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I hereby recommend that the thesis prepared under my supervision by H. Fred Oehlschlaeger

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by

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To

Betty D. Oehlschlaeger

for her unfailing encouragement, this work is affectionately dedicated.

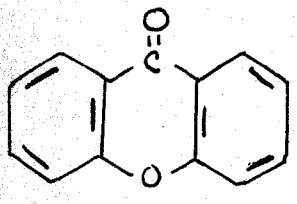
I INTRODUCTION

In the proposed work the heterocyclic molecule thiaxanthene will be utilized as a nucleus to prepare a number of compounds which might reasonably be expected to be of some value as chemotherapeutic agents. A correlation between structure and physiological activity will be attempted in so far as allowed by the rather meager information furnished in the literature.

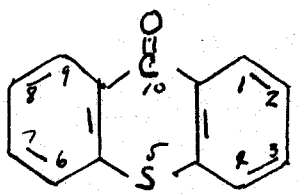
It is beyond the scope of this work to attempt to report and classify all of the derivatives of thiaxanthene and related compounds that have been reported. However, some knowledge of the chemistry of thiaxanthene and its corresponding ketone, thiaxanthone, is desirable in order to understand the nature of the problem and the difficulties encountered in its solution. No attempt will be made by the author to include any ring substituted compounds, most of which are prepared by ring closure. Only two cases of substitution on any thiaxanthene type structure have been reported. We will, however, attempt to discuss the chemistry of thiaxanthene which contains both an oxidizable methylene group and a sulfur atom as bridges between two aromatic rings. It will also be necessary to present a partial review of the 10-substituted thiaxanthenes since these relate directly to the problem.

II HISTORY OF THIAXANTHONE AND DERIVATIVES

Thiaxanthone. (II) Thiaxanthone, the sulfur analogue of the better known xanthone (I), was first prepared by Ziegler in 1890 (1).

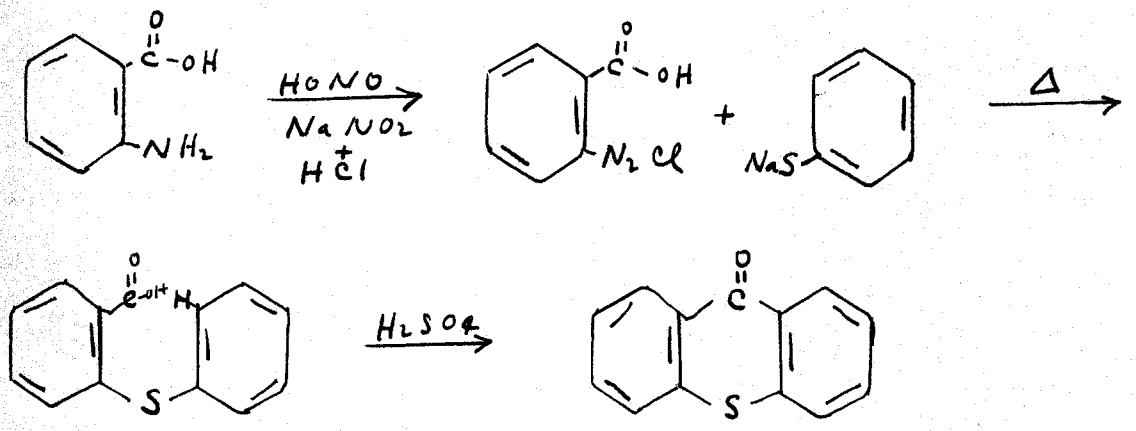


Xanthone
(I)



Thiaxanthone
(II)

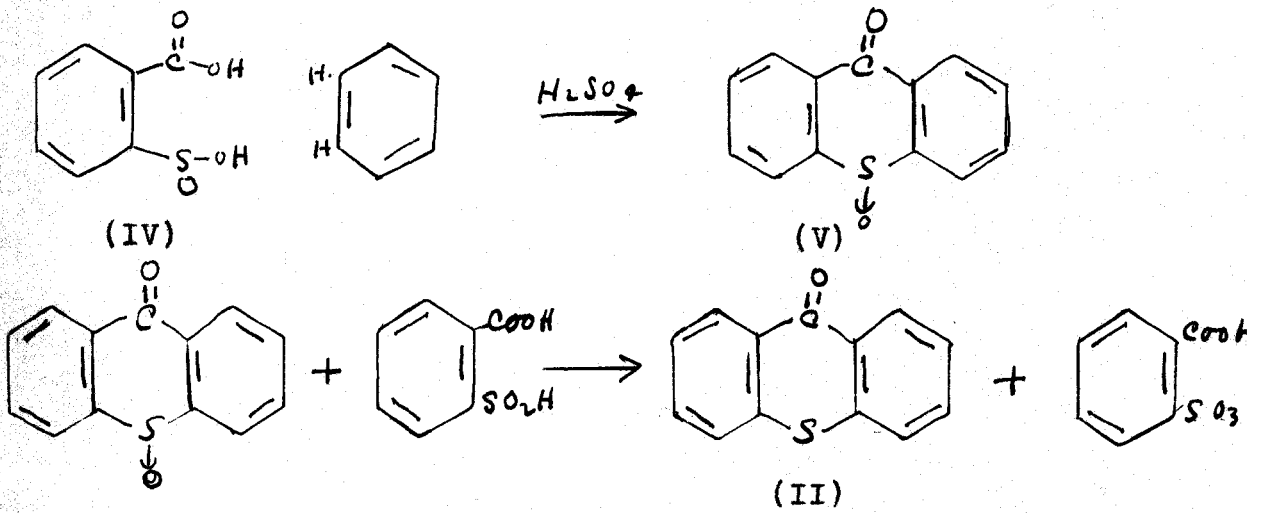
He coupled diazotized anthranilic acid with thiophenol in alkaline solution to obtain 2-carboxyldiphenylsulfide (III). Ring closure of this compound to thiaxanthone was accomplished by heating with concentrated sulfuric acid for a few minutes.



(III)

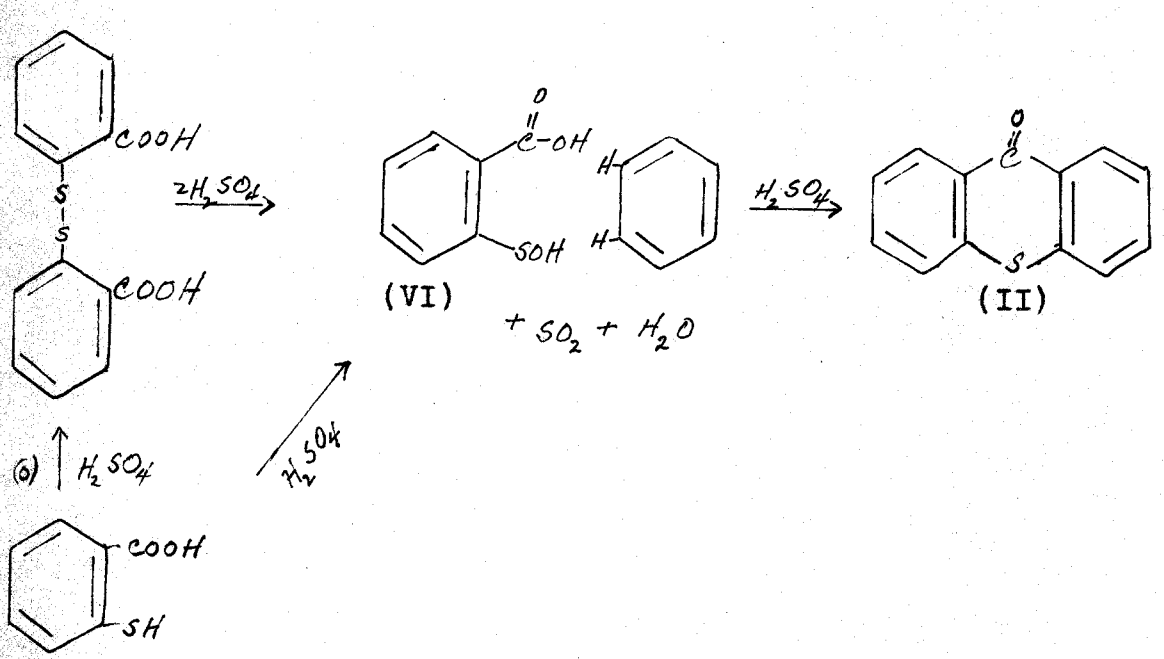
The compound may also be prepared in rather poor yields by prolonged heating of thiosalicylic acid with acetic anhydride or by dry distillation of the phenyl ester of thiosalicylic acid (2). Smiles (3)(4)(5) and his colleagues, over a period of years, synthesized thiaxanthone and some

substituted derivatives by direct condensation of either o-carboxybenzene sulfinic acid, dithiosalicylic acid or thiosalicylic acid with benzene or other aromatic compounds in concentrated sulfuric acid. The mechanisms postulated by Smiles for these condensations are rather interesting. The reaction of o-carboxybenzene sulfinic acid (IV) with benzene is straightforward enough; thiaxanthone-oxide (V) is formed as an intermediate by loss of two molecules of water between the acid groups and the benzene molecule. The sulfoxide is then reduced to (II) by the original sulfinic acid which is in turn oxidized to the corresponding sulfonic acid.



While this method yielded a satisfactory product it is not very efficient since it requires the use of two moles of the sulfinic acid for every mole of thiaxanthone produced. As o-carboxybenzene sulfinic acid is only prepared with some difficulty, this synthesis did not prove very practical from a preparatory standpoint. In the condensation of dithiosalicylic acid or thiosalicylic acid with benzene, an unisolatable

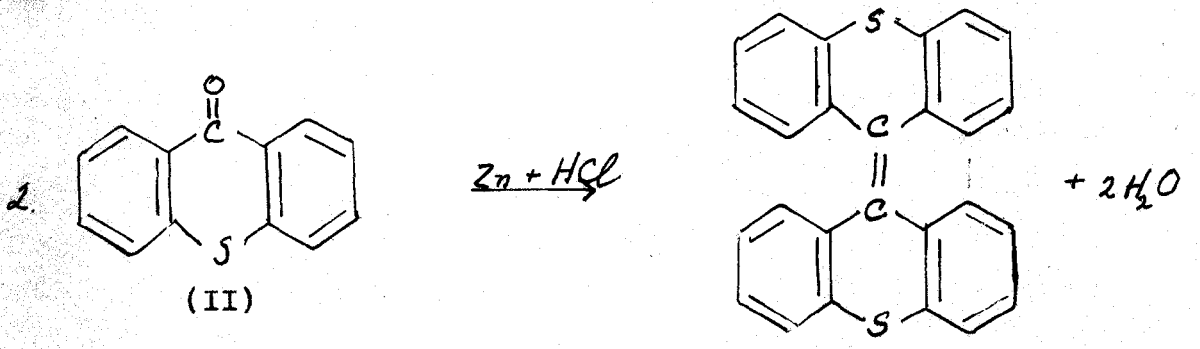
o-carboxyl sulfenic acid (VI) is formed as an unstable intermediate. This intermediate then condenses with the benzene ring by loss of two moles of water as shown in the accompanying diagram. The thiosalicylic acid may be first oxidized to the dithiosalicylic acid or converted directly to the unstable intermediate. There is no evidence to indicate which reaction actually occurs.



The yields in these condensation reactions were reported, surprisingly enough, as excellent. For example thiaxanthone was obtained in a ninety per cent yield by the condensation of thiosalicylic acid with benzene. The yields using dithiosalicylic acid and benzene were slightly lower, but since thiosalicylic acid is usually prepared by the reduction of dithiosalicylic acid, the overall yield of thiaxanthone from the condensation using either the mono or dithiosalicylic acid is about the same. However many side products were

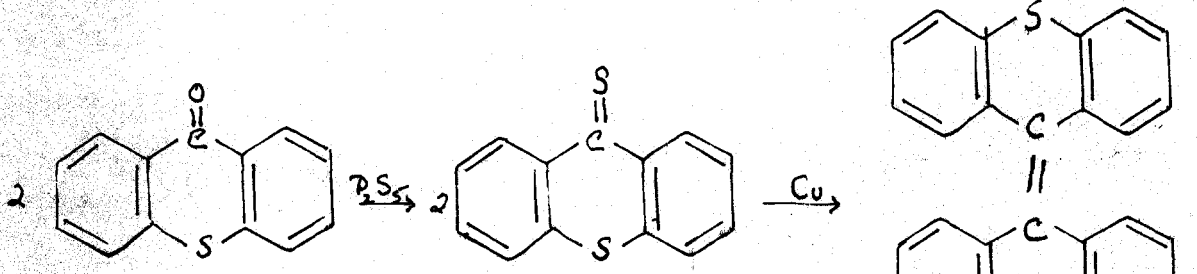
produced when phenol was substituted for benzene to form 2-hydroxythiaxanthone and the yield was therefore very low.

Fritz Mayer (2) reported the condensation of two molecules of thiaxanthone to form dithiaxanthylene (VII). This reaction is analogous to one carried out in the xanthone series to form dixanthylene (6); zinc and hydrochloric acid are the reagents used to carry out the reaction.



(II) (VII)

As might be predicted of a condensed molecule of this type, dithiaxanthylene was reported as being a high melting (346°) microcrystalline solid which was insoluble in most organic solvents. Dithiaxanthylene was later prepared, evidently in purer form, by Ardnt(7). He prepared the sulfur analogue of thiaxanthone, thiaxanthione (VIII), by the action of phosphorus pentasulfide on the former compound. He then condensed two molecules of thiaxanthione by the use of copper bronze.

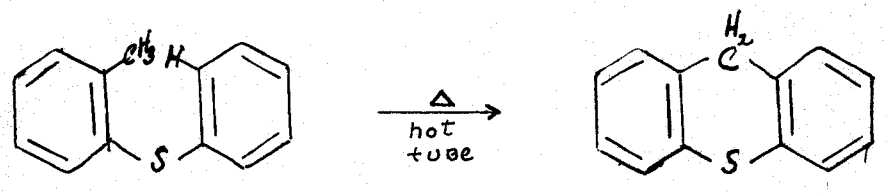


(II) (VIII) (VII)

Dithiaxanthylene prepared by this synthesis melted at 365° to a clear colorless melt. Ardnt found that the condensed compound would not add bromine across the double bond; instead six atoms of bromine added to the compound to form a perbromide. Dithiaxanthylene was oxidized to dithiaxanthylene dioxide, a compound which is described as darkening somewhere between 380° and 500° and melting to a brown liquid at the glowing point of platinum foil. The double bond in this compound was inactive and thus was unaffected by bromine. Schoenberg has prepared and studied these condensed type compounds for many years and recently a review has been published containing references to some of his many papers (8).

Several investigators (1)(9) tried unsuccessfully to prepare an oxime or a phenylhydrazone of thiaxanthone, however, the ketone is active enough to react with the Grignard reagent (10)(11).

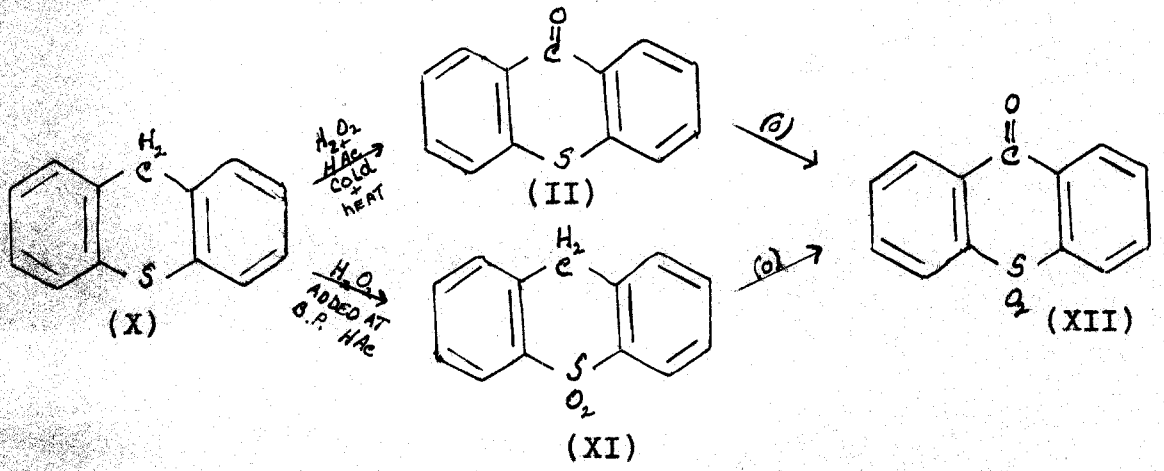
Thiaxanthene. (X) Around the turn of the century, Graebe and Schulthess (9) continued Ziegler's investigation of phenylthiosalicylic acid and its derivatives. They repeated Ziegler's synthesis of thiaxanthone and then reduced the ketone by means of hydriodic acid or red phosphorus and iodine to diphenylmethane sulfide or as it is now called, thiaxanthene. They also synthesized the compound by passing phenyl-o-tolyl sulfide (IX) through a red-hot tube.



