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Five-Membered 2,3-Dioxo Heterocycles: LX.* Reaction of 3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with Cyclic Enehydrazino Ketones. Crystalline and Molecular Structure of *N*-[3′-Benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-3-nitrobenzamide

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Abstract—3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones react with N′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)benzohydrazides to give the corresponding *N*-[3′-aroyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]benzamides. The molecular and crystalline structure of one of the products, *N*-[3′-benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-3-nitrobenzamide, was determined by X-ray analysis.

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Nucleophilic transformations of 1*H*-pyrrole-2,3-diones, including those fused at the [*a*] side to various heterocycles, by the action of O- and N-mono- and N,N-, N,O-, and N,S-binucleophiles underlie convenient methods for the synthesis of carbonyl derivatives of five- and six-membered nitrogen-containing heterocycles, ensembles of such heterocycles, and fused heterocyclic systems which attract interest from the viewpoint of biological activity [2, 3].

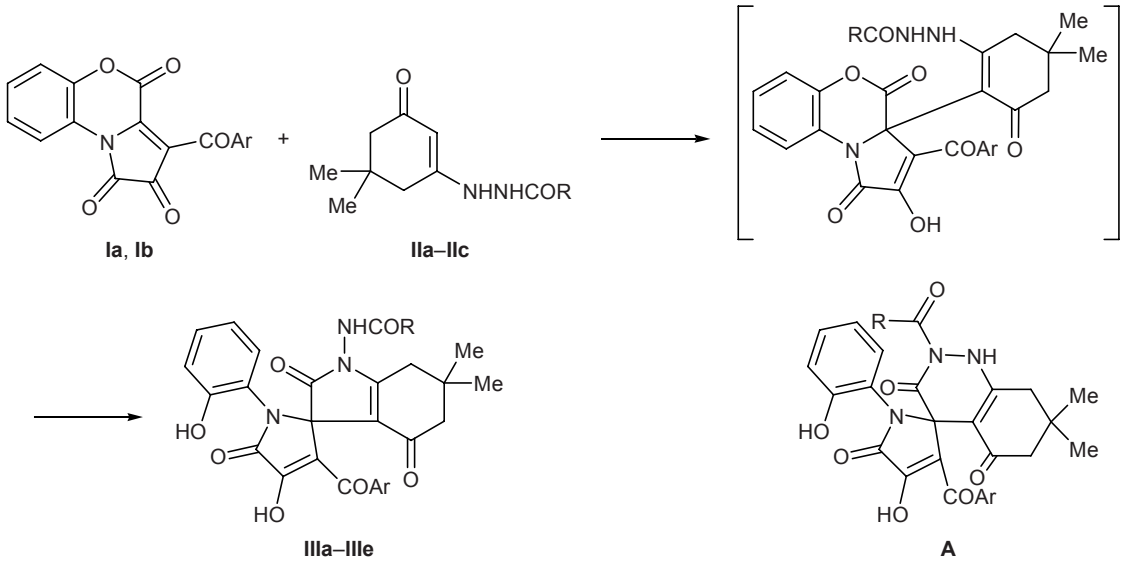
We previously showed that 4-acyl-2,3-dihydro-1*H*-pyrrole-2,3-diones fused to a 1,4-benzoxazine fragment, namely 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia** and **Ib**, react with substituted alkyl 3-aminoprop-2-enoates (β-enamino esters), as well as with 1,3-C,N-binucleophiles, via addition of the activated β-CH group in the enamino fragment at the C^{3a} carbon atom of pyrrolobenzoxazine **I**, followed by pyrrole ring closure as a result of intramolecular attack by the side-chain amino group on the lactone carbonyl carbon atom in the benzoxazine fragment and cleavage of the C^4–O^5 bond. The products of these reactions were alkyl 4-aroyl-3-hydroxy-1-(2-hydroxyphenyl)-2,6-dioxo-1,7-diazaspiro[4.4]nona-3,8-diene-9-carboxylates [1].

