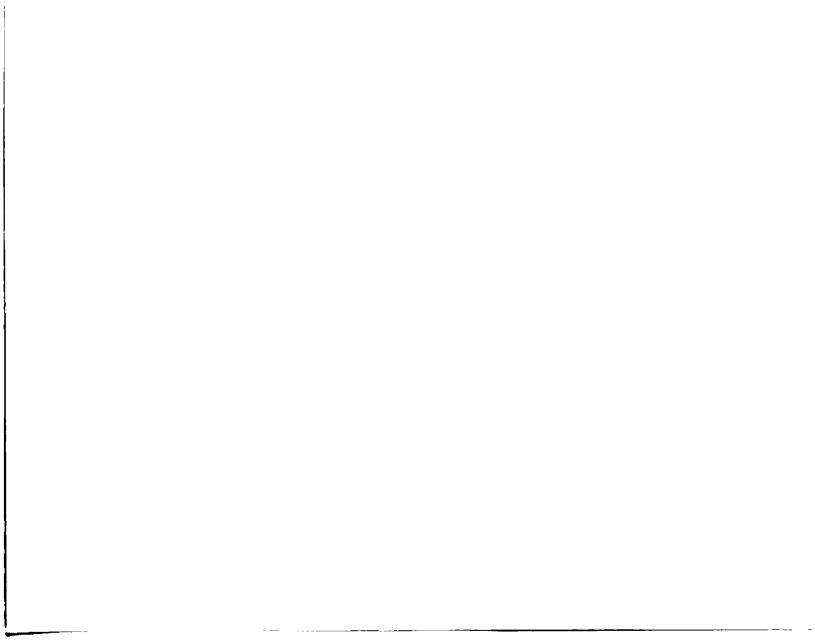

THE PREPARATION OF SOME HETEROCYCLIC OMEGA-(N,N-DIALKYLAMINO) ALKYL SULFIDES

By

JANET N. PAIGE

A THESIS

Submitted to the College of
Science and Arts of Michigan
State University of Agriculture
and Applied Science in Partial
Fulfillment of the Requirements
for the Degree of

MASTER OF SCIENCE

Department of Chemistry

1963

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The author wishes to express her appreciation for the guidance given by Professor Robert D. Schuetz during the course of this investigation.

THE PREPARATION OF SOME HETEROCYCLIC OMEGA-(N,N-DIALKYLAMINO) ALKYL SULFIDES

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AN ABSTRACT

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ABSTRACT

The objective of this investigation was to synthesize previously undescribed heterocyclic omega-(N,N-dialkylamino) alkyl sulfides. The work was undertaken as part of a continuing study of sulfur-containing organic compounds of potential pharmacological value as local anesthetics. Earlier investigations from these laboratories in this area were concerned with dialkylaminoalkyl derivatives of thiophenol (1), 2- and 3-thiophenethiol (2,3), substituted thiophenols (4), α- and β-naphthalenethiols (5), and thianaphthenethiols (6).

The experimental procedure utilized in the present work involved the interaction, in an alkaline solution, of the heterocyclic thiol with a dialkylaminoalkyl chloride hydrochloride for two to three hours at the reflux temperature of the reaction mixture. In this manner, seventeen new heterocyclic omega-(N,N-dialkylamino) alkyl sulfides were prepared. The amines were customarily isolated as their hydrochloride salts.

The commercially available heterocyclic thiols used in this investigation were 2-mercaptobenzothiazole, 5-mercapto-1-phenyl-1,2,3,4-tetrazole, 2-mercaptopyrimidine, 2-mercaptoimidazole, 2-mercaptobenzoxazole, and 2-mercaptobenzimidazole. The ω-(N,N-dialkylamino) alkyl moiety of the sulfides was obtained from β-diethylaminoethyl chloride, β-morpholinoethyl chloride, β-piperidinoethyl chloride, γ-morpholino-n-propyl chloride, γ-piperidino-n-propyl chloride, α-methyl-β-morpholinoethyl chloride, and α-methyl-β-piperidinoethyl chloride.

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INTRODUCTION

The present study is concerned with an investigation of heterocyclic omega-(N,N-dialkylamino) alkyl sulfides. These were synthesized and studied since it had been previously observed that the analogous phenyl compounds showed local anesthetic activity comparable with that of procaine, 2-diethylaminoethyl 4-aminobenzoate (1). Previous studies directed towards the preparation of sulfur-containing organic compounds of potential value as local anesthetics were concerned with dialkylaminoalkyl derivatives of thiophenol (1), 2- and 3-thiophenethiol (2,3), substituted thiophenols (4), α- and β-naphthalenethiols (5), and thianaphthenethiols (6). Thus, the present study represents a departure from the previous work inasmuch as heterocyclic thiols containing more than a single hetero atom were utilized. The heterocyclics used in the present investigation included the 2-mercapto derivatives of benzothiazole, benzimidazole, benzoxazole, pyrimidine, 1-methylimidazole, and 5-mercapto-1-phenyl-1,2,3,4-tetrazole.

To determine the effect of structure on physiological activity by having different atoms in the one position of the heterocyclic portion of the molecule, the 2-mercapto derivatives of benzothiazole, benzimidazole and benzoxazole were allowed to interact with γ-piperidino-n-propyl chloride hydrochloride.

X = S, NH, or O

However, the effect of these different structures on pharmacological activity can be determined only by laboratory and clinical tests which have not been conducted as part of the present study, and such studies will be reported elsewhere.

DISCUSSION

There are two general synthetic methods available for the preparation of 2-(N,N-dialkylaminoalkylthio) benzothiazoles and similar compounds. These are shown in the following reaction sequences.

1. $RSNa + Cl(CH_2)_nOH \longrightarrow RS(CH_2)_nOH$

$RS(CH_2)_nOH + SOCl_2 \longrightarrow RS(CH_2)_nCl$

$RS(CH_2)_nCl + 2\ R_2NH \longrightarrow RS(CH_2)_nNR_2 + R_2NH\cdot HCl$

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

$R_2N(CH_2)_nOH + SOCl_2 \longrightarrow R_2N(CH_2)_nCl\cdot HCl$

$R_2N(CH_2)_nCl\cdot HCl + RSNa \longrightarrow RS(CH_2)_nNR_2 + NaCl$

In the present study, the latter method was utilized. There were several reasons for this choice. First, and most important, previous experience in the synthesis of this general type of compound had shown that the first process was considerably more difficult to handle experimentally (3). The yields, especially from the second step, were apt to be rather poor. Houff and Schuetz reported that the Darzens reaction (7), involved in the second step, resulted in the formation of considerable amounts of intractable material (3). They also observed that the final products obtained in that general procedure contained impurities that were quite difficult to remove; this caused considerable

difficulty in purification of the hydrochlorides by recrystallization procedures. These problems were not encountered in the second process. Another advantage of the second reaction sequence was the fact that several ω-(N,N-dialkylamino) alkyl chlorides, as their hydrochlorides, were commercially available. Thus, it was often possible to start with the third step in the second series of reactions.

