THE SYNTHESIS AND STUDY OF SOME THIANAPHTHENETHIOLS AND GJ-(N, N-DHALKYLAMINO) ALKYL THIANAPHTHYL SULFIDES

> Thats for the Degree of Ph. D. MICHIGAN STATE UNIVERSITY Charles E. Hoyd 1986



THESIS

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#### thesis entitled

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presented by

Charles E. Heyd

has been accepted towards fulfillment of the requirements for

Ph.D. degree in Chemistry

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THE SYNTHESIS AND STUDY OF SOME THIANAPHTHENETHIOLS AND  $\omega-({\rm N},{\rm N}-{\rm Dialkylamino})$  Alkyl thianaphthyl sulfides

By Charles E. Heyd

#### A THESIS

Submitted to the School of Graduate Studies of Michigan State University of Agriculture and Applied Science in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

### ACKNOWLEDGHENT

125 60

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#### VITA

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Doctor of Philosophy

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By

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### AN ABSTRACT

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Department of Chemistry

Year

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### ABSTRACT

This study deals with an investigation of the heretofore unknown thianaphthenethiols, and the synthesis from them of thianaphthyl alkyl sulfides having a tertiary amino group on the terminal carbon of the alkyl chain. This study was undertaken for the purpose of extending the work previously done in the field of synthetic local anesthetics containing the thic ether linkage (1,2,3). These compounds can be represented by the general formula,



The thianaphthenethiols, 2-thianaphthenethiol, 3-methyl-2-thianaphthenethiol, 3,5-dimethylthianaphthenethiol, and 3,7-cimethylthianaphthenethiol, were prepared by the metalation of the appropriate thianaphthene derivative with n-butyl lithium, and subsequent reaction with powdered sulfur. The general reaction scheme is illustrated for the preparation of 2-thianaphthenethiol,



The mercaptan 3-thianaphthenethiol was synthesized by employing a Grignard reaction starting with 3-iodothianaphthene,



The preparation of thiols by the reduction of sulfonyl chlorides with lithium aluminum hydride was found inapplicable to thianaphthene as a synthetic approach due to the sensitivity of the latter towards chlorosulfonic acid.

The preparation of the tertiary aminoalkyl thianaphthyl sulfides can be represented by the general equation,



The tertiary amino alkyl chloride hydrochlorides, Q-dimethylaminoethyl, Q-diethylaminoethyl, X-dimethylamino-n-propyl, A-methyl-Q-dimethylaminoethyl, Q-morpholinoethyl, Y-morpholino-n-propyl, Q-piperdinoethyl, Y-piperdino-n-propyl, Q-thiomorpholinoethyl, and Y-thiomorpholino-n-propyl chloride hydrochlorides, were used in the present investigation.



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#### INTRODUCTION

Thianaphthene was first prepared by Gattermann and Lockhart in the year 1893 (4). Since that time many investigations dealing with thianaphthene have been recorded in the chemical literature. However, there are numerous problems dealing with this material yet to be solved. Most of the studies in thianaphthene chemistry have been on the hydroxythianaphthenes and quinones as these materials are essential intermediates in the synthesis of the commercially important thioindigo dyes. Other derivatives of thianaphthene have not received nearly the attention given the hydroxy compounds, and as a consequence many phases of thianaphthene chemistry are still in need of study.

One such phase that has received only the most limited amount of work is that of the sulfur derivatives of thianaphthene. No sulfides, sulfoxides, sulfones or thiols have been reported, and only a few random cases of sulfonation have been published in the chemical literature.

The main objectives of this study were to investigate possible methods of obtaining thianaphthenethiols, and to then employ the thiols in the synthesis of compounds which should have potential use as local anesthetics.

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#### HISTORICAL

There are two general groups of drugs used for the production of local anesthesia. To the first group belong such substances as ethyl chloride which causes anesthesia by refrigeration. The second group of drugs comprises substances which produce a selective paralysis of sensory nerves.

The second group may be divided into two classes. Into the first fall substances almost insoluble in water and which are therefore used as dusting powders or in the form of cintments. An example of this class is ethyl p-amino benzoate or benzocaine. The members of the second class are soluble in water. The best known example of this class is procaine hydrochloride or 2-diethylamino ethyl p-amino benzoate hydrochloride.

The use of local anesthetics in medicine dates back to the last two decades of the nineteenth century when cocaine was introduced by Karl Koller (5) as an anesthetic for the eye. However, the fact that a large number of people show a dangerously high degree of addiction to cocaine has been one of the main reasons for seeking substitutes for cocaine as a local anesthetic.

The science of synthetic local anesthetics dates from the discovery of Einhorn (6) that esters of p-aminobenzoic acid produces surface anesthesia. Since that time numerous investigations have been directed

toward the preparation of compounds having the general features indicated in the formula,

$$A-M-(C)_n-N$$

Here A represents an aryl group, and M is a heteroatom or heterogroup. These features are considered to be responsible for the local anesthetic properties of cocaine.

Until recent years, most of the compounds prepared showing activity as local anesthetics were related to cocaine or novocaine. Studies made in the past few years have shown that compounds possessing widely different structures also possess anesthetic activity. These include anino alcohols, sterols, and ethers containing a tertiary amino group.

More recently, Schuetz (1,2,7) and Campaigne (8) have investigated the activity of various organic sulfur compounds possessing a tertiary amino group. A group of phenyl sulfides was prepared having the following structure (1),

$$C_6H_5$$
-S-( $CH_2$ )<sub>n</sub>-R·HCl

where n varied from two to six and R was equivalent to piperdino, morpholino, diethylamino and dimethylamino. All of these compounds were found to possess anesthetic activity in the range of procaine.

Due to the chenical similarity of benzene and thiophene, Campaigne and LeSuer (8) prepared a series of esters having the following structure,

CO<sub>2</sub>-(CH<sub>2</sub>)<sub>n</sub>-R.HCl

where n varied from two to three and R was equivalent to morpholino, dimethylamino, diethylamino, di-n-propylamino, and di-n-butylamino. Only the Y -di-n-butyl-n-propyl derivative showed any anesthetic activity. The toxicity of these compounds is similar to the p-aminobenzoates.

Houff and Schuetz (7) studied the properties of some derivatives of 2-thenoic acid.



where n was either two or three and R was piperdino or morpholino. These compounds were comparable to procaine in wheal tests in guinea pigs and possessed low toxicity. Later studies by these same workers were carried out on derivatives of 3-thiophenethiol (2),



Here, n varied in these compounds from two to five and R was piperdino or morpholino. Pharmacological tests indicated a high activity.

An interesting group of compounds was prepared by Burrows and Reid (9) having the tertiary amine group in the form of a thiomorpholino ring,

with n equal to two or three. The n-propyl derivative was found to be about as effective as procaine, but less toxic.

Burtner and Lehmann (10) prepared a derivative of dibenzothiophene of the following structure.

It showed a weak anesthetic action in the rabbit cornea test.

Since both the benzene and thiophene nuclei have been incorporated separately in numerous compounds studied over recent years as local anesthetics, it was thought that the preparation of derivatives containing these features combined in a single molecule, as is found in thianaphthene, would be of interest.

Thianaphthene is the name currently used for the ring system (I) by <u>Chemical Abstracts</u>. The alternate numbering system (II) is found occasionally in early literature. Prior to 1937, the name



benzothiophene, which was first used by the original German workers, was employed by <u>Chemical Abstracts</u>, and the <u>British Abstracts</u> still use this form.

Detailed descriptions of the Chemistry of thianaphthene may be found in books by Steinkopf (11), and Fukushima (12). Recently, an excellent coverage by Hartough and Meisel (13) has been published, which contains the majority of references through the first half of 1952.

The first derivative of thianaphthene, 4-hydroxythianaphthene, was prepared in 1886 by Biedermann (14) from thiophene-2-aldehyde and sodium succinate. This reaction is similar to that used to prepare **A**-naphthol from benzaldehyde.



Thianaphthene was obtained synthetically before it was isolated from natural sources. Gattermann and Lockhart (4) first prepared it by heating at its reflux temperature an alkaline alcoholic solution of o-mercapto- Q-chlorostyrene.



It was not until 1902 that Boes (15) was able to isolate thianaphthene from coal tar. He separated it from the naphthalene fraction by means of its picrate derivative.

Thianaphthene can be produced by the dehydrogenation of ethylbenzene (16) and subsequent reaction of the styrene with hydrogen sulfide, or from styrene and hydrogen sulfide (17).

Friedlander (18) prepared thianaphthene by the oxidation of o-mercaptocinnamic acid with potassium ferricyanide.



A synthesis of thianaphthene widely used is the reduction of 3-hydroxythianaphthene by means of zinc dust (19).



There has been no systematic study of the halogenation of thianaphthene. Komppa (20) was the first to chlorinate thianaphthene. He obtained a dichlorothianaphthene, presumably the 2,3-derivative. Schlesinger (21) obtained 3-chlorothianaphthene in low yield by the chlorination of thianaphthene in carbon tetrachloride as a solvent. The perchloro derivative of thianaphthene, 2,3,4,5,6,7-hexachlorothianaphthene, was prepared by Barger (22) as indicated in the equation,



Bromination of thianaphthene yields a variety of products depending upon the reaction conditions. Mono, di, tri, and tetrabromo derivatives

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are known. A monobromo derivative, 3-bromothianaphthene was prepared by treating thianaphthene with bromine in chloroform as a solvent at a temperature of  $30^{\circ}$ C. (20). A 2-bromothianaphthene results from the interaction of 2-thianaphthyllithium with bromine in ether solution (23).

Only three iodo derivatives are reported in the chemical literature. The 2-iodothianaphthene results from the treatment, in an ether solution, of 2-thianaphthyllithium with iodine (24). The 3-iodo-derivative results from the treatment of thianaphthene with iodine and mercuric oxide (24). 2,3-diiodothianaphthene has been prepared by treating 2,3-thianaphthenedimercurichloride with iodine in carbon tetrachloride (25).

Metalation of thianaphthene with sodamide in liquid ammonia (26), or with n-butyl lithium in ether (27) occurs in the two position. That metalation occurs in the two position has been verified by the fact that the methylthianaphthene obtained from the reaction of thianaphthyllithium with methyl p-toluenesulfonate, and the 2-methylthianaphthene prepared by Noth and Kiss (28) by the following unequivocal synthesis are identical.



The alkylthianaphthenes are formed by either a ring closure reaction or the direct alkylation of the thianaphthene nucleus. The compound 2-methylthianaphthene is obtained from the reaction of 2-thianaphthenyllithium with methyl p-toluenesulfonate (23). It has also been prepared in low yield by the vapor phase dehydrogenation of o-npropylbenzenethiol (29). The alkyl derivative, 3-methylthianaphthene, was obtained by Werner (30) by the dehydration of phenyl acetonyl sulfide.



The alkylthianaphthene, 3-t-butylthianaphthene, recently reported by Corson (31), was prepared by the reaction of thianaphthene with isobutylene,



The structure of this derivative of thianaphthene was established by desulfurization with Raney nickel.

The use of Raney nickel as a desulfurizing agent has found popular use in the structure proof of several thianaphthene compounds. Table I lists the compounds that have been subjected to such a reaction.

A very limited amount of work has been done on the sulfur derivatives of thianaphthene. No thiols, sulfides, sulfoxides, or sulfones have as yet been recorded in the chemical literature. Komppa (20) treated thianaphthene with 75% sulfuric acid and obtained a



Compound Reduced	Products	Reference
Thianaphthene	Ethylbenzene	32
3-Hydroxythianaphthene	Ethylbenzene	32
2-Thianaphthene carboxylic acid	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H	33
3-Thianaphthene carboxylic acid	C <sub>6</sub> H <sub>5</sub> CH(CH <sub>3</sub> )CO <sub>2</sub> H	33
3-t-Butylthianaphthene	$C_{e}H_{5}CH(CH_{3})C(CH_{3})_{3}$	31
$\dot{\mu}$ -Hydroxythianaphthene	o-Sthylphenol, o-Ethylthiophenol	34

TAULE I

## RANEY NICKEL REDUCTION OF THIANAPHTHEME COMPOUNDS

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monothianaphthenesulfonic acid, isolated as its sodium salt. He also reported that some disulfonic acid was formed during the reaction. However, he reported no structure study on any of these compounds.

Only one thianaphthene derivative containing a sulfonic acid group in the benzene ring has been reported. Fieser (35) prepared it by the following sequence of reactions,


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## DISCUSSION

The preparation of 3-thianaphthenethiol was accomplished by the reaction of 3-thianaphthenemagnesium iodide with powdered sulfur.



The iodo derivative was used in the Grignard reaction in preference to the 3-bromothianaphthene since it is more reactive towards magnesium. However, with both 3-iodo and 3-bromothianaphthene an appreciable amount of unreacted magnesium was always present at the conclusion of the Grignard reaction. The use of 3-bromothianaphthene in the Grignard reaction requires the presence of a simple alkyl halide to promote the reaction. The yield of 3-thianaphthenethiol was not particularly good, in any of the several experiments carried out for its preparation. A yield of thirty percent was never attained; the maximum being about twenty-six percent. The mercaptan, 3-thianaphthenethiol is a yellow colored liquid possessing a characteristic mercaptan like odor.

