NEUROTROPIC ACTIVITY OF DI-(α-CARBALKOXYMETHOXY)-DIETHYLSILANES AND CARBALKOXYALKYL(ARYL)-OXYTRIALKYLSILANES

L. M. Obvintseva, E. L. Pidémskii, R. V. Alikina, T. N. Povarnitsyna, and N. A. Kozlova

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The neutrotropic action of organic compounds of silicon has been reported by many investigators [1-5].

The presence of tranquilizing properties in diethyldialkoxy(aroxy)silanes was shown by us previously [6]. This served as a basis in the search for new neurotropic preparations among organosilicon compounds of similar chemical structure.

In the present work the materials for investigating neurotropic activity were di-(α-carbalkoxymethoxy)-diethylsilanes of general formula $(AlkCOOCH_2O)_2Si(C_2H_5)_2$ and carbalkoxyalkyl(aryl)oxytrialkylsilanes of general formula $Alk'COOCH(R)OSi(Alk)_3$ (I). Compounds were synthesized in the Organic Chemistry Department of Perm University.

Esters of α-trialkylsiloxycarboxylic acids were obtained by the interaction of equimolar amounts of α-hydroxyacid esters and trialkylsilanes in the presence of colloidal nickel [7].

$$RCH(OH)COOAlk' + HSi(Alk)_3 \xrightarrow[-H_2]{} I$$

The physicochemical properties of (I) are given in Table 1.

Di-(α-carbalkoxymethoxy)diethylsilanes were synthesized from esters of oxalic acid and diethylsilane; zinc chloride was used as catalyst [8].

$$(C_2H_5)_2SiH_2 + 2RCH_2OCOCOOCH_2R \xrightarrow[-2RHCO]{} (C_2H_5)_2Si(OCH_2COOCH_2R)_2 + 2H_2$$

II

The properties of (II) are given in Table 2.

EXPERIMENTAL

Chemical

IR spectra of thin films of compounds on a cuvette window were taken on a UR-20 spectrophotometer.

TABLE 1. Esters of α-Trialkylsiloxycarboxylic Acids

Compound	R	Alk	Alk'	Yield, %	bp, °C (mm)	Found, % Si	Empirical formula	Calculated, %	IR spectra, cm⁻¹ C=O	IR spectra, cm⁻¹ (Si–O)
Ia	CH_3	C_3H_7	iso-C_5H_{11}	54	138—40 (4)	8,79	$C_{17}H_{36}O_3Si$	8,87	1743	1145
Ib	C_6H_5	C_2H_5	CH_3	71	149—50 (8)	10,20	$C_{15}H_{24}O_3Si$	10,02	1755	1125
Ic	C_6H_5	C_3H_7	CH_3	38	169—73 (11)	8,72	$C_{18}H_{30}O_3Si$	8,71	1750	1122
Id	C_6H_5	C_2H_5	C_2H_5	82	150—2 (7)	9,69	$C_{16}H_{26}O_3Si$	9,54	1747	1125
Ie	C_6H_5	C_4H_9	C_2H_5	43	199—202 (12)	7,59	$C_{22}H_{38}O_3Si$	7,42	1748	1125
If	o-$CH_3C_6H_4$	C_2H_5	C_2H_5	68	159—61 (8)	9,20	$C_{17}H_{28}O_3Si$	9,10	1748	1126
Ig	m-$CH_3C_6H_4$	C_2H_5	C_2H_5	57	150—2 (5)	8,80	$C_{17}H_{28}O_3Si$	9,10	1747	1122
Ih	p-$CH_3C_6H_4$	C_2H_5	C_2H_5	68	172—4 (11)	8,59	$C_{17}H_{28}O_3Si$	9,10	1747	1125

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α-Trialkysiloxycarboxylic Acid Esters (I). A mixture of α-hydroxyacid ester (0.1 mole), trialkylsilane (0.1 mole), and colloidal nickel, obtained by reducing $NiCl_2$, was heated for 5-6 h at the boiling point of the trialkylsilane used. At the end of the reaction (I) was isolated and purified by redistillation in vacuum.

Di-(α-carbalkoxymethoxy)diethylsilanes (II). A mixture of dialkyl oxalate (0.2 mole), diethylsilane (0.1 mole), and catalyst anhydrous zinc chloride (0.2 g) was heated for 2-3 h at 50-60°C. The flask contents were dissolved in ether, transferred to a separatory funnel, and washed with water. After drying the ether solution and distilling off the solvent the product (II) was redistilled in vacuum.

Pharmacological

Investigation of the neurotropic action of di-(α-carbalkoxymethoxy)diethylsilanes and carbalkoxyalkyl-(aryl)oxytrialkylsilanes was carried out in experiments on tetrahybrid mice and Wistar strain rats. Activity of compounds was assessed by their ability to suppress the orienting reaction [9] and conditioned defensive reflex [10], to potentiate Hexenal narcosis, to show hypothermic and analgesic action [11], to protect animals from convulsions and death after administration of Corazole or by the influence of an electric current [12], and by antagonism of the m-cholinomimetic arecoline. The neurotropic action of compounds was compared with the action of the known tranquilizer trioxazine.

