2-(HETEROATOM-SUBSTITUTED)METHYL PENEMS.
I. SULPHUR DERIVATIVES

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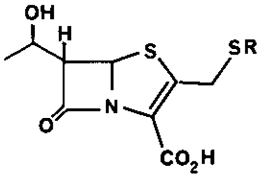
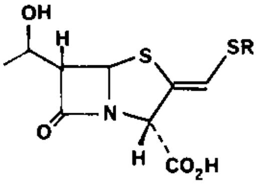
Abstract - Chemical strategies for the synthesis of "2-CH_2X" penems wherein X is a (substituted) alkylthio or heterocyclylthio radical are reviewed. The rationale at the basis of the programme is checked against the obtained microbiological data.

Following the discovery of a natural active structure, a great deal of research work has usually to be spent altering the original molecule in order to achieve optimal biological effects; this task is further aggravated when dealing with man-made structures, such as penems. Even so, the poorness of consolidated structure-activity relationships inside the penem family does appear surprising: while the importance of the hydroxyethyl chain at C-6 was soon recognized, the role of substituents at position 2 in modulating the antibacterial activity is still matter of conjecture. On the subject, it has been recently written that "..variation of the 2-substituent exerts only a modest effect on in vitro activity..", the main differences appearing rather "to reflect the effect [of the substituent] on the lipophilicity of the molecule."[1] A quite opposite rationale was adopted by us in approaching this field: we surmised that, because of the enamine system common to penems and cephalosporins, the inductive effect of the 2-position side chain would strongly influence the reactivity of the ß-lactam carbonyl and therefore be of the utmost relevance. This holds true for cephalosporins, where not only the average Gram-negative activity can be correlated to the inductive substituent constants for the C-3 side chain[2], but a heteroatom-substituted methyl in this position is usually more beneficial than a heteroatom attached directly to the nucleus[3]: hence our particular interest in 2-CH_2X (X= S,O,N) penem derivatives. We wish here to report our unpublished results in the area, and point out some discrepancies with the general statement referred to above.

The sulphur derivatives we considered can be divided in two families, I and II, according to whether the sulphur atom is further linked to a heterocyclyl or alkyl residue. The former family was pursued first, since it bears obvious relationships with the majority of cephalosporins present on the market, and preliminary studies on a representative lacking the C-6 side chain had been encouraging.[5]



