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SYNTHESIS OF BENZOXAZOLE SULFANILAMIDE DERIVATIVES

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A number of hitherto undescribed 2-(p-aminobenzenesulfamide) benzoxazoles are prepared by treating 2-aminobenzoxazole or its 6-substituted compounds with p-carbomethoxyaminobenzenesulfochloride or p-acetylaminobenzenesulfochloride, followed by alkaline hydrolysis. A similar reaction with 6-amino-2-hydroxy- and 2-mercaptobenzoxazoles gives 6-(p-aminobenzenesulfamido)-2-hydroxy- and 2-mercapto-benzoxazoles.

The object of the present work was synthesis of sulfanilamide compounds where the nitrogen of the sulfamide group carried a benzoxazole ring substituent.

Hitherto, such compounds have not been reported in the literature. There are only indications of the preparation of 2-(benzenesulfamido)benzoxazoles, with Cl or p-$CH_3-C_6H_4SO_2O$ at the para position in the benzene ring [1].

We synthesized the benzoxazole 2-sulfanilamide derivatives in the usual way, by condensing p-carbomethoxy-amino- or p-acetylaminobenzenesulfochloride with the appropriate 2-aminobenzoxazoles, in which position 6 was occupied by Br, NO_2, NH_2, OMe, and OEt. 6-Alkoxy-2-sulfanilamide derivatives of benzoxazole were of especial interest, it being known that, for example, introduction of alkoxy groups into the heterocyclic ring in the pyrimidine series promotes prolonging of the action of sulfanilamide preparations [2]. The condensation was run in pyridine at 60° - 80° C, and the resultant 2-p-carbomethoxyamino or p-acetylaminobenzenesulfamido) benzoxazoles were then submitted to alkaline hydrolysis.

To obtain water-soluble compounds, Na- and diethylamino salts of 2-(p-aminobenzenesulfamido) benzoxazole were synthesized.

An attempt to prepare 6-nitro-2-(p-aminobenzenesulfamido) benzoxazole by nitrating unsubstituted 2-sulfanil-amidobenzoxazole with nitric acid (d 1.5) or nitrating mixture gave a mixture of nitro compounds from which 6-nitro-2-(p-aminobenzenesulfamido) benzoxazole could not be isolated. The latter was obtained by condensing 6-nitro-2-aminobenzoxazole with p-acetylaminobenzenesulfochloride, followed by alkaline hydrolysis of the acetyl group. However, due to the effect of the nitro group, the condensation gave only a yield of ~ 20%, and a considerable amount of starting amine was recovered. In general, it proved impossible to prepare the 6-nitro compound when starting with p-carbomethoxyaminobenzenesulfochloride.

An attempt to reduce the nitro group in 6-nitro-2-(p-acetylaminobenzenesulfamido) benzoxazole to an amino group using hydrogen and Raney nickel was unsuccessful; consequently, 6-amino-2-(p-aminobenzenesulfamido) benzoxazole was prepared from 6-acetylamino-2-aminobenzoxazole [3] by the usual method.

It was also of interest to prepare 6-sulfanilamide derivatives of benzoxazole. For that purpose, 6-amino-2-hydroxybenzoxazole and6-amino-2-mercaptobenzoxazole were caused to react with p-carbomethoxyaminobenzenesulfochloride, to give correspondingly 6-(p-aminobenzenesulfamido)-2-mercapto- and 2-hydroxybenzoxazoles.

The presence of a free mercapto group in 6-(p-aminobenzenesulfamido) mercaptobenzoxazole was confirmed by the ease with which an aqueous ethanolic solution of the compound decolorized a solution of iodine.

An investigation of the bacteriostatic activity and chemotherapeutic action of 2-(p-aminobenzenesulfamido)-benzoxazole and its derivatives showed that a number of preparations have high activity in vitro for Escherichia coli and dysentery bacilli, as well as being active in experiments with mice infected with pneumococcus.

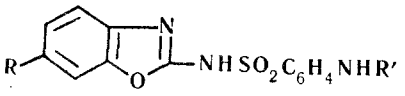
A maximum effect was shown by 2-(p-aminobenzenesulfamido) benzoxazole and 6-methoxy-2-(p-aminoben-zenesulfamido) benzoxazole. However, 2-sulfanilamidobenzoxazole derivatives possess no real advantages over known sulfanilamide derivatives. Introduction of a nitro group at position 6 sharply lowers the activity. 6-Sulfanilamido-benzoxazoles lack appreciable bacteriostatic activity.

Experimental

2-(p-Carbomethoxyaminobenzenesulfamido) benzoxazole. 2 g (0.015 mole) 2-aminobenzoxazole [3] was dis-

*The work was done by E. N. Padeiska of the Chemotherapy Division of VNIKhFI (All-Union Pharmaceutical Chemistry Research Institute).

