ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 1, pp. 115–118. © Pleiades Publishing, Ltd., 2009.
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Reduction of 2-Amino-3- and -5-nitropyridine Derivatives with Hydrazine Hydrate

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Received March 18, 2007

Abstract—The reactions of 2-amino-3-nitropyridine and 2-amino-5-nitropyridine with hydrazine hydrate resulted in elimination of the amino group and reduction of the nitro group with formation of 3-aminopyridine. A probable reaction mechanism involves addition of hydrazine hydrate at the N–C^2 bond, followed by elimination of ammonia and reduction of the nitro group to amino. 2-Amino-4-methyl-3-nitropyridine and 2-amino-5-methyl-3-nitropyridine reacted with hydrazine hydrate in a similar way.

DOI: 10.1134/S107042800901014X

We previously showed that reactions of 3- and 5-nitropyridin-2(1*H*)-ones with hydrazine hydrate led to the formation of pyrazole, and (pyrazole-3-yl)acetohydrazide, respectively [1, 2]. While continuing studies in this line we found that heating of 3-nitropyridin-4(1*H*)-one with hydrazine hydrate under analogous conditions yields 3-acetylpyrazole hydrazone [3]. The latter was also formed in the reaction of 4-amino-3-nitropyridine with hydrazine hydrate [3]. A probable mechanism was proposed for the observed recyclization, and its details were confirmed by experiments with model compounds [4].

It was interesting to elucidate whether analogous recyclication is possible in the reactions of 5- and 3-nitro-2-aminopyridines **I** and **II** with hydrazine hydrate. The reaction of 2-amino-5-nitropyridine (**I**) with excess hydrazine hydrate on heating at 110–120°C (7–10 h) was accompanied by evolution of ammonia, and the product was 3-aminopyridine (**III**, yield 35%) which was identified on the basis of its elemental composition and ^{1}H NMR data, as well as by comparing with an authentic sample (no depression of the melting point was observed on mixing, and the ^{1}H NMR spectra of both samples were identical). Likewise, in the reaction of 2-amino-3-nitropyridine with hydrazine hydrate we isolated 25% of the same product, 3-aminopyridine (**III**) [5] (Scheme 1).

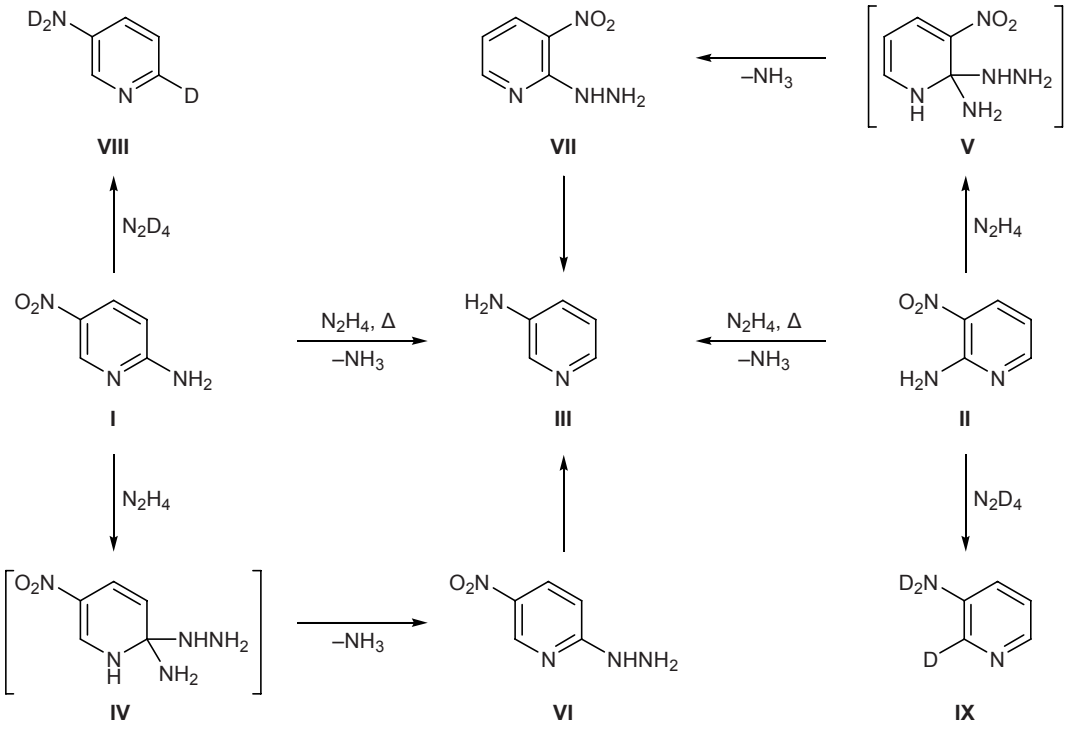
Thus the reduction of the nitro group in molecules **I** and **II** with hydrazine hydrate is accompanied by elimination of the amino group from the 2-position. Taking into account that neither 2,5- nor 2,3-diaminopyridine reacted with hydrazine hydrate, we presumed that elimination of the 2-amino group from **I** and **II** precedes complete reduction of the nitro group in their molecules. It is quite probable that in the initial step hydrazine molecule adds at the N–C^2 bond of aminonitropyridine **I** or **II**, and next follows elimination of ammonia molecule leading to 2-hydrazino-5- and 2-hydrazino-3-nitropyridines **VI** and **VII**. Presumably, the hydrazino group in **VI** and **VII** is oxidized with nitro group, and subsequent reduction of intermediates thus formed with excess hydrazine hydrate finally yields 3-aminopyridine (**III**). To verify this assumption we synthesized intermediate hydrazinopyridines **VI** and **VII** according to the procedure described in [6, 7]. In fact, heating of compounds **VI** and **VII** with hydrazine hydrate under the same conditions as in the reduction of nitro derivatives **I** and **II** resulted in the formation of 3-aminopyridine **III** [8].

