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Five-Membered 2,3-Dioxo Heterocycles: LXII.* Reaction of 3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones with *N*,*N*′-Dihydroxycyclohexane-1,2-diamine. Unusual Rearrangement in the Spiro[quinoxaline-2,2′-pyrrole] System

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Abstract—3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones reacted with *N*,*N*′-dihydroxycyclohexane-1,2-diamine to give 3-aroyl-1′,4,4′-trihydroxy-1-(2-hydroxyphenyl)-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[pyrrole-2,2′-quinoxaline]-3′,5(1*H*,4′*H*)-diones which underwent rearrangement into 1′-aroyloxy-4,4′-dihydroxy-1-(2-hydroxyphenyl)-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-3′,4,5(4′*H*)-triones via [1,4]-migration of the aroyl group. The product structure was proved by X-ray analysis.

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2,3-Dihydro-1*H*-pyrrole-2,3-diones fused at the [*a*] side to various heterocycles react with difunctional nucleophiles to give polyoxo heterocyclic systems that are difficult to obtain by other methods [2]. We previously found that reactions of 3-aroyl-1*H*-pyrrolo-[2,1-*c*][1,4]benzoxazine-1,2,4-triones **I** with *o*-phenylenediamine and *o*-aminobenzenethiol [3, 4] under mild conditions lead to recyclization products as a result of successive attacks by the two nucleophilic centers on the C^{3a} and C^4 atoms in compound **I** and opening of the oxazine ring at the C^4–O^5 bond and pyrrole ring at the C^{3a}–N^{10} bond. It was interesting to involve in these reactions another type of nitrogen-centered binucleophiles, *N*,*N*′-dihydroxy-1,2-diamines. It is known that reactions of the latter with polycarbonyl compounds and enones underlie convenient procedures for the synthesis of functionally substituted derivatives of *N*-hydroxypyrazine [5] and *N*-hydroxy-1,4-diazepine [6] or the corresponding *N*-oxides.

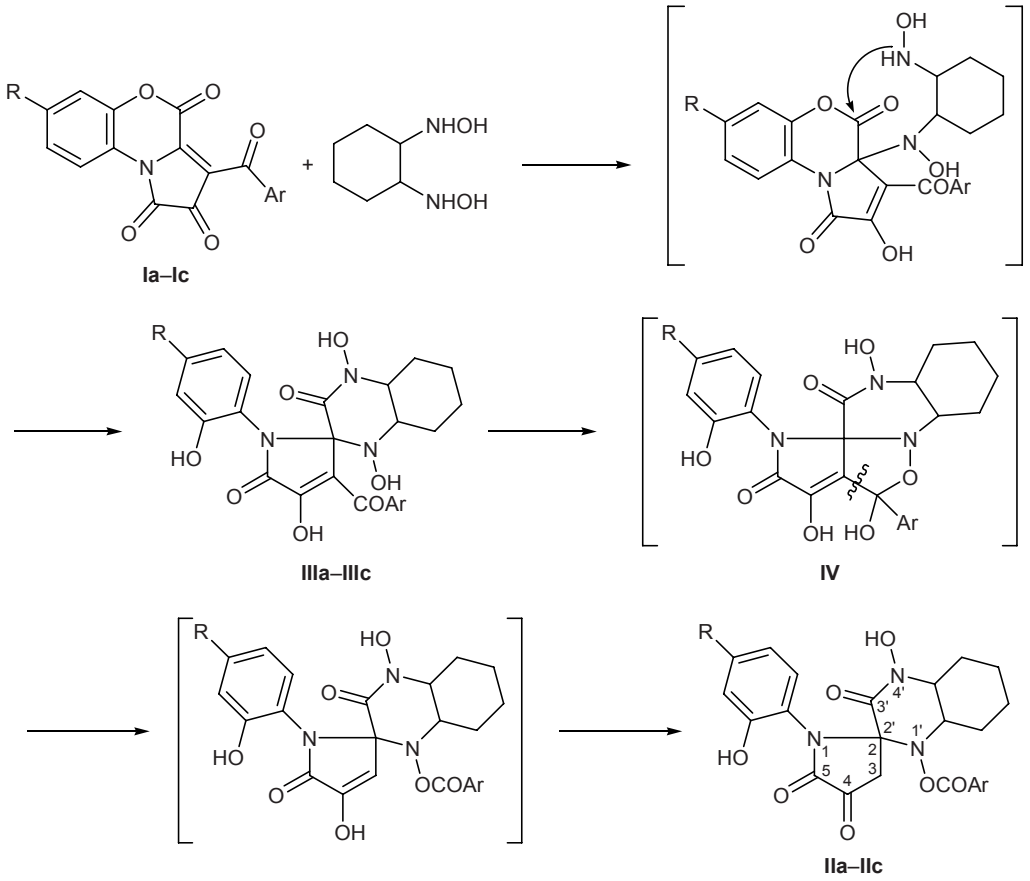
By reactions of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]-benzoxazine-1,2,4-triones **Ia**–**Ic** with *N*,*N*′-dihydroxycyclohexane-1,2-diamine [7] at a ratio of 1:1 (boiling anhydrous acetonitrile, 2–3 min [3, 4]) we obtained compounds **IIa**–**IIc** whose spectral parameters did not allow us to unambiguously determine their structure. On the basis of the X-ray diffraction data for compound **IIa** (Fig. 1) the products were assigned the structure of 1′-aroyloxy-4′-hydroxy-1-(2-hydroxyphenyl)hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-3′,4,5(4′*H*)-triones (Scheme 1).

