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REVIEW

Neurotropic activity of organogermanium compounds

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Neurotropic activity of several classes of organogermanium compounds (namely germatranes, germanols, germsesquioxanes, germyladamantanes, germylamides, germylimides and germyl-substituted amines, imines and hydroxamic acids) and their synthesis are reviewed.

Keywords: Organogermanium compounds, toxicity, neurotropic activity

CONTENTS

1 INTRODUCTION

Numerous organogermanium and coordinative germanium compounds possessing analgesic, hypotensive, fungistatic, bactericidal, antiviral, antimalarial, radio-protective, antitumour, interferon-inducing and immunomodulating properties have been synthesized.[1] Two organogermanium compounds—spirogermanium and 2-carboxyethylgermsesquioxane (Ge-132)—have been tested clinically as antitumour remedies. Unfortunately, they exhibited insufficient activity. Ge-132 has been tested for osteoporosis and viral diseases, and spirogermanium as an antimalarial remedy. A number of tetra- and penta-coordinated germanium derivatives have been found to possess neurotropic activity.

This review presents data on the neurotropic activity of organogermanium compounds synthesized by Professor V. F. Mironov's group (State Institute of Chemistry and Technology of Organoelemental Compounds, Moscow) and in the organometallic chemistry laboratory of the Institute of Organic Synthesis, Latvian Academy of Sciences in Riga; all the biological tests have been performed in the pharmacology laboratory of this Institute.

The neurotropic activity of germatranes (Sections 2–5), germsesquioxanes (Section 6), germyl-substituted amines, imines and hydroxamic acids (Section 7) and germanium-containing adamantanes (Section 8) has been studied.

All tests aiming at the elucidation of the neurotropic activity of germanium compounds were carried out on BALB/c, Icr:Icl, CBA mice and on white mongrel rats. Solutions or aqueous suspensions of the compounds, prepared with Tween-80, were administered i.p. 30–60 minutes prior to the corresponding test. For more detailed studies some compounds were administered orally. In all cases the control animals received an isotonic solution of sodium chloride or distilled water with the addition of the corresponding Tween concentrations administered i.p. or injected into the stomach in the same doses and at the same time. The experimental study of the neurotropic properties of germanium compounds was carried out in accordance with previous work.[2]

The data obtained were processed statistically and the mean effective (ED_{50}) and the mean lethal (LD_{50}) doses were determined.

To evaluate the mean duration of hexenal and phenamine anaesthesia, protective properties against Corazole-induced convulsions and

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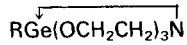
hypoxia, volume of reserpine-induced ptosis and hypothermia, the mean arithmetical values and their standard deviation ($M \pm m$) were calculated. The significance of deviations between the mean values was defined using Student's t test. Deviations were considered reliable at $P \leq 0.05$. The criteria found permit the neurotropic activity of the compounds under study to be analysed precisely.

2 HYDROXY, SILOXY AND GERMOXY DERIVATIVES OF GERMATRANE

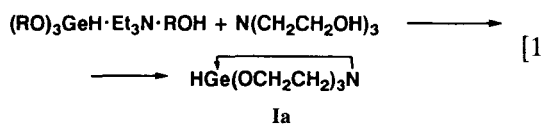
Several methods for the preparation of germatranes



I

(**I**; tricyclic organogermanium derivatives of triethanolamine 1-germa-2,8,9-trioxa-5-azatricyclo-[3.3.3.$0^{1,5}$]undecane) have been elaborated. Interaction of tetra-alkoxy- or trialkoxy-germanes with triethanolamine occurring under mild conditions in the presence of a catalyst giving 70–90% yield is considered the simplest and most available.[3]

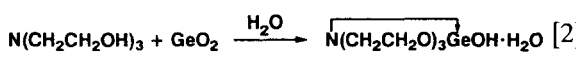
The synthesis of 1-hydrogermatrane (**Ia**) is also based on transalkoxylation but instead of trialkoxygermanes their stable complexes with triethylamine and alcohol (Eqn [1]) are used as starting substances:[4]



[1]

Ia

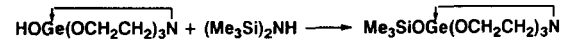
1-Hydroxygermatrane hydrate (**II**) was obtained surprisingly easily and differently: it is sufficient to boil germanium dioxide with triethanolamine in water (Eqn [2]) in order to obtain the monohydrate of 1-hydroxygermatrane.[5] No hydrolysis of Ge—O—C bonds in the atrane rings was observed (the yield of the compound was quantitative).



[2]

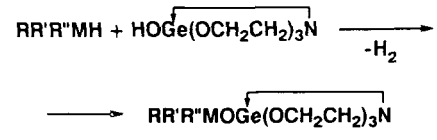
II

Complete dehydration of the monohydrate to 1-hydroxygermatrane is achieved by drying compound **II** in vacuum or over P_2O_5.[5] The existence of the sufficiently stable atrane ring permits us to realize some conversions with 1-hydroxygermatrane, resulting in germatranes with M—O—Ge groups.[6] For example, 1-hydroxygermatrane, splits the Si—N bond in hexamethyldisilazane, generating trimethylsiloxygermatrane (Eqn [3]) (**III**):



III [3]

It has been found that hydroxygermatrane enters into condensation with hydro-silanes or -germanes affording the corresponding siloxy- or germoxy-germatranes (viz. compounds **IV–XI**).[7]



[4]

IV–XI

IV	M = Si; R = R′ = R″ = 2-thienyl
V	M = Si; R = R′ = 2-thienyl; R″ = Me
VI	M = Si; R = 2-thienyl; R′ = R″ = Me
VII	M = Si; R = R′ = R″ = Ph
VIII	M = Si; R = R′ = Ph; R″ = Me
IX	M = Si; R = Ph; R′ = R″ = Me
X	M = Si; R = α-naphthyl; R′ = Ph; R″ = H
XI	M = Ge; R = R′ = R″ = Ph

Biological study of compounds **II–XI** has demonstrated that they are low-toxicity substances, their LD_{50} exceeding 1000 mg kg^{-1}, whilst the LD_{50} for hydrogermatrane is 320 mg kg^{-1} (Table 1).

The action of siloxy- and germoxy-germatrane on locomotor activity and muscle tone parameters is less strong; trimethylsiloxygermatrane (**III**), triphenylsiloxygermatrane (**VII**) and triphenylgermoxygermatrane (**XI**) in doses up to 500 mg kg^{-1} do not affect the parameters mentioned. In rotating-rod, tube and traction tests, dithienyl- (**V**), trithienyl- (**IV**) and α-naphthylphenylsiloxy- (**X**) germatranes have ED_{50} within the 178–410 mg kg^{-1} range, dimethylthienylsiloxygermatrane (**VI**) is between 70 and 250 mg kg^{-1} and germatranol hydrate (**II**) is at 30–35 mg kg^{-1}. Hydrogermatrane (**Ia**) (ED_{50} 0.0015 mg kg^{-1}) exhibits the highest depressant activity on the central nervous system (CNS). Thus, the therapeutic index for this compound is rather high (>200 000).

The hypothermic action of the compounds

Table 1 Neurotropic activity of germatrane, its hydroxy-, siloxy- and germoxy-derivatives

Compound	LD_{50} (mg/kg)	ED_{50} (mg kg^{-1})[a]			Neurotropic activity, $M \pm m$ (% of control)[a]					
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Ethanol anaesthesia	Phenamine stereotype	ME, $\bar{s}$ [b] RA (%)[c]
I	320 (221–464)	0.0015 (0.0004–0.006)	0.0015 (0.0004–0.006)	—	45 (31–65)	—	—	—	—	—
II	<5000	32.5 (21.9–45.5)	34.6 (12.0–66.2)	35.5 (24.9–46.1)	29.6 (9.3–61.2)	186.5*	132.2	89.4	47.7*	95.8 ± 10.8* (97.7)
III	3500 (2490–4610)	>500	>500	>500	>500	148.1*	95.5	151.0*	31.4*	5.0 ± 1.9 (28.5)
IV	Approx. 2500	274 (99–524)	>500	>500	274 (99–524)	136.2*	—	—	91.4	51.0 ± 16.6* (70.0)
V	Approx. 1000	355 (249–461)	282 (159–419)	410 (268–552)	282 (159–419)	114.8	97.8	156.6*	165.9*	30.5 ± 13.8 (50.0)
VI	>2500	109 (40.6–205.8)	70.8 (50–92.5)	>250	218 (81–411)	111.1	117.8	140.9*	129.6	79.1 ± 14.2* (75.0)
VII	>1000	>500	>500	>500	>500	120.1*	129.4*	87.4	87.7	72.0 ± 15.2* (80.0)
VIII	>10 000	690 (242–1303)	564 (387–743)	815 (567–1110)	815 (567–1110)	108.2	92.0	75.6	101.6	46.5 ± 16.4* (62.5)
X	>1000	>500	178 (136–230)	137 (50–262)	141 (108–209)	90.3	115.2	—	—	20.0 ± 3.5 (57.1)
XI	Approx. 2000	>500	>500	>500	>500	116.4	133.3*	46.2*	226.9*	92.7 ± 12.4* (77.7)

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] Values are means ± SD, or means with range in parentheses.

[b] ME = Memory enhancement

[c] RA = Retrogradal amnesia

studied, with the exception of hydrogermatrane (**Ia**) and germatranol (**II**), is expressed weakly and is approximately at the same doses as their action on locomotor activity. Hypothermic activity one order of magnitude higher has been found in hydrogermatrane (**Ia**) and germatranol hydrate (**II**). Comparison of triphenylgermoxygermatrane (**XI**) with the corresponding derivatives of siloxygermatrane (**VII**) shows that they differ insignificantly.

The effect of germatranol hydrate (**II**), administered orally, on the behaviour of rats in open-field tests and on body temperature confirms the results previously obtained, namely that these compounds in doses up to 250 mg kg^{-1} do not significantly change the parameters of vertical and horizontal locomotor activity, learning response and body temperature.

