N-Alicyclic-Substituted Derivatives of 2-Aminoethanethiol and Related Compounds as Antiradiation Agents†

Robert D. Elliott,* James R. Piper, Carl R. Stringfellow, Jr., and Thomas P. Johnston

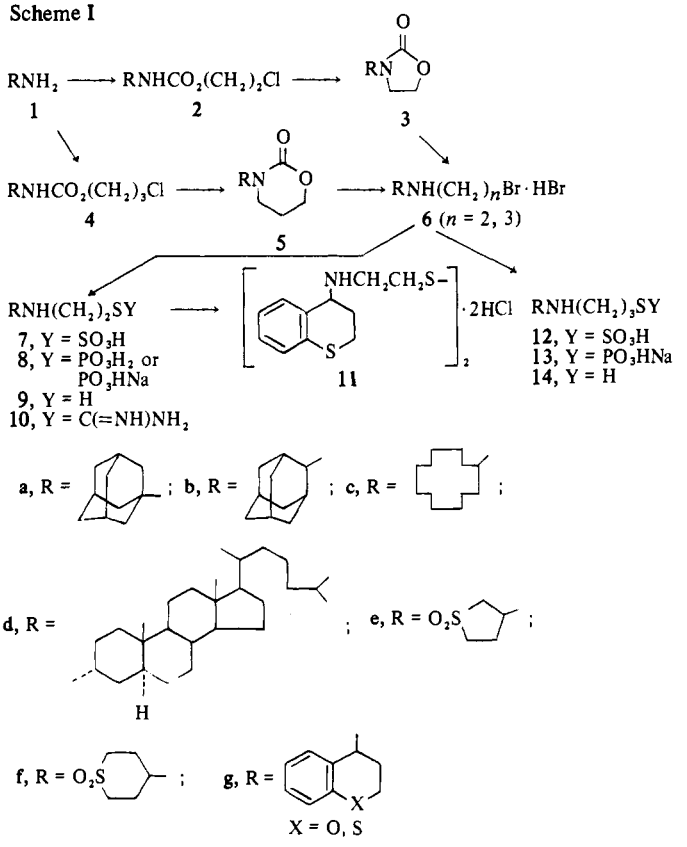
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205. *Received December 14, 1971*

A number of 2-aminoethanethiol derivatives, $RNH(CH_2)_2SY$, in which R is an alicyclic or heteroalicyclic group and SY is a suitable S function (*e. g.*, thiol, thiosulfate, or phosphorothioate), were synthesized for evaluation as antiradiation agents. The intermediate N-substituted 2-bromoethylamines were prepared from either 3-substituted 2-oxazolidinones derived from primary amines or N-substituted 2-aminoethanols derived from cyclic ketones. The adaptability of the first approach to the synthesis of 3-aminopropanethiol derivatives was demonstrated. Eight of the 38 compounds tested in mice by ip administration showed good radioprotection as judged by >45% 30-day survival; these compounds were the 1-adamantyl derivatives **7a** ($Y = SO_3H$) and **8a**·H_2O ($Y = PO_3H_2$); the 2-adamantyl derivative **7b** ($Y = SO_3H$); the cyclododecyl derivative **7c** ($Y = SO_3H$); the tetrahydro-2*H*-thiopyran-4-yl 1,1-dioxide derivative **7f** ($Y = SO_3H$); and the 2-bornyl derivatives **28**·HCl (Y = H), **29** ($Y = SO_3H$), and **30**·H_2O ($Y = PO_3HNa$). Of the active compounds, **8a**·H_2O rated best on the basis of indices relating dose and toxicity.

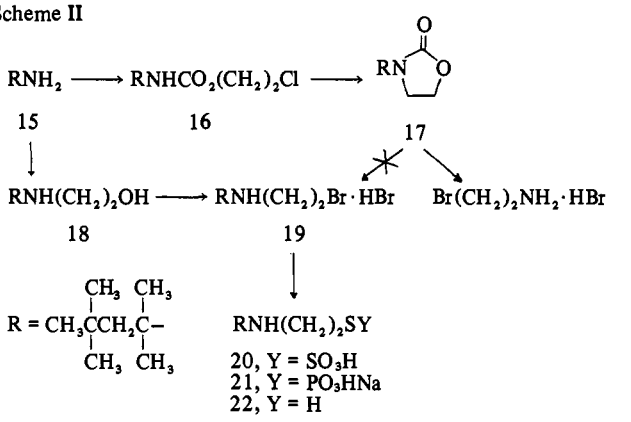
In the continuing search for effective modifications of known radioprotective agents, two general approaches were developed for the synthesis of derivatives of 2-aminoethanethiol and 3-aminopropanethiol in which the amino group is substituted by alicyclic or heteroalicyclic groups. The more versatile of the 2 routes, applicable to primary amines as illustrated in Scheme I, was based on reported 2-oxazolidinone ring closures[1-3] and dry HBr ring openings of 3-substituted 2-oxazolidinones.[4] The second route, applicable to cyclic ketones and illustrated in Scheme III, was suggested by the reported two-step conversion of 3-bromo-2-bornanone to 2-(2-bornylamino)ethanol;[5] but troublesome condensations (first step) limited its usefulness.

The acylation step in Scheme I was achieved with K_2CO_3 in Me_2CO [as in conversions leading to the 1-adamantyl derivatives **7-10a** and the thiochroman-4-yl derivatives **7-10g** (X = S)], Schotten-Baumann conditions (as in conversions leading to the tetrahydro-3-thienyl dioxide derivatives **7**, **8**, **10e**, and the tetrahydro-2*H*-thiopyran-4-yl dioxide derivatives **7-9f**) and excess amine in PhH (as in the conversion leading to the cyclododecyl derivatives **7-9c**). Oxazolidinone ring closure was effected with NaH in DMF;[6] oxazolidinone ring opening, with 30% dry HBr in AcOH.[4] Ring-opening conditions were modified so as to minimize cleavage of the ring C-N bond in the 1-adamantyl and thiochroman-4-yl series, but the problem of C-N cleavage was not overcome in the ring opening of 3-(4-chromanyl)-2-oxazolidinone (**3g**, X = O) because of inseparable mixtures. This undesired cleavage occurred even more readily with the related tertiary-branched, alkyl-substituted oxazolidinone **17**, whose treatment with limited amounts of dry HBr under mild conditions resulted in the isolation of good yields (77-86%) of 2-bromoethylamine·HBr. The target compounds **20-22** were obtained, however, by an alternative route involving hydroxyethylation of the amine **15**[7] (see Scheme II).

