One-Step Synthesis of α-Amido-α-methoxy-β-lactams as Cephamycin Analogs

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Activity against many gram negative bacteria and resistance to β-lactamases have placed cephamycins (1) in the category of valuable antibiotics. Two members (2, 3) of this family of antibiotics have already been introduced to medicine. More recently, sulfazecin (4) and related monobactam antibiotics have been discovered.

![Chemical structures of cephamycin and sulfazecin](image)

We were interested in preparing monocyclic and polycyclic analogs of cephamycins for X-ray diffraction studies and chemical reactivity measurements for a better understanding of the relationship between molecular and chemical parameters and biological activity. A number of methods have been devised for introducing a 7α-methoxy group in 7-aminocephalosporanic acid-type compounds. Christensen and coworkers have prepared α-azido-α-bromo-β-lactams as intermediates for the synthesis of 3-amino-3-methoxy-2-azetidinones. We have described earlier a one-step synthesis of 3-acetyl-3-aryl-2-azetidinones and 3-alkoxycarbonylaminom-2-azetidinones. Recently Gluchowski, Cooper, Bergbreiter, and Newcomb have prepared 3-amido-3-alkyl-2-azetidinones in one step.

We report here a convenient synthesis of 3-methoxy-3-amido-2-azetidinones by the annelation of Schiff bases. This method appears to be the first example of a one-step synthesis of β-lactams with the cephamycin-type side chain. The starting materials for our synthesis are the α-hydroxyhippuric acid derivatives (8) described by Zoller and Ben-Ishai. These compounds are prepared in high yield by the condensation of glyoxylic acid (6) with certain amides (5) and subsequent treatment of 7 with acidic methanol.

![Chemical structures of reaction intermediates](image)

When the diion 9 of 8 (R=C,H2), prepared by reaction with two equivalents of lithium diisopropylamide in tetrahydrofuran, was allowed to react with a Schiff base (10) from an aromatic aldehyde and an arylamine, a single isomer of a compound (11) was obtained in high yield. On the basis of spectral properties, the α-methoxy-α-amido-β-lactam structure was assigned to 11 and the alternative oxazolidinone structure (12) was eliminated.

We have noted previously that when the 3-methoxy group is cis to a phenyl group at C-4 in a β-lactam, the methyl signal in the N.M.R. spectrum resonates at δ = 3.20 ppm. The ring current of the phenyl group is responsible for this higher than normal chemical shift for the methyl protons; in contrast, the
methyl sig al of the 7α-methoxy group in cephamycins appears further downstream at δ = 3.52 ppm. On the basis of N.M.R. data for 11 and related compounds (Table) we can tentatively assign the (Z)-configuration to the β-lactam 11 (R = C₆H₅). Nuclear Overhauser effect studies on 11 did not provide any definitive information on its configuration. Single crystal X-ray analysis of 11 (R = Ar₁ = Ar₂ = C₆H₅) is in progress.

To obtain 4-lactams of type 11 but with other N-acyl groups in the side chain, it should be possible to react sequences in the literature. We have observed, however, that 8 (R = OCH₃) can also be used for 4-lactamization. This type of β-lactam provides easy access (by hydrolysis) to 3-amino-3-methoxy-2-azetidinones which can be acylated to other side chains of choice.

One of the limitations of this method appears to be the requirement that the Schiff base be derived from an aromatic amine and an aromatic aldehyde. Further work is in progress to extend the scope of this stereospecific synthesis of 3,3-disubstituted 2-azetidinones.

Melting points were determined in open capillary tubes using a Mel-Temp apparatus and are uncorrected. I.R. spectra were obtained with a Perkin-Elmer Infracord and Perkin-Elmer 247 grating spectrometers. H-N.M.R. spectra were recorded on a Varian EM 390 spectrometer in CDCl₃ solvents, at 7.54 mT. Mass spectra were obtained with a CIMS-Biospect (Scientific Research Institute) mass spectrometer using methane or ammonia as reagent gas.

Microanalyses were performed by Guelph Chemical Laboratories, Guelph, Canada and Schwarzkopf Microanalytical Laboratory, Inc., Woodside, New York.