(IX) (X)

Recently Fehnel (12) reduced thiaxanthone to thiaxanthene by the Huang-Minlon (13) modification of the Wolf-Kishner reduction. To this day no synthesis capable of being adapted to fairly large scale preparation has been reported for this compound. This fact precludes work on substitution or other reactions of thiaxanthene.

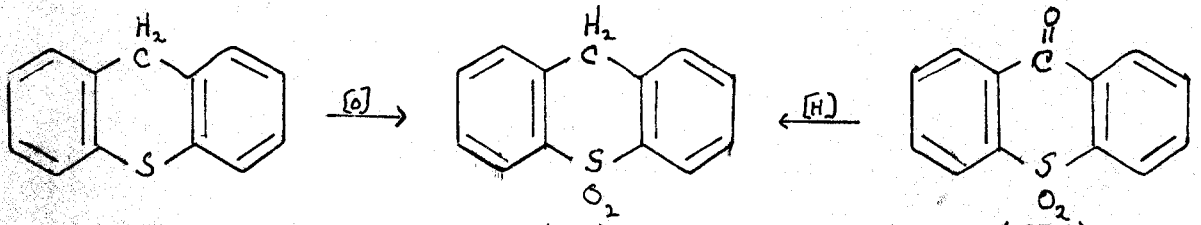
According to Hilditch and Smiles (14) thiaxanthene acts in an unusual manner toward oxidation. They report that by adding hydrogen peroxide to a solution of thiaxanthene in cold acetic acid, warming to the boiling point and isolating the oxidation product they obtained the expected thiaxanthone (II). However, by adding the same strength of hydrogen peroxide to a solution of thiaxanthene in boiling acetic acid they obtained thiaxanthene-5-dioxide (XI) and no other product. Both of these compounds can be converted to thiaxanthone dioxide (XII) by further oxidation.



(X) (II) (XI) (XII)

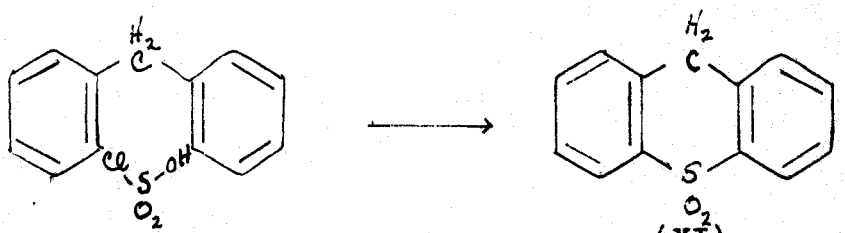
Thiaxanthene crystallizes as white needles from a mixture of alcohol and chloroform; its melting point is 128°.

Thiaxanthene-5-dioxide. (XI) Thiaxanthene-5-dioxide is intermediate in the oxidation of thiaxanthene to XII or in the reduction of XII to XI. It can actually be isolated either in the oxidation or in the reduction process (9)(14) as illustrated in the following diagram:



(X) (XI) (XII)

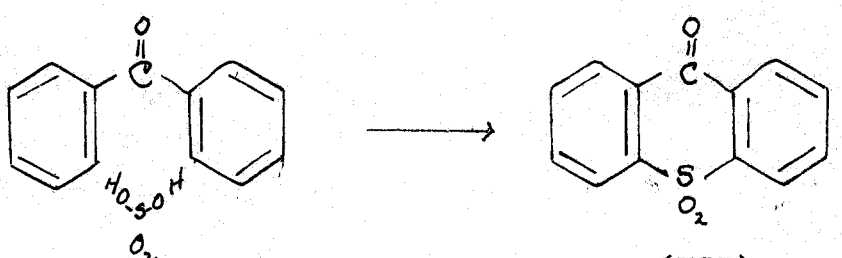
The material can also be prepared in rather small yields by treatment of diphenylmethane with chlorosulfonic acid (15)(16).



(XI)

It crystallizes from alcohol in colorless needles which melt sharply at 169-170°.

Thiaxanthone-5-dioxide. (XII) This substance was first described by Beckmann (17) who obtained it as a by-product in the treatment of benzophenone with fuming sulfuric acid.

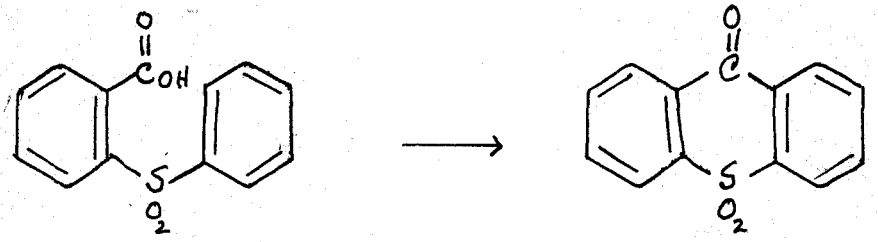


(XII)

Ziegler (1) and later Graebe and Schulthess (9) prepared the compound by oxidation of thiaxanthone. All of these investigators reported the material as being yellow crystals. Later investigators (18) found that the compound crystallizes as colorless needles from alcohol or chloroform and melts at 187°.

Thiaxanthone-5-dioxide is the end product of the oxidation of any of the thiaxanthene intermediates such as thiaxanthene (9)(15), thiaxanthene-5-dioxide (9) or thiaxanthone (9)(15) etc. The oxidation of thiaxanthone to XII in particular has been investigated thoroughly and the oxidation carried out with numerous oxidizing agents including chromic acid in acetic acid, sodium dichromate in sulfuric acid (9)(15), hydrogen peroxide in acetic acid, and potassium persulfate (18).

At approximately the same time, and by independent investigators, the compound was prepared by ring closure of diphenylsulfone-2-carboxylic acid (19)(20).



(XII)

Ullmann and Lehner (19) closed the ring by the use of concentrated sulfuric acid at fairly high temperatures, while Weedon and Doughty (20) cyclized the compound by heating

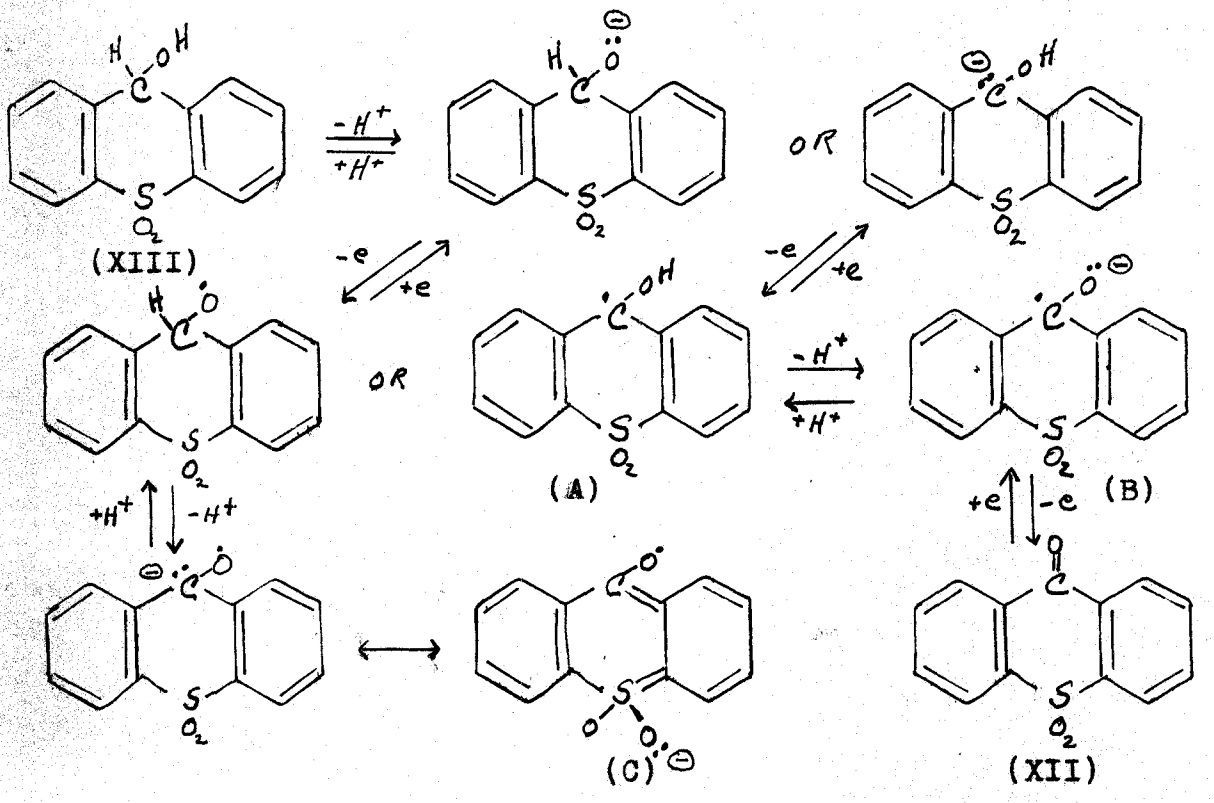
with concentrated sulfuric acid for a longer period at lower temperatures.

The color reactions reported by Graebe and Schulthess for the partial identification of this compound were fully verified by Weedon and Doughty (20). The compound, upon being heated with alcohol and strong potassium hydroxide solution, develops a deep blue coloration which disappears when the solution is cooled and reappears when heated. By heating with aqueous alkali and zinc dust the same color is temporarily developed but is destroyed by continued action. According to Ullmann (19) the color is also produced by vatting with sodium hydrosulfite much as the blood-red color of vatted anthraquinone is produced. If the solution is filtered and allowed to stand fine crystals appear.

Thiaxanthenol-5-dioxide. (XIII) Recently the peculiar color reaction of thiaxanthone-dioxide attracted the attention of several American investigators and thiaxanthenol-dioxide (XIII) and other derivatives were isolated independently. Heymann (21) reduced thiaxanthone-dioxide by means of zinc dust and dilute acetic acid. Fehnel (12) obtained the compound by the same method of reduction and in addition used sodium hydrosulfite as a reducing agent. It seems then, that thiaxanthenol-dioxide can be obtained by reduction of thiaxanthone-dioxide in either acid or alkaline medium.

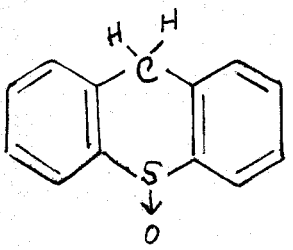
Thiaxanthenol-dioxide or the corresponding acetate

give the same intense blue color in alkaline solutions which Graebe first noticed with solutions of thiaxanthone-dioxide in zinc dust and alkali. The color reaction of Graebe is due therefore not to the thiaxanthone-dioxide but to its reduction product the thiaxanthenol-dioxide. Upon shaking the blue alkaline solution of thiaxanthenol-dioxide in air the color is discharged and thiaxanthone-dioxide precipitates. This reaction is no doubt due to air oxidation. The investigators of this phenomenon seem to favor the formation of a free radical (A) intermediate between the thiaxanthenol-dioxide and the completely oxidized form, which is converted to a semiquinone ion radical structure (B) which is, in turn, easily oxidized to thiaxanthone-dioxide. The following scheme is due to Heymann (21).

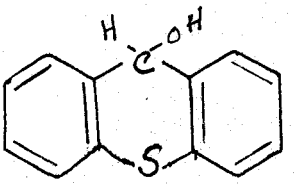


Fehnel (12) has studied this reaction and has arrived at essentially the same conclusion as to the structure of the intermediate ion in the oxidation of thiaxanthenol-dioxide to thiaxanthone-dioxide. However Fehnel tends to support a divalent semi-quinone ion similar to the one shown in the diagram (IC) where sulfur has expanded its valence shell to include ten electrons.

Thiaxanthene-5-oxide. (XIV) Hilditch and Smiles (14) first prepared this interesting intermediate by mild oxidation of thiaxanthene. They used hydrogen peroxide in acetic anhydride below 35° or the theoretical amount of potassium permanganate with a little sulfuric acid in acetone at its boiling point. The mild oxidative conditions were necessary to prevent formation of the sulfone (XI). Thiaxanthene-5-oxide crystallizes from benzene and melts at 109-111° which is rather close to the melting point of its isomer thiaxanthenol (XV) previously prepared by other investigators.



(XIV)



(XV)

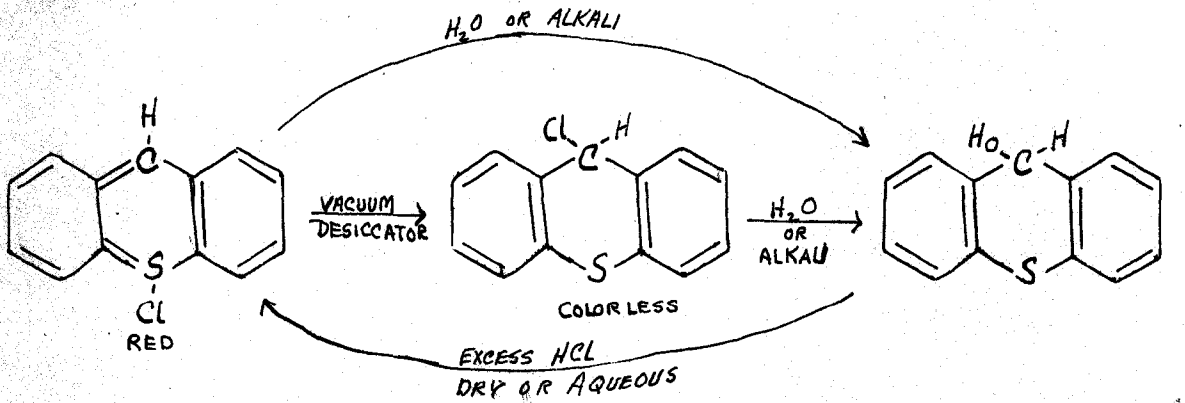
In order to differentiate between the compounds, Hilditch and Smiles first resorted to a mixed melting point (70-80° indefinite); further they showed that the compound melting at 109-111° did not form a benzoyl or acetyl derivative and that further oxidation with the theoretical amount of

potassium permanganate in cold glacial acetic acid yielded the corresponding sulfone, thiaxanthene-5-dioxide, while the compound melting at 103-105° and presumed to be thiaxanthenol, easily formed a benzoyl derivative and further oxidation of this compound yielded thiaxanthone. Both compounds formed thiaxanthylium salts with mineral acids but only the thiaxanthenol formed a stable red ferrichloride complex. Thiaxanthene-oxide formed the normal yellow addition compound with ferric chloride.

Thiaxanthenol or 10-Hydroxythiaxanthene. (XV) Thiaxanthenol is a rather unstable compound which was first prepared by Werner in 1901 (22) by reduction of thiaxanthone with alcoholic sodium hydroxide and zinc dust. He found that the material dissolved in mineral acid solution with the formation of an intense orange-red color. This intense color was presumed to be due to the formation of thiaxanthylium salts. Werner also prepared a crystalline perbromide of the compound by passing bromine vapors into a solution of the hydrobromide of thiaxanthenol. The resulting compound had the formula $C_{13}H_9SBr_3$ and might have several conceivable structures.

