colored oil. Attempts to crystallize this material were not successful. Paper and thin-layer chromatography of the material, however, revealed a single radioactivity zone in each case corresponding to the mobility of the hydroxypropyl metabolites and several fluorescence-quenching zones which were not radioactive. The oily material was taken up in Et_2O and the soln was subjected to preparative tlc on a 20 × 20 cm film of silica gel§ 2-mm thick. The silica gel corresponding to the zone of radioactivity was removed from the plate and eluted with four 10-ml portions of Me_2CO. The residue obtained upon evapn of the Me_2CO was recrystd once from Et_2O and once from EtOH–H_2O with the aid of charcoal (Darco G-60) to obtain 0.036 g of white solid material. The uv and ir spectra corresponded to those of IV, although there was a weak peak at 1045 cm^{-1} in the ir attributable to a primary alcohol. Paper and thin-layer chromatography revealed a single fluorescence quenching and radioactivity zone in each case corresponding to the mobility of IV. *Anal.* ($C_{10}H_{13}N_2O_4ClS$) C, H, N.

The nmr spectrum of the material was obtained†† and compared to those of chlorpropamide and IV. Instead of the Me-hydrogen triplet at δ 0.80 and the methylene absorption at 1.45, observed for chlorpropamide, this material gave a doublet at 1.06, typical of IV and a quintet at 1.62 attributable to a 3-hydroxypropyl metabolite, 1-[(*p*-chlorophenyl)sulfonyl]-3-(3-hydroxypropyl)urea (V). The ratio of areas under the δ 1.06 and 1.62 peaks indicated the material was a mixt of 75% IV and 25% V.

Analysis of the material by glc confirmed that the product was a mixt of the 2 isomers, 76% IV and 24% V.

††A 2.0-mg sample of the material in 0.4 ml of acetone-d_6 was employed. The spectrum was an average of 233 scans employing a Varian C-1024 time-averaging computer attached to a Varian HA-100 nmr spectrometer.

Acknowledgments. We are indebted to members of the Physical and Analytical Chemistry Unit for the analytical results reported and to Dr. H. L. Oster for clinical aspects of this study. Special thanks are due Dr. G. Slomp and Mr. J. F. Zieserl for detg the location of the hydroxyl group in the hydroxypropyl metabolites by micro-nmr techniques and Dr. D. G. Kaiser for helping develop the gas chromatographic assay used to quantify these metabolites.

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Effect of the Sulfur-Covering Group on the Antiradiation Activity of Substituted 2-Aminoethanethiols†

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Highly effective N-substituted derivatives of *S*-2-aminoethyl hydrogen thiosulfate as antiradiation agents have been modified to include the corresponding thiols, disulfides, and thiazolidines. In addition, many new substituents have been included. Based on intraperitoneal administration, Bunte salts had the best activity and thiazolidines the poorest. Thiols and disulfides were intermediate in their action. Of the new Bunte salts, *S*-2-{5-[(2-isopropyl-5-methylcyclohexyl)oxy]pentyl}amino)-ethyl hydrogen thiosulfate (7) derived from L-menthol was the most active. The best 3-substituted thiazolidine was 3-[5-(*o*-tolyloxy)pentyl]thiazolidine (62). *S*-2-{[4-(*o*-Cumenyloxy)butyl]amino}-ethyl hydrogen thiosulfate (11) was highly effective against tapeworm infections in mice, and the corresponding disulfide, *N,N'*-(dithiodiethylene)bis[4-(*o*-cumenyloxy)butylamine] dihydrochloride (49), had broad spectrum antibacterial activity in *in vitro* systems. 1-Substituted aziridines served as useful intermediates to Bunte salts and thiols by ring opening with $(NH_4)_2S_2O_3$ and H_2S. The thiols were oxidized to disulfides and treated with sodium formaldehyde bisulfite to give 3-substituted thiazolidines. Alkylation of ethylenimine using alkyl bromides and 7–10 molar excesses of ethylenimine in the presence of powdered K_2CO_3 was found to be a convenient route to 1-substituted aziridines.

Substituted 2-aminoethanethiol remains the most important structural type having antiradiation effectiveness.[1] Extensive work in many laboratories has been devoted to varying the substituents on nitrogen and sulfur. We previously have published several series of N-substituted *S*-2-aminoethyl hydrogen thiosulfates (I) as antiradiation agents.[2] Cycloalkylalkyl, alicyclic ether, aralkyl, and aryloxyalkyl groups were used as nitrogen substituents. Included in those series are some of the most active and best tolerated radioprotectors known. Antiradiation effectiveness was found to be especially sensitive to minor structural modifications of the nitrogen substituent. It remained to be determined what effect changes in the sulfur-covering function would have on radioprotective properties. Sulfur-containing groups of active radioprotectors in the main have included the parent thiol, disulfide, thiosulfates, and phosphorothioates (esters of H_3PO_3S). A summary including other miscellaneous types has been published.[3] Because of the importance of Bunte salts, we now report some additional thiosulfates along with modifications of the thiosulfate ester

$$RNHCH_2CH_2SSO_3H$$
I

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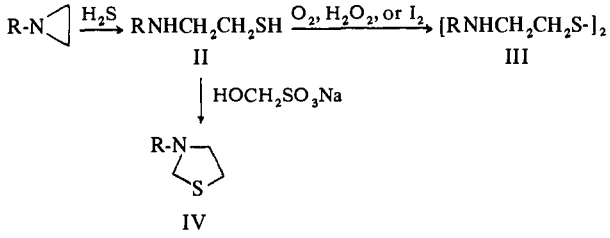
portion of some of the new compounds as well as of Bunte salts previously reported by us. Comparisons of antiradiation properties have been made of Bunte salts (I), thiols (II), disulfides (III), and thiazolidines (IV). In five cases compounds with all four sulfur-covering groups having the same nitrogen substituent were prepared. In several other cases either two or three sulfur-covering functions were used with the same nitrogen substituent. A few substituted thiazolidines have been included in other antiradiation studies,[4-6] but aside from thiazolidine itself, these compounds are either 2-substituted thiazolidines or highly substituted and unusual structures. In view of the importance of the nitrogen substituent for good radioprotective properties of N-substituted 2-aminoethanethiols (II), a study of N-substituted thiazolidines was needed. Very few 3-monosubstituted thiazolidines have been reported. 3-Methyl- and 3-ethylthiazolidines[7,8] and 3-arylthiazolidines[9,10] are the simplest types known. 3-Phenethylthiazolidine,[11] the closest analogy to our work, and 3-thiazolidineacetic acid[12] are known. 3,3'-Methylenebisthiazolidine has been used to prepare α-3-thiazolidinyl-*o*-cresol and 3-[(benzylthio)methyl]thiazolidine.[13]

Some of the Bunte salts‡ (Table I) were prepared by alkylation of *S*-2-aminoethyl hydrogen thiosulfate, but most were obtained from 1-substituted aziridines by ring opening with $(NH_4)_2S_2O_3$[15] or free $H_2S_2O_3$.[16] 1-Substituted aziridines were useful intermediates leading to thiols[17] (II) (Table II), which in turn were converted to disulfides (III) (Table III) and thiazolidines[13] (IV) (Table IV).



