# Selective Esterification of N-Benzyl-L-aspartic Acid. (II). Synthesis of α- and β-Benzyl Esters of N-Benzyl-L-aspartic Acid

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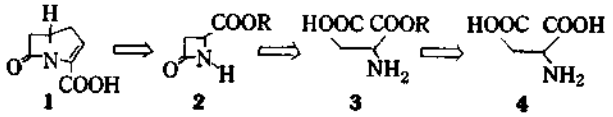
The four different preparative methods of α-benzyl and β-benzyl esters of N-benzyl-L-aspartic acid from L-aspartic acid are described.

## Introduction

In the previous paper[1], we have reported the modified methods for the preparption of N-benzylaspartic anhydride hydrobromide from racemic N-benzylaspartic acid, which was obtained in three steps from maleic anhydride.

As discussed in that report, the (5R)-configuration of the recently discovered carbapenems **1** could be derived from the naturally occurring optically active L-aspartic acid (**4**). Intramolecular cyclization of L-aspartic acid α-esters (**3**), the β-amino acids, gives rise to 4-substituted β-lactams **2** possessing the correct stereochemistry at the 4-position, which corresponds to the (5R)-configuration of carbapenems **1**.



There are, however, two synthetic inefficiency when the β-lactam rings are directly elaborated from L-aspartic acid α-esters (**3**); First, direct cyclization of the β-amino acids having primary amino group usually affords β-lactams in poor to moderate yield, and secondly, the N-H bond of the β-lactams **2** should be protected when the 2- and 3-positions are functionalized.

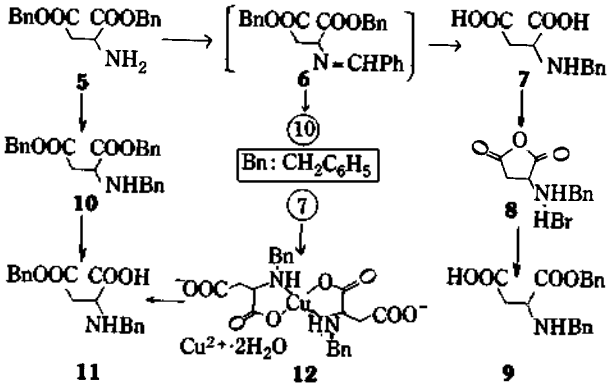
These inefficiency can easily be overcome if one uses N-benzyl-L-aspartic acid α-esters, since the β-lactam formation is more effective due to the more reactive secondary amino group and the protection of the amide nitrogen of the resulting β-lactams is not necessary since it is already tertiary amide. This N-benzyl group is also readily removable by hydrogenolysis over 10% Pd-C or by reductive cleavage with sodium or lithium in liquid ammonia[2].

On the basis of above synthetic viewpoint, we have studied the preparative methods of N-benzyl-L-aspartic acid α-and β-esters starting from L-aspartic acid.

## Results and Discussion

Esterification of L-aspartic acid (**4**) with benzyl alcohol in the presence of p-toluenesulfonic acid produced dibenzyl L-aspartate p-toluenesulfonic acid salt[3] in excellent yield, from which p-toluenesulfonic acid was removed by neutralization with aqueous sodium bicarbonate. The resulting dibenzyl L-aspartate (**5**) was reacted with benzaldehyde to afford the Schiff base **6**, which without separation was hydrogenolized over 5% Pd-C (40 psi, 20 min). At this stage, the dibenzyl ester groups were hydrogenolized along with hydrogenation of the imino group, providing N-benzyl-L-aspartic acid (**7**) in 70% yield.

Reduction of the Schiff base **6** with sodium cyanoborohydride, on the other hand, afforded dibenzyl N-benzyl-L-aspartate (**10**) without cleavage of the benzyl esters. This N-benzyl diester **10** was also prepared from the compound **5** by reaction with benzyl bromide in the presence of sodium carbonate.



**Scheme 1.** Synthesis of α-and β-benzyl N-benzyl-L-aspartates.

Anhydride formation of N-benzyl-L-aspartic acid (**7**) could be accomplished by employing Kovacs' procedure[4] for the preparation of L-aspartic anhydride hydrobromide, or by the modified methods discussed in the previous paper[1]. Thus, salt formation of N-benzyl-L-aspartic-acid (**7**) with 40% hydrobromic acid and treatment of the salt with acetic anhydride after water removal, or sequential treatment of N-benzyl-L-aspartic acid (**7**) with 30% HBr in acetic acid followed by acetic anhydride (one-pot reaction) provided N-benzyl-L-aspartic anhydride hydrobromide (**8**) in 75% yield. Alcoholysis of this anhydride salt **8** with benzyl alcohol then afforded α-benzyl N-benzyl-L-aspartate (**9**) in 90% yield.

