SYNTHESIS AND SUGAR REDUCING ACTIVITY OF DIOXAMOYL DERIVATIVES OF SULFANILAMIDE

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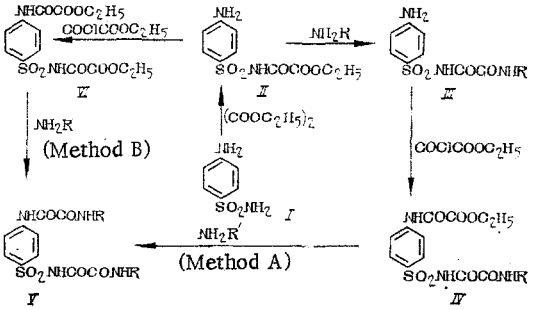
It has already been shown that the introduction of the oxamoyl residue into a molecule of streptocide positively affects the sugar reducing activity and decreases its toxicity [1-5].

It was desirable to synthesize and study the sugar reducing activity of dioxamoyl derivatives of sulfanilamide containing simultaneously two oxamoyl residues in its composition. The synthesis of these compounds was carried out according to the following scheme, starting from sulfanilamide (I):



Esters II and amides III were obtained by methods described in [6]. In the reaction of amides III with monoethyl oxalate monoacid chloride (ethoxalyl chloride), N-R-amides of 4-(ethoxalylamino)benzenesulfonyloxamic acid (IV, Table 1) are formed in yields of 72-86%. The latter with primary alkylamines form N-R-amides of 4-(N-R'-oxamido)benzenesulfonyloxamic acid (V, Table 2) in yields of 67-90%. Compounds IV and V are colorless crystalline compounds, which are insoluble in water and readily soluble in aqueous alkalies.

In the reaction of ester II with ethoxalyl chloride, ethyl ester of 4-(ethoxalylamino)-benzenesulfonyloxamic acid (VI) is formed in 93% yield, which gives compounds V (R = R') with primary alkylamines. Ester VI is readily saponified by 5% sodium hydroxide, and converts

TABLE 1. N-R-Amides of 4-(Ethoxalylamino)benzenesulfonyloxamic Acids (IV)

Compound	R	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
				N	S		N	S
IVa	H	79,1	237—8	12,46	9,52	$C_{12}H_{13}N_3O_7S$	12,24	9,34
IVb	HO	72,4	223—4	11,78	9,06	$C_{12}H_{13}N_3O_8S$	11,69	8,92
IVc	CH_3	82,0	290	11,89	8,99	$C_{13}H_{15}N_3O_7S$	11,76	8,97
IVd	CH_2OHCH_2	77,6	225—6	11,10	8,34	$C_{14}H_{17}N_3O_8S$	10,85	8,28
IVe	n-C_3H_7	81,2	214—5	11,16	8,44	$C_{15}H_{19}N_3O_7S$	10,90	8,32
IVf	n-C_4H_9	81,7	197—8	10,76	8,16	$C_{16}H_{21}N_3O_7S$	10,52	8,03
IVg	iso-C_4H_9	82,1	211—2	10,61	8,24	$C_{16}H_{21}N_3O_7S$	10,52	8,03
IVh	cyclo-C_6H_{11}	86,0	229—30	10,22	7,58	$C_{18}H_{23}N_3O_7S$	9,88	7,54
IVi	$C_6H_5CH_2$	84,2	212—3	9,84	7,47	$C_{19}H_{19}N_3O_7S$	9,69	7,40

Note. Compounds IVa, IVd, IVi were crystallized from glacial acetic acid; IVf, IVh from methanol; remaining compounds from aqueous dimethylformamide.

