2-(HETEROATOM-SUBSTITUTED)METHYL PENEMS. II[1]. SULPHINYL AND SULPHONYL DERIVATIVES

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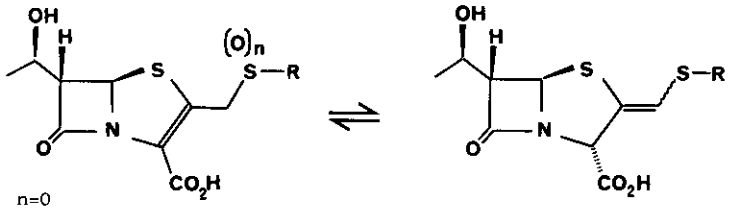
Abstract - Thermodynamic control of the endo-exo double bond equilibration in 2-(thio-substituted)methyl penems allowed the synthesis of the sulphinyl and sulphonyl derivatives, which proved to be potent antibacterial agents.

Recently[1] we reported on the chemistry and biological activity of 2-thiomethyl penem derivatives I, pointing out that some incongruities of the microbiological results could be ascribed to their equilibration to the isomeric thiomethylene penam structure II.



I n=0
III n=1
IV n=2

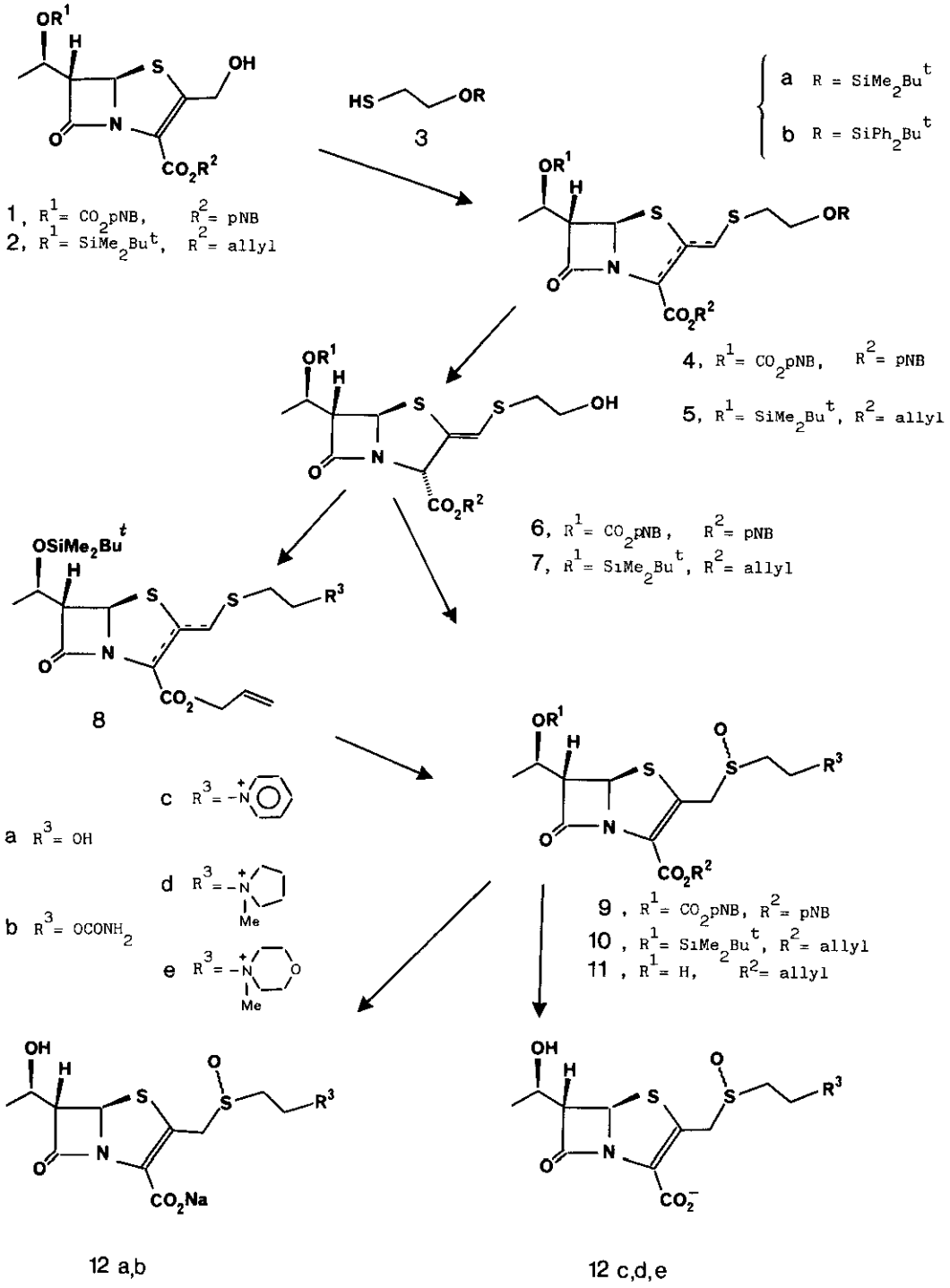
II

To complete the "sulphur series" of 2-CH_2X penems, we looked for substituents possessing an increased electron-withdrawing ability coupled with the intrinsic aptitude to stabilize the endo over the exo-cyclic ene form. These requirements are fulfilled by the sulphinyl and sulphonylmethyl penems III, IV, which are the object of the present communication.

For the preparation of sulphoxide derivatives III a straightforward method was found in the regio-selective oxidation of the easily accessible thiomethylene penams II. Accordingly, Bu_4NF-mediated desilylation of the penem 4b[1] afforded the penam 6, whose treatment with 1 eq MCPBA (CH_2Cl_2, -40°C) followed by workup with aqueous sodium metabisulphite led to isolation of penem 9a as a mixture of sulphoxide epimers in virtually quantitative yield (Scheme 1). Regioselectivity in the oxidation is accounted for by the preferential attack of MCPBA to the sterically less hindered sulphur atom, while the exo-endo double bond isomerization results from thermodynamic