A NEW CLASS OF PENEMS —C-2-*N*-SUBSTITUTED COMPOUNDS— SYNTHESIS AND ANTIBACTERIAL ACTIVITY

Sir:

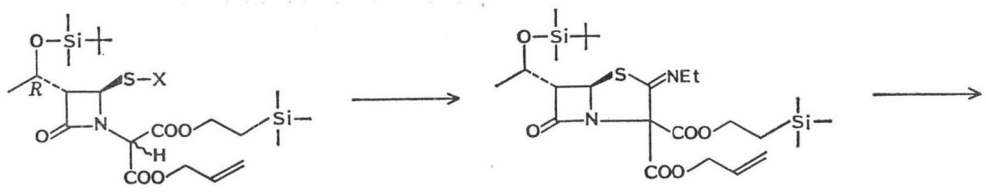
Penems are a novel class of highly active β-lactam antibiotics, extensively investigated for the past ten years. From a structure and activity point of view, presence of a hydroxyethyl substituent (6*S*,8*R*) at C(6) is well recognized to be beneficial for the β-lactamase stability and broad-spectrum activity of penems[1~3] and carbapenems[4]. A variety of substituents bearing a sulfur, carbon or oxygen at C(2) have been synthesized and their effect on the antimicrobial activity is readily available in the literature[5,5~7]. There is, however, little information forthcoming on the C(2)-nitrogen substituted penems. Here, we wish to report the synthesis and biological activities of C(2)-nitrogen linked penems.

Two types of compounds have been investigated in our laboratories, *viz* C(2)-mono-*N*-alkyl penems and C(2)-*N*-heterocyclic penems. The former was synthesized by employing a combination of previously reported procedures[8,9], Scheme 1.

The β-lactam thiol (**2**), obtained by treating the silver salt[9] (**1**) with H_2S, was reacted with dibromo-*N*-ethylketimine[8] in methylene chloride in the presence of triethylamine to afford the penam (**3**) (50% after HPLC). The allyl, 2-trimethylsilyl ethyl mixed esters are diastereomeric at C(3) and complicates the NMR data, the salient features of which are very similar to the di-trimethylsilyl ethyl ester. For simplicity the spectral data of the latter is given: NMR ($CDCl_3$) δ 5.35 (1H, d, J=1.5 Hz), 4.2~4.5 (5H, m), 3.5 (1H, dd, J=1.5, 6 Hz), 3.4 (2H, q), 1.15~1.45 (6H), 0.95 (9H, s), 0.1~0.05 (6H, 2s); FAB-MS m/z 617 $(M+1)^+$ (base peak). Treatment of (**3**) with tetrabutyl ammonium fluoride in THF effected the cleavage of both the silyl protecting groups with concomitant loss of CO_2 yielding the penem/penam allyl ester (**4**, **5**). Inseparable enamine - imine (1 : 1) mixture resulted in split peaks: salient peaks in the NMR ($CDCl_3$) δ 5.9 (1H, m), 5.4~5.5 (2d, J=1.5, 2 Hz, C(5)-H), 5.1~5.4 (2H, m), 4.6 (2H, m), 4.25 (1H, m), 3.5 (1H, dd, split), 3.45 (2H, m, split), 1.35 (3H, d, J=8 Hz), 1.2 (3H, t, split); FAB-MS m/z 299 $(M+1)^+$ (base peak). Deblocking the allyl group[10] using Pd^0 in the presence of sodium 2-ethyl hexanoate afforded the penem/penam sodium salt (**6**, **7**) (the free acid was found to decarboxylate spontaneously when 2-ethyl hexanoic acid was used): NMR (D_2O) δ 5.5 (1H, d, J=1.5 Hz), 4.4 (1H, m), 3.65 (1H, dd, J=1.5, 8 Hz), 3.4 (2H, q, br), 1.1~1.45 (6H); FAB-MS m/z 281 $(M+1)^+ + Na$, 215 $(M+1)^+ - COONa$.

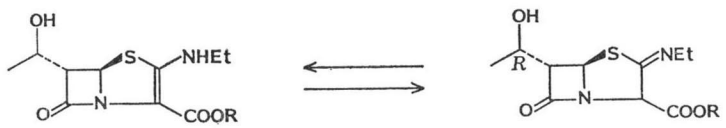
The C(2)-*N*-heterocyclic penems were made by the outlined general procedure in Scheme 2, exemplified by a 2-imidazol-1-yl penem. Reaction of the silver thiolate[11] (**8**) with an appropriate

Scheme 1.



1 X = Ag
2 X = H

3



4 R = Allyl
6 R = Na

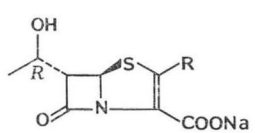
5 R = Allyl
7 R = Na

Table 1. *In vitro* antibacterial activity of selected penems.

