N-Substituted S-2-Aminoethyl Thiosulfates as Antiradiation Agents[1]

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An extensive series of N-substituted derivatives of S-2-aminoethyl thiosulfate has been prepared for the purpose of finding a useful radioprotective agent. Cycloalkylalkyl, cycloalkylalkyloxyalkyl, cycloalkyloxyalkyl, aralkyl, and aryloxyalkyl groups were included as substituents on nitrogen. The length of the linear alkyl group separating the cyclic portion from the amine was varied from zero to nine carbon atoms. Branched chains also were used as insulating groups. Alkylation of S-2-aminoethyl thiosulfate with alkyl halides was used extensively, although alkylations with epoxides and a tosyl ester also were employed. Other preparations of internal Bunte salts utilized in this work include oxidation of disulfides with sulfite ion and reaction of N-substituted aminoethyl halides with thiosulfate ion. Intermediates for the alkylation reactions were prepared by various conventional methods, including numerous chain-lengthening and chain-branching reactions. Antiradiation activity in mice has been found throughout the series, and it is apparent that several compounds can be administered to obtain a good radioprotective effect at one-tenth to one-fifteenth of toxic (LD_{50}) doses. Activity by oral administration also was obtained for some compounds.

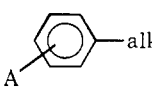
It is apparent from recent reports[2] that less toxic antiradiation agents are needed. We discovered that N-cyclohexylalkyl substitution of S-2-aminoethyl thiosulfate results in radioprotectants having a larger margin of safety than can be obtained by ordinary alkyl substitution. Variation of the substituent on nitrogen followed. We replaced the cyclohexyl group with cyclobutyl, cyclopentyl, and cycloheptyl groups. The length of the insulating linear alkyl group was increased to nine carbon atoms and decreased to the point of simply having N-cycloalkyl derivatives.

Nitrogen substitution by alicyclic ethers and various aralkyl and aryloxyalkyl groups also were included in the study. Compounds having branched chains as insulating groups were prepared for the cycloalkylalkyl series and both aromatic series. The five general classes of compounds prepared are represented below.

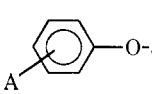
$RNHCH_2CH_2SSO_3H$

R = $(CH_2)_nCH$-alkyl- (Table I),

$(CH_2)_{n_1}CH(CH_2)_{n_2}O(CH_2)_{n_3}$– (Table II),



(Table III),



(Table IV),

and miscellaneous substituents (Table V).

Bunte salts isolated as final products were prepared principally by alkylation of sodium S-2-aminoethyl thiosulfate with alkyl halides.[3] Alkyl chlorides used in the alkylation reactions were prepared from the corresponding alcohols and thionyl chloride, with or without pyridine. Phosphorus tribromide in the presence of up to 0.33 molar equiv of pyridine was used to prepare primary alkyl bromides from the corresponding alcohols. For the bromides reaction conditions varied from 15 hr at room temperature to 4 hr at 100°. Generally, better yields of alkyl bromides were obtained using higher reaction temperatures, providing the compounds are stable to these conditions. Lower temperatures frequently resulted in appreciable formation of phosphate ester.

Throughout this work it was necessary to lengthen carbon chains of intermediates leading to alkyl halides by one-, two-, or three-carbon fragments. Reaction of Grignard reagents with CO_2 served to extend a chain by one carbon atom. Reaction of Grignard reagents with ethylene oxide was the most direct route used for the addition of a two-carbon fragment, although the method suffers from the disadvantage of giving several side products.[4] The more conventional and less direct alkylation of diethyl malonate served to extend a chain by two carbon atoms. A three-carbon fragment was conveniently introduced by the addition of a Grignard reagent to trimethylene oxide.[5,6]

Preparation of alkyl halides having a cycloalkyl group attached to a branched carbon chain was accomplished by first performing a Reformatsky reaction between a cycloalkanone or an appropriate aldehyde and an α-bromo ester. Dehydration and reduction reactions of the Reformatsky products afforded branched alcohols which were easily converted to the halides. The branched halide [2-(bromomethyl)propyl]cyclohexane was converted to the known *sec*-butylcyclohexane in order to rule out rearrangement during the halogenation step.

Preparation of aryl-substituted branched-chain compounds required a different approach. Aryl malonates were treated with an alkyl halide in the presence of NaH and the product was successively saponified, decarboxylated, reduced, and halogenated to provide branched alkyl bromides for alkylation of S-2-aminoethyl thiosulfate.

Incorporation of the *trans*-2-phenylcyclopropane-

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(2) W. D. Foye in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press Inc., New York, N. Y., 1966, Chapter 30.

(3) A series primarily of N-alkyl derivatives of S-2-aminoethyl thiosulfate has been reported, but no antiradiation data were given: D. L. Klayman and W. F. Gilmore, *J. Med. Chem.*, **7**, 823 (1964).

(4) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 961.

(5) C. G. Derick and D. W. Bissell, *J. Am. Chem. Soc.*, **38**, 2478 (1916).

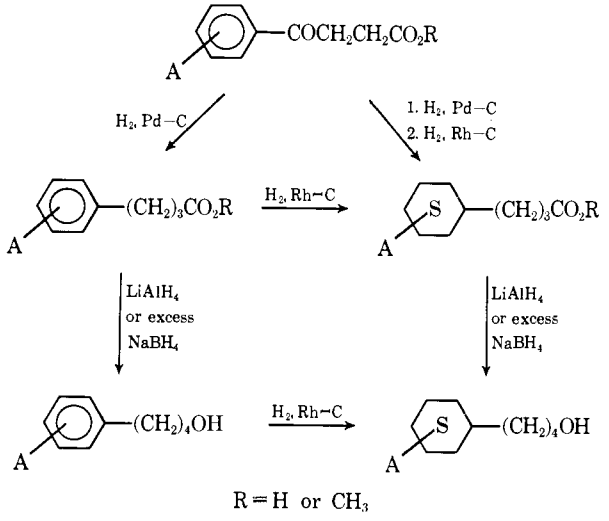
(6) S. Searles, *ibid.*, **73**, 124 (1951).

methyl group as a nitrogen substituent of S-2-aminoethyl thiosulfate required yet another approach: *trans*-2-phenylcyclopropanecarbonyl chloride + $H_2NCH_2CH_2OH$ → 2-hydroxyethylamide + $LiAlH_4$ → 2-(substituted amino)ethanol + $SOCl_2$ → 2-(substituted amino)ethyl chloride hydrochloride + $Na_2S_2O_3$ → Bunte salt.

The high order of antiradiation activity of S-2-{[4-(cyclohexyl)butyl]amino}ethyl thiosulfate (**16**) prompted a study of the effects on biological activity of substitution of the cyclohexane ring. Two synthetic approaches were considered: (1) catalytic hydrogenation of aromatic intermediates and (2) use of the three cyclohexenyl derivatives as intermediates for addition reactions giving rise to substituted cyclohexanes. Hydrogenation of di- and trisubstituted benzenes gives mixtures of isomeric products requiring physical methods to separate racemates. However, since aryl-substituted S-2-alkylaminoethyl thiosulfates are effective antiradiation agents, it seemed desirable to use the hydrogenation approach in order at the same time to study substituted phenyl compounds as antiradiation agents. Substitution of the cyclohexane ring is not a technique used widely by medicinal chemists in studying structure–activity relationships. In our opinion the lack of precedence justified the preparation and testing of a limited selection of mixtures of isomeric substituted cyclohexanes. Vapor phase chromatographic analysis indicated that some of the alcohols and halides used to prepare S-2-alkylaminoethyl thiosulfates were largely one component and others were mixtures. In the case of **31**, racemates of the intermediate 4-(4-chlorobutyl)-cyclohexyl methyl ether were separated using preparative gas chromatography. Enough of one racemate was obtained to prepare the desired Bunte salt.

Friedel–Crafts reactions were used to prepare the di- and trisubstituted benzenes for conversion to substituted cyclohexanes. We selectively employed succinic anhydride, monomethyl succinate, and methyl 3-(chloroformyl)propionate to acylate the various substituted benzenes. The resulting α-keto acids or esters were reduced in stages to obtain 4-aryl-1-butanols and 4-(substituted cyclohexane)butanols (Scheme I). Friedel–Crafts acylation of *p*-chlorophenetole with succinic anhydride resulted in cleavage of the ether and isolation of only 3-(5-chlorosalicyloyl)propionic acid. The chlorine atom was removed in the hydrogenation step which followed, giving as a final product the 4-(*o*-hydroxyphenyl)butyl derivative **66**. Ether cleavage of *p*-(4-chlorobutyl)anisole using BBr_3[7] gave *p*-(4-chlorobutyl)phenol for the preparation of **67**, a position isomer of **66**.

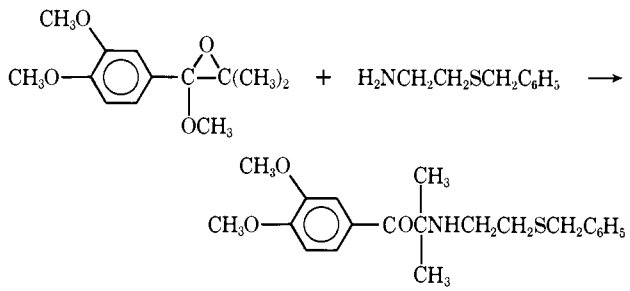
Scheme I



The series of alicyclic ethers found in Table II required as intermediates alkyl halides which were prepared in benzene or toluene from cycloalkanols or cycloalkylalkanols, excess α,ω-dibromoalkanes, and NaH. In some cases an α-bromo-ω-chloroalkane was used in the reaction.

The aryl ethers in Table IV required intermediate halo ethers which were prepared from appropriately substituted phenols and α,ω-dibromoalkanes in the presence of K_2CO_3. Branched-chain compounds in this aryl ether series were prepared similarly from α-bromo esters. Dehydrohalogenation of the α-bromo ester could be expected in this case, but apparently K_2CO_3 is not a strong enough base for dehydrohalogenation to compete successfully with substitution by phenoxide ion. If formed, an α,β-unsaturated ester would add phenoxide ion to give a β-substituted ether. Homogeneous products were obtained and structures were confirmed by nmr spectra. Precedence for the desired α substitution has been reported in early literature.[8]

Several hydroxy-substituted compounds were synthesized. Compound **140** is an example of the use of an epoxide to alkylate S-2-aminoethyl thiosulfate. Another case is the reaction of 2-(benzylthio)ethylamine with 1-(3,4-dimethoxyphenyl)-1,2-epoxy-1-methoxy-2-methylpropane[9] leading to a compound related

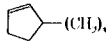
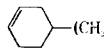
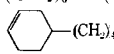


to epinephrine. The following transformations afforded a Bunte salt from the ring-opened product: ketone + $LiAlH_4$ → alcohol + Na–NH_3 → thiol + O_2 → disulfide + SO_3^{2-} → Bunte salt (**143**). Structures with this degree of substitution are almost devoid of analeptic activity.

Biological Activity.—The Bunte salts were tested in mice[10] for antiradiation activity at Walter Reed Army Institute of Research.[11] Protection data are given for intraperitoneal administration of the compounds.

(7) D. L. Manson and O. C. Musgrave, *J. Chem. Soc.*, 1011 (1963).
(8) C. A. Bischoff, *Ber.*, **33**, 1249 (1900).
(9) The compound [bp 101–103° (0.2 mm)] was supplied by Dr. R. W. Fleming, Parke-Davis. For preparation of epoxy ethers of this type see C. L. Stevens, W. Malik, and R. Pratt, *J. Am. Chem. Soc.*, **72**, 4758 (1950).
(10) Female albino mice 6–8 weeks old are used in the test. For the initial screening results the maximum and one-half the maximum tolerated doses are injected intraperitoneally into two groups of 15 mice each, and ten control mice are injected with the vehicle only.
(11) For a description of the test method see W. L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964), and E. R. Atkinson G. R. Handrick, R. J. Bruni, and F. E. Granchelli, *ibid.*, **8**, 29 (1965).

