New approach to the synthesis of 4-amino-2-pyridone and 1-phenyl-1,6-naphthyridinone derivatives based on substituted 3- and 5-formyl-2-pyridones

N. Z. Tugusheva,[a] L. M. Alekseeva,[a] A. S. Shashkov,[b] and V. G. Granik[a]★

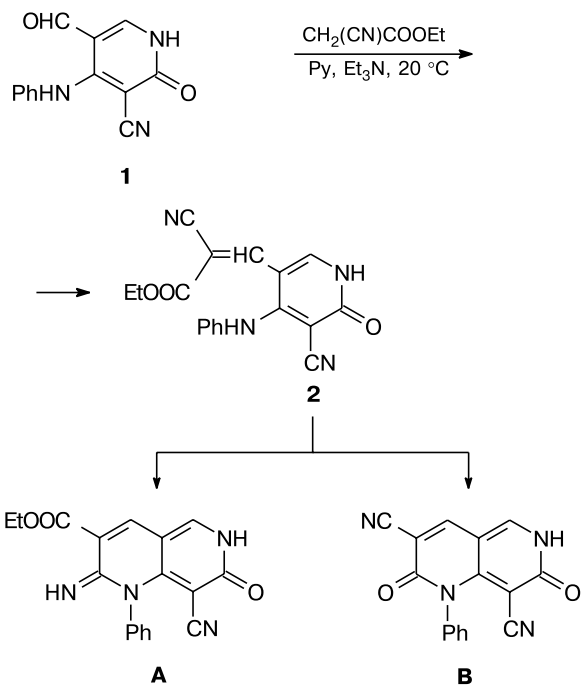
[a]State Research Center of Antibiotics,
3a ul. Nagatinskaya, 117105 Moscow, Russian Federation.
Fax: +7 (495) 231 4284. E-mail: vggranik@mail.ru
[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 135 5328

The reactions of 3-cyano-3(5)-formyl-2-oxo-4-(phenylamino)-1,2-dihydropyridines with CH acids were studied. The previously unknown fused 2-pyridone derivatives containing the 4-aminopyridine fragment were synthesized by the Knoevenagel reaction.

Key words: 3-cyano-3(5)-formyl-2-oxo-4-(phenylamino)-1,2-dihydropyridines, 2,7-dioxo-1-phenyl-1,2,6,7-tetrahydro-1,6-naphthyridines, 2-imino-5(7)-oxo-1-phenyl-1,6-naphthyridines, Knoevenagel reaction, NMR spectroscopy.

Compounds containing the 4-aminopyridine or 4-aminopyridone fragment are of interest because of their potential biological (including psychotropic, nootropic, or antiepileptic) activity.[1—3] A large number of substituted naphthyridines having different biological activities (diuretics, herbicide components, *etc*.) were synthesized by condensation of *ortho*-aminopyridinecarbaldehydes with CH acids in the presence of bases (Knoevenagel-type reaction).[4,5] Earlier,[6,7] we have developed a procedure for the synthesis of 3- and 5-formyl-substituted 4-arylamino-2-pyridones and examined the possibilities of performing their modifications and functionalization primarily by the reactions with various amines. In the present study, we investigated the reactions of these aldehydes with compounds containing activated methylene groups (Knoevenagel reaction). We prepared compound **2** in 96% yield by the reactions of 5-formyl-2-pyridone **1** with cyanoacetic ester in pyridine in the presence of triethylamine at 20 °C. Presumably, the Knoevenagel reaction affords a bicyclic product **A** (Scheme 1). The electrospray (ES) mass spectrum of compound **2** has peaks at *m/z* 335 $[M + H]^{+\bullet}$ and 669 $[2 M + H]^{+\bullet}$ corresponding to the molecular weights of **2** or **A** but not of the form **B**. The ^{1}H NMR spectroscopic data are also consistent with the structures **2** or **A**. These spectra show signals of the COOEt group: a triplet at δ 1.35 ($COOCH_2C\underline{H}_3$) and a quartet at δ 4.35 ($COOC\underline{H}_2CH_3$).

