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Synthesis of 5-Aryl-4-aroyl-3-hydroxy-1-carboxymethyl-3-pyrroline-2-ones

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Abstract—The reaction of methyl aroylpyruvate with a mixture of aromatic aldehyde and glycocol in a dioxane–water mixture (1 : 1) leads to the formation of a new series of 5-aryl-4-aroyl-3-hydroxy-1-carboxymethyl-3-pyrroline-2-ones. Structure of the obtained compounds was determined by IR and ^{1}H NMR spectroscopy methods.

Keywords: 5-aryl-4-aroyl-3-hydroxy-1-carboxymethyl-3-pyrrolin-2-ones, glycocol, tetrahydropyrrole-2,3-diones, three-component reactions

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Pyrrole core is presented both in the most important natural molecular systems (chlorophyll, hemoglobin, hormones, dyes, pheromones, antibiotics, oxidoreductase enzymes), and in various well-known drugs, such as piracetam, atropine, captopril, lincomycin, etc. For example, atorvastatin containing a completely substituted pyrrole ring lowers plasma cholesterol and lipoprotein levels and is one of the best-selling drugs in the world [1]. In addition, the pyrroline fragment is included into the structure of fluorophores, optoelectronic and other progressive materials. The development of technologies in various fields of human activity requires the production of new heterocyclic compounds with the necessary properties for the creation of new materials, drugs, chemical sensors and the implementation of effective processes for converting solar energy. Within the framework of this general problem, the preparation of pyrrole derivatives occupies an important place and constantly requires the development of effective methods for their synthesis from available raw materials on the basis of new step-economic approaches without isolation of intermediate compounds [2].

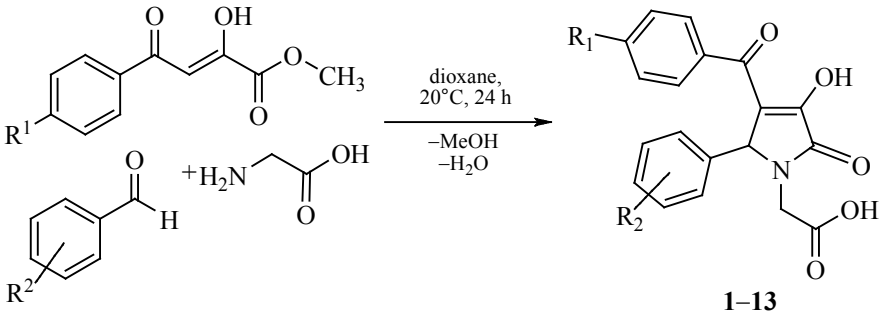
Tetrahydropyrrole-2,3-diones are important class of available and stable organic compounds. They easily react with various nucleophilic reagents due to the highly reactive 3-carbonyl group. The presence of the latter, as well as the carbonyl group of the side chain, make it possible to generate various fused systems from the heterocycles in reactions with binucleophilic reagents [3, 4].

1,4,5-Trisubstituted tetrahydropyrrole-2,3-diones are promising substrates in the synthesis of biologically active substances. Previously, it has been found that 1,4,5-trisubstituted 3-hydroxy-3-pyrrolin-2-ones show anti-inflammatory, analgesic, antimicrobial, nootropic, antiplatelet, antiviral [5, 6], and antifungal activity [7]. It has also been shown that the substituent in the position 1 of the heterocycle significantly affects the biological activity and chemical properties of 1,4,5-trisubstituted 3-hydroxy-3-pyrroline-2ones [8, 9].

