SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF PYRAZOLE-4-CARBOXYLIC ACID HYDRAZIDES AND N-(4-PYRAZOYL)HYDRAZONES OF AROMATIC AND HETEROAROMATIC ALDEHYDES

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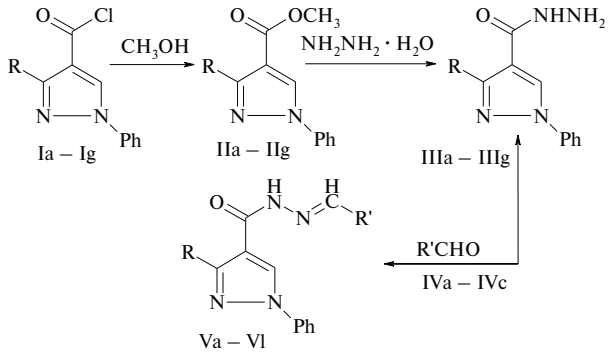
Proceeding from the fact that some widely used antibacterial preparations (furacilin, furazolidone, ftivazide) contain hydrazone groups, we decided to synthesize a series of pyrazole-4-carboxylic acid hydrazides, modify these compounds so as to obtain N-(4-pyrazoyl)hydrazones, and study the antibacterial properties of the products.

Hydrazides IIIa – IIIg were synthesized based on the previously described pyrazole-4-carboxylic chloroanhydrides (Ia – Ig) [1]. Treated with methanol in the presence of an organic base, compounds Ia – Ig converted with a quantitative yield into the corresponding methyl esters IIa – IIg. Interaction of these intermediates with hydrazine hydrate (on heating in ethanol) led to a high yield of hydrazides IIIa – IIIg. The yields and physicochemical characteristics of methyl esters IIa – IIg and hydrazides IIIa – IIIg are listed in Table 1.



I – III: R = C_6H_5 (a), 4-FC_6H_4 (b), 4-ClC_6H_4 (c), 4-BrC_6H_4 (d), 4-$C_2H_5C_6H_4$ (e), 4-$CH_3OC_6H_4$ (f), 2-thienyl (g);
IV: R′ = 3-CH_3O-4-HOC_6H_3 (a), 3-(4H-chromenon-4-yl) (b), 5-nitrofur-2-yl (c);
V: R = C_6H_5, R′ = 3-CH_3O-4-HOC_6H_3 (a); R = C_6H_5, R′ = 3-(4H-chromenon-4-yl) (b); R = C_6H_5, R′ = 5-nitrofur-2-yl (c); R = 4- FC_6H_4, R′ = 3-CH_3J-4-HOC_6H_3 (d); R = 4-FC_6H_4, R′ = 5-nitrofur-2-yl (e); R = 4-C1C_6H4, R′ = 3-CH_3O-4-HOC_6H_3 (f); R = 4-ClC_6H_3, R′ = 5-nitrofur-2-yl (g); R = 4-BrC_6H_4, R′ = 3-CH_3O-4-HOC_6H_3 (h); R = 4-BrC_6H_4, R′ = 5-nitrofur-2-yl (i); R = 4-$C_2H_5C_6H_4$, R′ = 5-nitrofur-2-yl (j); R = 4-CH_3O C_6H_4, R′ = 5-nitrofur-2-yl (k); R = thienyl-2, R′ = 5-nitrofur-2-yl (l).

The target N-(4-pyrazoyl)hydrazones (Va – Vl) (Table 1) were obtained by the condensation of hydrazides IIIa – IIIg with aryl(heteryl)aldehydes (IVa – IVc) in boiling ethanol. The proposed compositions were confirmed by elemental analyses and the proposed structures, by the IR spectra of the products, which displayed absorption bands due to the stretching vibrations of NH (3200 – 3280 cm^{-1}), as well as C=O and C=N (1670 – 1640 cm^{-1}) groups.

EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were measured on an UR-20 spectrophotometer (Germany) using samples pelletized with KBr. The ^1H NMR spectra of esters IIa – IIg and hydrazides IIIa – IIIg were recorded with a 100-MHz Bruker spectrometer using deuterated DMSO as the solvent and HMDS as the internal standard. The course of reactions was monitored and the purity of products checked by TLC on Silufol UV-254 plates (Czech Republic) eluted in an ethyl acetate – diethyl ether (10 : 1) system and developed by exposure to iodine vapors.

