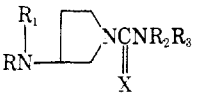
TABLE I

1-CARBAMOYL- AND 1-THIOCARBAMOYLPYRROLIDINES



No.	R	R_1	R_2	R_3	X	Prepn method[a]	% yield	Mp, °C	Purificn[b] solvent	Formula	Analyses
1	C_6H_5	H	H	H	O	2	57	133–135	W	$C_{11}H_{15}N_3O$	C, H, N
2	C_6H_5	CH_3	H	H	O	2	62	130–132	B–O	$C_{12}H_{17}N_3O$	C, H, N
3	C_6H_5	CH_3	CH_3	H	O	1	97	126–128	B–O	$C_{13}H_{19}N_3O$	C, H, N
4	C_6H_5	CH_3	C_2H_5	H	S	4	82	82–84	B–E	$C_{14}H_{21}N_3S$	C, H, N
5	C_6H_5	CH_3	*m*-C_4H_9	H	S	4	68	176–178	I	$C_{16}H_{26}ClN_3S$[d]	C, H, N
6	C_6H_5	H	C_2H_5	C_2H_5	O	3	84	102–104	O	$C_{15}H_{23}N_3O$	C, H, N
7	C_6H_5	CH_3	C_2H_5	C_2H_5	O	3	81	154–160	I–E	$C_{16}H_{27}Cl_2N_3O$[e]	C, H, N
8	C_6H_5	CH_3	C_6H_5	H	O	1	81	142–144	B–O	$C_{18}H_{21}N_3O$	C, H, N
9	C_6H_5	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	O	1	89	176–178	I–E	$C_{21}H_{28}ClN_3O_4$[d]	H, N; C[f]
10	C_6H_5	CH_3	*p*-$CH_3OC_6H_4$	H	O	1	69	107–109	B–O	$C_{19}H_{23}N_3O_2$	C, H, N
11	C_6H_5	CH_3	*m*-$CF_3C_6H_4$	H	S	4	54	137–138	M–W	$C_{19}H_{20}F_3N_3S$	C, H, N
12	C_2H_5	C_2H_5	*m*-ClC_6H_4	H	O	1	81	187–190	I	$C_{15}H_{23}Cl_2N_3O$[d]	C, H, N
13	C_2H_5	C_2H_5	*m*-$CF_3C_6H_4$	H	O	1	60	212–214	I	$C_{16}H_{23}ClF_3N_3O$[d]	C, H, N
14	C_6H_5	CH_3	C_6H_5	H	S	4	79	61–63	B–O	$C_{18}H_{21}N_3S$	N
15	C_6H_5	CH_3	*m*-$CF_3C_6H_4$	H	O	1	75	196–198	B–O	$C_{19}H_{21}ClF_3N_3O$[d]	C, H, N
16	C_6H_5	CH_3	C_6H_5	*m*-C_3H_7	O	3	33	132–135	I	$C_{21}H_{25}ClN_3O$[d]	C, H, N
17	C_2H_5	C_2H_5	C_6H_5	CH_3	O	3	59	162–164	I–E	$C_{16}H_{26}ClN_3O$	C, H, N
18	C_2H_5	C_2H_5	C_6H_5	C_6H_5	O	3	40	137–140	I	$C_{25}H_{31}N_3O_9$[e]	C, H, N
19	*o*-$CH_3OC_6H_4$	H	C_6H_5	C_6H_5	O	3	77	72–74	B–O	$C_{24}H_{25}N_3O_2$	C, H, N
20	C_6H_5	H	C_6H_5	C_6H_5	O	3	84	125–126	B–O	$C_{24}H_{23}N_3O$	C, H, N
21	C_6H_5	CH_3	C_6H_5	C_6H_5	O	3	85	124–126	B–O	$C_{25}H_{23}N_3O$	C, H, N

[a] See Experimental Section. [b] B = C_6H_6, E = *i*-Pr_2O, I = *i*-PrOH, M = MeOH, W = H_2O, O = isooctane. [c] Dihydrochloride. [d] Hydrochloride. [e] Dioxalate. [f] C: calcd, 59.78; found, 59.16.

