NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS. 151.* SYNTHESIS, NMR SPECTRA, AND BIOLOGICAL ACTIVITY OF HETARYLAMINOALKYLSILOXANES AND THEIR HYDROCHLORIDES AND METHIODIDES

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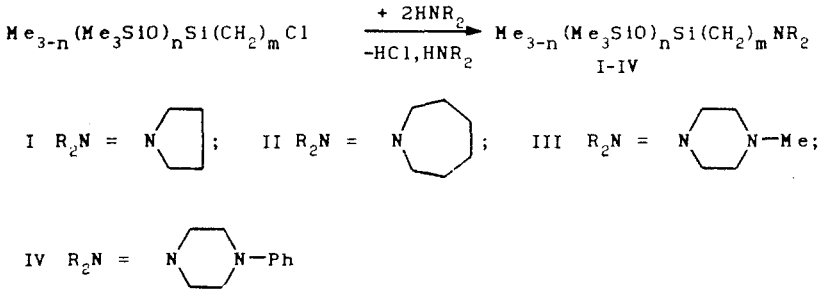
Hetarylaminoalkylsiloxanes and their hydrochlorides and methiodides were synthesized. Their neurotropic, antitumorigenic, and antimicrobial properties were studied. It was established that the character of the heteroring, the number of siloxy groups, and the length of the methylene chain between the nitrogen and silicon atoms in the molecule affect the biological activity. It is shown that the changes in the chemical shifts in the ^{13}C, ^{15}N, ^{17}O, and ^{29}Si NMR spectra of the synthesized compounds are determined chiefly by the presence of siloxy substituents, i.e., the effects in the Si—O—Si fragment prevail.

We have previously shown that hetarylaminoalkylsilanes $R_3Si(CH_2)_mNR_2$, which contain an alkyl group attached to the silicon atom, have neurotropic and bacteriostatic activity [2]. According to the NMR data [3, 4], an interaction between the nitrogen and silicon atoms through space is observed in these compounds. To determine the effect on the biological activity of replacement of the alkyl groups attached to the silicon atom by siloxy groups and to ascertain the contribution of competitive effects to the N→Si interaction we synthesized pyrrolidino-, perhydroazepino-, and N-methyl(phenyl)piperazinoalkylsiloxanes $Me_{3-n}(Me_3SiO)_nSi(CH_2)_mNR_2$, in which a $(p—d)_\pi$ interaction in the Si—O bond is assumed [5].

The hetarylaminoalkylsiloxanes were obtained (in 54-72% yields) by heating the chloromethyl(propyl)siloxane with a twofold excess of pyrrolidine, hexamethyleneimine, and N-methyl(phenyl)piperazine in toluene for 20-30 h:



* See [1] for communication 150.

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TABLE 1. ^{13}C, ^{15}N, ^{17}O, and ^{29}Si NMR Spectra of Siloxanes $Me_{3-n}(Me_3{*}Si{*}O)_nSi(CH_2)_mR$

Compound	n	m	δ ^{17}O, ppm	$\Delta\nu_{1/2}$, Hz*2	δ ^{29}Si, ppm		δ ^{15}N, ppm	δ $^{13}C_{Me}$, ppm		δ $^{13}C_{(CH_2)m}$, ppm			δ $^{13}C_R$, ppm		
					Si	Si*		Me	Me*	CH_2Si	$-CH_2-$	CH_2N	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$
Ib	2	1	52,6	140	−27,0	7,4	−337,0	0,31	2,23	—	47,72	—	58,25	24,45	—
Ic	2	3	53,2	220	−21,9	6,9	—	0,08	2,23	16,03	23,16	60,51	54,70	23,90	
Id	3	1	52,5	250	−71,5	7,7	−334,4	—	2,16	—	44,38	—	57,35	24,50	—
Ie	3	3	53,1	280	−65,9	7,0	—	—	2,10	12,88	23,41	60,46	54,67	24,00	—
IIb	2	1	53,0	190	−26,7	7,4	−345,0	0,24	2,16	—	51,26	—	59,94	28,64	27,44
IIc	2	3	—	—	−21,6	6,7	—	0,12	2,23	15,74	21,49	62,05	56,01	28,52	27,60
IId	3	1	52,7	230	−71,8	7,7	−345,6	—	2,06	—	48,47	—	59,34	28,81	27,44
IIe	3	3	53,4	330	−65,6	7,0	—	—	1,90	12,30	21,72	61,76	55,84	28,61	27,25
IIIb	2	1	53,0	230	−27,1	7,3	−345,5; −345,6	0,41	2,29	—	50,97	—	57,40	56,10	46,55
IIIc	2	3	52,8	250	−22,1	6,6	—	0,15	2,29	15,81	20,88	62,41	53,76	55,84	46,55
IIId	3	1	53,0	300	−72,0	7,8	−345,0; −345,8	—	2,19	—	48,0	—	57,19	56,02	46,56
IIIe	3	3	51,8	370	−65,9	7,0	—	—	2,16	12,62	21,14	62,28	53,76	55,84	46,61
IVb	2*3	1	53,2	310	−26,7	7,9	−317,2; −344,9	0,54	2,29	—	51,07	—	49,80	57,40	—
IVd	3*4	1	54,0	210	−71,9	8,2	−317,1; −345,6	—	2,20	—	48,80	—	49,77	57,20	

*Ib-e R = pyrrolidino, IIb-e R = perhydroazepino, IIIb-e R = N-methylpiperazino, IVb, d R = N-phenylpiperazino.