The preparation of the ω-(N,N-dialkylamino) alcohols was carried out by heating a stirred mixture of the chlorohydrin and secondary amine in absolute alcohol at its reflux temperature for an entire day; the molar ratio of the reactants was two moles of amine for each mole of chlorohydrin (8). A small quantity of sodium iodide was added to facilitate the reaction. During the reaction, secondary amine hydrochloride by-product precipitated. This was removed by filtration. The alcohols were colorless liquids, easily purified by vacuum distillation, and were obtained in yields varying from 49 to 74 percent.

The ω-(N,N-dialkylamino) alkyl chlorides were prepared by the reaction of the corresponding alcohols with thionyl chloride in dry chloroform (9). A quarter molar excess of thionyl chloride was used. This reagent was added to the chloroform solution of the alcohol at a rate sufficient to maintain a reaction temperature of 50 to 55°C. Frequently, solid products commenced to precipitate from the reaction mixture during the addition of the thionyl chloride. Upon completing the addition of the chlorinating reagent, the reaction mixture was stirred at 50 to 60° for an additional two hours. In most cases, toward the end of the reaction, it was necessary to add additional

chloroform to the reaction mixture in order to permit continuous stirring. The solid α-(N,N-dialkylamino) alkyl chloride hydrochlorides were recrystallized from absolute alcohol and were obtained in yields ranging from 42 to 70 percent. Although others have attained improvement in yields by passing a current of dry air across the surface of the reaction mixture, such a procedure was not found particularly helpful in the course of this work.

The 2-(N,N-dialkylaminoalkylthio) benzothiazoles were prepared by the interaction of the α-(N,N-dialkylamino) alkyl chloride with an excess of 2-mercaptobenzothiazole dissolved in aqueous sodium hydroxide. Following the complete addition of the chloride, the reaction mixture was kept at its reflux temperature for two hours. During this time, the product separated from solution as a heavy oil; these oils varied in color from a light yellow to a dark brown. The crude, oily product was separated, and the aqueous layer was extracted with three portions of ether. The combined ether extracts and oil were dried over anhydrous sodium sulfate. The hydrochlorides were prepared by passing dry hydrogen chloride gas into the cooled ether solutions of the amines. In all cases, the amine salts were obtained as white solids; the addition of excessive amounts of hydrogen chloride caused the amine salts to become sticky and very difficult to handle.

With a single exception, the final products were purified by recrystallization from isopropyl alcohol. 2-(α-Methyl-β-piperidinoethylthio) benzothiazole was purified by a single washing with hot cyclohexane. The following solvents were ineffective in the recrystal-

lization of this material: isopropyl alcohol, ethanol, 1:1 cyclohexane-isopropyl alcohol, 1:1 benzene-isopropyl alcohol, n-butyl alcohol, chloroform, and benzene-isopropyl alcohol containing a small amount of ether. In the preparation of this material, it was difficult to avoid excess hydrogen chloride; precipitation was complete within a very short time. Possibly because of these difficulties, the yield of this product was one of the lowest (31 percent).

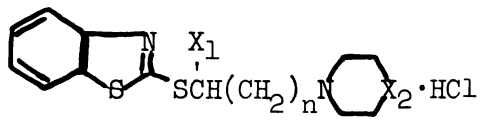
Yields of the thioamine hydrochloride products varied from 14 to 80 percent. The lowest yield was obtained for 2-(α-methyl-β-morpholino-ethylthio) benzothiazole hydrochloride. The third and largest quantity of this material, obtained from the mother liquors after its recrystallization, could not be further purified by additional recrystallization, and the recovered product had a 10° melting point range. Thus, the yield reported for this compound included only the material obtained in the initial two recrystallizations.

Altogether, six previously unreported 2-(dialkylaminoalkylthio) benzothiazole hydrochlorides were prepared. Some of their properties are summarized in Table I.

The same general procedure was employed in the preparation of three new 1-phenyl-5-(dialkylaminoalkylthio) 1,2,3,4-tetrazole hydrochlorides. In all three cases, the tertiary amines separated from the reaction mixtures as dark colored oils. These crude, oily products were converted into their solid hydrogen chloride salts by treatment with gaseous hydrogen chloride as already described. The crude products were recrystallized without difficulty from either absolute or isopropyl alcohol. Yields of these materials in pure form ranged from 37 to 53 percent.

TABLE I

2-(N,N-Dialkylaminoalkylthio) Benzothiazoles



X_1	n	X_2	M.P., °C.	% Yield	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
H	1	O	169-70.5	Mechanical loss	$C_{13}H_{17}ClN_2OS_2$	49.29	49.45	5.38	5.43	20.22	19.18
H	1	CH_2	213-15	81	$C_{14}H_{19}ClN_2S_2$	53.40	53.25	6.04	5.99	20.35	20.35
H	2	O	178-80	62	$C_{14}H_{19}ClN_2OS_2$	50.83	50.63	5.75	5.76	19.37	19.40
H	2	CH_2	137-8.5	60	$C_{15}H_{21}ClN_2S_2$	54.80	54.74	6.40	6.54	19.50	19.36
CH_3	1	O	146-8	14	$C_{14}H_{19}ClN_2OS_2$	50.83	50.76	5.75	5.92	19.37	19.36
CH_3	1	CH_2	118-22	31	$C_{15}H_{21}ClN_2S_2$	54.80	54.88	6.40	6.46	19.50	19.36

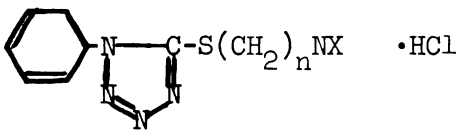
In one case, the effect on product yield of the ratio of the starting materials was checked. Ordinarily, a slight excess of the tetrazole was used. However, in one preparation of 1-phenyl-5-(β-diethylaminoethylthio) 1,2,3,4-tetrazole hydrochloride, equimolar quantities of the tetrazole and the dialkyl compounds were employed. The yield of the thioamine hydrochloride product obtained was the same as when an excess of tetrazole was used in its preparation. Some of the properties of these compounds are shown in Table II.

A series of 2-(N,N-dialkylaminoalkylthio) pyrimidine hydrochlorides was prepared following the general procedure already described for the synthesis of heterocyclic thioalkyl amine salts. In the preparations of the hydrochlorides of 2-(γ-piperidino-n-propylthio)- and 2-(β-diethylaminoethylthio) pyrimidine, oily, dark products separated from solution during the reaction of excess 2-mercaptopyrimidine with the dialkyl compound. The hydrochlorides of these tertiary amines were prepared, by the general procedures already described, in yields of 25 and 28 percent respectively.

Insoluble material failed to separate from the reaction mixture during the preparation of 2-(γ-morpholino-n-propylthio) pyrimidine. During the final stages of the reaction, the reaction mixture took on a dark coloration and became turbid, but, even after cooling, there was no separation of the reaction mixture into distinct layers. The mixture was thrice extracted with an 80 ml. portion of ether. Upon treatment of the dried ethereal solution with dry hydrogen chloride gas, a rather small quantity of the hydrochloride was obtained. The yield of this material was 15 percent.

