[Contribution from the Department of Pathology, Georgetown
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DITHIOLS AND DERIVATIVES[1]

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In continuation of the investigation of the synthesis and study of the physiological properties of bis-polar *alpha-omega* type compounds, we have synthesized the polymethylene dithiols up to the dodecane member and have prepared several series of derivatives from them. Of particular interest to us were the series embracing the bis-(dialkylaminoalkylthio)alkanes their salts and quaternary salts.

Several series of polymethylene derivatives terminally substituted by groups which can be quaternerized have been shown to possess curarizing activity. Smith and Cavallito (1) found curare activity when the terminal substituent was 2-thenylamino or benzylamino. Collier (2) compared the curare activity of the terminal groups 1,2,3,4-tetrahydro-2-methylisoquinoline and 6,7-dimethoxy and 6,7,8-trimethoxy analogs. Ehrhart (3) claimed that when the terminal group was dialkylaminophenyl, or ring substituted mono-, di-, and tri-methylphenyl, several agents having more potent muscular relaxant properties than curare resulted.

Marszak, *et al.* (4) studied the effects on the curarizing activity of introducing oxygen and triple bonds into the central chain of a group of polymethylene bis-quaternary salts. Cavallito, *et al.* (5) report considerable neuroblocking activity of several series of *alpha-omega* bis-(dialkylamino)alkanes which they quaternerized with fluorene, carbazole, and phenothiazine halides. A recent British patent (6) claims use of the quaternary salts of the bis-(dialkylaminoalkoxy)alkanes in the control of muscular tonus. These compounds are the oxygen isologs of our corresponding sulfur series. Fakstorp and Christiansen (7) recently reported the preparation of quaternary salts of bis-(dialkylaminoethyl)sulfides with ganglionic blocking properties. The relation of structure to curare activity has been the subject of several reviews among the more recent of which are those of Riker (8) and the excellent paper of Cheymol (9).

The starting materials in our syntheses were the polymethylene dithiols and the dialkylaminoalkyl halides. The bases were prepared in good yields by refluxing the appropriate halides with the bis-sodium mercaptides in absolute ethanol. The dialkylaminoalkyl halides were obtained from the chloride-hydrochloride salts when these were commercially available or were prepared from the appropriate dialkylaminoalkanols with thionyl chloride.

The dithiols were obtained by the alkaline hydrolysis of the corresponding diisothiuronium dihydrohalide salts which were available from a previous investigation (10). A review of the early literature of the methods of thiol

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synthesis was given by Malisoff, *et al.* (11). Since the work of Backer (12) the alkaline hydrolysis of isothiuronium salts has been increasingly employed in the synthesis of thiols. Hall and Reid (13) compared the hydrolysis of potassium xanthates, thiolbenzoates, and von Braun's (14) dithiourethan method with the alkali metal sulfhydryl method and obtained yields in the range 40–50%. The thiourea method gave yields of 80–85% for the C_4 and C_5 members which gave poor yields by the alkali metal sulfhydryl method. Meadow and Reid (15) had previously shown that yields were lowered in this procedure due to the formation of ring compounds and polymers by reaction of generated dithiols and mercaptides with unreacted dihalides. Stoken (16) concluded that of the many methods available for the preparation of thiols only the ammonium and alkali metal sulfhydryl method with halogen compounds gave good results when applied to the synthesis of dithiols. We have, therefore, made a careful study of the production of the polymethylene dithiols from the corresponding diisothiuronium salts.

Following the procedure outlined in Organic Syntheses (17) ethane dithiol was obtained in 55 and 58% yield on two separate runs. The yield was increased to around 70% by elimination of the steam-distillation and extraction of the dithiol with ether from the aqueous medium saturated with sodium chloride or sulfate. The yields of ethane and other dithiols prepared were increased to around 90% when prepared in quantities greater than 10 g. by further modification of the procedure so that 3 molar equivalents of alkali, in lieu of 4, were used per isothiuronium salt group (which liberates the thiol in the free state rather than as the alkali metal mercaptide); neutralization and acidification were done with 1:1 HCl, and the hydrolysis, neutralization, and distillation steps were carried out under an atmosphere of nitrogen.