To a stirred solution of 0.1 mole of the 3-aminopyrrolidine in 100 ml of dry C_6H_6 at room temperature was added slowly 0.1 mole of the alkyl or aryl isocyanate in 20 ml of dry C_6H_6. After the addition was complete, the mixture was stirred for several minutes and the solvent was evaporated at reduced pressure. Crude products were purified by recrystallization.

Procedure 2. By Reaction of 3-Aminopyrrolidine and Potassium Cyanate.—A solution of 0.03 mole of 3-substituted aminopyrrolidine in 31 ml of 1 *N* HCl was treated all at once with 0.03 mole of KNCO in 5 ml of H_2O. The mixture was stirred for 4–16 hr at room temperature, then the resulting precipitate was separated by filtration, washed (H_2O), and purified by recrystallization.

Procedure 3. By Reaction of 3-Aminopyrrolidine and Substituted Carbamoyl Chlorides.—A solution of 0.045 mole of the 3-substituted aminopyrrolidine in 50 ml of $CHCl_3$ was added to a solution of 10 g of K_2CO_3 in 50 ml of H_2O. The stirred mixture was then treated dropwise with 0.045 mole of the substituted carbamoyl chloride in 50 ml of $CHCl_3$ and stirring was continued for 1–16 hr. The $CHCl_3$ layer was separated and dried ($MgSO_4$) and the solvent was evaporated. The crude product was purified by recrystallization.

3-Amino-1-thiocarbamoylpyrrolidines. Procedure 4. By Reaction of Alkyl or Aryl Isothiocyanate and 3-Substituted Aminopyrrolidine.—The general procedure was essentially the same as procedure 1 except in some cases the reactants were stirred at room temperature for 2–16 hr or heated at reflux for several hours.

1-Benzyl-3-diethylaminopyrrolidine Difumarate.—A mixture of Et_2NH (250 g) and 170 g (0.61 mole) of 1-benzyl-3-pyrrolidinol benzenesulfonate ester was placed in a bomb and heated at 100° for 16 hr. After the excess amine was evaporated, the residue was treated with 200 ml of 6 *N* HCl and extracted (Et_2O). The acidic layer was made basic and then extracted (Et_2O). The combined extracts were washed (H_2O) and dried ($MgSO_4$) and the solvent evaporated. The residual oil was distilled at reduced pressure and the fraction boiling at 88–90° (0.10 mm) was collected. The nonviscous oil weighed 87.5 g (62% yield).

A portion of the free base (11.7 g, 0.05 mole) was added to a solution of 11.6 g (0.01 mole) of fumaric acid in warm *i*-PrOH. The salt which separated on cooling was recrystallized from *i*-PrOH–EtOH. The white product melted at 159.5–162° and weighed 13.6 g. *Anal.* ($C_{23}H_{32}N_2O_8$) C, H, N.

3-Diethylaminopyrrolidine Dihydrochloride.—A solution of 72 g (0.31 mole) of 1-benzyl-3-diethylaminopyrrolidine, 150 ml of absolute EtOH and 50 ml of 12 *N* HCl was shaken with 8 g of Pd–C catalyst at about 70° until 1 equiv of H_2 was absorbed. After cooling, the suspension was filtered and the solvent was evaporated at reduced pressure. The residual oil was made basic with 50% NaOH and the resulting suspension was filtered. The organic layer was separated, dried (NaOH pellets), and distilled at reduced pressure. The fraction boiling at 82–84° (12 mm) was collected. The water white, nonviscous oil weighed 21.2 g (49% yield). A portion of the free base was converted to the hydrochloride and recrystallized (*i*-PrOH). The white product melted at 181.5–183.5°. *Anal.* ($C_8H_{20}Cl_2N_2$) C, H, N.