TABLE 1: S-2-(CYCLOALKYLALKYLAMINO)ETHYL THIOSULFATES $RNHCH_2CH_2S_2O_3H$

No.	R	RX Source	RX Bp, °C (mm)	RX Ghpc, %	Method[a]	Recrystn solvents[b]	Yield, %	Mp, °C	Formula[m,n]	Antiradiation act.[c,e,o] Ca. LD_{50}, mg/kg	Drug dose, mg/kg	Min preir-radiation	Radiation, dose, R	Survival, %	Rating
1	$(CH_2)_5CH$				I[d]	A	9	222–224	$C_8H_{17}NO_3S_2$	175	100			0	0
2	$(CH_2)_3CH(CH_2)_3$	*c, f*			II	B, A	33	211–212.5	$C_9H_{19}NO_3S_2$	200	25	30	1000 G	7	0
3	$(CH_2)_5CHCH_2$				I[g]	B	26	210–216	$C_9H_{19}NO_3S_2$	350	125	15	825 X	20	+
4	$(CH_2)_4CH(CH_2)_3$				I[h]	A	31	200–202.5	$C_{10}H_{21}NO_3S_2$	>150	112	15	1000 G	13	0
5	$(CH_2)_5CH(CH_2)_2$				III	C	19	194–195	$C_{10}H_{21}NO_3S_2$	90	50	15	1000 G	27	+
6		*i, j*	80–86 (11)	80	II	A, D	28	177–184	$C_{11}H_{21}NO_3S_2$						
7		*i, k*	89–90 (12)	87	II	A	27	186–194	$C_{11}H_{21}NO_3S_2$		40			13	0
8	$(CH_2)_3CH(CH_2)_5$	*c, f*	111–113 (19)	90	II	A	13	218–221	$C_{11}H_{23}NO_3S_2$	150	25	15	1000 G	87	++++
9	$(CH_2)_4CH(CH_2)_4$	*i, l*	100–102 (21)		II	A	8	200–203	$C_{11}H_{23}NO_3S_2$	175	37.5*	15	1000 G	90	+++
10	$(CH_2)_4CHCH(C_2H_5)CH_2$	*c, m*	80–84 (1.7)	50	II	A	10	163–168	$C_{11}H_{23}NO_3S_2$	140	50	30	1000 G	40	++
11	$(CH_2)_5CH(CH_2)_3$	*c, n*			II	C	22	227–228	$C_{11}H_{23}NO_3S_2$	150	100	15	825 X	86	+
12	$(CH_2)_5CHCH(CH_3)CH_2$	*c, o*	53–55 (0.5)	90	II	A	7	206–211	$C_{11}H_{23}NO_3S_2$	120	50	15	1000 G	40	+
13	$(CH_2)_6CH(CH_2)_2$	*c, p*	62–72 (0.5)		II	A	24	210–214	$C_{11}H_{23}NO_3S_2$	80	50	15	1000 G	40	+
14		*i, q*	112–113 (14)	90	II	D, A	19	177–183	$C_{12}H_{23}NO_3S_2$	75	25	15	1000 G	100	++++
											12.5	15	1000 G	87	
15	$(CH_2)_5CH(CH_2)_4$, Na salt					E	70	*Ca.* 80–100	$C_{12}H_{24}NNaO_3S_2 \cdot H_2O$[m,n]	15	10	30	1000 G	93	++
											5	15	1050 G	79	
16	$(CH_2)_5CH(CH_2)_4$	*i, r*			I[p]	A	44	225–227	$C_{12}H_{25}NO_3S_2$	50	10	18	825 X	87	++++
					II	A	26				5	18	825 X	80	
17	$(CH_2)_4CH(CH_2)_5$	*i, s*	56–66 (0.6)		II	B, A	10	209–212	$C_{12}H_{25}NO_3S_2$	25	10	15	1000 G	53	++
18	$(CH_2)_5CHCH(C_2H_5)CH_2$	*c, f*	110–111 (13)	99	II	A	16	184–187	$C_{12}H_{25}NO_3S_2$	300	50	30	1000 G	80	+++
19	$(CH_2)_4CH(CH_2)_6$	*i, l*	74–80 (1)	100	II	A	9	212–216	$C_{13}H_{27}NO_3S_2$						
20	$(CH_2)_4CHCH(C_4H_9)CH_2$	*c, u*		98	II	A	35	200–203	$C_{13}H_{27}NO_3S_2$	135	50	30	1000 G	40	+
21	$4\text{-}CH_3[(CH_2)_5CH](CH_2)_4$	*i, f*	69–72 (0.8)	60–40	II	F, A	18	222–223	$C_{13}H_{27}NO_3S_2$	7	5	30	1000 G	80	+
22	$(CH_2)_5CH(CH_2)_5$	*c, v*	78 (0.3)		II	A	19	217–220	$C_{13}H_{27}NO_3S_2$	10	5	15	825 X	7	0
23	$3\text{-}CH_3[(CH_2)_5CH](CH_2)_4$	*c, w*	63–71 (0.5)		II	G, A, D	4	226–227.5	$C_{13}H_{27}NO_3S_2$	8	5	30	1000 G	100	+
											2.5	30	1000 G	60	
24	$(CH_2)_5CHCH(CH_3)(CH_2)_3$	*c, x*	78–80 (0.6)		II	A, D, A	23	213–216	$C_{13}H_{27}NO_3S_2$	80	20	30	1000 G	100	+++
											10	30	1000 G	53	
25	$(CH_2)_5CHCH(C_2H_5)(CH_2)_2$	*c, x*	68–72 (0.2)	90	II	A	7	167–169	$C_{13}H_{27}NO_3S_2$	150	50	15	1000 G	66	++++
											25	15	1000 G	60	
26	$(CH_2)_5CHCH_2CH(C_2H_5)CH_2$	*c, y*			II	H, I	21	174–175	$C_{13}H_{27}NO_3S_2$	140	50	30	1000 G	100	++++
											25	30	1000 G	73	
27	$(CH_2)_5CHCH(C_3H_7)CH_2$	*c, o*	70–77 (0.5)	94	II	A	50	198–199	$C_{13}H_{27}NO_3S_2$	300	75	30	1000 G	13	0
28	$3\text{-}CH_3[(CH_3)_5CH]CH(C_2H_5)CH_2$	*c, o*	72–74 (0.5)	80	II	A	10	160–162	$C_{13}H_{27}NO_3S_2$	170	100	30	1000 G	93	++++
											25	30	1000 G	53	
29	$(CH_2)_6CH(CH_2)_4$	*c, z*	87 (0.5)		II	A	11	212–216	$C_{13}H_{27}NO_3S_2$	15	5	30	1000 G	87	++
30	$2\text{-}CH_3O[(CH_2)_5CH](CH_2)_4$	*c, f*	75–85 (0.2)		II	A, D, A	11	204–207	$C_{13}H_{27}NO_4S_2$	175	25	15	1000 G	93	+++
31	$4\text{-}CH_3O[(CH_2)_5CH](CH_2)_4$	*i, f*	*f*	91	II	A	10	203–204	$C_{13}H_{27}NO_4S_2$	200	50	15	1000 G	33	+
32	$(CH_2)_4CH(CH_3)_7$	*i, aa*	75–100 (0.3)		II	A	15	216–220	$C_{14}H_{29}NO_3S_2$	13	5	30	1000 G	7	0
33	$(CH_2)_5CH(CH_2)_6$				I[q]	A	22	218–220	$C_{14}H_{29}NO_3S_2$	10	5	30	825 X	53	+
34	$4\text{-}C_2H_5[(CH_2)_5CH](CH_2)_4$	*i, bb, cc*			II	A	15	224–226	$C_{14}H_{29}NO_3S_2$	7	3	15	1000 G	13	0
35	$2,4\text{-}(CH_3)_2[(CH_2)_5CH](CH_2)_4$	*i, dd*	73–78 (0.7)		II	J, A	16	212–213	$C_{14}H_{29}NO_3S_2$	25	20	15	1000 G	73	+
36	$2,5\text{-}(CH_3)_2[(CH_2)_5CH](CH_2)_4$	*i, bb, cc*			II	A	6	208–210	$C_{14}H_{29}NO_3S_2$	25	15	15	1000 G	87	+
											7.5	15	1000 G	33	
37	$(CH_3)_5CHCH(C_2H_5)(CH_2)_3$	*c, ff*	96–98 (1)	70	II	K, H	30	184–185	$C_{14}H_{29}NO_3S_2$	75	25	30	1000 G	80	+
38	$(CH_2)_5CH(CH_2)_2CH(C_2H_5)CH_2$	*c, bb, gg*			II	H	40	178–179	$C_{14}H_{29}NO_3S_2$	44	30	30	1000 G	87	+++
											7.5	30	1000 G	73	
39	$(CH_2)_6CH(CH_2)_5$	*i, hh*	66–78 (0.2)		II	A	16	216–220	$C_{14}H_{29}NO_3S_2$	18	5	30	1000 G	80	++
40	$(CH_2)_4CH(CH_2)_8$	*i, ii*	90–95 (0.4)		II	A	22	213–216	$C_{15}H_{31}NO_3S_2$	13	6	30	1050 G	33	+
41	$(CH_2)_6CH(CH_2)_7$	*i, jj*	79–87 (0.2)		II	A	14	206–210	$C_{15}H_{31}NO_3S_2$	25	8	30	1000 G	87	+
42	$(CH_2)_5CHCH(C_6H_5)CH_2$	*e*		90	II	A, M	6	208	$C_{16}H_{25}NO_3S_2$	>400	50	30	1000 G	27	++

43	$(CH_2)_4CH(CH_2)_9$	,[kk]	104–115 (0.8)	II	A	15	189–193	$C_{16}H_{33}NO_3S_2$					
44	Decahydro-2-naphthyl-$(CH_2)_4$	*i*, *f*	177–178 (19)	II	A, L, N	8	217–220	$C_{16}H_{31}NO_3S_2$	18	8	30	1000 G	53	+
45	$(CH_2)_5CH(CH_2)_8$	*bb*, *ll*		II	L, A	33	222–225	$C_{16}H_{33}NO_3S_2$		5			73	
46	4-Cyclohexylcyclohexyl-$(CH_2)_4$	*i*, *f*	205–209 (19)	II	L, A	7	224–226	$C_{18}H_{35}NO_3S_2$	20	10	30	1000 G	27	+

