Synthesis of β-(*sec*-Amino)alanines

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Preparation of β-(*sec*-amino)alanines (3) by acid hydrolysis of diethyl (*sec*-aminomethyl)formamidomalonates (2) was studied. Although high reaction temperature resulted in low yield, low reaction temperature (below 30 °C) gave good to excellent yields. The hydrolysis of diethyl formamido(piperidinomethyl)malonate (2a) was followed by ^{1}H-NMR, and a plausible mechanism involving the condensation of ethyl hydrogen aminomalonate (7) with 1-piperidinemethanol (5) is proposed.

Key words ethyl hydrogen aminomalonate; 1-piperidinemethanol; Mannich reaction; hydrolysis; mechanism; diethyl formamidomalonate

As a part of our work on the synthesis of Mannich bases[1] with pharmacological activities, we were interested in the title Mannich bases (**3**). To our knowledge, only β-piperidinoalanine dihydrochloride (**3a**) has so far been synthesized,[2] *via* the condensation of diethyl formamidomalonate (**1**) with piperidine and formaldehyde, followed by hydrolysis of the piperidinomethylated product (Mannich base **2a**) (Chart 1).

We tried the above method for the preparation of β-(*sec*-amino)alanines (**3a**—**d**), but obtained quite low yields. In the hydrolysis of the Mannich bases **2**, the yield of **3** seemed to depend on the reaction temperature. For instance, after the addition of concentrated hydrochloric acid (HCl) to the Mannich base **2a**, heating of the reaction mixture resulted in the formation of **3a** (37% yield), together with piperidine hydrochloride and glycine hy-

