Tetrahedron Letters Vol. 21, pp 561 - 564 0040-4039/80/0201-0561$02.00/0

CONVERSION OF CLAVULANIC ACID INTO THIADEOXA NUCLEAR ANALOGUES

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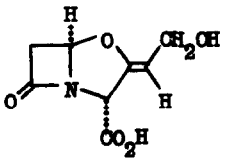
Summary: 1,4-Addition of sulphur nucleophiles to the diene (12) derived via the pen-2-em (5) from clavulanic acid provides the thiadeoxa analogues (14-15). X-ray analysis of the ester (14) shows the thermodynamically stable isomers to have the same relative stereochemistry as clavulanic acid.

Over the past few years there has been considerable effort directed toward the preparation of nuclear analogues of penicillins and cephalosporins in which the sulphur atom has been replaced by oxygen. Following the isolation of clavulanic acid (1),[1] the first naturally occurring example of such an analogue, the replacement of the ring oxygen atom of this novel bicyclic structure by sulphur was of similar interest. Recent reports have described the syntheses of the thiadeoxa analogues (2-4) which, although similar, do not exactly correspond with the carbon skeleton and stereochemistry of clavulanic acid.[2,3] We now present the preparation of analogues of thiadeoxaclavulanic acid [2-(2-substituted-ethylidene)penams] with the correct carbon skeleton and relative stereochemistry. Furthermore, these analogues are prepared from the pen-2-em (5) which itself has been derived from clavulanic acid (1).[4] Thus the overall result of the reaction sequence is the replacement of the ring oxygen atom of clavulanic acid by sulphur, while retaining all eight of the carbon atoms constituting the skeleton.

Treatment of 4-nitrobenzyl (5RS)-2-(2-hydroxyethyl)pen-2-em-3-carboxylate (5) in EtOAc at 0° for 30 min. with mesyl chloride (1.63 equiv.) and triethylamine (TEA) (1.63 equiv.) afforded the corresponding mesylate (6, 96%) m.p. 103-104° (EtOAc/petrol), $\lambda_{max}(CHCl_3)$ 266 (ε 12,550) and 317.5 nm (ε 9,100), $\nu_{max}(CHBr_3)$ 1786 (β-lactam) and 1705 cm^{-1} (ester), $\tau(CDCl_3)$ 4.28 (dd, 2 and 4 Hz, C5-H), 5.60 (t, 7 Hz, $CH_2\underline{CH_2}OMes$), 6.4 - 7.1 (m, $\underline{CH_2}CH_2OMes$) and 6.97 (s, CH_3). Hydrogenolytic deprotection of the ester (6) over 10% Pd/C gave the corresponding acid which was isolated as the potassium salt (7). The salt was unstable on storage and cyclised to the lactone (11), $\lambda_{max}(CHCl_3)$ 268



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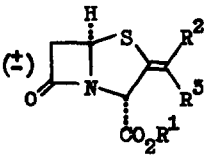
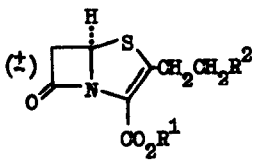
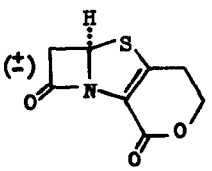


2 R^1 = H R^2 = Ph R^3 = H
3 R^1 = H R^2 = SCH_3 R^3 = H
4 R^1 = CH_2Ph R^2 = H R^3 = CO_2CH_3



5 R^1 = pNB R^2 = OH
6 R^1 = pNB R^2 = OSO_2CH_3
7 R^1 = K R^2 = OSO_2CH_3
8 R^1 = K R^2 = H
9 R^1 = pNB R^2 = $SCOCH_3$
10 R^1 = K R^2 = $SCOCH_3$



