PRODUCTION OF SURFACE-ACTIVE AGENTS WITH PRONOUNCED PHARMACOLOGICAL ACTIVITY

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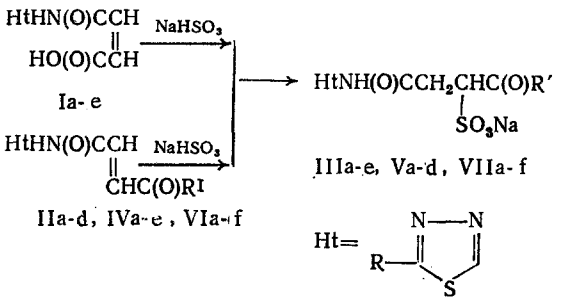
The broad spectrum of pharmacological activity of dicarboxylic acids [7, 9] and also possible chemical transformations of their structure served as a basis for developing new surface active agents (SAA) with a pronounced pharmacological effect.

Our investigations showed that the most promising trend in this respect is sulfonation of the acyl fragment of the heteryl amides of dicarboxylic acids and their derivatives



I, II, III: R = H (a), C_2H_5 (b), n-C_3H_7 (c), iso-C_3H_7 (d), n-C_4H_9 (e); R^1 = OH; IV, V: R = H (a), n-C_3H_7 (b), n-C_4H_9 (c), iso-C_4H_9 (d), SO_2NH_2 (e); R' = OCH_3; VI, VII: R = H (a), n-C_3H_7 (b), n-C_4H_9 (d), iso-C_3H_7 (e), iso-C_4H_9 (f); R' = NH_2 (a-c), $NHCH_3$ (d-f).

The initial heterylmaleinamino (I) and heterylfumaramic (II) acids and their esters (IV) and amides (VI) were obtained by the method described in [8, 10].

The sodium salts of heteryl amides of sulfosuccinic acid (III) were obtained by boiling heterylmaleinamino acids I in an aqueous solution of sodium hydrosulfite. The identification and the structure of the compounds obtained were confirmed by the data of elemental analysis and alternative synthesis by the reaction of heterylfumaramic acids II with sodium hydrosulfite.

TABLE 1. Heteryl Amides of Sulfosuccinic Acid and Its Derivatives

Compound	Yield, %	mp, °C	Calc. %		Empirical formula	Found, %	
			N	S		N	S
IIIa	72	218—220	13,86	21,14	$C_6H_6N_3O_6S_2Na$	13,67	21,03
IIIb	52	199—201	12,68	19,35	$C_8H_{10}N_3O_6S_2Na$	12,50	19,14
IIIc	80	150—152	12,17	18,57	$C_9H_{12}N_3O_6S_2Na$	12,12	18,44
IIId	68	165—167	12,17	18,57	$C_9H_{12}N_3O_6S_2Na$	12,06	18,53
IIIe	84	178—180	11,69	17,84	$C_{10}H_{14}N_3O_6S_2Na$	11,62	17,73
Va	81	224—225	13,24	20,21	$C_7H_8N_3O_6S_2Na$	13,15	20,11
Vb	72	185—187	11,69	17,84	$C_{10}H_{14}N_3O_6S_2Na$	11,73	17,60
Vc	44	182—183	11,25	17,17	$C_{11}H_{16}N_3O_6S_2Na$	11,34	17,06
Vd	42	164—165	11,25	17,17	$C_{11}H_{16}N_3O_6S_2Na$	11,31	17,10
Ve	69	230 разл.	14,14	24,27	$C_7H_9N_4O_8S_3Na$	14,11	24,13
VIIa	90	232—233	18,54	21,21	$C_7H_7N_4O_5S_2Na$	18,36	20,43
VIIb	65	178—181	16,27	18,62	$C_9H_{13}N_4O_5S_2Na$	15,98	18,49
VIIc	82	213—214	56,63	17,89	$C_{10}H_{15}N_4O_5S_2Na$	15,36	17,63
VIId	92	181—183	15,63	17,89	$C_{10}H_{15}N_4O_5S_2Na$	15,48	17,55
VIIe	85	170—172	15,68	17,89	$C_{10}H_{15}N_4O_5S_2Na$	15,36	17,67
VIIf	94	220—222	15,05	17,22	$C_{11}H_{17}N_4O_5S_2Na$	14,80	17,02

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TABLE 2. Surface Tension and Pharmacological Activity of Heteryl Amides of Sulfosuccinic Acid and Their Derivatives

Compound	% suppression of inflammation	% reduction of sugar level in blood with respect to initial data after ... hours					LD_{50} at intraperitoneal administration, mg/kg	Surface tension 10^{-4} J/m^2 of 1% aqueous solutions
		2	4	6	8	10		
IIIa	25	0	30	34	33	30	3000	68,1
IIIb	20	4	22	27	23	21	1000	65,3
IIIc	15	3	32	29	20	14	1560	56,8
IIId	21	7	19	33	28	9	1720	51,9
IIIe	—	22	29	32	27	13	800	43,5
Va	17	0	0	+2	0	3	...	63,0
Vb	19	+2	+1	0	+3	2	6000	48,3
Vc	19	11	12	15	17	5	2300	56,1
Vd	14	2	5	26	3	0	...	64,1
Ve	8	3	18	25	18	17	...	67,1
VIIa	—	10	21	18	5	0	...	59,2
VIIb	—	15	20	27	30	15	...	58,0
VIIc	—	8	10	7	15	18	...	51,9
VIId	5	0	0	1	2	0	...	51,9
VIIe	10	13	29	33	33	30	1500	53,2
VIIf	15	22	34	26	30	24	800	56,3
Butadione	17	—	—	—	—	—	128	—
Butamide	—	21	25	30	24	23	700	—
Control	—	0	0,5	0	+0,5	+1	—	—

Similarly, the corresponding sodium salts of esters (V) and amides (VII) of the heteryl amides of sulfosuccinic acid were obtained from methyl esters IV and amides VI of heteryl-fumarimic acids.

