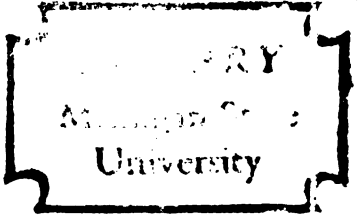
THE PREPARATION OF THE THIENOBENZO (B) THIOPHENES AND THE SYNTHESIS OF SOME W-(N, N-DIALKYLAMINO) ALKYL NAPHTHYL SULFIDES

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Edward Paul Dunigan

1961



THE PREPARATION OF SOME THIANAPHTHENO[2,3-b]THIOPHENES AND THE SYNTHESIS OF SOME ω-(N,N-DIALKYLAMINO) ARYL NAPHTHYL SULFIDES

By

EDWARD PAUL DUNIGAN

AN ABSTRACT OF A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

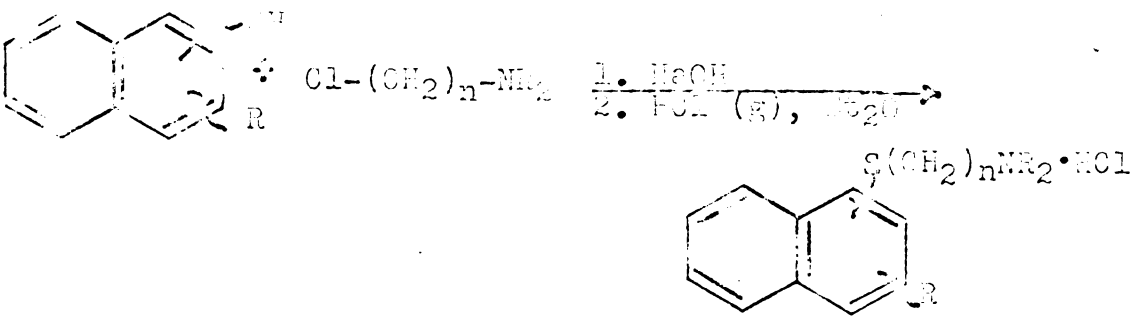
1961

...DUCTION

The work discussed here has been divi... into two parts. It is an investigation of synthetic routes l...ding to the thienobenzo[...]thiophene isomers and the pre...ration of some ω(N,N-disubstituted amino) alkyl naphthyl sul...des.

The thienobenzo[b]thiophene isomers were prepar... successfully by the synthetic route following the method of Tilak but could not be isolated by other attempted proc...dures.

The amine derivatives were prepared in a simple reaction involving heating the naphthalene halide with aminoalkyl chloride hydrochlorid... in an alkaline medium, at its reflux temperature, and isolating the products as their hydrochlor...de sal...



Twelve previously unreported compounds were prepared by this ...ethod.

THE PREPARATION OF THE THIENOBENZO[b]THIOPHENES AND THE SYNTHESIS OF SOME ω-(N,N-DIMETHYLAMINO)ALKYL NAPHTHYL SULFIDES

By

EDWARD PAUL DUNIGAN

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TABLE OF CONTENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

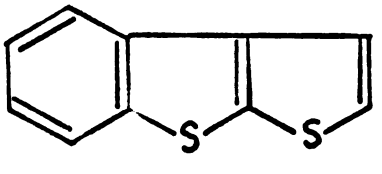
Benzo[b]thiophene has been known for somewhat over a half century, but aryl derivatives of it having a second thiophene ring fused to the molecule have had little reported on them in the chemical literature. The first part of this thesis deals with two attempts to prepare the thienobenzo[b]thiophene in fairly good yields.

The remainder of the work herein reported deals with the preparation of tertiary amine derivatives of α and β naphthalenethiols. Considerable work has been done on aryl or heterocyclic dialkylamino alkyl sulfides but none has been reported in which naphthalene is part of the molecule. A general investigation of such materials was started by Kim and Schuetz (1) when they observed that certain ω-(N,N-disubstituted amino)-alkyl-phenyl sulfides possessed local anesthetic properties. Epstein and Meyer (2), and Luduena and Hoppe (3) broadened this work to other types of compounds, all containing a tertiary amine group. Additional work has since been reported from these laboratories by Houff and Schuetz (4), Schuetz and Baldwin (5) and Heyd (6) on other possible anesthetic compounds of this general type.

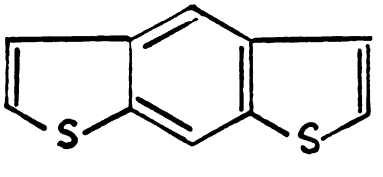
HISTORICAL

Lanfry (7) first claimed to have isolated a thienobenzo[b]thiophene isomer. In 1911, he reported the product obtained from the high temperature reaction of sulfur and naphthalene (iron tube) gave positive tests for a thiophene ring with isatin (indophenine test) and phenanthraquinone (Liebermann test). The material melted at 118.5° and on oxidation yielded a sulfone, $C_{10}H_6O_2S_2$ (m.p. 130°) and a disulfone, $C_{10}H_6O_4S_2$ (m.p.125°). It also formed a tetranitro derivative (m.p. 300°d) and a tetrabromide (m.p. 247-248°).

On these very limited data, he proposed two structures for this compound.



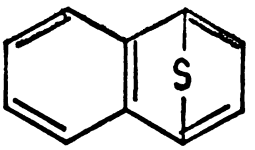
or



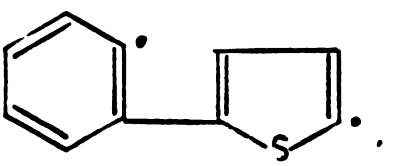
Hartough and Meisel (8) do not accept either structure since they claim that both of these compounds would require a drastic skeletal rearrangement of the naphthalene structure. They quote the work of Herzfelder (9) as contradictory evidence and propose a different structure.

Herzfelder treated 1-nitronaphthalene with sulfur under milder conditions to obtain a compound $C_{10}H_6S$ which

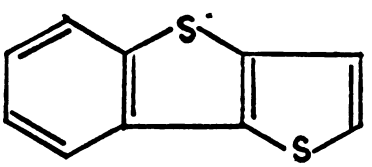
he assigned an endo formula.



Hartough and Meisel propose that if this material is initially formed, a second sulfur may attack either the 1-8a or the 4-4a carbon bond to yield an intermediate



which could react with an additional sulfur atom, with skeletal rearrangement to yield, not thieno[2,3-b]benzo[b]thiophene, but rather, its isomer, thieno[3,2-b]benzo[b]thiophene.



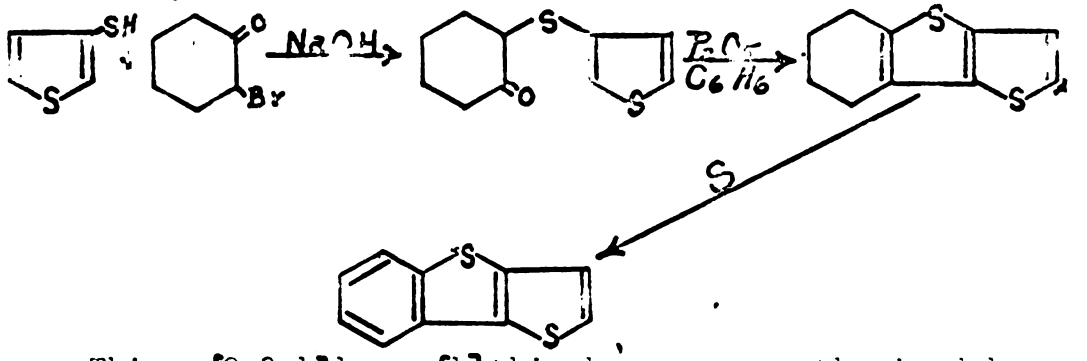
Interesting as this may be, it appears from the journals that little was done on these isomeric compounds until about six years ago when Tilak and co-workers, in India, undertook a study of the carcinogenesis of thiophene isosters of polycyclic hydrocarbons.

Most of this work has been published in the Indian journals and in abstract form in Chemical Abstracts. However, Tilak has published a summary article of this work in English (10).

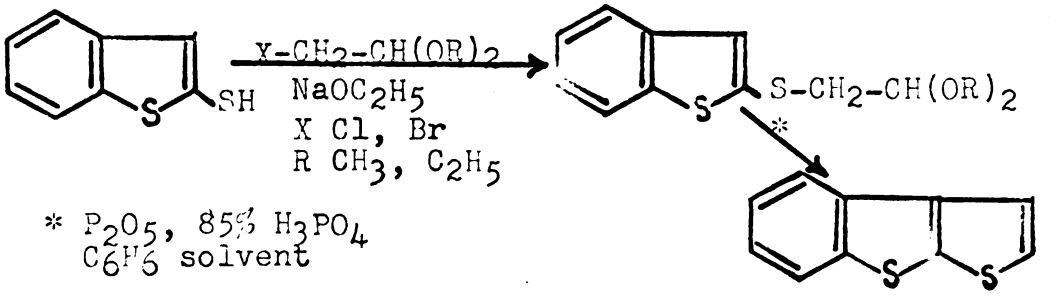
Tilak and co-workers (11, 12, 13) describe the

preparation of both isomers.

Thieno[3,2-b]benzo[b]thiophene was obtained by the reaction of 3-mercaptothiophene with 2-bromocyclohexanone, cyclodehydration and sulfur dehydrogenation to the aromatic structure.



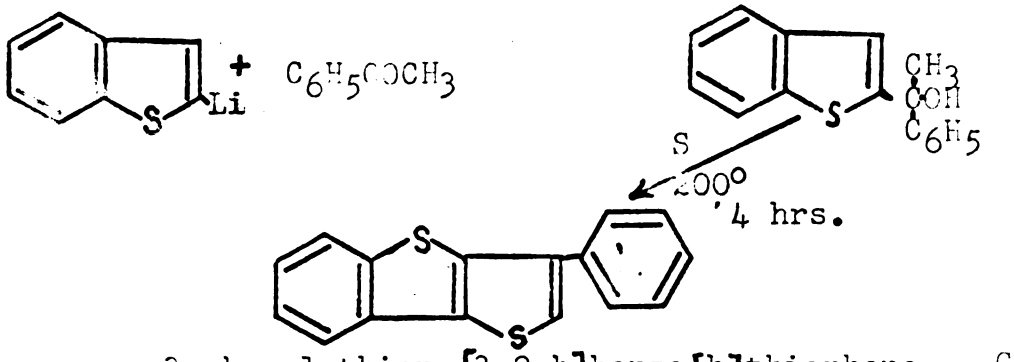
Thieno[2,3-b]benzo[b]thiophene was synthesized by the reaction of benzo[b]thiophene with n-butyl lithium, addition of sulfur and hydrolysis to the mercaptan, followed by interaction of the latter with a haloacetaldehyde dialkylacetal and subsequent ring closure with phosphorus pentoxide.



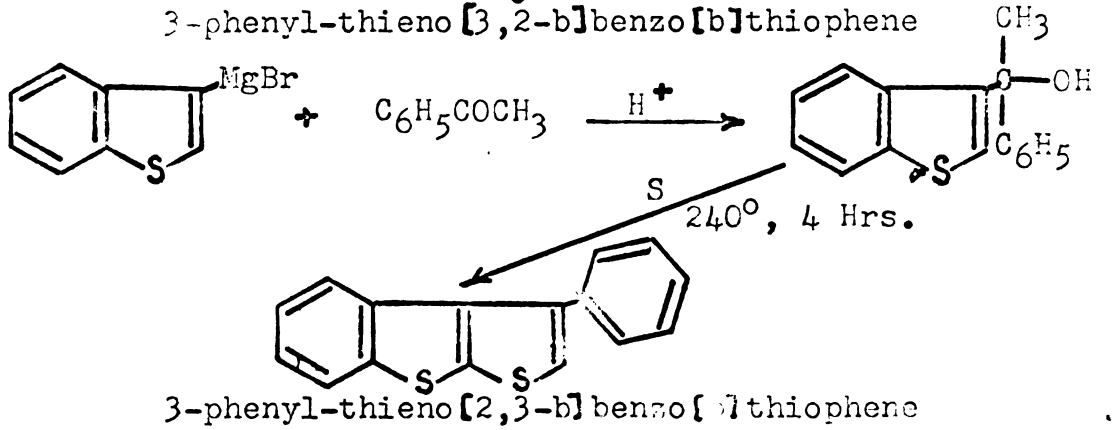
The work of Horton (14) on the mechanism of the reaction of sulfur with several hydrocarbons has led to the more recent work of Parham and Gadsby (15). They attempted to prepare thieno[2,3-b]benzo[b]thiophene by

the interaction of sulfur and 3-vinylbenzo[b]thiophene at moderately high temperatures. Distillation of the crude reaction mixture yielded a bright orange colored oil but chromatographic techniques gave only a series of oils.

However, they were able to prepare two phenyl substituted derivatives. Their work may be summarized in the following equations:

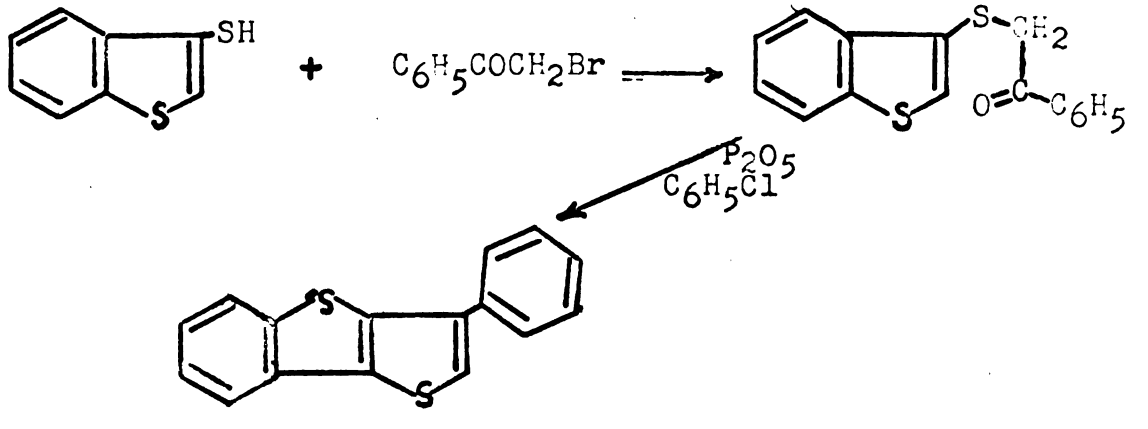


3-phenyl-thieno[3,2-b]benzo[b]thiophene



3-phenyl-thieno[2,3-b]benzo[b]thiophene

These structures were confirmed by the unequivocable synthesis of the two isomers.



PART II

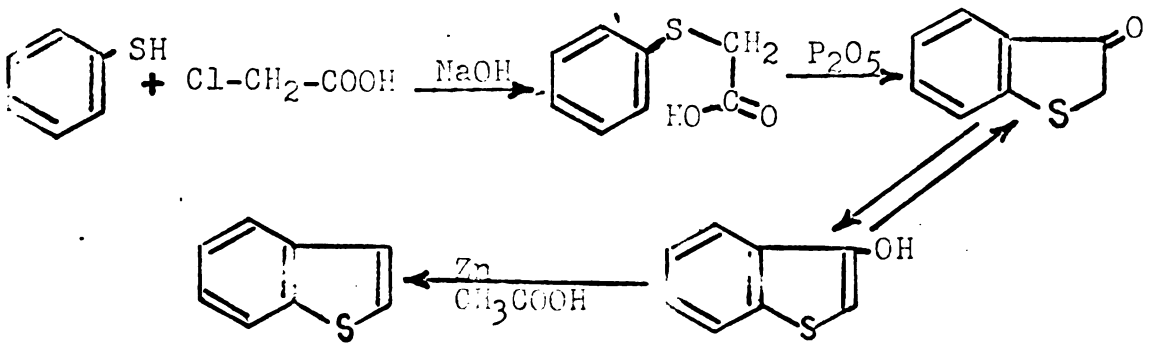
The historical background of tertiary amine hydrochloride derivatives of aromatic sulfides has already been exhaustively reviewed by Kim (16), Houff (17), Baldwin (18) and Heyd (6) in their respective theses.

