SUBSTITUTED AMIDES AND HYDRAZIDES OF 1,4-DICARBOXYLIC ACIDS. PART 8.[1] SYNTHESIS AND HYPOGLYCEMIC ACTIVITY OF SUBSTITUTED SUCCINIC ACID AMIDES AND HYDRAZIDES

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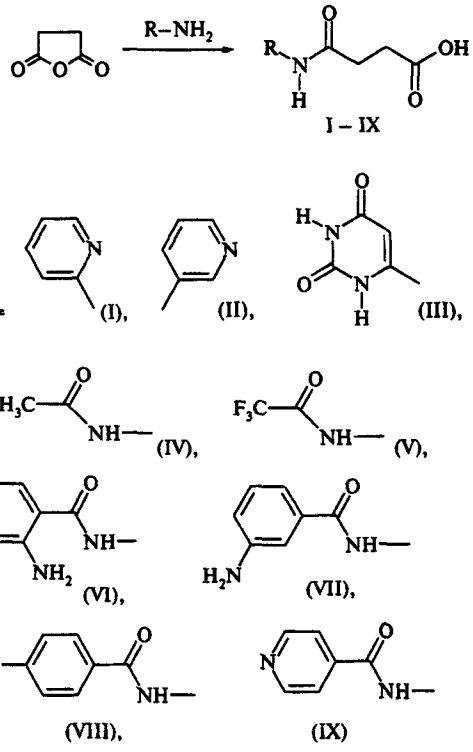
It was reported that amides and hydrazides of 1,4-dicarboxylic acids contain compounds possessing hypoglycemic properties [2 – 7], this activity being most pronounced in substituted hydrazides of succinic acid with heterylamide terminal fragments [6, 8].

In continuation of the search for new hypoglycemic agents, we have synthesized a series of heterylamides (I – III) and acylhydrazides (IV – IX) of succinic acid and studied their properties.



Compounds I – IX were synthesized by acylating the corresponding heterylamines and hydrazides of carboxylic acids with succinic anhydride under mild conditions as described in [1, 8].

The proposed structures of originally synthesized compounds I – III and IX were confirmed by the results of spectroscopic measurements in comparison with data for the previously reported succinic acid acylhydrazides [1].

EXPERIMENTAL CHEMICAL PART

The ^{1}H NMR spectra of the synthesized compounds were measured on the RYa-2310 (60 MHz) and Varian VPX-300 (300 MHz) spectrometers using samples dissolved in DMSO-d_6, with HMDS or TMS as the internal standard. The course of reactions was monitored and the purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted in an ethyl acetate – hexane (5 : 1) system and visualized by exposure to iodine vapors. The data of elemental analyses agree with the results of analytical calculations according to the empirical formulas.

Succinic acid heterylamides (I – III). To a solution of 10 mmole of the corresponding heterylamine in 30 – 50 ml of ethyl acetate (6-aminouracyl was dissolved in water on heating) was added, with stirring and short-time heating to 50 – 60°C, a solution of 1.0 g (10 mmole) of succinic anhydride in 50 ml of ethyl acetate (for the synthesis of compound III, succinic anhydride was dissolved in in 30 ml of water). The mixture was allowed to stand for 2 h, after which the precipitate was filtered and recrystallized from an ethyl acetate – dioxane (1 : 1) mixture for compound I, dioxane for compound II, or water – ethanol (10 : 1) mixture for compound III.

Succinic acid N-(2-pyridyl)amide (I). Yield, 80 %; m.p., 142 – 143°C; ^{1}H NMR spectrum at 300 MHz in

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DMSO-d_6 (δ, ppm): 2.43 (s, 4H, CH_2–CH_2), 6.46 (m, 2H, H4′ and H5′ in C_5H_4N), 7.35 (t, 1H, H3′ in C_5H_4N), 7.89 (s, 1H, H6′ in C_5H_4N), 5.70 (bs, 1H, CONH).

Succinic acid N-(3-pyridyl)amide (II). Yield, 80 %; m.p., 188 – 189°C; ^{1}H NMR spectrum at 300 MHz in DMSO-d_6 (δ, ppm): 2.57 (2t, 4H, CH_2–CH_2), 7.31 (q, 1H, H5′ in C_5H_4N), 7.97 (t, 1H, H4′ in C_5H_4N), 8.23 (d, 1H, H6′ in C_5H_4N), 8.73 (s, 1H, H2′ in C_5H_4N), 10.00 (s, 1H, CONH), 11.90 (bs, 1H, COOH).

