APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 10, 113–123 (1996)

New Germaheterocycles, Germadithioacetals and a Germylated Oxide and Sulfide Derived from Cysteamine, Methylcysteamine and *N*-Substituted Cysteamine: Synthesis and Radioprotective Activity

G. Rima,* J. Satgé,* H. Sentenac-Roumanou,† M. Fatome,‡ J. D. Laval,‡ C. Lion§ and R. Dagiral*

* Laboratoire de Chimie des Organominéraux, URA 477 du CNRS, Université Paul Sabatier, 118 Route de Narbonne, 31062 Toulouse Cedex, France, † Direction des Recherches, Etudes et Techniques, 26 bd Victor, 00460 Armées, France, ‡ Division de Radiobiologie et Radioprotection, Centre de Recherches du Service de Santé des Armées, 24 avenue des Maquis du Grésivaudan, 38702 La Tronche Cedex, France, and § Institut de Topologie et de Dynamique des Systèmes de l'Université de Paris VII, Associé au CNRS, 1 rue Guy de la Brosse, 75005 Paris, France

Further to our work concerning organometallic compounds active in chemical radioprotection, we report the synthesis and pharmacological study (radioprotective activity, toxicity) of new germathiazolidines and germadithioacetals derived from cysteamine, methylcysteamine and *N*-substituted cysteamine. A germylated oxide and sulfide with methylcysteamine hydrochloride as ligand were also investigated.

A notable decrease in the toxicity and a fairly large increase in the radioprotective activity of these new organogermylated compounds were observed compared with cysteamine, methylcysteamine and *N*-substituted cysteamine.

Keywords: germathiazolidines; germadithioacetals; germylated oxide; germylated sulfide; *N*-substituted cysteamine; toxicity; radioprotective activity

INTRODUCTION

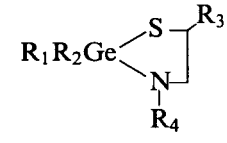
During a research program in the field of the pharmacological activity of organogermanium compounds, several derivatives were chemically synthesized and tested for their radioprotection properties. The great majority of these compounds were metalla-thiazolidines and -dithioacetals of *N*-substituted cysteamine, methylcysteamine, *N*-(2-thioethyl)-1,3-diaminopropane and naphthylmethylimidazoline. Seventy compounds of these derivatives have a dose reduction factor (DRF) between 1.4 and 1.75.[1–8]

In Fig. 1 we cite some compounds synthesized in our laboratory by way of example:

We have broadened our research program and completed our study on the germathiazolidines and germadithioacetals series. Various organogermanium compounds of these types with different substituents on germanium and nitrogen have been prepared and tested.

In this work we present the study of the synthesis, toxicity and radioprotective activity of some new germathiazolidines and germadithioacetals, and a germylated oxide and sulfide, as listed below.

(a) *Germathiazolidines*

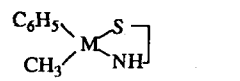


$R_1 = R_2 = i\text{-}C_5H_{11}$, $R_3 = H$,
$R_4 = (CH_2)_3NHCH_2CH = CH_2$ **1**

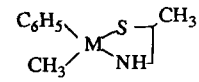
$R_1 = p\text{-}CH_3 - C_6H_4$, $R_2 = CH_3$, $R_3 = H$,
$R_4 = (CH_2)_3NHCH_2CH = CH_2$ **2**

CCC 0268–2605/96/020113–11

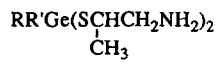
Received 14 April 1995
Accepted 7 July 1995



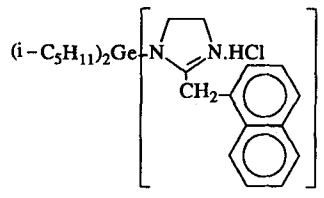
M = Si, DRF = 1.6
M = Ge, DRF = 1.6



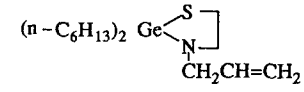
M = Si, DRF = 1.5
M = Ge, DRF = 1.75



R, R' = i-C_5H_{11}, DRF > 1.6
R = CH_3, R' = C_6H_5, DRF > 1.5



DRF= 1.5



DRF = 1.4

Figure 1 Some germanium- and silicon-containing heterocycles and their dose reduction factors (DRF)