The present author's work dealt with the preparation of tertiary amine hydrochloride derivatives of the naphthalenethiol series, and was mainly concerned with β-naphthalenethiol derivatives. However, α-piperidino, morpholino and dialkyl amino derivatives of α-naphthalenethiol were prepared in addition. Two cases of methoxy substituted naphthalene nuclei were also obtained with the aim of determining whether position substitution had an effect on the pharmacological activities of such materials.

The tertiary amines used in this work included β-piperidinoethyl, γ-piperidino-n-propyl, β-morpholinoethyl, γ-morpholino-n-propyl, α-methyl-β-dimethylaminoethyl, β-dimethylaminoethyl and β-diethylaminoethyl.

DISCUSSION

One of the purposes of the study described here was to prepare the two isomers of thienobenzo[b]thiophene from the readily available benzo[b]thiophene. One of the first methods considered feasible to investigate was the cyclic dehydration of the arylthioglycolic acid with phosphorus pentoxide to the corresponding cyclic alcohol. This could then be reduced to the unsubstituted compound, and is illustrated by the preparation of benzo[b]thiophene.



This method would involve the use of readily available materials and it was considered desirable to determine how easily, and under what conditions, the ring closure occurred.

The investigation was initiated with thiophenol as it appeared reasonable that useful conclusions could be drawn from this series as to its applicability to the benzo[b]thienylthiols synthesis.

Thiophenol was easily converted to phenylthioglycolic

acid by reacting it with a molar excess of chloroacetic acid in aqueous sodium hydroxide.

From that point on, however, results were negative in the attempted ring closure. Several different procedures were employed; refluxing a benzene solution of the acid with an eight to ten molar excess of phosphorus pentoxide yielded only a red colored oil as the product. Johns Manville Celite Analytical Filter Aid was added in an attempt to obtain a good suspension of the phosphorus pentoxide but this again gave the same red colored oil instead of the expected solid compound. The use of a higher boiling solvent, chlorobenzene, once again gave the same oily material.

In a final attempt, a benzene solution of the phenylthioglycolic acid was added slowly to a refluxing benzene, phosphorus pentoxide suspension but this too proved unsuccessful.

It was impossible toseparate any product by vacuum distillation indicating that none of the desired product had been formed since the three hydroxy compound boils low enough (95-100° at 1 mm.) to have been quite easily isolated. Attempted extraction with several different solvents failed to isolate any pure compound.

This preliminary work indicated that another method would have to be employed in the synthesis of the thieno-benzo[b]thiophenes.

Tilak (11, 12, 13) had previously prepared the two isomers by a relatively simple procedure. His method employed the benzo[b]thienylmercaptans as a starting material and since Heyd (6) had already studied the chemistry and preparation of these materials, it was a simple matter to obtain them.

Heyd used 3-iodobenzo[b]thiophene which he converted to the corresponding Grignard, reacted this with sulfur and hydrolyzed the product to the corresponding 3-benzo-[b]thienylmercaptan. This synthesis was employed on two occassions but was abandoned for the more easily prepared 3-bromobenzo[b]thiophene which could be converted to a Grignard reagent in almost as good yields as the iodo compound.

The yield of 3-benzo[b]thienylmercaptan was improved considerable over those of Heyd's by immediate distillation of the mercaptan following hydrolysis of the magnesium halide salt of the mercaptan. The halomagnesium salt was stored under nitrogen prior to hydrolysis to reduce to a minimum, oxidation of these salts to the corresponding disulfide.

The pure mercaptan could be stored in the dark (0°) for several hours with no apparent oxidation as indicated by its complete solubility in 15% potassium hydroxide.

Tilak reacted the 3-benzo[b]thienylmercaptan with bromoacetaldehyde dimethylacetal and obtained the expected 2,2-dimethoxyethyl-2-benzo[b]thienyl sulfide. Bromoacetaldehyde diethylacetal was used, because of its availability, in the first synthesis of the intermediate compound but chloroacetaldehyde diethylacetal was used successfully thereafter.

Initially, considerable experimental difficulty was encountered in attempting to purify the 2,2-diethoxyethyl-2-benzo[b]thienyl sulfide by distillation, even at very low pressures.

Fortunately, it was found that the desired heterocyclic could be prepared by refluxing the undistilled compound in a benzene solution of phosphorus pentoxide and 85% phosphoric acid. The crude product could be cleaned up easily by treating it with small quantities of norite while recrystallizing it from an isopropyl alcohol-water mixture. The purified compound had a melting point in agreement with that reported by Tilak for the same material.

The isomeric thieno[2,3-b]benzo[b]thiophene was also prepared using the procedure just described. The 2-benzo[b]thienylmercaptan was obtained as an unpleasant smelling

solid by preparing 2-benzo[b]thienyl lithium from benzo[b]thiophene and freshly prepared n-butyl lithium, adding sulfur to the ethereal solution of the organo lithium compound and hydrolyzing the lithium mercaptide to obtain the free mercaptan. It was not purified by recrystallization since Heyd(6) reports that it is readily air oxidized to the disulfide during recrystallization. It was recovered from the hydrolysis solution by filtration and dried in a dessicator under a nitrogen atmosphere. It was always checked for contamination by disulfide by its melting point before use, (the mercaptan melts about 70° lower than the disulfide) and its solubility in aqueous base.

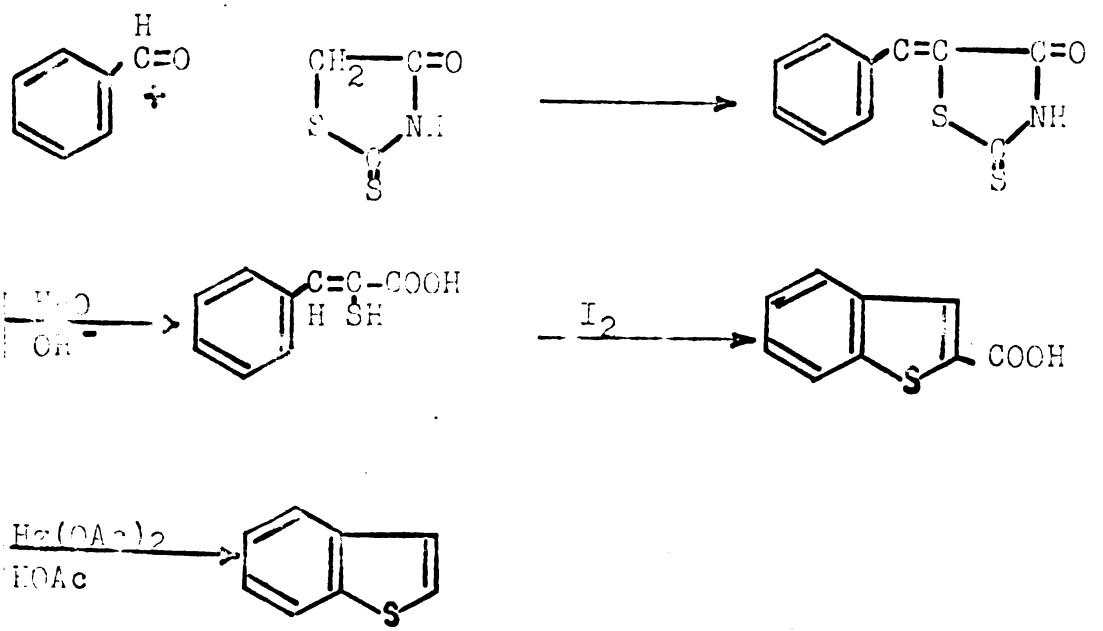
The mercaptan was converted to the acetal and cyclized to thieno[2,3-b]benzo[b]thiophene with phosphorus pentoxide and 85% phosphoric acid in boiling benzene. This isomer was more difficult to purify as only an oil was initially isolated on removal of the ether from the combined ether extracts. It could not be induced to crystallize nor could it be distilled (vacuo). However, it was isolated by extraction of the oil with boiling methanol and treatment of the latter with small quantities of norite.

Banfield (19) reported some work on the ring closures of arylthioacetaldehyde diethylacetals. In his work,

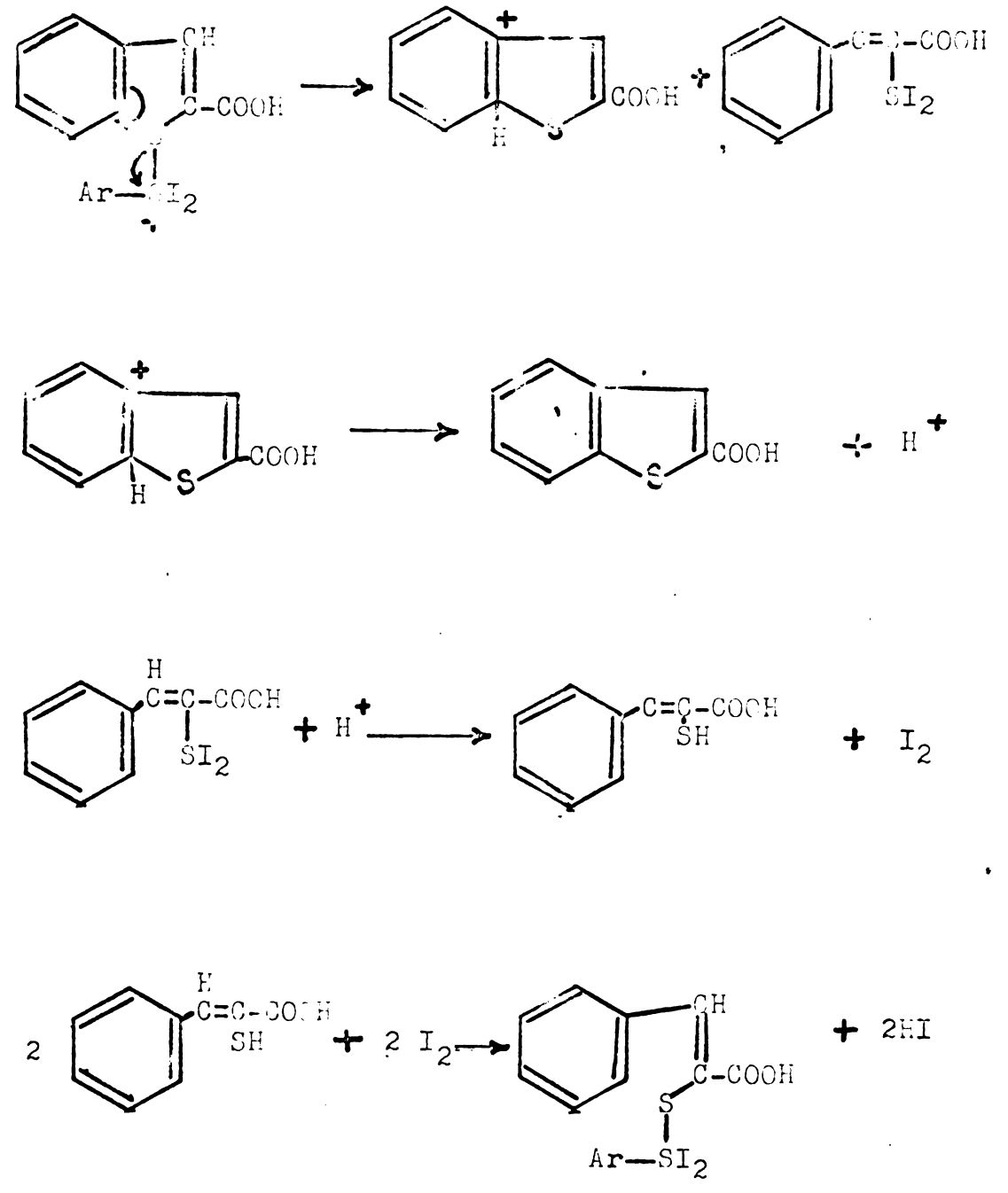
he cyclized naphtho[2,3-b]thiophene in 92% yield from 2-naphthylthioacetaldehyde diethylacetal using anhydrous stannic chloride as their reagent.

This method, when applied to the benzo[b]thienyl-thioacetaldehyde diethylacetal somers gave thieno[3,2-b] benzo[b]thiophene in a very pure state. However, the [2,3-b]isomer could not be isolated using the same procedure.

Campaigne (20,21) reported the preparation of several condensed thiophenes by the ring closures of some β-aryl-α-mercaptoacrylic acids and their related disulfides. In this work they condensed several aromatic aldehydes with rhodanine, hydrolyzed the rhodanine derivatives with dilute base to their respective β-aryl-α-mercaptoacrylic acids and then oxidized the latter with iodine to a fused thiophene ring compound.



The authors suggest the following mechanism for this reaction.



Campaigne supported the disulfide intermediate by ring closure reactions of both the α-mercapto acids and some of their related disulfides. Iodine, was in the main, used as the oxidizing agent for both the direct ring closure and conversion to the disulfide. Solvents and reaction conditions varied greatly. Iodine in ethanol at room temperature (14 hrs.) oxidized 5-phenyl-2-mercapto-2-4-pentadienoic acid to 5-phenyl-2-thenoic acid. Naphtho[1,2-b]thiophene-2-carboxylic acid was isolated in 60% yield by treating β-2-naphthyl-α-mercaptoacrylic acid with iodine in dioxane at 50° (24 hrs.). When the disulfide was used in the ring closure, the final product was isolated in 90% yield in a 50% longer reaction period.

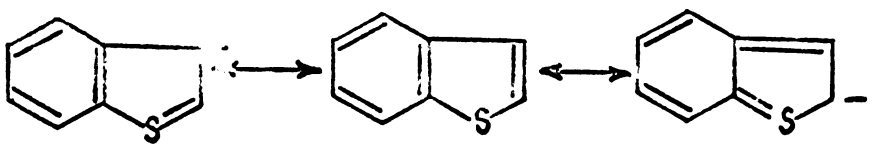
Rather vigorous conditions were used to synthesize benzo[b]thiophene-2-carboxylic acid. An iodine-nitrobenzene solution was heated to just below its boiling point (210.5°) prior to adding the α-mercaptocinnamic acid. A very short reaction time (1 min.) was used to obtain the product in 68% yield. Decarboxylation of the acid with mercuric acetate in glacial acetic acid gave a 16% yield of benzo[b]thiophene.

These procedures appeared to be applicable to the preparation of thienobenzo[b]thiophenes starting with

the appropriate aldehydes. The 2-benzo[b]thienylaldehyde was easily prepared by reacting 2-benzo[b]thienyllithium with N-methylformanilide. The aldehyde was converted easily to the high melting rhodanine derivative in 84.4% yield. The rhodanine derivative was hydrolyzed to α-mercapto-β-benzo[b]thienylacrylic acid in 62.5% yield.

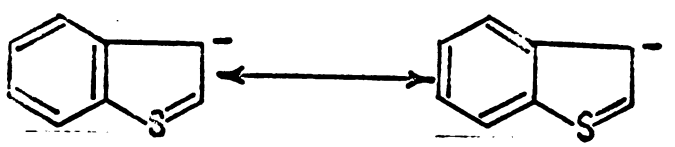
The acid was recrystallized with difficulty only from chloroform and was obtained as a powdery yellow colored solid, which was analyzed as its 2-4-dinitrophenyl derivative. Campaigne reported similar difficulties in the recrystallization of the α-mercapto carboxylic acids.

Hartough (8) states that resonance considerations of the benzo[b]thiophene system predicts that electrophilic substitution should occur preferentially in the 3 position.