In continuation of our studies on reactions of hetareno[*a*]pyrrole-2,3-diones with nucleophiles, in the present work we examined transformations of 3-aroyl-substituted 1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia** and **Ib** in reactions with cyclic enehydrazino ketones. As the latter we used *N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-2-hydroxybenzohydrazide (**IIa**), 2-amino-*N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-benzohydrazide (**IIb**), and *N*′-(5,5-dimethyl-3-oxocyclohex-1-en-1-yl)-3-nitrobenzohydrazide (**IIc**). Pyrrolobenzoxazinetriones **Ia** and **Ib** reacted with substituted benzohydrazides **IIa**–**IIc** at a ratio of 1:1 on heating in boiling anhydrous *m*-xylene to give in 8–15 min the corresponding *N*-[3′-aroyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]benzamides **IIIa**–**IIIe** (Scheme 1) whose structure was confirmed by X-ray analysis of compound **IIIe****

* For communication LIX, see [1].

** For preliminary communication, see [4].

Scheme 1.



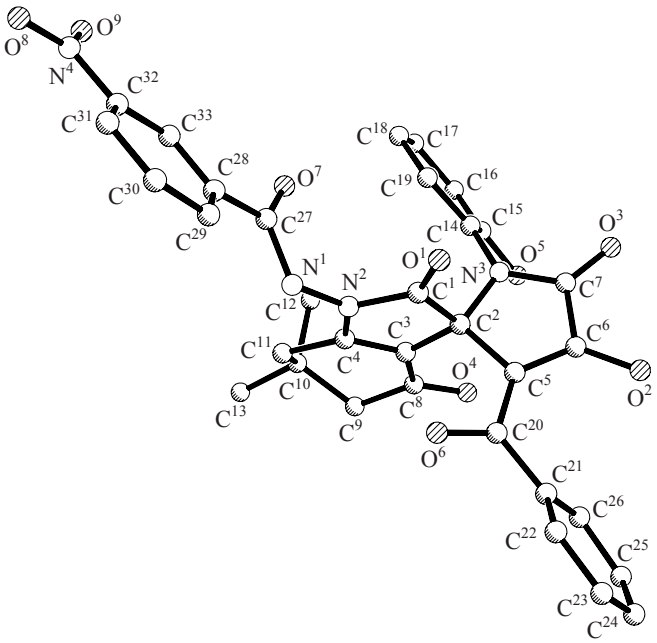
Ia, **Ib** **IIa–IIc** **IIIa–IIIe** **A**

I, Ar = Ph (**a**), 4-BrC_6H_4 (**b**); **II**, R = 2-HOC_6H_4 (**a**), 2-$H_2NC_6H_4$ (**b**), 3-$O_2NC_6H_4$ (**c**); **III**, R = 2-HOC_6H_4, Ar = Ph (**a**), 4-BrC_6H_4 (**b**); R = 2-$H_2NC_6H_4$, Ar = Ph (**c**), 4-BrC_6H_4 (**d**); Ar = Ph, R = 3-$O_2NC_6H_4$ (**e**).

(Fig. 1). Compounds **IIIa**–**IIIe** are light yellow crystalline substances which melt with decomposition at a high temperature; they are readily soluble in DMF and DMSO, poorly soluble in common organic solvents, and insoluble in saturated hydrocarbons and water. The presence of enolic and phenolic hydroxy groups in their molecules was confirmed by a positive color test (cherry color) with an alcoholic solution of iron(III) chloride.