Regarding the action of anaesthetic substances, it has been shown that the duration of hexenal anaesthesia is increased only under the influence of triphenylsiloxy- (**VII**) and triphenylgermoxygermatrane (**XI**) by 29.4 and 33.3%, respectively (*Table* 1). Ethanol anaesthesia is strengthened under the influence of trimethyl- (**III**), dimethylthienyl- (**VI**) and dithienylmethyl-siloxygermatrane (**V**) derivatives, while under the influence of triphenylgermoxygermatrane (**XI**) it is (quite the reverse) decreased by 53.8%. The duration of ethanol anaesthesia under the influence of germtranol hydrate (**II**) is little changed both under i.p. and p.o. administrations. The duration of hexenal, sodium barbital and chloral hydrate anaesthesia is increased upon p.o. administration of germtranol (**II**) in doses of 5–250 mg kg^{-1} by a factor of almost two, depending on the dose administered (Table 2).

Germatranol (**II**), trimethylsiloxygermatrane (**III**), trithienylsiloxygermatrane (**IV**) and triphenylsiloxygermatrane (**VII**) exhibit noticeable antihypoxic activity (i.p. administration, 50 mg kg^{-1}) (Table 1). Compound **II** also shows high antihypoxic activity during oral administration. The prolongation of life-span for a mouse under hypoxic hypoxia is more than doubled under the influence of germatranol (**II**) (Table 2).

The pharmacological effects of phenamine are depressed by germatranol hydrate (**II**) and siloxygermatrane (**III**) by 52.3 and 68.6%, respectively. However, dithienylsiloxygermatrane (**V**) and triphenylgermoxygermatrane (**XI**), on the contrary, strengthen stimulating action on phenamine locomotor activity and phenamine stereotype behaviour duration by 65.9 and 126.7%, respectively. The stereotype behaviour duration has not been changed reliably during p.o. administration of germatranol hydrate in doses from 5 to 250 mg kg^{-1}.

Reserpine-induced ptosis was reduced only under the influence of trimethylsiloxy- (**III**) and dimethylthienylsiloxy-germatranes (**VI**), and also of triphenylgermoxygermatrane (**XI**) by 42.9, 22.5 and 41.5 %, respectively.

All derivatives of siloxygermatrane, except for the trithienyl derivative (**IV**), reveal some anti-Corazole activity; germoxygermatrane (**XI**) and the siloxygermatrane (**IV**), on the contrary, strengthen the convulsive action of Corazole by 35.3 and 23.7%, respectively. Siloxy- and germoxy-germatranes do not exhibit any protective properties in the tests of maximal electric shock. Germatranol (**II**) (p.o. administration) has been shown to lack any protective activity in corasol-, maximal electric shock- and strychnine-induced convulsions. Germatranol hydrate does not prevent tremor caused by N- and M-ergic substances—nicotine and arecoline. However, when thiosemicarbazide was used as a convulsion-inducing agent, germatranol (**II**) in doses of 100 and 250 mg kg^{-1} noticeably increased the latent period of the beginning of the first tremor attack. This fact provides indirect evidence for the participation of GABA in the neurotropic mechanism of the compound (Table 2). In the same dose, germatranol hydrate (**II**) displays serotonin-blocking activity (Table 2).

All the derivatives studied of siloxygermatrane and germoxygermatrane in comparatively small doses (50 mg kg^{-1}) enhance memory processes to some extent and reduce or even completely prevent retrogradal amnesia caused by electric shock. Germatranol hydrate (**II**), triphenylgermoxy- (**XI**), triphenylsiloxy- (**VII**), trithienylsiloxy- (**IV**) and dimethylthienyl-siloxygermatranes (**VI**) show the highest activities preventing retrogradal amnesia by 75–97% and increasing the difference of latent periods (Δt) to passage a darkened chamber after 24 h from 46.5 to 95.8 s, whereas the control Δt is equal to 6.8 s (Table 1).

Germatranol (**II**) administer p.o. in doses of 5, 100 and 250 mg kg^{-1} also exhibits high activity in the passive-avoidance test (Table 2).

The data obtained permit us to conclude that, during the transition from germatrane (**Ia**) to hydroxygermatrane (**II**), CNS depressant activity is noticeably decreased. The substitution of the hydroxyl group in the germatranol molecule by

Table 2 Neurotropic activity of 1-germatranol hydrate (**II**) administered into the stomach 1 h prior to tests on BALB/c male mice weighing 18–20 g and on white mongrel male rats weighing 195 g ($n = 6$; temperature 21 ± 5 °C)

Tests	Neurotropic activity, $M \pm m$[a]				
	Dose (mg/kg): 0	5	50	100	250
Hypoxic hypoxia	34.2 ± 1.6 (100)	51.7 ± 9.7 (151.1)	71.5 ± 11.5* (209.1)	74.5 ± 7.9* (218.9)	65.8 ± 8.1* (194.2)
ME, s	2.0 ± 1.1	80.0 ± 29.5*	—	119.8 ± 33.9*	74.4 ± 25.7*
Hexenal anaesthesia, min	65.0 ± 10.5 (100)	120.0 ± 6.2* (184.0)	100.8 ± 15.9* (155.1)	—	95.0 ± 4.2* (146.2)
Sodium barbital anaesthesia, min	76.3 ± 3.9 (100)	137.5 ± 14.4* (180.2)	151.7 ± 11.9 (196.2)	151.7 ± 11.9* (198.9)	124.2 ± 14.2 (169.3)
Chloral hydrate anaesthesia, min	50.3 ± 3.2 (100)	87.5 ± 8.7* (173.1)	96.7 ± 3.1* (192.2)	63.3 ± 8.5 (125.8)	58.4 ± 8.6 (115.9)
No. of 'head shakings' caused by 5-hydroxy-tryptophan	21.3 ± 1.5 (100)	24.5 ± 4.7 (115.0)	18.5 ± 2.7 (86.8)	—	10.7 ± 0.9* (50.2)
Thiosemicarbazide convulsions, min	61.0 ± 2.0 (100)	65.8 ± 3.5 (107.5)	—	91.7 ± 2.4* (149.8)	80.8 ± 5.5* (132.9)

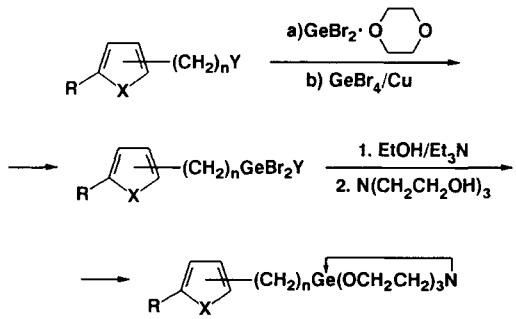
* Differences are statistically reliable vs control at $P \leq 0.05$

[a] Mean ± SD. Values in parentheses are percentages of control, i.e. response to 0 mg kg^{-1} dose.

trimethylsiloxy- (**III**), triphenylsiloxy- (**VII**) or triphenylgermoxy- (**XI**) groups leads to the complete loss of CNS depressant activity in rotating-rod, tube, traction and hypothermia tests, their ED_{50} being $>500\ mg\ kg^{-1}$. A comparative study of the pharmacological activity of the triphenylsiloxygermatrane (**VII**) derivative with the analogous derivative of germoxygermatrane (**XI**) has shown that, in the spectrum of neurotropic activity of the latter, the activating components prevail. Germatranes of this series are characterized by high activity in the elaboration of conditioned responses of passive avoidance and in the prevention of retrogradal amnesia.

3 VINYL, FURYL- AND THIENYL-GERMATRANES

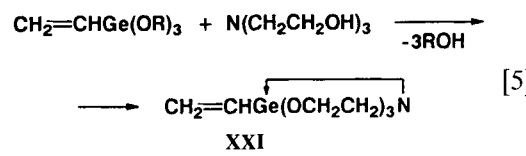
Furyl- and thienyl-germatranes were obtained as a result of the following conversions: insertion of germanium dibromide into the carbon–halogen bond in the corresponding halo-furans and -thiophenes, alcoholysis of the obtained trihalogermylfurans and -thiophenes into trialkoxy derivatives, and their transalkoxylation with triethanolamine into atranes Scheme 1).[8]



XII	X = O; Y = 2-Br; R = H; $n = 0$
XIII	X = O; Y = 3-Br; R = H; $n = 0$
XIV	X = O; Y = 2-Cl; R = H; $n = 1$
XV	X = O; Y = 2-Br; R = COOEt; $n = 0$
XVI	X = S; Y = 2-Br; R = H; $n = 0$
XVII	X = S; Y = 3-Br; R = H; $n = 0$
XVIII	X = S; Y = 2-Br; R = Me; $n = 0$
XIX	X = S; Y = 2-Br; R = Et; $n = 0$
XX	X = S; Y = 2-Br; R = Br; $n = 0$

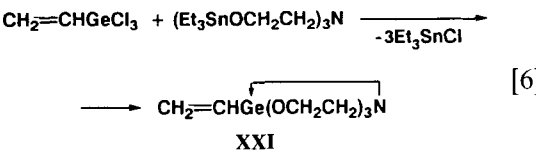
Scheme 1

Synthesis of vinylgermatrane is also based on the reaction of transalkoxylation (Eqn [5]).[9]



XXI [5]

One other route of vinylgermatrane synthesis based on organotrihalogermanes is possible (Eqn [5]).[10]



XXI [6]

All derivatives of furylgermatrane examined (**XII–XV**) are low-toxicity substances, their LD_{50} exceeding $1000\ mg\ kg^{-1}$.[8] The derivatives of thienylgermatrane **XVI–XX** are highly toxic compounds; LD_{50} values for thienylgermatranes **XVI–XVIII** are within the 16–89 $mg\ kg^{-1}$ range. 5-Ethyl-2-thienylgermatrane (**XIX**) is an exception (Table 3). The comparison of 5-methyl- (**XVIII**), 5-ethyl- (**XIX**) and 5-bromo-2-thienylgermatranes demonstrates that the substitution of a methyl group for an ethyl noticeably reduces the acute toxicity of compound **XIX**. Introduction of a bromine atom instead of the methyl group does not change the toxicity of the compound. It is worthy of note that all furyl- and thienylgermatranes are less toxic than the corresponding silatranes.[11,12] At the same time, 2-isomers belonging to the thiophene series appear to be the most toxic, but 2-isomers of the furan series, on the contrary, are less toxic than 3-substituted derivatives (Table 3).