The Gabriel synthesis and the Wenker modification of it are the most general methods[18,19] (elimination of HX from substituted 2-aminoethyl halides or sulfates) available for the preparation of 1-substituted aziridines. We were led to a study of the direct alkylation of ethylenimine because of a need for 1-(aryloxyalkyl)aziridines. Preparations leading to a Gabriel synthesis of these compounds were considered first. However, in our hands attempts to prepare 2-(aryloxyalkylamino)ethanols from aryloxyalkyl halides and 2-aminoethanol resulted in cleavage of the aryl ethers. In order to avoid this problem by use of a direct alkylation procedure, investigations were made of the effects of various solvents and acid scavengers on the yields of 1-substituted aziridines obtained by direct alkylation of ethylenimine using alkyl bromides.[20] Monoalkylation of ethylenimine has generally been limited to the use of reactive halides[21-24] such as α-halocarbonyl compounds,[23,24] β-chloro ethers or thioethers,[25] haloazines,[26] benzyl halides,[19] β-haloethylamines,[19,22] and allylic halides.[27] Some notable exceptions to this generalization have been reported in patents which describe the use of alkyl halides and ethylenimine in the presence of an inorganic base.[28-31] Other aspects of this reaction have been discussed by Dermer and Ham in their comprehensive review.[19] Polymer formation is probably the most serious side reaction when using the direct alkylation approach.[19,22] Also, in our hands incomplete alkylation was often found. This is particularly troublesome because the starting halide and 1-substituted aziridine are not readily separated by distillation, and, in fact, can react with one another. We were able to obtain complete alkylation using a 7-10 to 1 ratio of ethylenimine to alkyl bromide. Reactions were performed in refluxing ethanol containing powdered anhydrous K_2CO_3. The 1-substituted aziridines prepared by this method are shown in Table V. Even though analysis by glpc indicated high purity, only a few good quality analytical samples were obtained. Nitrogen values usually were high and carbon values were low. When nitrogen values were high by as much as 1–2%, a problem especially with low-boiling products, the nmr spectra had extraneous signals centered at δ 2.7 ppm. This was attributed to poly(ethylenimine) or perhaps a polymer involving the 1-substituted aziridine. Integrations of the area in the region of δ 2.7 ppm were generally so small as to be insignificant.

The compounds shown in Tables I-IV were tested in mice for antiradiation activity. The test method has been described[32] and comments pertinent to our evaluation of the antiradiation test data are found elsewhere.[2] Ratings and comparisons are based on protective indices.§

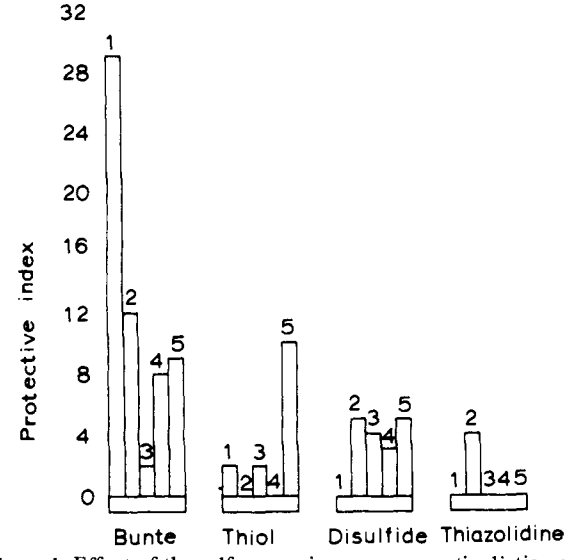


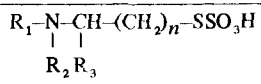
Figure 1. Effect of the sulfur-covering group on antiradiation activity in mice, using intraperitoneal administration. 1, R = $(CH_2)_5CHCH(C_2H_5)CH_2$; 2, R = $(CH_2)_5CHCH(CH_3)(CH_2)_3$; 3, R = = 2,3,6-$(CH_3)_3C_6H_2O(CH_2)_4$; 4, R = 2-[$(CH_3)_2CH$]$C_6H_4O(CH_2)_4$; 5, R = $(CH_2)_7CHO(CH_2)_7$. Bunte = $RNHCH_2CH_2S_2O_3H$; thiol = $RNHCH_2CH_2SH$; disulfide = $[RNHCH_2CH_2S-]_2$; thiazolidine = R-N, S

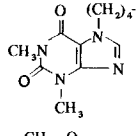
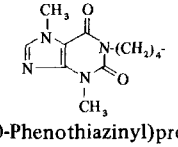
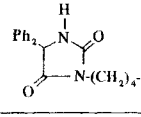
A comparison of antiradiation test data (intraperitoneal administration) for the five cases in which all four sulfur-covering functions were used with each of five different nitrogen substituents is shown in Figure 1. Generally, use of Bunte salts (I) resulted in the best activity and thiazolidines (IV) the poorest. Thiols (II) and disulfides (III) were intermediate in their action. These general trends prevailed in

‡A comprehensive review of organic thiosulfates has been published.[14]

§ Protective index = (protection factor) × (LD_{50}/minimum effective dose), where doses are in mg/kg and the protection factor is 1.3 for 30% survival, 1.4 for 40% survival, etc. 2-Aminoethanethiol (MEA) can be considered the standard for comparison. At 150 mg/kg ip of MEA 87% survival of mice can be obtained in the 30-day test. Its ip LD_{50} is *ca.* 250 mg/kg and it is rated ++. The po LD_{50} is *ca.* 625 mg/kg. At 300 mg/kg 73% survival can be obtained in the po test giving MEA a rating of ++.