factors favouring allyl sulphoxides over the isomeric vinyl sulphoxides[2]. In fact, in the absence of the peripheral sulphur, oxidation of methylene penams uneventfully occurs on the nucleus with preservation of the exo structure[3]. An intra-annular counterpart of this double bond shift is the well-known conversion of Δ^2 cephems into Δ^3 cephem-1-oxides.

Removal of the pNB protecting groups from 9a by catalytic hydrogenation proved unexpectedly diffi-

SCHEME 1


1, R1 = CO2pNB, R2 = pNB
2, R1 = SiMe2But, R2 = allyl
3
a R = SiMe2But
b R = SiPh2But
4, R1 = CO2pNB, R2 = pNB
5, R1 = SiMe2But, R2 = allyl
6, R1 = CO2pNB, R2 = pNB
7, R1 = SiMe2But, R2 = allyl
8
a R3 = OH
b R3 = OCONH2
c R3 = -N+
d R3 = -N+ Me
e R3 = -N+ O Me
9, R1 = CO2pNB, R2 = pNB
10, R1 = SiMe2But, R2 = allyl
11, R1 = H, R2 = allyl
12 a,b
12 c,d,e

cult. To overcome this problem, the differently protected methylene penam 7 was preferred to 6 as the key intermediate for the synthesis of 12a~e. Reaction of the alkyl thiol 3a (3b)[1] with hydroxymethyl penem 2[4] under a slightly modified Mitsunobu-Volante[5] procedure (slow addition of a preformed PPh_3-DEAD complex to a mixture of 2 and 3 in refluxing dichloromethane) furnished a 1:1 penem-penam mixture 5a (5b) in 73% (81%) yield. Selective cleavage of the primary silyl ether in 5a and 5b (1.5 eq $Bu_4NF \cdot 3H_2O$, 5 eq HOAc, THF, few hours)occurred as expected with concomitant double bond isomerization, affording 7 in satisfactory yield (68-75%). When 7 was subjected to MCPBA oxidation, penem 10a (1:1 mixture of epimeric sulphoxides) was exclusively obtained. In accordance with well-established procedures, 10a underwent desilylation and deblocking of the allyl group[6] to furnish the sodium salt 12a in 65% yield.

