Rearrangement of 2-Aminofuro[3,2-*b*]pyridine-3-carboxylic Esters

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Ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate rearranges with sodium ethoxide in ethanol to 2-oxo-3-cyano-2,3-dihydro[3,2-*b*]furopyridine; the corresponding *p*-nitrophenyl ester undergoes the same rearrangement by dilute aqueous sodium hydroxide. In the first case it was possible to isolate the labile intermediate, which was shown to be the hemiacetal of the above mentioned cyanolactone.

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Meth-Cohn and Narine (1) pointed out the role of different substituents in position 3 in the rearrangement of 2-aminothiophenes to 3-cyanothiophenes; thus, an electron withdrawing group favours the nucleophilic cleavage of the ring by increasing the acidity of the amino group and then accepting the thiolate anion formed during the rearrangement. When the substituent is an ester group, 3-cyano-γ-thiolactones or their 2-hydroxy tautomers are formed, the latter species being favored when a phenyl, acetyl or ethoxycarbonyl group is present in position 5.

The reverse rearrangement of 4,5-disubstituted 3-cyano-γ-lactones to 2-amino-3-carbethoxy-4,5-dihydrofurans has been reported: it has been shown that the equilibrium between cyanolactone and aminodihydrofuran depends on the amount of base (2,3).

In a previous work (4) we have shown that 2-amino-3-carbethoxyfuro[3,2-*b*]pyridine (**1**) does not behave as a β-enaminoester (5), probably because of an hydrogen bond interaction between the amino group and the ester carbonyl group. Therefore, it seemed of interest to investigate the ability of the above molecule to rearrange.

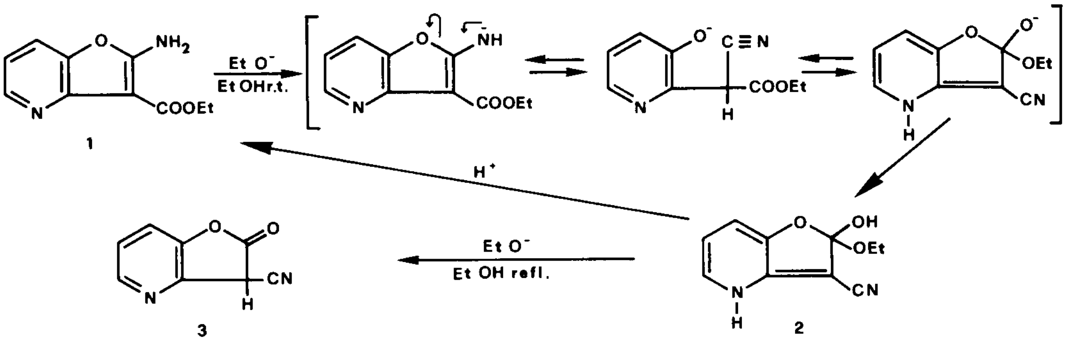
When **1** was refluxed in ethanolic sodium ethoxide (molar ratio 1:1), it rearranged to 2-oxo-3-cyano-2,3-dihydrofuro[3,2-*b*]pyridine (**3**). The reaction pathway reported in Scheme 1 is supported by the isolation of the labile intermediate **2**.

Compound **2** was obtained by reacting **1** with equimolar amounts of sodium ethoxide in ethanol at room temperature: a precipitate formed, which was shown to be 2-hydroxy-2-ethoxy-3-cyano-4*H*-furo[3,2-*b*]pyridine. It appears to be the first isolated and characterized lactone hemiacetal. The ir spectrum of **2** shows the cyanide band at 2170 cm^{-1} and a strong broad NH and OH absorption band at 3450 cm^{-1}. The nmr spectrum in DMSO-d$_6$ shows two broad signals, one of the NH proton at 13.2-12.8, the other of the OH proton at 3.5-3.7 ppm; a quadruplet for 2H at 4.05 and a triplet for 3H at 1.15 ppm belong to the ethyl group. The upfield displacement of the H$_5$ and H$_7$ protons at 6.70 ppm (dd, 2H) with respect to those of ester **1**, and the downfield displacement of the H$_6$ proton at 7.75 ppm (q, 1H) can be explained as due to the disappearance of aromaticity in the pyridine ring.

