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Reaction of Anthranilic Acid 2-*N*-Phenylhydrazide with Cyclic Anhydrides

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Abstract—In the reaction with cyclic anhydrides the anthranilic acid 2-*N*-phenylhydrazide depending on conditions yielded either anthranilic acid 2-*N*-acyl-2-*N*'-phenylhydrazides, 2-R-3-anilinoquinazolin-4(3*H*)-ones, or derivatives of 1-phenylpyridazino[3,2-*b*]quinazoline-2,10-dione.

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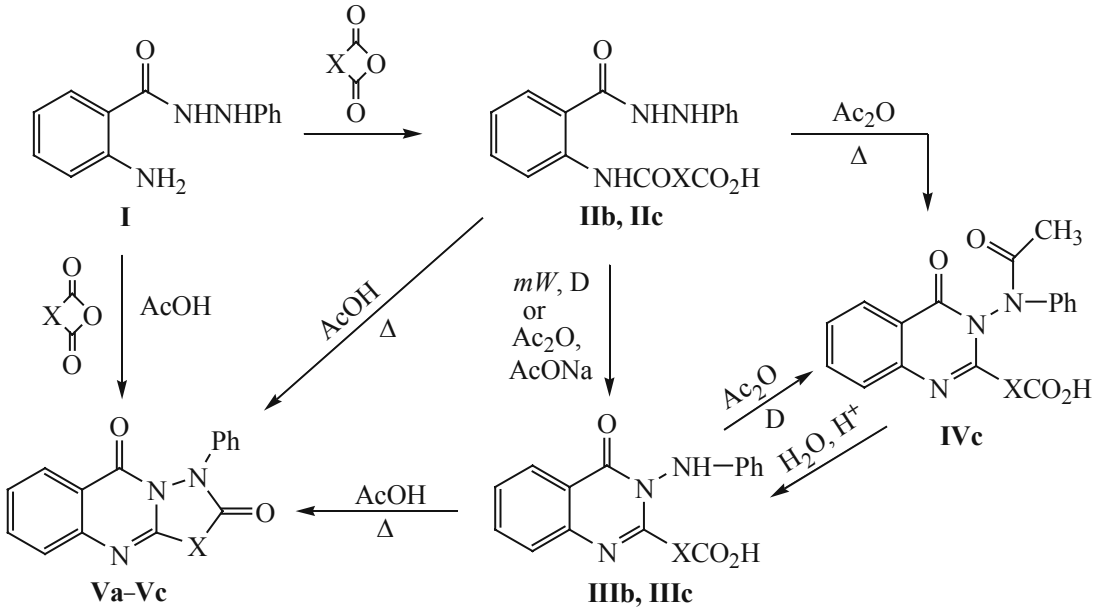
Several procedures are known for the synthesis of compounds containing pyridazino[3,2-*b*]quinazolinone system. The first method employs as initial compounds the anthranilohydrazide and cyclic anhydrides of dicarboxylic acids [1]. Other procedures are based on intramolecular cyclization of 2-R-3-amino-4-oxo-3,4-dihydroquinazoline derivatives having substituents in the position *2* either with a double bond or with a functionally substituted carboxy group [2], and also on intermolecular condensation of 3-amino-2-chloromethyl-4-oxo-3,4-dihydroquinazolines with reagents containing an activated double bond (maleimides, nitroalkenes) [3]. The existing methods for designing the pyridazino[3,2-*b*]quinazolinone system come mainly to the application of anthranilohydrazide and 3-aminoquinazolinones unsubstituted by the amino group. The described reaction of anthranilic acid *N*-isopropylidenehydrazide with phthalic anhydride [4] led to the formation of the corresponding imide or of phthalazino-[1,2-*b*]quinazoline-5,8-dione in a low yield (10%).

We investigated the reaction of anthranilic acid 2-*N*-phenyl-hydrazide (**I**) with cyclic anhydrides of dicarb-oxylic acids (see the scheme).

Scheme.



X = $(CH_2)_2$ (**a**), CH=CH (**b**), *o*-C_6H_4 (**c**).

Initial hydrazide **I** was prepared by acylating the phenylhydrazine with isatoic anhydride. The reaction of hydrazide **I** with cyclic anhydrides under mild conditions (in the glacial acetic acid without heating) resulted in acids **IIb** and **IIc**. We failed to isolate acid **IIa** both in these conditions and at their modification (lower temperature, replacement of the glacial acetic acid with other solvents: dioxane, DMF). The ^{1}H NMR spectrum of the oily substance obtained revealed that it contained alongside acid **IIa** its cyclization products.

