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Synthesis and psychotropic properties of 1-triorganylsiloxy- and 1-triorganylgermoxy-germatranes

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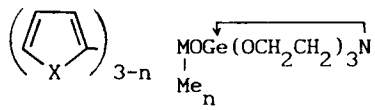
Triorganylsiloxy- and triorganylgermoxy-germatranes have been prepared by the interaction of the easily available 1-hydroxygermatrane with various hetaryl-silanes and -germanes. The compounds were of the general structure:



M = Si; X = S, CH = CH (viz. phenyl); $n = 0, 1, 2$
M = Ge; X = CH = CH (viz. phenyl); $n = 0$

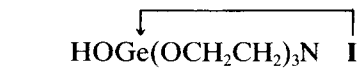
All siloxy- and germoxy-germatranes obtained were subjected to psychotropic assays. Some of phenylsiloxygermatranes are effective for memory enhancement (inhibition of retrogradal amnesia by triphenylsiloxygermatrane was 80%).

Keywords: Phenylsiloxygermatranes, thienylsiloxygermtranes, triphenylgermoxygermatrane, toxicity, psychotropic activity

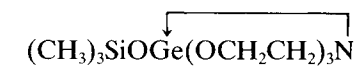
INTRODUCTION

We have embarked on a systematic investigation of the biologial activities of organogermanium compounds.[1–3] Recently it has been demonstrated that furyl- and thienyl-germatranes whose molecules contain a heterocycle and atrane cycles with a pentacoordinated germanium atom are endowed with neurotropic activity. It has also been found that compounds with a hetaryl group linked directly to the germanium atom are highly toxic substances.[2] The introduction of one methylene group separating the germanium atom and heterocycle dramatically decreases the toxicity of the compounds while maintaining a sufficiently high neurotropic activity.

To elucidate the influence of hetarylgermane structure on this activity we decided to exchange the methylene group between the germanium atom and the heterocycle by siloxy and germoxy groups. We used the mildly toxic 1-hydroxy-germatrane which appears to be one of the most readily available germatranes containing the functional group at the germanium atom. Boiling a mixture of germanium dioxide and triethanolamine in the presence of a small amount of water until dissolution of GeO_2 is complete after cooling leads to compound **I**



in crystalline form.[4,5] It contains a pentacoordinated germanium atom with a sufficiently short Ge–N bond.[6] 1-Hydroxygermatrane readily reacts with hexamethyldisilazane or hexamethyldigermazane to afford 1-trimethylsiloxy (**II**),



or 1-trimethylgermoxy derivatives.[7] The compounds obtained possess antitumour activity.[8] 1-Hydroxygermatrane **I** reacts with various trialkylhalogeno-silanes, -germanes and -stannanes, triphenylsilanol and *o*-aminophenol to give compounds containing an M-O-Ge group.[5,9]

It has been shown that 1-hydroxygermatrane (**I**) reacts with phenyl- and thienyl-hydrosilanes and -hydrogermanes to yield hydrogen in the presence of chloroplatinic acid or Amberlyst 15 (Fluka), while in the case of more active hydrosilanes the reaction occurs even without catalyst. The new siloxy- (**III–IX**) and germoxy- (**X**) germatranes obtained were tested biologically.

EXPERIMENTAL

NMR spectra were recorded on a Bruker WM-360 spectrometer operating at 12.56 (^{73}Ge), 71.55 (^{29}Si) and 90.56 MHz (^{13}C) on solutions in

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Table 1 Influence of the reaction conditions on the yield of products

Compound	Reaction time (h)	Yield (%) Without catalyst	With $H_2PtCl_6.6H_2O$[a]	With A 15[b]
III	1	62	80	47
IV	1	45	50	40
V	10	6	9	2
VI	10	0	48	—
VII	10	0	2	25
VIII	20	0	0	2
IX	10	—	14	—
X	10	0	13	40

[a]

[b] A 15, Amberlyst 15 ion-exchange resin containing 4.6 mg kg^{-1} SO_3H groups per g. 1.6 w%.

DMSO. Chemical shifts were measured relative to $Me_4Ge(^{73}Ge)$, $Me_4Si(^{29}Si)$ and $C_6H_{12}(^{13}C)$.

^1H NMR spectra were also recorded conventionally on a Bruker WH-90/DS spectrometer for 5–7% solutions in DMSO with TMS as internal standard.

Phenyl- and thienyl-hydrosilanes were prepared according to the known methods.[10]

Yields, melting points and analytical data for the new compounds obtained are summarized in Tables 1 and 2. A list of the compounds (**III–X**) prepared is also given in the Results and discussion section below.

