Antiradiation Agents. 3-[(Alkylthio)alkyl]thiazolidines and Substituted 2-{[(3-Thiazolidinyl)alkyl]thio}pyridines and -quinolines†

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5-Halo- and 3,5-dihalo-2-{[(3-thiazolidinyl)alkyl]thio}pyridine hydrochlorides [alkyl = $(CH_2)_{3-8,10}$] and substituted and unsubstituted 2-{[(3-thiazolidinyl)alkyl]thio}quinoline hydrochlorides [alkyl = $(CH_2)_{5,6}$] have been prepared by alkylation of 2(1*H*)-pyridinethiones and 2(1*H*)-quinolinethiones with 3-(chloroalkyl)thiazolidines. The series was extended to 3-[(alkylthio)alkyl]thiazolidine hydrochlorides [$CH_3(CH_2)_{n_1}$-S-$(CH_2)_{n_2}$, involving 27 combinations of n_1 = 0–9 and n_2 = 2–7] by alkylation of alkanethiols. Several compounds exhibited promising antiradiation activity, either by ip or po administration. Generally the compounds were more active in the po test. 5-Chloro-2-{[7-(3-thiazolidinyl)heptyl]thio}-pyridine hydrochloride (**19**) given po at 75 mg/kg (*ca.* 0.13 LD_{50}) afforded 60% survival in the 30-day test. 3-[5-(Pentylthio)pentyl]thiazolidine hydrochloride (**43**) resulted in 92% survival (30-day) of the mice when given po at 125 mg/kg (0.2 LD_{50}).

A principal objective in the search for antiradiation agents has been to develop a drug which is effective on oral administration. In contrast with the many compounds effective by parenteral dosing, few agents have been reported active when given orally.[1-7] Selected pyridyloxyalkyl derivatives of thiazolidine were active in the po test[4] and, in fact, 5-halo-2-{[5-(3-thiazolidinyl)pentyl]oxy}pyridine and the corresponding hexyl derivative were more active po than ip. We now report a related series of thioethers, substituted 2-{[(3-thiazolidinyl)alkyl]thio}pyridines I (Table I) and -quinolines II (Table I), and a new group of simple alkyl thioethers, 3-[(alkylthio)alkyl]thiazolidines III (Table II). The same type of potentially useful antiradiation activity has been found.

3-(Chloroalkyl)thiazolidines were synthesized for alkylations of the 2(1*H*)-pyridinethiones, 2(1*H*)-quinolinethiones, and alkanethiols. 3-Thiazolidinealkanol hydrochlorides IV suspended in THF were readily converted ($SOCl_2$) to alkyl chlorides V. Other solvents or lack of solvent led to decomposition of the sensitive thiazolidine ring. Alkylation of thiols using these alkyl chlorides was accomplished in DMF (NaH).

Figure 1 shows correlations between the length of the thioether alkyl chain of the 5-halopyridine compounds and antiradiation activity in mice in the ip and po tests.[8] The

IV V

activity is expressed as protective index values‡ which incorporate both dose response and therapeutic index factors. In both test systems the 5-chloro and 5-bromo derivatives were more active than the 5-iodopyridines, with 5-chloro substitution being preferred for optimum activity by the oral route. With appropriate halogen substitution on the pyridine ring, good activity was obtained with pentyl, hexyl, or heptyl thioethers, regardless of route (ip or po) of administration. 5-Chloro-2-{[7-(3-thiazolidinyl)heptyl]-thio}pyridine·HCl (**19**) is the compound of choice in the

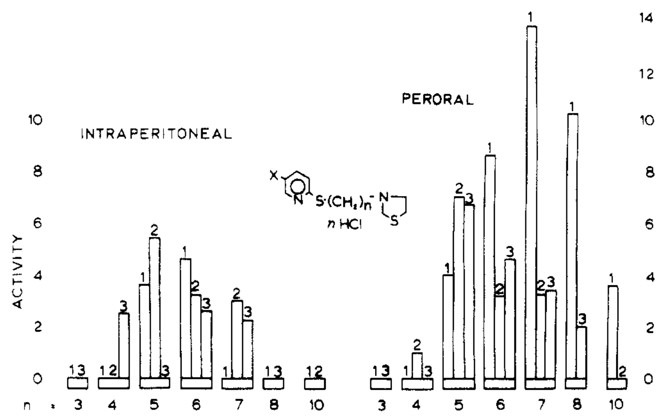


Figure 1. Effect of halogen substitution and chain length on antiradiation activity (activity expressed as protective index values‡) of 5-halo-2-{[(3-thiazolidinyl)alkyl]thio}pyridine hydrochlorides: **1**, X = Cl; **2**, X = Br; **3**, X = I.

