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Asymmetric Syntheses of β-Amino Acids by the Addition of Chiral Amines to C=C Double Bonds

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Asymmetric syntheses of β-amino acids were achieved by the addition of chiral amines, $R(+)$- and $S(-)$-α-methylbenzylamines (**1b** and **1c**), to crotonitrile, methyl crotonate (**5a**), *l*-menthyl crotonate (**5b**), ethyl cinnamate (**5c**), and methacrylonitrile, and by the addition of benzylamine (**1a**) to **5b**, in the range of 2—19% optical purities. Among them, the configuration of the resulting β-amino acids was same as **1b** and **1c** used, in the reactions with crotonitrile and **5c**, but was different in the cases of **5a** and **5b** and methacrylonitrile.

Keywords——asymmetric synthesis; β-amino acid; addition of chiral amine; configuration; optical purity

Several naturally occurring β-amino acids having an asymmetric carbon atom and peptides possessing β-amino acids as the component have hitherto been isolated,[2] and these have attracted attention on the field of biochemistry. Although a variety of studies on the asymmetric syntheses of optically active α-amino acids have hitherto been known,[3] investigations to prepare optically active β-amino acids, by asymmetric syntheses, are quite scare: Terentev[4] prepared optically active β-aminobutyric acids by the addition of chiral amines to crotonic acid in the range of 7—9% optical purities. Recently we found that optically active β-amino acids were formed by the reaction of chiral Schiff bases with Reformatsky reagent in the range of 2—28% optical purities.[5]

In this paper, we tried to study on the asymmetric syntheses of optically active β-amino acids, such as β-aminobutyric acids(**4**, **6a**), β-amino-β-phenylpropionic acid(**6b**), and α-methyl-β-alanine(**11**), by the addition of chiral amines(**1b** and **1c**) to C=C double bond compounds having nitrile or ester groups in the α-position. As the chiral amines, $R(+)$-α-methylbenzylamine(**1b**) and $S(-)$-α-methylbenzylamine(**1c**) were used. The C=C double bond compounds were as follows: crotonitrile, methyl crotonate(**5a**), *l*-menthyl crotonate(**5b**), ethyl cinnamate(**5c**), and methacrylonitrile. First, the asymmetric synthesis of optically active β-aminobutyric acid(**4**) was successfully carried out by the addition of **1** to crotonitrile, as shown in Chart 1.

The resulting β-N-benzylaminobutyronitriles(**2**) were hydrolyzed with 6N hydrochloric acid to convert into β-N-benzylaminobutyric acids(**3**), which were hydrogenolyzed with 10%

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[2] *a*) H.R. Crumpler, C.E. Dent, H. Harris, and R.G. Westall, *Nature*, **167**, 307 (1951); *b*) N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Tetrahedron Letters*, **1965**, 1411; *c*) N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, *Agr. Biol. Chem.* (Tokyo), **30**, 132 (1966); *d*) T.P. Hettinger, and L.C. Craig, *Biochemistry*, **7**, 4153 (1968); *e*) M. Sato and T. Tatsuno, *Chem. Pharm. Bull.* (Tokyo), **16**, 2182 (1968); *f*) H. Yoshioka, T. Aoki, H. Goto, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, *Tetrahedron Letters*, **1971**, 2043; *g*) S. Kondo, S. Shibahara, S. Takahashi, K. Maeda, H. Umezawa, and M. Ohno, *J. Am. Chem. Soc.*, **93**, 6305 (1971); *h*) S. Shibahara, S. Kondo, K. Maeda, H. Umezawa, and M. Ohno, *J. Am. Chem. Soc.*, **94**, 4353 (1972); *i*) T. Wakamiya, T. Shiba, and T. Kaneko, *Bull. Chem. Soc. Japan*, **45**, 3668 (1972); *j*) H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, and T. Takeuchi, *J. Antibiotics* (Tokyo), Ser. A **29**, 97 (1976).

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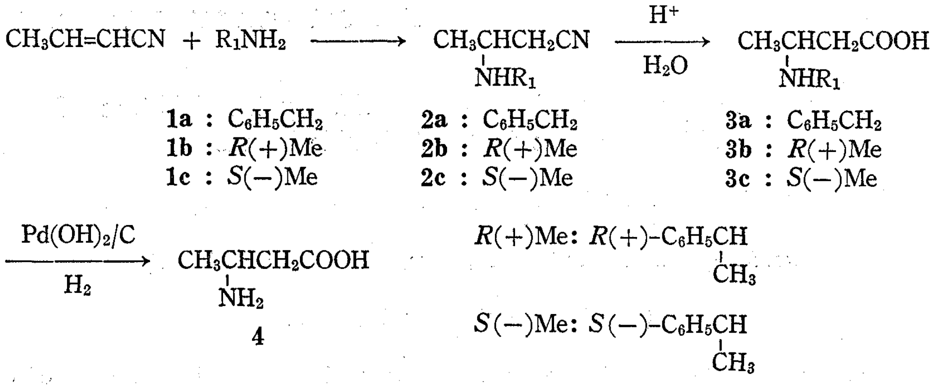


$$CH_3CH{=}CHCN + R_1NH_2 \longrightarrow \underset{NHR_1}{CH_3CHCH_2CN} \xrightarrow[H_2O]{H^+} \underset{NHR_1}{CH_3CHCH_2COOH}$$