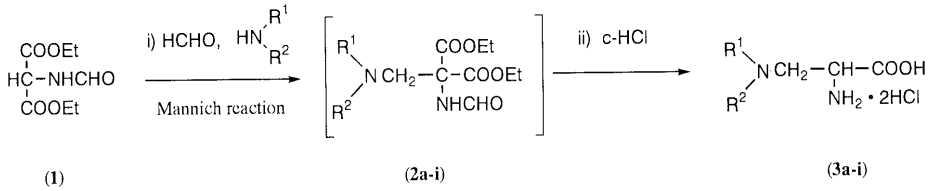

Chart 1

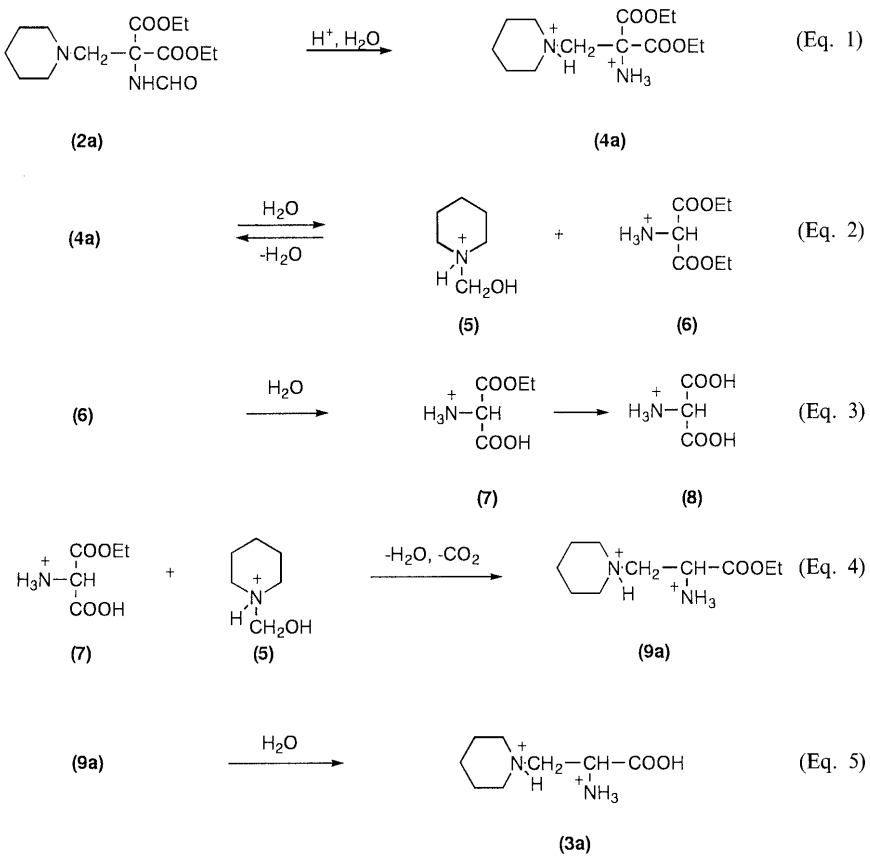

Chart 2

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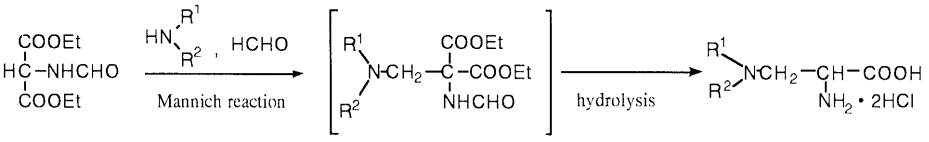
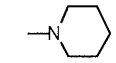
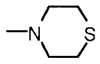
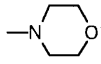
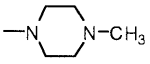
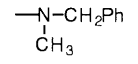
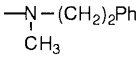
Table 1. Preparation of β-(*sec*-Amino)alanines



1 2a-i 3a-i

$NH\langle^{R^1}_{R^2}$	Mannich reaction: Conditions[a]	Mannich reaction: Compd. 2	mp (°C)	Reaction time (d) at 30 °C	Hydrolysis of 2: Compd. 3	Hydrolysis of 2: Yield (%)	mp (dec.) (°C) (solvent)
	A, 5 min	**2a**	76—77[b]	4	**3a**	84	173[c] (EtOH)
	B, 5 min	**2b**	60—63	4	**3b**	78	138 (MeOH)
	A, 5 min	**2c**	106—107	4	**3c**	71	178 (EtOH)
	A, 5 min	**2d**	113—115[d]	4	**3d**	79	158 (EtOH)
	B, 6 h	**2e**	76—80	5	**3e**[e]	56	198 (MeOH–acetone)
	B, 2 min	**2f**	73—77	5	**3f**	76	155 (EtOH)
	B, 5 min	**2g**	[f]	4	**3g**	73	124 (EtOH)
	B, 2 h	**2h**	47—49	5	**3h**[g]	55	203 (MeOH)
	B, 2 h	**2i**	[f]	5	**3i**[g]	39	193 (MeOH)

a) A, room temperature → heating on a water bath; B, room temperature. *b*) Lit.[2] mp 77 °C. *c*) Lit.[2] mp (dec.) 175 °C. *d*) Lit.[2] mp 108 °C. *e*) Obtained as the 3HCl salt. *f*) Obtained as an oil. *g*) Obtained as the free amino acid.

drochloride.

To understand these results, we studied the hydrolysis of **2a** in detail. The reaction was carried out under mild conditions (at 30 °C) and the reaction mixture was monitored by ^{1}H-NMR spectroscopy (see Experimental).

The treatment of **2a** with concentrated HCl for 2 h resulted in complete hydrolysis of the formamido group (Eq. 1 in Chart 2) and gave a mixture of the amino-intermediate **4a**, 1-piperidinemethanol hydrochloride (**5**), and diethyl aminomalonate hydrochloride (**6**) (**4a**:**5**:**6**=1:1:1)[3] (Eq. 2 in Chart 2), affording **3a** in 87% yield after 6 d. This finding suggested the cleavage of the Mannich base **4a** and the formation of another Mannich base leading to **3a**.