Table 1

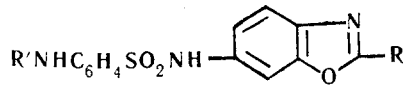


R	R′	Mp, °C	Formula	C, %		H, %		N, %		S, %		Yield, %
				Found	Calculated	Found	Calculated	Found	Calculated	Found	Calculated	
H	$COCH_3$	246—248	$C_{15}H_{13}N_3O_4S$	54.51	54.36	3.92	3.95	12.43	12.68	9.75	9.68	82.5
H	$COOCH_3$	247—248,5	$C_{15}H_{13}N_3O_5S$	51.64	51.87	3.83	3.75	12.04	12.10	9.06	9.22	90.8
H	H	261—262	$C_{13}H_{11}N_3O_3S$	53.77	53.96	4.18	3.83	—	—	10.83	11.08	85.7
Br	$COOCH_3$	274	$C_{15}H_{12}BrN_3O_5S$	—	—	—	—	9.98	9.86	7.49	7.52	84
Br	H	269—270	$C_{13}H_{10}BrN_3O_3S$	42.19	42.40	2.78	2.73	—	—	8.63	8.71	65
NO_2	$COCH_3$	281—286	$C_{15}H_{12}N_4O_6S$	48.03	47.86	3.49	3.21	14.95	14.88	8.84	8.52	20
NO_2	$COOCH_3$	249—253	$C_{15}H_{12}N_4O_7S$	46.24	45.91	3.45	3.08	14.92	14.28	8.21	8.17	50
NO_2	H	230—231	$C_{13}H_{10}N_4O_5S$	46.82	46.70	3.00	3.01	16.57	16.76	9.60	9.59	77
CH_3CONH	$COOCH_3$	288	$C_{17}H_{16}N_4O_6S$	50.59	50.51	4.10	3.98	13.91	13.85	7.85	7.93	56
NH_2	H	240—242	$C_{13}H_{12}N_4O_3S$	—	—	—	—	18.05	18.41	10.37	10.53	83
OC_2H_5	$COOCH_3$	246—248	$C_{17}H_{17}N_3O_6S$	52.10	52.16	4.23	4.37	10.76	10.73	8.50	8.19	92
OC_2H_5	H	236—238	$C_{15}H_{15}N_3O_4S$	53.72	54.04	4.27	4.53	12.81	12.60	9.68	9.62	77
OCH_3	$COOCH_3$	251—253	$C_{16}H_{15}N_3O_6S$	51.07	50.91	4.28	4.01	11.26	11.14	8.75	8.50	76
OCH_3	H	228	$C_{14}H_{13}N_3O_4S$	52.83	52.65	4.37	4.10	13.10	13.16	10.10	10.04	82

solved in 7 ml dry pyridine, the temperature held at not over 30° C, and 3.91 g (0.016 mole) p-(carbomethoxyamino)-benzenesulfochloride added in portions, after which the mixture was heated for 2 hr 30 min at 90° C, and left overnight. Then 25 ml water was added, and the products made slightly acid to congo red with 10% HCl. The precipitate was filtered off and washed with water, when 4.71 g (90.8%) of almost white, crystalline material was obtained, mp 247°–248.5° (ex EtOH) (see Table 1).

2-(p-Aminobenzenesulfamido) benzoxazole. A solution of 4.71 g (0.014 mole) 2-(p-carbomethoxyaminobenzenesulfamido) benzoxazole in 19 ml 10% NaOH was held at 60°–70° for 2 hr 30 min, then decolorizing charcoal added and the mixture heated for a further 15 min, after which 3.42 g dry NaCl was added. The mixture was cooled to + 5° C, the precipitate plus charcoal filtered off, washed with saturated brine, dissolved in water, heated to 70° C, the charcoal filtered off and, after cooling, the filtrate acidified with 70% AcOH. The almost colorless precipitate which separated was washed with water until neutral, yield 2.47 g crystalline compound mp 261°–262° C (see Table 1). On acidification with AcOH, the alkaline mother liquor gave an additional 0.87 g of the same compound, total yield 85.7%.

Table 2



R	R′	Mp, ° C	Formula	C, %		H, %		N, %		S, %		Yield, %
				Found	Calculated	Found	Calculated	Found	Calculated	Found	Calculated	
SH	$COOCH_3$	209	$C_{15}H_{13}N_3O_5S_2$	47.40	47.48	3.73	3.45	11.06	11.08	—	—	98
SH	H	235	$C_{13}H_{11}N_3O_3S_2$	48.08	48.58	3.62	3.45	12.76	13.07	—	—	51.5
OH	$COOCH_3$	268—269	$C_{15}H_{13}N_3O_6S$	49.57	49.58	3.58	3.61	11.14	11.56	8.62	8.82	96
OH	H	227—228	$C_{13}H_{11}N_3O_4S$	50.82	51.14	3.76	3.64	13.81	13.76	10.60	10.50	62

The other 2-(p-aminobenzenesulfamido) benzoxazoles (see Table 1), as well as 6-(p-aminobenzenesulfamido)-2-hydroxy- and 2-mercaptobenzoxazoles (see Table 2) were prepared similarly.

Diethylamine salt of 2-(p-aminobenzenesulfamido) benzoxazole. A mixture of 5 g (0.017 mole) 2-(p-aminobenzenesulfamido) benzoxazole, 15 ml EtOH, and 1.89 g (0.026 mole) Et_2NH was heated until the solid dissolved, the solution treated with decolorizing charcoal, and then cooled; yield 4.32 g slightly yellowish crystalline material, decomp 172° C (ex EtOH), readily soluble in water. Found: C 56.56; H 6.02; N 15.38; S 8.93%. Calculated for $C_{17}H_{22}N_4O_3S$: C 56.35; H 6.07; N 15.47; S 8.84%.

Na salt of 2-(p-aminobenzenesulfamido) benzoxazole. This was prepared by saturating an alkaline solution of 2-(p-aminobenzenesulfamido) benzoxazole with NaCl. As it was highly soluble in water, it was purified by recrystallization from 10% NaCl solution. Found: C 47.52; H 3.35; N 13.01; Cl′ 2.87%. Calculated for $C_{13}H_{10}N_3O_3SNa$ + 0.255 mole NaCl: C 47.84; H 3.06; N 12.87; Cl′ 2.87%.

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