The strong antibacterial activity of 12a (Table III)prompted us to synthesize some analogues bearing functionalities whose beneficial effect had been previuosly observed in the penem area[7,8]. Preparation of the carbamate 12b entailed condensation of the alcohol 10a with trichloroacetyl isocyanate (CH_2Cl_2, 1 minute, quant.) followed by simultaneous removal of the secondary silyl ether and trichloroacetyl group ($Bu_4NF \cdot 3H_2O$, HOAc-THF, overnight) and final unmasking of the allyl ester (38% overall). A quaternary ammonium group was conveniently introduced at an earlier stage. Thus, reaction of the penam carbinol 7, *in situ* activated as its triflate (trifluoromethanesulphonic anhydride, 2.5 eq. pyridine, CH_2Cl_2, -70°C → 0°C), with an excess of the selected tertiary nitrogen nucleophile occurred with partial exo-endo double bond isomerization[9] providing 8c~e, which underwent mild oxidation (1 eq. MCPBA, CH_2Cl_2, -70°C → -30°C, 15 min) to the epimeric sulphoxides 10c~e, uncontaminated[10] by any penam isomer. Subsequent routinary desilylation and catalytic transallylation with excess acetic acid ($Pd(PPh_3)_4$, PPh_3, CH_3CN-CH_2Cl_2, 30 min., 12% overall from the alcohol 7) yielded the zwitterions 12c~e. The carbamate 12b exhibited excellent antimicrobial activity, superior to the hydroxy analog 12a and to the reference compound FCE 22101[7], while an adverse effect was associated with the introduction of quaternary ammonium groups (entries 12c~e, Table III).

Table I - Spectral data of key intermediates

Compd.	ir (ν max, cm^{-1})[1]	^1H nmr (δ, ppm)[2]
9a	1795,1745,1710	2.96(2H,m),3.99(1H,dd,J=1.8 and 7.5Hz),4.05(2H,m),4.01,4.06, 4.56,4.61(2H, each d,J=13.3Hz),5.67(1H,d,J=1.8Hz)
10a	1790,1700	3.0-3.2(2H,m),3.83(1H,dd,J=1.7 and 4.1Hz),4.1-4.3(2H,m),4.11, 4.26,4.64,4.74(2H, each d,J=13.3Hz),5.72(1H,d,J=1.7Hz)
14	3420,1425,1120, 1010,950,700	(DMSO-d_6)1.00(9H,s),2.29 and 3.88(each 2H,t,J=7.0Hz),7.25-7.78(10H,m)
15c	3550,1790,1700 (KBr)	2.61(1H,br,s),3.3-3.4(2H,m),3.79(1H,dd,J=1.7 and 4.0Hz),4.13 (2H,m),4.47 and 4.93(2H, each d,J=14.4Hz),5.69(1H,d,J=1.7Hz)

[1] In $CHCl_3$ unless otherwise stated. [2] In $CDCl_3$ unless otherwise stated. Signals due to C_6 side chain and to protecting groups have been omitted.

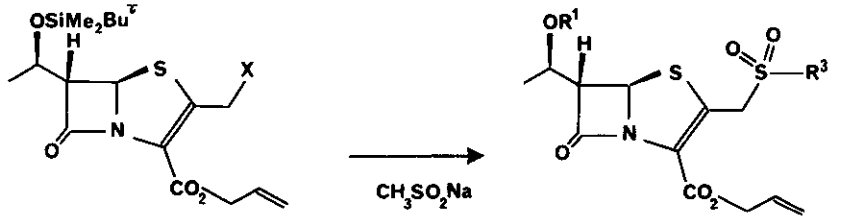
Table II - Spectral data of 2-sulphinyl and 2-sulphonylmethylpenem-3-carboxylic acids (sodium or internal salts)

