Studies on the Hydrogenation of 6-(Hydroxymethyl)pyridine-2-carboxylates and its Application to the Synthesis of 6-(Hydroxymethyl)piperidine-2-carboxylic Acid Derivatives

Jordi Bolós*, Santiago Gubert, Lluís Anglada, Angel Pérez,

Aurelio Sacristán and José A. Ortiz

Medicinal Chemistry Department,
Centro de Investigación Grupo Ferrer,
Juan de Sada, 32, 08028-Barcelona, Spain
Received April 5, 1994

The synthesis of the novel amino acid 6-(hydroxymethyl)-2-piperidinecarboxylic acid (**1a**) and its ethyl ester **1b** is reported. In the hydrogenation of 6-(hydroxymethyl)pyridine-2-carboxylates, hydrogenolysis of the alcohol group appeared as an unusual side reaction. Optimization of the reaction conditions allowed us to minimize hydrogenolysis and afforded pure **1**.

As a part of our program on the preparation of new anti-hypertensive drugs, we were interested in the synthesis of the previously unknown amino acid *cis*-6-(hydroxymethyl)-piperidine-2-carboxylic acid (**1a**) and its ethyl ester **1b**. To achieve the required *cis* stereochemistry it was found advantageous to afford the synthesis by hydrogenation of a pyridine precursor.

The key intermediate, ethyl 6-hydroxymethylpyridine-2-carboxylate (**2**) was prepared by essentially the same method as described in a Japanese patent [1]. Thus, ethyl 6-methylpyridine-2-carboxylate *N*-oxide (**3**) [2] was rearranged in the presence of acetic anyhdride to give ethyl 6-(acetyloxymethyl)pyridine-2-carboxylate (**4**). Alternatively, this compound was either submitted to alcoholysis to afford hydroxyester **5** or to hydrolysis to afford acid **6**.

Scheme 1
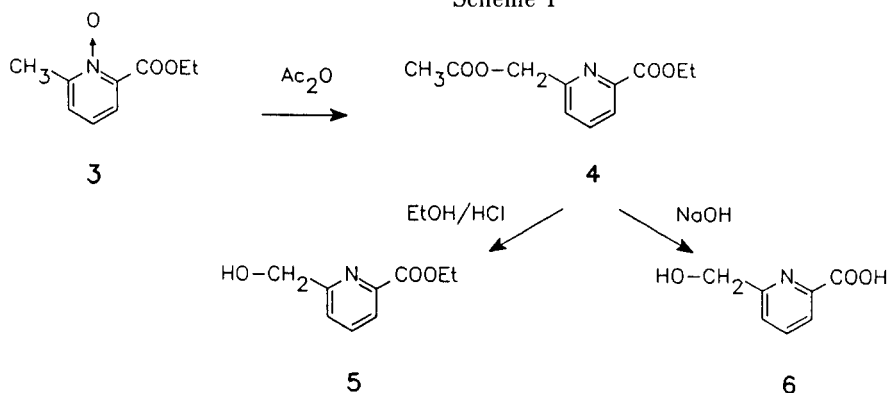
Scheme 2
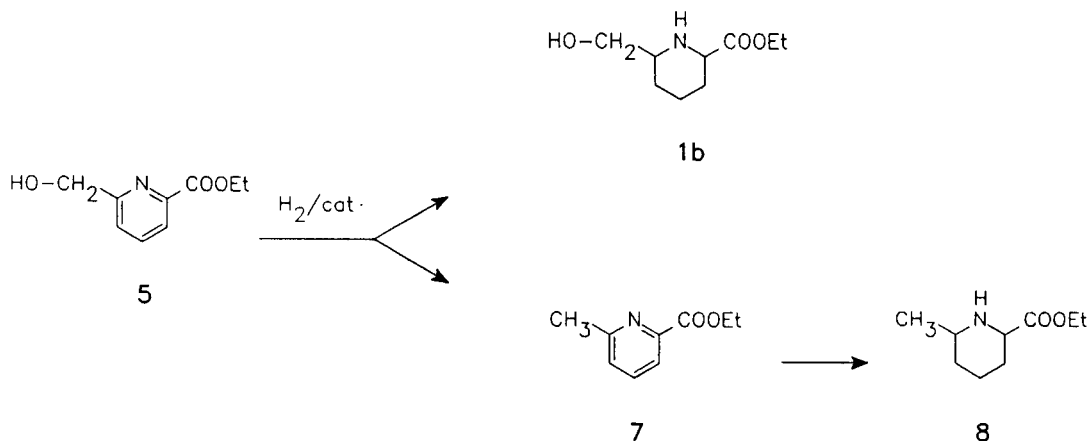
Unexpectedly, on hydrogenation of acetate **4**, the hydrogenolysis compounds 6-methylpyridine **7** and 6-methylpiperidine **8** were obtained as the major products. In order to reduce this undesirable side reaction, a study was conducted on the reaction conditions, which included the nature of the starting pyridine compound, hydrogenation catalyst and the *pH* of the reduction medium. Initial attempts, on the hydrochlorides of acetate **4** or alcohol **5** using several hydrogenation catalysts, gave either poor or negligible amounts of the desired compounds **1**. Platinum and rhodium catalysts gave the best results, although in all cases yields of **1** were lower than 30% (see Table 1). As a control experiment, after submitting **1b** to the same hydrogenation conditions it was recovered unchanged. This provided evidence that hydrogenolysis occurs prior to pyridine ring reduction, as a competitive reaction.

