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DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. V.

2-(FUNCTIONALIZED METHYL)PENEMS FROM 3-METHYLENECEPHAM-1-OXIDES

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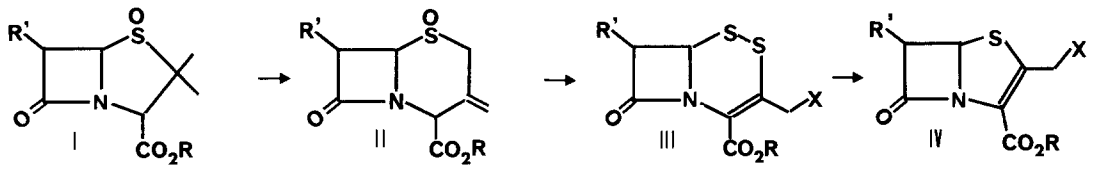
Abstract : 3-Methylenecepham-1-oxides are converted into 3-(functionalized methyl)-2-thiacephems, direct precursors of a group of valuable penem antibiotics.

The feasibility of straightforward ring transformations between penams, cephems and their nuclear analogs constitutes a fascinating aspect of the chemistry of ß-lactam antibiotics. We wish here to describe a route to functionalized penems IV which, starting from penams I, expeditiously involves cephams II and 2-thiacephems III as intermediates.



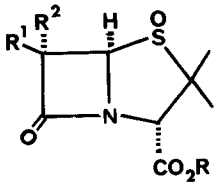
Previously[1], we had described the synthesis of 3-methyl-2-thiacephems (III, X=H) and their ring-contraction to 2-methylpenems (IV, X=H); thermolysis of penam-1-oxides I in the presence of 2-mercaptobenzothiazole (MBT) to give disulphides 6 was the starting move in this process. Very attractive to us was the recent report that 3-methylenecepham-1-oxides II undergo an allyl sulphoxide-sulphenate [2,3]sigmatropic rearrangement wherein the sulphenate species can be intercepted by MBT[2] to give disulphide-alcohols 7 ; we surmised that substitution of cephams II for penams I in our former sequence would provide an entry to 2-thiacephems functionalized on the C-3 methyl group[3] (III, X=OH, $OCOCH_3$, OCONHR), and thence to penems which rank among the most interesting compounds of this class under current investigation.[4~6]

From penams to cephams - The well-known Kukolja reaction[7] (NCS, refluxing toluene; then $SnCl_4$) enables a high-yield conversion of I into II to be achieved when R'=phthalimido. Our first attempts to extend this procedure to substrates bearing the hydroxyethyl side chain (1c,d) met often (particularly in experiments exceeding the millimole scale) with sudden decomposition of all the ß-lactam material. A capricious side reaction[8] is known

to interfere with ring expansion of classical (i.e., 6-acylamino) penams; acid acceptors were recommended, but the most appropriate experimental conditions never published. We had found the presence of sodium metabisulphite very profitable in these instances[9], and a convenient one-pot procedure for preparing 2c,d which capitalizes on those experiences is here presented.[10]

