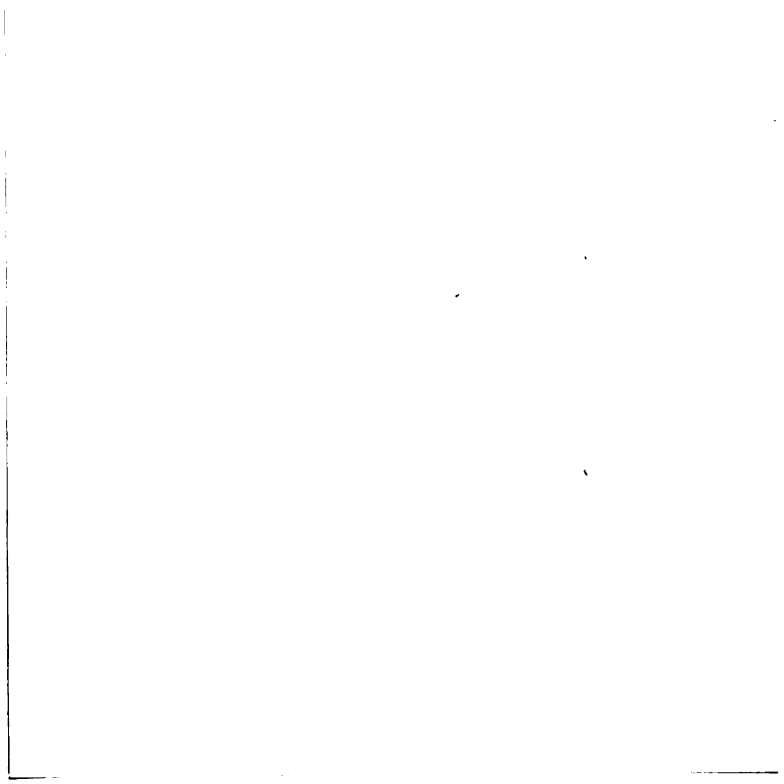
THE SYNTHESIS AND STUDY OF SOME SUBSTITUTED PHENYL W-(N, N-DIALKYLAMINO) ALKYL SULFIDES

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Roger Allan Baldwin

1956



THE SYNTHESIS AND STUDY OF SOME SUBSTITUTED PHENYL ω-(N,N-DIALKYLAMINO) ALKYL SULFIDES

By

Roger Allan Baldwin

A THESIS

Submitted in partial fulfillment of the

requirements for the degree of

MASTER OF SCIENCE

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AN ABSTRACT

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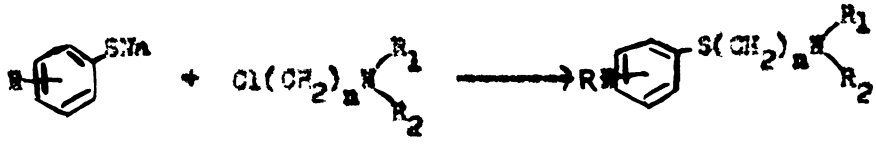
ABSTRACT

The present study deals with an investigation of substituted phenyl alkyl sulfides having a tertiary amine group on the terminal carbon of the alkyl chain. The study was undertaken since certain ω(N,N-disubstituted amino) alkylphenyl sulfides (1) and similarly related compounds (2,3) have been reported as useful local anesthetics.

Using a general procedure which involved the interaction, in an alkaline solution, of an o- or p-substituted thiophenol with an aminoalkyl chloride hydrochloride at the reflux temperature of the reaction mixture for a two hour period resulted in the formation of a total of thirty previously unreported ω(N,N-Disubstituted amino) alkyl -o- or p- substituted phenyl sulfides.



The sulfides were characterized either as their hydrochloride salts or as their quaternary methyl iodides.

The readily available aminoalkyl chloride hydrochlorides used for the preparation of the ω (N,N-dialkylamino) alkyl moiety of the sulfides were β -diethylaminoethyl chloride, γ -dimethylamino-n-propyl chloride, β -dimethylamino-α-methylethyl chloride, γ-piperidino-n-propyl chloride, and γ -morpholino-n-propyl chloride. The substituents on the benzene ring occupied positions either ortho or para to the sulfide linkage and included such atoms or groups as chloro-, methyl, amino, acetylamino, and methoxy.

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1. M. H. Kim and R. D. Schuetz, J. Am. Chem. Soc., 74, 5102 (1952).
2. F. P. Luduena and J. O. Hoppe, J. Pharmacol. Exp. Therap., 104, 40 (1952).
3. E. Epstein and M. Meyer, J. Am. Chem. Soc., 77, 4059 (1955).

INTRODUCTION

The present study deals with an investigation of a series of new substituted phenyl alkyl sulfides having a tertiary amine group on the terminal carbon of the alkyl chain. This investigation was prompted first, by the report of Kim and Schuetz (1) that certain ω-(N,N-disubstituted amino)-alkyl-phenyl sulfides possess activity as local anesthetics; secondly, that derivatives of 2-alkoxy-4-aminobenzoates containing tertiary nitrogen groups (2) have been reported as excellent anesthetics and finally Epstein and Meyer (3) report that mono- and dialkylaminoethyl esters of m-aminoalkoxybenzoic acids proved to be highly effective and non-irritating as local anesthetics with relatively low toxicities. As a consequence of these reports, it was anticipated that by varying the substituents on the benzene ring and, also, the tertiary amino group in the side chain of substituted phenyl tertiary-aminoalkyl sulfides it should be possible to prepare compounds exhibiting high anesthetic activity with low toxicity, and low irritation.

Only the pharmacological studies, which will be conducted by another group of investigators, and are thus not a part of this thesis can evaluate these compounds as local anesthetics.

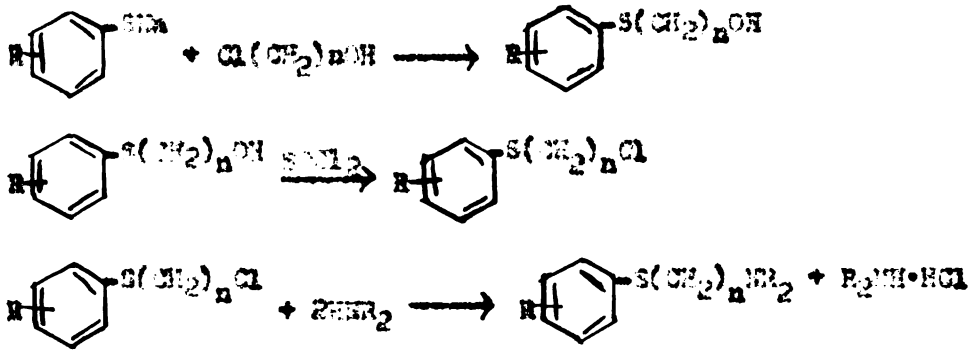
Since amino- and alkoxyl- groups were prominent in the compounds shown by Epstein and Meyer to have local anesthetic properties, it was of interest to prepare a series of ortho- and para- amino and alkoxyl substituted thiophenols for the purpose of converting these to substituted phenyl alkyl sulfides. In addition, other ortho and para substituted thiophenols containing methyl, chloro, and acetylamino groups

were used. The tertiary nitrogen containing alkyl groups used included, β-diethylamino, γ-dimethylamino-n-propyl, α-methyl-β-dimethylamino-ethyl, γ-piperidino-n-propyl, and γ-morpholino-n-propyl. In general, the desired mixed sulfides were obtained as their hydrochloride salts, but a few were converted to their corresponding quaternary salts with methyl iodide.

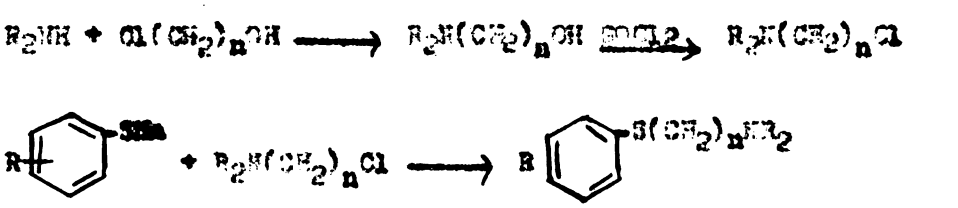
DISCUSSION

There are two good general methods by which the desired ω-(N,N-disubstituted amino) alkyl -2, 3 or 4-substituted phenyl sulfides could be prepared. These are indicated in the following equations.

Starting with a substituted thiophenol,



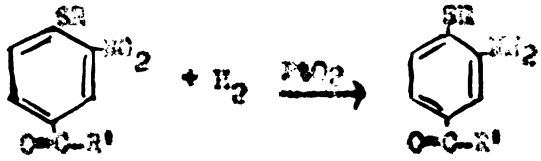
Or starting with a tertiary amine,



The latter method was utilized due to the ready availability of the necessary aminoalkyl chlorides and since good yields of the sulfide were anticipated from the last step in this synthetic sequence.

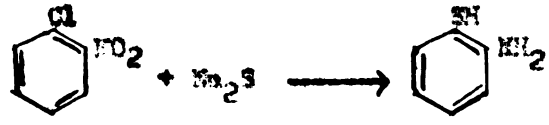
Recorded in the literature are a wide variety of methods for preparing the substituted thiophenols needed in the synthesis of the substituted phenyl aminoalkyl sulfides. Donleavy and Condit (4) prepared aminophenylalkylsulfides by the catalytic reduction, which they claimed to be quantitative, of the corresponding nitro compounds using platinum

oxide and an initial hydrogen pressure of twenty-five pounds.