$R_1 = R_2 =$ i-C_5H_{11}, $R_3 = H$,
$R_4 = (CH_2)_3$N **3**

$R_1 = R_2 =$ n-C_6H_{13}, $R_3 = H$,
$R_4 = (CH_2)_3$N  **4**

$R_1 = R_2 =$ n-C_6H_{13}, $R_3 = CH_3$, $R_4 = H$ **5**

$R_1 = R_2 =$  , $R_3 = R_4 = H$ **6**

$R_1 = R_2 =$  , $R_3 = CH_3$, $R_4 = H$ **7**

$R_1 = R_2 = SCH(CH_3)CH_2NH_2.HCl$,
$R_3 = H$, $R_4 = (CH_2)_3$N  **8**

$R_1 = R_2 = SCH_2CH_2NH_2.HCl$,
$R_3 = H$, $R_4 = (CH_2)_3$N  **9**

(b) *Germadithioacetals*

$$R_1R_2Ge[SCH(R_3)CH_2NHR_4]_2$$

$R_1 = p$-$CH_3C_6H_4$, $R_2 = CH_3$, $R_3 = H$,
$R_4 = (CH_2)_3NHCH_2CH = CH_2$ **10**

$R_1 = R_2 =$ i-C_5H_{11}, $R_3 = H$,
$R_4 = (CH_2)_3$N  **11**

$R_1 = R_2 =$ n-C_6H_{13}, $R_3 = H$,
$R_4 = (CH_2)_3$N  **12**

$R_1 = R_2 =$ n-C_6H_{13}, $R_3 = CH_3$, $R_4 = H$ **13**

$R_1 = R_2 =$  , $R_3 = R_4 = H$ **14**

$R_1 = R_2 =$  , $R_3 = CH_3$, $R_4 = H$ **15**

$R_1 = R_2 = SCH(CH_3)CH_2NH_2.HCl$, $R_3 = H$
$R_4 = (CH_2)_3$N  **16**

$R_1 = R_2 = SCH_2CH_2NH_2.HCl$, $R_3 = H$,
$R_4 = (CH_2)_3$N  **17**

(c) *Germylated oxide and sulfide (i.e. a germoxane and a germathiane)*

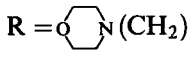
$$([HCl.H_2NCH_2CH(CH_3)S]_2GeX)_3$$

X=O **18**

X=S **19**

(d) N-*Substituted cysteamine*

$$R - NHCH_2CH_2SH$$

R =  **20**

$R = CH_2 = CHCH_2NH(CH_2)_3$ **21**

EXPERIMENTAL

General methods

All the syntheses were performed under nitrogen or argon. Solvents were freshly distilled from sodium/benzophenone before use. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. ^1H NMR spectra were recorded on a Brüker AC-80 spectrometer. Mass spectra, under electron impact (EI) conditions at 70 eV, were recorded on a Hewlett–Packard 5989 spectrometer. Elemental analyses (C, H, N) were performed at the Laboratoire de Microanalyses de l'Ecole Nationale Supérieure de Chimie de Toulouse.

Syntheses of germathiazolidines

Germathiazolidines were prepared by two methods: A and B.

Synthesis of compound 1 (method A)
To a solution of di(isoamyl)dichlorogermane (4 g, 14 mmol) in 50 ml of tetrahydrofuran (THF) were added freshly distilled *N*-substituted cysteamine (0.44 g, 14 mmol) and triethylamine (3.03 g, 30 mmol). The mixture was refluxed for 4 h with stirring. After the mixture had cooled to room temperature it was filtered under argon and the filtrate concentrated *in vacuo*.

Synthesis of compound 2 (method B)
Bis(diethylamino)di-isoamylgermane (2 g, 5.6 mmol) was dissolved in 50 ml of THF and *N*-substituted cysteamine (0.975 g, 5.6 mmol) was added from a syringe. The solution was refluxed under an argon atmosphere for 3 h with stirring, and concentrated *in vacuo*.

Syntheses of germadithioacetals

These compounds were also synthesized by two methods: C and D.

Synthesis of compound 12 (method C)
To a stirred mixture of *N*-substituted cysteamine (2.88 g, 14.1 mmol), triethylamine (1.6 g, 15.84 mmol) and 70 ml of THF, a solution of dichlorodihexylgermane (2.21 g, 7.05 mmol) in 40 ml of THF was added slowly. The reaction mixture was refluxed for 8 h, filtered at ambient temperature under argon, and concentrated *in vacuo*.

Synthesis of compound 13 (method D)
To a solution of methylcysteamine (0.945 g, 10.38 mmol) in 50 ml of THF was added dropwise with a stirring bis(diethylamino)dihexylgermane (2 g, 5.19 mmol) in 50 ml of anhydrous THF. The mixture was refluxed for 4 h. Removal of the solvent and work-up was as before.

Physicochemical data of derivatives **1–17** synthesized in this paper are reported in Table 1.

Synthesis of dichlorobis(2-thienyl)germane

A solution of 1.6 M BuLi (10.25 g, 0.16 mmol) in hexane was added dropwise to a solution of thiophene (13.44 g, 0.16 mmol) in 200 ml ether prepared according to Ref. 9. The mixture was added dropwise with stirring to a solution of tetrachlorogermane (17.15 g, 80 mmol) in ether (300 ml) cooled to −78 °C. The reaction mixture was allowed to stand overnight and was filtered at ambient temperature, then concentrated, and the residue was redissolved in pentane (100 ml) and filtered again. The solvent was removed by evaporation under reduced pressure. The residue was distilled through a 30 cm vacuum-jacketed vigreux column. A fraction of b.p. 115–120 °C/0.05 mm Hg (6.92 g, 28% yield) was obtained.

^1H NMR (δ in $CDCL_3$, ppm): 7.28 (d of d, 2H, J=3.5 and 4.7 Hz), 7.54 (d of d, 2H, J=1 and 3.5 Hz), 7.79 (d of d, 2H, J=*1* and 4.7 Hz).
Mass spectrum (GC/MS): m/z=310 [M^+·].

