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# Synthesis and Some Transformations of 5-Aryl-4-(4-halogenaroyl)-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones

**V. L. Gein[a,*], E. V. Pastukhova[a], A. N. Korol[a], N. V. Dozmorova[a], and E. V. Voronina[a,b]**

[a] *Perm State Pharmaceutical Academy, Perm, 614990 Russia*
[b] *Perm Institute, Plekhanov Russian University of Economics, Perm, 614990 Russia*
**e-mail: geinvl48@mail.ru*

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**Abstract**—5-Aryl-4-aroyl-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones were synthesized by a three-component reaction of aroylpyruvic acid methyl ester with a mixture of aromatic aldehyde and 2-aminoacetonitrile sulfate in glacial acetic acid in the presence of anhydrous sodium acetate. The possibility of their reactions with *p*-toluidine and hydrazine hydrate was shown.

**Keywords:** 5-aryl-4-aroyl-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones, 2-aminoacetonitrile hydrogensulfate, tetrahydropyrrole-2,3-diones, three-component reactions

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Substituted 3-hydroxy-3-pyrrolin-2-ones are five-membered nitrogen-containing heterocyclic compounds that are components of a number of biologically active substances and drugs, which determines their interest for medicine and pharmacy [1, 2].

They are of interest in organic synthesis due to possibility to react with various nucleophiles owing to the presence of two carbonyl groups at position 3 of the heterocycle and a side chain at position 4, which allows the formation of various heterocyclic fused systems [1, 2].

Previously, it has been found that the substituent at position 1 of the heterocycle significantly affects the biological activity and reactivity of 1,4,5-trisubstituted 3-hydroxy-3-pyrrolin-2-ones [1, 3].

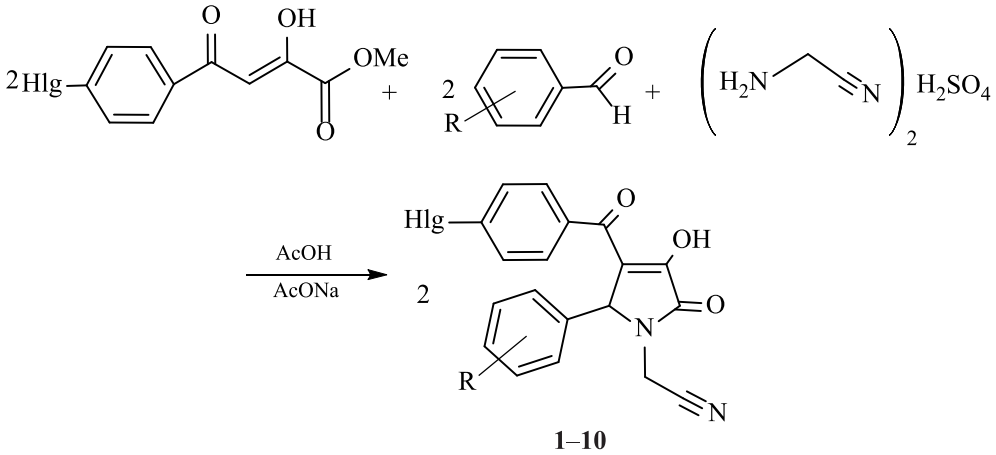
Cyano group is a part of a number of currently used drugs [4]. Therefore, it was of interest to introduce a cyanomethyl group into the position 1 of the heterocycle and further evaluate its effect on the reactivity and biological activity of newly synthesized compounds. The synthesis of 5-aryl-4-aroyl-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones has been previously described in [5]. In order to assess the effect of the halogen in the *para*-position of aroylpyruvic acid methyl ester on the reactivity and biological activity of the obtained compounds, we studied the three-component reaction of *p*-halobenzoylpyruvic acids methyl esters with a mixture of aromatic aldehyde and 2-aminoacetonitrile sulfate. The reaction proceeds upon short-term heating of an equimolar amount of reagents in the presence of anhydrous sodium acetate in glacial acetic acid to form 5-aryl-4-(-4-halogenaroyl)-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones **1**–**10** (Scheme 1).

2-Aminoacetonitrile, which does not exist in free form under normal conditions, was obtained in situ by reacting 2-aminoacetonitrile sulfate with anhydrous sodium acetate in acetic acid medium. Presumably, the reaction proceeds with the formation of an intermediate Schiff base. Further addition of methyl *p*-halobenzoylpyruvate followed by cyclization of the intermediate 4-aryl-4-amino-2-oxobutanoic acid ester furnished the corresponding 3-hydroxy-3-pyrrolin-2-ones **1**–**10** (Scheme 2).

