SYNTHESIS AND PHYSIOLOGICAL ACTIVITY OF 1-(2-POLYFLUOROALKYL-1-IODOETHYL)SILATRANES

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Fluoroorganic compounds occupy an important place in the drug arsenal [8, 32]. However, the physiological activity of fluoroorganic derivatives of silicon has not yet been investigated. The silatranes $RSi(OCH_2CH_2)_3N$ are known to have a wide spectrum of biological activity [3, 30]. Thus, 1-organylsilatranes (R = Me, CH_2=CH, C_6H_5) exhibit a sedative effect and potentiate the narcotic effect of hexabarbital [14]. Introduction of polyfluoroalkyl groups or fluorine atoms into the molecules of physiologically active compounds intensifies their inherent psychotropic or anti-inflammatory effect [8]. This prompted us to develop methods of synthesis and to study the pharmacological action of 1-(2'-polyfluoroalkyl-1'-iodoethyl)silatranes. To prepare them, we chose the addition reaction of polyfluoroiodoalkanes to 1-vinylsilatrane and its eso-methyl derivatives.

Perfluoroiodoalkanes add to the double bond on UV irradiation [23], or on heating [23] in the presence of radical initiators [15], or electrochemically [20]. This process is also accelerated by mercury, copper salts or amines at 135°C [16, 21]. The radical reaction of primary and secondary perfluoroalkyl iodides at room temperature is initiated by sodium aryl and alkyl sulfinates in aprotic bipolar solvents [22]. The UV-light-initiated photochemical addition of trifluoroiodomethane to vinyl trimethylsilane is accomplished after 102 h to the extent of 79%, and vinyltrichlorosilane to the extent of 35% after 9.5 days [23].

We found that polyfluoroiodoalkanes add to 1-vinylsilatrane and its eso-C-substituted derivatives in a $CHCl_3$ medium according to the following scheme:

$$RI + CH_2{=}CH\overbrace{Si(OCHMeCH_2)_n(OCH_2CH_2)_{3-n}N}\rightarrow$$

$$\rightarrow RCH_2CHI\overbrace{Si(OCHMeCH_2)_n(OCH_2CH_2)_{3-n}N}$$

R=CF_3, n=0 (I); R=C_3F_7, n=0 (II); R=C_3F_7, n=1 (III); R=C_3F_7, n=3 (IV); R=$H(CF_2)_4$, n=0 (V); R=$CF_3(CF_2)_5$, n=0 (VI); R=$H(CF_2)_6$, n=0 (VII); R=C_6F_{13}, n=0 (VIII); R=$H(CF_2)_8$, n=0 (IX); R=$CF_3(CF_2)_7$, n=0 (X).

The reaction proceeds slowly (60-120 h) even in scattered light, while under UV irradiation it is concluded after 2-3 h. The yield of the adducts I-X is 78-100% (Table 1).

The strong electron donor effect of the silatrane grouping $\overbrace{N(CH_2CH_2O)_3Si}$ (σ_1 = −0.56 [6]) possibly activates the addition to it of the more electron-deficient radical $I^{\cdot}$ by increasing the electron density on the α-carbon atom of the vinyl group:

$$RI \rightleftharpoons R^{\cdot} + I^{\cdot}$$

$$I + CH_2{=}CH\overbrace{Si(OCH_2CH_2)_3N}\rightarrow CH_2{-}\overset{\cdot}{C}H\overbrace{Si(OCH_2CH_2)_3N}$$

$$R^{\cdot} + CH_2{-}\overset{\cdot}{C}HI\overbrace{Si(OCH_2CH_2)_3N}\rightarrow RCH_2CHI\overbrace{Si(OCH_2CH_2)_3N}$$

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TABLE 1. Reaction Conditions of 1-Vinylsilatrane and Its eso-C-Methyl Substituted Derivatives (A) with Polyfluoroalkyl Iodides and Characteristics of Synthesized 1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes I-X

