THE SYNTHESIS OF SOME ω-(N, N-DIALKYLAMINO) ALKYL-3-THIENYL SULFIDE HYDROCHLORIDES

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By

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INTRODUCTION

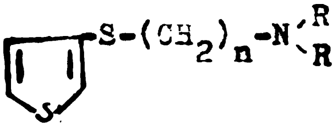
Extensive chemical research has had as its object the elucidation of the structural relationship of compounds to their physiological activity. Numerous investigations have been directed toward the preparation of compounds structurally related to naturally occurring active substances, with the aim of finding some relationship between chemical structure and biological activity. Such studies have, in a few cases, led to the synthesis of important new drugs. Compounds which embody the following features in their structures,

$$A\text{-}M\text{-}(C)_n\text{-}N=$$

where A represents an aryl group, and M is a heteroatom or heterogroup, have been the keen object of these investigations since Einhorn's[1] historic synthesis of "Novocain".

Based on the results of many investigations, an important prediction was made by Pyman[2], who generalized the relationship for compounds of this general structure with respect to their physiological actions. Following this, Lofgren[3] gave the detailed structural requirements of a compound which should possess local anesthetic properties.

Because of the similarity in chemical structure of the organic sulfides to the ethers, the pharmaceutical usefulness of certain aryl ethers which contain a tertiary amino group, and the reported lower toxicity of the thiophene nucleus compared to that of benzene[4,5], the investigation herein reported was undertaken to synthesize a series of mixed tertiary amino thienyl alkyl sulfides. These compounds can be represented by the general formula:



In the present study, a systematic attempt was made to vary the length of the polymethylene chain, attached between the thienyl group and the amino nitrogen, from two to five carbon atoms. The terminal amino groups in the compounds prepared were piperidine and morpholine.

Compounds of this type can be regarded as potential local anesthetics. However, only laboratory and clinical tests, which have not been conducted, as a part of the present work, will determine the usefulness of such compounds.

HISTORICAL

Part I

Local anesthetics, according to Chen and Scott[6], are drugs which block pain impulses at the periphery, while general anesthetics produce anesthesia by blocking pain sensation in the brain accompanied by loss of consciousness.

Attempts to produce local anesthesia have been known for a great many years. The earliest of these employed the use of manual pressure. A serious objection to this practice is that it often resulted in permanent paralysis or anemia.

A later development depended on spraying the area to be anesthesized with easily volatilized organic liquids which freeze the skin by rapid evaporation. However, a painful period of initiation usually preceeds complete anesthesia and serious damage to the frozen area was often objectionable in this procedure.

The use of local anesthetics in medicine began in 1884, with Karl Koller's[7] use of cocaine in opthamological practice and surgery. Serious objections to the alkaloid are its toxicity and habit forming properties. Also it is unstable to the action of microorganisms and purification by heat results in chemical decomposition.

Following Willstatter's[8] characterization of cocaine at the beginning of the twentieth century, a large number of compounds structurally related to cocaine were prepared and studied to determine what structural features of the cocaine molecule are responsible for its activity. These investigations led the way for Einhorn's[1] discovery of novocaine, an excellent local anesthetic of much lower toxicity than cocaine.

Until recently most compounds possessing local anesthetic activity were structurally related to cocaine or novocaine. A thorough review of the field, up to 1930, is given by Hirschfelder and Bieter.[9]

Recently, however, compounds related only slightly or not at all to Pyman's basic structure have been reported as local anesthetics. These include certain sterols, amino alcohols, n-hexyl amine and phenylethyl alcohol. This indicates a need for a revision of Pyman's hypothesis.

Lofgren[10] proposed a scheme which accounted for the local anesthetic property of a larger number of compounds. According to this scheme the structures of local anesthetics should contain the following three units:

Lipophillic center--Intermediate chain--Hydrophillic center

Lofgren believes that the following are desirable factors in active compounds:

First, the lipophillic center should be aromatic.

Secondly, the intermediate chain should consist of a hydrocarbon residue joined to the aromatic group through an ester, amide, ether oxygen, amino nitrogen, or ketonic carbonyl linkage.

Next, the hydrophillic end should consist of a tertiary or secondary amino group.

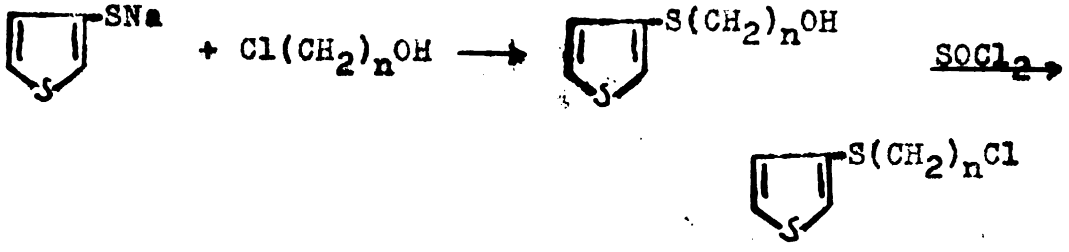
Finally, it is important to achieve a balance between the lipophillic and hydrophillic centers. There is given no definition as to the meaning of the term "balance" nor are the factors governing this "balance" explained.

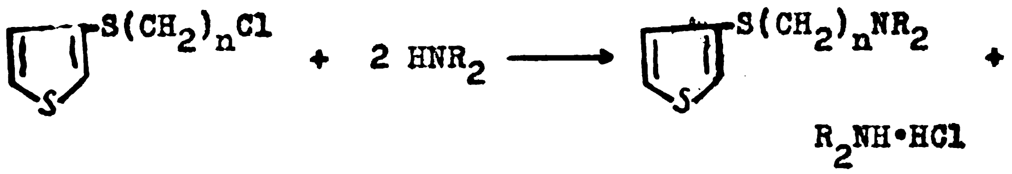
Part II

At the present time no information is available on the physiological and pharmacological effects of tertiary amine derivatives of mixed 3-thienyl alkyl sulfides. However, some work has been done regarding the same effects in the phenyl analogs and a good deal more information has been reported on the other analogs of the phenyl compounds.

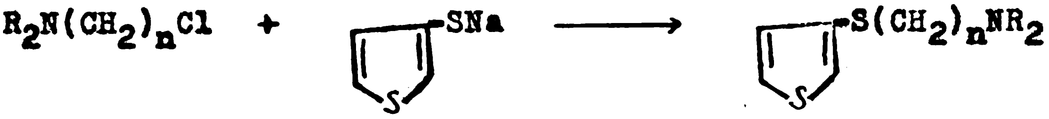
A review of the feasible methods available for the synthesis of tertiary amine derivatives of mixed thienyl alkyl sulfides as well as the intermediates used in their preparation will be discussed to indicate why the methods used in the present investigation were chosen.

There were available two methods or variations of these by which the molecule could be constructed. These are shown in the two sequences of reactions:



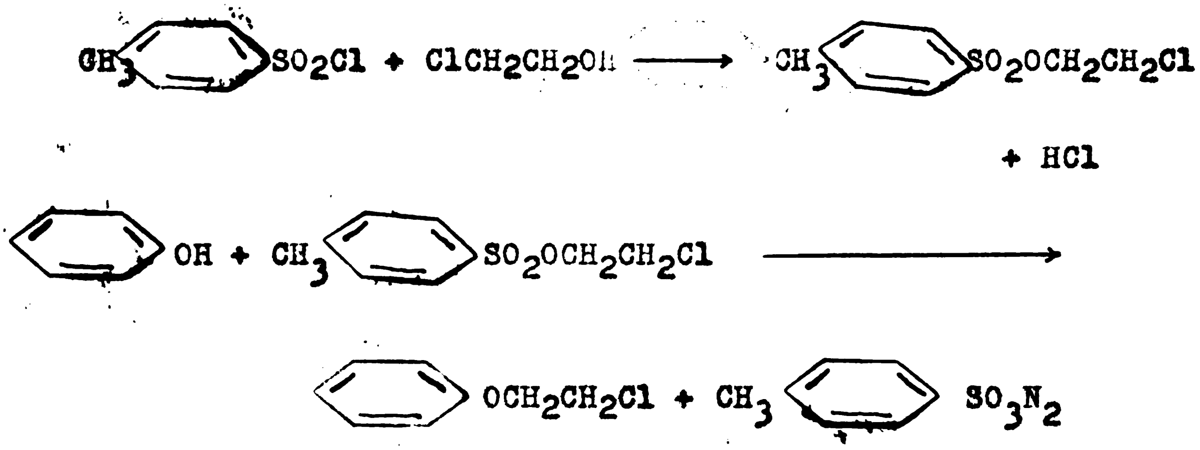


$$R_2NH + Cl(CH_2)_nOH \longrightarrow R_2N(CH_2)_nOH \xrightarrow{SOCl_2} \underset{HCl}{R_2N(CH_2)_nCl}$$

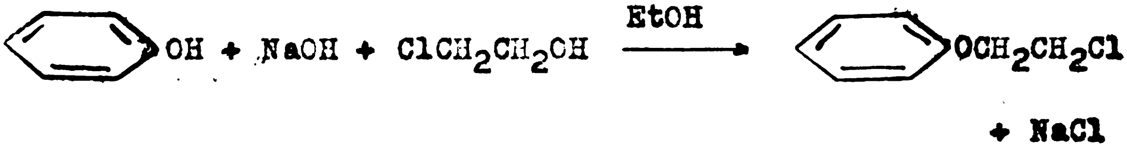


Considerably more information was available describing the former of these methods.

Marvel[11] reported that the reactions between sodium phenoxide and 1,2-dichloroethane or 1,3-dibromopropane gave 55-56 percent and 84-85 percent yields respectively of the ω-chloroalkyl phenyl ethers, but there was no evidence that the reaction would be applicable to the more reactive sodium salt of 3-thiophenethiol. A better yield of the β-chloroethyl phenyl ether is obtained by the use of β-chloroethyl-p-toluene sulfonate as a chloroalkylating agent for sodium phenoxide as initially employed by Clemo and Perkin[12].

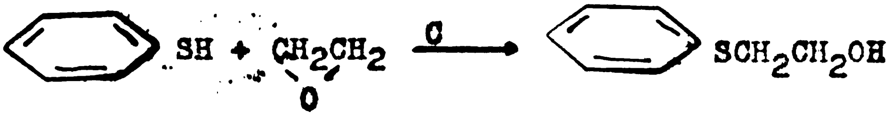


The β-chloroethyl phenyl ether was obtained in a 76 percent yield by Steinkopf[13] on passing gaseous hydrogen chloride into a heated mixture of phenol, sodium hydroxide and ethylene chlorohydrin in alcoholic solution.

