Synthesis of 2,3-Benzo-fused 1-Oxacephems

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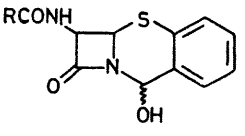
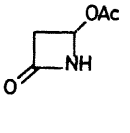
Summary 4-Acetoxyazetidin-2-one (**2**) reacted with salicylaldehyde and 2-hydroxyphenyl ketones to give tricyclic hydroxy-amine products, and the reaction with ethyl 2-hydroxyphenylacetate was employed in the synthesis of a 2,3-benzo-fused ethoxycarbonyl 1-oxa analogue of the cephems.

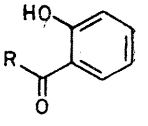
THE antibiotic properties[1] of the synthetic tricyclic β-lactam (**1**), which bears formal similarities to the cephalosporins, prompted us to investigate a potentially brief route to 1-oxa† analogues of (**1**), which is now described. In addition, we report a related synthesis of the 1-oxa-4-carboxylate (**17**), of interest because of recent disclosures on the antibiotic properties of 1-oxacephems.[2] 4-Acetoxyazetidin-2-one (**2**), which has been a key synthon in the β-lactam area,[3] reacted in ethanol–sodium ethoxide with salicylaldehyde (**3**), to give directly, (**10**)‡ (42% after recrystallisation); i.r. (KBr) 1745 cm^{-1}; δ ($CDCl_3$) 2·95 (1H, dd, *J* 1, 14 Hz, *trans* 7-H), 3·40 (1H, dd, *J* 3, 14 Hz, *cis* 7-H), 5·41 (1H, dd, *J* 1, 3 Hz, 6-H), and 5·78 (1H, s, 4-H). *X*-Ray crystallographic analysis[4] established that the 4-OH was *cis* to H-6, and adopted a pseudo-axial conformation with respect to the flattened boat form of the 1,3-oxazine ring. Similar reaction with 2-hydroxyacetophenone (**4**), 2-hydroxybenzophenone (**5**), and with ethyl 2-hydroxybenzoylformate (**6**), led in good yield to the corresponding tricyclic adducts (**7**),‡ (**8**),‡ and (**9**),‡ in which the stereochemistry at C-4 was not rigorously established. The existence of (**7**), (**8**), (**9**), and (**10**) entirely in the cyclic hydroxy-amine form in solution may be compared with similar observations in related five-[5] and six-membered[6] ring systems.



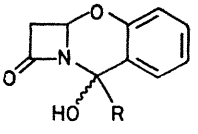
(1)



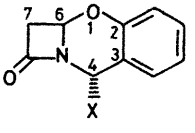
(2)



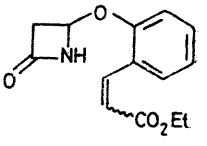
(3) R = H
(4) R = Me
(5) R = Ph
(6) R = CO_2Et



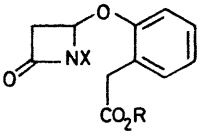
(7) R = Me
(8) R = Ph
(9) R = CO_2Et



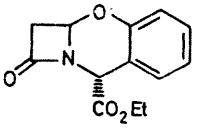
(10) X = OH
(11) X = OAc
(12) $X = N_3$



(13)



(14) X = H, R = Me
(15) X = Br, R = Me
(16) X = H, R = Et



(17)

Displacement reactions of the acetate (**11**)‡ were compared with those[7] of the acetate (**2**). Azide displacement on (**11**) proceeded relatively slowly, to give (**12**)‡ (stereochemistry not defined), compared with the extremely rapid

† The cephalosporin numbering system is employed.

‡ New compounds had satisfactory elemental analyses and/or high resolution mass measurement.

displacement from (**2**). Carbanion displacements on (**11**), intended to give a potential 4-carboxy group, were unsuccessful.

In further pursuit of carbon functionality on C-4, ethyl 2-hydroxycinnamate was condensed with (**2**) to give, as a mixture of geometrical isomers, the adduct (**13**).‡ All attempts to effect intramolecular Michael cyclization were unsuccessful because of competing elimination of the 2-hydroxycinnamate unit.§

An alternative strategy, involving the methyl 2-hydroxyphenylacetate adduct (**14**)‡ was frustrated because attempts to form a benzylic bromide invariably led to the *N*-bromoazetidin-2-one (**15**) (characterized spectroscopically) which could not be cyclized under thermal, free radical, or photochemical conditions. However, the ethyl ester (**16**)‡ was quantitatively brominated in the benzylic position, and cyclization was achieved in dimethylformamide–potassium carbonate to give the target compound (**17**)‡ (10%), i.r. (film) 1773 cm^{-1}; δ ($CDCl_3$) 3·03 (1H, dd, *J* 1, 16 Hz, 7-H), 3·42 (1H, dd, *J* 4, 16 Hz, *cis* 7-H), 5·32 (1H, s, 4-H), and 5·51 (1H, dd, *J* 1, 4 Hz 6-H); *m/e* 247 (M^+), 174 (100%, $M - CO_2Et$), and 132 ($M - CO_2Et - CH_2CO$). The stereochemistry of (**17**) is presumably as depicted.

The tricyclic compounds reported in this study were not significantly active as antibiotics, but structural elaborations are in progress towards this end.

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§ Attempts to circumvent this problem by epoxidation of (**13**) followed by cyclisation led to difficulties because of lack of reproducibility. Similar difficulties were encountered during attempted addition of bromine followed by eliminative cyclization.

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