SYNTHESIS AND RADIOPROTECTIVE PROPERTIES OF NEW METALLATHIAZOLIDINES, DIALKYLOXATHIAGERMOLANES, DIALKYLGERMOCANES AND METALLADITHIOACETALS

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Abstract

New organogermanium and organosilicon compounds 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 derivatives are noted in comparison with the starting organic compounds.

Introduction

We have realized a considerable work in the field of the pharmacological activity and chemical radioprotection of organogermanium and organosilicon compounds. In these investigations we have developed the synthesis and study of the biological activity of some organometallic compounds such as metallathiazolidines and metalladithioacetals of cysteamine, N-substituted cysteamine, methylcysteamine, N-(2-thioethyl)-1,3-diaminopropane and naphthyl-methylimidazoline.

All these derivatives have been tested in the field of radioprotection and they have shown a lower toxicity and led to a dose reduction factor (DRF) with values in the range of 1.4 and 1.75 [1-9].

We report in this paper the synthesis, toxicity and radioprotective activity of some new sila- and germathiazolidines, dialkyloxathiagermolanes, dialkyldithiagermocanes, sila- and germadithioacetals.

Sila- and germathiazolidines

Dialkylloxathiagermolanes

R = n-C₆H₁₃ **5**

R = -SCH₂CH₂NH₂·HCl **6**

Dialkyldithiagermolanes

X = S, R = i-C₅H₁₁ **7**, R = n-C₆H₁₃ **9**

X = O, R = i-C₅H₁₁ **8**, R = n-C₆H₁₃ **10**

Sila- and germadithioacetals

R₁ = R₂ = -SCH₂CH₂NH₂·HCl **11**

R₁ = R₂ = i-C₅H₁₁ **12**

R₁ = R₂ = n-C₆H₁₃ **13**

R₁ = p-CH₃C₆H₄, R₂ = CH₃ **14**

2,2'-thiodiethanethiol (Sigma-Aldrich Chimie) **2,2'-oxydiethanethiol** (Sigma-Aldrich Chimie) **3-[N-(2-mercaptoethyl)]aminopropanamide** WR-2529 [10]

