THE SYNTHESIS OF A 6-CARBAMOYL SUBSTITUTED CARBAPENEM

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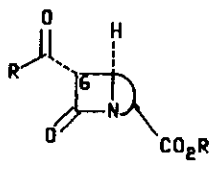
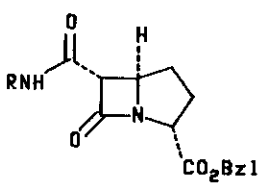
Abstract- A 6-(1-pyrrolidinylcarbonyl)substituted carbapenem was prepared. This compound has a half-life of 1.3 h (pH 7.4, 37°C) and exhibits moderate activity against Gram-positive bacteria.

Few examples of bicyclic ß-lactams which bear an acyl function adjacent to the ß-lactam carbonyl group, e.g. 1, have been reported.[1,2] This appears to be a result of the poor stability exhibited by this class of ß-lactams. For example, the carbapenam[1] (2) was described as being labile at room temperature and the thiopenam[2] (3) as only having a solution half-life of several hours at room temperature. Presumably this is why attempts to prepare the more strained carbapenem analog of 2 has not been described. Recent work[3] in these laboratories has provided us with access to the useful carbapenem precursor (5). We decided to see if the 6-carbamoyl-1-ß-methyl substituted carbapenem (13) could be prepared from 5 using the Merck carbapenem synthesis.[4] It was hoped that the presence of the 1ß-methyl group,[4] a feature which significantly increases the chemical stability of carbapenems, would impart a useful stability to 13. It was also decided to restrict this effort to the preparation of a 6-(1-pyrrolidinylcarbonyl)substituted carbapenem. This compound should possess a hydrogen atom at C-6 which is kinetically less acidic[5] and therefore would not participate in undesired side-reactions during transformations conducted under basic conditions.



(1)



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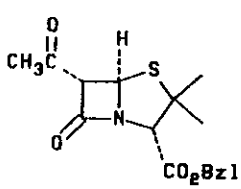

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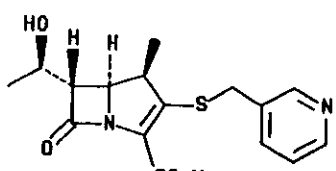
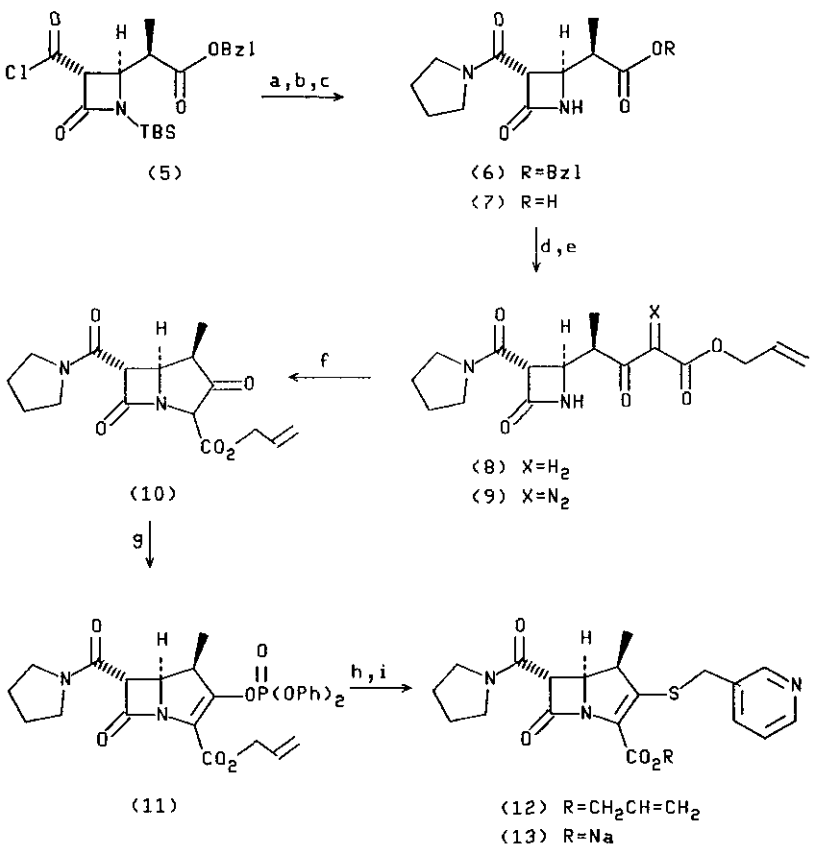


