The introduction of a chlorine atom in either the ortho or para positions of the benzene ring (compounds Ib, c) leads to an essential change in the spectra of pharmacological activities by comparison with other amidoximes studied. The indicated change in the spectrum of activity is characterized by central serotonin-positive action with weak effectiveness with respect to potentiation of phenamine and antagonism to reserpine.

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NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS. CXXII. SYNTHESIS AND PHARMACOLOGICAL STUDIES OF TRIALKYLSILYLALKYLAMINOETHYL DICARBOXYLATE METHIODIDES

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UDC 615.216.5:[547.245:547.582.2].012.1

In the course of studying the biological activity of organosilicon derivatives of aminoalcohols [1-5], we synthesized the methiodides of esters of organosilicon choline derivatives and dicarboxylic acids.

The organosilicon aminoalcohols Ia-g were synthesized from trialkyl(chloroalkyl)silanes and N-methylaminoethanol in the presence of triethylamine in a butanol medium. The products of reaction of trialkyl(2-hydroxyethylaminoalkyl)silanes with succinic, adipic, suberic, azelaic, and sebacic chlorides were treated with methyl iodide to obtain the methiodides III-VII.

$$RR'_2Si(CH_2)_nN(CH_3)CH_2CH_2OH \xrightarrow{(CH_2)_m[COCl]_2} \underset{I\ a\text{-}g}{} \longrightarrow \underset{II}{\left[RR'_2Si(CH_2)_nN(CH_3)CH_2CH_2OCO\right]_2(CH_2)_m} \xrightarrow{CH_3I} \left[RR'_2Si(CH_2)_n\overset{+}{N}(CH_3)_2CH_2CH_2OCO\right]_2(CH_2)_m \cdot 2I^-$$

IIIa-g–VIIa-g

a: $n = 1$, $R = R' = CH_3$; b: $n = 1$, $R = R' = C_2H_5$; c: $n = 3$, $R = C_2H_5$, $R' = CH_3$; d: $n = 3$, $R = CH_3$, $R' = C_2H_5$; e: $n = 3$, $R = CH_3$, $R' = C_3H_7$; f: $n = 3$, $R = CH_3$, $R' = C_4H_9$; g: $n = 3$, $R = R' = C_2H_5$.

III: $m = 2$; IV: $m = 4$; V: $m = 6$; VI: $m = 7$; VII: $m = 8$.

Hydrocarbon analogs of the succinic acid derivatives, containing 7- or 10-carbon chain substituents at the N atom, were also synthesized. Dimethiodides of di[2-(N-methyl-N-alkyl)-aminoethyl] succinates were obtained according to the same scheme as for the organosilicon derivatives:

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 11, pp. 1314-1318, November, 1984. Original article submitted May 3, 1984.

0091-150X/84/1811-0754$08.50

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TABLE 1. Aminosilanes and Aminoalcohols

Compound	Yield, %	bp, °C (mm Hg)	n_D^{20}	d_4^{20}	MR	
					expt.	calc.
Ic	59	101–103 (5)	1,4553	0,8764	63,01	63,42
Ie	57	127—130 (3)	1,4604	0,8747	76,93	77,31
If	60	145—146 (2)	1,4611	0,8709	86,22	86,57
VIIIa	54	86–89 (2)	1,4478	0,8669	53,50	53,79
VIIIb	56	127 (2)	1,4528	0,8629	67,44	67,68

TABLE 2. Methiodides of Aminoethyl Dicarboxylates

Compound	mp, °C	Expt., %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
IIIa	216—219	35,26	6,59	3,89	$C_{20}H_{16}I_2N_2O_4Si_2$	34,88	6,73	4,06
IIIc	145—148	41,08	7,50	3,88	$C_{26}H_{58}I_2N_2O_4Si_2$	40,41	7,57	3,63
IIId	168—170	41,59	7,73	3,65	$C_{28}H_{62}I_2N_2O_4Si_2$	42,00	7,80	3,50
IIIe	103,5—105	45,24	8,33	3,42	$C_{32}H_{70}I_2N_2O_4Si_2$	44,85	8,23	3,27
IIIf	87—89	47,72	8,36	3,11	$C_{36}H_{78}I_2N_2O_4Si_2$	47,36	8,61	3,07
IIIg	121—123	42,95	8,24	3,15	$C_{30}H_{66}I_2N_2O_4Si_2$	43,47	8,03	3,38
IVb	152—155	42,47	7,41	3,72	$C_{28}H_{62}I_2N_2O_4Si_2$	42,00	7,80	3,50
Vb	156—159	42,83	7,80	3,19	$C_{30}H_{66}I_2N_2O_4Si_2$	43,47	8,02	3,37
VIb	112—115	44,49	8,27	3,23	$C_{31}H_{68}I_2N_2O_4Si_2$	44,17	8,13	3,32
VIIb	101—103	45,27	8,32	3,20	$C_{32}H_{70}I_2N_2O_4Si_2$	44,85	8,23	3,27
Xa	159—160,5	43,96	7,33	4,07	$C_{26}H_{54}I_2N_2O_4$	43,83	7,64	3,93
Xb	82—85	47,89	8,68	3,81	$C_{32}H_{66}I_2N_2O_4$	48,24	8,35	3,52

$$RN(CH_3)CH_2CH_2OH \xrightarrow{(CH_2)_2[COCl]_2} [RN(CH_3)CH_2CH_2OCO]_2(CH_2)_2 \xrightarrow{CH_3I}$$

