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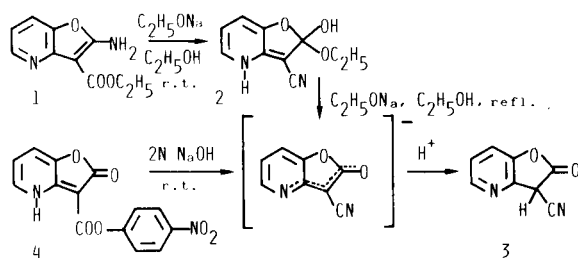
The rearrangement of 2-amino-3-carbethoxy-4-ethylfuro[3,2-*b*]pyridinium iodide in basic solution was studied. The reaction product is 2-oxo-3-cyano-4-ethyl-4*H*-furo[3,2-*b*]pyridine which was obtained also by alkylation with ethyl iodide and sodium hydride in dimethylformamide of 2-oxo-3-cyano-3*H*-furo[3,2-*b*]pyridine or of *p*-nitrophenyl-3-acetoxypyridine-2-cyanacetate.

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There is still lively interest in the chemistry of furopyridines [1]. In the search for new antimicrobial and anti-tumor products we initiated a program to prepare substituted γ -lactones of 3-hydroxypyridine-2-acetic acid, for instance 3-cyano- or 3-methylene-2-oxo-3*H*-furo[3,2-*b*]pyridines. In a previous paper [2] we described the rearrangement in ethanolic sodium ethoxide of ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**1**) to 2-oxo-3-cyano-3*H*-furo[3,2-*b*]pyridine (**3**) through the labile intermediate 2-hydroxy-2-ethoxy-3-cyano-4*H*-furo[3,2-*b*]pyridine; we found also that the corresponding *p*-nitrophenyl ester (**4**) rearranged readily in 2*N* sodium hydroxide at room temperature.

Evidently the rearrangement to α -cyanolactone took place easier with the increase in acidity of the group in the 2 position of furo[3,2-*b*]pyridine and of the intermediate **2** (Scheme 1).

Scheme 1

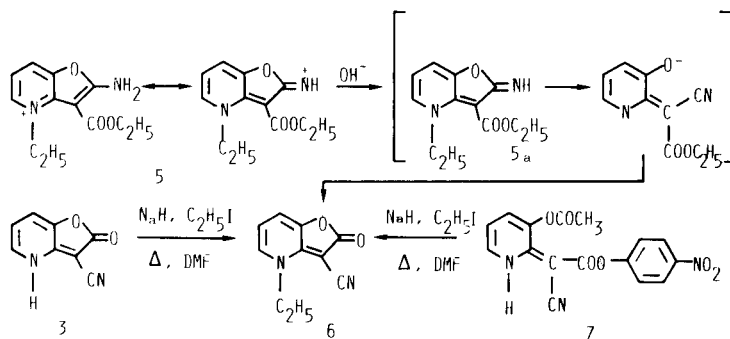


In the nmr spectrum of **3** in deuteriodimethylsulfoxide (DMSO) all three possible chemical shifts for the acidic hydrogen were present in equal proportions [2], corresponding to the suggested charge delocalization of the anion; the spectra of the esters, at least in DMSO, showed that the ethyl ester **1** exists in the amino form [3], whereas the *p*-nitrophenyl ester **4** is in the imino form [2].

Therefore we wanted to verify if the alkylation on the pyridine nitrogen could have a favourable effect to the ease of rearrangement. We studied such a reaction on 2-amino-3-carbethoxy-4-ethylfuro[3,2-*b*]pyridinium iodide (**5**), which was obtained by treatment of ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**1**) with ethyl iodide in dimethylformamide (DMF) at 120°. In basic solution the reactive species originating from **5** is **5a**, resembling the structure of **4**. We found that the rearrangement also proceeds in this case with diluted sodium hydroxide at room temperature. Product **6** is identical to that obtainable from cyanolactone **3** by treatment with sodium hydride and ethyl iodide in DMF, or directly by cyclization and concurrent ethylation of the *p*-nitrophenyl ester of 3-acetoxypyridine-2-cyanacetic acid (**7**) [2] (Scheme 2).

