# N-Substituted S-2-Aminoethyl Thiosulfates as Antiradiation Agents<sup>1</sup>

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Received March 14, 1968

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, cycloalkylalkyl, cycloalkylakyl, 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<sup>2</sup> that less toxic antiradiation agents are needed. We discovered that Ncyclohexylalkyl 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5,6</sup>

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  $\alpha$ 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-

<sup>(1)</sup> This investigation was supported by the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2306. We appreciate the interest and support of Drs. D. P. Jacobus and T. R. Sweeney of Walter Reed Army Institute of Research.

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

<sup>(3)</sup> 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).

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

<sup>(5)</sup> C. G. Derick and D. W. Bissell, J. Am. Chem. Soc., 38, 2478 (1916).

<sup>(6)</sup> 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 +  $H_2NCH_2$ - $CH_2OH \rightarrow 2$ -hydroxyethylamide + LiAl $H_4 \rightarrow 2$ -(substituted amino)ethanol + SOCl<sub>2</sub>  $\rightarrow 2$ -(substituted amino)ethyl chloride hydrochloride + Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>  $\rightarrow$  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 diand 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  $\alpha$ -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 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<sub>3</sub><sup>7</sup> 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 cycloalkanols or cycloalkylalkanols, excess  $\alpha, \omega$ -dibromoalkanes, and NaH. In some cases an  $\alpha$ -bromo- $\omega$ -chloroalkane was used in the reaction.

The aryl ethers in Table IV required intermediate halo ethers which were prepared from appropriately substituted phenols and  $\alpha, \omega$ -dibromoalkanes in the presence of K<sub>2</sub>CO<sub>3</sub>. Branched-chain compounds in this aryl ether series were prepared similarly from  $\alpha$ bromo esters. Dehydrohalogenation of the  $\alpha$ -bromo ester could be expected in this case, but apparently K<sub>2</sub>CO<sub>3</sub> is not a strong enough base for dehydrohalogenation to compete successfully with substitution by phenoxide ion. If formed, an  $\alpha,\beta$ -unsaturated ester would add phenoxide ion to give a  $\beta$ -substituted ether. Homogeneous products were obtained and structures were confirmed by nmr spectra. Precedence for the desired  $\alpha$  substitution has been reported in early literature.<sup>8</sup>

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<sup>9</sup> leading to a compound related



to epinephrine. The following transformations afforded a Bunte salt from the ring-opened product: ketone + LiAlH<sub>4</sub>  $\rightarrow$  alcohol + Na-NH<sub>3</sub>  $\rightarrow$  thiol + O<sub>2</sub>  $\rightarrow$  disulfide + SO<sub>3</sub><sup>2-</sup>  $\rightarrow$  Bunte salt (143). Structures with this degree of substitution are almost devoid of analeptic activity.

**Biological Activity.**—The Bunte salts were tested in mice<sup>10</sup> for antiradiation activity at Walter Reed Army Institute of Research.<sup>11</sup> 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).

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TABLE 1: S-2-(Cycloalkylabkylamino)ethyl Thiosuleates RNHCH2CH3S\_0,H

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 <sup>10</sup> (NHRUHAE) + 80(-1)
 <sup>10</sup> (MIRUHAE) + 80(-1)
 <sup>11</sup> (MIRUHAE) + 80(-1)
 <l + $233 \\ 273$ 1000 G 1000 G 80 30 ++++, 16–29. The ratings are a measure of t ug for which a high rate of survival was obtained.  $\infty$  is  $\overline{0}$ 18 20 C<sub>16</sub>H<sub>31</sub>NO<sub>3</sub>S<sub>2</sub> C<sub>16</sub>H<sub>33</sub>NO<sub>3</sub>S<sub>2</sub> C<sub>18</sub>H<sub>35</sub>NO<sub>3</sub>S<sub>5</sub>  $193 \\ 220 \\ 225 \\ 226$ 189 - 1217 - 2 222 - 2 224 - 2  $\rightarrow$  cyclohexaneoctanoic acid (reference in footnote r); RCO<sub>2</sub>H + LiAIH. <sup>mm</sup> All compounds were analyzed for ( ng ranges of protective indices (footnote 12 in the text): 0, 0–1; +, 2–5; ++, 6–10; +++, 11–15; +-radiation activity was obtained. The per cent survival given in the table represents the lowest dose of drug ⊴ % % ⊳ A L' 104-115 (0.8) 177-178 (19)205-209 (19) 4-Cyclohexylcyclohexyl-(CII2)4 Decahydro-2-naphthyl-(CH<sub>2</sub>)<sub>4</sub> (CH<sub>2</sub>)<sub>5</sub>CH(CH<sub>2</sub>)<sub>8</sub> antiradiation activity was obtained. (CH\*),CH(CH\*) 

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  $\gamma$  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.<sup>12</sup> 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 doseresponse 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-cvclohexenyl 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-

<sup>(12) &</sup>quot;Protective index" is a term used by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. Protective index = (protection factor)(LD<sub>50</sub>/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.

kg tion dose, R val. % Rating 15 1000 (3 0 0 0 15 825 X 47 + 15 825 X 87 +1	15 1000 (; 0 0 15 825 X 47 + 15 825 X 87 +1	15 825 N 47 + 15 825 N 47 + 15 825 N 87 + 1	15 825 X 47 + 15 825 X 87 ++	15 895 V 87 ±±		5 15 825 X 60	15 1000 G 60 ++	15 1000 G 87 +	15 1000 G 33 ++	5 15 1000 G 47 +	30 1000 G 53 +	30 1050 G 13 0	27	15 1000 G 80 +++	15 1000 G 87 +	30 1000 G 80 +++	5 15 1050 G 87 ++	15 1000 G 80 +	15 1050 G 67 +	imental Section. All are alkyl bromides	ere analyzed for C, H, N, S.
con 'cerrrie	mg/kg mg/	150 50	100	125 75	150 75	37	150 50	150 75	150 20	18 12	38 15	75 x	12	150 25	35 25	250 50	50 12	110 60	15 10	ther in Expe	compounds v
-	Formula <sup>g</sup>	C <sub>11</sub> H <sub>23</sub> NO <sub>4</sub> S <sub>2</sub>	C12H25NO4S2	$C_{12}H_{25}NO_4S_2$	$C_{13}H_{27}NO_4S_2$		$C_{13}H_{27}NO_4S_2$	$C_{13}H_{27}NO_4S_2$	$C_{14}H_{29}NO_4S_2$	$C_{14}H_{29}NO_4S_2$	$\mathrm{C}_{14}\mathrm{H}_{29}\mathrm{NO}_4\mathrm{S}_2$	$\mathrm{C}_{14}\mathrm{H}_{29}\mathrm{NO}_4\mathrm{S}_2$	C <sub>16</sub> H <sub>29</sub> NO <sub>4</sub> S <sub>2</sub>	$C_{14}H_{29}NO_4S_2$	$C_{14}H_{29}NO_4S_2$	$C_{14}H_{29}NO_4S_2$	C <sub>15</sub> H <sub>31</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>15</sub> H <sub>31</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>16</sub> H <sub>33</sub> NO <sub>4</sub> S <sub>2</sub>	utyl cyclohexyl c	97 (1959). # AH
	Mp, °C	156 - 157	200 - 202	198-200	$200 \ 202$		197-200	198-200	209-211	201 - 203	192 - 195	213-215	209-210	196 - 199	196-202	194 - 195	200-203	170-171	188-191	of 4-bromobu	hem. Soc., N
	Yield, $\%$	12	15	2	3		11	20	Π	14	21	x	9	10	14	68	40	12	10	paration o	nett, J. C
Recrystn	solvents"	0, P	Q, G, C, D	D, A	R, D		D, H	А	1), X	<b>T</b> , D	Q, D	V	G, A	G, J, C, J	A, D	H	II	1)	Λ, Ι.	I. <sup>4</sup> See pre	and N. E. N
	Method"	II	II	II	II		II	II	II	Π	II	II	II	II	Π	Π	Ш	II	II	o, Table	d. Davis,
ĺ	Glpc, $%$		95				<u>9</u> 9				20					<u>95</u>	95	8	96 0	s c and c	Joffins, A
	Bp, °C (mm)	120 130 (15)	82-95 (0.4)	$56-67 \ (0.1)$	65.75(0.1)		100-120 (0.4)	95 - 115 (0.6)	87-97 (0.1)	98-100 (0.6)	97-102 (0.05	87-92 (0.3)	$90{-}100(0.5)$	$93-105\ (0.6)$	97-110 (0.4)	108-117 (0.5)	130-137 (0.4)	112-120 (1.2)	126 - 140(0.5)	<sup>c</sup> See footnote	Ashley, R. F. (
•	Source	p	lh h	,	d, f		l,	p	p	lh I	d	p	d	p	p	ų	lh l	<i>q</i>	p	b, Table I.	1. J.J. N.
	R	(CH <sub>2</sub> ),CHO(CH <sub>2</sub> ),	$(CH_2)_4 CHO(CH_2)_5$	(CH <sub>2</sub> ) <sub>5</sub> CHO(CH <sub>2</sub> ) <sub>4</sub>	(CH <sub>2</sub> ) <sub>5</sub> CHO(CH <sub>2</sub> ) <sub>5</sub>		$(CH_2)_4CHO(CH_2)_6$	$(CH_2)_6CHO(CH_2)_4$	(CH <sub>2</sub> ) <sub>6</sub> CHO(CH <sub>2</sub> ) <sub>6</sub>	(CH <sub>2</sub> ) <sub>5</sub> CHCH <sub>2</sub> O(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ),CH(CH <sub>2</sub> ),O(CH <sub>2</sub> ),	2-CH <sub>3</sub> [(CH <sub>2</sub> ) <sub>5</sub> CH]O(CH <sub>2</sub> ) <sub>5</sub>	$4-CH_3[(CH_2)_5CH]O(CH_2)_5$	1-CH <sub>3</sub> [(CH <sub>2</sub> ) <sub>5</sub> CH]O(CH <sub>2</sub> ) <sub>5</sub>	(CH <sub>2</sub> ) <sub>6</sub> CHO(CH <sub>2</sub> ) <sub>5</sub>	$(CII_2)_7CHO(CII_2)_4$	$(CH_2)_7 CHO(CH_2)_5$	(CH <sub>2</sub> ),CHCH(C <sub>2</sub> H <sub>6</sub> )O(CH <sub>2</sub> ),	$(CH_2)_{5}^{3}CHO(CH_2)_{5}$	otnote a, Table I. <sup>6</sup> See footnote i	noted. * See Experimental Section
	No.	47	48	49	50		51	52	53	54	55	56	57	58	59	60	61	62	69	" See for	xcept as 1

