A New Route to 4-Alkylthio-3-phenylacetamidoazetidin-2-ones

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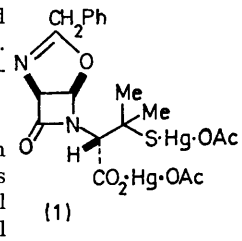
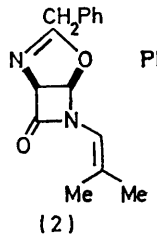
Summary The oxazoline-azetidinone (**2**) reacts with alkanethiols in the presence of toluene-*p*-sulphonic acid to give mixtures of (3*R*,4*R*)-[*e.g.* (**4a**)] and (3*R*,4*S*)-[*e.g.* (**5a**)] 4-alkylthio-1-(2-methylpropenyl)-3-phenylacetamidoazetidin-2-ones.

RECENTLY it was shown[1] that the salt (**1**), obtained from potassium benzylpenicillinate and mercury(II) acetate, was converted into the oxazoline-azetidinone (**2**) by dimethyl sulphoxide. The derivative (**2**) is a potentially useful precursor of β-lactam antibiotic analogues if nucleophiles can be introduced at position 1 with retention of configuration. A study of the reaction of the oxazoline–azetidinone (**2**) with acidified alcohols or with organic acids has demonstrated that, although 1,2-bond cleavage occurred, the nucleophiles entered with inversion of configuration at position 1; thus, the *trans*-azetidinone (**3**) was formed with methanol in the presence of toluene-*p*-sulphonic acid.[2]

When treated with methanethiol containing a trace of toluene-*p*-sulphonic acid, the oxazoline–azetidinone (**2**) was converted into a less-polar product (41% after silica gel chromatography). Although a single entity on t.l.c., the material was shown to be a mixture (1·8:1) of two components by n.m.r. spectroscopy. The major constituent, m.p. 120—122°, $[\alpha]_D$ −19° ($CHCl_3$), which crystallised from the mixture on addition of ether, was considered to be the *cis*-azetidinone (**4a**).† Careful fractionation of the mother liquor by silica-gel chromatography (benzene–ether as eluant; fractions were monitored by n.m.r. spectroscopy) yielded the minor constituent as a syrup, $[\alpha]_D$ −12° ($CHCl_3$); it was considered to be the *trans*-azetidinone (**5a**).†

The oxazoline-azetidinone (**2**) reacted with several other thiols under corresponding conditions (Table). In each


(1)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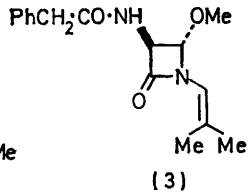
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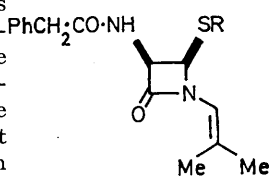
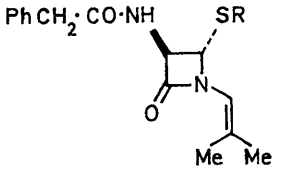
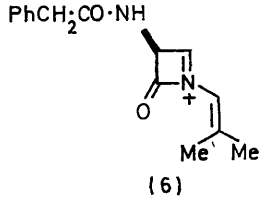

(4)

a; R=Me
b; R=Et
c; R=Bu^n
d; R=EtCH(Me)
e; R=Bu^t


(5)

f; R=CH_2:CH·CH_2
g; R=HS·CH_2·CH_2
h; R=AcO·CH_2·CH_2
i; R=MeO_2C·CH_2
j; R=MeO_2C·CH_2·CH_2


(6)

† The composition of new compounds was confirmed by elemental analysis and/or by mass spectroscopy. Structural assignments are based upon i.r. and n.m.r. spectroscopic evidence.

TABLE

Reaction of the oxazoline–azetidinone (**2**) with thiols

Thiols	Azetidinones produced	Yield/%[a]	Ratio (*cis*:*trans*)[b]
Ethanethiol	(**4b**) and (**5b**)	52	1·5:1
Butane-1-thiol	(**4c**) and (**5c**)	46	1·5:1
Butane-2-thiol	(**4d**) and (**5d**)	30	2·0:1
2-Methylpropane-2-thiol	(**4e**) and (**5e**)	20	1·5:1
Allylthiol	(**4f**) and (**5f**)	34	1·8:1
Ethane-1,2-dithiol	(**4g**) and (**5g**)	57	1·2:1
2-Mercaptoethyl acetate	(**4h**) and (**5h**)	34	1:1
Methyl mercaptoacetate	(**4i**) and (**5i**)	18	1:1·5
Methyl 3-mercaptopropionate	(**4j**) and (**5j**)	29	1:1·1

[a] Based upon the weight of the azetidinones isolated after silica gel chromatography. [b] Estimated by n.m.r. spectroscopy.

case a mixture of the *cis*- and the *trans*-azetidinone was produced.

The foregoing reactions are of interest in two respects. First, they illustrate that the 1,2-bond of the oxazoline-azetidinone (**2**) can be cleaved by thiols with inversion or with retention of configuration. This result, which contrasts with that observed for alcohols[2] [in which the 1,2-bond of the derivative (**2**) was ruptured with inversion of configuration], suggests that the cation (**6**) is an intermediate in the reaction. Secondly, they exemplify a new general route to 1-substituted *cis*- and *trans*-4-alkylthio-3-phenylacetamidoazetidin-2-ones. 1-Substituted *cis*-azetidin-2-ones bearing 3-acylamino- and 4-alkylthio-substituents are of considerable current interest.[3] They have been previously prepared from 3-hydroxypenams,[4] penicillanic acid esters,[5] penicillin esters[6] and their sulphoxides,[7] a cepham,[8] and by total synthesis.[9]

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[1] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181.
[2] D. F. Corbett and R. J. Stoodley, *J.C.S. Perkin I*, 1974, 185.
[3] 'Cephalosporins and Penicillins,' ed. E. H. Flynn, Academic Press, New York, 1972; R. J. Stoodley, *Progr. Org. Chem.*, 1973, **8**, 102.
[4] K. Heusler, *Helv.Chim. Acta.*, 1972, **55**, 388.
[5] J. P. Clayton, J. H. C. Nayler, R. Southgate, and P. Tolliday, *Chem. Comm.*, 1971, 590.
[6] M. Yoshimoto, S. Ischihara, E. Nakayama, E. Shoji, H. Kumano, and N. Soma, *Tetrahedron Letters*, 1972, 4387; N. Numato, Y. Imashiro, I. Minamida, and M. Yamaoka, *ibid.* p. 5097.
[7] I. Ager, D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, G. H. Hewitt, B. E. Looker, A. Mowatt, C. A. Robson, and W. G. E. Underwood, *J.C.S. Perkin I*, 1973, 1187.
[8] R. J. Stoodley and N. S. Watson, *J.C.S. Perkin I*, 1973, 2105.
[9] R. Lattrell, *Angew. Chem. Internat. Edn.*, 1973, **12**, 925.