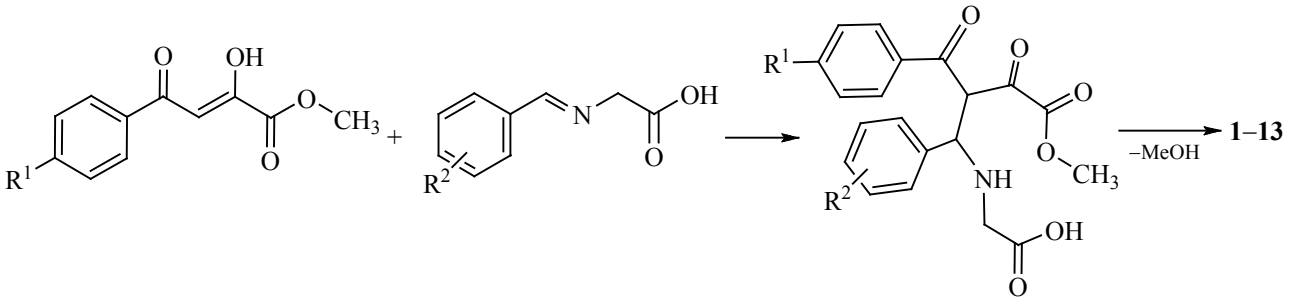
Herein, we reported the synthesis of new 5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones containing a carboxymethyl substituent in the position 1 of the heterocycle by the three-component reaction of methyl esters of aroylpyruvic acids with a mixture of aromatic aldehyde and glycol. This reaction is of interest because it can be used as a method for determining the *N*-terminal amino acid in peptides and proteins [8, 9].

The three-component reaction of aroylpyruvic acid methyl ester with aromatic aldehydes and glycocol in dioxane–water medium (1 : 1) led to the formation of 5-aryl-4-acyl-3-hydroxy-1-carboxymethyl-3-pyrrolin-2-ones **1**–**13** with a yield of 10–78% (Scheme 1).

Scheme 1.



Scheme 2.



Presumably, the reaction proceeds with the formation of an intermediate Schiff base, at the double bond of which the starting ester is added. Further cyclization of the intermediate 4-amino-4-aryl-2-oxobutanoic acid ester results in the formation of the corresponding 3-hydroxy-3-pyrrolin-2-ones **1**–**13** (Scheme 2).

The obtained compounds **1**–**13** are white or weakly colored crystalline substances, soluble in DMSO, DMF, dioxane, and when heated in ethanol and glacial acetic acid, insoluble in water.

The IR spectra of compounds **1**–**13** exhibit absorption bands of the lactam carbonyl group at 1698–1676 cm^{-1} and a strong absorption band of the enol hydroxyl group at 3187–3109 cm^{-1}. The absorption band of the side chain carbonyl group is observed at 1739–1726 cm^{-1}.

The ^1H NMR spectra of compounds **1**–**13** contain signals of aromatic protons in the range of 6.77–7.81 ppm, a singlet of the methine proton at C^5 atom in the range of 5.34–5.86 ppm, doublets of enantiotropic protons of the methylene group of the carboxymethyl substituent in the ranges of 3.19–3.39 (1H, $C^{\alpha}H_A\underline{H}_B$, J = 16.0 Hz) and 4.18–4.30 ppm (1H, $C^{\alpha}\underline{H}_AH_B$, J = 16.0 Hz), and a broadened signal of the enol hydroxyl group at 12.77–12.96 ppm (1H, C^3OH).

All the obtained compounds reacted with an alcoholic solution of iron(III) chloride to give purple coloration. The results of ^1H NMR spectroscopy and a positive ferric chloride test indicate the existence of the obtained compounds **1**–**13** mainly in the enol form.

In summary, the reaction of aroylpyruvic acid methyl ester with a mixture of aromatic aldehyde and glycol in aqueous dioxane gave 5-aryl-4-aroyl-3-hydroxy-1-carboxymethyl-3-pyrrolin-2-ones containing a carboxymethyl substituent at position 1 of the heterocycle.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrometer from KBr pellets. ^1H NMR spectra were recorded on a Bruker AM-400 instrument with an operating frequency of 400 MHz in DMSO-d_6 relative to internal tetramethylsilane. Melting points were determined on a MeltingPointM-565 apparatus. Elemental analysis was performed on a PerkinElmer 2400 instrument.