Succinic acid N-(2,4-dioxo-6-pyrimidyl)amide (III). Yield, 87 %; m.p., > 310°C (decomp.); ^{1}H NMR spectrum at 60 MHz in DMSO-d_6 (δ, ppm): 2.40 (s, 4H, CH_2–CH_2), 4.36 (s, 1H, C^5H), 6.25 (s, 2H, N^1H, N^3H), 10.25 (bs, 1H, CONH); ^{1}H NMR spectrum at 60 MHz in DMSO-d_6 + CF_3COOH ~ 10 : 1 (δ, ppm): 2,40 (s, 4H, CH_2–CH_2), 4.55 – 4.71 (bs, 1H, C^5H), 6.55 – 7.71 (bs, 2H, N^1H, N^3H), 10.55 (bs, 1H, CONH). In the presence of trifluoroacetic acid, the ^{1}H NMR spectrum exhibits significant broadening of the proton signals from methine and from amide groups of the pyrimidine ring; in addition, these signals shift toward weaker fields.

Succinic acid isonicotinoyl hydrazide (IX). To a solution of 1.37 g (10 mmole) of isonicotinic acid hydrazide in 50 ml of water was added with intensive stirring a solution of 1.0 g (10 mmole) of succinic anhydride in 50 ml of ethyl acetate. The mixture was allowed to stand for 5 h, after which the precipitate was filtered and recrystallized from a water – ethanol (1 : 1) mixture. Yield of compound IX, 2.18 g (92 %); m.p., 222 – 224°C (decomp.); ^{1}H NMR spectrum at 60 MHz in DMSO-d_6 (δ, ppm): 2.45 (s, 4H, CH_2–CH_2), 7.71, 8.68 (2d, 4H, C_5H_4N), 10.38 (bs, 1H, CONH), 10.68 (bs, 1H, CONH), 11.71 (bs, 1H, COOH).

Syntheses of the other succinic acid acylhydrazides (IV – VIII) and their physicochemical characteristics and spectral parameters were reported previously [1].

TABLE 1. Hypoglycemic Activity of Succinic Acid Heterylamides and Acylhydrazides I – IX in Rats