β-Benzyl N-benzyl-L-aspartate (**11**) was prepared in different ways. Hydrogenolysis of the dibenzyl N-benzyl-L-aspartate (**10**) in methanol over 5% Pd-C at the hydrogen pressure of 40 psi for 15 min surprisingly resulted in the generation of β-benzyl N-benzyl-L-aspartate (**11**). β-Benzyl ester **11** was also prepared from N-benzyl-L-aspartic acid (**7**) by employing the copper-mediated esterification method[5]. Thus, treatment of N-benzyl-L-aspartic acid (**7**) with copper (II) acetate monohydrate produced blue copper salt **12**, which was reacted with 1,1,3,3-tetramethylguanidine follow-

ed by benzyl bromide. Conventional work-up with EDTA disodium salt gave the β-benzyl ester **11** in 83% yield.

The α- and β-benzyl esters were clarified by analyzing their $^1$H-nmr spectral data, as discussed in the previous report[1], and the α-ester **9** was utilized for the elaboration of N-benzyl-4-benzyloxycarbonyl-2-azetidinone and its further derivatization.

## Experimental

**General.** All the chemicals used were of reagent grade and purified prior to use, if necessary, by the methods reported in the literature. Melting points were measured on Buchi-510 type mp apparatus and are uncorrected. Ir spectra were obtained by JASCO A202 ir spectrophotometer and $^1$H-nmr spectra were recorded on a Varian EM 360A (60MHz) nmr spectrometer. The internal standard was TMS in organic solvent or DSS in $D_2O$. Optical rotation was measured by JASCO DIP 181 polarimeter and elemental analysis was performed by the instrument laboratory, Korea Research Institute of Chemical Technology.

**Dibenzyl L-aspartate (5).** A mixture of L-aspartic acid (**4**, 13.3 g, 10 mmol), benzyl alcohol (73 m*l*), p-toluenesulfonic acid monohydrate (14 g, 10 mmol) and benzene (70 m*l*) was refluxed for 4 hr with separation of the generated water. Solvent removal followed by quenching with diethyl ether resulted in the precipitation of dibenzyl L-aspartate p-toluenesulfonic acid salt[3] in 80% yield (43.7 g). The salt was separated, dissolved in hot water (70°C) and treated with aqueous sodium bicarbonate. Extraction with diethyl ether and usual work-up produced oily product **5** in 95% yield (36.8 g), which was used without futher purification. $[\alpha]_D^{20} = -6.5°$ (c=0.2, 1N HBr). IR ($CHCl_3$); $\nu$=3420 (-$NH_2$), 1730 cm$^{-1}$ (ester carbonyl). $^1$H-nmr ($CDCl_3$); $\delta$=6.90 (s, 10H, phenyl), 4.85, 4.80 (each s, 4H, two -$OCH_2$-), 3.60 (t, J=5 Hz, 1H, -NCH-), 2.60 (d, J=5 Hz, 2H, -$COCH_2$-), 1.95 ppm (s, 2H, -$NH_2$).

**N-Benzyl-L-aspartic acid (7).** A solution of dibenzyl L-aspartate (**5**, 9.40 g, 30 mmol) and benzaldehyde (3.80 g, 30 mmol) in dry methanol (120m*l*) was refluxed for 3 hr and cooled to rt. 5% Pd-C (1.0 g) was added and the mixture was hydrogenolyzed at the hydrogen pressure of 40 psi for 20 min. Triethylamine (4.18 m*l*, 30 mmol) was added, the precipitate was filtered off, and methanol was evaporated. The residue was dissolved in water (50 m*l*) followed by acidification with 1N hydrochloric acid to pH 3 and kept at 0°C for 24 hr. The precipitate was collected by filration and recrystallized from water. Yield: 70% (4.68 g), mp: 214-216°C, $[\alpha]_D^{20} = +0.6°$ (c=0.15, 1N HCl). IR (KBr); $\nu$=3200-2500 (broad), 1720cm$^{-1}$ (acid carbonyl). $^1$H-nmr ($CF_3COOH$); $\delta$=7.25 (s, 5H, phenyl), 4.25 (s, 2H, -$NCH_2$-), 4.18 (t, J=5 Hz, 1H, -NCH-), 3.10 ppm (d, J=5 Hz, 2H, -$COCH_2$-).

