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

The Synthesis and Properties of Some Substituted Phenyl ω-(N,N-Dialkylamino)-alkyl Sulfides[1]

BY ROBERT D. SCHUETZ AND ROGER A. BALDWIN[2]

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The synthesis and properties of a series of tertiary amine derivatives of mixed substituted phenyl alkyl sulfides are described.

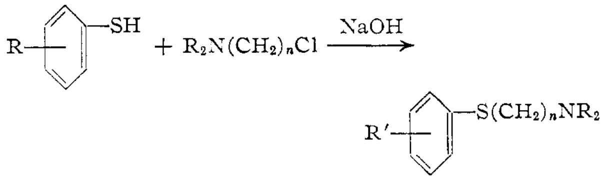
In previous communications from these laboratories there have been described several series of organic sulfur compounds, dialkylaminoalkyl derivatives of thiophenol,[3] 2- and 3-thiophenethiol[4,5] and 2-thenoic acid,[6] prepared in a search for more active local anesthetics.

As part of a continuing study of sulfur-containing organic compounds of potential pharmacological value, several series of substituted phenyl ω-(N,N-dialkylamino)-alkyl sulfides were prepared because of the activity of certain closely related compounds.

Prior investigations[3] have shown that certain ω-(N,N-dialkylamino)-alkyl phenyl sulfides possessed activity as local anesthetics comparable to procaine, 2-diethylaminoethyl 4-aminobenzoate. The dialkylaminoalkyl 2-alkoxy-4-aminothiolbenzoates were found by Clinton[7] and his collaborators to possess very high local anesthetic activity. Epstein and Meyer[8] recently reported that both mono- and dialkylaminoethyl esters of *m*-aminoalkoxybenzoic acids were found to be highly effective local anesthetics with relatively low toxicities.

Since amino and alkoxyl groups, substituted in the aromatic moiety, were prominent in the active compounds, it was deemed of interest to prepare a series of *o*- and *p*-amino and -alkoxylphenyl ω-(N,N-dialkylamino)-alkyl sulfides. In addition it was thought to be advisable to examine the effect of additional substituents, methyl and chloro, in the aromatic portion of such molecules on their local anesthetic activity.

The dialkylaminoalkyl *o*- or *p*-substituted phenyl sulfides were synthesized readily in good yields from the parent substituted thiophenol and the dialkylaminoalkyl chloride by a procedure used for the preparation of the corresponding thienyl[5] analogs.



The resulting sulfides were characterized as their hydrochloride or methyl iodide salts, whose properties are summarized in Tables I-IV.

The acetylamino derivatives listed in Table I were prepared by the direct acylation of the amino sulfide obtained from the interaction of the aminothiophenols and dialkylaminoalkyl chlorides.

No difficulties were encountered in the reactions of the ω-(N,N-dialkylamino)-alkyl halides with the substituted aryl mercaptans with the exception of α-methyl-β-dimethylaminoethyl chloride. This latter chloride could, in alkaline media, on interaction with a mercaptan have resulted in the formation of two isomeric sulfides. It has been shown that on treatment of either of the amine hydrochlorides β-methyl-β-diethylaminoethyl chloride or α-methyl-β-diethylaminoethyl chloride with dilute sodium hydroxide, the free amine β-methyl-β-diethylaminoethyl chloride is formed.[9]

Evidence for a mixture of products was indicated by the fact that it was difficult to obtain a crystalline product with a sharp melting point. A broad melting range was found in several preparations, involving α-methyl-β-dimethylethylaminoethyl chloride, after repeated recrystallization from various solvent combinations. At the present time, it is not known with certainty which isomer forms or if there is actually a mixture in these cases.

Pharmacological Results.—All compounds were tested as local anesthetics. In preliminary examination none of the sulfides were found to exceed procaine in activity in the guinea pig wheal test. We are indebted to the Department of Pharmacology of Abbott Laboratories for the preliminary pharmacological results reported here.