S-2-Aminoethyl S′-ω-Carboxyalkyl Dithiocarbonate Hydrochlorides as Potential Antiradiation Agents[1]

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The synthesis of S-2-aminoalkyl S′-ω-carboxyalkyl dithiocarbonate hydrochlorides (V) was undertaken as an extension of previous modifications of the radioprotective agent 2-aminoethanethiol in which the mercapto group is combined in dithiocarbonate esters.[2] Two of the previously prepared dithiocarbonates (I and II)[2a] afforded "fair" protection to mice exposed

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2028.

(2) (a) T. P. Johnston and A. Gallagher, *J. Org. Chem.*, **29**, 2442 (1964); (b) T. P. Johnston and C. R. Stringfellow, Jr., *J. Med. Chem.*, **9**, 921 (1966).

$H_2NCH_2CH_2SCOSCH_2CH_2NH_2 \cdot 2HBr$
I

$CH_2(CH_2SCOSCH_2CH_2NH_2)_2 \cdot 2HCl$
II

to radiation that was lethal to unprotected mice[3] (see Table I), whereas two aminoethyl sulfoalkyl dithiocarbonates[2b] were inactive.

TABLE I

RADIOPROTECTIVE ACTIVITIES OF SELECTED S-2-AMINOETHYL DITHIOCARBONATES[a]

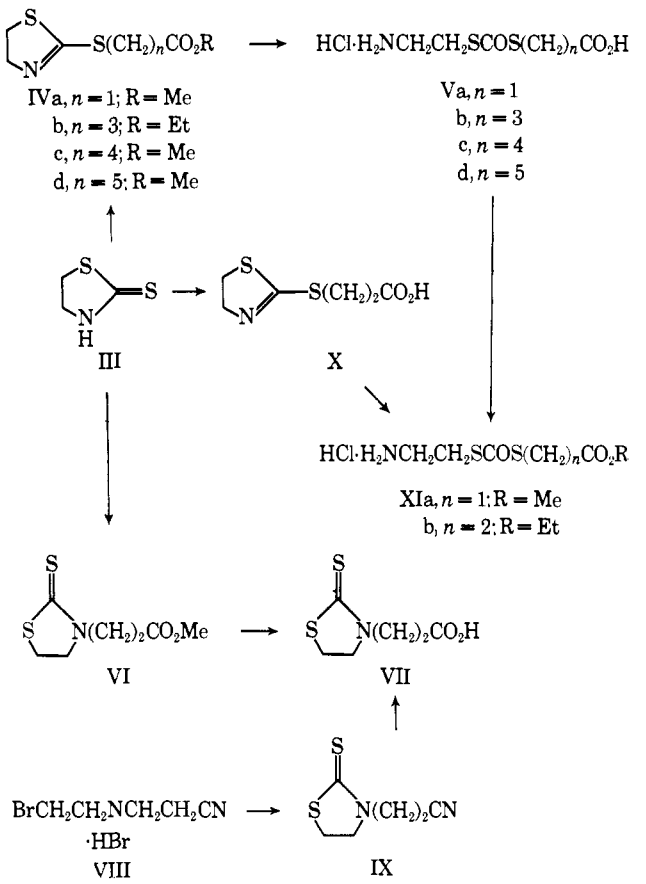
Compd	Approx LD_{50}, mg/kg	Drug dose, mg/kg[b]	Vehicle of admin	30-day survival, %[c]
I	425	300	Saline[d]	40
		150	Saline	7
II	>150	90	Saline	40
		45	Saline	0
Vb	1300	1000	CMC-Tw[e]	67
		500	CMC-Tw	33
Vc	560	320	CMC-Tw	0
Vd	1000	560	CMC-Tw	33
		280	CMC-Tw	0
A[f]	300	200	Saline	20
B[g]	500	300		20
		150		10

