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Synthesis and Antibacterial Activity of 4-Aryl-2-hydroxy-4-oxo-2-butenoic (Aroylpyruvic) Acids *N*-(4-Guanidylsulfonylphenyl)amides

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Abstract—Reaction of methyl aroylpyruvates with 4-aminobenzolsulfonylguanidine in acetic acid in the presence of anhydrous sodium acetate afforded *N*-(4-guanidylsulfonylphenyl)amides of 4-aryl-2-hydroxy-4-oxo-2-butenoic acids. Antibacterial activity of the synthesized compounds was studied.

Keywords: aroylpyruvic acids *N*-(4-guanidylsulfonylphenyl)amides, 4-aminobenzenesulfonylguanidine, sulgin, antibacterial activity

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Currently an urgent problem of pharmaceutical chemistry consists in search for biologically active compounds which are promising for the drugs design.

Aroylpyruvic acids amides, polycarbonyl compounds, are of interest due to the presence in the structure of several reaction sites providing a possibility to use them in a targeted synthesis of organic compounds of different classes containing pharmacophoric groups [1]. Furthermore, some aroylpyruvic acids amides and their derivatives showed analgesic, anticonvulsant, anti-inflammatory, and antimicrobial activity [1–3].

The most frequent method of these amides preparaton is based on the reaction of 5-aryl-2,3-dihydrofurane-2,3-diones with amines in anhydrous dioxane, toluene or other inert solvent [4, 5]. It should be noted that the direct interaction of arylamines with aroylpyruvic acids [6] or their esters [7, 8] led to the formation of the corresponding anils at the α-carbonyl group. Amides were formed in low yields only as a byproduct or not formed at all.

We have previously shown that reaction of methyl aroylpyruvates with sodium 4-aminobenzenesulfonylacetamide (sodium sulfacetamide) in glacial acetic acid under reflux afforded 4-aryl-2-hydroxy-4-oxo-2-butenoic acids *N*-(4-acetylaminosulfonylphenyl)amides [9].

In this work we studied the reaction of methyl aroylpyruvates with 4-aminobenzenesulfonylguanidine (sulgin), whose molecule contains an aromatic amino group and guanidine moiety, in the presence of sodium acetate.

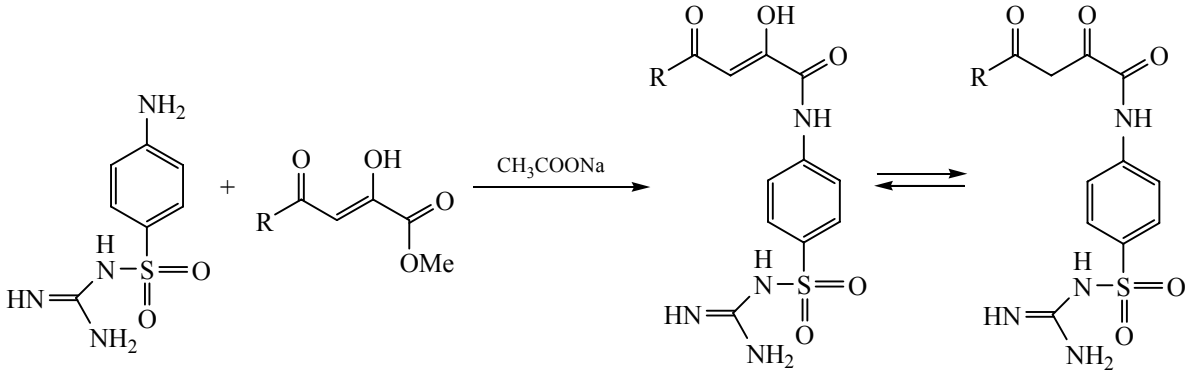
Sulgin is known to react with β-dicarbonyl compounds to form pyrimidine derivatives [10].

We found that interaction of sulgin with methyl aroylpyruvates involves aromatic amino group to give 4-aryl-2-hydroxy-4-oxo-2-butenoic acids *N*-(4-guanidylsulfonylphenyl)amides **I**–**VI**. The reaction proceeded for 15–20 min at reflux in glacial acetic acid in the presence of an equivalent amount of anhydrous sodium acetate.

The obtained compounds **I**–**VI** were crystalline solids, soluble in dimethylsulfoxide and dimethylformamide, in dioxane and acetic acid upon heating, and insoluble in water.