Compounds **IIa**–**IIc** are colorless high-melting (with decomposition) crystalline substances which are readily soluble in dimethylformamide and dimethyl sulfoxide, poorly soluble in common organic solvents, and insoluble in saturated hydrocarbons and water; they show a positive test (dark cherry color) for phenolic hydroxy group on treatment with an alcoholic solution of iron(III) chloride.

Compounds **IIa**–**IIc** displayed in the IR spectra absorption bands belonging to stretching vibrations of OH group (broad bands in the regions 3360–3410 and 3100–3320 cm^{-1}), OCOAr ester carbonyl group (1770–1780 cm^{-1}), C^5=O lactam carbonyl group (1740–

* For communication LXI, see [1].

Scheme 1.



R = H, Ar = Ph (**a**), 4-MeC$_6$H$_4$ (**b**); R = Me, Ar = 4-MeC$_6$H$_4$ (**c**).

1760 cm^{-1}), C^4=O (1730–1740 cm^{-1}), and C$^{3'}$=O lactam carbonyl groups (1650–1690 cm^{-1}). The ^{1}H NMR spectra of **IIa**–**IIc** in DMSO-d_6 contained signals from aromatic protons, methyl protons in tolyl groups, 5′-H–8′-H methylene protons (δ 1.62–1.65 ppm, m, 8H), 3-H (δ 3.06–3.77 ppm, d.d, *AB* system), 4a-H and 8a-H (δ 3.64–3.85 ppm), OH (δ 8.65–8.83 ppm, s), and N–OH (δ 10.51–10.54 ppm, s). In the ^{13}C NMR spectrum of compound **IIb** in DMSO-d_6 the following signals were present, δ_C, ppm: 195.0 (C^4), 170.3 (C$^{3'}$), 162.9 (OCO), 158.5 (C^5), 153.4 (C$^{2''}$), 144.7 (C$^{4'''}$), 122.8 (C$^{1''}$), 129.5–116.2 (C$_{arom}$), 85.2 (C$_{spiro}$), 59.7 (C^{8a}), 59.3 (C^{4a}), 40.1 (C^3), 39.1 (C$^{8'}$), 38.9 (C$^{5'}$), 25.7 (C$^{6'}$), 21.9 (C$^{7'}$), 20.7 (Me).

Figure 1 shows the structure of molecule **IIa** as determined by X-ray analysis (hydrogen atoms are not shown). All bond lengths conform to the corresponding standard values. The pyrazine ring adopts a weakly distorted *envelope* conformation. The bend angle along the N^2···C^{12} line is 53.2°, and the C^{13} atom deviates by 0.71 Å from the mean-square plane formed by the other five atoms. The N^1 atom has almost planar configuration (the sum of the bond angles at N^1 is 359.4°) which is stabilized by intramolecular hydrogen bond O^1–H^1···O^2 [2.635(5) Å]. The N^2 atom is pyramidal; the sum of the bond angles at that atom is 320.7°. The planar benzoyl group on N^2 occupies bisector position relative to the pyrazine ring, and the C^{18}=O^6 bond is directed toward the unshared electron pair on the nitrogen atom. Molecules duplicated by the glide reflection plane *n* are linked through intermolecular hydrogen bond O^1–H^1···O^4 [2.872(6) Å] so that the O^1–H^1 hydroxy group is involved in bifurcate hydrogen bond (intra- and intermolecular). The hydrogen bond O^1–H^1···O^2 is characterized by the following parameters: D–H 1.06(7), H···A 2.17(6), D···A 2.635(5) Å; ∠DHA 104(4)° (here, D and A stand for the donor and acceptor atoms, respectively). The solvate acetone molecule is linked to molecule **IIa** by the hydrogen bond O^7–H^7···O^8 [2.887(7) Å]. No other shortened intermolecular contacts were found in the crystalline structure of compound **IIa**.