(4)

Reaction of the acid chloride (5) with excess pyrrolidine (Scheme I) followed by desilylation with TBAF afforded the 3-(1-pyrrolidinylcarbonyl)azetidinone (6). Hydrogenolysis of the benzyl ester (6) gave the carboxylic acid (7) which was converted to the ß-keto ester (8) using the procedure of Masamune.[4,6] Base-catalyzed diazotransfer proceeded smoothly to give

Scheme I[a]



(5)

(6) R=Bzl
(7) R=H

(8) $X=H_2$
(9) $X=N_2$

(10)

(11)

(12) $R=CH_2CH=CH_2$
(13) R=Na

[a] a. pyrrolidine, CH_2Cl_2 b. TBAF (67%) c. H_2,10%Pd-C, EtOAc(75%) d. imidazole, magnesium monoallyl malonate, MeCN(72%) e. toluenesulfonyl azide, TEA, MeCN(85%) f. Rh(octanoate)$_2$ dimer g. $ClPO(OPh)_2$, DIPEA, MeCN h. pyridin-3-ylmethanethiol, DIPEA i. PhNHMe, $Pd(PPh_3)_4$, PPh_3 then $NaHCO_3$ (7%)

the carbapenem precursor (9). The bicyclic ketone (10) was obtained by rhodium-catalyzed cyclization and was converted to the phosphate (11) under basic conditions. The latter reaction is noteworthy in that it was not complicated by the acidic hydrogen atom at C-6. Unfortunately, the next step, displacement of the phosphate group by ethanethiol, did not give rise to an isolatable carbapenem. It was assumed that this was due to both the substrate and the desired product being unstable and not surviving the relatively long time required for reaction between the phosphate and an alkanethiol. Upon turning to a more reactive thiol,[7] 3-picolylthiol, the carbapenem (12) was obtained. This compound was relatively unstable and chromatographic purification had to be conducted at low temperature so that product decomposition would not be too extensive. The final palladium-catalyzed removal of the carboxyl protecting group was conducted at ice-bath temperature and the impure acid 13 was isolated by reverse phase chromatography. A second chromatographic purification gave the final product which was still contaminated with a trace of an unidentified aromatic impurity. The half-life (pH 7.4, 37°C) of this 6-carbamoylcarbapenem is 1.3 h. This compares with a half-life of 65 h for the analogous carbapenem[8] (4) which bears the more common 1(R)-hydroxyethyl chain at position 6. The 6-carbamoylcarbapenem (13) exhibited moderate activity[9] against Gram-positive bacteria but was essentially inactive against Gram-negative bacteria. In summary, the first synthesis of a 6-carbamoylcarbapenem was achieved. However, due to the poor stability and <u>in vitro</u> antibacterial activity of this compound, further work in this area is not planned.

EXPERIMENTAL[10]

(3R,4S)-4-[(1R)-1-Carboxyethyl]-3-(1-pyrrolidinylcarbonyl)azetidin-2-one 7. A solution of (3<u>R</u>,4<u>S</u>)-4-[(1<u>R</u>)-1-benzyloxycarbonylethyl]-1-(<u>t</u>-butyldimethylsilyl)-3-chlorocarbonylazetidin-2-one[3] (5) (8.11 g, 19.8 mmol) in dry CH_2Cl_2 (40 ml) was cooled in an ice bath. Pyrrolidine (3.47 ml, 41.6 mmol) was then added dropwise with stirring. After 15 min, a solution of tetrabutylammonium fluoride (20.8 ml, 1.0 M in THF, 20.8 mmol) was added. After an additional 15 min, the reaction mixture was diluted with CH_2Cl_2 and H_2O. The pH of the aqueous phase was adjusted to 7.0 with aq. HCl (1N). Workup followed by chromatography afforded (3<u>R</u>,4<u>S</u>)-4-[(1<u>R</u>)-1-benzyloxycarbonylethyl]-3-(1-pyrrolidinocarbonyl)azetidin-2-one (6) as an oil (4.41 g, 67%): Rf 0.23 (EtOAc:hexane, 3:1); ir (film) 3200, 1765, 1735, 1625 cm^{-1};