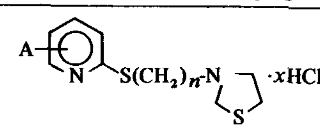
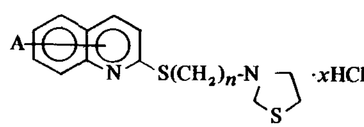
pyridine series because of its strikingly good peroral activity, but it is rated inactive when given ip. Perorally a dose of 75 mg/kg (*ca.* 0.13 LD_{50}) of **19** resulted in 60% survival in the 30-day test. The corresponding hexyl (**15**) and octyl (**21**) ethers also were highly active perorally. The 5-bromo derivative as a pentyl ether **10** is a good agent, in view of its effectiveness in both test systems. Fair activity was obtained with the 3,5-dichloropyridine derivatives (Table I), but corresponding dibromo compounds were only slightly active. Results using pyridine substituents other than halogen in the oxygen ethers discouraged us from employing those substituents in this thioether series. Of the quinoline thioether derivatives (Table I) 2-{[5-(3-thiazolidinyl)pentyl]-thio}quinoline·2HCl (**26**) was the most active compound, although the hexyl thioether **29** compared favorably in the po test.

Certain 3-[(alkylthio)alkyl]thiazolidines III (Table II) also

†This investigation was supported by the U. S. Army Medical Research and Development Command, Contract No. DA-49-193-MD-2306.

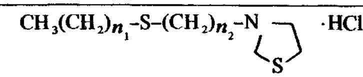
‡Protective index = (protection factor) × (LD_{50}/min effective dose), where doses are in mg/kg and the protection factor is 1.4 for 40% survival, 1.5 for 50% survival, etc. 30% survival is the smallest value used for the calculations. 2-Aminoethanethiol (MEA) is the standard for comparison. At 150 mg/kg ip of MEA, 87% survival of mice can be obtained in the 30-day test. Its ip LD_{50} is *ca.* 250 mg/kg and it is rated ++. The po LD_{50} is *ca.* 625 mg/kg. At 300 mg/kg, 73% survival can be obtained in the po test giving MEA a rating of ++.

Table I. Substituted 2-{[(3-Thiazolidinyl)alkyl]thio}pyridines (I) and -quinolines (II)

No.	A	*n*	Recrystn solvents	Yield, %	Mp, °C	Formula[a]	Antiradiation activity[b]: Intraperitoneal data: LD_{50}, *ca.* mg/kg	Intraperitoneal: Drug dose, mg/kg	Intraperitoneal: Survival, %	Intraperitoneal: Rating	Peroral data: LD_{50}, *ca.* mg/kg	Peroral: Drug dose, mg/kg	Peroral: Survival, %	Peroral: Rating
														