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 medioere.

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), mchlorophenoxybutyl (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**<sup>13</sup>

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<sup>9</sup> 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<sub>2</sub>O was warmed and filtered. Dry HCl was added to the light yellow filtrate, precipitating a semisolid salt. The Et<sub>2</sub>O layer was decanted and the product was triturated with 200 ml of warm Me<sub>2</sub>CO to effect crystallization. The mixture was chilled and filtered to give 21 g (51%) of crystalline product, mp 177-180°. Recrystallization from Me<sub>2</sub>CO provided 16 g of product with no increase in melting point. Anal. (C21H27NO3S. HCl) C, H, N. A 0.2-mole preparation gave 40.5 g (50%) of the same product, mp 177-179°

 $\alpha$ -(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<sub>2</sub>O-C<sub>5</sub>H<sub>6</sub> (1:1) was treated with 50 ml of 1 N NaOH. The organic layer was separated, washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and concentrated. The residual oil was reduced with 1.9 g of LiAlH<sub>4</sub> in 250 ml of Et<sub>2</sub>O.<sup>14</sup> 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 materiał was washed well with H<sub>2</sub>O. 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°. Anatl. (C<sub>21</sub>H<sub>29</sub>NO<sub>8</sub>S) C, H, N, S.

 $\alpha, \alpha'$ -[Dithiobis(ethyleniminoisopropylidene)]bis(3,4-dimethoxybenzyl Alcohol).—Debenzylation of 12.2 g (0.032 mole) of  $\alpha$ -(1-{[2-(benzylthio)ethyl]amino}-1-methylethyl)-3,4-dimethoxybenzyl alcohol was effected by the use of Na in liquid NH<sub>3</sub>.<sup>16,16</sup> The solid obtained from the decomposed (H<sub>2</sub>O–NH<sub>4</sub>Cl) mixture was washed well (H<sub>2</sub>O) and recrystallized from EtOH giving 6.5 g of crude product in several crops, mp 144–152°. The combined

<sup>(13)</sup> 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  $\pm 0.4\%$  of the theoretical values.

<sup>(14)</sup> W. G. Brown, Org. Reactions. 6, 469 (1951).

<sup>(15)</sup> J. Baddiley and E. M. Thain, J. Chem. Soc., 800 (1952).

