# Synthesis of Furo[2,3-*b*]pyridine

*J. W. McFarland, R. P. Wollerman (1), W. C. Sadler, and G. N. Coleman*

Department of Chemistry, DePauw University, Greencastle, Indiana 46135

Received May 21, 1971

Two routes were employed to synthesize unsubstituted furo[2,3-*b*]pyridine (IV). The first method started with ethyl 5-aminofuro[2,3-*b*]pyridine-2-carboxylate (I) and involved successive deamination, hydrolysis, and decarboxylation. The second method began with 5-nitrofuro[2,3-*b*]-pyridine-2-carboxylic acid (V) and consisted of successive decarboxylation, reduction, and deamination reactions.

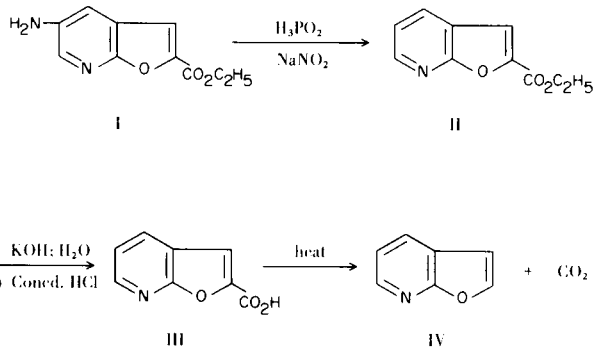
There are six possible chemical structures possessing a furan ring fused to a pyridine ring. Although all six systems have been known in the literature for several years, no completely unsubstituted furopyridine had been isolated until Sliwa's recent synthesis of furo[2,3-*b*]pyridine (IV) (2) and the synthesis of the furo[3,2-*c*]pyridine skeleton by Eloy and Deryckere (3). The furo[2,3-*b*]pyridine ring system was first reported in the literature in 1932 (4) but it was not until 1966 that Snyder and Ebetino (5) prepared substituted ring compounds in anything approaching practical syntheses. Other methods by which such substituted bicyclic systems have been obtained are difficult and give low yields (6,7). Other substituted isomeric furopyridines have been prepared by various workers (8-13). None of the methods were, however, successful in preparing the parent compounds.

Sliwa (2) started with 3-(bromoacetyl)-2-pyridone and through a series of reactions, including cyclization, reduction, acetylation, and pyrolysis, obtained the parent compound, furo[2,3-*b*]pyridine. Before the publication of Sliwa's work we were involved in the synthesis of the unsubstituted furopyridines and in the study of their physical and chemical properties. We report herein our synthesis of furo[2,3-*b*]pyridine (IV) by entirely different synthetic routes from that used by Sliwa.

In the first route the starting material was ethyl 5-aminofuro[2,3-*b*]pyridine-2-carboxylate (I), a disubstituted bicyclic compound first prepared by Snyder and Ebetino (5). The amino group was removed by dissolving I in 50% aqueous hypophosphorous/acid and adding sodium nitrite. The resultant ethyl furo[2,3-*b*]pyridine-2-carboxylate (II) was easily hydrolyzed to furo[2,3-*b*]pyridine-2-carboxylic acid (III) in aqueous base. The bicyclic acid was obtained in 87% yield and appeared to be stable toward strong base and strong acid conditions.

Furo[2,3-*b*]pyridine (IV) was obtained in 54% yield by pyrolyzing acid III. No other products were identified from the pyrolysis but tar formation was evident.

SCHEME I

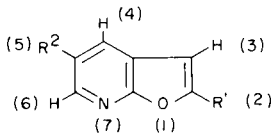



Alternative to the deamination, hydrolysis, and decarboxylation sequence shown in Scheme 1, another route was found also to be successful (Scheme 2). Following the method of Snyder and Ebetino (5), 5-nitrofuro[2,3-*b*]-pyridine-2-carboxylic acid (V) was synthesized. The nitro acid was decarboxylated to 5-nitrofuro[2,3-*b*]pyridine (VI) by heating in the presence of quinoline and copper powder.

