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Five-Membered Dioxoheterocycles: XCIX.* Reaction of 1-Aryl-4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones with Indoles. Crystal and Molecular Structure of Substituted 2-(Indol-3-yl)pyrrole

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Abstract—1-Aryl-4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones react with indole and 2-methylindole with the formation of methyl 1-aryl-3-aroyl-4-hydroxy-2-(1*H*-indol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylates. Crystal and molecular structure of methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate was examined.

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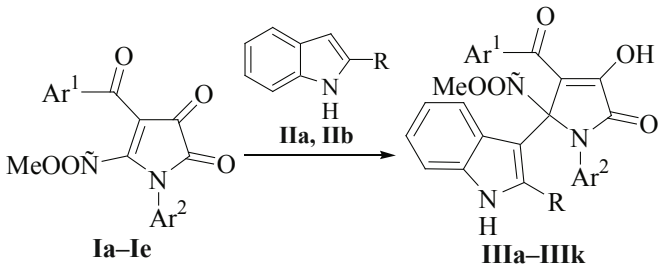
We formerly described spiro-bis-heterocyclizations of 1-aryl-4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones at the action of acyclic, carbocyclic, and heterocyclic enamines proceeding with the primary addition of the β-CH group of the enamino fragment to the C^5 atom of pyrroledione followed by the intramolecular cyclization through the attack of the amino group of the enamino fragment of enamines on the ester carbonyl group in the position *5* of pyrrolediones [2–4]. With the goal to prove the above scheme we chose heterocyclic enamines with the fixed (*E*)-location of the β-CH and NH groups of the enamino fragment thus excluding their intramolecular cyclization of the above described type.

At boiling 1-aryl-4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones **Ia–Ie** with indole (**IIa**) and 2-methylindole (**IIb**) in 1 : 1 ratio in anhydrous benzene within 10–20 min (when the intense red color of initial pyrrolediones disappeared) methyl 1-aryl-3-aroyl-4-hydroxy-2-(1*H*-indol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylates **IIIa–IIIk** were obtained whose structure was confirmed by X-ray diffraction (XRD) study by an example of compound **IIIf**.

Compounds **IIIa–IIIk** are colorless or light-yellow crystalline substances of high melting points, readily soluble in DMSO and DMF, sparingly soluble in alcohols and haloalkanes, insoluble in water and alkanes, showing a positive test for enol hydroxy group with the alcohol solution of iron(III) chloride.

The IR spectra of compounds **IIIa–IIIk** contain absorption bands of the stretching vibrations of the secondary amino group of indole as a narrow peak (3280–3436 cm^{-1}), of the enol OH group as a broad band



I, Ar^1 = Ph, Ar^2 = C_6H_4Br-4 (**a**), C_6H_4Me-4 (**b**), C_6H_4OMe-4 (**c**); Ar^1 = C_6H_4Br-4, Ar^2 = C_6H_4Me-4 (**d**); Ar^1 = C_6H_4Me-4, Ar^2 = C_6H_4OMe-4 (**e**); **II**, R = H (**a**), Me (**b**); **III**, R = H: Ar^1 = Ph, Ar^2 = C_6H_4Br-4 (**a**), C_6H_4Me-4 (**b**), C_6H_4OMe-4 (**c**); Ar^1 = C_6H_4Br-4, Ar^2 = C_6H_4Me-4 (**d**); Ar^1 = C_6H_4Me-4, Ar^2 = C_6H_4OMe-4 (**e**); R = Me: Ar^1 = Ar^2 = Ph (**f**); Ar^1 = Ph, Ar^2 = C_6H_4Br-4 (**g**), C_6H_4Me-4 (**h**), C_6H_4OMe-4 (**i**); Ar^1 = C_6H_4Br-4, Ar^2 = C_6H_4Me-4 (**j**); Ar^1 = C_6H_4Me-4, Ar^2 = C_6H_4OMe-4 (**k**).

* For Communication XCVIII, see [1].

(3141–3280 cm^{-1}), of methoxycarbonyl group (1731–1764 cm^{-1}), lactam carbonyl group (1686–1705 cm^{-1}), and aroyl carbonyl group in the region 1652–1674 cm^{-1}.

In the ^1H NMR spectra of solutions of compounds **IIIa–IIIe** in DMSO-d_6 along with proton signals of the aromatic rings and of groups bound to them signals are observed from the protons of the methoxycarbonyl group (3.74–3.76 ppm), the doublet of the indole proton H^2 (7.86–7.92 ppm), doublet of the proton of indole amino group (11.11–11.21 ppm), and the broadened singlet of the proton of OH group at 12.23–12.56 ppm.