[a] I, $(RNHCH_2CH_2S-)_2 + SO_3^{2-} + O_2 \rightarrow RNHCH_2CH_2S_2O_3H$; II, $RX + H_2NCH_2CH_2S_2O_3Na \rightarrow RNHCH_2CH_2S_2O_3H$; III, $RBr + H_2NCH_2CH_2OH \rightarrow RNHCH_2CH_2OH + HBr$ or $SOCl_2 \rightarrow RNHCH_2CH_2X \cdot HX + Na_2S_2O_3 \rightarrow RNHCH_2CH_2S_2O_3H$. [b] A, EtOH; B, 95% EtOH; C, H_2O; D, Me_2CO; E, THF; F, 80% EtOH; G, EtOAc; H, EtCOMe; I, Me_2CO–EtOH; J, MeCN; K, *t*-BuCOMe–H_2O; L, MeOH; M, EtOH–DMF; N, *n*-PrOH; O, *n*-PrOH–Et_2O; P, *n*-BuOH; Q, Me_2CO–Et_2O; R, EtOH–Et_2O; S, EtOH–H_2O; T, Me_2CO–H_2O; U, Me_2CO–2,2-dimethoxypropane. [c] The radiation dose in Roentgens was supplied by either X-rays (indicated by X) or cobalt-60 γ rays (indicated by G). For each test 15 mice were treated with drug and irradiated. When fewer than 15 mice were used (generally 6) the drug dose is marked with an asterisk. [d] Thiol: F. Yu. Rachinskii, N. M. Slavachevskaya, and D. V. Ioffe, *Zh. Obshch. Khim.*, **28**, 2998 (1958); *Chem. Abstr.*, **53**, 9045 (1959). [e] ROH + PBr_3–pyridine. [f] See Experimental Section. [g] Thiol: R. D. Westland, J. L. Holmes, B. Green, and J. R. Dice, *J. Med. Chem.*, **11**, 824 (1968). [h] Thiol: R. J. Wineman, M. H. Gollis, J. C. Jaines, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962). [i] ROH + $SOCl_2$–pyridine. [j] ROH: J. A. Arvin and R. Adams, *J. Am. Chem. Soc.*, **50**, **59**, 1790 (1928). [k] 4-(Chloromethyl)cyclohexene: M. F. Clarke and N. L. Owen, *J. Chem. Soc.*, 2108 (1950). $RMgCl + (CH_2)_2O$. [l] ROH: G. R. Yohe and R. Adams, *J. Am. Chem. Soc.*, **50**, 1503 (1928). RCl: *Anal.* ($C_9H_{17}Cl$) C, H. [m] Ethyl α-ethylcyclopentane-Δ^1,α-acetate [H. A. R. Kon and B. T. Narayanan, *J. Chem. Soc.*, 1536 (1927)] + H_2/20% Pd–C $\rightarrow$ crude ester + $LiAlH_4$ $\rightarrow$ ROH [bp 72–80° (0.5 mm). *Anal.* ($C_9H_{18}O$) C, H]. [n] Aldrich Chemical Co. [o] Reformatsky reaction involving cyclohexanone or an aldehyde and an α-bromo ester. Dehydration of the condensation product was followed by two reductions (H_2/Pd–C, $LiAlH_4$). Each of the intermediates was distilled and characterized by its ir spectrum and gas chromatogram. See Experimental Section and O. Wallach, *Ann.*, **360**, 59 (1908). [p] ROH: O. Wallach, *ibid.*, **353**, 301 (1907). [q] ROH [bp 120–130° (12 mm)] from 3-cyclohexenemethylmagnesium chloride and trimethylene oxide. [r] ROH: G. S. Hiers and R. Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926). [s] ROH: L. F. Fieser, *et al.*, *ibid.*, **70**, 3195 (1948). [t] ROH: K. Bursehkies and J. Scholl, *Arch. Pharm.*, **281**, 328 (1943); *Chem. Abstr.*, **38**, 5801 (1944). RCl: *Anal.* ($C_{11}H_{21}Cl$) C, H. [u] ROH: α-ethylcyclopentaneacetic acid (footnote *n*) + $LiAlH_4$; bp 89–90° (1.2 mm). [v] R. F. Collins and M. Davis, *J. Chem. Soc.*, 1863 (1961). [w] 3-Methylcyclohexanecthanol [F. Becherer, *Helv. Chim. Acta*, **8**, 184 (1925)] $\rightarrow$ RBr + Mg + $(CH_2)_2O \rightarrow$ ROH, bp 73–85 (0.5 mm). [x] Resolved forms; P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **97**, 563 (1932). [y] ROH: K. Folkers, *J. Am. Chem. Soc.*, **58**, 1558 (1936). Crude halide was used. [z] 2-(Bromoethyl)cyclohcptane + Mg + $(CH_2)_2O$. [aa] S. Pilat and N. Turkiewicz, *Ber.*, **72B**, 1527 (1939). [bb] Crude alkyl halide was used for the alkylation. [cc] See process for **31**; the halide was not subjected to preparative glpc. [dd] See process for **30**. 4-(*o*,*p*-Dimethylphenyl)butyric acid: P. Karrer, P. Portman, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948); P. Karrer and P. Portman, *ibid.*, **31**, 2088 (1948). [ee] See process for **21**. 4-(*o*,*p*-Dimethylphenyl)-1-butanol: W. E. Truce and F. D. Hoerger, *J. Am. Chem. Soc.*, **76**, 5357 (1954). [ff] ROH: [2-(bromomethyl)propyl]cyclohexane (Experimental Section) + Mg + $(CH_2)_2O$; bp 83–93° (0.3 mm) and glpc 80%. [gg] See footnote *o*. ROH: bp 87–93° (0.6 mm) and glpc 98%. [hh] ROH: (4-bromobutyl)cyclohcptane (*cf.* **29**) + Mg + CO_2; $LiAlH_4$. [ii] ROH: see process for **47**; bp 92–110° (0.4 mm). [jj] (4-Bromobutyl)cyclohcptane (footnote *z*) + Mg + $(CH_2)_2O$. [kk] (7-Chloroheptyl)cyclopentane (footnote *aa*) + Mg + $(CH_2)_2O$. [ll] (7-Chloroheptyl)cyclohexane + Mg + $CO_2 \rightarrow$ cyclohexaneoctanoic acid (reference in footnote *r*); $RCO_2H + LiAlH_4$. [mm] All compounds were analyzed for C, H, N, S. [nn] Additional analyses: H_2O, Na. [oo] Ratings are based on the following ranges of protective indices (footnote 12 in the text): 0, 0–1; +, 2–5; ++, 6–10; +++, 11–15; ++++, 16–29. The ratings are a measure of the lowest dose for which some antiradiation activity was obtained. The per cent survival given in the table represents the lowest dose of drug for which a high rate of survival was obtained.

Highly active compounds also were tested by oral administration and these data are used in some of the evaluations which follow.

The antiradiation activity data given in Tables I–V 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. Data for more than one dose of drug are included for selected compounds which exhibited good protection at more than one dose. Irradiation of the mice with X-rays or cobalt-60 γ rays was not always at the same level, but the radiation was consistently lethal for all control animals well within the 30-day period. The number of minutes the drugs were administered preirradiation was varied upward from 15 min. Ratings in Tables I–V are based on protective indices.[12] A high survival rate and a low rating (low protective index) indicates that the compound did not protect well at doses lower than those shown. The protective index in a sense is a measure of protection at the lowest dose for which some antiradiation activity was obtained. Twenty per cent survival is the smallest value used to determine ratings.

Table VI shows a comparison of the most active compounds. Most of these were active at more than one dose and it was possible, therefore, to obtain dose–response curves. The effective dose given in Table VI is the dose estimated to give 50% survival of the animals in the 30-day test. The therapeutic index as given in the table is the LD_{50} value divided by the effective dose. Among the group of cycloalkylalkyl derivatives highly active compounds were obtained by incorporating cyclobutyl, cyclopentyl, and cyclohexyl groups. The best activity in this series was obtained when the alkyl group insulating the ring from the amino group was butyl, pentyl, or hexyl. It is interesting that branching of the insulating group in this series, rather than decreasing biological effectiveness, in some cases actually increases the therapeutic index. Substitution of the cyclohexane ring results in highly active compounds, although it should be noted that a 3-cyclohexenyl derivative (**14**) is one of the most highly effective agents. The presence of mixtures of isomers in the group of substituted cyclohexanes complicates interpretation of the test data.

Activity by oral administration of the drugs (Table VII) does not correlate with high therapeutic indices based on parenteral administration. Several compounds showed slight or fair protection at doses close to toxic limits, but only a few gave good protection and then at only a single dose. Among the alicyclic alkyl compounds, the cyclopentanehexyl derivative **19** is the most promising candidate for oral administration.

Use of 1-methylcyclohexyl and cyclooctyl groups in the series of alicyclic ethers resulted in compounds giving radiation protection. The cyclooctyl derivative **61** was reasonably effective when given by the oral route.

General activity was found among aralkyl derivatives (Table III), but therapeutic indices are lower for the group. The *p*-anisylbutyl derivative **70** is an exception. It has a therapeutic index of 10, but its protec-

(12) "Protective index" is a term used by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. Protective index = (protection factor)(LD_{50}/minimum effective dose), where doses are in mg/kg and the protection factor is 1.2 for 20% survival, 1.3 for 30% survival, etc.

TABLE II: S-2-(CYCLOALKYLOXY- AND CYCLOALKYLALKYLOXY)ALKYLAMINO)ETHYL THIOSULFATES $RNHCH_2CH_2S_2O_3H$

No.	R	Source	Bp, °C (mm)	Cpd, %	Method[b]	Recrystn solvents[c]	Yield, %	Mp, °C	Formula[d]	Ca. LD_{50}, mg/kg	Drug dose, mg/kg	Min preirradiation	Radiation dose, R	Survival, %	Ratio
47	$(CH_2)_5CHO(CH_2)_4$	*d*	120–130 (15)		II	O, P	12	156–157	$C_{11}H_{25}NO_4S_2$	150	50	15	1000 G	0	0
48	$(CH_2)_4CHO(CH_2)_5$	*d*	82–95 (0.4)	95	II	Q, G, C, D	15	200–202	$C_{12}H_{25}NO_4S_2$		100			67	
49	$(CH_2)_5CHO(CH_2)_4$	*e*	56–67 (0.1)		II	D, A	7	198–200	$C_{12}H_{25}NO_4S_2$	125	75	15	825 X	47	+
50	$(CH_2)_5CHO(CH_2)_5$	*d, f*	65–75 (0.1)		II	R, D	18	200–202	$C_{13}H_{27}NO_4S_2$	150	75	15	825 X	87	++
											37.5	15	825 X	60	+
51	$(CH_2)_4CHO(CH_2)_6$	*d*	100–120 (0.4)	65	II	D, H	11	197–200	$C_{13}H_{27}NO_4S_2$	150	50	15	1000 G	60	+
52	$(CH_2)_6CHO(CH_2)_4$	*d*	95–115 (0.6)		II	A	20	198–200	$C_{13}H_{27}NO_4S_2$	150	75	15	1000 G	87	++
53	$(CH_2)_5CHO(CH_2)_6$	*d*	87–97 (0.1)		II	D, S	11	209–211	$C_{14}H_{29}NO_4S_2$	150	20	15	1000 G	33	+
54	$(CH_2)_5CHCH_2O(CH_2)_5$	*d*	98–100 (0.6)		II	T, D	14	201–203	$C_{14}H_{29}NO_4S_2$	18	12.5	15	1000 G	47	++
55	$(CH_2)_5CH(CH_2)_2O(CH_2)_4$	*d*	97–102 (0.05)	70	II	Q, D	21	192–195	$C_{14}H_{29}NO_4S_2$	38	15	30	1000 G	53	+
56	$2\text{-}CH_3[(CH_2)_5CH]O(CH_2)_5$	*d*	87 92 (0.3)		II	A	8	213–215	$C_{14}H_{29}NO_4S_2$	75	8	30	1050 G	13	0
57	$4\text{-}CH_3[(CH_2)_5CH]O(CH_2)_5$	*d*	90–100 (0.5)		II	G, A	6	209–210	$C_{14}H_{29}NO_4S_2$		12			27	
58	$1\text{-}CH_3[(CH_2)_5CH]O(CH_2)_5$	*d*	93–105 (0.6)		II	G, J, C, J	10	196–199	$C_{14}H_{29}NO_4S_2$	150	25	15	1000 G	80	+
59	$(CH_2)_6CHO(CH_2)_5$	*d*	97–110 (0.4)		II	A, D	14	196–202	$C_{14}H_{29}NO_4S_2$	35	25	15	1000 G	87	+
60	$(CH_2)_7CHO(CH_2)_4$	*d*	108–117 (0.5)	95	II	H	39	194–195	$C_{14}H_{29}NO_4S_2$	250	50	30	1000 G	80	+
61	$(CH_2)_7CHO(CH_2)_5$	*d*	130–137 (0.4)	95	II	H	40	200–203	$C_{15}H_{31}NO_4S_2$	50	12.5	15	1050 G	87	+
62	$(CH_2)_5CHCH(C_2H_5)O(CH_2)_4$	*d*	112–120 (1.2)	92	II	D	12	170–171	$C_{15}H_{31}NO_4S_2$	110	60	15	1000 G	80	+
63	$(CH_2)_5CHO(CH_2)_5$	*d*	126–140 (0.5)	96	II	A, L	5	188–191	$C_{16}H_{33}NO_4S_2$	15	10	15	1050 G	67	+

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See footnotes *c* and *m*, Table I. [d] See preparation of 4-bromobutyl cyclohexyl ether in Experimental Section. All are alkyl bromides except as noted. [e] See Experimental Section. [f] J. N. Ashley, R. F. Collins, M. Davis, and N. E. Sirett, *J. Chem. Soc.*, 897 (1950). [g] All compounds were analyzed for C, H, N, S.

tive effect when given orally is the more important feature. The *p*-ethylphenyl (**73**) and *p*-ethoxyphenyl (**76**) derivatives also exhibited significant activity by oral administration, even though parenteral data are mediocre.