Scheme 1

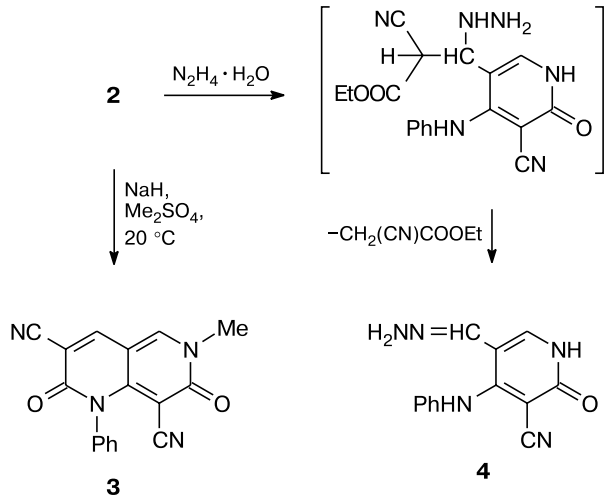


It was impossible to measure the ^{13}C NMR spectrum of compound **2**, which could allow us to unambiguously assign its structure to the open or bicyclic form, because of low solubility of **2** in DMSO. To solve this problem, compound **2** was subjected to alkylation (Me_2SO_4, NaH, 20 °C) to prepare compound **3** (Scheme 2). The mass spectrum of the latter has peaks at *m/z* 302 $[M + H]^{+\bullet}$ and 325 $[M + Na]^{+\bullet}$. The ^{13}C NMR spectrum shows two

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1416—1420, August, 2006.

signals of the CN groups at δ 111.6 (CN(C(8))) and 115.0 (CN(C(3))). The position of the CH_3 group was established by the HMBC spectrum, which shows signals at δ 3.58/149.7 (Me(C(6))/C(5)) and 3.58/160.6 (Me(C(6))/C(7)). Analysis of the ^1H and ^{13}C NMR and HMBC spectra (see the Experimental section) demonstrated that compound **3** is 3,8-dicyano-6-methyl-7-oxo-1-phenyl-1,2,6,7-tetrahydro-1,6-naphthyridine, which can be derived only from open form **2**.

Scheme 2



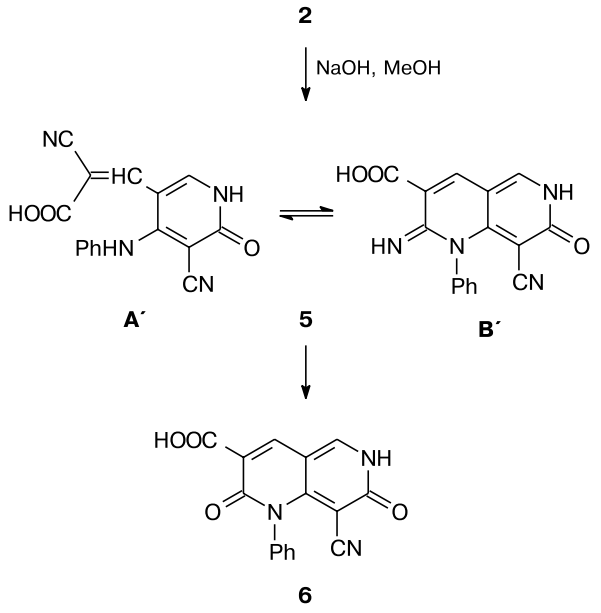
Storage of compound **2** in ethanol in the presence of hydrazine hydrate at 20 °C (see Scheme 2) afforded hydrazone **4** (its ^1H NMR and mass spectra are completely identical to those of hydrazone prepared from 5-formylpyridone **1** and hydrazine hydrate[7]), which is also evidence for the monocyclic structure of compound **2**.

The ethoxycarbonyl group in substituted vinylpyridone **2** is easily hydrolyzed with bases (NaOH in aqueous methanol or an aqueous $NaHCO_3$ solution) at 20 °C (Scheme 3). The ^1H NMR spectrum of the resulting compound **5** shows two singlets (1 H each) at δ 8.73 and 8.81, signals for the protons of the phenyl ring at δ 7.67—7.74 (m, 5 H) and the NH=C(2) fragment at δ 8.39 (strongly br.s), and strongly broadened signals of the OH and N(6)H groups at δ 13.44 and 13.58, respectively. The ES mass spectrum has peaks at m/z 307 $[M + H]^+$, 289 $[M - OH]^+$, and 261 $[M - COOH]^+$. Compound **5** can have either an open (**A´**) or cyclic (**B´**) structure, or alternatively can exist as a tautomeric mixture.

Refluxing of pyridone **2** in an alkali smoothly affords naphthyridinedione **6** in 77% yield. The electron impact (EI) mass spectrum of compound **6** shows peaks at m/z 307 ($[M^+]$) and 263 ($[M - CO_2]^+$), and the ES mass spectrum has a peak at m/z 330 $([M + Na]^+)$.

