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2-SELENACEPHEMS AND 1-DETHIA-1-SELENAPENEMS

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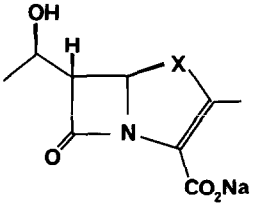
Abstract - The first selena nuclear analogues of ß-lactam antibiotics have been synthesized and compared with their sulphur counterparts.

During the last decade, the quest for an expanded antimicrobial spectrum has prompted several synthetic endeavours aimed at the skeletal modification of the naturally occurring ß-lactam antibiotics. The nuclear sulphur of penicillins and cephalosporins has been replaced by different atoms (O,N,C) and the chemophysical and microbiological effects of these substitutions have become object of investigation. We wish here to describe the synthesis of the optically active 1-dethia-1-selenapenem 2, and its antibacterial activity[1] in comparison with the sulphur counterpart 1. Although substitution of selenium for sulphur in the periphereal side chains of cephalosporins has been claimed[2], to our best knowledge the 1-selenapenem 2 and the closely related 2-selenacephem 6 are the first bicyclic selena ß-lactams ever reported.



1, X= S
2, X= Se

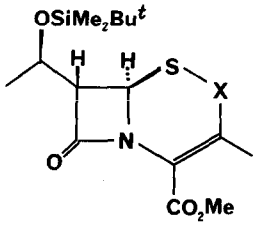
MICROORGANISM	MICs (µg/ml)		
	1	**2**	Ampicillin
Staphylococcus aureus Smith	0.39	0.39	≤ 0.19
Streptococcus pyogenes ATCC 12384	0.09	0.19	3.12
Klebsiella aerogenes 1522 E	3.1	12.5	-
K. aerogenes 1082 E (ß-lact.+)	3.1	12.5	>100
Enterobacter cloacae 1321 E	3.1	12.5	-
E. cloacae P 99 (ß-lact.+)	3.1	12.5	-
Escherichia coli B	3.1	12.5	0.39
E. coli B cef R (ß-lact.+)	3.1	12.5	>100
Salmonella typhimurium ATCC 14028	1.55	6.25	0.78
Shigella flexneri ATCC 11836	3.1	12.5	≤0.19
Proteus mirabilis FI 7474	6.2	25	-
P. morganii ATCC 25830	6.2	25	-

For the synthesis of 2, 1,5-ring-closing strategies were preferred to the classical Woodward's cyclization pattern, which would have required the preparation of 4-azetidinyl

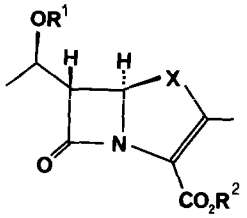
selenoester intermediates[3]. Substitution of sodium selenide for sodium sulfide in our original 2-thiacephem approach[4] allowed the conversion of the disulphide-mesylate 4a (Na_2Se 1 equiv., DMF-H_2O, 5 min 10°C, followed by prompt quenching with $AgNO_3$ 2 equiv., H_2O) into the novel 2-selenacephem 6 in 12% isolated yield[5]. In analogy with ring-contraction experiments carried out on the sulfur isoster 5[4,6], it was hoped that treatment of 6 with PPh_3 would preferentially give the selenapenem 8a; however, the undesidered (5S)-epimer 10a (as indicated by the large coupling constant of the ß-lactam protons, J= 4.13 Hz) was exclusively formed (78%). An identical sample of 10a was obtained (47%) from 4a by chlorinolysis to 4b (Cl_2 2 equiv., CH_2Cl_2, -40°C) and displacement of the mesyloxy group[7] with Na_2Se (DMF, argon, 45 min 20°C).

The above results indicated the (4S)-chloroazetidinone 4e as the most appropriate key intermediate for obtaining the desired (5R)-1-dethia-1-selenapenem 2. Chlorinolysis of 4-alkylthioazetidinones can be reagent-approach controlled when the hydroxyethyl group at C_3 is unprotected[8]. A convenient precursor was therefore envisaged in the thioether 4d, prepared from the threonine-derived benzoyloxyazetidinone 3a[9] by sequential displacement with butylmercaptan (NaH, DMF, 82%), N-alkylation (pNB iodoacetate, Cs_2CO_3, MeCN, overnight, 83%), C-acylation ($LiN(SiMe_3)_2$ 2 equiv., CH_3COCl 1.1 equiv., THF, 30 min -78°C, 75%), enol mesylation (MsCl, NEt_3, CH_2Cl_2, -20°C, 90%) and desilylation ($BF_3.Et_2O$ 1.2 equiv., MeCN, -15°C, 80%). As expected, chlorinolysis of this material (Cl_2 in CCl_4 1.2 equiv., CH_2Cl_2, 30 min -40°C) gave the 3,4-cis azetidinone 4e (41% after flash-chromatography), which reacted with sodium selenide to afford the (5R)-selenapenem 8b, albeit in poor yield (14%). Removal of the p-nitrobenzyl group was best achieved by reduction with iron powder in a buffered medium (NH_4Cl, THF-H_2O 1:1, 35 min 20°C) and the product required for microbiological evaluation was isolated as the sodium salt 2 (33%) after ion exchange and reverse-phase chromatography.

