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Synthesis and psychotropic properties of furyl- and thienyl-germatranes

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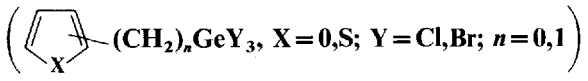
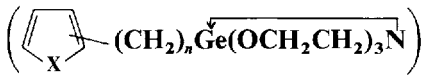
Trihalogermyl-furans and -thiophenes



were prepared by inserting germanium dibromide ($GeBr_2$) generated from the dibromogermane(II) dioxanate complex into the carbon–halogen bond of halo-furans and -thiophenes. Their ethanolysis and transesterification by triethanolamine yielded the germatranes



which were subjected to psychotropic activity assays. The psychotropic properties of germatranes were found to depend on the type of the heterocycle and on the position of the germatrane moiety.

Keywords: Furyltribromogermanes, thienyltribromogermanes, furylgermatranes, thienylgermatranes, toxicity, psychotropic activity

INTRODUCTION

Recent years have seen an upsurge of interest in the biological properties of germsesquioxanes and germazaspiranes, largely due to the discovery of antitumour and immunomodulating activity in some of their derivatives (Ge-132, 'spirogermanium').[1–5] We have embarked on a systematic investigation of the biological activities of two other organogermanium systems, viz. germatranes[6–9] and hetarylgermanes.[10] The present communication deals with the synthesis and psychotropic properties of organogermanium compounds (furyl- and thienyl-germatranes) whose molecules combine fragments characteristic of these two classes—the atrane cycle with a pentacoordinated germanium atom and a heterocycle linked to the germatrane residue. Synthesis is via the respective trihalofuryl- and trihalothienyl-germanes (**I–VI**).

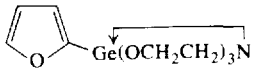
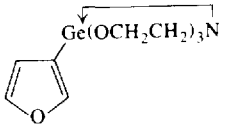
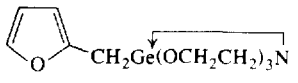
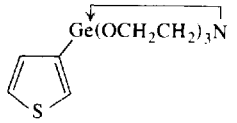
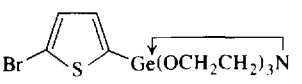
EXPERIMENTAL

PMR spectra were conventionally recorded on a Bruker WH-90/DS spectrometer for 5–7% solutions in deuterochloroform with TMS as internal standard. Mass spectra were recorded on a Kratos MS-25 apparatus at 70 eV. 2-Bromofuran, 3-bromofuran and 2-furfuryl chloride were prepared according to known methods.[11–13] 2-Bromo- and 3-bromo-thiophene were Fluka products.

2-Furylgermatrane (VII)

2-Bromofuran (11.5 g, 0.078 mol) and the dioxane complex of germanium(II) dibromide (23.1 g, 0.072 mol) were heated in a sealed ampoule for 2 h at 200°C. The resultant yellow solution was distilled *in vacuo*, and a fraction boiling at 66–70°C/3 mm Hg was collected to yield 2-furyltribromogermane (20 g, 67%). To a 2-furyltribromogermane solution (2.7 g, 0.007 mol) in ether (20 cm^3), cooled to 0°C, was added dropwise an ethanolic solution (10 cm^3) of triethylamine (2.5 g, 0.025 mol), followed by heating to room temperature and boiling for 2 h. After cooling, the triethylamine salt was filtered off. To the filtrate cooled to 0°C was added dropwise triethanolamine (1.04 g, 0.007 mol). The reaction mixture was stirred at room temperature for 2 h, cooled to 0°C and 2-furylgermatrane **VII** (1.2 g, 60%) was filtered off. Recrystallization from chloroform–hexane (1:1) mixture was carried out. Found: C, 42.18; H, 5.18; N, 4.83. Calcd for $C_{10}H_{15}NGeO_4$: C, 42.01; H, 5.29; N, 4.90%. M.p. 166–167°C. ^1H NMR and mass-spectroscopic data are summarized in Table 1.