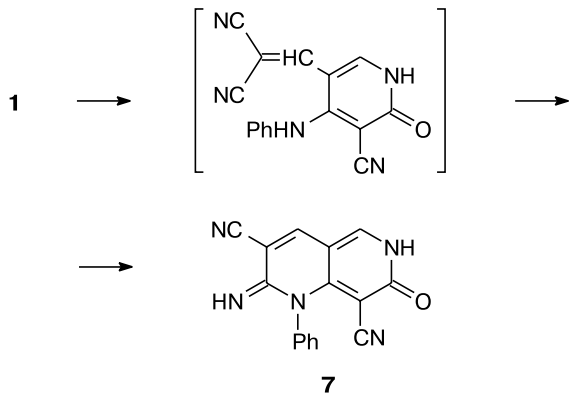
Under analogous conditions (Py, Et_3N, 20 °C), the reaction of compound **1** with another CH acid, *viz.*,

Scheme 3



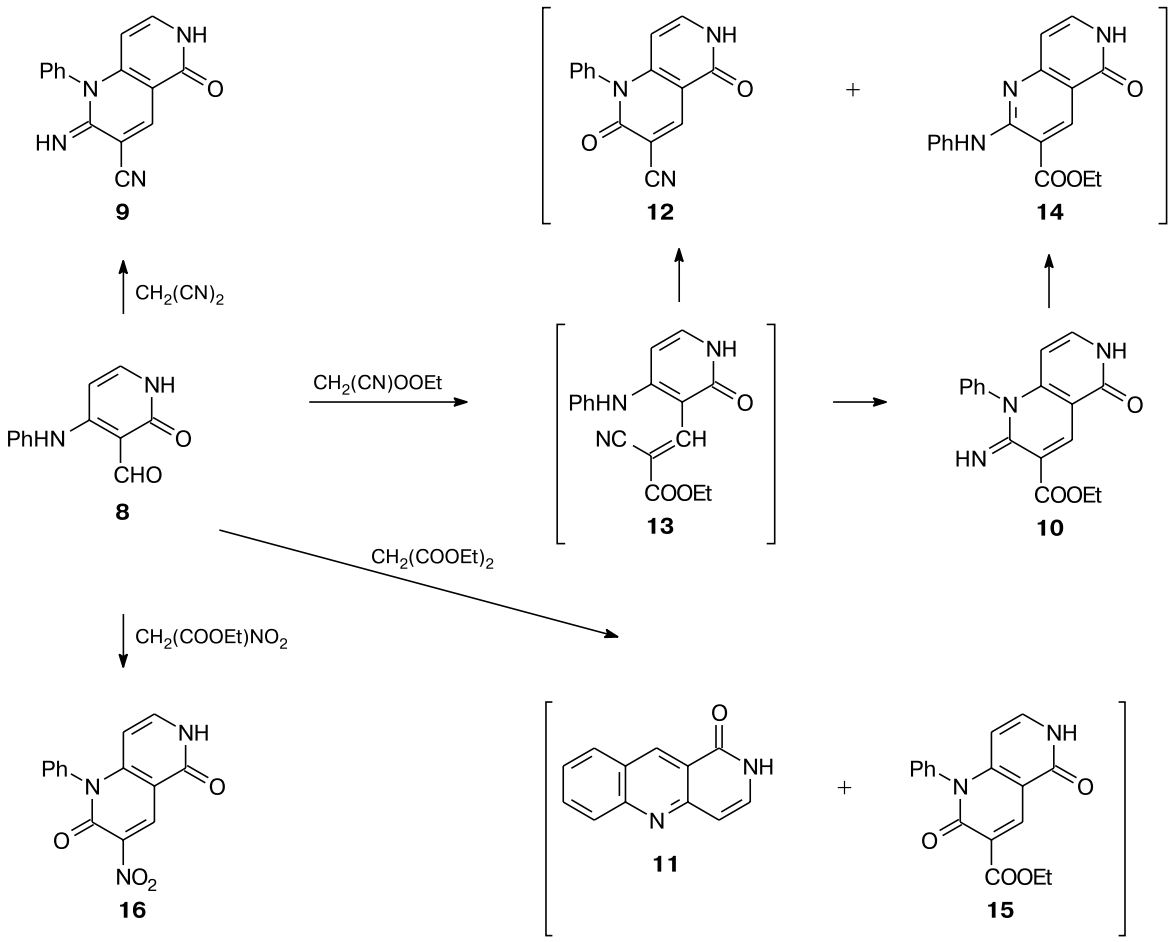
malononitrile, leads to cyclization of the Knoevenagel reaction product to give naphthyridinone **7** in 96% yield (Scheme 4). This conclusion was drawn based on analysis of the ^{13}C NMR spectrum (see the Experimental section). The cyclic structure is evidenced by the presence of signals for the C atoms of two (rather than three) CN groups at δ 112.3 (CN(C(8))) and 115.7 (CN(C(3))). The assignment of the signals in the ^{13}C NMR spectrum was made based on correlation peaks in the 2D HMBC spectrum presented in the Experimental section.