4-Benzoyl-1-carboxymethyl-3-hydroxy-5-(4-methylphenyl)-3-pyrrolin-2-one (1). To a mixture of 0.01 mol of glycocol dissolved in 5 mL of distilled water and 0.01 mol of 4-methylbenzaldehyde in 5 mL of dioxane was added 0.01 mol of benzoylpyruvic acid methyl ester. The reaction mixture was heated until the components were dissolved and kept at room temperature for 1 day. The precipitate formed upon cooling was filtered off and recrystallized from ethanol. Yield 0.92 (26%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3119 (OH), 1736 (COOH), 1685 (CON), 1612 (CO). ^1H NMR spectrum, δ, ppm: 2.24 s (3H, CH_3), 4.30 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.36 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.51 s (1H, C^5H), 7.12–7.74 m (9H, CH_{Ar}), 12.85 s (1H, C^3OH). Found, %: C 68.37; H 4.88; N 3.99. $C_{20}H_{17}NO_5$. Calculated, %: C 68.12; H 4.62; N 3.70.

Compounds **2**–**13** were prepared similarly.

4-Benzoyl-1-carboxymethyl-5-(4-ethylphenyl)-3-hydroxy-3-pyrroline-2-one (2). Yield 0.35 g (10%), mp 199–202°C. IR spectrum, ν, cm^{-1}: 3161 (OH), 1732 (COOH), 1680 (CON), 1618 (CO). ^1H NMR spectrum, δ, ppm: 1.14 t (3H, $CH_2C\underline{H}_3$, J = 8.0 Hz), 2.55 q (2H, $C\underline{H}_2CH_3$, J = 8.0 Hz), 4.28 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.28 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.46 s (1H, C^5H), 7.14–7.74 m (9H, CH_{Ar}), 12.90 s (1H, C^3OH). Found, %: C 69.03; H 5.24; N 3.83. $C_{21}H_{19}NO_5$. Calculated, %: C 69.00; H 5.26; N 3.81.

4-Benzoyl-1-carboxymethyl-3-hydroxy-5-(4-isopropylphenyl)-3-pyrroline-2-one (3). Yield 0.65 g (17%), mp 198–200°C. IR spectrum, ν, cm^{-1}: 3109 (OH), 1736 (COOH), 1676 (CON), 1620 (CO). ^1H NMR spectrum, δ, ppm: 1.21 d [6H, $(C\underline{H}_3)_2CH$, J = 8.0 Hz], 2.83 q [1H, $(CH_3)_2C\underline{H}$, J = 8.0 Hz], 4.30 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.28 d (1H, $C_\alpha H_A\underline{H}_B$, CH_2CO, J = 16.0 Hz), 5.49 s (1H, C^5H), 7.18–7.74 m (9H, CH_{Ar}), 12.96 s (1H, C^3OH). Found, %: C 69.64; H 5.58; N 3.69. $C_{22}H_{21}NO_5$. Calculated, %: C 69.66; H 5.57; N 3.71.

4-Benzoyl-1-carboxymethyl-3-hydroxy-5-(2-methoxyphenyl)-3-pyrroline-2-one (4). Yield 1.42 g (37%), mp 164–166°C. IR spectrum, ν, cm^{-1}: 3150 (OH), 1732 (COOH), 1691 (CON), 1626 (CO). ^1H NMR spectrum, δ, ppm: 3.73 s (3H, CH_3O), 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.19 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.86 s (1H, C^5H), 6.81–7.81 m (9H, CH_{Ar}), 12.77 s (1H, C^3OH). Found, %: C 65.38; H 4.67; N 3.79. $C_{20}H_{17}NO_6$. Calculated, %: C 65.39; H 4.66; N 3.81.

4-Benzoyl-1-carboxymethyl-3-hydroxy-5-(3-methoxyphenyl)-3-pyrroline-2-one (5). Yield 0.57 g (15%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3145 (OH), 1738 (COOH), 1692 (CON), 1626 (CO). ^1H NMR spectrum, δ, ppm: 3.64 s (3H, CH_3O), 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.34 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.46 s (1H, C^5H), 6.77–7.67 m (9H, CH_{Ar}), 12.85 s (1H, C^3OH). Found, %: C 65.38; H 4.67; N 3.79. $C_{20}H_{17}NO_6$. Calculated, %: C 65.39; H 4.66; N 3.81.