Synthesis of compound 18

To a refluxing solution of $(HCl.H_2NCH_2CH(CH_3)S)_2GeCl_2^4$ (5 g, 12.6 mmol) in 150 ml of freshly distilled pyridine was added dropwise with stirring a solution of NaSH (1.41 g,

Table 1 Physicochemical data of some germathiazolidines and germadithioacetals

Compound	Method of synthesis	Yield (%)	Properties
1	A	55	^{1}H NMR (δ in $CDCL_3$, ppm): 0.9–1.7 (m, 24H), 2.48–2.93 (m, 8H), 3.12 (m, 2H), 5.16
	B	80	(m, 2H), 5.86 (m, 1H). Analysis: Calcd: C, 55.87; H, 9.83; N, 7.24. Found: C, 55.65; H, 9.81; N, 7.17%.
2	A	60	^{1}H NMR (δ in $CDCl_3$, ppm): 0.87 (s, 3H), 1.26 (m, 4H), 2.30 (s, 3H), 2.5 (m, 8H), 3.19
	B	82	(m, 2H), 5.10 (m, 2H), 5.88 (m, 1H). Analysis: Calcd: C, 54.76; H, 7.42; N, 7.98. Found: C, 54.37; H, 7.09; N, 7.57%.
3	A	79	^{1}H NMR (δ in $CDCl_3$, ppm): 0.84–1.82 (m, 24H), 2.38 (m, 6H), 2.93 (m, 6H), 3.66 (m, 4H).
	B	89	Mass spectrum (EI): $m/z = 419$ [$M^+ + 1$]. Analysis: Calcd: C, 54.73; H, 9.60; N, 6.72. Found: C, 54.38; H, 9.43; N, 6.57%.
4	A	65	^{1}H NMR (δ in $CDCL_3$, ppm): 1.21 (m, 26, H), 1.57 (q, 2H, $J = 6.4$ Hz); 2.3 (m, 6H), 2.68
	B	88	(m, 6H), 3.58 (m, 4H). Analysis: Calcd: C, 56.68; H, 9.90; N, 6.30. Found: 56.48; H, 9.84; N, 6.17%.
5	A	70	^{1}H NMR (δ in $CDCl_3$, ppm): 0.87–1.31 (m, 29H), 2.31–2.97 (m, 3H). Mass spectrum (EI):
	B	83	$m/z = 433$ [M^+]. Analysis: Calcd: C, 54.28; H, 9.95; N, 4.22. Found: C, 54.15; H, 9.87; N, 4.12%.
6	A	89	^{1}H NMR (δ in $CDCl_3$, ppm): 2.65–2.73 (m, 4H), 7.25 (d of d, 2H, $J = 3.4$ and 4.7 Hz), 7.49 (d of d, 2H, $J = 1$ and 3.4 Hz), 7.69 (d of d, 2H, $J = 1$ and 4.7 Hz). Mass spectrum (EI): $m/z = 315$ [M^+].
7	A	86	^{1}H NMR (δ in $CDCl_3$, ppm): 1.17 (d, 3H, $J = 6.2$ Hz), 2.5–3.17 (m, 3H), 7.39 (d of d, 2H, $J = 3.45$ and 4.72 Hz), 7.64 (d of d, 2H, $J = 1$ and 3.45 Hz), 7.84 (d of d, 2H, $J = 1$ and 4.72 Hz). Mass spectrum (EI): 329 [M^+]. Analysis: Calcd: C, 40.66; H, 3.97; N, 4.27. Found: C, 40.37; H, 3.86; N, 4.15%.
8	A	51	^{1}H NMR (δ in D_2O, ppm): 1.39 (d, 6H, $J = 6.6$ Hz), 2.14 (q, 2H, $J = 6.6$ Hz), 2.9–3.75 (m, 18H), 3.93 (m, 4H). Mass spectrum (EI): $m/z = 366$ [$M^+ - 90$]. Analysis: Calcd: C, 34.12; H, 6.82; N, 10.61. Found: C, 33.82; H, 6.49; N, 10.27%.
9	A	60	^{1}H NMR (δ in D_2O, ppm): 1.95 (q, 2H, $J = 6.23$ Hz), 2.56–3.34 (m, 16H), 3.80 (m, 4H). Analysis: Calcd: C, 31.19; H, 6.40; N, 11.20. Found: C, 30.88; H, 6.37; N, 10.93%.
10	C	64	^{1}H NMR (δ in $CDCl_3$): 0.89 (s, 3H), 1.22 (q, 4H, $J = 6.5$ Hz), 2.18 (s, 3H), 2.47 (m, 16H), 3.14 (m, 4H), 5.20 (m, 4H), 5.82 (m, 2H), 7.33 (m, 4H). Analysis: Calcd: C, 54.90; H, 8.40; N, 10.67. Found: C, 54.68; H, 8.36; N, 10.55%.
11	D	80	^{1}H NMR (δ in $CDCl_3$, ppm): 0.77–1.38 (m, 22H), 1.69 (q, 4H, $J = 6.7$ Hz), 2.35 (m, 12H), 2.80 (m, 12H), 3.62 (m, 8H). Mass spectrum (EI): $m/z = 551$ [$M^+ - 71$]. Analysis: Calcd: C, 54.06; H, 9.65; N, 9.01. Found: C, 54.47; H, 10.17; N, 9.25%.
12	C	87	^{1}H NMR (δ in $CDCl_3$, ppm): 1.22 (m, 26H), 1.57 (q, 4H, $J = 6.4$ Hz), 2.33 (m, 12H), 2.57 (m, 12H), 3.60 (m, 8H). Mass spectrum (EI): $m/z = 533$ [$M^+ - 117$]. Analysis: Calcd: C, 55.42: H, 9.85; N, 8.62. Found: C, 55.21; H, 9.73; N, 8.57%.
13	D	65	^{1}H NMR (δ in $CDCl_3$, ppm): 0.84–1.24 (m, 32H), 2.6–3.06 (m, 6H). Mass spectrum (EI): $m/z = 433$ [$M^+ - 91$]. Analysis: Calcd: C, 51.11; H, 9.94; N, 6.63. Found: C, 51.07; H, 9.74; N, 6.38%.
14	D	52	^{1}H NMR (δ IN $CDCl_3$, ppm): 1.38 (s, 4H), 2.6–2.82 (m, 8H), 7.24 (d of d, 2H, $J = 3.4$ and 4.7 Hz), 7.49 (d of d, 2H, $J = 1$ and 3.4 Hz), 7.70 (d of d, 2H, $J = 1$ and 4.7 Hz). Mass spectrum (EI): $m/z = 358$ [$M^+ - 34$]. Analysis: Calcd: C, 36.86; H, 4.61; N, 7.17. Found: C, 37.09; H, 4.67; N, 7.12%.
15	D	71	^{1}H NMR (δ in $CDCl_3$, ppm): 1.04 (d, 6H, $J = 6$ Hz), 1.41 (s, 4H), 2.50–3.22 (m, 6H), 7.24 (d of d, 2H, $J = 3.4$ and 4.7 Hz), 7.50 (d of d, 2H, $J = 1$ and 3.4 Hz), 7.70 (d of d, 2H, $J = 1$ and 4.7 Hz). Analysis: Calcd: C, 40.13; H, 5.25; N, 6.70. Found: C, 39.91; H, 5.19; N, 6.57%.
16	C	60	^{1}H NMR (δ in D_2O, ppm): 1.39 (d, 6H, $J = 6.6$ Hz), 2.18 (q, 4H, $J = 6$ Hz), 2.84–3.72 (m, 30H), 4.00 (m, 8H). Analysis: Calcd: C, 39.32; H, 7.64; N, 11.50. Found: C, 39.18; H, 7.47, N, 11.36%.
17	C	42	^{1}H NMR (δ in D_2O, ppm): 1.96 (q, 4H, $J = 6.23$ Hz), 2.51–3.48 (m, 32H), 3.81 (m, 8H). Analysis: Calcd: C, 37.47; H, 7.38; N, 11.92%. Found: C, 37.43; H, 7.31; N, 11.86%.

