A Novel Photochemical Route to Functionalised β-Lactams

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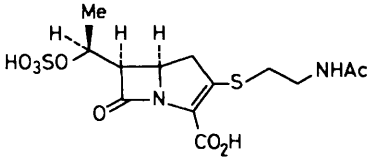
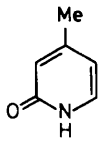
Summary 2-Methyl-5-azabicyclo[2.2.0]hex-2-en-6-one, a photoisomer of 4-methyl-2-pyridone, is transformed upon ozonolysis and reduction into two diastereoisomeric azetidin-2-ones, substituted at the 3- and 4-positions.

ANTIBIOTICS of the olivanic acid series,[1] *e.g.* (**1**), differ most significantly from the related thienamycins in their *cis* disposition of the two hydrogen atoms on the β-lactam ring.



(1)



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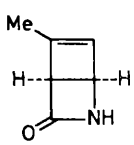

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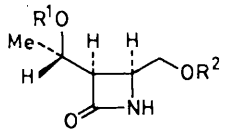
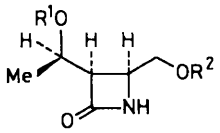
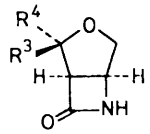


(4a) $R^1 = R^2 = H$
(5a) $R^1 = R^2 = Ac$
(6a) $R^1 = H$, $R^2 = Si(Me)_2Bu^t$



(4b) $R^1 = R^2 = H$
(5b) $R^1 = R^2 = Ac$
(6b) $R^1 = H$, $R^2 = Si(Me)_2Bu^t$



(7)
a; $R^3 = H$, $R^4 = Me$
b; $R^3 = Me$, $R^4 = H$

In an effort to develop a general synthetic approach to structures related to (**1**) the utility of 4-methyl-2-pyridone (**2**) was examined, since manipulation of its photoisomer, 2-methyl-5-azabicyclo[2.2.0]hex-2-en-6-one (**3**),[2] ought to allow access to disubstituted β-lactams of defined relative stereochemistry.

Thus, irradiation of (**2**) at 310 nm gave (**3**) in 50—60% yield.† Ozonolysis (−78 °C, MeOH) followed by *in situ* reduction ($NaBH_4$) of the ozonolysis product gave a mixture of the monocyclic β-lactams (**4a**) and (**4b**) (75%, *ca.* 1:1)‡ which could be separated chromatographically. The ^1H n.m.r. spectra of these compounds§ confirmed their gross structures, while conversion into the *OO'*-diacetates (**5a**) and (**5b**) (Ac_2O, pyridine) allowed confirmation that the *cis* stereochemistry across the C(3) and C(4) positions of the ring had been retained ($J_{3,4}$ 5 Hz)[3].

The important ability to discriminate chemically between the primary and secondary alcohol groups was demonstrated by the reaction of (**4a**) and (**4b**) with t-butyldimethylsilyl chloride (0 °C, pyridine) which in each case yielded the desired silyl ethers (**6a**) and (**6b**) (each 80%).¶ The relative stereochemistries of the C(3) hydroxyethyl side-chains were indicated by the ^1H n.m.r. $J_{3,5}$ values observed for (**6a**) and (**6b**) which were 10·5 Hz and 6 Hz, respectively, and which correlate with reported values[3] for *cis* (*S**) and *cis*-(*R**) hydroxyethyl side-chains in related structures. Further support for these assignments was obtained by monotosylation-cyclisation reactions on (**4a**) and (**4b**) which gave rise to the isomeric bicyclic structures (**7a**) and (**7b**), respectively. Since only one isomer was formed in each case selective functionalisation was assumed to have taken place, as previously, on the primary hydroxy-group. On the basis of ^1H n.m.r. shifts of the methyl groups of (**7a**) and (**7b**)[4] the structures were assigned as shown, and thus the stereostructures of (**4a**) and (**4b**) were confirmed.

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† Higher yields of (**3**) (> 60%) were obtained by using higher dilution of (**2**) (< 1 g l^{-1}); 1·5 g l^{-1} of (**2**) gave (**3**) in 55% yield.

‡ All compounds are racemic mixtures of which one enantiomer is shown. New compounds gave satisfactory spectrocopic and analytical data.

§ The structures of the lactams (**4**), (**5**), and (**6**) were confirmed on the basis of their 220 MHz ^1H n.m.r. spectra.

¶ This selectivity was confirmed by acetylation of the remaining hydroxy-group and observing the ^1H n.m.r. chemical shift of the α-methine multiplet move to the position observed for the diacetate; silylation did not result in significantly different n.m.r. shifts from those observed in the alcohols.

[1] A. J. G. Baxter, P. Davis, R. J. Ponsford, and R. Southgate, *Tetrahedron Lett.*, 1980, **21**, 5071, and references therein.
[2] The synthesis of similar bicyclic photoisomers had been reported: R. C. De Selms and W. R. Schleigh, *Tetrahedron Lett.*, 1972, 3563; H. Furrer, *Chem. Ber.*, 1972, **105**, 2780; C. Kaneko, K. Shiba, H. Fujii, and Y. Momose, *J. Chem. Soc., Chem. Commun.*, 1980, 1177.
[3] Related azetidin-2-ones bearing carbon substituents upon C(3) and C(4) show ^1H n.m.r. $J_{3,4}$ values of 1·5 Hz in the *trans* case and 5 Hz in the *cis* case: F. A. Bouffard, D. B. R. Johnston, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1130.
[4] It was assumed that the *endo* methyl group would experience a deshielding effect resulting from the proximity of the carbonyl group; this is in accord with ^1H n.m.r. data for 2,2-dimethylbicyclo[3.2.0]heptan-7-one derivatives: A. Hassner, R. M. Cory, and N. Sartoris, *J. Am. Chem. Soc.*, 1976, **98**, 7898.