In a recent patent, p-aminothiophenol was prepared by the high pressure hydrogenation of mercaptobenzothiazole using a cobalt sulfide catalyst (5).

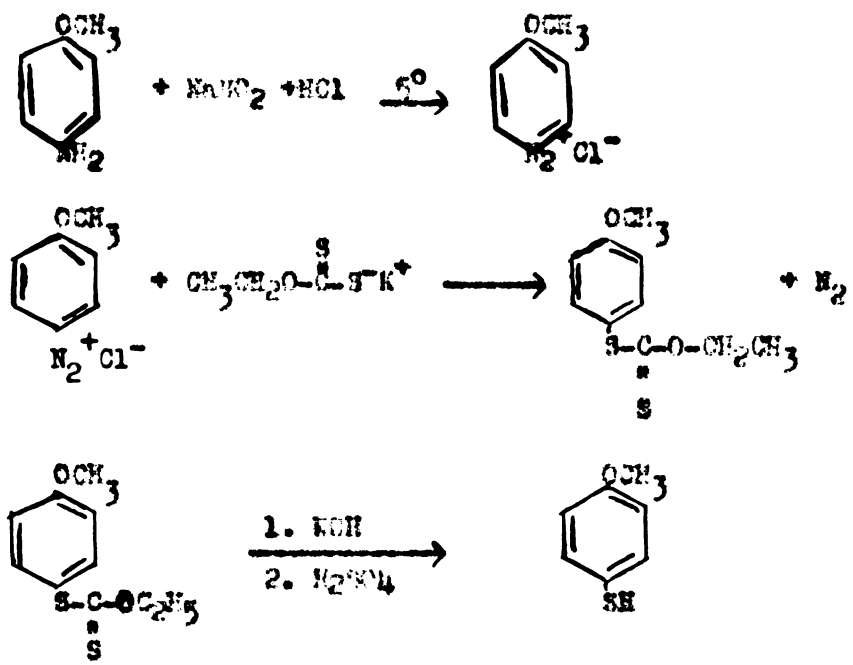
Aminothiophenols were also prepared in a convenient method by Gilman and Gainer (6). In their method, an aqueous solution of the 1-chloro-2 or 4-nitrobenzene and sodium sulfide hydrate was refluxed for eight hours, followed by acidification which gave the aminothiophenols in good yields and this method was employed in present work.



In carrying out the interaction of the aminothiophenols and ω (N,N-dialkylamino) alkyl chlorides to obtain the ω (N,N-dialkylamino) alkyl -o or p-amino phenyl sulfides, a nitrogen atmosphere was required since the aminothiophenols were readily oxidized to their disulfides. In all but one case with sulfides of the type used, it was found that in order to obtain a crystalline hydrochloride derivative of the tertiaryaminoalkyl aminophenyl sulfides, it was necessary to acetylate the amino group. Three sulfides of this series were characterized as their quaternary methyl iodide salt rather than as the hydrochloride salt. Five previously unreported ω (N,N-dialkylamino) alkyl -o or p-acetylaminophenyl sulfides were prepared in this series, and their

properties are summarized in Table I. In addition two ω (N,N-dialkylamino) alkyl-o-aminophenyl sulfides were prepared and their properties are summarized in Table I.

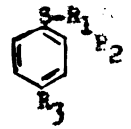
The methoxythiophenols were prepared successfully employing the procedure of Suter and Hansen (7) although in low yields. In this method ortho or para anisidine was diazotized and then treated with potassium ethyl xanthate. Alkaline hydrolysis of the xanthate followed by acidification, and then steam distillation of the reaction mixture yielded the crude methoxythiophenol which was purified by distillation under reduced pressure.



The sodium salts of the methoxythiophenols on reaction with the ω (N,N-dialkylamino) alkyl chlorides resulted in the synthesis of ten new ω (N,N-dialkylamino) alkyl -o or p-methoxyphenyl sulfides. A few of the physical and chemical properties of these compounds are indicated in Table II.

TABLE I

ω(N,N-Dialkylamino) alkyl -2 or p-acetylaminophenyl sulfide quaternary methyl iodides or hydrochlorides

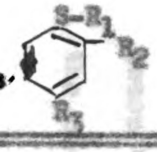


R_1	R_2	R_3	M.P. °C.	Yield %	Formula	Analyses % Calculated C	H	S	Found C	H	S
$-(CH_2)_2N(CH_2CH_3)_2$ [a,e]	-H	$-NHCOCH_3$	155-6	21	$C_{15}H_{25}ON_2SI$	44.2	6.2	7.85	44.25	6.31	7.55
$-(CH_2)_2N(CH_2CH_3)_2$ [a,e]	$-NHCOCH_3$	-H	124-5.5	24.6	$C_{15}H_{25}ON_2SI$	44.2	6.2	7.85	44.7	6.11	7.88
$-(CH_2)_3N(CH_3)_2$ [a,f]	-H	$-NHCOCH_3$	198-200	49	$C_{14}H_{23}ON_2SI$	42.7	5.9	8.12	42.73	5.98	7.97
$-(CH_2)_3N(CH_3)_2$ [a,e]	$-NH_2$	-H	120-1	33.5	$C_{12}H_{21}N_2SI$	41.0	6.0	9.1	41.01	6.08	9.01
$-(CH_2)_3$-morpholine [b,d]	-H	$-NHCOCH_3$	184-5	35.2	$C_{15}H_{23}O_2N_2SCl$	54.4	7.0	9.7	54.70	6.87	9.54
$-(CH_2)_3$-morpholine [c,e]	$-NH_2$	-H	198-200	31	$C_{13}H_{22}ON_2SCl_2$	48.0	6.83	9.9	47.92	6.88	9.88
$-(CH_2)_3$-piperidine [b,d]	-H	$-NHCOCH_3$	174.5-5.5	50	$C_{16}H_{25}ON_2SCl$	58.5	7.65	9.7	58.54	7.67	9.6

a. Quaternary methyl iodide salt. b. Hydrochloride. c. Dihydrochloride. d. Recrystallized from isopropyl alcohol. e. Recrystallized from absolute ethanol. f. Recrystallized from methanol.

TABLE II

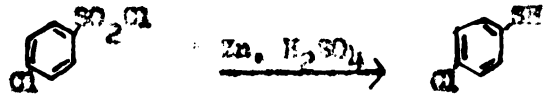
ω(N,N-Dialkylamino) alkyl -o or p-methoxyphenyl sulfide hydrochlorides.



R_1	R_2	R_3	M.P. °C.	Yield %	Formula	Analyses % Calculated C	H	S	Found C	H	S
$-(CH_2)_2N(CH_2CH_3)_2$ [a]	$-OCH_3$	-H	127-9	43.5	$C_{12}H_{22}ONSCl$	56.7	8.05	11.7	56.61	7.87	11.42
$-(CH_2)_2N(CH_2CH_3)_2$ [a]	-H	$-OCH_3$	132-3.5	69	$C_{12}H_{22}ONSCl$	56.7	8.05	11.7	56.63	8.16	11.50
$-(CH_2)_3N(CH_3)_2$ [a]	$-OCH_3$	-H	113-4	52	$C_{12}H_{22}ONSCl$	55.0	7.7	12.2	54.94	7.72	12.22
$-(CH_2)_3N(CH_3)_2$ [a]	-H	$-OCH_3$	130-1.5	69	$C_{12}H_{20}ONSCl$	55.0	7.7	12.2	55.28	7.73	12.18
$-(CH_2)_3N$⟨O⟩ [a]	$-OCH_3$	-H	155-6	73.5	$C_{14}H_{22}O_2NSCl$	55.4	7.3	10.5	55.67	7.37	10.45
$-(CH_2)_3N$⟨O⟩ [a]	-H	$-OCH_3$	146.5-8	78	$C_{14}H_{22}O_2NSCl$	55.4	7.3	10.5	55.47	7.34	10.7
$-(CH_2)_3N$⟨⟩ [a]	$-OCH_3$	-H	150-1	83.5	$C_{15}H_{24}ONSCl$	59.6	8.0	10.6	59.33	8.24	10.68
$-(CH_2)_3N$⟨⟩ [a]	-H	$-OCH_3$	128-9	73.5	$C_{15}H_{24}ONSCl$	59.6	8.0	10.6	59.87	8.07	10.81
$-CHCH_2N(CH_3)_2$ [a] (CH3)	-H	$-OCH_3$	173-4.5	36	$C_{12}H_{20}ONSCl$	55.0	7.7	12.2	54.99	7.91	11.96
$-CHCH_2N(CH_3)_2$ [b] (CH3)	$-OCH_3$	-H	110-2	41	$C_{12}H_{20}ONSCl$	55.0	7.7	12.2	55.22	7.87	12.10

Solvents for recrystallization: a - Isopropyl alcohol. b - Isopropylalcohol and cyclohexene.

The chlorothiophenols could be prepared from the aminochlorobenzenes through the S-aryl ethyl xanthates as previously described for the corresponding methoxythiophenols. However, only the p-chlorothiophenol used in this work was prepared in this manner. Since the method of Benesr, Dupport, and Kospfli (8) gave better yields, it was employed for the preparation of p-chlorothiophenol. In this procedure, p-chlorobenzenesulfonyl chloride was reduced with sulfuric acid and zinc powder to give yields as high as 73 percent of p-chlorothiophenol.