1-Trithienylsiloxygermatrane (III)

Trithienylsilane (1.17 g, 0.005 mol) and 1-hydroxygermatrane (1.39 g, 0.005 mol) were refluxed in xylene (20 cm^3) for 60 min. Then the isolated compound **III** was filtered off and dried *in vacuo* [yield 1.6 g (62%)]. Recrystallization from ethanol was carried out. ^1H NMR δ, ppm: 2.89 (t, 6H, N–CH_2); 3.68 (t, 6H, O—CH_2); 7.21 (q, 3H, H^4); 7.41 (q, 3H, H^3); 7.84 (q, 3H, H^5); $J_{3,5}=0.9$; $J_{3,4}=3.2$; $J_{4,5}=4.7$ Hz; ^{13}C NMR δ, ppm: 50.84 (N–CH_2); 56.32 (O–CH_2); 127.65; 132.11; 136.71; 137.47 (C_{Ar}).

Compounds **IV–X** were prepared analogously from the appropriate silane and 1-hydroxygermatrane, and had the properties shown below and in Tables 1 and 2.

1-Dithienylmethylsiloxygermatrane (IV)

^1H NMR δ, ppm: 0.54 (s, 3H, Si—CH_3); 2.88 (t, 6H, N—CH_2); 3.68 (t, 6H, O—CH_2); 7.19 (q, 2H, H^4); 7.38 (q, 2H, H^3); 7.80 (q, 2H, H^5); $J_{3,5}=1.0$; $J_{3,4}=3.4$; $J_{4,5}=4.7$ Hz. ^{13}C NMR δ, ppm: 3.69 (Si—CH_3); 51.87 (N—CH_2); 57.38 (O—CH_2); 128.71; 132.20; 136.24; 140.40 (C_{Ar}). ^{73}Ge NMR δ, ppm: −70.5; $\Delta\nu_{1/2}=180$ Hz (in $CDCl_3$); ^{29}Si NMR δ, ppm: −22.13.

1-Thienyldimethylsiloxygermatrane (V)

^1H NMR δ, ppm: 0.12 (s, 6H, Si—CH_3); 2.73 (t, 6H, N—CH_2); 3.56 (t, 6H, O—CH_2); 7.13 (q, 1H, H^4); 7.21 (q, 1H, H^3); 7.65 (q, 1H, H^5); $J_{3,5}=1.0$;

Table 2 Analytical data for compounds **III–X**

Compound	Molecular formula	M.p. (°C)	Analysis: found (calc.) (%) C	H	N
III	$C_{18}H_{21}GeNO_4S_3Si$	217–218	42.64 (42.21)	3.97 (4.13)	2.66 (2.73)
IV	$C_{15}H_{21}GeNO_4S_2Si$	140–142	40.56 (40.83)	4.76 (4.75)	3.15 (2.89)
V	$C_{12}H_{21}GeNO_4SSi$	120–121	38.17 (38.33)	5.57 (5.63)	3.76 (3.72)
VI	$C_{24}H_{27}GeNO_4Si$	273–274	58.43 (58.33)	5.63 (5.51)	2.78 (2.83)
VII	$C_{19}H_{25}GeNO_4Si$	160–162	52.87 (52.81)	5.89 (5.83)	3.07 (3.24)
VIII	$C_{14}H_{23}GeNO_4Si$	156–158	45.49 (45.44)	6.44 (6.26)	3.75 (3.78)
IX	$C_{22}H_{25}GeNO_4Si$	186–188	55.97 (56.45)	5.37 (5.38)	2.89 (2.99)
X	$C_{24}H_{27}Ge_2NO_4$	230–232	53.84 (53.51)	4.95 (5.05)	2.30 (2.60)

$J_{3,4}=3.4$; $J_{4,5}=4.7$ Hz. ^{13}C NMR δ, ppm: 2.55 ($Si—CH_3$); 50.73 ($N—CH_2$); 56.21 ($O—CH_2$); 127.62; 130.27; 133.86; 141.25 (C_{Ar}).

1-Triphenylsiloxygermatrane (VI)

^1H NMR δ, ppm: 2.82 (t, 6H, $N—CH_2$); 3.62 (t, 6H, $O—CH_2$); 7.21–7.63 (m, 15H, C_6H_5). ^{13}C NMR δ, ppm: 51.93 ($N—CH_2$); 57.38 ($O—CH_2$); 128.21; 129.91; 135.83; 139.26 (C_{Ar}). ^{73}Ge NMR δ, ppm: −75.8; $\Delta\nu_{1/2}=110$ Hz (in C_6H_6).