Experimental

Intermediates.—The *o*- and *p*-amino-,[10] methoxy-[11] and chloro-[12,13] substituted thiophenols were obtained by methods described in the literature. The *o*- and *p*-methylthiophenols were obtained from Eastman Kodak Co. as their white label products and were used as received. The ω-(N,N-dialkylamino)-alkyl chlorides, β-diethylaminoethyl, γ-dimethylamino-*n*-propyl and α-methyl-β-dimethylaminoethyl, were obtained as generous samples from the Michigan Chemical Corp., Saint Louis, Mich. The γ-morpholino-*n*-propyl and γ-piperidino-*n*-propyl chlorides were prepared by the method of Adams and Whitmore,[14] which involved the interaction of trimethylene chlorobromide and morpholine or piperidine in dry benzene as a solvent.

Substituted Phenyl ω-(N,N-Dialkylaminoalkyl) Sulfide Hydrochlorides.—In a typical experiment, 22 g. (0.15 mole)

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(1) Abstracted in part from the M.S. Thesis, Michigan State University, of R. A. Baldwin, 1956.

(2) Presented before the Division of Medicinal Chemistry of the American Chemical Society, New York, N. Y., Sept. 13–18, 1957.

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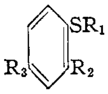
TABLE I

ω-(N,N-DIALKYLAMINO)-ALKYL *o*- OR *p*-ACETYLAMINO- AND -AMINOPHENYL SULFIDES QUATERNARY METHYL IODIDES OR HYDROCHLORIDES

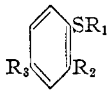


R_1	R_2	R_3	Formula	M.p., °C.	Yield, %	Analyses, %[g]					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_2)_2N(CH_2CH_3)_2^{a,e}$	H	$NHCOCH_3$	$C_{15}H_{25}ON_2SI$	155–156	21.0	44.23	44.25	6.21	6.31	7.85	7.55
$(CH_2)_2N(CH_2CH_3)_2^{a,e}$	$NHCOCH_3$	H	$C_{15}H_{25}ON_2SI$	124–125.5	24.6	44.23	44.7	6.21	6.11	7.85	7.88
$(CH_2)_3N(CH_3)_2^{a,f}$	H	$NHCOCH_3$	$C_{14}H_{23}ON_2SI$	198–200	49.0	42.73	42.73	5.91	5.98	8.12	7.97
$(CH_2)_3N(CH_3)_2^{a,e}$	NH_2	H	$C_{12}H_{21}N_2SI$	120–121	33.4	41.02	41.01	6.03	6.08	9.11	9.01
$(CH_2)_3N(CH_2CH_2)_2O^{b,d}$	H	$NHCOCH_3$	$C_{15}H_{23}O_2N_2SCII$	184–185	35.2	54.43	54.70	7.04	6.87	9.73	9.54
$(CH_2)_3N(CH_2CH_2)_2O^{c,e}$	NH_2	H	$C_{13}H_{22}ON_2SCl_2$	198–200	31.0	48.03	47.92	6.83	6.88	9.92	9.88
$(CH_2)_3N(CH_2)_5^{b,d}$	H	$NHCOCH_3$	$C_{16}H_{25}ON_2SCl$	174.5–175.5	50.0	58.51	58.54	7.65	7.67	9.73	9.60

[a] Quaternary methyl iodide salt. [b] Hydrochloride. [c] Dihydrochloride. Recrystallized from[d] isopropyl alcohol, [e] absolute ethanol, [f] methanol. [g] Micro Tech Lab., Skokie, Ill.

