RADIOPROTECTIVE ACTIVITY AND SYNTHESIS OF SILADITHIOACETALS AND GERMADITHIOACETALS DERIVED FROM N-SUBSTITUTED NAPHTHYLETHYLIMIDAZOLINE

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ABSTRACT
A number of organosilicon and organogermanium derivatives and some related compounds including the N-substituted 2-[1-naphthylmethyl]-2-imidazoline and 2-[1-(1-naphthyl)ethyl]-2-imidazoline have been prepared and the toxicity of some compounds have been determined in mice. In this paper we report the synthesis and the evaluation of the pharmacological activity of new organosilicon and organogermanium compounds such as sila- and germadithioacetals derived from N-substituted naphthylimidazoline.

INTRODUCTION
Recently, it has been reported that medetomidine [1] is a new imidazole drug that possesses selective and potent α2-adrenergic properties. α2-Adrenergic stimulation is known to mediate a variety of biological actions including hypertension, sedation, antianxiety, analgesia, hypothermia, decreased salivary secretions and mydriasis [2].

The selection of the naphthalene ring system was due to its presence in the potent α1-adrenergic stimulant naphazoline. The presence of a methyl group attached at the benzylic position of medetomidine is important for optimal α2-adrenergic activity [3].

Our group has already reported a considerable work in the field of the chemical radioprotection and pharmacological activity of organosilicon and organogermanium compounds [4-16]. Several organometallic classes derived from N-substituted naphthylimidazoline showed a potent radioprotective activity.

Concerning the mechanism of the radioprotective activity of these compounds, it is well established that the main mechanisms of radioprotection are tissue oxygen tension decrease, free radical scavenging and hydrogen transfer [17]. However, the radioprotective action mechanism of naphthylimidazoline remains unclear. Some recent and preliminary investigations seem to indicate that at least in vitro, it has no effect on lipidic peroxidation. Perhaps it acts through its vasoconstrictive effects, which can lower the tissue oxygen supply and hence decrease the radiation-induced lesions.

Another possible explanation of excellent activity of naphthylimidazoline, the first non-sulfur radioprotective compound, is its evolution in vivo of the compound that forms anti-inflammatory products of naphthyl-1-acetic acid type [18]. Further studies are necessary to determine the precise mechanism of action.

Accordingly our objective, we have investigated a new series of organosilicon and organogermanium compounds derived from N-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline.

Experimental section
General procedures
All manipulations were performed under an inert atmosphere of argon using standard Schlenck, glove box and high-vacuum-line techniques. All solvents used were freshly dried using standard techniques and all glassware was oven-dried. 1H-NMR spectra were recorded on a Bruker AC 80 spectrometer operating at 80.13 MHz (chemical shifts are reported in parts per million relative to internal Me4Si as reference) and 13C-NMR spectra on an AC 200 spectrometer (50.32 MHz). The multiplicity of the 13C-NMR signals was determined by the APT technique. Mass spectra under electron impact (EI) or chemical ionisation (CI/CH3) conditions at 70 and 30 eV were obtained on Hewlett-Packard 5989 and Nermag R10-10H spectrometers. IR and UV spectra were recorded on Perkin-Elmer 1600 FT-IR and Lambda-17 spectrophotometers.
Table 1  Physicochemical data and analyses of derivatives 1-12

