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SILYL MODIFICATION OF BIOLOGICALLY ACTIVE COMPOUNDS. 10*. LIPID TYPE ORGANOSILICON DERIVATIVES OF 8-HYDROXY-QUINOLINE AND N-(2-HYDROXYETHYL)-1,2,3,4-TETRAHYDRO(SILA, ISO)QUINOLINES

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Organosilicon alkylation of the primary alcoholic groups of N-(2-hydroxyalkyl) derivatives of 1,2,3,4-tetrahydroquinoline, tetrahydroisoquinoline, and 4,4-dimethyltetrahydro-4-silaisoquinoline, and also the hydroxyl group of 8-hydroxyquinoline by trialkyl-chloroalkylsilanes under conditions of phase-transfer catalysis has been investigated. The neurotropic properties and acute toxicity of the synthesized compounds have been investigated.

Keywords: tetrahydroisoquinoline, tetrahydroquinoline, alkylation, phase-transfer catalysis, psychotropic activity, silylation.

As a result of numerous investigations [1-10] it has been shown that silylation significantly increases the lipophilicity of biologically active compounds and therefore assists their transport within the organism. This is true not only in relation to reversibly silylated (hydrolytically unstable) compounds but also to compounds containing a triorganosilyl(oxy) group stable to hydrolysis under physiological conditions.

According to literature data certain tetrahydro(iso)quinoline-containing ligands reveal affinity towards serotonin (5-HT_{1A}) [11, 12], dopamine [13], and N-methyl-D-aspartate (NMDA) [14] receptors, and certain opiate alkaloids contain hydrogenated residues of quinoline and isoquinoline [15]. In addition it was noted that on silylation of both aliphatic and heterocyclic amino alcohols, and also their salts, which are structural analogs of the neuromediators choline and colamine (2-aminoethanol), psychotropic activity is increased [16, 17], and the acute toxicity of the synthesized compounds is reduced [18].

With the aim of improving the pharmacological properties of biologically active molecules *in vivo* we propose to extend this principle to organosilicon derivatives of N-heterocyclic amino alcohols, simultaneously pursuing the aim of constructing lipid type bipolar compounds, consisting of derivatives of hydroxyquinoline or tetrahydroquinoline, tetrahydroisoquinoline, and tetrahydrosilaisoquinoline as hydrophilic "heads", and lipophilic trimethylsilylpropoxyethyl "tails".

We have developed a method of obtaining 8-(3-trimethylsilylpropoxy)quinoline **1** by the interaction of 8-hydroxyquinoline with (3-chloropropyl)trimethylsilane under phase-transfer catalysis conditions [19].

* For Part 9 see [1].

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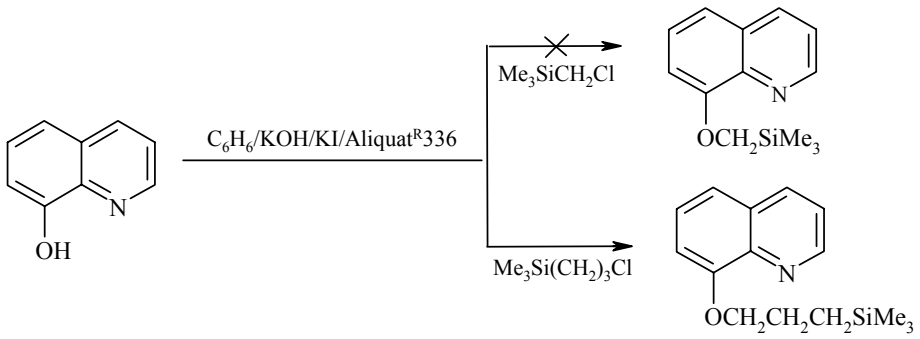
Organosilicon alkylation was carried out in the system benzene/KOH/KI/Aliquat^R 336 and according to our experimental data proved to be more efficient than synthesis from the lithium salt of 8-hydroxyquinoline. From the data of physicochemical investigations reaction proceeds with the formation of the O-alkyl derivative.

Scheme 1



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The developed method was used for the organosilicon alkylation of the primary alcoholic groups of N-(2-hydroxyethyl) derivatives of 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline in the synthesis of the corresponding N-trialkylsilylalkoxyethyl derivatives (**4-7**, **11-14**). The interaction of compounds **1**, **5**, **11**, and **15** with methyl iodide gave their iodomethylates **18-21** respectively.

The initial amino alcohols of 1,2,3,4-tetrahydroquinoline (**2**) and 1,2,3,4-tetrahydroisoquinoline (**9**) were obtained by the hydroxyethylation of the appropriate heterocyclic base with ethylene iodohydrin [18] or ethylene bromohydrin (Schemes 2 and 3).

In addition to the products of hydroxyethylation with ethylene iodohydrin N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline and N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline [18], we detected in the reaction mixture the products of double O-alkylation **3** and **10** in 4 and 14% yield, respectively. These were isolated and characterized by ^{1}H NMR spectroscopy and chromato-mass spectrometry.