VIIIa, b IXa, b

$$[RN^{+}(CH_3)_2CH_2CH_2OCO]_2(CH_2)_2 \cdot 2I^{-}$$

Xa, b

a: $R = C_7H_{15}$; b: $R = C_{10}H_{21}$

The 2-(N-methyl-N-alkyl)aminoethanols VIIIa and VIIIb were synthesized from the corresponding alkyl bromide and N-methylaminoethanol in the presence of triethylamine in butanol. Reactions of the aminoalcohols with succinic chloride gave the esters IXa and b, from which the methiodides Xa and b were obtained by treatment with methyl iodide.

Physical constants, yields, and analytical data for the new aminoalcohols and their derivatives are presented in Tables 1 and 2.

The curare-like and ganglioblocking activities of the synthesized methiodides, their effect on the cardiovascular system, and their influence on the hemodynamic effects of biogenic amines were investigated. Acute toxicity was also determined. The results of pharmacological studies showed that in experiments with narcotized cats, a number of the compounds exhibited a curare-like effect when given iv (Table 3). However, the doses for this are relatively large, with the ED_{50} being 0.74 mg/kg only for the methiodide of the adipic acid ester (IVb). In contrast to the other compounds, Xa in doses close to the ED_{50} value causes a significant decrease in the depth of respiration simultaneously with decreased neuromuscular conductivity in skeletal musculature, i.e., it blocks the neuromuscular conductivity in the respiratory muscles.

In experiments on cats, only succinic acid derivatives show an effect on arterial pressure, causing it to decrease in the majority of cases. The most active in this respect was the dimethiodide of di[2-(N-methyl-N-3-methyldiethylsilylpropyl)aminoethyl] succinate (IIId), which decreased arterial pressure to 20-60 mm Hg in 2-6 min at doses of 0.6-2 mg/kg. Compound IIIg at doses of 0.1-10 mg/kg either does not change or temporarily increases (by 10-30 mm Hg) arterial pressure. The pulse frequency in this case is somewhat increased. Compound IIIa causes a weak hypotensive response.

All compounds studied show a ganglioblocking action on the parasympathetic ganglia of the heart in cats. Compounds IIId and IIIe, with methyldiethyl- and methyldipropylsilicon groups, respectively, show the most significant activity (see Table 3).

TABLE 3. Pharmacological Activity of Methiodides of Esters of Aminoalcohols and Dicarboxylic Acids

Compound	Acute toxicity, LD_{50}, mg/kg	Curare-like activity		Hypotensive effect, ED_{30}, mg/kg	Ganglioblocking activity	
		ED_{50}, mg/kg	duration of effect, min		ED_{50}, mg/kg	duration of effect, min
IIIa	45 (37,5—54)	1,1	10	—	4,5	—
IIIc	86 (61,4—120,4)	5,6	10	5,0	1,0	25
IIId	35 (25,9—47,25)	1,1	4	1,0	0,05	30
IIIe	43 (28,1—65,8)	>8	—	7,5	0,06	15
IIIf	62 (41,3—93)	>8	—	7,0	0,35	8
IIIg	61 (49,2—75,6)	5,0	5	—	0,3	7
IVb	35 (26,1—46,9)	0,74	5,5	—	4	—
Vb	76 (67,8—85,1)	7,5	4	—	8	—
VIb	87 (76,9—98,3)	8,0	3	—	7	—
VIIb	84 (73,4—93,8)	7,4	2,8	—	5	—
Xa	36 (20,2—64)	4,5	8	4,0	0,4	5
Xb	81 (72,3—90,7)	8,5	12	7,0	0,9	12

Note. The limits of variation are in parentheses.

The majority of the compounds studied exhibit a slight m-cholinolytic activity, decreasing the depressor effect of acetylcholine. The most active in this respect was compound Xa, which almost completely (by 90—95%) decreased the depressor effect of acetylcholine at doses of 3-5 mg/kg. Compounds IIIc, IIIf, and IIIg at doses of 0.05-0.5 mg/kg show some m-cholinomimetic activity but show a slight cholinolytic activity at higher doses.

