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INFLUENCE OF TRIALKYLSILYL- AND SILATRANYLMETHYLESTERS OF ARYLOXY-, ARYLTHIO-, AND ARYLAMINOACETIC ACIDS ON THE AGGREGATION OF THROMBOCYTES

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The primary effect of chemical agents on cells is the disruption of the cell membrane [1]. In this connection, the search for membrane-stabilizing agents is of significant theoretical and practical interest. These materials are conveniently investigated by the ADP-induced aggregation of thrombocytes. Organic compounds of silicon significantly affecting the coagulation system of the blood are particularly attractive in the role of cell membrane stabilizers [2]. In a search for new aggregation inhibitors, we synthesized previously-unknown trialkylsilyl- and silatranylmethyl esters of aryloxy-, arylthio-, and arylaminoacetic acids.

These compounds were synthesized by the following schemes:

$$ArOCH_2COOK + ClCH_2SiR_3 \xrightarrow{DMF} ArOCH_2COOCH_2SiR_3 + KCl$$

I – III

Ia: Ar = C_6H_5, R = CH_3; Ib: Ar = C_6H_5, R = C_2H_5; Ic: Ar = C_6H_5, R = C_3H_7; II: Ar = 2,4-$Cl_2C_6H_3$, R = C_2H_5; III: Ar = 2, 4, 5-$Cl_3C_6H_2$, R = C_2H_5.

$$ArXCH_2COOCH_2Si(OCH_3)_3 + (HOCH_2CH_2)_3N \xrightarrow{CH_3ONa}$$

$$ArXCH_2COOCH_2Si(OCH_2CH_2)_3N + 3CH_3OH$$

IV – IX

IV: ArX = 2-$CH_3C_6H_4O$; V: ArX = 4-ClC_6H_4O; VI: ArX = 2,4-$Cl_2C_6H_4O$; VII: ArX = 2, 4, 5-$Cl_3C_6H_2O$; VIII: ArX = 2-$CH_3C_6H_4S$; IX: ArX = 2,4-$(CH_3)_2C_6H_3NH$.

EXPERIMENTAL CHEMISTRY

Trialkylsilylmethyl Aryloxyacetates (I-III). A mixture of 0.01 mole of potassium aryloxyacetate, 0.015 mole of chloromethyltrialkylsilane and 100 ml of dimethylformamide was boiled for 1 h. The resulting precipitate of KCl was filtered off, the solution was concentrated at reduced pressure and the residue was distilled under vacuum.

1-Silatranylmethyl Aryloxy-, Arylthio-, and Arylaminoacetates (IV-IX). A mixture of 0.01 mole of the trimethoxysilylmethyl ester of the corresponding acid, 0.015 mole of freshly-dis-

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TABLE 1. Physicochemical Properties, Yields, and Analytical Data for Compounds I-IX

Compound	Yield, %	bp, °C (mm) or mp, °C	n_D^{20}	d_4^{20}	Found, %						Empirical formula	Calculated, %					
					C	H	Cl	N	S	Si		C	H	Cl	N	S	Si
Ia	59,0	144—145 (9)	1,4949	1,0407	61,30	7,99	—	—	—	10,91	$C_{12}H_{18}O_3Si$	60,50	7,26	—	—	—	11,75
Ib	45,1	171—172 (6)	1,4970	1,0142	63,69	8,63	—	—	—	9,40	$C_{15}H_{24}O_3Si$	64,20	8,57	—	—	—	10,00
Ic	66,1	225 (28)	1,4915	0,9861	68,00	10,03	—	—	—	8,03	$C_{18}H_{30}O_3Si$	67,20	9,33	—	—	—	8,68
IIb	56,5	204—205 (6)	1,5190	1,1626	52,99	6,98	20,36	—	—	8,98	$C_{15}H_{22}Cl_2O_3Si$	53,20	6,32	20,31	—	—	8,03
IIIb	75,0	168 (1,0)	1,5280	—	46,01	5,35	27,24	—	—	7,21	$C_{15}H_{21}Cl_3O_3Si$	46,94	5,48	27,77	—	—	7,30
IV	53,0	146—147	—	—	54,01	6,41	—	3,81	—	7,81	$C_{16}H_{23}NO_6Si$	54,38	6,56	—	3,96	—	7,95
V	65,0	85	—	—	47,98	5,10	9,01	3,46	—	7,02	$C_{15}H_{20}ClNO_6Si$	48,19	5,35	9,50	3,75	—	7,50
VI	55,0	157	—	—	43,83	5,01	17,03	3,38	—	6,29	$C_{15}H_{19}Cl_2NO_6Si$	44,1	4,67	17,40	3,43	—	6,86
VII	165,0	165	—	—	40,24	4,21	23,85	3,15	—	5,98	$C_{15}H_{18}Cl_2NO_6Si$	40,68	4,07	24,07	3,16	—	6,33
VIII	138,0	138	—	—	51,59	6,73	—	3,96	8,57	8,07	$C_{16}H_{23}NO_4SSi$	52,03	6,29	—	3,79	8,67	7,59
IX	61,0	158	—	—	54,98	7,19	—	7,25	—	7,01	$C_{17}H_{26}N_2O_3Si$	55,59	6,81	—	7,67	—	7,67

TABLE 2. Change of Thrombocyte Aggregation upon Contact of the Plasma with Compounds I-IX

