Ion Radicals. VII. The Reactions of Thianthrene Oxide in Hydrochloric Acid[1,2]

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The reaction of thianthrene monoxide with concentrated hydrochloric acid gave thianthrene and 2-chlorothianthrene. The thianthrene cation radical was also formed. Chlorine was detected above the surface of the reaction solution. The same reaction in the presence of phenol gave *p*-chlorophenol, thianthrene, and the monohydrate of *p*-hydroxyphenylthianthrenylium chloride; no 2-chlorothianthrene was formed. Attempts to chlorinate thianthrene suspended in hydrochloric acid with chlorine and hypochlorous acid failed. The products were thianthrene oxides. The reductive chlorination is, therefore, regarded as not arising from reduction to thianthrene followed by electrophilic chlorination. Instead, nucleophilic substitution by chloride ion on the hydroxysulfonium cation is proposed. The formation of chlorine in the reductive chlorination is regarded as coincident with, but not responsible for, the formation of 2-chlorothianthrene. A nucleophilic substitution is also applied to interpreting the chlorination of thianthrene in dry chloroform.

The reaction of an aromatic sulfoxide with hydrochloric acid or hydrobromic acid may cause both reduction to the sulfide and reductive halogenation to the ring-halogenated sulfide. This reaction has been applied for the most part to the oxides of phenothiazines and thianthrenes. In the latter case Fries and Vogt[3] reported that thianthrene monoxide (I) dissolved slowly in concentrated hydrochloric acid to give a colored solution from which 2-chlorothianthrene precipitated slowly. This reaction was discussed in an earlier publication in the present series,[4] where it was pointed out that the colored solution had an absorption maximum at 546 mμ, the characteristic absorption of the thianthrene cation radical (II). The presence of II in solutions of I in hydrochloric acid was subsequently confirmed by e.s.r. spectroscopy in this laboratory. It was evident that the reaction of I with hydrochloric acid had a striking resemblance to its behavior in 96% sulfuric acid.[4,5] In each case, the ion radical II is formed, although to a much greater extent in the sulfuric than in the hydrochloric acid. In the hydrochloric acid ring halogenation occurs, while in 96% sulfuric acid ring hydroxylation takes place.

Two possible mechanisms for reductive halogenation have been proposed by Schmalz and Burger in work with 10-methylphenothiazine 5-oxide.[6] One of them consists of the electrophilic chlorine chlorination of preformed 10-methylphenothiazine, and the other, formulated originally by Page and Smiles,[7] involves the nucleophilic attack of chloride ion on a phenazothionium ion. The latter course has also been proposed by Craig[8] for the conversion of 3-chlorophenothiazine 5-oxide to 3,7-dichlorophenothiazine in a mixture of acetic and hydrochloric acids.

However, Gilman and Eisch[9] proposed that reductive halogenation occurred by electrophilic substitution, on the following evidence. The reaction of 10-ethylphenothiazine 5-oxide with hydrobromic acid gave 3-bromo-10-ethylphenothiazine. The same reaction in the presence of phenol gave *p*-bromophenol, 3-bromo-10-ethylphenothiazine, and 10-ethylphenothiazine. The reaction of 10-ethylphenothiazine oxide with hydrochloric acid gave 3-chloro-10-ethylphenothiazine, but the attempted trapping of chlorine with phenol was unsuccessful, and it was concluded that chlorination of the 10-ethylphenothiazine was too rapid to permit competitive chlorine capture by added phenol. Gilman and Eisch considered that the postulation of highly charged dications, such as the N-alkylphenazothionium ions, as intermediates in the nucleophilic chlorination mechanism was undesirable.

