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LETTERS TO THE EDITOR

Reactions of 5-Aryl-4-acyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrroline-2-ones with Butylamine, Hydroxylamine, and Semicarbazide

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Some 1,4,5-trisubstituted tetrahydropyrrole-2,3-diones exhibit nootropic, analgesic, and anti-inflammatory activity [1]. Earlier, 5-aryl-4-acyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-ones have been obtained [2], and their interaction with arylamines was studied [3].

Extending the study of reactivity of substituted 3-pyrrolin-2-ones, herein we report on reactions of 5-aryl-4-acyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-ones with hydroxylamine, semicarbazide, and butylamine.

Refluxing a 1 : 2 mixture of 5-aryl-4-aroyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-ones and hydroxylamine in glacial acetic acid during 3 h resulted in formation of 4-aroyl-1-(4-hydroxyphenyl)-5-aryltetrahydropyrrole-2,3-diones 3-oximes **Ia**–**Ic**. Compounds **Ia**–**Ic** were crystalline substances, soluble in DMF and DMSO as well as (upon heating) in ethanol and isopropanol.

Structures of the obtained compounds were confirmed by NMR and IR spectroscopy, and mass spectrometry. The spectral data indicated that compounds **Ia**–**Ic** existed predominantly in the oxime, being apparently stabilized by an intramolecular hydrogen bond.

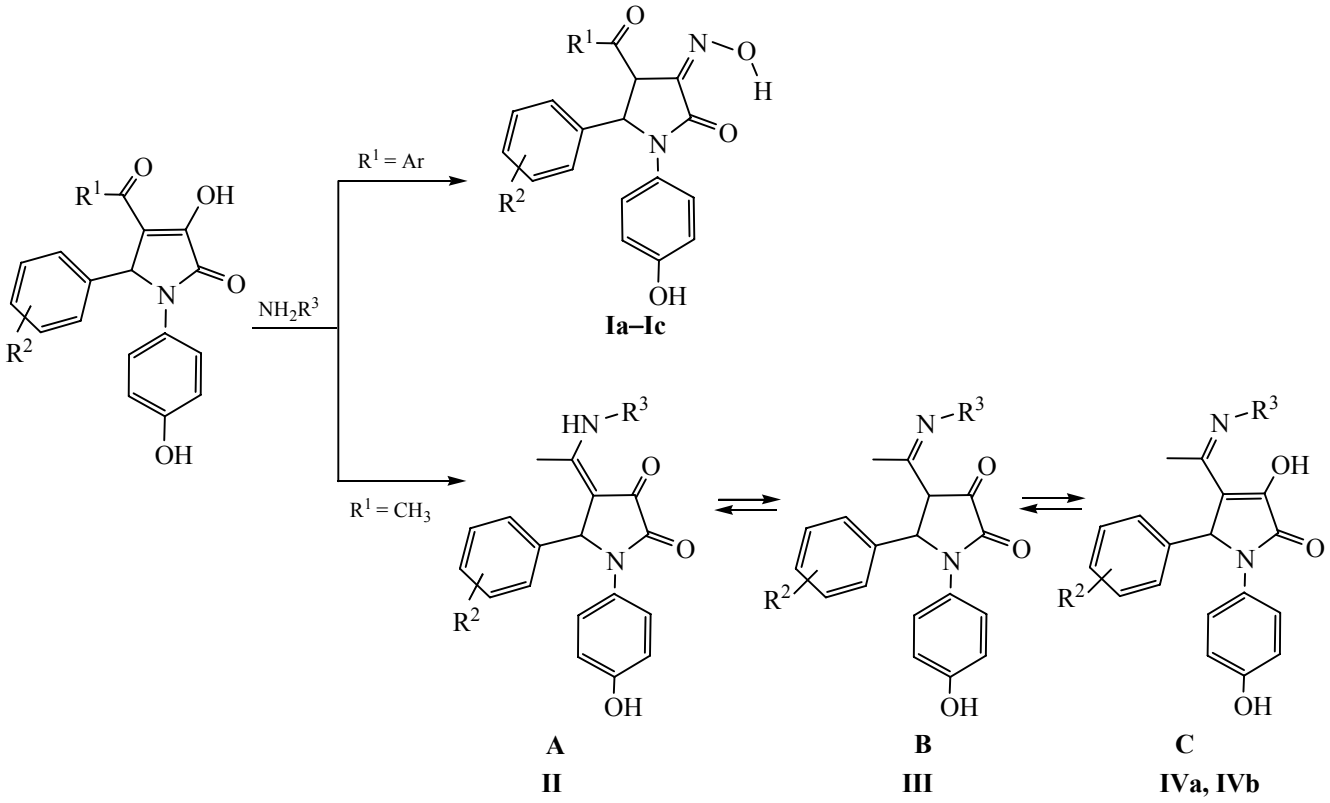
Refluxing a mixture of 5-phenyl-4-acetyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-one and butylamine in glacial acetic acid during 3 h resulted in formation of 4-(1-butylaminoethylene)-1-(4-hydroxyphenyl)-5-phenylpyrrolidine-2,3-dione **II**. The spectroscopy data suggested that compound **II** existed in the enamine form **A** stabilized by an intramolecular hydrogen bonding.

