Synthesis of Antibacterial Pen-2-em-3-carboxylic Acids from Clavulanic Acid

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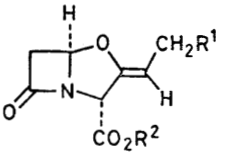
Summary The antibacterially active potassium salt (**7b**) has been synthesised from clavulanic acid (**1a**) by two routes involving either base-catalysed or thermolytic cyclisations of novel monocyclic azetidinones; protection of the hydroxy group of clavulanic acid followed by an analogous thermolytic cyclisation gave the corresponding 2-hydroxyethylpen-2-em ester (**7d**) from which a series of antibacterially active *O*-substituted derivatives was available.

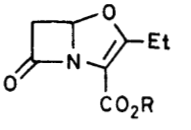
WE have recently reported[1] the conversion of the natural β-lactamase inhibitor clavulanic acid (**1a**)[2,3] into potassium 3-ethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (**2a**). This salt was also found to be a potent inhibitor of β-lactamases and, as part of a programme directed towards the synthesis of nuclear analogues,[4] we now report a generally applicable transformation of derivatives of clavulanic acid into the appropriately substituted pen-2-em-3-carboxylic acids in high yields. This novel bicyclic system, which has been described in the form of the 6-acylamino derivative (**3a**)[5] and, more recently, as the 6-unsubstituted analogues (**3b**),[6] incorporates structural features of both penicillins and cephalosporins which are responsible for their chemical reactivity and potency as antibiotics.

Our syntheses utilised either a base-catalysed or thermolytic cyclisation of monocyclic β-lactams, and were based on observations made in the preparation of the 7-oxo-4-oxa-1-azabicyclo[3.2.0]hept-2-ene ring system. Thus, reaction of 4-nitrobenzyl (2*R*,5*R*,*Z*)-3-ethylidene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (**1c**) with triethylamine



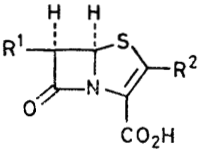
(1)

a; R^1 = OH, R^2 = H
b; R^1 = OH, R^2 = pNB
c; R^1 = H, R^2 = pNB
d; R^1 = OCH(Me)OEt; R^2 = pNB



(2)

a; R = K
b; R = pNB



(3)

a; R^1 = $PhOCH_2CONH$, R^2 = Me
b; R^1 = H

pNB = 4-Nitrobenzyl

(2 equiv.) gave the crystalline betaine (**4a**; 62%) which readily cyclised to the $\alpha\beta$-unsaturated ester (**2b**; 78%) on thermolysis.[1] Treatment of (**2b**) with n-butanethiol (5 equiv.) in tetrahydrofuran (THF) under reflux for 4·5 h gave the β-oxo ester† (**6a**; 95%) which, from spectroscopic

† Satisfactory spectroscopic data were obtained for all new compounds.

data, is largely enolised as indicated. A dichloromethane solution of (**6a**) was treated with 3 equiv. of chlorine in carbon tetrachloride in the presence of powdered acetamide at −70 °C to give the 4-chloroazetidin-2-one (**6b**; 100%); m.p. 99—100 °C. This material, when treated with 1 equiv. of triethylamine in THF at 0 °C, smoothly recyclised to (**2b**)‡ (20%).

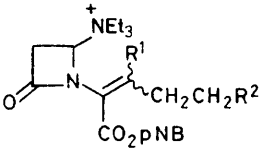
Treatment of a dichloromethane solution of the enol (**6a**) with methanesulphonyl chloride and triethylamine at 0 °C gave the mesylate (**6c**; 95%). Chlorinolysis of this derivative followed by purification by silica gel chromatography gave the corresponding 4-chloroazetidin-2-one (**6d**; 65%). Treatment of (**6d**) with hydrogen sulphide and triethylamine in THF at 0 °C brought about a smooth conversion into the desired 4-nitrobenzyl 2-ethylpen-2-em-3-carboxylate (**7a**) in 67% yield; m.p. 107—112 °C; λ_{max} (EtOH) 265 (ϵ 12,400) and 313·5 nm (ϵ 9,400); ν_{max} ($CHBr_3$) 1788 (β-lactam) and 1710 cm^{-1} (ester); τ ($CDCl_3$) values include 4·38 (dd, J 4 and 2 Hz, C-5H).

