DOI 10.1007/s11094-015-1248-2
Pharmaceutical Chemistry Journal, Vol. 49, No. 3, June, 2015 (Russian Original Vol. 49, No. 3, March, 2015)

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-ARYL-4-ACYL-3-HYDROXY-1-[2-(2-HYDROXYETHOXY)-ETHYL]-3-PYRROLIN-2-ONES

V. L. Gein,[1] T. F. Odegova,[1] S. N. Rogachev,[1] A. A. Bobyleva,[1] and L. F. Gein[2]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 49, No. 3, pp. 32 – 34, March, 2015.

Original article submitted June 17, 2014.

Interaction of 2-(2-aminoethoxy)ethanol with a mixture of an aromatic aldehyde and the methyl esters of acetylpyruvic acids yielded 5-aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones. The antimicrobial activity of the compounds synthesized here was studied.

Keywords: 5-aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones; synthesis; antimicrobial activity.

Tetrahydropyrrol-2,3-diones and their derivatives are present in the fragments of many medicinal agents (piracetam, atropine, Iminem, glimepiride, etc. [1]. Published data indicate that 3-hydroxypyrrolin-2-ones with alkoxyalkyl substituents in position 1 are low-toxicity compounds and have various types of biological activity [2]. With the aim of synthesizing novel 3-hydroxypyrrolin-2-ones and studying the effects of structure on their chemical properties and antimicrobial actions, we have prepared tetrahydropyrrol-2,3-diones containing a hydrophilic 2-(2-hydroxyethoxy)ethyl substituent in position 1 of the heterocycle to identify how structural changes affect the water solubility and antimicrobial activity of these compounds.

Using a known method [3], we studied the interaction of 2-(2-aminoethoxy)ethanol with a mixture of an aromatic aldehyde and an acylpyruvic acid methyl ester at an equimolar ratio in dioxane or glacial acetic acid at room temperature. In these conditions, the sole product was a 5-aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-one (Table 1).

The resulting compounds (I – XIV) were yellow crystalline substances, soluble in ethanol, dimethysulfoxide (DMSO), and dimethylformamide, and insoluble in water. Substances I – V, containing the acetyl fragment, were soluble in water on heating.

The ^{1}H NMR spectra of compounds I – XIV contained signals from aromatic protons at 6.82 – 7.62 ppm, a singlet

TABLE 1. Yields and Melting Temperatures of 5-Aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones

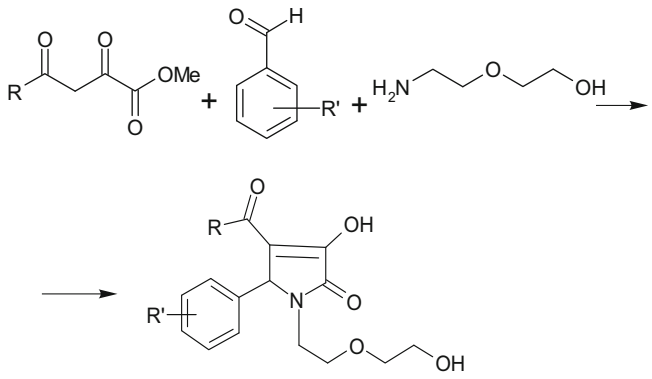
Compound	Yield, %	T_m, °C	Molecular formula	[M$^+$]
I	53.1	110 – 112	$C_{16}H_{19}NO_5$	305.33
II	64.5	122 – 124	$C_{16}H_{18}FNO_5$	
III	61.8	139 – 141	$C_{16}H_{18}N_2O_8$	350.33
IV	70.9	147 – 149	$C_{16}H_{19}NO_6$	321.33
V	61.7	116 – 118	$C_{18}H_{23}NO_5$	
VI	75.4	190 – 192	$C_{21}H_{21}NO_6$	
VII	26.8	188 – 190	$C_{23}H_{25}NO_5$	
VIII	54.0	183 – 185	$C_{21}H_{21}NO_5$	
IX	56.4	180 – 182	$C_{21}H_{20}FNO_5$	
X	34.8	193 – 195	$C_{21}H_{20}N_2O_8$	412.40
XI	45.2	180 – 182	$C_{22}H_{23}NO_6$	
XII	30.8	192 – 194	$C_{22}H_{23}NO_7$	
XIII	38.8	190 – 192	$C_{21}H_{20}BrNO_5$	
XIV	48.7	183 – 185	$C_{21}H_{21}NO_6$	

[1] Perm State Pharmaceutical Academy, Russian Ministry of Health, Perm, Russia; e-mail: geinv148@mail.ru; rogachevsergei@mail.ru.
[2] Academician E. A. Vagner Perm State Medical Academy, Russian Ministry of Health, Perm, Russia.

