SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF N-(ALKYLIDENE)ARYLIDENEHYDRAZONES OF FORMIC ACID AMIDES

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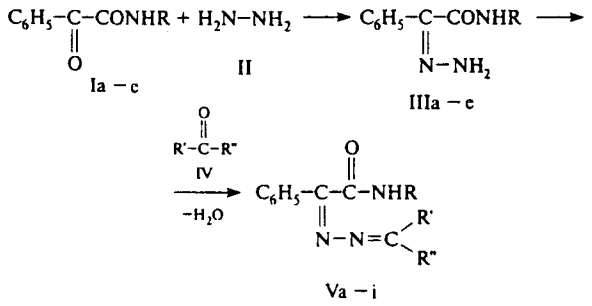
Hydrazones and arylhydrazones are known to exhibit biological activity [1, 2] and are used as reagents in the analysis and synthesis of some pharmacological products [3, 4].

In a search for the biologically active compounds of this class, we have synthesized hydrazones of benzoylformic acid amides (IIIa – e) and, on this basis, obtained N-(alkylidene)arylidenehydrazones of benzoylformic acid amides (Va – i). The latter compounds were characterized for the antimicrobial activity with respect to *St. aureus* and *E. coli*.

The synthesis of the target compounds was performed according to the following scheme



where R = H, CH_3, C_6H_5, $C_6H_5CH_2$, $C_6H_4CH_3$-4;
R′ = H, CH_3; R″ = C_6H_4Br-4; $C_6H_4CH_3$-4, $C_6H_4N(CH_3)_2$-4.

Compounds Ia – e interact with hydrazine hydrate II (a 97% solution) to form hydrazones of benzoylformic acid amides (IIIa – IIIe). Combining the the latter with ketones and aldehydes (IV), we obtain N-(alkylidene)arylidenehydrazones of benzoylformic acid amides (Va – Vi).

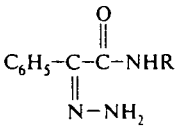
The reaction is carried out in an alcohol medium at room temperature and, depending on the chemical structures of combined components III and IV, may or may not require the presence of an inhibitor (H+). Compounds Va – Vi appear as yellow or orange substances, sparingly soluble in organic solvents and insoluble in water. The substances exhibit the properties of an acid-base indicator: on dissolution in concentrated sulfuric acid, compounds Va, b, g – i pass from the benzoid state V into the chinoid state VI, whereby the color changes from yellow-orange to red.

Tables 1 and 2 give data on the structures and physicochemical characteristics of compounds III and V. The structures were confirmed by data of IR, UV, and ^{1}H NMR spectroscopies.

The IR spectra of compounds IIIa – e contain absorption bands at 3120 – 3180 and 3420 – 3350 cm^{-1}, belonging to the stretching vibrations of the NH and NH_2 groups, respectively, and the bands at 1660 – 1680 cm^{-1} assigned to the stretching vibrations of C=N and CO groups. A decrease in the frequency of stretching vibrations of the carbonyl and amino groups is indicative of their participation in the formation of intermolecular hydrogen bonds.

The structure of compounds Va – i was confirmed by the results of UV and ^{1}H NMR measurements. In the ^{1}H NMR spectra, the signal due to the protons of NH groups corresponds to a weak field and is observed at 8.3 – 8.5 ppm, the multiplet signal of protons of the aromatic system is centered at 6.5 – 7.6, and the signal due to the protons of alkyl groups

TABLE 1. Hydrazones of Benzoylformic Acid Amides



III

Compound	R	M.p., °C	Yield, %	Empirical formula	IR spectrum, ν_{max}, cm^{-1}		
					NH	NH_2	CO
IIIa	H	104 – 105	63	$C_8H_9N_3O$	3180	3420	1680
IIIb	CH_3	115	84	$C_9H_{11}N_3O$	3160	3380	1675
IIIc	C_6H_5	128 – 129	96	$C_{14}H_{13}N_3O$	3120	3360	1660
IIId	$C_6H_5CH_2$	192 – 193	95	$C_{15}H_{15}N_3O$	3160	3350	1670
IIIe	$C_6H_4CH_3$-4	162 – 163	83	$C_{15}H_{15}N_3O$	3180	3400	1680

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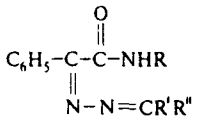
TABLE 2. N-Alkylidene(arylidene)hydrazones of Benzoylformic Acid Amides



