*Russian Journal of General Chemistry, Vol. 73, No. 7, 2003, pp. 1147–1150. Translated from Zhurnal Obshchei Khimii, Vol. 73, No. 7, 2003, pp. 1216–1219.*


# Condensation of Isatoic Anhydride with Hetarylguanidines

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Received July 10, 2001

**Abstract** — Condensation of isatoic anhydride with 4-methylquinazolin-2-yl-, 2-benzoxazolyl-, 2-benzothiazolyl-, and 4,6-dimethylpyrimidin-2-ylguanidines leads to the corresponding 2-hetarylamino-4-hydroxyquinazolines as a result of cyclization of intermediate anthranilic acid hetarylguanidides. These intermediates can be isolated as individual compounds.

Derivatives of quinazoline and quinazolinone exhibit antimicrobial [1], anticonvulsant [2, 3], immunostimulating [4], antiviral [5], and other kinds of pharmacological activity, which stimulates further studies in the field of synthesis of such compounds. Isatoic anhydride (**I**) possesses some synthetic potential in this respect due to its ability to undergo various cyclization reactions [3, 7, 8]. In this work, we studied the condensation of isatoic anhydride (**I**) with hetarylguanidines.

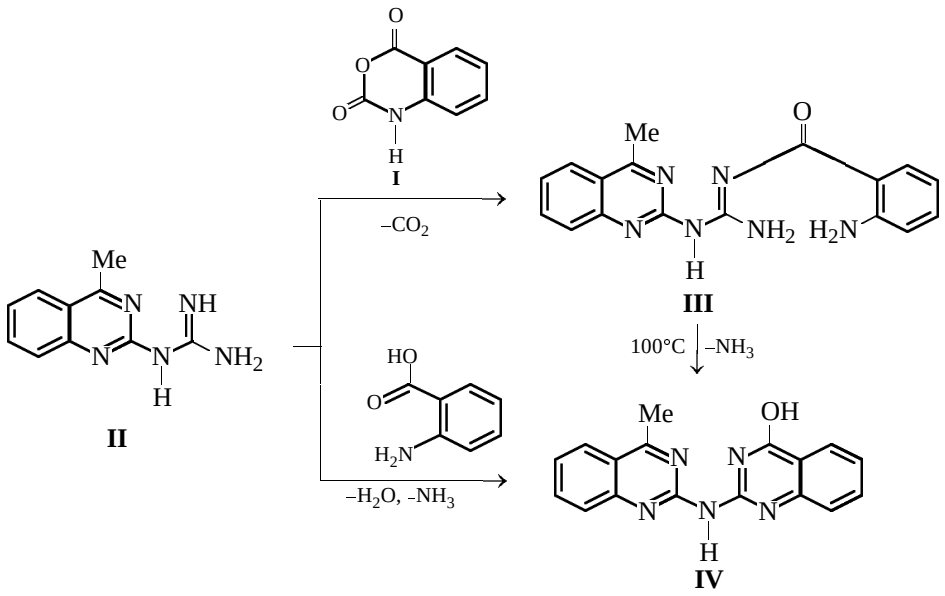
Initial 4-methylquinazolin-2-ylguanidine (**II**) was prepared by the procedure reported in [9]. 2-Benzoxa-(thia)zolylguanidines **Va** and **Vb** were synthesized by cyclization of *o*-aminophenol or *o*-aminobenzenethiol with dicyanodiamide [10]. *N*-(4,6-Dimethylpyrimidin-2-yl)-*N*'-*p*-tolylguanidine (**X**) was obtained by addition of *p*-toluidine hydrochloride to 2-cyanamino-4,6-dimethylpyrimidine (**XI**) which was synthesized by cyclization of acetylacetone with dicyanodiamide in aqueous medium.

The reaction of quinazolylguanidine **II** with isatoic anhydride (**I**) in dimethylformamide (DMF) at room temperature afforded anthranilic acid quinazolylguanidide **III** (Scheme 1). When the reaction mixture was heated to 100°C, 2-(4-methylquinazolin-2-ylamino)-4-hydroxyquinazoline (**IV**) was obtained. Compound **IV** was synthesized previously by cyclization of guanidine **II** with anthranilic acid [11].

Guanidides **VIa** and **VIb** were obtained from 2-benzoxa(thia)zolylguanidines **Va** and **Vb** by heating with anhydride **I** in dioxane or by keeping at room temperature in DMF (Scheme 2).