**^{17}O NMR spectrum.

***δ $^{13}C_{Ph}$ = 152.11 [$C_{(i)}$], 116.35 [$C_{(o)}$], 129.55 [$C_{(m)}$], 119.88 [$C_{(p)}$].

****δ $^{13}C_{Ph}$ = 152.19 [$C_{(i)}$], 116.45 [$C_{(o)}$], 129.61 [$C_{(m)}$], 119.92 [$C_{(p)}$].

TABLE 2. ^{13}C, ^{15}N, ^{17}O, and ^{29}Si NMR Spectra of Siloxane Hydrochlorides $Me_{3-n}(Me{*}Si{*}O)_nSiCH_2\overset{+}{N}HR_2Cl^-$

Compound	NR_2	n	δ ^{17}O, ppm	$\Delta\nu_{1/2}$, Hz*	δ ^{29}Si, ppm		δ ^{15}N, ppm	δ $^{13}C_{Me}$, ppm		δ $^{13}C_{CH_2}$, ppm	δ $^{13}C_R$, ppm		
					Si	Si*		Me	Me*		$C_{(1)}$	$C_{(2)}$	$C_{(3)}$
Vb	Pyrrolidino	2	57,0	240	−32,6	11,2	—	1,38	2,26	45,64	56,65	24,13	—
VIb	Perhydroazepino	2	57,3	240	−32,1	11,5	—	1,67	2,26	48,99	57,69	24,52	27,15
VIIb	N-Methylpiperazino	2	57,0	400	−30,5	10,2	—	0,93	2,23	49,02	53,24	53,83	44,60
VIId	N-Methylpiperazino	3	56,9	300	−81,9	12,9	−338,2; −339,4	—	2,29	47,78	51,62	50,42	43,46
VIIIb	N-Phenylpiperazino	2**	59,2	520	−32,5	11,8	—	1,77	2,29	47,72	47,72	54,48	—
VIIId	N-Phenylpiperazino	3***	57,5	340	−79,9	12,3	−334,9; −335,0	—	2,19	44,63	47,78	53,18	—

*^{17}O NMR spectrum.

**δ $^{13}C_{Ph}$ = 150.36 [$C_{(i)}$], 117.97 [$C_{(o)}$], 130.06 [$C_{(m)}$], 122.20 [$C_{(p)}$].

***δ $^{13}C_{Ph}$ = 150.24 [$C_{(i)}$], 117.91 [$C_{(o)}$], 130.12 [$C_{(m)}$], 122.20 [$C_{(p)}$].

TABLE 3. ^{13}C, ^{15}N, ^{17}O, and ^{29}Si NMR Spectra of Aminoalkylsiloxane Methiodides $Me_{3-n}(Me_3{*}Si{*}O)_nSi(CH_2)_m\overset{+}{N}MeR_2I^-$

Compound	R_2N	n	m	$\delta\,^{17}O$, ppm	$\Delta\nu_{1/2}$ Hz*	$\delta\,^{29}Si$, ppm		$\delta\,^{15}N$, ppm	$\delta\,^{13}C_{Me}$, ppm		$\delta\,^{13}C_{(CH_2)m}$, ppm			$\delta\,^{13}C_R$, ppm			$\delta\,^{13}C_{\overset{+}{N}Me}$, ppm
						Si	Si*		Me	Me*	CH_2Si	$-CH_2-$	CH_2N	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	
IXa	Pyrrolidino	1	3	—	—	6,6	8,5	—	0,92	2,52	15,25	18,80	67,57	65,49	22,44	—	50,16
IXc	Pyrrolidino	2	3	52,3	260	−23,9	8,4	−305,0	0,31	2,42	14,51	18,60	67,31	65,49	22,47	—	50,16
IXd	Pyrrolidino	3	1	—	—	−81,9	12,8	—	—	2,42	—	54,67	—	68,39	22,50	—	53,05
IXe	Pyrrolidino	3	3	—	—	−68,4	8,9	—	—	2,29	11,45	18,93	66,96	65,46	22,44	—	49,99
Xa	Perhydroazepino	1	3	—	—	6,7	8,4	—	0,93	2,49	15,16	17,69	68,26	65,53	22,76	27,40	52,07
Xd	Perhydroazepino	3	1	56,7	380	−82,1	18,6	−320,8	—	2,42	—	55,68	—	68,87	23,28	27,31	54,89
Xe	Perhydroazepino	3	3	51,2	350	−68,3	8,8	−317,1	—	2,29	11,32	17,76	67,41	65,53	22,83	27,44	52,46
XIb	N-Methylpiperazino	2	1	56,4	500	−28,4	8,9	−332,6	0,63	1,48	—	49,25	—	49,73	62,67	—	51,94
XId	N-Methylpiperazino	3	1	54,7	480	−73,9	9,3	−333,1	—	2,20	—	47,36	—	49,41	63,51	—	50,45

*^{17}O NMR spectrum.