Compound	The A:B ratio	Duration of reaction, h (solvent)	Mp, °C	Yield, %	Empirical formula
I	1:1,34	30 ($CHCl_3$)	119,5	95	$C_9H_{15}F_3INO_3Si$
II	1:2	120 ($CHCl_3$)	137—8	97	$C_{11}H_{15}F_7INO_3Si$
	1:1,67	3 ($CHCl_3$)		98	
III	1:1,4	70 ($CHCl_3$)	89—90	78	$C_{12}H_{17}F_7INO_3Si$
IV	1:2	120 ($CHCl_3$)	125—6	86	$C_{14}H_{21}F_7INO_3Si$
V	1:0,57	70 ($CHCl_3$)	99—100	100	$C_{12}H_{16}F_8INO_3Si$
	1:1	22 (C_6H_6)*		31	
VI	1:1,28	60 ($CHCl_3$)	138—8,5	100	$C_{12}H_{15}F_9INO_3Si$
VII	1:1,25	120 ($CHCl_3$)	103,5—4	79	$C_{14}H_{16}F_{12}INO_3Si$
VIII	1:1,5	48 ($CHCl_3$)	135—6	91	$C_{14}H_{15}F_{13}INO_3Si$
IX	1:1,24	32 ($CHCl_3$)	115—5,5	100	$C_{16}H_{16}F_{16}INO_3Si$
	1:1,5	9,5 (C_6H_6)*		28	
X	1:1,26	80 ($CHCl_3$)	137—9	100	$C_{16}H_{15}F_{17}INO_3Si$

*During UV irradiation.

TABLE 2. Neurotropic Activity Indexes of 1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes V-X

Compound	Motoric activity, points			Rectal temperature, °C			Inhibition of pain reaction during thermal effect, sec		
	After 30 min	After 60 min	After 120 min	After 30 min	After 60 min	After 120 min	After 15 min	After 30 min	After 60 min
V	2,4±0,1*	2,1±0,2*	2,2±0,3*	35,2±0,2*	35,5±0,2*	35,1±0,2*	213±28	238±15	198±35
VI	2,2±0,4	2,9±0,4*	3,5±0,6*	34,6±0,3*	35,1±0,2*	35,0±0,3	340±57*	212±63	131±27
VII	1,8±0,1	1,3±0,1	1,7±0,2	35,6±0,4*	35,9±0,3	35,9±0,2	245±26	185±26	168±21
VIII	1,2±0,1	1,2±0,1	1,2±0,1	33,3±0,4	33,9±0,4	34,1±0,6	380±33*	244±47	393±30*
IX	1,6±0,2	2,5±0,3*	2,4±0,3*	34,4±0,4	34,0±0,4	34,0±0,5	256±16	169±12	111±25
X	1,6±0,1	1,5±0,1	2,9±0,2*	35,8±0,3*	35,9±0,3	36,0±0,3	269±25	114±26	119±34
Control	1,6±0,2	1,7±0,3	1,9±0,2	36,6±0,3	36,1±0,3	35,9±0,2	210±18	170±21	149±38

* $P=0,05$.

The photochemical addition of polyfluoroiodoalkanes to 1-vinyl-silatrane in benzene medium is sharply retarded and is accompanied by strong resinification. In analogy with this, the reaction of norbornene with perfluorooctyl iodide, initiated by p-toluenesulfonate, also proceeds noticeably slowly in benzene [22]. The slowing down of reactions in which halogen radicals participate in an aromatic solvent is caused by the formation of π-complexes of these radicals with aromatic molecules having lower reactivity [1].

The 1-(2'-polyfluoroalkyl-1'-iodoethyl)silatranes I-X obtained are white crystalline substances with a yellowish tinge which are insoluble in water, and readily soluble in $CHCl_3$. The melting points of compounds I-X are given in Table 1.

The chemical shifts of the ^1H nuclei of the OCH_2 and NCH_2 groups in the PMR spectra of silatranes I, II, V-X are observed at 3.84-3.85 and 2.89-2.90 ppm (in $CDCl_3$), respectively. This nearly coincides with the influence on the resonance of protons of these groups in the spectrum of 1-iodomethylsilatrane (3.84 and 2.86 ppm, respectively [3]).

In the IR spectra of compounds I-X intense ν(C-F) absorption bands are observed in the 1100-1280 cm^{-1} region, which overlap at the low frequency side with the vibration bands of the Si—O—C grouping. The vibrations of the bonds in the silatrane skeleton in I-X appear in the usual region [4] and are inappreciably shifted with a change in R.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were run on a "Tesla BS487 C" spectrometer, using TMS as internal standard. The IR spectra were obtained on a "Specord IR" spectrophotometer in KBr tablets.

