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DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. II. 4-ACYLDITHIOAZETIDIN-2-ONES FROM PENICILLIN DERIVED SULPHENIMIDES, THIOLSULPHONATES AND DISULPHIDES.

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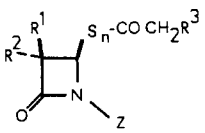
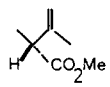
Abstract: Displacement of different leaving groups from a number of 2-oxo-azetidin-4-ylthio derivatives with thioacids, followed by sulphur extrusion, provides a facile access to ß-lactam thioesters and hence to penems.

In the preeceding paper of this series[1] we dealt about the convenience of generating acyldithioazetidinones of type 2, 4 as precursors of thioesters 1, 3, 5 to be used in penem syntheses, and described a new access to this class of compounds. We wish here to report the results of a more systematic approach to our target. Asymmetrical disulphides are usually obtained by reaction of sulphenyl halides with thiols; replacing thiols with thioacids in this reaction has been sometimes expedient for the preparation of acyl alkyl disulphides[2]. Attempted generation of sulphenyl chlorides 7a-c from Kamija[3] disulphides 8a-c[4,5] (a very handy class of 1,2-secopenicillins) was however unrewarding; even when excess Cl_2 was avoided (CCl_4 solution of Cl_2, 1 mol equiv., -50° to r.t., $CHCl_3$) the 4-chloroazetidinones 9a[6], 9b[7] and 9c[8] were formed instead. In the search for easily accessible and stable synthetic equivalents of sulphenyl chlorides, we turned our attention to sulphenimides[9] and thiolsulphonates[10,11]. Indeed compounds 7d and 7e, prepared by minor modifications of published procedures, when exposed to thioacid 10 (1 mol equiv., MeCN, 0°C) smoothly afforded the hoped-for acyldithioazetidinone 2a[1] in virtually quantitative yield. The eventual finding that disulphides 8 themselves undergo rapid and quantitative exchange with thioacids under surprisingly mild conditions endowed the foregoing results with a still greater preparative appeal; thus, 8c and 10 gave 6a and 2-mercaptobenzothiazole (1 mol equiv. each, THF, 0°C, less than 1 min). Sulphur extrusion from 2a, as previously described[1], or from 6a gave the corresponding thioesters 1a, 5a; on the contrary, reductive acylations of azetidinyl benzothiazolyl disulphides according to Woodward[12] (AcOH, Ac_2O, pyridine, PPh_3) or Prasad[13] (RCOOH, PPh_3) were reported[13,14] to be abortive on a number of ß-lactams not bearing the classical, cis-oriented acylamino side chain (O-acylazetidinones and/or monosulphides being formed instead)[15].



1 ; n = 1, **2** ; n = 2, Z = 

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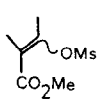
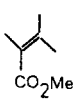
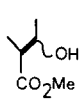
13 ; n = 1, **14** ; n = 2, Z = 

3 ; n = 1, **4** ; n = 2, Z = 

11 ; n = 1, **12** ; n = 2, Z = 

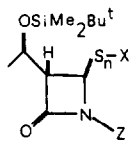
a ; R^1 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl, R^3 = $OSiPh_2Bu^t$

b ; R^1 = R^3 = H, R^2 = 1(R)-hydroxyethyl

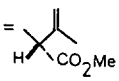
c ; R^1 = 1(R)-hydroxyethyl; R^2 = R^3 = H

