A Convenient Synthesis of 1-Methyl-4-oxopipecolic Acid Methyl Ester

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An efficient and convenient synthesis of the title compond **1** is described. The approach to the synthesis is based on hydride reduction of the 4-methoxypyridinium salt **5**, followed by acid hydrolysis of the resulting vinyl ether intermediate **6**.

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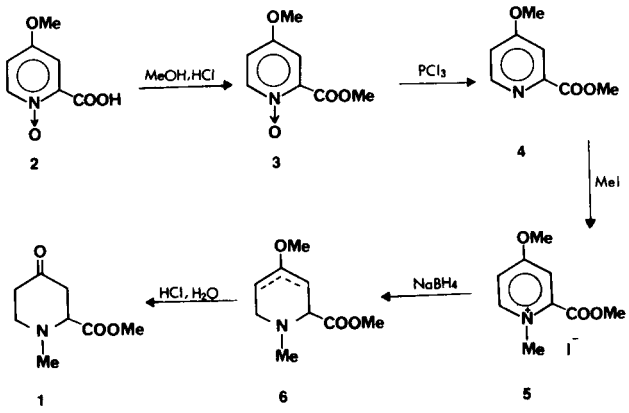
Pipecolic acid (2-piperidinecarboxylic acid) analogues can be used as a valuable tool to investigate its physiological role in the central nervous system (1). Although a number of ring-substituted pipecolic acid derivatives can be prepared by catalytic hydrogenation of the corresponding picolinic acid, this approach is only of limited application because reduction proceeds with difficulty (2,3). Alternatively, 4-substituted analogues can be prepared from a suitably protected 4-oxopipecolic acid (4). To that purpose, we report on a convenient synthesis of 4-oxopipecolic acid ester **1**.

Since efforts to synthesize **1** using the conventional Dieckmann cyclization procedures proved difficult, this compound was prepared from 4-methoxypicolinic acid *N*-oxide **2** which was readily obtained by a reported procedure from picolinic acid (5). As illustrated in Scheme 1, the approach to the synthesis is based on hydride reduction of the quaternary 4-methoxypyridinium salt to give Δ^3- and Δ^4-tetrahydropyridines (6) which, as vinyl ethers, can be hydrolyzed readily to the 4-piperidones. Thus, Fisher esterification of **2**, followed by *N*-deoxygenation using phosphorus trichloride (7) afforded the 4-methoxypicolinate ester **4**. This intermediate was reacted with excess iodomethane to give the 4-methoxypyridinium iodide **5**. Reduction of **5** using sodium borohydride in methanol gave **6** which, according to nmr analysis, was a mixture ($\sim$2:1) of Δ^3- and Δ^4-tetrahydropyridines. Hydrolysis of **6** in aqueous hydrochloric acid afforded **1**. The overall yield of **1** from **2** was about 25% and was obtained in about 95% purity (glc).

Scheme 1



The synthetic approach described here may prove applicable in the synthesis of other piperidones which otherwise are difficult to prepare.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elemer 237B or 281 spectrometer. Proton nmr spectra were obtained on Varian T-60 D or XL-100 spectrometer, using tetramethylsilane as an internal standard. Mass spectral analyses were performed on AEI MS-30 spectrometer. Elemental analysis were carried out by M-H-W Laboratories, Phoenix, Arizona. The glc analyses were conducted on a Varian 2100 Aerograph. Removal of solvents was carried out under reduced pressure on a rotary evaporator.

4-Methoxy-2-methoxycarbonylpyridine *N*-Oxide (**3**).

Dry hydrogen chloride gas was bubbled into a cooled (−10°) suspension of **2** (5) (14.3 g, 0.0846 mole) in methanol (500 ml) for 45 minutes. The mixture was refluxed in a steam bath for 3 hours and methanol was evaporated. The residue was dissolved in water (500 ml), basified with sodium carbonate and extracted with chloroform (3 × 150 ml). The extract was dried over anhydrous sodium sulfate and chloroform was evaporated. The solid residue was crystallized from chloroform-petroleum ether (30-60°) to give 9.91 g (64%) of **3**, mp 135-137°; ir (potassium bromide): 1750 cm^{-1} (carbonyl); nmr (deuteriochloroform): 3.86 (s, 3H, OCH_3), 6.83 (q, J = 3 and 7 Hz, H-5), 7.06 (d, J = 3 Hz, H-3), 8.1 (d, J = 7 Hz, H-6); ms: 183 (M^+ 1.7).

Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.64. Found: C, 52.55; H, 4.96; N, 7.65.

4-Methoxy-2-pyridinecarboxylic Acid Methyl Ester (**4**).

To a solution of **3** (6.7 g, 0.0366 mole) in chloroform (75 ml) was added dropwise with stirring phosphorus trichloride (7) (6 ml, 0.0687 mole) while the temperature was kept below 10°. The mixture was stirred at room temperature for 1 hour then was heated at 45° for 45 minutes. The solvent was evaporated, the solid residue was dried *in vacuo*, and crystallized from chloroform-petroleum ether (30-60°) to give 5.5 g (74%) of **4**·hydrochloride, mp 138-139°; ir (potassium bromide): 1735 cm^{-1} (carbonyl); ms: 167 (M^+ − HCl, 3.9). The base **4** was obtained from **4**·hydrochloride using sodium carbonate and was crystallized from ethyl acetate-ether, mp 47-50°; nmr (deuteriochloroform): 3.88 (s, 3H, OCH_3), 6.88 (q, J = 6 and 2.2 Hz, H-5), 7.56 (d, J = 2.2 Hz, H-3), 8.51 (d, J = 6 Hz, H-6).

Anal. Calcd. for $C_8H_9NO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 45.18; H, 5.21; N, 6.61. Found: C, 45.04; H, 5.10; N, 6.41.

4-Methoxy-2-methoxycarbonylpyridinium Iodide (**5**).

To a solution of **4** (7.4 g, 0.044 mole) in acetone (7 ml) was added iodomethane (25 ml, 0.401 mole) and the mixture was stirred at room temperature for 24 hours. The precipitated product was collected and crystallized from methanol-ether to give 11.9 g (87%) of **5**, mp 120-122°; ir (potassium bromide): 1735 cm^{-1} (carbonyl); nmr (deuterium oxide): 4.06 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 4.33 (s, 3H, NCH_3), 7.5 (q, J = 3 and 7 Hz, H-5), 7.91 (d, J = 3 Hz, H-3), 8.65 (d, J = 7 Hz, H-6).

Anal. Calcd. for $C_9H_{12}NO_3I$: C, 34.97; H, 3.91; N, 4.53. Found: C, 35.06; H, 3.92; N, 4.36.

1-Methyl-4-oxo-2-piperidinecarboxylic Acid Methyl Ester (**1**).

To an ice-cooled solution of **5** (12 g, 0.0388 mole) in methanol (100 ml) was added portionwise with stirring sodium borohydride (2.35 g, 0.0621 mole) over a period of 1 hour. Stirring was continued at room temperature for 1 hour followed by evaporation of methanol. The oily residue was mixed with water (100 ml) and extracted with ether (2 × 100 ml). The ether layer was dried over anhydrous sodium sulfate and evaporated to give 6.0 g (84%) of crude **6** as an oil; ir (neat): 1750 (carbonyl), 1675 cm^{-1} (C = C—OCH_3); nmr (deuteriochloroform): 4.48 (m, 1H, width at half height = 6 Hz, olefinic proton), 3.9-2.93 (m, 9H), 2.86-2.2 (m, 5H); ms: 185 (M^+, 0.4), 126 ($M^+ - 59$, 100). This product (6.69 g, 0.036 mole) was mixed with water (35 ml), concentrated hydrochloric acid (5 ml) was added with cooling, and the mixture was stirred at room temperature for 48 hours. The mixture was cooled (0°) basified with sodium carbonate, and extracted with ether (3 × 50 ml). The ether layer was dried over anhydrous sodium sulfate, ether was removed and the resulting residue was dried *in vacuo* to give 4.51 g (73%) of **1** as an oil; glc (~95% pure): R_t 5.2 minutes (glass column; 6 ft × 2 mm, packing; 3% OV-1 on 100/120 chromosorb W-HP, column temperature; 140°, detector temperature; 225°, flow rate; 15 ml/minute of nitrogen); ir (neat): 1750-1725 cm^{-1} (carbonyl); nmr (deuteriochloroform): 3.9-3.62 (m, 4H, OCH_3 and H-2), 3.5-2.2 (m, 9H); ms: 171 (M^+, 2.7), 112 ($M^+ - 59$, 100).

Anal. Calcd. for $C_8H_{13}NO_3$: N, 8.18. Found: N, 8.03.

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