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SILYL MODIFICATION OF BIOLOGICALLY ACTIVE COMPOUNDS. 9*. SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL 1,3-DISILA-BENZO[5,6]CYCLOHEXENE DERIVATIVES

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We have synthesized a series of 1,3-disilabenzo[5,6]cyclohexene derivatives starting from (o-bromomethylphenyl)dimethylchlorosilane. Based on NMR data, we have concluded that there is a transannular N → Si interaction in the 3',3'-5-trimethyl-2,8-dioxa-5-aza-1-silacyclooctane-1-spiro-1'-(1',3'-disilabenzo-[4',5']cyclohexene) obtained. We have studied the psychotropic activity of this compound and its iodomethylate and also 3-(3-chloropropyl)-1,1,3-trimethyl-1,3-disilabenzo[5,6]cyclohexene, and we have shown that they have a sedative effect.

Keywords: 1,3-disilabenzo[5,6]cyclohexene, organosilicon compounds, spirocycle, chlorosilane, psychotropic activity, transannular interaction, cyclization, ^{29}Si NMR.

Compounds containing a tetrahydroisoquinoline moiety have a broad spectrum of biological action [2-7]. Inserting a silicon atom into the ring in place of a carbon atom is a well-established method for modifying biologically active substances that promotes an increase in their lipophilicity, which is needed to better penetrate the lipid layer of the cell membrane and also to cross the blood–brain barrier in the case of compounds acting *via* the central nervous system [8]. Earlier we obtained a series of silicon analogs of tetrahydroisoquinoline derivatives with one silicon atom in place of the $C_{(4)}$ atom of the heterocycle, and we showed that they have a sedative effect [6, 7, 9, 10]. In continuing these studies, it seems to certainly be of interest to introduce a second silicon atoms into the molecule of such analogs in place of the nitrogen atom, and to study the biological activity of the products of such modification: 1,3-disilabenzo[5,6]cyclohexene derivatives.

Among compounds of this series, only 1,1,3,3-tetramethyl-1,3-disilabenzo[5,6]cyclohexene and its tetrachloro-substituted analog are known. The first compound was synthesized by homolytic cyclization of silyl radicals formed from 2,4,4-trimethyl-5-phenyl-2,4-disilapentane upon heating in the presence of di-*tert*-butyl peroxide [11]. The second compound was obtained by treatment of *o*-xylene with dichlorosilylene, appearing upon decomposition of polychlorosilanes $Cl_3Si(SiCl_2)nSiCl_3$ in the gas phase [12].

* For Communication 8, see [1].

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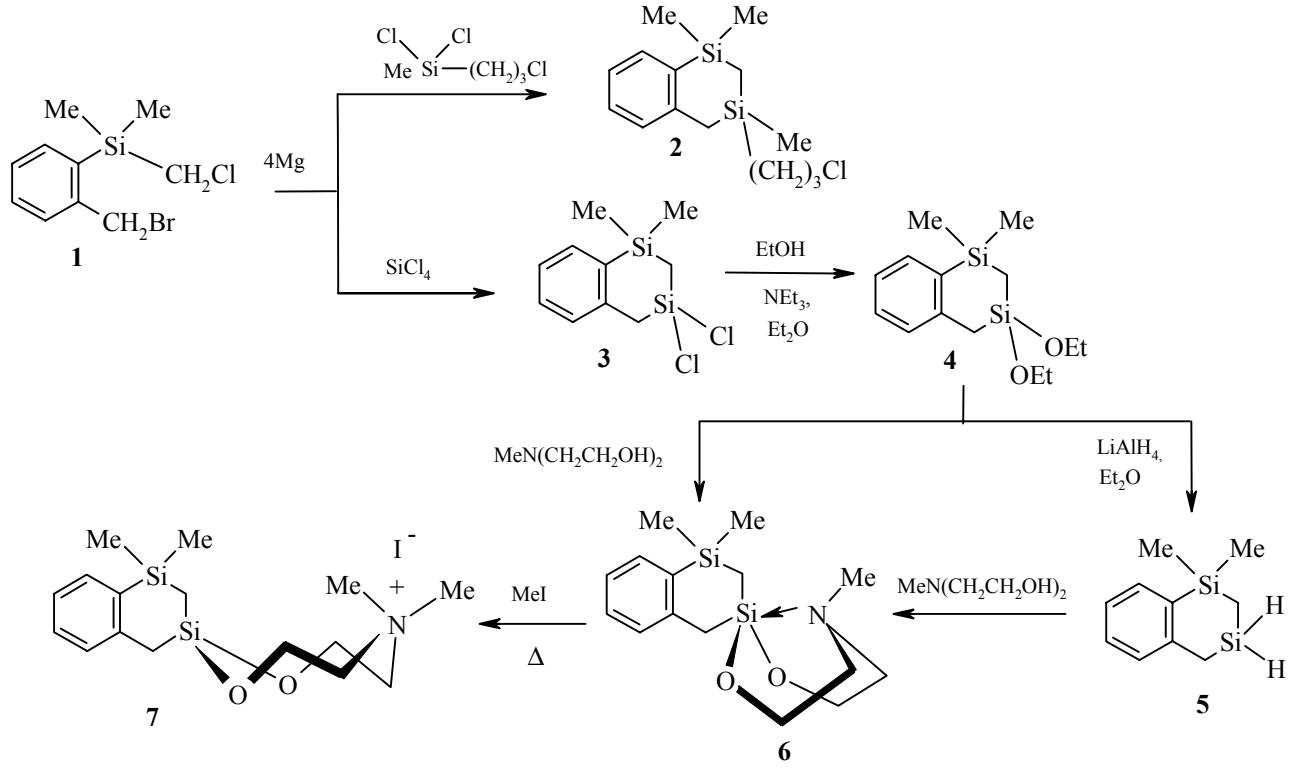
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In this paper, we propose a novel approach to synthesis of various 1,3-disilabenzocyclohexene derivatives starting from (*o*-bromomethylphenyl)dimethylchloromethylsilane (**1**) [13]. The possibilities of the synthesis are demonstrated in the examples of synthesis of compounds **2-7** (see Scheme).

