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Synthesis and Radiopharmacological Study of New Metallated Thiazolidines and Dithioacetals of *N*-Allyl-substituted Cysteamine and Methylcysteamine

G. Rima,* J. Satge,* H. Sentenac-Roumanou,† M. Fatome,‡ J. D. Laval,‡ C. Lion,§ O. Alazard* and P. Chabertier§

* 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

New germa- and silathiazolidines or germa- and siladithioacetals with *N*-allyl-substituted cysteamine and methylcysteamine ligands have been synthesized and their pharmacological properties (toxicity, radioprotective activity) have been studied. A notable decrease in the toxicity and a rather large increase in the radioprotective activity of these new organometallic derivatives compared to *N*-allyl-substituted cysteamine and methylcysteamine were observed.

Keywords: Germa- and silathiazolidines, germa- and siladithioacetals, toxicity, *N*-allylcysteamine, *N*-allylmethylcysteamine, radioprotective activity

INTRODUCTION

The pharmacological activity of organogermanium compounds is now well known, and many articles and reviews have been published on the subject.[1–9]

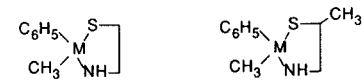
These describe the activity of organogermanium compounds as antitumour, psychotropic, neurotropic, cardiovascular, antiarthritic and immunoregulatory agents, in addition to their behaviour as specific enzyme inactivators, their inhibitory activity towards encephalin and also their bactericidal, and fungicidal properties. Organogermanium and organosilicon compounds have been shown to be more active than their carbon analogues. Moreover, the majority of organogermanium compounds are less toxic than their silicon analogues.

We have already demonstrated that the substitution of a carbon atom by a germanium atom in certain biologically active molecules significantly increases their radioprotective power.[10–16]

During the last few years we have reported a large number of germa- and silathiazolidines[10,11] and germadithioacetals, variously *N*-substituted.[11,12]

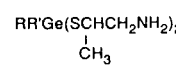
We will summarize here some interesting results on organometallic compounds, active in chemical radioprotection, synthesized in our laboratory.

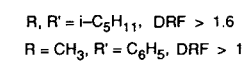
In this field of radioprotection[10–16] we have broadened our study to include the new organogermylated and silylated structures: we have synthesized new *N*-allyl-substituted germa- and silathiazolidines and germa- and sila-*N*-allyl-substituted dithioacetals. The aim of this study was to compare the radioprotective activity and toxicity of these new organometallic derivatives



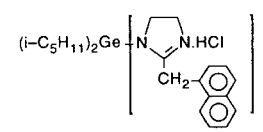
M = Si, DRF = 1.6
M = Ge, DRF = 1.6

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



Dose reduction factor (DRF) = 1.5

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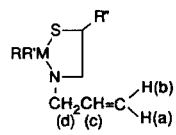
with those of basic organic compounds (*N*-allyl-substituted cysteamine and methylcysteamine).

We report in this paper the synthesis and pharmacological study of some molecules with the following structures which have been prepared and tested.

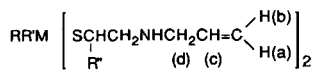


M=Ge ; R"=H ; R=R'=CH_3 **1** ; R=R'=i-C_5H_{11} **2** ; R=R'=n-C_6H_{13} **3**
R=p-$CH_3C_6H_4$, R'=CH_3 **4**

R"=CH_3 ; R=R'=n-C_6H_{13} **5** ; R=R'=i-C_5H_{11} **6**
R=p-$CH_3C_6H_4$, R'=CH_3 **7**

M=Si ; R"=H ; R=R'=n-C_6H_{13} **8** ; R=C_6H_5, R=-$CH_2CH=CH_2$ **9**
R"=CH_3 ; R=R'=n-C_6H_{13} **10** ; R=C_6H_5, R'=-$CH_2CH=CH_2$ **11**

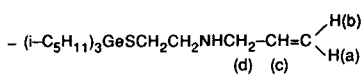
- Germa- and siladithioacetals



M=Ge ; R"=H ; R=R'=CH_3 **12** ; R=R'=i-C_5H_{11} **13**
R=R'=n-C_6H_{13} **14** ; R=p-$CH_3C_6H_4$, R'=CH_3 **15**

R"=CH_3 ; R=R'=i-C_5H_{11} **16** ; R=R'=n-C_6H_{13} **17**
R=p-$CH_3C_6H_4$, R'=CH_3 **18**

M=Si ; R"=H ; R=R'=n-C_6H_{13} **19** ; R=C_6H_5, R'=-$CH_2CH=CH_2$ **20**
R"=CH_3 ; R=R'=n-C_6H_{13} **21** ; R=C_6H_5, R'=-$CH_2CH=CH_2$ **22**



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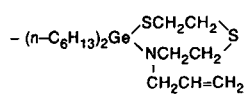

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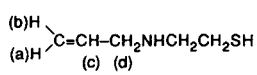

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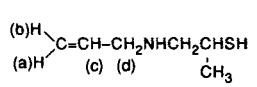

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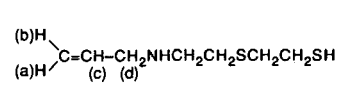

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EXPERIMENTAL

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 FT-IR 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 Microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse and were within ±0.4% of calculated values.