Table I. *S*-(Substituted amino)alkyl Hydrogen Thiosulfates



No.	R_1	R_2	R_3	n	Method[a]	Recrystn solvents	Yield, %	Mp, °C	Formula[b]	Antiradiation activity[c] *Ca.* LD_{50}, mg/kg	Drug dose,[d,e] mg/kg	Survival, %	Protect. index[f]	Rating[g]
						***S*-{[(Cycloalkyl)alkyl]amino}alkyl Hydrogen Thiosulfates**								
1	$(CH_2)_5CH(C_2H_5)CH_2$	H	H	1	A	EtOH	17	180–184	$C_{12}H_{25}NO_3S_2$[h]	300	17	73	29	++++
2	4-(2-Norbornyl)butyl	H	H	1	B	EtOH	15	211–213	$C_{13}H_{25}NO_3S_2$	80	20	87[i]	7	++
3	$(CH_2)_5CH(C_2H_5)CH_2$	H	H	2	A[j]	EtOH	25	180–181	$C_{13}H_{27}NO_3S_2$	140	80	33	2	+
4	2-(3-Methylcyclohexyl)butyl	H	CH_3	1	A[k]	EtOH–H_2O	19	173–175	$C_{14}H_{29}NO_3S_2$	320	180*	50	3	+
5	$(CH_2)_5CHCH(C_2H_5)CH_2$	C_2H_5	H	1	A[l]	EtOH	10	155–158	$C_{14}H_{29}NO_3S_2$	560	150*	17	0	–
						***S*-({[(Cycloalkyl)oxy]alkyl}amino)alkyl Hydrogen Thiosulfates**								
6	$(CH_2)_7CHO(CH_2)_5$	H	H	2	A[j]	EtOH	30	170–174	$C_{16}H_{33}NO_4S_2$	110	40	27	3	+
7	5-(L-*p*-Menth-3-yloxy)pentyl	H	H	1	B	EtOH	29	156–180	$C_{17}H_{35}NO_4S_2$	60	15	100	10	++
						***S*-[(Aralkyl)amino]alkyl Hydrogen Thiosulfate**								
8	$4\text{-}BrC_6H_4(CH_2)_4$	H	H	1	A[m]	DMF–EtOH	35	182–184	$C_{12}H_{18}BrNO_3S_2$	43	32*	17	0	–
						***S*-({[(Aryl)oxy]alkyl}amino)alkyl Hydrogen Thiosulfates**								
9	$C_6H_5O(CH_2)_2O(CH_2)_2$	H	H	1	C	Me_2CO	29	80–83	$C_{12}H_{19}NO_5S_2$	250	100	0	0	–
10	$2\text{-}CH_3\text{-}4\text{-}Br\text{-}6\text{-}ClC_6H_2O(CH_2)_4$	H	H	1	B	EtOH	19	170–175	$C_{13}H_{19}BrClNO_4S_2$	75	50*	0	0	–
11	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	H	H	1	B	EtOH–H_2O, EtOH	40	164–167	$C_{15}H_{25}NO_4S_2$	320	50*	33	8	++
12	$2,3,6\text{-}(CH_3)_3C_6H_2O(CH_2)_4$	H	H	1	B	EtOH–H_2O	27	182–187	$C_{15}H_{25}NO_4S_2$	>100	50	50[n]	2	+
13	$2\text{-}CH_3C_6H_4O(CH_2)_5$	H	CH_3	1	A[k]	EtOH	48	145–150	$C_{15}H_{25}NO_4S_2$	240	180*	0	0	–
14	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	H	H	2	A[j]	EtOH	24	171–176	$C_{16}H_{27}NO_4S_2$	150	80	60[i]	3	+
15	$2\text{-}[(CH_3)_3C]\text{-}4\text{-}CH_3C_6H_3O(CH_2)_4$	H	H	1	B	EtOH–H_2O, EtOH	23	180–182	$C_{17}H_{29}NO_4S_2$	38	5	7	0	–
16	$2,4\text{-}[(CH_3)_2CH]_2C_6H_3O(CH_2)_4$	H	H	1	A[o]	EtOH, Me_2CO	12	168–172	$C_{18}H_{31}NO_4S_2$	75	30	0	0	–
17	$3,5\text{-}[(CH_3)_2CH]_2C_6H_3O(CH_2)_4$	H	H	1	B	EtOH, EtOH–H_2O	23	168–170	$C_{18}H_{31}NO_4S_2$	300	200*	0	0	–
						***S*-{[(Heterocyclyl)alkyl]amino}alkyl Hydrogen Thiosulfates**								
18	4-(3-Thienyl)butyl	H	H	1	A[p]	EtOH, MeOH	30	173–174	$C_{10}H_{17}NO_3S_3$	200	50	60[i]	6	+
19	3-(3-Methyl-2-thienyl)propyl	H	H	1	A[q]	EtOH, *i*-BuCOMe–EtOH	17	180–181	$C_{10}H_{17}NO_3S_3$	75	20	0	0	–
20		H	H	1	C	H_2O	20	196–198	$C_{13}H_{21}N_5O_5S_2$	100	50	0	0	–
21		H	H	1	C	DMF–EtOH	50	169–179	$C_{13}H_{21}N_5O_5S_2$[r]	130	100*	17	0	–
22	3-10-Phenothiazinyl)propyl	H	H	1	A[s]	MeOH–Me_2CO	6	188–190	$C_{17}H_{20}N_2O_3S_3$[t]		50	0	0	–
23		H	H	1	A[u]	H_2O	11	179–182	$C_{21}H_{23}N_3O_5S_2$	380	90	0	0	–

[a] A, RX + sodium *S*-2-aminoalkyl thiosulfate; B, $RNC_2H_4 + (NH_4)_2S_2O_3$; C, $RNC_2H_4 + H_2S_2O_3$. References for prepns of alkyl halides used for A are found in ref 2 if no ref is given in this table. Refs for alkyl halides used to prep 1-substituted aziridine are given in Table V. [b] All compds were analyzed for C, H, N, and S. [c] Data are given for intraperitoneal administration of the compds. The antiradiation data generally represent the lowest dose of drug for which a high rate of survival was obtained. The per cent survival (30 days) of the test animals is given for the dose specified. [d] For each test 15 mice were

treated with drug and irradiated either 15 or 30 min later. When fewer than 15 mice were used (generally 6) the drug dose is marked with an asterisk. [e]The radiation dose was supplied by either X-rays (800–825 rads, also indicated by the asterisks) or ^{60}Co γ rays (950 rads, except as noted). γ radiation less than 950 rads was generally sublethal for control animals. [f]See footnote § in the text. [g]Ratings are based on the following ranges of protective indices: –, 0–1; +, 2–5; ++, 6–10; +++, 11–15; ++++, 16–29. The ratings are a measure of the lowest drug dose for which some antiradiation activity was obtained. A high survival rate and a low rating (low protective index) indicates that the compd did not protect well at doses lower than those shown. Twenty per cent survival is the smallest value used to det ratings. [h]L(–) form. [i]Survival of controls, 10%. [j]$H_2N(CH_2)_3S_2O_3H$, ref 43. [k]$H_2NCH(CH_3)CH_2S_2O_3H$, see ref 43. [l]$C_2H_5NHCH_2CH_2S_2O_3H$, ref 34. [m]1-Bromo-4-(4-bromobutyl)benzene, Dr. H. A. DeWald, Parke, Davis and Co. [n]781 rads; survival of controls, 20%. [o]Halide: 2,4-diisopropylphenol + 1,4-dibromobutane. [p]3-Bromomethylthiophene (ref 44) + $CH_2(CO_2Et)_2$ → diethyl (3-thienylmethyl)malonate [*Anal.* ($C_{12}H_{16}O_4S$) C, H] + H_2O, OH^- + Δ → crude 3-(3-thienyl)propionic acid + LAH → crude 3-(3-thienyl)propanol + PBr_3 → crude 3-(3-bromopropyl)thiophene + Mg + CO_2 → 4-(3-thienyl)butyric acid [*Anal.* ($C_8H_{10}O_2S$) C, H] + LAH → crude 4-(3-thienyl)butanol + PBr_3 → 3-(4-bromobutyl)thiophene [*Anal.* ($C_8H_{11}BrS$) C, H]. [q]RX: 2-bromo-3-methylthiophene (ref 45) + Mg + 3-chloropropyl *p*-toluenesulfonate. [r]S: calcd, 16.38; found, 15.89. [s]RX, ref 46. [t]S: calcd, 24.26; found, 23.78. [u]5,5-Diphenylhydantoin, Na salt, + $Br(CH_2)_5Br$ → 3-(4-bromobutyl)-5,5-diphenylhydantoin [*Anal.* ($C_{19}H_{19}BrN_2O_2$) C, H, N].