Scheme I



Scheme II



The end products were usually thiosulfates, phosphorothioates, and thiols with an occasional disulfide and isothiuronium salt. Acid hydrolysis[6,8] of phosphorothioates afforded the thiols **9a-c**, **9f**, and **9g** (X = S). A $FeCl_3$-catalyzed air oxidation of **9g** (X = S) in neutral aqueous solution afforded the disulfide **11**.

The use of 3-chloropropyl chloroformate[6] in the acylation step led to the cyclododecyl derivatives **12-14c** and demonstrated an effective access to 3-aminopropanethiol deriva-

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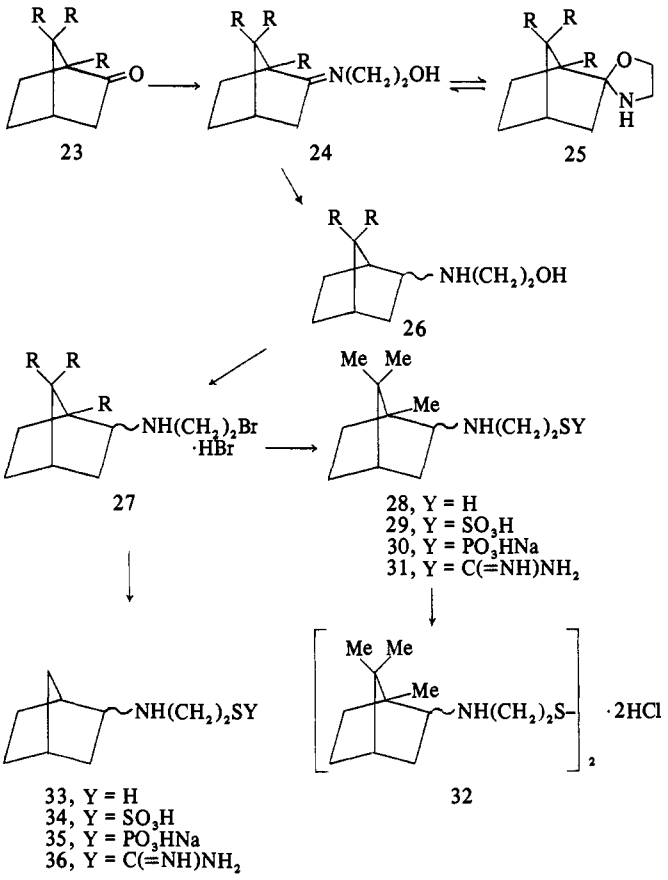
tives. The ring opening of 3-cyclododecyltetrahydro-2*H*-1,3-oxazin-2-one (**5c**) with dry HBr required heat, since this ring undergoes decarboxylative cleavage very slowly at ordinary temp. (Heat was used in the ring opening of the corresponding 2-oxazolidinone **3a** primarily to promote solubility.) In the case of the 1-adamantyl derivative **5a**, however, forcing conditions ruptured the bridgehead C-N bond more readily than the ring, the products being 1-bromoadamantane and 3-bromopropylamine·HBr.

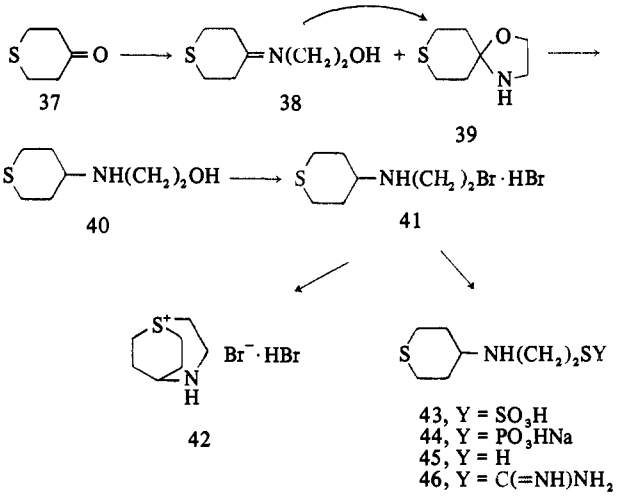
The condensation of *d*-camphor (**23**, R = Me) with 2-aminoethanol (Scheme III) in DMF at 96° (after unsuccessful trials in toluene) probably gave a mixture of the Schiff base **24** and the oxazolidine **25** (as indicated, in subsequent related examples, by ir spectral data[9]), the $NaBH_4$ reduction of which provided the aminoethanol **26** required in the synthesis of the 2-bornyl derivatives **28–32**. The condensation and reduction steps leading to the 2-norbornyl derivatives **33–36** were also troublesome. The thiols **28** and **33**, which were characterized as hydrochlorides, were obtained by direct displacement reactions with NaSH; acid hydrolysis of the thiosulfate **34** also gave **33**·HCl, but in low yield.

Scheme III



The tetrahydro-2*H*-thiopyran-4-yl derivatives **43–46** were prepared according to Scheme IV, which, in practice, was an adaptation of the second approach discussed above. The condensation of tetrahydro-4*H*-thiopyran-4-one (**37**) with 2-aminoethanol was effected in DMF in the presence of a molecular sieve, and the distilled product eventually crystallized with complete conversion of the Schiff base **38** to the oxazolidine **39**. Cortese treatment[10] of the aminoethanol **40** resulted in the formation of the cyclic sulfonium salt **42**, the structure proof of which involved the development of a convenient bromide ion determination (as AgBr) in the presence of a reactive C-Br covalent bond. The desired bromide **41** was subsequently obtained by the action of PBr_3 on **40**·HBr. Acid hydrolysis of the phosphorothioate **44** provided the thiol **45**.

Scheme IV



Antiradiation Evaluation. Radioprotective activity of these compounds in mice, as judged by test[11] results provided by Walter Reed Army Institute of Research was found to vary widely with the N substituent and, to a lesser degree, with the S substituent. Among the alicyclic derivatives administered ip, good protection (>45% 30-day survival) was observed with several adamantyl (**7a**, b; **8a**) and bornyl (**28–30**) derivatives and fair protection (**25–44%** survival) with norbornyl (**35**), adamantyl (**10a**·2HBr), and cyclododecyl (**7c**) derivatives; the cholestanyl derivative **7d** was only slightly protective. Among the S-containing heteroalicyclic derivatives, the good protection shown by one tetrahydro-2*H*-thiopyran-4-yl 1,1-dioxide derivative (**7f**) and slight protection by 2 others (**8f**, **9f**) contrasted sharply with the lack of protection observed with tetrahydro-3-thienyl *S,S*-dioxide (**7**, **8**, **10e**), thiocroman-4-yl (**7–10g**, X = S; **11**), and tetrahydro-2*H*-thiopyran-4-yl (**43–45**) derivatives. Thiosulfates (**7a–c, e**; **29**) provided more examples of good or fair protection than phosphorothioates (**8a**, **30**, **35**), and one thiol (**28**·HCl) showed good protection and one isothiuronium salt (**10a**·2HBr) fair protection. Of the compounds tested by oral administration (**7b, f**; **8a–c**; **13c**; **14c**; and **29**), all were nonprotective except **8a**, which was slightly protective.

