Antiradiation Compounds. IV. Trithiocarbonates of β-Mercaptoethylguanidines[1]

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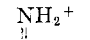
β-Mercaptoethylguanidine and N-substituted derivatives, prepared in aqueous solution by rearrangement of the corresponding β-aminoethylisothiuronium compounds, gave insoluble adducts with carbon disulfide. Both infrared and ultraviolet absorption spectral characteristics as well as chemical evidence showed the adducts to be trithiocarbonates rather than dithiocarbamates or cyclic structures. N,S-Diacyl derivatives of β-mercaptoethylguanidine were prepared from the trithiocarbonate by reaction with acyl chlorides. Several of the trithiocarbonates, as well as one of the diacyl derivatives, furnished significant protection to mice against an otherwise lethal dose of X-irradiation.

Conversion of mercaptan bases to compounds with reactive sulfur-containing functional groups has produced effective radiation-protective agents for animals. This has been demonstrated in the case of 2-mercaptoethylamine (MEA) and 2-mercaptoethylguanidine (MEG) by conversion to Bunte salts,[2] thiophosphates,[3] and acyl thioesters.[4] The trithiocarbonates of MEA and MEG have now been prepared and found to have appreciable radiation-protective ability in mice. The trithiocarbonate zwitterion of MEA was previously believed to be a dithiocarbamic acid,[4,5] but evidence for the trithiocarbonate structure has been presented.[6]

Reaction of carbon disulfide with an aqueous solution of 2-mercaptoethylguanidine, prepared from the alkaline rearrangement of 2-(2-aminoethyl)-2-thiopseudourea dihydrobromide (AET), gave immediate precipitation of an insoluble yellow adduct. The product is most likely the trithiocarbonate zwitterion, as has been found from the corresponding reactions with MEA and 2-diethylaminoethanethiol.[6] However, since a dithiocarbamate (I) or trithiocarbonate (II) structure, both theoretically possible from this reaction, give the same elemental analysis, it was necessary to distinguish between the possible structures.


$\mathrm{HSCH_2CH_2NH}\overset{\mathrm{NH_2^+}}{\overset{\|}{\mathrm{C}}}\mathrm{NHCS_2^-}$

I

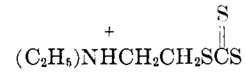

$^-\mathrm{S}\overset{\mathrm{S}}{\overset{\|}{\mathrm{C}}}\mathrm{SCH_2CH_2NH}\overset{\mathrm{NH_2^+}}{\overset{\|}{\mathrm{C}}}\mathrm{NH_2}$

II

Examination of the infrared absorption spectra of the MEG adduct showed definite trithiocarbonate absorption[7] at 1038 cm.$^{-1}$. The corresponding N,N,N′-trimethyl derivative of MEG, where dithiocarbamate formation would be less likely, also showed this absorption at 1026 cm.$^{-1}$. The trithiocarbonate zwitterion of MEA (III) showed this peak at 1018 cm.$^{-1}$, and the carbon disulfide adduct of 2-diethylaminoethanethiol (IV), which can be only a trithiocarbonate, absorbed at 1032 cm.$^{-1}$. Furthermore, no absorption near 2550 cm.$^{-1}$, due to a mercapto group, was evident with any of these compounds.


$^+\mathrm{NH_3CH_2CH_2S}\overset{\mathrm{S}}{\overset{\|}{\mathrm{C}}}\mathrm{S}^-$

III


$(\mathrm{C_2H_5})\overset{+}{\mathrm{N}}\mathrm{HCH_2CH_2S}\overset{\mathrm{S}}{\overset{\|}{\mathrm{C}}}\mathrm{S}^-$

