

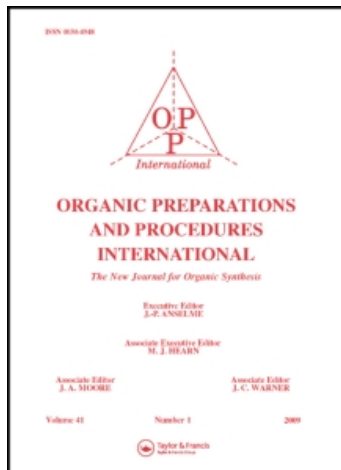
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### PREPARATION OF METHYL 2-METHOXYCARBONYLMETHYL-6-OXO-1,6-DIHYDROPYRIDINE-3-CARBOXYLATE

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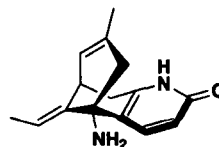
**PREPARATION OF METHYL 2-METHOXYCARBONYLMETHYL-  
6-OXO-1,6-DIHYDROPYRIDINE-3-CARBOXYLATE**

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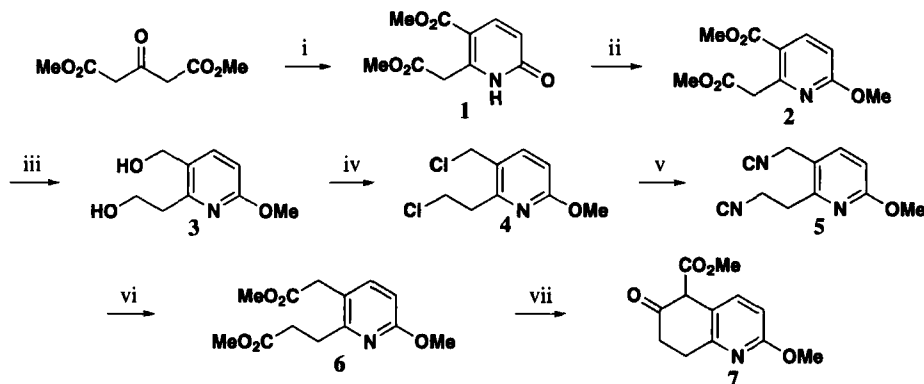
Huperzine A,<sup>1</sup> a *Lycopodium* alkaloid isolated from Chinese folk medicine, *Huperia serrata*(Thunb.) Trev., is a potent, reversible inhibitor of acetylcholinesterase. In China, it has been approved as a drug for the treatment of Alzheimer's disease. Several groups have achieved the total synthesis of huperzine A,<sup>2-7</sup> in which the protected tetrahydroquinolone  $\beta$ -keto ester **7** is a common key intermediate. A number of methods have been developed for the preparation of **7** from different starting materials. In the first total synthesis of huperzine A, compound **7** was prepared by Ji *et al.* from ethyl 2-methyl-6-hydroxynicotinate *via* a somewhat laborious sequence of reactions. Kozikowski's group<sup>2,8</sup> developed a one-pot, three-component condensation by simply admixing the mono-ethylene ketal of 1,4-cyclohexanedione, methyl propiolate in ammonia-saturated methanol in a Parr reactor,<sup>10</sup> followed by  $\alpha$ -carbomethoxylation to obtain **7**.<sup>3</sup> Recently, Langlois *et al.*<sup>6,9</sup> reported that **7** was obtained from 2-methoxy-6-methylpyridine in five steps with a 43% overall yield. However, the overall yields of **7** obtained by these methods were not satisfactory, requiring the use of organometallic and expensive reagents and under critical reaction conditions. This paper describes a new approach to **7** from dimethyl acetone-1,3-dicarboxylate in 7 steps (*Scheme*).