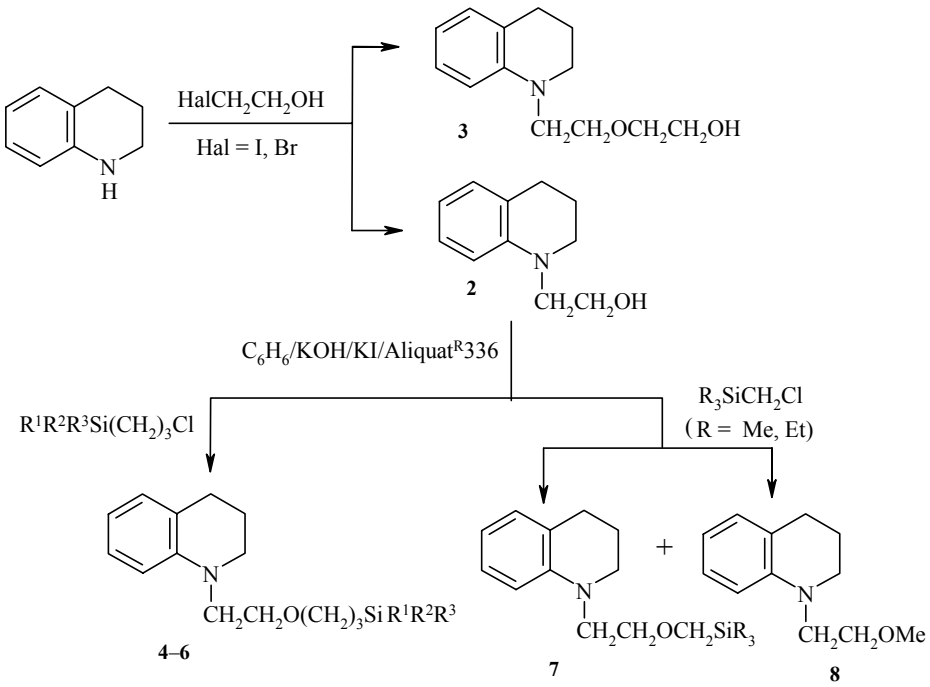
By replacing ethylene iodohydrin by ethylene bromohydrin in the hydroxyethylation reaction an increase was noted in the yield of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline and N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline of more than twofold in comparison with the published data [18].

When obtaining compound **4** the phase-transfer organosilicon alkylation of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline with trimethyl(3-chloropropyl)silane was carried out in two systems: C_6H_6/KOH/KI/Aliquat 336^R and C_6H_6/K_2CO_3/KI/18-crown-6 with variation of the reactant ratio and of the reaction time and temperature. The system C_6H_6/KOH/KI/Aliquat 336^R proved to be more efficient (Table 1).

TABLE 1. Synthesis of N-[2-(3-trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline **4**

Ratio [THQ] : [silane], mole/mole	Catalyst	Reaction time, h	Temperature, °C	Yield, %
2:1	KOH/Aliquat^R 336	4	20	—
2:1	KOH/Aliquat^R 336	7	80	4
1:2	KOH/Aliquat^R 336	14	80	5
1:1.05	KOH/KI/Aliquat^R 336	14	80	32
1:1	K_2CO_3/KI/18-Crown-6	7	80	19

Scheme 2



4 $R^1R^2R^3 = Me_3$; **5** $R^1R^2 = Am_2$, $R^3 = Me$; **6** $R^1R^2 = Me_2$, $R^3 = Hp$; **7** R = Me

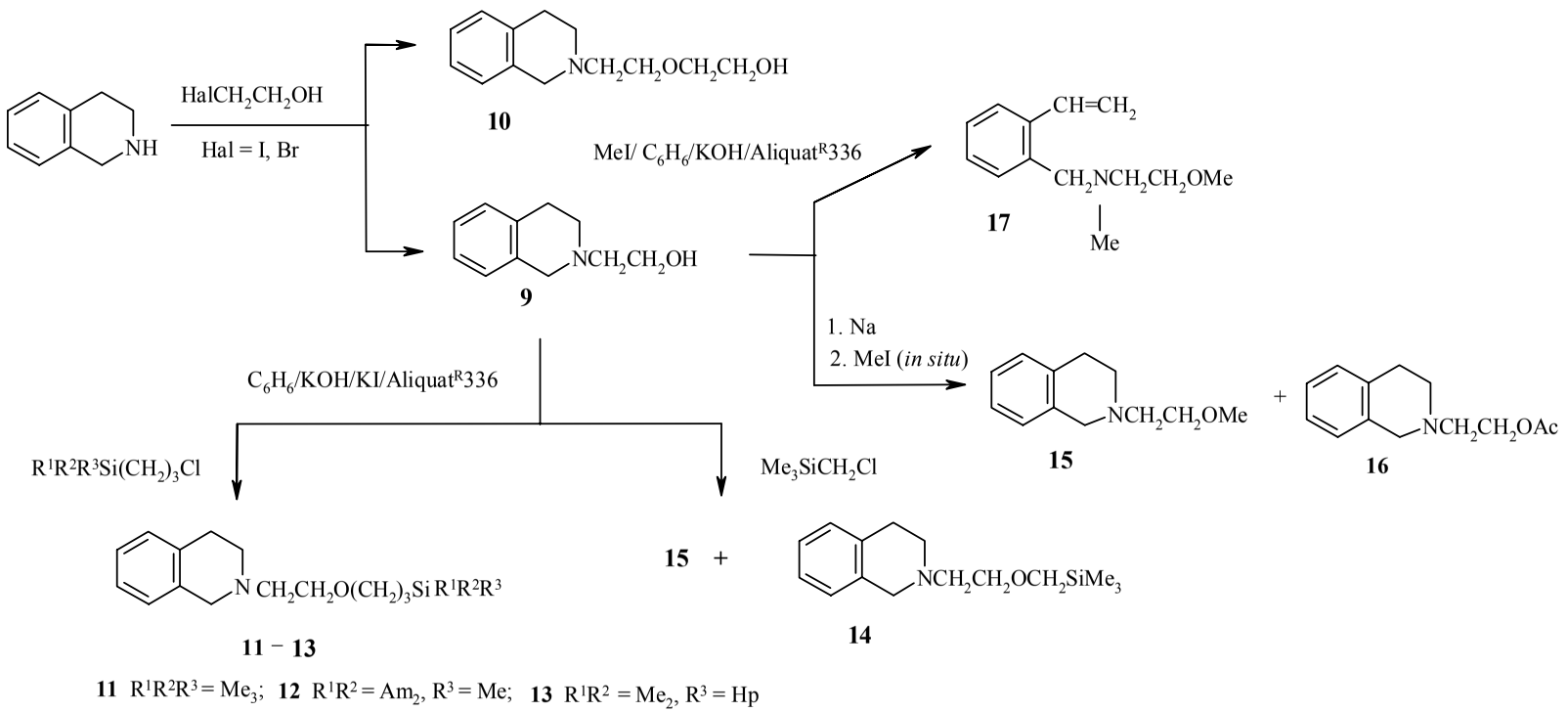
It has revealed that interaction of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoline with N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline with chloromethyltrialkylsilanes under these conditions (Schemes 2 and 3) resulted in the formation of desired N-[2-(trimethylsilylmethoxy)ethyl]-1,2,3,4-tetrahydroquinoline (**7**) and N-2-(trimethylsilylmethoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (**14**) formed in trace amounts of 4 and 0.4%, respectively.

