ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 5, pp. 697–700. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © Yu.N. Bannikova, Yu.S. Rozhkova, Yu.V. Shklyaev, A.N. Maslivets, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 5, pp. 706–709.

# Five-Membered 2,3-Dioxoheterocycles: LVIII.* Reaction of Methyl 1-Aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrol-2-carboxylates with Substituted 1-Methyl-3,4-dihydroisoquinolines. New Approach to the Synthesis of Steroid 13-Azaanalogs

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Received May 16, 2006

**Abstract**—Methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates reacted with substituted 1-methyl-3,4-dihydroisoquinolines with the formation of substituted 3-oxo-2,3,5,6-*tetra*-hydropyrrolo[2,1-*a*]-isoquinoline-2-spiro-2'-(1-aryl-3-aroyl-4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrroles). A new approach was developed to the synthesis of 13-azagonanes, substituted benzo[f]pyrrolo[2,1-*a*]isoquinoline-9-spiro-2'-pyrroles.

**DOI:** 10.1134/S1070428008050102

We formerly described the reaction of monocyclic 1*H*-pyrrole-2,3-diones (methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates) with cyclic enaminoketones (3-alkylamino- and 3-anilino-5,5-dimethyl-2-cyclohexen-1-ones) leading to the formation of substituted 6,6-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-*1H*-indole-3-spiro-2'-(1-aryl-3-aroyl-4-hydroxy-5-oxo-2,3-dihydro-1*H*-pyrroles) whose structure was confirmed by XRD analysis [2]. The reaction proceeds through successive attacks by two nucleophilic sites (β-CH and NH groups) on the enamino fragment of the cyclic enaminoketone at the carbon atom in position *5* and carbonyl carbon of the methoxycarbonyl substituent in position *5* of 1*H*-pyrrole-2,3-diones with methanol elimination.

