ARYLSULFONIC ACID DERIVATIVES. SYNTHESIS AND ANTITUMOR ACTIVITY OF DI- AND TETRA(BENZYLSULFONYL)DIAMINES

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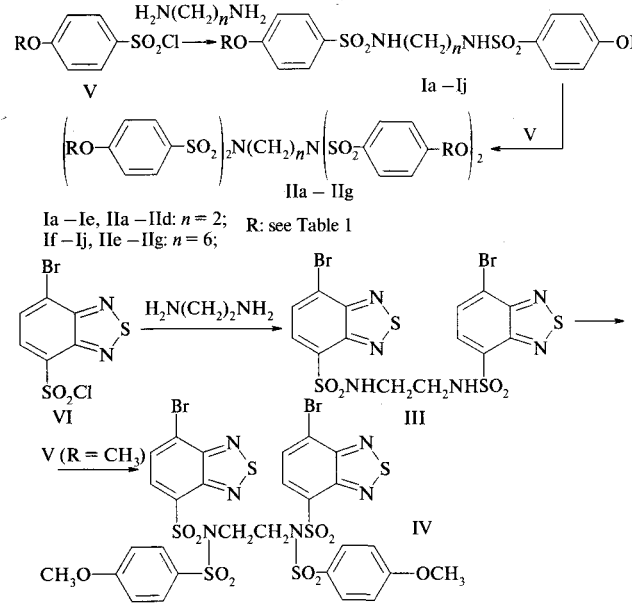
In continuation of the previous investigation of sulfonylamide derivatives [1] known to possess antitumor activity [2], we have synthesized and characterized a series of new di- and tetrasulfonylamides (I – IV) by the following scheme:



Selecting these compounds for the synthesis was inspired by data on the antitumor activity of alkanesulfonic acid esters and aliphatic diols, where the maximum efficacy was observed for 1,4-bis(methanesulfonyloxy)butane (myelosan) [3]. The effect of structural features on the antitumor activity was elucidated by replacing oxygen in the sulfonic acid esters by sulfur and nitrogen [4]. Taking into account these data and the fact that the antileukemic activity can be increased by introducing electron-acceptor groups [5], we synthesized disulfonylamides I using reactions of alkoxybenzenesulfochlorides V with ethylene- and hexamethylenediamines in the presence of a 10% aqueous solution of sodium hydroxide.

As is known, the antitumor activity of these compounds increases with the number of sulfamide groups [6]. For this reason, we have synthesized tetrasulfonamides II by heating compounds I with alkoxybenzenesulfochlorides in an anhydrous DMF medium in the presence of lithium hydride. The yields of compounds II did not exceed 30%. Our attempts at improving this characteristic by increasing the temperature and duration of heating were unsuccessful.

In order to find a relationship between the antitumor properties and chemical structure of the synthesized substances, it was also of interest to study the effect of including a heterocyclic ring. By analogy with the above reactions, we used 4-bromobenzo-2,1,3-thiadiazole-7-sulfochloride (VI) and ethylenediamine to obtain sulfonamide III. Heating this compound with methoxybenzenesulfochloride leads to formation of the desired compound IV.

Purity of the synthesized compounds was checked by TLC; the proposed compositions and structures were confirmed by the results of elemental analyses and by the IR and ^{1}H NMR spectroscopic data.

EXPERIMENTAL CHEMICAL PART

The TLC analyses were performed on Silufol UV-254 plates; the spots were visualized by exposure to the UV radiation. The IR absorption spectra were recorded on an UR-20 spectrophotometer (Germany). The ^{1}H NMR spectra were measured on a Varian T-60 spectrometer (working frequency, 60 MHz) using DMSO as the solvent and TMS as the internal standard.