In the ^1H NMR spectra of solutions of compounds **IIIf–IIIk** in DMSO-d_6 along with proton signals of the aromatic rings and of groups bound to them the following signals are present: a singlet of methyl protons of the 2-methylindole fragment (1.92–2.03 ppm), a singlet of the protons of the methoxycarbonyl group (3.50–3.54 ppm), a singlet of the proton of indole amino group (10.98–11.07 ppm), and a broadened singlet of the hydroxy group proton in the region 11.70–12.13 ppm.

According to XRD data compound **IIIf** crystallized in a centrosymmetric space group (Fig. 1). The bond lengths and bond angles in the molecule are close to standard values. The dihydropyrrole fragment of the molecule is flat within 0.016 Å. The phenyl and benzoyl substituents are turned at considerable angles with respect to the plane of the dihydropyrrole fragment and they are not involved in the conjugation with this heterocycle. In the crystal the molecules due to the contacts of the polar groups form polymeric chains (Fig. 2), and two types of contacts are present: a strong hydrogen bond of a "dimer" type between the carboxy groups and weaker interactions between the indole ring and the carbonyl of the benzoyl group C=O···H–N (*–x*, *–y*, *–z*). Evidently just this interaction governs the conformation of the benzoyl fragment where the carbonyl is deviated both from the plane of the dihydropyrrole ring and the plane of the phenyl substituent.

The described reaction confirms the previous assumption that the spiro-bis-heterocyclization of 1-aryl-4-aroyl-5-methoxycarbonyl-1*H*-pyrrole-2,3-diones at the action of enamines proceeds with the primary addition of β-CH group of the enamino fragment of enamines to the C^5 atom of the pyrrolediones.

EXPERIMENTAL

IR spectra of compounds obtained were recorded on a spectrophotometer Perkin Elmer Spectrum Two from mulls in mineral oil. ^1H NMR spectra were registered on a spectrometer Bruker WP-400 in DMSO-d_6, internal reference TMS. The homogeneity of compounds obtained was checked by TLC on Silufol plates, eluent ethyl acetate, development in iodine vapor.

Methyl 3-benzoyl-1-(4-bromophenyl)-4-hydroxy-2-(1*H*-indol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIa). A solution of 1 mmol of compound **Ia** and 1 mmol of pyrazole (**IIa**) in 10 mL of anhydrous benzene was boiled for 15 min, cooled, the separated precipitate was filtered off. Yield 91%, mp 235–236°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3356 (NH), 3189 br (OH), 1755 (COOMe), 1693 (C^2=O), 1668 (COPh). ^1H NMR spectrum, δ, ppm: 3.76 s (3H, COOMe), 7.02–7.55 group of signals (13H, Ph + $2C_6H_4$), 7.92 d (1H, H^2_{indole}, *J* 2.2 Hz), 11.21 d (1H, NH, *J* 2.2 Hz),

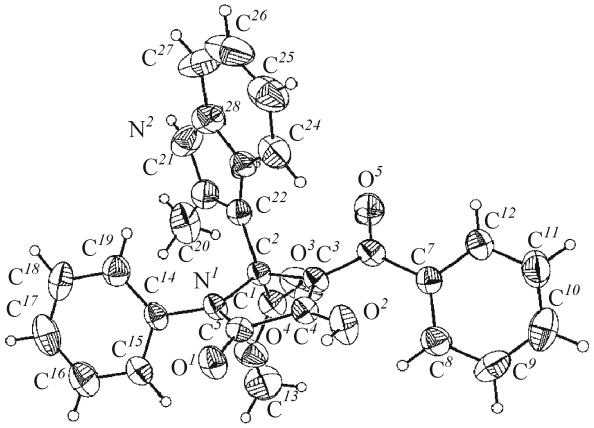


Fig. 1. General view of the molecule of methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (**IIIf**).

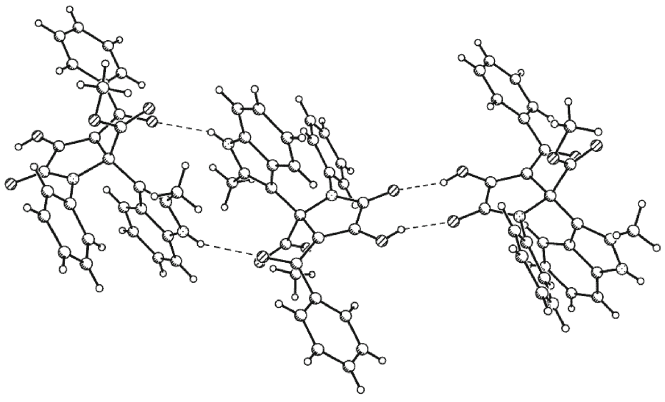


Fig. 2. Interaction of polar groups in the crystal of methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (**IIIf**).

12.41 br.s (1H, OH). Found, %: C 61.05; H 3.58; N 5.29. $C_{27}H_{19}BrN_2O_5$. Calculated, %: C 61.03; H 3.60; Br 15.04; N 5.27.