The hydrogenation of VI gave two different products depending upon the solvent. With a mixture of ethanol and benzene as solvent not only was the nitro group reduced to the amino group but also the furan ring added a mole of hydrogen. The product in 74% yield was 5-amino-2,3-dihydrofuro[2,3-*b*]pyridine (VII). On the other hand, with only benzene as solvent and the same catalyst (5% Pd/C) the furan ring was not reduced and 5-aminofuro[2,3-*b*]pyridine (VIII) was obtained in 75% yield. The hydrogenation of the furan ring in ethanol is similar to the finding of Sliwa that IV itself consumes a mole of hydrogen in the presence of platinum oxide catalyst and ethanol (2). Treatment of VIII with sodium nitrite in an excess of 50% aqueous hypophosphorous acid led to deamination and the resultant furo[2,3-*b*]pyridine (IV) in 50% yield of pure product. The fact that IV was

TABLE I

Nmr Assignments (δ-values) for the Furopyridines (a)



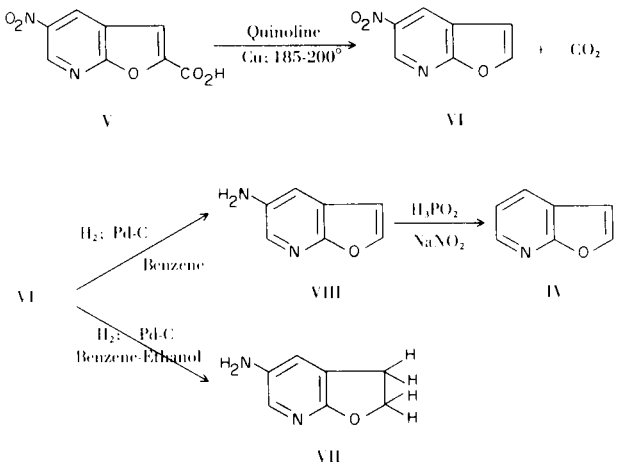
| Compound No. | R′ | $R^2$ | H-2 | H-3 | H-4 | H-5 | H-6 | Others |
|---|---|---|---|---|---|---|---|---|
| I | $CO_2C_2H_5$ | $NH_2$ | ---- | 7.49s | 7.31d | ---- | 7.91d | $NH_2$ - 4.80s<br>$C_2H_5$ - 4.32q; 1.38t |
| II | $CO_2C_2H_5$ | H | ---- | 7.47s | 8.03q | 7.25q | 8.48q | $C_2H_5$ - 4.42q; 1.42t |
| III | $CO_2H$ | H | ---- | 7.64s | 8.25q | 7.40q | 8.46q | |
| IV | H | H | 7.75d | 6.79d | 7.92q | 7.19q | 8.35q | |
| V | $CO_2H$ | $NO_2$ | ---- | 7.85s | 9.14d | ---- | 9.34d | |
| VI | H | $NO_2$ | 7.93d | 6.98d | 8.82d | ---- | 9.30d | |
| VIII | H | $NH_2$ | 7.72d | 6.67d | 7.29d | ---- | 7.84d | $NH_2$ - 3.64s |

s = singlet; d = doublet; t = triplet; q = quartet.

(a) Spectra for all compounds except III and V were obtained in deuteriochloroform. Spectra for III and V were obtained in deuterioacetone and DMSO-$d_6$ and in all cases rapid exchange with carboxyl hydrogen occurred.

isolated under such acidic conditions indicates that the furan ring is considerably more stable than in furan itself. Apparently the fused pyridine ring has a stablilzing effect on furan such as that caused by electron-withdrawing groups like nitro, carboxyl, carbalkoxy, and others. A more thorough study of the stability of IV is now being pursued.

SCHEME 2




The nmr absorption peaks for the furopyridines herein reported and the assignments for the various protons are given in Table I.

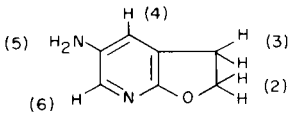
The peaks and their assignments in compound IV, furo[2,3-*b*]pyridine, are consistent with those of Sliwa (2). Assignments were primarily made on the basis of decouplings, coupling constants, and logic. As an example, the coupling constants for compound IV are: $J_{2-3}$ = 2.5 cps; $J_{4-5}$ = 7.8; $J_{5-6}$ = 4.75; $J_{4-6}$ = 1.8. This same sort of pattern holds for the substituted compounds and may be used to determine the position of substitution. Furo[2,3-*b*]pyridine-2-carboxylic acid (III) gave coupling constants $J_{4-5}$ = 8.0; $J_{5-6}$ = 4.6; $J_{4-6}$ = 1.8; and 5-nitrofuro[2,3-*b*]pyridine (VI) had values $J_{2-3}$ = 2.45 and $J_{4-6}$ = 2.0.

It is reasonable to expect H-2 to absorb further downfield than H-3 because of the adjacent electronegative oxygen atom. Likewise, in the pyridine ring, H-6 absorbs further downfield than either H-4 or H-5 due to the influence of the nitrogen atom. Note also that H-4 absorbs consistently further downfield than H-5 in those compounds in which both are present. The exact positions of absorption of H-4 and H-6 are dependent upon the substituent in position 5. When $R^2$ is an electron-withdrawing group, as expected the absorption is shifted downfield, and when $R^2$ is electron-donating the absorptions are upfield with respect to those in IV. It is interesting that the nmr spectrum of IV is remarkably similar to that of thieno[2,3-*b*]pyridine (14).