Products of similar bicyclic structure as **6**, but with a chlorine atom or an aryl group in place of a cyano group, were obtained for the first time in 1980 by Katritzky *et al.* [4], by addition of 1-substituted 3-oxidopyridinium compounds to dichloroketenes or arylbromoketenes across the C(4)-O and the C(2)-O positions. Consequently the reac-

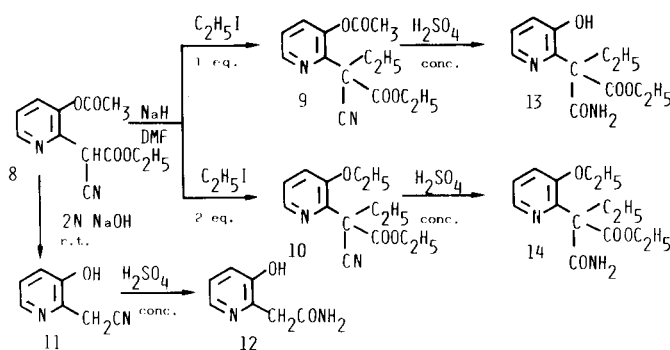
Scheme 2



tion products were a mixture of *N*-alkyl-2-oxofuro[3,2-*b*] and [3,4-*c*]pyridines, except for a few instances where only one pathway of addition was followed.

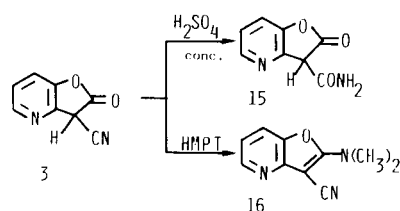
In contrast to the *p*-nitrophenyl ester **7**, the ethyl ester **8** upon treatment with one equivalent each of sodium hydride and ethyl iodide was ethylated at the methine hydrogen, giving **9**, whereas with two equivalents of the same reagents the acetyl group was also exchanged with the ethyl group and **10** was obtained. In diluted aqueous sodium hydroxide at room temperature no cyclization took place, but hydrolysis and decarboxylation occurred; the product obtained was the 3-hydroxypyridine-2-acetonitrile (**11**) [4a]. The corresponding acetic acid has already been described by our research group [5] (Scheme 3).

Scheme 3



Compound **11** treated with concentrated sulfuric acid gave the amide **12** and did not cyclize into 2-amino-3*H*-furo[3,2-*b*]pyridine, probably on account of the instability of 3-unsubstituted 2-aminofuranes [6]; analogously we obtained the amides **13** and **14** starting from **9** and **10** and the amide **15** from 3-cyano-2-oxo-3*H*-furo[3,2-*b*]pyridine. Treatment of this last compound with hexamethylphosphortriamide (HMPT) gave 2-dimethylamino-3-cyanofuro[3,2-*b*]pyridine (**16**) (Scheme 4), as in the case of 2-oxo-3*H*-benzo[*b*]furan, which yielded 2-dimethylaminobenzo[*b*]furan [7].

Scheme 4



The products **1**, **3**, **7**, **15** and **16** were tested against some Gram positive and Gram negative bacteria, but concentrations up to 50 µg/ml were inactive.

2-Oxo-3-cyano-3*H*-furo[3,2-*b*]pyridine (**3**) was tested by the National Cancer Institute of Bethesda, USA, also

against P-388 lymphocytic leukemia in mouse, but no activity was found.

EXPERIMENTAL

Melting points were determined with a Büchi SMP-20 capillary melting point 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 internal standard. Elemental analyses were performed by Microanalysis Laboratory, Department of Pharmaceutical Science, University of Padova, Italy.

2-Amino-3-carbethoxy-4-ethylfuro[3,2-*b*]pyridinium Iodide (**5**).

Ethyl 2-aminofuro[3,2-*b*]pyridine-3-carboxylate (**1**) [3] (0.01 mole) was dissolved in dimethylformamide (15 ml) by heating, ethyl iodide (0.04 mole) was added and the solution was heated at 120° with stirring for 5 hours. After cooling, ether was added and the precipitate was filtered and crystallized from ethanol/ethyl acetate, yield 96%, mp 187-88°; ir (potassium bromide): 3330, 1710 cm⁻¹; ¹H nmr (deuteriodimethylsulfoxide): δ 9.55-9.15 (bs, 2H, NH₂), 8.55 (d, 1H, H₅), 8.30 (d, 1H, H₇), 7.55 (dd, 1H, H₆), 5.05 (q, 2H, NCH₂), 4.40 (q, 2H, OCH₂), 1.4 (m, 6H, 2CH₃).

Anal. Calcd. for C₁₂H₁₅N₂O₃: C, 39.79; H, 4.17; N, 7.74. Found: C, 39.55; H, 4.32; N, 7.86.