The elemental analyses of the liquid thicls prepared in this study were carried out on their respective  $2, l_i$ -dinitrophenyl sulfides since the thicls were observed to be quite unstable. It was found that the

base soluble thicl obtained immediately following its vacuum distillation soon exhibited some degree of insolubility in alkaline solution, even when kept in a refrigerator in a tightly closed container. For this reason, the infrared spectra of the thicls were recorded on a sample obtained immediately after distillation and which had been checked for complete solubility in an alkaline solution.

The infrared absorption spectrum of 3-thianaphthenethicl is shown in Figure I. Inspection of the curve reveals the sulfhydryl band near 4  $\mu$ ; the strong, selective band for thianaphthene at 9.5  $\mu$ ; and the wide band at 13  $\mu$  indicative of monosubstitution in the three position. A band in the 7.95  $\mu$  - 8.15  $\mu$  region usually identifies sulfur in a five membered ring. The strong band at 3.25  $\mu$  is characteristic of the carbon hydrogen stretching vibration. Figure II shows the infrared absorption spectrum of 3-(2,4-dinitrophenyl) thianaphthylsulfide in carbon disulfide. The strong band at 7.5  $\mu$  is characteristic of the aromatic nitro group.

2-Methyl-3-thianaphthenethiol was prepared from the previously unknown 2-methyl-3-iodothianaphthene by the following sequence of reactions.



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The thiol was characterized by the preparation of its 2,4-dimitrophenylsulfide derivative. The infrared spectrum of this derivative in carbon disulfide is shown in Figure III.

The necessary intermediate, 2-methyl-3-iodothianaphthene, was prepared by the direct iodination of 2-methylthianaphthene. The position of halogenation was established by the carbonation of the Grignard reagent 2-methylthianaphthene-3-magnesium iodide to the known 2-methyl-3-thianaphthene carboxylic acid (36).

The heretofore unknown 3-thianaphthenethiols propared in the course of this investigation and their 2,4-dinitrophenyl sulfide derivatives are reported in Table II.

The previously unknown 2-thianaphthenethiols prepared during this study and their 2,4-dinitrophenyl sulfide derivatives are listed in Table III. All of these hetrocyclic mercaptans were prepared from the appropriate thianaphthenes by means of a metalation reaction. The several reaction steps used in the synthesis of these compounds can be presented as follows,



The metalation of thianaphthene with n-butyl lithium has been described by Shirley (23). The 2-thianaphthenethiol is a white crystalline, low



Figure III

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TABLE II

3-THIANAPHIHENETHIOLS



lsulfi.de nd E	2.56	3 <b>.</b> 01	
itropheny Fou	50.45	51.93	
s (2,4-Din ated H	2.42	2.91	
Analysis Calcul C	50 <b>.</b> 59	52.01	
Fercent Yield (Thiol)	26	;	
ï.Ρ.,°C. (2,4-Dinitro phenylsulfide)	163 <b>-</b> 16it	179-181	
B.P. (Thiol) C. Man.	116 <b>-</b> 117 3	:	
Formula (2,4-Dinitrophenyl- sulfide)	c <sub>14</sub> H <sub>a</sub> O <sub>4</sub> N <sub>2</sub> S <sub>2</sub>	C <sub>15</sub> H <sub>10</sub> C₄N₂S₂ <sup>a</sup>	
(Thiol)	C <sub>a</sub> ∺ <sub>6</sub> S₂	ς C <sub>9Ha</sub> S <sub>2</sub>	
<u>74</u>	Н	CH <sub>3</sub>	

Solvents for Recrystallization: a-Methanol Analysis by Micro-Tech. Lab., Skokie, Ill.

TABLE III

2-THIANAPHTHEN STRIOLS

<u> </u>	ЗH	
		C
		R11
- <b>L</b>		

ಗ್ರ	Ж	<b>।</b> स	(Tiniol)	Formula (2,4-Dinitrophenyl sulfide)	B.P. o <sup>(Thio</sup>	1) En (2, ph	M.F.,°C. ,4-Dinitro-	Percent Yield (Thiol)	(2,1+-D) Calcu	Anal initrop lated H	.ysis henylsu G	lfide) ound H
г	щ	Η	CaHeSz	C <sub>14</sub> H <sub>6</sub> O <sub>4</sub> N <sub>2</sub> S <sup>a</sup>	211-LI	(M.P.)	159-160	22	50.60	2./,1	50. 1 <sub>1</sub> 8	2.51
CII3	Ē	<u>;;;</u> ;	C <sub>9</sub> H <sub>8</sub> Sz	0 <sub>16</sub> H <sub>10</sub> 04N <sub>2</sub> S2 <sup>a</sup>	116-118	2	216-213	0	51 <b>.</b> 99	2.91	51.94	<b>2</b> .00
cII3	CH3	Н	Clo <sup>H</sup> lo <sup>S</sup> z	C <sub>16</sub> H <sub>1</sub> 204NzSz <sup>b</sup>	11,2-145	30	215-215	Ę	53.32	Эб	53.53	С. С.
СНЗ	ш	CH <sub>3</sub>	CloHloS2	c <sub>1c</sub> H <sub>12</sub> O <sub>4</sub> N <sub>2</sub> S <sub>2</sub> <sup>b</sup>	133-135	23	157-158	ŝ	53.32	3•36	5.32	
Solv Ana	vents f lysis b	Cor reci y Micro	rystallizat o-Tech. Lab	ion: a-Methanol, b-di ., Skokie, Ill.	lute diox	ane						

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melting solid, whereas, the other 2-thiol compounds are all liquids at room temperature. They are all sensitive to air oxidation.

The infrared spectrum of 2-thianaphthemethicl in carbon tetrachloride is shown in Figure IV.

The position of metalation of 3-methylthianaphthene was established as the two position by carbonating a small quantity of the metalation reaction mixture with solid carbon dioxide. The melting point of the acid obtained Following hydrolysis of the product was the same as that reported for 3-methyl-2-thianaphthene carboxylic acid by Gaertner (37).

The infrared spectrum of 3-methyl-2-thianaphthenethicl in carbon tetrachloride is shown in Figure V.

The position of metalation of the dialkylthianaphthenes is presumed to also occur as is usual in the two position.

The 3-alkylthianaphthenes used for the preparation of the 3-alkyl 2-thianaphthenethiols were prepared by a ring closure reaction using phosphorous pentoxide with the appropriate acetonyl phenyl sulfides. The method of Werner (30) for the synthesis of alkylthianaphthenes was successfully extended to acetonyl-p-tolyl and acetonyl-o-tolyl sulfides. The extension of this synthetic method to p-methoxy and o-methoxy phenyl acetonyl sulfides was not successful. The ring closure reaction was always accompanied by extreme darkening of the reaction mixture and apparent decomposition.

The thianaphthene derivative obtained by the ring closure of acetonyl-o-tolyl sulfide was a previously unknown dialkylthianaphthene.

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Figure IV





The structure for this compound was established by its desulfurization with Raney nickel.



The expected desulfurization product, m-cymene, was identified by its boiling point, refractive index, and a comparison of its infrared spectrum with that of an authentic sample, of m-cymene kindly supplied by the National Bureau of Standards. The curves shown in Figure VI shows the infrared absorption spectrum of the compound obtained by desulfurization and also the curve of the authentic m-cymene.

In addition to the Grignard and metalation synthesis of thianaphthenethiols, another route to their preparation was desirable since the former two methods would be limited in their usefulness to obtain derivatives of the thianaphthenethiols in cases where a reactive group was already present in the thianaphthene nucleus prior to the introduction of the mercapto group. A well known synthesis of thiols is by the reduction of the corresponding sulfonyl chloride. In the aromatic series, the sulfonyl chlorides are readily obtained by treating the aromatic compound with chlorosulfonic acid. This sequence of reaction for the introduction of the mercapto group into heterocyclic compounds has been recently applied to thiophene derivatives by R. J. Fawcett (Ph. D. Thesis, Michigan State University).

The initial studies on the chlorosulfonation of thianaphthene compounds were carried out on the parent compound. It became evident



<sup>3 4 5 6 7 8 9 10 11 12 13 14</sup> WAVELENGTH IN MICRONS HMETHYL-3-ISOPROPYLBENZENE NATIONAL BUREAU OF STANDARDS SAMPLE

after a few experiments that this reaction when applied to thianaphthene was quite sensitive to both temperature and the quantities of reagents. The chlorosulfonation reaction mixture usually became very dark colored after a small amount of thianaphthene had been added to it. It was apparent after removing the solvent layer that very little thianaphthene was being converted directly to its sulfonyl chloride derivative. A reasonable possibility seemed to be that a thianaphthene sulfonic acid was actually the product being formed and of course would be expected to be found in the water layer. The aqueous layer was neutralized first with barium carbonate, filtered, and the filtrate treated with sodium carbonate, filtered to remove the precipitated barium carbonate, and evaporated to dryness. The resulting solid residue was treated with phosphorous pentachloride with the intention of converting the sodium sulfonate to the sulfonyl chloride. This procedure yielded a dark oil which was very difficult to distill even at very low pressures due to its rapid thermal decomposition. Reduction of the crude oil with lithium aluminum hydride was not successful because of excessive furing and sparking during the course of the reaction which necessitated stopping the experiment. However, during one of the distillations on the crude oil, a small amount of distillate was obtained. This material analyzed correctly for a monosulfonyl chloride, formed a sulfonamide and has an infrared spectrum showing two strong bands at 8.54 µ and 7.25 µ. Schrieber (38) noted that benzene sulfonyl chloride exhibited two strong bands at 8.42  $\mu$  and 7.46  $\mu$ . However, very little spectral data has been reported on the organic

sulfonyl chlorides as a class of compounds.

A small sample of this distilled sulfonyl chloride was reduced with lithium aluminum hydride and the resulting thiol characterized as its 2,4-dinitrophenyl sulfide. The infrared spectrum of this derivative in carbon disulfide is shown in Figure VII. The mixed melting points of this derivative with the 2,4-dinitrophenyl sulfide derivatives prepared from known samples of 2- and 3-thianaphthenethiol showed no depression with the 3-substituted derivative and an appreciable depression with the 2-substituted derivative. These results indicate that the sulfonation of thianaphthene occurred as expected in the three position of the thianaphthene nucleus. This conclusion is further supported by a comparison of the infrared curves (Figures II and VII) of the 2,4-dinitrophenyl sulfide derivative of 3-thianaphthenethiol, the latter material having been prepared by an independent synthesis already discussed. These curves are seen to be identical.

Several chlorosulfonations of thianaphthene were carried out at lower temperatures in an attempt to reduce the amount of decomposition occurring during the reaction. An experiment on the chlorosulfonation of thianaphthene carried out at a temperature of  $-37^{\circ}$ C. resulted in no reaction and recovery of the starting material. Another such reaction conducted at a temperature of  $-15^{\circ}$ C. yielded a product having no halogen present, but which gave an elemental analysis close to that of dithianaphthyl sulfone, and the product had an infrared curve in chloroform with maxima at 7.58, 8.70, and 8.85  $\mu$ . Schrieber (38) proposed the ranges 8.62-8.92 and 7.12-7.69  $\mu$ , for the characterization of normal sulfones.







The chlorosulfonation of 3-methylthianaphthene with an excess of chlorosulfonic acid gave a product which had the correct elemental analysis for a disulfonyl chloride derivative of 3-methylthianaphthene. The infrared spectrum of this compound in carbon tetrachloride shows strong peaks at 7.20 and  $8.50 \,\mu$ . It also formed an amide having the correct elemental analysis for a disulfonamide of 3-methylthianaphthene.

The position of one of the sulfonyl chloride groups in the thisnaphthene ring is very probably in the two position. The location of the second group in the benzene portion of the thianaphthene nucleus was not determined.

The chlorcsulfonation of 2-methylthianaphthene yielded a variety of products depending upon the experimental conditions of the reaction. In an experiment carried out by adding the 2-methylthianaphthene to the chlorosulfonic acid yielded a product which analyzed very closely for a disulfonyl chloride derivative of 2-methylthianaphthene. This latter compound formed an amide which gave a very good analysis for a disulfonamide of 2-methylthianaphthene and the product had an infrared absorption curve with strong absorptions maxima at 7.19 and  $8.47 \mu$ .

Other chlorosulfonation experiments on 2-methylthianaphthene yielded products which gave elemental analysis that were not in agreement with either mono or disubstitution, although the analytical results approached the values for disubstitution more than for a monosubstituted product. A single chlorosulfonation reaction on 2-methylthianaphthene conducted at room temperature resulted only in extreme decomposition and tar formation.

By employing the technique of reverse addition of reagents, that is, by adding the chlorosulfonic acid to the alkyl thianaphthene compound, it was possible to obtain a monosubstituted product from 2-methylthianaphthene. The product gave the correct analysis for a mono-sulfonyl chloride and a monosulfonamide of 2-methylthianaphthene.

To establish that substitution occurred in the three position of the thianaphthene nucleus during the chlorosulfonation of 2-methylthianaphthene the product of the reaction was reduced by means of lithium aluminum hydride to its corresponding mercaptan and the latter was then converted to its 2,4-dinitrophenyl sulfide derivative. This sulfide was then compared with the 2,4-dinitrophenyl sulfide of 2-methyl-3-thianaphthenethiol whose structure has been established by an unequivocal synthesis developed in the course of this investigation and previously discussed. These reactions establishing the position of substitution in the chlorosulfonation of 2-methylthianaphthene are shown in the following sequences of reactions.