From cephams to 2-thiacephems - Ring opening of the cephams 2a-d [11] was readily accomplished by simple thermolysis in the presence of MBT; however, the resulting carbinols proved prone to lactonization (e.g., 7a,b give 18), and mixtures of alcohols and lactones were isolated. Lactonization was promoted not only by double bond isomerization (e.g., after NEt_3 treatment), but by prolonged heating and SiO_2 chromatography as well; it could be repressed most efficiently ($\leqslant$10%) on the phthalimido-susbstituted compounds (hereinafter selected as model substrates)[12] by using excess MBT under high concentration (to speed up the thermolysis; $\leqslant$30min, refluxing toluene) and by avoiding purification. Thus, one-pot ring opening and acetylation (AcCl, pyr, r.t.), tetrahydropyranylation (DHP, TsOH cat.,r.t.), or carbamoylation (EtNCO, overnight) of 2a, 2b, gave 8b, 9a, 9b, 10b in 70%- 80% isolated yields. Ozonolysis (O_3stream in CH_2Cl_2-MeOH, -70°; then Me_2S, r.t.) worked satisfactorily for 10b, affording 14b; poor results were elsewhere obtained, owing primarily to overoxidation (to give oxoamides 19, and thence the 1-H azetidinone 20 after SiO_2 chromatography) and cleavage (of the acyloxy and tetrahydropyranyloxy moieties in 12b, 13b, to give the diol 11b). The very recovery of 11b, testifying a remarkable resistance of this substrate to lactonization (in sharp contrast with 7b) suggested the opportunity of performing a direct ozonation of the crude thermolysis mixture from 2a,b and MBT. The diols 11a, 11b thus prepared (65%) could be selectively reacted on the allylic hydroxyl; 12a (Ac_2O/NEt_3 in CH_2Cl_2, 55% overall), 13a, 13b (DHP excess, TsOH cat., CH_2Cl_2, 60% overall). Mesylation (MsCl/pyr or NEt_3, CH_2Cl_2) of 13a, 13b, 14b and brief treatment with $NaSH \cdot H_2O$ (DMF, r.t.) gave moderate yields ($\leqslant$15%) of the 2-thiacephems 22a, 22b, 23b; cyclization of the unstable acetoxy compound 15a could not be achieved. Unmasking of the hydroxyl group in 22a, even under mild conditions (PPTS, EtOH 65°, 1 h)[13], afforded directly the 2-thiacephem lactone 24 (80%).

From 2-thiacephems to penems - Desulphuration of the 2-thiacephems 22a and 23b to give the penems 27a and 29b occurred cleanly and instantaneously upon treatment with PPh_3; 24 afforded the remarkable tricyclic penem structure 25 .[14] In each case complete inversion was observed at C-6 (thiacephem numbering), the unfavourable stereochemical outcome depending on the 7ß-phthalimido side chain rather than on the particular substitution at the C-3 methyl group.[15] To complete the feasibility study, hydrolysis of the THP ether in 27a (PPTS, EtOH 55°, 90min) and hydrogenolysis of the pNB ester in 29b (H_2 1 atm, 5% Pd on C, AcOEt-H_2O) were performed, thus liberating a versatile[5,6] allyl alcohol (28a, 75%) and a free penem carboxylate[16] (29c, 60%). New methods for yield improvement in the ring closure and for stereochemical control in the ring contraction, now under advanced investigation in our laboratories , will complement the results so far obtained on C-3 methyl functionalization.



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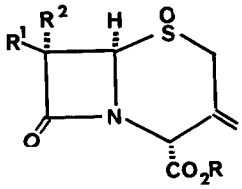

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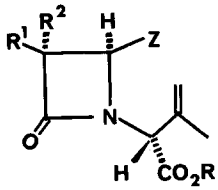
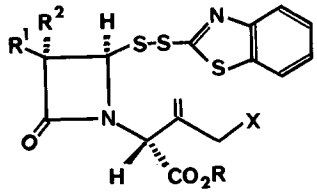
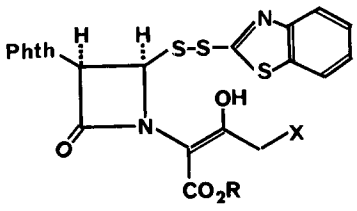


3 Z = SOCl
4 Z = Cl
5 Z = SO_2H

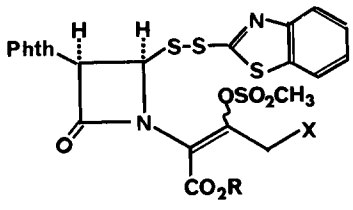


6 X = H
7 X = OH
8 X = OAc
9 X = OTHP
10 X = OCONHEt

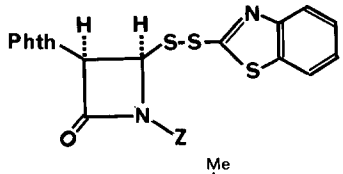
a series, R^1=*Phth*, R^2=*H*, *R*=*Me*
b " R^1=*Phth*, R^2=*H*, *R*=*pNB*
c " R^1=*H*, R^2=*(1R)-t-Butyldimethylsilyloxyethyl*, *R*=*Me*
d " R^1=*H*, R^2=*(1R)-Trichloroethoxycarbonyloxyethyl*, *R*=*Me*

