SYNTHESIS AND ANTIBLASTIC ACTIVITY OF ORGANOSILICON DERIVATIVES OF QUINOLINE, ISOQUINOLINE, AND N-METHYLPIPERAZINE*

É. Lukevits, T. V. Lapina,
I. D. Segal, I. S. Augustane,
and V. N. Verovskii

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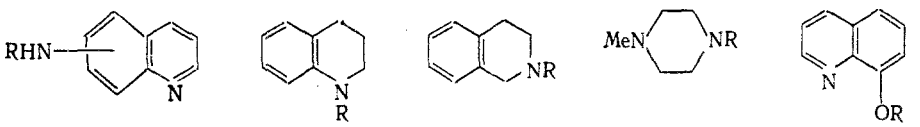
It has been shown that 4-[3-(1-silatranyl)propylamino]quinolines [1, 2], and 3-(triethylsilyl)- and 3-(1-silatranyl)propylamides of quinolinecarboxylic acids [3] possess some antiblastic activity. Continuing these studies, we have synthesized the N-substituted amides of γ-trialkylsilylbutyric acids with aminoquinolines (Ia-f), with 1,2,3,4-tetrahydroquinoline (IIa, b), with 1,2,3,4-tetrahydroisoquinoline (IIIa, b), and with N-methylpiperazine (Va-c), the ester of 8-hydroxyquinoline with γ-trimethylsilylbutyric acid (VI), N-trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline (IV), and the 4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinolines (VIIa-c), and examined their antiblastic activity.



Ia, f IIa, b IIIa, b, IV Va-c VI

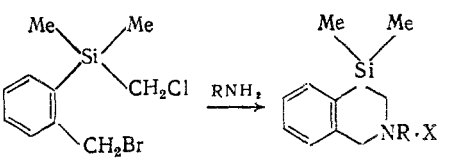
R = $CO(CH_2)_3SiMe_3$ (Ia at $C_{(3)}$, Ib at $C_{(4)}$, Ic at $C_{(6)}$ If at $C_{(8)}$, IIa, IIIa, Va, VI); $CO(CH_2)_3SiMeEt_2$ (Id at $C_{(6)}$, IIb, IIIb, Vb); $CO(CH_2)_3SiEt_3$ (Id at $C_{(6)}$, Vc); CH_2SiMe_3 (IV); Ia-f, IV, VI — hydrochlorides.

Heating γ-trialkylsilylbutyryl chlorides with aminoquinolines in heptane gave the amides (Ia-f), which were isolated as their hydrochlorides.

1,2,3,4-Tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, and N-methylpiperazine were more reactive, reacting with γ-trialkylsilylbutyryl chlorides in an inert solvent (ether or hexane) at 0 to −10°C to give the amides (IIa, b), (IIIa, b), and (Va, b).

The reaction between 8-hydroxyquinoline and γ-trimethylsilylbutyryl chloride in ether in the presence of Et_3N gave the ester, which was converted into its hydrochloride (VI).

N-trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline (IV) was obtained by reacting trimethylchloromethylsilane with 1,2,3,4-tetrahydroisoquinoline in DMF, and isolated as its hydrochloride.



VIIa-c

a: R = Am, X = HCl; b: R = CH_2CH_2OCOPh, X = HCl; c; R = EtCl, X = MeJ.

The 4-sila-1,2,3,4-tetrahydroisoquinolines were synthesized by reacting dimethylchloromethyl(2-bromomethylphenyl)silane with an excess of the primary amine, then converted into the hydrochlorides (VIIa, b) or methiodide (VIIc).

Examination for antitumor activity was carried out in B16 cell culture, and in mice with grafted P388 lympholeukemia and Lewis lung cancer (LLC). The first test was used for a preliminary selection (prescreening) of potential antitumor drugs in a range of cytotoxic agents. All the highly cytotoxic compounds with $EC_{50} \leqslant 3.2$ mg/kg were subjected to further screening in two types of mouse tumor.

