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# SYNTHESIS AND NEUROTROPIC ACTIVITY OF GERMATRANYLMETHYLAMIDES AND -IMIDES

É. Lukevits, S. K. Germane, M. A. Trushule, V. F. Mironov, T. K. Gar, O. A. Dombrova, and N. A. Viktorov

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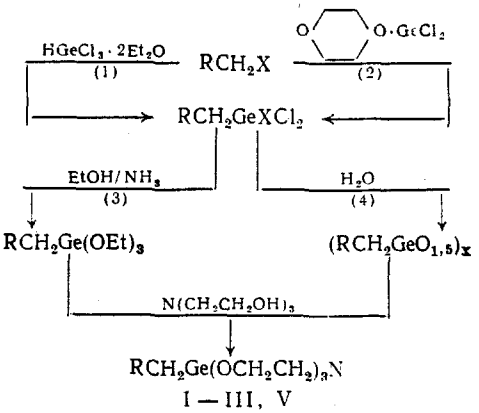
Continuing investigations into the neurotropic properties of organogermanium compounds [4-6], we have synthesized the sila- and germatranyl-methylamides (I-V), 1,5-dimethyl-3-(1-germatranyl)methyl-5-(cyclohexen-1-yl)-barbituric acid (VI), and 1(bromomethyl)germatrane (VII), and examined their effects on the central nervous system.

In order to obtain the germatranylmethylamides (and imides) of carboxylic (and dicarboxylic) acids, the following route was adopted. The starting halomethylamides (or imides) were converted by condensation with trichlorogermane etherate (reaction (1)) or by inserting dichlorogermane at the carbon-halogen bond (reaction (2)) into the trihalogermylmethylamides (or imides). The latter were subjected to alcoholysis (reaction (3)) or hydrolysis (reaction (4)) to give the corresponding triethoxygermyl compounds and germsesquioxanes, which on treatment with triethanolamine readily afforded the germatranes (I-III) and (V).




I — III, V

R = $C_6H_5CONH$ (I), *n*-$ClC_6H_4CONH$ (II), N-phthalimido (III), N-succinimido (V);
X = Cl, Br

To obtain N-[(1-germatranyl)methyl]benzamide (I), N-[(1-germatranyl)methyl]phthalimide (III), and N-[(1-germatranyl)methyl]succinimide (V), a combination of reactions (1) and (3) was used [3], and in the preparation of N-[(1-germatranyl)methyl]-p-chlorobenzamide (II), reactions (2) and (4).

N-[(1-siltranyl)methyl]phthalimide (IV) was obtained by heating potassium phthalimide with chloromethyltriethoxysilane in dimethylformamide, and transetherification with triethanolamine.

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Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. State Research Institute of the Chemistry and Technology of Heteroorganic Compounds, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 2, pp. 163-167, February, 1988. Original article submitted October 8, 1986.

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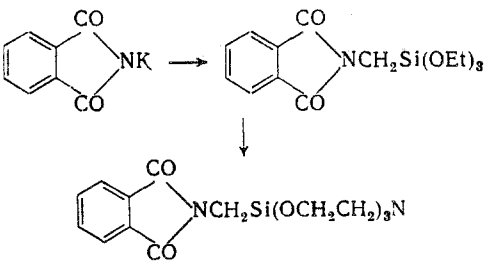
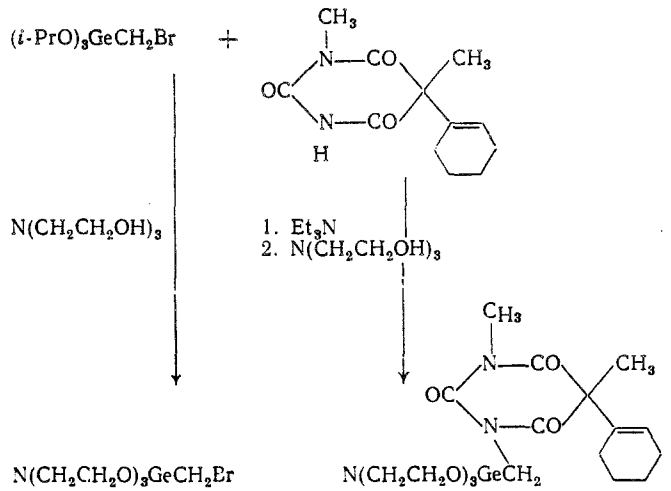


IV

1,5-Dimethyl-3-(1-germatranyl)methyl-5-(cyclohexen-1-yl)barbituric acid (VI) was synthesized by heating hexobarbital with bromomethyltriisopropoxygermane in the presence of triethylamine, followed by transetherification with triethanolamine.



VII VI

1-(Bromomethyl)germatrane (VII) was obtained as described in [1, 2].

The results of examination of the neurotropic activity of the germatranylmethylamides and imides are given in Table 1. All the test compounds were of low toxicity ($LD_{50}$ > 1000 mg/kg), except for (VII) ($LD_{50}$ 355 mg/kg).