Compound	Concentration, M	Character of thrombocyte aggregation	Change in degree of aggregation, %
Ia	10^{-6}	Inhibition	15,0
	10^{-7}		15,0
Ib	10^{-6}	Inactive	—
	10^{-7}		
Ic	10^{-6}	Inhibition	10,0
	10^{-7}		10,0
II	10^{-6}	Inhibition	21,4
	10^{-7}		21,4
III	10^{-6}	Inhibition	6,7
	10^{-7}		
IV	10^{-6}	Inhibition	17,8
	10^{-7}		10,7
	10^{-8}		10,7
V	10^{-6}	Inhibition	15,0
	10^{-7}		15,0
	10^{-8}		20,0
VI	10^{-6}	Inhibition	12,0
	10^{-7}		12,0
VII	10^{-6}	Inactive	—
	10^{-7}		
VIII	10^{-6}	Activation	21,0
	10^{-7}		27,0
IX	10^{-6}	Activation	11,0
	10^{-7}		16,0

tilled triethanolamine and several drops of methanolic sodium methoxide were vigorously stirred for 1 h at room temperature. The resulting precipitate was filtered off, washed with ether, dissolved in alcohol, and precipitated with ether. Recrystallization was from alcohol.

Yields, physical constants, and elemental analyses for compounds I-IX are given in Table 1. Their structure was checked by PMR and IR spectroscopy [3-6].

EXPERIMENTAL BIOLOGY

The investigations were conducted on concentrated rabbit blood plasma thrombocytes. The blood was extracted from the outer vein of the ears. The plasma was separated from the erythrocytes by centrifugation at g = 550 ml/sec^2 for 3 min. Thrombocyte aggregation was determined by the method of Born [3] by measurement of the change in optical density at a wavelength of 490 nm before and after introduction of the aggregation inducer (adenosine diphosphate, ADP) at a concentration of 200 μg/ml.

The substances to be studied were added to the plasma at concentrations of 10^{-6}-10^{-8} M. The results were expressed as percent change of optical density relative to the control.

As shown in Table 2, the biological effect of the trialkylsilylmethyl esters of aryloxyacetic acids (I-III) depends on the nature of the substituents both on the silicon atom and on the aromatic ring. Trimethylsilylmethyl phenoxyacetate (Ia) more effectively inhibits the aggregation of thrombocytes than the tripropylsilylmethyl ester (Ic). At the same time, the triethylsilylmethyl ester (Ib) is practically without effect on the functional activity of thrombocytes. However, triethylsilylmethyl-2,4-dichlorophenoxyacetate (II) shows sufficient activity, but the introduction of still another chlorine atom into position 5 reduces the inhibitory activity (III).

In the series of exochloro derivatives of silatranylmethyl phenoxyacetate (V-VII), the accumulation of chlorine atoms leads to a decreased inhibitory activity. Thus, the 4-monochloro derivative V inhibits aggregation by 20% at a concentration of 10^{-8} M, while the 2,4-derivative VI acts only at higher concentrations and is less active. Finally, the 2,4,5-trichloro-substituted derivative VII does not influence the adhesive function of thrombocytes. The oxygen compound IV differs from compound VIII only in the nature of the heteroatom (O and S, respectively). Ester IV is an aggregation inhibitor, but its thioanalog VIII stimulates the action of ADP.

An inductor effect also is shown by the nitrogen-containing ester (IX, X = NH).

Thus, compounds Ia, Ic, II, III, IV, V, and VI at low concentrations showed moderate inhibition of ADP-induced thrombocyte aggregation.

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EFFECTS OF METHYLETHYL(SILATRAN-1-YLMETHYL)SULFONIUM IODIDE ON THE HEALING OF EXPERIMENTAL PEPTIC ULCER IN RATS

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It was established earlier that certain silatranes stimulate the proliferative-repair function of connective tissue during the healing of wounds [1-3] and are capable of inhibiting the development of experimental peptic ulcers induced by histamine, serotonin, reserpine, as well as "stress ulcers" [4, 5]. In particular, an antiulcerogenic action of diorganyl(silatran-1-ylmethyl)sulfonium halides has been demonstrated [6].

This communication presents data on the action of one of the representatives of the latter group of silatranes — methylethyl(silatran-1-ylmethyl)sulfonium iodide (I) [7] — on the healing of experimental peptic ulcer in rats on the basis of a biochemical analysis of the dynamics of the connective tissue components. The investigations were conducted in comparison with a known antiulcer drug — hydroxyferriscorbone (II) [8, 9].

EXPERIMENTAL PHARMACOLOGY

The experiments were conducted on 180 rats weighing 150-180 g. For reproduction of chronic experimental peptic ulcer, we used a somewhat modified method, described in [10]. The abdominal cavity of the animals was opened under ether anesthesia, the stomach was drawn out,

TABLE 1. Influence of I and II on the Course of the Ulcer Process, Induced by Acetic Acid in the Stomachs of White Rats (M ± m)

Preparation	Day of observation				
	3rd	7th	10th	20-th	30-th
II	98,1±15,7	87,0±24,0	58,7±14,7	13,5±4,4	4,7±3,8
I	91,0±10,2	53,0±5,7	38,0±3,5	1,0±0,5	0
Intact animals	117,6±6,5	119,8±9,5	36,1±3,5	34,5±4,1	11,0±2,5

Note. The area of visible ulceration (in mm^2) is indicated.

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