Table I - Physicochemical data of derivatives 1-14

Compound	Method of synthesis	Yield (%)	Physical Properties and Elemental Analyses
1		60	¹ H NMR (δ in D ₂ O, ppm) : 2.09 (quintet, 2H, J = 5 Hz), 2.75 - 3.5 (m, 20H), 3.90 (t, 4H, J = 5 Hz). Analysis : Calcd : C, 34.27 ; H, 7.08 ; N, 12.30. Found : C, 34.18 ; H, 7.17 ; N, 12.26.
2	A or B	83	¹ H NMR (δ in CDCl ₃ , ppm) : 0.86 (d, 12H, J = 5.5 Hz), 0.98 - 1.76 (m, 10H), 2.37 - 3.21 (m, 8H). ¹³ C NMR (δ in CDCl ₃ , ppm) : 17.15 (-), 18.24 (-), 22.13 (+), 26.41 (-), 32.19 (+), 33.30 (-), 44.87 (-), 50.60 (-), 174.83 (C=O). IR (CCl ₄ , cm ⁻¹) : ν _{NH₂} = 3290, 3185 ; ν _{C=O} = 1670. Mass spectrum (EI) : m/z = 363 [M ⁺ +1]. Analysis : Calcd : C, 49.89 ; H, 8.93 ; N, 7.76. Found : C, 49.82 ; H, 8.97 ; N, 7.71.
3	A or B	97	¹ H NMR (δ in CDCl ₃ , ppm) : 0.86 (t, 6H, J = 5Hz), 1.1-1.32 (m, 20H), 2.54 - 2.90 (m, 8H). ¹³ C NMR (δ in CDCl ₃ , ppm) : 14.14 (+), 19.65 (-), 20.74 (-), 22.56 (-), 23.34 (-), 24.63 (-), 31.38 (-), 32.34 (-), 44.80 (-), 50.47 (-), 174.66 (C=O). IR (CCl ₄ , cm ⁻¹) : ν _{NH₂} = 3315, 3183 ; ν _{C=O} = 1670. Mass spectrum (EI) : m/z = 391 [M ⁺ +1]. Analysis : Calcd : C, 52.47 ; H, 9.32 ; N, 7.20. Found : C, 52.38 ; H, 9.33 ; N, 7.13.
4	A or B	87	M.P. = 53 - 55°C. ¹ H NMR (δ in CDCl ₃ , ppm) : 0.96 (s, 3H), 2.34 (s, 3H), 2.42-3.01 (m, 8H), (C ₆ H ₄ , syst. AB) δ _A = 7.40 (2H), δ _B = 7.30 (2H), J _{AB} = 8Hz. ¹³ C NMR (δ in CDCl ₃ , ppm) : 2.94 (+), 21.58 (+), 27.64 (-), 34.94 (-), 44.88 (-), 50.50 (-), 129.47 (+), 132.98 (+), 140.23 (C _{quat}), 140.73 (C _{quat}), 174.93 (C=O). IR (CCl ₄ , cm ⁻¹) : ν _{C=O} = 3344, 3214 ; ν _{C=O} = 1666. Mass spectrum (EI) : m/z = 326 [M] ⁺ . Analysis : Calcd : C, 48.05 ; H, 6.20 ; N, 8.62. Found : C, 47.85 ; H, 6.22 ; N, 8.56.
5		91	¹ H NMR (δ in CDCl ₃ , ppm) : 0.83 (t, 6H, J = 5 Hz), 1.24 - 1.52 (m, 20 H), 6.90 (dd, 1H, J = 4.5 and 7 Hz), 6.98 (dd, 1H, J = 1.7 and 7 Hz), 7.91 (dd, 1H, J = 1.7 and 4.5 Hz). Mass spectrum (EI) : m/z = 369 [M] ⁺ . Analysis : Calcd : C, 55.47 ; H, 7.94 ; N, 3.80. Found : C, 55.48 ; H, 7.97 ; N, 3.86.
6		98	¹ H NMR (δ in DMSO-d ₆ , ppm) : 2.98 - 3.21 (m, 8H), 7.37-7.76 (m, 3H). Mass spectrum (EI) : m/z = 274 [M ⁺ -77]. Analysis : Calcd : C, 25.56 ; H, 4.05 ; N, 9.93. Found : C, 25.51 ; H, 4.14 ; N, 9.86.
7		98	¹ H NMR (δ in CDCl ₃ , ppm) : 0.83 (d, 12H, J = 5.6 Hz), 1.2-1.72 (m, 10H), 2.74 - 2.79 (m, 8H). Mass spectrum (EI) : m/z = 369 [M+1] ⁺ . Analysis : Calcd : C, 45.80 ; H, 8.23. Found : C, 45.67 ; H, 8.26.