Syntheses of germathiazolidines and silathiazolidines

Germathiazolidines and silathiazolidines were prepared by two methods: A and B.

Synthesis of 3-allyl-2,2-diisopentyl 2-germa 1,3-thiazolidine 2 (method A)

To a solution of di(isoamyl)dichlorogermane (4 g, 14 mmol) in 50 ml of THF were added freshly distilled *N*-allylcysteamine (1.64 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* and then distilled.

Synthesis of 3-allyl 2,2-diisoamyl 5-methyl-2-germa 1,3-thiazolidine 6 (method B)

Bis(diethylamino)diisoamylgermane (2 g, 5.6 mmol) was dissolved in 50 ml of THF and *N*-allylcysteamine (0.73 g, 5.6 mmol) was added from a syringe. The solution was refluxed under an argon atmosphere for 3 h with stirring, concentrated, and then, in certain cases, distilled.

Syntheses of germa- and siladithioacetals

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

Synthesis of bis(2-allylaminoethylthio)dihexylsilane 19 (method C)

To a stirred mixture of *N*-allylcysteamine (1.65 g, 14.1 mmol), triethylamine (1.6 g, 15.84 mmol)

and 70 ml of THF a solution of dichlorodihexylsilane (1.9 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, concentrated *in vacuo* and the residue distilled, depending on the particular case.

Synthesis of bis(2-allylamino-1-methylethylthio)dihexylgermane 17 (method D)
To a solution of *N*-allylmethylcysteamine (2 g, 10.38 mmol) in 50 ml of THF was added, dropwise with stirring bis(diethylamino)dihexylgermane (1.35 g, 5.17 mmol) in 50 ml of anhydrous THF. The mixture was refluxed for 4 h. Removal of the solvent and work-up was as before.

Synthesis of compound 23

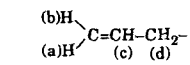
To a solution of *N*-allylcysteamine (1.1 g, 9.4 mmol) in 50 ml of anhydrous THF and excess triethylamine (1 g, 10 mmol) was added, dropwise with stirring, chlorotriisoamylgermane (3.02 g; 9.4 mmol) in 30 ml of THF. The reaction mixture was refluxed for 4 h under argon, after which the mixture was filtered and concentrated. The residue was distilled *in vacuo* to give the product (see Table 1).

Synthesis of compound 24

Dichlorodihexylgermane (3.21 g, 14.12 mmol) dissolved in 20 ml of anhydrous THF was added dropwise to a stirred mixture of *N*- and *S*-substituted cysteamine, CH_2=$CHCH_2NHCH_2CH_2SCH_2CH_2SH$, (2.5 g, 14.12 mmol) and triethylamine (3.15 g, 3.12 mmol) in 50 ml of THF. After stirring and refluxing for 4 h under argon the mixture was filtered and concentrated *in vacuo*. The product was not distilled because it was not thermally stable. Physicochemical data of all derivatives synthesized in this paper are reported in Table 1.

Synthesis of compounds 25 and 26

To a refluxing solution of allylamine (57 g, 1 mol) in 150 ml of anhydrous toluene was added, dropwise with stirring, thiirane or methylthiirane (1 mol). The mixture was refluxed for 48 h. During this time the reaction was monitored by Gr.C. After 48 h, thiirane or methylthiirane were almost absent. Solvent was removed *in vacuo*, and the remaining liquid was distilled under reduced pressure to afford compound **25** CH_2=$CHCH_2NHCH_2CH_2SH$ (47 g; 40%) in the form of a liquid, b.p. 88–89 °C at 50 mm Hg.



For **25**: ^{1}H NMR (δ in $CDCl_3$): 1.35 (s, 2H), 2.68 (m, 4H), 3.12–3.19 (dt, 2H, J_{ad} = 1.21 Hz; J_{cd} = 5.75 Hz); 5.79 (m, 1H), J_{bc} = 17.24 Hz, J_{ac} = 9.82 hz; 5.05 (m, 2H). IR In $CDCl_3$ (cm^{-1}): ν_{NH} = 3305; ν_{SH} = 2559. Mass spectrum: m/z = 117 $[M]^{+\cdot}$.

For **26**: (55 g; 42%) of CH_2=$CHCH_2NHCH_2(CH_3)CHSH$, b.p. 102–103 °C at 32 mm Hg. ^{1}H NMR (δ in $CDCl_3$): 1.16 (d, 3H, J_{H-H} = 6.72 Hz), 1.43 (s, 2H), 2.53 (m, 3H), 3.11 (m, 2H, J_{ad} = 1.24 Hz, J_{cd} = 5.93 Hz); 5.78 (m, 1H), J_{ac} = 10.1 Hz, J_{bc} = 17.21 Hz; 5(m, 2H). IR in $CDCl_3$ (cm^{-1}): ν_{NH} = 3317; ν_{SH} = 2472. Mass spectrum: m/z = 131 $[M]^{+\cdot}$.