Mayer (2) later prepared XV by substituting potassium ethylate for the corresponding sodium derivative and he reported a smoother reduction by adding the zinc dust portionwise. Hilditch and Smiles (14) using Mayer's method reported erratic results and low yields. The yield was improved somewhat by excluding air from the vessel and

maintaining careful temperature control. In addition to differentiating between the isomers (XV) and (XIV), Hilditch and Smiles (14) extended Werner's work on the action of acids on thiaxanthenol. They obtained a brick-red crystalline precipitate when they saturated an ethereal solution of thiaxanthenol with dry hydrogen chloride gas. The material was not stable enough to analyze (hydrolyzed almost immediately back to XV) but did form a stable red ferrichloride complex compound of formula $C_{13}H_9Cl \cdot FeCl_3$ which melted at 192-193°. The ferrichloride salt also was easily converted to thiaxanthenol by an alkaline medium or even by water.. Upon allowing the thiaxanthylium chloride (XVI) to stand in a desiccator the material was converted into an isomeric colorless compound shown to be the stable thiaxanthyl chloride (XVII) melting at 112-113°. The relationship between these compounds can be shown more easily by the following diagram:

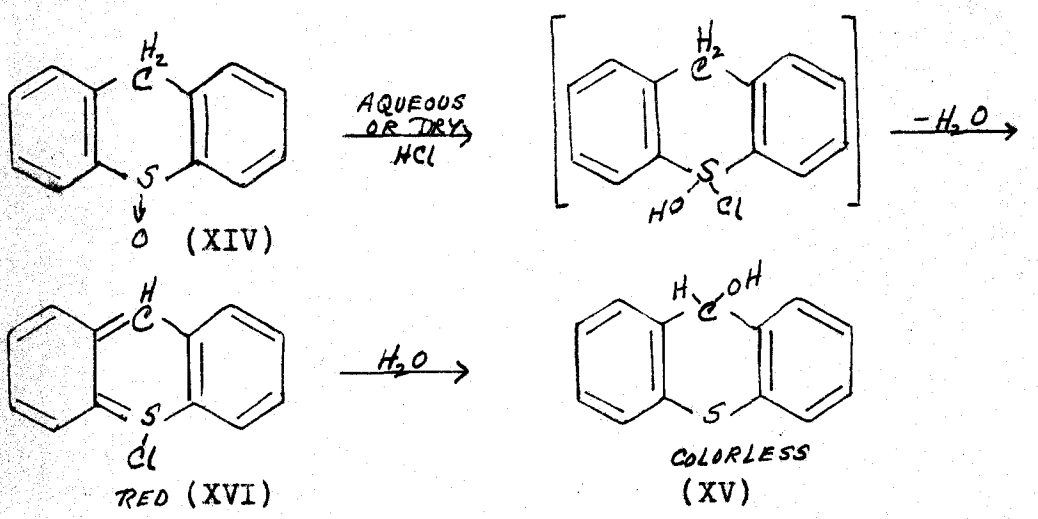


(XVI) (XVII) (XV)

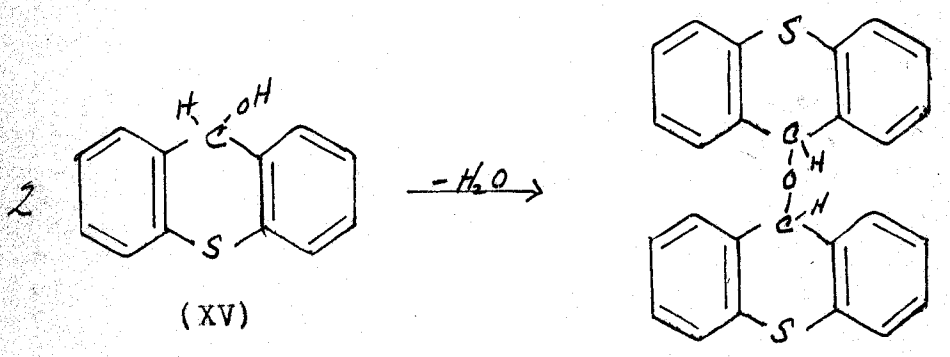
In view of later evidence introduced by Gomberg(11) and others in their work on 10-phenylthiaxanthenol and reasoning

by analogy it seems likely that the compound postulated as thiaxanthylium chloride might in reality be a chloride-hydrochloride such as is formed by the 10-phenylthiaxanthenol. The 10-phenylthiaxanthenol forms a brick-red phenylsulfonium chloride-hydrochloride which loses a molecule of hydrogen chloride to yield the corresponding colorless 10-phenylthiaxanthenyl chloride. Further it also forms a ferrichloride salt whose analysis corresponds to that of the sulfonium ferrichloride salt. The thiaxanthylium chloride was not analyzed by Hilditch and Smiles but the formula was inferred from the analysis of the ferrichloride addition compound. As can be seen from the work on 10-phenylthiaxanthenol this might easily lead to erroneous conclusions as to the composition of the compound. Only an analysis of the red thiaxanthylium chloride compound will reveal its true nature.

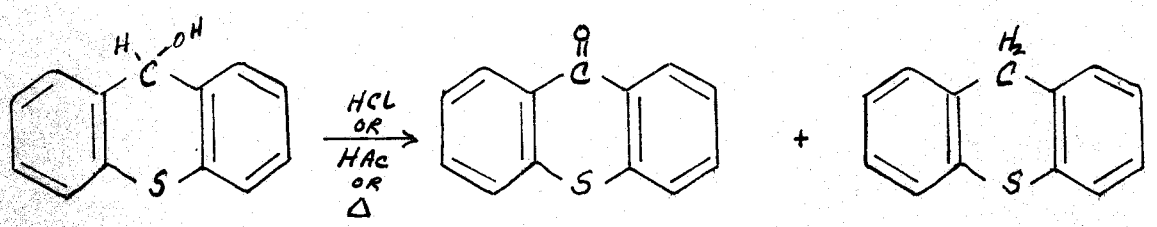
Like thiaxanthenol (XV), the isomeric thiaxanthene-oxide (XIV) is converted into the same highly colored thiaxanthylium salt (XVI) by the action of mineral acid, although the reaction is somewhat slower than in the case of thiaxanthenol. Thiaxanthene-oxide can thus be converted into thiaxanthenol by the alternative treatment with acid, then water or alkali. Hilditch and Smiles postulated the following mechanism.



Thiaxanthenol when heated alone or in acetic acid, acetic anhydride or other solvents (acetyl chloride and pyridine) intramolecularly dehydrated to form the thiaxanthenyl ether, a pale yellow crystalline compound which melted at 314-315°.

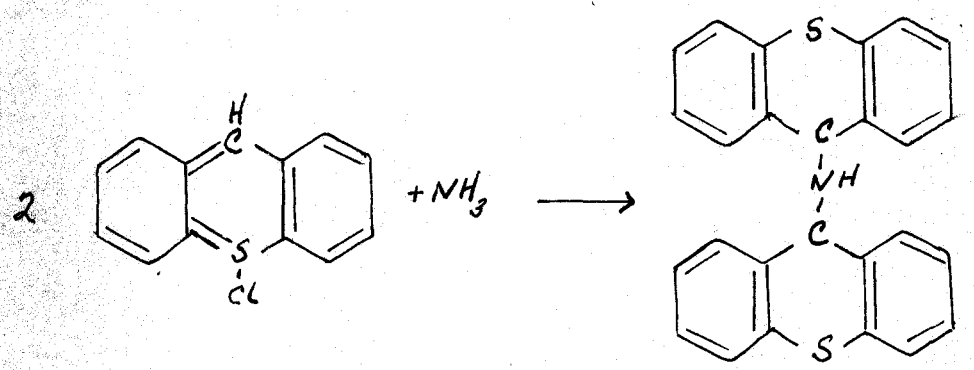


Later work by Finzi (23) conflicts with some of the results of Hilditch and Smiles. Finzi claimed that thiaxanthenol upon heating, or by refluxing with acetic acid, yielded a mixture of thiaxanthone and thiaxanthene rather than the thiaxanthenyl ether as reported by Hilditch and Smiles. He also reported the production of thiaxanthone and thiaxanthene by refluxing thiaxanthenol with very dilute (.01N) hydrochloric acid.



(XV) (II) (X)

Recently Schoenberg (24) reported that by heating thiaxanthenol to 120-130° for one hour he obtained thiaxanthene, thiaxanthone, and dithiaxanthylene. In addition Finzi found that thiaxanthenol is easily oxidized to thiaxanthone by sulfuric acid or atmospheric oxygen. Thiaxanthenol or the corresponding thiaxanthyl chloride are converted by an excess of ammonia to dithiaxanthylamine, melting point 168°. (XVIII)



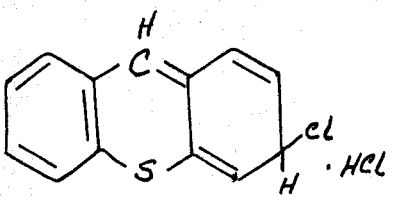
(XVIII)

10-Alkyl or aryl derivatives of thiaxanthenol. It has been previously mentioned that the Grignard reagent reacts with thiaxanthone to produce 10-alkyl or aryl thiaxanthenols. Several of these compounds have been prepared and, as one of them is of special interest as an intermediate, a study of these compounds is indicated.

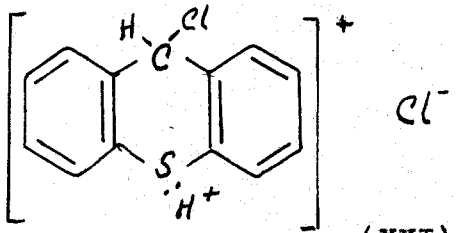
Phenylthiaxanthenol. (XIX) This compound was first prepared by Bürnzly and Decker (10) who introduced a benzene solution of thiaxanthone into an ethereal solution of phenylmagnesium bromide. They isolated the product as white compact crystals of melting point 105-106°. They also found that the compound was similar to thiaxanthenol in its chemical action since it forms dark red sulfonium salts in mineral acid solutions and a stable red ferrichloride complex which crystallizes from acetic acid saturated with hydrogen chloride gas. The latter crystals are tiny dark red needles melting sharply at 169°. Like thiaxanthenol, it reacts with the requisite inorganic salts to form the corresponding mercuric chloride salt or the cadmium bromide salt, both of which are stable red compounds. A tribromide of 10-phenylthiaxanthenol was also prepared by these investigators; it was reported to melt at approximately 180°. According to Bürnzly and Decker (10), when the material was crystallized from absolute alcohol it was converted to the ethyl ether which they reported as melting at 76-77°. No analysis of the compound was advanced to substantiate their proposed structure.

Several years later Gomberg and Cone (11) repeated the work of Bürnzly and Decker and improved the yields of 10-phenylthiaxanthenol by adding dry pulverized solid thiaxanthone to phenylmagnesium bromide in the Grignard addition reaction. They prepared a stable chloride-hydrochloride of

the material by saturating a chloroform solution of 10-phenylthiaxanthenol, containing a few drops of acetyl chloride, with dry hydrogen chloride gas. The solution was intensely colored and deposited dark red crystals upon treatment with dry ligroin. Gomberg and Cone (11) assigned a quinoid type structure to this compound and called it phenylquinothiaxanthenol chloride-hydrochloride (XX). A more logical structure might be a simple sulfonium salt (XXI). At any rate, the analysis of the compound showed the presence of at least one molecule of hydrogen chloride. The total chlorine content agreed with the theoretical amount.

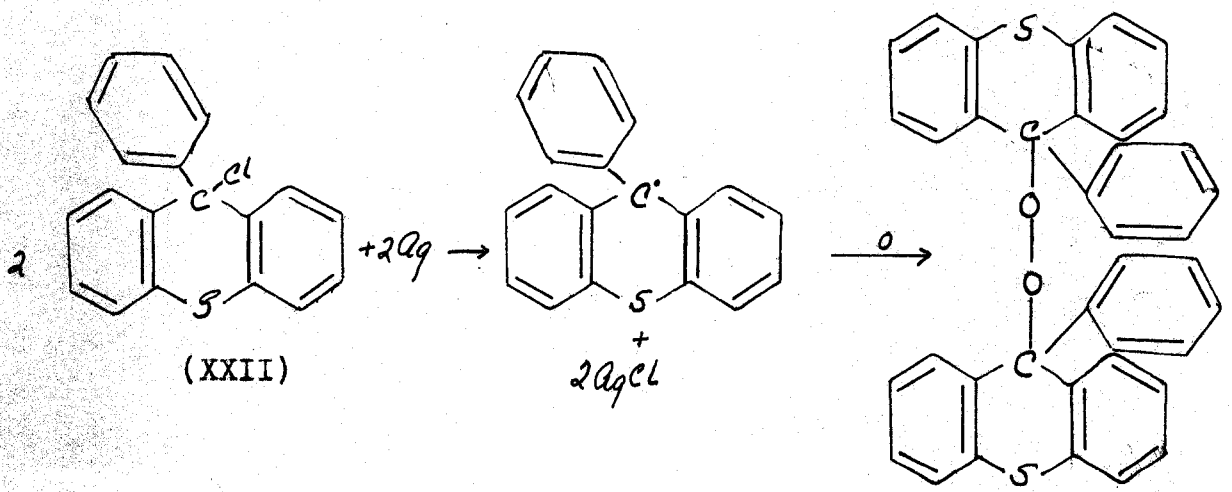


(XX)



(XXI)

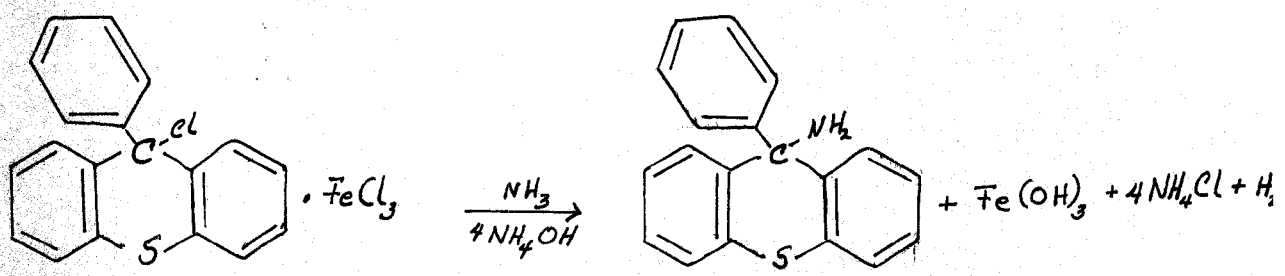
10-Phenyl-10-chlorothiaxanthene. (XXII) It was further found by Gomberg and Cone (11) that dry air passed through a heated suspension of the sulfonium salt of 10-phenylthiaxanthenol in dry benzene removed a molecule of hydrogen chloride leaving 10-phenyl-10-chlorothiaxanthene in solution. The material was isolated as pink-tinged crystals (m.p. 114-115°) which quickly hydrolyzed to the corresponding 10-phenylthiaxanthenol. Treatment of the chloride with finely divided silver gave a brown-red solution of the free radical phenylthiaxanthyl in benzene (11); a peroxide was precipitated when air was forced through the solution.



(XXII)

The melting point of this peroxide was not sharp although the compound was isolated as colorless hexagonal prisms which sintered at 175-180° and finally melted with decomposition at 187-188°.

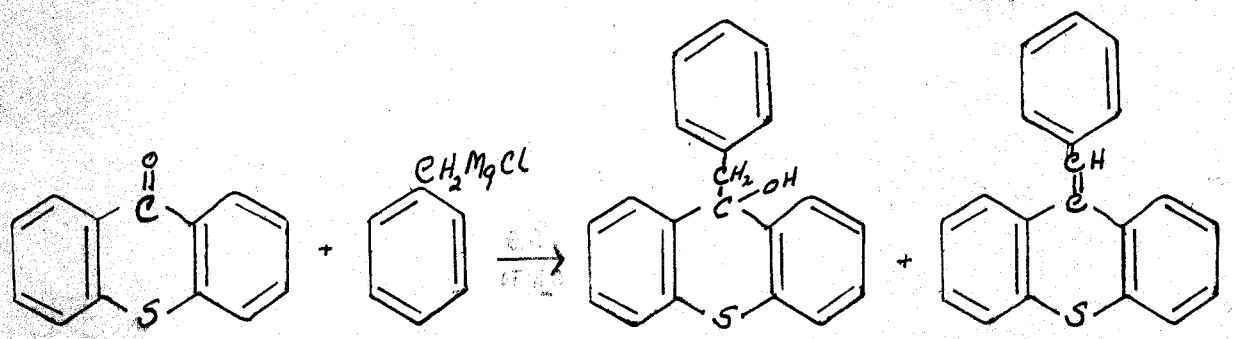
10-Phenyl-10-aminothiaxanthene. (XXIII) Treatment of the chloride-hydrochloride of 10-phenylthiaxanthenol with aqueous ammonia gave a mixture of 10-phenylthiaxanthenol and 10-phenyl-10-aminothiaxanthene. (25). The pure amino compound can be obtained by the reaction of ammonia and the ferrichloride salt of 10-phenyl-10-chlorothiaxanthene.



(XXIII)

This substance recrystallizes from benzene-ligroin as yellowish red prisms, melting point 118-120°.

10-Benzylthiaxanthenol. (XXIV) Decker (26) also investigated the action of benzyl magnesium chloride on thiaxanthone. He succeeded in separating two compounds from this reaction; the expected 10-benzylthiaxanthenol and 10-benzalthiaxanthene (XXV). The latter compound is undoubtedly formed by dehydration of the former, a tertiary alcohol.



(II) (XXIV) (XXV)

The alcohol can be recrystallized from ethyl alcohol or a high boiling petroleum ether as a white crystalline compound melting at 133°. The compound dissolved in glacial acetic acid to form a colorless solution, but addition of a mineral acid introduced the familiar intense red color of a thiaxanthonium salt. Unlike the corresponding 10-phenyl homologue this material did not form an ethyl ether by recrystallization from absolute alcohol.

10-Benzylidenethiaxanthene or 10-Benzalthiaxanthene. (XXVI) This material, as mentioned above, was formed as a by-product during the reaction of benzylmagnesium chloride with thiaxanthone. It was rather easily separated from the other product, 10-benzylthiaxanthenol, by virtue of its greater solubility in low-boiling petroleum ether. The carbinol could

be easily converted into benzalthiaxanthone by heating to 140° or by refluxing in glacial acetic acid. The benzal compound separated as slightly colored needles melting at 114-115°. It was soluble in glacial acetic acid forming a colorless solution, but like 10-benzylthiaxanthenol formed the intensely colored sulfonium salts with mineral acids. It seems likely that one molecule of acid first adds across the double bond. Addition of a solution of ferric chloride to a concentrated hydrochloric acid solution of either 10-benzylthiaxanthenol or 10-benzalthiaxanthene yielded red leaflets of the ferrichloride double salt (melting point 155°). Both compounds yielded the same mercuric chloride double salt.