TABLE 4. Neurotropic Properties of Aminoalkylsiloxane Methiodides in Tests on Male Mice of the $I_{cr}:I_{cl}$ Strain with Masses of 18-21 g

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg				M ± m, % relative to the control (100%)*				
		rotating-rod test	tube test	pulling-up-to-a-horizontal-bar test	hypothermia test	hypoxic hypoxia	hexenal narcosis	ethanol narcosis	phenamine stereotypy	corazole spasms
IXa	65 (43,8 ... 88,6)	41 (28,8 ... 55,21)	17,8 (13,6 ... 23)	35,5 (24,9 ... 46,1)	17,8 (13,6 ... 29)	104,6	75,1	51,4**	113,4	157,1**
IXb	44,7 (31,3 ... 59,6)	7,1 (4,3 ... 10,2)	5,6 (3,9 ... 7,4)	11,8 (2,9 ... 24)	6,9 (2,4 ... 13)	110,9	168,5**	139,4	100,0	113,7
IXc	12,9 (8,4 ... 17,9)	7,1 (5 ... 9,3)	6,5 (4,4 ... 8,9)	8,1 (4,5 ... 12,5)	6,5 (4,4 ... 8,9)	220,7**	123,5	353,0**	88,3	176,2**
IXd	58 (20,2 ... 109,9)	7,3 (2,6 ... 13,7)	6,5 (4,4 ... 8,9)	20,5 (14,6 ... 28,8)	5,9 (1,7 ... 12)	318,4**	117,3	120,2	106,6	104,4
IXe	51,5 (36,1 ... 69,2)	15 (9,6 ... 30,8)	11,2 (7,9 ... 14,7)	11,2 (7,9 ... 14,7)	14,7 (9,2 ... 20,9)	140,7**	126,1	61,1	76,9**	193,9**
Xa	28,2 (18,3 ... 37,2)	14,1 (6,8 ... 20,9)	12,9 (8,4 ... 17,9)	17,8 (13,8 ... 23)	4,5 (3,1 ... 5,9)	156,3**	166,7**	289,1**	93,9	87,9
Xb	44,7 (31,3 ... 59,6)	2,6 (1,5 ... 4,0)	1,7 (0,7 ... 3,3)	3,5 (2,5 ... 4,6)	2,8 (1,6 ... 4,2)	190,3**	142,7**	104,6	60,1**	167,9**
Xc	6,5 (3,4 ... 10,0)	0,7 (0,4 ... 1,0)	0,7 (6,4 ... 0,9)	0,6 (0,4 ... 0,8)	0,7 (0,4 ... 0,9)	231,7**	202,3**	185,7**	78,3	135,6**
Xd	22,4 (14,4 ... 28,5)	17,2 (7,3 ... 33,2)	10,3 (5,8 ... 15,7)	11,2 (6,5 ... 16,4)	8,9 (6,3 ... 11,9)	146,2**	87,7	39,5**	83,5	167,3**
Xe	41 (21,2 ... 62,2)	11,8 (2,9 ... 24)	12,9 (8,4 ... 17,9)	8,2 (4,5 ... 12,5)	8,2 (5,7 ... 11,1)	183,6**	132,7	262,0**	93,1	159,2**
XId	46 (15,3 ... 86,1)	7,3 (2,6 ... 13,7)	5,6 (3,4 ... 8,1)	5,9 (1,7 ... 12)	1,1 (0,8 ... 1,5)	133,6**	124,3	268,5**	117,1	119,3
XIe	16,3 (10,2 ... 22,7)	5,6 (3,9 ... 7,4)	4,1 (2,1 ... 6,2)	4,5 (2,7 ... 6,4)	2,6 (1,7 ... 3,4)	254,0**	72,2	84,1	40,4**	115,5

*The investigated compounds were introduced in a 5 mg/kg dose.

**The differences with respect to the control were statistically reliable with $P < 0.05$.

TABLE 5. Neurotropic Properties of Aminoalkylsiloxane Hydrochlorides in Tests on Male Mice of the BALB/C Strain with Masses of 18-22 g

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg				M ± m, % relative to the control (100 %)*				
		rotating-rod test	tube test	pulling-up-to-a-horizontal-bar	hypothermia test	hypoxic hypoxia	hexenal narcosis	ethanol narcosis	phenamine stereotypy	corazole spasms
Vd	89 (56 ... 129)	0,5 (0,3 ... 0,8)	1,8 (1,1 ... 2,5)	1,8 (1,1 ... 2,5)	0,6 (0,3 ... 0,9)	141,9**	198,4**	211,2**	21,8**	116,7**
VIc	20,5 (14,6 ... 28,8)	0,6 (0,2 ... 1,0)	1,4 (0,5 ... 2,6)	0,9 (0,6 ... 1,2)	0,5 (0,1 ... 1,0)	162,8**	228,0**	—	84,8	103,7
VId	137 (50 ... 262)	2,1 (1,5 ... 2,9)	2,8 (1,6 ... 4,2)	2,8 (1,6 ... 4,2)	2,6 (1,7 ... 3,6)	185,5**	246,6**	212,8**	63,7**	86,6**
VIIb	224 (114 ... 285)	4,3 (1,6 ... 8,2)	4,1 (2,7 ... 5,5)	4,5 (3,1 ... 6,0)	3,7 (1,1 ... 7,9)	125,0	168,4**	42,3**	95,1	105,1
VIId	224 (144 ... 285)	8,9 (5,6 ... 12,9)	10,5 (4,1 ... 20,8)	10,5 (4,1 ... 20,8)	12,9 (8,4 ... 17,9)	173,3**	186,6**	81,2	53,9**	95,9
VIIId	2240 (1200 ... 3320)	23,9 (12,4 ... 38,3)	20,5 (14,6 ... 28,8)	28,2 (15,9 ... 41,9)	25,8 (16,8 ... 35,7)	161,4**	180,0**	72,5	94,3	191,8**

*The investigated compounds were introduced in a 5 mg/kg dose.

