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DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. I.

4-ACYLDITHIOAZETIDIN-2-ONES VIA THERMOLYSIS OF PENICILLIN-DERIVED SULPHOXIDES

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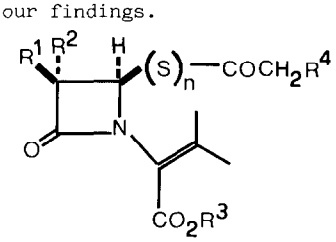
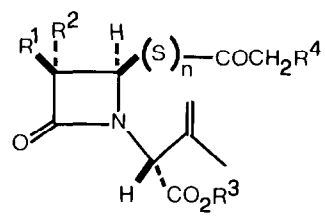
Abstract: Thermolysis of penicillin-derived sulphoxides in the presence of thioacids offers a simple route to 4-acyldithioazetidin-2-ones, whose desulphurisation yields key intermediates for the synthesis of penem antibiotics.

During the course of a programme devoted to the chemistry of penicillin-derived sulphinic acids[1], a few acyl azetidinyl disulphides of general type 1 were synthesized[2]. The representatives of this new class of 1,2-secopenicillin prepared on that occasion were readily desulphurised by PPh_3 to afford thioesters 2 in virtually quantitative yield and with substantial retention of the azetidinone C-4 configuration. Since the latter compounds are key intermediates in Woodward's strategy[3] to penems, we were interested to further extend the scope of this desulphurative approach, devising alternative routes to disulphide precursors 1, 3, and here and in accompanying paper report our findings.



1 ; n=2
2 ; n=1



3 ; n=2
4 ; n=1

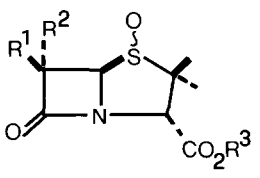
a; R^1 = $PhOCH_2CONH$, R^2=R^4 = H, R^3 = Me

b; R^1 = R^4 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl, R^3 = Me

c; R^1 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl, R^3 = Me, R^4 = Bu^tPh_2SiO

d; R^1 = H, R^2 = 1(R)-benzyloxycarbonyloxyethyl, R^3 = $PhCH_2$, R^4 = Bu^tPh_2SiO

Some structurally related azetidinyl disulphides had been previously obtained by Barton[4] and Kamiya[5] by trapping a thermally generated sulphenic acid with alkyl and heteroaryl thiols. In the hope that thioacids may behave not differently from thiols in a similar reaction, methyl phenoxyacetamidopenicillanate-1-oxide 5a was thermolyzed in the presence of thioacetic acid (1 mol equiv., refluxing toluene, 1 h), and indeed the disulphide 3a[6] was thereby isolated in 34% yield as the sole ß-lactam product[7]. The acylamino side chain present in 5a takes part in parasite reactions, as revealed by concomitant formation of a relevant amount of the thiazole 6[8]; not surprisingly, therefore, when similar thermolysis was performed on 5b the anticipated disulphide 3b was isolated in good yield. The easy derivation of compounds 3c and 3d, obtained from thioacid 7[9] and sulphoxides 5b,c in 70-80% yields after chromatographic purification, can serve to illustrate the generality of the reaction and its potentiality for preparing highly functionalized precursors of penem antibiotics. Sulphur extrusion from 3a-d (PPh_3 1-2 mol equiv., $CHCl_3$, r.t.) smoothly furnished the thioesters 4a-d; the high diastereoselectivity of this step is particularly significant in the case of the cis-substituted ß-lactam 3a, where a trans-directing effect from the C-3 substituent is expected[10]. Finally, the target conjugated butenoates 2a-d were obtained following brief exposure of 4a-d to triethylamine; reversal of this sequence (i.e., double bond migration first and desulphurisation second) was sometimes thwarted by sensitiveness of the acyldithio compounds 3 towards the base.



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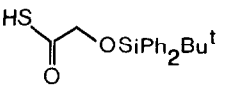

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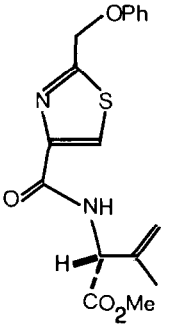

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a; $R^1 = PhOCH_2CONH$, $R^2 = H$, $R^3 = Me$

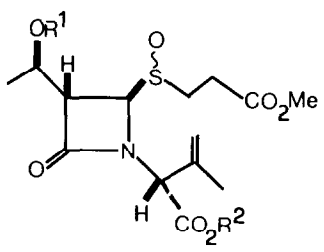
b; $R^1 = H$, $R^2 = 1(R)$-tert-butyldimethylsilyloxyethyl, $R^3 = Me$

c; $R^1 = H$, $R^2 = 1(R)$-benzyloxycarbonyloxyethyl, $R^3 = PhCH_2$

In principle, sulphoxides different from 5, but still bearing a hydrogen substituent at a ß-carbon atom, can generate sulphenic acids and olefins, and the former be trapped with thioacids. Experimental evidence was sought by heating the monocyclic sulphoxides 8a,b, obtained from 5b,c and methyl acrylate according to a general method[11], in the presence of thioacid 7; the anticipated acyldithio compounds 3c,d were again isolated in good yields.