Disilabenzocyclohexenes **2** and **3** were synthesized in 70% and 51% yields by reaction of the dimagnesium derivative obtained from silane **1** with dichloro(3-chloropropyl)methylsilane or tetrachlorosilane respectively. After the Grignard reagent began to form in the reaction mixture, silane **1** and the corresponding chlorosilane were added simultaneously to the reaction mixture and thus the dimagnesium derivative was reacted *in situ*, which promoted formation of the cyclization product. Such conditions were used in [14] for synthesis of a series of bicyclic structures containing one silicon atom.

Dichlorodisilabenzocyclohexene **3** was then converted by alcoholysis to the corresponding diethoxy derivative **4** (40% yield), which then was completely reduced by lithium aluminum hydride in ether to 1,1-dimethyl-1,3-disilabenzo[5,6]cyclohexene (**5**).

Synthesis of spirocyclic derivatives of N-methyldiethanolamine **6** and **7** was of special interest for detecting the proposed coordination interaction between the nitrogen and silicon atoms (noted previously for a number of silicon-containing derivatives of N-methyldiethanolamine [15]), and also for bioassays of these compounds, since we know that the ethanolamine moiety is an important structural element for a number of biologically active substances [7, 16-18].

Trimethyl-substituted 2,8-dioxa-5-azasilacyclooctane-1-spiro-1'-(1',3'-disilabenzo[4',5']cyclohexene) **6** was obtained via two routes: A – by dehydrocondensation of compound **5** with N-methyldiethanolamine in ether without a catalyst (58% yield; B (a more convenient method) – by transesterification of substituted diethoxysilane **4** with N-methyldiethanolamine in hexane in the presence of sodium hydroxide as a catalyst (60% yield).

Iodomethylate **7** was obtained by treatment of compound **6** with methyl iodide.

The structure of the synthesized compounds was confirmed by ^{1}H, ^{13}C, ^{29}Si NMR spectra and mass spectrometry.

In the ^{29}Si NMR spectrum of compound **6**, there are signals at -4.52 ppm ($^{29}Si_{(1)}$ atom) and at -18.48 ppm ($29Si_{(3)}$ atom included in the spirocycle). In [15], NMR was used to establish the existence of a nitrogen – silicon transannular interaction in 1,3-dioxa-6-aza-2-silacyclooctanes $R^1R^2Si(OCH_2CH_2)_2NR$, and the effect of substituents at the N and Si atoms on the strength of this interaction was demonstrated. One factor supporting the existence of the indicated interaction is the upfield shift (by 5.8-9.5 ppm) of the signal from the 29Si atom relative to the analogous signal for model diethoxysilanes. The compound that is structurally most similar to compound **6** among the studied azasilacyclooctanes is the diethanolamine derivative $Me_2Si(OCH_2CH_2)_2NMe$; the chemical shifts are δ = -10.1 ppm for its ^{29}Si atom and δ = -4.3 ppm for the ^{29}Si atom of the corresponding diethoxysilane. Thus the signal for the $^{29}Si_{(3)}$ atom of compound **6** is shifted upfield relative to the signals from the indicated compounds.