**The differences with respect to the control were statistically reliable with $P < 0.05$.

TABLE 6. Cytotoxicity and Antitumorigenic Activity of Aminoalkylsiloxane Hydrochlorides and Methiodides

Compound	B16, EC_{50}, μg/ml	P388, MTD, mg/kg	Compound	B16, EC_{50}, μg/ml	P388, MTD, mg/kg	Compound	B16, EC_{50}, μg/ml	P388 MTD, mg/kg
Va	10	100	VIIId	>32	—	Xa	32	3,2
Vb	0,32	100	IXa	>32	32	Xb	3,2	10
VIc	5,6	10	IXb	32	10	Xc	1,0	1,0
VId	3,2	100	IXc	10	1,0	Xd	3,2	10
VIIb	5,6	100	IXd	10	3,2	Xe	0,32	3,2
VIId	1,8	100	IXe	1,0	3,2	XId	10	3,2
						XIe	3,2	10

TABLE 7. Antimicrobial Activity of Aminoalkylsiloxane Methiodides [minimal suppressing concn. (MSC), μg/ml]

Compound	*Staphylococcus aureus* 209	*Staphylococcus aureus* ATCC 25923	*Micrococcus luteus*	*Escherichia coli* K-12	*Hafnia alvei* 773	*Klebsiella pneumoniae* 5054	*Pseudomonas aeruginosa* 136	*Serratia marcescens* 1266
IXa	125	62,5	15,6	500	500	>500	500	250
IXb	7,8	62,5	1,96	500	500	31,2	500	7,8
IXd	250	500	250	>500	>500	500	>500	0,24
IXe	7,8	1,96	0,24	125	250	125	250	0,98
Xa	62,5	31,2	7,8	500	500	>500	250	125
Xb	15,6	31,2	15,6	500	500	500	500	62,5
Xd	15,6	31,2	7,8	500	500	125	500	0,48
Xe	1,96	0,98	0,24	125	250	250	250	0,98
XId	1,96	1,96	0,24	250	125	125	250	0,48
XIe	0,48	1,96	0,24	62,5	125	62,5	125	0,24

The parameters of the NMR spectra of the investigated compounds are presented in Tables 1-3. The ^{29}Si chemical shifts (CS) vary within two ranges: the first from −21 to −27 ppm and the second from −65 to −72 ppm. The distance between these ranges is determined by the number of siloxy substituents (two or three), and the variations in the CS in each range are due to a change in the length of the methylene chain between the silicon and nitrogen atoms. The m = 1→3 transition gives rise to a 5 ppm strong-field shift of the ^{29}Si resonance vis-à-vis a constant number of siloxy groups. Within the limits of the experimental error, the type of amino substituent does not affect the ^{29}Si CS because of remoteness from the silicon atom. The formation of hydrochlorides and methiodides causes strong-field shifts of the ^{29}Si resonance of the central silicon atom and a weak-field shift of the silicon atom in the siloxy substituent; the shifts are more pronounced in the case of the hydrochlorides. In aminoalkylsilanes the effect due to salt formation is less pronounced [4].

Within the limits of the experimental error, the ^{17}O CS of the investigated compounds are virtually independent of the number of siloxy groups and the type of amino substituent or the number of CH_2 groups that separate the silicon and nitrogen atoms, i.e., the location of the ^{17}O resonance signal is determined primarily by the directly bonded Me_3Si substituent, and the effect of more remote substituents is sensed to a lesser extent (see Table 1). In the spectra of the salts (see Tables 2 and 3) the half width of the ^{17}O resonance signal ($\Delta\nu_{1/2}$) is significantly greater than in the spectra of the corresponding siloxanes; this is probably associated with an increase in the volume of the molecule. The $\Delta\nu_{1/2}$ value is determined by the quadrupole-relaxation time T_2 and is proportional to the rotational correlation time of the molecule τ_c [6]. Since τ_c is associated with the volume of the molecule, the formation of salts broadens the ^{17}O resonance signal. In the spectra of the hydrochlorides the ^{17}O resonance signal is shifted ~4 ppm to weak field. This shift also does not change as a function of the amino substituent or the length of the alkyl chain between the silicon and nitrogen atoms. The weak-field shifts are less pronounced in the formation of the methiodides.

As in the case of piperidinoalkylsiloxanes [5], the ^{15}N CS are less sensitive to variations in the number of siloxy groups, and they were therefore measured only for a few compounds. As compared with the corresponding trimethylsilylalkylamines, the introduction of a siloxy substituent into the molecule has little affect on the ^{15}N CS. The location of the ^{15}N resonance signal is determined primarily by the type of ring in which the nitrogen atom is involved. An increase in the ring size from a five-membered ring to a six-membered ring gives rise to a 4-5 ppm strong-field shift [5], and passing to a seven-membered ring shifts the ^{15}N signal another 3 ppm to strong field. In the piperazine ring replacement of a methyl

TABLE 8. Physicochemical Properties of Aminoalkylsiloxanes $Me_{3-n}(Me_3SiO)_nSi(CH_2)_mNR_2$