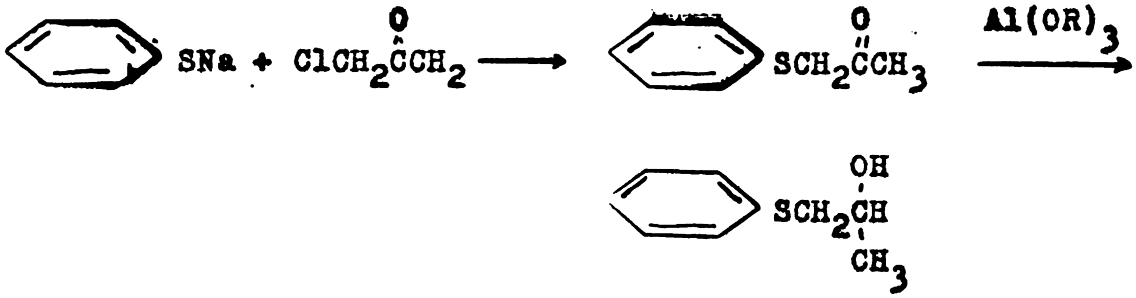


Leder and Stocklin[14] reported the production of β-chloroethyl phenyl sulfide in good yield by passing ethylene gas into an anhydrous carbon tetrachloride solution of phenylsulfenyl chloride.

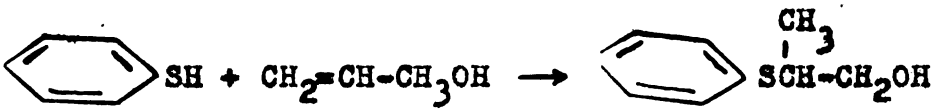
The condensation of ethylene oxide with thiophenol in the presence of activated charcoal is reported to yield β-hydroxyethyl phenyl sulfide.[15]



Fuson and Koehneke[16] prepared β-methyl-β-hydroxyethyl phenyl sulfide by the Meerwein, Ponndorf, Verly reduction of thiophenyl acetone, obtained by the reaction of sodium thiophenolate with chloroacetone.



They also obtained the isomeric α-methyl-β-hydroxyethyl phenyl sulfide by treating thiophenol with allyl alcohol in the presence of sulfur as a catalyst.



Renshow and co-workers[17] prepared dialkylaminomethyl alkyl sulfides in good yields by the reaction of mercaptans and secondary amines with formaldehyde, but this method has not been applied to aromatic or heterocyclic mercaptans.

$$RSH + H\overset{O}{\overset{\|}{C}}H + R_2NH \longrightarrow RSCH_2NR_2 + H_2O$$

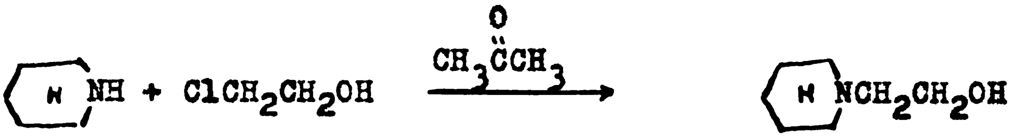
Bennett and Berry[18], in a method similar to Steinkopf's[13], successfully prepared β-hydroxyethyl phenyl sulfide by the addition of ethylene chlorohydrin to a sodium thiophenolate solution. They further reported that distillation of the product resulted in an unsaturated compound. However, Kirner[19] was unable to confirm this instability of β-hydroxyethyl phenyl sulfide. Bennett[20] reported the reaction of the acetates of the longer chained chlorohydrins with sodium thiophenolate to yield ω-acetoxy alkyl phenyl sulfides which were hydrolyzed and easily converted to the ω-chloro compounds by means of thionyl chloride.

One method employed in the present investigation was analogous to that suggested by Powell[22] and developed by Kirner[23], for the preparation of β-hydroxylethyl and γ-hydroxy-n-propyl phenyl sulfides. It involved the reaction of the sodium salt of the mercaptan with a chlorohydrin at reflux temperature and gave excellent yields of the intermediates, ω-hydroxyalkyl-3-thienyl sulfides, used in this work.

Brooks[24] reported the preparation of a number of derivatives of 3-thiophenethiol and among these was the synthesis of β-hydroxyethyl 3-thienyl sulfide which was prepared by the interaction of 3-thiophenethiol with ethylene chlorohydrin in the presence of aqueous potassium hydroxide. No information was given concerning the experimental conditions of this preparation.

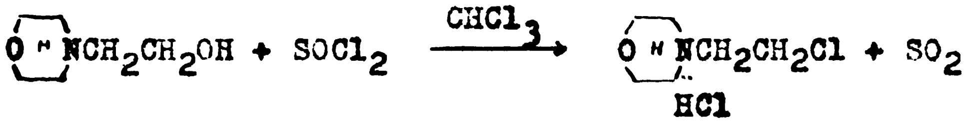
A second general method of synthesis was based on the preparation of the dialkylamino alcohols, their conversion to the corresponding chlorocompound and then treatment of the latter with the sodium salt of the mercaptan.

Bram et al[25] reported a satisfactory method for the synthesis of the dialkylamino alcohols by the reaction of piperidine with ethylene chlorohydrin in acetone.

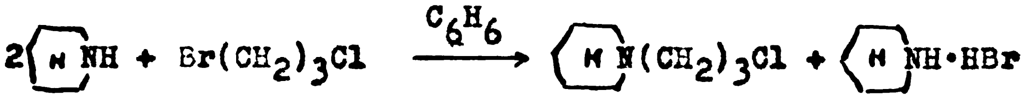


Clinton et al[26] employed a similar method, obtaining 95 percent yields, using ethyl alcohol as a solvent and a small quantity of sodium iodide. The latter reagent served the purpose of shortening the reaction time by exchange of iodine for the chlorine atom in the chlorohydrin.

A successful conversion of β-hydroxyethyl morpholine into the corresponding chloro compound was accomplished by Mason and Block[27] who used thionyl chloride in anhydrous chloroform. By careful control of the temperature β-chloroethyl morpholine hydrochloride is obtained in a good yield.



An elegant synthesis of γ-chloropropyl morpholine is reported by Adams and Clark[28], which involved the interaction of morpholine and trimethylene chlorobromide in absolute benzene, yielding the desired product and the hydrobromide of morpholine in stoichiometric quantities.



DISCUSSION

After consideration of the several methods available for the synthesis of N,N-dialkylaminoalkyl 3-thienyl sulfide hydrochlorides the procedure, used initially in the present investigation, is shown in the following sequence of reactions.

$$2\ \mathrm{R_2NH + Cl(CH_2)_nOH \xrightarrow[EtOH]{NaI} R_2N(CH_2)_nOH + R_2NH\cdot HCl}$$

$$\mathrm{R\ N(CH_2)_nOH + SOCl_2 \xrightarrow{CHCl_3} \underset{HCl}{R_2N(CH_2)_nCl} + SO_2}$$

This method had the advantages of ready availability of reagents, excellent yields, few side-reactions and easy purification of the product.

The preparation of the N(ω -hydroxyalkyl) morpholines and piperidines was carried out by refluxing a stirred mixture of the secondary amine and chlorohydrin in absolute ethanol to which a small quantity of sodium iodide had been added. The latter accelerated the reaction by replacing the organic chlorine with iodine. The molar ratio of reactants employed was two of amine to one of chlorohydrin, and the reaction time was 23 to 24 hours. The precipitate of secondary amine hydrochloride, proportional to the amount of product, separated during the reaction. In general, piperidine, due to its greater basicity, reacted somewhat more rapidly than did morpholine. The yields obtained varied between 63 and 86 percent. The -hydroxy compounds were obtained as colorless liquids by vacuum distillation.

The N(ω-chloroalkyl) piperidines and morpholines were obtained from the corresponding ω-hydroxy compounds by means of the Darzens reaction using dry chloroform as a solvent. Yields ranging from 50 to 95 percent were obtained by treating the N(ω-hydroxyalkyl) amines with a 25 percent excess of thionyl chloride under conditions which prevented any sudden reaction temperature rise during the addition of thionyl chloride. The reaction was completed by refluxing at the boiling point of chloroform for an additional hour, during which the reaction mixture generally became dark red in color and the hydrochloride salt of the product crystallized from the reaction medium. It was found that yields were considerably improved by sweeping a current of dry air across the reaction surface to remove sulfur dioxide which seemed to cause greater coloration in the reaction mixture.

Five of the ω(dialkylamino)alkyl chlorides have not been previously reported and some of their physical properties are recorded in Table 1.

The tertiary amine derivatives of the mixed 3-thienyl

TABLE 1

ω-(N,N-DIALKYLAMINO)-ALKYL CHLORIDE HYDROCHLORIDES

Compound: Chloride hydrochloride	Formula	m.p. °C	Percent nitrogen	
			Calc'd.	Found
α-Methyl-β piperidinoethyl	$C_8H_{17}NCl_2$	207.5-209	7.07	6.95 6.99
ε-Piperidino-n-amyl	$C_{10}H_{21}NCl_2$	138.5-140	6.19	6.21 6.33
α-Methyl-β morpholinoethyl	$C_7H_{15}ONCl_2$	180 -181.5	6.99	6.91 7.13
δ-Morpholino-n-butyl	$C_8H_{17}ONCl_2$	120 -121	6.54	6.63 6.61
ε-Morpholino-n-amyl	$C_9H_{19}ONCl_2$	122.5-124	6.13	6.30 6.19

alkyl sulfides were obtained from the N(ω-chloroalkyl) amines by treatment of the latter with an excess of 3-thiophenethiol dissolved in aqueous sodium hydroxide solution. The reaction mixture was refluxed for one to two hours during which the product separated as a heavy yellowish oil. This was separated and the reaction mixture extracted three times with ether. The combined oil and ether extracts were dried over anhydrous sodium sulfate. Addition of dry hydrogen chloride to the cooled ether solution converted the amines to their salts which, in certain instances, separated as a yellowish oil. Crystallization was induced only after allowing the oil to set at room temperature for some time with occasional scratching of the walls of the vessel. Isopropyl alcohol was suitable for recrystallization of some of the products. In others, a mixture of equal parts of isopropyl alcohol and benzene, to which a small quantity of ether was added while the benzene-alcohol mixture was still hot, served more adequately.

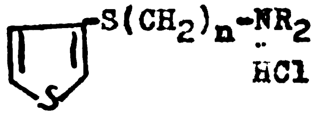
Altogether, ten new N,N-dialkylaminoalkyl 3-thienyl sulfide hydrochlorides which have not previously been reported were prepared and some of their properties are summarized in Table 2.