[a] Antiradiation screening tests in mice against lethal radiation (800-825R, X-rays) were performed at Walter Reed Army Institute of Research, Washington, D. C., under the direction of Dr. D. P. Jacobus. [b] Administered intraperitoneally 15 min before irradiation as a solution or suspension ranging from 0.9% for the most toxic compound to 5% for the least toxic (pH 5–7). [c] No survival among control mice. [d] Physiological saline. [e] Compound suspended in physiological saline containing 0.3% sodium carboxymethylcellulose and 0.1% Tween 80. [f] $CH_3SCOSCH_2CH_2NH_2 \cdot HCl$.[4] [g] $C_6H_5CH_2SCOSCH_2CH_2NH_2 \cdot HCl$.[4]

The general approach to the preparation of the title compounds (see Scheme I) was based, as were the examples of S-2-aminoethyl dithiocarbonates already mentioned, on the dithiocarbonate synthesis developed by Crawhall and Elliott[4] and involved concurrent hydrolytic ring cleavage and ester hydrolysis of the alkyl ω-(2-thiazolin-2-ylthio)alkanoates (IV). The required intermediate esters were prepared by the alkylation of 2-thiazolidinethione (III) with the corresponding alkyl ω-bromoalkanoates in DMF with K_2CO_3 as acid acceptor, but the alkylation of III with methyl 3-bromopropionate under the same conditions gave anomalous results: ir transparency at ~1565 cm^{-1} (C=N) indicated that the product was methyl 2-thioxo-3-thiazolidinepropionate (VI), acid hydrolysis of which gave 2-thioxo-3-thiazolidinepropionic acid (VII) without ring cleavage. The assigned structure was confirmed by an umambiguous synthesis of VII consisting of a base-promoted CS_2 ring closure of 3-(2-bromoethylamino)propionitrile hydrobromide (VIII) and subsequent acid hydrolysis of the resultant crude 2-thioxo-3-thiazolidinepropionitrile (IX). The reported[5] synthesis of VII *via* the cyanoethylation of III with acrylonitrile suggests that the anomalous alkylation with methyl 3-bromopropionate was a result of the intermediate formation of methyl acrylate.

3-(2-Thiazolin-2-ylthio)propionic acid (X), a suitable

SCHEME I



intermediate for the preparation of the corresponding dithiocarbonate, was obtained in crude form by the reported action of propiolactone on III in alkaline solution.[5,6] Recrystallization (EtOH) of the crude product from the acid hydrolysis of X, however, produced the pure ethyl ester, S-2-aminoethyl S′-2-(ethoxycarbonyl)ethyl dithiocarbonate hydrochloride (XIb). The acid hydrolysis of methyl (2-thiazolin-2-ylthio)-acetate (IVa) also failed to give a product isolable in pure form, but esterification with MeOH enabled the isolation of the methyl ester XIa, although in minute yield. Variations of the procedure leading to XIa, including esterification with EtOH neither improved the yield nor gave a pure product.

Among the dithiocarbonates tested thus far, only S-2-aminoethyl S′-3-carboxypropyl dithiocarbonate hydrochloride (Vb) has shown "good" radioprotection of mice.[3] A comparison of the antiradiation activity of Vb with other selected dithiocarbonates is given in Table I; Vb is apparently the least toxic dithiocarbonate listed and hence can be administered at a relatively higher nontoxic dose.

Experimental Section[7]

Alkyl ω-(2-Thiazolin-2-ylthio)alkanoates (IV).—A mixture of equimolar amounts (~0.15 mole) of III and K_2CO_3 was stirred in DMF (~90 ml) for ~20 min and then treated dropwise with a solution of an equimolar amount of the appropriate alkyl ω-bromo-

(3) "Fair" denotes 26–44% survival and "good" >45% survival of mice in standard antiradiation screening tests (see Table I).

(4) J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952).

(5) R. J. Gaul, W. J. Fremuth, and M. N. O'Connor, *J. Org. Chem.*, **26**, 5106 (1961).

(6) J. E. Jansen and R. A. Mathes, U. S. Patent 2,483,416 (1949); *Chem. Abstr.*, **44**, 1544 (1950).

(7) Melting points were determined with a Mel-Temp apparatus. Infrared spectra were determined in pressed KBr disks (solids) or films (oils) with a Perkin-Elmer 521 spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.4% of the theoretical values.