TABLE II

ω-(N,N-DIALKYLAMINO)-ALKYL *o*- OR *p*-METHOXYPHENYL SULFIDE HYDROCHLORIDES

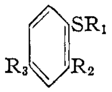


R_1	R_2	R_3	Formula	M.p., °C.	Yield, %	Analyses, %[c]					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_2)_2N(CH_2CH_3)_2^a$	OCH_3	H	$C_{13}H_{22}ONSCl$	127-129	43.5	56.60	56.61	8.04	7.87	11.62	11.42
$(CH_2)_2N(CH_2CH_3)_2^a$	H	OCH_3	$C_{13}H_{22}ONSCl$	132-132.5	69.0	56.60	56.63	8.04	8.16	11.62	11.50
$(CH_2)_3N(CH_3)_2^a$	OCH_3	H	$C_{12}H_{20}ONSCl$	113-114	52.0	55.04	55.94	7.72	7.72	12.23	12.22
$(CH_2)_3N(CH_3)_2^a$	H	OCH_3	$C_{12}H_{20}ONSCl$	130-131.5	69.0	55.04	55.28	7.72	7.73	12.23	12.18
$(CH_2)_3N(CH_2CH_2)_2O^a$	OCH_3	H	$C_{14}H_{22}O_2NSCl$	155-156	73.5	55.33	55.67	7.29	7.37	10.55	10.45
$(CH_2)_3N(CH_2CH_2)_2O^a$	H	OCH_3	$C_{14}H_{22}O_2NSCl$	146.5-148	78.0	55.33	55.47	7.29	7.34	10.55	10.70
$(CH_2)_3N(CH_2)_5^a$	OCH_3	H	$C_{15}H_{24}ONSCl$	150-151	83.5	59.64	59.33	8.02	8.24	10.61	10.68
$(CH_2)_3N(CH_3)_5^a$	H	OCH_3	$C_{15}H_{24}OSNCl$	128-129	73.5	59.64	59.87	8.02	8.07	10.61	10.81
$CH_3CHCH_2N(CH_3)_2^a$	H	OCH_3	$C_{12}H_{20}ONSCl$	173-174.5	36.0	55.03	54.99	7.71	7.91	12.22	11.96
$CH_3CHCH_2N(CH_3)_2^b$	OCH_3	H	$C_{12}H_{20}ONSCl$	110-112	41.0	55.03	55.22	7.71	7.87	12.22	12.10

[a] Recrystallized from isopropyl alcohol, [b] isopropyl alcohol and cyclohexene (1:1). [c] Micro Tech. Lab., Skokie, Ill.

TABLE III

ω-(N,N-DIALKYLAMINO)-ALKYL *o*- OR *p*-CHLOROPHENYL SULFIDE HYDROCHLORIDES

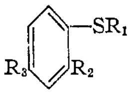


R_1	R_2	R_3	Formula	M.p., °C.	Yield, %	Analyses, %[c]					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_2)_2N(CH_2CH_3)_2^a$	Cl	H	$C_{12}H_{19}NSCl_2$	148-149	83.0	51.51	51.49	6.85	6.86	11.43	11.27
$(CH_2)_2N(CH_2CH_3)_2^a$	H	Cl	$C_{12}H_{19}NSCl_2$	123-124.5	78.0	51.51	51.28	6.85	6.93	11.43	11.26
$(CH_2)_3N(CH_3)_2^a$	Cl	H	$C_{11}H_{17}NSCl_2$	127-128	36.4	49.63	49.72	5.40	6.54	12.01	11.95
$(CH_2)_3N(CH_3)_2^a$	H	Cl	$C_{11}H_{17}NSCl_2$	126.5-127.5	71.0	49.63	49.82	6.45	6.56	12.01	12.18
$(CH_2)_3N(CH_2CH_2)_2O^a$	Cl	H	$C_{13}H_{19}ONSCl_2$	147.5-148.5	86.0	50.62	50.68	6.21	6.46	10.42	10.21
$(CH_2)_3N(CH_2CH_2)_2O^a$	H	Cl	$C_{13}H_{19}ONSCl_2$	184.5-186	81.0	50.62	50.44	6.21	6.24	10.42	10.42
$(CH_2)_3N(CH_2)_5^a$	Cl	H	$C_{14}H_{21}NSCl_2$	148-149	55.0	55.04	55.00	6.93	7.38	10.54	10.26
$(CH_2)_3N(CH_2)_5^a$	H	Cl	$C_{14}H_{12}NSCl_2$	157-158	90.5	55.04	55.02	6.93	7.05	10.54	10.70
$CH_3CHCH_2N(CH_3)_2^b$	H	Cl	$C_{11}H_{17}NSCl_2$	90-91	84.0	49.65	48.95	6.45	6.59	12.03	12.36

Recrystallized from [a] isopropyl alcohol, [b] isopropyl alcohol and cyclohexane (1:1). [c] Micro Tech. Lab., Skokie, Ill.

