The height of the reduction wave is proportional to the concentration of the nitrofuran compound. The logarithm of the heights was plotted against the time in a diagram of the type presented in Figure 1, from which per cent reduced compound after 1 hr reaction could be calculated. The values in Table II are the mean values with calculated 95% confidence limits assuming the same variation in measurements with all compounds.

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Antiradiation Agents. Substituted 2-Pyridyloxy and 2-Quinolyloxy Derivatives of *S*-2-(Alkylamino)ethyl Hydrogen Thiosulfates and 3-Alkylthiazolidines and Substituted 2-Pyridyloxy Derivatives of 2-(Alkylamino)ethanethiols and Corresponding Disulfides†

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Substituted 2-pyridyloxy and 2-quinolyloxy derivatives of *S*-2-(alkylamino)ethyl hydrogen thiosulfates (Table II), 3-alkylthiazolidines (Table V), and substituted 2-pyridyloxy derivatives of 2-(alkylamino)-ethanethiols (Table III) and corresponding disulfides (Table IV) were synthesized as antiradiation agents by the appropriate aziridine ring-opening reactions of substituted 2-{[(1-aziridinyl)alkyl]oxy}pyridines and -quinolines. 5-Substituted 2-chloropyridines and substituted 2-chloroquinolines were prepared for heterocyclic ether-forming reactions by treatment with the Na salts of 1-aziridinealkanols to give the aziridinylalkyloxy derivatives. 5-Halo-2-pyridyl ethers resulted in the highest antiradiation activity regardless of route of administration or type of sulfur-covering group. *S*-2-({5-[(5-Chloro-2-pyridyl)oxy]-pentyl}amino)ethyl hydrogen thiosulfate (**15**) and *S*-2-({5-[(3,5-dichloro-2-pyridyl)oxy]pentyl}amino)-ethyl hydrogen thiosulfate (**11**) afforded 87% survival of mice in the 30-day test at 19 ($^1/_{12}$ of LD_{50} dose) and 12.5 mg/kg ip ($^1/_{14}$ of LD_{50} dose), respectively. In view of the dearth of agents effective perorally, remarkable good radioprotection was found on oral administration of thiazolidines substituted in the 3 position with 5-halo-2-pyridyloxypentyl or -hexyl groups; 5-chloro- (**102**) and 5-iodo-2-{[6-(3-thiazolidinyl)hexyl]oxy}pyridine (**103**) hydrochlorides resulted in survival rates of 73% at 150 mg/kg po (0.25 of LD_{50} dose) and 93% at 300 mg/kg po (0.5 of LD_{50} dose), respectively.

Expansion of several series of antiradiation agents[1-3] of the substituted 2-aminoethanethiol type led to derivatives of 2-pyridyl and 2-quinolyl ethers as highly effective antiradiation compounds. Thiols, disulfides, thiazolidines, and Bunte salts were compared to determine which sulfur-covering group would result in optimum activity. An objective of the antiradiation program has been to produce a drug which is effective when administered orally. Extensive development of the present series was undertaken because several compounds, thiazolidines in particular, showed remarkably good activity in the peroral test.

N-Substituted aziridines (Table I) were key intermediates leading to Bunte salts **1-54** (Table II) by reaction[3,4] with $(NH_4)_2S_2O_3$ and to thiols **55-69** (Table III) by reaction[3,5] with H_2S. Thiols were oxidized[3] to disulfides **70-80** (Table IV) and treated[3,6] with sodium formaldehyde bisulfite to give thiazolidines **81-134** (Table V). The required 1-aziridinealkanols [$HO(CH_2)_nN(CH_2)_2$] were conveniently prepared from polymethylene chlorohydrins using the displacement reaction previously described[3] for simpler 1-alkylaziridines. Substituted 2-chloro- or 2-bromopyridines and -quinolines were treated with the Na salt of 1-aziridinealkanols in refluxing THF to synthesize the heterocyclic ethers Het-O-$(CH_2)_nN(CH_2)_2$. No attempt was made to rigorously purify the new 1-substituted aziridines given in Table I.

Several novel 2-chloropyridines were prepared, although not all were used successfully in the displacement reaction. Reductive methylation of 3,3′-(methylenediimino)bis(6-chloropyridine) gave 2-chloro-5-(dimethylamino)pyridine;

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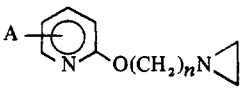
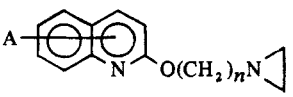
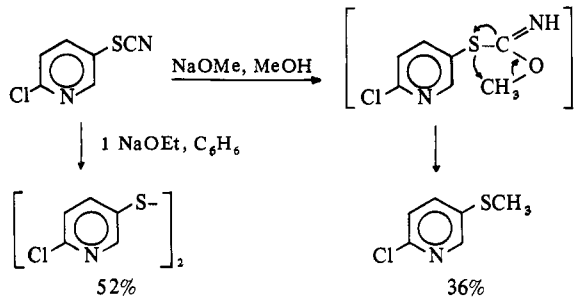
Table I. 1-Substituted Aziridines

Intermediate for compd no.	A	*n*	Yield, %	Bp (mm) or mp, °C	Glc, %
					
98	H	5	62	68–84 (0.001)	
12, 75, 91	3-Br	5	72	106–108 (0.1)	99
4	3-Cl	3	76	86–89 (0.3)	99
10, 59, 73, 89	3,5-Br_2	5	60	150–160 (0.2)	94
18, 99	3,5-Br_2	6	50	144–155 (0.05)	97
11. 60, 74, 90	3,5-Cl_2	5	66	118–132 (0.1)	82
1, 55, 70, 81	5-Br	2	55	95–97 (0.2)	99
3, 56, 71, 83	5-Br	3	65	91–102 (0.01)	
8, 57, 86	5-Br	4	67	100–105 (0.08)	96
13, 61, 62, 76, 92, 93	5-Br	5	72	109–118 (0.01)	98
22, 65, 78, 100	5-Br	6	60	120–133 (0.5)	98
24, 106	5-Br	7	76	125–130 (0.1)	97
110	5-Br	8	48	157–162 (0.3)	99
26, 69, 80, 111	5-Br	10	45	167–169 (0.1)	
14, 94	6-Br	5	75	118–119 (0.01)	94
2, 82	5-Cl	2	80	95–100 (0.2)	99
5, 72, 84	5-Cl	3	72	92–97 (0.3)	96
9, 58, 87	5-Cl	4	68	97 (0.1)	95
15, 63, 77, 95, 96	5-Cl	5	83	114–117 (0.1)	98
23, 66, 79, 102	5-Cl	6	71	114–117 (0.05)	99
107	5-Cl	7	73	122–125 (0.2)	94
85	5-I	3	40	105–110 (0.05)	93
88	5-I	4	44	115–120 (0.06)	99
16, 64, 97	5-I	5	32	135–140 (0.2)	91
103	5-I	6	30	157–160 (0.05)	94
25, 108	5-I	7	68	41–45	100
21	5-CN	5	43	133–143 (0.1)	75
19, 67	4-CH_3	5	48	113–118 (0.2)	99
20, 68, 104	5-CH_3	5	58	112–122 (0.3)	93
109	5-CH_3	6	19	104 (0.02)	75
105	5-CH_3S	5	48	126–132 (0.3)	94
6	3-NO_2	3	21	122–124 (0.2)	99
7	5-NO_2	3	31	122–126 (0.2)	99
28	*a*	5	67	132–135 (0.7)	97
115	*b*		62	98–100 (0.1)	89
29	*c*	5	7	164–174 (0.01)	95
113	*d*	5	38	103–108 (0.1)	88
27	*e*	5	50	140–150 (0.1)	75
112	*f*	3	25	94–100 (0.1)	100
					