Structure **2** is confirmed by the mass spectrum, which shows the molecular peak M$^+$ at m/e 206 and a characteristic fragmentation pattern, where the most abundant peak is at m/e 160 (M - C_2H_5OH); other peaks are at m/e 132 (M - C_2H_5OH - CO) and at m/e 105 (M - C_2H_5OH - CO - HCN). Moreover a peak at m/e 205 (M-H) shows the presence of a hydroxyl group.

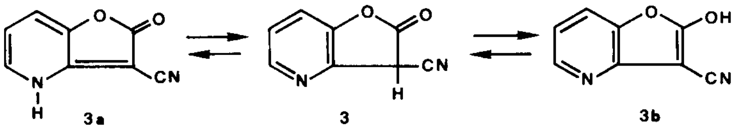
The intermediate anion shown in Scheme 1 is clearly a stronger base than the ethoxide anion, since by proton abstraction from ethanol it gives compound **2**, which is

SCHEME 1



0022-152X/81/061085-03$02.25

SCHEME 2



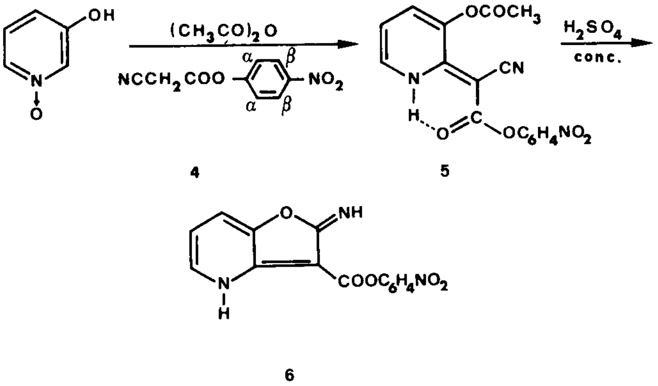
stable enough in the solid state: refluxing is required for the elimination of ethanol and conversion to lactone **3**. Compound **2** rearranged back to ester **1** when dissolved in 2*N* hydrochloric acid at room temperature.

Upon prolonged refluxing of 1 mole of **3** in ethanol containing 0.1 mole of sodium ethoxide, only a small amount of the aminoester **1** is formed; this shows the less electropositive nature of the carbonyl carbon in comparison with that of the dihydrolactones studied by Pacini and Ghirardelli (2).

Compound **3** in the solid state consists only of the lactone form as shown by the ir spectrum; however in DMSO-d_6 solution, the simultaneous presence of the carbonyl (**3**), amino (**3a**) and enol (**3b**) forms is indicated by the presence in the nmr spectrum of three broad signals at 6.75 (0.3 H), 7.35 (0.3 H) and 7.90 (0.3 H) ppm; they disappear with deuterium oxide.

In order to increase the amino group acidity and to make the rearrangement easier in type **1** compounds, the *p*-nitrophenyl ester **6** was employed. *p*-Nitrophenyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**6**) was obtained with the reaction pathway described in our preceeding paper (4).

