

N-Substituted S-2-Aminoethyl Thiosulfates as Antiradiation Agents¹

ROGER D. WESTLAND, JOYCE L. HOLMES, MARY LOU MOUK, DOUGLAS D. MARSH,
RICHARD A. COOLEY, JR., AND JOHN R. DICE

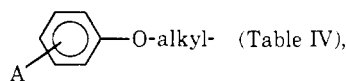
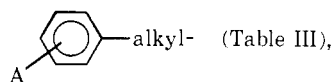
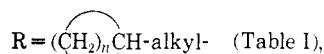
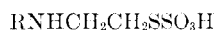
Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106

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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, cycloalkylalkoxyalkyl, 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 (LD₅₀) doses. Activity by oral administration also was obtained for some compounds.

It is apparent from recent reports² that less toxic anti-radiation 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.



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 with-

out 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 CO₂ 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.

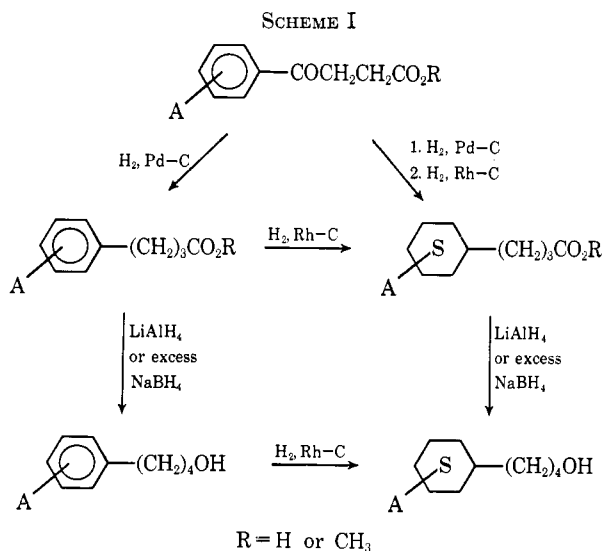
(5) C. G. Derick and D. W. Bissell, *J. Am. Chem. Soc.*, **38**, 2478 (1916).

(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 + $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH} \rightarrow$ 2-hydroxyethylamide + $\text{LiAlH}_4 \rightarrow$ 2-(substituted amino)ethanol + $\text{SOCl}_2 \rightarrow$ 2-(substituted amino)ethyl chloride hydrochloride + $\text{Na}_2\text{S}_2\text{O}_3 \rightarrow$ Bunte salt.

The high order of antiradiation activity of S-2-[4-(cyclohexyl)butyl]aminoethyl 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). Frie-



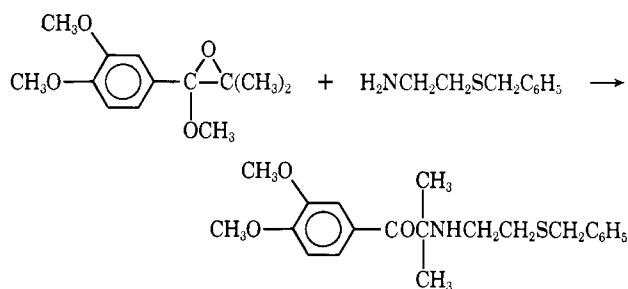
del-Crafts acylation of *p*-chlorophenetole with succinic anhydride resulted in cleavage of the ether and isola-

tion 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**.

The series of alicyclic ethers found in Table II required as intermediates alkyl halides which were prepared in benzene or toluene from cycloalkanol 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-methylpropane⁹ leading to a compound related



to epinephrine. The following transformations afforded a Bunte salt from the ring-opened product: ketone + $\text{LiAlH}_4 \rightarrow$ alcohol + $\text{Na-NH}_3 \rightarrow$ thiol + $\text{O}_2 \rightarrow$ disulfide + $\text{SO}_3^{2-} \rightarrow$ Bunte salt (**143**). Structures with this degree of substitution are almost devoid of analeptic activity.

Biological Activity.—The Bunte salts were tested in mice¹⁰ 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 I. S-2-(CYCLOALKYLALKYLAMINO)ETHYL THIOSULFATES RNHC(CH₂)₂SO₂H