The formation of the corresponding methyl ethers **8** and **15** (yields 42 and 48%) proceeds in significant amounts in this reaction [20, 21]. The structure of the latter was confirmed by alternate syntheses: a) using 2-chloroethyl methyl ether as alkylating agent under conditions of phase-transfer catalysis in the system toluene/K_2CO_3/KI/18-crown-6 [20], and b) by alkylation of N-(2-hydroxyethyl)tetrahydroisoquinoline sodium salt with methyl iodide *in situ*. In the latter case, besides of the main product **15** (56% yield), compound **16**, containing C=O group was isolated (10% yield) from the reaction mixture and characterized by ^{1}H NMR, IR, and chromato-mass spectroscopy. The characteristic absorption band at 1745 cm^{-1} confirmed C=O group presence in the molecule.

It could be speculated that compound **16** is formed by the interaction of unreacted N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline sodium salt with ethyl acetate under the conditions of chromatography on silica gel.

It could be noted that attempts to avoid the formation of the iodomethylate and to carry out methylation of the primary alcoholic group of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline with methyl iodide under phase-transfer catalysis conditions in the system benzene/KOH/Aliquat^R 336, lead, besides O- and N-methylation, to opening of the hydrogenated ring of the tetrahydroisoquinoline system with the formation of compound **17** in 32% yield, the structure of which was established by ^{1}H NMR and chromato-mass spectroscopy.

Scheme 3



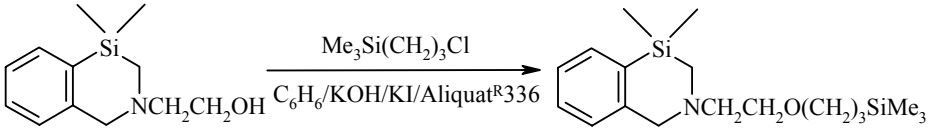
11 $R^1R^2R^3 = Me_3$; **12** $R^1R^2 = Am_2$, $R^3 = Me$; **13** $R^1R^2 = Me_2$, $R^3 = Hp$

