SYNTHESIS AND BIOLOGICAL ACTIVITY OF 3-PERFLUOROACYLOXY-, 3,3,3-TRIFLUORO-, AND 3-FLUOROPROPYLSILATRANES

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The synthesis and study of new classes of organofluorine silicon compounds are interesting not only from the theoretical point of view, but also because of any possible combination of pharmacologically valuable properties in them that are specific of both silicon and organofluorine compounds.

It is known that 1-alkyl- and 1-phenylsilatranes have a weak analgesic effect [2, 5, 8, 9]. Introduction of a fluoride atom into the molecule of an organic compound with a psychotropic action leads, in general, to intensification of this effect [1]. We have already reported on the high toxicity of trifluoropropylsilatrane, causing depression of the central nervous system in animals, and in particular, of the respiratory center [4, 7].

The present work deals with the synthesis and study of the neurotropic action of previously unknown (3-perfluoroacyloxy)propylsilatranes (I-VIII), and also of 3,3,3-trifluoro- and 3-fluoropropylsilatranes (IX-XIII), whose synthesis we have already described [7].

Compounds I-VIII were obtained by the reaction of trimethylsilyl ethers of triethanolamine and its C-methyl substituted derivatives with the corresponding (perfluoroacyloxypropyl)trifluorosilanes:

$$R_FCOO(CH_2)_3SiF_3 + (CH_3)_3Si(OCH_2CH_2)_n(OCHRCH_2)_{3-n}N \longrightarrow$$

$$\longrightarrow R_FCOO(CH_2)_3Si(OCH_2CH_2)_n(OCHRCH_2)_{3-n}N + 3(CH_3)_3SiF.$$

I — VIII

I: $R_F = CF_3$, R — none, $n = 3$; II: $R_F = C_3F_7$, R — none, $n = 3$;

III: $R_F = C_4F_9$, R — none, $n = 3$; IV: $R_F = CF_3$, $R = CH_3$, $n = 0$; V: $R_F = CF_3$, $R = CH_3$, $n = 1$; VI: $R_F = CH_3$, R — none, $n = 3$; VII: $R_F = CF_3$, R = H, $n = 2$;

VIII: $R_F = C_3F_7$, R = H, $n = 2$.

In contrast to acyloxypropyl silatranes $RCOO(CH_2)_3Si(OCH_2CH_2)_3N$, where R = CH_3, C_6H_5, ClC_6H_4, etc., n = 1-3, these compounds could not be obtained by transesterification of perfluoroacyloxypropyltrialkoxysilanes with hydroxyalkylamines [6].

The process was carried out in the absence of a solvent and catalysts by heating the reaction mixture at 90-100°C until no more gaseous trimethylfluorosilane was evolved, followed by addition of hexane and boiling the reaction mixture for 10-20 h. The yield of the end products were 60-70% (see Table 1).

The compounds obtained are low-melting crystalline substances of oily odorless liquids. They readily dissolve in chloroform and in ether. The C-methyl derivatives distill *in vacuo*.

Unexpectedly, 3-perfluoroacyloxypropylsilatrane I has a higher melting point than acetoxypropylsilatrane VI (see Table 1). Increase in the number of fluorine atoms in the molecule of compounds I-VIII did not lead to increase in toxicity (Table 2).

In the IR spectra of compounds I-VIII, and anomalous shift of the characteristic $\nu_{C=O}$ frequencies and deformational vibrations of the atrane polyhedron to the high frequencies region is observed (see Table 1). The C—F bands are represented by intense singlets in the

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TABLE 1. Physicochemical Characteristics of 3-Perfluoroacyloxypropylsilatranes I-VIII

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				ν, cm⁻¹			
			C	H	Si	F		C	H	Si	F	atrane	C=O	Si—O—C	C—F
I	72	84—6	39,95	5,28	8,13	17,67	$C_{11}H_{18}F_3NO_5Si$	40,11	5,51	8,53	17,31	570	1690	1028 1100	1210 1328
II	74	51—3	36,46	4,71	6,15	30,67	$C_{13}H_{18}F_7NO_5Si$	36,36	4,22	6,54	30,97	570	1680	1038 1120	1212 1342
III	73	63—5	35,31	3,85	5,75	35,37	$C_{14}H_{18}F_9NO_5Si$	35,08	3,75	5,86	35,67	575	1688	1022 1138	1210 1345
IV*	69	94—6	45,18	6,73	7,53	15,60	$C_{14}H_{24}F_3NO_5Si$	45,27	6,51	7,56	15,35	560	1688	1070 1116	1210 1345
V	55	58—9	44,32	7,07	8,03	16,51	$C_{13}H_{22}F_3NO_5Si$	43,68	6,20	7,86	15,95	560	1680	1028 1130	1210 1320
VI	60	65—7	47,68	8,13	9,81	—	$C_{11}H_{21}O_5SiN$	47,97	7,69	10,20	—	585	1732	1030 1105	—
VII	51	—	Oil, decomposes on distillation									545	1675	1026 1130	1210 1325
VIII	56	—	Oil, decomposes on distillation									560	1788	1038 1120	1212 1342

*bp 133-140°C/2.5 mm Hg; n_D^{20} 1.4552; d_4^{20} 1.2259.