The obtained compounds **1**–**10** are crystalline substances, soluble in DMSO, DMF, in ethanol and glacial acetic acid with heating, and insoluble in water. The IR spectra of compounds **1**–**10** show absorption bands of the lactam carbonyl group at 1696–1664 $cm^{-1}$ and a strong absorption band of the enol hydroxyl group at 3200–3040 $cm^{-1}$. The absorption band of the side chain carbonyl group is observed at 1632–1604 $cm^{-1}$.

It should be noted that we were unable to detect the absorption band of the C≡N group in the IR spectra of compounds **1**–**10**. Apparently, this is explained by the

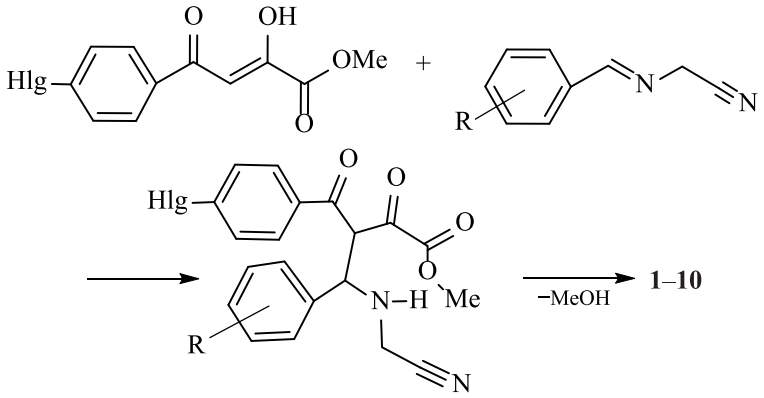
**Scheme 1.**



**1–10**

Hlg = Br, R= H (**1**), 4-MeO (**2**), 4-EtO (**3**), 4-HO-3-EtO (**4**); Hlg = Cl, R = H (**5**), 4-MeO (**6**), 4-EtO (**7**); Hlg = F, R= H (**8**), 4-MeO (**9**), 4-EtO (**10**).

**Scheme 2.**



fact that the introduction of an oxygen-containing group into the molecule leads to a significant decrease in the intensity of the C≡N absorption band [6], and the effect of this group is greater when it is attached to the same carbon atom as the nitrile, and can be indistinguishable at all.

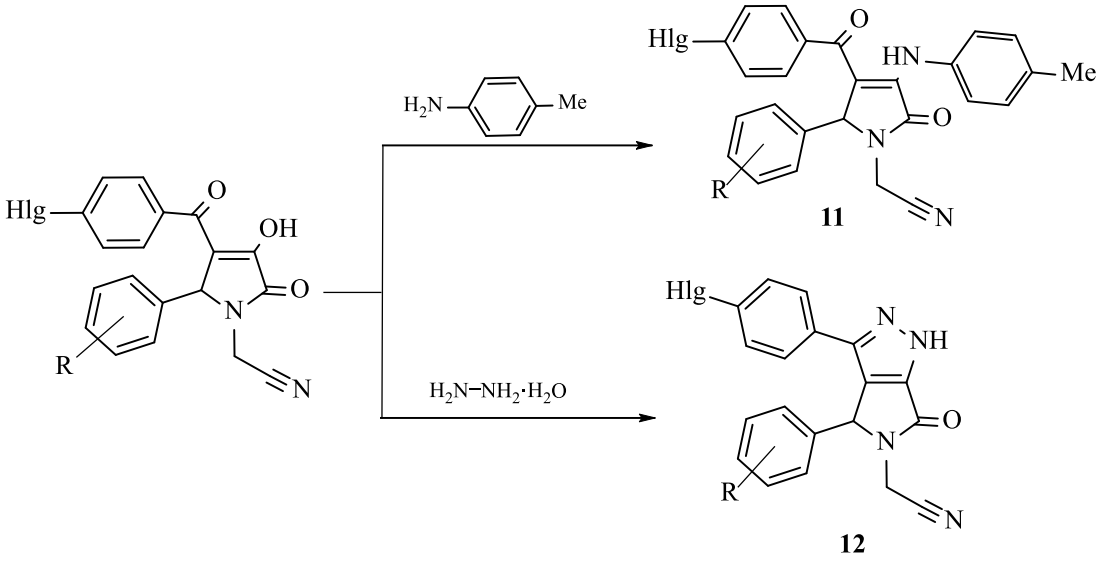
The $^1$H NMR spectra of compounds **1**–**10** contain signals of aromatic protons (6.35–8.46 ppm), a characteristic singlet of the methine proton at position 5 of the heterocycle (5.36–5.69 ppm), two doublets of cyanomethyl group protons at the nitrogen atom of the heterocycle (3.96–4.54 ppm, $J$ = 16.7–18.6 Hz) and the signal of the OH-group proton in position 3 of the heterocycle (11.98–12.31 ppm). The signal of the OH group proton in position 3 of the heterocycle in the spectra of compounds **1**–**10** is strongly broadened due to deuterium exchange [2].

