NEUROTROPIC AND ANTI-INFLAMMATORY ACTION OF THIOESTERS

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It is known that certain organosulfur compounds exhibit pronounced biological activity [1-5]. Earlier we showed [6] that aromatic thioesters with the general formula ArCAr'Ar"SAr are relatively nontoxic and exhibit an analgesic action. Continuing a study of the pharmacological properties of sulfur compounds, we investigated the biological properties of a series of aliphatic-aromatic sulfides with general formula 4-$CH_3OC_6H_4CH(R)SC_6H_4R'$-4 (I-VII), in order to detect their neurotropic and anti-inflammatory activity.

EXPERIMENTAL CHEMISTRY

The method of production of aliphatic-aromatic bioesters I-VII was based on the interaction of halomagnesium alcoholates with halomagnesium thiophenolates in the presence of ethyl formate in anhydrous diethyl ether medium [7].

General Method of Production of Sulfides. To 0.2 mole of alkyl or arylmagnesium bromide, 0.1 mole of the carbonyl compound, dissolved in a triple volume of anhydrous ether, was added dropwise with cooling, and after the reaction was completed, 0.1 mole of thiophenol, also in ether solution, was added. To complete the formation of bromomagnesium carbinolate and bromomagnesium thiophenolate, the mixture obtained was heated for 10-15 min. After cooling, 0.1 mole ethyl formate was added to the mixture, the reaction mixture mixed and left for 24 h at room temperature. Then the reaction mass was hydrolyzed with water and with 10% sulfuric acid. The layers were separated and the aqueous layer extracted twice with ether. All the ether layers were mixed, and to remove the unreacted thiophenol, washed with a 10% solution of sodium hydroxide and then with water to a neutral pH, dried with anhydrous sodium sulfate, the ether distilled off, and the sulfide obtained purified by redistillation under vacuum or by recrystallization from a suitable solvent (Table 1).

EXPERIMENTAL BIOLOGY

An investigation of the biological activity of thioesters was conducted on tetrahybrid mice of both sexes, weighing 16-20 g, and on rats of the Wistar line of both sexes, weighing 160-200 g. The neurotropic activity of the preparations was evaluated according to their ability to influence the orientative response of animals by the "throttle valve" method [8], on hexenal anesthesia by the test of "lateral position," on the pain protective reflex by the "hot plate" method [9], and on experimental convulsions induced by electric current or arecoline [10, 11]. Trioxazine, amidopyrine, cyclodol, and chloracon were used as standards of neurotropic action.

The anti-inflammatory activity of the compounds was studied on models of formalin, dextran, serotonin, histamine, and agar inflammation. The value of the inflammatory response was determined oncometrically ac-

TABLE 1. Aliphatic-Aromatic Sulfides I-VII

Compound	R	R'	Yield, %	Melting point, °C*	Found, % S	Gross formula	Calculated, % S
I	C_3H_7	H	97	39—40	11,73	$C_{17}H_{20}OS$	11,76
II	C_3H_7	CH_3	95	38—9	11,09	$C_{18}H_{22}OS$	11,19
III	C_4H_9	H	85	27—9	11,06	$C_{18}H_{22}OS$	11,19
IV	C_5H_{11}	H	83	38—9	11,00	$C_{19}H_{24}OS$	10,66
V	iso-C_3H_7	H	92	42—3	11,28	$C_{17}H_{20}OS$	11,76
VI	C_2H_5	H	94	48—50	12,13	$C_{16}H_{18}OS$	12,44
VII	CH_3	H	92	31—2	13,18	$C_{15}H_{16}OS$	13,10

* Compounds I-VI were recrystallized from petroleum ether, compound VII from alcohol.

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TABLE 2. Neurotropic and Anti-inflammatory Activity and Acute Toxicity of Organosulfur Compounds

Compound	Potentiation of hexenal anesthesia – duration of "lateral position," min (M ± m)	Analgesic activity (latent period of protective reflex), sec (M ± m)	Influence on the orientative reaction of animals		Antitremor activity		Anticonvulsive activity		Anti-inflammatory activity according to test of formalin inflam-		LD_{50}, mg/kg
			time of stay of animals in first chamber, sec (M ± m)	number of open valves	protection from hyperkinesis, %	duration of hyperkinesis min (M ± m)	Protection from convulsions, %	survival of animals in experiment, %	3 h	6 h	
Control	25,5±7,0	13,1±1,1	87,3±28,4	2,3	0	8,0±0,6	0	15	148	79	—
						12,1±3,9	0	15	65	25	400,0
I	26,8±13,4	15,1±2,0	174,0±13,8	0,3	0						(298,5–536,0)*
II	20,0±17,7	15,6±2,7	138,5±21,6	1,4	0	8,1±0,3	0	15	82	47	500
III	21,6±19,5	19,3±2,8	162,0±29,4	0,9	0	11,6±1,0	0	15	53	15	500
IV	29,5±18,1	18,7±1,4	172,0±12,4	0,6	0	12,1±0,5	0	0	107	70	500
V	84,3±45,5	16,3±1,7	164,0±27,2	0,5	0	15,0±3,6	0	0	75	64	500
VI	35,6±16,7	16,8±1,1	163,5±30,5	0,7	0	16,8±4,9	0	0	71	79	500
VII	39,5±14,9	18,0±0,8	156,0±36,1	1,0	0	19,8±2,0	0	15	100	91	500
Amidopyrine (100 mg/kg)	—	27,6±1,3	—	—	—	—	—	—	—	—	—
Trioxazine (100 mg/kg)	48,2±17,6	—	133,0±31,3	1,0	—	—	—	—	—	—	—
Chloracon (200 mg/kg)	—	—	—	—	—	—	100	70	—	—	—
Cyclodol (30 mg/kg)	—	—	—	—	40	4,2±1,7	—	—	—	—	—
Phenylbutazone (30 mg/kg)	—	—	—	—	—	—	—	—	55	44	—

