted with two portions of 1% sodium hydroxide solution. The aqueous layer was washed with ether.

By the application of water aspirator vacuum the dissolved ether was expelled from the aqueous solution. The latter was clarified by treatment with Norit-A, followed by filtration. Carbon dioxide was bubbled into the alkaline salt solution, but no phenolic material separated. The clear solution was acidified with hydrochloric acid and there was

collected 10.2 g. of white solid melting over the range 134-174°. During the course of attempts to separate the components of the mixture by crystallization from methanol, extraction with petroleum ether (b.p. 60-70°) and digestion with benzene, much of the product was lost. It was found that the lower-melting acid was soluble in benzene and that the other acid could be retained as a residue upon filtration of the hot benzene digestion mixture. By concentration of the benzene solution there was obtained 6.2 g. of solid, melting range 128-142°, which was recrystallized from methanol-water to yield 4.3 g. of crystals melting over the range 138-142°. Upon recrystallization from benzene there was obtained 3.0 g. (8.1%) of 2-carboxy-2'-thioldiphenyl ether, m.p. 142-143°.

Anal. Calcd. for $C_{13}H_{10}O_3S$: S, 13.02; neut. equiv., 123. Found: S, 13.08, 12.97; neut. equiv., 130, 130.

The assignment of the value of 123 for the theoretical neutralization equivalent is based upon the assumption that the thiol group is sufficiently acidic to be titrated with sodium hydroxide using phenolphthalein as the indicator. It may be that oxidation occurs during the titration and that some of the thiol groups are "tied up" as the disulfide.

The fraction of crude acid which was insoluble in benzene melted at 229-231°. After two recrystallizations from

methanol there was obtained 1.1 g. of crystals melting at 235-235.5°. The compound is believed to be the disulfide of 2-carboxy-2'-thioldiphenyl ether.

Anal. Calcd. for $C_{26}H_{18}O_6S_2$: S, 13.07; neut. equiv., 245. Found: S, 13.17, 13.24; neut. equiv., 242, 243.

The infrared spectra of the two acids from the reaction mixture were almost identical. This was evidence that the two acids bear the thiol-disulfide relationship to each other.

DISCUSSION

Metalation Reactions

The investigator who has made a cursory survey of the literature of phenoxathiin would visualize a field of chemistry for which the pioneering research had been done. At least one derivative had been prepared for each of the four monosubstitution positions. The lithium atom could be introduced into the 1-[59] or the 4-[54] position by metalation of phenoxathiin-10-oxide and phenoxathiin, respectively. The product of bromination[35], 2-bromophenoxathiin, could be converted, by the halogen-metal interconversion reaction, to phenoxathiinyllithium, a valuable intermediate.[54] Therefore, the lithiophenoxathiins appeared to be the ideal starting materials for the preparation of other phenoxathiin derivatives.

The literature contains no data from which can be made an accurate estimation of the amount of 4-phenoxathiinyllithium that was produced by the metalation of phenoxathiin with n-butyllithium. The crude carbonation product has been obtained in yields of 56 and 63%, but the yield of pure 4-phenoxathiincarboxylic acid has not been reported.[54]

It was shown in this work that the crude carbonation product contained considerable amounts of phenoxathiindi-

carboxylic acids. The amount of metalation product which formed a neutral derivative was considered sufficiently small to be neglected. The extent of monometalation could have been estimated from the neutralization equivalent of the crude mixture. Unfortunately, this determination was not made on the crude product obtained in 76.2% yield (based upon 4-phenoxathiincarboxylic acid). From this mixture there were isolated yields of 36.9 and 1.4% of pure 4-phenoxathiincarboxylic acid and 1,6-phenoxathiindicarboxylic acid, respectively. In addition to the isolation of the 1,6-diacid, there are other data which indicate that the amount of monometalation was less than 76.2%, and that more than 76.2% of the n-butyllithium was used in metalation. First, the average yield of crude dicarboxylic acids in the dimetalation experiments was greater than 90%; indicating that almost all of the n-butyllithium was used in metalation. Second, in these experiments the pure 4,6-diacid was isolated in a yield approximately 3.5 times greater than that of the 1,6-diacid. Therefore, it would be expected that some of the 4,6-diacid was formed in the monometalation experiments, even though none was isolated. This dicarboxylic acid, being less soluble than the 4-acid and more soluble than the 1,6-diacid, could have easily escaped isolation. On the basis of these facts, one can estimate conservatively that at least 85% of the

n-butyllithium effected metalation in the reaction in which a 76.2% yield of crude product was obtained. Using these two figures, it was calculated that 63.6% of the n-butyllithium was used in monometalation and 21.4% in dimetalation. Stated in another manner, the crude acid must have consisted of six moles of 4-phenoxathiincarboxylic acid per mole of phenoxathiindicarboxylic acids.

Attempts were made to limit the metalation to the formation of the monolithium derivative. Some dimetalation took place when n-butyllithium was used at low temperature for a short period of time. Even when the reaction was carried out with phenylcalcium iodide, an organometallic compound which is not an effecient metalating agent, but one which has effected an anomalous metalation[81], 4-phenoxathiincarboxylic acid and 4,6-phenoxathiindicarboxylic acid were isolated in small amounts. Methyllithium showed the greatest promise as a monometalating agent since no interferring dimetalation occurred even though two equivalents of the reagent were employed. Though the crude acid was obtained in a low yield (11.6%), it was in a relatively high state of purity.

If it can be assumed that n-butyllithium metalates phenoxathiin only in the positions which are ortho to the hetero atoms, there are four phenoxathiindicarboxylic acids which would result upon carbonation. They are the 1,4-,

1,6-, 1,9- and 4,6- derivatives. One of the positions ortho to the oxygen is known to be especially reactive since monometalation occurs at the 4- position.

The two phenoxathiindicarboxylic acids prepared simultaneously by way of dimetalation of phenoxathiin were obtained in yields of 8.9 and 34.7%. The acid melting at 266-267° was proved to be the 4,6- derivative when it yielded 2,2'-dicarboxydiphenyl ether upon desulfurization with Raney nickel. Though the phenoxathiindicarboxylic acid melting at ca. 350°, with decomposition, was obtained in the lower yield, it was the more interesting of the two isomers. This acid was also a product when phenoxathiin-10-oxide was treated with n-butyllithium at room temperature. The higher melting isomer yielded 2,3'-dicarboxydiphenyl ether upon hydrogenolysis with Raney nickel. Though this product could be obtained upon cleavage of either 1,6- or 3,6-phenoxathiindicarboxylic acid, the latter acid was not considered as a possible dimetalation product since the 3- position is not ortho to a hetero atom. Therefore, dimetalation of phenoxathiin occurs in the 1,6- and 4,6- positions.