No.	Source	R	RX		Method ^u	Recrystn solvent ^d	Yield, %	Mp, °C	Formula ^{mm}	Antiradiation act., ^{mm}			
			Bp, °C (mm)	Clpc, %						Cu, LD ₅₀ , mg/kg	Drug dose, mg/kg	Radia- tion, dose, R	Survival, %
1	<i>e, f</i>	(CH ₂) ₅ CH	80-86 (11)	80	II	A, D	28	177-184	C ₁₁ H ₂₁ NO ₃ S ₂	175	100	1000 G	0
2		(CH ₂) ₅ CH(CH ₂) ₃			II	A	13	211-224	C ₁₄ H ₂₇ NO ₃ S ₂	200	25	30	7
3		(CH ₂) ₅ CH(CH ₂) ₄			II	B, A	33	211-212	C ₁₅ H ₂₉ NO ₃ S ₂	350	125	825 X	20
4		(CH ₂) ₅ CH(CH ₂) ₅			II	B	26	210-216	C ₁₆ H ₃₁ NO ₃ S ₂	>150	112	15	13
5		(CH ₂) ₅ CH(CH ₂) ₆			II	A	31	200-202	C ₁₇ H ₃₃ NO ₃ S ₂	90	50	15	27
6	<i>i, j</i>	(CH ₂) ₅ CH(CH ₂) ₇			III	C	19	194-195	C ₁₈ H ₃₅ NO ₃ S ₂				
7	<i>i, k</i>	(CH ₂) ₅ CH(CH ₂) ₈			II	A, D	28	177-184	C ₁₉ H ₃₇ NO ₃ S ₂				
8	<i>e, f</i>	(CH ₂) ₅ CH(CH ₂) ₉			II	A	27	186-194	C ₂₀ H ₃₉ NO ₃ S ₂	150	25	15	87
9	<i>i, l</i>	(CH ₂) ₅ CH(CH ₂) ₁₀			II	A	13	218-224	C ₂₁ H ₄₁ NO ₃ S ₂	175	37.5*	15	90
10	<i>e, m</i>	(CH ₂) ₅ CH(CH ₂) ₁₁			II	A	8	200-203	C ₂₂ H ₄₃ NO ₃ S ₂	140	50	30	40
11	<i>e, n</i>	(CH ₂) ₅ CH(CH ₂) ₁₂			II	C	22	163-168	C ₂₃ H ₄₅ NO ₃ S ₂	150	100	15	86
12	<i>e, o</i>	(CH ₂) ₅ CH(CH ₂) ₁₃			II	A	7	227-228	C ₂₄ H ₄₇ NO ₃ S ₂	120	50	15	40
13	<i>e, p</i>	(CH ₂) ₅ CH(CH ₂) ₁₄			II	A	24	206-211	C ₂₅ H ₄₉ NO ₃ S ₂	80	50	15	40
14	<i>i, q</i>	(CH ₂) ₅ CH(CH ₂) ₁₅			II	D, A	19	177-183	C ₂₆ H ₅₁ NO ₃ S ₂	75	25	15	100
15		(CH ₂) ₅ CH(CH ₂) ₁₆			II	E	70	80-100	C ₂₇ H ₅₃ NO ₃ S ₂	15	10	30	87
16	<i>i, r</i>	(CH ₂) ₅ CH(CH ₂) ₁₇			II	A	44	225-227	C ₂₈ H ₅₅ NO ₃ S ₂	50	10	15	93
17	<i>i, s</i>	(CH ₂) ₅ CH(CH ₂) ₁₈			II	A	26	209-212	C ₂₉ H ₅₇ NO ₃ S ₂	5	15	1030 G	79
18	<i>e, f</i>	(CH ₂) ₅ CH(CH ₂) ₁₉			II	B, A	10	184-187	C ₃₀ H ₅₉ NO ₃ S ₂	25	10	15	80
19	<i>i, t</i>	(CH ₂) ₅ CH(CH ₂) ₂₀			II	A	9	212-216	C ₃₁ H ₆₁ NO ₃ S ₂	300	50	30	53
20	<i>e, u</i>	(CH ₂) ₅ CH(CH ₂) ₂₁			II	A	35	200-203	C ₃₂ H ₆₃ NO ₃ S ₂	135	50	30	80
21	<i>i, f</i>	(CH ₂) ₅ CH(CH ₂) ₂₂			II	F, A	18	222-223	C ₃₃ H ₆₅ NO ₃ S ₂	7	5	15	40
22	<i>e, v</i>	(CH ₂) ₅ CH(CH ₂) ₂₃			II	A	19	217-220	C ₃₄ H ₆₇ NO ₃ S ₂	10	5	15	7
23	<i>e, w</i>	(CH ₂) ₅ CH(CH ₂) ₂₄			II	G, A, D	4	226-227	C ₃₅ H ₆₉ NO ₃ S ₂	8	5	30	100
24	<i>e, x</i>	(CH ₂) ₅ CH(CH ₂) ₂₅			II	A, D, A	23	213-216	C ₃₆ H ₇₁ NO ₃ S ₂	80	20	30	60
25	<i>e, y</i>	(CH ₂) ₅ CH(CH ₂) ₂₆			II	A	7	167-169	C ₃₇ H ₇₃ NO ₃ S ₂	150	10	30	53
26	<i>e, z</i>	(CH ₂) ₅ CH(CH ₂) ₂₇			II	H, I	21	174-175	C ₃₈ H ₇₅ NO ₃ S ₂	140	50	30	66
27	<i>e, o</i>	(CH ₂) ₅ CH(CH ₂) ₂₈			II	A	50	198-199	C ₃₉ H ₇₇ NO ₃ S ₂	300	75	30	100
28	<i>e, o</i>	(CH ₂) ₅ CH(CH ₂) ₂₉			II	A	10	160-162	C ₄₀ H ₇₉ NO ₃ S ₂	170	100	30	73
29	<i>e, z</i>	(CH ₂) ₅ CH(CH ₂) ₃₀			II	A	11	212-216	C ₄₁ H ₈₁ NO ₃ S ₂	15	25	30	93
30	<i>e, f</i>	(CH ₂) ₅ CH(CH ₂) ₃₁			II	A, D, A	11	204-207	C ₄₂ H ₈₃ NO ₃ S ₂	175	25	15	87
31	<i>i, f</i>	(CH ₂) ₅ CH(CH ₂) ₃₂			II	A	10	203-204	C ₄₃ H ₈₅ NO ₃ S ₂	200	50	15	93
32	<i>i, aa</i>	(CH ₂) ₅ CH(CH ₂) ₃₃			II	A	15	216-220	C ₄₄ H ₈₇ NO ₃ S ₂	13	5	30	33
33	<i>i, bb, cc</i>	(CH ₂) ₅ CH(CH ₂) ₃₄			II	A	22	218-220	C ₄₅ H ₈₉ NO ₃ S ₂	10	5	30	7
34	<i>i, dd, ee</i>	(CH ₂) ₅ CH(CH ₂) ₃₅			II	A	15	224-226	C ₄₆ H ₉₁ NO ₃ S ₂	7	3	30	53
35	<i>i, ff, gg</i>	(CH ₂) ₅ CH(CH ₂) ₃₆			II	J, A	16	212-213	C ₄₇ H ₉₃ NO ₃ S ₂	25	20	15	13
36	<i>i, hh, ii</i>	(CH ₂) ₅ CH(CH ₂) ₃₇			II	A	6	208-210	C ₄₈ H ₉₅ NO ₃ S ₂	25	15	15	73
37	<i>e, ff</i>	(CH ₂) ₅ CH(CH ₂) ₃₈			II	K, H	30	184-185	C ₄₉ H ₉₇ NO ₃ S ₂	75	25	30	87
38	<i>e, bb, gg</i>	(CH ₂) ₅ CH(CH ₂) ₃₉			II	H	40	178-179	C ₅₀ H ₉₉ NO ₃ S ₂	44	30	30	80
39	<i>i, hh</i>	(CH ₂) ₅ CH(CH ₂) ₄₀			II	A	16	216-220	C ₅₁ H ₁₀₁ NO ₃ S ₂	18	5	30	73
40	<i>i, ii</i>	(CH ₂) ₅ CH(CH ₂) ₄₁			II	A	22	213-216	C ₅₂ H ₁₀₃ NO ₃ S ₂	13	6	30	80
41	<i>i, jj</i>	(CH ₂) ₅ CH(CH ₂) ₄₂			II	A	14	206-210	C ₅₃ H ₁₀₅ NO ₃ S ₂	23	8	30	33
42	<i>e</i>	(CH ₂) ₅ CH(CH ₂) ₄₃			II	A, M	6	208	C ₅₄ H ₁₀₇ NO ₃ S ₂	>400	50	30	87