In a control experiment, most of **6** was hydrolyzed within 1 d to give a mixture of ethyl hydrogen aminomalonate (**7**) and aminomalonic acid hydrochloride (**8**)[4] (Eq. 3 in Chart 2). Although compounds **5** and **6** could be detected throughout the hydrolysis process of **2a**, neither **7** nor **8** was detected at any stage during the hydrolysis. These results suggested that Eq. 2 (in Chart 2) was an equilibrium reaction[5] and that Mannich reaction of **5** with **7** took place (Eq.4 in Chart 2). Hydrolysis of **9a** gave rise to the final product **3a** (Eq. 5 in Chart 2).

Heating of the reaction mixture presumably promotes the loss of formaldehyde from unstable **5**[6] and results in a low yield of **3a**, while an excess of **7** is decarboxylated and hydrolyzed to give glycine.

From the above observations and the fact that most of the Mannich bases **2** are unstable in solution, we used **2** for the hydrolysis step without further purification. Thus, *in situ*-generated Mannich base **2a** was treated with concentrated HCl at around 30 °C for 4 d and then heated for 2 h to give an 84% yield of **3a**. In a similar manner, other compounds (**3b**—**i**) were obtained. As shown in Table 1, our modified method provides a useful synthetic procedure for β-(*sec*-amino)alanines (**3**).

Experimental

Melting points are uncorrected. Infrared (IR) spectra were measured with a Shimadzu FTIR-8100 spectrometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-GX400 (400 MHz) or Hitachi R-90H (90 MHz) spectrometer using tetramethylsilane or sodium 3-(trimethylsilyl)propionic 2,2,3,3-d_4 acid (in D_2O) as the internal standard. FAB-MS were obtained with a JEOL JMS-HX110 mass spectrometer.

General Procedure for the Synthesis of Compounds 3a—g Mannich Reaction: Diethyl formamidomalonate (5 g, 0.0246 mol) was added to a mixture of a *sec*-amine (0.0246 mol) and a 37% solution of formaldehyde (2.19 g, 0.027 mol) and the whole was stirred at room temperature for a few minutes. In the cases of **2a**, **2c**, and **2d**, the reaction mixture was

heated in a water bath for a few minutes (see Table 1).

Hydrolysis of the Mannich Base: The resulting Mannich reaction mixture was treated in situ with concentrated HCl (50 ml) at 30 °C for 4—5 d, and then heated at 90 °C in a water bath for 2 h. After concentration, the crystallized product was washed with EtOH to give **3a—g**.

α-Amino-1-piperidinepropionic Acid Dihydrochloride (3a) IR (KBr) cm^{-1}: 3420, 2660—2350, 1750, 1648. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.55 (br s, 2H), 1.82 (t, 4H, J=5.9 Hz), 2.6—4.3 (br, 3H), 3.17 (br s, 2H), 3.39—3.54 (m, 3H), 3.62—3.66 (m, 1H), 4.68—4.71 (m, 1H), 8.4—10.2 (br, 2H). FAB-MS m/z: 173 (MH^+). *Anal.* Calcd for $C_8H_{16}N_2O_2 \cdot 2HCl$: C, 39.20; H, 7.40; N, 11.43. Found: C, 39.39; H, 7.64; N, 11.48.

α-Amino-1-pyrrolidinepropionic Acid Dihydrochloride (3b) IR (KBr) cm^{-1}: 3326, 2690—2350, 1945, 1715, 1620. ^{1}H-NMR (90 MHz, D_2O) δ: 1.96—2.33 (m, 4H), 3.17—3.99 (m, 6H), 4.17—4.39 (m, 1H). FAB-MS m/z: 159 (MH^+). *Anal.* Calcd for $C_7H_{14}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 33.75; H, 7.28; N, 11.24. Found: C, 33.87; H, 7.22; N, 11.11.