1a : $C_6H_5CH_2$ **2a** : $C_6H_5CH_2$ **3a** : $C_6H_5CH_2$
1b : *R*(+)Me **2b** : *R*(+)Me **3b** : *R*(+)Me
1c : *S*(−)Me **2c** : *S*(−)Me **3c** : *S*(−)Me

$$\xrightarrow[H_2]{Pd(OH)_2/C} \underset{NH_2}{CH_3CHCH_2COOH}$$

4

R(+)Me: $R(+)\text{-}\underset{CH_3}{C_6H_5CH}$

S(−)Me: $S(-)\text{-}\underset{CH_3}{C_6H_5CH}$

Chart 1

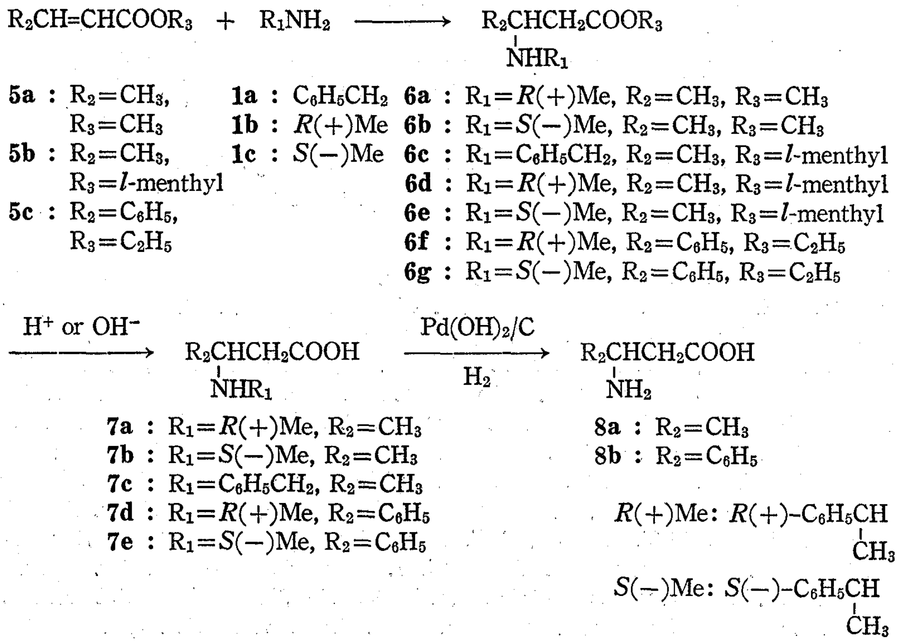
palladium hydroxide on charcoal after treated with IR 120 (H^+ form) without isolation to avoid the fractionation during purification. The specific rotation of **4** thus obtained was measured in the crude state without purification. The specific rotations, configurations, optical purities, and overall yields are shown in Table I.

Table I. Optically Active β-Aminobutyric Acid (**4**) by the Reaction of Crotonitrile with **1b**—**c**

Config. of **1**	Config. of **4**	$[\alpha]_D^{15}$ (H_2O)	Optical purity (%)$^{a)}$	Overall yield (%)
R(+)	*R*	−3.2°(*c* =5.6)	8.3	22
S(−)	*S*	+3.8°(*c* =7.5)	9.8	20

a) The optical purity is defined as $[\alpha]_D^{obsd.}/[\alpha]_D^{b)}\times 100$.
b) *S*(+)-β-aminobutyric acid, $[\alpha]_D^{15}+38.8°$ (H_2O)$^{c)}$
c) K. Balenovic, D. Cerar, and Z. Fuks, *J. Chem. Soc.*, **1952**, 3316

When *R*(+)-and *S*(−)-amines(**1b** and **1c**) were used, *R*(−)-and *S*(+)-β-aminobutyric acids(**4**) were obtained in 8.3 and 9.8 % optical purities, respectively. These results are consistent with those[4] that Terentev observed in the addition of chiral amines(**1b** and **1c**) to crotonic acid.



