ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 10, pp. 1541–1545. © Pleiades Publishing, Ltd., 2009.
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Reaction of 5,5-Dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles with Morpholine

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Received February 17, 2009

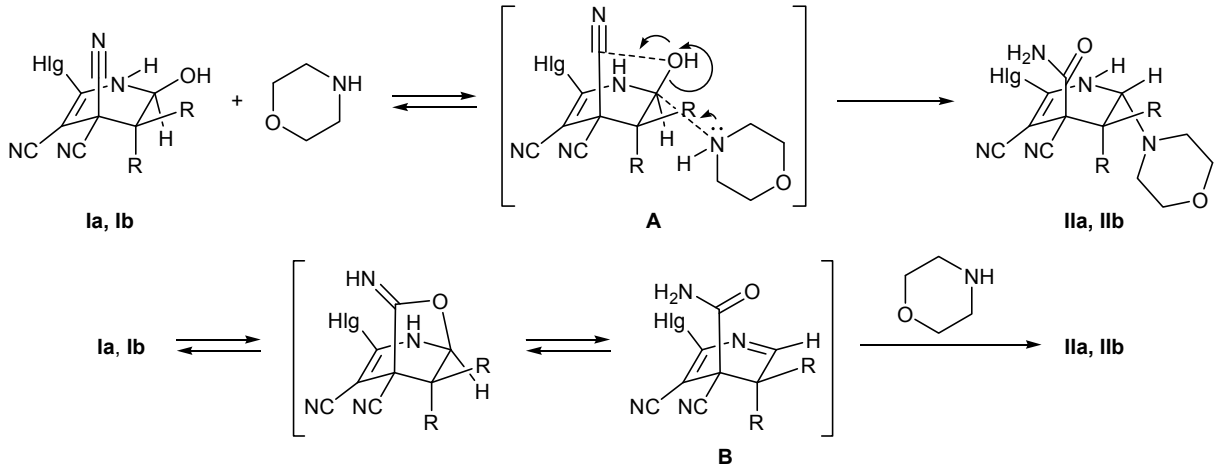
Abstract—5,5-Dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles reacted with morpholine in aprotic solvent to give the corresponding 3,3-dialkyl-4,5-dicyano-6-halo-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamides, while analogous reaction in amphiprotic solvent resulted in the formation of 8,8-dialkyl-3-halo-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitriles.

DOI: 10.1134/S1070428009100212

Intramolecular reactions between cyano and hydroxy groups underlie syntheses of heterocyclic compounds [1–6]. As shown in [7–9], spatially close (1,3-diaxial) location of hydroxy and cyano groups favors their mutual activation toward nucleophiles. Due to effect of the cyano group, the hydroxy group becomes a readily departing group, while the cyano group readily undergoes hydrolysis. For example, the hydroxy group in 2-aryl-6-hydroxy-5,6-tetramethylenepiperidine-3,3,4,4-tetracarbonitriles is readily replaced by amino by the action of aqueous ammonia, and the reaction is accompanied by hydrolysis of one cyano group to carbamoyl [7]. Analogous transformations were observed in the reactions of 5,5-dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles with methanol [8] and aldehyde oximes [9]. We believe that the above processes are favored by electrophilic assistance by cyano group to nucleophilic replacement of the hydroxy group.

We previously reported on the synthesis of 5,5-dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles [10]. According to the X-ray

Scheme 1.



R = Me, Hlg = Cl (**a**), Br (**b**).

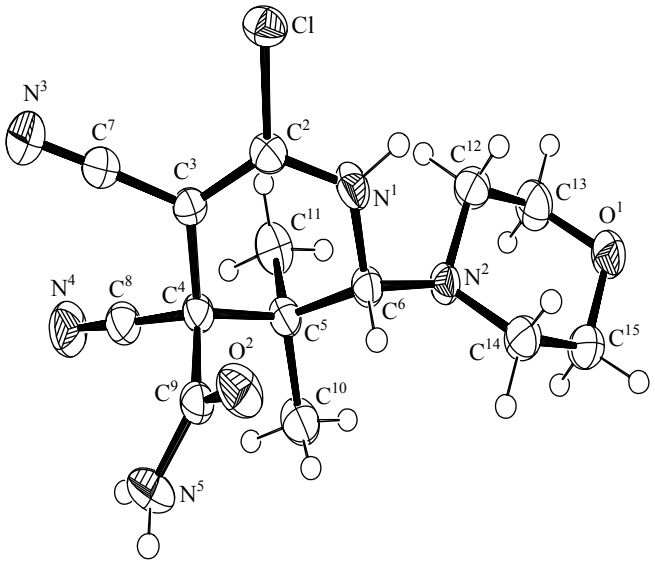


Fig. 1. Structure of the molecule of 6-chloro-4,5-dicyano-3,3-dimethyl-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamide (**IIa**) according to the X-ray diffraction data.

