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Reactions of 1-(4-Aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones with Arylamines and Hydrazine Hydrate

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Abstract—Depending on the reaction condition, 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones reacted with aromatic amines to yield 3-arylamino-3-pyrrolin-2-ones or 4-[aryl (arylamino) methylene]tetrahydropyrrole-2,3-diones. Reactions of 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones with hydrazine hydrate afforded pyrrolo[3,4-*c*]pyrazol-6-ones.

Keywords: 3-hydroxy-3-pyrrolin-2-ones, arylamines, hydrazine hydrate, tetrahydropyrrole-2,3-dione, pyrrolo-[3,4-*c*]pyrazol-6-ones

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1,4,5-Trisubstituted tetrahydropyrrole-2,3-diones and their derivatives are of interest due to their biological activity and synthetic capabilities. Tetrahydropyrrole-2,3-dione reacted readily with various mono- and binucleophiles to give amino derivatives and fused heterocyclic systems [1].

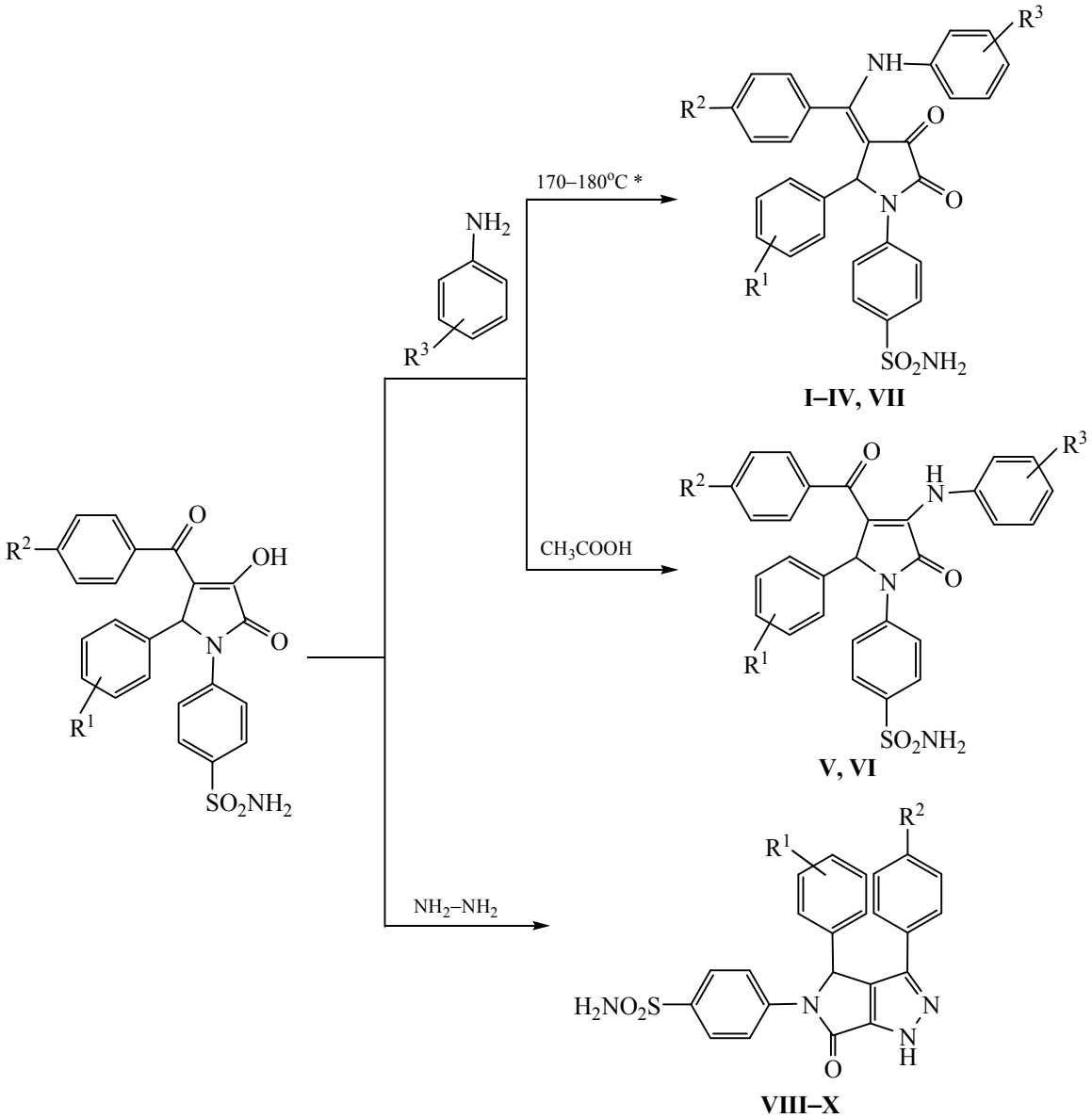
In continuation of our studies on the reactivity of 3-hydroxy-3-pyrrolin-2-ones, we have investigated the reactions of 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones [2] with various aromatic amines (*p*- and *o*-toluidines, *o*-aminophenol, 4-ethylaniline). Depending on the reaction conditions and the structure of the starting compounds, the reactions afforded 1-(4-aminosulfonylphenyl)-5-aryl-4-[aryl(arylamino)methylene]tetrahydropyrrole-2,3-diones **I**–**IV**, **VII** or 1-(4-aminosulfonylphenyl)-5-aryl-3-arylamino-4-aroyl-3-pyrrolin-2-ones **V**, **VI**. Thus, maintaining the starting reactants at 170–180°C for 5–10 min in the solvent-free conditions resulted in only 1-(4-aminosulfonylphenyl)-5-aryl-4-[aryl(arylamino)methylene]-tetrahydropyrrole-2,3-diones **I**–**IV**. Compound **VII** was formed when the reaction was performed in acetic acid. Tetrahydropyrrole-2,3-diones **I**–**IV**, **VII** were bright yellow or orange crystalline substances. They were soluble in dimethyl sulfoxide and dimethylformamide; in glacial acetic acid and dioxane under heating, slightly soluble in alcohol and insoluble in water.

