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SYNTHESIS AND RADIOPROTECTIVE PROPERTIES OF 2-ARYLETHYLAMMONIUM SALTS OF SULFINIC ACIDS

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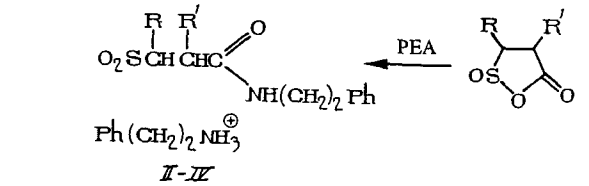
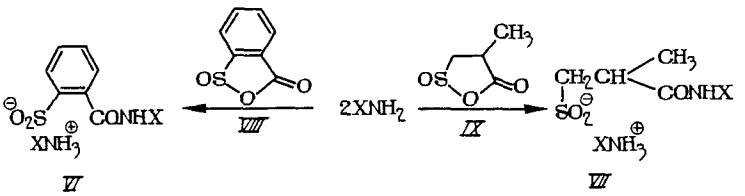
We previously showed that the 2-phenylethylammonium salt of the 2-phenylethylamide of o-sulfinobenzoic acid (I) has low toxicity and exhibits moderate radioprotective action [1]. With the object of studying the influence of the nature of the sulfinic acid on the anti-radiation activity, as well as searching for new more effective anti-radiation agents, we accomplished the synthesis of new aliphatic analogs of the compounds (I). The reaction of 1,2-oxathiolan-5-on-2-oxides with 2-phenylethylamine (PEA) afforded the 2-phenylethylammonium salts of 2-phenylethylamides of β-sulfinoalkanoic acids (II)-(IV). For the comparison with the amide (II), the bis(2-phenylethylammonium) salt of β-sulfinopropionic acid (V) was also obtained by the neutralization of this acid with PEA.



II—IV:

R=R′=H (II); R=Me, R′=H (III); R=H, R′=Me (IV)

$^{-}O_2S(CH_2)_2COO^{-}$ $2Ph(CH_2)_2NH_3^{+}$ V



X= p-$FC_6H_4CH_2CH_2$

The structure of the compounds synthesized was confirmed by the data of the IR spectra. Strong absorption, characteristic of the sulfinate anion, is observed for all the salts (II)-(VII) in the region of 950-1045 cm^{-1}. In the carbonyl region (1410-1635 cm^{-1}) the character of the absorption is different for the bis-salt (V) and the amides (II)-(IV), (VI), and (VII) (Table 1). The spectra of the fluorine-containing salts (VI) and (VII), and the unfluorinated analogs (I) and (IV), only differ by the presence of the ν(C−F) band in the region of 1230-1250 cm^{-1}.

It is known that the introduction of fluorine atoms into derivatives of mercaptoethylamine increases the radioprotective effect and the therapeutic index of the substances [2]. Therefore, we synthesized fluorine-containing sulfinates of the aromatic [compound (VI)] and aliphatic [compound (VII)] series by the reaction of 2-(4′-fluorophenyl)ethylamine (F-PEA) with 2,1-benzoxathiol-3-on-1-oxide (VIII) or with 4-methyl-1,2-oxathiolan-5-on-2-oxide (IX) correspondingly.

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TABLE 1. Physicochemical Properties of the Compounds (II)-(VII)