All of the thiols were assayed for free sulfhydryl content which was more meaningful as a criterion of purity than elemental analysis. Representative thiols prepared by this modified procedure are listed in Table I. Usually only

TABLE I

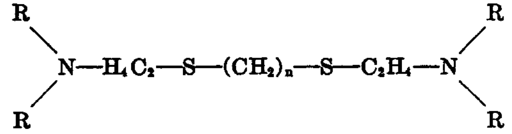
POLYMETHYLENE DITHIOLS

Thiol	B.p., °C./mm.	Yield, %	Midcut B.P., °C./mm.	Yield, %	SH, % of Theory
β-Mercaptoethanol	155–160/760	89	157–158.5/760	78	99.8
1,2-Ethanedi[a]	76–81/150	70	78–80/150	58	98.7
1,2-Ethanedi[b]	76–81/150	86	78–80/150	72	99.3
1,3-Propanedi	92–98/56	84	94–95/56	62	99.4
1,4-Butanedi	108–114/50	88	110–112/50	68	99.7
1,5-Pentanedi	135–140/75	88	137.5–138.5/75	73	99.2
1,6-Hexanedi	139–142/44	90	140–140.5/44	75	99.6
1,9-Nonanedi	175–178/50	87	—	—	99.4
1,10-Decanedi	207–209/57–58	88	—	—	99.2

[a] Prepared according to reference (17) except that steam-distillation was omitted and the dithiol was extracted with ether from the aqueous medium saturated with NaCl. [b] Prepared according to the modified procedure which is detailed in the experimental section.

TABLE II

BIS-DIALKYLAMINOALKYL DERIVATIVES OF DITHIOLS



$R_2N-H_4C_2-S-(CH_2)_n-S-C_2H_4-NR_2$

Number	R	n	B.P., °C./mm.	Analyses C Calc'd	Analyses C Found	Analyses H Calc'd	Analyses H Found	Analyses N Calc'd	Analyses N Found	n_D^{25}	d_4^{24}
1	Ethyl	2	108–113/0.05	57.47	57.83	11.03	10.87	9.58	9.50	1.5015	0.948
2	Ethyl	3	125–130/0.10	58.76	58.69	11.18	11.28	9.14	8.93	1.4990	.942
3	Ethyl	4	122–132/0.04	59.94	60.17	11.32	11.08	8.74	8.97	1.4977	.947
4	Ethyl	5	—	61.02	60.91	11.45	11.50	8.37	8.58	1.4972	.944
5	Ethyl	6	—	62.01	61.90	11.56	11.53	8.04	8.17	1.4952	.933
6	Ethyl	9	—	64.55	64.47	11.87	12.19	7.17	7.27	1.4915	.925
7	Ethyl	10	—	65.28	65.58	11.95	11.91	6.92	6.48	1.4916	.921
8	Methyl	2	88–94/0.05	50.80	50.91	10.23	10.10	11.85	11.50	1.5100	.988
9	Morpholino[a]	2	64–65[b]	52.46	52.70	8.81	8.77	8.74	8.42	—	—
10	Piperidino[a]	2	—	60.70	60.81	10.10	10.05	8.85	[c]	1.5352	—
11	Ethyl	[d]	—	54.49	54.67	10.29	10.18	7.94	8.09	1.5218	1.001

[a] When R is morpholino or piperidino, only one R group is present. [b] Melting point, recrystallized from methanol-petroleum ether. [c] Apparently there is some difficulty in determining nitrogen on this compound as figures from two microanalytical laboratories ran from 7.9–9.5%. Calc'd for $C_{16}H_{32}N_2S_2$; S, 20.25. Found S, 20.16. [d] Central chain derived from "mustard dithiol"—C_2H_4—S—C_2H_4—

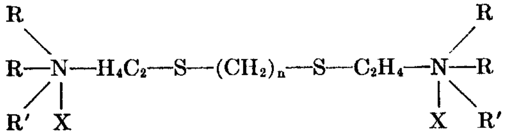
the midcut was analyzed; but analysis of the lower and higher fraction for the C_6 and C_3 members yielded sulfhydryl values between 98.5–99.5% of theoretical.

The dialkylaminoalkyl derivatives of the dithiols are listed in Table II together with pertinent characteristics. Only those members possessing short central chains and with methyl or ethyl nitrogen substituents could be distilled. There was slight decomposition on distilling #3 of Table II. The morpholinoethyl member, #9, was a white crystalline solid. All the others were colorless oily liquids that gradually developed yellow tints at room temperature. When stored under nitrogen in the refrigerator they were stable for long periods.