Judged on the basis of protective and therapeutic indices, much of the radioprotection provided by appreciably active compounds of this series (Table I) was achieved at relatively high fractions of the LD_{50} dose. *S*-2-(1-Adamantylamino)ethyl dihydrogen phosphorothioate (**8a**) monohydrate showed the highest protective index‡ (12.5 for 79% survival, 18 for 29%) and therapeutic index (index defined by Westland, *et al.*[12]) (9.6) in the series.

Experimental Section§

ω-Chloroalkyl carbamates (Table II) were prepd by one of the representative procedures described below or by one similar as designated in the table.

‡An index used at Walter Reed Army Institute of Research to relate radioprotection with drug dose and toxicity: [[1 + (% survival/100)] × ~LD_{50} (mg/kg)]/dose (mg/kg).

§Melting points recorded without a range were determined with a Kofler Heizbank; those with a range, with a Mel-Temp apparatus. Ir spectra were determined with a Model 521 Perkin-Elmer spectrophotometer. Analytical results indicated only by element or function symbols were within ±0.4% of the theor values. Microanalyses were performed for the most part by Galbraith Laboratories, Knoxville, Tenn.

Procedure A. 2-Chloroethyl 1-Adamantanecarbamate (2a). A stirred mixt of **1a**·HCl (15.0 g, 80.0 mmoles), $ClCO_2(CH_2)_2Cl$ (12.8 g, 89.5 mmoles), anhyd K_2CO_3 (40.0 g, 0.290 mole), and Me_2CO (400 ml) was refluxed for 4.5 hr, cooled, and filtered. The solid on the funnel was retained for isolation of unchanged 1a. The filtrate was evapd, and the solid residue was stirred with H_2O and recrystd from EtOH–H_2O to give 8.2 g of pure **2a**. The solid filtered from the reaction mixt was stirred with H_2O (200 ml), and the insol solid (1a) was dried, and subjected again to the procedure described above, but with a prolonged reflux time (17 hr), to give addnl pure 2a (11.2 g).

Procedure B. 2-Chloroethyl Tetrahydro-2*H*-thiopyran-4-carbamate *S,S*-Dioxide (2f). $ClCO_2(CH_2)_2Cl$ (4.72 g, 33.0 mmoles) was added dropwise during 15–20 min to a stirred soln of 1f·HCl (5.72 g, 30.8 mmoles) and NaOH (2.70 g, 67.5 mmoles) in H_2O (100 ml) at ~25°. Stirring was contd 1 hr before the cryst 2f was collected and dried *in vacuo* (25°, P_2O_5).

Procedure C. 2-Chloroethyl Cyclododecanecarbamate (2c). A soln of $ClCO_2(CH_2)_2Cl$ (19.5 g, 0.136 mole) in PhH (200 ml) was added dropwise to a stirred soln of 1c (50.0 g, 0.272 mole) in PhH

Table I. Radioprotective Activities of Selected N-Substituted 2-Aminoethanethiol Derivatives, $RNH(CH_2)_2SY$[a]

No.	R	Y	Approx LD_{50}, mg/kg	Drug dose, mg/kg[b]	Preirradiation interval, min[c]	30-Day survival, %[d]	Protective index[e]	Approx ED_{50}, mg/kg[f]	Therapeutic index[g]
7a	1-Adamantyl	SO_3H	560	160	15	67	5.8	140	4.0
				80	30	50	10.5		
8a·H_2O	1-Adamantyl	PO_3H_2	560	80	30	79	12.5	54	9.6
				80	60	20	8.4		
				40	30	29	18.1		
10a·2HBr	1-Adamantyl	C(=NH)NH_2	240	90	15	33	3.5		
7b	2-Adamantyl	SO_3H	275	70	30	60	6.3	275	5.5
				70	60	27	5.0		
				35	30	20	9.4		
7c	Cyclododecyl	SO_3H	100	50	30	47	2.9	53	1.9
				50	60	27	2.5		
				35	30	20	3.4		
				35	60	60	4.6		
				25	30	33	5.3		
				17.5	30	27	7.3		
7f	Tetrahydro-2*H*-thiopyran-4-yl 1,1-dioxide	SO_3H	>800	500	30	67	2.7	430	1.9
				500	60	20	1.9		
28·HCl	2-Bornyl	H	74	56	30	67	2.2	50	1.5
29	2-Bornyl	SO_3H	430	80	30	60	8.6	72	6.0
				80	60	27	6.8		
30·H_2O	2-Bornyl	PO_3HNa	430	320	30	50	2.0	320	1.3
35	2-Norbornyl	PO_3HNa	240	90	30	33	3.5		

[a] Antiradiation tests in mice against lethal radiation [950 R (γ rays ^{60}Co) or 825 R (X-rays)]; tests results provided by Walter Reed Army Institute of Research, Washington, D. C.; results for 1,1,3,3-tetramethylbutyl derivatives 20–22 not included. [b] Ip injection of drug as 0.3–2.5% soln of pH 5–7.5, usually unadjusted; usual medium: physiological saline soln contng 0.3% methylcellulose and 0.1% Tween 80. [c] Time between drug admin and irradiation, 15 or 30 min in primary test. [d] No survival among control mice. [e] See footnote ‡. [f] Dose required for 50% survival estimated from log dose–probit survival plots. [g] See ref 12; calcd only for compds giving >45% survival.

Table II. ω-Chloroalkyl Carbamates

No.[a]	Procedure	Yield, %	Mp, °C	Formula	Analyses
2a	A	94[b]	85	$C_{13}H_{20}ClNO_2$	C, H, Cl
2b	A	88	82	$C_{13}H_{20}ClNO_2$	C, H, N
2c	C	83	136–137	$C_{15}H_{28}ClNO_2$	C, H, N
2d	A	36	120–122	$C_{30}H_{52}ClNO_2$	C, H, N
2e	B	81	102	$C_7H_{12}ClNO_4S$	C, H, N
2f	B	72	171	$C_8H_{14}ClNO_4S$	C, H, Cl, S
2g (X = O)	B	93	126	$C_{12}H_{14}ClNO_3$	C, H, N
2g (X = S)	A	93[b]	107	$C_{12}H_{14}ClNO_2S$	C, H, N
4a	B[c]	86	78–79	$C_{14}H_{22}ClNO_2$	C, H, N
4c	C	89	123–125	$C_{16}H_{30}ClNO_2$	C, H, N
16	B[d]	74		$C_{11}H_{22}ClNO_2$	C, H, N

[a] Starting amines not obtained from com sources prepd according to lit. procedures: 1d,[13] 1e·HCl,[14] 1f·HCl,[15] and 1g (X = O)·HCl.[16] [b] Total yield after recycling recovered unchanged 1. [c] Solns of 1a·HCl (in H_2O) and $ClCO_2(CH_2)_3Cl$ (in Me_2CO) were added dropwise and simultaneously to the stirred NaOH soln; remainder of procedure same as in example given. [d] The free amine 15 was used with proportionately less NaOH. An Et_2O ext of the reaction mixt was washed with 2 *N* HCl, dried ($MgSO_4$), and evapd at 100° *in vacuo* to an oil; $n^{24}D$ 1.4613.

