

Five-Membered 2,3-Dioxo Heterocycles: LIV.* Double Spiro Heterocyclization of Methyl 1-Aryl- 3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates with 3-Arylamino-5,5-dimethylcyclohex-2-en-1-ones

Yu. N. Bannikova^a, A. N. Maslivets^a, and Z. G. Aliev^b

^a Perm State University, ul. Bukireva 15, Perm, 614990 Russia
e-mail: koh2@psu.ru

^b Institute of Chemical Physics Problems, Russian Academy of Sciences, Chernogolovka, Moscow oblast, Russia

Received December 28, 2005

Abstract—Methyl 1-aryl-3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates reacted with 3-aryl-amino-5,5-dimethylcyclohex-2-en-1-ones in boiling benzene to give the corresponding 1,1'-diaryl-3'-benzoyl-4'-hydroxy-6,6-dimethyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-triones and 1'-aryl-4-aryl-amino-3-benzoyl-6',6'-dimethyl-1',2',4',5',6',7'-hexahydro-5*H*-spiro[furan-2,3'-indole]-2',4',5'-triones whose structure was proved by X-ray analysis.

DOI: 10.1134/S1070428007090126

We previously described reactions of methyl 1-aryl-3-aryloxy-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates with 1,3-C,N-difunctional nucleophiles (cyclic enamines, N-substituted 3-amino-5,5-dimethylcyclohex-2-en-1-ones). These reactions involved successive nucleophilic attacks by the CH and NH groups of the enamine on the carbon atom in position 2 and ester carbonyl carbon atom in the dioxopyrrolecarboxylate, respectively, and resulted in the formation of 1,1'-diaryl-3'-aryloxy-4'-hydroxy-6,6-dimethyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-triones whose structure was confirmed by the X-ray diffraction data [2, 3].

The reaction of methyl 1-aryl-3-benzoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **Ia** and **Ib** with 3-arylamino-5,5-dimethylcyclohex-2-en-1-ones **IIa** and **IIb** (molar ratio 1:1) in boiling anhydrous benzene in 0.5–10 min gave both expected 1,1'-diaryl-3'-benzoyl-4'-hydroxy-6,6-dimethyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-triones **IIIa–IIIc** and 1'-aryl-4-arylamino-3-benzoyl-6',6'-dimethyl-1',2',4',5',6',7'-hexahydro-5*H*-spiro[furan-2,3'-indole]-2',4',5'-triones **IVa–IVc** (Scheme 1). The structure of compound **IVa** was unambiguously determined by X-ray analysis.

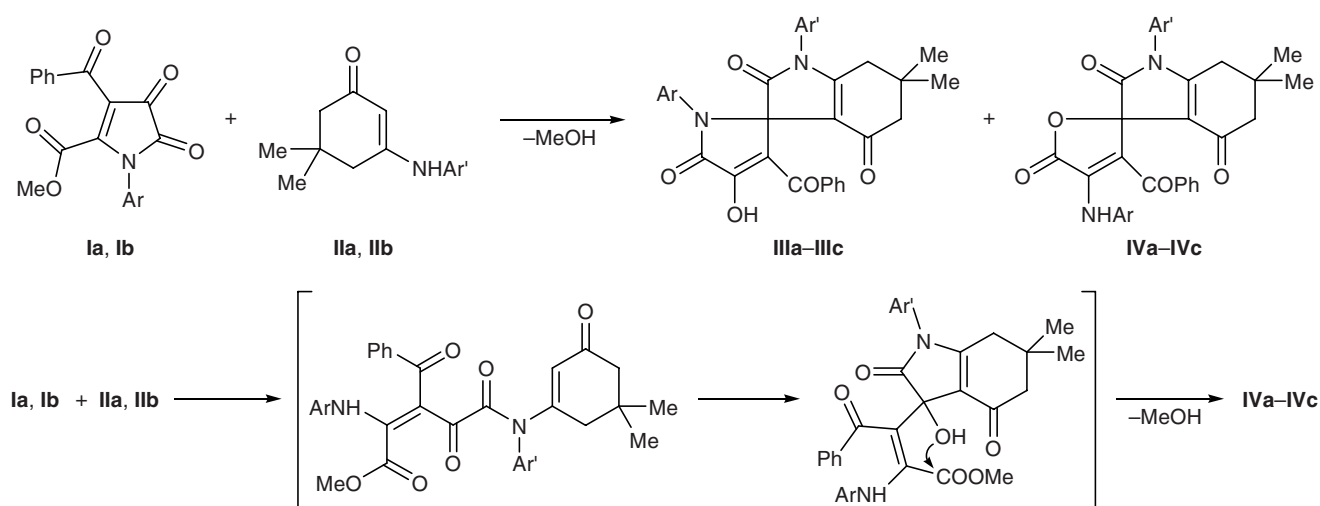
Compounds **IIIa–IIIc** are colorless or light yellow high-melting crystalline substances which are readily soluble in DMF and DMSO, poorly soluble in other organic solvents, and insoluble in alkanes and water. They showed a positive test for enolic hydroxy group (cherry color) with an alcoholic solution of iron(III) chloride. The IR spectra of **IIIa–IIIc** contained absorption bands due to stretching vibrations of the enolic OH group (a diffuse band at 3150–3170 cm^{−1}), lactam carbonyl groups in the indole and pyrrole fragments (1761–1763 and 1717–1726 cm^{−1}, respectively), and conjugated ketone carbonyl groups in the indole fragment and benzoyl group (one or two bands in the region 1626–1663 cm^{−1}).