The IR spectra of spiro compounds **IIIa**–**IIIe** contained absorption bands belonging to stretching vibrations of the OH and NH groups (a broad band in the region 3165–3458 cm^{-1}), two lactam carbonyl groups (two peaks at 1698–1778 cm^{-1}), and ArC=O, $NHCOC_6H_4$, and C^4=O groups (1605–1666 cm^{-1}); also, amide II band was present at 1524–1578 cm^{-1}. Compounds **IIIa**–**IIIe** showed in the ^1H NMR spectra (DMSO-d_6) signals from protons in the aromatic rings and substituents therein, two singlets from the methyl groups in the cyclohexenone fragment (δ 0.78–0.86 ppm), signals from two methylene groups in the cyclohexenone fragment (δ 2.01–2.42 ppm), a singlet from the phenolic hydroxy proton (δ 9.20–9.35 ppm), a singlet from the exocyclic amide NH proton (δ 11.33–12.03 ppm) and a broadened singlet from the enolic hydroxy proton (δ 12.40–12.60 ppm). The ^{13}C NMR spectrum of **IIIb** in DMSO-d_6 contained the following signals, δ_C, ppm: 190.26 (C^4); 187.92 (**C**OC_6H_4); 172.57, 167.58, 165.79, 165.21 (C^2O, C^{7a}, $C^{5'}$, $C^{4'}$); 158.92 (NH**C**OC_6H_4); 153.23 ($C^{3'}$); 136.69–107.91 (C_{arom}); 67.61 [$C^3(C^{2'})$], 50.59 (C^5); 48.57 (C^7), 33.59 (C^6); 27.57 (CH_3).

According to the X-ray diffraction data, compound **IIIe** crystallizes as solvate with methanol at a ratio of 1 : 1.5. One methanol molecule is located in the general position. The oxygen atom in the second methanol



Structure of the molecule of *N*-[3′-benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-3-nitrobenzamide (**IIIe**) according to the X-ray diffraction data (hydrogen atoms are not shown).

Parameters of hydrogen bonds D–H···A in the crystalline structure of *N*-[3′-benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-3-nitrobenzamide (**IIIe**).

D–H	*d*(D–H), Å	*d*(H···A), Å	∠DHA, deg	*d*(D···A), Å	A
O^5–H^5	1.016	2.036	133.97	2.838	O^4
O^5–H^5	1.016	2.138	124.94	2.844	N^3
N^1–H^1	0.836	2.084	176.29	2.918	O^3 [$x + 1, y, z$]
O^{10}–H^{10}	1.076	1.687	170.64	2.754	O^6
O^2–H^2	1.019	1.644	144.06	2.540	O^{10} [$x - 1, y, z$]

molecule occupies the symmetry center, its carbon atom is statistically disordered by two positions, and the molecule is characterized by large thermal vibrations. All bond lengths and bond angles in molecule **IIIe** conform to the corresponding standard values. The planes of the benzene rings in the hydroxyphenyl and benzoyl fragments are almost parallel (the corresponding dihedral angle is 178.1°) and are turned through dihedral angles close to 60° (62.6 and 61.2°, respectively) with respect to the pyrrole ring plane. The benzoyl fragment is not planar: the torsion angle $O^6C^{20}C^{21}C^{22}$ is equal to –40.9°. The benzoyl oxygen atom deviates from the benzene ring plane by 0.83 Å, and from the pyrrole ring plane, by 0.58 Å. The orientation of the benzoylamino group is characterized by the torsion angles $C^1N^2N^1C^{27}$ 84.8, $N^2N^1C^{27}O^7$ 13.3, and $N^1C^{27}C^{28}C^{29}$ 25.1°. The bend along the $C^9\cdots C^{11}$ line is 45.3° toward the hydroxyphenyl group on N^3. The hydroxy proton in the hydroxyphenyl fragment is likely to be involved in intramolecular hydrogen bond with O^4 and N^3 (bifurcate bond). The molecule of methanol occupying the general crystallographic position forms hydrogen bonds O^{10}–$H^{10}\cdots O^6$ and O^2–$H^2\cdots O^{10}$ with molecules **IIIe**, giving rise to an infinite chain along the *a* axis. Molecules **IIIe** in that chain are also linked through intramolecular hydrogen bonds N^1–$H^1\cdots O^3$; however, the $H^1\cdots O^3$ distance suggests that this bond is relatively weak. The hydrogen bond parameters are given in table.

Presumably, the process involves addition of the β-CH group of cyclic enehydrazino ketone **II** at the C^{3a} atom of the pyrrolobenzoxazine system (as in reactions of compounds **I** with mononucleophiles) [2, 3], followed by nucleophilic attack by the NH group on the lactone carbonyl carbon atom (C^4) and cleavage of the C^4–O^5 bond. Closure of pyridazine ring with formation of structure **A** does not occur, presumably because of lower nucleophilicity of the NH group adjacent to the benzoyl carbonyl group.