1	3,5-Cl_2	3	*n*-BuOH	63	134–137	$C_{11}H_{14}Cl_2N_2S_2 \cdot HCl$	225	100	7	0	950	500	7	0
2	5-Cl	3	EtOH	27	134–137	$C_{11}H_{15}ClN_2S_2 \cdot HCl$	200	50	0	0	625	170	0	0
3	5-I	3	*i*-PrOH, EtOH	17	175–179	$C_{11}H_{15}IN_2S_2 \cdot HCl$	350	150	13	0	>600	300	0	0
4	3,5-Cl_2	4	*n*-BuOH	75	150–153	$C_{12}H_{16}Cl_2N_2S_2 \cdot HCl$	350	150	7	0	>650	300	7	0
5	5-Br	4	*n*-BuOH	38	108–110	$C_{12}H_{17}BrN_2S_2 \cdot HCl$	275	100	7	0	650	300	26	0
6	5-Cl	4	EtOAc, BuOH	19	106–109	$C_{12}H_{17}ClN_2S_2 \cdot HCl$	250	100	13	0	550	300	20	0
7	5-I	4	MeCN, EtOH	23	150–153	$C_{12}H_{17}IN_2S_2 \cdot HCl$	225	125[c]	47	+	600	300	27	0
8	3,5-Br_2	5	MeCN, *i*-PrOH	11	153–160	$C_{13}H_{18}Br_2N_2S_2 \cdot HCl$	>500	200	7	0	>600	400	0	0
9	3,5-Cl_2	5	*n*-BuOH	37	147–149	$C_{13}H_{18}Cl_2N_2S_2 \cdot HCl$	>300	100	53	+	1000	500	27	0
10	5-Br	5	*n*-BuOH	50	128–130	$C_{13}H_{19}BrN_2S_2 \cdot HCl$	275	100	93	++	800	200	73	++
11	5-Cl	5	EtOH, MeCN	50	149–153	$C_{13}H_{19}ClN_2S_2 \cdot 2HCl$	180	90	80	+	675	300	80	+
12	5-I	5	MeCN	24	149–152	$C_{13}H_{19}IN_2S_2 \cdot HCl$	175	50	20	0	700	300	80	++
13	3,5-Cl_2	6	*n*-BuOH	80	145–147	$C_{14}H_{20}Cl_2N_2S_2 \cdot HCl$	275	140	87	+	1000	400	80	+
14	5-Br	6	MeCN, EtOH	28	143–146	$C_{14}H_{21}BrN_2S_2 \cdot HCl$	300	200, 100	93, 20	+	500	400, 200	80, 40	+
15	5-Cl	6	EtOH, *n*-BuOH	53	142–144	$C_{14}H_{21}ClN_2S_2 \cdot HCl$	225	100	100	+	700	150	80	++
16	5-I	6	*i*-PrOH	40	150–154	$C_{14}H_{21}IN_2S_2 \cdot HCl$[d]	225	125	53	+	>430	250	80	+
17	3,5-Cl_2	7	MeCN	68	134–136	$C_{15}H_{22}Cl_2N_2S_2 \cdot HCl$	275	125	60	++	>1050	800[c]	0	0
18	5-Br	7	MeCN	48	135–140	$C_{15}H_{23}BrN_2S_2 \cdot 2HCl$	115	75	93	+	450	250	90	+
19	5-Cl	7	Me_2CO–MeCN, MeCN	57	125–127	$C_{15}H_{23}ClN_2S_2 \cdot HCl$	56	30	20	0	650	150, 75	87, 60	+++
20	5-I	7	EtOH	46	141–143	$C_{15}H_{23}IN_2S_2 \cdot HCl$	125	100	73	+	300	200	60	+
21	5-Cl	8	MeCN	53	135–137	$C_{16}H_{25}ClN_2S_2 \cdot HCl$	125	70	8	0	500	125	80	+++
22	5-I	8	MeCN	19	120–122	$C_{16}H_{25}IN_2S_2 \cdot HCl$	150	100	20	0	250	200[c]	53	+
23	3,5-Cl_2	10	EtOH	68	145–148	$C_{18}H_{28}Cl_2N_2S_2 \cdot HCl$	525	250[c]	0	0	>2000	1000[c]	0	0
24	5-Br	10	Me_2CO	51	102–107	$C_{18}H_{29}BrN_2S_2 \cdot 2HCl$	130	60	13	0	>600	400[c]	13	0
25	5-Cl	10	Me_2CO, Me_2CO–MeCN	26	103–106	$C_{18}H_{29}ClN_2S_2 \cdot 2HCl$[e]	135	45	7	0	>750	300	47	+
														
26	H	5	EtOH–Et_2O, EtOH	28	168–173	$C_{17}H_{22}N_2S_2 \cdot 2HCl$	160	80	80	+	>600	400	73	+
27	4-Me, 6-Cl	5	*i*-PrOH	22	215–217	$C_{18}H_{23}ClN_2S_2 \cdot 2HCl$	225	100	7	0				
28	4-Me	5	EtOH	24	215–218	$C_{18}H_{24}N_2S_2 \cdot 2HCl$	300	150	0	0				
29	H	6	MeCN, EtOH	22	98–110	$C_{18}H_{24}N_2S_2 \cdot 2HCl \cdot H_2O$[f]	175	60	47	+	900	500	13	0
30	4,6-Me_2	5	*i*-PrOH	12	209–213	$C_{19}H_{26}N_2S_2 \cdot 2HCl$	275	100	0	0	800	400	73	+

