The Reaction of 3-Hydroxypyridine *N*-Oxide with Active Hydrogen Compounds and the Synthesis of 3-Substituted 2-Aminofuro[3,2-*b*]pyridines

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3-Hydroxypyridine *N*-oxide reacts readily in acetic anhydride with ethyl cyanoacetate, cyanoacetone and malononitrile. The three reaction products (2-substituted-3-acetoxypyridines) show different equilibria between tautomeric structures; in strong acids they undergo cyclization to 3-substituted 2-aminofuro[3,2-*b*]pyridines.

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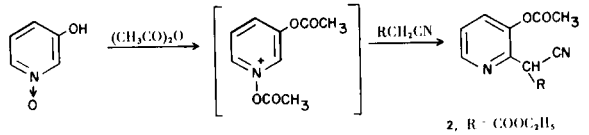
Hamana, *et al.*, (1) have demonstrated the reactivity of the 2-carbon atom of quinoline *N*-oxide toward nucleophilic substitution with active hydrogen compounds, in the presence of acylating agents, pointing out that the nature of the acylating agent and the acidity of the active hydrogen compound play an essential role for the initiation of the reaction. Similarly 1,5-naphtyridine *N*-oxide easily gave substituted products (2). On the contrary, pyridine *N*-oxide and 2-picoline *N*-oxide gave the substituted compounds in very low yield (1).

We have found that the reaction occurs readily when applied to 3-hydroxypyridine *N*-oxide in acetic anhydride, which suggests an activation not only by the positive charge on the pyridine nitrogen but also by the acetylated 3-hydroxy group of the intermediate (1) (Scheme 1).

Scheme 1



1

2, R = $COOC_2H_5$,
3, R = $COCH_3$
4, R = CN

The reaction of 3-hydroxypyridine *N*-oxide with ethyl cyanoacetate, cyanoacetone or malononitrile in acetic anhydride was carried out under nitrogen at room temperature and gave the corresponding products in good yields; only traces of unidentified compounds were obtained with diethyl malonate and ethyl acetoacetate. The contribution of the 3-acetoxy group to the activation of the nucleophilic substitution is also proved by the fact that 3-benzyloxypyridine *N*-oxide does not react with ethyl cyanoacetate under similar conditions.

Spectroscopic evidence show the presence of tautomeric forms for ethyl (3-acetoxy-2-pyridyl)cyanoacetate (**2**) and α-acetyl-(3-acetoxy-2-pyridyl)acetonitrile (**3**), as already indicated by the presence of two spots in the thin layer chromatogram of the recrystallized products, a yellow one, with higher Rf value, and the other one blue-fluorescent. Each tautomer rapidly transforms into a mixture of the two forms, according to the equilibria:

2 2a

3 3a

The nmr spectrum of compound **2** in DMSO-d_6 shows a broad signal at 14.3 ppm (0.75 H), typical of hydrogen-bonded protons, and a signal at 8.1 ppm (0.25 H) of the methine proton, which is markedly deshielded by the α cyano and ester groups. The nmr evidence clearly calls for the predominance of tautomeric form **2a**, stabilized by an intramolecular hydrogen bond. The nmr spectrum in deuteriochloroform shows a one-proton broad signal at 10.3 ppm, proving the presence of the **2a** form only; the downfield displacement of the H-6 pyridine proton from 8.0 ppm in DMSO-d_6 to 8.65 ppm in deuteriochloroform could be explained with a decrease of hydrogen bonding between the NH proton and the solvent and with an increase of the nitrogen polarity. This interpretation is in agreement with the data available for analogous compounds (3,4).

The infrared spectrum of **2** in the solid state shows NH weak absorption bands between 2890 and 2980 cm^{-1}, strong hydrogen-bonded carbonyl absorption at 1650 cm^{-1}, a conjugate nitrile band at 2200 cm^{-1}, and acetyl absorption at 1755 cm^{-1}. The infrared spectrum in chloroform solution is essentially unchanged.

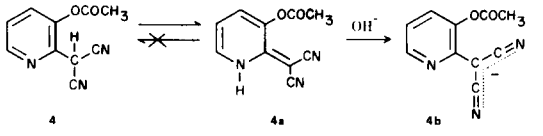
The nmr spectrum of **3** in DMSO-d_6 shows also a broad signal for 0.75 H, but it falls at 16.75-17.35 ppm as for hydrogen-bonded enolic protons; at 8.3 ppm there is a signal for 1.25 H, due to the methine hydrogen (0.25 H) of the cheto tautomer, overlapping on the signal of the pyridine α-proton. The spectrum in deuteriochloroform shows an upfield displacement of the H-6 proton at 7.98 ppm, in agreement with a decrease of the pyridine nitrogen polarity, whereas the broad OH signal is shifted to 17.9-18.3 ppm. In this case, tautomeric equilibrium is shifted

toward the enol form **3a**, in accordance with the conclusion drawn for α-acetyl-(2-pyridyl)acetonitrile (5) and similar products (6-9).