8		98	¹ H NMR (δ in CDCl ₃ , ppm): 0.87 (d, 12H, J = 5.6 Hz), 1.25 - 1.55 (m, 10H), 2.84 (m, 4H, J = 6.4 Hz), 3.66 (m, 4H, J = 6.4 Hz). Mass spectrum (EI): m/z = 281 [M ⁺ - 71]. Analysis: Calcd: C, 47.89; H, 8.61. Found: C, 47.79; H, 8.70.
9		98	¹ H NMR (δ in CDCl ₃ , ppm): 0.84 (t, 6H, J = 5.5 Hz), 0.98-1.45 (m, 20H), 2.79(s, 8H). Mass spectrum (EI): m/z = 396 [M ⁺]. Analysis: Calcd: C, 48.62; H, 8.67. Found: C, 48.59; H, 8.82.
10		92	¹ H NMR (δ in CDCl ₃ , ppm): 0.84 (t, 6H, J = 5.2 Hz), 0.98-1.52 (m, 20H), 2.81 (m, 4H, J = 6.2 Hz), 3.59 (m, 4H, J = 6.2 Hz). Mass spectrum (EI): m/z = 381 [M ⁺ +1]. Analysis: Calcd: C, 50.68; H, 9.04; O, 4.22. Found: C, 50.91; H, 9.18; O, 4.11.
11		48	¹ H NMR (δ in D ₂ O, ppm): 2.02 (quintet, 4H, J = 7.3 Hz), 2.71 - 3.52 (m, 32H, J = 5.4 Hz), 3.85 (t, 8H, J = 4.6 Hz). Analysis: Calcd: C, 40.04; H, 7.94; O, 4.85. Found: C, 39.85; H, 8.04; O, 4.76.
12	C or D	81	M.P.: 145 - 146°C. ¹ H NMR (δ in DMSO-d ₆ , ppm): 0.91 (d, 12H, J = 5.5 Hz), 1.40 (m, 10H), 2.52 - 2.68 (m, 6H, 6.2 Hz), 3.03 - 3.32 (m, 12H). ¹³ C NMR (δ in DMSO-d ₆ , ppm): 16.35 (-), 21.90 (+), 22.04 (-), 29.70 (+), 30.58 (-), 32.77 (-), 42.79 (-), 48.50 (-), 171.23 (C=O). IR (Nujol, cm ⁻¹): ν _{NH₂} = 3351, 3251; ν _{C=O} = 1670. Mass spectrum (EI): m/z = 363 [M ⁺ -147]. Analysis: Calcd: C, 47.16; H, 8.71; N, 11.00. Found: C, 46.97; H, 8.79; N, 10.88.
13	C or D	92	¹ H NMR (δ in CDCl ₃ , ppm): 0.86 (t, 6H, J = 5.6 Hz), 1.21-1.45 (m, 20H), 2.23-3.25 (m, 16H). ¹³ C NMR (δ in CDCl ₃ , ppm): 14.07 (+), 19.79 (-), 22.58 (-), 24.63 (-), 27.53 (-), 31.33 (-), 32.32 (-), 35.53 (-), 45.04 (-), 50.97 (-), 175.29 (C=O). IR (CCl ₄ , cm ⁻¹): ν _{NH₂} = 3358, 3179; ν _{C=O} = 1667. Mass spectrum (EI): m/z = 391 [M ⁺ -147]. Analysis: Calcd: C, 49.17; H, 9.00; N, 10.43. Found: C, 48.86; H, 9.02; N, 10.35.
14	C or D	59	M.P. = 215-217°C. ¹ H NMR (δ in DMSO-d ₆ , ppm): 1.15 (s, 3H), 2.33 (s, 3H), 2.36-3.5 (m, 16H), C ₆ H ₄ , δ _A = 7.52, δ _B = 7.31, J _{AB} = 7.2 Hz, sy st. AB. ¹³ C NMR (δ in DMSO-d ₆ , ppm): 1.90 (+), 21.02 (+), 22.53 (-), 30.54 (-), 42.77 (-), 48.28 (-), 129.49 (+), 132.27 (C _{quat}), 132.66 (+), 140.40 (C _{quat}), 171.22 (C=O). IR (Nujol, cm ⁻¹): ν _{NH₂} = 3399, 3191. ν _{C=O} = 1658. Mass spectrum (EI): m/z = 327 [M ⁺ -147]. Analysis: Calcd: C, 45.69; H, 6.81; N, 11.84. Found: C, 45.51; H, 6.82; N, 11.37.

Materials and methods

All manipulations were carried out under dry nitrogen or argon. Solvents were freshly distilled from sodium/benzophenone before use. IR spectra were recorded on a Perkin-Elmer 1600FT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 80 MHz and AC-200 spectrometer; the multiplicity of the ^{13}C NMR signals was determined by the APT technique and quoted as (+) for CH_3 and CH , and (-) for CH_2 and C_{quat} for quaternary carbon atoms. Mass spectra under electron impact (EI) conditions at 70 eV and 10 eV were recorded on a Hewlett-Packard 5989 and Nermag R10-10H spectrometers. Melting points were taken on a hot-plate microscope apparatus Leitz Biomed. Elemental analyses (C, H, N, O) were performed at the Laboratoire de Microanalyse de l'Ecole Nationale Supérieure de Chimie de Toulouse.