The hydrochloride salts and a number of quaternary salts prepared from these bases are listed in Table III. All quaternerized readily at room temperature with an excess of alkyl iodide in absolute methanol or ethanol. Even with a large excess of alkyl iodide and long standing there was little evidence of sulfonium salt formation except in the case derived from β,β'-dimercaptodiethyl sulfide, "mustard dithiol". Here attempts to quaternerize the nitrogens alone always gave oily products that could not be readily crystallized or resolved into pure substances. An excess of alkyl iodide always yielded the bis-quaternary nitrogen sulfonium salt. Since none of the other bases yielded quaternary nitrogen and sulfonium salts, it is assumed that the site of sulfonium salt formation is the central sulfur atom.

TABLE III

Bis-(dialkylaminoalkylthio)alkane Hydrochlorides and Quaternary Salts



$$R_2R'N^{+}X^{-}\text{—}H_4C_2\text{—}S\text{—}(CH_2)_n\text{—}S\text{—}C_2H_4\text{—}N^{+}R_2R'X^{-}$$

Hydrochlorides, R′ = H, X = Cl						Quaternary Salts X = I				
R	n	Formula	M.P., °C.	Ionic Chlorine, %		R′	Formula	M.P., °C.	Ionic Iodine, %	
				Calc'd	Found				Calc'd	Found
Ethyl	2	$C_{14}H_{34}Cl_2N_2S_2$	193	19.40	19.35	Methyl	$C_{16}H_{38}I_2N_2S_2$	212	44.03	44.11
Ethyl	2	—	—	—	—	Ethyl	$C_{18}H_{42}I_2N_2S_2$	217.5–218.5*	42.00	41.78
Ethyl	2	—	—	—	—	Allyl	$C_{20}H_{42}I_2N_2S_2$	158.5–160	40.38	40.30
Methyl	2	$C_{10}H_{26}Cl_2N_2S_2$	251.5	22.90	22.65	Methyl	$C_{12}H_{30}I_2N_2S_2$	272–273*	48.78	48.48
Methyl	2	—	—	—	—	Ethyl	$C_{14}H_{34}I_2N_2S_2$	210–210.6*	46.29	46.25
Methyl	2	—	—	—	—	Allyl	$C_{16}H_{34}I_2N_2S_2$	128–130	44.34	43.89
Ethyl	3	$C_{15}H_{36}Cl_2N_2S_2$	123.5–125	18.68	18.74	Methyl	$C_{17}H_{40}I_2N_2S_2$	144.5–145	42.99	42.80
Ethyl	4	$C_{16}H_{38}Cl_2N_2S_2$	130.8–131.3	18.02	18.15	Methyl	$C_{18}H_{42}I_2N_2S_2$	136–137	41.99	42.01
Ethyl	5	$C_{17}H_{40}Cl_2N_2S_2$	128.5–129.5	17.39	16.99	Methyl	$C_{19}H_{44}I_2N_2S_2$	162.8–163.5	41.04	41.33
Ethyl	6	$C_{18}H_{42}Cl_2N_2S_2$	127.5–128.5	16.82	16.80	Methyl	$C_{20}H_{46}I_2N_2S_2$	115–116.5	40.13	40.15
Ethyl	9	$C_{21}H_{48}Cl_2N_2S_2$	117.3–118	15.29	15.54	Methyl	$C_{23}H_{52}I_2N_2S_2$	119	37.62	37.88
Ethyl	10	$C_{22}H_{50}Cl_2N_2S_2$	131–132	14.84	14.81	Methyl	$C_{24}H_{54}I_2N_2S_2$	140–141	36.85	36.90
Morpholino[a]	2	$C_{14}H_{30}Cl_2N_2O_2S_2$	275–276.5*	18.02	18.18	Methyl	$C_{16}H_{34}I_2N_2O_2S_2$	158–160	41.99	42.04
Piperidino[a]	2	$C_{16}H_{34}Cl_2N_2S_2$	286–288*	18.20	18.27	Methyl	$C_{18}H_{38}I_2N_2S_2$	206–207	42.27	42.53
Ethyl	[b]	$C_{16}H_{38}Cl_2N_2S_3$	103–104[c]	16.66	16.84	Methyl	$C_{19}H_{45}I_3N_2S_3$	129–131*	48.90[d]	48.41

* Melting with decomposition. [a] In the cases where R is morpholino or piperidino, only one R group is present. [b] The central chain is diethyl sulfide, derived from "mustard dithiol". [c] Very hygroscopic. [d] Calculated for the dimethonium sulfonium triiodide.