The data gathered in the course of this work prompt the writer to view with amazement the report that 2-phenoxathiincarboxylic acid acid was isolated subsequent to the reaction of 2-bromophenoxathiin (m.p. reported 58-59°) with four

equivalents of n-butyllithium.[54] (See p. 88.) In the first place, there is the very important question as to whether the material which was designated as 2-bromophenoxathiin was a pure compound or a mixture. (This question is discussed under Halogenation Reactions.) However, given the benefit of the doubt that there are two crystalline forms of 2-bromophenoxathiin, one melting at ca. 60° and the other at ca. 90°, there must be considered the possibility of metalation accompanying the halogen-metal interconversion reaction. It was shown, by carrying out the reaction between phenoxathiin and n-butyllithium under the conditions employed for the interconversion reaction, that metalation occurred to the extent of 0.71 equivalent of n-butyllithium. This figure was calculated from the 64% yield (based upon 4-phenoxathiincarboxylic acid) of crude acid and the neutralization equivalent of the mixture. Highly significant is the fact that 16% of the weight of crude acid was due to phenoxathiindicarboxylic acids. It shows that dilithiophenoxathiins can be formed under these conditions. This writer does not believe that 2-phenoxathiinyllithium, the halogen-metal interconversion product, would be resistant to metalation. The 6- position, ortho to oxygen in the other ring, should be sufficiently reactive to allow the formation of a large amount of 2,6-dilithiophenoxathiin. A comparison of the yields of the phenoxathiindicarboxylic

acids in the dimetalation experiments with those of 4-phenoxathiincarboxylic acid in the monometalation experiments reveals that a lithium atom in one ring does not inhibit metalation in the other. However, granting that some of the 2-phenoxathiincarboxylic acid was formed in a significant amount, its separation from the dicarboxylic acids would have been a formidable task.

The structure of the acid prepared by way of the halogen-metal interconversion reaction was proved in a peculiar fashion (See p. 88.). Curiously enough, the "pure" acid (melting range 260-265°) was not compared with an authentic specimen of the 2-acid (m.p. reported[35] 259-260°), though such a sample was available since it was mentioned in another part of the article.

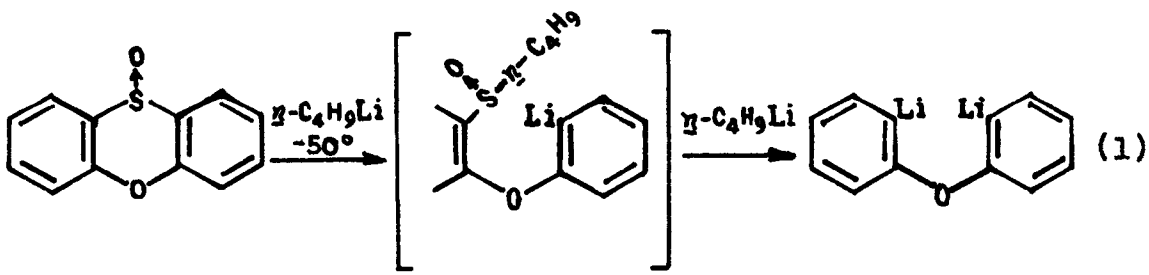
The action of n-butyllithium on phenoxathiin-10-oxide had been studied in this Laboratory by Messrs. T. L. Reid and D. L. Esmay, who had isolated an unknown acid. This writer, knowing that a complex reaction or series of reactions occurred, resorted to the low reaction temperature of -50° in hopes of minimizing the secondary reactions. It was believed that metalation and reduction occurred as in the case of dibenzothiophene-5-oxide and n-butyllithium.[72] It appeared feasible that if metalation preceded reduction, and if the metalated phenoxathiin-10-oxide were a sufficiently

stable intermediate, this organometallic compound could be derivatized by carbonation and a phenoxathiincarboxylic acid 10-oxide would result. This compound was not found, however. The products isolated were phenoxathiin, 2-carboxydiphenyl ether, n-butyl mercaptan and 1-phenoxathiincarboxylic acid. The yield of the last compound was less than 5%.

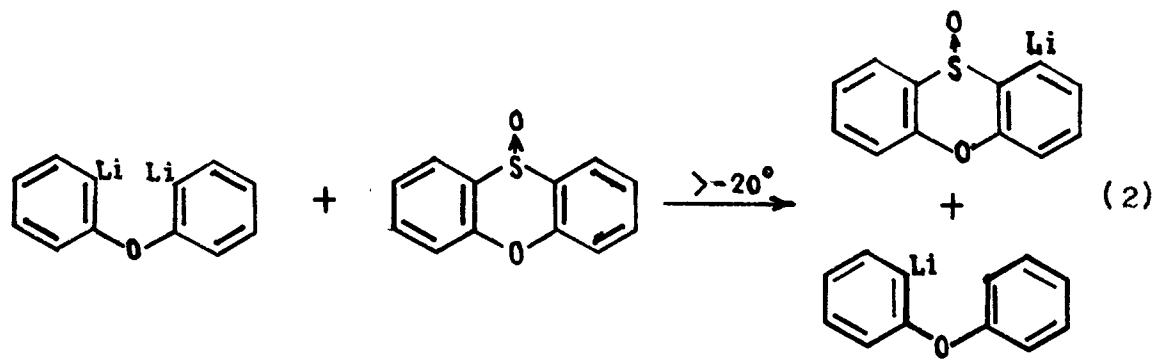
When it was learned that Shirley and Lehto[59] had carried out the above reaction at -20° to room temperature and obtained a 22% yield of 1-phenoxathiincarboxylic acid, the reaction was repeated under these conditions and a comparable yield of the 1-acid isolated. Thus, it appeared that more cleavage had occurred under the milder conditions. Then, with the isolation of diphenyl ether from both reaction mixtures, it was apparent that the reaction was not affected anomalously by changes in conditions. A comparison of the overall yields (see Table 9, p. 137) under the two conditions reveals approximately the same amount of cleavage, but more metalation of the heterocycle at the higher temperature.

In order to prove that the formation of 2-lithio- and 2,2'-dilithiodiphenyl ether did not occur by way of a two-step process involving cleavage to diphenyl ether, followed by metalation, the action of n-butyllithium on diphenyl ether at -50° was investigated. No metalation took place at this temperature.

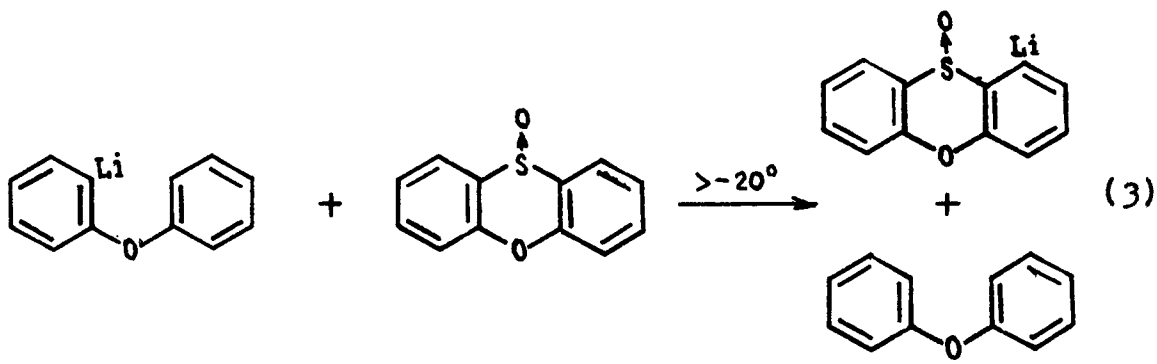
2-Carboxydiphenyl ether, 2,2'-dicarboxydiphenyl ether and n-butyl mercaptan are logical cleavage products of phenoxathiin-10-oxide, but the mechanism by which diphenyl ether is formed is not clear. Any cleavage of the heterocycle would be expected to produce 2-lithio- or 2,2'-dilithiodiphenyl ether or a lithio derivative similar to the intermediate in Equation 1. These organometallic compounds would yield carboxylic acids upon carbonation. Appreciable amounts of the acids corresponding to the first two lithium derivatives were isolated, but only when the metalation reactions were carried out at -50°. At the higher temperatures the lithium atoms were apparently replaced by hydrogen prior to the carbonation reaction. Since the absence of the carboxydiphenyl ether paralleled the formation of 1-phenoxathiincarboxylic acid, it appeared that 2-lithio- or 2,2'-dilithiodiphenyl ether may have metalated phenoxathiin-10-oxide. The cleavage and metalation reactions are illustrated by Equations 1-3.