In one case it was possible to prepare the -chloroalkyl amine in excellent yield by a simple direct procedure indicated in the following equation.

$$2\ R_2NH + Br(CH_2)_3Cl \xrightarrow{C_6H_6} R_2N(CH_2)_3Cl + R_2NH \cdot HBr$$

TABLE 2

ω(N,N-DIALKYLAMINO)ALKYL-3-THIENYL SULFIDE HYDROCHLORIDES

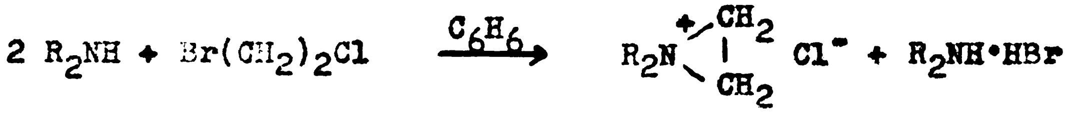


Compound: -3-Thienyl sulfide hydrochloride	Formula	m.p. °C	Percent nitrogen		Percent sulfide	
			Calc'd.	Found	Calc'd.	Found
β-Piperidinoethyl[a]	$C_{11}H_{18}S_2NCl$	149.5-150.5	5.31	5.38 5.27	12.15	12.26 12.41
α-Methyl-β-piperidino-ethyl[b]	$C_{12}H_{20}S_2NCl$	172 -173.5	5.04	5.01 5.16	11.54	11.76 11.81
γ-Piperidino-n-propyl[a]	$C_{12}H_{20}S_2NCl$	120 -121	5.04	5.09 5.17	11.54	11.36 11.67
δ-Piperidino-n-butyl[c]	$C_{13}H_{22}S_2NCl$	131 -133	4.80	4.72 4.68	10.98	10.61 10.72
ε-Piperidino-n-amyl[d]	$C_{14}H_{24}S_2NCl$	89.5- 91.5	4.58	4.52 4.68	10.48	10.54 10.67
β-Morpholinoethyl[b]	$C_{10}H_{16}OS_2NCl$	109 -110.5	5.27	5.20 5.31	12.06	11.96 11.81
α-Methyl-β-morpholino-ethyl[d]	$C_{11}H_{18}OS_2NCl$	95 - 96	5.00	4.91 5.18	11.46	11.62 11.70
γ-Morpholino-n-propyl[b]	$C_{11}H_{18}OS_2NCl$	157 -158.5	5.00	4.92 5.09	11.46	11.65 11.79
δ-Morpholino-n-butyl[b]	$C_{12}H_{20}OS_2NCl$	148 -150	4.77	4.88 4.92	10.93	11.19 11.16
ε-Morpholino-n-amyl[d]	$C_{13}H_{22}OS_2NCl$	135 -136.5	4.55	4.51 4.69	10.41	10.28 10.64

Solvents employed for recrystallization:

a - ethanol	c - ethanol and benzene
b - isopropyl alcohol	d - isopropyl alcohol and benzene

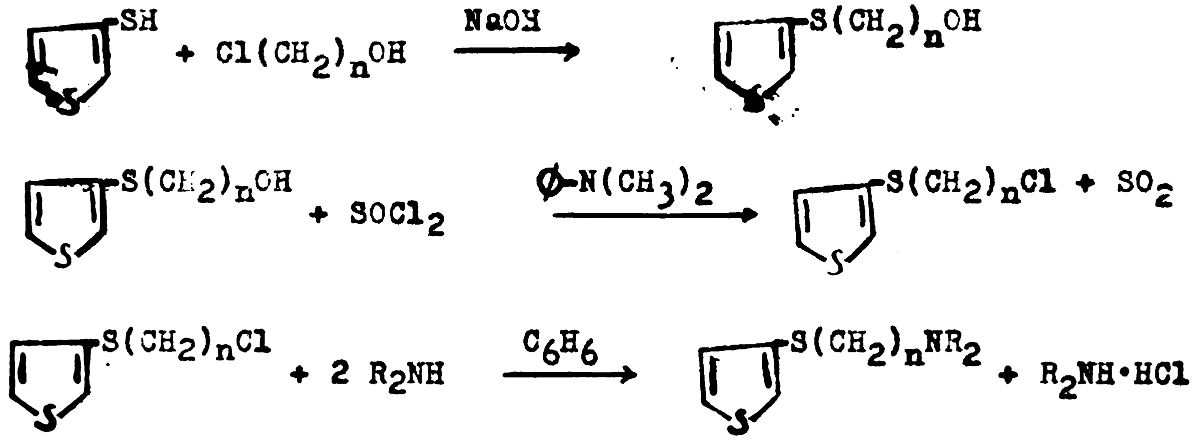
This reaction was found applicable only in the case of the trimethylene chlorobromide since by using either ethylene or propylene chlorobromide the product had the properties of a quaternary ammonium salt and was probably an ethyl immonium halide.



$$2\ R_2NH + Br(CH_2)_2Cl \xrightarrow{C_6H_6} R_2\overset{+}{N}\left<\begin{matrix}CH_2\\ |\\ CH_2\end{matrix}\right.\ Cl^- + R_2NH\cdot HBr$$

This difficulty was not encountered when the trimethylene derivative was employed and this may be attributed to the much greater difficulty involved in the formation of azetidenium compounds. The method employed involved the interaction of trimethylene chlorobromide and the secondary amine in approximately a one to two mole ratio. The reaction was carried out in dry benzene and upon raising the temperature an exothermic reaction took place causing the mixture to reflux for about one-half hour without the application of heat. The reaction was completed by heating at reflux temperature for an additional three hours. The greater reactivity of an alkyl bromide compared to that of a chloride resulted in almost exclusive formation of the N(ω-chloroalkyl) amine.

In an effort to improve the yields of the final product and to shorten the time required for their preparation a second general method of synthesis was studied, and is indicated in the following series of reactions.



While this method could be carried out in a shorter period of time, there were several objections to it. The final product contained an impurity which was very difficult to remove, and caused considerable difficulty in the crystallization of the hydrochlorides. It was further found that the Darzens reaction, involved in the second step, resulted in charring and poor yields. As noted above, this method was economical of time since the ω-chloroalkyl 3-thienyl sulfide could be reacted with various secondary amines in the last step permitting the preparation of a variety of final compounds.

The first step of the reaction followed closely the procedure of Kirner and Holmes[23], who prepared phenyl derivatives, and was found to be applicable to the derivatives of thiophene. The procedure involved the careful addition of a slight excess of the polymethylene chlorohydrin to an aqueous 20 percent sodium hydroxide solution of 3-thiophenthiol. The reaction mixture was refluxed for an hour in which time the ω-hydroxyalkyl 3-thienyl sulfide separated as an oil. The purified product was obtained, in yields of 85 to 95 percent, as a straw colored oil by vacuum distillation.

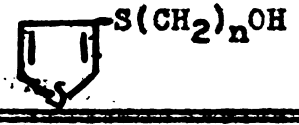
Three ω-hydroxyalkyl-3-thienyl sulfides, two of which have not been reported, were prepared and some data on their physical properties is recorded in Table 3. These alcohols were further characterized by the preparation of their p-phenylazo benzoates. Some information concerning the properties of these derivatives is reported in Table 5.

Replacement of the hydroxyl group in the ω-hydroxyalkyl 3-thienyl sulfides by chlorine was successfully carried out by treatment of the alcohols with a half molar excess of purified thionyl chloride dissolved in dimethyl aniline. The temperature of the reaction was kept at 0° C during the addition of thionyl chloride by means of an ice bath. This was followed by heating for a half hour at reflux temperature, to complete the reaction, following the procedure developed by Bennett and Berry[18] for the preparation of ω-chloroalkyl phenyl sulfides. The ω-chloroalkyl 3-thienyl sulfide separated from the reaction medium as a thick oil. After extraction with ether, drying and removal of the ether, the product was obtained, in low yields as a straw colored oil, by vacuum distillation. The yield was not substantially increased by reverse addition of the reagents.

One ω-chloroalkyl-3-thienyl sulfide, not previously reported, was prepared by this method and some of its physical

TABLE 3

ω-HYDROXYALKYL-3-THIENYL SULFIDES

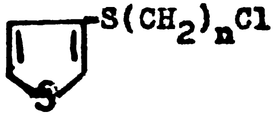


Compound: 3-Thienyl sulfides	Formula	b.p. °C/mm	Percent sulfide Calc'd.	Percent sulfide Found
δ-Hydroxy-n-butyl	$C_8H_{12}OS_2$	134-135/1.5	16.49	16.02 16.42
β-Methyl- β-hydroxyethyl	$C_7H_{10}OS_2$	111/4	18.40	18.26 18.81
β-Hydroxyethyl*	$C_6H_8OS_2$	116-117/2	20.02	20.56 20.23

*Reported by Brooks[24].

TABLE 4

ω-CHLOROALKYL-3-THIENYL SULFIDES



Compound: 3-Thienyl sulfides	Formula	b.p. °C/mm	Percent sulfide Calc'd.	Percent sulfide Found
δ-Chloro-n-butyl	$C_8H_{11}S_2Cl$	135/1.5	15.51	15.78 15.92
β-Chloroethyl	$C_6H_7S_2Cl$	123/8	17.93	18.38 17.71

TABLE 5

p-PHENYL-AZOBENZOATES OF THE -HYDROXYALKYL-3-THIENYL SULFIDES

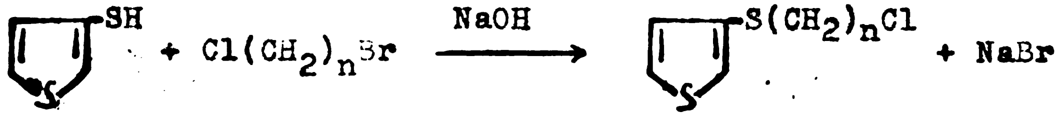
Derivative* of 3-thienyl sulfides	Formula	m.p. °C	Percent nitrogen	
			Calc'd.	Found
δ-Hydroxy-n-butyl	$C_{21}H_{20}O_2S_2N_2$	79- 80	7.06	7.12 6.91
β-Methyl- β-hydroxyethyl	$C_{20}H_{18}O_2S_2N_2$	224-225	7.32	7.31 7.48
β-Hydroxyethyl	$C_{19}H_{16}O_2S_2N_2$	98- 98.5	7.60	7.69 7.52

*All recrystallized from ethanol

properties are reported in Table 4.

The N,N-dialkylaminoalkyl 3-thienyl sulfides were prepared by reacting the ω-chloroalkyl 3-thienyl sulfides with twice the molar quantity of secondary amine in dry benzene. At the end of about four hours of heating at reflux, the reaction mixture, which then contained the insoluble hydrochloride salt of the excess secondary amine, was cooled and made basic. The excess secondary amine was completely removed from this mixture by steam distillation as shown by the application of the Simon's color test[29] to the distillate. Acidification of the distillation residue and extraction with ether removed any unreacted ω-chloroalkyl 3-thienyl sulfide. Following this, the aqueous solution was again made basic whereupon the tertiary amine separated as an oil which was taken up in ether and dried. Dry hydrogen chloride was passed slowly into the ethereal solution to yield the hydrochloride of the product as a heavy oil which was difficult to obtain in a crystalline form. Isopropyl alcohol or a mixture of isopropyl alcohol, benzene and ether was used as a solvent for recrystallization of the amine salts.

