Synthetic Studies on 1,2-Dehydro-1-carbacephem Compounds

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7-Azido-1,2-dehydro-1-carbacephem 13 was efficiently synthesized by employing ketene-imine cycloaddition, intramolecular Horner-Emmons reaction and elimination of a phenylsulfoxide group or an ammonium group. 7-Acylamino 1,2-dehydro-1-carbacephem, 18 and 19, were obtained from 13. Infrared absorption frequencies of the β-lactam carbonyl in 1,2-dehydro-1-carbacephem compounds thus prepared are equal to or higher than those of the corresponding 1-carbacephem compounds. However, 18 and 19 exhibited very poor antibacterial activity.

Keywords β-lactam; carbacephem; 1,2-dehydro-1-carbacephem; ketene-imine cycloaddition; intramolecular Horner-Emmons reaction; infrared absorption; acylation; Michael addition

In the preceding paper13 we reported the first synthesis of optically active 3-H-1-carbacephem compounds 1 and an examination of their antibacterial activity. In the course of our extensive studies on the synthesis of carbacephem compounds we were interested in 1,2-dehydro-3-H-1-carbacephem compounds 2. The 1,2-dehydro-1-carbacephem nucleus is considered to have so great a ring strain as to increase the chemical reactivity of the β-lactam carbonyl14 toward nucleophiles, and this is expected to lead to an increased antibacterial activity. In addition, the 1,2-dehydro ring system is unique to the 1-carbacephem nucleus (it is not available in cephem or 1-oxacephem compounds).

The 1,2-dehydro-1-carbacephem compound 3 was first synthesized by Doyle et al.15 and after the completion of our work4 by Uyoe and Ona5. The compounds with limited acyl groups synthesized by Uyoe and Ona have a common 3-CH3 group which is considered to diminish their antibacterial activities. In the preceding paper the favorable biological features of 3-H-1-carbacephem over the conventional 3-substituted methyl-1-carbacephem compound were demonstrated.13 We now wish to report the synthesis and antimicrobial activity of 1,2-dehydro-3-H-1-carba-
cephem compounds.

1,2-Dehydro-3-H-1-carba-cephem was divided into three
synthons, namely a C₃ unit with an amine precursor 4
(e.g. azidoacetyl chloride or phthalaldehyde chloride), tert-
butyl diethylphosphonoglycinate 5, and 4,4-dimethoxy-2-
butenal 6.

Although many methods are known for the preparation of
diethylphosphonoglycinate, except for the tert-butyl ester, none of them are suitable for a large-scale synthesis.
A practical synthesis of tert-butyl diethylphosphonoglycinate 5, which has played a significant role throughout our
carba-cephem project, was reported in a separate paper. 7

The aldehyde 6, prepared from furan in two steps, was
condensed with the amine 5 to give the Schiff’s base 7
quantitatively. Addition of azidoacetyl chloride to an ice-
cold solution of the Schiff’s base 7 and triethylamine in
benzene-cyclohexane resulted in stereoselective cyclod-
dition 8 to give the desired 3,4-cis-azetidinone 8. The acetal
9 was readily hydrolyzed to the corresponding carba-cephem 9
quantitatively.

Since the double bond of 9 adopts trans form, isomerization
to the cis form was examined. All attempts, however,
were unsuccessful. Conjugate addition of sodium thiophen-
nolate 9a) or preferably thionphenol with a catalytic amount of
piperidine 9b) to 9 gave 10 as a diastereomeric mixture. Cyclic
olefination of 10 was smoothly effected upon treatment with
sodium hydride or triethylamine to afford the bicycle products
11a and 11b as a mixture of C₁-stereoisomers in the ratio of ca. 2.5 : 1; these were easily separated by silica
gel column chromatography. In both isomers the coupling constant (5.0 Hz) between C₆-H and C₇-H was indicative of
the C₆=C₇ cis-stereochemistry. The coupling constant be-
tween C₆-H and C₀-H was 11.0 Hz for the major isomer
and, 3.0 Hz for the minor isomer. On the basis of Dreiding
models, the coupling constant of C₁-β-H is expected to be
larger than that of C₁-α-H. Thus, the major and minor
isomers can be assigned as the 1α-phenylsulfide 11a and the
1β-phenylsulfide 11b, respectively. Oxidation of 11a and
11b with m-chloroperbenzoic acid (MCPBA) or NaIO₄
afforded the corresponding sulfones 12a and 12b almost
quantitatively. The sulfone 12a was obtained as a mixture of
stereoisomers at the sulfur atom. Pyrolysis of 12a at
105—110°C gave the desired 1,2-dehydro-1-carba-cephem
13 in moderate yield. The ratios of elimination of the two
isomers of 12a were indistinguishable. In the case of the
sulfone 12b obtained as a single isomer, the elimination
was more smoothly effected upon heating at 70°C, to give
13 in fairly good yield. Prolonged reaction time decreased
the yield of 13. The objective 1,2-dehydro-1-carba-cephem
skeleton was thus synthesized through four steps from the
aldehyde 9 in 32% overall yield.

