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Oxidation of 3-hydroxy-6-methyl-2-hydroxymethylpyridine with manganese dioxide yielded the corresponding aldehyde, the condensation of which with diethyl bromomalonate furnished hydroxydihydrofuro[3,2-*b*]pyridinedicarboxylic acid ester. Saponification of the diester with concentrated hydrochloric acid afforded the hydrochloride of 5-methylfuro[3,2-*b*]pyridine carboxylic acid.

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The ready availability of 2-methyl-5-hydroxypyridine (1) prompted an attempt to use this compound as a convenient starting material for synthesis of the furo[3,2-*b*]pyridine system. There are relatively few reports dealing with the synthesis of this ring system, although many of the isomeric furopyridines have been extensively investigated (2).

During the course of work on 3-hydroxy-2-pyridine-carboxaldehydes, a facile synthesis of 5-methyl-3-hydroxy-2-pyridinecarboxaldehyde was developed. Hydroxymethylation of 1 was carried out essentially according to a known procedure (3) by treating 1 with an aqueous solution of formaldehyde in the presence of triethylamine, furnishing 6-methyl-2-hydroxymethyl-3-hydroxypyridine (2) (Scheme 1). The nmr assignments of the protons of

chloroform, reaction proceeded rather sluggishly (6). Condensation of the aldehyde 3 with diethyl bromomalonate in the presence of potassium carbonate afforded the substituted dihydrofuro[3,2-*b*]pyridine 4. The nmr spectrum was in agreement with the assigned structure, showing two doublets for H-4 and H-5, a coupling constant of $J_{4-5} = 8.0$ Hz and a singlet for the secondary proton in the dihydrofuran ring at $\delta = 5.70$.

Further confirmation was obtained by heating 4 with concentrated hydrochloric acid, whereby dehydration and decarboxylation of the disubstituted malonic acid derivative yielded the hydrochloride of the furopyridine carboxylic acid 5 which was recrystallized from 20% hydrochloric acid. The free acid was obtained by treating an aqueous solution of 5 with a Dowex-OH ion exchange resin. The acid 6 showed a pK of 4.6 and its structure was confirmed from the nmr spectrum which exhibited a singlet for the furan ring and a doublet for the H-4 and the H-5 protons of the pyridine ring with a coupling constant of $J_{4-5} = 8.0$ Hz.

EXPERIMENTAL

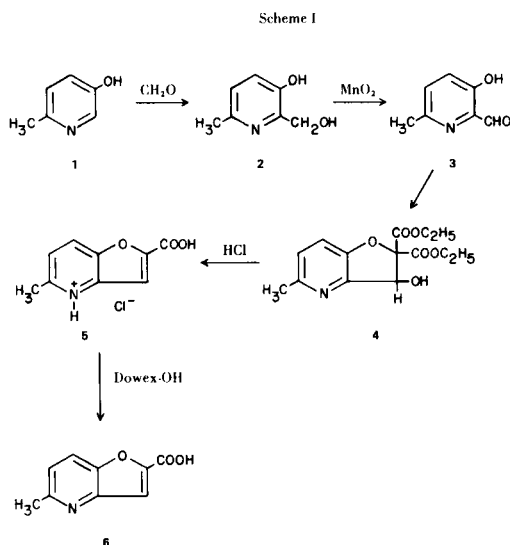
Melting points are uncorrected. Infrared spectra were recorded in potassium bromide discs on a Perkin Elmer-221 instrument and the nmr spectra were determined on a Varian HA-100D instrument, using TMS as the internal standard.

3-Hydroxy-6-methyl-2-hydroxymethylpyridine (2).

A suspension of 617 g. (5.66 moles) of 2-methyl-5-hydroxypyridine (1) in 448 ml. (170 g., 5.5 moles) of an aqueous solution containing 38% of formaldehyde, 572 g. (5.66 moles) of triethylamine and 1130 ml. of water was stirred and refluxed for a period of 6.5 hours. The solution was concentrated on a rotary evaporator to half its volume and the resulting suspension cooled to 0°. Filtration gave 631 g. of almost pure material. Crystallization of 200 g. of product from 600 ml. of ethanol yielded 145 g. of 2, m.p. 157-159° (lit. 156°); ir cm^{-1} : ν 3049, 2762, 1587, 1160, 1125, 1010; uv (methanol) : $\lambda_{\text{max}} (\epsilon)$ 223 (7,100), 288 (5,400); nmr (dimethylsulfoxide- d_6): δ 7.10 (d, H-4), 6.98 (d, H-5), 4.53 (s, CH_2OH), 2.36 (s, CH_3).

3-Hydroxy-6-methyl-2-pyridinecarboxaldehyde (3).