30, 116	4-CH_3	2	65	138–148 (0.2)	92
31, 117	H	3	63	130–134 (0.3)	100
32, 118	4-CF_3	3	31	104–107 (0.05)	83
33, 119	6-Cl, 4-CH_3	3	60	100–134 (0.2)	92
34, 120	8-Cl, 4-CH_3	3	65	149–159 (0.3)	
35, 122	4-CH_3	3	81	128–134 (0.01)	60
36	6-CH_3O, 4-CH_3	2	42	56–62	
37, 121	4-CH_3	3	58	154–174 (0.05)	85
38, 123	4-Cl	5	46	165–174 (0.1)	
39, 126	H	5	64	136–143 (0.2)	100
40, 124	4,6-$(CH_3)_2$	3	57	140–150 (0.05)	92
41, 125	4-CH_3	4	67	139–145 (0.2)	92
42, 127	6-CH_3O, 4-CH_3	3	43	178–194 (0.1)	
43, 128	4-CF_3	5	57	135–147 (0.2)	88
44, 129	6-Cl, 4-CH_3	5	66	66–68	
45, 130	8-Cl, 4-CH_3	5	62	52–54	
46, 131	4-CH_3	5	85	126–142 (0.01)	96
47	4-$(CH_2)_2CH_3$	3	44	156–163 (0.2)	92
48, 132	4-CH_3	5	45	165–186 (0.05)	97
49, 134	4-CH_3	6	47	163–168 (0.05)	99
50, 133	4,6-$(CH_3)_2$	5	65	150–165 (0.05)	94
51	4-$(CH_2)_2CH_3$	5	57	145–157 (0.2)	97
52	7-Cl[g]	5			
53	H[h]	3	45	110–114 (0.1)	94
54	H[i]	5	80	144–150 (0.1)	85

[a] 5-Br-2-pyridyl-$O(CH_2)_5$-$N[CH_2CH(CH_3)]$. [b] 5-Cl-2-pyridyl-$O(CH_2)_2C(CH_3)H(CH_2)_2$-$N(CH_2)_2$. [c] 6-$[(CH_2)_2N$-$(CH_2)_5$-$O]$-2-pyridyl-$O(CH_2)_5$-$N(CH_2)_2$. [d] 4-Pyridyl-$O(CH_2)_5$-$N(CH_2)_2$. [e] 3-Br-4-pyridyl-$O(CH_2)_5$-$N(CH_2)_2$. [f] 3-Pyridyl-$O(CH_2)_3$-$N(CH_2)_2$. [g] 7-Cl-4-quinolyl-$O(CH_2)_5$-$N(CH_2)_2$; crude material was used. [h] 1-Isoquinolyl-$O(CH_2)_3$-$N(CH_2)_2$. [i] 1-Isoquinolyl-$O(CH_2)_5$-$N(CH_2)_2$.

the bis compound, $[(6\text{-Cl-3-Py})NH]_2CH_2$, was precipitated immediately on mixing 5-amino-2-chloropyridine with formalin. Nitrosation of 5-amino-2-chloropyridine using a variety of conditions resulted in new derivatives potentially useful for 2-(1-aziridinylalkoxy)pyridines. However, well-established Schiemann reaction procedures failed to yield 2-chloro-5-fluoropyridine. In one case decomposition of 2-chloro-5-pyridinediazonium tetrafluoroborate in $(Me_2N)_3PO$ gave in low yield only 2-chloro-5-(3,3-dimethyl-1-triazeno)-pyridine [5-(2-Cl-Py)N=NNMe$_2$], indicating either reaction with the solvent or with Me_2NH contained in the solvent. This appears to be the first reported example of a diazo-amino derivative of pyridine. 2-Chloro-5-hydroxypyridine was formed by decomposing 2-chloro-5-pyridinediazonium sulfate in the presence of Cu^{2+}, and 5-azido-2-chloropyridine was prepared by nitrosating 2-chloro-5-hydrazinopyridine. A synthetic method[7] for thioanisole was extended to 2-chloro-5-pyridyl thiocyanate to give 2-chloro-5-(methylthio)pyridine (Scheme I). Reaction of the thiocyanate with only 1 molar equiv of NaOEt in C_6H_6 gave a disulfide rather than a thioether (Scheme I). Diphenyl disulfide was prepared similarly by Ross.[7]

Scheme I



Compounds were tested[8] for antiradiation activity in mice. In this study Bunte salts substituted with pyridine and quinoline ethers (Table II) resulted in no compound active in the po test, but potential drugs for parenteral use were found. In the pyridine series 5-halo-2-pyridyl ethers were most active. The effect of chain length and halogen substitution on antiradiation activity of Bunte salts is shown in Figure 1. Activities given in Figures 1 and 2 are protective index‡ values, and ratings shown in Tables II-V are based on these values. Dose-response and therapeutic index factors are incorporated in the protective index. Pentyl ethers resulted in maximum activity. The 5-chloro-2-pyridyl ether **15** afforded 87% survival of mice in the 30-day test at 19 mg/kg ($^1/_{12}$ of LD_{50} dose) ip, and the same survival rate was obtained from the corresponding 3,5-dichloro derivative **11** at 12.5 mg/kg ($^1/_{14}$ of LD_{50} dose) ip. Propyl ethers **31**, **35**, and **40** were most active in the analogous quinoline series (Table II).

Compounds representing different structural types have been selected for po administration in the antiradiation test, but few examples have been reported[1-3,9] to be highly active when given orally. No relationship correlating high ip activity with even slight po activity is apparent from published data. Furthermore, generalizations correlating ip and po data for a given sulfur-covering group may not apply to other groups. Thiazolidines (Table V) corresponding to the Bunte salts substituted with 2-pyridyl ethers were only moderately active when given ip, based on standards established for the ip test. However, in the po test 79-90% survival rates were obtained with some of these compounds at 150-300 mg/kg (0.25-0.5 of LD_{50} dose). Again, 5-halo-2-pyridyl ethers were most active, and in this case hexyl ethers rather than pentyl ethers resulted in maximum activity perorally (Figure 2). The 5-iodo-2-pyridyl ethers **97** and **103** compared favorably with the 5-Cl compounds (*e.g.*, **102**). Also, within this

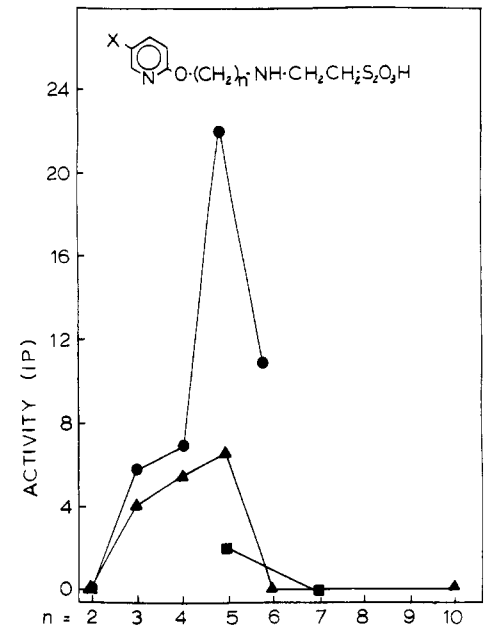


Figure 1. Effect of halogen substitution and chain length on antiradiation activity (expressed as protective index values‡) of *S*-2-({[(5-halo-2-pyridyl)oxy]alkyl}amino)ethyl hydrogen thiosulfates given intraperitoneally: (●–●) X = Cl; (▲–▲) X = Br; (■–■) X = I.