Aryloxyalkyl compounds as a class are highly effective. Methyl substitution, either *ortho* or di-*ortho*, leads the list. The insulating alkyl group can be butyl, pentyl, or hexyl for the *o*-tolyl ether (Table VI). Activity by oral administration was not obtained with these compounds, however. *p*-Tolyloxybutyl (**100**), *m*-chlorophenoxybutyl (**88**), and *p*-ethyl-*o*-methoxyphenoxybutyl (**118**) derivatives showed moderate activity by oral dosing. In the case of unsubstituted phenyl the butyl ether **94** and hexyl ether **114** were inactive, whereas the pentyl ether **101** displayed good activity. Branching of the alkyl group in the aryl ether series gave compounds devoid of antiradiation properties.

It is apparent that within these several series are numerous compounds which in the mouse can be administered to obtain a good radioprotective effect at one-tenth to one-fifteenth the toxic (LD_{50}) doses.

Experimental Section[13]

2-{[2-(Benzylthio)ethyl]amino}-3',4'-dimethoxy-2-methylpropiophenone Hydrochloride.—A solution containing 24 g (0.1 mole) of 1-(3,4-dimethoxyphenyl)-1,2-epoxy-1-methoxy-2-methylpropane[9] and 33 g (0.2 mole) of 2-(benzylthio)ethylamine was allowed to stand at room temperature for 3 days and then at steam-bath temperature for 3 days. Excess 2-(benzylthio)-ethylamine was removed by distillation, recovering 12 g of liquid, bp 100–103° (0.1 mm). A mixture of the pot residue and charcoal in 400 ml of Et_2O was warmed and filtered. Dry HCl was added to the light yellow filtrate, precipitating a semisolid salt. The Et_2O layer was decanted and the product was triturated with 200 ml of warm Me_2CO to effect crystallization. The mixture was chilled and filtered to give 21 g (51%) of crystalline product, mp 177–180°. Recrystallization from Me_2CO provided 16 g of product with no increase in melting point. *Anal.* ($C_{21}H_{27}NO_3S\cdot HCl$) C, H, N. A 0.2-mole preparation gave 40.5 g (50%) of the same product, mp 177–179°.

α-(1-{[2-(Benzylthio)ethyl]amino}-1-methylethyl)-3,4-dimethoxybenzyl Alcohol.—A slurry of 20.5 g (0.05 mole) of 2-{[2-(benzylthio)ethyl]amino}-3',4'-dimethoxy-2-methylpropiophenone hydrochloride in Et_2O–C_6H_6 (1:1) was treated with 50 ml of 1 *N* NaOH. The organic layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated. The residual oil was reduced with 1.9 g of $LiAlH_4$ in 250 ml of Et_2O.[14] Filtration of the decomposed (NaOH) mixture and concentration of the filtrate afforded only 1 g of oily material. A slurry of the separated solid (mostly inorganic) in 15% NaOH solution was filtered and the insoluble material was washed well with H_2O. Two recrystallizations of the solid from EtOH gave 13 g (70%) of product, mp 146–149°. Another 2.2-g sample (mp 146–149°) was obtained from the crystallization liquors; total yield, 15 g (82%). A 1-g sample was recrystallized from EtOH giving 0.95 g of product, mp 145–148°. *Anal.* ($C_{21}H_{29}NO_3S$) C, H, N, S.

α,α'-[Dithiobis(ethyleniminoisopropylidene)]bis(3,4-dimethoxybenzyl Alcohol).—Debenzylation of 12.2 g (0.032 mole) of α-(1-{[2-(benzylthio)ethyl]amino}-1-methylethyl)-3,4-dimethoxybenzyl alcohol was effected by the use of Na in liquid NH_3.[15,16] The solid obtained from the decomposed (H_2O–NH_4Cl) mixture was washed well (H_2O) and recrystallized from EtOH giving 6.5 g of crude product in several crops, mp 144–152°. The combined

(13) Melting points 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 are within ±0.4% of the theoretical values.

(14) W. G. Brown, *Org. Reactions*, **6**, 469 (1951).

(15) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 800 (1952).

(16) F. I. Carroll, D. White, and M. E. Wall, *J. Org. Chem.*, **28**, 1236 (1963).

Table III

S-2-(Aralkylamino)ethyl Thiosulfate

$RNHCH_2CH_2S_2O_3H$

No.	R	RX Source	RX Bp, °C (mm)	RX Glpc, %	Method[a]	Recrystn solvents[b]	Yield, %	Mp, °C	Formula[z]	Antiradiation act.[c] Ca. LD_{50}, mg/kg	Drug dose, mg/kg	Drug dose, min preirradiation	Radiation, dose, R	Survival, %	Rating
64		*d*			III	M	78	188–190	$C_{12}H_{17}NO_3S_2$	75	50	15	1000 G	13	0
65	4-$ClC_6H_4CH(C_2H_5)CH_2$	*e*, *f*	83–86 (0.5)		II	B, A	29	198–200	$C_{12}H_{18}ClNO_3S_2$	140	75	15	1000 G	73	+
66	2-$HOC_6H_4(CH_2)_4$	*e*, *g*	110–115 (0.1)		II	C, M	6	186–187	$C_{12}H_{19}NO_4S_2$	300	100	15	1000 G	13	0
67	4-$HOC_6H_4(CH_2)_4$	*e*, *h*	141–145 (2)		II	C, J, A	13	187–188	$C_{12}H_{19}NO_4S_2$	250	150	15	1000 G	27	+
68	2-$CH_3OC_6H_4(CH_2)_3$	*e*, *i*			II	A	11	179–180	$C_{12}H_{19}NO_4S_2$	175	75	15	1000 G	20	+
69	4-$CH_3OC_6H_4(CH_2)_3$	*e*, *j*	106–110 (0.4)		II	L	18	180–181	$C_{12}H_{19}NO_4S_2$	200	75	30	1050 G	47	+
70	4-$CH_3OC_6H_4(CH_2)_4$	*h*, *k*, *l*		95	II	A	7	181–182	$C_{13}H_{21}NO_4S_2$	120	50*	15	825 X	100	+++
											30	15	1000 G	87	
71	3-$CH_3OC_6H_4(CH_2)_4$	*e*, *m*	115–117 (0.3)		II	A	41	167–169	$C_{13}H_{21}NO_4S_2$	150	37.5	15	1000 G	80	++
72	3-$CH_3OC_6H_4CH(C_2H_5)CH_2$	*e*, *n*	96–102 (0.7)		II	B, C	18	130–135	$C_{13}H_{21}NO_4S_2$	100	40	15	1000 G	20	+
73	4-$C_2H_5C_6H_4(CH_2)_4$	*h*, *k*, *o*			II	C	15	210–212	$C_{14}H_{23}NO_3S_2$	15	5	15	1000 G	60	+
74	2,4-$(CH_3)_2C_6H_3(CH_2)_4$	*h*, *k*, *p*			II	A	14	214–215	$C_{14}H_{23}NO_3S_2$	38	15	30	1000 G	73	+
75	2,5-$(CH_3)_2C_6H_3(CH_2)_4$	*e*, *q*	79–85 (0.5)		II	A	22	214–215	$C_{14}H_{23}NO_3S_2$	20	10	30	1000 G	73	+
76	4-$C_2H_5OC_6H_4(CH_2)_4$	*e*, *r*	115–123 (0.3)		II	A	19	206–207	$C_{14}H_{23}NO_4S_2$	22	15	15	1000 G	47	+
77	4-$CH_3OC_6H_4(CH_2)_5$	*e*, *s*	100–107 (0.03)		II	B, A	36	181–184	$C_{14}H_{23}NO_4S_2$	45	15	30	1050 G	80	+
78	3,4-$(CH_3O)_2C_6H_3(CH_2)_4$	*t*	120–142 (0.3)		II	A	8	166–168	$C_{14}H_{23}NO_5S_2$	350	200*	15	825 X	83	+
79	4-$CH_3OC_6H_4(CH_2)_6$	*e*, *u*	128–135 (0.7)		II	B, D, A, D	19	183–186	$C_{15}H_{25}NO_4S_2$	>40	10	30	1000 G	80	++
80	4-$[(CH_2)_5CH]C_6H_4(CH_2)_4$	*h*, *k*, *v*			II	L, A	10	223–225	$C_{18}H_{29}NO_3S_2$	15	8	15	1000 G	53	+
81	2-Phenanthryl-$(CH_2)_4$	*h*, *k*, *w*			II	A	17	208–211	$C_{20}H_{23}NO_3S_2$	100	75	30	1000 G	0	0
82	9,10-Dihydro-2-phenanthryl-$(CH_2)_4$	*h*, *k*, *x*			II	M	15	216–217	$C_{20}H_{25}NO_3S_2$[y]	750	25	30	1000 G	0	0

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] See footnotes *c* and *oo*, Table I. [d] See Experimental Section. [e] RBr. [f] ROH: 2-(*p*-chlorophenyl)butyric acid [M. A. Spielman, A. D. Geiszler, and W. J. Close, *J. Am. Chem. Soc.*, **70,** 4189 (1948)] + $LiAlH_4$. [g] Reaction between *p*-chlorophenetole and succinic anhydride (Friedel–Crafts conditions using $AlCl_3$ in $C_2H_2Cl_4$–$C_6H_5NO_2$) gave 3-(5-chlorosalicyloyl)propionic acid [S. L. Dalal, J. J. Trivedi, and N. Z. Patel, *J. Indian Chem. Soc.*, **35,** 745 (1958)]; catalytic (20% Pd–C) hydrogenation gave 4-(*o*-hydroxyphenyl)butyric acid [G. Schroeter, German Patent 562,827 (1928); *Chem. Abstr.*, **27,** 1224 (1933)]; $LiAlH_4$ reduction gave ROH [I. G. Baddeley, N. H. P. Smith, and M. A. Vickars, *J. Chem. Soc.*, 2455 (1956)]. Reaction between ROH and PBr_3 was effected in Et_2O at 25° for 18 hr. [h] RCl. [i] Aldrich Chemical Co. [j] A. Horeau, *Bull. Soc. Chim. France,* **15,** 414 (1948). [k] Crude alkyl halide was used for the alkylation. [l] H. Morren, D. Zivkovic, R. Linz, H. Strubbe, and L. Marchal, *Ind. Chim. Belge,* **28,** 123 (1963); *Chem. Abstr.*, **59,** 8732 (1963). [m] ROH: R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79,** 3114 (1957). [n] ROH [bp 95° (0.3 mm)] from diethyl ethyl(*m*-methoxyphenyl)malonate [H. Tsukamoto, H. Yoshimura, and S. Toki, *Pharm. Bull.* (Tokyo), **3,** 239 (1955); *Chem. Abstr.*, **50,** 11, 246 (1956)]. [o] 3-(*p*-Ethylbenzoyl)propionic acid + H_2/Pd–C → 4-(*p*-ethylphenyl)butyric acid [F. G. Baddar and F. L. Warren, *J. Chem. Soc.*, 944 (1939)] + $LiAlH_4$ → ROH, bp 165–172° (21 mm). [p] ROH: 4-(*o*,*p*-dimethylphenyl)butyric acid [I. M. Heilbron and B. G. Wilkinson, *ibid.*, 2537 (1930)] + $LiAlH_4$. [q] ROH: see ref in footnote *cc*, Table I. [r] ROH: *p*-chlorophenetole + (1) Mg–$(CH_2)_2O$, (2) PBr_3–Et_2O, (3) Mg–$(CH_2)_2O$. [s] J. M. von der Zanden, *Rec. Trav. Chim.*, **60,** 291 (1941), gave bp 144–145° (2 mm). [t] See footnote *o* for process. ROH (ref in footnote *m*) + $(C_6H_5O)_3PBr_2$ → RBr. [u] ROH: 6-(*p*-methoxyphenyl)hexanoic acid (ref in footnote *s*) + $LiAlH_4$. [v] ROH: see footnote *o* for process; bp 220–230° (20 mm). [w] Methyl 2-phenanthrenebutyrate [W. E. Bachman and W. S. Struve, *J. Org. Chem.*, **4,** 456 (1939)] + $LiAlH_4$. [x] ROH: $LiAlH_4$ → methyl 9,10-dihydro-2-phenanthrenebutyrate [structure was verified by conversion to acid; A. Burger and E. Mosettig, *J. Am. Chem. Soc.*, **59,** 1302 (1937)]; bp 194–195° (0.4 mm). [y] S: calcd, 16.38; found, 15.86. [z] All compounds were analyzed for C, H, N, S.

