arterial pressure, the effects of (IIa) and (IIIa) being the greatest. All the compounds reduced the depressor effect, the most active compounds in this respect being (IIa) and (IIIa). The compounds showed some β-adrenoblocking ((IIc) and (IIIb)) and antihistaminic (IIb) effects.

LITERATURE CITED

1. R. Tacke and R. Niedner, Z. Naturforsch., 33B, 412 (1978).
2. R. Tacke and U. Wannagat, Top. Curr. Chem., 84, 68 (1979).

NITROGENOUS ORGANOSILICON COMPOUNDS.

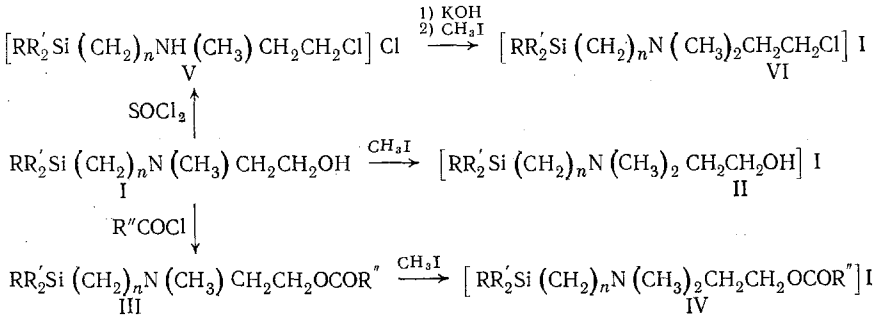
CX. SYNTHESIS AND PHARMACOLOGICAL STUDY OF ORGANOSILICON AMINOALCOHOLS AND THEIR DERIVATIVES

É. Lukevits, M. M. Veveris, Z. A. Atare, I. D. Segal, L. N. Khokhlova, and A. A. Kimenis

UDC 615.216.5'217.4:547.245'238

In continuation of studies of the biological activity of organosilicon derivatives of aminoalcohols [1, 2], we have synthesized some new organosilicon derivatives of choline, acetylcholine, and "chlorocholine," and studied their pharamacology.

The organosilicon compounds (Ic-f) were synthesized from trialkyl(chloroalkyl)silanes and N-methylaminoethanol in the presence of triethylamine, in butanol solution. The methiodides (IId-f), (IVh-k, m, n), (Vc, e, f), and (VIc, e, f) were obtained by treating trialkyl(2-hydroxyethylaminoalkyl)silanes and all the intermediate products of the reaction of the latter with thionyl chloride and acyl halides, with methyl iodide. These reactions may be shown as follows:



a: $n = 1$, $R = R' = CH_3$; b: $n = 1$, $R = CH_3$, $R' = C_2H_5$; c: $n = 1$, $R = R' = C_2H_5$; d: $n = 3$, $R = R' = CH_3$; e: $n = 3$, $R = CH_3$, $R' = C_2H_5$; f: $n = 3$, $R = R' = C_2H_5$; g: $n = 1$, $R = R' = CH_3$, $R'' = CH_3$; h: $n = 1$, $R = R' = C_2H_5$, $R'' = CH_3$; i: $n = 3$, $R = R' = CH_3$, $R'' = CH_3$; j: $n = 3$, $R = CH_3$, $R' = C_2H_5$, $R'' = CH_3$; k: $n = 3$, $R = R' = C_2H_5$, $R'' = CH_3$; l: $n = 1$, $R = R' = CH_3$, $R'' = C_6H_5$; m: $n = 3$, $R = R' = CH_3$, $R'' = C_6H_5$; n: $n = 3$, $R = R' = C_2H_5$, $R'' = C_6H_2(OCH_3)_3 = 3, 4, 5$.

The physical constants, yields, and analytical figures for the new organosilicon aminoalcohols and their derivatives are shown in Tables 1 and 2.