The ^{1}H NMR spectra of **I**–**IV**, **VII** contained the signals of aromatic protons and sulfamide group (6.20–7.80 ppm). The signals of the methine proton in the position 5 of the heterocycle appeared in the range of 6.11–6.37 ppm. The NH protons resonated at 12.40–12.53 ppm. The signals of other groups were observed in the expected areas (Scheme 1).

In the IR spectra of **I**–**IV**, **VII** there were the absorption bands of amino (3439–3280, 3320–3185, 3200–3100 cm^{-1}), lactam carbonyl (1712–1696 cm^{-1}), ketone carbonyl (1632–1616 cm^{-1}), and SO_2 (1380–1352, 1168–1160 cm^{-1}).

The reactions of 1-(4-aminosulfonylphenyl)-5-aryl-3-hydroxy-4-(4-chlorobenzoyl)-3-pyrrolin-2-ones with 4-ethylaniline occurred under reflux in glacial acetic acid for 1–2 h to give 1-(4-aminosulfonylphenyl)-5-aryl-4-(4-chlorobenzoyl)-3-(4-ethylphenylamino)-3-pyrrolin-2-ones **V** and **VI**. The latter were yellow crystalline substances, soluble in DMF and DMSO, under heating in glacial acetic acid, dioxane and acetonitrile, insoluble in water.

Scheme 1.



