SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-HETERYLOXAMIC ACID HYDRAZONES

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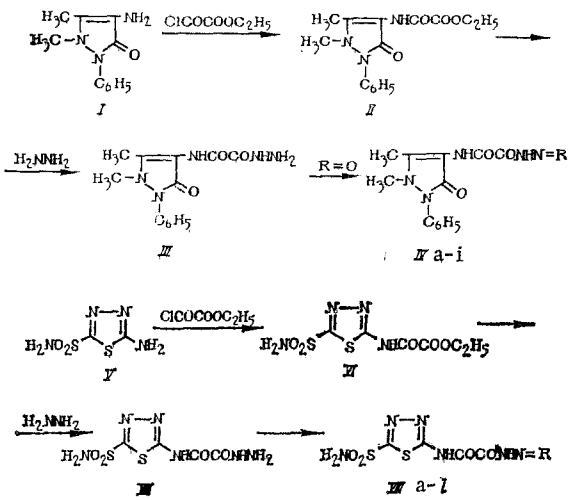
We have previously reported [1] the synthesis and biological activity of 1,3,5-thiadiazolyloxamic acid amides. We established that the hypoglycemic and antibacterial activity depend on the character of the substituents bonded to the amide nitrogen atom. It seemed of interest to obtain new derivatives of oxamic acid, viz., N-heteryloxamic acid hydrazones, and to investigate their biological activity. The synthesis of this group of compounds was realized via the scheme



Esters II [2] and VI [3], which were obtained by reaction of the corresponding heterocyclic amines I and V with ethoxalyl chloride, were used as the starting compounds for the preparation of hydrazones IV and VIII. The reaction of esters II and VI with hydrazine hydrate in alcohol solutions led to the corresponding hydrazides III [2] and VII, which upon heating with aliphatic, aromatic, and heterocyclic aldehydes or ketones in dimethylformamide (DMF) gave hydrazones IV and VIII. The compounds obtained were identified from the results of elementary analysis, their IR spectra, and data from thin-layer chromatography (TLC).

The IR spectra of IVa-i and VIIIa-l (Table 1) are characterized above all by the presence of a number of intense absorption bands at 1600-1700 cm^{-1} due to the stretching vibrations of carbonyl groups. The difficulty in the assignment of these bands is explained by the presence in the molecules of three (IVa-g and VIIIi-l) and four (IVh-i) carbonyl groups, as well as by the presence of an absorption band of an O=N group in this region. For the reliable interpretation of this range of frequencies we recorded the spectra of three model compounds, viz., antipyrine, 4-dimethylaminoantipyrine, and hydroxy-2,3-dihydroindol-2-on-3-ylidene [sic], each of which is a terminal grouping in IVa-i and VIIIi-l and gives at 1662-1714 cm^{-1} an absorption band corresponding to the stretching vibrations of an exocyclic carbonyl group.

A $\nu_{C=N}$ band at 1660 cm^{-1} is present in the spectra of compounds with an antipyrine grouping, except for IVa and IVf, in the spectra of which it shows up in the form of inflections on the more intense band of an aliphatic C=O group.

The band at 1660-1698 cm^{-1} is due to the asymmetrical stretching vibrations of two α-carbonyl groups situated in the aliphatic part of the molecule. From the ν_{CO} values of this band it may be assumed that they are found in the S-trans conformation, since the ν_{CO} band at

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TABLE 1. N-Heteryloxamic Acid Hydrazones

