converted to the N-phenylcarbamates as described above.

Degradation Procedures.—The amines and N-phenylcarbamates were oxidized to the corresponding benzoic acids by conventional procedures.[15] Alkaline permanganate was employed for the unsubstituted and 4-methoxy compounds while chromic acid oxidation was necessary for the 4-nitro derivatives. In some experiments, the 4-methoxybenzoic acid appeared to be contaminated with 4-hydroxybenzoic acid and the material was converted to and purified as the anilide.

CAMBRIDGE 39, MASSACHUSETTS

(15) R. L. Shriner and R. C. Fuson, "Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 198.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE COLLEGE]

The Preparation and Properties of Some ω-(N,N-Dialkylamino) Alkyl-3-thienyl Sulfide Hydrochlorides[1]

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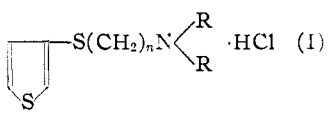
The synthesis and properties of a series of ω-(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides, and the intermediates involved, are described.

Several ω-(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides were prepared as a consequence



(I)

of the observation[3] that some analogous phenyl compounds showed local anesthetic activity comparable with that of procaine.

The aminoalkyl-3-thienyl sulfides of the present investigation were prepared by the sequence of reactions

$$R_2NH + Cl(CH_2)_nOH \xrightarrow[EtOH]{NaI} R_2N(CH_2)_nOH \quad (II)$$

$$\xrightarrow[CHCl_3]{SOCl_2} R_2N(CH_2)_nCl\cdot CHl \quad (III) \xrightarrow[NaOH]{C_4H_3SSH} I$$

The N-(ω-hydroxyalkyl) amines II, where the amine was piperidine or morpholine and the alkyl chain contained two to five carbon atoms, including a branched alkyl chain of three carbon atoms, were prepared by the reaction of a two-molar excess of the secondary amine with the corresponding chlorohydrin in dry ethanol, following the procedure employed by Clinton, *et al.*[4]

The N-(ω-chloroalkyl)-amine hydrochlorides (III) were obtained from the corresponding N-(ω-hydroxyalkyl)-amines by an adaptation of the method, described by Mason and Block,[5] employing thionyl chloride and dry chloroform as a solvent.

One of the N-(ω-chloroalkyl)-amines, namely, γ-morpholine-*n*-propyl chloride, was prepared in a single step reaction by the method of Adams and Whitmore,[6] which involved the reaction of a two-mole excess of morpholine with trimethylene chlorobromide in dry benzene. An attempt was made to adapt this shorter procedure for preparing N-(ω-chloroalkyl)-amines to the use of ethylene and propylene chlorobromide, but was unsuccessful due to the formation of a quaternary ammonium salt which may have been an ethylimmonium halide.

The properties of five N-(ω-chloroalkyl)-amine hydrochlorides which have not previously been reported are listed in Table I.

The ω-(N,N-dialkylamino) alkyl-3-thienyl sulfides were obtained, in yields of 77 to 93%, from the N-(ω-chloroalkyl)-amine hydrochlorides by interaction with a slight excess of 3-thiophenethiol dissolved in aqueous sodium hydroxide. The tertiary amines were converted to their hydrochloride salts and isolated and characterized as such. Altogether, ten new ω-(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides, were prepared and some of their properties are summarized in Table II.

A second general method of synthesis for the preparation of the ω-(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides was studied with the aim of obtaining better yields and permitting the preparation of more than one type of final compound from the intermediates. This method may be represented by the series of reactions

$$C_4H_3S{-}SH + Cl(CH_2)_nOH \xrightarrow[H_2O]{NaOH}$$

$$C_4H_3S{-}S(CH_2)_nOH(V) \xrightarrow[C_5H_5N]{SOCl_2}$$

$$C_4H_3S{-}S(CH_2)_nCl \quad (VI) \xrightarrow[C_6H_6]{R_2NH} I$$

Three new ω-hydroxyalkyl-3-thienyl sulfides (V) were readily prepared by the interaction of the corresponding chlorohydrin and 3-thiophenethiol dissolved in aqueous sodium hydroxide. Brooks in some unpublished work[7] reported, without experimental details, the preparation of β-hydroxyethyl-3-thienyl sulfide from ethylene chlorohydrin and 3-thiophenethiol, giving only the boiling point of the material. A few of the properties of these compounds are summarized in Table III.

(1) Presented before the Division of Medicinal Chemistry of The American Chemical Society at Atlantic City, N. J., on September 15, 1952.

(2) Abstracted in part from the M.S. Thesis, Michigan State College, of Wm. H. Houff, 1952.

(3) M. H. Kim and R. D. Schuetz, THIS JOURNAL, **74**, 5102 (1952).

(4) R. O. Clinton, U. S. Salvador and S. C. Laskowski, *ibid.*, **71**, 3366 (1949).