A mixed melting point of samples of the 2,h-dinitrophonyl sulfides prepared by both sequences of reaction showed no depression in melting point. The infrared absorption spectrum in carbon disulfide of the 2,h-dinitrophenyl sulfide obtained from the chlorosulfonated product of 2-methylthianaphthene is shown in Figure VIII. A comparison of the infrared absorption curve with the infrared absorption curve of 2-methylthianaphthyl-3-(2,h-dinitrophenyl) sulfide shown in Figure III reveals the identity of these two compounds.

An examination of the results obtained from the chlorosulfonation reactions of various thianaphthenes indicates that the nature of the product, its purity and yield in such reactions is very dependent on the experimental conditions. The thianaphthene nucleus is quite sensitive towards chlorosulfonic acid. Eany of the reactions of thianaphthene and its simple alkyl derivatives were accompanied by tar formation with the resultant development of excessive quantities of dark colored material in the reaction solution. Chlorosulfonation does not appear to be practical as a synthetic method in the thianaphthene series for obtaining the sulfonyl chlorides derivatives needed as intermediates in the preparation of thianaphthenethiels.

The **U**-(N,N-Dialkylamino) skyl thianaphthyl sulfides were prepared by the interaction of a basic solution of the appropriate thiol with an aqueous solution of a tertiary amino alkyl chloride hydrochloride. No particular difficulty was experienced with this reaction, except in a few cases during the precipitation of the sulfide hydrochloride salt. The product would separate from the reaction solution as an oil which



Figure VIII

solidified on standing in some cases. In others, the entire experiment had to be repeated.

Isopropyl alcohol was found to be a satisfactory solvent for the recrystallization of the majority of tertiary amine hydrochlorides salts.

During the course of these preparations it was found that the best results were obtained if the thicl was used as soon after its preparation as possible. In all cases the mercaptan oxidized in a short time to a base insoluble material.

Tables IV, V, and VI lists a total of twenty-one previously unreported CD-(N,N-Dialkylamino)alkyl thianaphthyl sulfides, together with some of their physical properties and analytical data on their elemental analysis. These compounds will be submitted to an independent laboratory for their pharmacological evaluation.

TABLE IV

W-(Dialkylamino) Alkyl-2-Thianaphthyl Sulfide Hydrochloridos

st-licit

CH.	Formula	N.P.°C	Percent Yield	Perce C	nt Calc <b>H</b>	ulated S	Ъ С	rrcent Fo H	und. S
$-(GH_z)_z N(C_2H_c)_z^a$	C <sub>14</sub> H <sub>20</sub> NS <sub>2</sub> 01	133-4	50	55 • 70	6 <b>.</b> 58	21•2)t	55 . 53	6.62	20.56
$-(\operatorname{CH}_{z})_{z}^{\operatorname{M}}(\operatorname{CH}_{3})_{z}^{\operatorname{a}}$	012H16HS201	164-5	69	52.63	ы С. С.	23.142	72 •09	6 <b>.</b> 02	23.31
-(CH2) <sub>3</sub> N(CH <sub>3</sub> )2 <sup>a</sup>	C <sub>leHla</sub> US <sub>2</sub> Cl	125-7	<u>บ</u> า บา	54.24	6.30	22.28	54.08	6.31	22.20
cH <sub>3</sub> -CH-UH <sub>2</sub> N(CH <sub>3</sub> )2 <sup>a</sup>	CleHleXS <sub>2</sub> 01	1),0-51	67	5.	6.30	22 • 23	10. - 03	9 <sup>-16</sup>	22.31
-(OII2)2N (a	014H18CNS201	181-3	у, М	53.23	1.	20.30	53.50	7. • ?\$	20.02
-(CH <sub>2</sub> ) <sub>5</sub> N	C18H200.S201	132-41	27	54.56	6.11	19.44	54.78	<b>6.</b> 05	19 • 25
-(CII2) 2 M	CleNS201	220-2	71:	57.39	6.42	20 <b>.</b> \43	57.57	6.53	20.46
-(CH2)3N	C <sub>le</sub> H22NS2Cl	1/;6-8	C /Li	58.60	6.70	19.56	<u>र</u> ि • र 0	6.71	
-(GII2)2M Sa	$c_{14}H_{16}NS_{3}cl$	191-3	10	5u <b>.</b> 66	5.47	23.93	50.75	یر ت	29.17
- $(\operatorname{Gll}_2)_{\mathfrak{I}} \bigvee S^{\mathfrak{A}}$	$c_{15}H_{zc}$ i:S_3U1	123-4	77	52 <b>.</b> 07	5 <b>.</b> 83	27.80	51.5)	5 • 52	27.51

Solvents for Recrystallization: a - Isopropyl Alcohol, b - absoluts ethanol Analysis by Ricro-Tech. Lab., Shokie, Ill.

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TABLE V

C - (DIALKYLAMINO) ALKYL-3-METHYL-2-THIANAPHTHYL SULFIDE HYDROGILORIDE

CH3 SR.HC1

c:	Formula	M.P. <sup>o</sup> C.	Percent Yield	Percen C	t Calcul H	ated S	Pe1	rcent Fou H	nd S
-(CH <sub>2</sub> ) <sub>2</sub> N(C <sub>2</sub> N <sub>5</sub> ) <sub>2</sub> <sup>a</sup>	C <sub>le</sub> H22 <sup>NS</sup> 2Cl	178-9	24	56 <b>.</b> 89	7.00	20.25	57 <b>.</b> 21	7.16	20.05
-(CH2) 2N(CH3) 2 <sup>a</sup>	C <sub>13</sub> H <sub>18</sub> NS <sub>2</sub> Cl	214-5	51	51.24	6.30	22.28	50°	6.12	22.33
-(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>5</sub> ) <sub>2</sub> <sup>a</sup>	C <sub>14</sub> H <sub>20</sub> NS <sub>2</sub> Cl	160-2	т Л	55.70	6.63	21.2 <sup>1</sup>	<u>5</u> 5.61	6.73	21.5%
cH <sub>a</sub> -CH-CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>a</sup>	C14HzoliSzCl	172-4	74	J. 70	6.58	21 <b>.</b> 24	- t - し い	6.83	20.95
$-(CH_2)_2N O^a$	CleHzoOWSz01	200-2	212	54.61	11 <b>.</b> 3	19.44		6.39	19.72
$-(CH_2)_2 M a$	ClelleRNS.01	222-24	68	58.60	6 <b>.</b> 76	19.55	50 • 52	• •	19.74
-(CH <sub>2</sub> ) <sub>3</sub> N a	C17112411S2C1	160-62	63	59.71	7.07	13.75		7.C5	18 <b>.</b> 65
-(CH2) 2N Sa	CleHeows. 7	205-3	51	52 <b>.</b> 07	0 2 2 1 1	27.80	51.87	6•C2	26.05
-(CH2)3NS <sup>a</sup>	CleH22IIS, M	126-0	62	53.38	6 <b>.</b> 16	26.72	13 °12	6.30	23.44

Solvents for decrystallization: a - Isopropyl Alcohol Analysis by Micro-Tech. Lab., Skokie, Ill.

TABLE VI

CDIALKYLANINO) ALKYL-3-THIIANAPHTHYL SULFIDE HYDROCHLORIDES



ц	Formula	M.P.°C	Percent Yield	Perce	nt Calcu H	lated S	Pe	rcent Fo	and S
-(CH2) 2N(CH3) 2 <sup>a</sup>	CleHenser	7-2µL	72	52.63	5.89	23.42	52.73	10°9	LL.62
-(CH <sub>2</sub> ) <sub>2</sub> N	C <sub>14</sub> H <sub>16</sub> ONS <sub>2</sub> C1	. 9-2µL	37	53.23	5.74	20.30	53.45	5.74	20.05

Solvents for Recrystallization: a - 'Isopropyl Alcohol Analysis by Micro-Tech. Lab., Skokle, Ill.

EXPERIMENTAL

## Halothianaphthenes

3-Iodothianaphthene



In a two-liter three necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 700 ml. (7.8 moles) of benzene and 224 g. (1.68 moles) of thianaphthene. The stirred mixture was heated to  $60^{\circ}$ C. by means of an electric mantel and 270 g. (1.08 moles) of yellow mercuric oxide and 380 g. (1.49 moles) of iodine was added alternately in small portions. The reaction mixture was stirred for two hours following the addition of reagents. The solution was allowed to cool to room temperature and then filtered to remove the insoluble mercuric iodide. The dark red filtrate was treated with three 100 ml. portions of saturated sodium thiosulfate solution to destroy unreacted iodine. The benzene solution was still dark following this treatment. However, a golden yellow colored solution was obtained by use of activated alumina. The benzene was removed by distillation at atmospheric pressure and the residue was distilled at reduced pressure to yield 124 g. (0.48 moles, 35%) of a light yellow oil which boiled at lló-llô<sup>o</sup>C./2 mm. The reported boiling point for 3-iodothianaphthene is 120-121°C./1.6 mm. (24).

3-Bromo-2-methylthianaphthene



This compound was prepared using the method employed by Gaertner for the bromination of 3-methylthianaphthene (37).

In a 500 ml. three necked flask fitted with a stirrer, reilux condenser and dropping funnel was placed 14.8 g. (0.1 mole) of 2-methylthianaphthene dissolved in 50 ml. of carbon tetrachloride. The reaction vessel was placed in an ice bath and cooled to  $3^{\circ}$ C. To this solution was added over a period of an hour, 16 g. (0.1 mole) of bromine contained in 25 ml. of carbon tetrachloride. When the addition of the bromine solution was complete the reaction mixture was heated to 50°C. and the carbon tetrachloride removed with a water aspirator. The residue obtained was stirred overnight at 65°C. with 200 ml. of 10% potassium hydroxide solution. The organic layer was separated and the aqueous layer extracted with 25 ml. of carbon tetrachloride. The organic layer was combined with the carbon tetrachloride extract, washed with distilled water and dried over calcium chloride. Removal of the solvent and vacuum distillation of the residue gave 15.2 g. (0.067 moles, 67%) of a pale yellow colored liquid having a boiling point of 125-125°C./4 mm.

Calc'd. for C<sub>9</sub>M<sub>7</sub>SBr: C, 4759; H, 3.11; Br, 35.18. Found: C, 47.80; H, 3.24; Br, 35.45.
Attempted Preparation of a Grignard Reagent from 3-Bromo-2-methylthianaphthene

In an eight inch test tube fitted with a condenser was placed 0.24 g. (0.01 moles) of magnesium turnings and 5 ml. of anhydrous ether. To this mixture was added 2.3 g. (0.01 moles) of 3-bromo-2-mothylthianaphthene dissolved in 15 ml. of dry ether. The reaction mixture was heated at its reflux temperature but the reaction could not be initiated. The addition of a drop of methyl fielde produced only a momentary refluxing of the reaction mixture. The reaction was discontinued.

3-Iodo-2-methylthianaphthene



The method employed by Clartner for the iodination of thianaphthene was used in the synthesis of this material (24).

In a 500 ml. three necked flask fitted with a stirrer, reflux condenser and thermometer was placed life g. (C.1 woles) of 2-methylthianaphthene and 100 ml. of benzene. The solution was heated to  $60^{\circ}$ C. and 15.2 g. (0.07 moles) of yellow mercuric oxide and 25.4 g. (0.1 moles) of iodine were added alternately in small portions. The red reaction solution was stirred for four hours at  $60^{\circ}$ C. after the addition of reagents was complete. The reaction mixture was cooled and filtered to remove the mercuric iodide. The filtrate was treated with 100 ml. of a saturated sodium thiosulfate solution, washed with distilled water and

dried over calcium chloride. Removal of the benzene and distillation of the residue gave 16.2 g. (0.059 moles, 59%) of a yellow colored liquid having a boiling point of 127-128°C./2 mm.

Calc'd. for C<sub>9</sub>H<sub>7</sub>SI: C, 39.43; H, 2.57; I, L6.29.

Found: C, 39.25; H, 2.81; I, 46.60.

Acetonyl Phenyl Sulfides

Acetonyl phenyl sulfide

In a one liter three necked flask fitted with a stirrer, reflux condenser, and dropping funnel was placed h0 g. (1.0 moles) of sodium hydroxide dissolved in 100 ml. of distilled water. The sodium hydroxide solution was cooled to  $25^{\circ}$ C. and 110 g. (1.0 moles) of thiophenol was quickly added. To the alkaline thiophenol solution, 92 g. (1.0 moles) of chloroacetone was then added over a half hour period, during which time the reaction temperature was maintained in the range of  $20-25^{\circ}$ C. The reaction mixture was stirred for an hour after the addition of the chloroacetone was complete. The reaction product was taken up in 200 ml. of ether, washed with 100 ml. of water, and then dried over calcium chloride. Following the removal of the ether on a steam bath, the residue was vacuum distilled to yield 13h g. (0.61 moles, 81%) of a clear yellow liquid boiling at 139-1h0°C./16 mm. The reported boiling point of acetonyl phenyl sulfide is  $1h2^{\circ}C./17$  mm. (30).

Acetonyl-o-tolyl sulfide

 $CH_{3}$ СH<sub>3</sub>-С-СH<sub>2</sub>-S

This compound was prepared by utilizing the experimental procedure described above for acetonyl phenyl sulfide. The amounts of the several reagents used were, 22 g. (0.55 moles) of sodium hydroxide dissolved in 50 ml. of distilled water, 62.1 g. (0.5 moles) of o-toluene-thiol and  $\mu$ 6.3 g. (0.5 moles) of chloroacetone. Vacuum distillation of the crude product gave 67.8 g. (0.37 moles, 755) of a pale yellow colored liquid having a boiling point of 154-155°C./15 mm.