* CH_3COOH for **VII**. $R^1 = R^2 = H$, $R^3 = 4\text{-}CH_3$ (**I**), $R^1 = 3\text{-}NO_2$, $R^2 = H$, $R^3 = 4\text{-}CH_3$ (**II**), $R^1 = R^2 = H$, $R^3 = 2\text{-}CH_3$ (**III**), $R^1 = R^2 = H$, $R^3 = 2\text{-}OH$ (**IV**), R^1 =4-Cl, $R^2 = Cl$, $R^3 = 4\text{-}C_2H_5$ (**V**), $R^1 = 4\text{-}F$, $R^2 = Cl$, $R^3 = 4\text{-}C_2H_5$ (**VI**), $R^1 = 4\text{-}NO_2$, $R^2 = Cl$, $R^3 = 4\text{-}C_2H_5$ (**VII**), $R^1 = R^2 = H$ (**VIII**), $R^1 = 2,5\text{-}(CH_3O)_2$, $R^2 = H$ (**IX**), $R^1 = 3\text{-}F$, $R^2 = H$ (**X**).

In the ^1H NMR spectra of **V** and **VI** there were the signals of aryl and sulfonamide groups at 6.66–7.71 ppm. The methine proton in the position 5 of the heterocycle resonated at 6.36 ppm. The signals of NH group were observed in the range of 8.74–8.76 ppm. The protons of CH_3CH_2-group appeared at 1.08–1.09 and 2.38–2.44 ppm.

The IR spectra of **V** and **VI** contained the absorption bands of the amino (3296–3288, 3220–3210 cm^{-1}), the lactam carbonyl (1700 cm^{-1}), ketone carbonyl (1640–1635 cm^{-1}), and SO_2 (1376–1352, 1168–1164 cm^{-1}) moieties.

The obtained data indicate that compounds **I–VII** exist predominantly in the enamine form.

The reactions of 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones with aromatic amines proceed in two directions, presumably, due the fact that the oxalyl-containing substrates react with

nucleophiles in the keto form, although they exist preferably in the enol form [3, 4]. Therefore, under solvent-free conditions the reaction occurs via substitution of the oxygen atom of the side chain in the position 4, since the carbonyl group exists in the ketone form, to give compounds **I**–**IV**. When the reaction is carried out in acetic acid, the isomerization of the starting 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones into the ketone form occurs. The aromatic amine attacks the carbonyl group in the position *3* to form 1-(4-aminosulfonylphenyl)-5-aryl-3-arylamino-4-aroyl-3-pyrrolin-2-ones **V** and **VI**. The formation of 1-(4-aminosulfonylphenyl)-5-(4-nitrophenyl)-4-[4-chlorophenyl(4-ethylphenylamino)methylene]tetrahydropyrrole-2,3-dione **VII** in this reaction may be presumably due to a strong electron-withdrawing effect of NO_2-group on the side-chain carbonyl group.

Analysis of the ^{1}H NMR spectra of **V** and **VI** indicates the formation of a minor product (less than 1–2%) 1-(4-aminosulfonylphenyl)-5-aryl-4-[aryl(arylamino)methylene]tetrahydropyrrole-2,3-dione.

Aiming to synthesize fused systems we investigated the reactions of 1-(4-aminosulfonylphenyl)-5-aryl-4-benzoyl-3-hydroxy-3-pyrrolin-2-ones with hydrazine hydrate. The reactions proceeded in glacial acetic acid under reflux for 1–2 h to afford 5-(4-aminosulfonylphenyl)-4-aryl-3-phenyl-4,6-dihydropyrrolo[3,4-*c*]-pyrazol-6-ones **VIII**–**X**. Compounds **VIII**–**X** were white or pale yellow crystalline substances, soluble in DMSO and DMF, under heating in dioxane, glacial acetic acid, isopropanol and ethanol, and insoluble in water.

The ^{1}H NMR spectra of **VIII**–**X** contained the signals of the aryl and sulfamide moieties (6.46–8.00 ppm), of the methine proton in the position *4* of the heterocycle (6.78–6.86 ppm), and the NH-group (13.96–14.05 ppm).