The direct preparation of the ω-chloroalkyl 3-thienyl sulfide by the interaction of appropriate polymethylene chlorobromides and 3-thiophenethiol was also studied with the aim of elimination of the Darzen's reaction.



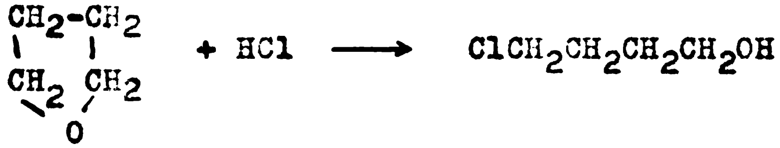
However, yields were not good and mixtures of products were obtained from which it was difficult to isolate pure products. This reaction depended upon the greater reactivity of the bromine in a polymethylene chlorobromide. The procedure involved the careful addition of an aqueous solution of sodium 3-thiophenethiolate to a stirred and refluxed mixture of polymethylene chlorobromide and water. The product was isolated by extraction with ether, drying, and distillation under vacuum.

One ω-chloroalkyl sulfide was prepared for the first time by this method and some of its properties are reported in Table 4.

A study of the methods of preparation employed reveals that the first general method is most applicable to the synthesis of the desired series of compounds. The yields are, in general, better, isolation is simpler, the purity of the products is more satisfactory, and fewer side-reactions are involved in the synthesis.

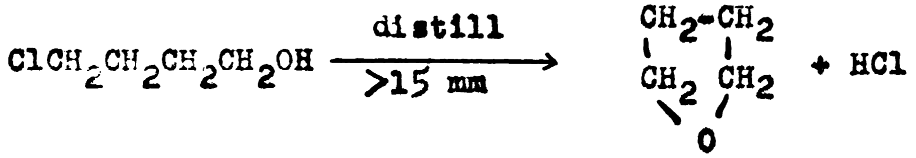
Of the polymethylene chlorohydrins used for the preparations just described, ethylene chlorohydrin, prophylene chlorohydrin, trimethylene chlorohydrin, and pentamethylene chlorohydrin were available.

Tetramethylene chlorohydrin was prepared by treating tetrahydrofuran with gaseous hydrogen chloride according to the method described by Starr and Hixson.[30]



Contrary to the report of Starr and Hixson[30], who reported that only five hours of passing hydrogen chloride into the reaction mixture were required to reach a constant temperature of 105° C, it was found that twenty-four hours were necessary before a constant temperature of 103° C was attained.

The tetrahydrofuran was heated to its boiling point, then a slow stream of hydrogen chloride was passed into it. As the reaction proceeded the temperature of the reaction mixture rose, indicating an increase in the high-boiling product. When the temperature of the refluxing solution remained constant the constituents of the reaction were separated by fractional distillation at a pressure less than 15 mm, since at a higher pressure the tetramethylene chlorohydrin was dehydrohalogenated to give tetrahydrofuran.



The possible side reactions which could be ascribed to the low yields have been reported.[31]

CHEMICAL REAGENTS

3-Thiophenethiol - (App. 50%) Courtesy of Socony-Vacuum, purified by extraction with sodium hydroxide solution, neutralization of the aqueous portion with hydrochloric acid and vacuum distillation, b.p., 64° C/17 mm.

Piperidine - Practical grade, Eastman Kodak Co.

Morpholine - Technical grade, Matheson Co.

Ethylene chlorohydrin - White label, Eastman Kodak Co.

Propylene chlorohydrin - White label, Eastman Kodak Co.

Trimethylene chlorohydrin - Practical grade, Matheson Co.

Ethylene chlorobromide - Practical grade, Matheson Co.

Trimethylene chlorobromide - Practical grade, Matheson Co.

Pentamethylene chlorohydrin - Obtained as student preparation.

Tetrahydrofuran - Courtesy of E. I. DuPont de Nemours Co.

Thionyl chloride - C. P. grade, purified by distillation from quinoline followed by distillation from boiled linseed oil.

Ethanol - C. P. grade, absolute, dried by distillation from magnesium powder.

Chloroform - C. P. grade, absolute, Merck & Co.

Benzene - C. P. grade, dried by distillation from sodium.

Ether - C. P. grade, absolute, dried in contact with sodium.

2-Morpholino-ethanol - Courtesy of Carbide and Carbon Chemicals Co.

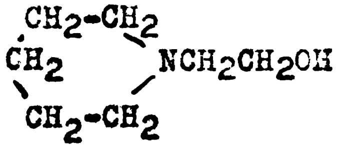
Isopropyl alcohol - C. P. grade, absolute.

Hydrogen chloride - Anhydrous gas, obtained in a pressure cylinder from Matheson Co.

EXPERIMENTAL

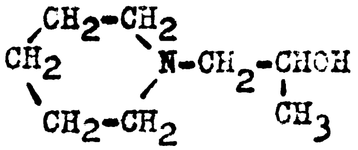
ω(N,N-Dialkylamino)alkyl Alcohols

β-Piperidinoethyl alcohol



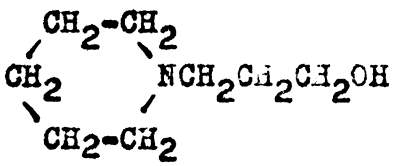
In a 500 ml three-necked flask fitted with a stirrer and reflux condenser was placed 80 g (1.0 mole) of ethylene chlorohydrin, 166 g (2.0 moles) of piperidine and 7.5 g of sodium iodide dissolved in 225 ml of absolute ethanol. The stirred mixture was heated moderately with an electric mantel. Within an hour, precipitation of piperidine hydrochloride commenced. Reaction was continued for 24 hours, at the end of which time there was no further precipitation, indicating completeness of reaction. After allowing the reaction mixture to cool to room temperature, it was treated with a solution containing 200 ml of absolute ethanol and 22 g of dissolved sodium metal. The precipitate of inorganic salts was filtered and washed with three 50 ml portions of dry ethyl ether. The combined filtrate and washings were distilled until a temperature of 110° C was reached in the column head to remove ether, alcohol, and unreacted piperidine. At this point the remaining inorganic salts were removed by filtration and washed with ether which was combined with the filtrate. Following removal of the ether on a steam bath, the residue was vacuum distilled in a column 30 cm in height, 12 mm in diameter packed with 1/8" glass helices, to yield 109 g (0.845 moles, 84.5% yield) of a clear oily liquid having an unpleasant odor and boiling at 90-92° C/16-17 mm. A small amount of unreacted chlorohydrin was obtained in the forerun. The reported boiling point of the product is 89-91° C/20 mm.[32]

α-Methyl-β-piperidinoethyl alcohol



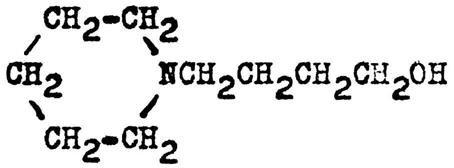
Using the apparatus and procedure described above, 94 g (1.0 mole) of propylene chlorohydrin and 166 g (2.0 moles) of piperidine were dissolved in 225 ml of absolute ethanol containing 7.5 g of sodium iodide. The stirred mixture was heated under reflux for 24 hours and then cooled. After neutralization, filtration, and distillation as previously described, the crude oil was fractioned giving 112 g (0.785 moles, 78.5% yield) of a clear product boiling at 63-65° C/4-5 mm. The reported boiling point is 194° C.[33]

γ-Piperidino-n-propyl alcohol



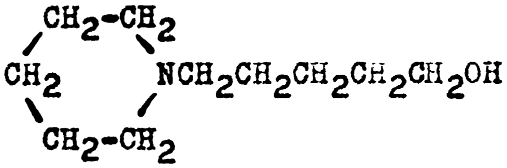
The apparatus and procedure employed here were the same as in the previous preparations. This compound was prepared by refluxing for 24 hours a stirred mixture of 166 g (2.0 moles) of piperidine, 94 g (1.0 mole) of trimethylene chlorohydrin and 7.5 g of sodium iodide in 200 ml of absolute ethanol as a solvent. Following the separation procedure used in the former preparations, the crude product was fractioned, yielding 117 g (0.82 moles, 82% yield) of a pure produce which boiled in the range 83-86° C/8-9 mm. Its reported boiling point is 93.5-95° C/9 mm.[26]

δ-Piperidino-n-butyl alcohol



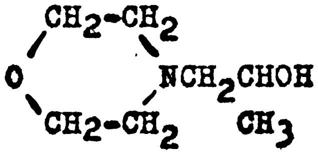
Using the same general procedure discussed above, 70 g (0.65 mole) of tetramethylene chlorohydrin, 108 g (1.3 moles) of piperidine and 6 g of sodium iodide dissolved in 150 ml of absolute ethanol were heated under reflux with stirring for 22 hours. Fractionation of the crude product yielded 78 g (0.495 moles, 76% yield) of the pure product which distilled at 114-116° C/6 mm. The reported boiling point for this compound is 142-144° C/15 mm.[34]

ε-Piperidino-n-amyl alcohol



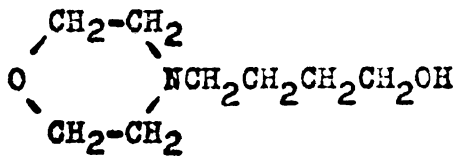
Following the same technique as that used in the foregoing experiments, the interaction of 25 g (0.205 mole) of pentamethylene chlorohydrin, 33.8 g (0.40 mole) of piperidine, and 3 g of sodium iodide dissolved in 100 ml of absolute ethanol, gave, after purification and fractionation, 22.5 g (0.128 moles, 64% yield) of a clear colorless liquid product. The boiling point at a pressure of 10 mm was 134-135° C. The literature value for the boiling point of the compound is 163-165° C/15 mm.[34]

α-Methyl-β morpholinoethyl alcohol



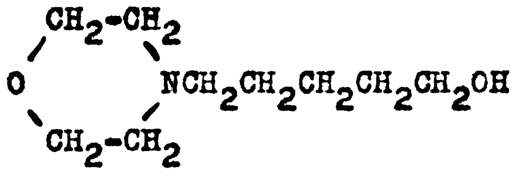
By reacting 57 g (0.5 mole) of propylene chlorohydrin, 87 g (1.0 mole) of morpholine and 4 g of sodium iodide in 125 ml of absolute ethyl alcohol, there was obtained, according to the previously described procedure, 62 g (0.43 moles, 86% yield) of a colorless liquid which distilled at 96-97° C/12 mm. The reported boiling point of this substance is 81-82° C/5 mm.[35]