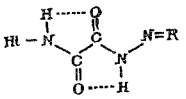
Compound	R	Yield, %	T. mp, °C	Found, %		Empirical formula	Calc., %		R_f	IR spectra, ν, cm^{-1}	
				N	S		N	S		CO (amide)	CO (oxalyl)
IVa	p-Methoxybenzylidene	79	236—238	17,18	—	$C_{21}H_{21}N_5O_4$	17,19	—	0,68	Плечо	1681
IVb	p-Dimethylaminobenzylidene	68	264—265	20,08	—	$C_{22}H_{24}N_6O_3$	19,99	—	0,73	1666	1677
IVc	o-Nitrobenzylidene	85	254—255	20,08	—	$C_{20}H_{18}N_6O_5$	19,89	—	0,53	1668	Shoulder
IVd	Veratrolidene	91	238—239	16,18	—	$C_{22}H_{23}N_5O_5$	16,01	—	0,43	1663	Shoulder
IVe	Vanillylidene	73	267—268	16,21	—	$C_{21}H_{21}N_5O_5$	16,44	—	0,64	1650	1683
IVf	Furfurylidene	68	252—253	19,35	—	$C_{18}H_{17}N_5O_4$	19,06	—	0,39	Плечо	1672
IVg	5-Nitrofurfurylidene	71	298—300	20,35	—	$C_{18}H_{16}N_6O_6$	20,38	—	0,48	1653	1688
IVh	2,3-Dihydroindol-2-on-3-ylidene	88	259—261	20,18	—	$C_{21}H_{18}N_6O_4$	20,09	—	0,53	1660	1697
IVi	1-Methyl-2,3-dihydroindol-2-on-3-ylidene	87	300	19,62	—	$C_{22}H_{20}N_6O_4$	19,43	—	0,65	1650	1698
VIIIa		42	253—255	23,91	18,29	$C_{11}H_{10}N_6O_4S_2$	23,71	18,09	0,29	—	1659
VIIIb	Benzylidene	39	232—234	21,88	16,73	$C_{12}H_{12}N_6O_5S_2$	21,86	16,68	0,80	—	1663
VIIIc	p-Methoxybenzylidene	37	256—257	24,87	16,26	$C_{13}H_{15}N_7O_4S_2$	24,67	16,13	0,50	—	1671
VIIId	p-Dimethylaminobenzylidene	60	252—253	24,67	16,19	$C_{11}H_9N_7O_6S_2$	24,55	16,05	0,85	—	1689
VIIIe	o-Nitrobenzylidene	41	238—239·	20,39	15,63	$C_{13}H_{14}N_6O_6S_2$	20,27	15,47	0,35	—	1660
VIIIf	Veratrolidene	48	248—250	21,09	16,21	$C_{12}H_{12}N_6O_6S_2$	20,98	16,01	0,43	—	1662
VIIIg	Vanillylidene	61	300	24,60	18,81	$C_9H_8N_6O_5S_2$	24,40	18,62	0,75	—	1689
VIIIh	Furfurylidene	66	278—280	25,36	16,70	$C_9H_7N_7O_7S_2$	25,18	16,42	0,30	—	1693
VIIIi	5-Nitrofurfurylidene	65	300	24,86	16,42	$C_{12}H_9N_7O_5S_2$	24,79	16,21	0,70	1711	Covered band
VIIIj	2,3-Dihydroindol-2-on-3-ylidene	61	300	24,07	15,83	$C_{13}H_{11}N_7O_5S_2$	23,94	15,66	0,32	1711	1691
VIIIk	1-Methyl-2,3-dihydroindol-2-on-3-ylidene	73	300	20,83	13,71	$C_{12}H_8BrN_7O_5S_2$	20,67	13,52	0,42	1710	covered band
VIIIl	5-Bromo-2,3-dihydroindol-2-on-3-ylidene	56	280—282	22,63	14,73	$C_{14}H_{11}N_7O_6S_2$	22,41	14,66	0,50	1711	1690
	1-Acetyl-2,3-dihydroindol-2-on-3-ylidene										

Note: IV and VIII were crystallized from aqueous DMF.

TABLE 2. Hypoglycemic and Antibacterial Activity of N-Heteryloxamic Acid Hydrazones

Compound	Time after introduction of prep., h: decrease in the sugar level in the blood, % of the starting level							Test culture of microorganisms			
	2	4	6	8	10	12	24	E. coli	Bacillus pyocyaneus	pathogenic staphylococcus	hay bacillus
IVa	7	4	5	8	7	5	1	1:8 000	1:8 000	1:4 000	1:8 000
IVb	3	7	10	11	13	10	4	1:8 000	1:8 000	1:4 000	1:4 000
IVc	9	11	14	15	11	7	5	1:8 000	1:8 000	1:4 000	1:8 000
IVd	11	15	13	11	8	5	3	1:16 000	1:8 000	1:2 000	1:2 000
IVe	15	15	13	10	10	8	7	1:8 000	1:8 000	1:8 000	1:8 000
IVf	11	13	15	13	10	5	1	1:4 000	1:8 000	1:4 000	1:8 000
IVg	8	5	5	7	5	3	3	1:16 000	1:8 000	1:8 000	1:4 000
IVh	10	8	15	15	17	13	7	1:8 000	1:16 000	1:8 000	1:16 000
IVi	13	12	14	12	13	10	8	1:2 000	1:8 000	1:2 000	1:2 000
VIIIa	15	13	13	14	10	8	7	1:4 000	1:8 000	1:4 000	1:4 000
VIIIb	10	7	6	6	3	3	1	1:8 000	1:8 000	1:2 000	1:8 000
VIIIc	11	13	18	15	10	10	3	1:16 000	1:8 000	1:8 000	1:4 000
VIIId	6	17	15	13	13	6	3	1:4 000	1:16 000	1:4 000	1:8 000
VIIIe	7	10	15	11	8	5	2	1:8 000	1:8 000	1:16 000	1:16 000
VIIIf	13	19	18	13	15	15	8	1:4 000	1:8 000	1:8 000	1:8 000
VIIIg	8	7	13	10	10	8	7	1:2 000	1:8 000	1:8 000	1:4 000
VIIIh	10	15	13	8	8	3	1	1:16 000	1:16 000	1:4 000	1:8 000
VIIIi	6	15	15	13	10	8	5	1:4 000	1:8 000	1:8 000	1:2 000
VIIIj	7	7	13	10	7	5	1	1:8 000	1:4 000	1:4 000	1:4 000
VIIIk	3	15	16	15	13	10	8	1:8 000	1:8 000	1:2 000	1:8 000
VIIIl	5	9	18	21	10	8	5	1:8 000	1:8 000	1:16 000	1:4 000
Butamide	21	25	30	24	23	23	5	—	—	—	—