Heating of compounds **VI** in boiling DMF led to cyclization with elimination of ammonia molecule and

**Scheme 1.**

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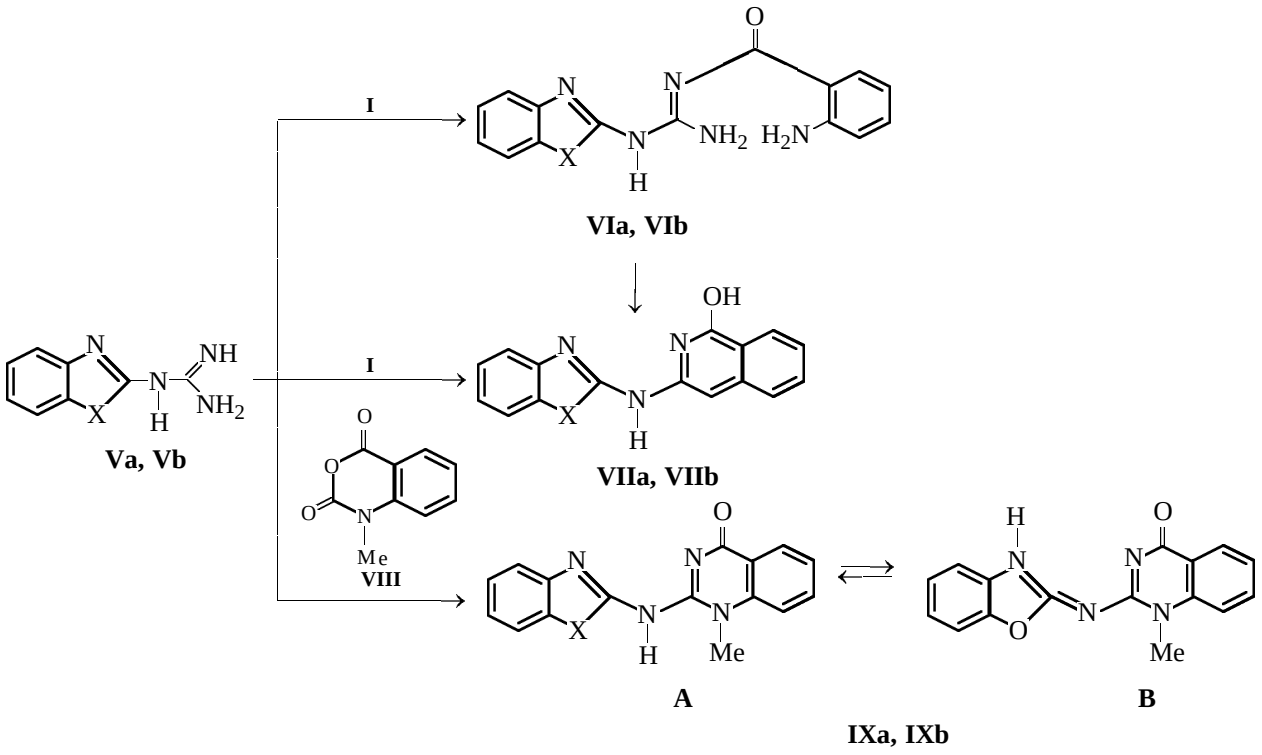
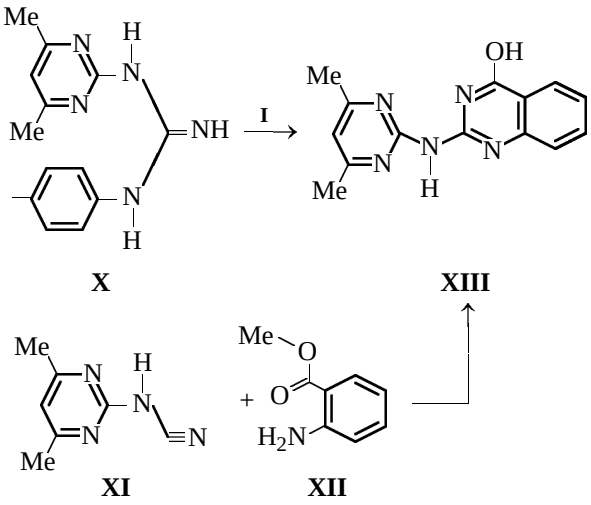
**Scheme 2.**




X = O (**a**), S (**b**).

formation of 2-[1,3-benzoxa(thia)zol-2-ylamino]-4-hydroxyquinazolines **VIIa** and **VIIb**. The same products were formed directly from compounds **V** and **I** in boiling DMF. The condensation of guanidines **V** with *N*-methylisatoic anhydride (**VIII**) gave 2-[1,3-benzoxa(thia)zol-2-ylamino]-1-methyl-1,4-dihydroquinazolin-4-ones **IXa** and **IXb**. These data suggest that elimination of ammonia involves nitrogen atom of the guanidine fragment. An additional proof for cleavage of the C–N bond in guanidine is the formation of 2-(4,6-dimethylpyrimidin-2-ylamino)-4-hydroxyquinazoline (**XIII**) from *N*-(4,6-dimethylpyrimidin-2-yl)-*N*'-*p*-tolylguanidine (**X**) and isatoic anhydride (**I**), which is accompanied by elimination of *p*-toluidine (Scheme 3). Quinazoline **XIII** was also synthesized by condensation of cyanamide **XI** with anthranilic acid methyl ester (**XII**). The structure of the products was proved by elemental analysis and $^1$H NMR spectroscopy.