$$R_2CH{=}CHCOOR_3 + R_1NH_2 \longrightarrow \underset{NHR_1}{R_2CHCH_2COOR_3}$$

5a : $R_2=CH_3$, $R_3=CH_3$
5b : $R_2=CH_3$, $R_3=l$-menthyl
5c : $R_2=C_6H_5$, $R_3=C_2H_5$

1a : $C_6H_5CH_2$
1b : *R*(+)Me
1c : *S*(−)Me

6a : $R_1=R(+)$Me, $R_2=CH_3$, $R_3=CH_3$
6b : $R_1=S(-)$Me, $R_2=CH_3$, $R_3=CH_3$
6c : $R_1=C_6H_5CH_2$, $R_2=CH_3$, $R_3=l$-menthyl
6d : $R_1=R(+)$Me, $R_2=CH_3$, $R_3=l$-menthyl
6e : $R_1=S(-)$Me, $R_2=CH_3$, $R_3=l$-menthyl
6f : $R_1=R(+)$Me, $R_2=C_6H_5$, $R_3=C_2H_5$
6g : $R_1=S(-)$Me, $R_2=C_6H_5$, $R_3=C_2H_5$

$$\xrightarrow{H^+ \text{ or } OH^-} \underset{NHR_1}{R_2CHCH_2COOH} \xrightarrow[H_2]{Pd(OH)_2/C} \underset{NH_2}{R_2CHCH_2COOH}$$

7a : $R_1=R(+)$Me, $R_2=CH_3$
7b : $R_1=S(-)$Me, $R_2=CH_3$
7c : $R_1=C_6H_5CH_2$, $R_2=CH_3$
7d : $R_1=R(+)$Me, $R_2=C_6H_5$
7e : $R_1=S(-)$Me, $R_2=C_6H_5$

8a : $R_2=CH_3$
8b : $R_2=C_6H_5$

R(+)Me: $R(+)\text{-}\underset{CH_3}{C_6H_5CH}$

S(−)Me: $S(-)\text{-}\underset{CH_3}{C_6H_5CH}$

Chart 2.

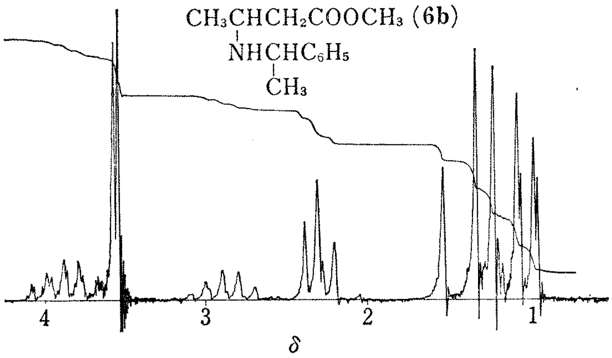


Fig. 1

Next, the asymmetric syntheses of optically active β-amino acids by the addition of **1** to α,β-unsaturated carboxylic esters (**5**), methyl and *l*-menthyl crotonate(**5a** and **5b**) and ethyl cinnamate (**5c**), were examined, as shown in Chart 2.

Heating of **1** with **5** in ethanol gave the corresponding adducts, β-N-benzylamino esters(**6**). Figure 1 shows the ^1H-nuclear magnetic resonance (^1H-NMR) spectrum of methyl β-N-S-α-methylbenzylaminobutyrate(**6b**), which was prepared from **1c** and **5a**.

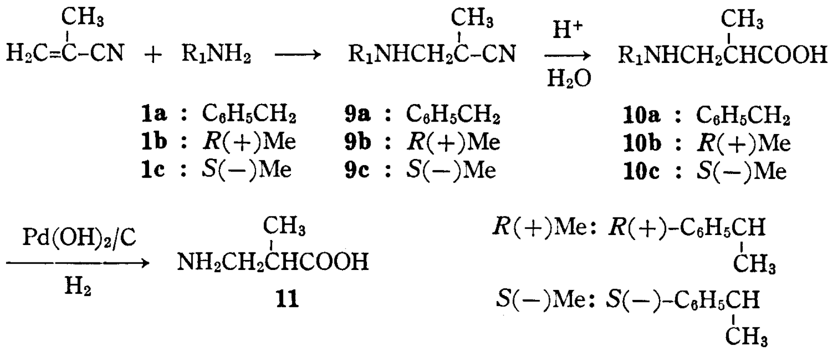
The signals of methyl,methylene,methine, and methoxy groups were observed to be splitted under the influence of the *S*(−)-amino moiety. The β-N-benzylamino esters(**6**) were hydrolyzed to β-N-benzylamino acids(**7**), followed by hydrogenolysis with 10% palladium hydroxide on charcoal to afford β-amino acids(**8**). Their specific rotations, configurations, optical purities, and overall yields are summarized in Table II.