V, 4-*para*

Compound	R	R′	R″	M.p., °C	Yield, %	Empirical formula	Antimicrobial activity (MIC), μg/ml	
							B.coli M-17	*St.aureus* 209-P
Va	H	CH_3	CH_3	130 – 132	80	$C_{11}H_{13}N_3O$	500	1000
Vb	CH_3	CH_3	CH_3	219 – 220	75	$C_{12}H_{15}N_3O$	500	1000
Vc	H	H	C_6H_4Br-4	245 – 246	70	$C_{15}H_{12}BrN_3O$	1000	Inactive
Vd	CH_3	H	C_6H_4Br	195 – 196	65	$C_{16}H_{14}BrN_3O$	Inactive	Inactive
Ve	H	H	$C_6H_4OCH_3$-4	204 – 206	67	$C_{16}H_{15}N_3O_2$	1000	1000
Vf	H	H	$C_6H_4N(CH_3)_2$	216 – 217	72	$C_{17}H_{18}N_4O$	–	–
Vg	CH_3	H	$C_6H_4N(CH_3)_2$	218 – 219	71	$C_{18}H_{20}N_4O$	500	500
Vh	C_6H_5	H	$C_6H_4OCH_3$-4	173 – 174	78	$C_{22}H_{19}N_3O_2$	2000	500
Vi	C_6H_5	H	$C_6H_4N(CH_3)_2$	187 – 189	70	$C_{23}H_{22}N_4O$	–	–

has the form of a doublet at 2.5 – 3 ppm; the spectra of compounds Vc – i also exhibit a broadened signal due to the proton of the methine group at 3.7 – 4.2 ppm.

The UV spectra of the alcohol solutions of compounds V exhibit three absorption bands, 220 – 228, 308 – 310, and 330 – 375 nm, with peak intensities in the intervals log ε = 4.60 – 4.95, 4.90 – 5.22, and 4.60 – 4.85, respectively. The longwave absorption maximum (330 – 375 nm) has a large width of 4 – 6 nm indicative of the presence of a conjugation system in compounds V, in agreement with the data published earlier [3].

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Carl Zeiss, Germany) using samples prepared as vaseline oil suspensions. The ^1H NMR spectra were recorded at 25°C on a PC-60 spectrometer operated at 60 MHz, using DMSO-d_6 and acetone-d_6 as solvents and TMS as the internal standard.

Hydrazone of benzoylformic acid amide (IIIa, R = H). Benzoylformic acid amide (1.49 g or 0.01 mole), obtained as described in [6], is placed into a 50-ml cone-shaped flask and mixed with 30 ml of ethanol. Then 0.7 g (0.02 mole) of a 97% hydrazine hydrate solution is added on stirring, which results in the formation of a white precipitate. The precipitate is separated by filtering, washed with water until a neutral reaction, dried, and crystallized. Yield, 1.0 g (63% of the theoretical value); m.p., 103 – 104°C (benzoyl); IR spectrum, λ_{max}, cm^{-1}: 3180 (NH), 3420 (NH_2), 1680 (CO).

A similar procedure is used to obtain compounds IIIb – e.

N-(4-Bromobenzylidene)hydrazones of benzoylformic acid amide (Vc, R = H, R′ = H, R″ = C_6H_4Br-4). To 1.63 g (0.01 mole) of compound IIIa, placed into a 50-ml cone-shaped flask, are added 50 ml of ethanol, 1.87 g (0.01 mole) of of bromobenzaldehyde, and 2 – 3 drops of concentrated hydrochloric acid, and the reaction mixture is stirred until the formation of a precipitate. The precipitate is separated by filtering, washed with ethanol, dried, and crystallized. Yield, 2.31 g (70% of the theoretical value); m.p., 245 – 246°C (DMSO). A similar procedure is used to obtain compounds Va, b, and d – i.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the compounds Va – i was studied by the method described in [5], based on consecutive double dilutions of the medium.

Experiments were performed with two types of bacteria, Gram-positive *Staphylococcus aureus* strain 209-P and Gram-negative *Escherichia coli* strain M-17.

The antibacterial activity was characterized by the minimum inhibiting concentration (MIC) of the compound (in μg/ml) leading to complete suppression of the growth of the test microbe under standard conditions.

As is seen from data presented in Table 2, the compounds exhibit weak antibacterial activity.

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