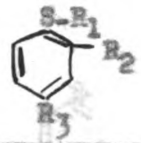
Interaction of the sodium chlorothiophenolates with ω(N,N-dialkylamino) alkyl chlorides resulted in the preparation of nine ω(N,N-dialkylamino) alkyl -o or p-chlorophenyl sulfides which are not recorded in the chemical literature and data on some of their physical properties are summarized in Table III.

Further, reactions of several ω(N,N-dialkylamino) alkyl chlorides with o and p-methylthiophenols in an alkaline reaction resulted in the preparation of an additional four previously undescribed ω(N,N-dialkylamino) alkyl o- or p-methylphenyl sulfides and these, as their hydrochloride salts, with a few of their physical properties are indicated in Table IV.

Using the excellent method of Adams and Whitmore (9), γ-chloropropyl morpholine and piperidine were prepared from the interaction of trimethylene chlorobromide and morpholine or piperidine employing pure dry benzene, as a reaction medium.

TABLE III

ω (N,N-Dialkylamino) alkyl -o or p-chlorophenyl sulfide hydrochlorides

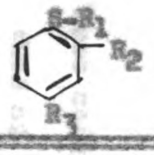


R_1	R_2	R_3	M.P.°C.	Yield %	Formula	Analyses % Calculated C	H	S	Found C	H	S
$-(CH_2)_2N(CH_2CH_3)_2$ [a]	-Cl	-H	148-9	83	$C_{12}H_{19}NSCl_2$	51.5	6.85	11.4	51.49	6.86	11.27
$-(CH_2)_2N(CH_2CH_3)_2$ [a]	-H	-Cl	123-4.5	78	$C_{12}H_{19}NSCl_2$	51.5	6.85	11.4	51.28	6.93	11.26
$-(CH_2)_3N(CH_3)_2$ [a]	-Cl	-H	127-8	36.4	$C_{11}H_{17}NSCl_2$	49.6	6.45	12.0	49.72	6.54	11.95
$-(CH_2)_3N(CH_3)_2$ [a]	-H	-Cl	126.5-7.5	71	$C_{11}H_{17}NSCl_2$	49.6	6.45	12.0	49.82	6.56	12.18
$-(CH_2)_3N$  [a]	-Cl	-H	147.5-8.5	86	$C_{13}H_{19}ONSCl_2$	50.6	6.2	10.4	50.68	6.46	10.21
$-(CH_2)_3N$  [a]	-H	-Cl	184.5-6	81	$C_{13}H_{19}ONSCl_2$	50.6	6.2	10.4	50.44	6.24	10.42
$-(CH_2)_3N$  [a]	-Cl	-H	148-9	55	$C_{14}H_{21}NSCl_2$	55.0	6.9	10.5	55.0	7.38	10.26
$-(CH_2)_3N$  [a]	-H	-Cl	157-8	90.5	$C_{14}H_{21}NSCl_2$	55.0	6.9	10.5	55.02	7.05	10.7
$-CHCH_2N(CH_3)_2$ (CH3) [b]	-H	-Cl	90	84	$C_{11}H_{17}NSCl_2$	49.6	6.45	12.0	48.95	6.59	12.36

Solvents for recrystallization: a - isopropyl alcohol, b - isopropyl alcohol and cyclohexene.

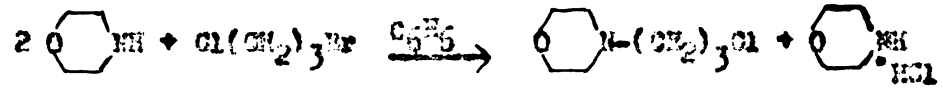
TABLE IV

ω (N,N-Dialkylamino) alkyl -o or p-methylphenyl sulfide hydrochlorides

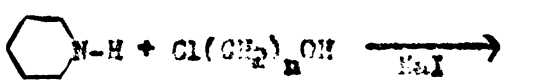


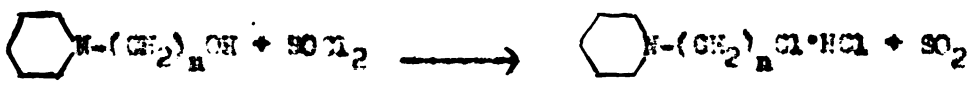
R_1	R_2	R_3	M.P.°C.	Yield %	Formula	Analyses % Calculated C	H	S	Found C	H	S
$-(CH_2)_2N(CH_2CH_3)_2$ [a]	-H	$-CH_3$	120-1	89	$C_{13}H_{22}NSCl$	60.0	8.5	12.2	60.08	8.51	12.23
$-(CH_2)_2N(CH_2CH_3)_2$	$-CH_3$	-H	154-5	72	$C_{13}H_{22}NSCl$	60.0	8.5	12.2	60.15	8.46	12.07
$-(CH_2)_3N$⟨O⟩	-H	$-CH_3$	168.5-169.5	78	$C_{14}H_{22}ONSCl$	58.4	7.7	11.1	58.6	7.61	11.01
$-(CH_2)_3N$⟨O⟩	$-CH_3$	-H	167-9	59	$C_{14}H_{22}ONSCl$	58.4	7.7	11.1	58.47	7.60	10.93

a - recrystallized from isopropyl alcohol.



These chlorides could have also been prepared by the more drawn out method of first preparing the alcohol from the chlorohydrin (10), by treating the latter with an appropriate secondary amine, and then converting the alkanolamine to its corresponding chloride by means of thionyl chloride in anhydrous chloroform (11), as a reaction media.





The general method employed in the synthesis of the substituted phenyl tertiaryamino sulfides from the dialkylamino-alkyl chlorides and substituted phenylthiol was carried out in the following manner. The substituted aryl mercaptan was dissolved in sufficient sodium hydroxide to neutralize both it and the ω (N,N-dialkylamino) alkyl chloride hydrochloride. The alkaline solution of the mercaptide was heated to its reflux temperature and a water solution of the dialkylamino alkyl chloride hydrochloride salt was added dropwise. Since methoxy- and amino- substituted thiophenols oxidize readily in base, reactions involving such compounds were carried out in a nitrogen atmosphere. Following the addition of the aqueous amine hydrochloride solution, the reaction mixture was kept at its reflux temperature for two hours, after which it was allowed to cool to room temperature. The oily layer which had formed was extracted with three portions of ether and the combined ether extracts were washed with ten percent sodium hydroxide,

then with water, followed by drying over anhydrous magnesium sulfate. The ether solution of the sulfide was filtered, cooled in an ice bath and then saturated with dry hydrogen chloride gas. The resulting hydrochloride salt of the sulfide was collected by filtration and the ether filtrate was tested for complete removal of the amino sulfide by passing additional hydrogen chloride gas into the ether filtrate. Isopropyl alcohol was used to recrystallize the hydrochloride salt generally.

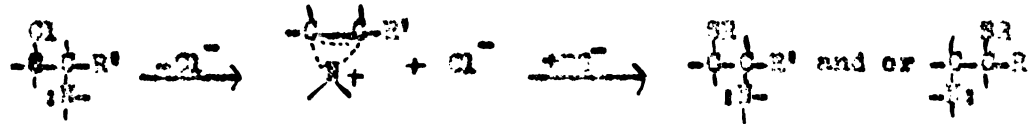
In preparing the quaternary methyl iodide salts of the amino sulfides, the ether was removed by evaporation and the resulting dry oily amine sulfide was treated with methyl iodide. Methyl or ethyl alcohol was the solvent used to purify these compounds by recrystallization.

No difficulties were encountered in the reactions of β-diethylaminoethyl chloride, γ-dimethylamino-n-propyl chloride, γ-morpholino-n-propyl chloride, or γ-piperidino-n-propyl chloride with the substituted aryl mercaptans. However, the reactions of α-methyl-β-dimethylaminoethyl chloride in alkaline media could very likely have resulted in the formation of two isomeric sulfides. It is known, for example, that 1-diethylamino-2-chloropropane hydrochloride yields the rearranged product, 2-diethylamino-1-propanol, upon basic hydrolysis(12).

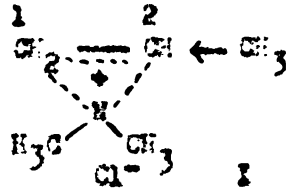
$$H_3C-\underset{Cl}{\overset{H}{\underset{|}{\overset{|}{C}}}}-CH_2N(CH_2CH_3)_2\cdot HCl \longrightarrow H_3C\underset{N(CH_2CH_3)_2}{\overset{OH}{\underset{|}{\overset{|}{C}}}}-CH_2$$

This rearrangement is an example of participation by a neighboring group, the nucleophilic amino group, in a displacement reaction. The initial step in the mechanism of this type of reaction is a preliminary

intramolecular displacement reaction or ionization effected by the nucleophilic nitrogen to form a cyclic onium salt (13).