Compound	Yield	mp, °C (solvent of crystallization)	Empirical formula	IR spectrum, ν, cm^{-1}				
				C=O	SOβ	N—H	val. $^{\oplus}NH_3$	other bands
II	64	137—9 (ethanol–petroleum ether)[a]	$C_{19}H_{26}N_2O_3S$	1635, 1645	950—970 (sym.) 1000—1020 (asym.)	3300	2500—3100	1520—1558[b]
III	90	149—52 (ethanol)[a]	$C_{20}H_{28}N_2O_3S$	1635	975, 1010, 1030	3235	2600—3100	1560—1575[b]
IV	96	123[c]	$C_{20}H_{28}N_2O_3S$	1645	970 (sym.) 1015 (asym.)	3315	2500—3200	1540—1590[b]
V	75	125—6 (abs. ethanol–petroleum ether)[d]	$C_{19}H_{28}N_2O_4S$	1410, 1555	950 (sym.) 1045 (asym.)	3300	2600—3100	1555, 1590[b]
VI	83	170—2 (ethanol)[d]	$C_{23}H_{24}F_2N_2O_3S$	1645	950—960 (sym.) 1010—1020 (asym.)	3250	2600—3100	1520—1565[b], 1230 (C—F)
VII	100	148—150 (ethanol— — ether)	$C_{20}H_{26}F_2N_2O_3S$	1635	970—980 (sym.) 1015—1030 (asym.)	3235	2500—3200	1525, 1580[b] 1245—1250 (C—F)

Notes. a) Soluble in water, alcohol, and DMF and insoluble in ether, petroleum ether, and benzene; b) def. $^{\oplus}NH_3$, Ar; c) soluble in water, alcohol, DMF, and hot $CHCl_3$ and insoluble in acetone, ether, petroleum ether, and hexane; d) soluble in water and alcohol.

EXPERIMENTAL (CHEMICAL)

The IR spectra were obtained on the UR-20 instrument (Germany) using tablets with KBr. Data on the yields, constants, solubility, and IR spectra of the new compounds (II)-(VII) are presented in Table 1. All reactions were conducted utilizing dry solvents and reagents. The initial 1,2-oxathiolan-5-on-2-oxides and the benzanhydride (VIII) were obtained as described in [3]. The data of the elemental analysis satisfy the calculated values.

2-Phenylethylammonium Salt of the 2-Phenylethylamide of β-Sulfinopropionic Acid (II). To the solution of 2.3 g (0.019 mole) of 1,2-oxathiolan-5-on-2-oxide in 30 ml of benzene is added, with stirring, the solution of 4.6 g (0.038 mole) of PEA in 40 ml of benzene. On the following day, the precipitated residue is filtered off, washed with ether, and dried over P_2O_5 prior to the isolation of 4.4 g of (II).

2-Phenylethylammonium Salt of the 2-Phenylethylamide of β-Sulfinobutyric Acid (III). To the solution of 4.36 g (0.036 mole) of PEA in 20 ml of ether is added, with stirring at 6°C, the solution of 2.13 g (0.016 mole) of 3-methyl-1,2-oxathiolan-5-on-2-oxide in 30 ml of ether. The reaction mass is treated as described above for (II) prior to the isolation of 5.4 g of (III).

2-Phenylethylammonium Salt of the 2-Phenylethylamide of β-Sulfinoisobutyric Acid (IV). This was obtained from 4.36 g of (IX) and PEA (2.13 g) under the conditions of the synthesis of the benzylammonium salt of the benzylamide of β-sulfinoisobutyric acid [1]. The yield of (IV) was 5.4 g.

Bis(2-phenylethylammonium) Salt of β-Sulfinopropionic Acid (V). To the suspension of 2.75 g (0.02 mole) of β-sulfinopropionic acid [4] in 45 ml of benzene is added, while cooling the mixture with cold water, the solution of 5.57 g (0.046 mole) of PEA in 30 ml of benzene. On the following day, the residue is filtered off and washed with ether. The yield of 5.7 g of (V), with the mp 119-120°C, is obtained; it is purified by the solution of the substance in boiling abs. ethanol with the precipitation by petroleum ether and the drying in a vacuum exsiccator over P_2O_5.

2-(4′-Fluorophenyl)ethylammonium Salt of the 2-(4′-Fluorophenyl)ethylamide of o-Sulfinobenzoic Acid (VI). To the solution of 2.1 g (0.0125 mole) of (VIII) in 35 ml of $CHCl_3$ are added 3.5 g (0.025 mole) of F–PEA (obtained as an oil with the bp 110°C/30 mm by the action of EtONa on F–PEA hydrochloride in alcohol) in 20 ml of $CHCl_3$. On the following day, the reaction mass is subjected to vacuum treatment and cooled. The yield of 4.65 g of (VI), with the mp 166°C, is obtained. After the recrystallization from alcohol, 4.2 g of (VI) are isolated.