Alternatively, mesylation of the betaine (**4a**) in 1,2-dichloroethane (DCE) in the presence of pyridine at 0—20 °C gave the crystalline salt (**5a**; 97%). Reaction of (**5a**) with hydrogen sulphide and triethylamine in DCE at 0 °C gave the crystalline thioenolate salt (**4c**) in 55% yield. This derivative readily eliminated triethylamine on heating briefly in DCE and (**7a**) was isolated in high yield (69%). The betaine (**4a**) could be conveniently converted into the pen-2-em ester (**7a**) in 60% yield without the isolation of the intermediates (**5a**) or (**4c**).

Deprotection of (**7a**) by hydrogenation over 10% palladium on charcoal gave the crystalline acid which could be isolated as the potassium salt (**7b**; 38%); λ_{max} (H_2O) 257 (ϵ 3,915) and 300 nm (ϵ 5,170); ν_{max} (Nujol) 1756 (β-lactam) and 1572 cm^{-1} (carboxylate).

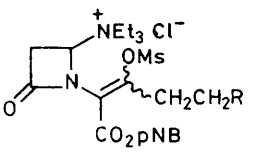
Using ethyl vinyl ether–4-toluenesulphonic acid in ethyl acetate, the hydroxy group of 4-nitrobenzyl clavulanate (**1b**)[3] was protected as the ether (**1d**; 100%);[7] treatment of this derivative with triethylamine in ethyl acetate for 2 h resulted in the deposition of the crystalline betaine (**4b**; 88%); $[\alpha]_D$ 0 ± 1° (c 1·0, Me_2SO); m.p. 112—114 °C (decomp.). Repetition of the above sequence without isolation of the intermediate mesylate (**5b**) or the thioenolate salt (**4d**) gave the corresponding pen-2-em ester (**7c**; 74%); m.p. 77·8 °C. Hydrolysis of the ether group using pH 0·91 buffer–THF mixtures afforded the hydroxy-ester (**7d**; 55%); m.p. 146·2 °C; this was de-esterified to the corresponding acid and isolated as the potassium salt (**7e**; 49%).

Reaction of (**7d**) with diazomethane–BF_3 etherate, carboxylic acid chlorides, isocyanates, and isothiocyanates



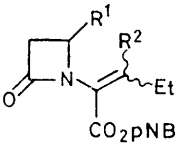
(4)

a; R^1 = O^-, R^2 = H
b; R^1 = O^-, R^2 = OCH(Me)OEt
c; R^1 = S^-, R^2 = H
d; R^1 = S^-, R^2 = OCH(Me)OEt



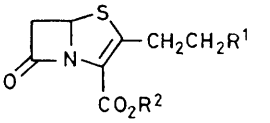
(5)

a; R = H
b; R = OCH(Me)OEt



(6)

a; R^1 = SBu^n, R^2 = OH
b; R^1 = Cl, R^2 = OH
c; R^1 = SBu^n, R^2 = OMs
d; R^1 = Cl, R^2 = OMs



(7)

a; R^1 = H, R^2 = pNB
b; R^1 = H, R^2 = K
c; R^1 = OCH(Me)OEt, R^2 = pNB
d; R^1 = OH, R^2 = pNB
e; R^1 = OH, R^2 = K

pNB = 4-Nitrobenzyl
Ms = $MeSO_2$—

gave substituted oxyethylpen-2-em esters which were deprotected (by catalytic hydrogenation or by dissolving metal reduction) to the corresponding acids and isolated as their potassium salts (**7**; R^1 = OMe, OCOMe, OCOPh, $OCOCH_2Ph$, $OCONH_2$, OCONHMe, OCONHPh, or OCSNHMe, R^2 = K).

The pen-2-em potassium salts prepared above exhibit good broad spectrum antibacterial activity and are stable to the action of β-lactamases, including the staphyloccocal penicillinase PCl and the P99 enzyme from *Enterobacter cloacae*.[8]

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‡ Similar 4-chloroazetidinones, prepared by total synthesis, have been shown to undergo analogous cyclisations: P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, *J.C.S. Chem. Comm.*, 1977, 905.

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[2] Glaxo Laboratories Ltd., German OLS No. 2,604,697.
[3] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[4] C. M. D. Beels, M. S. Abu-Rabie, P. Murray-Rust, and J. Murray-Rust, following communication.
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