Compound	R_2N	n	m	bp, °C (mm)	n_D^{20}
Ia	Pyrrolidino	1	3	80...82 (1,5)	1,4382
Ib	Pyrrolidino	2	1	75...76 (1,5)	1,4228
Ic	Pyrrolidino	2	3	86...88 (2,5)	1,4280
Id	Pyrrolidino	3	1	75...78 (2,5)	1,4192
Ie	Pyrrolidino	3	3	113...115 (1,5)	1,4224
IIa	Perhydroazepino	1	3	95...97 (1,5)	1,4452
IIb	Perhydroazepino	2	1	80...81 (1,5)	1,4335
IIc	Perhydroazepino	2	3	112...114 (2,5)	1,4360
IId	Perhydroazepino	3	1	85...86 (2,5)	1,4305
IIe	Perhydroazepino	3	3	120...122 (2,5)	1,4270
IIIa	N-Methylpiperazino	1	3	74...76 (1,5)	1,4522
IIIb	N-Methylpiperazino	2	1	79...81 (1,5)	1,4328
IIIc	N-Methylpiperazino	2	3	99...101 (3,5)	1,4348
IIId	N-Methylpiperazino	3	1	114...116 (1,5)	1,4260
IIIe	N-Methylpiperazino	3	3	129...131 (3,5)	1,4300
IVb	N-Phenylpiperazino	2	1	166...168 (1,5)	1,4845
IVd	N-Phenylpiperazino	3	1	138...140 (1,5)	1,4510

TABLE 9. Physicochemical Properties of Hetarylaminoalkylsiloxane Hydrochlorides $Me_{3-n}(Me_3SiO)_nSi(CH_2)_m\overset{+}{N}HR_2Cl^-$

Compound	Empirical formula	n	m	R_2N	mp, °C
Va	$C_{12}H_{30}ClNO_2Si_2$	1	3	Pyrrolidino	214...216
Vb	$C_{12}H_{32}ClNO_2Si_3$	2	1	Pyrrolidino	106...108
Vd	$C_{14}H_{38}ClNO_3Si_4$	3	1	Pyrrolidino	106...108
VIb	$C_{14}H_{36}ClNO_2Si_3$	2	1	Perhydroazepino	80...82
VIc	$C_{16}H_{20}ClNO_2Si_3$	2	3	Perhydroazepino	141...143
VId	$C_{16}H_{42}ClNO_3Si_4$	3	1	Perhydroazepine	86...88
VIIb	$C_{13}H_{35}ClN_2O_2Si_3$	2	1	N-Methylpiperazino	150...152
VIId	$C_{15}H_{41}ClN_2O_3Si_4$	3	1	N-Methylpiperazine	169...170
VIIIb	$C_{18}H_{37}ClN_2O_2Si_3$	2	1	N-Phenylpiperazino	142...143
VIIId	$C_{20}H_{43}ClN_2O_3Si_4$	3	1	N-Phenylpiperazino	89...91

TABLE 10. Physicochemical Properties of Aminoalkylsiloxane Methiodides $Me_{3-n}(Me_3SiO)_n(CH_2)_m\overset{+}{N}MeR_2I^-$

Compound	R_2N	n	m	Empirical formula	mp, °C
IXa	Pyrrolidino	1	3	$C_{13}H_{32}INOSi_2$	183...185
IXb	Pyrrolidino	2	1	$C_{13}H_{34}INO_2Si_3$	169...171
IXc	Pyrrolidino	2	3	$C_{15}H_{38}INO_2Si_3$	83...85
IXd	Pyrrolidino	3	1	$C_{15}H_{40}INO_2Si_4$	173...175
IXe	Pyrrolidino	3	3	$C_{17}H_{44}INO_3Si_4$	221...223
Xa	Perhydroazepino	1	3	$C_{15}H_{36}INOSi_2$	178...180
Xb	Perhydroazepine	2	1	$C_{15}H_{38}INO_2Si_3$	173...175
Xc	Perhydroazepine	2	3	$C_{17}H_{42}INO_2Si_3$	204...205
Xd	Perhydroazepine	3	1	$C_{17}H_{44}INO_3Si_4$	180...182
Xe	Perhydroazepino	3	3	$C_{19}H_{48}INO_3Si_4$	230...232
XId	N-Methylpiperazino	3	1	$C_{16}H_{43}IN_2O_3Si_4$	178...180
XIe	N-Methylpiperazino	3	3	$C_{18}H_{47}IN_2O_3Si_4$	190...192

group attached to a nitrogen atom by a phenyl group causes an appreciable weak-field shift (18 ppm), while the ^{15}N CS of the second nitrogen atom remains virtually unchanged. Salt formation also causes weak-field shifts of the resonance signal of nitrogen; this is a common property in amines [7].

The changes in the ^{13}C CS of the siloxy group in the investigated compounds are insignificant. An increase in the number of CH_2 groups from one to three slightly shifts the ^{13}C signal of the methyl group attached to the central silicon atom to strong field. In contrast to aminoalkylsilanes [4], the formation of salts shifts the resonance signal of these carbons to weak field. An increase in the number of siloxy substituents from two to three gives rise to a 3 ppm strong-field shift of the signal of the α-CH_2 group, which is also characteristic for siloxanes with other $(CH_2)_mR$ substituents [5], i.e., it is a common property of compounds of this type. The formation of hydrochlorides causes a small strong-field shift of the CH_2 (m = 1)

signal. In the case of methiodides, on the other hand, one observes an appreciable weak-field shift of the signal of these carbons, while the signals of the CH_2—Si and CH_2 groups are shifted to strong field.

The ^{13}C CS of the carbons of the amine ring are more sensitive to the length of the methylene chain and, in the piperazine ring, also to substitution at the nitrogen atom. In view of the remoteness of the siloxy substituents, varying their number has virtually no effect on the ^{13}C CS of these carbons. The formation of methiodides also has an alternating effect on the ring carbons: one observes a weak-field shift of the carbon atoms in the α position and a strong-field shift of the carbons in the β position from the center of addition of methyl iodide. In the case of the hydrochlorides the ^{13}C CS of the ring carbons are shifted somewhat to strong field as compared with the starting aminoalkylsiloxanes.