| Cpd | Yield (%) | Physical properties and elemental analyses |
|-----|-----------|------------------------------------------|
| 1   | R = 'R = n-C₃H₁₁; 'R = CH₃; M = Ge | H-NMR (CDCl₃): 0.88 (t, 6H, J = 6.6 Hz, CH₂CH₃); 1.09 - 1.56 (m, 26H, (CH₂)₅ and CH₃-CHS); 7.12 - 7.50 (m, 8H, C₆H₅); 7.63 - 8.09 (m, 2H, C₆H₅). 13C-NMR (CDCl₃): 14.12 (CH₃CH₂); 19.07 (CH₃); 21.09 (CH₂CH₃); 22.58 (CH₂Ge); 23.41 (CH₃CH₂CH₂); 31.10 (CH₃CH₂CH₂); 34.79 (CH₂CH₃); 50.28 (CH₃N); 50.49 (CH₃N); 123.09 (aromatic CH); 124.72 (aromatic CH); 125.61 (aromatic CH); 126.18 (aromatic CH); 126.80 (aromatic CH); 131.12 (aromatic CH); 134.09 (aromatic CH); 137.10 (aromatic CH); 167.21 (N-C=N). Mass Spectrum: m/z 525 [M - 283]+. Analysis (C₄₆H₆₄N₄S₂Ge): Calcd.%: C, 68.85; H, 8.13; N, 6.69. Found %: C, 69.02; H, 8.17; N, 6.61. |
| 2   | R = 'R = n-C₃H₁₁; 'R = H; M = Ge | H-NMR (CDCl₃): 0.86 (t, 6H, J = 6.8 Hz, CH₂CH₃); 1.02 - 1.47 (m, 20H, (CH₂)₅); 2.26 - 2.84 (m, 4H, CH₂S); 3.02 - 3.84 (m, 12H, C₆H₅); 4.43 (q, 2H, J = 6.9 Hz, CH₂CH₃); 7.21 - 7.62 (m, 8H, C₆H₅); 7.68 - 7.92 (m, 4H, C₆H₅); 8.00 - 8.20 (m, 2H, C₆H₅). 13C-NMR (CDCl₃): 14.22 (CH₃CH₂); 19.13 (CH₃); 21.26 (CH₂CH₃); 22.70 (CH₂Ge); 23.39 (CH₃CH₂); 31.21 (CH₃CH₂CH₂); 34.89 (CH₂); 50.34 (CH₃); 50.61 (CH₃); 52.74 (CH₃N); 124.17 (aromatic CH); 124.86 (aromatic CH); 125.73 (aromatic CH); 126.12 (aromatic CH); 126.23 (aromatic CH); 127.93 (aromatic CH); 129.31 (aromatic CH); 130.12 (aromatic CH); 131.18 (aromatic CH); 134.14 (aromatic CH); 137.18 (aromatic CH); 167.36 (N-C=N). Mass Spectrum: m/z 525 [M - 283]+. Analysis (C₄₆H₆₄N₄S₂Ge): Calcd.%: C, 68.33; H, 8.00; N, 7.05. |
| 3   | R = 'R = i-C₃H₁₁; 'R = H; M = Ge | H-NMR (CDCl₃): 0.87 (t, 12H, J = 5.6 Hz, (CH₃)₂CH); 1.05 - 1.49 (m, 16H, CH₂CH₃CH and CH₂CH₃S); 1.69 (d, 6H, J = 6.8 Hz, CH₃CH₂); 2.30 - 2.80 (m, 2H, CH₂S); 3.06 - 3.88 (m, 12H, C₆H₅); 4.44 (q, 2H, J = 6.7 Hz, CH₂CH₃); 7.22 - 7.60 (m, 8H, C₆H₅); 7.65 - 7.92 (m, 4H, C₆H₅); 8.00 - 8.20 (m, 2H, C₆H₅). 13C-NMR (CDCl₃): 18.28 (CH₃); 19.10 (CH₃); 22.09 (CH₂CH₃); 32.25 (CH₂); 34.83 (CH₂); 50.26 (CH₃N); 50.51 (CH₃N); 52.65 (CH₃N); 124.01 (aromatic CH); 125.41 (aromatic CH); 125.73 (aromatic CH); 126.49 (aromatic CH); 126.64 (aromatic CH); 127.69 (aromatic CH); 128.66 (aromatic CH); 132.12 (aromatic CH); 132.56 (aromatic CH); 166.31 (N-C=N). Analysis (C₄₆H₆₄N₄S₂Ge): Calcd.%: C, 68.32; H, 7.91; N, 6.93. Found %: C, 68.33; H, 8.00; N, 7.05. |
| 4   | R = 'R = i-C₃H₁₁; 'R = H; M = Ge | H-NMR (CDCl₃): 0.87 (d, 12H, J = 5.6 Hz, (CH₃)₂CH); 1.06 - 1.44 (m, 10H, CH₂CH₃CH and CH₂CH₃S); 1.71 (d, 6H, J = 6.7 Hz, CH₃CH₂); 2.36 - 2.77 (m, 4H, CH₂S); 3.07 - 3.79 (m, 12H, CH₃N); 4.45 (q, 2H, J = 6.7 Hz, CH₂CH₃); 7.20 - 7.58 (m, 8H, C₆H₅); 7.64 - 7.90 (m, 4H, C₆H₅); 8.05 - 8.23 (m, 2H, C₆H₅). 13C-NMR (CDCl₃): 17.19 (CH₃); 18.28 (CH₂); 19.10 (CH₃); 22.09 (CH₂); 30.52 (CH₂); 32.25 (CH₂); 34.83 (CH₂); 50.26 (CH₃N); 50.51 (CH₃N); 52.65 (CH₃N); 124.01 (aromatic CH); 125.41 (aromatic CH); 125.73 (aromatic CH); 126.49 (aromatic CH); 126.64 (aromatic CH); 127.69 (aromatic CH); 128.66 (aromatic CH); 132.12 (aromatic CH); 132.56 (aromatic CH); 166.31 (N-C=N). Analysis (C₄₆H₆₄N₄S₂Ge): Calcd.%: C, 68.32; H, 7.91; N, 6.93. Found %: C, 68.33; H, 8.00; N, 7.05. |
| 5   | R = p-CH₃-C₆H₄; 'R = CH₃; M = Ge | H-NMR (CDCl₃): 0.95 (s, 3H, CH₃); 1.35 (d, 6H, J = 6.7 Hz, CH₂CH₃); 1.74 (d, 6H, J = 6.8 Hz, CH₂CH₃); 2.20 - 2.63 (m, 5H, p-CH₃ and CH₂S); 3.08 - 3.80 (m, 12H, C₆H₅); 4.51 (q, 2H, J = 6.8 Hz, CH₂CH₃); 7.09 - 8.18 (m, 18H, C₆H₅). 13C-NMR (CDCl₃): 9.02 (CH₃); 20.11 (CH₃); 20.75 (CH₂); 21.21 (CH₂); 21.65 (CH₂); 34.22 (CH₂); 45.92 (CH₃N); 46.40 (CH₃N); 46.73 (CH₃N); 123.20 (aromatic CH); 125.74 (aromatic CH); 125.96 (aromatic CH); 128.41 (aromatic CH); 128.84 (aromatic CH); 129.39 (aromatic CH); 129.47 (aromatic CH); 129.70 (aromatic CH); 130.02 (aromatic CH); 131.79 (aromatic CH). |
(arom. Cquat); 132.26 (arom. Cquat); 136.21 (arom. Cquat); 140.29 (arom. Cquat); 146.49 (arom. Cquat); 170.93 (N-C=N). Analysis (C₄₄H₅₂N₄S₂Ge): Calcd. %: C, 68.16; H, 6.71; N, 27.23. Found %: C, 68.22; H, 6.87; N, 7.19.

