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A NEW β-LACTAM EXPANSION REACTION OF A SPIROPENICILLANIC ACID

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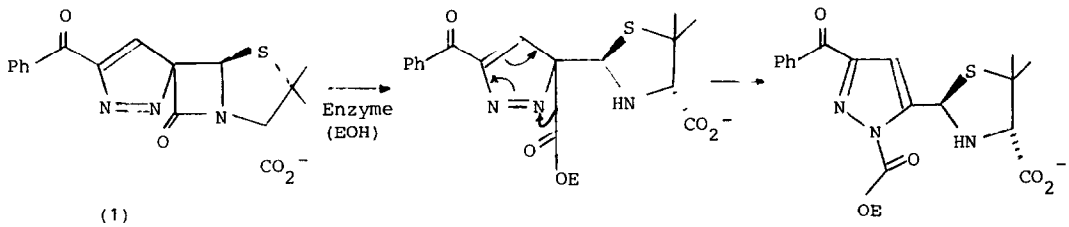
Summary. A new rearrangement reaction of the penicillin nucleus is described which involves migration of the 6,7-bond.

Studies on 6β-bromopenicillanic acid indicate that a rapid rearrangement to a dihydrothiazine derivative accompanies binding of the active site of β-lactamases of the serine proton type.[1] The rearranged dihydrothiazine esters are only hydrolysed from the active site with difficulty and this is assumed to be caused by electronic and steric stresses which reduce the normal catalysed reactions associated with the active site.[2]

Further examples of substrates which might undergo irreversible rearrangements after binding to the active site of β-lactamases are being sought One possibility, considered in our work, is outlined in Scheme 1. The choice of compounds such as (1) was based on the reasoning that, after opening of the β-lactam ring, acyl migration should take place, either to carbon or, as indicated, to nitrogen Such acyl migration can occur very rapidly[3] and would lead to derivatives of the type (2), bearing an 'unnatural' acyl residue attached to the serine hydroxyl group of the β-lactamase enzymes.

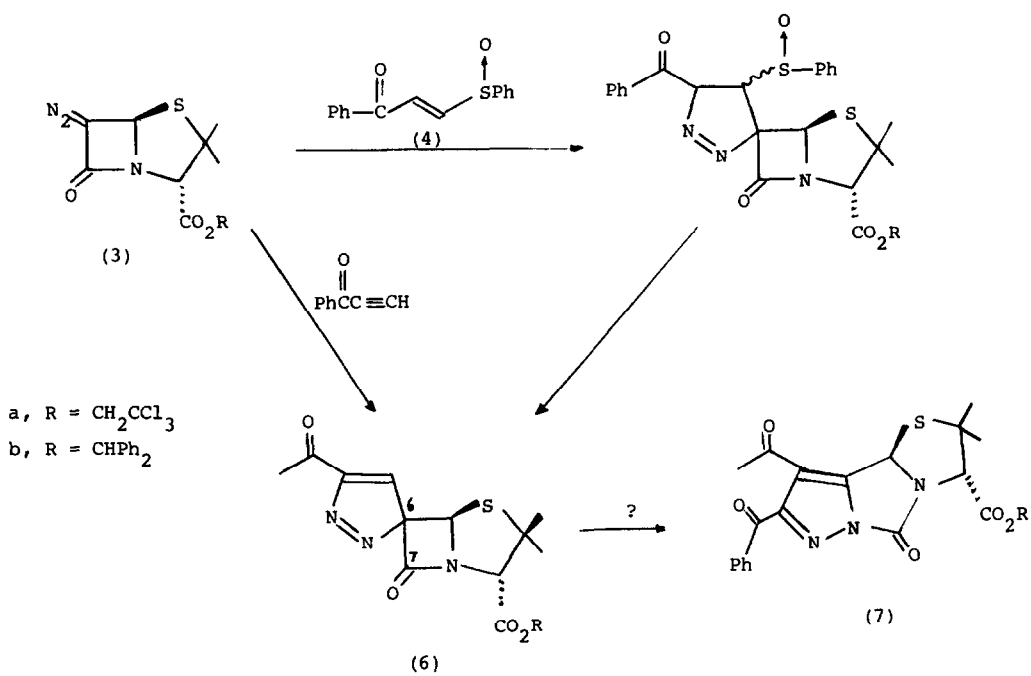


(1) (2)

Scheme 1

Although the activity of penicillin derivatives is known to be sensitive to substitution at position 6α, small groups, such as the methoxy group can be accommodated.[4] Little work has been reported on 6,6-spiro-derivatives of the type (1) but, for these, the steric bulk of the 6α-substituent is kept to a minimum by the spiro-ring itself.