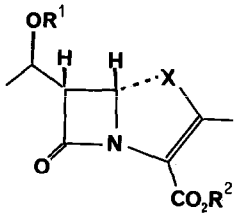
Interestingly, the selenapenem 2 closely reproduced the antibacterial spectrum of the penem 1, but with a constant (about 4 fold) decrease in potency (see Table). These data suggest that the isosteric systems differ not for their mode of action but for the intrinsic acylating activity of the ß-lactam ring. It is reasonable to assume that substitution of selenium for sulphur brings about a partial release of the structural strain associated with the combination of four- and five-membered rings[10]. This is probably reflected in the IR carbonyl stretching frequency, which is consistently (~10 cm^{-1}) lower in the selena compounds. Differences between the components of the isosteric pairs 2-1, 6-5, 10a-9a were also observed in ^1H-NMR and UV spectroscopy: the selena derivatives were characterized by a 0.23÷0.28 downfield shift for the heteroatom-adjacent ß-lactam proton, and by a strong absorption at 280 nm, either accompanying (in selenapenems) or submerging (in selenacephems) the long-wavelenght maximum proper of their sulphur counterparts (310 and 327 nm, respectively).



5, X= S
6, X= Se

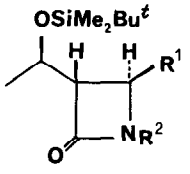


7, X= S
8, X= Se



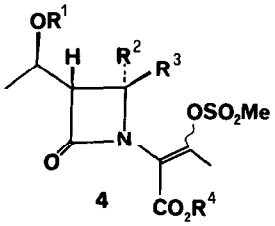
9, X= S
10, X= Se

a, R^1= TBDMS, R^2= Me
b, R^1= OH, R^2= pNB



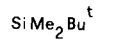
3

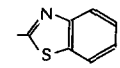
a, R^1= OCOPh, R^2= H
b, R^1= SBu, R^2= H
c, R^1= SBu, R^2= CH_2CO_2pNB

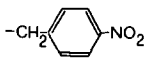


4

a, R^1= TBDMS, R^2= H, R^3= SSBt, R^4= Me
b, R^1= TBDMS, R^2= H, R^3= Cl, R^4= Me
c, R^1= TBDMS, R^2= H, R^3= SBu, R^4= pNB
d, R^1= R^2= H, R^3= SBu, R^4= pNB
e, R^1= R^3= H, R^2= Cl, R^4= pNB

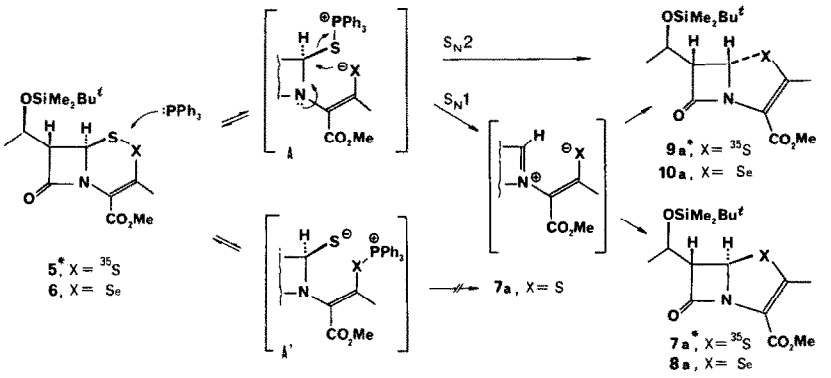
TBDMS = 

Bt = 

pNB = 

The desulphurative ring-contraction of 5 and 6 bears the most relevant chemical difference between the sulphur and selena isosters object of our study. In parallel experiments[6] carried out on ^{35}S analogues (i.e., 5* instead of 6) we found a single regiochemical result (incorporation of the radiolabel in the penem product) accompanying different stereochemical outcomes (7a* and 9a* formed in relative amounts of 1:1 or 2.4:1, depending on the solvent; see Scheme overleaf). Therefore, the observed discrepancy should not be attributed to chemoselectivity factors in the PPh_3 attack (A vs. A' on replacing Se for S) but rather depends on differences in the fate of the thiophosphonium intermediate A. The observed exclusive formation of 10a from 6 corroborates our analysis[4,6] of the ring contraction in terms of a competition between S_N2 and S_N1 mechanisms: changing the entering nucleophile from $-S^-$ to $-Se^-$ cannot affect the latter but obviously promotes[11] the former.