TABLE II

ALKYL ω-(2-THIAZOLIN-2-YLTHIO)ALKANOATES (IV)

Compd	Yield, %	Bp, °C (mm)	$n^{25}D$	$\bar{\nu}$ (C=N),[a] cm^{-1}	Formula	Analyses
IVa	23	122–126 (0.4)	1.5613[27]	1570	$C_6H_9NO_2S_2$	C, H, N, S
IVb	76	122–128 (0.05)	1.5553[24]	1565	$C_7H_{11}NO_2S_2$	C, H, S
IVc	55	137–143 (0.4)	1.5400[24]	1570	$C_8H_{13}NO_2S_2$	C, H, N, S
IVd	29	133–137 (0.2)	1.5350[26]	1565	$C_{10}H_{17}NO_2S_2$	C, H, N, S

[a] Strong absorption.

TABLE III

S-2-AMINOETHYL S′-ω-CARBOXYALKYL DITHIOCARBONATE HYDROCHLORIDES (V)

Compd	Yield, %	Mp, °C	$\bar{\nu}$, cm^{-1} C=O[a] CO_2H	C=O[a] SCOS	SCS[a]	Formula	Analyses
Vb	31	167–169	1710	1640	870	$C_7H_{13}NO_3S_2 \cdot HCl$	C, H, N, S, Cl
Vc[b]	19	142–144	1715	1645	870	$C_8H_{15}NO_3S_2 \cdot HCl$	C, H, N, S, Cl
Vd	18	132–135	1715	1645	860	$C_9H_{17}NO_3S_2 \cdot HCl$	C, H, N, S

[a] Strong absorption; *cf.* ref 2a. [b] Recrystallized from 6 *N* HCl.

alkanoate in DMF (1 ml/g of ester) at such a rate that the reaction temperature did not rise above 50°. The resulting mixture was stirred for 1–4 hr and filtered to remove inorganic salts; DMF was removed from the filtrate under reduced pressure (water aspirator) at 70–75° (hot-water bath). The residual, crude, oily products were sufficiently pure for use as intermediates in the preparation of the corresponding dithiocarbonates, but successive vacuum distillations (short path) were required in order to obtain analytically pure samples as colorless oils (see Table II).

S-2-Aminoethyl S′-ω-Carboxyalkyl Dithiocarbonate Hydrochlorides (V).—Mixtures of IVb–d (~0.1 mole) and 6 *N* HCl (2.5 ml/g of IV) were refluxed for 4 hr. The resulting solutions, while still hot, were clarified by filtration and chilled. The dithiocarbonate hydrochlorides (see Table III) were collected as white crystals, washed (cold EtOH), and dried (P_2O_5) *in vacuo*.

Methyl 2-Thioxo-3-thiazolidinepropionate (VI).—A solution of methyl 3-bromopropionate (42.9 g, 0.257 mole) in DMF (50 ml) was added dropwise to a stirred mixture of III (30.0 g, 0.252 mole), K_2CO_3 (38.5 g, 0.252 mole), and DMF (150 ml), the rate of addition being controlled so that the reaction temperature did not exceed 50°. After the exothermic reaction the mixture was stirred at room temperature for 4 hr and then filtered. *In vacuo* concentration of the filtrate left a residual yellow oil, which was purified by vacuum distillation; the yield of VI as a colorless oil, bp 180–188° (0.07 mm), was 26.1 g (42%). *Anal.* ($C_7H_{11}NO_2S_2$) C, H, S.

2-Thioxo-3-thiazolidinepropionic Acid (VII). A. From VI.—A mixture of VI (26.1 g, 0.127 mole) and 6 *N* HCl (600 ml) was refluxed for 4 hr. The resulting solution, filtered hot and then chilled, deposited VII as white crystals, which were dried (P_2O_5) *in vacuo;* yield 6.73 g (22%), mp 99–101°. *Anal.* ($C_6H_9NO_2S_2$) C, H, N, S.

