

Cyclization of Aroylacetic Acids 2-Carboxyphenylamides into 2-[(Z)-2-Aryl-2-hydroxy-1-ethenyl]-4*H*-3,1-benzoxazin-4-ones. Crystal and Molecular Structure of 2-[(Z)-2-Hydroxy-2-phenyl-1-ethenyl]-4*H*-3,1-benzoxazin-4-one

E. S. Vostrov^a, A. A. Novikov^a, A. N. Maslivets^a, and Z. G. Aliev^b

^aPerm State University, Perm 614990 Russia

e-mail: koh2@psu.ru

^bInstitute of Problems of Chemical Physics, Russian Academy of Sciences, Chernogolovka

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Abstract—2-Carboxyphenylamides of aroylacetic acids undergo cyclization when treated with dehydrating agents to give 2-[(Z)-2-aryl-2-hydroxy-1-ethenyl]-4*H*-3,1-benzoxazin-4-ones. Crystal and molecular structure of the latter phenyl derivative was studied by X-ray crystallography.

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Heterocyclic enaminoketones, namely, 3-acylmethylene-3,4-dihydro-2*H*-1,4-benzoxazin-2-ones [1], 3-acylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones [2], 3-acylmethylene-3,4-dihydro-2-phenylquinoxalines [3], 2-acylmethylene-3-aryl-1,2,3,4-tetrahydro-4-quinazolones [4], and 3-acylmethylenepiperazin-2-ones [5], exist in enaminoketone form as demonstrated by X-ray diffraction studies. In all compounds investigated an intramolecular hydrogen bond of H-chelate type was observed between the NH group of the heterocycle and the carbonyl of acylmethylene fragment; therewith the hydrogen involved into the hydrogen bond was localized at the nitrogen of the enaminoketone moiety.

In extension of studies on the synthesis of new classes of heterocyclic enaminoketones and on investigating fine features of their structure we performed intramolecular cyclization of aroylacetic acids 2-carboxyanilides by treating them with dehydrating agents. The arising benzoxazinones are polyfunctional reagents and can serve as starting compounds for the synthesis of representatives of new classes of extensively studied nowadays dioxo-heterocycles and heterocumulenes based thereon.

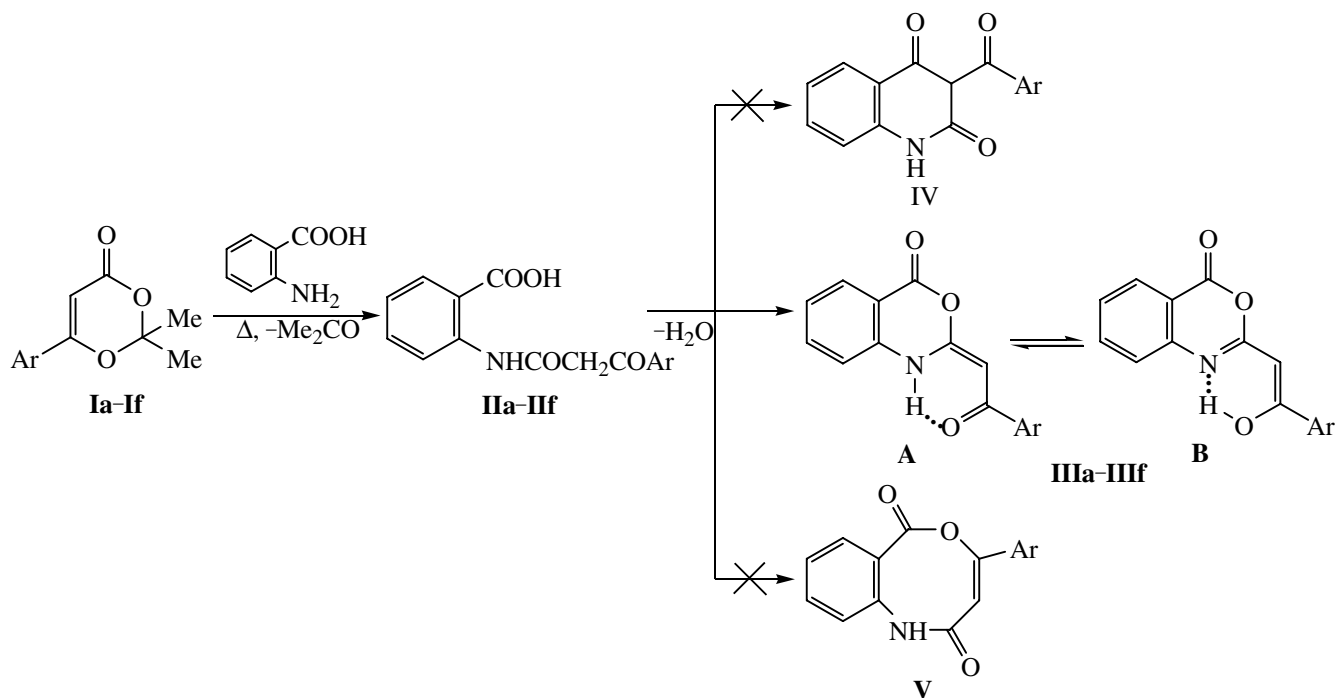
Two convenient methods were published for preparation of aroylacetyl amides: aroylacylation of amines [6] and amides [7] with aroylketenes generated by thermolysis of 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones, and reaction of ethyl benzoylacetate with arylamines [8].