Table II. Optically Active β-Amino Acid(**8**) through the Intermediate (**6**)

6	$[\alpha]_D^{25}$ (EtOH)	Config. of **8**	Optical purity (%)	Overall yield (%)
6a	+2.5°(*c* =6.4)	*S*	6.5	40
6b	−2.8°(*c* =3.6)	*R*	7.2	47
6c	−0.9°(*c* =5.0)	*R*	2.3	26
6d	+1.8°(*c* =2.2)	*S*	4.6	28
6e	−5.8°(*c* =2.0)	*R*	15.0	25
6f	+19.4°(*c* =2.0)[a]	*R*	16.9	16
6g	−22.0°(*c* =3.1)[a]	*S*	19.2	14

a) The specific rotations were measured as formyl derivatives.[b]
b) F.Bergel and J. Butler, *J. Chem. Soc.*, **1961**, 4047.

When *R*(+)-and *S*(−)-amines(**1b** and **1c**) were allowed to react with **5a**, *S*(+)-and *R*(−)-β-aminobutyric acids(**8a**) were formed in 6.5 and 7.2% optical purities, respectively. The configuration of **8a** was in the reverse order, compared with those in the case of the addition of **1** to crotonitrile. The addition of **1b** and **1c** to **5b** also gave the same results in the configurations. *S*(+)-and *R*(−)-**8a** were formed from **1b** and **1c** in the optical purities of 4.6 and 15.0%, respectively, while the addition of **1a** to **5b** gave *R*(−)-**8a** in 2.2% optical purity. On the addition to **5b**, two chiral groups can participate each other. It is of interest that



$$H_2C{=}\overset{CH_3}{C}{-}CN + R_1NH_2 \longrightarrow R_1NHCH_2\overset{CH_3}{C}{-}CN \xrightarrow[H_2O]{H^+} R_1NHCH_2\overset{CH_3}{C}HCOOH \xrightarrow[H_2]{Pd(OH)_2/C} NH_2CH_2\overset{CH_3}{C}HCOOH$$

1a : $C_6H_5CH_2$ **9a** : $C_6H_5CH_2$ **10a** : $C_6H_5CH_2$
1b : *R*(+)Me **9b** : *R*(+)Me **10b** : *R*(+)Me
1c : *S*(−)Me **9c** : *S*(−)Me **10c** : *S*(−)Me

11

R(+)Me: $R(+)\text{-}C_6H_5\underset{CH_3}{CH}$
S(−)Me: $S(-)\text{-}C_6H_5\underset{CH_3}{CH}$

Chart 3

the participation serves as the increase of the optical purity in the use of **1c**, but as the decrease in the case of **1b**.

The reactions of **1b** and **1c** with **5c** resulted in the formation of *R*(+)-and *S*(−)-β-amino-β-phenylpropionic acids(**8b**) in the optical purities of 16.9 and 19.2%, respectively. In comparison with the case of **5a**, the increased values of the optical purities will be due to the bulkiness of the phenyl group rather than methyl group.

The asymmetric synthesis of optically active α-methyl-β-alanine(**11**) was achieved by heating **1** with methacrylonitrile in ethanol.

The resulting β-N-benzylamino-α-methylpropionitriles(**9**) were hydrolyzed to the corresponding carboxylic acids(**10**), followed by hydrogenolysis with 10% palladium hydroxide on charcoal to give **11**. In this case, when *R*(+)-and *S*(−)-amines(**1b** and **1c**) were used, *S*(+)-and *R*(−)-α-methyl-β-alanines(**11**) were formed in the optical purities of **11** and 12%, respectively. The specific rotations, configurations, optical purities, and overall yields are shown in Table III.

Table III. Optically Active α-Methyl-β-alanine(**11**) by the Reaction of Methacrylonitrile with **1b**—**c**

Config. of **1**	Config. of **11**	$[\alpha]_D^{15}$ (H_2O)	Optical purity (%)	Overall yield (%)
R(+)	*S*	+1.5°(*c* =2.3)	11	10
S(−)	*R*	−1.7°(*c* =2.3)	12	9

a) *R*(−)-α-mehyl-β-alanine, $[\alpha]_D$ −14.0° (H_2O).[b]
b) K. Balenovic and N. Bregant, *Tetrahedron*, **5**, 44(1959).

The addition of chiral amines(**1b** and **1c**) to C=C double bonds has been investigated on the asymmetric syntheses of aspartic acid using fumaric and maleic acid derivatives in detail.[6] These reactions would be the diastereoface differentiating reaction,[7] which proceed *via* the salt intermediates.[6] Similarly, the asymmetric synthesis of optically active **4** by the addition of **1b** and **1c** to crotonic acid[4] belongs to the diastereoface differentiating reaction, in which **1b** and **1c** are asymmetrically added to the initially formed salt of crotonic acid and **1b** and **1c**. On the other hand, the asymmetric syntheses of β-amino acids in our present studies are different from these reactions in the asymmetric induction, though these are formally alike. The reaction shown in Chart 1 and 2 are enantioface differentiating reaction, and the reaction of Chart 3 belongs to enantiotopos differentiating reaction. In the addition of **1b** and **1c** to **5b**, enantioface and diastereoface differentiating reactions participate in the reaction simultaneously.