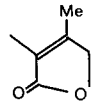


11 X = OH
12 X = OAc
13 X = OTHP
14 X = OCONHEt

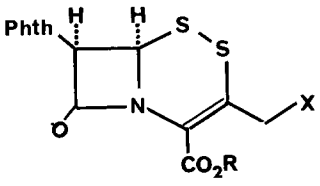


15 X = OAc
16 X = OTHP
17 X = OCONHEt

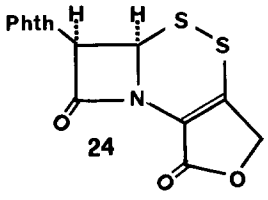




18 Z =
19 Z = $COCO_2R$
20 Z = H



21 X = H
22 X = OTHP
23 X = OCONHEt



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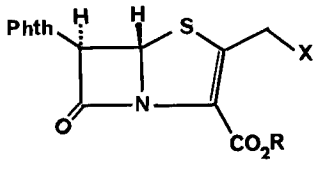
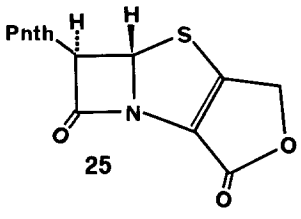


26 X = H
27 X = OTHP
28 X = OH
29 X = OCONHEt



25

a series, *R*=*Me*
b " *R*=*pNB*
c " *R*=*H*

References and Notes

1. E. Perrone, M. Alpegiani, A. Bedeschi, M. Foglio, and G. Franceschi, Tetrahedron Lett., 1983, 1631.
2. This rearrangement and trapping occurred in a 6α-benzamidopenam (1, R^1 =H, R^2 =PhCONH, R=$CHPh_2$; 40% yield); H. Yanagisawa and A. Ando, Tetrahedron Lett., 1982, 3379.
3. Another method for functionalizing the C-3 methyl group of 2-thiacephems was unexpectedly discovered during the course of the present work : E. Perrone, M. Alpegiani, A. Bedeschi, F. Giudici, M. Foglio, and G. Franceschi, Tetrahedron Lett., 1983, 3283. Efforts to directly functionalize the C-2 methyl group of a penem were unrewarding.
4. A. Sanfilippo, C. Della Bruna, D. Jabes, E. Morvillo, G. Schioppacassi, G. Franceschi, F. Arcamone, C. Battistini, M. Foglio, and F. Zarini, J. Antibiotics , 1982, 35, 1248.