The 2,4-dinitrophenylhydrazone of this ketosulfide was prepared and after recrystallization from ethanol it melted at  $113-115^{\circ}C$ .

Calc'd. for C<sub>16</sub>H<sub>16</sub>O<sub>4</sub>N<sub>4</sub>S: C, 53.32; H, 4.48; S, 8.90.

Found: C, 53.09; H, 4.48; S, 8.81.

Acetonyl-p-tolyl sulfide



This compound was prepared following the experimental procedure previously described for the synthesis of acetonyl phenyl sulfide. The quantities of reagents used were, 22 g. (0.55 moles) of sodium hydroxide dissolved in 50 ml. of water, 62.1 g. (0.5 moles) of p-toluenethiol, and h6.3 g. (0.5 moles) of chloroacetone. The yield obtained was 67.2 g. (0.37 moles, 74.5%) of a pale yellow liquid which boiled at 160-162°C./17 mm. The reported boiling point of this sulfide is 150-151°C./15 mm. (39).

Acetonyl-p-methoxyphenyl sulfide

0 И СН<sub>3</sub>-С-СН<sub>2</sub>-S-

This compound was prepared in the same experimental manner as described above for acetonyl phenyl sulfide. The quantities of reagents used were, 20 g. (0.5 moles) of sodium hydroxide dissolved in 200 ml. of distilled water, 70.1 g. (0.5 moles) of p-methoxythiophenol and  $\frac{1}{46.3}$  g. (0.5 moles) of chloroacetone. Vacuum distillation of the crude product after isolation from the reaction mixture, as previously described, yielded 73.8 g. (0.38 moles, 75%) of a pale yellow colored liquid having a boiling point of  $154-156^{\circ}$ C./2 mm.

The 2,4-dinitrophenylhydrazone prepared from this ketonic sulfide melted at 119-120°C. following recrystallization from ethanol.

Calc'd. for C<sub>16</sub>H<sub>16</sub>O<sub>5</sub>N<sub>4</sub>S: C, 51.05; H, 4.29; S, 8.52.

Found: C, 51.03; H, 4.36; S, 8.36.

Alkylthianaphthenes

2-Methylthianaphthene

In a three liter three necked flask fitted with a stirrer, dropping funnel, nitrogen gas inlet tube, thermometer and calcium chloride drying tube was placed 25 g. (3.6 moles) of lithium chips contained in 400 ml. of anhydrous ether. The reaction vessel was cooled to  $-10^{\circ}$ C.

in a dry ice-isopropyl alcohol bath and then a solution of 247 g. (1.8 mole) of redistilled n-butyl bromide dissolved in 250 ml. of dry ether was added slowly over a period of an hour. The solution was stirred for two hours after completing the addition of the bromide. The reaction solution was then filtered under a nitrogen atmosphere through glass wool into a three-liter flask which had been previously chilled. To the filtered solution of n-butyl lithium, precooled to -10°C., was added, during a period of three quarters of an hour, 214.6 g. (1.6 moles) of thianaphthene dissolved in 200 ml. of anhydrous ether. The reaction mixture was then stirred an additional hour at a reaction temperature kept between  $-10^{\circ}$ C. and  $-5^{\circ}$ C. To this solution was then added 279 g. (1.5 mole) of methyl p-toluenesulfonate dissolved in 150 ml. of anhydrous ether over a period of an hour, after which the reaction mixture was stirred for an additional hour. The dry ice bath was removed and the stirred reaction solution was allowed to warm to room temperature. It was then poured onto 2000 g. of crushed ice. The pale yellow colored ether layer was separated, washed with water and then dried over calcium chloride. Removal of the ether on a steam bath yielded a white solid which on recrystallization from dilute ethanol gave 113 g. (0.76 mole, 51%) of a pure white solid having a melting point of 50-52°C. The reported melting point of this compound is 51.5-52°C. (23). The boiling point of the purified compound was observed to be 73-74°C./2 mm. The literature reports no boiling point for 2-methylthianaphthene.

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CH<sub>2</sub>

In a 500 ml. three necked flask fitted with a stirrer, reflux condenser and dropping funnel, was placed 22 g. (0.15 mole) of phosphorous pentoxide. In the dropping funnel was placed 64.5 g. (0.39 mole) of acetonyl phenyl sulfide. Approximately a quarter of the sulfide was added initially and then the reaction mixture was cautiously heated with a Bunson burner to initiate the spontaneous reaction. This occurred when the reaction mixture had reached a temperature of about 100°C. The exothermic reaction caused the temperature to rise to about 200°C. and resulted in the reaction mixture becoming very dark in color. After allowing the reaction temperature to fall to 170°C., the balance of the sulfide was added dropwise, after which the reaction mixture was stirred and heated at  $160-160^{\circ}C$ . for an additional three guarters of an hour. The dark colored reaction mixture was cooled to room temperature and 200 ml. of water added. The reaction mixture was then extracted with three 100 ml. portions of ether. The combined extracts were washed with water and dried over calcium chloride. The ether was removed on a steam bath and the residual oil distilled under reduced pressure to yield 34.5 g. (0.23 mole, 60%) of a pale yellow liquid which had a boiling point of 75.78°C./2 mm. The reported boiling point for 3-methylthianaphthene is  $63-72^{\circ}C./0.3$  mm. (30).

3,5-Dimethyl thianaphthene



This compound was prepared in a 36% yield employing the experimental procedure previously described for the synthesis of 3-methylthianaphthene. The reagents used were, 15 g. (0.11 mole) of phosphorous pentoxide, 32 g. (0.18 mole) of acetonyl-p-tolyl sulfide. Distillation of the crude product under reduced pressure gave 10.3 g. (0.063 mole) of a pale yellow liquid boiling at  $133-135^{\circ}0./15$  mm. The reported boiling point of this material is  $118^{\circ}0./9$  mm. (h0).

A picrate of this thianaphthene derivative was prepared and after recrystallization from ethanol it melted at  $ll_3-ll_1^{00}$ . which is the same as that reported in the literature (40) for this picrate.

3,7-Dimethylthianaphthene



Preparation of this compound was accomplished by following the experimental method used for the synthesis of the methylthianaphthenes which have already been described. The following quantities of reagents were used, 25 g. of phosphorous mentoxide and 68 g. (0.38 mole) of acetonyl-o-tolyl sulfide. Distillation of the impure product gave 39.5 g. (0.24 mole, 64%) of a nearly colorless liquid which boiled at

133-136°C./14-15 mm.

Calc'd. for C<sub>10</sub>H<sub>10</sub>S: C, 74.05; H, 6.66; S, 19.77.

Found: C, 74.20; H, 6.70; S, 19.65.

A picrate prepared from the 3,7-dimethylthianaphthene had a melting point of ll4-ll5 $^{\circ}$ C. after recrystallization from 95% ethanol.

Calc'd. for  $C_6H_3O_7N_3.C_{10}H_{10}S$ : C, 49.11; H, 3.35; S, 8.20.

Found: C, 49.21; H, 3.28; S, 8.31.

Desulfurization of 3,7-dimethylthianaphthene with Raney-nickel

The method of Blicke and Sheets (32) was used in this desulfurization reaction. A 5 g. (0.031 mole) quantity of 3,7-dimethylthianaphthene dissolved in 250 ml. of methanol was refluxed for three hours with 25 g. of Raney-nickel, prepared according to Hozingo's procedure (41). The cooled reaction mixture was filtered and the catalyst washed with methanol. The filtrate and washings were diluted with 1.5 liters of distilled water and extracted with three 100 ml. portions of chloroform which were combined and dried over calcium chloride. Removal of the chloroform by distillation yielded 4.5 g. (0.33 mole) of a colorless liquid having the odor of p-cymene. The boiling point of the product was  $170-173^{\circ}$ C. at atmospheric pressure, and its refractive index was,  $n_D^{25} = 1.4912$ . The physical constants, for m-cymene, reported in the literature are, boiling point,  $175-176^{\circ}$ C.,  $n_D^{25} = 1.4922$  (42).

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3-Nothyl-5-mothoxythianaphthene



In a 500 ml. three necked flask fitted with a stirror, condenser and dropping funnel, was placed 25 g. (0.18 mole) of phosphorous pentoxide. In the dropping funnel was placed 73 g. (0.37 mole) of acetonyl-p-methoxyphenyl sulfide. A small amount, approximately fifteen grams of the sulfide, was added to the reaction flask and the reaction mixture heated cautiously with a Bunsen burner. When its temperature reached 110°C.. the reaction mixture started to fume and the reaction became spontaneous. The burner was removed and reaction temperature rose to 150°C. The balance of the sulfide was then added dropwise over a half hour period during which time the reaction mixture became black in color. Stirring was continued for an additional half hour keeping the reaction temperature between 160°C. and 180°C. The viscous solution was cooled and 100 ml. of water added after which it was extracted with 3-100 ml. portions of other. Some difficulty was encountered in distinguishing between the water and other layers. The combined ether extracts were dried over calcium chloride. Removal of the other on a steam bath yielded only a small amount of a dark colored oil. Vacuum distillation of this material gave 5 g. (0.028 mole, 85) of pale yellow colored liquid having a boiling point of 130-133°C./5 mm.

The picrate of this product was prepared and had a molting point of 105-108°C. after being recrystallized from 95% ethanol.

Calc'd. for C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub>·O<sub>10</sub>H<sub>10</sub>SO: C, 17,17; H, 3.22; N, 10.32. Found: C, 16.95; H, 3.39; N, 10.11.

## Thianaphthenethiols

3-Thianaphthenethiol



In a 500-ml. three necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 2.7 g. (0.11 mole) of magnesium chips and 25 ml. of dry ether. To this mixture was added dropwise a solution of 26 g. (0.1 mole) of 3-iodothianaphthene dissolved in 50 ml. of dry ether. The Grignard reaction started after a few ml: had been added. An atmosphere of dry nitrogen was maintained throughout the course of the reaction. The reaction solution was refluxed for two hours following the addition of the 3-iodothianaphthene solution and yet a considerable amount of the magnesium was still unreacted. To the Grignard solution was gradually added 3.2 g. (0.1 g.-atom) of powdered sulfur which caused the reaction mixture to reflux spontaneously during the addition of the latter. The reaction solution was then refluxed for seven hours, cooled, and hydrolyzed with 75 ml. of 3N hydrochloric acid. The ether layer was separated and extracted twice with 50 ml. portions of 10% potassium hydroxide solution. The combined alkaline extracts were acidified to Congo Red paper with 3N hydrochloric acid. A dark oil, having a distinctive mercaptan-like odor, separated.

The acidic aqueous solution was extracted twice with 50 ml. portions of ether. The combined ether extracts were washed with cold water and then dried over calcium chloride. The ether was removed with a water aspirator and the residual dark oil was distilled under reduced pressure, to yield h.h g. (0.0265 mole, 26.5%) of a pure product boiling at 116-117°C./3 mm.

A 2,1-dinitrophenyl sulfide was prepared from this mercaptan and 2,1-dinitrochlorobenzene. After a single recrystallization from methanol it melted at  $163-16h^{\circ}C$ .

Calc'd. for C14H804N2S2: C, 50.59; H, 2.42.

Found: C, 50.45; H, 2.56.

2-Thianaphthenethiol



Thianaphthene was metalated according to the method of Shirley (23).

A 500 ml. three necked flask was fitted with a stirrer and two Yadaptor arms. One of the adaptors carried a calcium chloride drying tube and thermometer and the other was fitted with a dropping funnel and a nitrogen gas inlet. In the flask was placed 4.5 g. (0.65 mole) of lithium chips and 100 ml. of dry ether. A solution of 41.1 g. (0.3 mole) of redistilled n-butyl bromide dissolved in 60 ml. of dry ether was added slowly. As soon as the reaction started, the reaction flask

was immersed in an isopropyl alcohol-ary ice bath to lower the temperature of the reaction mixture to  $-10^{\circ}$ C. The remainder of the n-butyl bromide solution was added over a period of an hour, after which the reaction solution was stirred for an additional hour and a half. The n-butyl lithium solution was filtered through glass wool into a 500 ml. three necked flask which had been swept out with nitrogen and chilled in an ice bath. The filtered n-butyl lithium solution was cooled to -10°C. and 26.8 g. (0.2 mole) of thianaphthene dissolved in 50 ml. of dry ether was added over a period of twenty minutes after which the reaction mixture was stirred for an additional hour and a half at -10°C. The quantity, 6.7 g. (0.21 g-atom), of powdered sulfur was added in small portions from a 50 ml. Erlenmoyer flask which was connected to the reaction vessel through a piece of wide rubber tubing. A slight rise in temperature was noted during the addition of the sulfur. The cooling bath was removed and the reaction mixture allowed to warm to room temperature after which it was heated at its reflux temperature for an hour. The reaction vessel was cooled in an ice bath and hydrolysis of the reaction mixture was carried out with 200 ml. of 2N hydrochloric acid. The yellow colored ether layer was separated and extracted with two 75 ml. portions of 15% potassium hydroxide solution. The combined alkaline extracts were cooled in an ice bath and acidified to Congo Red with 2N hydrochloric acid. An oil separated which solidified after a short period of stirring. The solid was filtered under a stream of nitrogen, washed with distilled water and dried in a vacuum desiccator. A small portion of the dried product was recrystallized

from isopropyl alcohol. The product was insoluble in base and had a melting point of 112-113°C. The mercaptan apparently oxidized to the disulfide during recrystallization.