R = p-CH₃C₆H₄; R = CH₃; M = Ge

H-NMR (CDCl₃): 0.99 (s, 3H, CH₃); 2.13 - 2.58 (m, 7H, CH₃ and CH₃S); 3.06 - 3.73 (m, 12H, CH₂N₃); 4.51 (q, 2H, J = 6.8 Hz, CH₂CH₃); 6.85 - 8.18 (m, 18H, C₁₀H₈ and C₁₀H₉). ¹³C-NMR (CDCl₃): 9.06 (CH₃Ge); 17.09 (p-CH₃); 21.61 (CH₃-H); 27.90 (CH₃S); 34.32 (CH₂C₆H₄); 45.84 (CH₂N₃); 46.02 (CH₂N₃); 47.26 (CH₂N₃); 123.20 (aromatic CH); 125.20 (aromatic CH); 125.78 (aromatic CH); 128.62 (aromatic CH); 128.89 (aromatic CH); 129.22 (aromatic CH); 129.36 (aromatic CH); 132.23 (aromatic CH); 133.11 (aromatic CH); 134.07 (aromatic CH); 135.87 (aromatic CH); 138.26 (aromatic CH); 141.35 (aromatic CH); 147.32 (aromatic CH); 163.09 (N-C=N). Analysis (C₄₂H₄sN₄S₂Ge): Calcd. %: C, 67.51; H, 6.43; N, 7.50. Found %: C, 67.44; H, 6.14; N, 7.47.

R = R = t-CH₃; R = CH₃; M = Si

H-NMR (CDCl₃): 0.83 (t, 6H, J = 5.7 Hz, CH₂CH₃); 1.00 - 1.49 (m, 20H, CH₂CH₃ and CH₂CH₂CH₂); 1.75 (d, 6H, J = 6.9 Hz, CH₃); 2.36 - 2.79 (m, 2H, CH₂CH₂CH₂); 3.04 - 3.81 (m, 12H, CH₂N₃); 7.28 - 7.63 (m, 8H, C₁₀H₈); 7.64 - 7.88 (m, 4H, C₁₀H₉); 7.92 - 8.26 (m, 2H, C₁₀H₉). ¹³C-NMR (CDCl₃): 14.12 (CH₃C₆H₄); 16.18 (CH₃Si); 18.48 (CH₃CH₂); 18.67 (CH₃CH₂); 19.58 (CH₃Si); 20.85 (CH₃CH₂); 22.56 (CH₃CH₂CH₂); 25.58 (CH₃CH₂CH₂CH₂); 31.58 (CH₃CH₂); 33.44 (CH₃CH₂); 44.02 (CH₃N₃); 46.16 (CH₃N₃); 50.13 (CH₃CH₂); 123.18 (aromatic CH); 125.38 (aromatic CH); 125.79 (aromatic CH); 127.0 (aromatic CH); 127.02 (aromatic CH); 127.28 (aromatic CH); 127.28 (aromatic CH); 127.81 (aromatic CH); 128.0 (aromatic CH); 130.96 (aromatic CH); 133.68 (aromatic CH); 134.08 (aromatic CH); 173.80 (N-C=N). Mass Spectrum: m/z 792 [M⁺]; 704 [M-44⁺]. Analysis (C₄₈H₆₈N₄S₂Si): Calcd. %: C, 72.73; H, 8.59; N, 7.07. Found %: C, 72.69; H, 8.65; N, 7.03.

R = R = n-C₆H₁₃; R = CH₃; M = Si

H-NMR (CDCl₃): 0.81 (t, 6H, J = 5.9 Hz, CH₂CH₃); 1.01 - 1.44 (m, 26H, CH₂CH₃ and CH₂CH₂CH₂); 1.75 (d, 6H, J = 6.9 Hz, CH₃); 2.36 - 2.79 (m, 2H, CH₂CH₂); 3.04 - 3.81 (m, 12H, CH₂N₃); 4.53 (q, 2H, J = 6.9 Hz, CH₂CH₃); 7.25 - 7.56 (m, 8H, C₁₀H₈); 7.61 - 7.86 (m, 4H, C₁₀H₉); 7.90 - 8.21 (m, 2H, C₁₀H₉). ¹³C-NMR (CDCl₃): 14.12 (CH₃C₆H₄); 16.18 (CH₃Si); 18.48 (CH₃CH₂); 18.67 (CH₃CH₂); 19.58 (CH₃Si); 20.85 (CH₃CH₂); 22.56 (CH₃CH₂CH₂); 25.58 (CH₃CH₂CH₂CH₂); 31.58 (CH₃CH₂); 33.44 (CH₃CH₂); 44.02 (CH₃N₃); 46.16 (CH₃N₃); 50.13 (CH₃CH₂); 123.18 (aromatic CH); 125.38 (aromatic CH); 125.79 (aromatic CH); 127.0 (aromatic CH); 127.02 (aromatic CH); 127.28 (aromatic CH); 127.28 (aromatic CH); 127.81 (aromatic CH); 130.96 (aromatic CH); 133.68 (aromatic CH); 134.08 (aromatic CH); 173.80 (N-C=N). Mass Spectrum: m/z 792 [M⁺]; 704 [M-44⁺]. Analysis (C₄₈H₆₈N₄S₂Si): Calcd. %: C, 72.73; H, 8.59; N, 7.07. Found %: C, 72.69; H, 8.65; N, 7.03.
Melting points were taken uncorrected on a Leitz Biomed hot-plate microscope apparatus or, in capillary tubes, on a digital Electrothermal apparatus. Elemental analyses (C, H, N) were performed at the "Laboratoire de Microanalyse de l’Ecole Nationale Supérieure de Chimie" of Toulouse.

