Synthesis and Properties of Cyanomethyl Derivatives of Imidazo[1,2-*a*]pyridine, Imidazo[1,2-*a*]pyrimidine, and Imidazo[2,1-*b*]thiazole

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Abstract—2-Cyanomethyl derivatives were obtained of imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, and imidazo[2,1-*b*]thiazole, and their reactivity was investigated by an example of imidazo[1,2-*a*]pyridine: It was subjected to nitration, bromination, azo coupling and nitrosation. Acylation of the methylene group effected by amino acids esters with a subsequent addition of the amino group to the cyano group resulted in the formation of 5-amino-4-imidazo[1,2-*a*]-pyridin-2-yl-1-phenyl-1,2-dihydro-3*H*-pyrrol-3-one and 2-amino-1-ethyl-3-imidazo[1,2-*a*]pyridin-2-yl-4(1*H*)-quinolinone.

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Derivatives of imidazoheterocycles can exhibit a versatile biological activity: Nonsteroid antiphlogistic drugs [1], cardiotonic and antiarrhithmic pharmaceuticals [2], substances with a neurotropic action [3, 4], and those possessing cytoprotective and antitumor activity [5] are found among these compounds. Therefore the development of new preparation procedures for these fused systems is very promising.

The bromomethyl derivatives of imidazo[1,2-a]-pyridine, imidazo[1,2-a]pyrimidine, and imidazo[2,1-b]thiazole **I**, **II** [6, 7] that we have previously synthesized can be by a known procedure converted into the corresponding cyanomethyl heterocycles **III** [8].

Methylene group in these compounds is less reactive than in the 1-methyl-2-cyanomethylbenzimidazole [9]. It is not acylated with anhydrides and chlorides of carboxylic acids. However in reaction of diazonium salts with compound **IIIa** formed bisazo dyes of **IVa** and **IVb** type (Scheme 2). In the ¹H NMR spectra of compounds **IVa** and **IVb** the signal of proton H⁵ is shifted downfield by 0.9 ppm. This abnormal paramagnetic shift indicates that these compounds are present prevailingly in the *syn*conformation [10]. No signals from the position 3 of the bicycle and CH₂ group and also the chemical shifte and intensities of the other signals in the ¹H spectrum confirm the assumed structures of the azo dyes **IVa** and **IVb**. At equivalent ratio of the reactant an intractable mixture was obtained containing along with other compounds (TLC data) bisazo dye **IV** and free base **IIIa**.

The nitrosation of imidazo[1,2-*a*]pyridine-2-ylacetonitrile (**IIIa**) led to the formation of 2-(hydroxyimino)(3nitrosoimidazo[1,2-*a*]pyridine-2-yl)-acetonitrile (**VII**).

Scheme 1.



Ia–IIIa, $R^1 = R^2 = H$, Y = CH=CH, $R^3 = H$; **II, III**, $R^1 = Cl$, $R^2 = H$, Y = CH=CH, $R^3 = Cl$ (b); $R^1 = R^2 = H$, Y = CH=CH, $R^3 = Br$ (c); $R^1 = H$, $R^2 = CH_3$, $Y = CH_3-CN=CH$, $R^3 = H$ (d); $R^1 = H$, $R^2 = H$, Y = S, $R^3 = Br$ (e).

[†] Deceased.

In the ¹H NMR spectrum of this compound a slightly broadened singlet of the hydroxy group proton appeared in the region 15 ppm, and it disappeared at treatment with deuterium oxide. The signal of H⁵ proton is shifted downfield by 1.4 ppm compared to the spectrum of the initial compound **IIIa** indicating that this substance is present prevailingly in the *syn*-conformation [10].

The bromination and nitration of compound **IIIa** occurred only in the position 3. Salt **V** isolated after bromination in dioxane (Scheme 2) treated with 2 M alkali solution was readily converted into (3-bromo-imidazo[1,2-*a*]pyridine-2-yl)acetonitrile (**IIIc**).