Table II. 2-(Substituted amino)ethanethiols

						$RNHCH_2CH_2SH \cdot xHCl$					
							Antiradiation activity[c]				
No.	R	Method[a]	Recrystn solvents	Yield, %	Mp, °C	Formula[b]	*Ca.* LD_{50}, mg/kg	Drug dose,[d,e] mg/kg	Survival, %	Protect. index[f]	Rating[g]
					2-{[(Cycloalkyl)alkyl]amino}ethanethiols						
24	$(CH_2)_4CH(CH_2)_4$	A	MeCN	22	197–200	$C_{11}H_{23}NS \cdot HCl$	70	40	87	3	+
25	$(CH_2)_5CH(CH_2)_3$	A	EtOH–Et_2O, MeCN	11	199–203	$C_{11}H_{23}NS \cdot HCl$	75	25	13	0	–
26	$(CH_2)_5CHCH(C_2H_5)CH_2$	A	*i*-PrOH–Et_2O	60	160–162	$C_{12}H_{25}NS \cdot HCl$[h]	70	40	40	2	+
27	$(CH_2)_5CH(CH_2)_4$	B	Concd HCl	45	208–211	$C_{12}H_{25}NS \cdot HCl$	50	40	67	9	++
28	$(CH_2)_4CH(CH_2)_6$	A	MeCN	17	204–207	$C_{13}H_{27}NS \cdot HCl$	75	40	45[i]	2	+
29	$(CH_2)_5CHCH(CH_3)(CH_2)_3$	A	MeCN	24	194–196	$C_{13}H_{27}NS \cdot HCl$[j]	75	50*	17	0	–
30	2-(3-Methylcyclohexyl)butyl	A	MeCN	60	115–118	$C_{13}H_{27}NS \cdot HCl$[k]	62	25	0	0	–
31	4-(2,4-Dimethylcyclohexyl)butyl	A	MeCN	32	204–211	$C_{14}H_{29}NS \cdot HCl$	40	17.5*	0	0	–
					2-({[(Cycloalkyl)oxy]alkyl}amino)ethanethiol						
32	$(CH_2)_7CHO(CH_2)_5$	A	*i*-PrOH–Et_2O	51	164–169	$C_{15}H_{31}NOS \cdot HCl$	180	50*	83	10	++
					2-({[(Aryl)oxy]alkyl}amino)ethanethiols						
33	$4\text{-}CH_3C_6H_4O(CH_2)_4$	A	MeCN	38	153–155	$C_{13}H_{21}NOS \cdot HCl$	75	40	80	4	+
34	$4\text{-}CH_3C_6H_4O(CH_2)_4 \cdot$ citric acid	A	EtOH	82	138–140	$C_{13}H_{21}NOS \cdot C_6H_8O_7$	300	50*	0	0	–
35	$2\text{-}CH_3C_6H_4O(CH_2)_5$	A	*i*-PrOH–Et_2O	57	116–118	$C_{14}H_{23}NOS \cdot HCl$	100	56*	50	5	+
36	$2,6\text{-}(CH_3)_2C_6H_3O(CH_2)_4$	A	MeCN	44	109–111	$C_{14}H_{23}NOS \cdot HCl$	75	50	80	3	+
37	$2\text{-}CH_3C_6H_4O(CH_2)_6$	A	*i*-PrOH–Et_2O	20	114–116	$C_{15}H_{25}NOS \cdot HCl$	150	40	35[i]	5	+
38	$2,3,6\text{-}(CH_3)_3C_6H_2O(CH_2)_4$	A	MeCN	60	116–120	$C_{15}H_{25}NOS \cdot HCl$	130	100*	33	2	–
39	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	A	Et_2O–*i*-PrOH	66	98–100	$C_{15}H_{25}NOS \cdot HCl$[l]	90	50	21[m]	0	–

[a]A, $RNC_2H_4 + H_2S$; B, $RNHCH_2CH_2S_2O_3H$ + concd HCl → $RNHCH_2CH_2SH \cdot HCl$ (ref 47). [b]All compds were analyzed for C, H, N, and SH (34 was analyzed for S rather than for SH); greater tolerance was allowed for the thiol values. [c–g]See Table I, footnotes *c–g*. [h]SH: calcd, 13.13; found, 13.93. [i]781 rads; survival of controls, 10%. [j]SH: calcd, 12.43; found, 11.53. [k]SH: calcd, 12.44; found, 11.89. [l]C: calcd, 59.28; found, 58.77. [m]781 rads; survival of controls, 20%.

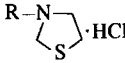
Table III. *N,N'*-(Dithiodiethylene)bis(substituted amine) Hydrochlorides