The infrared spectrum in potassium bromide shows a weak absorption band at 2600 cm^{-1} (strongly hydrogen-bonded enol) which in chloroform undergoes a shift, giving weak bands between 2880 and 2980 cm^{-1}; the other bands are for the conjugated nitrile at 2190 cm^{-1}, the enol moiety at 1630 cm^{-1}, and the acetyl carbonyl at 1765 cm^{-1}.

Ultraviolet and visible spectroscopy in methanol for compound **2** indicates a highly conjugated system, with absorption maxima at 293 and 375 nm. The spectrum taken just after dissolution in acidic methanol is virtually unchanged, whereas in the presence of alkali it shows new absorption maxima at 243, 384 and 396 nm, probably due to a contribution of a pyridone structure in equilibrium with the 3-pyridinol anion formed by deacylation. Under such conditions, the product slowly cyclizes to 2-amino-3-carbethoxyfuro[3,2-*b*]pyridine (**5**), as shown by the spectrum registered after one hour. Absorption maxima at 384 and 396 nm are weaker, and the band at 293 nm is shifted to 306 nm, the characteristic absorption of the bicyclic compound. The same behaviour is observed for compound **3**.

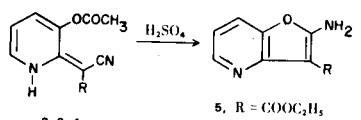
Spectral data of 3-acetoxypyridine-2-malononitrile (**4**) indicate the presence of structure **4a** only. The nmr spectrum shows a broad signal at 2.9-4.1 ppm (1H) and an upfield displacement of the H-6 proton of the pyridine ring as compared with the same signal for compounds **2** and **3**. The ir spectrum displays absorptions assignable to doubly split cyanide bands at 2200 and 2170 cm^{-1}, characteristic of conjugated dicyanomethylene groups (10,11), NH stretching at 3100 cm^{-1} and the carbonyl band of the acetyl group at 1760 cm^{-1}. The ultraviolet and visible spectra in methanol show absorption maxima at 292 and 366 nm, which indicate an extended conjugation, while in alkaline solution a hypsochromic shift of the band at 366 nm to 348 nm is observed. Clearly the free anion of the cyanocarbon acid (**4b**) does not show a great resonance interaction with the heterocycle ring and the whole molecule is probably less planar than **4a**.



4 4a 4b

In concentrated acid even at room temperature, **2**, **3** and **4** rapidly cyclize to ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**5**), 2-amino-3-acetylfuro[3,2-*b*]pyridine (**6**) and 2-amino-3-cyanofuro[3,2-*b*]pyridine (**7**), respectively (Scheme 2).

Scheme 2



2, 3, 4

5, R = $COOC_2H_5$
6, R = $COCH_3$
7, R = CN

Other substituted furo[3,2-*b*]pyridines have been prepared by more or less complicated procedure (12-15), while 2-aminoderivatives were not known. However, the isomeric 3-aminofuro[2,3-*b*]pyridines have already been described (16).

The nmr and ir spectra show that in compounds **5** and **6**, the amino group is hydrogen-bonded with the carbonyl in the adjacent position. Acetylation of **5** yields the acetylamino derivative (**8**) showing the ir absorption of the ester carbonyl at 1735 cm^{-1} in addition to the amidic one at 1675 cm^{-1}. The ester group of **5** is in fact stable to acid hydrolysis and to ammonolysis; when compound **5** is heated in 2*N* sodium hydroxide, 3-hydroxy-2-methylpyridine is obtained as the final product. The amide (**10**) was prepared from the cyano derivative **7** by reaction with concentrated ammonia and 36% hydrogen peroxide at room temperature. When **5** was refluxed with formamide, 4-hydroxypyrido[2′,3′:3,2]furo[5,4-*d*]pyrimidine (**9**) was obtained.

The mass spectrum of **5** shows a molecular peak M^+ at m/e 206, coinciding with the molecular weight, and a characteristic fragmentation pattern, where the most abundant peak is at m/e 160 (M-C_2H_5OH); the others are at m/e 132 (M-C_2H_5OH-CO) and m/e 105 (M-C_2H_5OH-CO-HCN). This fragmentation is similar to that of corresponding substituted benzofurane (17).

EXPERIMENTAL

Melting points are determined with a Büchi SMP-20 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer-177 instrument, nmr spectra were determined on a Varian EM-390 instrument, using TMS as internal standard, and the mass spectra were recorded on an Hewlett-Packard 5908-A massa spectrometer with an electron beam energy of 70eV. 3-Hydroxypyridine *N*-oxide was prepared as in reference (18).