TABLE III

S-2-(ARALKYLAMINO)ETHYL THIOSULFATE

RNHC(CH₂)₂SO₂CH₃

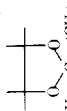
No.	R	RX			Recrystn solvents ^b	Yield, %	Mp, °C	For. anal. ^c	Cl, LD ₅₀ , mg/kg	Drug dose		Survival, %	Rating
		Source	Bp, °C (mm)	Gipc, %	Method ^a					mg/kg	preirradiation		
64	C ₆ H ₅ —  —CH ₃	d			III	M	188-190	C ₁₂ H ₁₇ NO ₃ S ₂	75	50	15	1000 G	0
65	4-ClC ₆ H ₄ CH(C ₂ H ₅)CH ₃	e, f	83-86 (0.5)		II	B, A	198-200	C ₁₂ H ₁₃ ClNO ₃ S ₂	140	75	15	1000 G	+
66	2-HOC ₆ H ₄ (CH ₂) ₄	e, g	110-115 (0.1)		II	C, M	186-187	C ₁₂ H ₁₉ NO ₃ S ₂	300	100	15	1000 G	0
67	4-HOC ₆ H ₄ (CH ₂) ₄	e, h	141-145 (2)		II	C, J, A	187-188	C ₁₂ H ₁₉ NO ₃ S ₂	250	150	15	1000 G	+
68	2-CH ₃ OC ₆ H ₄ (CH ₂) ₃	e, i			II	A	179-180	C ₁₂ H ₁₉ NO ₃ S ₂	175	75	15	1000 G	+
69	4-CH ₃ OC ₆ H ₄ (CH ₂) ₃	e, j	106-110 (0.4)		II	L	180-181	C ₁₂ H ₁₉ NO ₃ S ₂	200	75	30	1050 G	+
70	4-CH ₃ OC ₆ H ₄ (CH ₂) ₄	h, k, l		95	II	A	181-182	C ₁₃ H ₂₁ NO ₃ S ₂	120	50*	15	825 X	++
71	3-CH ₃ OC ₆ H ₄ (CH ₂) ₄	e, m	115-117 (0.3)		II	A	167-169	C ₁₃ H ₂₁ NO ₃ S ₂	150	30	15	1000 G	87
72	3-CH ₃ OC ₆ H ₄ CH(C ₂ H ₅)CH ₃	e, n	96-102 (0.7)		II	B, C	130-135	C ₁₃ H ₂₁ NO ₃ S ₂	100	40	15	1000 G	20
73	4-C ₂ H ₅ OC ₆ H ₄ (CH ₂) ₄	h, k, o			II	C	210-212	C ₁₄ H ₂₃ NO ₃ S ₂	15	5	15	1000 G	60
74	2,4-(CH ₃) ₂ C ₆ H ₃ (CH ₂) ₄	h, k, p			II	A	214-215	C ₁₄ H ₂₃ NO ₃ S ₂	38	15	30	1000 G	73
75	2,5-(CH ₃) ₂ C ₆ H ₃ (CH ₂) ₄	e, q	79-85 (0.5)		II	A	224-225	C ₁₄ H ₂₃ NO ₃ S ₂	20	10	30	1000 G	73
76	4-C ₂ H ₅ OC ₆ H ₄ (CH ₂) ₃	e, r	115-123 (0.3)		II	A	206-207	C ₁₄ H ₂₃ NO ₃ S ₂	22	15	15	1000 G	47
77	4-CH ₃ OC ₆ H ₄ (CH ₂) ₃	e, s	100-107 (0.03)		II	B, A	181-184	C ₁₄ H ₂₃ NO ₃ S ₂	45	15	30	1050 G	80
78	3,4-(CH ₃) ₂ C ₆ H ₃ (CH ₂) ₄	t	120-142 (0.3)		II	A	166-168	C ₁₄ H ₂₃ NO ₃ S ₂	350	200*	15	825 X	83
79	4-CH ₃ OC ₆ H ₄ (CH ₂) ₆	e, u	128-135 (0.7)		II	B, D, A, D	183-186	C ₁₆ H ₂₅ NO ₃ S ₂	>40	10	30	1000 G	80
80	4-[(CH ₃) ₂ CH]C ₆ H ₄ (CH ₂) ₄	h, k, v			II	L, A	223-225	C ₁₈ H ₂₉ NO ₃ S ₂	15	8	15	1000 G	53
81	2-Phenanthryl-(CH ₂) ₄	h, k, w			II	A	208-211	C ₂₀ H ₂₃ NO ₃ S ₂	100	75	30	1000 G	0
82	9,10-Dihydro-2-phenanthryl-(CH ₂) ₄	h, k, x			II	M	216-217	C ₂₀ H ₂₃ NO ₃ S ₂	750	25	30	1000 G	0

