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DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. III.

SYNTHESIS AND DESULPHURISATION OF 3-METHYL-2-THIACEPHEM-4-CARBOXYLATES

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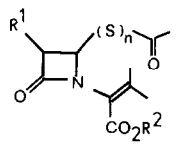
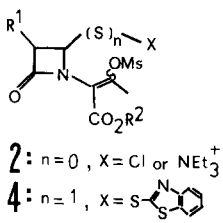
Abstract: Displacement of leaving groups from a number of 2-oxo-azetidin-4-ylthio derivatives with sulphide or hydrosulphide salts conveniently affords 2-thiacephem, whose desulphurisation gives penems.

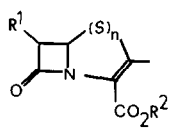
The penem ring system 5 has been constructed by two major routes: internal Wittig reaction, starting from type 1 intermediates[1], or intramolecular displacement of leaving groups at azetidinone C-4 by a thioenolate moiety, starting from type 2 compounds[2]. In the previous papers of this series[3,4] disulphides of general formula 3, 4, differing from said penem precursors for an extra sulphur atom, have been described; analogously, they can be considered precursors of sulphur homologs of penems, 2-thiacephems 6[5]. Since desulphurative ring contraction of cyclic disulphides has precedents[6], we were intrigued by the prospect of deriving penems from what looks formally as the reversal of the desulphurisation-cyclisation sequence previously exploited. The recent communication that two penem representatives have been prepared through a similar route[7] prompts us to report our first results along this line.



1: n=1
3: n=2



2: n=0, X=Cl or NEt_3^+
4: n=1, X=S-

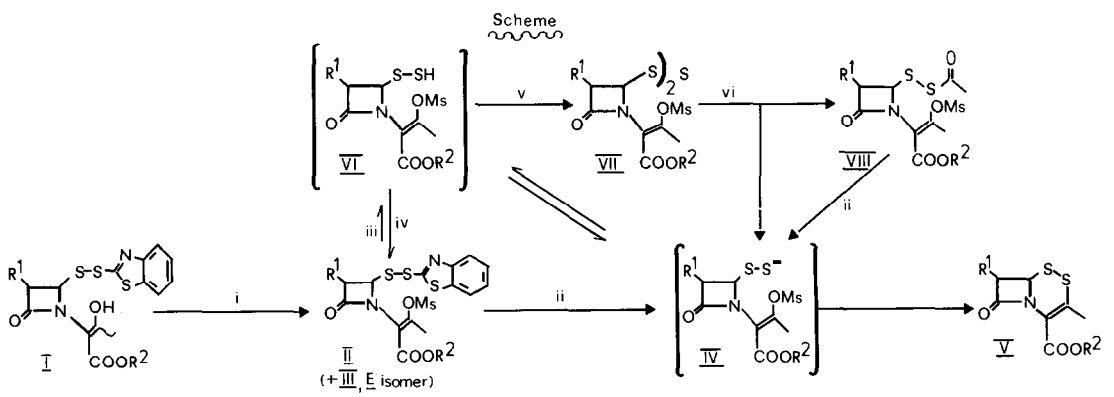


5: n=1
6: n=2

Since the benzothiazolylthio group in azetidinonedisulphides acts as a leaving group towards sulphur nucleophiles[4], we assumed as a working hypothesis that by omitting the chlorinolysis step in Glaxo's procedure[2] a 2-thiacephem 6 instead of a penem 5 should be obtained. In fact, rapid bubbling of excess H_2S into a diluted MeCN solution of 7a and NEt_3 (1 mol equiv.), followed after 1 min[8] by partition in H_2O/EtOAc and chromatography, did afford the hoped-for 2-thiacephem 8a as crystals (20%): mp 85-87°C; λ_{max}(EtOH) 233(ε 4,773),277(6,335) and 326(2,922) nm; ν_{max} 1785 and 1730 cm^{-1}; δ ($CDCl_3$)0.08(6H,s), 0.88(9H,s), 1.25(3H,d,J=6Hz), 2.22(3H,s),3.07(1H,dd,J=2.2 and 3.5Hz),3.8(3H,s),4.35(1H,m) and 4.62ppm(1H,d,J=2.2Hz). To gain better insight into this novel cyclisation, which suffered from low yields and lack of reproducibility, a series of experiments

