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Synthesis of 1-Aminocarbonylmethyl-5-aryl-4-aroyl-3-hydroxy-3-pyrroline-2-ones

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Abstract—A series of new 1-aminocarbonylmethyl-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones has been synthesized through a three-component reaction of aroylpyruvic acid methyl ester with a mixture of aromatic aldehyde and glycinamide hydrochloride in glacial acetic acid in the presence of anhydrous sodium bicarbonate.

Keywords: 1-aminocarbonylmethyl-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones, glycinamide hydrochloride, tetrahydropyrrol-2,3-diones, three-component reactions

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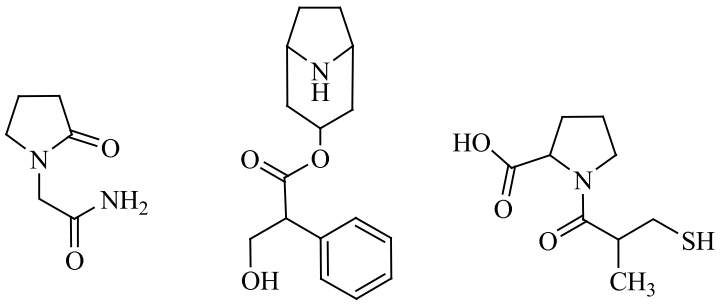
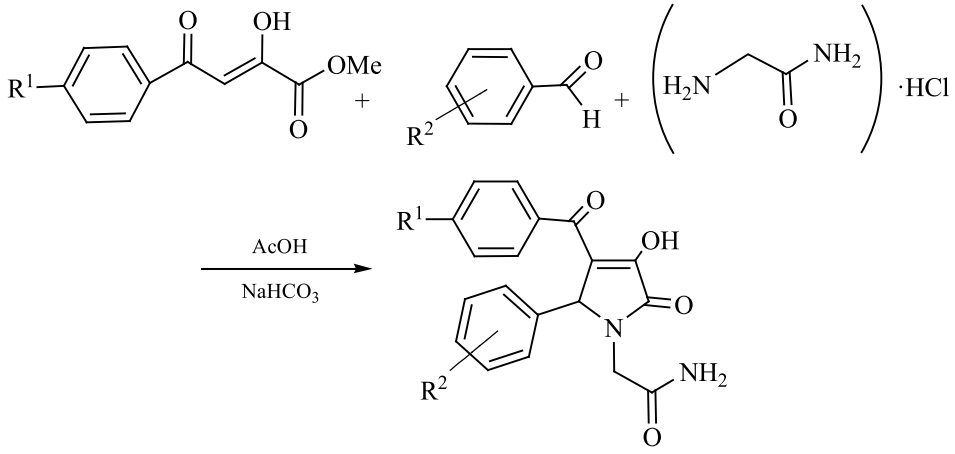
The search for new highly active substances with specified pharmacological and biological properties and low toxicity is one of the main tasks of pharmaceutical chemistry. 3-Hydroxy-3-pyrrolin-2-one derivatives are of particular interest, since the pyrroline moiety is included into various known drugs, such as piracetam, atropine, captopril, lincomycin, etc., as well as enzyme molecules such as oxidoreductase [1] (Scheme 1). 3-Hydroxy-3-pyrrolin-2-one derivatives have a wide spectrum of biological activity: nootropic, antihypoxic, analgesic, anti-inflammatory, antiplatelet and antiviral [2]. The presence of several reaction sites in the structure of 3-hydroxy-3-pyrrolin-2-ones allows them to be involved into reactions with various nucleophilic reagents, such as urea and hydrazine hydrate [3]. Thus, the development of methods for the synthesis of 3-hydroxy-3-pyrrolin-2-one derivatives containing an aminocarbonylmethyl fragment at position 1 of the heterocycle and the study of their biological activity is a topical area of pharmaceutical chemistry [3, 4]. In order to synthesize 4,5-disubstituted 1-aminocarbonylmethyl-3-hydroxy-3-pyrrolin-2-ones, we performed the three-component reaction of aroylpyruvic acid methyl ester with a mixture of aromatic aldehyde and glycinamide [5]. This reaction proceeds upon short-term heating of an equimolar amount of reagents in the presence of anhydrous sodium bicarbonate in glacial acetic acid to form 1-aminocarbonylmethyl-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones **1**–**15** (Scheme 2). Glycinamide, which does not exist in a free form under normal conditions, was obtained *in situ* by the known reaction of glycinamide hydrochloride with anhydrous sodium bicarbonate in an acetic acid

Scheme 1.



