Synthesis of 2-R-3-Hydroxy[1,2,4]triazino[6,1-*b*]-quinazoline-4,10-diones

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Abstract—A preparation method was developed for [1,2,4]triazino[6,1-*b*]quinazoline-4,10-diones using isatoic anhydride, carboxylic acids hydrazides, ethyl oxalyl chloride, and hydroxylamine.

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Application of anthranilic and dicarboxylic acids derivatives for building up a quinazolinone ring furnishes structures that open wide opportunities for constructing thereon new heterocyclic systems, in particular, those with fused heterocyclic rings [1].

The simplest methods suggested nowadays for the synthesis of compounds from the triazinoquinazolinone series are based mainly on the application as an initial substance of ethyl 3-amino-4-oxo-3,4-dihydroquinazoline-2-carboxylate [2] which is commonly obtained by reaction of the anthranilohydrazide with the diethyl oxalate [3].

We report here on the synthesis of 2-R-3-hydroxy-[1,2,4]triazino[6,1-*b*]quinazoline-4,10-diones **VIIa–VIIf**, a new group of substances with a potential biologic action (see the scheme). First the presumed initial synthons for their preparation were 3,1-benzoxazin-4-ones derivatives, isatoic anhydride (**I**) or 3,1-benzoxazin-4-on-2-carboxylic acid *N*-hydroxyamide (**VIII**).

From the two assumed synthetic procedures the one involving isatoic anhydride (I) proved to be more successful. Its reaction with carboxylic hydrazides provided 2-*N*-acylanthranilohydrazides **Ha–Hf**. The hydrazinolysis was carried out in DMF; the reaction occurred cleaner in the presence of triethylamine. A similar condensation with arylcarboxylic hydrazides in the presence of the *p*-toluene-sulfonic acid was formerly applied to the one-stage preparation of 2-aryl-3-aminoquinazolin-4-ones [4].

Acylhydrazides **Ha–Hf** obtained were treated with ethyl oxalyl chloride in DMF or acetic acid in the presence of triethylamine. Different products were isolated depending on the reaction temperature. The reaction

carried out at 0°C afforded ester IIIb, and without cooling the reaction mixture self-heated and alongside the acylation occurred also cyclodehydration furnishing 3-acylamino-2-ethoxycarbonylquinazolin-4-ones IVa–IVf. A short (4–6 min) heating of ester IIIb also results in formation of quinazolinone IVb. In the ¹H NMR spectrum of ester IVb lack the signals from two NH groups existing in the ¹H NMR spectrum of ester IIIb.

Considering that the yields of acylhydrazides are virtually quantitative and that the hydrazinolysis and acylation can be performed under similar conditions (DMF in the presence of triethylamine) we have decided to prepare esters IIIb, IVa—IVf omitting the isolation of intermediate products IIa—IIf. This reduced the experimental time due to decreasing the number of stages involving separation and purification of the reaction products, and also improved the yields of esters IIIb, IVa—IVf calculated on the initial anhydride.

The reaction of esters IIIb, IVa–IVf with hydroxylamine furnished in good yields the corresponding hydroxamic acids Vb, VIa–VIf which readily underwent cyclization at heating in acetic anhydride. In both cases the reaction products were diones VIIa–VIIf. In reaction of hydroxamic acid Vb quinazoline and triazine rings close simultaneously. We failed to stop the reaction at the stage of the quinazoline ring closure (we did not succeed in hydroxyamide VIb isolation). The ease of the closure of both rings apparently is due to the enhanced nucleophilic properties of the hydrazide and N-hydroxyamide groups (α -effect) [5].

In keeping with the second scheme we planned to synthesize the triazinoquinazoline system proceeding from

Scheme.

N-hydroxyamide **VIII**; however this route turned out to be less favorable because of complications in the preparation of compound **VIII** by cyclization of 2-carboxyoxanilic acid *N*-hydroxyamide in acetic anhydride by method [6]. The target products were obtained in a low yield with impurity of acetylation products.

EXPERIMENTAL

 1 H NMR spectra were registered on a spectrometer Varian M200, operating frequency 200 MHz, from solutions in DMSO- d_6 with TMS as internal reference. Elemental analyses were performed on an analyzer Carlo Erba CHNS-O EA 1108.