Presumably, the primary recyclization products, spiro compounds **III**, are formed according to a scheme analogous to that described by us previously [3, 4], i.e., via successive nucleophilic attacks by the NH groups of *N*,*N*′-dihydroxycyclohexane-1,2-diamine on the C^{3a} and C^4 atoms in **Ia**–**Ic** and opening of the oxazine ring at the C^4–O^5 bond. We succeeded in isolating one intermediate product, compound **IIIc**, as individual substance; it underwent rearrangement to **IIc** upon attempted recrystallization.

Compound **IIIc** is a light yellow crystalline substance which is readily soluble in common organic solvents and insoluble in unsaturated hydrocarbons and water. The presence of enolic and phenolic hydroxy groups in molecule **IIIc** was confirmed by positive color test (cherry color) with an alcoholic solution of iron(III) chloride. The spectral parameters of **IIIc** are very consistent with those reported by us previously for structurally related spiro[indole-3,2′-pyrroles] [8] whose structure was proved by X-ray analysis.

Compounds **III** are unstable, and their rearrangement into final products **IIa**–**IIc** is likely to involve intramolecular addition of the 1′-OH group at the carbonyl carbon atom in the aroyl group with formation of intermediate tricyclic isoxazolidine derivatives **IV** [9]; cleavage of the C^4–C^5 bond in the isoxazolidine ring yields compounds **II**. Thus initially formed spiro compounds **III** are stabilized via unexpected [1, 4] C→O migration of the aroyl group rather than via opening of the pyrrole ring as described in [3, 4].

With a view to elucidate whether the above rearrangement is possible we compared the thermodynamic stabilities of the ketone and enol tautomers of intermediate and final compounds **IIIa** and **IIa** on the basis of the results of *ab initio* calculations [10]. Conformational analysis of each tautomer using STO-3G basis set gave a structure corresponding to the global minimum on the potential energy surface (Fig. 2, see table). As followed from the calculated *ab initio* [6-31G(*d*)] energies of formation of the most stable conformers, the ketone tautomer of **II** is more thermodynamically stable, the energy difference being 16.3 kcal/mol.

EXPERIMENTAL

The IR spectra were recorded on an FSM-1201 spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 instrument at 400.13 and 100.2 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The purity of the products was checked by thin-layer chromatography on Silufol plates using ethyl acetate or ethyl acetate–benzene (1:5) as eluent; the chromatograms were developed by treatment with iodine vapor.

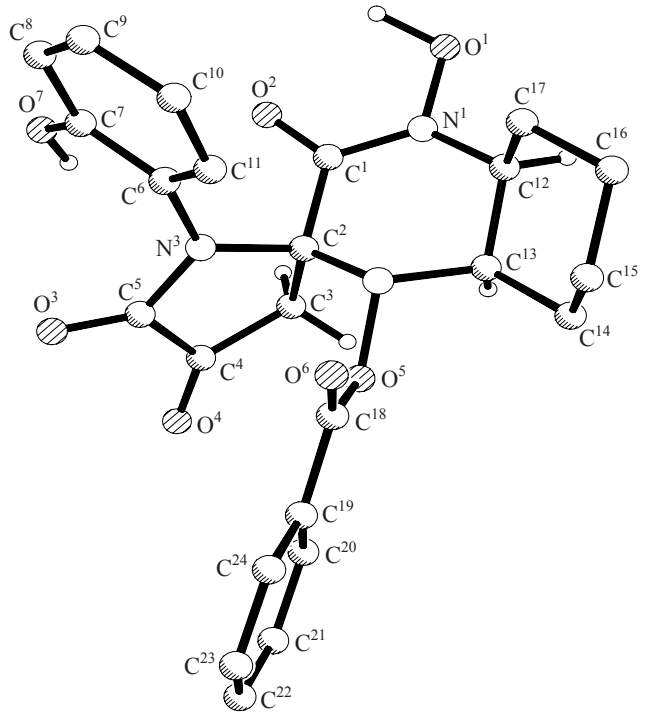


Fig. 1. Structure of the molecule of 1′-benzoyloxy-4′-hydroxy-1-(2-hydroxyphenyl)hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-3′,4,5(4′*H*)-trione (**IIa**) according to the X-ray diffraction data.