Huperzine A

Commercially available dimethyl acetone-1,3-dicarboxylate was treated with propioly amide in 5% Na<sub>2</sub>CO<sub>3</sub> solution, affording 2-pyridone in 61% yield. After O-methylation of pyridone **1** with CH<sub>3</sub>I/Ag<sub>2</sub>CO<sub>3</sub> in CHCl<sub>3</sub>, compound **2** was smoothly reduced with LiAlH<sub>4</sub> in THF furnishing diol **3** in 85% yield. Diol **3** was then transformed into **7** *via* the sequence of reactions reported by Qian *et al.*<sup>8</sup> Diol **3** was treated with SOCl<sub>2</sub> in CHCl<sub>3</sub> for 2.5 h, leading to dichloride **4**

in 92% yield. Reaction of **4** with sodium cyanide in DMSO gave cyanide **5** a 99% yield of **6** which was esterified by refluxing in HCl-saturated CH<sub>3</sub>OH for 3 h, to afford diester **6** in 85% yield. Finally, intramolecular Dieckmann condensation of **6** in a suspension of NaH in THF produced **7** regioselectively in 92% yield. The undesired regio-isomer was not detected. The overall yield of **7** is 33% in seven steps.



i) propioly l amide, rt, 61%; ii) Ag<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>I, CHCl<sub>3</sub>, 45°C, 90%; iii) LAH, THF, reflux, 85%; iv) SOCl<sub>2</sub>, CHCl<sub>3</sub>, reflux, 92%; v) NaCN, DMSO, 80°C, 99%; vi) dry HCl, CH<sub>3</sub>OH, 60°C, 85%; vii) NaH (60%), THF, rt, 92%

In comparison to other approaches to **7**, a new 2-pyridone intermediate **1** was obtained by a novel method for the construction of 2-pyridone ring. All the reactions proceeded under mild conditions with satisfactory and reproducible yields and no organometallic and other expensive reagents were required.

## EXPERIMENTAL SECTION

Mps were determined on a Büchi 510 apparatus and are uncorrected. Elemental analyses were performed on a Elementar vario EL instrument. IR spectra were taken on a Nicolet Magna 750 spectrophotometer. <sup>1</sup>H-NMR spectra were recorded in Bruker AMX-400 and GEMINI-300 spectrometers and the values of chemical shifts (δ) are given in ppm. Mass spectral data were obtained at MAT-711 and MAT-5 mass spectrometers. Column chromatography was performed using silica gel (200-300 mesh). All solvents were dried and redistilled before use.

**Methyl 2-(Methoxycarbonylmethyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (1).**- To a stirred solution of dimethyl acetone-1,3-dicarboxylate (9.40 g, 5.4 mmol) in H<sub>2</sub>O (10 mL), Na<sub>2</sub>CO<sub>3</sub> was added to adjust the pH of the solution between 8-9, then propioly l amide (3.11 g, 4.5 mmol) in H<sub>2</sub>O (3 mL) was added, and the reaction mixture was stirred at 0°C for 24 h. To the mixture acetic acid was added to adjust the pH to 6. The mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, then concentrated under reduced pressure. The solid residue was recrystallized from ethyl acetate to afford **1** as white crystals (6.18 g, 61%), mp. 145-146°C. IR (KBr): 3428, 1749, 1718, 1649, 1433, 1286, 1213, 1134, 1009, 844 cm<sup>-1</sup>; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 12.18

## METHYL 2-METHOXYCARBONYLMETHYL-6-OXO-1,6-DIHYDROPYRIDINE-3-CARBOXYLATE

(br.s, 1H, NH), 7.85 (d,  $J = 9.6\text{Hz}$ , 1H, ArH), 6.33 (d,  $J = 9.9\text{Hz}$ , 1H, ArH), 3.99 (s, 2H,  $\text{CH}_2$ ), 3.72 (s, 3H,  $\text{OCH}_3$ ), 3.63 (s, 3H,  $\text{OCH}_3$ ); EI-MS ( $m/z$ ): 225 ( $\text{M}^+$ , 20%), 193 (100%), 136, 94.

