A Convenient Synthesis of 4-Hydroxy-2-pyridone

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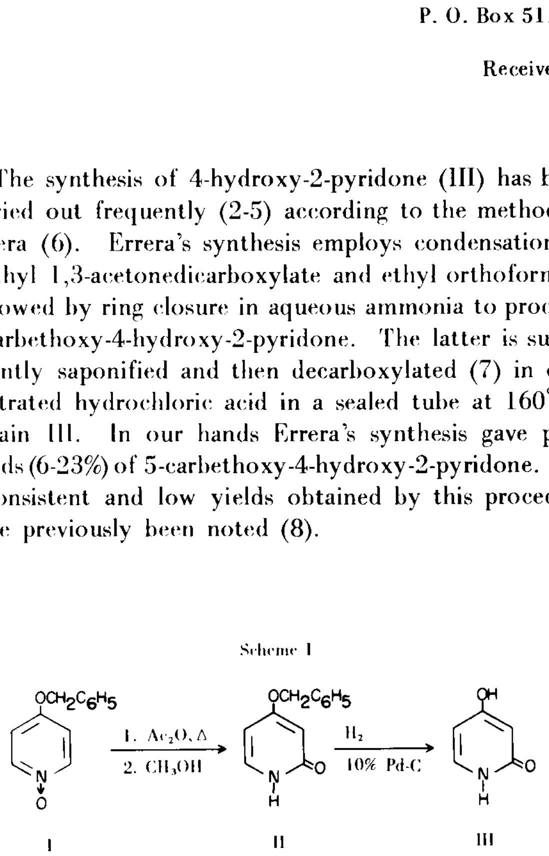
Received October 25, 1974

The synthesis of 4-hydroxy-2-pyridone (III) has been carried out frequently (2-5) according to the method of Errera (6). Errera's synthesis employs condensation of diethyl 1,3-acetonedicarboxylate and ethyl orthoformate followed by ring closure in aqueous ammonia to produce 5-carbethoxy-4-hydroxy-2-pyridone. The latter is subsequently saponified and then decarboxylated (7) in concentrated hydrochloric acid in a sealed tube at 160° to obtain III. In our hands Errera's synthesis gave poor yields (6-23%) of 5-carbethoxy-4-hydroxy-2-pyridone. The inconsistent and low yields obtained by this procedure have previously been noted (8).

Scheme I



We would like to present an alternate synthesis (Scheme I) of III that utilizes a preformed pyridine, 4-benzyloxypyridine 1-oxide (I), as a starting point. This route was suggested by the reported syntheses of both 4-ethoxy-2-pyridone and 4-methoxy-2-pyridone (9) by acetic anhydride rearrangement (10) of the corresponding 4-alkoxypyridine 1-oxides in 50% yield. The preparation of I may be carried out on a large scale (> 1.0 mole) and in high yield (90-95%) from the commercially available 4-nitropyridine 1-oxide by the method of Ochiai (11).

Rearrangement of I in refluxing acetic anhydride followed by methanolysis of the crude intermediate, 2-acetoxy-4-benzyloxypyridine, furnished pure 4-benzyloxy-2-pyridone, II, in 35% yield (12) after recrystallization. Subsequent debenzylation of II by hydrogenation gave III in near quantitative yield. The advantages of the present synthesis are its brevity and convenience for preparation of large amounts (> 0.1 mole) of 4-hydroxy-2-pyridone.

EXPERIMENTAL

4-Benzyloxy-2-pyridone (II).

A solution of 185 g. (0.92 mole) of 4-benzyloxypyridine 1-oxide in 1.1 l. of acetic anhydride was refluxed for 1.5 hours (solution darkens). The acetic anhydride was removed *in vacuo* and the dark residue dissolved in 1.0 l. of ethyl acetate. Insoluble solids were removed by filtration, 50 ml. of methanol added to the filtrate and the mixture heated to 60°. After cooling the crude solid was collected by filtration and washed once with ethyl acetate to furnish 98 g. (53%). Recrystallization and treatment with Norit in 3 l. of 3:1 ethyl acetate-ethanol gave 52 g. of pure 4-benzyloxy-2-pyridone as vanilla flakes. Removal of the mother liquors *in vacuo* and a repeat recrystallization of the residual solid from 1.2 l. of solvent gave an additional 18.5 g., total yield, 70.5 g. (38%), m.p. 198-200°; uv, max (methanol): 278 nm (log ϵ 3.65); nmr (DMSO-d_6): δ 5.10 (2H, s, benzylic H's), 5.83-6.05 (2H, multiplet, pyridone 3-H and 5-H), 7.25 (1H, d, $J_{5\text{-}6}$ = 7 Hz, pyridone 6-H), 7.42 (5H, s, phenyl H's), 11.17 (1H, broad s, N-H).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.69. Found: C, 71.79; H, 5.60; N, 6.97.

4-Hydroxy-2-pyridone (III).

A solution of 26.1 g. (0.13 mole) of 4-benzyloxy-2-pyridone in 1 l. of 1:1 tetrahydrofuran-methanol was hydrogenated at room temperature and 2 psi with 10% palladium on carbon catalyst in a 2 l. Parr bomb. After 45 minutes hydrogen uptake had ceased, the catalyst was removed by filtration, and the solvent was removed *in vacuo* to furnish 14.2 g. (99%) of 4-hydroxy-2-pyridone, m.p. 278° (DSC) as colorless plates; uv max (methanol): 278 nm (log ϵ 3.64); nmr (DMSO-d_6): δ 5.62 (1H, d, $J_{3\text{-}5}$ = 2 Hz, 3-H), 5.87 (1H, d of d, $J_{3\text{-}5}$ = 2 Hz and $J_{5\text{-}6}$ = 7 Hz, 5-H), 7.27 (1H, d, $J_{5\text{-}6}$ = 7 Hz, 6-H), 10.83 (2H, broad s, O-H and N-H).

Anal. Calcd. for $C_5H_5NO_2$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.00; H, 4.62; N, 12.48.

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(12) The yield of pure II is an average value obtained from four different preparations. Crude II is obtained in 45-55% yield and contains 4-hydroxypyridine 1-oxide as an impurity. The 1-oxide was identified by thin layer chromatography and pmr comparisons with authentic material.

(13) Gratitude is expressed for the work carried out in support of this research by A. J. Damascus, W. Selby, and E. Zelinski, heads of the Spectroscopy, Hydrogenation and Microanalytical Departments respectively of Searle Laboratories.

(14) Melting points are uncorrected and were determined using a Fisher-Johns melting point block or a Dupont 900 differential thermal analyzer. Uv and nmr spectra were recorded with a Beckman Dk-2 and a Varian A-60A spectrometer.