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

# November 1968

S-2-(Aralkylamino)ethyl Th:osulfate

TABLE III

RNHCH2CH2S2O3H

1195

Rating	0	+	0	+	+	+	+++++++++++++++++++++++++++++++++++++++		++	+	+	+	+	+	+	+	++	-+-	0		0	Cleiszler, Oz) gave yric acid (1956)]. used for n. Chem. $l. Abstr.,(65-172°netole +netole +ote m) +to butyratecid; A.$
Survi- val, %	13	73	13	27	20	47	100	87	80	20	60	73	7:3	47	80	53 25	ŝ	53	•		0	an, A. D. $\mathcal{U}_{-}C_{6}H_{5}N$ $\mathcal{U}_{-}C_{6}H_{5}N$ $\mathcal{Sec}$ , 2455 $\mathcal{Sec}$ , 2455 $\mathcal{Sec}$ , 2455 $\mathcal{Sec}$ , $\mathcal{A}^{1}$
liation act. <sup>c-</sup> Radiation, dose, R	1000 G	1000 G	1000 G	1000 G	1000 G	1050  G	825 X	1000  G	1000 G	1000 G	1000 G	1000 G	1000 G	1000 G	1050 G	825 X	1000 G	1000 G	1000 G		1000 G	A. Spielm I <sub>a</sub> in C <sub>2</sub> H <sub>3</sub> C AryCoryph J. Chem. A de alkyl h. Chem. A de alkyl $\rightarrow$ J. Shem. A de alkyl h. A de alkyl $\rightarrow$ 1 alHI <sub>4</sub> $\rightarrow$ 1 ROH. $p^{-1}$ ROH. $p^{-1}$ ROH. $(reihyl)$ 2-phen Lby conveil
-Antirac iose min preir- radia- tion	15	15	15	15	15	30	15	15	15	15	15	30	30	15	30	15	30	15	30		30	acid [M ing AlC vickars, vickars, vickars, vickars, vickars, vickars, blow, vickars, vickara
Drug d mg/kg	50	75	100	150	75	75	50*	30	37.5	40	ŗ	15	10	15	15	200*	10	x	75		25	(b) butyrid initions us initions us M. A. M. M. A. M. M. A. M. M. A. M. M. M
Ca. LD <sub>50</sub> , mg/kg	75	140	300	250	175	200	120		150	100	15	38	20	22	45	350	>40	15	100		750	orophenyl rafts cond n hydrogen mith, and ce, 15, 41- 3). " R( 3). " R( 3). " R( 3). " R( 3). " R( 3). " R( 20-230° tute [struct analyzed analyzed
For anda <sup>2</sup>	$\mathrm{C}_{12}\mathrm{H}_{17}\mathrm{NO}_3\mathrm{S}_2$	C <sub>12</sub> H <sub>18</sub> CINO <sub>3</sub> S <sub>2</sub>	C <sub>12</sub> H <sub>19</sub> NO4S <sub>2</sub>	$C_{12}H_{19}NO_4S_2$	C <sub>12</sub> H <sub>19</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>12</sub> H <sub>19</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>		C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	$C_{14}H_{23}NO_3S_2$	$C_{14}H_{23}NO_3S_2$	$C_{14}H_{23}NO_3S_2$	$C_{14}H_{23}NO_4S_2$	$C_{14}H_{23}NO_4S_2$	$C_{14}H_{23}NO_5S_2$	C <sub>15</sub> H <sub>25</sub> NO <sub>4</sub> S <sub>2</sub>	$\rm C_{18}H_{29}NO_3S_2$	$\mathrm{C}_{20}\mathrm{H}_{23}\mathrm{NO}_3\mathrm{S}_2$		$\mathrm{C}_{20}\mathrm{H}_{25}\mathrm{NO}_{3}\mathrm{S}_{2}^{\mu}$	/ ROH: $2$ -( $p$ -chl hride (Friedel-C) tric (20% Pd-C) eley, N. H. P. S. Soc. <i>Chim. Fran.</i> Soc. <i>Chim. Fran.</i> Soc. <i>Chim. Fran.</i> <i>tr.</i> , <b>59</b> , 8732 (196 nura, and S. Toki nura, and S. Toki nura, and S. Toki 1. Warren, <i>J. Cl</i> a ROH: see ref <i>i</i> anthrenebutyrr ompounds were sompounds were
Mp, °C	188-190	198-200	186 - 187	187-188	179 - 180	180-181	181-182		167 - 169	130 - 135	210 - 212	214 - 215	214 - 215	206 - 207	181-184	166 - 168	183-186	223 - 225	208-211		216 - 217	<ul> <li>m. * RBr.</li> <li>normality and the second secon</li></ul>
Yield, $\%$	78	29	9	13	11	18	7		41	18	15	14	22	19	36	×	19	10	17		15	al Sectic la al Sectic <b>5</b> , 745 (1) <b>6</b> , 745 (1) <b>7</b> , 14. H <b>7</b> , 1933) (1941), 1 (1941), 1 (1941), 2 (1941), 2 (1941), 1 (1941), 1 (1941
Recrystn solvents <sup>b</sup>	М	B, A	C, M	С, Ј, А	V.	L	Α		Α	В, С	C	Α	A	Α	B, A	A	B, D, A, D	L, A	A		Μ	æ Experiment shloropheneto <i>Chem. Soc.</i> , <b>3</b> reduction gan Chemical Coa <i>Chemical Coa</i> <i>Chemical Coa</i> <i>Belge</i> , <b>28</b> , 12 alonate [H. T. butyric acid [ on, <i>ibid.</i> , 253 <i>Juim.</i> , <b>60</b> , 291 LiAIH. $^{\circ}$ R UH <sub>4</sub> → meth.
4ethoda	III	II	II	II	II	II	II		II	Π	II	II	II	Π	Ш	II	II	II	II		II	e I. $^{d}S$ ween $p^{-d}$ ween $p^{-d}$ ween $p^{-d}$ ween $p^{-d}$ Indian LiAlH, Aldrich Aldrich A. <i>Chim</i> nenyl)m: pphenyl) (phenyl) (
Glpc, %							95															1 oo, Tabl ction bet 0 for bet J. T at $J$ . L (1933)]; L (1933)]; L (1933)]; L (2010 L ( $p$ -ethy M, $Ee(p-ethyM$ , $Ee(p-ethyM$ , $Ee(p-ethyM$ , $Ee(0.4 mm)(0.4$ mm)
RX- Bp. °C (mm)		83 - 86 (0.5)	110-115 (0.1)	141 - 145(2)		106 - 110(0.4)			115-117 (0.3)	$96 - 102 \ (0.7)$			79-85(0.5)	$115-123 \ (0.3)$	100-107 (0.03)	120-142(0.3)	128 - 135 (0.7)					be footnotes c and - LiAllt, " Reavised, and N. Z. Abstr., 27, 1224 t 25° for 18 hr. t 25° for 18 hr. trubbe, and L. Mi liethyl ethyl(m-m [+ H <sub>2</sub> /Pd-C $\rightarrow$ 4 [L. M. Heilbron a - M. von der Zan texanoic acid (ref 6 (1939)] + LiAl 57)]; bp 194-195'
Source	ą	e, f	e, g	e, h	e, i	e, j	h, k, l		e, m	e, n	h, k, o	h, k, p	е, д	е, т	с, s	ł	e, u	h, k, v	h, k, w		h, k, x	Table I. $e_{1}^{c}$ 89 (1948)   $\rightarrow$ 981 J. J. T. 981 J. J. T. 28); <i>Chem.</i> 46 in Et <sub>2</sub> O a 28); <i>Chem.</i> 4. Linz, H. S mm)] from c ropionic acid putyric acid CH <sub>2</sub> ) <sub>2</sub> O. * J 00 Cytem., 4, 455 59, 1302 (19)
~	C,H <sub>5</sub> CH <sub>2</sub>	4-ClC <sub>6</sub> H <sub>4</sub> CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	$2-HOC_6H_4(CH_2)_4$	$4-HOC_6H_4(CH_2)_4$	$2-CH_3OC_6H_4(CII_2)_3$	$4-CH_3OC_6H_4(CH_2)_3$	$4-CH_3OC_6H_4(CH_2)_4$		$3-CH_3OC_6H_4(CH_2)_1$	3-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	$4-C_2H_5C_6H_4(CH_2)_4$	$2,4-(CH_3)_2C_6H_3(CH_2)_4$	$2,5-(CH_3)_2C_6H_3(CH_2)_4$	$4-C_2H_5OC_6H_4(CH_2)_4$	$4-CH_3OC_6H_4(CH_2)_5$	$3,4-(CH_3O)_2C_6H_3(CH_2)_4$	$4-CH_{3}OC_{6}H_{4}(CH_{2})_{6}$	$4-[(CH_2)_5CH]C_6H_4(CH_2)_4$	2-Phenanthryl-(CH <sub>2</sub> ) <sub>4</sub>	9,10-Dihydro-2-phenanthryl-	$(CH_2)_4$	otnote a, Table I. *See footnote $b_i$ , Close, J. Am. Chem. Soc., <b>70</b> , 41 osalicyloyl)propionic acid [S. L. T eter, German Patent 562,827 (19 between ROH and PBr <sub>3</sub> was effect tion. <sup>1</sup> H. Morren, D. Zivkovic, 1 114 (1957). <sup>a</sup> ROH [bp 95° (0.3; j (1956)]. <sup>a</sup> 3-(p-Ethylbenzoyl)pi <sup>p</sup> ROH: 4-(o,p-dimethylphenyl) <sup>p</sup> ROH: 4-(o,p-dimethylphenyl) <sup>p</sup> ROH: 4-(o,p-dimethylphenyl) <sup>p</sup> Br <sub>2</sub> $\rightarrow$ RBr. <sup>a</sup> ROH: 6-(p-meth chman and W. S. Struve, J. Org., <sup>d</sup> HE. Mosettig, J. Am. Chem. Soc., <sup>d</sup> HE.
Š	64	65	99	67	68	69	20		71	72	73	74	75	76	27	78	62	9 <u>8</u>	81	82		<sup>a</sup> See for and W. J. 3-(5-chlor) 1(1, Schron   Reaction   Reaction   Reaction   10, 246 50, 11, 246 50, 11, 246 10, 266 11, 246 10, 266 10, 266 1