Experimental

Infrared (IR) spectra were recorded with JASCO IRA-1 Grating Infrared Spectrometer. ^{1}H-NMR spectra were taken with a JEDL High Resolution NMR Instrument C-60H at 60 MHz. Hydrogenations were carried out by Skita and Parr catalytic hydrogenation apparatus. Specific rotations were measured by JASCO DIP-4 Polarimeter using 10 mm cell.

β-N-Benzylaminobutyronitrile (2a—c)——A solution of crotonitrile (2.7 g, 0.04 mole) and amine (**1a**—**c**) (0.04 mole) in EtOH (50 ml) was refluxed for 6 hr. After removal of EtOH, the residue was distilled under reduced pressure to give **2a**—**c**. Their boiling points, specific rotations, yields, IR spectra, ^{1}H-NMR spectra, and elemental analyses are shown in Table IV.

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[6] *a*) A.P. Terentev, R.A. Gracheva, L.F. Titova, and T.F. Dendeko, *Dokl. Akad. Nauk. S.S.S.R*, **154**, 1406 (1964); *b*) K. Harada and K. Matsumoto, *J. Org. Chem.*, 31, 2985 (1966); *c*) Y. Liwschitz and A. Singlrmann, *J. Chem. Soc.*, **1966**, 1200.

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TABLE IV. Optically Active β-N-Benzylaminobutyronitrile(**2a**—**c**)

	bp (mmHg)	$[\alpha]_D^{15}$ (c,EtOH)	Yield (%)	Formula	Analysis (%) Calcd. (Found)			IR ν_{max}^{film} cm^{-1} (CN)	^{1}H-NMR spectra (δ) in CDCl$_3$
					C	H	N		
2a	121°(2.5)	—	35	$C_{11}H_{14}N_2$	75.82 (75.48)	8.10 (8.27)	16.08 (16.31)	2230	7.21(s, 5H, arom), 3.72(s, 2H, CH$_2$), 2.95(m, 1H, J=6.0 Hz, CH), 2.35(d, 2H, J=6.0 Hz, CH$_2$), 1.36(s, 1H, NH), 1.20(d, 3H, J=6.0 Hz, CH$_3$)
2b	126°(4.0)	+60.2°(2.7)	26	$C_{12}H_{16}N_2$	76.55 (76.87)	8.57 (8.94)	14.88 (15.23)	2230	7.16(s, 5H, arom), 3.79(q, 1H, J=6.0 Hz, CH), 2.78(m, 1H, J=6.0 Hz, CH), 2.31 and 2.14 (d, 2H, J=6.0 Hz, CH$_2$), 1.42 (s, 1H, NH), 1.29(d, 3H, J=7.0 Hz, CH$_3$), 1.17 and 1.07 (d, 3H, J=2.5 Hz, CH$_3$)
2c	126°(4.0)	−57.2°(2.0)	29	$C_{12}H_{16}N_2$	76.55 (76.39)	8.57 (8.44)	14.88 (14.42)	2230	7.16(s, 5H, arom), 3.82(q, 1H, J=6.0 Hz, CH), 2.80(q, 1H, J=6.0 Hz, CH), 2.33 and 2.17 (d, 2H, J=5.0 Hz, CH$_2$), 1.46 (s, 1H, NH), 1.30(d, 3H, J=7.0 Hz, CH$_3$), 1.18 and 1.08(d, 3H, J=2.5 Hz, CH$_3$)

β-N-Benzylaminobutyric Acid (3a—c)——N-Benzylaminobutyronitrile (**2a**) (1.7 g, 0.01 mole) was refluxed with 6N HCl (30 ml) for 10 hr. The mixture was extracted with ether (20 ml), and the aqueous layer was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and the solution was applied to IR 120 column (H$^+$ form, 2.2×26.5 cm). The column was eluted with 1.5N aqueous ammonia and the fractions containing amino acid were combined and evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH to give **3a**—**c**. **3a**: yield, 1.7 g, 88%, mp 188—189°; IR ν_{max}^{film} cm^{-1}: 1550 (COO$^-$). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.23; H, 8.00; N, 7.13; NMR δ (D_2O): 7.32 (s, 5H, arom), 4.17 (s, 2H, CH$_2$), 3.49 (m, 1H, J=7.0 Hz, 1H), 2.50 (d, 2H, J=6.0 Hz, CH$_2$), 1.36 (d, 3H, J=6.0 Hz, CH$_3$).