* Limit of fluctuations.

TABLE 3. Anti-inflammatory Action of Thioesters on Various Models of Inflammation

Compound	Dextran inflammation				Serotonin inflammation				Histamine inflammation				Agar inflammation			
	enlargement of foot (in % of initial) after															
	30 min	1 h	3 h	6 h	30 min	1 h	3 h	6 h	30 min	1 h	3 h	6 h	1 h	3 h	5 h	24 h
Control	70,4	69,7	66,0	72,7	161,4	170,3	115,7	66,9	73,0	67,9	65,9	52,8	40,3	108,7	130,2	87,7
I	46,2	40,6	32,4	28,9	127,1	124,6	71,6	43,6	55,2	51,8	42,8	38,7	54,7	115,0	115,0	90,4
P	0,05	<0,05	<0,02	<0,02	<0,05	>0,05	<0,02	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05	>0,05
III	73,9	73,1	62,7	57,8	130,0	114,7	69,2	40,0					65,2	122,2	125,4	82,5
P	>0,05	>0,05	>0,05	>0,05	<0,05	<0,02	<0,02	<0,05					>0,05	>0,05	>0,05	>0,05

cording to the method of L. S. Salyamon. The phlogolytic activity of the compounds was compared with the action of phenylbutazone.

The toxicity of the thioesters was studied by determining LD_{50}, recording death of the animals for a period of ten days. The degree of toxicity of the preparations was determined according to the classification of I. V. Sanotskii [13].

The investigated preparations were administered to the experimental animals intraperitoneally in the form of a suspension in 2% starch mucilage in doses of 200 mg/kg (neurotropic action) and 50 mg/kg (anti-inflammatory action). The control animals received equal amounts of the starch mucilage; hexenal and arecholine were injected intraperitoneally in doses of 70 and 12 mg/kg, respectively. The results obtained were subjected to statistical treatment and considered significant at $P \leq 0.05$ [14].

RESULTS AND DISCUSSION

The results of experiments investigating the toxicity and neurotropic activity of thioesters are presented in Table 2, from which it is evident that the values of LD_{50} of the tested compounds exceed 500 mg/kg, and only in preparation I is LD_{50} equal to 400 mg/kg. According to the classification of acute toxicity of chemical substances [12], the compounds studied can be classified as relatively nontoxic.

The organosulfur compounds studied gave a pronounced sedative effect, which was manifested in their ability to inhibit the orientative reaction in mice. In this respect they surpass the tranquilizer trioxazine (see Table 2). The time of stay of the animals in the first chamber after the introduction of the investigated substances was increased by 60-100% in comparison with the control. The greatest activity was exhibited by preparations I and IV, which almost entirely inhibited the orientative reflex in mice. After the introduction of the tested compounds, the number of valves opened by the animals during their passage along the "runway" was decreased 2 to 4-fold, which was also evidence of inhibition of the orientative response [15].

The sulfides of the trithane series studied had a weak analgesic effect, increasing the time of the protective reflex by 25-50% in comparison with the control. The most distinct analgesic effect was exhibited by preparation III.

A significant lengthening of hexenal anasthesia was induced by preparation V; the remaining compounds were ineffective in this respect.

The investigated compounds had no influence on experimental convulsions (electric shock, arecholine hyperkinesis).

In a study of thioesters on a model of formalin inflammation, it was noted that they have a distinct anti-inflammatory effect (see Table 2). In strength of phlogolytic effect, some of these compounds (I and III) are not inferior to phenylbutazone. These substances have propyl and butyl groups as the radicals, respectively. An increase in the number of carbon atoms in this radical (compound IV), like a decrease in them (compounds VI and VII), leads to a decrease in the anti-inflammatory activity. It was also noted that the replacement of one of the hydrogens of the phenyl radical at the sulfur atom by a methyl group (II) is accompanied by a decrease in the anti-inflammatory action.