Synthesis of compound 27

Following the previous procedure with allylamine (28.5 g, 0.5 mol) and thiirane (60 g, 1 mol), the desired product was distilled off, giving 57 g of **27** (65%) as a liquid, b.p. 120–125 °C at 25 mm Hg. ^{1}H NMR (δ in $CDCl_3$): 1.45 (s, 2H), 2.62 (m, 8H), 3.1–3.17 (dt, 2H J_{ad} = 1.41 Hz, J_{cd} = 5.79 Hz), 5.77 (m, 1H), J_{ac} = 9.82 Hz; J_{bc} = 17.8 Hz, 5.02 (m, 2H). IR in $CDCl_3$ (cm^{-1}): ν_{NH} = 3307, ν_{SH} = 2552. Mass spectrum: m/z = 177 $[M]^+$.

Pharmacology

Evaluation of radioprotection
Male CD1 mice (Charles River, France), 25 g body weight, were used. Compounds were injected intra peritoneally 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 d 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

Table 1 Physicochemical data of some derivatives synthesized

Compound	Method	b.p./mm Hg	^{1}H NMR (δ in $CDCl_3$)	Yield (%)
1	A or B	38–40/0.2	0.65 (s, 6H); 2.9 (m, 4H); 3.42 (dt, 2H); 5.15 (m, 2H); 5.89 (m, 1H). Analysis: Calcd., C, 38.60; H, 6.89; N, 6.43. Found, C, 38.35; H, 6.57; N, 6.12.	65
2	A or B	156/1	1.14 (m, 22H); 2.77 (m, 4 H); 3.23 (dt, 2H); 5.11 (m, 2H); 5.87 (m, 1H). Analysis: Calcd., C, 54.61; H, 9.40; N, 4.25. Found, C, 54.22; H, 9.15; N, 3.92.	65
3	A or B	166/0.6	1.14 (m, 26 H), 2.87 (m, 4H), 3.43 (dt, 2H); $^3J_{dc} = 5.93$ Hz, $^4J_{db} = {}^4J_{ad} = 1.22$ Hz, 5.12 (m, 2H); 5.87 (m, 1H); $^3J_{ac} =$ 9.5 Hz, $^3J_{dc} = 5.93$ Hz, $^3J_{bc} = 16.3$ Hz. Analysis: Calcd., C, 57.04; H, 9.78; N, 3.91. Found, C, 56.78; H, 9.35; N, 3.62.	50
4	A or B		0.92 (s, 3 H); 1.24 (d, 3 H, $^3J_{H-H} = 7.12$ Hz); 2.82 (m, 3 H); 2.36 (s, 3 H); 3.24 (dt, 2 H); $^3J_{cd} = 5.93$ Hz; $^4J_{ad} = {}^4J_{bd} =$ 1.48 Hz, 5.77 (m, 1 H); $J_{ac} = 9.5$ Hz; $^3J_{bc} = 15.3$ Hz; 5 (m, 2 H) (syst. AB) $\delta_a = 7.58$ (2 H); $\delta_B = 7.32$; $^3J_{AB} = 8.8$ Hz. Analysis: Calcd., C, 53.13; H, 6.47; N, 4.76. Found, C, 52.93; H, 6.25; N, 4.35.	48
5	A or B		1.14 (m, 26 H); 3.18 (m, 3H; $^3J_{HH} = 7.2$ Hz); 1.41 (d, 3H, $^3J_{H-H} = 7.2$ Hz); 3.3 (dt, 2H); $^3J_{dc} = 5.95$ Hz, $^4J_{db} = {}^4J_{ad} =$ 1.48 Hz; 6.02 (m, 1 ZH), $^3J_{dc} = 5.95$ Hz, $^3J_{ac} = 9.5$ Hz, $^3J_{bc} =$ 17.2 Hz; 5.42 (m, 2H). Mass spectrum: $m/z = 373$ $M^{+\cdot}$. Analysis: Calcd., C, 58.13; H, 9.95; N, 3.76. Found, C, 57.67; H, 9.65, N, 3.25.	60
6	A or B		1.26 (m, 22 H); 1.35 (d, 3 H, $^3J_{H-H} = 7.12$ Hz); 2.8 (m, 3 H); 3.22 (dt, 2 H); $^3J_{dc} = 5.93$ Hz; $^4J_{db} = {}^4J_{ad} = 1.8$ Hz; 5.09 (m, 2H); 5.85 (m, 1 H), $^3J_{dc} = 5.93$ Hz; $^3J_{ac} = 10.1$ Hz, $^3J_{bc} =$ 17.2 Hz. Mass spectrum: $m/z = 345$ $M^{+\cdot}$. Analysis: Calcd., C, 55.88; H, 9.60; N, 4.07. Found, C, 55.45; H, 9.28; N, 3.72.	75
7	A or B		0.73 (s, 3 H); 2.1 (s, 3 H); 2.85 (m, 4 H); 3.3 (dt, 2 H); $^3J_{cd} = 5.93$ Hz; $^4J_{ad} = {}^4J_{bd} = 1.48$ Hz; 4.94 (m, 2H); 5.7 (m, 1 H); $^3J_{ac} = 10.1$ Hz; $^3J_{bc} = 17.2$ Hz; (syst. AB) $\delta_A = 7.55$ (2 H), $\delta_B = 7.05$ (2H); $^3J_{AB} = 8$ Hz. Analysis: Calcd., C, 54.62; H, 6.83; N, 4.55. Found, C, 54.20; H, 6.45; N, 4.19.	24
8	A		1.05 (m, 26 H); 2.9 (m, 4 H); 3.43 (dt, 2 H); $^3J_{dc} = 5.63$ Hz; $^4J_{db} = {}^4J_{ad} = 1.48$ Hz; 5.09 (m, 2H); 5.75 (m, 1 H); $^3J_{dc} =$ 5.63 Hz, $^3J_{ac} = 10.1$ Hz, $^3J_{bc} = 17.8$ Hz. Mass spectrum: $m/z = 313$ $M^{+\cdot}$. Analysis: Calcd., C, 65.17; H, 11.18; N, 4.47. Found, C, 64.82; H, 10.65; N, 4.14.	65
9	A		2.17 (m, 2H); 2.93 (m, 4 H); 3.43 (m, 2H); 5.03 (m, 2 H) 5.83 (m, 2H); 7.55 (m, 5H). Mass spectrum: $m/z = 261$ $M^{+\cdot}$. Analysis: Calcd., C, 64.36; H, 7.28; N, 5.36. Found C, 64.05; H, 6.95; N, 5.02.	60
10	A		1.32 (d, 3 H, $^3J_{H-H} = 7.12$ Hz); 1.42 (m, 26 H) 2.93 (m, 3 H); 3.44 (dt, 2H); 5.08 (m, 2H); 5.76 (m, 1 H). Mass spectrum: $m/z = 327$ $M^{+\cdot}$. Analysis: Calcd., C, 66.05; H, 11.31; N, 4.28. Found, C, 65.60; H, 10.98; N, 3.95.	84
11	A		1.25 (d, 3 H, $^3J_{H-H} = 7.12$ Hz); 2.14 (m, 2 H); 2.87 (m, 3H); 3.37 (m, 2H); 4.97 (m, 4H); 5.82 (m, 2H); 6.53 (m, 5H). Mass spectrum: $m/z = 275$ $M^{+\cdot}$. Analysis: Calcd., C, 65.45; H, 7.63; N, 5.09. Found, C, 65.08; H, 7.27; N, 4.69.	65
12	C or D	$150/8 \times 10^{-2}$	0.75 (s, 6H); 1.45 (s, 2 H); 2.75 (m, 8H); 3.2 (dt, 4H); 5.05 (m, 4H); 5.83 (m, 2 H). Analysis: Calcd., C, 43.04; H, 7.77; N, 8.37. Found, C, 42.82; H, 7.73, N, 8.25.	72

