ELSEVIER

Journal of Organometallic Chemistry 659 (2002) 165–171

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Synthesis, molecular structure and biological activity of bromobenzylgermatranes

Edmunds Lukevics *, Luba Ignatovich, Tatyana Shul'ga, Olga Mitchenko, Sergey Belyakov

Latvian Institute of Organic Synthesis, Aizkraukles 21, Riga LV-1006, Latvia

Received 20 May 2002; received in revised form 11 July 2002; accepted 11 July 2002

Abstract

The new series of benzylgermatranes $RC_6H_4CH_2Ge(OCH_2CH_2)_3N$, R = H (**I**), 2-Br (**II**), 3-Br (**III**), 4-Br (**IV**), has been obtained to study the influence of a substituent position on coordination of the germanium atom, the values of bond angles and neurotropic activity. Compounds **I**–**IV** were prepared by insertion of $GeBr_2$ into carbon–bromine bond of the corresponding benzylbromide or bromobenzylbromide in refluxing toluene, conversion of benzyl- or bromobenzyltribromogermanes into triethoxy derivatives by alcoholysis, and transalkoxylation with triethanolamine. The crystal structure of compounds **I**–**IV** was studied via the X-ray diffraction method. The intramolecular donor–acceptor bond N→Ge in benzylgermatranes (2.175–2.219 Å) is shorter than that in tolylgermatranes (2.212–2.230 Å). Biological investigations have demonstrated that all benzylgermatranes (**I**–**IV**) are low toxic compounds ($LD_{50} > 1000$ mg kg^{-1}) with high anaesthetic and anti-Corazol activity. Benzylgermatrane (**I**), 3-bromobenzylgermatrane (**III**) and 4-bromobenzylgermatrane (**IV**) improve memory processes and completely prevent animals from retrogradal amnesia (RA) caused by electroshock. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Benzyltribromogermane; Bromobenzyltribromogermane; Germatrane; Crystal structures; Toxicity; Neurotropic activity

1. Introduction

Germatranes (CAS name: 5-aza-2,8,9-trioxa-1-germatricyclo[3.3.3.0]undecane) contain hypervalent germanium atom with transannular bond to nitrogen (bond length 2.01–2.29 Å) which is responsible for their chemical stability [1,2]. The nature of substituent at germanium atom influences the strength of the transannular N→Ge bond, the values of bond angles [1,2] and biological properties [3–6]. Recently we found that arylgermatranes are less toxic compounds than corresponding thienylgermatranes [6], at the same time the N→Ge bond is longer in arylgermatranes than in furyl- and thienylgermatranes [1,2,7]. It has been found that in furyl- and thienylgermatranes the introduction of one methylene group between heterocycle and germatranyl group dramatically lowers the acute toxicity of the compound, while the neurotropic activity remains high [4–6]. One can expect that in phenyl–benzyl series it will lead to the low toxic compounds and thus to the increase of their therapeutic index. Therefore, in this investigation we focused our attention to the benzylgermatranes.

The first step of their synthesis is preparation of benzyltribromogermanes by the insertion of $GeBr_2$ into the C–Br bond. As the starting bromobenzylbromides contain two different carbon–bromine bonds (C_{sp^3}–Br and C_{sp^2}–Br) we could expect the formation of bromobenzylgermatranes or even bis(germatranyl)derivatives. The influence of the position of bromine atom in the phenyl ring on the reactivity of the starting bromides and on the properties of the obtained germatranes has been studied.

2. Results and discussion

Benzylgermatranes (**I**–**IV**) were obtained as a result of the following conversions: insertion of germanium dibromide into carbon–bromine bond of the corre-

* Corresponding author. Tel.: +371-75-51-822; fax: +371-75-50-338

E-mail address: ign@osi.lv (E. Lukevics).

0022-328X/02/$ - see front matter
PII: S0022-328X(02)01723-0

sponding benzyl- or bromobenzylbromides in refluxing toluene, conversion of benzyl- or bromobenzyltribromogermanes into triethoxy derivatives by alcoholysis, and transalkoxylation with triethanolamine to germatranes **I**–**IV** (yields 66.7, 61.0, 56.5, and 35.0, respectively) (Scheme 1).