Table 1 ^{1}H NMR and mass spectral data for furyl- and thienyl-germatranes

Compound	Chemical shift, δ (ppm); J (Hz)	m/z (relative intensity [%])
VII 	2.91 (t, 6H, β-CH_2), 3.91 (t, 6H, α-CH_2), 6.36 (q, 1H, H^4), 6.76 (q, 1H, H^3), 7.69 (q, 1H, H^5); $J_{3,5}$ 3.5, $J_{3,4}$ 0.9, $J_{4,5}$ 1.8	287 (M^+, 24), 257 (17), 227 (13), 204 (12), 160 (14), 146 (100), 86 (25), 68 (10), 56 (40), 42 (21)
VIII 	2.91 (t, 6H, β-CH_2), 3.87 (t, 6H, α-CH_2), 6.53 (q, 1H, H^4), 7.47 (q, 1H, H^5), 7.57 (q, 1H, H^2); $J_{2,4}$ 0.7, $J_{2,5}$ 1.3, $J_{4,5}$ 1.7	287 (M^+, 40), 257 (33), 227 (45), 146 (100), 86 (49), 70 (11), 56 (47), 42 (28)
IX 	2.41 (s, 2H, CH_2), 2.83 (t, 6H, β-CH_2), 3.80 (t, 6H, α-CH_2), 6.01 (m, 1H, H^3), 6.26 (m, 1H, H^4), 7.27 (q, 1H, H^5); $J_{3,4}$ 2.9, $J_{3,5}$ 0.6, $J_{4,5}$ 1.8	301 (M^-, 8), 220 (100), 160 (12), 81 (27), 56 (16)
XI 	2.90 (t, 6H, β-CH_2), 3.88 (t, 6H, α-CH_2), 7.34 (m, 1H, H^4), 7.34 (m, 1H, H^5), 7.69 (q, 1H, H^2)	303 (M^+, 41), 273 (34), 258 (11), 243 (45), 220 (10), 160 (39), 146 (100), 91 (13), 86 (38), 70 (13), 56 (54), 42 (27)
XII 	2.89 (t, 6H, β-CH_2), 3.84 (t, 6H, α-CH_2), 6.98 (d, 1H, H^4), 7.11 (d, 1H, H^3); $J_{3,4}$ 3.4	381 (M^+, 51), 351 (29), 321 (30), 160 (28), 146 (100), 82 (34), 56 (26), 42 (17)

3-Furylgermatrane (VIII)

From 3-bromofuran (4.2 g, 0.029 mol) and germanium(II) dioxane dibromide (4.0 g, 0.0125 mol) was obtained 3-furyltribromogermane (3.9 g) in 41% yield, b.p. 99–100°C/8 mm Hg (the reaction conditions were analogous to those in the preparation of 2-furyltribromogermane). To a solution of 3-furyltribromogermane (2.4 g, 0.0063 mol) in ether (20 cm^3), cooled to 0°C, was added dropwise triethylamine (1.9 g, 0.019 mol) dissolved in ethanol (10 cm^3). After reaching room temperature the mixture was boiled for 2 h, then cooled, and the triethylamine salt was filtered off. Triethanolamine (0.94 g, 0.0063 mol) in absolute ethanol (5 cm^3) was added dropwise to the filtrate. The reaction mixture was stirred at room temperature for 2 h, cooled and filtered to yield the germatrane **VIII** (1.0 g, 56%), recrystallized from chloroform. Found: C, 41.65; H, 5.21; N, 5.01. Calcd for $C_{10}H_{15}NGeO_4$: C, 42.01; H, 5.29; N, 4.90%. M.p. 168–170°C. ^{1}H NMR and mass-spectroscopic data are summarized in Table 1.

2-Furfurylgermatrane (IX)

Germanium(II) dioxane dibromide (5.4 g, 0.017 mol) was added in small portions to furfuryl chloride (4.0 g, 0.034 mol) with cooling (0°C) in an argon atmosphere, and after warming up to room temperature the mixture was stirred for 5 h. A fraction boiling at 84–85°C/2.5 mm Hg was collected during distillation *in vacuo* to yield 2-furfuryldibromochlorogermane (2.6 g, 44%). The 2-furfuryldibromochlorogermane (1.9 g, 0.0054 mol) was converted to the corresponding triethoxy derivative from which germatrane **IX** was obtained by transesterification with triethanolamine (0.81 g, 0.0054 mol). Recrystallization from chloroform gives 2-furfurylgermatrane (1.2 g, 64%) with m.p. 195–197°C. Found: C, 43.91; H, 5.68; N, 4.57. Calcd for $C_{11}H_{17}NGeO_4$: C, 44.06; H, 5.71; N, 4.67%. ^{1}H NMR and mass-spectroscopic data are summarized in Table 1.