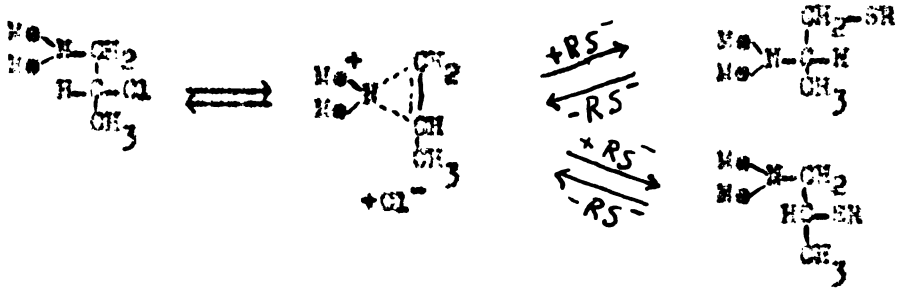


In the case of dimethylaminoisopropyl chloride, this would yield the intermediate,



I

Attack by a nucleophilic ion would very probably occur at the least substituted carbon(1) due to the inductive effect of the methyl group to give the rearranged product. However, if the initial step in the formation of cyclic ethylene iminonium ion is a reversible process,



due to internal nucleophilic attack by the β-amino group and the product step is also a reversible attack by a nucleophilic thiolate ion then the above equilibrium scheme would be obtained due to the principle of microscopic reversibility and the product isolated would be the most thermodynamically stable.

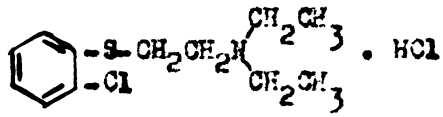
Evidence for a mixture of products was indicated by the fact that it was difficult or impossible in some cases to obtain a crystalline

product with a sharp melting point. A broad melting range was found in several preparations after repeated recrystallizations from various solvent combinations. At the present time, it is not known which isomer predominates or if there is actually a mixture indeed.

EXPERIMENTAL

ω (N,N-Dialkylamino) alkyl -o or p-substituted phenyl Sulfide Hydrochlorides and Methiodides

β -Diethylaminoethyl-o-chlorophenyl sulfide hydrochloride



Into a three-necked 500 ml flask equipped with a reflux condenser, stirrer, and dropping funnel was poured 22 g. (0.15 mole) of o-chlorothiophenol dissolved in a solution containing 20 g. of sodium hydroxide in 50 ml. of water. To this was added dropwise from the dropping funnel 18 g. (0.1 mole) of diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of water. The stirred reaction solution was held at its reflux temperature during this addition and then for an additional two hours, at the end of which time a light yellow oil had separated. The oil was removed and the aqueous layer was extracted three times with 100 ml. portions of ether. The combined ether extracts and oil were washed with 100 ml. of a 5 percent sodium hydroxide solution and then with 100 ml. of distilled water. The ether was dried over anydrous sodium sulfate.

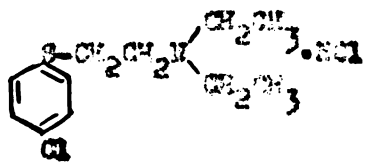
After drying, the ether solution of aminosulfide was filtered into a dry three-necked 500 ml. flask fitted with a stirrer, condenser, and a delivery tube for admission of dry hydrogen chloride gas. After cooling in an ice bath, hydrogen chloride was bubbled slowly through the stirred ether solution. The white hydrochloride was removed by suction filtration and the filtrate tested with additional gaseous

hydrogen chloride for completeness of reaction. After recrystallization from isopropyl alcohol, 23.3 g. (0.083 moles, 83% yield) of a white crystalline material which melted at 148-9°C. were recovered. Analysis of the compound for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{12}H_{19}NSCl_2$: H, 6.85; C, 51.5; S, 11.4.

Found: H, 6.86; C, 51.49; S, 11.27.

β-Diethylaminoethyl-p-chlorophenyl sulfide hydrochloride

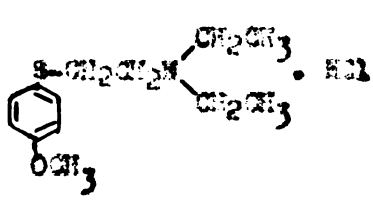


Following the procedure described above, 22 g. (0.15 mole) of p-chlorothiophenol dissolved in 80 ml. of water containing 20 g. of sodium hydroxide were treated with a solution of 18 g. (0.1 mole) of diethylaminoethyl chloride hydrochloride in 100 ml. of distilled water. The reddish-yellow oil was treated as in the previously described preparation of the o-chloro isomer. The white hydrochloride which melted at 123-124.5°C., was recrystallized from dry isopropyl alcohol and weighed 21.8 g. (0.078 mole, 78% yield). Analysis of the compound for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{12}H_{19}NSCl_2$: H, 6.85; C, 51.5; S, 11.4.

Found: H, 6.93; C, 51.28; S, 11.26.

β-Diethylaminoethyl-p-methoxyphenyl sulfide hydrochloride

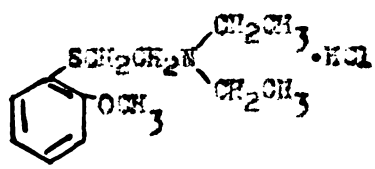


Using 20 g. (0.143 mole) of p-methoxythiophenol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide, and 100 ml. of a water solution containing 23 g. (0.134 mole) of diethylaminoethylchloride hydrochloride and following the experimental procedure described above, there was obtained 25.6 g. (0.093 mole, 69% yield) of a white hydrochloride. The latter material was recrystallized from isopropyl alcohol and had an observed melting point of 132-133.5°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{12}H_{22}NOCl$: C, 56.7; H, 8.05; S, 11.7.

Found: C, 56.63; H, 8.16; S, 11.70.

β-Diethylaminoethyl-o-methoxyphenyl sulfide hydrochloride

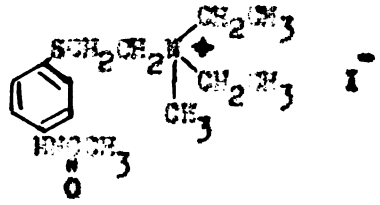


To the aqueous alkaline suspension of an insoluble white salt resulting from 20 g. (0.143 mole) of o-methoxythiophenol being placed in 100 ml. of 20 percenty by weight aqueous sodium hydroxide, was added 23.5 g. (0.136 mole) of diethylaminoethylchloride hydrochloride dissolved in 100 ml. of water. After carrying out the reaction as described above, a yellow oil separated. The crude hydrochloride, 16.3 g. (0.059 mole, 43.5% yield) on recrystallization from isopropyl alcohol, separated from solution as a gum which was crystallized by stirring in an ice bath. Its melting point was 127-9°C. Analysis for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{12}H_{22}O_3N_2$: C, 56.7; H, 8.05; S, 11.7.

Found: C, 56.61; H, 7.87; S, 11.42.

β-Diethylaminoethyl-p-acetylaminophenyl sulfide methyl iodide



To a solution made by dissolving 12.5 g. (0.1 mole) of p-aminothiophenol in 100 ml. of 20 percent by weight aqueous sodium hydroxide and contained in a 500 ml. flask fitted with stirrer, reflux condenser, dropping funnel, and a nitrogen gas delivery tube was added 16.5 g. (0.096 mole) of diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of water. The stirred reaction mixture was mildly heated for a four hour period while a gentle stream of nitrogen gas was bubbled through it. When the reaction mixture had cooled to room temperature it was extracted with three 100 ml. portions of ether. The combined ether extracts were washed with 100 ml. of 10 percent sodium hydroxide and then with 100 ml. of water after which the ether solution was dried over anhydrous sodium sulfate, and filtered.

After removal of the ether by evaporation 20 ml. (0.20mole) of acetic anhydride was added to the residual oil. The reaction mixture was heated to its boiling point and then poured into water. The resulting solution was made slightly basic with sodium hydroxide causing an oil to separate which was extracted with ether and dried over anhydrous magnesium sulfate.

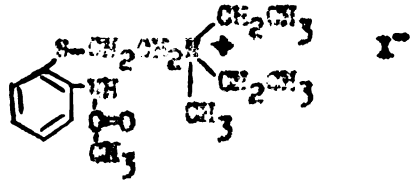
The ether solution after decantation from the drying agent and treatment with dry hydrogen chloride gas resulted only in the formation of a non-crystalline gummy product. This material was neutralized with 10 percent sodium hydroxide, dissolved in ether, washed with water and then dried over anhydrous magnesium sulfate.

The ether was removed by evaporation and the free amine was treated with methyl iodide to yield a brown solid which on recrystallization from absolute ethanol yielded 8.2 g. (0.02 mole, 21% yield) of the quaternary methyl iodide salt which melted at 175-6°C. Analysis for carbon hydrogen, and sulfur gave the following results:

Calculated for $C_{15}H_{25}N_2OIS$: H, 6.2; C, 44.2; S, 7.85.

Found: H, 6.31; C, 44.25; S, 7.55.

β-Diethylaminoethyl-g-acetylaminophenyl sulfide methyl iodide



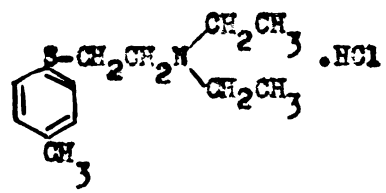
Following the method of the previous preparation, a 100 ml. aqueous solution containing 16.5 g. (0.096 mole) of diethylaminoethyl chloride hydrochloride was added to a refluxing solution of 12.5 g. (0.1 mole) of g-aminothiophenol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide. The resulting oily amine, after isolation, was acetylated by means of 20 ml. of acetic anhydride and then converted to its quaternary salt with methyl iodide to yield, after several recrystallizations from absolute ethanol, 10 g. (0.0246 mole, 24.6% yield)

of white product which melted at 124-25.5°C. Analysis for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{15}H_{25}SN_2OI$: H, 6.2; C, 44.2; S, 7.85.

Found: H, 6.11; C, 44.7; S, 7.88.