β-N-*R*- and *S*-α-Methylbenzylaminobutyric acids (**3b** and **3c**) were used in the next hydrogenolysis without isolation to avoid the fractionation during purification.

β-Aminobutyric Acid (4)——A solution of **3a**—**c** (0.005 mole) in 50% aqueous EtOH (30 ml) was hydrogenolyzed with 10% palladium hydroxide (0.7 g) on charcoal for 12 hr. After the reaction was over, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from MeOH to give **4**: yield, 0.46 g (89% from **3a**); mp 190—192°. IR ν_{max}^{KBr} cm^{-1}: 1550 (COO$^-$). NMR δ: (D_2O): 3.56 (m, 1H, J=6.0 Hz, CH), 2.46 (d, 2H, J=6.5 Hz, CH$_2$), 1.32 (d, 3H, J=7.0 Hz, CH$_3$). *Anal.* Calcd. for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.67; H, 8.43; N, 13.80.

The specific rotations of optically active β-aminobutyric acids (from **2b** and **2c**) were measured in the crude state without isolation to avoid the fractionation. A part of **4** (from **2c**) was recrystallized from MeOH for elemntal analysis. mp 193—195°. *Anal.* Calcd. for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.62; H, 8.53; N, 13.50.

***l*-Menthyl Crotonate (5b)**——A mixture of crotonic acid (8.6 g, 0.1 mole), *l*-menthol (15.6 g, 0.1 mole), *p*-toluenesulfonic acid (0.2 g), and toluene (60 ml) was refluxed for 10 hr in a Dean-Stark separator until the calculated amount of water was separated. The toluene solution was washed with 1% aq. NaHCO$_3$ (30 ml) and then with water (30 ml), and dried over anhydrous Na$_2$SO$_4$. After the solvent was removed, the residue was distilled under reduced pressure: yield, 15 g (67%); bp 101°/2.0 mmHg; $[\alpha]_D^{15}$ −85.7° (c=2.9, EtOH). IR ν_{max}^{film} cm^{-1}: 1710 (C=O), 1650 (C=C). *Anal.* Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.79.

***l*-Menthyl β-N-Benzylaminobutyrate (6c)**——A solution of **5b** (4.4 g, 0.02 mole) and **1a** (2.2 g, 0.02 mole) in EtOH (40 ml) was refluxed for 12 hr. After the solvent was removed, the residue was distilled under reduced pressure: yield, 2.6 g (39%); bp 163—164°/3.0 mmHg; $[\alpha]_D^{15}$ −54.6° (c=3.1, EtOH).

β-N-Benzylaminobutyrates (**6a**—**e**) prepared from **1a**—**c** and **5a**—**b** by the same procedure described above are listed in Table V, along with boiling points, specific rotations, yields, elemental analyses, IR spectra, and ^{1}H-NMR spectra.

TABLE V. β-N-Benzylaminobutyrate (**6**)