(1)



(2)



(3)

The metalation reactions may not occur to a significant extent until the mixture is allowed to warm above -20°. Such a situation would explain the presence of large amounts of the carboxydiphenyl ethers, yet little of 1-phenoxathiincarboxylic acid when the reaction mixture was carbonated after a short reaction period at low temperature.

The mechanism was tested by adding a mixture of 2-lithio- and 2,2'-dilithiodiphenyl ether to phenoxathiin-10-

oxide at -20° and allowing the reaction mixture to warm to room temperature before carbonation. The work-up of the mixture was attended by considerable difficulty due to the number and character of the products. A small quantity of phenolic material was separated, but could not be isolated in sufficient quantity to be identified. The isolated quantity of 1-phenoxathiincarboxylic acid 10-oxide was small, but sufficient to give support to the postulated mechanism. This acid may have been formed by a reaction such as is illustrated by Equation 2 or 3. Since no 1-phenoxathiincarboxylic acid was isolated, it appears that reduction of the metalated compound is effected by n-butyllithium, but not by the lithiodiphenyl ethers. It is not known whether the isolated 2-carboxydiphenyl ether resulted from the 2-lithiodiphenyl ether which was originally present in the mixture or from that which may have been produced by the reaction illustrated by Equation 2. Both alternatives are possible. Such a difficulty can be avoided by the use of only one metalating agent. 2,2'-Dilithiodiphenyl ether could be prepared conveniently from 2,2'-dibromodiphenyl ether by the halogen-metal interconversion reaction. The latter compound was not available during this work.

The lithium atom can be introduced into the 1- position of the phenoxathiin ring system by metalation of either

phenoxathiin-10-oxide or phenoxathiin-10-dioxide. Metalation of the former compound is of limited synthetic value for several reasons. The optimum reaction conditions are difficult to achieve; the yield is poor; cleavage occurs and many interfering by-products are formed. Fortunately, the metalation of phenoxathiin-10-dioxide is not accompanied by cleavage. However, the sulfone group activates both the 1- and the 9-positions to such an extent that dimetalation accompanied monometalation under the conditions which were employed. Though Shirley and Lehto reported only 1-phenoxathiincarboxylic acid 10-dioxide from the reaction of phenoxathiin-10-dioxide with one equivalent of n-butyllithium, it is believed that the dicarboxylic acid could have been formed but easily escaped isolation. The work of Shirley and Lehto demonstrated that the yield of 1-phenoxathiincarboxylic acid 10-dioxide could not be increased above 46% by the use of 1.5 equivalents of n-butyllithium. The results which this writer found upon using 1.5 equivalents of n-butyllithium revealed that it would be extremely detrimental to use an excess of the metalating agent. The yields of 15% mono- and 48% dicarboxylic acid show that much of the monolithium derivative is converted to the dilithio compound upon the addition of excess metalating agent.

When 1,9-phenoxathiindicarboxylic acid 10-dioxide was prepared by way of dimetalation of phenoxathiin-10-dioxide the yield of crude product was 92.5%. Though there was undoubtedly a considerable amount of monocarboxylic acid formed, the extent of dimetalation was greater than the 52.2% yield of pure 1,9-diacid indicates. There are two reasons why the yield of pure dicarboxylic acid in this experiment is only slightly greater than that obtained when 1.5 equivalents of n-butyllithium were employed. In the latter case a slightly higher reaction temperature was employed and an improved method of separation of the products was used.

The structure of 1,9-phenoxathiindicarboxylic acid 10-dioxide was proved by hydrogenolysis to 3,3'-dicarboxydiphenyl ether. The isolation of this cleavage product is considered to be adequate proof that the acid is the 1,9- derivative even though two other phenoxathiindicarboxylic acids, the 1,7- and the 3,7- derivatives, would also yield the same product. It is unlikely that metalation occurred in the 7-position, one which is not ortho to either the sulfone group or the ether linkage.

The behavior of phenoxathiin towards organolithium compounds is similar to that of dibenzo-p-dioxin. Metalation of the latter heterocycle was limited to the formation of the monolithium derivative only when methyllithium was

employed. Two dicarboxylic acids of dibenzo-p-dioxin were formed as the result of reaction with 2.5 equivalents of n-butyllithium.[94]

The oxygen and sulfur heterocycles can be arranged in order of the decreasing extent of dimetalation. On the basis of the decreasing yields of the dicarboxylic acids, the order is: phenoxathiin > dibenzo-p-dioxin > thianthrene > dibenzofuran > dibenzothiophene. As far as the ease* of dimetalation is concerned, dibenzo-p-dioxin ranks above phenoxathiin since a monocarboxylic acid could not be isolated from the mixture formed when dibenzo-p-dioxin was treated with one equivalent** of n-butyllithium.[94]

No thianthrenedicarboxylic acid was isolated from the mixture of acids obtained when 1-thianthrenecarboxylic acid was prepared by way of the reaction of thianthrene with one equivalent of n-butyllithium.[123] This writer believes that

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[123]D. R. Swayampati, Unpublished Ph.D. Thesis, Iowa State College Library, 1955.

*Dimetalation of phenoxathiin occurs principally in the two positions ortho to the ether linkage. Since the structure of dibenzo-p-dioxin contains two ether linkages, this heterocycle would be expected to be more easily dimetalated than phenoxathiin.

**When phenoxathiin was metalated with one equivalent of n-butyllithium the dicarboxylic acids which were produced did not prevent the isolation of 4-phenoxathiincarboxylic acid.

interfering amcunts* of thianthrenedicarboxylic acid were responsible for the difficulty encountered in obtaining the pure product.

When dibenzofuran was metalated with a slight excess of one molar equivalent of n-butyllithium, high yields of crude 4-dibenzofurancarboxylic acid were obtained.[124] Both the melting range of the crude product and the small loss upon purification indicate lack of contamination by dicarboxylic acids.

The monometalation of dibenzofuran by n-butyllithium was described in an article[125] which deals primarily with the dimetalation of this heterocycle with n-butylsodium. A 77% yield of the dicarboxylic acid was obtained by carbonation of 4,6-disodiodibenzofuran. Dimetalation of dibenzofuran by n-butyllithium was not mentioned.