* See footnote a, Table I. * See footnote b, Table I. * See footnotes c and d, Table I. * See Experimental Section. * RBr: 2-(p-chlorophenyl)butyric acid [M. A. Spielman, A. D. Geisler, and W. J. Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948)] + LiAlH₄. * Reaction between p-chlorophenol and succinic anhydride (Friedel-Crafts conditions using AlCl₃ in C₂H₅Cl-C₆H₅NO₂) gave 3-(5-chlorosalicyloyl)propionic acid [S. L. Dabai, 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)]; LiAlH₄ reduction gave ROH [I. G. Baddeley, N. H. P. Smith, and M. A. Vickars, *J. Chem. Soc.*, 2455 (1956)]. Reaction between ROH and PBr₃ was effected in Et₂O at 25° for 18 hr. * RCl: Aldrich Chemical Co. * A. Horeau, *Bull. Soc. Chim. France*, **15**, 414 (1948). * Crude alkyl halide was used for the alkylation. * H. Morren, D. Zivkovic, R. Linz, H. Strubbe, and L. Marchal, *Ind. Chim. Belge*, **28**, 123 (1963); *Chem. Abstr.*, **59**, 8732 (1963). * ROH: R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3114 (1957). * ROH [bp 95° (0.3 mm)] from diethyl ethyl(m-methoxyphenyl)malonate [H. Tsukamoto, I. Yoshimura, and S. Toki, *Pharm. Bull. (Tokyo)*, **3**, 239 (1955)]; *Chem. Abstr.*, **50**, 11, 246 (1956)]. * 3-(p-ethylbenzoyl)propionic acid + H₂/Pd-C → 4-(p-ethylphenyl)butyric acid [F. G. Baddeley and F. L. Warren, *J. Chem. Soc.*, 944 (1939)] + LiAlH₄ → ROH, bp 165-172° (21 mm). * ROH: 4-(o,p-dimethylphenyl)butyric acid [I. M. Heilbron and B. G. Wilkinson, *ibid.*, 2537 (1930)] + LiAlH₄. * ROH: see ref in footnote c, Table I. * ROH: p-chlorophenol + (1) Mg-(CH₂)₂O, (2) PBr₃-Et₂O, (3) Mg-(CH₂)₂O. * J. M. von der Zanden, *Rec. Trav. Chim.*, **60**, 291 (1941), gave bp 144-145° (2 mm). * See footnote o for process. ROH (ref in footnote m) + (C₆H₅O)₂PBr₂ → RBr. * ROH: 6-(p-methoxyphenyl)hexanoic acid (ref in footnote s) + LiAlH₄. * ROH: see footnote o for process; bp 220-230° (20 mm). * Methyl 2-phenanthrenebutyrate [W. E. Bachman and W. S. Struve, *J. Org. Chem.*, **4**, 456 (1939)] + LiAlH₄. * ROH: LiAlH₄ → methyl 9,10-dihydro-2-phenanthrenebutyrate [structure was verified by conversion to acid; A. Burger and E. Mosetig, *J. Am. Chem. Soc.*, **59**, 1302 (1937)]; bp 194-195° (0.4 mm). * S: calcd, 16.38; found, 15.86. * All compounds were analyzed for C, H, N, S.