B. From VIII.—K_2CO_3 (4.86 g, 34.1 mmoles) was added in portions to a stirred solution of VIII (4.00 g, 15.5 mmoles), CS_2 (4.0 ml, 66 mmoles), and DMF (30 ml), the reaction temperature being kept below 35° by intermittent use of an ice–water bath. The mixture was stirred overnight at room temperature, then poured into H_2O (100 ml), and extracted with three 75-ml portions of Et_2O. The Et_2O phase, washed with H_2O and dried ($MgSO_4$), was concentrated under reduced pressure, leaving crude 2-thioxo-3-thiazolidinepropionitrile (IX) as a yellow oil. A solution of the oil in 6 *N* HCl (10 ml) was refluxed for 4 hr, filtered hot, and chilled. The off-white, crystalline VII that precipitated was collected, washed (cold EtOH), and dried (P_2O_5) *in vacuo;* yield 0.42 g (14%), mp 105–107°, mmp 103–106°, with product from A, lit.[5] mp 103.3–104.6°. *Anal.* ($C_6H_9NO_2S_2$) C, H.

3-(2-Bromoethylamino)propionitrile Hydrobromide (VIII).—1-Aziridinepropionitrile[8] (19.2 g, 0.200 mole) was added dropwise to cold (−5 to 0°) 48% HBr (50 ml) with vigorous stirring. The solution was evaporated to dryness under reduced pressure, and the crystalline residue was reprecipitated from MeOH by the addition of Et_2O; yield 49.0 g (95%), mp 96–98°. *Anal.* ($C_5H_9BrN_2 \cdot HBr$) C, H, Br.

S-2-Aminoethyl S′-(Methoxycarbonyl)methyl Dithiocarbonate Hydrochloride (XIa).—A solution of IVa (2.00 g, 10.5 mmoles) in 6 *N* HCl (20 ml) was refluxed for 6 hr and then evaporated to dryness *in vacuo*. A solution of the residue in MeOH (20 ml) was refluxed for 2 hr, treated with Norit, and filtered. The filtrate was concentrated *in vacuo* to a viscous oil, which crystallized. Recrystallization (MeOH–Et_2O) afforded 0.47 g (17%) of XIa: mp 134–137° dec with presoftening; $\bar{\nu}$ (in cm^{-1}) 1730 (s, C=O of CO_2Me), 1640 (s, C=O of SCOS), and 870 (s, SCS). *Anal.* ($C_6H_{11}NO_3S_2 \cdot HCl$) C, H, N, Cl.

S-2-Aminoethyl S′-2-(Ethoxycarbonyl)ethyl Dithiocarbonate Hydrochloride (XIb).—A mixture of crude 3-(2-thiazolin-2-ylthio)propionic acid[5] (mp 62–65°, lit.[5] mp 76.6–77.5°; 10.0 g, 48.7 mmoles) and 6 *N* HCl (100 ml) was refluxed for 6 hr; and the resulting solution was concentrated under reduced pressure to an oil, which crystallized on standing. A solution of the crude solid (S-2-aminoethyl S′-2-carboxyethyl dithiocarbonate hydrochloride) in boiling EtOH (50 ml), cooled and diluted with Et_2O (100 ml), deposited 5.09 g (38%) of XIb as sparkling, white crystals: mp 111–112°; $\bar{\nu}$ (in cm^{-1}) 1725 (s, C=O of CO_2Et), 1645 (s, C=O of SCOS), and 870 (s, SCS). *Anal.* ($C_8H_{15}NO_3S_2 \cdot HCl$) C, H, N, S, Cl.

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(8) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).

Synthesis and Antifertility Activity of 4- and 5-(ω-Arylalkyl)oxazolidinethiones

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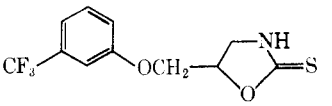
The substituted oxazolidinethione **1** has been shown previously to be an effective antifertility agent in the rat.[1] The relatively low potency of that compound led us to prepare additional analogs. The unexpected finding that the phenolic oxygen could be replaced by a



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