**Synthesis of metasiladithioacetals 1-12**

All these compounds were prepared by a method already described.

**Siladithioacetal 8 (method A)**

To a stirred mixture of freshly distilled triethylamine (0.96 g, 9.5 mmol) and 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline (2.70 g, 9.5 mmol) in 30 ml of THF was added dropwise with stirring a solution of diisoamyldichlorosilane (1.28 g, 4.75 mmol) in 30 ml of THF. The reaction mixture was refluxed under an argon atmosphere for 5 hours. After filtration, the residue was concentrated under vacuum to give 8 (3.2 g, 88%).

**Germadithioacetal 4 (method B)**

A solution of bis(diethylamino)diisoamylgermane (1.71 g, 4.75 mmol) in 30 ml of THF was added slowly with stirring to a solution of 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline (2.70 g, 9.5 mmol) in 30 ml of THF. The reaction mixture was refluxed under argon atmosphere for 5 hours. After cooling to room temperature, the volatile material was removed under vacuum to afford 4 (3.38 g, 91%).

The physiochemical data and the analyses are reported in Table 1.

**Synthesis of selenodiazadihexylgermetane 13**

Method C

To a solution of 1,3-bis(trimethylsilyl)selenourea (2.2 g, 8.23 mmol) in 100 ml of THF was added slowly with stirring a solution of bis(diethylamino)dihexylgermane (3.18 g, 8.23 mmol) in 10 ml of THF. The reaction mixture was refluxed under argon atmosphere for 5 hours. After cooling to room temperature, the volatiles were removed under vacuum to afford 13 (1.88 g, 45%) as a yellow oil.

Method D

To a solution of 1,3-bis(trimethylsilyl)selenourea (2.2 g, 8.23 mmol) and triethylamine (1.67 g, 16.46 mmol) freshly distilled in 100 ml of THF was added dropwise with stirring a solution of dichlorodihexylgermane (2.58 g, 8.23 mmol) in 10 ml of THF. The reaction mixture was refluxed for 5 hours. After cooling to room temperature, the mixture was filtered and the volatiles were removed under vacuum to give 13 (1.59 g, 38%).

13: 1H-NMR (CDCl3): 0.15 (s, 18H, (CH3)3Si); 0.86 (t, 6H, J = 5.6 Hz, CH2CH3); 1.10-1.50 (m, 20H, (CH2)n). 13C-NMR (CDCl3): 1.06 ([CH3]2Si); 14.08 (CH2CH3); 22.57 (CH2CH3); 25.76 (CH2CH2CH2CH3); 31.39 (CH2CH3Ge); 32.13 (CH3Ge); C-Se not detected.

Mass spectrum: m/z 508 [M]+; 431 [M - Se + 1]. Analysis (C60H34N4S2Si2Ge): Calcd. %: C, 44.79; H, 8.64; N, 5.50. Found %: C, 44.86; H, 8.69; N, 5.49.
Synthesis of selenodiazadisosaamonylgermane 14

Using the same experimental procedure as for the synthesis of 13, the reaction of dichlorodisamonylgermane (3.13 g, 10.96 mmol) in the presence of triethylamine (2.22 g, 21.92 mmol) or bis(diethylamino)disosaamonylgermane (3.93 g, 10.96 mmol) with 1,3-bis(trimethylsilyl)selenourea (2.93 g, 10.96 mmol) does not lead to 14 but afford only the selenagermadamantane 15 (2.50 g, 87%) as a yellow solid, and 1,3-bis(trimethylsilyl)carbodiimide.

Synthesis of hexaselenatetrakis(isamylgerma)adamantane 15

A solution of LiEt3BH (57.20 mmol in 57.2 mol of THF) was added dropwise to elemental selenium (2.26 g, 28.60 mmol) via syringe. The mixture was stirred for 1 hour at room temperature. A solution of trichloroisamylgermane (4.77 g, 19.07 mmol) in 25 mol of anhydrous THF was added at 0°C for 1 hour. After the addition the reaction mixture was warmed to room temperature and stirred until the red color of the selenium salt had disappeared (5 days). The solvent was removed in vacuo and the residue was extracted with toluene. After filtration and concentration the residue solid was crystallized from pentane to afford 15 (4.5 g, 90%).

15: H-NMR (CDCl3): 0.90 (d, 24H, J = 5.4 Hz, (CH3)2CH); 1.20-2.11 (m, 20H, CH-CH-CH). 13C-NMR (CDCl3): 21.96 (CH); 29.70 (C-H); 31.37 (C-H2); 32.69 (CH2). Mass spectrum (CI-C4): m/z 1079 [M+ 29]. Analysis (C20H4Se6Ge): Calcd. %: C, 22.90; H, 4.20. Found %: C, 22.93; H, 4.23.

This compound has been shown by X-Ray crystallographic methods to have an adamantane-type structure but the quality of crystal does not permit us to do a structure refinement.