(5) J. P. Mason and H. W. Block, *ibid.*, **66**, 1443 (1940).

(6) R. R. Adams and F. C. Whitmore, *ibid.*, **67**, 735 (1945).

(7) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 429.

TABLE I

ω-(N,N-DIALKYLAMINO)-ALKYL CHLORIDE HYDROCHLORIDES $\begin{matrix}R\\R\end{matrix}\!\!>\!N\!-\!(CH_2)_n\!-\!Cl\cdot HCl$

Chloride hydrochloride	Formula	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Found
α-Methyl-β-piperidinoethyl	$C_8H_{17}NCl_2$	207.5–209	53	7.07	6.97
ε-Piperidino-*n*-amyl	$C_{10}H_{21}NCl_2$	138.5–140	80.4	6.19	6.27
α-Methyl-β-morpholinoethyl	$C_7H_{15}ONCl_2$	180–181.5	79	6.99	7.05
δ-Morpholino-*n*-butyl	$C_8H_{17}ONCl_2$	120–121	97	6.54	6.62
ε-Morpholino-*n*-amyl	$C_9H_{19}ONCl_2$	122.5–124	95.5	6.13	6.25

TABLE II

ω-(N,N-DIALKYLAMINO) ALKYL-3-THIENYL SULFIDE HYDROCHLORIDES $C_4H_3S\!-\!S\!-\!(CH_2)_n\!-\!N\begin{matrix}R\cdot HCl\\R\end{matrix}$

Recrystallized from: (a) ethanol, (b) isopropyl alcohol, (c) ethanol and benzene, (d) isopropyl alcohol and benzene

3-Thienyl sulfide Hydrochloride	Formula	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Found	Sulfide-sulfur, % Calcd.	Found
β-Piperidinoethyl[a]	$C_{11}H_{18}NS_2Cl$	149.5–150.5	83	5.31	5.32	12.15	12.34
α-Methyl-β-piperidinoethyl[b]	$C_{12}H_{20}NS_2Cl$	172–173.5	83	5.04	5.09	11.54	11.79
γ-Piperidino-*n*-propyl[a]	$C_{12}H_{20}NS_2Cl$	120–121	81	5.04	5.13	11.54	11.52
δ-Piperidino-*n*-butyl[c]	$C_{13}H_{22}NS_2Cl$	131–133	89	4.80	4.70	10.98	10.67
ε-Piperidino-*n*-amyl[d]	$C_{14}H_{24}NS_2Cl$	89.5–91.5	93	4.58	4.60	10.48	10.61
β-Morpholinoethyl[b]	$C_{10}H_{16}ONS_2Cl$	109–110.5	77.5	5.27	5.26	12.06	12.24
α-Methyl-β-morpholinoethyl[d]	$C_{11}H_{18}ONS_2Cl$	95–96	77	5.00	5.03	11.46	11.66
γ-Morpholino-*n*-propyl[b]	$C_{11}H_{18}ONS_2Cl$	157–158.5	85	5.00	5.01	11.46	11.72
δ-Morpholino-*n*-butyl[b]	$C_{12}H_{20}ONS_2Cl$	148–150	92	4.77	4.90	10.98	11.18
ε-Morpholino-*n*-amyl[d]	$C_{13}H_{22}ONS_2Cl$	135–136.5	87.5	4.55	4.60	10.41	10.46

TABLE III

ω-HYDROXYALKYL-3-THIENYL SULFIDES, $C_4H_3S\!-\!S(CH_3)_nOH$

3-Thienyl sulfides	Formula	B.p., °C.	Mm.	Yield, %	Sulfide-sulfur, % Calcd.	Found
δ-Hydroxy-*n*-butyl	$C_8H_{12}OS_2$	134–135	1.5	85	16.49	16.22
α-Methyl-β-hydroxyethyl	$C_7H_{10}OS_2$	111	4	97	18.40	18.54
β-Hydroxyethyl	$C_6H_8OS_2$	116–117	2	84	20.02	20.40

These compounds were further characterized by the preparation by known methods[8] of their *p*-phenylazo benzoate derivatives and the properties of these are reported in Table V.

One of the ω-chloroalkyl-3-thienyl sulfides, namely, δ-chloro-*n*-butyl, was prepared from the corresponding ω-hydroxyalkyl-3-thienyl sulfide by a modification of the method of Darzens.[9] However, the yield was poor and considerable variations of the reaction conditions resulted in no marked improvement.

The direct preparation of the ω-chloroalkyl-3-thienyl sulfide by the interaction of the appropriate polymethylene chlorobromide and 3-thiophenethiol was also studied with the aim of eliminating the Darzens reaction. However, a mixture of products, due to the reaction of both halogens, was obtained from which it was difficult to isolate the desired product and thus no advantage was gained over the previous method of preparation.