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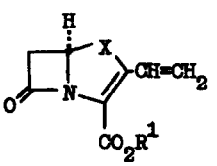
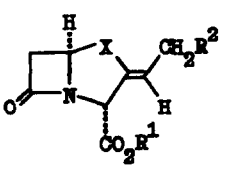
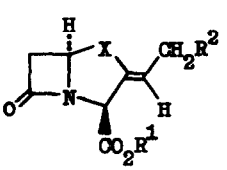


12 (±) X = S R^1 = pNB
15 X = O R^1 = pNB



(X = O 5R; X = S 5S)
14 (±) X = S R^1 = pNB R^2 = SPh
15 (±) X = S R^1 = pNB R^2 = $SCOCH_3$
16 X = O R^1 = pNB R^2 = $SCOCH_3$
17 (±) X = S R^1 = K R^2 = $SCOCH_3$
18 X = O R^1 = Na R^2 = $SCOCH_3$



(X = O 5S; X = S 5R)
19 (±) X = S R^1 = pNB R^2 = $SCOCH_3$
20 X = O R^1 = pNB R^2 = $SCOCH_3$

pNB = 4-Nitrobenzyl

(ε 2,600) and 315 nm (ε 6,400), $\nu_{max}(CHBr_3)$ 1797 (β-lactam) and 1722 cm^{-1} (lactone), τ(DMSO-d_6) 4.18 (dd, 2 and 4 Hz, C5-H), 5.58 (t, 7 Hz, $C\underline{H}_2CH_2O$) and 7.16 (m, $CH_2C\underline{H}_2O$).

In the presence of TEA (5 equiv.) in EtOAc at 20°, the mesylate (6) was converted within 30 min. into the diene (12, 65%), m.p. 123-126° (ether), λ_{max}(EtOH) 264 (ε 16,280) and 348 nm (ε 8,270), $\nu_{max}(CHBr_3)$ 1786 (β-lactam)

and 1706 cm^{-1} (ester), $\tau(CDCl_3)$ 2.45 (dd, 12 and 17 Hz, $C\underline{H}=CH_2$), 4.40 (dd, 2 and 4 Hz, C5-H) and 4.3 - 4.5 (m, $CH=C\underline{H}_2$). The diene (12) was more conveniently obtained directly from the alcohol (5) in 95% yield by the action of mesyl chloride (1.75 equiv.) and TEA (5 equiv.) in EtOAc at 20^o for 30 min. Catalytic hydrogenation of the diene-ester over 10% Pd/C afforded 2-ethylpen-2-em-3-carboxylic acid, isolated as the previously described potassium salt (8).[4]

The 2-vinylpen-2-em (12), like the corresponding 2-vinylclav-2-em (13) derived from clavulanic acid,[5] readily undergoes 1,4-additions of sulphur nucleophiles and provided the 2-ethylidenepenam system. Thus, treatment with thiophenol (3.3 equiv.), 18-crown-6 (0.63 equiv.) and potassium carbonate (0.6 equiv.) in CH_2Cl_2 at 20^o gave 4-nitrobenzyl (3SR,5RS,Z)-2-(2-phenylthioethylidene)penam-3-carboxylate (14, 66%), m.p. 83.5 - 84.5 (ether) λ_{max}(EtOH) 253 nm (ε 18,900), $\nu_{max}(CHBr_3)$ 1780 (β-lactam) and 1746 cm^{-1} (ester), $\tau(CDCl_3)$ 2.6 - 2.8 (m, Ph), 4.20 (dt, 1 and 7 Hz, -CH=), 4.65 (m, C3-H and C5-H) and 6.46 (d, 7 Hz, CH_2S). X-ray crystallographic analysis of (14) confirmed that the relative stereochemistries at C-3 and C-5 and the geometry about the double bond were the same as in clavulanic acid (1).