δ-Morpholino-n-butyl alcohol



The same procedure and apparatus was used as in the preparations described earlier. By stirring and maintaining at reflux temperature, a mixture of 70 g (0.65 mole) of tetramethylene chlorohydrin, 111 g (1.3 moles) of morpholine and 6 g of sodium iodide in 150 ml of dry ethanol, there resulted, after purification and fractionation, 82 g (0.514 moles, 79% yield) of a pure liquid product distilling at 131-133° C/7 mm. The boiling point given in the literature is 116-117° C/5 mm.[35]

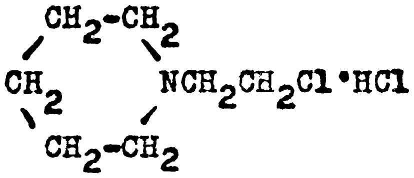
ε-Morpholino-n-amyl alcohol



By a similar procedure, involving the interaction of 25 g (0.205 mole) of pentamethylene chlorohydrin, 34 g (0.4 mole) of morpholine, and 3 g of sodium iodide in 100 ml of absolute ethanol, there was obtained after purification and fractionation 22 g (0.126 moles, 63% yield) of a liquid product boiling at 151-151.5° C/11 mm. The reported boiling point is 133-134° C/5 mm.[35]

ω-N,N-Dialkylamino)alkyl Chloride Hydrochlorides

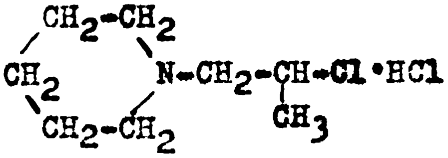
β-Piperidinoethyl chloride hydrochloride



In a 500 ml three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel were placed 65 g (0.5 mole) of β-piperidinoethyl alcohol. Provision was made to draw a slow stream of dry air through the reaction flask. To the reaction flask was added a solution of 72 g (0.6 mole) of purified thionyl chloride dissolved in 100 ml of dry chloroform at a rate sufficient to maintain the reaction temperature between 50 and 55° C. Following the addition of the thionyl chloride solution, which required two hours, the reaction mixture was heated on a steam bath at reflux temperature for a half hour. Upon cooling to room temperature, a crystalline solid separated from the reaction mixture. This was collected on a filter and washed with dry ether. The combined ether washings and filtrate was evaporated to one-third of its original volume and on cooling a second crop of crystals was obtained. The two quantities of crystalline material were combined and recrystallized from 250 ml of absolute ethanol, using 5 g of Norit A. to remove colored material. The crystals, after washing with ether and drying, weighed 60 g (0.33 moles, 66% yield) and had a melting point of 206.5-208° C.

The reported melting point of this material is 208° C.[36]

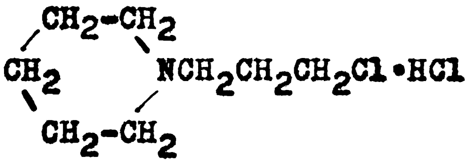
α-Methyl-β piperidinoethyl chloride hydrochloride



The reaction of 71 g (0.5 mole) of α-methyl-β-piperidinoethyl alcohol with 89 g (0.75 mole) of thionyl chloride dissolved in 100 ml of dry chloroform, following the previously described procedure, resulted in the formation of a slightly yellow crystalline product. After recrystallization from 150 ml of absolute ethanol, there was obtained 52 g (0.265 moles, 53% yield) of colorless crystals which melted at 207.5-209° C. Analysis of the compound for nitrogen gave the following results:

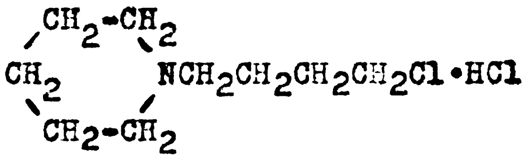
Calc'd. for $C_8H_{17}NCl_2$: N, 7.07. Found: N, 6.95; 6.99.

γ-Piperidino-n-propyl chloride hydrochloride



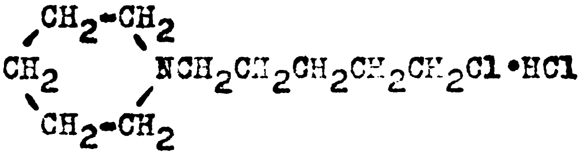
Following the procedure employed in previous preparation, 70 g (0.5 mole) of γ-piperidino-n-propyl alcohol were treated with a solution of 75 g (0.65 mole) of thionyl chloride dissolved in 75 ml of dry chloroform. The slightly brown crude product was treated as in the foregoing preparations, and after recrystallization from 180 ml of dry ethanol, 60 g (0.305 moles, 61% yield) of a white crystalline product melting at 218-219.5° C was obtained. Its reported melting point is 220° C.[37]

δ-Piperidino-n-butyl chloride hydrochloride



The same general procedure as previously described was employed, using 15.7 g (0.10 mole) of δ-piperidino-n-butyl alcohol and 15 g (0.125 mole) of thionyl chloride dissolved in 50 ml of dry chloroform. Recrystallization of the crude product from a mixture of equal parts of ethanol andether resulted in 16 g (0.094 moles, 93.5% yield) of a white crystalline product. The melting point was 160.5-161.5° C, and the reported literature value is 162° C.[38]

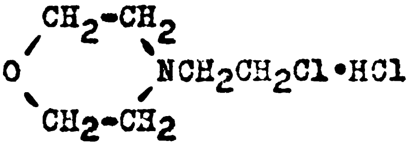
ε-Piperidino-n-amyl chloride hydrochloride



Adding, during a one hour period, 13.1 g (0.11 mole) of thionyl chloride dissolved in 25 ml of dry chloroform to 15 g (0.088 mole) of ε-piperidino-n-amyl alcohol in 25 ml of the same solvent and heating this reaction mixture at reflux for an additional half hour resulted in 17.5 g of a crude yellow crystalline product. After recrystallization from a mixture of equal volumes of benzene and ethanol, there was obtained 16 g (0.071 moles, 80.4% yield) of a pure crystalline material melting at 138.5-140° C. Analysis of the compound for nitrogen gave the following data:

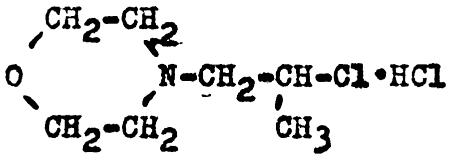
Calc'd. for $C_{10}H_{21}NCl_2$: N, 6.19. Found: N, 6.21; 6.33.

β-Morpholinoethyl chloride hydrochloride



The reaction of 64 g (0.5 mole) of β-morpholinoethyl alcohol with 72 g (0.605 mole) of thionyl chloride using 100 ml of dry chloroform as a solvent over a one hour period resulted in the precipitation of the product as the hydrochloride. By means of the previously described separation procedure and recrystallization from isopropyl alcohol, there was obtained 67.5 g (0.395 moles, 79% yield) of a white crystalline product which melted at 186-187.5° C. The melting point given in the literature for this substance is 182-182.5° C.[27]

α-Methyl-β-morpholinoethyl chloride hydrochloride

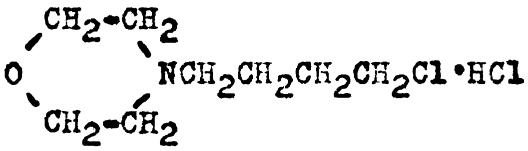


Treatment of 35 g (0.24 mole) of α-methyl-β-morpho-

linoethyl alcohol with 36 g (0.3 mole) of thionyl chloride in 100 ml of dry chloroform according to the previously discussed procedure resulted in the formation of the crude yellow product. Recrystallization from dry ethanol gave 36 g (0.19 moles, 79% yield) of a white crystalline solid melting at 180-181.5° C. A nitrogen analysis of the compound resulted in the following data:

Calc'd. for $C_7H_{15}NOCl_2$: N, 6.99. Found: N, 6.91; 7.18.

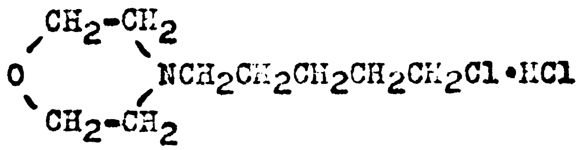
δ-Morpholino-n-butyl chloride hydrochloride



Addition from a dropping funnel of 31 g (0.26 mole) of thionyl chloride dissolved in 25 ml of dry chloroform to 40 g (0.226 mole) of δ-morpholino-n-butyl alcohol dissolved in 25 ml of the same solvent during a period of one hour followed by 30 minutes of heating at reflux temperature gave a slightly colored reaction mixture. After the usual isolation procedure and recrystallization from a mixture of equal parts of benzene and ethanol, there resulted 47 g (0.22 moles, 97% yield) of a white crystalline solid whose melting point is 120-121° C. Analysis of the compound for nitrogen resulted in the following information:

Calc'd. for $C_8H_{17}NOCl_2$: N, 6.54. Found: N, 6.63; 6.61.

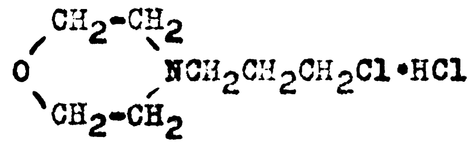
ε-Morpholino-n-amyl chloride hydrochloride



The reaction of 15 g (0.087 mole) of ε-morpholino-n-amyl alcohol with 13.1 g (0.11 mole) of thionyl chloride dissolved in 50 ml of absolute chloroform resulted in a practically colorless reaction mixture. After separation of the crude product and purification by recrystallization from an isopropyl alcohol-benzene mixture of equal parts, there was obtained 19 g (0.083 moles, 95.5% yield) of the pure crystalline product which melted at 122.5-124° C. A nitrogen analysis gave the following information:

Calc'd. for $C_9H_{19}NOCl_2$: N, 6.13. Found: N, 6.30; 6.19.

