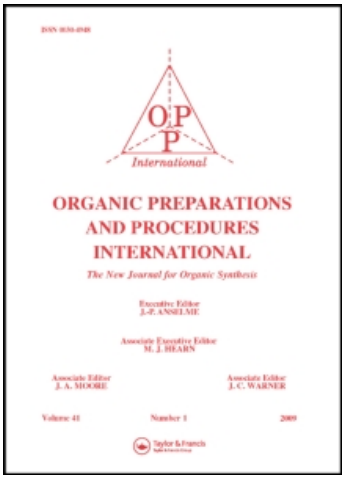

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D-α-AMINOADIPIC ACID FROM CEPHALOSPORIN C

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D-α-AMINOADIPIC ACID FROM CEPHALOSPORIN C

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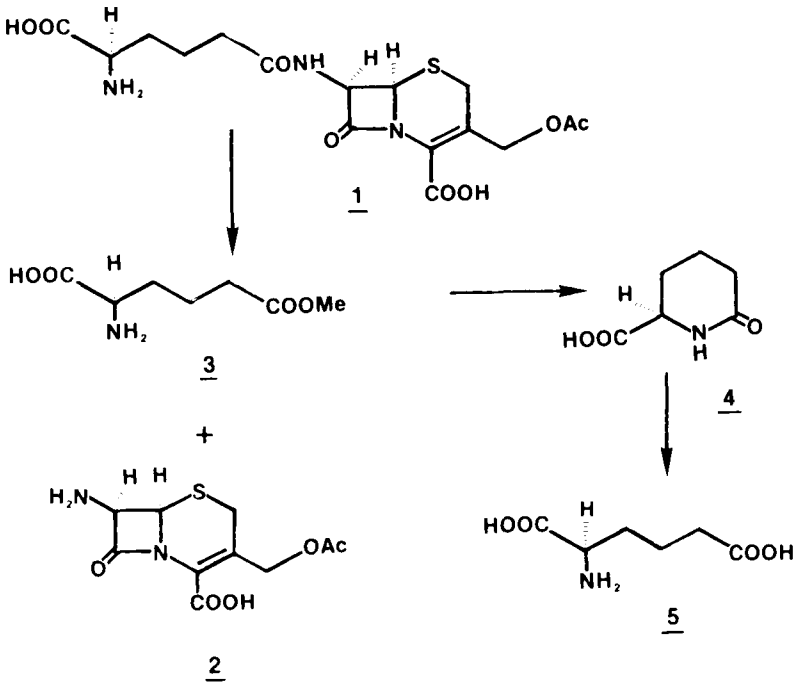
In connection with ongoing work, an efficient method was needed to prepare large quantities of D-α-aminoadipic acid (5). Interest in 5 stems from its implication in the biosynthesis of cephalosporins and penicillins.[1] In addition, it was recently reported that 6-oxo-piperidine-2-carboxylic acid, the lactam of racemic 5, is produced in substantial amounts in commercial penicillin fermentations.[2] The classical method[3] for the preparation of 5 involves an enzymatic resolution which is inefficient and unreliable, especially on a large scale. Syntheses of L-α-aminoadipic acid from L-lysine or L-aspartic acid have been reported,[4,5] but are impractical for the preparation of 5 due to the difficulty in obtaining sufficient quantities of the corresponding D-aminoacids. A method for resolving 6-oxo-piperidine-2-carboxylic acid *via* quinine salts is also known.[6] However, the low concentrations required to selectively crystallize the salt of the D-isomer render this methodology unsuitable for large scale.

Cephalosporin C (1) provides an excellent potential source of 5 since it contains this moiety as a removable side-chain. Utilizing the well-known chemical deacylation technology used to prepare commercial quantities of 7-aminocephalosporanic acid (2),[7] we developed a practical procedure for preparing 5 from the filtrate obtained after



separating 2 from the reaction mixture. Treatment of the filtrate with base (pH 10) converts D-α-aminoadipic acid methyl ester (3), the product from the deacylation reaction, to D-6-oxo-piperidine-2-carboxylic acid (4).[8] Compound 4 is then extracted from the aqueous solution with n-butanol[9] and, after solvent removal, crystallized from water in 48% yield based on cephalosporin C. Hydrolysis of 4[3] gives good quality 5 in 92% yield. Attempts to hydrolyze 3 or 4 in situ and isolate 5 directly have provided poor quality material in low yield. The isolation of unchanged 3 also proved to be impractical due to its instability under the conditions necessary to purify the complicated mother liquor.