The nitration of nitrile IIIa gave (3-nitroimidazo-1,2-a]pyridine-2-yl)acetonitrile (VI).

Neither salt V nor base **IIIc** entered into the reactions of azo coupling, nitrosation, bromination, and nitration.

Imidazo[1,2-*a*]pyridine-2-ylacetonitrile (**IIIa**) was acylated at the methylene group with methyl 2-(ethylamino)benzoate in the presence of sodium *tert*-butylate (structure **VIII**), but we failed to isolate this substance for the ethylamino group underwent an intramolecular addition to the cyano group (Scheme 3). The product of the reaction was 2-amino-3-(imidazo[1,2-*a*]pyridine-2yl)-1-ethyl-4(1*H*)-quinolinone (**X**). Similarly compound **IIIa** reacted with ethyl N-phenylglycinate yielding 5amino-4-imidazo[1,2-*a*]pyridine-2-yl-1-phenyl-1,2dihydro-3*H*-pyrrol-3-one (**XIII**).

At the treatment of crude products **X** and **XIII** with dilute hydrochloric acid bishydrochlorides **IX** and **XII** were obtained that on adding aqueous ammonia provided analytically pure 2-amino-(3-imidazo[1,2-a]pyridin-2-yl)-1-ethyl-4(1*H*)-quinolinone (**X**) and 5-amino-(4-

imidazo[1,2-*a*]pyridine-2-yl)-1-phenyl-1,2-dihydro-3*H*-pyrrol-3-one (**XIII**).

The treatment of 2-amino-3-aryl-4-quinolones in acetic acid solution with sodium nitrite is known to lead to the formation of the derivatives of a quino[2,3-*c*]-cinnolone heterocyclic system [11]. However the treatment of amine **X** with sodium nitrite in dilute hydrochloric acid resulted in the nitrosation in the position 3 of imidazopyridine giving a dihydrochloride of nitroso derivative **XIV** converted into compound **XV** with aqueous ammonia. This reaction route is due to the electron-donor effect of the nitrogen atom in the position 2 of the imidazo[1,2-*a*]pyridine fragment [12]. The intramolecular coordination of the amino group proton in 2-amino-3-(3-nitrosoimidazo[1,2-*a*]pyridine-2-yl)-1-ethyl-4(1*H*)-quinolinone (**XV**) hampers the reciprocal rotation of both heterocycles.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Pye-Unicam SP3-300 from KBr pellets. ¹H NMR spectra were registered on a spectrometer Varian Mercury 400 (400 MHz), internal reference TMS. The reaction progress was monitored and the purity of products obtained was checked by TLC on Silufol UV-254 plates.

Imidazo[1,2-*a***]pyridin-2-ylacetonitrile (IIIa).** To a dispersion of 21.2 g (0.073 mol) of 2-bromomethyl-1H-imidazo[1,2-*a*]pyridinium bromide in 140 ml of methanol a solution was added of 7.42 g (0.07 mol) of sodium hydrogen carbonate in 56 ml of water. A colorless precipitate formed, the mixture was stirred for 5 min, then 7.6 g (0.12 mol) of potassium cyanide was added.





Scheme 4.



The stirring was continued for 6 h, the precipitate was filtered off and washed with ethanol. The mother liquor was evaporated to dryness, and the reaction product was extracted with ether from the dry residue. The insoluble residue was alkalinized with 2 M solution of NaOH and several times treated with ether. The ether was distilled off on a rotary evaporator, the crystals of the nitrile were dried and recrystallized from 2-propanol. Yield 5.72 g (51%), mp 91–92°C (92°C [8]). IR spectrum, v, cm⁻¹: 2254 (CN). ¹H NMR spectrum (DMSO- d_6), δ , ppm: 8.47 d (1H, *J* 6.1 Hz), 7.88 s (1H), 7.46 d (1H, *J* 8.8 Hz), 7.22 m (1H), 6.84 m (1H), 3.99 s (2H). Found, %: C 68.56; N 26.54. C₉H₇N₃. Calculated, %: C 68.78; N 26.74.