TABLE II

1-Phenyl-5-(N,N-Dialkylaminoalkylthio) 1,2,3,4-Tetrazoles



n	X	M.P., °C.	% Yield	Formula	Carbon, %		Hydrogen, %		Sulfur, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
3	C_4H_8O	187-9.5	43	$C_{14}H_{20}ClN_5OS$	49.19	49.56	5.86	6.12	9.37	9.52
3	C_5H_{10}	156-8.5	37	$C_{15}H_{22}ClN_5S$	53.02	53.16	6.48	6.45	9.42	9.52
2	Diethyl	180-2	53	$C_{13}H_{20}ClN_5S$	49.76	49.60	6.38	6.29	10.20	10.48

Two of the crude hydrochloride products were recrystallized from isopropyl alcohol. Washing with ether was found to be the most suitable method of purification for 2-(β-diethylaminoethylthio) pyrimidine hydrochloride. Some of the properties of these compounds are given in Table III.

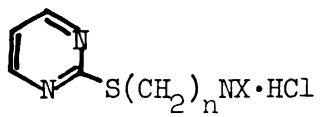
Similar reactions were run with 1-methyl-2-mercaptoimidazole, 2-mercaptobenzoxazole, and 2-mercaptobenzimidazole with the aim of obtaining additional examples of heterocyclic thioalkylamine salts. On the whole, the reactions with the first of these materials were probably the least successful. The general experimental procedures used were the same as those previously described.

The reaction of the imidazole with γ-morpholino-n-propyl chloride hydrochloride resulted in no product formation. During the reaction period, there was no evidence that any reaction had occurred, such as oil formation or cloudiness; the reaction solution was discarded.

A similar reaction with γ-piperidino-n-propyl chloride hydrochloride yielded crude product as a dark oil. The hydrochloride of this tertiary amine was prepared, but no satisfactory method of purification was found. Due to the hygroscopic nature of the product, attempted recrystallization resulted only in formation of an oily material. The compound was stored under nitrogen.

TABLE III

2-(N,N-Dialkylaminoalkylthio) Pyrimidines



n	X	M.P., °C.	% Yield	Formula	Carbon, %		Hydrogen, %		Sulfur, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
3	C_4H_8O	174-7	15	$C_{11}H_{18}N_3OS$	47.91	48.00	6.53	6.68	11.61	11.64
3	C_5H_{10}	158.5-60	25	$C_{12}H_{20}ClN_3S$	52.65	52.61	7.31	7.18	11.70	12.23
2	Diethyl	125-8	28	$C_{10}H_{18}ClN_3S$	48.48	48.26	7.27	7.72	12.93	12.80

During the reaction of the imidazole with β-diethylaminoethyl chloride hydrochloride, a light oily material separated as the upper layer of the reaction mixture. However, on cooling, the oil disappeared. The reaction mixture was extracted with ether. Treatment of the ethereal extracts with hydrogen chloride resulted in the formation of the dihydrochloride, verified by elemental analyses, of 1-methyl-2-(β-diethylaminoethylthio) imidazole. This material, also, was extremely hygroscopic, and its purification was unsuccessful. After it had been stored three months in an amber bottle under nitrogen, the material had lost its crystallinity.

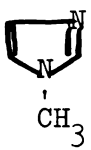
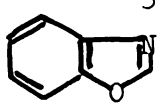
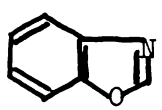
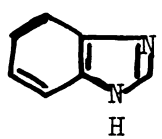
Some of the properties of these compounds are summarized in Table IV.

Throughout the study of these miscellaneous reactions, it appeared that the morpholino derivatives had the least tendency to form. This was also true of 2-mercaptobenzoxazole. In the reaction of this material with β-morpholinoethyl chloride hydrochloride, only a very small quantity of supernatant oily material formed. This dissolved as soon as the mixture was cooled. Extraction of the mixture with ether yielded a solution containing a small amount of the desired tertiary amine. This was converted to its hydrochloride and a quantity sufficient for elemental analyses was obtained after its recrystallization from isopropyl alcohol.

TABLE IV

Miscellaneous Heterocyclic Thioalkylamine Hydrochlorides

$RS(CH_2)_nNX \cdot HCl$

R	n	X	M.P., °C.	% Yield	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
	3	C_5H_{10}	144-50	29	$C_{12}H_{22}ClN_3S$	52.27	49.75	7.95	7.72	11.62	11.10
	2	Diethyl	115-20	24	$C_{10}H_{21}Cl_2N_3S$	41.96	42.85	7.35	7.67	24.82*	23.04*
	2	C_4H_8O	215-8	-	$C_{13}H_{17}ClN_2O_2S$	51.91	51.80	5.66	5.82	10.65	10.53
	3	C_5H_{10}	167-70	-	$C_{15}H_{21}ClN_2OS$	57.60	56.95	6.72	7.04	10.24	10.46
	3	C_5H_{10}	103-8	72	$C_{15}H_{21}N_3S$**	65.45	62.20	7.63	7.96	11.64	11.20

*% Chlorine

**Tertiary amine

The interaction of 2-mercaptobenzoxazole with γ-piperidino-n-propyl chloride was considerably more successful than were the previous cases. During the reaction, a large amount of a dark red-colored product separated from the reaction mixture. A fair yield (38%) of the crude hydrochloride was obtained by treatment of a dry ethereal solution of this material with gaseous hydrogen chloride. A small scale recrystallization of the hydrochloride from isopropyl alcohol yielded the pure compound. Due to excessive humidity in the laboratories, the major amount of this material was lost during recrystallization. A summary of some of the properties of these compounds is recorded in Table IV.

An attempt to prepare 2-(γ-dimethylamino-n-propylthio) benzoxazole hydrochloride was unsuccessful. Upon completion of the initial reaction, a cloudy mixture was present. This was extracted with ether, and when hydrogen chloride was passed into the dried ether solution of it, a small amount of a sticky red-colored oily material formed. Attempts at crystallization of the oil failed.

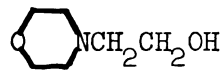
One new derivative of 2-mercaptobenzimidazole, 2-(γ-piperidino-n-propylthio) benzimidazole, was prepared. This differed from the compounds previously described in that the tertiary amine was a solid. Thus, conversion to a hydrochloride was unnecessary. Some of the properties of this compound are listed in Table IV.

An attempt to prepare 2-(β-morpholinoethylthio) benzimidazole was a failure. There was no evidence, whatsoever, of any reaction.