Calc'd. for C16H10S4: C, 58.16; H, 3.05; S, 38.30.

Found: C, 57.91; H, 3.16; S, 38.76.

Vacuum sublimation of the crude mercaptan yielded 18.5 g. (0.11 mole, 57%) of a white crystalline product with a melting point of h1-h3<sup>o</sup>C.

Calc'd. for C<sub>8</sub>H<sub>e</sub>S<sub>2</sub>: C, 57.79; H, 3.64; S, 38.56.

Found: C, 57.48; H, 3.81; S, 38.64.

A 2,4-dimitrophenyl sulfide of the mercaptan was prepared and had a melting point of 159-160 $^{\circ}$ C. after recrystallization from methanol.

Calc'd. for C14H604N2S2: C, 50.60; H, 2.41; S, 19.31.

Found: C, 50.48; H, 2.51; S, 19.25.

2-Methyl-3-Thianaphthenethiol

In a 500 ml. three necked flask fitted with a stirrer, condenser and dropping funnel, was placed 0.73 g. (0.03 g-atom) of magnesium turnings. To this was added 6.3 g. (0.023 mole) of 3-iodo-2-methylthianaphthene dissolved in 50 ml. of anhydrous ether. A small crystal of iodine was added to initiate the reaction. The reaction solution began to reflux gently after about ten minutes of stirring. The reaction Was allowed to proceed at its reflux temperature for four hours, at the end of which time, 0.7h g. (0.023 g-atom) of sulfur was added to the reaction mixture. The reaction solution was kept at its reflux temperature for an additional three hours, cooled and then hydrolyzed with 50 ml. of 3N of hydrochloric acid. The yellow colored ether solution was separated and extracted with two 20 ml. portions of 10% potassium hydroxide solution. The combined alkaline extracts were cooled and acidified with 3N hydrochloric acid. The resulting acidified solution was then extracted with two 25 ml. portions of ether which were then combined, washed with water, and dried over calcium chloride. Removal of the ether gave about a gram of a dark colored solid having a mercaptan like odor.

A 2,4-dimitrophonylsulfide derivative was prepared from this mercaptan and recrystallized from methanol. Its observed melting point was 179-181°C.

Calc'd. for C<sub>15</sub>H<sub>10</sub>C<sub>4</sub>N<sub>2</sub>S<sub>2</sub>: C, 52.01; H, 2.91; N, 8.09.

Found: C, 51.93; H, 3.01; N, 8.17.

3-Methyl-2-thianaphthenethiol



In a 500 ml. three necked flask fitted as described for the proparation of 2-thianaphthemethicl, was placed 4.5 g. (0.65 mole) of lithium chips and 100 ml. of anhydrous other. The reaction vessel was

placed in a dry ice-isopropyl alcohol bath to maintain the temperature approximately at -15°C. A solution containing 41.1 g. (0.3 mole) of redistilled n-butyl bromide dissolved in 60 ml. of dry ether was added dropwise over a period of an hour. The reaction mixture was then stirred for an additional two hours, after which, it was filtered through glass wool into a 500-ml. three necked flask. To the n-butyl lithium solution was added 29.6 g. (0.2 mole) of 3-methylthianaphthene dissolved in 50 ml. of dry ether, over a period of an hour. The resulting solution was stirred for an additional hour, and the 6.7 g. (0.21 g-atom) of sulfur was added at a rate sufficient to maintain the reaction temperature between -15°C. and -10°C. After adding the sulfur the dry ice-isopropyl alcohol bath was removed and the reaction mixture was heated at its reflux temperature for an hour. Subsequently, it was cooled in an ice bath and hydrolyzed with 100 ml. of cold 3N hydrochloric acid. The yellow colored ether layer was separated and extracted with two 100 ml. portions of cold 15% potassium hydroxide solution. The combined alkaline extracts were cooled in an ice bath and acidified to Congo Red paper with 3N hydrochloric acid. The dark unpleasant smelling oil which separated was extracted with two 75 ml. portions of ether. The combined ether extracts were washed with cold water and dried for about a half an hour over calcium chloride. The ether was removed with a water aspirator and the residual oil distilled under reduced pressure to yield 14.5 g. (0.08 mole, 40%) of yellow oil boiling at 116-118°C./2 rm.

A 2,4-dinitrophenyl sulfide prepared from the mercaptan melted at 216-219°C. after recrystallization from methanol.

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Calc'd. for C<sub>16</sub>H<sub>12</sub>O<sub>4</sub>N<sub>2</sub>S<sub>2</sub>: C, 53.32; H, 3.36. Found: C, 53.53; H, 3.56.

3,7-Dimethyl-2-thianaphthenethiol



A solution of n-butyl lithium was prepared as previously described using 1.8 g. (0.25 mole) of lithium chips contained in 40 ml. of dry ether and 15.1 g. (0.11 mole) of redistilled n-butyl bromide dissolved in 25 ml. of dry ether. To this filtered solution, maintained at a temperature of  $-10^{\circ}$ C., was added over a half hour period 12 g. (0.062 mole) of 3,7-dimethylthianaphthene dissolved in 25 ml. of dry ether. The reaction mixture was then stirred for an hour, maintaining its temperature at  $-5^{\circ}$ C. to  $-10^{\circ}$ C. Sulfur, 2.5 g. (0.078 g-atom), was then gradually added, after which the cold bath was removed and the reaction solution was stirred for an additional hour. The solution was cooled to  $-10^{\circ}$ C. and hydrolyzed with 25 ml. of 6N hydrochloric acid. The ether layer was separated and the impure product isolated using the experimental technique previously described for the metalation reactions. Vacuum distillation of the crude product gave h g. (0.02 mole, 33%) of a yellow colored liquid having a boiling point of 133-135<sup>o</sup>C./23 mm.

The 2,4-dinitrophenyl sulfide derivative prepared from the mercaptan had a melting point of  $157-158^{\circ}$ C. after a single recrystallization from dilute dioxane.

Calc'd. for C<sub>16</sub>H<sub>12</sub>O<sub>4</sub>N<sub>2</sub>S<sub>2</sub>: C, 53.32; H, 3.36. Found: C, 53.32; H, 3.44.

Reduction of 2,21-thianaphthyl disulfide with LiAlH4 (43).

The reduction of the disulfide was carried out employing a Soxhlet extractor due to its insolubility in ether. The quantity, 0.4 g. (0.015 mole) of lithium aluminum hydride dissolved in 150 ml. of dry ether was placed in the Soxhlet flask and 6.6 g. (0.02 mole) of the disulfide was placed in the thimble. The ether was refluxed for two and a half hours and after cooling the reaction mixture was then hydrolyzed by treating it first with 20 ml. of cold distilled water, followed by 25 ml. of 15% sulfuric acid. The ether layer was separated and the aqueous layer extracted with two 25 ml. portions of ether. The combined ether extracts were washed with cold distilled water and dried for about fifteen minutes over anhydrous sodium sulfate. The ether was removed with a water aspirator to yield 5.3 g. (0.03 mole, 79%) of a base soluble product. Vacuum sublimation gave a near colorless material having a melting point of h2-h3°C. A mixed melting point with the 2-thianaphthenethiol obtained directly from the metalation reaction gave no depression in the melting point.

Reduction of 2-Methylthianaphthenemonosulfonyl chloride

This reduction was carried out according to the method reported by Marvel and Caesar (hh).

In a 200 ml. single necked round bottom flask fitted with a condenser, was placed 0.9 g. (0.021 mole) of lithium aluminum hydride



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and 15 ml. of dry ether. Two grams (0.008 mole) of 2-methylthianaphthenemonosulfonyl chloride dissolved in 75 ml. of dry ether was added gradually over a period of an hour. The reaction solution refluxed vigorously with each addition of acid chloride. The reaction was allowed to proceed at its reflux temperature for three hours. The reaction solution was cooled and hydrolyzed first with water, then with 1K hydrochloric acid. The resulting mixture was filtered through glass wool and after separating the ether layer it was extracted with two 25 ml. portions of 10% sodium hydroxide. The combined basic extracts were cooled and acidified with 3N hydrochloric acid. The acidified solution was extracted with two 25 ml. portions of ether which were combined, dried over calcium chloride, after which the ether was removed with a water aspirator. The residue consisted of 0.6 g, of a tan colored solid.

A 2,4-dinitrophenylsulfide derivative was prepared from this product and had a melting point of  $181-183^{\circ}C$ . after recrystallization from methanol.

Calc'd. for  $C_{16}H_{10}O_4N_2S_2$ : C, 52.01; H, 2.91; N, 8.07. Found: C, 51.85; H, 2.90; N, 8.20.

A mixed melting point with the 2,4-dinitrophenylsulfide prepared, as described above, from 3-iodo-2-methylthianaphthene was 179-181°C.

Reduction of Thianaphthenemonosulfonyl chloride

In a 150 ml. single necked flask fitted with a condenser, was placed 0.7 g. (0.018 mole) of lithium aluminum hydride contained in 10 ml. of dry ether. To this solution was added over a period of a half hour, 1.h g. (0.006mole) of thianaphthenemonosulfonyl chlcride dissolved in 30 ml. of dry ether. The reaction mixture was heated at its reflux temperature for three hours and then treated experimentally as described above for the reduction of 2-methylthianaphthenemonosulfonyl chloride. Removal of the ether after drying yielded a few tenths of a gram of dark oil having a mercaptan like odor.

A 2,L-dinitrophenylsulfide derivative was prepared and recrystallized from methanol. Its melting point was 160-162°C.

Calc'd. for C14H604S2: C, 50.50; H, 2.43; N, 8.43.

Found: C, 50.39; H, 2.57; N, 8.20.

A mixed melting point of this derivative with the 2,4-dinitrophenylsulfide prepared from 3-thianaphthenethiol was  $162-164^{\circ}$ C. A mixed melting point of this derivative with the 2,4-dinitrophenylsulfide prepared from 2-thianaphthenethiol was  $130-146^{\circ}$ C.

3-Methyl-2-thianaphthene carboxylic acid



A small gliquot of the solution containing 3-methyl-2-thianaphthene lithium, prepared during the synthesis of 3-methyl-2-thianaphthenethiol, was carbonated by means of dry ice and the white solid obtained after recrystallization from acetic acid melted at 2µl-2µ3°C. The reported melting point of this acid is 2µ3-2µµ°C. (37).



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2-Methyl-3-Thianaphthene Carboxylic Acid



In a 50 ml. round bottom flask fitted with a condenser, was placed 0.24 g. (0.01 g-atom) of magnesium chips and 5 ml. of aniydrous ether. To this mixture was added 2.7 g. (0.01 mole) of 3-iodo-2-methylthianaphthene dissolved in 20 ml. of dry ether. After a few minutes of initial heating at its reflux temperature the reaction mixture continued to reflux spontaneously. The reaction was allowed to proceed at its reflux temperature for two hours and then the yellow brown reaction solution was poured onto crushed dry ice. The reaction product was isolated in the usual manner, and the crude product was purified by vacuum sublimation. The observed melting point was 192-193°C. Its reported melting point is  $195^{\circ}$ C. (36). The yield obtained was o.6 g. (0.003 mole, 31%).

Calc'd. for C<sub>10</sub>H<sub>6</sub>O<sub>2</sub>S: C, 62.47; H, 4.20. Found: C, 62.21; H, 4.40.

# Reaction of Thiaanaphthene with Chlorosulfonic Acid

Method A

In a 500 ml. three necked flask fitted with a stirrer, condenser and dropping funnel was placed 35 g. (0.3 mole) of rodistilled chlorosulfonic acid and 25 ml. of chloroform. The reaction flask was immersed in an ice bath and 28 g. (0.2 mole) of thianaphthene dissolved in 25 ml.

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of chloroform was added dropwise over a period of an hour. The rate of addition of the thianaphthene solution was sufficient to keep the reaction temperature from exceeding 10°C. There was an abundant evolution of hydrogen chloriae during the addition of the thianaphthene. When the addition of the thianaphthene solution had been completed, 100 ml. of distilled water was added to the reaction mixture. The chloroform layer was separated, washed with two 50 ml. portions of distilled water followed by drying over calcium chloride. Removal of the chloroform yielded about two grams of a dark oil having an odor similar to thianaphthene. The aqueous layer was neutralized with barium carbonate and the precipitate of barium sulfate was removed by filtration. The resulting filtrate was treated with sodium carbonate until the precipitation of the barium carbonate was complete. The barium carbonate was removed by filtration and the pale yellow filtrate evaporated to dryness on a hot plate. The residual solid was dried overnight in an oven at 110°C. The weight of the dry, light yellow solid was 35 g.

The dry solid was finely ground, and combined with 35 g. (0.17 mole) of phosphorous pentachloride in a 500 ml. three necked flask fitted with a condenser, stirror and thermometer. The stirred reaction mixture was immersed in an oil bath at 100°C. for three hours. The solid reaction mixture liquified to a dark red solution shortly after being placed in the oil bath. The reaction apparatus was arranged for distillation and the phosphorous oxychloride formed during the reaction was removed by distillation. Its observed boiling point was 103-104°C. and the reported (h5) boiling point of this material is 105.3°C.



The cooled residue was extracted with 75 ml. of dry benzone and the extract was dried over calcium chloride. The benzene was removed with a water aspirator to yield 32 g. (0.14 mole) of a dark, yellow colored oil.

