Preparation of 8-Oxo-7-(1-hydroxyethyl)-3-oxa-1-azabicyclo[4.2.0]octane Derivatives: Intermediates for Thienamycin Synthesis

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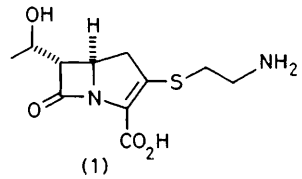
Summary Readily available tetrahydro-1,3-oxazines on acylation with diketen followed by diazo exchange, irradiation, and reduction give 8-oxo-7-(1-hydroxyethyl)-3-oxa-1-azabicyclo[4.2.0]octane derivatives having *trans*-substituents about the β-lactam ring.

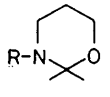
THIENAMYCIN[1] (**1**) is a novel β-lactam antibiotic having a 6α-hydroxyethyl substituent on the β-lactam ring. The total synthesis[2] of (**1**), *via* (**4b**), provides for hydroxyethylation by an aldol reaction α to the β-lactam carbonyl of unsubstituted (**4**; R = H). A similar method has been used to prepare novel C-6(7) substituted penicillins and cephalosporins.[3] Interest in these compounds prompts us to report an alternative preparation of (**4b**) and also the new derivative (**5b**), starting from the tetrahydro-1,3-oxazines (**2a**)[4] and (**3a**),[5] readily available from 3-aminopropan-1-ol and acetone or cyclohexanone.

Reaction of (**2a**) with diketen gave the oily acetoacetamide (**2b**) (60%). Diazo exchange with toluene-*p*-sulphonyl azide and triethylamine readily occurred forming (**2c**) (89%), which on irradiation[6] cyclised† to give exclusively the *trans*-substituted β-lactam product (**4a**) (55%), ν_{max} ($CHCl_3$) 1750 cm^{-1} (β-lactam carbonyl). Reduction of the ketone with sodium borohydride (0 °C, ethanol) resulted in a mixture of the two isomers of the alcohol (**4b**), which on acylation with phenoxyacetyl chloride led to (**4c**) seen as a 1:1 mixture of isomers in the ^1H n.m.r. spectrum.[7] The isomers of (**4b**) correspond to the same mixture prepared by the aldol route.[2]

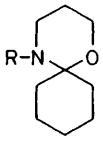
Similarly the tetrahydro-1,3-oxazine (**3a**) was converted *via* (**3b**) into (**3c**). Irradiation of (**3c**) gave a 73% yield of the *trans*-β-lactam (**5a**). Reduction and acylation



(1)

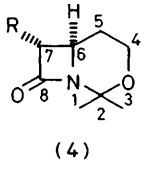


(2)

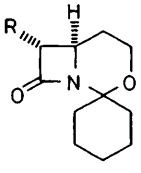


(3)

a; R = H
b; R = $COCH_2COMe$
c; R = $COCN_2COMe$

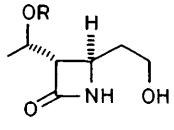


(4)



(5)

a; R = COMe
b; R = $^9CH(OH)Me$
c; R = $^9CH(OCOCH_2OPh)Me$



(6)

† Cyclisation of the diazo compounds (**2c**) and (**3c**) has also been successful (75%) using $Rh_2(OAc)_4$ in dichloromethane (room temperature); with Cu in toluene (90 °C) yields were lower (25%).

provided the two isomers of (**5c**), which could be separated by chromatography on silica gel. Both (**4c**) and (**5c**) gave the same mixture of isomers of the azetidin-2-one (**6**; R = $COCH_2OPh$) on treatment with aqueous acid. All compounds gave satisfactory i.r., n.m.r., and mass spectral data.

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[2] D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1978, **100**, 313.
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[4] J. S. Eden, U.S.P. 2,960,433; (*Chem. Abs.*, 1961, **55**, P8437f).
[5] E. M. Hancock, E. M. Hardy, D. Heyl, M. E. Wright, and A. C. Cope, *J. Amer. Chem. Soc.*, 1944, **66**, 1747.
[6] At −60 °C using a Hanovia 450W medium-pressure lamp. See D. M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc.* (*C*), 1971, 3756.
[7] In $CDCl_3$ using Me_4Si as internal standard; as judged by the intensity of the C7-H signals; δ 2·86 (dd, $J_{6,7}$ 2 Hz, $J_{7,9}$ 8·5 Hz) and δ 2·98 (dd, $J_{6,7}$ 2 Hz, $J_{7,9}$ 5 Hz). See also ref. 2.