EXPERIMENTAL

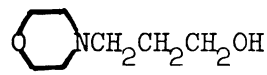
A. Preparation of (N,N-Dialkylamino) Alcohols

1. β-Morpholinoethyl Alcohol



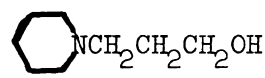
A 1-liter, three-necked flask equipped with reflux condenser, stirrer, and thermometer was charged with 26.0 g. (3.0 moles) of morpholine, 120.0 g. (1.5 moles) of ethylene chlorohydrin, and 11.3 g. (0.075 mole) of sodium iodide dissolved in 350 ml. of absolute alcohol. The stirred reaction mixture was heated at 50-60° for 24 hours. After cooling, the mixture was treated with a sodium ethoxide solution prepared from 300 ml. of absolute alcohol and 33.0 g. (1.45 g. at.) of metallic sodium. The insoluble material was removed from the reaction mixture by filtration and washed with 225 ml. of ether. The filtrate and ether washings were combined and distilled until the temperature in the distillation head reached 160°. The residue was filtered to remove the remaining insoluble material. The latter was washed on the filter with ether. The ether washings were combined with the filtrate, and the ether was removed by evaporation on a steam bath. The residue was vacuum distilled to obtain 96 g. (0.73 mole; 49%) of a pure product boiling at 158-162°/27 mm., n_D^{20} = 1.4760. Literature values, b.p. = 118-120°/24 mm., n_D^{25} = 1.4770 (10).

2. γ-Morpholino-n-propyl Alcohol



To a 1-liter, three-necked flask equipped as described in the preceding synthesis was added 174.0 g. (2.0 moles) of morpholine, 94.5 g. (1.0 mole) of trimethylene chlorohydrin, and 8.0 g. (0.055 mole) of sodium iodide dissolved in 175 ml. of absolute alcohol. The stirred reaction mixture was heated at 60-65° for 24 hours, cooled, and then neutralized with a sodium ethoxide solution prepared by dissolving 22.0 g. (0.96 g. at.) of sodium in 200 ml. of absolute alcohol. The insoluble material was removed by filtration and washed on the filter with dry ether. The ether washings and filtrate were combined and distilled at atmospheric pressure until the still head temperature reached 145°. The residue was treated in the same manner as described in the previous preparation to obtain 99.6 g. (0.69 mole; 69%) of a pure product boiling at 135-139°/24 mm., n_D^{20} = 1.4742. Literature values, b.p. = 134-136°/24 mm., n_D^{25} = 1.4752 (10).

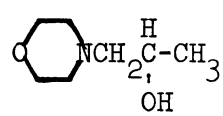
3. γ-Piperidino-n-propyl Alcohol



The experimental apparatus was the same as that described in the preceding reaction. To a solution of 249.0 g. (3.0 moles) of piperidine and 141.8 g. (1.5 moles) of trimethylene chlorohydrin was added 11.3 g. (0.075 mole) of sodium iodide dissolved in 350 ml. of absolute alcohol.

The reaction was run in the manner already described. After the reaction mixture had cooled, it was treated with a sodium ethoxide solution prepared from 33 g. (1.43 g. at.) of metallic sodium and 350 ml. of absolute alcohol. The insoluble secondary amine hydrochloride was removed by filtration and washed with dry ether. The filtrate and ether washings were combined and distilled at atmospheric pressure until a still head temperature of 180° was reached. The residue tended to solidify during filtration. The solid was dissolved in 200 ml. of absolute alcohol and distilled at atmospheric pressure until the still head temperature reached 100°. The residue from this distillation was subjected to vacuum distillation to obtain 136.0 g. (0.95 mole; 63.5%) of a pure product boiling at 151-154°/11 mm., n_D^{20} = 1.4750. Literature values, b.p. = 93.5-95°/9 mm.; n_D^{20} = 1.4755 (8).

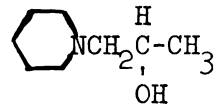
4. α-Methyl-β-morpholinoethyl Alcohol



Using the apparatus previously described, the reaction flask was charged with 57.0 g. (0.6 mole) of propylene chlorohydrin, 87.0 g. (1.0 mole) of morpholine, and 4.0 g. (0.27 mole) of sodium iodide dissolved in 125 ml. of absolute alcohol. The reaction was conducted in the manner discussed above. Following completion of the reaction, the mixture was treated with a solution containing 11.0 g. (0.47 g. at.) of sodium dissolved in 100 ml. of absolute alcohol. After removal of a small amount of solid by filtration and washing with ether, the washings and the filtrate were combined and distilled at atmospheric pressure.

The remaining residue was vacuum-distilled to obtain 53.5 g. (0.37 mole; 74%) of a clear liquid boiling at 160-163°/14 mm., n_D^{25} = 1.4629. Literature values, b.p. = 82-4°/1.5 mm., n_D^{20} = 1.4638 (11).

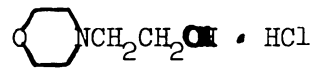
5. α-Methyl-β-piperidinoethyl Alcohol



This alkanolamine was synthesized in a manner similar to that discussed above using 170.0 g. (2.0 moles) of piperidine, 94.5 g. (1.0 mole) of propylene chlorohydrin, and 7.5 g. (0.05 mole) of sodium iodide dissolved in 175 ml. of absolute alcohol. The reaction was carried out as previously described. After the reaction mixture had cooled, it was treated with a sodium ethoxide solution prepared by dissolving 22.0 g. (0.96 g. at.) of sodium in 200 ml. of absolute alcohol. The insoluble salt was removed by filtration and washed with ether. These ether washings were combined with the filtrate; this was distilled at atmospheric pressure until a still head temperature of 130° was reached. The residue was then vacuum-distilled to obtain 80.0 g. (0.56 mole; 56%) of a clear liquid product which boiled at 74-78°/9 mm. Literature value, b.p. = 194° (12).

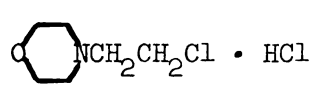
B. Preparation of ω-(N,N-Dialkylamino) Alkyl Chlorides

1. β-Morpholinoethyl Chloride Hydrochloride



A 65.5 g. (0.5 mole) quantity of β-morpholinoethyl alcohol was placed in a 500 ml. three-necked flask equipped with a reflux condenser, stirrer, thermometer, and dropping funnel. The apparatus was also provided with a gas inlet tube for drawing a stream of dry nitrogen through the reaction flask. A 72.1 g. (0.6 mole) quantity of thionyl chloride was dissolved in 100 ml. of dry chloroform and added dropwise to the amino alcohol at a rate sufficient to maintain the reaction temperature between 50-55°. The addition of the acid chloride required an hour and 10 minutes. Following the addition of the acid chloride, the reaction mixture was heated and stirred at a temperature of 52-61° for an additional two hours. During this period, it was necessary to add 50 ml. of chloroform to the reaction mixture to keep it fluid. After cooling the reaction mixture, a gray solid was removed by filtration. This was recrystallized from 470 ml. of absolute alcohol and 5 g. of Norit to obtain 39.1 g. (0.21 mole; 42%) of an off-white colored product that melted at 177-181°. Literature value, m.p. = 182-182.5° (9).