TABLE 2. ^{1}H NMR Spectra of Compounds **1**, **3-6**, **8**, **10-13**, **15-21**, **23**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)
1	0.18 (9H, s, $Si(CH_3)_3$; 0.79 (2H, m, $SiCH_2$); 2.07 (2H, m, CH_2); 4.32 (2H, t, *J* = 7.5, OCH_2); 7.09-9.09 (6H, m, arom.)
3	1.91 (2H, m, 3-CH_2); 2.44 (1H, br. s, OH); 2.72 (2H, t, *J* = 6, 4-CH_2); 3.12-3.71 (10H, m, 2-CH_2+NCH_2+OCH_2); 6.42-7.28 (4H, m, arom.)
4	0.02 (9H, c, $Si(CH_3)_3$; 0.49 (2H, m, $SiCH_2$); 0.89 (2H, br. s, CH_2); 1.93 (2H, m, 3-CH_2); 2.73 (2H, t, *J* = 6, 4-CH_2); 3.16-3.90 (8H, m, NCH_2+OCH_2+2-CH_2); 6.35-7.14 (4H, m, arom.)
5	-0.04 (3H, s, $SiCH_3$); 0.51 (6H, m, $SiCH_2$); 0.90 (6H, t, *J* = 6.5, CH_3); 1.31 (14H, br. s, CH_2); 1.97 (2H, m, 3-CH_2); 2.77 (2H, t, *J* = 6, 4-CH_2); 3.27-3.66 (8H, m, NCH_2+ OCH_2+ 2-CH_2); 6.44-7.17 (4H, br. s, arom.)
6	-0.02 (6H, s, $Si(CH_3)_2$); 0.51 (4H, m, $SiCH_2$); 0.90 (3H, t, *J* = 6.5, CH_3); 1.29 (10H, br. s, CH_2); 1.98 (2H, m, 3-CH_2); 2.78 (2H, t, *J* = 6, 4-CH_2); 3.23-3.65 (8H, m, NCH_2+OCH_2+2-CH_2); 6.40-7.20 (4H, br. s, arom.)
8	1.92 (2H, m, 3-CH_2); 2.75 (2H, t, *J* = 6, 4-CH_2); 3.23-3.66 (9H, m, OCH_3+OCH_2+2-CH_2+ NCH_2); 6.47-7.31 (4H, m, arom.)
10	2.58-3.01 (8H, m, 3,4-CH_2+NCH_2+OCH_2); 3.35-4.01 (6H, m, OCH_2 + 1-CH_2); 6.88-7.13 (4H, m, arom.)
11	0.018 (9H, s, $Si(CH_3)_3$); 0.52 (2H, m, $SiCH_2$); 1.64 (2H, m, CH_2); 2.80 (2H, t, *J* = 6, NCH_2), 2.91 (4H, m, 3,4-CH_2); 3.49 (2H, t, *J* = 7, OCH_2); 3.69 (2H, t, *J* = 6, OCH_2); 3.80 (2H, s, 1-CH_2); 7.13 (4H, m, arom.)
12	-0.06 (3H, s, $SiCH_3$); 0.49 (6H, m, $SiCH_2$); 0.89 (6H, t, *J* = 6.5, CH_3); 1.33 (12H, br. s, CH_2); 1.60 (2H, m, CH_2); 2.78 (2H, t, *J* = 6, NCH_2); 2.90 (4H, m, 3,4-CH_2); 3.56 (4H, m, OCH_2); 3.73 (2H, br. s, 1-CH_2); 7.09 (4H, m, arom.)
13	0.01 (6H, s, $Si(CH_3)_2$); 0.51 (4H, m, $SiCH_2$); 0.91 (3H, t, *J* = 6.5, CH_3); 1.27 (10H, br. s, CH_2); 1.62 (2H, m, CH_2); 2.78 (2H, t, *J* = 6, NCH_2); 2.81 (2H, t, *J* = 6, 4-CH_2); 2.92 (2H, t, *J* = 6, 3-CH_2); 3.44 (2H, m, OCH_2); 3.67 (2H, t, *J* = 6, OCH_2); 3.73 (2H, br. s, 1-CH_2); 7.10 (4H, m, arom.)
15	2.77 (2H, t, *J* = 6, NCH_2); 2.83 (4H, m, 3,4-CH_2); 3.37 (3H, s, OCH_3); 3.47 (2H, t, *J* = 6, OCH_2); 3.72 (2H, s, 1-CH_2); 6.92-7.12 (4H, m, arom.)
16	2.06 (H, s, $COCH_3$); 2.60-2.99 (6H, m, 3,4-CH_2+NCH_2); 3.68 (2H, s, 1-CH_2); 4.17-4.36 (2H, t, *J* = 6, OCH_2); 6.87-7.19 (4H, m, arom.)
17	2.24 (3H, s, NCH_3); 2.62 (2H, t, *J* = 7, NCH_2); 3.34 (3H, s, OCH_3); 3.49 (3H, t, *J* =7, OCH_2); 3.57 (2H, s, $ArCH_2N$); 5.20 (1H, dd, *J* = 12, *J* = 2, *cis*=CH_2), 5.60 (1H, dd, *J* = 18, *J* = 2, *trans* =CH_2); 7.03-7.67 (5H, m, =CH + arom.)
18	0.04 (9H, s, $Si(CH_3)_3$); 0.62 (2H, m, $SiCH_2$); 1.93 (2H, m, CH_2); 4.18 (2H, t, *J* = 7.5, OCH_2); 5.07 (3H, s, N^+Me); 7.49-10.11 (6H, m, arom.)
19	-0.07 (3H, s, $SiCH_3$); 0.49 (6H, m, $SiCH_2$); 0.91 (6H, t, *J* = 6.5, CH_3); 1.33 (14H, br. s, CH_2); 2.33 (2H, m, 3-CH_2); 3.02 (2H, t, *J* = 6, 4-CH_2); 3.29 (2H, m, NCH_2); 3.51-4.04 (4H, m, OCH_2); 4.00 (3H, s, N^+Me); 4.60 (2H, m, 2-CH_2); 7.27-8.31 (4H, m, arom.)
20	0.04 (9H, s, $Si(CH_3)_3$); 0.48 (2H, m, $SiCH_2$); 1.51 (2H, m, CH_2); 3.16-3.51 (4H, m, 3,4-CH_2); 3.58 (3H, s, N^+Me); 3.83-4.34 (6H, m, NCH_2+OCH_2); 4.97 (2H, s, 1-CH_2); 7.00-7.50 (4H, m, arom.)
21	2.72-2.91 (6H, m, 3,4-CH_2+NCH_2); 3.22 (3H, s, OCH_3); 3.54 (2H, t, *J* = 6, OCH_2), 4.02 (3H, s, N^+Me); 5.02 (2H, s, 1-CH_2); 7.15-7.34 (4H, m, arom.)
23	0.01 (9H, s, $Si(CH_3)_3$); 0.21 (6H, s, $Si(CH_3)_2$); 0.42 (2H, t, *J* = 6.5, $SiCH_2$); 1.29 (2H, br. s, CH_2); 1.80 (2H, s, $SiCH_2N$); 2.22 (2H, t, *J* = 6, NCH_2); 2.44 (2H, m, OCH_2); 3.49 (2H, s, 1-CH_2); 3.90 (2H, m, OCH_2); 6.99-7.51 (4H, br. s, arom.)

The developed method of silicoalkylation of a hydroxyl group under conditions of phase-transfer catalysis was also used to obtain the 2-(trimethylsilylpropoxy)ethyl derivative of tetrahydroisoquinoline with a silicon atom in the ring (**23**) from N-(2-hydroxyethyl)-4,4-dimethyl-1,2,3,4-tetrahydro-4-silaisoquinoline (**22**) [22] and (3-chloropropyl)trimethylsilane.