Evidence in support of the electrophilic halogenation mechanism was given in the thianthrene system by Gilman and Swayampati,[10] in that the bromine bromination of thianthrene in boiling glacial acetic acid and the reaction of the oxide I with boiling hydrobromic acid each gave 2-bromothianthrene, but, in contrast, the action of chlorine on thianthrene in hot 90% acetic acid gave only thianthrene di- and trioxides. It is this observation which stood out to us as being apparently anomalous in the scheme of reductive halogenation which depended on electrophilic substitution. In the reductive chlorination of I by hydrochloric acid no mention has ever been made of the formation of the higher oxides. The reaction of chlorine with thianthrene is the recognized way of preparing the dioxide.[11] Now, it is possible to prepare 2-chlorothianthrene by the action of chlorine on thianthrene, but the reaction does not definitely appear to be an electrophilic substitution. Fries and Vogt[3] found that, if chlorine was passed into a solution of thianthrene in dry chloroform or dry acetic acid the solid, red chlorosulfonium chloride (thianthrene dichloride) was formed. If the suspensions of the red solid were allowed to stand overnight, out of contact with moist air, the solid dissolved with the fading of the color, hydrogen chloride was liberated, and 2-chlorothianthrene was formed, but, if water was added to a freshly prepared suspension, the red solid became hydrolyzed to I. It seemed to us, from these observations, that the likelihood of chlorinating thianthrene electrophilically in aqueous hydrochloric acid was questionable. Because of this and our interest in cation radical formation we have investigated the behavior of I in hydrochloric acid.

Results

Thianthrene Monoxide (I) in Hydrochloric Acid.—As described earlier,[4] I suspended in hydrochloric acid was

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(2) This work was supported by the Directorate of Chemical Sciences, Air Force Office of Scientific Research (Grant AF-AFOSR-23-63), and the Robert A. Welch Foundation, to whom we express our thanks.

(3) K. Fries and W. Vogt, *Ann.*, **381**, 312 (1911).

(4) H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1962).

(5) H. J. Shine and T. A. Robinson, *J. Org. Chem.*, **28**, 2828 (1963).

(6) A. C. Schmalz and A. Burger, *J. Am. Chem. Soc.*, **76**, 5455 (1954).

(7) H. J. Page and S. Smiles, *J. Chem. Soc.*, **97**, 1112 (1910).

(8) J. C. Craig, M. E. Tate, and F. W. Donovan, *J. Med. Pharm. Chem.*, **2**, 669 (1960).

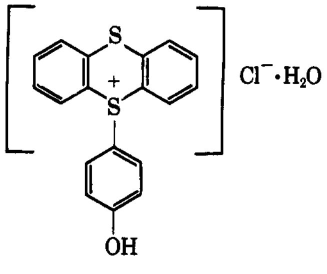
(9) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **77**, 3852 (1955).

(10) H. Gilman and D. R. Swayampati, *ibid.*, **77**, 5944 (1955).

(11) K. Fries and W. Vogt, *Ber.*, **44** 756 (1911).

found to disappear slowly with the continuous formation of a precipitate containing thianthrene and 2-chlorothianthrene. The pink color of the solution, formed very quickly on adding I to the acid, has now been found to be associated with the five-line e.s.r. spectrum of the thianthrene cation radical. We have now found also, by starch-iodide test, that chlorine is in the vapor above the reaction mixture.

The reaction of I with hydrochloric acid containing phenol was very rapid. The I dissolved immediately, in contrast to the system with no phenol, and a second, pink, semisolid phase separated. This phase was found to contain *p*-chlorophenol, thianthrene, and a new compound which we deduce is the hydrated sulfonium chloride III. The presence of 2-chlorothianthrene was not detected. The sulfonium chloride was easily converted to the corresponding anhydrous acid sulfate by the action of concentrated sulfuric acid.



III

The addition of I to a solution of phenol in water also caused the separation of a second, but fluid and colorless, phase, from which only I was recovered.

The blowing of nitrogen gas through a suspension of I in concentrated hydrochloric acid prevented the formation of 2-chlorothianthrene. About 85% of the I was recovered and the concentration of the acid was diminished to 26.5%. Thianthrene was formed in 15% yield.

