2-Methyl-3-(p-chlorophenyl)-6-diethylaminoethoxybenzofuran Hydrochloride (XVIII). This was prepared like compound XVI in 80% yield, mp 142-144°C (from acetone—ether). Found, %: C 63.39, H 6.33, Cl 17.94. $C_{21}H_{24}ClNO_2 \cdot HCl$. Calculated, %: C 66.50, H 6.40, Cl 18.02.

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SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF N-ALKYL-N'-(2-AMINO-1,3,4-THIADIAZOL-5-YLSULFONYL)- AND N-ALKYL-N'-(5-SULFAMOYL-1,3,4-THIADIAZOL-2-YL)-OXAMIDES

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N-Substituted N'-arylsulfonyloxamides display marked sugar-reducing activity and are relatively nontoxic [1-3].

We thought it relevant to structure—activity studies to examine the biological activity of N-alkyl-N'-(2-amino-1,3,4-thiadiazol-5-ylsulfonyl)- and N-alkyl-N'-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)oxamides, in which the sulfonyl group is attached to a heterocycle.

We synthesized these groups of compounds by the reactions

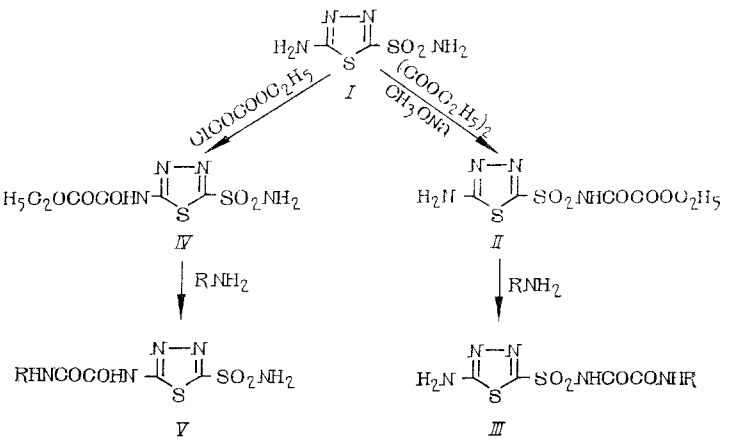

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TABLE 1. N-Alkyl-N'-(2-amino-1,3,4-thiadiazol-5-ylsulfonyl)-(III) and N-Alkyl-N'-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-oxamides (V)