α-Aminotetrahydro-4*H*-1,4-thiazine-4-propionic Acid Dihydrochloride (3c) IR (KBr) cm^{-1}: 3375, 2660—2330, 1746, 1645. ^{1}H-NMR (400 MHz, DMSO-d_6+D_2O) δ: 2.84 (s, 4H), 3.06—3.13 (m, 3H), 3.20—3.30 (m, 3H), 4.31—4.33 (m, 1H). FAB-MS m/z: 191 (MH^+). *Anal.* Calcd for $C_7H_{14}N_2O_2S \cdot 2HCl$: C, 31.95; H, 6.13; N, 10.64. Found: C, 32.20; H, 6.10; N, 10.64.

α-Amino-4-morpholinepropionic Acid Dihydrochloride (3d) IR (KBr) cm^{-1}: 3395, 3247, 2658—2335, 1752, 1640. ^{1}H-NMR (400 MHz, DMSO-d_6+D_2O) δ: 3.09—3.14 (m, 2H), 3.29—3.40 (m, 3H), 3.60—3.63 (m, 1H), 3.81—3.86 (m, 4H), 4.56—4.59 (m, 1H). FAB-MS m/z: 175 (MH^+). *Anal.* Calcd for $C_7H_{14}N_2O_3 \cdot 2HCl \cdot H_2O$: C, 31.71; H, 6.84; N, 10.57. Found: C, 31.83; H, 6.94; N, 10.49.

α-Amino-4-methyl-1-piperazinepropionic Acid Trihydrochloride (3e) IR (KBr) cm^{-1}: 3315, 2705—2350, 1742, 1630. ^{1}H-NMR (90 MHz, D_2O) δ: 2.91 (s, 3H), 2.74—3.76 (m, 10H), 4.14—4.29 (m, 1H). FAB-MS m/z: 188 (MH^+). *Anal.* Calcd for $C_8H_{17}N_3O_2 \cdot 3HCl$: C, 32.39; H, 6.8; N, 14.17. Found: C, 32.65: H, 6.82; N, 13.95.

2-Amino-3-dimethylaminopropionic Acid Dihydrochloride (3f) IR (KBr) cm^{-1}: 3401, 3295, 2689—2480, 1752, 1628. ^{1}H-NMR (90 MHz, DMSO-d_6) δ: 2.91 (s, 6H), 3.67—3.74 (m, 2H), 4.62—4.74 (m, 1H). FAB-MS m/z: 133 (MH^+). *Anal.* Calcd for $C_5H_{12}N_2O_2 \cdot 2HCl \cdot 0.2H_2O$: C, 28.78; H, 6.96; N, 13.42. Found: C, 28.90: H, 7.22; N, 13.29.

2-Amino-3-diethylaminopropionic Acid Dihydrochloride (3g) IR (KBr) cm^{-1}: 3434, 3314, 2676—2350, 1754, 1619. ^{1}H-NMR (90 MHz, D_2O) δ: 1.35 (t, 6H, J=7.3 Hz), 3.39 (q, 4H, J=7.3 Hz), 3.52—3.68 (m, 2H), 4.27—4.44 (m, 1H). FAB-MS m/z: 161 (MH^+). *Anal.* Calcd for $C_7H_{16}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 33.48; H, 8.03; N, 11.15. Found: C, 33.50; H, 8.06; N, 11.17.

Procedure for the Synthesis of Compounds 3h and 3i Diethyl formamidomalonate (5 g, 0.0246 mol) was added to a mixture of *N*-methylbenzylamine (2.98 g, 0.0246 mol) or *N*-methylphenethylamine (3.32 g, 0.0246 mol) and a 37% solution of formaldehyde (2.19 g, 0.027 mol) at room temperature. The whole was stirred for 2 h, then concentrated HCl (50 ml) was added. The resulting mixture was allowed to stand at room temperature for 5 d, and then heated in a water bath for 1 h. After concentration, the oily residue was passed through a column packed with ion exchange resin (AG 11A8®, Bio-Rad Laboratories) to give a crystalline material. The crude product was recrystallized from MeOH.