The compounds synthesized (Table 1) are colorless, crystalline substances, readily soluble in water and alcohol, and insoluble in acetone. Considering the spectrum of the pharmacological activity of the initial heterylmaleinamino and heterylfumarimic acids and their derivatives, the compounds synthesized were screened for antiinflammatory, diuretic, sugar-reducing, and antihypoxic activity.

EXPERIMENTAL CHEMICAL SECTION

Sodium Salt of 5-n-Propyl-2-(1,3,4-thiadiazolyl)amide of Sulfosuccinic Acid (IIIc).

Method A. A 2.41-g portion (0.01 mole) of 5-n-propyl-2-(1,3,4-thiadiazolyl)maleinamino acid and 1.04 g (0.01 mole) of sodium hydrosulfite are dissolved in 20 ml of water, the solution is heated for 2 h, and then excess solvent is distilled off. The precipitate is filtered and the product is purified by reprecipitation by acetone from concentrated solution. Plates mp 151-152°C.

Method B. A mixture of 2.41-g (0.01 mole) of 5-n-propyl-2-(1,3,4-thiadiazolyl)fumaramic acid, 1.04 g (0.01 mole) of sodium hydrosulfite, 20 ml of water, and 20 ml of isopropanol is heated for 4 h. The excess solvent is then distilled off. The precipitate is filtered and purified by reprecipitation from acetone from concentrated aqueous solution plates. mp 150-152°C. Mixed probes of compounds obtained by methods A and B do not depress the melting points.

Compounds IIIa, b, d, e were obtained in a similar way.

Sodium Salt of Methyl Ester of 5-n-propyl-2-(1,3,4-thiadiazolyl)amide of Sulfosuccinic Acid (Vb). A solution of 1.04 g (0.01 mole) of sodium hydrosulfite in 30 ml of water and 30 ml of isopropanol is added to 2.54 g (0.01 mole) of the methyl ester of 5-n-propyl-2-(1,3,4-thiadiazolyl)fumaramic acid. The mixture is heated to complete homogenization, and then for another 4-6 h, and cooled. The precipitate is filtered and dried, and then crystallized from water. Needles. mp 184-187°C.

Methyl esters Va, c-d and amides VIIa-f of heteryl amides of sulfosuccinic acid were obtained in a similar way (see Table 1).

EXPERIMENTAL PHARMACOLOGICAL SECTION

The acute toxicity was determined on white mice with intraperitoneal administration. The LD_{50} was calculated according to Prozorovskii [2]; the antiinflammatory activ-

ity was studied by the method of Strel'nikov in a dose of 100 mg/kg [6]; the sugar-reducing action of the compounds synthesized was studied in a dose of 50 mg/kg according to [3]; stability with respect to hypoxic hypoxia was determined in experiments on rats [5]. The results of the pharmacological experiments were statistically treated [1].

For a primary estimation of surface activity, the surface tension was determined of 1% aqueous solutions of the compounds synthesized at a temperature of 25 ± 1°C by the method described in [4].

The results of the investigations are listed in Table 2, which shows that compounds IIIc, Va-e, VIIId-f have a pronounced antiinflammatory activity (5-19%), comparable with the effect of butadione used in medicine. Compounds IIIb-d, Vd-e, VII have a sugar-reducing activity at the level of the antidiabetic butamide.

A study of the antihypoxic activity of the heteryl amides of sulfosuccinic acid and their derivatives showed that they cannot prolong the life of the animals under conditions of acute hypoxia hypoxia. Diuretic activity was also absent.

The acute toxicity of the compounds synthesized varies over wide range from 800 to 6000 mg/kg, so that they can be considered to be slightly or practically nontoxic compounds.

The above data show that the surface activity depends on the character of the hydrophobicity and hydrophilicity of the individual fragments of the molecule. In this series of compounds, increase in hydrophobicity of the heteryl amide fragment was most expedient. According to the Taube rule, this is achieved by elongation of alkyl radicals in compounds IIIa-e. The introduction of a more hydrophilic group to the heterocyclic ring of compound Ve leads to a sharp decrease in surface tension.

Hydrophilic groups COOH and SO_3Na are advisable for the acyl fragment of the molecule. This supposition is confirmed by the fact that increase in the hydrophobicity of the carboxylic group by esterification of compounds Va-e or amidation of compounds VIIa-f leads to a decrease in the surface-active properties.

Based on the above regularities, compound IIIe was synthesized. This compound includes in its structure an optimal combination of the above structural features, and correspondingly has a minimal surface tension coefficient.

Our investigations thus indicate the practical possibility of producing SAA with given technological and biological properties and may serve as a basis for further research.

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