Piracetam Atropine Captopril

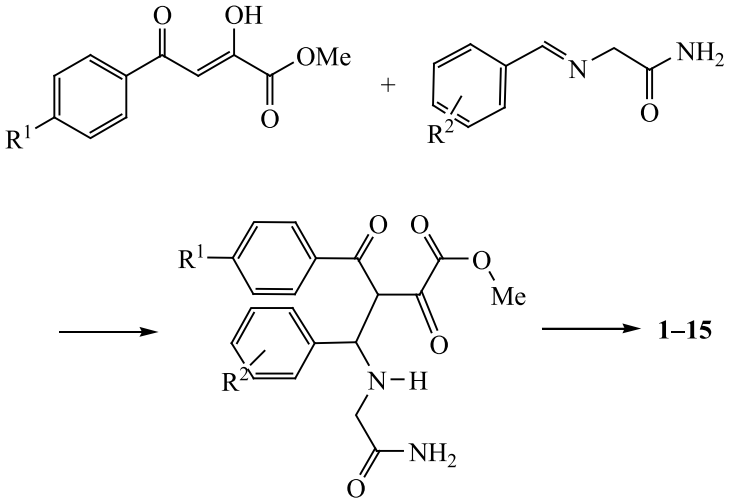
Scheme 2.



1–15

R^1 = Cl, R^2 = H (**1**); R^1 = Cl, R^2 = 4-Cl (**2**); R^1 = Cl, R^2 = 2-Cl (**3**); R^1 = Cl, R^2 = 3-NO_2 (**4**); R^1 = Cl, R^2 = 2-NO_2 (**5**); R^1 = Cl, R^2 = 4-Et (**6**); R^1 = Cl, R^2 = 4-*i*-Pr (**7**); R^1 = Cl, R^2 = 4-MeO (**8**); R^1 = 4-Cl, R^2 = 4-Me (**9**); R^1 = Cl, R^2 = 4-F (**10**); R^1 = H, R^2 = 2-Cl (**11**); R^1 = H, R^2 = 2-NO_2 (**12**); R^1 = H, R^2 = 3-NO_2 (**13**); R^1 = H, R^2 = 4-*i*-Pr (**14**); R^1 = H, R^2 = 4-Me (**15**).

Scheme 3.



medium [5, 6]. Presumably, the reaction proceeds with the formation of an intermediate Schiff base, at the double bond of which the initial ester is added, followed by cyclization of the intermediate 4-aryl-4-amino-2-oxobutanoic acid ester to the corresponding 3-hydroxy-3-pyrrolin-2-ones **1**–**15** (Scheme 3). The obtained compounds **1**–**15** are white 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**–**15** contain absorption bands of the lactam carbonyl group at 1765–1703 cm^{-1} and an absorption band of the amide group at 1713–1664 cm^{-1}. The absorption band of the carbonyl group of the side chain is observed in the 1635–1624 cm^{-1} region. A strong absorption band of the enol hydroxyl group is recorded at 3250–3150 cm^{-1}, and the absorption band of NH_2 groups appears at 3568–3441 cm^{-1}. The ^1H NMR spectra of compounds **1**–**15** contain signals of aromatic protons (6.27–7.94 ppm), a singlet of the methine proton at the C^5 atom (5.40–5.90 ppm), and doublets of the methylene group of the aminocarbonylmethyl substituent (3.07–3.24 ppm, $C_\alpha H_A \underline{H}_B$; 4.12–4.88 ppm, $C_\alpha \underline{H}_A H_B$). The absence of the signal of the enol hydroxyl group in the spectra of the obtained compounds is explained

by exchange intramolecular processes. In addition, the spectra of compounds **1**–**15** contain two singlets of the protons of the primary amide amino group at 6.07–7.21 and 6.68–7.22 ppm. The obtained compounds give a characteristic coloration upon reaction with iron(III) chloride. One can conclude that these compounds predominantly exist in the enol form.