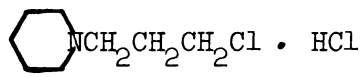
2. γ-Morpholino-n-propyl Chloride Hydrochloride



A solution containing 72.5 g. (0.5 mole) of γ-morpholino-n-propyl alcohol dissolved in 20 ml. of dry chloroform was placed in a half liter, three-necked flask equipped as described in the previous preparation

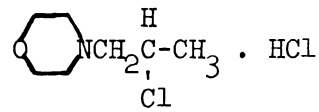
except for the omission of the gas inlet tube. A chloroform solution containing 72.0 g. (0.6 mole) of thionyl chloride dissolved in 100 ml. of the solvent was added to the alkanolamine in the manner described above during three and a quarter hours. Following the addition of the acid chloride, the reaction mixture was heated at its reflux temperature a half hour. Concentration of the reaction solution resulted in the formation of a yellow precipitate. This was recovered by filtration and recrystallized from 150 ml. of absolute alcohol to obtain 62.4 g. (0.31 mole; 62%) of a cream-colored powder having a melting point of 171-174°. Literature value, m.p. = 168-170° (13).

3. γ-Piperidino-n-propyl Chloride Hydrochloride



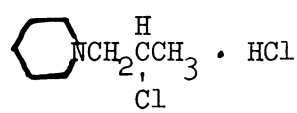
Following the experimental procedure used in similar syntheses, a solution containing 70.0 g. (0.5 mole) of γ-piperidino-n-propyl alcohol dissolved in 50 ml. of dry chloroform was treated with 75.0 g. (0.65 mole) of thionyl chloride dissolved in 100 ml. of chloroform. The crude product was isolated as described previously and recrystallized from 200 ml. of absolute alcohol to obtain 61.2 g. (0.31 mole; 62%) of an off-white colored solid which melted at 224-228°. Literature value, m.p. = 208-209° (13).

4. α-Methyl-β-morpholinoethyl Chloride Hydrochloride



A 350 g. (0.24 mole) quantity of α-methyl-β-morpholinoethyl alcohol was dissolved in 50 ml. of dry chloroform and allowed to interact with 36.0 g. (0.3 mole) of thionyl chloride. The latter was added to the alkanolamine by dissolving it in 100 ml. of chloroform. Concentration of the reaction solution precipitated the crude product. This was recrystallized from 125 ml. of absolute alcohol to obtain 33.7 g. (0.17 mole; 71%) of an off-white colored solid product which melted at 181-183°. Literature value, m.p. = 180-181.5° (3).

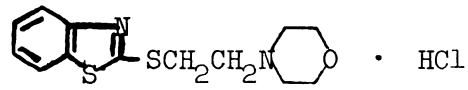
5. α-Methyl-β-piperidinoethyl Chloride Hydrochloride



Following the procedure previously described, a 57.2 g. (0.4 mole) quantity of α-methyl-β-piperidinoethyl alcohol was dissolved in 25 ml. of dry chloroform and treated with a chloroform solution of 72.0 g. (0.6 mole) of thionyl chloride. The reaction and product isolation were conducted as described in previous preparations. The crude product was recrystallized from 150 ml. of absolute alcohol to obtain 47.1 g. (0.24 mole; mechanical loss during recrystallization) of a gold-colored crystalline product melting at 209-211°. Literature value, m.p. = 207-209° (3).

C. Preparation of 2-(Dialkylaminoalkylthio) Benzothiazoles

1. 2-(β-Morpholinoethylthio) Benzothiazole Hydrochloride

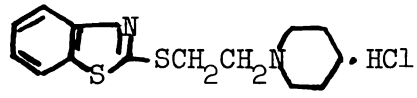


A 13.4 g. (0.08 mole) quantity of 2-mercaptobenzothiazole was dissolved in a sodium hydroxide solution prepared by dissolving 10 g. (0.25 mole) of sodium hydroxide in 90 ml. of water; the resulting basic solution was transferred to a 500 ml., three-necked flask equipped with a stirrer, dropping funnel, reflux condenser and thermometer. The reaction solution was heated to its reflux temperature, and an aqueous solution of 9.3 g. (0.05 mole) of β-morpholinoethyl chloride hydrochloride was added to it during an hour. After the mixture had been stirred at its reflux temperature for an additional two hours, it was cooled to room temperature. The sticky yellow-colored oil that had settled out was separated, and the aqueous layer was extracted with three 80 ml. portions of ether. The ether extracts and the oil were combined and washed with 100 ml. of 5% sodium hydroxide, then with 100 ml. of water, and dried in contact with anhydrous sodium sulfate.

The ether solution was filtered into a 500 ml., three-necked flask fitted with an inlet tube and a stirrer, cooled in an ice-bath, and treated, while being stirred, with hydrogen chloride gas. The white hydrochloride salt was removed by filtration, and the filtrate was tested with gaseous hydrogen chloride for complete precipitation of the amine salt. It was necessary to avoid the use of excess hydrogen chloride since this caused the amine hydrochlorides to become sticky and

almost impossible to recrystallize. The crude product was recrystallized from 100 ml. of isopropyl alcohol to obtain 7.3 g. (0.023 mole; mechanical loss during purification) of a white crystalline product melting at 169-170.5°. Calc'd. for $C_{13}H_{17}ClN_2OS_2$: C, 49.29; H, 5.38; S, 20.22. Found: C, 49.45; H, 5.43; S, 19.18.

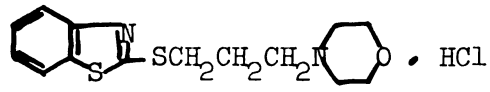
2. 2-(β-Piperidinoethylthio) Benzothiazole Hydrochloride



A basic solution of 13.4 g. (0.08 mole) of 2-mercaptobenzothiazole was prepared in the same manner as described in the preceding synthesis and poured into a 500 ml., three-necked flask equipped with a stirrer, thermometer, dropping funnel, and reflux condenser. The stirred solution was heated to its reflux temperature, and a solution containing 9.0 g. (0.05 mole) of β-piperidinoethyl chloride hydrochloride dissolved in 100 ml. of water was added to it over a period of an hour. Following another two hours of heating at its reflux temperature, the reaction mixture was cooled to room temperature; a dark oil had separated, and this was removed. The aqueous layer was extracted with three 80 ml. portions of ether. The combined ether extracts and oil were washed as previously described and dried over anhydrous sodium sulfate.

The amine hydrochloride was prepared in the same manner as described in the preceding synthesis. After recrystallization from 540 ml. of isopropyl alcohol, 12.8 g. (0.041 mole; 81%) of a white powder melting at 213-215° was obtained. Calc'd. for $C_{14}H_{19}ClN_2S_2$: C, 53.40; H, 6.04; S, 20.35. Found: C, 53.25; H, 5.99; S, 20.35.