Table 1

Hydrogenation Products from Esters **4** and **5**

Substrate	Catalyst	Yield of Products (%)			
		1	**8**	**7**	**5**
4 [a]	Pd–C	0	2	98	0
4	PtO₂	15	77	2	0
4	Rh–Al₂O₃	18	38	30	0
4	Rh–C	14	63	0	0
4	Ru–C	0	0	5	95
5 [b]	PtO₂	28	72	0	0
5	Rh–Al₂O₃	7	4	56	33
5	Rh–C	24	20	0	0

[a] Used as the hydrochloride.   [b] One equivalent of hydrochloric acid added to the solvent.

A survey of the recent literature revealed a number of examples of hydrogenations of substituted 2-hydroxymethylpyridines without alcoholic hydrogenolysis [3]. Hydrogenation of 2-hydroxymethylpyridine itself has been reported [4] to afford 2-hydroxymethylpiperidine in high yield. Thus, the results obtained on our compounds suggested an interference due to the electron-attracting effect of the carboxylate ester group. Assuming this, a carboxylate ion would exert a lesser potenciating effect on hydrogenolysis. Therefore, it was decided to undertake hydrogenation of the corresponding acid **6** at several *pH* conditions. Results are shown in Table 2.

Table 2

Hydrogenation Products from Acid **6**

| Catalyst	Acid/base added	Yield of Products [a] (%)			
		1	**8**	**7**	**5**
PtO₂	–	68	13	5	3
PtO₂	HCl	48	54	0	0
PtO₂	NaOAc	0	0	0	100
Rh–Al₂O₃	–	14	9	12	0
Rh–C	–	8	7	10	0

[a] Determined after conversion to ethyl esters.