In conclusion, a series of new 1-aminocarbonylmethyl-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones was obtained by the reaction of aroylpyruvic acid methyl ester with a mixture of aromatic aldehyde and glycinamide in glacial acetic acid in the presence of sodium bicarbonate.

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrometer from KBr pellets. ^{1}H NMR spectra were recorded on a Bruker Avance III HD 400 spectrometer with an operating frequency of 400 MHz in DMSO-d_6. Elemental analysis was performed on a Perkin Elmer 2400 apparatus. Melting points were determined on a Melting Point M-565 apparatus.

1-Aminocarbonylmethyl-3-hydroxy-5-phenyl-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (1). To a solution of 0.55 g (0.005 mol) of glycinamide hydrochloride in 10 mL of acetic acid was added 0.42 g (0.005 mol) of sodium bicarbonate. The resulting mixture stirred until complete dissolution. Then a mixture of 0.51 mL (0.005 mol) of benzaldehyde and 1.2 g (0.005 mol) of methyl *p*-chlorobenzoylpyruviate was added. The reaction mixture was heated until the components were dissolved and kept at room temperature for 1 day. The formed precipitate was filtered off and recrystallized from ethanol. Yield 0.95 g (51%), mp 256–257°C. IR spectrum, ν, cm^{-1}: 1695 (CON), 1668 ($CONH_2$), 1606 (CO), 3200 (OH), 3445 (NH_2). ^{1}H NMR spectrum, δ, ppm: 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.12 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.51 s (1H, C^5H), 7.12–7.73 m (9H, CH_{Ar}), 7.05 s and 7.15 s (2H, NH_2). Found, %: C 61.82; H 4.34; N 7.82. $C_{19}H_{15}ClN_2O_4$. Calculated, %: C 61.55; H 4.08; N 7.56.

Compounds **2**–**15** were prepared similarly and purified by recrystallization from ethanol.

1-Aminocarbonylmethyl-3-hydroxy-4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-3-pyrrolin-2-one (2). Yield 0.5 g (25%), mp 242–244°C. IR spectrum, ν, cm^{-1}: 1707 (CON), 1687 ($CONH_2$), 1635 (CO), 3150 (OH), 3451 (NH_2), ^{1}H NMR spectrum, δ, ppm: 4.21 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), 5.51 s (1H, C^5H), 7.11–7.73 m (8H, CH_{Ar}), 7.09 s and 7.11 s (2H, NH_2). Found, %: C 56.63; H 3.74; N 7.19. $C_{19}H_{14}Cl_2N_2O_4$. Calculated, %: C 56.31; H 3.48; N 6.91.

1-Aminocarbonylmethyl-3-hydroxy-4-(4-chlorobenzoyl)-5-(2-chlorophenyl)-3-pyrrolin-2-one (3). Yield 0.6 g (30%), mp 227–229°C. IR spectrum, ν, cm^{-1}: 1709 (CON), 1685 ($CONH_2$), 1626 (CO), 3180 (OH), 3445 (NH_2). ^{1}H NMR spectrum, δ, ppm: 4.18 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.11 d (1H, $C_\alpha H_A\underline{H}_B$, CH_2CO, J = 16.0 Hz), 5.67 s (1H, C^5H), 7.13–7.77 m (8H, CH_{Ar}), 7.11 s and 7.13 s (2H, NH_2). Found, %: C 56.57; H 3.73; N 6.65. $C_{19}H_{14}Cl_2N_2O_4$. Calculated, %: C 56.31; H 3.48; N 6.91.

1-Aminocarbonylmethyl-3-hydroxy-5-(3-nitrophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (4). Yield 0.45 g (22%), mp 206–208°C. IR spectrum, ν, cm^{-1}: 1765 (CON), 1703 ($CONH_2$), 1620 (CO), 3198 (OH), 3568 (NH_2). ^{1}H NMR spectrum, δ, ppm: 4.2 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), 5.63 s (1H, C^5H), 7.06–8.77 m (8H, CH_{Ar}), 7.06 s and 7.08 s (2H, NH_2). Found, %: C 55.14; H 3.62; N 10.39. $C_{19}H_{14}ClN_3O_6$. Calculated, %: C 54.89; H 3.39; N 10.11.