**Scheme 3.**




## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Bruker AC-300 spectrometer operating at 300 MHz; tetramethylsilane was used as internal reference. The progress of reactions and the purity of products were monitored by TLC on UV-254 plates (Merck).

***N*-Anthraniloyl-*N*'-(4-methylquinazolin-2-yl)-guanidine (III).** Isatoic anhydride (**I**), 1.79 g, was added with stirring to a suspension of 2.01 g of quinazolylguanidine **II** in 15 ml of DMF. The mixture was stirred for 8 h at room temperature, and the precipitate was filtered off and recrystallized from warm chloroform. Yield 2.56 g (80%), colorless crystals, mp 165°C. $^1$H NMR spectrum (DMSO-$d_6$–$CCl_4$), δ, ppm: 2.91 s (3H, $CH_3$); 6.80 br.s (2H, $NH_2$); 6.83–

8.15 m (8H, $H_{arom}$); 9.50 br.s, 9.92 br.s, 11.95 br.s (3H, NH). Found, %: C 64.05; H 4.86; N 26.52. $C_{17}H_{16}N_6O$. Calculated, %: C 63.75; H 5.00; N 26.25.

**4-Hydroxy-2-(4-methylquinazolin-2-ylamino)-quinazoline (IV).** *a.* A mixture of 3.2 g of compound **III** and 15 ml of DMF was heated for 30 min under reflux. After cooling, the colorless product was filtered off and recrystallized from chloroform. Yield 2.10 g (70%), colorless needles, mp 295°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 2.80 s (3H, $CH_3$), 6.40–8.12 m (8H, $H_{arom}$), 11.06 br.s (1H, NH), 13.38 br.s (1H, OH). Found, %: C 66.93; H 4.48; N 23.15. $C_{17}H_{13}N_5O$. Calculated, %: C 67.33; H 4.29; N 23.10.

*b.* A mixture of 2.01 g of compound **II** and 1.50 g of anthranilic acid in 15 ml of DMF was heated for 8–10 h under reflux. After cooling, the precipitate was filtered off and recrystallized from chloroform. Yield 2.24 g (75%), colorless crystals, mp 295°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 2.82 s (3H, $CH_3$), 6.41–8.08 m (8H, $H_{arom}$), 11.02 br.s (1H, NH), 13.48 br.s (1H, OH). Found, %: C 66.85; H 4.56; N 23.52. $C_{17}H_{13}N_5O$. Calculated, %: C 67.33; H 4.29; N 23.10.

***N*-Anthraniloyl-*N*'-(2-benzoxazolyl)guanidine (VIa).** A mixture of 1.76 g of compound **Va** and 1.63 g of isatoic anhydride (**I**) in 15 ml of dioxane was heated for 10 h under reflux. The precipitate was filtered off and recrystallized from DMF. Yield 1.92 g (65%), colorless crystals, mp 217°C. $^1$H NMR spectrum (DMSO-$d_6$–$CCl_4$), δ, ppm: 6.51 br.s (2H, $NH_2$), 6.55–7.82 m (8H, $H_{arom}$), 9.10 br.s (2H, NHCN$H_2$), 11.82 br.s (1H, N$H$C$NH_2$). Found, %: C 60.85; H 4.56; N 23.52. $C_{15}H_{13}N_5O_2$. Calculated, %: C 61.02; H 4.41; N 23.73.

***N*-Anthraniloyl-*N*'-(2-benzothiazolyl)guanidine (VIb).** A mixture of 1.92 g of compound **Vb** and 1.63 g of isatoic anhydride (**I**) in 10 ml of DMF was kept for 48 h at room temperature. The precipitate was filtered off and recrystallized from DMF. Yield 1.93 g (62%), colorless crystals, mp 268°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 6.51 br.s (2H, $NH_2$), 6.55–7.82 m (8H, $H_{arom}$), 9.10 br.s (2H, NHCN$H_2$), 11.82 br.s (1H, N$H$C$NH_2$). Found, %: C 58.02; H 4.31; N 22.63; S 9.95. $C_{15}H_{13}N_5OS$. Calculated, %: C 57.88; H 4.18; N 22.51; S 10.29.