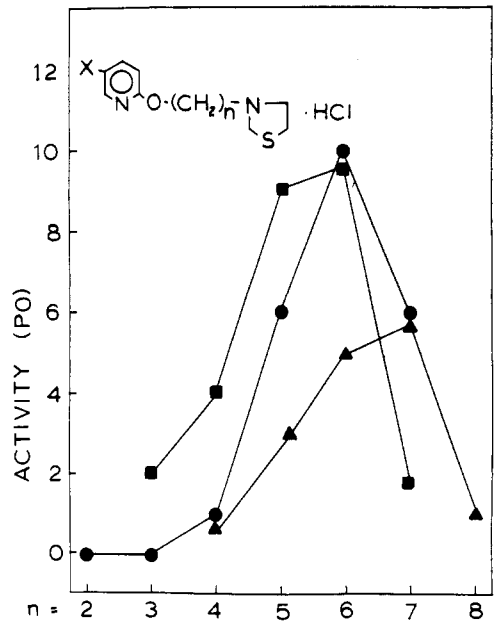
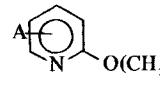
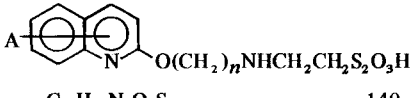


Figure 2. Effect of halogen substitution and chain length on antiradiation activity (expressed as protective index values‡) of 5-halo-2-[(3-thiazolidinylalkyl)oxy]pyridines given perorally: (●–●) X = Cl; (▲–▲) X = Br; (■–■) X = I.

‡"Protective index" is a term used by the Division of Medicinal Chemistry, Walter Reed Army Institute of Research. Protective index = (protection factor) X (LD_{50}/min effective dose), where doses are in mg/kg and the protection factor is 1.4 for 40% survival, 1.5 for 50% survival, etc. Antiradiation results can be compared with the activity of 2-aminoethanethiol (MEA). At 150 mg/kg ip (LD_{50} *ca.* 250 mg/kg ip) of MEA 87% survival of mice in the 30-day test can be obtained. It is rated ++ in the ip test. The po LD_{50} for MEA is *ca.* 625 mg/kg. At 300 mg/kg 73% survival can be obtained in the po test, giving MEA a rating of ++. Ratings in Tables II-IV are based on the following ranges of protective indices: 0, 0-1; +, 2-5; ++, 6-10; +++, 11-14; ++++, 15-26.

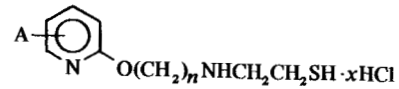
Table II. *S*-2-(Substituted amino)ethyl Hydrogen Thiosulfates

No.	A	*n*	Recrystn solvents	Yield, %	Mp, °C dec	Formula[a]	Antiradiation activity[b]							
							Intraperitoneal data				Peroral data			
							LD_{50}, *ca.* mg/kg	Drug dose, mg/kg	Survival, %	Rating	LD_{50}, *ca.* mg/kg	Drug dose, mg/kg (min preirrad)	Survival, %	Rating
														
1	5-Br	2	95% EtOH, MeCN	30	150–157	$C_9H_{13}BrN_2O_4S_2$	175	100	0	0				
2	5-Cl	2	MeCN, EtOH	23	145–147	$C_9H_{13}ClN_2O_4S_2$	150	75	0	0				
3	5-Br	3	H_2O, EtOH	38	181–183	$C_{10}H_{15}BrN_2O_4S_2$	125	80	73	+	>900	500 (30)	0	0
4	3-Cl	3	H_2O, EtOH	50	171–175	$C_{10}H_{15}ClN_2O_4S_2$	160	80	0	0				
5	5-Cl	3	MeOH, H_2O	55	171–173	$C_{10}H_{15}ClN_2O_4S_2$	150	45	67	+	800	400 (60)	20	0
6	3-NO_2	3	MeCN	7	162–165	$C_{10}H_{15}N_3O_6S_2$	175	80	0	0				
7	5-NO_2	3	H_2O	18	196–198	$C_{10}H_{15}N_3O_6S_2$	180	90	21	0				
8	5-Br	4	EtOH, H_2O	53	185–188	$C_{11}H_{17}BrN_2O_4S_2$	180	100, 50	93, 60	+++	>900	500 (30)	0	0
9	5-Cl	4	H_2O, MeOH	54	178–180	$C_{11}H_{17}ClN_2O_4S_2$	190	100, 50	100, 73	++	>1200	600 (30)	0	0
10	3,5-Br_2	5	20% EtOH	42	204–209	$C_{12}H_{18}Br_2N_2O_4S_2$	163	50, 25	93, 67	++++	>1200	800 (30)	0	0
11	3,5-Cl_2	5	EtOH	56	209–210	$C_{12}H_{18}Cl_2N_2O_4S_2$	175	12.5	93	++++				
12	3-Br	5	EtOH	49	178–183	$C_{12}H_{19}BrN_2O_4S_2$	170	45	47	+				
13	5-Br	5	DMF–H_2O, HMPA–EtOH	25	186–187	$C_{12}H_{19}BrN_2O_4S_2$	90	25	73	+++				
14	6-Br	5	DMF–EtOH, DMF–H_2O, DMF, DMSO, DMSO–H_2O, HMPA–EtOH	33	184–185	$C_{12}H_{19}BrN_2O_4S_2$[c]	140	100	0	0				
15	5-Cl	5	H_2O	63	164–168	$C_{12}H_{19}ClN_2O_4S_2$	225	19	87	++++	>1000	800 (30)	7	0
16	5-I	5	DMF–EtOH	28	187–193	$C_{12}H_{19}IN_2O_4S_2$	100	50	27	0				
17	5-NO_2	5	MeCN, H_2O	9	150–156	$C_{12}H_{19}N_3O_6S_2$	150	80	53	+				
18	3,5-Br_2	6	EtOH	29	206–210	$C_{13}H_{20}Br_2N_2O_4S_2$	250	15	20	0				
19	4-CH_3	5	EtOH	25	135–139	$C_{13}H_{22}N_2O_4S_2$	185	100	0	0				
20	5-CH_3	5	EtOH	26	134–139	$C_{13}H_{22}N_2O_4S_2$	125	35	80	++	>900	600 (30)	7	0
21	5-CN	5	EtOH	34	158–160	$C_{13}H_{19}N_3O_4S_2$	175	80	13	0				
22	5-Br	6	DMF–EtOH, H_2O	46	175–187	$C_{13}H_{21}BrN_2O_4S_2$	225	50	0	0				
23	5-Cl	6	H_2O, MeOH	28	196–198	$C_{13}H_{21}ClN_2O_4S_2$	120	30	67	+++	>800	600 (30)	0	0
24	5-Br	7	MeOH	36	180–182	$C_{14}H_{23}BrN_2O_4S_2$	50	20	13	0				
25	5-I	7	MeOH, 95% EtOH	50	169–177	$C_{14}H_{23}IN_2O_4S_2$	100	20	0	0				
26	5-Br	10	EtOH, DMF–H_2O, MeOH	33	147–189	$C_{17}H_{29}BrN_2O_4S_2$	160	80	0	0				
27	*d*	5	MeOH–Et_2O, H_2O	35	168–174	$C_{12}H_{19}BrN_2O_4S_2$	450	25	7	0				
28	*e*		EtOH	80	175–177	$C_{13}H_{21}BrN_2O_4S_2$	>400	200	0	0				
29	*f*	5	H_2O	29	175–177	$C_{19}H_{35}N_3O_8S_4$	150	50	7	0				
														