*Anal.* Calcd.  $\text{C}_{10}\text{H}_{11}\text{NO}_5$ : C, 53.33; H, 4.92; N, 6.22. Found: C, 53.35; H, 4.97; N, 6.22

**Methyl 6-Methoxy-2-(methoxycarbonylmethyl)nicotinate (2).**- A stirred mixture of **1** (4.01 g, 1.8 mmol),  $\text{CH}_3\text{I}$  (2.8 mL) and  $\text{Ag}_2\text{CO}_3$  (4.68 g), in  $\text{CHCl}_3$  (35 mL) was warmed at  $45^\circ\text{C}$  for 8 h, then cooled to room temperature. A little silica gel was added to the mixture and then was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether/EtOAc: 88/12) to afford compound **2** as a yellowish oil (3.8 g, 90%).<sup>8</sup> IR (film): 2995, 2953, 1743, 1720, 1595, 1483, 1425, 1263, 1136, 1074, 1032,  $960\text{ cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.19 (d,  $J = 8.7\text{ Hz}$ , 1H, ArH), 6.69 (d,  $J = 8.7\text{ Hz}$ , 1H, ArH), 4.20 (s, 2H,  $\text{CH}_2$ ), 3.96 (s, 3H,  $\text{OCH}_3$ ), 3.73 (s, 3H,  $\text{OCH}_3$ ); EIMS ( $m/z$ ): 239 ( $\text{M}^+$ , 76%), 207, 179 (100%), 164, 150, 136.

**2-(2-Hydroxyethyl)-3-(hydroxymethyl)-6-methoxypyridine (3).**- To a stirred suspension of  $\text{LiAlH}_4$  (1.66 g, 42.6 mmol) in THF (40 mL) cooled in an ice-water bath, was added dropwise a solution of **2** (3.49 g, 14.6 mmol) in THF (10 mL) and the reaction mixture was heated to reflux for 1h. To the cooled mixture,  $\text{H}_2\text{O}$  (3.2 mL), 15% sodium hydroxide (1.6 mL) and  $\text{H}_2\text{O}$  (8 mL) were added successively and carefully. The mixture was stirred at room temperature for 2.5 h, the solid material formed was removed by suction and washed with THF (2 x 30 mL). The filtrate was evaporated *in vacuo* and the residue was purified by flash chromatography (petroleum ether/EtOAc: 50/50) to give **3** as a pale oil (2.65 g, 85%).<sup>8</sup> IR (film): 3330, 2928, 1597, 1477, 1421, 1294, 1263, 1043,  $827\text{ cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.56 (d,  $J = 8.4\text{Hz}$ , 1H, ArH), 6.62 (d,  $J = 8.4\text{ Hz}$ , 1H, ArH), 4.60 (s, 2H,  $\text{CH}_2\text{OH}$ ), 4.04 (t,  $J = 5.4\text{Hz}$ , 2H,  $\text{CH}_2\text{OH}$ ), 3.91 (s, 3H,  $\text{OCH}_3$ ), 3.00 (t,  $J = 5.3\text{Hz}$ , 2H,  $\text{CH}_2$ ); 2.12 (br., 2H, OH); EI-MS( $m/z$ ): 183 ( $\text{M}^+$ , 55%), 168, 153, 150, 138 (100%), 136, 122, 104.

**2-(2-Chloroethyl)-3-(chloromethyl)-6-methoxypyridine (4).**- A mixture of thionyl chloride (10 mL), **3** (2.09 g, 11.4 mmol) in  $\text{CHCl}_3$  (100 mL) was stirred at room temperature for 1 h and heated to reflux for an additional 1.5 h, then cooled to room temperature. Crushed ice was added into the mixture, and its pH to 8-9 was adjusted with solid  $\text{NaHCO}_3$ . The aqueous layer was extracted with methylene chloride (3 x 50 mL) and the combined organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After concentration, the crude product was purified by column chromatography (petroleum ether/EtOAc: 80/20) to afford product **4** as a yellowish oil (2.30 g, 92%). IR(film): 2941, 1733, 1599, 1579, 1481, 1425, 1304, 1263, 1084, 1038, 829,  $685\text{ cm}^{-1}$ ;  $^1\text{H-NMR}$ ( $\text{CDCl}_3$ ):  $\delta$  7.52 (d,  $J = 8.4\text{Hz}$ , 1H), 6.61 (d,  $J = 8.4\text{Hz}$ , 1H), 4.61 (s, 2H), 4.02 (t,  $J = 7.0\text{Hz}$ , 2H), 3.93 (s, 3H), 3.27 (t,  $J = 7.1\text{Hz}$ , 2H); EIMS ( $m/z$ ): 220 ( $\text{M}^+$ , 12%), 186, 184 (100%), 148.