TABLE IV: S-2-(ARYLOXYALKYLAMINO)ETHYL THIOSULFATES $RNHCH_2CH_2S_2O_3H$

No.	R	RX Source	RX Bp, °C (mm)	RX Glpc, %	Method[a]	Recrystn solvents[b]	Yield, %	Mp, °C	Formula[c]	Anti-radiation act.[d] Ca. LD_{50}, mg/kg	Drug dose, mg/kg	Min pre-irradiation	Radiation, dose, R	Survival, %	Rating
83	4-$ClC_6H_4O(CH_2)_2$	*d*			IV[e]	C	5	188–190	$C_{10}H_{14}ClNO_4S_2$	150	100	30	1000 G	20	+
84	$C_6H_5O(CH_2)_3$	*f, g*			II	C, A	7	189–190	$C_{11}H_{17}NO_4S_2$	150	50	15	1000 G	7	0
85	2,4-$Cl_2C_6H_3O(CH_2)_4$	*h–j*			II	A	26	179–181	$C_{12}H_{17}Cl_2NO_4S_2$	125	25	30	1000 G	93	+++
											12.5	30	1000 G	33	
86	4-$BrC_6H_4O(CH_2)_4$	*f, k*	134–150 (0.3)	95	II	M	13	187–188	$C_{12}H_{18}BrNO_4S_2$	>150	50	30	1000 G	0	0
87	2-$ClC_6H_4O(CH_2)_4$	*f, k*	124–133 (0.4)	98	II	J, A	16	165–166	$C_{12}H_{18}ClNO_4S_2$	150	50	30	1000 G	80	++
											25	30	1000 G	20	
88	3-$ClC_6H_4O(CH_2)_4$	*f, k*	181–187 (19)		II	C, A	25	158–159	$C_{12}H_{18}ClNO_4S_2$	150	50	15	1000 G	73	+
89	4-$ClC_6H_4O(CH_2)_4$	*f, k, l*	115–130 (0.3)	98	II	M	30	171–172	$C_{12}H_{18}ClNO_4S_2$	175	75	30	1000 G	33	++
90	3-$ClC_6H_4OCH(C_2H_5)CH_2$	*f, m*	112–114 (1.5)	98	II	A	35	168–169	$C_{12}H_{18}ClNO_4S_2$	120	80	15	1000 G	13	0
91	4-$NO_2C_6H_4O(CH_2)_4$	*f, n*	156–169 (0.3)	50	II	A	19	157–159	$C_{12}H_{18}N_2O_6S_2$	250	50	30	1000 G	80	+++
											25	30	1000 G	33	
92	2-$CH_3C_6H_4O(CH_2)_3$	*h, o*	75–84 (0.7)	85	II	M	22	208–209	$C_{12}H_{19}NO_4S_2$	150	75	15	1000 G	6	0
93	3-$CH_3C_6H_4O(CH_2)_3$	*h, o*	143–148 (20)		II	A, C	11	179–181	$C_{12}H_{19}NO_4S_2$	230	80*	15	825 X	83	+
94	$C_6H_5O(CH_2)_4$	*h, g*			II	A	22	178–181	$C_{12}H_{19}NO_4S_2$	>250	200	15	1000 G	0	0
95	2-$C_2H_5OC_6H_4O(CH_2)_2$	*f, p*			II	A	10	139–143	$C_{12}H_{19}NO_5S_2$	150	100	15	1000 G	0	0
96	3-$CF_3C_6H_4O(CH_2)_4$	*h, k, q*	148–158 (20)		II	A, C	17	190–193	$C_{13}H_{18}F_3NO_4S_2$	45	30	30	1000 G	80	+
97	$C_6H_5S(CH_2)_5$	*f, r*	131–145 (0.3)		II	M	35	177–178	$C_{13}H_{21}NO_3S_3$	300	50			20	0
98	2-$CH_3C_6H_4O(CH_2)_4$	*h, g*			II	A	12	173–178	$C_{13}H_{21}NO_4S_2$	150	25	15	1000 G	78	+++
99	3-$CH_3C_6H_4O(CH_2)_4$	*h, g*			II	B, C	4	168–170	$C_{13}H_{21}NO_4S_2$	175	50	15	825 X	100	++
											25	30	825 X	7	
100	4-$CH_3C_6H_4O(CH_2)_4$	*h, g*			II	A, D	12	180–182	$C_{13}H_{21}NO_4S_2$	35	25	30	1000 G	73	+
101	$C_6H_5O(CH_2)_5$	*f, k, s*	107–117 (0.2)	95	II	J	25	157–158	$C_{13}H_{21}NO_4S_2$	>50	50	30	1000 G	80	+
											25	30	1000 G	73	
102	2-$CH_3C_6H_4OCH(C_2H_5)CH_2$	*f, m*	92–97 (1.5)	98	II	A	43	172–173	$C_{13}H_{21}NO_4S_2$	150	50	15	1000 G	0	0
103	3-$CH_3C_6H_4OCH(C_2H_5)CH_2$	*f, m*	88–91 (0.5)	95	II	A	47	176–177	$C_{13}H_{21}NO_4S_2$	90	50	30	1000 G	0	0
104	4-$CH_3C_6H_4OCH(C_2H_5)CH_2$	*f, m*	82–87 (0.6)	98	II	A, M	55	214–215	$C_{13}H_{21}NO_4S_2$	87	50	15	1000 G	0	0
105	4-$CH_3OC_6H_4O(CH_2)_4$	*f, k, l*	130–142 (0.4)		II	M	41	154–156	$C_{13}H_{21}NO_5S_2$	200	90	30	1000 G	93	++
											45	30	1000 G	60	
106	4-$CH_3OC_6H_4OCH(C_2H_5)CH_2$	*f, r*	106–113 (0.6)	97	II	A, M	46	194–195	$C_{13}H_{21}NO_5S_2$	100	112*	15	825 X	17	0
107	1-Naphthyl-O$(CH_2)_2$	*f*	mp 113–121		II	M	24	220–230	$C_{14}H_{17}NO_4S_2$	700	25	30	1000 G	0	0
108	2,3-$(CH_3)_2C_6H_3O(CH_2)_4$		113–117 (0.4)	99	II	A	32	198–200	$C_{14}H_{23}NO_4S_2$	22	7.5	30	1000 G	73	+
109	3,4-$(CH_3)_2C_6H_3O(CH_2)_4$	*f, k*	142–149 (1.5)		II	C	7	187–189	$C_{14}H_{23}NO_4S_2$	45	30	30	1000 G	87	+
											15	30	1000 G	47	
110	2,4-$(CH_3)_2C_6H_3O(CH_2)_4$	*f, k*	122–126 (1)		II	A, C	5	206–208	$C_{14}H_{23}NO_4S_2$	20	10	30	1000 G	87	++
											5	30	1000 G	40	
111	2,5-$(CH_3)_2C_6H_3O(CH_2)_4$	*f, k*	126–131 (0.7)	99	II	A	35	185–187	$C_{14}H_{23}NO_4S_2$	>40	30	30	1000 G	93	+
											15	30	1000 G	27	
112	2,6-$(CH_3)_2C_6H_3O(CH_2)_4$	*f, k*	110–123 (0.4)	99	II	M	32	213–214	$C_{14}H_{23}NO_4S_2$	250	100	30	1000 G	100	++++
											25	30	1000 G	73	
113	2-$CH_3C_6H_4O(CH_2)_5$	*f, k*	121–137 (0.6)	98	II	A	38	185–187	$C_{14}H_{23}NO_4S_2$	200	70	15	1000 G	87	+++
											18	30	1050 G	67	
114	$C_6H_5O(CH_2)_6$	*f, k, o*	115–117 (0.4)	95	II	M	16	181–182	$C_{14}H_{23}NO_4S_2$	500	50	60	1000 G	0	0
115	3-CH_3, 4-$CH_3SC_6H_3O(CH_2)_4$	*f, i, k*		90	II	D	14	174–175	$C_{14}H_{23}NO_4S_3$	187	50	15	1000 G	53	++

116	2-$CH_3C_6H_4O(CH_2)_6$	*f, k*	130–143 (0.3)	98	II	A, D	43	181–183	$C_{15}H_{25}NO_4S_2$	135	25	30	1000 G	93	++++
											12.5	30	1000 G	53	
117	4-$C_3H_7OC_6H_4O(CH_2)_4$	*f, r*	143–155 (1)	98	II	D	12	188–190	$C_{15}H_{25}NO_5S_2$	95	40	30	1000 G	100	++
											25	30	1000 G	67	
118	2-CH_3O, 4-$C_2H_5C_6H_3O(CH_2)_4$	*f, k*	128–136 (0.5)	93	II	G	6	134–137	$C_{18}H_{25}NO_5S_2$	125	75	15	1000 G	87	+
											27.5	15	1000 G	20	
119	4-[$(CH_2)_5CH$]$C_6H_4O(CH_2)_4$	*f, k*	141–157 (0.3)		II	S	14	210–212	$C_{18}H_{29}NO_4S_2$	50	10	30	1050 G	0	0
120	$[C_6H_5O(CH_2)_3-]_2$[v]				II[w]	*x*	4	130–132	$C_{20}H_{27}NO_5S_2$	>1000	800	30	1000 G	0	0
121	[4-$ClC_6H_4O(CH_2)_4-]_2$[v]				II[w]	I	8	149–151	$C_{22}H_{29}Cl_2NO_5S_2$	1300	100*	15	825 X	17	0
122	$[C_6H_5O(CH_2)_2O(CH_2)_2-]_2$[v]	*g*			II[w]	A, D	9	106–108	$C_{22}H_{32}NO_7S_2$	450	400	15	1000 G	0	0
123	$[C_6H_5S(CH_2)_5-]_2$[v]				II[w]	A	4	121–123	$C_{24}H_{35}NO_3S_4$	1100	50	30	1000 G	0	0
124	$[C_6H_5O(CH_2)_5-]_2$[v]				II[w]	J	10	163–164	$C_{24}H_{35}NO_4S_2$	>400	100	30	1000 G	0	0
125	[4-$CH_3OC_6H_4O(CH_2)_4-]_2$[v]				II[w]	A	9	106–108	$C_{24}H_{35}NO_7S_2$	1300	640*	15	825 X	33	+
126	[4-$C_3H_7OC_6H_4O(CH_2)_4-]_2$[v]				II[w]	A	10	126–127	$C_{26}H_{43}O_5S_2$	>150	50	30	1000 G	0	0