Compounds **IIIb–IIIk** were synthesized analogously.

Methyl 3-benzoyl-4-hydroxy-2-(1*H*-indol-3-yl)-5-oxo-1-(4-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIb). Yield 85%, mp 234–235°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3385 (NH), 3141 br (OH), 1755 (COOMe), 1693 (C^2=O), 1664 (COPh). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, Me), 3.75 s (3H, COOMe), 6.91–7.55 group of signals (13H, Ph + 2C$_6$H$_4$), 7.89 d (1H, H$^2_{indole}$, *J* 2.2 Hz), 11.13 d (1H, NH, *J* 2.2 Hz), 12.32 br.s (1H, OH). Found, %: C 72.11; H 4.74; N 6.02. $C_{28}H_{22}N_2O_5$. Calculated, %: C 72.09; H 4.75; N 6.01.

Methyl 3-benzoyl-4-hydroxy-2-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIc). Yield 80%, mp 178–179°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3280 (NH, OH), 1756 (COOMe), 1705 (C^2=O), 1669 (COPh). ^{1}H NMR spectrum, δ, ppm: 3.66 s (3H, MeO), 3.76 s (3H, COOMe), 6.79–7.57 group of signals (13H, Ph + 2C$_6$H$_4$), 7.88 d (1H, H$^2_{indole}$, *J* 2.2 Hz), 11.13 d (1H, NH, *J* 2.2 Hz), 12.34 br.s (1H, OH). Found, %: C 69.68; H 4.59; N 5.83. $C_{28}H_{22}N_2O_6$. Calculated, %: C 69.70; H 4.60; N 5.81.

Methyl 3-(4-bromobenzoyl)-4-hydroxy-2-(1*H*-indol-3-yl)-5-oxo-1-(4-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIId). Yield 91%, mp 201–203°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3460 (NH), 3179 br (OH), 1754 (COOMe), 1697 (C^2=O), 1674 (COAr). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, Me), 3.75 s (3H, COOMe), 6.88–7.62 group of signals (12H, 3C$_6$H$_4$), 7.88 d (1H, H$^2_{indole}$, *J* 2.2 Hz), 11.13 d (1H, NH, *J* 2.2 Hz), 12.56 br.s (1H, OH). Found, %: C 61.64; H 3.89; Br 14.60; N 5.16. $C_{28}H_{21}BrN_2O_5$. Calculated, %: C 61.66; H 3.88; Br 14.65; N 5.14.

Methyl 4-hydroxy-2-(1*H*-indol-3-yl)-3-(4-methylbenzoyl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIe). Yield 86%, mp 217–218°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3375 (NH), 3128 br (OH), 1754 (COOMe), 1686 (C^2=O), 1660 (COAr). ^{1}H NMR spectrum, δ, ppm: 2.29 s (3H, Me), 3.66 s (3H, MeO), 3.74 s (3H, COOMe), 6.78–7.48 group of signals (12H, 3C$_6$H$_4$), 7.86 d (1H, H$^2_{indole}$, *J* 2.2 Hz), 11.11 d (1H, NH, *J* 2.2 Hz), 12.23 br.s (1H, OH). Found, %: C 70.16; H 4.85; N 5.65. $C_{29}H_{24}N_2O_6$. Calculated, %: C 70.15; H 4.87; N 5.64.

Methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIf). Yield 89%, mp 217–218°C (decomp., *m*-xylene–ethyl acetate, 1 : 1). IR spectrum, ν, cm^{-1}: 3436 (NH), 3147 br (OH), 1764 (COOMe), 1692 (C^2=O), 1671 (COPh). ^{1}H NMR spectrum, δ, ppm: 1.97 s (3H, Me), 3.52 s (3H, COOMe), 6.89–7.56 group of signals (14H, 2Ph + C$_6$H$_4$), 11.00 s (1H, NH), 11.92 br.s (1H, OH). Found, %: C 72.11; H 4.73; N 6.02. $C_{28}H_{22}N_2O_5$. Calculated, %: C 72.09; H 4.75; N 6.01.