The described reaction is a rare example of synthesis of a difficultly accessible spiro[indole-3,2′-pyrrole] heterocyclic system with various substituents in both heterocyclic fragments.

EXPERIMENTAL

The IR spectra were recorded in mineral oil on an FSM-1201 spectrometer. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer at 400 MHz for ^{1}H using DMSO-d_6 as solvent and TMS as internal reference. The purity of the products was checked by TLC on Silufol plates using ethyl acetate and ethyl acetate–benzene (1:5) as eluents; spots were visualized by treatment with iodine vapor.

***N*-[3′-Benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-2-hydroxybenzamide (IIIa).** A solution of 1.0 mmol of compound **Ia** and 1.0 mmol of cyclic enehydrazine **IIa** in 10 ml of anhydrous *m*-xylene was heated for 10 min under reflux. The mixture was cooled, and the precipitate was filtered off. Yield 86%, mp 205–206°C (from methanol). IR spectrum, ν, cm^{-1}: 3450, 3264 br (NH, OH); 1762, 1715 (C^2=O, $C^{5'}$=O); 1650 (1-NHC=O), 1625 (C^4=O, 3′-C=O), 1578 (δNH). ^{1}H NMR spectrum, δ, ppm: 0.78 s (3H, Me), 0.86 s (3H, Me), 2.04 d.d and 2.12 d.d (1H each, 7-H, J = 16.0 Hz), 2.23 d.d and 2.40 d.d (1H each, 5-H, J = 18.3 Hz), 6.73–7.93 m (13H, H_{arom}), 9.32 s (1H, OH), 11.33 s (1H, NH), 11.46 s (1H, OH), 12.40 br.s (1H, 4′-OH). Found, %: C 64.60; H 3.48; N 6.06. $C_{33}H_{27}N_3O_8$. Calculated, %: C 66.77; H 4.58; N 7.08.

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

***N*-[3′-(4-Bromobenzoyl)-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,-6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-2-hydroxybenzamide (IIIb).** Yield 85%, mp 239–240°C

(from methanol). IR spectrum, ν, cm^{-1}: 3455, 3233 br (NH, OH); 1762, 1708 (C^2=O, $C^{5'}$=O); 1650, 1624 (C^4=O, 3′-C=O, 1-NHC=O), 1541 (δNH). ^{1}H NMR spectrum, δ, ppm: 0.79 s (3H, Me), 0.86 s (3H, Me), 2.04 d.d and 2.09 d.d (1H each, 7-H, *J* = 15.9 Hz), 2.24 d.d and 2.41 d.d (1H each, 5-H, *J* = 18.2 Hz), 6.79–7.90 m (12H, H_{arom}), 9.39 s (1H, OH), 11.34 s (1H, NH), 11.43 s (1H, OH), 12.60 br.s (1H, 4′-OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 190.26 (C^4=O); 187.92 (**C**OC_6H_4); 172.57, 167.58, 165.79, 165.21 (C^2, C^{7a}, $C^{5'}$, $C^{4'}$); 158.92 (NHCO); 153.23 ($C^{3'}$); 136.69–107.91 (C_{arom}); 67.61 (C_{spiro}); 50.59 (C^5); 48.57 (C^7); 33.59 (C^6); 27.57 (CH_3). Found, %: C 57.60; H 3.90; Br 12.70; N 5.25. $C_{33}H_{26}BrN_3O_3$. Calculated, %: C 58.94; H 3.90; Br 11.88; N 6.25.

2-Amino-*N*-[3′-benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,-6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-benzamide (IIIc). Yield 91%, mp 202–204°C (from methanol). IR spectrum, ν, cm^{-1}: 3457, 3165 br (NH, OH); 1778, 1715 (C^2=O, $C^{5'}$=O); 1666, 1613 (C^4=O, 3′-C=O, 1-NHCO), 1561 (δNH). ^{1}H NMR spectrum, δ, ppm: 0.81 s (3H, Me), 0.85 s (3H, Me), 2.01 d.d and 2.13 d.d (1H each, 7-H, *J* = 15.7 Hz), 2.17 d.d and 2.37 d.d (1H each, 5-H, *J* = 18.1 Hz), 6.53–7.75 m (13H, H_{arom}), 7.76 br.s (2H, NH_2), 9.21 s (1H, OH), 11.34 s (1H, NH), 12.40 br.s (1H, 4′-OH). Found, %: C 66.88; H 3.99; N 9.01. $C_{33}H_{28}N_4O_7$. Calculated, %: C 66.88; H 4.76; N 9.45.

