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Five-Membered 2,3-Dioxo Heterocycles: CII.* Spiro Heterocyclization of 3-Aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones by the Action of Tetrahydroquinoline

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Abstract—3-Aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones reacted with 1,2,3,4-tetrahydroquinoline to give 3-aroyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-diones.

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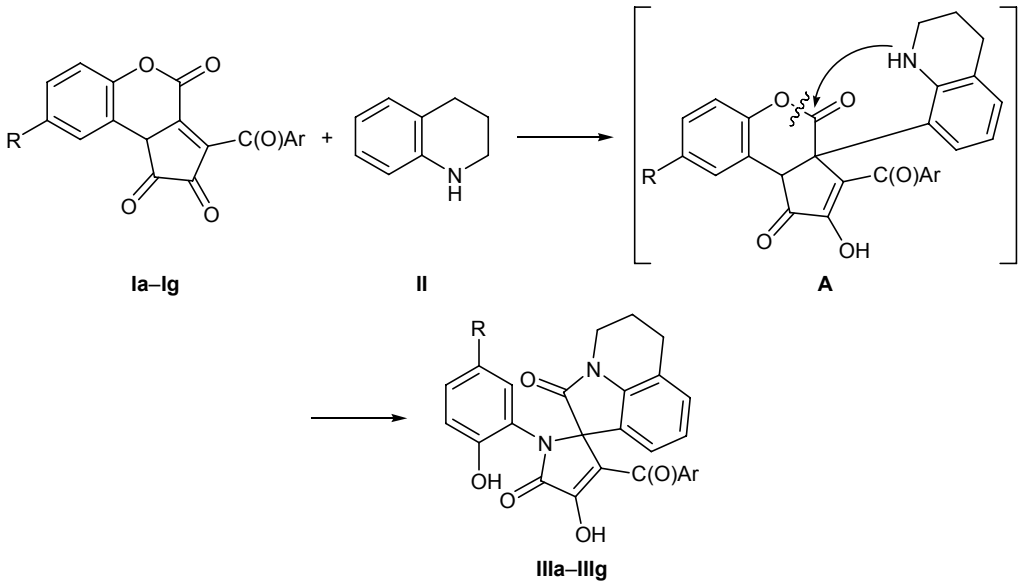
Nucleophilic heterocyclizations and recyclizations of 1*H*-pyrrole-2,3-diones fused at the N^1–C^5 bond to heterocyclic systems in reactions with binucleophiles provide a convenient synthetic route to various five-, six-, and seven-membered aza heterocycles and fused, bridged, and spiro heterocyclic systems [2, 3]. Recyclizations of 3-acylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones by the action of 1,4-N,N- [4, 5], 1,4-S,N- [6], and 1,3-C,N- binucleophiles [7] follow a common scheme including successive nucleophilic attacks on the 3a-carbon atom and carbonyl carbon atom in position *4* of pyrrolobenzoxazinetrione. The reactions with N,N- and S,N-binucleophiles are accompanied by opening of the oxazine and pyrrole rings at the C^4–O^5 and N^{10}–C^{3a} bonds, respectively. In continuation of our studies on nucleophilic recyclizations of pyrrolobenzoxazinetriones in the present article we report on their reaction with 1,2,3,4-tetrahydroquinoline.

Scheme 1.



Ar = Ph (**a**, **g**), 4-BrC_6H_4 (**b**), 4-FC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), 4-$MeOC_6H_4$ (**e**), 4-$EtOC_6H_4$ (**f**); R = H (**a**–**f**), Cl (**g**).

* For communication CI, see [1].

The reactions of 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia**–**Ig** with 1,2,3,4-tetrahydroquinoline (**II**) were carried out with equimolar amounts of the reactants which were heated in boiling benzene (79–80°C) for 30–60 min, the progress of the reaction being monitored by HPLC. As a result, we isolated 3-aroyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-diones **IIIa**–**IIIg** [8] as colorless high-melting (with decomposition) crystalline substances which were readily soluble in DMF and DMSO, poorly soluble in alcohols and chlorinated hydrocarbons, and insoluble in alkanes and water. The products showed a positive color test (cherry color) for enolic and phenolic hydroxy groups on treatment with an alcoholic solution of iron(III) chloride.

