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## Five-Membered 2,3-Dioxo Heterocycles: CI.\* Reaction of 3-Aroylpyrrolo[2,1-c][1,4]benzoxazine-1,2,4-triones with Arylhydrazines. Crystal and Molecular Structure of Substituted 2-Hydrazonopyrrolo[2,1-c][1,4]benzoxazine

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**Abstract**—A new direction of nucleophilic attack was revealed in the reactions of 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with *o*-tolylhydrazine and 2-hydrazinylbenzoic acid hydrochloride, which afforded the corresponding hydrazones at the  $C^2$ =O carbonyl group, substituted 2-(2-*o*-tolylhydrazono)pyrrolo[2,1-*c*]-[1,4]benzoxazine-1,4(2*H*)-diones and pyrrolo[2,1-*c*][1,4]benzoxazin-2(4*H*)-ylidenehydrazinylbenzoic acids. The structure of (*Z*)-2-{2-[3-benzoyl-1,4-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acid was determined by X-ray analysis.

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We previously showed [2] that hetareno[*e*]pyrrole-2,3-diones react with both mono- and binucleophiles according to only two paths of initial nucleophilic addition, at the carbon atom in position I or 3a of the substrate molecule. Unexpectedly, the reactions of 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with *ortho*-substituted phenylhydrazines gave products of nucleophilic attack at the C<sup>2</sup> atom, the corresponding arylhydrazones.

The reactions were carried out by heating 3-aroylpyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **Ia**–**Ic** with 2-hydrazinylbenzoic acid or *o*-tolylhydrazine at a ratio of 1:1 in boiling anhydrous acetonitrile (1-3 min; TLC and HPLC monitoring). As a result, we isolated (Z)-2-{2-[3-aroyl-1,4-dioxo-1*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acids **IIa**, **IIc**, and **IIe** and (Z)-3-aroyl-2-(2-*o*-tolylhydrazono)-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,4(2*H*)-diones **IIb** and **IId** (Scheme 1). Their structure was confirmed by X-ray analysis of **IIa** [3] (see figure).

Compounds **IIa–IIe** are dark red high-melting crystalline substances which are soluble in DMF and DMSO, sparingly soluble in alcohols and haloalkanes, and insoluble in water and saturated hydrocarbons. The



I, Ar = Ph(a), 4-MeC<sub>6</sub>H<sub>4</sub> (b), 4-MeOC<sub>6</sub>H<sub>4</sub>O (c); II, Ar = Ph, R = COOH(a); Ar = 4-MeC<sub>6</sub>H<sub>4</sub>, R = Me(b), COOH (c); Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>, R = Me(d), COOH (e).

<sup>\*</sup> For communication C, see [1].



Structure of the molecule of (Z)-2-{2-[3-benzoyl-1,4-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acid (**Ha**) according to the X-ray diffraction data with atom numbering. Non-hydrogen atoms are shown as thermal vibration ellipsoids at the 50% probability level.

IR spectra of **Ha–He** contained absorption bands at 3300–3200 cm<sup>-1</sup> due to stretching vibrations of the OH and NH groups and carbonyl absorption bands at 1715–1732 (lactone, COOH in **Ha**, **Hc**, **He**), 1662–1669 (lactam carbonyl involved in intramolecular hydrogen bond), and 1626–1636 cm<sup>-1</sup> (3-C=O). Compounds **Ha–He** displayed in the <sup>1</sup>H NMR spectra signals from protons in the aromatic rings and substituents therein, a singlet at  $\delta$  14.60–14.97 ppm from the NH proton, and a broadened singlet at  $\delta$  13.60–13.72 ppm from the COOH proton (**Ha**, **Hc**, **He**). The 9-H signal appeared as a doublet in the region  $\delta$  8.61–8.82 ppm due to deshielding effect of the C<sup>1</sup>=O carbonyl group.

The structure of compound **IIa** was determined by X-ray analysis (see figure). It crystallized as a 1:1 solvate with DMF in the centrosymmetric space group

Parameters of intra- and intermolecular hydrogen bonds in the crystal structure of (*Z*)-2-{2-[3-benzoyl-1,4-dioxo-1*H*pyrrolo[2,1-*c*][1,4]-benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acid (**Ha**)

D–H…A	d(D–H), Å	$d(\mathbf{H}\cdots\mathbf{A}),$ Å	∠DHA, deg	$d(\mathbf{D}\cdots\mathbf{A}),$ Å
$N^1$ – $H^1$ ···· $O^4$	0.956(14)	1.912(14)	135(1)	2.678(2)
$N^1$ – $H^1$ ···· $O^1$	0.956(14)	2.117(14)	125(1)	2.778(2)
$O^6 - H^6 \cdots O^{1S}$	0.98(2)	1.60(2)	163(1)	2.548(2)
[-x, -y+2, -z+1]				

belonging to the triclinic crystal system. The bond lengths and bond angles in molecule **Ha** showed no appreciable differences from the corresponding standard values. The  $C^1-C^2$ ,  $C^3-C^4$ , and  $C^4-C^5$  bond lengths in the heteroring are within 1.45(2) Å and are typical of single bonds in conjugated chains rather than of classical aromatic bonds. Thus, the examined heterocyclic system should be regarded as heteropolyene rather than heteroaromatic structure.

