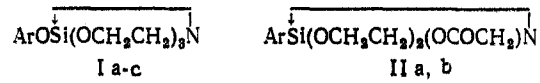
BIOLOGICAL ACTIVITY OF 1-AROXYSILATRANES AND 1-AROXYSILATRAN-3-ONES

V. B. Kazimirovskaya, L. A. Mansurova,
T. P. Torshina, T. V. Nefedova,
E. V. Bakhareva, L. A. Ageeva,
P. Hencsei, J. Nad', and
M. G. Voronkov

UDC 615.27:547.271].015.4

Earlier we showed that certain 1-substituted silatranes $RSi(OCH_2CH_2)_3N$ possess high specific activity [3, 4, 13, 16, 17]. In particular, they are stabilizers of the erythrocyte membranes, inhibitors of platelet aggregation, anticoagulants, inhibitors of lipid peroxidation, stimulators of the proliferative-repair function of connective tissue, pilotropic agents, etc. [5, 7, 10].

In this communication we consider the results of investigations of the biological activity of 1-aroxysilatranes (Ia-c) and 1-aroxysilatran-3-ones (IIa, b), their influence on certain aspects of the system of homeostasis, the proliferative-repair function of the connective tissue, and the pilotropic activity.



I a-c II a, b

Ia: Ar = C_6H_4Cl = 3; Ib: Ar = $C_6H_3(NO_2)_2$ = 2,4; Ic: Ar = $C_6H_3(NO_2)_2$ = 2,5; IIa: Ar = = C_6H_4F-4; IIb: Ar = C_6H_4F-3.

EXPERIMENTAL (CHEMICAL)

1-Aroxysilatranes (Ia-c) were produced by the reaction of tetraethoxysilane and triethanolamine with the corresponding substituted phenol in xylene medium [15].

1-Fluorophenylsilatran-3-ones (IIa, b) were produced by the reaction of N-bis(2-hydroxyethyl)aminoacetic acid with 3- and 4-fluorophenyltrimethoxysilanes in DMFA and benzene medium, taken in the 3:1 ratio.

The compounds obtained were recrystallized from the following solvents: from acetone (Ia), ethanol (Ib, c), and a benzene-heptane mixture (IIa, b). Data on the compounds obtained are cited in Table 1.

EXPERIMENTAL (BIOLOGICAL)

Methods of Investigation. The toxicity of compounds I and II was determined after intraperitoneal injection into laboratory white mice [2]. The coagulogic indices of the resistance of the erythrocytes and the functional activity of the platelets was studied on blood of rabbits taken from the marginal vein of the ear into 3.8% sodium citrate (in a 9:1 ratio).

The proliferation-repair function of the connective tissue and the pilotropic activity were studied on laboratory white rats and guinea pigs.

In an investigation of the resistance of erythrocytes, the coagulogic indices, and the aggregating ability, the substances were dissolved in 0.85% physiological saline solution with Tween-80, incubated in the substrate for 15 min at 37°C in doses of 10^{-4}-10^{-10} M (in

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR. Budapest Technical University, Hungary. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 7, pp. 815-818, July, 1986. Original article submitted February 25, 1985.

 0091-150X/86/2007-0472$12.50

TABLE 1. Physicochemical Characteristics of 1-Aroxysilatranes Ia-c and 1-Arylsilatran-3-ones IIa, b

Compound	mp, °C	Yield, %	Gross formula	Calculated (found), %			
				C	H	N	Si
Ia	243—5	57	$C_{12}H_{16}ClNO_4Si$	47,45 (47,76)	5,44 (5,34)	4,66 (4,64)	9,30 (9,31)
I	235—40	24	$C_{12}H_{15}N_3O_8Si$	40,19 (40,33)	4,22 (4,23)	11,75 (11,76)	7,43 (7,86)
I	218—24	37	$C_{12}H_{15}N_3O_8Si$	40,41 (40,33)	4,22 (4,23)	11,53 (11,76)	7,50 (7,86)
IIa	185—6	...	$C_{12}H_{14}FNO_4Si$	50,94 (50,87)	5,35 (4,98)	4,97 (4,94)	9,72 (9,91)
II	135—7	...	$C_{13}H_{14}F_3NO_4Si$	47,15 (46,84)	4,36 (4,23)	4,52 (4,20)	(8,43)

TABLE 2. Primary Pharmacological Characteristics of Compounds Ia-c and IIa, b

Compound	LD_{50}, mg/kg	Motor Activity	Respiration frequency	Conclusion
Ia	3000	Strong inhibition from a higher dose	Normal	Relatively nontoxic
Ib	3000	Negligible inhibition	The same	The same
Ic	1340	The same	Fast respiration	Virtually nontoxic
IIa	445	Strong inhibition	The same	Low toxicity
IIb	1830	Inhibition	Convulsive respiration	The same

Note. Pain reflex and reflex of the outer ear in the normal state.