1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes (I-X). A solution of 10 mmoles of 1-vinylsilatrane and 5.7-20 mmoles of the corresponding polyfluoroalkyl iodide was held in a sealed pyrex glass ampule with a scattered natural illumination, or was irradiated by UV light (a PRK-2 lamp). The ratio of the reagents, the solvent, method of initiation of the reaction and

TABLE 3. Influence of 1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes V-X on the Narcotic Effect of Hexenal Chloral Hydrate and Barbamyl

Compound	Duration of narcosis (in min) after the introduction of		
	hexenal	chloral hydrate	barbamyl
V	61,8±9,1	61,0±5,4	49,7±3,9
VI	54,2±4,8	63,8±6,9	51,3±4,1
VII	69,1±4,3*	70,1±8,1	57,0±5,2
VIII	57,0±9,0	67,3±7,8	54,5±6,0
IX	61,0±8,0	174,4±13,2*	75,1±6,9*
XX	50,6±6,6	77,0±6,2	62,0±4,9*
Control	47,1±3,4	54,3±6,8	44,4±0,1

* $p=0,05$.

TABLE 4. Frequency of Appearance of Stimulating Effect of 1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes V-IX on Various Subpopulations of Human Peripheral Blood Lymphocytes

Subpopulation of lymphocytes	Compound					K
	V	VI	VII	VIII	IX	
Total T-lymphocytes	62±12*	56±13*	81±10*	56±13*	69±12*	46±9
Active T-lymphocytes	56±13	62±12	75±11*	62±12	56±13	50±11
Active multireceptor T-lymphocytes	62±12*	56±13	81±10*	67±13*	62±12*	42±8
Active low-receptor T-lymphocytes	25±11	38±12	50±13	43±13	31±12	30±12
Thermostable T-lymphocytes	38±12*	43±13*	56±13*	43±13*	18±8	18±6
Autorosette-forming T-lymphocytes	25±14	38±12*	75±11*	25±14	12±10	16±6
Theophylline-resistant T-lymphocytes	56±13*	50±13*	62±12*	43±13	81±10*	27±11
B-Lymphocytes related to mice erythrocytes	19±10	50±13*	38±12	25±11	12±8	29±13

Note. Here and in Table 5 the asterisk designates $p < 0.05$ or 0.05.

its duration are given in Table 1. The reaction mixture was heated to boiling, filtered, the solution was evaporated, and the crystals of I-X that separated out were filtered off, washed with pentane, and dried. The elemental analysis data of I-X corresponded to the calculated values.

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity and neurotropic activity of compounds I-X were studied on nonpedigree white mice of both sexes, each weighing 20-24 g, with intraperitoneal administration.

The neurotropic activity was evaluated from the ability of compounds V-X to change the spontaneous motoric activity, the rectal temperature and the reaction to the pain irritant during a thermal effect, and also from the simultaneous influence on the central nervous system of silatranes V-X and of compounds producing on it both a depressive (reserpine, sodium barbital, chloral hydrate) and activating action (phenamine, corazole) [5, 9]. The influence of the gamma-aminergic systems was determined from the ability to prevent spasms caused by thiosemicarbazide [10]. The M-cholinergic action was studied with arecoline treatment [5].

The immunomodulating properties of silatranes V-IX on the T- and B-lymphocytes was studied on human lymphocytes (6 healthy donors and 10 patients with lymphoproliferative and allergic diseases with manifestations of secondary immunodeficiency) according to the methods described in [2, 11, 13, 17-19, 24, 26, 27, 29]. The lymphocytes were isolated by gradient centrifugation with verographine [25] and were brought up to a concentration of $5 \cdot 10^5$ cells/ml.