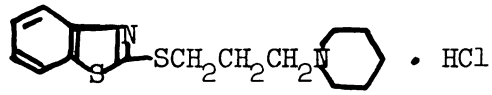
3. 2-(γ-Morpholino-n-propylthio) Benzothiazole Hydrochloride



By means of the experimental procedure previously described, a basic solution of 13.4 g. (0.08 mole) of 2-mercaptobenzothiazole was allowed to interact with an aqueous solution of 10.0 g. (0.05 mole) of γ-morpholino-n-propyl chloride hydrochloride. Upon completion of the reaction, a very sticky dark oil had separated. This was removed from the cooled reaction mixture and combined with the extracts obtained by ether extraction of the aqueous layer. This material was washed and dried as described in the first synthesis.

Dry hydrogen chloride was passed into the ether solution precipitating the crude amine hydrochloride. The crude material was recrystallized from 90 ml. of isopropyl alcohol to obtain 10.2 g. (0.031 mole; 62%) of a white powder melting at 178-180°. Calc'd. for $C_{14}H_{19}ClN_2OS_2$: C, 50.83; H, 5.75; S, 19.37. Found: C, 50.63; H, 5.76; S, 19.40.

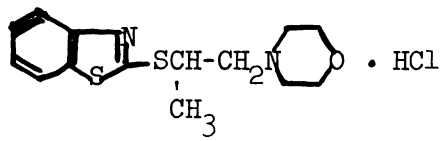
4. 2-(γ-Piperidino-n-propylthio) Benzothiazole Hydrochloride



The reaction of 13.4 g. (0.08 mole) of 2-mercaptobenzothiazole with 9.9 g. (0.05 mole) of γ-piperidino-n-propyl chloride hydrochloride was carried out in the usual manner. Using the procedure previously described, the amine was converted to its hydrochloride salt. After recrystallization from 120 ml. of isopropyl alcohol, 9.8 g. (0.03 mole;

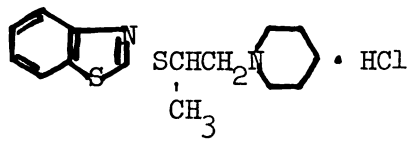
60%) of a white powder was obtained. The melting point of the pure amine hydrochloride was 137-138.5°. Calc'd. for $C_{15}H_{21}ClN_2S_2$: C, 54.80; H, 6.40; S, 19.50. Found: C, 54.74; H, 6.54; S, 19.36.

5. 2-(α-Methyl-β-morpholinoethylthio) Benzothiazole Hydrochloride



This compound was prepared from 2-mercaptobenzothiazole and α-methyl-β-morpholinoethyl chloride hydrochloride utilizing the procedure previously described for the synthesis of 2-(β-morpholinoethylthio) benzothiazole hydrochloride. The crude amine hydrochloride was recrystallized from 30 ml. of isopropyl alcohol to obtain 2.2 g. (0.0067 mole; 13.5%) of a white powder which melted at 146-148°. Calc'd. for $C_{14}H_{19}ClN_2OS_2$: C, 50.83; H, 5.75; S, 19.37. Found: C, 50.76; H, 5.92; S, 19.36.

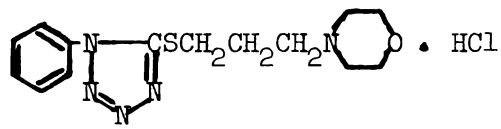
6. 2-(α-Methyl-β-piperidinoethylthio) Benzothiazole Hydrochloride



This compound was prepared from 2-mercaptobenzothiazole and α-methyl-β-piperidinoethyl chloride hydrochloride utilizing the procedure previously described. The crude amine hydrochloride was purified by washing with hot cyclohexane to obtain 5.0 g. (0.015 mole; 30.5%) of a white powder which melted at 118-122°. Calc'd. for $C_{15}H_{21}ClN_2S_2$: C, 54.80; H, 6.40; S, 19.50. Found: C, 54.88; H, 6.46; S, 19.36.

D. Preparation of 1-Phenyl-5-(Dialkylaminoalkylthio) 1,2,3,4-Tetrazoles

1. 1-Phenyl-5-(γ-Morpholino-n-propylthio) 1,2,3,4-Tetrazole Hydrochloride

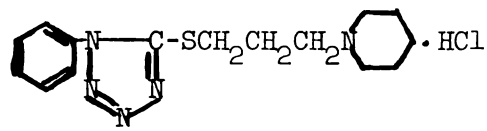


An 8.9 g. (0.05 mole) quantity of 5-mercapto-1-phenyl-1,2,3,4-tetrazole was dissolved in a sodium hydroxide solution prepared from 10.0 g. (0.25 mole) of sodium hydroxide and 90 ml. of water. This basic solution was poured into a 500 ml., three-necked flask equipped with a stirrer, thermometer, reflux condenser, and dropping funnel. The stirred solution was heated to its reflux temperature, and an aqueous solution of 10.0 g. (0.05 mole) of γ-morpholino-n-propyl chloride hydrochloride was added to it during an hour and 45 minutes. After the mixture had been stirred at its reflux temperature for another two hours, it was cooled to room temperature. The dark oil that had settled out of solution was separated, and the aqueous layer was extracted with three 80 ml. portions of dry ether. The oil and the ether extracts were combined and washed with 100 ml. of 5% sodium hydroxide, then with 100 ml. of water, and dried over anhydrous sodium sulfate.

The ether solution was poured into a 500 ml., three-necked flask equipped with an inlet tube and a stirrer. The stirred solution was cooled to 0-5° in an ice-bath and treated carefully with anhydrous hydrogen chloride gas until there was no further precipitation of amine hydrochloride. After separation of the crude product by filtration, it was recrystallized from 135 ml. of absolute alcohol to obtain 7.3 g. (0.021 mole; 42.5%) of a white powder which melted at 187-189.5°.

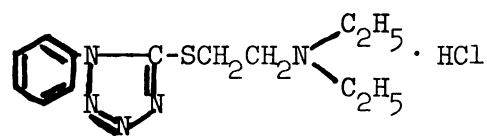
Calc'd. for $C_{14}H_{20}ClN_5OS$: C, 49.19; H, 5.86; S, 9.37. Found: C, 49.56; H, 6.12; S, 9.52.

2. 1-Phenyl-5-(γ-Piperidino-n-propylthio) 1,2,3,4-Tetrazole Hydrochloride



γ-Piperidino-n-propyl chloride hydrochloride and 5-mercapto-1-phenyl-1,2,3,4-tetrazole were allowed to interact as previously described in the synthesis of 1-phenyl-5-(γ-morpholino-n-propylthio) 1,2,3,4-tetrazole. The amine hydrochloride was recrystallized from 85 ml. of isopropyl alcohol. A 6.2 g. (0.018 mole; 36.5%) quantity of a white powder of melting point 156-158.5° was obtained. Calc'd. for $C_{15}H_{22}ClN_5S$: C, 53.02; H, 6.48; S, 9.42. Found: C, 53.16; H, 6.45; S, 9.52.