Scheme 4



The reaction of 3-formylpyridone **8** with malononitrile in the presence of Et_3N both in ethanol and pyridine (in the absence of a catalyst) produces 2-iminonaphthyridin-5-one **9** (in 61 and 86% yields, respectively), the virtually analytically pure product being isolated from ethanol

Scheme 5



(Scheme 5). The structure of compound **9** was confirmed by the HMBC spectrum (δ): 5.15/105.7 (H(8)/C(4a)), 5.15/139.7 (H(8)/C(7)), 7.36/96.1 (H(7)/C(8)), 7.36/102.3 (H(7)/C(4a)), 7.36/151.8 (H(7)/C(8a)), 7.36/159.3 (H(7)/C(5)), 8.15/96.1 (H(4)/C(8)), 8.15/102.3 (H(4)/C(3)), 8.15/116.4 (H(4)/CN(C(3))), 8.15/151.8 (H(4)/C(8a)), and 8.15/159.3 (H(4)/C(5)). The IR spectrum of compound **9** shows signals at 3319 (NH=) and 2200 (CN) cm^{-1}.

The reaction of 3-formylpyridone **8** with cyanoacetic ester in the presence of Et_3N in ethanol requires prolonged refluxing (24 h). In this case, we prepared compound **10** in 54% yield (it should be noted that traces of tricyclic compound **11**, which we have prepared earlier,[7] were detected in the mother liquor by chromatography). The IR spectrum of compound **10** shows signals at 3302 (NH=), 1734 (COOEt), and 1693 (CO) cm^{-1} but the signal of the CN group is absent. The above facts and the ^1H NMR spectroscopic data (see the Experimental section) provide evidence that compound **10** has a bicyclic structure, *i.e.*, it is 3-ethoxycarbonyl-2-imino-1-phenylnaphthyridin-5-one.

This reaction in pyridine as the solvent affords a mixture consisting primarily of two products (in a ratio of 1 : 1). One of these products, naphthyridinone **12**, is generated through intramolecular cyclization involving the phenylamino and ethoxycarbonyl groups. Another product contains the ethyl group but it is not compound **10**. The ^1H NMR spectrum of the mixture shows two doublets (1 H each) at δ 5.28 and 5.38 and two singlets (1 H each) at δ 8.82 and 8.91, as well as a triplet (3 H) and a quartet (2 H) corresponding to one ethyl group. The ES mass spectrum has ion peaks at *m/z* 264 $[M^1 + H]^+$ (**12**), 310 $[M^2 + H]^+$, and 281 $[M^2 - C_2H_4]^+$. These data suggest that the reaction of 3-formylpyridine **8** with cyanoacetic ester in pyridine produces a mixture of naphthyridinones **12** and **14**. The formation of the latter is apparently attributed to the transformation of intermediate **13** into compound **10** and then into **14** through Dimroth recyclization. We failed to isolate naphthyridinone **14** from the reaction mixture in individual form.

We also used diethyl malonate and ethyl nitroacetate as compounds containing activated methylene groups in condensation with 3-formylpyridone **8**. In the former case,

refluxing in isopropyl alcohol in the presence of a catalytic amount of piperidine afforded a mixture containing (^{1}H NMR spectroscopic data) tricyclic compound **11** as the major product (signals of this compound are completely identical to those observed in the ^{1}H NMR spectrum of tricyclic compound **11**, which we have prepared earlier[7]). The ^{1}H NMR spectrum of the minor component shows the following signals (δ): 1.25 (t, 3 H, CH_3), 4.21 (q, 2 H, $C\underline{H}_2CH_3$), 5.28 (d, 1 H, H(8)), 7.32 (d, 2 H, Ph), 8.62 (s, 1 H, H(4)). Based on these data, it can be suggested that the minor product has the structure of 3-ethoxycarbonyl-1-phenylnaphthyridine-2,5-dione **15**. The ES mass spectrum of the mixture has signals at *m/z* 197 $[M^1 + H]^+$, 311 $[M^2 + H]^+$, 333 $[M^2 + Na]^+$, and 643 $[2\ M^2 + Na]^+$, where M^1 corresponds to the molecular ion of tricyclic compound **11** and M^2 corresponds to naphthyridinone **15**.

It should be noted that 3-formylpyridone **8** readily undergoes cyclization[7] to give tricyclic compound **11** upon refluxing in isopropyl alcohol in the presence of piperidine.