Table 1 *Cont.*

Compound	Method	b.p./mm Hg	^{1}H NMR (δ in $CDCl_3$)	Yield (%)
13	C or D	160/0.7	1.08 (m, 22 H); 1.43 (s, 2H); 2.71 (m, 8 H); 3.2 (m, 4 H); 5.07 (m, 4 H); 5.83 (m, 2 H). Analysis: Calcd., C, 53.74; H, 9.40; N, 6.27. Found, C, 53.40; H, 9.15; N, 5.89.	66
14	C or D	$80/6\times10^{-2}$	1.23 (m, 26H); 1.82 (s, 2H); 2.8 (m, 8H); 3.25 (dt, 4H); $^3J_{dc}=5.93$ Hz, $^4J_{ab}=^4J_{db}=1.42$ Hz; 5.14 (m, 4H); 5.9 (m, 2H); $^3J_{bc}=17.2$ Hz, $^3J_{ac}=10$ Hz. Analysis: Calcd., C, 55.62; H, 9.69. N, 5.90. Found, C, 55.40; H, 9.54, N, 5.89.	24
15	C or D	140/0.5	0.95 (s, 3H); 1.46 (s, 2H); 2.32 (s, 3H) 2.74 (m, 8H): (dt, 2H); $^3J_{dc}=5.93$ Hz; $^4J_{db}=^4J_{da}=1.48$ Hz; 5.06 (m, 4H); 6.84 (m, 2H); $^3J_{bc}=17.8$ Hz, $^3J_{ac}=10$ Hz, $^3J_{dc}=5.93$ Hz. (syst. AB); $\delta_A=7.5$ (2H); $\delta_B=7.2$ (2H); $J_{AB}=7.2$ Hz. Analysis: Calcd., C, 52.60; H, 7.31; N, 6.82. Found, C, 52.38; H, 7.29; N, 6.75.	42
16	C or D		1.2 (m, 22 H); 1.32 (d, 6 H, $^3J_{H\text{-}H}=7.12$ Hz); 2.78 (m, 6 H); 3.23 (dt, 4 H); $^3J_{dc}=5.64$ Hz, $^4J_{db}=^4J_{ad}=1.78$ Hz; 5.12 (m, 4H); 5.9 (m, 2 H); $^4J_{dc}=5.64$, $^3J_{ac}=10.38$ Hz; $^3J_{bc}=17.21$ Hz. Analysis: Calcd., C, 55.62; H, 9.69; N, 5.90. Found, C, 55.41; H, 9.44, N, 5.82.	64
17	C or D		1.23 (m, 26 H); 1.35 (d, 6H, $^3J_{H\text{-}H}=7.1$ Hz); 2.82 (m, 6H); 3.25 (dt, 4H); $^3J_{dc}=5.93$ Hz, $^4J_{db}=^4J_{ad}=1.48$ Hz; 5.11 (m, 4H); 5.88 (m, 2 H); $^3J_{dc}=5.93$ Hz, $^4J_{ac}=10.4$ Hz; $^3J_{bc}=$ 17.2 Hz. Analysis: Calcd., C, 57.30; H, 9.95; N, 5.57. Found, C, 57.15; H, 9.87; N, 5.52.	47
18	C or D		1.02 (s, 3 H); 1.24 (d, 6 H, $^3J_{HH}=7.12$ Hz); 2.32 (s, 3 H); 2.8 (m, 6 H); 3.24 (dt, 4 H); $^3J_{dc}=5.93$ Hz; $^4J_{ab}=^4J_{bd}=$ 1.40 Hz; 4.92 (m, 4H); 5.66 (m, 2 H); $^3J_{ac}=10$ Hz; $^3J_{bc}=$ 7.1 Hz; (syst. AB) $\delta_A=7.58$ (2 H); $\delta B=7.32$ (2 H); $\delta_B=$ 7.32 (2 H); $^3J_{AB}=8.8$ Hz. Analysis: Calcd., C, 54.72; H, 7.75, N, 6.38. Found, C, 54.58; H, 7.55; N, 6.32.	60