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TABLE 1. Organosilicon Derivatives of Quinoline and 1,2,3,4-Tetrahydroisoquinoline

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %		
			C	H	N		C	H	N
Ia	65	194—5	59,3	7,4	9,0	$C_{16}H_{23}ClN_2OSi$	59,6	7,2	8,7
Ib	60	212—4	59,7	7,4	9,0	$C_{16}H_{23}ClN_2OSi$	59,6	7,2	8,7
Ic	62	210—2	59,5	6,9	9,2	$C_{16}H_{23}ClN_2OSi$	59,6	7,2	8,7
Id	53	188—90	61,6	8,1	8,0	$C_{18}H_{27}ClN_2OSi$	61,6	7,8	7,5
Ie	58	174—6	62,9	7,7	8,1	$C_{19}H_{29}ClN_2OSi$	62,5	8,0	7,7
If	60	110—1	59,1	7,3	9,1	$C_{16}H_{23}ClN_2OSi$	59,6	7,2	8,7
IV	34	178—9	60,9	8,8	5,5	$C_{13}H_{22}ClNSi$	61,0	8,7	5,5
VI	30	96—8	59,5	7,0	4,1	$C_{16}H_{22}ClNO_2Si$	59,3	6,8	4,3
VIIa	38	177—8	63,9	9,6	5,0	$C_{15}H_{26}ClNSi$	63,5	9,2	4,9
VIIb	39	190—3	63,0	6,2	3,8	$C_{19}H_{24}ClNO_2Si$	63,0	6,7	3,9
VIIc	15	217—8	40,9	5,6	3,7	$C_{13}H_{21}ClINSiJ$	40,9	5,5	3,6

TABLE 2. Organosilicon Amides of 1,2,3,4-Tetrahydroquinoline, 1,2,3,4-Tetrahydroisoquinoline, and N-Methylpiperazine

Compound	Yield, %	bp, °C (mm)	n_D^{20}	Purity by GLC, %	Found, %			Empirical formula	Calc., %		
					C	H	N		C	H	N
IIa	80	152—4/2	1,523	97,8	70,19	9,50	4,78	$C_{16}H_{25}NOSi$	69,78	9,15	5,08
IIb	69	155—7/2	1,517	86,6	72,15	10,45	4,01	$C_{18}H_{29}NOSi$	71,23	9,63	4,61
IIIa	79	171—3/2	1,526	95,8	69,26	8,78	5,46	$C_{16}H_{25}NOSi$	69,78	9,15	5,08
IIIb	70	174—86/2	1,522	96,7	70,81	9,91	5,02	$C_{18}H_{29}NOSi$	71,23	9,63	4,61
Va	87	112—4/2	1,470	97,1	59,83	10,68	11,75	$C_{12}H_{26}N_2OSi$	59,45	10,81	11,56
Vb	68	134—6/2	1,481	96,5	62,61	11,49	10,03	$C_{14}H_{30}N_2OSi$	62,16	11,18	10,38
Vc	81	168—70/2	1,488	99,1	63,80	11,77	9,73	$C_{16}H_{32}N_2OSi$	63,32	11,30	9,87

In the P388 test, the compounds were introduced on the second and ninth days to assess antitumor activity, corresponding to $\geq$1.0 log death of the tumor cells. In the LLC test, a highly-sensitive version of the grafted tumor (beneath the perirenal fat) was employed, antitumor activity in the range 0.1-1.0 log death of tumor cells being observed. The test results for cytotoxicity and antitumor activity are shown in Table 3. Most of the compounds displayed high cytotoxicity towards B16 cells, only (IV) and (VII) being of low toxicity (EC_{50} 10-180 μg/ml). With P388 lympholeukemia, no antitumor activity was found in the test compounds. In the case of LLC solid tumors, (Ic) and (IIIa) had significant antitumor activity.

Increasing the size of the alkyl group attached to silicon in most cases reduced activity, and the tetrahydroisoquinoline derivatives were more active than the tetrahydroquinolines. Examination of the maximum tolerated doses (MTD) shows that the tetrahydroquinoline and tetrahydroisoquinoline amides are considerable less toxic than the other compounds.

EXPERIMENTAL CHEMISTRY

PMR spectra were obtained on a Brucker WH-90/DS (West Germany) in $CDCl_3$ or DMSO-d_6 (internal standard CH or TMS), and IR spectra on a Perkin-Elmer 580 B (Great Britain) with solid samples in Vaseline oil.

The γ-trialkylsilylbutyramides (Ia-f), (IIa, b), (IIIa,b) and (Va-c), the 8-hydroxyquinoline ester of γ-trimethylsilylbutyric acid, and its hydrochloride (VI) had the following proton chemical shifts (δ, ppm): —0.07—0.06 (Si — CH_3), 0.33—0.93 (Si — CH_2 — C), 0.89—2.13 (C — CH_2 — C), 6.95—9.46 (Ar).

N-trimethylsilylmethyl-1,2,3,4-tetrahydroquinoline and its hydrochloride (IV) gave the following proton shifts (δ, ppm): 0.12, 0.36 (Si — CH_3), 1.68, 2.12 (Si — CH_2 — N), 3.47—3.89, 4.45-4.87 (Ar —CH_2 — N), 6.70-7.34, 6.92-7.44 (C_6H_4).