1-Aminocarbonylmethyl-3-hydroxy-5-(2-nitrophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (5). Yield 0.55 g (26%), mp 176–178°C. IR spectrum, ν, cm^{-1}: 1703 (CON), 1682 ($CONH_2$), 1630 (CO), 3160 (OH), 3451 (NH_2). ^{1}H NMR spectrum, δ, ppm: 4.28 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 4.26 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.31 s (1H, C^5H), 7.00–8.20 m (8H, CH_{Ar}), 7.00 s and 7.01 s (2H, NH_2). Found, %: C 55.13; H 3.61; N 10.36. $C_{19}H_{14}ClN_3O_6$. Calculated, %: C 54.89; H 3.39; N 10.11.

1-Aminocarbonylmethyl-3-hydroxy-4-(4-chlorobenzoyl)-5-(4-ethylphenyl)-3-pyrrolin-2-one (6). Yield 1.05 g (55%), mp 253–254°C. IR spectrum, ν, cm^{-1}: 1707 (CON), 1687 ($CONH_2$), 1630 (CO), 3185 (OH), 3451 (NH_2). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, $CH_2C\underline{H}_3$), 2.53 q (2H, $C\underline{H}_2CH_3$), 4.22 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.11 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.48 s (1H, C^5H), 7.11–7.73 m (12H, CH_{Ar}), 7.18 s and 7.21 s (2H, NH_2). Found, %: C 63.51; H 5.05; N 7.28. $C_{21}H_{17}ClN_2O_4$. Calculated, %: C 63.24; H 4.80; N 7.02.

1-Aminocarbonylmethyl-3-hydroxy-5-(2-isopropylphenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (7). Yield 0.95 g (46%), mp 262–263°C. IR spectrum, ν, cm^{-1}: 1709 (CON), 1687 ($CONH_2$), 1633 (CO), 3225 (OH), 3447 (NH_2), ^{1}H NMR spectrum, δ, ppm: 1.17 d [6H, $(C\underline{H}_3)_2CH$], 2.85 q [1H, $(CH_3)_2C\underline{H}$], 4.22 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.10 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.48 s (1H, C^5H), 7.12–7.75 m (15H, CH_{Ar}), 7.20 s and 7.21 s

(2H, NH_2). Found, %: C 64.27; H 5.40; N 7.05. $C_{22}H_{21}ClN_2O_4$. Calculated, %: C 64.00; H 5.13; N 6.79.

1-Aminocarbonylmethyl-3-hydroxy-5-(4-methoxyphenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (8). Yield 0.6 g (30%), mp 242–245°C. IR spectrum, ν, cm^{-1}: 1709 (CON), 1691 ($CONH_2$), 1633 (CO), 3195 (OH), 3441 (NH_2). ^1H NMR spectrum, δ, ppm: 3.72 s (3H, OCH_3), 4.21 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.14 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.46 s (1H, C^5H), 6.86–7.74 m (11H, CH_{Ar}), 7.21 s and 7.22 s (2H, NH_2). Found, %: C 60.21; H 4.56; N 7.25. $C_{20}H_{17}ClN_2O_5$. Calculated, %: C 59.93; H 4.28; N 6.99.

1-Aminocarbonylmethyl-3-hydroxy-5-(4-methylphenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (9). Yield 0.75 g (39%), mp 209–211°C. IR spectrum, ν, cm^{-1}: 1707 (CON), 1674 ($CONH_2$), 1635 (CO), 3168 (OH), 3451 (NH_2). ^1H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.12 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.48 s (1H, C^5H), 7.09–8.09 m (11H, CH_{Ar}), 7.09 s and 7.12 s (2H, NH_2). Found, %: C 65.54; H 4.09; N 7.61. $C_{20}H_{17}ClN_2O_4$. Calculated, %: C 65.27; H 3.83; N 7.35.

1-Aminocarbonylmethyl-3-hydroxy-5-(4-fluorophenyl)-4-(4-chlorobenzoyl)-3-pyrrolin-2-one (10). Yield 0.85 g (44%), mp 264–266°C. IR spectrum, ν, cm^{-1}: 1707 (CON), 1682 ($CONH_2$), 1633 (CO), 3190 (OH), 3453 (NH_2). ^1H NMR spectrum, δ, ppm: 4.21 d (1H, $C_\alpha\underline{H}_AH_B$, CH_2CO, J = 16.0 Hz), 3.17 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.52 s (1H, C^5H), 7.10–8.10 m (8H, CH_{Ar}), 7.10 s and s 7.12 (2H, NH_2). Found, %: C 58.91; H 3.87; N 7.47. $C_{19}H_{14}ClFN_2O_4$. Calculated, %: C 58.70; H 3.63; N 7.21.