When hydrogen chloride gas was blown through a suspension of I in hydrochloric acid, the I dissolved quickly. From the deep blue solution there separated a solid which was found to contain more 2-chlorothianthrene than was obtained from the use of hydrochloric acid alone.

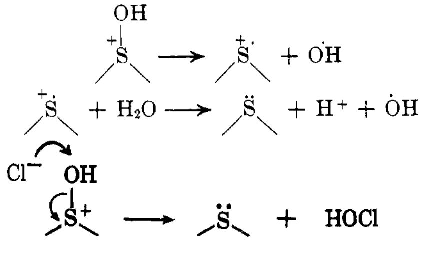
Attempts to Chlorinate Thianthrene.—The reaction of a small amount of chlorine with thianthrene suspended in hydrochloric acid slowly caused the yellow-colored solution to become pink. The solution had the five-line e.s.r. spectrum of II. The thianthrene did not appear to dissolve. A similar observation was made when a small amount of hydrogen peroxide was added to a suspension of thianthrene in hydrochloric acid. When larger amounts of chlorine or hydrogen peroxide were used the thianthrene underwent further oxidation. Chlorine gave a mixture of the *cis*-dioxide and the trioxide. The hydrogen peroxide reaction gave the trioxide. In neither case did the unrecrystallized product solid contain halogen. In neither case did the amount of suspended matter appear to diminish during reaction.

The addition of sodium hypochlorite to a suspension of thianthrene in hydrochloric acid also gave the *cis*-dioxide and trioxide as products. No ring halogenation was observed.

Discussion

The visible[4] and e.s.r. spectra leave little doubt that the thianthrene cation radical, II, is formed from I in hydrochloric acid. We have reported on the analogous behavior of I in concentrated sulfuric acid and of the phenothiazine and phenoxathiin oxides in aqueous sulfuric and phosphoric acids (previous papers in this series). In those cases and in this it seems that the homolysis of the protonated oxide (eq. 1) may be the reaction which leads to the cation radical. It may be argued that the cation radical is formed by a one-electron oxidation only after the protonated oxide is reduced to its parent compound. In the present case, for example, where thianthrene precipitates from solution, the formation of the thianthrene may be represented as in eq. 3, and the formation of the cation radical II by a subsequent one-electron oxidation of some of the thianthrene. We feel that the major portion of the thianthrene which precipitates is formed by the reduction shown in eq. 3, but we do not believe that the II comes from its partial reoxidation. The action of a small amount of chlorine on a suspension of thianthrene in hydrochloric acid produced II only slowly. In contrast, when I is suspended in hydrochloric acid, II is produced almost immediately. It seems that in the reaction with a small amount of chlorine the thianthrene is first oxidized to I and that some of the I leads to II. We were also unable to produce II by adding a small amount of chlorine to a benzene solution of thianthrene. A light orange solution was obtained, which gave no e.s.r. signal; the color was undoubtedly due to the presence of thianthrene dichloride. The homolysis of the protonated oxide seems the better answer to cation radical formation in this and the other cases, even though the proposed formation of hydroxyl radicals is intuitively unattractive.

The concentration of II obtained from I in hydrochloric acid is never high. Some of the II may become hydrolyzed to thianthrene (eq. 2).[4] The main reaction of the I is its reductive chlorination. The reduction is formulated in eq. 3. It is unlikely that much of the hypochlorous acid can exist in the highly acidic solution of chloride ion,[12] but that it is instead converted to chlorine (eq. 4). This is one of the ways in which chlorine can be formed in the acid solution of I. Chlorine may also be formed from the reaction of hydroxyl radicals with chloride ion.