6	bp (mmHg)	$[\alpha]_D^{25}$ (c,MeOH)	Yield (%)	Formula	Analysis (%) Calcd. (Found)			IR ν_{max}^{film} cm^{-1} (CN)	^{1}H-NMR spectra (δ) in CDCl$_3$
					C	H	N		
6a	104°(2.0)	+42.8° (6.2)	63	$C_{13}H_{19}O_2N$	70.55 (70.42)	8.65 (8.81)	6.33 (6.36)	3300 (NH) 1720 (C=O)	7.12(s, 5H, arom), 3.94 and 3.92(m, 1H, J=6.0 Hz, CH), 3.53 and 3.57(s, 3H, OCH$_3$), 2.92(m, 1H, J=6.0 Hz, CH), 2.31 and 2.26(d, 2H, J=5.0 Hz, CH$_2$), 1.58(s, 1H, NH), 1.33(d, 3H, J=7.0 Hz, CH$_3$), 1.07 and 1.05 (d, 3H, J=6.0 Hz, CH$_3$)
6b	105°(2.2)	−44.1° (5.9)	54	$C_{13}H_{19}O_2N$	70.55 (70.99)	8.65 (8.95)	6.33 (6.19)	3300 (NH) 1720 (C=O)	7.13(s, 5H, arom), 3.93 and 3.91(m, 1H, J=6.0 Hz, CH), 3.52 and 3.56(s, 3H, OCH$_3$), 2.90(m, 1H, J=6.0 Hz, CH), 2.35 and 2.24(d,2H,J=5.0 Hz, CH$_2$), 1.56 (s, 1H, NH), 1.29(d, 3H, J=7.0 Hz, CH$_3$), 1.05 and 1.02 (d, 3H, J=6.0 HZ, CH$_3$)
6c	163—164° (3.0)	−54.6° (3.2)	35	$C_{21}H_{33}O_2N$	76.09 (75.93)	10.03 (10.06)	4.23 (4.62)	3290 (NH) 1720 (C=O)	7.22(s, 5H, arom), 4.67(m, 1H, CH), 3.75(s, 2H, CH$_2$), 3.15(q, 1H, J=6.0 Hz, CH), 2.39 and 2.36(d, 2H, J=7.0 Hz, CH$_2$), 2.10—1.40 (m, 6H,3×CH$_2$), 1.74(s, 1H, NH),1 .13(d, 3H, J=6.0 Hz, CH$_3$), 0.88(d, 6H, J=7.0 Hz, 2×CH$_3$), 0.75(d, 3H, J=7.0 Hz, CH$_3$)
6d	172°(2.0)	−29.9° (2.5)	32	$C_{22}H_{25}O_2N$	76.47 (76.19)	10.21 (10.55)	4.05 (4.29)	3310 (NH) 1730 (C=O)	7.25(s, 5H, arom), 4.67 (m, 1H, CH), 3.88 and 3.85(q, 1H, J=7.0 Hz, CH), 2.92(m, 1H, J=7.0 Hz, CH), 2.37 and 2.27(d, 2H, J=4.0 Hz, CH$_2$), 2.12(s, 1H, NH), 2.08—1.64(m, 6H, 3×CH$_2$), 1.34 (d, 3H, J=7.0 Hz, CH$_3$), 1.06(d, 3H, J=6.5 Hz, CH$_3$), 0.89(d, 6H, J=7.0 Hz, 2×CH$_3$), 0.77(d, 3H, J=7.0 Hz, CH$_3$)
6e	172°(2.0)	−80.3° (2.3)	35	$C_{22}H_{25}O_2N$	76.47 (76.52)	10.21 (10.15)	4.05 (4.31)	3310 (NH) 1730 (C=O)	7.24(s, 5H, arom), 4.68(m, 1H, CH), 3.90 and 3.86(q, 1H, J=7.0 Hz, CH), 2.95(m, 1H, J=7.0 Hz, CH), 2.38 and 2.26(d,2H, J=4.0 Hz, CH$_2$), 1.98 (s, 1H, NH), 2.14—1.64(m, 6H, 3×CH$_2$), 1.33(d, 3H, J=6.5 Hz, CH$_3$), 1.05(d, 3H, J=6.5 Hz, CH$_3$), 0.89 (d, 6H, J=7.0 Hz, 2×CH$_3$), 0.77 (d, 3H, J=7.0 Hz, CH$_3$)

β-N-Benzylaminobutyric Acid (7c)——*l*-Menthyl β-N-benzylaminobutyrate (**6c**) (1.7 g, 0.005 mole) was dissolved in a mixture of EtOH (25 ml) and 10% aq. NaOH (25 ml). After allowed to stand for 3 days at room temperature, the reaction mixture was dissolved in H_2O (25 ml) and the aqueous solution was extracted with ether (20 ml). The aqueous layer was acidified with 6N HCl and evaporated to dryness under reduced pressure. The residue was extracted twice with ab. EtOH (20 ml). After evaporation of EtOH, the residue was treated with the same method as described in a procedure of **3a**—**c**. The half part of the crude **7c** thus obtained was recrystallized from EtOH for elemental analysis. The yield was 0.43 g (89%). $[\alpha]_D^{25}$ −2.5° (c=2.4, EtOH). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.58; H, 7.82; N, 6.91.

The rest was used in the next hydrogenation. The optically active *l*-methyl β-N-*R*- and *S*-α-methylbenzylaminobutyrate (**6d** and **6e**) were also treated with the same method.

Methyl β-N-*R*- and *S*-α-methylbenzylaminobutyrates (**6a** and **6b**) were hydrolyzed with 6N HCl. The resulting hydrolyzates were worked up in the same method described in the procedure of **4**. The resulting **7a** and **7b** were used in the next hydrogenation without isolation to avoid the fractionation during purification.

β-Aminobutyric Acid (8a)——The residue **7c** obtained by the procedure described above was dissolved in 50% aq. EtOH (30 ml), and the solution was treated with the same method described in the procedure of **4**. The yield was 0.19 g (83%); mp 193—194°. *Anal.* Calcd. for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.64; H, 8.95; N, 13.27.

β-Amino-β-phenylpropionic Acid (8b)——A mixture of **5c** (1.8 g, 0.01 mole) and **1b** (2.4 g, 0.02 mole) was heated at 80—90° for 10 hr. After excess amine was removed by evaporation, the residue was hydrolyzed with 6N HCl (30 ml), and then hydrogenolyzed by the same method described in the procedure of **4**. A part of the resulting **8b** was recrystallized from 50% aq. EtOH; mp 243—244°. *Anal.* Calcd. for $C_9H_{11}O_2N$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.04; H, 6.77; N, 8.46.

