

2-(HETEROATOM-SUBSTITUTED)METHYL PENEMS.

 II¹. SULPHINYL AND SULPHONYL DERIVATIVES

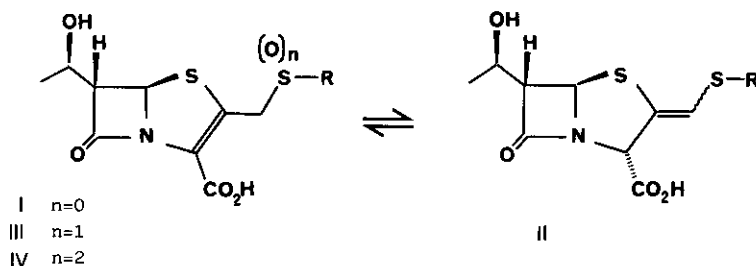
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Abstract - Thermodynamic control of the endo-exo double bond equilibration in 2-(thio-substituted)methyl penems allowed the synthesis of the sulphinyl and sulphonyl derivatives, which proved to be potent antibacterial agents.

Recently¹ 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.

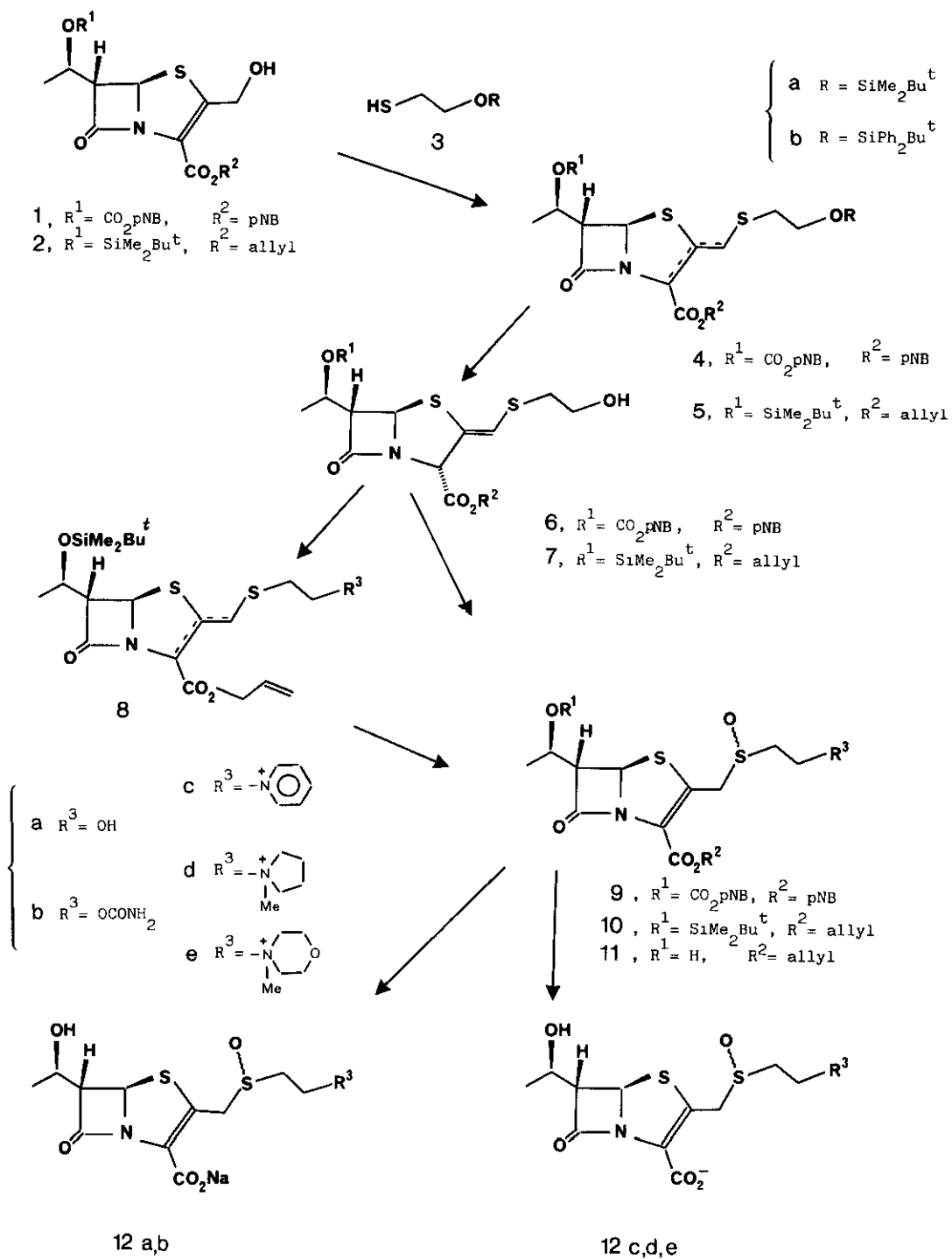


To complete the "sulphur series" of 2-CH₂X penems, we looked for substituents possessing an increased electron-withdrawing ability coupled with the intrinsic aptitude to stabilize the endo over the exo-cyclic ene form. These requirements are fulfilled by the sulphinyl and sulphonylmethyl penems III, IV, which are the object of the present communication.

For the preparation of sulphoxide derivatives III a straightforward method was found in the regioselective oxidation of the easily accessible thiomethylene penems II. Accordingly, Bu₄NF-mediated desilylation of the penem 4b¹ afforded the penam 6, whose treatment with 1 eq MCPBA (CH₂Cl₂, -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 endo-exo double bond isomerization results from thermodynamic factors favouring allyl sulphoxides over the isomeric vinyl sulphoxides². In fact, in the absence of the peripheral sulphur, oxidation of methylene penams uneventfully occurs on the nucleus with preservation of the exo structure³. An intra-annular counterpart of this double bond shift is the well-known conversion of Δ^2 cepems into Δ^3 cepem-1-oxides.

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

SCHEME 1