The results of an investigation of the neurotropic activity of the aminoalkylsiloxane methiodides are presented in Table 4, while the results for the corresponding hydrochlorides are given in Table 5. All of the investigated compounds display a depressive effect on the tonus of the skeletal musculature, the coordination of movements, and the body temperature. The highest depressive activity was observed for perhydroazepine derivative Xc, which contains two trimethylsiloxy groups and a chain made up of three methylene groups. For the remaining perhydroazepine derivatives Xa, b, d, e the depressive activity in the tests mentioned above is manifested to a lesser extent by a factor of 4 to 24. The aminoalkylsiloxanes that contain a pyrrolidine (IXa-d) or N-methylpiperazine group have depressive activity over the range 5-15 mg/kg (ED_{50}).

With respect to hypothermic activity, all of the investigated compounds are more active than in the rotating-rod test.

In doses of 5 mg/kg all of the compounds have rather high antihypoxic activity. It is highest for IXc, d, Xb, c, e, and XIe, which prolongs the lives of the animals by a factor of 1.9-3.2. Pyrrolidine derivative IXa, with one trimethylsiloxy group, is distinguished by the lowest activity in all of these tests.

A potentiating effect on Hexenal narcosis was observed for perhydroazepine derivatives Xa, b, c. With respect to ethanol narcosis, both a potentiating effect and an antagonizing effect were established. A prolonging effect was established for IXc, Xa, c, e, and XId, while an antagonizing effect was observed for IXa and Xd.

A neurotropic effect, which is associated with the effect of the compound on the dopaminergic structure of the cerebrum, is manifested to the greatest degree by the siloxane with a piperazine radical and three methylene groups (XIe). Perhydroazepine derivatives, as well as some compounds with a pyrrolidine group (IXa, e, Xa-e), display protective properties in the case of Corazole spasms. The methiodides of the N-methylpiperazine derivatives do not have anti-Corazole activity.

Not one of the investigated compounds displayed protective properties in the case of electroshock spasms.

The aminoalkylsiloxane methiodides are relatively toxic substances. Their lethal doses (LD_{50}) range from 6.5 to 65 mg/kg. Heptamethyl-3-(3-perhydroazepinopropyl)trisiloxane (Xc) displays the highest acute toxicity, while pentamethyl(3-pyrrolidinopropyl)disiloxane (IXa) exhibits the lowest acute toxicity. The remaining methiodides do not differ substantially from one another with respect to toxic properties.

A study of the aminoalkylsiloxane hydrochlorides shows that, with respect to the spectrum of pharmacological activity, they do not differ substantially from the corresponding methiodides. However, their absolute activity with respect to the individual tests is considerably greater, while their acute toxicity is lower. Thus, for example, a comparison of pyrrolidinomethyltrisiloxane hydrochloride Vd (see Table 5) and its methiodide IXd (see Table 4) shows that the hydrochloride has significantly higher depressive activity in all of the investigated tests. The hydrochlorides of N-methyl- and N-phenylpiperazine derivatives VIIb, d and VIIId (see Table 2) also have higher neurotropic activity than the corresponding methiodides (see Table 4); the hydrochlorides of the piperazine derivatives have lower LD_{50} values by a factor of 5-50 than the corresponding methiodides. As compared with the corresponding methiodide Xd, perhydroazepinomethyltetrasiloxane hydrochloride VId has approximately five to nine times higher neurotropic activity, and its toxicity is lower to the same extent. There are no such pronounced differences in activity for another pair of perhydroazepinotrisiloxane derivatives VIc and Xc.

Depending on the character of the heteroring, the acute toxicities of aminomethyltetrasiloxanes (V, VI, VII, VIIId) decrease in the order pyrrolidino > perhydroazepino > N-methylpiperazino > N-phenylpiperazino. Their neurotropic activities decrease in the same order. It follows from the studies that, in addition to the number of siloxy groups and the type of amine, the environment itself of the nitrogen atom in the heteroring plays a substantial role in the manifestation of neurotropic properties by aminoalkylsiloxane derivatives.

The cytotoxicity of the investigated compounds (Table 6) depends on the number of siloxy groups in the molecules and, in the pyrrolidine IXa, c, e and perhydroazepine Xa, c, e series, increases on passing from di- to tri- and tetrasiloxanes. An increase in the number of methylene groups between the nitrogen and silicon atoms from one to three increases the cytotoxicity of the compounds in the pyrrolidine (compare IXb and IXc, IXd and IXe), perhydroazepine (compare Xb and Xc, Xd and Xe),

and N-methylpiperazine (compare XId and XIe) series. Of the methiodides, the perhydroazepine derivatives have the greatest cytotoxicity, and the pyrrolidine and N-methylpiperazine derivatives (compare X and IX and XIb, d and XIe) have somewhat lower cytotoxicity. Aminomethyltetrasiloxane hydrochlorides V, VI, and VIIId are arranged in a different order: pyrrolidino > N-methylpiperazino > perhydroazepino > N-phenylpiperazino.

The investigated compounds do not have antitumorigenic activity with respect to lympholeucosis P388 and Lewis lung carcinoma.

The antimicrobial activity of the synthesized aminoalkylsiloxane methiodides was determined in vitro in strains of Gram-positive bacteria (*Staphylococcus aureus* 209 and ATCC 25923, *Micrococcus luteus*) and Gram-negative bacteria (*Escherichia coli* K-12, *Hafnia alvei* 773, *Klebsiella pneumoniae* 5054, *Pseudomonas aeruginosa* 136, and *Serratia marcescens* 1266) (Table 7).