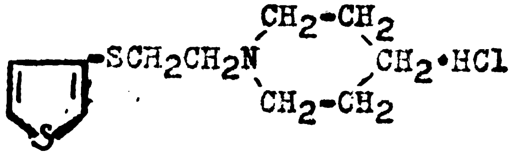
γ-Morpholino-n-propyl chloride hydrochloride



Into a dry three-necked 500 ml flask fitted with a reflux condenser, dropping funnel and stirrer was placed 60 g (0.38 mole) of trimethylene chlorobromide dissolved in 150 ml of dry benzene. To this solution 50 g (0.6 mole) of morpholine was added with stirring. After the addition of the morpholine was completed the reaction mixture was heated gently until an exothermic reaction took place which caused the solution to reflux for about a half hour without the application of heat. Morpholine hydrobromide had begun to precipitate almost immediately and after a further half hour of heating at reflux temperature the reaction appeared to be complete as indicated by no further salt formation. The crystalline morpholine hydrobromide was removed by filtration and washed thoroughly with dry ether. The ether washings were combined with the benzene solution and then were extracted with 3N hydrochloric acid. The aqueous acid extract was made basic with 10N sodium hydroxide and the oil layer which separated was removed in a separatory funnel. The aqueous layer was extracted once with ether. The combined ether extract and oil were dried over anhydrous sodium sulfate. Gaseous hydrogen chloride was passed slowly into the chilled ether solution to form the insoluble amine hydrochloride which was filtered and washed with dry ether. After recrystallization from isopropyl alcohol 45 g (0.22 moles, 73% yield) of a white crystalline material was obtained which melted at 162.5-164° C. The free base, obtained by making basic an aqueous solution of the amine salt and extraction with ether, boiled at 101-102° C/20 mm. The reported boiling point is 113-115° C/25 mm.[28]

ω(N,N-Dialkylamino)alkyl-3-Thienyl Sulfide Hydrochlorides

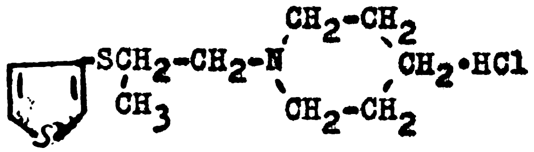
β-Piperidinoethyl-3-thienyl sulfide hydrochloride



Into a dry three-necked 500 ml flask equipped with stirrer, reflux condenser and dropping funnel was poured 33 g (0.25 mole) of 3-thiophenethiol dissolved in a solution containing 30 g of sodium hydroxide in 100 ml of water. To this was added from a dropping funnel 28 g (0.15 mole) of -piperidinoethyl chloride hydrochloride dissolved in 100 ml of water. The stirred reaction mixture was maintained at reflux temperature during the addition of the salt solution which required an hour. Reaction was continued for an additional hour and a half, at the end of which a yellowish oil had separated. This was removed and the aqueous layer was extracted three times with 100 ml portions of ether. The combined ether extracts and oil was washed with a 5 percent sodium hydroxide solution and then with water to remove any unreacted 3-thiophenethiol. After drying with anhydrous sodium sulfate, the ether solution, while being kept cold, was treated with a gentle stream of dry hydrogen chloride until there was no further precipitation of amine hydrochloride. Difficulties were frequently encountered in filtering the sticky white hydrochloride. These were best overcome by using just sufficient hydrogen chloride for completing the precipitation. The bulky precipitate was collected on a Buchner funnel and the filtrate tested with hydrogen chloride gas for complete removal of amine. The crude hydrochloride was dissolved in 100 ml of hot, dry isopropyl alcohol and decolorized with Norit. Two recrystallizations from isopropyl alcohol and a final washing with dry ether followed by drying gave 29 g (0.124 moles, 83% yield) of a white crystalline product which melted at 149.5-150.5° C. Analysis of the compound for nitrogen and sulfide sulfur gave the following results:

Calc'd. for $C_{11}H_{18}NS_2Cl$: N, 5.31; S, 12.15. Found: N, 5.38; 5.27. S, 12.26; 12.41.

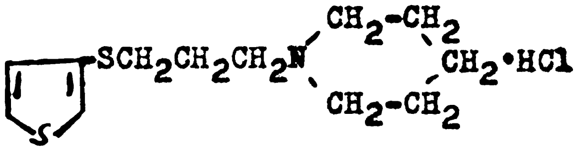
α-Methyl-β-piperidinoethyl-3-thienyl sulfide hydrochloride



Following the same procedure as described above, 33 g (0.25 mole) of 3-thiophenethiol dissolved in a solution containing 30 g of sodium hydroxide in 100 ml of water were treated with 20 g (0.10 mole) of α-methyl-β-piperidinoethyl chloride hydrochloride dissolved in 100 ml of water. The addition of the latter reactant required an hour and was followed by a half hour of heating, with good stirring, at reflux temperature. The product was purified in the previously described manner. The hydrochloride was recrystallized from dry isopropyl alcohol giving 20 g (0.083 moles, 83% yield) of a crystalline salt which melted at 172-173.5° C. The analysis of the compound for nitrogen and sulfide sulfur gave the following results:

Calc'd. for $C_{12}H_{20}NS_2Cl$: N, 5.04; S, 11.54. Found: N, 5.01; 5.16. S, 11.76; 11.81.

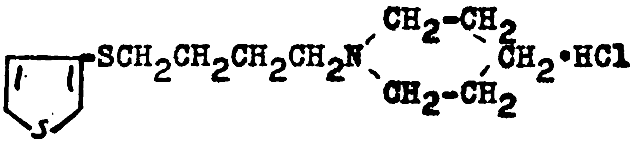
γ-Piperidino-n-propyl-3-thienyl sulfide hydrochloride



The procedure was the same as that employed in the previous preparations. A quantity of 40 g (0.2 mole) of γ-piperidino-n-propyl chloride hydrochloride in 100 ml of water was added to a well-stirred solution, at its reflux temperature, of 66 g (0.50 mole) of 3-thiophenethiol dissolved in 100 ml of water containing 40 g of sodium hydroxide. Two hours were required for the reaction to be completed. After the usual operations, the crude hydrochloride was recrystallized from absolute ethanol. The pure crystalline product weighed 45 g (0.162 moles, 81% yield) and had a melting point of 120-121° C. The analysis of the compound for nitrogen and sulfide sulfur resulted in the following data:

Calc'd. for $C_{12}H_{20}NS_2Cl$: N, 5.04; S, 11.54. Found: N, 5.09; 5.17. S, 11.36; 11.67.

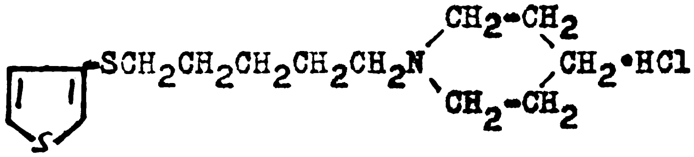
δ-Piperidino-n-butyl-3-thienyl sulfide hydrochloride



Interaction of 13.2 g (0.10 mole) of 3-thiophenethiol dissolved in a solution of 10 g of sodium hydroxide in 30 ml of water with 19 g (0.05 mole) of δ-piperidino-n-butyl chloride hydrochloride in 30 ml of water resulted in the separation of an oily product after heating for an hour and a half at reflux temperature. After the usual purification procedure the hydrochloride salt of the product was recrystallized twice from a mixture of equal parts of ethanol and benzene to yield 13 g (0.045 moles, 89% yield) of a pure crystalline product melting at 131-133° C. Analysis of the compound for nitrogen and sulfide sulfur gave the following data:

Calc'd. for $C_{13}H_{22}NS_2Cl$: N, 4.89; S, 10.98. Found: N, 4.72; 4.68. S, 10.61; 10.72.

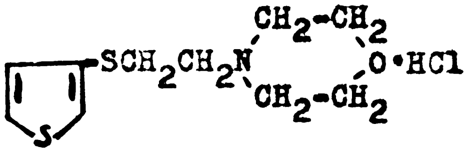
ϵ-Piperidino-n-amyl-3-thienyl sulfide hydrochloride



Employing 12 g (0.053 mole) of ϵ-piperidino-n-amyl chloride hydrochloride in 50 ml of water and 7 g (0.06 mole) of 3-thiophenethiol dissolved in a solution containing 6 g of sodium hydroxide in 50 ml of water and following the previous procedure, there was obtained, after recrystallization from an isopropyl alcohol and benzene mixture of equal parts, 15 g (0.048 moles, 93% yield) of a crystalline product. The observed melting point was 89.5-91.5° C. Analysis for nitrogen and sulfide sulfur gave the following data:

Calc'd. for $C_{14}H_{24}NS_2Cl$: N, 4.58; S, 10.48. Found: N, 4.52; 4.68. S, 10.54; 10.67.

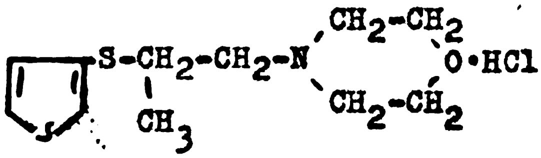
β-Morpholinoethyl-3-thienyl sulfide hydrochloride



Using 11 g (0.083 mole) of 3-thiophenethiol dissolved in a solution of 10 g of sodium hydroxide in 50 ml of water and treating it with 10.5 g (0.056 mole) of β-morpholinoethyl chloride hydrochloride in 25 ml of water, there was obtained an insoluble oil after two hours of heating at reflux temperature. After separation and conversion to its hydrochloride salt, it was recrystallized from isopropyl alcohol. The crystalline product weighed 11.5 g (0.043 moles, 77.5% yield) and gave an observed melting point of 109-110.5° C. The following data was obtained by analysis for nitrogen and sulfide sulfur:

Calc'd. for $C_{10}H_{16}NS_2OCl$: N, 5.27; S, 12.06. Found: N, 5.20; 5.31. S, 11.96; 11.81.

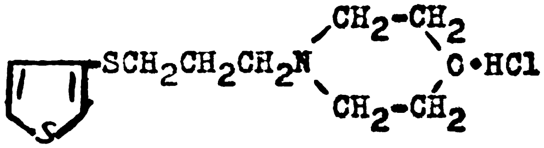
α-Methyl-β-morpholinoethyl-3-thienyl sulfide hydrochloride



The addition of 18 g (0.15 mole) of 3-thiophenethiol dissolved in a solution containing 10 g of sodium hydroxide and 25 ml of water, to 14 g (0.070 mole) of α-methyl-β-morpholinoethyl chloride hydrochloride dissolved in 25 ml of water resulted in the formation of an insoluble oily layer after an hour and a half of heating and stirring at reflux temperature. Using the same isolation procedure and recrystallizing from a one to one isopropyl alcohol-benzene mixture containing a small amount of ether gave 15 g (0.054 moles, 77% yield) of a pure product melting at 95-96° C. Analysis for nitrogen and sulfide sulfur gave the following results:

Calc'd. for $C_{11}H_{18}NS_2OCl$: N, 5.00; S, 11.46. Found: N, 4.91; 5.18. S, 11.62; 11.70.