In the IR spectra of **VIII**–**X** there were the absorption bands of the amino (3432–3328, 3392–3245, 3296–3152 cm^{-1}), the lactam carbonyl (1716–1696 cm^{-1}), and SO_2-groups (1380–1328, 1172–1168 cm^{-1}).

Therefore, depending on the reaction conditions 1-(4-aminosulfonylphenyl)-5-aryl-4-aroyl-3-hydroxy-3-pyrrolin-2-ones react with arylamines to form 3-arylamino-3-pyrrolin-2-ones or 4-[aryl(arylamino)methylene]tetrahydropyrrole-2,3-diones. The reactions with hydrazine hydrate afforded pyrrolo[3,4-*c*]pyrazol-6-ones.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-300 (300 MHz) and Bruker DRX 500 (500.13 MHz) spectrometers in DMSO-d_6, internal reference TMS. The IR spectra were registered on a Specord M-80 instrument frommulls in mineral oil. Elemental analysis was performed on a Perkin Elmer 2400 instrument. Mass spectra were obtained on a Finnigan MAT INCOS-50 spectrometer at ionization electrons energy of 70 eV. Melting points were determined on a Melting Point M-565 instrument.

1-(4-Aminosulfonylphenyl)-5-phenyl-4-[phenyl-(4-methylphenylamino)methylene]tetrahydropyrrole-2,3-dione (I). A mixture of 0.005 mol of 1-(4-aminosulfonylphenyl)-4-benzoyl-3-hydroxy-5-phenyl-3-pyrrolin-2-one and 0.0055 mol of *p*-toluidine was heated at 170–180°C for 5–10 min in the absence of a solvent until gas evolution stopped and the reaction mixture solidified. After cooling, the residue was treated with ethanol, filtered off and recrystallized from glacial acetic acid. Yield 1.07 g (41%), mp 274–275°C. IR spectrum, ν, cm^{-1}: 3280, 3185, 3100 (NH_2, NH), 1708 (CON), 1620 (C=O), 1368, 1160 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.15 s (3H, CH_3), 6.14 s (1H, C^5H), 6.51–7.74 m (20H, CH_{arom}, SO_2NH_2), 12.53 s (1H, NH). Found, %: C 68.94, 68.67; H 4.80, 4.88; N 8.08, 7.98; S 6.04, 6.21. $C_{30}H_{25}N_3O_4S$. Calculated, %: C 68.82; H 4.81; N 8.02; S 6.12.

1-(4-Aminosulfonylphenyl)-5-(3-nitrophenyl)-4-[phenyl(4-methylphenylamino)methylene]tetrahydropyrrole-2,3-dione (II) was obtained similarly. Yield 1.82 g (64%), mp 323–324°C. IR spectrum, ν, cm^{-1}: 3336, 3264, 3168 (NH_2, NH), 1712 (CON), 1632 (C=O), 1364, 1168 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.12 s (3H, CH_3), 6.37 s (1H, C^5H), 6.65–7.80 m (19H, CH_{arom}, SO_2NH_2), 12.48 s (1H, NH). Found, %: C 63.48, 63.25; H 4.31, 4.18; N 9.80, 9.93; S 5.56, 5.72. $C_{30}H_{24}N_4O_6S$. Calculated, %: C 63.37; H 4.25; N 9.85; S 5.64.

1-(4-Aminosulfonylphenyl)-5-phenyl-4-[phenyl-(2-methylphenylamino)methylene]tetrahydropyrrole-2,3-dione (III) was obtained similarly. Yield 1.28 g (49%), mp 274–275°C. IR spectrum, ν, cm^{-1}: 3304, 3192, 3136 (NH_2, NH), 1704 (CON), 1616 (C=O), 1368, 1160 (SO_2). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 6.16 s (1H, C^5H), 6.53–7.76 m (20H, CH_{arom}, SO_2NH_2), 12.53 s (1H, NH). Found, %: C 68.81, 68.88; H 4.79, 4.86; N 8.08, 7.96; S 6.05, 6.21. $C_{30}H_{25}N_3O_4S$. Calculated, %: C 68.82; H 4.81; N 8.02; S 6.12.