The nmr spectrum of 5-amino-2,3-dihydrofuro[2,3-*b*]-pyridine (VII) was quite reasonable in light of the above discussion. Doublets representing one hydrogen each

were at δ 7.05 and δ 7.40 which could be assigned to H-4 and H-6, respectively. Triplets, each representing two hydrogens, occurred at δ 4.45 and δ 3.14 which could be assigned to H-2 and H-3, respectively. In addition, the $NH_2$ group gave a broad peak at δ 4.28.

Infrared spectra were also used to further confirm the assigned structures for the furopyridines.




VII

## EXPERIMENTAL

Elemental analyses were performed by the Midwest Microanalytical Laboratory, Indianapolis, Indiana. Melting points were determined on a Mel-Temp metal block and are not corrected. The infrared spectra were determined on a Perkin-Elmer Infracord as potassium bromide disks and nmr spectra were recorded on a Hitachi R-20 spectrometer.

Ethyl Furo[2,3-*b*]pyridine-2-carboxylate (II).

To a 250-ml. 3-necked flask fitted with a dropping funnel, stirrer, thermometer, and air condenser, were added 4.3 g. (0.021 mole) of ethyl 5-aminofuro[2,3-*b*]pyridine-2-carboxylate (I) (5) and 43 g. of a cold 50% aqueous solution of hypophosphorous acid. A 13% aqueous solution of sodium nitrite was slowly added to the flask with vigorous stirring while keeping the temperature at 0°. The sodium nitrite solution was added until starch-potassium iodide paper indicated a slight excess of nitrous acid. The contents of the flask were allowed to stand 15 hours at 0° and a solid precipitate was collected by filtration.

To the filtrate was added 10 ml. of chloroform and the layers separated. The aqueous layer was washed with 2 x 10 ml. portions of chloroform. The combined organic extracts were washed to neutrality with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was combined with the original precipitate from the reaction mixture. Distillation gave 2.1 g. (52%) of ethyl furo[2,3-*b*]-pyridine-2-carboxylate (II), b.p. 138-140° (5.6 mm), m.p. 56.6-57.5°.

*Anal.* Calcd. for $C_{10}H_9NO_3$: C, 62.81; H, 4.75; N, 7.32. Found: C, 62.45; H, 4.70; N, 7.50.

Furo[2,3-*b*]pyridine-2-carboxylic Acid (III).

A suspension of 1.9 g. (0.01 mole) of II, 0.65 g. (0.012 mole) of solid potassium hydroxide, and 10 ml. of 95% ethanol was added to a 25-ml. flask fitted with a reflux condenser. After heating at reflux for three hours, the mixture was cooled to 0° and the potassium furo[2,3-*b*]pyridine-2-carboxylate collected by filtration. The salt was dissolved in the minimum amount of water and acidified with cold concentrated hydrochloric acid. Filtration of the cooled mixture yielded 1.4 g. (87%) of furo[2,3-*b*]pyridine-2-carboxylic acid (III), m.p. 280° dec.

*Anal.* Calcd. for $C_8H_5NO_3$: C, 58.89; H, 3.09; N, 8.58. Found: C, 58.10; H, 3.10; N, 8.35.

Furo[2,3-*b*]pyridine (IV).

One g. of acid III was pyrolyzed using a soft flame in a 5-ml. flask equipped with a still head and air condenser. To the suspension collected was added 5 ml. of chloroform. The insoluble material was removed by filtration and the chloroform removed from the filtrate by distillation at atmospheric pressure. Distillation of the residue under reduced pressure afforded 0.39 g. (54%) of IV, b.p. 70° (2.5 mm); literature (2) b.p. 95° (22 mm).

*Anal.* Calcd. for $C_7H_5NO$: C, 70.56; H, 4.23; N, 11.76. Found: C, 70.75; H, 4.63; N, 11.61.

5-Nitrofuro[2,3-*b*]pyridine (VI).

To a 500-ml. 3-necked flask equipped with a reflux condenser, mechanical stirrer, and thermometer, were added 23.0 g. (0.11 mole) of 5-nitrofuro[2,3-*b*]pyridine-2-carboxylic acid (V) (5), 100 ml. of freshly-distilled quinoline, and 1.56 g. of copper powder. While stirring the mixture was heated at 185-200° during three hours. The flask was cooled to 60° and the reflux consenser replaced by a still head and condenser for downward distillation. Under reduced pressure 45 ml. of quinoline was distilled off, after which the residue was filtered and the filtrate added to 500 ml. of chloroform. The resultant solution was concentrated to 100 ml. and petroleum ether (b.p. 30-60°) added until precipitation was complete (*ca.* 150 ml.). Crude VI was collected by filtration and recrystallized from benzene, using charcoal to remove the color. The yield of pure VI was 7.1 g. (39%), m.p. 159-160.5°.