Table III. 3-Substituted 2-Oxazolidinones and Tetrahydro-2*H*-1,3-oxazin-2-ones

No.	Recrystn solvent[a]	Yield, %	Mp, °C	Formula	Analyses
3a	A	99	124–125	$C_{13}H_{19}NO_2$	C, H
3b	A	85	90	$C_{13}H_{19}NO_2$	C, H, N
3c	B	57	105–106	$C_{15}H_{27}NO_2$	H, N; C[b]
3d	C	91	144–147	$C_{30}H_{51}NO_2$	H, N; C[c]
3e	D	74	107	$C_7H_{11}NO_4S$	C, H, N
3f	D	90	160–161	$C_8H_{13}NO_4S$	C, H, N
3g (X = O)	A, E	86	112	$C_{12}H_{13}NO_3$	C, H, N
3g (X = S)	E	92	157	$C_{12}H_{13}NO_2S$	C, H, N
5a	B	75	115–117	$C_{14}H_{21}NO_2$	C, H, N
5c	B	37	151–153	$C_{16}H_{29}NO_2$	C, H, N
17	A, E	86	75–76	$C_{11}H_{21}NO_2$	C, H, N

[a] A, cyclohexane; B, EtOH–H_2O; C, MeOH; D, EtOH; E, PhH. [b] C: calcd, 71.10; found, 70.62. [c] C: calcd, 78.72; found, 76.24.

Table IV. Bromoalkylamine Hydrobromides

No.	Yield, %	Mp, °C dec	Formula	Analyses
6a, *n* = 2	60	289–291	$C_{12}H_{20}BrN·HBr$	C, H, Br, N
6b, *n* = 2	69	306–307	$C_{12}H_{20}BrN·HBr$	C, H, N
6c, *n* = 2	94	227–228	$C_{14}H_{28}BrN·HBr$	C, H, N
6c, *n* = 3	93	248–250	$C_{15}H_{30}BrN·HBr$	C, H, N
6d, *n* = 2	35	304–308	$C_{29}H_{52}BrN·HBr$	C, H, N
6e, *n* = 2	80	115–116	$C_6H_{12}BrNO_2S·HBr$	C, H, N
6f, *n* = 2	100	215–216	$C_7H_{14}BrNO_2S·HBr$	C, H, N
6g (X = S), *n* = 2	55	187	$C_{11}H_{14}BrNS·HBr$	C, H, N
19	80	200	$C_{10}H_{22}BrN·HBr$	C, H, N
27 (R = Me)	92	268–269	$C_{12}H_{22}BrN·HBr$	C, H, N
27 (R = H)	69	253–254	$C_9H_{16}BrN·HBr$	C, H, Br, N
41	51	201	$C_7H_{14}BrNS·HBr$	C, H, Br, N

(500 ml) kept at 25–30°. The mixt was stirred at ~25° for 1 hr longer, then refluxed 1 hr, cooled, and filtered from 1c·HCl. The clear filtrate was evapd to ~350 ml and then dild with ligroin (bp 30–60°) (~150 ml). The refrigd mixt deposited pure 2c.

3-Substituted 2-oxazolidinones and tetrahydro-2*H*-1,3-oxazin-2-ones (Table III) were prepd by the following general procedure. A soln of the appropriate 2 or 4 in DMF (200–300 ml/0.1 mole) was added dropwise to a stirred suspension of NaH (dispersion in oil, amt equimolar with 2 or 4) in DMF (~50 ml/0.1 mole) kept at ~25°. The mixt was stirred ~18 hr, filtered, and evapd *in vacuo*; the residue was recrystd from the indicated solvent.

N-(ω-Bromoalkyl)amine hydrobromides (Table IV) were prepd by the following procedures.

A. *N*-(2-Bromoethyl)-1-adamantanamine Hydrobromide (6a, $n = 2$). A soln of 3a (10.0 g, 45.3 mmoles) in 5% dry HBr–AcOH soln, prepd by diln of 30% dry HBr–AcOH (50 g) with glac AcOH (250 g), was immersed in a bath at 78°, kept at 78–80° for 1 hr, and then cooled rapidly to 20–25°. The cryst ppt was collected with the aid of AcOH, washed with Et_2O, and dried *in vacuo* (77°, P_2O_5) to give 8.31 g of crude product. The Et_2O-dild filtrate deposited addnl impure solid (3.21 g). The combined crops were stirred 10 min with H_2O (50 ml) at ~90° in order to remove $Br(CH_2)_2NH_2 \cdot HBr$. Pure 6a ($n = 2$), which was filtered from the cooled aqueous mixt and dried *in vacuo* (77°, P_2O_5), amounted to 8.06 g, and concn of the aqueous filtrate gave an addnl crop (0.82 g). Evapn of the Et_2O-dild filtrate from the reaction mixt and extn of the dark residue with Et_2O left insoluble solid (1.08 g), which was recrystd from H_2O to give another small amount of product (0.25 g). The final Et_2O filtrate was evapd and the dark semisolid residue was sublimed under reduced pressure (H_2O aspirator, bath at 80–90°) to give 1-bromoadamantane (1.83 g, 19% yield), mp 116–118° (lit.[17] mp 118°).

B. *N*-(ω-Bromoalkyl)cyclododecylamine Hydrobromides (6c, $n = 2,3$). A mixt of 3c (or 5c for the prepn of 6c, $n = 3$) in 30% dry HBr–AcOH (2.5 ml/mmole of 3c or 5c) was gradually heated during 1.5–2 hr to boiling and refluxed 1 hr. The cooled soln was dild with Et_2O and the cryst product was washed with Et_2O and dried *in vacuo* (100°, P_2O_5).