2-(4′-Fluorophenyl)ethylammonium Salt of the 2-(4′-Fluorophenyl)ethylamide of β-Sulfinoisobutyric Acid (VII). To the solution of 2.3 g (0.017 mole) of F–PEA in 15 ml of ether is added 1.1 g (0.008 mole) of (IX) in 10 ml of ether. On the following day, the precipitated residue is filtered off prior to the isolation of 3.5 g of (VII) with the mp 142-150°C. The substance is purified by the solution in hot ethanol and the precipitation with ether for the isolation of 2.5 g of (VII).

TABLE 2. Acute Toxicity and Radioprotective Activity (RPA) of the 2-Arylethylammonium Salts of Sulfinic Acids

Substance	Method of introduction	LD_{50}	Dose of substance	Excess of survival over the control, %
		mg/kg		
I	A	1640	410	22—40 [1]
II	A	650	250	25
	B		250	40
III	A	310	150	60
	A		100	55
	A		50	30
	B		300	40
IV	A	260	200	80
	A		100	60
	A		50	26
V	A	50	20	47
	A		10	53
	A		5	33
VI	A	1080	400	21
	A		200	16
VII	A	650	300	50
	A		200	40
	A		100	15
	B		300	57

Notes. A) ip at 30 min before exposure; B) po at 1 h before exposure.

EXPERIMENTAL (BIOLOGICAL)

The toxicity of the compounds investigated was studied using experiments on white hybrid mice. The anti-radiation action was studied on (CBA × C57B1)F_1 hybrid mice of the mass 19-23 g. Compounds were introduced ip in the aqueous solution using 0.2-0.4 ml at 30 min before exposure, or po at 1 h before exposure. The irradiation of the animals was performed on the IGUR equipment at the dose of 850 rd and the dose rate of 210 rd/min. The anti-radiation effect of the compounds was judged from the survival of the animals in the course of 30 days after the irradiation. The death of the control animals under the given conditions of irradiation comprised 100%.

It follows from Table 2, in which data on the acute toxicity and RPA of the compounds synthesized as well as the phenylethylammonium salt (I) which we obtained previously [1] are presented, that most of them possess medium toxicity. Only the bisphenylethylammonium salt (V) stands out; in its toxicity (50 mg/kg), it even surpasses PEA (146 mg/kg). Among the amides, the arenesulfinates (I) and (VI) are less toxic (LD_{50} > 1000 mg/kg) than alkanesulfinates. The data presented on the radioprotector activity indicate that all the compounds studied possess RPA. The fluorine-containing analog (VI) does not have advantages by comparison with the known compound (I). It is evident that the arylethylammonium salts of alkanesulfinic acids (II)-(V) and (VII) are more effective than the arenesulfinates (I) and (VI): at lower doses, they exhibit the analogous (and often higher) RPA. Among the alkanesulfinates, the maximal therapeutic index (13.3) is shown by the bis-salt (V); it is however toxic. The corresponding amide (mono-salt) (II) has low toxicity, but is also less effective. Of all the amides, the best protection with the ip application (80%) is given by the isobutyric acid derivative (IV) in the subtoxic dose. An important advantage of the alkanesulfinates is also the marked or good RPA (40-57% at doses of 250-300 mg/kg) with the po method of application, whereas the preparation cystamine guarantees the survival of 20-48% at high doses (400-500 mg/kg po) with a lower irradiation dose (700 rd) [5]. The most effective compound with low toxicity for po utilization proved to be the fluorine-containing amide of isobutyric acid (VII) (the 57% survival of the animals).

Therefore, the combination of 1,2-oxathiolan-5-on-2-oxides with arylethylamines permits a decrease in the toxicity of the latter with the retention (or increase) of their RPA. Among the alkanesulfinates studied, the most promising anti-radiation compounds are C-arylethylamides based on isobutyric acid (IV) and (VII).

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