TABLE IV

ω-(N,N-DIALKYLAMINO)-ALKYL *o*- OR *p*-METHYLPHENYL SULFIDE HYDROCHLORIDES



R_1[a]	R_2	R_3	Formula	M.p., °C.	Yield, %	Analyses, %[b]					
						Carbon		Hydrogen		Sulfur	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
$(CH_2)_2N(CH_2CH_3)_2$	H	CH_3	$C_{13}H_{22}NSCl$	120–121	89.0	60.03	60.08	8.51	8.51	12.24	12.23
$(CH_2)_2N(CH_2CH_3)_2$	CH_3	H	$C_{13}H_{22}NSCl$	153–154	72.0	60.03	60.15	8.51	8.46	12.24	12.07
$(CH_3)_3N(CH_2CH_2)_2O$	H	CH_3	$C_{14}H_{22}ONSCl$	168.5–169.5	78.0	58.42	58.60	7.72	7.61	11.12	11.01
$(CH_3)_3N(CH_2CH_2)_2O$	CH_3	H	$C_{14}H_{22}ONSCl$	167–169	59.0	58.42	58.47	7.72	7.60	11.12	10.93

[a] Recrystallized from isopropyl alcohol. [b] Micro Tech. Lab., Skokie, Ill.

of *p*-chlorothiophenol dissolved in a solution containing 20 g. (0.5 mole) of sodium hydroxide and 80 ml. of water, was placed in a three-neck flask fitted with a dropping funnel, stirrer and reflux condenser. The stirred alkaline mercaptan solution was heated to its reflux temperature and a solution, containing 18 g. (0.1 mole) of diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of water, was added dropwise to it over a period of an hour. The reaction mixture was kept at its reflux temperature for 2 hours after the addition of the amine salt solution had been completed. At this point a yellow oil had separated from the solution. 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 100 ml. of 5% sodium hydroxide, then with 100 ml. of water and dried in contact with anhydrous sodium sulfate. The ether solution of amino sulfide was filtered, cooled in an ice-bath, and while being stirred was carefully treated 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. The use of excess hydrogen chloride had to be avoided as it caused the amine hydrochlorides to become sticky and very difficult, if not impossible, to recrystallize. After recrystallization from isopropyl alcohol, 21.8 g. (78% yield) of a white crystalline product was obtained which melted at 123–124.5°. Analytical results are given in Table III.

Acetylated Aminophenyl ω-(N,N-Dialkylamino)-alkyl Sulfide Methyl Iodides.—In a typical experiment, 12.5 g. (0.1 mole) of *p*-aminothiophenol was dissolved in 100 ml. of 20% by weight sodium hydroxide contained in a flask fitted with a stirrer, reflux condenser, dropping funnel and a nitrogen gas delivery tube. To this alkaline solution was added 16.5 g. (0.096 mole) of diethylaminoethyl chloride hydrochloride dissolved in 100 ml. of water. The stirred reaction mixture was heated mildly for a 4-hour period while a gentle stream of nitrogen was bubbled through it. After cooling the reaction mixture it was extracted with three 100-ml. portions of ether which were combined, washed with 100 ml. of 10% sodium hydroxide, then with 100 ml. of water and dried in contact with anhydrous sodium sulfate and filtered. After removal of the ether by evaporating, 20 ml. (0.20 mole) of acetic anhydride was added to the residual oil and the mixture was heated to its boiling point and then poured into water. The resulting solution was made slightly alkaline with sodium hydroxide, causing an oil to separate, which was extracted with ether and dried with 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 5.2 g. (21% yield) of the quaternary methyl iodide salt melting at 155–56°. Analytical results are given in Table I.