The molecular fragment including the heterocycle, hydrazone moiety, and carboxyphenyl substituent is planar; deviations of atoms from the mean-square plane do not exceed 0.250 Å (for O<sup>4</sup> in the carboxy group). Taking into account the extent of this fragment and its conformational mobility, its fairly planar structure is determined by formation of bifurcate intramolecular hydrogen bond between the N<sup>1</sup>H proton in the hydrazone fragment, on the one hand, and carbonyl oxygen atoms O<sup>1</sup> and O<sup>4</sup>, on the other (see table). The planar molecular fragments in crystal are packed so that to form stacks with an interplanar distance of ~3.3 Å, which suggests essential  $\pi$ - $\pi$  interactions.

The benzoyl fragment in molecule **IIa** is turned through a dihedral angle of  $73.1(2)^{\circ}$  (C<sup>4</sup>C<sup>3</sup>C<sup>12</sup>C<sup>13</sup>) with respect to the heterocyclic system, and the dihedral angle between the mean-square planes O<sup>3</sup>C<sup>12</sup>C<sup>13</sup>C<sup>3</sup> and C<sup>13</sup>C<sup>14</sup>C<sup>15</sup>C<sup>16</sup>C<sup>17</sup>C<sup>18</sup>, which characterizes rotation of the phenyl ring about the carbonyl group, is 29.4(2)°. As a result, the phenyl ring appears in close proximity to polar fragments of the neighboring molecule [-x, 2 - y, 1 - z] so that short intermolecular contact H<sup>14.4</sup>...O<sup>1</sup> 2.540 Å is observed. Unfortunately, the available structural data do not allow us to estimate the nature of this contact.

The crystal packing of **Ha** may be described as layered, where the planar molecular fragments are oriented approximately parallel to the [15 15 16] plane while benzoyl fragments deviate from that plane. Solvation DMF molecules occupy voids in the crystal packing and are held via intermolecular hydrogen bonds between the carbonyl group of DMF molecule and carboxy group of **Ha**. The crystallographic data for compound **Ha** were deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 990590; *http://www.ccdc.cam.uk*).

## **EXPERIMENTAL**

The IR spectra were recorded on Perkin Elmer Spectrum Two and FSM-1201 spectrometers from samples dispersed in mineral oil. The <sup>1</sup>H NMR spectra were measured on a Bruker AM-400 instrument at 400 MHz using DMSO- $d_6$  as solvent and TMS as reference. The reaction conditions were optimized with the aid of ultra-HPLC (Waters Acquity UPLC BEH C<sub>18</sub> column, 1.7 µm; eluents methanol–water and acetonitrile–water, flow rate 0.3–0.5 mL/s; ESI MS Hevo TQD detector). The purity of the isolated compounds was checked by ultra-HPLC and TLC on Silufol plates (ethyl acetate, ethyl acetate–benzene, 1:5; development with iodine vapor).

(Z)-2-{2-[3-Benzoyl-1,4-dioxo-1*H*-pyrrolo[2,1-*c*]-[1,4]benzoxazin-2(4H)-ylidene]hydrazinyl}benzoic acid (IIa). A solution of 1.0 mmol of 2-hydrazinylbenzoic acid hydrochloride in 30 mL of a 10:1 mixture of anhydrous acetonitrile and DMSO was added to a solution of 1.0 mmol of compound Ia in 30 mL of anhydrous acetonitrile. The mixture was heated for 2 min under reflux and cooled, and the precipitate was filtered off and recrystallized from acetonitrile. Yield 47%, mp 275–277°C (from MeCN). IR spectrum, v, cm<sup>-1</sup>: 3300 br, 3200 (OH, NH); 1732 (C<sup>4</sup>=O, COOH), 1669 (C<sup>1</sup>=O), 1636 (3-C=O). <sup>1</sup>H NMR spectrum, δ, ppm: 7.23–8.12 m (12H,  $H_{arom}$ ), 8.63 d (1H, 9-H, J =8.0 Hz), 13.60 br.s (1H, COOH), 14.87 s (1H, NH). Found, %: C 66.21; H 3.31; N 9.25. C<sub>25</sub>H<sub>15</sub>N<sub>3</sub>O<sub>6</sub>. Calculated, %: C 66.23; H 3.33; N 9.27.