1,3-Diphenylpyrazole-4-carboxylic acid methyl ester (IIa). To 10 mmole (2.8 g) of 1,3-diphenylpyrazole-4-carboxylic acid chloroanhydride (Ia) in 10 ml of anhydrous methanol was added 10 mmole (1,0 g) triethylamine and the mixture was boiled for 2 h. Then the solvent was evaporated and the residue washed with water, filtered, dried, and crystallized from ethanol. Yield of compound IIa, 2.5 g (95%).

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Compounds IIb – IIg were obtained using analogous procedures (Table 1).

1,3-Diphenylpyrazole-4-carboxylic acid hydrazide (IIIa). To a suspension of 5 mmole (1.3 g) of 1,3-diphenylpyrazole-4-carboxylic acid methyl ester (IIa) in 10 ml of ethanol was added 1 ml of 85% hydrazine hydrate and the mixture was boiled for 4 h. Then the solvent was evaporated and the residue washed with water, filtered, dried, and crystallized from 80% ethanol. Yield of compound IIIa, 1.0 g (75%).

TABLE 1. Yields and Physicochemical Characteristics of Methyl Esters (IIa – IIg) and Hydrazides (IIIa – IIIg) of Pyrazole-4-carboxylic Acids

Compound	M.p., °C	Yield, %	Empirical formula	IR spectrum: ν, cm^{-1}		^{1}H NMR spectrum: δ, ppm
				C=O	N–H	
IIa	107 – 108	95	$C_{17}H_{14}N_2O_2$	1740	–	9.01 (s, 1H, CH=), 6.42 – 7.70 (m, 10H, H_{arom}), 3.75 (s, 3H, CH_3O)
IIb	130 – 131	96	$C_{17}H_{13}FN_2O_2$	1735	–	8.82 (s, 1H, CH=), 7.04 – 8.18 (m, 9H, H_{arom}), 3.87 (s, 3H, CH_3O)
IIc	137 – 138	97	$C_{17}H_{13}ClN_2O_2$	1735	–	9.11 (s, 1H, CH=), 7.11 – 7.85 (m, 9H, H_{arom}), 3.54 (s, 3H, CH_3O)
IId	153 – 154	94	$C_{17}H_{13}BrN_2O_2$	1745	–	9.07 (s, 1H, CH=), 7.21 – 7.94 (m, 9H, H_{arom}), 3.63 (s, 3H, CH_3O)
IIe	94 – 95	96	$C_{19}H_{18}N_2O_2$	1740	–	8.99 (s, 1H, CH=), 7.15 – 7.63 (m, 9H, H_{arom}), 2.44 (q, 2H, CH_2), 1.33 (t, 3H, CH_3), 3.70 (s, 3H, CH_3O)
IIf	102 – 103	92	$C_{18}H_{16}N_2O_3$	1740	–	9.14 (s, 1H, CH=), 7.24 – 7.85 (m, 9H, H_{arom}), 3.84 (s, 3H, CH_3O), 3.69 (s, 3H, CH_3O)
IIg	82 – 83	98	$C_{15}H_{12}N_2O_2S$	1735	–	8.87 (s, 1H, CH=), 6.99 – 7.83 (m, 8H, H_{arom}), 4.01 (s, 3H, CH_3O)
IIIa	157 – 158	75	$C_{16}H_{14}N_4O$	1655	3240	9.53 (s, 1H, NH), 8.94 (s, 1H, CH=), 6.54 – 7.79 (m, 10H, $H_{arom.}$), 4.57 (bs, 2H, NH_2)
IIIb	203 – 204	79	$C_{16}H_{13}FN_4O$	1660	3240	9.44 (s, 1H, NH), 8.87 (1H, CH=), 7.10 – 8.24 (m, 9H, H_{arom}), 4.64 (bs, 2H, NH_2)
IIIc	181 – 182	81	$C_{16}H_{13}ClN_4O$	1665	3230	9.59 (s, 1H, NH), 9.04 (s, 1H, CH=), 7.17 – 7.90 (m, 9H, H_{arom}), 4.54 (bs, 2H, NH_2)
IIId	196 – 198	76	$C_{16}H_{13}BrN_4O$	1660	3260	9.37 (s, 1H, NH), 8.92 (s, 1H, CH=), 7.22 – 7.84 (m, 9H, H_{arom}), 4.44 (bs, 2H, NH_2)
IIIe	166 – 168	61	$C_{18}H_{18}N_4O$	1670	3240	9.46 (s, 1H, NH), 9.00 (s, 1H, CH=), 7.03 – 7.52 (m, 9H, H_{arom}), 4.55 (bs, 2H, NH_2), 2.47 (q, 2H, CH_2), l.33 (t, 3H, CH_3)
IIIf	157 – 158	72	$C_{17}H_{16}N_4O$	1665	3250	9.29 (s, lH, NH), 8.92 (s, lH, CH=), 7.30 – 7.92 (m, 9H, H_{arom}), 4.62 (bs, 2H, NH_2), 3.76 (3H, CH_3O)
IIIg	154 – 155	77	$C_{14}H_{13}N_4OS$	1660	3260	9.50 (s, 1H, NH), 8.86 (1H, CH=), 6.88 – 7.56 (m, 8H, H_{arom}), 4.56 (bs, 2H, NH_2)