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TABLE 1. Characteristics of Compounds Ia – IIj and IIa – IIg

Compound	*R*	Yield, %	M.p., °C	R_f (benzene – acetone, 3 : 1)	Empirical formula
Ia	CH_3	87	152 – 153	0.62	$C_{16}H_{20}N_2O_6S_2$
Ib	C_2H_5	74	155 – 156	0.66	$C_{18}H_{24}N_2O_6S_2$
Ic	C_3H_7	70	166 – 167	0.70	$C_{20}H_{28}N_2O_6S_2$
Id	C_4H_9	82	150 – 151	0.73	$C_{22}H_{32}N_2O_6S_2$
Ie	*iso*-C_4H_9	72	159 – 160	0.75	$C_{22}H_{32}N_2O_6S_2$
If	CH_3	87	119 – 120	0.68	$C_{20}H_{28}N_2O_6S_2$
Ig	C_2H_5	72	160 – 162	0.72	$C_{22}H_{32}N_2O_6S_2$
Ih	C_3H_7	80	135 – 136	0.74	$C_{24}H_{36}N_2O_6S_2$
Ii	C_4H_9	81	133 – 134	0.77	$C_{26}H_{40}N_2O_6S_2$
Ij	*iso*-C_4H_9	82	127 – 128	0.81	$C_{26}H_{40}N_2O_6S_2$
IIa	CH_3	30	228 – 230	0.60	$C_{30}H_{32}N_2O_{12}S_4$
IIb	C_2H_5	29	204 – 205	0.73	$C_{34}H_{40}N_2O_{12}S_4$
IIc	C_3H_7	25	223 – 225	0.80	$C_{38}H_{48}N_2O_{12}S_4$
IId	C_4H_9	26	184 – 185	0.83	$C_{42}H_{56}N_2O_{12}S_4$
IIe	CH_3	28	193 – 194	0.66	$C_{34}H_{40}N_2O_{12}S_4$
IIf	C_2H_5	27	208 – 209	0.77	$C_{38}H_{48}N_2O_{12}S_4$
IIg	C_3H_7	23	179 – 180	0.81	$C_{42}H_{56}N_2O_{12}S_4$

TABLE 2. Antitumor Activity of Arylsulfonic Acid Derivatives (Ia – Ij, IIa, IIc, IIe, III and IV)

Compound	Tumor growth inhibition, % of control					
	Dose, mg/kg	Sarcoma 37	*p*	Dose, mg/kg	WCS	*p*
Ia	200	57	< 0.05	100	49	< 0.05
Ib	250	47	< 0.05	100	41	= 0.05
Ic	250	45	< 0.05	100	30	= 0.05
Id	200	60	< 0.05	120	0	
Ie	250	45	< 0.05	100	0	
If	200	52	< 0.05	100	22	> 0.05
Ig	250	57	< 0.05	120	21	> 0.05
Ih	150	54	< 0.05	100	48	< 0.05
Ii	150	48	< 0.05	100	0	
Ij	250	48	< 0.05	120	33	= 0.05
IIa	150	57	< 0.05	120	25	> 0.05
IIc	200	66	< 0.05	120	29	> 0.05
IIe	200	55	< 0.05	100	20	> 0.05
III	200	37	= 0.05	100	39	= 0.05
IV	175	70	< 0.05	120	56	< 0.05

N,N′-Di(*p*-alkoxybenzenesulfonyl)alkyldiamines (Ia – Ij). A mixture of 10 mmole of 4-alkoxybenzenesulfochloride V [7], 5 mmole of the corresponding amine, 1 ml of water, and 4 ml of 10% aqueous sodium hydroxide solution was heated with stirring for 3 h on a boiling water bath. Upon cooling, the precipitated crystals were separated by filtration and recrystallized from 80% aqueous ethanol solution (Table 1).

The IR spectra of compounds Ia – Ij (ν_{max}, cm^{-1}): 1160 – 1165 (SO_2 symm.), 1380 – 1385 (SO_2, antisymm.), 3285 – 3300 (NH).

N,N′-Di(4-bromobenzo-2,1,3-thiadiazole-7-sulfonyl)ethylenediamine (III). Compound III was synthesized by a procedure analogous to that described above, proceeding from 1.6 g (5 mmole) of chloroanhydride VI [8], 0.3 ml (2.5 mmole) of a 50% aqueous ethylenediamine solution, 1 ml of water, and 5 ml of 10% aqueous potassium hydroxide solution.

Yield, 1.3 g (86%); m.p., 214 – 215°C (from acetone); R_f 0.74 (C_6H_6 – acetone, 2 : 1); $C_{14}H_{16}Br_2N_6O_4S_4$; IR spectrum ($\nu_{max}$, cm^{-1}): 1180 (SO_2 symm.), 1390 (SO_2, antisymm.), 1590 (C=C, arom.), 1630 (C=N), 3300 (NH, amide).