In the ^{29}Si NMR spectrum of iodomethylate **7**, there are two signals: -4.35 ppm ($^{29}Si_{(1)}$) and -0.66 ppm ($^{29}Si^{(3)}$). Thus the signal from the $^{29}Si_{(3)}$ atom of compound **7** is shifted downfield relative to the signal from $^{29}Si_{(3)}$ of the base **6**. A similar shift was observed earlier in the case of the iodomethylate $[Me_2Si(OCH_2CH_2)_2N^+Me_2]I^-$ (δSi = -1.4 ppm) relative to the starting amine (δSi = -10.1 ppm), and was explained by the effect of the positively charged N^+Me_2 group [15]. All the data given above support the hypothesis that an N $\rightarrow$ Si interaction exists in spirocyclic compound **6**. This is also indirectly supported by the fairly low yield (39%) of its iodomethylate **7** even upon heating.

We determined the acute toxicity and studied the psychotropic activity using a number of tests for the synthesized disilabenzocyclohexene derivatives **2, 6,** and **7**. The results obtained are presented in Table 1.

Spiro compound **6** is virtually nontoxic (LD_{50} is 5000 mg/kg), while the toxicity of both its iodomethylate **7** and also disilabenzocyclohexene **2** is an order of magnitude higher, and it can be classified as moderately toxic (LD_{50} is 355 mg/kg).

TABLE 1. Psychotropic Activity of Compounds **2, 6**, and **7**

Test number	Test	Compound*		
		2	**6**	**7**
1	LD_{50}, mg/kg	*355*	*5000*	*355*
2	Hypoxic hypoxia, %*[2]	159.8	*106.5*	*113.7*
3	Hypothermia, °C	+1.2 (30')	-1.2 (60')	-1.1 (60')
4	Phenamine-induced hyperactivity, %*[2]	76.3 (30') 59.7 (60')	71.8 (30') 108.3 (60')	81.3 (30') 59.0 (60')
5	Hexenal narcosis	140.0	152.3	91.3
6	Ethanol narcosis, %*[2]	81.1	106.5	188.9
7	Corazole-induced convulsions, % (clonic/tonic)*[2]	129.0/136.0	161.0/115.5	128.7/199.7
8*[3]	Passive avoidance conditioned reflex, sec	132.5 (84.9)	147.8 (76.8)	137.3 (76.8)
9*[3]	Retrograde amnesia, %	83.3 (63.3)	83.3 (33.3)	83.3 (33.3)
10	Porsolt's test, %	*101.8*	156	49.1

* Results are statistically significant ($p \leq 0.05$), except for the values marked in italics.
*[2] Control, %: 100.
*[3] Control data are given in parentheses.

The data in the table show that the studied compounds have a sedative effect. They all are phenamine antagonists, and also exhibit pronounced anticonvulsive activity and have an appreciable effect on memory processes (compound **6** is the most active in this regard, and it also has a rather strong antistress effect).

EXPERIMENTAL

The NMR spectra were taken for solutions in $CDCl_3$ on a Varian Mercury 200 (200 MHz), internal standard $(Me_3Si)_2O$. The mass spectra were recorded on an HP6890 GC-MS.

GLC analysis was conducted on a Chrom-42 chromatograph with flame-ionization detector and glass column (1.2 m × 3 mm) with 5% OV-17 on Chromosorb W-AW (60-80 mesh).

(*o*-Bromomethylphenyl)dimethylchloromethylsilane (1) was synthesized by the procedure in [13].