Silathiazolidine 1

To a suspension of $(\text{HCl} \cdot \text{H}_2\text{NCH}_2\text{CH}_2\text{S})_2\text{SiCl}_2$ [4] (5 g, 15.42 mmol) in tetrahydrofuran (100 ml) was added dropwise with stirring (3.15 g, 15.42 mmol) of 4-[(2-thioethyl)-3-aminopropyl]morpholine [9] in 70 ml of anhydrous tetrahydrofuran. The resulting reaction mixture was refluxed for 3 h, followed by cooling to room temperature and filtration. The precipitate was washed twice with anhydrous pentane (50 ml) and then dried in vacuo. A white solid, compound **1** (4.22 g, 60 %) was collected.

Syntheses of germathiazolidines 2-4

These compounds were prepared by two methods : A and B

Method A

Di(isoamyl)dichlorogermane (3.96 g, 13.86 mmol) in THF (70 ml) was added to $\text{HSCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$ (2.05 g, 13.85 mmol) and triethylamine (3.08 g, 30.50 mmol) in THF (100 ml). The mixture was refluxed for 2 h with stirring. After filtration to remove the precipitate $\text{Et}_3\text{N} \cdot \text{HCl}$, the filtrate concentrated under reduced pressure, afforded a white pasty product **2** (4.16 g, 83 %).

Method B

Bis(diethylamino)diisoamylgermane (4 g, 11.15 mmol) was added dropwise to a stirring mixture of $\text{HSCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{C}(\text{O})\text{NH}_2$ (1.65 g, 11.15 mmol) in anhydrous THF (100 ml). The mixture was refluxed under argon for 3 h with stirring. The solution was concentrated in vacuo to afford the compound **2** (3.42 g, 85 %).

2,2-di-n-hexyl-4,5-pyridino-1,3,2-oxathiagermolane

Di-n-hexyldichlorogermane (5.97 g, 19.03 mmol) in 20 ml of THF was added dropwise to a stirring solution of 2-mercapto-3-pyridinol (2.42 g, 19.03 mmol) and freshly distilled triethylamine (4.24 g, 42.86 mmol) in THF (100 ml). The mixture was refluxed for 2 h with stirring. After the mixture had cooled to room temperature it was filtered under argon to remove the precipitate $\text{Et}_3\text{N} \cdot \text{HCl}$. Removal of volatiles (under reduced pressure) from the filtrate, afforded a yellow liquid product **5** (6.36 g, 91 %).

2,2-(2-thioethylaminohydrochloride)-4,5-pyridino-1,3,2-oxathiagermolane

Compound	R_1	R_2	R_3	M	LD ₅₀ mg.Kg ⁻¹ (mmol)	Injected dose mg.Kg ⁻¹	Irradiation Gy(t, min) ^a	Survival rate %	DRF ^b
1	HCl.H ₂ NCH ₂ -CH ₂ S-	HCl.H ₂ NCH ₂ CH ₂ S-	-(CH ₂) ₃ -N(CH ₂) ₃ -C	Si	600 (1.32)	300 75 300 300	7.5 (15) 7.5 (15) 7.5 (90) 9.5 (15)	100 30 50 90	1.6
2	i-C ₅ H ₁₁	i-C ₅ H ₁₁	-(CH ₂) ₂ -C(=O)-NH ₂	Ge	> 1500 (4.15)	1000 1000	8 (15) 8 (90)	40 40	1.2
3	n-C ₆ H ₁₃	n-C ₆ H ₁₃	-(CH ₂) ₂ -C(=O)-NH ₂	Ge	> 1500 (3.86)	1000 1000	8 (15) 8 (90)	30 40	1.2
4	p-CH ₃ C ₆ H ₄	CH ₃	-(CH ₂) ₂ -C(=O)-NH ₂	Ge	> 1500 (4.62)	1000 1000 1000	8.25 (15) 8.25 (90) 10.25 (15)	70 60 20	1.4

^at = time between administration of the compound and irradiation. ^bdose reduction factor : (LD₅₀(30) treated/LD₅₀(30) untreated).