N,N,N′N′-Tetra(*p*-alkoxybenzenesulfonyl)alkyldiamines (II). To a solution of 2.5 mmole of the corresponding diamide I in 25 ml of anhydrous DMF were added 0.04 g (5.5 mmole) of lithium hydride and the reaction mass was heated with stirring for 40 min on a boiling water bath. Then 5.5 mmole of 4-alkoxybenzenesulfochloride V was added and the mixture was additionally heated for 10 h. Upon cooling, the reaction mixture was poured into a glass with ice and allowed to stand for 10 – 12 h. Then the precipitated crystals were filtered and purified by boiling in ethanol, whereby unreacted disulfonamide I dissolved in the alcohol.

The IR spectra of compounds IIa – IIg (ν_{max}, cm^{-1}): 1170 – 1180 (SO_2 symm.), 1390 – 1395 (SO_2 antisymm.), no bands in the region of characteristic NH absorption (Table 1).

N,N′-Di(*p*-methoxybenzenesulfonyl)-N,N′-di(4-bromobenzo-2,1,3-thiadiazole-7-sulfonyl)ethylenediamine (IV). Compound IV was synthesized by a procedure analogous to that described above, proceeding from 1 g (2.6 mmole) of diamide III, 0.04 g (5.6 mmole) of lithium hydride, and 1.6 g (5.6 mmole) of chloroanhydride V (R = CH_3) in 30 ml of anhydrous DMF. Yield, 1.4 g (63%); m.p., 138 – 140°C (from ethanol); R_f 0.55 (C_6H_6 – acetone, 2 : 1); $C_{18}H_{22}Br_2N_6O_{10}S_6$; IR spectrum ($\nu_{max}$, cm^{-1}): 1160 (SO_2 symm.), 1390 (SO_2 antisymm.), 1590 (C=C, arom.), 1620 (C=N), no bands in the region of characteristic NH absorption.

EXPERIMENTAL BIOLOGICAL PART

The antitumor properties were studied by conventional methods [9, 10] using rats and mice inoculated with sarcoma 37 and Walker's carcinosarcoma (WCS). Substances showing activity with respect to these solid tumors were additionally tested on a hemocytoblastosis Ia model. The therapeutic effect was evaluated as percentage inhibition (TGI) of the solid tumor growth (for sarcoma and 37 and WCS) or as percentage increase in the lifetime of test animals (for hemocytoblastosis Ia).

Because of poor solubility in water, all the synthesized compounds were injected as suspensions in an 0.5%

carboxymethyl cellulose solution. The intraperitoneal injections were made daily over a period of 8 (rats) and 5 – 6 (mice) days. The experimental data were processed by the Student – Fisher method.

The results of investigation of the therapeutic efficacy of dibenzosulfonylamides Ia – Ij are summarized in Table 2. Similar to myelosan, some of these compounds (in particular, the compounds containing methoxy, ethoxy, and butoxy radicals) exhibit significant antitumor activity with respect to sarcoma 37 ($TGI = 57 – 60\%$; $p < 0.05$). WCS was much less sensitive to the drugs tested: only some of the derivatives studied (Ia, Ic, Ih, Ij) produced a weak effect ($TGI = 30 – 48\%$; $p \leq 0.05$). Note, however, that the therapeutic action of myelosan on this model also did not exceed 50% [11]. On the whole, ethylene and hexamethylene derivatives (IIIa – IIIe and IIIf – IIIj, respectively) showed approximately equal activity levels on the tumor models studied.

Tetrabenzenesulfonylamides IIa, IIc, and IIe also significantly inhibited the growth of sarcoma 37 ($TGI = 57 – 66\%$; $p < 0.05$) while virtually not affecting the WCS growth (Table 2).

Compound III (containing a benzothiazole cycle) exhibits weak antitumor activity with respect to both sarcoma 37 and WCS ($TGI = 37$ and 39%, respectively; $p = 0.05$) Compound IV (with methoxybenzenesulfonyl substituent) showed a pronounced effect upon sarcoma 37 ($TGI = 70\%$, $p < 0.05$) and moderately inhibited the WCS growth ($TGI = 56\%$, $p < 0.05$).

Compounds showing activity with respect to sarcoma 37 and WCS (Ia, Id, Ig, Ih, IIa, IIc, and IV) exhibited no reliable antitumor effect when tested on the hemocytoblastosis Ia model.

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