2-N-Benzoylanthranilohydrazide (IIb). In 3 ml of DMF was dissolved 0.01 mol (1.63 g) of isatoic anhydride (**I**), thereto was added 0.01 mol (1.4 ml) of triethylamine and a solution of 0.01 mol (1.36 g) of benzoic hydrazide in 3 ml of DMF. After 4 h the mixture was diluted with cold water. Yield 2.51 g, mp 210–212°C (from AcOH). 1 H NMR spectrum, δ , ppm: 6.45 br.s (2H, NH₂), 6.55–7.65 m (9H_{arom}), 10.45 br.s (2H, NHNH). Found, %: C 65.62; H 4.95; N 16.51. C₁₄H₁₃N₃O₂. Calculated, %: C 65.87; H 5.13; N 16.46.

Hydrazides **IIa**, **IIc–IIf** were obtained in the same way.

2-N-Acetylanthranilohydrazide (IIa). Yield 80%, mp 235–237°C. 1 H NMR spectrum, δ , ppm: 2.55 s (3H, CH₃), 6.30 br.s (2H, NH₂), 7.16 t (1H_{arom}), 7.28 t (1H_{arom}), 7.42 d (1H_{arom}), 7.76 d (1H_{arom}), 10.60 br.s (2H, NHNH). Found, %: C 56.23; H 5.57; N 21.69. C₉H₁₁N₃O₂. Calculated, %: C 55.95; H 5.74; N 21.75.

2-N-(2-Hydroxybenzoyl)anthranilohydrazide (**Hc**). Yield 95%, mp 208–210°C. 1 H NMR spectrum, δ , ppm: 6.40 br.s (2H, NH₂), 6.50–7.80 m (8H_{arom}), 10.30 br.s (2H, NHNH), 11.05 br.s (1H, OH). Found, %: C 62.40; H 5.01; N 15.52. $C_{14}H_{13}N_{3}O_{3}$. Calculated, %: C 61.99; N 15.49; H 4.83.

2-N-(4-Isonicotinoyl)anthranilohydrazide (IId). Yield 71%, mp 195–197°C. ^1H NMR spectrum, δ , ppm: 6.30 br.s (2H, NH₂), 6.25–7.55 m (8H_{arom}), 10.30 br.s (2H, NHNH). Found, %: C 60.65; H 4.84; N 21.91. C₁₃H₁₂N₄O₂. Calculated, %: C 60.93; H 4.72; N 21.86.

2-N-(2-Furoyl)anthranilohydrazide (IIe). Yield 78%, mp 285–287°C. 1 H NMR spectrum, δ , ppm: 6.45 br.s (2H, NH₂), 6.65–8.10 m (7H_{arom}), 10.40 br.s (2H, NHNH). Found, %: C 59.07; H 4.43; N 17.05. C₁₂H₁₁N₃O₃. Calculated, %: C 58.77; H 4.52; N 17.13.

3-Hydroxy-4-oxo-3,4-dihydroquinazoline-2-carboxylic 2-*N***-(2-aminobenzoyl)hydrazide (IIf)**. Yield 67%, mp 186–188°C. ¹H NMR spectrum, δ, ppm: 6.50 br.s

(2H, NH₂), 7.45–8.60 m (8H_{arom}), 10.35 br.s (2H, NHNH), 12.20 br.s (1H, OH). Found, %: C 56.51; H 3.98; N 20.59. $C_{16}H_{13}N_5O_4$. Calculated, %: C 56.64; H 3.98; N 20.64.

Benzoic 2-N-[2-(ethoxalylamino)benzoyl]-hydrazide (IIIb). *a*. In 3 ml of the glacial acetic acid (or DMF) was dissolved 0.01 mol (2.55 g) of acylhydrazide **IIb**, 0.01 mol (1.4 ml) of triethylamine was added, the mixture was cooled to 0°C, and 0.01 mol (1.2 ml) of ethyl oxalyl chloride was added. After 3 h the reaction mixture was diluted with cold water. Yield 3.42 g, mp 101–103°C (from acetic acid).

b. In 3 ml of DMF was dissolved 0.01 mol (1.63 g) of isatoic anhydride (**I**), thereto was added 0.01 mol (1.4 ml) of triethylamine and a solution of 0.01 mol (1.36 g) of benzoic hydrazide in 3 ml of DMF. After 4 h the mixture was cooled to 0°C, and 0.01 mol (1.2 ml) of ethyl oxalyl chloride was added. After 3 h the reaction mixture was diluted with cold water. Yield 3.46 g, mp 102–104°C (from AcOH). ¹H NMR spectrum, δ, ppm: 1.15 t (3H, CH₂CH₃), 4.10 m (2H, CH₂CH₃), 6.80–7.95 m (9H_{arom}), 9.50 br.s (1H, NH), 10.95 br.s (2H, NHNH). Found, %: C 61.19; H 5.02; N 11.89. $C_{18}H_{17}N_3O_5$. Calculated, %: C 60.84; H 4.82; N 11.82.