Compounds IIIb–IIIe. *General procedure*. To 0.1 mol of base **II** in 140 ml of methanol 7.6 g (0.12 mol) of

RUSSIAN JOURNAL OF ORGANIC CHEMISTRY Vol. 44 No. 2 2008

potassium cyanide was added. The mixture was stirred for 5–6 h, the precipitate was filtered off and washed with ethanol. The mother liquor was evaporated to dryness, and the nitrile was extracted with ether from the dry residue. The insoluble residue was alkalinized with 2 M solution of NaOH and several times treated with ether. The ether was distilled off on a rotary evaporator.

(3,6-Dichloroimidazo[1,2-*a*]pyridin-2-yl)acetonitrile (IIIb). Yield 8.54 g (50%), mp 130°C (ethanol). ¹H NMR spectrum (DMSO- d_6), δ , ppm: 8.39 s (1H), 7.66 d (1H, *J* 9.6 Hz), 7.37 d (1H, *J* 9.6 Hz), 4.06 s (2H, CH₂). Found, %: C 47.45; Cl 31.22; N 18.14. C₉H₅Cl₂N₃. Calculated, %: C 47.82; Cl 31.37; N 18.59.

(3-Bromoimidazo[1,2-*a***]pyridin-2-yl)acetonitrile (IIIc)**. *a*. Yield 9.56 g (56%), mp 149°C (2-propanol). ¹H NMR spectrum (DMSO-*d*₆), δ, ppm: 8.25 d (1H, *J* 6.8, *J* 9.6 Hz), 7.59 d (1H, *J* 9.2 Hz), 7.36 m (1H), 7.08 m (1H), 4.03 s (2H, CH₂). Found, %: Br 34.52; N 17.60. C₉H₆BrN₃. Calculated, %: Br 33.85; N 17.80.

b. To 0.64 g (0.002 mol) of salt V in 10 ml of water was added at room temperature 2 M solution of NaOH till pH 8. The separated precipitate was filtered off, washed with water, dried, and crystallized from 2-propanol. Yield 0.43 g (99%), mp 149°C. ¹H NMR spectrum (DMSO- d_6), δ , ppm: 8.25 d (1H, *J* 6.8 Hz), 7.59 d (1H, *J* 9.2 Hz), 7.36 m (1H), 7.08 m (1H), 4.03 s (2H, CH₂). Found, %: Br 34.68. N 17.67. C₉H₆BrN₃. Calculated, %: Br 33.85; N 17.80.

(5,7-Dimethylimidazo[1,2-*a*]pyrimidin-2-yl)acetonitrile (IIId). Yield 9.63 g (68%), mp 184–186°C (ethanol). IR spectrum, v, cm⁻¹: 2235.99 (CN). ¹H NMR spectrum (DMSO- d_6), δ, ppm: 7.88 s (1H), 6.84 s (1H), 3.99 s(2H, CH₂), 2.57 s (6H, CH₃ and CH₃). Found, %: C 64.56; N 30.27. C₁₀H₁₀N₄. Calculated, %: C 64.50; N 30.09;.

(5-Bromoimidazo[2,1-*b*][1,3]thiazol-6-yl)acetonitrile (IIIe). Yield 7.18 g (46%), mp 110°C (2-propanol). IR spectrum, v, cm⁻¹: 2245 (CN). ¹H NMR spectrum (DMSO– d_6), δ , ppm: 7.72 d (1H, *J* 4.8 Hz), 7.38 d (1H), 3.86 s (2H, CH₂). Found, %: N 17.36; S 13.24. C₇H₄BrN₃S. Calculated, %: N 17.47; S 13.63.

Azo dyes IVa and IVb. General procedure. The diazonium salt was obtained at 0°C from 7.6 mmol of amine, 0.54 g (7.8 mmol) of sodium nitrite, 1.91 ml (22.8 mmol) of hydrochloric acid, and 6.34 ml of water, sodium acetate was added till neutral reaction toward Congo, and the mixture obtained was added to the ethanol solution of 0.52 g (3.3 mmol) of nitrile (IIIa) cooled on

an ice bath. After 1 h 9 mg (0.1 mmol) of Na_2CO_3 was added, the separated precipitate was filtered off, washed with ethanol, dried, and crystallized.