TABLE 3. Influence of Compounds Ia-c on the Hemocoagulating Activity of Rabbit Blood Plasma

Concentration	Ia			Ib			Ic		
	1	2	3	1	2	3	1	2	3
10^{-4}	122±11	45±2	38±1	93±3	39±2	44±2	118±8	42±2	34±1
10^{-5}	124±6	46±2	37±2	91±4	39±1	43±2	115±10	44±4	36±2
10^{-6}	125±7	48±1	40±1	87±7	39±2	43±1	138±11	42±2	37±1
10^{-7}	130±11	49±4	41±3	91±4	39±1	40±1	130±15	48±4	37±2
10^{-8}	127±10	49±2	41±4	103±7	40±1	42±1	126±5	50±1	36±1
10^{-9}	115±12	49±1	40±1	104±12	42±1	41±1	123±9	51±2	40±2
10^{-10}	120±5	50±5	40±1	122±7	41±1	41±1	120±12	49±1	40±1

Note. 1) Recalcification time, sec; 2) thrombin time, sec; 3) thromboplastin time, sec.

a 1:9 ratio); an equivalent amount of physiological saline solution with Tween-80 was introduced into the control samples.

The coagulogic indices in vitro (the time of recalcification, thrombin and prothrombin times according to Quick) were studied by the classical methods.

The antihemolytic activity was determined by a modified method of chemical erythrograms [12]. As the hemolytics we used 0.004% HCl and a 0.007% solution of saponins from Merck.

TABLE 4. Indices of Effectiveness of 1-Aroxysilatranes Ia-c

Compound	Hemolytic	Doses, M						
		10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}	10^{-9}	10^{-10}
Ia	HCl	0,87	0,96	1,04	1,10	1,06	1,02	1,01
	Saponins	1,00	1,00	1,07	1,13	1,04	1,03	1,00
Iб	HCl	0,38	0,57	0,87	0,98	0,99	0,99	1,00
	Saponins	0,10	0,43	0,47	0,79	0,86	0,97	1,00
Iв	HCl	0,92	0,94	1,01	1,00	1,00	1,00	1,00
	Saponins	0,97	0,97	1,01	1,01	1,02	1,00	1,00

TABLE 5. Influence of 3% Liniments Ia and III on the Biochemical Indices of GFT

Index	Control	LC	LC + Ia (3 %)	LC + III (3 %)
Tissue mass	1,17±0,01	1,40±0,07	1,65±0,81	2,04±0,20
DNA	2,91±0,66	2,70±0,20	3,10±0,19	3,34±0,30
RNA	2,37±0,25	2,31±0,27	2,56±0,20	2,88±0,26
Hydroxyproline	2,04±0,04	2,20±0,09	2,86±0,15	4,03±0,29
Tyrosine	2,17±0,05	3,03±0,31	3,07±0,29	3,02±0,21
Hexosamines	0,57±0,08	0,87±0,05	1,16±0,07	1,23±0,08
Hexuronic acids	0,64±0,07	0,42±0,07	0,60±0,04	0,79±0,09
Hexoses	2,13±0,17	2,38±0,18	2,60±0,17	2,97±0,23
Sialic acids	0,17±0,12	0,92±0,12	0,78±0,06	0,57±0,06

Note. The tissue mass is given in grams, the remaining indices in grams per 100 g of dried defatted tissue. LC) Mixture of lanolin and castor oil.

The activity of the compounds was estimated according to the index of effectiveness (the ratio of the time of 50% hemolysis of the experimental sample and the time of 50% hemolysis of the control sample). An investigation of the antiaggregation activity of the thrombocytes was conducted by the method of I. Born [14]. The functional activity of the blood platelets was also evaluated according to the electrokinetic potential.

The pilotropic activity was investigated on guinea pigs on which part of the fur was removed with a 2% epilin salve. A histologic substantiation of such a method was described earlier [1]. The investigation compound was applied after one day on a portion of skin prepared in this way in the form of a 2% salve with a lanolin-petrolatum base.

The controls were the group of intact animals and the group of animals on the epilated portion of the skin of which a 3% salve of 1-(chloromethyl)silatrane (III), possessing pronounced pilotropic properties, was applied. The pilotropic activity of the preparation was estimated according to the time of appearance of the first bristles.