C. *N*-(2-Bromoethyl)-2-adamantanamine hydrobromide (6b, $n = 2$), *N*-(2-bromoethyl)tetrahydro-3-thiophenamine 1,1-dioxide hydrobromide (6e, $n = 2$), and *N*-(2-bromoethyl)tetrahydro-2*H*-thiopyran-4-amine 1,1-dioxide hydrobromide (6f, $n = 2$) were prepd by treatment of the appropriate 3 with 30% dry HBr–AcOH (2 ml/mmole of 3) at 25–30°; resp reaction times (hr) were: 84 (3b), 44 (3e), and 48 (3f). Products were isolated as in part B, but 6e ($n = 2$) was recrystd twice from EtOH.

D. *N*-(2-Bromoethyl)thiochroman-4-amine Hydrobromide (6g, X = S, $n = 2$). A soln of 3g (X = S) (45.2 g, 0.192 mole) in glac AcOH (800 ml) was treated with 30% dry HBr–AcOH (98 ml), and the resulting soln was heated at 80° until CO_2 evolution had ceased (~45 min). The cryst product, which sepd from the cooled soln, was washed with AcOH and then Et_2O and dried *in vacuo* (25–30° P_2O_5).

E. *N*-(2-Bromoethyl)-5α-cholestan-3α-amine Hydrobromide (6d, $n = 2$). A soln of 3d (6.40 g, 14.0 mmoles) in glac AcOH (50 ml) and 30% dry HBr–AcOH (50 ml) was stirred at 25–30° for 64 hr. Addn of Et_2O caused sepn of cryst product, which was recrystd from EtOH.

F. *N*-(2-Bromoethyl)-1,1,3,3-tetramethylbutylamine Hydrobromide (19). A soln of 18 (50.0 g, 288 mmoles) in Et_2O (1.45 l.) was treated with 30% dry HBr–AcOH (75.7 ml) and refrigd to give cryst 18·HBr. A mixt of the dry hydrobromide and PBr_3 (142 ml) was refluxed under N_2 for 18 min, cooled to 25°, and stirred with Et_2O (300 ml). Recrystn of the crude ppt from EtOH (300 ml) gave pure 19.

G. *N*-(2-Bromoethyl)tetrahydrothiopyran-4-amine hydrobromide (41) was prepd from 40 (182 mmoles) by procedure F except that the 40·HBr was stirred with PBr_3 (100 ml) at 100° for 45 min and the resulting crude 41 was recrystd from 48% HBr (145 ml).

H. *N*-(2-Bromoethyl)bornylamine Hydrobromide (27, R = Me) and *N*-(2-Bromoethyl)-2-norbornanamine Hydrobromide (27, R = H). A soln of 26 (10 mmoles) in 48% HBr (10 ml) was evapd to dryness (H_2O aspirator). The residue was redissolved in 48% HBr (56 ml) and concd to ~6 ml by the intermittent distn procedure of Cortese.[10] The reaction mixt was refrigd; the cryst ppt was washed with cold EtOH and dried *in vacuo* (P_2O_5).

S-Substituted Hydrogen Thiosulfates (Table V). General Procedure. $Na_2S_2O_3 \cdot 5H_2O$, in solid form or in aqueous soln, was added to a hot soln of an equimolar amt of the appropriate bromoalkylamine hydrobromide in H_2O or, in some cases, H_2O contg EtOH. (Amts and the total vol of solvents used are given in the table.) The mixt was heated at ~90° for ~30 min. Products generally crystd from the mixt and required no further purification. Compd 7c was prepd in an analogous manner from 6c ($n = 2$) and $MgS_2O_3 \cdot 6H_2O$ in boiling MeOH (1-hr reflux).

Table V. S-Substituted Hydrogen Thiosulfates

No.	Scale, mmoles	Amt of H_2O, ml	Yield, %	Mp, °C dec	Formula[a]
7a	11.8	70	94	238–240	$C_{12}H_{21}NO_3S_2$
7b	10.0	80[b]	94	255	$C_{12}H_{21}NO_3S_2$
7c	10.8[c]	30[d]	77	215–216	$C_{14}H_{29}NO_3S_2$
7d	4.55	75[b]	60	225–226	$C_{29}H_{33}NO_3S_2$
7e	10.0	20[e]	77	222	$C_6H_{13}NO_5S_3$
7f	11.0	11[e]	86	210–211	$C_7H_{15}NO_5S_3$
7g (X = S)	10.0	40	86	207	$C_{11}H_{15}NO_3S_3$
12c	10.3	320	91	215–216	$C_{18}H_{31}NO_3S_2$
20	31.5	90[b]	80	188	$C_{10}H_{23}NO_3S_2$
29	10.0	30[b]	79	245	$C_{12}H_{23}NO_3S_2$
34	15.0	25	81	245	$C_9H_{17}NO_3S_2$
43	16.4	20	76	201–202	$C_7H_{15}NO_3S_2$

[a] *Anal.* C, H, N, S. [b] Milliliters of EtOH added to promote solubility of reactant: 2 (7b), 50 (7d), 4 (20), and 15 (29). [c] $MgS_2O_3 \cdot 6H_2O$ used instead of $Na_2S_2O_3 \cdot 5H_2O$. [d] MeOH used instead of H_2O. [e] Product crystd after addn of EtOH (~100 ml).

N-Substituted 2-aminoethanethiol hydrohalides (Table VI) were prepd by the following general procedures.

Method A. A mixt of the appropriate phosphorothioate and 3 *N* HBr or HCl was stirred at 90–100° for 5–10 min and refrigd (9f was dild with EtOH before cooling). The cryst product was recrystd and dried *in vacuo* (P_2O_5).

Method B. A soln of NaOMe (2.05 mmoles/mmole of 19 or 27) in MeOH (~3 ml/mmole of NaOMe) was satd with H_2S at −20°, treated in small portions with the appropriate bromide (19 or 27), and stirred until the temp rose to 0°. The soln was kept at 0° in a tightly stoppered flask for 18 hr and evapd to dryness *in vacuo* (H_2O aspirator). A filtered $CHCl_3$ soln of the residue was concd *in vacuo* and distd (Claisen head) to give the aminothiol [22, bp 77–79° (1.8 mm); 28, bp 70° (0.08 mm); 33, bp 56° (0.07 mm)], which was converted to a cryst hydrochloride by treatment in Et_2O with