**3-[(3-(Cyanomethyl)-6-methoxypyridin-2-yl)]propionitrile (5).**- To a solution of sodium cyanide (1.34 g, 27 mmol) in DMSO (5 mL), **4** (2.01 g, 9.1 mmol) in DMSO (10 mL) was added dropwise at  $50\text{-}70^\circ\text{C}$ . The reaction mixture was stirred at  $80\text{-}90^\circ\text{C}$  for an additional 2 h, then was cooled to room temperature. Crushed ice (60 g) was slowly added at  $0^\circ\text{C}$ . The mixture was

extracted with diethyl ether (3 x 50 mL), the combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous  $\text{MgSO}_4$ , and concentrated in vacuum. The crude product was purified by column chromatography (petroleum ether/EtOAc: 70/30) to afford the compound **5** as a colorless oil (1.83 g, 99%).<sup>8</sup> IR (film): 2943, 2249, 1718, 1599, 1479, 1427, 1302, 1269, 1088, 1036, 829  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.55 (d,  $J$  = 8.4Hz, 1H), 6.69 (d,  $J$  = 8.4Hz, 1H), 3.96 (s, 3H), 3.65 (s, 2H), 3.08 (t,  $J$  = 6.9Hz, 2H), 2.94 (t,  $J$  = 6.8Hz, 2H); EIMS ( $m/z$ ): 201 ( $\text{M}^+$ , 100%), 184, 173, 161, 149, 131.

**Methyl 3-[(6-Methoxy-3-(methoxycarbonylmethyl)pyridin-2-yl)]-propionate (6).**- Cyanide **5** (1.70 g, 8.5 mmol) was added under stirring to MeOH saturated with HCl (20 mL). The mixture was heated to reflux for 8 h and cooled to room temperature. Solid  $\text{NaHCO}_3$  was added in portions to basify the mixture to pH 8-9. The mixture was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL), the combined extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated *in vacuo* and the residue was purified by short column chromatography (petroleum ether/EtOAc: 75/25) to yield compound **6** as a colorless oil (1.90 g, 85%).<sup>8,9</sup> IR (film): 2953, 1740, 1599, 1581, 1477, 1429, 1298, 1159, 1038, 816  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.39 (d,  $J$  = 8.2Hz, 1H), 6.56 (d,  $J$  = 8.4Hz, 1H), 3.88 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.61 (s, 2H), 3.05 (t,  $J$  = 6.9Hz, 2H), 2.85 (t,  $J$  = 6.9Hz, 2H); EIMS ( $m/z$ ): 267 ( $\text{M}^+$ , 21%), 236, 208 (100%), 148.

**Methyl 2-Methoxy 6-oxo-5,6,7,8-tetrahydro-5-quinolinecarboxylate (7).**- To a suspension of NaH (60%; 0.84 g, 21 mmol) and the mixture was stirred at room temperature overnight. After quenching with saturated aqueous  $\text{NH}_4\text{Cl}$ , the solvent was evaporated in vacuum, and the residue was extracted into diethyl ether (3 x 50 mL). The combined organic phase was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated. The solid residue was recrystallized from  $\text{CH}_3\text{OH}$  to give pyridone **7** as yellowish crystals (1.30 g, 92%), mp. 70-71°C, *lit.*<sup>8,11</sup> 70°C, 71-72°C. IR (KBr): 3423, 2960, 1739, 1635, 1606, 1570, 1479, 1448, 1425, 1315, 1240, 1200, 1122, 1036, 820  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  13.17 (s, 1H), 7.90 (d,  $J$  = 8.8Hz, 1H), 6.57 (d,  $J$  = 8.8Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.94 (t,  $J$  = 7.8, 2H), 2.63 (t,  $J$  = 7.9, 2H); EIMS ( $m/z$ ): 255 ( $\text{M}^+$ , 35%), 203 (100%), 174, 146, 118.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}_4$ : C, 61.66; H, 5.64; N, 5.91; Found: C, 61.27; H, 5.57; N, 5.95

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