2-mercapto-3-pyridinol (0.5 g, 3.93 mmol) in THF (50 ml) was added dropwise to a stirring suspension of bis(2-thioethylaminohydrochloride)dichlorogermanium (1.45 g, 3.93 mmol) in 50 ml of THF. The mixture was refluxed for 2 h with stirring. After which the time the mixture was filtered and the yellow precipitates of **6** were collected (1.63 g, 98%), washed with pentane, and dried in vacuo.

Dialkylgermocanes

2,2-di-isoamyl-6-thia-1,3,2-dithiagermocane

To a solution of 2,2'-thiodiethanethiol (4.09g, 26.50mmol) and triethylamine (5.9 g, 58.31 mmol) in 100 ml anhydrous tetrahydrofuran was added, dropwise with stirring, di-isoamyl-dichlorogermane (7.57 g, 26.50 mmol) in 70 ml of THF. A white precipitate was gradually formed. The mixture was refluxed for 2 h with stirring. Filtration, followed by removal of the solvents in vacuo gave a quantitative yield of **7**.

Compounds **8-10** were prepared analogously from the appropriate dichlorogermane and diethanethiol $X(CH_2CH_2SH)_2$ ($X = O, S$).

Siladithioacetal

4-[(2-thioethyl)-3-aminopropyl]morpholine (5.04 g, 24.68 mmol) in THF (70 ml) was added dropwise to a stirring suspension of $(HCl.H_2NCH_2CH_2S)_2SiCl_2$ (4.00 g, 12.34 mmol) in THF (100 ml). The mixture was refluxed for 3 h with stirring. The white precipitate was filtered, washed twice with pentane (50 ml), and dried in vacuo. A white solid, compound **11** (3.9 g, 48 %) was collected.

Germadithioacetals

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

Method C

To a stirred mixture of 3-[N-(2-mercaptoethyl)]aminopropanamide (2.76 g, 18.61 mmol), triethylamine (2.07 g, 20.47 mmol) and 150 ml of THF a solution of dichlorodihexylgermane (2.92 g, 9.30 mmol) in 50 ml of THF was added slowly. The reaction mixture was refluxed for 2 h, filtered at ambient temperature under argon, concentrated in vacuo to afford the compound **13** (4.6g, 92 %).

Method D

To a stirred mixture of 3-[N-(2-mercaptoethyl)]aminopropanamide (2.76 g, 18.61 mmol) in 100 ml of THF was added, dropwise with stirring bis(diethylamino)dihexylgermane (3.6 g, 9.31 mmol) in 50 ml of THF. The mixture was refluxed for 2 h. Removals of volatiles (under reduced pressure) to afford compound **13**.

Physicochemical data of derivatives **1-14** synthesized in this paper are reported in Table I.

Pharmacology : evaluation of radioprotection

Male CD1 mice (Charles River, France), 25 g body weight, were used. Compounds were injected intraperitoneally 15 of 90 min before irradiation. The irradiation dose was LD_{100/30}, days for untreated control mice (7.5, 8 or 8.25 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 LD₅₀ 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 6.5 and 7.25 Gy, according to the date).

Irradiation was applied using a cobalt-60 source at a dose rate of 0.3-0.4 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 x 28.5 cm in area. Dosimetry was checked with an ionization chamber dosimeter. The different LD₅₀ values were determined by probit analysis.

Table III - Dialkyl pyridino-oxathia-germolane

 R_2Ge

Compound	R	LD ₅₀ mg·Kg ⁻¹ (mmol)	Injected dose mg·Kg ⁻¹	Irradiation Gy (t,min)	Survival rate %	DRF
5	n-C ₆ H ₁₃	800	400 100 400	7.5 (15) 7.5 (15) 7.5 (90)	40 20 50	1.3
6	HCl·H ₂ NCH ₂ -CH ₂ S-	400	200	7.5 (15)	50	1.1