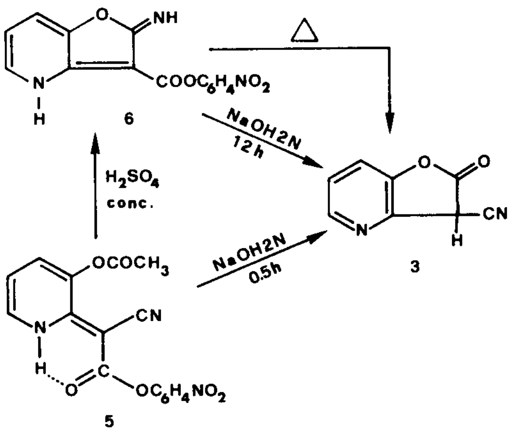
SCHEME 3



The synthesis of *p*-nitrophenyl cyanoacetate has been accomplished by heating cyanoacetic acid with *p*-nitrophenol in acetic anhydride, since the methods used for the synthesis of the *o*-nitrophenyl ester (6) gave very poor yields.

The ir and nmr spectra of *p*-nitrophenyl β-(3-acetoxy-2-pyridyl)cyanoacetate (see Experimental) show that it is exclusively in the tautomeric form **5**, stabilized by intramolecular hydrogen bonding. In concentrated acid, cyclization to *p*-nitrophenyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**6**) occurs; the spectral data indicate the presence of form **6** only. This compound is converted to 2-oxo-3-cyano-2,3-dihydrofuro[3,2-*b*]pyridine (**3**) by simple action of 2*N* sodium hydroxide at room temperature; this indicates that the amino group of this ester is able to donate a proton to a base weaker than the ethoxide anion. Lactone **3** was also obtained from compound **5** with 2*N* sodium hydroxide, as the anion formed during deacetylation is accepted by the carbonyl carbon atom as in the rearrangement of **6**. Under the same conditions the ethyl ester **1** gives a complex mixture, containing only trace of **3**.

SCHEME 4



EXPERIMENTAL

Melting points were determined with a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 297 instrument, nmr spectra were determined on a Varian EM-390 instrument, using TMS as the internal standard, and the mass spectra were recorded on an Hewlett-Packard 5908-A mass spectrometer with an electron beam energy of 70 eV.

2-Hydroxy-2-ethoxy-3-cyano-4*H*-furo[3,2-*b*]pyridine (**2**).

To a solution of sodium (55 mg, 0.0024 mole) in 5 ml of absolute ethanol, 2-amino-3-carbethoxyfuro[3,2-*b*]pyridine (**1**) (500 mg. 0.0024 mole) was added. The solid rapidly dissolved by stirring and after few minutes a precipitate was formed. The mixture was kept overnight at 0°, the precipitate was filtered and washed with absolute ethanol. It darkened at 190-195°, decomposing. It was impossible to crystallize **2** since it rearranged easily into **1**; ir (potassium bromide): 3700-3300, 2170 cm^{-1}; nmr (DMSO-d_6): δ 13.20-12.80 (s, 1H, NH), 7.75 (q, 1H, H-6), 6.70 (dd, 2H, H-5, H-7), 4.05 (q, 2H, CH_2), 3.50-3.70 (s, 1H, OH), 1.15 (t, 3H, CH_3); ms: m/e 206 (M^+, 94), 205 (31), 162 (51), 161 (46), 160 (100), 132 (19), 105 (29), 104 (34).

2-Oxo-3-cyano-2,3-dihydrofuro[3,2-*b*]pyridine (**3**).

a) Compound **1** (500 mg, 0.0024 mole) was added to a solution of sodium (55 mg, 0.0024 mole) in 5 ml of absolute ethanol; the suspension was refluxed for 3 hours. After cooling, the solution was evaporated under reduced pressure; the residue was dissolved in water and acidified to *p*H 5 with 2*N* hydrogen chloride. The precipitate was filtered, washed with water and crystallized from ethanol after decoloration with charcoal, mp 316-317° (yield, 65%).

b) Compound **5** (500 mg) was dissolved in 5 ml of 2*N* sodium hydroxide. After 30 minutes at room temperature, the solution was acidified to *p*H 5 with 2*N* hydrogen chloride. The precipitate was treated as in a) (yield, 66%).

c) A suspension of **6** (500 mg) in 5 ml of 2*N* sodium hydroxide was stirred at room temperature for 12 hours. The solution obtained was acidified with 2*N* hydrogen chloride. The precipitate was treated as in a) (yield, 53%; ir (potassium bromide): 2220, 1750 cm^{-1}; nmr (DMSO-d_6): δ 7.95-7.85 (s, 0.3 H, NH), 7.85 (d, 1H, H-5), 7.55 (d, 1H, H-7), 7.40-7.30 (s, 0.3 H, OH), 7.00 (t, 1H, H-6), 6.80-6.70 (s, 0.3 H, CH).