As can be seen from Table 3, 2- (**XVI**) and 3-substituted (**XVII**) derivatives of thienylgermatrane possess the highest CNS depressant activity. Both compounds have the same results in rotating-rod, tube, traction and hypothermia tests (ED_{50} being within the 1–2.7 $mg\ kg^{-1}$ range). However, the 3-substituted derivative (**XVII**) has 5.4 times less toxicity than compound **XVI**. At the same time, 2- (**XII**) and 3-substituted (**XIII**) furylgermatranes possess 40–80 times less CNS depressant activity than the corresponding thienyl compounds.

Insertion of a CH_2 group between the furan ring and the germanium atom increases the depriming activity of compound **XIV** by a factor of two. 5-Methyl-2-thienylgermatrane (**XVIII**) (ED_{50} $10\ mg\ kg^{-1}$) displays the highest CNS depressant activity in the series of 5-substituted 2-

Table 3 Neurotropic activity of vinyl, furyl- and thienyl-germatrane derivatives

Compound	LD_{50} (mg/kg)	ED_{50} (mg kg^{-1})[a]			Neurotropic activity, $M \pm m$ (% of control)[a]						
		Rotating rod test	Tube test	Traction test	Hypothermia	Anaesthesia	Hypoxia	Hexenal anaesthesia	Ethanol anaesthesia	Phenamine stereotype	ME, $\bar{s}$ RA, (%)
XII	2050 (1460–2880)	41 (26.8–55.2)	41 (26.8–55.2)	35.5 (24.9–46.1)	47.7 (26.5–64.3)	70.8 (80.1–92.5)	184.8*	191.8**	72.9	90.4	—
XIII	1630 (1090–2270)	70.8 (43.0–101.9)	81.5 (44.9–125.2)	81.5 (56.7–111.0)	51.5 (29.1–78.6)	>100	150.5*	171.4*	61.5*	104.5	—
XIV	2960 (930–6120)	20.5 (14.6–28.8)	28.4 (14.4–28.5)	17.8 (13.6–23.0)	22.4 (12.0–33.2)	>50	169.1*	236.6*	79.6	94.6	—
XV	1030 (674–1384)	708 (430–1019)	590 (167–1203)	650 (367–1004)	870 (304–1649)	>100	108.6	113.4	—	80.0	—
XVI	16.5 (1–25)	1.0 (0.6–1.8)	1.0 (0.6–1.8)	—	2.7 (1.9–3.8)	17 (9–31)	—	58.0*	—	131.4*	—
XVII	89 (56–129.1)	1.2 (0.73–1.9)	2.2 (1.4–2.8)	1.5 (0.3–2.4)	1.2 (0.3–2.4)	>50	141.3*	164.3*	121.4	101.6	—
XVIII	20.5 (14.6–28.8)	9.5 (5.0–15.1)	8.9 (5.6–12.9)	10.3 (6.7–13.8)	12.9 (6.1–20.2)	>10	181.0*	150.0*	51.6*	71.7*	35.5 ± 26.6 (20)
XIX	>1000	141 (92–209)	282 (159–419)	205 (122–311)	178 (136–230)	>200	126.6*	205.0*	161.3*	193.4*	103.5 ± 32.5 (40*)
XX	20.5 (14.6–28.8)	20.5 (12.2–31.1)	16.3 (10.8–22.7)	20.5 (14.6–28.8)	17.8 (13.6–23.1)	>50	111.3	158.7*	82.8	78.6	—
XXI	5600 (2150–10565)	>500	>500	>500	>500	—	—	231.3*	—	—	—

* Difference vs control are statistically reliable at $P \leq 0.05$. [a] See footnote to Table 1.

Table 4 Neurotropic activity of halomethyl- and alkoxycarbonylalkyl-germatranes

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg/kg)[a]			Neurotropic activity $M \pm m$ (% of control)[a]					
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Ethanol anaesthesia	Phenamine stereotype	RA (%)
XXII	2960 (936–6120)	205 (146–288)	—	—	178 (136–230)	142.4*	86.7	124.1*	94.7	45.0 ± 9.5* (66.7)
XXIII	355 (249–461)	36.8 (11.3–67.9)	35.5 (20.2–50.8)	35.5 (20.2–50.8)	29.6 (9.6–61.2)	142.4*	85.5	—	172.1*	—
XXIV	6820 (1585–14 560)	590 (167–1203)	564 (342–814)	564 (342–814)	690 (242–1303)	156.6*	84.6	51.1*	145.6	—

* Differences are statistically reliable vs control at $P \leq 0.05$. [a] See footnotes to Table 1.

thienylgermatranes. Introduction of the ethyl group in position 5 of thienylgermatrane (**XIX**) decreases considerably (by 14–18-fold compared with **XVIII**) the CNS depressant activity of the compound, whilst the introduction of bromine in this position decreases the neurotropic properties of compound **XX** by only a factor of two. Vinylgermatrane (**XXI**) in doses up to 500 mg kg^{-1} has been found to lack CNS depressant activity.

Hexenal anaesthesia is prolonged by vinyl, thienyl and furyl derivatives of germatrane. In contrast, 1-(2-thienyl)germatrane (**XVI**) is an exception and reduces by 42% the duration of hexenal anaesthesia. The interaction of 2-thienylgermatrane (**XVI**) and phenamine evidences the activating effects of the former, i.e. the duration of phenamine stereotype behaviour is increased by 31.4%. Similar properties with respect to phenamine have been found in 5-ethyl-2-thienylgermatrane (**XIX**), whilst 5-methyl-2-thienylgermatrane (**XVIII**), on the contrary, cuts the duration of phenamine stereotype behaviour by 29.3%.

3-Furylgermatrane (**XIII**) and 5-methyl-2-thienylgermatrane (**XVIII**) have been shown to reduce the duration of ethanol anaesthesia. The other compounds also decrease the duration of ethanol anaesthesia (although the difference in their action is minimal). 5-Ethyl-2-thienylgermatrane differs considerably from other germatranes also by its influence on ethanol anaesthesia, i.e. it increases this parameter by 61.3%.

The interaction of furyl- and thienylgermatranes (**XII–XX**) with corazole and reserpine is small.

All derivatives studied—furylgermatrane at a dose of 50 mg kg^{-1} and derivatives of thienylgermatrane at a dose of 5 mg kg^{-1}—exhibit pronounced antihypoxic activity: 2-furylgermatrane (**XII**) is the most active in the furylgermatrane series and prolongs the life of animals under hypoxia by almost two-fold, and 2-furfurylgermatrane (**XIV**) and 3-furylgermatrane (**XIII**) follow in diminishing order. 5-Methyl-2-thienylgermatrane (**XVIII**), 3-thienylgermatrane (**XVII**) and 5-ethyl-2-thienylgermatrane (**XIX**), all belonging to the thienylgermatrane series, show the highest antihypoxic activity.

5-Methyl- and 5-ethyl-2-thienylgermatrane (**XVIII** and **XIX**) combine antihypoxic activity, high activity in the conditioned response of passive avoidance, and a preventive influence on retrogradal amnesia.

Vinylgermatrane (**XXI**) possesses insignificant neurotropic potency. Compound **XXI** at a dose of 50 mg kg^{-1} considerably increases only the duration of hexenal anaesthesia (Table 3).

4 HALOGENMETHYL- AND ALKOXYCARBONYLALKYLGERMATRANES

1-(Chloromethyl)- and 1-(bromomethyl)-germatranes (**XXII**, **XXIII**) and 1-[2-(methoxycarbonyl)propyl]germatrane (**XXIV**) were obtained using the routine method of transalkoxylation (Eqn [7]):[13]

$$RGe(OR')_3 + N(CH_2CH_2OH)_3 \xrightarrow[-3R'OH]{} R\overline{Ge(OCH_2CH_2)_3N} \quad [7]$$

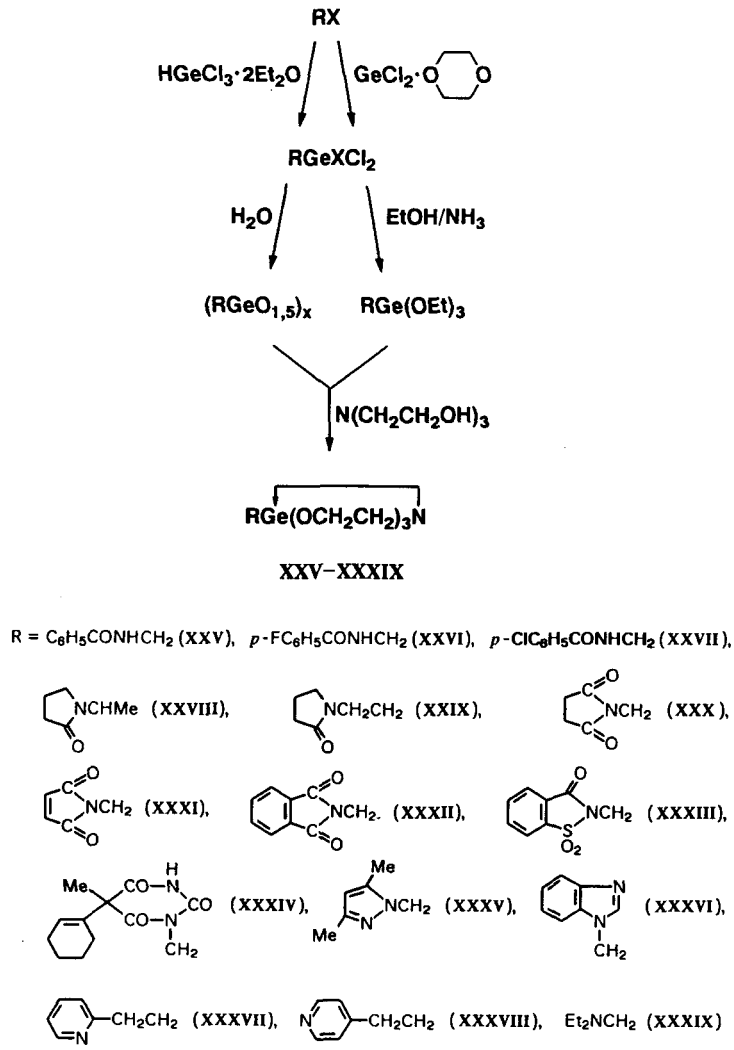
XXII–XXIV

R = CH_2Cl (**XXII**), CH_2Br (**XXIII**), $CH_2CH(CH_3)COOCH_3$ (**XXIV**)