Esmay[109] obtained an excellent yield of 4-dibenzothiophenecarboxylic acid, but isolated no dimetalation product after treating dibenzothiophene with 2.2 equivalents of n-butyllithium. The results were expected since dibenzothiophene

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[124] H. B. Willis, Unpublished Ph.D. Thesis, Iowa State College Library, 1943.

[125] H. Gilman and R. V. Young, J. Am. Chem. Soc., 57, 1121 (1935).

*The yields of crude acid and pure 1-thianthrenecarboxylic acid were 83 and 28%, respectively.

has been shown to be less readily metalated than dibenzofuran.[54]

More vigorous conditions are required for metalation and dimetalation of the three sulfur heterocycles than for the corresponding dioxides: phenoxathiin-10-dioxide, thianthrene-5-dioxide and dibenzothiophene-5-dioxide. The two dioxides in which the sulfone group is in six-membered rings appear to be more readily dimetalated than dibenzothiophene-5-dioxide.

Acetylation of Phenoxathiin

After the many fruitless attempts to prepare 2-bromophenoxathiin by the direct bromination of phenoxathiin, its synthesis was accomplished by a four-step process which began with the preparation of 2-acetylphenoxathiin. Though it was believed (and this belief was subsequently confirmed) that the second product, the oxime, would be more easily purified than the ketone, intensive efforts were made to obtain a pure sample of 2-acetylphenoxathiin in order to verify one of the two melting points (111-112°[35] and 117.5-118°[52]) reported for this compound. The pure sample melted at 116.5-118.5°.

The recovery of a large amount of phenoxathiin, the isolation of 2,8-diacetylphenoxathiin and the difficulty

encountered in obtaining pure 2-acetylphenoxathiin suggest that the acetylation may have occurred in a random fashion. It would appear that the three materials named above, which are most expected to be present in the crude reaction mixture, would be sufficiently different in solubility and boiling point to allow a clean separation. Either this was not the case or another product was present in the mixture. There are several reasons why the latter alternative appears probable. First, there is the possibility that the 2-acetylphenoxathiin (m.p. 111-112°) of Suter and coworkers[35] could have contained a small amount of another acetyl derivative, since it yielded an oxime (m.p. 142-143°) which did not agree in melting point with that (m.p. 158-159.5°) found by Nobis and coworkers[52] and (m.p. 156-158°) by this worker.

In this thesis is described the isolation of 2,8-diacetylphenoxathiin from the residue which remained after distillation of phenoxathiin and 2-acetylphenoxathiin. Suter and coworkers did not employ a distillation in the work-up procedure by which 2-acetylphenoxathiin was obtained, but purified the product by three recrystallizations from ethanol. Unless 2,8-diacetylphenoxathiin was removed previously by trituration or as a first fraction from a dilute solution, this compound probably would have crystallized along with the more soluble 2-acetylphenoxathiin.

Second, since the Friedel-Crafts reaction of phenoxathiin with succinic anhydride yielded both the 2- and the 3- derivatives, it is not unlikely that the very similar reaction, acetylation, would yield both 2- and 3-acetylphenoxathiin.

Third, it would not be illogical to expect some acetylation of phenoxathiin to occur at all of the four positions. Acetylation at the position ortho to the sulfur is not without precedence since the acetylation of dibenzothiophene yielded a mixture from which both 2- and 4-acetyldibenzothiophene were isolated.[126,127]

Reactions of 2-Substituted Phenoxathiin-10-dioxides

Nitration of phenoxathiin-10-dioxide appears to be the most convenient method of introducing a functional group into the 2- position of the phenoxathiin ring system. The reaction is easily performed and a relatively pure product can be isolated without employing an extensive purification procedure. Other mononitration products which may be difficultly separable should not be formed in significant amounts. The

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[126] A. Burger, W. B. Wartman, Jr. and R. E. Lutz, J. Am. Chem. Soc., 60, 2628 (1938).

[127] A. Burger and H. W. Bryant, J. Org. Chem., 4, 119 (1939).

2- position, which is both meta to the ring-deactivating sulfone group and para to the ether linkage, should be the principal position susceptible to attack by electrophilic reagents.

Though the melting points found for 2-aminophenoxathiin-10-dioxide (169-176°, 175.5-176°) were different from those reported[52] (163-164.5°, 164-165°), this difference may be due to polymorphism. The higher-melting sample contained the theoretical percentage of sulfur and was converted in good yield to the known 2-chlorophenoxathiin-10-dioxide. This amine was also used as the starting material for the preparation of 2-bromo- and 2-iodophenoxathiin-10-dioxide, two new compounds.

Reduction of the Sulfone Group by Lithium Aluminum Hydride

The reduction of phenoxathiin-10-dioxide to phenoxathiin, a hitherto unreported reaction, was accomplished by the use of lithium aluminum hydride. Though the yield was moderate and it is probable that some cleavage occurred, it is likely that the conditions can be modified to give a large yield. It did not appear that dehalogenation accompanied the reduction of 2-chloro- and 2-bromophenoxathiin-10-dioxide to 2-chloro- and 2-bromophenoxathiin.

The two most convenient reactions for the introduction of groups into the 1- and the 2- position, metalation and nitration, respectively, are substitution reactions of phenoxathiin-10-dioxide. The value of these reactions has been increased considerably by the demonstration that phenoxathiin-10-dioxides can be reduced to the corresponding phenoxathiin derivatives.

Halogenation Reactions

The reaction of phenoxathiin with sulfuryl chloride in pentane yielded a mixture from which two compounds were isolated. One of these (m.p. 168-169°) was undoubtedly the same as the _,_-dichlorophenoxathiin (m.p. 167-168°) which Irie[50] obtained from the reaction of phenoxathiin with chlorine. The other compound (m.p. 79-81°) was designated as 3-chlorophenoxathiin after a re-examination of an old product from a Ferrario reaction.

Suter and Green[34] obtained from the Ferrario reaction of 3-chlorodiphenyl ether a material which was reported to melt at 59-60°. Depending upon whether ring-closure occurred through the 2- or 6- position in 3-chlorodiphenyl ether, the product would have been 1- or 3-chlorophenoxathiin, respectively. The investigators believed the product was

3-chlorophenoxathiin. On this basis they designated the chlorophenoxathiin (m.p. 81-82°) obtained by chlorination of phenoxathiin as the 1- derivative.

Irie[50], by an unambiguous synthesis, prepared 1-chlorophenoxathiin (m.p. 78-80°), the other expected product of the above-mentioned Ferrario reaction. Since the 1-derivative did not melt at 59-60°, this confirmed Suter and Green's choice of the 3-derivative as the product from the ring-closure reaction. However, when Irie found (by a mixed m.p. depression) that the product of chlorination (m.p. 78-79°) was not 1-chlorophenoxathiin, he was reluctant to designate it as the 3- derivative, since this compound was reported to melt at 59-60°.

A sample of the product (m.p. reported 59-60°) from the Ferrario reaction was further investigated in the present work. This material (m.p. found 61-67°) was found to be a mixture of two compounds, one of which (m.p. 80-82°) was the same as the chlorophenoxathiin obtained from the reaction of phenoxathiin with sulfuryl chloride. The other compound was not identified. Therefore, both the Ferrario reaction of 3-chlorodiphenyl ether and chlorination of phenoxathiin produced 3-chlorophenoxathiin, m.p. ca. 80°.

