1-Oxadethiapenicillins: Synthesis and Stereochemical Assignments using Lanthanide Induced Shifts

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Summary (3*S*,4*S*)-4-Acetoxy-3-phenoxyacetamidoazetidin-2-one has been converted into 1-oxadethiapenicillins, the stereochemistry at C(3) being determined by n.m.r. and lanthanide induced shift studies.

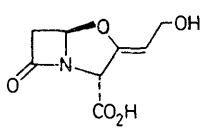
THE isolation and structural elucidation of clavulanic acid[1] (**1**) has been followed by the synthesis of the 7-oxo-4-oxa-1-azabicyclo[3.2.0.]heptane ring system.[2] Structurally related novel 1-oxapenam derivatives have now been prepared from the optically active (3*S*,4*S*)-4-acetoxy-3-

TABLE

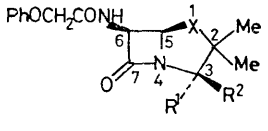
Structure	Shift[c] (p.p.m.) and shift ratios (relative to 6-H) 1·0 mol substrate: 0·9 mol Eu(fod-d_9)$_3$							
	OCH_2CO	NH	6-H	5-H	Me	Me	3-H	CO_2CH_2Ph
(**2b**)								
[a]4·47, [b]5·18	5·57	4·79	6·79	1·50	1·29	0·66	1·44	0·24
	0·82	0·71	1·00	0·22	0·19	0·10	0·21	0·04
(**2d**)								
[a]4·30, [b]5·32	5·31	4·31	6·30	1·43	1·22	0·67	1·42	0·27
	0·84	0·68	1·00	0·23	0·19	0·11	0·23	0·04
(**2c**)								
[a]3·86, [b]5·33	5·77	4·93	7·12	1·36	1·38	0·63	1·15	1·15
	0·81	0·69	1·00	0·19	0·19	0·09	0·16	0·16

[a] Position of 3-H. [b] Position of CO_2CH_2 (δ) in normal spectrum. [c] Spectra were recorded in $CDCl_3$ on a Perkin Elmer R32 instrument using Me_4Si as internal standard.

phenoxyacetamidoazetidin-2-one (**3b**),[3] m.p. 144 °C, $[\alpha]_D^{24}$ −49·8° (*c* 1·04, $CHCl_3$). The β-lactam (**3b**) was conveniently prepared by oxidative removal[3] of the *N*-substituent from the acetoxy derivative (**3a**),† m.p. 161 °C, readily obtained from methyl phenoxymethylpenicillinate

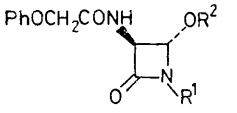


(1)

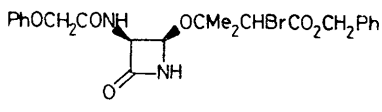


(2)

a; $R^1 = CO_2Me$, R^2=H, X = S
b; $R^1 = CO_2CH_2Ph$, R^2=H, X = S
c; R^1 = H, $R^2 = CO_2CH_2Ph$, X = O
d; $R^1 = CO_2CH_2Ph$, R^2=H, X = O
e; $R^1 = CO_2Na$, R^2=H, X = O

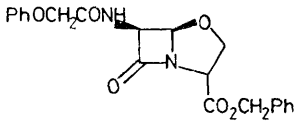


(3)



(4)

a; $R^1 = C(:CMe_2)\cdot CO_2Me$, R^2 = COMe
b; R^1 = H, R^2 = COMe
c; R^1 = H, $R^2 = CMe_2\cdot CHBr\cdot CO_2CH_2Ph$



(5)

(**2a**) by the method of Stoodley.[4] Reaction of (**3b**) with benzyl 2-bromo-3-hydroxy-3-methylbutyrate in the manner reported for 4-acetoxyazetidin-2-one[2] gave a separable mixture of the *cis*- and *trans*-β-lactams (**4** and **3c**, 20%, 1:1·2). Treatment of (**4**) with K_2CO_3 in dimethylformamide (24 h; room temp.) resulted in cyclisation to the 1-oxadethiapenicillin epimers (**2c**) and (**2d**) (32%) having the same stereochemistry as penicillin about the β-lactam ring (J_{5-6} 3 Hz).‡ The assignment of configuration at C(3) for each isomer was made on the basis of ^{1}H n.m.r. shift values and the use of lanthanide induced shifts.