Substitution of three terminal hydrogen atoms by fluorine atoms in the nontoxic 1-propylsilatrane molecule gives a very toxic (LD_{50} 5 mg/kg intraperitoneally for white mice) 1-(3',3",3"'-trifluoropropyl)silatrane [3, 30]. Its closest analogs – 1-(2'-perfluoroalkyl-1'-iodoethyl)silatranes with R = CF_3(I), C_3F_7 (II) and C_4F_9 (VI) – have moderate toxicity, which decreases with the elongation of the perfluoroalkyl group (LD_{50} 120, 180 and 400 mg/kg, respectively). At the same time, substitution of only one terminal

TABLE 5. Frequency of Appearance of Suppressing Effect on 1-(2'-Polyfluoroalkyl-1'-iodoethyl)silatranes V-IX on Various Subpopulations of Human Peripheral Blood Lymphocytes

Subpopulation of lymphocytes	Compound					K
	V	VI	VII	VIII	IX	
Theophylline sensitive T-lymphocytes	56±13	50±13	56±13	43±13*	75±11	60±17
Thermostable T-lymphocytes	6±6	12±8	12±8	6±6	0±6	12±4
Autorosette-forming T-lymphocytes	6±6	0±6	25±14	6±6	6±6	29±13

fluorine atom in the C_4F_9 group for a hydrogen atom sharply decreases the toxicity (in compound V the LD_{50} is 2000 mg/kg). Silatranes VII-X with the RC_6 and C_9 length are practically nontoxic (LD_{50} 3000 mg/kg).

In a dose of 0.2 LD_{50}, compound II has a depressive action, decreasing the pain sensitivity and the motoric activity [3, 30]. In contrast to II, silatrane VIII in a dose of 1/150 LD_{50} has weaker neurotropic action when the evaluation is carried out with respect to the same factors. Among the nontoxic silatranes VII-X, compound VIII exhibits the highest analgesic effect (Table 2). All the compounds V-X studied decrease the motoric activity and the rectal temperature. However, only silatranes V and IX decrease these two indexes over all periods of observation. Silatrane IX prolongs the narcosis produced by chloral hydrate and barbamyl (by 3.2 and 1.7 times, respectively; Table 3). The weakest potentiating effect is exhibited by the more toxic compounds V and VI. Silatranes V, VII and X intensify the hypothermal effect of apomorphine in contrast to compounds VI, VIII and IX, which weaken this effect. However, the development of reserpine-induced hypothermia is inhibited by both silatrane IX and X. Compounds V-X considerably decrease the head-shaking phenomenon provoked by 5-hydroxytryptophan. Silatrane IX intensifies the phenamine stereotypy. Treatment with thiosemicarbazide (an inhibitor of the glutamate decarboxylase enzyme) indicates the absence of the influence of silatranes V-X on the gamma-aminergic systems. At the same time the prolongation of the arecoline-induced spasms by these compounds indicates their M-cholinomimetic activity.

The presence of a stimulating effect of 1-(2'-polyfluoroalkyl-1'-iodoethyl)silatranes V-IX on subpopulations of human peripheral blood lymphocytes is illustrated in Table 4, and the suppressing effect in Table 5. The results were processed by the method of cybernetic sampling [7]. The stimulating effect on total T-lymphocytes is observed by the action of all the compounds studied, but is most significant in VII. The growth in the number of T-cells occurs mainly due to the highly-avid active T-lymphocytes (a twofold excess), and especially their multireceptor variety. Silatranes V-VIII also have a pronounced stimulating effect on the key immature T-lymphocytes and effector cells (the thermostable and autorosette-forming lymphocytes). In this, compound VII is the most active. Compounds V-IX also display a stimulating effect on the theophylline-resistant T-lymphocytes – the assistants, correspondingly decreasing the relative content of theophylline-sensitive T-lymphocytes – the suppressors. Silatrane VIII has the highest activity in this respect. The parameters of B-lymphocytes related to mice erythrocytes practically do not change, but silatrane VI stimulates this subpopulation of lymphocytes in vitro. The same compound has a weak stimulating effect on the A cells of the blood.

Thus, 1-(2'-polyfluoroalkyl-1'-iodoethyl)silatranes V-X influence the neurochemical processes to a certain extent, while silatranes V-IX modulate the cell unit of immunogenesis.