(II) (I) (III)

Formation of III requires a resonance interaction between the benzene and the heterocyclic ring which is not necessary for the formation of II, resulting in two ionic forms with a negative charge in the 3 position,



while the 2 anion can have only a single form.

These resonance considerations suggested that perhaps the thieno[3,2-b]thiophene-2-carboxylic acid could be closed under much milder conditions than the benzo[b]thiophene-2-carboxylic acid.

Consequently, the first attempted ring closure reactions were done in absolute ethanol at room temperature using iodine as the oxidizing agent. This procedure, however, resulted in only base insoluble material being isolated.

Next, iodine was used in hot dioxane (steam bath) as the ring closure media, but again only base insoluble material was isolated.

The high temperature (200°) use of nitrobenzene and iodine again yielded no cyclization product.

Since Campaigne had shown that the mechanism involved a disulfide intermediate, it was considered best to attempt to prepare the disulfide of the benzo[b] thiophene unsaturated acid first and then to proceed with the ring closure. Treatment of the mercapto acid with iodine in absolute ethanol at temperatures between -15 to 0° failed to yield any disulfide.

Following these failures, an attempt was made to find a more efficient oxidizing agent which would selectively

convert the free mercaptan to its disulfide without oxidatively attacking the side chain.

It was anticipated that bromine might accomplish this task well but it would be best to first compare it with Campaigne's work with iodine and benzo[b]thiophene-2-carboxylic acid.

α-Mercaptocinnamic acid was prepared by hydrolyzing the condensation product of benzaldehyde and rhodanine. The iodine oxidation proceeded smoothly to the disulfide as reported by Campaigne. When bromine was used, the disulfide was formed in 92% yield. A mixture melting point of the two disulfides obtained by the iodine and bromine oxidations was identical.

This initial success led to an attempt to prepare the benzo[b]thiophene-2-carboxylic acid directly from the substituted cinnamic acid using bromine in place of the iodine, conducting the cyclization reaction in nitrobenzene.

More difficulty was encountered with bromine in reaching the higher temperature and severe spattering of the bromine-nitrobenzene mixture forced the addition of the α-mercaptocinnamic acid at 165°. The melting point and unsaturation tests on material obtained in this reaction indicated that although some desired

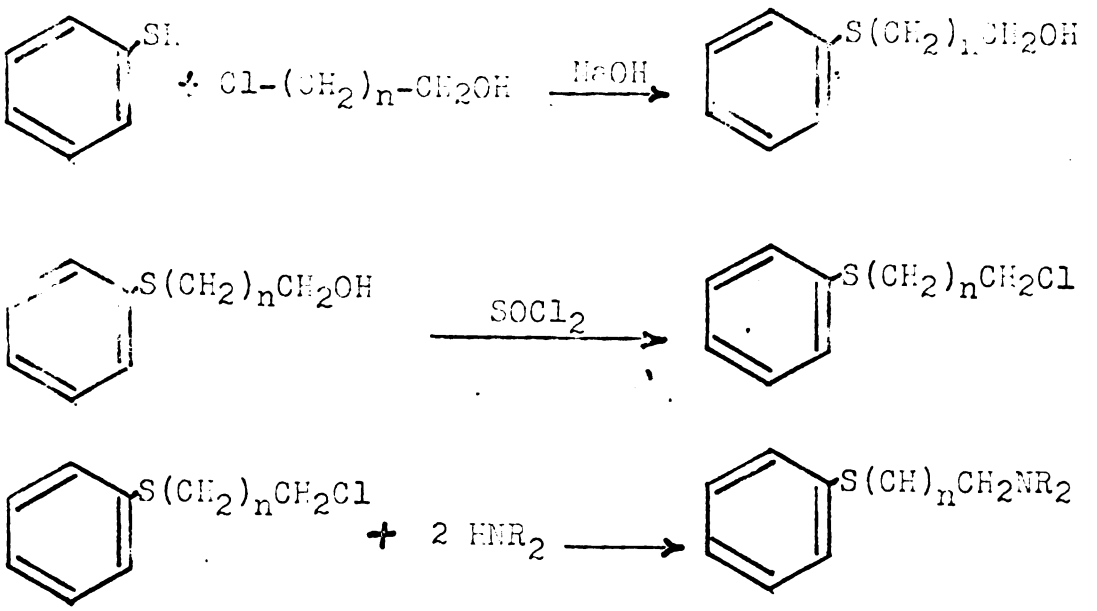
product had been formed, it did not compare favorably with that obtained by iodine oxidative cyclization.

Since the bromine oxidation of α-mercaptocinnamic acid to the disulfide had proceeded smoothly and in high yield, it was used in absolute ethanol to attempt to oxidize α-mercapto-β-2-benzo[b]thienylacrylic acid to its disulfide, but without success.

At this juncture the investigation to develop new synthetic procedures to obtain thienobenzo[b]thiophenes was discontinued.

PART II

There are two methods for preparing ω-(N,N di-substituted amino) aryl sulfides. Kim (1) used a method which can be summarized as follows.



This method suffered from several disadvantages. The ω-hydroxy compounds were easily prepared from the corresponding chlorohydrins but conversion of these to their ω-chloro compounds always had to be carried out under carefully controlled temperatures or considerable tarry material was formed. Reaction of the omega chloroalkyl phenyl sulfide with secondary amines usually resulted in low yields and it was often necessary to carry these reactions out in sealed tubes at elevated temperatures.

Despite the general procedures shortcomings, a few ω-hydroxyalkyl naphthyl sulfides were prepared to ascertain whether the yields obtainable would compare favorably

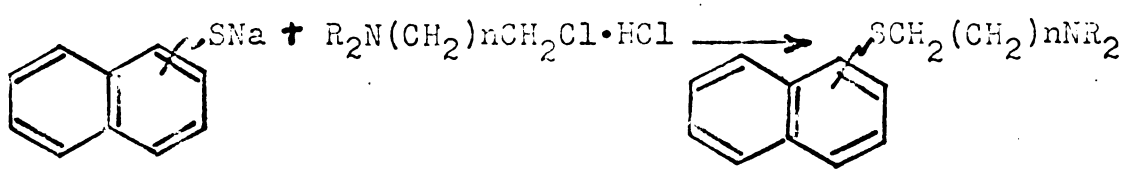
with those reported for the lower molecular weight aromatics. Further, a literature search revealed that β(β' thionaphthoxy) ethyl alcohol was the only compound of this homologous series that had been reported. The n-propyl and iso-propyl alcohols were prepared and characterized in the present study.

An attempt to convert β-naphthyl-γ-hydroxy propyl sulfide to its corresponding chloride with thionyl chloride revealed clearly the difficulties reported in such preparations and urged immediate abandonment of this general approach since it depended on the intermediate chlorides. Further, previous work in these laboratories had made available a good number of ω-(N,N dialkylamino) alkyl halides for an alternate procedure.

The second method for the synthesis of disubstituted amino alkyl naphthyl sulfides involves the interaction of a ω-chloro tertiary amine hydrochloride with the sodium salt of the thiol compound.

$$R_2NH + Cl(CH_2)nCH_2OH \longrightarrow R_2N(CH_2)nCH_2OH$$

$$R_2N(CH_2)nCH_2OH \xrightarrow{SOCl_2} R_2NCH_2)nCH_2Cl \cdot HCl$$

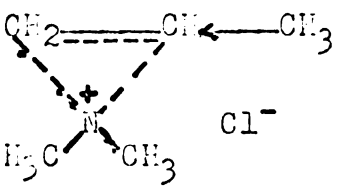


This latter general method was the one employed in the present study to obtain the ω-(N,N disubstituted amino) alkyl naphthyl sulfides.

β-Naphthalenethiol was prepared quantitatively by the reduction of β-naphthalenesulfonyl chloride, and some of it was purchased from commercial sources.

Table I summarizes the several tertiary amines substituted for the hydrogen of the sulfhydryl group. The amino sulfides were isolated as their hydrochlorides and were all recrystallized from dry isopropyl alcohol with the exception of the piperidinoethyl compound which was recrystallized from absolute ethanol.

The structure of the dimethylamino-isopropyl naphthyl sulfide was not definitely established. Baldwin(18) has reviewed the possibility of an intramolecular displacement reaction or ionization resulting from neighboring group participation of the nitrogen to form a cyclic onium salt in nucleophilic substitution involving β-dialkylamino-α-alkylethyl halides. Such an intermediate



on a bimolecular attack by naphthyl sulfide ions would probably give a rearranged product, while if the initial

step in product formation was the ionization of the cyclic ethylene imonium ion, the most thermodynamically stable product would predominate. Two cases of the interaction of β-naphthalenethiol and β-dimethylamino-β-methyl ethyl chloride gave one product which recrystallized very easily, melted sharply and analyzed correctly indicating a single isomer had resulted.

The preparation of the α-naphthalenethiol presented some difficulties. Several methods were attempted but all were abandoned in favor of the procedure involving the reaction of sulfur with an α-naphthalene Grignard reagent, followed by hydrolysis, steam distillation and purification of the arylthiol by distillation in vacuo. Even this procedure resulted in low yields of the thiol with an extremely unpleasant smelling residue remaining after the distillation when steam distillation was not employed first.

Three amino sulfides were prepared from α-naphthalene-thiol and are summarized in Table II.

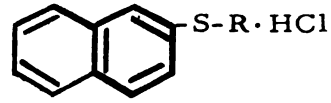
From a synthetic point, perhaps the most interesting compound prepared was α-mercapto-β-methoxynaphthalene, since it involved the preparation of α-thiocyano-β-methoxy-naphthalene as an intermediate. Kaufmann (22) prepared this latter material from β-methoxynaphthalene and a solution

of the free thiocyanogen. A few years later, he reported that several thiocyanate compounds could be synthesized by liberating the thiocyanogen with bromine from the sodium salt directly in the reaction mixture. He had previously established that thiocyanogen united with unsaturated compounds with an activity between bromine and iodine. He explained the bromine liberated thiocyanogen substitution reaction in the following manner (23).

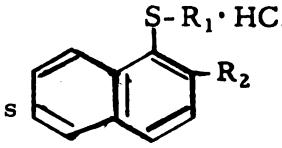
If aniline, for example, in a strongly acidic solution containing sodium thiocyanate, is treated in the cold with bromine, the reaction $2NaSCN + Br_2 \longrightarrow 2NaBr + (SCN)_2$, being ionic, proceeds so rapidly that the reaction $C_6H_5NH_2 + Br_2 \longrightarrow BrC_6H_4NH_2 \cdot HBr$ is negligible if an excess of sodium thiocyanate is used. The hydrolysis reaction, $3(SCN)_2 + 4H_2O \longrightarrow 5HSCN + H_2SO_4 + HCN$ is greatly retarded in the presence of the acid and the same is true of the polymerization so that under those conditions the $p\text{-}NCSC_6H_4NH_2$ is formed.

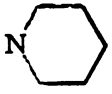
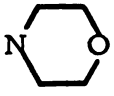
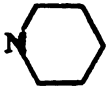
The α-mercapto-β-methoxynaphthalene compound was prepared by forming thiocyanogen in a glacial acetic acid solution of β-methoxynaphthalene. The product was recovered by filtration and after drying its melting point was 30° lower than reported in the literature (22, 24). An infrared spectrum of this material indicated both an α, β substituted naphthalene structure and a free sulfhydryl

group. Analysis of the material based on a mercapto-methoxynaphthalene structure, for carbon, hydrogen and sulfur showed agreement within 0.2%. From this data it was concluded that Kaufmann's reported melting point of 98° is incorrect and that the true melting point of α-mercapto-β-methoxynaphthalene is 68°.

Table I--ω(N, N-Dialkylamino)alkyl-β-naphthy sulfide hydrochlorides 

R	M.P. °C	Formula	Carbon %		Hydrogen %		Sulfur %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
-CH_2-CH_2-N⟨⟩	205	$C_{17}H_{22}ClNS$	66.32	66.36	7.20	7.03	10.42	10.44
-CH_2-CH_2-CH_2-N⟨⟩	148	$C_{18}H_{24}ClNS$	67.16	67.18	7.52	7.52	9.96	9.80
-CH_2-CH_2-N⟨O⟩	151-152	$C_{16}H_2ClNOS$	61.62	63.29	6.46	6.34	10.28	10.40
-CH_2-CH_2-CH_2-N⟨O⟩	189.5-190	$C_{17}H_{22}ClNOS$	63.04	62.82	6.85	6.78	9.90	9.60
-CH_2-CH-$N(CH_3)_2$ CH_3	149	$C_{15}H_{20}\cdot ClNS$	63.92	64.05	7.15	7.14	11.38	11.38
-CH_2-CH_2-$N(CH_3)_2$	151	$C_{14}H_{18}ClNS$	62.78	62.53	6.77	6.68	11.97	12.09
-CH_2-CH_2-$N(C_2H_5)_2$	147	$C_{16}H_{22}ClNS$	64.95	64.82	7.50	7.49	10.84	10.61

Table II--ω(N, N-Dialkylamino)alkyl-α-napthyl sulfide hydrochlorides 

R_1	R_2	M.P. °C.	Formula	Carbon %		Hydrogen %		Sulfur %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
$-CH_2-CH_2-N$ 	H	183.5	$C_{17}H_{22}ClNS$	66.32	66.26	7.20	7.32	10.42	10.19
$-CH_2-CH_2-CH_2-N$ 	H	157-157.5	$C_{17}H_{22}ClNOS$	63.04	63.01	6.85	6.98	9.90	9.75
$-CH_2-CH_2-N$ 	$-OCH_3$	184.75	$C_{18}H_{24}ClNOS$	63.97	64.09	7.15	7.07	9.48	9.43
$-CH_2-CH_2-C(C_2H_5)$	H	144.5-145	$C_{16}H_{22}ClNS$	64.95	62.47	7.50	7.30	10.84	10.66
$-CH_2-CH_2-N(C_2H_5)$	$-OCH_3$	138	$C_{17}H_{24}ClNOS$	62.65	62.51	7.42	7.37	9.84	9.91

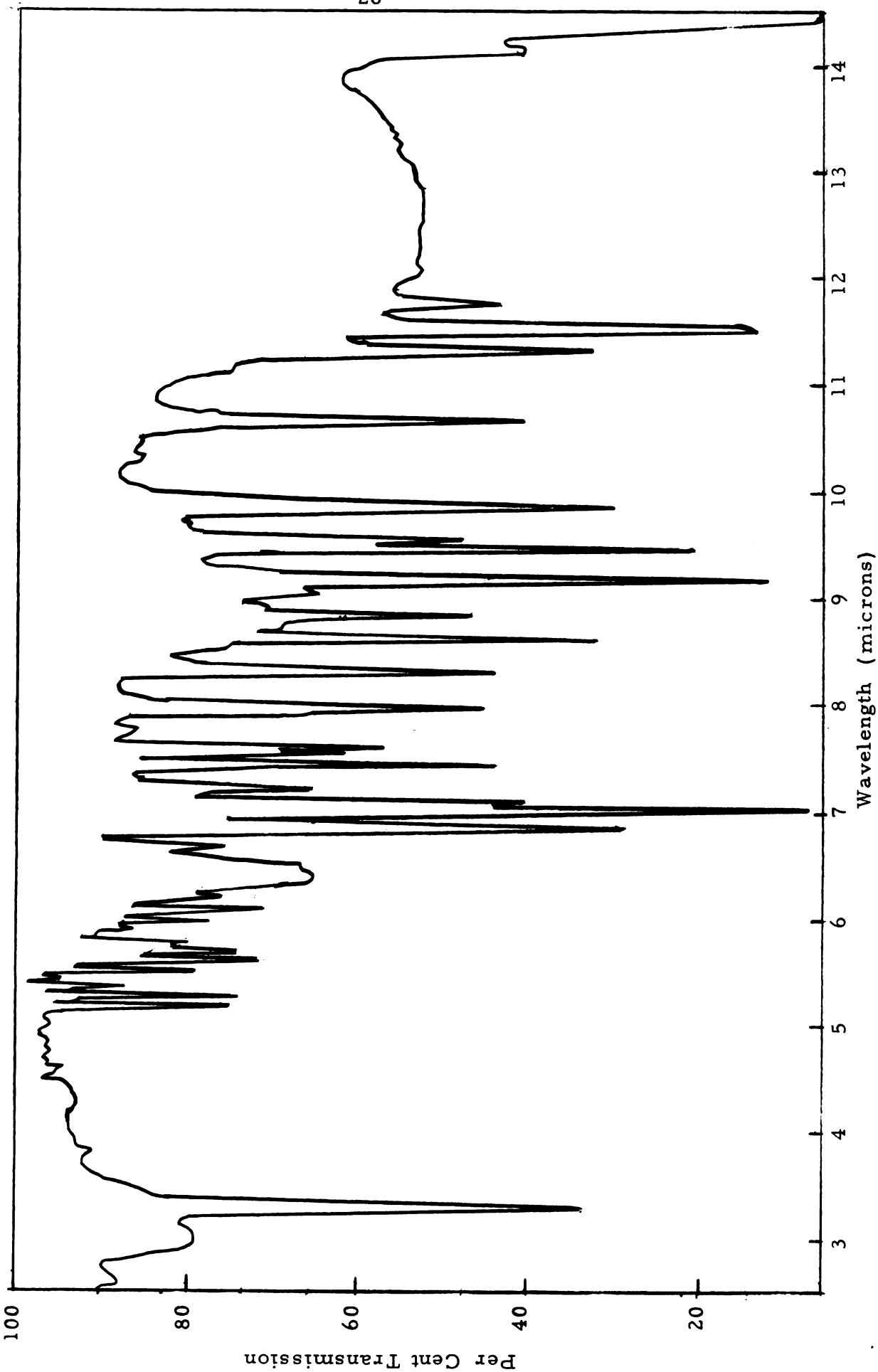


Figure 1. Infrared spectrum of benzo[b]thiophene (CCl_4 solution).