The IR spectra of **IIIa**–**IIIg** contained absorption bands typical of stretching vibrations of phenolic and enolic hydroxy groups (one broadened band in the region 3325–3177 cm^{-1}), lactam carbonyl groups (one or two bands in the region 1720– 1687 cm^{-1}), and ketone carbonyl group (3-C=O, 1637–1626 cm^{-1}). In the ^1H NMR spectra of **IIIa**–**IIIg** in DMSO-d_6 we observed signals from protons in the aromatic rings and substituents therein, three multiplets from methylene protons in the tetrahydroquinoline fragment at δ 1.73–1.91, 2.60–2.64, and 3.64–3.68 ppm (5′-H, 6′-H, and 4′-H, respectively), a singlet from the phenolic OH proton at δ 9.42–9.61 ppm, and a broadened singlet from the enolic hydroxy proton at δ 12.00–12.67 ppm.

Presumably, in the first step addition of the activated C^8H group of tetrahydroquinoline **II** to the carbon atom in position *3a* of pyrrolobenzoxazinetrione **I** yields intermediate **A**, and the subsequent intramolecular attack by the NH group of the tetrahydroquinoline on the lactone carbonyl carbon atom of the oxazine ring is accompanied by cleavage of the latter at the C^4–O^5 bond and closure of a new pyrrole ring (Scheme 1).

The described reaction is an example of regioselective synthesis of difficultly accessible spiro[pyrrole-2,1′-pyrrolo[3,2,1-*ij*]quinoline] system. Molecules **IIIa**–**IIIg** contain a fused heterocyclic lilolidine system (pyrrolo[3,2,1-*ij*]quinoline) which rarely occurs in nature and constitutes the base fragment of hippadine [9, 10] and lycorine alkaloids [11]. These alkaloids exhibit antitumor activity and are also active toward cardiovascular system. Thus, the described reaction may be regarded as a new synthetic approach to lilolidine derivatives.

EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer Spectrum Two spectrometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were obtained on a Bruker WP-400 spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The reactions conditions were optimized using a Waters Acquity UPLC I Class instrument (BEH C18 column, grain size 1.7 μm; eluents methanol–water and acetonitrile–water, flow rate 0.3–0.5 mL/s; ESI MS Xevo TQD detector). The purity of the products was checked by UPLC and TLC (Silufol plates; benzene, ethyl acetate–benzene, 1:5; development with iodine vapor).

3-Benzoyl-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIa). A solution of 3.1 mmol of compound **Ia** and 3.1 mmol of 1,2,3,4-tetrahydroquinoline (**II**) in 40 mL of anhydrous benzene was heated for 30 min under reflux (HPLC monitoring). The mixture was cooled, and the precipitate was filtered off. Yield 84%, mp 260–262°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3325 br (OH), 1716, 1698 (C^5=O, $C^{2'}$=O), 1630 (COPh). ^1H NMR spectrum, δ, ppm: 1.75 m and 1.91 m (2H, 5′-H), 2.62 m (2H, 6′-H), 3.68 m (2H, 4′-H), 6.67–7.73 m (12H, H_{arom}), 9.59 s (1H, 2″-OH), 12.00 br.s (1H, 4-OH). Found, %: C 71.75; H 4.44; N 6.12. $C_{27}H_{20}N_2O_5$. Calculated, %: C 71.67; H 4.46; N 6.19.

Compounds **IIIb**–**IIIg** were synthesized in a similar way.

3-(4-Bromobenzoyl)-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIb). Yield 76%, mp 264–267°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3262 br (OH), 1711 (C^5=O, $C^{2'}$=O), 1637 (3-C=O). ^1H NMR spectrum, δ, ppm: 1.73 m and 1.90 m (2H, 5′-H), 2.60 m (2H, 6′-H), 3.67 m (2H, 4′-H), 6.66–7.72 m (11H, H_{arom}), 9.58 s (1H, 2″-OH), 12.67 br.s (1H, 4-OH). Found, %: C 60.56; H 3.52; Br 15.07; N 5.37. $C_{27}H_{19}BrN_2O_5$. Calculated, %: C 61.03; H 3.60; Br 15.04; N 5.27.