Synthesis of 2-[1-(1-naphthyl)ethyl]-2-imidazoline 16

a) N-Boc 2-[1-(1-naphthylmethyl)-2-imidazoline

To a stirred solution of 2-(1-naphthylmethyl)-2-imidazoline (19 g, 90.35 mmol) in 200 mol of THF was added dropwise a solution of di-tertbutylcarbonate (21 mol, 91.64 mmol) in 20 mol of THF. The mixture was stirred at room temperature for 8 hours. The volatiles were removed under vacuum to afford N-Boc 2-[1-(1-naphthylmethyl)-2-imidazoline (25.52 g, 91%).

13C-NMR (CDCl3): 1.35 (s, 9H, (CH3)3C); 3.76 (s, 4H, CH2N); 4.49 (s, 2H, CH-CO2H); 7.33-7.92 (m, 7H, C10H7).

b) N-Boc 2,[1-(1-naphthyl)ethyl]-2-imidazoline

To a stirred solution of N-Boc 2-(1-naphthylmethyl)-2-imidazoline (25.52 g, 82.22 mmol) in 300 mol of THF, at -78°C, was added dropwise a solution of n-butyllithium 1.6M in hexane (51.4 ml, 82.22 mmol). The mixture was stirred at that temperature for 3 hours. A solution of methyl iodide (5.9 ml, 94.9 mmol) in 30 mol of THF was added dropwise. The mixture was then stirred at room temperature for a night. The volatiles were removed in vacuo and the residue was extracted with of a mixture ether/pentane (1/1, 400 mol). After filtration, the solvent was removed under reduced pressure to afford N-Boc 2-[1-(1-naphthyl)ethyl]-2-imidazoline (23.86 g, 90%).

H-NMR (CDCl3): 0.99 (s, 9H, (CH3)3C); 1.41 (d, 3H, J = 7.0 Hz, CH3-CH); 3.57 (s, 4H, CH2N); 5.15 (q, 1H, J = 7.0 Hz, CH3-CH); 7.20-7.90 (m, 7H, C10H7). 13C-NMR (CDCl3): 19.09 (CH3-CH); 27.87 ((CH3)3C); 35.80 (CH3-CH); 47.76 (CH2-N); 51.40 (CH3-CH); 83.05 ((CH3)3C); 123.01 (aromatic CH); 123.30 (aromatic CH); 125.63 (aromatic CH); 125.96 (aromatic CH); 126.67 (aromatic CH); 128.13 (aromatic CH); 131.24 (aromatic C-quat); 133.87 (aromatic C-quat); 138.10 (aromatic C-quat); 156.42 (C-C). Mass spectrum: m/z 324 [M+].

16: H-NMR (CDCl3): 1.70 (d, 3H, J = 7.1 Hz, CH3-CH); 3.53 (s, 4H, CH2N); 4.39 (q, 1H, J = 7.1 Hz, CH3-CH); 7.09 (s, H, Nil); 7.40-7.61 (m, 4H, C10H7); 7.60-7.81 (m, 2H, C10H7); 7.82-8.15 (m, 1H, C10H7). 13C-NMR (CDCl3): 18.95 (CH3-CH); 35.50 (CH3-CH); 47.76 (CH2-N); 123.08 (aromatic CH); 124.61 (aromatic CH); 125.63 (aromatic CH); 125.96 (aromatic CH); 126.67 (aromatic CH); 128.13 (aromatic CH); 129.00 (aromatic CH); 131.24 (aromatic C-quat); 133.87 (aromatic C-quat); 136.71 (aromatic C-quat); 171.80 (N-C=N). I.R. (cm-1): νNH = 3430. Mass spectrum: m/z 223 [M-1]. Analysis (C13H10N2): Calcd. %: C, 80.36; H, 7.14; N, 12.50. Found %: C, 80.70; H, 7.21; N, 12.09.

Synthesis of 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline 17

A solution of 2-[1-(1-naphthylmethyl)-2-imidazoline (3.66 g, 16.32 mmol) in 60 mol of dry toluene was mixed with a solution of ethylene sulfide (1.15 ml, 19.58 mmol) in 20 mol of dry toluene (sealed tube, argon flushed). The reaction mixture was then heated (110°C oven) for 22 hours. After cooling, 100 ml of cold diethyl ether was added with stirring to the reaction mixture and a small amount of polyethylene sulfide was filtered. The solvent was removed under reduced pressure to give a yellow pasty product 17 (3.25 g, 70%).

17: H-NMR (CDCl3): 1.68 (d, 3H, J = 6.8 Hz, CH3-CH); 2.43 (s, 1H, SH); 2.54-2.84 (m, 2H, CH2-S); 3.02-3.91 (m, 6H, CH2N); 4.41 (q, 1H, J = 6.8 Hz, CH3-CH); 7.38-7.50 (m, 4H, C10H7); 7.58-7.79 (m, 2H, C10H7).
Radioprotective Activity ad Synthesis of Siladithioacetals and Germadithioacetals Derived from N-Substituted Naphthylethylimidazoline

C_{10}H_{12}: 7.80-8.13 (m, 1H, C_{10}H_{12}). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 19.09 (CH\textsubscript{3}-CH); 23.40 (CH\textsubscript{2}-S); 35.12 (CH-CH\textsubscript{3}); 48.85 (CH\textsubscript{2}-N); 49.09 (CH\textsubscript{2}-N); 52.41 (CH\textsubscript{2}-N); 122.81 (arom. CH); 124.54 (arom. CH); 125.43 (arom. CH); 125.80 (arom. CH); 126.09 (arom. CH); 127.78 (arom. CH); 129.12 (arom. CH); 130.14 (arom. C\textsubscript{quat}); 133.85 (arom. C\textsubscript{quat}); 136.67 (arom. C\textsubscript{quat}); 168.36 (N-C=\textsubscript{N}). I.R. (cm\textsuperscript{-1}): \nu_{SH} = 2542. Mass spectrum: m/z 283 [M-1]. Analysis (C_{16}H_{22}N_{5}S): Calcd. %: C, 71.83; H, 7.04; N, 9.86. Found %: C, 71.89; H, 7.17; N, 9.77.