We used the former procedure for preparation of aroyl-acetic acids 2-carboxyphenylamides, initial compounds for investigation of intramolecular cyclization.

Boiling at 137–138°C for 15–20 min of solutions in *m*-xylene of 6-aryl-2,2-dimethyl-4*H*-1,3-dioxin-4-ones **Ia–If** in the presence of an equivalent amount of anthranilic acid led to the formation of aroylacetic acids 2-carboxyphenylamides **IIa–IIIf**. Spectral characteristics of anilides **IIa–IIIf** are reported in EXPERIMENTAL and are well consistent with those of similar in structure aroylacetic acids amides [6–8].

Anilides **IIa–IIIf** taken in the ratio 1:1 with dehydrating agents, e.g., at boiling in benzene with acetic anhydride for 1.5–2 h (method *a*) or at boiling in dichloroethane with dicyclohexylcarbodiimide for 25–30 min (method *b*) yielded light-yellow crystalline compounds **IIIa–IIIIf**. For the obtained products of the intramolecular cyclization of anilides **IIa–IIIf** we failed to make unambiguous choice among isomeric structures: based only on spectral data 2-aroylmethylene-1,2-dihydro-4*H*-3,1-benzoxazin-4-ones (**A**, **B**), 3-aroyl-1,2,3,4-tetrahydroquinolin-2,4-diones **IV**, or 4-aryl-1,6-dihydro-2*H*-benzo[*C*][1,5]oxazocine-2,6-diones **V**, and also to establish the localization in the compounds of the hydrogen involved into the intramolecular hydrogen bond. Therefore the application of X-ray crystallography was necessary. The X-ray diffraction analysis showed that compound **IIIa** was 2-[(Z)-2-hydroxy-2-phenyl-1-ethenyl]-4*H*-3,1-benzoxazin-4-one.

Scheme.



Ar = Ph (**a**), 4-MeC₆H₄ (**b**), 4-MeOC₆H₄ (**c**), 4-EtOC₆H₄ (**d**), 4-ClC₆H₄ (**e**), 4-BrC₆H₄ (**f**).

A single crystal of compound **IIIa** was specially grown from benzene for the X-ray diffraction study. The general view of **IIIa** molecule is presented on the figure.

The main bond lengths in the molecule are given below. The analysis of these interatomic distances unambiguously shows that the hydrogen atom is localized on the oxygen. The molecule is virtually planar containing an intramolecular hydrogen bond O—H $\cdots$ N. The distance N $\cdots$ H³ equals 1.71 Å, and the angle at the hydrogen is 146°.

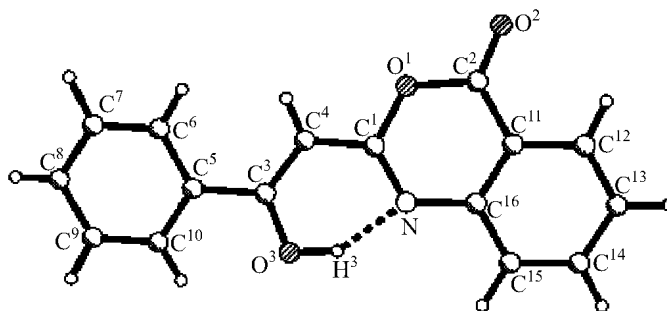
Bond	<i>d</i> , Å
O ¹ —C ¹	1.368(3)
O ¹ —C ²	1.393(3)
O ² —C ²	1.199(3)
O ³ —C ³	1.311(3)
N—C ¹	1.305(3)
C ¹ —C ⁴	1.411(4)
C ³ —C ⁴	1.366(4)
C ³ —C ⁵	1.486(4)