Compounds **IIIa–IIIc** showed in the ¹H NMR spectra signals from protons in the aromatic substituents, two singlets from two nonequivalent methyl groups, two pairs of doublets of doublets from two nonequivalent methylene groups in the cyclohexane fragment at δ 1.97–2.16 and 2.05–2.32 ppm, respectively, and a broadened singlet from the enolic hydroxy proton at δ 12.70–12.80 ppm.

Compounds **IVa–IVc** are bright yellow high-melting crystalline substances which are readily soluble in DMF and DMSO, poorly soluble in other common organic solvents, and insoluble in alkanes and water.

* For communication LIII, see [1].

Scheme 1.



I, Ar = Ph (**a**), 4-ClC₆H₄ (**b**); **II**, Ar' = 4-MeOC₆H₄ (**a**), 4-ClC₆H₄ (**b**); **III**, **IV**, Ar = Ph, Ar' = 4-MeOC₆H₄ (**a**); Ar = 4-ClC₆H₄, Ar' = 4-MeOC₆H₄ (**b**); Ar = Ar' = 4-ClC₆H₄ (**c**).

They showed a negative test for enolic hydroxy group with an alcoholic solution of iron(III) chloride. The IR spectra of **IVa–IVc** contained absorption bands due to stretching vibrations of the NH group (narrow peak at 3256–3283 cm⁻¹), lactone carbonyl group in the furan fragment (1790–1792 cm⁻¹), lactam carbonyl group in the indole fragment (1761–1764 cm⁻¹), and ketone carbonyl groups in the indole fragment and benzoyl group (one or two bands in the region 1626–1655 cm⁻¹).

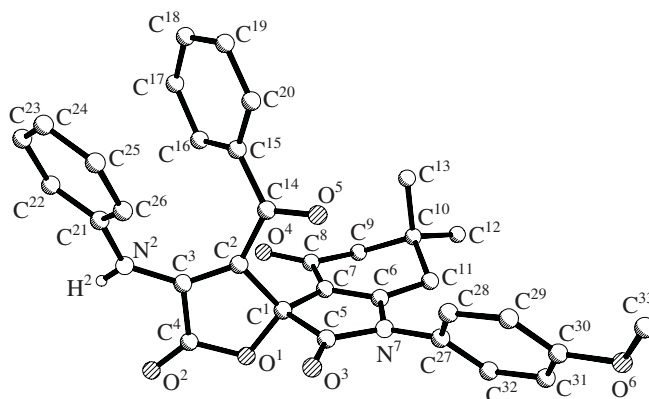
Compounds **IVa–IVc** showed in the ¹H NMR spectra signals from protons in the aromatic substituents, two singlets from two nonequivalent methyl groups, two pairs of doublets of doublets from two nonequivalent methylene groups in the cyclohexane fragment at δ 1.98–2.37 and 2.15–2.76 ppm, respectively, and a singlet from the NH proton at δ 9.31–9.48 ppm.