IV

Evidence from comparison of the ultraviolet absorption spectra of dithiocarbamates and trithiocarbonates also favored a trithiocarbonate structure (see Table I). The trithiocarbonate zwitterion of 2-diethylaminoethanethiol showed trithiocarbonate absorption peaks[8] at 226 mμ (log $\epsilon_{\max}$ 4.07) and 303 mμ (log $\epsilon_{\max}$ 4.18), and the trithiocarbonate zwitterion of MEA showed very similar absorption at 226 mμ (log $\epsilon_{\max}$ 3.96) and 304 mμ (log $\epsilon_{\max}$ 4.15). The potassium salts of ethyl and hexyl trithiocarbonates, however, absorbed at 300 mμ (log $\epsilon_{\max}$ 3.46) and 333 mμ (log $\epsilon_{\max}$ 3.10) and at 302 mμ (log $\epsilon_{\max}$ 3.61) and 333 mμ (log $\epsilon_{\max}$ 3.24), respectively. The carbon disulfide adduct of MEG showed absorption in the ultraviolet resembling that of the alkyl trithiocarbonates when observed in neutral solvent (C_2H_5OH), with peaks at 304 mμ (log $\epsilon_{\max}$ 3.36) and 353 mμ (log $\epsilon_{\max}$ 2.43). When observed in alkaline ethanol, however, the MEG·CS_2 adduct revealed ultraviolet absorption similar to that of the MEA and diethyl MEA zwitterions, with peaks at 225 mμ (log $\epsilon_{\max}$ 4.00) and 303 mμ (log $\epsilon_{\max}$ 4.11). The N-alkylated MEG trithiocarbonates showed closely similar absorption in the ultraviolet.

Moreover, the characteristic ultraviolet absorption[8,9] of dithiocarbamates at 240–260 mμ, 290–310 mμ, and 340-360 mμ was not in evidence with the carbon disulfide adducts of MEG and its alkyl derivatives. As seen from Table I, dithiocarbamate zwitterions showed absorption peaks at these wave lengths, as did the dithiocarbamate of the S-methyl ether of MEA (V). In this connection, the S-heptyl ether of N,N′-dicyclohexyl MEG gave a reaction with carbon disulfide in the usual manner to give an insoluble adduct (VI) that showed characteristic dithiocarbamate peaks in the ultraviolet at 243 mμ (log $\epsilon_{\max}$ 4.42) and 288 mμ (log $\epsilon_{\max}$ 2.77).

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[1] This project was carried out under a contract (DA-49-193-MD-2029) with the Office of the Surgeon General, U. S. Army Medical Research and Development Command.

[2] B. Holmberg and B. Sorbo, *Nature*, **183**, 832 (1959); A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiation Res.*, **14**, 23 (1961).

[3] B. Sorbo, *Arch. Biochem. Biophys.*, **98**, 342 (1962); D. P. Jacobus, O. B. Ramsay, R. E. Spalding, and D. C. Dittmer, Abstracts, 141st National Meeting, American Chemical Society, March, 1962, p. 30N.

[4] W. O. Foye, R. N. Duvall, and J. Mickles, *J. Pharm. Sci.*, **51**, 168 (1962).

[5] W. O. Foye and J. Mickles, *J. Med. Pharm. Chem.*, **5**, 846 (1962).

[6] W. O. Foye, J. R. Marshall, and J. Mickles, *J. Pharm. Sci.*, **52**, 406 (1963).

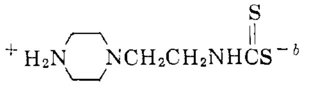
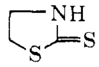
[7] J. I. Jones, W. Kynaston, and J. L. Hales, *J. Chem. Soc.*, 614 (1957).

[8] J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Am. Chem. Soc.*, **76**, 4348 (1954); M. J. Janssen, *Rec. trav. chim.* **79**, 454, 464, 1068 (1960); F. Challenger, E. A. Mason, E. C. Holdsworth, and R. Emmott, *J. Chem. Soc.*, 292 (1953).

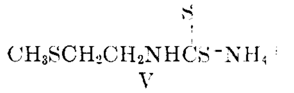
[9] H. P. Koch, *ibid.*, 401 (1949).