When reaction was effected on the hydrochloride of **6**, results were similar to the hydrogenation of the ester **5**, as expected for an unionized carboxylate group. On the other side, when reaction was effected in the presence of sodium acetate, no reduction took place since unprotonated pyridines are poorly activated for reduction. However, in the absence of any acid or base, the zwitterionic form should predominate, thus being activated for pyridine reduction but not for alcohol hydrogenolysis. As a confirmation of this, under neutral conditions, the desired alcohol **1** was obtained as the major compound. In a larger scale experiment, after esterification, one recrystallization afforded pure **1b**. In the nmr spectra, the values of the coupling constants for the protons of positions 2 (12.3 Hz) and 6 (12.8 Hz) and their chemical shifts were the expected ones for an axial disposition, which is consistent with the *cis* stereochemistry for compound **1**.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Infrared (ir) spectra were registered on a Perkin-Elmer 1710 spectrometer as potassium bromide pellets, and only noteworthy absorptions are listed. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm downfield (δ scale) from tetramethylsilane. Microanalyses were performed on a Perkin-Elmer 2400 elemental analyzer. Gas chromatography was performed on a Hewlett Packard 5890 Series II Gas Chromatograph fitted with an HP-17 capillary column. Hydrogenation catalysts were purchased from Aldrich Chemical Co. and were used without further purification. For column chromatography, silica gel (Merck, 70-230 mesh) was used. An authentic sample of ethyl *cis*-6-methylpiperidine-2-carboxyl-

Scheme 3
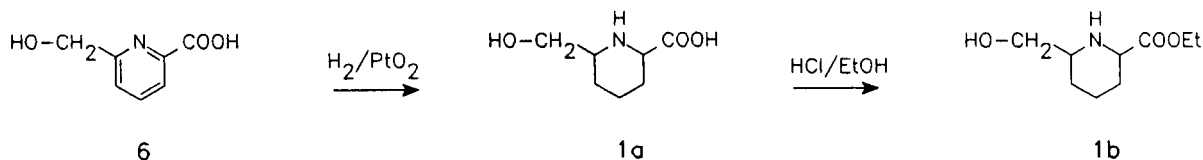
ate (**8**) was prepared by hydrogenation and esterification of 6-methylpyridine-2-carboxylic acid as described in the literature [5].

Ethyl 6-(Acetyloxymethyl)pyridine-2-carboxylate (**4**).

A solution of **3** (238 g, 1.31 moles) in 1 liter of acetic anhydride was kept at 60° for 2 hours. Then, the solvent was removed under vacuum, dissolved in dichloromethane, and washed with saturated solution of sodium bicarbonate. The organic extract was evaporated to afford 269 g (92%) of crude **4**. A sample was purified on column chromatography (chloroform as eluent) to afford pure **4** as an oil; ir: 1745, 1720, 1600, 1320, 1230 cm^{-1}; ^{1}H nmr (deuteriochloroform): 1.44 (t, J = 7.2 Hz, 3H, CH$_2$C**H**$_3$), 2.17 (s, 3H, COC**H**$_3$), 4.47 (q, J = 7.2 Hz, 2H, C**H**$_2$CH$_3$), 5.33 (s, 2H, Pyr–CH$_2$), 7.53 (dd, J = 7.5 and 2 Hz, 1H, 5–H), 7.83 (t, J = 7.5 Hz, 1H, 4–H), 8.06 (dd, J = 7.5 and 2 Hz, 1H, 3–H).

Anal. Calcd. for C$_{11}$H$_{13}$NO$_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 58.94; H, 6.02; N, 6.15.

Ethyl 6-Hydroxymethylpyridine-2-carboxylate (**2**).

A solution of **4** (3 g, 13 mmoles) in 30 ml of absolute ethanol and 3 ml of concentrated hydrochloric acid was stirred overnight at room temperature, and then the solvent was removed under vacuum. The resulting oil was dissolved in acetone to afford, on standing, **2** hydrochloride (2 g, 68%) as white crystals. An analytical sample was obtained by recrystallization from ethanol-diethyl ether, mp 131-133°; ir: 3100-3700, 2200-3000, 1745, 1630, 1210 cm^{-1}; ^{1}H nmr (deuteriomethanol): 1.47 (t, J = 7.1 Hz, 3H, CH$_3$), 4.58 (q, J = 7.1 Hz, 2H, C**H**$_2$CH$_3$), 5.03 (s, 2H, CH$_2$OH), 8.35 (dd, J = 7.5 and 2 Hz, 1H, 5–H), 8.46 (dd, J = 7.5 and 2 Hz, 1H, 3–H), 8.70 (t, J = 7.5 Hz, 1H, 4–H).