Scheme 4



22 **23**

The neurotropic properties and the acute toxicity of the synthesized compounds have been investigated. The action of substances on the CNS was assessed according to indicators of the rotating rod, tube, and traction tests, characterizing the effect of compounds on the tone of the skeletal musculature and motor coordination, and also according to tests of rectal temperature, analgesia, hypoxic hypoxia, Phenamine hyperactivity, hexenal and ethanol narcosis, Corazole convulsions, electroshock, conditioned avoidance response and retrograde amnesia, and the Porsolt test.

The results of the study of neurotropic properties and acute toxicity of the synthesized compounds are given in Tables 3 and 4.

It follows from the data of Table 3 that the acute toxicity depends on the substituent in the 2-hydroxyethyl sidechain, and silicoalkylation contributes to a reduction of toxicity. In the series of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinolines **11-15** the toxicity falls on going from compound **15** containing no organosilicon substituent to a compound with trimethylsilyl- (**11**), heptyldimethylsilyl- (**13**), and diamylmethylsilylpropyl group (**12**) tenfold. Approximately the same rule became apparent on investigating derivatives of 1,2,3,4-tetrahydroquinoline **4-8**. The influence of the nature of the heterocycle may be noticed on comparing derivatives of 1,2,3,4-tetrahydroquinoline and 1,2,3,4-tetrahydroisoquinoline. The toxicity of the first was lower in some cases with analogous substituents at the nitrogen atom (see **6** and **13**, **8** and **15**). The

TABLE 3. Effect of Organosilicon Derivatives of 8-Hydroxyquinoline and N-(2-Hydroxyethyl)tetrahydro(sila, iso)quinolines on the Tone of Skeletal Musculature and Motor Coordination

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg					
		Test					
		rotating rod	tube	rectal temperature	narcosis	analgesia	traction
1	447	>500	>500	410	>500	258	>500
4	650	>500	>500	>500	>500	410	>500
5	>2500	>500	355	>500	>500	>500	346
6	2820	258	346	>400	>400	172	163
8	1030	355	355	355	>500	435	355
11	650	>500	355	>500	>500	>500	325
12	2820	325	355	355	>500	>500	325
13	2240	>500	410	447	>500	325	325
15	282	205	112	>250	>250	178	129
18	20.5	16.3	10.3	12.9	>20	8.9	14.1
19	65	56.4	51.5	51.5	>50	44.7	44.7
20	70.8	14.1	8.1	14.1	>50	8.9	16.3
21	65	44.7	35.5	27.4	>50	35.5	>50
23	815	410	325	355	>500	>500	325

TABLE 4. Neurotropic Activity of Organosilicon Derivatives of 8-Hydroxyquinoline and N-(2-Hydroxyethyl)-tetrahydro(sila, iso)quinolines

Compound	*M*±*m*, % control (100%)								
	Test								
	hypoxic hypoxia	phenamine hypothermia, °C (60 min)	phenamine hyperactivity, (60 min)	hexenal narcosis	ethanol narcosis	corazole spasms (clonic/tonic)	retrograde amnesia	training	Porsolt
1	133*	-1.3*	44.8*	162*	101	28.6*/113.9*	50	111.0±29.2	89.2*
4	—	-0.1	89.9	107.5	67.6*	113.5/155.5*	83.3	145.0±7.0	94.5
5	128.4*	-0.7	70.7	95.7	215.4	157.6*/232*	100*	135.1*±8.1	73.4*
6	123.6*	-1.3	75.0	98.6	147.4*	177.4*/234.2*	83.3*	130.0*±10.3	137.9*
8	83*	-2.6*	89.0	120.5	139*	137.4*/183.1*	33.4	71.2±12.2	185*
11	117.7	-0.7	69.5*	119.2	187.1*	155.9*/179*	83.3	128.7±11.1	69.3*
12	127.9*	-1.6	75.9*	119*	187.6*	117.6*/148.1*	50	62.3±25.9	83.3
13	114.2	-0.1	85.2	123*	115.7	132.6*/202*	33.3	53.3±21.7	125*
15	123.2	-0.9	91.0	135.4*	187*	141*/123	83.3	122.3±11.6	95.4
18	146*	-2.1*	31.4*	226.7*	95	142.6*/187*	100*	145.8*±5.7	116*
19	127*	-0.2	108.0	123.8	187.6	151.2*/200.3*	50	25.5±6.9	147*
20	138.7*	0.1	41*	136.9*	249.4*	180.7*/130.9*	100*	142.3*±7.7	85.6
21	114.2*	-0.7	166.4*	123.8*	112.5	—	—	—	–
23	91.8	-1.4*	83.0	121	215.7*	132.3*/158.3*	67	99.5±9.6	114.6

* Differences from control are statistically reliable at $P \leq 0.05$.

introduction of a silicon atom into the tetrahydroisoquinoline ring (**23**) also assists a reduction in the acute toxicity compared with the carbon analog **11**. As a result of quaternization at nitrogen (**18-21**) the acute toxicity of compounds **1**, **5**, **11**, and **15** is increased.

Depriming activity in the rotating rod, tube, and traction tests was expressed weakly for the synthesized compounds, and as a rule was displayed at doses close to lethal. However salts **18-20** of silicoalkylated derivatives of 8-hydroxyquinoline, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline possessed clearly expressed depriming activity and analgesic action.

In difference to compound **8**, containing no trialkylsilylalkyl substituent and reliably reducing the lifespan of mice under conditions of hypoxia by 17%, all the investigated silicoalkylated derivatives displayed antihypoxic properties and prolonged the life of mice under conditions of hypoxia by 15-46%. The most active antihypoxic agents were salts **18-21**.