30	4-CH_4	2	MeCN, H_2O	39	205–208	$C_{14}H_{18}N_2O_4S_2$		140	0	0				
31	H	3	H_2O, DMF–H_2O, EtOH	24	186–187	$C_{14}H_{18}N_2O_4S_2$	220	25	93	++++				
32	4-CF_3	3	95% EtOH	33	203–205	$C_{15}H_{17}F_3N_2O_4S_2$	160	30	33	0				
33	6-Cl, 4-CH_3	3	95% EtOH	40	195–197	$C_{15}H_{19}ClN_2O_4S_2$	75	30, 15	86, 27	++	>600	600 (30)	0	0
34	8-Cl, 4-CH_3	3	DMSO–H_2O	45	214–215	$C_{15}H_{19}ClN_2O_4S_2$	300	10	0	0				
35	4-CH_3	3	MeOH–H_2O	32	200–201	$C_{15}H_{20}N_2O_4S_2$	180	25, 12.5	86, 27	++++	900	400 (30)	0	0
36	6-CH_3O, 4-CH_3	2	EtOH, MeOH–Et_2O	7	189–191	$C_{15}H_{20}N_2O_5S_2$	100	12	73	+++				
37	4-CH_3O	3	EtOH, 95% EtOH	28	185–186	$C_{15}H_{20}N_2O_5S_2$	175	80	33	0				

38	4-Cl	5	MeOH	30	178–185	$C_{16}H_{21}ClN_2O_4S_2$	275	10	0	0			
39	H	5	DMF–EtOH	54	173–175	$C_{16}H_{22}N_2O_4S_2$	25	12.5	27	0			
40	4,6-$(CH_3)_2$	3	EtOH	37	192–194	$C_{16}H_{22}N_2O_4S_2$	125	19	93	++++	>900	600 (60)	7	0
41	4-CH_3	4	EtOH	17	130–138	$C_{16}H_{22}N_2O_4S_2$	225	50, 25	93, 47	+++	>750	500 (30)	0	0
42	6-CH_3O, 4-CH_3	3	MeCN	42	189–195	$C_{16}H_{22}N_2O_5S_2$	130	25, 12.5	80, 33	++				
43	4-CF_3	5	EtOH, MeCN	41	186–188	$C_{17}H_{21}F_3N_2O_4S_2$	250	5	0	0				
44	6-Cl, 4-CH_3	5	EtOH	39	192–194	$C_{17}H_{23}ClN_2O_4S_2$	175	35	7	0				
45	8-Cl, 4-CH_3	5	DMF–H_2O, EtOH	15	193–194	$C_{17}H_{23}ClN_2O_4S_2$	325	20	0	0				
46	4-CH_3	5	95% EtOH, DMF–H_2O, DMF–Et_2O	20	167–169	$C_{17}H_{24}N_2O_4S_2$	740	560	0	0				
47	4-C_3H_7	3	MeCN, EtOH	25	146–148	$C_{17}H_{24}N_2O_4S_2$	125	30	53	+	>600	400 (60)	7	0
48	4-CH_3O	5	MeCN, 95% EtOH	34	154–156	$C_{17}H_{24}N_2O_5S_2$	225	100, 50	93, 47	++	>900	600 (60)	0	0
49	4-CH_3	6	EtOH	27	180–183	$C_{18}H_{26}N_2O_4S_2$	90	7.5	7	0				
50	4,6-$(CH_3)_2$	5	EtOH	47	178–179	$C_{18}H_{26}N_2O_4S_2$	115	30	0	0				
51	4-C_3H_7	5	EtOH	29	170–172	$C_{19}H_{28}N_2O_4S_2$	120	30	0	0				
52	*g*	5	EtOH, EtOH–H_2O, MeOH	22	172–176	$C_{16}H_{21}ClN_2O_4S_2$	250	150	0	0				
53	*h*	3	DMF–H_2O, 95% EtOH	36	185–189	$C_{14}H_{18}N_2O_4S_2$	175	80	13	0				
54	*h*	5	EtOH	50	159–161	$C_{16}H_{22}N_2O_4S_2$	175	30	0	0				

[a] All compounds were analyzed for C, H, N, and S. [b] Data are given for ip and po administration of the compounds. The antiradiation data generally represent the lowest dose of drug for which a high rate of survival was obtained. The per cent survival (30 days) of the test animals is given for the dose specified. For each test, usually 15 mice were treated with drug and irradiated either 15 or 30 min later with ip dosing, and 15, 30, or 60 min perorally. Preirradiation peroral dosage schedules are given in the table. The radiation dose was 950 rads (30–50 rads/min) of γ radiation from a Cobalt 60 source. Exceptions are noted. Ratings are described in footnote ‡ of the text. [c] C: calcd, 36.09; found, 36.62. S: calcd, 16.06; found, 15.55. [d] 3-Br-4-pyridyl-$O(CH_2)_5NHCH_2CH_2S_2O_3H$. [e] 5-Br-2-pyridyl-$O(CH_2)_5NHCH(CH_3)CH_2S_2O_3H$. [f] 6-$[HO_3S_2(CH_2)_2NH(CH_2)_5O]$-2-pyridyl-$O(CH_2)_5NHCH_2CH_2S_2O_3H$. [g] 7-Cl-4-quinolyl-$O(CH_2)_5NHCH_2CH_2S_2O_3H$. [h] 1-Isoquinolyl-$O(CH_2)_nNHCH_2CH_2S_2O_3H$.

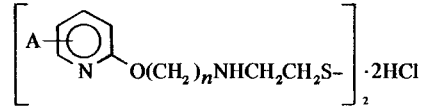
Table III. 2-({[(Substituted pyridyl)oxy]alkyl}amino)ethanethiols



							Antiradiation activity[b]							
							Intraperitoneal data				Peroral data			
No.	A	*n*	Recrystn solvents	Yield, %	Mp, °C	Formula[a]	LD_{50}, *ca.* mg/kg	Drug dose, mg/kg	Survival, %	Rating	LD_{50}, *ca.* mg/kg	Drug dose, mg/kg (min preirrad)	Survival, %	Rating
55	5-Br	2	EtOH	36	167–170	$C_9H_{13}BrN_2OS \cdot HCl$	110	50	0	0				
56	5-Br	3	MeCN	54	152–165	$C_{10}H_{15}BrN_2OS \cdot HCl$	150	50	7	0				
57	5-Br	4	EtOH	37	145–150	$C_{11}H_{17}BrN_2OS \cdot HCl$	125	50	0	0				
58	5-Cl	4	MeCN	42	148–160	$C_{11}H_{17}ClN_2OS \cdot HCl$	100	35	7	0	250	100 (30)	7	0
59	3,5-Br_2	5	EtOH	35	163–166	$C_{12}H_{18}Br_2N_2OS \cdot HCl$	150	40	7	0				
60	3,5-Cl_2	5	EtOH	57	162–166	$C_{12}H_{18}Cl_2N_2OS \cdot HCl$	130	70	30	0	510	250 (30)	0	0
61	5-Br	5	MeCN	46	159–164	$C_{12}H_{19}BrN_2OS \cdot HCl$	240	90	40	+				
62	5-Br	5	MeCN	40	126–132	$C_{12}H_{19}BrN_2OS \cdot 2HCl$	240	90	67[c]	+	>550	300 (30)	7	0
63	5-Cl	5	EtOH	49	144–156	$C_{12}H_{19}ClN_2OS \cdot HCl$	110	60	80	+	700	300 (15)	47	+
64	5-I	5	EtOH	28	140–152	$C_{12}H_{19}IN_2OS \cdot HCl$	150	25	20	0	400	150 (30)	0	0
65	5-Br	6	MeCN, EtOH	30	160–166	$C_{13}H_{21}BrN_2OS \cdot HCl$	140	60	87	++	350	200 (30)	47	+
66	5-Cl	6	MeCN–EtOH, MeCN	69	143–148	$C_{13}H_{21}ClN_2OS \cdot HCl$[d]	140	60	53	+	350	150 (15)	40	+
67	4-CH_3	5	MeCN	90	112–124	$C_{13}H_{22}N_2OS \cdot HCl$	97	40	0	0				
68	5-CH_3	5	MeCN	52	102–110	$C_{13}H_{22}N_2OS \cdot HCl$[e]	80	45	0	0				
69	5-Br	10	EtOH, MeCN	30	173–183	$C_{17}H_{29}BrN_2OS \cdot HCl$	52	30	20	0				