[a] All compounds were analyzed for C, H, N, and S. [b] The antiradiation data represent the lowest dose of drug for which a high rate of survival in the 30-day test was obtained. For each test (see ref 7), usually 15 mice were treated with drug and irradiated either 15 or 30 min later. The radiation dose was 950 rads (30–50 rads/min) of γ radiation from a Cobalt-60 source. Faster radiation doses are noted. Ratings are based on the following ranges of protective indices (footnote ‡ in the text): 0, 0–1; +, 2–5; ++, 6–10; +++, 11–14. [c] *Ca.* 200 rads/min, 975 rads total. [d] S: calcd, 14.41; found, 15.18. A high S analysis is attributed to the interference of free I_2 in the sample preparation. Additional analysis for Cl. [e] S: calcd, 14.38; found, 14.84. [f] Additional analysis for H_2O by nmr showed 1 molar equiv.

Table II. 3-[(Alkylthio)alkyl]thiazolidines (III)



							Antiradiation activity[b]							
							Intraperitoneal data				Peroral data			
No.	n_1	n_2	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	Survival, %	Rating
31	5	2	EtOAc	46	166–168	$C_{11}H_{23}NS_2 \cdot HCl$	250	62	33	+	>600	300	67	+
32	6	2	Me_2CO	34	167–170	$C_{12}H_{25}NS_2 \cdot HCl$	250	100	33	+	550	250	33	+
33	7	2	Me_2CO	36	166–170	$C_{13}H_{27}NS_2 \cdot HCl$	150	100	13	0	>600	400	53	+
34	8	2	Me_2CO	39	166–169	$C_{14}H_{29}NS_2 \cdot HCl$	250	100	7	0	>350	300	0	0
35	3	3	Me_2CO	11	134–137	$C_{10}H_{21}NS_2 \cdot HCl$	300	80	0	0	>600	300	7	0
36	5	3	Me_2CO	41	147–154	$C_{12}H_{25}NS_2 \cdot HCl$	120	75[c]	67	+	>300	200[c]	60	+
37	6	3	Me_2CO, EtOAc		149–156	$C_{13}H_{27}NS_2 \cdot HCl$	175	50	13	0	500	300	60	+
38	7	3	Me_2CO, EtOAc	5	158–162	$C_{14}H_{29}NS_2 \cdot HCl$	125	50	7	0	>600	400	80	+
39	8	3	Me_2CO, EtOAc	10	159–165	$C_{15}H_{31}NS_2 \cdot HCl$	250	100	47	+	>600	600	73	+
40	6	4	Me_2CO, EtOAc	17	161–165	$C_{14}H_{29}NS_2 \cdot HCl$	175	80	67	+	600	300	40	+
41	2	5	EtOAc	16	145–147	$C_{11}H_{23}NS_2 \cdot HCl$	300	75	0	0	>600	300	7	0
42	3	5	EtOAc	43	151–155	$C_{12}H_{25}NS_2 \cdot HCl$	160	60	73	+	900	500	40	+
43	4	5	EtOAc	24	160–163	$C_{13}H_{27}NS_2 \cdot HCl$	125	50	67	+	650	125, 63	92, 40	+++
44	5	5	Me_2CO	38	162–166	$C_{14}H_{29}NS_2 \cdot HCl$	75	30	73	+	500	125	87	++
45	6	5	EtOAc	55	161–166	$C_{15}H_{31}NS_2 \cdot HCl$	100	50	80	+	500	150	60	+
46	7	5	EtOAc	35	164–169	$C_{16}H_{33}NS_2 \cdot HCl$	120	60	33	+	>525	400	80	+
47	9	5	EtOAc, MeCN	43	171–174	$C_{18}H_{37}NS_2 \cdot HCl$	125	80	0	0	>900	300	0	0
48	1	6	Me_2CO	34	133–139	$C_{11}H_{23}NS_2 \cdot HCl$	300	100	0	0	>600	300	0	0
49	2	6	EtOAc	22	109–125	$C_{12}H_{25}NS_2 \cdot HCl$	160	75	13	0	>500	200	0	0
50	3	6	EtOAc	7	139–143	$C_{13}H_{29}NS_2 \cdot HCl$	>150	50	7	0	>300	300	33	0
51	4	6	EtOAc	39	159–161	$C_{14}H_{29}NS_2 \cdot HCl$	150	80, 40	60, 38	+	500	200, 100	67, 47	++
52	5	6	Me_2CO	27	158–162	$C_{15}H_{31}NS_2 \cdot HCl$[d]	125	60, 30	50, 47	++	175	90	53	+
53	6	6	Me_2CO, EtOAc	14	161–164	$C_{16}H_{33}NS_2 \cdot HCl$	130	50	13	0	> 1000	400	27	0
54	7	6	Me_2CO	33	159–164	$C_{17}H_{35}NS_2 \cdot HCl$	>200	100	0	0	650	300	13	0
55	8	6	Me_2CO, MeCN	11	166–169	$C_{18}H_{37}NS_2 \cdot HCl$	150	80	7	0	> 600	200	0	0
56	0	6	EtOAc–Me_2CO	12	116–121	$C_{10}H_{21}NS_2 \cdot HCl$	100	60	13	0	500	300	0	0
57	3	7	EtOAc	54	150–153	$C_{14}H_{29}NS_2 \cdot HCl$	175	80, 40	73, 46	++	650	300	67	+