The substances studied did not have significant α- or β-adrenoblocking or antihistamine activities at the doses tested.

In general, the acute toxicity of the compounds when administered ip to mice correlates with their curare-like activity. Compounds IVb, IIId, and IIIa were the most toxic, which is apparently related to their curare-like effect. Compound Xa is also highly toxic, which is apparently explained not only by its moderate curare-like activity but also by its significant m-cholinolytic activity.

When analyzing the results of pharmacological studies of these substances, one may note several characteristic changes in biological activity with changes in the compound structure. Substitution of the ethyl group on the silicon atom in methyldialkylsilylpropyl derivatives of succinic acid (IIId-f) by propyl or butyl groups leads to decreased curare-like, hypotensive, and ganglioblocking activities as well as decreased toxicity. Triethylsilyl derivatives of succinic (IIIg) as well as other acids (IVb-VIIb) do not show a hypotensive effect and are rather weak ganglioblockers.

In all cases, the dimethylethylsilyl derivative IIIc is not highly active. This compound is the weakest ganglioblocker among the trialkylsilylpropyl derivatives of succinic acid; its curare-like activity is comparable to that of the triethylsilyl derivative IIIg, and its hypotensive activity is significantly less than that of the methyldiethylsilyl derivative IIId. Compound IIIc is the least toxic within this group of compounds.

Comparison of succinic, adipic, suberic, azelaic, and sebacic acid derivatives shows that the adipic acid derivative has the strongest curare-like action in relation to the triethylsilylmethyl derivatives (cf. IVb and Vb-VIIb) as well as all compounds studied. The succinic acid derivatives are the strongest ganglioblockers. Within the triethylsilylmethyl derivatives, the strongest ganglioblocker is the adipic acid derivative IVb, the activity of which is comparable to that of the trimethylsilylmethyl derivative of succinic acid, IIIa. Derivatives of adipic and succinic acids have approximately equal toxicity when they are similar according to the magnitude of curare-like effect (cf. IVb, IIId, and IIIa). In the remaining cases, the toxicity of the adipic acid derivative somewhat surpasses that of derivatives of other acids, including triethylsilylmethyl (cf. IVb and Vb-VIIb) and triethylsilylalkyl derivatives (cf. IVb and Vb-VIIb, IIIg). An increase in the number of methylene groups between the ester functions to six markedly decreases the curare-like activity, the ganglioblocking action, and the toxicity of the compounds. Further increase in the distance between the ester groups has little effect on the biological activity.

When comparing compound IIIg with its carbon analog Xb, one may note that the latter shows a weaker curare-like and ganglioblocker activity but has a more prolonged duration of action and is less toxic. Compound Xa has a somewhat higher curare-like and ganglioblocking activity compared to compound Xb, but at the same time its activity is significantly less than that of IIId, the most active compound in the series of organosilicon derivatives of succinic acid.

EXPERIMENTAL CHEMISTRY

Trialkyl[(N-methyl-N-2-hydroxyethyl)aminomethyl]silanes (Ia, b) are obtained according to the method described in [3] and trialkyl[3-(N-methyl-N-2-hydroxyethylamino)propyl]silanes (Id, g) according to the method described in [2].

Trialkyl[3-(N-methyl-N-2-hydroxyethylamino)propyl]silanes (Ic, e, f). A mixture of trialkyl(3-chloropropyl)silane (0.05 mole) 2-(N-methylamino)ethanol (0.05 mole), triethylamine (0.1 mole), and 1-butanol (20 ml) is boiled for 23-25 h. The salt which is precipitated by cooling is removed by filtration. Solvent and unreacted reagents are distilled off in the vacuum of a water-jet pump. The reaction product is isolated by further vacuum distillation of the residue. The product yield may be boosted by treatment of filtered precipitate and residue in the vacuum distillation flask with a 20% NaOH solution followed by ether extraction. The ether extracts are dried under KOH. The residue obtained after distilling off ether and triethylamine are vacuum distilled and additional product is isolated.

2-[(N-Methyl-N-alkyl)amino]ethanols (VIIIa, b) are obtained according to the above method by boiling a mixture of alkyl bromide (0.1 mole), 2-(N-methylamino)ethanol (0.1 mole), triethylamine (0.15 mole), and 1-butanol (30 ml) for 4 h.

The yields and physical constants of the silanes and aminoalcohols obtained are presented in Table 1.