(2*Z*)-{3-[(*E*)-Phenyldiazenyl]imidazo[1,2-*a*]pyridin-2-yl}(phenylhydrazono)acetonitrile (IVa). Yield 1.14 g (72%), mp 191°C (decomp.) (aqueous DMF). IR spectrum, v, cm⁻¹: 2212.39 (CN). ¹H NMR spectrum (acetone- d_6), δ , ppm: 9.30 d (1H, *J* 5.6, *J* 9.6 Hz), 8.82 t (1H, *J* 8.8 Hz), 8.37 d (1H, *J* 8.4 Hz), 8.21 m (2H, H^o, PhN=N), 8.05 t (1H, *J* 6.5 Hz), 7.93–7.71 m (8H, protons PhNH, H^{m,p}, PhN=N). Found, %: C 69.25; N 26.97. C₂₁H₁₅N₇. Calculated, %: C 69.03; N 26.83.

2-{3-[(*E***)-2-(4-Methoxyphenyl)diazenyl]-imidazo-[1,2-***a***]pyridin-2-yl}-2-[(***Z***)-2-(4-methoxyphenyl)hydrazono]acetonitrile (IVb). Yield 1.00 g (65%), mp 288°C (decomp.). IR spectrum, v, cm⁻¹: 2218 (CN), 1722 (C=O). ¹H NMR spectrum (acetone-d_6), \delta, ppm: 9.36 d (1H,** *J* **5.6 Hz), 8.88 t (1H,** *J* **8.8 Hz) 8.65 m (2H, H°, PhN=N), 8.47–8.34 m (5H, H^{m,m'}, PhN=N, H⁸), 8.12– 8.05 t (3H, H°, PhN=N,** *J* **6.5 Hz), 4.27 s (3H, OCH₃), 4.23 s (1H, OCH₃). Found, %: C 62.56; N 20.43. C₂₅H₁₉N₇O₄. Calculated, %: C 62.37; N 20.36.**

3-Bromo-2-(cyanomethyl)-1*H***-imidazo[1.2-***a***]pyridin-4-ium bromide (V)**. To 0.8 g (5 mmol) imidazo[1,2-*a*]pyridin-2-ylacetonitrile (**IIIa**) in 20 ml of dioxane was added at room temperature 0.26 ml (5 mmol) of bromine, and the mixture was stirred for 4 h. The separated precipitate was filtered off, washed with dioxane, dried, and crystallized from 2-propanol. Yield 0.98 g (93%), mp 142°C. ¹H NMR spectrum (DMSO*d*₆), δ , ppm: 8.40 d (1H, *J*6.8 Hz), 7.74 d (1H, *J* 8.8 Hz), 7.56 m (1H), 7.25 m (1H), 5.4 br.s (H₂O, exchange with a proton), 4.16 s (2H, CH₂). Found, %: C 34.19; Br 50.52; N 13.31. C₉H₇Br₂N₃. Calculated, %: C 34.10; Br 50.42; N 13.26.

(3-Nitroimidazo[1,2-*a*]pyridin-2-yl)acetonitrile (VI). To a nitrating mixture composed of 0.5 ml (7.5 mmol) of 70% nitric acid and 10 ml of conen. H₂SO₄ was added 0.8 g (5 mmol) of nitrile **IIIa**, and the reaction mixture was stirred for 3 h at room temperature. Then it was poured on ice, and 12 mg (0.1 mmol) of sodium sulfate was added. The separated precipitate was filtered off, washed with water, dried, and crystallized. Yield 0.14 g (18%), mp 173°C (decomp.) (2-propanol). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 9.4 d (1H, *J* 6.8 Hz), 7.96 d (1H, *J* 9.2 Hz), 7.84 m (1H), 7.50 m (1H), 4.52 s (2H, CH₂). Found, %: C 53.40; N 28.01. C₉H₆N₄O₂. Calculated, %: C 53.47; N 27.71.