													diation act.'		
											2	Min			
		,	RX		- Me-	Recrystn	Yield,			$Ca. LD_{56}$	dose,	preu- radia-	Radiation,	Survi-	
No.	R	Source	Bp, °C (mm)	Glpe, %	5 thod"	$solvents^{b}$	%	$M_{p, \circ C}$	$Formula^{\mu}$	mg/kg	mg/kg	tion	dose, R	val, %	Rating
	$4-CIC_6II_4O(CII_2)_2$	q			$W^{\prime}$	C	13	188 - 190	C <sub>10</sub> H <sub>14</sub> CINO <sub>4</sub> S <sub>2</sub>	150	100	30	1000 G	20	+
<u>8</u>	$C_6H_5O(CH_2)_3$	f, g			Ш	С, Л	7	189190	$C_{11}H_{17}NO_4S_2$	150	50	15	1000 G	1	c
85	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> O(CH <sub>2</sub> ) <sub>4</sub>	$h^{-j}$			II	V	26	179 - 181	C <sub>12</sub> H <sub>17</sub> Cl <sub>2</sub> NO <sub>4</sub> S <sub>2</sub>	125	25	30	1000 G	93	+ + +
											12.5	30	1000 G	æ	
86	$4-BrC_6H_4O(CH_2)_4$	f, k	$134 - 150 \ (0.3)$	<u>95</u>	II	М	1:3	187-188	C <sub>12</sub> H <sub>18</sub> BrNO <sub>4</sub> S <sub>2</sub>	>150	50	30	1000 G	0	c
87	$2-\mathrm{ClC_6H_O(CH_2)_4}$	f, k	124 - 133(0.4)	<b>8</b> 6	Π	J, A	91	165 - 166	C <sub>12</sub> 11 <sub>18</sub> CINO <sub>4</sub> S <sub>2</sub>	150	50	30	1000 (}	80	++
											25	30	1000 G	20	
88	$3-\mathrm{ClC_6H_4O(CH_2)_4}$	f, k	181 - 187 (19)		II	С, А	25	158-159	C <sub>12</sub> H <sub>18</sub> CINO4S <sub>2</sub>	150	50	5	1000 G	73	+
89	$4-\mathrm{CMC_6H_4O(CH_2)_4}$	f, k, l	$115 - 130 \ (0.3)$	98 86	II	Ν	30	171-172	C <sub>12</sub> H <sub>18</sub> CINO4S <sub>2</sub>	175	7.5	30	1000 G	<b>:</b> ;;	+ +
<del>0</del> 6	3-CIC <sub>6</sub> H <sub>4</sub> OCH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	ſ, m.	112 114 (1.5)	86 8	Ξ	V	35	168 - 169	C <sub>12</sub> II <sub>18</sub> CINO4S <sub>2</sub>	120	80	15	1000 G	13	0
16	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> O(CH <sub>2</sub> ) <sub>4</sub>	l', n	156-169 $(0.3)$	50	11	ν	61	157 - 159	$\mathrm{C_{12}H_{18}N_2O_6S_2}$	250	50	30	1000 C	80	+++++
											25	30	1000 G	엻	
92	$2-CH_{a}C_{6}H_{4}O(CH_{2})_{3}$	h, o	75-84 (0.7)	85	П	М		$208 \ 209$	$C_{12}H_{19}NO_4S_2$	150	75	15	1000 G	9	0
<b>93</b>	$3-CH_3C_6II_4O(CH_2)_3$	h, o	143 - 148 (20)		Ш	Α, C	11	181 621	$C_{12}H_{19}NO_4S_2$	230	$80^{*}$	15	825 X	8	+
94	$C_bH_bO(CH_2)_4$	h, g			11	A		178-181	C <sub>12</sub> H <sub>19</sub> NO <sub>4</sub> S <sub>2</sub>	>250	200	15	1000 G	0	0
95	$2-C_{2}H_{5}OC_{6}H_{4}O(CH_{2})_{2}$	f, p			II	Α	01	139 - 143	$C_{12}H_{19}NO_5S_2$	150	100	Ъ	1000 G	0	c
<del>9</del> 6	$3-CF_3C_6H_4O(CH_2)_4$	h, k, q	148 - 158 (20)		Π	Λ, C	17	190-193	C13H18F3NO4S2	45	30	30	1000 G	80	+
26	$C_6H_5S(CH_2)_5$	f, r	131 145 (0.3)		Π	М	22	177-178	C <sub>13</sub> H <sub>21</sub> NO <sub>3</sub> S <sub>3</sub>	300	50			20	c
9S	$2-CH_{s}C_{6}H_{4}O(CH_{2})_{4}$	h, g			II	V	현	173-178	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	150	25	5	1000 G	78	+ + + +
66	3-CH <sub>3</sub> C <sub>6</sub> II <sub>4</sub> O(CH <sub>2</sub> ) <sub>4</sub>	h, g			II	В, С	4	168-170	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	175	50	15	825 N	001	+ +
											25	30	825 X	7	
001	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> O(CH <sub>2</sub> ) <sub>4</sub>	h, g			Ш	A, 1)	현	180-182	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	56	25	30	1000 G	23	+
101	$C_6 \Pi_5 O(C \Pi_2)_5$	f, k, s	107-117 (0.2)	<del>.</del> 8	II	ſ	55	157 158	C <sub>13</sub> H <sub>21</sub> NO4S <sub>2</sub>	>50	50	30	1000 G	80	+
											25	30	1000 G	73	
102	2-CH <sub>3</sub> C <sub>6</sub> H4OCH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	<i>f, m</i>	$92 \ 97 \ (1.5)$	86 86	II	V	<del>.</del> 5	172-173	C <sub>13</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	150	50	5	1000 G	C	c
103	3-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OCH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	Г, т	88-91 (0.5)	56	II	V	47	176-177	CI3H21NO4S2	06	50	98 8	1000 G	0	0
104	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OCH(C <sub>2</sub> H <sub>5</sub> )CH <sub>2</sub>	, т	$82-87 \ (0.6)$	86	II	Α, Μ	18	214-215	$C_{13}H_{21}NO_4S_2$	87	$\overline{50}$	9	1000 G	0	¢
105	$4-\mathrm{CH}_3\mathrm{OC}_6\mathrm{H}_4\mathrm{O}(\mathrm{CH}_2)_4$	f, k, t	130 - 142(0, 4)		П	М	41	154-156	C <sub>13</sub> H <sub>21</sub> NO <sub>5</sub> S <sub>2</sub>	200	06	98	1000	<del>3</del> 3	+
											45	30	1000	60	
106	4-CH <sub>8</sub> OC <sub>6</sub> H <sub>4</sub> OCH(C2H <sub>5</sub> )CH <sub>8</sub>	ſ, r	106-113 (0.6)	26	II	А, М	46	<u>194195</u>	C <sub>13</sub> H <sub>21</sub> NO <sub>5</sub> S <sub>2</sub>	100	112*	15	825 N	21	¢
107	$1-Naphthyl-O(CH_2)_2$	<u> </u>	mp 113 -121		Ξ	М	24	229-230	C <sub>14</sub> H <sub>17</sub> NO <sub>4</sub> S <sub>2</sub>	200	25	30	1000	e	0
108	$2,3-(CH_3)_2C_6H_3O(CH_2)_4$		113 - 117(0.4)	66	= ;	Ł	걿	198-200	$C_{14}H_{23}NO_4S_2$		С. Г	30 20	1000 G	23	+
601	3,4-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> O(CH <sub>2</sub> ) <sub>4</sub>	F, F	142 - (49)(1.5)		Ξ	Û		187 -180	C <sub>14</sub> H <sub>23</sub> NO <sub>4</sub> S <sub>2</sub>	4.)	8	80	1000	27	+
							,			;	1	80	1000	47	
0	2,4-(CH3)2C6H3O(CH2)4	J, K	122-126 (1)		Н	Α, (	¢	206-208	Cullan0422	20	10	02	1000	87	+-
									:		10	30	1000 (3	40	
Π	$2,5-(CH_3)_2O_6H_3O(CH_2)_4$	f, k	126-131 (0.7)	66	11	V	12	185 -187	C14H23NO4S2	>40	%0 %0	30	1000 (3	66	- <b>†</b> -
											12	30	1000 (}	27	
112	$2,6-(CH_3)_2C_6H_3O(CH_2)_4$	f, k	110 123 (0.4)	66	Π	М		213 214	C <sub>14</sub> H <sub>23</sub> NO <sub>4</sub> N	250	100	98	1000 G	100	+++++++++++++++++++++++++++++++++++++++
											25	30	1000 G	73	
<u>:</u>	2-C11 <sub>3</sub> C4114O(C11 <sub>2</sub> ) <sub>5</sub>	f, k	121 - 137 (0.6)	ŝ.	II	¥	X	180-181	C141128NO4S2	007	20	15	1000 C	x1 x	+++++++++++++++++++++++++++++++++++++++
				1						i	x	<u>8</u>	1050 C	67	
+	(56/H,(0)(C)H_2)6 2011 - 2011 - 2011 - 2020	I, K, n	11.0 - 117(0.4)	36	= :	7.	91 :	181 - 182 11 - 182	ChillaNO.Sz	000	9: 1	00	1000	0	= .
115	3-CH3, 4-CH3SC6H3O(CH2)4	$I_{2}, I_{2}, K_{1}$		06	=	2	4	174 475	C <sub>14</sub> H <sub>23</sub> NO <sub>2</sub> S <sub>3</sub>	181	00	<u>:</u>	1000 C	13	+

