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Selective Esterification of N-Benzyl-L-aspartic Acid. (I). Some Modified Methods for the Preparation of N-Benzylaspartic Anhydride Hydrobromide

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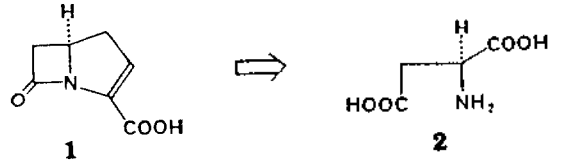
Racemic N-benzylaspartic acid (**4**) was prepared from maleic anhydride and used to modify and develop some efficient methods for the preparation of N-benzylaspartic anhydride hydrobromide (**5**). Thus, successive treatment of the compound **4** with 30% HBr in acetic acid and acetic anhydride afforded the title compound **5** in 75% yield. From this compound **5**, α-benzyl and α-methyl N-benzylaspartates were also prepared.

Introduction

The recently discovered carbapenems (**1**, derivatives of (5R)-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid)[1] possess the characteristic (5R)-configuration, which can be derived from naturally occurring L-aspartic acid (**2**). Thus far several reports[2] have described the elaboration of β-lactam rings from L-aspartic acid.



1 **2**

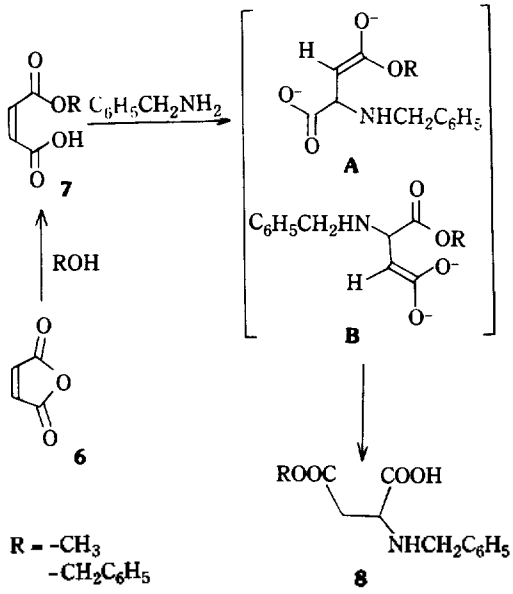
Intramolecular cyclization of α-alkyl L-aspartates, the β-amino acids, gives rise to 4-substituted β-lactams possessing the correct stereochemistry at 4-position, which corresponds to the (5R)-configuration of carbapenems.

These α-alkyl L-aspartates are readily available by the alcoholysis[3] of L-aspartic anhydride hydrobromide (**3**). The compound **3** has thus far been prepared by deprotection of N-benzyloxycarbonyl-L-aspartic anhydride with 30% HBr in acetic acid[3], by direct dehydration of L-aspartic acid with thionyl chloride in trifluoroacetic acid followed by the treatment with HBr in acetic anhydride[4], and by direct dehydration and salt formation of L-aspartic acid with PBr_3 in THF[5].

In this paper, we would like to report the modified methods for the preparation of N-benzylaspartic anhydride hydrobromide (**5**) from N-benzylaspartic acid (**4**) and the synthesis of α-and β-esters of N-benzylaspartic acid.

Results and Discussion

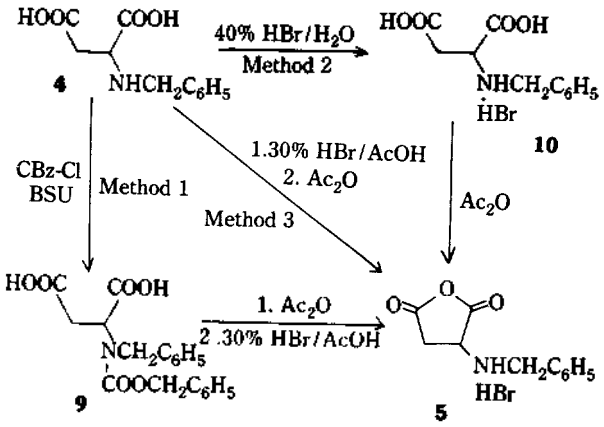
Alcoholysis of maleic anhydride (**6**) in methanol or benzyl alcohol produced in excellent yield methyl maleate (**7a**) or benzyl maleate (**7b**), which was treated with benzylamine to obtain the Michael-type addition products. The addition reaction proceeded by attacking β-position to the ester group rather than that to the free carboxylic acid, affording in excellent yield β-methyl N-benzylaspartate (**8a**)[6] or β-benzyl N-benzylaspartate (**8b**), respectively. This regioselectivity would probably be derived from the greater stability of the generated dianion **A** compared to that of the dianion **B**, in which the negative charges are accumulated (see Scheme 1). Hydrolysis of the ester groups of the compounds **8a** and **8b** gave rise to racemic N-benzylaspartic acid (**4**).