A number of the bis-quaternary salts of these bases were found to possess curare-like activity.

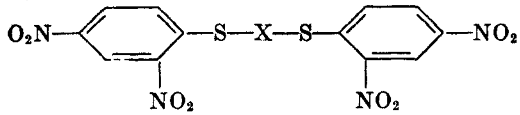
Since we possessed a group of dithiols of high purity, it was of interest to prepare several series of crystalline derivatives from them for purposes of characterization. For one series we selected the 2,4-dinitrophenyl derivatives. Several of these had been prepared by Bost, *et al.* (18, 19) who stated that the 2,4-dinitrophenyl derivatives of dithiols were amorphous (18). We have studied several methods of preparation and crystallization of these derivatives and have obtained them in crystalline form for all of our dithiol samples.

It was also of interest to us to compare the 2,4-dinitrophenyl derivatives, which contain two sulfide linkages per molecule, with the corresponding derivatives prepared from 2,4-dinitrobenzenesulfenyl chloride which derivatives differ only in that they contain two disulfide groups per molecule. A further modification in structure was attained by preparing the derivatives from 2-nitrobenzenesulfenyl chloride in which the two *para* nitro groups are removed from the molecule. These three series of dithiol derivatives are listed in Tables IV, V, and VI respectively.

The melting points of these three series of derivatives are plotted in Figure 1.

TABLE IV

2,4-DINITROPHENYL DERIVATIVES OF DITHIOLS

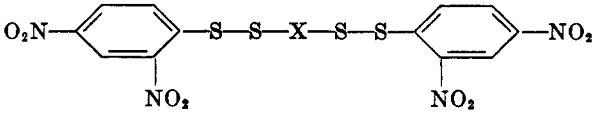


Number	X	Formula	M.P., °C.	Analyses			
				C		H	
				Calc'd	Found	Calc'd	Found
1	-ethanol*	$C_8H_8N_2O_5S^{a, b, c}$	101–102[d]	39.34	39.39	3.31	3.19
2	ethylene	$C_{14}H_{10}N_4O_8S_2^{a, c}$	249–250	39.43	39.65	2.36	2.63
3	trimethylene	$C_{15}H_{12}N_4O_8S_2^{a}$	199–200	40.90	41.21	2.75	2.85
4	tetramethylene	$C_{16}H_{14}N_4O_8S_2^{a}$	229–230	42.28	42.58	3.11	3.23
5	pentamethylene	$C_{17}H_{16}N_4O_8S_2^{a}$	175–176	43.58	43.78	3.44	3.58
6	hexamethylene	$C_{18}H_{18}N_4O_8S_2^{a}$	221.5–222.3	44.81	44.97	3.76	3.82
7	heptamethylene	$C_{19}H_{20}N_4O_8S_2$	138–139	45.96	46.24	4.06	4.14
8	octamethylene	$C_{20}H_{22}N_4O_8S_2$	186–187	47.05	47.45	4.34	4.61
9	nonamethylene	$C_{21}H_{24}N_4O_8S_2$	131–132	48.08	48.33	4.61	4.87
10	decamethylene	$C_{22}H_{26}N_4O_8S_2$	174.5–175	49.06	49.08	4.87	4.84
11	dodecamethylene	$C_{24}H_{30}N_4O_8S_2$	173–174	50.86	50.68	5.33	5.60
12	thio(diethylene)	$C_{16}H_{14}N_4O_8S_3$	159.5–160	39.50	39.79	2.91	3.07

* From β-mercaptoethanol. [a] Reference 18 gives #1, m.p. 100.5°; #2, m.p. 248°; #3, m.p. 194°; #4, m.p. 176°; #5, m.p. 170°; #6, m.p. 218°. [b] Bennett and Whincop, *J. Chem. Soc.*, **119,** 1860 (1921), m.p. 99–100°. [c] Bost, Starnes, and Wood, *J. Am. Chem. Soc.*, **73,** 1968 (1951), from halides and 2,4-dinitrothiophenol: #1, m.p. 100°; #2, m.p. 248° dec. [d] Long needles from methanol-water; all others mostly golden leaflets, occasionally needles, from methyl ethyl ketone or mixtures of methanol or ethanol and methyl ethyl ketone.