In order to study the reactivity of the obtained compounds **1**–**10**, we performed their reactions with *p*-toluidine and hydrazine hydrate [7, 8]. Thus, the reaction of 5-phenyl-4-(4-chlorobenzoyl)-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-one **5** with *p*-toluidine upon refluxing in acetic acid for 2 h yielded 5-phenyl-4-(4-chlorobenzoyl)-3-(4-methylphenylamino)-1-cyanomethyl-3-pyrrolin-2-one **11** (Scheme 3). Structure of compound **11** was confirmed by $^1$H NMR data.

The $^1$H NMR spectrum of compound **11** contains signals of aromatic protons in the range of 6.78–7.33 ppm, a singlet of the methine proton at the C$^5$ atom at 5.64 ppm, and two doublets of methylene group protons in the α-position of the cyanomethyl substituent at 4.20, 4.24 ppm ($C^{\alpha}H_AH_B$) and 4.48, 4.53 ppm ($C^{\alpha}H_AH_B$). The NH-proton of the aminotolyl substituent in position 3 of the heterocycle resonates at 9.04 ppm; the singlet at 1.92 ppm corresponds to the protons of the *p*-methyl group.

5-Aryl-4-(4-halogenaroyl)-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-ones have two reaction sites

**Scheme 3.**




Hlg = Cl, R= H (**11**); Hlg = Br, R = H (**12**).

at positions 3 and 4 of the pyrrole ring. Therefore, reactions of these compounds with such a binucleophilic agent as hydrazine hydrate allows to obtain a fused heterocyclic system [8]. So, the reaction of 5-phenyl-4-bromobenzoyl-3-hydroxy-1-cyanomethyl-3-pyrrolin-2-one **1** and hydrazine hydrate in glacial acetic acid produced 6-*p*-bromophenyl-5-phenyl-4-cyanomethyl-3,5-dihydropyrrolo[3,4-*c*]pyrazol-3-one **12** (Scheme 3).

Structure of compound **12** was confirmed by $^1$H NMR spectroscopy data. The $^1$H NMR spectrum of compound **12** contains signals of aromatic protons in the range of 7.26–7.54 ppm, a singlet of the NH proton at 13.88–13.96 ppm, a singlet of the methine proton at the $C^5$ atom in the range of 6.0 ppm, as well as two doublets of the methylene protons at the α-position of the cyanomethyl substituent at 4.56, 4.52 ppm ($C^{\alpha}H_AH_B$) and 4.20, 4.15 ppm ($C^{\alpha}H_AH_B$).

Thus, the introduction of a halogen at the *p*-position of aroylpyruvic acid methyl ester does not significantly affect the formation of a fused heterocyclic system and the reactivity of the carbonyl group at position 3 of the heterocycle.

## EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrometer from KBr pellets. $^1$H NMR spectra were registered on a Bruker AM-300 (300 MHz) instrument from DMSO-$d_6$ solutions relative to internal TMS.

**General procedure for the preparation of compounds 1–10.** To a solution of 0.05 mol of aminoacetonitrile hydrogen sulfate in acetic acid was added 0.1 mol of sodium acetate. The resulting mixture was stirred until complete dissolution. Then a mixture of 0.1 mol of aromatic aldehyde and 0.01 mol of 4-aroylpyruvic acid methyl ester in dioxane was added. The resulting mixture was heated until the components dissolved and kept at room temperature for 1 day. The precipitate formed upon cooling was filtered off and recrystallized from ethanol.

**4-Bromobenzoyl-3-hydroxy-5-phenyl-1-cyanomethyl-3-pyrrolin-2-one (1).** Yield 77%, mp 252–256°C. IR spectrum, ν, cm$^{-1}$: 3160 (OH), 1698 (CON), 1638 (CO). $^1$H NMR spectrum, δ, ppm: 4.36 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.21 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.43 s (1H, $C^5H$), 7.27–7.55 m (9H, $CH_{Ar}$), 11.62 s (1H, OH). Found, %: C 57.45; H 3.30; N 7.05. $C_{19}H_{13}BrN_2O_3$. Calculated, %: C 57.15; H 3.00; N 6.75.