The substances most active in the anti-inflammatory effect (I and III) were subjected to an expanded investigation to determine their phlogolytic activity on models of dextran, serotonin, histamine, and agar inflammation (Table 3). It was noted that the phlogolytic action of preparations I and III was manifested not only in formalin, but also in dextran (I) and serotonin (III) edemas [16].

The low toxicity of the investigated thioesters, and the rather high phlogolytic activity of some of them (I, III), in conjunction with the general depressive (sedative) and analgesic action, permit us to consider a further synthesis of compounds of this type as potential agents for the treatment of inflammatory processes advisable.

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THE RELATIONSHIP OF CHEMICAL STRUCTURE OF UREA DERIVATIVES TO ANTISPASMODIC ACTIVITY

IV. SUBSTITUTED BENZHYDRYL UREAS

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We found earlier [1] that benzhydryl ureas show high antispasmodic activity in screening tests. The present work describes the synthesis of a series of new benzhydryl ureas having substituents on the benzene ring. The synthesis of the substituted benzhydryl ureas was carried out according to the following scheme:

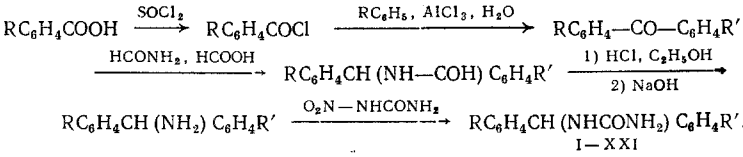

TABLE 1. Substituted Benzhydryl Ureas

Compound	R	R′	Melting point, °C	Found, %			Empirical found	Calculated, %		
				C	H	N		C	H	N
I	H	H	143—5	74,21	6,11	12,08	$C_{14}H_{14}N_2O$	74,33	6,19	12,38
II	2-CH_3	H	134—5	74,44	6,80	11,88	$C_{15}H_{16}N_2O$	75,00	6,66	11,66
III	3-CH_3	H	99—100	74,88	6,73	11,41	$C_{15}H_{16}N_2O$	75,00	6,66	11,66
IV	4-CH_3	H	160—2	75,41	6,91	11,81	$C_{15}H_{16}N_2O$	75,00	6,66	11,66
V	3-NH_2	H	100—1	70,29	5,43	17,14	$C_{14}H_{15}N_3O$	69,81	6,25	17,57
VI	4-$(CH_3)_2N$	H	160—2	70,72	6,74	16,39	$C_{16}H_{19}N_3O$	71,37	7,06	15,61
VII	3-OH	H	194—5	69,59	5,88	11,54	$C_{14}H_{14}N_2O_2$	69,42	5,78	11,57
VIII	4-OH	H	207—8	69,86	5,97	11,75	$C_{14}H_{14}N_2O_2$	69,42	5,78	11,57
IX	4-CH_3O	H	158—9	70,05	6,68	11,45	$C_{15}H_{16}N_2O_2$	70,31	6,25	11,67
X	3-NO_2	H	180—2	62,28	5,15	15,47	$C_{14}H_{13}N_3O_3$	61,99	4,80	15,49
XI	4-NO_2	H	218—9	62,50	5,11	16,29	$C_{14}H_{13}N_3O_3$	61,99	4,80	15,49
XII	4-C_6H_5	H	165—7	80,12	5,88	9,44	$C_{20}H_{18}N_2O$	79,47	5,99	9,27
XIII	2-CH_3	5-CH_3	143—4	75,63	7,03	11,37	$C_{16}H_{18}N_2O$	75,59	7,08	11,02
XIV	3-CH_3	4-CH_3	131—3	76,10	7,09	11,23	$C_{16}H_{18}N_2O$	75,59	7,08	11,02
XV	2-CH_3	4-CH_3	157—9	76,10	6,94	10,90	$C_{16}H_{18}N_2O$	75,59	7,08	11,02
XVI	3-CH_3	4-CH_3	153—4	75,39	7,18	11,24	$C_{16}H_{18}N_2O$	75,59	7,08	11,02
XVII	4-CH_3	4-CH_3	174—5	76,00	7,18	11,12	$C_{16}H_{18}N_2O$	75,59	7,08	11,02
XVIII	2-F	4-CH_3	165—6	70,39	6,00	10,83	$C_{15}H_{15}FN_2O$	69,45	6,18	10,81
XIX	3-F	4-CH_3	149—0	69,19	6,03	10,63	$C_{15}H_{15}FN_2O$	69,45	6,18	10,81
XX	4-F	4-CH_3	175—6	70,07	6,28	10,85	$C_{15}H_{15}FN_2O$	69,45	6,18	10,81
XXI	2-NH_2	5-Cl	233—5	61,31	5,28	15,28	$C_{14}H_{14}ClN_3O$	60,81	4,75	15,25

Note. Literature data: mp for I, 143°C [3]; IV, 158°C [4]; XVII, 152°C [4].

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