TABLE V

2,4-DINITROPHENYLTHIO DERIVATIVES OF DITHIOLS

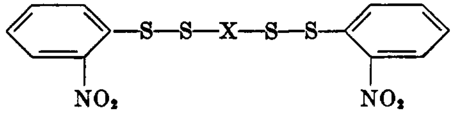


Number	X	Formula	M.P., °C.	Analyses			
				C		H	
				Calc'd	Found	Calc'd	Found
1	-ethanol*	$C_8H_8N_2O_5S_2$	108–109[a]	34.77	35.10	2.91	3.00
2	ethylene	$C_{14}H_{10}N_4O_8S_4$	202.5–203	34.28	34.28	2.05	2.39
3	trimethylene	$C_{15}H_{12}N_4O_8S_4$	159–160	35.71	35.77	2.40	2.62
4	tetramethylene	$C_{16}H_{14}N_4O_8S_4$	194.5–195	37.05	37.41	2.72	2.95
5	pentamethylene	$C_{17}H_{16}N_4O_8S_4$	147.5–148	38.33	38.36	3.03	2.89
6	hexamethylene	$C_{18}H_{18}N_4O_8S_4$	158.5–160	39.55	39.72	3.32	3.51
7	heptamethylene	$C_{19}H_{20}N_4O_8S_4$	126–127	40.70	40.56	3.60	3.37
8	octamethylene	$C_{20}H_{22}N_4O_8S_4$	151–152	41.80	41.86	3.86	4.01
9	nonamethylene	$C_{21}H_{24}N_4O_8S_4$	114–115.5	42.84	42.90	4.11	4.23
10	decamethylene	$C_{22}H_{26}N_4O_8S_4$	145.5–147	43.84	43.61	4.35	4.65
11	dodecamethylene	$C_{24}H_{30}N_4O_8S_4$	141–142	45.70	46.04	4.79	4.89
12	thio (diethylene)	$C_{16}H_{14}N_4O_8S_5$	147–148	34.90	34.72	2.56	2.71

* From β-mercaptoethanol. [a] Needles from methanol-water; all others from methyl ethyl ketone or methanol or ethanol and methyl ethyl ketone.

TABLE VI

2-NITROPHENYLTHIO DERIVATIVES OF DITHIOLS



Number	X	Formula	M.P., °C.	Analyses			
				C		H	
				Calc'd	Found	Calc'd	Found
1	-ethanol*	$C_8H_9NO_3S_2$	Oil	41.54	41.73	3.92	4.10
2	ethylene	$C_{14}H_{12}N_2O_4S_4$	185.5–186.5	41.98	42.06	3.02	3.14
3	trimethylene	$C_{15}H_{14}N_2O_4S_4$	102.5–103	43.46	43.41	3.40	3.62
4	tetramethylene	$C_{16}H_{16}N_2O_4S_4$	113.5–114	44.84	45.06	3.76	4.05
5	pentamethylene	$C_{17}H_{18}N_2O_4S_4$	87	46.13	46.29	4.10	4.28
6	hexamethylene	$C_{18}H_{20}N_2O_4S_4$	117.5–118	47.34	47.33	4.41	4.67
7	heptamethylene	$C_{19}H_{22}N_2O_4S_4$	77–77.5	48.49	48.66	4.71	4.91
8	octamethylene	—	—	—	—	—	—
9	nonamethylene	$C_{21}H_{26}N_2O_4S_4$	80	50.58	50.91	5.25	5.33
10	decamethylene	$C_{22}H_{28}N_2O_4S_4$	108	51.53	51.55	5.50	5.51
11	dodecamethylene	$C_{24}H_{32}N_2O_4S_4$	108.5–109	53.30	53.55	5.96	6.26
12	thio(diethylene)	$C_{16}H_{16}N_2O_4S_5$	89.5	41.72	41.89	3.50	3.68

* From β-mercaptoethanol.