*Anal.* Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.59; H, 2.75; N, 16.85.

Starting material (2.0 g.; 9%) was isolated by triturating the original solid residue with water, filtering, and acidifying the filtrate with concentrated hydrochloric acid.

5-Amino-2,3-dihydrofuro[2,3-*b*]pyridine (VII).

To a 500-ml. pressure bottle were added 1.5 g. (0.0092 mole) of VI, 125 ml. of absolute ethanol, 25 ml. of benzene, and 1.0 g. of 5% Pd/C catalyst. On a Parr Low Pressure Apparatus, hydrogenation was allowed to proceed at 25° until the hydrogen uptake remained unchanged (15 minutes; 2.7 psi total uptake). The catalyst was filtered and the filtrate concentrated under reduced pressure to give 0.9 g. (74%) of VII, m.p. 141-142°. Recrystallization from benzene-petroleum ether did not change the m.p.

*Anal.* Calcd. for $C_7H_8N_2O$: C, 61.76; H, 5.88. Found: C, 61.52; H, 5.70.

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

The procedure was identical to that above except that the solvent was 200 ml. of benzene. The total uptake of hydrogen was 1.6 psi and remained unchanged after 45 minutes. After concentrating the solution, the residue was triturated with cold benzene and then with cold 5% sodium hydroxide. The solid which remained was dried and amounted to 0.9 g. (75%) of VIII, m.p. 85.5-87°.

*Anal.* Calcd. for $C_7H_6N_2O$: C, 62.69; H, 4.48. Found: C, 62.55; H, 4.56.

Furo[2,3-*b*]pyridine (IV) from VIII.

5-Aminofuro[2,3-*b*]pyridine (VIII; 2.5 g.; 0.186 mole), 37.2 g. of cold aqueous 50% hypophosphorous acid and 10 ml. of water were added to a 250-ml. 3-necked flask equipped with a gas outlet, calibrated dropping funnel, thermometer, and mechanical stirrer. While cooling the flask contents at 0° 24.4 ml. (0.018 mole) of aqueous sodium nitrite solution (prepared by dissolving 2.0 g. of sodium nitrite in 30 ml. of water) was slowly added from the dropping funnel. The solution was stirred an additional hour at 0° and the crude IV extracted with 2 x 10 ml. portions of carbon tetrachloride. The aqueous layer was maintained at 0° and ex-

tracted at 15, 28, and 40 hours using each time 2 x 10 ml. portions of carbon tetrachloride. All of the carbon tetrachloride extracts were combined and concentrated under reduced pressure. The oily residue was distilled under reduced pressure, yielding 1.1 g. (50%) of pure IV. The ir and nmr spectra were identical with those of IV prepared above. The b.p. was also the same (70°, 2.5 mm).

## REFERENCES

(1) Abstracted in part from the M. S. Thesis of R. P. Wollerman, DePauw University, 1971.

(2) H. Sliwa, *Bull. Soc. Chim.* France, 646 (1970).

(3) F. Eloy and A. Deryckere, *J. Heterocyclic Chem.*, **8**, 57 (1971).

(4) K. Matejka, R. Robinson, and J. S. Watt, *J. Chem. Soc.*, 2019 (1932).

(5) H. R. Snyder, Jr. and F. F. Ebetino, *J. Heterocyclic Chem.*, **3**, 202 (1966).

(6) J. Reisch, *Arch. Pharm.*, **297**, (12) 754 (1964); *Chem. Abstr.*, **62**, 7742c (1965).

(7) E. Bullock, B. Gregory, and A. W. Johnson, *J. Chem. Soc.*, 1632 (1964).

(8) S. A. Mladenovic and C. E. Castro, *J. Heterocyclic Chem.*, **5**, 227 (1964).

(9) W. Herz and S. Tocker, *J. Am. Chem. Soc.*, **77**, 3554 (1955).

(10) T. Kametani, Y. Nomura, and K. Morita, *J. Pharm. Soc. Japan*, **76**, 652 (1956).

(11) T. Kametani, Y. Ito, and H. Isaka, *ibid.*, **74**, 1298 (1954).

(12) M. Descamps and F. Binon, *Bull. Soc. Chim, Belges*, **71**, 579 (1962).

(13) M. P. Mertes, R. F. Borne, and L. E. Hare, *J. Org. Chem.*, **33**, 133 (1968).

(14) L. H. Klemm, C. E. Klopfenstein, R. Zell, D. R. McCoy, and R. A. Klemm, *ibid.*, **34**, 347 (1969).