25.2 mmol) in pyridine (25 ml). The mixture was stirred at room temperature for 4 h under argon. The solvent was removed by evaporation under reduced pressure. The residue was precipitated by addition of 50 ml of anhydrous methanol, filtered and washed twice with 50 ml of pentane and then dried *in vacuo* for 1 h. The resulting white solid was compound **18** (3.2 g, 71% yield).

^{1}H NMR (δ in D_2O, ppm): 1.46 (d, 6H, J = 6.6 Hz), 2.09–3.66 (m, 6H).
Mass spectrum: m/z = 286 [$M^{+\cdot}$]
Analysis: Calcd: C, 20.13; H, 5.03; N, 7.83. Found: C, 19.93; H, 4.93, N, 7.75%.

Synthesis of compound 19

To a suspension of $(HCl.H_2NCH_2CH(CH_3)S)_2$ $Ge(OMe)_2^4$ (3 g, 7.74 mmol) in ether (50 ml) was added 2 g of water. The reaction mixture was stirred for 15 min at room temperature. The solvents were removed by evaporation under reduced pressure.

The pasty product was precipitated in anhydrous THF (100 ml) and left overnight with stirring. After filtration, the precipitate was washed twice with anhydrous pentane (50 ml) and then dried *in vacuo*. A white solid (1.85 g, 70% yield) was collected.

^{1}H NMR (δ in D_2O, ppm): 1.37 (d, 6H, J = 6.6 Hz), 2.84–3.70 (m, 6H).
Analysis: Calcd: C, 21.08; H, 5.27; N, 8.20. Found: C, 21.04; H, 5.22; N, 8.27%.

Synthesis of *N*-substituted cysteamines

Synthesis of compound 20

To a refluxing solution of 4-(3-aminopropyl)morpholine (30 g, 0.21 mol) in 150 ml of anhydrous toluene was added, dropwise with stirring, thiirane (12.51 g, 0.21 mol). The mixture was refluxed for 48 h. During this time the reaction was monitored by GC. After 48 h, thiirane was almost absent. Solvent was removed *in vacuo*, and the remaining liquid was distilled under reduced pressure to afford compound **20** in the form of a liquid, b.p. 91–92 °C/0.05 mm Hg (19 g, 44% yield).