Thus the intramolecular cyclization of anilides **II** effected by dehydrating agents resulted in formation of benzoxazinones **IV**. At the same time the localization of hydrogen in the enaminoketone fragment at the oxygen atom of the hydroxyenimine fragment tautomeric to the enaminoketone one is not only quite unexpected, but

obviously contrasts with the structure of the formerly studied heterocyclic enaminoketones [1–5]; the reason of this phenomenon requires a separate study. It should also be noted that the established localization of the hydrogen suggests new interpretation of the abnormal results of reactions between some heterocyclic enaminoketones with oxalyl chloride leading to the closure of a furandione [9, 10] and not a pyrroledione ring.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ¹H and ¹³C NMR spectra were registered on a spectrometer Bruker AM-400 (400 MHz), internal reference TMS. Mass spectra were taken



Structure of 2-[(Z)-2-hydroxy-2-phenyl-1-ethenyl]-4H-3,1-benzoxazin-4-one (**IIIa**).

on MKh-1320, ionizing electrons energy 70eV. The homogeneity of compounds synthesized was confirmed by TLC on Silufol plates, eluent benzene–ethyl acetate, 5:1, development in iodine vapor.

Benzoylactic acid *N*-(2-carboxyphenyl)amide (IIa). A solution of 4.9 mmol of dioxinone **Ia** and 4.9 mmol of anthranilic acid in 2 ml of *m*-xylene was boiled for 10–15 min, cooled, the precipitate was filtered off. Yield 1.10 g (79%), mp 177–178°C (ethanol). IR spectrum, ν , cm^{-1} : 3160 br (NH, COOH), 1698 (COOH), 1685 br (CONH, C(=O)Ph), 1540 (“amide II”). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 4.31 s (2H, CH_2), 7.18–8.44 group of signals (9H, C_6H_4 + Ph), 11.26 s (1H, NH), 13.60 br.s (1H, COOH). Found, %: C 67.76; H 4.60; N 5.00. $\text{C}_{16}\text{H}_{13}\text{NO}_4$. Calculated, %: C 67.84; H 4.63; N 4.94.

Compounds **IIb–IIf** were similarly obtained.

4-Toluoylactic acid *N*-(2-carboxyphenyl)amide (IIb). Yield 1.12 g (77%), mp 157–158°C (ethanol). IR spectrum, ν , cm^{-1} : 3150 br (NH, COOH), 1700 (COOH), 1675 br (CONH, COC_6H_4), 1535 (“amide II”). ^1H NMR spectrum (CDCl_3), δ , ppm: 2.40 s (3H, Me), 4.16 s (2H, CH_2), 7.11–8.69 group of signals (8H, $2\text{C}_6\text{H}_4$), 11.38 s (1H, NH). Found, %: C 68.70; H 5.08; N 4.73. $\text{C}_{17}\text{H}_{15}\text{NO}_4$. Calculated, %: C 68.68; H 5.09; N 4.71.

4-Methoxybenzoylactic acid *N*-(2-carboxyphenyl)amide (IIc). Yield 1.07 g (70%), mp 175–176°C (ethanol). IR spectrum, ν , cm^{-1} : 3145 br (NH, COOH), 1703 (COOH), 1670 br (CONH, COC_6H_4), 1533 (“amide II”). ^1H NMR spectrum ($\text{DMSO}-d_6$), δ , ppm: 3.86 s (3H, MeO), 4.22 s (2H, CH_2), 7.05–8.44 group of signals (8H, $2\text{C}_6\text{H}_4$), 11.26 s (1H, NH), 13.58 br.s (1H, COOH). Found, %: C 65.25; H 4.80; N 4.45. $\text{C}_{17}\text{H}_{15}\text{NO}_5$. Calculated, %: C 65.17; H 4.83; N 4.47.

4-Ethoxybenzoylactic acid *N*-(2-carboxyphenyl)amide (IId). Yield 1.11 g (69%), mp 192–193°C (ethanol). IR spectrum, ν , cm^{-1} : 3145 br (NH, COOH), 1680 (COOH), 1660 br (CONH, COC_6H_4), 1533 (“amide II”). ^1H NMR spectrum (CDCl_3), δ , ppm: 1.44 t (3H, MeCH_2O , J 7.0 Hz), 4.10 q (2H, MeCH_2O , J 7.0 Hz), 4.10 s (2H, CH_2), 6.91–8.71 group of signals (8H, $2\text{C}_6\text{H}_4$), 11.41 s (1H, NH). Found, %: C 66.04; H 5.24; N 4.30. $\text{C}_{18}\text{H}_{17}\text{NO}_5$. Calculated, %: C 66.05; H 5.23; N 4.28.