The rest of **8b** were converted to formyl derivatives and measured in the crude state without isolation to avoid the fractionation during purification.

α-Methyl-β-N-benzylpropionitrile (9a—c)——A solution of methacrylonitrile (5.2 g, 0.06 mole) and **1** (0.08 mole) in EtOH (40 ml) was refluxed for 48 hr. After removal of EtOH by evaporation, the residue was distilled under reduced pressure. The resulting **9a—c** are listed in Table VI, along with boiling points, specific rotations, yields, elemental analyses, IR spectra, and ^{1}H–NMR spectra.

TABLE VI. α-Methyl-β-N-benzylaminopropionitrile (**9**)

	bp (mmHg)	$[\alpha]_D^{15}$ (c,EtOH)	Yield (%)	Formula	Analysis (%) Calcd. (Found)			IR ν_{max}^{film} cm^{-1}	^{1}H–NMR spectra (δ) in $CDCl_3$
					C	H	N		
9a	100°(2.0)	—	33	$C_{11}H_{14}N_2$	75.82 (75.46)	8.10 (8.25)	16.08 (15.76)	3320 (NH) 2210 (CN)	7.17(s, 5H, arom), 3.73(s, 2H, CH_2), 2.68(d, 2H, $J=2.0$ Hz, CH_2), 2.65 (m, 1H, CH), 2.02(s, 1H, NH), 1.22 (d, 3H, $J=7.0$ Hz, CH_3)
9b	112—113° (2.5)	+48.2° (2.5)	14	$C_{12}H_{16}N_2$	76.55 (76.24)	8.57 (8.42)	14.88 (14.98)	3310 (NH) 2215 (CN)	7.18(s, 5H, arom), 3.74(q, 1H, $J=6.0$ Hz, CH), 2.59(d, 2H, $J=1.5$ Hz, CH_2), 2.56 (m, 1H, CH), 1.79 (s, 1H, NH), 1.34(d, 3H, $J=6.5$ Hz, CH_3), 1.21(d, 3H, $J=6.0$ Hz, CH_3)
9c	118—119° (3.0)	—48.6° (4.7)	12	$C_{12}H_{16}N_2$	76.55 (76.28)	8.57 (8.39)	14.88 (14.74)	3310 (NH) 2215 (CN)	7.15(s, 5H, arom), 3.71(q, 1H, $J=6.0$ Hz, CH), 2.56(d, 2H, $J=1.5$ Hz, CH_2), 2.52(m, 1H, CH), 1.77(s, 1H, NH), 1.34(d, 3H, $J=6.5$ Hz, CH_3), 1.18(d, 3H, $J=6.0$ Hz, CH_3)

α-Methyl-β-N-benzylalanine (10a—c)——The nitrile (**9a—c**) (0.01 mole) was refluxed with 6N HCl (30 ml) for 10 hr. The resulting hydrolyzate was worked up in the same method described in the procedure of **3a—c**. **10a** (recryst. from EtOH): yield, 62%; mp 146—147°. IR ν_{max}^{KBr} cm^{-1}: 1550 (COO^-). NMR δ (D_2O): 7.40 (s, 5H, arom), 4.20 (s, 2H, CH_2), 3.11 and 3.00 (d and s, 2H, $J=3.0$ Hz, CH_2), 2.74 (m, 1H, CH), 1.14 (d, 3H, $J=7.0$ Hz, CH_3). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.08; H, 7.87; N, 7.31.

The optically active α-methyl-β-N-*R*- and *S*-α-methylbenzylaminoalanines (**10b** and **10c**) were used in the next hydrogenation without isolation to avoid the fractionation during purification.

α-Methyl-β-alanine (11)——**10a—c** (0.05 mole) dissolved in 50% aq. EtOH (30 ml) was hydrogenolyzed with 10% paladium hydroxide on charcoal and worked up in the same method described in the procedure of **4**. **11a** (recryst. from 50% aq. EtOH): yield, 78%; mp 173—174°. IR ν_{max}^{KBr} cm^{-1}: 1550 (COO^-). NMR δ (D_2O): 3.09 and 2.96 (d and s, 2H, $J=2.0$ Hz, CH_2), 2.61 (m, 1H, CH), 1.17 (d, 3H, $J=7.0$ Hz, CH_3). *Anal.* Calcd. for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.21; H, 8.85; N, 13.43. **11b** (recryst. from 50% aq. EtOH): mp 181—183°. *Anal.* Calcd. for $C_4H_9O_2N$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.49; H, 8.83; N, 13.39.

The specific rotations of optically active **11b** and **11c** were measured in the crude state.