Crystal data: $C_{21}H_{18}N_2O_5S_2$, triclinic, $P\bar{1}$, a=12.69(5), b=12.55(5), c=8.01(5)Å, α=67.04(5), β=91.49(5), γ=66.73(5)°. 3108 Data were collected for hk0-6 with $\Theta_{max}=25^o$ on a STADI-2 diffractometer (Mo-Kα radiation). 2081 Reflections with $I > 3\sigma(I)$ were used in the refinement. The structure was solved by direct phasing methods with MULTAN-78 and by refinement with the SHELX-76 crystallographic program system to give an R value of 0.067.[6]

Under similar conditions, an analogous 1,4-addition of thioacetic acid to the diene (12) gave 4-nitrobenzyl (3SR,5RS,Z)-2-(2-acetylthioethylidene)penam-3-carboxylate (15, 69%), λ_{max}(EtOH) 247.5 nm (ε 16,300), λ_{inf} 257 nm (ε 15,600), $\nu_{max}(CHBr_3)$ 1780 (β-lactam) and 1748 cm^{-1}(ester), $\tau(CDCl_3)$ 4.26 (dt, 1 and 7 Hz, -CH=) 4.61 (dd, 2 and 4 Hz, C5-H), 4.64 (s, C3-H), 6.50 (d, 7 Hz, CH_2S) and 7.69 (s, CH_3). Examination of the crude product resulting from a similar reaction at 0^o revealed the presence of a minor component (1:3) which, under the reaction conditions or in the presence of TEA, was transformed into the major product (15). This second component was formulated as the thermodynamically unstable (3RS,5RS,Z)-epimer (19), $\tau(CDCl_3)$ 4.30 (dt, 1 and 7 Hz, -CH=), 4.87 (dd, 2 and 4 Hz, C5-H) and 5.45 (s, C3-H).

A reinvestigation of the 1,4-addition reactions of the diene (13) derived from clavulanic acid showed that under low temperature conditions (-10°), the corresponding thermodynamically unstable 3S-isomers (e.g. 20) could be detected

in the crude reaction products along with the previously isolated 3R-isomers (e.g. 16).[5] Thus, although 1,4-addition of sulphur nucleophiles to the dienes (12 and 13) usually results in products (e.g. 15 and 16) with high stereospecificity at C3, the reaction appears to proceed, at least in part, via the thermodynamically unstable epimers (e.g. 19 and 20). The pairs of C3-epimers of the ethylidene penams and clavams showed the large characteristic downfield shift reported for C3-protons on epimerisation of (3SR,5RS)-clavam-3-carboxylates to the more stable (3RS,5RS)-isomers.[7,8]

More prolonged action of TEA on the ethylidenepenam (15) resulted in isomerisation of the double bond to afford the 2-(2-acetylthioethyl)pen-2-em (9, 74%), $\lambda_{max}(CHCl_3)$ 265 (ε 13,100) and 320 nm (ε 8,100), $\nu_{max}(CHBr_3)$ 1786 (β-lactam) and 1708 cm^{-1} (ester), $\tau(CDCl_3)$ 4.34 (dd, 2 and 4 Hz, C5-H), 6.8 - 7.1 (m, $C\underline{H}_2C\underline{H}_2$) and 7.69 (s, CH_3). The esters (15) and (9) were deprotected by hydrogenolysis over 10% Pd/C and isolated as the corresponding potassium salts (17), λ_{max}(pH6 buffer) 235 nm (ε 10,270), ν_{max}(Nujol) 1727 (β-lactam) and 1634 cm^{-1} (carboxylate), and (10), λ_{max}(pH6 buffer) 232.5 (ε 6,400) and 302.5 nm (ε 5,100), ν_{max}(Nujol) 1758 (β-lactam) and 1602 cm^{-1} (carboxylate).

The racemic acetylthioethylidenepenam (17) was less active than the corresponding clavulanic acid derivative (18)[5] as an antibacterial and β-lactamase inhibitor. However, the acetylthioethylpenem (10), in common with other 6-unsubstituted pen-2-ems,[2,4,9] showed good antibacterial activity.

Acknowledgement: One of us (J.M.R.) thanks Glaxo Group Research Ltd. for financial assistance.

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(Received in UK 16 November 1979)