The cyclization of acids **IIb** and **IIc** was carried out under several different conditions. At heating to the melting point, under the effect of microwave irradiation, or at stirring without heating in acetic anhydride in the presence of sodium acetate acids **IIb** and **IIc** were converted into 2-R-3- anilinoquinazolin-4(3*H*)-ones **IIIb** and **IIIc**. In the ^{1}H NMR spectra of quinazolinones **IIIb** and **IIIc**, in contrast to the spectra of acids **IIb** and **IIc**, signals appeared from a single NH group and from OH group.

The boiling of acid **IIc** in acetic anhydride led to the formation of 2-{3-[acetyl(phenyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}benzoic acid (**IVc**) obtained also from quinazolinone **IIIc** under similar conditions. The acid hydrolysis of compound **IVc** yielded again quinazolinone **IIIc**.

The heating of acid **IIb** and **IIc** or quinazolinones **IIIb** and **IIIc** in the glacial acetic acid provided pyridazino[3,2-*b*]quinazolinones **Vb** and **Vc** as indicated by the absence in their ^{1}H NMR spectra signals of NH and OH groups. Diones **Va–Vc** were also obtained by heating hydrazide **I** with an appropriate anhydride in glacial acetic acid; the reaction was carried out without isolation of acids **IIa–IIc** and quinazolones **IIIa–IIIc**.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian M-200 (200 MHz), from solutions in DMSO-d_6 using TMS as internal reference. The microwave irradiation was carried out in a microwave oven of a power 800 W. Elemental analyses were performed on an analyzer Carlo Erba CHNS-O EA 1108.

Anthranilic acid 2-*N*-phenylhydrazide I. *a.* In a small quantity of DMF was dissolved 1.63 g (0.01 mol) of isatoic anhydride, 1.4 ml (0.01 mol) of triethylamine, and 2.4 ml (0.01 mol) of phenylhydrazine was added. After 1 h the reaction mixture was diluted with cold water, the separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.8 g (79%), mp 170–171°C.

b. A mixture of 1.63 g (0.01 mol) of isatoic anhydride and 2.4 ml (0.01 mol) of phenylhydrazine was heated to the melting point and then maintained for 30 min. On cooling the melt was dissolved in 5 ml of ethanol, and the product was precipitated by adding 20 ml of cold water. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.87 g (82%), mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 6.40 br.s (2H, NH_2), 6.55–7.65 m ($9H_{arom}$), 10.2 br.s (1H, CONH) [5]. Found, %: C.68; H 5.80; N 18.50. $C_{13}H_{13}N_3O$. Calculated, %: C 68.71; H 5.77; N 18.49.

2-[(3-Carboxyacryloyl)amino]-2-*N*-phenylbenzohydrazide (IIb). In 5 ml of glacial acetic acid was dissolved 2.27 g (0.01 mol) of hydrazide **I**, and 0.98 g (0.01 mol) of maleic anhydride was added. After 30 min the mixture was diluted with 50 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.3 g (71%), mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 6.35–7.65 m ($9H_{arom}$), 6.50–7.25 m (2H, CH=CH), 8.65 s (1H, NHPh), 10.45 s (1H, CONH), 10.80 s (1H, NHCO), 12.15 s (1H, OH). Found,%: C 62.77; H 4.67; N 12.88. $C_{17}H_{15}N_3O_4$. Calculated, %: C 62.76; H.65; N.92.

2-[(2-Carboxybenzoyl)amino]-2-*N*-phenylbenzohydrazide (IIc) was similarly prepared. Yield 3.0 g (80%), mp 172–174°C. ^{1}H NMR spectrum, δ, ppm: 6.45–8.05 m ($13H_{arom}$), 8.50 s (1H, NHPh), 10.55 s (1H, CONH), 11.45 s (1H, NHCO), 12.95 s (1H, OH). Found, %: C 67.18; H 4.53; N 11.17. $C_{21}H_{17}N_3O_4$. Calculated, %: C 67.19; H.56; N 11.19.