(1)

(2)

(3)

$$H_2\overset{+}{O}Cl + Cl^- \longrightarrow H_2O + Cl_2 \qquad (4)$$

In these ways chlorine is made available for the electrophilic chlorination of the reductively formed thianthrene. Several of our results appear to support the proposal that this is the mode of chlorination. They are the trapping of chlorine with phenol and the

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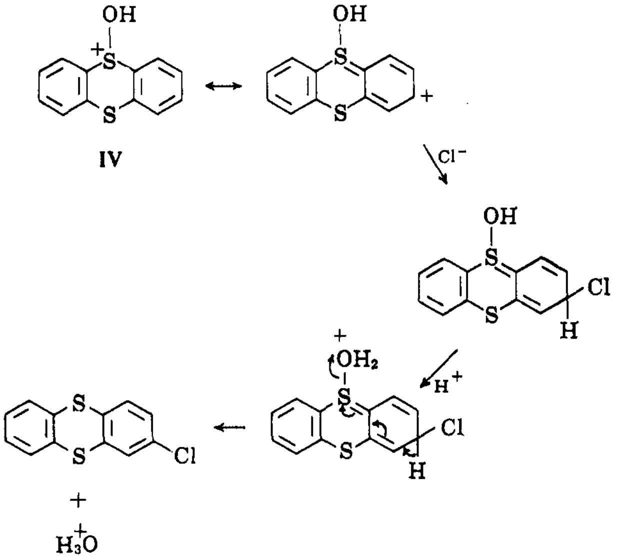
[12] J. Hine, "Physical Organic Chemistry," 2nd Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 363.

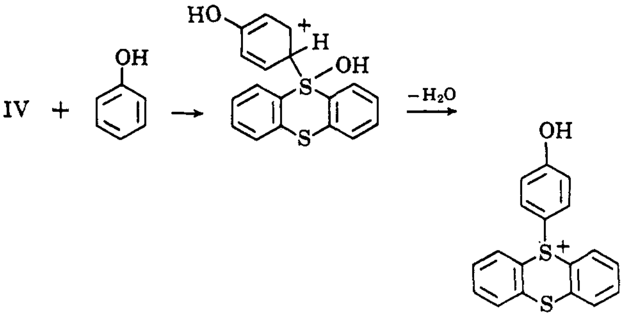
absence of 2-chlorothianthrene in the product; the formation of some thianthrene but not 2-chlorothianthrene when nitrogen was blown through the acid (and so, perhaps, stripped the solution of chlorine); and the increased formation of 2-chlorothianthrene when hydrogen chloride was blown through the acid (where the increase in hydrogen chloride content may have led rapidly, by the routes outlined above, to a higher concentration of chlorine).

Yet, all of our attempts to chlorinate thianthrene suspended in hydrochloric acid have failed. Instead, only mixtures of higher oxides were obtained. These attempts, carried out as they were on suspensions (and, therefore, saturated solutions) of thianthrene, may be thought not to be valid comparisons with the reductive chlorination. In the reductive halogenation thianthrene precipitates from solution; the solution, presumably, is saturated in thianthrene. In each case, therefore, thianthrene should be available for ring chlorination by chlorine in solution if that were the mode of chlorination.[13] The results do not encourage the acceptance of electrophilic chlorination as the route to product.

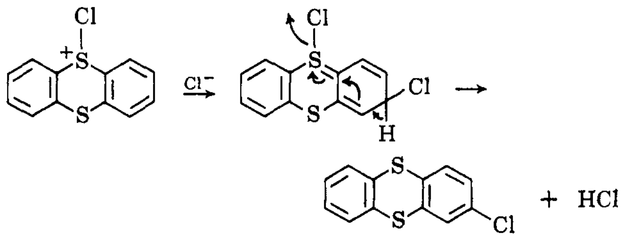
All of our results can be fitted to the nucleophilic halogenation of a thianthrenylium cation, formulated with the protonated oxide.