Compound	R	Yield, %	Melting point, °C (aqueous DMF)	Found, %		Formula	Calc., %		pK_a in 60% aqueous dioxane	R_f	IR spectra, cm^{-1}			
				N	S		N	S			ν_{NH}	ν_{CO}	$\nu^{as}_{SO_2}$	$\nu^{s}_{SO_2}$
IIIa	H	90	300	27,98	25,73	$C_4H_5N_5O_4S_2$	27,90	25,52	6,55	0,32	3360	1720	1360	1180
IIIb	CH_2CH_2OH	78	211—2	23,93	21,94	$C_6H_9N_5O_5S_2$	23,71	21,71	6,45	0,18	3365	1705	1360	1175
IIIc	C_3H_7	90	220—1	23,88	21,91	$C_7H_{11}N_5O_4S_2$	23,87	21,86	6,68	0,36	3370	1675	1365	1170
IIId	iso-C_3H_7	89	207—8	23,99	21,90	$C_7H_{11}N_5O_4S_2$	23,87	21,86	5,99	0,28	3320	1730	1365	1180
IIIe	CH_2=CH—CH_2	76	214—5	24,30	22,30	$C_7H_9N_5O_4S_2$	24,04	22,00	5,56	0,21	3280	1710	1360	1175
IIIf	C_4H_9	95	222—3	22,90	20,99	$C_8H_{13}N_5O_4S_2$	22,78	20,86	6,63	0,44	3350	1680	1355	1179
IIIg	iso-C_4H_9	95	230—1	22,87	21,01	$C_8H_{13}N_5O_4S_2$	22,78	20,86	6,62	0,41	3360	1678	1355	1175
IIIh	iso-C_5H_{11}	73	215—6	21,87	19,98	$C_9H_{15}N_5O_4S_2$	21,79	19,95	5,48	0,39	3320	1730	1365	1180
IIIj	cyclo-C_6H_{11}	84	220—1	21,30	19,53	$C_{10}H_{15}N_5O_4S_2$	21,00	19,23	6,72	0,32	3320	1720	1360	1170
IIIk	$CH_2C_6H_5$	82	221—2	20,71	18,93	$C_{11}H_{11}N_5O_4S_2$	20,51	18,78	6,73	0,36	3290	1680	1360	1175
Va	H	96	215—6	27,98	25,73	$C_4H_5N_5O_4R_2$	27,90	25,52	6,03	0,43	3355	1715	1355	1170
Vb	CH_3	85	225—6	26,48	24,58	$C_5H_7N_5O_4S_2$	26,40	24,47	6,06	0,25	3340	1710	1365	1180
Vc	CH_2CH_2OH	52	214—5	23,87	22,80	$C_6H_9N_5O_4S_2$	23,71	21,71	6,13	0,33	3340	1685	1360	1180
Vd	C_3H_7	73	229—30	23,99	22,00	$C_7H_{11}N_5O_4S_2$	23,87	21,86	6,48	0,43	3375	1680	1385	1170
Ve	iso-C_3H_7	69	213—4	29,88	21,93	$C_7H_{11}N_5O_4S_2$	23,87	21,86	6,52	0,57	3375	1675	1370	1175
Vf	CH_2=CH—CH_2	59	209—10	24,34	22,13	$C_7H_9N_5O_4S_2$	24,04	22,01	5,86	0,22	3320	1730	1370	1180
Vg	C_4H_9	57	223—4	22,90	20,93	$C_8H_{13}N_5O_4S_2$	22,78	20,86	6,45	0,39	3360	1690	1360	1180
Vh	iso-C_5H_{11}	56	213—4	21,90	20,08	$C_9H_{15}N_5O_4S_2$	21,79	19,95	5,75	0,37	3375	1675	1365	1170
Vj	cyclo-C_6H_{11}	83	204—5	21,21	19,47	$C_{10}H_{15}N_5O_4S_2$	21,00	19,23	6,52	0,45	3370	1715	1365	1170
Vk	$CH_2C_3H_5$	56	218—9	20,73	18,93	$C_{11}H_{11}N_5O_4S_2$	20,51	18,78	6,37	0,37	3340	1690	1370	1175

TABLE 2. Hypoglycemic Activity of N-Alkyl-N'-(2-amino-1,3,4-thiadiazol-5-ylsulfonyl)- (III) and N-Alkyl-N'-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)-oxamides (V)

Compound	Time after administration of the preparation, h							LD_{50}, mg/kg (intraperitoneal)
	2	4	6	8	10	12	24	
	reduction in sugar level, % of original							
III a	6	8	7	11	15	11	4	937
III b	5	8	13	10	11	8	3	
III c	4	8	8	7	6	6	5	728
III d	3	5	8	17	20	14	6	
III e	7	9	11	10	10	8	5	
III f	12	14	14	13	18	12	6	836
III g	7	8	8	7	9	9	8	
III h	15	20	22	32	26	17	11	
III j	14	15	12	14	14	8	7	1235
III k	27	28	28	26	17	10	9	
V a	26	24	25	26	20	16	9	736
V b	8	13	14	15	10	8	5	
V c	8	7	19	15	14	9	4	
V d	4	9	8	10	13	11	3	628
V e	5	7	10	12	11	7	5	640
V f	2	8	10	9	6	5	3	
V g	16	18	26	28	31	18	15	920
V h	21	29	27	25	24	19	8	
V j	16	18	24	24	24	25	27	1120
V k	7	8	16	15	17	12	7	
Butamide	21	25	30	24	23	19	5	700

Reaction of 2-amino-5-sulfamoyl-1,3,4-thiadiazole (I) with diethyl oxalate (in the presence of sodium methoxide) or ethoxalyl chloride gave esters II and IV, respectively, which formed alkylamides III and V with aliphatic amines.

Alkylamides III and V are white crystalline substances, highly soluble in organic solvents and also in alkali solutions.

We verified the homogeneity and structure of the synthetic compounds by elemental analysis, chromatography, and spectroscopy (Table 1).

The IR spectra of alkylamides III and V contain the characteristic stretching bands at 1660-1730 cm^{-1} (ν_{CO}) and 3290-3375 cm^{-1} (ν_{NH}). The SO_2 modes appear as two intense bands, at 1170-1180 cm^{-1} ($\nu_{SO_2}{}^{s}$) and at 1355-1370 cm^{-1} ($\nu_{SO_2}{}^{as}$).