Interaction of 4-acetyl-1-(4-hydroxyphenyl)-5-phenyl-3-hydroxy-3-pyrrolin-2-one with hydroxylamine involved carbonyl group of the acetyl moiety that was more reactive than the aroyl group, presumably due to the absence of conjugation with the aromatic ring. The reaction resulted in formation of 5-phenyl-1-(4-hydroxyphenyl)-4-(1-hydroxyiminoethylene)pyrrolidine-2,3-dione **III**. According to the spectral data, the resulting oxime existed in the imine form **B**.

Reaction of 5-aryl-4-acetyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-one with semicarbazide proceeded similarly to give 4-(1-aminocarbonylamino-iminoethylene)-5-aryl-1-(4-hydroxyphenyl)pyrrolin-2-ones **IVa** and **IVb**. Reaction of the latter with iron(III) chloride was accompanied with red coloration of the mixture. The results suggested that the obtained compounds **IVa** and **IVb** existed in the imino form **C** with enolization of the carbonyl group at the position 3 of the heterocycle (Scheme 1).

4-Benzoyl-1-(4-hydroxyphenyl)-5-(4-chlorophenyl)-pyrrolidine-2,3-dione-3-oxime (Ia). A mixture of 0.01 mol of 4-benzoyl-1-(4-hydroxyphenyl)-3-hydroxy-5-(4-chlorophenyl)-3-pyrrolin-2-one and 0.02 mol of hydroxylamine was refluxed in glacial acetic acid during 3 h, then cooled, and treated with ethanol. The precipitate was filtered off and recrystallized from

Scheme 1.



R^1 = Ph, R^2 = 4-Cl (**Ia**); R^1 = 4-$CH_3C_6H_4$, R^2 = 4-Br (**Ib**), R^2 = 3-NO_2 (**Ic**); R^1 = CH_3, R^2 = H, R^3 = C_4H_9 (**II**); R^1 = CH_3, R^2 = H, R^3 = OH (**III**); R^1 = CH_3, R^2 = H, R^3 = $NHCONH_2$ (**IVa**); R^1 = CH_3, R^2 = 2-Cl, R^3 = $NHCONH_2$ (**IVb**).

ethanol. Yield 0.16 g (38%), mp 220–221°C. IR spectrum, ν, cm^{-1}: 1630 (CO), 1695 (CON), 3160 (OH), 3320 (NOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 7.08 m ($13H_{arom}$), 9.37 s (1H, OH), 8.27 s (1H, NOH), 5.93–5.97 d (1H, C^4H, *J* 10.0), 4.78–4.85 d (1H, C^5H, *J* 10.0). Found, %: C 65.64; H 4.27; N 6.56. $C_{23}H_{17}ClN_2O_4$. Calculated, %: C 65.55; H 4.25; N 6.43.

5-(4-Bromophenyl)-1-(4-hydroxyphenyl)-4-(4-methylbenzoyl)pyrrolidine-2,3-dione-3-oxime (Ib) was prepared similarly. Yield 0.20 g (42%), mp 222–223°C. IR spectrum, ν, cm^{-1}: 1630 (C=O), 1695 (CON), 3163 (OH), 3300 (NOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 6.90 m ($12H_{arom}$), 9.51 s (1H, OH), 8.31 s (1H, NOH), 6.14 d (1H, C^4H, *J* 9.85), 4.83 d (1H, C^5H, *J* 10.0), 2.26 s (3H, CH_3). Mass-spectrum, *m*/*z* (I_{rel}, %): 480 (100) $[M]^+$. Found, %: C 60.15; H 4.05; N 5.89. $C_{24}H_{19}BrN_2O_4$. Calculated, %: C 60.14; H 4.00; N 5.84.