$[RNHCH_2CH_2S-]_2 \cdot xHCl$

No.	R	Method[a]	Recrystn solvents	Yield, %	Mp, °C	Formula[b]	Antiradiation activity[c] *Ca.* LD_{50}, mg/kg	Drug dose,[d,e] mg/kg	Survival, %	Protect. index[f]	Rating[g]
					(Cycloalkyl)alkyl Derivatives						
40	$(CH_2)_5CHCH(C_2H_5)CH_2$	A	EtOH–MeCN	57	159–161	$C_{24}H_{48}N_2S_2 \cdot 2HCl$	45	25	5	0	–
41	$(CH_2)_4CH(CH_2)_6$	A	EtOH, MeCN	15	240–248	$C_{26}H_{52}N_2S_2 \cdot 2HCl$	26	10	5[h]	0	–
42	$(CH_2)_5CHCH(CH_3)(CH_2)_3$	B	EtOH		215–217	$C_{26}H_{52}N_2S_2 \cdot 2HCl$	45	10	85[i]	5	+
					[(Cycloalkyl)oxy]alkyl Derivative						
43	$(CH_2)_7CHO(CH_2)_5$	A	Et_2O–*i*-PrOH	80	198–200	$C_{30}H_{60}N_2O_2S_2 \cdot 2HCl$	560	160*	50	5	+
					[(Aryl)oxy]alkyl Derivatives						
44	$4\text{-}CH_3C_6H_4O(CH_2)_4$	A	DMSO	53	249–256	$C_{26}H_{40}N_2O_2S_2 \cdot 2HCl$	430	160*	33	4	+
45	$4\text{-}CH_3OC_6H_4O(CH_2)_4$	A	EtOH	12	254–257	$C_{26}H_{40}N_2O_4S_2 \cdot 2HCl$	430	160*	50	4	+
46	$2,5\text{-}(CH_3)_2C_6H_3O(CH_2)_4$	B	EtOH–MeCN		217–221	$C_{28}H_{44}N_2O_2S_2 \cdot 2HCl$	45	15	35[j]	0	–
47	$2,6\text{-}(CH_3)_2C_6H_3O(CH_2)_4$	A	EtOH, EtOH–MeCN	55	160–175	$C_{28}H_{44}N_2O_2S_2 \cdot 2HCl$[k]	560	160*	17	0	–
48	$2\text{-}CH_3C_6H_4O(CH_2)_6$	B	*l*	23	199–205	$C_{30}H_{48}N_2O_2S_2 \cdot 2HCl$	74	25*	67	7	+
49	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	A	MeCN	56	136–138	$C_{30}H_{48}N_2O_2S_2 \cdot 2HCl$	240	90*	83	4	+
50	$2,3,6\text{-}(CH_3)_3C_6H_2O(CH_2)_4$	A	EtOH	73	191–193	$C_{30}H_{48}N_2O_2S_2 \cdot 2HCl$	56	32*	50	4	+

[a] A, $RNC_2H_4 + H_2S \rightarrow RNHCH_2CH_2SH + I_2\text{–MeOH} \rightarrow [RNHCH_2CH_2S-]_2$; B, isolated as a side-product from prepn of thiol. [b] Except as noted all compds were analyzed for C, H, N, and S. [c-g] See Table I, footnotes *c–g*. [h] 781 rads; survival of controls, 10%. [i] 600 rads; survival of controls, 65%. [j] 677 rads; survival of controls, 35%. [k] No analysis for S. Additional analysis for Cl. [l] Unoxidized thiol was washed from the solid disulfide with hot MeCN.

Table IV. 3-Substituted Thiazolidine Hydrochlorides[a]



·HCl, R

No.	R	Recrystn solvents	Yield, %	Mp or bp (mm), °C	Formula[b]	Antiradiation activity[c] *Ca.* LD_{50}, mg/kg	Drug dose,[d,e] mg/kg	Survival, %	Protect. index[f]	Rating[g]
				3-[(Cycloalkyl)alkyl]thiazolidines						
51	$(CH_2)_5CH(CH_2)_4$	MeCN	24	195–200	$C_{13}H_{25}NS \cdot HCl$	>125	20	10[h]	0	–
52	$(CH_2)_5CHCH(C_2H_5)CH_2$	MeCN	39	194–198	$C_{13}H_{25}NS \cdot HCl$	125	40	0	0	–
53	$(CH_2)_4CH(CH_2)_6$	MeCN	24	189–192	$C_{14}H_{27}NS \cdot HCl$	80	25	100	6	+
54	$(CH_2)_5CHCH(CH_3)(CH_2)_3$	MeCN	30	194–197	$C_{14}H_{27}NS \cdot HCl \cdot 0.5H_2O$	180	100	13	0	–
55	$(CH_2)_5CH(CH_2)_6$	MeCN–Et_2O	60	183–186	$C_{15}H_{29}NS \cdot HCl$	140	40	75[i]	6	+
				3-[(Cycloalkyloxy)alkyl]thiazolidines						
56	$(CH_2)_5CHO(CH_2)_5$	EtOH	28	157–159	$C_{14}H_{27}NOS \cdot HCl$	160	70	93	4	+
57	$(CH_2)_7CHO(CH_2)_5$	MeCN–Et_2O	13	135–139	$C_{16}H_{31}NOS \cdot HCl$	>120	30	7	0	–
58	5-(*p*-Menth-3-yloxy)pentyl		52	165–168 (0.2)	$C_{18}H_{35}NOS$	300	150	47	4	+
				3-(Aralkyl)thiazolidine						
59	4-[*p*-(2-Bornyloxy)phenyl]butyl	EtOH	28	195–197	$C_{23}H_{35}NOS \cdot HCl$	125	20	0	0	–
				3-{[(Aryl)oxy]alkyl}thiazolidines						
60	$3\text{-}ClC_6H_4O(CH_2)_4$	EtOH	67	125–126	$C_{13}H_{18}ClNOS \cdot HCl$	200	90	67	4	+
61	$4\text{-}CH_3C_6H_4O(CH_2)_4$	MeCN	29	117–120	$C_{14}H_{21}NOS \cdot HCl$	175	50	20	0	–
62	$2\text{-}CH_3C_6H_4O(CH_2)_5$	MeCN	20	152–154	$C_{15}H_{23}NOS \cdot HCl$	430	80	47	8	++
63	$2,3,6\text{-}(CH_3)_3C_6H_2O(CH_2)_4$	MeCN–Et_2O	26	111–113	$C_{16}H_{25}NOS \cdot HCl$	180	100	13	0	–
64	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	MeCN–Et_2O	37	110–112	$C_{16}H_{25}NOS \cdot HCl$	75	50*	0	0	–
65	$2\text{-}CH_3O\text{-}4\text{-}C_2H_5C_6H_3O(CH_2)_4$	EtOH	35	117–119	$C_{16}H_{25}NO_2S \cdot HCl$	135	70	27	2	+
66	$3,5\text{-}[(CH_3)_2CH]_2C_6H_3O(CH_2)_4$	MeCN–Et_2O	28	147–149	$C_{19}H_{31}NOS \cdot HCl$	200	40	0	0	–

[a] $RNC_2H_4 + H_2S \rightarrow RNHCH_2CH_2SH + HOCH_2SO_2Na \rightarrow RX$ (X is 3-thiazolidinyl); 37% formalin was used for 55. Thiol for 55: ref 35. [b] All compds were analyzed for C, H, N, and S. [c-g] See Table I, 750 footnotes *c–g*. [h] 750 rads; survival of controls, 5%. [i] 781 rads; survival of controls, 10%.