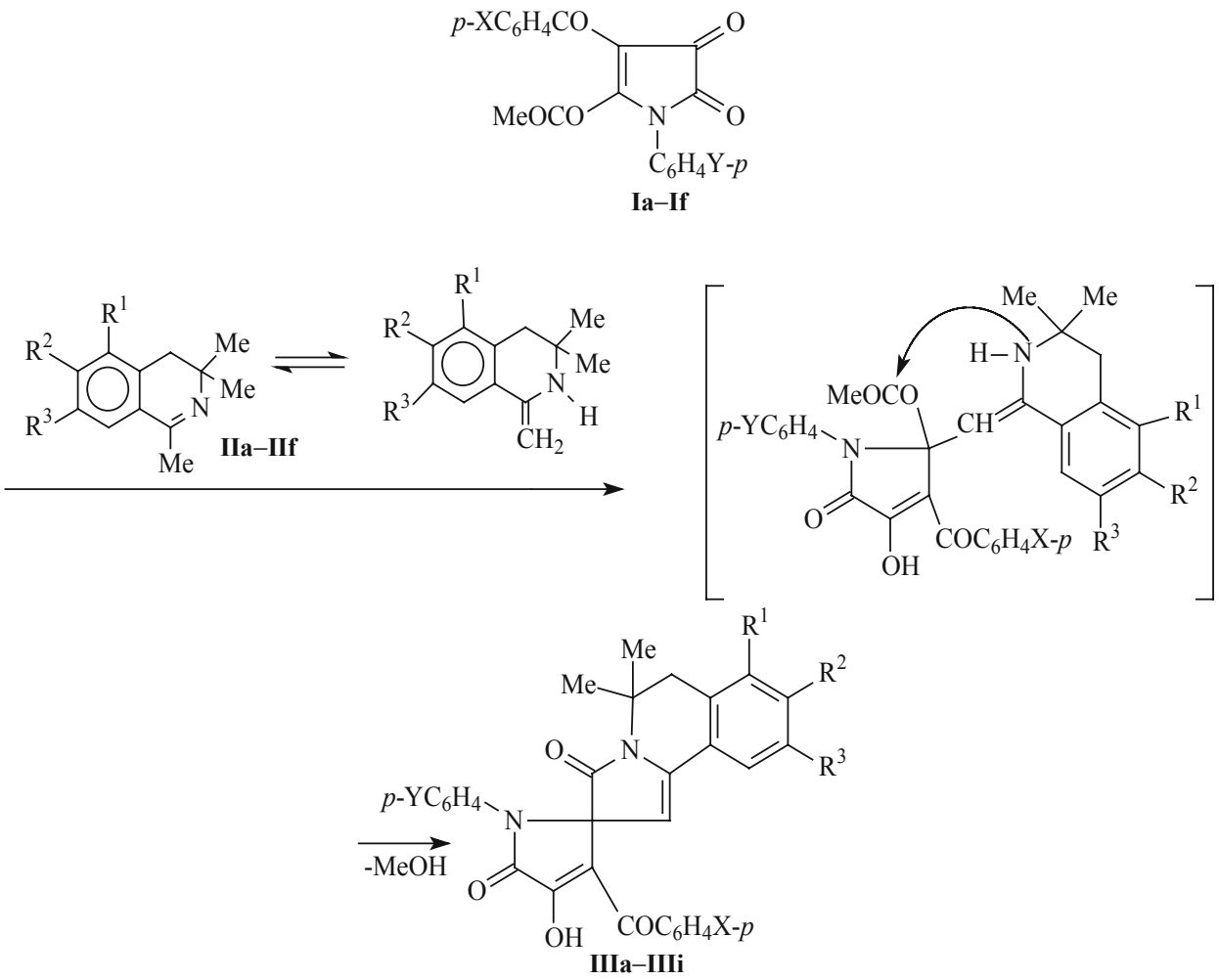
In extension of research on recyclization and heterocyclization of acyl-substituted 1*H*-pyrrole-2,3-diones under the action of CH,NH-binucleophilic reagents we studied reactions of methyl 1-aryl-3-aroyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **Ia–If** with substituted 1-methyl-3,4-dihydroisoquinolines **IIa–IIc**. 1-Methyl-3,4-dihydroisoquinolines in the tautomeric form of 1-methylene-1,2,3,4-tetrahydroisoquinolines contain an enamino fragment with two nearly equivalent nucleophilic groups, and they give products of nucleophilic attack on highly electrophilic 2,3-dioxoheterocycles both by NH [3] and β-CH [4] groups of this fragment. The direction of the primary nucleophilic attack of one of these groups on one among the several electrophilic centers of compounds **Ia–If** (atoms $C^4$, $C^5$, MeOCO) would have decided the structure of products obtained.

The reaction of compounds **Ia–If** with equimolar amount of isoquinolines **IIa–IIc** at boiling in anhydrous benzene for 0.5-2 min provided in practically quantitative yield substituted 5,5-dimethyl-3-oxo-2,3,5,6-tetrahydro-pyrrolo[2,1-*a*]isoquinoline-2-spiro-2c-(1-aryl-3-aroyl-4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrroles) **IIIa–IIIi**; the structure of compound **IIIb** was proved by XRD analysis [5].

Compounds **IIIa-IIIi** are colorless or light-yellow crystalline substances melting at high temperature, sparingly soluble in common organic solvents, readily soluble in DMF and DMSO, insoluble in alkanes and water, positive test with iron(III) chloride on the presence of enol hydroxy group (cherry-red coloration).

The IR spectra of spiro-compounds **IIIa–IIIi** recorded from mulls in mineral oil contain the bands of the stretching vibrations of enol OH group as a broad peak in the region 3180–3220 $cm^{-1}$, of two lactam carbonyl groups as one or two peaks in the region

* For communication LVII, see [1].




1688–1730 cm$^{-1}$, of aroyl carbonyl in the region 1625–1636 cm$^{-1}$.

In the $^1$H NMR spectra of solutions of compounds **IIIa–IIIi** in DMSO-$d_6$ alongside the signals of aromatic rings protons appear two singlets of methyl groups in the region 1.01–1.61 ppm, signals from two protons of $CH_2$ group of the isoquinoline fragment in the form of doublet of doublets (AB-system) in the region 3.12–3.63 ppm split due to the nonequivalence because of adjacent chiral center, and a signal of vinyl CH proton in the region 6.01–6.98 ppm.