**4-Bromobenzoyl-3-hydroxy-5-(4-methoxyphenyl)-1-cyanomethyl-3-pyrrolin-2-one (2).** Yield 59%, mp 234–236°C. IR spectrum, ν, cm$^{-1}$: 3176 (OH), 1698 (CON), 1638 (CO). $^1$H NMR spectrum, δ, ppm: 3.66 s (3H, $OCH_3$), 4.33 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.7 Hz), 4.19 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.37 s (1H, $C^5H$), 6.75–7.55 m (8H, $CH_{Ar}$), 12.15 s (1H, OH). Found, %: C 56.22; H 3.54; N 6.56. $C_{20}H_{15}BrN_2O_4$. Calculated, %: C 55.92; H 3.24; N 6.26.

**4-Bromobenzoyl-3-hydroxy-1-cyanomethyl-5-(4-ethoxyphenyl)-3-pyrrolin-2-one (3).** Yield 64%, mp 230–234°C. IR spectrum, ν, $cm^{-1}$: 3180 (OH), 1698 (CON), 1638 (CO). $^1H$ NMR spectrum, δ, ppm: 1.34 t (5H, $OCH_2CH_3$), 3.96 q (5H, $OCH_2CH_3$), 4.33 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 18.6 Hz), 4.19 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 16.7 Hz), 5.37 s (1H, $C^5H$), 6.75–7.56 m (8H, $CH_{Ar}$), 12.09 s (1H, OH). Found, %: C 57.16; H 3.88; N 6.35. $C_{21}H_{17}BrN_2O_4$. Calculated, %: C 56.86; H 3.58; N 6.05.

**4-Bromobenzoyl-3-hydroxy-5-(4-hydroxy-3-ethoxyphenyl)-1-cyanomethyl-3-pyrrolin-2-one (4).** Yield 70%, mp 239–242°C. IR spectrum, ν, $cm^{-1}$: 3054 (OH), 1712 (CON), 1632 (CO). $^1H$ NMR spectrum, δ, ppm: 4.32 d ($C\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.21 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.33 s (1H, $C^5H$), 6.69–7.58 m (7H, $CH_{Ar}$), 11.40 s (1H, OH). Found, %: C 55.16; H 3.75; N 6.13. $C_{21}H_{17}BrN_2O_5$. Calculated, %: C 54.86; H 3.45; N 5.83.

**3-Hydroxy-5-phenyl-4-chlorobenzoyl-1-cyanomethyl-3-pyrrolin-2-one (5).** Yield 68%, mp 217–226°C. IR spectrum, ν, $cm^{-1}$: 3176 (OH), 1696 (CON), 1638 (CO). $^1H$ NMR spectrum, δ, ppm: 4.35 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.20 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 18.5 Hz), 5.41 s (1H, $C^5H$), 7.26–7.68 m (9H, $CH_{Ar}$), 11.49 s (1H, OH). Found, %: C 64.69; H 3.71; N 7.94. $C_{19}H_{13}ClN_2O_3$. Calculated, %: C 64.39; H 3.41; N 7.64.

**3-Hydroxy-5-(4-methoxyphenyl)-4-chlorobenzoyl-1-cyanomethyl-3-pyrrolin-2-one (6).** Yield 62%, mp 205–210°C. IR spectrum, ν, $cm^{-1}$: 3160 (OH), 1700 (CON), 1636 (CO). $^1H$ NMR spectrum, δ, ppm: 3.67 s (3H, $OCH_3$), 4.33 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.4 Hz), 4.17 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 16.7 Hz), 5.36 s (1H, $C^5H$), 7.17–7.69 m (8H, $CH_{Ar}$), 11.28 s (1H, OH). Found, %: C 62.75; H 3.95; N 7.32. $C_{20}H_{15}ClN_2O_4$. Calculated, %: C 62.45; H 3.65; N 7.02.

**3-Hydroxy-4-chlorobenzoyl-1-cyanomethyl-5-(4-ethoxyphenyl)-3-pyrrolin-2-one (7).** Yield 52%, mp 210–215°C. IR spectrum, ν, $cm^{-1}$: 3180 (OH), 1700 (CON), 1636 (CO). $^1H$ NMR spectrum, δ, ppm: 1.26 t (5H, $OCH_2CH_3$), 3.88 q (5H, $OCH_2CH_3$), 4.33 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.7 Hz), 4.20 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.38 s (1H, $C^5H$), 6.73–7.69 m (8H, $CH_{Ar}$), 11.37 s (1H, OH). Found, %: C 63.56; H 4.32; N 7.06. $C_{21}H_{17}ClN_2O_4$. Calculated, %: C 63.26; H 4.02; N 6.76.

