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Synthesis and Antihypoxic Activity of 5-Aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones

V. L. Gein[a], S. N. Rogachev[a], A. A. Bobyleva[a], D. Yu. Apushkin[a], G. A. Veikhman[a], and O. E. Nasakin[b]

[a] *Perm State Pharmaceutical Academy, Ministry of Health of the Russian Federation, ul. Polevaya 2, Perm, 614990 Russia*
e-mail: geinvl48@mail.ru

[b] *Ulyanov Chuvash State University, Cheboksary, Russia*

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Abstract—Reactions of 2-(2-aminoethoxy)ethanol with mixtures of an aromatic aldehyde and aroylpyruvic acid methyl ester have afforded 5-aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones. Antihypoxic activity of the synthesized compounds has been studied.

Keywords: 5-aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxy)ethyl]-3-pyrrolin-2-one, antihypoxic activity

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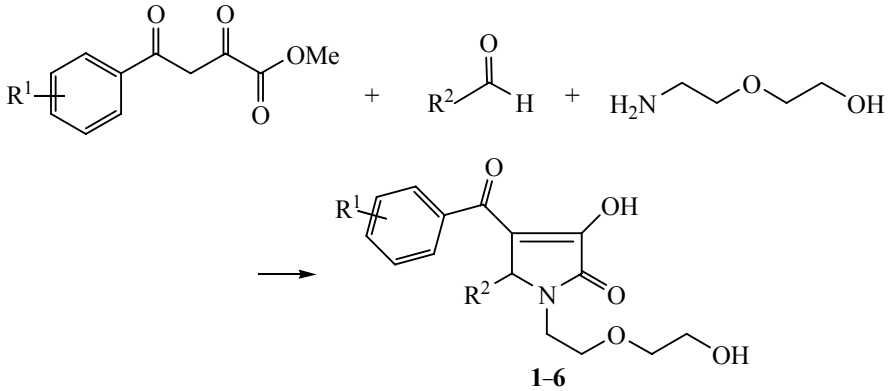
Search for substances enhancing the body resistance to negative environmental factors is a topical issue nowadays. Study of antihypoxic activity of pyrrole-2,3-diones derivatives is of interest, since representatives of this class exhibit nootropic activity [1], and combination of these two properties would be promising for practical applications.

We targeted at preparation of tetrahydropyrrole-2,3-diones with a hydrophilic 2-(2-hydroxyethoxy)ethyl substituent at the position 1 of the heterocycle and at elucidation of the structural changes effects on solubility in water and antihypoxic activity of the obtained compounds.

Using the known method [2], we performed reactions of 2-(2-aminoethoxy)ethanol with mixtures of an aromatic aldehyde and methyl aroylpyruvate taken in equimolar ratio, in dioxane medium at room temperature. Under those conditions, 5-aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethyl)ethyl]-3-pyrrolin-2-ones **1**–**6** were obtained as the only reaction products (Scheme 1, Table 1).

Scheme 1.



1–**6**

R^1 = 4-CH_3 (**1**, **3**, **4**), H (**2**), 4-Cl (**5**, **6**); R^2 = 2,4-$Cl_2C_6H_3$ (**1**), 3-OHC_6H_4 (**2**), 3-pyridyl (**3**), 2-FC_6H_4 (**4**), 4-FC_6H_4 (**5**), 2-$CH_3OC_6H_4$ (**6**).

Table 1. Physico-chemical parameters of compounds **1**–**6**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
1	61.5	215–217 (EtOH)	59.28	5.34	3.05	$C_{23}H_{25}Cl_2NO_5$	59.24	5.40	3.00
2	75.2	193–195 (EtOH)	65.80	5.54	3.68	$C_{21}H_{21}NO_6$	65.79	5.52	3.65
3	64.8	191–193 (EtOH)	66.05	5.70	7.35	$C_{21}H_{22}N_2O_5$	65.96	5.80	7.33
4	61.6	232–234 (EtOH)	66.08	5.47	3.50	$C_{22}H_{22}FNO_5$	66.16	5.55	3.51
5	70.7	231–233 (EtOH)	60.14	4.55	3.29	$C_{21}H_{19}ClFNO_5$	60.08	4.56	3.34
6	58.8	174–176 (EtOH)	61.22	5.15	3.17	$C_{22}H_{22}ClNO_6$	61.19	5.13	3.24

Table 2. ^{1}H NMR (DMSO-d_6) data for compounds **1**–**6**

Comp. no.	δ, ppm					
	H_{Ar} (m)	OH (s)	$C^1\underline{H}_AH_B$ (m)	$C^1H_A\underline{H}_B$ (m)	$CH_2OCH_2CH_2OH$ (m)	other signals (s)
1	7.20	11.90	3.80	2.80	3.40	2.35 ($3H^1$, CH_3)
2	7.25	11.90	3.80	2.80	3.45	
3	7.20	12.00	3.80	2.70	3.40	2.34 ($3H^1$, CH_3)
4	7.25	11.80	3.80	2.80	3.50	2.34 ($3H^1$, CH_3)
5	7.25	12.00	3.75	2.75	3.40	
6	6.80	11.70	3.80	2.70	3.35	2.35 ($3H^1$, CH_3O)

The resulting compounds **1**–**6** were white crystalline substances, soluble in ethanol, dimethyl sulfoxide, and dimethylformamide and insoluble in water (Table 1).