Figure shows the structure of molecule **IVa** according to the X-ray diffraction data. The double bonds in structure **IVa** are localized with no appreciable effect of π conjugation. All interatomic distances and bond angles approach the corresponding standard values. The cyclohexene ring adopts an *envelope* conformation folded along the C⁹...C¹¹ axis through an angle of 137.6°. The benzene ring in the methoxyphenyl group with the pyrrole ring plane forms a dihedral angle of 56.0°, and the torsion angle C⁶N¹C²⁷C²⁸ is 117.2°. Orientation of the benzoyl fragment with respect to the furan ring is characterized by the following torsion angles: C¹C²C¹⁴O⁵ -29.2 and C²C¹⁴C¹⁵C¹⁶ -24.0°; the torsion angles formed by the phenylamino group and the furan ring are C²C³N²C²¹ 17.4 and C³N²C²¹C²²

145.9°. Molecules **IVa** in crystal are linked through intermolecular hydrogen bonds N²-H²...O⁴ (2.943 Å) to give centrosymmetric dimers.

Presumably, compounds **IVa–IVc** are formed via initial addition of the activated NH group of enamine **II** to the carbon atom in position 5 of pyrroledione **I**, followed by cleavage of the pyrrole ring at the N¹-C⁵ bond and intramolecular closure of new pyrrole ring as a result of nucleophilic addition of the β -CH group in the enamine fragment to the ketone carbonyl group. Attack by the hemiacetal hydroxy group on the ester carbonyl in the intermediate thus formed leads to cyclization with elimination of methanol.

It should be emphasized that the described reactions are quite rare examples of formation of difficultly



Structure of the molecule of 3-benzoyl-1'-(4-methoxyphenyl)-6',6'-dimethyl-4-phenylamino-1',2',4',5',6',7'-hexahydro-5*H*-spiro[furan-2,3'-indole]-2',4',5-trione (**IVa**) according to the X-ray diffraction data.

accessible spiro-heterocyclic systems including indole and pyrrole or furan fragments with various functional substituents in several positions of both heterocyclic fragments.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer from samples dispersed in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz) from solutions in $\text{DMSO}-d_6$ using tetramethylsilane as internal reference. The purity of the products was checked by TLC on Silufol plates using ethyl acetate–benzene (1:5) or ethyl acetate as eluent; development with iodine vapor.

3'-Benzoyl-4'-hydroxy-1-(4-methoxyphenyl)-6,6-dimethyl-1'-phenyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-trione (IIIa) and 3-benzoyl-1'-(4-methoxyphenyl)-6',6'-dimethyl-4-phenylamino-1',2',4',5',6',7'-hexahydro-5H-spiro[furan-2,3'-indole]-2',4',5-trione (IVa). A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of enamine **IIa** in 10 ml of anhydrous benzene was heated for 10 min under reflux. The mixture was cooled, and the precipitate (compound **IIIa**) was filtered off. Yield 36%, mp 213–215°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3170 br (OH), 1761 ($\text{C}^2=\text{O}$), 1717 ($\text{C}^5=\text{O}$), 1663 ($\text{C}^4=\text{O}$), 1626 (COPh). ^1H NMR spectrum, δ , ppm: 0.52 s (3H, Me), 0.80 s (3H, Me), 1.97 d.d and 2.12 d.d (1H each, 7-H, $J = 16.0$ Hz), 2.08 d.d and 2.32 d.d (1H each, 5-H, $J = 17.9$ Hz), 3.83 s (3H, MeO), 7.10–7.73 m (14H, H_{arom}), 12.70 br.s (1H, OH). Found, %: C 72.22; H 5.18; N 5.17. $\text{C}_{33}\text{H}_{28}\text{N}_2\text{O}_6$. Calculated, %: C 72.25; H 5.14; N 5.11.