2-Amino-3-[methyl(phenylmethyl)amino]propionic Acid (3h) IR (KBr) cm^{-1}: 3453, 2793, 2620—2361, 1609, 1603, 1516. ^{1}H-NMR (90 MHz, D_2O) δ: 2.43 (s, 3H), 2.97 (d, 2H, J=7.9 Hz), 3.84 (s, 2H), 7.45 (s, 5H). FAB-MS m/z: 209 (MH^+). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.54: H, 7.76; N, 13.40.

2-Amino-3-[methyl(2-phenylethyl)amino]propionic Acid (3i) IR (KBr) cm^{-1}: 3425, 2788, 2583—2164, 1619, 1586, 1510. ^{1}H-NMR (90 MHz, D_2O) δ: 2.60 (s, 3H), 3.00—3.07 (m, 6H), 3.61—3.77 (m, 1H), 7.42 (s, 5H). FAB-MS m/z: 223 (MH^+). *Anal.* Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.62; H, 8.21; N, 12.55.

1-Piperidinemethanol Hydrochloride (5) Two equivalents of 30% methanolic HCl was added to 1-piperidinemethanol,[6] and the solvent was evaporated to give a mixture of **5** and piperidine hydrochloride, as a white solid. Since compound **5** was unstable, this was subjected to IR, MS and ^{1}H-NMR analyses without purification. IR (KBr) cm^{-1}: 3425 (OH). FAB-MS m/z: 116 (MH^+). ^{1}H-NMR (400 MHz, DMSO-d_6): δ: 1.34—1.37 [m, 1H, C(4)-$\underline{H}_a H_b$], 1.65—1.78 [m, 5H, C(4)-$H_a\underline{H}_b$ and C(3,5)-H_2], 2.77—2.78 [m, 2H, C(2,6)-$\underline{H}_a H_b$], 3.26—3.32 [m, 2H, C(2,6)-$H_a\underline{H}_b$], 4.41 (br s, 2H, NC$\underline{H}_2$OH), 7.62—7.69 (br, 1H, OH), 10.20—10.24 (br, 1H, NH^+).

Ethyl Amino(piperidinomethyl)malonate (Free Base of 4a) The Mannich base **2a** (5 g, 0.0166 mol) was treated with 50 ml of concentrated HCl, and the mixture was allowed to stand at 30 °C. After 2 h, 1 ml of the reaction solution was harvested and made basic (pH > 11) with 28% NH_4OH under cooling. The resulting mixture was extracted with Et_2O (5 ml × 3). The combined ethereal solution was dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to give the free base of **4a** as an oil (33%). IR (KBr) cm^{-1}: 3384, 1738, 1640—1550. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26 (dd, 6H, J=6.8, 7.3 Hz), 1.29—1.31 (m, 2H), 1.47—1.53 (m, 4H), 2.44 (t, 4H, J=5.4 Hz), 2.96 (s, 2H), 4.17—4.22 (m, 4H).

Hydrolysis of 2a The Mannich base **2a** (5 g, 0.0166 mol) was treated with 50 ml of concentrated HCl and the mixture was allowed to stand at 30 °C. At intervals (0.5, 1, 2, 4 h, 1—6 d), 1 ml samples of the reaction solution were taken and evaporated *in vacuo* and the products were subjected to ^{1}H-NMR analysis.

