Tetrahedron Letters No. 52, pp 5063 - 5066. 0040-4039/79/1222-5063$02.00/0

SYNTHESIS OF 2,3-BENZO-1-OXAOCTEM-4-CARBOXYLIC ACID

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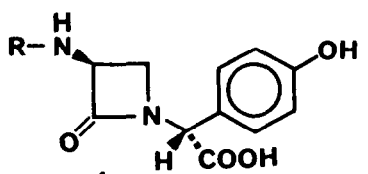
The synthesis, in a form suitable for biological testing, of the parent compound 4 of a new series of tricyclic β-lactams is described.

The recently discovered antibiotic nocardicin A (1) is the only monocyclic β-lactam known to possess *significant* antibacterial activity[1] and, since it was found by a parallel screening technique employing both a parent strain of *E. coli* and a derived mutant strain highly sensitive to β-lactam antibiotics, most likely retains the mode of action of the penicillins and cephalosporins. The moderate level of *in vitro* activity of nocardicin A against a range of Gram-negative bacteria[2] is thus unusual in that the structural elements which reduce amide resonance and thus activate the β-lactam bond in penicillins and cephalosporins[3] are lacking. However the fact that nocardicin A is more active *in vivo*[4] than expected from its *in vitro* MIC's, that its *in vitro* activity increases in the presence of serum and that it appears to act synergistically with polymorphonuclear leucocytes[2] (cells working oxidatively during phagocytosis and leaking oxidants into their environment[5]) suggested to us that the antibacterially active form of nocardicin may be the oxidised form 2. In structure 2, the unshared pair of electrons on the β-lactam nitrogen are now in conjugation with a quinoid system, consequently



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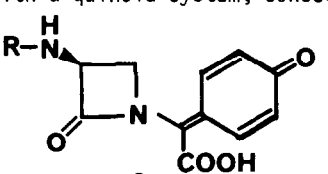

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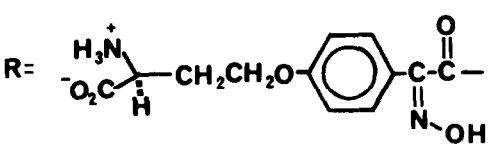
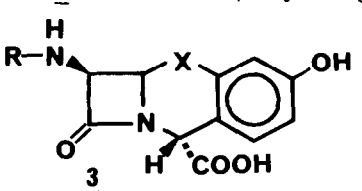


weakening the amide bond[6]. In biological terms this oxidation could correspond to the rearrangement of (inactive) Δ^2-cephalosporins to (active) Δ^3-cephalosporins[3]. To complete the analogy structures such as 3 in which the phenyl ring of nocardicin has been bonded onto the azetidi-



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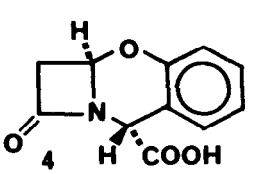
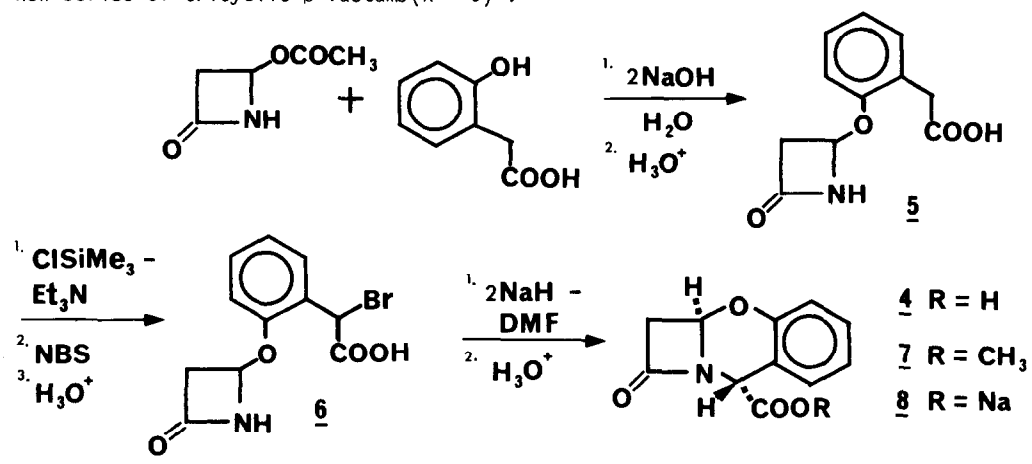


4

none could be envisaged. In this note, we report the synthesis of 4, the parent compound in this new series of tricyclic β-lactams(X = O)[7].



An ice cold solution of 2-hydroxyphenylacetic acid (41.6 mmol, 6.32 g) in 1 N sodium hydroxide (83.2 ml) is added to a solution of 4-acetoxyazetidin-2-one[6] (41.6 mmol, 5.37 g) in water (40 ml) previously cooled to 5°C. After 5 hr. at 0-5°C the solution is extracted once with ethyl acetate and the organic phase is discarded. The ice-cooled aqueous phase is layered with ethyl acetate and acidified to pH 2 by the addition of 1 N HCl. The organic phase is decanted, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.46 g (38 %) of 4-(2-carboxymethyl-phenoxy) azetidin-2-one 5[9] as a white powder m.p. 127-8°C ; infrared max (KBr), 1725 cm^{-1} (-COOH), 1750 cm^{-1} (C = O), 3240 cm^{-1} (N-H) ; pmr ($CDCl_3$-DMSO-d_6), 3-3.2 m (2 H), 3.55 s (2 H), 5.55 m (1 H), 6.7-7.6 m (4 H), 8.55 br, exch. (2 H).