diffraction data [10], the distance between the hydroxy oxygen atom and carbon atom in the cyano group in 2-chloro-6-hydroxy-5,5-dimethyl-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitrile is 2.722 Å, which is shorter than the sum of the corresponding van der Waals radii. Such close location of the reaction centers could give rise to assistance by cyano group to nucleophilic replacement of the hydroxy group, the cyano group being converted into carboxamide functionality.

We examined reactions of 5,5-dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles with morpholine and found that the depth of their transformation depends on the conditions. Here, an important factor is solvent nature. Aprotic solvents, such as acetone and acetonitrile, favor 1,3-diaxial assistance to nucleophilic replacement of the hydroxy group, and the products are 3,3-dialkyl-4,5-dicyano-6-halo-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamides **IIa** and **IIb** (yield 78–87%; Scheme 1). Presumably, the substitution process and hydrolysis of the cyano group occur simultaneously through transition state **A**. This assumption is supported by the fact that the entering morpholino group appears in the *trans* position with respect to the carboxamide group (according to the X-ray diffraction data; see Fig. 1). An alternative path involves formation of dihydropyridine intermediate **B**. However, in this case compounds **IIa** and **IIb** could be formed as mixtures of isomers with *cis* and *trans* arrangement of the morpholino and carbamoyl groups (Scheme 1).

In keeping with the proposed mechanism, morpholine as nucleophile attacks the C^2 atom. Close location of the nucleophilic (OH) and electrophilic (CN) centers in initial compounds **I** favors transformation of n,π-interaction [10] between these fragments into σ-bond upon the action of nucleophile. We believe that these processes are synchronous; therefore, the reaction should be stereoselective. Our assumption is confirmed by exclusive formation of the product with *trans* orientation of the carbamoyl and morpholino groups in the six-membered ring in the reaction with morpholine in acetone (Fig. 1).

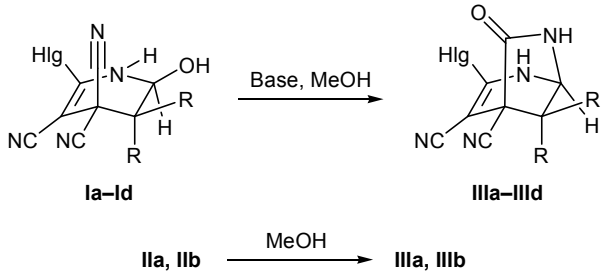
The structure of compound **IIa** was determined by X-ray analysis (Fig. 1), and compound **IIb** was assigned analogous structure by comparing its IR and ^{1}H NMR spectra with those of **IIa**. The morpholine ring in molecule **IIa** has a *chair* conformation, and the tetrahydropyridine adopts a C^5-*envelope* conformation. The C^4–C^5 bond length [1.589(3) Å] suggests steric repulsion between the substituents on C^4 and C^5. The C^5–C^6 bond is shortened [1.561(3) Å], presumably as a result of partial compensation of the repulsion between the bulky substituents on C^5 and C^6 due to interaction between H^{11A} and H^{10C} in the methyl groups on C^5 and lone electron pair on the nitrogen atom in the morpholine ring. This interaction is reflected in the interatomic distances $N^2\cdots H^{11A}$ 2.632 and $N^2\cdots H^{10C}$ 2.662 Å. Among intermolecular contacts, hydrogen bonds N^5–$H^{5B}\cdots O^1$ ($0.5 - x$, $-0.5 + y$, $-0.5 - z$) and N^1–$H^1\cdots O^2$ ($1 - x$, $-y$, $-z$) should be noted: $H^{5B}\cdots O^1$ 2.15 Å, $\angle N^5H^{5B}O^1$ 151°; $H^1\cdots O^2$ 2.20 Å, $\angle N^1H^1O^2$ 137°.

