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THE CONVERSION OF SECOPENICILLANIC ACID DERIVATIVES INTO NEW AZETIDINONES AND OXAZOLINE-AZETIDINONES.

David H. Bremner, Malcolm M. Campbell,* and Graham Johnson
Department of Chemistry,
Heriot-Watt University,
Riccarton, Edinburgh EH14 4AS.

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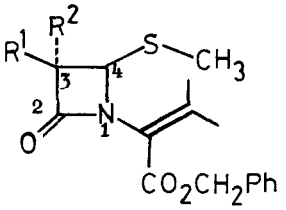
The isolation of a naturally occurring antibiotic 7α-methoxy cephem[1] has prompted much recent research[2] into the introduction of 6α-substituents in penams and 7α-substituents in cephems. We have recently demonstrated[3] a facile one step method of introducing a carbamate moiety at C-6 of the penam nucleus and have further shown[4] that certain penam sulphoxides can be similarly transformed into 6,6-disubstituted systems in which the original acylamino side chain has been displaced. We now report the formation of the 3,3-disubstituted azetidin-2-ones (7,9,10,11) and the novel 5-substituted oxazoline azetidinones (12) and (13) which may be of importance as precursors of β-lactam antibiotic analogues.

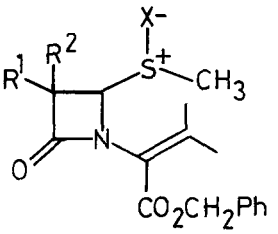
The secopenicillanic acid derivatives (1-3) did not react with N-chloro-N-sodiourethane (N.C.N.S.U.) in contrast to related penicillanates[3,4]. The sulphoxides (4,5) derived from (1,2), however, underwent facile reaction. For example, the acetamido sulphoxides (4)[4] (an inseparable mixture of two diastereoisomers) reacted readily with N.C.N.S.U. in acetonitrile to give two separable sulphoxide products which were shown by analytical and spectroscopic analysis to be the 3,3-disubstituted azetidin-2-ones (7)≠ differing only in sulphoxide chirality.

The sulphoxide diastereoisomers (7) were converted into a common sulphone (11)≠ $[\alpha]_D^{20}$ -76° by reaction with m-chloroperbenzoic acid. Similarly, the phenoxyacetamidoazetidin-2-one sulphoxides (5)[5] were transformed into separable products shown to be diastereoisomers of structure (7). The phthalimidoazetidin-2-ones (6) were unreactive towards N.C.N.S.U., indicating the involvement of the secondary amide sidechain in the reactions of compounds (4) and (5).

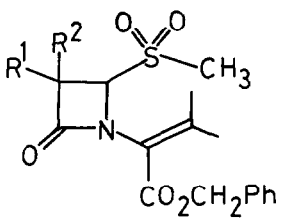
* Author to whom correspondence should be addressed.



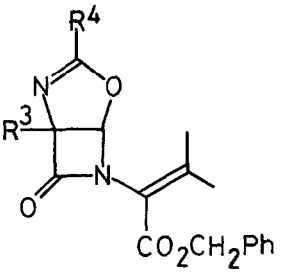
1) R^1 = MeCONH, R^2=H
2) R^1 = $PhOCH_2CONH$, R^2=H
3) R^1 = Phthalimido, R^2=H



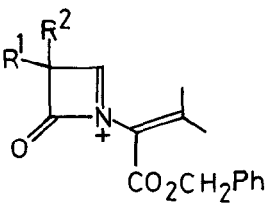
4) R^1 = MeCONH, R^2 = H , X = 0
5) R^1 = $PhOCH_2CONH$, R^2 = H , X = 0
6) R^1 = Phthalimido, R^2 = H , X = 0
7) R^1 = R^2 = EtO_2CNH, X = 0
8) R^1 = MeCONH, R^2 = H , X = NTOS
9) R^1 = MeCONH, R^2 = EtO_2CNH , X = NTOS
10) R^1 = R^2 = EtO_2CNH, X = NTOS



11) R^1 = R^2 = EtO_2CNH



12) R^3 = EtO_2CNH, R^4 = OEt
13) R^3 = EtO_2CNH, R^4 = Me



14) R^1 = R^2 = EtO_2CNH

With the objective of synthesising novel 5-substituted oxazoline azetidinones, the corresponding reactions of the sulphimides (8)# with N.C.N.S.U. were investigated. In addition to the expected 3,3-disubstituted sulphimides (10)≠, the 3-acetamido-3-urethane sulphimides (9)≠ were also isolated. Products (9) and (10) were obtained as an inseparable mixture of diastereoisomers. Utilising the facile oxidative elimination of the sulphimide group by m-chloroperbenzoic acid[5], the diastereoisomers (10) were converted into the 5-substituted oxazoline azetidinone (12)≠ $[\alpha]_D^{20}$ 0° whereas the diastereoisomers (9) afforded product (13)≠ $[\alpha]_D^{20}$ +20.8°. It is possible that the product (12) is a racemate, which could arise from the symmetrical intermediate (14). Such an intermediate is not possible in the reaction of (9).

The detailed mechanism of the reaction of penicillin derivatives with N.C.N.S.U. is not yet clear, although a probable pathway includes initial N-chlorination followed by dehydrohalogenation to the 3-imino intermediate, and subsequent nucleophilic attack of 'urethane' anion.

The modes of reaction of secopenicillanic acid derivatives with N.C.N.S.U. complement the reactions of penams[3,4], and highlight the difference in activation of the methine proton at C-6 in penams and C-3 in secopenicillanate derivatives.

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References and Footnotes

≠ All new compounds gave correct elemental analyses and/or molecular ion, high resolution mass measurement.

Although it is possible to prepare a single sulphimide in certain reactions it was found more convenient in this study to work with the diastereoisomeric mixture.

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