4-Chlorobenzoylactic acid *N*-(2-carboxyphenyl)amide (IIe). Yield 1.18 g (76%), mp 170–171°C (ethanol). IR spectrum, ν , cm^{-1} : 3225 br (NH, COOH), 1718 (COOH), 1685 br (CONH, COC_6H_4), 1536 (“amide II”). ^1H ($\text{DMSO}-d_6$), δ , ppm: 4.31 s (2H, CH_2), 7.18–8.40 group of signals (8H, $2\text{C}_6\text{H}_4$), 11.23 s (1H,

NH), 13.58 br.s (1H, COOH). Found, %: C 60.50; H 3.80; Cl 11.20; N 4.42. $\text{C}_{16}\text{H}_{12}\text{ClNO}_4$. Calculated, %: C 60.48; H 3.81; Cl 11.16; N 4.41.

4-Bromobenzoylactic acid *N*-(2-carboxyphenyl)amide (IIf). Yield 1.38 g (78%), mp 190–191°C (ethanol). IR spectrum, ν , cm^{-1} : 3335 br (NH, COOH), 1698 (COOH), 1680 br (CONH, COC_6H_4), 1533 (“amide II”). ^1H NMR spectrum (CDCl_3), δ , ppm: 4.12 s (2H, CH_2), 7.13–8.76 group of signals (8H, $2\text{C}_6\text{H}_4$), 11.38 s (1H, NH). Found, %: C 53.04; H 3.35; Br 22.10; N 3.85. $\text{C}_{16}\text{H}_{12}\text{BrNO}_4$. Calculated, %: C 53.06; H 3.34; Br 22.06; N 3.87.

2-[(*Z*)-2-Hydroxy-2-phenyl-1-ethenyl]-4*H*-3,1-benzoxazin-4-one (IIIa). *a.* A solution of 3.35 mmol of anilide **IIa** and 3.35 mmol of acetic anhydride in 10 ml of benzene was boiled for 2 h, evaporated, and the residue was crystallized from 2-propanol. Yield 0.89 g (100%).

b. A solution of 3.35 mmol of anilide **IIa** and 3.35 mmol of dicyclohexylcarbodiimide in 20 ml of 1,2-dichloroethane was boiled for 39 min, cooled, the precipitate of dicyclohexylurea was filtered off, the filtrate was evaporated, and the residue was crystallized from 2-propanol. Yield 0.89 g (100%), mp 141–142°C (2-propanol). IR spectrum, ν , cm^{-1} : 3050 br (OH_{bound}), 1762 ($\text{C}=\text{O}$), 1634 ($\text{C}=\text{N}$). ^1H NMR spectrum (CDCl_3), δ , ppm: 5.96 s (1H, CH), 7.37–8.15 group of signals (9H, Ph + C_6H_4), 14.26 s (1H, OH). Found, %: C 72.39; H 4.15; N 5.30. $\text{C}_{16}\text{H}_{11}\text{NO}_3$. Calculated, %: C 72.45; H 4.18; N 5.28.

X-ray crystallography. Crystals of compound **IIIa**, $\text{C}_{16}\text{H}_{11}\text{NO}_3$, monoclinic, *a* 14.182(3), *b* 9.443(2), *c* 9.404(2) Å, β 97.86(3)°, *V* 1247.6(5) Å³, *M* 265.26, d_{calc} 1.412 g/cm³, *Z* 4, space group *P*2₁/*n*. The set of experimental reflections was obtained on an automatic four-circle diffractometer QM-4 (KUMA DIFFRACTION) with κ -geometry by $\omega/2\theta$ scanning on $\text{MoK}\alpha$ -radiation with a monochromator ($2\theta \leq 50.1^\circ$). Overall 2349 reflections were measured, 2206 among them independent (R_{int} 0.0495). The correction for extinction was not done (μ 0.10 mm^{−1}). The structure was solved by the direct method by the program SIR92 [11] followed by calculation of a series of electron density charts. Hydrogen atoms were revealed from the difference synthesis of the electron density. Full-matrix refining in anisotropic approximation for nonhydrogen atoms was performed by the least-mean-squares method using SHELXL-97 software [12] and was completed at R_1 0.0393, wR_2 0.1070 using 1027 reflections with $I \geq 2\sigma(I)$ and R_1 0.1340, wR_2 0.1744 using all 2206 reflections.

Analogously were prepared compounds **IIIb–IIIf**.