Compounds **IIa** and **IIb** displayed in the IR spectra an absorption band at 1590 cm^{-1} due to stretching vibrations of the conjugated double C=C bond, a strong carbonyl absorption band (amide I) in the region 1675–1690 cm^{-1}, strong bands belonging to conjugated cyano groups at 2210–2220 cm^{-1}, a medium-intensity band at 2260 cm^{-1} corresponding to stretching vibrations of unconjugated cyano group, and several medium-intensity N–H bands in the region 3190–3370 cm^{-1}. The ^{1}H NMR spectra of **IIa** and **IIb** contained a doublet at δ 9.2–9.1 ppm from the enamine NH proton, two singlets in the region δ 7.9–7.7 ppm from two protons in the carboxamide fragment, a doublet at δ 4.6–3.9 ppm from the CH proton, multiplet signals at δ 3.6–2.7 ppm from protons in the morpholine ring, and two singlets at δ 1.3–0.9 ppm from protons in the methyl groups.

Unlike polar aprotic solvents (acetonitrile and acetone), the reaction of compounds **I** with morpholine

in amphiprotic solvents (e.g., methanol or ethanol) did not stop at the stage of formation of compounds **II** but further transformations occurred and were accompanied by deamination. An indirect support to the reaction path involving intermediate formation of carboxamide **II** is that dissolution of compounds **II** in methanol led to the formation of 8,8-dialkyl-3-halo-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitriles **III** in 98–99% yield (Scheme 2).

Scheme 2.



R = Me, Hlg = Cl (**a**), Br (**b**); R = Et, Hlg = Cl (**c**), Br (**d**).

The structure of compound **IIId** was determined by the X-ray diffraction data (Fig. 2), and compounds **IIIa**–**IIIc** were identified by IR and ^{1}H NMR spectra. The bond lengths and bond angles in molecule **IIId** almost do not differ from the corresponding standard values. Molecules **IIId** in crystal are linked through centrosymmetric hydrogen bonds involving the carboxamide group N^1–$H^1\cdots O^{1'}$ (–*x*, 3 – *y*, 1 – *z*) with the following parameters: $H^1\cdots O^{1'}$ 2.25 Å, $\angle N^1H^1O^{1'}$ 176°. The N^2 atom is also involved in intermolecular hydrogen bond N^2–$H^2\cdots O^{1'}$ (1 + *x*, *y*, *z*; $H^2\cdots O^{1'}$ 2.25 Å, $\angle N^2H^2O^{1'}$ 179°). These hydrogen bonds give rise to chains linked to each other and directed along the *a* crystallographic axis (Fig. 3).

The ^{1}H NMR spectra of compounds **IIIa**–**IIId** contain two doublets in the region δ 9.9–9.1 ppm due to NH protons, a triplet at δ 4.5–4.6 ppm due to CH proton, and two singlets at δ 1.3–0.9 ppm from protons in the methyl groups (**IIIa**, **IIIb**) or two triplets at δ 1.0–0.9 ppm (**IIIc**, **IIId**). Compounds **IIIc** and **IIId** also displayed multiplet signals from each methylene proton in the ethyl groups in the region δ 1.85–1.35 ppm.

Thus the presence of spatially close cyano and hydroxy groups in 5,5-dialkyl-2-halo-6-hydroxy-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitriles gives rise to stereoselective synchronous electrophilic assistance by the cyano group to nucleophilic replacement of the hydroxy group, as shown experimentally in their reactions with morpholine.

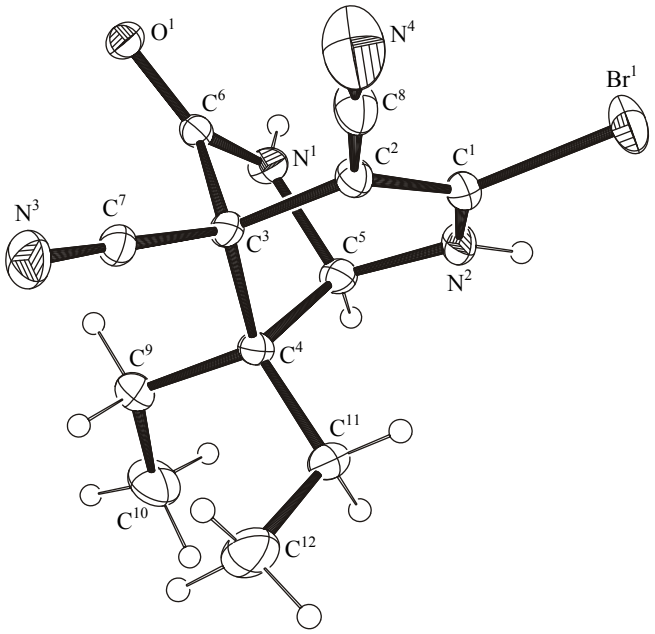


Fig. 2. Structure of the molecule of 3-bromo-8,8-diethyl-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitrile (**IIId**) according to the X-ray diffraction data.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker AM-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The IR spectra were measured on an FSM-1202 spectrometer with Fourier transfrom from samples dispersed in mineral oil. The mass spectra (electron impact, 70 eV) were obtained on a Shumadzu QP-2010 DI instrument. All solvents were distilled prior to use. The purity of the isolated compounds was checked by thin-layer chromatography on Silufol UV-254 plates; spots were visualized under UV light, by treatment with iodine vapor, or by heating.