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TABLE 2. N-R-Amides of 4-(N-R'-Oxamido)-benzenesulfonyloxamic Acids (V)

Compound	R'	R	Yield, %		mp, °C	Found, %		Empirical formula	Calculated, %	
			method A	method B		N	S		N	S
Va	H	H	84,1	87,3	283 (dec.)	18,02	10,32	$C_{10}H_{10}N_4O_6S$	17,83	10,20
Vb	CH_3	CH_3	74,6	76,2	312 (dec.)	16,54	9,52	$C_{12}H_{14}N_4O_6S$	16,37	9,37
Vc	$CH_2=CH-CH_2$	$CH_2=CH-CH_2$	78,2	79,0	230—1	14,42	8,29	$C_{16}H_{18}N_4O_6S$	14,21	8,13
Vd	$C_6H_5CH_2$	$C_6H_5CH_2$	67,7	67,1	281—3	11,57	6,51	$C_{24}H_{22}N_4O_6S$	11,33	6,48
Ve	n-C_7H_{15}	n-C_7H_{15}	81,2	82,4	239	11,21	6,34	$C_{24}H_{38}N_4O_6S$	10,97	6,28
Vf	n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	80,6	82,2	228—9	9,67	5,52	$C_{30}H_{50}N_4O_6S$	9,42	5,39
Vg	cyclo-C_6H_{11}	iso-C_4H_9	86,2		260—2	12,50	7,21	$C_{20}H_{28}N_4O_6S$	12,38	7,08
Vh	HO	iso-C_4H_9	79,7		188 (dec.)	14,76	8,39	$C_{14}H_{18}N_4O_7S$	14,50	8,30
Vi	H	CH_2OHCH_2	76,2		252	15,82	9,12	$C_{12}H_{14}N_4O_7S$	15,64	8,95
Vj	CH_3	CH_2OHCH_2	76,1		267—8	15,26	8,74	$C_{13}H_{16}N_4O_7S$	15,05	8,61
Vk	iso-C_4H_9	CH_2OHCH_2	77,6		229—30	13,74	7,86	$C_{16}H_{22}N_4O_7S$	13,52	7,74
Vl	n-C_7H_{15}	CH_2OHCH_2	81,4		237—8	12,51	7,24	$C_{19}H_{28}N_4O_7S$	12,27	7,02
Vm	n-$C_{10}H_{21}$	CH_2OHCH_2	72,8		213—4	11,46	6,61	$C_{22}H_{34}N_4O_7S$	11,24	6,43
Vn	$C_6H_5CH_2$	CH_2OHCH_2	82,4		218—9	12,72	7,18	$C_{19}H_{20}N_4O_7S$	12,49	7,15
Vo	H	CH_3	81,1		270—2	17,35	10,02	$C_{11}H_{12}N_4O_6S$	17,06	9,77
Vp	n-C_3H_7	CH_3	78,0		290—1	15,44	8,74	$C_{14}H_{18}N_4O_6S$	15,13	8,66
Vq	n-C_4H_9	CH_3	81,2		265—6	14,84	8,55	$C_{15}H_{20}N_4O_6S$	14,57	8,34
Vr	iso-C_4H_9	CH_3	84,6		296—8	14,88	8,51	$C_{15}H_{20}N_4O_6S$	14,57	8,34
Vs	CH_2OHCH_2	CH_3	90,1		283—4	15,27	8,82	$C_{13}H_{16}N_4O_7S$	15,05	8,61
Vt	cyclo-C_6H_{11}	CH_3	82,2		262—3	13,81	7,98	$C_{17}H_{22}N_4O_6S$	13,65	7,81
Vu	n-C_7H_{15}	CH_3	80,7		219—20	13,16	7,71	$C_{18}H_{26}N_4O_6S$	13,14	7,52
Vv	n-$C_{10}H_{21}$	CH_3	72,3		164—6	12,02	7,02	$C_{21}H_{32}N_4O_6S$	11,96	6,84
Vw	$C_6H_5CH_2$	CH_3	74,6		262—3	13,70	7,80	$C_{18}H_{18}N_4O_6S$	13,40	7,66
Vx	HO	n-C_3H_7	73,5		188 (dec.)	15,33	8,80	$C_{13}H_{16}N_4O_7S$	15,05	8,61
Vy	HO	$C_6H_5CH_2$	79,1		200 (dec.)	13,60	7,76	$C_{17}H_{16}N_4O_7S$	13,33	7,63
Vz	HO	H	80,2		224 (dec.)	17,08	9,90	$C_{10}H_{10}N_4O_7S$	16,96	9,71