Table IV - Dialkylthia- or oxadithia-germocanes R₂Ge(SCH₂CH₂)₂X

Compound	R	X	LD ₅₀ mg Kg ⁻¹ (mmol)	Injected dose mg·Kg ⁻¹	Irradiation Gy(t,min)	Survival rate %	DRF
7	i-C ₅ H ₁₁	S	> 1500 (4.08)	1000 250 1000	7.5 (15) 7.5 (15) 7.5 (90)	60 60 50	1.3
8	i-C ₅ H ₁₁	O	> 1500 (4.27)	1000 250 1000	7.5 (15) 7.5 (15) 7.5 (90)	40 20 40	1.2
9	n-C ₆ H ₁₃	S	> 1500 (3.79)	1000 250 1000	7.5 (15) 7.5 (15) 7.5 (90)	30 40 40	1.2
10	n-C ₆ H ₁₃	O	> 1500 (3.95)	1000 250 1000	7.5 (15) 7.5 (15) 7.5 (90)	60 10 20	1.2

Results and discussion

Sila- and germathiazolidines

Silathiazolidine has been prepared by the reaction of the corresponding dichlorosilane with an appropriate N-substituted cysteamine in stoichiometric molar ratio in refluxing anhydrous tetrahydrofuran, Scheme 1 :

Scheme 1

Germathiazolidines have been prepared according to two methods of heterocyclisation already described in the literature [1, 11, 12].

Method A

The action of diorganogermayldichloride [12] (in stoichiometric amounts) on N-substituted cysteamine in refluxing anhydrous THF in the presence of freshly distilled triethylamine gave by a cyclisation reaction, with elimination of hydrochloric acid from M-Cl, SH and NH [13] groups, the corresponding products, Scheme 2 :

Scheme 2

Method B

Treatment of N-substituted cysteamine, in stoichiometric amounts, with bis(diethylamino) dialkylgermane in anhydrous THF resulted in the cleavage of Ge-N bonds by the N-H and SH groups (a transamination reaction) [1, 12, 14] forming the corresponding germathiazolidines, Scheme 3 :

Scheme 3

Sila- and germadithioacetals

Siladithioacetal has been prepared by action of diorganosilyldichloride [4] on 2 mol of N-substituted cysteamine in refluxing anhydrous tetrahydrofuran, Scheme 4 :

Table V - Sila- and Germa-dithioacetals $R_1R_2M[SCCH_2CH_2NHR_3]_2$

Compound	R_1	R_2	R_3	M	LD50 $mg \cdot kg^{-1}$ (mmol)	Injected dose $mg \cdot kg^{-1}$	Irradiation Gy(t, mn)	Survival rate %	DRF
11	$HCl \cdot H_2NCH_2CH_2S \cdot$	$HCl \cdot H_2NCH_2CH_2S \cdot$		Si	500 (0.76)	250 62.5 250 250	7.5 (15) 7.5 (15) 7.5 (90) 9.5 (15)	60 30 10 20	1.3
12	$i-C_5H_{11}$	$i-C_5H_{11}$		Ge	> 1500 (2.95)	1000 1000	8.25 (15) 10.25 (15)	100 30	1.4
13	$n-C_6H_{13}$	$n-C_6H_{13}$		Ge	> 1500 (2.79)	1000 1000	8.25 (15) 8.25 (90)	90 20	1.3
14	$p-CH_3C_6H_4$	CH_3		Ge	> 1200 (2.54)	600	8.25 (15)	90	1.2

Table VI - 2,2'-thiodiethanethiol, 2,2'-oxydiethanethiol and 3-[N-(2-mercaptoethyl)]am nopropylamide

Compound	LD50 $mg \cdot kg^{-1}$ (mmol)	Injected dose $mg \cdot kg^{-1}$	Irradiation Gy (t,min)	Survival rate %	DRF
15 $S[CH_2CH_2SH]_2$	75 (0.49)	37.5 9.4	8 (15) 8 (15)	20 0	1
16 $O[CH_2CH_2SH]_2$	150 (1.09)	75 18.8 75	8 (15) 8 (15) 8 (90)	70 10 0	1.1
$HSCH_2CH_2NHCH_2CH_2C(=O)NH_2$	700 (4.73)	350 350	8 (15) 10 (15)	93 33	1.3

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Scheme 4

Germadithioacetals of N-substituted cysteamine were prepared by two methods, C and D [4].