General Synthesis of Compounds **2**, **3** and **4**.

3-Hydroxypyridine *N*-oxide (0.01 mole) was dissolved in 1.5 ml. of acetic anhydride by gently heating. After cooling, 0.011 mole of ethyl cyanoacetate or cyanoacetone were added to the solution and the mixture was allowed to stand at room temperature under nitrogen in the dark for 3 days. The crystalline precipitate was filtered; the mother liquor yielded more product after some days, which was added to the first. Reaction with malononitrile proceeds rapidly and already after 1 hour the mixture crystallized. The three compounds were recrystallized from ethyl acetate.

Ethyl α-(3-Acetoxy-2-pyridyl)cyanoacetate (**2**).

This compound was synthesized in 65% yield, m.p. 156-157°;

ir (potassium bromide): cm^{-1} ν 2980-2890, 2200, 1755, 1650, 1630; uv (methanol): λ max (ϵ), 224 (9,862), 293 (16,356), 375 (9,620); (methanol-hydrochloric acid *p*H $\simeq$ 3): λ max (ϵ) 227 (9,429), 289 (13,855), 370 (10,102); (methanol-sodium hydroxide *p*H $\simeq$ 12): λ max (ϵ) 224 (9,621), 243 (9,621), 293 (8,418), 384 (9,140), 396 (8,418); nmr (DMSO-d_6): ppm 14.50-14.10 (s, 0.75 H, NH), 8.00 (t, 1.25 H, H-6, CH), 7.55 (d, H-4), 6.80 (t, H-5), 4.10 (q, CH_2), 2.28 (s, $COCH_3$), 1.20 (t, CH_3); (deuteriochloroform): ppm 10.34-10.30 (s, NH), 8.65 (d, H-6), 7.78 (d, H-4), 7.19 (dd, H-5), 4.50 (q, CH_2), 2.35 (s, $COCH_3$), 1.45 (t, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.01; H, 5.01; N, 11.12.

α-Acetyl-(3-acetoxy-2-pyridyl)acetonitrile (**3**).

This compound was synthesized in 40% yield, m.p. 178-179°; ir (potassium bromide): cm^{-1} ν 2600, 2190, 1765, 1630; (chloroform): cm^{-1} ν 2980-2880, 2200, 1780, 1630; uv (methanol): λ max (ϵ) 226 (3,783), 294 (6,335), 374 (4,047); (methanol-sodium hydroxide *p*H $\simeq$ 12): λ max (ϵ), 225 (s) (3,871), 242 (4,311), 292 (3,343), 329 (2,551), 384 (2,727), 396 (s) (2,462); nmr (DMSO-d_6): ppm 17.75-17.35 (s, 0.75 H, OH), 8.30 (d, 1.25 H, H-6, CH), 7.85 (d, H-4), 7.22 (dd, H-5), 2.25 (s, CH_3), 2.20 (s, CH_3); (deuteriochloroform): ppm 18.30-17.90 (s, OH), 7.98 (d, H-6), 7.58 (d, H-4), 7.10 (dd, H-5), 2.45 (s, CH_3), 2.40 (s, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.33; H, 4.69; N, 12.76.

This compound was also obtained by the following procedure: to a solution of 1.24 g. (0.005 mole) of **2** in 10 ml. of 2*N* sodium hydroxide cooled in an ice bath, acetic anhydride (4-5 ml.) was added dropwise with stirring. The precipitate was filtered and crystallized from ethyl acetate.

3-Acetoxypyridine-2-malononitrile (**4**).

This compound was synthesized in 95% yield, m.p. 204-205°; ir (potassium bromide): cm^{-1} ν 3100, 2200, 2170, 1760, 1620, 1600; uv (methanol): λ max (ϵ), 227 (s) (5,979), 292 (13,540), 366 (4,748); (methanol-sodium hydroxide *p*H $\simeq$ 12) 226 (8,616), 291 (14,596), 348 (4,748); nmr (DMSO-d_6): ppm 7.80 (d, H-6), 7.60 (d, H-4), 6.88 (dd, H-5), 4.10-2.90 (s, NH), 2.25 (s, $COCH_3$).

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.56; H, 3.53; N, 20.95.

General Synthesis of Compounds **5**, **6** and **7**.

Compounds **2**, **3** or **4** (0.01 mole) were dissolved portionwise in 20 ml. of cooled concentrated sulphuric acid; after two hours the mixture was poured into ice and the *p*H was adjusted to *ca.* 6 with 2*N* ammonium hydroxide. The precipitate was filtered and washed with some water; the aqueous solution was extracted with chloroform. The residue combined with the precipitate was crystallized. The products show a blue fluorescence at the ultraviolet light.