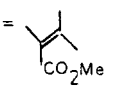
d ; R^1 = H, R^2 = 1(R)-hydroxyethyl, R^3 = $OSiPh_2Bu^t$

e ; R^1 = R^3 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl



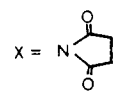
n=1, **7**
n=0, **9**

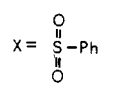
a ; X = Cl, Z = 

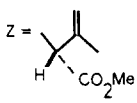
b ; X = Cl, Z = 

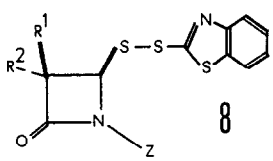
c ; X = Cl, Z = H

n=1, **7**

d ; X = 

e ; X = 

Z = 



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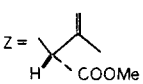
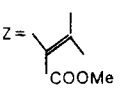
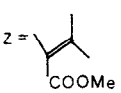
a ; R^1 = H, R^2 = 1(R)-tert-butyldimethyisilyloxyethyl Z = 

b ; R^1 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl Z = 

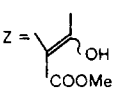
c ; R^1 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl Z = H

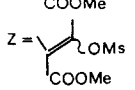
d ; R^1 = H, R^2 = 1(R)-hydroxyethyl

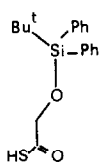
e ; R^1 = 1(R)-hydroxyethyl, R^2 = H

Z = 

f ; R^1 = H, R^2 = 1(R)-hydroxyethyl Z = H

g ; R^1 = H, R^2 = 1(R)-hydroxyethyl Z = 

h ; R^1 = H, R^2 = 1(R)-tert-butyldimethylsilyloxyethyl Z = 



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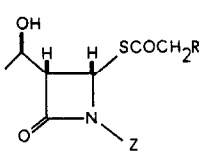

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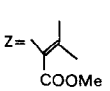
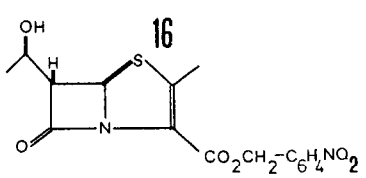
a ; R = H, Z = 

b ; R = Z = H

c ; R = $OSiPh_2Bu^t$, Z = H



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Different considerations support our belief that the foregoing exchange-desulphurisation sequence constitutes the most general route to 4-azetidinylthioesters available at the moment. First, its mildness allows almost every available thioester to be used; prolonged heating[1] or hydrolytic conditions[16] are no longer required. Second, introduction of the acylthio radical can be achieved regardless of the type of substitution on the azetidinone nitrogen. Thus, exchange of mercaptobenzothiazole with tert-butyldiphenylsilyloxythioacetic acid and/or thioacetic acid was easily performed not only on 8c but also on the 3-butenoate 8a, the 2-butenoates 8b,d,e, the 1-H-azetidinone 8f, the enol 8g and the mesylate 8h, thereby obtaining 2a[1], 4a,b,c, 6b or 6d, 12b and 14e. Sulphur extrusion (PPh_3, $CHCl_3$ or CH_2Cl_2) from all the tert-butyldimethylsilyloxyethyl substituted ß-lactams so far prepared was found to be highly diastereoselective, affording 1a[1], 3a, 5a and 13e. However, contrasting results were obtained in the desulphurisation of the free-hydroxyethyl substituted ß-lactams 4b, 4c, 6b, 6d and 12b; partial or complete epimerisation of the azetidinone C-4 chiral centre occurred for 4b, 6b, 6d, the 4S derivatives 15a-c being obtained along with 3b, 5b,d, but retention still occurred for 12b, which afforded 11b, and, most intriguingly[17], even for the cis-subsitituted ß-lactam 4c which yielded 3c. Further work is in progress in the attempt of elucidating the manifold factors involved in the stereochemistry of the desulphurative step. The type of solvent can play an important role, and the desired diastereoselectivity in sulphur extrusion from 6b,d was restored by simply performing the reaction in DMSO.

The compatibility with reactive functional groups of the present route to thioesters is noteworthy and can be exploited with advantage. Thus, methyl 6-[1(R)-hydroxyethyl] penicillanate was converted into 8f and thence, as above indicated, into 5d, from which the penem 16[18] could be obtained, albeit in moderate yields, by minor modifications of Woodward's procedure; to our knowledge, this is the first reported preparation of a penem of this type which thoroughly avoids protection of the side-chain alcohol.

