Tetrahedron Letters,Vol.25,No.8,pp 877-880,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

THE SYNTHESIS OF MONOBACTAM ANALOGUES BEARING CARBAPENEM SIDE-CHAINS ON C(3)

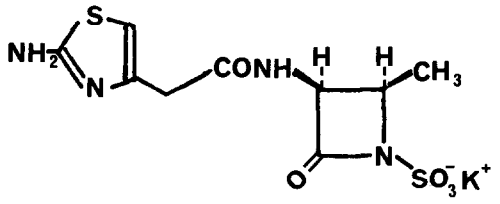
By Christopher J. Ashcroft,[a] John Brennan,[a*] Christopher E. Newall[b] and Stanley M. Roberts[b]

[a] Department of Chemistry, UMIST, P.O.Box 88, Manchester M60 1QD

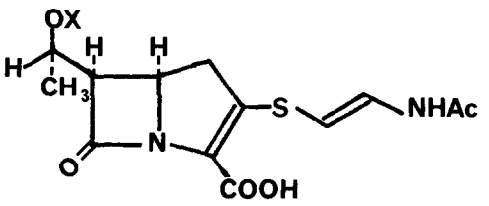
[b] Glaxo Group Research Ltd., Greenford Road, Greenford, Middlesex UB6 0HE

Summary: A series of monobactam analogues lacking 3-acylamino side chains has been synthesised from the photoisomer of 4-methyl-2-pyridone; none of these analogues showed any useful biological activity.

A major development in β-lactam antibiotic chemistry has been the discovery of a highly antibacterially active group of monocyclic β-lactams (monobactams) e.g. (1)[1] in which, apparently, activation of the azetidinone is effected by the electron withdrawing N-sulphonate group instead of the second fused ring found in penicillins, cephalosporins, penems and carbapenems.



(1)

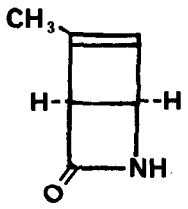


(2a) X = H

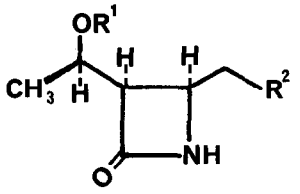
(2b) X = SO_3H

In an attempt to assess the importance of the acylamino side-chains of the monobactams we undertook the synthesis of analogues in which this side-chain was replaced by the cis-1-hydroxyethyl and cis-1-sulphooxyethyl side-chains found in epithienamycins or olivanic acids e.g. (2a)[2] and (2b)[3].

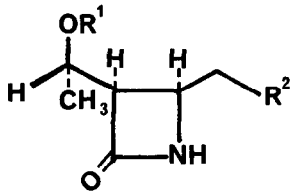
We chose as our starting material 2-methyl-5-azabicyclo[2.2.0]hex-2-en-6-one (3), a photoisomer of 4-methyl-2-pyridone, which has been shown to be a potential precursor for the required functionality and cis stereochemistry[4]. Our approach therefore anticipated cleavage of (3) to the dihydroxy isomers (4) which could be converted by appropriate protection and functional transformation to the partially protected and unprotected intermediates (10) and (11) and then to their respective N-mono- or O,N-bis-sulphonated derivatives.



(3)



(a)



(b)

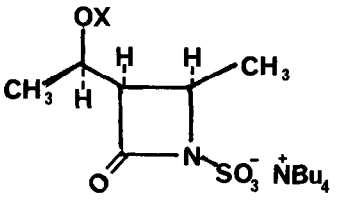
(4)	R^1=H	R^2=OH
(5)	R^1=H	R^2=OTBDMS
(6)	R^1=$PhCH_2OCO$	R^2=OTBDMS
(7)	R^1=$PhCH_2OCO$	R^2=OH
(8)	R^1=$PhCH_2OCO$	R^2=OMs
(9)	R^1=$PhCH_2OCO$	R^2=I
(10)	R^1=$PhCH_2OCO$	R^2=H
(11)	R^1=H	R^2=H

Thus 2-methyl-5-azabicyclo[2.2.0]hex-2-en-6-one (3)[5] was ozonised and reduced (O_3, MeOH, -78°; $NaBH_4$, -78° ⟶ 0°) to a mixture of the diastereoisomers (4a) and (4b), (1:1, 65%) which were separated chromatographically. Each was then separately subjected to the same reaction sequence and yields are for the (a) and (b) series respectively. Selective formation of the primary t-butyldimethylsilyl (TBDMS) ethers of (4) (TBDMS-Cl, pyridine, 97%, 91%) yielded the partially protected alcohols (5) which were reacted at their secondary hydroxyl groups with benzyl chloroformate ($PhCH_2OCOCl$, CH_2Cl_2, N,N-4-dimethylaminopyridine). The silyl ether functions of (6) were then hydrolysed to give (7)[6] ($n\text{-}Bu_4N^{\oplus}F^{\ominus}$, AcOH, THF, each 55% from (5). Mesylation of (7) gave (8) (MsCl, py, each 90%) which were transformed into the corresponding iodides (9) (NaI, $(CH_3)_2CO$, reflux, each 72%); reduction of these afforded the 4-methyl derivatives (10)[6] (Bu_3SnH, $PhCH_3$, each 70%).