The relative stereochemistry at C(3) and C(5) in penicillins and synthetic 7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane 2-carboxylates has been related to the chemical shift of the C(3) proton. This correlation indicates that the C(3) proton resonance in (**2d**) will be at lower field (*ca.* 0·5 p.p.m.) than in (**2c**). Separation of the 1-oxapenam epimers gave (**2c**)† (22%), $[\alpha]_D^{23}$ + 81·5° (*c* 1·03, $CHCl_3$), having the C(3) proton at δ 3·86. In (**2d**)† (12%), $[\alpha]_D^{23}$ + 34·1° (*c* 0·92, $CHCl_3$), the shift was at δ 4·30. The latter (**2d**) therefore has the natural penicillin chemistry at all three asymmetric carbon atoms.§

Confirmation of these assignments was obtained from a comparison of the lanthanide induced shifts (Table) observed in the n.m.r. spectra of (**2c**), (**2d**), and the benzyl ester of phenoxymethylpenicillin (**2b**). Since the dominant shifts are in agreement the same substrate–lanthanide shift reagent complex geometry is indicated for both the penicillin¶ (**2b**) and the 1-oxapenams (**2c**) and (**2d**). That the configuration of the penicillin ester (**2b**) and (**2d**) are the same is clearly reflected in the similarity of the shifts and shift ratios for the C(3) substituents. Thus (**2b**) shows a downfield shift of 1·44 p.p.m. for the C(3) proton and 0·24 p.p.m. for the methylene protons of the benzyl ester, while downfield shifts of 1·42 and 0·27 p.p.m. were observed for the corresponding signals in (**2d**). In contrast (**2c**) shows a greatly enhanced shift (1·15 p.p.m.) for the methylene protons and a corresponding reduction in the shift of the C(3) proton. The assignments of configuration in (**2c**) and (**2d**) parallel those made on the basis of shift values for the corresponding racemic compounds lacking the acylamino side chain.[2]

Repetition of the sequence using the benzyl ester of 2-bromo-3-hydroxypropionic acid gave the corresponding epimers of the 1-oxapenam (**5**)† lacking the geminal methyl groups. Hydrogenolysis of the benzyl ester (**2d**) allowed the isolation of the sodium salt (**2e**),** which was considerably less active than phenoxymethylpenicillin against the same range of bacteria. All compounds showed the expected spectroscopic properties.

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† Satisfactory elemental analysis or accurate mass data.

‡ Penicillin numbering; less than the normal penicillin coupling of 4—5 Hz for *cis*-β-lactams, but clavulanic acid (ref. 1) has J_{cis} 2·8 and J_{trans} 0·8 Hz. Cyclisation of the *trans*-isomers (**3c**) gave the corresponding 5-*epi*-isomers with J_{5-6} <1 Hz.

§ B. G. Christensen and R. W. Ratcliffe, have patented, *e.g.* German Offenlegungsschrift 2411856, 1974, a total synthesis of (±)-1-oxadethiapenicillins, but only isomers having the C(3) proton at δ 3·8—3·9 are described.

¶ Other penicillin esters show the same dominant shifts.

** Attempted removal of the ester group of (**2c**) gave only non-β-lactam material; re-esterification of (**2e**) with benzyl bromide in dimethylformamide gave pure (**2d**).

[1] T. T. Howarth, A. G. Brown, and T. J. King, *J.C.S. Chem. Comm.*, 1976, 266.
[2] A. G. Brown, D. F. Corbett, and T. T. Howarth, *J.C.S. Chem. Comm.*, 1977, in the press.
[3] E. G. Brain, A. J. Eglington, J. H. C. Nayler, M. J. Pearson, and R. Southgate, *J.C.S. Perkin I*, 1976, 447.
[4] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1973, 32.