Evidently in the first stage of the reaction the activated β-CH group of the tautomeric enamino form of isoquinolines **IIa–IIc** adds to the carbon atom in the position *5* of compounds **Ia–If** followed by the closure of the pyrrole ring through an intramolecular attack of the amino group of the enamino form of isoquinolines on the ester carbonyl of the substituent in the position *5* of pyrrolediones and by methanol elimination.

The described reaction is a rare example of building up a difficultly accessible spiro-bis-heterocyclic system containing purposefully variable functional substituents in several positions of both heterocycles.

It should be stressed that substituted benzo[*f*]pyrrolo[2,1-*a*]isoquinoline-9-spiro-2'-pyrroles **IIIb, IIIh**, and **IIIi** are 13-azagonanes, heterocyclic analogs of steroids containing a spiro-heterocyclic substituent in the position *16* of the tetracyclic system, and the described reaction constitutes the new approach to their synthesis.

## EXPERIMENTAL

IR spectra of compounds synthesized were recorded on a spectrophotometer UR-20 from mills in mineral oil. $^1$H and $^{13}$C NMR spectra were registered on a spectrometer Bruker AM-400 (operating frequency 400 MHz) from solutions in DMSO-$d_6$, internal reference TMS. Mass spectra were measured on a MKh-1320, instrument, energy of ionizing electrons 70 eV. The homogeneity of

compounds synthesized was checked by TLC on Silufol plates, eluents ethyl acetate–benzene, 1:5, ethyl acetate, development in iodine vapor.

**5,5-Dimethyl-8,9-dimethoxy-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-(3-benzoyl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole) (IIIa).** A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of enamine **IIa** in 10 ml of anhydrous benzene was boiled for 1 min, cooled, the separated precipitate was filtered off. Yield 72%, mp 220–223°C (decomp., from ethyl acetate). IR spectrum, cm$^{-1}$: 3205 br (OH), 1730, 1702 (C$^{3}$=O, C$^{5}$=O), 1635 (COPh). $^1$H NMR spectrum, δ, ppm: 1.25 s (3H, Me), 1.52 s (3H, Me), 2.61,2.77 d.d (2H, H$^{6}_{2}$, *J* 15.7 Hz), 3.72 s (3H, OMe), 3.75 s (3H, OMe), 5.76 s (1H, H$^{1}$), 6.76–7.77 group of signals (12H, 2Ph + H$^{7,10}$), 12.20 br.s (1H, OH). Found, %: C 71.61; H 5.18; N 5.31. $C_{32}H_{28}N_2O_6$. Calculated, %: C 71.63; H 5.26; N 5.22.

Compounds **IIIb–IIIi** were similarly synthesized.

**6,6-Dimethyl-8-oxo-5,6,8,9-tetrahydro-benzo-[*f*]pyrrolo[2,1-*a*]isoquinoline-9-spiro-2'-(3-benzoyl-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole) (IIIb)** Yield 86%, mp 255-257°C (decomp., from ethyl acetate-dichloroethane). IR spectrum, cm$^{-1}$: 3220 br (OH), 1728, 1703 (C$^{5}$=O, C$^{8}$=O), 1638 (COPh). $^1$H NMR spectrum, δ, ppm: 1.28 s (3H, Me), 1.63 s (3H, Me), 3.14, 3.28 d.d (2H, H$^{5}_{2}$, *J* 16.5 Hz), 6.05 s (1H, H$^{10}$), 7.27–8.12 group of signals (16H, 2Ph + H$^{1-4,11,12}$), 12.22 br.s (1H, OH). Mass spectrum, m/z ($I_{rel}$, %): 526 (50) [M$^{+\cdot}$], 421 (18), 407 (58), 406 (100), 379 (15), 105 (96) [PhCO]$^+$, 77 (35) [Ph]$^+$. Found, %: C 77.38; H 4.93; N 5.40. $C_{34}H_{26}N_2O_4$. Calculated, %: C 77.55; H 4.98; N 5.32.