We thank Dr. G. Franceschi for helpful discussions, and Mr. A. Fiumanò for technical assistance.

References and Notes

1) M. Alpegiani, A. Bedeschi, M. Foglio and E. Perrone, submitted for publication in Tetrahedron Letters.

2) L. Field, W.S. Hanley, I. McVeight and Z. Evans, J.Med.Chem., 1971, 14, 202; L. Field, W.S. Hanley and I. McVeight, J.Org.Chem., 1971, 36, 2735.

3) I. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, Tetrahedron Lett., 1973, 3001.

4) These compounds, as well as the other disulphides 8 exploited in this work as starting materials, were obtained from the appropriately 6-substituted methyl penicillanate-1-oxides by following well established procedures.

5) All new compounds showed i.r. and H^1 n.m.r. spectra consistent with the proposed structure and gave satisfactory combustion analyses, apart from 8e and 14e, which are further reacted as crude materials, and 9c, which is unstable on SiO_2. Selected data include ν_{max} C=O (film unless otherwise stated) and δppm relative to ß-lactam protons ($CDCl_3$ unless otherwise stated). 3b: 1765, 1725, 1700 cm^{-1}: δ3.30 (dd, 6 and 2.5 Hz), 5.63 (d, 2.5 Hz); 3c: 1760, 1720, 1700 sh cm^{-1}; δ3.65 (dd, 3 and 5 Hz), 5.83 (d, 5 Hz); 4b: 1765, 1730 br cm^{-1}, δ3.17 (dd, 5 and 2.5 Hz), 5.12 (d, 2.5 Hz) 4c: 1755, 1735 br cm^{-1}; δ3.52 (dd, 3 and 5 Hz), 4.97 (d, 5 Hz); 5a: mp 118-122°C; 1765, 1685 cm^{-1} (in KBr); δ3.23 (dd, 4.0 and 2.5 Hz), 5.24 (d, 2.5 Hz); 5b: 1763, 1690 cm^{-1}; δ(CD_3CN) 3.10 (dd, 5.5 and 2.5 Hz), 5.10 (d, 2.5 Hz); 5d: 1765, 1690 cm^{-1}; δ(d_6-DMSO) 3.20 (dd, 5.5 and 2.2 Hz), 5.28 (d, 2.2 Hz); 6a: 1765, 1728 cm^{-1}; δ3.18 (dd, 4.5 and 2 Hz), 4.87 (d, 2 Hz); 6b: 1750, 1705 cm^{-1}; δ(CD_3CN) 2.93 (dd, 5 and 2 Hz), 4.65 (d, 2 Hz); 6d: 1760, 1730 cm^{-1}; δ 3.22 (dd, 4.5 and 2 Hz), 4.83 (d, 2 Hz); 7d: 1772, 1730, 1710 sh, 1680 cm^{-1}; δ3.29 (dd, 4 and 3 Hz), 4.85 (d, 3 Hz); 7e: mp 105-106°C; 1770, 1750 cm^{-1} (in KBr); δ 3.22 (t, 2 Hz), 5.37 (d, 2 Hz); 8a: 1770, 1743 cm^{-1}; δ3.38 (dd, 3.5 and 2 Hz), 5.42 (d, 2 Hz); 8b: 1770, 1726 cm^{-1}; δ 3.36 (dd, 4 and 2.2 Hz), 5.56 (d, 2.2 Hz); 8c: mp 79-81°C; 1770 cm^{-1}; δ 3.30 (dd, 2.5 and 2 Hz), 5.10 (d, 2 Hz); 8d: 1765, 1725 cm^{-1}; δ3.45 (dd, 5.5 and 2.8 Hz), 5.43 (d, 2.8 Hz); 8f: mp 157-160°C decomp.; 1740 cm^{-1} (in KBr); δ3.28 (dd, 5 and 2 Hz), 5.15 (d, 2 Hz); 8g: amorphous; 1765 and 1730 cm^{-1} (in KBr); δ3.44 (dd, 5 and 2 Hz), 5.29 (d, 2 Hz); 8h (1:1 mixture of E, Z isomers): 1775, 1732 cm^{-1}; δ 3.42 (m), 5.60 and 5.64 (each d, 2.5 Hz); 9a: 1778, 1745 cm^{-1}; δ 3.38 (dd, 4.2 and 1.6 Hz), 5.95 (d, 1.6 Hz); 9b: 1782, 1727 cm^{-1}; δ 3.41 (dd, 5 and 2 Hz), 5.90 (d, 2 Hz); 9c: 1780 cm^{-1}; δ3.41 (dd, 3 and 1 Hz); 5.84 (d, 1 Hz); 11b: 1765, 1705 br, 1650 cm^{-1}; δ3.29 (dd, 6 and 2.5 Hz), 5.63 (d, 2.5 Hz); 12b: 1765, 1740 br, 1660 cm^{-1}; δ3.13 (dd, 5 and 2.5 Hz), 4.99 (d, 2.5 Hz); 13c: 1770, 1730, 1700 cm^{-1}; δ3.2 (obscured), 5.7 (d, 2 Hz); 15a: 1765, 1725, 1700 cm^{-1}; δ3.75 (dd, obscured), 5.88 (d, 5 Hz); 15b: 1763, 1690 cm^{-1}; δ(CD_3CN) 3.30 (dd, 8 and 5 Hz), 5.32 (d, 5 Hz); 15c: 1765, 1690 cm^{-1}; δ 3.50 (dd, 8.5 and 5.5 Hz), 5.33 (d, 5.5 Hz).