Method C

The reaction of diorganogermayldichloride and 2 mol of N-substituted cysteamine in the presence of triethylamine in refluxing anhydrous THF lead to the acyclic derivatives, Scheme 5 :

Scheme 5

Method D

The action of 2 mol of N-substituted cysteamine with bis(diethylamino)dialkylgermane in anhydrous THF (a cleavage reaction of Ge-N bonds by the S-H groups) lead to the formation of the desired products, Scheme 6 :

Scheme 6

Dialkyloxathiagermolanes

Reactions of diorganogermayldichloride with 2-mercapto-3-pyridinol in refluxing anhydrous THF in 1:1 molar ratios yield quantitatively oxathiagermolanes derivatives according to the following reactions, Scheme 7 :

Scheme 7

Dialkyldithiagermocanes

These compounds were obtained by the reaction of 2,2' -thiodiethanethiol or of 2,2' -oxydiethanethiol with dialkylgermyldichloride in equimolar amounts in anhydrous tetrahydrofuran in the presence of freshly distilled triethylamine, Scheme 8 :

Scheme 8**Conclusions**

The analysis of the results reported in tables II-V shows that the organogermylated and organosilylated derivatives described have a radioprotective activity greater than or sometimes equal to that of the starting organic derivatives and always a lower toxicity.

The organosilylated and organogermylated compounds **1**, **4**, **7**, **11**, **12** and **13** have an interesting radioprotective activity (DRF between 1.3-1.6) compared with the starting organic compounds for example :

- derivative **1** (DRF = 1.6), LD₅₀ = 600 mg. Kg⁻¹ (1.32 mmol, injected) ; derivative **11** (DRF = 1.3), LD₅₀ = 500 mg.Kg⁻¹ (0.76 mmol) compared with the starting organic derivative (DRF = 1.2), LD₅₀ = 450 mg.Kg⁻¹ (2.20 mmol) [9].

- derivative **4** (DRF = 1.4), LD₅₀ > 1500 mg.Kg⁻¹ (4.62 mmol) compared with derivative **17** (DRF = 1.3), LD₅₀ = 700 mg.Kg⁻¹ (4.73 mmol).

- derivative **7** (DRF = 1.3), LD₅₀ > 1500 mg.Kg⁻¹ (4.08 mmol) compared with derivative **15** LD₅₀ = 75 mg.Kg⁻¹ (0.49 mmol). We observed in this case an important decrease of toxicity with the organogermanium derivative **7** compared with the starting one **15**.

Concerning the derivatives **12** and **13** we have noted a lower toxicity compared with the WR-2529 **17** and a low increase of radioprotective activity : derivative **12** (DRF = 1.4) LD₅₀ > 1500 mg.Kg⁻¹ (2.95 mmol) ; derivative **13** (DRF = 1.3) LD₅₀ > 1500 mg.Kg⁻¹ (2.79 mmol) ; derivative **17** LD₅₀ = 700 mg.Kg⁻¹ (4.73 mmol).

With the other organometallic compounds **2**, **3**, **5**, **6**, **8**, **9**, **10** and **14** we have always observed a low increased activity in chemical radioprotection and a notable decrease of the toxicity compared with unsubstituted organic derivatives.

We have to underline that in all cases the greater radioprotective activity is obtained with organosilylated and organogermylated in spite of lower injected dosages expressed in mmol fractions.

At last, it is important to note the significant radioprotective activity of germa and silathiazolidines, dialkylxathiagermolanes and dialkylgermocanes when their injection is practiced 90 minutes before the irradiation. It confirms the sustained activity found for thiazolidines and indicates that the hydrolysis leading to the cysteamine release is an important mechanism in radioprotection.

In short, the radioprotective activity of organosilylated and organogermylated compounds can be increased compared with unsubstituted organic derivatives by the presence in these molecules of organometallic groups which increase the hydrosolubility and the organic ligands which increase the liposolubility and globally the biological activity of these molecules, thereby favoring their passage through the cellular membranes.

The results presented in this paper confirm the positive contribution of germanium and silicon in this field in agreement with previous work [1-9] and the interesting biological activity of organosilicon and organogermanium compounds in different fields [15-22].

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