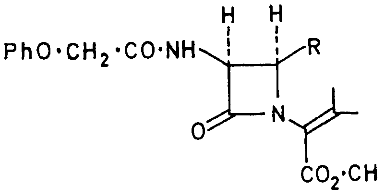
Oxidation of Some 1,2-Seco-penicillins

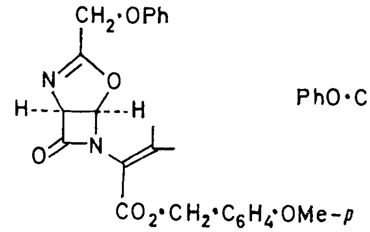
By E. G. Brain, A. J. Eglington, J. H. C. Nayler,* M. J. Pearson, and R. Southgate
(*Beecham Research Laboratories, Brockham Park, Betchworth, Surrey* RH3 7AJ)

Summary Lead tetra-acetate attacks (3*R*:4*R*)-1-(1-*p*-methoxybenzyloxycarbonyl-2-methylprop-1-enyl)-4-methylthio-3-(phenoxyacetamido)azetidin-2-one (I) at the sulphur atom and the adjacent carbon atoms, whereas osmium tetroxide and potassium permanganate remove the complete substituent from the β-lactam nitrogen of (I) and other 1,2-seco-penicillins.

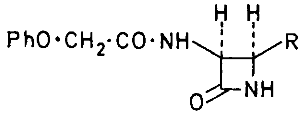
A RECENT report[1] described certain non-fused β-lactams obtained *via* a novel cleavage of the 1,2-bond of 6-tritylaminopenicillanates. Although these 1,2-seco-penicillins [*e.g.* (I) and the corresponding acid] have no significant antibacterial activity, they could prove valuable as intermediates for new fused β-lactams which might be active. A possible first step in such a scheme would be the introduction of functionality into the isopropylidene group, either by allylic substitution or by addition to the double bond. Some results of our attempts to introduce various oxygenated substituents are reported here.



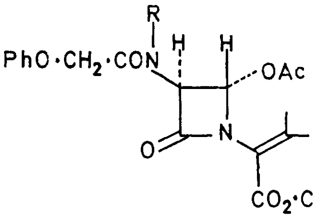
(I) R = SMe
(II) R = SO·Me
(III) R = SCH_2OAc



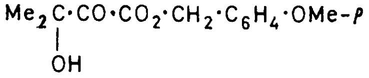
(VI)



(VII) R = SMe
(VIII) R = SAc

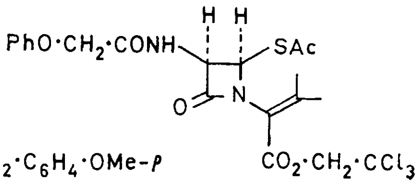


(IV) R = SMe
(V) R = H

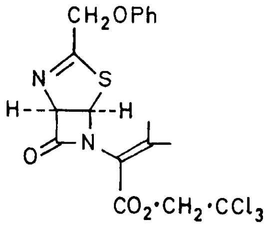


$\mathrm{Me_2\underset{\displaystyle OH}{\underset{|}{C}}\cdot CO\cdot CO_2\cdot CH_2\cdot C_6H_4\cdot OMe}$-*p*

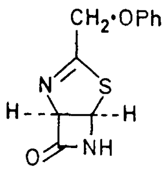
(IX)



(X)



(XI)



(XII)

Treatment of the ester (I) with lead tetra-acetate (1·5 mol) in refluxing benzene for 15 min gave products which, after silica gel chromatography, were identified† as the sulphoxide (II) (15%), an oil, the 4*R*-(acetoxymethylthio)-azetidinone (III), (35%), an oil, and two structures in which the methylthio-group had been displaced by oxygen. The more abundant of the latter was an amorphous solid (40%) considered to be the product (IV) of a remarkable migration of the methylthio-group. The n.m.r. signals of the β-lactam protons in both (IV) and the secondary amide (V) which it yielded readily on reduction (Ph_3P; $CHCl_3$) showed a coupling constant of 1·5 Hz characteristic of a *trans*-configuration.[2] A minor product from (I) and either lead tetra-acetate or *N*-bromosuccinimide was the oxazoline (VI), identical with a specimen prepared by treating the *p*-methoxybenzyl ester of penicillin V with t-butyl hypochlorite and triethylamine as described for penicillin G methyl ester.[3] The inertness of the allylic methyl groups in (I) has parallels in the chemistry of anhydropenicillins[4] and desacetoxy-Δ^3-cephalosporins.[5]

Reaction of (I) with oxidants capable of adding to the double bond apparently resulted in spontaneous cleavage of the initial product. Thus treatment with an excess of osmium tetroxide in dry benzene containing 20% pyridine at room temperature for 15 h followed by work-up with H_2S and silica gel chromatography gave, in addition to a little of the sulphone corresponding to (I), the (3*R*:4*R*)-azetidinone (VII) (24%), m.p. 170—172°, and the liquid ester (IX) (25%).

Oxidative removal of the substituent on the β-lactam nitrogen of (I) was also effected by treatment with potassium permanganate, and we have extended this procedure to various compounds derived from penicillins by fission of the 1,2-bond. Thus the acetylthio-compound[6] (X) in aqueous acetone buffered at pH 7 gave (VIII) (56%), m.p. 138—141°, while the thiazoline[7] (XI) in acetone–pyridine gave (XII) (37%), m.p. 156—158°. Removal of the *N*-substituent with permanganate constitutes a simple alternative to the recently reported[8] procedure of adding diazomethane to the double bond and subsequently eliminating a pyrazoline.

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† The composition of all new compounds was confirmed either by elemental analysis or by mass spectroscopy. Structural assignments are based on i.r. and n.m.r. spectral evidence.

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