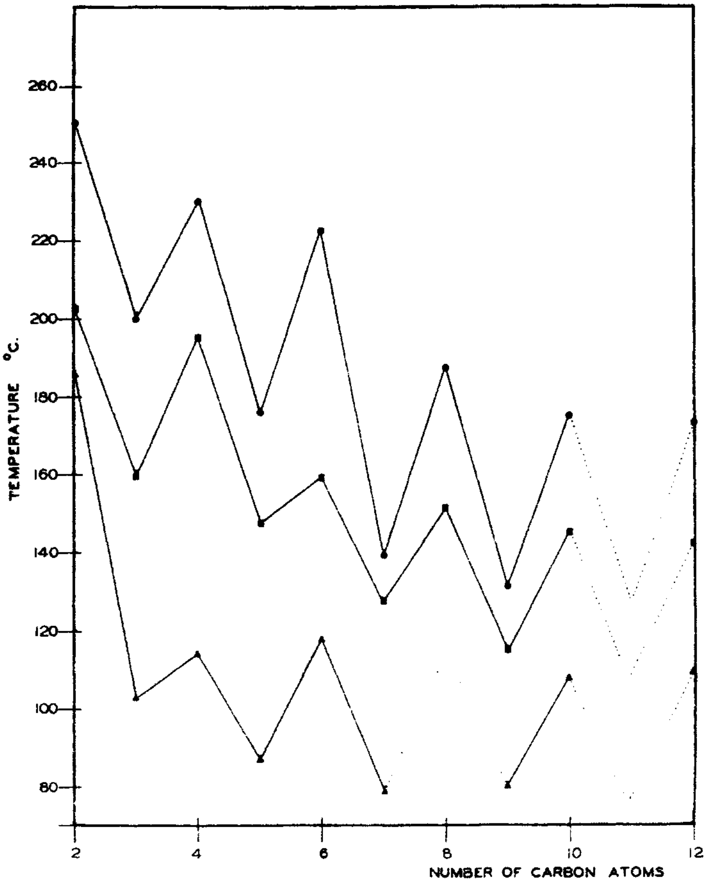


FIG. 1. MELTING POINTS OF DITHIOL DERIVATIVES AS A FUNCTION OF CENTRAL CHAIN LENGTH.
Upper Curve: 2,4-dinitrophenyl derivatives
Central Curve: 2,4-dinitrophenylthio derivatives
Lower Curve: 2-nitrophenylthio derivatives

All series exhibit regular attenuation patterns and are remarkable for the wide swing in attenuation. In homologous series, in which the elemental percentage composition differs little from one member to the next, regularities in the melting point pattern are frequently a better criterion of identity and purity than analytical data. It is interesting to note that the derivatives of diethyl sulfide central chain melt, in two of the series, at almost the same temperature as those of pentamethylene. It is unusual for the —CH_2— group to be equivalent to the —S— linkage.

EXPERIMENTAL

Preparation of thiols. All of the thiols prepared for the present study were obtained by the alkaline hydrolysis of the corresponding isothiuronium hydrohalide salts under the conditions discussed. The synthesis of the butane member will illustrate the procedure.

Butane-1,4-dithiol. Into a one-liter three-necked reaction flask equipped with a stirrer, dropping-funnel, and reflux condenser were placed 100 g. (0.358 mole) of butane-1,4-diisothiuronium dihydrochloride dissolved in 300 ml. of water. Stirring was started and a solution of 121 g. (2.15 mole) of KOH in 125 ml. of water was run in. The reaction flask was flushed out with N_2 until gentle refluxing started and NH_3 was being freely emitted. The mixture was refluxed until NH_3 was no longer evolved. This generally required 4–7 hours. Nitrogen was again admitted and the reaction mixture cooled in an ice-bath. The calculated amount and 25% excess of 1:1 HCl was run in with rapid stirring. Nitrogen was admitted until the mixture had cooled below room temperature, 15–20°. If precipitated NaCl was not evident, the mixture was saturated with NaCl and extracted with three 100-ml. portions of ether. The ether extracts were dried over Na_2SO_4, the ether was stripped off, and the dithiol was distilled at reduced pressure under an atmosphere of nitrogen. There was obtained 38.6 g., b.p. 108–114°/50 mm., 88%. The midcut, b.p. 110–112°/50 mm., assayed 99.7% of theoretical sulfhydryl content. (See below.)