**N-Benzyl-L-aspartic anhydride hydrobromide (8).** A solution of N-benzyl-L-aspartic acid (**7**, 22.3 g, 100 mmol) and 30% HBr in acetic acid (27.0 g, 100 mmol) in acetic acid (15 m*l*) was stirred vigorously for 30 min, and acetic anhydride (25.0 g, 250 mmol) was added. The solution was stirred at 35°C for 3 hr. treated with diethyl ether (500m*l*) and stirred for an additional hr. The precipitate was collected by filtration and dried in vacuo over $P_2O_5$. Yield: 75% (21.5 g), mp: 178-180°C (dec.), $[\alpha]_D^{20} = +16.0°$, (c=0.1, DMSO). IR (KBr); $\nu$=1875, 1805 cm$^{-1}$ (anhydride carbonyl). $^1$H-nmr (DMSO-$d_6$); $\delta$=10.50 (broad, -$NH_3$), 7.20 (s, 5H, phenyl), 4.55 (t, J=5 Hz, 1H, -NCH-), 4.20 (s, 2H, -$NCH_2$-), 3.25 ppm (d, J=5 Hz, 2H, -$COCH_2$-).

**α-Benzyl N-benzyl-L-aspartate (9).** N-Benzyl-L-aspartic anhydride hydrobromide (**8**, 14.3 g, 50 mmol) was added to dry benzyl alcohol (300 m*l*) and the mixture was stirred at rt for 12 hr. Triethylamine (5.0g, 50 mmol) was added follow ed by ethanol and the mixture was kept at -20°C for 12 hr. The precipitate was collected by filtration, washed with methanol and dried in vacuo. Yield: 90% (14.1 g), mp: 128-130°C, $[\alpha]_D^{20} = -6.7°$ (c=0.15, 1N HCl). IR (KBr); $\nu$=3100-2500 (broad), 1760 cm$^{-1}$ (ester carbonyl). $^1$H-nmr ($CF_3COOH$); $\delta$=7.00 (s, 10H, phenyl), 5.00 (s, 2H, -$OCH_2$-), 4.20 (s, 2H, -$NCH_2$-), 3.95 (t, J=5 Hz, 1H, -COCH-), 3.10 ppm (d, J=5 Hz, 2H, -$COCH_2$-).

**Dibenzyl N-benzyl-L-aspartate (10).** *Method* **1**. From Schiff base **6**: A Solution of dibenzyl L-aspartate (**5**, 3.13 g, 13 mmol) and benzadehyde (1.06 g, 10 mmol) in methanol (30 m*l*) was refluxed for 3 hr and cooled to rt. Sodium cyanoborohydride (0.63 g, 10 mmol) was added and the mixture was stirred at rt for 48 hr. Methanol was evaporated and water (50 m*l*) was added. Extraction with diethyl ether and usual work-up produced the oily product **10**, which was dissolved in diethyl ether and treated with 30% HBr in acetic acid (1.16 g). The HBr salt of the product **10** was collected by filtration, dried in vacuo and characterized. Yield 65% (3.16 g).

*Method* **2.** From dibenzyl aspartate (**5**): A mixture of dibenzyl L-aspartate (**5**, 3.13g 10mmol), anhydrous sodium carbonate (3.10 g, 30 mmol) and benzyl bromide (1.70 g, 10 mmol) in dry DMF (30m*l*) was stirred at rt for 12 hr and diluted with water (300 m*l*). Extraction with diethyl ether (50 m*l*) and usual work-up produced the oily product **10**, which was dissolved in diethyl ether and treated with 30% HBr in acetic acid (2.16 g). The HBr salt of the product **10** was collected by filtration, dried in vacuo and characterized. Yield: 78% (3.79 g), mp: 152-153°C (dec.), $[\alpha]_D^{22} = -9.5°$ (c=0.2, MeOH). IR (KBr); $\nu$=3190-2400 (broad, amine salt), 1740 cm$^{-1}$ (ester carbonyl). $^1$H-nmr ($CDCl_3$); $\delta$=7.55-7.05 (m, 15H, phenyl), 5.05, 4.95 and 4.30 (each s, 6H, three -$CH_2$Ph), 4.20 (t, J=5 Hz, 1H, -NCH-), 3.25 ppm (d, J=5 Hz, 2H, -$COCH_2$-).

**N-Benzyl-L-aspartic acid copper (II) complex copper (II) salt dihydrate (12).** Copper (II) acetate monohydrate (2.06 g, 10.3 mmol) was added to an hot (80°C) solution of N-benzyl-L-aspartic acid (**7**, 2.23 g, 10 mmol) in water (110 m*l*). The solution was cooled to rt and stirred for 2 days. The precipitate was collected by filtration, washed with water, ethanol, and diethyl ether, and dried at 50°C in vacuo. The blue crystalline product **12** was obtained in 83% yield (5.15 g). mp: 239-241°C(dec.), $[\alpha]_D^{20} = +133°$ (c=0.1, DMF). Anal. for Cu($C_{11}H_{13}NO_4$)$_2$·Cu·2$H_2O$; Calcd; **C**: 43. 64, H: 4.33, N: 4.63, Cu: 20.98, $H_2O$: 5.95, Found; C: 42.70, H: 4.50, N: 4.88, Cu: 19.80, $H_2O$: 6.60%.

