NITROGENOUS ORGANOSILICON COMPOUNDS. 140. SYNTHESIS AND PHARMACOLOGY OF TRIETHYLSILYLPROPYLAMINOALKANECARBOXYLIC QUINOLYLAMIDES

É. Lukevits, T. V. Lapina, and S. K. Germane

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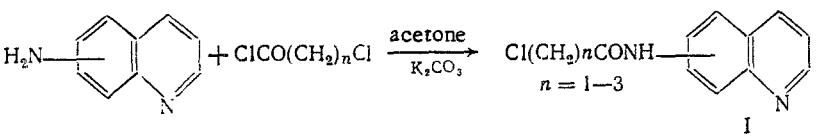
Continuing an examination of the biological activity of organosilicon derivatives of quinoline [1], we have obtained some triethylsilylpropylaminoalkanecarboxylic quinolylamides and examined their neurotropic properties. Such properties have been previously observed in organosilicon derivatives of tetrahydroisoquinoline [2].

We first of all obtained the ω-chloroalkanecarboxylic quinolylamides by reacting 3-, 5-, 6-, and 8-aminoquinolines with chloroacetyl, β-chloropropionyl, and γ-chlorobutyryl chlorides.



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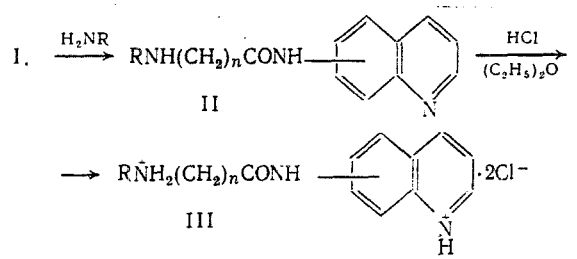
Condensation of the products with γ-triethylsilylpropylamine afforded the abovementioned organosilicon derivatives of quinoline, which were isolated as their hydrochlorides.



IIIa-f: $R = (CH_2)_3Si(C_2H_5)_3$; position of substituent in quinoline ring - 3 (a), 5 (b, c), 6 (d, e), 8 (f); $n = 1$ (a, b, d, f), 2 (c, e)

The γ-chlorobutyric and some of the β-chloropropionic acid derivatives hydrolyzed rapidly in air. Six compounds were stable (IIIa-f). Biological test results are given in Tables 1 and 2. It will be seen that the acute toxicities of (IIIa-d) do not differ significantly from each other. An exception is (IIIe), the LD_{50} value of which is one third of the remainder; the toxicity of (IIIc) is also slightly greater. The propionic acid derivatives are therefore more toxic than the acetic acid derivatives.

The effects of the compounds on skeletal musculature tonus and motor coordination (the rotating rod, tube, and pull-up to crossbar tests) depend on the position of the substituent in the quinoline ring. It will be seen from Table 1 that the greatest activity is shown by (IIId-f), in which the substituents are in the 6- and 8-positions of the quinoline ring. Compounds with substituents in positions 3 and 5 are slightly less active, and the distance between the amino nitrogen atom and the carboxyl group is not important in this instance. A similar pattern is apparent in studies of hypothermic effects.

None of the test compounds showed analgesic properties, and they did not prevent convulsions induced by maximum electric shock and corazole. An exception with respect to cora-

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TABLE 1. Acute Toxicity, Effects on Motor Coordination and Skeletal Tonus of Compounds (IIIa-f)