Table I

Ultraviolet Absorption Characteristics of Dithiocarbamates and Trithiocarbonates[a]

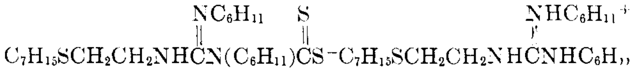
Compound	Absorption maxima, mμ	Log ϵ_{max}
$(C_2H_5)_2NCSCl$	250	4.22
$(C_2H_5)_2N\overset{\overset{S}{\|}}{C}S^-Na^+$	257 290	3.78 3.78
	255 292 344	3.49 3.48 2.35
$HOCH_2CH_2NH_2^+CH_2CH_2NH\overset{\overset{S}{\|}}{C}S^{-b}$	239 295 342	3.79 3.37 2.82
$CH_3SCH_2CH_2NH\overset{\overset{S}{\|}}{C}S^-NH_4^+$	257 292 345	3.92 4.06 1.95
$C_7H_{15}SCH_2CH_2NH\overset{\overset{NC_6H_{11}}{\|}}{C}N(C_6H_{11})\overset{\overset{S}{\|}}{C}S^-$ $C_7H_{15}SCH_2CH_2NHC(=NHC_6H_{11})NHC_6H_{11}^+$	243 288	4.42 2.77
$C_7H_{15}SCH_2CH_2NH\overset{\overset{S}{\|}}{C}S^-C_7H_{15}SCH_2CH_2NH_3^+$	256 293 343	3.88 3.85 3.04
$CH_3CH_2S\overset{\overset{S}{\|}}{C}S^-K^+$	300 333	3.46 3.10
$CH_3(CH_2)_5S\overset{\overset{S}{\|}}{C}S^-K^+$	302 333	3.61 3.24
$^+NH_3CH_2CH_2S\overset{\overset{S}{\|}}{C}S^{-c,d}$	226 304	3.96 4.15
$(C_2H_5)_2NH^+CH_2CH_2S\overset{\overset{S}{\|}}{C}S^{-d}$	226 303	4.07 4.18
$NH_2\overset{\overset{NH_2^+}{\|}}{C}NHCH_2CH_2S\overset{\overset{S}{\|}}{C}S^-$	304 353 225[d] 303[d]	3.36 2.43 4.00 4.11
$(CH_3)_2N\overset{\overset{NHCH_3^+}{\|}}{C}NHCH_2CH_2S\overset{\overset{S}{\|}}{C}S^-$	305 352	3.03 2.54
$C_6H_{11}NH\overset{\overset{NHC_6H_{11}^+}{\|}}{C}NHCH_2CH_2S\overset{\overset{S}{\|}}{C}S^-$	304 352	3.20 2.69
	276	4.17
$(CH_3)_2N\overset{\overset{S}{\|}}{C}SS\overset{\overset{S}{\|}}{C}N(CH_3)_2$	260–280	4.23

[a] Measured with the Beckman DU spectrophotometer using a 1 cm. cell and 95% ethanol as solvent. [b] See ref. 5. [c] See ref. 6. [d] Measured in 0.1 N ethanolic KOH solution.



$CH_3SCH_2CH_2NH\overset{\overset{S}{\|}}{C}S^-NH_4^+$

V



$C_7H_{15}SCH_2CH_2NH\overset{\overset{NC_6H_{11}}{\|}}{C}N(C_6H_{11})\overset{\overset{S}{\|}}{C}S^-C_7H_{15}SCH_2CH_2NH\overset{\overset{NHC_6H_{11}^+}{\|}}{C}NHC_6H_{11}$

VI

Chemical evidence in favor of trithiocarbonate rather than dithiocarbamate formation was found in the reaction of the disulfide of MEG with carbon disulfide. The degree of alkalinity required for a reaction to take place also cleaved the disulfide linkage, giving the same MEG trithiocarbonate zwitterion as before. In this connection, no dithiocarbamates of the guanidine group have previously appeared in the literature, with the exception of aminoguanidine dithiocarbamates.[10]

The marked tendency for zwitterion formation in the preparation of these trithiocarbonates was brought out by the behavior of N,N′-dicyclohexyl MEG hydrobromide. Although a hydrohalide of MEG or its derivatives had not previously been isolated, this compound was sufficiently insoluble in aqueous media to permit its isolation, after rearrangement of the corresponding AET derivative with aqueous ammonia. Reaction of the MEG derivative with carbon disulfide, however, removed the hydrogen bromide, giving the trithiocarbonate zwitterion. Furthermore, reaction of N,S-diacyl MEG derivatives with carbon disulfide in alkaline media gave no insoluble adduct until both acyl groups were removed during hydrolysis.