TABLE IV. S-2-(ARYLOXYALKYLAMINO)ETHYL THIOSELENYATES R.NHCH₂CHL₂S₂O₃H

No.	R	Source	R-N		Mp, °C (mm)	Glyce. %	Me- thod ^a	Reerystm solvents ^b	Yield, %	Mp, °C	Formula ^a	Cu, LD ₅₀ , mg/kg	Drug dose, mg/kg	Min preir- radia- tion	Radiation, dose, R	Surviv- al, %	Rating
			Bp, °C (mm)														
83	4-ClC ₆ H ₄ O(CH ₂) ₂	<i>d</i>					IV ^c	C	5	188-190	C ₁₀ H ₁₄ ClNO ₄ S ₂	150	100	30	1000 G	20	+
84	C ₆ H ₅ O(CH ₂) ₃	<i>f, g</i>					II ^c	C, A	7	189-190	C ₁₀ H ₁₇ NO ₄ S ₂	150	50	15	1000 G	7	0
85	2,4-Cl ₂ C ₆ H ₃ O(CH ₂) ₄	<i>h-j</i>					II	A	26	179-181	C ₁₂ H ₁₇ Cl ₂ NO ₄ S ₂	125	25	30	1000 G	93	++
												12.5	30	1000 G	33	++	
86	4-BrC ₆ H ₄ O(CH ₂) ₄	<i>f, k</i>	134-150 (0.3)	95	II		M		13	187-188	C ₁₂ H ₁₈ BrNO ₄ S ₂	>150	50	30	1000 G	0	0
87	2-ClC ₆ H ₄ O(CH ₂) ₄	<i>f, k</i>	124-133 (0.4)	98	II		J, A		16	165-166	C ₁₂ H ₁₈ ClNO ₄ S ₂	150	50	30	1000 G	80	++
												25	30	1000 G	20		
88	3-ClC ₆ H ₄ O(CH ₂) ₄	<i>f, k</i>	181-187 (19)		II		C, A		25	158-159	C ₁₂ H ₁₈ ClNO ₄ S ₂	150	50	15	1000 G	73	+
89	4-ClC ₆ H ₄ O(CH ₂) ₄	<i>f, k, l</i>	115-130 (0.3)	98	II		M		30	171-172	C ₁₂ H ₁₈ ClNO ₄ S ₂	175	75	30	1000 G	33	++
90	3-ClC ₆ H ₄ OCH(CH ₂) ₃ CH ₂	<i>f, m</i>	112-114 (1.5)	98	II		A		35	168-169	C ₁₂ H ₁₈ ClNO ₄ S ₂	120	80	15	1000 G	13	0
91	4-NO ₂ C ₆ H ₄ O(CH ₂) ₄	<i>f, n</i>	156-169 (0.3)	50	II		A		19	157-159	C ₁₂ H ₁₈ N ₂ O ₆ S ₂	250	50	30	1000 G	80	++
												25	30	1000 G	33	++	
92	2-CH ₃ C ₆ H ₄ O(CH ₂) ₃	<i>h, o</i>	75-84 (0.7)	85	II		M		22	208-209	C ₁₂ H ₁₉ NO ₄ S ₂	150	75	15	1000 G	6	0
93	3-CH ₃ C ₆ H ₄ O(CH ₂) ₃	<i>h, o</i>	143-148 (20)		II		A, C		11	179-181	C ₁₂ H ₁₉ NO ₄ S ₂	230	80*	15	825 X	83	+
94	C ₆ H ₅ O(CH ₂) ₄	<i>h, g</i>			II		A		22	178-181	C ₁₂ H ₁₉ NO ₄ S ₂	>250	200	15	1000 G	0	0
95	2-C ₂ H ₅ OC ₆ H ₄ O(CH ₂) ₂	<i>f, p</i>			II		A		10	139-143	C ₁₂ H ₁₉ NO ₄ S ₂	150	100	15	1000 G	0	0
96	3-CF ₃ C ₆ H ₄ O(CH ₂) ₄	<i>h, k, q</i>	148-158 (20)		II		A, C		17	190-193	C ₁₃ H ₁₈ F ₃ NO ₄ S ₂	45	30	30	1000 G	80	+
97	C ₆ H ₅ S(CH ₂) ₃	<i>f, r</i>	131-145 (0.3)		II		M		35	177-178	C ₁₃ H ₂₁ NO ₄ S ₂	300	50	15	1000 G	20	0
98	2-CH ₃ C ₆ H ₄ O(CH ₂) ₄	<i>h, g</i>			II		A		12	173-178	C ₁₃ H ₂₁ NO ₄ S ₂	150	25	15	1000 G	78	++
99	3-CH ₃ C ₆ H ₄ O(CH ₂) ₄	<i>h, g</i>			II		B, C		4	168-170	C ₁₃ H ₂₁ NO ₄ S ₂	175	50	15	825 X	100	++
												25	30	825 X	7		
100	4-CH ₃ C ₆ H ₄ O(CH ₂) ₄	<i>h, g</i>			II		A, D		12	180-182	C ₁₃ H ₂₁ NO ₄ S ₂	35	25	30	1000 G	73	+
101	C ₆ H ₅ O(CH ₂) ₃	<i>f, k, s</i>	107-117 (0.2)	95	II		J		25	157-158	C ₁₃ H ₂₁ NO ₄ S ₂	>50	50	30	1000 G	80	+
												25	30	1000 G	73		
102	2-CH ₃ C ₆ H ₄ OCH(CH ₂) ₃ CH ₂	<i>f, m</i>	92-97 (1.5)	98	II		A		43	172-173	C ₁₃ H ₂₁ NO ₄ S ₂	150	50	15	1000 G	0	0
103	3-CH ₃ C ₆ H ₄ OCH(CH ₂) ₃ CH ₂	<i>f, m</i>	88-91 (0.5)	95	II		A		47	176-177	C ₁₃ H ₂₁ NO ₄ S ₂	90	50	30	1000 G	0	0
104	4-CH ₃ C ₆ H ₄ OCH(CH ₂) ₃ CH ₂	<i>f, m</i>	82-87 (0.6)	98	II		A, M		55	214-215	C ₁₃ H ₂₁ NO ₄ S ₂	87	50	15	1000 G	0	0
105	4-CH ₃ OC ₆ H ₄ O(CH ₂) ₄	<i>f, k, t</i>	130-142 (0.4)		II		M		41	154-156	C ₁₃ H ₂₁ NO ₄ S ₂	200	90	30	1000 G	93	++
												45	30	1000 G	60		
106	4-CH ₃ OC ₆ H ₄ OCH(CH ₂) ₃ CH ₂	<i>f, r</i>	106-113 (0.6)	97	II		A, M		46	194-195	C ₁₃ H ₂₁ NO ₄ S ₂	100	112*	15	825 X	17	0
107	1-Naphthyl-O(CH ₂) ₂	<i>f</i>	mp 113-121		II		M		24	229-230	C ₁₄ H ₁₇ NO ₄ S ₂	700	25	30	1000 G	0	0
108	2,3-(CH ₃) ₂ C ₆ H ₃ O(CH ₂) ₄		113-117 (0.4)	99	II		A		32	198-200	C ₁₄ H ₂₃ NO ₄ S ₂	22	7.5	30	1000 G	73	+
109	3,4-(CH ₃) ₂ C ₆ H ₃ O(CH ₂) ₄	<i>f, k</i>	142-149 (1.5)		II		C		7	187-189	C ₁₄ H ₂₃ NO ₄ S ₂	45	30	30	1000 G	87	+
												15	30	1000 G	47		
110	2,4-(CH ₃) ₂ C ₆ H ₃ O(CH ₂) ₄	<i>f, k</i>	122-126 (1)		II		A, C		5	206-208	C ₁₄ H ₂₃ NO ₄ S ₂	20	10	30	1000 G	87	++
												5	30	1000 G	40		
111	2,5-(CH ₃) ₂ C ₆ H ₃ O(CH ₂) ₄	<i>f, k</i>	126-131 (0.7)	99	II		A		35	185-187	C ₁₄ H ₂₃ NO ₄ S ₂	>40	30	30	1000 G	93	+
												15	30	1000 G	27		
112	2,6-(CH ₃) ₂ C ₆ H ₃ O(CH ₂) ₄	<i>f, k</i>	110-123 (0.4)	99	II		M		32	213-214	C ₁₄ H ₂₃ NO ₄ S ₂	250	100	30	1000 G	100	++
												25	30	1000 G	73		
113	2-CH ₃ C ₆ H ₄ O(CH ₂) ₃	<i>f, k</i>	121-137 (0.6)	98	II		A		38	185-187	C ₁₄ H ₂₃ NO ₄ S ₂	200	70	15	1000 G	87	++
												18	30	1050 G	67		
114	C ₆ H ₅ O(CH ₂) ₆	<i>f, k, n</i>	115-117 (0.4)	95	II		M		16	181-182	C ₁₄ H ₂₃ NO ₄ S ₂	500	50	60	1000 G	0	0
115	3-CH ₃ , 4-CH ₃ C ₆ H ₃ OCH(CH ₂) ₄	<i>f, i, k</i>		90	II		D		14	174-175	C ₁₄ H ₂₃ NO ₄ S ₂	187	50	15	1000 G	53	++