LITERATURE CITED

1. A. L. Buchachenko and O. P. Sukhanova, Usp. Khim., No. 3, 475 (1967).
2. Kh. M. Veksler, P. M. S'yakste, É. Ya. Sprukule et al., Immunological Hemostasis and Immunoregulating Therapy [in Russian], Zinatne, Riga (1979), pp. 116-118.
3. M. G. Voronkov and V. M. D'yakov, Silatranes [in Russian], Nauka, Novosibirsk.
4. M. G. Voronkov, S. G. Shevchenko, E. M. Brodskaya, et al., Atlas of Spectra of Organic Compounds [in Russian], No. 31, Novosibirsk (1985).
5. G. G. Gatsura, Methods of Primary Pharmacological Investigation of Biologically Active Compounds [in Russian], Meditsina, Moscow (1974).
6. V. I. Glukhikh, M. G. Voronkov, O. G. Yarosh, et al., Dokl. Akad. Nauk SSSR, 258, 387 (1981).

7. V. S. Genes, Some Simple Methods of Cybernetic Treatment of Data of Diagnostic Physiological Investigations [in Russian], Nauka, Moscow (1967).
8. N. Isikawa and E. Kobayasi, Fluorine, Chemistry and Application [Russian translation], Mir, Moscow (1982).
9. M. D. Mashkovskii, N. I. Andreeva, and A. I. Polezhaeva, Pharmacology of Antidepressants [in Russian], Meditsina, Moscow (1983).
10. D. Mecler, Biochemistry [Russian translation], Vol. 3, Mir, Moscow (1980).
11. I. M. Remez, Industry and Immunological State of Organism [in Russian], No. 3, Part 2, All-Union Scientific-Research Medical Institute, Moscow (1983), pp. 43-47.
12. E. K. Slavcheva, "Tetracycline and primary immune response," Antibiotiki, No. 1, 75-79 (1976).
13. A. N. Cheredeev, General Problems of Pathology [in Russian], Part 4, All-Union Scientific-Research Medical Institute, Moscow (1976), pp. 124-126.
14. E. Bien, Pharmazie, 26, Part 6, 224 (1971).
15. N. O. Brace, J. Fluorine Chem., 20, 313 (1982).
16. D. J. Burton, and L. J. Kehoe, Tetrahedron Lett. 5163 (1966).
17. J. Caraux, C. Thierg, C. Esteve, et al., Cell. Immunol., 45, 36-48 (1979).
18. J. Dolen and B. H. Park, Immunological Communications, 6, 677-689 (1973).
19. E. Elliot and J. S. Haskill, Eur. J. Immunol., 3, 68-75 (1973).
20. European Patent Appl. 43758; Chem. Abstr., 96, 132156x (1982).
21. European Patent Appl. 43757; Chem. Abstr., 96, 199075 (1982).
22. A. E. Feiring, J. Org. Chem., 50, 3269 (1985).
23. A. M. Geyer, R. N. Haszeldine, L. Leedham, et al., J. Chem. Soc., 4472 (1957).
24. L. Holm, Immunol. Methods, 8, 277-281 (1975).
25. J. Holowiecki, H. J. Tiliger, and A. Felden, Arch. Immunol. Therap. Exp., 22, 177-180 (1974).
26. M. Jondal, G. Hoim, and H. Wigzell, J. Exp. Med., 136, 207-215 (1972).
27. S. Limatibul, A. Shore, H. M. Dosch, et al., Clin. Exp. Immunol., 33, 503-513 (1978).
28. W. A. Sheppard and C. M. Sharts, Organic Fluorine Chemistry, New York, 189-193 (1969).
29. R. Smith, R. Kerman, G. Erdinli, et al., J. Immunol. Methods, 8, 175-184 (1975).
30. M. G. Voronkov, Topics in Current Chemistry, 84, 77 (1979).
31. M. H. Wansbrough-Jones, G. H. Sculiarg, A. Nicholson, et al., Clin. Exp. Immunol., 35, 390-396 (1979).
32. J. Welch, tetrahedron, 43, 3123-3197 (1987).

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF γ-BROMOPROPARGYL ESTERS OF CARBAMIC ACIDS

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In order to study the reactivity of the terminal hydrogen atom in propargyl carbamates that we have previously synthesized [1], and also to prove their structure, we have carried out their bromination. The substitution of the acetylenic hydrogen in propargyl carbamates by bromine proceeds with the participation of equimolar amounts of propargyl carbamates and $CuBr_2$ in an organic solvent medium.

It should be noted that this method of bromination differs from the hypohalite method [2]. It is simpler, since the reaction proceeds in one step at room temperature.

The bromination was carried out at room temperature in a methanol medium according to the following scheme:

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