Synthesis of 1-(2-thiopropyl)-2-[1-(1-naphthyl)ethyl]imidazoline 18

Using the same experimental procedure as for the synthesis of 17, the reaction of 16 (3.66 g, 16.32 mmol) leads to a yellow pasty product 18 (3.17 g, 65%). 18: \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 1.24 (d, 3H, J 6.6 Hz, CH\textsubscript{3}-CH); 1.65 (d, 3H, J 6.9 Hz, CH\textsubscript{3}-CH); 2.48 (s, 1H, SH); 2.58-2.86 (m, 1H, CH\textsubscript{2}-CH\textsubscript{3}); 3.06-4.02 (m, 6H, CH\textsubscript{2}N); 4.46 (q, 1H, J 6.9 Hz, CH\textsubscript{2}-CH\textsubscript{3}); 7.11-7.52 (m, 4H, arom.CH); 7.66-7.82 (m, 2H, arom.CH); 7.84-8.16 (m, 1H, arom.CH). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 19.13 (CH\textsubscript{3}-CH); 21.75 (CH-CH\textsubscript{3}); 23.08 (CH\textsubscript{2}-CH\textsubscript{3}); 35.17 (CH-CH\textsubscript{3}); 48.89 (CH\textsubscript{2}-N); 49.21 (CH\textsubscript{2}-N); 52.46 (CH\textsubscript{2}-N); 123.01 (arom. CH); 124.61 (arom. CH); 125.51 (arom. CH); 125.90 (arom. CH); 126.13 (arom. CH); 127.83 (arom. CH); 129.19 (arom. CH); 131.09 (arom. C\textsubscript{quat}); 134.06 (arom. C\textsubscript{quat}); 137.02 (arom. C\textsubscript{quat}); 168.61 (N-C=\textsubscript{N}). I.R. (cm\textsuperscript{-1}): \nu_{SH} = 2548. Mass spectrum: m/z 297 [M-1]. Analysis (C_{18}H_{26}N_{5}S): Calcd. %: C, 72.48; H, 7.38; N, 9.40. Found %: C, 72.57; H, 7.61; N, 9.32.

Synthesis of 1,3-bis(trimethylsilyl)selenourea 19

To a stirred solution of selenourea (10 g, 81.29 mmol) and triethylamine (36 ml, 186.96 mmol) in 200 ml of THF was added dropwise a solution of chlorotrimethylsilane (20.6 ml, 81.29 mmol) in 50 ml of THF. The reaction mixture was refluxed under an argon atmosphere for 8 hours. After filtration, the residue was concentrated in vacuo to afford 19 (18.47 g, 85%). mp: 146-148°C (dec.). 19: \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 0.35 (s, 18H, (CH\textsubscript{3})\textsubscript{3}Si); 6.20 (s, 2H, NH). \textsuperscript{13}C-NMR (CDCl\textsubscript{3}): 1.02 ((CH\textsubscript{3})\textsubscript{3}Si); C=Se not detected. Mass spectrum: m/z 267 [M\textsuperscript{+}]. Analysis (C\textsubscript{7}H\textsubscript{14}N\textsubscript{2}SeSi\textsubscript{2}): Calcd. %: C, 31.41; H, 7.51; N, 10.41. Found %: C, 31.41; H, 7.51; N, 10.41.

Pharmacology: evaluation of radioprotection

Three-month-old male mice (Swiss, France), 25 g body weight, were used. The radioprotective effect of a compound was evaluated by determining the dose reduction factor (DRF), defined as the ratio of 50% lethal-dose irradiation 30 days (LD\textsubscript{50}/30 days) of injected mice to that of control mice. Initially the survival rate was determined 30 days after irradiation in different groups of 10 mice receiving an intraperitoneal (i.p.) injection of a dose equal to half or one-eighth of its LD\textsubscript{50} 15 or 90 min before whole-body irradiation delivered with a dose equal to the LD\textsubscript{50}/30 days of control mice (7.5, 7.75 or 8 Gy according to the irradiation date), or with a dose equal to this dose + 2 Gy. When necessary, other irradiation doses were tested in order to evaluate the irradiation LD\textsubscript{50} of protected mice by the Kraberm method (calculated or graphic). [19]

The radiosensitivity of the strain was regularly monitored by the determination of lethality curves of males and females. The LD\textsubscript{50}/30 days was between 6.5 ± 0.3 and 6.75 ± 0.3 Gy according to the date (P < 0.05). Under these conditions significant protection was observed with a DRF value superior to 1.15.

The toxicity was evaluated by a Probit analysis of the LD\textsubscript{50}. [20-21] the dose range being determined in a preliminary study. Five groups of ten mice were then injected with different doses within this range.