Although in the case of *p*-dibromobenzene the insertion of $GeBr_2$ in to C_{sp^2}–Br took place ('Pierce'vial, ~200 °C, 25 h) [8], all our attempts to insert $GeBr_2$ into C_{sp^2}–Br bond of bromobenzylbromides were unsuccessful even with excess of $GeBr_2$, long time heating in solvent, or without solvent at ~200 °C under pressure in 'Pierce' vial. It means that the introduction of CH_2GeBr_3 group completely deactivated the C_{sp^2}–Br bond in bromobenzyltribromogermanes to the further insertion of germylene.

Yields, melting points, element analysis, mass-spectra and ^{1}H-NMR data for new compounds obtained are summarized in Table 1. After recrystallization from chloroform (**I**, **III**, **IV**) or ethanol (**II**), they were obtained as colorless crystals suitable for X-ray diffraction study.

In extension of our structural investigation of atranes the crystals of germatranes **I**–**IV** were analyzed by means of X-ray diffraction. Figs. 1–3 show a perspective view of molecular structures **I**, **II**, **IV** with atomic labels. Table 3 lists the main geometrical characteristics of molecules **I**–**IV**.

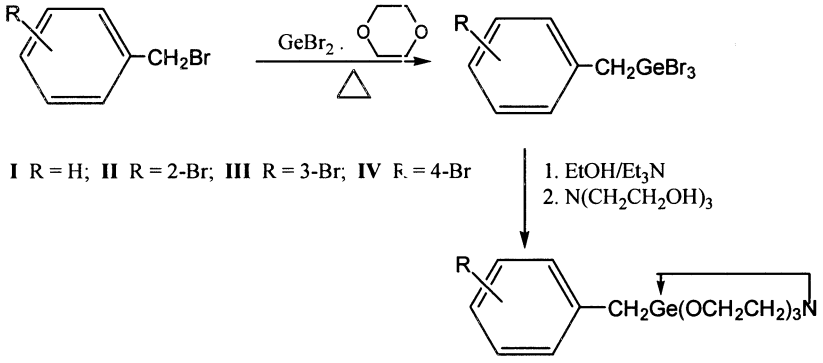
For crystal structures **I**, **II**, **IV** the disorder is observed. This phenomenon is usual for crystals of atranes. The disordered atoms are carbons C4, C6 and C11 in germatrane cage. In the structure **I** for atoms C4, C6, C11 the occupation *g*-factor equals 0.72 (respectively, $g = 0.28$ for $C4_x$, $C6_x$ and $C11_x$). In the structure **II** for all disordered atoms $C4_1$, $C6_1$, $C11_1$ and $C4_2$, $C6_2$, $C11_2$ the *g*-factor is 0.5. For structure **IV** the disorder is observed only in one of two crystallographically independent molecules, namely in molecule **B** (see Fig. 4). The values of *g* are 0.75 for C4, C6, C11 and 0.25 for $C4_x$, $C6_x$, $C11_x$.

The values of intramolecular N→Ge donor–acceptor bond lengths for **I**–**IV** lie in the interval of 2.175–2.219 Å. It has been shown [9] that the N→Ge distance depends on packing effect, because only a little energy is needed to change the N→Ge bond length on a few tenths of angstrom from optimum. At the same time, the parameters of temperature factors for germanium and nitrogen are relatively low and the thermal ellipsoids of Ge and N are correspondingly small. Though 'no indication was found for unusually flexible cage or for an impact of the crystal packing on the N→Ge linkage' [10], however, these thermal displacement parameters correspond to crystal state where molecules are compressed. In the free state thermal displacements along the N→Ge directions should be considerable because in isolated molecules of germatranes and silatranes the potential curve for deformation of transannular bond is very shallow [9,11]. The experimental investigations of atranes in the gas-phase [12,13] conform to this fact. The significant atom displacements along transannular bond lead to a large error for value of the bond length in gas-phase electronography studies. The influence of crystal packing effect is displayed for structure **IV** where there are two symmetrically non-equivalent molecules (see Fig. 4). For the molecules **B** the packing effect is less than for **A**: the shortest intermolecular contacts for molecule **A** are 2.67 Å (for H7B···H6B) and 2.69 Å (for H4A···O2), whilst for molecule **B** they are 2.79 Å (for H6′A···O8′) and 2.91 Å (for H6′B···H16′). Therefore, unlike molecule **A** the molecule **B** is disordered and N→Ge bond for **B** is longer (2.219 (3) Å) than for **A** (2.176 (3) Å).