Scheme 1. Synthesis of β-Alkyl N-Benzylaspartates

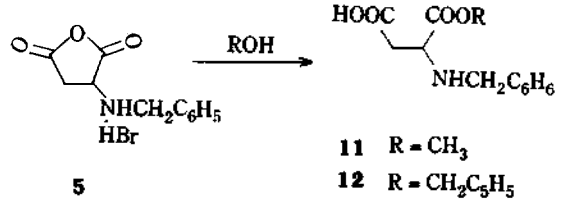
By using this racemic N-benzylaspartic acid (**4**), we have modified and developed an efficient method for the preparation of N-benzylaspartic anhydride hydrobromide (**5**). First, we have exactly followed Kovacs' procedure[3] for the preparation of L-aspartic anhydride hydrobromide (**3**) from L-aspartic acid (**2**). Thus, N-benzyloxycarbonyl-N-benzylasparic acid (**9**) was prepared from N-benzylaspartic acid (**4**) and treated with acetic anhydride. Without any purification, the N-benzyloxycarbonyl group of the resulting anhydride was removed with 30% HBr in acetic acid to produce N-benzylaspartic anhydride hydrobromide (**5**) in 69% overall yield (see Method 1 of Scheme 2).

In Kovacs' procedure[3], the reactive amino group was first deactivated with benzyloxycarbonyl unit and then removed with HBr in acetic acid after the anhydride formation. From this point of view, we deactivated the amino group of N-benzylaspartic acid (**4**) through the formation of HBr salt. Treatment of the compound **4** with 40% hydrobromic acid and water removal afforded N-benzylaspartic acid hydrobromide (**10**), which was dehydrated with acetic anhydride at 35°C. This procedure gave the same N-benzylaspartic anhydride hydrobromide (**5**) in 77% overall yield (see Method 2 of Scheme 2).



Scheme 2. Synthesis of N-Benzylaspartic Anhydride Hydrobromide

In method 2, water had to be removed after the formation of HBr salt. By employing Kovacs' deprotection reagent (30% HBr in acetic acid) instead of 40% hydrobromic acid, however, one-pot reaction could be feasible. Thus, N-benzylaspartic acid (**4**) was treated with equimolar amounts of 30% HBr in acetic acid with vigorous stirring and without separation of the resulting hydrobromide salt **10**, the mixture was reacted with 2.5 equivalents of acetic anhydride at 35°C for 3 hr. Usual work-up then produced N-benzylaspartic anhydride hydrobromide (**5**) in 75% yield (see Method 3 of Scheme 2).



Scheme 3. Synthesis of α-Alkyl N-Benzylaspartates

Alcoholysis of the hydrobromide **5** with methanol or benzyl alcohol then afforded α-methyl N-benzylaspartate (**11**) and α-benzyl N-benzylaspartate (**12**), respectively (see Scheme 3). The chemical shifts of the methyl protons of α-and β-methyl N-benzylaspartates (**8a** and **11**), and of the methylene protons of the benzyl group of α- and β-benzyl N-benzylaspartates (**8b** and **12**) are clearly differentiated; α-esters show the chemical shifts at the downfields (methyl protons at δ3.82 ppm and methylene protons of the benzyl group at 5.00 ppm) compared to those of β-esters (δ 3.40 and 4.75 ppm, respectively), probably due to the distance effects of the electronegative nitrogen atoms.

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 (60 MHz) nmr spectrometer. The internal standard was TMS in organic solvent or DSS in D_2O.