The reaction of 3-formylpyridine **8** with nitroacetic ester in isopropyl alcohol (refluxing, 4.5 h) in the presence of piperidine produced 3-nitro-1-phenylnaphthyridinedione **16** in 72% yield.

Experimental

The IR spectra were recorded on a FSM-1201 instrument in Nujol mulls. The ^{1}H NMR spectra were measured on Bruker AC-300 and Bruker DRX-500 spectrometers in DMSO-d_6 and DMSO-d_6—CCl_4. The HMBC spectra were recorded on a Bruker DRX-500 spectrometer in DMSO-d_6. The EI mass spectra (70 eV) were obtained on a Finnigan SSQ-710 mass spectrometer using a direct inlet system. The ES mass spectra were recorded on a Waters ZQ-2000 mass spectrometer using a direct inlet system without the use of a chromatographic column. The course of the reactions was monitored and the purity of the compounds was checked by TLC on Merck 60 F_{254} plates. The melting points were determined on an Electrotermal 9100 instrument (UK).

3-Cyano-5-(2-cyano-2-ethoxycarbonylvinyl)-2-oxo-4-(phenylamino)-1,2-dihydropyridine (2). A mixture of formylpyridone **1** (3 g, 0.012 mol), cyanoacetic ester (2.72 g, 0.021 mol), and triethylamine (0.5 mL) in pyridine (25 mL) was kept at 20 °C for 72 h. The reaction mixture was concentrated *in vacuo*, the residue was triturated in anhydrous EtOH (20 mL), and the precipitate that formed was filtered off and washed with EtOH. Compound **2** was obtained in a yield of 3.27 g (96%), m.p. 303—305 °C (DMF). Found (%): C, 64.39; H, 4.52; N, 16.58. $C_{18}H_{14}N_4O_3$. Calculated (%): C, 64.67; H, 4.19; N, 16.77. ^{1}H NMR (DMSO-d_6), δ: 1.35 (t, 3 H, $COOCH_2C\underline{H}_3$, J_o = 7.5 Hz); 4.35 (q, 2 H, $COOC\underline{H}_2CH_3$, J_o = 7.5 Hz); 7.53—7.66 (m, 5 H, Ph); 8.68 and 8.75 (both s, 1 H each, H(6), H(5′)); 9.38 (br.s, 1 H, NHPh). IR, ν/cm^{-1}: 3147 (NH), 2208 (CN), 1697 (CO), 1665 (CO). ES MS, *m/z*: 335 $[M + H]^{+\bullet}$, 669 $[2\ M + H]^{+\bullet}$, 691 $[2\ M + Na]^{+\bullet}$, 305 $[M - CHO]^{+\bullet}$, 288 $[M - EtOH]^{+\bullet}$.

3,8-Dicyano-6-methyl-2,7-dioxo-1-phenyl-1,2,6,7-tetrahydro-1,6-naphthyridine (3). A 80% NaH solution (0.5 g, 1.8 mmol) was added portionwise to a solution of compound **2** (0.2 g, 0.6 mmol) in DMSO (4 mL) at 19 °C for 1 h so that the temperature of the reaction mixture did not rise above 24 °C, after which the solution turned dark-red. Then Me_2SO_4 (0.26 g, 2.1 mmol) was added to the resulting salt, and the reaction mixture was stirred at 20 °C for 1 h and poured into cold water. The precipitate that formed was filtered off and washed with isopropyl alcohol and petroleum ether. Compound **3** was obtained in a yield of 0.074 g (41%), m.p. 184 °C (sublim.). Found (%): C, 65.04; H, 4.03; N, 17.62; H_2O, 2.90. $C_{18}H_{14}N_4O_3 \cdot 0.5H_2O$. Calculated (%): C, 65.18; H, 4.15; N, 17.89; H_2O, 2.87. ^{1}H NMR (DMSO-d_6), δ: 3.58 (s, 3 H, Me); 7.41—7.57 (m, 5 H, Ph); 8.62, (s, 1 H, H(4)); 8.88 (s, 1 H, H(5)). ^{13}C NMR (DMSO-d_6), δ: 39.2 (Me(C(6))); 83.6 (C(8)); 100.7 (C(3)); 103.9 (C(4a)); 111.6 (CN(C(8))); 115.0 (CN(C(3))); 129.0, 130.0, 130.5, 135.4 (Ph); 148.6 (C(4)); 149.7 (C(5)); 150.9 (C(8a)); 158.8 (C(2)); 160.6 (C(7)). HMBC (DMSO-d_6), δ: 3.58/149.7 (Me(C(6))/C(5)); 3.58/160.6 (Me(C(6))/C(7)); 8.62/149.7 (H(4)/C(5)); 8.62/150.9 (H(4)/C(8a)); 8.62/158.8 (H(4)/C(2)); 8.62/100.7 (H(4)/C(3)); 8.62/103.9 (H(4)/C(4a)); 8.62/115.0 (H(4)/C(C(3)N)); 8.88/103.9 (H(5)/C(4a)); 8.88/148.6 (H(5)/C(4)); 8.88/150.9 (H(5)/C(8a)); 8.88/160.6 (H(5)/C(7)). IR, ν/cm^{-1}: 2230 (CN), 1696 (CO), 1628 (CO). ES MS, *m/z*: 302 $[M + H]^{+\bullet}$, 325 $[M + Na]^{+\bullet}$, 627 $[2\ M + Na]^{+\bullet}$, 275 $[M - CO]^{+\bullet}$.