It is reasonable to believe that 3-chlorophenoxathiin was not the only monochlorination product of phenoxathiin.

Other chlorophenoxathiins may have been formed but escaped isolation. It is likely that the 2- isomer was produced since 2-bromophenoxathiin was one of the products of the bromination of phenoxathiin. The lack of 2-chlorophenoxathiin would be considered anomalous in view of the high reported yields of 2-bromophenoxathiin. However, the bromination experiments in this work revealed that the 2-position was not as reactive as had been believed.

In the initial stages of this work 2-bromophenoxathiin was considered a key compound, one which would serve as a useful starting material. However, after the unsuccessful attempts to repeat the bromination of phenoxathiin, a reaction which was reported[35] to give an 83% yield of 2-bromophenoxathiin (m.p. 59-60°), the compound became more important as a product than as a starting material. When 2-bromophenoxathiin was prepared by two unambiguous syntheses (See "Preparation of 2-bromophenoxathiin" and "Preparation of 2-bromophenoxathiin from 2-aminophenoxathiin by the Sandmeyer reaction".) and found to melt at 90-91°, the bromination reaction became open to considerable speculation.

Since the materials which had been obtained during the work on the bromination mixtures melted at temperatures higher than the melting point reported for 2-bromophenoxathiin, it was believed that some high-melting impurity was

present. However, since no pure product had been isolated from the mixture and it did not appear promising, the writer did not return to it after finding that 2-bromophenoxathiin melted at 90-91°. It is likely, however, that some pure 2-bromophenoxathiin could be isolated by a fractional recrystallization process in which seeds of the authentic compound are employed. That 2-bromophenoxathiin was formed by bromination was proved when 2-bromophenoxathiin-10-dioxide was isolated from the products which resulted upon oxidation of the crude bromination mixture. It is doubtful that 2-bromophenoxathiin was produced in a yield which would approach the reported 83%. If such had been the case, it is likely that the compound could have been easily purified since the number and amount of impurities would have been quite low. The results of the sulfur analysis of one crude fraction indicated that some dibromophenoxathiin was present. Also, it would not be illogical to suspect that the mixture contained some 3-bromophenoxathiin since 3-chlorophenoxathiin was produced upon chlorination of phenoxathiin.

Since 2-bromophenoxathiin melted at 90-91° and fractions of the crude dibromination mixture melted at temperatures over 115°, this writer views with suspicion the reported[35,58], melting points (92° and 92-93°) of 2,8-dibromophenoxathiin. However, something must explain the seeming lack of difference

in solubility between the mono- and dibromophenoxathiins, and if 2,8-dibromophenoxathiin does melt at 92°, it is likely that it would be very similar in solubility to 2-bromophenoxathiin. The isolation of a pure dibromophenoxathiin may not have been a problem of merely separating bromo- and dibromophenoxathiins. The mixture may have contained 2,7- and 2,8-dibromophenoxathiin.

Iodophenoxathiins have been prepared from 2- and 3-aminophenoxathiin and from 4-phenoxathiinyllithium.[75] There has been no report of an iodination of the phenoxathiin ring system or of the preparation of an iodophenoxathiin-10-dioxide. In this work is described the nitric-acid catalyzed iodination of phenoxathiin-10-dioxide, the third successful substitution reaction which has been performed on this compound. 2-Iodophenoxathiin-10-dioxide was isolated in a low yield from a mixture which was believed to contain only starting materials and the one organic product. The yield did not suffer from losses incurred in separation of the product from isomers and polyhalogen derivatives, a situation which prevailed in the case of bromination and chlorination of phenoxathiin. The recovery of a large amount of iodine indicated that the reaction was quite sluggish. It is believed that more powerful iodination conditions can be employed and the yield of 2-iodophenoxathiin-10-dioxide can

be increased without the danger of diiodination occurring. Herein lies the advantage of phenoxathiin-10-dioxide over phenoxathiin as a starting material in substitution reactions. The meta-directing and ring-deactivating sulfone group may limit substitution to the 2- position and inhibit disubstitution.

Oxidation Reactions

The hypochlorite oxidation of 2,8-diacetylphenoxathiin was carried out according to the method employed by Tomita[65], Irie[50] and Suter, McKenzie and Maxwell[35] in order to determine whether the sulfide linkage would be oxidized. The isolation of 2,8-phenoxathiindicarboxylic acid 10-dioxide (68.7%) is in agreement with the work of Tomita and Irie, both of whom found that oxidation of the sulfide to the sulfone accompanied the conversion of the acetyl to the carboxyl group. Suter and coworkers had reported that 2-phenoxathiincarboxylic acid was the product of the hypochlorite oxidation of 2-acetylphenoxathiin. Since oxidation to the sulfone was observed in three of the instances, attention is focused upon that preparation which is not in agreement.

First, the only analytical datum reported for 2-phenoxathiincarboxylic acid was a neutralization equivalent of 239,

which is 5 units below the theoretical value of 244. Whether the low neutralization equivalent was due to experimental error or to a phenoxathiindicarboxylic acid is a matter of speculation. Such an acid would have arisen from a diacetylphenoxathiin in the sample of the material oxidized. Though such a compound was not mentioned as a by-product in the preparation of 2-acetylphenoxathiin, it is likely that its presence may have been undetected. (See the discussion of the acetylation of phenoxathiin.)

Two facts indicate that there may be little difference between the reported 2-phenoxathiincarboxylic acid and the 2-phenoxathiincarboxylic acid 10-dioxide (m.p. 268-269°) which Irie prepared by the same method. An authentic specimen of the former acid (m.p. reported 259-260°) melted over the range 265-274°. This range includes the temperature reported by Irie for the melting point of the 10-dioxide. The infrared spectrum of a sample of the acid contained a band at 8.6μ which is characteristic of the sulfone group. Therefore the material would be expected to contain some 2-phenoxathiindicarboxylic acid 10-dioxide.

The acid from the haloform reaction was designated[35] as 2-phenoxathiincarboxylic acid since it did not depress the melting point of a sample of acid (m.p. reported 260-262°) prepared from 2-bromophenoxathiin (m.p. reported 59-60°) by

way of the Grignard reaction.[35] This preparation is open to question since the melting point of the starting material was ca. 30° lower than that found for 2-bromophenoxathiin (m.p. 90-91°) in this work.

A sample of the material which had been prepared by the Grignard reaction melted over the range 188-260°. It is probable that the compound could have changed in the twenty-year interval since its preparation. However, since this sample was reported to melt at approximately the same temperature as the one from the haloform reaction, it is peculiar that one should now melt over a 70°-range below, and the other over a 9°-range above the original melting point.

Cleavage Reactions

Raney nickel cleavage of the sixteen phenoxathiindicarboxylic acids would yield eleven dicarboxydiphenyl ethers. The structures of seven of the phenoxathiindicarboxylic acids could be proved unambiguously by this reaction. The other nine acids would yield the remaining four dicarboxydiphenyl ethers. Supplementary data are necessary in order for the cleavage reaction to be used in the proof of the structures in those cases where more than one phenoxathiindicarboxylic acid would yield the same product upon cleavage.

