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A NOVEL SYNTHESIS OF SUBSTITUTED 3-AMINOPENEMS

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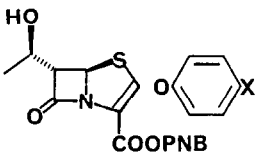
Summary: Displacement of phenol leaving groups at the C-3 position of penems by amines provides a general route to substituted 3-aminopenems

The penems, a group of highly active antibiotics, have been studied extensively over the last decade. High antibacterial activity and beta-lactamase stability in the penem series is provided by a 6-[1(R)-hydroxyethyl] group in the thienamycin-like 5,6-trans configuration. The C-3 position of the penems is more tolerant of substituent variation and a large number of penems bearing substituents bonded via sulphur[1], oxygen[2] and carbon[3] at this position have been prepared: several of these compounds are undergoing intensive study at present[4,5]. Conversely penem systems bearing substituents bonded through nitrogen at C-3 have received little attention[6a,b]. In this paper we describe a facile route to a range of these molecules.

As a result of other work in the penem area[2] a series of 3-aryloxypenems was available to us and we decided to investigate the possibility of using the phenol as a leaving group in such systems in an attempt to prepare 3-aminopenems. Displacements of leaving groups at the C-3 position of carbapenems is well known and has led to a range of molecules possessing sulphur side chains[7]; with one exception similar processes in penems have been little studied[8].

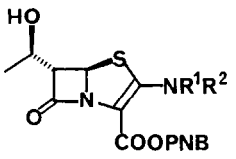
When the p-cyanophenoxypenem (1a) was treated with 1.05 equiv. of n-propylamine in DMF as solvent at room temperature a reaction occurred to liberate p-cyanophenol and form a slightly less polar product. Isolation of the product by silica gel chromatography afforded a golden yellow foam which was identified as the n-propylamino-penem (2a) on the basis of spectral data. The material exhibited infra-red absorptions (KBr disc) at 1780 and 1773 cm^{-1} and a ^1H n.m.r. spectrum which showed δ ($CDCl_3$) 8.22, 7.63 (4H, AA' BB', J=8.8Hz, Ar-H), 7.82 (1H, br, NH), 5.53 (1H,d,J=1.3Hz, H-5), 5.48, 5.16 (2H, ABq, J=14.2Hz,-CH_2Ar), 4.34-4.18 (1H, m, H-8), 3.61 (1H, dd, J=7.1, 1.3Hz, H-6), 3.33-3.10 (2H, m, -NHCH_2), 1.74 (1H,OH), 1.47 (2H, m,



(1)

a ; X = CN

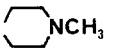
b ; X = NO_2



(2)

a ; R^1 = n-Pr, R^2 = H

b ; R^1 = CH_3, R^2 = H

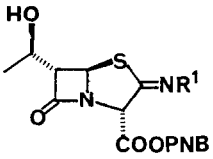
c ; R^1, R^2 = 

d ; R^1 = R^2 = CH_3

e ; R^1 = CH_3, R^2 = 

f ; R^1 = CH_3, R^2 = CH_2CO_2Et

g ; R^1 = Ph, R^2 = H



(3)

a ; R^1 = n-Pr

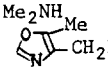
b ; R^1 = CH_3

g ; R^1 = Ph

$CH_2\underline{CH_2}CH_3$), 1.40 (3H, d, J=6.3Hz, $>CH\underline{CH_3}$), 0.96 (3H, t, J=7.3Hz, $-CH_2\underline{CH_3}$) p.p.m. and $^m/_e$ = 407 (M+). This data was entirely consistent with the proposed structure (2a) and in accordance with data published by Schering chemists for a similar compound[6b]. The ^1H n.m.r. spectrum did show some splitting of the peaks due to the presence of a small amount (ca. 20%) of the imino-penam tautomer (3a), which was inseparable from (2a) by chromatography.

We were gratified to find that this reaction represented a general route to various substituted 3-aminopenems and the results of other experiments are presented in the Table. In cases in which a primary amine was used inseparable mixtures of the aminopenems (2a, b) and the tautomeric imino-penams (3a, b) were obtained with the former predominating. Secondary amines gave the expected aminopenem products (2c-f). The reactions were slower in less polar solvents whilst the use of the p-nitrophenoxypenem (1b) to prepare aminopenem (2a) resulted in a significantly faster reaction than the analogous process using (1a). We anticipate the reaction occurs by a Michael addition - elimination process.