cult. To overcome this problem, the differently protected methylene penam 7 was preferred to 6 as the key intermediate for the synthesis of 12a *v.e.* Reaction of the alkyl thiol 3a (3b)¹ with hydroxymethyl penem 2⁴ under a slightly modified Mitsunobu-Volante⁵ procedure (slow addition of a preformed PPh₃-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 Bu₄NF·3H₂O, 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 group⁶ 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 previously observed in the penem area^{7,8}. Preparation of the carbamate 12b entailed condensation of the alcohol 10a with trichloroacetyl isocyanate (CH₂Cl₂, 1 minute, quant.) followed by simultaneous removal of the secondary silyl ether and trichloroacetyl group (Bu₄NF·3H₂O, 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, CH₂Cl₂, -70°C → 0°C), with an excess of the selected tertiary nitrogen nucleophile occurred with partial exo-endo double bond isomerization⁹ providing 8c *v.e.*, which underwent mild oxidation (1 eq. MCPBA, CH₂Cl₂, -70°C → -30°C, 15 min) to the epimeric sulphoxides 10c *v.e.*, uncontaminated¹⁰ by any penam isomer. Subsequent routinary desilylation and catalytic transallylation with excess acetic acid (Pd(PPh₃)₄, PPh₃, CH₃CN-CH₂Cl₂, 30 min., 12% overall from the alcohol 7) yielded the zwitterions 12c *v.e.* The carbamate 12b exhibited excellent antimicrobial activity, superior to the hydroxy analog 12a and to the reference compound FCE 22101⁷, while an adverse effect was associated with the introduction of quaternary ammonium groups (entries 12c *v.e.*, Table III).

Table I - Spectral data of key intermediates

Compd.	ir (ν _{max} , cm ⁻¹) ¹	¹ H nmr (δ, ppm) ²
<u>9a</u>	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)
<u>10a</u>	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)
<u>14</u>	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)
<u>15c</u>	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 CHCl₃ unless otherwise stated. ² In CDCl₃ unless otherwise stated. Signals due to C₆ side chain and to protecting groups have been omitted.