Ethyl 3-(benzoylamino)-4-oxo-3,4-dihydroquinazo-line-2-carboxylate (IVb). *a*. In 3 ml of the glacial acetic acid (or DMF) was dissolved 0.01 mol (2.55 g) of acylhydrazide **IIb**, 0.01 mol (1.4 ml) of triethylamine and 0.01 mol (1.2 ml) of ethyl oxalyl chloride was added. After 3 h the reaction mixture was diluted with cold water. Yield 3.29 g, mp 118–120°C (from ethanol).

b. In 3 ml of the glacial acetic acid 0.01 mol (3.55 g) of ester **IIIb** was boiled for 5 min and on cooling was diluted with cold water. Yield 3.33 g, mp 118–120°C (from ethanol).

c. In 3 ml of DMF was dissolved 0.01 mol (1.63 g) of isatoic anhydride (**I**), thereto was added 0.01 mol (1.4 ml) of triethylamine and a solution of 0.01 mol (1.36 g) of benzoic hydrazide in 3 ml of DMF. In 4 h 0.01 mol (1.2 ml) of ethoxalyl chloride was added. After keeping the mixture for 3 h it was diluted with cold water. Yield 3.35 g, mp 117–119°C (from AcOH). ¹H NMR spectrum, δ , ppm: 1.10 t (3H, CH₂CH₃), 4.00 m (2H, CH₂CH₃), 6.95–7.80 m (9H_{arom}), 12.05 br.s (1H, NH). Found, %: C 63.88; H 4.32; N 12.52. C₁₈H₁₅N₃O₄. Calculated, %: C 64.09; H 4.48; N 12.46.

Esters **IVa**, **IVc–IVf** were obtained by similar procedures.

Ethyl 3-(acetylamino)-4-oxo-3,4-dihydroquinazo-line-2-carboxylate (IVa). Yield 65%, mp 141–143°C. ¹H, δ, ppm: 1.05 t (3H, CH₂CH₃), 4.05 m (2H, CH₂CH₃), 2.55 s (3H, COCH₃), 7.00 t (1H_{arom}), 7.30 d (1H_{arom}), 7.55 t (1H_{arom}), 7.80 d (1H_{arom}), 11.50 br.s (1H, NH). Found, %: C 57.01; H 4.63; N 15.20. C₁₃H₁₃N₃O₄. Calculated, %: C 56.73; H 4.76; N 15.27.

Ethyl 3-(2-hydroxybenzoylamino)-4-oxo-3,4-di-hydroquinazoline-2-carboxylate (IVc). Yield 93%, mp 132–134°C. ¹H NMR spectrum, δ, ppm: 1.15 t (3H, CH₂CH₃), 4.05 m (2H, CH₂CH₃), 6.40–7.55 m (8H_{arom}), 11.55 br.s (1H, NH), 11.20 br.s (1H, OH). Found, %: C 61.26; H 4.20; N 11.97. C₁₈H₁₅N₃O₅. Calculated, %: C 61.19; H 4.28; N 11.89.

Ethyl 3-(2-isonicotinoylamino)-4-oxo-3,4-dihydro-quinazoline-2-carboxylate (IVd). Yield 82%, mp 128–130°C. 1 H NMR spectrum, δ, ppm: 1.10 t (3H, CH₂CH₃), 4.10 m (2H, CH₂CH₃), 6.35–7.80 m (8H_{arom}), 11.70 br.s (1H, NH). Found, %: C 60.48; H 4.26; N 16.48. C₁₇H₁₄N₄O₄. Calculated, %: C 60.35; H 4.17; N 16.56.

Ethyl 3-(2-furoylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (IVe). Yield 89%, mp 220–222°C. 1 H NMR spectrum, δ, ppm: 1.10 t (3H, CH₂CH₃), 4.15 m (2H, CH₂CH₃), 6.80–8.10 m (7H_{arom}), 11.90 br.s (1H, NH). Found, %: C 58.92; H 4.00; N 12.84.

Ethyl 3-(3-hydroxy-4-oxo-3,4-dihydro-quinazolin-2-ylcarbonylylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylate (IVf). Yield 87%, mp 118–120°C. 1 H NMR spectrum, δ, ppm: 1.10 t (3H, CH₂CH₃), 4.05 m (2H, CH₂CH₃), 7.35–8.60 m (8H_{arom}), 11.00 br.s (1H, NH), 12.35 br.s (1H, OH). Found, %: C 56.84; H 3.72; N 16.70. C₂₀H₁₅N₅O₆. Calculated, %: C 57.01; H 3.59; N 16.62.