Table V. 1-Substituted Aziridines, RNC_2H_4

Intermediate for compd no.	R	Alkyl halide,[a] source	Yield %[b]	Bp (mm) or mp, °C	Approximate purity, glpc analysis, %[c]
24	$(CH_2)_4CH(CH_2)_4$	*d*	76	66–69 (0.5)	95
25	$(CH_2)_5CH(CH_2)_3$	*d*	83	96–97 (9)	98
27	$(CH_2)_5CH(CH_2)_4$	*d*	71	76–83 (0.9)	96
26, 40, 52	$(CH_2)_5CHCH(C_2H_5)CH_2$	*d*	78	113–115 (13)	97
28, 41, 53	$(CH_2)_4CH(CH_2)_6$	*d*	44	88–92 (0.9)	91
29, 42, 54	$(CH_2)_5CHCH(CH_3)(CH_2)_3$	*d*	71	75–90 (0.5)	92
30	2-(3-Methylcyclohexyl)butyl	*d*	89	58–61 (0.2)	90
2	4-(2-Norbornyl)butyl	*e*	58	82–87 (0.5)	80
31	4-(2,4-Dimethylcyclohexyl)butyl	*d, f*	37	87–92 (0.9)	100
56	$(CH_2)_5CHO(CH_2)_5$	*d*	65	85–103 (0.1)	91
32, 43, 57	$(CH_2)_7CHO(CH_2)_5$	*d*	69	108–112 (0.05)	99
7, 58	5-(*p*-Menth-3-yloxy)pentyl	*g*	84	112–120 (0.1)	95
59	4-[*p*-(2-Bornyloxy)phenyl]butyl	*h*	71	181–187 (0.1)	94
60	$3\text{-}ClC_6H_4O(CH_2)_4$	*d*	92	105–108 (0.2)	100
9	$C_6H_5O(CH_2)_2O(CH_2)_2$	*i*	34	109–110 (0.5)	80
10	$2\text{-}CH_3\text{-}4\text{-}Br\text{-}6\text{-}ClC_6H_2O(CH_2)_4$	*j*	67	144–146 (0.3)	50
33, 44	$4\text{-}CH_3C_6H_4O(CH_2)_4$	*d*	71	109–119 (0.5)	95
45	$4\text{-}CH_3OC_6H_4O(CH_2)_4$	*d*	62	111–113 (0.2)	95
35, 62	$2\text{-}CH_3C_6H_4O(CH_2)_5$	*d*	67	106–110 (0.3)	99
46	$2,5\text{-}(CH_3)_2C_6H_3O(CH_2)_4$	*d*	62	95–103 (0.2)	96
36, 47	$2,6\text{-}(CH_3)_2C_6H_3O(CH_2)_4$	*d*	84	98–105 (0.2)	98
37, 48	$2\text{-}CH_3C_6H_4O(CH_2)_6$	*d*	71	120–125 (0.4)	99
11, 39, 49, 64	$2\text{-}[(CH_3)_2CH]C_6H_4O(CH_2)_4$	*k*	74	100–103 (0.1)	97
12, 38, 50, 63	$2,3,6\text{-}(CH_3)_3C_6H_2O(CH_2)_4$	*l*	61	120–126 (0.1)	98
65	$2\text{-}CH_3O\text{-}4\text{-}C_2H_5C_6H_3O(CH_2)_4$	*d*	79	134–141 (0.3)	98
15	$2\text{-}[(CH_3)_3C]\text{-}4\text{-}CH_3C_6H_3O(CH_2)_4$	*m*	87	122–132 (0.1)	93
17, 66	$3,5\text{-}[(CH_3)_2CH]_2C_6H_3O(CH_2)_4$	*n*	70	140–145 (0.2)	93
20	4-(7-Theophyllinyl)butyl	*o*	86	76–80	
21	4-(1-Theobrominyl)butyl	*p*	51	95–102	

[a] Alkyl halide used to alkylate ethylenimine. [b] Distd yield of material having glpc analysis indicated. [c] Most samples contained some polyethylenimine which seemingly could not be detected by glpc analysis. Nmr signals at about δ 2.7 ppm and high analysis for N suggested polyethylenimine. [d] Ref 2 in the text. [e] Crude RX: *exo*-2-norbornanemethyl bromide + Mg + $(CH_2)_3O \rightarrow$ *exo*-2-norbornanebutanol + $PBr_3 \rightarrow$ 2-(4-bromobutyl)-*exo*-norbornane. [f] Wenker synthesis was used. [g] From L-menthol (ref 48): *Anal.* ($C_{17}H_{33}NO$) C, H, N. [h] Camphene + *p*-(4-chlorobutyl)-phenol (ref 2) + $BF_3 \cdot Et_2O \rightarrow$ 2-bornyl 4-(4-chlorobutyl)phenyl ether, bp 169–170° (0.1 mm) and glpc 97%. *Anal.* ($C_{20}H_{29}ClO$) C, H. The general method has been published.[49] [i] Eastman Kodak Co. [j] $2\text{-}CH_3\text{-}4\text{-}Br\text{-}6\text{-}ClC_6H_2OH + Br(CH_2)_4Br + K_2CO_3\text{-}Me_2CO \rightarrow RX$, bp 150–162° (0.1 mm). *Anal.* ($C_{11}H_{13}Br_2ClO$) C, H. [k] $2\text{-}[(CH_3)_2CH]C_6H_4OH + Br(CH_2)_4Br + K_2CO_3\text{-}Me_2CO \rightarrow RX$, bp 90–96° (0.1 mm) and glpc 94%. [l] $2,3,6\text{-}(CH_3)_3C_6H_2OH + Br(CH_2)_4Br + K_2CO_3\text{-}Me_2CO \rightarrow RX$, bp 125–139° (0.2 mm). [m] $2\text{-}[(CH_3)_3C]\text{-}4\text{-}CH_3C_6H_3OH + Br(CH_2)_4Br + K_2CO_3\text{-}Me_2CO \rightarrow RX$, bp 115–127° (0.03 mm) and glpc 98%. *Anal.* ($C_{15}H_{23}BrO$) C, H. [n] $3,5\text{-}[(CH_3)_2CH]C_6H_3OH + Br(CH_2)_4Br + K_2CO_3\text{-}Me_2CO \rightarrow RX$, bp 120–135° (0.5 mm) and glpc 87%. [o] RCl, ref 50. [p] Theobromine + NaOEt-EtOH + $Br(CH_2)_4Cl \rightarrow$ RX, mp 104–107°.

cases where two or three of the sulfur-covering functions were used with each of several other nitrogen substituents. The correlations apply only to intraperitoneal administration of the drug.