[u] See footnote *a*, Table I. IV: RO-tosyl + $H_2NCH_2CH_2S_2O_3Na \rightarrow RNHCH_2CH_2S_2O_3H$. [b] See footnote *b*, Table I. [c] See footnotes *c* and *oo*, Table I. [d] (*p*-Chlorophenoxy)ethyl *p*-toluenesulfonate: C. Narayanan Nair and D. H. Peacock, *J. Indian Chem. Soc.*, **12**, 318 (1935). [e] Reaction conditions were the same as those used for method II. [f] RBr. [g] Aldrich Chemical Co. [h] RCl. [i] Crude alkyl halide. [j] ROH: B. J. Heywood and W. G. Leeds, British Patent 837,372 (1960); *Chem. Abstr.*, **54**, 14188 (1960). [k] See Experimental Section for preparation of 1-[1-(bromomethyl)propoxy]-4-methoxybenzene in the Experimental Section. Ethyl 2-(*m*-chlorophenoxy)butyrate, bp 99–109° (0.5 mm). 1-[1-(Bromomethyl)propoxy]-3-chlorobenzene: *Anal.* ($C_{10}H_{12}BrClO$) C, H. [l] F. C. Copp and G. G. Coker, British Patent 924,961 (1963); *Chem. Abstr.*, **59**, 9883 (1963); bp 156–169° (0.3 mm). [m] 1-Bromo-3-chloropropane. [n] CIBA Ltd., British Patent 879,342 (1959); *Chem. Abstr.*, **56**, 7215 (1962). [o] 1-Bromo-4-chlorobutane. [p] See Experimental Section. [q] P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 4 (1937), gave bp 160–165° (11 mm). [r] N. J. Leonard, D. L. Felley, and E. D. Nicolaides, *J. Am. Chem. Soc.*, **74**, 1700 (1952), gave mp 42–43°. [s] Bp 155–165° (3 mm). [t] $R_2NCH_2CH_2S_2O_3H$. [u] Refer to the corresponding monoalkylation product for the alkyl halide. These products, obtained as side products in the alkylation reactions, usually were isolated from crystallization liquors. In some cases extraction of the crude reaction mixtures with boiling Me_2CO or EtOH dissolved these products from less soluble monoalkylation material. [v] This material remained insoluble when the crude product was washed with boiling H_2O. Additional washing with EtOH gave pure material. [w] All compounds were analyzed for C, H, N, S.

crops (6.5 g) were triturated with 250 ml of hot EtOH leaving 4.3 g (23%) of insoluble product, mp 150–152°. Recrystallization from EtOH gave 2.8 g of disulfide as the hemihydrate, mp 148–150°. *Anal.* ($C_{28}H_{44}N_2O_6S_2 \cdot 0.5H_2O$) C, H, N.

A 0.5-g sample of one of the first crops from above was oxidized by air in EtOH solution. The oxidized product was identical with the 2.8-g crop.

S-2-[(β-Hydroxy-3,4-dimethoxy-α,α-dimethylphenethyl)amino]ethyl Thiosulfate (143).—A solution of 4.8 g of crude α,α′-[dithiobis(ethyleniminoisopropylidene)]bis(3,4-dimethoxybenzyl alcohol) (recovered from crystallization liquors and may have contained some thiol) in 1.6 l. of hot EtOH was oxidized to the Bunte salt using $(NH_4)_2SO_3$.[15] The solution was concentrated to 100–150 ml under reduced pressure and the residual mixture was chilled and filtered to remove a first crop of solid which probably contained most of the unoxidized disulfide. The filtrate was concentrated to dryness and a slurry of the residue with H_2O was chilled and filtered. The wet solid was recrystallized from EtOH–DMF giving 3.9 g (63%) of the Bunte salt **143**, mp 212–213°.

2-Amino-1-decanol.—Methyl 2-aminodecanoate hydrochloride[18] (mp 90–92°) was prepared from diethyl acetamidomalonate and 1-bromooctane. Two 75-g (0.32 mole) lots of the hydrochloride salt were converted (NaOH) to free base and reduced with $LiAlH_4$ in Et_2O.[14] The crude products were combined and distilled to give 84 g (76%) of 2-amino-1-decanol which solidified, bp 90–95° (0.03 mm). *Anal.* ($C_{10}H_{23}NO$) C, H, N.

Diethyl (Cyclobutylmethyl)malonate.—Diethyl malonate (80 g, 0.5 mole) was alkylated[19] with 68.4 g (0.43 mole) of (bromomethyl)cyclobutane.[20] Crude product was distilled to give 14 g of forerun, bp 135–140° (20 mm), and 56 g (57%) of product: bp 140–145° (20 mm); nmr (CCl_4), δ 4.13 (q, 4, J = 7 Hz, CH_2CH_3), 3.09 [t, 1, J = 7 Hz, $CH(CO_2C_2H_5)_2$], 1.9 (m, 9), and 1.23 ppm [t, 6, J = 7 Hz, $(CH_3)_2$].

The preparation was repeated using 87.5 g (0.55 mole) of (bromomethyl)cyclobutane and 97.5 g (0.61 mole) of diethyl malonate to give 90 g (72%) of the substituted malonate, bp 137–147° (20 mm).

Cyclobutanepropanol. A.—Diethyl (cyclobutylmethyl)malonate was saponified[21] and the white solid which separated from the acidified solution amounted to 109 g, mp 182–185° dec. A solution of the solid in 500 ml of C_5H_5N was heated under reflux until foaming ceased (1 hr). The cooled solution was diluted with 1.5 l. of Et_2O; the resulting solution was washed with 10% HCl and H_2O, and then dried ($MgSO_4$) and concentrated to dryness giving 41 g of crude solid cyclobutanepropionic acid. The wash solutions were concentrated and then extracted with Et_2O to give 31 g of additional product, yield 72 g (80%).

Reduction of 71 g (0.55 mole) of crude cyclobutanepropionic acid was effected with 21 g (0.55 mole) of $LiAlH_4$ in Et_2O solution (16 hr at 25° and 2 hr under reflux). The crude product was distilled to give 25 g (40%) of cyclobutanepropanol: bp 87–97° (17 mm); glpc, 95%; nmr (CCl_4), δ 3.93 (s, 1, O*H*), 3.49 (m, 1, O*H*), 3.49 (m, 2, CH_2O), and 1.2–2.5 ppm (m, 11).

B.—A Grignard reagent prepared in THF from 121 g (0.8 mole) of (bromomethyl)cyclobutane was allowed to react with 37 g (0.85 mole) of ethylene oxide.[4] The crude product was distilled to give 49 g [bp 60–82° (21 mm)] of a multi-component mixture and 44 g [bp 83–91° (21 mm)] of a two-component mixture. Ir analyses of all fractions showed extraneous olefin.[22] The main component of the 44-g fraction was the same as the product obtained in A and, furthermore, conversion to the alkyl bromide gave nearly homogeneous (glpc) 1-bromo-3-cyclobutylpropane [bp 71–76° (18 mm). *Anal.* ($C_7H_{13}Br$)Br] free of olefin and identical with material described below.

(17) D. H. Ball, J. M. Williams, and L. Long, Jr., *J. Org. Chem.*, **28**, 1589 (1963).

(18) F. Martin Panizo, *Publ. Inst. Quím. "Alonso Barba"* (Madrid), **4**, 302 (1950); *Chem. Abstr.*, **46**, 8009 (1952).

(19) R. Adams and R. M. Kamm in "Organic Syntheses," Coll. Vol. I, H. Gilman, Ed., 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 250.

(20) H. G. Kuivila and W. L. Masterton, *J. Am. Chem. Soc.*, **74**, 4953 (1952). Our product (bp 125–128° and glpc 97%) contained no bromocyclopentane as shown by the nmr analysis suggested by H. G. Richey, Jr., and E. A. Hill, *J. Org. Chem.*, **29**, 421 (1964).

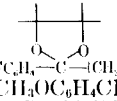
(21) G. B. Heisig and F. H. Stodola in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 213.

(22) The olefin is likely to be 6-hepten-1-ol [E. A. Hill, H. G. Richey, Jr., and T. C. Rees, *J. Org. Chem.*, **28**, 2161 (1963)].

TABLE V

MISCELLANEOUS S-2-(SUBSTITUTED AMINO)ETHYL THIOSULFATES

$RNHCH_2CH_2S_2O_3H$

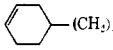
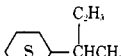
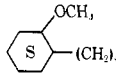
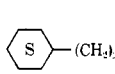
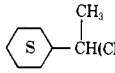
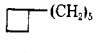
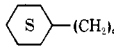
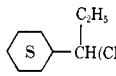
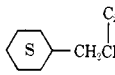
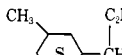
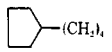
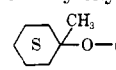
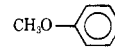
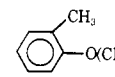
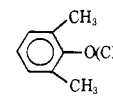
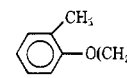
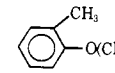
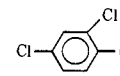
No.	R	RX Source	RX Bp, °C (mm)	Method[a]	Recrystn solvent(s)[b]	Yield, %	Mp, °C	Formula	Analyses	Anti-irradiation act.[c] Cu. LD$_{50}$, mg/kg	Drug dose min pretreatment, mg/kg	Pretreatment	Radiation dose, R	Survival, %	Ratings
127	$CH_2{=}CH(CH_2)_3$	*d*	122–130	II	A, I	12	149–150	$C_7H_{15}NO_3S_2$	C, H, N, S	225	100	15	1000 G	0	0
128	$CH_3O(CH_2)_4$	*d*, *e*	55–65 (13)	II	A	10	118–119	$C_7H_{17}NO_4S_2$	C, H, N, S	375	250	15	825 X	0	0
129	$(CH_3)_2CHCH_2CH(CH_3)$			I[d]	R	25	148–152	$C_5H_{13}NO_3S_2$	C, H, S	175	50	15	825 X	0	0
130	$HO(CH_2)_7$	*g*, *h*	56–66 (0.2)	II	A, B	4	144–149	$C_9H_{21}NO_4S_2$	C, H, N, S	550	300	15	825 X	7	0
131	$(CH_3)_2CHO(CH_2)_3$	*d*, *i*	78 (2)	II	D	5	124–125	$C_{10}H_{21}NO_3S_2$	C, H, N, S	350	200	15	825 X	0	0
132	$(C_2H_5)_3CCH_2$			III[e]	A	52	190–195	$C_{10}H_{23}NO_3S_2$	C, H, N, S	120	50	15	825 X	60	+
133	$HO(CH_2)_8$	*g*, *h*	68 (0.1)	II	B, A	5	118–120	$C_{10}H_{23}NO_4S_2$	C, H, N, S	625	200	60	1000 G	54	+
134	$CH_3(CH_2)_5CH(CH_2OH)$			I[f]	A	25	173–176	$C_{10}H_{23}NO_4S_2$	C, H, N, S	140	80	15	825 X	20	+
135	$HO(CH_2)_9$	*g*, *h*	79–83 (0.1)	II	A	23	150–154	$C_{11}H_{25}NO_4S_2$	C, H, N, S	350	200	30	825 X	27	+
136	$CH_3O(CH_2)_8$	*d*, *e*	95–105 (1.5)	II	B, A	18	180–183	$C_{11}H_{25}NO_4S_2$	C, H, N, S	150	75	15	1000 G	20	++
137	$CH_3O(CH_2)_9$	*d*, *e*	123–133 (14)	II	A	27	192–196	$C_{12}H_{27}NO_4S_2$	C, H, N, S	80	60*	30	1000 G	90	+
											30	30	825 X	40	
138	$HO(CH_2)_{10}$	*g*, *h*	97–100 (0.3)	II	A	17	135–138	$C_{12}H_{27}NO_4S_2$	C, H, N, S	>200	100	15	825 X	0	0
139	$CH_3(CH_2)_7CH(CH_2OH)$			I[g]	A	10	180–185	$C_{12}H_{29}NO_4S_2$	C, H, N, S	25	10	15	825 X	13	0
140	$HO(CH_2)_9CH(OH)CH_2$			V[h]	A	35	164–167	$C_{13}H_{29}NO_5S_2$	C, H, N, S	400	250	15	1000 G	0	0
141		*g*, *m*		II	A	8	202–203	$C_{13}H_{29}FNO_3S_2$	C, H, N, S	150	75	15	1000 G	13	0
142	$4\text{-}CH_3OC_6H_4CH_2O(CH_2)_4$	*d*, *n*		II	U	1.4	117–119	$C_{14}H_{23}NO_5S_2$	C, H, N; S[o]	200	100	15	1000 G	47	+
143	$3,4\text{-}(CH_3O)_2C_6H_3CH(OH)C(CH_3)_2$			I[i]	M	63	212–213	$C_{14}H_{23}NO_6S_2$	C, H, N; S[p]	300	100	15	1000 G	0	0
144	$(C_6H_5)_2CHO(CH_2)_2$	*g*		II	C	10	189–190	$C_{17}H_{23}NO_4S_2$	C, H, N, S	600	150	30	825 X	0	0

[a] See footnote *a*, Table I. V: $RCH\overset{O}{\diagdown\diagup}CH_2 + H_2NCH_2CH_2S_2O_3Na \rightarrow RCH(OH)CH_2NHCH_2CH_2S_2O_3H$. [b] See footnote *b*, Table I. [c] See footnotes *c* and *oo*, Table I. [d] RBr. [e] From the α,ω-dibromide according to the method of H. Schmid, *Helv. Chim. Acta*, **27**, 127 (1944). [f] See footnote *g*, Table I. [g] RCl. [h] From the diol according to the method of T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953). [i] F. Bohlmann, H. Bornowski, and P. Herbst, *Ber.*, **93**, 1951 (1960), gave bp 111–112° (12 mm). [j] See Experimental Section. [k] Crude thiol was prepared from 2-amino-4-decanol (Experimental Section). [l] Reaction conditions using 10,11-epoxy-1-undecanol were the same as for method II. [m] The ketal, bp 100–103° (0.5 mm), was prepared from 4-chloro-4′-fluorobutyrophenone. [n] Crude alkyl halide. [o] S: calcd, 18.35; found, 17.90. [p] S: calcd, 17.55; found, 16.76.