1-Diphenylmethylsiloxygermatrane (VII)

^1H NMR δ, ppm: 0.48 (s, 3H, $Si—CH_3$); 2.87 (t, 6H, $N—CH_2$); 3.67 (t, 6H, $O—CH_2$); 7.22–7.67 (m, 10H, C_6H_5). ^{13}C NMR δ, ppm: 1.11 ($Si—CH_3$); 51.84 ($N—CH_2$); 57.32 ($O—CH_2$); 128.24; 129.61; 134.71; 141.40 (C_{Ar}). ^{73}Ge NMR δ, ppm: −73.9; $\Delta\nu_{1/2}=94$ Hz. ^{29}Si NMR δ, ppm: −14.55.

1-Phenyldimethylsiloxygermatrane (VIII)

^1H NMR δ, ppm: 0.17 (s, 6H, $Si—CH_3$); 2.85 (t, 6H, $N—CH_2$), 3.66 (t, 6H, $O—CH_2$); 7.26–7.76 (m, 5H, C_6H_5). ^{13}C NMR δ, ppm: 1.52 ($Si—CH_3$); 50.70 ($N—CH_2$); 56.15 ($O—CH_2$); 127.12; 128.30; 129.23; 132.93 (C_{Ar}).

α-Naphthylphenylhydrosiloxygermatrane (IX)

^1H NMR δ, ppm: 2.82 (t, 6H, $N—CH_2$); 3.62 (t, 6H, $O—CH_2$); 5.71 (s, 1H, $Si—H$); 7.13–8.26 (m, 12H, C_6H_5, $C_{10}H_7$).

1-Triphenylgermoxygermatrane (X)

^1H NMR δ, ppm: 2.68 (t, 6H, $N—CH_2$); 3.47 (t, 6H, $O—CH_2$); 7.23–7.67 (m, 15H, C_6H_5).^{13}C NMR δ, ppm: 52.07 ($N—CH_2$); 57.20 ($O—CH_2$); 128.71; 129.97; 135.12; 139.67 (C_{Ar}).

PHARMACOLOGICAL STUDY

Neurotropic activity was studied on Icr:Ice BALB/c and CBA mice. Ambient temperature (22 ± 1 °C) was maintained in the laboratory and in the animal colony. The tested substances were administered intraperitoneally as aqueous suspensions prepared with the aid of Tween 80, 30 or 60 min prior to the assay. Control animals received injections of equal amounts of distilled water with Tween 80.

Tests were indicated and determined acording to Ref. 2.

Conventional reflex of passive avoidance was applied to evaluate the influence of the substances in question on memory and antiamnesic activity. Retrogradal amnesia was caused transcorneally my maximal electric shock administered just after learning.

RESULTS AND DISCUSSION

Triorganylsilanes react with hydroxyl-containing compounds in the presence of acids, bases, metals and their complexes.[11] In the last case the reaction rate increases with increasing electron density at the oxygen atom of the hydroxyl-containing compound and with an increase of the electron-accepting properties of the substituents at the silicon atom. Due to the large positive inductive effect of the germatranyl group, the oxygen atom of the hydroxyl group of 1-hydroxygermatrane (**I**) is susceptible to nucleophilic attack of the silicon atom in arylhydrosilanes (Eqn [1]):

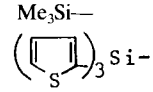
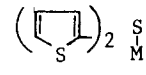
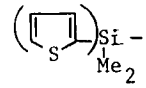
$$RR'R''MH + HOGe(OCH_2CH_2)_3N \xrightarrow{-H_2} RR'R''MOGe(OCH_2CH_2)_3N \quad [1]$$

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

In the presence of hexachloroplatinic acid, the reaction rate increases during the transition from phenyl to thienyl derivatives and with the increase of the number of these groups in the hydrosilane molecule, i.e. with the increase of the total electron-accepting effect of the substituents at the silicon atom. At the same time the dehydrocondensation reaction with the more active thienylsilanes proceeds even in the absence of catalysts. In this case the reaction rate increases with the number of thienyl groups in the hydrosilane molecule.