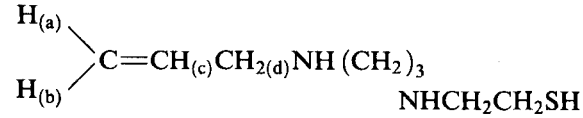
^{1}H NMR (δ in $CDCl_3$, ppm): 1.54 (s, 2H), 1.65 (q, 4H, J = 6.4 Hz), 2.40 (m, 6H), 2.66 (m, 6H), 3.68 (m, 4H).
IR in $CDCl_3$ (cm^{-1}: ν_{NH} = 3312, ν_{SH} = 2520.
Mass spectrum (EI): m/z = 205 [$M^{+\cdot}$ + 1].

Synthesis of *N*-allyldiaminopropane $CH_2{=}CHCH_2NH(CH_2)_3NH_2$

To a solution of allylamine (61 g, 1.078 mol) in 180 ml of water was added, dropwise with stirring, 3-chloropropylamine hydrochloride (28.1 g, 0.216 mol) in 25 ml of water. The reaction mixture was refluxed for 12 h. After the mixture had returned to room temperature, NaOH was added until the solution was saturated. Then 200 ml of ether was added and the organic phase was separated; the aqueous phase was extracted twice with ether in this way. The combined organic phase was dried over anhydrous KOH and filtered, and the volatile solvents were removed by evaporation under reduced pressure. The residue was distilled through a 10 cm vacuum-jacketed vigreux column. A central fraction (b.p. 175–177 °C/1 atm) was obtained (11 g, 45% yield).

^{1}H NMR (δ in DMSO ppm): 1.31 (s, 2H), 1.46 (m, 2H), 2.52 (m, 4H), 3.1 (m, 2H), 5.22 (m, 2H), 5.82 (m, 1H).
IR in CCl_4 (cm^{-1}): ν_{NH} = 3079, ν_{NH_2} = 3300, 3379.

Synthesis of compound 21



21

Following previous procedure with $CH_2{=}CHCH_2NH(CH_2)_3NH_2$ (31 g, 0.272 mol) and thiirane (16.32 g, 0.272 mol) with work-up as above, distillation gave $CH_2 = CHCH_2NH(CH_2)_3NHCH_2CH_2SH$ (25 g, 53% yield) as a colorless liquid boiling at 140–142 °C/13 mm Hg.

^{1}H NMR (δ in DMSO ppm): 1.33 (s, 2H), 1.47 (q, 2H, J = 6.5 Hz), 2.53 (m, 8H), 3.11 (m, 2H, J_{ad} = 5.6 Hz), 5.20 (m, 2H), 5.75 (m, 1H, J_{ac} = 10.5 Hz, J_{bc} = 16.95 Hz).
IR In CCl_4 (cm^{-1}): ν_{SH} = 2550, $_{NH}$ = 3294.

Pharmacology: evaluation of radioprotection

Male CD1 mice (Charles River, France), 25 g body weight, were used. Compounds were injected intraperitoneally 15 or 90 min before irradiation. The irradiation dose was $LD_{100}/30$, days for non-treated control mice (8.5, 9 or 9.5 Gy, according

to the irradiation date) or a 2 Gy greater dose. The injected dose of compound was equal to either one-half or one-eighth of the LD_{50} value which had been determined previously. The radioprotective effect was evaluated by the dose reduction factor (DRF), which is the ratio between the $LD_{50}/30$ days of treated mice and that of control mice (between 7.5 and 8.5 Gy, according to the date).

Irradiation was applied using a cobalt-60 source at a dose rate of 7–8 Gy min^{-1} according to the date. During irradiation, animals were placed in a Plexiglass box with 30 cells in a homogeneous field 28.5 cm × 28.5 cm in area. Dosimetry was checked with an ionization chamber dosimeter. The different LD_{50} values were determined by probit analysis.

RESULTS AND DISCUSSION

Synthesis of some germathiazolidines of *N*-substituted cysteamine and methylcysteamine

Germathiazolidines of *N*-substituted cysteamine and methylcysteamine were prepared according to two methods of heterocyclization already described in the literature.[1,10,11]

Method A

The action of the diorganogermanium dichloride[11] (in stoichiometric amounts) on *N*-substituted cysteamine or methylcysteamine in refluxing anhydrous THF in the presence of freshly distilled triethylamine gave by a cyclization reaction, with elimination of hydrochloric acid from M—Cl and SH and NH groups,[12] the corresponding products in yields of 51–89% (Scheme 1).

Method B

The reaction of *N*-substituted cysteamine and methylcysteamine, in stoichiometric amounts, with the bis(diethylamino)dialkylgermane in anhydrous THF resulted in the cleavage of Ge—N bonds by the NH and SH groups, forming the corresponding germathiazolidines in good yields (83–89%) (Scheme 2).