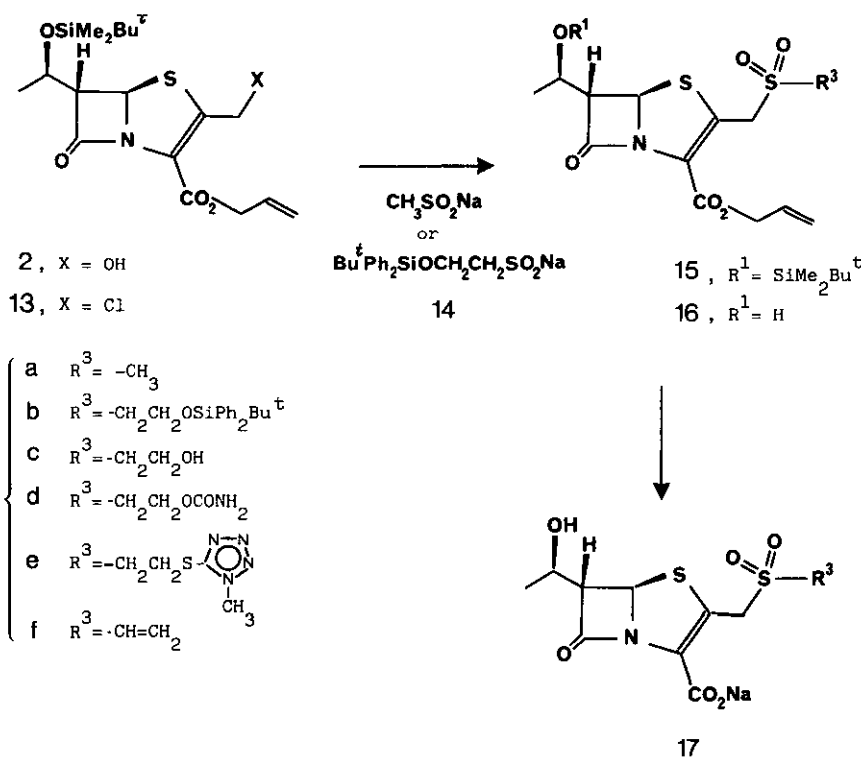
Table II - Spectral data of 2-sulphinyl and 2-sulphonylmethylpenem-3-carboxylic acids (sodium or internal salts)

Compound	ir(KBr) ν max (cm) ⁻¹	uv (H ₂ O) λ max (nm)	¹ H nmr (D ₂ O unless otherwise stated) δ (ppm)
<u>12a</u>	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, $J=13.0$ Hz), 5.05(1H,br s,exch.D ₂ O), 5.11(1H,br s,exch.D ₂ O), 5.42-5.44(1H, each d, $J=1.5$ Hz)
<u>12b</u>	1760,1715,1605	255($\epsilon=4185$), 315($\epsilon=6004$)	(DMSO-d ₆) 1.13(3H,d, $J=6.3$ Hz), 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, $J=13.0$ Hz), 5.11(1H,d, $J=4.9$ Hz, exch D ₂ O), 5.43, 5.44(1H, each d, $J=1.5$ Hz)
<u>12c</u>	1760,1620-1590	259,316	1.30(3H,d, $J=6.3$ Hz), 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, $J=13.6$ Hz), 5.19(2H,m), 5.69(1H,d, $J=1.7$ Hz), 8.14(2H,dd, $J=5.6$ and 7.0Hz), 8.63(1H,t, $J=7.0$ Hz), 8.99(2H,d, $J=5.6$ Hz)
<u>12d</u>	1765,1605	259,317	1.29(3H,d, $J=6.4$ Hz), 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, $J=13.6$ Hz), 5.73(1H,d, $J=1.5$ Hz)
<u>12e</u>	1770,1605	261,316	1.30(3H,d, $J=6.4$ Hz), 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, $J=13.4$ Hz), 5.73, 5.74(1H, each d, $J=1.6$ Hz)
<u>17a</u>	1765,1610	258,314	1.30(3H,d, $J=6.4$ Hz), 3.16(3H,s), 3.98(1H,dd, $J=1.5$ and 5.7Hz), 4.26(1H,m), 4.69, 5.09(2H, each d, $J=14.2$ Hz), 5.73(1H,d, $J=1.5$ Hz)
<u>17c</u>	1765,1600	256($\epsilon=5212$), 314($\epsilon=6900$)	1.30(3H,d, $J=6.3$ Hz), 3.54(2H,t, $J=5.6$ Hz), 3.98(1H,dd, $J=1.6$ and 6.0Hz), 4.07(2H,t, $J=5.6$ Hz), 4.26(1H,dq, $J=6.0$ and 6.3Hz), 4.70, 5.13(2H, each d, $J=14.1$ Hz), 5.73(1H,d, $J=1.6$ Hz)
<u>17d</u>	1760,1715 1605	259,313	1.32(3H,d, $J=6.4$ Hz), 3.73(2H,t, $J=5.2$ Hz), 4.01(1H,dd, $J=1.6$ and 6.0Hz), 4.28(1H,dq, $J=6.0$ and 6.4Hz), 4.52(2H,t, $J=5.2$ Hz), 4.73, 5.24(2H, each d, $J=14.2$ Hz), 5.75(1H,d, $J=1.6$ Hz)
<u>17e</u>	1765,1605	313($\epsilon=6275$)	1.34(3H,d, $J=6.4$ Hz), 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, $J=14.6$ Hz), 5.74(1H,d, $J=1.6$ Hz)