The three acids prepared by dimetalation of phenoxathiin and phenoxathiin-10-dioxide were cleaved by Raney nickel. Cleavage of 1,6- and 4,6-phenoxathiindicarboxylic acid yielded 2,3'- and 2,2'-dicarboxydiphenyl ether, respectively. The isolation of the latter acid furnished unambiguous proof of the structure of the 4,6- derivative. Theoretically, the 2,3'-dicarboxydiphenyl ether could result from desulfurization of either 1,6- or 3,6-phenoxathiindicarboxylic acid. The Raney nickel hydrogenolysis of 1,9-phenoxathiindicarboxylic acid 10-dioxide yielded 3,3'-dicarboxydiphenyl ether, an acid which could be produced by cleavage of the 1,7-, 3,7- and 1,9-diacids. The data involved in the elimination of the 3,6-, 1,7- and 3,7- derivatives were presented in the discussion of the dimetalation reactions.

The yields of the dicarboxydiphenyl ethers were low since the desulfurization reaction was accompanied by some cleavage of the ether linkage. This side reaction produced benzoic and hydroxybenzoic acids. Though the hydroxy acids were not isolated, positive tests for the phenolic hydroxyl group indicated their presence. Not only was the yield decreased by the ether cleavage, but the problem of isolating the dicarboxydiphenyl ethers was magnified by the presence of the two acids from the secondary reaction. It may be

possible to minimize the ether cleavage by decreasing the amount of the catalyst, the temperature or the reaction time.

The ether cleavage may not have been as great when 75% ethanol instead of 0.5% sodium carbonate was employed as the solvent for the reaction. However, the first method was abandoned when it was found that most of the product remained adsorbed on the nickel following filtration. Several extractions of the catalyst were required before a significant amount of the product could be obtained.

Cleavage of a carbon-sulfur bond occurred when phenoxathiin was treated with lithium in refluxing ether. The product of the cleavage was designated as the lithium salt of 2-lithio-2'-thioldiphenyl ether. This compound gave a positive Color Test I[111] and was converted into 2-thioldiphenyl ether by hydrolysis and into 2-carboxy-2'-thioldiphenyl ether by carbonation. The positive color test and the formation of the carboxylic acid proved that the cleavage product contained a carbon-lithium bond.

The above hydrolysis product was shown to be identical with an authentic specimen of 2-thioldiphenyl ether which was prepared by the reaction of sulfur with 2-lithiodiphenyl ether. Partial proof that the product was the thiol and not the oxidation product thereof, the disulfide, lay in the presence of the thiol band in the infrared spectrum of the

compound. Additional proof was provided by oxidation of the thiol to the disulfide by means of iodine in ethanol. This oxidation product, bis-(2-phenoxyphenyl)disulfide, afforded an infrared spectrum which was, with the exception of the absence of the thiol band, identical with that of 2-thioldiphenyl ether.

A second derivative of 2-thioldiphenyl ether was prepared by the reaction of the thiol with chloroacetic acid. The designation of the product as 2-phenoxyphenylmercaptoacetic acid was based upon the reaction by which it was prepared and upon the agreement between the experimental and theoretical values for the neutralization equivalent and the percentage of sulfur.

The proof of the structure of 2-carboxy-2'-thioldiphenyl ether is based upon the following evidence. First, the acid contained the theoretical percentage of sulfur. Second, the compound was easily oxidized, a reaction characteristic of thiols. Third, there was isolated from the same reaction mixture an acid which was the disulfide of 2-carboxy-2'-thioldiphenyl ether. The experimental values of the percentage of sulfur and the neutralization equivalent were in good agreement with the calculated values for this dicarboxylic acid. The infrared spectra of 2-carboxy-2'-thioldiphenyl ether and its disulfide were almost identical, a

property which would be expected of compounds bearing the thiol-disulfide relationship to one another.

The yield of the carbonation product was much lower than that of the hydrolysis product. No attempt is made to explain this since each reaction was carried out only one time.

The cleavage by lithium shows no promise as a reaction for the proof of the structures of phenoxathiin derivatives. After cleavage of an unsymmetrically substituted phenoxathiin there would be the problem as to which phenyl ring contained the thiol group. Also, the cleavage product would likely be an unknown compound which would be difficult to synthesize by another route.

The most commonly employed method for preparing an organometallic compound involves the reaction of a halo compound with a metal such as magnesium or lithium. Whether a phenoxathiinyllithium could be prepared from a halophenoxathiin and lithium without accompanying cleavage would depend upon the reactivity of the halogen. Such a reaction would be of value only if it would take place at a temperature below that at which cleavage occurs.

Melting Points*

Some of the variables which determine the melting point of a compound are symmetry, crystal structure, dipole moment and intermolecular forces. However, quantitative data concerning these factors are frequently lacking for the compounds which concern the synthetic organic chemist. Therefore, if one makes predictions or correlations based upon the one known physical constant, melting point, he relies upon intuition and simple analogy.

Upon examination of the tables of the melting points of derivatives of phenoxathiin one observes trends in this constant, two different melting points reported for some compounds and those melting points which appear "out of line". This discussion may bring to attention the possibility that some of the compounds exhibit polymorphism, that stereoisomerism may exist or that a compound may not actually be as designated.

There appears to be a trend in the melting points of the monosubstituted derivatives of phenoxathiin. In the majority of the available examples, the 4- derivative has the lowest and the corresponding 2- derivative the highest

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*References for all the melting points discussed in this section are listed in Tables 4-8.

melting point. The 1- and the 3- derivatives melt at approximately the same temperature. This relationship is shown in Table 10.

Exceptions to the above generalization are exhibited by the methyl- and acetamidophenoxathiins. The melting point

Table 10. Relationship between melting point and position of the substituent

Compound	Melting points of the four isomers			
	1-	2-	3-	4-
Chlorophenoxathiin	78-80	88-9	81-2	liquid
Bromophenoxathiin	---	90-1	---	---
Iodophenoxathiin	---	92-4	70-2	42.5-3
Aminophenoxathiin	---	93-5	81.5-3	liquid
Phenoxathiincarboxylic acid	223-4	260-2	223-4	171-3
Methyl phenoxathiin-carboxylate	95-6	---	---	liquid
Phenoxathiincarboxylic acid hydrazide	197-8	---	---	127-8
✓-Oxo-phenoxathiin-butyric acid	---	191-2	159-61	---
Methylphenoxathiin	---	38-9	83-4	liquid
Acetamidophenoxathiin	---	129-30	181-2.5	---

of 2-acetamidophenoxathiin appears low not only in comparison with that of 3-acetamidophenoxathiin, but upon consideration that acetamides usually melt at temperatures higher than 35° above the melting point of the corresponding low-melting amine. The melting point of 3-methylphenoxathiin (?) appears high in comparison with that of the 2- derivative. Though the melting point of 83-84° is in agreement with that of the 3-chloro-, iodo-, and amino- derivatives, one would not expect the methyl group to have the same effect as the amino and halo groups upon the melting point. It is shown in Table 11 that this compound is the only mono-methyl-substituted phenoxathiin which melts above the parent compound.

The introduction of a methyl group into a derivative containing no methyl groups lowers or has no effect on the melting point of the derivative. Since the 2,8-dimethyl-derivatives are symmetrically substituted, they would be expected to melt higher than the parent compounds.

