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BIOLOGICALLY ACTIVE SUBSTANCES IN HYDRAZIDE DERIVATIVES OF SUCCINIC HETERYLAMIDES

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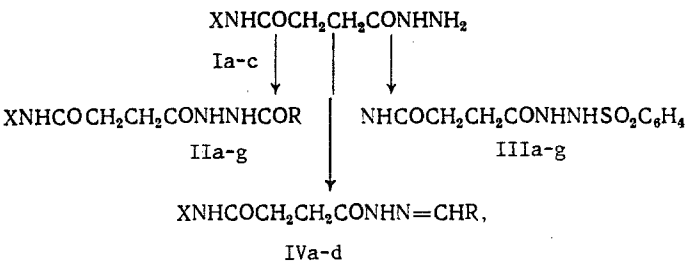
The present study was undertaken as a result of the results of our own observations [12-14] as well as the data from descriptor-statistical analysis [10] which indicated that the hydrazide derivatives of succinic heterylamides represent a promising series of substances that exhibit antiinflammatory, hydroglycemic, antimicrobial, and other pharmacological effects.

The purpose of the present study was to work out methods for the synthesis of acyl- (arensulfo- and ilidene-) hydrazides of succinic heterylamides, to examine their pharmacological properties, and identify any possible structure-pharmacological action relationships, i.e., for obtaining a theoretical basis for further research on biologically active substances.

The synthesis of the described groups of compounds was performed in accordance with the following patern:



where X = 2-(1,3,4-thiadiazolyl) (Ia, IIIa-d, IV, a, b); 5-n-propyl-2-(1,3,4-thiadiazolyl) (Ib, IIa-d); thiazolyl-2 (Ic, IId-g, IIId-h, IVc, d); R = C_2H_5 (IIa); C_3H_7(IIb, e); CH_2CH_2-COOH (IIc, f); 2-$CH_3C_6H_4$ (IId, g); 4-OCH_3 (IIIa, e); 4-$NHCOOCH_3$ (IIIb, f); 4-Cl (IIIc, g); 2-NO_2 (IIId); C_6H_5 (IVa, c); 4-OHC_6H_4 (IVb, d).

The starting hydrazides (Ia-c) were obtained by methods [4, 6]. Acylation of the hydrazides by carboxylic anhydrides and chloroanhydrides in dioxane as well as by arensulfochlorides in a pyridine medium was accompanied by the formation of the corresponding acyl- and arensulfohydrazides (IIa-g and IIIa-g, respectively). The ilidene hydrazides (IVa-d), obtained by reacting the hydrazides I and aldehydes in boiling DMFA, turned out to be the purest end products with the highest yield.

Structural and purity confirmation for the synthesized compounds was obtained by element analysis, counter synthesis, IR-spectroscopy, and chromatographic constants (Table 1).

The IR-spectra of compounds I-IV exhibited absorption bands in the 1759-1638 cm^{-1} region which corresponded to the stretching vibrations of the C=O ($\nu C{=}O$), and at 1646-1527 cm^{-1}, corresponding to the deformation vibrations of the NH (δNH) group. The bands of the asymmetric and symmetric stretching vibrations of the CH_2 group were in the 2974-2912 cm^{-1} ($\nu^{as}_{CH_2}$) range and in the 2890-2830 cm^{-1} ($\nu^{s}_{CH_2}$), whereas the deformation vibrations of the indicated group were in the 1435-1407 cm^{-1} (ρ_{CH_2}). Group C–H is characterized by shell vibrations in the 1226-1110 cm^{-1} (ν_{C-H}) range. The arensulfohydrazides IIIa-g exhibit intensive bands corresponding

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TABLE 1. Hydrazide Derivatives of Succinic Acid Heterylamides

Compound	Yield, %	mp, °C*	Empirical formula	R_f
Ia	99	183 (dec.)	$C_6H_9N_5O_2S$	0,80
Ib	88	185—7	$C_9H_{15}N_5O_2S$	0,75
Ic	82	180—2	$C_7H_{10}N_4O_2S$	0,90
IIa	62	198—9	$C_{12}H_{19}N_5O_3S$	0,76
IIb	67	203—5	$C_{13}H_{21}N_5O_3S$	0,78
IIc	75	198 (dec.)	$C_{13}H_{19}N_5O_5S$	0,79
IId	96	191 (dec.)	$C_{17}H_{21}N_5O_3S$	0,85
IIe	65	212 (dec.)	$C_{11}H_{16}N_4O_3S$	0,76
IIf	72	210 (dec.)	$C_{11}H_{14}N_4O_5S$	0,44
IIg	98	188 (dec.)	$C_{15}H_{16}N_4O_3S$	0,88
IIIa	73	168 (dec.)	$C_{13}H_{15}N_5O_5S_2$	0,79
IIIb	79	230 (dec.)	$C_{14}H_{16}N_6O_6S_2$	0,81
IIIc	82	227 (dec.)	$C_{12}H_{12}N_5O_4S_2Cl$	0,82
IIId	69	189 (dec.)	$C_{12}H_{12}N_6O_6S_2$	0,80
IIIe	76	197 (dec.)	$C_{14}H_{16}N_4O_5S_2$	0,80
IIIf	79	199 (dec.)	$C_{15}H_{17}N_5O_6S_2$	0,81
IIIg	78	207 (dec.)	$C_{13}H_{13}N_4O_4S_2Cl$	0,85
IVa	85	228 (dec.)	$C_{13}H_{13}N_5O_2S$	0,78
IVb	89	245 (dec.)	$C_{13}H_{13}N_5O_3S$	0,75
IVc	85	215 (dec.)	$C_{14}H_{14}N_4O_2S$	0,82
IVd	90	230 (dec.)	$C_{14}H_{14}N_4O_3S$	0,75