β-Diethylaminoethyl-p-methylphenyl sulfide hydrochloride

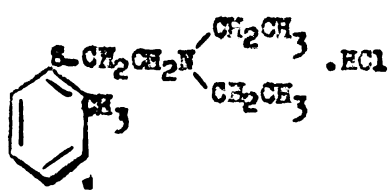


Following the experimental method previously described, 17 g. (0.1 mole) of β-diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of water was added to 12.4 g. (0.1 mole) of p-toluenethiol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide. Heating this reaction mixture at its reflux temperature in a nitrogen atmosphere gave an insoluble, yellow oily amine. Following the usual separation and conversion to a hydrochloride salt resulted in 23.2 g. (0.089 mole, 89% yield) of the hydrochloride which was obtained as white needles after recrystallization from isopropyl alcohol. The product melted at 120-1°C. The following data was obtained by analysis for carbon, hydrogen, and sulfur:

Calculated for $C_{13}H_{22}SNCl$: C, 60; H, 8.5; S, 12.2.

Found: C, 60.08; H, 8.51; S, 12.23.

β-Diethylaminoethyl-o-methylphenyl sulfide hydrochloride

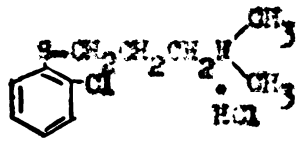


To 12.4 g. (0.1 mole) of o-toluenethiol dissolved in 100 ml. of water containing 20 g. of sodium hydroxide was added 17 g. (0.1 mole) of β-diethylaminoethylchloride hydrochloride dissolved in 100 ml. of water. After the reaction mixture had been refluxed under nitrogen for two hours, a yellow colored insoluble oil separated from the reaction mixture. From this oily material, by following the previously described method of isolation and amine salt formation there was obtained 18.7 g. (0.072 mole, 72% yield) of a white hydrochloride of the amino sulfide which on recrystallization from isopropyl alcohol melted at 154–155.5°C. Analysis for carbon, hydrogen and sulfur gave the following results:

Calculated for $C_{13}H_{22}ClNS$: C, 60; H, 8.5; S, 12.2.

Found: C, 60.15; H, 8.46; S, 12.07.

γ-Dimethylamino-n-propyl-o-chlorophenyl sulfide hydrochloride



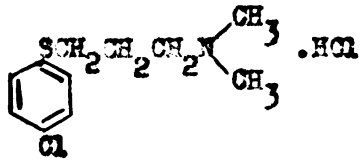
From 13 g. (0.09 mole) of o-chlorothiophenol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide and adding to it 14 g. (0.088 mole) of γ-dimethylaminopropyl chloride hydrochloride dissolved in 100 ml. of water, there was obtained an insoluble oil after a two hour reaction period at the reflux temperature of this mixture. The oily amine was converted to its hydrochloride and the latter on recrystallization from isopropyl alcohol, gave a white crystalline product which weighed 8.5 g. (0.032 mole, 36.4% yield)

and melted at 127-8°C. The following data was obtained by analysis for carbon, hydrogen, and sulfur:

Calculated for $C_{11}H_{17}NSCl_2$: C, 49.6; H, 6.45; S, 12.0.

Found: C, 49.72; H, 6.54; S, 11.95.

γ-Dimethylamino-n-propyl-p-chlorophenyl sulfide hydrochloride

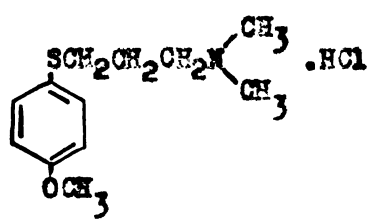


Interaction of 14.5 g. (0.1 mole) of p-chlorothiophenol dissolved in 100 ml. of water containing 20 g. of sodium hydroxide with 15.8 g. (0.1 mole) of γ-dimethylamino-n-propyl chloride hydrochloride in 100 ml. of water resulted in the formation of an oily amine after a reaction period of two hours at the reflux temperature of the reaction mixture. Reaction of the amine in ether with gaseous hydrogen chloride gave 18.9 g. (0.071 mole, 71% yield) of a pure white hydrochloride product melting at 126.5-127.5°C. after recrystallization from isopropyl alcohol. Analysis of the compound for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{11}H_{17}NSCl_2$: C, 49.6; H, 6.45; S, 12.0.

Found: C, 49.82; H, 6.56; S, 12.13.

γ-Dimethylamino-n-propyl-p-methoxyphenyl sulfide

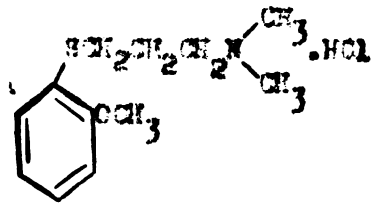


To 20 g. (0.14 mole) of p-methoxythiophenol dissolved in 100 ml. of water containing 20 g. of sodium hydroxide was added 22 g. (0.14 mole) of γ-dimethylamino-n-propylchloride hydrochloride contained in 100 ml. of water. The amine separated as an oil after two hours of heating at the reflux temperature of the reaction mixture. Conversion of the amine to its hydrochloride as previously described gave, 25.2 g. (0.096 mole, 69% yield) of the hydrochloride which melted at 130-131.5°C. after recrystallization from isopropyl alcohol. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{12}H_{20}NSOCl$: C, 55.0; H, 7.7; S, 12.2.

Found: C, 55.2%; H, 7.73; S, 12.18.

γ-Dimethylamino-n-propyl-p-methoxyphenyl sulfide hydrochloride



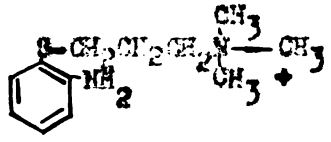
The addition of 21 g. (0.134 mole) of γ-dimethylamino-n-propyl chloride hydrochloride dissolved in 100 ml. of water to 20 g. (0.143 mole) of p-methoxythiophenol which had previously been dissolved in 100 ml. of water containing 20 g. of sodium hydroxide resulted in the formation of a pink oily layer after a two hour reaction period at the reflux temperature of the reaction mixture. Solution of the amine and conversion of it to its hydrochloride followed by recrystallization of the latter from isopropyl alcohol yielded 18.3 g. (0.07 mole, 52% yield) of a pure product which melted at 113-4°C. Analysis for

carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{12}H_{20}N_2OSI$: C, 55.0; H, 7.7; S, 12.2.

Found: C, 54.44; H, 7.72; S, 12.22.

γ-Dimethylamino-n-propyl-g-aminophenyl sulfide methyl iodide



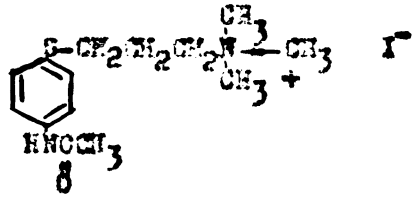
From 12.5 g. (0.1 mole) of g-aminothiophenol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide and adding to this solution 15 g. (0.095 mole) of γ-dimethylamino-n-propylchloride hydrochloride in 100 ml. of water, under an atmosphere of nitrogen yielded an oily amine after heating the reaction mixture at its reflux temperature for two hours. The oil was extracted with ether and dried over anhydrous magnesium sulfate.

After removal of the ether by evaporation, the residual oil on reaction with methyl iodide resulted in a yellow solid, which on recrystallization from absolute ethanol gave 11.2 g. (0.032 mole, 33.5% yield) of a white crystalline product have a melting point of 130-1°C. Analysis for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{12}H_{21}N_2SI$: C, 41.0; H, 6.0; S, 9.1.

Found: C, 41.01; H, 6.08; S, 9.01.

γ-Dimethylamino-n-propyl-g-acetylaminophenyl sulfide methyl iodide

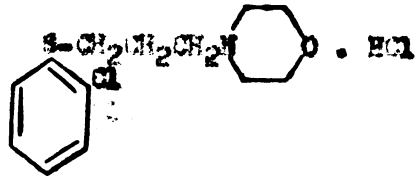


Employing the previously described procedure, 12.5 g. (0.1 mole) of p-aminothiophenol dissolved in a 100 ml. of 20 percent by weight aqueous sodium hydroxide were allowed to react with 15 g. (0.095 mole) of δ-diethylamino-n-propylchloride hydrochloride, added to the basic arylmercaptan solution, in the form of a 100 ml. aqueous solution. The liquid diamine obtained from the ether extract was acylated by heating it with 20 ml. (0.2 mole) of acetic anhydride and then the reaction mixture was poured into 500 ml. of water. Neutralization of this solution with 10N sodium hydroxide resulted in the separation of an oily material which after isolation and drying reacted vigorously with methyl iodide to give a white solid quaternary salt that recrystallizes easily from methanol. The quaternary salt, 18.3 g. (0.0465 mole, 49% yield), melts at 198-200°C. and tended to turn yellow on standing. Analyses for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{14}H_{23}SN_2OI$: C, 42.7; H, 5.9; S, 8.12.

Found: C, 42.73; H, 5.98; S, 7.97.

δ-Morpholino-n-propyl-p-chlorophenyl sulfide hydrochloride.