3-Cyano-5-(hydrazonomethyl)-2-oxo-4-phenylamino-1,2-dihydropyridine (4). A mixture of compound **2** (0.005 g, 0.015 mmol) and hydrazine hydrate (0.2 mL) in anhydrous EtOH (1 mL) was kept at 20 °C for 1 h. The precipitate that formed was filtered off and washed with EtOH. Hydrazone **4** was obtained in a yield of 0.036 g (95%), m.p. 293—294 °C (DMF). ^{1}H NMR (DMSO-d_6), δ: 6.66 (br.s, 2 H, NH_2); 7.25 and 7.39 (both m, 3 H and 2 H, Ph); 7.62 (s, 1 H, H_α); 7.75 (s, 1 H, H(6)); 11.39 (br.s, 1 H, C(4)NH); 11.63 (br.s, 1 H, N(1)H). IR, ν/cm^{-1}: 3400, 3200 (NH), 2200 (CN), 1690 (CO), 1620, 1570 (C=C, C=N). ES MS, *m/z*: 254 $[M + H]^{+\bullet}$, 276 $[M + Na]^{+\bullet}$, 529 $[2\ M + Na]^{+\bullet}$. EI MS, *m/z* (I_{rel} (%)): 253 $[M]^{+\bullet}$ (50), 222 $[M - NH_2NH]^{+\bullet}$ (100).

5-(2-Carboxy-2-cyanovinyl)-3-cyano-2-oxo-4-phenylamino-1,2-dihydropyridine (5). Compound **2** (0.325 g, 0.97 mmol) was added to a solution of NaOH (1.53 g) in 30% aqueous methanol (25 mL), and the reaction mixture was stirred at 20 °C until complete dissolution was achieved. The resulting solution of the sodium salt was acidified with concentrated HCl to pH 1 and kept at 5 °C for 0.5 h. The precipitate that formed was filtered off and washed with water. Compound **3** was obtained in a yield of 0.25 g (84%), m.p. 328—330 °C. Found (%): C, 60.11; H, 3.56; N, 17.39; H_2O, 4.92. $C_{16}H_{10}N_4O_3 \cdot 0.9H_2O$. Calculated (%): C, 59.63; H, 3.69; N, 17.38; H_2O, 4.75. IR, ν/cm^{-1}: 3426 (OH), 2230 (CN), 1655 (CO). ES MS, *m/z*: 307 $[M + H]^{+\bullet}$, 329 $[M + Na]^{+\bullet}$, 635 $[2\ M + Na]^{+\bullet}$, 289 $[M - OH]^{+\bullet}$, 261 $[M - HOOC]^{+\bullet}$. EI MS, *m/z* (I_{rel} (%)): 260 $[M - HCOOH]^{+\bullet}$ (100), 232 $[M - HCOOH - CO]^{+\bullet}$ (13), 205 $[M - HCOOH - CO - CN]^{+\bullet}$ (10).

8-Cyano-2,7-dioxo-1-phenyl-1,2,6,7-tetrahydro-1,6-naphthyridine-3-carboxylic acid (6) was prepared analogously to compound **5** from compound **2** (0.15 g, 0.45 mmol) at 76 °C. The reaction mixture was refluxed for 6 h. The yield was 77%, m.p. 314—315 °C. Found (%): C, 62.34; H, 3.00; N, 13.49. $C_{16}H_9N_3O_4$. Calculated (%): C, 62.54; H, 2.95; N, 13.68. ^{1}H NMR (DMSO-d_6), δ: 7.40—7.56 (m, 5 H, Ph); 8.71 and

8.77 (both s, 1 H each, H(4), H(5)); 12.95 and 13.30 (both br.s, 1 H each, N(6)H, COOH). IR, ν/cm^{-1}: 2217 (CN), 1731 (COOH), 1650 (CO), 1600 (C=C, C=N). ES MS, *m/z*: 330 $[M + Na]^{+\bullet}$, 637 $[2 M + Na]^+$. EI MS, *m/z* (I_{rel} (%)): 307 $[M]^{+\bullet}$ (30), 263 $[M - CO_2]^{+\bullet}$ (100), 234 $[M - CO_2 - CO - H]^{+\bullet}$ (10), 206 $[M - HCOOH - CO - CN]^{+\bullet}$ (15).