The N,S-diacyl derivatives of MEG were prepared by utilizing the trithiocarbonate, which could be isolated from aqueous solution. Previously, MEG had been isolated only as the flavianate.[11] Heating the trithiocarbonate with acyl chlorides having chain lengths of six or more carbons gave solid N,S-diacyl derivatives with loss of carbon disulfide. Physical constants

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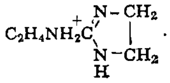
(10) D. J. Fry and A. J. Lambie, British Patent 737,567 (1955).

(11) J. X. Khym, R. Shapira, and D. G. Doherty, *J. Am. Chem. Soc.*, **79**, 5663 (1957).

TABLE II

PHYSICAL PROPERTIES OF THE β-MERCAPTOETHYLGUANIDINE DERIVATIVES

Compound	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
N,S-Dihexanoyl MEG·HCl	83–86	26	$C_{15}H_{30}ClN_3O_2S$	51.21	51.13	8.53	8.41	11.95	11.68	9.10	9.52
N,S-Diheptanoyl MEG·HCl	87–89	22	$C_{17}H_{34}ClN_3O_2S$	53.75	54.07	8.96	9.06	11.07	11.31	8.43	8.96
N,S-Dioctanoyl MEG·HCl	94–95	54	$C_{19}H_{38}ClN_3O_2S$	55.95	56.16	9.33	9.48	10.31	10.20	7.85	8.25
N,S-Dimyristoyl MEG·HCl	107–109	45	$C_{31}H_{62}ClN_3O_2S$	64.64	64.16	10.77	10.40	7.30	7.16	5.56	6.09
N,N′-Dicyclohexyl MEG·HBr	209–210	49	$C_{15}H_{30}BrN_3S$	49.45	49.27	8.24	7.31	11.54	11.21	8.79	8.76
TRITHIOCARBONATES,  $RS\overset{S}{\overset{\|}{C}}S^-$											
R											
$C_2H_4NHC(=NH_2^+)NH_2$	140–142	74	$C_4H_9N_3S_3$	24.60	25.00	4.64	4.80	21.51	21.85	49.29	49.00
$C_2H_4NHC(=NH_2^+)NHCH_3$	159–161	71	$C_5H_{11}N_3S_3$	28.71	28.71	5.26	5.15	20.10	20.08	45.93	45.46
$C_2H_4NHC(=NH_2^+)NHNH_2$	131–132	21	$C_4H_{10}N_4S_3$	22.86	23.00	4.76	4.67	26.67	26.77	45.71	46.55
$C_2H_4NHC(=NH^+CH_3)N(CH_3)_2$	116–118	58	$C_7H_{15}N_3S_3$	35.44	35.37	6.33	6.53	17.72	16.65	40.50	40.21
$C_2H_4NHC(=NH^+C_6H_{11})NHC_6H_{11}$	156–159	56	$C_{16}H_{29}N_3S_3$	53.48	53.60	8.08	8.17	11.70	11.52	26.74	26.30
$C_3H_6NHC(=NH_2^+)NH_2$	133–135	80	$C_5H_{11}N_3S_3$	28.71	29.09	5.26	5.53	20.10	20.55	45.93	45.98
$C_2H_4NHC(=NH_2^+)$- $NHCH_2CH=CH_2$	150–152	80	$C_7H_{13}N_3S_3$	35.74	35.49	5.53	5.65	17.87	17.50	40.85	40.89
	142–144	67	$C_6H_{13}N_3OS_3$[a]	30.10	30.94	5.47	5.72	17.55	17.98	40.19	40.71

[a] *Anal.* Calcd. H_2O: 7.10. Found: 6.32 (by loss of weight).

of the compounds prepared are listed in Table II.

Antiradiation Properties.—Tests for the ability of some of the compounds discussed to protect mice against a lethal dose of X-irradiation (800 r.) have been carried out at the Walter Reed Army Institute of Research under the direction of Dr. D. P. Jacobus. Tests were carried out as previously indicated,[4] and the trithiocarbonate of MEG was described as giving good protection, comparable to that from MEG itself, in the dose range of 350–750 mg./kg. The trithiocarbonates of the N-amino derivative (N′-amino-2-guanidinoethyltrithiocarbonate zwitterion) and the N-methyl derivative also gave good protection, as well as did the trithiocarbonate of 3-mercaptopropylguanidine (MPG). The trithiocarbonates of the dicyclohexyl and imidazole derivatives gave only slight protection, whereas the trithiocarbonate of the trimethyl derivative gave no protection. The hydrobromide of dicyclohexyl MEG also gave no protection, but the latter two compounds were too toxic for appreciable doses to be employed (doses of less than 50 mg./kg. were used). It appears, therefore, that two or three alkyl groups on the guanidine nitrogens seriously diminish or remove radioprotective ability.