The products structure was confirmed by the data of IR and ^{1} H NMR spectroscopy (Table 2). ^{1}H NMR spectra of compounds **1**–**6** contained the signals of aromatic protons (6.80–7.25 ppm), two multiplets of enantiotopic protons of the methylene group at position 1 (2.75–2.80, 3.75–3.80 ppm), a multiplet of other methylene protons (3.35–3.50 ppm), and a singlet assigned to the hydroxyl group at position 3 of the pyrroline ring (11.70–12.00 ppm) (Table 2).

IR spectra of compounds **1**–**6** (Table 3) contained absorption bands due stretching of the lactam (1652–1696 cm^{-1}), ketone (1620–1632 cm^{-1}), enol (3096–3128 cm^{-1}), and alcohol (3400–3470 cm^{-1}) groups.

Solutions of all the obtained compounds revealed deep cherry coloration after treatment with alcoholic solution of iron(III) chloride. That reaction along with the spectroscopy data indicated existence of compounds **1**–**6** in the enol form.

All the synthesized compounds were assayed for antihypoxic activity. The results revealed the highest antihypoxic activity of compounds **4** and **6**. The results of 5-aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethoxy)-ethyl]-3-pyrrolin-2-ones **1**–**6** assay under normobaric hypoxia conditions are shown in Table 4.

EXPERIMENTAL

^{1}H NMR spectra of the solutions in DMSO-d_6 were recorded using a Bruker AM-500 instrument at operat-

Table 3. IR spectral data for compounds **1**–**6**

Comp. no.	ν, cm^{-1}			
	CO	CON	OH	CH_2OH
1	1620	1692	3096	3400
2	1624	1696	3120	3470
3	1624	1652	3112	3430
4	1625	1682	3128	3450
5	1632	1692	3118	3432
6	1632	1664	3112	3470

Table 4. 5-Aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethoxy)ethyl]-3-pyrrolin-2-ones **1**–**6** towards antihypoxic activity under normobaric hypoxia conditions

Exp. no.	Reference	**1**	**2**	**3**	**4**	**5**	**6**
1	25.00	30.00	32.00	22.00	32.00	26.00	32.00
2	26.00	25.00	28.00	24.00	31.00	28.00	34.00
3	25.00	24.00	25.00	21.00	28.00	24.00	30.00
4	30.00	23.00	29.00	23.00	30.00	25.00	29.00
5	22.00	20.00	35.00	25.00	29.00	27.00	31.00
6	29.00	24.00	30.00	25.00	33.00	29.00	32.00
Average	26.17	24.33	29.83	23.33	30.50	26.50	31.33
Confidence interval	23.10–29.24	20.91–27.76	26.23–33.43	21.62–25.05	28.54–32.46	24.54–28.46	29.50–33.17
% increase relative to the reference group		–7.01	14.01	–10.83	16.56	1.27	19.75

ing frequency of 500 MHz relative to internal TMS. IR spectra of the suspensions in mineral oil were registered with a SPECORD M-80 spectrometer. Melting points were determined using a Melting-PointM-565 apparatus. Elemental analysis was performed with a Perkin Elmer 2400 instrument.

5-Aryl-4-aroyl-3-hydroxy-1-[2-(2-hydroxyethoxy)-ethyl]-3-pyrrolin-2-ones (1–6). A solution of 0.05 mol of methyl aroylpyruvate in 10 mL of dioxane was mixed with equimolar amounts of an aromatic aldehyde and 2-(2-aminoethoxy)ethanol and incubated at room temperature during 1 day. The precipitate formed was filtered off, recrystallized from ethanol, and dried.

Antihypoxia activity was studied taking advantage of the model of normobaric hypoxia with hypercapnia [3]. The experiments were performed with white mice (18–20 g) kept under standard vivarium conditions. The tested compounds were injected intraperitoneally 30 min prior to the experiment at a dose of 100 mg kg^{-1} as a suspensions with isotonic sodium chloride solution. Depending on the weight, the reference group was injected with a required amount of 0.9% sodium chloride solution. Lifetime of the mice (in minutes) was determined.

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REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Wolna, 2005.
2. Gein, V.L., *Tetragidropirrol- i tetragidrofuran-2,3-diony* (Tetrahydropyrrole- and Tetrahydrofuran-2,3-diones), Perm: PGFA, 2004.
3. Mironov, A.N., Bunyatyan, N.D., and Vasilieva, A.N., *Rukovodstvo po provedeniyu doklinicheskikh sredstv* (Guidelines for Pre-Clinical Studies of Drugs), Moscow: Grif i K, 2012.
4. Belen'kii, M.L., *Elementy kolichestvennoi otsenki farmakologicheskogo effekta* (Elements of Quantitative Assessment of Pharmacological Effect), Leningrad: Medgiz, 1963.