4-Benzoyl-1-carboxymethyl-3-hydroxy-5-(4-hydroxy-3-ethoxyphenyl)-3-pyrroline-2-one (6). Yield 0.95 g (24%), mp 205–207°C. IR spectrum, ν, cm^{-1}: 3144 (OH), 1739 (COOH), 1688 (CON), 1615 (CO). ^1H NMR spectrum, δ, ppm: 1.20 t (5H, $C\underline{H}_3CH_2O$, J = 8.0 Hz), 3.90 q (5H, $CH_3C\underline{H}_2O$, J = 8.0 Hz), 4.18 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.33 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.34 s (1H, C^5H), 6.81–7.81 m (8H, CH_{Ar}), 12.77 s (1H, C^3OH). Found, %: C 65.38; H 4.67; N 3.79. $C_{20}H_{17}NO_6$. Calculated, %: C 65.39; H 4.66; N 3.81.

4-Benzoyl-1-carboxymethyl-5-(4-fluorophenyl)-3-hydroxy-3-pyrroline-2-one (7). Yield 0.37 g (11%), mp 222–224°C. IR spectrum, ν, cm^{-1}: 3119 (OH), 1726 (COOH), 1695 (CON), 1626 (CO). ^1H NMR spectrum, δ, ppm: 4.25 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.36 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.48 s (1H, C^5H), 7.10–7.74 m (9H, CH_{Ar}), 12.90 s (1H, C^3OH). Found, %: C 64.23; H 3.97; N 3.94. $C_{19}H_{14}FNO_5$. Calculated, %: C 64.25; H 3.96; N 3.97.

1-Carboxymethyl-4-(4-chlorobenzoyl)-3-hydroxy-5-(4-methylphenyl)-3-pyrroline-2-one (8). Yield 0.39 g (78%), mp 240–242°C. IR spectrum, ν, cm^{-1}: 3154 (OH), 1732 (COOH), 1691 (CON), 1630 (CO). ^1H NMR spectrum, δ, ppm: 2.51 s (3H, CH_3), 4.28 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.33 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.46 s (1H, C^5H), 7.12–7.73 m (8H, CH_{Ar}), 12.85 s (1H, C^3OH). Found, %: C 62.24; H 4.20; N 3.62. $C_{20}H_{16}ClNO_5$. Calculated, %: C 62.26; H 4.18; N 3.63.

1-Carboxymethyl-4-(4-chlorobenzoyl)-5-(4-ethylphenyl)-3-hydroxy-3-pyrroline-2-one (9). Yield 2.10 (53%), mp 198–200°C. IR spectrum, ν, cm^{-1}: 3136 (OH), 1732 (COOH), 1695 (CON), 1626 (CO). ^1H NMR spectrum, δ, ppm: 1.14 t (3H, $CH_2C\underline{H}_3$, J = 8.0 Hz), 2.53 q (2H, $C\underline{H}_2CH_3$, J = 8.0 Hz), 4.28 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.31 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.47 s (1H, C^5H), 7.15–7.74 m (8H, CH_{Ar}), 12.90 s (1H, C^3OH). Found, %: C 63.08; H 4.54; N 3.50. $C_{21}H_{18}ClNO_5$. Calculated, %: C 63.07; H 4.57; N 3.48.

1-Carboxymethyl-4-(4-chlorobenzoyl)-3-hydroxy-5-(4-isopropylphenyl)-3-pyrroline-2-one (10). Yield 2.25 g (54%), mp 203–205°C. IR spectrum, ν, cm^{-1}:

3125 (OH), 1730 (COOH), 1697 (CON), 1630 (CO). ^{1}H NMR spectrum, δ, ppm: 1.23 d [6H, $(C\underline{H}_3)_2CH$, J = 8.0 Hz], 2.85 q [1H, $(CH_3)_2C\underline{H}$, J = 8.0 Hz], 4.29 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.32 d (1H, $C_\alpha H_A\underline{H}_B$, CH_2CO, J = 16.0 Hz), 5.48 s (1H, C^5H), 7.19–7.74 m (8H, CH_{Ar}), 12.92 s (1H, C^3OH). Found, %: C 63.64; H 4.90; N 3.25. $C_{22}H_{20}ClNO_5$. Calculated, %: C 63.85; H 4.87; N 3.38.