[a] All compounds were analyzed for C, H, N, and SH. [b] See Table II, footnote *b*. [c] The mice were challenged with 825 rads supplied by X-rays. [d] SH: calcd, 10.17; found, 9.72. [e] SH: calcd, 11.37; found, 10.39.

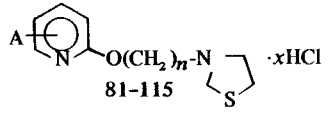
Table IV. 2,2'-[Dithiobis(ethyleneiminoalkyleneoxy)]bis(substituted pyridines)

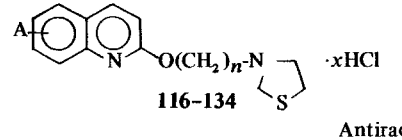


No.	A	n	Recrystn solvents	Yield, %	Mp, °C dec	Formula[a]	Antiradiation activity[b] Intraperitoneal data: LD_{50}, *ca.* mg/kg	Drug dose, mg/kg	Survival, %	Rating	Peroral data: LD_{50}, *ca.* mg/kg	Drug dose, mg/kg (min preirrad)	Survival, %	Rating
70	5-Br	2		45	223–230	$C_{18}H_{24}Br_2N_4O_2S_2 \cdot 2HCl$	140	35	7	0				
71	5-Br	3	MeOH	14	248–250	$C_{20}H_{28}Br_2N_4O_2S_2 \cdot 2HCl$	150	80	40	+				
72	5-Cl	3	MeOH	65	248–250	$C_{20}H_{28}Cl_2N_4O_2S_2 \cdot 2HCl$	100	50	13	0				
73	3,5-Br_2	5	MeOH	23	230–234	$C_{24}H_{34}Br_4N_4O_2S_2 \cdot 2HCl$	40	20	0	0				
74	3,5-Cl_2	5	MeOH	47	239–241	$C_{24}H_{34}Cl_4N_4O_2S_2 \cdot 2HCl$	70	40	0	0	>1500	1500 (30)	7	0
75	3-Br	5	EtOH	52	199–202	$C_{24}H_{36}Br_2N_4O_2S_2 \cdot 2HCl$	60	40	0	0				
76	5-Br	5	MeOH	68	244–246	$C_{24}H_{36}Br_2N_4O_2S_2 \cdot 2HCl$	320	90	47	+	>750	600 (30)	7	0
77	5-Cl	5	MeOH	77	240–242	$C_{24}H_{36}Cl_2N_4O_2S_2 \cdot 2HCl$	80	50	79	+	>900	420 (60)	7	0
78	5-Br	6	MeOH	58	236–242	$C_{26}H_{40}Br_2N_4O_2S_2 \cdot 2HCl$	78	20	20	0				
79	5-Cl	6	MeOH	35	243–246	$C_{26}H_{40}Cl_2N_4O_2S_2 \cdot 2HCl$	75	35	7	0				
80	5-Br	10	MeOH	43	239–242	$C_{34}H_{56}Br_2N_4O_2S_2 \cdot 2HCl$	50	7.5	0	0				

[a] All compounds were analyzed for C, H, N, and S. [b] See Table II, footnote *b*.

Table V. 3-Substituted Thiazolidines





No.	A	n	Recrystn solvent	Yield, %	Mp, °C	Formula[a]	Antiradiation activity[b] Intraperitoneal data: LD_{50}, *ca.* mg/kg	Drug dose, mg/kg	Survival, %	Rating	Peroral data: LD_{50}, *ca.* mg/kg	Drug dose, mg/kg (min preirrad)	Survival, %	Rating
81	5-Br	2	EtOH	54	179–183	$C_{10}H_{13}BrN_2OS \cdot HCl$	150	80	0	0				
82	5-Cl	2	MeCN, EtOH	49	176–178	$C_{10}H_{13}ClN_2OS \cdot HCl$	150	75	0	0	400	200 (30)	0	0
83	5-Br	3	MeCN	41	177–180	$C_{11}H_{15}BrN_2OS \cdot HCl$	250	100	33	0				
84	5-Cl	3	MeCN, EtOH	60	168–171	$C_{11}H_{15}ClN_2OS \cdot HCl$	125	60	0	0				
85	5-I	3	MeCN	18	168–170	$C_{11}H_{15}IN_2OS \cdot HCl$	175	80	13	0	>900	600	40	+
86	5-Br	4	MeCN	45	151–153	$C_{12}H_{17}BrN_2OS \cdot HCl$	250	100	80	+	600	250 (60)	27	0
87	5-Cl	4	MeCN	43	110–115	$C_{12}H_{17}ClN_2OS \cdot HCl$	275	120	47	+	750	300 (60)	33	0
88	5-I	4	*i*-PrOH	33	165–167	$C_{12}H_{17}IN_2OS \cdot HCl$	>300	100	20	0	>1000	400 (30)	53	+
89	3,5-Br_2	5	MeCN	39	170–172	$C_{13}H_{18}Br_2N_2OS \cdot HCl$	>320	200	13	0				
90	3,5-Cl_2	5	EtOH	62	173–175	$C_{13}H_{18}Cl_2N_2OS \cdot HCl$	150	50	0	0	>900	450 (30)	53	+
91	3-Br	5	MeCN	37	150–153	$C_{13}H_{19}BrN_2OS \cdot HCl$	280	100	0	0				
92	5-Br	5	MeCN	23	138–140	$C_{13}H_{19}BrN_2OS \cdot HCl$	240	100	67	+	900	500 (15)	60	+
93	5-Br	5	Me_2CO	60	104–106	$C_{13}H_{19}BrN_2OS \cdot C_6H_8O_7$[c]	300	100	87	++	>400	400 (15)	67	+
94	6-Br	5	MeCN	37	116–118	$C_{13}H_{19}BrN_2OS \cdot HCl$	240	180	67[d]	+				
95	5-Cl	5	MeOH–Et_2O	40	122–125	$C_{13}H_{19}ClN_2OS \cdot HCl$	160	80	87	+				
96	5-Cl	5	EtOH	63	143–145	$C_{13}H_{19}ClN_2OS \cdot 2HCl$	160	80	93	+	650	300 (30)	73	++