While the above reported thermolysis of penicillin sulphoxides with thioacids is related in mechanism to the Barton and Kamiya experiments, as a whole the trapping-desulphurisation sequence appeared to us reminiscent of other well-known reductive acylations performed on penicillin sulphoxides, i.e. the ones described by Hatfield[12] and Suarato[13]. In order to confirm these analogies, as well as to merely simplify the operative procedures leading to type 4 products, a tervalent phosphorus compound (triphenylphosphine, trimethylphosphite) was ab initio added to the mixture of 5b,c and the thioacid. Sequential thermolysis, exposure to triethylamine and chromatography rewardingly afforded compounds 2c and 2d in 50 and 60% yield. The presence of a relevant amount (up to 24%) of the corresponding cis-substituted diastereoisomers 9a,b suggests in this case similarities with the mechanism[14] of the Suarato procedure, its oxygen counterpart in reagents and products, rather than a simple temporal sequence of sulphenic acid trapping and sulphur extrusion.

As the formation of 10 (instead of 4b) from reaction of 5b with acetic anhydride/trimethylphosphite exemplifies, Hatfield's reductive acylation suffers from serious limitations in what concerns both the acylating agent and the nature of the C-6 penicillin substituent[15]. Other classical routes to thioesters, such as the reductive acylation of Kamiya-type disulphides, have recently shown their limits[16]. We are confident that the methodologies illustrated above can find their place among other tools of practical value in the derivation of penem antibiotics from penicillin[17].



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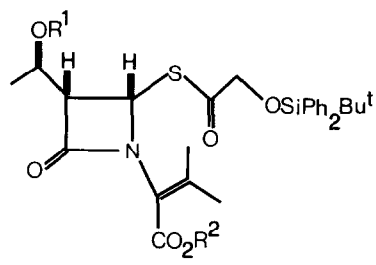

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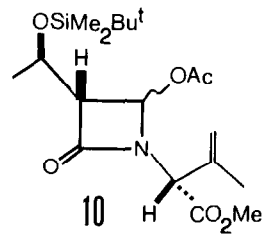
a; $R^1 = Bu^t Me_2Si$, $R^2 = Me$

b; $R^1 = PhCH_2OCO$, $R^2 = PhCH_2$



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We thank Dr. G. Franceschi and Prof. F. Arcamone for their interest in this work.

References and Notes

1) C.M. Pant, J. Steele and R.J. Stoodley, J.Chem.Soc., Perkin Trans. 1, 1982, 595, and references therein.

2) J.R. Irving, E. Perrone and R.J. Stoodley, unpublished results.

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6) All new compounds showed i.r. and H^1 n.m.r. spectra consistent with the proposed structure and gave satisfactory high-resolution mass spectra and/or combustion analysis. Purification of compounds 1 and 4 was not attempted; all products isolated as foams. Selected data include ν_{max} C=O (film) and δppm ($CDCl_3$) relative to β-lactam protons. 2b: 1765, 1725-1695 br cm^{-1}; δ3.15 (dd, 5.0 and 2.5 Hz); 2c: 1775, 1727, 1703 cm^{-1}; δ 3.30 (dd, 6 and 2.5 Hz), 5.72 (d, 2.5 Hz); 2d: 1779, 1745, 1700 cm^{-1}; δ 3.46 (dd, 7 and 2.5 Hz), 5.64 (d, 2.5 Hz); 3a: 1773, 1740, 1700 cm^{-1}; δ 5.51 (dd, 9 and 4.5 Hz), 5.1 (obscured); 3b: 1770, 1740 cm^{-1}; δ3.11 (dd, 3.5 and 2 Hz), 5.02 (d, 2 Hz); 3c: 1775, 1750, 1725 cm^{-1}; δ 3.13 (dd, 3.5 and 2 Hz), 5.08 (d, 2 Hz); 3d: 1777, 1750 sh, 1740, 1720 sh cm^{-1}; δ 3.32 (dd, 5.5 and 2 Hz), 4.92 (d, 2 Hz); 8a: 1770, 1738 cm^{-1}; δ 3.80 (dd, 5 and 2 Hz), 4.98 (d, 2 Hz); 8b: 1778, 1755 sh, 1740 cm^{-1}; δ 3.93 (dd, 8 and 2 Hz), ~5 (obscured); 9a: 1770, 1725 and 1690 cm^{-1}; δ 3.64 (dd, 4 and 5 Hz), 5.89 (d, 5 Hz); 9b: 1775, 1747, 1725, 1705 sh cm^{-1}; δ 3.72 (dd, 9 and 5 Hz), 5.89 (d, 5 Hz); 10: 1780, 1745 cm^{-1}; δ (trans isomer) 3.14 (dd, 4.5 and 1.5 Hz), 4.84 (d, 1.5 Hz); δ (cis isomer) 3.42 (dd, 8.5 and 4.5 Hz), 4.78 (d, 4.5 Hz).

7) This first experiment was performed by E.P. at Newcastle University under the skilled tuitionship of R.J. Stoodley, here gratefully aknowledged.

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16) I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler and R.B. Woodward, J.Am.Chem.Soc., 1978, 100, 8214. The alternative Zn/HOAc reduction therein proposed suffers from unsatisfactory yields.

17) The properties of highly active penem antibiotics, code-named FCE 21420 and 22101, derivable from synthon 2c will be published shortly.

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