19	C		1.05 (m, 26 H); 2.85 (m, 8 H); 3.4 (dt, 4 H); $^3J_{dc}=5.93$ Hz, $^4J_{db}=^4J_{ad}=1.48$ Hz; 5.09 (m, 4H); 5.82 (m, 2 H); $^3J_{dc}=$ 5.93 Hz, $^3J_{ac}=10.1$ Hz; $^3J_{bc}=17.21$ Hz. Analysis: Calcd., C, 61.39; H, 10.70; N, 6.51. Found, C, 61.80; H, 11.22; N, 6.75.	30
20	C		2.18 (m, 2H); 2.87 (m, 8 H); 3.43 (m, 4H); 5.03 (m, 6 H); 5.81 (m, 3 H); 7.58 (m, 5H); Analysis: Calcd., C, 60.32; H, 7.93; N, 7.41. Found, C, 61.32; H, 7.65; N, 6.86.	54
21	C		1.05 (d, 6 H, $^3J_{H\text{-}H}=7.12$ Hz); 1.09 (m, 26H); 2.83 (m, 6 H); 3.36 (m, 4 H); 5.09 (m, 4H); 5.79 (m, 2 H). Analysis: Calcd., C, 62.88; H, 10.92; N, 6.11. Found, C. 62.68; H, 10.72; N, 5.98.	75
22	C		2.13 (m, 2 H); 2.91 (m, 6H); 3.37 (m, 4 H); 4.97 (m, 6H); 5.82 (m, 3 H); 7.5 (m, 5H). Analysis: Calcd., C, 62.07; H, 8.37; N, 6.89. Found, C, 61.85; H, 8.12; N, 6.87.	65
23		138/1	1.23 (m, 33H); 2.73 (m, 4H); 3.23 (dt, 2H); 5.02 (m, 2H); 5.87 (m, 1H). Analysis: Calcd., C, 59.76; H, 10.71; N, 3.48. Found, C, 59.58; H, 10.69; N, 3.27.	64
24		$140/5\times10^{-2}$	1.12 (m, 26H); 2.75 (m, 8H); 3.26 (dt, 2H); $^3J_{dc}=5.93$ Hz, $^4J_{db}=^4J_{db}=^4J_{ad}=1.4$ Hz; 5.13 (m, 2H); 5.92 (m, 1H); $^3J_{dc}=$ 5.93 Hz, $^3J_{ac}=10$ Hz; $^3J_{bc}=16.32$ Hz. Mass spectrum: $m/z=419$ $M^{+\cdot}$. Analysis: Calcd., C, 54.60; H, 9.34; N, 3.35. Found, C, 54.38; H, 9.28; N, 3.26.	20

field 28.5 × 28.5 cm in size. Dosimetry was checked with an ionization chamber dosimeter. The different LD 50 values were determined by probit analysis.

RESULTS AND DISCUSSION

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

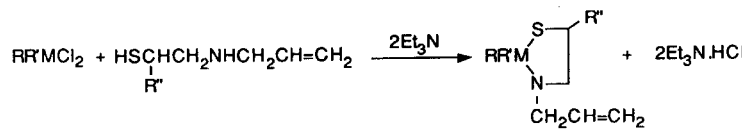
Germa- and silathiazolidines of *N*-allyl-substituted cysteamine and methylcysteamine were prepared according to two methods of heterocyclisation already described in the literature.[10, 17, 18]

Method A

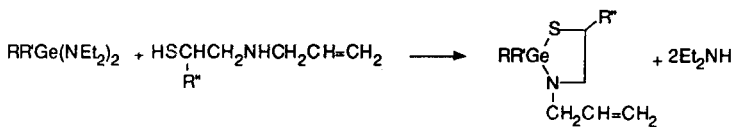
the action of diorganogermyl[18] or silyl dichloride (in stoichiometric amounts) on *N*-substituted cysteamine or methylcysteamine in refluxing anhydrous THF in the presence of freshly distilled triethylamine gave by a cyclisation reaction, with elimination of hydrochloric acid from M-Cl and SH and NH[19] groups, the corresponding products, Scheme 1, yields 24–75%.