A number of compounds (IXe, Xe, XId, e) suppress the growth of the Gram-positive bacteria at a concentration of 0.24-0.48 μg/ml. Many of the investigated aminoalkylsilane methiodides are inactive with respect to the Gram-negative bacteria. Pyrrolidine derivative IXd, which is inactive with respect to most of the Gram-positive and Gram-negative bacteria, displayed selective high activity against *Serratia marcescens* 1266 [minimal suppressing concentration (MSC) 0.24 μg/ml]. Compounds Xd and XId, e also displayed high activity (0.24-0.48 μg/ml) with respect to this microbe.

In an analysis of the dependence of the MSC on the structure of the tested compounds it was observed that the character of the heteroring in the compound has the principal effect. In the case of *Staphylococcus aureus* 209 the order of activity is as follows: pyrrolidine < hexamethyleneimine < N-methylpiperazine (IX < X < XI; IXe < Xe < XIe). The number of trimethylsiloxy groups [$IXa_{(n=1)} < IXe_{(n=3)}$; $Xa_{(n=1)} < Xe_{(n=3)}$] and the length of the chain of methylene groups [$IXd_{(m=1)} < IXe_{(m=3)}$; $Xd_{(m=1)} < Xe_{(m=3)}$; $XId_{(m=1)} < XIe_{(m=3)}$]. The most active compound is 3-(N-methylpiperazino)propyltetrasiloxane (XIe), which suppresses the growth of *Micrococcus luteus* and *Serratia marcescens* 1266 in a concentration of 0.24 μg/ml and *Staphylococcus aureus* 209 in a concentration of 0.48 μg/ml.

EXPERIMENTAL

The ^{17}O NMR spectra were obtained with a Bruker WM-360 spectrometer (operating frequency 48.82 MHz, pulse duration 40 μsec, number of accumulations from 10^4 to 10^5, computer resolution 0.1 ppm/point, external standard H_2O). The ^{13}C NMR spectra were recorded with a Bruker WH-90/DS spectrometer [operating frequency 22.53 MHz, complete proton decoupling, pulse duration 5 μsec, internal standard tetramethylsilane (TMS)]. The ^{29}Si NMR spectra were obtained with a Bruker WH-90/DS spectrometer (operating frequency 17.88 MHz, complete proton decoupling, pulse duration 5 μsec, internal standard TMS) and with a Bruker WM-360 spectrometer (operating frequency 71.5 MHz, complete proton decoupling, pulse duration 15 μsec). The ^{15}N NMR spectra were recorded with a Bruker WM-360 spectrometer (operating frequency 36.5 MHz, complete proton decoupling, pulse duration 15 μsec, external standard nitromethane).

The chloroalkylsiloxanes were obtained by a known method [8].

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

1,1,1,5,5,5-Hexamethyl-3-trimethylsiloxy-3-(pyrrolidinomethyl)trisiloxane (Id). A solution of 5.17 g (15 mmole) of 3-chloromethyl-3-trimethylsiloxytrisiloxane and 2.49 g (35 mmole) of pyrrolidine in 30 ml of toluene was heated for 30 h, after which the precipitate was removed by filtration, and the solvent was removed by distillation. Twofold fractional distillation in vacuo gave 3.60 g (63%) of Id.

Compounds Ia, b, c, e, IIa-e, and IIIa-e (Table 8) were similarly obtained.

Hydrochloride Vd. Ether saturated with HCl was added gradually with cooling to a solution of 2 g (5.27 mmole) of siloxane Ib in dry ether, after which the white precipitate was removed by filtration, washed with ether, and dried in vacuo.

The remaining **V-VII** (Table 9) were similarly obtained.

Methiodide IXd. A solution of 0.75 g (5.27 mmole) of methyl iodide in ether was added gradually to a solution of 2 g (5.27 mmole) of siloxane Ib in ether, after which the mixture was heated. It was then cooled, and the resulting white precipitate was removed by filtration and washed with dry ether and hexane.

The remaining **IX-XI** (Table 10) were similarly obtained.

The action of the synthesized compounds was investigated in experiments on male mice of the BAIB/c and I_{cr}:I_{cl} strains with masses of 18-22 g and on white, mongrel, male rats with masses of 210 ± 15 g. The investigated substances were introduced intraperitoneally for 30 min prior to setting up the corresponding test. The action of the substance on the central nervous system (CNS) was investigated with respect to the following indexes. 1) **With respect to the effect on the**