Methiodides of 2-[(N-Methyl-N-trialkylsilylpropyl)amino]ethyl Succinates (IIIc-g). To a stirred solution of aminoalcohol Ic-g (0.04 mole) and triethylamine (0.04 mole) in 30 ml of absolute ether at a temperature of 0-10°C, a solution of succinic chloride (0.02 mole) in 10 ml of absolute ether is added dropwise. The precipitate is removed by filtration and washed with ether. The filtrate is neutralized by a soda solution and the ether layer dried under magnesium sulfate. The precipitate is treated with 100 ml of a 20% NaOH solution followed by ether extraction. The ether extracts are combined and dried under magnesium sulfate. Unreacted initial aminoalcohol is separated *in vacuo* from the residue obtained from both ether solutions after removal of solvent and triethylamine. The remaining high-boiling ester II is dissolved in 10 ml of absolute ether. To the solution obtained are added 3 ml of methyl iodide in 10 ml ether. The reaction mixture is heated in a water bath at 35-40°C for 2-3 h and is left to stand at room temperature for 16 h. The precipitate is removed by filtration, washed with ether, and recrystallized from a mixture of absolute ether and absolute ethanol.

Dimethiodides of Di[2-(N-methyl-N-alkyl)aminoethyl] Succinate (Xa, b). These were obtained by the above method.

Methiodides of (Trialkylsilylmethyl)aminoethyl Esters of Dicarboxylic Acids (IIIa, IVb-VIIb). To a stirred solution of aminoalcohol (0.05 mole) and triethylamine (0.05 mole) in 40 ml of benzene which is cooled by ice water, dicarboxylic acid chloride (0.025 mmole) in 10 ml benzene is added dropwise. The mixture is heated in a water bath for 12-15 h. The precipitate is removed by filtration and washed with benzene. The filtrate is concentrated by boiling, unreacted aminoalcohol is separated from the residue *in vacuo*. The residual high-boiling ester II is dissolved in 15 ml of acetone. To the resulting solution are added 3 ml of methyl iodide in 5 ml acetone with cooling. The reaction mixture is heated in a water bath for 4-5 h and then left to stand for 16 h at room temperature. The precipitate is filtered off, washed with ether, and reprecipitated by ether from its solution in absolute ethanol which was previously passed through Al_2O_3.

The melting points and analytical data for the resulting methiodides are presented in Table 2.

EXPERIMENTAL PHARMACOLOGY

In acute experiments on cats weighing 2.5-4.0 kg, narcotized by α-glucochloralose (90 mg/kg) and urethane (200 mg/kg, ip), arterial pressure from the common carotid artery, respiration, the EKG II from a standard lead, and contraction of the anterior tibial muscle upon stim-

ulation of the sciatic nerve by supramaximal orthogonal impulses (0.5 msec, 0.2 Hz) were registered using the DMP-4B Narco Bio-Systems physiograph. In a number of experiments, the peripheral segment of the vagus was stimulated by supramaximal orthogonal impulses (0.2 msec, 30 Hz) for 5 sec. The capabilities of various concentrations of the substances under study to change the neuromuscular conductivity, to prevent the depression of arterial pressure in response to stimulation of the vagus, and to influence the hemodynamic effects caused by acetylcholine, isoproterenol, noradrenaline, and histamine were determined. Aqueous solutions of the substances were injected into the femoral vein.

The acute toxicity of the substances was studied in experiments with white mice weighing 18-26 g, with ip administration of the compounds. Values of LD_{50} and their limits of reliability were calculated according to the method of Litchfield and Wilcoxon.

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SYNTHESIS AND BIOLOGICAL STUDY OF THE cis- AND trans-ISOMERS OF CLOMIPHENE CITRATE AND SOME INTERMEDIATES OF ITS SYNTHESIS

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UDC 615.256.51.012.1

The dihydrocitrate of 1-chloro-2-[4-(2-diethylaminoethoxy)phenyl]-1,2-diphenylethylene (I) (clomiphene citrate, clomid, chlostilite [?]) is an effective drug, widely used in medicine for the treatment of patients with endocrine-related infertility, and a number of other diseases, in particular cancer of the mammary gland [1, 6]. The original method for the synthesis of clomiphene citrate was developed at the All-Union Scientific-Research Institute of Pharmaceutical Chemistry; the preparation was licensed for use in the USSR.

Experimental data on the character of the biological activity of clomiphene citrate led to the formulation of the probable mechanism of its action, which lies mainly in selective action on the hypothalamus and pituitary gland [9]. As compound I is a mixture of cis- and trans-isomers, containing 50-70% of the trans-isomer [12], interest centered on the differences between the biological properties of the isomers. The literature reports that the cis-isomer possesses estrogenic activity, and the trans-isomer antiestrogenic activity [4].

To study the biological properties of the isomers of I and some intermediates of its synthesis, we obtained the individual cis- and trans-isomers of I and also clomiphene base (II) and the dealkylated derivative (III).

The cis-isomer of clomiphene base II-Z was isolated by recrystallization of a mixture of the isomers [12] from petroleum ether. Evaporation of the mother liquors gave the trans-isomer

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 11, pp. 1318-1324, November, 1984. Original article submitted November 15, 1983.

0091-150X/84/1811-0758$08.50

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