2-Thienyltribromogermane (V)

2-Bromothiophene (13.05 g, 0.08 mol) and the dioxane complex of germanium(II) dibromide (12.2 g, 0.04 mol) were heated in a sealed ampoule for 3 h at 200°C. A fraction boiling at 72–74°C/2 mm Hg was collected during distillation *in vacuo* to yield 2-thienyltribromogermane (9.1 g, 55%), whose physicochemical characteristics were identical to those described elsewhere.[14] The preparation of 2-thienylgermatrane is described in Ref. 6.

3-Thienylgermatrane (XI)

3-Bromothiophene (3.2 g, 0.02 mol) and

germanium(II) dioxane dibromide (3.2 g, 0.01 mol) were boiled in a sealed ampoule for 4 h at 200°C. A fraction boiling at 104–106°C/2.5 mm Hg was collected during distillation to give 3-thienyltribromogermane (2.3 g, 58%). 3-Thienylgermatrane was obtained from 3-thienyltribromogermane (2.0 g, 0.005 mol) and triethanolamine (0.75 g, 0.005 mol) via the appropriate triethoxy derivative. Recrystallization from chloroform yielded 3-thienylgermatrane (0.7 g, 46%), m.p. 178–179°C. Found: C, 40.02; H, 4.99; N, 4.51. Calcd for $C_{10}H_{15}NGeO_3S$: C, 39.79; H, 5.00; N, 4.64%. ^{1}H NMR and mass-spectroscopic data are summarized in Table 1.

5-Bromo-2-thienylgermatrane (XII)

2,5-Dibromothiophene (4.4 g, 0.018 mol) and germanium(II) dioxane dibromide (6.08 g, 0.018 mol) were boiled in a sealed ampoule for 4 h at 200–250°C to give a clear yellow solution. A fraction boiling at 129–132°C/4 mm Hg was collected during distillation to yield 5-bromo-2-thienyltribromogermane (5.9 g, 69%). 5-Bromo-2-thienylgermatrane was obtained from 5-bromo-2-thienyltribromogermane (5.3 g, 0.011 mol) and triethanolamine (1.6 g, 0.011 mol) via the corresponding triethoxy derivative. Recrystallization from chloroform–hexane (1:1) yielded 5-bromo-2-thienylgermatrane (4.0 g, 95%) with m.p. 210–212°C. Found: C, 31.86; H, 3.49; N, 3.43. Calcd for $C_{10}H_{14}NBrGeO_3S$: C, 31.54; H, 3.71; N, 3.68%. ^{1}H NMR and mass-spectroscopic data are summarized in Table 1.

PHARMACOLOGICAL ACTIVITY

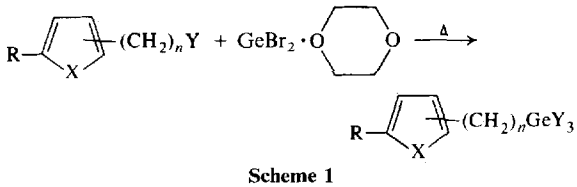
Neurotropic activity was studied on BALB/c mice of both sexes weighing 18–24 g and on white randomly-bred rats weighing 170–190 g in the spring season. Ambient temperature in the laboratory and in the animal colony during experiments was maintained at 21.5±1°C. The test-substances were administered intraperitoneally, 30 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.

Statistical evaluation of experimental findings was carried out and the values of mean lethal (LD_{50}) and mean effective (ED_{50}) doses were determined according to Ref. 15. Average values and standard deviations ($M \pm m$) were calculated in assessing the mean duration of the anaesthetic action of hexobarbital and amphetamine stereotypy, in evaluating the capacity to reverse Corazol-induced convulsions and hypoxia, reserpine-induced ptosis and hypothermia. Student's t-test was applied to evaluate the statistical significance of differences between the mean values. Variation was considered significant at the probability level $P \leqq 0.05$.