To obtain granulation-fibrous tissue (GFT) we used an experimental model – an open skin defect. 1-(3-Chlorophenoxy)silatrane (Ia) was applied daily in the form of a 3% liniment based on a mixture of lanolin and castor oil (LC) in a 1:3 ratio. For a comparison of equal healing effects we used the oil base of LC and 3% liniment III in the same base, exhibiting a significant therapeutic efect [8, 9].

For an investigation of GFT we used a complex system of quantitative biochemical analysis [11]. The results of the biochemical analyses were calculated as the concentration in grams per 100 g of dried defatted tissue. For statistical treatment of these data we used the Wilcoxon-Mann-Whitney nonparametric U-criteria [6].

DISCUSSION OF RESULTS

An analysis of the data of the primary pharmacological examination of compounds I and II (Table 2) permitted the selection only of compounds Ia-c for the study of biological activity.

The introduction of compounds Ia-c into donor blood plasma was accompanied chiefly by a negligible shift in the direction of hypercoagulation at concentrations of 10^{-4}-10^{-5} M (Table 3).

The duration of the coagulation reactions of the control plasmas, with which the comparison was performed, was as follows: recalcification time 125 ± 8 sec, thrombin time 49 ± 2 sec, thromboplastin time 40 ± 3 sec.

In an investigation of the resistance of the erythrocyte membranes to acid and saponin hemolysis established that of the 1-aroxysilatranes studied, only compound Ia has an antihemolytic effect (6-13%) in a sufficiently low concentration 10^{-6}-10^{-8} M; compound Ib causes destruction of the erythrocyte stroma, while compound Ic has no effect on hemolysis (Table 4).

The results obtained permitted the selection only of 1-(3-chlorophenoxy)silatrane Ia for further investigations.

The membranotropic effect of Ia is confirmed by its influence on the functional activity of the blood platelets. This compound, in concentrations of 10^{-4}-10^{-6} M, inhibits platelet aggregation and increases the electrokinetic potential by 10-25 and 6-9%, respectively.

Compound Ia also possesses pilotropic activity. When a 2% salve with Ia was rubbed on, the appearance of bristles was observed five days earlier than in the control. In comparison with animals in which a portion of skin was treated with a 3% salve with III, restoration of the fur began three days earlier. Complete restoration of the fur of the guinea pigs after epilation was observed at the same time, both in the experimental group and in the group where a slave with III was used (after one month). However, to unambiguously answer the question of whether compound Ia has an advantage over III, longer and more detailed investigations using histological methods of investigation are needed.

We studied the influence of Ia on the biochemical indices of the connective tissue, in a state of active proliferation of GFT. It was established that compound Ia has a positive influence on the biochemical indices of GFT in comparison with placebo (Table 5). The accumulation of collagen and noncollagen proteins is observed in the GFT. Moreover, the entire proliferative-repair process is intensified as a result of stimulation of cell proliferation, as indicated by the increase in DNA content in the granuloma. Moreover, synthetic processes in the cells of the GFT are also intensified, which is indicated by an increase in the RNA content, as well as that of glycoproteins and glycosaminoglycans.

However, in a comparative investigation of the radiohealing effect of compound III, it was found that the biochemical indices of the GFT are substantially improved under the action of this preparation. The concentration of the leading biochemical indicator and the maturation of the collagen of the GFT (hydroxyproline) are statistically significantly increased. A decrease is noted in the accumulation of sialoglycoproteins in the collagen, reflecting an inhibition of acute inflammatory processes.

The data obtained are evidence of the promise of the further study of the biological activity of 1-aroxysilatranes, in particular, 1-(3-chlorophenoxy)silatrane.