Chloromethyl- (**XXII**), and methoxycarbonyl- (**XXIV**) germatranes are low-toxicity compounds, their LD_{50} values exceeding 3000 mg kg^{-1}. Bromomethylgermatrane (**XXIII**) is considerably more toxic than compounds **XXII** and **XIV** (Table 4). Comparison of hydrogermatrane (Compound **Ia**, Table 1) with chloromethyl- (**XXII**) and bromomethyl- (**XXIII**) germatranes shows that the introduction of the chloromethyl group decreases the acute toxicity of the compound by almost 10-fold, whilst the bromomethyl group maintains approximately the same level of toxicity.

Bromomethylgermatrane (**XXIII**) exhibits comparatively high CNS depressant potency on locomotor activity, muscle tone and body temperature. Besides, bromomethylgermatrane possesses some activating effects strengthening phenamine locomotor activity by 72.1% and prolonging the life of animals under hypoxia by 42.4% (Table 4).

The action of chloromethylgermatrane (**XXII**) on locomotor activity, muscle tone and body temperature is less pronounced ($ED_{50} \sim 200$ mg kg^{-1}), and at a dose of 50 mg kg^{-1} exhibits some antihypoxic activity, prolonging, to some extent, ethanol anaesthesia; it prevents reserpine-induced ptosis by 45–88%. It is interesting to note that chloromethylgermatrane (**XXII**) at the same dose reveals a noticeable influence on memory processes and prevents the



Scheme 2

retrogradal amnesia caused by maximal electric shock.

1-[2-(Methoxycarbonyl)propyl]germatrane (**XXIV**) has lesser toxicity and neurotropic activity. Compound **XXIV**, at a dose of 50 mg kg^{-1} possesses average antihypoxic and antiethanol activities, i.e. prolonging the life of animals under hypoxia by 56.6% and decreasing the toxic action of ethanol by 48.9%.

Thus, the introduction of halogen-containing groups in the germatrane structure considerably decreases the CNS depressant properties (Tables 1, 4).

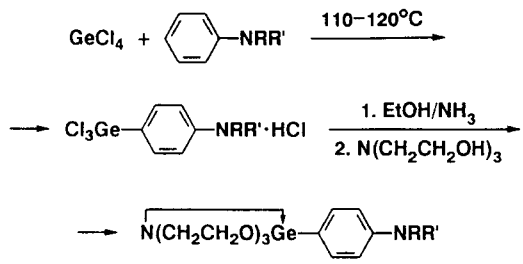
5 AMINOALKYL-, AMIDOALKYL- AND AMINOARYL-GERMATRANES

Germatranylmethylamides (imides) of carboxylic acid were obtained in accordance with Scheme 2.

The initial halomethylamides, by means of condensation with trichlorogermane etherate or by the insertion of dichlorogermane into the carbon–halogen bond, are converted into trihalogermylmethylamides (imides). The latter undergo alcoholysis or hydrolysis into the corresponding triethoxygermyl derivatives and germsesquiox-

anes, which on treatment with triethanolamine afford germatranes (**XXV–XXXIX**).[3, 14, 15]

Aminoarylgermatranes are synthesized according to Scheme 3.



XL R = R′ = Me
XLI R = R′ = Et

Scheme 3

4-(Dialkylamino)phenyltrihalogengermanes are converted into germatranes (**XL, XLI**) using routine methods.

Study of the toxic properties of nitrogen-containing germatranes has demonstrated that they are low-toxicity substances; their mean lethal doses exceeds 1000 mg kg^{-1}. Diethylaminomethylgermatrane (**XXXIX**) is the sole exception, having acute toxicity (LD_{50} = 355 mg kg^{-1}).

It has been found that the depriming activity of aminoalkyl-, amidoalkyl- and aminoarylgermatranes in rotating-rod, tube, traction and hypoxia tests depends on the substituents and differs to some extent (Table 5). Thus, comparison of isomeric pyrrolidonylethylgermatranes (**XXVIII** and **XXIX**) shows that the depriming activity of 2-pyrrolidonylethylgermatrane (**XXIX**) is two-fold less than that of the 1-isomer **XXVIII** in all the tests mentioned. The 2-isomer (**XXXVII**), belonging to the pyridylethylgermatrane series at doses of 20–50 mg kg^{-1} possesses sedative properties, whilst the 4-substituted derivative (**XXXVIII**) (which has the same toxicity) almost completely lacks any depriming effects. The substitution of the methylene group in diethylaminomethylgermatrane (**XXXIX**) by phenyl (**XLI**) between the nitrogen and germanium atoms decreases both depriming activity and the acute toxicity of the compound by approximately 10-fold in all tests. The comparison of maleimido- (**XXXI**) and phthalimidomethylgermatranes (**XXXII**) shows that the condensation effect with the benzene ring does not lead to increase of neurotropic properties of the compounds. In turn, the transition from unsaturated imide (**XXXI**) to saturated imide (**XXX**) increases to some extent the sedative potency of the compound. The introduction of fluorine or chlorine atoms in the *para*-position of the benzene ring in benzamidomethylgermatrane changes dramatically the depriming activity (**XXV**, **XXVI** and **XXVII**). *p*-Fluorobenzamidomethylgermatrane (**XXVI**) (its ED_{50} being within the 10–14 mg kg^{-1} range) exhibits the highest activity in rotating-rod, tube, traction and hypothermia tests. The substitution of the fluorine atom in the *para*-position of the phenyl ring by a chlorine atom produces a sharp decrease (10-fold) in depriming activity (**XXVII**). An analogous pattern is observed during the substitution of chlorine by hydrogen (**XXV**) from the *p*-chlorobenzamidomethylgermatrane (**XXVII**) molecule. The comparison of the depriming activity of 4-dimethylaminophenylgermatrane with that of the 4-diethylamino derivative (**XLI**) shows that the depriming activity of the latter is 5–6 times higher in rotating-rod, tube, traction and hypothermia tests.

All nitrogen-contining derivatives of methylgermatrane at a dose of 50 mg kg^{-1} exhibit antihypoxic activity; diethylaminomethylgermatrane (**XXXIX**) and 1,5-dimethyl-3-(1-germatranyl)-methyl-5-cyhclohexenylbarbituric acid (**XXXIV**) are the most active among them, prolonging life by 56.6 and 63.2%, respectively.

4-(Dimethylamino)phenylgermatrane (**XL**), belonging to the series of nitrogen-containing phenylgermatranes, shows reliable antihypoxic activity, prolonging life by 55.4%.

The anaesthetic action of hexenal is increased (by 75%) only under the influence of 4-fluorobenzamidomethylgermatrane (**XXVI**) in the series of nitrogen-containing methylgermatranes. The other compounds of this series considerably reduce the duration of hexenal anaesthesia. For example, phthalimidomethylgermatrane (**XXXII**) (its anaesthesia duration being only 59.6% vs the control) has been found to possess the highest antihexenal properties. At the same time nitrogen-containing derivatives of ethylgermatrane prolong hexenal anaesthesia.

For the duration of phenamine stereotype behaviour, the examined compounds, in both the methylgermatrane and the ethylgermatrane series, show different potencies. The majority of compounds of the methylgermatrane series decrease the duration of phenamine stereotype behaviour by 25–40%. With regard to this property 1-germatranylmethylsuccinimide (**XXX**), 1,5-dimethyl-3-(1-germatranyl)-methyl-5-