The proton chemical shifts for the silatetrahydroisoquinolines, their hydrochlorides (VIIa, b) and methiodide (VIIc) (δ, ppm) were: 0.24-0.51 (Si — CH_3), 3.44-4.71 (Ar — CH_2 — N), 7.13-7.87 (C_6H_4). The proton shifts δ in the groupings Si—CH_2—N and N—CH_2—C overlapped, and lay in the region 2.09-4.37 ppm.

In the IR spectra of the carbonyl compounds $\nu_{C=O}$ absorption was seen at 1650-1765 cm^{-1}.

TABLE 3. Antiblastic Activity of Organosilicon Derivatives of Quinoline, Isoquinoline, and N-Methylpiperazine

Compound	B16, EC_5, μg/ml	P388		LLC	
		MTD, mg/kg	T/C, %	daily dose, mg/kg	T/C, %
Ia	5,6	100	104	32	105
Ib	3,2	10	101	3,2	100
Ic	3,2	320	81	100	68
Id	3,2	320	82	100	92
Ie	3,2	320	87	100	100
If	3,2	320	110	100	100
IIa	5,6	1000	115	320	98
IIb	3,2	1000	103	320	93
IIIa	3,2	1000	116	320	53
IIIb	3,2	1000	91	560	88
Va	32	100	88	32	84
Vb	10	100	90	32	98
Vc	10	100	83	56	87
VI	3.2	100	98	32	96

3-[4-(Trimethylsilyl)butyrylamino]quinoline Hydrochloride (Ia). γ-Trimethylsilylbutyryl chloride (1.78 g, 10 mmole) in 10 ml of dry heptane was added dropwise to 2.16 g (15 mmole) of 3-aminoquinoline in 20 ml of dry heptane, with vigorous stirring. The mixture was boiled for 2 h, and the bright yellow solid which separated was filtered off and washed well with dry ether. The ether solution was passed through an alumina column, then ether saturated with dry HCl was added dropwise with care. The solid which separated was recrystallized from a mixture of absolute alcohol and ether (1:1) to give 2.1 g (65.2%) of (Ia). Compounds (Ib-f) were obtained similarly. The physicochemical constants and elemental analyses of the compounds are given in Table 1.

N-[4-(Trimethylsilyl(butyryl]-1,2,3,4-tetrahydroquinoline (IIa). γ-Trimethylsilylbutyryl chloride (1.78 g, 10 mmole) in 10 ml of dry ether was added dropwise to 1.33 g (10 mmole) of 1,2,3,4-tetrahydroquinoline and 1.01 g (10 mmole) of triethylamine in 20 ml of dry ether at −5 to −10°C with vigorous stirring. The mixture was then stirred for one hour at room temperature, and the solid which separated filtered off. The ether solution was treated with a small amount of HCl in ether to remove unreacted quinoline and Et_3N, filtered through alumina, the ether removed, and the residue distilled in vacuo to give 2.2 g (80%) of (IIa). Compounds (IIb) and (IIIa, b) were obtained similarly (Table 2).

N-Trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline Hydrochloride (IV). A mixture of 10 g (81 mmole) of 1,2,3,4-tetrahydroquinoline, 9.9 g (81 mmole) of trimethylchlorosilane, and 23 ml of triethylamine in 30 ml of DMF was heated at 110-120°C for 5 h. The solid which separated was filtered off, and the excess triethylamine and solvent removed from the filtrate. Vacuum distillation of the residue gave N-trimethylsilylmethyl-1,2,3,4-tetrahydroisoquinoline, bp 119-121°C (5 mm). This was dissolved in ether, and treated with ether saturated with dry HCl. The precipitate of (IV) (6.1 g, 34%) was filtered off.

N-Methyl-N'[4-(trimethylsilyl)butyryl]piperazine (Va). γ-Trimethylsilylbutyryl chloride (1.78 g, 10 mmole) in 10 ml of dry hexane was added dropwise to 2 g (20 mmole) of N-methylpiperazine in 20 ml of dry hexane at 0°C with vigorous stirring. Stirring was continued at room temperature for 5 h, then the solid which had separated was filtered off, the ether removed, and the residue distilled in vacuo to give 2.1 g (87%) of (Va). Compounds (Vb) and (Vc) were obtained similarly (Table 2).