10-Benzylthiaxanthene.(XXVII) Decker (26) reduced 10-benzylthiaxanthenol to benzylthiaxanthene by the use of hydriodic acid in acetic anhydride. The material was reported to be oxidized to thiaxanthone and benzaldehyde by the use of ferric chloride. It crystallized from alcohol and melted at 127°.

10-Methylthiaxanthenol. (XXVIII) This compound has never been isolated in pure form. When methyl magnesium iodide was reacted with thiaxanthone (26) an uncrystallizable oil was obtained which partly solidified at 17° and remelted at 45°. Decker claimed this compound to be 10-methylene thiaxanthene and stated that the 10-methylthiaxanthenol could not be isolated because it dehydrated to the corresponding methylene compound. The 10-methylthiaxanthenol compound

being unstable could not be analyzed; however the complex mercuric chloride salt of this compound was isolated as red brown crystals (melting point 156-160°) and analyzed. A ferric chloride salt was also prepared. Curiously enough, the methyl ether of 10-methylthiaxanthenol also resulted as a product in the Grignard reaction of methyl magnesium iodide with thiaxanthone. It was obtained as colorless hexagonal plates which melted at 198-199° with the evolution of gas. The compound was unusual in its behaviour in that it lost methyl alcohol when heated to 50-60° and was thereby converted into the unsaturated uncrystallizable oil 10-methylene-thiaxanthene (XXIX).

10-Methylene-thiaxanthene. (XXIX) A by-product of the Grignard reaction previously mentioned, this material was unstable in air and rapidly oxidized to thiaxanthone; it was therefore difficult to purify and crystallize. It formed red sulfonium salts with mineral acids and complex salts with the usual inorganic compounds.

10-Methylthiaxanthene. (XXX) Reduction of 10-methylene thiaxanthene with hydriodic acid and red phosphorus yielded the colorless 10-methylthiaxanthene. This compound melted at 74° and was easily oxidized to thiaxanthone.

10-Benzhydryl-thiaxanthenol. (XXXI) Bergemann and Corte (27) prepared 10-benzhydryl-thiaxanthenol by the action of diphenylmethyl sodium on thiaxanthone. The material crystallized from propyl alcohol in long needles melting at 208°.

10-Benzhydrylidene-thiaxanthene. (XXXII) Dehydration of 10-benzhydryl-thiaxanthenol by heating with acetyl chloride gave a quantitative yield of 10-benzhydrylidene-thiaxanthene as colorless crystals of melting point 243°. These crystals showed unusual thermochromic properties; upon heating in melted naphthalene or esters of phthalic acid they assumed a strong yellow color which disappeared upon cooling. This property seems to be common to some aromatic substituted ethylenes. Bromine added to the double bond to yield a rather unstable red dibromide which readily lost bromine.

10-Phenylthiaxanthenol-dioxide. (XXXIII) This material can be prepared either by the oxidation of 10-phenylthiaxanthenol or by the action of the phenyl Grignard reagent on thiaxanthone-dioxide. (23). The latter reaction gives a mixture of the desired product and unreacted thiaxanthone-dioxide so the former reaction is to be preferred. 10-Phenylthiaxanthenol could not be smoothly oxidized to the corresponding dioxide by the use of the usual reagent, hydrogen peroxide, but chromic acid in acetic acid gave an excellent yield of 10-phenylthiaxanthenol-dioxide. The compound recrystallized from acetic acid or from a mixture of chloroform and absolute alcohol as white needles which melted at 224-225°.

10-Phenylthiaxanthene-dioxide. (XXXIV) Reduction of 10-phenylthiaxanthenol-dioxide (XXXIII) with stannous chloride and hydrochloric acid yielded 10-phenylthiaxanthene-dioxide.

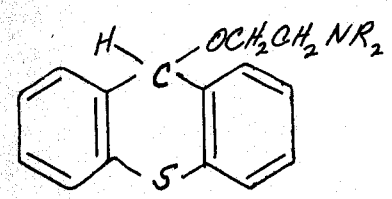
The material recrystallized from acetic acid as colorless needles melting at 193-194°. Gomberg and Britton (28) were unable to oxidize this compound to 10-phenylthiaxanthenol-dioxide, a behaviour which is not shown by the closely related triphenylmethane compounds.

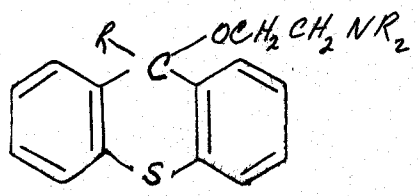
10-Phenyl-10-chlorothiaxanthene-dioxide.(XXXV) Unlike triphenylchloromethane which is easily prepared from the corresponding triphenylcarbinol, 10-phenyl-10-chlorothiaxanthene-dioxide is prepared from 10-phenylthiaxanthenol-dioxide (XXXIII) only with great difficulty. Gomberg and Britton (28) found that treatment of the carbinol with hydrogen chloride in ether or benzene, boiling acetyl chloride, thionyl chloride or phosphorus trichloride did not yield the expected chloro compound. The compound was finally prepared by fusion of the carbinol with phosphorus pentachloride. A small quantity of red impurity of unknown structure always accompanied the formation of 10-phenyl-10-chlorothiaxanthene-dioxide. This chloro compound was soluble in a large number of organic solvents, recrystallized from high boiling ligroin as white crystals and melted at 160-161°. It could be hydrolyzed to the carbinol by boiling with 80% acetic acid or with dilute alcohol.

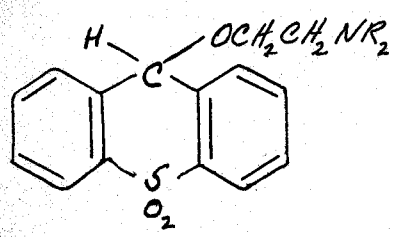
III PROCEDURE AND DISCUSSION

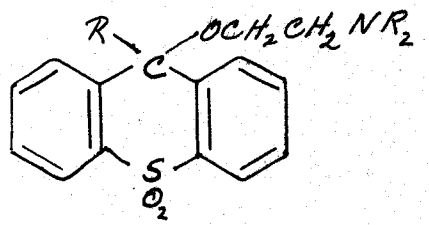
STATEMENT OF THE PROBLEM

It is proposed to prepare a series of alkamine ethers of thiaxanthene and derivatives for use as possible chemotherapeutic agents. We will attempt to synthesize the following series of ethers.









In the following pages we will attempt to point out facts which lead us to believe that these alkamine ethers of thiaxanthene will exhibit chemotherapeutic activity.

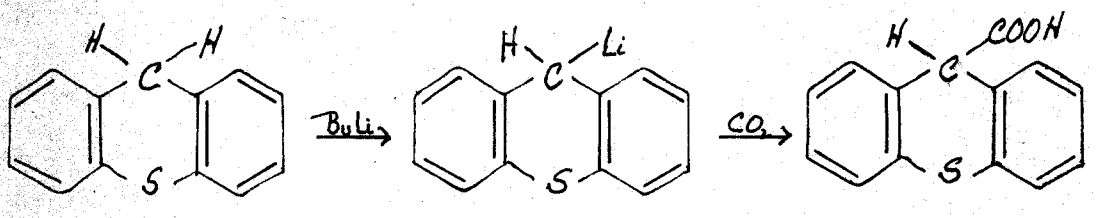
The use of dialkylaminoalkyl ethers as medicinals is comparatively recent and not enough work has been completed to correlate structure to physiological activity to any great degree. The main use of alkamine ethers has been as antispasmodics or more specifically antihistaminics.

Compounds with proven therapeutic value and with structures similar to the structures of the derivatives we intend to prepare will be mentioned. In addition thiaxanthene derivatives which have shown promise as medicinals will be discussed.

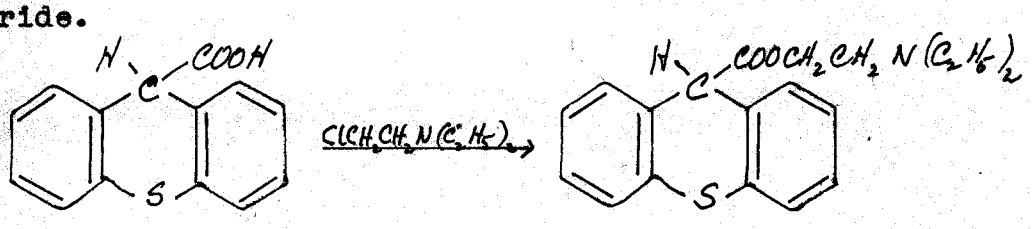
THIAXANTHENE DERIVATIVES AS MEDICINALS

Only three simple derivatives of thiaxanthene have been reported in the literature as being active as chemotherapeutic agents. Since we are endeavoring to prepare medicinals utilizing the thiaxanthene nucleus, the structure, synthesis and physiological action of the previously mentioned compounds will be examined and any correlation possible will be drawn.

<u>β-diethylaminoethyl-thiaxanthene-10-carboxylate</u>. Thiaxanthene-10-carboxylic acid was prepared by treatment of thiaxanthene with butyl lithium. The lithium derivative was then reacted with carbon dioxide in the usual manner to yield the carboxylic acid.

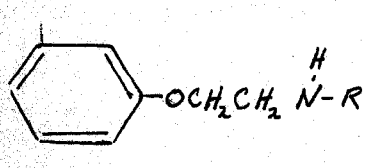
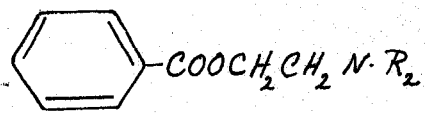


The acid was esterified by reaction with β-diethylaminoethyl chloride.

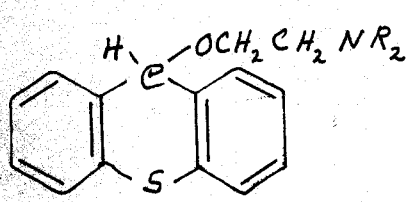
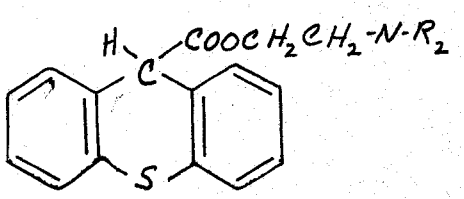


This work was carried out by Burtner and Cusic (29) and was by no means confined to thiaxanthene derivatives. These investigators prepared alkamine esters of the acids of unsaturated and partially saturated derivatives of naphthalene, anthracene, xanthene, thiaxanthene, acridine and phenanthrene. Of the compounds prepared, β-diethylaminoethyl xanthene-10-carboxylate proved to possess the greatest activity against spasm induced by acetyl choline. Recently Cusic (30) reported this compound, when administered as the methobromide, to be as active as atropine as an antispasmodic and to be equal to tetra ethyl ammonium bromide as an autonomic blocking agent in the sympathetic nervous system. Esters of 9, 10-dihydroanthracene-9-carboxylic acid proved to be highly superior to all others when tested against histamine. Esters of thiaxanthene-10-carboxylic acid were only about one-sixth as active as either of these derivatives but were much better than most of the other compounds tested. Encouragingly, the thiaxanthene derivatives proved to have a very low toxicity indicating that there is no inherent toxicity in the thiaxanthene molecule.

Philbrook (31) indicated that replacement of the carboxylic group in alkaminoalkyl esters by the ether linkage was not accompanied by loss of activity. He found alkaminoalkyl ethers of phenol to be about as active as anesthetics as the corresponding alkaminoalkyl esters.

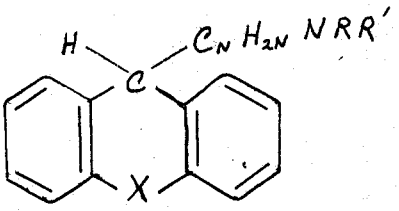



In an analogous manner, alkaminoethers of 10-thiaxanthenol might reasonably be expected to be as active or perhaps more active than the corresponding alkaminoesters of 10-thiaxanthene-carboxylic acid, compounds which have been shown to possess antispasmodic activity.

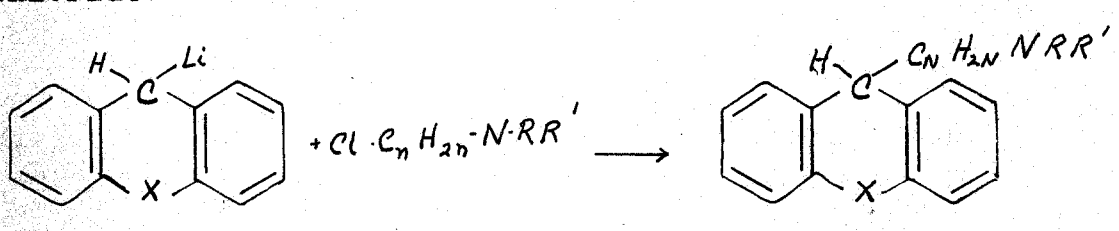
It will be interesting to note the weighting effect of an aromatic group on the number 10 carbon of alkamine ethers of thiaxanthenol. Only a few compounds with an alkamine ether linkage to a tertiary carbon have been reported. Similarly the oxidation of the sulfide linkage in these ethers of thiaxanthenol to the sulfone should introduce some new and interesting properties. Sulfones have long been used as drugs in combating a wide variety of diseases and their effect here might be expected to be advantageous.

10-Alkaminoalkyl thiaxanthene. Recently Cusic (32) investigated and patented a series of xanthene and thiaxanthene derivatives for use as antispasmodics. The compounds correspond to the following general formula:



In the formula, X represents oxygen or sulfur, n equals two or three, and R and R' are unsubstituted alkyl groups of not more than four carbon atoms.

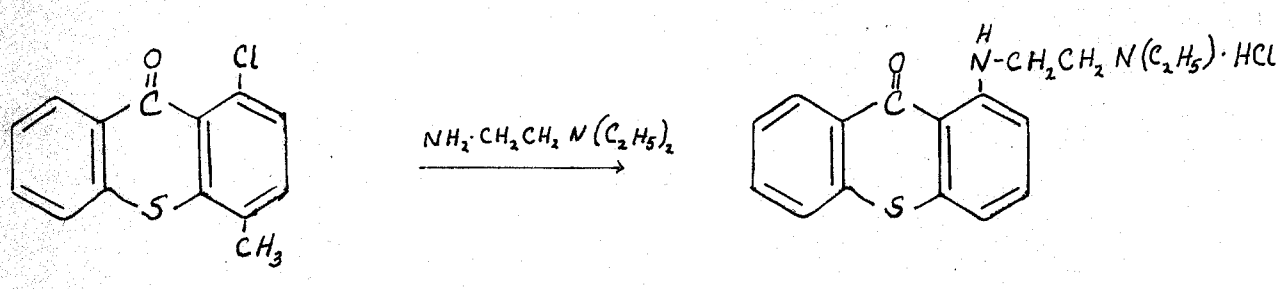
The compounds were prepared from the reaction of the corresponding 10-lithium compound and an alkaminoalkyl chloride.



The diethylaminoethyl derivatives of thiaxanthene and xanthene were both found to be superior to the diethylaminoethyl ester of fluorene-9-carboxylic acid in anti-spasmodic activity.

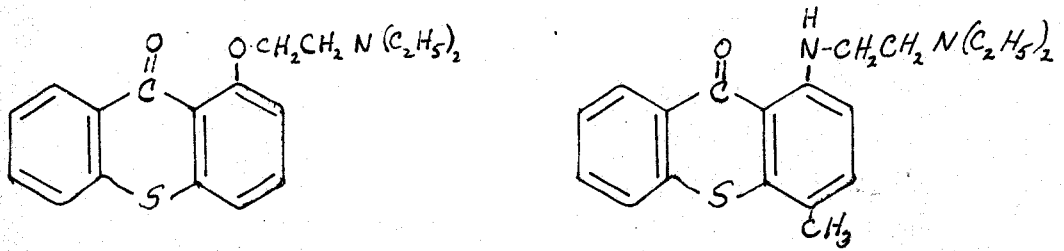
Miracil. During the last war, German investigators prepared a compound which has proven to be extremely active against some Schistosomiasis in animals. The drug was particularly effective against S. manosi in mice and monkeys, less so against S. haemotobium and had no effect upon S. japonica. No method of preparation for this substance, 4-methyl-1-(2-diethylaminoethylamino)-thiaxanthone, was given by the investigators reporting on its pharmacology and physiological activity (33). However, since Ullmann and Glenck (18) showed

that the chlorine in 4-methyl-1-chlorothiaxanthone could be easily replaced by any one of a number of primary amines or ammonia, it is reasonable to suppose that the compound was prepared in a similar manner from the reaction of the 4-methyl-1-chloro compound and diethylaminoethylamine.



The toxicity of this compound was not high. Wood (33) states that mice and rats easily tolerate doses of 20 mgm. per kg. and that 5 mgm. per kg. might be considered a safe dose over prolonged periods.