A solution of 5 (35.7 mmol, 7.9 g) in anhydrous THF (100 ml) is treated with triethylamine (140 mmol, 19.6 ml) and trimethylchlorosilane (140 mmol, 15.2 g) at 0°C for 2 hr. The solution is then filtered from precipitated triethylamine hydrochloride and the solvent is replaced by carbon tetrachloride (150 ml). N-Bromosuccinimide (38.5 mmol, 6.85 g) is then added and the suspension is heated at reflux and irradiated with a 250 W tungsten lamp for 50 mn. The solution is filtered from the succinimide and the solvent is replaced by ether (200 ml). This solution was stirred with cold 0.5 N HCl (60 ml) for 15 mn, then decanted, washed with water, dried ($MgSO_4$) and evaporated to give 5.7 g (55 %) of 6 as a low melting solid ; infrared max (KBr), 1710 cm^{-1} (COOH), 1755 cm^{-1} (C=O), 3260 cm^{-1} (N-H) ; pmr ($CDCl_3$-DMSO-d_6), 3.06 m (1 H), 3.22 m (1 H), 5.69 m (1 H), 5.80 s (1 H), 6.8-7.7 m (4 H), 8.95 br, exch (2 H).

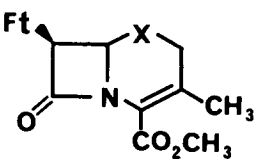
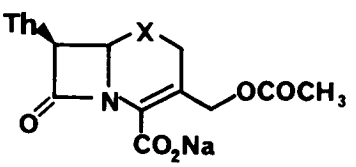
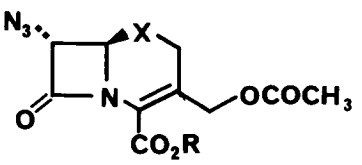
A solution of 6 (8.5 mmol, 2.56 g) in dry DMF (10 ml) contained in a refrigerated addition funnel cooled to 0°C is added dropwise to a stirred suspension of sodium hydride (18 mmol, 0.432 g) in DMF cooled in an ice bath. The solution is diluted with cold phosphate buffer (pH 4.5) and then layered with a mixture of ethylacetate/ether and acidified to pH 2. The organic phase is back extracted with aq. sodium bicarbonate which is then washed with ethyl acetate, acidified to pH 2.5 and extracted with ethyl acetate. After drying and evaporation of solvent the crude 4 (0.96 g) is chromatographed on silica gel (50 g) eluted with methylene chloride-methanol (13:1 v/v) to give 0.52 g (28 %) of pure 2,3-benzo-1-oxaoctem-4-carboxylic acid[9,10] 4 m.p. 155-158°C.

Infrared max (KBr), 1705 cm^{-1} (COOH), 1750 cm^{-1} (C=O) ; pmr ($CDCl_3$-DMSO-d_6, ppm), 3.00 d $J_{7\beta-7\alpha}$ 16 Hz ($H_{7\beta}$), 3.48 dd $j_{7\beta-7\alpha}$ 3.0 Hz and $J_{6-7\alpha}$ 3 Hz ($H_{7\alpha}$), 5.25 s (H_4), 5.56 d $j_{6-7\alpha}$ 3.0 Hz, 6.8-7.5 m (4 arom. H), 11.75 br, exch (1 H).

Diazomethane treatment of 4 gave the methyl ester 7 m.p. 80-81°C ; infrared max (CH_2Cl_2), 1740 cm^{-1} ($COOCH_3$) and 1775 cm^{-1} (C=O).

The coupling constants of the β-lactam protons in 4 (J_{cis}= 3.0 Hz, J_{trans}= 0 Hz) and in 7 (J_{cis}= 3.3 Hz, J_{trans}= 0 Hz) are smaller than those found in penams and cephems (J_{cis}= 4-5 Hz, J_{trans}= 1.5-3 Hz)[11] ; it seems to be a general rule that coupling constants for the β-lactam protons in oxapenam (clavam) and oxacephem systems are always smaller than in the corresponding sulfur compounds. Some examples in the cephem series are given in Table 1.

Table 1. β-Lactam coupling constants (Hz) in cephems and oxacephems.

Structure	X	J_{cis}	J_{trans}	ref.
	S	4.4		12
	O	3.8		13
	S	4.8		14
	O	4.0		15
	X = S R = PMB		1.8	16
	X = O R = Bz		1.0	15

Ft = phthalimido ; Th : thienylacetamido ; PMB = p-methoxybenzyl ; Bz = benzyl.

The relative stereochemistry of compound 4 (H_4 *anti* to H_6, i.e. $H_{4\beta}$ and $H_{6\alpha}$) is based on the following observations :

1. Very few Δ^2 cephems in which the carboalkoxy group at C-4 is in the β position are known ; those which have been isolated readily isomerise to the α position[17-19] .

2. In 4-carboalkoxy Δ^2 cephems[17-19], $H_{4\beta}$ resonates at higher field (5.00-5.27 ppm) than $H_{4\alpha}$ (4.68-4.97). In 4 H_4 appears at 5.25 ppm and in 7 at 5.34 ppm.

3. In both cephem[16-17] and cepham[19] systems $H_{4\alpha}$ is coupled to $H_{7\alpha}$ (1-2 Hz). In 4 and 7 no coupling between H_4 and $H_{7\alpha}$ is detected.

The sodium salt 8 showed no activity *in vitro* or *in vivo* against a series of Gram-positive and Gram-negative bacteria[21].

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19. In related work, we have isolated both 4α and 4β epimers of C-7-substituted 2,3-benzo-1-oxaoctem-4-carboxylates. The 4β compound readily isomerises to the 4α epimer.
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21. We thank Dr. T.D. HENNESSEY, ICI Pharmaceuticals Division, Alderley Park, U.K., for the microbiological assays.

(Received in France 17 October 1979)