Sulfhydryl analysis. The free sulfhydryl content of the thiol samples was determined by oxidation with a N/10 KIO_3 solution. All reagents used were prepared in water that was redistilled in an all glass apparatus from alkaline permanganate. The use of KIO_3, which can be obtained in high purity and gives a stable solution, avoids the preparation and continuous standardization of iodine solutions. A N/10 solution of the dried reagent grade salt (3.567 g./liter) checked within 3/1000 against a dichromate primary standard.

Several drops (20–75 mg.) of thiol were weighed into a small flask (equipped with a ground glass stopper), dissolved in absolute ethanol (that had been distilled over Ag_2O), and cooled to 15–20°. The following precooled reagents were then added: 3–5 ml. of 10% KI and sufficient 10% HCl to give a 4–5% concentration in the final volume. The thiol was then rapidly titrated with KIO_3 until a faint persistence of iodine color was evident. When employing a 2-ml. semi-micro buret and a daylight lamp against a white background, the end point could be repeated to within ±0.005 ml. without the use of starch indicator.

Bis-(dialkylaminoalkylthio)alkanes. These were all prepared by the reaction of the bissodium mercaptides with the corresponding dialkylaminoalkyl chlorides in absolute ethanol. Only those members that had short central chains, to approximately butane, and in which the N-alkyl substituent was either methyl or ethyl could be distilled without decomposition (*i.e.* compounds 1, 2, 3 and 8, Table II). The synthesis of compound 1, Table II, will illustrate the procedure.

Bis-(diethylaminoethylthio)ethane. Sodium (3 g., 0.130 mole) was dissolved in absolute ethanol (100 ml.) under dry conditions. After solution had been effected, 6.14 g. (0.065 mole) of ethane dithiol in 20 ml. of ethanol was added. To the resulting clear solution was added 17.7 g. (0.130 mole) diethylaminoethyl chloride. The mixture was refluxed gently for 2 hours, cooled, the NaCl filtered off, the ethanol stripped off under reduced pressure, and the resultant oil dissolved in ether. The base was extracted from the ether into an aqueous phase containing 10% HCl, and washed with ether. The aqueous phase was made alkaline with 10% NaOH and the base was extracted into a new ether phase. The ether extract was dried over Na_2SO_4, filtered, the ether stripped off, and the base distilled *in vacuo* to yield 15 g. of colorless oil, 78%, b.p. 108–113/0.05 mm. Compounds 4, 5, 6, 7, 10, and 11, which could not be distilled without decomposition, were subjected to the extraction steps and final drying *in vacuo* to remove traces of ether. Compound 9, which was a solid on stripping off the ethanol, was recrystallized from methanol-30–60° petroleum ether.

Quaternary salts. The quaternary salts were formed by dissolving the bases in either anhydrous ethanol or methanol and treatment with an excess of alkyl iodide under anhydrous conditions followed by precipitation with anhydrous ether. They were recrystallized from absolute methanol-ether.

Hydrochlorides. These were formed from the bases, dissolved in absolute methanol or ethanol, with an excess of a saturated solution of HCl in ethanol; and were precipitated with anhydrous ether. They were recrystallized from absolute methanol-ether.

Ionic halogen analyses. Chloride and iodide analyses of the salts and quaternary salts were carried out using the adsorption indicator method of Fajans and the polyethylene glycol 400 colloidal stabilizer recommended by Dean, *et al.* (20) except that the stabilizer-dichlorofluorescein reagent was prepared in absolute methanol instead of water. Dichlorofluorescein has not been recommended for the titration of iodides; but rather the corresponding diiodofluorescein. We found that iodides (as well as bromides and chlorides) could be readily titrated, frequently to 2/5000 and routinely to 2/1000, by employing the reagent in methanol at a concentration of 1 drop per 10 ml. of titration mixture. In the case of bromides and iodides, the yellow colors of the silver halides formed could be largely discharged by adding more methanol (an acetone-free reagent grade) to the titration mixture—5–10 ml. up to 50-ml. or 10–25 ml. up to 100-ml. volumes, dependent on the amount of halide formed—and permitted sharply defined end points.

Bis-2,4-dinitrophenyl derivatives. These were prepared by two procedures: *A*. That of Bost, *et al.* (18, 19) in which the thiol, dissolved in the minimum amount of alcohol, is converted to the sodium mercaptide by adding the equivalent of NaOH in a small volume of water and then the equivalent of 2,4-dinitrochlorobenzene in alcohol and warming 10 minutes on a steam-bath.