We also found a notably efficient alternative method for
the preparation of the 1,2-dehydro-1-carba-cephem 13
directly from the aldehyde 9. That is, treatment of the
aldehyde 9 with trialkylamine surprisingly afforded the 1,2-
dehydro-1-carba-cephem 13 in fairly good yield. Among
various bases examined for this novel type of cyclization
(Table 1), dimethylthanolamine and diazabicyclooctane
gave the most satisfactory results.

A possible reaction mechanism for the cyclization is
detailed in Chart 4, i.e., conjugate addition of an amine to the
aldehyde 9, followed by proton shift, Horner–Emmons
ring closure and subsequent elimination of amine, results in
the formation of the 1,2-dehydro-1-carba-cephem compound
13. Recently dimerization of α,β-unsaturated ketones and
nitriles catalyzed by diazabicyclooctane (DABCO) was suggested to involve the conjugate addition of
DABCO. 11 In this manner the target compound 13
became readily available. Since 13 can be easily reduced to
7-amino-3-H-1-carba-cephem 14, this method is also ef-
cient as an alternative synthetic method for the useful 3-
H-1-carba-cephem nucleus. Besides tert-butyl ester, tri-
chloroethyl and p-nitrobenzyl ester analogues of 13 were
similarly obtained from corresponding diethylphosphonoglycinate (Chart 5).

Hydrolysis of the tert-butyl ester of 13 with trifluo-
roacetic acid (TFA) gave the acid 15, which was reduced to
the zwitterionic amine 16a. Reduction of 13 with hydrogen
sulfide and triethylamine followed by hydrolysis of the ester
group with TFA also afforded 16b as the TFA salt.
Acylation of 16a with 2-thienylacetyl chloride gave the
corresponding amide 18. Similarly the amide 19 was ob-

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\text{Chart 4}
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\text{Chart 5}
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tained by acylation of 16b with 2-(2-chloroacetamidothiazol-4-yl)-2-syn-methoxyiminocacetyl chloride followed by de-protection. The amino ester 17 was acylated with Boc-(R)-phenylglycine by means of a mixed anhydride method to give the amide 20, but subsequent deprotection of the Boc group was unsuccessful.

As expected, the infrared (IR) absorption frequencies of the β-lactam carbonyl in 1,2-dehydro-1-carbacephem compounds are equal to or higher than those of the corresponding 1-carbacephem compounds as shown in Table II. However, 18 and 19 exhibited very poor antibacterial activity. The six-membered ring of 1,2-dehydro-1-carbacephem is nearly planar, being quite different from the cephem or 1-carbacephem ring system. This may imply the strict requirement of an appropriate molecular form (besides the reactive β-lactam ring) for the recognition of the β-lactam compound by target enzymes of the microorganism.

**Experimental**

IR spectra were measured with a JASCO IR-810, proton nuclear magnetic resonance (1H-NMR) spectra were measured on Varian T-60 and JEOL GNM PS-100 spectrometers, and mass spectra (MS) were measured with a JEOL JMS-01SG-I-2. Wako-gel C-200 was used for silica gel chromatography.

**Preparation of the Schiff's Base 7** tert-Butyl α-aminodiethyolphosphonooacetate 5 (1.80 g, 4 mmol) was dissolved in 100 ml of anhydrous CH₂Cl₂ and 4,4-dimethoxy-tranu-2-butenal 6 (580 mg, 4.4 mmol) dissolved in 20 ml of anhydrous CH₂Cl₂ was added thereto. The mixture was stirred at room temperature for 1 h. After addition of anhydrous MgSO₄ (600 mg), the resulting solution was filtered and the filtrate was evaporated under reduced pressure to obtain 1.63 g of an oily product. Yield 100%. NMR (CDCl₃) ppm: 8.00 (1H, d), 6.67 (1H, d), 4.93 (1H, d), 3.97—4.33 (4H, m), 3.33 (6H, s), 1.50 (9H, s), 1.33 (6H, t). MS m/z: 380 (M⁺+1).