1-(4-Hydroxyphenyl)-4-(4-methylbenzoyl)-5-(3-nitrophenyl)pyrrolidine-2,3-dione-3-oxime (Ic) was prepared similarly. Yield 0.25 g (56%), mp 218–219°C. IR spectrum, ν, cm^{-1}: 1630 (C=O), 1695 (CON), 3163 (OH), 3300 (NOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 7.24 m (5H, C_6H_5), 9.58 s (1H, OH), 8.47 s (1H, NOH), 6.14 d (1H, C^4H), 4.83 d (1H, C^5H), 2.24 s (1H, CH_3). Mass-spectrum, *m*/*z* (I_{rel}, %): 445 (100) $[M]^+$. Found, %: C 64.70; H 4.25; N 9.40. $C_{24}H_{19}N_3O_6$. Calculated, %: C 64.72; H 4.30; N 9.43.

4-(1-Butylaminoethylene)-1-(4-hydroxyphenyl)-5-phenylpyrrolidine-2,3-dione (II) was prepared similarly from 0.01 mol of 5-phenyl-4-acetyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrroline-2-one and 0.02 mol of butylamine. Yield 0.14 g (38%), mp 202–204°C. IR spectrum, ν, cm^{-1}: 1705 (COCON), 3152 (OH), 3283 (NH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 7.20 m ($9H_{arom}$), 9.32 s (1H, OH), 11.20 t (1H, NHBut), 5.95 s (1H, C^5H), 1.15 t (3H, CH_3But), 1.85 s (3H,CH_3CO). Found, %: C 72.53; H 6.63; N 7.66. $C_{22}H_{24}N_2O_3$. Calculated, %: C 72.51; H 6.64; N 7.69.

1-(4-Hydroxyphenyl)-4-(1-hydroxylaminoethylene)-5-phenylpyrrolidine-2,3-dione (III) was prepared similarly. Yield 0.18 g (55%), mp 223–225°C. IR

spectrum, ν, cm^{-1}: 1650 (C=O), 3560 (OH), 3350 (NOH). ^1H NMR spectrum, δ, ppm: 7.18 m ($9H_{arom}$), 9.27 s (1H, OH), 7.95 s (1H, NOH), 5.85 s (1H, C^4H), 4.00 s (1H, C^5H), 1.11 s (3H, CH_3). Found, %: C 66.62; H 4.99; N 8.66. $C_{18}H_{16}N_2O_4$. Calculated %: C 66.66; H 4.97; N 8.64.

4-(1-Aminocarbonylaminoiminoethylene)-5-phenyl-1-(4-hydroxyphenyl)pyrrolidine-2,3-dione (IVa). 1.23 g (0.011mol) of semicarbazide hydrochloride and 1.82 g (0.01 mol) of 5-phenyl-4-acetyl-1-(4-hydroxyphenyl)-3-hydroxy-3-pyrrolin-2-one were added to a solution of MeONa prepared from 0.25 g (0.011 mol) of Na and 15 mL of MeOH. The reaction mixture was refluxed for 15 min. After cooling, the precipitate was filtered off and recrystallized from ethanol. Yield 1.8 g (53%), mp 215–216°C. IR spectrum, ν, cm^{-1}: 1672 (C=O), 1624 (CONH), 3056 (OH), 3288 (NH). ^1H NMR spectrum, δ, ppm: 7.27 m ($9H_{arom}$), 10.62 s (1H, OH), 6.43 s (2H, NH_2), 6.20 s (1H, C^5H), 2.05 s (3H, CH_3). Found, %: C 56.77; H 5.23; N 11.52. $C_{20}H_{19}N_3O_4$. Calculated, %: C 56.74; H 5.24; N 11.50.

4-(1-Aminocarbonylaminoiminoethylene)-1-(4-hydroxyphenyl)-5-(2-chlorophenyl)pyrrolidine-2,3-dione (IVb) was prepared similarly. Yield 0.15 g (37%), mp 218–219°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 1610 (CONH), 3160 (OH), 3300 (NH). ^1H NMR spectrum, δ, ppm: 7.13 m ($8H_{arom}$), 10.61 s (1H, OH), 6.47 s (2H, NH_2), 6.16 s (1H, C^5H), 2.11 s (3H, CH_3). Found, %: C 56.90; H 4.28; N 13.90. $C_{19}H_{17}ClN_4O_4$. Calculated, %: C 56.94; H 4.28; N 13.98.

IR spectra were recorded with a Specord M-80 spectrophotometer in paraffin oil. ^1H NMR spectra were recorded with Bruker AM-300 (300 MHz) and Bruker AM-500 (500 MHz) spectrometers in DMSO-d_6, relative to internal TMS. Mass spectra were registered with a Finnigan MAT INCOS-50 instrument (70 eV). Elemental analysis was performed using a Perkin Elmer 2400 instrument. Melting points were determined with a Melting Point M-565 apparatus.

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