Note. Compounds Vh, Vk-n, Vx-z were crystallized from glacial acetic acid; remaining compounds were crystallized from aqueous dimethylformamide.

TABLE 3. IR and UV Spectra of N-R-Amides of 4(N-R'-Oxamido)benzenesulfonyloxamic Acids (V)

Compound	IR spectra: ν_{max}, cm^{-1}				UV spectra: λ_{max}, nm (log ε)		R_f
	OH	NH	CO	SO_2			
Vh	3520, 3270	3320, 3260	1720, 1670	1360, 1170	274	(4,23)	0,58
Vj	3530, 3265	3350, 3255	1735, 1660	1355, 1160	270	(3,74)	0,72
Vq		3335, 3260	1730, 1660	1360, 1165	272	(4,22)	0,65
Vt		3355, 3260	1735, 1665	1360, 1160	275	(4,17)	0,60
Vx	3525, 3270	3350, 3255	1730, 1660	1355, 1160	270	(4,21)	0,75
Vy	3530, 3265	3355, 3260	1730, 1660	1360, 1160	270	(4,07)	0,64

after acidification into 4-sulfanyloxanilic acid, melting at 215°C. The purity of the compounds obtained was controlled by determining the chromatographic constant (R_f).

The UV spectra of sulfamides (Table 3) are characterized by the presence of one or two highly intense absorption maxima in the 270-275 nm region (log ε 3.74-4.23).

In the IR spectra of sulfamides V (see Table 3) there are characteristic stretching vibration frequencies of the OH, NH- CO- and SO_2 groups. The lowered frequencies of the stretching vibrations of the OH, NH, and CO groups, and also the broad absorption bands of the NH group indicate the presence of hydrogen bonds [7]. The presence of the CONHOH group in compoundes IVb, Vh, Vx, Vy, Vz was confirmed by complex formation reactions with Fe^{3+} and Cu^{2+} salts [8].

Biological tests (Tables 4 and 5) were carried out in comparison with butamide. The data in Tables 4 and 5 show that the sugar reducing activity depends on the nature and position of the substituents in the oxamide residues. The greatest effect is attained when hydroxyl, hydroxyethyl, propyl, butyl, and cyclohexyl radicals are introduced into the sulfonyloxamide and benzene-oxamide parts of the molecules.

According to the K. K. Sidorov classification [9], all the compounds studied can be considered as practically nontoxic materials. No death of the animals was observed after peroral administration in doses of 10-15 g/kg.

EXPERIMENTAL CHEMICAL PART

The UV spectra were run on SF-4 apparatus in ethanol, c = $1 \cdot 10^{-3}$ to $1 \cdot 10^{-5}$ mole/liter; IR spectra were taken on the UR-20 apparatus in KBr tablets (concentration of the material, 0.5%) with sodium chloride and lithium fluoride prisms. The R_f was determined on Silufol-UV 254 plates, using the following systems of solvents: n-butanol—25% NH_3 (9:1) for compounds Vh, Vj, Vx, Vy and n-butanol—25% NH_3 (8:1) for compounds Vq and Vt. The spots on the chromatogram were detected with UV irradiation.

Ethyl Ester of p-(N-ethoxalylamino)benzenesulfonyloxamic Acid (VI). A 1.01 g portion of triethylamine and 1.5 g of ethoxalyl chloride was added with cooling to a solution of 2.72 g of ester II in 10 ml of glacial acetic acid, and the mixture was left to stand for 6 h at room temperature. It was then diluted with a 5-fold amount of water, the precipitate was filtered and crystallized from aqueous dimethylformamide. Needles, mp 220-221°C. Yield, 3.47 g (93.2%). Found, %: N 7.65. $C_{14}H_{16}N_2O_8S$. Calculated, %: N 7.52.