Triphenylgermane in the presence of $H_2PtCl_6.6H_2O$ exhibited a lower reactivity than

Table 3 Effects of germatranes $ROGe(OCH_2CH_2)_3N$ on locomotor coordination and muscle tone

Compd	R	ED_{50} (mg kg^{-1})[a] Test: Rotating rod	Tube	Traction	Hypothermia
II	Me_3Si—	>500	>500	>500	>500
III		274 (99–524)	>500	>500	274 (99–524)
IV		355 (249–461)	282 (159–419)	410 (268–552)	282 (159–419)
V		109 (40.6–205.8)	70.8 (50–92.5)	>250	218 (81–411)
VI	Ph_3Si—	>500	>500	>500	>500
VII	Ph_2Si(Me)—	690 (242–1303)	564 (387–743)	>500	815 (567–1100)
IX	α-NpPhSiH—	>500	178 (136–230)	137 (50–262)	141 (108–209)
X	Ph_3Ge—	>500	>500	>500	>500

[a] The mean effective dose.

triphenylsilane, while the reaction with triethylsilane, methyldihexylsilane, pentamethyldisiloxane, heptamethyltrisiloxane and triethylgermane failed to occur.

In the reactions with thienylsilanes Amberlyst 15 appeared to be less effective than hexachloroplatinic acid, but the reaction rate also increased with the number of thienyl groups in the hydrosilane. Nevertheless, the changes occurring during the transition from di- to tri-thienylsilane (as well as in the reactions without catalyst) are insignificant if compared with those in the reaction in the presence of the platinum catalyst. In the case of methyldiphenylsilane and triphenylgermane, Amberlyst 15 catalyses the reaction with 1-hydroxygermatrane more effectively than hexachloroplatinic acid.

This series of siloxy- (**III–IX**) and germoxy- (**X**) germatranes, differing from the usual siloxygermanes and digermoxanes (one of the germanium atoms being pentacoordinated in the M—O—Ge group, M = Si, Ge) has been synthesized by the reaction of phenyl- and thienyl-silanes and triphenylgermane with 1-hydroxygermatrane (**I**) in the presence of hexachloroplatinic acid or Amberlyst 15 in boiling xylene. According to X-ray data the Si—O—Si angle in hexa-aryldisiloxanes[12,13] and in some hexaorganyldigermoxanes[14–16] is 180°. The Si—O—Ge group in triphenylsiloxygermatrane (**VI**) has also been found to be linear. The length of the coordinated Ge—N bond is 2.126(6) Å, i.e. somewhat smaller than in the initial 1-hydroxygermatrane (2.146 Å).

The experimental evaluation of acute toxicity and neurotropic properties is presented in Tables 3 and 4.

All siloxy(germoxy)germatranes **II–X** under study exhibit low toxicity, their LD_{50} lying within the range 1000–5000 mg kg^{-1}.

The effect of siloxygermatranes on locomotor coordination parameters and muscle tone is insignificant. Thus, compounds **III**, **IV** and **IX** in rotating-rod, tube and traction tests have ED_{50} in

Table 4 Neurotropic activity of aryl- and thienylgermatranes $ROGe(OCH_2CH_2)_3N$

	Activity (% of control)					
Compd	Hypoxia	Hexobarbital anaesthesia	Ethanol anaesthesia	Amphetamine stereotypy	Corazole-induced spasms	Memory enhancement; retrogradal amnesia (s)
II	148.1[a]	95.5	151.0[a]	131.4[a]	108.5	5.0 ± 1.9; 28.5
III	136.2[a]	—	—	91.4	76.3[a]	51.0 ± 16.6[a]; 70.0
IV	114.8	97.8	145.2[a]	165.9[a]	174.9[a]	30.5 ± 13.8[a]; 50.0
V	111.4	117.8	140.9[a]	129.6	137.7[a]	79.1 ± 14.9[a]; 75.0
VI	120.1[a]	129.4	87.4	87.7	154.6[a]	72.0 ± 15.2[a]; 80
VII	108.2	92.0	75.6	101.6	168.5	46.5 ± 16.4[a]; 62.5
IX	90.3	115.2	—	—	—	20.0 ± 3.5[a]; 57.1
X	116.4	133.3[a]	46.2[a]	226.7[a]	64.7[a]	92.7 ± 12.4[a]; 77.7

[a] Statistically significant difference with respect to control, $P \leq 0.05$.

the 178–410 mg kg^{-1} range and compound **V** in the 70.8–250 mg kg^{-1} range. The other test compounds in doses up to 500 mg kg^{-1} do not entirely cause skeletal muscle relaxation and disturbance of locomotor coordination. Hypothermic action of the compounds synthesized is little expressed and is revealed in approximately the same doses as the influence on locomotor coordination.

Concerning the action of the anaesthetic hexobarbital, it has been found that only triphenylsiloxy- (**VI**) and triphenylgermoxy-germatrane (**X**) increase the duration of anaesthesia by 29.4–33.3%. The others do not increase the duration. Siloxygermatrane derivatives **II**, **IV**, **V** increase ethanol anaesthesia, while germoxygermatrane **X**, on the contrary, decreases the duration of ethanol anaesthesia by 53.8%. In this respect the germanium derivative **X** is more active than its sila analogue.