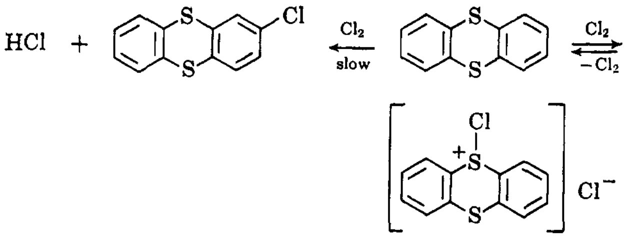
It is possible that the decrease in acidity caused by blowing nitrogen through the acid prevented this sequence of reactions, while the blowing of hydrogen chloride into the acid enhanced it. The reason that no 2-chlorothianthrene was formed where phenol trapped chlorine may be that IV was removed too quickly by reaction with phenol for reaction with chloride to occur.



The chlorination of thianthrene in chloroform[3] may also be formulated as a slow, nucleophilic substitution on the chlorosulfonium ion.



The alternative is an equilibrium, predominantly to the right, shown below, from which thianthrene is slowly removed by ring chlorination. In the aqueous, hydrochloric acid systems the chlorosulfonium chloride obtained from thianthrene, which was either formed *in situ* or was added, would be removed rapidly, we believe, by hydrolysis to the oxide. Therefore, the equilibrium and chlorination shown above would not be applicable.



Our conclusion is that the reductive chlorination of thianthrene oxide may well be nucleophilic rather than electrophilic.

Experimental

The thianthrene, m.p. 155–157°, and thianthrene monoxide (I), m.p. 142–143°, used in this work were obtained as described earlier.[5]

The Reaction of I with Concentrated Hydrochloric Acid. A.—I (5 g.) was added over a period of 5 min. to 200 ml. of acid stirred at room temperature. At the first addition, the mixture took on a purple color which intensified with time. A piece of moist starch–iodide paper held above the mixture turned blue. Within 10 min. a white, powdery solid was observed among the long needles of suspended I. After 20 hr. the needles of I were no longer present. The suspension was filtered to give 2.9 g. of white, powdery solid. The purple filtrate had an absorption maximum at 546 mμ and an e.s.r. spectrum of five symmetrical lines with a *g* value of 2.0081, the characteristics of the thianthrene cation radical (II). The purple filtrate was added to a large volume of cold water to precipitate a mixture of a white, flocculent solid and a yellow oil, totaling 1.8 g. This and the powdery solid were combined and crystallized from methanol to give 2.2 g. of white needles, m.p. 125–140°. The methanol filtrate is designated A. The white needles were recrystallized three times from acetone to give 0.3 g. of thianthrene, m.p. and m.m.p. 154–155°. The filtrates from the acetone crystallizations were combined with A and concentrated by evaporation to give a yellow, oily solid, m.p. 57–78°. Two crystallizations from methanol gave 0.2 g. of white crystals, m.p. 82–83°. The melting point of a mixture with 2-chlorothianthrene (m.p. 84°[14]) was not depressed while that with 1-chlorothianthrene (m.p. 85°[14]) was 68–75°.

B. Under Nitrogen Flow.—I (2 g.) and 100 ml. of acid were used. Nitrogen gas was bubbled vigorously through the stirred

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[13] A referee has suggested that chlorination occurs by a slow attack of HO_2Cl^+ on thianthrene, while the thianthrene is in an oxidation–reduction equilibrium with thianthrene monoxide. It is our feeling that the concentration of HO_2Cl^+ in the hydrochloric acid solutions will be so low[12] as to make its participation in the chlorination highly unlikely.

[14] H. J. Shine, C. F. Dais, and R. J. Small, *J. Org. Chem.*, **29**, 21 (1964).

acid during the addition of the I and continuously thereafter for 24 hr. The first addition of I caused the acid to become purple. The visible spectrum had a maximum at 546 mμ. After 7 hr. most of the needle-like crystals of the I had been replaced by a powdery solid. The supernatant solution was still purple and gave the five-line e.s.r. spectrum of II. After 24 hr. the supernatant was colorless and the solid (B) was entirely powdery. No e.s.r. signal was detected in the supernatant. The collected solid weighed 1.91 g. and had m.p. 135–148°. A Beilstein halogen test was negative. Fractional crystallization from methanol gave thianthrene, m.p. 155–156°, and I, m.p. 141–143°. Mixture melting points with authentic samples were the same. Spectrophotometric analysis[4] of B in cyclohexane solution showed that the composition of B was 15.4% of thianthrene and 84.6% of I.