3-(4-Fluorobenzoyl)-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pirrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIc). Yield 81%, mp 274–276°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3265 br (OH), 1709 (C^5=O, $C^{2'}$=O), 1635 (3-C=O). ^1H NMR spectrum, δ, ppm: 1.74 m and 1.90 m (2H, 5′-H), 2.62 m (2H, 6′-H), 3.67 m (2H,

4′-H), 6.67–7.89 m (11H, H_{arom}), 9.57 s (1H, 2″-OH), 12.53 br.s (1H, 4-OH). Found, %: C 68.75; H 4.14; F 3.9; N 6.08. $C_{27}H_{19}FN_2O_5$. Calculated, %: C 68.93; H 4.07; F 4.04; N 5.95.

4-Hydroxy-1-(2-hydroxyphenyl)-3-(4-nitrobenzoyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′H)-dione (IIId). Yield 74%, mp 256–257°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3318 br (OH), 1707, 1687 (C^5=O, $C^{2'}$=O), 1636 (3-C=O). ^{1}H NMR spectrum, δ, ppm: 1.75 m and 1.91 m (2H, 5′-H), 2.64 m (2H, 6′-H), 3.67 m (2H, 4′-H), 6.67–8.32 m (11H, H_{arom}), 9.61 s (1H, 2″-OH), 12.10 br.s (1H, 4-OH). Found, %: C 65.21; H 3.79; N 8.51. $C_{27}H_{19}N_3O_7$. Calculated, %: C 65.19; H 3.85; N 8.45.

4-Hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxybenzoyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIe). Yield 82%, mp 269–271°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3182 br (OH), 1708 (C^5=O, $C^{2'}$=O), 1626 (3-C=O). ^{1}H NMR spectrum, δ, ppm: 1.74 m and 1.90 m (2H, 5′-H), 2.62 m (2H, 6′-H), 3.67 m (2H, 4′-H), 3.83 s (3H, OMe), 6.66–7.74 m (11H, H_{arom}), 9.56 s (1H, 2″-OH), 12.15 br.s (1H, 4-OH). Found, %: C 69.87; H 4.54; N 5.99. $C_{28}H_{22}N_2O_6$. Calculated, %: C 69.70; H 4.60; N 5.81.

3-(4-Ethoxybenzoyl)-4-hydroxy-1-(2-hydroxyphenyl)-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIf). Yield 79%, mp 204–206°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3230 br (OH), 1709 (C^5=O, $C^{2'}$=O), 1634 (3-C=O). ^{1}H NMR spectrum, δ, ppm: 1.33 t (3H, $CH_2C\mathbf{H}_3$), 1.73 m and 1.90 m (2H, 5′-H), 2.60 m (2H, 6′-H), 3.64 m (2H, 4′-H), 4.11 q (2H, OCH_2), 6.63–7.21 m (11H, H_{arom}), 9.42 s (1H, 2″-OH), 12.02 br.s (1H, 4-OH). Found, %: C 70.01; H 4.76; N 5.53. $C_{29}H_{24}N_2O_6$. Calculated, %: C 70.15; H 4.87; N 5.64.

3-Benzoyl-1-(5-chloro-2-hydroxyphenyl)-4-hydroxy-5′,6′-dihydrospiro[pyrrole-2,1′-pyrrolo-[3,2,1-*ij*]quinoline]-2′,5(1*H*,4′*H*)-dione (IIIg). Yield 77%, mp 274–276°C (decomp., from benzene). IR spectrum, ν, cm^{-1}: 3177 br (OH), 1720 and 1696 (C^5=O, $C^{2'}$=O), 1632 (3-C=O). ^{1}H NMR spectrum, δ, ppm: 1.75 m and 1.94 m (2H, 5′-H), 2.65 m (2H, 6′-H), 3.70 m (2H, 4′-H), 6.67–7.73 m (11H, H_{arom}), 10.02 s (1H, 2″-OH), 12.51 br.s (1H, 4-OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 188.69 (3-C=O); 171.53, 165.29, 153.14 (C^4, $C^{2'}$, C^5); 140.41–117.80 (C_{arom}), 71.23 (C^{spiro}), 31.10 ($C^{4'}$), 23.66 ($C^{6'}$), 20.69 ($C^{5'}$). Found, %: C 66.78; H 4.11; Cl 7.32; N 5.73. $C_{27}H_{19}ClN_2O_5$. Calculated, %: C 66.60; H 3.93; Cl 7.28; N 5.75.

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