Table 5 Neurotropic activity of amino-, amidoalkyl- and aminoaryl-germatranes

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg/kg)[a]			Neuroactivity, *M* (% of control)[a]				
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Phenamine stereotype	Corazole convulsions
XXV	1290 (840–1790)	650 (438–886)	950 (502–1516)	755 (389–1215)	755 (389–1215)	130.7*	72.4*	110.3	85.6
XXVI	>5000	14.1 (3.5–29.4)	14.1 (3.5–29.4)	10.3 (6.7–13.8)	14.1 (6.8–20.9)	120.3*	175.0*	73.3*	152.7*
XXVII	2050 (1460–2880)	141 (43–258)	89 (63.1–119.7)	95 (50.2–151.6)	108 (40–198)	106.9	70.3*	140.9*	118.9
XXVIII	6500 (4380–8860)	137 (50–262)	129 (84–179)	112 (79–147.4)	56 (21–106)	122.8	125.1*	50.3*	92.6
XXIX	>10 000	1290 (840–1790)	1120 (790–1474)	890 (631–1197)	1290 (616–2020)	116.6	101.3	118.4	83.1
XXX	>2500	28.2 (15.9–41.9)	20.5 (14.6–28.8)	22.4 (14.4–28.5)	25.8 (16.8–35.7)	136.0*	86.4	59.6*	85.6
XXXI	>1000	>100	>100	>100	>100	145.5*	84.4	>50	>100
XXXII	4100 (2680–5520)	>1000	1030 (582–1573)	>1000	815 (449–1252)	114.1	59.6*	85.7	99.4
XXXIII	>1000	28.2 (15.9–41.9)	25.8 (14.5–40.4)	23.5 (5.8–48.3)	29.6 (9.3–61.2)	139.7*	119.5	60.9*	178.9*
XXXIV	>10 000	564 (342–814)	708 (430–1019)	564 (387–743)	515 (362–692)	163.2*	65.9*	62.5*	90.6
XXXV	3600 (1000–7100)	755 (389–1215)	870 (304–1649)	600 (317–930)	870 (304–1649)	119.4	88.1	136.8	89.9
XXXVI	1780 (550–3500)	69 (24.2–130.3)	51.5 (36.2–69.2)	54.7 (20–102.7)	60 (31.7–93)	147.7*	74.9	113.2	91.2
XXXVII	2820 (1830–3720)	32.5 (21.9–45.5)	28.2 (18.3–37.2)	32.5 (21.9–45.5)	35.5 (20.2–50.8)	98.4	125.1*	54.7*	90.3
XXXVIII	2580 (1680–3570)	937 (262–1914)	1030 (647–1384)	1120 (790–1947)	650 (434–886)	81.8	131.1*	77.4	102.3
XXXIX	355 (249–461)	22.4 (14.4–28.5)	20.5 (14.6–28.8)	20.5 (14.6–28.8)	20.5 (14.6–28.8)	156.6*	123.7	68.1*	155.9*
XL	3680 (1130–6790)	708 (501–925)	650 (438–886)	815 (567–1110)	564 (332–814)	155.4*	169.7*	156.6*	144.1*
XLI	3250 (2190–4556)	163 (85–250)	137 (50–262)	120 (73–191)	129 (84–179)	112.6	148.9*	80.9	89.3

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] Values are means, with ranges in parentheses.

cyclohexenylbarbituric acid (**XXXIV**) are among the compounds appearing to be the most potent. It is worth noting that the substitution of the fluorine atom for the chlorine in benzamidomethylgermatranes changes the activity of the compound. Thus, for example, 4-fluorobenzamidomethylgermatrane, by all the parameters (hypoxia, hexenal anaesthesia, phenamine stereotype behaviour), at a dose of 50 mg kg^{-1} shows a sedative effect, whereas the 4-*chloro* derivative (**XXVII**) shows an activating effect, i.e. it reduces the duration of hexenal anaesthesia and increases the duration of phenamine stereotype behaviour.

Concerning corazole convulsions, diethylaminomethylgermatrane (**XXXIX**), *N*-(1-germatranyl)methylsaccharine (**XXXIII**), 4-fluorobenzamidomethylgermatrane (**XXVI**) and 4-dimethylaminophenylgermatrane (**XL**) have been found to increase the Corazole dose necessary for tonic convulsions followed by a lethal outcome.

4-(Dimethylamino)phenylgermatrane (**XL**) has been studied more thoroughly by its administration into the stomach. The results of these investigations are presented in Table 6. Compound **XL**, in doses exceeding 50 mg kg^{-1}, increases both horizontal and vertical locomotor activity. Oral administration of the **XL** in the doses mentioned increases the duration of anaesthesia caused by hexenal, sodium barbital and ethanol. Its activity is strengthened proportion-

Table 6 Neurotropic activity of 4-(dimethylamino)phenylgermatrane administered into the stomach 1 h prior to tests on BALB/c male mice weighing 18–22 g and on white mongrel male rats weighing 212 ± 10 g ($n = 6$; temperature = 21 ± 1.5 °C)

	$M \pm m$[a]				
	Dose (mg kg^{-1})				
Test	0	5	50	100	250
Hypoxic hypoxia	28.7 ± 1.6	44.3 ± 2.2* (154.3)	46.7 ± 4.0* (162.7)	68.0 ± 4.7* (236.9)	53.3 ± 3.7* (185.7)
Thermal hypoxia	27.1 ± 1.2	29.7 ± 1.8* (109.0)	38.8 ± 2.8* (140.2)	38.3 ± 2.8* (141.3)	28.3 ± 1.7 (104.4)
ME, s	2.0 ± 1.1	—	97.8 ± 34.6*	76.1 ± 30.8*	101.3 ± 31.4*
Ethanol anaesthesia, min	55.9 ± 3.9	105.8 ± 11.4* (189.3)	150.0 ± 12.4* (268.3)	170.8 ± 14.1* (305.5)	196.6 ± 13.1* (351.7)
Hexenal anaesthesia, min	65.0 ± 10.5	110.8 ± 12.8* (170.5)	—	141.7 ± 13.9* (218.0)	126.0 ± 10.9* (193.8)
Sodium barbital anaesthesia, min	76.3 ± 3.9	135.0 ± 12.8* (176.9)	131.7 ± 14.0* (171.6)	126.7 ± 7.6* (166.5)	176.7 ± 13.1* (231.6)
Chloralanhydrate anaesthesia, min	50.3 ± 3.2	59.2 ± 13.1 (117.7)	63.3 ± 13.2 (125.8)	71.7 ± 14.2 (142.5)	65.0 ± 10.0 (129.2)
Phenamine stereotype behaviour	173.3 ± 7.2	174.2 ± 9.6 (100.5)	192.5 ± 17.7 (111.1)	206.7 ± 13.1 (119.9)	156.7 ± 13.2 (90.4)
No. of 'head shakings' caused by 5-hydroxytryptophan	9.2 ± 1.4	4.3 ± 1.8 (46.7)	2.5 ± 1.2* (27.2)	—	2.2 ± 0.8* (23.9)
Strychnine convulsions	1.06 ± 0.06	1.67 ± 0.12* (157.5)	—	2.23 ± 0.18* (210.4)	1.48 ± 0.16* (139.6)
Arecoline tremor	11.7 ± 1.1	20.2 ± 0.54* (172.6)	22.8 ± 1.0* (194.6)	—	25.8 ± 0.54* (220.5)
Thiosemicarbazide convulsions	61.2 ± 2.0	66.7 ± 3.6 (109.0)	—	76.7 ± 5.7* (125.3)	76.7 ± 5.0* (125.3)
Horizontal locomotor activity	48.5 ± 1.2	56.8 ± 3.3 (117.1)	62.5 ± 5.0* (128.9)	68.1 ± 6.1* (140.4)	55.8 ± 10.2 (115.1)
Vertical locomotor activity	7.2 ± 0.1	3.5 ± 1.3 (48.6)	7.3 ± 2.3 (101.4)	12.2 ± 3.0* (169.4)	15.7 ± 4.4* (218.1)

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] Mean ± SD, with percentage of control value (dose 0 mg kg^{-1}) in parentheses.

ally to its dose up to 100 mg kg^{-1} in most tests. If the compound is applied at higher doses (250 mg kg^{-1}), its activity decreases.

The duration of phenamine stereotype behaviour upon administration of 4-(dimethylamino)-phenylgermatrane (**XL**) into the stomach is not consistently increased. As for anticonvulsive activity, compound **XL** has been found to possess protective properties under strychnine action when the latter is used as convulsive agent.

4-(Dimethylamino)phenylgermatrane (**XL**) in doses from 5 to 250 mg kg^{-1} exhibits a pronounced antagonistic effect during hypoxic hypoxia and a lesser activity during haemic hypoxia. The antihypoxic activity of the compound is combined with a pronounced effect on the elaboration of a conditioned reaction of passive avoidance, thus showing evidence for a positive influence on the memory processes. The neurotropic action of 4-(dimethylamino)-phenylgermatrane is characterized by serotonin-blocking as well as by M-cholinemimetic and GABA-ergic mechanisms.

6 GERMANOLS AND GERMSESQUIOXANES

In principle, the hydrolysis of halogengermanes can lead to the formation of the corresponding germanols (Eqn [8]):

$$R_3GeX \xrightarrow{H_2O} R_3GeOH + HX \qquad [8]$$

However, these germanols are usually unstable and undergo dehydration to the corresponding germoxanes (Eqn [9]):

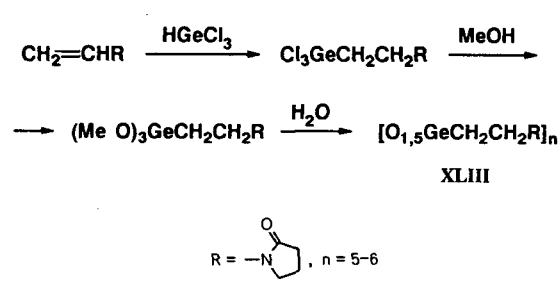
$$2R_3GeOH \rightarrow R_3GeOGeR_3 + H_2O \qquad [9]$$

Tricyclohexylgermatranol (**XLII**) is the sole example which we have successfully isolated and studied.

To obtain compounds of the sesquioxane type with nitrogen-containing heterocycle fragments, the reaction of $HGeCl_3$ addition to the multiple bonds followed by alcoholysis and hydrolysis has been employed (Scheme 4).[13]

Germsesquioxane substituted with a pyrazole heterocycle was obtained in accordance with Scheme 5.[19]

Tricyclohexylgermanol (**XLII**) and 1-(2-pyrrolidonyl)ethylgermsesquioxane (**XLIII**) are low-toxicity compounds, their LD_{50} values

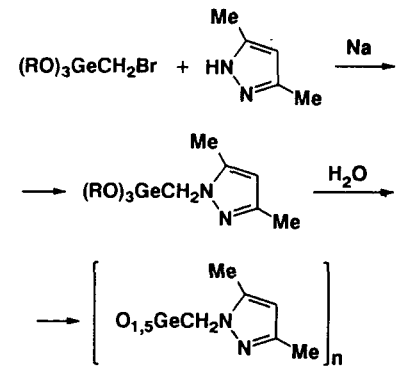


Scheme 4

exceeding 5000 mg kg^{-1}. Hydroxamic acid $(O_{1.5}GeCH_2CH_2CONHOH)_n$ (**XLV**) and its sodium salt (**XLVI**) appear to be low-toxicity substances also (Table 7). 3,5-Dimethylpyrazolylmethylgermsesquioxane (**XLIV**) exhibits acute toxicity with a mean value of $LD_{50} = 708$ (501–925) mg kg^{-1}.[14]

Tricyclohexylgermanol (**XLII**) in doses of 35–100 mg kg^{-1} shows some sedative activity, i.e. reduces the duration of phenamine stereotype behaviour, and in a dose of 35 mg kg^{-1} lowers the body temperature by 3 °C (or even more) in 50% of the experimental animals.