[a]All compounds were analyzed for C, H, N, and S. [b]See footnote *b*, Table I. [c]*Ca.* 200 rads/min, 975 rads total. [d]S: calcd, 19.67; found, 19.12.

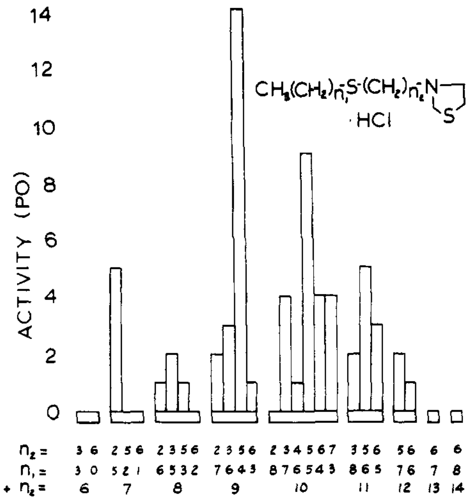


Figure 2. Effect of chain length on antiradiation activity (activity expressed as protective index‡) of 3-[(alkylthio)alkyl]thiazolidine hydrochlorides given perorally.

Table III. 3-Thiazolidinealkanol Hydrochlorides, $HO(CH_2)_n$-N(thiazolidine)·HCl (IV)

n	Yield, %	Mp, °C	Formula	Analyses
2	49	80–84	$C_5H_{11}NOS \cdot HCl$	C, H, N, S
3	55	92–94	$C_6H_{13}NOS \cdot HCl$	C, H, N, S
4	13	93–99	$C_7H_{15}NOS \cdot HCl$	C, H, N, S
5	50	96–98	$C_8H_{17}NOS \cdot HCl$	C, H, N, S
6	71	112–116	$C_9H_{19}NOS \cdot HCl$	C, H, N, S
7	50	101–105	$C_{10}H_{21}NOS \cdot HCl$	C, H, N, S
8	53	128–130	$C_{11}H_{23}NOS \cdot HCl$	C, H, N, S
10	32	140–143	$C_{13}H_{27}NOS \cdot HCl$	C, H, N, S

Table IV. 3-(Chloroalkyl)thiazolidine Hydrochlorides, $Cl(CH_2)_n$-N(thiazolidine)·HCl (V)

n	Recrystn solvents	Yield, %	Mp, °C	Formula	Analyses
2	THF	94	129–131	$C_5H_{10}ClNS \cdot HCl$	H, N, S; C[a]
3	*n*-BuOH	88	133–135	$C_6H_{12}ClNS \cdot HCl$	C, H, N, S
4	THF, Me_2CO	27	120–124	$C_7H_{14}ClNS \cdot HCl$	C, H, N, S
5	THF	89	133–135	$C_8H_{16}ClNS \cdot HCl$	C, H, N
6	THF	40	117–122	$C_9H_{18}ClNS \cdot HCl$	C, H, N, S
7	MeCN	35	132–134	$C_{10}H_{20}ClNS \cdot HCl$	C, H, N, S
8	EtOAc	50	130–132	$C_{11}H_{22}ClNS \cdot HCl$	C, H, N, S
10	Me_2CO	92	144–147	$C_{13}H_{26}ClNS \cdot HCl$	C, H, N, S