Ethyl 2-Aminofuro[3,2-*b*]pyridine-3-carboxylate (**5**).

This compound was synthesized in 60% yield, m.p. 190-191°, crystallized from benzene; ir (potassium bromide): cm^{-1} ν 3360, 1650; uv (methanol): λ max (ϵ) 221 (4,038), 259 (11,046), 306 (11,521); nmr (DMSO-d_6): ppm 8.22-7.92 (m, 3H, NH_2, H-6), 7.52 (d, H-4), 6.90 (dd, H-5), 4.25 (q, CH_2), 1.32 (t, CH_3); ms: m/e 206 (M^+), 178, 161, 160, 134, 132, 105, 104.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.33; H, 4.69; N, 12.76.

2-Amino-3-acetylfuro[3,2-*b*]pyridine (**6**).

This compound was synthesized in 60% yield, m.p. 200-201°, crystallized from benzene; ir (potassium bromide): cm^{-1} ν 3330, 1640, 1620; uv (methanol): λ max (ϵ) 208 (23,226), 251 (8,946), 297 (12,387); nmr (DMSO-d_6): ppm 8.68 (s, NH_2), 8.32 (d, H-6), 7.70 (d, H-4), 7.05 (dd, H-5), 2.60 (s, CH_3).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.39; H, 4.60; N, 15.86.

2-Amino-3-cyanofuro[3,2-*b*]pyridine (**7**).

This compound was synthesized in 50% yield, m.p. 215-217°, crystallized from ethyl acetate; ir (potassium bromide): cm^{-1} ν 3420, 2210, 1650, 1620; uv (methanol): λ max (ϵ) 209 (6,773), 215 (s) (5,147), 258 (11,406), 310 (8,624); nmr (DMSO-d_6): ppm 8.32 (d, H-6), 8.02 (s, 1H, NH_2), 7.68 (d, H-4), 7.32 (s, 1H, NH_2), 7.02 (dd, H-5).

Anal. Calcd. for $C_8H_5N_3O \cdot H_2O$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.00; H, 4.23; N, 23.66.

Ethyl 2-Acetamidofuro[3,2-*b*]pyridine-3-carboxylate (**8**).

A suspension of 0.2 g. of **5** and 0.01 g. of sodium acetate in 5 ml. of acetic anhydride was heated at 60-70° until dissolution. After cooling the precipitate was filtered and the solution neutralized with ammonium hydroxide gave more product which was crystallized from benzene, m.p. 202-204°; ir (potassium bromide): cm^{-1} ν 3250, 1735, 1675, 1620; nmr (DMSO-d_6): ppm 14.30 (s, NH), 8.60 (m, H-6, H-4), 7.70 (dd, H-5), 4.45 (q, CH_2), 2.37 (s, $COCH_3$), 1.40 (t, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.00; H, 4.68; N, 11.15.

4-Hydroxypyrido[2',3':3,2]furo[5,4-*d*]pyrimidine (**9**).

A suspension of 1.02 g. (0.005 mole) of **5** in 5 ml. of formamide with 3-4 drops of acetic anhydride was refluxed for a period of 2 hours. The precipitate was filtered and extracted with ethyl alcohol; the extracts were concentrated under reduced pressure until compound **9** crystallized. Recrystallized from methanol, it did not melt under 350°; nmr (deuterioacetic acid): ppm 9.00-8.85 (m, H-2, H-7, H-9), 8.20 (dd, H-8).

Anal. Calcd. for $C_9H_5N_3O_2$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.60; H, 2.71; N, 22.30.

2-Aminofuro[3,2-*b*]pyridine-3-carboxamide (**10**).

A mixture of 18 ml. of 35% ammonium hydroxide with 1.3 ml. of 36% hydrogen peroxide was added to a solution of 1.59 g. (0.01 mole) of **7** in 20 ml. of ethyl alcohol and allowed to stand at room temperature for 3 days. The precipitate was filtered and crystallized from ethyl alcohol, m.p. 259-260°; ir (potassium bromide): cm^{-1} ν 3200, 1640; uv (methanol): λ max (ϵ) 209 (12,124), 217 (7,876), 256 (20,709), 306 (16,195); nmr (DMSO-d_6): ppm 8.29 (d, H-6), 7.98 (s, 2H, quickly exchangeable, NH_2), 7.70 (d, H-4), 7.60 (s, 1H, slowly exchangeable, $CONH_2$), 7.28 (s, 1H, slowly exchangeable, $CONH_2$), 7.02 (dd, H-5).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.23; H, 3.85; N, 23.81.

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