During the transition from germatranes (**XXIX** and **XXXV**) to germsesquioxanes with the same substituent at the germanium atom (**XLIII** and **XLIV**), the effect of the latter on locomotor activity, muscle tone and body temperature is increased to some extent. It must be noted that germsesquioxanes **XLIII** and **XLIV** within their neurotropic activity spectrum have the elements of activating action, in that they strengthen the phenamine stimulation by 55.3 and 34.5%, respectively, and reduce reserpine-depressant activity (ptosis and hypothermia).



XLIV $n = 5–6$

Scheme 5

Table 7 Neurotropic activity of germanols and germsesquioxanes

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1})[a]			Neurotropic activity, $M \pm m$ (% of control)[a]				
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Phenamine stereotype behaviour	Corazole convulsions, tonic phase
XLII	>5000	92 (33–175)	89 (56–129)	92 (33–175)	35.5 (25–46)	95.2	119.2	41.5*	83.0
XLIII	>5000	56 (18–110)	71 (26–132)	54 (21–99)	71 (24–139)	87.2	117.8	155.3*	112.0
XLIV	708 (501–925)	205 (146–288)	590 (167–1203)	590 (167–1203)	282 (159–419)	117.7	88.1	134.6	71.3
XLV	>5000	>500	447 (313–596)	>500	>500	95.0	62.9*	44.1*	126.0*
XLVI	>2500	>500	>500	>500	>500	151.6*	125.8	46.3*	108.4

* Differences are statistically reliable vs control at $P \leq 0.05$.
[a]See footnote to Table 5.

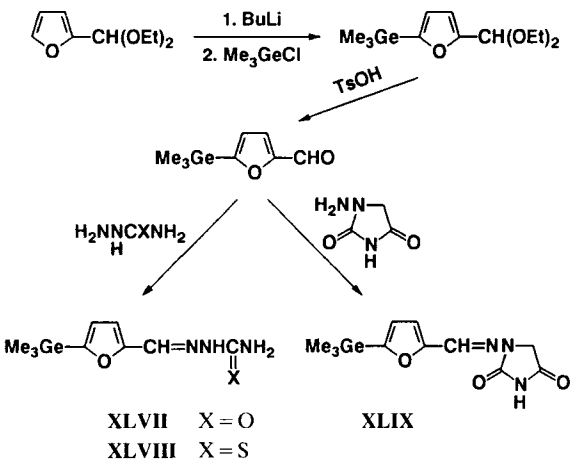
Table 8 Neurotropic activity of germyl-substituted amines and imines

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg kg)[a]			$M \pm m$ (% of control)[a]				
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Phenamine stereotype	Corazole convulsions
XLVII	—	51.5 (36.2–69.2)	65 (43.8–88.6)	51.5 (36.2–69.2)	70.8 (50.1–92.5)	106.6	92.6	37.8*	—
XLVIII	205 (146–288)	>20	>20	>20	>20	121.1	—	—	—
XLIX	224 (144–285)	18.7 (5.3–38.3)	22.4 (14.4–28.5)	28.2 (18.3–37.2)	28.2 (15.9–41.9)	164.0*	—	—	—
L	81.5 (56.7–111)	23.5 (5.8–48.3)	28.2 (15.9–41.9)	29.6 (9.3–61.2)	34.6 (12–66.2)	157.4*	86.3	46.3*	123.0
LI	81.5 (56.7–111)	4.1 (2.7–5.5)	2.6 (1.5–4.0)	4.5 (13.1–6)	4.5 (3.1–6)	158.9*	139.3	46.7*	136.0*
LV	325 (219–455)	37.9 (19.3–59.4)	20.5 (14.6–28.8)	41 (26.8–55)	32.5 (21.9–45.9)	128.3	214.9*	60.4*	113.8

* Differences are statistically reliable vs control at $P \leq 0.05$.
[a] See footnote to Table 5.

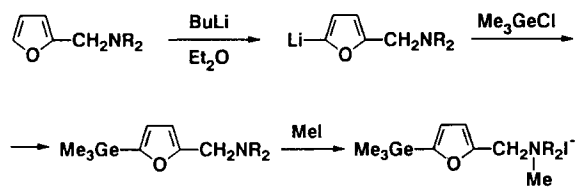
7 GERMYL-SUBSTITUTED AMINES, IMINES AND HYDROXAMIC ACIDS

Furan-containing germyl-substituted amines were obtained according to Schemes 6 and 7:[16]



XLVII X = O XLIX
XLVIII X = S

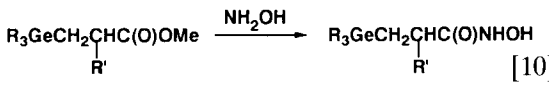
Scheme 6



L R = Me
Li R = Et

Scheme 7

β-Germyl-substituted hydroxamic acids **LII–LIV** were synthesized from esters of the corresponding acids (Eqn 10).[17]



[10]

LII R = Me; R′ = H **LII–LIV**
LIII R = Me; R′ = Me
LIV R = Et; R′ = Me

The nitrogen-containing substituent is responsible for the acute toxicity in compounds **XLVIII–LI**. Iodomethylammonium species **L** and **LI** have been found to possess the highest toxicity, their LD_{50} being 81.5 mg kg^{-1}; both compounds have similar LD_{50} values (Table 8).

5 - Trimethylgermylfurfurylidenethiocarbazide (**XLVIII**), 1-(5-trimethylgermyl-2-furfurylidene)-hydantoin (**XLIX**), 2-(pyridyl)ethyltrimethylgermane hydrochloride (**LV**) and 2-triethylgermylisobutyrohydroxamic acid (**LIV**) have mean LD_{50} values within the 205–355 mg kg^{-1} range. β-Trimethylgermylpropiohydroxamic acid (**LII**) exhibits the lowest toxicity; the corresponding germsesquioxanes are even less toxic. Comparison of compounds **LII**, **LII** and **LIV** (Table 9) shows that the substitution of a propiohydroxamic group for the isobutyrohydroxamic one decreases the LD_{50} more than twofold, whereas the introduction of a triethyl group in position 2 instead of the trimethyl group in the germylisobutyrohydroxamic structure increases the acute toxicity also twofold.[18]

Iodomethylammonium compound **LI** shows the highest depressant activity in rotating-rod, tube, traction and hypothermia tests. The substitution of a diethyl group for the dimethyl one in the structure of the iodomethylammonium species evokes a considerable decrease in depressant activity component with iodomethylammonium species **L**. For the derivatives of propiohydroxamic acid (**LII**) and isobutyrohydroxamic acids (**LIII** and **LIV**), approximately the same correlations were observed as had been found earlier for the acute toxicity in these compounds.

Hexenal anaesthesia is reliably strengthened only under the influence of 2-(4-pyridyl)ethyltrimethylgermane hydrochloride (**LV**).

Concerning the pharmacological effects of phenamine, all the compounds examined, except hydroxamic acid **LII**, have antagonist properties. Iodomethylammonium species **L** and **LI** and compound **XLVII** reveal the highest activities in this test. β-Trimethylgermylpropiohydroxamic acid (**LII**), on the contrary, increases the pharmacological effects of phenamine by 126.6%.

These compounds affect Corazole-induced convulsions slightly, the derivatives of isobutyrohydroxamic acid (**LIII** and **LIV**) being the only exception; they increase the dose of Corazole causing the tonic phase of convulsive attack by 56.8 and 57.7%. With regard to convulsions evoked by electric shock, trimethylgermylfurfurylidenehydantoin (**XLIX**) has been found to exhibit pronounced activity [ED_{50} 32.5 (21.9–45.5) mg kg^{-1}], which is obviously stipulated by the presence of the hydantoin group.

Using the experimental model of hypoxic hypoxia, all the compounds studied display antihypoxic activity (21–74%) in doses of 5–50 mg kg^{-1}.

β-Trimethylgermylpropiohydroxamic acid (**LII**) was tested more extensively for p.o. administration. The data in Table 10 confirm the antihy-

Table 9 Neurotropic activity of germyl-substituted hydroxamic acids

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1})[a]			$M \pm m$ (% of control)[a]				
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexanal anaesthesia	Phenamine stereotype	Corazole convulsions
LII	>2000	205 (146–288)	239 (124–383)	224 (120–332)	224 (120–332)	160.3*	141.7	226.6*	101.2
LIII	815 (567–1110)	81.5 (56.7–111)	60 (31.7–93)	56.4 (34.2–81.4)	69 (24.2–130)	174*	97.4	91.3	156.8*
LIV	355 (249–461)	51.5 (36.2–69.2)	44.7 (31.3–59.6)	60 (31.7–93)	137 (50–262)	141.5	80.5	89.7	157.7*

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] See footnote to Table 5.