LITERATURE CITED

1. E. V. Bakhareva, M. G. Voronkov, and M. K. Vasil'tsov, Byul. Éksp. Biol. Med., No. 5, 100-101 (1983).
2. M. L. Belen'kii, Elements of the Quantitative Evaluation of the Pharmacological Effect [in Russian], Leningrad (1963), pp. 81-106.
3. M. G. Voronkov and V. M. D'yakov, Silatrans [in Russian], Novosibirsk (1978).
4. M. G. Voronkov, G. I. Zelchan, and É. Ya. Lukevits, Silicon and Lift [in Russian], Riga (1978).
5. M. G. Voronkov, E. V. Bakhareva, and I. G. Kuznetsov, Dokl. Akad. Nauk SSSR, 262, No. 3, 319 (1982).
6. E. V. Gubler and A. A. Genkin, The Use of Nonparametric Criteria of Statistics in Medicobiological Investigation [in Russian], Leningrad (1973), pp. 5-15.
7. L. A. Mansurova, M. G. Voronkov, L. I. Slutskii, et al., Dokl. Akad. Nauk SSSR, 262, No. 6, 1505-1506 (1982).
8. L. A. Mansurova, M. G. Voronkov, L. I. Slutskii, et al., Byul. Éksp. Biol. Med., No. 3, 100-102 (1983).
9. L. A. Mansurova, M. G. Voronkov, L. I. Slutskii, et al., ibid., No. 9, 97-98.
10. T. V. Nefedova, B. Shirchin, V. B. Kazimirovskaya, et al., Khim.-farm. Zh., No. 3, 319-321 (1984).

11. L. I. Slutskii, The Biochemistry of Normal and Pathologically Changed Connective Tissue [in Russian], Leningrad (1969).
12. I. A. Terskov and I. I. Gitel'zon, Biofizika, No. 2, 259-266 (1957).
13. T. V. Shelkova, V. B. Kazimirovskaya, and L. A. Lyapina, Vopr. Med. Khim., No. 2, 118-120 (1983).
14. G. V. R. Born, Nature, 194, 927-929 (1962).
15. P. Hencsei, L. Bihatsi, G. Kovacs, et al., Acad. Sci. Acta Chim. Hung., 112, 261-267 (1983).
16. M. G. Voronkov, In: Biochemistry of Silicon and Related Problems, G. Bendzand and I. Lindciref, eds., New York (1978), p. 335.
17. M. G. Voronkov, Topics Current Chem., 84, 77-135 (1979).

SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF N-ACYL-5-METHOXYTRYPTAMINES

L. M. Grin, L. N. Khlaponina, N. S. Pivnenko, A. G. Selichenko, and V. D. Brutov

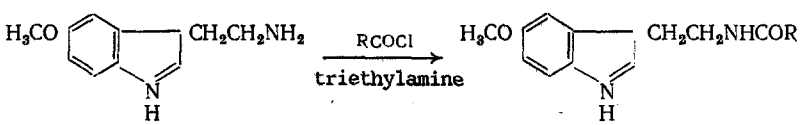
UDC 547.582.4+543.422:615.25.349

The search for new synthetic antidiabetic drugs is currently of great importance. This is due to the constantly-increasing numbers of patients with sugar diabetes, and to the inadequacies of current drugs.

Unlike the investigations carried out in the 1950's and 1960's in the search for hypoglycemic agents, when biguanides and sulfonylureas were the subjects of study [2], in the 1970's and 1980's the search for antidiabetic drugs was concentrated on derivatives of organic acids of various types.

Indole derivatives are of special interest. For example, there have been literature reports of the hypoglycemic effect of 5-hydroxytryptophan [5] and substituted indolecarboxylic acids [4], which provide grounds for believing that studies of compounds containing this heterocycle hold promise.

It was considered promising to synthesize derivatives of 5-methoxytryptamine (I), which is a structural heteroanalog of β-phenylethylamine, a constituent of some highly active hypoglycemic drugs (phenformin, glybenclamid, and glyburid). N-Acyl derivatives of 5-methoxytryptamine (II-V) have been obtained which contain acyl residues of α-methylcinnamic, hydrocinnamic, m-chlorcinnamic, and 2-methoxy-5-chlorobenzoic acids. These compounds were synthesized as follows:



II: R = $C_6H_5CH{=}C(CH_3)$—; III: R = $C_6H_5CH_2CH_2$—; IV: R = m-$ClC_6H_4CH{=}CH$—; V: R = 2-CH_3O-5-ClC_6H_3—.

The compositions and structures of the products were confirmed by their elemental analyses and their IR and PMR spectra (Tables 1 and 2).

The IR spectra, obtained in the solid phase, showed absorption for the amino-group of the indole ring at 3420-3390 cm^{-1}, in agreement with literature reports. Stretching vibrations of the NH group of the amide moiety were shifted to longer wavelengths by approximately 100 cm^{-1}. Attention is drawn to the considerable shift of the NH stretching vibrations (by more than 50 cm^{-1}) in the spectrum of (V), possibly due to intramolecular hydrogen bonding:

Kharkov Scientific-Research Institute for Endocrinology and Hormone Chemistry. Kharkov University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 7, pp. 819-822, July, 1986. Original article submitted April 11, 1985.

 0091-150X/86/2007-0476$12.50