Figure 2. Infrared spectrum of thieno[2, 3-b]benzo[b]thiophene (CCl_4 solution).

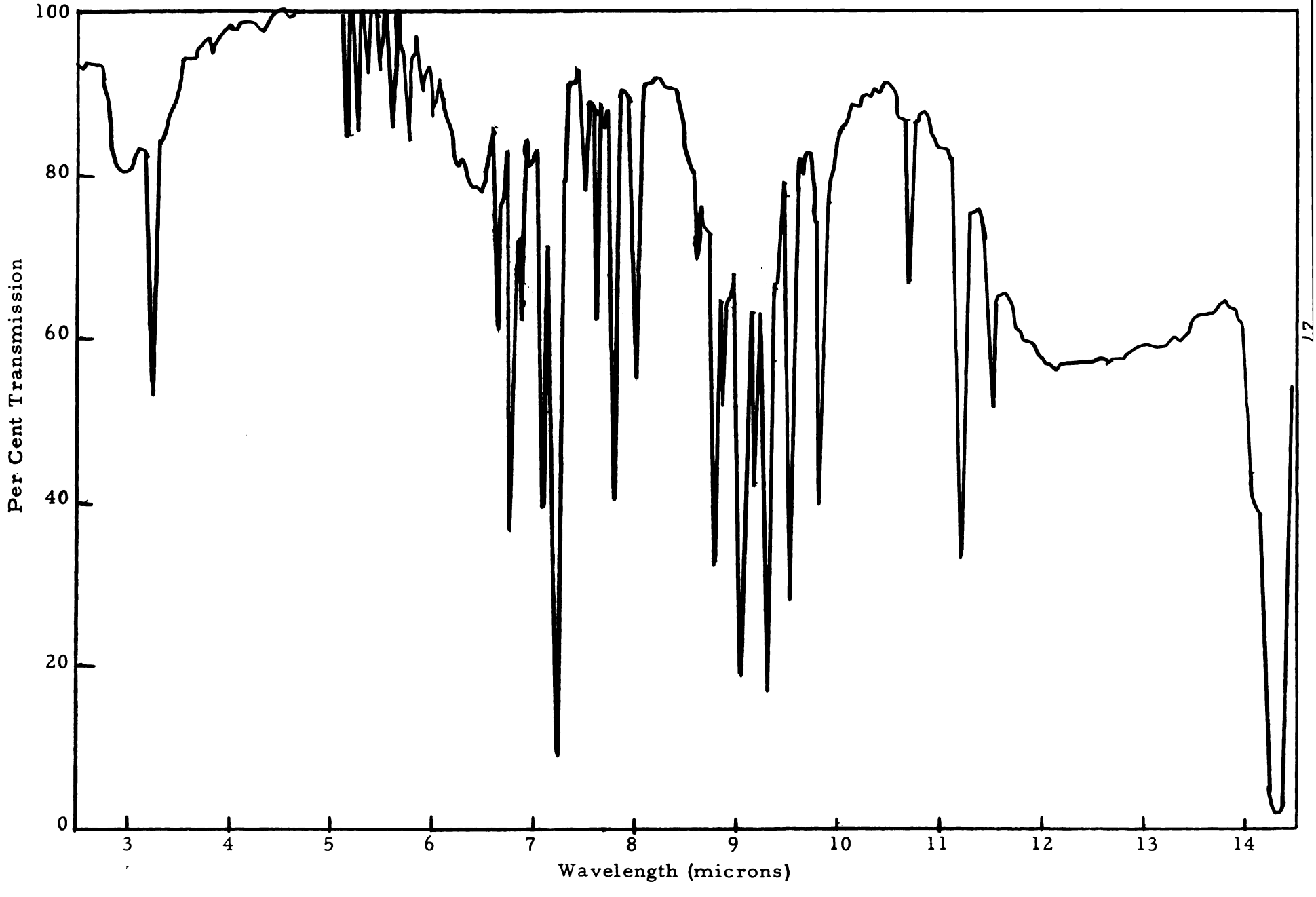
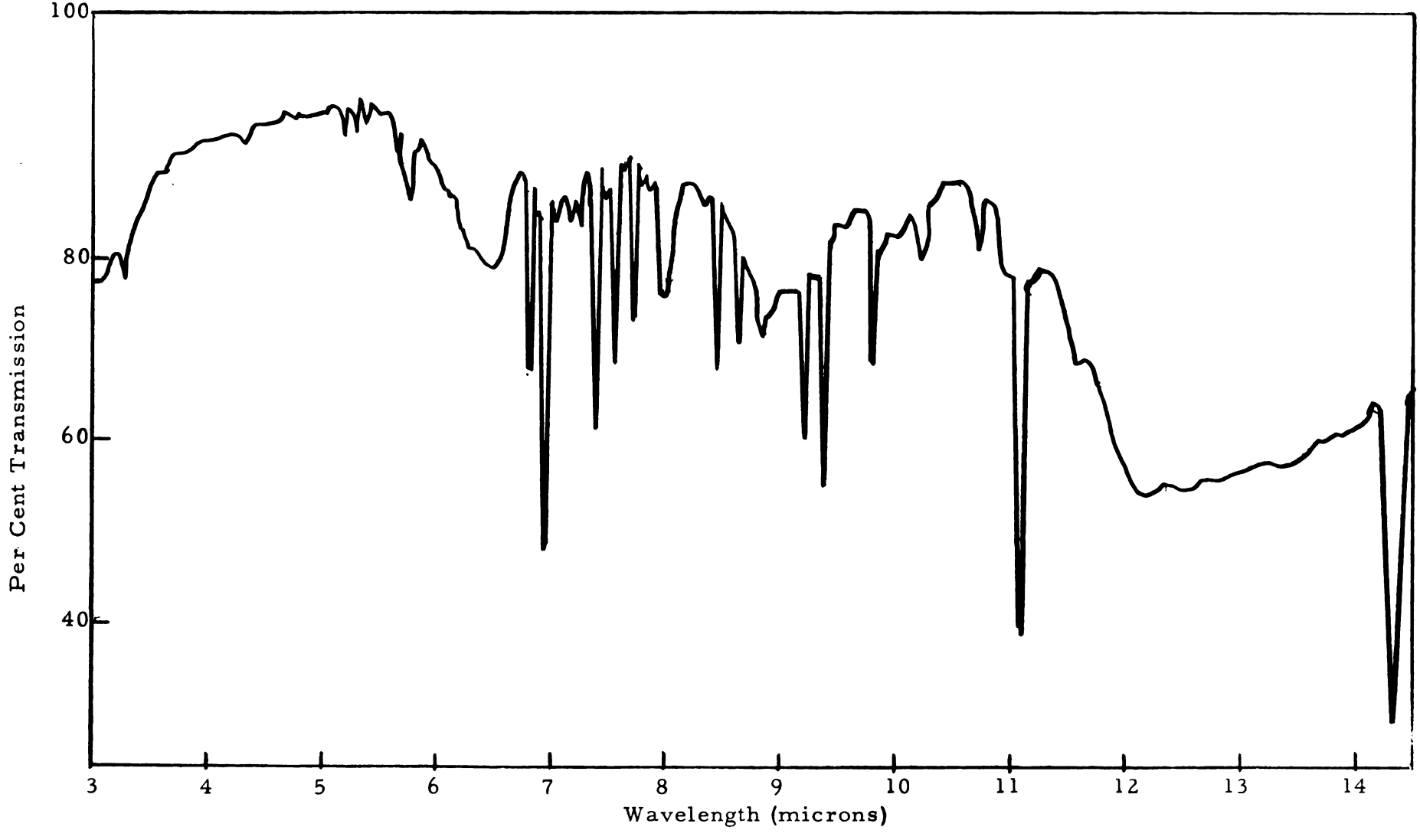
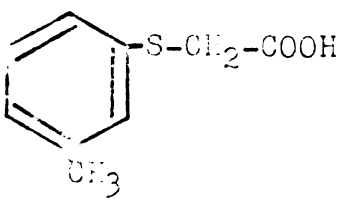


Figure 3. Infrared spectrum of thieno[3, 2-b]benzo[b]thiophene (CCl_4 solution).



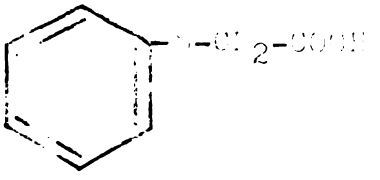
EXPERIMENTAL

m-Thiocresoxyacetic acid



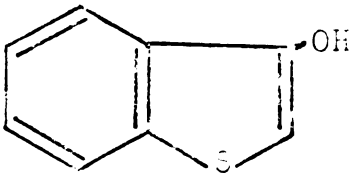
To a stirred, warm solution containing 10 g. (0.08 mole) of m-thiocresol dissolved in 50 ml. of 33% aqueous NaOH solution, was added slowly, 15 g. (0.16 mole) of chloroacetic acid. The reaction mixture was warmed on the steam bath for an hour, cooled, strongly acidified with 6 M H_2SO_4 and extracted twice with ether. The combined etheral extracts were in turn extracted with two portions of 5 % aqueous Na_2CO_3 solution. The basic solution was acidified with 6 M H_2SO_4 and cooled (ice bath) to precipitate the product. Recrystallization from petroleum ether (30 - 60°) gave 11.7 g. (0.057 mole, 71%) of the product melting at 66-68°. Literature value, m.p. 67.5-68° (25).

Phenylthioglycolic acid



Following the previously described procedure, 11 g. (0.1 mole) of thiophenol was dissolved in dilute alkali and 18.5 g. (0.2 mole) of chloroacetic acid was added. Isolation of the product yielded 17.2 g. (0.095 mole, 95%) which after recrystallization from hot water melted at 63°. Literature value, m.p. 61-62° (26).

3-Hydroxybenzo[b]thiophene



Attempted Preparations

A. In a one liter two necked flask equipped with a condenser and Hershberg wire paddle stirrer, was placed 4.5 g. (0.0268 mole) of phenylthioglycolic acid dissolved in 100 ml. of dry benzene. To the latter solution was added with stirring, 30 g. (0.211 mole) of P_2O_5, causing a yellow coloration to develope in the solution. The reaction flask was heated, during 1.5 hrs., in an oil bath to 80° and was maintained at that temperature for another

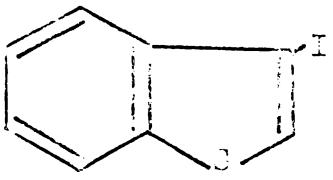
1.5 hrs. After cooling to room temperature, the reaction mixture was filtered and the P_2O_5 washed several times with dry benzene. The combined benzene fractions were evaporated in vacuo to obtain two ml. of a deep red colored oil from which no pure compound could be isolated.

B. The above reaction was repeated with the following modifications:

A 10 g. (0.0595 mole) quantity of phenyl thioglycolic acid and 30 g. (0.211 mole) of P_2O_5 were added to 200 ml. of dry chlorobenzene. To this mixture was added 15 g. of "Johns Manville Celite Analytical Filter Aid" to suspend the P_2O_5 in the reaction medium. The reaction mixture was heated at 132° for 4.0 hrs., cooled to room temperature, and filtered. The P_2O_5-Celite slurry was washed several times with chlorobenzene and these washings were added to the reaction solution. The solvent was removed by heating the mixture on a steam bath while directing a stream of dry air into the beaker to prevent foaming. Approximately 20 ml. of a viscous, red colored oil remained as a residue, which could not be crystallized, distilled, nor extracted with pentane or hot water.

C. A final attempt was made to prepare the hydroxybenzo[b]thiophene by adding the phenylthioglycolic acid dissolved in 75 ml. of benzene to a refluxing solution of benzene-celite-P_2O_5. This procedure lead to results very similar to those just described.

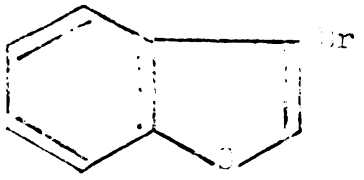
3-Iodobenzo[b]thiophene



In a 500 ml. three necked flask equipped with mechanical stirrer and reflux condenser, was placed 100 ml. of sodium dried benzene and 50 g. (0.37 mole) of benzo[b]thiophene dissolved in an additional 75 ml. of benzene. The stirred solution was heated to 50-55° (oil bath) and 68 g. (0.27 mole) of mercuric oxide and 95 g. (0.38 mole) of iodine were added gradually, in alternate portions, during 70 minutes. The reaction mixture was stirred for an additional 2 hrs., cooled to room temperature, filtered and treated with three 100-ml. portions of saturated sodium thiosulfate (to destroy the unreacted iodine). The red colored benzene solution was poured through a column (3"X2") filled with 1.5 lbs. of alumina (acid free). The column was eluted with benzene and the first golden-yellow colored fraction was collected as a pure benzene solution of the 3-iodobenzo[b]thiophene.

The benzene was removed in a Rinco rotary to obtain a golden orange colored oil which on distillation in vacuo gave a product boiling at 96-104° at 2 mm. Literature value, b.p. 120-121° at 1.6 mm. (27).