Table VI

Comparison of Highly Effective Antiradiation Agents

$RNHCH_2CH_2SSO_3H$

No.	R	Effective dose, mg/kg[a]	Therapeutic index[b]
	Cycloalkylalkyl Derivatives		
14		5	15
18		23	13
30		17	10
38		5	9
24		9	9
8		20	7
16		5	7
25		20	7
26		20	7
28		23	7
9		25	7
	Cycloalkyloxyalkyl Derivatives		
58		20	7
60	$(CH_2)_5CHO(CH_2)_4$	35	7
	Aralkyl Derivatives		
70		10	10
	Aryloxyalkyl Derivatives		
113		15	13
112		20	12
116		14	11
98		18	8
85		16	8

[a] The dose estimated to give 50% survival. [b] LD_{50} in mg/kg divided by effective dose in mg/kg.

1-Bromo-3-cyclobutylpropane.—To 25 g (0.22 mole) of cyclobutanepropanol containing 2 ml of C_5H_5N was added below 0° 21 g (0.077 mole) of PBr_3.[23] After stirring for 16 hr at room temperature the mixture was poured onto ice and the product was extracted into Et_2O. The extract was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated. Distillation of the residue provided 22 g (58%) of 1-bromo-3-cyclobutylpropane: bp 72–77° (19 mm); glpc, >93%; nmr (CCl_4), δ 3.32 (t, 2, J = 7 Hz, CH_2Br) and 1.3–2.6 ppm (m, 11).

(23) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, p 91.

Table VII

Radiation Protection by Oral Administration

No.	LD_{50}, mg/kg	Dose, mg/kg	Dose, min preirradiation	Survival, %
8	>1250	800	30	20
		800	60	13
9	938	500	30	20
		500	60	33
14	900	500	15	0
		500	30	13
17	800	500	30	13
		500	60	33
19	>1000	800	30	47
		800	60	50
		800	120	0
21	900	800	30	27
		800	60	20
30	>1250	750	30	20
		1000	60	7
50	>800	600	30	27
61	1800	1000	30	33
		1000	60	40
		1000	120	7
		1000	180	0
70	>1000	1000	15	7
		1000	30	87
		500	30	20
		250	30	0
73	1000	500	30	53
		500	60	57
76	980	800	30	0
		800	60	27
88	>1250	1000	30	0
		1000	60	20
100	1400	1000	15	0
		1000	30	53
118	>2400	800	30	27
		800	60	13
137	>1000	1000	30	7
		1000	60	13

S-2-[(3-Cyclobutylpropyl)amino]ethyl Thiosulfate (2).—Sodium S-2-aminoethyl thiosulfate (43 g, 0.24 mole) was alkylated[3] in 95% EtOH with 22 g (0.12 mole) of 1-bromo-3-cyclobutylpropane. The solvent was removed under vacuum and a slurry of the solid residue with 100 ml of H_2O was filtered, giving 31 g of crude product. The solid was triturated with H_2O and then recrystallized twice from 95% EtOH and once from absolute EtOH to give 10.8 g (33%) of **2** as shiny white crystals, mp 211–212.5° dec.

S-2-[(5-Cyclobutylpentyl)amino]ethyl Thiosulfate (8).—A Grignard reagent prepared in THF from 43 g (0.24 mole) of 1-bromo-3-cyclobutylpropane was treated with 11.7 g (0.27 mole) of ethylene oxide to give 22 g (65%) of impure cyclobutanepentanol, bp 110–114° (20 mm). Treatment of the alcohol with PBr_3 in the presence of C_5H_5N gave 15 g (46%) of 1-bromo-5-cyclobutylpentane: bp 111–113° (19 mm); glpc, 90%. Ir analysis ruled out any olefinic alkyl halide. This product was used to prepare[3] the Bunte salt **8**.

***trans*-N-(2-Hydroxyethyl)-2-phenylcyclopropanecarboxamide** was prepared in CH_2Cl_2 from 100 g (0.55 mole) of *trans*-2-phenylcyclopropane-1-carboxylic acid and 74 g (1.2 moles) of 2-aminoethanol: 91 g (80%), mp 110–111°. *Anal.* ($C_{12}H_{15}NO_2$) C, H, N.

***trans*-N-(2-Chloroethyl)-2-phenylcyclopropanemethylamine Hydrochloride.**—Reduction of *trans*-N-(2-hydroxyethyl)-2-phenylcyclopropanecarboxamide (80 g, 0.39 mole) was effected in 1.5 l. of refluxing (24 hr) THF containing 30 g (0.78 mole) of $LiAlH_4$. Distillation of the product afforded 57 g (76%) of 2-[*trans*-(2-

phenylcyclopropyl)methyl]amino}ethanol: bp 140–146° (0.3 mm); nmr (CCl_4), δ 6.95 (m, 5, C_6H_5), 3.40 (m, 4, NH, CH_2OH), 2.58 (m, 4, CH_2NCH_2), and 0.62–1.83 ppm (m, 4, $CHCH_2CH$).

To 20 g (0.11 mole) of 2-{[*trans*-(2-phenylcyclopropyl)methyl]amino}ethanol was added dropwise at 0° 25 g (0.2 mole) of $SOCl_2$. The mixture was stirred at room temperature for 16 hr and then at 40–50° for 0.5 hr. The solvent was removed under vacuum and a solution of the solid residue in EtOH was treated with charcoal and reconcentrated. Crystallization from EtOH–Et_2O gave 15 g (60%) of *trans*-N-(2-chloroethyl)-2-phenylcyclopropanemethylamine hydrochloride, mp 117–119°. The sample for analysis melted at 120–122°. *Anal.* ($C_{12}H_{16}NCl \cdot HCl$) C, H, N, Cl.

S-2-{[*trans*-(2-Phenylcyclopropyl)methyl]amino}ethyl Thiosulfate (64).—*trans*-N-(2-Chloroethyl)-2-phenylcyclopropanemethylamine hydrochloride (15 g, 0.06 mole) was converted to the Bunte salt using $Na_2S_2O_3 \cdot 5H_2O$.[3] Two recrystallizations of the crude product from EtOH–DMF gave 13.5 g (78%) of **64**, mp 188–190°.

S-2-[(2,2-Diethylbutyl)amino]ethyl Thiosulfate (132).—Reduction of 50 g (0.32 mole) of 2,2-diethylbutyric acid by $LiAlH_4$ in Et_2O gave 44 g of crude liquid 2,2-diethyl-1-butanol. Reaction (24 hr of reflux) of this alcohol with 62 g (0.23 mole) of PBr_3 in the presence of 48 g of quinoline and 350 ml of bromobenzene gave 32 g of liquid: bp 53–58° (14 mm); glpc analysis, 1-bromo-2,2-diethylbutane and PhBr in a ratio of 1:1. A solution containing 250 ml of 2-aminoethanol and the crude 1-bromo-2,2-diethylbutane was refluxed for 16 hr. An ethereal extract of the solution was washed (H_2O), dried ($MgSO_4$), concentrated, and distilled giving 7 g of 2-[(2,2-diethylbutyl)amino]ethanol, bp 125° (15 mm). A solution of this amino alcohol in 21 ml of 48% HBr was refluxed for 1 hr. The crude HBr salt (8.4 g, 65%) on reaction with 6.3 g (0.026 mole) of $Na_2S_2O_3 \cdot 5H_2O$ in 20 ml of H_2O afforded 3.6 g (52%) of the Bunte salt **132**: mp 190–195° dec; nmr (D_2O–NaOD), δ 2.8–3.3 (m, 4, NCH_2CH_2S), 2.31 (s, 2, Et_4C-CH_2N), and 0.50–1.48 ppm [m, 15, (C_2H_5)$_3$].

4-(4-Chlorobutyl)bicyclohexyl.—A solution of 225 g (0.86 mole) of 3-(*p*-cyclohexylbenzoyl)propionic acid[24] in 1 l. of MeOH was hydrogenated at about 3 atm in the presence of 5 ml of concentrated H_2SO_4 and 5 g of 20% Pd–C. The reduction was allowed to proceed for 17 hr (H_2 uptake corresponded to reduction of carbonyl group) and then 10 g of 10% Rh–C was added followed by hydrogenation for 48 hr (H_2 uptake corresponded to reduction of the aromatic ring). A slurry of the filtered solution with 10 g (0.094 mole) of anhydrous Na_2CO_3 was allowed to stand for 16 hr. The solvent was removed under reduced pressure, the residue was extracted with 500 ml of Et_2O, and the ethereal extract was washed with small portions of H_2O and dried ($MgSO_4$).

The solution containing 4-cyclohexylcyclohexanebutyric acid was reduced with 35.8 g (0.89 mole) of $LiAlH_4$ giving 149 g (70%) of 4-cyclohexylcyclohexanebutanol: bp 209–215° (8 mm); glpc, 99%. Conversion of the alcohol to the chloride ($SOCl_2$, C_5H_5N)[25] resulted in 157 g of crude product. Distillation of 117 g of crude product gave 97 g of 4-(4-chlorobutyl)bicyclohexyl: bp 205–209° (19 mm); glpc, 80:20 mixture of isomers. *Anal.* ($C_{16}H_{29}Cl$) C, H, Cl.

2-(4-Bromobutyl)cyclohexyl Methyl Ether.—4-(*o*-Methoxyphenyl)butyric acid[26] (80 g, 0.41 mole) was hydrogenated (3 atm) for 20 hr in 400 ml of MeOH containing 5 g of 10% Rh–C. Concentration of the filtered solution gave 77 g of crude 2-methoxycyclohexanebutyric acid. Reduction of 50 g (0.25 mole) of the crude acid with 9.5 g (0.25 mole) of $LiAlH_4$ in Et_2O solution gave 32 g (71%) of 2-methoxycyclohexanebutanol, bp 83–95° (0.4 mm). The substituted butanol (32 g, 0.18 mole) was converted (PBr_3 and C_5H_5N at 25°) to 2-(4-bromobutyl)cyclohexyl methyl ether: 18 g (40%), bp 75–85° (0.2 mm). *Anal.* ($C_{11}H_{21}BrO$) C, H, Br.