Cyclohexyl Amide of p-(ethoxalylamino)benzenesulfonyloxamic Acid (IVh). A 1.01 g portion of triethylamine and 1.5 g of ethoxalyl chloride were added with cooling to a solution of 3.25 g of sulfanilamide III (R = cyclo-C_6H_{11}) in 10 ml of glacial acetic acid, and the mixture was left to stand for 6 h at room temperature. It was then diluted with a 5-fold amount of water, and the precipitate was filtered off, and recrystallized. Yield, 3.65 g (85.9%). Compounds IVa-g and IVi were obtained similarly.

Benzyl Amide of p-(benzyloxamido)benzenesulfonyloxamic Acid (Vd). Method A. A 2.14 g portion of benzylamine was added to a solution of 4.33 g of benzyl amide of p-(N-ethoxalyl-

TABLE 4. Hypoglycemic Activity of N-R-Amides of 4-(ethoxalylamino)benzenesulfonyloxamic acids (IV)

Compound	R	Period of investigation, h					
		2	4	6	8	10	24
		reduction in sugar level in blood, % with respect to initial data					
IVa	H	9	18	10	16	21	9
IVb	HO	2	2	21	17	19	5
IVc	CH_3	0	9	7	7	20	0
IVd	CH_2OHCH_2	28	22	16	23	14	10
IVe	n-C_3H_7	20	22	26	21	22	12
IVf	n-C_4H_9	8	15	15	23	20	11
IVg	iso-C_4H_9	19	24	22	28	26	7
IVh	cyclo-C_6H_{11}	24	21	12	14	12	2
IVi	$C_6H_5CH_2$	4	10	21	18	26	6
Butamide		21	25	30	24	23	5

TABLE 5. Hypoglycemic Activity of N-R-Amides of 4-(N-R'-oxamido)benzenesulfonyloxamic acids (V)

Compound	R'	R	Period of investigation, h					
			2	4	6	8	10	24
			reduction in sugar level in blood, % with respect to initial data					
Va	H	H	0	5	3	3	1	
Vb	CH_3	CH_3	3	7	4	8	5	
Vc	CH_2=CH—CH_2	CH_2=CH—CH_2	4	8	2	12	6	
Vd	$C_6H_5CH_2$	$C_6H_5CH_2$	2	7	14	2	3	
Ve	n-C_7H_{15}	n-C_7H_{15}	0	9	7	11	4	
Vf	n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	3	0	2	4	1	
Vg	cyclo-C_6H_{11}	iso-C_4H_9	12	21	27	25	20	12
Vh	HO	iso-C_4H_9	11	19	28	26	24	8
Vi	H	CH_2OHCH_2	10	18	21	14	22	12
Vj	CH_3	CH_2OHCH_2	18	6	17	28	16	7
Vk	iso-C_4H_9	CH_2OHCH_2	20	27	26	22	18	14
Vl	n-C_7H_{15}	CH_2OHCH_2	7	24	13	27	15	4
Vm	n-$C_{10}H_{21}$	CH_2OHCH_2	16	21	24	12	27	11
Vn	$C_6H_5CH_2$	CH_2OHCH_2	12	22	18	27	20	6
Vo	H	CH_3	0	+2	17	6	21	0
Vp	n-C_3H_7	CH_3	14	20	24	17	25	10
Vq	n-C_4H_9	CH_3	18	21	30	22	26	7
Vr	iso-C_4H_9	CH_3	14	22	28	23	17	15
Vs	CH_2OHCH_2	CH_3	12	21	32	21	14	5
Vt	cyclo-C_6H_{11}	CH_3	8	26	29	18	27	14
Vu	n-C_7H_{15}	CH_3	2	8	14	2	0	
Vv	n-$C_{10}H_{21}$	CH_3	0	6	18	4	1	
Vw	$C_6H_5CH_2$	CH_3	2	12	3	16	4	
Vx	HO	n-C_3H_7	19	26	18	31	20	8
Vy	HO	$C_6H_5CH_2$	7	4	16	18	10	2
Vz	HO	H	4	12	8	26	17	3
	Butamide		21	25	30	24	23	5