Method B

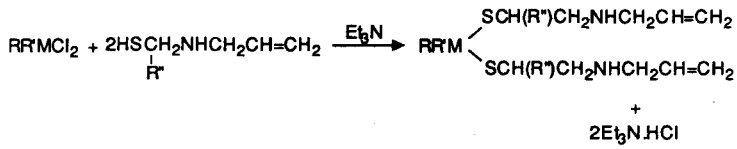
Treatment of *N*-substituted cysteamine and methylcysteamine, in stoichiometric amounts, with bis-



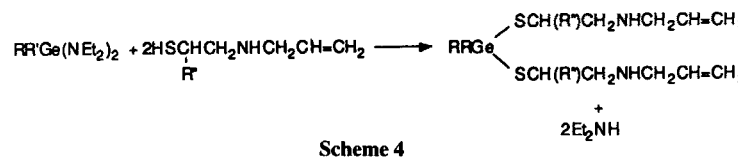
Scheme 1



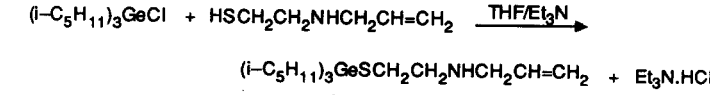
Scheme 2



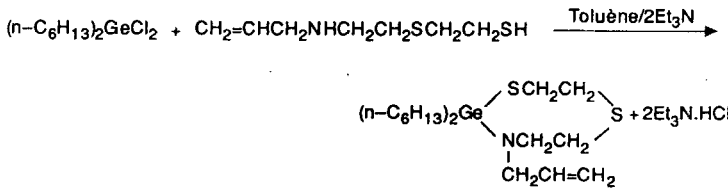
Scheme 3



Scheme 4



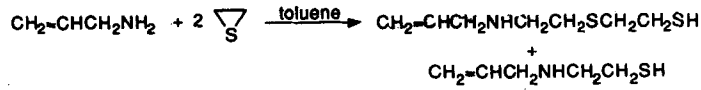
Scheme 5



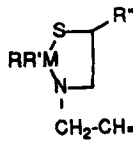
Scheme 6

R = H **25**; R = CH_3 **26**

Scheme 7



Scheme 8

Table 2 Germa- and silathiazolidines 

Compound	R	R′	R″	M	LD_{50} mg kg^{-1} (mmol)	Injected dose (mg kg^{-1})	irradiation (Gy)(t, min)[a]	Survival rate (%)	DRF[b]
1	CH_3	CH_3	H	Ge	500	250	9 (15)	90	1.2
					(2.3)	250	11 (15)	0	
2	i-C_5H_{11}	i-C_5H_{11}	H	Ge	800	400	9 (15)	20	1.1
					(2.43)	100	9 (15)	0	
						400	9 (90)	10	
						400	11 (15)	10	
3	n-C_6H_{13}	n-C_6H_{13}	H	Ge	700	350	8.5 (15)	70	1.4
					(1.96)	87.5	8.5 (15)	0	
						350	8.5 (90)	80	
						350	10.5 (15)	40	
4	*p*-CH_3-C_6H_4	CH_3	H	Ge	400	200	9 (15)	10	1
					(1.36)	200	11 (15)	0	
5	n-C_6H_{13}	n-C_6H_{13}	CH_3	Ge	1500	1000	8.5 (15)	30	1.1
					(4.03)	1000	10.5 (15)	0	
6	i-C_5H_{11}	i-C_5H_{11}	CH_3	Ge	1200	600	8.5 (15)	90	1.2
					(3.49)	600	8.5 (90)	70	
						600	10.5 (15)	0	
7	*p*-CH_3-C_6H_4	CH_3	CH_3	Ge	1200	600	7.75 (15)	7	1.2
					(3.9)	150	7.75 (15)	0	
						600	7.75 (90)	0	
								50	
8	n-C_6H_{13}	n-C_6H_{13}	H	Si	1000	500	8.5 (15)	70	1.2
					(3.2)	125	8.5 (15)	20	
						500	8.5 (90)	40	
9	C_6H_5	CH_2=$CHCH_2$	H	Si	1000	500	7.5 (15)	40	1.2
					(3.83)	125	7.5 (15)	60	
						500	7.5 (90)	70	
						500	9.5 (15)	0	
10	n-C_6H_{13}	n-C_6H_{13}	CH_3	Si	1500	1000	8.5 (15)	70	1.25
					(4.6)	250	8.5 (15)	30	
						1000	8.5 (90)	70	
11	C_6H_5	CH_2=$CHCH_2$	CH_3	Si	1000	500	8.5 (15)	40	1.2
					(3.64)	125	8.5 (15)	50	

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

(diethylamino)dialkylgermane in anhydrous THF resulted in the cleavage of Ge—N bonds by the N—H and SH groups (a transamination reaction)[10, 18–20] forming the corresponding germathiazolidines, Scheme 2, in good yields 50–75%.

Synthesis of germa- and siladithioacetals

These derivatives of *N*-allyl-substituted cysteamine and methylcysteamine were prepared by two methods, C and D[13].