TABLE V
MISCELLANEOUS N-2-(SUBSTITUTED AMINO)ETHYL THIOSULFATES
 $RNHC_2H_4CH_2S_2O_3H$

No.	R	RX		Method ^a	Recrystn solvents ^b	Yield, %	Mp, °C	Formula	Analyses	C, L/D ₅₀ , mg/kg	Drug dose		Survival, %	Rating	
		Source	Bp, °C (mm)								min	preirradiation			Radiation dose, R
127	CH ₂ =CH(CH ₂) ₃	d	122-130	II	A, I	12	149-150	C ₇ H ₁₅ NO ₃ S ₂	C, H, N, S	225	100	15	1000 G	0	0
128	CH ₃ O(CH ₂) ₄	d, e	55-65 (13)	II	A	10	118-119	C ₇ H ₁₇ NO ₃ S ₂	C, H, N, S	375	250	15	825 X	0	0
129	(CH ₃) ₂ CHCH ₂ CH(CH ₃)			I ^f	R	25	148-152	C ₉ H ₁₉ NO ₃ S 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 ₉ H ₂₁ NO ₃ S ₂	C, H, N, S	550	300	15	825 X	7	0
131	Γ-O ⁻ (CH ₃) ₂ CHOCH ₃	d, i	78 (2)	II	D	5	124-125	C ₁₀ H ₂₁ NO ₃ S ₂	C, H, N, S	350	200	15	825 X	0	0
132	(C ₂ H ₅) ₃ CCH ₂			III ^j	A	52	190-195	C ₁₀ H ₂₃ NO ₃ S 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 ₃ S ₂	C, H, N, S	625	200	60	1000 G	74	+
134	CH ₃ (CH ₂) ₅ CH(CH ₂ OH)			I ^f	A	25	173-176	C ₁₀ H ₂₃ NO ₃ S ₂	C, H, N, S	140	80	15	825 X	20	+
135	HO(CH ₂) ₆	g, h	79-83 (0.1)	II	A	23	150-154	C ₁₀ H ₂₅ NO ₃ S ₂	C, H, N, S	350	200	30	825 X	27	+
136	CH ₃ O(CH ₂) ₈	d, e	95-105 (1.5)	II	B, A	18	180-183	C ₁₀ H ₂₅ NO ₃ S ₂	C, H, N, S	150	75	15	1000 G	20	+
137	CH ₃ O(CH ₂) ₉	d, e	123-133 (14)	II	A	27	192-196	C ₁₂ H ₂₇ NO ₃ S ₂	C, H, N, S	80	60*	30	1000 G	90	+
138	HO(CH ₂) ₁₀	g, h	97-100 (0.3)	II	A	17	135-138	C ₁₂ H ₂₇ NO ₃ S ₂	C, H, N, S	>200	30	30	825 X	40	0
139	CH ₃ (CH ₂) ₇ CH(CH ₂ OH)			I ^k	A	10	180-185	C ₁₂ H ₂₇ NO ₃ S ₂	C, H, N, S	25	10	15	825 X	13	0
140	HO(CH ₂) ₉ CH(OH)CH ₂			V ^l	A	35	164-167	C ₁₃ H ₂₉ NO ₃ S ₂	C, H, N, S	400	250	15	1000 G	0	0
141		g, m		II	A	8	202-203	C ₁₁ H ₂₉ NO ₃ S ₂	C, H, N, S	150	75	15	1000 G	13	0
142	4-FC ₆ H ₄ C(CH ₃) ₂ CH ₂ O(CH ₂) ₄			II	U	1.4	117-119	C ₁₉ H ₃₃ NO ₃ S ₂	C, H, N, S	200	100	15	1000 G	47	+
143	3,4-(CH ₃ O) ₂ C ₆ H ₃ CH(OH)C(CH ₃) ₂	d, n		I ^f	M	63	212-213	C ₂₁ H ₃₅ NO ₃ S ₂	C, H, N, S	300	100	15	1000 G	0	0
144	(C ₆ H ₅) ₂ CHO(CH ₂) ₂	g		II	C	10	180-190	C ₂₁ H ₂₃ NO ₃ S ₂	C, H, N, S	600	150	30	825 X	0	0

^a See footnote a, Table I. V: $RCHCH_2 + H_2NCH_2CH_2S_2O_3Na \rightarrow RCH(OH)CH_2NHC_2H_4CH_2S_2O_3H$. ^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**, 1931 (1960), gave bp 111-112° (12 mm). ^j See Experimental Section. ^k Crude thiol was prepared from 2-amino-1-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'-fluorobutylphenone. 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
RNHCH₂CH₂SSO₃H

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		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 LD₅₀ 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 C₅H₅N was added below 0° 21 g (0.077 mole) of PBr₃.²³ After stirring for 16 hr at room tem-

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
70	>1000	1000	180	0
		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

perature the mixture was poured onto ice and the product was extracted into Et₂O. The extract was washed with saturated NaHCO₃, dried (MgSO₄), and concentrated. Distillation of the residue provided 22 g (58%) of 1-bromo-3-cyclobutylpropane: bp 72–77° (19 mm); glpc, >93%; nmr (CCl₄), δ 3.32 (t, 2, J = 7 Hz, CH₂Br) and 1.3–2.6 ppm (m, 11).