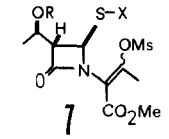
was undertaken. Improved results were obtained with a freshly prepared solution of NaSH in DMF; the 2-thiacephem 8a was thereby isolated in about 40% yield not only from 7a, but even from the sulphenimide 7b[4] and the thiolsulphonate 7c[4], this last entry offering the advantage of a simple final purification from water soluble by-products. The instantaneous displacement of mercaptobenzothiazole by hydrosulphide anion observed on 7a even at -50°C suggests that, different from the reaction of chloro-mesylates (e.g. 9) to afford penems, the first reaction occurs on the sulphur and not on the mesylate moiety[9], presumably to generate the transient species IV depicted in the Scheme. Analysis of the crude reaction mixture under different experimental conditions revealed that two products are competitively formed. When a solution of a sulphide (Na_2S, NaSH, Bu_4NSH) was added in one portion into a diluted solution of type II mesylate, the 2-thiacephem V was the main isolated product; on the other hand, introduction of H_2S into a concentrated solution of II containing a trace of a base (e.g., NEt_3) overwhelmingly afforded a new, more polar product, which was assigned the trisulphide structure VII after full characterisation was gained on entry 10: ν_{max} ($CHCl_3$) 1777, 1765 sh, 1726, 1640, 1375, 1250 and 1166 cm^{-1}; δ ($CDCl_3$) 1.51(3H,d,J=6.5Hz), 2.63 (3H,s), 3.24(3H,s), 3.60(1H,dd,J≈2 and 6Hz), 3.83(3H,s), 4.75(2H,s), 5.28(1H,m) and 5.42ppm (1H,d,J=2Hz); FD/MS[10] = m/z 1056 ($M^{+\cdot}$). Found: S, 14.78%; $C_{28}H_{34}Cl_6N_2O_{18}S_5$ requires S, 15.13%. Formation of trisulphide VII instead of 2-thiacephem V can be tentatively accounted for in terms of an intermolecular versus intramolecular reaction, presumably involving the unreacted starting disulphide II. Polysulphides of type VII were described by Hoechst's chemists[11], and used in their two-step preparation of 2-thiacephems from mesylates II,III, the reagent of choice being potassium thioacetate. Now, we could easily anticipate[4] the acetyldisulphide VIII as the first result of a similar reaction, this being accompanied by the release of an equimolecular amount of IV, the true 2-thiacephem precursor.

Scheme

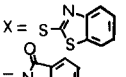


Reagents: i, MsCl/base; ii, Na_2S; iii, H_2S; iv, 2-mercaptobenzothiazole; v, compound II, cat. SiO_2; vi, CH_3COSH/base

Indeed, when trisulphide 10 was treated with CH_3COSNa (THF, 0°C), the acetyldisulphide 11 was isolated in 48% yield together with the anticipated 2-thiacephem 8b, and found identical with a sample prepared by direct displacement of mercaptobenzothiazole from 7d and thioacetic acid: ν_{max} (film) 1770 br, 1735 br, 1640, 1375, 1250 and 1165 cm^{-1}; $\delta(CDCl_3)$ 1.50(3H,d), 2.48(3H,s), 2.62 (3H,s), 3.29(3H,s), 3.44(1H,dd,J=2 and 5Hz), 3.83(3H,s), 4.77(2H,ABq), 5.24(1H,d,J=2Hz), 5.25 (1H,m). Moreover, we envisaged that this latter disulphide, though less reactive, could in turn react with hydrosulphide anion developing IV and thence a further amount of 2-thiacephem. This again was shown to be true: thus, the recovered 11 reacted with Bu_4NSH in THF yielding 8b, albeit in moderate yield. Speculations concerning the possible influence of the alkene geometry in type 7 intermediates were also formulated. Compound 7a (1:1 mixture of E, Z isomers) was first separated into the single components by repeated chromatography; we assigned the Z geometry (type II in the Scheme) to the isomer possessing the butenoate terminal methyl resonating at lower fields in the H^1 n.m.r. spectrum[12]. Whereas the Z isomer reacted with freshly prepared solutions of NaSH in DMF to directly afford 8a in up to 60% yields, only a minor amount of the latter (10-15%) was obtained from the E isomer, accompanied by other mesylate-free by-products, in particular a dimeric ß-lactam which was attributed structure 12: ν_{max}(film) 1770 and 1710 cm^{-1}; $\delta(CDCl_3)$ 0.05 and 0.07 (each 3H,s), 0.85(9H,s), 1.23(3H,d,J=5.8Hz), 2.39(3H,s), 2.98(1H,dd,J=2.8 and 5.5Hz), 3.80(3H,s), 4.18(1H,m) and 5.66 ppm (1H,d,J=2.8Hz); FD-MS: m/z 778 (M^+), 721 ($M^+-C_4H_9$). Here again, this finding was converted into a significant methodology improvement, since it turned out that mesylation in THF (instead of the ubiquitously used CH_2Cl_2) is expedient in raising the Z/E isomeric ratio from 1:1 to about 9:1. Finally, sulphur extrusion from the 2-thiacephem ring system was examined, and it was rewarding to follow the smooth conversion of 8a (PPh_3, $CDCl_3$) into the penem 13a, contamined by only a small amount of its 5S diastereomer 14a: λ_{max} (EtOH) 257 and 314 nm; ν_{max} (nujol) 1800 and 1715 cm^{-1}; $\delta(CDCl_3)$ 0.09(6H,s), 0.88(9H,s), 1.23(3H,d), 2.35(3H,s), 3.61(1H,dd,J=2 and 4.5Hz), 3.89(3H,s), 4.23(1H,m), and 5.51ppm(1H,d,J=2Hz). The observed substantial retention of configuration at azetidinone C-4 is crucial in conferring a practical value to this new access to penem compounds, otherwise not easily apparent[13]; this can be appreciated by comparison with the original Glaxo's strategy[2] exploiting type 4 disulphides, which gave the sole, useless 5S penem 14a: ($CDCl_3$) inter alia 1.39(3H,d), 2.37(3H,s), 3.80(1H,dd,J=4 and 10Hz) and 5.61ppm(1H,d,J=4Hz). The profound effect of the 7-substitution and of the solvent on the stereochemistry of the ring contraction became apparent when susbtrates other than 8a were examined (Table). While a closer investigation is in progress, we believe that the reported results are enough to enlighten the 2-thiacephem approach with new prospects of usefulness for the synthesis of biologically active penem antibiotics[14].