3,8-Dicyano-2-imino-7-oxo-1-phenyl-1,2,6,7-tetrahydro-1,6-naphthyridine (7). A mixture of formylpyridone **1** (1.2 g, 5 mmol), malononitrile (0.33 g, 5 mmol), and triethylamine (0.5 mL) in pyridine (25 mL) was kept at 20 °C for 20 h. The reaction mixture was concentrated *in vacuo*, the residue was triturated with anhydrous EtOH (20 mL), and the precipitate that formed was filtered off and washed with EtOH. Compound **7** was obtained in a yield of 1.3 g (96%), m.p. > 315 °C (DMF). Found (%): C, 66.59; H, 3.25; N, 24.25. $C_{16}H_9N_5O$. Calculated (%): C, 66.90; H, 3.14; N, 24.39. ^{1}H NMR (DMSO-d_6), δ: 7.47 and 7.57—7.66 (both m, 2 H and 3 H each, Ph); 8.23 (s, 1 H, H(4)); 8.30 (s, 1 H, H(5)); 11.00—12.00 (strongly br.s, 1 H each, N(6)H, HN=C(2)). ^{13}C NMR (DMSO-d_6), δ: 83.1 (C(8)); 100.0 (C(3)); 104.8 (C(4a)); 112.3 (CN(C(8))); 115.7 (CN(C(3))); 130.6, 131.6, 134.7 (Ph); 144.1 (C(4)); 145.4 (C(5)); 151.0 (C(8a)); 152.0 (C(2)); 162.3 (C(7)). HMBC NMR (DMSO-d_6), δ: 8.23/115.7 (H(4)/CN(C(3))); 8.23/151.0 (H(4)/C(C(8a))); 8.30/104.8 (H(5)/C(4a)); 8.30/144.1 (H(5)/C(4)); 8.30/151.0 (H(5)/C(8a)), 8.30/162.3 (H(5)/C(7)). IR, ν/cm^{-1}: 3304 (NH), 2218 (CN), 1654 (CO). ES MS, *m/z*: 288 $[M + H]^{+\bullet}$, 310 $[M + Na]^{+\bullet}$, 575 $[2 M + Na]^{+\bullet}$.

3-Cyano-2-imino-5-oxo-1-phenyl-1,2,5,6-tetrahydro-1,6-naphthyridine (9). A mixture of 3-formylpyridone **8** (0.1 g, 0.47 mmol), malononitrile (0.03 g, 0.47 mmol), and triethylamine (0.05 mL) in EtOH (2 mL) was refluxed for 1 h. The precipitate that formed upon refluxing was filtered off and washed with EtOH. Compound **9** was obtained in a yield of 0.073 g (61%), m.p. 340 °C (Pr^iOH—DMF, 1 : 1). Found (%): C, 68.97; H, 3.94; N, 21.55. $C_{15}H_{10}N_4O$. Calculated (%): C, 68.69; H, 3.84; N, 21.36. ^{1}H NMR (DMSO-d_6), δ: 5.15 (d, 1 H, H(8), J_o = 7.4 Hz); 7.34—7.41 (both m, 3 H each, Ph, H(7)); 8.15, (s, 1 H, H(4)); 11.20—12.40 (strongly br.s, 1 H each, N(6)H, HN=C(2)). ^{13}C NMR (DMSO-d_6), δ: 96.1 (C(8)); 102.3 (C(3)); 105.7 (C(4a)); 116.4 (CN(C(3))); 129.0, 130.1, 131.1, 135.8 (Ph); 139.7 (C(7)); 141.1 (C(4)); 151.8 (C(8a)); 153.2 (C(2)); 159.3 (C(5)). IR, ν/cm^{-1}: 3319, 3087 (NH); 2230 (CN); 1674, 1625 (CO). EI MS, *m/z* (I_{rel} (%)): 261 $[M - H]^{+\bullet}$ (100).