Table. α-Amino-α-methoxy-β-lactams 11a–e prepared

<table>
<thead>
<tr>
<th>Product No.</th>
<th>R</th>
<th>Ar¹</th>
<th>Ar²</th>
<th>Yield [%]</th>
<th>m.p. [°C]</th>
<th>ν₁,₂,₃ [cm⁻¹] (β-lactam)</th>
<th>δOCH₃ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td></td>
<td></td>
<td></td>
<td>84</td>
<td>190–191°</td>
<td>1760</td>
<td>3.22</td>
</tr>
<tr>
<td>11b</td>
<td></td>
<td></td>
<td></td>
<td>88</td>
<td>223–224°</td>
<td>1750</td>
<td>3.28</td>
</tr>
<tr>
<td>11c</td>
<td>Cl</td>
<td></td>
<td>Cl</td>
<td>91</td>
<td>204–205°</td>
<td>1760</td>
<td>3.26</td>
</tr>
<tr>
<td>11d</td>
<td>CH₂OH</td>
<td></td>
<td>Cl</td>
<td>91</td>
<td>173–175°</td>
<td>1750</td>
<td>3.26</td>
</tr>
<tr>
<td>11e</td>
<td>CH₂OH</td>
<td></td>
<td>Cl</td>
<td>91</td>
<td>156–157°</td>
<td>1750</td>
<td>3.26</td>
</tr>
</tbody>
</table>

Methyl α-methoxyhippurate (R = C₂H₅) and methyl α-methoxy-N-benzoylcarbonylglucinate (R = C₆H₅CH₂O) were prepared from benzamide and benzyl carbamate, respectively, by the method of Zoller and Ben-Ishai.

**β-Lactams 11; General Procedure:** A solution of disopropylamine (2.2 g, 22 mmol) in anhydrous tetrahydrofuran (20 ml) is stirred under nitrogen atmosphere at ice bath temperature while a 1.5 molar hexane solution of n-butyllithium (14.7 ml, 22 mmol) is added dropwise over a 5 min period. The contents are stirred for an additional 15 min and cooled in a Dry ice/acetone bath. A solution of the appropriate α-methoxy-α-midoacetic acid ester (10 mmol) in dry tetrahydrofuran (20 ml) is added dropwise with stirring. After about 20 min, a solution of a Schiff base 10 (10 mmol) in dry tetrahydrofuran (20 ml) is added dropwise. Stirring is continued at −78°C for 4 h and then at room temperature for 10 h. The solvent is then evaporated under reduced pressure and the residue redissolved in dichloromethane (100 ml). This solution is washed with 10% acetic acid, water, saturated sodium hydrogen carbonate solution, brine and dried with magnesium sulfate. Evaporation of the dichloromethane gives the crude product which is chromatographed on silica gel with appropriate solvents.

**1,4-Diphenyl-3-benzoylamino-3-methoxyazetidin-2-one (11a):** Reaction of the diamion from methyl α-methoxyhippurate (2.23 g, 10 mmol) and benzaldehyde (1.81 g, 10 mmol) after chromatography on Davison silica gel (100–200 mesh) using chloroform/hexane (8:2) as eluent gives the title compound as a white solid; yield: 3.12 g (84%); m.p.: 190–191°C.

C₆H₅N₂O₃ calc. C 74.18 H 5.41 N 7.52 (372.4) found C 74.02 H 5.34 N 7.43

1R (nujol): ν = 3250, 1760, 1660 cm⁻¹

1H-N.M.R. (CDCl₃): δ = 3.22 (s, 3 H); 5.72 (s, 1 H); 6.7–8.3 ppm (m, 16 H).

E.I.M.S.: m/e = 372 (M⁺). C.I.M.S. (NH₃): m/e = 390 (M⁺ + NH₃)⁺, 373 (M⁺ + H)⁺.

1-(1-Naphthyl)-3-benzoylamino-3-methoxy-4-phenyl-azetidin-2-one (11b): The liithium enolate of methyl α-methoxyhippurate (2.23 g, 10 mmol) and N-benzylidene-1-naphthylamine (2.31 g, 10 mmol) affords the title compound as viscous oil. Trituration with ether and benzene (8:2) gives a white solid which on recrystallization from chloroform/hexane (1:1) gives the pure product; yield: 3.7 g (88%); m.p.: 223–224°C.

C₆H₅N₂O₃ calc. C 76.76 H 5.25 N 6.63 (422.5) found C 76.81 H 5.05 N 6.57

1R (nujol): ν = 3210, 1750, 1655 cm⁻¹

1H-N.M.R. (CDCl₃): δ = 3.28 (s, 3 H); 5.95 (s, 1 H); 7.0–8.25 ppm (m, 18 H).

C.I.M.S. (NH₃): m/e = 440 (M⁺ + NH₃)⁺, 423 (M⁺ + H)⁺.