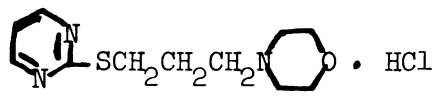
3. 1-Phenyl-5-(β-Diethylaminoethylthio) 1,2,3,4-Tetrazole



This compound was obtained from the reaction of β-diethylaminoethyl chloride hydrochloride with 5-mercapto-1-phenyl-1,2,3,4-tetrazole utilizing the procedure previously described. After recrystallization from 90 ml. of absolute alcohol, 8.3 g. (0.026 mole; 53%) of a cream-colored crystalline product was obtained. The melting point of the pure compound was 180-182°. Calc'd. for $C_{13}H_{20}ClN_5S$: C, 49.76; H, 6.38; S, 10.20. Found: C, 49.60; H, 6.29; S, 10.48.

E. Miscellaneous Preparations

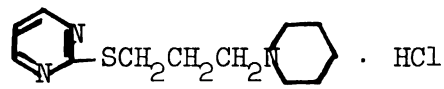
1. 2-(γ-Morpholino-n-propylthio) Pyrimidine Hydrochloride



The experimental apparatus was the same as that described in the preceding syntheses. During an hour, an aqueous solution of 6.0 g. (0.033 mole) of γ-morpholino-n-propyl chloride hydrochloride was added to a stirred basic solution of 6.0 g. (0.054 mole) of 2-mercaptopyrimidine. Upon completing the addition of the hydrochloride, the reaction mixture was kept at its reflux temperature for another two hours and then cooled to room temperature. The mixture was dark and cloudy, but no oil separated. The reaction mixture was extracted with three 80 ml. portions of ether, and these ether extracts were dried over anhydrous sodium sulfate.

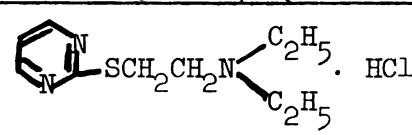
The ether solution was cooled to 0-5° and treated with anhydrous hydrogen chloride until there was no further precipitation of amine hydrochloride. After recrystallization from 30 ml. of isopropyl alcohol, a 1.3 g. (0.0047 mole; 14.5%) yield of a cream-colored crystalline product was obtained. The pure compound melted at 174-177°. Calc'd. for $C_{11}H_{18}ClN_3OS$: C, 47.91; H, 6.53; S, 11.61. Found: C, 48.00; H, 6.68; S, 11.64.

2. 2-(γ-Piperidino-n-propylthio) Pyrimidine Hydrochloride



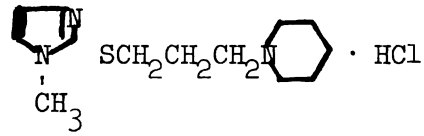
Utilizing the procedure previously described, a basic solution of 8.9 g. (0.08 mole) of 2-mercaptopyrimidine was allowed to interact with 9.9 g. (0.05 mole) of γ-piperidino-n-propyl chloride hydrochloride. A dark oil settled out of solution and was separated from the aqueous layer. The aqueous portion was extracted with ether, and the ether extracts were combined with the oil, washed, and dried in contact with anhydrous sodium sulfate. The amine hydrochloride was prepared in the same manner as described in the synthesis of 2-(γ-morpholino-n-propylthio) pyrimidine hydrochloride. This compound was purified by recrystallization from 50 ml. of isopropyl alcohol to obtain 3.4 g. (0.0125 mole; 25%) of a cream-colored crystalline material which melted at 158.5-160°. Calc'd. for $C_{12}H_{20}ClN_3S$: C, 52.65; H, 7.31; S, 11.70. Found: C, 52.61; H, 7.18; S, 12.23.

3. 2-(β-Diethylaminoethylthio) Pyrimidine Hydrochloride



This compound was prepared from 2-mercaptopyrimidine and β-diethylaminoethyl chloride hydrochloride using the procedure described for the synthesis of 2-(γ-piperidino-n-propylthio) pyrimidine hydrochloride. The crude amine hydrochloride was purified by washing with dry ether. A 3.5 g. (0.014 mole; 28%) quantity of a white powder which melted at 125-128° was obtained. Calc'd. for $C_{10}H_{18}ClN_3S$: C, 48.48; H, 7.27; S, 12.93. Found: C, 48.26; H, 7.72; S, 12.80.

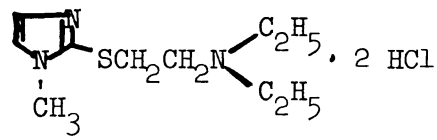
4. 1-Methyl-2-(γ-Piperidino-n-propylthio) Imidazole Hydrochloride



A 9.12 g. (0.08 mole) quantity of 1-methyl-2-mercaptoimidazole was dissolved in a sodium hydroxide solution prepared from 10.0 g. (0.25 mole) of sodium hydroxide and 90 ml. of water. This basic salt solution was transferred to a 500 ml. three-necked flask equipped with a stirrer, thermometer, reflux condenser, and dropping funnel. The reaction solution was heated to its reflux temperature, and an aqueous solution containing 9.9 g. (0.05 mole) of γ-piperidino-n-propyl chloride hydrochloride was added to it during an hour. Following the addition of the amine salt solution, the reaction mixture was kept at its reflux temperature for an additional two hours to complete the reaction. When the mixture was cooled, the supernatant dark oil that had formed during the reaction settled out of solution. This was separated, and the aqueous layer was extracted with three 80 ml. portions of ether. The ether extracts and the oil were combined, washed with 100 ml. of 5% sodium hydroxide, then with 100 ml. of water, and dried over anhydrous sodium sulfate.

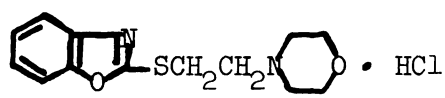
The amine hydrochloride was prepared in the manner described in the foregoing syntheses. The crude product was very hygroscopic and was dried in a vacuum oven for several days in the presence of phosphorus pentoxide. Attempts at purification by recrystallization from various solvents were unsuccessful. A 4.0 g. (0.0145 mole; 29%) quantity of a hygroscopic white powder which melted at 144-150° was obtained. Calc'd. for $C_{12}H_{22}ClN_3S$: C, 52.27; H, 7.95; S, 11.62. Found: C, 49.75; H, 7.72; S, 11.10.

5. 1-Methyl-2-(β-diethylaminoethylthio) Imidazole Dihydrochloride



Following the procedure described above, 9.12 g. (0.08 mole) of 1-methyl-2-mercaptoimidazole was treated with an aqueous solution of 8.6 g. (0.05 mole) of β-diethylaminoethyl chloride hydrochloride. A supernatant oil appeared during the reaction but disappeared when the reaction mixture was cooled. The mixture was extracted with three 80 ml. portions of ether, and these extracts were combined, washed, and then dried over anhydrous sodium sulfate. The amine was converted to its dihydrochloride by treatment with dry hydrogen chloride gas. Inasmuch as the dried material was extremely hygroscopic, recrystallization wasn't successful. A 3.0 g. (0.0105 mole; 21%) quantity of the crude product was obtained. This amine dihydrochloride was a white powder which melted at 115-120°. Calc'd. for $C_{10}H_{21}Cl_2N_3S$: C, 41.96; H, 7.35; Cl, 24.82. Found: C, 42.85; H, 7.67; Cl, 23.04.