By treatment of 2-amino-5-nitropyridine (**I**) with excess hydrazine-d_4 we obtained 2-deutero-5-dideuteroaminopyridine (**VIII**). Under analogous conditions, 2-amino-3-nitropyridine (**II**) was converted into 2-deutero-3-dideuteroaminopyridine (**IX**) (Scheme 1). The structure of compounds **VIII** and **IX** was unambiguously confirmed by the ^{1}H NMR data.

While developing our studies on reactions of nitro-substituted 2-aminopyridines **I** and **II** with hydrazine hydrate we tried to elucidate the effect of methyl

[†] Deceased.

Scheme 1.



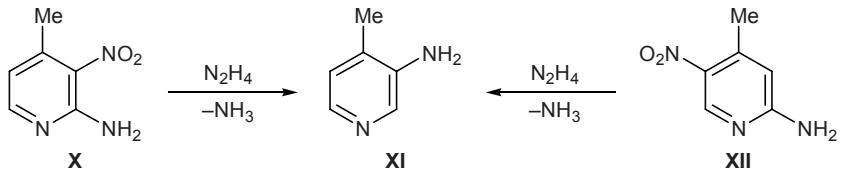
groups in position *3*, *4*, or *6* of the pyridine ring. The reaction of 2-amino-4-methyl-3-nitropyridine (**X**) [9, 10] with excess hydrazine hydrate on heating at 110–120°C was accompanied by evolution of ammonia, and the product was assigned the structure of 3-amino-4-methylpyridine (**XI**) on the basis of analytical and spectral data (Scheme 2). The product (yield 57%) was identical to an authentic sample [11] in the melting point. Likewise, the reduction of 2-amino-4-methyl-5-nitropyridine (**XII**) [9, 10] with hydrazine hydrate gave 59% of 3-amino-4-methylpyridine (**XI**).

2-Amino-5-methyl-3-nitropyridine (**XIII**) [12, 13] reacted with hydrazine hydrate with evolution of ammonia to produce 3-amino-5-methylpyridine (**XIV**) [14] (Scheme 3). The product showed a positive test for amino group and no depression of the melting point on mixing with an authentic sample. Compound **XIV** was also formed in the reaction of 2-amino-3-methyl-5-nitropyridine (**XV**) [14] with hydrazine hydrate under similar conditions. Treatment of 2-amino-6-methyl-3-nitropyridine (**XVI**) with hydrazine hydrate resulted in the formation of 5-amino-2-methylpyridine (**XVII**), while the reaction with 2-amino-6-methyl-5-nitropyridine (**XVIII**) gave 3-amino-2-methylpyridine (**XIX**) [15, 16].