Ethyl 2-imino-5-oxo-1-phenyl-1,2,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate (10). A mixture of 3-formylpyridone **8** (0.354 g, 1.65 mmol), cyanoacetic ester (0.237 g, 2.61 mol), and triethylamine (0.13 mL) in EtOH (18 mL) was refluxed for 24 h. The reaction mixture was concentrated *in vacuo*, the residue was triturated in anhydrous EtOH (10 mL), and the residue was filtered off and washed with EtOH. Compound **10** was obtained in a yield of 0.275 g (54%), m.p. 264—265 °C (EtOH). Found (%): N, 13.57. $C_{17}H_{15}N_3O_3$. Calculated (%): N, 13.58. ^{1}H NMR (DMSO-d_6), δ: 1.32 (t, 3 H, $COOCH_2C\underline{H}_3$, J_o = 7.5 Hz); 4.27 (q, 2 H, $COOC\underline{H}_2CH_3$, J_o = 7.5 Hz); 5.12 (d, 1 H, H(8), J_o = 7.4 Hz); 7.34 (d, 1 H, H(7), J_o = 7.4 Hz); 7.26, 7.48, and 7.51 (all m, 2 H each, 1 H, 2 H, Ph); 8.42 (s, 1 H, H(4)); 8.77 and 11.56 (both br.s, 1 H each, N(6)H, NH=C(2)). IR, ν/cm^{-1}: 3302, 3087 (NH); 1734, 1693, 1651, 1620 (CO). ES MS, *m/z*: 310 $[M + H]^{+\bullet}$, 332 $[M + Na]^{+\bullet}$, 641 $[2 M + H]^{+\bullet}$, 296 $[M + H - 14]^{+\bullet}$, 264 $[M + H - C_2H_5OH]^{+\bullet}$.

3-Nitro-2,5-dioxo-1-phenyl-1,2,5,6-tetrahydro-1,6-naphthyridine (16). A mixture of 3-formylpyridone **8** (0.1 g, 0.47 mmol), nitroacetic ester (0.12 g, 0.9 mol), and piperidine (0.086 g) in isopropyl alcohol (5 mL) was refluxed for 4 h. The precipitate that formed was filtered off and washed with isopropyl alcohol. Compound **16** was obtained in a yield of 0.093 g (72%), m.p. 335 °C (decomp., EtOH). Found (%): C, 59.36; H, 3.23; N, 14.76. $C_{14}H_9N_3O_4$. Calculated (%): C, 59.38; H, 3.20; N, 14.84. ^{1}H NMR (DMSO-d_6), δ: 5.35 (d, 1 H, H(8), J_o = 7.4 Hz); 7.41—7.84 (m, 6 H, Ph, H(7)); 8.91 (s, 1 H, H(4)); 11.56 (br.s, 1 H, N(6)H). IR, ν/cm^{-1}: 3158 (NH); 1659, 1631 (CO); 1518 (NO_2). ES MS, *m/z*: 284 $[M + H]^{+\bullet}$, 306 $[M + Na]^{+\bullet}$, 589 $[2 M + H]^+$.

This study was financially supported by the Federal Agency for Science and Innovations of the Russian Federation (Contract No. 1/05).

References

1. M. I. Rodriguez-Franco, M. I. Fernandez-Bachiller, C. Perez, B. Hernandez-Ledezma, and B. Bartolome, *J. Med. Chem.*, 2006, **49**, 459.
2. P. Munor-Ruiz, L. Rubio, E. Garcio-Palomero, I. Dorronsoro, M. Del Monte-Millan, L. Valezuela, P. Usan, C. de Austria, M. Bartolini, V. Adrisano, A. Bidon-Chanal, M. Orozco, F. J. Ligue, M. Medina, and A. Martinez, *J. Med. Chem.*, 2005, **48**, 7223.
3. Germ. Pat. DE 19835918A1, 2000; *Chem. Abstr.*, 2000, **132**, p137285.
4. V. P. Litvinov, S. V. Roman, and V. D. Dyachenko, *Usp. Khim.*, 2000, **69**, 218 [*Russ. Chem. Rev.*, 2000, **69** (Engl. Transl.)].
5. A. S. Ivanov, N. Z. Tugusheva, and V. G. Granik, *Usp. Khim.*, 2005, **74**, 1001 [*Russ. Chem. Rev.*, 2005, **74** (Engl. Transl.)].
6. A. S. Ivanov, N. Z. Tugusheva, L. M. Alekseeva, and V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 837 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 873].
7. N. Z. Tugusheva, L. M. Alekseeva, A. S. Shashkov, V. V. Chernyshev, and V. G. Granik, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 1421 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1475].

Received May 26, 2006;
in revised form July 12, 2006