2-Oxo-3-cyano-4-ethyl-4*H*-furo[3,2-*b*]pyridine (**6**).

a) 2-Amino-3-carbethoxy-4-ethylfuro[3,2-*b*]pyridinium iodide (**5**) (0.01 mole) was dissolved in 2*N* sodium hydroxide (30 ml). After 24 hours at room temperature, the product was filtered. A further amount of **6** was obtained from the filtrate by acidification with 2*N* hydrochloric acid and continuous extraction with ethyl acetate, yield 59%.

b) A solution of 2-oxo-3-cyano-3*H*-furo[3,2-*b*]pyridine (**3**) [2] or of *p*-nitrophenyl α-(3-acetoxypyridine-2)cyanoacetate (**7**) [2] (0.01 moles) in dry dimethylformamide (50 ml) was added dropwise to a suspension of sodium hydride (0.01 moles) in dry dimethylformamide (50 ml). The mixture was stirred at room temperature for 30 minutes, ethyl iodide (0.02 moles) was added and the solution was heated at 70° for 5.5 hours. After cooling, ether was added and the precipitate was filtered, washed with water and crystallized from ethanol, yield 85%, mp 217-218°; ir (potassium bromide): 2200, 1730 cm⁻¹; ¹H nmr (deuteriodimethylsulfoxide): δ 8.05 (d, 1H, H₅), 7.6 (d, 1H, H₇), 7.1 (dd, 1H, H₆), 4.5 (q, 2H, CH₂), 1.45 (t, 3H, CH₃).

Anal. Calcd. for C₁₀H₈N₂O₂: C, 63.82; H, 4.29; N, 14.89. Found: C, 64.03; H, 4.25; N, 15.21.

Ethyl α-Ethyl(3-acetoxypyridine-2)cyanoacetate (**9**) and ethyl α-ethyl(3-ethoxypyridine-2)cyanoacetate (**10**).

A solution of ethyl α-(3-acetoxypyridine-2)cyanoacetate (**8**) [3] (0.01 moles) in dry *N,N*-dimethylformamide (35 ml) was added to a suspension of sodium hydride (0.01 moles) in dry *N,N*-dimethylformamide (20 ml). The mixture was stirred at room temperature until gas evolution ceased; ethyl iodide (0.01 or 0.02 mole respectively for **9** or **10**) was added and the suspension was heated at 70° for 5 hours under stirring. After cooling, water was added and the solution was extracted with ether. The extract was washed with water, dried (sodium sulphate) and evaporated. The obtained oil was chromatographed on silica gel by eluting with ethyl acetate. The products were crystallized from ethyl ether/petroleum ether.

Compound **9**.

This compound was obtained in a yield of 72%, mp 46-47°; ir (potassium bromide): 2240, 1780, 1740 cm⁻¹; ¹H nmr (carbon tetrachloride): δ 8.45 (dd, 1H, H₆), 7.6 (dd, 1H, H₄), 7.3 (dd, 1H, H₅), 4.2 (q, 2H, OCH₂), 2.6-2.2 (m, 5H, CH₂, COCH₃), 1.35-1.00 (m, 6H, 2CH₃).

Anal. Calcd. for C₁₄H₁₆N₂O₄: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.63; H, 5.79; N, 10.30.

Compound **10**.

This compound was obtained in a yield of 95%, mp 63-64°; ir (potassium bromide): 2240, 1740 cm⁻¹; ¹H nmr (carbon tetrachloride): δ 8.1 (m, 1H,

H₂), 7.15 (m, 2H, H₄, H₅), 4.35-3.9 (m, 4H, 2OCH₂), 2.7-2.1 (m, 2H, CH₂), 1.55-1.05 (m, 9H, 3CH₃).

Anal. Calcd. for C₁₇H₁₈N₂O₃: C, 64.10; H, 6.92; N, 10.68. Found: C, 64.29; H, 6.91; N, 10.73.

3-Hydroxypyridine-2-acetonitrile (11).

Ethyl α -(3-acetoxypyridine)-2-cyanoacetate (**8**) [3] (0.01 mole) was dissolved in 2*N* sodium hydroxide (30 ml). After 30 minutes at room temperature, the solution was neutralized with 2*N* hydrochloric acid, the precipitate was filtered and crystallized from ethyl acetate. More product was obtained from the filtrate by evaporation under reduced pressure and extraction of the residue with hot ethyl acetate, yield 70%, mp 142-143°; ir (potassium bromide): 2750-2500, 2250 cm⁻¹; ¹H nmr (deuteriodimethylsulfoxide): δ 10.6-9.8 (s, 1H, OH), 8.05 (m, 1H, H₆), 7.25 (m, 2H, H₄, H₅), 4.00 (s, 2H, CH₂).