Scheme



References and Notes

1. We thank Dr. G. Meinardi for the antimicrobial test.
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3. Selenocarboxylic acids are difficult to handle and stable only in the presence of excess hydrogen selenide: K.A. Jensen, Quart. Reports Sulphur Chem., 5, 45 (1970).
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5. Salient data for new compounds: 2: ν_{max}(KBr) 1750 cm^{-1}; δ(D_2O) 1.28(3H,d,J=6.4Hz), 2.34(3H,s), 3.87(1H,dd,J=1.4, 4.3Hz), 4.22(1H,qd,J=6.4,4.3Hz), 5.86(1H,d,J=1.4Hz); λ_{max}(H_2O) 277,311 nm; 3b: mp 74°C; ν_{max}(KBr) 1765 cm^{-1}; δ($CDCl_3$) 0.04 and 0.05(each 3H,s), 0.85(9H,s), 0.92(3H,d,J=7.2Hz), 1.21(3H,d,J=6.3Hz), 1.31-1.62(4H,m), 2.60(2H,t, J=7.2Hz), 3.09(1H,ddd,J=0.9,2.4,3.5Hz), 4.22(1H,qd,J=6.3,3.5Hz), 4.80(1H,d,J=2.4Hz); 3c: ν_{max}($CHCl_3$) 1765sh, 1750 cm^{-1}; δ($CDCl_3$)inter alia 3.10(1H,dd), 4.0(2H,ABq), 4.87(1H,d), 5.22(2H,s); 4c(mixture of E,Z isomers): ν_{max} ($CHCl_3$) 1765,1725 cm^{-1}; δ($CDCl_3$) 0.01 and 0.05(each 3H,s), 0.79-0.89(12H,m), 1.24(3H,d,J=6.4Hz), 1.3-1.6(4H,m), 2.30 and 2.61(3H,each s,=CMe of E and Z,respect.), 2.4-2.8(2H,m), 3.09-3.13(1H,two dd), 3.16 and 3.25(3H,each s, SO_2Me of E and Z,respect.), 4.22-4.34(1H,m), 5.17-5.22(1H,two d), 5.28-5.34(2H,two ABq), 7.54-7.60(2H, two d), 8.20-8.26(2H,two d); 4e(mixt.of E,Z isomers): ν_{max}($CHCl_3$) 1780,1730 cm^{-1}; δ($CDCl_3$) 1.45(3H,d,J=6.3Hz), 2.45 and 2.70(3H,each s), 3.27 and 3.30(3H,each s), 3.35-3.75(1H,each dd), 4.1-4.5(1H,m), 5.35(2H,s), 6.05 and 6.10(1H, each d,J=4.5Hz), 7.5 and 8.25(each 2H,d,J=8.5Hz); 6: ν_{max}($CHCl_3$) 1775,1725 cm^{-1}; δ($CDCl_3$) 0.1(6H,s), 0.88(9H,s), 1.27(3H,d,J=6.2Hz), 2.23(3H,s), 3.08(1H,dd,J=2.0 and 4.0Hz), 3.82(3H,s), 4.30(1H,m), 4.88(1H,d,J=2.0Hz); λ_{max} (n.hexane) 284 nm; MS(FD) 437 $m/_z$; 8b: ν_{max}($CHCl_3$) 1775,1705 cm^{-1}; δ($CDCl_3$) 1.33(3H,d,J=6.3Hz), 2.46(3H,s), 3.77 (1H,dd,J=1.6 and 6.6Hz), 4.20(1H,qd,J=6.3 and 6.6Hz), 5.30(2H,ABq,J=13.9Hz), 5.83(1H,d,J=1.6Hz), 7.59 and 8.19 (4H,each d,J=8.6Hz); MS(FD) 412,410 $m/_z$; 10a: ν_{max}($CHCl_3$) 1780,1707 cm^{-1}; δ($CDCl_3$) 0.08(6H,s), 0.86(9H,s), 1.40 (3H,d,J=6.0Hz), 2.48(3H,s), 3.77(1H,dd,J=4.1 and 10.0Hz), 3.78(3H,s), 4.29(1H,dq,J=6.0 and 10.0Hz), 5.86(1H,d,J= 4.1Hz); λ_{max}(EtOH) 250,286,318 nm; MS(FD) 405 $m/_z$.
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11. For a comparison between thiolate and selenoate nucleophilicities see H.J. Reich and M.L. Cohen, J. Org. Chem., 44, 3148 (1979), and references therein.

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