One of the N,S-diacyl derivatives, the dioctanoyl, gave fair protection in the 150–350 mg./kg. dose range. In addition, more detailed data for the protective ability of MEG trithiocarbonate (GET) *vs.* 800 and 900 r. in mice is presented in Table III. These results were obtained through the courtesy of Dr. Richard I. H. Wang of Roswell Park Memorial Institute, who plans to publish a more complete study elsewhere. The protective ability of the compound is obscured somewhat in these results by the toxicity of the propylene glycol solutions employed; the LD_{50} of GET in propylene glycol is about 0.1 ml. of a 4% solution by the intraperitoneal route.

TABLE III

RADIOPROTECTIVE ABILITY OF 2-GUANIDINOETHYLTRITHIOCARBONATE (GET) IN MICE[a]

Compound; amount administered[b]	Dose, r.	No. of mice used	No. of mice died	% mortality (30 days)
0.1 ml. 3% GET	900	20	11	55
.1 ml. 2% GET	900	20	6	30
.3 ml. 0.8% AET[c]	900	20	0	0
Control	900	20	20	100
0.1 ml. 3% GET	800	20	11	55
.1 ml. 2% GET	800	20	0	0
.3 ml. 0.8% AET[c]	800	20	0	0
.1 ml. propylene glycol	800	20	16	80
Control	800	20	17	85

[a] Determined at Roswell Park Memorial Institute by Dr. R. I. H. Wang. [b] In propylene glycol; administered 15 min. prior to radiation exposure. [c] In saline solution.

Experimental[12]

2-Guanidinoethyltrithiocarbonate Zwitterion.—S-(2-Aminoethyl)-isothiuronium bromide hydrobromide (5.6 g., 0.02 mole) (Matheson Coleman and Bell) was dissolved in 15 ml. of water and treated with 3 ml. of concentrated ammonium hydroxide. The resulting solution of 2-mercaptoethylguanidine was added dropwise with stirring to 4 ml. of carbon disulfide surrounded by an ice bath. A bright yellow precipitate was isolated and was washed with water and ethanol and was air dried. The yield was 2.9 g. (74%) of product which melted at 140–142°. Trithiocarbonates of the N-alkyl MEG derivatives were prepared in similar fashion.

N,S-Diacyl-2-mercaptoethylguanidine Hydrochlorides.—The acid chloride (15 ml.) and 3.5 g. (0.018 mole) of 2-guanidinoethyltrithiocarbonate zwitterion were heated on a steam bath for 1 hr. after the mixture became homogeneous. The solution was cooled, and 200 ml. of ether was added. The resulting solution was refrigerated, and the crystals which appeared were filtered and washed with ether. In the case of the N,S-dimyristoyl derivative, the product could be recrystallized from absolute alcohol. In general, the compounds were slightly soluble in water, very soluble in alcohol, and gave negative tests for a sulfhydryl group with dilute iodine solution.

2-Guanidinoethyl Disulfide Dihydrobromide.[13]—S-(2-Amino-

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[12] Melting points were taken on either a Fisher–Johns or Mel-Temp block. Analyses for carbon, hydrogen, and nitrogen were done by Weiler and Strauss, Oxford, England.

[13] The disulfide of MEG has been tested for radioprotective ability by E. E. Schwartz and B. Shapiro, *Radiation Res.*, **13**, 768 (1960), but no synthetic procedure was described.

ethyl)isothiuronium bromide hydrobromide (28 g., 0.1 mole) was dissolved in 25 ml. of concentrated ammonia water, and 200 ml. of 3% hydrogen peroxide was added in four portions over a period of 2 hr. The solution was heated on a water bath during the addition. It solidified during the night, and the solid was pulverized, washed with absolute alcohol, and recrystallized from ethanol. The yield was 14.8 g. (75%) of product which melted at 195–197°.