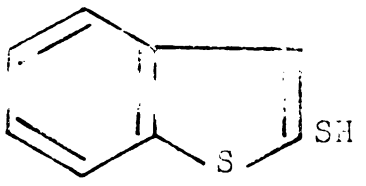
3-Bromobenzo[b]thiophene



In a two liter three necked flask equipped with mechanical stirrer, dropping funnel, reflux condenser (with drying tube) and thermometer was placed 360 ml. of dry chloroform containing 71.9 g. (0.536 mole) of benzo[b]thiophene and 71.0 g. (0.832 mole) of anhydrous sodium acetate. Bromine, 87.3 g. (0.546 mole) dissolved in 70 ml. of chloroform was added during 50 minutes, keeping the reaction temperature between 20-26° by external cooling. During the next hour, the stirred reaction mixture took on a cream coloration and became quite thick, necessitating the addition of 100 ml. of distilled water to dissolve inorganic salts. The mixture was transferred to a separatory funnel and extracted with chloroform. The chloroform layer was separated, washed with 200 ml. of water, twice with 100-ml. portions of 5% aqueous NaOH, again with 200 ml. of water and finally with 200 ml. of saturated sodium chloride after which it was filter through anhydrous sodium sulfate. The solvent was removed in a rotary evaporator and the residue was distilled in vacuo

to obtain the product boiling at 95-102°/1.5 mm. Literature value, b.p. 90-106°/1.5 mm. (28).

2-Mercaptobenzo[b]thiophene



In a 500 ml. flask equipped with mechanical stirrer and two 2 necked adapters (one fitted with a nitrogen gas inlet and low temperature thermometer; the other with a dropping funnel and bulb condenser), was placed (after sweeping the apparatus with nitrogen gas) 100 ml. of sodium dried ether and 4.5 g. (0.65 mole) of lithium metal.

The dropping funnel was charged with 41.1 g. (0.3 mole) of previously redistilled n-butyl bromide dissolved in 60 ml. of dry ether.

The reaction was initiated by adding a few ml of the etheral n-butyl bromide solution and at the first turbidity, the reaction flask was immersed in a dry ice-isopropyl alcohol bath. Addition of the n-butyl bromide was continued at a rate sufficient to maintain a reaction temperature of -10°. The reaction was completed by

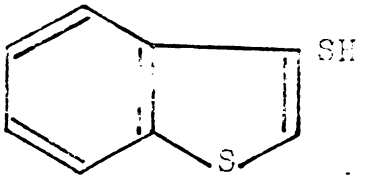
stirring at -10° for 1.25 hrs. following the addition of the allyl bromide. The n-butyl lithium solution was filtered directly, by means of a dry trapped water aspirator, into a 500 ml. flask presweot with nitrogen and cooled in a dry ice-isopropyl alcohol bath. The flask was equipped with a straight vacuum takeoff and a piece of glass tubing with a sintered glass end. The latter was connected by teflon tubing to a 90° standard taper takeoff stopcock, which had been plugged with glass wool. The 500 ml. flask was equipped similar to the initial one described above while its contents were kept cold.

To the stirred ethereal solution of n-butyl lithium was added 26.8 g. (0.2 mole) of benzo[b]thiophene dissolved in 50 ml. of dry ether during 0.33 hrs. The reaction mixture was stirred for an additional 1.5 hrs. and then refluxed for another half hour.

It was then recooled to -10° and, while the reaction flask was being swept with nitrogen gas, the dropping funnel was removed and 6.7 g. (0.21 g. atoms) of finely powdered sulfur was added in small portions causing spontaneous refluxing of the reaction mixture to occur. After stirring the lithium sulfide solution for a short time (10 min.), external cooling was removed and it was heated at its reflux temperature for an hour. The solution was transferred to a liter beaker, cooled (ice bath) and

hydrolyzed with 200 ml. of 2 N HCl. The yellow ether layer was separated, extracted with 100 ml. of 15% NaOH and carefully acidified (congo red paper) with 2 N HCl. A brown colored oil separated and, upon continued stirring and cooling, solidified to an unpleasant smelling solid. The latter was recovered by filtration and dried under a nitrogen atmosphere. The product, without further purification, melted at 40-42° and was completely soluble in 15% NaOH. Literature value, m.p. 41-43 (29, 6)

3-Mercaptobenzo[b]thiophene



In a one liter flask equipped with a mechanical stirrer, condenser (with drying tube), dropping funnel and nitrogen gas inlet, was placed 9.7 g. (0.4 mole) of magnesium chips and 50 ml. of dry ether. To this was added dropwise, over 1.5 hrs., 98.9 g. (0.38 mole) of 3-iodobenzo[b]thiophene dissolved in 75 ml. of ether. A crystal of iodine was added to initiate the reaction. After adding the heterocyclic iodide, the reaction mixture was refluxed for 2 hrs. at which point a considerable

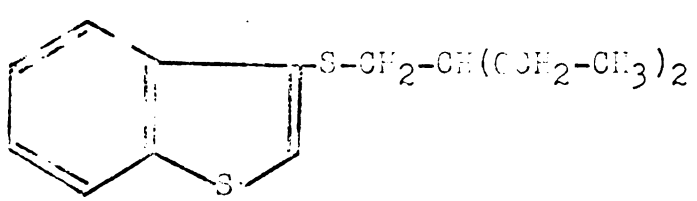
amount of magnesium still remained. After cooling the Grignard solution to room temperature, 12.16 g. (0.38 g. atom) of sulfur was added in small portions to control the exothermic reaction. The halomagnesium sulfide solution was heated at its reflux temperature for 7.5 hrs., and stored overnight under a nitrogen atmosphere. Hydrolysis of the Grignard complex was done with 350 ml. of 3 N HCl. The ethereal layer was separated, extracted twice with two 150-ml. portions of 15% KOH and these were combined and acidified (congo red paper) with 3 N HCl causing a dark colored oil to separate from solution. The latter was taken up in ether, dried over magnesium sulfate and the ether was removed in a rotary evaporator. The dark colored oily residue was distilled in vacuo yielding 33.9 g. (0.201 mol 53.6%) of a light yellow oil boiling at 110-120°/3-4 mm. Literature value, b.p. 116-117°/3 mm. (6).

2,2-Diethoxyethyl-2'-benzo[b]thienyl sulfide

A 0.15 mole quantity of sodium ethoxide was prepared from 100 ml. of absolute ethanol and 3.45 g. of sodium metal.

To the sodium ethoxide-ethanol solution was added 19 g. (0.1145 mole) of 2-mercaptobenzo[b]thiophene. The reaction flask was cooled (ice bath) and 29.6 g. (0.15 m ole) of previously redistilled bromoacetaldehyde diethylacetal was added from a dropping funnel during 0.5 hrs. External cooling was removed and the stirred reaction mixture was heated at its reflux temperature for 3.5 hrs. The major portion of the alcohol was removed by distillation and 100 ml. of distilled water was added. The aqueous solution was extracted with two 100-ml. portions of ether. These were combined, dried over magnesium sulfate, filtered and the ether was removed (steam bath) to yield 24.3 g. of a reddish orange colored liquid. The aqueous portion was concentrated to half its volume and extracted with ether to obtain another two ml. of the oily product. The combined product was fractionated (vacuo) to yield 6.3 g. of unreacted bromoacetaldehyde diethylacetal. The residual acetal was undistillable even at a temperature of 200° under 1.0 mm. of vacuum.

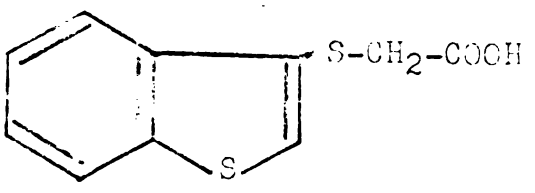
2,2-Diethoxyethyl-3'-benzo[b]thienyl sulfide



A 0.189 molar quantity of sodium ethoxide was prepared in a 500 ml. flask, by the cautious addition of 4.35 g. of sodium metal into 200 ml. of absolute ethyl alcohol. To the latter solution, while still warm, was added, in one portion, 31.5 g. (0.189 mole) of 3-mercaptobenzo[b] thiophene. The stirred alkaline reaction solution was cooled (ice bath) and 21.3 g. (0.189 mole) of chloroacetaldehyde diethylacetal was added slowly from a dropping funnel, causing the mixture to take on a reddish brown coloration.

When the acetal had been added, external cooling was removed and the reaction flask was set aside overnight at room temperature. It was then kept at its reflux temperature for 4 hrs., and the alcohol was removed in a rotary evaporator to yield 38 g. of a red colored liquid product. Fractionation of this in vacuo gave 9.2 g. of unreacted starting materials. The residual product could not be vacuum distilled at a temperature of 190° and 0.2 mm. pressure.

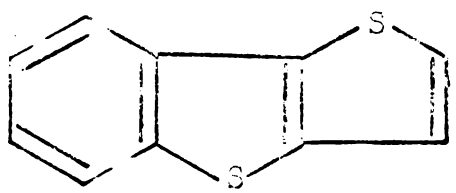
S-3-Benzo[b]thienylthioglycolic acid



3-Mercaptobenzo[b]thiophene, 2.5 g. (0.0157 mole), was dissolved in 15 ml. of 33% aqueous NaOH and to this, 2.95 g. (0.0314 mole) of chloroacetic acid was added in small portions. The alkaline mixture was heated on the steam bath for 1.75 hrs., cooled, and acidified with 6 N H_2SO_4, to precipitate a red colored oil. The oil was taken up in ether, the latter was extracted with 5% aqueous Na_2CO_3 and acidified (congo red paper), which reprecipitated the red oil. It was again extracted with ether, dried and the ether removed in a Pinco evaporator.

The oil would not solidify upon cooling in the refrigerator, but when a jet of air was blown into it, a solid formed. Recrystallization from about 2 liters of water gave 2 g. (0.0094 mole, 57%) of product melting at 87-89°.

Thieno[2,2-b]benzo[b]thiophene



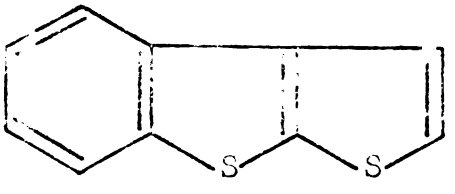
In a one liter flask equipped with mechanical stirrer, reflux condenser and thermometer was placed 25 g. (0.1 mole)

of 2,2-diethoxy-3-benzo[b]thienyl sulfide dissolved in 250 ml. of dry benzene. To this was added 60.7 g. of P_2O_5 and 37 ml. of 85% phosphoric acid. After the initial exothermic reaction subsided, the stirred mixture was heated at 80° for 5 hrs. and allowed to cool to room temperature (1 hr.). The black syrupy phosphoric acid was removed by filtration, dissolved in water and extracted with benzene, adding this extract to the original benzene filtrate. The latter was washed twice with 5% aqueous Na_2CO_3, then 4-5 times with distilled water until neutral (litmus paper), dried over calcium chloride and the benzene was removed in a Rinco evaporator to yield 13.4 g. (0.0705 mole, 70.5%) of a black solid. Recrystallization from a isopropyl alcohol-water (1:1) mixture and treatment with norite yielded a write crystalline material melting sharply at 86-87°. Literature value, m.p. 87-88° (13).

In a second preparation of thieno[3,2-b]benzo[b]thiophene, a 50 ml. flask, immersed in an ice bath, was charged with 3.35 g. (0.015 mole) of 2,2-diethoxy-3-benzo[b]thienyl sulfide dissolved in 20 ml. of dry chloroform. The catalyst, 1.34 ml. (0.015 mole) of anhydrous stannic chloride, was added with a syringe. The reaction mixture was allowed to warm to room temperature and left, with occasional shaking

for 40 hrs., diluted with 25 ml. of [illegible]Cl, and the chloroform layer separated with some difficulty. The latter was dried over calcium chloride and on removal of the solvent in a rotary evaporator, solid residue was obtained. This was dissolved in boiling isopropyl alcohol, treated with norite and filtered. The filtrate was evaporated to dryness and the residue was again dissolved in isopropyl alcohol (2-3 ml.), heated on a steam bath and diluted with water (2-3 ml.). Upon cooling, a crystalline material in the form of needles separated from the solution. It melted at 85.5-87°.

Thieno[2,3-b]benzo[b]thiophene



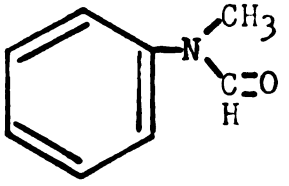
A 6.3 g. (0.0224 mole) quantity of 2,2-diethoxy-2-benzo[b]thienyl sulfide was placed in a 300 ml. flask, equipped with mechanical stirrer and reflux condenser, and containing 50 ml. of dry benzene. To this was added 14.2 g. of P_2O_5 and 7.5 ml. of 85% phosphoric acid. After the initial exothermic reaction subsided, the stirred reaction mixture was heated at its reflux temperature for 4.5 hrs.

and cooled to room temperature. The black syrupy phosphoric acid was filtered from the benzene solution, slowly dissolved in 150 ml. of water and extracted with benzene. The extract and initial benzene filtrate were combined, washed twice with 5% aqueous Na_2CO_3 and then with water until neutral (litmus paper). It was dried over calcium chloride and the benzene was removed in a Rinco evaporator leaving approximately 10 ml. of a red colored liquid, which could not be crystallized. An attempted distillation at 165° at 2 mm. gave only a few drops of material collecting in the distillation head, which solidified on cooling and had a melting point of 56-58°.

As the distillation flask cooled, additional yellow crystalline material formed in various upper parts of the flask. Thus, residue in the flask was warmed on the steam bath with a small volume of methyl alcohol, treated with norite, filtered and concentrated on the steam bath while a stream of air was blown into the flask. When the volume had been reduced to 7-8 ml., the alcohol became cloudy. On cooling this solution to room temperature, it soon deposited a yellowish-white crystalline material. This was collected by filtration and dried to obtain 0.9 g. (0.00474 mole, 21.2%) of product that had a melting point of 61.2°. Literature value, m.p. 61.0-61.5° (12).

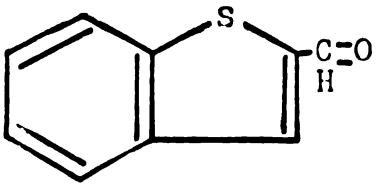
A second attempt to obtain this product, using stannic chloride as the cyclization catalyst in place of phosphoric acid failed.

N-Methylformanilide



In a three liter flask equipped for azeotropic distillation, was placed 321 g. (3.0 mole) of N-methylaniline, 300 g. 90% aqueous formic acid solution and 1800 ml. of toluene. The reaction mixture was heated at 84° to initiate the azeotropic distillation and was continued until the temperature of the distillate (in the distillation head) reached 108°, at which point 1,325 ml. of toluene and 159 ml. of water had been collected. The remainder of the toluene was removed under reduced pressure and the product was distilled in vacuo with the fraction boiling between 112-116° at 8 mm. being collected as pure product. It had a refractive index (29°) of 1.5532-1.5559. Literature value, b.p. 114-121 at 8 mm. n_D^{29} 1.553-1.555 (30).

2-Benzo[b]thienylaldehyde



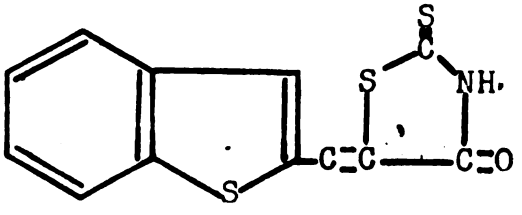
A 20 g. (0.149 mole) quantity of benzo[b]thiophene was metalated with freshly prepared n-butyl lithium in an ether medium.

To the cold, stirred solution of 2-benzo[b]thienyl lithium, was slowly added, 20 g. (0.149 mole) of N-methylformanilide. The reaction mixture was heated at its reflux temperature for 5 hours. and hydrolyzed by pouring it into 80 ml. of cold 3 N HCl. The colored ether layer was separated and the aqueous phase was extracted twice with ether and these extracts were combined with the ether phase. The ether solution was washed thrice with 100-ml. portions of 1 N HCl, once with 200 ml. of 10% aqueous $NaHCO_3$, dried over magnesium sulfate and the ether was removed in a Rinco evaporator. The residue was diluted with a small volume of 95% ethyl alcohol and 125 ml. of saturated sodium bifulfite and set aside for 10 min. to insure complete precipitation. The bisulfite addition compound was recovered by filtration and washed with ether.