TABLE 2. Spectral Characteristics of Compounds I – XIV

Compound	^{1}H NMR spectrum, ppm					
	Aromatic protons (m)	C^5H (s)	$C^1\underline{H}_AH_B$ (m)	$C^1H_A\underline{H}_B$ (m)	$CH_2OCH_2CH_2OH$ (m)	CH_3CO (s)
I	7.17	5.22	3.78	2.62	3.42	2.25
II	7.14	5.23	3.83	2.84	3.63	2.29
III	7.62	5.42	3.82	2.82	3.43	2.27
IV	6.82	5.15	3.75	2.63	3.38	2.26
V	7.05	5.16	3.45	2.55	3.42	1.73
VI	7.45	5.45	3.75	2.65	3.50	
VII	7.30	5.35	3.55	2.75	3.70	
VIII	7.25	5.55	3.45	2.75	3.75	
IX	7.30	5.45	3.50	2.70	3.85	
X	7.40	5.70	3.45	2.65	3.80	
XI	7.40	5.45	3.60	2.70	3.75	
XII	7.30	5.40	3.55	2.85	3.75	
XIII	7.40	5.50	3.45	2.80	3.70	
XIV	7.45	5.40	3.40	2.80	3.80	

from the methine group at position 5 of the heterocycle at 5.15 – 5.70 ppm, two multiplets from protons in the methylene group at position 1 at the nitrogen atom at 2.55 – 2.85 and 3.40 – 3.83 ppm, and a multiplet from the three methylene groups at 3.38 – 3.80 ppm.



I – XIV

R = CH_3 (I – V), C_6H_5 (VI – XIV)
R' = H (I, VIII), 4-F (II, IX), 3-NO_2 (III, X), 3-OH (IV, VI, XIV), 4-C_2H_5 (V, VII), 4-CH_3O (XI), 4-HO, 3-CH_3O (XII), 3-Br (XIII).

The IR spectra of compounds III – XI (Table 3) contained absorption bands due to stretch vibrations of the lactam carbonyl group at 1680 – 1700 cm^{-1}, the ketone carbonyl group at 1620 – 1650 cm^{-1}, the enol hydroxyl group at 3080 – 3170 cm^{-1}, and the alcohol hydroxyl group at 3370 – 3470 cm^{-1}.

The mass spectra of the compounds synthesized here (I, III, IV, and X) showed a molecular ion peak (see Table 1) and ion fragment peaks confirming the structures.

All compounds gave an intense cherry color with ethanolic iron (III) chloride solution. Spectral data and qualitative reactions with ethanolic iron (III) chloride provided evidence that compounds I – XIV were in the enol form.

EXPERIMENTAL CHEMICAL SECTION

^{1}H NMR spectra were recorded on a Bruker AM-300 and a Bruker AM-500 with working frequencies of 300 and 500 MHz in DMSO-d_6 with tetramethysilane as internal standard. IR spectra were recorded on a Specord M-80 in Vaseline grease. Mass spectra were taken on a Finnigan MAT ICOS-50 instrument (ionizing energy 70 eV). Melting temperatures were measured on a Melting Point M-565 instrument. Elemental analysis data were consistent with molecular formulas.

TABLE 3. IR Spectra of Compounds III – XI

Compound	IR Spectrum, ν, cm^{-1}			
	CH_2OH	CNO	CH_3CO	OH
III	3450	1700	1650	3170
IV	3430	1680	1630	3100
V	3470	1690	1640	3110
VI	3370	1700	1640	3090
VIII	3400	1690	1620	3090
X	3430	1700	1640	3100
XI	3400	1690	1640	3080

TABLE 4. Antimicrobial Activity of 5-Aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones (III – XIV)

Compound	MIC, μg/ml	
	S. aureus	*E. coli*
III	1000	500
IV	500	250
V	500	500
VI	1000	1000
VII	500	500
VIII	500	1000
IX	1000	500
X	inactive	1000
XI	500	500
XII	250	500
XIII	1000	inactive
XIV	1000	1000
Mercury dichloride	1000	1000

5-Aryl-4-acyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones (I – XIV).

General method. Equimolar quantities of aromatic aldehyde and 2-(2-aminoethoxy)ethanol were added to 0.05 mol of acetylpyruvic acid methyl ester or benzoylpyruvic acid dissolved in 10 ml of dioxane for compounds I – V or 10 ml of acetic acid for compounds VI – XIV. The reaction mixture was held at room temperature for one day. The resulting precipitate was collected by filtration and recrystallized from ethanol.

EXPERIMENTAL BIOLOGICAL SECTION

Antimicrobial activity against strains of *E. coli* and *S. aureus* was determined by twofold serial dilutions in meat-peptone broth with a bacterial load of 250,000 microbial units per ml of solution. The active dose was taken as the minimum inhibitory concentration (MIC) of the compound, i.e., the maximum dilution leading to complete suppression of test microbe growth. Reference agents were mercury dichloride and ethacridine lactate.

The study compounds had low levels of antimicrobial activity against both strains. Some increase in the antimicrobial activity of compound XII against *S. aureus* and compound IV against *E. coli* should be noted, apparently due to the presence of the phenol hydroxyl in these compounds.

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