The figures for the effects of the test compounds on motor coordination, muscle tone, and body temperature in the animals may be divided into two groups. In compounds of the

TABLE 1. Neurotropic Activity of Germatransylmethylamides and -imides

| Compound | $LD_{50}$, mg/kg | $ED_{50}$, mg/kg | | | | As % of control (100%) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | rotating rod test | tube test | pull-up to cross bar test | hypothermia test | hypoxic hypoxia | hexobarbital narcosis | amphetamine stereotypy | corazol convulsions tonic phase |
| I | 1290 (840—1790) | 650 (438—886) | 950 (502—1516) | >1000 | 755 (389—1215) | 130,7* | 72,4* | 110,3 | 85,6 |
| II | 2050 (1460—2880) | 141 (43—258) | 89 (63—120) | 95 (50—152) | 108 (40—198) | 106,9 | 70,3* | 140,9* | 118,9 |
| III | 4100 (2680—5520) | >1000 | 1030 (582—1573) | >1000 | 815 (449—1252) | 114,1 | 59,6* | 85,7 | 99,4 |
| IV | 4470 (3130—5960) | 103 (58—157) | 112 (65—164) | 103 (58—157) | 103 (58—157) | 129,9 | 81,0 | 105,2 | 90,7 |
| V | >2500 | 28 (16—42) | 21 (15—29) | 22 (14—29) | 26 (17—36) | 136,0* | 86,4 | 59,6* | 85,6 |
| VI | >10000 | 564 (342—814) | 708 (430—1019) | 564 (387—743) | 515 (362—692) | 163,2* | 65,9* | 62,5* | 90,3 |
| VII | 355 (249—461) | 37 (11—68) | 36 (20—51) | 36 (20—51) | 30 (10—61) | 142,4* | 85,5 | 172,1* | 96,1 |

Note. Range of variation given in brackets. An asterisk denotes statistically different from the controls, P < 0.05.

first group the depressant activity is more pronounced, i.e., the mean effective doses ($ED_{50}$) in the rotating rod, tube, pull-up to the crossbar, and hypothermia tests are between 20 and 100 mg/kg (II, IV, V, VII), whereas in compounds of the second group the depressant activity is slight, the $ED_{50}$ values for the above tests being 500-1000 mg/kg (I, III, VI).

It was also found that none of the test compounds had analgesic activity, or diminished the convulsant effects of electric shock or corazole.

All these germatranylmethylamides (and imides) shorted to a greater or lesser extent the duration of hexobarbital marcosis. Statistically significant shortening of hexobarbital narcosis was observed with compounds (I-III) and (VI). Antihypoxic activity was greatest in (VI). On treatment with (VI), the lifespan of animals under hypoxic conditions was increased by 63.2%. Antihypoxic activity was also shown in decreasing order by (VII) (42.4%), (V) (36%), and (I) (30.7%).

The test compounds had varying effects on amphetamine stereotypy. For example, (II) and (VII) extended the stereotypy by 40.9 and 72.1%, respectively, whereas (V) and (VI) shortened it by 40.4 and 37.5%, respectively. These compounds had a slight antagonistic effect (by 15-20%) on the central effects of reserpine (they decreased reserpine ptosis).

Comparison of the acute toxicity of (III) with its sila-analog (IV) shows that the compounds differ little in this respect, but depressant activity is shown by (IV) at doses one tenth those of the germanium compound (III). N-[(1-germatranyl)methyl]phthalimide further differs from its silicon analog in that it shortens by 40% the duration of the narcotic effects of hexobarbitone. Consideration of these results shows that in the compound containing silicon, depressant activity is predominant, whereas in the germanium analog stimulant activity predominates.

## EXPERIMENTAL (CHEMICAL)

N-[(1-Germatranyl)methyl]benzamide (I). To a suspension of 9.5 g of N-[(trichlorogermyl)-methyl]benzamide in a mixture of dry ether and dry benzene was added 5.3 g of absolute ethanol, and ammonia bubbled through for 1 h with vigorous stirring and cooling to 20-30°C. Excess ammonia was removed by heating to 80°C for 0.5 h, the mixture cooled, and the precipitated ammonium chloride filtered off. The filtrate was evaporated, and the viscous residue (7.9 g) mixed with 4.2 g of triethanolamine and 40 ml of benzene. After 1.5 h, the colorless crystalline solid was filtered off, washed with ether, and dried in vacuo to give 6.1 g of (I), yield 75%, mp 189-191°C. Found, %: C 48.00; H 5.70; Ge 20.10. $C_{14}H_{20}O_4N_2Ge$. Calculated, %: C 47.54; H 5.71; Ge 20.56. PMR spectrum, δ, ppm: 3.81 t ($OCH_2$), 2.78 t ($NCH_2$), 3.22 s ($CH_2Ge$), 7.35-7.82 M ($C_6H_4$).