^{1}H NMR spectra of **I**–**VI**, along with the signals of aromatic protons, contained a broadened singlet of four protons of guanidine residue [NHC(=NH)NH_2] (6.64–6.74 ppm), a singlet of the methine proton (7.13–7.45 ppm), and a singlet of the amide proton (10.78–10.91 ppm). In addition, in the ^{1}H NMR spectra of compounds **I**–**VI** there was a signal of low intensity in the region of 4.40–4.64 ppm corresponding to the methylene protons of β-diketone form. Based on the

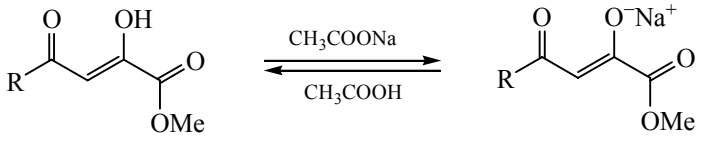
Scheme 1.



I–VI

R = 4-BrC_6H_4 (**I**), 4-$CH_3OC_6H_4$ (**II**), 4-$CH_3C_6H_4$ (**III**), 4-FC_6H_4 (**IV**), $C_6H_5CH{=}CH$ (**V**), 4-$C_2H_5OC_6H_4$ (**VI**).

Scheme 2.



ratio of the signal integral intensities of β-methylene group and the CH= proton, the compounds obtained exist predominantly in the enol form **A** (≈90%). The absence of the proton signal of enol hydroxy group in the ^{1}H NMR spectra is apparently due to its significant broadening as a result of exchange processes observed also for the other derivatives of aroylpyruvic acids [9, 11] (Scheme 1).

In the IR spectra of **I–VI** there were absorption bands of the stretching vibrations of the amino (3448–3376 cm^{-1}), hydroxyl (3220–3176 cm^{-1}), amide (1704–1692 cm^{-1}), ketone fragments (1656–1608 cm^{-1}), and SO_2-group (1384–1336, 1140–1136 cm^{-1}).

Reaction of all obtained compounds with an alcohol solution of iron chloride(III) was accompanied with characteristic coloration of the mixture.

The exclusive formation of amides **I–VI** was apparently due to the exchange interaction of sodium acetate [9] with the original aroylpyruvate to form sodium derivative where the deactivation of the α-positioned carbonyl group took place. In this regard, an attack of the ester carbonyl moiety with the primary amino group of 4-aminobenzenesulfonyl guanidine is possible (Scheme 2).

Guanidine residue was not involved into the reaction, which appears to be associated with a significant decrease in its basicity and nucleophilicity due to the nature of the electron-withdrawing sulfonyl group.

Taking into account that sulgin belongs to sulfanilamide drugs and is effective for the treatment of intestinal infections [12], we investigated antibacterial activity of the compounds obtained towards the test cultures of *Staphylococcus aureus* ATCC 6538-P and *Escherichia coli* ATCC 25922. The tests were performed by serial two-fold dilution in liquid nutrition medium with bacterial load of 250 thousand microbial units per 1 mL [13]. Minimum inhibitory concentration (MIC) was determined by the absence of visible bacterial growth. Dioxidine and chloramine B were used as a reference. The test results are shown in the table.

According to the data obtained, 4-aryl-2-hydroxy-4-oxo-2-butenoic acids *N*-(4-guanidylsulfonylphenyl) amides show moderate activity against the strain *St. aureus* ATCC 6538-P and low activity against the strain *E. coli* ATCC 25922.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer (500.13 MHz) in DMSO-d_6, internal reference TMS. IR spectra were registered on a

Specord M-80 spectrophotometer from KBr pellets. Elemental analysis was performed on a Perkin Elmer 2400 instrument. Melting points were determined on a Melting Point M-565 apparatus.

4-(4-Bromophenyl)-2-hydroxy-4-oxo-2-butenoic acid *N*-(4-guanidylsulfonylphenyl)amide (I). A solution of 0.01 mol of methyl 4-brombenzoylpyruvate and 0.01 mol of anhydrous sodium acetate in 10 mL of glacial acetic acid were added to a solution of 0.01 mol of 4-aminobenzenesulfonylguanidine in 15 mL of glacial acetic acid. The reaction mixture was refluxed for 20 min. The precipitate was filtered off upon cooling and recrystallized from a mixture of acetic acid–dioxane (1 : 1). Yield 3.78 g (81%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3448, 3392 (NH_2), 3336 (NH), 3190 (OH), 1692 (CONH), 1628 (C=O), 1372, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 4.64 s (2H, $COCH_2CO$), 6.70 s [4H, $NHC(=NH)NH_2$], 7.19 s (1H, CH=), 7.71–8.01 m (8H, CH_{Ar}), 10.91 s (1H, CONH). Found, %: C 43.59, 43.82; H 3.19, 3.28; N 11.91, 12.06; *I*S 6.80, 6.91. $C_{17}H_{15}BrN_4O_5S$. Calculated, %: C 43.70; H 3.24; N 11.99; S 6.86.