For other covalent bonds, the crystal packing influence is not significant, therefore, their values of bond lengths are near to standard, except for C–C and C–N bonds in atrane system of *m*-bromobenzylgermatrane (**III**). These bonds are shortened due to the strong liberated thermal vibration [14] of the carbon atoms, which are connected with nitrogen atom.

The intramolecular donor–acceptor bond N→Ge in benzylgermatranes **I**–**IV** (2.175–2.219 Å) is shorter than that in tolylgermatranes (2.212–2.230 Å) [1].

The experimental evolution of acute toxicity and neurotropic activity of benzylgermatranes is presented



Scheme 1.

Table 1
Analytical data for benzylgermatranes $RGe(OCH_2CH_2)_3N$

R	Reaction time (*h*)	M.p. (°C)	Molecular formula	Anal. Found: (Calc.) (%)			^{1}H-NMR (δ ppm)	GS–MS (%)	Yield (%)
				C	H	N			
$C_6H_5CH_2$ (**I**)	4	224–226	$C_{13}H_{19}GeNO_3$	50.22 (50.39)	6.16 (6.18)	4.52 (4.52)	2.31(2H, s, CH_2); 2.64 (6H, t, N–CH_2); 3.59(6H, t, O–CH_2); 6.79–7.26 (4H, m, C_6H_5)	311[M^+, 5], 220[$M^+ - C_6H_5CH_2$, 100], 160(35), 146(18), 130(7), 116(5), 100(5), 91(50), 65(20), 56(35), 42(30)	66.7
2-Br-$C_6H_4CH_2$ (**II**)	3	195–197	$C_{13}H_{18}BrGeNO_3$	40.05 (40.16)	4.66 (4.67)	3.63 (3.60)	2.53(2H, s, CH_2); 2.62(6H, t, N–CH_2); 3.62(6H, t, O–CH_2); 6.62–7.42(4H, m, C_6H_4)	389[M^+, 3], 220[$M^+ - Br\ C_6H_5CH_2$, 100], 160(30), 146(15), 130(7), 117(5), 102(5), 90(30), 56(35), 42(30)	61.0
3-Br-$C_6H_4CH_2$(**III**)	6	189–190	$C_{13}H_{18}BrGeNO_3$	40.20 (40.16)	4.60 (4.67)	3.52 (3.60)	2.28(2H, s, CH_2); 2.64(6H, t, N–CH_2); 3.62(6H, t, O–CH_2); 6.77–7.37 (4H, m, C_6H_4)	389[M^+,3], 310[$M^+ - Br$, 3], 220[$M^+ - BrC_6H_5CH_2$, 100], 190(6), 160(28), 146(14), 130(10), 117(7), 102(5), 89(30), 56(35), 42(30)	56.5
4-Br-$C_6H_4CH_2$(**IV**)	5	225–228	$C_{13}H_{18}BrGeNO_3$	40.17 (40.16)	4.59 (4.67)	3.56 (3.60)	2.26(2H, s, CH_2); 2.66 (6H, t, N–CH_2); 3.60 (6H, t, O–CH_2); 6.86–7.28(4H, m, C_6H_4)	389[M^+,5], 220[$M^+ - BrC_6H_5CH_2$, 100], 190(5), 160(30), 146(16), 130(10), 117(7), 102(5), 90(35), 56(35), 42(30)	35.0