Table VI. N-Substituted 2-Aminoethanethiol Hydrohalides

No.	Method	Scale, mmoles	Amt of 3 *N* HX in method A, ml	Recrystn solvent	Yield, %	Mp, °C	Formula[a]
9a·HCl	A	9.28	115		88	243–244 dec	$C_{12}H_{21}NS \cdot HCl$[b]
9b·HBr	A	19.6	33		91	>260	$C_{12}H_{21}NS \cdot HBr$
9c·HBr	A	8.33	75	EtOH–Et_2O	86	216–218 dec	$C_{14}H_{29}NS \cdot HBr$
9f·HCl[c]	A	3.50	3	MeOH	37	204–205 dec	$C_7H_{15}NO_2S_2 \cdot HCl$
9f·HCl[d]	A	9.16	10	MeOH	79	206–207 dec	$C_7H_{15}NO_2S_2 \cdot HCl$[e]
9g (X = S)·HBr	A	23.3	20	EtOH	81	197	$C_{11}H_{15}NS_2 \cdot HBr$
14c·HBr	A	11.6	100	*i*-PrOH–Et_2O	66	200 dec	$C_{15}H_{31}NS \cdot HBr$
22·HCl	B	63.1			45	~199[f]	$C_{10}H_{23}NS \cdot HCl$
28·HCl	B	14.7			39	260 dec	$C_{12}H_{23}NS \cdot HCl$
33·HCl[g]	B	23.4			53	205	$C_9H_{17}NS \cdot HCl$
45·HBr	A	15.0	11		80	196	$C_7H_{15}NS_2 \cdot HBr$[b]

[a] *Anal.* C, H, N, S, SH. [b] % SH could not be detd iodometrically. [c] *Anal.* C, H, N only. [d] From 8f (Y = PO_3H_2). [e] From 8f (Y = PO_3HNa). [f] Detd with Mettler FP1 apparatus. [g] 33 was also prepd in 5% yield by hydrolysis of 34 in refluxing 4 *N* HCl.

Table VII. S-Substituted Thiopseudoureas

No.	Yield, %	Mp, °C	Formula	Analyses
10a	75	>260	$C_{13}H_{23}N_3S \cdot 2HBr$	C, H, Br, N, S
10e	84	~241	$C_7H_{15}N_3O_2S_2 \cdot 2HBr$	C, H, N, S
10g	80	~159	$C_{12}H_{17}N_3S_2 \cdot 2HBr$	C, H, N, S
31	83	~256	$C_{13}H_{25}N_3S \cdot 2HBr$	C, H, N, S
36	61	226–227	$C_{10}H_{19}N_3S \cdot 2HBr$	C, H, N, S
46	81	259–261	$C_8H_{17}N_3S_2 \cdot 2HBr$	C, H, N, S

dry HCl–EtOH. The product was washed with Et_2O and dried *in vacuo* (P_2O_5).

S-Substituted Thiopseudoureas (Table VII). A soln of equimolar amts of thiourea and $RNH(CH_2)_2Br \cdot HBr$ in EtOH (2 ml/mmole of thiourea) was refluxed 30 min. The cooled soln deposited pure crystn product.

***S*-2-(1-Adamantylamino)ethyl Dihydrogen Phosphorothioate (8a) Monohydrate.** The mixt obtained from addn of powd 6a (n = 2) (3.00 g, 8.85 mmoles) to a soln of Na_3PSO_3 (1.59 g, 8.83 mmoles) in H_2O (40 ml) was stirred at 25–30° for 2 hr, treated with DMF (20 ml), and stirred 1 hr longer. Complete soln did not occur. EtOH (150 ml) was added, and the solid was collected, washed with EtOH, suction dried, and then stirred into H_2O (40 ml). The resulting nearly clear soln was filtered through Celite, and the filtrate was treated with AcOH (0.60 g). Gradual sepn of cryst (needles) 8a occurred, and, after refrign, the product was collected, washed with cold H_2O, and dried *in vacuo* (25–30°, P_2O_5); yield 64% (1.75 g), mp 162–164°. *Anal.* ($C_{12}H_{22}NO_3PS \cdot H_2O$) C, H, N, S; P: calcd, 10.01; found, 10.6.

***S*-2-(2-Adamantylamino)ethyl Sodium Hydrogen Phosphorothioate (8b).** Powd 6b (n = 2) (3.39 g, 10.0 mmoles) was added in small portions to a stirred mixt of Na_3PSO_3 (1.80 g, 10.0 mmoles) and H_2O (40 ml) at 10°. The mixt was treated dropwise with DMF (20 ml) and EtOH (20 ml), stirred at 25° for 1 hr, dild with DMF (50 ml), and stirred for 30 min longer. The cryst product was washed successively with cold DMF–H_2O (3:1), DMF, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 2.96 g (96%), mp indef. *Anal.* ($C_{12}H_{21}NNaO_3PS$) C, H, N, P, S.

***S*-2-(Tetrahydro-3-thienylamino)ethyl Sodium Hydrogen Phosphorothioate *S,S*-Dioxide (8e) Monohydrate.** Powd 6e (n = 2) (3.23 g, 10.0 mmoles) was added in small portions to a stirred mixt of Na_3PSO_3 (1.80 g, 10.0 mmoles) in H_2O (15 ml) at 10°. The mixt was stirred at 25° for 1.5 hr, treated dropwise with DMF (5 ml) and stirred for 30 min, and finally dild with EtOH (5 ml) and stirred for 30 min. The cryst product was washed successively with 1:1 EtOH–H_2O, cold EtOH, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 2.83 g (90%), mp indef. *Anal.* ($C_6H_{13}NNaO_5PS_2 \cdot H_2O$) C, H, N, P, S.

***S*-2-(Tetrahydrothiopyran-4-ylamino)ethyl Dihydrogen Phosphorothioate *S,S*-Dioxide (8f) Sesquihydrate.** Solid 6f (n = 2) (6.74 g, 20.0 mmoles) was added to a stirred mixt of Na_3PSO_3 (3.60 g, 20.0 mmoles) in H_2O (20 ml), and, after soln had occurred, DMF (10 ml) was added. After ~10 min, product sepn occurred. EtOH (250 ml) was added, and the solid was collected and repptd from H_2O soln by addn of EtOH. The air-dried, white solid (hydrated Na salt of 8f, 6.36 g) analyzed unsatisfactorily. *Anal.* ($C_7H_{15}NNaO_5PS_2 \cdot 2.5H_2O$) C, N, P; H: calcd, 5.66; found, 4.82; S: calcd, 18.00; found, 19.06. A portion (2.95 g) of this material was dissolved in H_2O (6 ml), and the clarified (Norit, Celite) soln was treated with AcOH (6 ml). The cryst 8f that sepd from the refrigd soln was washed successively with cold H_2O–AcOH (1:1), EtOH, and Et_2O, and was then air-dried; yield 2.35 g, mp 170–171°. *Anal.* ($C_7H_{16}NO_5PS \cdot 1.5H_2O$) C, H, N, P, S. The remainder of the impure Na salt was successfully converted to the thiol 9f.