Preparation of the methanol solution of hydroxylamine. In a minimal volume of methanol was dissolved 0.012 mol (0.28 g) of sodium, and at cooling a solution of 0.012 mol (0.84 g) hydroxylamine hydrochloride was added. After 15 min the precipitate was removed, and the filtrate was used in further reactions.

Benzoic *N'*-[2-(ethoxalylamino)benzoyl]-hydrazide *N*-hydroxyamide (Vb). In 5 ml of methanol was dissolved 0.01 mol (3.55 g) of ester IIIb, and 0.012 mol of hydroxylamine in methanol solution was added. The mixture was stirred for 30 min at 50°C. After 6 h the precipitate formed was separated. Yield 3.27 g, mp 183–185°C (from AcOH). 1 H NMR spectrum, δ, ppm: 6.95–8.20 m (9H_{arom}), 9.50 br.s (1H, NH), 10.90 m (2H, NHNH), 11.85 br.s (1H, NHOH), 12.15 br.s (1H, NHOH). Found, %: C 55.78; H 4.22; N 16.40. C₁₆H₁₄N₄O₅. Calculated, %: C 56.14; H 4.12; N 16.37.

3-(Benzoylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid *N***-hydroxyamide (VIb)**. In 5 ml of methanol was dissolved 0.01 mol (3.37 g) of ester **IVb**, and 0.012 mol of hydroxylamine in methanol solution was added. The mixture was stirred for 30 min at 50°C. After 6 h the precipitate formed was separated. Yield 3.19 g, mp 205–207°C (from acetic acid). ¹H NMR spectrum, δ, ppm: 6.95–8.05 m (9H_{arom}), 10.15 br.s (1H, NNH), 10.40 br.s (1H, NHOH), 11.50 br.s (1H, NHOH). Found, %: C 59.41; H 3.52; N 17.20. C₁₆H₁₂N₄O₄. Calculated, %: C 59.26; H 3.69; N 17.28.

N-Hydroxyamides **VIa**, **VIc–VIf** were obtained by the same procedure.

- **3-(Acetylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid** *N***-hydroxyamide (VIa).** Yield 96%, mp 210–212°C. 1 H NMR spectrum, δ , ppm: 2.60 s (3H, CH₃), 6.85 t (1H_{arom}), 7.05 d (1H_{arom}), 7.25 t (1H_{arom}), 7.60 d (1H_{arom}), 10.35 br.s (1H, NNH), 11.00 br.s (1H, NHOH), 11.95 br.s (1H, NHOH). Found, %: C 50.27; H 3.99; N 21.31. C₁₁H₁₀N₄O₄. Calculated, %: C 50.38; H 3.84; N 21.37.
- **3-(2-Hydroxybenzoylamino)-4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid** *N***-hydroxyamide (VIc)**. Yield 92%, mp 192–194°C. ¹H NMR spectrum, δ, ppm: 6.65–7.80 m (8H_{arom}), 10.20 br.s (1H, NNH), 10.80 br.s (1H, <u>NH</u>OH), 11.05 br.s (1H, <u>OH</u>), 11.45 br.s (1H, NH<u>OH</u>). Found, %: C 56.57; H 3.42; N 16.51. C₁₆H₁₂N₄O₅. Calculated, %: C 56.47; H 3.55; N 16.46.
- **3-(Isonicotinoylamino)-4-oxo-3,4-dihydroquinazo-line-2-carboxylic acid** *N***-hydroxyamide (VId)**. Yield 81%, mp 208–210°C. 1 H NMR spectrum, δ, ppm: 6.55–8.25 m (8H_{arom}), 10.30 br.s (1H, NNH), 10.50 br.s (1H, NHOH), 11.65 br.s (1H, NHOH). Found, %: C 54.93; H 3.32; N 21.47. C₁₅H₁₁N₅O₄. Calculated, %: C 55.39; H 3.41; N 21.53.
- **3-(2-Furoylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid** *N***-hydroxyamide (VIe)**. Yield 91%, mp 264–266°C. ¹H NMR spectrum, δ , ppm: 6.90–8.20 m (7H_{arom}), 10.35 br.s (1H, NNH), 11.55 br.s (1H, <u>NHOH</u>), 11.55 br.s (1H, NH<u>OH</u>). Found, %: C 53.07; H 3.14; N 17.89. C₁₄H₉N₄O₅. Calculated, %: C 53.51; H 3.21; N 17.83.
- 3-(3-Hydroxy-4-oxo-3,4-dihydroquinazoline-2-carbonylamino)-4-oxo-3,4-dihydroquinazoline-2-carboxylic acid *N*-hydroxyamide (VIf). Yield 93%, mp 188–190°C. 1 H NMR spectrum, δ , ppm: 7.20–8.00 m (8H_{arom}), 10.75 br.s (1H, NNH), 11.20 br.s (1H, <u>NHOH</u>), 12.05 br.s (1H, NOH), 12.30 br.s (1H, NH<u>OH</u>). Found,