1-Aminocarbonylmethyl-4-benzoyl-3-hydroxy-5-(2-chlorophenyl)-3-pyrrolin-2-one (11). Yield 1.00 g (69%), mp 247–249°C. IR spectrum, ν, cm^{-1}: 1759 (CON), 1713 ($CONH_2$), 1624 (CO), 3188 (OH), 3451 (NH_2). ^1H NMR spectrum, δ, ppm: 4.19 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.11 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.69 s (1H, C^5H), 6.73–7.69 m (9H, CH_{Ar}), 6.07 s and 6.68 s (2H, NH_2). Found, %: C 61.83; H 4.31; N 7.80. $C_{19}H_{15}ClN_2O_4$. Calculated, %: C 61.55; H 4.08; N 7.56.

1-Aminocarbonylmethyl-4-benzoyl-3-hydroxy-5-(2-nitrophenyl)-3-pyrrolin-2-one (12). Yield 0.42 g (22%), mp 179–181°C. IR spectrum, ν, cm^{-1}: 1707 (CON), 1685 ($CONH_2$), 1630 (CO), 3192 (OH), 3456 (NH_2). ^1H NMR spectrum, δ, ppm: 4.25 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.35 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 6.09 s (1H, C^5H), 7.15–7.98 m (9H, CH_{Ar}), 6.81 s and 7.15 s (2H, NH_2). Found, %: C 60.09; H 4.22; N 11.27. $C_{19}H_{15}N_3O_6$. Calculated, %: C 59.84; H 3.96; N 11.02.

1-Aminocarbonylmethyl-4-benzoyl-3-hydroxy-5-(3-nitrophenyl)-3-pyrrolin-2-one (13). Yield 0.41 g (21%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 1703 (CON), 1680 ($CONH_2$), 1633 (CO), 3185 (OH), 3451 (NH_2). ^1H NMR spectrum, δ, ppm: 4.21 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), 5.70 s (1H, C^5H), 7.41–8.18 m (9H, CH_{Ar}), 7.08 s and s 7.10 (2H, NH_2). Found, %: C 60.05; H 4.22; N 11.26. $C_{19}H_{15}N_3O_6$. Calculated, %: C 59.84; H 3.96; N 11.02.

1-Aminocarbonylmethyl-4-benzoyl-3-hydroxy-5-(4-isopropylphenyl)-3-pyrrolin-2-one (14). Yield 0.43 g (23%), mp 270–272°C. IR spectrum, ν, cm^{-1}: 1703 (CON), 1674 ($CONH_2$), 1635 (CO), 3250 (OH), 3451 (NH_2). ^1H NMR spectrum, δ, ppm: 1.17 d [6H, $(C\underline{H}_3)_2CH$], 2.84 q [1H, $(CH_3)_2C\underline{H}$], 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.11 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.49 s (1H, C^5H), 7.11–7.73 m (16H, CH_{Ar}), 7.11 s and 7.21 s (2H, NH_2). Found, %: C 70.08; H 6.12; N 7.63. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.83; H 5.86; N 7.40.

1-Aminocarbonylmethyl-4-benzoyl-3-hydroxy-5-(4-methylphenyl)-3-pyrrolin-2-one (15). Yield 0.35 g (20%), mp 250–252°C. IR spectrum, ν, cm^{-1}: 1703 (CON), 1664 ($CONH_2$), 1624 (CO), 3220 (OH), 3464 (NH_2), ^1H NMR spectrum, δ, ppm: 2.25 s (3H, CH_3), 4.23 d (1H, $C_\alpha\underline{H}_AH_B$, J = 16.0 Hz), 3.11 d (1H, $C_\alpha H_A\underline{H}_B$, J = 16.0 Hz), 5.49 s (1H, C^5H), 7.12–8.09 m (12H, CH_{Ar}), 7.09 s and s 7.12 (2H, NH_2). Found, %: C 68.81; H 5.39; N 8.27. $C_{20}H_{18}N_2O_4$. Calculated, %: C 68.56; H 5.18; N 8.00.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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