Anal. Calcd. for $C_8H_4N_2O_2$: C, 60.00; H, 2.52; N, 17.50 Found: C, 60.19; H, 2.51; N 17.34.

p-Nitrophenyl cyanoacetate (**4**)

A solution of 4-nitrophenol (8 g., 0.058 mole) and cyanoacetic acid (5 g., 0.058 mole) in 30 ml. of acetic anhydride was refluxed for 1 hour; the excess of acetic anhydride was distilled at reduced pressure. The residue was poured into ice and extracted with ether. The ethereal solution was dried (sodium sulfate) and evaporated under reduced pressure. From the resulting oil the *p*-nitrophenyl acetate was extracted with petroleum ether (40-70°) until the undissolved *p*-nitrophenyl cyanoacetate crystallized; it was recrystallized from chloroform, mp 100-101° (yield, 50%); ir (potassium bromide): 2250, 1750, 1520, 1340 cm^{-1}; nmr (dueteriochloroform): δ 8.35 (d, 2H, H-β), 7.40 (d, 2H, Hα), 3.85 (s, 2H, CH_2).

Anal. Calcd. for $C_9H_6N_2O_4$: C 52.43; H, 2.93; N, 13.59. Found: C, 52.24; H, 2.82; N, 13.21.

p-Nitrophenyl β-(3-Acetoxy-2-pyridyl)cyanoacetate (**5**).

A solution of 3-hydroxypyridine *N*-oxide (500 mg, 0.0045 mole) in 1.5 ml of acetic anhydride was obtained by gentle warming. After cooling, compound **4** (1 g, 0.0048 mole) was added and the mixture was allowed to stand under nitrogen in the dark for 2 days at room temperature. The crystalline precipitate was filtered and recrystallized from ethyl acetate/ethanol (1:1), mp 170-173° (yield, 45%); ir (potassium bromide): 2980-2890, 2200, 1760, 1510, 1310 cm^{-1}, nmr (DMSO-d_6): δ 11.80-11.20 (s, 1H, NH), 8.70 (m, 3H, H-β, H-6), 8.35 (d, 1H, H-4), 7.95 (d, 2H, H-α), 7.60 (t, 1H, H-5), 2.90 (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{14}N_3O_6$: C, 56.31; H, 3.25; N, 12.31. Found: C, 56.25; H, 3.39; N, 12.29.

p-Nitrophenyl 2-Aminofuro[3,2-*b*]pyridine-3-carboxylate (**6**).

Compound **5** (500 mg) was added portionwise to 3 ml of concentrated sulfuric acid; after 30 minutes the solution was poured into ice; the suspension of **6** sulfate was neutralized first with concentrated ammonium hydroxide and then with 2*N* ammonium hydroxide. The light yellow precipitate was filtered, washed with water and crystallized from ethyl acetate (yield 62%); mp 204-205° with conversion to compound **3**; ir (potassium bromide): 3420, 1700, 1520, 1310 cm^{-1}; nmr (DMSO-d_6): δ 8.65-8.40 (s, 1H, NH), 8.35 (m, 3H, H-β, H-5), 7.75 (d, 1H, H-7), 7.55 (d, 2H, H-α), 7.10 (q, 1H, H-6), 7.70-6.60 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_9N_3O_5$: C, 56.19; H, 3.03; N, 14.04. Found: C, 56.31; H, 3.19; N, 13.96.

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