Anal. Calcd. for $C_6H_{18}Br_2N_6S_2$: C, 18.09; H, 4.52; N, 21.11; S, 16.09. Found: C, 17.38; H, 4.48; N, 21.10; S, 15.93.

N,N′-Dicyclohexyl-N″-(2-mercaptoethyl)guanidine Hydrobromide.—N,N′-Dicyclohexylthiourea (10.0 g., 0.042 mole) (prepared by the method of Schmidt[14]) and 2-bromoethylamine hydrobromide (10.0 g., 0.049 mole) were refluxed in 60 ml. of absolute ethanol for 3 hr. after solution took place. After cooling, 200 ml. of water was added, and the solution was chilled in an ice bath. Unreacted dicyclohexylthiourea (1.1 g.) was removed by filtration. Concentrated ammonium hydroxide (10 ml.) was added dropwise with stirring to the chilled filtrate, and the resulting solution was refrigerated. A fine, white precipitate was filtered, washed with water, and dried. The yield was 7.5 g. (49%) of material melting at 210°. The compound was insoluble in water, soluble in ethanol, and gave a positive iodine test for a mercapto group.

Anal. Calcd. for $C_{15}H_{30}BrN_3S$: C, 49.45; H, 8.24; Br, 21.98; N, 11.54; S, 8.79. Found: C, 49.27; H, 7.31; Br, 22.14; N, 11.21; S, 8.76.

N′-Amino-2-guanidinoethyltrithiocarbonate Zwitterion.—A mixture of thiosemicarbazide (4.6 g., 0.05 mole) and absolute ethanol (80 ml.) was refluxed for 30 min., 2-bromoethylamine hydrobromide (10.25 g., 0.05 mole) (K and K Laboratories, Inc.) was added, and the mixture was refluxed until it became homogeneous. The solution was cooled in an ice bath, and to it were added an equal volume of water and 15 ml. of concentrated ammonium hydroxide. Carbon disulfide (4 ml., 0.05 mole) was added dropwise with stirring, and the yellow precipitate was isolated and washed repeatedly with water. The yield was 2.2 g. (21%) of material melting at 131–132°.

2-Methylthioethylamine Hydrochloride.—A mixture of 25.0 g. (0.58 mole) of ethyleneimine and 100 g. (0.48 mole) of methanethiol was placed in 200 ml. of alcohol in a large steel pressure reaction vessel and heated to 60° for 48 hr. The reaction vessel was opened and anhydrous hydrogen chloride was generated in for 30 min. The ethanol was distilled leaving a grayish white solid. The solid was recrystallized from ethanol–acetone to yield 43.0 g. (34%) of the desired compound; m.p. 146–148° (reported m.p.[15] 146–148°).

Ammonium 2-Methylthioethyldithiocarbamate.—Carbon disulfide (14 ml., 0.2 mole) and 44 ml. (0.64 mole) of concentrated ammonium hydroxide were placed in a flask which was immersed in an ice–rock salt bath. While this two-phase system was stirred, an aqueous solution containing 25.6 g. (0.2 mole) of 2-methylthioethylamine hydrochloride was slowly added by a dropping funnel over a period of 30 min. The grayish white precipitate was isolated, washed with ethanol, and dried by stirring the crystals rapidly on a sheet of drying paper, giving 26 g. (70%) of material melting at 104–106°. This compound was found to be unstable on exposure to air, losing ammonia and carbon disulfide within 24 hr.

Anal. Calcd. for $C_4H_{12}N_2S_3$: C, 26.09; H, 6.51; N, 15.27; S, 52.17. Found: C, 24.62; H, 6.91; N, 15.06; S, 51.38.

2-Diethylaminoethyltrithiocarbonate Zwitterion.—A solution of carbon disulfide (2 ml., 0.025 mole) and concentrated ammonium hydroxide (5.5 ml., 0.35 mole) was cooled, and a solution of 2-diethylaminoethanethiol hydrochloride (4.2 g., 0.1 mole) (Evans Chemetics, Inc.) in 5 ml. of water was added dropwise with stirring. A yellow product precipitated at once and was isolated, washed with water and ethanol, and allowed to dry. A yield of 4.7 g. (90%) was obtained, m.p. 114–115° (with effervescence). The compound was slightly soluble in ethanol, and reduced iodine solution, indicating that it is not a thiocarbonyl disulfide.

