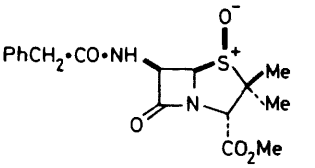
(3*R*,4*R*)-4-t-Butylthio-3-phenylacetamidoazetidin-2-one: a Useful Precursor of Penicillin Analogues

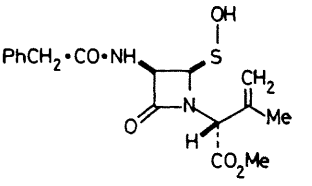
By ARUN C. KAURA, CHRISTOPHER D. MAYCOCK, and RICHARD J. STOODLEY*
(*Department of Organic Chemistry, The University, Newcastle upon Tyne* NE1 7RU)

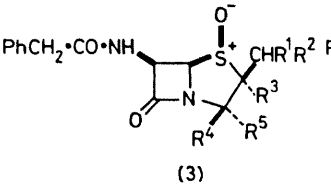
Summary The preparation of the title azetidinone and its conversion into (1*S*,5*R*,6*R*)-2,2-dimethyl-6-phenylacetamidopenam 1-oxide are described.

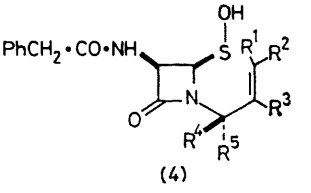
IT is well established[1] that penicillin ester sulphoxides, *e.g.* (**1**), afford low equilibrium concentrations of sulphenic acids, *e.g.* (**2**), at *ca.* 80 °C. In principle, therefore, it should be possible to prepare modified penicillins of type (**3**) from sulphenic acids of type (**4**). Two problems must be solved to achieve such an objective. First, it is necessary to unmask the reactive sulphenic acid group under conditions in which it will react intramolecularly with the double bond and, secondly, the modified *N*-substituent must be capable of being elaborated in the presence of the latent sulphenic acid group. The t-butylsulphinyl group is known to serve as a precursor of the sulphenic acid function and, indeed, 5-t-butylsulphinylpent-1-ene has been shown[2] to afford *cis*-2-methylthiolan 1-oxide when thermolysed; furthermore, the *N*-alkylation,[3] *N*-hydroxylation,[4] and *N*-acetylation[5] of 1-unsubstituted azetidin-2-ones are established reactions. These considerations led to the selection of the azetidinone (**5a**) as the candidate to test the afore-mentioned possibilities.

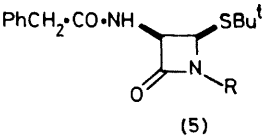
Treatment of the readily available propenyl derivative (**6a**)[6] with *N*-bromoacetamide in aqueous acetone afforded the bromohydrin (**6b**)† (68%), m.p. 111—114 °C, as a 3:1 mixture of isomers (n.m.r. spectroscopy). Compound

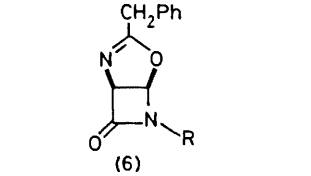

(1)


(2)


(3)


(4)


(5)
(a) R = H
(b) R = CH_2·CMe=CH_2

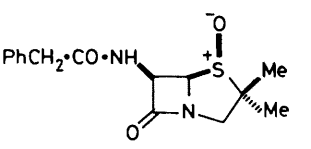

(6)
(a) R = CH=CMe_2
(b) R = CH(OH)·CMe_2Br

† This compound was identified by its spectral properties; its composition was confirmed by elemental analysis and/or by mass spectroscopy.

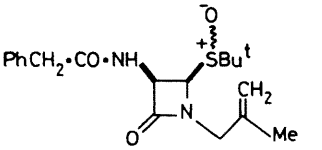
(**6b**) was converted, in the presence of t-butayl thiol and triethylamine, into the required azetidinone (**5a**)† (40% after silica gel chromatography), m.p. 57—58 °C, $[\alpha]_D$ −34° ($CHCl_3$).‡

To evaluate the feasibility of employing the azetidinone (**5a**) as a precursor of penicillin analogues, the compound (**7**) was selected as a target system. In this example, the opportunity for the intermediate sulphenic acid to undergo the prescribed cyclization was expected to be particularly favourable.

Treatment of the azetidinone (**5a**) with methallyl bromide and potassium t-butoxide in *NN*-dimethylformamide afforded the derivative (**5b**)† (46% after silica gel chromatography), m.p. 146 °C, $[\alpha]_D$ −16° (EtOH). Oxidation of the compound (**5b**) with sodium periodate in aqueous methanol yielded the sulphoxide (**8**) (90%), as a 2:1 mixture of isomers; silica gel fractionation afforded the more mobile minor isomer,† m.p. 118 °C, $[\alpha]_D$ +24° (EtOH), and the less mobile major isomer,† m.p. 108 °C, $[\alpha]_D$ +151° (EtOH). When heated in dry benzene under nitrogen (44 h), the sulphoxide (**8**), as a mixture of isomers, was converted into the penam sulphoxide (**7**)†§ (64% after silica gel chromatography), m.p. 123—125 °C, $[\alpha]_D$ +205° (EtOH).



(7)



(8)

The foregoing results reveal that the *N*-alkylation of monocyclic azetidinones can be achieved in the presence of the 4-t-butylthio function and that the t-butylsulphinyl group provides a means of unmasking the sulphenic acid group under conditions which are mild enough for intramolecular trapping reactions to be achieved. Clearly, the azetidinone (**5a**) holds considerable promise as a precursor of a wide range of bicyclic analogues of the β-lactam antibiotics.

We thank Dr. J. H. C. Nayler for his interest, Beecham Pharmaceuticals for a research studentship (to A.C.K.), and the S.R.C. for a CASE award (to C.D.M.).

(*Received*, 1*st October* 1979; *Com.* 1047.)

‡ The crude product contained both (**5a**) and its *trans*-isomer (*ca.* 5:1).

§ The stereochemistry of the sulphinyl group of this compound was established by benzene-induced chemical shift studies (see D. H. R. Barton, F. Comer, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1969, **91**, 1529).

[1] D. H. R. Barton, F. Comer, D. G. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Comm.*, 1970, 1059; R. D. G. Cooper, *J. Amer. Chem. Soc.*, 1970, **92**, 5010.
[2] D. N. Jones and D. A. Lewton, *J.C.S. Chem. Comm.*, 1974, 457.
[3] E. Testa, L. Fontanella, and V. Aresi, *Annalen*, 1964, **673**, 60.
[4] C. Cignarelli, C. F. Cristiani, and E. Testa, *Annalen*, 1963, **661**, 181.
[5] E. Testa, G. Pifferi, L. Fontanella, and V. Aresi, *Annalen*, 1966, **696**, 108.
[6] R. J. Stoodley and N. R. Whitehouse, *J.C.S. Perkin I*, 1974, 181.