N-[(Trichlorogermyl)methyl]benzamide was obtained by adding 13.5 g of trichlorogermane etherate with stirring to a suspension of 7 g of N-chloromethylbenzamide in dry ether. The amide dissolved, the temperature rising to 35°C, and a colorless crystalline solid then separated. The mixture was stirred at 20°C for 2.5 h, and the solid was filtered off, washed with ether, and dried in vacuo to give 12.5 g of product (85%), mp 183-185°C.

N-[(1-Germatranyl)methyl]-p-chlorobenzamide (II). A mixture of 40.8 g of N-chloromethyl-p-chlorobenzamide and 46 g of dichlorogermane dioxanate in 100 ml of dioxane was heated for 1 h at 80°C with stirring. The solvent was removed under reduced pressure from the resulting emulsion, and the polymeric residue treated with an excess of aqueous ammonia to give 32 g of a colorless powder, which was placed in a flask fitted with a Dean and Stark apparatus. Benzene (120 ml) and triethanolamine (17.5 g) were added, and the mixture boiled for 2.5 h with removal of water. On cooling, 26.2 g of colorless crystalline (II) was obtained, yield 58%, mp 205-210°C. Found, %: C 42.91; H 5.07; Ge 18.67. $C_{14}H_{19}O_4N_2ClGe$. Calculated, %: C 43.20; H 5.18; Ge 18.66. PMR spectrum, δ, ppm): 3.80 t ($OCH_2$), 2.86 t ($NCH_2$), 3.21 s ($CH_2Ge$), 7.45-7.75 m ($C_6H_4$).

N-[(1-Silatranyl)methyl]phthalimide (IV). A mixture of 18.6 g of potassium phthalimide, 21.3 g of chloromethyltriethoxysilane, and 100 g of dry DMF was heated for 8 h at 150°C, cooled, and distilled under reduced pressure. To the fraction, bp 173-210°C/1 mm Hg, (15.2 g) was added 6.7 g of triethanolamine and 30 ml of benzene, and the mixture boiled with simultaneous removal of the benzene–ethanol azeotrope. On cooling, there was obtained 14.3 g (42%) of colorless crystalline (IV), mp 241-243°C (acetonitrile). Found, %: 51.80, H 6.10; Si 8.00. $C_{15}H_{18}N_2O_5Si$. Calculated, %: C 53.00; H 5.67; Si 8.38. PMR spectrum, δ, ppm ($CDCl_3$): 2.82 t ($CH_2N$), 3.06 s ($NCH_2Si$), 3.77 t ($OCH_2$), 7.27-7.82 m ($C_6H_4$).

This compound was also obtained by heating an equimolar mixture of chloromethylsilatrane and potassium phthalimide in DMF at 150-158°C for 12 h. Yield 19%, mp 240-243°C.

N-[(1-Germatranyl)methyl]succinimide (V). N-bromomethylsuccinimide (15.4 g) and trichlorogermane etherate (22.9 g) were heated in o-xylene at 90°C for 14 h. There was obtained 15 g of a mixture of halogermanes as a viscous, undistillable liquid, which was converted into the required germantrane (V) as in the case of (I). Yield 54%, mp 213-215°C. PMR spectrum, δ, ppm: 3.76 t ($OCH_2$), 2.82 t ($NCH_2$), 3.34 s ($CH_2Ge$), 2.66 s $(CH_2)_2$.

1,5-Dimethyl-3-(1-germatransyl)methyl-5-(cyclohexen-1-yl)barbituric Acid (VI). A mixture was stirred, and the solid was filtered off and washed with 20 ml of ether. The filtrate was amine was boiled for 6 h at 110-130°C. After cooling, 40 ml of dry ether was added, the mixture stirred, and the solid filtered off and washed with 20 ml of ether. The filtrate was evaporated to 75°C/2 mm Hg (vapor temp.), to give 12 g of a viscous, dark-colored oil, which was boiled with 3.6 g of triethanolamine in 50 ml of benzene, 14 g of the isopropanol–benzene azeotrope being distilled off. Following evaporation of the benzene, the solid was filtered off, washed with benzene and ether, and dried in vacuo to give 7.9 g (74.7%) of (VI), mp 209-210°C. Found, %: C 47.54; H 6.11; Ge 15.88. $C_{19}H_{29}N_3O_6Ge$. Calculated, %: C 48.76; H 6.25; Ge 15.50. PMR spectrum, δ, ppm: 3.13 s ($NCH_3$), 1.43 s ($CCH_3$), 3.42 d ($CH_2Ge$), 5.56 m (cyclohexene CH), 1.3-2.2 m (–$CH_2$–), 3.52 t (atrane $OCH_2$), 2.78 t ($NCH_2$).

The (III) and (VII) used had mp: 218-210 and 195-200°C respectively.

## EXPERIMENTAL (BIOLOGICAL)

Neurotropic activity was examined in mice of strain BALB/c and in female mongrel white rats, described in [6].

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