Trimethyl- (**II**), trithienyl- (**III**) and triphenylsiloxygermatranes (**VI**) possess antihypoxic activity (Table 3).

Stimulating effects of amphetamine are strengthened under the influence of trimethylsiloxygermatrane (**II**) and of methyldithienylsiloxygermatrane (**IV**) by 31.4 and 65.9% respectively, while triphenylgermoxygermatrane **X** exhibits the highest effect (126.7%). Trimethylsiloxygermatrane **II** and dimethylthienylsiloxygermatrane **V** reduce reserpine-induced ptosis by 42.9 and 22.5%. Triphenylgermoxygermatrane (**X**) decreases reserpine-induced ptosis by 41.5%.

All siloxygermatrane derivatives tested, except the trithienyl derivative **III**, possess anti-Corazole activity. Triphenylgermoxygermatrane **X**, as well as trithienylsiloxygermatrane **III**, on the contrary, promote the stimulating effects of Corazole by 35.3 and 23.7%, respectively. None of the compounds synthesized exhibits anticonvulsive activity in the tests of maximal electric shock.

Siloxygermatrane and germoxygermatrane derivatives enhance, to a certain extent, memory processes and decrease the degree of retrogradal amnesia induced by maximal electric shock (Table 4). Triphenylgermoxy- (**X**), triphenylsiloxy- (**VI**) and dimethylthienylsiloxygermatrane (**V**) reveal the highest activity; they prevent retrogradal amnesia by 75–80% and considerably increase the difference of latent periods (Δt) for passage of a darkened chamber after 24 h from 72 to 92.7 s, with control Δt being equal to 3.8 s. Trithienyl- (**III**) and methyldiphenyl-siloxygermatrane (**VII**) exhibit, to some extent, a lesser activity in this test.

Thus, siloxygermatrane derivatives possess neurotropic activity comprising both depriming and activating components. Comparison of triphenylsiloxygermatrane (**VI**) with the corresponding germanium analogue (**X**) has shown that activating pharmacological effects prevail in the latter.

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REFERENCES

1. Lukevics, E, Gar, T K, Ignatovich L M and Mironov, V F *Biological Activity of Germanium Compounds*, Zinatne, Riga, 1990 (in Russian)

2. Lukevics, E, Ignatovich, L, Porsiurova, N and Ğērmane, S *Appl. Organomet. Chem.*, 1988, 2: 115 and references cited therein
3. Lukevics, E and Ignatovich, L M *Metalloorg. Khim.*, 1989, 2: 184
4. Mironov, V F, Gar, T K, Khromova, N Yu and Frid, O D *Zh. Obshch. Khim.*, 1986, 56: 638
5. Gar, T K and Mironov, V F *Metalloorg. Khim.*, 1988, 1: 260
6. Gurkova, S N, Gusev, A J, Alekseev, N V, Gar, T K and Khromova, N Yu *Zh. Strukt. Khim.*, 1985, 6: 154
7. Gar, T K, Khromova, N Yu, Sonina, N N, Nikitin, V S, Polyakova, M V and Mironov, V F *Zh. Obshch. Khim.*, 1979, 49: 1516
8. Lukevics, E Ya, Ğērmane, S K, Zidermane, A A, Dauvarte, A Z, Kravchenko, J M, Trushule, M A, Mironov, V F, Gar T K, Khromova, N Yu, Victorov, N A and Shiryaev, V I *Khim.-Farm. Zh.*, 1984, 2: 154
9. Mironov, V F *Chemistry Reviews: Soviet Scientific Rev.*, Sect. B, Harwood Academic Publishers, London, 1989, 12: 341
10. Bazant, V *Organosilicon Compounds*, Prague Publishing House, Prague, 1965
11. Lukevics, E and Dzintara, M *J. Organomet. Chem.*, 1985, 295: 265
12. Glidewell, C. and Liles, D C *Acta Cryst., B*, 1978, 34: 124
13. Glidewell, C and Liles, D C *J. Chem. Soc., Chem. Commun.*, 1977, 18: 632
14. Glidewell, C and Liles, D C *J. Organomet. Chem.*, 1979, 174: 275
15. Glidewell, C and Liles, D C *Acta Cryst., B*, 1978, 34: 119
16. Glidewell, C and Liles, D C *J. Chem. Soc., Chem. Commun.*, 1973, 3: 93