S-2-[(3-Cyclobutylpropyl)amino]ethyl Thiosulfate (2).—Sodium S-2-aminoethyl thiosulfate (43 g, 0.24 mole) was alkylated³ 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 H₂O was filtered, giving 31 g of crude product. The solid was triturated with H₂O 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 PBr₃ in the presence of C₅H₅N 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 prepare³ the Bunte salt **8**.

trans-N-(2-Hydroxyethyl)-2-phenylcyclopropanecarboxamide was prepared in CH₂Cl₂ 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. (C₁₂H₁₅NO₂) 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 LiAlH₄. Distillation of the product afforded 57 g (76%) of 2-[*trans*-(2-

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

phenylcyclopropyl)methyl]amino]ethanol: bp 140–146° (0.3 mm); nmr (CCl₄), δ 6.95 (m, 5, C₆H₅), 3.40 (m, 4, NH, CH₂OH),

2.58 (m, 4, CH₂NCH₂), and 0.62–1.83 ppm (m, 4, CHCH₂CH).

To 20 g (0.11 mole) of 2- $\{[trans-(2\text{-phenylcyclopropyl})methyl]amino\}$ ethanol was added dropwise at 0° 25 g (0.2 mole) of SOCl₂. 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 re-concentrated. Crystallization from EtOH–Et₂O gave 15 g (60%) of *trans*-N-(2-chloroethyl)-2-phenylcyclopropanemethylamine hydrochloride, mp 117–119°. The sample for analysis melted at 120–122°. *Anal.* (C₁₂H₁₆NCl·HCl) C, H, N, Cl.

S-2- $\{[trans-(2\text{-Phenylcyclopropyl})methyl]amino\}$ ethyl Thiosulfate (64).—*trans*-N-(2-Chloroethyl)-2-phenylcyclopropanemethylamine hydrochloride (15 g, 0.06 mole) was converted to the Buente salt using Na₂S₂O₃·5H₂O.³ Two recrystallizations of the crude product from EtOH–DMF gave 13.5 g (78%) of **64**, mp 188–190°.

S-2- $\{[2,2\text{-Diethylbutyl})amino\}$ ethyl Thiosulfate (132).—Reduction of 50 g (0.32 mole) of 2,2-diethylbutyric acid by LiAlH₄ in Et₂O 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 PBr₃ 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 (H₂O), dried (MgSO₄), concentrated, and distilled giving 7 g of 2- $\{[2,2\text{-diethylbutyl})amino\}$ 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 Na₂S₂O₃·5H₂O in 20 ml of H₂O afforded 3.6 g (52%) of the Buente salt **132**: mp 190–195° dec; nmr (D₂O–NaOD), δ 2.8–3.3 (m, 4, NCH₂CH₂S), 2.31 (s, 2, Et₂C–CH₂N), and 0.50–1.48 ppm [m, 15, (C₂H₅)₃].

4-(4-Chlorobutyl)bicyclohexyl.—A solution of 225 g (0.86 mole) of 3-(*p*-cyclohexylbenzoyl)propionic acid²⁴ in 1 l. of MeOH was hydrogenated at about 3 atm in the presence of 5 ml of concentrated H₂SO₄ and 5 g of 20% Pd–C. The reduction was allowed to proceed for 17 hr (H₂ uptake corresponded to reduction of carbonyl group) and then 10 g of 10% Rh–C was added followed by hydrogenation for 48 hr (H₂ uptake corresponded to reduction of the aromatic ring). A slurry of the filtered solution with 10 g (0.094 mole) of anhydrous Na₂CO₃ was allowed to stand for 16 hr. The solvent was removed under reduced pressure, the residue was extracted with 500 ml of Et₂O, and the ethereal extract was washed with small portions of H₂O and dried (MgSO₄).

The solution containing 4-cyclohexyleyclohexanebutyric acid was reduced with 35.8 g (0.89 mole) of LiAlH₄ giving 149 g (70%) of 4-cyclohexyleyclohexanebutanol: bp 209–215° (8 mm); glpc, 99%. Conversion of the alcohol to the chloride (SOCl₂, C₆H₅N)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.* (C₁₆H₂₆Cl) C, H, Cl.

2-(4-Bromobutyl)cyclohexyl Methyl Ether.—4-(*o*-Methoxyphenyl)butyric acid²⁶ (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 LiAlH₄ in Et₂O solution gave 32 g (71%) of 2-methoxycyclohexanebutanol, bp 83–95° (0.4 mm). The substituted butanol (32 g, 0.18 mole) was converted (PBr₃ and C₆H₅N at 25°) to 2-(4-bromobutyl)cyclohexyl methyl ether: 18 g (40%), bp 75–85° (0.2 mm). *Anal.* (C₁₁H₂₁BrO) C, H, Br.

1-(4-Chlorobutyl)-4-methylcyclohexane.—A solution containing 75 g (0.45 mole) of 4-*p*-tolyl-1-butanol²⁷ and 2 ml of concentrated H₂SO₄ 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 H₂SO₄ in 250 ml of MeOH was completed in 24 hr over 4 g of 10% Rh–C. The H₂SO₄ in the two lots was neutralized with Na₂CO₃ as described above. The products were combined giving 79 g (71%) of crude oily product. The alcohol was chlorinated (SOCl₂, C₆H₅N) to give 39 g (45%) of 1-(4-chlorobutyl)-4-methylcyclohexane: bp 69–72° (0.8 mm); glpc, 60:40 mixture of isomers. *Anal.* (C₁₁H₂₁Cl) C, H.