It would be of interest to see if dialkylaminoethers of 4-methyl-1-hydroxythiaxanthone showed activity in the same type of infections.

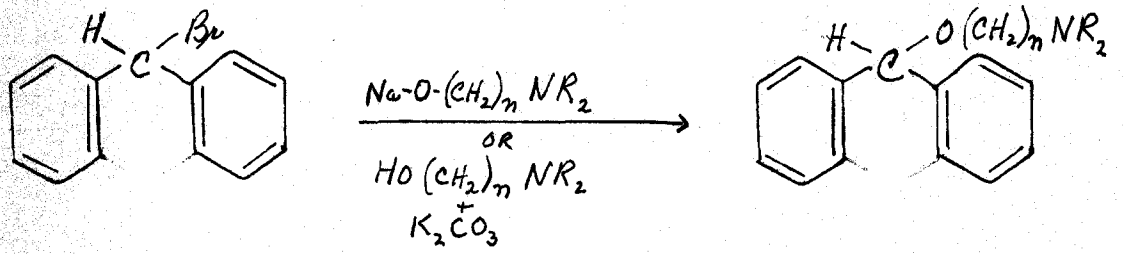


Again the structures are much the same, a polar -NH- group has been replaced by another polar group, -O-; activity of the two compounds might be similar, although in some cases replacement of an ether linkage by the amino linkage results in a surprising loss of activity (see page 34).

COMPOUNDS HAVING STRUCTURES SIMILAR TO ALKAMINE ETHERS OF THIAXANTHENOL

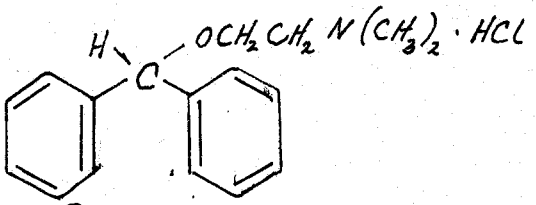
Many of the antihistaminic and other compounds of proven therapeutic value are structurally related to the thiaxanthene derivative that we hope to prepare, therefore, it seems reasonable to assume that the physiological activities of the two classes of compounds should also be similar.

Huber and Rieveschl (34) first prepared a series of alkamine ethers of benzhydrol which were later patented by Rieveschl for Parke-Davis and Co. (35). The compounds were of the following general formula and were prepared by the condensation of benzhydryl bromide with either the sodium salt of the alkamine alcohol or with the alkamine alcohol itself in the presence of anhydrous potassium carbonate.



A large series of these ethers was tested (36) and many compounds were found to be active as antihistaminics, antispasmodics, and antagonists to anaphylactic shock. -Dimethylaminoethyl-benzhydryl ether hydrochloride proved to be the most active compound when tested against bronchospasm induced in guinea pigs by vaporized histamine diphosphate. Accordingly it was marketed under the trade name

Benadryl for use in combating the role of histamine in gastric secretions, vasodilation, capillary permeability, pain mediation, smooth muscle spasm and various allergic conditions including the common cold.



BENADRYL

The β-piperidinoethyl ether was only slightly less active than Benadryl and both were at least several times more active than the β-morpholinoethyl derivative. The main disadvantage of the drug is the extreme drowsiness which accompanies its use in some persons. Recently the hydrochloride and methiodide salts of β-pyrrolidylethyl benzhydryl ether have been reported to exhibit an antihistaminic activity greater than that of Benadryl (37).

From the results of the testing of this series of alkamine ethers of benzhydryl some conclusions can be drawn as to the relationship of chemical structure to anti-histamine activity.

(1). A chain length of two carbons between the ether linkage and the tertiary nitrogen atom seems to give maximum activity. Branched or longer chained compounds are definitely less active.

(2). Ethers containing a tertiary amino group proved to be more active than those prepared using secondary aminoalcohols which in turn were more active than the

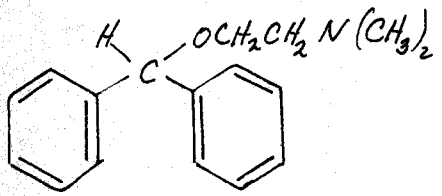
primary amine compounds.

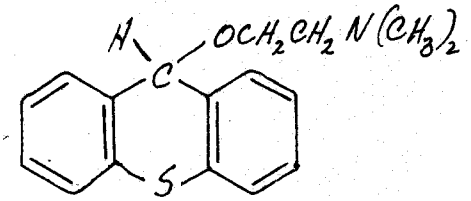
(3). An increase in the alkyl groups on the nitrogen atom led to less active compounds in both the tertiary and primary series.

(4). A substituent on the ring (Cl) reduced the activity but also reduced toxicity to a greater degree. However, only one ring substituted compound was tested so generalities can not be drawn.

(5). The replacement of the ether linkage (-O-) by the secondary amino linkage (-NH-) deprived the compounds of almost all antihistaminic activity.

The introduction of a bridge of -S-, -O-, $-CH_2-$ or a direct linkage between aromatic rings in a compound which possesses physiological activity, greatly enhances the activity of the resulting fused ring compound (29)(38). Thus, the introduction of a sulfur bridge in the Benadryl molecule to form the β-dimethylaminoethyl ether of thiaxanthenol might be expected to increase the activity of the compound.



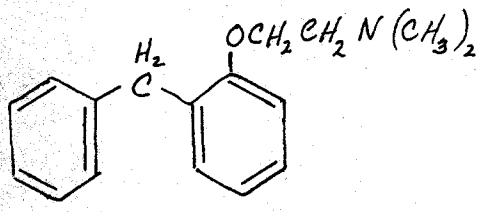


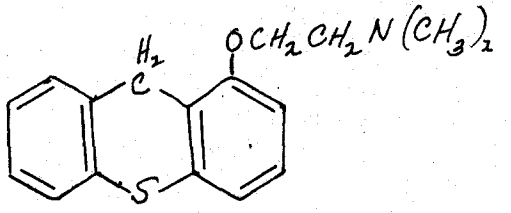
Again the effect of a phenyl or p-chlorophenyl group attached to the carbon atom carrying the ether linkage might prove interesting. The introduction of a sulfone linkage

for the sulfide linkage also might be expected to have a drastic effect on the physiological activity of the compound. The sulfone linkage is, of course, prominent in many therapeutic agents in use today. Hence the similarity in structure between alkamine ethers of benzhydryl and thiaxanthyl, 10-aryl thiaxanthyl and thiaxanthyl-5-dioxide indicates the likelihood of chemotherapeutic activity in the latter compounds.

A very promising alkamine ether derivative was reported last year. Cheney and his colleagues (39) synthesized a series of 2-benzylphenyl and 4-benzylphenyl alkamine ethers of which 2-benzylphenyl-β-dimethylaminoethyl ether

ethers of which 2-benzylphenyl-β-dimethylaminoethyl ether ound was water soluble, relatively non-toxic and possessed a high order of antihistaminic and local anesthetic activity.

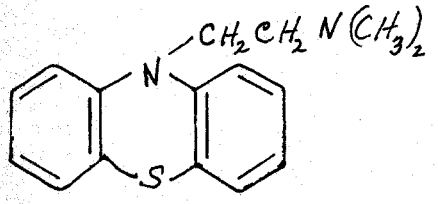




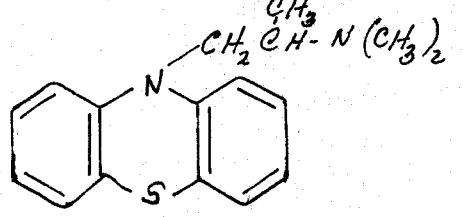
Although it is beyond the scope of this problem to prepare a series of thiaxanthene ethers analogous to this compound, it would be of interest to determine the similarity of this series to the corresponding alkamine ether of 1-thiaxanthone described on page 31. Both series should be active.

Shortly after the end of the war, the laboratories

of Rhone Poulenc in France reported the synthesis and pharmacological properties of several alkaminoalkyl derivatives of phenothiazine (40). These compounds, dimethylaminoethyl- and 2-dimethylamino-2-methylethylphenothiazine



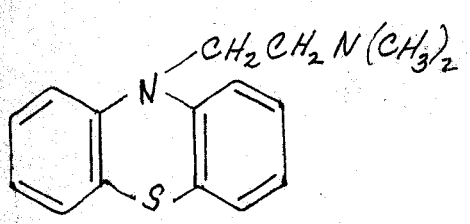
DIPARACOL

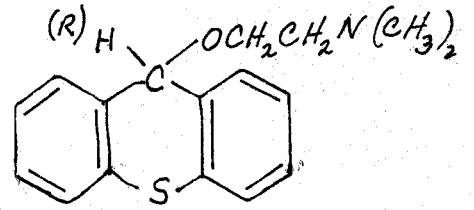


PHENERGAN

were reported to be many times more effective as antihistamines than any other drug then on the market. Phenergan, for example is said to be approximately 90 times more effective than Benadryl as an antihistaminic. The Upjohn Company has recently marketed β-pyrrolidinoethylphenothiazine under the trade name Pyrrolazote. (41)

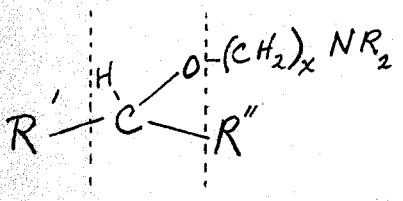
The similarity of the structures of these therapeutic agents to alkamine ethers of thiaxanthenol can be seen by examining the following formulae.

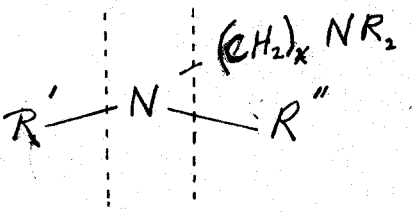




Of the two general classes of antihistamines on the market today the carbon-oxygen ether linkage and the nitrogen atom are interchangeable. That is, it is possible to replace the -C-O- linkage by an -N- linkage without appreciable loss of

activity. This principle may be more clearly understood by a glance at the following general formulae which represent the two main classes of antihistamines.



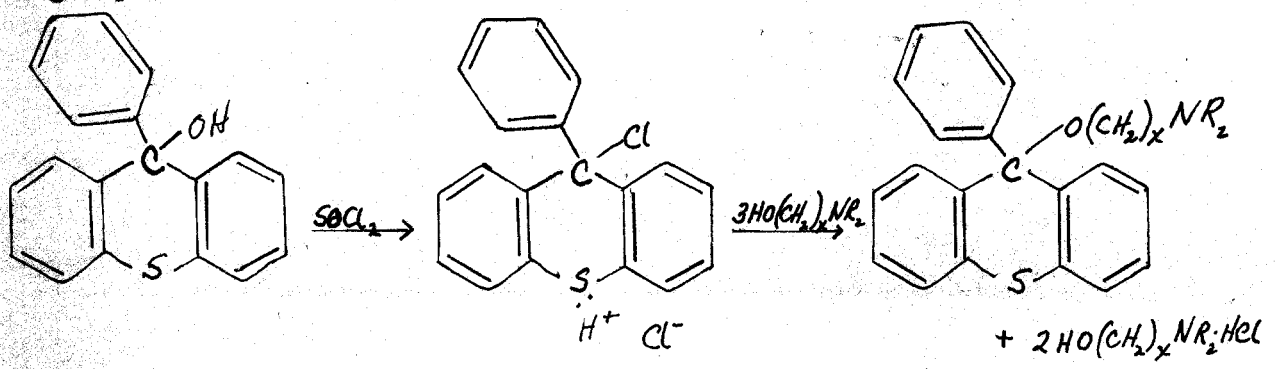


In these formulae R' is usually an aromatic or aryl-alkyl radical and R" is either aromatic or of a certain type of heterocyclic radical such as -pyridyl, -thienyl, etc.

By replacing the -N- linkage of the phenothiazine derivatives by the -C-O- linkage in the thiaxanthenol compounds comparable activity should be obtained. Hence here is more evidence that alkyl aminoalkyl ethers of thiaxanthenol and aryl thiaxanthenols should be active as antihistamines.

ALKAMINE ETHERS

The alkamine ethers of 10-phenylthiaxanthenol were successfully prepared by several modifications of the condensation of 10-phenyl-10-chlorothiaxanthene hydrochloride with the corresponding aminoalcohol according to the following equation:



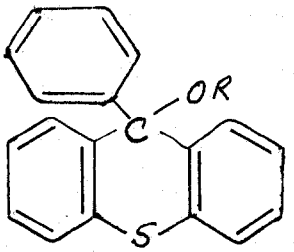
Condensation took place readily and the alkamine alcohol hydrochloride separated almost immediately. The first method involved the use of ten moles of the aminoalcohol to one mole of the crystalline chloride-hydrochloride which had been previously isolated. The aminoalcohol thus had three functions; it served as reagent, as a solvent, and as a neutralizing agent for the two moles of liberated hydrogen chloride, forcing the reaction to completion. After the completion of the reaction, the aminoalcohol hydrochlorides were neutralized by means of a solution of sodium hydroxide, and the free bases were extracted with ether. The ether solution was washed well with water to remove any excess aminoalcohol, and was then dried. Upon evaporation of the solvent a red oil resulted. This oil proved to be a mixture of the free base of the desired ether and unreacted 10-phenylthiaxanthenol. The mixture was dissolved in alcohol and a methyl iodide salt of the free base of the ether was prepared. The methiodide salt of the free bases were prepared for two reasons: first, they were crystalline compounds and thus were used for purposes of analysis; secondly, several investigators (42)(43)(44) have recently reported that quaternary derivatives of β-dimethylaminoethyl benzhydryl ether and other compounds are effective antihistaminic and antispasmodic agents. The final products being quaternary ammonium salts did not melt in the true sense, but decomposed

(between 190 and 215°). The decomposition point could be raised or lowered about five degrees depending upon the rate of heating. Attempts to prepare a methylbenzenesulfonate salt yielded only an oily material which we were unable to crystallize.

Other methods which were used to prepare the ethers utilized less aminoalcohol. A ratio of six moles of aminoalcohol to one mole of the 10-phenyl-10-chlorothiaxanthene hydrochloride (200% excess aminoalcohol) in either chloroform or ethyl acetate as the solvent was used. The solvent had to be absolutely dry or the yield was decreased radically. The yields were approximately the same for all the methods; they varied between forty and sixty per cent for the three step process of conversion of carbinol to chloride-hydrochloride to alkamine ether and thence to quaternary ammonium salt.

The use of other solvents such as ether or benzene proved less satisfactory, probably because of the insolubility of the chloride-hydrochloride in these materials. Chlorobenzene could be substituted for chloroform or ethyl acetate but there was danger of decomposition of the desired compound when the solvent was removed by evaporation after the reaction was complete. The use of 10-phenyl-10-bromothiaxanthene hydrobromide in place of the chemically less active chloro compound did not increase the yield of alkamine ether.

The following four compounds of this series were prepared:



(1) R - β-dimethylaminoethyl methiodide

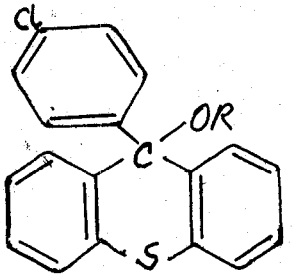
(2) R - β-piperidinoethyl methiodide

(3) R - β-morpholinoethyl methiodide

(4) R - β-diethylaminoethyl methiodide

Since the first three aminoalcohols proved to yield the most active antihistamines and antispasmodics in the benzhydryl series, they were used in this investigation because it was thought that they would again prove to be the most valuable. The β-diethylaminoethyl compound was prepared because this aminoalcohol occurs so often in such a wide variety of medicinals that it is always wise to include it in any series of potential chemotherapeutics prepared.