(2)-(Hydroxyimino)(3-nitrosoimidazo[1,2-*a*]pyridin-2-yl)acetonitrile (VII). To 0.39 g (0.025 mol) of nitrile **IIIa** in 4 ml of glacial acetic acid was added by small portions a solution of 0.2 g (0.029 mol) of sodium nitrite in 1 ml of water. The reaction proceeded for 15 min, then 8–10 ml of water was added. The separated precipitate was filtered off, washed with water, and dried. To the mother liquor 0.5 g of additional dry sodium nitrite was added. The separated precipitate was identical to the preceding portion. Yield 0.42 g (79%), mp 236°C (aqueous DMF). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 15.05 br.s (1H, OH), 9.70 d (1H, *J* 6.8 Hz), 8.09 m (2H), 7.58 m (1H). Found, %: C 50.57; N 32.41. C₉H₅N₅O₂. Calculated, %: C 50.24; N 32.55.

2-Amino(3-imidazo[1,2-*a*]pyridin-2-yl)-1-ethyl-4(1*H*)-quinolinone dihydrochloride (X). A mixture of 1.57 g (1 mmol) of nitrile IIIa, 2.17 g (1 mmol) of ethyl N-ethylanthranilate, and 4 g of sodium *tert*-butylate was boiled in 30 ml of pyridine, the pyridine was distilled off in a vacuum, and the residue was ground in 100 ml of water. To the reaction mixture 27 ml of 3.5% HCl was added at stirring, and some hours later the precipitate obtained was filtered off. Yield 2.02 g (57%), mp 190°C. IR spectrum, v, cm⁻¹: 1651(C=O). ¹H NMR spectrum (DMSO-*d*₆), δ , ppm: 9.08 d (1H, *J* 6.71 Hz*), 8.66 s (1H*), 8.44 br.s (2H, NH₂), 8.24 d (1H, *J* 7.93 Hz*), 7.95 m (4H), 7.45 m (2H), 4.32 t (2H, CH₂, *J* 7.32 Hz), 1.35 t (3H, CH₃). Found, %: N 14.92; Cl 18.97. C₁₈H₁₈Cl₂N₄O. Calculated, %: N 14.85; Cl 18.79.

2-Amino-(3-imidazo[1,2-*a***]pyridin-2-yl)-1-ethyl-4(1***H***)-quinolinone (XI). In water was dissolved 0.5 g (0.0013 mol) of salt X, a base was added, and some hours later the precipitate obtained was filtered off. Yield 0.29 g (73%), mp 139–140°C. IR spectrum, v, cm⁻¹: 1626 (C=O). ¹H NMR spectrum (DMSO-***d***₆), \delta, ppm: 9.36 br.s (2H, NH₂), 9.21 s (1H*), 8.66 d (1H,** *J* **6.71 Hz*), 8.32 d (1H,** *J* **7.93 Hz*), 7.61 m (2H**), 7.28 m (2H*,**), 6.90 m (1H*), 4.32 t (1H, CH₂-N,** *J* **7.2 Hz), 1.35 t (3H, CH₃). Calculated, %: C 71.04; N 18.41. C₁₈H₁₆N₄O. Found, %: C 71.21; N 18.68;.**