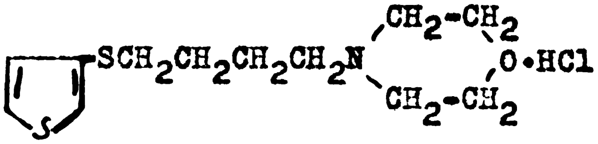
γ-Morpholino-n-propyl-3-thienyl sulfide hydrochloride



To 14 g (0.07 mole) of γ-morpholino-n-propyl chloride hydrochloride dissolved in 25 ml of water was added 18 g (0.15 mole) of 3-thiophenethiol in 25 ml of 10N sodium hydroxide. After the reaction was carried out as described above, a yellow oil separated. This, after separation, purification and recrystallization from isopropyl alcohol, gave 16.5 g (0.060 moles, 85% yield) of the hydrochloride salt which melted at 157-158.5° C. Analysis for nitrogen and sulfide sulfur gave the following results:

Calc'd. for $C_{11}H_{18}NS_2OCl$: N, 5.00; S, 11.46. Found: N, 4.92; 5.09. S, 11.65; 11.79.

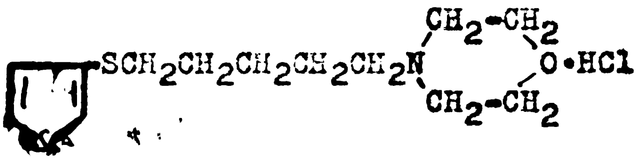
δ-Morpholino-n-butyl-3-thienyl sulfide hydrochloride



The quantity, 7 g (0.06 mole) of 3-thiophenethiol was dissolved in a solution containing 6 g of sodium hydroxide dissolved in 50 ml of water. To this, by means of a dropping funnel, was added a solution of 8 g (0.037 mole) of δ-morpholino-n-butyl chloride hydrochloride in 50 ml of water. Purification and recrystallization from isopropyl alcohol gave 9.5 g (0.034 moles, 92% yield) of crystalline hydrochloride having a melting point of 148-149° C. Analysis for nitrogen and sulfide sulfur resulted in the following analytical data:

Calc'd. for $C_{12}H_{20}NS_2OCl$: N, 4.77; S, 10.98. Found: N, 4.88; 4.92. S, 11.19; 11.16.

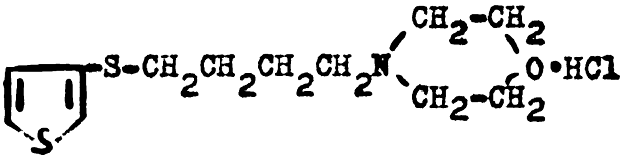
ε-Morpholino-n-amyl-3-thienyl sulfide hydrochloride



The interaction of 12 g (0.052 mole) of ε-morpholino-n-amyl chloride hydrochloride in 50 ml of water and 7 g (0.06 mole) of 3-thiophenethiol dissolved in a solution of 6 g of sodium hydroxide and 50 ml of water, produced an insoluble oil in a reaction period of one hour. Following the usual separation procedure and recrystallization of the product from a benzene-isopropyl alcohol mixture of equal parts, gave 14 g (0.045 moles, 87.5% yield) of a crystalline hydrochloride which melted at 135-136.5° C. Analysis for nitrogen and sulfide sulfur gave the following data:

Calc'd. for $C_{13}H_{22}NS_2OCl$: N, 4.55; S, 10.41. Found: N, 4.51; 4.69. S, 10.28; 10.64.

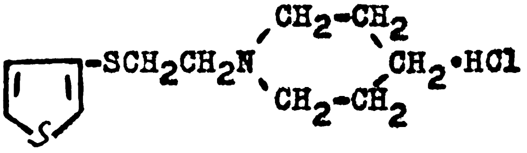
δ-Morpholino-n-butyl-3-thienyl sulfide hydrochloride



In order to test the second general method of synthesis, 7 g (0.034 mole) of δ-chloro-n-butyl-3-thienyl sulfide and 6 g (0.070 mole) of morpholine were added to 50 ml of dry benzene and allowed to stand with occasional shaking for a one-half hour period. Following this the solution was heated at its reflux temperature for four hours, at the end of which no additional formation of morpholine hydrochloride was observed. After cooling to room temperature, the reaction was made basic and steam distilled until the Simon's test for secondary amines indicated the complete removal of excess morpholine. The solution remaining in the distillation flask was made acidic with 4N hydrochloric acid and extracted twice with ether to remove unreacted δ-chloro-n-butyl-3-thienyl sulfide. On neutralization with 4N sodium hydroxide a brownish oil separated which was extracted twice with ether and dried over anhydrous sodium sulfate. Dry hydrogen chloride was slowly passed into the chilled ether solution to form the hydrochloride, which separated as a clear oil. Considerable difficulty was experienced in crystallizing the product and was accomplished only by seeding the oil with a crystal of the compound prepared previously by the first general method. After recrystallization from isopropyl alcohol, there was obtained 1.0 g (0.0035 moles, 10.5% yield) of a crystalline product melting at 146.5-148° C. There was no depression in melting point when a sample of this product was mixed with a sample of the substance prepared in the previously described manner. Analysis for nitrogen gave the following data:

Calc'd. for $C_{12}H_{20}NS_2OCl$: N, 4.77. Found: N, 4.56; 4.51.

β-Piperidinoethyl-3-thienyl sulfide hydrochloride



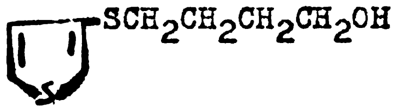
According to the method employed in the previous preparation, 14 g (0.079 mole) of β-chloroethyl-3-thienyl sulfide and 12 g (0.14 mole) of piperidine were added to 100 ml of dry benzene and allowed to stand for a half hour followed by heating at the reflux temperature of the solution for five hours at the end of which there was no further separation of piperidine hydrochloride. After the usual separation procedure the hydrochloride was obtained as a clear oil which could be crystallized only by seeding with a crystal of the compound prepared by the first method. The solid product was recrystallized once from dry isopropyl alcohol by seeding the hot solution with a few crystals of the material. The yield of crystalline material obtained was 4 g (0.015 moles, 19% yield). The substance melted at 148-150° C and gave no depression in melting point when mixed with a sample of the same compound prepared previously.

Analysis for nitrogen gave the following results:

Calc'd. for $C_{11}H_{18}NS_2Cl$: N, 5.31. Found: N, 5.21; 5.19.

ω-Hydroxyalkyl-3-thienyl Sulfides

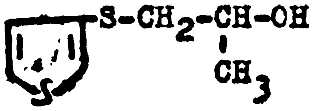
δ-Hydroxy-n-butyl-3-thienyl sulfide



In a 500 ml three-necked flask fitted with a stirrer and reflux condenser was placed 87 g (0.75 mole) of 3-thiophenethiol dissolved in a solution prepared from 35 g of sodium hydroxide and 150 ml of water. To this stirred solution was added dropwise, over a half hour period, 65 g (0.60 mole) of tetramethylene chlorohydrin. Immediately after the addition of the chlorohydrin was completed the reaction mixture was heated to its reflux temperature for an hour and then allowed to cool to room temperature, at which point a yellow oil separated. The oily layer was separated in a separatory funnel and the aqueous fraction extracted twice with ether. The combined ether extracts and oil were washed twice with water and dried over anhydrous sodium sulfate followed by removal of the ether by distillation. The oil was vacuum distilled using the column previously described and resulted in 96 g (0.51 moles, 85% yield) of a clear slightly yellow liquid product. A few ml of unreacted chlorohydrin were obtained in the fore-run. The product boiled at 134-135° C/1.5 mm. Analysis for sulfide sulfur gave the following results:

Calc'd. for $C_8H_{12}S_2O$: S, 16.49. Found: S, 16.02; 16.42.

β-Methyl-β-hydroxyethyl-3-thienyl sulfide

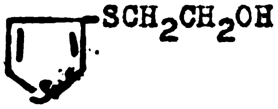


Employing the previously described procedure, 58 g (0.50 mole) of 3-thiophenethiol dissolved in 30 g of sodium hydroxide and 150 ml of water was reacted with 57 g (0.60 mole) of propylene chlorohydrin. After the afore mentioned separation the liquid product was distilled in vacuo to yield 70 g (0.485 moles, 97% yield) of clear yellowish oil boiling at 116° C/5 mm. Analysis for sulfide sulfur gave the following results:

Calc'd. for $C_7H_{10}S_2O$: S, 18.40. Found: S, 18.26; 18.81.

A second preparation gave a yield which was 85 percent of the theoretical and the product distilled at 111° C/4 mm.

β-Hydroxyethyl-3-thienyl sulfide

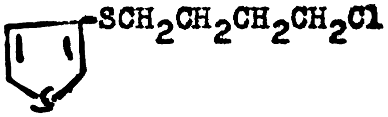


By the interaction of 35 g (0.30 mole) of 3-thiophenethiol dissolved in a solution of 15 g of sodium hydroxide and 150 ml of water with 28 g (0.35 mole) of ethylene chlorohydrin a yellow oily layer was obtained after a reaction period of one hour. Separation and vacuum distillation gave 40.5 g (0.25 moles, 84% yield) distilling at 116-117° C/2 mm. Only the boiling point, 125° C/1 mm, is given in some unpublished work.[24] Analysis of the compound for sulfide sulfur gave the following results:

Calc'd. for $C_6H_8S_2O$: S, 20.02. Found: S, 19.76; 20.23.

ω-Chloroalkyl-3-thienyl Sulfides

δ-Chloro-n-butyl-3-thienyl sulfide

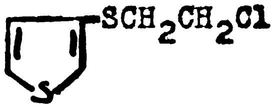


The quantity, 54 g (0.45 mole) of thionyl chloride was added dropwise to a solution of 68 g (0.36 mole) of δ-hydroxy-n-butyl-3-thienyl sulfide dissolved in 35 g of pyridine. The reaction was carried out in an apparatus consisting of a three-necked flask fitted with a stirrer, dropping funnel, and reflux condenser. Provision was made to allow a stream of dry air to be drawn across the surface of the reaction mixture. Stirring was maintained during the addition of the thionyl chloride and at various time intervals the reaction flask was immersed in an ice bath to control the exothermic reaction. Addition of the thionyl chloride required an hour after which the reaction mixture was allowed to cool to room temperature. The crude, brown, oily product was washed twice with water, dissolved in 200 ml of ether and dried over anhydrous sodium sulfate. After removal of the ether by distillation, the oil was distilled under vacuum to give 17 g (0.086 moles, 24% yield) of greenish yellow oil boiling at 131° C/1.5 mm. Analysis of the product for sulfide sulfur gave the following results:

Calc'd. for $C_8H_{11}S_2Cl$: S, 15.51. Found: S, 15.78; 15.92.

A second preparation employing reversed addition of the reagents resulted in a 29 percent yield of product which distilled at 135° C/2.5 mm.