Table 10 Neurotropic activity of β-Trimethylgermylpropiohydroxamic acid (**LII**) administered into the stomach 1 h prior to tests on BALB/c male mice weighing 18–24 g and in white mongrel rats weighing 200 ± 15 g ($n = 6$; temperature = 21 ± 1.5 °C)

Test	$M \pm m$[a] Dose (mg kg^{-1}): 0	5	50	100	250
Hypoxic hypoxia	58.5 ± 5.2 (100)	71.5 ± 13.8 (122.2)	100.0 ± 15.7* (170.9)	116.5 ± 14.6* (197.6)	141.7 ± 13.0* (249.2)
Thermal hypoxia	41.6 ± 7.7 (100)	56.8 ± 7.0 (136.5)	61.0 ± 10.1* (146.6)	38.3 ± 3.7 (92.1)	32.8 ± 1.3 (78.8)
ME, s̄	2.0 ± 1.1	111.7 ± 25.5*	33.0 ± 24.1	—	7.7 ± 5.3
Ethanol anaesthesia	55.9 ± 3.9	62.5 ± 7.9 (111.8)	105.8 ± 14.2* (189.3)	145.0 ± 16.3* (259.4)	235.8 ± 15.0* (421.8)
Hexenal anaesthesia	45.8 ± 7.1	30.0 ± 1.2* (65.5)	36.6 ± 1.0* (79.9)	46.6 ± 20.3 (101.7)	175.8 ± 9.7 (382.1)
Phenamine stereotype behaviour	65.8 ± 9.3	63.3 ± 10.0	82.5 ± 12.5 (125.4)	—	58.3 ± 19.0 (88.6)
No. of 'head shaking' caused by 5-hydroxytryptophan	20.5 ± 3.3	9.2 ± 2.5* (44.9)	6.8 ± 2.1* (33.2)	—	4.2 ± 0.5* (20.5)
Strychnine convulsions	0.94 ± 0.1	1.49 ± 0.05* (158.3)	2.01 ± 0.15* (213.8)	2.02 ± 0.21* (214.9)	1.49 ± 0.13* (158.3)
Nicotinic tremor	1.30 ± 0.1	—	1.39 ± 0.21 (106.9)	—	2.02 ± 0.23* (155.4)
Arecoline tremor	17.8 ± 1.6	14.7 ± 2.4 (82.6)	15.3 ± 1.9 (95.9)	15.0 ± 2.9 (84.3)	15.5 ± 2.9 (87.1)
Thiosemicarbazide convulsions	63.3 ± 2.6	65.0 ± 4.2 (100.7)	63.3 ± 10.1 (100)	90.0 ± 3.6* (142.2)	148.3 ± 9.3 (243.3)

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] See footnote to Table 6.

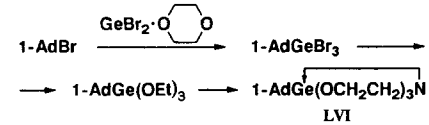
poxic activity expressed. Compound **LII** in doses from 50 to 250 mg kg^{-1} prolongs the life of animals under hypoxic hypoxia by 70–149.2% and by 46.6% (in a dose of 50 mg kg^{-1}) under haemic hypoxia.

β-Trimethylgermylpropiohydroxamic acid (**LII**) favourably affects the elaboration of passive conditional responses (only in very low doses, i.e. 5 mg kg^{-1}). Increasing the dose of compound **LII** (50–250 mg kg^{-1}) leads to the emergence of depressant activity. This is confirmed by the hexenal anaesthesia test. Thus, acid **LII** in doses of 5 and 50 mg kg^{-1} reduces the duration of hexenal anaesthesia by 34.5 and 20.1%, respectively, whereas a larger dose (250 mg kg^{-1}) prolongs this parameter by 282.1%. Concerning the phenamine stereotype behaviour, the action of compound **LII** administered p.o. is not reliable. The pronounced protective action of β-trimethylgermylpropiohydroxamic acid (**LII**) on strychnine-induced convulsions is evidence for its influence on the spinal cord.

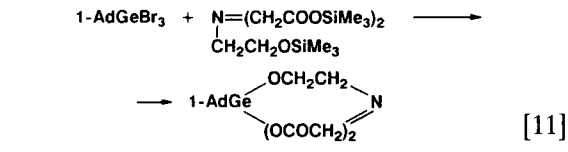
Obviously, the mechanism of β-trimethylgermylpropiohydroxamic acid (**LII**) action implies an influence on the central serotoninergic processes. During its application in large doses (100 and 250 mg kg^{-1}) GABAergic processes are involved as well.

8 ORGANOGERMANIUM DERIVATIVES OF ADAMANTANE

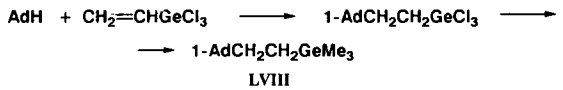
Organogermanium derivatives of adamantane have been obtained according to Schemes 8–11 and Eqns [11] and [12].[14]



Scheme 8

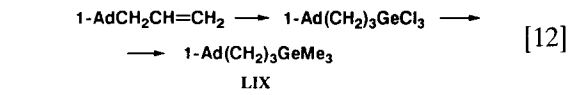


LVII [11]



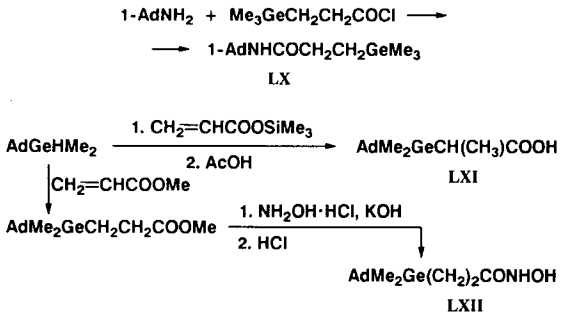
LVIII

Scheme 9



LIX [12]

Scheme 10



LX

LXI

LXII

Scheme 11

All the organogermanium derivatives of adamantane studied are low-toxicity substances; their mean lethal doses exceed 1000 mg kg^{-1} (Table 11). However, some patterns governing the toxic properties and neurotropic activity of these compounds have been revealed. Thus, comparison of adamantylgermatrane (**LVI**) with adamantylgermatranedione (**LVII**) has shown that the introduction of two carbonyl groups into the germatrane ring increases to some extent the toxicity and decreases the depressant activity of the compound. Compound **LVIII**, with two methylene groups between the adamantane group and the germanium atom, is more toxic than the corresponding substance containing three methylene groups (**LIX**). At the same time the latter has the highest depressant activity among adamantylgermatranes. During the transition from 2-(adamantyldimethylgermyl)propionic acid (**LXI**) to β-(adamantyldimethylgermyl)propiohydroxamic acid (**LXII**), the toxicity of the compound is increased 1.8-fold, and its depressant activity grows 4–7-fold.

The substitution of one methyl group in trimethylpropiohydroxamic acid (**LII**) for adamantyl (**LXII**) increases approximately twofold the depriming activity, but decreases by a factor of 2.5 the phenamine effect of the compound. No one compound of this group possesses noticeable analgesic activity, changes the pharmacological effects of phenamine or exhibits protective properties during convulsions caused by electric shocks.

It has been found that adamantanes **LIX**, **LVI** and **LX** increase the Corazole dose causing tonic convulsions with lethal outcome by 85.2, 55.4 and 43.3%, respectively. Hexenal anaesthesia is statistically increased by 2-(adamantyldimethylgermyl)propionic acid (**LXI**) and 1-adamantylgermatranedione (**LVII**), while under the influence of adamantylethylgermane (**LVIII**) it is decreased.

All the organogermanium derivatives of adamantane studied (except **LVIII**) at a dose of 50 mg kg^{-1} exhibit antihypoxic activity, mostly expressed in adamantylgermatrane (**LVI**), germatrandione (**LVII**) and germyladamantane (**LIX**). Adamantylgermatrane (**LVI**) and the adamantylamide of trimethylgermylpropionic acid (**LX**) in a dose of 50 mg kg^{-1} decrease hypothermia by 1–3 °C and reserpine-induced ptosis by 15–25%.

Adamantylgermatrane (**LVI**) has been studied more thoroughly during its administration to the stomach in doses from 5 to 250 mg kg^{-1}. Administered p.o., it also reveals pronounced antihypoxic activity which increases with dose (Table 12). Compound **LVI** in doses of 50–250 mg kg^{-1} also reveals antihypoxic potency at haemic hypoxia. Nevertheless, adamantylgermatrane does not noticeably influence the elaboration of the conditional response of passive avoidance. Its high activity for anaesthesia caused by sodium barbital (which is known not to cause any metabolic transformations and not to influence the central nervous system) is evidence for neurotropic potency.

A reproducible effect of adamantylgermatrane on the pharmacological activity of phenamine, 5-oxytryptophan and strychnine has been observed. Compound **LVI** fails to affect noticeably the horizontal component of locomotor activity, but in doses of 100 and 200 mg kg^{-1} it decreases to some extent the vertical component of locomotor activity.

In the mechanism of action of adamantyl-

Table 11 Neurotropic activity of organogermanium derivatives of adamantane

Compound	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1})[a]			$M \pm m$ (% of control)[a]				
		Rotating rod test	Tube test	Traction test	Hypothermia	Hypoxia	Hexenal anaesthesia	Phenamine stereotype behaviour	Corazole convulsions
LVI	>5000	205 (146–280)	224 (144–285)	258 (168–357)	>500	173.8*	139.5	78.1	155.4*
LVII	3250 (1720–5020)	>500	>500	>500	447 (313–596)	165.5*	160.6*	78.2	148.7
LVIII	1480 (350–2940)	>1000	>1000	>1000	>1000	96.5	62.5*	124.3	90.7
LIX	>5000	32.5 (21.9–45.5)	47.7 (24.8–76.7)	47 (14–96.6)	47.7 (24.8–76.7)	174.0*	84.0	77.8	185.2*
LX	3600 (1200–6700)	23.5 (15.8–48.3)	23.2 (15.9–41.9)	29.6 (9.3–61.2)	23.2	124.7	113.6	100.0	143.3*
LXI	5150 (3620–6920)	515 (362–694)	447 (313–569)	650 (438–886)	410 (268–552)	132.0*	167.9*	94.8	96.6
LXII	2820 (1830–3720)	109 (40.6–205.8)	116 (40.5–219.8)	89 (63.8–119.7)	103 (58.2–157.3)	145.5	144.8	90.2	131.3

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] See footnote to Table 5.