The curariform and ganglion-blocking activity of the compounds were studied, together with their effects on the blood circulatory system and modification of the effects of biogenic amines. Acute toxicities were also determined. The pharmacological studies showed that in experiments with narcotized cats, several of the compounds showed curariform activity when administered by the intravenous route (Table 3), but the doses were relatively high, and only with methyldiethyl-[3-(N-methyl-N-2-chloroethylamino)propyl]silane (VIe) was the ED_{50} 0.7 ± 0.2 mg/kg. In experiments with pigeons, paralysis of the neck muscles occurred with all the compounds except (Ve), which in doses up to 20 mg/kg had no curariform activity (see

Institute for Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 10, pp. 1204-1209, October, 1982. Original article submitted February 16, 1982.

0091-150X/82/1610-0764$07.50

TABLE 1. Organosilicone Aminoalcohols and Their Esters

Compound	Yield, %	bp, °C (mm Hg)	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated
Id	66	111 (15)	1,4503	0,8660	58,79	58,80
Ie	69	110—112 (3,5)	1,4601	0,8806	67,62	68,05
If	54	105—106 (3)	1,4650	0,8893	71,94	72,32
IIIg	48	157—159 (35)	1,4560	0,9120	72,96	72,90
IIIh	52	120—121 (15)	1,4401	0,8895	68,58	68,27
IIIi	53	131—133 (3)	1,4501	0,9012	77,39	77,53
IIIk	55	121—122 (5)	1,4552	0,9102	81,52	81,80
IIIm	60	195 (15)	1,4950	0,9717	88,07	88,03

TABLE 2. Hydrochlorides and Methiodides of Organosilicon Aminoalcohols and Their Derivatives

Compound	Yield, %	mp, °C	Found, % C	Found, % H	Found, % N	Molecular formula	Calculated, % C	Calculated, % H	Calculated, % N
IId	63	116	35,89	7,89	4,07	$C_{10}H_{26}JNOSi$	36,25	7,91	4,23
IIe	40	179—182	40,90	8,81	4,19	$C_{12}H_{30}JNOSi$	40,11	8,41	3,90
IIf	54	223—225	42,20	8,49	3,80	$C_{13}H_{32}JNOSi$	41,82	8,64	3,75
IVg	40,5	93—96	40,52	7,74	3,27	$C_{13}H_{30}JNO_2Si$	40,30	7,81	3,62
IVh	80	160	38,61	7,55	4,06	$C_{12}H_{28}JNO_2Si$	38,60	7,56	3,75
IVi	65	145—146	41,38	7,84	3,27	$C_{14}H_{32}JNO_2Si$	41,89	8,04	3,49
IVj	72	147—149	42,79	8,38	3,34	$C_{15}H_{34}JNO_2Si$	43,36	8,25	3,37
IVm	58	96,5—98	47,32	7,31	3,49	$C_{17}H_{30}JNO_2Si$	46,89	6,94	3,22
IVn	33,5	118—120	46,60	6,83	2,24	$C_{23}H_{45}JNO_5Si$	46,67	7,46	2,47
Vc	27	137—140	45,80	9,46	5,20	$C_{10}H_{25}Cl_2NSi$	46,49	9,76	5,42
Ve	13	139,5—140,5	48,81	9,87	5,51	$C_{11}H_{27}Cl_2NSi$	48,51	9,99	5,14
Vf	70	132—135	50,60	10,22	5,08	$C_{12}H_{29}Cl_2NSi$	50,33	10,21	4,89
VIc	36	218—220	35,79	7,38	3,53	$C_{11}H_{27}ClJNSi$	36,31	7,48	3,85
VIe	23	176—178	40,59	7,86	4,25	$C_{12}H_{29}ClJNSi$	41,21	8,36	4,01
VIf	44	200—203	39,58	7,82	3,25	$C_{13}H_{21}ClJNiS$	39,84	7,97	3,57

Table 3). The most active compound, both in pigeons and cats, was (VIe), the ED_{50} being only 0.2 mg/kg. Intravenous administration to pigeons of (VIe) in doses of 0.1-0.3 mg/kg disturbed neuromuscular conductivity, the effect developing slowly over a period of 7-15 min following administration, reaching a maximum over 30-40 min. The paralysis was of the flaccid type, and persisted for 2-3 h.