Several alkamine ethers of 10-p-chlorophenylthiaxanthenol were prepared in a similar manner by condensation of the appropriate aminoalcohol with 10-p-chlorophenylthiaxanthyl chloride in chloroform solution. These compounds were also characterized as methiodides which were obtained as white crystalline compounds after several recrystallizations. The following compounds were prepared:

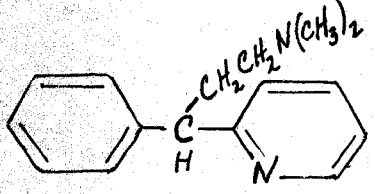


(1) R - β-dimethylaminoethyl methiodide

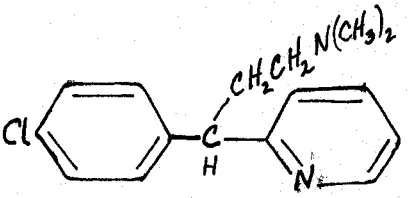
(2) R - β-piperidinoethyl methiodide

(3) R - β-morpholinoethyl methiodide

The para-chlorophenyl group was included in an attempt to attain the increase in activity which seems to accompany the introduction of a chlorine into a position para to the ether or amine linkage. For example: Chlorothen is reported to be more active than the corresponding Thenylene (45)



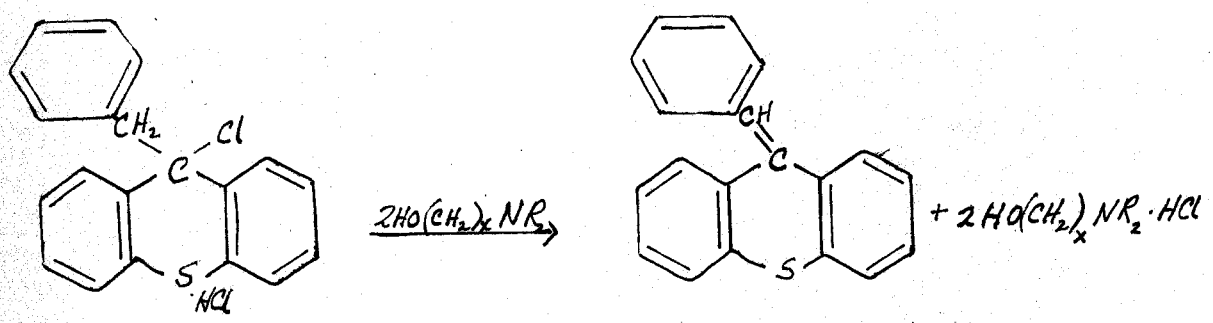
TRIMETON



CHLOROTRIMETON

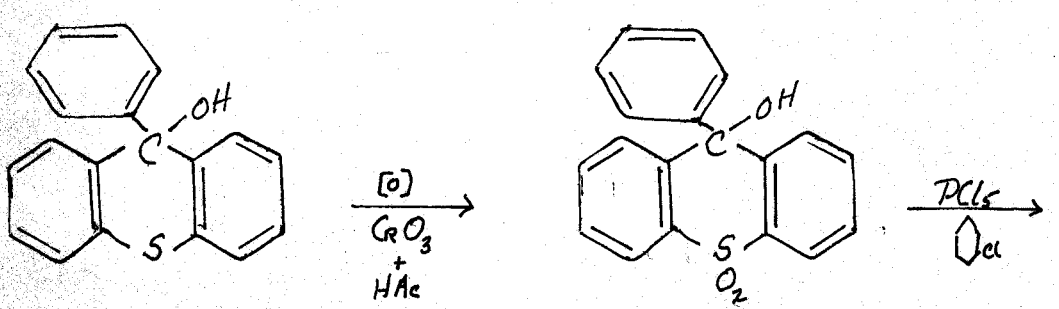
while Chlorotrimeton is reported to be superior to Trimeton (46) as antihistaminics.

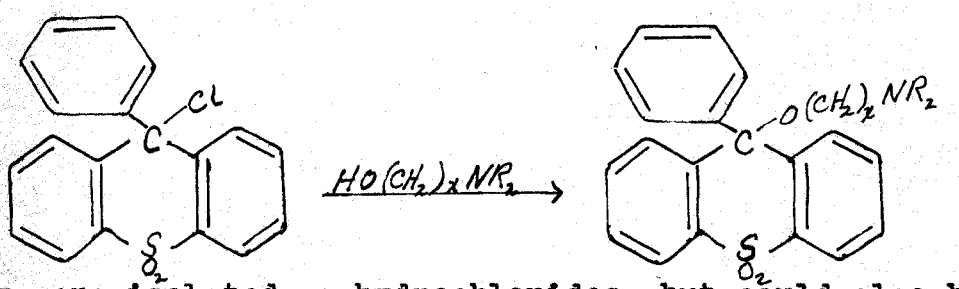
Since the benzyl group has been advantageously introduced into drugs that are useful antihistamines, we attempted to prepare a series of ethers of 10-benzylthiaxanthenol. However, due to the ease of dehydrohalogenation of 10-benzyl-10-chlorothiaxanthenol in the presence of the basic aminoalcohol, only 10-benzalthiaxanthene could be isolated.



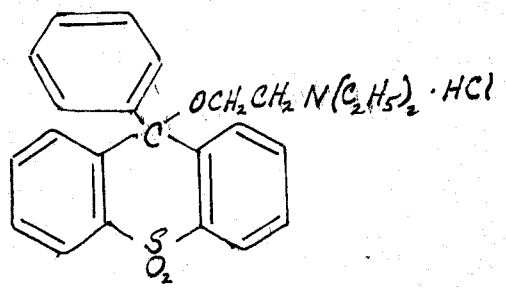
This ease of dehydrohalogenation of the tertiary alkyl halide would probably preclude the preparation of any series of alkamine ethers of 10-alkyl or aralkyl thiaxanthenol.

Attempts to oxidize the alkaminoethers of 10-phenylthiaxanthenol to the corresponding alkamine ethers of 10-phenylthiaxanthenol dioxide failed; only 10-phenylthiaxanthenol was obtained as a product, indicating cleavage of the ether linkage. The alkamine ether series of 10-phenylthiaxanthenol dioxide was prepared by first oxidizing 10-phenylthiaxanthenol to the corresponding dioxide; treatment of this compound with phosphorus pentachloride using chlorobenzene as a solvent yielded 10-phenyl-10-chlorothiaxanthene. When this chloro compound was refluxed with 10 times the molar quantities of alkamine alcohols, the desired compounds were obtained.

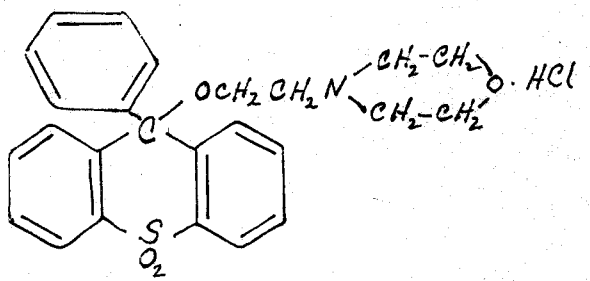




They were isolated as hydrochlorides, but could also be crystallized as free bases. Only two compounds of this series were prepared:



β-diethylaminoethyl-10-phenylthiaxanthyl-dioxide ether hydrochloride



β-morpholinoethyl-10-phenylthiaxanthyl-dioxide ether hydrochloride

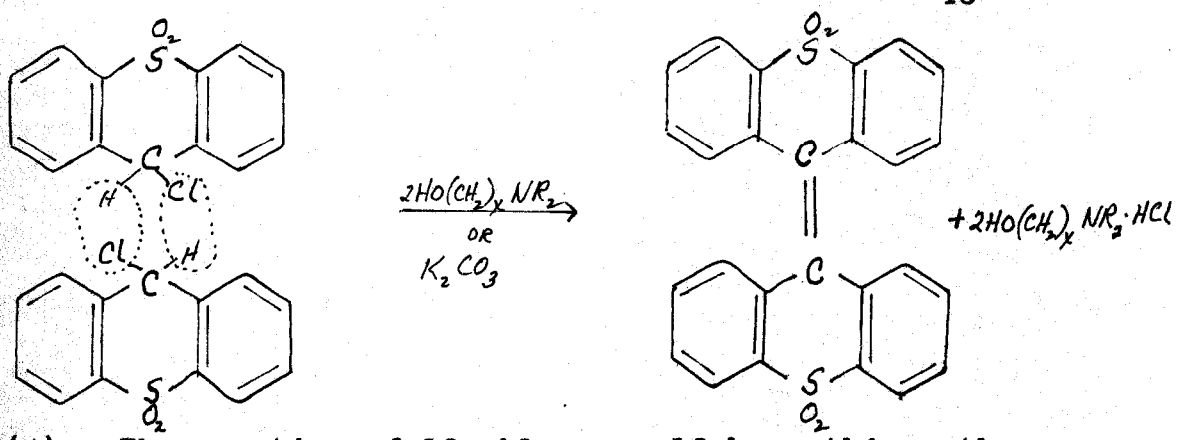
Efforts to prepare a series of alkamine ethers of either thiaxanthenol or thiaxanthenol-dioxide were unsuccessful. Reviewing the work on the thiaxanthenol-dioxide molecule first; we attempted to prepare alkamine ethers of this compound by the following methods:

(1). Condensation of thiaxanthenol-dioxide with a dialkylaminoalkyl chloride in the presence of various basic

condensing agents such as potassium carbonate or pyridine was attempted, but the desired product could not be isolated in either case.

(2). Reaction of the sodium salt of thiaxanthenol dioxide with a dialkylaminoalkyl chloride in a neutral solvent such as toluene or xylene also was tried. The reaction was run under nitrogen to protect against air oxidation but was unsuccessful. Huber (34) was also unsuccessful in attempts to prepare alkamine ethers of the sodium salt of benzhydryl by this method.

(3). The attempted condensation of 10-chlorothiaxanthene dioxide (or the more reactive bromo derivative) with a dialkylaminoalkyl alcohol, or with the sodium salt of such an alcohol, was carried out in a variety of ways. The alkylaminoalcohol was used as both reactant and solvent in some cases. In other cases relatively non-polar substances such as benzene or ether were tried as solvents, and finally polar materials such as pyridine or acetone were used. In all attempts a finely crystalline material, colored from yellow to red, precipitated within a short time. This material was insoluble in almost all organic solvents and did not melt at 360°, consequently it was believed to be dithiaxanthylene dioxide which was formed by splitting out hydrogen chloride from two molecules of 10-chlorothiaxanthene dioxide under the influenee of the strongly basic aminoalcohol.



(4). The reaction of 10-chloro or 10-bromothiaxanthene dioxide with ethylene chlorohydrin in the presence of potassium carbonate was attempted. We had hoped to react the intermediate resulting from the foregoing reaction, β-chloroethylthiaxanthene-dioxide with a series of tertiary amines. However, an extremely high melting compound again resulted. This was also presumed to be the same product as obtained above, dithiaxanthylene dioxide.

It has been mentioned previously (see pages 13, 16 and 17) that thiaxanthenol is a material which is extremely sensitive to oxidation. In addition it has been found to disproportionate very readily to thiaxanthone and thiaxanthene. These reasons seem to explain why we were unable to prepare alkamine ethers from the reaction of the sodium salt of thiaxanthenol with an alkaminoalkyl chloride.

The reaction of thiaxanthylium chloride with an alkaminoalcohol produced a large amount of thiaxanthone and a very small amount of an oily methiodide salt which could not be crystallized. Since the material was insoluble in water it probably was not the methyl iodide salt of the aminoalcohol. It dissolved in alcohol, however, and showed the

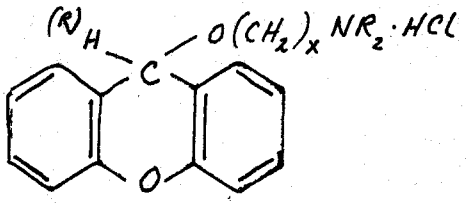
presence of ionizable iodide, a behaviour shown by the corresponding 10-arylthiaxanthenol derivative. Consequently, it was probably the desired alkamino ether of thiaxanthenol. The yield, however, was so small as to render this synthesis useless. Even when the reaction was carried out under an inert atmosphere such as nitrogen, no increase in yield was noticed, therefore, efforts to prepare a series of ethers of thiaxanthenol were abandoned.

IV SUGGESTIONS FOR FUTURE THESIS PROBLEMS

(1) The structure of the compound described by Smiles (14) as thiaxanthylium chloride has never been fully verified. The compound may be a thiaxanthylium chloride as postulated or it may be a chloride-hydrochloride as explained on pages 14-15. An accurate analysis of this compound for chlorine should clear up the problem of structure. Smiles described the compound as being too unstable to analyze, however the compound is stable for a short time in solution and we believe that it may be possible to work out a method for analyzing the material in solution.

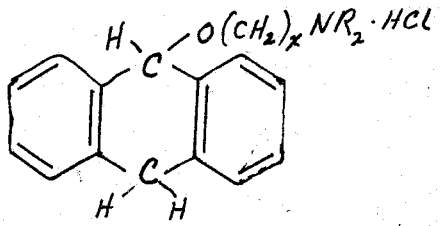
(2) The structures of the ferrichloride salt of 10-phenylthiaxanthenol and the chloride-hydrochloride of 10-phenylthiaxanthenol have been in doubt since their preparation forty years ago. (see pages 18-19). It is possible that electrical conductivity measurements may help to elucidate the structures of these two compounds. In addition, the effect of introducing groups in the para position of the phenyl group on the color of the complex compound may be of interest as well as help in determining structure.

(3) Although the alkamine ethers of thiaxanthenol could not be prepared because of the instability of the compound, it may be possible to prepare an alkamine ether series of xanthenol or substituted xanthenol of the following type.

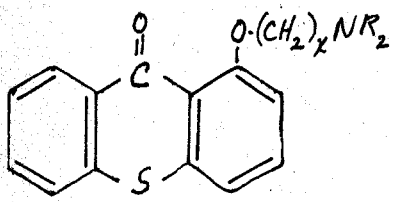


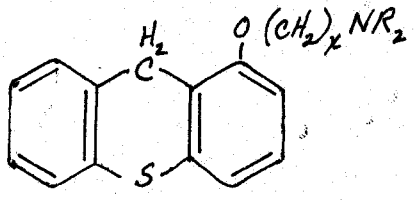
These ethers should be more active as antihistamines than the thiaxanthenol compounds which we could not prepare. The alkamine ethers of xanthene-carboxylic acid proved to be more active antihistaminics than the corresponding thiaxanthene compounds (see page 28).

(4) In a similar manner, alkamine ethers of 9, 10-dihydroanthracene should be prepared for possible use as antispasmodics (see page 28).



(5) As explained on pages 31 and 35, it would be of interest to prepare the following ring substituted alkamine ethers of thiaxanthone and thiaxanthene for use as chemotherapeutic agents.

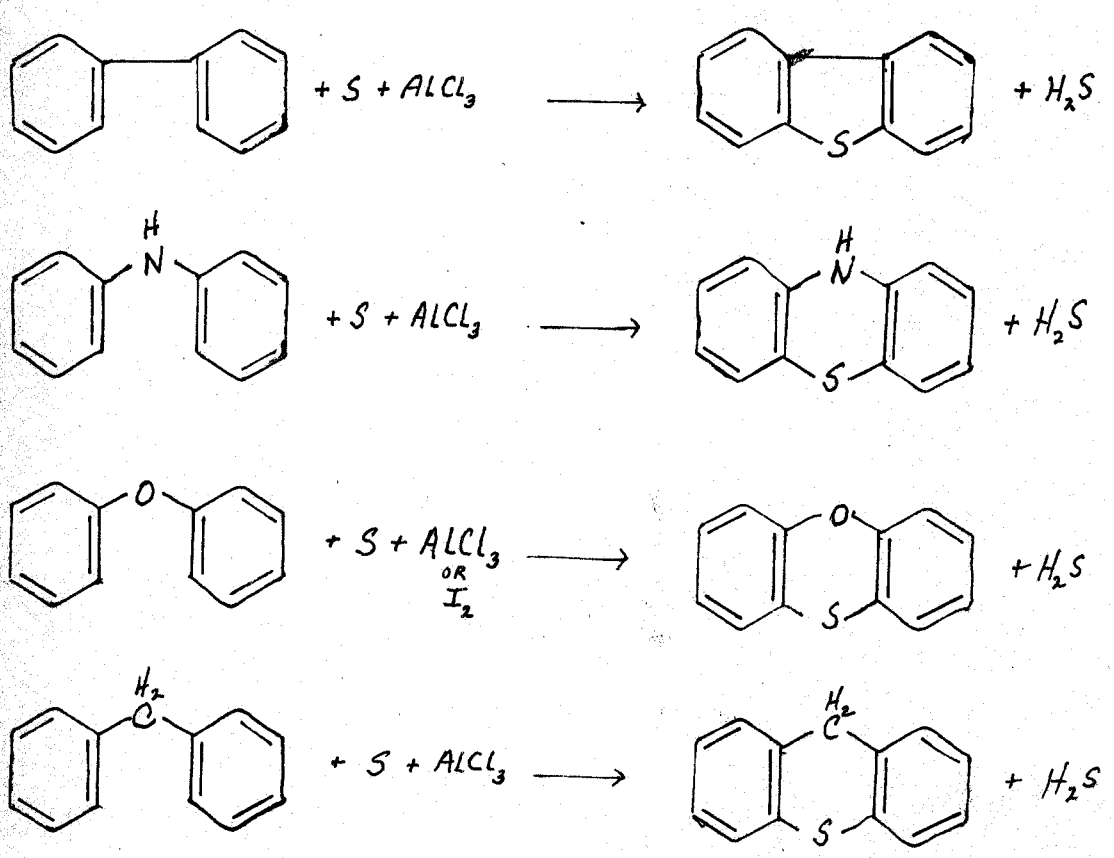




(6) A method for the preparation of thiaxanthene on a large scale is needed. Substitution studies on thiaxanthene have never been carried out, largely because of the

difficulty of preparing this compound. The following methods may prove useful.