1-(4-Aminosulfonylphenyl)-5-phenyl-4-[phenyl-(2-hydroxyphenylamino)methylene]tetrahydropyrrole-2,3-dione (IV) was obtained similarly. Yield 1.18 g (45%), mp 258–260°C. IR spectrum, ν, cm^{-1}: 3410, 3320, 3200 (NH_2, NH), 3150 (OH), 1696 (CON), 1620 (C=O), 1380, 1164 (SO_2). ^1H NMR spectrum, δ, ppm: 6.11 s (1H, C^5H), 6.20–7.74 m (20H, CH_{arom}, SO_2NH_2), 10.16 s (1H, OH), 12.51 s (1H, NH). Found, %: C 66.17, 66.38; H 4.46, 4.36; N 7.89, 7.91; S 6.17, 6.03. $C_{29}H_{23}N_3O_5S$. Calculated, %: C 66.27; H 4.41; N 7.99; S 6.10.

1-(4-Aminosulfonylphenyl)-4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-3-(4-ethylphenylamino)-3-pyrrolin-2-one (V). A mixture of 0.01 mol of 1-(4-aminosulfonylphenyl)-3-hydroxy-4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-3-pyrrolin-2-one and 0.011 mol of 4-ethylaniline in 15 mL of glacial acetic acid was refluxed for 1–2 h, then cooled and treated with ethanol. The precipitate was filtered off and recrystallized from ethanol. Yield 3.95 g (65%), mp 206–208°C. IR spectrum, ν, cm^{-1}: 3296, 3210 (NH_2, NH), 1700 (CON), 1640 (C=O), 1376, 1168 (SO_2). ^1H NMR spectrum, δ, ppm: 1.08 t (3H, $\underline{CH_3}CH_2$, *J* 7.52 Hz), 2.44 q (2H, $CH_3\underline{CH_2}$, *J* 7.52 Hz), 6.36 s (1H, C^5H), 6.66–7.71 m (18H, CH_{arom}, SO_2NH_2), 8.76 s (1H, NH). Found, %: C 61.50, 61.27; H 4.09, 4.21; N 6.84, 7.01; S 5.38, 5.20. $C_{31}H_{25}Cl_2N_3O_4S$. Calculated, %: C 61.39; H 4.15; N 6.93; S 5.29.

1-(4-Aminosulfonylphenyl)-5-(4-fluorophenyl)-4-(4-chlorobenzoyl)-3-(4-ethylphenylamino)-3-pyrrolin-2-one (VI) was obtained similarly. Yield 3.72 g (63%), mp 168–170°C. IR spectrum, ν, cm^{-1}: 3288, 3220 (NH_2, NH), 1700 (CON), 1635 (C=O), 1352, 1164 (SO_2). ^1H NMR spectrum, δ, ppm: 1.09 t (3H, $\underline{CH_3}CH_2$, *J* 7.43 Hz), 2.38 q (2H, $CH_3\underline{CH_2}$, *J* 7.43 Hz), 6.36 s (1H, C^5H), 6.68–7.71 m (18H, CH_{arom}, SO_2NH_2), 8.74 s (1H, NH). Found, %: C 62.98, 63.23; H 4.22, 4.33; N 7.04, 7.21; S 5.51, 5.36. $C_{31}H_{25}Cl{\cdot}FN_3O_4S$. Calculated, %: C 63.10; H 4.27; N 7.12; S 5.43.