Monobenzyl maleate (7b). A solution of equimolar amounts of maleic anhydride and benzyl alcohol was stirred at 70°C for 2 hr and cooled to rt. The resulting solid was dissolved in methanol and treated with cold water. The colorless solid was collected by filtration and dried in vacuo. Yield: 95%, mp; 52-54°C. ^{1}H-nmr ($CDCl_3$); δ = 11.5 (broad, 1H, COOH), 7.25 (s, 5H, phenyl) 6.25 (s, 2H, -CH=CH-), 5.15 ppm (s, 2H, -OCH_2-). IR (KBr); ν = 1720 cm^{-1} (ester).

β-Benzyl N-benzylaspartate (8b). To a solution of monobenzyl maleate (**7b**, 10.3g, 50 mmol) in pyridine (10 m*l*), was added dropwise benzylamine (5.35g, 50 mmol) with maintaining the temperature below 40°C. The mixture was refluxed for 1 hr, cooled to rt and treated with methanol (50 m*l*). The colorless solid was collected by filtration and recrystallized from water. Yield: 76% (11.9g), mp: 224-226°C. ^{1}H-nmr (CF_3COOH); δ = 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 = 5Hz, 2H, -$COCH_2$-). IR (KBr); ν = 1740 cm^{-1} (ester).

β-Methyl N-benzylaspartate (8a). A solution of maleic anhydride (4.90g, 50 mmol) in methanol (15 m*l*) was refluxed for 30 min and methanol was evaporated. The residue was dissolved in pyridine (10 m*l*) and benzylamine (5.35g, 50 mmol) was added. The solution was refluxed for 1 hr, cooled to rt, treated with methanol (20 m*l*), and the precipitate was collected by filtration. Recrystallization from water afforded colorless solid. Yield: 65% (7.71g), mp: 219-221°C (lit[6]: 109°C). ^{1}H-nmr (CF_3COOH); δ = 7.05 (s, 5H, phenyl), 4.05 (s, 2H, -NCH_2-), 3.90 (t, J = 5Hz, 1H, -COCH-), 3.40 (s, 3H, -OCH_3), 2.85 ppm (d, J = 5Hz, 2H, -$COCH_2$-). IR (KBr); ν -1740 cm^{-1} (ester).

N-Benzylaspartic acid (4). A solution of β-benzyl N-benzylaspartate (**8b**, 3.13g, 10 mmol) or β-methyl N-benzylaspartate (**8a**, 2.37g, 10 mmol) in 1N aqueous sodium hydroxide (20m*l*) was refluxed for 3 hr, cooled to rt. acidified to pH 3 with 6N hydrochloric acid, and stirred at 0-5°C for 2 hr. The precipitate was collected by filtration and recrystallized from water. Yield: 91% (2.03g), mp: 210-212°C. ^{1}H-nmr (CF_3COOH); δ = 7.25 (s, 5H, phenyl), 4.25 (s, 2H,

-NCH_2-), 4.18 (t, J=5Hz, 1H, -NCHCO-), 3.10 ppm (d, J=5Hz, 2H, -$COCH_2$-). IR (KBr); ν=3200-2500 (broad), 1720 cm^{-1} (acid carbonyl).

N-Benzyloxycarbonyl-N-benzylaspartic acid (9). A suspension of N-benzylaspartic acid (**4**, 11.2g, 50 mmol) and 1,3-bis (trimethylsilyl)urea (BSU, 10.2g, 50 mmol) in dichloromethane (100 m*l*) was refluxed for 30 min and cooled to 0°C. Triethylamine (10.1g, 100 mmol) was added followed by benzyl chloroformate (8.53g, 50 mmol) and the solution was stirred at rt for 5 hr. Ten % aqueous sodium carbonate solution (100 m*l*) was added and the aqueous layer was separated, washed successively with ethyl acetate and diethyl ether, and acidified to pH 2 with 6N hydrochloric acid. Extraction with ethyl acetate and evaporation afforded 16.4g (92% yield) of colorless solid, mp: 113-115°C. ^{1}H-nmr (acetone-d_6); δ=7.60 (s, 5H, phenyl), 6.50 (s, 5H, phenyl), 3.75-3.30 (m, 5H, two -CH_2-, -COCH-), 2.55 ppm (d, J=5Hz, 2H, -CO_2CH_2-). IR (KBr); ν=3500-2500 (broad), 1715 (acid carbonyl), 1650 cm^{-1} (amide carbonyl)