**3-Hydroxy-5-phenyl-4-fluorobenzoyl-1-cyanomethyl-3-pyrrolin-2-one (8).** Yield 71%, mp 223–227°C. IR spectrum, ν, $cm^{-1}$: 3056 (OH), 1712 (CON), 1625 (CO). $^1H$ NMR spectrum, δ, ppm: 4.36 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.22 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.43 s (1H, $C^5H$), 7.07–7.73 m (9H, $CH_{Ar}$), 11.57 s (1H, OH). Found, %: C 67.85; H 3.90; N 8.33. $C_{19}H_{13}FN_2O_3$. Calculated, %: C 67.55; H 3.60; N 8.03.

**3-Hydroxy-5-(4-methoxyphenyl)-4-fluorobenzoyl-1-cyanomethyl-3-pyrrolin-2-one (9).** Yield 94%, mp 210–214°C. IR spectrum, ν, $cm^{-1}$: 3064 (OH), 1712 (CON), 1607 (CO). $^1H$ NMR spectrum, δ, ppm: 3.68 s (3H, $OCH_3$), 4.34 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.20 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.40 s (1H, $C^5H$), 6.75–7.91 m (8H, $CH_{Ar}$), 11.64 s (1H, OH). Found, %: C 65.57; H 4.13; N 7.65. $C_{20}H_{15}FN_2O_4$. Calculated, %: C 65.27; H 3.83; N 7.35.

**3-Hydroxy-4-fluorobenzoyl-1-cyanomethyl-5-(4-ethoxyphenyl)-3-pyrrolin-2-one (10).** Yield 85%, mp 201–206°C. IR spectrum, ν, $cm^{-1}$: 3168 (OH), 1712 (CON), 1604 (CO). $^1H$ NMR spectrum, δ, ppm: 1.26 t (5H, $OCH_2CH_3$), 3.96 q (5H, $OCH_2CH_3$), 4.34 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 17.6 Hz), 4.21 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 17.6 Hz), 5.39 s (1H, $C^5H$), 6.74–7.80 m (8H, $CH_{Ar}$), 12.29 s (1H, OH). Found, %: C 66.31; H 4.50; N 7.36. $C_{21}H_{17}FN_2O_4$. Calculated, %: C 66.01; H 4.2; N 7.06.

**3-(4-Methylphenylamino)-5-phenyl-4-(4-chlorobenzoyl)-1-cyanomethyl-3-pyrrolin-2-one (11).** To a solution of 0.002 mol of compound **5** in 10 mL of glacial acetic acid was added 0.004 mol of *p*-toluidine. The resulting mixture was refluxed for 2 h. The precipitate that formed upon cooling was filtered off and recrystallized from acetic acid. Yield 35%, mp 150–156°C. $^1H$ NMR spectrum, δ, ppm: 1.92 s (3H, $CH_3$), 4.22 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 20.0 Hz), 4.51 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 16.0 Hz), 5.64 s (1H, $C^5H$), 6.78–7.33 m (14H, $CH_{Ar}$), 11.82 s (1H, OH), 9.04 s (1H, NH). Found, %: C 70.67; H 4.56; N 9.51. $C_{26}H_{20}ClN_3O_2$. Calculated, %: C 70.37; H 4.26; N 9.21.

**6-(4-Bromophenyl)-5-phenyl-4-cyanomethyl-3,5-dihydropyrrolo[3,4-*c*]pyrazol-3-one (12).** To a solution of 0.002 mol of compound **1** in 10 mL of glacial acetic acid was added 0.002 mol of hydrazine hydrate. The resulting mixture was refluxed for 2 h. The precipitate that formed upon cooling was filtered off and recrystallized from acetic acid. Yield 57%, mp 265–267°C. $^1H$ NMR spectrum, δ, ppm: 4.18 d ($\underline{H}_AH_B$, $CH_2CN$, $J$ = 16.0 Hz), 4.54 d ($H_A\underline{H}_B$, $CH_2CN$, $J$ = 20.0 Hz), 6.0 s (1H, $C^5H$), 7.26–7.54 m (9H, $CH_{Ar}$). Found, %: C 58.03; H 3.33; N 14.25. $C_{19}H_{13}BrN_4O$. Calculated, %: C 57.73; H 3.03; N 13.95.

## CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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