2-Hydroxy-4-(4-methoxyphenyl)-4-oxo-2-butenoic acid *N*-(4-guanidylsulfonylphenyl)amide (II) was obtained similarly. Yield 3.01 g (72%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 3440, 3384 (NH_2), 3344 (NH), 3200 (OH), 1704 (CONH), 1608 (C=O), 1336, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 3.88 s (3H, CH_3O) 4.59 s (2H, $COCH_2CO$), 6.71 s [4H, $NHC(=NH)NH_2$], 7.14 s (1H, CH=), 7.10–8.08 m (8H, CH_{Ar}), 10.84 s (1H, CONH). Found, %: C 51.54, 51.78; H 4.30, 4.39; N 13.33, 13.44; S 7.59, 7.74. $C_{18}H_{18}N_4O_6S$. Calculated, %: C 51.67; H 4.34; N 13.39; S 7.66.

2-Hydroxy-4-(4-methylphenyl)-4-oxo-2-butenoic acid *N*-(4-guanidylsulfonylphenyl)amide (III) was obtained similarly. Yield 3.66 g (91%), mp 223–225°C. IR spectrum, ν, cm^{-1}: 3440, 3392 (NH_2), 3352 (NH), 3220 (OH), 1696 (CONH), 1620 (C=O), 1384, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 4.62 s (2H, $COCH_2CO$), 6.70 s [4H, $NHC(=NH)NH_2$], 7.19 s (1H, CH=), 7.39–8.00 m (8H, CH_{Ar}), 10.89 s (1H, CONH). Found, %: C 53.61, 53.85; H 4.47, 4.56; N 13.86, 13.99; S 7.92, 8.03. $C_{18}H_{18}N_4O_5S$. Calculated, %: C 53.72; H 4.51; N 13.92; S 7.97.

2-Hydroxy-4-(4-fluorophenyl)-4-oxo-2-butenoic acid *N*-(4-guanidylsulfonylphenyl)amide (IV) was obtained similarly. Yield 3.61 g (89%), mp 229–231°C. IR spectrum, ν, cm^{-1}: 3432, 3384 (NH_2), 3336 (NH), 3176 (OH), 1696 (CONH), 1656 (C=O), 1380, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 4.60 s (2H, $COCH_2CO$), 6.64 s [4H, $NHC(=NH)NH_2$], 7.13 s (1H, CH=), 7.31–8.09 m (8H, CH_{Ar}), 10.78 s (1H, CONH). Found, %: C 50.13, 50.23; H 3.76, 3.72; N 13.70, 13.80; S 7.97, 7.84. $C_{17}H_{15}FN_4O_5S$. Calculated, %: C 50.24; H 3.72; N 13.79; S 7.89.

Antibacterial activity of compounds **I–VI**

Compound	MIC, μg mL^{-1}	
	St. aureus ATCC 6538-P	*E. coli* ATCC 25922
I	500	500
II	500	1000
III	250	500
IV	500	1000
V	1000	1000
VI	250	1000
Dioxidine	62.5–1000	3.9–62.5
Chloramine B	500	250

2-Hydroxy-4-oxo-6-phenyl-2,5-hexadioic acid *N*-(4-guanidylsulfonylphenyl)amide (V) was obtained similarly. Yield 3.52 g (85%), mp 246–248°C. IR spectrum, ν, cm^{-1}: 3440, 3392 (NH_2), 3336 (NH), 3210 (OH), 1692 (CONH), 1632 (C=O), 1376, 1140 (SO_2). ^1H NMR spectrum, δ, ppm: 4.40 s (2H, $COCH_2CO$), 6.74 s [4H, $NHC(=NH)NH_2$], 7.15 s (1H, CH=), 7.45–7.99 m (11H, CH=CH, CH_{Ar}), 10.86 s (1H, CONH). Found, %: C 54.92, 55.19; H 4.36, 4.42; N 13.47, 13.56; S 7.69, 7.80. $C_{19}H_{18}N_4O_5S$. Calculated, %: C 55.06; H 4.38; N 13.52; S 7.74.

2-Hydroxy-4-(4-ethoxyphenyl)-4-oxo-2-butenoic acid *N*-(4-guanidylsulfonylphenyl)amide (VI) was obtained similarly. Yield 3.33 g (77%), mp 222–224°C. IR spectrum, ν, cm^{-1}: 3424, 3376 (NH_2), 3344 (NH), 3184 (OH), 1704 (CONH), 1620 (C=O), 1380, 1136 (SO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.36 t (3H, CH_3CH_2O, *J* 6.7), 4.16 q (2H, CH_3CH_2O, *J* 6.7), 4.59 s (2H, $COCH_2CO$), 6.69 s [4H, $NHC(=NH)NH_2$], 7.17 s (1H, CH=), 7.09–8.08 m (8H, CH_{Ar}), 10.87 s (1H, CONH). Found, %: C 52.88, 52.66; H 4.71, 4.60; N 12.87, 13.06; S 7.34, 7.49. $C_{19}H_{20}N_4O_6S$. Calculated, %: C 52.77; H 4.66; N 12.96; S 7.41.

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