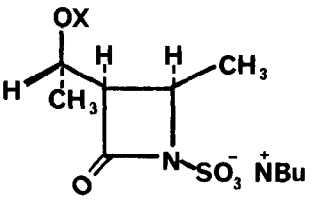
Sulphonation[6] of (10) gave the N-sulphonates (12) (3 equiv. pyridine-SO_3,

$Bu_4N^{\oplus}$ $HSO^{\ominus}_4$, 44%, 37%) and hydrogenolysis of the benzyloxycarbonyl groups yielded the desired isomers (13)[6] (Pd-C, H_2, EtOH, 95%, 83%); in order to obtain the O,N-bis-sulphonated derivatives (14)[6] deprotection, as for (12), preceded sulphonation (6 equiv. pyridine-SO_3, $Bu_4N^{\oplus}$ $HSO^{\ominus}_4$, 32%, 49%).

Antibacterial testing showed none of the compounds (13a), (13b), (14a), or (14b) to possess any significant activity, while testing for β-lactamase inhibition showed only (13a) to possess a low level of activity.



(a)



(b)

(12) X = $PhCH_2OCO$
(13) X = H
(14) X = $SO_3^{\ominus}$ $^{\oplus}NBu_4$

These results strongly suggest that, in common with penicillins and cephalosporins, the acylamino side-chain is an essential feature for useful antibacterial activity in the N-sulphonated monocyclic β-lactam series.

We thank Glaxo Group Research and the SERC for a CASE award to C.J.A. and the former for carrying out biological testing.

References and Notes

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2) S.J. Box, J.D. Hood, and S.R. Spear, J. Antibiot., 1979, 32, 1239

3) A.G. Brown, D.F. Corbett, A.J. Eglington and T.T. Howarth, J. Chem. Soc., Chem. Commun., 1977, 523

4) J. Brennan, J. Chem. Soc., Chem. Commun., 1981, 880

5) All compounds (3) to (14) are racemic mixtures of which only one isomer is shown; all new compounds exhibited satisfactory microanalytical and/or spectroscopic properties

6) Selected spectroscopic data: (7a), ir (nujol), 1770 cm^{-1} β-lactam C=O, nmr ($CDCl_3$) δ, 7.41 (5H,s,Ph), 6.95 (1H, br.s,NH), 5.30 (1H,m,CH_3CH-O),

5.20 (2H,s,PhC$\underline{H}_2$), 3.75 (4H,m,C$\underline{H}_2$OH, $\underline{H}$-C-NH,CH$_2$O$\underline{H}$), 3.30 (1H,m,H-C-C=O), 1.35 (3H,d,C$\underline{H}_3$CH, J=7Hz); (10a) ir (nujol), 1750 cm^{-1},br., both C=O, nmr(CDCl$_3$) δ, 7.38 (5H,s,Ph), 6.40 (1H,s,NH), 5.15 (2H,s,PhC$\underline{H}_2$), 5.08 (1H,dq CH$_3$C$\underline{H}$-O- J=6Hz,7Hz), 3.83 (1H,dq,$\underline{H}$-C-NH, J=6Hz,7Hz), 3.25 (1H,dd, H-C-C=O, J=6Hz,6Hz), 1.40 (3H,d,C$\underline{H}_3$CH-O, J=7Hz), 1.25 (3H,d,C$\underline{H}_3$CHNH, J=7Hz); (13a) ir (CHBr$_3$ solution), 1745 cm^{-1}, β-lactam C=O, nmr (CDCl$_3$) δ, 4.15 (2H,m,CH$_3$C$\underline{H}$-O, $\underline{H}$-C-N-), 3.24 (8H,m,4(CH$_2$N)), 2.95 (1H,dd H-C-C=O, J=6Hz,8Hz), 2.71 (1H,br.s.,OH), 1.8-1.2 (22H,br.m.,4(C$\underline{H}_2$C$\underline{H}_2$), C$\underline{H}_3$-CH-N-, C$\underline{H}_3$-CH-OH, the latter being clearly discernable at δ 1.23, J-7Hz), 1.10 (12H,t.,4(C$\underline{H}_3$CH$_2$-), J. 7.5Hz); (14a) ir (CHBr$_3$ solution), 1750 cm^{-1}, β-lactam C=O.

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(Received in UK 9 December 1983)