^{1}H nmr ($CDCl_3$) δ 1.26 (d, J=7.0 Hz, 3H,), 1.90 (m, 4H), 2.80 (q, J=7.0 Hz, 1H), 3.23 (m, 1H), 3.43 (m, 2H), 3.85 (m, 1H), 4.07 (d, J=2.4 Hz, 1H,), 4.39 (dd, J=7.0, 2.4 Hz, 1H,), 5.11 (s, 2H), 6.05 (br s, 1H), 7.34 (m, 5H).

Hydrogenolysis (Parr apparatus, 45 p.s.i. H_2) of the benzyl ester (6) (723 mg, 2.19 mmol) with 10% Pd/C (70 mg) in EtOAc (60 ml) was allowed to proceed for 1.5 h. The catalyst was removed by filtration and was then washed with warm acetonitrile. Removal of the solvent from the combined filtrate and washings left the acid (7) (396 mg, 75%) as a solid which was crystallized from acetonitrile: mp 147-149°C; $[\alpha]_D^{24}$ + 125° (c 0.13, DMSO); ir (KBr disc) 3100, 1760, 1730, 1610 cm^{-1}; ^{1}H nmr (DMSO-d_6 + 1 drop D_2O) δ 1.05 (d, J=7.0 Hz, 3H,), 1.71-1.87 (m, 4H), 2.57 (dq, J=7.0, 8.2 Hz, 1H,), 3.24-3.67 (m, 4H), 3.88 (dd, J=2.2, 8.2 Hz, 1H,), 4.11 (d, J=2.2 Hz, 1H,). Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.97; H, 6.60; N, 11.31.

Sodium (4R,5S,6S)-4-methyl-7-oxo-3-(pyridin-3-yl-methylthio)-6-(1-pyrrolidinylcarbonyl)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (13). The acid (7) (1.50 g, 6.25 mmol) and carbonyldiimidazole (1.22 g, 1.2 equiv.) were suspended in dry acetonitrile (30 ml). After 1 h, magnesium monoallyl malonate (2.03 g, 1.05 equiv.) was added to the resulting solution and this was left for 20 h. Removal of the solvent left a gum which was dissolved in a mixture of EtOAc and H_2O. The pH of the aqueous phase was adjusted to 3.0 with aqueous HCl (1.0 N). The organic phase was separated and the aqueous phase was extracted with a little EtOAc. The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ and then brine. After the solution was dried (Na_2SO_4), the solvent was removed. Chromatography afforded (3R,5S)-4-[(1R)-3-allyloxycarbonyl-2-oxo-1-methylpropyl]-3-(1-pyrrolidinylcarbonyl)azetidin-2-one (8) (1.45 g, 72%) as an oil: Rf 0.41 (EtOAc:MeOH, 19:1); ir (film) 3240, 1755, 1710, 1630 cm^{-1}.

An ice-cooled solution of the ß-keto ester (8) (1.30 g, 4.04 mmol), toluenesulfonyl azide (0.62 ml, 1 equiv.) and TEA (0.56 ml, 1 equiv.) in dry MeCN (10 ml) was left for 1.5 h. Removal of the solvent followed by chromatography afforded (3R,4S)-4-[(1R)-3-allyloxycarbonyl-3-diazo-2-oxo-1-methylpropyl]-3-(1-pyrrolidinylcarbonyl)azetidin-2-one (9) (1.20 g, 85%) as a foam: Rf 0.70 (developed twice, EtOAc:MeOH, 19:1); ir (film) 3250, 2140, 1765, 1710, 1635 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.18 (d, J=7.0 Hz, 3H,), 1.94 (m, 4H), 3.47 (m, 3H), 3.99 (m, 2H), 4.05 (d, J=2.4 Hz, 1H,), 4.46 (dd, J=4.2, 2.4 Hz, 1H,), 4.73 (m, 2H), 5.35 (m, 2H), 5.95 (m,

1H), 6.04 (br s, 1H).