amino)benzenesulfonyloxamic acid in 10 ml of ethanol. The mixture was left to stand for 12 h at room temperature, a large part of alcohol was distilled off, and the residue diluted with a 5-fold amount of water, and acidified with HCl (1:1) to pH 2.0. The precipitate was filtered off and recrystallized. Yield, 3.36 g. Compounds Va-c, Ve-z were obtained similarly.

Method B. A 3.21 g portion of benzylamine was added to a solution of 3.72 g of ester VI in 10 ml of ethanol. The mixture was kept at room temperature, and a large part of the alcohol was distilled off. The residue was acidified with HCl (1:1) to pH 2.0. The precipitate was filtered off and recrystallized to yield 3.31 g of Vd. Compounds Va-c, Ve, Vf were obtained similarly.

EXPERIMENTAL BIOLOGICAL PART

The sugar reducing activity of compounds IV and V was determined perorally on rabbits by the ortho-toluidine method [10] in doses of 0.05 g/kg. In each experiments 6 rabbits were used.

The toxicity was studied on white mice with a peroral method of administration. LD_{50} was determined by the method described in [11].

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF ISONICOTINOYLHYDRAZONES OF CERTAIN DI- AND TRICARBONYL COMPOUNDS

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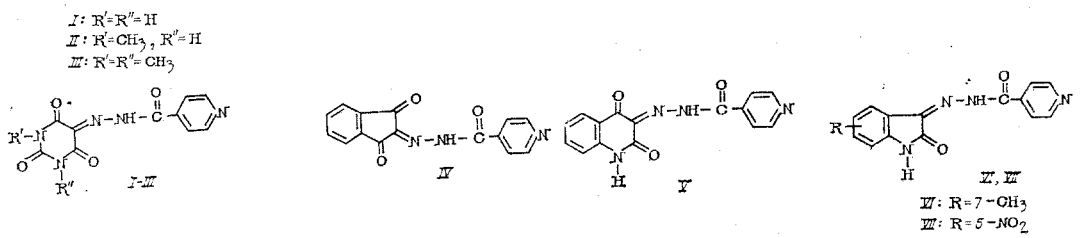
In the literature papers continue to be published on the synthesis of derivatives of isonicotinic acid hydrazide (isoniazid) to obtain compounds with a higher tuberculostatic activity than that of isoniazid itself [1-4]. This search is necessary because of the existence of patients infected with stable mycobacteria [5].

For the synthesis of the new isoniazid derivatives we used cyclic 1,2,3-tricarbonyl compounds: alloxan, 1-methyl- and 1,3-dimethylalloxan, ninhydrin, quinisatin, as well as dicarbonyl compounds: 7-methyl- and 5-nitroisatin. The reaction of these polycarbonyl compounds with isoniazid was carried out by mixing aqueous or alcoholic solutions containing equimolar amounts of the reagents. In all cases the formation of precipitates of the condensation products (I-VII) was observed already at room temperature, or after short-term (15-30 min) heating.

The compounds obtained, crystallized with one molecule of water, are moderately soluble in dimethylformamide and slightly soluble in ethanol and in water. To increase the solubility they were converted into the corresponding pyridinium salts (Ia-VIIa) by reacting equimolar amounts of hydrochloric acid and the hydrazone solutions in an ethanol–dioxane mixture (1:1). In the hydrochloride form the compounds are more stable on storage.



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