The bubbling of nitrogen through a control sample of hydrochloric acid caused a drop in hydrogen chloride content from 36.3 to 26.5%. I did not dissolve in the weaker acid and no color developed during 24 hr.

C. **Under Hydrogen Chloride Flow.**—Hydrogen chloride was bubbled through 100 ml. of concentrated acid while 1.7 g. of I was added and was continued thereafter. The I dissolved almost instantly to give a deep blue, almost black, solution. A fine white powder began to precipitate within 10 min. The gas flow was stopped after 5 hr. The white powder and highly colored solution were poured into 200 ml. of cold water. The filtered, dried solid weighed 1.5 g., m.p. 65–105°. A Beilstein halogen test was positive. Two crystallizations from ethanol gave 0.4 g. of 2-chlorothianthrene, m.p. and m.m.p. 82–83°.

D. **In the Presence of Phenol.**—Experiment A was repeated with hydrochloric acid in which 5 g. of phenol had first been dissolved. On adding portions of I the solution became turbid and pink immediately. Globules of oil formed rapidly. Within a few minutes of adding all of the I the oil globules had coalesced to a soft ball which settled at the bottom of the solution. The orange-colored solution did not give an e.s.r. signal. No change in the appearance of the flask contents occurred during 2 hr., after which the soft lump was removed and stirred for 4 hr. with 100 ml. of 5% sodium hydroxide solution. A white, powdery solid formed, which was collected and dried to give C, 3.2 g., m.p. 136–146°. A Beilstein test for halogen was negative. It was found in earlier work[14] on the preparation of 2-hydroxythianthrene from 2-chlorothianthrene that halogen displacement by sodium hydroxide could not be caused even by boiling with sodium hydroxide solution.

The filtrate from C was acidified with 10% hydrochloric acid to precipitate 1.6 g. of red oil having a strong phenolic odor. This oil is designated D. Crystallization of C twice from acetone gave 1.5 g. of thianthrene, m.p. and m.m.p. 154–155°.

To the oil D was added 50 ml. of acetone, causing the precipitation of 0.6 g. of white crystals, E, m.p. 226–227.5°. The red-brown acetone filtrate is designated F. Crystallization of E gave 0.4 g. of shiny, white crystals of III, m.p. 231.5–232° dec.

The filtrate F was evaporated to give an oily, phenolic residue. This was dissolved in dry ether; the solution was dried over magnesium sulfate and evaporated to give an oil. The benzoate, m.p. 87–88°, and 1-naphthylurethan, m.p. 162–164°, were made. The reported melting points of the benzoate and 1-naphthylurethan from *p*-chlorophenol are 88 and 166°, respectively.[15] An authentic sample of *p*-chlorophenyl benzoate was made. Admixture with the above benzoate did not depress the melting point.

The Characteristics of III.—Prior to its melting, crystalline III became powdery and gave off water vapor, which condensed in the upper part of the melting point capillary and was identified by its turning anhydrous copper sulfate blue. Thermogravimetric analysis, kindly made available to us by Dr. W. W. Wendlandt, showed that a sample of III lost 4.97% of its weight between 120–210°. The calculated water of hydration in III is 4.96%. Between 210 and 232° the weight remained constant but at the latter temperature weight loss became rapid and a strong phenolic odor was detected.

Anal. Calcd. for $C_{18}H_{15}ClO_2S_2$ (362.9): C, 59.57; H, 4.20; Cl, 9.77; S, 17.67. Found[16]: C, 59.40; H, 4.34; Cl, 9.69; S, 17.69.

Analysis for ionic chloride was carried out separately in our laboratory by the method of Diehl and Smith[17]: found, 9.88%.

A solution of III in 96% sulfuric acid remained colorless for many hours. A faint purple color developed only after standing overnight, and the solution then displayed the five-line e.s.r. spectrum characteristic of II, but with very low intensity.