Anal. Calcd. for C$_9$H$_{11}$NO$_3$·HCl: C, 49.66; H, 5.56; N, 6.44; Cl, 16.29. Found: C, 49.43; H, 5.41; N, 6.33; Cl, 15.96.

6-Hydroxymethylpyridine-2-carboxylic Acid (**6**).

A solution of **4** (380 g, 1.7 moles) in 1.3 liter of ethanol and 1.3 liter of aqueous 1 *M* sodium hydroxide was stirred overnight at room temperature. Then, it was concentrated under vacuum to remove most of the ethanol, and the resulting aqueous solution was washed with diethyl ether. The aqueous solution was treated with 0.65 liter of 3 *M* sulfuric acid, and was evaporated under vacuum. The solid residue was washed with diethyl ether, and the product was extracted with methanol. Evaporation afforded 253 g (97%) of acid **6**. A sample was recrystallized from acetone, mp 135-137° (lit [6] 136-137°); ir: 2500-3400, 1740, 1625, 1220, 1085 cm^{-1}; ^{1}H nmr (deuteriomethanol): 5.08 (s, 2H, CH$_2$OH), 8.30 (dd, J = 7.5 and 2 Hz, 1H, 5–H), 8.45 (dd, J = 7.5 and 2 Hz, 1H, 3–H), 8.72 (t, J = 7.5 Hz, 1H, 4–H).

Anal. Calcd. for C$_7$H$_7$NO$_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.63; H, 4.77; N, 8.96.

General Procedure for Small Scale Hydrogenation of Pyridines.

A sample equivalent to 0.5 mmole of the corresponding pyridine was dissolved in 10 ml of absolute ethanol. In some experiments, 0.5 ml of a 1 *M* solution of ethanolic hydrogen chloride or 41 mg (0.5 mmole) of sodium acetate was added. Then, 20 mg of the appropriate catalyst (2 mg in the case of platinum oxide) was added, and the suspension was stirred under hydrogen for 16 hours at atmospheric pressure and room temperature. When hydrogenation was performed on acid **6**, 1 ml of 1 *M* solution of eth-

anolic hydrogen chloride was added, and the solution was refluxed overnight. The solutions were filtered, diluted with ethanol to a volume of 20 ml, and the resulting mixtures were analyzed by gas chromatography. The results are summarized in Tables 1 and 2.

6-Hydroxymethylpiperidine-2-carboxylic Acid (**1a**).

To a solution of **6** (72 g, 0.47 mole) in 1 liter of ethanol and 0.5 liter of water was added 0.6 g of platinum oxide and was stirred under hydrogen at a pressure of 40 psi for 48 hours. The catalyst was filtered off, and the solution was evaporated under vacuum. The residue was extracted with 3 portions of ethanol, and the alcoholic extracts were evaporated under vacuum. The residue was suspended in diethyl ether and stirred overnight. Then, the solid was filtered, washed with ether, and immediately transferred to a vacuum desiccator to afford 61.7 g (82%) of **1a** as a hygroscopic solid, mp 231-233° dec; ir: 3200-3700, 2500-3200, 1600, 1430, 1400, 1060 cm^{-1}; ^{1}H nmr (deuterium oxide): 1.29 (br q, J = 12.8 Hz, 1H, 4–Hax), 1.48 (2 overlapped q, 2H, 3–Hax and 5–Hax), 1.71 (br d, J = 15 Hz, 1H, 4–Heq), 1.83 (m, 1H, 5–Heq), 2.14 (m, 1H, 3–Heq), 3.10 (m, 1H, 6–H), 3.50 (dd, J = 11 and 8 Hz, 1H, CHOH), 3.67 (dd and m, 2H, CHOH and 2–H).