**5,5-Dimethyl-8,9-dimethoxy-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[4-hydroxy-3-(*p*-nitrobenzoyl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole] (IIIc)**. Yield 58%, mp 234-236°C (decomp., from ethyl acetate). IR spectrum, cm$^{-1}$: 3190 br (OH), 1725, 1686 (C$^{3}$=O, C$^{5}$=O), 1640 (COAr). $^1$H NMR spectrum, δ, ppm: 1.27 s (3H, Mε); 1.50 s (3H, Mε); 2.62, 2.78 d.d (2H, H$^{6}_{2}$, *J* 15.9 Hz); 3.73 s (3H, OMe), 3.76 c (3H, OMe), 5.78 c (1H, H$^{1}$); 6.79–8.34 group of signals (11H, Ph + $C_6H_4$ + H$^{7,10}$); 12.28 br.s (1H, OH). Found, %: C 66.13; H 4.66; N 7.37. $C_{32}H_{27}N_3O_8$. Calculated, %: C 66.09; H 4.68; N 7.23.

**5,5-Dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[4-hydroxy-3-benzoyl-5-oxo-1-(*p*-tolyl)-2,5-dihydro-1*H*-pyrrole] (IIId)**. Yield 75%, mp 249-251°C (decomp., from ethyl acetate-dichloroethane). IR spectrum, cm$^{-1}$: 3198 br (OH), 1731, 1705 (C$^{3}$=O, C$^{5}$=O), 1639 (COPh). $^1$H NMR spectrum, δ, ppm: 1.26 s (3H, Me); 1.53 s (3H, Me); 2.25 s (3H, $C_6H_4$Me-4); 2.66, 2.86 d.d (2H, H$^{6}_{2}$, *J* 15.9 Hz); 5.88 s (1H, H$^{1}$); 6.98-7.75 group of signals (13H, Ph + 2$C_6H_4$); 12.30 br.s (1H, OH).Found, %: C 76.09; H 5.46; N 5.74. $C_{31}H_{26}N_2O_4$. Calculated, %: C 75.90; H 5.34; N 5.71.

**5,5-Dimethyl-8,9-dimethoxy-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[4-hydroxy-3-benzoyl-5-oxo-1-(*p*-tolyl)-2,5-di-hydro-1*H*-pyrrole] (IIIe)**. Yield 58%, mp 160–161°C (decomp., from ethyl acetate). IR spectrum, cm$^{-1}$: 3208 br (OH), 1726, 1701 (C$^{3}$=O, C$^{5}$=O), 1634 (COPh). $^1$H NMR spectrum, δ, ppm: 1.19 s (3H, Me), 1.51 s (3H, Me), 2.35 s (3H, $C_6H_4$Me-4); 2.62,2.77 d.d (2H, H$^{6}_{2}$, *J* 15.6 Hz), 3.72 s (3H, OMe), 3.75 s (3H, OMe), 5.73 s (1H, H$^{1}$), 6.77–7.76 group of signals (11H, Ph+$C_6H_4$ + H$^{7,10}$), 12.24 br.s (1H, OH). Found, %: C 71.87; H 5.41; N 5.11. $C_{33}H_{30}N_2O_6$. Calculated, %: C 71.99; H 5.49; N 5.09.

**5,5-Dimethyl-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[3-benzoyl-4-hydroxy-5-oxo-1-(*p*-chlorophenyl)-2,5-dihydro-1*H*-pyrrole] (IIIf)**. Yield 58%, mp 280-281°C (decomp., from ethyl acetate). IR spectrum, cm$^{-1}$: 3215 br (OH), 1724, 1698 (C$^{3}$=O, C$^{5}$=O), 1638 (COPh). $^1$H NMR spectrum, δ, ppm: 1.23 s (3H, Me); 1.52 s (3H, Me); 2.73, 2.86 d.d (2H, H$^{6}_{2}$, *J* 16.0 Hz); 5.87 s (1H, H$^{1}$); 7.24–7.76 group of signals (13H, Ph + 2$C_6H_4$); 12.27 br.s (1H, OH).Found, %: C 70.62; H 4.57; Cl 7.03; N 5.56. $C_{30}H_{23}ClN_2O_4$. Calculated, %: C 70.52; H 4.54; Cl 6.94; N 5.48.