East Lansing, Michigan

[Contribution from the Severance Chemical Laboratory, The College of Wooster]

The Salt Effect in the Aromatic Nucleophilic Substitution Reaction[1a,b]

By John D. Reinheimer, William F. Kieffer, Stanley W. Frey, John C. Cochran and
Edward W. Barr

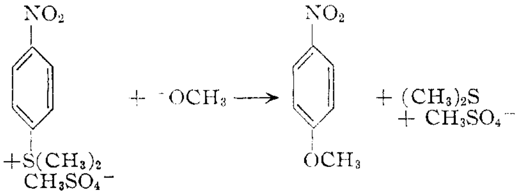
Received July 12, 1957

The effect of added salts on the rate constant of the ion dipole reaction, $MOCH_3$ + 2,4-dinitrochlorobenzene, was investigated. The rates were studied in absolute methanol as a function of the reactant ($LiOCH_3$, $KOCH_3$ and $NaOCH_3$) in the presence of added lithium, sodium and potassium salts. The change in rate constant is not due to ionic strength alone, but an additional factor which is believed to be ion pairing must be involved.

The effect of ionic strength upon aromatic nucleophilic substitution reactions has been investigated.[2] The Debye–Hückel relationship of

$$\log k/k_0 = 2AZ_aZ_b\sqrt{u} \qquad (1)$$

is obeyed for the replacement of bromine on an aromatic cation, 4-bromo-3-nitro-N,N,N-trimethylanilinum chloride, by the methoxide ion.[2a] This is an example of reaction of ions of opposite charge in which the center of charge of the aryl cation is not the site of the reaction. Another example is the ion–ion reaction



(2)

in which the anion attacks the aryl carbon directly attached to the positive sulfur.[2b] "The linear relationship of Debye–Hückel law is obeyed in this reaction, though the slope does not agree precisely with that calculated from theory." The salt effect for the ion–dipole nucleophilic reaction was investigated by Lulofs.[2c] He added water and salts to the reaction mixture of 2,4-dinitrobromobenzene and sodium ethoxide. The addition of NaAc had little effect upon the rate constant, but addition of NaBr resulted in a decreased reaction rate. In solvents that contained more water, the change in reaction rate constant was greater. The purpose of the present research was to explore the effect of added salts upon the ion–dipole reaction of $MOCH_3$ and 2,4-dinitrochlorobenzene (2,4-DNCB).

Experimental

Materials.—Methanol, Fisher certified, A.C.S., was dried over Drierite two times and distilled in all-glass apparatus.[3] Drying tubes containing Drierite and NaOH were used to exclude HOH and CO_2 during distillation. The acidity of the distillate was checked.

2,4-Dinitrochlorobenzene, Eastman Kodak Co., white label, was recrystallized once from ethanol, then from benzene. A second sample was recrystallized twice from ether. No difference in rate constant was observed with these samples.

All salts, except the hydrates, were dried at 75° in a vacuum apparatus; LiCl, $LiNO_3$, NaCl, NaBr, KI, KBr, KAc and NaI were A.C.S. reagent grade compounds; $NaClO_4 \cdot HOH$ and $LiClO_4 \cdot 3HOH$ were C.P.; while $LiI \cdot 3HOH$, $LiAc \cdot 2HOH$, $LiBr \cdot n HOH$ were purified grades. The $LiBr \cdot n HOH$ was dried to constant weight in the vacuum apparatus before use.

Solutions.—Salt solutions were prepared by placing the salt into a weighed volumetric flask, reweighing and diluting to volume. This method was necessary since the anhy-

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[1] (a) This research supported by a grant from the Petroleum Research Fund administered by the American Chemical Society and the donors of which are the Shell Oil Co., Inc., Standard Oil Co. of California, Standard Oil Co. (Indiana), Standard Oil Co. (New Jersey), The Texas Co., N. V. de Bataafsche Petroleum Maatschappij and Phillips Petroleum Company. (b) A preliminary report was given in This Journal, **79**, 1263 (1957).

[2] (a) B. Bolto, M. Liveris and J. Miller, *J. Chem. Soc.*, 750 (1956). (b) B. Bolto and J. Miller, *Australian J. Chem.*, **9**, 74 (1956); (c) M. P. K. Lulofs, *Rec. trav. chim.*, **20**, 292 (1901).

[3] J. A. Riddick and E. E. Toops, Jr., "Technique of Organic Chemistry," Vol. 7, 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1955, p. 335.