Furo[3,2-*b*]pyridines (1)

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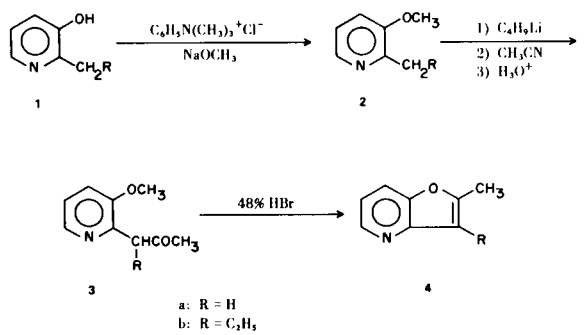
Although many of the isomeric furopyridines have been the subject of rather extensive study (2), there is only one recent report on the synthesis of the furo[3,2-*b*]pyridine system. Mladenovic and Castro (3) described the preparation of 2-substituted furo[3,2-*b*]pyridines by the reaction of cuprous acetylides with 2-iodo-3-pyridinol. The only previous mention of this ring system in the literature involves the fully hydrogenated form. Koepfli, Brockman and Moffat (4) suggested that the structure of the alkaloid febrifugine contained a substituted octahydrofuro[3,2-*b*]-pyridine system, and Fried, Wintersteiner, Moore, Iselin and Klingsberg (5) demonstrated that the perhydro system constituted part of the structure of the alkaloid jervine.

During the course of our work on febrifugine analogs (6), a facile conversion of 1-(3-methoxy-2-pyridyl)-2-propanone (**3a**) to 2-methylfuro[3,2-*b*]pyridine (**4a**) was discovered. Attempts to demethylate **3a** by heating a solution in 48% hydrogen bromide under reflux gave **4a** in good yield, apparently by spontaneous cyclization and dehydration of the hydrolysis product. Similar treatment of 3-(3-methoxy-2-pyridyl)-2-pentanone (**3b**) afforded 3-ethyl-2-methylfuro[3,2-*b*]pyridine (**4b**).

The intermediate ketones were prepared by adding acetonitrile to the lithio derivative of the appropriate 2-alkyl-3-methoxypyridine (**2**) (7).



EXPERIMENTAL

2-Methylfuro[3,2-*b*]pyridine (4a).

A solution of 1-(3-methoxy-2-pyridyl)-2-propanone (**3a**) (4.75 g., 0.029 mole) in 50 ml. of 48% hydrogen bromide was heated under reflux for 18 hours. The reaction mixture was made basic with sodium hydroxide and extracted with chloroform. The extracts were washed with water and with saturated aqueous sodium chloride, dried (sodium sulfate), and concentrated *in vacuo*. Distillation of the residue gave 2.2 g. (56%) of 2-methylfuro[3,2-*b*]-pyridine (9), b.p. 65-67° (0.7 torr); n_D^{20} 1.5505; nmr (deuteriochloroform): δ 2.43 (doublet, 3, J = 1 Hz, CH_3), 6.58 (quartet, 1, J = 1 Hz, 3-*H*), 7.05 (pair of doublets, 1, J = 8.5 and 4.5 Hz, 6-*H*), 7.61 (pair of doublets, 1, J = 8.5 and 1.5 Hz, 7-*H*) and 8.46 (pair of doublets 1, J = 4.5 and 1.5 Hz, 5-*H*); uv max (95% C_2H_5OH) 236 (ϵ 10,600), 266 (ϵ 9,600) and 302 (ϵ 8,900).

Anal. Calcd. for C_8H_7NO: C, 72.2; H, 5.30; N, 10.5. Found: C, 71.9; H, 5.27; N, 10.2.

A sample of **4a** was dissolved in ether and anhydrous hydrogen chloride was added to precipitate the hydrochloride, m.p. 214-215° after recrystallization from ethanol.

Anal. Calcd. for C_8H_8ClNO: C, 56.7; H, 4.75; N, 8.26. Found: C, 56.5; H, 4.68; N, 8.28.

3-Ethyl-2-methylfuro[3,2-*b*]pyridine (4b).

In a procedure identical to that described above, 3-(3-methoxy-2-pyridyl)-2-pentanone (**3b**) was converted in 36% yield to **4b** (9): b.p. 68-70° (0.7 torr); n_D^{20} 1.5682; nmr (deuteriochloroform): δ 1.31 (triplet, 3, J = 8 Hz, CH_2CH_3), 2.42 (singlet, 3, 2-CH_3), 2.77 (quartet, 2, J = Hz, CH_2CH_3), 7.08 (pair of doublets, 1, J = 8.5 and 4.5 Hz, 6-*H*), 7.58 (pair of doublets, 1, J = 8.5 and 1.5 Hz, 7-*H*), 8.47 (pair of doublets, 1, J = 4.5 and 1.5 Hz, 5-*H*).

Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.5; H, 6.88; N, 8.69. Found: C, 74.4; H, 7.16; N, 8.83.

3-(3-Methoxy-2-pyridyl)-2-pentanone (3b).

The procedure of Barringer and Berkelhammer (7) was used to convert 3-methoxy-2-propylpyridine to **3b**. The crude product, b.p. 70-80° (0.05 torr), was characterized by ir (neat), 1290 (OCH_3), 1450, 1470, 1610, 1625 (pyridine) and 1750 cm^{-1} (C=O) and was used without further purification for conversion to **4b**.

3-Methoxy-2-propylpyridine (2b).

The methylation procedure of Baker and McEvoy (10) was used for preparation of this compound. A solution of 2-propyl-3-pyridinol (11) (28.6 g., 0.165 mole), phenyltrimethylammonium chloride (40.0 g., 0.232 mole), and sodium methoxide (13.0 g., 0.241 mole) in 250 ml. of dimethylformamide (DMF) was heated under reflux for 16 hours. The DMF was removed on a flash evaporator, and the residue was distilled yielding 21.2 (85%) of 3-methoxy-2-propylpyridine, b.p. 88° (1.1 torr); nmr (deuteriochloroform): δ 0.98 (triplet, 3, J = 7 Hz, $CH_2CH_2CH_3$), 1.75 (multiplet, 2, $CH_2CH_2CH_3$), 2.85 (triplet 2, J = 7.5 Hz, $CH_2CH_2CH_3$), 3.78 (singlet, 3, OCH_3), 7.06 (doublet, 2, J = 3 Hz) and 8.12 (triplet, 1, J = 3 Hz); ir (neat): 1280 (OCH_3), 1450, 1470, 1610, and 1625 cm^{-1} (pyridine).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.5; H, 8.67; N, 9.26. Found: C, 71.2; H, 8.67; N, 9.34.

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REFERENCES

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(2) For a summary of prior work see J. W. McFarland, R. P. Wollerman, W. C. Sadler and G. N. Coleman, *J. Heterocyclic Chem*, **8**, 735 (1971).

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(8) Melting points and boiling points are uncorrected. The nmr spectra were obtained with a Varian A-60 Spectrometer and the uv spectrum with a Cary Model 14 Spectrophotometer.

(9) This compound slowly discolors even when stored under nitrogen at 2°.

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