Reaction Mixture after 2 h: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.21—1.26 (m, 6H, $COOCH_2C\underline{H}_3$), 1.34—1.91 (m, 6H, C(3,4,5)-H_2 of piperidine ring), 4.23—4.32 (m, 4H, $COOC\underline{H}_2CH_3$), 4.42 (br s, 2H × 1/2, NC$\underline{H}_2$OH), 5.05 (s, 1H × 1/2, C(α)-H in **6**). FAB-MS m/z: 273 (MH^+, for **4a**), 176 (MH^+, for **6**), 116 (MH^+, for **5**).

Hydrolysis of Diethyl Aminomalonate (6) Compound **6** (Sigma-Aldrich Japan K.K., 3.51 g, 0.0166 mol), was hydrolyzed by the methods described above.

Reaction Mixture after 24 h: ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.25 (3H × 0.6, dd, J=7.0, 7.3 Hz, $COOCH_2C\underline{H}_3$), 3.65 [2H × 0.05, s, C(α)-H_2 in glycine], 3.75 [2H × 0.03, s, C(α)-H_2 in glycine ethyl ester], 4.19—4.31 (2H × 0.6, m, $COOC\underline{H}_2CH_3$), 4.64 [1H × 0.45, s, C(α)-H in **8**], 4.81 [1H × 0.39, s, C(α)-H in **7**], 5.00 [1H × 0.09, s, C(α)-H in **6**]. FAB-MS m/z: 176 (MH^+, for **6**), 148 (MH^+, for **7**), 120 (MH^+, for **8**).

Ethyl α-Amino-1-piperidinepropionate Dihydrochloride (9a) Ethanolic HCl (30%) was added to a solution of **3a** in anhydrous ethanol and the mixture was held for 24 h at room temperature, then evaporated to dryness *in vacuo*. After three such treatments with ethanolic HCl, the residue crystallized completely. It was recrystallized from anhydrous ethanol to give an analytical sample of **9a** as hygroscopic prisms, mp 168 °C (dec.) lit.,[2] mp 145—147 °C. IR (KBr) cm^{-1}: 1752. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.27 (dd, 3H, J=6.8, 7.3 Hz), 1.55—1.56 (m, 2H), 1.81—1.86 (m, 4H), 3.20—3.71 (m, 6H), 4.22—4.28 (m, 2H), 4.85—4.88 (m, 1H). *Anal.* Calcd for $C_{10}H_{20}N_2O_2 \cdot 2HCl \cdot 0.1\ H_2O$: C, 43.68; H, 8.14; N, 10.19. Found: C, 43.62; H, 8.39; N, 10.21.

References and Notes

1) *a*) Miyano S., Abe N., *Chem. Pharm. Bull.*, **20**, 1588—1589 (1972); *b*) *Idem*, Ger. Offen. 2323301 [*Chem. Abstr.*, **80**, 70539*h* (1974)].
2) Butenandt A., Hellmann H., *Hoppe-Seyler's Z. Physiol. Chem.*, **284**, 168—175 (1949).
3) The ^{1}H-NMR spectrum of the mixture showed two characteristic singlet signals at δ 4.42 and 5.05, due to C(α)-H in **5** and C(α)-H in **6**, respectively. The ratio of the integral values of methyl in –COOEt in **4a** and **6**, C(α)-H in **5**, and C(α)-H in **6** was about 12 : 2 : 1, which roughly indicated a composition of **4a** : **5** : **6** = 1 : 1 : 1. Since these two methyl signals in **4a** and two methyl signals in **6** completely overlap each other, half the total integration (6H) is assigned to those of **4a**.
4) The ^{1}H-NMR spectrum of the mixture showed two singlet signals at δ 4.81 and 4.65 which were ascribable to C(α)-H in **7** and C(α)-H in **8**, respectively.
5) A solution of a mixture of **5**, obtained by the method of Hellmann and Opitz,[6] and **6** in concentrated HCl was allowed to stand at room temperature for 20 min, resulting in a mixture containing **4a**.
6) Hellmann H., Opitz G., *Chem. Ber.*, **89**, 81—95 (1956).