Synthesis of germadithioacetals

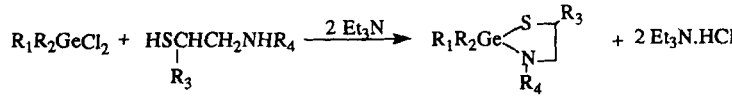
These compounds of *N*-substituted cysteamine and methylcysteamine were also prepared by two methods, C and D.[4]

Method C

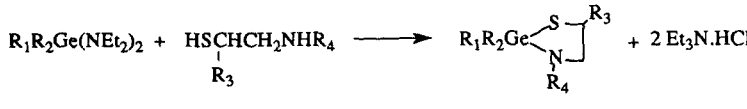
The action of the diorganogermanium dichloride on 2 mol of *N*-substituted cysteamine or methylcysteamine in refluxing anhydrous THF in the presence of triethylamine gave the acyclic derivatives (Scheme 3) in yields of 42–87%.

Method D

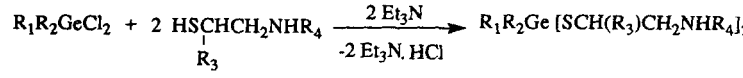
The reaction of 2 mol of *N*-substituted cysteamine or methylcysteamine with the bis(diethylamino)-dialkylgermane in anhydrous THF (a cleavage reaction of Ge—N bonds by the SH groups) gave the corresponding germylated derivatives (Scheme 4) in yields of 52–80%.



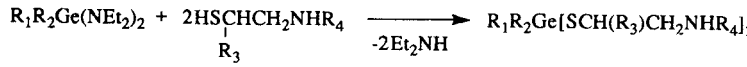
Scheme 1



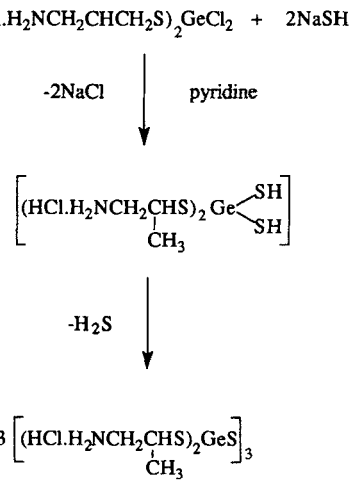
Scheme 2



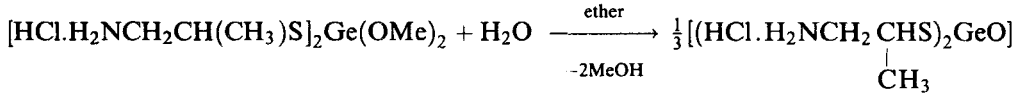
Scheme 3



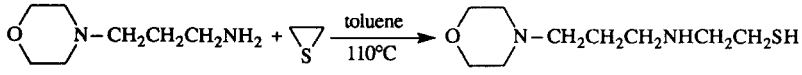
Scheme 4



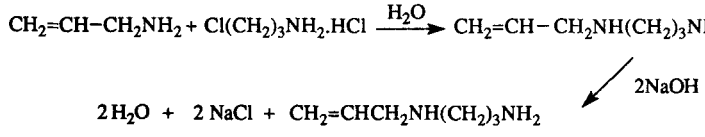
Scheme 5



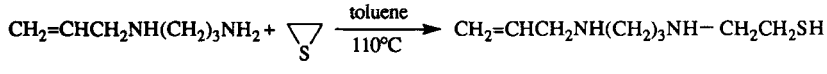
Scheme 6



Scheme 7



Scheme 8



Scheme 9

Table 2 Germathiazolidines R_1R_2Ge(S–R_3)(N–R_4)

Compound	R_1	R_2	R_3	R_4	LD_{50} (mg kg^{-1}) (mmol)	Injected dose (mg kg^{-1}	Irradiation dose (Gy) (t, min)[a]	DRF[b]
1	i-C_5H_{11}	i-C_5H_{11}	H	$(CH_2)_3NHCH_2CH{=}CH_2$	400	400	7.75 (15)	60 1.2
					(1.035)	400	7.75 (90)	10
2	*p*-$CH_3C_6H_4$	CH_3	H	$(CH_2)_3NHCH_2CH{=}CH_2$	500	250	7.75 (15)	60
					(1.43)	250	7.75 (90)	40 1.2
						250	9.75 (15)	10
3	i-C_5H_{11}	i-C_5H_{11}	H	$(CH_2)_3$N(O)	800	800	7.75 (15)	80 ~1.3
					(1.92)	800	7.75 (90)	80
4	n – C_6H_{13}	n – C_6H_{13}	H	$(CH_2)_3$N(O)	1500	750	7.5 (15)	100
					(3.37)	187	7.5 (90)	40 1.5
						750	7.5 (90)	90
5	n – C_6H_{13}	n – C_6H_{13}	CH_3	H	1500	1000	7.5 (15)	80
					(4.52)	1000	7.5 (90)	90 1.5
						1000	9.5 (15)	80
6	S	S	H	H	500	250	7.75 (15)	70 1.2
					(1.59)	250	7.5 (90)	40
7	S	S	CH_3	H	600	300	7.75 (90)	50 1.1
					(1.83)			
8	$SCH(CH_3)CH_2NH_2.HCl$	$SCH(CH_3)CH_2NH_2.HCl$	H	$(CH_2)_3$N(O)	900	450	7.75 (15)	30 1.1
					(1.70)	450	7.5 (90)	10
9	$SCH_2CH_2NH_2.HCl$	$SCH_2CH_2NH_2.HCl$	H	$(CH_2)_3$N(O)	500	250	7.5 (15)	100 1.2
					(1.00)	250	7.5 (90)	20

[a] t = time between administration of the compound and irradiation. [b] Dose reduction factor (see Pharmacology section).