*All of the synthesized compounds were recrystallized from aq. DMFA.
**R_f was calculated in a 9:1 chloroform—ethanol system for compounds Ia-c and IIa-g, and in a 2:3:3 ethanol—chloroform—hexane system for compounds IIIa-g and IVa-d.

to the asymmetric ($\nu^{as}_{SO_2}$) and symmetric ($\nu^{s}_{SO_2}$) stretching vibrations of the sulfo group within the range of 1340-1321 cm^{-1} and 1175-1160 cm^{-1}, respectively. The stretching vibrations of the methyl group, which is present in the 5-n-propylsubstituted analogs of compounds Ib, IIa-d, were observed in the 2974-2956 cm^{-1} ($\nu^{as}_{CH_3}$) and 2878-2862 cm^{-1} ($\nu^{s}_{CH_3}$) range.

In accordance with the "Oracle" prediction system the synthesized compounds were pharmacologically screened for hypoglycemic, antiinflammatory, diuretic, and antimicrobial activity.

The results of the biological tests (Table 2) indicate that compounds I-II elicit pronounced hypoglycemia in animals. The level of hypoglycemia ranged from 7-28% within a 24-h period, although it does not exceed the activity of butamide (30%).

As illustrated by the I-III hydrazide derivatives, one can see that the magnitude and duration of the hypoglycemic effect is proportional to the nature of the heterocyclic fragment and structure of the molecule's hydrazide derivative component. Thus, the most active acyl hydrazides II are those in which the heterocycle is represented by a thiazole (IIe-g). Changes in the acyl hydrazide fragment, such as an elongation of the alkyl chain to 3 carbon atoms (IIb) or the introduction of aromatic radicals (IId, g) while retaining the nature of the heterocyclic component, was accompanied by an attenuation of hypoglycemic activity (by 1.5-4.3 times).

In analyzing the experimental data one should note that most of the examined compounds can inhibit inflammatory edema. Pronounced antiinflammatory activity was exhibited by compounds IIb, d, g, and IIIb, d which reduced inflammatory edema by 19-29% which is comparable to the effect of butadione (17-25%) and somewhat lower than the effect of indomethacin (55%).

Among the acyl hydrazides II the effect that the nature of the heterocycle had on the degree of antiexudative activity was not clear. In one case the thiazole fragment (IIg) proved to be advantageous, while in another case the thiadiazole fragment (IIb, d) was advantageous.

The arensulfohydrazides III exhibited a tendency to increase antiinflammatory activity when acceptor substituents (IIId) were introduced into the benzene ring or when a thiadiazole (IIIb-d) was introduced into the heterocyclic fragment.

The tests demonstrated that the arensulfohydrazides III manifested the most pronounced diuretic activity of all the investigated substances. A single administration of those substances increased diuresis by 100 to 229% in comparison to the control which was 1.6 times greater than a similar effect produced by the acyl hydrazides II, although they did not exceed the activity of hypothiazide (230%). In that respect the thiadiazole derivatives IIIa-c have a certain advantage over the thiazole analogs IIIe-g.

TABLE 2. Hypoglycemic, Antiinflammatory, and Diuretic Activity of Hydrazide Derivatives of Succinic Acid Heterylamides

Compound	Blood sugar reduction, as % of the initial data						Reduction of inflammatory edema, %	Urine volume excreted by animals during experiment, %
	after 2 h	after 4 h	after 6 h	after 8 h	after 10 h	after 24 h		
Ib	3	10	22	21	7	—	17	80
IIa	2	11	11	16	22	8	13	90
IIb	2	14	10	11	6	—	29	90
IIc	23	10	5	2	—	—	15	100
IId	7	—	—	—	—	—	19	100
IIe	16	24	6	20	28	10	13	125
IIf	13	22	10	20	17	6	5	130
IIg	10	8	12	8	2	—	27	145
IIIa	3	7	12	10	4	—	—	195
IIIb	8	9	5	4	3	—	19	229
IIIc	9	6	3	—	—	—	4	100
IIId	3	—	—	—	—	—	21	145
IIIe	2	—	—	—	—	—	4	182
IIIf	4	2	2	1	—	—	—	—
IIIg	—	3	—	—	—	—	—	—
Butamide	21	25	30	24	23	5	—	—
Butadione	—	—	—	—	—	—	17	—
Hypothiazide	—	—	—	—	—	—	—	230

Note. Dash denotes no activity.