Table IV: S-2-(Aryloxyalkylamino))ethyl Thiosuleyfes RNH0H\_00H\_80,0H

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$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	116	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> O(CH <sub>2</sub> ) <sub>6</sub>	f, k	130-143 (0.3)	98	II	Α, D	43	181 - 183	C <sub>15</sub> H <sub>25</sub> NO <sub>4</sub> S <sub>2</sub>	135	25	30	1000 G	93	++++
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$												12.5	30	1000 G	<u>8</u>	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	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	++
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$												25	30	1000 G	67	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	118	2-CH <sub>3</sub> O, 4-C <sub>2</sub> H <sub>5</sub> C <sub>6</sub> H <sub>3</sub> O(CH <sub>2</sub> ) <sub>4</sub>	f, k	$128 - 136 \ (0.5)$	93	II	IJ	9	134-137	$\mathrm{C_{15}H_{25}NO_5S_2}$	125	75	15	1000 G	87	÷
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$												27.5	15	1000 G	20	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	119	4-[(CH <sub>2</sub> ) <sub>5</sub> CH]C <sub>6</sub> H <sub>4</sub> O(CH <sub>2</sub> ) <sub>4</sub>	f, k	141 - 157 (0.3)		II	s	14	210 - 212	C <sub>18</sub> H <sub>29</sub> NO,S <sub>2</sub>	50	10	30	1050 G	0	0
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	120	$[C_6H_5O(CH_2)_{3-}]_{2^v}$				Шw	x	4	130 - 132	$\mathrm{C_{20}H_{27}NO_5S_2}$	>1000	800	30	1000  G	0	0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	121	$[4-ClC_6H_4O(CH_2)_{4-}]_2^{v}$				$\prod^{w}$	I	×	149 - 151	C22H29Cl2NO5S2	1300	100*	15	825  X	17	0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	122	$[C_6H_5O(CH_2)_2O(CH_2)_2-]_2^n$	g			IIw	Α, D	6	106-108	$C_{22}H_{32}NO_7S_2$	450	400	15	1000 G	0	0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	123	$[C_6H_5S(CH_2)_5-]_2^v$				u I I	Y	4	121 - 123	$C_{24}H_{35}NO_3S_4$	1100	50	30	1000 G	0	0
$ \begin{array}{llllllllllllllllllllllllllllllllllll$	124	$[C_6H_5O(CH_2)_{5-}]_2^n$				u I I w	ſ	10	163 - 164	$C_{24}H_{35}NO_5S_2$	>4()()	100	30	1000 G	0	e
126 $[4-C_3H_2OC_4H_O(CH_2)_4]_2^w$ >150 50 30 * See footnote a, Table I. IV: RO-tosyl + H <sub>3</sub> NCH <sub>2</sub> CH <sub>3</sub> S <sub>2</sub> O <sub>3</sub> Na $\rightarrow$ RNHCH <sub>2</sub> CH <sub>3</sub> S <sub>2</sub> O <sub>3</sub> II. <sup>b</sup> See footnote b, Table I. <sup>c</sup> See footnotes c and oo, Table I. <sup>d</sup> (p-Chloroph C. Narayanan Nair and D. H. Peacock, J. Indian Chem. Soc., 12, 318 (1935). <sup>e</sup> Reaction conditions were the same as those used for method II. <sup>f</sup> RBr. <sup>e</sup> Aldrich	125	$[4-\mathrm{CH}_3\mathrm{OC}_6\mathrm{H}_4\mathrm{O}(\mathrm{CH}_2)_{4-}]_2^v$				IIw	Υ	6	106 - 108	$C_{24}H_{35}NO_7S_2$	1300	640*	15	825 X	<u>89</u>	+
"See footnote a, Table I. IV: RO-tosyl + H <sub>3</sub> NCH <sub>3</sub> CH <sub>3</sub> S <sub>3</sub> O <sub>3</sub> Na -> RNHCH <sub>3</sub> CH <sub>3</sub> S <sub>3</sub> O <sub>3</sub> M -> RNHCH <sub>3</sub> CH <sub>3</sub> S <sub>3</sub> O <sub>3</sub> M -> RNHCH <sub>3</sub> CH <sub>3</sub> S <sub>3</sub> O <sub>3</sub> M -> Route b, Table I. <sup>a</sup> (p-Chloroph C. Narayanan Nair and D. II. Peacock, <i>J. Indian Chem. Soc.</i> , <b>12</b> , 318 (1935). <sup>a</sup> Reaction conditions were the same as those used for method II. <sup>J</sup> RBr. <sup>a</sup> Aldrich	126	$[4-C_3\Pi_7OC_6\Pi_4O(CH_2)_{4-}]_{2^n}$				uII w	Υ	10	126 - 127	$\mathrm{C}_{26}\mathrm{H}_{48}\mathrm{O}_7\mathrm{S}_2$	>150	50	30	1000 G	0	0
C. Narayanan Nair and D. H. Peacock, J. Indian Chem. Soc., 12, 318 (1935). Reaction conditions were the same as those used for method II. / RBr. "Aldrich	" See for	otnote a, Table I. IV: RO-tosyl +	- H <sub>2</sub> NCH <sub>2</sub>	CH <sub>2</sub> S <sub>2</sub> O <sub>3</sub> Na → RNH	ICH <sub>2</sub> CI	I <sub>2</sub> S <sub>2</sub> O <sub>3</sub> II	I. b See for	otnote b,	Table I. « S	See footnotes c and o	o, Table I.	$^{d}(p-Chld$	orophen	toxy)ethyl p	-toluen	sulfonate:
	C. Narayi	man Nair and D. H. Peacock, J.	Indian Ch	em. Soc., 12, 318 (19	(35). *	Reactic	on conditic	ons were	the same as	those used for meth	od II. / I	{Br. ∥Al	ldrich C	hemical Co.	ARC	· · Crude

November 1968

Experimental Section. Ethyl 2-(*m*-chlorophenoxy)butyrate, bp 99–109° (0.5 mm). 1-[1-(Bromonethyl)propoxy]-3-chlorobenzene: Anal. (C<sub>0</sub>H<sub>13</sub>BrClO) C, H. <sup>n</sup> F. C. Copp and G. G. Coker, British Patent 924,961 (1963); Chem. Abstr., **59**, 9883 (1963); bp 156–169° (0.3 mm). <sup>o</sup> 1-Bromo-3-chloropropane. <sup>p</sup> CIBA Ltd., British Patent 879,342 (1959); Chem. Abstr., **56**, 7215 (1962). <sup>o</sup> 1-Bromo-4-chlorobutane. <sup>r</sup> See Experimental Section. <sup>e</sup> P. Gaubert, R. P. Linstead, and H. N. Rydon, J. Chem. Soc., 4 (1937), gave bp 160–165° (11 mm). <sup>e</sup> N. J. Leonard, D. L. Felley, and E. D. N. I. Plaromo-4-chlorobutane. <sup>r</sup> See Experimental Section. <sup>e</sup> P. Gaubert, R. P. Linstead, and H. N. Rydon, J. Chem. Soc., 4 (1937), gave bp 160–165° (11 mm). <sup>e</sup> N. J. Leonard, D. L. Felley, and E. D. N. Olaides, J. Am. Chem. Soc., 74, 1700 (1952), gave mp 42–43°. <sup>e</sup> Bp 155–165° (3 mm). <sup>e</sup> R<sub>3</sub>NCH<sub>2</sub>CH<sub>2</sub>S<sub>2</sub>O<sub>3</sub>H. <sup>e</sup> Refer to the corresponding monoalkylation product for the alkyl halide. These alkyl halide. <sup>7</sup> ROH: B. J. Heywood and W. G. Leeds, British Patent 837,372 (1960); *Chem. Astr.*, **54**, 14188 (1960). <sup>\*</sup> See Experimental Section for preparation of **117**. <sup>4</sup> A. V. Topchiey, I. F. Baev, and L. A. Morozov, *Dokl. Akad. Nauk SSSR*, **118**, 306 (1958); *Chem. Astr.*, **52**, 10936 (1958). <sup>m</sup> For the method see 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<sub>0</sub>H<sub>1</sub>,BrCIO) C, H. <sup>a</sup> F. C. Copp and G. G. Coker, In some cases extraction of the crude reaction mixtures with boiling Me<sub>2</sub>CO or <sup>i</sup> Crude Additional washing with EtOH A ROI # I. " (p-Uniorphenoxy )ethyl p-1 / RBr. # Aldrich Chemical Co. EfOII dissolved these products from less soluble monoalkylation material. \* This material remained insoluble when the crude product was washed with boiling H<sub>2</sub>O. \* Reaction conditions were the same as those used for method II. products, obtained as side products in the alkylation reactions, usually were isolated from crystallization liquors. ŵ <sup> $\mu$ </sup> All compounds were analyzed for  $\dot{C}$ , H, N, gave pure material. ಲ

crops (6.5 g) were triturated with 250 ml of hot EtOH leaving 4.3 g (23%) of insoluble product, mp 150–152°. Recrystal lization 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-[ $(\beta$ -Hydroxy-3,4-dimethoxy- $\alpha,\alpha$ -dimethylphenethyl)amino]ethyl Thiosulfate (143).—A solution of 4.8 g of crude  $\alpha,\alpha'$ -[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<sub>4</sub>)<sub>2</sub>SO<sub>3</sub>.<sup>47</sup> 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<sub>2</sub>O 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<sup>18</sup> (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<sub>4</sub> in Et<sub>2</sub>O.<sup>14</sup> 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<sub>10</sub>H<sub>23</sub>NO) C, H, N.