**2-(1,3-Benzoxazol-2-ylamino)-4-hydroxyquinazoline (VIIa).** A mixture of 1.76 g of compound **Va** and 1.63 g of isatoic anhydride (**I**) in 15 ml of DMF was heated for 15 h under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from DMF. Yield 1.61 g (58%), colorless crystals melting above 330°C. $^1$H NMR spectrum (DMSO-$d_6$–$CCl_4$), δ, ppm: 7.15–8.05 m (8H, $H_{arom}$), 12.41 br.s (1H, NH), 12.55 br.s (1H, OH). Found, %: C 64.85; H 3.56; N 20.02. $C_{15}H_{10}N_4O_2$. Calculated, %: C 64.75; H 3.60; N 20.14.

**2-(1,3-Benzothiazol-2-ylamino)-4-hydroxyquinazoline (VIIb).** A mixture of 1.92 g of compound **Vb** and 1.63 g of isatoic anhydride (**I**) in 15 ml of DMF was heated for 5 h under reflux. The mixture was cooled, and the precipitate was filtered off and recrystallized from DMF. Yield 2.09 g (71%), colorless crystals melting above 330°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 7.23–8.10 m (8H, $H_{arom}$), 12.38 br.s (1H, NH), 12.66 br.s (1H, OH). Found, %: C 60.90; H 3.31; N 19.63; S 10.95. $C_{15}H_{10}N_4OS$. Calculated, %: C 61.22; H 3.40; N 19.05; S 10.88.

**2-[1,3-Benzoxa(thia)zol-2-ylamino]-1-methyl-1,4-dihydroquinazolin-4-ones IXa and IXb** were synthesized as described above for compounds **VIIa** and **VIIb** using *N*-methylisatoic anhydride (**VIII**) instead of isatoic anhydride (**I**).

Compound **IXa**. Yield 1.74 g (54%), mp 296°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 3.78 d (3H, $NCH_3$), 6.55–8.15 m (8H, $H_{arom}$), 13.21 d (1H, NH). Found, %: C 66.88; H 5.56; N 18.02. $C_{18}H_{18}N_4O_2$. Calculated, %: C 67.08; H 5.59; N 17.39.

Compound **IXb**. Yield 2.16 g (64%), mp 302°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 3.79 d (3H, $NCH_3$), 6.58–8.31 m (8H, $H_{arom}$), 13.40 d (1H, NH). Found, %: C 64.10; H 5.31; N 16.63; S 10.11. $C_{18}H_{18}N_4OS$. Calculated, %: C 63.91; H 5.33; N 16.57; S 9.47.

**2-(4,6-Dimethylpyrimidin-2-ylamino)-4-hydroxyquinazoline (XIII).** *a.* A mixture of 2.31 g of compound **X** and 1.63 g of isatoic anhydride (**I**) in 15 ml of DMF was kept for 0.5 h at room temperature. The precipitate was filtered off and recrystallized from dioxane. Yield 1.60 g (60%), colorless crystals, mp 239°C. $^1$H NMR spectrum (DMSO-$d_6$–$CCl_4$), δ, ppm: 2.39 s (6H, $CH_3$), 6.76 s (1H, 5-H, pyrimidine), 7.25–8.07 m (4H, $H_{arom}$), 10.55 br.s (1H, NH), 13.27 br.s (1H, OH). Found, %: C 62.83; H 5.02; N 26.02. $C_{14}H_{13}N_5O$. Calculated, %: C 62.92; H 4.87; N 26.22.

*b.* Compound **XII**, 1.51 g, was dissolved in 20 ml of isopropyl alcohol, and 1.48 g of cyanamide **XI** and 0.92 ml of concentrated hydrochloric acid were added. The mixture was heated for 2 h under reflux and was then treated with a solution of 0.56 g of potassium hydroxide in 200 ml of water. The precipitate was filtered off and recrystallized from dioxane. Yield 1.79 g (67%), colorless crystals, mp 238°C. $^1$H NMR spectrum (DMSO-$d_6$–$CCl_4$), δ, ppm: 2.41 s (6H,

$CH_3$), 6.79 s (1H, 5-H, pyrimidine), 7.20–8.02 m (4H, $H_{arom}$), 10.55 br.s (1H, NH), 13.25 br.s (1H, OH). Found, %: C 63.18; H 4.56; N 26.36. $C_{14}H_{13}N_5O$. Calculated, %: C 62.92; H 4.87; N 26.22.

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