X-ray diffraction analysis of compound IIIf was carried out on an automatic single crystal diffractometer Xcalibur 3 at 295(2) K (MoK_α-radiation, graphite monochromator, ω/2θ-scanning in the range $2.59° < \theta < 26.39°$). Crystallographic data: monoclinic system, *a* 15.5819(16), *b* 9.5948(11), *c* 17.2380(13) Å, β 115.312(9)°, space group $P2_1/c$, *Z* 4, d_{calc} 1.330 g/cm^3. Intensity of 11290 reflections was measured, among them 4585 independent (R_{int} 0.0658), in particular, 1760 with $I > 2\sigma(I)$. The completeness of the data array for the angles $\theta < 26.0°$ is 96.5%. No correction for extinction was introduced because of its negligible value (μ 0.092 mm^{-1}). The structure was solved by the direct method and refined by least-squares method in the anisotropic-isotropic (for H atoms) approximation applying the SHELXTL-97 software [5]. The position of hydrogen atoms was calculated geometrically (rider model) save atoms of the NH and OH groups whose positions were refined in the isotropic approximation. The final values of the divergence factors are as follows: wR_2 0.0751, R_1 0.0427 for 2926 reflections with $I > 2\sigma(I)$ and wR_2 0.1193, R_1 0.1594 for all reflections at the quality factor S 1.001. The maximum and minimum peaks of the residual electron density are 0.324 and –0.286 e Å^{-3} respectively. The complete set of crystallographic data was deposited to Cambridge Crystallographic Data Center (CCDC no. 982524) and it is available at the address ww.ccdc.cam.ac.uk/conts/retrieving.html.

Methyl 3-benzoyl-1-(4-bromophenyl)-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIg). Yield 81%, mp 211–213°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3302 (NH), 3165 br (OH), 1756 (COOMe), 1691 (C^2=O), 1671 (COPh). ^{1}H NMR spectrum, δ, ppm: 2.03 s (3H, Me), 3.53 s (3H, COOMe), 6.90–7.63 group of signals (13H, Ph + 2C$_6$H$_4$), 11.07 c (1H, NH), 11.96 br.s (1H, OH). Found, %: C 61.65; H 3.86; Br 14.71; N 5.15. $C_{28}H_{21}BrN_2O_5$. Calculated, %: C 61.66; H 3.88; Br 14.65; N 5.14.

Methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-(4-tolyl)-2,5-dihydro-1*H*-pyrrole-2-

carboxylate (IIIh). Yield 84%, mp 224–225°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3410 (NH), 3152 br (OH), 1755 (COOMe), 1690 (C^2=O), 1667 (COPh). ^{1}H NMR spectrum, δ, ppm: 1.96 s (3H, Me), 2.22 s (3H, Me), 3.52 s (3H, COOMe), 6.76–7.63 group of signals (13H, Ph + $2C_6H_4$), 10.99 s (1H, NH), 11.89 br.s (1H, OH). Found, %: C 72.51; H 5.02; N 5.85. $C_{29}H_{24}N_2O_5$. Calculated, %: C 72.49; H 5.03; N 5.83.

Methyl 3-benzoyl-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIi). Yield 91%, mp 231–232°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3373 (NH), 3158 br (OH), 1743 (COOMe), 1691 (C^2=O), 1652 (COPh). ^{1}H NMR spectrum, δ, ppm: 1.94 s (3H, 2-Me), 3.52 s (3H, COOMe), 3.68 s (3H, MeO), 6.73–7.56 group of signals (13H, Ph + $2C_6H_4$), 10.99 s (1H, NH), 11.89 br.s (1H, OH). Found, %: C 70.17; H 4.86; N 5.63. $C_{29}H_{24}N_2O_6$. Calculated, %: C 70.15; H 4.87; N 5.64.

Methyl 3-(4-bromobenzoyl)-4-hydroxy-2-(2-methyl-1*H*-indol-3-yl)-5-oxo-1-(4-tolyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIj). Yield 83%, mp 198–199°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3422 (NH), 3158 br (OH), 1731 (COOMe), 1693 (C^2=O), 1669 (COAr). ^{1}H NMR spectrum, δ, ppm: 1.95 s (3H, 2-Me), 2.22 s (3H, 4-Me), 3.54 s (3H, COOMe), 6.74–7.67 group of signals (12H, $3C_6H_4$), 11.00 s (1H, NH), 12.13 br.s (1H, OH). Found, %: C 62.24; H 4.12; Br 14.22; N 4.99. $C_{29}H_{23}BrN_2O_5$. Calculated, %: C 62.26; H 4.14; Br 14.28; N 5.01.

Methyl 4-hydroxy-3-(4-methylbenzoyl)-2-(2-methyl-1*H*-indol-3-yl)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1*H*-pyrrole-2-carboxylate (IIIk). Yield 80%, mp 217–218°C (decomp., benzene). IR spectrum, ν, cm^{-1}: 3362 (NH), 3153 br (OH), 1736 (COOMe), 1694 (C^2=O), 1672 (COAr). ^{1}H NMR sectrum, δ, ppm: 1.92 s (3H, 2-Me), 2.33 s (3H, 4-Me), 3.50 s (3H, COOMe), 3.68 s (3H, MeO), 6.72–7.47 group of signals (12H, $3C_6H_4$), 10.98 c (1H, NH), 11.70 br.s (1H, OH). Found, %: C 70.60; H 5.14; N 5.47. $C_{30}H_{26}N_2O_6$. Calculated, %: C 70.58; H 5.13; N 5.49.

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