5. G. Franceschi, M. Foglio, M. Alpegiani, C. Battistini, A. Bedeschi, E. Perrone, F. Zarini, F. Arcamone, C. Della Bruna, and A. Sanfilippo, J. Antibiotics, 1983, 36, 938.
6. G. Franceschi, M. Alpegiani, A. Bedeschi, M. Foglio, E. Perrone, G. Meinardi, S. Grasso, and I. de Carneri, J. Antibiotics, in press.
7. S. Kukolja, S. R. Lammert, M.R.B. Gleissner, and A.I. Ellis, J. Am. Chem. Soc., 1976, 98, 5040.
8. T.S. Chou, W.A. Spitzer, D.E. Dorman, S. Kukolja, I.G. Wright, N.D. Jones, and M.O. Chaney, J. Org. Chem., 1978, 43, 3835.
9. M. Foglio and G. Franceschi, unpublished results.
10. The sulphoxide 1d (4.29 g), CaO (1 g), Na_2SO_3 (2 g), propylene oxide (10 ml) and NCS (1,47 g) in dry toluene (130 ml) were refluxed under stirring for 4 h (no st. material left, TLC); the suspension was concentrated to about 20 ml through a Dean-Stark arm under slight depression and cooled to r.t.; dry Et_2O (1,5 ml) and $SnCl_4$ (2.4 ml, two portions at 30 min intervals) were added; the gummy solid was separated from the liquours and partitioned between AcOEt and 1M HCl; the organic layer was then washed with aq. $NaHCO_3$ and evaporated to give 3.92 g (91 %) of virtually pure 2d; νmax($CHCl_3$) 1775, 1745cm^{-1}; δ($CDCl_3$) 1,50(3H, d, CH_3), 3.6-3.9(6H, m, 2-H, 7-H and OCH_3), 4.80(3H, d+s, 6-H and CH_2CCl_3), 5.12(1H, s, 4-H), 5.25(1H, m, 8-H), 5.4 and 5.67(each 1H, s, $=CH_2$). The major by-product, chloroazetidinone 4d (130 mg, 3%), remained in the toluene liquours. Moisture in the st. materials is responsible for the formation of 4d whereas exposure to moisture after depletion of NCS gives sulphinic acid 5d.
11. All new compounds were characterized by NMR, IR and mass spectroscopy. Salient data for key compounds are as follows : 2c: mp 122°; νmax(KBr) 1775, 1740 cm^{-1}; δ($CDCl_3$) 3.5(1H, dd, 2.0 and 3.5 Hz, 7-H), 3.70(5H, s+ABq, 2-H and OCH_3), 4.73(1H, d, 2 Hz, 6-H), 5.10, 5.30, and 5.56(each 1H, s, 4-H and $=CH_2$); 7b: νmax($CHCl_3$ film) 1780 br, 1750, 1720 cm^{-1}; δ($CDCl_3$) 3.20(1H, br s, exch. D_2O), 4.97(2H, s, CH_2OH), 5.22(1H, s, NCHCO), 5.31 (2H, s, OCH_2 Ar), 5,47(2H, m, $=CH_2$), 5.78 and 5.86(each 1H, d, 4 Hz, 4-H and 3-H); 11b: mp 184-185°; νmax (KBr) 1790, 1780, 1725, 1660 sh, 1605 cm^{-1}; δ($CDCl_3$) 4.72(2H, br s, CH_2OH), 5.30(2H, ABq, 13 Hz, CH_2Ar), 5.40 (2H, br s, OH), 5.70 and 5.92(each 1H, d, 5 Hz, 4-H and 3-H); 18: mp 145-147°; νmax(KBr) 1785, 1775, 1755, 1720, 1680 cm^{-1}; δ($CDCl_3$) 4.60(2H, ABq, CH_2O), 5.85 and 6.20(each 1H, d, 5.5 Hz, 4-H and 3-H); 22a (1:1 diast. mixture): mp 173-176°; νmax(KBr) 1810, 1780, 1728 cm^{-1}; δ($CDCl_3$) 1.51-1.83(6H, m, $OCH_2(CH_2)_3CHO$), 3.49-3.59 (1H, m, OCH_2, Heq), 3.83-3.91(1H, m, OCH_2, Hax), 3.90(3H, s, OCH_3), 4.61 and 4.63(2H, each ABq, 14 Hz, 3-CH_2), 4.67 and 4.71(1H, m, OCHO), 5.09 and 6.09(each 1H, d, 5 Hz, 6-H and 7-H); λmax($CHCl_3$) nm(ε) 280(11,392) and 338(4,710); 23b: νmax($CHCl_3$) 1805, 1780, 1728 