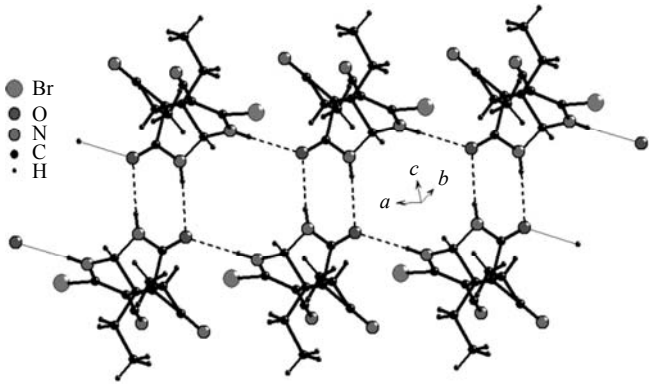


Fig. 3. Intermolecular hydrogen bonds formed by molecules of 3-bromo-8,8-diethyl-6-oxo-2,7-diazabicyclo[3.2.1]oct-3-ene-4,5-dicarbonitrile (**IIId**) in crystal.

4,5-Dicyano-6-halo-3,3-dimethyl-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamides IIa and IIb (*general procedure*). Morpholine, 0.01 g (0.001 mol), was added to a solution of 0.001 mol of 2-halo-6-hydroxy-5,5-dimethyl-5,6-dihydro-1*H*-pyridine-3,4,4-tricarbonitrile **Ia** or **Ib** in 1 ml of acetone. After 1–2 h, the precipitate was filtered off and washed with acetone.

6-Chloro-4,5-dicyano-3,3-dimethyl-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamide (IIa). Yield 0.36 g (87%), mp 245–246°C. IR spectrum, ν, cm^{-1}: 3370, 3320, 3260 (N–H, NH_2); 2260, 2210 (C≡N); 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.05 s and 1.21 s (3H each, CH_3), 2.67 t (2H, NCH_2), 3.52 t (2H, CH_2O), 4.61 d (1H, CH), 7.68 s and 7.85 s [1H each, $C(O)NH_2$], 9.15 d (1H, NH). Mass spectrum: *m*/*z* 323 (I_{rel} = 3%). Found, %: C 51.90; H 5.65; N 21.57. $C_{14}H_{18}ClN_5O_2$. Calculated, %: C 51.93; H 5.60; N 21.63.

6-Bromo-4,5-dicyano-3,3-dimethyl-2-morpholino-1,2,3,4-tetrahydropyridine-4-carboxamide (IIb). Yield 0.27 g (78%), mp 255–256°C. IR spectrum, ν, cm^{-1}: 3370, 3320, 3260 (N–H, NH_2); 2260, 2220 (C≡N); 1715 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.01 s and 1.18 s (3H each, CH_3), 2.72 t (2H, NCH_2), 3.57 t (2H, CH_2O), 4.32 d (1H, CH), 7.72 s and 7.89 s [1H each, $C(O)NH_2$], 9.21 d (1H, NH). Mass spectrum: *m*/*z* 367 (I_{rel} = 4%). Found, %: C 45.62; H 4.86; N 19.08. $C_{14}H_{18}BrN_5O_2$. Calculated, %: C 45.66; H 4.93; N 19.02.

8,8-Dialkyl-3-halo-6-oxo-2,7-diazabicyclo[3.2.1]-oct-3-ene-4,5-dicarbonitriles IIIa–IIId (*general procedure*). *a*. One drop of morpholine was added to a solution of 0.001 mol of compound **Ia**–**Id** in 5 ml of methanol. After cooling, the precipitate was filtered off and washed with alcohol.

b. Compound **IIa** or **IIb**, 0.001 mol, was dissolved in 5 ml of methanol on heating. After cooling, the precipitate was filtered off and washed with alcohol.