97	5-I	5	EtOH	45	173–175	$C_{13}H_{19}IN_2OS \cdot HCl$[e]	230	100	93	+	>900	300 (30), 150 (30)	80 53	++
98	H	5	MeCN	46	141–144	$C_{13}H_{20}N_2OS \cdot 2HCl$	>200	50	7	0				
99	3,5-Br_2	6	MeCN	17	152–154	$C_{14}H_{20}Br_2N_2OS \cdot HCl$	274	130	0	0				
100	5-Br	6	MeCN	40	124–126	$C_{14}H_{21}BrN_2OS \cdot HCl$	200	100	73	+	>525	300 (30), 150 (30)	93 47	+
101	5-Br	*f*	MeCN	59	172–175	$C_{14}H_{21}BrN_2OS \cdot HCl$	220	80	0	0	690	250 (30)	7	0
102	5-Cl	6	MeCN	30	132–135	$C_{14}H_{21}ClN_2OS \cdot HCl$	220	100	93	+	>600	150 (30), 75 (30)	73 33	+++
103	5-I	6	EtOH	43	149–152	$C_{14}H_{21}IN_2OS \cdot HCl$	125	75	47	+	>600	300 (30), 150 (30)	93 47	+++
104	5-CH_3	5	MeCN, EtOH	25	164–167	$C_{14}H_{22}N_2OS \cdot 2HCl$	190	70	33	0	700	375 (15)	20	0
105	5-CH_3S	5	MeCN, EtOH–Et_2O	30	128–130	$C_{14}H_{22}N_2OS_2 \cdot 2HCl$	200	60	0	0	550	300 (15)	0	0
106	5-Br	7	MeCN	55	133–136	$C_{15}H_{23}BrN_2OS \cdot HCl$	225	150	47	+	800	400 (30), 200 (30)	67 47	++
107	5-Cl	7	MeCN	56	119–123	$C_{15}H_{23}ClN_2OS \cdot HCl$	100	50	0	0	500	200 (30)	79	+
108	5-I	7	*i*-PrOH	36	160–163	$C_{15}H_{23}IN_2OS \cdot HCl$	200	100	47	+	>750	600 (30)	73	+
109	5-CH_3	6	MeCN	9	149–151	$C_{15}H_{24}N_2OS \cdot 2HCl$	200	60	0	0	500	150 (15)	53	+
110	5-Br	8	Me_2CO, EtOAc	24	135–137	$C_{16}H_{25}BrN_2OS \cdot HCl$	230	50	20	0	>600	150 (15)	40	+
111	5-Br	10	Me_2CO, EtOAc	28	145–147	$C_{18}H_{29}BrN_2OS \cdot HCl$	50	12.5	7	0				
112	3-Pyridyl-O$(CH_2)_3$		EtOH	26	168–171	$C_{11}H_{16}N_2OS \cdot 2HCl$	150	75	0	0				
113	4-Pyridyl-O$(CH_2)_5$		MeCN	12	140–146	$C_{13}H_{20}N_2OS \cdot 2HCl$	150	80	0	0	500	200 (30)	0	0
114	5-Br	*g*	$CHCl_3$–EtOH	14	167–170	$C_{14}H_{22}BrN_2OSX$ (X = Cl)	15	8	0	0				
115	5-Cl	*h*	Me_2CO, MeCN	16	142–146	$C_{14}H_{21}ClN_2OS \cdot HCl$								
116	4-CH	2	95% EtOH, EtOH	15	167–171	$C_{15}H_{18}N_2OS \cdot HCl$	250	50	13	0				
117	H	3	EtOH	26	124–130	$C_{15}H_{18}N_2OS \cdot 2HCl$	120	60	20	0	375	150 (30)	0	0
118	4-CF_3	3	*i*-PrOH, EtOH	32	96–97	$C_{16}H_{17}F_3N_2OS$	>360	40	0	0	>900	600 (60)	7	0
119	6-Cl, 4-CH_3	3	EtOH	43	175–178	$C_{16}H_{19}ClN_2OS \cdot HCl$	350	70	33	0	>900	600 (60)	7	0
120	8-Cl, 4-CH_3	3	EtOH	62	195–196	$C_{16}H_{19}ClN_2OS \cdot HCl$	>400	50	33	0	>900	500 (30)	33	0
121	4-CH_3O	3	EtOH	48	70–71	$C_{16}H_{20}N_2O_2S$	225	100	7	0				
122	4-CH_3	3	EtOH	32	158–161	$C_{16}H_{20}N_2OS \cdot 2HCl$	320	180	0	0	>900	500 (30)	42	+
123	4-Cl	5	MeCN	10	154–156	$C_{17}H_{21}ClN_2OS \cdot HCl$	350	75	7	0	>900	500 (30)	0	0
124	4,6-$(CH_3)_2$	3	EtOH	41	63–65	$C_{17}H_{22}N_2OS$	500	50	53	++	>500	500 (60)	40	+
125	4-CH_3	4	EtOH	41	158–160	$C_{17}H_{22}N_2OS \cdot 2HCl$	260	110	0	0	600	300 (15)	7	0
126	H	5	EtOH	34	131–133	$C_{17}H_{22}N_2OS \cdot 2HCl$	225	100	40	+	400	200 (30)	73	+
127	6-CH_3O, 4-CH_3	3	EtOH	3	103–105	$C_{17}H_{22}N_2O_2S$	200	100	0	0				
128	4-CF_3	5	EtOH	42	156–157	$C_{18}H_{21}F_3N_2OS \cdot HCl$	200	50	7	0	800	400 (60)	20	0
129	6-Cl, 4-CH_3	5	EtOH	57	149–151	$C_{18}H_{23}ClN_2OS \cdot HCl$	>375	300	27	0	>450	400 (30)	0	0
130	8-Cl, 4-CH_3	5	EtOH	39	177–178	$C_{18}H_{23}ClN_2OS \cdot HCl$	180	60	0	0				
131	4-CH_3	5	EtOH	45	151–153	$C_{18}H_{24}N_2OS \cdot 2HCl$	430	320	7	0	>600	300 (30)	0	0
132	4-CH_3O	5	*i*-PrOH, EtOH	53	77–78	$C_{18}H_{24}N_2O_2S$	>450	50	0	0				
133	4,6-$(CH_3)_2$	5	*i*-PrOH, EtOH	28	58–60	$C_{19}H_{26}N_2OS$	500	6	0	0				
134	4-CH_3	6	MeCN–EtOH, MeCN	24	144–146	$C_{19}H_{26}N_2OS \cdot 2HCl$	200	100	7	0				

[a]All compounds were analyzed for C, H, N, and S. [b]See Table II, footnote *b*. [c]Citric acid salt prepared from the free base of **92**. [d]The mice were challenged with 825 rads supplied by X-rays. [e]S: calcd, 7.73; found, 7.26. [f]5-Br-2-pyridyl-O$(CH_2)_5$-N(S)-$CH_3 \cdot HCl$. [g]5-Br-2-pyridyl-O$(CH_2)_5$-$(Me)^+$N(S) Cl^-. [h]5-Cl-2-pyridyl-O$(CH_2)_2C(CH_3)H(CH_2)_2$-N(S) $\cdot HCl$.

series of thiazolidines, **90**, **107**, and **109** were active when given orally but inactive parenterally. Inactivity in the ip test for compounds active in the po test is very unusual.

The thiols and disulfides listed in Tables III and IV were only moderately active when given ip and even less active in the po test. Quinoline ethers as thiazolidines **116–134** (Table V) showed some activity in the po test but were more active generally when given intraperitoneally.

5-Chloro-2-{[5-(3-thiazolidinyl)pentyl]oxy}pyridine hydrochloride (**95**) was administered iv to anesthetized dogs to check for activity on the autonomic nervous and cardiovascular systems.§ A cumulative dose of 63 mg/kg (iv) resulted in no adrenergic or ganglionic blockade, no anticholinergic or antibradykinin effects, and no major respiratory effects. Only a slight hypotensive effect was observed.