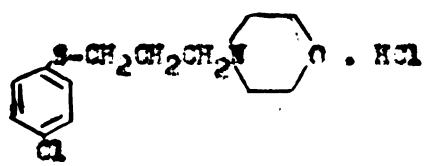
The addition to a solution containing 11 g. (0.076 mole) of p-chlorothiophenol, 100 ml. of water, and 15 g. sodium hydroxide, of 14.6 g. (0.073 mole) of δ-morpholino-n-propylchloride hydrochloride dissolved in 100 ml. of water resulted in the separation of an oily amine after a two hour period of heating at the reflux temperature of the

reaction mixture. Treatment of the oily amine, dissolved in dry ether, with gaseous hydrogen chloride produced a gum which solidified on being set aside for sometime. This material yielded, after recrystallization from isopropyl alcohol, 19.4 g. (0.063 mole, 86% yield) of a hydrochloride with a melting point of 147.5-148.5°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{13}H_{19}NOSCl_2$: C, 50.6; H, 6.2; S, 10.4.

Found: C, 50.68; H, 6.46; S, 10.21.

γ-Morpholino-n-propyl-p-chlorophenyl sulfide hydrochloride

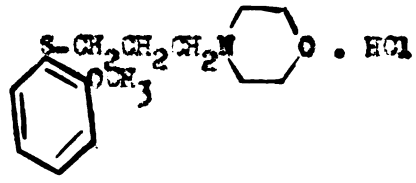


The addition of 15 g. (0.075 mole) of γ-morpholino-n-propyl chloride hydrochloride dissolved in 100 ml. of water to 11 g. (0.076 mole) of p-chlorothiophenol in a solution of 13 g. of sodium hydroxide and 100 ml. of water followed by heating the reaction mixture at approximately 100°C. for two hours, resulted in the formation of an insoluble oil. After separation as previously indicated and conversion to the hydrochloride salt, there was obtained 18.6 g. (0.0605 mole, 81% yield) of product which was rather insoluble in isopropyl alcohol. The crystalline hydrochloride melted at 184.5-185°C. The following data was obtained by analysis for carbon, hydrogen, and sulfur:

Calculated For $C_{13}H_{19}NOSCl_2$: C, 50.6; H, 6.2; S, 10.4.

Found: C, 50.44; H, 6.24; S, 10.42.

γ-Morpholino-n-propyl-p-methoxyphenyl sulfide hydrochloride

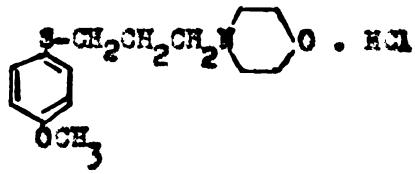


The quantity, 21 g. (0.105 mole) of γ-morpholino-n-propyl chloride hydrochloride contained in 100 ml. of water was added to 15 g. (0.107 mole) of p-methoxythiophenol dissolved in a solution prepared from 20 g. sodium hydroxide and 100 ml. of water. Following the previously described general procedure, 23.3 g. (0.77 mole, 73.5% yield) of a white crystalline hydrochloride was obtained which after recrystallization from isopropyl alcohol melted at 155-6°C. The following data was obtained by analysis for carbon, hydrogen, and sulfur:

Calculated for $C_{14}H_{22}O_2NSCl$: C, 55.4; H, 7.3; S, 10.5.

Found: C, 55.67; H, 7.37; S, 10.45.

γ-Morpholino-n-propyl-p-methoxyphenyl sulfide hydrochloride



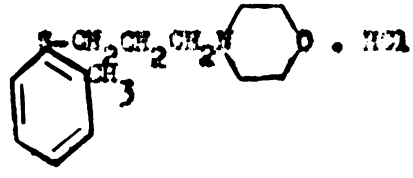
Following the procedure employed above, 18 g. (0.09 mole) of γ-morpholino-n-propylchloride hydrochloride contained in 100 ml. of water was added to a refluxing solution of 13 g. (0.093 mole) of p-methoxythiophenol dissolved in 100 ml. of water containing 12 g. of sodium hydroxide. The hydrochloride, prepared as described previously, weighed 21.3 g. (0.07 mole, 78% yield) and was found to melt in the range of 146.5-148°C. Isopropyl alcohol was used to recrystallize

the compound. Analysis for carbon, hydrogen, and sulfur gave the following results:

Calculated for $C_{14}H_{22}O_2NSCl$: C, 55.4; H, 7.3; S, 10.5.

Found: C, 55.47; H, 7.34; S, 10.7.

γ-Morpholino-n-propyl-o-methylphenyl sulfide hydrochloride

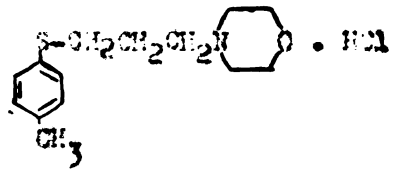


From 12.4 g. (0.1 mole) of o-toluenethiol dissolved in 100 ml. of 20 percent by weight aqueous sodium hydroxide and adding to it 20 g. (0.1mole) of γ-morpholino-n-propylchloride hydrochloride in 100 ml. of water, a colorless oil was obtained after two hours heating at the reflux temperature of the reaction mixture. The oily amine was purified and converted to its hydrochloride which had a pink color. This crystalline hydrochloride after being dissolved in isopropyl alcohol, treated with Norite A and allowed to crystallize gave 16.9 g. (0.059 mole, 59% yield) of white product in the form of needles which melted at 167-9°C. A mixed melting point of this material with the starting halide, γ-morpholino-n-propylchloride, with which it was similar in appearance, was found to be in the range 125-135°C. which showed they were not identical. Analysis of the product for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{14}H_{22}NSOCl$: C, 58.4; H, 7.7; S, 11.1.

Found: C, 58.47; H, 7.60; S, 10.93.

γ-Morpholino-n-propyl-p-methylphenyl sulfide hydrochloride

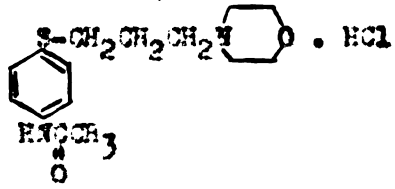


To a refluxing solution prepared from 12.4 g. (0.1 mole) of p-toluenethiol, 100 ml. of water, and 20 g. of sodium hydroxide was added 20 g. (0.1 mole) of γ-morpholino-n-propyl chloride hydrochloride dissolved in 100 ml. of water. The oil which separated after a two hour reaction period was purified and converted, in the general manner employed above, to a slightly pink colored hydrochloride which after being dissolved in hot isopropyl alcohol, treated with Norite A, and allowed to crystallize gave 22.4 g. (0.78 mole, 78% yield) of a pure product with a melting point of 168.5-169.5°C. A mixed melting point of this material with its ortho isomer depressed the melting point ten degrees. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{14}H_{22}NSOCl$: C, 58.4; H, 7.7; S, 11.1.

Found: C, 58.6; H, 7.61; S, 11.01.

γ-Morpholino-n-propyl-p-acetylaminophenyl sulfide hydrochloride.



A 100 ml. aqueous solution containing 19 g. (0.095 mole) of γ-morpholino-n-propyl chloride hydrochloride was added to a refluxing solution prepared from 12.5 g. (0.1 mole) of p-aminothiophenol, 100 ml. of water and 20 g. of sodium hydroxide. The resulting insoluble oily

amine obtained during a two hour reaction period was extracted with ether and dried over anhydrous sodium sulfate. After the ether was removed by evaporation, acetic anhydride was added to the amine and the mixture was warmed almost to its boiling point and then poured into water. The resulting solution was neutralized with 10% sodium hydroxide and the solid which precipitated was recovered by suction filtration. The acetylated amine after recrystallization from isopropyl alcohol melted at 98.5–99.5°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{15}H_{22}N_2SO_2$: C, 61.6; H, 7.55; S, 10.9.

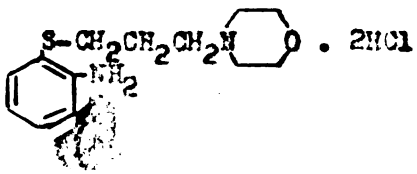
Found: C, 61.4; H, 7.57; S, 10.84.

The free amine was dissolved in ether and hydrogen chloride gas was passed through the solution resulting in the formation of 11 g. (0.034 mole, 35.2% yield) white, ether insoluble hydrochloride. The hydrochloride, after being recrystallized from isopropyl alcohol, melted at 184–5°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{15}H_{23}N_2SO_2Cl$: C, 54.4; H, 7.0; S, 9.7.

Found: C, 54.70; H, 6.87; S, 9.54.

γ-Morpholino-n-propyl-o-aminophenyl sulfide dihydrochloride



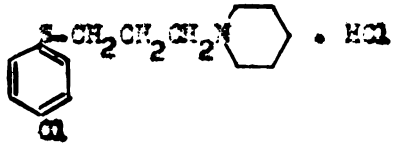
A 19 g. quantity (0.095 mole) of γ-morpholino-n-propyl chloride hydrochloride dissolved in 100 ml. of water was added to a solution

prepared by dissolving 12.5 g. (0.1 mole) of o-aminothiophenol in 100 ml. of 20 percent by weight aqueous sodium hydroxide. After a two hour reaction period, under a nitrogen atmosphere, the reaction mixture yielded an insoluble oily amine. The oil was separated, dried, and converted to its hydrochloride in the manner described above to give 9.6 g. (0.029 mole, 31% yield) of a white hydrochloride. The pure product, obtained by recrystallization of the hydrochloride from ethanol, melted at 198-200°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{13}H_{22}ON_2SCl_2$: C, 48.0; H, 6.83; S, 9.9.

Found: C, 47.92; H, 6.88; S, 9.88.