Two of the ω-chloroalkyl-3-thienyl sulfides which have not been previously reported have a few of their properties listed in Table IV.

Two of the ω-(N,N-dialkylamino) alkyl-3-thienyl sulfides were obtained from the ω-chloroalkyl-3-thienyl sulfides by treatment with a two molar excess of the proper secondary amine. The reactions were carried out in benzene and the products were

(8) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 164.

(9) G. Darzens, *Compt. rend.*, **152**, 1314 (1911).

TABLE IV

ω-CHLOROALKYL-3-THIENYL SULFIDES, $C_4H_3S\!-\!S(CH_2)_nCl$

3-Thienyl sulfides	Formula	B.p., °C.	Mm.	Yield, %	Sulfide, % Calcd.	Found
δ-Chloro-*n*-butyl	$C_8H_{11}ClS_2$	135	1.5	29	15.51	15.85
β-Chloroethyl	$C_6H_7ClS_2$	123	8	72	17.93	18.05

isolated and characterized as the hydrochlorides. This method was not as satisfactory as the first one employed due to the difficulty of obtaining the final product as a crystalline solid. The ω-(N,N-dialkylamino) alkyl-3-thienyl sulfide hydrochlorides prepared by this procedure were found to be identical with those prepared by the first method.

Pharmacological Results.—All compounds were tested as antihistaminics at a dose level of 2 mg. per cat, and none of them were effective except δ-piperidino and δ-morpholino-*n*-butyl-3-thienyl sulfides which showed a slight effect. As local anesthetics they were found in preliminary examination to equal or exceed procaine in activity in the guinea pig wheal test.

Experimental

Intermediates.—A generous sample of crude 3-thiophenethiol was supplied by Socony–Vacuum Oil Company and was purified by extraction with sodium hydroxide solution, neutralization of the aqueous portion with hydrochloric acid and vacuum distillation; b.p. 64° (17 mm.). The Electrochemical division of the du Pont Company furnished a sample of tetrafuran. The N-(ω-hydroxyalkyl)-piperidines and morpholines were prepared in yields of 63 to 86% by the interaction of the proper secondary amine with the corresponding chlorohydrin in alcoholic sodium iodide solution.[4] The N-(ω-chloroalkyl)-piperidine and morpholine hydrochlorides were obtained by treating the corresponding hydroxy derivative with thionyl chloride in chloroform following a method already described[5] with a modification of the experimental procedure. The apparatus was arranged so as to allow a stream of dry air to be drawn across the surface of the reaction mixture. The latter served to remove sulfur dioxide which decreased the amount of tarring in the reaction mixture and improved the yields.

The γ-morpholino-*n*-propyl chloride was prepared according to the method described by Adams and Clark[6] by the interaction of trimethylene chlorobromide with morpholine in dry benzene.

ω-(N,N-Dialkylamino) Alkyl-3-thienyl Sulfide Hydrochlorides. Method A.—In a typical experiment, 33 g. (0.25 mole) of 3-thiophenethiol dissolved in a solution containing 30 g. of sodium hydroxide and 100 ml. of water, was placed in a three-necked flask fitted with a dropping funnel, reflux condenser and stirrer. To this was added dropwise 28 g. (0.15 mole) of β-piperidinoethyl chloride hydrochloride dissolved in 100 ml. of water. The stirred reaction mixture was maintained at reflux temperature during the addition of the amine salt solution which required an hour. Reaction was continued for an additional hour and a half, at the end of which a yellowish oil had separated. This was removed and the aqueous layer was extracted three times with 100-ml. portions of ether. The combined ether extracts and oil were washed with a 5% sodium hydroxide, then with water and dried over anhydrous sodium sulfate. The ether solution, while kept cold, was treated with hydrogen chloride gas until there was no further precipitation of amine hydrochloride. After filtration, the crude hydrochloride was dissolved in 100 ml. of hot, dry isopropyl alcohol and decolorized with Norite. Two additional recrystallizations from isopropyl alcohol gave 29 g. (83%) of a white crystalline product which melted at 149.5–150.5°.

Anal. Calcd. for $C_{11}H_{18}NS_2Cl$: N, 5.31; S, 12.15. Found: N, 5.33; S, 12.34.

