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Synthesis of 3-Carboxyisopenam Sulphone: an Analogue of Penicillanic Acid Sulphone

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Summary The title compound has been prepared by a five-step sequence from 4-iodomethylazetidin-2-one

PENICILLANIC ACID SULPHONE (CP-45 899) (**1**) is a powerful semi-synthetic inhibitor of β-lactamases produced by many pathogenic bacteria [1] By analogy with clavulanic acid,[2] it seems likely that the inhibitory action of compound (**1**) is associated with the formation of the aminoacrylate (**2**) Because of its vinylogous urethane character, hydrolysis of the ester linkage of species (**2**) is impeded, hence, the

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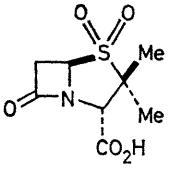
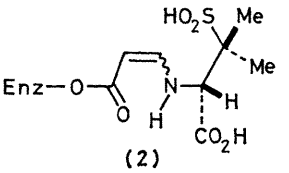
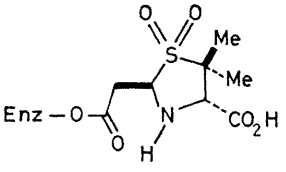
enzyme remains bound to the substrate and becomes inactivated. The aminoacrylate (**2**) is probably formed by way of intermediates (**3**) and (**4**); since *N*-unsubstituted thiazolidine sulphones have never, as far as we are aware, been isolated, the (**3**) → (**4**) transformation may well be spontaneous.



(1)



(2)



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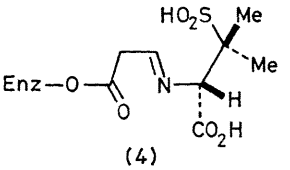

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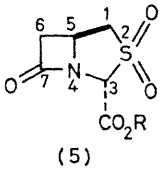
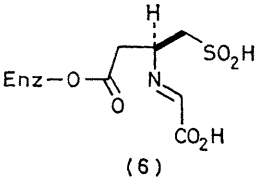


(5)

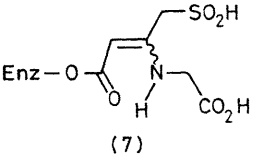
a; R = H
b; R = Na
c; R = Bu^t
d; R = $CH_2C_6H_4NO_2$-*p*



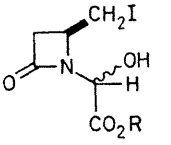
(6)

In theory, the isopenam† sulphone (**5a**) might also act as a β-lactamase inhibitor if opening of the β-lactam were followed by formation of an acyclic intermediate (**6**) which then rearranged to the aminoacrylate (**7**). We now describe the synthesis of the sulphone (**5b**) and report its biological properties.

Sequential treatment of the azetidinone (**8a**)[3] with lutidine–thionyl chloride (tetrahydrofuran, −40 °C),[4] hydrogen sulphide (CH_2Cl_2, 0 °C), and triethylamine led to two major products which were separated by silica gel chromatography. The more mobile material (30%) was the isopenam (**9a**)‡ and the less mobile material (15%) was the isopenam (**10a**).‡ By a similar reaction sequence, the isopenams (**9b**)‡ (20%) and (**10b**)‡ (30%), m.p. 108—112 °C, were derived from the azetidinone (**8b**). The relative configuration of the 3- and 5-positions of the isopenams was indicated by n.m.r. spectroscopy;[5,6] in compounds (**9a**) and (**9b**) the 3-hydrogen atom absorbed ($CDCl_3$) at δ 5·35 and 5·56, respectively, whilst in compounds (**10a**) and (**10b**) it resonated at δ 4·50 and 4·74, respectively. Furthermore, when treated with a trace of 1,5-diazabicyclo[4.3.0]non-5-ene, compounds (**10a**) and (**10b**) were converted into the isomers (**9a**) and (**9b**); the *cis* orientation of the 3-carboxylate and the 5-hydrogen represents the thermodynamically preferred situation in related systems.[6]

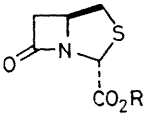


(7)



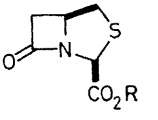
(8)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*



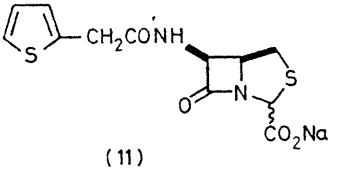
(9)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*
c; R = Na



(10)

a; R = Bu^t
b; R = $CH_2C_6H_4NO_2$-*p*



(11)

Oxidation ($KMnO_4$, HOAc–H_2O)[7] of a 1:1 mixture of compounds (**9a**) and (**10a**) led to the sulphone (**5c**)‡ (59% after SiO_2 chromatography), m.p. 120—122 °C; under similar conditions, the isopenams (**9b**) and (**10b**) afforded the sulphone (**5d**)‡ (55% and 63%, respectively). Clearly, epimerisation of the isopenams (**10a**) and (**10b**) (or of the derived sulphones) occurred under the experimental conditions.

An attempt to convert the ester (**5c**) into the acid (**5a**), by the action of trifluoroacetic acid, was unrewarding; cleavage of the β-lactam ring occurred prior to the loss of the t-butyl ester unit. Hydrogenolysis (H_2, Pd/C) of the ester (**5d**) in the presence of sodium hydrogen carbonate, however, proved to be successful and afforded the salt (**5b**)‡ (60%).

In contrast with the sulphone (**1**), compound (**5b**) did not inactivate the β-lactamase from *Pseudomonas aeruginosa*. Evidently, the location of the sulphonyl group at position 1 of compound (**1**) is an essential requirement for bioactivity.

† The trivial name 'isopenam' has been proposed for 7-oxo-4-thia-1-azabicyclo[3.2.0]heptane (M. S. Manhas and A. K. Bose, in 'Synthesis of Penicillin, Cephalosporin C, and Analogs,' Marcel Dekker, New York, 1966, p. 53); this system is numbered in the same way as a penicillin [see (**5**)].

‡ This compound, obtained as a racemate, was characterised by its spectral properties.

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Recently, it was reported[8] that the racemate of the isopenicillin (**11**), as a mixture of C-3 epimers, inhibited the growth of several bacteria including *Staphylococcus aureus*. Hydrogenolysis (H_2, Pd/C) of the ester (**9b**) in the presence of sodium hydrogen carbonate afforded the salt (**9c**)‡ (80%) which showed no antimicrobial activity against *Staphylcoccus aureus* or *Salmonella typhi*. Clearly, the presence of a *cis*-orientated acylamino group at position 6 is necessary for the bioactivity of isopenam-3-carboxylic acids.

We thank Professor E. P. Abraham, F.R.S. for testing the salts (**5b**) and (**9c**). We are also grateful to the N.R.D.C. for the award of a research fellowship (to C. M. P.).

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