**Diethyl (Cyclobutylmethyl)malonate.**—Diethyl malonate (80 g, 0.5 mole) was alkylated<sup>19</sup> with 68.4 g (0.43 mole) of (bromomethyl)cyclobutane.<sup>20</sup> 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<sub>4</sub>),  $\delta$  4.13 (q, 4, J = 7 Hz,  $CH_2CH_3$ ), 3.09 [t, 1, J = 7 Hz,  $CH(CO_2C_2H_3)_2$ ], 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

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<sup>21</sup> 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<sub>5</sub>H<sub>5</sub>N was heated under reflux until foaming ceased (1 hr). The cooled solution was diluted with 1.5 l. of Et<sub>2</sub>O; the resulting solution was washed with 10% HCl and H<sub>2</sub>O, and then dried (MgSO<sub>4</sub>) and concentrated to dryness giving 41 g of crude solid cyclobutanepropionic acid. The wash solutions were concentrated and then extracted with Et<sub>2</sub>O 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<sub>4</sub> in Et<sub>2</sub>O 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<sub>4</sub>),  $\delta$  3.93 (s, 1, OH), 3.49 (m, 1, OH), 3.49 (m, 2, CH<sub>2</sub>O), 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.<sup>4</sup> 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.<sup>22</sup> 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-cyclobutyl-propane [bp 71–76° (18 mm). Anal. (CrH<sub>13</sub>Br)Br] free of olefin and identical with material described below.

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(1950); Chem. Abstr., 46, 8009 (1952).
(19) R. Adams and R. M. Kamm in "Organic Syntheses," Coll. Vol. I,

(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 glpe 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)].

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# MISCELLANEOUS S-2-(SUBSTITUTED AMINO)ETHYL THOSULEATES

# RNHCH<sub>2</sub>CH<sub>2</sub>S<sub>2</sub>O<sub>3</sub>H

Drug dose

Rat- íng	:	2 :	=	=	0	C	+-	-+-		+	+-	÷		=	=	¢	•	+	- 0	0	
Survi- val, <sup>7</sup> ,		> :	=	÷	-	C	60	Ţ.	ର ମ	27	20	9 <del>6</del>	40	c	<u>::</u>	¢	2	1-	÷	0	
Radiation, dose, R		1000	N 078	825 N	825 N	825 N	825 N	1000	825 N	825 N	1000	1000 G	825 N	825 N	N 178	1000	1000	1000 (3	1000 G	825 N	
min preir- radia- tion	<u>}</u>	<u>-</u>	<u>.</u>	2	<u></u>	5	2	09	12	8	13	80	9 <u>8</u>	ŝ	13	5	12	17	12	8	
m#/ke		8	220	<u>9</u>	300	200	50	200	<u>8</u>	200	13	£09	80	100	2	250	13	100	001	150	
$C_{a}$ . L $\mathrm{D}_{bb}$ , me/ke	1	7.7.	375	175	000	350	120	62.5	140	350	150	ž		>200	5	400	021	200	300	600	
Analyses		C, H, Z, Z	C, H, N, S	С, П, S	C, H, N, S	C, H, N, S	C, H, N, S	C, H, N, S	C, H, N, S	C, H, N, S	C, H, N, X	C, H, N, Y	-	C, H, N, N	C, H, N, S	C, H, N, S	С, Н, N, S	C. H. N. X.		C, H, N, S	
Formula		CHENO'S	C <sub>4</sub> H <sub>17</sub> NO <sub>4</sub> Z	C <sub>6</sub> H <sub>10</sub> NO <sub>3</sub> S <sub>2</sub>	C <sub>9</sub> H <sub>21</sub> NO <sub>4</sub> S <sub>2</sub>	$\mathrm{C}_{16}\mathrm{H}_{21}\mathrm{NO}_{5}\mathrm{S}_{2}$	C <sub>10</sub> H <sub>23</sub> NO <sub>3</sub> S <sub>2</sub>	C <sub>10</sub> H <sub>23</sub> NO <sub>4</sub> S <sub>2</sub>	$C_{10}H_{23}NO_4S_2$	C <sub>11</sub> H <sub>25</sub> NO <sub>4</sub> S <sub>2</sub>	$C_{11}H_{25}NO_4S_2$	$C_{12}H_{27}NO_4S_2$		CleH <sub>27</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>12</sub> H <sub>27</sub> NO <sub>4</sub> S <sub>2</sub>	C <sub>13</sub> H <sub>29</sub> NO <sub>5</sub> S <sub>2</sub>	$C_{\rm E} H_{20} { m FNO}_{\rm sS_2}$	C.H.,NO.S.	CuH-NO.S.	C <sub>17</sub> H <sub>21</sub> NO,S <sub>2</sub>	
D° aM		149 - 150	118 - 119	148 - 152	144 149	124 125	190 -195	118 - 120	173-176	150 154	180 183	192196		135-138	180 -185	164-167	202 $203$	611-211	212 213	061-681	
Vield - 9	// 'miari	21	10	25	4	13	22	1¢	25	53 53	<u>x</u>	27		17	10	35	x	<del>.</del>	3	10	
Recrystn solvents <sup>b</sup>		Α, Ι	V	ž	А, В	1	V	B, A	Ā	V	B, A	Ā		A	V	V	Ł	11	2	c	
Methoda	101111	II	11	1,	Ш	II		11	/1	Π	II	11		II	14	1.1	Π	Ц	1	II	
	amm) > 'da	122-130	55-65 (13)		56 $66$ $(0.2)$	78 (2)		68 (0.1)		79 83 (0.1)	95 105 (1, 5)	123 133 (14)		07-100 (0.3)							
Sumo		<i>q</i>	1, c		g, h	d, i		a. h		a. h	d. c	d. c		a. h			d, m	<i>"</i> "	11 (an	9	
2	-	$CH_{2^{m-1}}CH(CH_2)_{3}$	CH <sub>3</sub> O(CH <sub>2</sub> ),	(CIIIa)bCHCH.CH(CHa)	$HO(CH_2)_7$	LOT (CH.).CHO(CH.).	(C.H.),OCH.	HO(CH)	CH, (CH,), CH (CH, OH)	HO(CH <sub>a</sub> ),	CH.O(CH.)	CH.O(CH.).		HO(CH <sub>3</sub> ) <sub>10</sub>	CH <sub>2</sub> (CII <sub>2</sub> ),CH(CH-OH)	HO(CH <sub>2</sub> ) <sub>5</sub> CH(OH)CH <sub>2</sub>	 –q –ď	4-FC,H,—C —(CH,), 4. AM AAC H APH AACHLA	3.4_(CH_O)_C_H_C(H(OH)C2(CH_)_	(C <sub>6</sub> H <sub>5</sub> ) <sup>2</sup> CHO(CH <sub>2</sub> ) <sub>2</sub>	•<
	.0N	127	128	()(7)	130	131	681	12	134	12	981	1321		Ser	681	140	141	644	4 1 1 1	144	

<sup>\*</sup> Sec footnote a, Table I. V: RCHCH<sub>2</sub> + H<sub>2</sub>NCH<sub>2</sub>CH<sub>3</sub>S<sub>4</sub>O<sub>8</sub>Na → RCH(OH)CH<sub>2</sub>CH<sub>2</sub>S<sub>4</sub>O<sub>4</sub>N. <sup>\*</sup> Sec footnote b, Table I. <sup>\*</sup> Sec footnote s cand  $\infty$ , Table I. <sup>\*</sup> RBr. <sup>\*</sup> From the aco-dibromide according to the method of H. Schmid, *Hele. Chim. Acta*, **27**, 127 (1944). <sup>\*</sup> Sec footnote g, Table I. <sup>\*</sup> Sec footnote b, Table I. <sup>\*</sup> Sec footnote s cand  $\infty$ , Table I. <sup>\*</sup> RBr. <sup>\*</sup> From the acording to the method of H. Schmid, *Hele. Chim. Acta*, **27**, 127 (1944). <sup>\*</sup> Sec footnote g, Table I. <sup>\*</sup> RCH. <sup>\*</sup> From the diol according to the method of T. D. Perrine, J. Org. Chem., **18**, 1356 (1953). <sup>\*</sup> F. Bohlmann, H. Bornowski, and P. Herbst, Ber, **93**, 1931 (1960), gave bp 111–112<sup>\*</sup> (12 mn). <sup>\*</sup> Sec Experimental Section. <sup>\*</sup> Crude thiol was prepared from 2-amino-1-decanol (Experimental Section). <sup>\*</sup> Reaction conditions using 10,11-epoxy-1-undecanol were the same as for method II. <sup>\*\*</sup> The ketal, bp 100–103<sup>\*</sup> (0.5 mm), was prepared from 4-chloro-4'-fluorobutyrophenone. <sup>\*</sup> Crude alkylhalide. <sup>\*</sup> S: caled, 17.35; found, 17.50. <sup>\*</sup> S: caled, 17.55; found, 16.76.

