

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

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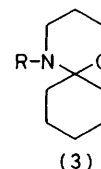
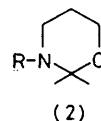
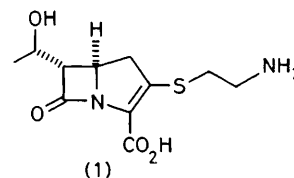
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Summary Readily available tetrahydro-1,3-oxazines on acylation with diketen followed by diazo exchange, irradiation, and reduction give 8-oxo-7-(1-hydroxyethyl)-3-oxa-1-azabicyclo[4.2.0]octane derivatives having *trans*-substituents about the β -lactam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

THIENAMYCIN¹ (**1**) is a novel β -lactam antibiotic having a 6 α -hydroxyethyl substituent on the β -lactam ring. The total synthesis² of (**1**), *via* (**4b**), provides for hydroxy-ethylation 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-amino-propan-1-ol and acetone or cyclohexanone.

Reaction of (**2a**) with diketen gave the oily aceto-acetamide (**2b**) (60%). Diazo exchange with toluene-*p*-sulphonyl azide and triethylamine readily occurred forming (**2c**) (89%), which on irradiation⁶ cyclised† to give exclusively the *trans*-substituted β -lactam product (**4a**) (55%), ν_{\max} (CHCl₃) 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

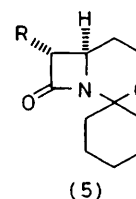
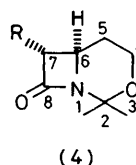
Similarly the tetrahydro-1,3-oxazine (**3a**) was converted *via* (**3b**) into (**3c**). Irradiation of (**3c**) gave a 73% yield of the *trans*- β -lactam (**5a**). Reduction and acylation



a; R = H

b; R = COCH₂COMe

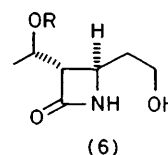
c; R = COCN₂COMe



a; R = COMe

b; R = ⁹CH(OH)Me

c; R = ⁹CH(OCOCH₂OPh)Me



† Cyclisation of the diazo compounds (**2c**) and (**3c**) has also been successful (75%) using Rh₂(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 = COCH₂OPh) on treatment with aqueous acid. All compounds gave satisfactory i.r., n.m.r., and mass spectral data.

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¹ U.S.P. 3,950,358. Abstracts, Sixteenth Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 1976.

² D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, and B. G. Christensen, *J. Amer. Chem. Soc.*, 1978, **100**, 313.

³ F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.*, 1977, **42**, 2960.

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 CDCl₃ using Me₄Si 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.