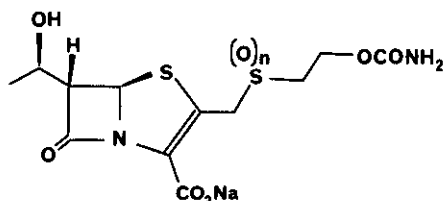
At this point we turned our attention to the synthesis of sulphonylmethylpenems IV, which offered further reasons for interest. Not only thermodynamic control favours allyl sulphones over vinyl sulphones, thereby inhibiting the penem \rightarrow penam isomerization as for the corresponding sulphoxides, but the sulphonyl group compared to the sulphinyl group enhances the β -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 13¹¹, followed by displacement with the appropriate alkanesulphinat anion.

Thus, treatment of 13 with sodium methanesulphonate and with sodium *t*-butyldiphenylsilyloxyethane-sulphonate 14¹² (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). Cleavage of the primary silyl ether on the fully protected penem 15b could be achieved selectively (1.2 eq, Bu₄NF·3H₂O, 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 (CH₂Cl₂, -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 conditions⁵ (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



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 18¹, only differing in the oxidation state of the extranuclear sulphur atom are worth noticing. In line with our original working hypothesis¹, 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.
<u>12a</u>	0.045	0.005	0.78	1.56	0.78	0.78	1.56
<u>12b</u>	0.045	0.011	0.19	0.39	0.78	0.39	0.78
<u>12c</u>	0.09	—	6.25	3.12	3.12	6.25	6.25
<u>12d</u>	0.19	—	6.25	6.25	6.25	6.25	25
<u>12e</u>	0.39	—	6.25	6.25	6.25	6.25	25
<u>17a</u>	0.19	0.045	0.39	0.78	0.39	0.19	1.56
<u>17c</u>	0.09	0.045	0.78	1.56	0.78	0.78	1.56
<u>17d</u>	0.09	0.022	0.39	1.56	1.56	0.39	0.78
<u>17e</u>	0.09	0.022	3.12	3.12	12.5	6.25	3.12
<u>18</u>	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

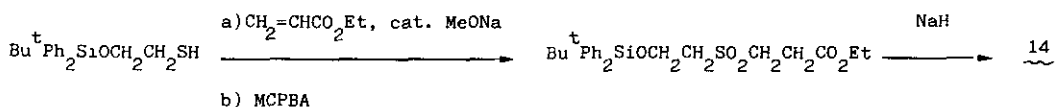
- 1) Minimal inhibitory concentrations (MICs, ug/ml) were determined by the standard two-fold agar dilution method in Bacto Antibiotic Medium 1 (Difco).
- 2) Organisms included in this Table are: S.a., Staphylococcus aureus Smith; S.p., Streptococcus pyogenes ATCC 12384; E.c., Escherichia coli B; E.c.⁺, E. coli B β -lactamase producer; E.cl.⁺, Enterobacter cloacae P99 β -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):



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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