To 5 ml. of 96% sulfuric acid was added 0.23 g. of III. Dissolution was immediate with much effervescence. The colorless solution was poured immediately onto ice. Small white crystals formed in the aqueous solution. Filtration, washing with water and ethanol, and drying gave 0.22 g. of the sulfonium bisulfate, m.p. 236° dec.

Anal. Calcd. for $C_{18}H_{14}O_5S_3$ (406.5): C, 53.18; H, 3.47; S, 23.66. Found[16]: C, 53.10; H, 3.67; S, 23.53.

The Reaction of I with Phenol in Water.—I (2 g.) was added over a 5-min. period to a stirred solution of 5 g. of phenol in 100 ml. of water. A colorless oily globule settled out. This did not become a viscous lump as in experiment D. The supernatant was decanted after stirring for 4 hr. and the oil was stirred with 5% sodium hydroxide solution as in D. The white solid was removed, washed, and dried to give 1.9 g. of I, m.p. and m.m.p. 142–143° with authentic I.

The Reaction of Thianthrene with Chlorine in Hydrochloric Acid.—The addition of a small amount of chlorine to a suspension of thianthrene in concentrated hydrochloric acid caused the acid to become yellow. After about 1 hr. of stirring the solution was faintly pink. After 3 hr. the pink supernatant liquid had a maximum at 545 mμ and gave the five-line e.s.r. spectrum of II.

Chlorine gas was bubbled intermittently into a suspension of 2 g. of thianthrene in 110 ml. of acid. The pink color of the supernatant disappeared after 1 hr. There seemed at no time to be a decrease in the amount of solid matter in suspension. After 4 hr. the white solid was filtered to give 1.33 g., m.p. 207–240°. Dilution of the filtrate gave 0.59 g. of white solid, m.p. 231–240°. In both solids a Beilstein test for halogen was negative. The solids were combined and fractionally crystallized from ethanol to give 0.3 g., m.p. and m.m.p. 216–217°, with authentic thianthrene trioxide and 1.1 g., m.p. and m.m.p. 274–276° with authentic thianthrene *cis*-dioxide.

The Reaction of Thianthrene with Hypochlorous Acid.—To a stirred suspension of 3.40 g. of thianthrene in 160 ml. of concentrated hydrochloric acid was added, in portions over a 30-min. period, 60 ml. of a 10% solution of sodium hypochlorite. Each addition was exothermic; the solution became yellow temporarily and chlorine was detected above the surface. At no time did the solution become free of suspended solid. After stirring for 24 hr. the suspension was filtered to give 3.74 g. of white product, m.p. 207–210°. A Beilstein test for halogen was negative. The filtrate was diluted with a large volume of water; nothing further precipitated. Crystallization of the product from ethanol gave 3.1 g., m.p. 212–214°. Four further crystallizations from acetone gave 1.85 g. of thianthrene trioxide, m.p. 216–217°, and 0.20 g. of the *cis*-dioxide, m.p. 279–280°.

The Reaction of Thianthrene with Hydrogen Peroxide in Hydrochloric Acid.—The addition of a few drops of 30% hydrogen peroxide solution to a stirred suspension of 3 g. of thianthrene in 150 ml. of concentrated hydrochloric acid caused a pink color to appear after 30 min. The e.s.r. signal and the 546-mμ absorption maximum characteristic of II were recorded. The pink color in the supernatant persisted for over 1 week.

When 15 ml. of 10% hydrogen peroxide was added to a similar suspension over a period of 30 min., chlorine gas was detected above the surface. The suspended solid did not appear to change. After 4 hr. it was collected to give 3.4 g., m.p. 216–217°. A Beilstein test for halogen was negative. The melting point was not depressed by admixture with thianthrene trioxide.

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(15) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 680.

(16) Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(17) H. Diehl and G. F. Smith, "Quantitative Analysis," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 113.