N-Substituted [(5-halo-2-pyridyl)oxy]alkyl derivatives of *S*-2-aminoethyl hydrogen thiosulfate are potential antiradiation agents for parenteral use. The corresponding N-substituted thiazolidines are effective perorally. A long-sought goal to increase the number of radioprotective compounds effective by oral administration has been realized.

Experimental Section#

Substituted 2-Bromo- and 2-Chloropyridines. The following compounds were obtained from Aldrich Chemical Co.: 2-bromo-4-methylpyridine, 2-chloro-3-nitropyridine, 2-chloro-5-nitropyridine, 4-chloropyridine, 2,5-dibromopyridine, 2,6-dibromopyridine, and 2,3-dichloropyridine. 2,5-Dichloropyridine was obtained from Olin Corp. The following compounds were prepared according to published methods: 3-bromo-2-chloropyridine,[10] 2-bromo-3,5-dichloropyridine,[11] 2-bromo-5-iodopyridine,[12] 2-bromo-5-methylpyridine,[11] 2-chloro-5-cyanopyridine,[13] 3,4-dibromopyridine,[14] and 2,3,5-tribromopyridine.[15]

5-Amino-2-chloropyridine. The catalytic method described here is an improvement over known[16] methods. A solution of 168 g (1.04 mol) of 2-chloro-5-nitropyridine in 1.6 l. of MeOH containing 5 g of Raney Ni was treated with H_2 at 50 psi for 13.5 hr at room temperature. The catalyst was removed, the filtrate was concentrated under reduced pressure, and the solid residue was recrystallized from H_2O (charcoal) to give 117 g (87%) of 5-amino-2-chloropyridine, mp 78–81° (lit.[16] mp 83°). The benzylidene derivative [5-(benzylideneamino)-2-chloropyridine] had mp 69–70°. *Anal.* ($C_{12}H_9ClN_2$) C, H, N.

2-Chloro-5-(3,3-dimethyl-1-triazeno)pyridine. Nitrosation of 5-amino-2-chloropyridine in 95% EtOH–40% HBF_4 was effected using EtONO.[17] A suspension of 12 g of the brilliant yellow solid diazonium tetrafluoroborate in 100 ml of Et_2O and 10 ml of $(Me_2N)_3PO$ was stirred at room temperature for 2 days (deep red coloration and gas evolution). The supernatant was decanted and the insoluble solid complex was decomposed with 1.0 *N* NaOH and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated giving acid-soluble solid. Recrystallization from H_2O and then 50% EtOH gave 200 mg of the title compound, mp 54–56°, and characteristic nmr and mass spectra. *Anal.* ($C_7H_9ClN_4$) C, H, Cl, N.

3,3′-(Methylenediimino)bis(6-chloropyridine). A mixture of 25 g (0.2 mol) of 5-amino-2-chloropyridine, 31 g of 37% formalin, and 250 ml of EtOH was stirred for 1 hr at room temperature giving 20 g of a precipitated solid, mp 206–208°. Recrystallization from 1.5 l. of MeCN gave 11.4 g (32%) of the bis derivative, mp 208–210°, characterized by ir and nmr spectra. *Anal.* ($C_{11}H_{10}Cl_2N_4$) C, H, N.

3,3′-(Methylenediimino)bis(6-chloropyridine) in alcoholic dry HCl for 1 hr at 25° gave 5-amino-2-chloropyridine·HCl, mp 184–187° dec, identical with an authentic sample.

2-Chloro-5-(dimethylamino)pyridine. Reductive methylation of 100 g (0.8 mol) of 5-amino-2-chloropyridine was effected in 1 l. of absolute EtOH using 138 g of 37% formalin (immediate precipitation of the bis derivative), 2 × 10 g of 10% Pt/C, and H_2 pressure of 50 psi. Concentration of the filtered mixture and distillation of the residue gave 90.4 g (72%) of the dimethylamino derivative, bp 100–110° (0.5 mm), mp 45–46.5°, and characteristic nmr spectrum. *Anal.* ($C_7H_9ClN_2$) C, H, N.

5-Azido-2-chloropyridine. HNO_2 diazotization of 13.8 g (0.096 mol) of 2-chloro-5-hydrazinopyridine[18] (prepared here in 43% yield by $SnCl_2$–HCl reduction of 2-chloro-5-pyridinediazonium chloride) gave 6.2 g (42%) of 5-azido-2-chloropyridine, bp 54° (0.3 mm) and mp (2,2,3-trimethylpentane) 34–35°. *Anal.* ($C_5H_3ClN_4$) C, H. N.

2-Chloro-5-pyridyl thiocyanate was prepared from 5-amino-2-chloropyridine using conditions reported[19] for 2-chloro-3-pyridyl thiocyanate. Crystallization from cyclohexane gave 72% of the thiocyanate product, mp 75–77°. *Anal.* ($C_6H_3ClN_2S$) C, H, N.

2-Chloro-5-(methylthio)pyridine. A solution of 25 g (0.15 mol) of 2-chloro-5-pyridyl thiocyanate in 450 ml of absolute MeOH was added rapidly to cold NaOMe in MeOH (from 6 g, 0.15 mol, of 57% NaH and 150 ml of MeOH). The mixture was stirred for 24 hr at room temperature and then concentrated under reduced pressure. The residue was extracted with several portions of Et_2O, totaling *ca.* 1 l. The combined extracts were filtered and concentrated to give 13.3 g of oily product. Distillation resulted in a 36% yield, bp 56–58° (0.05 mm). *Anal.* (C_6H_6ClNS) C, H, Cl, N.

3,3′-Dithiobis(6-chloropyridine). To a cold oily emulsion containing NaOEt (from 6.4 g, 0.27 mol, of 57% NaH and 15.7 ml, 0.27 mol, of absolute EtOH) was slowly added below 10° a solution of 46.1 g (0.27 mol) of 2-chloro-5-pyridyl thiocyanate in 300 ml of C_6H_6. The mixture was stirred without cooling for 1 hr; filtration through Celite, concentration under reduced pressure, and recrystallization from Et_2O gave 20.3 g (52%) of crystalline disulfide, mp 118–120°. *Anal.* ($C_{10}H_6Cl_2N_2S_2$) C, H, N.

2-Chloro-5-hydroxypyridine. A suspension of 2-chloro-5-pyridinediazonium sulfate (from 5 g, 0.039 mol, of 5-amino-2-chloropyridine in 125 ml of 2 *N* H_2SO_4) was added over 20 min to a vigorously stirred solution at 85–98° of 9.7 g (0.039 mol) of $CuSO_4 \cdot 5H_2O$ in 125 ml of 2 *N* H_2SO_4. The mixture was made nearly neutral with cold 50% NaOH and then slightly basic by the addition of solid K_2CO_3. The slurry was continuously extracted for 16 hr with Et_2O, and the nearly colorless extract was dried ($MgSO_4$) and concentrated to give 2.8 g of pale yellow solid. Recrystallization from C_6H_6 resulted in 1 g (20%) of product: mp 152–159° dec; uv max (MeOH) 289 nm (ε 3930), 226 (9900); uv max (MeOH–KOH) 313 nm (ε 4000), 247 (13,950). *Anal.* (C_5H_4ClNO) C, H, N.