1-(4-Chlorobutyl)-4-methylcyclohexane.—A solution containing 75 g (0.45 mole) of 4-*p*-tolyl-1-butanol[27] and 2 ml of concentrated H_2SO_4 in 400 ml of MeOH was hydrogenated for 2 days at 3 atm over 5 g of 10% Pt–C. An additional 2.5 g of 10% Pt–C was added and hydrogenation was continued for 3.5 days in order to complete the reduction. Another hydrogenation using 32 g (0.19 mole) of 4-*p*-tolyl-1-butanol and 1 ml of concentrated H_2SO_4 in 250 ml of MeOH was completed in 24 hr over 4 g of 10% Rh–C. The H_2SO_4 in the two lots was neutralized with Na_2CO_3 as described above. The products were combined giving 79 g (71%) of crude oily product. The alcohol was chlorinated ($SOCl_2$–C_5H_5N) to give 39 g (45%) of 1-(4-chlorobutyl)-4-methylcyclohexane: bp 69–72° (0.8 mm); glpc, 60:40 mixture of isomers. *Anal.* ($C_{11}H_{21}Cl$) C, H.

4-(4-Chlorobutyl)cyclohexyl Methyl Ether.—A methanolic solution containing 125 g (0.56 mole) of methyl 3-*p*-anisoylpropionate[28] was hydrogenated in a stepwise manner as in the reduction given above for 3-(*p*-cyclohexylbenzoyl)propionic acid. Only 8 hr was required to saturate the aromatic ring in this case.[29] The crude oily methyl 4-methoxycyclohexanebutyrate (100 g) was further reduced with 180 g (4.7 moles) of $NaBH_4$ in 2 l. of absolute EtOH.[30] The mixture was allowed to stir for 18 hr[31] before dilution in 7 l. of H_2O. The product was extracted into $CHCl_3$ and the crude 4-methoxycyclohexanebutanol (65 g, 74%) was converted to 46 g of impure 4-(4-chlorobutyl)cyclohexyl methyl ether, bp 110–140° (15 mm). Fractional distillation gave a forerun, bp 24–118° (6 mm); 8 g, bp 118–130° (6 mm), glpc 45:8 mixture of A and B; 17 g, bp 130–137° (6 mm), glpc 73:18 mixture of A and B. Components A and B were separated from the two fractions by preparative gas chromatography (F & M Model 770): component A, 5.8 g (contaminated with 1.8% of B), nmr (CCl_4) δ 3.48 (t, 2, J = 6 Hz, CH_2Cl), *ca.* 3.3 (m, 1, MeOCH), and 3.21 ppm (s, 3, CH_3O); component B, 1.1 g (contaminated with 2.8% of A), nmr (CCl_4) δ *ca.* 3.5 (m, 1, MeOCH), 3.47 (t, 2, J = 6 Hz, CH_2Cl), and 3.23 ppm (s, 3, CH_3O). Elemental analytical data confirmed that A and B are the two racemates of 4-(4-chlorobutyl)cyclohexyl methyl ether. *Anal.* A ($C_{11}H_{21}ClO$) C, H, Cl. B ($C_{11}H_{21}ClO$) C, H.

***p*-(4-Chlorobutyl)phenol.**—A solution of 79.5 g (0.40 mole) of *p*-(4-chlorobutyl)anisole[32] in 1.2 l. of CH_2Cl_2 was treated with 100 g (0.40 mole) of BBr_3[5] to give 57 g (77%) of *p*-(4-chlorobutyl)-phenol, bp 141–145° (2 mm). *Anal.* ($C_{10}H_{13}ClO$) C, H, Cl.

[2-(Bromomethyl)propyl]cyclohexane.—Reduction of 200 g (1.18 moles) of α-ethylcyclohexaneacetic acid in Et_2O with 44.6 g (1.18 moles) of $LiAlH_4$ gave 135 g (72%) of α-ethylcyclohexaneethanol: bp 78–84° (0.6 mm) [lit.[33] L form, bp 119–121° (18 mm)]; nmr (CCl_4), δ 3.49 (d, 2, J = 4 Hz, CH_2O), 3.09 (s, 1, OH), and 0.75–1.92 ppm (m, 17). Conversion of the alcohol to the alkyl bromide (PBr_3–C_5H_5N, 2 hr at 100°) gave 39.6 g (67%) of [2-(bromomethyl)propyl]cyclohexane: bp 125–131° (28 mm); glpc, 94%; nmr (CCl_4), δ 3.49 (d, 2, J = 4 Hz, CH_2Br) and 0.75–1.98 ppm (m, 17). *Anal.* ($C_{10}H_{19}Br$) C, H, Br.

***sec*-Butylcyclohexane.**[34]—Reduction of 39.6 g (0.18 mole) of [2-(bromoethyl)propyl]cyclohexane with 2.3 g (0.06 mole) of $LiAlH_4$ was allowed to proceed for 18 hr in 300 ml of refluxing Et_2O. The crude oily product (32.8 g) was distilled to give 7.3 g of *sec*-butylcyclohexane: bp 79–81° (28 mm) [lit.[35] bp 177° (760 mm)]; glpc, 98%. Ir and nmr spectra of the hydrocarbon were nearly superimposable with a commercial sample (glpc, 96%) of *sec*-butylcyclohexane.

1-[1-(Bromomethyl)propoxy]-4-methoxybenzene.—A mixture of 80 g (0.64 mole) of *p*-methoxyphenol, 136 g (0.7 mole) of ethyl 2-bromobutyrate, 96 g (0.7 mole) of anhydrous K_2CO_3, and 500 ml of absolute EtOH was refluxed for 18 hr. The filtered solution was concentrated and the residue was diluted with 400 ml of H_2O before being extracted into Et_2O. The ethereal solution was washed (H_2O), dried ($MgSO_4$), and distilled giving 6.5 g of forerun and 119 g (78%) of ethyl 2-(*p*-methoxyphenoxy)-butyrate: bp 118–121° (0.5 mm); glpc, 90%; nmr (CCl_4), δ 1.03 ppm (t, 3, J = 7 Hz, CH_3CH_2CH).

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(30) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963).

(31) At one point vigorous evolution of hydrogen occurred. We prefer $LiAlH_4$ for these reductions.

(32) See Table III, footnote *l*.

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(34) This preparation provided evidence that no rearrangement of branched-chain compounds occurred in the synthesis of alkyl bromides from alcohols using PBr_3 and pyridine.

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Reduction of 119 g (0.5 mole) of ethyl 2-(*p*-methoxyphenoxy)-butyrate with 10.6 g (0.28 mole) of $LiAlH_4$ was effected in 1 l. of Et_2O to give 94 g (95%) of crude 2-(*p*-methoxyphenoxy)-1-butanol; glpc, 99%; nmr (CCl_4), δ 0.90 ppm (t, 3, J = 7 Hz, CH_3CH_2CH).

A mixture of 52 g (0.26 mole) of 2-(*p*-methoxyphenoxy)-1-butanol, 7.8 ml of pyridine, and 27 g (0.1 mole) of PBr_3 was heated at 95–110° for 2 hr and then stirred at room temperature for 16 hr giving 39 g (52%) of 1-[1-(bromomethyl)propoxy]-4-methoxybenzene: bp 106–113° (0.6 mm); glpc, 97%. *Anal.* ($C_{11}H_{15}BrO_2$) C, H, Br.

1-(4-Bromobutoxy)-4-propoxybenzene.—Alkylation of 100 g (0.66 mole) of *p*-propoxyphenol with 1,4-dibromobutane (339 g, 1.57 moles) was effected in Me_2CO in the presence of K_2CO_3.[36] Distillation of the crude product gave 25 g of forerun and 95.6 g (50%) of material: bp 143–155° (0.5–1 mm); glpc, 98%; the nmr peaks were as expected. *Anal.* ($C_{13}H_{19}BrO_2$) C, H, Br.

4-Bromobutyl Cyclohexyl Ether.—Alkylation of 50 g (0.5 mole) of cyclohexanol as the Na salt (NaH) with 162 g (0.75 mole) of 1,4-dibromobutane was effected in a benzene–toluene mixture. Distillation gave 44 g (38%) of product, bp 56–67° (0.1 mm); the nmr peaks were as expected. *Anal.* ($C_{10}H_{19}BrO$) C, H, Br.

5-Bromopentyl Phenyl Sulfide.—Thiophenol (55 g, 0.5 mole) was alkylated with 1,5-dibromopentane (345 g, 1.5 moles) in absolute EtOH containing 27 g (0.5 mole) of $NaOCH_3$.[36] Distillation of crude product gave 37 g (28%) of material: bp 120–140° (0.3 mm); glpc, 95%; uv, λ_{max}^{MeOH} 254 mμ (ε 8700); the nmr peaks were as expected. *Anal.* ($C_{11}H_{15}BrS$) Br.

In addition, 34 g of 1,5-di(phenylthio)pentane was obtained: bp 177–192° (0.3 mm); uv, λ_{max}^{MeOH} 254 mμ (ε 15,000).

(36) Reference 23, pp 226–228.

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Synthetic Schistosomicides. X. Bis(4-arylazo-1-naphthylamines)

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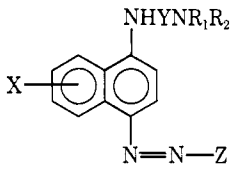
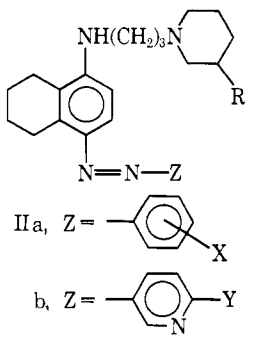
Fifteen bis(4-arylazo-1-naphthylamines) were synthesized for evaluation as potential antischistosomal and antimycobacterial agents. Various N,N-[bis(phenyleneazo-1,4-naphthylene)]bis(N',N'-dialkylalkylenediamines) (III) were prepared by coupling a tetrazotized dianiline derivative with the appropriate N,N-dialkyl-N'-1-naphthylalkylenediamine. Likewise, several bis[(4-phenylazo-1-naphthylamino)alkyl]amines (IVa–c) were obtained from benzenediazonium chloride and the corresponding bis[(1-naphthylamino)alkyl]amines. Condensation of diazotized N-[4-(4-amino-1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacetamide (VII) with an N,N-dialkyl-N'-1-naphthylalkylenediamine followed by alkaline hydrolysis of the intermediate trifluoroacetamides afforded a series of N',N'-diethyl-N''',N'''-dialkyl-N,N''-[1,4-naphthylenebis(azo-1,4-naphthylene)]bis(alkylenediamines) (IXa–c). Five compounds (1, **2**, and IXa–c) effected a 94–100% reduction of live *Schistosoma mansoni* in mice at drug-diet doses ranging from 110–692 mg/kg daily for 14 days. Six compounds (**2**, **3**, **5**, **7**, IVa, and VII) were active against *Mycobacterium tuberculosis* $H_{37}Rv$ *in vitro*.

In previous communications various N-mono- and N,N-dialkyl-N'-(4-arylazo- and 4-heterocyclic azo-1-naphthyl)alkylenediamines (Ia and b) and related



Ia, Z = Ar
b, Z = Het



IIa, Z =

b, Z =

substances were reported to have strong therapeutic effects against *Schistosoma mansoni*[1–7] and *Schistosoma japonicum*[8] in experimental animals. Further, certain 1-(3-{[5,6,7,8-tetrahydro-4-(phenylazo- and 3-pyridylazo)-1-naphthyl]amino}propyl)piperidines (IIa and b) are highly active against *Mycobacterium tuberculosis* $H_{37}Rv$ and *Mycobacterium lepraemurium in vitro* and in mice.[9,10] In a further extension of this work, representative bis(4-arylazo-1-naphthylamines) were synthesized for antischistosomal and antimycobacterial evaluation. Several of the bis(4-arylazo-1-naphthylamines) showed good activity against *S. mansoni* in mice.

A group of N,N-[bis(phenyleneazo-1,4-naphthylene)]-bis(N',N'-dialkylalkylenediamines) (III) (Table I) was prepared by coupling a tetrazotized dianiline derivative with the appropriate N,N-dialkyl-N'-1-naph-

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