Table 2
Crystal data, measurement conditions and refinement results for compounds **I**–**IV**

	I	**II**	**III**	**IV**
Molecular formula	$C_{13}H_{19}GeNO_3$	$C_{13}H_{18}BrGeNO_3$	$C_{13}H_{18}BrGeNO_3$	$C_{13}H_{18}BrGeNO_3$
Molecular weight	309.88	388.79	388.79	388.79
Crystal size (mm)	0.07 × 0.32 × 0.37	0.08 × 0.2 × 0.45	0.24 × 0.25 × 0.47	0.10 × 0.18 × 0.28
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P\bar{1}$
Cell parameters				
a (Å)	10.4871(3)	7.6738(2)	6.7780(1)	6.9587(2)
b (Å)	11.6149(4)	17.4535(5)	12.2271(3)	11.1650(3)
c (Å)	13.7570(5)	12.5238(4)	17.9044(5)	19.0717(6)
α (°)	90.0	90.0	90.0	86.853(1)
β (°)	126.420	18.130(2)	100.614(1)	82.352(1)
γ (°)	90.0	90.0	90.0	83.796(2)
Unit cell volume V (Å^3)	1348.41(8)	1479.24(8)	1458.44(6)	1458.74(7)
Calculated density D_x (g.cm^{-3})	1.527	1.746	1.771	1.770
$F(000)$	640	776	776	776
Absorbtion coefficient μ (mm^{-1})	2.27	4.77	4.84	4.84
Data collection: $2\theta_{max}$ (°)	55	55	60	55
Number of measured reflections	5864	5741	7401	10383
Number of independent reflections	3423 [$R_{int} = 0.031$]	3547 [$R_{int} = 0.032$]	4266 [$R_{int} = 0.033$]	7086 [$R_{int} = 0.033$]
Number of observed reflections	1975 [$I > 3\sigma(I)$]	2135 [$I > 3\sigma(I)$]	2961 [$I > 2\sigma(I)$]	4632 [$I > 3\sigma(I)$]
Refinement data: R-factor	0.038	0.040	0.051	0.043
$R(F)$ for all data	0.071	0.090	0.083	0.071
$wR(F^2)$ for all data	0.080	0.119	0.121	0.101
$\Delta\rho_{max}$, (e Å^{-3})	0.49	1.25	1.21	0.99
Number of parameters	175	197	172	359
Programs used	DIRDIF [17], MAXUS [18], ORTEP [19]	DIRDIF [17], MAXUS [18], ORTEP [19]	SHELXS-86 [20], SHELXL-97 [21], ORTEP [19]	SIR97 [22], MAXUS [18], ORTEP [19]
Deposition number	185 760	185 761	in [16]	185 762

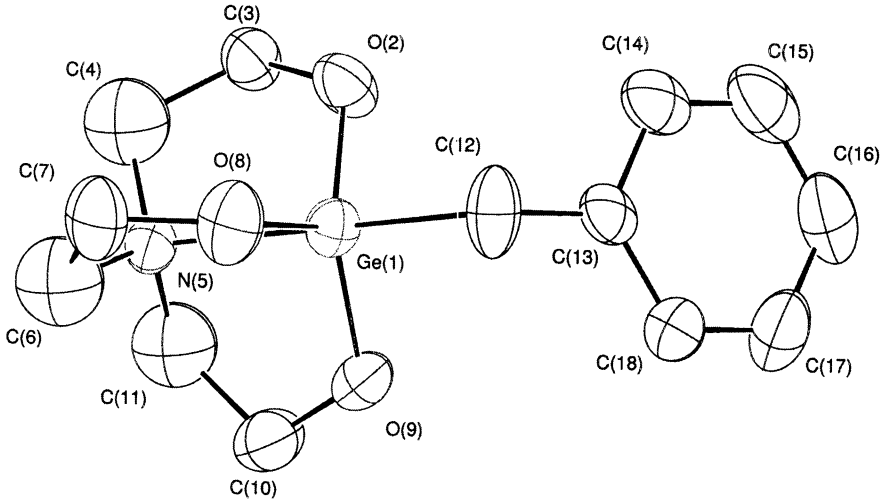


Fig. 1. Perspective view and atom numbering scheme of molecule **I**.