Action of the drugs on the central nervous system was assessed by observing the effects on locomotor coordination and muscle tone using the 'rotating rod' technique on a Ugo Basile apparatus (8 rpm for 2 min), the 'tube' test (a glass tube measuring 30 cm × 2 cm for 30 s) and the 'traction' test (on a metal wire 2 mm in diameter for 5 s). Temperature variation was measured intrarectally with the aid of an electrothermometer; a drop in rectal temperature by 3°C and more was considered a positive effect. The 'hot plate' test was applied to assess analgesic properties. Anticonvulsant activity was measured in the maximum electric shock test with alternating current of 50 mA and 50 Hz s^{-1} frequency (stimulation duration, 0.2 s) and by reversing Corazol-induced convulsions caused by intravenous injection of a 1% Corazol solution given at the 0.01 cm^3 s^{-1} rate. The drugs were also tested for their effects on animal survival under hypoxia conditions (single animals were placed in air-tight chambers of 220 cm^3 capacity without carbon dioxide absorption), for the duration of amphetamine stereotypy (10 mg kg^{-1}, s.c.), on reserpine-induced hypothermia and ptosis (2.5 mg kg^{-1}, i.p. for 2.5 h). In the last three cases the test substances were injected intraperitoneally one, two and three hours prior to the assays. Effects on the duration of ethanol anaesthesia (5 g kg^{-1}, i.p.) were assessed.

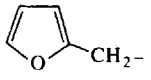
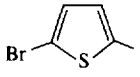
RESULTS AND DISCUSSION

We have established that insertion of germanium dibromide ($GeBr_2$) into the carbon–halogen bond[16] of halo-furans and -thiophenes provides a convenient route to trihalofuryl- and trihalothienyl-germanes (**I–VI**), enabling one to



Scheme 1

Table 2 Acute toxicity of germatranes $R'Ge(OCH_2CH_2)_3N$ and their effects on locomotor coordination and muscle tone in BALB/c mice (18–24 g)

Compound	R'	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1})				
			Test				
			Rotating rod	Tube	Traction	Analgesia	Hypothermia
VII		2050 (1460–2880)	41 (37–55)	41 (37–55)	35 (25–46)	71 (50–93)	45 (26–64)
VIII		1630 (1090–2270)	71 (43–102)	82 (45–125)	82 (57–111)	100	51 (29–79)
IX		2960 (930–6122)	21 (15–29)	22 (14–28)	18 (14–29)	100	22 (12–33)
X[a]		16.5 (11–25)	1.0 (0.6–1.8)	1.0 (0.6–1.8)	—	17 (9–31)	2.7 (1.9–3.8)
XI		89 (56–129)	1.2 (0.7–1.9)	2.2 (1.4–2.8)	1.5 (0.4–2.9)	50	1.2 (0.3–2.4)
XII		21 (15–29)	20 (12–31)	16 (11–23)	20 (15–29)	>10	18 (14–23)

[a]Ref. 6.

Table 3 Neurotropic activity of furyl and thienylgermatranes in male BALB/c mice (body weight 18–24 g) and randomly bred female white rats (body weight 170–200 g) ($n=6$, $T=22 \pm 1°C$)

Compound	% of control					
	Hypoxia	Hexobarbital anaesthesia	Ethanol anaesthesia	Amphetamine stereotypy	Corazol-induced spasms	
					Clonic	Tonic
VII	184.8[a]	191.8[a]	72.9	90.4	105.4	81.7
VIII	150.3[a]	171.4[a]	61.5[a]	101.5	120.8	120.2
IX	169.1[a]	236.6[a]	79.6	94.6	107.1	122.2
XI	141.3[a]	164.3[a]	121.4	101.6	122.5	150.4[a]
XII	111.3	158.7[a]	82.8	78.6	125.8	102.1

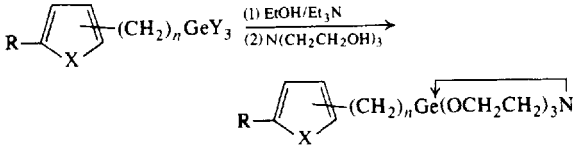
[a]Statistically valid difference with respect to control.

introduce a germyl substituent both in position 2 and position 3 of these heterocycles (Scheme 1).