coordination of motion and muscular tonus in accordance with "rotating rod" methods with an Ugo Basile apparatus operating at 8 rpm for 2 min and with respect to the "tube" test (with a 30 by 2 cm glass tube for 30 sec) and the "pulling up to a horizontal bar" test (with a metal rod with a diameter of 2 mm in 5 sec) prior to and 30 and 60 min after intraperitoneal introduction of the substance. 2) **With respect to the effect on the duration of the action of narcotic substances — Hexenal and ethanol.** The duration of narcosis was determined from the instant of loss of the "turnover" reflex to its restoration. Hexenal was introduced intraperitoneally in a dose of 70 mg/kg, and ethanol was introduced intraperitoneally in a dose of 5 g/kg 30 min after injection of the investigated substances. 3) **With respect to the effect on the spasm-inducing action of electric current and Corazole.** The animal was subjected to alternating current with a strength of 50 mA and a frequency of 50 pulses/sec for a stimulus duration of 0.2 sec (maximum electroshock), and a 1% solution of Corazole was introduced intraperitoneally at a rate of 0.01 ml/sec 30 min after administration of the compound. The antispasmodic effect was evaluated from the degree of prevention of the clonic and tonic phases of the spasmodic paroxysm and the death of the animal after introduction of the spasmodic agent. 4) **With respect to the effect on the body temperature** measured in the rectum of the animals with an electric thermometer prior to and 30, 60, and 180 min after introduction of the investigated substances. A decrease in the rectal temperature by 3°C or more as compared with the corresponding indexes of the animals of the control groups served as the criterion of the evaluation. 5) **With respect to the analgesic action.** The "hot plate" method with an Ugo Basile apparatus was used to evaluate the analgesic effect. The thresholds of pain sensitivity during thermal stimulation were determined prior to and 30, 60, and 180 min after injection of the investigated substances. 6) **With respect to the effect on hypoxic hypoxia.** Hypoxic hypoxia was induced in an isolated 220 cm^3 hermetic chamber without CO_2 absorption; the manifestation of the first symptoms of respiratory disturbances, the development of hypoxic spasms, and the time of death of each animal in the hermetic chamber were recorded. 7) **With respect to the effect on the central adrenergic and dopaminergic processes**, which were evaluated from the duration of phenamine stereotypy in the rats after subcutaneous injection of phenamine in a dose of 10 mg/kg. 8) **With respect to the influence on the depressive effects of reserpine.** Reserpine in a dose of 2 mg/kg was introduced intraperitoneally for 1 h prior to injection of the investigated substance. The hypothermia and degree of ptosis induced by reserpine were determined 1, 2, and 3 h after their administration. 9) In addition, the toxic properties of all of the substances were also investigated by determining the mean LD_{50} values in the case of intraperitoneal administration.

Cultivation of melanoma B16 cells was carried out at 37°C in an atmosphere of 10% CO_2 in a Dulbeko complete medium (DCM) containing 25 mM HEPES buffer, 10% fetal serum, and a standard mixture of streptomycin, penicillin, and Fungizone (Gibco). In the cytotoxic test the first 10 passages of B16 cells obtained from the tumorous material of the melanoma strain [9] were used.

The cytotoxic test was carried out in 96-cell flat-bottomed plates (Linbro) in 300 μl of DCM. A total of $5 \cdot 10^3$ to $10 \cdot 10^3$ melanoma B16 cells were sown in the cells, and the next day the investigated compounds in tenfold dilutions over a concentration range of 0.32-32 μg/ml were introduced. After 4 days the number of cells in the plate cells was determined with respect to DNA by a microfluorimetric method by means of Choest N 33342 dye (Calbiochem). The B16 cells were fixed in 70% ethanol and lysed in 0.5 M NaOH at 55°C for 1 h. The cell lysate was neutralized with 0.6 M KH_2PO_4 containing 2 M NaCl in the presence of the Choest dye in a final concentration of 0.1 μg/ml. The excitation and emission wavelengths (360 and 460 nm, respectively) were used in the fluorimetry.

The cytotoxicity of the compounds was evaluated from the effectiveness of the concentration (in micrograms per milliliter) that suppresses the cell growth by 50 (EC_{50}). The calculation and analysis with respect to the statistical (0.25 log) and functional (1.0 log) ranks of cytotoxicity on a logarithmic scale of the concentration were carried out by the method of linear regression with an Apple IIe computer. The functional thresholds of high and moderate cytotoxicity were 3.2 and 32 μg/ml, respectively.

The antitumorigenic activity of the compounds was studied with respect to lympholeucosis P388 and Lewis lung carcinoma (LLC) in mice. Lympholeucosis P388 was implanted intraperitoneally in C57BL/6×DBA/2 male hybrids (with masses 18-20 g) in the amount of 10^6 cells per mouse. The compounds were introduced intraperitoneally on the second and ninth days in doses that increased by 0.5 log on the logarithmic scale until toxicity developed. Lewis lung carcinoma was implanted intraperitoneally in C57BL/6×DBA/2 male hybrids (with masses of 18-22 g) in the amount of 10^6 cells per mouse. The compounds were introduced on the first to third and eighth to tenth days in doses amounting to 0.32-0.56 of the optimal doses (OD) in the case of active substances or of the maximally tolerable doses (MTD) in the absence of activity as determined with respect to lympholeucosis P388.

The antitumorigenic activity was evaluated from the life span of the mice in the test groups (T) as compared with the control (C) and was expressed in percent (T/C, %). The number of mice in the test group with lympholeucosis P388 was three and in the test group with LLC was five, which makes it possible to determine the reliable effect ($P < 0.05$) of the toxicity and antitumorigenic activity at 80% and 120% levels, respectively. The functional thresholds of moderate and high antitumorigenic activity were 150% and 200%, respectively.

The study of the antimicrobial activity was carried out by the widely used method of twofold serial cultures in beef-extract broth at pH 7.2-7.4 [10, 11]. The following standard strains were used as test microbes: *Staphylococcus aureus* 209, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* K-12, *Pseudomonas aeruginosa* 136, *Serratia marcescens* 1266, etc. — a total of eight strains. The microbe charge was $(1\text{-}5)\cdot 10^6$ microbial bodies per milliliter of a diurnal broth culture of the test microbes [12]. The minimal suppressing concentration (MSC) was determined. The substances for the tests were dissolved in DMSO and 87% sodium chloride solution up to a final concentration of 1000 μg/ml.

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