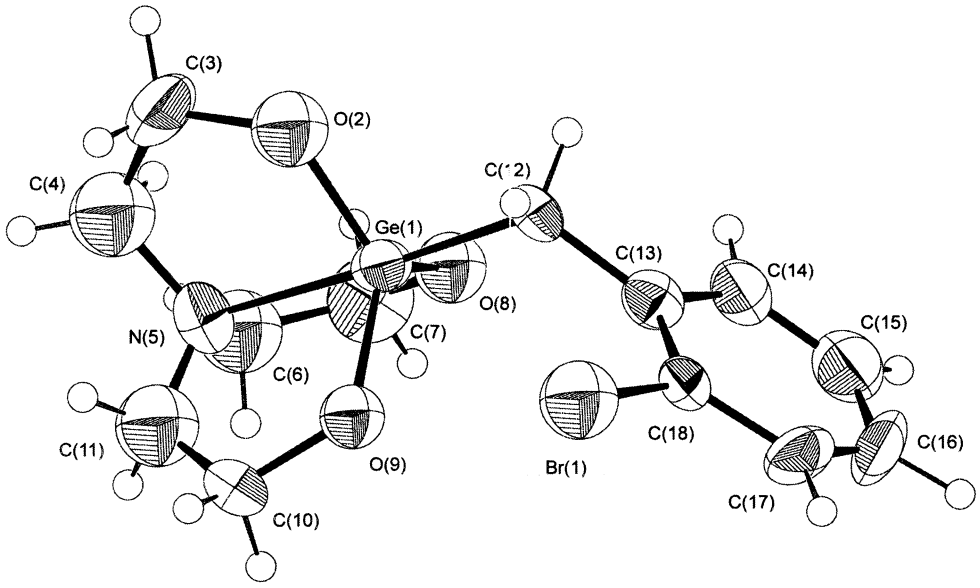


Fig. 2. Perspective view and atom numbering scheme of molecule **II**.

in Table 4. Biological investigations have demonstrated that all compounds **I**–**IV** are low toxic compounds ($LD_{50} > 1000$ mg kg^{-1}). Like in furyl- and thienylgermatranes [4,6] introduction of CH_2-group between aromatic ring and germatranyl group significantly lowers the toxicity of germatrane (LD_{50} for phenylgermatrane 35.5 mg kg^{-1} [1], for 4-bromophenylgermatrane −65 mg kg^{-1} [8]). All benzylgermatranes (**I**–**IV**)