Anal. Calcd. for C₇H₆N₂O: C, 62.68; H, 4.51; N, 20.89. Found: C, 63.03; H, 4.52; N, 21.20.

Synthesis of Amides 12-15.

Compounds **11**, **9**, **10** or **3** (0.01 mole) were dissolved portionwise in cooled concentrated sulphuric acid (20 ml). After 30 minutes at room temperature, the mixture was poured into ice and neutralized with 2*N* ammonium hydroxide. The precipitate was filtered, washed with water and crystallized; where an oil was obtained, it was extracted with ethyl acetate, the organic layer was dried (sodium sulphate) and evaporated.

3-Hydroxypyridine-2-acetamide (12).

This compound was obtained in a yield of 60%. Crystallization from ethanol gave mp 180-182°; ir (potassium bromide): 3470, 3300, 2750-2250, 1670 cm⁻¹; ¹H nmr (deuteriodimethylsulfoxide): δ 10.5-9.8 (bs, 1H, OH), 8.1 (m, 1H, H₆), 7.75-7.45 (bs, 1H, NH), 7.35-7.00 (m, 3H, H₄, H₅, NH), 3.65 (s, 2H, CH₂).

Anal. Calcd. for C₇H₈N₂O₂: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.07; H, 5.24; N, 18.67.

α -Carbethoxy- α -ethyl(3-hydroxypyridines-2)-acetamide (13).

This compound was obtained in a yield of 88%. Crystallization from ethanol gave mp 138-140°; ir (potassium bromide): 3400, 3200, 1720, 1670 cm⁻¹; ¹H nmr (deuteriodimethylsulfoxide): δ 10.2-9.7 (bs, 1H, OH), 8.25-7.95 (m, 2H, H₆, NH), 7.5-7.3 (bs, 1H, NH), 7.15 (m, 2H, H₄, H₅), 4.1 (q, 2H, OCH₂), 2.6-2.1 (m, 2H, CH₂), 1.05 (t, 3H, CH₃), 0.8 (t, 3H, CH₃).

Anal. Calcd. for C₁₂H₁₆N₂O₄: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.36; H, 6.43; N, 11.28.

α -Carbetoxy- α -ethyl(3-ethoxypyridine-2)acetamide (14).

This compound was obtained in a yield of 75%. Crystallization from ethyl ether/petroleum ether gave mp 150-155°; ir (potassium bromide): 3380, 3250, 1720, 1660 cm⁻¹; δ ¹H nmr (deuteriodimethylsulfoxide): δ 8.3-7.9 (m, 2H, NH, H₆), 7.6-7.05 (m, 3H, NH, H₄, H₅), 4.35-3.85 (m, 4H, 2OCH₂), 2.6-2.05 (m, 2H, CH₂), 1.4-0.65 (m, 9H, 3CH₃).

Anal. Calcd. for C₁₄H₂₀N₂O₄: C, 59.98; H, 7.19; N, 9.99. Found: C, 60.15; H, 7.23; N, 10.14.

2-Oxo-3*H*-furo[3,2-*b*]pyridine-3-carboxamide (15).

This compound was obtained in a yield of 90%. Crystallization from ethanol gave mp 298-299° dec; ir (potassium bromide): 3420, 3290, 1730, 1680 cm⁻¹; ¹H nmr (deuteriodimethyl sulfoxide): δ 7.7 (d, 1H, H₅), 7.5 (d, 1H, H₇), 7.25-6.7 (m, 4H, H₃, H₆, NH₂).

Anal. Calcd. for C₈H₆N₂O₃: C, 53.93; H, 3.40; N, 15.73. Found: C, 53.63; H, 3.48; N, 15.38.

2-Dimethylamino-3-cyanofuro[3,2-*b*]pyridine (16).

A solution of cyanolactone **3** (0.01 mole) in 12.5 ml of hexamethylphosphoramide was heated at 160° for 30 minutes and for another 30 minutes at 230°. After purification by chromatography on silica gel, eluting with ethyl acetate, the product was crystallized from ethanol, yield 70%, mp 157-158°; ir (potassium bromide): 2200 cm⁻¹; ¹H nmr (deuteriodimethyl sulfoxide): δ 8.3 (dd, 1H, H₅), 7.7 (dd, 1H, H₇), 7.05 (m, 1H, H₆), 3.3 (s, 3H, CH₃), 3.25 (s, 3H, CH₃).

Anal. Calcd. for C₁₀H₈N₂O: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.32; H, 4.90; N, 22.57.

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