6) Compound 9a was detected as the major component of a mixture containing at least other two ß-lactam products by comparison with an authentical sample prepared by oxidative chlorination of penicillin sulphoxides; W.A. Spitzer, T. Goodson, R.S. Lammert and S. Kukolja, J.Org.Chem., 1981, 46, 3568. The eventuality of further reaction of 9a to afford a 2-chloromethylpenam and possibly a 3-methylcephem has been anticipated (see refer. 3).

7) Compound 9b was formed in good yield and found identical with a material obtained by chlorination of the penicillanic precursor according to S. Kukolja and S.R. Lammert, Croatia Chemica Acta, 1972, 44, 299. The chlorine atom in this compound is completely inert towards exchange with thioacids.

8) Compound 9c was not stable to silica gel chromatography. It reacted with thioacid 10 to afford the ß-lactam thioester 5a in moderate yield.

9) J. Verweij and H.S. Tan, 'Fifth International Congress on Heterocyclic Chemistry', Ljubljana (Yugoslavia), July 13-8, 1975.

10) R.D. Allan, D.H.R. Barton, M. Girijavallbhan and P.G. Sammes, J.Chem.Soc., Perkin Trans. 1, 1974, 1456; J. Gosteli, Chemia, 1976, 30, 13.

11) Reaction of thiolsulphonates with thiocarboxylic acids has precedents: L. Field and J.D. Buckman, J.Org.Chem., 1967, 32, 3467.

12) 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.

13) K. Prasad, H. Hamberger, P. Stütz and G. Schulz, Helvetica Chim. Acta, 1981, 64, 279.

14) M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest and R.B. Woodward, J.Am.Chem.Soc., 1979, 101, 6296.

15) Disulphides bearing the hydroxyethyl chain make no exception. The zinc/acid alternative devised by Woodward et al. on that occasion gave on our substrates unsatisfactory yields.

16) K. Clauss, D. Grimm and G. Prossel, Justus Liebigs Ann. Chem., 1974, 539.

17) In this instance, the result is apparently against the intermediacy of an azetidinium ion, which has been postulated in related desulphurisations.

18) Racemic 16 has been described in Dutch Patent Appl. 7,909,056 NL (Bristol Myers)

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