# WESTLAND, HOLMES, MOUK, MARSH, COOLEY, AND DICE

# TABLE VI Comparison of Highly Effective Antiradiation Agents RNHCH, CH, SSO, H

TABLE VII RADIATION PROTECTION BY ORAL ADMINISTRATION

D . .

No.	R	Effective dose, mg/kg <sup>a</sup>	Thera- peutic index <sup>b</sup>	
	Cycloalkylalkyl Derivativ	res		
14	(CH <sub>2</sub> ),	5	15	
18	s - chch	23	13	
20	OCH <sub>3</sub>		10	
30	C <sub>3</sub> H <sub>4</sub>	17	10	
38	$\langle \mathbf{S} \rangle - (CH_2)_2 CHCH_2$	õ	9	
24	$S \rightarrow CH_3 \\ CH(CH_2)_3$	9	9	
8	(CH <sub>2</sub> ) <sub>5</sub>	20	7	
16		5	7	
25	$C_2H_s$ CH(CH <sub>2</sub> ),	20	7	
	C <sub>2</sub> H <sub>5</sub>	-0	·	
26	S CH <sub>2</sub> CHCH <sub>2</sub>	20	7	
28		23	7	
9		25	7	
	Cycloalkyloyyalkyl Derivat	11700		
KQ		20	7	
50	$S - O - (CH_2)_5$	20	1	
60	(CH <sub>2</sub> ) <sub>7</sub> CHO(CH <sub>2</sub> ) <sub>4</sub>	35	7	per ext
70	$CH_{3}O \longrightarrow (CH_{2})_{4}$	10	10	res bp
	Aryloxyalkyl Derivative	s		Hz
113	CH <sub>3</sub>	15	12	diu in
110	CH CH2)3	10	10	pro of
112		20	12	oi rec Et(
	CH <sub>3</sub>			212
116	O(CH <sub>2</sub> ) <sub>6</sub>	14	11	Gri bro of
98		18	8	per PB
				cyc ana
85	$Cl \longrightarrow O(CH_2)_4$	16	8	use

 $^a$  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  $C_3H_3N$  was added below 0° 21 g (0.077 mole) of PBr<sub>3</sub>.<sup>23</sup> After stirring for 16 hr at room tem-

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

			Dose,	
	$LD_{\delta 0}$ ,	Dose,	min preir-	Survival,
No.	mg/kg	mg/kg	radiation	%
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
<b>76</b>	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 Et<sub>2</sub>O. The extract was washed with saturated NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), and concentrated. Distillation of the residue provided 22 g (58%) of 1-bromo-3-cyclobutylpropane: bp 72-77° (19 mm); glpc, >93%; nmr (CCl<sub>4</sub>),  $\delta$  3.32 (t, 2, J = 7 Hz, CH<sub>2</sub>Br) and 1.3-2.6 ppm (m, 11).

\$-2-[(3-Cyclobutylpropyl)amino]ethyl Thiosulfate (2).—Sodium S-2-aminoethyl thiosulfate (43 g, 0.24 mole) was alkylated<sup>3</sup> 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<sub>2</sub>O was filtered, giving 31 g of crude product. The solid was triturated with H<sub>2</sub>O 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 1bromo-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<sub>8</sub> in the presence of  $C_5H_3N$  gave 15 g (46%) of 1-bromo-5cyclobutylpentane: bp 111-113° (19 mm); glpc, 90%. Ir analysis ruled out any olefinic alkyl halide. This product was used to prepare<sup>3</sup> the Bunte salt **8**.

trans-N-(2-Hydroxyethyl)-2-phenylcyclopropanecarboxamide was prepared in CH<sub>2</sub>Cl<sub>2</sub> from 100 g (0.55 mole) of trans-2phenylcyclopropane-1-carboxylic acid and 74 g (1.2 moles) of 2-aminoethanol: 91 g (80%), mp 110-111°. Anal. (C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>) 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<sub>4</sub>. Distillation of the product afforded 57 g (76%) of 2-{[trans-(22.58 (m, 4, CH<sub>2</sub>NCH<sub>2</sub>), and 0.62–1.83 ppm (m, 4, CHCH<sub>2</sub>CH).

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<sub>2</sub>. 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<sub>2</sub>O gave 15 g ( $60C_{\ell}$ ) of *trans*-N-(2-chloroethyl)-2-phenylcyclopropanemethylamine hydrochloride, mp 117–119°. The sample for analysis melted at 120–122°. Anal. (Ct<sub>2</sub>H<sub>15</sub>NCl·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<sub>4</sub> in Et<sub>2</sub>O 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  $48~{\rm g}$  of quinoline and  $350~{\rm ml}$  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-2,2diethylbutane was refluxed for 16 hr. An ethereal extract of the solution was washed (H<sub>2</sub>O), dried (MgSO<sub>4</sub>), concentrated, and distilled giving 7 g of 2-[(2,2-diethylbutyl)amino]ethanol, bp  $125^{\circ}$  (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<sub>2</sub>S<sub>2</sub>O<sub>3</sub>·5H<sub>2</sub>O in 20 ml of H<sub>2</sub>O afforded 3.6  $\tilde{\mathbf{g}}$  (52 $C_{\ell}$ ) of the Bunte salt 132: mp 190–195° dec; nmr (D<sub>2</sub>O-NaOD),  $\delta$  2.8-3.3 (m, 4, NCH<sub>2</sub>CH<sub>2</sub>S), 2.31 (s, 2, Et<sub>3</sub>C-CH<sub>2</sub>N), 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<sup>24</sup> in 1 l. of MeOH was hydrogenated at about 3 atm in the presence of 5 ml of concentrated H<sub>2</sub>SO<sub>4</sub> and 5 g of  $20^{\circ}$ / Pd–C. The reduction was allowed to proceed for 17 hr (H<sub>2</sub> uptake corresponded to reduction of carbonyl group) and then 10 g of  $10^{\circ}$ / Rh–C was added followed by hydrogenation for 48 hr (H<sub>2</sub> uptake corresponded to reduction of the aromatic ring). A shurry of the filtered solution with 10 g (0.094 mole) of anhydrous Na<sub>2</sub>CO<sub>8</sub> was allowed to stand for 16 hr. The solvent was removed under reduced pressure, the residue was extracted with 500 ml of Et<sub>2</sub>O, and the ethereal extract was washed with small portions of H<sub>2</sub>O and dried (Mg–SO<sub>4</sub>).

The solution containing 4-cyclohexylcyclohexanebutyric acid was reduced with 35.8 g (0.89 mole) of LiAlH<sub>4</sub> giving 149 g (70%) of 4-cyclohexylcyclohexanebutanol: bp 209–215° (8 mm); glpc, 99%. Conversion of the alcohol to the chloride (SOCl<sub>2</sub>,  $C_5H_5N)^{25}$  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. (CusHayCl) C, H, Cl.

**2**-(4-**B**romobuty])cyclohexyl Methyl Ether.—4-(*o*-Methoxyphenyl)butyric acid<sup>26</sup> (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 2methoxycyclohexanebutyric acid. Reduction of 50 g (0.25 mole) of the crude acid with 9.5 g (0.25 mole) of LiAlH<sub>4</sub> in Et<sub>2</sub>O 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<sub>8</sub> and C<sub>8</sub>H<sub>5</sub>N at 25°) to 2-(4-bromobutyl)cyclohexyl methyl ether: 18 g (40%), bp 75-85° (0.2 mm). Anal. (C<sub>11</sub>H<sub>21</sub>-BrO) C. H. Br.