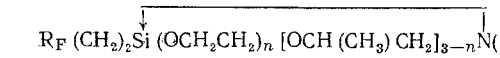
TABLE 2. Pharmacological Activity of 3-Perfluoroacyloxypropylsilatranes I-IV

Compound	LD_{50}, mg/kg	Rectal temperature, °C			Motor activity			Index of prolongation of hexenal-induced sleep
		after 30 min	after 60 min	after 120 min	after 30 min	after 60 min	after 120 min	
I	2000	35,6±0,4	36,3±0,3	36,8±0,4	3,0±0,2	3,2±0,3	3,3±0,3	1,44
II	3000	33,2±0,24*	33,8±0,28*	35,8±0,4	3,1±0,2	3,6±0,4	3,2±0,4	1,98
III	4000	33,6±0,23*	34,5±0,22*	33,8±0,4*	3,9±0,56*	4,0±0,56*	4,0±0,45	1,39
IV	3678	35,2±0,52	34,8±0,53*	33,1±1,04*	2,5±0,7	3,7±0,56*	4,25±0,7*	2,9

*Differences are statistically significant.

1130-1370 cm^{-1} region, while the Si—O—C grouping is characterized by moderately intense bands at 800-810 and 1050-1130 cm^{-1}.

We also studied the neurotropic action of previously synthesized [7] 3,3,3-trifluoro- and 3-fluoropropylsilatranes:



IX-XIII; IX: $R_F = CH_2F$, $n = 3$; X: $R_F = CF_3$, $n = 3$; XI: $R_F = CF_3$, $n = 2$; XII: $R_F = CF_3$, $n = 1$; XIII: $R_F = CF_3$, $n = 0$) (see Table 3)

EXPERIMENTAL CHEMISTRY

The IR spectra were run on the UR-20 spectrophotometer (GDR) in KBr tablets or in solutions in $CHCl_3$.

A mixture of 0.05 mole of tris(2-trimethylsiloxyethyl)amine and 0.05 mole of the corresponding organyltrifluorosilane was heated until no more gaseous trimethylfluorosilane was evolved. Then, 50 ml of hexane were added and the mixture was boiled for 12 h. Hexane was distilled at reduced pressure, the residue was dissolved in chloroform and crystals were precipitated by ether, or it was distilled *in vacuo*.

1-(3-Trifluoroacetoxypropyl)silatrane (I). A 6.9-g portion (0.018 mole) of tris(2-trimethylsiloxyethyl)amine and 4.32 g (0.018 mole) of (3-trifluoroacetoxypropyl)trifluorosilane were mixed in a four-necked flask, fitted with a stirrer, thermometer, dropping funnel, and a reflux condenser connected to a bubbler. The reaction mixture was stirred for 15 min to cessation of bubbling of trimethylfluorosilane formed. Then, 20 ml of hexane were added, and the mixture was heated for 12 h at 60°C. Hexane was distilled in a water-jet pump vacuum, the residue was dissolved in chloroform, precipitated by ether, and filtered by suction *in vacuo*. Yield, 4.2 g (72%) of I, mp 84-86°C.

Silatranes IX-XIII and also VI were obtained by the reaction of the corresponding organyltrialkoxysilanes with tris(2-hydroxyalkanol)amines in the presence of a catalytic amount of sodium alcoholate.

1-(3,3,3-Trifluoropropyl)silatrane (X). An 18.2-g portion (0.07 mole) of 3,3,3-trifluoropropyltriethoxysilane was added dropwise to a boiling solution of 10.8 g (0.07 mole) of triethanolamine in 30 ml of absolute ethanol. When cool, 10 ml of hexane were added dropwise, and its mixture with ethanol formed was distilled off. The precipitate formed was washed with ether and dried *in vacuo*. After recrystallization from chloroform, 14.5 g of compound X, mp 108°C , were isolated.

EXPERIMENTAL PHARMACOLOGY

The acute toxicity of 3-perfluoroacyloxy-, 3,3,3-trifluoro-, and 3-fluoropropylsilatrane and the character of their action on the central nervous system were studied on nonpedigree white mice with interperitoneal administration. We also studied the influence of these compounds on the resistance factors of the organism (the complement titer, content of lysozyme and β-mesines and bactericidal activity of blood serum).

The neurotropic effect of the compounds was estimated from the ability to change the spontaneous motor activity, to potentiate the hexenal-induced narcosis, and to exhibit a hypothermal action [3].

It was thus found that 3-perfluoroacyloxypropylsilatranes are practically nontoxic (see Table 3). However, 3-fluoro- and 3,3,3-trifluoropropylsilatranes are highly and moderately toxic compounds (Table 4).