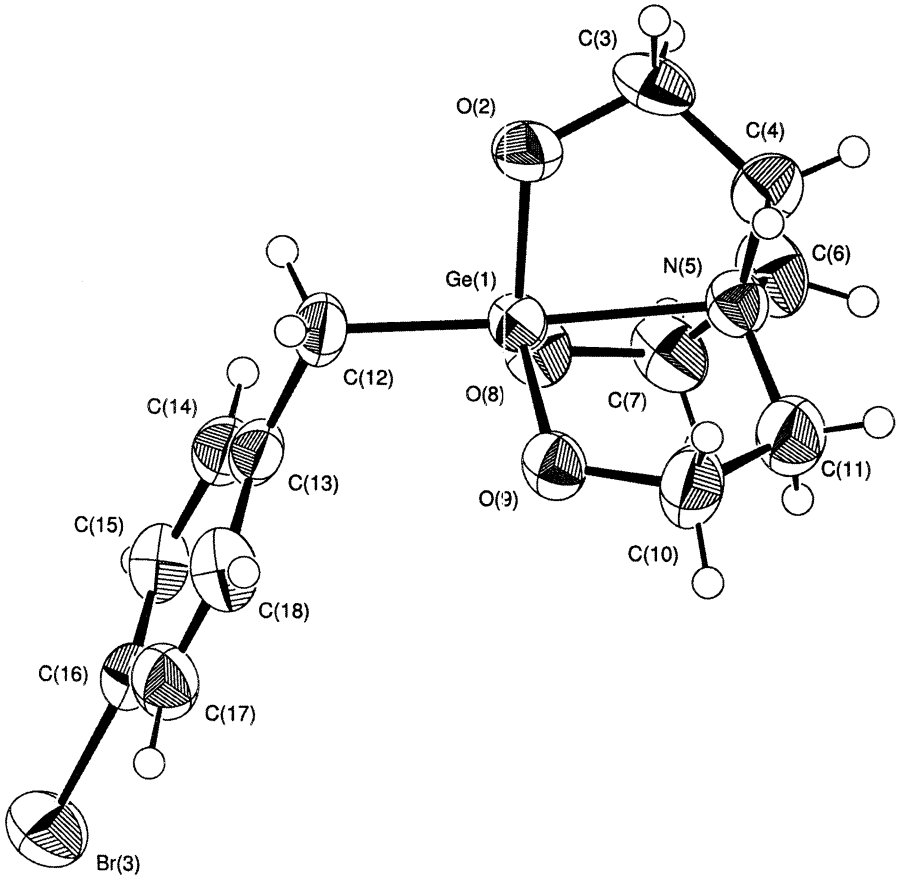


Fig. 3. Perspective view and atom numbering scheme of molecule **IV**.

Table 3
The principal geometrical parameters of molecules **I**–**IV**

	I	**II**	**III**	**IV** (Molecule **A**)	**IV** (Molecule **B**)
N–Ge (Å)	2.183(2)	2.175(3)	2.183(3)	2.176(3)	2.219(3)
Ge–C (Å)	1.956(3)	1.954(3)	1.962(4)	1.962(3)	1.952(3)
Ge–O(mean) (Å)	1.798(2)	1.803(2)	1.800(3)	1.799(2)	1.797(2)
O–C(mean) (Å)	1.408(4)	1.413(4)	1.411(5)	1.420(4)	1.404(4)
C–C(mean) (Å)	1.517(3)	1.521(10)	1.471(8)	1.516(6)	1.490(7)
C–N(mean) (Å)	1.478(4)	1.487(9)	1.445(6)	1.476(4)	1.471(5)
C–Br (Å)		1.894(3)	1.895(4)	1.910(3)	1.899(4)
N–Ge–C (°)	178.46(9)	176.4(1)	175.6(2)	177.7(1)	177.3(1)
C–Ge–O(mean) (°)	97.3(1)	97.2(1)	97.3(2)	97.1(1)	98.0(1)
Ge–C–C (°)	115.7(2)	118.0(2)	117.8(3)	116.5(2)	116.1(2)
ΔGe (Å)	0.2295(4)	0.2273(6)	0.2266(18)	0.2219(4)	0.2493(5)
ΔN (Å)	0.381(3)	0.375(5)	0.380(5)	0.387(4)	0.362 (4)

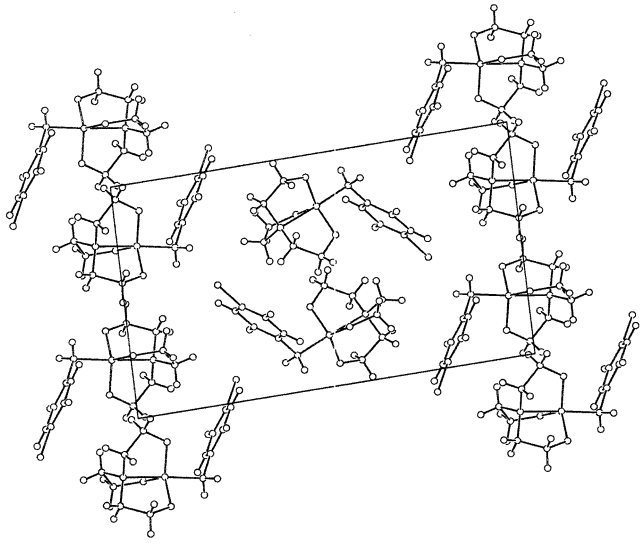


Fig. 4. Crystal structure of compound **IV** projection along [100].