1′-Benzoyloxy-4′-hydroxy-1-(2-hydroxyphenyl)-hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-

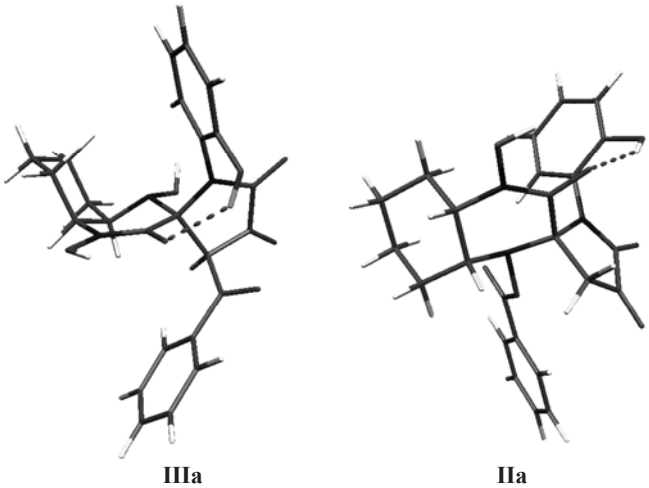


Fig. 2. Conformations of molecules **IIIa** (ketone) and **IIa** (ketone) simulated by HF/6-31G(*d*) calculations.

Energies of formation (a.u.) of structures **IIa** and **IIIa**, calculated *ab initio* using STO-3G and 6-31G(*d*) basis sets

Compound no.	STO-3G	6-31G(*d*)
IIa (ketone)	–1589.22841	–1608.84735
IIIa (ketone, *R*)	–1589.20091	–1608.82142
IIIa (ketone, *S*)	–1589.19190	
IIIa (enol)	–1589.18807	

3′,4,5(4′*H*)-trione (IIa). A solution of 1.0 mmol of *N*,*N*′-dihydroxycyclohexane-1,2-diamine in 30 ml of anhydrous acetonitrile was added dropwise to a solution of 1.0 mmol of compound **Ia** in 30 ml of anhydrous acetonitrile. The mixture was heated for 2–3 min at 60°C and cooled, and the precipitate was filtered off. Yield 78%, mp 210–212°C (decomp., from acetone). IR spectrum, ν, cm^{-1}: 3410, 3320 br (OH); 1780 (OCO); 1760 (C^5=O); 1740 (C^4=O); 1690 ($C^{3'}$=O). ^{1}H NMR spectrum, δ, ppm: 1.65 m (8H, 5′-H, 6′-H, 7′-H, 8′-H), 3.65 m (1H, 8a′-H), 3.85 m (1H, 4a′-H), 3.10 d.d and 3.66 d.d (1H each, 3-H, *AB* system, *J* = 15.3 Hz), 7.27 m (9H, H_{arom}), 8.83 s (1H, 2″-OH), 10.54 s (1H, 4′-OH). Found (after drying at 90–95°C under reduced pressure), %: C 61.86; H 4.98; N 8.95. $C_{24}H_{23}N_3O_7$. Calculated, %: C 61.93; H 4.97; N 9.03.

Compounds **IIb** and **IIc** were synthesized in a similar way.

4′-Hydroxy-1-(2-hydroxyphenyl)-1′-(4-methylbenzoyloxy)-hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-3′,4,5(4′*H*)-trione (IIb). Yield 80%, mp 161–162°C (decomp., from acetone). IR spectrum, ν, cm^{-1}: 3360, 3100 br (OH); 1770 (OCO); 1740 (C^5=O); 1730 (C^4=O); 1650 ($C^{3'}$=O). ^{1}H NMR spectrum, δ, ppm: 1.64 m (8H, 5′-H, 6′-H, 7′-H, 8′-H), 2.38 s (3H, Me), 3.09 d.d and 3.77 d.d (1H each, 3-H, *AB* system, *J* = 15.3 Hz), 3.64 m (1H, 8a′-H), 3.85 m (1H, 4a′-H), 7.29 m (7H, H_{arom}), 8.81 s (1H, 2″-OH), 10.52 s (1H, 4′-OH). Found, %: C 62.59; H 5.21; N 8.71. $C_{25}H_{25}N_3O_7$. Calculated, %: C 62.62; H 5.26; N 8.76.