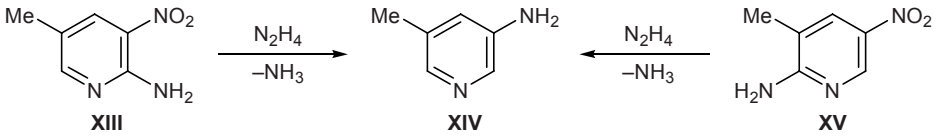
EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-467 instrument (80 MHz) using trifluoroacetic acid as solvent and on a Varian Gemini-200 spectrometer (200 MHz) in $CDCl_3$; the chemical shifts were determined relative to hexamethyldisiloxane as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using ethanol or chloroform as eluent; spots were visualized under UV light or by treatment with iodine vapor. Initial compounds **I** and **II** were synthesized according to the procedure described in [17].

Scheme 2.



Scheme 3.



Pyridin-3-amine (III). *a*. A mixture of 1.5 g (10.8 mmol) of 5-nitropyridin-2-amine (**I**) and 5 ml (~100 mmol) of hydrazine hydrate was heated for 7–10 h at 110–120°C. The reaction was accompanied by evolution of ammonia. When the reaction was complete, excess hydrazine hydrate was distilled off in a stream of argon. The tarry residue was extracted with diethyl ether, and the extract was evaporated to obtain a light lilac material which was purified by recrystallization from hexane. Yield 0.32 g (35%), mp 64°C. ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 4.18 s (2H, NH_2), 6.87 d (1H, 4-H, J = 6.0 Hz), 6.97 d (1H, 5-H, J = 6.0 Hz), 7.98 m (1H, 6-H), 8.03 m (1H, 2-H). Found, %: C 63.62; H 6.38; N 29.58. $C_5H_6N_2$. Calculated, %: C 63.81; H 6.43; N 29.76.

b. A mixture of 1.5 g (10.8 mmol) of 3-nitropyridin-2-amine (**II**) and 5 ml (~100 mmol) of hydrazine hydrate was heated for 7–10 h at 110–120°C. Ammonia evolved during the process. When the reaction was complete, the product was isolated as described above in *a*. Yield 0.25 g (25%), mp 64°C. ^{1}H NMR spectrum (CF_3COOH), δ, ppm: 4.15 s (2H, NH_2), 6.89 d (1H, 4-H, J = 6.0 Hz), 6.98 d (1H, 5-H, J = 6.0 Hz), 7.96 m (1H, 6-H), 8.01 m (1H, 2-H). Found, %: C 63.67; H 6.39; N 29.62. $C_5H_6N_2$. Calculated, %: C 63.81; H 6.43; N 29.76.

c. A solution of 1.65 g (10.7 mmol) of 5-nitropyridin-2-ylhydrazine (**VI**) in 5 ml (~100 mmol) of hydrazine hydrate was heated for 7–10 h at 110–120°C. The product was isolated as described above in *a*. Yield 0.35 g (35%), mp 64°C. It showed no depression of the melting point on mixing with an authentic sample of pyridin-3-amine.

d. 3-Nitropyridin-2-ylhydrazine (**VII**), 1.65 g (10.7 mmol), was dissolved in 5 ml (~100 mmol) of hydrazine hydrate, and the solution was heated and then treated as described above in *a*. Yield 0.25 g (25%), mp 64°C. The product showed no depression of the melting point on mixing with an authentic sample of pyridin-3-amine.