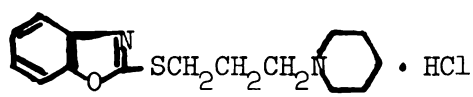
6. 2-(β-Morpholinoethylthio) Benzoxazole Hydrochloride



The apparatus employed for this synthesis was the same as that previously described. A 12.0 g. (0.08 mole) quantity of 2-mercapto-benzoxazole was dissolved in a sodium hydroxide solution prepared from 10.0 g. (0.25 mole) of sodium hydroxide and 90 ml. of water. The basic solution was heated to its reflux temperature and allowed to interact

with an aqueous solution of 9.3 g. (0.05 mole) of β-morpholinoethyl chloride hydrochloride. Upon completion of the reaction, a supernatant oil was visible. This disappeared when the reaction mixture was cooled. The reaction mixture was extracted with three 80 ml. portions of ether, and the dried ether solution was treated with anhydrous hydrogen chloride gas. A very small amount of the crude amine hydrochloride was isolated, and this was recrystallized from 5 ml. of absolute alcohol. The pure compound was cream-colored and melted at 215-218°. Calc'd. for $C_{13}H_{19}ClN_2O_2S$: C, 51.91; H, 5.66; S, 10.65. Found: C, 51.80; H, 5.82; S, 10.53.

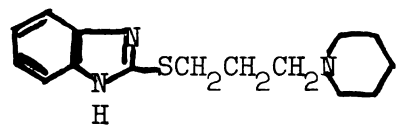
7. 2-(γ-Piperidino-n-propylthio) Benzoxazole Hydrochloride



Following the method of the preceding synthesis, a basic solution of 12.1 g. (0.08 mole) of 2-mercaptobenzoxazole was treated with 9.9 g. (0.05 mole) of γ-piperidino-n-propyl chloride hydrochloride. A large amount of a red-colored oil settled out of solution during the reaction and was separated after the reaction mixture had cooled. The aqueous layer was extracted with ether in the usual manner. The oil and ether extracts were combined, and dry hydrogen chloride gas was passed into the resulting ether solution. A 6.0 g. quantity of crude amine hydrochloride was obtained; a small quantity of this was recrystallized from isopropyl alcohol. (Due to humid conditions within the laboratory, most of the material was lost during a large-scale recrystallization.)

The pure compound was a pink-colored powder which melted at 167-170°. Calc'd. for $C_{15}H_{21}ClN_2OS$: C, 57.60; H, 6.72; S, 10.24. Found: C, 56.95; H, 7.04; S, 10.46.

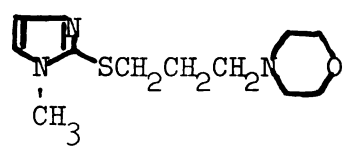
8. 2-(γ-Piperidino-n-propylthio) Benzimidazole



Utilizing the procedure and apparatus previously described, a 10.5 g. (0.07 mole) quantity of 2-mercaptobenzimidazole was dissolved in a sodium hydroxide solution and allowed to interact with 13.9 g. (0.07 mole) of γ-piperidino-n-propyl chloride hydrochloride. Upon completion of the reaction, a gray solid had settled out. The solid was removed by filtration and recrystallized from 225 ml. of acetone. A 13.9 g. (0.05 mole; 72%) quantity of a white crystalline material of melting point 103-8° was obtained. Calc'd. for $C_{15}H_{21}N_3S$: C, 65.45; H, 7.63; S, 11.64. Found: C, 62.20; H, 7.96; S, 11.20.

F. Attempted Preparations

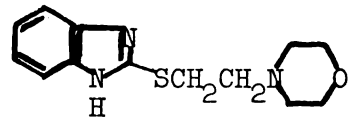
1. 1-Methyl-2-(γ-Morpholino-n-propylthio) Imidazole



A 9.12 g. (0.08 mole) quantity of 1-methyl-2-mercaptoimidazole was dissolved in a sodium hydroxide solution prepared from 10.0 g. (0.25 mole) of sodium hydroxide and 90 ml. of water. The basic salt solution was poured into a 500 ml. three-necked flask equipped as previously

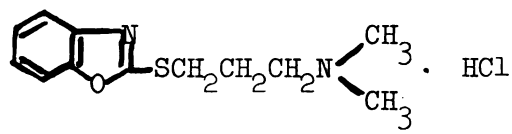
described and heated to its reflux temperature. An aqueous solution of 10.0 g. (0.05 mole) of γ-morpholino-n-propyl chloride hydrochloride was added during an hour, but there was no evidence of reaction. Nothing separated from solution when the reaction solution was cooled.

2. 2-(β-Morpholinoethylthio) Benzimidazole



Following the procedure described above, 12.0 g. (0.08 mole) of 2-mercaptobenzimidazole was dissolved in a sodium hydroxide solution and treated with an aqueous solution of 9.3 g. (0.05 mole) of β-morpholino-ethyl chloride hydrochloride. There was no evidence that a reaction had occurred.

3. 2-(γ-Dimethylamino-n-propylthio) Benzoxazole Hydrochloride



Following the experimental procedure used in the synthesis of 2-(β-morpholinoethylthio) benzoxazole hydrochloride, 2-mercapto-benzoxazole was allowed to react with γ-dimethylamino-n-propyl chloride hydrochloride. The cloudy reaction mixture was cooled and extracted with ether. Upon treatment of the ether extracts with hydrogen chloride, there was formed a small amount of a sticky red oil which could not be made to crystallize.

SUMMARY

1. Six previously undescribed 2-(N,N-dialkylaminoalkylthio) benzothiazoles were prepared. These were characterized as their hydrochloride salts.

2. Three previously unreported 1-phenyl-5-(N,N-dialkylaminoalkylthio) 1,2,3,4-tetrazoles were prepared and characterized as their hydrochlorides.

3. Three previously unreported 2-(N,N-dialkylaminoalkylthio) pyrimidines were prepared and characterized as their hydrochlorides.

4. 1-Methyl-2-(γ-piperidino-n-propylthio) imidazole hydrochloride was prepared and its properties determined. This compound was previously undescribed.

5. 1-Methyl-2-(β-diethylaminoethylthio) imidazole was prepared and characterized as its dihydrochloride. This compound was previously unreported.

6. Two previously undescribed 2-(N,N-dialkylaminoalkylthio) benzoxazoles were prepared. These were characterized as their hydrochloride salts.

7. 2-(γ-Piperidino-n-propylthio) benzimidazole was prepared and characterized for the first time.

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