3-Chloro-8,8-dimethyl-6-oxo-2,7-diazabicyclo-[3.2.1]oct-3-ene-4,5-dicarbonitrile (IIIa). Yield 0.22 g (95%) (*a*), 0.23 g (99%) (*b*), mp 300–301°C. IR spectrum, ν, cm^{-1}: 3260, 3120 (NH); 2260, 2210 (C≡N); 1710 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.04 s and 1.22 s (3H each, CH_3), 4.52 t (1H, CH), 9.17 d (1H, NH), 9.73 s (1H, NH). Mass spectrum: *m*/*z* 236 (I_{rel} = 3%). Found, %: C 50.68; H 3.87; N 23.68. $C_{10}H_9ClN_4O$. Calculated, %: C 50.75; H 3.83; N 23.67.

3-Bromo-8,8-dimethyl-6-oxo-2,7-diazabicyclo-[3.2.1]oct-3-ene-4,5-dicarbonitrile (IIIb). Yield 0.27 g (97%) (*a*), 0.28 g (99%) (*b*), mp 298–299°C. IR spectrum, ν, cm^{-1}: 3280, 3160 (NH); 2260, 2210 (C≡N); 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 9.74 s (1H, NH), 9.15 d (1H, NH), 4.55 t (1H, CH), 1.25 s and 1.01 s (3H each, CH_3). Mass spectrum: *m*/*z* 280 (I_{rel} = 4%). Found, %: C 42.65; H 3.26; N 19.97. $C_{10}H_9BrN_4O$. Calculated, %: C 42.73; H 3.23; N 19.93.

3-Chloro-8,8-diethyl-6-oxo-2,7-diazabicyclo-[3.2.1]oct-3-ene-4,5-dicarbonitrile (IIIc). Yield 0.25 g (94%), mp 307–308°C. IR spectrum, ν, cm^{-1}: 3280, 3200 (NH); 2260, 2210 (C≡N); 1690 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.95 t (6H, $CH_2C\mathbf{H}_3$), 1.36 m (3H, $C\mathbf{H}_2CH_3$), 1.85 m (1H, $C\mathbf{H}_2CH_3$), 4.62 t (1H, CH), 9.91 s (1H, NH), 9.25 d (1H, NH). Mass spectrum: *m*/*z* 264 (I_{rel} = 2%). Found, %: C 54.38; H 4.87; N 21.12. $C_{12}H_{13}ClN_4O$. Calculated, %: C 54.45; H 4.95; N 21.17.

3-Bromo-8,8-diethyl-6-oxo-2,7-diazabicyclo-[3.2.1]oct-3-ene-4,5-dicarbonitrile (IIId). Yield 0.30 g (96%), mp 303–304°C. IR spectrum, ν, cm^{-1}: 3260, 3190 (NH); 2260, 2210 (C≡N); 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.96 t (6H, $CH_2C\mathbf{H}_3$), 1.37 m (3H, $C\mathbf{H}_2CH_3$), 1.84 m (1H, $C\mathbf{H}_2CH_3$), 4.56 t (1H, CH), 9.22 d (1H, NH), 9.85 d (1H, NH). Mass spectrum: *m*/*z* 308 (I_{rel} = 2%). Found, %: C 46.68; H 4.28; N 18.18. $C_{12}H_{13}BrN_4O$. Calculated, %: C 46.62; H 4.24; N 18.12.

Crystallographic parameters. Compound **IIa**: a = 8.992(2), b = 16.099(3), c = 10.936(3) Å; β = 191.44(2)°; Z = 4; space group $P2_1/n$. The structure was refined in full-matrix anisotropic approximation for non-hydrogen atom using 2711 reflections measured in the range $2\theta < 144°$ and characterized by $I > 2\sigma(I)$. Hydrogen atoms were localized by the Fourier difference syntheses, and their positions were refined in isotropic approximation. Final divergence factor R = 0.048.

Compound IIId: a = 6.9560(8), b = 7.9550(1), c = 12.5812(10); Z = 2; space group P-1. The structure was refined in full-matrix anisotropic approximation for non-hydrogen atom using 2711 reflections measured in the range $2\theta < 144°$ and characterized by $I > 2\sigma(I)$. Hydrogen atoms were localized by the Fourier difference syntheses, and their positions were refined in isotropic approximation. Final divergence factor R = 0.041.

All calculations were performed using SHELXL-97 software package. The complete sets of crystallographic data for compounds **IIa** and **IIId** were deposit-

ed to the Cambridge Crystallographic Data Centre (entry nos. CCDC 675190 and CCDC 675205, respectively).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 08-03-97015r-Povolzh'e-a). The authors thank the Nanotechnology Collective Use Center of the Chuvash Republic for recording the IR and mass spectra.

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