B. Alternatively, it was found that a mixture of the thiol and the equivalent of 2,4-dinitrochlorobenzene in alcohol could be titrated with an alcoholic solution of KOH. Thus: 0.005 mole of dithiol and 0.01 mole of 2,4-dinitrochlorobenzene were dissolved in 15–25 ml. of ethanol and titrated with a 0.1 *molar* alcoholic solution of KOH. The reaction was instantaneous and the end point could be readily seen in most cases since an excess of alkali caused an orange or dirty gray-green color to persist. An excess of alkali was avoided. The mixture was diluted with 10 or more volumes of water, boiled, and filtered hot. This procedure yielded products which were readily cleaned up. These derivatives had a tendency to be deposited in an amorphous state as noted by Bost, *et al.* (18). They were generally insoluble in ordinary solvents. They were only very slightly soluble in the lower alcohols, slightly soluble in benzene, chloroform, acetone, and ethyl acetate, and soluble in methyl ethyl ketone. The latter solvent proved to be the best single solvent for recrystallization. Most of the materials were deposited slowly from this solvent and tended to be amorphous until the second or third recrystallization. However, if the crude product was warmed with a little methanol, the methanol decanted, and the residue dissolved in a methyl ethyl ketone-ethanol or methanol mixture, a single recrystallization yielded a crystalline product with nearly constant melting point. The odd numbered carbon chain derivatives were more soluble than those of even number.

Bis-2,4-dinitrophenylthio derivatives. A. The method of Kharasch, *et al.* (21) for the preparation of derivatives of 2,4-dinitrobenzenesulfenyl chloride and alcohols, in which pyridine was used as an HCl acceptor, was tried and always resulted in a considerable residue insoluble in ethylene chloride or carbon tetrachloride. The products were more difficult to clean up than those prepared in *B* below. *B*. To 0.005 mole of dithiol dissolved in anhydrous ethylene chloride or carbon tetrachloride in a 500-ml. wide-mouth flask (which facilitated removal of solvent by aspiration later) was added 0.01 mole of 2,4-dinitrobenzenesulfenyl chloride in 10 ml. of the same solvent. They were mixed well and stoppered lightly (or provided with a drying tube) and warmed on a hot plate with shaking until the evolution of HCl was completed. Toward the end of the reaction, the mixture was heated slowly to the boiling point, boiled gently for a minute or two, stoppered, and allowed to cool. In some cases the even numbered carbon chain members were obtained in crystalline form from the reaction mixture. In most cases the solvent was removed at the aspirator with the flask immersed in a water-bath. The solid or oil that resulted was re-dispersed or dissolved in about 20 ml. of acetone which was removed rapidly at the aspirator (heat) to remove the last traces of reaction solvent by entrainment. The flask was filled with water, boiled, and filtered hot. The products were recrystallized from methyl ethyl ketone-ethanol or methanol mixtures.

Bis-2-nitrophenylthio derivatives. These derivatives were obtained from 2-nitrobenzenesulfenyl chloride and the dithiols in a manner analogous to the 2,4-dinitrophenylthio derivatives. The even numbered carbon chain members all were obtained in crystalline form from the reaction solvent. The odd members all were obtained as oils after solution of the crude product in acetone and precipitation with water. They were solidified on cooling under water-acetone in the refrigerator. The even members were relatively insoluble and were recrystallized from methyl ethyl ketone-ethanol. The odd members were recrystallized from ethanol. All members of this series in general were more soluble than the corresponding 2,4-dinitrophenylthio series.

The sample of *o*-nitro(2-nitro)benzenesulfenyl chloride was kindly furnished by Monsanto Chemical Company.

SUMMARY

A careful study of the formation of polymethylene dithiols by the alkaline hydrolysis of the diisothiuronium salts has been made. All of the thiols were obtained in yields of better than 80% and in high purity. Several bis-(dialkylaminoalkylthio)alkanes have been prepared from the dithiols and dialkylaminoalkyl chlorides. A number of the bis-quaternary salts of these bases possessed curare-like activity. The dithiols have been characterized as the 2,4-dinitrophenyl, 2,4-dinitrophenylthio, and 2-nitrophenylthio derivatives.

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