I R = H; X = O; 2-furyl; Y = Br; $n = 0$
II R = H; X = O; 3-furyl; Y = Br; $n = 0$
III R = H; X = O; 2-furyl; $Y_3 = Br_2Cl$; $n = 1$
IV R = H; X = S; 3-thienyl; Y = Br; $n = 0$
V R = H; X = S; 2-thienyl; Y = Br; $n = 0$
VI R = Br; X = S; 2-thienyl; Y = Br; $n = 0$.

In the case of 2,5-dibromothiophene, $GeBr_2$ can only be inserted into one of the carbon–bromine bonds at an equimolar ratio of reagents.

The presence of a germanium–halogen bond in furyl- and thienyl-germanes offers new synthetic pathways to other classes of organogermanium compounds in the furan and thiophene series. For instance, we effected ethanolysis of compounds **I–VI** with subsequent transesterification by triethanolamine to obtain furyl- and thienyl-germatranes, **VII–XII** (Scheme 2).



Scheme 2

VII R = H; X = O; 2-furyl; $n = 0$
VIII R = H; X = O; 3-furyl; $n = 0$
IX R = H; X = O; 2-furyl; $n = 1$
X R = H; X = S; 2-thienyl; $n = 0$
XI R = H; X = S; 3-thienyl; $n = 0$
XII R = Br; X = S; 2-thienyl; $n = 0$.

^{1}H NMR and mass-spectroscopic data obtained for the germatranes are summarized in Table 1.

Experimental evaluation of acute toxicity and neurotropic properties is depicted in Tables 2 and 3.

All the furylgermatranes in the study exhibit low toxicity, their LD_{50} ranging within 1630–2050 mg kg^{-1}. The toxicity is further decreased (2960 mg kg^{-1}) if the germatranyl group is removed from the furan ring by one methylene group (**IX**). The thiophene derivatives are much more toxic. For example, 2-thienylgermatrane (**X**) is 124 times more toxic than 2-furylgermatrane (**VII**), while the corresponding 3-derivative (**XI**) exceeds the toxicity of **VIII** 18.3-fold. All the germatranes examined here appeared considerably less toxic than the appropriate silatranes (Table 4). Interestingly, the highest toxicity in the thiophene series was displayed by the 2-derivatives, whereas in the furan series they were less toxic than their 3-substituted counterparts.

The highest neurotropic activity among the furylgermatranes was noted for 2-furfuryl-germatrane (**IX**) whose mean effective doses found in the 'rotating rod', 'tube' and 'pull-up' (traction) tests were 21, 22 and 18 mg kg^{-1}, respectively. These tests indicate its high or potent pharmacological action. 2-Furyl-germatrane (**VII**) shows a neurotropic activity half that of 2-furfurylgermatrane, but exhibits analgesic properties (Table 2).

All furylgermatranes applied in doses up to 50 mg kg^{-1} prolong hexobarbital-induced anaesthesia by 70–136%, protect against hypoxia, bring about hypothermia and somewhat shorten the duration of ethanol anaesthesia. At the same time, the pharmacological manifestations of amphetamine, reserpine and Corazol are not affected by these compounds.

Thienylgermatranes exhibit a much higher neurotropic activity than the corresponding furyl-germatranes. The mean effective doses in our assays were 1–2.2 mg kg^{-1} for **X** and **XI**. The 2- and 3-derivatives were almost equipotent, whilst the 5-bromo-2-thienylgermatrane (**XII**) was markedly less active. 3-Thienylgermatrane in the 10 mg kg^{-1} dose was found to prolong somewhat hexobarbital and ethanol anaesthesia, and it also protected against hypoxia and Corazol toxicity, whereas 2-thienylgermatrane possessed analgesic properties.

Table 4 Acute toxicity of atranes $R'M(OCH_2CH_2)_3N$ following intraperitoneal administration to white mice

R'	LD_{50} (mg kg^{-1})	
	M = Si[a]	M = Ge
	125	2050
	14.5	1630
	0.3	16.5
	1.8	89

[a]Ref. 6.

Consequently, it can be concluded that the furyl- and thienyl-germatranes in this study are endowed with neurotropic activity of the depressant type, the scope of the therapeutic effects showing dependence on the heterocycle type and location of the germatranyl moiety.

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