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg			
		rotating rod test	tube test	pull-up to crossbar test	hypothermia
IIIa	355 (202—508)	56,4 (34,2—81,4)	44,7 (31,3—59,6)	44,7 (31,3—59,6)	51,5 (36,3—69,2)
IIIb	346 (120—662)	22,4 (14,4—28,5)	17,8 (13,6—23,0)	32,5 (17,2—50,2)	25,8 (14,5—45,5)
IIIc	258 (168—357)	25,8 (16,8—35,7)	28,2 (15,9—41,9)	20,5 (14,6—28,8)	22,4 (14,4—28,5)
IIId	289 (159—419)	3,0 (0,3—6,1)	4,1 (2,1—6,2)	4,4 (1,6—8,2)	2,2 (1,4—2,8)
IIIe	103 (67—138)	7,1 (4,3—10,2)	7,1 (4,3—10,2)	8,2 (5,7—15,2)	7,4 (2,2—15,2)
IIIf	325 (219—455)	4,1 (2,7—5,5)	3,6 (2,5—4,6)	5,2 (3,6—6,9)	4,5 (3,1—6,0)

Note. The tests were carried out with mice of strain BALB/c weighing 18-24 g.

TABLE 2. Neurotropic Activity of (IIIa-f)

Compound	Percent of the controls (100%)				
	hypoxic hypoxia	hexobarbital narcosis	ethanol narcosis	amphetamine stereotypy	corazole convulsions (tonic phase)
IIIa	103,3	274,4*	102,5	151,1	90,5
IIIb	123,8	266,3*	39,7*	181,6*	127,4
IIIc	110,6	411,7*	111,7	208,0*	175,1*
IIId	121,9	307,5*	67,6	167,2*	130,7
IIIe	128,3	305,9*	93,0	195,1*	108,6
IIIf	110,6	251,4*	127,9	162,4*	117,5

*The difference from the control is statistically significant at $P < 0.05$.
**The tests were carried out using male mice of the BALB/c strain weighing 18-20 g, and mongrel white female rats weighing 180-200 g ($n = 6$, $t = 22°C$).

zole shock was (IIIc), which increased by 75% the dose of corazole required to produce a lethal outcome in mice (Table 2). Compounds of this type likewise failed to have any significant effect on the pharmacological effects of reserpine, and they had no antihypoxic activity. However, as will be seen from Table 2, all the compounds in doses of 25 mg/kg increased by a factor of 2.5-4 the duration of hexobarbital narcosis. With respect to alcohol narcosis, it was found that only (IIIb) (10 mg/kg) shortened the duration of narcosis by 60.3% ($P < 0.02$), and (IIId) (10 mg/kg) by 32.3% ($P > 0.25$), i.e. decreased the toxic effects of ethanol.

In a dose of 10 mg/kg, the compounds extended amphetamine stereotypy in rats by 51-108%, the most active being the propionic acid derivatives (IIIc) and (IIIe) (Table 2).

It appears that the activity of these compounds with respect to the pharmacological effects of amphetamine and hexobarbital is due to their influence on the microsomal enzymes of the liver.

EXPERIMENTAL (CHEMISTRY)

The structures of the new compounds were established by their PMR and IR spectra. PMR spectra were obtained on a Bruker WH-90/DS, and IR spectra on a Perkin-Elmer 580B.

The ω-chloroalkanecarboxylic quinolylamides were obtained as described in [3].

3-[3-(Triethylsilyl)propylaminoacetylamino]quinoline Dihydrochloride (IIIa). A mixture of 2.2 g (0.01 mole) of 3-(α-chloroacetylamino)quinoline, 1.7 g (0.01 mole) of 3-triethylsilylpropylamine, 1 ml of triethylamine, and 30 ml of dry xylene was boiled under reflux for 6 h. The triethylamine hydrochloride which separated was filtered off, and the solvent removed in a rotary evaporator. The resinous product obtained was dissolved in ether, purified by passing through a column of alumina, and saturated ethereal hydrogen chloride was added to the ether solution, whereupon (IIIa) separated as a pale yellow solid. This was quickly filtered off, washed with ether, and dried in vacuo. Compounds (IIIb-f) were obtained similarly. The physical properties and elemental analyses of the compounds are given in Table 3.