Among the Bunte salts (I) (Table I), use of the levorotatory *N*-2-cyclohexylbutyl compound (**1**) with a protective index of 29 resulted in the best activity and was comparable with the racemic compound reported[2] earlier. An *N*-(*p*-menth-3-yloxy)pentyl derivative **7** derived from L-menthol was a highly active (protective index = 13) alicyclic ether within the new group of Bunte salts. There were no new highly active Bunte salts with aryloxyalkyl or aralkyl groups as nitrogen substituents, although we have previously reported good radioprotectants of this type, notably *S*-2-{[4-(*p*-methoxyphenyl)butyl]amino}ethyl hydrogen thiosulfate.[2] Bunte salts **18–23** bearing the heterocyclic substituents shown in Table I are of no interest as antiradiation agents. Among the thiols (II) (Table II) cyclopentylbutyl (**32**) (protective index = 3), cyclohexylbutyl (**27**) (protective index = 9), cyclooctyloxypentyl (**32**) (protective index = 10), and *p*-tolyloxybutyl (**33**) (protective index = 4) as nitrogen substituents on 2-aminoethanethiol were the most effective; in each case the corresponding Bunte salt was active.[2] Several related disulfides (III) (Table III) exhibited moderate activity, but no exceptional compounds were found.

Modest activity was obtained using the new N-substituted thiazolidines (IV) (Table IV) in the ip test system. Again optimum activity depends on the nitrogen substituent. The best thiazolidine was the 3-(*o*-tolyloxy)pentyl derivative **62** with a protective index of 8. Antiradiation activity has been reported[6,33] for the parent unsubstituted thiazolidine, some 2-substituted thiazolidines, and 2,3-disubstituted thiazolidines.

Antiradiation activity based on oral administration of the drugs has been reported[2] for 16 Bunte salts. This development, significant because few radioprotective agents are effective when given by the oral route, stimulated continued exploration of these series. In this study as in others, only those compounds which were highly active intraperitoneally were tested perorally. Of the compounds tested, thiazolidines (IV) **56**, **60**, and **62** (Table VI) had protective index values of 3–4 when given by mouth.

The earlier structure-activity study[2] of N-substituted derivatives of *S*-2-aminoethyl hydrogen thiosulfate produced many antiradiation agents having very high protective index

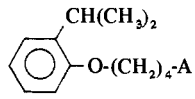
Table VI. Radiation Protection by Oral Administration

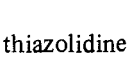
No.	LD_{50}, mg/kg	Dose, mg/kg	Dose, min preir-radiation	Survival, %
56	>600	200	15	27
		200	30	20
60	650	300	15	27
		300	30	47
62	>1000	300	30	29
		300	60	0

values in the ip test and some compounds with good activity on oral administration. The extension of that work to other Bunte salts and to thiols, disulfides, and thiazolidines has resulted in many active radioprotectants, but none so effective as the original Bunte salts.

The antiradiation drug development program sponsored by Walter Reed Army Institute of Research, in addition to the discovery of new radioprotective substances, has given rise to compounds having other useful biological properties. Antibacterial agents,[34,35] a unique and highly potent schistosomicide,[36] potential antiarthritic compounds,[37] and an α-adrenergic blocking agent[38] which may be useful in the treatment of hemorrhagic shock have been reported.

In this instance also, other potentially useful biological properties were uncovered. The 4-(*o*-cumenyloxy)butyl substituent in comparison with other derivatives of the sulfur-containing compounds imparted unusual potency in two additional biological systems. Antibacterial activity was again found and, for the first time among antiradiation agents, potent anthelmintic properties against tapeworm infections were discovered. The Bunte salt **11** was effective# against tapeworm infections in mice when given in the diet at 26 mg/kg per day for 2 days. The possibility of a useful tapeworm drug was indicated by the data, but unfortunately efficacy could not be demonstrated in dogs. A positive correlation was observed between intraperitoneal toxicity and anthelmintic potency among a series of related Bunte salts. However, the most active anthelmintic Bunte salt, **11**, with an ip LD_{50} of *ca.* 300 mg/kg provided the single exception to that generalization. Most other antiparasitic Bunte salts had ip LD_{50} values of less than *ca.* 50 mg/kg. The Bunte salts tested were generally rather nontoxic when given orally (LD_{50} > 500 mg/kg) and, therefore, were of interest in the treatment of intestinal parasites.



11, A = $-NHCH_2CH_2S_2O_3H$
39, A = $-NHCH_2CH_2SH \cdot HCl$
49, A = $[-NHCH_2CH_2S-]_2 \cdot HCl$
64, A =  $\cdot HCl$

The thiol **39**, disulfide **49**, and thiazolidine **64** also having the 4-(*o*-cumenyloxy)butyl substituent were active antibacterial agents in *in vitro* systems[39] and inactive as anthelmintic agents, whereas the corresponding anthelmintic Bunte salt (**11**) possessed no antibacterial activity. The disulfide **49** had the best antibacterial activity and would be considered broad spectrum in its effect in the *in vitro* system; it inhibited the growth of seven out of eight bacterial organisms. Inhibition of *Escherichia coli* and *Streptococcus pyogenes* at 0.08 μg/ml and of *Pseudomonus aeruginosa* at 0.31 μg/ml were the most significant results. All of these compounds were inactive in *in vivo* test systems.

Experimental Section**

1-Substituted Aziridines. 1-[5-(Cyclooctyloxy)pentyl]aziridine. A mixt of 40 g (0.14 mole) of 5-bromopentyl cyclooctyl ether,[2] 23 g (0.17 mole) of powdered anhyd K_2CO_3, and 400 ml of EtOH was stirred until the soln was basic. Ethylenimine (60 g, 1.4 moles) was added, and the resulting mixt was stirred and heated under reflux for 40 hr. The mixt was filtered, and the filtrate was concd under reduced pressure. A slurry containing the residual oil in 400 ml of Et_2O was filtered through Celite; the filtrate was reconcd giving 42 g of crude oil which was distd to give 24.6 g (74%) of 1-[5-(cyclooctyloxy)pentyl]aziridine: bp 110–116° (0.3 mm); glpc 96%. The nmr spectrum was as expected. *Anal.* ($C_{15}H_{29}NO$) C, H, N.

***S*-(Substituted amino)alkyl Hydrogen Thiosulfates. Method A.** The procedure of Klayman and Gilmore[40] was used to alkylate *S*-2-aminoalkyl hydrogen thiosulfates.

Method B. 1-Substituted aziridines were allowed to react with $(NH_4)_2S_2O_3$ in refluxing MeOH in a manner described by Klayman, *et al.*[15]

Method C.[16] ***S*-2-{[4-(1,2,3,6-Tetrahydro-3,7-dimethyl-2,6-dioxopurin-1-yl)butyl]amino}ethyl Hydrogen Thiosulfate (1-Substituted Theobromine).** A soln of 7.7 g (0.028 mole) of 1-[4-(1-aziridinyl)butyl]theobromine [*Anal.* ($C_{13}H_{19}N_5O_2$) C, H, N] in 25 ml of MeOH was added to 55 ml of cold (−45°) methanolic $H_2S_2O_3$[16] containing 3.2 g (0.028 mole) of $H_2S_2O_3$. The mixt was warmed slowly to room temp before being dild with 150 ml of Et_2O, causing pptn of a light yellow solid (10.5 g). A soln of this solid in a small vol of H_2O was poured into 400 ml of EtOH to give an oily product which was triturated with Et_2O to effect crystn. The white solid was repptd from EtOH–Et_2O and then from DMF–EtOH to give 4 g (36%) of **21**: mp 169–179°.