**β-Benzyl N-benzyl-L-aspartate (11).** *Method* **1**. From Dibenzyl aster **10**: A solution of the HBr salt of dibenzyl N-benzyl-L-aspartate (**10**, 4.84 g, 10 mmol) in methanol (50 m*l*) was neutralized with triethylamine (1.01 g, 10 mmol) and hydrogenolized over 5% Pd-C (0.5 g) at the hydrogen pressure of 40 psi for 15 min. Triethylamine (1.01 g, 10 mmol) was added and the precipitate was filtered off. The pH was adjusted to 6.2 with 1N hydrochloric acid and the solution was kept at 0.5°C for 12 hr. The precipitate was collected by filtration and recrystallized from water. Yield 69% (2.16 g).

*Method* **2.** From the copper complex **12**: To a solution of the copper complex **12** (3.03 g, 5 mmol), and 1,1,3,3-tetramethylguanidine (1.15 g, 10 mmol) in DMF (60 m*l*), was added benzyl bromide (1.71 g, 10 mmol) and the solution was stirred at rt for 24 hr. A solution of EDTA disodium salt (10 g, 20 mmol) in water (300 m*l*) was added and the mixture was stirred for 24 hr. The precipitate was collected by filtration and recrystallized from water. Yield: 83% (2.60 g), mp: 224-226°C, $[\alpha]_D^{20} = +13.5°$ (c=0.15, 1N HCl). IR (KBr); $\nu$=1740 $cm^{-1}$ (ester carbonyl). $^1$H-nmr ($CF_3COOH$); $\delta$=7.30-7.00 (m, 10H, phenyl), 4.75 (s, 2H, -$OCH_2$-), 4.35-4.00 (m, 3H, -COCH-, -$NCH_2$-) 3.05 ppm (d, J=5 Hz, 2H, -$COCH_2$-).

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# Turbidimetric and Nephelometric Studies on Aggregation of Cationic-Anionic Surfactants†

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The aggregation between cationic and anionic surfactants was studied by turbidimetric and nephelometric methods with emphasis on facile analysis of the surfactants and understanding of the mixed micellization. The turbidimetric titration of sodium dodecylsulfate (SDS) with cetyltrimethylammonium bromide (CTAB) or cetylpyridinium bromide (CPB) showed maximum turbidity at equimolar composition in the SDS concentration range of 0.1-0.9mM. The nephelometric titration of the same systems extended the limit of analysis to 0.001mM. The sodium salts of decylsulfate and sulfonate gave similar maxima, but not at equimolar composition. The coexistence of equimolar aggregates and mixed micelles were shown over broad composition range. The aggregation and mixed micellization of the anionic/cationic surfactants mixtures depended sensitively on the hydrophobic character of the surfactants.

## Introduction

Ionic surfactants are widely used in both industrial and domestic applications, and drained into neighboring rivers. The analysis of the surfactants in the environmental water can be a mean for monitoring water pollution from domestic waste water.

Two analytical methods are most frequently used for the determination of ionic surfactants. One is "two phase titration" which is based upon stoichiometric reaction between cationic and anionic surfactants.[2-4] The cationic-anionic surfactants aggregates are either insoluble or sparingly soluble in water, but readily soluble in organic solvent. Chlorinated hydrocarbons such as chloroform are typically utilized. Also mixed indicators e.g. dimidium bromide and disulfine blue VN 150 are commonly used for visual end point detection. The other method is spectrophotometric determination after extracting the oppositely charged surfactant-dye complexes with organic solvent.[5-7] These methods can be very precise when they are strictly applied, but they are basically liquid-liquid extraction of cationic/anionic complexes, of which efficiency is effected by experimental manipulation and this has an effect upon the final result. Also the requirement of controlled pH due to the use of dyes and environmental hazard in the laboratory arised from uses of organic solvent are disadvantages of these methods.

The above mentioned analytical methods are based on the aggregation phenomena of surfactant ions with oppositely charged other surfactant ions or dyes. The aggregation can be utilized directly for the analysis of ionic surfactants by turbidimetric and/or nephelometric method. However, little is known on the scope and limitation in analysis.[8] Furthermore, the formation of mixed micelles from surfactant mixtures is of great current interest.[9-11] In this paper, we present the results of the turbidimetric and nephelometric studies on the aggregation of cationic-anionic surfactants in views of facile analysis of ionic surfactants and understanding of mixed micelle formation from cationic-anionic surfactants mixtures.

## Experimental

Sodium salts of dodecylsulfate (SDS), decylsulfate (SDeS) and decylsulfonate (SDeSo), and Triton X-100 were obtained

† Part III of the series on the studies on the formation and stability of colloids. Part II; *Bull. Kor. Chem. Soc.*, **8** (2), 118 (1987).