Compound	ir(KBr) ν max $(cm)^{-1}$	uv (H_2O) λ max (nm)	^{1}H nmr (D_2O unless otherwise stated) δ (ppm)
12a	1765,1600	258,316	(DMSO-d_6)1.12(3H,d,6.3Hz),2.7-3.0(2H,m),3.49 (1H,dd,J=1.5 and 6.9Hz),3.73(2H,m),3.87(1H,m), 4.07,4.32,4.49,4.79(2H, each d,J=13.0Hz),5.05 (1H,br s,exch.D_2O),5.11(1H,br s,exch.D_2O),5.42-5.44(1H, each d,J=1.5Hz)
12b	1760,1715,1605	255(ε=4185), 315(ε=6004)	(DMSO-d_6)1.13(3H,d,J=6.3Hz),2.8-3.2(2H,m),3.50 (1H,dd,J=1.5 and 6.9Hz),3.87(1H,m),4.1-4.3(2H, m),4.06,4.35,4.61,4.95(2H, each d,J=13.0Hz), 5.11(1H,d,J=4.9Hz, exch D_2O),5.43,5.44(1H,each d,J=1.5Hz)
12c	1760,1620-1590	259,316	1.30(3H,d,J=6.3Hz),3.6-3.7(2H,m),3.95(1H,dd,J= 1.7 and 5.9Hz),4.25(1H,dq,J=5.9 and 6.3Hz), 4.33,4.72(2H, each d,J=13.6Hz),5.19(2H,m),5.69 (1H,d,J=1.7Hz),8.14(2H,dd,J=5.6 and 7.0Hz),8.63 (1H,t,J=7.0Hz),8.99(2H,d,J=5.6Hz)
12d	1765,1605	259,317	1.29(3H,d,J=6.4Hz),2.26(4H,m),3.13(3H,s),3.60 (4H,m),3.5-4.0(4H,m),3.99(1H,dd,J=1.5 and 6.0Hz) 4.26(1H,dq,J=6.0 and 6.4Hz),4.36,4.40,4.72,4.76 (2H, each d,J=13.6Hz),5.73(1H,d,J=1.5Hz)
12e	1770,1605	261,316	1.30(3H,d,J=6.4Hz),3.29(3H,s),3.60(4H,m),3.5-4.0 (4H,m),4.09(4H,m),4.26(1H,dq,J=5.9 and 6.4Hz), 4.37,4.74(2H, each d,J=13.4Hz),5.73,5.74(1H,each d,J=1.6Hz)
17a	1765,1610	258,314	1.30(3H,d,J=6.4Hz),3.16(3H,s),3.98(1H,dd,J=1.5 and 5.7Hz),4.26(1H,m),4.69,509(2H, each d,J=14.2 Hz),5.73(1H,d,J=1.5Hz)
17c	1765,1600	256(ε=5212), 314(ε=6900)	1.30(3H,d,J=6.3Hz),3.54(2H,t,J=5.6Hz),3.98(1H,dd, J=1.6 and 6.0Hz),4.07(2H,t,J=5.6Hz),4.26(1H,dq,J= 6.0 and 6.3Hz),4.70,5.13(2H,each d,J=14.1Hz),5.73 (1H,d,J=1.6Hz)
17d	1760,1715 1605	259,313	1.32(3H,d,J=6.4Hz),3.73(2H,t,J=5.2Hz),4.01(1H,dd, J=1.6 and 6.0Hz),4.28(1H,dq,J=6.0 and 6.4Hz),4.52 (2H,t,J=5.2Hz),4.73,5.24(2H, each d,J=14.2Hz), 5.75(1H,d,J=1.6Hz)
17e	1765,1605	313(ε=6275)	1.34(3H,d,J=6.4Hz),3.7-3.9(4H,m),3.97(1H,dd,J=1.6 and 6.0Hz),4.04(3H,s),4.27(1H,dq,J=6.0 and 6.4Hz), 4.83,5.13(2H, each d,J=14.6Hz),5.74(1H,d,J=1.6Hz)

At this point we turned our attention to the synthesis of sulphonylmethylpenems IV, which offerred further reasons for interest. Not only thermodynamic control favours allyl sulphones over vinyl sulphones, thereby inhibiting the penem → penam isomerization as for the corresponding sulphoxides, but the sulphonyl group compared to the sulphinyl group enhances the ß-lactam reactivity by exerting a stronger electron-withdrawing power, and avoids handling with epimeric mixtures. In Scheme 2 a practical synthetic route to sulphonylmethyl penems is outlined, involving conversion of 2 into the chloromethyl penem 13[11], followed by displacement with the appropriate alkanesulphinate anion.

Thus, treatment of 13 with sodium methanesulphinate and with sodium t-butyldiphenylsilyloxyethanesulphinate 14[12] (DMF, 3h, 50-70%) afforded the crystalline[13] sulphones 15a and 15b, respectively. Stepwise removal of protecting groups from 15a uneventfully gave 16a and 17a (48% over the two steps). Clevage of the primary silyl ether on the fully pretected penem 15b could be achieved selectively (1.2 eq, $Bu_4NF \cdot 3H_2O$, HOAc, THF, 6h) furnishing the carbinol 15c (73%), together with appreciable amounts of the diol 16c (~20%), obtained as the only product (82%) after prolonged exposure (24h) to excess (6 eq) reagent. Conventional Pd-mediated deallylation gave the sodium salt 17c. The preparation of the carbamoyl derivatives 17d from the alcohol 15c paralleled the route followed in the sulphoxide series (10a ⟶ 12b). However, 15c failed to behave like its analogue 10a when treated with triflic anhydride /N-methylpyrrolidine (CH_2Cl_2, -70°C ⟶ 0°C), the main isolated product being the vinyl sulphone 15f (30% yield). In this case the leaving ability of the triflate and quaternary ammonium groups, associated with the acidity of the α-sulphonyl protons, accounts for the occurrence of a competitive elimination reaction. Activation of the alcohol 15c under Mitsunobu-Volante conditions[5] (preformed TPP/DEAD complex, THF, 1 min.) in the presence of 5-mercapto-1-methyl-1,2,3,4-tetrazole led to the formation of the correspondent heterocyclyl thioester 15e in 90% yield, the remainder being the elimination product 15f. Finally 15e was converted into the sodium salt 17e (35% overall) by following the usual deprotection protocol.