The aldehyde was regenerated by treating an aqueous

solution of the bisulfite addition product with an excess of saturated Na_2CO_3, and setting it aside overnight at 0°. The precipitated aldehyde was collected by filtration and dried in a vacuum dessicator to obtain 16.6 g. (0.101 mole, 68%) of product melting at 32.0-32.5°. Literature value, m.p. 34.0-34.5° (31).

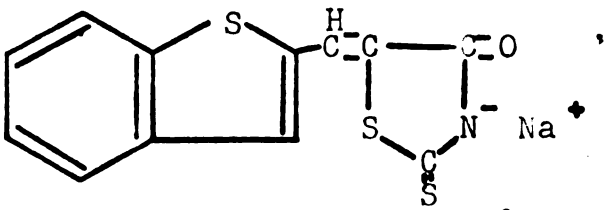
5(2-Benzo[b]thienylidene) rhodanine



In a 50 ml. flask fitted with reflux condenser, 4.0 g. (0.03 mole) of rhodanine and 7.5 g. (0.09 mole) of fused anhydrous sodium acetate was dissolved in 30 ml. of glacial acetic acid by heating the latter. A 4.86 g. (0.03 mole) quantity of 2-benzo[b]thienylaldehyde was added to the hot acid solution. In approximately 15 minutes, the rhodanine derivative began to precipitate and the acetic acid solution was poured into one liter of cold water. The reddish orange colored crystals were recovered by filtration and dried in a vacuum dessicator. The product weighed 6.7 g. (0.0242 mole, 80.6%). After three recrystallizations from 95% ethanol it melted at 286-287°.

Anal. Calc'd. for $C_{12}H_7NOS_3$: C, 51.96; H, 2.54; S, 34.68.
Found: C, 51.88; H, 2.76; S, 34.80.

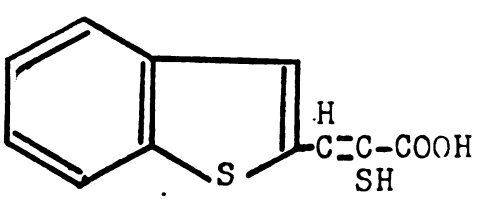
Sodium salt of
5(2-Benzo[b]thienylidene) rhodanine



In a 250 ml. beaker, cooled to 0° by an ice-salt bath, and equipped with magnetic stirrer, was placed 1 g. (0.00362 mole) of the rhodanine derivative. To this was added 100 ml. of water and 11 ml. of 5% aqueous NaOH.

After stirring the alkaline solution for 20 min., the sodium salt was removed by filtration and used directly in the preparation of α-mercapto-β-(2-benzo[b] thienyl) acrylic acid.

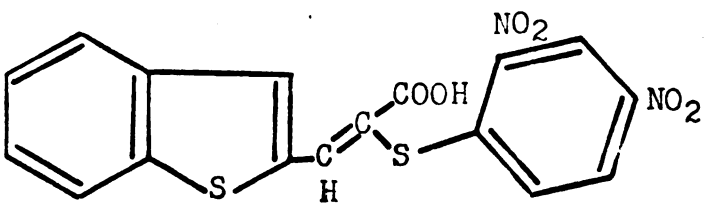
α-Mercapto-β-(2-benzo[b]thienyl) acrylic acid



The sodium of the 1 g. of 5(2-benzo[b]thienylidene) rhodanine was added to one liter three necked

flask containing 350 ml. of water and 40 ml. of 5% aqueous NaOH. The stirred alkaline solution was heated on a steam bath to 75-85° for 0.5 hrs., rapidly cooled to 25° and filtered through a norite pad into a two liter beaker. A 40 ml. volume of 3 N HCl was added rapidly to the stirred filtrate. A flocculent precipitate separated. This was collected by filtration and weighed 0.275 g. (0.000862 mole, 52.2%). It melted at 214-216° after a single recrystallization from chloroform. A second preparation of this product was carried out with an improved yield (63%).

α[2,4-Dinitrothiophenoxy]-β-(2-benzo[b]thienyl) acrylic acid

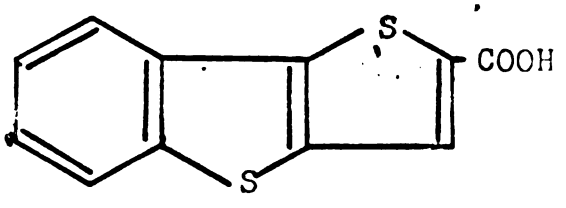


A solution prepared from 0.34 g. (0.0017 mole) of 2,4-dinitrochlorobenzene and 100 ml. of ethyl alcohol was added to a 250 ml. round bottom flask containing 0.4 g. (0.0017 mole) of α-mercapto-β-(2-benzo[b]thienyl) acrylic acid dissolved in a small volume of warm absolute ethanol. A 1.5 ml. volume of 10% aqueous NaOH was added and the alkaline solution was heated at its reflux temperature on a steam bath for 50 min., cooled to room

temperature, acidified with 2 N HCl (congo red paper) which caused a yellow solid to precipitate. This was recovered by filtration and recrystallization from absolute ethanol gave a yellow crystalline solid in the form of needles which melted above 297°.

Anal. Calc'd. for $C_{17}H_{10}N_2O_6S$: C, 49.48; H, 2.57.
Found. C, 50.54; H, 2.71.

Thieno[3,2-b]benzo[b]thiophene-2-carboxylic acid



Iodine, 4.0 g. (0.01575 mole), was added to 100 ml. of absolute ethanol in a 250 ml. flask. To the iodine solution, 1.9 g. (0.00805 mole) of α-mercapto-β-(2-benzo[b]thienyl) acrylic acid was added and the reaction solution was kept at its reflux temperature on a steam bath for 2.5 hrs. and set aside, at room temperature, for 45 hrs.

It was then poured into two liters of water and excess iodine was destroyed with a saturated sodium bisulfite solution. A very dark green colored precipitate was collected by vacuum filtration. This material could not be recrystallized from any available solvent nor could it be oxidized to the desired thiophene carboxylic acid derivative by potassium permangate in varying concentrations of NaOH.

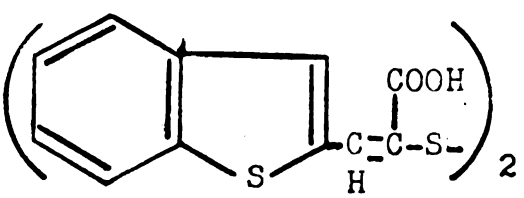
In a second attempted preparation of this material, a 50 ml. flask equipped with condenser, was charged with 0.9 g. (0.00381 mole) of α-mercapto-β-(2-benzo[b]thienyl) acrylic acid and 1.93 g. (0.00762 mole of iodine dissolved in 30 ml. of dioxane. After heating the reaction mixture on a steam bath for 2½ hrs., it was poured into two liters of water and a saturated sodium bisulfite solution was added to destroy excess iodine. However, the solution retained a dark brown coloration. On acidification of this solution (congo red paper) with concentrated HCl, it precipitated a brown colored solid. The latter was insoluble in all concentrations of alkalie.

In a third attempted preparation of this compound, 3.6 g. (0.0152 mole) of the α-mercapto acid was dissolved in 400 ml. of dioxane and 7.72 g. (0.032 mole) of iodine was added to the solution. It was set aside, at room temperature, and two ml. samples were taken daily for 12 days and tested for ring closure product. No product was isolated during that time. At the end of that period, the remainder of the solution was poured into water and decolorized with bisulfite, to yield only the starting α-mercapto acid.

In a final attempt to obtain the thienobenzo[b] thiophene carboxylic acid, 4.0 g. (0.0158 mole) of iodine was added to 30 ml. of nitrobenzene and the latter was heated to 197° at which point 0.52 g. (0.0022 mole) of α-mercapto-β-(2-benzo[b]thienyl) acrylic acid was quickly added to the iodine solution. The reaction mixture was stirred rapidly for one minute, quickly cooled to 30° and extracted with 10% NaOH. This resulted in the formation of a bright orange colored mixture in which it was very difficult to detect the liquid-liquid interface.

On acidification of the alkaline phase with conc. HCl a black powdery material precipitated. It was recovered by filtration and dried. It had no definite melting point up to 297°. When heated in an oven for a short time at 110°, it gave off dense iodine vapors. It was insoluble in various concentrations of sodium hydroxide.

1-Carboxy-2-(2'-benzo[b]thienyl) ethylene disulfide



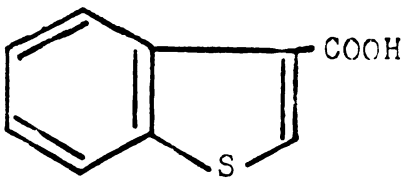
A 0.9 g (0.0038 mole) quantity of α-mercapto-β-(2-benzo[b]thienyl) acrylic acid was dissolved in a minimum volume of absolute ethanol and cooled, in a small flask,

to 0°. To this stirred solution, one g. (0.0039 mole) of iodine was added. The reaction flask was maintained at -15 to 0° for 3.5 hrs. during which time no precipitate formed. The reaction was set aside for 26 hrs., at room temperature, but it failed to yield any disulfide after decolorization with sodium bisulfite.

In a second attempt to prepare this disulfide, a 250 ml. beaker, cooled to 0° (ice-salt bath), and supported over a magnetic stirrer was charged with 0.4 g. (0.0017 mole) of the α-mercapto acid was dissolved in a minimum volume of absolute ethanol. Bromine, 0.088 ml. (0.0017 mole), was added with a syringe to the stirred alcohol solution. After 1.5 hrs., no disulfide had formed as indicated by its lack of precipitation. It was poured into 600 ml. of cold water and the solution turned yellow but the disulfide product could not be isolated.

In a final attempt to prepare the disulfide, the procedure just described was repeated using a 1:1 absolute ethanol-dioxane mixture and iodine as the oxidizing agent. After keeping the reaction mixture at 0° for 1.5 hrs., no precipitate had formed. Pouring the mixture into cold water resulted in the precipitation of the starting α-mercapto acid as shown by its m.p. (212-214°).

3-Benzo[b]thienyl carboxylic acid



A one liter three necked flask equipped with a reflux condenser (drying tube), mechanical stirrer and dropping funnel was charged with 3.35 g. (0.22 g. atoms) of magnesium chips and the latter were covered with 200 ml. of dry ether. 3-Bromobenzo[b]thiophene, 44.2 g. (0.198 mole), was dissolved in 50 ml. of ether and several ml. of this solution was added to the reaction flask. It was necessary to use a methyl Grignard to initiate the reaction. The 3-bromobenzo[b]thiophene was then added rapidly so as to maintain spontaneous refluxing of the reaction solution. After the haloheterocyclic had been added, the mixture was kept at its reflux temperature for 2 hrs. and then dry carbon dioxide was bubbled into the etheral solution for 45 min. This caused a thick brown oil to separate from solution. It was then poured into an ether-dry ice solution and hydrolyzed with 3 N HCl.

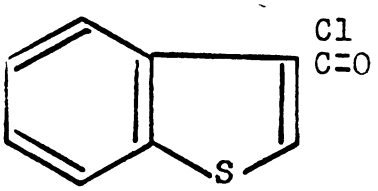
The ether layer was separated and the aqueous portion was extracted with ether, combined with the ether layer and dried over magnesium sulfate.

The ether was removed in a rotary evaporator leaving 32.5 g. of an impure yellow colored solid. This was dissolved in 150 ml. of 33% aqueous NaOH, diluted with water to 500 ml., throughly stirred and filtered to remove insoluble materials.

The basic solution was acidified with concentrated HCl, extracted with ether, dried and the ether was removed in a rotary evaporator.

The product was recrystallized from a 1:1 ethyl alcohol-water mixture and melted at 172°. Literature value, m.p. 174-175°. (32).

3-Benzo[b]thienyl acid chloride

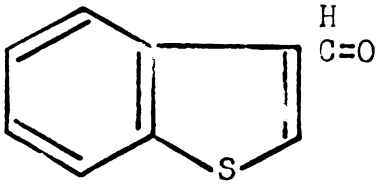


A 10 g. (0.0562 mole) quantity of 3-benzo[b]thienyl carboxylic acid was placed in a 100 ml. flask and 40 g. of thionyl chloride was added to it. The reaction mixture was warmed on a steam bath to effect solution and then brought to its reflux temperature and kept there for 1.25 hrs.

Excess thionyl chloride was removed by vacuum distillation and the product was distilled under reduced

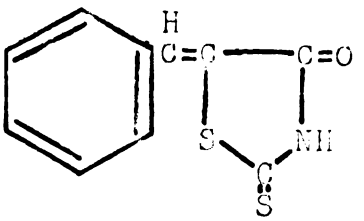
pressure to yield 10.6 g. (0.0541 mole, 96.4%) of acid chloride melting at 49-50°. Literature value, m.p. 50° (32).

Attempted Preparation of
3-Benzo[b]thiophene carboxaldehyde



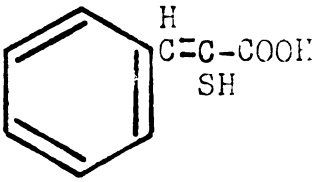
In a 500 ml. three necked flask equipped with mechanical stirrer, reflux condenser (with drying tube) and dropping funnel was placed 8.8 g. (0.0448 mole) of 3-benzo[b]thienyl acid chloride dissolved in 155 ml. of dry diglyme. The stirred solution was cooled to -73° (2-propanol-dry ice) and 45.6 ml. (0.045 mole) of lithium alumino-tri-t-butoxy hydride dissolved in 50 ml. of dry diglyme was added during a 45 min. period while dry ice was added intermittedly to maintain a temperature of -72 to -73°. Following the addition of the reducing agent, the well stirred reaction mixutre was allowed to warm to room temperature (1 hr.), poured into 500 g. of crushed ice in water and set aside overnight. A white solid precipitated which proved quite difficult to filter. It was insoluble in ether, acetone and 95% ethanol. An attempted bisulfite addition compound of the solid gave no product.

5(1-Benzyladine) rhodanine



A 700 ml. volume of glacial acetic acid containing 66.5 g. (0.5 mole) of rhodanine and 123 g. (1.5 mole) of fused anhydrous sodium acetate was placed in a 1 l. flask. The mixture was warmed to effect solution and 53.0 g. (0.5 mole) of benzaldehyde was added in portions with intermittent shaking of the solution. When the aldehyde had been added the reaction mixture was heated to just below its reflux temperature and kept there for 0.75 hrs. It was poured into five liters of distilled water and the resulting yellow colored precipitate was recovered by filtration. It melted at 206-207°. Literature value, m.p. 204-205° (20).

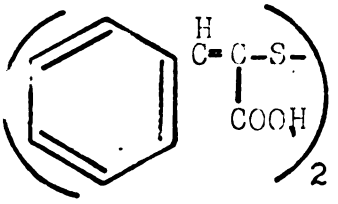
α-Mercaptocinnamic acid



A 74.0 g. (0.34 mole) quantity of 5(1-benzyladine) rhodanine was placed in two liters of stirred, warm (60-65°) water and 54 g. of NaOH dissolved in 500 ml. of water

was added. After stirring the alkaline solution for 45 min. at 60-65°, it was cooled to room temperature, filtered through a norite pad, and acidified with conc. HCl to precipitate 44.1 g. (0.245 mole, 7[illegible].6%) of the unsaturated acid. It melted at 123-124°. Literature value, m.p. 125-129° (20).

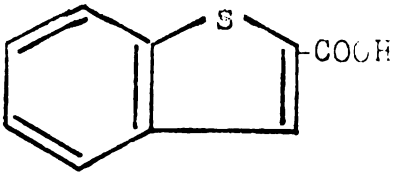
2,2'-Dithiobis(3-phenylacrylic)acid



α-Mercaptocinnamic acid, 1.0 g. (0.00555 mole), was dissolved in a minimum amount of well stirred absolute ethanol, cooled (ice-salt bath) and 1.44 g. (0.00555 mole) of iodine was added to the ethanol solution. The reaction mixture was stirred for 1.5 hrs. and poured into cold water. This produced a brownish colored precipitate which was collected by filtration. It melted at 184-187°. Literature value, m.p. 186-187° (20).