applied in doses 5 mg kg^{-1} prolong hexobarbital-induced anaesthesia by 62–95%, possess high *anti*-Corazol activity (75–136%). Bromobenzylgermatranes **II** and **III** protect against hypoxia (50–58%). Duration of ethanol anaesthesia is decreased by 40% under influence of compound **III** (Table 4). Benzylgermatrane (**I**), 3-bromobenzylgermatrane (**III**) and 4-bromobenzylgermatrane (**IV**) improve memory processes and completely prevent animals from retrogradal amnesia (RA) caused by electroshock (Table 4).

3. Experimental

Standard inert atmosphere techniques were used for all synthesis and sample manipulations. The solvents were dried by standard methods and distilled prior use. Arylhalogenides—commercially available compounds-were distilled prior use under vacuo. The dioxane complex of germanium (**II**) dibromide was prepared by reduction of $GeBr_4$ with tetramethyldisiloxane in 1,4-dioxane by known procedure [15].

^{1}H-NMR spectra were conventionally recorded on a Varian 200 Mercury instrument (200 MHz) using $CDCl_3$ as a solvent and hexamethyldisiloxane (HMDSO) as internal standard. Mass spectra were registered on GC–MS HP 6890 (70 eV).

For X-ray crystal structure analysis of compounds **I**–**IV** an authomatic 'Nonius KappaCCD' diffractometer with Mo radiation ($\lambda = 0.71073$ Å) was used. The crystallographic, measurement and refinement data for **I**–**IV** are given in Table 2. Preliminary data for 3-bromobenzylgermatrane (**III**) have been described in [16].

Neurotropic activity was studied on Icr:Ice BALB/c and CBA mice. Ambient temperature (22+1 °C) was

Table 4
Acute toxicity and neurotropic activity of $RGe(OCH_2CH_2)_3N$

R	Hypoxia (%)	Corazol induced spasms (%)	Phenamine, stereotypy (%)	Anaesthesia of control (%)		RA(%)
				Hexo-barbital	Ethanol	
$C_6H_5CH_2$ (**I**)	127	213	104	162	116	100
2-$BrC_6H_4CH_2$ (**II**)	158	226	129	162	91	100
3-$BrC_6H_4CH_2$ (**III**)	116	237	91	167	60	60
4-$BrC_6H_4CH_2$ (**IV**)	150	175	129	195	80	100

maintained in the laboratory and in the animal colony. The tested substances were administered intraperitoneally 30 or 60 min prior to the assay as aqueous suspensions prepared with the aid of Tween 80. Control animals received injections of equal amounts of distilled water with Tween 80. Tests were indicated and determined according to Ref. [23]. Conventional reflex of passive avoidance was applied to evaluate the influence of the substances in question on memory and antiamnesic activity. RA was caused transcorneally by maximal electric shock administered just after learning.

3.1. Benzylgermatrane

Benzylbromide (3.7 g, 0.022 mol) and dioxane complex of germanium (II) dibromide (6.98 g, 0.022 mol) in 20 ml toluene were refluxed for 4 h under argon atmosphere. The resultant yellow solution was cooled to room temperature (r.t.) and analyzed by GC–MS (m/z, %): 404 [M^+, 5], 325 [$M^+ - Br$, 3], 153 (Ge–Br, 10), 91(100). An ethanolic solution (5 ml) of triethylamine (6.1 g, 0.06 mol) was added dropwise to a benzyltribromogermane, cooled to 0 °C, followed by heating to r.t. and boiling for 2 h. After cooling triethylamine salt was filtered off. Triethanolamine (3.28 g, 0.022 mol) in ethanolic solution was added to the filtrate. The reaction mixture was stirred at r.t. for 10 h, cooled to 0 °C and benzylgermatrane (4.55 g, 66.7%) was filtered off. Recrystallization from chloroform was carried out. Analytical data are summarized in Table 1.

Compounds **II**–**IV** were prepared analogously. After recrystallization from chloroform, compounds had properties shown in Table 1.