8-[4-(Trimethylsilyl)butyryl]oxyquinoline Hydrochloride (VI). To 1.45 g (10 mmole) of 8-hydroxyquinoline and 1.01 g (10 mmole) of triethylamine in 20 ml of dry ether was added dropwise 1.78 g (10 mmole) of γ-trimethylsilylbutyryl chloride in 10 ml of dry ether at room temperature, with vigorous stirring. The mixture was boiled for 5 h. The solid which separated was filtered off, and the ethereal solution passed through a column of alumina. Removal of the ether and distillation in vacuo gave 8-[4-(trimethylsilyl)butryl]oxyquinoline, bp 100-105°C)1 mm), n_D^{20} 1.535, purity (GC) 98%. This was dissolved in ether, and treated dropwise with ether saturated with dry HCl, to give platelets of (VI) (1.8 g, 81%).

2-Pentyl-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline Hydrochloride (VIIa). To 1.13 g (130 mmole) of pentylamine was added dropwise with stirring 9.16 g (33 mmole) of dimethylchloromethyl-(2-bromomethylphenyl)silane. When evolution of heat was complete, the

mixture was heated for 2 h, then treated with 50 ml of 10% sodium hydroxide, extracted with ether, and dried over magnesium sulfate. The residue after removal of the ether and excess pentylamine was distilled in vacuo at 97-100°C (5 mm), and dissolved in ether. The ether solution was treated with ether saturated with dry HCl to give 3.5 g (38%) of (VIIa), which was recrystallized from a mixture of absolute alcohol and ether (Table 1).

2-[2-(1-Benzoyloxyethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline (VIIb) Hydrochloride. To 19.52 g (320 mmole) of 2-aminoethanol was added dropwise with vigorous stirring 20.54 g (37 mmole) of dimethylchloromethyl-(2-bromomethylphenyl)silane at such a rate that the temperature of the mixture did not exceed 80°C. Stirring was continued until the temperature fell to ambient, then the mixture was treated with 50 ml of 10% sodium hydroxide, extracted with ether, and dried over magnesium sulfate. The solvent was removed, and the residue vacuum distilled to give 8.96 g (54%) of 2-[2-(1-hydroxyethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline, bp 121-123°C (2 mm). To a mixture of 3.33 g (15 mmole) of this compound, 5 ml of triethylamine, and 25 ml of ether was added dropwise with stirring 2.4 g (17 mmole) of benzoyl chloride. After heating for 1 h, the mixture was filtered, and the filtrate washed with sodium carbonate solution and dried over magnesium sulfate. The residue was treated with 20% sodium hydroxide, extracted with ether, and dried over magnesium sulfate. The ether solutions were combined, the solvent removed, and the residue distilled in vacuo to give 3.6 g of 2-[2-(1-benzoyloxyethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline, bp 175-176°C (0.2 mm). This material was dissolved in ether, and treated dropwise with cooling with a solution of dry HCl in ether, to give 2.1 g (38.7%) of (VIIb), which was recrystallized from a mixture of absolute alcohol and ether.

2-[2-(1-Chloroethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline Methiodide (VIIc). To a solution of 3.5 ml of thionyl chloride in 5 ml of chloroform was added dropwise at 35-40°C 4.36 g of 2-[2-(1-hydroxyethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline in 6 ml of chloroform. The mixture was held at this temperature for 4 h, then excess thionyl chloride and solvent were removed under reduced pressure. The residue was washed with dry ether, and recrystallized from a mixture of ether and absolute alcohol to give 2.15 g of 2-[2-(1-chloroethyl)]-4,4-dimethyl-4-sila-1,2,3,4-tetrahydroisoquinoline hydrochloride. To a mixture of this compound with 25 ml of distilled water and 15 ml of ether was added dropwise with vigorous stirring and cooling 15 ml of 7% KOH. The ether layer was separated, and the aqueous layer extracted with ether. The combined ether extracts were dried over magnesium sulfate, concentrated to 10-15 ml, and 1.5 ml of MeI added dropwise. The mixture was heated on the water bath for 4-5 h, to give 1.14 g (15%) of (VIIc).