A second preparation of the disulfide was carried out as described except that 0.39 ml. of bromine was used as the oxidizing agent. The disulfide (m.p. 182°) was isolated in 92% yield. A mixed (1:1) melting point of the materials obtained in the two preparations melted at 182-183.5°

Benzo[b]thiophene-2-carboxylic acid



In a 100 ml. round bottom flask was placed 30 ml. of nitrobenzene and 4.0 g. (0.0158 mole) of iodine. A standard taper, plain glass tube (4" long) was connected to the flask to condense iodine vapors. The iodine solution was heated to 200° (determined by lowering a thermometer directly into the reaction solution). To the hot solution, 0.4 g. (0.00223 mole) of α-mercapto-cinnamic acid was quickly added, and the mixture was vigorously shaken for 60 seconds and then quickly cooled to room temperature (ice bath).

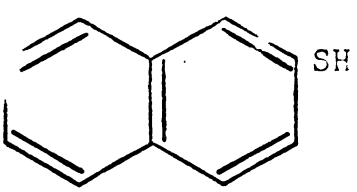
It was extracted thrice with 10% NaOH, decolorized with sodium bisulfite and the alkaline layer extracted with ether to remove the nitrobenzene which proved difficult to separate. The alkaline phase was acidified with concentrated HCl (congo red paper) and the precipitate was collected by filtration. After drying it melted at 233-236°. Literature value, m.p. 236° (32).

The synthesis of the carboxylic acid was repeated using the experimental procedure described except that

bromine was used in place of the iodine. The nitrobenzene-bromine began to spatter at 165° so the α-mercapto acid was added at this temperature. The reaction mixture was shaken for about a minute, cooled rapidly and the product was isolated as already described.

A dry sample of the material isolated had no definite melting point. Recrystallization of this material from chloroform gave a fine white crystalline substance that still melted over a broad temperature range. Tests for unsaturation with 2% potassium permanganate and bromine in several solvents gave contradictory results.

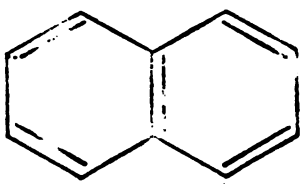
β-Naphthalenethiol



This compound was obtained in a quantitative yield by the reduction of 30 g. (0.132 mole) of β-naphthalene-sulfonyl chloride. The sulfonyl chloride was added to a rapidly stirred solution containing 54 ml. of concentrated sulfuric acid diluted with 280 ml. of water. The temperature of the acid chloride solution was held at 20° while 18 g. of zinc dust were added, (in portions) during

2.5 hrs. The reduction mixture was heated to approximately 50° at which temperature an exothermic reaction set in causing the temperature to rise rapidly to 96°, necessitating immersion of the reaction flask in a cold water bath. The reaction flask was then reheated to 70-80° for 1.5 hrs., then heated at its reflux temperature for another hour and allowed to cool to room temperature. The cool mixture was poured into cold water and the product was collected by filtration and recrystallized from absolute ethanol. Its melting point was 80.5-81°. Literature value, m.p. 81-82° (33, 34).

γ-Hydroxy-n-propyl-β-naphthyl sulfide



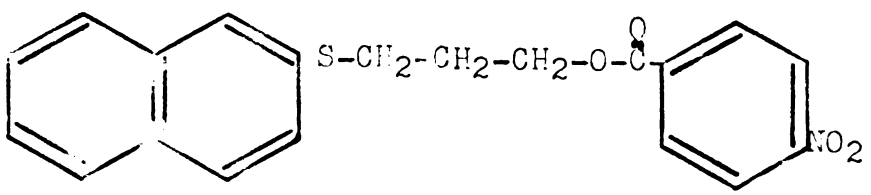
In a 100 ml. three necked round bottom flask was placed 1.2 g. (0.03 mole) of NaOH dissolved in 100 ml. of distilled water. To the slightly warmed alkaline solution was added 3.3 g. (0.0206 mole) of β-naphthalenethiol. After cooling the sodium β-naphthalenethiolate solution to room temperature, 2.85 g. (0.03 mole) of trimethylene chlorohydrin was added to it rapidly from a dropping funnel. The stirred reaction mixture was

heated at its reflux temperature for 3.5 hrs. during which time a brown colored oil separated from solution. On cooling the solution to room temperature the oil solidified. It was collected by filtration and dried in a vacuum desiccator to yield 3.90 g. (0.0179 mole, 87%) of product. This was recrystallized from a large volume of petroleum ether in the form of white crystals which melted at 62°.

Anal. Calc'd. for $C_{13}H_{14}OS$: C, 71.52; H, 6.46; S, 14.69.

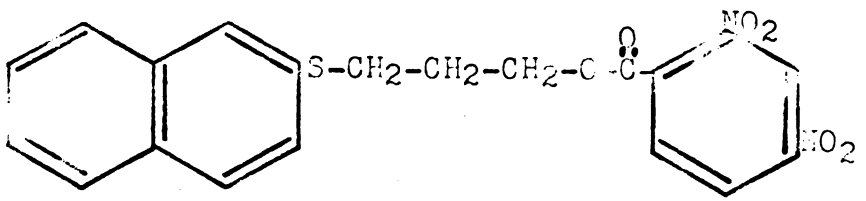
Found: C, 71.49; H, 6.54; S, 14.61.

γ-β'-Thionaphthoxy-n-propyl-p-nitrobenzoate



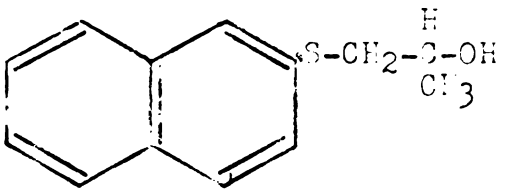
This compound was prepared by the method described by Shriner, Fuson and Curtin (35). A single recrystallization from absolute ethanol gave a product melting at 98-100°.

γ-β'-Thionaphthoxy-n-propyl-2,4-dinitrobenzoate



This material was prepared as previously described (35). A single recrystallization from absolute ethanol gave a product with a melting point of 115-117°.

β-Hydroxy-n-propyl-β'-naphthyl sulfide

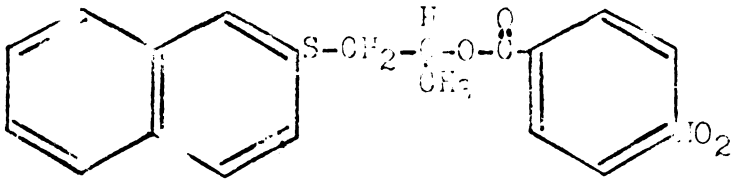


An 0.8 g. (0.005 mole) quantity of β-naphthalenethiol was dissolved in 50 ml. of water containing 0.7 g. (0.0057 mole) of sodium hydroxide. To this alkaline solution was added 0.55 g. (0.006 mole) of propylene chlorohydrin. The reaction mixture was heated at its reflux temperature for 1.6 hrs. during which time an insoluble oil precipitated from solution. On cooling, it solidified and was removed by filtration to yield 0.7 g. of product (0.00321 mole, 64.2%). Recrystallization of this material from petroleum ether gave a product with a melting point of 46.5-47.5°.

Anal. Calc'd. for $C_{13}H_{14}OS$: C, 71.52; H, 6.46; S, 14.69.

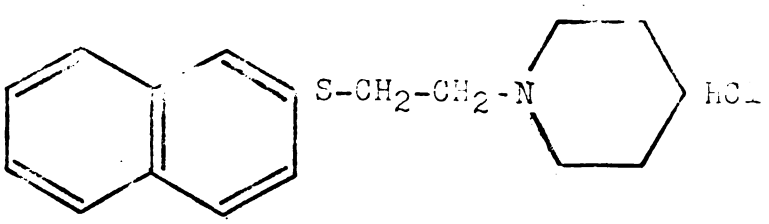
Found: C, 71.61; H, 6.59; S, 14.54.

β-β'-Thionaphthoxy-isopropyl-p-nitrobenzoate



This compound was prepared by procedures previously described in the literature(35). A single recrystallization from absolute ethanol gave a product with a melting point of 83-86°.

β-Piperidinoethyl-β'-naphthyl sulfide hydrochloride

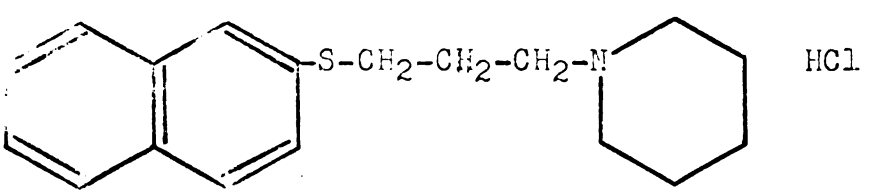


In a 500 ml. three necked flask equipped with a mechanical stirrer, reflux condenser and dropping funnel was placed 16.0 g. (0.1 mole) of β-naphthalenethiol dissolved in 100 ml. of 10% aqueous NaOH. The stirred alkaline solution was warmed to 55° and 18 g. (0.098 mole) of 2-piperidino-1-chloroethane hydrochloride dissolved in 100 ml. of distilled water was added during 55 min. After adding the hydrochloride salt, the reaction mixture was heated to its reflux temperature and kept at that temperature for two hours during which time an insoluble oil separated. After cooling the solution to

room temperature, the oil was separated and the aqueous portion was extracted twice with 200-ml. portions of ether. The ether extracts and oil were combined, washed with 100 ml. of 5% aqueous NaOH, 100 ml. of distilled water, then dried over sodium sulfate. The hydrochloride salt was precipitated from the ether solution by passing an intermittent stream of anhydrous hydrogen chloride into the solution (excess hydrogen chloride gives a material which is difficult to recrystallize). The ether insoluble hydrochloride was removed by filtration and dried in vacuum to yield 23.7 g. (0.077 mole, 78.6%) of the desired product. Recrystallization from absolute ethanol gave a white crystalline product in the form of needles melting at 205°.

Anal. Calc'd. for $C_{17}H_{22}ClNS$; C, 66.32; H, 7.20; N, 4.55; S, 10.42; Cl, 11.52.
Found: C, 66.36; H, 7.03; N, 4.48; S, 10.44; Cl, 11.54.

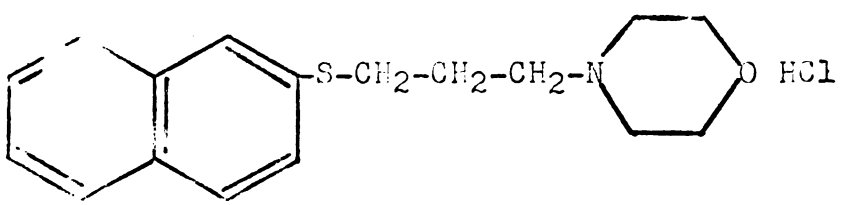
γ-Piperidino-n-propyl-α-naphthyl sulfide hydrochloride



This compound was prepared by dissolving 16.0 g. (0.1 mole) of 2-naphthalenethiol in 100 ml. of 10% NaOH, heating the solution to 70° and adding to it 19 g. (0.096 mole) of 3-piperidino-n-propylchloride hydrochloride dissolved in 100 ml. of water during a 20 min. period. The well stirred reaction mixture was then heated at its reflux temperature for 3 hrs. during which an insoluble oil formed. The oil was separated from the basic solution and combined with the ethereal extract of the reaction mixture, dried over anhydrous sodium sulfate, filtered and treated with anhydrous hydrogen chloride. This caused a gummy oil to separate which solidified on cooling to yield 25.4 g. (0.074 mole, 76%) of product. Recrystallization of the material from isopropyl alcohol yielded a cream colored crystalline solid in the form of needles which melted at 148-149°.

Anal. Calc'd. for $C_{18}H_{24}ClNS$: C, 67.16; H, 7.52; N, 4.35; S, 9.96; Cl, 11.01.
Found: C, 67.18; H, 7.52; N, 4.25; S, 9.80; Cl, 10.90.

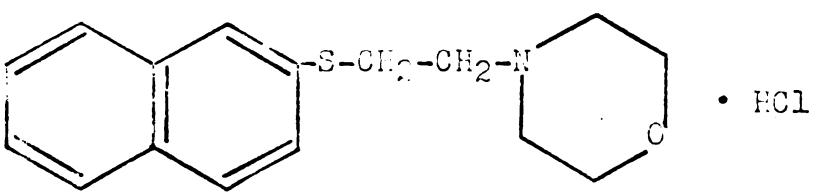
3-Morpholino-n-propyl-2-naphthyl sulfide hydrochloride



Following the previously described procedure used for the preparation of the γ-piperidino analogue of this material, 16 g. (0.1 mole) of β-naphthalenethiol was allowed to interact with 20 g. (0.1 mole) of γ-morpholino-n-propyl chloride hydrochloride. Employing the usual separation of the free amine and its conversion to a hydrochloride salt resulted in 26.3 g. (0.0815 mole, 81.5%) of a pink colored crystalline solid. After a single recrystallization from dry isopropyl alcohol, this product melted at 189.5-190°.

Anal. Calc'd. for $C_{17}H_{22}ClNOS$: C, 63.04; H, 6.85; N, 4.33; S, 9.90; Cl, 10.9%.
Found: C, 62.82; H, 6.78; N, 4.21; S, 9.60; Cl, 10.65.

β-Morpholinoethyl-β-naphthyl sulfide hydrochloride



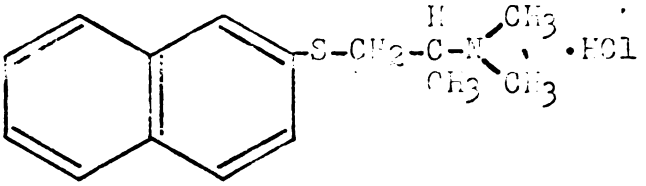
The interaction of 15.0 g. (0.081 mole) of β-morpholinoethyl chloride hydrochloride with 14.0 g. (0.0875 mole) of β naphthalenethiol in 10% aqueous NaOH as the reaction media, yielded the free oily amine. This was dissolved in ether, dried, and treated with dry hydrogen

chloride to precipitate 13.6 g. (0.0545 mole, 55%) of the amine salt. The latter, after recrystallization from isopropyl alcohol, melted at 151-152°.

Anal. Calc'd. for $C_{16}H_{20}ClNOS$: C, 61.62; H, 6.46; N, 4.49; S, 10.28; Cl, 11.37.

Found: C, 63.29; H, 6.34; N, 4.17; S, 10.40; Cl, 11.33.

β-Dimethylamino-isopropyl-β-naphthyl sulfide hydrochloride

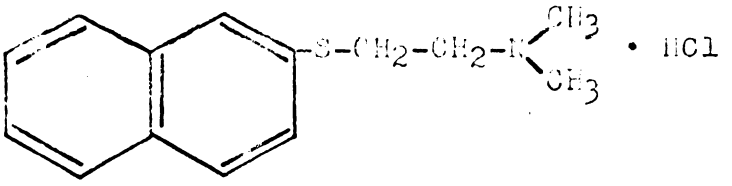


The formation of this compound resulted from the interaction of 16.0 g. (0.1 mole) of β-naphthalenethiol with 17.8 g. (0.1 mole) of dimethylaminoisopropyl chloride hydrochloride in an aqueous alkaline media as previously described. Isolation of the amine as its hydrochloride salt yielded 22.0 g. (0.0785 mole, 78.5%) of a white crystalline solid in the form of needles which melted at 149° following recrystallization from isopropyl alcohol.