5-Amino-4-imidazo[1,2-a]pyridin-2-yl-1-phenyl-1.2-dihydro-3H-pyrrol-3-one dihydrochloride XIII). A mixture of 1.57 g (1 mmol) of nitrile IIIa, 1.90 g (0.01 mol) ethyl *N*-phenylaminoacetate, and 4 g of sodium *tert*-butylate was boiled in 30 ml of pyridine for 2.5 h. The pyridine was distilled off in a vacuum, and the residue was ground in 100 ml of water. To the reaction mixture 3 ml of acetic acid was added at stirring, and some hours later the precipitate obtained was filtered off, the precipitate was dissolved in dilute hydrochloric acid (1:10), and some hours later the precipitate was filtered off. Yield 1.8 g (52%), mp 242°C. IR spectrum, v, cm⁻¹: 1623–1658 (C=O). ¹H NMR spectrum (DMSO- d_6), δ , ppm: 8.80 d (1H, J 5.8 Hz*), 8.76 s (1H*), 8.02 d (2H, NH₂), 8.99 d (1H, J 8.8 Hz*), 7.74 t (1H*), 7.51 t (2H, H^mPh), 7.45 d (2H, H^oPh, J 8.8 Hz), 7.36 m (2H, CH and H^aPh), 4.36 C (2H, CH₂). Found, %: C 56.34; Cl 19.71; N 15.56. C₁₇H₁₆Cl₂N₄O. Calculated, %: C 56.21; Cl 19.52; N 15.42.

5-Amino(4-imidazo[1,2-*a***]pyridin-2-yl)-1-phenyl-1,2-dihydro-3***H***-pyrrol-3-one (XIV). A solution of 0.5 g (1.4 mmol) of salt XIII in water was neutralized with a water solution of sodium hydrogen carbonate, the precipitate was filtered off. Yield 0.15 g (38%), mp 185°C. IR spectrum, v, cm⁻¹: 1578 (C=O). ¹H NMR spectrum (DMSO-***d***₆), δ, ppm: 8.55 d (1H,** *J* **6.4 Hz*), 8.32 s (1H*), 8.01 br.s (2H, NH₂), 7.62 d (1H,** *J* **8.8 Hz*), 7.49 t (1H*), 7.45 m (3H, H^{m,n}Ph), 7.30 d (2H, H^oPh,** *J* **8.8 Hz), 4.20 s (2H, CH₂). Found, %: C 70.63; N 19.38. C₁₇H₁₄N₄O. Calculated, %: C 70.33; N 19.30.**

2-Amino-1-ethyl-3-(3-nitrosoimidazo[1,2-*a*]pyridin-2-yl)-4(1*H*)-quinolinone dihydrochloride (XV). To 1 g (3 mmol) of amine XI in dilute hydrochloric acid was added 0.3 g (4.3 mmol) of sodium nitrite. Some hours later the precipitate obtained was filtered off, washed with acetone and ether. Yield 0.77 g (80%), mp 201°C (decomp.) (2-propanol). ¹H NMR spectrum (DMSO- d_6), δ , ppm: 9.76 d (1H, *J*6.71*), 8.64 br.s (2H, NH₂), 8.17 d (1H, *J*7.93 Hz*), 8.14 m (2H**), 7.00 m (2H**), 7.61m (2H*), 4.54 s (2H, CH₂), 1.39 t (3H). Found, %: C 53.32; Cl 17.56; N 17.38. C₁₈H₁₇Cl₂N₅O₂. Calculated, %: C 53.21; Cl 17.45; N 17.24.

2-Amino-1-ethyl-3-(3-nitrosoimidazo[1,2-*a***]pyridin-2-yl)-4(1***H***)-quinolinone (XVI). To a solution of 0.5 g (1.2 mmol) of salt XV in water several drops of aqueous ammonia was added, and the precipitate formed was filtered off. Yield 0.24 g (58%), mp 229°C (decomp.). IR spectrum, v, cm⁻¹: 1614 (C=O). ¹H NMR spectrum (DMSO-***d***₆), \delta, ppm: 9.80 d (1H,** *J* **8.00 Hz*), 7.95 m (2H*), 7.63 m (2H**), 7.49 br.s (2H, NH₂), 7.41 m (2H*), 7.29 m (1H**), 4.34 s (2H, CH₂), 1.43 t (3H, CH₃). Found, %: C 64.97; N 21.22. C₁₈H₁₅N₅O₂. Calculated, %: C 64.86; N 21.02.**

The signals from the imidazo[1.2-*a*]pyridine ring are marked with one asterisk, from the quinolone fragment, with two asterisks.

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