1-Phenyl-3-benzoylamino-3-methoxy-4-(p-chlorophenyl)-azetidin-2-one (11c): Methyl α-methoxyhippurate (2.23 g, 10 mmol) is converted to the cor-
responding diamin and then allowed to react with p-chlorobenzylidenacine (2.16 g, 10 mmol) to yield the product as a flaky white solid (2.6 g) after trituration with ether and benzene (8:2). The filtrate is evaporated under reduced pressure to give a crude product which is chromatographed on Davison silica gel (100-200 mesh) with an eluent of chloroform/ethyl acetate (9:1) to afford an additional 1.1 g of the \( \beta \)-lactam; total yield of the compound: 3.7 g (91%); m.p. 204-205°C (chloroform/hexane).

\[
C_9H_7ClN_2O_4 \quad \text{calc.} \quad C \ 67.89 \quad H \ 4.71 \quad N \ 6.89
\]

\[
(406.9) \quad \text{found} \quad 68.06 \quad 4.61 \quad 7.07
\]

I.R. (nujol) \( \nu = 3250, 1760, 1650 \) cm\(^{-1}\).

1H-N.M.R. (CDCl\(_3\)) \( \delta = 3.26 \) (s, 3H); 5.69 (s, 1H); 6.9-8.15 ppm (m, 15H).

C.I.M.S. (-NH\(_3\)) \( m/e = 424, 426 \) (M + NH\(_3\))\(^+\); 407, 409 (M + H\(^+\)).

1-(1-Naphthyl)-3-benzoylcarbonylaminoo-3-methoxy-4-phenylazetidin-2-one (11f):

Methyl \( \alpha\)-methoxy-N-benzoylcarbonylglycine diamin (2.53 g, 10 mmol), prepared in situ, with \( N\)-benzylidene-1-naphthylamine (2.31 g, 10 mmol) gives the \( \beta \)-lactam as an oily residue. On trituration with ether and benzene (7:3) a flaky white solid is formed which on recrystallization from chloroform/hexane (1:1) gives the pure product; yield: 3.8 g (84%); m.p. 173-175°C.

\[
C_{12}H_{15}N_2O_4 \quad \text{calc.} \quad C \ 74.32 \quad H \ 5.35 \quad N \ 5.19
\]

\[
(452.5) \quad \text{found} \quad 74.14 \quad 5.16 \quad 6.10
\]

I.R. (nujol) \( \nu = 3250, 1750, 1675 \) cm\(^{-1}\).

1H-N.M.R. (CDCl\(_3\)) \( \delta = 3.22 \) (s, 3H); 5.21 (s, 2H); 5.85 (2, 1H); 6.21 (s, 1H); 7.2-8.15 ppm (m, 17H).

1-Phenyl-3-benzoylcarbonylaminoo-3-methoxy-4-(p-chlorophenyl)-azetidin-2-one (11e):

Methyl \( \alpha\)-methoxy-N-benzoylcarbonylglycine diamin (2.53 g, 10 mmol) is converted to the corresponding diamin and then allowed to react with \( p\)-chlorobenzylidenacine (2.16 g, 10 mmol) to give the crude product; yield: 4 g (91%), which is purified by passing through a column of Davison silica gel (100-200 mesh) using chloroform/ethyl acetate (9:1); and obtained as a white crystalline solid; m.p. 156-157°C.

\[
C_{16}H_{15}ClN_2O_4 \quad \text{calc.} \quad C \ 65.98 \quad H \ 4.85 \quad N \ 6.41
\]

\[
(436.9) \quad \text{found} \quad 65.86 \quad 4.84 \quad 6.38
\]

I.R. (nujol) \( \nu = 3280, 1750, 1680 \) cm\(^{-1}\).

1H-N.M.R. (CDCl\(_3\)) \( \delta = 3.26 \) (s, 3H); 5.15 (s, 2H); 5.52 (s, 1H); 6.8-7.5 ppm (m, 15H).

C.I.M.S. (-NH\(_3\)) \( m/e = 454, 456 \) (M + NH\(_3\))\(^+\); 437, 439 (MH\(^+\)).

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For example: Compound 8 (Ar\(^1\) = Ar\(^2\) = C\(_6\)H\(_5\)).

I.R. (nujol) \( \nu = 3250, 1760 \) (\( \beta \)-Lactam CO), 1660 cm\(^{-1}\) (\( =CON=\)).

1H-N.M.R. (CDCl\(_3\)) \( \delta = 3.22 \) (s, 3H, OCH\(_3\)); 5.72 (s, 1H, C\(_6\)-H): 6.7-8.03 ppm (m, 16H, aromatic and NH).

C.I.M.S. (-NH\(_3\)) as reagent gas: \( m/e = 390 \) (M + NH\(_3\))\(^+\); 373 (M + H\(^+\)).