RESULTS AND DISCUSSION

Synthesis of metalladithioacetals \textsuperscript{1}R\textsuperscript{2}RM[SCH(\textsuperscript{4}R)CH\textsubscript{2}NEI\textsubscript{2}]

NE\textsubscript{I} = 2-[1-(1-naphthyl)ethyl]-2-imidazoline

The synthesis of sila- and germadithioacetals compounds derived from N-substituted 2-[1-(1-naphthyl)ethyl]-2-imidazoline was realised by two methods, A and B [4, 22].

Method A

The action of the dichlorodiorganometallane [22] on two equivalents of N-substituted naphthylethylimidazoline in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave the acyclic derivatives (Scheme 1) in yields of 85-90%.

\[ \text{ Scheme 1 } \]
Method B

The reaction of two equivalents of N-substituted naphthylimidazoline with the bis(diethylamino)dialkyllmetalane in anhydrous tetrahydrofuran (a cleavage of M-N bonds by the SH groups) [4, 22, 23] gave the corresponding organometallated derivatives (Scheme 2) in yield of 92-96%.

$$\text{IR}_2RM(NEt)_2 + 2\text{HSCH}_2\text{N.N} \rightarrow \text{IR}_2RM(\text{SCH}_2\text{N.N})_{\text{THF, refluxed}} - 2\text{Et}_2\text{NH}$$

Scheme 2

| M = Ge | M = Si |
|--------|--------|
| 1 \( R = n-C_6H_{13}; R = \text{CH}_3 \) | 7 \( R = n-C_6H_{13}; R = \text{CH}_3 \) |
| 2 \( R = n-C_6H_{13}; R = \text{H} \) | 8 \( R = n-C_6H_{13}; R = \text{H} \) |
| 3 \( R = i-C_6H_{13}; R = \text{CH}_3 \) | 9 \( R = i-C_6H_{13}; R = \text{CH}_3 \) |
| 4 \( R = i-C_6H_{13}; R = \text{H} \) | 10 \( R = i-C_6H_{13}; R = \text{H} \) |
| 5 \( R = p-C_6H_4; R = \text{CH}_3 \) | 11 \( R = p-C_6H_4; R = \text{CH}_3 \) |
| 6 \( R = p-C_6H_4; R = \text{H} \) | 12 \( R = p-C_6H_4; R = \text{H} \) |

Synthesis of selenodiazagermetane \( R_2Ge-N(SiMe_3)(C=Se)N(SiMe_3) \)

Case \( R = n-C_6H_{13} \):

This compound was also synthesised by two methods, C and D.

Method C

Treatment of 1,3-bis(trimethylsilyl)selenourea, in stoichiometric amounts, with bis(diethylamino)dihexylgermane in refluxing anhydrous tetrahydrofuran resulted with a cleavage of Ge-N bonds by the NH groups (a transamination reaction) [22-26] forming the corresponding diazagermetane (Scheme 3) in yield of 45%.

$$\text{(n-C}_6\text{H}_{13})_2\text{Ge(NEt)_2} + \text{Me}_3\text{Si(H)}\text{N=SN(H)SiMe}_3 \rightarrow \text{(n-C}_6\text{H}_{13})_2\text{Ge}$$

Scheme 3

Case \( R = i-C_5H_{11} \):

Method D

The action of dichlorodihexylgermane, in stoichiometric amounts, on 1,3-bis(trimethylsilyl)selenourea, in refluxing anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine gave by a cyclization reaction, with elimination of hydrochloric acid from Ge-Cl and NH [22,26] group, the corresponding product (Scheme 4) in yield of 38%.

$$\text{(n-C}_6\text{H}_{13})_2\text{GeCl}_2 + \text{Me}_3\text{Si(H)}\text{N=SN(H)SiMe}_3 \rightarrow \text{(n-C}_6\text{H}_{13})_2\text{Ge}$$

Scheme 4
Using the same procedures described above, the reaction between bis(diethylamino)diisooamylgermane or dichlorodiisooamylgermane and 1,3-bis(trimethylsilyl)selenoureia does not lead to stable heterocycle but gives only the selenagermaadamantane 15 and 1,3-bis(trimethylsilyl)carbodiimide probably via the intermediate selenodiazagermetane. (Scheme 5).

\[
\begin{align*}
(i\text-C_3\text{H}_{11})_2\text{Ge}(\text{Y})_2 & \quad + \quad \text{Me}_3\text{Si}(\text{H})\text{N}--\text{N}(\text{H})\text{SiMe}_3
\quad \xrightarrow{\text{THF, refluxed}} \quad \text{Me}_3\text{Si} \quad \text{(i\text-CsH}_{11}\text{)}_2\text{Ge}\quad \text{-}2\text{YH} \\
& \quad \downarrow \quad \text{N} \\
((i\text-CsH}_{11})_4\text{Ge}_2\text{Se}_6 & \quad + \quad \text{Me}_3\text{Si}--\text{N}--\text{SiMe}_3
\end{align*}
\]

Scheme 5

**Reaction mechanism**

The formation of the selenagermaadamantane may be explained by two ways as follows (Scheme 6).
Path A: The nucleophilic intramolecular attack of selenium on the germanium atom leads to a corresponding intermediate 14'. Then, this cyclic intermediate 14' undergoes a decomposition to give the germaneselone and 1,3-bis(trimethylsilyl)carbodiimide.