Almost all of the synthesized compounds at a dose of 5 mg/kg are synergists of hexenal and ethanol, reliably extending their narcotic action by 20-127% and by 40-150% respectively. The most reliable extension of narcotic action (by 2.3 times for hexenal and 2.5 times for ethanol) on introducing an organosilicon substituent was noted in the case of the iodomethylates of trimethylsilylpropyl derivatives of 8-hydroxyquinoline **18** and 1,2,3,4-tetrahydroisoquinoline **20** respectively. Tetrahydrosilaisoquinoline **23** is a stronger agonist of ethanol compared with its carbon analog **11**.

The only compound displaying a reliable reduction of the duration of narcosis (by 32%, ethanol) was N-[-2-(3-trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline (**4**).

All the compounds studied possess antispasmodic action in corazole spasm (clonic and tonic) increasing their threshold by 18-81% in the tonic and by 14-134% in the clonic phase. In the clonic phase of this test compounds in which more bulky or long organosilicon substituents are present (**5**, **6**, **13**, and **15**) are stronger anticonvulsants. The greatest antispasmodic activity was possessed by the diaminomethyl- (**5**) and heptyldimethylsilylpropyl- (**6**) derivatives of 1,2,3,4-tetrahydroquinoline. The investigated substances did not display protective properties in maximal electroshock.

Almost all the investigated compounds act as amphetamine antagonists, reducing the locomotor activity caused by administration of amphetamine by 24-69%. The greatest antagonistic effect on interacting with amphetamine was observed for the trimethylsilylpropyl derivatives of 8-hydroxyquinoline **1** and 1,2,3,4-tetrahydroisoquinoline **11** and has a tendency to strengthen with additional alkylation of the nitrogen (compounds **18** and **20**). The only compound reliably strengthening the action of amphetamine (by 1.7 times, 66.4%) was compound **21**, containing no organosilicon substituent.

Study of the effect of the investigated substances on memory processes showed that the greatest activity was displayed by compounds **5**, **18**, and **20**, which at a dose of 5 mg/kg completely (100%) prevented retrograde amnesia.

Antistress activity in the Porsolt test is a reliable characteristic of the majority of the investigated compounds (**6**, **8**, **13**, **18**, **19**, **23**), with the exception of **1**, **5**, and **11**. The introduction of a silicon atom into the tetrahydroisoquinoline ring (compound **23**) shows up positively on the display of sedative action compared with its carbon analog **11**.

As a result of the investigations carried out a dominant display is shown of a definite type of neurotropic properties depending on the nature of the heterocyclic base, and also on the presence of a silicon atom in the molecule. Tetrahydro-isoquinolines possess a tranquilizing/sedative action, tetrahydrosilaisoquinoline derivatives an antihypnotic action (reduction in the duration of sleep caused by the action of ethanol). Tetrahydroquinolines display an antispasmodic effect (pentylene-tetrazole-induced spasm test).

The data obtained show the expediency of a selected rational approach to the construction of new neurotropic substances among silicon-containing heterocyclic derivatives.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Bruker WH 90/DS (90 MHz) spectrometer in $CDCl_3$, internal standard was TMS, ^{29}Si NMR spectra were taken on a Mercury 200 Varian (40 MHz) spectrometer. Mass spectra were recorded on a HP 6890 GC-MS instrument. GLC analysis was carried out on a Chrom-42 chromatograph with a flame-ionization detector and a glass column (1.2 m x 3 mm) with 5% OV-17 on Chromosorb W-AW (60-80 mesh). Chromatographic separation of reaction products was carried out on an Acros column (carrier was silica gel 0.060-0.200 mm, pore diameter 4 nm). Elemental analysis was carried out with the aid of a Carlo Erba 1108 analyzer.

N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroquinoline (2) and N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (9) were synthesized by the procedure of [18].

N-(2-Hydroxyethyl)-4,4-dimethyl-1,2,3,4-tetrahydro-4-silaisoquinoline (22) was synthesized by the procedure of [22].

Salts of Compounds 18-21 were obtained by the procedure described in [23].

Silicoalkylation of 8-Hydroxyquinoline, N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroquinoline, N-(2-Hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline, and N-(2-Hydroxyethyl)-4,4-dimethyl-1,2,3,4-tetrahydro-4-silaisoquinoline Under Conditions of Phase-transfer Catalysis (General Procedure). A mixture of the heterocyclic 2-amino alcohol (1 equiv., 28 mmol), potassium hydroxide (5 equiv., 140 mmol), potassium iodide (2 equiv., 56 mmol), trialkylchloroalkylsilane (1.05 equiv., 29 mmol), and Aliquat^{R} 336 (0.05 equiv., 1.4 mmol) in dry benzene (25 ml) was stirred at the boiling point of the solvent for 10-14 h. The solid was then filtered off, and the solvent removed from the filtrate. The product was isolated by distillation in vacuum or by separation on a chromatographic column.

8-(3-Trimethylsilylpropoxy)quinoline (1) was isolated in 19% yield, bp 175°C (14 mm Hg). Found, %: C 68.72; H 9.22; N 5.23. $C_{15}H_{25}NOSi$. Calculated, %: C 68.38; H 9.56; N 5.32.

N-[2-(2-Hydroxyethoxy)ethyl]-1,2,3,4-tetrahydroquinoline (3) was isolated in 4% yield; bp 167-168°C (2 mm Hg). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}): 221 (18) $[M]^+$, 158 (4) $[M\text{-}OCH_2CH_2OH]^+$, 146 (100) $[M\text{-}CH_2OCH_2CH_2OH]^+$. Found, %: C 70.97; H 8.94; N 6.44. $C_{13}H_{19}NO$. Calculated, %: C 70.56; H 8.65; N 6.33.