After separation of compound **IIIa**, the filtrate was evaporated by half and cooled, and the precipitate (compound **IVa**) was filtered off. Yield 56%, mp 185–187°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3283 (NH), 1790 ($\text{C}^5=\text{O}$), 1761 ($\text{C}^2=\text{O}$), 1655 ($\text{C}^4=\text{O}$), 1626 (COPh). ^1H NMR spectrum, δ , ppm: 0.69 s (3H, Me), 1.01 s (3H, Me), 1.98 d.d and 2.36 d.d (1H each, 7'-H, $J = 16.0$ Hz), 2.16 d.d and 2.70 d.d (1H each, 5'-H, $J = 18.4$ Hz), 3.85 s (3H, MeO), 6.71–7.45 m (14H, H_{arom}), 9.31 s (1H, NH). ^{13}C NMR spectrum, δ_{C} , ppm: 28.86 (C^6), 33.95 (Me), 35.96 (C^7), 50.21 (C^5), 55.50 (MeO), 83.05 (C_{spiro}), 108.52, 114.95, 117.94, 120.16, 123.28, 125.16, 128.04, 128.36, 128.70, 132.84, 132.96, 137.23, 140.55, 159.58 (COMe), 167.97 ($\text{C}^{7a'}$), 169.07 (C^5), 173.16 (C^2), 190.11 (PhCO), 190.62 (C^4). Found, %: C 72.26;

H 5.15; N 5.13. $\text{C}_{33}\text{H}_{28}\text{N}_2\text{O}_6$. Calculated, %: C 72.25; H 5.14; N 5.11.

Compounds **IIIb**, **IVb** and **IIIc**, **IVc** were synthesized in a similar way.

3'-Benzoyl-1'-(4-chlorophenyl)-4'-hydroxy-1-(4-methoxyphenyl)-6,6-dimethyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-trione (IIIb). Yield 47%, mp 200–202°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3150 br (OH), 1762 ($\text{C}^2=\text{O}$), 1726 ($\text{C}^5=\text{O}$), 1637 ($\text{C}^4=\text{O}$, COPh). ^1H NMR spectrum, δ , ppm: 0.59 s (3H, Me), 0.79 s (3H, Me), 1.97 d.d. and 2.11 d.d (1H each, 7-H, $J = 16.1$ Hz), 2.05 d.d and 2.28 d.d (1H each, 5-H, $J = 18.0$ Hz), 3.83 s (3H, OMe), 7.12–7.72 m (13H, H_{arom}), 12.75 br.s (1H, OH). Found, %: C 67.99; H 4.65; Cl 6.11; N 4.78. $\text{C}_{33}\text{H}_{27}\text{ClN}_2\text{O}_6$. Calculated, %: C 67.98; H 4.67; Cl 6.08; N 4.80.

3-Benzoyl-4-(4-chlorophenylamino)-1'-(4-methoxyphenyl)-6',6'-dimethyl-1',2',4',5',6',7'-hexahydro-5H-spiro[furan-2,3'-indole]-2',4',5-trione (IVb). Yield 46%, mp 185–187°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3256 (NH), 1792 ($\text{C}^5=\text{O}$), 1764 ($\text{C}^2=\text{O}$), 1639 ($\text{C}^4=\text{O}$, COPh). ^1H NMR spectrum, δ , ppm: 0.68 s (3H, Me), 1.00 s (3H, Me), 1.98 d.d and 2.36 d.d (1H each, 7'-H, $J = 16.0$ Hz), 2.15 d.d and 2.69 d.d (1H each, 5'-H, $J = 18.4$ Hz), 3.84 s (3H, OMe), 6.70–7.46 m (13H, H_{arom}), 9.44 s (1H, NH). Found, %: C 67.96; H 4.68; Cl 6.10; N 4.81. $\text{C}_{33}\text{H}_{27}\text{ClN}_2\text{O}_6$. Calculated, %: C 67.98; H 4.67; Cl 6.08; N 4.80.