1-(4-Aminosulfonylphenyl)-5-(4-nitrophenyl)-4-[4-chlorophenyl(4-ethylphenylamino)methylene]-tetrahydropyrrole-2,3-dione (VII) was obtained similarly. Yield 3.64 g (59%), mp 275–277°C. IR spectrum, ν, cm^{-1}: 3439, 3300, 3125 (NH_2, NH), 1708 (CON), 1624 (C=O), 1352, 1160 (SO_2). ^1H NMR spectrum, δ, ppm: 1.05 t (3H, $\underline{CH_3}CH_2$, *J* 7.42 Hz), 2.55 q (2H, $CH_3\underline{CH_2}$, *J* 7.42 Hz), 6.33 s (1H, C^5H), 6.72–7.79 m (18H, CH_{arom}, SO_2NH_2), 12.40 s (1H, NH). Found, %: C 60.25, 60.44; H 4.04, 4.13; N 9.16, 9.00; S 5.26, 5.15. $C_{31}H_{25}ClN_4O_6S$. Calculated, %: C 60.34; H 4.08; N 9.08; S 5.20.

5-(4-Aminosulphonylphenyl)-3,4-diphenyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-6-one (VIII). To a suspension of 0.01 mol of 1-(4-aminosulfonylphenyl)-4-benzoyl-3-hydroxy-5-phenyl-3-pyrrolin-2-one in 15–20 mL of acetic acid was added 0.012 mol of hydrazine hydrate. The reaction mixture was refluxed for 1–2 h. After cooling, the precipitate was filtered off and recrystallized from propan-2-ol. Yield 2.97 g (69%), mp 269–271°C. IR spectrum, ν, cm^{-1}: 3432, 3328, 3248 (NH_2, NH), 1716 (CON), 1328, 1168 (SO_2). ^1H NMR spectrum, δ, ppm: 6.78 s (1H, C^4H), 7.08–7.79 m (16H, CH_{arom}, SO_2NH_2), 13.99 s (1H, NH). Found, %: C 64.05, 64.27; H 4.16, 4.25; N 13.07, 12.98; S 7.50, 7.40. $C_{23}H_{18}N_4O_3S$. Calculated, %: C 64.17; H 4.21; N 13.01; S 7.45.

5-(4-Aminosulfonylphenyl)-4-(2,5-dimethoxyphenyl)-3-phenyl-4,6-dihydropyrrolo[3,4-*c*]pyrazol-6-one (IX) was obtained similarly. Yield 3.49 g (71%), mp 290–292°C. IR spectrum, ν, cm^{-1}: 3328, 3245, 3152 (NH_2, NH), 1696 (CON), 1336, 1168 (SO_2). ^1H NMR spectrum, δ, ppm: 3.50 s (3H, CH_3O), 3.83 s (3H, CH_3O), 6.79 s (1H, C^4H), 6.46–7.95 m (14H, CH_{arom}, SO_2NH_2), 13.96 s (1H, NH). Found, %: C 61.32, 61.08; H 4.55, 4.47; N 11.49, 11.35; S 6.61, 6.48. $C_{25}H_{22}N_4O_5S$. Calculated, %: C 61.21; H 4.52; N 11.42; S 6.54.

5-(4-Aminosulfonylphenyl)-3-phenyl-4-(3-fluorophenyl)-4,6-dihydropyrrolo[3,4-*c*]pyrazol-6-one (X) was obtained similarly. Yield 2.82 g (63%), mp 280–282°C. IR spectrum, ν, cm^{-1}: 3432, 3392, 3296 (NH_2, NH), 1712 (CON), 1380, 1172 (SO_2). ^1H NMR spectrum, δ, ppm: 6.86 s (1H, C^4H), 7.15–8.00 m (15H, CH_{arom}, SO_2NH_2), 14.05 s (1H, NH). Found, %: C 61.69, 61.51; H 3.86, 3.79; N 12.55, 12.43; S 7.19, 7.10. $C_{23}H_{17}FN_4O_3S$. Calculated, %: C 61.60; H 3.82; N 12.49; S 7.15.

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