Anal. Calc'd. for $C_{15}H_{20}ClNS$: C, 63.92; H, 7.15; N, 4.97; S, 11.38; Cl, 12.58.

Found: C, 64.05; H, 7.14; N, 4.85; S, 11.38; Cl, 12.81.

, -Dimethylaminoethyl-β-naphthyl sulfide hydrochloride

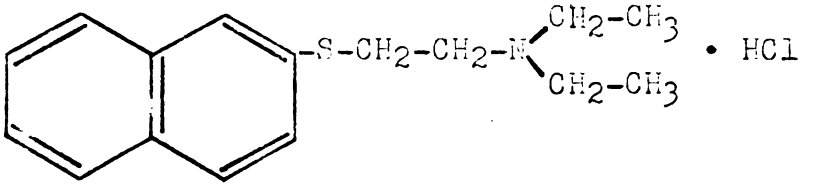


A 16.0 g. (0.1 mole) quantity of β-naphthalenethiol was allowed to react with 14.1 g. (0.1 mole) of β-dimethylaminoethyl chloride hydrochloride in a basic aqueous media to yield 23.2 g. (0.087 mole, 87%) of the hydrochloride salt. Recrystallization from isopropyl alcohol gave a product with a melting point of 151°.

Anal. Calc'd. for $C_{14}H_{18}ClNS$; C, 62.78; H, 6.77; N, 5.23; S, 11.97; Cl, 13.24.

Found: C, 62.53; H, 6.68; N, 5.13; S, 12.09; Cl, 13.59.

β-Diethylaminoethyl-β-naphthyl sulfide hydrochloride



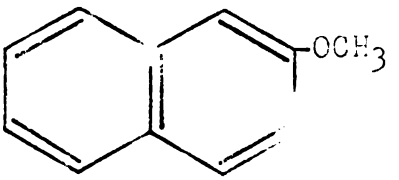
A 0.1 molar quantity of β-naphthalenethiol and an equal molar amount of β-diethylaminoethyl chloride hydrochloride, on interaction in a basic media, yielded the free amine as an oil. This was separated, dissolved

in ether, and dried. Treatment of the ether solution with dry hydrogen chloride caused the precipitation of 23.4 g. (0.0794 mole, 79.4%) of the amine salt as a creamish white crystalline solid. After recrystallization from isopropyl alcohol, this material melted at 147°.

Anal. Calc'd. for $C_{16}H_{22}ClNS$: C, 64.95; H, 7.50; N, 4.73; S, 10.84; Cl, 11.98.

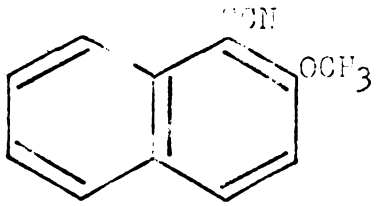
Found: C, 64.82; H, 7.49; N, 4.75; S, 10.61; Cl, 11.76.

β-Methoxynaphthalene



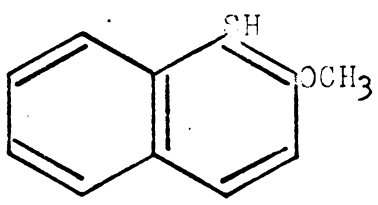
A 50 g. (0.347 mole) quantity of β-hydroxynaphthalene was added to 60 ml. of absolute methanol to which had previously been added 10 ml. of concentrated H_2SO_4. The reaction mixture was heated at its reflux temperature for 4 hrs. On cooling the solution to room temperature, the product precipitated from solution. It was recovered by filtration and after two recrystallizations from ethanol, melted at 72-72.5°. Literature value, m.p. 71-72° (36).

α-Thiocyano-β-methoxynaphthalene



A 7.35 g. (0.046 mole) quantity of β-methoxynaphthalene was dissolved in 40 ml. of glacial acetic acid and the latter was added to 14.6 g. (0.18 mole) of sodium thiocyanate dissolved in 100 ml. of glacial acetic acid. The reaction mixture was stirred with cooling (ice bath) and 2.3 ml. (0.046 mole) of bromine dissolved in 20 ml. of glacial acetic acid was added slowly during 10 min. The stirred solution was allowed to warm to room temperature and the yellow precipitate was collected by filtration. The acetic acid filtrate was poured into three times its volume of water and a second quantity of crystalline product was collected by filtration. A single recrystallization from ethanol gave a material with a melting point of 130°-132.5°. Literature value, m.p. 134° (22).

α-Mercapto-β-methoxynaphthalene

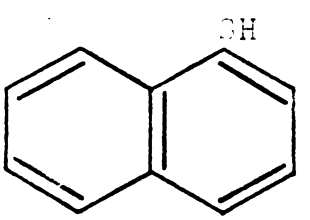


A 10.3 g. (0.05 mole) quantity of α-thiocyano-β-methoxynaphthalene was dissolved in 250 ml. of 95% ethanol by warming it on a steam bath. A 15 ml. volume of conc. hydrochloric acid was added to the alcohol solution. The reaction mixture was heated to its reflux temperature and 20 g. of zinc metal was added to it during 5 hrs. An additional 7 ml. of hydrochloric acid was added to the reaction mixture when about half of the metal had been added. The reaction solution was kept at its reflux temperature for 3 hrs. following the zinc addition. It was then poured into two liters of water containing 60 ml. of concentrated hydrochloric acid to precipitate 7.0 g. (0.039 mole, 78%) of product. This was collected by filtration and after recrystallization from ethanol melted at 68°. Literature value, m.p. 98° (22). The product was soluble in 15% potassium hydroxide.

Anal. Calc'd. for $C_{11}H_{10}OS$: C, 69.43; H, 5.29; S, 16.85.

Found: C, 69.51; H, 5.38; S, 16.61.

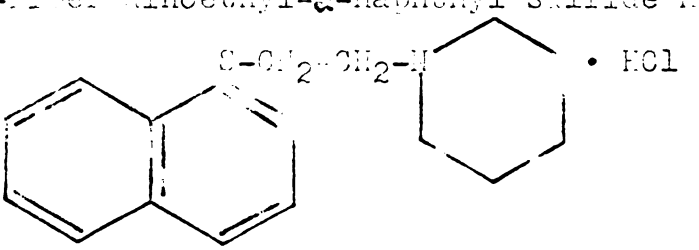
α-Naphthalenethiol



A 500 ml. three necked round bottom flask equipped with a reflux condenser (drying tube), mechanical stirrer and parallel sidearm connecting tube fitted with a dropping funnel and nitrogen gas inlet was charged with 7.4 g. (0.31 g. atom) of magnesium and covered with 150 ml. of dry ether. α-Bromonaphalene, 62.1 g. (0.3 mole), was dissolved in 40 ml. of ether and about one third of this solution was added directly to the ether-magnesium mixture. A one ml. quantity of methyl iodide was added to the reaction mixture and it was warmed to its reflux temperature for about one minute to initiate the reaction. After the initial reaction was under control, the remainder of the α-bromonarhthalene solution was added to the stirred reaction mixture at a rate sufficient to maintain a vigorous reflux of the reaction media. After adding the aromatic bromide, the mixture was warmed in a warm water bath for a half hr. during which time the Grignard mixture became quite thick. At this point, 9.6 g. (0.3 g. atoms) of sulfur was cautiously added while dry nitrogen was rapidly swept through the reaction flask. The addition of the sulfur caused the reaction media to spontaneously reflux and markedly lowered the viscosity of the reaction solution. It was again warmed at its reflux temperature for an additional half hour during which it again became quite pasty in consistency. The Grignard complex was hydrolyzed by

carefully pouring it, with vigorous stirring, into 500 ml. of a saturated ammonium chloride solution. The hydrolysis solution was made definitely acidic and steam distilled until five liters of distillate had been collected. The distillate was extracted with ether, dried over anhydrous magnesium sulfate and the ether was removed in a Rinco evaporator. Distillation of the residual oil yielded the pure mercaptan which boiled at 105°/1.5 mm. Literature value, b.p. 105-107°/1.5 mm. (32).

β-Piperidinoethyl-α-naphthyl sulfide hydrochloride

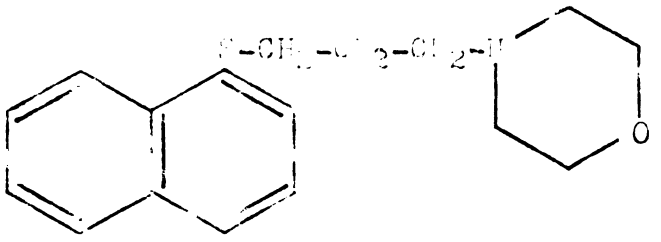


This compound was prepared using the procedure employed in the synthesis of its β-naphthyl analogue. The interaction of 3.7 g. (0.023 mole) of α-naphthalenethiol and 4.2 g. (0.0229 mole) of β-piperidinoethyl chloride hydrochloride in a basic media, isolation of the free oily amine and its conversion to a hydrochloride salt yielded 4.4 g. (0.0143 mole, 62.5%) of the expected product. After recrystallization from isopropyl alcohol, the product melted at 183.5-183.75°.

Anal. Calc'd. for $C_{17}H_{22}ClNS$: C, 66.32; H, 7.20; S, 10.42.

Found: C, 66.26; H, 7.32; S, 10.19.

γ-Morpholino-n-propyl-α-naphthyl sulfide hydrochloride

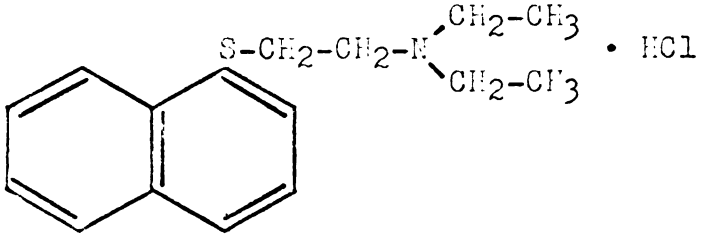


α-Naphthalenethiol, 7.0 g. (0.050 mole), was allowed to react with 11.2 g. (0.056 mol[illegible] of γ-morpholino-n-propyl chloride hydrochloride in a basic solution following the previously described procedure. Isolation of the hydrochloride salt of the amine in the usual manner yielded 9.9 g. (0.0306 mole, 54.6%) of product as a light pink crystalline solid melting at 157-157.5° following its recrystallization from isopropyl alcohol.

Anal. Calc'd. for $C_{17}H_{22}ClNOS$: C, 63.04; H, 6.85; S, 9.90.

Found: C, 63.01; H, 6.98; S, 9.75.

β-Diethylaminoethyl-α-naphthyl sulfide hydrochloride



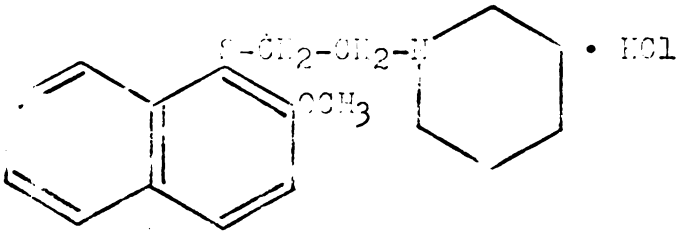
A 7.0 g. (0.0437 mole) quantity of α-naphthalenethiol was allowed to react with 5.4 g. (0.0437 mole) of β-diethylaminoethyl chloride hydrochloride in a basic media to

form an alkali insoluble oily amine. This was extracted with ether and dried over magnesium sulfate. Treatment of the ether solution with gaseous hydrogen chloride yielded 7.4 g. (0.016 mole, 75 %) of a white crystalline hydrochloride salt. Recrystallization of the latter from isopropyl alcohol yielded a pure product melting at 144.5-145.25°.

Anal. Calc'd. for $C_{16}H_{22}ClNS$: C, 64.95; H, 7.50; S, 10.84; N, 4.73; Cl, 11.98.

Found: C, 62.47; H, 7.30; S, 10.66; N, 4.75; Cl, 11.72.

β-Piperidinoethyl-α-[β-methoxynaphthyl] sulfide hydrochloride

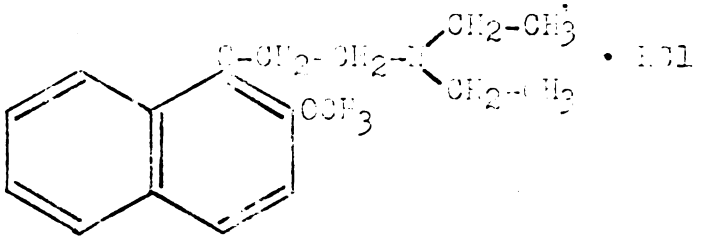


α-Mercapto-β-methoxynaphthalene, 2.3 g. (0.0122 mole), was allowed to react with an equimolar amount of β-piperidinoethyl chloride hydrochloride in 10% aqueous NaOH. Isolation of the free amine and its conversion, in the usual manner, to its hydrochloride salt yielded 1.4 g. (0.00415 mole, 34%) of the desired product. This material, after two recrystallizations from isopropyl alcohol, gave a product with a melting point of 184.9-185.3°.

Anal. Calc'd. for $C_{17}H_{24}ClNOS$: C, 63.47; H, 7.15; S, 9.94.

Found: C, 64.09; H, 7.07; S, 9.43.

β-Diethylaminoethyl-[α-(3-methoxynaphthyl)] sulfide hydrochloride



A 6.0 g. (0.0315 mole) quantity of α-mercapto-β-methoxynaphthalene was converted to its sodium salt by dissolving it in 100 ml. of 10% aqueous NaOH. To the stirred alkaline solution, heated to its reflux temperature, was slowly added 5.42 g. (0.0315 mole) of β-diethylaminoethyl chloride hydrochloride in 50 ml. of water. Isolation of the insoluble yellow colored oily amine and its conversion to its hydrochloride salt yielded 2.6 g. (0.008 mole, 25.4%) of product. The melting point of this material was 138° after its recrystallization from isopropyl alcohol.

Anal. Calc'd. for $C_{17}H_{24}ClNOS$: C, 62.65; H, 7.42; S, 9.84; N, 4.30; Cl, 10.88.

Found: C, 62.51; H, 7.37; S, 9.91; N, 4.49; Cl, 11.01.

SUMMARY

1. Thieno[2,3-b]benzo[b]thiophene and thieno[3,2-b]benzo[b]thiophene were successfully prepared by cyclization of their corresponding acetals.

2. An improved method for the preparation of β-mercapto-benzo[b]thiophene was developed.

3. The 5(2-benzo b thienylidene) rhodanine, its sodium salt and α-mercapto-β-2-benzo[b]thienylacrylic acid were prepared for the first time and some of their physical properties were investigated.

4. Investigation of the possible ring closure of α-mercapto-β-2-benzo[b]thienylacrylic acid to thieno[3,2-b]benzo[b]thiophene-2-carboxylic acid showed that it could not be cyclized by iodine or bromine oxidation.

5. Two ω-hydroxy-β-naphthyl sulfides were prepared for the first time and some of their physical properties were determined. The p-nitrobenzoyl derivatives of these alcohols were characterized as well as one 2,4-dinitrobenzoyl derivative of the ω-hydroxy-n-propyl aryl sulfide.

6. Seven ω-(N,N-dialkylamino) alkyl-β-naphthyl sulfide hydrochlorides were synthesized for the first time and some of their properties were investigated.

7. Three ω-(N,N-dialkylamino) alkyl-α-naphthyl sulfide hydrochlorides were prepared for the first time and some of their physical properties were investigated.

8. The (-(N,N-dialkylamino) alkyl β- naphthyl ketone methiodide hydrochlorides were prepared for the first time and some of their physical properties were determined.

9. The melting point of α- bromo-β- methoxynaphthalene was found to be 60° and not 91° as previously reported in the literature.

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