3-(3-Chloropropyl)-1,1,3-trimethyl-1,3-disilabenzo[5,6]cyclohexene (2). A solution of (18 g, 0.05 mol) silane **1** in ether (50 ml) was slowly added to Mg (4.8 g, 0.2 mol) in ether (30 ml). After the Grignard reagent began to form, dichloro(3-chloropropyl)methylsilane (9.6 g, 0.05 mol) in ether (5 ml) was added to the boiling mixture along with a solution of silane **1**, over an ~1 h period; after this, the reaction mixture was boiled for 38 h. The yellow color of the mixture became more intense and a significant amount of the inorganic salt was formed. Then a 50% NH_4Cl solution (~200 ml) was added until the precipitate was completely dissolved. The ether layer was removed, the aqueous layer was extracted with ether (2 × 100 ml). The combined extract was dried with anhydrous Na_2SO_4, filtered, and evaporated down. A viscous residue was obtained, from which by distillation we isolated 18.6 g (70%) of chromatographically pure product **2**; bp 136-138°C (2 mm Hg). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.06-7.56 (4H, m, H_{arom}); 3.47 (2H, t, *J* = 5.0, CH_2Cl); 2.13 (2H, s, $SiCH_2$); 1.76 (2H, m, $C\underline{H}_2CH_2Cl$); 0.62 (2H, m, $C\underline{H}_2(CH_2)_2Cl$); 0.36 (6H, s, $SiMe_2$), 0.04 (3H, s, SiMe), -0.13 (2H, s, $SiCH_2Si$). Mass spectrum, *m*/*z*: 282 [M^+], 267 [$M–CH_3^+$], 205 [$M–CH_2CH_2CH_2Cl^+$]. Found, %: C 59.35; H 8.46. $C_{14}H_{23}ClSi_2$. Calculated, %: C 59.43; H 8.19.

3,3-Dichloro-1,1-dimethyl-1,3-disilabenzo[5,6]cyclohexene (3) was obtained similarly to compound **2**, from silane **1** (27.7 g, 0.1 mol), $SiCl_4$ (17.1 g, 0.1 mol), and Mg (9.7 g, 0.4 mol). Instead of being treated with NH_4Cl, the reaction mixture was filtered and the filtrate was evaporated. From the oily residue, by distillation we isolated 13.3 g (51%) of chromatographically pure product **3**; bp 115-118°C (3.5 mm Hg). ^{1}H NMR spectrum, δ, ppm: 7.06-7.54 (4H, m, H_{arom}); 2.58 (2H, s, $SiCH_2$); 0.69 (2H, s, $SiCH_2Si$); 0.45 (6H, s, $SiMe_2$). Found, %: C 45.57; H 5.37. $C_{10}H_{14}Cl_2Si_2$. Calculated, %: C 45.98; H 5.36.

3,3-Diethoxy-1,1-dimethyl-1,3-disilabenzo[5,6]cyclohexene (4). A solution of compound **3** (6.5 g, 0.025 mol) in ether (13 ml) was carefully added to a mixture of ethanol (2.9 ml, 0.05 mol), triethylamine (7 ml, 0.05 mol), and ether (40 ml). The reaction mixture was stirred for 2 h and then filtered, and the filtrate was evaporated down. From the residue, by distillation we isolated 2.8 g (40%) of chromatographically pure product **4**; bp 140-143°C (7 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.04-7.63 (4H, m, H_{arom}); 3.78 (4H, q, *J* = 5.6, $2OCH_2$); 2.31 (2H, s, $SiCH_2$); 1.20 (6H, t, *J* = 5.6, $CH_2\underline{CH_3}$); 0.44 (6H, s, $SiMe_2$); 0.13 (2H, s, $SiCH_2Si$). Mass spectrum, *m*/*z*: 280 [M^+], 265 [$M–CH_3^+$], 221 [$M^+–CH_2CH_3$, $–CH_3$, $–CH_3$].

Compound **4** rapidly decomposes in air, and so it was immediately used to obtain products **5** and **6**.

1,1-Dimethyl-1,3-disilabenzo[5,6]cyclohexene (5). A solution of compound **4** (2.4 g, 8.57 mmol) in ether (20 ml) was added dropwise under an argon atmosphere to $LiAlH_4$ (0.76 g, 20 mmol) in ether (20 ml). The reaction mass was stirred at room temperature for 18 h (the completeness of the conversion of silane **4** to product **5** was monitored by GLC) and filtered. The filtrate was evaporated down; from the residue, by distillation we isolated 0.76 g (47%) of product **5** as a colorless liquid; bp 79-80°C (4 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.03-7.60 (4H, m, H_{arom}); 4.00 (2H, m, SiH_2); 2.26 (2H, t, *J* = 2.4, $SiCH_2$); 0.38 (6H, s, $SiMe_2$); 0.11 (2H, t, *J* = 3.0, $SiCH_2Si$). Mass spectrum, *m*/*z*: 192 [M^+], 177 [$M–CH_3^+$].

Compound **5** rapidly decomposes in air, and so it was used immediately to obtain product **6** (see below).