The yellow oil was placed in a small distillation apparatus and fractionated under reduced pressure. The material proved to be very difficult to distill due to excessive foaming and decomposition. The addition of a small amount of Dow antifoam agent did not reduce the foaming. Considerable charring of the material occurred during its distillation. However, a small amount, 5 g. (0.021 mole, 10%) of distillate, which solidified on cooling, was obtained having a boiling point of  $1h0-1h5^{\circ}$ C./2 mm. The green-yellow solid was treated with Norite in ligroin ( $30^{\circ}-60^{\circ}$ ) and the product obtained on crystallization from the latter solvent was white solid having a melting point of  $85-66^{\circ}$ C.

Calc'd. for C<sub>3</sub>H<sub>5</sub>O<sub>2</sub>S<sub>2</sub>Cl: C, hl.29; H, 2.17; Cl, 15.24; S, 27.56. Found: C, hl.30; H, 2.14; Cl, 15.00; S, 27.48.

A sulfonamide derivative was prepared from the sulfonyl chloride by adding a small amount of it to a beaker containing liquid ammonia. The liquid ammonia was allowed to evaporate at room temperature, and the residual solid was washed with distilled water. The product was recrystallized from boiling water and had a melting point of 158-160°C.

Calc'd. for C<sub>8</sub>H<sub>7</sub>O<sub>2</sub>NS<sub>2</sub>: C, 45.05; H, 3.31; N, 6.57. Found: C, 45.16; H, 3.13; N, 6.47.



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## Method B

To a solution containing 13.5 g. (0.1 mole) of thianaphthene dissolved in 500 ml. of chloroform and precooled to  $-370^{\circ}$ C., was added 23.3 g. (0.2 mole) of redistilled chlorosulfonic acid contained in 50 ml. of chloroform, over a period of two hours. The purple colored solution was poured onto crushed ice immediately after the addition of the acid chloride was complete. The chloroform layer was separated, washed first with 75 ml. of 10% sodium carbonate solution and then with 100 ml. of water. After drying the neutralized reaction mixture with calcium chloride the chloroform was removed by distillation, yielding 11 g. (0.082 mole) of a dark oil. The oil had a boiling point of  $60-62^{\circ}$ C./2 mm. and solidified in the received during distillation. It had an odor resembling thianaphthene and formed a picrate which melted at  $ll_6-ll_60^{\circ}$ C. The reported ( $l_66$ ) melting point for the picrate of thianaphthene is  $ll_8-ll_9^{\circ}$ C.

## Reaction of 2-Methylthianaphthene with Chlorosulfonic Acid

## Method A

In a 500 ml. three necked flask fitted with a stirrer, dropping funnel and calcium chloride drying tube, was placed ll g. (0.074 mole) of 2-methylthianaphthene dissolved in 50 ml. of carbon tetrachloride. The solution was cooled to  $0^{\circ}$ C. in an ice salt bath and 17.3 g. (0.148 mole) of redistilled chlorosulfonic acid was added over a period of forty-five minutes. There was considerable decomposition and darkening of the reaction mixture during the addition of the acid chloride.

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and the sulforyl chloride obtained in method A was  $ll5-ll6^{\circ}C.$  indicating the two compounds to be identical.

#### Method C

To a solution containing ll g. (0.0712 mole) of 2-methylthianaphthene dissolved in 75 ml. of chloroform and cooled to 0°C., was added 26 g. (0.223 mole) of radistilled chlorosulfonic acid over a period of an hour. The resulting reaction mixture was stirred for an additional hour and then poured onto 500 g. of crushed ice. The chloroform layer was separated and the aqueous layer extracted with two 75 ml. portions of chloroform. The combined extracts were washed with three 50 ml. portions of ice-cold water, dried over calcium chloride, and then combined with the original chloroform layer. Removal of the chloroform with a water aspirator left an impure solid product which was recrystallized from ligroin to yield 3 g. (0.012 mole, 16.1%) of a crystalline, white solid having a melting point of 115-116°C. A mixed melting point of this material with the product obtained in Nethod A was 115-117°C.

## Method D

To 94 g. (0.8 mole) of redistilled chlorosulfonic acid at  $10^{\circ}$ C. was added over a period of two hours, 30 g. (0.2 mole) of 2-methylthianaphthene dissolved in 25 ml. of chloroform. The reaction mixture was stirred for a period of four hours at 0 to  $10^{\circ}$ C. and then for an additional two hours at room temperature at the end of which time it was poured onto 1600 g. of crushed ice. The aqueous solution was extracted with two 100 ml. portions of chloroform. The combined extracts were



washed with two 50 ml. portions of cold water dried over calcium chloride and combined with the original chloroform layer. Removal of the chloroform yielded a small amount of a dark oil which solidified on being set aside at room temperature for several hours. This solid, after it had been recrystallized from dilute ethanol, melted at 120-122°C.

Calc'd. for monosulfonation,  $C_9H_7O_2S_2C1\text{: C, } \downarrow3.81\text{; } H\text{, } 2.86\text{; } C1\text{, } 11\text{,}37\text{.}$ 

- Calc'd. for disulfonation,  $C_{\rm p}H_{\rm G}O_4S_{\rm 2}Cl_2\colon$  C, 31.30; H, 1.75; Cl, 20.54.
- Found: C, 31.86; H, 2.27; Cl, 18.93.

A sulfonamide derivative was prepared from this product and concentrated armonium hydroxide. The melting point of the amide after recrystallization from dilute ethanol was 265-267°C.

- Calc'd. for monosulfonamide, C<sub>0</sub>H<sub>9</sub>O<sub>2</sub>HS<sub>2</sub>: C, 47.55; H, 3.99; N, 6.16.
- Calc'd. for disulfonamide,  $C_9H_{10}O_4N_2S_5$ : C, 35.28; H, 3.29; N, 9.1h.
- Found: C, 34.90; H, 3.21; N, 8.87.

The aqueous layer from the hydrolyzed reaction mixture was neutralized with sodium carbonate and evaporated to dryness. The resulting salt mixture was finely ground in a morter and then stirred vigorously for eighteen hours with 500 ml. of boiling methanol to extract the sodium salt of any sulfonic acid present. The solution was filtered to remove undissolved solid and the methanol was removed by distillation. The solid obtained weighed 21 g. after drying in an oven at  $110^{\circ}$ C. for three hours. 、

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The presumed sodium sulfonate obtained as described above was combined with 35 g. (0.17 mole) of phosphorous pentachloride. After stirring the solid mixture a few minutes it liquified to a dark red solution. This solution was stirred for four hours at  $100^{\circ}$ C., cooled, and extracted with two 75 ml. portions of benzene. The combined benzene extracts were washed with three 25 ml. portions of cold water, and then dried over calcium chloride. Removal of the benzene yielded 14 g. of a dark red oil. Attempted vacuum distillation of a small portion of this oil only resulted in extensive decomposition. When a small quantity of the oil was treated with concentrated armonium hydroxide, it gave a gummy material which could not be purified.

The remainder of the oil was allowed to react with lithium aluminum hydride using the following experimental procedure. To 6 g. (0.16 mole) of lithium aluminum hydride dissolved in 75 ml. of anhydrous ether, under a mitrogen atmosphere, was added over a period of an hour to 10 g. of the oil contained in 25 ml. of dry ether. As each drop of the ether solution came in contact with the hydride solution, large quantities of white fumes were evolved. Solid material was deposited on the walls of the reaction vessel, on the surface of which sparking occurred during the reaction. This experiment was discontinued when the sparking became more frequent as the reaction proceeded.

# Method E

To a solution containing 11 g. (0.074 mole) of 2-methyl-thianaphthene in 50 ml. of chloroform and kept at room temperature (25°C.) was added 17.3 g. (0.148 mole) of redistilled chlorosulfonic acid



dissolved in 50 ml. of chloroform. As the addition of the acid chloride proceeded, a black tarry material formed in the reaction mixture. In a short time the entire reaction solution was converted to a black, gummy like substance. The reaction was discontinued at this point.

## Method F

To 25 g. (0.21 mole) of redistilled chlorosulfonic acid precooled to -15°C., was added over a period of forty-five minutes, 14.8 g. (0.1 mole) of 2-methylthianaphthene dissolved in 35 ml. of chloroform. The reaction solution took on a dark brown color almost at once. The reaction temperature varied between -17°C. and -15°C. during the addition of the 2-methylthianaphthene. Large quantities of hydrogen chloride were evolved during the reaction. The dark reaction solution was poured onto 500 g. of ice immediately after completing the addition of the 2-methylthianaphthene. The chloroform layer was separated and the aqueous layer extracted twice with 50 ml. of chloroform. The combined chloroform extracts were washed with 50 ml. of cold water, dried over magnesium sulfate and combined with the original chloroform layer. The chloroform was removed with a water aspirator, yielding a yellow colored oil which solidified after being set aside for a few minutes, at room temperature. The product was recrystallized from a mixture of equal volumes of ethanol and cyclohexane. It had a melting point of 161-163°C. and weighed 6 g. (0.0167 mole, 16.7%). This material gave a positive sulfur test and a negative halogen test after carrying out a sodium fusion of the material.

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Calc'd. for a sulfone, C<sub>13</sub>H<sub>14</sub>C<sub>2</sub>S<sub>3</sub>: C, 60.33; H, 3.94; S, 26.86. Found: C, 59.71; H, 4.15; S, 26.72.

## Reaction of 3-Methylthianaphthene with Chlorosulfonic Acid

In a 500 ml. three necked flask fitted with a stirrer, condenser and dropping funnel, was placed 93 g. (0.8 mole) of redistilled chlorosulfonic acid. The acid was cooled to  $10^{\circ}$ C. and 15 g. (0.1 mole) of 3-methylthianaphthene was added over a period of an hour. The solution became almost black during the reaction, and copious quantities of hydrogen chloride were evolved. Stirring was continued for fifteen minutes after the addition of the 3-methylthianaphthene was completed. The reaction mixture was then poured onto 1000 g. of ice. The aqueous solution was extracted with two 100 ml. portions of chloroform. The combined extracts were dried over calcium chloride. Removal of the chloroform yielded only a trace of a dark cil.

The aqueous solution was neutralized with barium carbonate, filtered to remove the precipitated barium sulfate, and the filtrate treated with sodium carbonate until the precipitation of barium carbonate was complete. The solution was filtered and the filtrate evaporated to dryness. The solid residue was dried at  $110^{\circ}$ G. for four hours. The dried solid, weighing h3 g., was combined with h2 g. (0.2 mole) of phosphorous pentachloride contained in a 500 ml. three necked flask, fitted with a stirrer, condenser and thermometer, and stirred vigorously. The mixture liquified and was heated at  $100^{\circ}$ G. for an hour and a half. The dark red solution was cooled and poured onto 100 g. of ice. The aqueous solution was extracted with two 50 ml. portions of benzene and the extracts were



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washed with two 25 ml. portions of cold water. The washed benzene extracts were combined and dried over calcium chloride after which the benzene was removed with a water aspirator. The tan colored residue, 7.5 g. (0.022 mole, 22%), was recrystallized from ligroin following prior treatment with Norite. The purified material had a melting point of  $107-109^{\circ}C$ .

- Calc'd. for monosulfonation,  $C_9H_70_2S_2\text{Cl:}$  C, 43.61; H, 2.66; Cl, 14.37.
- Calc'd. for disulfonation,  $C_{\rm 5}{\rm H_6O_4S_3Cl_2}{:}$  C, 31.30; H, 1.75; Cl, 20.54.
- Found: C, 31.45; H, 1.95; Cl, 20.22.

A sulfonamide derivative was prepared from the sulfonyl chloride by boiling a small quantity of it with concentrated ammonium hydroxide for five minutes and then evaporating the reaction mixture to dryness. The crude product was washed with cold water and then recrystallized from boiling water. The melting point of the amide was  $258-260^{\circ}$ C.

- Calc'd. for monosulfonamide,  $\rm C_9H_9O_2NS_2$ : C, 47.55; H, 3.99; N, 6.16.
- Calc'd. for disulfonamide,  $C_9H_{10}O_4N_2S_3\colon$  C, 35.28; H, 3.29; N, 9.14.
- Found: C, 35.24; H, 3.30; N, 8.85.

(N.N-Dialkylamino)Alkyl Chlorides Hydrochlorides

B-Piperidinoethyl Chloride Hydrochloride


In a 500 ml. three necked flask fitted with a stirrer, reflux condenser, and dropping funnel were placed, 65 g. (0.5 mole) of **Q**-piperidinoethyl alcohol. A slow stream of dry air was drawn through the apparatus during the reaction. To the reaction vessel was added a solution of 72 g. (0.6 mole) of redistilled thionyl chloride dissolved in 100 ml. of dry chloroform at a rate sufficient to maintain the reaction temperature between 50 and 55°C. The solution was heated at its reflux temperature for a half hour following the addition of the thionyl chloride solution, which required two hours. The reaction solution was cooled and the solid collected by filtration, washed with cold ether and dried in a vacuum desiccator. Recrystallization from absolute ethanol gave 60 g. (0.32 mole, 65%) of a product having a melting point of 205-206°C. The reported melting point for this material is 205°C. (47).

Y-Piperdino-n-propyl chloride hydrochloride



The method of Adams and Whitmore was employed in the preparation of this material (48).