- %: C 53.16; H 3.08; N 20.51. C₁₈H₁₂N₆O₆. Calculated, %: C 52.95; H 2.96; N 20.58.
- **3-Hydroxy-2-phenyl**[1,2,4]**triazino**[6,1-*b*]**quinazoline-4,10-dione (VIIb)**. *a*. In 5 ml of acetic anhydride 0.01 mol (3.42 g) of N-hydroxyamide **Vb** was heated for 15 min. On cooling the mixture was diluted with cold water. Yield 2.97 g, mp 272–274°C (from AcOH). 1 H NMR spectrum, δ, ppm: 7.0–8.40 m (9H_{arom}), 11.45 br.s (1H, OH). Found, %: C 62.43; H 3.16; N 18.34. C $_{16}$ H $_{10}$ N $_{4}$ O $_{3}$. Calculated, %: C 62.75; H 3.29; N 18.29.
- b. In 5 ml of acetic anhydride 0.01 mol (3.24 g) of N-hydroxyamide **VIb** was heated for 5 min. On cooling the mixture was diluted with cold water. Yield 3.01 g, mp 273–275°C (from AcOH).

Compounds VIIa, VIIc-VIIf were prepared similarly.

- **3-Hydroxy-2-methyl[1,2,4]triazino[6,1-***b***]-quinazoline-4,10-dione (VIIa)**. Yield 92%, mp 268–270°C. ¹H NMR spectrum, δ, ppm: 2.50 s (3H, CH₃), 6.85 t (1H_{arom}), 7.05 d (1H_{arom}), 7.25 t (1H_{arom}), 7.60 d (1H_{arom}), 11.25 br.s (1H, OH). Found, %: C 53.78; H 3.14; N 22.96. $C_{11}H_{18}N_4O_3$. Calculated, %: C 54.10; H 3.30; N 22.94.
- **3-Hydroxy-2-(2-hydroxyphenyl)[1,2,4]triazino- [6,1-b]quinazoline-4,10-dione (VIIc)**. Yield 94%, mp 256–258°C. ¹H NMR spectrum, δ , ppm: 7.00–8.10 m (8H_{arom}), 10.85 br.s (1H, OH), 11.15 br.s (1H, NOH). Found, %: C 59.90; H 3.21; N 17.31. C₁₆H₁₀N₄O₄. Calculated, %: C 59.63; H 3.13; N 17.38.
- **3-Hydroxy-2-(4-pyridyl)**[1,2,4]triazino[6,1-*b*]-quinazoline-4,10-dione (VIId). Yield 85%, mp 273–275°C. 1 H NMR spectrum, δ, ppm: 6.70–8.05 m (8H_{arom}), 11.40 br.s (1H, OH). Found, %: C 58.44; H 2.69; N 22.77. C₁₅H₉N₅O₃. Calculated, %: C 58.63; H 2.95; N 22.79.
- 3-Hydroxy-2-(2-furyl)[1,2,4]triazino[6,1-b]-quinazoline-4,10-dione (VIIe). Yield 91%, mp > 290°C.

 1H NMR spectrum, δ , ppm: 7.05–8.30 m (7H_{arom}), 11.30 br.s (1H, OH). Found, %: C 56.84; H 2.79; N 18.92.
 C₁₄H₈N₄O₄. Calculated, %: C 56.79; H 2.72; N 18.91.
- **3-Hydroxy-2-(3-hydroxyquinazolin-4-on-2-yl)-**[1,2,4]triazino[6,1-*b*]quinazoline-4,10-dione (VIIf). Yield 89%, mp 240–242°C. ¹H NMR spectrum, δ, ppm: 7.35–8.15 m (8H_{arom}), 12.35 br.s (2H, 2OH). Found, %: C 55.59; H 2.47; N 21.50. $C_{18}H_{10}N_6O_5$. Calculated, %: C 55.39; H 2.58; N 21.53.

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