***S*-2-Cyclododecylaminoethyl Sodium Hydrogen Phosphorothioate (8c) Hydrate.** A warm (~35°) soln of 6c (n = 2) (3.71 g, 10.0 mmoles) in H_2O (50 ml) and EtOH (50 ml) was added to a stirred soln of Na_3PSO_3 (1.80 g, 10.0 mmoles) in H_2O (25 ml). The resulting soln was kept at 25–30° for 10 min, filtered, and treated with DMF (300 ml). Cryst 8c sepd as the mixt was refrigd overnight. The collected ppt was washed successively with DMF and Et_2O, then air-dried; yield 92% (3.74 g). *Anal.* ($C_{14}H_{29}NNaO_3PS \cdot 3.5H_2O$) C, N, P, S; H: calcd, 8.88; found, 8.38.

***S*-2-(Thiochroman-4-ylamino)ethyl Sodium Hydrogen Phosphorothioate (8g, X = S).** A stirred mixt of Na_3PSO_3 (1.80 g, 10.0 mmoles) and H_2O at 10° was treated successively, in small portions, with powd 6g (n = 2, X = S) (3.53 g, 10.0 mmoles), DMF (5 ml), and EtOH (5 ml), stirred at 25° for 1 hr, and then dild with EtOH (10 ml). The cryst product was washed successively with cold EtOH–H_2O (2:1), cold EtOH, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 2.68 g (82%), mp indef. *Anal.* ($C_{11}H_{15}NNaO_3PS_2$) C, H, N, P, S.

***N,N'*-(Dithiodiethylene)di(thiochroman-4-amine) Dihydrochloride (11).** A mixt of 9g·HBr (X = S) (3.81 g, 12.4 mmoles), 1 *N* NaOH (12.4 ml), $FeCl_3$ (~0.5 mg), and H_2O (20 ml) was stirred in contact with air for 2 weeks. An Et_2O ext of the reaction mixt (nitroprusside-negative) was washed with H_2O, dried ($MgSO_4$), and evapd *in vacuo* to a gum, a soln of which in EtOH (25 ml) was treated with dry HCl–EtOH (2.45 *N*, 12.3 ml) and then Et_2O (100 ml). The pptd 11 was washed with Et_2O and dried *in vacuo* (P_2O_5); yield 2.84 g (88%), mp indef. *Anal.* ($C_{22}H_{28}N_2S_4 \cdot 2HCl$) C, H, N, S.

***S*-3-Cyclododecylaminopropyl Sodium Hydrogen Phosphorothioate (13c) Hydrate.** Na_3PSO_3 (1.80 g, 10.0 mmoles) was dissolved in H_2O (100 ml); EtOH (50 ml) and DMF (10 ml) were then added. Powd 6c (n = 3) was gradually added in portions during 15 min, the mixt being stirred until a clear soln was obtained (~4 hr). Cryst 13c sepd when the soln was poured into EtOH (400 ml) and, after refrign, was collected, washed with a small amt of cold H_2O, and air-dried; yield 60% (2.65 g). *Anal.* ($C_{15}H_{31}NNaO_3PS \cdot 4.5H_2O$) C, H, N, P, S.

***S*-2-(1,1,3,3-Tetramethylbutylamino)ethyl Sodium Hydrogen Phosphorothioate (21) Monohydrate.** A stirred suspension of Na_3PSO_3 (3.60 g, 20.0 mmoles) in H_2O (60 ml) at 10° was treated successively in small portions with 19 (6.34 g, 20.0 mmoles), EtOH (30 ml), and DMF (30 ml). The mixt was stirred at 25° for 4 hr, cooled to 10°, dild with DMF (40 ml), and stirred for 10 min longer. The cryst product was washed successively with cold DMF–H_2O (5:3), cold DMF, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 5.43 g (88%), mp indef. *Anal.* ($C_{10}H_{23}NNaO_3PS \cdot H_2O$) C, H, N, P, S.

2-(2-Bornylamino)ethanol (26, R = Me) Hydrochloride. A soln of 23 (R = Me) (100 g, 658 mmoles), 2-aminoethanol (250 ml), and DMF (100 ml) was heated at 96° for 3 days and evapd to dryness (H_2O aspirator). A soln of the residue in EtOH (500 ml) was treated in small portions with $NaBH_4$ (62.3 g, 1.65 mole), stirred for 1 hr, and refluxed for 1.5 hr. The mixt was acidified with 6 *N* HCl, then made basic with 50% NaOH, and extd continuously with Et_2O for 18 hr. The ext was washed with a small amt of H_2O, dried ($MgSO_4$), treated with concd HCl (60 ml), and evapd to dryness (H_2O aspirator). Crystn of the residue from EtOH gave a 42% yield of 26·HCl (R = Me), mp 269–272° (lit.[5] mp 271–272°). ***S*-2-(2-Norbornylamino)ethanol (26, R = H),** prepd similarly, was fractionally distd; yield 18% [18.4 g from 0.659 mole of 23 (R = H)], bp 70–80° (0.12 mm), $n^{24}D$ 1.5018. *Anal.* ($C_9H_{17}NO$) C, H, N.

***S*-2-(2-Bornylamino)ethyl Sodium Hydrogen Phosphorothioate (30).** A stirred soln of Na_3PSO_3 (2.64 g, 14.7 mmoles) in H_2O (45 ml) and EtOH (45 ml) at 10° was treated in small portions with 27 (R = Me) (5.00 g, 14.7 mmoles) and stirred at 25° for 1.5 hr. The resulting soln was concd to ~35 ml *in vacuo* (rotary evaporator), filtered, and dild with DMF (25 ml) at 0°. The cryst product was washed successively with cold 3:2 DMF–H_2O, DMF, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 2.47 g (51%), mp indef. *Anal.* ($C_{12}H_{23}NNaO_3PS \cdot H_2O$) C, H, N, P, S.

2,2'-Dithiobis[*N*-(2-bornyl)ethylamine] Dihydrochloride (32). A mixt of 27 (R = Me) (2.12 g, 8.50 mmoles), 1 *N* NaOH (8.50 ml, 8.50 mmoles), $FeCl_3$ (~0.1 mg), EtOH (10 ml), and H_2O (10 ml) was stirred in contact with air for 5 days. An ext of the reaction mixt (nitroprusside-negative) with Et_2O (50 ml) was dried ($MgSO_4$), treated with 3.6 *N* dry HCl–EtOH (3.00 ml), stirred for 16 hr, and refrigd. The pptd 32 was dried *in vacuo* (P_2O_5); yield 1.95 g (92%), mp 261° dec. *Anal.* ($C_{24}H_{44}N_2S_2 \cdot 2HCl$) C, H, N, S.