In a two liter three necked flask fitted with a stirrer and reflux condenser, was placed 142 g. (0.9 mole) of trimethylene chlorobromide, 400 ml. of dry benzene, and 119 g. (1.4 moles) of piperidine. The solution was stirred intermittently for a half hour, during which time the reaction solution began to reflux. After the refluxing of the

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reaction solution had terminated, external heat was applied to keep it at its reflux temperature for three hours. The reaction solution was cooled and the piperdine hydrobromide was removed by filtration and washed with dry ether. The ether washings were combined with the benzene solution and extracted with three 125 ml. portions of 3N hydrochloric acid. The combined extracts were made basic with 10N sodium hydroxide and the oil which separated was extracted with three 100 ml. portions of ether. The ether extracts were dried with magnesium sulfate and then treated with dry hydrogen chloride gas. The resulting precipitate was recovered by filtration and dried in a vacuum desiccator. The crude product on recrystallization from absolute ethanol yielded 89 g. (0.15 mole, 50%) of white solid melting at 217-219°C. The reported melting point for this salt is 220°C. (h9).

P-Morpholinoethyl chloride hydrochloride



To 52.5 g. (0.4 mole) of **Q**-morpholinosthyl alcohol dissolved in 150 ml. of chloroform was added over a period of an hour, 60 g. (0.5 mole) of redistilled thionyl chloride dissolved in 75 ml. of chloroform. The product separated from solution during the addition of the thionyl chloride. The reaction mixture was stirred for fifteen minutes after the addition of the thionyl chloride was complete and then filtered. The orude product was washed with dry ether and dried in a vacuum desiccator. Recrystallization of the crude product from absolute ethanol

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gave 38.7 g. (0.21 mole, 52%) of a white solid having a melting point of 179-131°C. The reported melting point for this compound is 182-182.5°C. (50).

Y-Morpholino-n-propyl chloride hydrochloride

In a three liter three necked flask fitted with a reflux condenser, dropping funnel and stirrer was placed 300 g. (3.ht moles) of morpholine, 360 g. (2.29 moles) of trimethylene chlorobromide and 900 ml. of dry benzone. The reaction mixture was allowed to stand at room temperature for an hour with occasional stirring. The temperature of the reaction mixture was raised to its reflux temperature and then the heat was removed, after which the reaction mixture refluxed spontaneously for about a half hour. External heat was again applied and the reaction mixture was kept at its reflux temperature for three hours, cooled, and the insoluble morpholine hydrobroxide removed by filtration and washed with dry ether. The ether washings were combined with the benzone filtrate and the resulting solution was extracted with four 200 ml. portions of 3N hydrochloric acid. The combined acid extracts were made basic with 10N sodium hydroxide resulting in the separation of an oily layer. The aqueous layer was extracted with 100 ml. of ether. The combined ether extract and oil were dried over anhydrous sodium sulfate. Gaseous hydrogen chloride was passed slowly into the chilled ether solution to form the insoluble amine hydrochloride which was filtered

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and washed with dry ether. After recrystallization from isopropyl alcohol, 275 g. (1.37 moles,  $\delta D_{\sigma}$ ) of a white crystalline material was obtained which melted at 160-162°C. The reported melting point for this substance is 163-170°C. (h.8).

Q-Thiodiglycol



In a three liter three necked flask fitted with stirrer, reflux condenser and thermometer was placed 298 g. (3.7 moles) of ethylene chlorohydrin and 1200 ml. of distilled water. To this solution was added 493 g. (2.05 moles) of sodium sulfide over a period of forty-five minutes. The temperature of the reaction mixture was maintained at about 30°C., while it was stirred for a half hour after the addition of the sulfide was complete. The reaction solution was then heated to 90°C. on the steam bath for forty-five minutes, cooled, and neutralized to tumeric paper by adding concentrated hydrochloric acid dropwise. The water in the reaction mixture was removed by vacuum distillation and the residue extracted twice with 500 ml. portions of hot absolute ethanol. The combined yellow colored alcohol extracts were returned to the three liter flask and the ethanol removed under reduced pressure. The residual oil had a boiling point of 154-156°C./9 mm. and weighed 199 g. (1.63 moles, 88%). The reported boiling point of Q-thiodiglycol is 164-166°C./20 mm. (51).

β, β'-Dibromodiethyl sulfide

To 25 g. (0.21 mole) of  $\mathbf{Q}$ -thiodiglycol dissolved in 100 ml. of chloroform was added 42 g. (0.16 mole) of redistilled phosphorous tribromide over a period of an hour. The temporature of the reaction solution was kept at about 10°C. by means of an ice bath during the addition of the bromide. After the addition of phosphorous tribromide was completed, the ice bath was removed and the reaction solution was stirred for eight hours. The chloroform was removed by distillation and the residue poured into water. The product was extracted with ether and the latter was dried over calcium chloride. The ether solution was concentrated on the steam bath, cooled in an ice bath and the product which crystallized in white needles was removed by filtration, washed with cold ether, and dried in a vacuum desiccator. The yield was 38 g. (0.15 mole, 74.5%) and it melted at 31-33°C. The reported melting point of this dibromide is 32-3h°C. (52).

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Q-Thiomorpholinoethyl alcohol hydrochloride



In a two liter three necked flask fitted with a stirrer, reflux condenser and dropping funnel was placed 200 g. (0.61 mole) of **\$,\$**,\$d-dibromodiethyl sulfide and 900 ml. of chloroform. To this solution was

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added rapidly, lh8 g. (2.h2 moles) of monoethanolamine. The reaction mixture was heated while being stirred on the steam inth for fifteen hours. After cooling, it was filtered and the precipitated ethanol amine hydrobromide extracted with two 75 ml. portions of chloroform. The combined chloroform extracts and original chloroform filtrate were chilled and treated with gaseous hydrogen chloride. The hydrochloride product was filtered, washed with a small portion of dry ether and dried in a vacuum desiccator. Recrystallization of the product from absolute ethanol gave 93 g. (0.51 mole, 63%) of a white crystalline solid having a melting point of 159-161°C. The reported melting point of this salt is 162-163°C. (9).

3-Thiomorpholinoethyl chloride hydrochloride

A suspension of 14 g. (0.076 mole) of P-thiomorpholinoethyl alcohol hydrochloride in 75 ml. of chloroform was heated to  $\mu^{0}$ C. on a steam bath. To the heated solution, was added 9.5 g. (0.08 mole) of redistilled thionyl chloride dissolved in 15 ml. of chloroform at such a rate as to keep the reaction temperature below 55°C. The roaction mixture was heated at 50°C for a half hour after the addition of thionyl chloride was complete. After cooling, the solid was removed by filtration and washed with cold, dry ether. The orude product was treated with Norite in isopropyl alcohol, filtered, and allowed to crystallize from the isopropyl alcohol. The yield of pure product was



6 g. (0.03 mole,  $h(\beta)$  and it melted at 203-204°C. The reported melting point of this substance is 206-208°C. (53).

Y-Thiomorpholino-n-propyl chloride hydrochloride



A mixture of 137 g. (0.55 mole) of \$, \$'-dibromodiethyl sulfide, 500 ml. of chloroform and 124.4 g. (1.66 moles) of Y-propanolamine was heated at its reflux temperature on a steam bath for eight hours. The steam bath was removed and the reaction mixture was stirred overnight. The hydrobromide of the amino alcohol which had formed in the reaction was removed by filtration and washed with chloroform. The chloroform solutions were combined and then the chloroform was removed by distillation, yielding 81.6 g. of a yellow colored oil. To this crude X-thiomorpholino-n-propyl alcohol (9) dissolved in 100 ml. of chloroform at room temperature, was added 63 g. (0.53 mole) of redistilled thionyl chloride dissolved in 50 ml. of chloroform over a period of an hour. The dark reaction solution was heated at its reflux temperature for a half hour after the addition of the thionyl chloride had been completed. The reaction mixture was cooled and 150 ml. of distilled water was added to extract the hydrochloride. The aqueous extract was made basic with 20% sodium hydroxide and the yellow colored oil which separated was extracted with ether. The ether extract was washed with cold water and dried over calcium chloride. The ether solution was chilled and then



The ether extracts and oil were combined and washed first with a 10% sodium hydroxide solution and then with three 25 ml. portions of cold water. After drying the ether solution of the product with anhydrous magnesium sulfate it was cooled in an ice bath and treated with a gentle stream of dry hydrogen chloride until there was no further precipitation of amine hydrochloride. The use of excess hydrogen chloride was carefully avoided as it usually resulted in the formation of a very sticky product or a product which separated from the ether solution as an oil. The white precipitated product was collected on a Buchner funnel and washed with a small quantity of dry ether. Recrystallization of the hydrochloride from isopropyl alcohol gave 8 g. (0.029 mole, 89%) of a white crystalline product which melted at  $164-165^{\circ}$ c.

Cale'd. for C<sub>12</sub>H<sub>16</sub>NS<sub>2</sub>Cl: C, 52.63; H, 5.89; S, 23.42. Found: C, 52.89; H, 6.02; S, 23.31.

Q-(Diethylamino) ethyl-2-thianaphthyl sulfide hydrochloride

S-CH2CH2NC2H6 . HCl

Following essentially the same experimental procedure as described above, 8.3 g. (0.05 mole) of 2-thianaphthemethicl was dissolved in a solution containing 7.2 g. (0.18 mole) of sodium hydroxide contained in 30 ml. of distilled water. To this solution heated to its reflux temperature was added 6.9 g. (0.04 mole) of  $\mathbf{e}$  -diethylaminoethyl chloride hydrochloride dissolved in 30 ml. of water. The addition of isolated as previously described. Recrystallization of the hydrochloride salt from isopropyl alcohol gave 6.5 g. (0.021 mole, 52%) of a white solid which melted at 161-183°C.

Calc'd. for C14H18ONS2Cl: C, 53.23; H, 5.74; S, 20.30.

Found: C, 53.50; H, 5.96; S, 20.02.

Y-Morpholino-n-propyl-2-thianaphthyl sulfide hydrochloride

SCH2CH2CH2N 0.HCl

This compound was prepared employing the experimental procedure previously described. The quantity, eight grams (0.048 mole) of 2-thianaphthenethiol was dissolved in a solution containing 6 g. (0.15 mole) of sodium hydroxide in 75 ml. of distilled water. To this solution heated to its reflux temperature was added, over a period of a half hour, 8 g. (0.04 mole) of  $\Upsilon$ -morpholino-n-propylchloride hydrochloride dissolved in 25 ml. of distilled water. The product was isolated in the manner already described after a reaction period of two hours. Recrystallization of the amine hydrochloride product from isopropyl alcohol gave 7.5 g. (0.023 mole, 57%) of a white solid which melted at 139-1h°C.

Cale'd. for C<sub>15</sub>H<sub>20</sub>ONS<sub>2</sub>Cl: C, 54.56; H, 6.11; S, 19.44. Found: C, 54.78; H, 6.05; S, 19.25.

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 ${f Q}$  -Piperdinoethyl-2-thianaphthyl sulfide hydrochloride



To a solution of 6 g. (0.15 mole) of sodium hydroxide in 75 ml. of distilled water, was added 8.3 g. (0.05 mole) of 2-thianaphthenethiol. This solution was brought to its reflux temperature and 8.3 g. (0.045 mole) of  $\mathbf{e}$ -piperdinoethyl chloride hydrochloride dissolved in 40 ml. of distilled water was added over a period of a half hour. The reaction solution was kept at its reflux temperature for six hours after which the desired amine salt was isolated as previously described. Recrystallization of the product from absolute ethanol gave 10.5 g. (0.033 mole, 75.5%) of a white solid which melted at 220-222°C.

Cale'd. for C<sub>15</sub>H<sub>20</sub>NS<sub>2</sub>Cl: C, 57.39; H, 6.42; S, 20.43. Found: C, 57.57; H, 6.53; S, 20.46.

8 -Piperdino-n-propyl-2-thianaphthyl sulfide hydrochloride

SCH2CH2CH2N .HCl

The experimental procedure used in this preparation was the same as that already described. The quantity, eight grams (0.048 mole) of 2-thianaphthenethiol was dissolved in a solution made from 6 g. (0.15 mole) of sodium hydroxide and 75 ml. of distilled water. This alkaline solution of the mercaptan was brought to its reflux temperature and 8 g. (0.04 mole) of  $\checkmark$ -piperdino-n-propyl chloride hydrochloride dissolved in 30 ml. of water was added over a thirty minute period.



The resulting reaction solution was kept at its reflux temperature for three hours and the product was then isolated as previously described. Recrystallization of the product from isopropyl alcohol gave 6.5 g. (0.02 mole, 49.5%) of a white solid which melted at 146-148°C. Calc'd. for C<sub>16</sub>H<sub>22</sub>NS<sub>2</sub>Cl: C, 58.60; H, 6.76; S, 19.56. Found: C, 58.50; H, 6.71; S, 19.41.

Q-Thiomorpholinoethyl-2-thianaphthyl sulfide hydrochloride

sch\_ch\_N s. Hcl

A 6 g. (0.036 mole) quantity of 2-thianaphthenethicl was dissolved in a solution prepared from 6 g. (0.15 mole) of sodium hydroxide and 75 ml. of distilled water. To this alkaline solution of the sodium salt of 2-thianaphthenethicl was added 6.7 g. (0.033 mole) of e-thiomorpholinoethyl chloride hydrochloride dissolved in 40 ml. of distilled water, over a half hour period. Heating this reaction mixture at its reflux temperature for five hours resulted in the formation of the free amine as an oil. This was isolated and converted to its hydrochloride following the experimental procedures already discussed. Recrystallization of the product from isopropyl alcohol gave 7 g. (0.021 mole, 64%) of a white solid which melted at 191-193<sup>0</sup>C.