Compound	Glycemia level after drug introduction				
	Initial, mM	3 h		5 h	
		mM	%	mM	%
I	4.70 ± 0.08	5.14 ± 0.11	+ 9.4 ± 2.2^3	4.73 ± 0.13	+ 0.6 ± 3.6^1
Control	5.11 ± 0.10	4.69 ± 0.09	– 8.2 ± 2.7	4.22 ± 0.10	– 17.5 ± 5.4
VI	4.72 ± 0.12	4.76 ± 0.10	+ 0.9 ± 4.1	4.75 ± 0.09	+ 0.7 ± 2.3^1
Control	5.10 ± 0.12	4.70 ± 0.13	– 7.8 ± 4.5	4.51 ± 0.11	– 11.5 ± 4.1
IV	4.82 ± 0.13	4.07 ± 0.09	– 15.5 ± 2.2	4.60 ± 0.08	– 4.6 ± 2.6
Control	5.11 ± 0.10	4.69 ± 0.12	– 8.2 ± 2.7	4.22 ± 0.10	– 17.5 ± 5.4
VII	4.41 ± 0.15	3.74 ± 0.14	– 15.1 ± 0.9^1	4.03 ± 0.12	– 8.6 ± 1.3
Control	5.11 ± 0.10	4.69 ± 0.10	– 8.2 ± 2.7	4.22 ± 0.08	– 17.5 ± 5.4
IX	4.61 ± 0.12	4.02 ± 0.10	– 12.9 ± 5.5	3.73 ± 0.11	– 19.0 ± 3.1
Control	5.10 ± 0.12	4.70 ± 0.11	– 7.8 ± 4.5	4.51 ± 0.12	– 11.5 ± 4.1
V	4.03 ± 0.11	3.52 ± 0.08	– 12.6 ± 1.9	3.39 ± 0.12	– 15.9 ± 1.9
Control	5.11 ± 0.10	4.69 ± 0.10	– 8.2 ± 2.7	4.22 ± 0.11	– 17.5 ± 5.4
VIII	4.02 ± 0.31	3.58 ± 0.24	– 11.0 ± 4.5	3.03 ± 0.20	– 24.7 ± 4.0^2
Control	5.13 ± 0.07	4.58 ± 0.09	– 10.7 ± 1.4	4.47 ± 0.10	– 12.9 ± 2.7
II	4.81 ± 0.11	4.41 ± 0.14	– 8.3 ± 2.3	4.21 ± 0.12	– 12.4 ± 2.0
Control	5.11 ± 0.10	4.69 ± 0.09	– 8.2 ± 2.7	4.22 ± 0.11	– 17.5 ± 5.4
III	4.80 ± 0.08	4.49 ± 0.11	– 6.4 ± 1.7	4.06 ± 0.10	– 15.4 ± 3.1
Control	5.10 ± 0.12	4.70 ± 0.15	– 7.8 ± 4.5	4.51 ± 0.12	– 11.5 ± 4.1
Adebit	5.10 ± 0.10	3.67 ± 0.09	– 28.1 ± 7.0^1	2.96 ± 0.10	– 42.0 ± 7.3^2
Control	5.13 ± 0.07	4.58 ± 0.08	– 10.7 ± 1.4	4.47 ± 0.06	– 12.9 ± 2.7
Glidifen	3.95 ± 0.19	3.43 ± 0.17	– 13.2 ± 2.1^1	2.99 ± 0.14	– 24.2 ± 4.3^2
Control	3.65 ± 0.06	3.41 ± 0.05	– 6.5 ± 1.3	3.49 ± 0.07	– 4.4 ± 2.0
Gliclazide	4.28 ± 0.14	3.11 ± 0.15	– 27.3 ± 3.3^3	3.76 ± 0.15	– 12.1 ± 3.3
Control	4.00 ± 0.12	3.69 ± 0.10	– 7.8 ± 2.6	3.37 ± 0.10	– 15.8 ± 2.5
Carbutamide	4.10 ± 0.13	3.40 ± 0.15	– 17.1 ± 1.4^2	3.30 ± 0.19	– 19.5 ± 2.2^1
Control	4.73 ± 0.19	4.53 ± 0.17	– 4.2 ± 1.2	4.31 ± 0.24	– 8.9 ± 2.8

Notes. Number of experimental animals in all tests $n = 6$; differences from control are reliable for ^{1} $p < 0.05$, ^{2} $p < 0.01$, ^{3} $p < 0.001$.

EXPERIMENTAL BIOLOGICAL PART

The hypoglycemic activity was studied on intact white mongrel rats weighing 220 – 250 g. The levels of glycemia in the test groups were determined by the orthotoluidine technique before and after (3 and 5 h) drug introduction; animals in the control groups received an equivalent volume of pure 1 % starch jelly [9]. The animals were deprived of food 14 h before and during the experiment, while receiving water *ad libitum*. The reference preparations were represented by guanidine derivatives (adebit, glidifen) and sulfonylurea derivatives (gliclazide, carbutamide). All the compounds tested and the reference substances were introduced by intraperitoneal injections at a dose of 50 mg/kg.

It was found that succinic acid heterylamides II and III containing β-pyridyl and uracyl fragments do not affect the blood glucose level. However, the passage to succinic acid α-pyridylamide (I) led to the appearance of a hyperglycemic effect (Table 1).

Succinic acid acetylhydrazide (IV), trifluoroacetylhydrazide (V), and isonicotinoylhydrazide (IX) exhibited no significant influence on the blood glucose level at any observation time. The transition to succinic acid aroylhydrazides VI – VIII (isomeric with respect to the amino group position in the benzene ring) gave rise to either hyper- or hypoglycemic effects. The hypoglycemic activity of compound VIII was comparable with that of gliclazide and glidifen.

Thus, the results of our investigations showed that succinic acid heterylamides do not possess hypoglycemic activity. The level of sugar-decreasing effect for the succinic acid acylhydrazides studied depends on the character of substituent in the benzene ring, the maximum activity being observed for succinic acid *p*-aminobenzoylhydrazide VIII

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