2-Amino-*N*-[3′-(4-bromobenzoyl)-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,-5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]benzamide (IIId). Yield 89%, mp 227–230°C (from methanol). IR spectrum, ν, cm^{-1}: 3458, 3168 br (NH, OH); 1775, 1711 (C^2=O, $C^{5'}$=O); 1658, 1619, 1608 (C^4=O, 3′-C=O, 1-NHC=O); 1556 (δNH). ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, Me), 0.83 s (3H, Me), 2.02 d.d and 2.09 d.d (1H each, 7-H, *J* = 15.7 Hz), 2.19 d.d and 2.31 d.d (1H each, 5-H, *J* = 18.1 Hz), 6.52–7.73 m (12H, H_{arom}), 7.75 br.s (2H, NH_2), 9.20 s (1H, OH), 11.33 s (1H, NH), 12.40 br.s (1H, 4′-OH). Found, %: C 60.03; H 3.75; Br 10.92; N 8.50. $C_{33}H_{27}BrN_4O_7$. Calculated, %: C 59.03; H 4.05; Br 11.90; N 8.34.

***N*-[3′-Benzoyl-4′-hydroxy-1′-(2-hydroxyphenyl)-6,6-dimethyl-2,4,5′-trioxo-1′,4,5,5′,6,7-hexahydrospiro[indole-3,2′-pyrrol]-1(2*H*)-yl]-3-nitrobenzamide (IIIe).** Yield 87%, mp 230–232°C (from methanol). IR spectrum, ν, cm^{-1}: 3377 br, 3214 br (NH, OH); 1771, 1698 (C^2=O, $C^{5'}$=O); 1655, 1620, 1605 (3′-C=O, C^4=O, 1-NHC=O); 1524 (δNH). ^{1}H NMR spectrum, δ, ppm: 0.80 s (3H, Me), 0.86 s (3H, Me), 2.03 d.d and 2.14 d.d (1H each, 7-H, *J* = 15.9 Hz), 2.26 d.d and 2.42 d.d (1H each, 5-H, *J* = 18.5 Hz), 6.76–8.51 m (13H, H_{arom}), 9.35 s (1H, OH), 12.03 s (1H, NH), 12.40 br.s (1H, 4′-OH). Found, %: C 62.57; H 4.01; N 9.50. $C_{33}H_{26}N_4O_9$. Calculated, %: C 63.66; H 4.21; N 9.00.

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REFERENCES

1. Racheva, N.L., Aliev, Z.G., Belova, M.A., Mashevskaya, I.V., and Maslivets, A.N., *Russ. J. Org. Chem*., 2008, vol. 44, p. 701.
2. Maslivets, A.N. and Mashevskaya, I.V., *2,3-Digidro-2,3-pirroldiony* (2,3-Dihydropyrrole-2,3-diones), Perm: Perm. Gos. Univ., 2005, p. 126.
3. Mashevskaya, I.V. and Maslivets, A.N., *2,3-Digidro-2,3-pirroldiony, kondensirovannye s razlichnymi geterotsiklami storonoi [a], i ikh benzo[b]analogi: sintez, khimicheskie svoistva, prakticheskoe primenenie* (2,3-Dihydropyrrole-2,3-diones Fused at the [*a*] Side to Various Heterocycles and Their Benzo[*b*] Analogs: Synthesis, Chemical Properties, and Practical Applications), Perm: Perm. Gos. Sel'skokhoz. Akad., 2003, p. 140.
4. Racheva, N.L., Aliev, Z.G., and Maslivets, A.N., *Russ. J. Org. Chem*., 2008, vol. 44, p. 937.