The studied preparations were introduced intraperitoneally as a suspension in 2% starch paste 0.5 h before the investigation in doses of 100 mg/kg (for rats) and 200 mg/kg (for mice) which was 1/10 to 1/15 of the LD_{50} of the preparations. Control animals received an equal volume of starch paste. Hexenal, arecoline, and Corazole were given intraperitoneally in doses of 70, 12, and 70 mg/kg respectively. Trioxazine was applied in doses of 100 mg/kg (for mice) and 50 mg/kg (for rats) which are equieffective to the test doses of the silicon preparations. Results were processed statistically by the method of Litchfield and Wilcoxon [13].

Preparations active in neurotropic respects appeared in both series of organosilicon compounds. Preparations displayed the ability to suppress the orienting reaction in animals to some extent. The majority of compounds increased the residence time of animals in the first chamber and were not superseded by trioxazine in this respect. Another characteristic of the suppression of the orienting reflex is the reduction of the number of valves opened by animals in running a race. The silicon preparations reduced the number of valves opened 2-3-fold in comparison with the control. Preparations (Ia, c, IIa) proved to be the most active by this method.

The investigated compounds also inhibited the conditioned defensive reflex. The most active were preparations (Ic, g, IIa) under the action of which the residence time of animals in the dark chamber after developing the conditioned reflex was on average 90-165 min, i.e., as much again as untrained rats spent in it. The most active compounds surpassed trioxazine in activity. Some preparations (Ie, h, IIc) suppressed the developed conditioned reflex by 50% i.e. they were equal to trioxazine in activity.

With the exception of α-carbisopentoxyethyloxytriethylsilane all the tested compounds increased the duration of Hexenal narcosis by 2.8-3.8-fold. Preparations eliminated the Hexenal hyperkinesis observed in control animals when entering narcosis and emerging from it.

Compounds (Ia, b, g, IIa, b) significantly reduced (by 0.8-1.2°C) rectal temperature in rats. The hypothermic action reached a maximum after 2-4 h and remained for 2-3 h. Carbomethoxybenzyloxytripropylsilane (Ic) and carbethoxybenzyloxytriethylsilane (Id) displayed the greatest activity under the action of which the initial rectal temperature of animals was reduced by 2.9 and 2.1°C respectively.

The majority of the investigated preparations displayed an analgesic effect (by the hot plate test). This action was most marked for preparations (Ig, h) and was equal to that of trioxazine. The remaining compounds were less active than trioxazine. Maximal activity of the preparations was displayed 1.5-2 h after their administration and continued for 2 h.

No anticonvulsive action was detected for the investigated compounds, however preparations possessed the ability to protect animals from death caused by the action of an electric current or Corazole. The investigated compounds did not prevent arecoline tremor and had no influence on its duration

The ability of the studied compounds to suppress the conditioned reflex activity of animals, to potentiate Hexenal narcosis, to show hypothermic and analgesic action, and to protect animals from death under the action of an electric current or Corazole indicates the presence in them of neurotropic properties. Of all the compounds investigated preparations (Ic, g, h, IIa) showed activity in the majority of tests.

TABLE 2. Di-(α-carbalkoxymethoxy)diethylsilanes

Compound	R	Yield, %	bp, °C (mm)	Found, % Si	Empirical formula	Calculated, % Si	IR Spectra, cm^{-1}	
							C=O	(Si—O)
II	C_4H_9	52	160—2 (12)	7,98	$C_{16}H_{32}O_6Si$	8,06	1736	1194
IIb	iso-C_5H_{11}	48	190—2 (15)	7,50	$C_{18}H_{36}O_6Si$	7,46	1742	1182
IIc	C_6H_{13}	47	195—8 (15)	6,58	$C_{20}H_{40}O_6Si$	6,94	1735	1191
IId	C_9H_{19}	41	180—5 (5)	5,59	$C_{26}H_{52}O_6Si$	5,79	1737	1186

Study of the dependence of neutrotropic activity on the chemical structure of the compounds made it possible to establish that in the series of di-(α-carbalkoxymethoxy)diethylsilanes the most active was preparation (IIa) having a butoxy group. With an increasing number of carbon atoms in the alkoxy group the neurotropic activity of compounds fell (IId).

Substitution in the α-carbalkoxyalkyloxytriethylsilane molecule of the alkoxy group by a benzyloxy group led to a strengthening of the hypothermic action (Ic-e). The remaining types of activity were not appreciably changed. Inclusion of an o-, m-, or p-tolylmethoxy radical in the molecule was accompanied by a strengthening of the analgesic properties of compounds (If-h).

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