3'-Benzoyl-1,1'-bis(4-chlorophenyl)-4'-hydroxy-6,6-dimethyl-1,1',2,4,5,5',6,7-octahydrospiro[indole-3,2'-pyrrole]-2,4,5'-trione (IIIc). Yield 42%, mp 218–220°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3160 br (OH), 1763 ($\text{C}^2=\text{O}$), 1726 ($\text{C}^5=\text{O}$), 1640 ($\text{C}^4=\text{O}$, COPh). ^1H NMR spectrum, δ , ppm: 0.60 s (3H, Me), 0.79 s (3H, Me), 1.99 d.d and 2.16 d.d (1H each, 7-H, $J = 16.1$ Hz), 2.07 d.d and 2.31 d.d (1H each, 5-H, $J = 18.3$ Hz), 7.11–7.73 m (13H, H_{arom}), 12.80 br.s (1H, OH). Found, %: C 65.45; H 4.10; Cl 12.09; N 4.75. $\text{C}_{32}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}_5$. Calculated, %: C 65.43; H 4.12; Cl 12.07; N 4.77.

3-Benzoyl-1'-(4-chlorophenyl)-4-(4-chlorophenylamino)-6',6'-dimethyl-1',2',4',5',6',7'-hexahydro-5H-spiro[furan-2,3'-indole]-2',4',5-trione (IVc). Yield 46%, mp 194–196°C (decomp., from ethyl acetate). IR spectrum, ν , cm^{-1} : 3257 (NH), 1792 ($\text{C}^5=\text{O}$), 1764 ($\text{C}^2=\text{O}$), 1639 ($\text{C}^4=\text{O}$, COPh). ^1H NMR spectrum, δ , ppm: 0.67 s (3H, Me), 1.01 s (3H, Me),

2.02 d.d and 2.37 d.d (1H each, 7'-H, $J = 16.0$ Hz), 2.20 d.d and 2.76 d.d (1H each, 5'-H, $J = 18.4$ Hz), 6.68–7.44 m (13H, H_{arom}), 9.48 s (1H, NH). Found, %: C 65.42; H 4.13; Cl 12.08; N 4.78. $C_{32}H_{24}Cl_2N_2O_5$. Calculated, %: C 65.43; H 4.12; Cl 12.07; N 4.77.

X-Ray analysis of compound (IVa). $C_{33}H_{28}N_2O_6$; monoclinic crystal system, space group $P2_1/n$. Unit cell parameters: $a = 10.408(2)$, $b = 9.469(2)$, $c = 28.903(6)$ Å; $\beta = 96.03(3)^\circ$; $V = 2832.7(10)$ Å³; $M = 548.57$; $d_{\text{calc}} = 1.286$ g/cm³; $Z = 4$. The unit cell parameters and a set of experimental reflections were measured on a KM-4 (KUMA DIFFRACTION) automatic four-circle diffractometer (χ geometry, monochromatized MoK_α irradiation $\omega/2\theta$ scanning to $2\theta \leq 50.12^\circ$). Total of 5093 reflections were measured, 4816 of which were independent ($R_{\text{int}} = 0.0605$). Correction for absorption was not introduced ($\mu = 0.089$ mm⁻¹). The structure was determined by the direct method using SIR92 program [4], followed by a series of calculations of the electron density maps. The positions of hydrogen atoms were set from the geometry considerations, and only their positional parameters were refined by the least-squares procedure.

Full-matrix anisotropic least-squares refinement (for non-hydrogen atoms) was performed using SHELXL 97 program [5] and was complete at $R_1 = 0.0530$, $wR_2 = 0.1307$ [from 1789 reflections with $I \geq 2\sigma(I)$]; goodness of fit 0.851.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 04-03-96033) and by the Federal Education Agency (project no. A04-2.11-491).

REFERENCES

1. Racheva, N.L., Shklyayev, Yu.V., Rozhkova, Yu.S., and Maslivets, A.N., *Russ. J. Org. Chem.*, 2007, vol. 43, p. 1330.
2. Bannikova, Yu.N. and Maslivets, A.N., *Khim. Geterotsikl. Soedin.*, 2004, p. 124.
3. Bannikova, Yu.N., Maslivets, A.N., and Aliev, Z.G., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 1791.
4. Altomare, A., Cascarano, G., Giacovazzo, C., and Guarlardi, A., *J. Appl. Crystallogr.*, 1993, vol. 26, p. 343.
5. Sheldrick, G.M. SHELX-97. *Programs for Crystal Structure Analysis*, Gottingen: Univ. of Gottingen, 1998.