Anal. Calcd. for C$_7$H$_{13}$NO$_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.96; H, 8.25; N, 8.62.

Ethyl 6-Hydroxymethylpiperidine-2-carboxylate (**1b**).

A solution of **1a** (94 g, 0.59 mole) in 850 ml of absolute ethanol and 150 ml of a 4.8 *M* ethanolic solution of hydrogen chloride was refluxed overnight. After cooling, the solution was filtered and evaporated under vacuum. The residue was suspended in diethyl ether and stirred overnight. Then, it was filtered, washed with ether and vacuum dried, to afford crude **1b** hydrochloride (97 g, 73%), which contained 1% of **8** by gas chromatography. One recrystallization from ethanol afforded pure **1b**, mp 196-198°; ir: 3100-3700, 2400-2900, 1745, 1310, 1235 cm^{-1}; ^{1}H nmr (deuteriomethanol): 1.15 (t, J = 7.2 Hz, 3H, CH$_3$), 1.34 (br q, J = 12.8 Hz, 1H, 4–Hax), 1.52 and 1.56 (2 overlapped q, J = 12.8 Hz, 2H, 3–Hax and 5–Hax), 1.76 (br d, J = 15 Hz, 1H, 4–Heq), 1.86 (m, 1H, 5–Heq), 2.19 (m, 1H, 3–Heq), 3.18 (m, 1H, 6–H), 3.53 (dd, J = 12.5 and 7.4 Hz, 1H, C**H**–OH), 3.70 (dd, J = 12.5 and 4 Hz, 1H, C**H**–OH), 3.90 (dd, J = 12.3 and 3.3 Hz, 1H, 2–H), 4.16 (q, J = 7.2 Hz, 2H, COOCH$_2$); ^{13}C nmr (deuteriomethanol): 13.8 (CH$_3$), 21.8 (4–C), 24.3 (3–C), 26.1 (5–C), 58.0 and 59.0 (6–C and 2–C), 62.1 (C**H**$_2$CH$_3$), 64.0 (CH$_2$OH), 169.9 (COO).

Anal. Calcd. for C$_9$H$_{17}$NO$_3$·HCl: C, 48.32; H, 8.11; N, 6.26; Cl, 15.85. Found: C, 48.45; H, 7.82; N, 6.06; Cl, 15.53.

REFERENCES AND NOTES

[1] I. Matsumoto and K. Tomimoto, Japanese Patent **73** 05,591; *Chem. Abstr.*, **78**, 136084y (1973).

[2] P. Barczynski, B. Brzezinski and M. Szafran, *Rocz. Chem.*, **48**, 903 (1974).

[3a] D. I. C. Scopes, N. F. Hayes, D. E. Bays, D. Belton, J. Brain, D. S. Brown, D. B. Judd, A. B. McElroy, C. A. Meerholz, A. Naylor, A. G.

Hayes, M. J. Sheehan, P. J. Birch and M. B. Tyers, *J. Med. Chem.*, **35**, 490 (1992); [b] D. Mauleón, M. D. Pujol, C. Minguillón and J. Miquel, *J. Heterocyclic Chem.*, **26**, 693 (1989); [c] A. Delgado, S. Hospital, D. Mauleón and F. Pérez, *Synth. Commun.*, **18**, 2017 (1988); [d] D. Mauleón, M. D. Pujol and G. Rosell, *J. Med. Chem.*, **31**, 2122 (1988);

[e] D. A. Shamblee and J. S. Gillespie, *J. Med. Chem.,* **22**, 86 (1979).

[4] S. Kasuga and T. Taguchi, *Chem. Pharm. Bull.,* **13**, 233 (1965).

[5] A. R. Day and A. D. Lourie, U. S. Patent 3,388,128 (1965); *Chem. Abstr.,* **69**, 67419m (1968).

[6] T. H. Fife and T. J. Przystas, *J. Am. Chem. Soc.,* **104**, 2251 (1982).