Alkylamides III and V are nitrogen acids. We measured the ionization constants (pK_a) representing proton loss by potentiometric titration in 60% aqueous dioxane. Table 1 shows that the alkyl substituent in the amide part of the molecule only slightly affects the pK_a. As would be expected, the replacement of the aromatic radical by the thiadiazole residue in these substituted oxamides entails a considerable reduction in acidity.

We carried out the biological screening of the synthetic compounds for sugar-reducing activity by the ortho-toluidine method [4] and determined the toxicity in white mice by Litchfield and Wilcoxon's method in M. A. Belen'kii's modification. Our results for compounds III and V are summarized in Table 2 in comparison with butamide.

Table 2 shows that the test compounds have sugar-reducing and hypoglycemic effects, which depend on the nature of the alkyl substituent in the amide part of the molecule. The greatest reduction in blood sugar is caused by the alkylamides III containing the iso-pentyl (IIIh) and benzyl (IIIk) substituents and by compounds Vg, Vh, and Vj, which approach or equal butamide in hypoglycemic activity. Alkylamides IIIh, Vg, and Vj retain their sugar-reducing activity for 24 h, whereas by this time butamide scarcely causes any reduction in the blood sugar level.

Among the test compounds N-cyclohexyl-N'-(5-sulfamoyl-1,3,4-thiadiazole-2-yl)oxamide (Vj) demands particular attention; it causes stable hypoglycemia, which reaches its maximum 6 h after administration and lasts for 24 h. Tests of the acute toxicity revealed that this preparation, like several other compounds, is much less toxic than butamide (Table 2).

In general these compounds are inferior in sugar-reducing activity to the preparations currently used for the treatment of diabetes. However, our results will be relevant in further searches for effective preparations among analogs of these compounds.

EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on a UR-20 spectrophotometer in KBr tablets (c 0.5%); pK_a was measured with a pH-340 instrument in aqueous dioxane solution with mmole concentrations of the compounds. Thin-layer chromatography was carried out on Silufol plates in chloroform—methanol (9:1).

Ethyl (2-Amino-1,3,4-thiadiazol-5-ylsulfonyl)oxamate (II). To sodium methylate, prepared from sodium (0.23 g, 0.01 mole) and absolute methanol (25 ml), were added I (1.80 g, 0.01 mole) and dry diethyl oxalate (1.46 g, 0.01 mole). The reaction mixture was kept at room temperature for 1 h. The methanol was stripped off. The residue was diluted with water and filtered. The filtrate was acidified with dilute hydrochloric acid (1:1) to pH 5.0 and the precipitate was dried to give II (1.96 g, 70%) with mp 208-210°C (needles; from DMF—ethanol).

Ethyl (5-Sulfamoyl-1,3,4-thiadiazol-2-yl)oxamate (IV). To a solution of I (3.6 g, 0.02 mole) in glacial acetic acid (15 ml) and pyridine (1.74 g, 0.022 mole) was added oxalic acid monochloride monoethyl ester (3.2 g, 0.022 mole) with stirring and cooling. The reaction mixture was stirred for 1 h at the temperature of the boiling water bath. It was then cooled and diluted with water. The precipitate was filtered off and dried to give IV (3.52 g, 63%), mp 203°C (plates; from ethanol).

N-Butyl-N'-(2-amino-1,3,4-thiadiazol-5-ylsulfonyl)oxamide (IIIf). To a solution of IV (4.2 g, 0.015 mole) in ethanol (20 ml) was added n-butylamine (2.2 g, 0.03 mole). The reaction mixture was kept at room temperature for 12 h. Water (20 ml) was then added and the mixture was acidified with dilute hydrochloric acid (1:1) to pH 5.0. The precipitate was filtered off and dried. Recrystallization gave IIIf (4.38 g, 95%).

Compounds IIIa-e, g-k, and Va-k were prepared in the same way.

EXPERIMENTAL BIOLOGY

We assayed the hypoglycemic activity in male rabbits weighing 2-3 kg. The test compounds were administered perorally through a tube in 2% starch base in a dose of 0.05 g/kg. Blood samples for analysis were taken from an ear vein at various times during the 24 h after a single administration of the preparation. We evaluated the hypoglycemic activity in six to ten rabbits. Blood sugar was determined by the ortho-toluidine method [5] and Hagedorn and Jensen's method [5]. Our results were processed statistically. We made a parallel assay of the effect of butamide to compare sugar-reducing activity.

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