The last pair of compounds exhibits in Table 11 an exception to the generalization mentioned. It appears that 2-chlorophenoxathiin-10-dioxide, a well-established compound, has an anomalous melting point since 2-amino-, 2-bromo- and 2-iodophenoxathiin-10-dioxide melt in the range 171-176°. The structure of 2-chloro-8-methylphenoxathiin-10-dioxide was not proved, making the comparison between this compound

Table 11. Effect of the methyl group upon melting points

Parent compound	M.p., ^{o}	M.p., ^{o}	Methyl-substituted compound
Phenoxathiin	56	38-9	2-Methylphenoxathiin
Phenoxathiin	56	83-4	3-Methylphenoxathiin(?)
Phenoxathiin	56	liquid	4-Methylphenoxathiin(?)
Phenoxathiin	56	74	2,8-Dimethylphenoxathiin
2-Aminophenoxathiin	98	97	2-Amino-8-methylphenoxathiin
2-Nitrophenoxathiin	160	160	2-Methyl-8-nitrophenoxathiin
Phenoxathiin-10-dioxide	147-8	134-5	2-Methylphenoxathiin-10-dioxide
Phenoxathiin-10-dioxide	147-8	138-9	3-Methylphenoxathiin-10-dioxide
Phenoxathiin-10-dioxide	147-8	141-2	4-Methylphenoxathiin-10-dioxide
2-Nitrophenoxathiin-10-dioxide	196.5	196-7	2-Methyl-8-nitrophenoxathiin-10-dioxide
2-Chlorophenoxathiin-10-dioxide	158-9	173	2-Chloro-8-methylphenoxathiin-10-dioxide

and 2-chlorophenoxathiin-10-dioxide of limited value. However, this slight difference in melting point casts a doubt on the assignment of the structure 2-chloro-8-methylphenoxathiin-10-dioxide to the compound melting at 173^{o}.

An important compound for which have been reported two melting points differing by 53° is 2,8-diaminophenoxathiin. (Both syntheses have been described in the Historical section of this thesis.) In Table 12 these two melting points are compared with those of 1,3- and 3,7-diaminophenoxathiin. The

Table 12. Melting points of diamino- and dinitrophenoxathiins

Compound	Melting points of the three isomers		
	1,3-	2,8-	3,7-
Diaminophenoxathiin	158	118, 166-8, 171-3	167-8
Dinitrophenoxathiin	187	143	204-5

melting points of 118° and 143° for 2,8-diamino- and 2,8-dinitrophenoxathiin, respectively, are in the expected relationship to one another, but much lower than those of the analogous 1,3- and 3,7- derivatives. If the correct melting point for 2,8-diaminophenoxathiin is approximately 170°, 2,8-dinitrophenoxathiin would be expected to melt at approximately 200°.

The melting points of the 2-substituted-8-nitrophenoxathiins follow no discernible pattern. All of the four disubstituted derivatives listed in Table 13 were prepared by Irie.[50] The melting point of 128-129° for 2-chloro-8-nitrophenoxathiin was reported by Krishna.[67] It is not known which melting point for 2-chloro-8-nitrophenoxathiin is correct. Though Irie made no mention of the relationship between the melting temperatures for the following three compounds, the writer of this thesis would expect 2-methoxy-8-nitrophenoxathiin to melt lower, and 2,8-dinitrophenoxathiin to melt higher than 2-nitrophenoxathiin. If the melting points as reported are correct, the nitro and methoxy groups have very interesting effects upon the melting points.

Table 13. Melting points of 2-substituted- and 2-substituted-8-nitrophenoxathiins

Parent compound	M.p., °	M.p., °	Nitro derivative
2-Methylphenoxathiin	38-9	160	2-Methyl-8-nitrophenoxathiin
2-Chlorophenoxathiin	88-9	195 (128-9)	2-Chloro-8-nitrophenoxathiin
2-Methoxyphenoxathiin	----	ca. 300	2-Methoxy-8-nitrophenoxathiin
2-Nitrophenoxathiin	160	143	2,8-Dinitrophenoxathiin

The melting points of many of the derivatives of phenoxathiin, phenoxathiin-10-oxide and phenoxathiin-10-dioxide increase with the increase in oxidation state of the sulfur, i.e., the phenoxathiin derivative melts at the lowest, and the corresponding phenoxathiin-10-dioxide derivative melts at the highest temperature. However, the following pairs of compounds exhibit exceptions to this generalization: phenoxathiin-10-oxide (m.p. 155°) and phenoxathiin-10-dioxide (m.p. 147-148°), 1-nitro-3-phenoxathiincarboxylic acid (m.p. 262°) and the 10-oxide (m.p. 251-252°), 1-phenoxathiincarboxylic acid 10-oxide (m.p. 262°) and the 10-dioxide (m.p. 229-231°), 1,3-diaminophenoxathiin-10-oxide (m.p. 262°) and the 10-dioxide (m.p. 228°).

The lower of the two melting points, 136-137° and 193-194°, for 2-phenoxathiinacetic acid appears to be more probable to this writer. It is believed that the difference between the melting point of 2-phenoxathiincarboxylic acid (m.p. reported 259-260°, 260-262°) and 2-phenoxathiinacetic acid should be greater than 70°, but less than 125°. The reported melting point of 2-phenoxathiincarboxylic acid is questioned. It is predicted that the melting point of this compound would fall in the range 230-240°.

There is no doubt that 2-bromophenoxathiin has a melting point of 90-91°. There may be another crystalline form which

melts at 59-60°. The occurrence of two forms would account for the difficulty encountered by this worker in isolating a pure bromophenoxathiin from the bromination mixture. If the melting point of 2,8-dibromophenoxathiin is 92-93° as reported, and there is only one form each of 2-bromo- and 2,8-dibromophenoxathiin, the melting point of the dibromo compound is unexpectedly low.

Suggestions for Further Research

Aminophenoxathiins and aminophenoxathiin-10-dioxides are the best starting materials for the preparation of many derivatives of phenoxathiin. 2-Nitrophenoxathiin-10-dioxide can be readily reduced to 2-aminophenoxathiin-10-dioxide.[52] 1-Aminophenoxathiin-10-dioxide and 4-aminophenoxathiin[54] should be prepared from the corresponding lithium compounds and O-methylhydroxylamine. The 1- and 4- amines will be contaminated by diamines resulting from dilithio derivatives.

The value of the metalations of phenoxathiin and phenoxathiin-10-dioxide would be enhanced considerably if the ratio of mono- to dimetalation were increased. It is probable that this may be accomplished by employing lower temperatures and less than an equivalent amount of n-butyllithium. Since methyllithium showed promise as a

monometalating agent, this reagent should be employed in a multifold excess. If the methyllithium is prepared from methyl bromide the products of subsequent reactions contain fewer impurities than if methyl iodide is employed.