Only the sulfide sulfur was determined by quantitative oxidation with bromate–bromide, which had previously been applied only to alkyl sulfides and disulfides.[10]

Method B.—A solution composed of 7 g. (0.034 mole) of δ-chloro-*n*-butyl-3-thienyl sulfide and 6 g. (0.070 mole) of morpholine in 50 ml. of dry benzene was allowed to stand with occasional shaking for a half-hour. The solution was then heated at its reflux temperature for four hours, at the end of which time no additional formation of morpholine hydrochloride was observed. After cooling to room temperature, the reaction was made basic and steam distilled until the Simon[11] test for secondary amines indicated the complete removal of excess morpholine. The solution remaining in the distillation flask was made acidic with 4 *N* hydrochloric acid and extracted twice with ether to remove unreacted δ-chloro-*n*-butyl-3-thienyl sulfide. On neutralization with 4 *N* sodium hydroxide, a brownish oil separated which was extracted with ether and dried over anhydrous sodium sulfate. Hydrogen chloride gas was slowly passed into the chilled ether solution to form the hydrochloride, which separated as a clear oil. This was crystallized only by seeding with a crystal of the compound prepared by method A. After recrystallization from isopropyl alcohol, there was obtained 1.0 g. (10.5%) of a crystalline product melting at 146.5–148°. There was no depression in melting point when a sample of this product was mixed with a sample of the substance prepared in the previously described manner.

Anal. Calcd. for $C_{12}H_{20}ONS_2Cl$: N, 4.77. Found: N, 4.54.

ω-Hydroxyalkyl-3-thienyl Sulfides.—In a 500-ml. three-necked flask fitted with a stirrer and reflux condenser was placed 87 g. (0.75 mole) of 3-thiophenethiol dissolved in a solution prepared from 35 g. of sodium hydroxide and 150 ml. of water. To this stirred solution was added dropwise, over a half-hour period, 65 g. (0.60 mole) of tetramethylene chlorohydrin. After the addition was completed, the reaction mixture was heated to its reflux temperature for an hour and then allowed to cool to room temperature, at which point a yellow oil separated. The oily layer was separated and the aqueous fraction extracted twice with ether. The ether extract was combined with the oil and dried over anhydrous sodium sulfate. After removal of the ether, the oil was distilled under reduced pressure to obtain 96 g. (85%) of a clear, slightly yellow, liquid product which boiled at 134–135° (1.5 mm.).

Anal. Calcd. for $C_8H_{12}OS_2$: S, 16.49. Found: S, 16.22. Only the sulfide sulfur was determined.

TABLE V

p-PHENYL AZOBENZOATES OF THE ω-HYDROXYALKYL-3-THIENYL SULFIDES[8]

Derivative of -3-thienyl sulfides[a]	Formula	M.p., °C.	Nitrogen, % Calcd.	Found
δ-Hydroxy-*n*-butyl	$C_{21}H_{20}O_2N_2S_2$	79–80	7.06	7.02
α-Methyl-β-hydroxyethyl	$C_{20}H_{18}O_2N_2S_2$	224–225	7.32	7.40
β-Hydroxyethyl	$C_{19}H_{16}O_2S_2N_2$	98–98.5	7.60	7.61

[a] All recrystallized from ethanol.

ω-Chloroalkyl-3-thienyl Sulfides. Method A.—To 68 g. (0.36 mole) of δ-hydroxy-*n*-butyl-3-thienyl sulfide dissolved in 35 g. of pyridine was added 54 g. (0.45 mole) of thionyl chloride. The reaction was carried out in an apparatus consisting of a three-necked flask fitted with a stirrer, dropping funnel, and reflux condenser. Provision was made to allow a stream of dry air to be drawn across the surface of the reaction mixture. Stirring was maintained during the addition of the thionyl chloride and at various time intervals the reaction flask was immersed into an ice-bath to control the exothermic reaction. The addition of thionyl chloride required an hour after which the reaction mixture was allowed to cool to room temperature. The crude, brown, oily product was washed twice with water, dissolved in 200 ml. of ether and dried over anhydrous sodium sulfate. After removal of the ether, the oil was distilled to give 17 g. (24%) of a greenish-yellow oil boiling at 131° (1.5 mm.).

Anal. Calcd. for $C_8H_{11}ClS_2$: S, 15.51. Found: S, 15.85. Only the sulfide sulfur was determined.

Method B.—A stirred solution of 50 g. (0.43 mole) of 3-thiophenethiol in 200 ml. of water containing 18 g. of sodium hydroxide was heated to its reflux temperature and 73 g. (0.50 mole) of ethylene chlorobromide was added slowly over a period of a half-hour. The reaction was allowed to continue for an additional hour and cooled to room temperature. The heavy yellow oil which separated was removed, dissolved in ether and dried over anhydrous sodium sulfate. The yellow oil remaining after the removal of the ether was fractionated yielding 55 g. (72%) of slightly yellow oil which boiled at 123° (8 mm.).

Anal. Calcd. for $C_8H_7ClS_2$: S, 17.93. Found: S, 18.28. Only the sulfide sulfur was determined.

Tetramethylene Chlorohydrin.—This chlorohydrin was obtained from tetrahydrofuran by treatment with gaseous hydrogen chloride using the method of Starr and Hixon.[12]

Acknowledgment.—We are indebted to the Department of Pharmacology of Abbott Laboratories for preliminary pharmacological results reported here.

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