***S*-2-(2-Norbornylamino)ethyl Sodium Hydrogen Phosphorothioate (35).** A stirred suspension of Na_3PSO_3 (3.01 g, 16.7 mmoles) in H_2O (34 ml) and EtOH (8 ml) at 10° was treated in small portions with 27 (R = H) (5.00 g, 16.7 mmoles), stirred at 25° for 2 hr, filtered, and dild with DMF (34 ml) at 0°. The cryst product was washed successively with cold 3:2 DMF–H_2O, cold DMF, and Et_2O, and was dried *in vacuo* (P_2O_5); yield 4.01 g (88%), mp indef. *Anal.* ($C_9H_{17}NNaO_3PS$) C, H, N, P, S.

1-Oxa-8-thia-4-azaspiro[4.5]decane (39). A soln of 37 (46.8 g, 0.403 mole) and 2-aminoethanol (46.8 g, 0.765 mole) in DMF (90 ml) was stirred with Linde 3A Molecular Sieve (18 g) under N_2 at 81° for 24 hr. The soln was filtered, heated with fresh molecular sieve (20 g) at 81° for 40 hr, cooled to 25°, filtered, and concd (rotary evaporator). Fractional distn of the oily residue gave a 76% yield of a syrup, bp 70–75° (0.13 mm), $n^{24}D$ 1.5383, which was indicated by ir to be a mixt of the Schiff base 38 and the oxazolidine 39, absorption at 1670 cm^{-1} being assigned to 38 and triplet

absorption[9] at 1340 cm^{-1} to 39. *Anal.* ($C_7H_{13}NOS$) C, H, N. The oily mixt eventually crystd with apparently complete conversion to 39, mp ~28–31°.

2-(Tetrahydrothiopyran-4-ylamino)ethanol (40). A soln of 39 (34.5 g, 0.217 mole) in MeOH (150 ml) at 0° was treated with $NaBH_4$ (8.20 g, 0.217 mole) and worked up as in the prepn of 26 (R = Me). Evapn of the Et_2O ext up to 100° (H_2O aspirator) left a residue of cryst 40; yield 32.1 g (92%), mp 53–54°. *Anal.* ($C_7H_{15}NOS$) C, H, N.

1-Thionia-4-azabicyclo[3.2.2]nonane Bromide Hydrobromide (42). A soln of 40 (26.5 g, 161 mmoles) and 48% HBr (1 l.) was distd slowly over a period of 18 hr until 925 ml of distillate was collected. The residue was refrigd, and the cryst 42 was collected, washed with EtOH, and dried *in vacuo* (P_2O_5); wt 14.2 g, mp 254° dec. The above-described distn was repeated on the concd filtrate dissolved in 48% HBr (500 ml) to give addl 42 (11.0 g), mp 254° dec; total yield 51%. *Anal.* ($C_7H_{14}BrNS \cdot HBr$) C, H, N, S.

Br^- Determination. Analysis of 42 and *N*-(2-Bromoethyl)amine Hydrobromides. A soln of $AgNO_3$ (340 mg, 2.00 mmoles) in 2 *N* HNO_3 (5 ml) was added to a soln of 42 (305 mg, 1.00 mmoles) in 2 *N* HNO_3 (10 ml). The mixt was swirled for 1 min. The AgBr was collected by filtration in the dark, washed with 2 *N* HNO_3 and then EtOH, and dried *in vacuo* (P_2O_5); yield 379 mg (2.02 Br^- per mole).

The utility of this detn for distinguishing ionic from covalent Br was demonstrated by reactions of 6g (*n* = 2, X = S) with 2 $AgNO_3$ to give 1.01 AgBr, 27 (R = Me) with 2 $AgNO_3$ to give 1.08 AgBr, and *N,N'*-bis(2-bromoethyl)ethylenediamine dihydrobromide[8a] with $AgNO_3$ to give 2.03 AgBr.

***S*-2-(Tetrahydro-2*H*-thiopyran-4-ylamino)ethyl Sodium Hydrogen Phosphorothioate (44).** A stirred suspension of Na_3PSO_3 (2.36 g, 13.1 mmoles) in H_2O (26 ml) at 10° was treated in small portions with 41 (4.00 g, 13.1 mmoles), stirred 30 min, treated dropwise with *N,N*-dimethylacetamide (DMAC) (13 ml) at 10°, stirred at 25° for 2 hr, and filtered. Dropwise addn of DMAC (39 ml) to the filtrate at 0° gave a cryst product, which was washed successively with cold DMAC–H_2O (2:1), DMAC, and Et_2O, and dried *in vacuo* (P_2O_5); yield 3.33 g (91%), mp indef. *Anal.* ($C_7H_{15}NNaO_3PS_2$) C, H, N, P, S.

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Optically Active Dithiothreitol. Toxicity and Radiation-Protective Activity

Marvin Carmack,* Charles J. Kelley,† Steadman D. Harrison, Jr.,‡

Chemistry Laboratories, Indiana University, Bloomington, Indiana 47401

and Kenneth P. DuBois§

Toxicity Laboratory, The University of Chicago, Chicago, Illinois 60637. *Received October 4, 1971*

The optical isomers of dithiothreitol (DTT) (Cleland's reagent) and their oxidized forms were prepared from L_g-(+)- and D_g-(−)-tartaric acid by an improved procedure, and their toxicity and radiation-protective activity were investigated in mice. The LD_{50} (mg/kg) of D_g-DTT is 255 compared to 179 and 169 for L_g-DTT and *rac*-DTT, respectively. The radiation-protective activity of D_g-DTT (60, 120, 150, and 200 mg/kg) was determined in mice exposed to X-radiation (600, 625, 700, and 750 R). Administration of 200 mg/kg of D_g-DTT ip increased survival at the end of 30 days by 50% in mice exposed to 650 R. Comparable studies on L_g-DTT show that this enantiomer affords no protection. The oxidized forms of D_g- and L_g-DTT were less toxic (LD_{50} = 435 and 410 mg/kg, respectively) and exhibited no protective activity (200 and 300 mg/kg against 625, 650, and 750 R). This work indicates that attention should be given to molecular asymmetry in designing more potent, selective, and less toxic radiation-protective agents, and in investigating their mechanisms of action.

Research on the development of radiation-protective compounds and the elucidation of their mechanisms of action has been reviewed recently.[1-3] Little work has been reported in which the importance of molecular asymmetry in a protective agent was evaluated. In one study, Doherty and Shapira[4] reported that D_s-2-aminobutylisothiourea dihydrobromide is twice as protective against X-radiation in the mouse as the L_s enantiomer. Foye[2] points out that more information on the comparative activity of the enantiomers of optically active radiation-protective agents would allow one to assess the importance of stereochemistry in radiation protection.

Falconi, *et al.*,[5-7] have reported that *rac*-dithiothreitol

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