In the cat experiments, most of the compounds caused a reduction in arterial pressure (Table 3). The most active in this test was trimethyl-[3-(N-methyl-N-2-acetoxyethylamino)-propyl]silane (IVi), which in doses of 0.06-0.5 mg/kg reduced the arterial pressure by 15-40 mm Hg for 30-60 sec. In doses of 0.01-0.5 mg/kg, (VIe) either did not affect, or temporarily increased, the arterial pressure (by 5-15%), but in higher doses this compound also reduced the arterial pressure.

All the compounds in experiments on cats showed ganglion-blocking activity in the parasympathetic cardiac ganglia. The highest activity was shown by (IVj, IIe, IVi, and IVm) (Table 3).

In the doses studied, the compounds did not display significant α- or β-adrenoblocking or antihistamine activity. In doses of 0.5-3.0 mg/kg, (IId, IVm, and Ve) had some adrenosensitizing activity, and (Ve) increased by 10-20% the depressor effect of histamine. Most of the compounds showed weak m-cholinolytic activity, reducing the depressor effect of acetylcholine. The most active compounds in this test were (IVj and VIe), the ED_{50} values for these being 0.3 and 0.37 mg/kg respectively.

The acute toxicities in mice by the intravenous route parallel in general their curariform activity in the pigeon experiments (see Table 3). Compound (VIe) was highly toxic, apparently owing to its curariform effects.

TABLE 3. Pharamacological Activity of Methiodides and Hydrochlorides of Organosilicon Aminoalcohols

Compound	Acute toxicity, LD_{50}, mg/kg	Curariform activity				Hypotensive effect, ED_{30}, mg/kg	Ganglion-blocking activity	
		cats		pigeons			ED_{50}, mg/kg	duration of effect, min
		ED_{50}, mg/kg	duration of effect, min	ED_{50}, mg/kg	duration, of effect, min			
IId	101 (79,52—128,27)	6	—	11,58	5	1,9	0,38 (0,217—0,669)	10
IIe	64 (53,3—76,8)	2,6±0,5	3	6,3	3	1,75	0,28 (0,164—0,476)	12
IIf	37 (32,1—42,5)	2,3	4	4,55	2	10—12	0,6	—
IVh	46 (38,3—55,2)	6,8	$4\frac{1}{2}$	13,5	$1\frac{1}{2}$	8	2,5	—
IVi	92 (77,9—108,6)	>6	—	11,76	$\frac{1}{2}$	0,25	0,265 (0,21—0,357)	10
IVj	94 (75,2—117,5)	>5	—	12,0	$1\frac{1}{2}$	1,0	0,15 (0,075—0,30)	14
IVk	40 (32,5—49,2)	3,1	$5\frac{1}{2}$	5,6	3	9	0,8	—
IVm	152 (112,6—205,2)	>5	—	12,5	2	2,3	0,28 (0,164—0,476)	15
IVn	91 (79,2—104,6)	>5	—	5,8	1	1,2	3,5	—
Vc	62 (42,7—89,9)	>15	—	—	—	—	14	—
Ve	145 (103,57—203,0)	Inactive	—	>20	—	2,8	3,8 (1,26—11,4)	—
Vf	66 (45,5—95,7)	>15	—	—	—	—	9	11
VIc	44 (36—53,6)	5,3	$5\frac{1}{2}$	5,5	3	—	2,5	—
VIe	0,81 (0,548—1,013)	0,7±0,2	10	0,2	180	1,8	0,5 (0,235—0,875)	10
VIf	42 (31,5—55,8)	3,2	$5\frac{1}{2}$	4,8	2	—	0,5	—

Note. Range of variation given in parentheses.

An examination of the effects of the structures of organosilicon aminoalcohol methiodides and their acetates and benzoates, and the methiodides and hydrochlorides of organosilicon β-chloroethylamines, on their biological activity has shown* that in most cases replacement of methyl groups attached to the silicon atom by ethyl increases the acute toxicity (cf. IIa and IIc; IId, IIe, and IIf; IVg and IVh; IV and IVk; VIa, VIb, and VIf; Va and Vc), and also curariform activity (cf. IId, IIe, and IIf; IVi, IVj, and IVk; IIa and IIc; VIa and VIb), but reduces hypotensive activity (cf. IIa and IIc; VIa and VIb; IId and IIf; IVg and IVh; IVi, IVj, and IVk) and ganglion-blocking properties (cf. IIa and IIc; IId and IIf; IVg and IVh; IVi and IVk; VIa and VIc; Ve and Vf). However, the most active ganglion-blockers of the whole series are methyldiethylsilyl derivatives (IVj, IIe, VIb, and Ve).