**tert-Butyl (±)-2-[(cis-4-(3,3-Dimethoxy-1-propenyl)-3-azido-2-oxazolidin-1-yl)-2-diethylphosphonoacetate (8)** The Schiff's base 7 (39.2 g, 0.103 mol) was dissolved in 500 ml of anhydrous benzene and 500 ml of anhydrous cyclohexane and 21.2 ml (0.15 mol) of anhydrous triethylamine were added. To the mixture, azidoacetyl chloride (16.8 g, 0.14 mol) dissolved in 750 ml of cyclohexane was added dropwise slowly at 0°C over about 2 h. The mixture was further stirred at 0°C for 1 h. Benzene was added, and the reaction solution was washed with saturated NaHCO₃ and saturated NaCl. The resulting solution was dried over anhydrous MgSO₄ and concentrated under reduced pressure to obtain 45.5 g of a crude product. The product was purified by high performance liquid chromatography (HPLC) (System 500 n-hexane: AcOEt = 1:2) to obtain 30.9 g (70.7%) of the acetal compound 8. NMR(CDCl₃) ppm: 5.83—6.07 (2H, m), 4.50—5.00 (3H, m), 4.23 (4H, m), 3.33 (6H, s), 1.50 (9H, s), 1.37 (6H, s).
m. IR ν\text{\textit{cn}} em\text{-1}: 2120, 1780, 1745.

terr-Butyl (5R*,6S*,7S*)-7-Azido-oct-8-oxo-5-phenylthio-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (11a) A solution of 11a (71 mg, 0.06 mmol) in 170 ml of anhydrous dimethylformamide was reacted with 500 mg (12.4 mmol) of NaN₃ under ice-cooling. The mixture was stirred at 0°C for 30 min and at room temperature for 1 h. Then 100 mg of 60% NaH was added, and the mixture was stirred for a further 1 h at room temperature. AcOEt was added to the reaction solution and the mixture was washed with 8% HCl, saturated NaCl, and Na₂SO₄. The resulting solution was concentrated under reduced pressure to obtain 4.5 g of an oily product which was a mixture of stereoisomers at the 1-position of the desired compound.

The oily product was chromatographed (SiO₂; 160g; n-hexane: AcOEt = 1:2) to give the title compound 8.58 g (70.6%). IR ν\text{\textit{cn}} cm\text{-1}: 2120, 1780, 1735. MS m/z: 526 (M⁺).
27.2%. IR ν max cm⁻¹: 1790, 1780, 1695, 1655, 1630. NMR (CD₂OD) ppm: 7.2—7.3 (m, 1H), 6.93—6.97 (m, 2H), 6.72 (d, 1H, J = 5.8 Hz), 6.21 (ddd, 1H, J = 2.2, 5.8, 9.8 Hz), 5.89 (ddd, 1H, J = 1.5, 9.8 Hz), 5.72 (d, 1H, J = 4.6 Hz), 4.67—4.73 (m, 1H), 3.80 (s, 2H).

(6R,7S)⁻7-[2-(2-Amino-4-thiazolyl)-2-syn-methoxyminoacetamide]-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylic Acid (19) Triethylamine (45 μl) was added to a solution of 2-(N-chloroacetyl-2-amino-4-thiazoly)-2-syn-methoxyminoacetic acid (75 mg) in 1.4 ml of CH₂Cl₂, then 56 mg of PCl₅ was added and the mixture was stirred at room temperature for 30 min. After addition of 5 ml of n-hexane, the mixture was stirred and the supernatant was removed by decantation. To the residue, 2.7 ml of tetrahydrofuran was added. The mixture was added to a solution of 60 mg of 16b in 3 ml of 50% aqueous tetrahydrofuran and 120 μl of triethylamine under ice-cooling. The reaction mixture was stirred for about 2.5 h and acidified to a pH of 2 to 3 with 1 N HCl. The solution was extracted with AcOEt. The extract was washed with saturated NaCl, dried, and concentrated under reduced pressure. The residue was triturated with ether and 35 mg (39.0%) of N-protected acylated compound was obtained by filtration as a powder. IR ν max cm⁻¹: 1765, 1700—1710, 1690, 1660, 1550. NMR (CD₂OD) ppm: 7.50 (s, 1H), 6.8 (m, 1H), 6.1—6.4 (m, 2H), 5.9 (m, 1H), 4.3 (s, 2H), 4.0 (s, 3H).

The above product (15 mg) was dissolved in 0.3 ml of dimethylacetamide and 5.3 mg of thiourea was added. The mixture was stirred at room temperature for about 18 h. Ether was added to the mixture and the supernatant was removed by decantation. The residue was subjected to chromatography (HP-20 6 ml, H₂O:MeOH=4:1—1:1) to obtain 10.2 mg (77.2%) of the desired compound. IR ν max cm⁻¹: 1770, 1650—1670, 1630, 1540. NMR (D₂O) ppm: 7.05 (s, 1H), 6.54 (d, 1H, J=5.4 Hz), 6.25 (m, 1H), 6.06 (d, 1H), 5.85 (d, 1H, J=4.6 Hz), 4.01 (s, 3H).

References