Path B: The ring cleavage of 14 results in the formation of the monomeric species [(i-C₅H₁₁)₂Ge=N-SiMe₃] and [Me₃Si-N=C-Se] as an intermediate, which submits to a pseudo Wittig reaction to afford the intermediate 14'.

The germaneselone derivative showed a rearrangement to give preferentially the selenagermaadamantane 15 which has been completely characterised by usual spectroscopies, mass spectrometry and X-ray diffraction structure.

**Molecular modelisation study (ESSF field)**

This study showed the very important steric bulk of the isoamyl groups. The heterocycle 13 seems to benefit a protection of the reactive centre induced by the hexyl groups.

\[ R = i-C₅H₁₁ \quad \text{and} \quad R = n-C₆H₁₃ \]

**Synthesis of selenagermaadamantane 15**

The treatment of isoamyltrichlorogermane with lithium selenide gave tetragermahexaselenide 15 [27]. (Scheme 7). The structure was determined by X-ray crystallography.

\[
4 \text{ (i-C₅H₁₁)GeCl₃} + 6 \text{ LiSe} \xrightarrow{\text{THF refluxed}} \text{(i-C₅H₁₁)Se₆GeSiMe₃} \]

**Scheme 7**

**Synthesis of the 2-[1-(1-naphthyl)ethyl]-2-imidazoline 16**

This product was synthesised according to the following reaction scheme. (Scheme 8).
Synthesis of 17 and 18

The stoichiometric addition of thirane or methylthirane to 16 in toluene at 110 °C leads respectively to 1-(1-thioethyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline 17 and 1-(2-thiopropyl)-2-[1-(1-naphthyl)ethyl]-2-imidazoline 18 (i.e. by a cleavage of the C-S bond by the NH group [28]) (Scheme 9) in yields of 70 and 65%.

Synthesis of 1,3-bis(trimethylsilylselenourea) 19

The reaction between equimolar amounts of selenourea and chlorotrimethylsilane in the presence of triethylamine in anhydrous refluxing tetrahydrofuran gives 19 (Scheme 10) in yield of 85%.

\[
\begin{align*}
H_2N\text{-Se-C-NH}_2 + 2 \text{Me}_3\text{SiCl} & \xrightarrow{\text{THF} / 2 \text{B}_3\text{N}} \text{Me}_3\text{Si(H(N=Se)=N-H)}\text{SiMe}_3 + 2 \text{Et}_3\text{N,HCl}
\end{align*}
\]

Scheme 10
### Table 2  Toxicity in mice of some organic and organometallic derivatives

| Compound | \( \text{LD}_{50} \) (mg/kg) | \( \text{LD}_{50} \) (mmol/kg) |
|----------|-----------------------------|-----------------------------|
| \[
\begin{array}{c}
\text{Me}_3\text{Si}(\text{H})\text{N} \\
\text{N}(\text{H})\text{SiMe}_3
\end{array}
\] | 106 | 0.473 |
| \[
\begin{array}{c}
\text{Me}_3\text{Si}(\text{H})\text{N} \\
\text{N}(\text{H})\text{SiMe}_3
\end{array}
\] | 50 | 0.238 |
| \[
\begin{array}{c}
(i-C_6H_{11})_2\text{Ge} \\
\text{SCH}_2\text{CH}_2\text{N} \\
\text{N} \\
\text{CH}_3
\end{array}
\] | 80 | 0.106 |
| \[
\begin{array}{c}
(i-C_6H_{11})_2\text{Ge} \\
\text{SCH}_2\text{CH}_2\text{N} \\
\text{N} \\
\text{CH}_3
\end{array}
\] | 212 | 0.271 |
| \[
\begin{array}{c}
(n-C_6H_{11})_2\text{Ge} \\
\text{SCH}_2\text{CH}_2\text{N} \\
\text{N} \\
\text{CH}_3
\end{array}
\] | 185 | 0.221 |
| \[
\begin{array}{c}
(n-C_6H_{11})_2\text{Ge} \\
\text{SCH}_2\text{CH}_2\text{N} \\
\text{N} \\
\text{CH}_3
\end{array}
\] | 150 | 0.192 |
| \[
\begin{array}{c}
\text{Me}_3\text{Si}(\text{H})\text{N} \\
\text{N}(\text{H})\text{SiMe}_3
\end{array}
\] | > 75 | 0.281 |
| \[
\begin{array}{c}
\text{Me}_3\text{Si}(\text{H})\text{N} \\
\text{N}(\text{H})\text{SiMe}_3
\end{array}
\] | > 600 | 1.180 |

**Evaluation of the toxicity**

The toxicity obtained with the different compounds has been summarized in table 2. The biological protocol has been detailed in the *Experimental section*.

The 2-[1-(1-naphthyl)ethyl]-2-imidazoline (NEI) compounds seems to be less toxic than their 2-(1-naphthylmethyl)-2-imidazoline (NMI) homologous. For example, NEI (16) show a two times lower molar toxicity than NMI. The lower toxicity of organometallic compounds compared with basic materials is confirmed by comparison between the toxicity of 13 and 19. Indeed compound 13 is eight times less toxic (\( \text{LD}_{50} > 600 \) mg/Kg) than the starting derivative 19 (\( \text{LD}_{50} > 75 \) mg/Kg). This means that the organogermanium compound 13 have a toxicity four times lower than 19 one (expressed in mol fractions).

The results of the radioprotective activity will be reported at a later date.
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