Increasing the distance between the silicon and nitrogen atoms by two methylene groups in all the types of compound increases ganglion-blocking activity (cf. IIa and IId; IIc and IIf; IVg and IVi; IVh and IVk; IVl and IVm; VIc and VIf; Vc and Vf), increases to some extent curariform properties (cf. IVh and IVk; VIc and VIf), and also increases acute toxicity (cf. IIa and IId; IIc and IIf; IVg and IVi; IVl and IVm; VIb and VIe), although only to a small extent in the case of triethylsilyl compounds.

Replacement of the hydroxyl group of the organosilicon aminoalcohols by an acetoxy group or a chlorine atom has little effect on their biological activity. There is nevertheless some tendency to increased ganglion-blocking (cf. IVj, IIe, and VIe; IV and IId) and hypotensive (cf. IVg, VIa, IVl, and IIa; IVi, IId, and IVm; IVl, IIe, and VIe) activity in the acetoxy-compounds, and the toxicities of the trimethylsilylmethyl- and methyldiethylsilylpropyl derivatives are greater for the alcohols and chloro-derivatives than for the acetoxy- and benzoyloxy-derivatives (cf. IVl, IVg, IIa, and VIa; IVj, IIe, and VIe).

EXPERIMENTAL CHEMICAL SECTION

Triethyl[(N-methyl-N-2-hydroxyethyl)aminomethyl]silane (Ic) was obtained by the method described in [3].

Trialkyl[3-N-methyl-N-2-hydroxyethylamino)propyl]silanes (Id-f). A mixture of the trialkyl(-3-chloropropyl)silane (0.1 mole), 2-(N-methylamino)ethanol (0.1 mole), triethylamine (0.1 mole), and 1-butanol (25 ml) was heated at the boil for 20-22 h. The salt which separated on cooling was filtered off, and the solvent and unreacted starting materials distilled off under a water pump vacuum. Further vacuum distillation of the residue afforded the product. Yields can be increased by treating the filtered solid and the residue in a distillation flask with 20% NaOH solution, followed by extraction with ether. The ether extracts were dried over KOH, and the residue after removal of the ether and triethylamine was distilled *in vacuo* to give a further quantity of product.

The yields and physical constants of the silanes are given in Table 1.

Trialkyl[N-methyl-N-(2-acyloxyethyl)aminoalkyl]silanes (IIIh-k and m). To a solution of the aminoalcohol (Ic-f) (0.015 mole) and triethylamine (0.016 mole) in 30 ml of dry ether was added dropwise with stirring a solution of the acyl chloride (0.016 mole) in 5 ml of dry ether. The mixture was boiled for 3 h, and the solid filtered off and washed with ether. The filtrate was neutralized with sodium carbonate solution, and the ethereal layer dried over magnesium sulfate. The solvent was removed, and the residue distilled *in vacuo* to give the product.

The yields and physical constants of the esters are given in Table 1.

Methiodides of Organosilicon Aminoalcohols and Their Esters (IId-f, IVh-k and m). To a solution of (Id-f) or (IIIh-k, m) (0.01 mole) in 8 ml of dry ether was added a solution of 2 ml of methyl iodide in 5 ml of ether. When the exothermic reaction had ceased, the mixture was heated on the water bath at 35-40°C for 3-4 h, and kept for 16 h at ~20°C. The solid was filtered off, washed with ether, and recrystallized from a mixture of absolute ether and absolute alcohol.

The yields, melting points, and analyses of the methiodides are given in Table 2.

Triethyl[3-[N-methyl-N-2-(3',4',5'-trimethoxybenzoyloxy)enthylamino]propyl]silane Methiodide (IVn). To a benzene solution of 11.57 g (0.05 mole) of the aminoalcohol (If) and

*In discussing the results, use has been made of data on pharmacological activity of (IIa, IIc, IVg, IVl, Va, VIa, and VIb) given in [1].