The five oxygen and sulfur heterocycles, dibenzo-p-dioxin, phenoxathiin, thianthrene, dibenzothiophene and dibenzofuran, could be accurately compared on the basis of ease of dimetalation if all were subjected to the action of n-butyllithium under the same conditions. The neutralization equivalent of each mixture of crude acids would provide an estimate of the amounts of mono- and dicarboxylic acids present. The monocarboxylic acids could be removed from the mixture by trituration with benzene. The neutralization equivalent of the residue of crude dicarboxylic acids would reveal the efficiency of the trituration. Each of the first three heterocycles listed above will probably yield two dicarboxylic acids. (This has been demonstrated in the case of dibenzo-p-dioxin[94] and phenoxathiin.) If dibenzo-p-dioxin and thianthrene behave as did phenoxathiin, heteronuclear dimetalation will occur and the acid in which both carboxyl groups are ortho to the same hetero atom will be more soluble and lower-melting than the one in which a carboxyl group is ortho to each of the hetero atoms. The dimethyl esters would likely be more readily separated than the acids themselves.

This method was used by Gilman and Stuckwisch[94] for the separation of the two dicarboxylic acids of dibenzo-p-dioxin.

Since the reported[35] melting point of 2-phenoxathiin-carboxylic acid is open to question, this compound should be prepared by an unambiguous synthesis. The most convenient method would probably involve hydrolysis of the nitrile which could be prepared from 2-aminophenoxathiin by the Sandmeyer reaction.

It would be interesting to see whether the Grignard reagent could be prepared in good yield from 2-bromophenoxathiin (m.p. 90-91°). Suter and coworkers[35] employed ethylmagnesium iodide as a catalyst in the reaction between 2-bromophenoxathiin (m.p. 59-60°) and magnesium. One should avoid the use of an organometallic compound in this preparation since phenoxathiin is easily metalated.

Phenoxathiin-10-oxide is an ideal compound upon which organometallic compounds can be compared and tested as agents for metalation, reduction and cleavage. The postulated mechanism for the metalation of phenoxathiin-10-oxide can be tested if 2,2'-dilithiodiphenyl ether can be prepared from the dibromo compound by the halogen-metal interconversion reaction. The yield of the latter reaction should be tested by carbonation.

The reaction of phenoxathiin-10-oxide with phenyllithium should be investigated. This organometallic compound may not effect reduction as did n-butyllithium. However, if both reduction and cleavage occur, phenol and thiophenol may be products.

It has been postulated by Mr. D. R. Swayampati of This Laboratory that Grignard reagents do not cleave sulfoxides beyond the first stage illustrated in Equation 1 for the proposed mechanism of the reaction of n-butyllithium with phenoxathiin-10-oxide. If allylmagnesium bromide were employed as the cleavage atent, the presence of the allyl group in the cleavage product could be easily detected.

The action of n-butyllithium on diphenyl sulfoxide[109] should be further investigated. It may be advantageous to carry out the experiments on a larger scale than that used in the previous work[109] so that, if n-butyl mercaptan or disulfide is formed, it can be isolated in sufficient quantity to be identified. Since benzoic acid was the principal product when these reaction mixtures were carbonated, the action of phenyllithium on diphenyl sulfoxide should be investigated.

In order that the halogenation of phenoxathiin be of value in determining the relative directive influences of the sulfur and oxygen atoms, more data must be acquired.

On the basis of present information, the 2- and 3- positions are the sites of bromination and chlorination, respectively. Either this anomalous situation actually prevails or both positions are involved in each reaction. Since 3-bromophenoxathiin is a probable product of bromination, this compound should be first synthesized from the amine. Then, armed with the knowledge of its melting point, boiling point and solubility and with a seed crystal, one would be prepared to attack the problem of isolating 3-bromophenoxathiin from the bromination mixture.

Part of the difficulty in separating 2-bromophenoxathiin from the bromination mixture is due to the presence of a dibromophenoxathiin. By adding a seed crystal of 2,8-dibromophenoxathiin to a dilute solution of the bromination mixture one may be able to induce crystallization of this compound and thus separate it from the bromophenoxathiins and phenoxathiin. This would necessitate the prior synthesis of the compound from 2,8-diaminophenoxathiin. At the same time the unexpectedly low melting point (92-93°) which has been reported for 2,8-dibromophenoxathiin could be checked.

Both the reaction conditions for the acetylation of phenoxathiin and the methods of isolating the products are in need of improvement. If both 2- and 3-acetylphenoxathiin are formed, the corresponding oximes may be more readily separated than the ketones.

The only hydroxyphenoxathiin for which physical constants have been reported is the 4- derivative.[79] The others should be prepared from the corresponding amino- or lithiophenoxathiins and then be derivatized as the oxyacetic acids and methyl ethers. The effect of the methoxy group upon the melting point of phenoxathiin is interesting since 2-methoxy-8-nitrophenoxathiin was reported[50] to melt at ca. 300°.

During the Raney nickel desulfurization of the phenoxathiindicarboxylic acids cleavage of the ether linkage occurred. Raney nickel may cleave 2,2'-dicarboxydiphenyl ether and 4,6-dibenzofurandicarboxylic acid. The latter compound is suggested instead of 4-dibenzofurancarboxylic acid since there is the possibility that cleavage of this unsymmetrical acid would yield two products.

SUMMARY

A review of the literature of phenoxathiin was presented. Emphasis was placed on those preparations and reactions concerned with the identification of products of substitution reactions.

The known derivatives of phenoxathiin were listed in tables. Attempts were made to correlate the melting points of these derivatives.

A bibliography of the literature of phenoxathiin was compiled.

Phenoxathiin and phenoxathiin-10-dioxide were metalated with n-butyllithium, methyllithium and phenylcalcium iodide. The dimetalation products were identified and derivatized.

The structures of the three dicarboxylic acids prepared by way of dimetalation of phenoxathiin and phenoxathiin-10-dioxide were proved by hydrogenolysis with Raney nickel.

The action of n-butyllithium on phenoxathiin-10-oxide was found to be dependent upon temperature. Metalation, reduction and cleavage products were isolated. A mechanism of the metalation reaction was postulated and tested.

2-Bromophenoxathiin, a key compound, was prepared by two unambiguous syntheses and found to melt 30° higher than the reported melting point.

The first diazotization of an aminophenoxathiin-10-dioxide was performed.

Phenoxathiin-10-dioxide, 2-chloro- and 2-bromophenoxathiin-10-dioxide were reduced to phenoxathiin, 2-chloro- and 2-bromophenoxathiin, respectively, by lithium aluminum hydride.

The reaction of phenoxathiin with sulfuryl chloride was carried out and one of the products was proved to be 3-chlorophenoxathiin. A ring closure reaction was shown to yield the same product.

Bromination of phenoxathiin by a published method could not be duplicated. 2-Bromophenoxathiin-10-dioxide was isolated subsequent to oxidation of the crude bromination mixture.

The initial iodination of phenoxathiin-10-dioxide yielded 2-iodophenoxathiin-10-dioxide.

Oxidation of phenoxathiin in glacial acetic acid by dilute nitric acid produced good yields of phenoxathiin-10-oxide.

Several derivatives of phenoxathiin were oxidized to the corresponding 10-oxides and 10-dioxides by hydrogen peroxide.

2,8-Diacetylphenoxathiin was oxidized to 2,8-phenoxathiindicarboxylic acid 10-dioxide by sodium hypochlorite.

Phenoxathiin was cleaved by lithium in refluxing ether and the subsequent hydrolysis and carbonation products were identified.

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