[a]C: calcd, 31.92; found, 31.42.

were highly effective when given by mouth. Generally these are more effective perorally than parenterally. Figure 2 illustrates the effect of variations in chain length on po antiradiation activity. A total of 10–12 carbons in the side chain is the optimum chain length. As can be seen from Figure 2, however, even within this range large differences in activity are evident with various combinations of n_1 and n_2. The best compound is 3-[5-(pentylthio)pentyl]thiazolidine·HCl (**43**). Given orally 30-min preirradiation at 125 mg/kg (0.2 LD_{50}), **43** afforded 92% survival of the mice in the 30-day test. At 63 mg/kg (0.1 LD_{50}) 40% survival was obtained in the same test. 3-[5-(Hexylthio)pentyl]thiazolidine·HCl (**44**) had similar activity.

Thiazolidine substituted in the 3 position with (5-halo-2-pyridyl)thioalkyl, (substituted-2-quinolyl)thioalkyl, and alkylthioalkyl groups resulted in effective antiradiation agents in mice. A 5-chloropyridyl thioether **19** and a (pentylthio)pentyl derivative **43** can be considered candidates for further study in the search for an antiradiation agent which is effective by the oral route.

Experimental Section§

3-Thiazolidinealkanol hydrochlorides IV (Table III) were prepared from 1-aziridinealkanols using the general procedure described[4] previously. Crude products were recrystallized from MeCN.

3-(5-Chloropentyl)thiazolidine Hydrochloride (V, *n* = 5) (General Procedure for V, Table IV). To a slurry of 30.5 g (0.14 mol) of IV (*n* = 5) in 500 ml of THF was added in one portion 20 g (0.17 mol) of $SOCl_2$. The stirred mixture was purged continuously with a rapid stream of N_2, gradually heated to 45°, and kept at that temperature for 2–4 hr. The mixture, with continued stirring, was chilled and filtered. The solid was washed (as a slurry) in cold THF, dried, and recrystallized to give V (*n* = 5) (Table IV). In some cases Et_2O was added to the cold mixture to effect precipitation.

Substituted 2(1*H*)-pyridinethiones and 2(1*H*)-quinolinethiones (general procedure[9]): 5-chloro-,[9] 5-bromo-,[9] and 5-iodo-2(1*H*)-pyridinethione;[9] 3,5-dibromo-2(1*H*)-pyridinethione, mp 155–159° (methyl cellosolve at 120° was substituted for propylene glycol used in the general procedure;[9] this solvent was preferable to propylene glycol in most cases); 3,5-dichloro-2(1*H*)-pyridinethione, mp 153–156° [*Anal.* ($C_5H_3Cl_2NS$) C, H, N, S]; 6-chloro-4-methyl-2(1*H*)-quinolinethione, mp 296–311° [*Anal.* ($C_{10}H_8ClNS$) C, H, N]; 4-methyl-2(1*H*)-quinolinethione, mp 258–262° [*Anal.* ($C_{10}H_9NS$) C, H, N]; 4,6-dimethyl-2(1*H*)-quinolinethione, mp 298–302°.

Alkylation of Thiols (Preparation of I–III, Tables I and II). A mixture of the substituted 2(1*H*)-pyridinethione, substituted 2(1*H*)-quinolinethione, or alkanethiol and 2 molar equiv of NaH in DMF was treated portionwise in the cold with 1 molar equiv of solid V. Mixtures containing the heterocycles were kept at 80–90° for 4–6 hr, whereas those involving alkanethiols were kept on a steam bath for 4–5 days. The diluted (Et_2O) mixtures were washed with H_2O, dried ($MgSO_4$), and treated with 1 equiv of dry HCl giving I and II after recrystallization. The free bases of the aliphatic analogs were distilled under high vacuum before conversion to HCl salts (III).

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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, analytical results obtained for these elements are within ±0.4% of the theoretical values.