Almost all the 3-perfluoroacyloxypropylsilatranes decrease the rectal temperature and prolong hexenal-induced narcosis. The potentiating effect is most pronounced in IV (see Table 2). Silatranes I and IV change the complement titer and the lysozyme content in blood. Compound II exhibits a weakly expressed antistress action.

In the study on the relationship between the biological action of these compounds and the structure, it was found that elongation of the carbon chain and increase in the number

TABLE 3. Physicochemical Characteristics of 3-Fluoro- and 3,3,3-Trifluoropropylsilatranes IX-XIII

Compound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				ν, cm⁻¹	
			C	H	Si	F		C	H	Si	F	Si–O–C	C–F
IX	96	72	45,92	7,70	11,31	7,73	$C_9H_{18}FNO_3Si$	45,93	7,71	18,93	8,07	980 1035 1080	1129
X	78	108	39,63	5,93	11,18	21,15	$C_9H_{16}F_3NO_3Si$	39,98	5,94	10,35	21,00	980 1017 1066	1130 1360
XI*	91	36	42,07	6,40	10,12	19,70	$C_{10}H_{18}F_3NO_3Si$	42,09	6,36	9,84	19,98	782 1060 1118	1130 1382
XII†	90	32	45,49	6,75	9,37	18,62	$C_{11}H_{20}F_3NO_3Si$	44,13	6,73	9,38	19,04	980 1030 1120	1118 1382
XIII‡	98	58	46,00	7,10	8,90	17,94	$C_{12}H_{22}F_3NO_3Si$	45,90	7,07	8,96	18,18	980 1060 1118	1118 1388

*bp 121°C/1 mm Hg; n_D^{20} 1.4393; d_4^{20} 1.2329; MR_D: found 60.91; calculated 61.58.
†bp 150°C/4 mm Hg; n_D^{20} 1.4404.
‡bp 136°C/1.5 mm Hg.

TABLE 4. Pharmacological Activity of 3-Fluoro- and 3,3,3-Trifluoropropylsilatranes IX-XII

Compound	LD_{50}, mg/kg	Rectal temperature, °C			Motor activity			Index of prolongation of hexenal-induced sleep
		after 30 min	after 60 min	after 120 min	after 30 min	after 60 min	after 120 min	
IX	90	36,3±0,2	36,8±0,3	36,9±0,4	2,7±0,1	2.2±0,2	2,4±0,2	1,49
X	0,2	36,8±0,4	37,2±0,3	37,1±0,2	2,8±0,2	2,2±0,2	2,3±0,3	1,09
XI	260	36,2±0,3	35,8±0,2	35,0±0,2*	2,1±0,1	2,4±0,2	2,6±0,2	1,28
XII	260	36,7±0,3	35,2±0,2*	35,4±0,3*	2,9±0,1	3,2±0,1	3,9±0,2*	1,68

*Differences are statistically significant.

of fluorine atoms in the molecule of 3-perfluoroacyloxypropylsilatranes leads to decrease in the toxicity and a certain intensification of the neurotropic activity.

In contrast to these compounds, 3-fluoro- and 3,3,3-trifluoropropylsilatranes are considerably more toxic (see Table 4). The introduction of three methyl groups at positions 3, 7, and 10 of the silatrane skeleton decrease the toxicity, and is accompanied by the appearance of the hypothermal and potentiating ability (Table 2).

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SYNTHESIS AND LOCAL-ANESTHETIC ACTIVITY OF 6-[ω-AMINO-ω-ARYLALKYL]BENZO-1,4-DIOXANES

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A number of benzo-1,4-dioxane derivatives are known to exhibit local-anesthetic activity [3, 4]. Since ω-aminoalkylbenzene with a phenyl group in the side chain also exhibits activity of this type [11], we have synthesized a number of new benzo-1,4-dioxane analogs and studied their local anesthetic properties.

The 6-(ω-amino-ω-arylalkyl)benzo-1,4-dioxanes (IIa-e) were synthesized by Leuckart's reaction; the 6-(ω-aroylvinyl)benzo-1,4-dioxanes (Ia-e) were heated with ammonium formate, and the N-formyl derivatives then hydrolyzed with acid.

The ketone Ia was synthesized by acylation of benzo-1,4-dioxane (III) with benzoyl chloride, and the ketones Ib-e by hydrogenation of the 6-(2-aroylvinyl)benzo-1,4-dioxanes (V) in the presence of Raney nickel; the latter were obtained by condensation of 6-formylbenzo-1,4-dioxane (IV) [4] with acetophenone or its p-derivative in methanolic potassium hydroxide at 20°C by the usual method [7]. The chalcones Vb and c (An = C_6H_4Cl-p, C_6H_4F-p) were prepared for the first time.

Hydrogenation of the chalcone Vb ($_9$Ar = C_6H_4Cl-p) proceeded more slowly than for the other compounds, and uncontrolled hydrogenation of the chalcone Va (Ar = C_6H_5) gave 6-(3-hydroxy-3-phenylpropyl)benzo-1,4-dioxane (VI).

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