3',3',5'-Trimethyl-2,8-dioxa-5-aza-1-silacyclooctane-1-spiro-1'-(1',3'-disilabenzo[4',5']cyclohexene) (6). A. A mixture of compound **4** (5.1 g, 18.2 mmol) and N-methyldiethanolamine (2.1 ml, 18.2 mmol) in hexane (2 ml) was boiled for 2 h in the presence of a catalytic amount of NaOH powder and then evaporated down. From the residue, by distillation we isolated 3.36 g (60%) of product **6** as a viscous oil; bp 180-183°C (2 mm Hg). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.00-7.53 (4H, m, H_{arom}); 3.71 (4H, t, *J* = 4.1, OCH_2); 2.64 (4H, t, *J* = 4.1, 2 NCH_2); 2.48 (3H, s, NCH_3); 2.21 (2H, s, $SiCH_2$); 0.37 (6H, s, $SiMe_2$); 0.07 (2H, s, $SiCH_2Si$). ^{13}C NMR spectrum, δ, ppm: 146.1, 136.8, 133.2, 129.6, 129.3, and 123.9 (C_6H_4), 61.9 (OCH_2), 57.6 (NCH_2), 43.4 (NCH_3), 25.5 ($SiCH_2$), -0.30 ($SiCH_3$), -2.4 ($SiCH_2Si$). ^{29}Si NMR spectrum, δ, ppm: -4.52 (3'-Si), -18.48 (1-Si). Mass spectrum, *m*/*z*: 307 [M^+], 292 [$M–CH_3^+$], 264 [$M–CH_2NCH_3^+$]. Found, %: C 58.50; H 8.31; N 4.52. $C_{15}H_{25}NO_2Si_2$. Calculated, %: C 58.58; H 8.19; N 4.55.

B. Compound **5** (0.69 g, 3.6 mmol) was added by syringe through a septum to N-methyldiethanolamine (0.43 g, 3.6 mmol) with stirring at room temperature under an argon atmosphere. The mixture was stirred for 4 h at 60°C. Obtained 0.97 g (58%) of product **6**, which according to the NMR spectrum was identical to the sample obtained by procedure A.

Iodomethylate of 3',3',5-Trimethyl-2,8-dioxa-5-aza-1-silacyclooctane-1-spiro-1'-(1',3'-disilabenzo-[4',5']cyclohexene) (7). A mixture of (0.15 g, 4.9 mmol) of compound **6** and methyl iodide (0.69 g, 4.9 mmol) was stirred for 1 h at 40°C. The precipitate formed was filtered out, recrystallized from a 3:1 (by volume) mixture of ethanol–ether, and we obtained 0.85 g (39%) of product **7**; mp 79-80°C. ^{1}H NMR spectrum, δ, ppm: 7.08-7.50 (4H, m, H_{arom}); 4.26 (4H, m, $2OCH_2$); 4.15 (4H, m, $N^+(CH_2)_2$); 3.72 and 3.71 (3H+3H, s+s, N^+Me_2); 2.27 (2H, s, $SiCH_2$); 0.37 (6H, s, $SiMe_2$); 0.14 (2H, s, $SiCH_2Si$). ^{13}C NMR spectrum, δ, ppm: 141.9, 136.2, 133.7, 130.1, 130.0, and 125.1 (C_6H_4), 66.2 (OCH_2), 58.3 (N^+CH_2), 53.2 (N^+CH_3), 21.6 ($Si–CH_2$), -0.35 ($SiCH_3$), -3.6 ($Si–CH_2–Si$). ^{29}Si NMR spectrum, δ, ppm: -0.66 (1-Si), -4.35 (3'-Si). Found, %: C 42.55; H 6.23, N 3.28. $C_{16}H_{28}INO_2Si_2$. Calculated, %: C 42.76; H 6.28; N 3.12.

Biological Activity of Compounds 2, 6, 7. The neurotropic activity of compounds **2, 6, 7** was studied in mice of the BALB/c line and nonpedigree male rats. An oil solution of the test substance was injected intraperitoneally 30 min before observations began (in a dose of 5 mg/kg for tests 2-10, Table 1). The test drugs were not injected into the control group of animals. The experiments were conducted according to the procedures given in [19].

The experimental data were treated statistically. We used the well known fast method in [20] to determine the average LD_{50} and ED_{50} values from 12-20 observations. The differences between the average values (M+m) were evaluated based on Student's test. The differences were considered significant for probability level $p \leq 0.05$.

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