Anal. Calcd. for $C_7H_{15}NS_3$: C, 40.16; H, 7.22; N, 6.70; S, 45.94. Found: C, 40.74; H, 7.20; N, 6.76; S, 46.12.

2-Heptylthioethylammonium 2-Heptylthioethyldithiocarbamate.—Ethyleneimine (10 g., 0.23 mole) in 100 ml. of absolute ethanol and heptanethiol (33 g., 0.25 mole) (Eastman Organic Chemicals) were placed in a stainless steel pressure reactor and heated to 80° for 5 hr. The ethanol was distilled, leaving 39.0 g. (91%) of the oily amine. The product (8.8 g., 0.05 mole) was dissolved in 50 ml. of absolute ethanol, the solution was cooled, and 2.0 g. (0.025 mole) of carbon disulfide was added with stirring. After dilution with water, a pale yellow solid precipitated; it was washed with water and dried, giving 8.29 g. (76%); m.p. 48–50°.

Anal. Calcd. for $C_{19}H_{42}N_2S_4$: C, 53.50; H, 9.92; N, 6.56; S, 30.01. Found: C, 52.73; H, 9.75; N, 6.65; S, 29.88.

N-(2-Heptylthioethyl)-N′,N″-dicyclohexylguanidine.—Ethyleneimine (10 g., 0.23 mole) in 100 ml. of absolute ethanol, and heptanethiol (33 g., 0.25 mole) (Eastman Organic Chemicals) were placed in a stainless steel pressure reactor and heated to 80° for 5 hr. The product was isolated as in the previous case, and 17.5 g. (0.1 mole) of it, with dicyclohexylcarbodiimide (20.6 g., 0.1 mole) was placed in a glass-lined pressure reactor and heated at 100° for 6 hr. After the contents were cooled, 100 ml. of water was added and the mixture was boiled for 1 hr., and the insoluble dicyclohexylurea was removed. The resulting oil was separated, dissolved in dilute acid, and treated with dilute sodium hydroxide solution. A white precipitate (25.2 g., 66%) was obtained, m.p. 166–168°.

Anal. Calcd. for $C_{22}H_{43}N_3S \cdot H_2O$: C, 66.13; H, 11.33; N, 10.42; S, 8.00. Found: C, 67.13; H, 10.86; N, 9.26; S, 8.60.

N-(2-Heptylthioethyl)-N′,N″-dicyclohexylguanidinium N-(2-Heptylthioethyl)-N′,N″-dicyclohexylguanidinedithiocarbamate.—The previous compound (14.8 g., 0.05 mole) was distilled with excess carbon disulfide, giving a yellow solid which was recrystallized from ethanol–butanol (50:50). A white solid resulted in a yield of 4.8 g. (29%); m.p. 172–174°.

Anal. Calcd. for $C_{45}H_{86}N_6S_4$: C, 64.41; H, 10.33; N, 10.02; S, 15.25. Found: C, 63.63; H, 10.02; N, 10.34; S, 15.01.

Hydrolysis of N,S-Dioctanoyl-2-mercaptoethylguanidine.—N,S-Dioctanoyl-2-mercaptoethylguanidine hydrochloride (3.7 g., 0.009 mole) was dissolved in 15 ml. of absolute ethanol, a solution of 1.0 g. of sodium hydroxide in 5 ml. of water was added, and the solution was refluxed for 75 min. During this time 2-ml. samples were withdrawn at 15-min. intervals and treated with carbon disulfide and ammonium hydroxide, but no precipitation occurred. After the refluxing, the cooled gel was extracted with ether, which gave only a trace of oily residue after evaporation, and the residue was dissolved in water and treated with 4 ml. of carbon disulfide and 3 ml. of concentrated ammonium hydroxide. A copious precipitate of bright yellow solid was isolated which proved to be identical with 2-guanidinoethyltrithiocarbonate zwitterion, m.p. 138–140°.

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