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A STEREOSPECIFIC SYNTHESIS OF CIS-β-LACTAMS[1]

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A widely used method of β-lactam synthesis consists of the reaction of an acid chloride with an imine in presence of a base. The stereochemistry of the β-lactam formed in such a reaction is unpredictable — in most cases the product is either a trans-β-lactam, or a mixture of cis- and trans-β-lactams.[2] Other synthetic approaches, for example the reaction of an α-bromoester with a Schiff-base and zinc[3] or the photolysis of an unsaturated amide,[4] also give mixtures of isomers or only the trans-isomer. We wish to report a facile method for the stereospecific synthesis of cis-β-lactams.

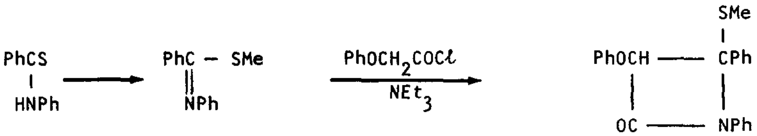
The reaction of the thioimidate (2) (prepared by treating the thioamide (1) with methyl iodide under alkaline conditions) with phenoxyacetyl chloride and triethylamine gave a single β-lactam (3)[5] in 80-90% yield.[6] Desulfurization of (3) with Raney nickel in boiling ethanol produced in about 50% yield a new β-lactam (4a) which was identified as cis-1,4-diphenyl-3-phenoxyazetidin-2-one described previously.[7] In a similar fashion several other cis-β-lactams (4b, 4c, 4d) were prepared.

A secondary product in the desulfurization reaction was the amide (5) which could arise by the cleavage of the C_4-S, C_4-N and C_3-OPh bonds. The use of acetone in place of ethanol as the solvent made the desulfurization reaction milder, improved the yields and reduced the cleavage of the β-lactam ring.

Using the appropriate cyclic imines, single isomers of fused β-lactams (6), (7), (8) incorporating a thiazolidine or a thiazine ring were obtained which upon desulfurization gave cis-β-lactams (9), (10) and (11) respectively. The sulfoxides corresponding to (6), (7) and (8) also underwent easy desulfurization to afford cis-β-lactams (9), (10) and (11).

In case of the cepham derivative (8), the resonance of the -OMe protons occurred at higher field (δ 3.10) than usual indicating that the phenyl group at the ring junction and the methoxy group were cis to each other. Since the cepham (8) and the corresponding sulfoxide afforded a *cis*-β-lactam, desulfurization must occur with retention of configuration.[8] The retention of configuration in these reactions was further confirmed by the desulfurization of the *trans*-β-lactam (12) using deuterated Raney nickel in CH$_3$OD. The product (13) showed about 70% deuterium incorporation as determined by mass spectroscopy and retained its *trans* stereochemistry. It can be concluded therefore that all the β-lactams prepared from thioimidates by treatment with acid chlorides have E-configuration. On the basis of the current views regarding the mechanism of β-lactam formation[9] it is not easy to account for the directive influence of the thioether function resulting in stereospecificity in β-lactam formation.[10]

The β-lactams in penicillin and cephalosporin C are *cis* in stereochemistry; their *trans*-isomers have little biological activity.[11] The preparative method described here for *cis*-β-lactams is therefore of potential value to synthetic and medicinal chemistry — especially as naturally occurring monocyclic β-lactams have been discovered recently.[12]



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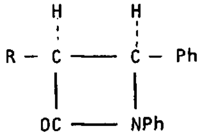

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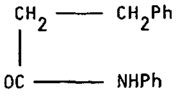

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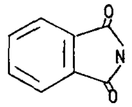
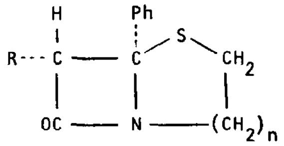
(a) R = PhO

(b) R = CH$_3$O

(c) R = Ph

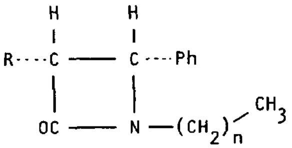
(d) R = 



(6) n = 1, R = PhO

(7) n = 2, R = PhO

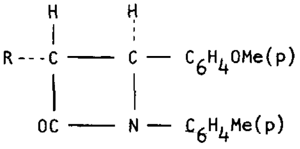
(8) n = 2, R = MeO



(9) n = 1, R = PhO

(10) n = 2, R = PhO

(11) n = 2, R = MeO



(12) R = $PhCH_2S$

(13) R = D

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