EXPERIMENTAL SECTION

D-6-oxo-piperidine-2-carboxylic Acid (4).- The deacylation of cephalosporin C was conducted as described in the literature[10,11] with minor

modifications. To a suspension of 80 g (162.4 mmoles) of cephalosporin C sodium salt (88.8% purity) in 910 ml methylene chloride at 20° was added 171.6 ml of N,N-dimethylaniline and 182.5 ml of chlorotrimethylsilane over 15 min. During the addition of the latter compound, the temperature rose to 38°. The mixture was stirred for 45 min, cooled to -60°, and then treated with 21.5 g of phosphorous pentachloride. After vigorous stirring at -40° for 2.5 hrs, the mixture was cooled to -70° and 282 ml of methanol was added over 15 min while the temperature was mainted below -40°. After stirring at -40° for 2 hrs, 715 ml of water and 358 ml of methanol was added over 15 min. During the methanol addition, the temperature was maintained below -5°. The layers were allowed to separate and the pH of the aqueous phase was adjusted to 3.5 by dropwise addition of 10M NaOH upon which crystallization commenced. After stirring for 45 min at ambient temperature, the crystals were collected by filtration, washed with acetone, and dried to give 34.6 g (78%) of 7-aminocephalosporanic acid (2).

The mother liquor, which contained D-α-aminoadipic acid methyl ester (3),[8] was adjusted to pH 10.0 by the dropwise addition of 10M NaOH and the mixture was stirred at room temperature for 16 hrs. The mixture was then extracted twice with 200 ml portions of methylene chloride and the pH of the resultant aqueous solution adjusted to 2.0 by the dropwise addition of 12N HCl. The solution was condensed *in vacuo* to about 400 ml and extracted with five 400 ml portions of *n*-butanol. The combined extracts were treated with 0.5 g of activated charcoal and after filtration, the solvent was evaporated *in vacuo*. The oily residue was dissolved in 25 ml 80° water, the solution seeded, and allowed to cool to room temperature upon which crystallization commenced. The mixture was kept at 0-5° for 16 hrs and the solid col-

lected by filtration, washed with 3.0 ml of ice water, and dried in a vacuum oven at 40° to give 11.18 g (48%) of the title compound, mp 125-128°. $[\alpha]_D$ = -38.5 (2% in 6N HCl) [lit.[3] $[\alpha]^{25}_D$ = -41.5° (2% in 6N HCl)]; ^{1}H nmr (DMSO-d_6): δ 1.52-2.05 (m, 4, 2 CH_2's), 2.15 (t, 2, $COCH_2$), 3.97 (m, 1, alpha proton), and 7.57 ppm (d, 1, NH); ^{13}C nmr (DMSO-d_6): δ 173.9, 170.6, 53.9, 31.1, 25.2, and 18.7 ppm.

For elemental analysis 5.0 g was recrystallized from 15 ml of water to give 4.52 g (81%) of crystalline monohydrate, mp 103-105°, Anal. Calcd. for $C_6H_9NO_3 \cdot H_2O$: C, 44.71; H, 6.88; N, 8.69; water, 11.18. Found: C, 44.36; H, 6.84; N, 8.59; water (KF), 10.57.

D-α-Aminoadipic Acid (5).- The hydrolysis of 4 was conducted as described in the literature.[3] To a solution of 1.43 g (10 mmoles) of 4 in 66.6 ml of water was added 33.3 ml of 6N HCl and the mixture refluxed for 2 hrs. After cooling to room temperature, the pH of the solution was adjusted to 3.0-3.5 with 10M NaOH. The mixture was cooled to 5° and stirred for 1.5 hrs. The separated crystals were collected by filtration, washed with 10 ml water, and dried in a vacuum oven at 40° to give 1.49 g (92%) of the title compound, mp. 205-205.5°; $[\alpha]^{25}_D$ = -25.7° (2% in 6N HCl) [lit.[3] $[a]^{25}_D$ = -25.0° (2% in 6N HCl)]; 'H nmr (D_2O-TFA): δ 1.62-1.88 (m, 2, CH_2), 1.88-2.15 (m, 2, CH_2), 2.50 (t, 2, CH_2CO_2H), and 4.12 (t, 1, alpha proton); ^{13}C nmr (D_2O-TFA): δ 178.0, 172.2, 53.5, 33.6, 29.8, and 20.5 ppm; Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.43; H, 6.86; N, 8.62. The material was homogeneous by HPLC (μBondapak-C_{18} 3.9 mm ID x 2.5 cm, 0.1% TFA in H_2O, 1 ml/min, UV 210 nm; retention time: 4.8 min).

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8. Compounds 2, 3, and 4 may be monitored by HPLC (μBondapak-C_{18} 3.9 mm ID x 25 cm, 0.1% AcOH in H_2O, 1 ml/min, UV 210 nm; retention times: 2, 9.0 mins, 3, 6.9 mins, and 4, 11.4 mins).

9. The partition coefficient of 4 between water and n-butanol is 1.4. Ethyl acetate, methylene chloride, or methylisobutylketone are not suitable solvents for this extraction.

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