Method C

The action of diorganogermyl or silyl dichloride on 2 mol of *N*-allyl-substituted cysteamine or methylcysteamine in refluxing anhydrous THF in the presence of triethylamine (a dehydrochlorination reaction with the SH group) gave the acyclic derivatives, (Scheme 3).

Method D

The reaction of 2 mol of *N*-allyl-substituted cysteamine or methylcysteamine with bis(diethylamino)dialkylgermane in anhydrous THF (a cleavage reaction of Ge—N bonds by the S—H groups) gave the corresponding germylated derivatives, Scheme 4.

Table 3 Germa- and siladithioacetals of *N*-allyl-substituted cysteamine and methylcysteamine $RR'M[SC(R'')HCH_2NHCH_2CH{=}CH_2]_2$

Compound	R	R′	R″	M	LD_{50} mg kg^{-1} (mmol)	Injected dose (mg kg^{-1})	Irradiation (Gy)(t, mn)[a]	Survival rate (%)	DRF[b]
12	CH_3	CH_3	H	Ge	300 (0.89)	200	9 (15)	70	1.25
						50	9 (15)	10	
						200	9 (90)	40	
						200	11 (15)	30	
13	i-C_5H_{11}	i-C_5H_{11}	H	Ge	450 (1.01)	225	8.5 (15)	20	1.2
						56.3	8.5 (15)	0	
						225	8.5 (90)	50	
						225	10.5 (15)	10	
14	n-C_6H_{13}	n-C_6H_{13}	H	Ge	1000 (2.11)	500	8.5 (15)	100	~1.3
						125	8.5 (15)	30	
						500	8.5 (90)	90	
						500	10.5 (15)	10	
15	*p*-CH_3-C_6H_4	CH_3	H	Ge	600 (1.46)	300	8.5 (15)	50	1.4
						75	8.5 (15)	50	
						300	8.5 (90)	30	
						300	10.5 (15)	50	
16	i-C_5H_{11}	i-C_5H_{11}	CH_3	Ge	1000 (2.11)	500	8.5 (15)	70	1.1
17	n-C_6H_{13}	n-C_6H_{13}	CH_3	Ge	1000 (1.99)	500	8.5 (15)	50	1.1
18	*p*-CH_3-C_6H_4	CH_3	CH_3	Ge	800 (1.82)	400	7.75 (15)	80	1.2
						100	7.75 (15)	60	
19	n-C_6H_{13}	n-C_6H_{13}	H	Si	1200 (2.79)	600	7.5 (15)	100	1.3
						150	7.5 (15)	60	
20	C_6H_5	$CH_2{=}CH{-}CH_2$	H	Si	800 (2.12)	400	7.5 (15)	50	1.2
						100	7.5 (15)	50	
						400	7.5 (90)	50	
						400	9.5 (15)	30	
21	n-C_6H_{13}	n-C_6H_{13}	CH_3	Si	800 (1.75)	400	7.75 (15)	90	1.25
						100	7.75 (15)	40	
22	C_6H_5	$CH_2CH{=}CH_2$	CH_3	Si	1200 (2.95)	600	7.5 (15)	90	1.25
						150	7.5 (15)	40	

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

Table 4 Radioprotective activity of germanium and starting organic derivatives

Compound	LD_{50} mg kg^{-1} (mmol)	Injected dose (mg kg^{-1})	Irradiation (Gy) (t, mn)[a]	Survival rate (%)	DRF[b]
23	800	400	9 (15)	40	1.1
	(1.99)	400	11 (15)	0	
24	800	400	8.5 (15)	60	1.2
	(1.92)	400	8.5 (90)	80	
		400	10.5 (15)	0	
25	400	200	8.5 (15)	100	~1.3
	(3.42)	50	8.5 (15)	20	
		200	8.5 (90)	80	
		200	10.5 (15)	20	
26	400	200	8.5 (15)	80	~1.2
	(3.05)	200	8.5 (90)	40	
27	250	125	8.5 (15)	50	~1.25
	(1.41)	31.3	8.5 (15)	50	
		125	8.5 (90)	70	
		125	10.5 (15)	10	

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

We assume a preliminary formation of germathiazolidine (see method A) in which the Ge—N bond is cleaved by a second molecule of *N*-allyl-substituted cysteamine or methylcysteamine. Yield 24–75%.

M = Si, Ge

R,R′ = alkyl or aryl groups

R′ = H, CH_3

Synthesis of compound 23

Compound **23** was obtained by the action of stoichiometric amounts of triorganochlorogermane on *N*-allyl-substituted cysteamine in refluxing anhydrous THF in the presence of triethylamine, Scheme 5.

Synthesis of compound 24

Compound **24** was prepared by the reaction of *N*- and *S*-substituted cysteamine with dihexylgermyldichloride in equimolar amounts in anhydrous toluene in the presence of freshly distilled triethylamine, Scheme 6.

Syntheses of compounds 25 and 26

The addition of thiirane to allylamine freshly distilled in toluene at 110 °C leads to **25** or **26** quantitatively, Scheme 7.

Synthesis of compound 27

The action of 2 mol thiirane on allylamine in refluxing anhydrous toluene gave the corresponding derivative, Scheme 8.