TABLE 2. Yields, Physicochemical Characteristics, and Antimicrobial Properties of Aromatic and Heteroaromatic Aldehydes

Compound	Yield, %	M.p., °C	Empirical formula	Antimicrobial activity			
				St. aureus 209-P		*E. coli*	
				MBSC, μg/ml	MBCC, μg/ml	MBSC, μg/ml	MBCC, μg/ml
Va	77	261 – 263	$C_{24}H_{20}N_4O_3$	62.5	125	250	500
Vb	72	201 – 202	$C_{27}H_{18}N_4O_3$	62.5	125	125	250
Vc	81	227 – 228	$C_{21}H_{15}N_5O_4$	62.5	125	125	250
Vd	84	279 – 280	$C_{24}H_{19}FN_4O_3$	31.2	62.5	125	250
Ve	79	252 – 253	$C_{21}H_{14}FN_5O_4$	31.2	62.5	> 500	> 500
Ve	80	270 – 271	$C_{24}H_{19}ClN_4O_3$	125	250	-“-	-“-
Vg	74	263 – 264	$C_{21}H_{14}ClN_5O_4$	125	-“-	-“-	-“-
Vh	85	256 – 257	$C_{24}H_{19}BrN_4O_3$	125	-“-	-“-	-“-
Vi	86	258 – 259	$C_{21}H_{14}BrN_5O_4$	125	-“-	-“-	-“-
Vj	73	205 – 206	$C_{23}H_{19}N_5O_4$	15.6	31.2	-“-	-“-
Vk	78	240 – 241	$C_{22}H_{17}N_5O_5$	62.5	125	125	250
Vl	82	234 – 235	$C_{19}H_{13}N_5SO_4$	31.2	62.5	250	500

Compounds IIIb – IIIg were obtained using analogous procedures (Table 1).

3-Methoxy-4-hydroxybenzaldehyde N-[4-(1,3-diphenyl)pyrazoyl]hydrazone (Va). A mixture of 2 mmole (0.6 g) of hydrazide IIIa and 2 mmole (0.32 g) of 3-methoxy-4-hydroxybenzaldehyde (IVa) in 10 ml of ethanol was boiled for 3 h. Then the precipitate was filtered, washed with ethanol, dried, and crystallized from acetic acid. Yield of compound Va, 0.64 g (77%).

Compounds Vb – Vl were obtained using analogous procedures (Table 2).

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of hydrazides IIIa – IIIg and hydrazones (Va – Vl) with respect to standard strains of *St. aureus* 209-P and *E. coli* was determined using a four-hour-grown suspension of each test culture in a liquid nutrient medium (microbial load $(1 – 2) \times 10^6$ cells/ml according to the turbidity standard). The activity was evaluated after incubation for 20 – 24 h at 37°C by determining the minimum bacteriostatic concentration (MBSC) inhibiting the growth and multiplication of the microbes. Then the minimum bactericidal concentration (MBCC) was determined by inoculating Petri dishes containing a meat-infusion agar with culture drops from the tubes exhibiting no visible growth of microbes. The samples of inoculated dense medium were incubated for two days at 37°C. A sector with a minimum concentration completely inhibiting the microbial growth was assumed to represent the MBCC.

As seen from the data presented in Table 2, all the synthesized compounds possess moderate bactericidal and bacteriostatic properties, the effect being more pronounced with respect to staphylococcal species than to *E. coli*.

REFERENCES

1. M. K. Bratenko, V. A. Chornous, and M. V. Vovk, *Zh. Org. Khim.*, **36**(5), 849 – 852 (2000).