TABLE 3. Physicochemical Properties of (IIIa-f)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %		
		C	H	N		C	H	N
IIIa	114—6	55,82	7,60	9,60	$C_{20}H_{33}Cl_2NO_3Si$	55,80	7,72	9,75
IIIb	120—2	55,65	7,72	9,42	$C_{20}H_{33}Cl_2NO_3Si$	55,80	7,72	9,75
IIIc	105—7	56,66	7,85	9,55	$C_{21}H_{35}Cl_2NO_3Si$	56,74	7,93	9,45
IIId	180—2	55,87	7,42	9,61	$C_{20}H_{33}Cl_2NO_3Si$	55,80	7,72	9,75
IIIe	134—6	56,55	8,14	9,45	$C_{21}H_{35}Cl_2NO_3Si$	56,74	7,93	9,45
IIIf	144—6	56,04	7,66	9,72	$C_{20}H_{33}Cl_2NO_3Si$	55,80	7,72	9,75

EXPERIMENTAL (PHARMACOLOGY)

Neurotropic activity was examined in mice of strain BALB/c of both sexes weighing 17-23 g, and in mongrel white female mice weighing 180-200 g in the winter-spring season. The temperature in the laboratory and vivarium was maintained during the tests at 22 ± 1.5°C. The test compounds, prepared as aqueous suspensions with Tween-80, were administered intraperitoneally 30 min before carrying out the appropriate test. Comparative evaluations of the effects of the compounds on hypoxia, hexobarbital narcosis, amphetamine stereotypy, corazole convulsions, and reserpine hypothermia and ptosis were carried out in groups of animals consisting of 6-8 individuals, the test compounds being administered in doses of 10-25 mg/kg. The control animals were injected with the same volume of distilled water into the abdominal cavity.

The test results were evaluated statistically. In order to find the mean LD_{50} or ED_{50} values from 12-25 observations the rapid method was used, and in evaluating the mean duration of the narcotic effects of hexobarbital and amphetamine stereotypy, protectant activity in corazole convulsions and hypoxia, and the magnitude of reserpine ptosis and hypothermia, the mean arithmetic values were calculated with the standard error (M ± m). To assess the significance of the differences between the mean values, Student's t-test was used. The differences were considered to be significant at the probability level $P < 0.05$.

The effects of the compounds on the central nervous system were assessed by the following tests: 1) by their effects on motor coordination and muscle tonus using the rotating rod test on an Ugo Basile apparatus (Italy), rotation frequency 8 rpm for 2 min, the tube test (a glass tube measuring 30 × 2 cm for 30 sec), and the pull-up to crossbar test (a metal wire of diameter 2 mm for 5 sec); 2) by their effects on body temperature, measured in the large intestine using an electrical thermometer, the criterion here being a drop in rectal temperature of 3°C or more; 3) by their analgesic effect as measured by the hot plate method on an Ugo Basile apparatus (Italy); 4) anticonvulsant activity, using the maximum electroshock method (alternating current at 5 cps and 50 mA, duration of stimulus 0.2 sec) and the corazole convulsion test, induced by intravenous titration with 1% corazole at a rate of 0.01 ml/sec; 5) by their effects on the duration of hexobarbital narcosis (a 0.4% solution of hexobarbital intravenously in a dose of 70 mg/kg); 6) by their effects on the lifespan of animals under conditions of hypoxic hypoxia obtained by placing mice (one at a time) in a hermetically sealed chamber of volume 220 cm^3 without absorption of CO_2; 7) by the change in the duration of amphetamine stereotypy (a 0.4% solution of amphetamine subcutaneously in a dose of 10 mg/kg); and 8) by their effects on reserpine hypothermia and ptosis (a 0.01% solution of reserpine intraperitoneally in a dose of 2.5 mg/kg, 2.5 h before administration of the test compound), measurement 1, 2, and 3 h following injection of the test compounds; the acute toxicities and the mean lethal doses (LD_{50}, mg/kg) were also found.

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