SCHEME 2

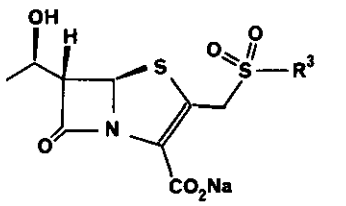


2, X = OH
13, X = Cl

14

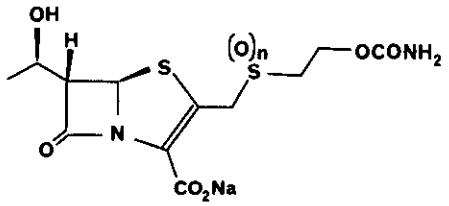
15, R^1 = $SiMe_2Bu^t$
16, R^1 = H

a R^3 = $-CH_3$
b R^3 = $-CH_2CH_2OSiPh_2Bu^t$
c R^3 = $-CH_2CH_2OH$
d R^3 = $-CH_2CH_2OCONH_2$
e R^3 = $-CH_2CH_2S$-(tetrazole)-CH_3
f R^3 = $-CH=CH_2$



17

With the exception of 17e, all the sulphonylmethyl penems showed a quite remarkable level of *in vitro* antimicrobial activity, comparable to that of their analogues in the sulphoxide series (Table III). The minimal inhibitory concentration (MIC) values exhibited by the structurally related carbamates 17d, 12b and 18[1], only differing in the oxidation state of the extranuclear sulphur atom are worth noticing. In line with our original working hypothesis[1], an improvement in antibiotic performance was observed on changing from the thioether representative 18 to the oxidated analogues, but the better profile exhibited by 12b in comparison with 17d could not be reduced in terms of straightforward structure-activity relationship.



12b n = 1
17d n = 2
18 n = 0

Table III - In vitro antibacterial activity[1,2] of penems

Compound	S.a.	S.p.	E.c.	E.c.+	E.cl.+	K.a.	P.m.
12a	0.045	0.005	0.78	1.56	0.78	0.78	1.56
12b	0.045	0.011	0.19	0.39	0.78	0.39	0.78
12c	0.09	———	6.25	3.12	3.12	6.25	6.25
12d	0.19	———	6.25	6.25	6.25	6.25	25
12e	0.39	———	6.25	6.25	6.25	6.25	25
17a	0.19	0.045	0.39	0.78	0.39	0.19	1.56
17c	0.09	0.045	0.78	1.56	0.78	0.78	1.56
17d	0.09	0.022	0.39	1.56	1.56	0.39	0.78
17e	0.09	0.022	3.12	3.12	12.5	6.25	3.12
18	0.045	0.011	6.25	6.25	25	12.5	6.25
FCE 22101	0.045	0.011	0.39	1.56	0.78	0.39	1.56

1) Minimal inhibitory concentrations (MICs, ug/ml) were determined by the standard two-fold agar dilution method in Bacto Antibiotic Medium 1 (Difco).

2) Organisms included in this Table are: S.a., Staphylococcus aureus Smith; S.p., Streptococcus pyogenes ATCC 12384; E.c., Escherichia coli B; E.c.+, E. coli B ß-lactamse producer; E.cl.+, Enterobacter cloacae P99 ß-lactamase producer; K.a., Klebsiella aerogenes 1522 E; P.m., Proteus morganii ATCC 25830.

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9. The penam/penem ratio ranged from approximately 3:1 to 4:1, depending on the nature of the nitrogen nucleophile.
10. As detected by ^1H NMR (200MHz) spectroscopy.
11. M. Alpegiani, A. Bedeschi, and E. Perrone, Gazz. Chim. Ital., 1985, 115, 393.
12. Compound 14 was obtained from the corresponding mercaptan [1] by exploiting the Michael adduct with ethyl acrylate as an oxidation blocker (81% overall):

$$Bu^tPh_2SiOCH_2CH_2SH \xrightarrow[b)\ MCPBA]{a)\ CH_2=CHCO_2Et,\ cat.\ MeONa} Bu^tPh_2SiOCH_2CH_2SO_2CH_2CH_2CO_2Et \xrightarrow{NaH} \mathbf{14}$$

13. Melting points of the crystalline sulphone intermediates are as follows: 15a, 65°C; 15b, 144-146°C; 15c, 120-122°C; 16a, 118-120°C.

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