Substituted 2-chloroquinolines: 2,4-dichloroquinoline,[20] 2,6-dichlorolepidine [68%, mp 150–151°. *Anal.* ($C_{10}H_7Cl_2N$) C, H] from 6-chloro-2-hydroxylepidine[21] using the general procedure of Buchmann and Hamilton;[20] 2,8-dichlorolepidine;[22] 2-chloro-6-methoxylepidine;[23] 2-chloro-4-methoxyquinoline [55%, mp 75–76°. *Anal.* ($C_{10}H_8ClNO$) C, H, N] from 4-methoxyquinoline 1-oxide[24] using the general method of Bachman and Cooper;[25] 2-chloro-4,6-dimethylquinoline [80%, mp 97–98°. *Anal.* ($C_{11}H_{10}ClN$) C, H, N] from $POCl_3$ and 4,6-dimethyl-2-hydroxyquinoline; 2-chloro-4-propylquinoline (80% crude yield, mp 74–75°) from $POCl_3$ and 2-hydroxy-4-propylquinoline; 2-chloro-4-(trifluoromethyl)quinoline [74%, mp 39–41° *Anal.* ($C_{10}H_5ClF_3N$) C, H, N] from $POCl_3$ and 2-hydroxy-4-(trifluoromethyl)quinoline; 1-chloroisoquinoline.[26]

The three carbostyrils immediately preceding were prepared from the required β-keto ester (see ref 23) and substituted aniline. These two reactants were heated together at 220–240° for 3–4 min, cooled, and mixed with 40 ml of concentrated H_2SO_4 for each 0.1-mol run; the resulting mixture was heated for 1 hr at 95°: 4,6-dimethyl-2-hydroxyquinoline [30%, mp 254–255°. *Anal.* ($C_{11}H_{11}NO$) C, H, N]; 2-hydroxy-4-propylquinoline [30%, mp 172–174°. *Anal.* ($C_{12}H_{13}NO$) C, H, N]; 2-hydroxy-4-(trifluoromethyl)quinoline [11%, mp 244–246°. *Anal.* ($C_{10}H_6F_3NO$) C, H, N].

1-Aziridinealkanols were prepared as previously described[3] in refluxing EtOH from chlorohydrins, ethylenimine, and powdered anhydrous K_2CO_3. Crude products were distilled through Vigreux columns (10–25 cm) to give 2–3 fractions which were subjected to nmr and glc analysis to determine purity: 1-aziridinepropanol, 70% yield, bp 70–82° (8 mm), glc 99%; 1-aziridinebutanol, 27%, bp 87–95° (8 mm), glc 62%; 1-aziridinepentanol, 52%, bp 130–140° (22 mm), glc 97%; 1-aziridinehexanol, 90%, bp 125–136° (14 mm), glc 96%; 1-aziridineheptanol, 60%, bp 82–85° (0.2 mm), glc 95%; 1-aziridineoctanol, 69%, bp 91–97° (0.4 mm), glc 97%; 1-aziridinedecanol, 80%, bp 117–122° (0.5 mm), glc 93%; 2-methyl-1-aziridinepentanol (from 2-methylaziridine), 81%, bp 124–130° (18 mm), glc 92%; and γ-methyl-1-aziridinepentanol, 55%, bp 120–123° (12 mm), glc 100%.

Substituted 2-[(1-Aziridinylalkyl)oxy]pyridines. 2-{[5-(1-Azir-

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#Melting points (uncorrected) were determined using a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions are within ±0.4% of the theoretical values. Nmr and/or ir spectra were used in making structural assignments of new compounds.

idinyl)pentyl]oxy}-5-chloropyridine. To a slurry containing 18.5 g (0.46 mol) of 60% NaH dispersion in 560 ml of THF was added slowly at reflux temperature 59.8 g (0.46 mol) of 1-aziridinepentanol. The mixture was stirred and heated under reflux for 2 hr, cooled, and then treated with 68.5 g (0.46 mol) of 2,5-dichloropyridine. The resulting mixture was heated under reflux for 4 hr and stirred overnight at room temperature. The mixture was cooled, diluted with Et_2O, and filtered through Celite. The filtrate was concentrated to give 117 g of residue; distillation gave 92.6 g (83%) of liquid product, bp 114–117° (0.01 mm) and glc 98%.

The reflux period was different for some of the other substituted pyridines: 3,4-dibromopyridine, 18 hr; 2,3,5-tribromopyridine, 9 hr; 2,6-dibromopyridine, stirred at 25° for 18 hr before being refluxed for 3 hr; 2,3-dichloropyridine, 8 hr; 2-chloro-5-methylpyridine, 18–64 hr; 2-chloro-4-methylpyridine, 40 hr; 2-chloro-5-(methylthio)-pyridine, 11 hr; and 2-chloro-3- and -5-nitropyridines, reaction started in Dry Ice–Me_2CO bath and allowed to warm to room temperature over several hours.

Substituted 2-[(1-Aziridinylalkyl)oxy]quinolines. Substituted 2-chloroquinolines and 1-aziridinealkoxides were heated in refluxing THF for 16–24 hr, except for the following: 2-chlorolepidine, 4 hr; 4,7-dichloroquinoline, 3 hr; and 2-chloro-4-(trifluoromethyl)quinoline was allowed to react only at room temperature for 16 hr.

3-[3-(1-Aziridinyl)propoxy]pyridine. A mixture of 39 g (0.41 mol) of 3-hydroxypyridine, 128 g (0.82 mol) of 1-bromo-3-chloropropane, 69 g (0.50 mol) of anhydrous K_2CO_3, and 500 ml of Me_2CO was heated under reflux for 2.5 hr. The dark mixture was filtered and the filtrate was concentrated under reduced pressure. Tars were separated by treatment with H_2O and extraction with several portions of Et_2O. The combined light brown extracts were dried ($MgSO_4$) and concentrated to give 36 g of crude 3-(3-chloropropoxy)pyridine which was used promptly to prepare 3-[3-(1-aziridinyl)propoxy]pyridine by reaction[3] with ethylenimine.

***S*-2-({[(Substituted 2-pyridyl- and 2-quinolyl)oxy]alkyl}amino)-ethyl hydrogen thiosulfates** were prepared[3,4] in MeOH from $(NH_4)_2S_2O_3$ and the 1-substituted aziridines.

2-({[(Substituted 2-pyridyl)oxy]alkyl}amino)ethanethiols were prepared[3,5] in EtOH from H_2S and the 1-substituted aziridines.

2,2′-[Dithiobis(ethyleneiminoalkyleneoxy)]bis(substituted pyridines) were prepared[3] in MeOH by I_2 oxidation of the corresponding aziridines.

2-[(3-Thiazolidinylalkyl)oxy]substituted pyridines and quinolines were prepared[3,6] from the corresponding thiols and $HOCH_2SO_3Na$.

3-{5-[(5-Bromo-2-pyridyl)oxy]pentyl}-3-methylthiazolidinium Chloride (91). A mixture of 20 g (0.06 mol) of 5-bromo-2-{[5-(3-thiazolidinyl)pentyl]oxy}pyridine (free base) and 8.6 ml (0.14 mol) of MeI was heated under reflux for 2 hr. The excess MeI was removed under reduced pressure, and the residue was crystallized from EtOH–EtOAc (50:12) to give 18.5 g of the quaternary salt. Recrystallization from the same solvent gave 14.8 g, mp 157–159°, which was dissolved in MeOH and passed through a column (diameter, 2 cm) packed with 300 ml of Dowex-1 resin (chloride form) in MeOH. The effluent (450 ml) was concentrated and the 15 g of residue was recrystallized twice from $CHCl_3$–EtOH to give 3.2 g (14%) of the thiazolidinium chloride **(91)**, mp 167–170°.

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