(6-^{2}H)-Pyridin-3-($^2H_2$)amine (VIII) was obtained from 1.5 g (10.8 mmol) of 5-nitropyridin-2-amine (**I**) and 5 ml (~100 mmol) of hydrazine-d_4 (N_2D_4) as described above for pyridin-3-amine (method *a*). When the reaction was complete, excess hydrazine-d_4 was distilled off in a stream of argon. The tarry residue was extracted with diethyl ether, and the solvent was distilled off from the extract. Yield 0.3 g (30%), mp 52°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.45 br.s (2D, ND_2), 6.95 d (1H, 4-H, J = 6.0 Hz), 7.03 d (1H, 5-H, J = 6.0 Hz), 8.00 m (1D, 6-D), 8.09 m (1H, 2-H). Found, %: C 61.62; H (D) 9.26; N 28.74. $C_5H_3D_3N_2$. Calculated, %: C 61.82; H (D) 9.34; N 28.84.

(2-^{2}H)-Pyridin-3-($^2H_2$)amine (IX) was obtained in a similar way from 1.5 g (10.8 mmol) of 3-nitropyridin-2-amine (**II**) and 5 ml (~100 mmol) of hydrazine-d_4. Yield 0.2 g (20%), mp 57°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.95 br.s (2D, ND_2), 6.89 m (1H, 4-H), 6.95 m (1H, 5-H), 7.96 m (1H, 6-H), 8.01 m (1D, 2-D). Found, %: C 61.72; H (D) 9.24; N 28.83. $C_5H_3D_3N_2$. Calculated, %: C 61.82; H (D) 9.34; N 28.84.

4-Methylpyridin-3-amine (XI). *a*. A mixture of 1.53 g (10 mmol) of 4-methyl-3-nitropyridin-2-amine (**X**) and 10 ml (~200 mmol) of hydrazine hydrate was heated for 3–5 h at 110–120°C. When the reaction was complete (ammonia no longer evolved), excess hydrazine hydrate was distilled off under reduced pressure in a stream of argon, the tarry residue was extracted with benzene or diethyl ether, and the extract was evaporated. Yield 0.53 g (49%), mp 105–106°C (from benzene–petroleum ether); published data [11]: mp 106–108°C. Found, %: C 66.42; H 7.40; N 25.81. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

b. A mixture of 1.53 g (10 mmol) of 4-methyl-5-nitropyridin-2-amine (**XII**) and 10 ml (~200 mmol) of hydrazine hydrate was heated for 3–5 h at 110–120°C. The mixture was then treated as described above in *a*. Yield 0.62 g (57%), mp 106–107°C (from benzene–hexane). Found, %: C 66.51; H 7.42; N 25.83. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

5-Methylpyridin-3-amine (XIV). *a*. Compound **XIV** was synthesized from 1.53 g (10 mmol) of 5-methyl-3-nitropyridin-2-amine (**XIII**) and 10 ml (~200 mmol) of hydrazine hydrate as described above for compound **XI** (method *a*). Yield 0.44 g (41%),

mp 56–57°C (from diethyl ether or petroleum ether); published data [18]: mp 57–59°C. Found, %: C 66.45; H 7.41; N 25.76. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

b. A mixture of 1.53 g (10 mmol) of 3-methyl-5-nitropyridin-2-amine (**XV**) and 10 ml (~200 mmol) of hydrazine hydrate was heated for 3–5 h. The mixture was then treated as described above for compound **XI** (method *a*). Yield 0.49 g (45%), mp 57–58°C (from diethyl ether or petroleum ether). Found, %: C 66.53; H 7.40; N 25.77. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

6-Methylpyridin-3-amine (XVII) was obtained from 1.53 g (10 mmol) of 6-methyl-3-nitropyridin-2-amine (**XVI**) and 10 ml (~200 mmol) of hydrazine hydrate as described above for compound **XI** (method *a*). Yield 0.4 g (37%), mp 94–95°C (from benzene–hexane); published data [16]: mp 96°C. Found, %: C 66.53; H 7.43; N 25.75. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

2-Methylpyridin-3-amine (XIX) was obtained from 1.53 g (10 mmol) of 6-methyl-5-nitropyridin-2-amine (**XVIII**) and 10 ml (~200 mmol) of hydrazine hydrate as described above for compound **XI** (method *a*). Yield 0.33 g (31%), mp 110–112°C (from benzene–petroleum ether); published data [15]: mp 112–114°C. Found, %: C 66.52; H 7.41; N 25.80. $C_6H_8N_2$. Calculated, %: C 66.64; H 7.46; N 25.90.

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