Table 3 Germadithioacetals $R_1R_2Ge[SCH(R_3)CH_2NHR_4]_2$

Compound	R_1	R_2	R_3	R_4	LD_{50} (mg kg^{-1}) (mmol)	Injected dose (mg kg^{-1})	Irradiation dose (Gy) (t, min)	DRF
10	*P*-$CH_3C_6H_4$	CH_3	H	$(CH_2)_3NHCH_2CH{=}CH_2$	1200 (2.29)	600	7.75 (15) 7.75 (90)	10 1.1 30
11	i-C_5H_{11}	i-C_5H_{11}	H	$(CH_2)_3$N O	900 (1.45)	750 187 750	7.75 (15) 7.75 (15) 7.75 (90)	100 40 1.5 90
12	n-C_6H_{13}	n-C_6H_{13}	H	$(CH_2)_3$N O	800 (1.23)	400 100 400	7.75 (15) 7.75 (15) 7.75 (90)	100 50 1.5 80
13	n-C_6H_{13}	n-C_6H_{13}	CH_3	H	800 (1.89)	800 800 800	7.75 (15) 7.75 (90) 7.75 (15)	100 70 ⩾1.6 90
14			H	H	500 (1.28)	250 250 250	7.75 (15) 7.75 (90) 7.75 (15)	80 70 1.4 50
15			CH_3	H	500 (1.194)	250 250 250	7.75 (15) 7.75 (90) 7.75 (15)	20 60 1.2 20
16	$SCH(CH_3)CH_2NH_2.HCl$	$SCH(CH_3)CH_2NH_2.HCl$	H	$(CH_2)_3$N O	400 (0.146)	400	7.75 (15)	50 1.1
17	$SCH_2CH_2NH_2.HCl$	$SCH_2CH_2NH_2.HCl$	H	$(CH_2)_3$N O	700 (0.994)	350	7.75 (15)	80 1.1

Synthesis of germylated sulfide

The action of NaSH on $[HCl.H_2NCH_2CH(CH_3)S]_2GeCl_2$[4] in anhydrous pyridine leads to the corresponding product, **19** (Scheme 5).

Synthesis of germylated oxide 18 (germoxane), compound 18

The germylated oxide was prepared by the action of water in excess on $[HCl.H_2NCH_2CH(CH_3)S]_2Ge(OMe)_2$[4] (Scheme 6).

Synthesis of *N*-substituted cysteamines

Synthesis of compound 20

Compound **20** was obtained by the reaction of stoichiometric amounts of 4-(3-aminopropyl)morpholine with thiirane in refluxing anhydrous toluene (i.e. by a cleavage of the C—S bond by the NH group).[14] This reaction leads to derivative **20** (Scheme 7).

Synthesis of compound 21

This compound could be obtained in water by adding *N*-allylamine to 3-chloropropylamine hydrochloride (commercially available), then saturating the solution with NaOH (Scheme 8) to give the intermediate *N*-allyldiaminopropane. The synthesis of diaminothiol **21** was then carried out in a similar manner to that of compound **20** (Scheme 9.

CONCLUSIONS

Analysis of the results reported in Tables 2 and 3 shows that the germylated derivatives described have generally a radioprotective activity greater than that of the basic organic derivatives, and a lower toxicity.

For example, compounds **3** and **4** have DRF values of 1.3 and 1.5, compared with **20** (DRF = 1.2) and **5** (DRF = 1.5), compared with methylcysteamine DRF.[4].

Furthermore we note the low toxicity of compounds **3**, **4** and **5** (LD_{50}, 800, 1500 and 1500 mg kg^{-1}) compared with **20** (LD_{50}, 450 mg kg^{-1}) and methylcysteamine (LD_{50}, 500 mg kg^{-1}).

Noteworthy also are the compounds **11**, **12**, **13** and **14**, which have an interesting radioprotective activity (DRF 1.4–1.6), compared with derivative **20** (DRF = 1.2). Derivatives **13** and **14**, compared with cysteamine and methylcysteamine,[4] have a greater radioprotective activity and a lower toxicity, in spite of lower injected dosages in the case of the germylated derivatives (expressed in mmol fractions): derivative **11** LD_{50} 900 mg kg^{-1} (1.45 mmol); derivative **12** LD_{50} 800 mg kg^{-1} (1.23 mmol) compared with derivative **20** LD_{50} 450 mg kg^{-1} (2.2 mmol); derivative **13** LD_{50} 800 mg kg^{-1} (1.89 mmol), compared with methylcysteamine LD_{50} 500 mg kg^{-1} (3.92 mmol); derivative **14** LD_{50} 500 mg kg^{-1} (1.28 mmol), compared with cysteamine[4] LD_{50} 450 mg kg^{-1} (3.96 mmol).