Also of interest is the fact that the hydrazide derivative heterylamides of succinic acid, like the compounds of the other groups [3, 15], exhibit a tendency to increase diuretic activity when the acidity of the compounds is increased. Whereas diuresis in the initial hydrazides I (pK_α 3.57-3.65) did not exceed 80%, that figure was 100-229% for the arensulfohydrazides III (pK_α 8.35-10.26).

The ilidene hydrazide IV tests for fungicidal activity showed that they would not be of interest as antimicrobial agents since their activity level did not significantly differ from the control.

In summing up the foregoing, one should note that the arensulfohydrazides would seem to represent a promising series in the search for new diuretic agents, and that the acyl hydrazides of succinic acid heteroylamides would seem to be a promising series for finding new hypoglycemic and antiinflammatory agents.

EXPERIMENTAL (CHEMICAL)

IR-spectra were recorded on a UR-20 instrument in the 3700-2500 cm^{-1} region (LiF prism) and the 1900-650 cm^{-1} (NaCl prism) in KBr pellets [5]. Element analysis data satisfied the calculated values.

Succinic 5-n-Propyl-(1,3,4-thiadiazolyl)-amide Propionyl Hydrazide (IIa). A 1.39 ml (0.011 mole) portion of triethylamine was added dropwise to a suspension of 2.57 g (0.01 mole) of compound Ib in 5 ml of dioxane to which 1.01 g (0.011 mole) of propionyl chloride was subsequently added upon intensive stirring. The resultant precipitate was left to stand for 2 h, filtered off, and dried. Yield was 1.94 g. Needles (from aq. DMFA), mp 198-199°C.

Compounds IIb-g were obtained in a similar manner.

Succinic 2-Thiazolylamide 4-Methoxybenzosulfohydrazide (IIIa). A mixture of 2.06 g (0.01 mole) of 4-methoxybenzolsulfochloride, 20 ml of pyridine, and 2.14 g (0.01 mole) of 4-methoxybenzolsulfochloride, 20 ml of pyridine, and 2.14 g (0.01 mole) of compound Ic was heated for 45 min with a reflux condenser. The precipitate was filtered off and dried. Yield was 3.84 g. Needles, mp 168°C (decomposition, from aq. DMFA).

Compounds IIIb-g were obtained in a similar manner.

Succinic 2-Thiazolylamide Benzylidene Hydrazide (IVc). A 1.06 g (0.01 mole) portion of benzaldehyde was added to a solution of 2.14 g (0.01 mole) of compound Ic in 10 ml of DMFA and the mixture was heated for 30 min after which it was diluted with a fivefold quantity of water. The precipitate was filtered off and dried. Yield was 2.48 g. Needles, mp 215°C (decomp.) (from aq. DMFA).

Compounds IVa, b, d, were obtained in a similar manner.

EXPERIMENTAL (BIOLOGICAL)

The hypoglycemic activity of the synthesized substances was tested on Chinchilla male rabbits of the same age weighing 2-2.5 kg. The animals' diet consisted of oats, hay, and water. The test substances were administered orally at a dose of 50 mg/kg. Analyzed blood was taken from the aural vein of rabbits at 2, 4, 6, 8, 10 and 24 h intevals following a single administration of the test preparation. Blood sugar content was measured by the toluidine method [8]. The test data was statistically processed by the Rakitskii method [9].

The compounds' antiinflammatory activity was judged by their antiexudative action which was measured on mice weighing 18-20 g in which a 2.5% solution of formalin was used as the inflammatory agent by method [11]. The compounds were administered at a dose of 0.3 g/kg [1].

The compounds' diuretic action was tested on rats weighing 160-200 g by method [2]. The substances were administered at a dose of 200 mg/kg.

Acute toxicity of the examined compounds administered ip (observations within a 24 h period) was calculated by method [7], and varied between 3000-4200 mg/kg.

The antifungal activity of compounds IV was tested by the dilution method on solid (Sabouraud's agar) and liquid (Sabouraud's extract) nutrient media at concentrations of 500, 250, 125, 62.5, and 31.25 μg per 1 ml of medium. The test cultures used were the most prevalent etiological agents of skin and adventitia mycoses as well as etiological agents of systemic mycoses (Microsporum canis 722, Triphophyton gymseum 308, and Candida albicans 781).

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