EXPERIMENTAL (PHARMACOLOGY)

Melanoma B16 cells were cultured at 37°C in an atmosphere of 10% CO_2 in complete Dulbecco medium (CDM) containing 25 ml of HEPES buffer, 10% fetal serum, and the usual mixture of streptomycin, penicillin, and Fungizone (Gibco). In the cytotoxicity test, the first five passages of B16 cells (obtained from tumor material of the melanoma strain) were used. The cytotoxicity test was carried out in 96-cell flat-bottomed plates (Linbro) in 300 ml of CDM. Into the cells were introduced $5 \cdot 10^3$-$10 \cdot 10^3$ B16 cells, and on the following day the compounds were added in tenfold dilutions, in the concentration range 3.2-320 μg/ml. After four days, the numbers of cells in the cells were determined by the microfluorimetric DNA method, using Hoechst N3442 dye (Calbiochem). The B16 cells were fixed in 70% ethanol, and lysed in 0.5 M sodium hydroxide 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 Hoechst dye in a final concentration of 0.1 μg/ml. In fluorimetry, the excitation (360 μm) and emission (460 μm) wavelengths were used.

The cytotoxicity of the compounds was assessed by the standard method as the concentration (in μg/ml) inhibiting the growth of the cells by 50% (EC_{50}). The calculation and analysis of the EC_{50} by statistical (0.25 log) and functional (1.0 log) ranking of cytotoxicity on a logarithmic scale of concentrations were carried out by linear regression on an Apple IIe computer [5]. The minimum criteria for high, moderate, and low cytotoxicity in B16 cell culture were 3.2, 32, and 320 μg/ml.

The antitumor activity of the compounds was determined in P388 lympholeukemia and Lewis lung carcinoma (LLC) in mice.

Lympholeukemia P388 was inoculated intraperitoneally (i/p) to male VDG hybrids (weighing 18-22 g) in amounts of 10^6 cells per mouse. The compounds were administered i/p on the second and ninth days in doses increasing on a logarithmic scale by 0.5 log until toxicity appeared.

LLC was inoculated beneath the perirenal fat to female VDG hybrids (weighing 20-23 g) in 2 microfragments weighing 1-2 mg, using a stereomicroscope and microsurgical technique. The compounds were administered i/p on the third, fourth, and fifth days at the MTD, amounting to 1/3-1/2 the daily MTD for lympholeukemia P388. The numbers of mice in the test groups were three in the first test and five in the repeats.

Antitumor activity was assessed by the mean mass of the tumors on the sixth day in the LLC test, or the mean lifespan in the P388 test, expressed as the test/control (t/c) ratio as a percentage. The statistical criteria for activity ($P < 0.05$) (t/c) were 75 and 120% in the LLC and P388 tests respectively. The statistical criterion for toxicity (t/c) in the P388 test was 80%.

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SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF NEW SUBSTITUTED GUANIDINES AND 2-AMINO-2-IMIDAZOLINES

R. G. Glushkov, L. A. Nikolaeva, L. N. Dronova, O. V. Kozlova, B. A. Medvedev, and M. D. Mashkovskii

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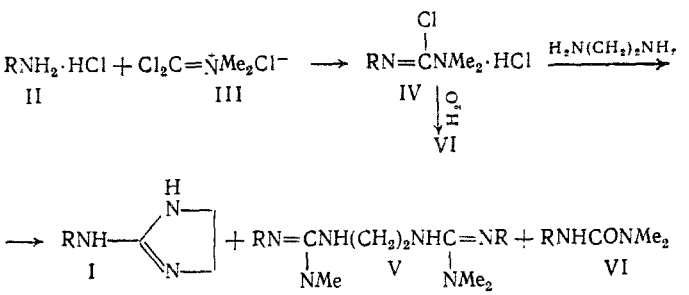
In continuation of our search for hypotensive agents [2] among the structural analogs of clofeline [1], we carried out the synthesis of new derivatives of 2-amino-2-imidazoline (I) and substituted guanidines (V, VII) containing lipophilic groups in their structure, such as p-cyclohexylphenyl and p-isobutylphenyl fragments, and studied their pharmacological activity.

The N-substituted 2-amino-2-imidazolines (Ia-c) were synthesized by a previously developed method [1] consisting in the reaction of the corresponding primary amine hydrochlorides (IIa-c) with N,N-dimethyl-N-dichloromethyleneimmonium chloride (III) [5, 6], followed by the reaction of the hydrochlorides of N-substituted N',N'-dimethyl-C-chloroformamidines (IVa-c) obtained with ethylenediamine in an acetonitrile medium.



I, II, IV—VI: a — R = p-cyclohexylphenyl, b — R = isobutylphenyl; c — R = 2-(p-isobutylphenyl)propyl.

Examination of the reaction of IVa, b with ethylenediamine showed that the process proceeds with the formation of a mixture of products, from which imidazolines Ia, b, bisguanidines

S. Ordzhonikidze All-Union Scientific Research Chemical Pharmaceutical Institute, Moscow.

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