(a) Since dibenzothiophene is prepared by the condensation of biphenyl with sulfur in the presence of aluminum chloride (47) and other compounds such as phenothiazine, phenoxathiin etc. are prepared by similar condensations, it is reasonable to assume that thiaxanthene could be prepared by a like condensation of diphenylmethane and sulfur in the presence of aluminum chloride or other catalysts. The following diagrams point out this analogy:



(b) The hot tube reaction of Graebe and Schulthess (9) in which phenyl-o-tolyl sulfide was converted to thiaxanthene should be re-examined. Modern techniques and knowledge of vapor phase reactions may be able to modify this synthesis to a successful laboratory preparation.

V EXPERIMENTAL DETAILS

A. PREPARATION OF DITHIOSALICYLIC ACID

The method of Allen and MacKay (48) was used to prepare dithiosalicylic acid and its reduction product thiosalicylic acid. In a four-liter beaker, 290 cc. of water were heated to boiling and 260 g. (1.08 moles) of crystalline sodium sulfide ($Na_2S \cdot 9H_2O$) and 34 g. (1.08 moles) of powdered sulfur were dissolved by heating and stirring. A solution of 40 g. (1.0 mole) of sodium hydroxide in 100 cc. of water was then added and the mixture cooled, first in cold water, and finally by a freezing mixture of ice and salt.

In a two-liter beaker, set in a freezing mixture and provided with a mechanical stirrer and a thermometer were placed 500 cc. of water, 137 g. (1.0 mole) of anthranilic acid and 200 cc. of concentrated hydrochloric acid; the stirrer was started and the mixture cooled to a temperature somewhere between 0-5°. Meanwhile 69 g. (1.0 mole) of sodium nitrite were dissolved in 280 cc. of hot water and the solution cooled in ice. The nitrite solution was slowly run into the anthranilic acid by means of a separatory funnel, the end of which extended below the surface of the anthranilic acid solution. During the addition of the nitrite solution about 500 g. of cracked ice were added at such a rate as to keep the temperature below 5°.

The stirrer and thermometer were transferred to the alkaline sulfide solution, the temperature of which was held below 5°. The diazo solution was added over a period of twenty to thirty minutes along with 950 g. of ice to prevent a rise above 5°. When the addition was complete, the ice-water bath was removed and the mixture was allowed to warm up to room temperature; after approximately two hours the evolution of nitrogen ceased. During the evolution of nitrogen it was sometimes necessary to control excessive foaming by addition of small amounts of ether or butanol. At this point the solution was made acid to Congo Red by the addition of approximately 180 cc. of concentrated hydrochloric acid. The crude dithiosalicylic acid was filtered off and washed well with water. To remove excess sulfur, the precipitate was dissolved by heating with a solution of 60 g. of anhydrous sodium carbonate in 2 l. of water, filtered while hot and the dithiosalicylic acid reprecipitated as before with concentrated hydrochloric acid. The solid was filtered, washed well with water and air dried. The crude product weighed 230 g. (75%) and was sufficiently pure to use directly to prepare thiaxanthone.

B. PREPARATION OF THIOSALICYLIC ACID

It is recommended in Organic Synthesis that the cake of dithiosalicylic acid be divided into five portions and reduced with zinc dust and acetic acid. This method of reducing in smaller quantities was found to be superior to

reducing the cake in one portion or to the alternate German method using iron or zinc dust and sodium carbonate (49).

One-fifth of the moist cake of dithiosalicylic acid from the above preparation was mixed with 27 g. of zinc dust and 300 cc. of glacial acetic acid in a one-liter round-bottomed flask, and the mixture was refluxed for about four hours. When reduction was complete the mixture was cooled and filtered by suction. It was sometimes necessary to add more zinc dust in the reduction as it did not always proceed smoothly due to lumping of the zinc dust. The cake was suspended in 200 cc. of water in a one-liter beaker and the suspension was heated to boiling. The hot solution was made strongly alkaline by the addition of about 40 cc. of 33 per cent aqueous sodium hydroxide solution. The alkaline solution was boiled for about twenty minutes to insure complete extraction of the product from the filter cake and then filtered from the insoluble residue. The thiosalicylic acid was precipitated by the addition of sufficient concentrated hydrochloric acid to make the solution acid to Congo Red paper. The product was filtered with suction, washed once with water and dried in an oven at 100 to 110°. The average yield of a product which melted at 162° was 110 g. (70%). For a purer product 5 g. of the material was dissolved in 20 cc. of hot alcohol (95%) and 40 cc. of hot water was added. The solution was treated with Darco, filtered hot and allowed to cool. The yield of almost white crystalline thiosalicylic

acid melting at 163-164° was 4.5 to 4.7 g. *

C. PREPARATION OF THIAXANTHONE

Smiles and his coworker (4) prepared thiaxanthone by several methods involving the condensation of benzene with thiosalicylic acid and derivatives (see page 3). Gomberg and Cone (11) simplified one of these methods and obtained thiaxanthone in excellent yields by reacting thiosalicylic acid, benzene and sulfuric acid. We have used Gomberg's method with little variation and have also simplified and improved another method of Smiles utilizing the condensation of dithiosalicylic acid with benzene in the presence of sulfuric acid.

1. Thiaxanthone from Dithiosalicylic Acid. A mixture of 40 g. (.13 mole) of dithiosalicylic acid and 120 cc. of benzene (1.3 moles) was stirred in a one-liter three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer and reflux condenser, the apparatus being kept under a hood. while stirring strongly, 400 cc. of concentrated sulfuric acid were added; an orange color developed almost immediately , the temperature rose to between 50-60°, and sulfur dioxide was evolved. Stirring was continued and the temperature was held at 55-60° for three hours by heating the flask in a hot water bath. During this time the color deepened and much of the solid material went into solution; sulfur

* We are indebted to the Eli Lilly Company for a generous complimentary supply of thiosalicylic acid.

dioxide was evolved at a steady rate. At the end of this time the temperature was raised and held at 70-80° for one hour; the solid material dissolved completely forming a dark red solution.

After cooling, the mixture was slowly poured into 500 g. of ice and 1000 g. of water with good mechanical stirring. The resulting white precipitate was filtered and washed twice with 100 cc. portions of 10% sodium hydroxide solution to remove any remaining dithiosalicylic acid, then washed with water until free from base. The crude white powdery material weighed 47.5 g. when air dried (86%). One recrystallization from 380 cc. of glacial acetic acid yielded light yellow needles of thiaxanthone which melted at 211-212° and weighed 40 g. This represents a yield of 72% of pure thiaxanthone or 54% of pure product from anthranilic acid.

2. Thiaxanthone from Thiosalicylic Acid. A mixture of 50 g. (.33 mole) of thiosalicylic acid, 150 cc. of benzene (1.5 moles) was stirred in a one-liter, three-necked, round-bottomed flask fitted with a mechanical stirrer, thermometer and reflux condenser. While stirring, 600 cc. of concentrated sulfuric acid were added, and the solution was stirred for twelve hours. During this time sulfur dioxide was evolved and the color of the suspension gradually darkened from yellow to deep orange. The solution was allowed to stand for an additional twelve hours and was then heated on the

steam bath for one additional hour to complete the reaction. The dark red clear solution was allowed to cool and then poured into 750 g. of ice and 1500 cc. of water with good mechanical stirring. The white precipitate was allowed to stand for twelve hours (filtration was easier due to crystal growth) and then was filtered and washed twice with 150 cc. portions of 10% sodium hydroxide solution. After washing with water and allowing to air dry the crude material was recrystallized from acetic acid and the purified product weighed 55 g. (79.5%). Hence the overall yield of pure thiaxanthone from anthranilic acid was 55.7%.

D. 10-PHENYL THIAXANTHENOL

Phenyl magnesium bromide was prepared in the usual manner by covering 7.2 g. (.3 mole) of dry magnesium chips with 60 cc. of dry Grignard ether. About 20-30 cc. of a solution of 47 g. (.3 mole-31.5 cc.) of freshly distilled bromobenzene in 300 cc. of dry ether was added and the reaction was initiated by cautious heating, stirring and usually by addition of a crystal of iodine. After the reaction had started the solution of the halide was run in at such a rate as to maintain a steady reflux of ether. After addition of all the bromobenzene solution the reaction was completed by an additional twenty minutes heating in a warm water bath.

Finely powdered thiaxanthone, 31.6 g. (.15 mole), was then added in small portions. A yellow solid of the magnesium complex compound precipitated from the reaction

solution. After addition of the thiaxanthone, stirring and warming in a warm water bath was continued for twenty minutes. The magnesium complex was hydrolyzed by pouring the entire reaction mixture into 24 cc. of concentrated hydrochloric acid, 400 cc. of water and 100 g. of ice. Any solid remaining in the flask was washed into the hydrolysis mixture with ether. The hydrolysis reaction was well stirred and enough ether added to dissolve the liberated 10-phenylthiaxanthenol. From 300-500 cc. of extra ether were required. The yellow ether layer was decanted and evaporated on a steam heated hot plate. An oil resulted which crystallized when treated with cold ligroin (40-60°) into a yellowish-tan material which weighed 36.5 g. (84%) and melted at 95-98°. After recrystallization from 100-120° ligroin the product was received as white clusters of crystals melting at 105-106° and weighing 31 g. (71.5%).

E. THE FERRICHLORIDE ADDITION COMPOUND OF 10-PHENYL THIAXANTHENOL

1. From Aqueous Solution. Crude 10-phenylthiaxanthenol, 5.8 g. (.02 mole), was dissolved in 40 cc. of concentrated hydrochloric acid. A solution of 40 cc. of 3N ferric chloride was added and a red amorphous solid precipitated immediately. The weight of this material was 7.2 g. (76.5%).

2. From Ether Solution. To a solution of 5.8 g. (.02 mole) of crude 10-phenylthiaxanthenol in 60 cc. of dry ether was added 4.8 g. of ferric chloride (.03 mole) in 60 cc. of

dry ether. Dry hydrogen chloride was passed into this solution causing precipitation of the crystalline blood red ferrichloride salt. The hydrogen chloride was passed in until precipitation was complete and the material was filtered off, washed well with ether and air dried. The product consisted of 8.8 g. (93.5%) of fine blood red crystals which melted at 166°.

F. β-DIETHYLAMINOETHYL-10-PHENYLTHIAXANTHYL ETHER METHIODIDE

Method 1. Into a 500 cc. three-necked round-bottomed flask fitted with a mercury sealed mechanical stirrer, a dropping funnel and a reflux condenser was placed a solution of 12 g. (.1 mole) of β-diethylaminoethyl alcohol in 500 cc. of benzene. The mixture was warmed and stirred while a solution of 9.4 g. (.02 mole) of the ferrichloride salt of 10-phenylthiaxanthenol in 30 cc. of acetone was added dropwise. A brown precipitate of complex ferric compounds resulted almost immediately. When addition of the complex salt was completed, the reaction mixture was refluxed for three hours and , after cooling, a solution of 50 cc. of 1N sodium hydroxide was added to remove the iron as ferric hydroxide. The iron oxides were filtered off by suction and the benzene layer was separated from the alkali. The benzene solution was then washed four times with equal volumes of water to remove all unreacted aminoalcohol. The benzene layer was dried over potassium carbonate and evaporated to a volume of about 3 cc. An excess of low boiling ligroin

was added and the cloudy solution allowed to stand overnight. A white material crystallizing in clusters was collected and identified by means of a mixed melting point as 10-phenyl thiaxanthenol; a total of 2.5 g. of the material was collected. A red oil remained after removal of 10-phenylthiaxanthenol; this material was dissolved in a few cubic centimeters of alcohol and about 1 cc. of methyl iodide was added. This solution was refluxed for fifteen minutes under an efficient reflux condenser and, after cooling, white needles of the methyl iodide salt of β-diethylaminoethyl-10-phenylthiaxanthyl ether were precipitated by the addition of ether. The material decomposed at 188-190° and weighed 1.3 g. (12.25%). The yield based on the amount of 10-phenylthiaxanthenol which entered into the reaction was 21.7%.

Anal. Calcd. for $C_{26}H_{30}OINS$: I, 23.92. N, 2.64. S, 6.03. Found. I, 24.22. N, 2.57. S, 6.12

Method 2. Into a 250 cc. Erlenmeyer flask fitted with a reflux condenser and a calcium chloride drying tube was placed 5.8 g. (.02 mole) of 10-phenylthiaxanthenol and 20 cc. of dry chloroform; the carbinol was dissolved by warming and gently rotating the flask. The drying tube at the top of the condenser was replaced by a short-stemmed dropping funnel and a solution of 2.4 g. (.02 mole) of thionyl chloride in 5 cc. of dry chloroform was added dropwise through the dropping funnel. A vigorous exothermic reaction began almost immediately. The solution developed

a dark red color and hydrogen chloride gas was slowly evolved. After addition of the thionyl chloride solution, the mixture was refluxed until the evolution of gaseous hydrogen chloride ceased (about one hour). At this time a solution of 14 g. (.12 mole) of β-diethylaminoethyl alcohol in 28 cc. of dry chloroform was added dropwise through the dropping funnel. During the addition of the aminoalcohol the color of the solution gradually lightened from an opaque red to a light yellow; white needles of the hydrochloride of the aminoalcohol were formed but later dissolved in the excess of solvent introduced. The mixture was refluxed for six hours to complete the reaction; during this time the solution again darkened to a cherry red. After cooling, the mixture was transferred to a separatory funnel and was shaken with 20 cc. of a solution of 6N sodium hydroxide. The chloroform layer was separated, washed four times with equal volumes of water to remove the unreacted aminoalcohol and sodium hydroxide, and dried overnight over anhydrous potassium carbonate or sodium sulfate. The chloroform was removed by evaporation and a red viscous oil was obtained. Since the free base could not be isolated in a crystalline form, 2 cc. of methyl iodide (.033 mole) and 5 cc. of absolute alcohol were added and the solution refluxed under an efficient condenser for one hour to form the methiodide salt. Addition of a large excess of dry ether precipitated a brownish-yellow oil which crystallized upon standing, the

yield varied from 5.8 to 6.4 g. (54.5-60%) of material which decomposed at about 184°. Two recrystallizations from alcohol-ether yielded white crystals which decomposed at 190°.

G. β-MORPHOLINOETHYL-10-PHENYLTHIAXANTHYL ETHER METHIODIDE

This material was prepared by a slight modification of Method 2 under the preparation of β-diethylaminoethyl ether (F). The chloride-hydrochloride of 5.8 g. (.02 mole) of 10-phenylthiaxanthenol in 20 cc. of dry chloroform was prepared in exactly the same manner as given under F-2. After refluxing for one hour to complete the replacement of the hydroxy group by chlorine, a solution of 15.7 g.(.12 mole) of β-morpholinoethyl alcohol in twice its volume of dry chloroform (ca. 30 cc.) was added dropwise. The color change from dark red to yellow was again observed and some hydrochloride of β-morpholino ethanol precipitated. After refluxing for six additional hours, the chloroform was evaporated off and 50 cc. of ether along with 20 cc. of 6N sodium hydroxide solution was added to the white crystalline residue. The mixture was agitated until all of the liberated free base dissolved in the ether layer, then the entire mixture was transferred to a separatory funnel and the alkali layer was separated and discarded. The ether layer was washed four times with equal volumes of water to remove excess aminoalcohol. The ether solution was dried overnight and the solvent removed by evaporation; a thick red oil of the free base

resulted. While the oil was still warm 3.8 cc. of methyl iodide and 5 cc. of absolute alcohol were added and the mixture was refluxed for one hour under an efficient condenser. Upon standing, 6.4 g. (60%) of the β-morpholinoethyl-10-phenylthiaxanthyl ether methiodide precipitated as faintly pink crystals whose decomposition point was 200°. Recrystallization from absolute alcohol using Darco yielded fine white crystals which decomposed at 208°.

Anal. Calcd. for $C_{26}H_{28}O_2INS$: I, 23.30. N, 2.57. Found. I, 23.31. N, 2.60.

H. β-PIPERIDINOETHYL-10-PHENYLTHIAXANTHYL ETHER METHIODIDE

This material was prepared by a method which differs from that previously given under F in that the chloride-hydrochloride of 10-phenylthiaxanthenol was isolated and treated directly with the dialkyl aminoalcohol which then acted both as reagent and solvent. A solution of 5.8 g. (.02 mole) in 20 cc. of dry chloroform was prepared and 2.4 g. (.02 mole) of thionyl chloride in 5 cc. of chloroform were added dropwise. The resulting red solution was refluxed for approximately one-half hour and then 100-150 cc. of dry ligroin (40-60°) were added, with agitation, to the solution. Red needles of the chloride-hydrochloride of 10-phenylthiaxanthenol were precipitated. After standing for about 15 minutes the precipitation seemed to be complete and the ligroin-chloroform-thionyl chloride solution was poured off. The crystals were washed with two 25 cc. portions

of dry ligroin and the 21 g. (.16 mole) of β-piperidinoethanol were added. A reaction took place immediately and crystals of β-piperidinoethanol hydrochloride appeared. Upon refluxing the mixture a clear red solution resulted. After one and one-half hours of heating under reflux the mixture was allowed to cool and 50 cc. of ether were added whereupon the hydrochloride of the excess aminoalcohol again precipitated as a white crystalline material. Upon addition of 20 cc. of a 6N solution of sodium hydroxide the white precipitate was reconverted to the oily free base which then dissolved in th ether layer. The ether layer was separated, washed and dried overnight over potassium carbonate. Evaporation of the ether left about 5.5 g. of a thick red oil which was converted to the methyl iodide salt in the usual manner using 3.8 cc. of methyl iodide. A crude product of dark yellow crystals weighing 5.5 g. (52%) was obtained. One recrystallization from absolute alcohol gave a faintly tan-colored product weighing 4.8 g. (44%) which decomposed at 208°.