2-(Substituted amino)alkanethiols. 1-Substituted aziridines were allowed to react in EtOH with excess H_2S.[17] Crude products were distd under reduced pressure and HCl salts were prepd from freshly distd thiols by treatment in Et_2O with dry HCl.

***N,N'*-(Dithiodiethylene)bis(substituted amines).**[41] ***N,N'*-(Dithiodiethylene)bis[5-(cyclooctyloxy)pentylamine]·2HCl (43).** A soln of 8.0 g (0.026 mole) of 2-{[(5-cyclooctyloxy)pentyl]amino}ethanethiol·HCl (**32**) in 300 ml of MeOH was treated with portions of a methanolic soln containing 3.4 g of I_2 until a yellow color persisted. The pH of the soln was adjusted to about 10 by the addn of 65 ml of 1 *N* NaOH. The solvent was removed under reduced pressure and the residue was taken up in *ca.* 200 ml of Et_2O. The ethereal soln was washed with satd NaCl, dried ($MgSO_4$), and treated with 6.1 ml of 4.4 *N* HCl in *i*-PrOH to give 6.5 g (88%) of **43** as a waxy solid: mp 198–200°.

Substituted Thiazolidines.[12] **3,4-(*m*-Chlorophenoxy)butyl]thiazolidine·HCl (60).** To a soln of about 12 g (0.3 mole) of H_2S in 75 ml of cold (−40°), abs EtOH was added 25.0 g (0.11 mole) of 1-[4-(*m*-chlorophenoxy)butyl]aziridine in 25 ml of EtOH. The soln was warmed to room temp over a period of 2 hr. The solvent was removed under reduced pressure and a soln of the residue in 150 ml of MeOH was combined with a soln of 149 g (1.11 moles) of sodium formaldehyde bisulfite in 150 ml of H_2O. The resulting mixt was stirred and heated under reflux overnight and then concd. The product was extd into Et_2O, and the combined exts were washed (H_2O and satd NaCl), dried ($MgSO_4$), and treated with 25 ml (0.11 mole) of 4.5 *N* HCl–*i*-PrOH. The white ppt was recrystd from abs EtOH to give 23 g (67%) of **60**: mp 125–126°.

Resolution of α-Ethylcyclohexaneacetic Acid. To a soln of 578 g (2.0 moles) of dehydroabietylamine dissolved in 4 l. of MeOH was added 340 g (2.0 moles) of racemic α-ethylcyclohexaneacetic acid. The stirred soln was slowly dild with 1 l. of H_2O and stored for 16 hr in the refrigerator. The crystals were collected and dried to give 744.7 g of salt, mp 134–141°. Four recrystns from MeOH containing a small quantity of H_2O successively gave the following fractions: 580 g, mp 136–142°; 348 g, mp 138–143°; 209 g, mp 142–145°; and 105 g, mp 143–146°. The final crop (105 g) was added to a mixt of 1 l. of satd NaCl and 1 l. of Et_2O. The layers were sepd, and the aqueous layer was washed several times with Et_2O. The aqueous layer was acidified with concd HCl and then extd with Et_2O. The combined exts were dried ($MgSO_4$) and concd giving 35.7 g of light yellow oil which was distd to give 31.4 g of oil which solidified: bp 110° (1 mm); and $[M]^{25}_{589}$ −0.27°, $[M]^{25}_{578}$ −0.207°, $[M]^{25}_{546}$ +0.051°, $[M]^{25}_{436}$ +2.48°, and $[M]^{25}_{365}$ 8.9° (*c* 19, heptane).†† The filtrate from the final crop (105 g) of α-ethylcyclohexaneacetic acid, dehydroabietylamine salt, was concd to dryness, and the residue was converted to the free acid by extn with satd Na_2CO_3, followed by washing the aqueous layer with Et_2O. The aqueous layer was acidified with concd HCl, and the α-ethylcyclohexaneacetic

#Anthelmintic tests were performed by Dr. P. E. Thompson and coworkers at Parke Davis. The cooperation of Dr. D. B. Capps is gratefully acknowledged.

**Melting points (uncorrected) were determined using a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

†† Molecular rotations reported[42] for *l*-α-ethylcyclohexaneacetic acid: λ 589.3, *ca.* −1.3°; λ 578.0, −1.267°; λ 546.0, −1.103°; λ 436.0, +1.509°; and λ 365.0 nm, +7.89° (*c* 19, heptane).

acid was extd with Et_2O. The crude oil resulting from concn of the ext was distd to give 29.4 g of acid: bp 108–110° (0.5 mm); $[M]^{25}_{589}$ −0.085°, $[M]^{25}_{578}$ −0.085°, $[M]^{25}_{546}$ +0.051°, $[M]^{25}_{436}$ +1.5°, and $[M]^{25}_{365}$ +3.08° (*c* 19, heptane). The 29.4-g and 31.4-g fractions were combined.

A small quantity of the other isomer was obtained by concg the filtrate from the first crystn of α-ethylcyclohexaneacetic acid, dehydroabietylamine salt, to dryness giving 141.6 g of solid, mp 128–138°. An attempt to recrystallize the solid from EtOH gave approximately 80 g of EtOH-insol product which was successfully recrystd twice from EtOAc to give the following quantities: 56.6 g, mp 139–144°; 21.6 g, mp 143–146° and mmp with levorotatory salt 134–139°. The 21.6-g fraction was converted to the free acid giving 2 g of distd product: $[M]^{25}_{589}$ −5°, $[M]^{25}_{578}$ −5.3°, $[M]^{25}_{546}$ −6.38°, $[M]^{25}_{436}$ −14.2°, and $[M]^{25}_{365}$ −29.9° (*c* 19, heptane).

α-Ethylcyclohexaneethanol. Active α-ethylcyclohexaneacetic acid (54 g, 0.32 mole) was treated with 10 g (0.26 mole) of LAH in 675 ml of THF to give 46.6 g (94%) of crude oily product which was characterized by ir spectrum.

Active [1-(Bromomethyl)propyl]cyclohexane. From 46.6 g (0.3 mole) of crude active α-ethylcyclohexaneethanol and 10.6 ml (0.11 mole) of PBr_3 was prepd[3] 47.3 g (72%) of active [1-(bromomethyl)propyl]cyclohexane: bp 125–133° (25 mm); glpc 100%; and $[M]^{25}_{589}$ +1.30°, $[M]^{25}_{578}$ +1.30°, $[M]^{25}_{546}$ +1.57°, $[M]^{25}_{436}$ +3.00°, and $[M]^{25}_{365}$ +5.10° (*c* 20, heptane). *Anal.* ($C_{10}H_{19}Br$) Br.

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