γ-Piperidino-n-propyl-p-chlorophenyl sulfide hydrochloride

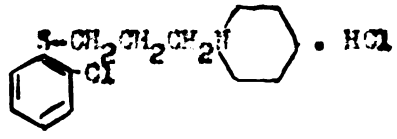


The quantity, 14.1 g. (0.071 mole), of γ-piperidino-n-propyl chloride hydrochloride dissolved in 100 ml. of water was added to a well-stirred solution, at its reflux temperature, of 10.5 g. (0.073 mole) of p-chlorothiophenol dissolved in a solution of 100 ml. of water and 15 g. of sodium hydroxide. The reaction was complete at the end of two hours. After the usual experimental operations employed above, the crude hydrochloride was recrystallized from isopropyl alcohol. The product weighed 19.7 g. (0.645 mole, 90.5% yield) and had a melting point of 157-158°C. The analysis of the compound for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{14}H_{21}NSCl_2$: C, 55.0; H, 6.9; S, 10.5.

Found: C, 55.02; H, 7.05; S, 10.7.

γ-Piperidino-n-propyl-o-chlorophenyl sulfide hydrochloride

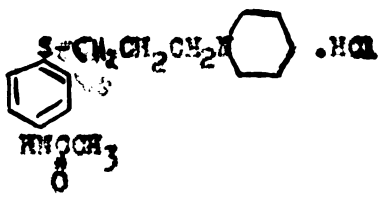


The addition, over a two hour period, from a dropping funnel of 15.3 g. (0.078 mole) of γ-piperidino-n-propyl chloride dissolved in 100 ml. of water to a stirred refluxing solution of 11.4 g. (0.079 mole of o-chlorothiophenol dissolved in 100 ml. of water containing 15 g. of sodium hydroxide resulted in the separation of an insoluble oily amine. The hydrochloride was prepared from this amine in the manner used above followed by its recrystallization from isopropyl alcohol. The pure crystalline hydrochloride weighed 12 g. (0.039 mole, 55% yield) an melted at 146-9°C. Analysis of the compound for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{14}H_{21}NSCl_2$: C, 55.0; H, 6.9; S, 10.5.

Found: C, 55.0; H, 7.38; S, 10.26.

γ-Piperidino-n-propyl-p-acetylaminophenyl sulfide hydrochloride.



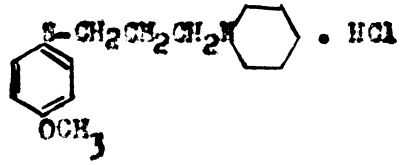
The addition of a 100 ml. aqueous solution containing 17 g. (0.096 mole) of γ-piperidino-n-propylchloride hydrochloride to a stirred

refluxing solution of 12.5 g. (0.1 mole) of p-aminothiophenol dissolved in 100 ml. of water and 20 g. of sodium hydroxide resulted in the formation of an insoluble oily amine. To prevent oxidation of the amine sulfide the reaction was carried out under a nitrogen atmosphere. The ether extracts of the reaction mixture were dried and the ether was removed by evaporation. The residual free amine was treated with 20 ml. (0.2 mole) of acetic anhydride, warmed to boiling, and poured into water. The resulting solution was neutralized with 10% sodium hydroxide and the solid hydrochloride which formed was recovered by filtration, dissolved in ether, and on treatment with hydrogen chloride gas gave a gum which solidified on being set aside for some time. The hydrochloride was recrystallized from isopropyl alcohol, had a melting point of 174.5-175.5°C, and weighed 16.2 g. (0.48 mole, 50% yield). Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{16}H_{25}N_2OSCl$: C, 58.5; H, 7.65; S, 9.7.

Found: C, 58.54; H, 7.67; S, 9.66.

γ-Piperidino-n-propyl-p-methoxyphenyl sulfide hydrochloride



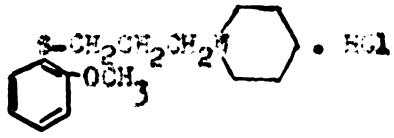
The interaction of 20.7 g. (0.105 mole) of γ-piperidino-n-propyl-chloride hydrochloride contained in 100 ml. of water with 15 g. (0.107 mole) of p-methoxythiophenol dissolved in 100 ml. of water and 20 g. of sodium hydroxide resulted in the formation of an amine which separated as an insoluble oil. The amine, dissolved in dry ether, was

converted to its hydrochloride with gaseous hydrogen chloride. It melted at 128-29°C. after being dissolved in hot isopropyl alcohol, treated with Norite A, and allowed to crystallize. The amount of pure hydrochloride product obtained was 23.3 g. (0.077 mole, 73.5% yield). Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{15}H_{24}NOSCl$: C, 59.6; H, 8.0; S, 10.6.

Found: C, 59.87; H, 807; S, 10.81.

γ-Piperidino-n-propyl-o-methoxyphenyl sulfide hydrochloride.

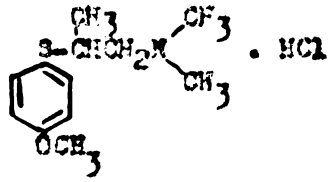


The experimental procedure utilized in the synthesis of this material was the same as that used in the previous preparations. The quantity, 15 g. (0.107 mole), of o-methoxythiophenol dissolved in 100 ml. of water and 20 grams of sodium hydroxide was allowed to react with 20.5 g. (0.104 mole) of γ-piperidino-n-propylchloride hydrochloride, added to the reaction flask as a 100 ml. aqueous solution, to yield an oily, insoluble amine. This on conversion to its hydrochloride in the usual manner separated from the ether solution as a gum which later solidified on being set aside for some time. The crude product on recrystallization from isopropyl alcohol gave 26.2 g. (0.087 mole, 83.5% yield) of a pure hydrochloride melting at 150-1°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{15}H_{24}NOSCl$: C, 59.6; H, 8.0; S, 10.6.

Found: C, 59.33; H, 8.24; S, 10.66.

α-Methyl-β-dimethylaminoethyl-p-methoxyphenyl sulfide hydrochloride

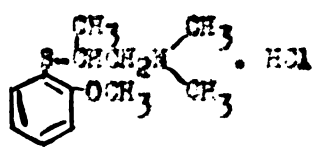


This compound, as the free amine, was obtained by the gradual addition of a solution of 22 g. (0.14 mole) of dimethylaminoisopropyl-chloride hydrochloride in 100 ml. of water to a stirred refluxing solution prepared from 20 g. (0.143 mole) of p-methoxythiophenol, 100 ml. of water, and 20 g. of sodium hydroxide. The initial attempt to prepare the hydrochloride resulted in the formation of an uncrystallizable gum. The gum was dissolved in 15 percent sodium hydroxide and the aqueous solution was extracted with ether and dried over anhydrous sodium sulfate. The ether solution was filtered and hydrogen chloride gas was bubbled through to form a gummy hydrochloride which solidified on being set aside for some time. The product after five recrystallizations from isopropyl alcohol weighed 13.2 g. (0.051 mole, 36% yield) and had a melting point of 173-174.5°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{12}H_{20}NOSCl$: C, 55.0; H, 7.7; S, 12.2.

Found: C, 54.99; H, 7.91; S, 11.96.

α-Methyl-β-dimethylaminoethyl-o-methoxyphenyl sulfide hydrochloride



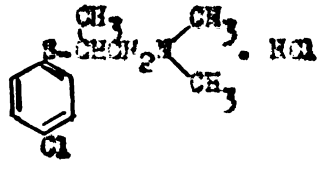
Following the previously described procedure, 15 g. (0.107 mole)

of o-methoxythiophenol dissolved in a solution of 20 g. of sodium hydroxide and 100 ml. of water was allowed to react with 16.5 g. (0.104 mole) of dimethylaminoisopropylchloride hydrochloride, added to the basic arylmercaptan solution, as a 100 ml. aqueous solution, to yield an insoluble oily amine. The free amine was converted to its hydrochloride in the usual manner, and due to its solubility in isopropyl alcohol was exceedingly difficult to purify. It had a melting point of 110-112°C. The amount of pure hydrochloride obtained weighed 11.1 g. (0.0425 mole, 41% yield). Analysis of the compound for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{12}H_{20}NOSCl$: C, 55.0; H, 7.7; S, 12.2.

Found: C, 55.22; H, 7.87; S, 12.10.

α-Methyl-β-dimethylaminoethyl-p-chlorophenyl sulfide hydrochloride.



The synthesis of this material was carried out in a nitrogen atmosphere. p-Chlorothiophenol, 14.5 g. (0.1mole), was dissolved in 100 ml. of water containing 20 g. of sodium hydroxide and 15 g. (0.095 mole) of dimethylaminoisopropyl chloride hydrochloride in 100 ml. of water was added to the refluxing alkaline solution of the haloarylmercaptan. The resulting oily amine, after isolation and drying was converted to its hydrochloride by bubbling gaseous hydrogen chloride through an ether solution of the amine. The hydrochloride was very

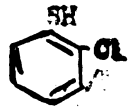
difficult to purify and was completely soluble in isopropyl alcohol. It was recrystallized by the addition of ether or cyclohexane to the compound dissolved in isopropyl alcohol. The amount of material obtained weighed 21.2 g. (0.08 mole, 84% yield) and had a melting point of about 90°C. Analysis for carbon, hydrogen, and sulfur gave the following data:

Calculated for $C_{11}H_{17}NSCl_2$: C, 49.6; H, 6.45; S, 12.0.