Cale'd. for C<sub>14</sub>H<sub>18</sub>NS<sub>3</sub>Cl: C, 50.66; H, 5.17; S, 28.98. Found: C, 50.75; H, 5.54; S, 29.17

𝕇 -Thiomorpholino-n-propyl-2-thianaphthyl sulfide hydrochloride

SCH2CH2CH2N S.HCL

The previously described experimental procedure was used for the preparation of this material. An 8 g. (0.048 mole) quantity of 2-thianaphthenethiol was dissolved in a solution prepared from 6 g. (0.15 mole) of sodium hydroxide and 75 ml. of distilled water. This alkaline solution was brought to its reflux temperature and 8.6 g. (0.04 mole) of  $\checkmark$ -thiomorpholino-n-propyl chloride hydrochloride contained in 50 ml. of distilled water was added over a period of a half hour. The reaction solution was maintained at its reflux temperature for two hours after which the product was isolated by methods previously described. Recrystallization of the amine hydrochloride salt from isopropyl alcohol gave 9.2 g. (0.027 mole, 77%) of a pure product which melted at 123-124°C.

Cale'd. for C<sub>15</sub>H<sub>20</sub>NS<sub>3</sub>Cl: C, 52.07; H, 5.83; S. 27.80. Found: C, 51.89; H, 5.62; S, 27.51.

& -Dimethylaminoethyl-3-methyl-2-thianaphthyl sulfide hydrochloride

CH3 SCH2CH2NCH3.HCl

This compound was prepared according to the previously described experimental procedure by combining 8.2 g. (0.045 mole) of 3-methyl-2thianaphthenethiol and 6 g. (0.15 mole) of sodium hydroxide dissolved

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in 75 ml. of distilled water with 5.6 g. (0.04 mole) of  $\mathbf{Q}$ -dimethylaminosthyl chloride hydrochloride contained in 40 ml. of water. The reaction mixture was kept at its reflux temperature for five hours and the desired product was isolated in a manner similar to that already described. The crude product after being recrystallized from isopropyl alcohol amounted to 6.2 g. (0.022 mole, 54%) of a white solid which melted at 214-215°C.

Cale'd. for C<sub>13</sub>H<sub>18</sub>NS<sub>2</sub>Cl: C, 54.24; H, 6.30; S, 22.28. Found: C, 54.09; H, 6.42; S, 22.33.

Q-Diethylaminoethyl-3-methyl-2-thianaphthyl sulfide hydrochloride

CH3 SCH2CH2NC2H5, HCL

A 9 g. (0.05 mole) quantity of 3-methyl-2-thianaphthenethiol was dissolved in a solution prepared from 8 g. (0.2 mole) of sodium hydroxide in 50 ml. of water. To this alkaline solution kept at its reflux temperature was added 8.6 g. (0.05 mole) of C-diethylaminoethyl chloride hydrochloride dissolved in 30 ml. of water. The reaction solution was heated at its reflux temperature for five hours and the product was i solated in the manner discussed above. Recrystallization of the product from isopropylalcohol gave 7.5 g. (0.024 mole, 47%) of a white solid which melted at 178-179°C.

Calc'd. for C<sub>15</sub>H<sub>22</sub>NS<sub>2</sub>Cl: C, 56.89; H, 7.00; S, 20.25. Found: C, 57.21; H, 7.16; S, 20.06. Y-Dimethylamino-n-propyl-3-methyl-2-thianaphthyl sulfide hydrochloride



The same experimental procedure as previously described was employed for the preparation of this material. The mercaptan, 8.2 g. (0.045 mole), was dissolved in a solution of 6 g. (0.15 mole) of sodium hydroxide dissolved in 75 ml. of water. The reaction solution was kept at its reflux temperature for four and a half hours after 6.3 g. (0.04 mole) of  $\checkmark$ -dimethylamino-m-propyl chloride hydrochloride contained in 25 ml. of water had been added to the alkaline solution of the sodium salt of the mercaptan. Following the isolation techniques described above, 6.5 g. (0.022 mole, 54%) of a white solid was obtained after recrystallization of the product from isopropyl alcohol following prior treatment of the alcoholic solution with Norite. The observed melting point of the pure product was  $160.5-162.5^{\circ}$ C.

Calc'd. for C14H20NS2Cl: C, 55.70; H, 6.68; S, 21.24.

Found: C, 55.61; H, 6.78; S, 21.54.

 ${\color{black} \blacktriangleleft}$  -Methyl- ${\color{black} Q}$  -dimethylaminosthyl-3-methyl-2-thianaphthyl sulfide hydrochloride



This compound was prepared by adding to a solution containing 8.2 g. (0.045 mole) of 3-methyl-2-thianaphthenethiol, 6 g. (0.15 mole) of

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sodium hydroxide and 75 ml. of water, a second solution prepared from 6.3 g. (0.04 mole) of dimethylaminoisopropyl chloride hydrochloride and 40 ml. of water. The resulting reaction solution was kept at its reflux temperature for a period of four hours. Recrystallization of the crude hydrochloride product from isopropyl alcohol gave 8.9 g. (0.03 mole, 71%) of a white solid which melted at  $172-171\%^{\circ}$ C.

Calc'd. for C<sub>14</sub>H<sub>20</sub>NS<sub>2</sub>Cl: C, 55.70; H, 6.68; S, 21.24. Found: C, 55.42; H, 6.88; S, 20.95.

Q -Morpholinoethyl-3-methyl-2-thianaphthyl sulfide hydrochloride

SCH<sub>2</sub>CH<sub>2</sub>N 0.HCL

The experimental procedure used in this synthesis was the same as previously described. The mercaptan 8.2 g. (0.045 mole), was dissolved in a solution of 6 g. (0.15 mole) of sodium hydroxide contained in 75 ml. of water. The alkaline solution was heated to its reflux temperature and 7.4 g. (0.04 mole) of **Q** -morpholinoothyl chloride hydrochloride dissolved in h0 ml. of water was added over a thirty-minute period after which the reaction solution was kept at its reflux temperature for four hours. Following the isolation procedure used above, the crude hydrochloride was obtained and following recrystallization from isopropyl alcohol gave 5.5 g. (0.017 mole, h2%) of a white solid which melted at 200-202<sup>9</sup>C.

Cale'd. for C<sub>15</sub>H<sub>20</sub>GNS<sub>2</sub>Cl: C, 54.61; H, 6.11; S, 19.44. Found: C, 54.48; H, 6.39; S, 19.72.

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8 -Piperdinoethyl-3-methyl-2-thianaphthyl sulfide hydrochloride

SCH2CH2N .HCL

To an alkaline solution of 3.2 g. (0.08 mole) of sodium hydroxide in 50 ml. of water, was added 5.h g. (0.03 mole) of 3-methyl-2-thianaphthenethiol. The solution was then heated to its reflux temperature and h.5 g. (0.02h mole) of  $\mathbf{g}$ -piperdinoethyl chloride hydrochloride contained in h0 ml. of water was added over a half hour period. The reaction solution was kept at its reflux temperature for three hours after which it was cooled and the product isolated in the manner already described. Recrystallization of the product from isopropyl alcohol yielded 5.h g. (0.016 mole, 68%) of a white solid which melted at 222-221°C.

Calc'd. for C<sub>16</sub>H<sub>22</sub>NS<sub>2</sub>Cl: C, 58.60; H, 6.76; S, 19.56.

Y-Piperdino-n-propyl-3-methyl-2-thianaphthyl sulfide hydrochloride

SCH2CH2CH2N .HC

This compound was prepared by adding to a solution containing 8.2 g. (0.045 mole) of 3-methyl-2-thianaphthenethiol, 6 g. (0.15 mole) of sodium hydroxide and 75 ml. of water, a solution prepared from 8 g. (0.04 mole) of  $\checkmark$ -piperdino-n-propyl chloride hydrochloride contained in 40 ml. of water. The reaction mixture was heated at its reflux

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temperature for three and a half hours and the product isolated in the manner described earlier. The crude hydrochloride product was recrystallized from isopropyl alcohol after prior treatment of its alcoholic solution with Norite. The yield of the product was 9.3 g. (0.027 mole, 60%), and its observed molting point was 160-162°C.

Calc'd. for C<sub>17</sub>H<sub>24</sub>NS<sub>2</sub>Cl: C, 59.71; H, 7.07; S, 18.75. Found: C, 59.49; H, 7.05; S, 18.56.

e-Thiomorpholinoethyl-3-methyl-2-thianaphthyl sulfide hydrochloride

CH3 SCH2CH2N S.HC1

A solution containing 3 g. (0.075 mole) of sodium hydroxide in 50 ml. of water was prepared and to it was added 2.7 g. (0.015 mole) of 3-methyl-2-thianaphthenethiol. A solution prepared from 3 g. (0.015 mole) of  $\mathbf{Q}$ -thiomorpholinoethyl chloride hydrochloride in 30 ml. of water was added over a half hour period. The resulting reaction solution was heated at its reflux temperature for three and a half hours and then the product was isolated as previously described. Recrystallization of the crude hydrochloride product from isopropyl alcohol yielded 2.6 g. (0.0075 mole, 51%) of a white solid which had a melting point of 206-208°C.

Cale'd. for C<sub>15</sub>H<sub>20</sub>NS<sub>3</sub>Cl: C, 52.07; H, 5.83; S, 27.80. Found: C, 51.87; H, 6.02; S, 28.05.

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Y-Thiomorpholino-n-propyl-3-methyl-2-thianaphthyl sulfide hydrochloride



This compound was prepared by adding to a solution containing 8.2 g. (0.045 mole) of 3-methyl-2-thianaphthenethiol, 6 g. (0.15 mole) of sodium hydroxide and 75 ml. of water, a second solution prepared by dissolving 8.6 g. (0.04 mole) of **V**-thiomorpholino-n-propyl chloride hydrochloride in 40 ml. of water. The resulting reaction mixture was kept at its reflux temperature for four and a half hours. Following the same procedure described above, the crude hydrochloride product was isolated and recrystallized from isopropyl alcohol to yield 9 g. (0.025 mole, 62%) of a material melting at 126-128°C.

Cale'd. for C<sub>16</sub>H<sub>22</sub>NS<sub>3</sub>Cl: C, 53.38; H, 6.16; S, 26.72. Found: C, 53.52; H, 6.30; S, 26.14.

Dimethylaminoethyl-3-thianaphthyl sulfide hydrochloride.



Following the previously described experimental procedure, the quantity, 4 g. (0.024 mole) of 3-thianaphthenethicl was added to a solution containing 2.4 g. (0.06 mole) of sodium hydroxide dissolved in 50 ml. of water. The alkaline solution was heated to its reflux temperature and 2.9 g. (0.02 mole) of  $\mathbf{Q}$ -dimethylaminoethyl chloride hydrochloride contained in 30 ml. of water was added over a half hour period.

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The reaction mixture was heated at its reflux temperature for three hours, cooled and the product isolated as already described. Recrystallization of the crude hydrochloride product from isopropyl alcohol following prior treatment of its alcoholic solution with Norite, gave 4 g. (0.015 mole, 73%) of a white solid which melted at 1½5-1½7°C. Calc'd. for C<sub>12</sub>H<sub>10</sub>NS<sub>2</sub>Cl: C, 52.63; H, 5.89; S, 23.½2. Found: C, 52.73; H, 6.01; S, 23.11.

8 -Korpholinoethyl-3-thianaphthyl sulfide hydrochloride

SCH2CH2 0.HCl

This hydrochloride salt was synthesized by adding to a solution containing h g. (0.02h mole) of 3-thianaphthemethiol, 2.h g. (0.06 mole) of sodium hydroxide and 50 ml. of water a second solution prepared from 3.3 g. (0.018 mole) of **Q** -morpholinocthyl chloride hydrochloride dissolved in 25 ml. of water. The resulting reaction solution was kept at its reflux temperature for a three hour period at the end of which it was cooled and the product isolated by the procedure already described. The crude hydrochloride product was recrystallized from isopropyl alcohol after first treating its alcoholic solution with Norite, to give 2.1 g. (0.0066 mole, 37%) of a white solid which melted at 1h5-1h6°C. Calc'd. for C<sub>14H16</sub>ONS<sub>2</sub>Cl<sub>3</sub> C, 53.23; H, 5.7h; S, 20.30.

Found: C, 53.45; H, 5.74; S, 20.05.

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## SUPPARY

- Six proviously unreported thianaphthenothiols were propared and Characterized.
- Ten previously unreported (Q-(dialkylamino) alkyl-2-thianaphthyl sulfide hydrochlorides were prepared.
- Nine ω-(dialkylamino) alkyl-3-methyl-3-thianaphthyl sulfide hydrochlorides were prepared for the first time and characterized.
- 4. Two Q-(dialkylamino) alkyl-3-thianaphthyl sulfide hydrochlorides were synthesized for the first time and characterized.
- 5. Thianaphthene, 3-methylthianaphthene, and 2-methylthianaphthene were all subjected to the action of chlorosulfonic acid. A variety of products were obtained, some of which were partially characterized.
- The position of substitution in the thianaphthene nucleus during mono-chlorosulfonation of thianaphthene and 2-methylthianaphthene was established.
- The previously unreported 3,7-dimethylthianaphthene was prepared and its structure established.



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