1760 cm^{-1} corresponds to an S-cis orientation (4). In addition, the S-trans conformer in this case is stabilized by the existence of an intramolecular hydrogen bond between the hydrogen atoms of the amino groups and each of the α-carbonyl oxygen atoms, as indicated by the character and frequency of the absorption of the NH groups. On the basis of the material set forth above, it may be assumed that a quasi-aromatic structure of the following type exists in these systems:



The stretching vibrations of the sulfonyl group in VIIIa-*l* are represented by two bands, viz., $\nu^{as}_{SO_2}$ (1251-1368 cm^{-1}) and $\nu^{s}_{SO_2}$ (1096-1182 cm^{-1}).

The results of a study of the biological activity of the compounds obtained are presented in Table 2. The hypoglycemic activity was determined by the o-toluidine method [5] as compared with butamide. Most of the compounds that we synthesized lower the percentage of sugar in the blood by 10-15% as compared with the starting level, and this amounts to 30-50% of the maximum reduction under the influence of butamide. Hydrazones VIIIc, VIIIf, and VIIIl, the maximum sugar-lowering effect of which is displayed at various time intervals, have the highest activity, which reaches 18-21%.

With respect to the duration of their effect, six hydrazones (IVb, IVh, IVi, VIIIc, VIIIf, and VIIIk) still retain their sugar-lowering action (up to 10-15%) after 12 h, while the rest of the compounds lose their activity after this period of time. Virtually all of the hydrazones lose their hypoglycemic activity after 24 h. The data on the sugar-lowering activity of hydrazones IVa-i presented above were unexpected, since some authors assume that the sulfonyl group is responsible for the sugar-lowering effect.

The antibacterial activity of the synthesized hydrazones was determined by the generally accepted method of twofold serial cultures in beef-extract broth (pH 7.2) with respect to pathogenic staphylococcus, *Bacillus pyocyaneus*, *Escherichia coli*, and the hay bacillus.

The bacteriostatic action was determined visually after the seedings had been heated in a thermostat at 37°C for 18-20 h. The experiments showed that hydrazones IV and VIII do not have pronounced bacteriostatic action with respect to the microorganisms cited above (see Table 2). The highest antibacterial activity is observed for IVg, IVh, VIIIc, VIIId, VIIIe, VIIIh, and VIIIl.

Thus it may be noted that the union of a heteryl residue with a hydrazonooxamoyl residue leads to substances that have little promise with respect to their physiological action (according to tests of their hypoglycemic and antibacterial activity).

EXPERIMENTAL

The IR spectra of potassium bromide pellets (1%) of the compounds were recorded with an IK-20 spectrometer. Thin-layer chromatography was carried out on Silufol UV-254 plates in a chloroform–methanol–DMF system (70:20:10).

5-Sulfamoyl-1,3,4-thiadiazolyl-2-oxamic Acid Hydrazide (VII). A solution of 2 g (0.04 mole) of hydrazine hydrate in 10 ml of methanol was added to a solution of 5.6 g (0.02 mole) of VI [3] in 25 ml of methanol, and the mixture was maintained at room temperature for 3 h. The methanol was removed by distillation and the residue was diluted with water and filtered. The filtrate was acidified to pH 5.0 with dilute hydrochloric acid (1:1) and the precipitate was separated and dried to give 4 g (75%) of VII with mp 233-234°C (plates from aqueous DMF).

5-Sulfamoyl-1,3,4-thiadiazolyl-2-oxamic Acid Benzylidenehydrazide (VIIIa). A 1.06-g (0.01 mole) sample of benzaldehyde was added to 2.6 g (0.01 mole) of hydrazide VII in 10 ml of DMF and the mixture was heated for 30 min. A fivefold amount of water was then added, and the precipitate was removed by filtration, dried, and crystallized.

Hydrazones VIIIb–l and IVa-i were similarly obtained.

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