β-Chloroethyl-3-thienyl sulfide



SCH_2CH_2Cl

The quantity, 50 g (0.43 mole) of 3-thiophenethiol was dissolved in a solution of 18 g of sodium hydroxide and 200 ml of water. The resulting solution was poured into a 1000 ml flask fitted with a reflux condenser, stirrer and dropping funnel. The stirred mixture was heated to reflux temperature and 73 g (0.50 mole) of ethylene chlorobromide was added slowly over a period of a half hour. The reaction was allowed to continue an additional hour after the addition of ethylene chlorobromide was complete. Upon cooling to room temperature, a heavy yellow oil separated and this was collected with the aid of a separatory funnel. The aqueous layer was extracted with a 100 ml portion of ether which was added to the oil. The resulting ether solution was washed with water followed by drying over anhydrous sodium sulfate. The ether was removed by distillation and the yellow oil remaining was fractionated under vacuum using the previously described column. There was a few ml of forerun followed by 55 g (0.31 moles, 72% yield) of a slightly yellow, clear oil which boiled at 123° C/8 mm. Analysis for sulfide sulfur gave the following data:

Calc'd. for $C_6H_7S_2Cl$: S, 17.93. Found: S, 18.38; 17.71.

Tetramethylene Chlorohydrin

A 1000 ml flask was equipped with a reflux condenser, thermometer, and gas diffusion tube extending to the bottom of the flask. The quantity, 400 g (6.45 moles) of tetrahydrofuran were added to the flask and heated to its reflux temperature (64° C) using an electric mantel. The introduction of gaseous hydrogen chloride being commenced at this point. The reaction was continued for 18 hours in which time the reaction temperature had risen to 103° C. Excess hydrogen chloride was removed from the reaction mixture with a water aspirator and the product was dried by the addition of anhydrous sodium sulfide. A small quantity, 5 g, of copper powder was added to the solution to prevent peroxide formation. The reaction mixture was distilled under vacuum producing 195 g of unreacted tetrahydrofuran as a forerun, followed by 158 g (3.29 moles, 51% yield) which distilled at 70-71° C/7 mm. Starr and Hixson[30] reported a 54-57 percent yield of product boiling at 87° C/10 mm.

ANALYSIS

Determination of Nitrogen

The analytical method used was that of Redemann[39] which employed the Kjeldahl method on a semimicro scale. Using a micro-Kjeldahl distilling apparatus, a mixture containing 20-60 mg of sample, 0.1 g quantity of equal parts of mercuric oxide and potassium sulfate in the ratio of 8 to 100, and 5 ml of concentrated sulfuric acid, was digested until a clear, colorless solution resulted. After cooling the digested mixture was diluted with 15 ml of 50 percent aqueous sodium hydroxide. The receiving flask consisted of a 200 ml conical flask containing a known amount of standard hydrochloric acid. After 40-50 ml of distillate was collected, a few drops of methylene blue-methyl red indicator were added and the solution was titrated with standard sodium hydroxide.

Determination of Sulfide

Following the procedure of Siggia and Edsberg[40], a sample containing about 0.002 mole of alkyl sulfide was weighed directly into a 250 ml conical flask and dissolved in 40 ml of acetic acid. To this solution was added about 10 ml of distilled water followed by 3 ml of concentrated hydrochloric acid. The solution was titrated with 0.1N bromate-bromide solution until the first yellow color due to excess bromine was visible. A blank was run on the solvents to correct for the amount of excess bromine needed to detect the endpoint.

SUMMARY

1. Two ω-piperidinoalkyl chloride hydrochlorides and three ω-morpholinoalkyl chloride hydrochlorides were prepared for the first time and some of their physical properties are reported.
2. Two ω-hydroxyalkyl-3-thienyl sulfides with two and four carbon atoms in the alkyl chain were prepared for the first time and some of their physical properties were determined. The p-phenyl azobenzoate derivatives of these were synthesized and their melting points are reported.
3. Two ω-chloroalkyl-3-thienyl sulfides having two and four carbons in the alkyl chain were prepared for the first time and some of their physical properties were determined.
4. Ten ω(N,N-dialkylamino)alkyl-3-thienyl sulfide hydrochlorides were synthesised for the first time and some of their properties were investigated.

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THE SYNTHESIS OF SOME ω(N,N-DIALKYLAMINO)ALKYL-3-THIENYL SULFIDE HYDROCHLORIDES

By

William H. Houff

AN ABSTRACT

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

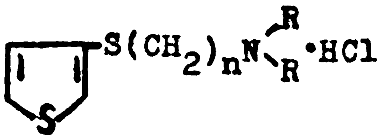
MASTER OF SCIENCE

Department of Chemistry
Year 1952

Approved Robert D. Schuetz

William H. Houff

As a study of sulfur containing compounds of pharmacological interest, some ω(N,N-dialkylamino)alkyl-3-thienyl sulfide hydrochlorides were prepared because of the interesting activity as local anesthetics possessed by the corresponding phenyl analogs and because of the reported lower toxicity of the thiophene nucleus when incorporated into such compounds as compared with that of benzene. These compounds may be represented by the general formula,

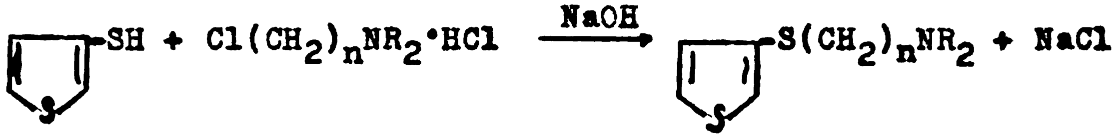


where $-N{<}^{R}_{R}$ is a morpholino or piperidino group and "n" varies from two to five.

The first general method of synthesis involved the following sequence of reactions:

$$2R_2NH + Cl(CH_2)_nOH \xrightarrow{EtOH} R_2N(CH_2)_nOH + R_2NH\cdot HCl$$

$$R_2N(CH_2)_nOH + SOCl_2 \xrightarrow{CHCl_3} R_2N(CH_2)_nCl\cdot HCl + SO_2$$

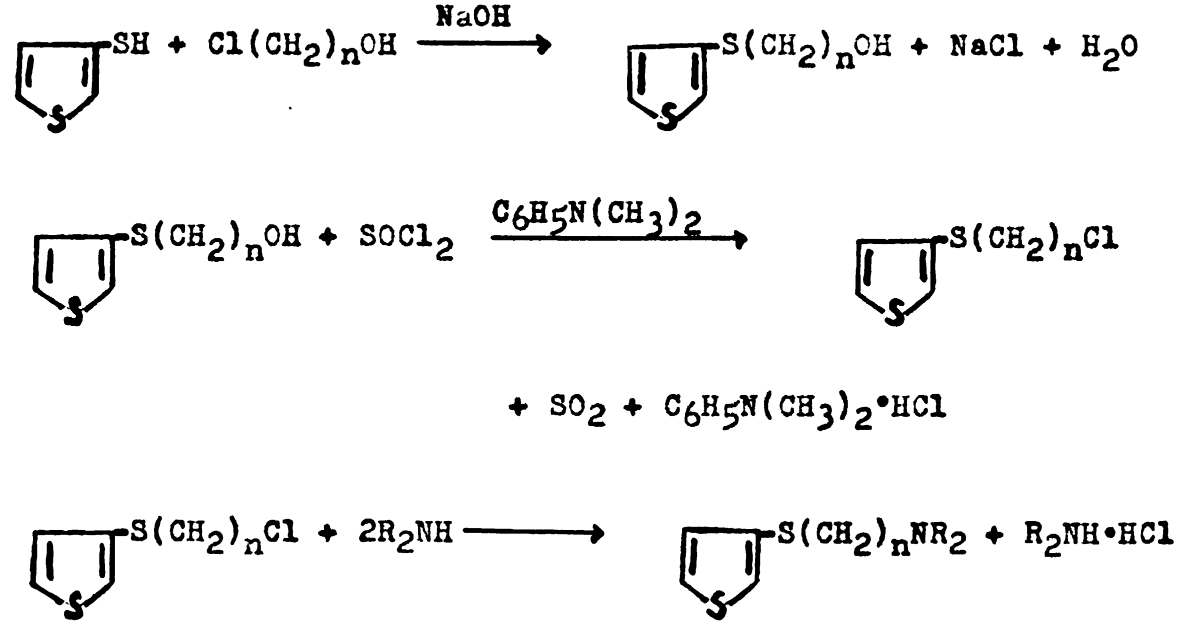


The first intermediates, ω(N,N-dialkylamino) alcohols, were prepared by refluxing the proper secondary amine and chlorohydrin in absolute ethanol.

The synthesis of the ω(N,N-dialkylamino)alkyl chloride hydrochlorides involved the careful addition of thionyl chloride to a chloroform solution of the ω{N,N-dialkylamino} alcohol. Five compounds which had not been previously reported were prepared and some of their physical properties were determined.

The ω{N,N-dialkylamino}alkyl-3-thienyl sulfide hydrochlorides were prepared by the interaction of the proper ω{N,N-dialkylamino}alkyl chloride with 3-thiophenethiol in aqueous sodium hydroxide solution. The products were isolated and characterized as the hydrochloride salts. Altogether, ten ω{N,N-dialkylamino}alkyl-3-thienyl sulfide hydrochlorides were prepared and some of their physical properties are reported.

In an effort to improve the yields of the final product and to shorten the time required for their preparation a second general method of synthesis was studied, and is indicated in the following series of reactions:



As represented by the first equation, 3-thiophenethiol was reacted with the appropriate chlorohydrin in aqueous sodium hydroxide to yield the ω-hydroxyalkyl-3-thienyl sulfide. Three ω-hydroxyalkyl-3-thienyl sulfides were prepared which had not been previously reported and some of their physical properties were determined.

The ω-hydroxyalkyl-3-thienyl sulfides were converted to the ω-chloroalkyl-3-thienyl sulfides by the addition of thionyl chloride employing dimethyl aniline as solvent. Two ω-chloroalkyl-3-thienyl sulfides which were not previously reported in the literature were synthesized and some of their properties were investigated.

By reacting the ω-chloroalkyl-3-thienyl sulfide with the appropriate secondary amine, the ω(N,N-dialkylamino)alkyl-3-thienyl sulfide was obtained and isolated as the hydrochloride. Two such compounds were prepared in this manner and were found to be identical with those prepared by the first general method.

A study of the methods of preparation employed revealed that the first general method was most applicable to the synthesis of the desired series of compounds. The yields were, in general, better, isolation was simpler, the purity of the products was more satisfactory and fewer side-reactions were involved in the synthesis.

No information concerning the pharmacological properties of the ω(N,N-dialkylamino)alkyl-3-thienyl sulfide hydrochlorides is given since this work deals only with the synthesis of these compounds.