Another very interesting result was obtained with the germylated sulfide **18** [DRF 1.6, LD_{50}

Table 4 Germylated sulfide and oxide. Starting organic derivatives

Compound		LD_{50} (mg kg^{-1}) (mmol)	Injected dose (mg kg^{-1})	Irradiation dose (Gy) (*t*, min)	Survival rate (%)	DRF
18	$([HCl.H_2NCH_2CH(CH_3)S]_2GeS)_3$	1000	500	7.5 (15)	100	1.6
		(0.93)	125	7.5 (15)	10	
			500	7.5 (90)	50	
			500	9.5 (15)	80	
19	$([HCl.H_2NCH_2CH(CH_3)S]_2GeO)_3$	800	400	7.5 (15)	50	1.2
		(0.78)	100	7.5 (15)	20	
			400	7.5 (90)	30	
20		450	225	7.75 (15)	50	1.2
		(2.20)	56.2	7.75 (15)	20	
			225	7.75 (90)	70	
21	$CH_2{=}CHCH_2NH(CH_2)_3NHCH_2CH_2SH$	150	75	7.75 (15)	30	1.1
		(0.862)	18.7	7.75 (15)	10	
			75	7.75 (90)	20	

1000 mg kg^{-1} (0.93 mmol)], compared with methylcysteamine.

In short, the radioprotective activity of germathiazolidines, germadithioacetals, and the germylated sulfide and oxide derived from cysteamine, methylcysteamine and *N*-substituted cysteamine can be increased compared with unsubstituted organic derivatives by the presence of organometallic groups which increase the hydrosolubility, the lipophilicity and the activity of these molecules, thereby favoring their passage through the cellular membranes.

These derivatives are generally less toxic and more active than the basic organic derivatives.

The results presented in this paper confirm the positive contribution of germanium in this field in agreement with previous work[1–8] and the interesting biological activity of organogermanium compounds.[15–19] We also observed that organogermylated groups decrease the toxicity of the basic molecules to which they are attached.

Acknowledgements The authors thank the Direction des Recherches, Etudes et Techniques, Département de Chimie–Pharmacologie du Ministère de la Défense Nationale, France, for their financial support and interest in this research.

REFERENCES

1. J. Satgé, A. Cazes, M. Bouchaut, M. Fatome, H. Sentenac-Roumanou and C. Lion, *Eur. J. Med. Chem.* **17**, 433 (1982).
2. M. Fatome, H. Sentenac-Roumanou, C. Lion, J. Satgé, M. Fourtinon and G. Rima, *Eur. Med. Chem.* **19**, 119 (1984).
3. M. Fatome, H. Sentenac-Roumanou, C. Lion, J. Satgé and G. Rima, *Eur. J. Med. Chem.* **23**, 257 (1988).
4. J. Satgé, G. Rima, M. Fatome, H. Sentenac-Roumanou and C. Lion, *Eur. J. Med. Chem.* **24**, 48 (1989).
5. G. Rima, J. Satgé, C. Lion, H. Sentenac-Roumanou and D. Guyot, *Synth. Réact. Inorg. Met.-Org. Chem.* **19**, 787 (1989).
6. G. Rima, J. Satgé, M. Fatome, J. D. Laval, H. Sentenac-Roumanou, C. Lion and M. Lazraq, *Eur. J. Med. Chem.* **26**, 291 (1991).
7. G. Rima, J. Satgé, H. Sentenac-Roumanou, M. Fatome, C. Lion and J. D. Laval, *Eur. J. Med. Chem.* **28**, 761 (1993).
8. G. Rima, J. Satgé, H. Sentenac-Roumanou, M. Fatome, J. D. Laval, C. Lion, O. Alazard and P. Charbertier, *Appl. Organomet. Chem.* **8**, 481 (1994).
9. D. Chadwick and C. Willbe, *J. Chem. Soc. Perkin*, 887 (1977).
10. G. Dousse, J. Satgé and M. Rivière-Baudet, *Synth. Inorg. Met. Org. Chem.* **3**, 11 (1973).
11. M. Lesbre, P. Mazerolles and J. Satgé in: *The Organic Compounds of Germanium*, Wiley, New York, 1973.
12. J. Satgé, M. Lesbre and M. Baudet, *C.R. Acad. Sci. Paris, Ser. C* **259**, 4733 (1964).
13. J. Satgé and M. Baudet, *C.R. Acad. Sci. Paris, Ser. C* **263**, 435 (1966).
14. J. Corbin, K. Miller, N. Pariyadath, S. Wherland and A. Bruce, *Inorg. Chim. Acta* **90**, 41 (1984).
15. G. Atassi, *Rev. Silicon Germanium Tin Lead Compd.* **8**, 219 (1985).
16. J. S. Thayer, *Rev. Silicon Germanium Tin Lead Compd.* **8**, 133 (1985); *Idem, Appl. Organomet. Chem.* **1**, 227 (1987).
17. T. K. Gar and V. F. Mironov, in: *Review of the Biological Activity of Germanium Compounds*, Niitekhim, 1982, Moscow.
18. E. Lukevics and L. Ignatovich, *Appl. Organomet. Chem.* **6**, 113 (1992).
19. E. Lukevics, L. Ignatovich, N. Shilena and S. Germane, *Appl. Organomet. Chem.* **6**, 261 (1992).