Table 12 Neurotropic activity of adamantylgermatrane (**LVI**) administered into the stomach 1 h prior to tests on BALB/c male mice weighing 18–29 g and on white mongrel rats weighing 210 ± 15 g ($n = 6$; temperature = 21 ± 1.5 °C)

	$M \pm m$[a]				
	Dose (mg kg^{-1}):				
Tests	0	5	50	100	250
Hypoxic hypoxia	45.5 ± 2.1 (100)	60.2 ± 12.4 (132.3)	71.7 ± 9.7* (157.6)	96.8 ± 8.9* (212.7)	108.2 ± 11.9* (237.8)
Thermal hypoxia	22.8 ± 0.4 (100)	23.7 ± 0.7 (103.9)	30.3 ± 0.9* (132.0)	28.8 ± 1.2* (126.3)	31.5 ± 0.6* (138.2)
RA, %	2.0 ± 1.1	4.5 ± 3.3	—	—	3.3 ± 0.8
Hexenal anaesthesia	65.0 ± 10.5 (100)	76.7 ± 5.3 (118.0)	—	78.3 ± 11.1 (120.5)	69.2 ± 11.5 (106.2)
Sodium barbital anaesthesia	76.3 ± 3.9 (100)	135.8 ± 3.8* (178.0)	135.8 ± 18.1* (178.0)	155.0 ± 20.8* (203.1)	128.3 ± 15.7* (168.1)
Chloral hydrate anaesthesia	50.3 ± 3.2 (100)	70.8 ± 9.0 (140.7)	65.8 ± 5.8 (130.8)	65.0 ± 9.2 (129.2)	68.3 ± 8.7 (135.9)
Phenamine stereotype behaviour	180.0 ± 11.2 (100)	177.7 ± 8.0 (98.6)	161.7 ± 10.7 (89.8)	150.8 ± 13.5 (83.8)	149.2 ± 16.8 (82.9)
No. of 'head shakings' caused by 5-hydroxytryptophan	6.8 ± 2.0 (100)	6.3 ± 2.3 (92.6)	4.0 ± 1.1 (58.8)	—	3.3 ± 1.0 (48.5)
Strychnine convulsions	1.06 ± 0.06 (100)	1.34 ± 0.12 (126.4)	—	1.34 ± 0.16 (126.4)	1.77 ± 0.18 (167.0)
Arecoline tremor	11.7 ± 1.1 (100)	29.3 ± 3.7* (250.4)	31.8 ± 1.7* (271.8)	—	14.8 ± 1.3 (126.5)
Thiosemicarbazide convulsions	61.2 ± 2.0 (100)	72.5 ± 4.6* (118.5)	—	81.7 ± 3.8* (133.5)	80.8 ± 5.6* (132.0)
Horizontal locomotor activity	48.5 ± 1.2 (100)	57.0 ± 3.4 (117.5)	53.8 ± 4.0 (110.9)	51.3 ± 5.1 (105.3)	44.3 ± 8.7 (91.3)
Vertical locomotor activity	7.2 ± 0.5 (100)	5.0 ± 1.6 (69.4)	3.7 ± 0.7 (51.3)	1.2 ± 0.7* (16.7)	1.3 ± 0.4* (18.1)

* Differences are statistically reliable vs control at $P \leq 0.05$.

[a] See footnote to Table 6.

germatrane a considerable role is played by its M-cholinemimetic influence (i.e. it strengthens the adrenaline tremor) and GABAergic structure.

9 CONCLUSION

To summarize the effects of the organogermanium compounds examined on the central nervous system, one can assert that the majority of the compounds possess neurotropic potency of the depressant type, causing attenuation in animals and decrease in locomotor activity and in learning activity, relaxation of skeletal muscle and lowering of body temperature.

All the compounds examined can be conditionally divided into four groups according to their influence on locomotor activity, mucle tone and body temperature. Compounds of the first group have the highest depressant activity, the mean values of the effective doses being less than 10 mg kg^{-1}. Thus, ED_{50} of 1-hydrogermatrane (Table 1) equals 0.0015 mg kg^{-1} in rotating-rod and tube tests. Thienylgermatranes (**XVI–XVIII**; Table 3) and iodomethylammonium derivatives of *N*,*N*-diethyl-5-trimethylgermyl-2-furfuryl amine (**LI**; Table 8) exhibit high depressant activity.

Compounds of the second group possess medium depressant activity; their ED_{50} values lie within the 10–100 mg kg^{-1} range in the tests mentioned above (compound **II**, Table 1; compounds **XII–XIV** and **XX**, Table 3; compound **XXIII**, Table 4; compounds **XXVI**, **XXX**, **XXXIII**, **XXXVI**, **XXXVII** and **XXXIX**, Table 5; com-

pounds **XLII** and **XLIII**, Table 7; compounds **XLVIII**, **XLIX** and **LV**, Table 8; compounds **LIII** and **LIV**, Table 9; compounds **LIX** and **LX**, Table 11). Compounds of the third group show insufficient depressant activity (their ED_{50} in the relevant tests being within the 100–500 mg kg^{-1} ranges) (compounds **IV–VI** and **X**, Table 1; compound **XIX**, Table 3; compound **XXII**, Table 4; compounds **XXVII**, **XXVIII**, **XXXI** and **XLI**, Table 5; compound **XLIV**, Table 7; compound **LII**, Table 9; compounds **LVI** and **LXI**, Table 11).

The ED_{50} values of the fourth group in rotating-rod, tube, traction, and hypothermia tests exceed 500 mg kg^{-1} (compounds **III**, **VII**, **VIII** and **XI**, Table 1; compounds **XV** and **XXI**, Table 3; compound **XXIV**, Table 4; compounds **XXV**, **XXIX**, **XXXII**, **XXXIV**, **XXXV**, **XXXVIII** and **XL**, Table 5; compounds **LVII** and **LVIII**, Table 11), i.e. their depressant activity is revealed only in the doses close to toxic.

The effect of organogermanium compounds on the duration of hexenal anaesthesia provides evidence for the sedative activity. Thus, for example, all derivatives examined of furyl- and thienylgermatranes with the exception of 1-(2-thienyl)germatrane (**XVI**) (Table 3), nitrogen-containing derivatives of methyl- and ethylgermatrane (Table 5) and germanium-containing adamantanes (Table 11) prolong hexenal anaesthesia 1.5–2-fold. Perhaps the compounds studied influence the metabolic processes of hexenal to some extent. Their tranquilizing activity is revealed in the Corazole convulsions test: organogermanium derivatives of adamantane (Table 11), some amidoalkylgermatranes (Table 5) and germyl-substituted hydroxamic acids exhibit the highest activity in this test (Table 9).

All the compounds examined in doses of 5–50 mg kg^{-1} show antihypoxic activity, expressed differently in the various groups of compounds. The most active among them are germatranol (**II**), which has been found to prolong the life of animals by 86.5%, 2-furylgermatrane (**XII**) by 84.8% and 5-methyl-2-thienylgermatrane (**XVIII**) by 81%; adamantylgermatrane (**LVI**), 1-(γ-trimethylgermyl)-propyladamantane (**LIX**) and β-trimethylgermylisobutyrohydroxamic acid (**LIII**) all prolonged life by 74%. The other derivatives of germanium show antihypoxic activity within the 30–68% range. According to antihypoxic activity indexes, germanium-containing compounds exceed the reference drug for nootropic action (i.e. Piracetam) when used in doses of 5, 50, 250, 500 mg kg^{-1} and prolong animal life by 29.5, 39.3, 35.4 and 64.1%, respectively. A statistically reliable value was obtained only in the case when Piracetam was applied in a dose of 500 mg kg^{-1}, i.e. at a 10-fold larger dose than germanium-containing compounds.

The interaction of compounds studied with phenamine is evidence for their influence on CNS dopaminergic processes. These compounds decrease the duration of phenamine stereotype behaviour; for example, 1-germatranol hydrate (**II**) reduces the phenamine stereotype behaviour to 47.7 versus the control (100%); trimethylsiloxygermatrane (**III**) reduces it to 31.4%, the majority of nitrogen-containing germanes and germatranes (see Tables 5 and 8) reduce it to 46–60%, and tricyclohexylgermanol (**XLII**) reduces it to 41.5%. On the other hand, triphenylgermoxygermatrane (**XI**) and β-trimethylgermylpropiohydroxamic acid increase the duration of phenamine stereotype behaviour by 126.7%, ethylthienylgermatrane (**XIX**) increases it by 93.4%, bromomethylgermatrane (**XXIII**) increases it by 72.1%, dithienylmethylsiloxygermatrane (**V**) increases it by 65.9%, germatranyldimethylaniline (**XL**) increases it by 56.6%, and pyrrolidonylethylsesquioxane (**XLIII**) increases it by 55.3%. The potentiating activity of the other compounds has been found to be less than 50%.

Data on the potentiating interaction with phenamine and also data on the antagonistic interaction with hexenal speak in favour of the activating components in their spectrum of action. Thus, 2-thienylgermatrane (**XVI**) shortens hexenal anaesthsia by 42%, phthalimidomethylgermatrane (**XXXII**) by 40.3%, germatranylmethylbenzamide (**XXV**) by 27.6%, chlorobenzamidomethylgermatrane (**XXVII**) by 29.7%, germatranylbarbituric acid (**XXXIV**) by 34.1% and trimethylgermyladamantane (**LVIII**) by 37.5%.

Detailed studies of 1-germatranol hydrate (Table 2), 4-(dimethylamino)phenylgermatrane (Table 6), β-trimethylgermylpropiohydroxamic acid (Table 10) and adamantylgermatrane (Table 12) confirm the high antihypoxic activity of these compounds administered p.o. in doses of 5–250 mg kg^{-1}. Antihypoxic activity for these compounds is combined with influence expressed on conditioned responses of passive avoidance, thus, providing evidence for the nootropic activity observed in germanium-containing compounds.

By the parameters mentioned, the germanium compounds studied exceed the reference preparation for nootropic action, Piracetam; statistically reliable results were obtained when it was used in 5–10-fold larger doses.

The mechanism of neurotropic action of the germanium derivatives studied, considering indirect indicators, seems to involve various neuromediator structures, e.g. cholinergic, dopaminergic, serotoninergic and GABAergic structures, and is expressed differently in the various compounds.

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