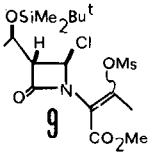
7

a; R = $SiMe_2Bu^t$ X = 

b; R = " X = 

c; R = " X = SO_2Ph

d; R = $CO_2CH_2CCl_3$, X = 



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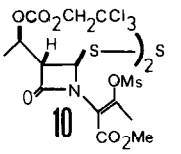

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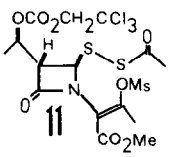

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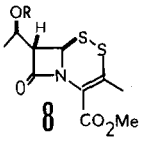

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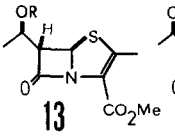

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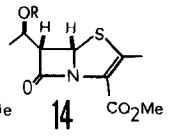
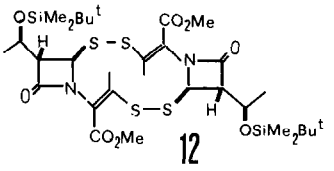


14

a; R = $SiMe_2Bu^t$

b; R = $CO_2CH_2CCl_3$

c; R = H



12

Starting 8	Solvent	Products/ratio
8a	$CHCl_3$	13a, 14a/4:1
8b	$CHCl_3$	- 14b -
8c	$CHCl_3$	13c, 14c/1:9
8c	Me_2CO	13c, 14c/1:1

References and Notes

1) 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.

2) P.C. Cherry, C.E. Newall and N.S. Watson, J.Chem.Soc., Chem.Commun., 1979, 663; C.M.D. Beels, M. Said Abu-Rabie, P. Murray-Rust and J. Murray-Rust, J.Chem.Soc., Chem.Commun., 1978, 665.

3) Part I of this series: M. Alpegiani, A. Bedeschi, M. Foglio and E. Perrone, submitted to Tetrahedron Letters.

4) Part II of this series: M. Alpegiani, A. Bedeschi, M. Foglio, F. Giudici and E. Perrone, submitted to Tetrahedron Letters

5) 7-Acylamino-2-thiacephems have been mentioned in the past (K. Burry and R.B. Woodward, unpublished results, 1970) without finding applications.

6) D.N. Harpp, J.G. Gleason and J.P. Snyder, J.Am.Chem.Soc., 1968, 90, 4181.

7) A. Henderson, G. Johnson, K.W. Moore and B.C. Ross, J.Chem.Soc., Chem.Commun., 1982, 809.

8) Delays in quenching the reaction resulted in extensive decomposition of the product.

9) Conversion from 9 into 14a (vide infra) is, by contrast, very sluggish at low temperatures. A similar difference in reactivity had been previously observed [4].

10) Field-desorption mass spectra were recorded on a Varian MAT 311-A mass spectrometer equipped with a combined FI/FD/EI ion source.

11) Interestingly, the reported preparation[7] of these products may be the accidental result of a chromatographic purification performed without first removing the excess H_2S. It is a fact that our substrates of type II, III failed to react with H_2S in C_6H_6 (in situ nmr analysis, recovering of the st. material upon evaporation) but easily yielded trisulphide VII under SiO_2 catalysis. We had previously observed silica gel catalyzed reactions of type; e.g., in structurally related azetidinyldisulphides mercaptobenzothiazole can be replaced by tritylmercaptane only by adsorbing the reagents on SiO_2.

12) These assignments follow from the general behaviour of isolate 2-butenoic systems, and are in keeping with Wolfe's results on a series of related 4-chloroazetidinones (S. Wolfe and C. Shaw, Can.J.Chem., 1982, 60, 144). Our confidence in extending this criterion to the 4-benzothiazolyldithio derivatives is supported by the experimental evidence that introduction of this group is not associated with any relevant anisotropic effect.

13) The 5R configuration in penem compounds is essential requisite for antimicrobial activity (I. Ernest, J. Gosteli and R.B. Woodward, J.Am.Chem.Soc., 1979, 101, 6301); Henderson et al. reported[7] to have obtained optically inactive p-nitrobenzyl 2-methylpenem-3-carboxylate and the 5S isomer of p-nitrobenzyl 6-chloro-2-methylpenem-3-carboxylate.

14) Part IV of this series, to be submitted.

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