4′-Hydroxy-1-(2-hydroxy-4-methylphenyl)-1′-(4-methylbenzoyloxy)-hexahydro-1′*H*-spiro[pyrrolidine-2,2′-quinoxaline]-3′,4,5(4′*H*)-trione (IIc). Yield 79%, mp 199–200°C (decomp., from acetone). IR spectrum, ν, cm^{-1}: 3360, 3250 (OH); 1780 (OCO); 1760 (C^5=O); 1740 (C^4=O); 1670 ($C^{3'}$=O). ^{1}H NMR spectrum, δ, ppm: 1.62 m (8H, 5′-H, 6′-H, 7′-H, 8′-H), 2.28 s (3H, Me), 2.49 s (3H, Me), 3.06 d.d and 3.75 d.d (1H each, 3-H, *AB* system, *J* = 15.3 Hz), 3.64 m (1H, 8a′-H), 3.84 m (1H, 4a′-H), 7.19 m (7H, H_{arom}), 8.65 s (1H, 2″-OH), 10.51 s (1H, 4′-OH). Found, %: C 63.25; H 5.48; N 8.49. $C_{26}N_{27}N_3O_7$. Calculated, %: C 63.28; H 5.52; N 8.51.

1′,4,4′-Trihydroxy-1-(2-hydroxy-4-methylphenyl)-3-(4-methylbenzoyl)-4a′,5′,6′,7′,8′,8a′-hexahydro-1′*H*-spiro[pyrrole-2,2′-quinoxaline]-3′,5(1*H*,4′*H*)-dione (IIIc). A solution of 1.0 mmol of *N*,*N*′-dihydroxycyclohexane-1,2-diamine in 30 ml of anhydrous acetonitrile was added dropwise to a solution of 1.0 mmol of compound **Ic** in 30 ml of anhydrous acetonitrile. The precipitate was filtered off and reprecipitated from 5 ml of dioxane with 1 ml of hexane. Yield 67%, mp 112–113°C (decomp.). IR spectrum, ν, cm^{-1}: 3410, 3100 br (OH), 1750 (C^5=O), 1695 ($C^{3'}$=O), 1680 (COC_6H_4Me-*p*). ^{1}H NMR spectrum, δ, ppm: 1.46 m (8H, 5′-H, 6′-H, 7′-H, 8′-H), 2.27 s (3H, Me), 2.38 s (3H, Me), 3.56 m (2H, 8a′-H, 4a′-H), 7.30 m (7H, H_{arom}), 8.09 s (1H, 4′-OH), 9.20 s (1H, 1′-OH), 10.30 s (1H, 2″-OH), 11.65 s (1H, 4-OH). ^{13}C NMR spectrum, δ_C, ppm: 191.1 (3-CO), 164.9 ($C^{3'}$), 159.5 (C^5), 154.3 (C^4), 151.7 ($C^{2''}$), 143.3 ($C^{4''}$), 131.3 ($C^{4'''}$), 130.25 (C^3), 128.8–117.3 (C_{arom}), 88.6 (C_{spiro}), 59.3 ($C^{8a'}$), 54.2 ($C^{4a'}$), 39.9 ($C^{4'}$), 39.1 ($C^{8'}$), 26.9 ($C^{5'}$), 23.6 ($C^{6'}$), 21.3 ($C^{7'}$), 21.1 and 20.9 (Me). Found, %: C 63.29; H 5.46; N 8.43. $C_{26}H_{27}N_3O_7$. Calculated, %: C 63.28; H 5.52; N 8.51.

X-Ray diffraction data for compound IIa. Monoclinic crystals, $C_{24}H_{23}N_3O_7 \cdot (CH_3)_2CO$; unit cell parameters: *a* = 13.706(3), *b* = 11.437(2), *c* = 17.046(3) Å; β = 108.50(3), γ = 104.32(3)°; *V* = 2589.0(9) $Å^3$; *M* 523.53; d_{calc} = 1.343 g/cm^3; *Z* = 2; space group *P*2(1)/*n*. Total of 5027 independent reflections (R_{int} = 0.0688) were measured on a KM-4 Kuma Diffraction automatic four-circle diffractometer (χ geometry, monochromatized CuK_α irradiation, ω/2Θ scanning, 2Θ ≤ 160.48°). No correction for absorption was introduced (μ = 0.834 mm^{-1}). The structure was solved by the direct method using SIR92 program [11] with subsequent calculation of electron density maps. Hydrogen atoms in the hydroxy groups were visualized objectively by difference synthesis of electron density, and positions of the other hydrogen atoms were set on the basis of geometry considerations. The positions of non-hydrogen atoms were refined by the least-squares procedure in full-matrix anisotropic approximation using SHELXL-97 software package [12]. The final divergence factor was R_1 = 0.0872 [19384 reflections with $I \geq 2\sigma(I)$]; goodness of fit 0.919.

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