Stability Problem of the 4-Hydroxy-azetidin-2-one System, a Possible Intermediate in 1-Oxacephem Synthesis

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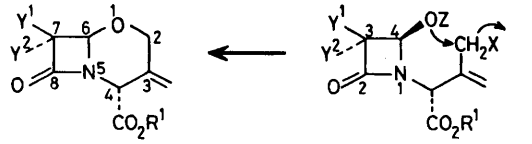
Summary Reduction of the 4-hydroperoxy-azetidin-2-one (**4**) at −50 °C gave the 4-hydroxy-azetidin-2-one (**6**) which was converted into the corresponding trifluoroacetate (**7**); the 4-hydroxy-azetidin-2-ones, which were not isolated, were unstable at room temperature, and appeared to be unpromising as intermediates for 1-oxacephem synthesis.

SINCE the 7α-methoxy-1-oxacephem compounds[1] were shown to have marked antibacterial activity, particularly against gram-negative micro-organisms including β-lactamase-producing, resistant strains, several efficient and practical synthetic methods[2] for new analogues of cephalosporins have been developed.

Our continuing efforts to find an alternative method for synthesizing 3-methylene-1-oxacepham derivatives (**1**) have been focused on utilizing the 4-hydroxy-azetidin-2-one system (**2**) as an intermediate leading to (**1**) by O(1)–C(2) ether bond formation (Scheme 1).

As the β-hydroxy carbonyl function constitutes part of the strained β-lactam ring system in (**2**) and easily undergoes β-lactam ring cleavage by reverse aldol-type reaction,[3] the stability of the 4-hydroxy-azetidin-2-one system is the key to such an approach. It is also interesting to know the nature of the 4-hydroxy-azetidin-2-one system in comparison with that of the 4-mercapto-azetidin-2-one system[4]



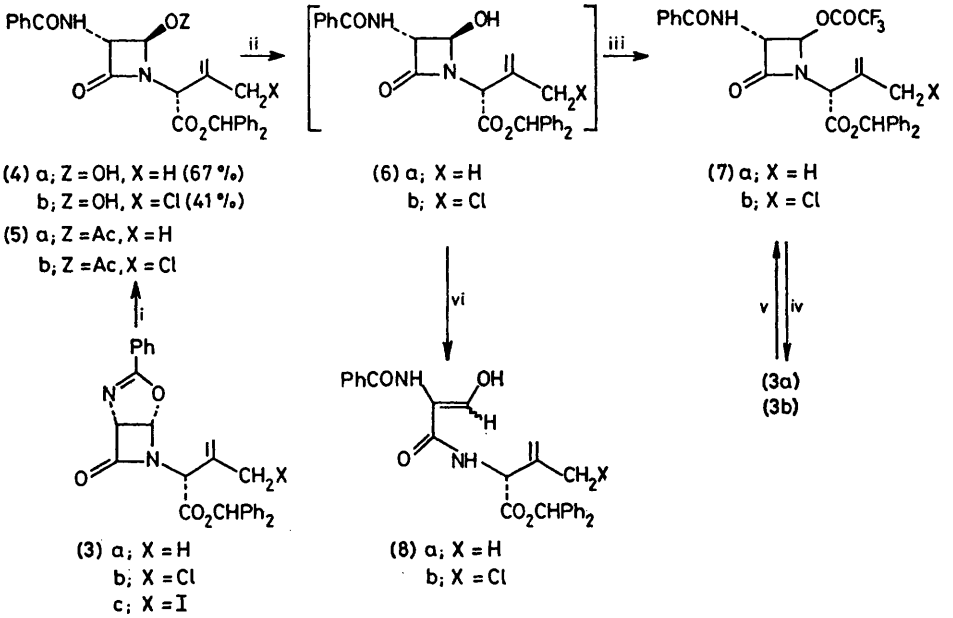
SCHEME 1

which, when appropriately substituted, was successfully used for the syntheses of some cephalosporins.[5] We have therefore investigated the preparation of the hydroxy-azetidinone system (**6**).

On treatment of the azetidinone-*epi*-oxazolines (**3a**) and (**3b**)[2b,6] with 30% aq. hydrogen peroxide in the presence of a catalytic amount of sodium tungstate in a dichloromethane–acetic acid (2 : 1) mixture, 4-hydroperoxy-azetidin-2-one derivatives, (**4a**) (67%) and (**4b**) (41%) were obtained, accompanied by small amounts of 4-acetoxy-azetidin-2-one derivatives, (**5a**) and (**5b**). The iodide (**3c**) failed to give the corresponding 4-hydroperoxy-azetidin-2-one derivative by the same reaction. These 4-hydroperoxy compounds could be expected to be reduced quite

easily under mild reaction conditions to the 4-hydroxy-azetidin-2-one derivatives, and thus the reaction of (**4a**) with dimethyl sulphide in deuteriochloroform at −50 °C was followed by n.m.r. spectroscopy at low temperatures.† The formation of the 4-hydroxy-azetidin-2-one derivative (**6a**) could be detected at −34 °C, [^{1}H n.m.r. spectroscopy in $CDCl_3$ at −34 °C: δ 1·82 (s, 3 H, CH_3), and 5·5—5·78 (br m, 1 H, >C*H*–OH)]. It decomposed slowly on being kept at −15 °C and rapidly while at room temperature to give (**8a**). The half life of (**6a**) at −15 °C is *ca.* 30 min to 1 h. partially reconverted to (**3a**) and (**3b**) on treatment with silica gel (see Scheme 2).

Several attempts which were aimed at synthesizing 3-methylene-1-oxacepham compounds (**1**) *via* the 4-hydroxy-azetidin-2-one intermediates (**2**), derived from appropriate precursors, for example (**2**) (Y^1 = H, Y^2 = PhCONH, R^1 = $CHPh_2$, Z = OH or COH, X = Cl, I or OH), have been unsuccessful. This failure has now been rationalized by the observed instability of the 4-hydroxy-azetidin-2-one intermediate leading to a non-β-lactam compound such as



SCHEME 2. Reagents: i 30 % aq. H_2O_2–Na_2WO_4 (cat.) in AcOH–CH_2Cl_2 (1 : 2), room temp., 4 h. ii CH_3SCH_3 in CH_2Cl_2, −50 to *ca.* −45 °C (**4a**) or −40 to *ca.* −35 °C (**4b**). iii $(CF_3CO)_2O$ in CH_2Cl_2, −50 to *ca.* 25 °C. iv SiO_2. v CF_3CO_2H in AcOEt, 0 °C, 1 h. vi Room temp. in CH_2Cl_2.

The alcohols (**6a**) and (**6b**) obtained by reduction of (**4a**) and (**4b**) with dimethyl sulphide in dichloromethane at low temperature could also be transformed to the corresponding trifluoroacetates (**7a**) and (**7b**) on treatment with trifluoroacetic anhydride at −50 to 25 °C. The esters (**7a**) and (**7b**) were also prepared from (**3a**) and (**3b**) by cleavage with trifluoroacetic acid in ethyl acetate at 0 °C and then were (**8**) under the same reaction conditions used for the intramolecular etherification. This result strongly suggests that such a route *via* the 4-hydroxy-azetidin-2-one intermediate is unpromising.

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† Broadening of the signals occurred below −34 °C owing to the restricted rotations of the amide and the substituent on the azetidinone nitrogen. We thank Dr. Tori for measurement of the spectra and discussions.

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