Found: C, 48.95; H, 6.59; S, 12.36.

o- or p- Substituted Thiophenols

o-Chlorothiophenol



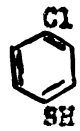
This haloarylmercaptan was prepared by following the method of Schwarzenbach and Egli (14). In a three-necked, 500 ml. flask fitted with a stirrer, thermometer, and dropping funnel, 51 g. (0.4 mole) of o-chloroaniline dissolved in 240 ml. of concentrated hydrochloric acid was diazotized using 28 g. (0.4 mole) of sodium nitrite contained in 80 ml. of water. The precooled sodium nitrite solution was added slowly to the stirred acid solution of o-chloroaniline held at a temperature of 0-5°C. by means of an ice-salt bath.

The diazoniumsalt solution was poured into a hot solution of potassium ethylxanthate, prepared from 160 g. (1.0 mole) of the xanthate and 600 ml. of water which had been heated to 80°C. This resulted in the formation of a heavy dark red oil, which was separated, and added to a mixture of 114 g. (2.0 moles) of potassium hydroxide,

200 ml. of ethanol and 100 ml. of water.

This reaction mixture after having been heated at its reflux temperature for three hours was diluted with two liters of water and neutralized with concentrated hydrochloric acid. The red oil which separated was distilled at about 3-4 mm. pressure to yield 23.5 g. (0.162 mole, 41% yield) of light yellow colored p-chlorothiophenol boiling at 75-80°C.

p-Chlorothiophenol



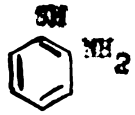
Using the procedure described by Senear, Rapport and Koepfli(6), 120 g. (1.84 mole) of zinc dust was added, in a half hour period, to a stirred mixture prepared from 72 g. (0.34 mole) of p-chlorobenzenesulfonyl chloride, 720 g. of ice and 130 ml. of concentrated sulfuric acid. The reaction mixture was held at 0°C. during the addition of the zinc and for two additional hours following the addition of the metal dust. The reaction mixture was then carefully warmed to its reflux temperature and an additional 130 ml. of concentrated sulfuric acid was added to it followed by the addition of, in small portions, of 120 g. of zinc dust. The reaction mixture was then set aside over night under an atmosphere of nitrogen.

Steam distillation of the reaction mixture resulted in the formation of a white crystalline solid in the distillate. The solid was filtered onto a Buchner funnel and dried over calcium chloride in a vacuum desiccator. The product weighed 36 g. (0.25 mole, 73% yield) and melted at 53-4°C.

p-Aminothiophenol

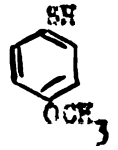
Following the technique developed by Gilman and Gainer (6), 128 g. (0.81 mole) of p-chloronitrobenzene was added to an aqueous solution containing 480 g. (2 moles) of sodium sulfide nonahydrate in two liters of water and the resulting mixture was heated at its reflux temperature for eight hours. The reaction mixture after being allowed to cool to room temperature was extracted with ether to remove a small amount of insoluble oil. The remaining aqueous solution was saturated with sodium chloride and then 240 g. (4 moles) of glacial acetic acid was added to it which caused an oil to separate from the solution. The oil removed by ether extraction, dried over anhydrous sodium sulfate and the ether removed by evaporation. Distillation of the oil yielded 62.4 g. (0.5 mole, 62% yield) of a colorless oil boiling at 143-47°C. at 11 mm. which solidified to a white solid on being set aside for some time. The product was stored under a nitrogen atmosphere.

o-Aminothiophenol



Following the same experimental procedure used for preparing p-aminothiophenol, the interaction of 128 g. (0.81 mole) of o-chloronitrobenzene and 480 g. (2 moles) of sodium sulfide nonahydrate yielded 59 g. (0.47 mole, 58% yield) of o-aminothiophenol, which had a melting point of 26°C and boiled at 125-7°C at 6 mm.

p-Methoxythiophenol



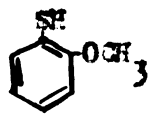
The procedure of Suter and Hansen (7) was utilized in the synthesis of this compound.

In a one liter three necked flask fitted with a stirrer, thermometer, and dropping funnel, 123 g. (1.0 mole) of p-anisidine dissolved in 250 ml. of concentrated hydrochloric acid was diazotized by adding 69 g. (1.0 mole) of sodium nitrite contained in 300 ml. of water. The reaction temperature was held at 0-5°C. during the diazotization. Sodium acetate was added to neutralize the excess acid and the cold diazonium salt solution was gradually poured into a hot solution, 70°C., prepared from 300 g. (1.87 mole) of potassium ethyl xanthate and 700 ml. of water. The stirred reaction mixture was then heated at its reflux temperature for an hour. The reaction mixture was allowed to cool to room temperature and the dark red oil which separated was removed.

The oil was added to a solution prepared from 115 g. of potassium hydroxide and 1 liter of 95% ethanol and the resulting mixture was heated at its reflux temperature for three hours at which point 20 g. of glucose was added to the refluxing reaction mixture. The volume of the reaction mixture was reduced to about 300 ml. by distillation of solvent and then acidified with sulfuric acid. A few grams of zinc dust was added and the reaction mixture was steamed distilled. The distillate was extracted with ether and the ether extract was dried over calcium chloride and the ether removed by evaporation. Distillation of the crude product under reduced pressure yielded 60 g. (0.43 mole, 43% yield) of material boiling at 100°C at 10 mm. Suter and

Hansen (7) reported a boiling point of 85–90°C at 5 mm.

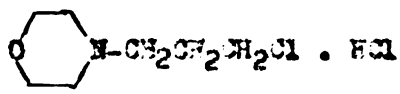
o-Methoxythiophenol



Following the experimental procedure just described for the preparation of p-methoxythiophenol, 123 g. (1.0 mole) of o-anisidine on diazotization and reaction with potassium ethyl xanthate yielded 50.2g. (0.36 mole, 36% yield) of o-methoxythiophenol which had a boiling point of 124–129°C. at 13 mm.

γ (N,N-Dialkylamino) alkyl Chloride Hydrochlorides

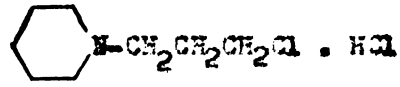
γ-Morpholino-n-propyl chloride hydrochloride.



This hydrochloride was prepared according to the method developed by Adams and Whitmore (9). A solution containing 300 g. (3.53 mole) of morpholine and 360 g. (2.29 mole) of trimethylene chlorobromide in 900 ml. of dry benzene was set aside at room temperature for one hour with an occasional shaking. Following this, the reaction mixture was heated at its reflux temperature for three hours during which time a heavy white precipitate formed. The precipitate was recovered by suction filtration and washed throughly with ether. The ether washings and benzene filtrate were combined and extracted with 500 ml. of 3N hydrochloric acid. The acid extract was made basic with 10N sodium hydroxide and the oil which separated was extracted with ether and dried over anhydrous sodium sulfate.

The dry ether solution was filtered into a one liter three-necked flask fitted with condenser, stirrer, and delivery tube for admission of gaseous hydrogen chloride. Saturation of the amine ether solution with hydrogen chloride gave 201 g. (1 mole, 43.5% yield) of a white solid hydrochloride which was recrystallized from isopropyl alcohol. The melting point of the hydrochloride was 157-8°C. Its reported melting point is 168-170°C.(9).

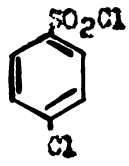
γ-Piperidino-n-propyl chloride hydrochloride



Following the procedure used for the preparation of γ-morpholino-n-propyl chloride hydrochloride, the interaction of 275 g. (1.75 mole) of trimethylenechlorobromide in 500 ml. of dry benzene with 298 g. (3.5 mole) of piperidine, followed by conversion of the free amine to its hydrochloride gave 150 g. (0.75 mole, 43.5% yield) of -piperidino-n-propyl chloride hydrochloride.

After a single recrystallization from absolute ethanol, the melting point of the pure hydrochloride was 215-6°C. Its reported melting point is 220°C. (15).

p-Chlorobenzenesulfonyl chloride



Using the method of Ullman and Borselt (16), 130 g. (1.56 mole, 102 ml) of chlorosulfonic acid contained in a half liter three-necked flask fitted with a stirrer, dropping funnel,

and thermometer, was cooled to -15°C. by means of an ice-salt bath. To the cold stirred chlorosulfonic acid, 60 g. (0.54 mole, 34.5 ml.) of chlorobenzene was added dropwise over a two hour period. The reaction temperature was kept between -10 and -5°C for an additional two hours after which the sulfonation mixture was set aside over night at room temperature.

The reaction mixture was then poured onto cracked ice and the solid product recovered by filtration and dried. The crude product, weighing 100 g. (0.47 mole, 85% yield) was used directly for reduction to p-chlorothiophenol.

SUMMARY

1. Five ω(N,N-dialkylamino) alkyl -o or p-acetylaminophenyl sulfides and two ω(N,N-dialkylamino) alkyl o-aminophenyl sulfides were prepared for the first time as either their hydrochloride salts or quaternary methyl iodides and some of their physical properties are reported.

2. Ten new ω(N,N-dialkylamino) alkyl -o or p-methoxyphenyl sulfide hydrochloride salts were prepared for the first time and their melting points are reported.

3. Nine ω(N,N-dialkylamino) alkyl -o or p-chlorophenyl sulfide hydrochloride salts were prepared which are not recorded in the chemical literature.

4. Four previously undescribed ω(N,N-dialkylamino) alkyl -o or p-methylphenyl sulfide hydrochlorides were synthesized. Some of their physical properties are listed.

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VITA

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