Two approaches to the formation of the spirocyclic lactam (1) were investigated. Reaction of trichloroethyl 6-diazopenicillinate (3)[5] with β-phenylsulphinylpropeno-phenone (4) (Scheme 2), in the dark, at room temperature for 2 days, gave a low yield of product, shown to be the adduct minus one mole of phenylsulphinic acid. The



Scheme 2

same product was also obtained directly by addition of the diazo-ester (3a) to propiolo-phenone (5), in 60% yield. The product was initially assigned structure (6a) showing $\nu_{max.}$ (Nujol) 1785, 1750 and 1660 cm^{-1}. Attempts to remove the trichloroethyl protecting group failed, so the corresponding benzhydryl ester (3b) (prepared in 75% yield from the diazo-ester) was utilised. Removal of the benzhydryl protecting group from the adduct, by use of trifluoroacetic acid in anisole, gave the corresponding acid, isolated as

its potassium salt. Unexpectedly, this acid was completely inert in both β-lactamase and antimicrobial assays,[6] indicating a non-β-lactam structure. X-ray crystallographic analysis of the trichloroethyl ester confirmed this deduction. The crystals of the ester are trigonal, space group $\underline{P3}_1$ with $\underline{a}$ = 1075.1(3), and $\underline{c}$ = 1658.6(4) pm, and $\underline{Z}$ = 3.

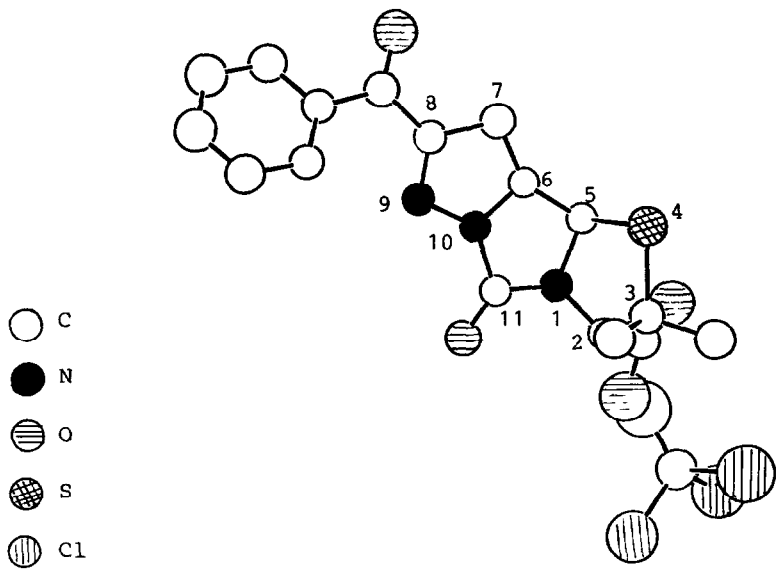


Figure X-ray crystallographic structure of (7a)

The structure analysis used the 1353 independent reflections with $I>2\sigma(I)$ and refinement of all non-hydrogen atoms with anisotropic vibration parameters converged at R = 0.085, R' = 0.092. The result of this analysis is depicted in the Figure, which shows that the anticipated acyl migration has taken place, to nitrogen, before β-lactam opening, resulting in the fused pyrazole (7).[7] Apparently the geometrical constraints imposed by the spiro-azetidinone ring are insufficient to inhibit the acyl migration. Although the penicillin nucleus is known to be involved in a wide range of molecular

rearrangements,[8] to our knowledge this is the first report in which the carbonyl group has undergone a shift breaking the 6,7-bond.

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6. We thank Dr. S.G. Waley, Sir William Dunn School of Pathology, University of Oxford for providing these assays

7. This ester showed m.p 203-208°, $[\alpha]_D^{25}$ + 189° (c 1 0, $CHCl_3$) ^1H δ 1.68 (6H, 2 x Me), 4.80, 4 90 (AB q, 2H), 4.87 (1H, s, H-3), 6.42 (1H, s, H-5), 7.04 (1H, s), 7.5 (3H, aromatic), 8.3 (2H, m, aromatic), $\lambda_{max.}$ (MeOH) 220, 267 nm Found. MW 486.99173; $C_{19}H_{16}Cl_3^{35}N_3O_4S$ requires 486.99269

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