4-(4-Chlorobutyl)cyclohexyl Methyl Ether.—A methanolic solution containing 125 g (0.56 mole) of methyl 3-*p*-anisoylpropionate²⁸ 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 NaBH₄ in 2 l. of absolute EtOH.³⁰ The mixture was allowed to stir for 18 hr³¹ before dilution in 7 l. of H₂O. The product was extracted into CHCl₃ 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 (CCl₄) δ 3.48 (t, 2, *J* = 6 Hz, CH₂Cl), *ca.* 3.3 (m, 1, MeOCH), and 3.21 ppm (s, 3, CH₃O); component B, 1.1 g (contaminated with 2.8% of A), nmr (CCl₄) δ *ca.* 3.5 (m, 1, MeOCH), 3.47 (t, 2, *J* = 6 Hz, CH₂Cl), and 3.23 ppm (s, 3, CH₃O). Elemental analytical data confirmed that A and B are the two racemates of 4-(4-chlorobutyl)cyclohexyl methyl ether. *Anal.* A (C₁₁H₂₁ClO) C, H, Cl. B (C₁₁H₂₁ClO) C, H.

***p*-(4-Chlorobutyl)phenol.**—A solution of 79.5 g (0.40 mole) of *p*-(4-chlorobutyl)anisole³² in 1.2 l. of CH₂Cl₂ was treated with 100 g (0.40 mole) of BBr₃³ to give 57 g (77%) of *p*-(4-chlorobutyl)phenol, bp 141–145° (2 mm). *Anal.* (C₁₀H₁₃ClO) C, H, Cl.

[2-(Bromomethyl)propyl]cyclohexane.—Reduction of 200 g (1.18 moles) of α -ethylcyclohexaneacetic acid in Et₂O with 44.6 g (1.18 moles) of LiAlH₄ gave 133 g (72%) of α -ethylcyclohexaneethanol: bp 78–84° (0.6 mm) [lit.³³ 1 form, bp 119–121° (18 mm)]; nmr (CCl₄), δ 3.49 (d, 2, *J* = 4 Hz, CH₂O), 3.09 (s, 1, OH), and 0.75–1.92 ppm (m, 17). Conversion of the alcohol to the alkyl bromide (PBr₃–C₆H₅N, 2 hr at 100°) gave 39.6 g (67%) of [2-(bromomethyl)propyl]cyclohexane: bp 125–131° (28 mm); glpc, 94%; nmr (CCl₄), δ 3.49 (d, 2, *J* = 4 Hz, CH₂Br) and 0.75–1.98 ppm (m, 17). *Anal.* (C₁₀H₁₉Br) C, H, Br.

***sec*-Butylcyclohexane.**³⁴—Reduction of 39.6 g (0.18 mole) of [2-(bromomethyl)propyl]cyclohexane with 2.3 g (0.06 mole) of LiAlH₄ was allowed to proceed for 18 hr in 300 ml of refluxing Et₂O. 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 K₂CO₃, 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 H₂O before being extracted into Et₂O. The ethereal solution was washed (H₂O), dried (MgSO₄), 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 (CCl₄), δ 1.03 ppm (t, 3, *J* = 7 Hz, CH₃CH₂CH).

(28) M. D. Soffer and M. C. Hunt, *J. Am. Chem. Soc.*, **67**, 692 (1945).

(29) Catalytic reduction of 4-(*p*-methoxyphenyl)-1-butanol using Rh–C resulted in only the unsubstituted S-2- $\{[4\text{-cyclohexyl})butyl\}$ amino[ethyl]thiosulfate as a final product. The ether must have been cleaved during catalytic reduction; dehydration and saturation of the ring must have followed.

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

(31) At one point vigorous evolution of hydrogen occurred. We prefer LiAlH₄ for these reductions.

(32) See Table III, footnote 1.

(33) E. Bowden and H. Adkins, *J. Am. Chem. Soc.*, **56**, 689 (1934).

(34) This preparation provided evidence that no rearrangement of branched-chain compounds occurred in the synthesis of alkyl bromides from alcohols using PBr₃ and pyridine.

(35) J. Timmermans, *Bull. Soc. Chim. Belges*, **36**, 502 (1927); *Chem. Abstr.*, **22**, 56 (1928).

(24) N. P. Bun-Hoi, P. Cogniant, and Ch. Mentzer, *Bull. Soc. Chim. France*, **11**, 127 (1944).

(25) Reference 23, p 92.

(26) J. Lockett and W. F. Short, *J. Chem. Soc.*, 787 (1939).

(27) R. Huisgen and V. Vossius, *Monatsh. Chem.*, **88**, 517 (1957).

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, $\text{CH}_3\text{CH}_2\text{CH}$).

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. ($\text{C}_{11}\text{H}_{13}\text{BrO}_2$) 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. ($\text{C}_{13}\text{H}_{19}\text{BrO}_2$) 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. ($\text{C}_{10}\text{H}_{19}\text{BrO}$) 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, $\lambda_{\text{max}}^{\text{MeOH}}$ 254 m μ (ϵ 8700); the nmr peaks were as expected. Anal. ($\text{C}_{11}\text{H}_{15}\text{BrS}$) Br.

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

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(36) Reference 23, pp 226–228.

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

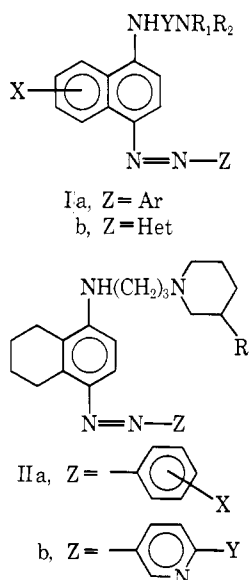
EDWARD F. ELSLAGER, DAVID B. CAPPS, DIANNE H. KURTZ, AND DONALD F. WORTH

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106

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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* H₃₇Rv *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



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* H₃₇Rv 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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