CONCLUSIONS

The analysis of the results reported in Tables 2–4 shows that the germylated and silylated derivatives described have a radioprotective activity equal to or greater than that of the basic organic derivatives (**25–27**) and a lower toxicity, whereas compounds **3**, **10**, **14** and **15** have a DRF = 1.4.

The average of LD50 for 24 germylated and silylated derivatives is about 850 mg kg^{-1} and 350 mg kg^{-1} for the three basic organic derivatives. Note that derivatives **3**, **14** and **15** have a radioprotective activity comparable to the basic compound **25** even at two-fold lower injected dosages in the case of the germylated derivatives (expressed in mmol). Noteworthy also is silylated compound **10** which has a radioprotective activity slightly greater and a lower toxicity than **26** (**10** LD 50:1500 mg kg^{-1} compared with **26** LD50:400 mg kg^{-1}).

The results presented in this paper show that the germylated and silylated derivatives have a considerably lower toxicity than that of the basic organic compounds (**25–27**) and a radioprotective

activity that is comparable, but with lower injected dosages expressed in mmol.

Equally interesting are the radioprotective activities at the LD 50/8 for derivatives **9**, **11**, **15**, **19** and **20** and the retarding effect for compounds **3**, **6**, **10** and **14**.

The results presented in this paper confirm the positive contribution of germanium and silicon to the field of chemical radioprotection, in agreement with our previous work.[10–16] We also observed that organogermanium and silicon groups decrease the toxicity of the basic molecules to which they are linked.

Among the organosilicon analogues, Voronkov *et al.* have shown that in a number of categories of biologically active derivatives, pharmacological activity was increased when O—, S—, N— and C— were substituted by organosilicon groups.[21]

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REFERENCES

1. G. Atassi, *Rev. Silicon Germanium Tin Lead Compd.* **8**, 219 (1985).
2. J. S. Thayer, *Rev. Silicon Germanium Tin Lead Compd.*, **8**, 133 (1985); *Appl. Organometal. Chem.* **1**, 227 (1987).
3. H. A. Meinema, A. M. J. Liebregts, H. A. Budding and E. J. Bulten, *Rev. Silicon Germanium Tin Lead Compd.* **8**, 157 (1985).
4. T. K. Gar and V. F. Mironov, in: *Review of the Biological Activity of Germanium Compounds*, Niitekhim, 1982, Moscow.
5. J. Satgé, *Rapport de Mise au point*, Assoc. Etude Problemes Avances (AEPA), 1981, Paris.
6. F. Rijkens, *Organogermanium Compounds*, TNO Germanium Research Committee, 1960, Utrech.
7. E. Lukevics and L. Ignatovich, *Appl. Organometal. Chem.* **6**, 113 (1992).
8. E. Lukevics, L. Ignatovich, N. Shilena and S. Germane, *Appl. Organometal. Chem.* **6**, 261 (1992).
9. F. Rijkens and G. J. M. Van der Kerk, in: *Investigation in the field of Organogermanium Chemistry*, TNO Germanium Research Committee, 1964, Utrech.
10. J. Satgé, A. Cazes, M. Bouchant, M. Fatome, H. Sentenac-Roumanou and C. Lion. *Eur. J. Med. Chem.* **17**, 433 (1982).
11. M. Fatome, H. Sentenac-Roumanou, C. Lion, J. Satgé, M. Fourtinon and G. Rima, *Eur. Med. Chem.* **19**, 119 (1984).
12. M. Fatome, H. Sentenac-Roumanou, C. Lion, J. Satgé and G. Rima, *Eur. J. Med. Chem.* **23**, 257 (1988).
13. J. Satgé, G. Rima, M. Fatome, H Sentenac-Roumanou and C. Lion, *Eur. J. Med. chem.* **24**, 48 (1989).
14. G. Rima, J. Satgé, C. Lion, H. Sentenac-Roumanou and D. Guyot, *Synth. React. Inorg. Met.-Org. Chem.* **19**, 787 (1989).
15. G. Rima, J. Satgé, M. Fatome, J. D. Laval, H. Sentenac-Roumanou, C. Lion and M. Lazraq, *Eur. J. Med. Chem.* **26**, 291 (1991).
16. G. Rima, J. Satgé, H. Sentenac-Roumanou, M. Fatome, C. Lion and J. D. Laval, *Eur. J. Med. Chem.* **28**, 761 (1993).
17. G. Dousse, J. Satgé, M. Rivière-Baudet, *Synth. Inorg. Metal-Org. Chem.* **3**, 11 (1973).
18. M. Lesbre, P. Mazerolles and J. Satgé, in: *The Organic Compounds of Germanium*, John Wiley and Sons, New York, 1973.
19. J. Satgé, M. Lesbre and M. Baudet, *C.R. Acad. Sci. Paris, Ser. C.* **259**, 4733 (1964).
20. J. Satgé and M. Baudet, *C.R. Acad. Sci. Paris Ser. C.* **263**, 435 (1966).
21. M. G. Voronkov, E. Lukevics, U. Wannagat, R. R. Levier, M. L. Chandler, S. R. Wendel and B. Strindberg, Biological and Pharmacological Effects of Organosilicon Compounds in the Biochemistry of Silicon and Related Problems, Beendz, G. and Lundquist, I. (eds), Plenum Press, NY, 1978, 395.