A suspension of 122.6 g. (0.88 mole) of 2 in 1300 ml. of 1,2-dimethoxyethane was refluxed until solution was obtained. The source of heating was then removed and 700 g. of manganese dioxide (Merck, Inc.) was added with stirring over a period of about 30 minutes at such a rate that reflux was maintained without further external heating. After the addition had been completed,



compound 2 were in agreement with this structure, showing two doublets for H-4 and H-5, respectively, with a coupling constant of $J_{4-5} = 8.0$ Hz, and a singlet for the proton of the aldehyde group, altogether in agreement with the nmr pattern of 2,3,6-trisubstituted pyridine-carboxaldehydes (4). Oxidation of the hydroxymethyl group to the aldehyde function (3) was best accomplished by gradual addition of commercial manganese dioxide (5) to a solution of 2 in dimethoxyethane. The reaction was exothermic and on large scale preparations took rather a violent course while in other solvents, such as benzene or

heating was continued for 45 minutes, the suspension was filtered by suction and the residue washed on the filter with three 100 ml. portions of hot dimethoxyethane. The filtrate was decolorized with 5 g. of decolorizing carbon and, after filtration, evaporated to dryness yielding 99.2 g. (81.7%) of pure material (100% by gc). Crystallization from 1300 ml. of cyclohexane gave 87.7 g. (69%) of crystals, m.p. 106-108°; ir cm^{-1} : ν 3003, 2880, 1653, 1587; uv (methanol): λ max (ϵ) 215 (9,100), 241 (3,300), 325 (3,600); nmr (benzene- d_6): 9.82 (s, CHO), 6.72 (d, H-4), 6.38 (d, H-5), 2.13 (s, CH_3).

Anal. Calcd. for $\text{C}_7\text{H}_7\text{NO}_2$: C, 61.27; H, 5.14; N, 10.20. Found: C, 61.30; H, 5.20; N, 10.14.

Diethyl 3-Hydroxy-5-methyl-2,3-dihydrofuro[3,2-*b*]pyridine-2,2-dicarboxylate (4).

To a solution of 41.1 g. (0.3 mole) of **3** and 86.4 g. (0.334 mole) of diethyl bromomalonate in 900 ml. of 1,2-dimethoxyethane was added 47.7 g. (0.34 mole) of anhydrous potassium carbonate, and the mixture stirred under reflux for a period of 3 hours. The hot suspension was filtered, and the residue on the filter washed with 500 ml. of boiling dimethoxyethane. The combined filtrates were evaporated to dryness, yielding 82.3 g. of product. A sample (10 g.) of the crude material was dissolved in 100 ml. of an ethanol-water mixture (1:1), decolorizing carbon added, and briefly heated to reflux. Filtration and cooling yielded 5.9 g. (59%) of crystals, m.p. 160-161°; ir cm^{-1} : ν 3050, 2980, 1775, 1736, 1616, 1590; uv (methanol): λ max (ϵ) 222 (5,500), 291 (6,500); nmr (DMSO- d_6): δ 7.36 (d, H-4), 6.72 (b, OH), 5.70 (s, H-3), 2.46 (s, CH_3 at position 5), 4.27 (q, CH_2) and 1.22 (t, CH_3) both signals for the ethyl ester group.

Anal. Calcd. for $\text{C}_{14}\text{H}_{17}\text{NO}_6$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.68; H, 5.93; N, 4.81.

5-Methylfuro[3,2-*b*]pyridine-2-carboxylic Acid Hydrochloride (5).

A suspension of 120 g. (0.4 mole) of crude **4** in 2400 ml. of concentrated hydrochloric acid was heated to reflux for a period of 2.5 hours. The hydrochloric acid was then removed on a rotary evaporator, and the solid residue dried over sodium hydroxide at 80°/20 mm. This was recrystallized from 185 ml. of 20% hydrochloric acid yielding, after filtration through a glass sintered funnel and drying at 90°/1 mm, 60 g. (69%) of slightly off white crystals,

m.p. 275-280° dec.; ir cm^{-1} : a series of bands with maximum at ν 2750, 1723 (COOH), 1633, 1625 (pyridine ring), 1570; uv (20% hydrochloric acid): λ max (ϵ) 230 (4,100), 258 (2,380), 267 (2,320), 315 (24,300); nmr (deuterium oxide): δ 7.95 (d, H-4); 8.72 (d, H-5); $J_{4,5} = 8.0$ Hz; 7.73 (s, H-2); 3.03 (s, CH_3).

Anal. Calcd. for $\text{C}_9\text{H}_8\text{ClNO}_3$: C, 50.60; H, 3.78; Cl, 16.60; N, 6.66. Found: C, 50.48; H, 3.72; Cl, 16.53; N, 6.52.

6-Methylfuro[3,2-*b*]pyridine-2-carboxylic Acid Monohydrate (6).

A solution of 5.2 g. (0.024 mole) of the hydrochloride (**5**) in 200 ml. of water was neutralized by adding Dowex-50-OH resin with stirring. The ion exchange resin was then filtered from the solution and washed with 500 ml. of water. The resin was suspended in a mixture of 200 ml. of acetic acid and 400 ml. of water, stirred for 30 minutes, filtered and the solution evaporated to dryness yielding 3.5 g. (73%) of crystalline product, m.p. 268° dec. An analytical sample was crystallized from water and dried at 100°/0.1 torr. Titration in water with 0.1 *N* tetramethylammonium hydroxide gave a *pK* of 4.6; ir cm^{-1} : ν 3380, 3050, 2760, 2550, 1710, 1640, 1620, 1570, 1383, 1290, 1170; uv (methanol): λ max (ϵ) 254 (7,450), 302 (15,900), 308 (14,300); nmr (deuterium oxide): δ 7.91 (d, H-4); 7.27 (d, H-5); 7.04 (s, H-4); 2.56 CH_3 .

Anal. Calcd. for $\text{C}_9\text{H}_9\text{NO}_4$: C, 55.38; H, 4.65; N, 7.18. Found: C, 55.41; H, 4.25; N, 7.20.

REFERENCES AND NOTES

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