3-(3-Anilino-4-oxo-3,4-dihydroquinazolin-2-yl)acrylic acid (IIIb). *a*. In 3 ml of acetic anhydride was dissolved 3.25 g (0.01 mol) of acid **IIb**, 0.01 mol (0.83 g) of sodium acetate was added, and the mixture was stirred for 15 min. On cooling the reaction mixture was diluted with 50 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.6 g (85%), mp 100–102°C.

b. Acid **IIb** (3.25 g, 0.01 mol) was heated to melting and thus kept for 19 min. On cooling the melt was dissolved in 5 ml of ethanol, and the product was precipitated by adding 20 ml of cold water. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.71 g (88%), mp 101–103°C.

c. Acid **IIb** (3.25 g, 0.01 mol) was subjected to microwave irradiation for 10 min. On cooling the melt

was dissolved in 5 ml of ethanol, and the product was precipitated by adding 20 ml of cold water. The precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.71 g (88%), mp 101–103°C. ^{1}H NMR spectrum, δ, ppm: 6.45–8.20 m ($9H_{arom}$), 6.60–6.85 m (2H, CH=CH), 9.30 s (1H, NHPh), 12.95 s (1H, OH) [6]. Found, %: C 66.42; H 4.30; N.66. $C_{17}H_{13}N_3O_3$. Calculated, %: C 66.44; H 4.26; N 13.67.

2-(3-Anilino-4-oxo-3,4-dihydroquinazolin-2-yl)benzoic acid (IIIc). *a*. Synthesis was carried out as described for compound **IIIb**. Yield 3.01 g (84%), mp 120–122°C.

b. Quinazolinone **IVc** (4.00 g, 0.01 mol) was boiled for 30 min in water acidified with HCl to pH 1. On cooling the precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.72 g (76%), mp 119–120°C. ^{1}H NMR spectrum, δ, ppm: 6.25–8.30 m ($13H_{arom}$), 9.00 s (1H, NHPh), 12.50 s (1H, OH). Found, %: C 70.61; H 4.26; N 11.75. $C_{21}H_{15}N_3O_3$. Calculated, %: C.58; H 4.23; N 11.76.

2-{3-[Acetyl(phenyl)amino]-4-oxo-3,4-dihydroquinazolin-2-yl}benzoic acid (IVc). *a*. Hydrazide **IIc** (3.57 g, 0.01 mol) was boiled in acetic acid for 30 min. On cooling the mixture was diluted with 20 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.83 g (71%), mp >200°C.

b. Quinazolinone **IIc** (3.57 g, 0.01 mol) was boiled in acetic anhydride for 15 min. On cooling the mixture was diluted with 20 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.9 g (73%), mp >200°C. ^{1}H NMR spectrum, δ, ppm: 2.00 s (3H, CH_3), 6.25–8.30 m ($13H_{arom}$), 11.65 s (1H, OH). Found, %: C 69.18; H 4.31; N 10.50. $C_{23}H_{17}N_3O_4$. Calculated, %: C 69.17; H 4.29; N 10.52.

1-Phenyl-3,4-dihydro-1*H*-pyridazino[6,1-*b*]-quinazoline-2,10-dione (Va). In 5 ml of glacial acetic acid was dissolved 2.27 g (0.01 mol) of hydrazide **I**, 1.00 g (0.01 mol) of succinic anhydride was added, and the mixture was boiled for 30 min. On cooling the mixture was diluted with 50 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.97 g (67%), mp 114–116°C. ^{1}H NMR spectrum, δ, ppm: 2.55–3.01 m (4H, CH_2CH_2), 6.45–8.00 m ($9H_{arom}$). Found, %: C 70.11; H 4.52; N 14.40. $C_{17}H_{13}N_3O_2$. Calculated,%: C 70.09; H 4.50; N 14.42.

1-Phenyl-1*H*-pyridazino[6,1-*b*]quinazoline-2,10-dione (Vb). *a*. Hydrazide **IIb** (3.25 g, 0.01 mol) was dissolved in 3 ml of acetic acid and was heated for 30 min. On cooling the mixture was diluted with 50 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 2.03 g (70%), mp 180–182°C.

b. Quinazolinone **IIIb** (3.07 g, 0.01 mol) was dissolved in 3 ml of acetic acid and was heated for 15 min. On cooling the mixture was diluted with 50 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. Yield 1.94 g (67%), mp 179–181°C. ^{1}H NMR spectrum, δ, ppm: 6.50–6.85 m (2H, CH=CH), 7.10–8.15 m ($9H_{arom}$). Found, %: C 70.61; H 3.80; N 14.51. $C_{17}H_{11}N_3O_2$. Calculated, %: C 70.58; H 3.83; N 14.52.

6-Phenyl-6*H*-phthalazino[1,2-*b*]quinazoline-5,8-dione (Vc) was obtained in the same way. Yield 2.54 g (75%), mp > 200°C. ^{1}H NMR spectrum, δ, ppm: 7.45–8.60 m ($13H_{arom}$) [7]. Found,%: C 74.30; H 3.89; N 12.40. $C_{21}H_{13}N_3O_2$. Calculated, %: C.33; H 3.86; N 12.38.

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