Anal. Calcd. for $C_{27}H_{30}OINS$; I, 23.39. N, 2.58. Found. I, 23.40. N, 2.67.

I. β-DIMETHYLAMINOETHYL-10-PHENYLTHIAXANTHYL ETHER METHIODIDE

A warm solution of 5.8 g. (.02 mole) of 10-phenylthiaxanthenol in 20 cc. of ethyl acetate, purified by the method of Fieser (50), was treated with 2.4 g. of thionyl chloride diluted with 3.5 cc. of ethyl acetate; the now

familiar dark red color and vigorous reaction was observed. The mixture was refluxed for 10 minutes and 9.0 g. (.12 mole) of β-dimethylaminoethyl alcohol* in 20 cc. of ethyl acetate were added in the usual manner. After refluxing for two hours, 50 cc. of ether and 20 cc. of 6N sodium hydroxide were added to the cooled solution. The ether layer was separated, washed four times and dried over sodium sulfate. The ether was evaporated and the free base converted to a yellow methyl iodide salt. Recrystallization from alcohol-ether yielded 4.8 g. (48%) of a very faintly yellow crystalline material which melted at 214° with decomposition.

Anal. Calcd. for $C_{24}H_{26}OINS$; I, 25.25. N, 2.78. Found. I, 25.46. N, 3.04.

J. PARA-BROMO-CHLOROBENZENE

The method of Mouneyrat and Pouret (51) was used to prepare this intermediate. Into a dry flask equipped with a reflux condenser and a hydrogen bromide trap were placed 125 g. (1.02 moles) of chlorobenzene and 160 g. (1 mole) of dry bromine. The contents of the flask were cooled by means of an ice bath and small portions (.15 to .2 g.) of anhydrous aluminum chloride were added at approximately fifteen minute intervals until a total of 2 g. of the catalyst had been added. The mixture was allowed to stand overnight and the almost solid mass of crystals was broken up and collected by suction filtration. The precipitate was washed with dilute sodium

* This alcohol was generously supplied by Sharples Inc.

carbonate solution followed by water. It was recrystallized from methyl alcohol yielding large flat white prisms which melted at 66° and weighed 173 g. (90%).

K. 10-(4-CHLOROPHENYL)-THIAXANTHENOL

The Grignard reagent, p-chlorophenyl magnesium bromide was prepared in the usual manner from 3.6 g. (.15 mole) of magnesium turnings and 28.8 g. (.15 mole) of p-chlorobromobenzene in 250 cc. of dry ether. After formation of the Grignard reagent, 21.2 g. (.1 mole) of dry pulverized thiaxanthone was added in small portions. The solution was heated after every addition and for one-half hour after addition was complete. A total of about 300 cc. of dry ether was added during the reaction to keep the mixture fluid. The reaction mixture which contained a heavy yellow precipitate was hydrolyzed by pouring it into a mixture of 16 cc. of concentrated hydrochloric acid, 400 cc. of water and 100g. of ice. Additional ether was used to help remove the heavy precipitate from the flask. The ether layer was separated and upon evaporation 34.8 g. of crude yellow crystalline material was collected. Recrystallization from high boiling ligroin, using Darco, yielded 28 g. (86%) of faintly yellow clusters of crystals which melted at 150°. The sample for analysis was recrystallized twice from ligroin and was obtained as pure white crystals which melted sharply at 154°. The compound formed a red ferrichloride complex compound

as red needles which melted at 194°.

Anal. Calcd. for $C_{19}H_{13}OClS$; Cl, 10.94. Found. Cl, 11.31.

L. β-MORPHOLINOETHYL-10-(4-CHLOROPHENYL)-THIAXANTHYL ETHER METHIODIDE

To a solution of 3.25 g. (.01 mole) of 10-(4-chlorophenyl)-thiaxanthenol in 25 cc. of dry chloroform was added portionwise a solution of 1.4 g. (.012 mole) of thionyl chloride in 2.5 cc. of chloroform. The usual vigorous reaction set in and the color of the solution turned to dark red. The reaction flask was stoppered with a calcium chloride drying tube to prevent the entrance of moisture, and was allowed to stand for one-half hour to complete the reaction. A solution of 8.2 g. (.06 mole) of β-morpholinoethyl alcohol in 15 cc. of dry chloroform was added slowly, during which time the color of the solution faded to an orange-yellow; the mixture was then refluxed for two hours, during which time the color became cherry red. After cooling, 200 cc. of ether and 20 cc. of a 6N sodium hydroxide solution were added with shaking and the ether layer was separated and washed four times with equal volumes of water. The ether solution was dried over sodium sulfate and the solvent evaporated. The red oil which remained was dissolved in 40 cc. of benzene with 2 cc. (.03 mole) of methyl iodide and the mixture was refluxed for one hour. After about 5 minutes, pale pink crystals of the methiodide salt appeared; the precipitate

gradually became heavier as refluxing continued. After the requisite time, 100 cc. of 40-60° ligroin was added to complete the precipitation of the methyl iodide salt. Upon cooling, 1.8 g. (33%) of a very faintly pink crystalline precipitate was collected which decomposed at 220°. After recrystallization from absolute ethyl alcohol the compound was obtained as fine pure white needles which decomposed at 223°.

Anal. Calcd. for $C_{26}H_{27}O_2ClINS$; I, 21.90. N, 2.42. Found. I, 22.18. N, 2.66.

M. β-DIMETHYLAMINOETHYL-10-(4-CHLOROPHENYL)-THIAXANTHYL ETHER METHIODIDE

This material was prepared in a manner identical to the method given for the corresponding β-morpholinoethyl ether (L). To a solution of 1.1 g. (.0033 mole) of 10-(4-chlorophenyl)-thiaxanthenol in 10 cc. of dry chloroform was added .3 cc. of thionyl chloride in 10 cc. of dry chloroform. A solution of 1.8 g. (.02 mole) of β-dimethylaminoethyl alcohol in 2.5 cc. of chloroform was added dropwise and the mixture was refluxed for two hours. The free base, β-dimethylaminoethyl-10-(4-chlorophenyl)-thiaxanthyl ether was isolated as a red oil in the usual manner and converted to the methiodide salt which was obtained as light yellow crystals. After recrystallization from isopropyl alcohol, a material which weighed .60 g. (33%) and decomposed at 198° was obtained.

Anal. Calcd. for $C_{24}H_{25}OClINS$; I, 23.60. N, 2.61. Found. I, 23.40. N, 2.78.

N. β-PIPERIDINOETHYL-10-(4-CHLOROPHENYL)-THIAXANTHYL ETHER METHIODIDE

This ether was prepared in exactly the same manner as that of the other two derivatives (L and M). The chloride-hydrochloride of 1.1 g. (.0033 mole) of 10-(4-chlorophenyl)-thiaxanthenol in chloroform was reacted with 2.6 g. of β-piperidinoethyl alcohol and the free base was isolated as usual. The methiodide salt was prepared as a yellow crystalline material which was recrystallized from isopropyl alcohol and decomposed at 196°. The yield was .65 g. (35%).

Anal. Calcd. for $C_{27}H_{29}OClINS$; I, 21.98. N, 2.43. Found. I, 21.91. N, 2.35.

O. 10-PHENYLTHIAXANTHENOL-DIOXIDE.

This oxidation was carried out as described by Gomberg and Britton (28). Into a solution of 11.6 g. (.04 mole) of 10-phenylthiaxanthenol in 80 cc. of hot glacial acetic acid was introduced a concentrated solution of 15 g. (.15 mole) of chromic acid in 20 cc. of water. The oxidizing agent was added at such a rate as to keep the temperature of the acetic acid above 100°. After addition of the chromic acid solution was complete, the dark-colored reaction mixture was refluxed for one hour, then 50 cc. of hot water were added and the 10-phenylthiaxanthenol-dioxide was allowed to crystallize. After the solution cooled, the resulting precipitate was collected and washed several times with hot water to remove chromic salts and then recrystallized from

glacial acetic acid and water. The material was obtained as fine white crystals which weighed 9.5 g. (74%) and melted at 224°.

P. 10-PHENYL-10-CHLOROTHIAXANTHENE-5-DIOXIDE

Into a 500 cc. three-necked round-bottomed flask fitted with a reflux condenser connected to a hydrogen chloride trap, and a mechanical mercury-sealed stirrer, was placed a solution of 19.3 g. (.06 mole) of 10-phenylthiaxanthenol dioxide in 100 cc. of dry chlorobenzene. The solution was brought to reflux temperature and 12.5 (.06 mole) of phosphorus pentachloride was added portionwise, but rapidly, by means of a powder funnel inserted into one of the necks of the flask. A light red color developed almost immediately and a small amount of a dark red by-product precipitated. After refluxing for one hour, the condenser was removed and the majority of the phosphorus oxychloride was boiled away. After treatment with activated charcoal, the solution was filtered, evaporated to 50 cc. and about 150 cc. of ligroin were added to precipitate the product. Upon standing, 17.7 g. (87%) of a pinkish crystalline material which melted at 153-155° was collected. Recrystallization from high boiling ligroin raised the melting point to 160-161°, and removed the color, leaving pure white crystals.

Q. β-DIETHYLAMINOETHYL-10-PHENYLTHIAXANTHYL DIOXIDE ETHER HYDROCHLORIDE

A mixture of 3.4 g. (.01 mole) of 10-phenyl-10-

chlorothiaxanthene dioxide and 11.7 g. of β-diethylaminoethyl alcohol (.1 mole) was refluxed for two hours. After cooling, the brown solution was treated with 20 cc. of 6N sodium hydroxide and was extracted with 250 cc. of ether. The ether layer was separated from a small amount of purplish amorphous material and washed four times with 100 cc. portions of water. After drying overnight, the ether solution was saturated with dry hydrogen chloride gas, and allowed to stand for several hours; fine white crystals formed which were collected and recrystallized from alcohol. The yield of material melting at 285° with decomposition was 2.0 g. (43.6%). The free base was prepared and after recrystallization from ethyl methyl ketone was obtained as fine white needles which melted at 120°.

Anal. Calcd. for $C_{25}H_{28}O_3ClNS$; Cl, 7.77. N, 3.06. Found. Cl, 7.52. N, 3.02.

R. β-MORPHOLINOETHYL-10-PHENYLTHIAXANTHYL DIOXIDE ETHER HYDROCHLORIDE

A mixture of 3.4 g. (.01 mole) of 10-phenyl-10-chlorothiaxanthene and 13.1 g. (.1 mole) of β-morpholinoethyl alcohol was refluxed for two hours and was then added with stirring to 200 cc. of water containing 20 cc. of 6N sodium hydroxide solution. The dark brown oil which precipitated soon solidified to a granular precipitate. This material was collected and dried overnight in a desiccator. The free base of β-morpholinoethyl-10-phenylthiaxanthyl ether

was extracted from this material by refluxing with two successive 100 cc. portions of isopropyl ether. A small quantity of tarry material remained and was discarded. Dry hydrogen chloride gas was passed into the isopropyl ether solution and a gummy precipitate of the hydrochloride formed. Recrystallization from alcohol yielded 1.8 g. of fine white needles (38.5%) which decomposed at 266°.

Anal. Calcd. for $C_{25}H_{26}O_4ClNS$; Cl, 7.53. N, 2.97. Found. Cl, 7.30. N, 3.10.

S. THIAXANTHENOL

Although efforts to prepare alkamine ethers of thiaxanthenol failed, an excellent synthesis of thiaxanthenol itself was discovered. Previous reductions of thiaxanthone to thiaxanthenol (22)(24)(14)(23) had given erratic results, impure products and low yields. An application of the method of Organic Synthesis (52) for the reduction of xanthone to xanthyrol to the reduction of thiaxanthone gave unusually pure thiaxanthenol in quantitative yields.

A mixture of 375 g. of mercury, 13.8 g. (.065 mole) of thiaxanthone and 80 cc. of 95% alcohol was placed in a pressure bottle and while shaking 4.6 g. (.2 mole) of sodium were added in small pieces over a fifteen minute period. During addition of the sodium, the temperature rose and a dark purple color developed which gradually disappeared as all of the thiaxanthone went into solution. The mixture was mechanically shaken for an additional fifteen minutes and the

alcohol layer was decanted. The mercury amalgam was extracted with two 15 cc. portions of hot alcohol and the combined alcoholic solutions were filtered to remove a gray residue and poured into one liter of water. A white precipitate of fine crystals was collected which weighed 13.2 g. (95.7%) to 13.4 g. (97%) when air dried. This material was pure enough for any subsequent reactions; it melted at 103-104°. The pure product is reported to melt at 105-106°. Since the material is very susceptible to air oxidation it should be stored in a sealed brown bottle.

VI SUMMARY

A. A method for the preparation of pure thiaxanthenol in quantitative yields has been described.

B. An improvement in the method for the preparation of 10-phenyl-10-chlorothiaxanthene dioxide has been reported.

C. Alkamine ethers of 10-phenylthiaxanthenol and 10-(4-chlorophenyl)-thiaxanthenol were prepared for possible use as chemotherapeutic agents and were characterized as methiodide salts.

D. Several alkamine ethers of 10-phenylthiaxanthenol dioxide were prepared as hydrochlorides for possible medicinal use,

E. The following new compounds were prepared:

(1) β-diethylaminoethyl-10-phenylthiaxanthyl ether methiodide dec. 184

(2) β-dimethylaminoethyl-10-phenylthiaxanthyl ether methiodide dec. 214

(3) β-morpholinoethyl-10-phenylthiaxanthyl ether methiodide dec. 206

(4) β-piperidinoethyl-10-phenylthiaxanthyl ether methiodide dec. 208

(5) 10-(4-chlorophenyl)-thiaxanthenol M.P. 154
10-(4-chlorophenyl)-thiaxanthyl chloride ferrichloride M.P. 194

(6) β-morpholinoethyl-10-(4-chlorophenyl)-thiaxanthyl ether methiodide dec. 223

(7) β-piperidinoethyl-10-(4-chlorophenyl)-thiaxanthyl ether methiodide dec. 196

(8) β-dimethylaminoethyl-10-(4-chlorophenyl)-thiaxanthyl ether methiodide dec. 198

(9) β-diethylaminoethyl-10-phenylthiaxanthyl dioxide ether hydrochloride dec. 285

(10) β-morpholinoethyl-10-phenylthiaxanthyl dioxide ether hydrochloride dec. 266

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SOME ETHERS OF 10-ARYLTHIAXANTHENOL

ABSTRACT

The purpose of this research was to prepare a series of alkamine ethers of thiaxanthenol and related compounds for possible use as pharmacological agents. The similarity in structure between these compounds and compounds of known antihistaminic and antispasmodic activity such as the alkamine ethers of benzhydrol led us to believe that the thiaxanthenol ethers would be effective medicinals.

The following work was accomplished:

(1) A method for the preparation of pure thiaxanthenol in quantitative yields has been worked out.

(2) An improvement in the method for the preparation of 10-phenyl-10-chlorothiaxanthene-dioxide has been demonstrated.

(3) Alkamine ethers of 10-phenylthiaxanthenol and 10-(4-chlorophenyl)-thiaxanthenol were prepared and characterized as methiodide salts.

(4) Several alkamine ethers of 10-phenylthiaxanthenol dioxide were prepared as hydrochlorides.

(5) A number of new compounds were prepared.

(6) Unsuccessful attempts were made to prepare ethers of unsubstituted and thiaxanthenol and the corresponding thiaxanthenol dioxide.

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Thesis Title. Alkamine Esters of 7-Amino-fluorenone-2-carboxylic Acid.

Major Field: Organic Chemistry

Departmental Minor: Physical Chemistry

Outside Minor: Physiology

Major Courses:

Organometallic Compounds
Heterocylic Compounds
Organic Medicinal Compounds
Terpenes
Carbohydrates, Fats and Proteins

Minor Field:

Physico-Organic Chemistry
Thermodynamics
Electrochemistry
Special Topics in Physical Chemistry

Outside Minor: General Physiology

Other Courses:

Industrial Bacteriology
Advanced Quantitative Analysis
Advanced Inorganic Chemistry

Books which the candidate has read or used as reference texts

F.E. May	Organic Chemistry
Brewster	Organic Chemistry
Wheland	Advanced Organic Chemistry
Watson	Modern Theories of Organic Chemistry
Gilman	Advanced Organic Chemistry
Getman and Daniels	Outline of Physical Chemistry
Glasstone	Elements of Physical Chemistry