Compound	Geometric mean MICs (μg/ml)*										
	Bacillus	*Escherichia coli*	*Entero-bacter*	*Kleb-siella*	*Morga-nella*	*Provi-dencia*	*Salmo-nella*	*Micrococcus*	*Serratia*	*Staphylo-coccus*	*Entero-coccus faecalis*
12a	0.12 (1)	0.94 (11)	2.5 (3)	1.1 (10)	4.0 (1)	3.0 (5)	0.63 (3)	0.12 (1)	6.7 (4)	0.21 (18)	4.0 (2)
12b	0.50 (1)	1.9 (11)	6.4 (3)	3.0 (10)	8.0 (1)	3.5 (5)	1.6 (3)	<0.02 (1)	16.0 (4)	0.30 (18)	5.7 (2)
12c	0.12 (1)	1.4 (11)	5.0 (3)	1.4 (10)	8.0 (1)	8.0 (5)	1.6 (3)	—	13.4 (4)	0.27 (17)	8.0 (2)
12d	0.06 (1)	0.94 (11)	5.0 (3)	1.1 (10)	8.0 (1)	4.6 (5)	1.6 (3)	—	9.5 (4)	0.06 (17)	2.8 (2)
12e	2.0 (1)	11.0 (11)	20.2 (3)	13.0 (10)	32.0 (1)	18.4 (5)	8.0 (3)	0.50 (1)	45.3 (4)	0.96 (18)	32.0 (2)
12f	0.06 (1)	0.68 (11)	3.2 (3)	0.81 (10)	2.0 (1)	2.3 (5)	0.50 (3)	—	5.7 (4)	0.12 (18)	5.7 (2)
12g	0.06 (1)	0.30 (11)	1.3 (3)	0.35 (10)	2.0 (1)	0.87 (5)	0.25 (3)	0.06 (1)	4.8 (4)	0.11 (18)	5.7 (2)

The figures in the parentheses indicate the number of strains examined.

* Mueller-Hinton agar, 24 hours.



12a ~ g

12a R = 

12b R = 

12c R = 

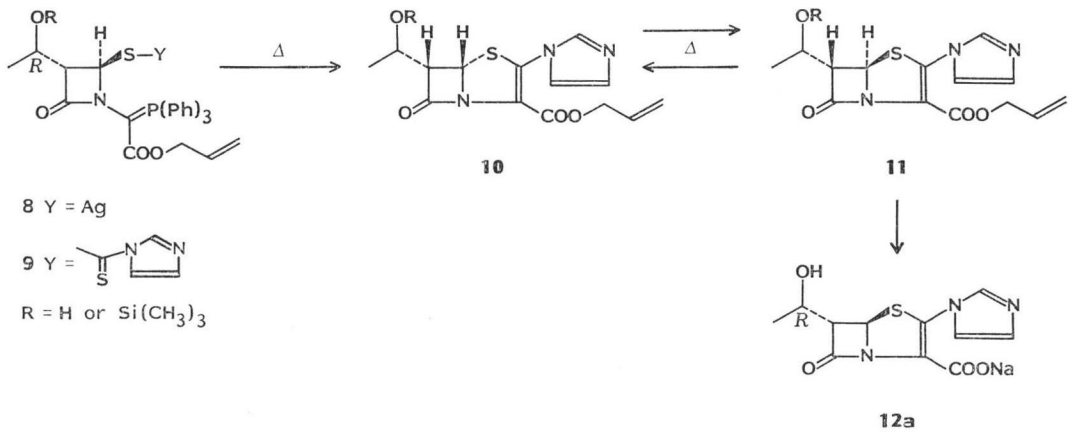
12d R = 
CH_2OH (4 or 5)

12e R = 
CH_3 (4 or 5)

12f R = CH_2OCONH_2
(FCE 22101)

12g R = $SCH_2CH_2OCONH_2$
(Sch 34343)

Scheme 2.



thiocarbonyl bis-heterocycle afforded the dithiocarbamate (**9**), which upon thermal cyclization yielded an isomeric mixture of *cis*/*trans* penems (**10**) and (**11**). The undesired *cis* isomer could be thermally isomerized[12,13] to the biologically active trans series.

Finally, Pd^0 catalyzed deblocking of the allyl protecting group[10] provided the corresponding penem carboxylates (**12a~e**) in good yield. **12a**: NMR (D_2O) δ 8.85 (1H, br s), 7.57 (1H, br s), 7.4 (1H, br s), 5.8 (1H, d, J=1.5 Hz), 3.8 (1H, dd, J=1.5, 8 Hz), 1.25 (3H, d, J=8 Hz); FAB-MS m/z 282 $(M+1)^+$.

Whereas the mono *N*-alkyl penem (**7**) turned out to be inactive in our tests (presumably due to the imine form, as well as decomposition under the test conditions), the *N*-heterocyclic penems (**12a~e**) were potent broad-spectrum antibiotics as compared to the activities of reference compounds FCE 22101 (**12f**) and Sch 34343 (**12g**) as shown in the Table 1.

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