cm^{-1}; δ($CDCl_3$) 1,14(3H, t), 3.20(2H, m), 5.13 and 6.10(each 1H, d, 5 Hz, 6-H and 7-H), 5.34(4H, m, CH_2Ar and 3-CH_2); λmax($CHCl_3$) nm(ε) 269(14,020) and 337(2,810); 24: mp 243-245° dec; νmax($CHCl_3$) 1815, 1780, 1765, 1735 cm^{-1}; δ($CDCl_3$) 5.03(2H, s, 3-CH_2), 5.11 and 6.24(each 1H, d, 5.2 Hz, 6-H and 7-H); λmax(EtOH) nm(ε) 223(37,800), 277(7,800), and 329(2,155); MS(FD) 360m/z $[M^{\cdot}]^+$; 25: mp 150° dec; νmax(KBr) 1805,1790,1775,1755,1720 cm^{-1}; δ($CDCl_3$) 4.97(2H,s,2-CH_2), 5.97 and 6.57(each 1H,d,2Hz, 5-H and 6-H); λmax($CHCl_3$) nm(ε) 301(5,335); 27a(1:1 diast. mixture): νmax($CHCl_3$) 1800, 1780, 1730 cm^{-1}; δ($CDCl_3$) 1.52-1.73 (6H, m, $OCH_2(CH_2)_3CHO$), 3.50-3.60(1H, m, OCH_2, Heq), 3.84-3.90(1H, m, OCH_2, Hax), 3.86(3H, s, OCH_3), 4.70 and 4.72(1H, each m, OCHO), 4.84 and 4.86(2H, each ABq, 16 Hz, 3-CH_2), 5.76 and 5.93(each 1H, d, 2.1 Hz, 5-H and 6-H); λmax($CHCl_3$) 308 nm; 28a: νmax($CHCl_3$) 1800, 1775, 1730, 1700 sh cm^{-1}; δ($CDCl_3$) 3.89(3H, s, OCH_3), 4.64(2H, ABq, 15.4 Hz, CH_2OH), 5.79 and 5.96(each 1H, d, 1.9 Hz, 5-H and 6-H); λ max($CHCl_3$) 308 nm; 29b: νmax($CHCl_3$) 1795, 1780 sh, 1720 cm^{-1}; δ($CDCl_3$) 5.79 and 5.97(each 1H, d, 2.0 Hz, 5-H and 6-H); λmax($CHCl_3$) nm(ε) 267(9,692), 305 sh(5,830), 324(4,555); 29c: νmax($CHCl_3$) 1780 br, 1720, 1690 cm^{-1}; δ($CDCl_3$) 1.15(3H,t), 4.25(2H, m), 5.34(2H, ABq, 16 Hz, 2-CH_2), 5.82 and 5.98(each 1H, d, 2 Hz, 5-H and 6-H); λmax($CHCl_3$) nm(ε) 244(9,072), 304(4,433), 318(3,560).
12. Both alcohols and lactones can be exploited in different syntheses aimed at the same penem compounds IV. Lactones bearing the hydroxyethyl side chain are dealt with in the following paper of this series.
13. N. Miyashita, A. Yoshikoshi, and P.A. Grieco, J. Org. Chem., 1972, 42, 3772.
14. Five-membered lactones fused with the penem ring system, such as 25, could not be prepared from 2-hydroxymethyl penem-3-carboxylates, or mesylates thereof , while a related six-membered lactone has been described (C.E. Newall, in Recent Advances in the Chemistry of β-Lactam Antibiotics, Chem. Soc. Spec. Publ., 1981, No.38, p150). On the other hand, five-membered lactones fused with the six-membered rings of cephems and 2-thiacephems[3] are spontaneously generated entities.
15. For example, desulphuration of 6,7-trans and 6,7-cis 2-thiacephems bearing the (1R)-tert-butyldimethylsilyl side chain proceeds with substantial retention of the 6-C configuration.
16. 6-Phthalimido penem esters have been previously prepared (I. Ernest et al., unpublished results; T. Kametani, N. Kanaya, T. Mochizuki, and T. Honda, Tetrahedron Lett., 1983, 1511) but, to our knowledge, their hydrolysis not accomplished. Chemical half-life measurements for 29c indicated a stability of the order observed in penems possessing the hydroxyethyl side chain (>100 h in pH 7.4 phosphate buffer, 37.5 °C).

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