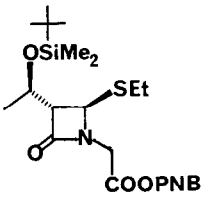
TABLE : Reaction of 3-arlyoxypenems with amines*

Starting Material	R^1R^2NH	Product	Isolated Yield
1a	n-$PrNH_2$	2a/3a (4:1)	75%
1b	n-$PrNH_2$	2a/3a (4:1)	57%
1a	$MeNH_2$	2b/3b (3:1)	39%
1a		2c	26%
1a	Me_2NH	2d	31%
1a		2e	33%
1a	EtO_2CCH_2NHMe	2f	78%†

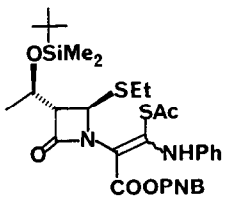
† Solvent acetonitrile

*Solvent DMF unless otherwise stated

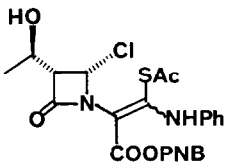
As might be expected from its lower nucleophilicity aniline did not react with the aryloxypenem (1a); however the phenylamino-penem (2g) could be prepared by a modification of some earlier chemistry performed in these laboratories[2]. Treatment of the



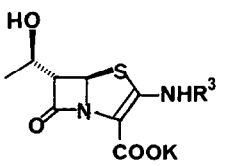
(4)



(5)



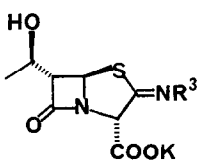
(6)



(7)

a ; R^3 = n-Pr

b ; R^3 = Ph



(8)

a ; R^3 = n-Pr

b ; R^3 = Ph

PNB = p-nitrobenzyl

azetidinone-acetate (4) with 2.5 equiv. of lithium hexamethyldisilazide in THF at -40°C followed by addition of phenyl isothiocyanate and then acetic anhydride afforded the ketene derivative (5). Hydrolysis of the silyl ether protecting group (5M aqueous HCl, THF, 20°C) followed by stereospecific chlorinolysis (Cl_2, CCl_4-$CHCl_3$, 0°C)[9] led to the cis-chloro compound (6) which on mild base treatment (imidazole, dioxane-H_2O) smoothly cyclised to give the phenylaminopenem (2g) together with ca. 15% of the tautomeric imino-penam (3g). The spectral data of the material was consistent with structure (2g); ν_{max} 1775 cm^{-1}, δ ($CDCl_3$) 8.21, 7.59 (4H, AA'BB', J=8.8Hz,-$C_6H_4NO_2$), 7.45-7.25 (5H,m,-Ph), 7.10 (1H, br, NH), 5.63 (1H, d, J=1.6Hz, H-5), 5.47, 5.26 (2H,ABq, J=13.6Hz, CH_2 Ar), 4.30-4.20 (1H,m,H-8), 3.84 (1H, dd, J=4.7, 1.6Hz, H-6),2.09 (1H, OH),1.34 (3H, d, J=6.4Hz, >$CHCH_3$) p.p.m. Clearly, in compounds (3a) and (3g) the reduced strain provided by the additional sp^3 centre is outweighed by the stabilisation resulting from better conjugation in (2a) and (2g) leading to a preponderance of the penem tautomer.

Attempted hydrogenolysis of the p-nitrobenzyl ester protecting group in these compounds (4 atm H_2, $KHCO_3$aq, EtOAc, 10%Pd-C) gave disappointing results. In many cases the conditions used led to decomposition; however both the n-propylaminopenem (2a) and the phenylaminopenem (2g) (together with small amounts of their imino-penam tautomers (3a) and

(3g)) did give moderate yields of the corresponding potassium salts under these conditions. Examination of the spectral properties of the potassium salt obtained from (2a) and (3a)[10] revealed that it existed as a 3:2 tautomeric mixture of the penem (7a) and the imino-penam (8a). The ^{1}H nmr spectrum of the potassium salt derived from (2g) and (3g) however showed that the phenylaminopenem tautomer (7b) was predominant (> 80%)[11] and only minor amounts of the imino-penam tautomer (8b) were present.

These aminopenem potassium salts exhibited only moderate antibacterial acitivity. This effect is possibly due to instability under the conditions of the test.

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10. 7a: δ (D_2O) 5.47 (d, J=1.2Hz, H-5), 4.40-4.21 (m, H-8), 3.65 (dd, J=6.2 and 1.2Hz, H-6), 3.27 (m, -NHCH_2-), 1.73-1.58 (m,-NHCH_2CH_2-), 1.34 (d, J=6.4Hz,>CHCH_3), 0.89 (t, J=7.4Hz, propyl-CH_3); many peaks show splitting. 8a : δ(D_2O) 5.40 (d, J=1.0Hz, H-5) and 1.26 (t, J=6.4Hz,>CHCH_3).
11. 7b : δ (D_2O) 7.52-7.30 (m, Ph), 5.59 (d, J=1.5Hz, H-5), 4.28-4.12 (m, H-8), 3.93 (dd, J=1.5 and 6.0Hz, H-6), 1.23 (d, J=6.4Hz,>CHCH_3); 8b : δ (D_2O) 5.52 (d, J=1.4Hz, H-6).

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