**5,5-Dimethyl-8,9-dimethoxy-3-oxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[3-benzoyl-4-hydroxy-5-oxo-1-(*p*-chlorophenyl)-2,5-dihydro-1*H*-pyrrole] (IIIg)**. Yield 58%, mp 225-227°C (decomp., from ethyl acetate). IR spectrum, cm$^{-1}$: 3218 br (OH), 1733, 1682 (C$^{3}$=O, C$^{5}$=O), 1628 (COPh). $^1$H NMR spectrum, δ, ppm: 1.29 s (3H, Me), 1.53 s (3H, Me), 2.67,2.79 d.d (2H, H$^{6}_{2}$, *J* 16.1 Hz), 3.72 s (3H, OMe), 3.76 s (3H, OMe), 5.76 s (1H, H$^{1}$), 6.80-7.77 group of signals (11H, Ph + $C_6H_4$ + H$^{7,10}$), 12.28 br.s (1H, OH). Found, %: C 67.44; H 4.72; Cl 6.25; N 4.83. $C_{32}H_{27}ClN_2O_6$. Calculated, %: C 67.31; H 4.77; Cl 6.21; N 4.91.

**6,6-Dimethyl-8-oxo-5,6,8,9-tetrahydrobenzo-[*f*]pyrrolo[2,1-*a*]isoquinoline-9-spiro-2'-[4-hydroxy-5-oxo-1-(*p*-tolyl)-3-(*p*-ethoxybenzoyl)-2,5-dihydro-1*H*-pyrrole] (IIIh)**. Yield 86%, mp 200-202°C (decomp., from ethyl acetate–dichloroethane). IR spectrum cm$^{-1}$:

3210 br (OH), 1730 ($C^5$=O, $C^8$=O), 1641 (COPh). $^1$H NMR spectrum, δ, ppm: 1.05 s (3H, Me), 1.28 t (3H, $CH_3CH_2O$), 1.59 s (3H, Me), 2.39 s (3H, $C_6H_4$Me-4), 2.96,3.18 d.d (2H, $H^5_2$, *J* 16.2 Hz), 3.84 q (2H, $CH_3CH_2O$), 6.32 s (1H, $H^{10}$), 7.20-8.23 group of signals (14H, $2C_6H_4$ + $H^{1-4,11,12}$), 12.45 br.s (1H, OH). Found, %: C 76.13; H 5.55; N 4.78. $C_{37}H_{32}N_2O_5$. Calculated, %: C 76.01; H 5.52; N 4.79.

**6,6-Dimethyl-8-oxo-5,6,8,9-tetrahydrobenzo-[*f*]pyrrolo[2,1-*a*]isoquinoline-2-spiro-2'-[4-hydroxy-5-oxo-1-(*p*-tolyl)-3-(*p*-chlorobenzoyl)-2,5-dihydro-1*H*-pyrrole] (IIIi).** Yield 95%, mp 257–259°C (decomp., from ethyl acetate-dichloroэtaνa). IR spectrum, $cm^{-1}$,: 3180 br (OH), 1722, 1688 ($C^5$=O, $C^8$=O), 1636 (COAr). $^1$H NMR spectrum, δ, ppm: 1.34 s (3H, Me), 1.61 s (3H, Me), 2.22 s (3H, $C_6H_4$Me-4), 3.12, 3.28 d.d (2H, $H^5_2$, *J* 16.3 Hz), 6.01 s (1H, $H^{10}$), 7.16-8.14 group of signals (14H, $2C_6H_4$ + $H^{1-4,11,12}$), 12.20 br.s (1H, OH). $^{13}$C NMR spectrum, δC, ppm: 20.53 (Me-*p*), 25.92, 26.20 (2Me isoquinoline), 39.50 ($C^5$), 53.43 (C spiro), 72.19 ($C^6$), 98.88–143.36 (Ar), 152.94 ($C^4$OH), 165.38 ($C^5$), 173.82 ($C^8$), 187.30 (COAr). Found, %: C 73.06; H 4.79; Cl 6.22; N 4.79. $C_{35}H_{27}ClN_2O_4$. Calculated, %: C 73.10; H 4.73; Cl 6.16; N 4.87.

The study was carried out under financial support of the Russian Foundation for Basic Research (grants nos. 07-03-96036, 04-03-96045).

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