A solution of the diazo compound (9) (523 mg, 1.50 mmol) in a mixture of EtOAc (7 ml) and hexane (14 ml) was heated to a gentle reflux. Rhodium(II) octanoate (16 mg) was added and a vigorous evolution of gas ensued. After 2 min, the reaction mixture was cooled to room temperature. The solvent was removed to leave the crude bicyclic ketone 10 as an oil. This was taken up in dry MeCN (15 ml) and the resulting solution was cooled (ice bath). Chlorodiphenylphosphate (326 µl, 1.05 equiv.) and Hünig's base (275 µl, 1.05 equiv.) were added to generate the vinyl phosphate (11). After 50 min, pyridin-3-ylmethanethiol (205 µl, 1.2 equiv.) and Hünig's base (275 µl, 1.05 equiv.) were added. The reaction was then left for 45 min afterwhich it was poured into a stirred, ice-cooled mixture of EtOAc (75 ml), water (7 ml) and brine (7 ml). The organic phase was removed, dried (Na_2SO_4), and the solvents were removed. Flash chromatography [gradient elution with cooled mixtures (ca.-20°C) of EtOAc:hexane, 1:1 to EtOAc:MeOH, 9:1] gave the impure carbapenem (12) as an oil (403 mg): Rf, 0.14 (EtOAc:MeOH, 19:11).

The carbapenem (12) (403 mg) and N-methylaniline (103 µl, 1 equiv.) were dissolved in EtOAc (10 ml) and this solution was cooled in an ice bath. A solution of tetrakistriphenylphosphine palladium (0) (54 mg, 0.05 equiv.) and triphenylphosphine (54 mg, 0.05 equiv.) in CH_2Cl_2 (5 ml) was added. A precipitate formed within 5 min. After 1 h, cold water (10 ml) was added and the pH of the aqueous phase was adjusted to 7.0 by the addition of an aqueous solution of $NaHCO_3$ (0.05 M). The aqueous phase was removed and put under high vacuum to remove any residual organic solvents. This solution was then applied onto a medium pressure reverse phase column and eluted with ice-cooled solvent mixtures (H_2O to H_2O:MeCN, 9:1). Lyophilization of the desired fractions gave the impure carboxylate salt (13) (170 mg). This was rechromatographed to give purer material (38 mg, 7%) as a pale yellow powder: Rf 0.23 (reverse phase tlc; H_2O:MeCN, 19:1); uv (pH 7.4 phosphate buffer) 304 nm (ε=7,600); ir (KBr disc) 3420, 1755, 1610 cm^{-1}; ^1H nmr (D_2O) δ 1.23 (d, J=7.2 Hz, 3H,), 1.95 (m, 4H), 3.41 (m, 4H), 3.68 (m, 1H), 4.08 (d, J=14 Hz, 1H), 4.19 (d, J=14 Hz, 1H), 4.32 (dd, J=2.5, 9.0 Hz, 1H,), 4.50 (d, J=2.5 Hz, 1H), 7.20-8.54 (m, 4H, arom), 7.40 (m, ca. 1H, impurity).

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7 Under the conditions employed, a normal 1ß-methylsubstituted vinyl phosphate will react about ten times faster with a picolylthiol than with ethanethiol.

8 We thank P. Dextraze for data on the stability of this compound.

9 Representative minimum inhibitory concentrations (nutrient broth, µg/ml): S.pneumoniae A9585, 4; S. aureus A9537, 2; E. coli A15119,63. The hydroxyethyl analog (4) exhibited MIC values of 0.016 against each of these organisms. We thank J. Fung-Tomc for this data.

10 The equipment and general experimental procedures that were employed were the same as those described previously: H. Mastalerz, M. Ménard, V. Vinet, J. Desiderio, J. Fung-Tomc, R. Kessler, and Y. Tsai, J. Med. Chem., 1988, 31,1190.

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