1-(4-Chlorobutyl)-4-methylcyclohexane.—A solution containing 75 g (0.45 mole) of 4-p-tolyl-1-butanol<sup>27</sup> and 2 ml of concentrated H<sub>2</sub>SO<sub>4</sub> 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

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

(25) Reference 23, p 92.

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

32 g (0.19 mole) of 4-*p*-tolyl-1-but and 1 ml of concentrated H<sub>2</sub>SO<sub>4</sub> in 250 ml of MeOH was completed in 24 hr over 4 g of  $10^{c}$ <sub>c</sub> Rh C. The H<sub>2</sub>SO<sub>4</sub> in the two lots was neutralized with Na<sub>2</sub>CO<sub>4</sub> as described above. The products were combined giving 79 g (71<sup>c</sup><sub>e</sub>) of crude oily product. The alcohol was chlorinated (SOCl<sub>2</sub>-C<sub>5</sub>H<sub>5</sub>N) to give 39 g (45<sup>c</sup><sub>e</sub>) of 1-(4-chlorobutyl)-4methylcyclohexane: bp 69 72° (0.8 mm); glpc, 60:40 mixture of isomers. Anal. (CutH<sub>21</sub>Cl) C, H.

4-(4-Chlorobutyl)cyclohexyl Methyl Ether .-- A methanolic solution containing 125 g (0.56 mole) of methyl 3-p-anisoylpropionate<sup>28</sup> 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.<sup>29</sup> The crude oily methyl 4-methoxycyclohexanebutyrate (100 g) was further reduced with 180 g (4.7 moles) of NaBH<sub>4</sub> in 2 l. of absolute EtOH.<sup>30</sup> The mixture was allowed to stir for 18 hr<sup>31</sup> before dilution in 7 l. of  $H_2O$ . The product was extracted into CHCl<sub>3</sub> and the crude 4-methoxycyclohexanebutanol (65 g,  $74^{\circ}_{c}$ ) 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<sub>4</sub>)  $\delta$  3.48 (t, 2, J = 6 Hz, CH<sub>2</sub>Cl), ca. 3.3 (m, 1, MeOCH), and 3.21 ppm (s, 3, CH<sub>3</sub>O); component B, 1.1 g (contaminated with  $2.8C_c$  of A), nmr (CCl<sub>4</sub>)  $\delta$  ca. 3.5 (m, 1, MeOCH), 3.47 (t, 2, J = 6 Hz, CH<sub>2</sub>Cl), and 3.23 ppm (s, 3,  $CH_{3}O$ ). Elemental analytical data confirmed that A and B are the two racemates of 4-(4-chlorobutyl)cyclohexyl methyl ether. Anal. A (C<sub>11</sub>H<sub>21</sub>ClO) C, H, Cl. B (C<sub>11</sub>H<sub>21</sub>ClO) C, H.

p-(4-Chlorobutyl)phenol.—A solution of 79.5 g (0.40 mole) of p-(4-chlorobutyl)anisole<sup>32</sup> in 1.2 l, of CH<sub>2</sub>Cl<sub>2</sub> was treated with 100 g (0.40 mole) of BBr<sub>3</sub><sup>7</sup> to give 57 g (77  $\stackrel{\frown}{\leftarrow}$ ) of p-(4-chlorobutyl)-phenol, bp 141–145° (2 mm). Anal. (C<sub>10</sub>H<sub>13</sub>ClO) C, H, Cl.

[2-(Bromonethyl)propyl]cyclohexane.—Reduction of 200 g (1.18 moles) of  $\alpha$ -ethylcyclohexaneacetic acid in Et<sub>2</sub>O with 44.6 g (1.18 moles) of LiAlH<sub>3</sub> gave 133 g (72%) of  $\alpha$ -ethylcyclohexaneethanol: bp 78–84° (0.6 mm) [lit.<sup>33</sup> L form, bp 119–121° (18 mm)]; nmr (CCl<sub>4</sub>),  $\delta$  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<sub>3</sub>–C<sub>5</sub>H<sub>3</sub>N, 2 hr at 100°) gave 39.6 g (67%) of [2-(bromomethyl)propyl]cyclohexane: bp 125–131° (28 mm); glpc, 94%; nmr (CCl<sub>4</sub>),  $\delta$  3.49 (d, 2, J = 4 Hz,  $CH_2Br$ ) and 0.75–1.98 ppm (m, 17). Anal. (C<sub>19</sub>H<sub>19</sub>Br) C, H, Br.

scc-Butylcyclohexane.<sup>34</sup>—Reduction of 39.6 g (0.18 mole) of [2-(bromoethyl)propyl]cyclohexane with 2.3 g (0.06 mole) of LiAlH<sub>4</sub> was allowed to proceed for 18 hr in 300 ml of refluxing Et<sub>2</sub>O. The crude oily product (32.8 g) was distilled to give 7.3 g of scc-butylcyclohexane: bp 79–81° (28 mm) [lit.<sup>35</sup> bp 177° (760 mm)]; glpc, 98°<sub>6</sub>. Ir and nmr spectra of the hydrocarbon were nearly superimposable with a commercial sample (glpc, 96°<sub>6</sub>) of scc-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<sub>2</sub>CO<sub>3</sub>, 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<sub>2</sub>O before being extracted into Et<sub>2</sub>O. The ethereal solution was washed (H<sub>2</sub>O), dried (MgSO<sub>4</sub>), 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%; mm (CCl<sub>4</sub>),  $\delta$  1.03 ppm (t, 3, J = 7 Hz, CH<sub>3</sub>CH<sub>2</sub>CH).

(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-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 LiAlH<sub>4</sub> for these reductions.

(32) See Table III. footnote l.

(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 PBrs and pyridine.

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

<sup>(26)</sup> J. Lockett and W. F. Short, J. Chem. Soc., 787 (1939).

Reduction of 119 g (0.5 mole) of ethyl 2-(p-methoxyphenoxy)butyrate with 10.6 g (0.28 mole) of LiAlH<sub>4</sub> was effected in 1 l. of Et<sub>2</sub>O to give 94 g (95%) of crude 2-(p-methoxyphenoxy)-1butanol; glpc, 99%; nmr (CCl<sub>4</sub>),  $\delta$  0.90 ppm (t, 3, J = 7 Hz,  $CH_3CH_2CH$ ).

A mixture of 52 g (0.26 mole) of 2-(p-methoxyphenoxy)-1butanol, 7.8 ml of pyridine, and 27 g (0.1 mole) of PBr<sub>3</sub> 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]-4methoxybenzene: 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-proposyphenol with 1,4-dibromobutane (339 g, 1.57 moles) was effected in Me<sub>2</sub>CO in the presence of  $K_2CO_3$ .<sup>36</sup> 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°

(36) Reference 23, pp 226-228.

(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<sub>3</sub>.<sup>36</sup> 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 $\mu$  ( $\epsilon$  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,  $\lambda_{\max}^{MeOH}$  254 m $\mu$  ( $\epsilon$  15,000).

Acknowledgment.—We wish to express appreciation to Mr. William M. Pearlman for performing the catalytic hydrogenations; to Mrs. Elizabeth C. Y. Huang for some experimental work; to Mr. C. E. Childs and his associates for the microanalytical data: to Dr. J. M. Vandenbelt, Mr. R. B. Scott, Mr. E. J. Schoeb, and Mrs. Carola Spurlock for nmr, ir, and uv analyses; and to the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, for the antiradiation test data.

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

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Received July 17, 1968

 $Fifteen\ bis (4-ary lazo-1-naphthylamines)\ were\ synthesized\ for\ evaluation\ as\ potential\ antischistosomal\ and\ antischistosomal\ antischistosomal\ and\ antischistosomal\ antischistosom$ mycobacterial 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'-1naphthylalkylenediamine. Likewise, several bis[(4-phenylazo-1-naphthylamino)alkyl]amines (IVa-c) were obtained from benzenediazonium chloride and the corresponding bis[(1-naphthylamino)alkyl]amines. Con-densation of diazotized N-[4-(4-amino 1-naphthylazo)-1-naphthyl]-N-(2-diethylaminoethyl)-2,2,2-trifluoroacet-amide (VII) with an N,N-dialkyl-N'-1-naphthylakylenediamine 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 HarRy in vitro.

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



substances were reported to have strong therapeutic effects against Schistosoma mansoni<sup>1-7</sup> and Schistosoma

(1) Previous paper: L. M. Werbel, E. F. Elslager, and D. F. Worth, J. Med. Chem., 11, 950 (1968).

japonicum<sup>8</sup> 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.<sup>9,10</sup> 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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