1-Carboxymethyl-4-(4-chlorobenzoyl)-3-hydroxy-5-(3-methoxyphenyl)-3-pyrroline-2-one (11). Yield 0.54 g (13%), mp 210–212°C. IR spectrum, ν, cm^{-1}: 3156 (OH), 1732 (COOH), 1698 (CON), 1624 (CO). ^{1}H NMR spectrum, δ, ppm: 3.66 s (3H, CH_3O), 4.30 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.36 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.41 s (1H, C^5H), 6.77–7.68 m (8H, CH_{Ar}), 12.85 s (1H, C^3OH). Found, %: C59.78; H4.01; N 3.49. $C_{20}H_{16}ClNO_6$. Calculated, %: C59.75; H 4.02; N 3.51.

1-Carboxymethyl-4-(4-chlorobenzoyl)-3-hydroxy-5-(4-hydroxy-3-methoxyphenyl)-3-pyrroline-2-one (12). Yield 0.55 g (13%), mp 113–115°C. IR spectrum, ν, cm^{-1}: 3187 (OH), 1730 (COOH), 1688 (CON), 1623 (CO). ^{1}H NMR spectrum, δ, ppm: 3.66 s (3H, CH_3O), 4.30 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.36 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.51 s (1H, C^5H), 7.12–7.74 m (7H, CH_{Ar}), 12.85 s (1H, C^3OH). Found, %: C 68.37; H 4.88; N 3.99. $C_{20}H_{17}NO_5$. Calculated, %: C 68.12; H 4.62; N 3.70.

1-Carboxymethyl-4-(4-chlorobenzoyl)-5-(4-fluorophenyl)-3-hydroxy-3-pyrroline-2-one (13). Yield 2.50 g (64%), mp 133–135°C. IR spectrum, ν, cm^{-1}: 3175 (OH), 1726 (COOH), 1697 (CON), 1647 (CO). ^{1}H NMR spectrum, δ, ppm: 4.26 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.39 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.49 s (1H, C^5H), 7.10–7.71 m (8H, CH_{Ar}), 12.90 s (1H, C^3OH). Found, %: C 58.39; H 3.36; N 3.59. $C_{19}H_{13}ClFNO_5$. Calculated, %: C 58.54; H 3.39; N 3.57.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2010.
2. Galenko, E.E., *Candidate Sci. (Chem.) Dissertation*, St. Petersburg, 2016.
3. Gein, V.L., *Tetragidropirrol- i tetragidrofuran-2,3-diony* (Tetrahydropyrrole- and Tetrahydrofuran-2,3-diones). Perm: PGFA, 2004.
4. Mar'yasov, M.A., *Tetragidropirrol-2,3-diony* (Tetrahydropyrrole-2,3-diones), Perm: PGFA, 2013.
5. Gein, L.F., *Candidate Sci. (Pharm.) Dissertation*, Perm, 2009.
6. Kylosova, I.A., *Candidate Sci. (Pharm.) Dissertation*, Perm, 2007.
7. Cordeiro, R.A., Teixeira, C.E.C., Brilhante, R.S.N., Castelo-Branco, D.S.C.M., Paiva, M.A.N., Leite, J.J.G., Lima, D.T., Monteiro, A.J., Sidrim, J.J.C., and Rocha, M.F.G., *Medical Mycology*, 2013, vol. 51, no. 1, p. 53. https://doi.org/10.3109/13693786.2012.692489
8. Gein, V.L., Gein, L.F., Porseva, N.Yu., Shchurova, I.G., Shchurov, S.N., Vakhrin, M.I., Voronina, E.V., Mardanova, L.G., and Kolla, V.E., *Pharm. Chem. J.*, 1997, vol. 31, no. 5, p. 251. https://doi.org/10.1007/BF02464106
9. Gein, V.L., Gein, L.F., Porseva, N.Yu., Voronina, E.V., Vakhrin, M.I., Potemkin, K.D., Kolla, V.E., Drovosekova, L.P., Milyutin, A.V., Shchuklina, N.S., and Veihman, G.A., *Pharm. Chem. J.*, 1998, vol. 32, no. 9, p. 477. https://doi.org/10.1007/BF02539221