5.05 g (0.05 mole) of triethylamine was added dropwise a benzene solution of 11.50 g (0.05 mole) of 3,4,5-trimethoxybenzoyl chloride. The reaction mixture was boiled for 30 h, the solid filtered off, and washed with benzene. The filtrate was treated with sodium carbonate solution, and the benzene solution was dried over magnesium sulfate. The high-boiling product was obtained on removal of the solvent. The product (8 g) was dissolved without further purification in 15 ml of acetone. To the resulting solution was added dropwise with ice-cooling 3 ml of methyl iodide in 5 ml of acetone. The resulting solid was filtered off, washed with ether, and reprecipitated from its acetone solution with ether to give 9.5 g of the methiodide (IVn), mp 118-120°C.

2-Chloroethylaminoalkylsilane Hydrochlorides (Vc, e, f). To a solution of 6 ml of thionyl chloride in 10 ml of chloroform, heated to 35-40°C, was added dropwise, slowly, with stirring, the aminoalcohol (Ic, e, or f) (0.037 mole) in 12 ml of chloroform. Stirring was continued at the same temperature for 3-4 h. The solvent and excess thionyl chloride were removed in a water pump vacuum, and the residue was washed with ether and recrystallized from benzene, a small volume of acetone, or a mixture of acetone and ether.

The yields, melting points, and analyses of the hydrochlorides are given in Table 2.

2-Chloroethylaminoalkylsilane Methiodides (VIc, e, and f). To a solution of the 2-chloroethylaminoalkylsilane hydrochloride (Vc, e, or f) (0.025 mole) in 30 ml of water was added 30 ml of ether, and a solution of 1.5 g of KOH in 30 ml of water was then added with continuous stirring and cooling. The aqueous layer was extracted with ether. To the combined ethereal extracts, dried over calcium chloride, was added a solution of 5 ml of methyl iodide in 10 ml of ether, and the mixture heated on the water bath for 3-4 h at 35-40°C. The mixture was kept for 16 h at 20°C, and if necessary placed in a freezing chamber until a solid separated. The solid was filtered off, washed with ether, and recrystallized from absolute ethanol or from a mixture of absolute ethanol and ether.

The yields, melting points, and analyses of the methiodides are given in Table 2.

EXPERIMENTAL PHARMACOLOGICAL SECTION

In acute experiments on chloralose-narcotized cats weighing 2.6-4.0 kg, using a Narco Biosystems physiograph, the arterial pressure in the common carotid artery, respiration, transthoracic ECG, and contractions of the anterior tibial muscle following stimulation of the sciatic nerves by supramaximal square wave pulses (0.5 msec, 0.2 Hz) were recorded. In a series of experiments, the peripheral region of the vagus nerve was stimulated by square wave pulses (0.2 msec, 30 Hz) for 5 sec. The ability of the compounds to modify neuromuscular conductivity, to prevent the depressant reaction of the arterial pressure in response to stimulation of the vagus nerve, and to influence the hemodynamic effects of acetylcholine, isadrin, noradrenalin, and histamine was determined. Aqueous solutions of the compounds were administered via the femoral vein.

Solutions of the compounds were administered intravenously to intact pigeons weighing 220-330 g. The doses which caused weakening of the neck muscles (in the case of flaccid paralysis) or spastic contractions of the rear limbs (in the case of spastic paralysis) were measured.

The acute toxicities of the compounds were measured in white rats weighing 18-26 g, by the intraperitoneal route. The LD_{50} values and the confidence limits were calculated by the Litchfield and Wilxocon method.

LITERATURE CITED

1. A. A. Kimenis, R. O. Vitolinya, É. Ya. Lukevits, et al., Izv. Akad. Nauk Latv. SSR, No. 12, 108-111 (1969).
2. L. N. Khokhlova, M. M. Veveris, and A. A. Kimenis, in: 5th All-Union Conference on the Chemistry and Applications of Organosilicon Compounds. Abstracts of Papers. Tbilisi, Part 2 (1980), p. 324.
3. E. Ya. Lukevits and M. G. Voronkov, Zh. Obshch. Khim., 38, No. 10, 2325-2337 (1968).