N-[2-(3-Trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline (4) was isolated in 32% yield; bp 164°C (3 mm Hg). Found, %: C 70.01; H 10.03; N 4.90. $C_{17}H_{29}NOSi$. Calculated, %: C 70.10; H 9.97; N 4.81.

N-[2-(3-Diamylmethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline (5) was isolated in 43% yield; bp 128 °C (3 mm Hg). Found, %: C 74.27; H 11.34; N 3.52. $C_{25}H_{45}NOSi$. Calculated, %: C 74.38; H 11.23; N 3.47.

N-[2-(3-Heptyldimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline (6) was isolated in 37% yield; bp 178-180°C (3 mm Hg). Found, %: C 73.29; H 11.24; N 3.82. $C_{23}H_{41}NOSi$. Calculated, %: C 73.54; H 11.00; N 3.73.

N-[2-(Trimethylsilylmethoxy)ethyl]-1,2,3,4-tetrahydroquinoline (7) was isolated in 4% yield by chromatographic separation on a column. Eluent was CH_2Cl_2. The content of main substance was 86% according to mass spectrometric data. Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 263 (10) $[M]^+$, 248 (1) $[M\text{-}Me]^+$, 190 (1) $[M\text{-}SiMe_3]^+$, 160 (4) $[M\text{-}OCH_2SiMe_3]^+$, 146 (100) $[M\text{-}CH_2OCH_2SiMe_3]^+$, 73 (11) $[M\text{-}ArCH_2CH_2CH_2NCH_2CH_2OCH_2]^+$.

N-(2-Methoxyethyl)-1,2,3,4-tetrahydroquinoline (8) was obtained by two procedures.

A. (Using Me_3SiCH_2Cl). Isolated in 41% yield by chromatographic separation of the reaction products on a column, eluent was ethyl acetate–hexane, 1:10.

B. (Using Et_3SiCH_2Cl). Isolated in 42% yield; bp 135-137°C (4 mm Hg). Content of main substance was 98.2% according to HPLC data (Symmetry C_{18}, 4.6 × 150 mm, system: 70% acetonitrile + 30% [0.1% H_3PO_4 + H_2O], pH 2.5), UV detector (λ = 220 nm). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 191 (17) $[M]^+$, 146 (100) $[M\text{-}CH_2OCH_3]^+$. Found, %: C 75.43; H 9.04; N 7.25. $C_{12}H_{17}NO$. Calculated, %: C 75.35; H 8.96; N 7.32.

N-[2-(2-Hydroxyethoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (10) was isolated in 14% yield; bp 194-195°C (3 mm Hg). Found, %: C 70.64; H 8.44; N 6.27. $C_{13}H_{19}NO$. Calculated, %: C 70.56; H 8.65; N 6.33.

N-[2-(3-Trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (11) was isolated in 66% yield; bp 179-181°C (4 mm Hg). ^{29}Si NMR spectrum ($CDCl_3$), δ, ppm: -0.70. Found, %: C 70.15; H 10.09; N 4.98. $C_{17}H_{29}NOSi$. Calculated, %: C 70.10; H 9.97; N 4.81.

N-[2-(3-Diamylmethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (12) was isolated in 58% yield; bp 225-227°C (3 mm Hg). Found, %: C 74.92; H 11.66; N 3.79. $C_{25}H_{45}NOSi$. Calculated, %: C 74.38; H 11.23; N 3.47.

N-[2-(3-Heptyldimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (13) was isolated in 72% yield; bp 200-202°C (3 mm Hg). Found, %: C 73.67; H 10.56; N 3.96. $C_{23}H_{41}NOSi$. Calculated, %: C 73.54; H 11.00; N 3.73.

N-[2-(3-Trimethylsilylmethoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline (14) was detected in the reaction in an analytical amount (0.4%). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}): 263 (1) $[M]^+$, 248 (2) $[M\text{-}Me]^+$, 160 (6) $[M\text{-}OCH_2SiMe_3]^+$, 146 (100) $[M\text{-}CH_2OCH_2SiMe_3]^+$, 132 (10) $[M\text{-}CH_2CH_2OCH_2SiMe_3]^+$, 73 (12) $[M\text{-}ArCH_2CH_2CH_2NCH_2CH_2OCH_2]^+$.

N-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinoline (15) was isolated in 48% yield; bp 126-128°C (3 mm Hg). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 191 (15) $[M]^+$, 146 (100) $[M\text{-}CH_2OCH_3]^+$. Found, %: C 75.10; H 9.07; N 7.52. $C_{12}H_{17}NO$. Calculated, %: C 75.35; H 8.96; N 7.32.

N-(2-Acetoxyethyl)-1,2,3,4-tetrahydroisoquinoline (16). A mixture of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (2.0 g, 11.3 mmol) and metallic sodium (0.14 g, 6.2 mmol) in dry benzene (4 ml) was heated with stirring until complete disappearance of sodium. The mixture was diluted with benzene (10 ml), cooled to +5°C, methyl iodide (0.81 g, 5.7 mmol) was added, and stirring continued at room temperature for 2 h. The solid was then filtered off, the solvent was removed from the filtrate, and the residue was chromatographed on silica gel, eluent was ethyl acetate. Two products were isolated, one of which (56% yield calculated on methyl iodide), according to data of ^1H NMR and chromato-mass spectrometry, was identical to compound **15**. Product **16** was isolated in 10% yield (calculated on the initial hydroxyethyltetrahydroisoquinoline). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}, %): 218 (1) $[M\text{-}H]^+$, 176 (1) $[M\text{-}COCH_3]^+$, 159 (10) $[M\text{-}OCOCH_3\text{-}H]^+$, 146 (100) $[M\text{-}CH_2OCOCH_3]^+$, 132 $[M\text{-}CH_2CH_2OCOCH_3]^+$. Found, %: C 71.55; H 7.81; N 6.08. $C_{13}H_{17}NO_2$. Calculated, %: C 71.23; H 7.76; N 6.39