N-Benzylaspartic acid hydrobromide (10). N-Benzylaspartic acid (**4**, 2.23g, 10 mmol) was dissolved in 40% hydrobromic acid (2.02g, 10 mmol) and water was evaporated in vacuo. The pale yellow solid was obtained in quantitative yield, mp: 198°C. ^{1}H-nmr (D_2O); δ=7.00 (s, 5H, phenyl), 4.00 (s, 2H, -NCH_2-), 3.90 (t, J=5Hz, 1H, -COCH-), 2.80 ppm (d, J=5Hz, 2H, -$COCH_2$-). IR (KBr); ν=2500-3500 (broad), 1710 cm^{-1} (acid carbonyl).

N-Benzylaspartic anhydride hydrobromide (5). Method 1; From N-benzyloxycarbonyl-N-benzylaspartic acid (**9**): A solution of N-benzyloxycarbonyl-N-benzylaspartic acid (**9**, 10.7g, 30 mmol) in acetic anhydride (50 m*l*) was stirred at 35°C for 3 hr and 30% HBr in acetic acid (20.2g, 75 mmol) was added. The solution was stirred at rt for 2 hr and treated with diethyl ether. The precipitate was collected by filtration and dried in vacuo over P_2O_5. Yield: 75% (6.44g), mp: 178-180°C. ^{1}H-nmr (DMSO-d_6); δ=10.50 (broad, -NH_2-), 7.20 (s, 5H, phenyl), 4.55 (t, J=5Hz, 1H, -NCH-), 4.20 (s, 2H, -NCH_2-), 3.25 ppm (d, J=5Hz, 2H, -$COCH_2$-). IR (KBr); ν=1875, 1805 cm^{-1} (anhydride carbonyl).

Method 2; From N-benzylaspartic acid hydrobromide (**10**): A solution of N-benzylaspartic acid hydrobromide (**10**, 15.2g 50 mmol) in acetic anhydide (20 m*l*) was stirred at 35°C for 3 hr and treated with diethyl ether (30m*l*). The precipitate was collected by filtration and dried in vacuo over P_2O_5. Yield: 77% (11.0g).

Method 3; From N-benzylaspartic acid (**4**): To a solution of N-benzylaspartic acid (**4**, 11.2g, 50 mmol) in acetic acid (10 m*l*), was added 30% HBr in acetic acid (13.5g, 50 mmol) with vigorous stirring. Acetic anhydride 12.5g (122 mmol) was added and the solution was stirred a 35°C for 3hr. Treatment of the solution with diethyl ether (50 m*l*) produced solid product which was collected by filtration and dried in vacuo over P_2O_5. Yield: 75% (10.7g).

α-Methyl N-benzylaspartate (11). A solution of N-benzylaspartic anhydride hydrobromide (**5**, 7.72g, 27 mmol) in dry methanol (120m*l*) was stirred at rt for 3 hr and triethylamine (2.73g, 27 mmol) was added at 0°C. The slurry was stirred at 0°C for 2 hr and the precipitate was collected by filtration and recrystallized from water. Yield: 73% (4.68g), mp: 156-158°C. ^{1}H-nmr (CF_3COOH); δ=7.00 (s, 5H, phenyl), 6.05 (s, 2H, -CH_2N-) 3.85 (s, 3H, -OCH_3), 2.95 ppm (d, J=5Hz, 2H, -$COCH_2$-). IR (KBr); ν=3100-2500 (broad), 1740 (ester carbonyl).

α-Benzyl N-benzylaspartate (12). A solution of N-benzylaspartic anhydride hydrobromide (**5**, 7.72g, 27 mmol) in dry benzyl alcohol (150m*l*) was stirred at rt for 12 hr and treated with triethylamine (2.73g, 27 mmol). Methanol was added 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: 77% (6.52g), mp: 127-130°C. ^{1}H-nmr (CF_3COOH); δ=7.00 (s, 10H, phenyl), 5.00 (s, 2H, -OCH_2-), 4.20 (s, 2H, -NCH_2-), 3.95 (t, 1H, -COCH-), 3.10 ppm (d, J=5Hz, 2H, -$COCH_2$-). IR (KBr); ν=3100-2500 (broad), 1760 cm^{-1} (ester carbonyl).

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