4. Supplementary material

Crystallographic data for the structures **I**–**IV** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary information, CCDC nos. 185760–185762 for compounds **I**, **II**, **IV** and no. 180000 for compound **III**. Copies of the data can be obtained free of charge on application from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Acknowledgements

The authors are grateful to Dr. Jury Popelis for recording ^{1}H-NMR spectra, Dr. Skaidrite Germane for biological investigations. We are grateful to the Latvian Council of Science (grant No. 180) for financial support.

References

[1] E. Lukevics, L. Ignatovich, S. Belyakov, J. Organomet. Chem. 588 (1999) 222.
[2] S.S. Karlov, G.S. Zaitseva, Chem. Heterocycl. Compd. 11 (2001) 1451.
[3] E. Lukevics, S. Germane, L. Ignatovich, Appl. Organomet. Chem. 6 (1992) 543.
[4] E. Lukevics, L. Ignatovich, S. Germane, Chem. Heterocycl. Compd. 31 (1995) 1241.
[5] E. Lukevics, L. Ignatovich, in: S. Patai (Ed.), The Chemistry of Organic Germanium, Tin and Lead Compounds, Wiley, 1995, pp. 857–863.
[6] E. Lukevics, L. Ignatovich, in: Z. Rappoport, Y. Apeloig (Eds.), The Chemistry of Organic Germanium, Tin and Lead Compounds, Wiley, 2002, pp. 1651–1682.
[7] E. Lukevics, L. Ignatovich, S. Belyakov, Main Group Metal. Chem. 25 (2002) 183.
[8] E. Lukevics, L. Ignatovich, A. Kemme, Main Group Metal. Chem. 25 (2002) 313.
[9] S. Belyakov, L. Ignatovich, E. Lukevics, J. Organomet. Chem. 577 (1999) 205.
[10] R. Eujen, E. Petrauskas, A. Roth, D.J. Brauer, J. Organomet. Chem. 613 (2000) 86.
[11] M.W. Schmidt, T.L. Windus, M.S. Gordon, J. Am. Chem. Soc. 117 (1995) 7480.
[12] Q. Shen, R.L. Hilderbrandt, J. Mol. Struct. 64 (1980) 257.
[13] G. Forgacs, M. Kolonits, I. Hargittai, Struct. Chem. 1 (1990) 245.
[14] W.R. Busing, H.A. Levy, Acta Crystallogr. 17 (1964) 142.
[15] M.K. Denk, M. Khan, A.J. Lough, K. Shuchi, Acta Crystallogr. Sect. C 54 (1998) 1830.
[16] E. Lukevics, L. Ignatovich, T. Shul'ga, S. Belyakov, Main Group Metal. Chem. 25 (2002) 325.
[17] P.T. Beurskens, G. Beurskens, W.P. Bosman, R.S. de Gelder, S. Garcia-Granda, R.O. Gould, J.M.M. Smits, The DIRDIF 96 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1996.
[18] S. Mackay, C.J. Gilmore, C. Edwards, N. Stewart, K. Shankland, MAXUS Computer Program for the Solution and Refinement of Crystal Structures, Bruker Nonius, The Netherlands, MacScience, Japan, The University of Glasgow, 1999.
[19] C.K. Johnson, ORTEP-II. A FORTRAN Thermal-Ellipsoid Plot Program. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, USA, 1976.
[20] G.M. Sheldrick, Acta Crystallogr. Sect. A 46 (1990) 467.
[21] G.M. Sheldrick, SHELXL 97. Program for the Refinement of Crystal Structures, University of Göttingen, Germany, 1997.
[22] A. Altomare, M.C. Burla, M. Camalli, G.L. Cascarano, C. Giacovazzo, A. Guagliardi, A.G.G. Moliterni, R. Spagna, J. Appl. Crystallogr. 32 (1999) 115–119.
[23] E. Lukevics, L. Ignatovich, N. Porsiurova, S. Germane, Appl. Organomet. Chem. 2 (1988) 115.