The X-ray diffraction data for compound **IIa** were acquired on an Xcalibur S (Oxford Diffraction) automatic four-circle diffractometer with a CCD detector. The unit cell parameters and experimental reflection intensities were measured at 295(2) K by  $\omega/2\theta$  scanning in the range 2.64 <  $\theta$  < 28.28 with a step of 1 deg under monochromatized  $MoK_a$  radiation. Triclinic crystal system,  $C_{28}H_{22}N_4O_7$ , with the following unit cell parameters: a = 8.463(2), b = 11.609(3), c =12.8717(19) Å;  $\alpha = 83.952(16), \beta = 76.505(17), \gamma =$  $85.75(2)^\circ$ ; V = 1221.3(5) Å<sup>3</sup>; M 526.50;  $d_{calc} =$ 1.432 g/cm<sup>3</sup>; Z = 2; space group P-1. Total of 7184 reflection intensities were measured, 5783 of which were independent ( $R_{int} = 0.0304$ ) and 2438 reflections were characterized by  $I > 2\sigma(I)$ ; completeness 0.966 for  $\theta = 26.00^{\circ}$ . No correction for absorption was applied ( $\mu = 0.105 \text{ mm}^{-1}$ ). The structure was solved by the direct statistical method and was refined against  $F^2$ by the full-matrix least-squares procedure in anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms in the OH and NH groups were visualized directly, and their positions were refined independently; the other hydrogen atoms were placed in geometrically calculated positions and were refined

in isotropic approximation with dependent thermal parameters. All calculations were performed using SHELX97 software package [6]. The final divergence factors were  $R_1 = 0.0394$ ,  $wR_2 = 0.0585$  for reflections with  $I > 2\sigma(I)$  and  $R_1 = 0.1167$ ,  $wR_2 = 0.0625$  for all reflections; goodness of fit S = 1.003; maximum and minimum residual electron densities 0.178 and  $-0.173 \ \bar{e}/\text{Å}^3$ .

Compounds **IIb–IIe** were synthesized as described above for **IIa**.

**3-(4-Methylbenzoyl)-2-[2-(2-methylphenyl)hydrazono]-1***H***-pyrrolo[2,1-***c***][1,4]benzoxazine-1,4(2***H***)-dione (IIb). Yield 57%, mp 244–246°C (from MeCN). IR spectrum, v, cm<sup>-1</sup>: 3300 br, 3200 (OH, NH); 1718 (C<sup>4</sup>=O); 1669 (C<sup>1</sup>=O); 1630 (3-C=O). <sup>1</sup>H NMR spectrum, \delta, ppm: 2.49 s (3H, Me), 2.51 s (3H, Me), 7.04–8.03 m (11H, H<sub>arom</sub>), 8.82 d (1H, 9-H, J = 8.0 Hz), 14.80 s (1H, NH). Found, %: C 71.38; H 4.37; N 9.59. C<sub>26</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>. Calculated, %: C 71.39; H 4.38; N 9.61.** 

(Z)-2-{2-[3-(4-Methylbenzoyl)-1,4-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acid (IIc). Yield 54%, mp 282– 284°C (from MeCN). IR spectrum, v, cm<sup>-1</sup>: 3300 br, 3200 (OH, NH); 1720 (C<sup>4</sup>=O, COOH); 1660 (C<sup>1</sup>=O); 1629 (3-C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 2.44 s (3H, Me), 7.03–8.04 m (11H, H<sub>arom</sub>), 8.61 d (1H, 9-H, *J* = 8.0 Hz), 13.70 br.s (1H, COOH), 14.60 s (1H, NH). Found, %: C 66.79; H 3.65; N 8.97. C<sub>26</sub>H<sub>17</sub>N<sub>3</sub>O<sub>6</sub>. Calculated, %: C 66.81; H 3.67; N 8.99.

(*Z*)-3-(4-Methoxybenzoyl)-2-(2-methylphenylhydrazono)-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,4(2*H*)-dione (IId). Yield 49%, mp 267–269°C (from MeCN). IR spectrum, v, cm<sup>-1</sup>: 3300 br, 3200 (OH, NH); 1715 (C<sup>4</sup>=O); 1667 (C<sup>1</sup>=O); 1633 (3-C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 2.52 s (3H, Me), 3.83 s (3H, OMe),7.03–8.08 m (11H, H<sub>arom</sub>), 8.73 d (1H, 9-H, *J* = 8.0 Hz), 14.97 s (1H, NH). Found, %: C 69.68; H 4.10; N 9.02. C<sub>27</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>. Calculated, %: C 69.67; H 4.11; N 9.03.

(Z)-2-{2-[3-(4-Methoxybenzoyl)-1,4-dioxo-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazin-2(4*H*)-ylidene]hydrazinyl}benzoic acid (IIe). Yield 59%, mp 227– 229°C (from MeCN). IR spectrum, v, cm<sup>-1</sup>: 3300 br, 3200 (OH, NH); 1710 (C<sup>4</sup>=O, COOH); 1662 (C<sup>1</sup>=O); 1626 (3-C=O). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 3.86 s (3H, OMe), 7.03–8.04 m (11H, H<sub>arom</sub>), 8.63 d (1H, 9-H, *J* = 8.0 Hz), 13.72 br.s (1H, COOH), 14.80 s (1H, NH). Found, %: C 64.58; H 3.53; N 8.67. C<sub>26</sub>H<sub>17</sub>N<sub>3</sub>O<sub>7</sub>. Calculated, %: C 64.60; H 3.54; N 8.69. This study was performed under financial support by the Ministry of Education and Science of the Russian Federation, by the Ministry of Education of Perm Krai (International Research Teams Competition), and by the Russian Foundation for Basic Research (project nos. 12-03-00696, 13-03-96009).

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