2-[(Z)-2-Hydroxy-2-(4-methylphenyl)-1-ethenyl]-4H-3,1-benzoxazin-4-one (IIIb). Yield 98 (a), 100% (α), mp 178–179°C (2-propanol). IR spectrum, ν, cm⁻¹: 3080 br (OH_{bound}), 1770 (C⁴=O), 1640 (C=N). ¹H NMR spectrum (CDCl₃), δ, ppm: 2.42 s (3H, Me), 5.93 s (1H, CH), 7.26–8.14 group of signals (8H, 2C₆H₄), 14.25 s (1H, OH). Found, %: C 73.10; H 4.67; N 5.03. C₁₇H₁₃NO₃. Calculated, %: C 73.11; H 4.69; N 5.01.

2-[(Z)-2-Hydroxy-2-(4-methoxyphenyl)-1-ethenyl]-4H-3,1-benzoxazin-4-one (IIIc). Yield 100% (a, b), mp 164–165°C (2-propanol). IR spectrum, ν, cm⁻¹: 3040 br (OH_{bound}), 1750 (C⁴=O), 1615 (C=N). ¹H NMR spectrum (CDCl₃), δ, ppm: 3.88 s (3H, MeO), 5.88 s (1H, CH), 6.96–8.13 group of signals (8H, 2C₆H₄), 14.27 s (1H, OH). ¹³C NMR spectrum (100 MHz, CDCl₃), δ, ppm: 55.48 (MeO), 83.93 (C²=CH), 114.10 (C^{4a}), 121.25–129.35 (ArH), 137.00 (C^{8a}), 162.12 (C⁴), 162.56 (C²), 177.30 (COC₆H₄). Mass spectrum, m/z (I_{rel}, %): 265 (32) [M]⁺, 188 (6) [M – C₆H₅]⁺, 146 (3) [M – C₆H₅COCH₂]⁺, 119 (19) [C₆H₅COCH₂]⁺, 105 (100) [C₆H₅CO]⁺, 77 (29) [C₆H₅]⁺. Found, %: C 69.17; H 4.48; N 4.75. C₁₇H₁₃NO₄. Calculated, %: C 69.15; H 4.44; N 4.74.

2-[(Z)-2-Hydroxy-2-(4-ethoxyphenyl)-1-ethenyl]-4H-3,1-benzoxazin-4-one (IIId). Yield 98 (a), 100% (b), mp 165–166°C (2-propanol). IR spectrum, ν, cm⁻¹: 3040 br (OH_{bound}), 1753 (C⁴=O), 1630 (C=N). ¹H NMR spectrum (CDCl₃), δ, ppm: 1.45 t (3H, MeCH₂O, J 7.0 Hz), 4.88 q (2H, MeCH₂O, J 7.0 Hz), 5.88 s (1H, CH), 6.94–8.12 group of signals (8H, 2C₆H₄), 14.27 s (1H, OH). Found, %: C 69.90; H 4.88; N 4.55. C₁₈H₁₅NO₄. Calculated, %: C 69.89; H 4.89; N 4.53.

2-[(Z)-2-Hydroxy-2-(4-chlorophenyl)-1-ethenyl]-4H-3,1-benzoxazin-4-one (IIIe). Yield 96 (a), 100% (b), mp 205–206°C (2-propanol). IR spectrum, ν, cm⁻¹: 3170 br (OH_{bound}), 1757 (C⁴=O), 1628 (C=N). ¹H NMR spectrum (CDCl₃), δ, ppm: 5.92 s (1H, CH), 7.36–8.15

group of signals (8H, 2C₆H₄), 14.24 s (1H, OH). Found, %: C 64.10; H 3.37; Cl 11.85; N 4.65. C₁₆H₁₀ClNO₃. Calculated, %: C 64.12; H 3.36; Cl 11.83; N 4.67.

2-[(Z)-2-Hydroxy-2-(4-bromophenyl)-1-ethenyl]-4H-3,1-benzoxazin-4-one (IIIf). Yield 95 (a), 100% (b), mp 204–205°C (2-propanol). IR spectrum, ν, cm⁻¹: 3340 br (OH_{bound}), 1760 (C⁴=O), 1625 (C=N). ¹H NMR spectrum (CDCl₃), δ, ppm: 5.91 s (1H, CH), 7.35–8.14 group of signals (8H, 2C₆H₄), 14.23 s (1H, OH). Found, %: C 55.83; H 2.95; Br 23.25; N 4.05. C₁₆H₁₀BrNO₃. Calculated, %: C 55.84; H 2.93; Br 23.22; N 4.07.

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