[N-(2-Methoxyethyl)-N-methyl]-2-vinylbenzylamine (17). A mixture of N-(2-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (0.60 g, 3.4 mmol), potassium hydroxide (0.95 g, 17.0 mmol), methyl iodide (0.52 g, 3.7 mmol), and Aliquat^R 336 (0.07 g, 0.17 mmol) in benzene (1.5 ml) was heated with stirring for 3.5 h. The solid was then filtered off, the solvent was removed from the filtrate, and the residue chromatographed on silica gel using ethyl acetate–methylene chloride, 1:1, as eluent. The product was isolated in 32% yield (calculated on methyl iodide). Mass spectrum (EI, 70 eV), *m/z* (I_{rel}): 205 (1) $[M]^+$, 174 (1) $[M\text{-}OCH_3]^+$, 160 (54) $[M\text{-}CH_3OCH_2]^+$, 147 (7) $[M\text{-}OCH_3\text{-}CH{=}CH_2]^+$, 130 (2), 117 (100) $[M\text{-}CH_3NCH_2CH_2OCH_3]^+$, 102 (4), 91 (26). Found, %: C 75.57; H 9.44; N 6.72. $C_{13}H_{19}NO$. Calculated, %: C 76.06; H 9.33; N 6.82.

8-(3-Trimethylsilylpropoxy)quinoline Iodomethylate (18) was isolated in 47% yield; mp 105-107°C (ethanol–diethyl ether). Found, %: C 47.56; H 6.02; N 3.45. $C_{16}H_{24}INOSi$. Calculated, %: C 47.88; H 5.98; N 3.49.

N-[2-(3-Diamylmethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroquinoline Iodomethylate (19) was isolated in 59% yield; mp 75-76°C (ethanol–diethyl ether). Found, %: C 56.92; H 8.65; N 2.71. $C_{26}H_{48}INOSi$. Calculated, %: C 57.17; H 8.80; N 2.57.

N-[2-(3-Trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydroisoquinoline Iodomethylate (20) was isolated in 52% yield; mp 80-82°C (ethanol–diethyl ether). Found, %: C 49.83; H 7.45; N 3.27. $C_{18}H_{32}INOSi$. Calculated, %: C 49.87; H 7.44; N 3.23.

N-(2-Methoxyethyl)-1,2,3,4-tetrahydroisoquinoline Iodomethylate (21) was isolated in 58% yield; mp 135-137°C (ethanol–diethyl ether). Found, %: C 46.63; H 6.01; N 4.19. $C_{13}H_{20}INO$. Calculated, %: C 46.82; H 6.00; N 4.20.

4,4-Dimethyl-N-[2-(3-trimethylsilylpropoxy)ethyl]-1,2,3,4-tetrahydro-4-silaisoquinoline (23) was isolated in 21% yield; bp 100-101°C (4 mm Hg). Found, %: C 64.53; H 10.00; N 4.13. $C_{18}H_{33}NOSi_2$. Calculated, %: C 64.28; H 9.82; N 4.17.

BIOLOGICAL EXPERIMENTAL

Neurotropic activity was studied in BALB/c strain mice and in random-bred male rats. An oil solution of the substance being investigated was administered intraperitoneally 30 min before carrying out the experiment. Comparative assessment of the action of the substance being investigated at a dose of 5 mg/kg was carried out on groups of 6 animals on the indicators of hypoxia, hexenal and ethanol narcosis, amphetamine hyperactivity, corazole spasm, training, and the Porsolt test.

The action of a substance on the central nervous system was assessed 1) by its effect on motor coordination and muscle tone (rotating rod, pipe, hanging on a beam); 2) on body temperature; 3) on analgesic effect (hot plate test); 4) on antispasmodic activity (maximal electroshock test, alternating current 50 mA, 50 imp./sec at stimulation time 0.2 sec, and corazole spasms caused by an intravenous titration with 1% corazole solution at 0.01 ml/sec); 5) on the duration of hexenal (0.4% hexenal solution at 70 mg/kg intravenously) and ethanol narcosis (4 g/kg intraperitoneally); 6) by the duration of life under conditions of hypoxic hypoxia caused by placing mice (singly) in a hermetically sealed chamber of volume 220 cm^3 without absorption of carbon dioxide gas; 7) by locomotor activity and body temperature on joint action with amphetamine (0.4% amphetamine solution subcutaneously 10 mg/kg); 8) by the unavoidable stress situation (Porsolt test) and the action on memory processes and retrograde amnesia.

The acute toxicity on intraperitoneal injection was also determined and the mean lethal dose (LD_{50}, mg/kg) established.

The experimental data were processed statistically. The express method [24] was used for calculating the mean effective (ED_{50}) and mean lethal (LD_{50}) doses. For assessing the mean duration of narcotic action of hexenal and alcohol, amphetamine hyperactivity, hypoxia, protective action on corazole spasm, the arithmetic mean values and their standard errors ($M \pm m$) in comparison with the appropriate control data were calculated. Assessment of the significance of the differences between the mean values was carried out on the basis of the Student criterion. Differences were regarded as significant at a level of probability $P \leq 0.05$.

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