I R= heterocyclyl
II R= alkyl

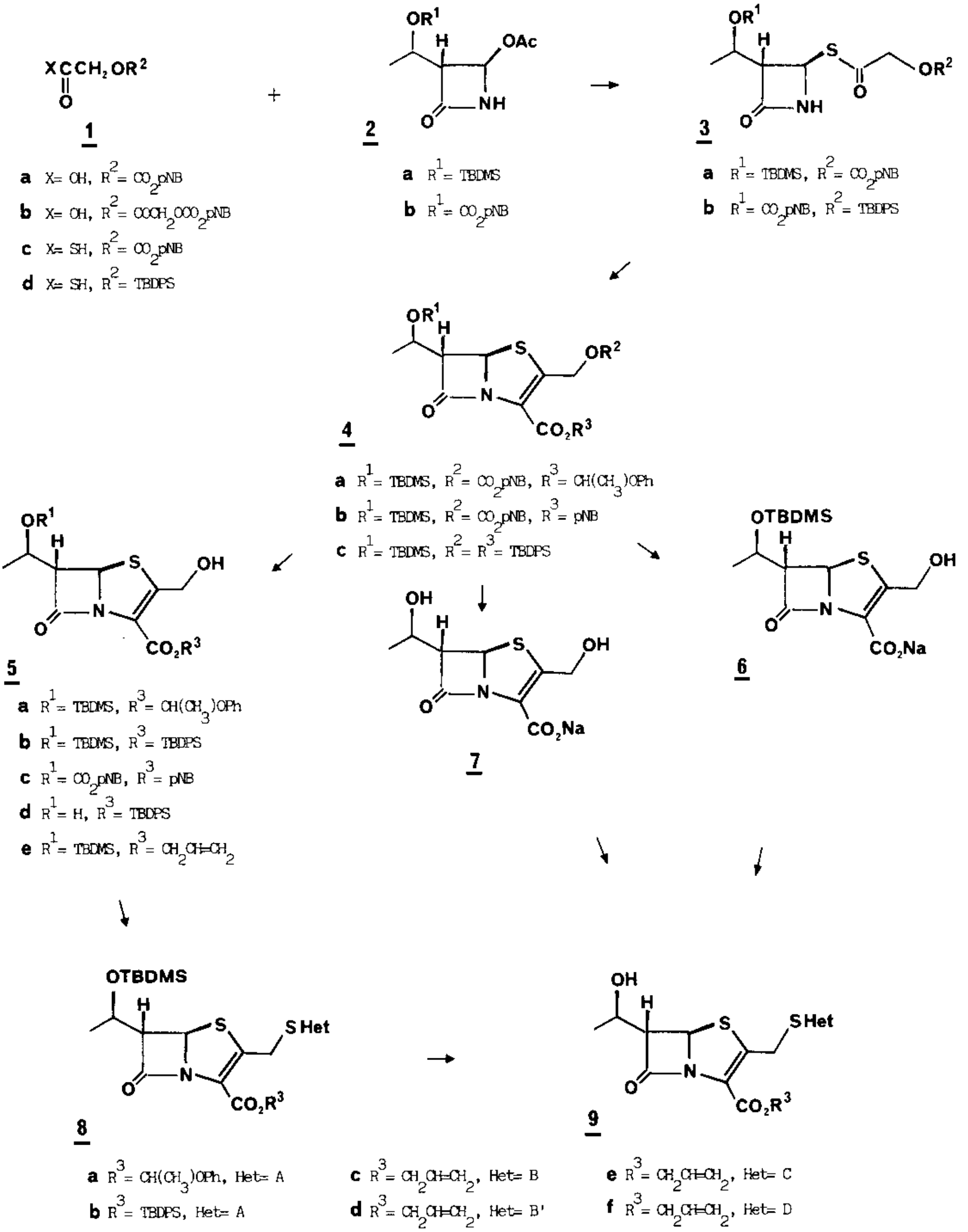


III R= heterocyclyl
IV R= alkyl

Initially, our synthetic plan closely duplicated Woodward's strategy;[6] i.e. a phosphorane, already incorporating the heterocyclylthio moiety, was cyclized to each individual target compound. This route, which suffered from low yields owing to the sensitiveness of the thioester intermediates and to the problematic choice of the multiple protecting groups, had been expedient for obtaining a sample of the first member of the series, the methyltetrazolyl derivative Ia,[7] but lacked the versatility and productivity required for the preparation of a consistent number of analogues. For this purpose we envisaged the possibility of exploiting a 2-hydroxymethylpenem as a late common intermediate and, since an expressly designed carboxyl protecting group[8] had proved invaluable for the first synthesis of Ia, this common precursor was sought in the 1-phenoxyethyl ester 5a (Scheme I). To our end, glycolic acid was treated with p-nitrobenzyl chloroformate to give the carbonate 1a (43%) and the dimeric derivative 1b; the former was converted into the thioacid 1c ($EtOCOCl/NEt_3$, CH_2Cl_2; then H_2S/NEt_3) and used for acetate displacement on azetidinone 2a.[9] The thioester 3a thus obtained was condensed with 1-phenoxyethyl glyoxylate and then processed along the popular phophorane sequence[6] to give the fully protected 2-hydroxymethylpenem 4a; the desired free alcohol 5a was thence unmasked in high yield by catalytic hydrogenation. The conversion of this compound into the thioether 8a, a key intermediate in the first synthesis of Ia, clearly demonstrated the potentiality of hydroxymethylpenems 5 in the preparation of a large number of heterocyclylthiomethyl derivatives; such conversion was accomplished either by sequential mesylation (CH_3SO_2Cl/NEt_3, CH_2Cl_2) and displacement with 5-mercapto-1-methyltetrazole (MMT sodium salt, THF, few hours, 0°C), or in a single step via the Mitsunobu reaction[10] (MMT/PPh_3/diethyl azodicarboxylate).

Having established the practicability of the new synthetic approach, the chemistry of the protecting groups and of the exchange reaction was more attentively examined. First, since hydrolysis of the ester group on the final compounds was one major problem, we devised to perform this step prior to thiol introduction. Thus, p-nitrobenzyl glyoxylate was substituted for the 1-phenoxyethyl analogue in the above sequence leading to 4a, thereby obtaining 4b; catalytic hydrogenation in a biphase EtOAc-aq.$NaHCO_3$ system (the carbonate being removed first) then afforded the sodium salt 6 in satisfactory yield. A convenient temporary protection for the carboxyl function of 6 was found in the labile tert-butyldiphenylsilyl group, which was selectively introduced by performing the silylation in THF (in CH_2Cl_2 formation of the trisilylated compound 4c could not be avoided); the obtained disilylated intermediate 5b was then activated on the free hydroxyl ($MsCl/NEt_3$, CH_2Cl_2) and reacted in situ with the thiol to give the desired thioether 8b. Unfortunately, double desilylation of 8b afforded Ia in very poor yields, presumably a consequence of the limited stability of penems under the conditions of silyl removal at position 8 whenever the carboxyl is unmasked first. In order to avoid this problem, selective activation of the primary alcohol was performed on the fully deprotected synthon 7. This material, easily accessible from azetidinone 2b via thioester 3b and penem 5c according to a previous methodology,[11] when temporarily protected as the TBDPS ester 5d[12] underwent mesylation and in situ displacement (MMT sodium salt/$CaCO_3$, THF-CH_2Cl_2) to afford 9b and thence Ia (HOAc-THF-H_2O, 3:1:1; 40 min, r.t.).[13] The extremely mild cleavage of allyl esters recently introduced by McCombie et al.[14] came welcome in this context; the allyl ester 5e often proved superior to 5a, 5c,[15] 5d as a precursor of 2-thiomethyl substituted penems, either through the mesylate

SCHEME I



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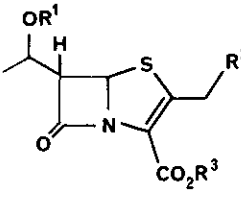
pNB= p-nitrobenzyl; TBDMS= $SiMe_2Bu^t$; TBDPS= $SiPh_2Bu^t$; heterocycles A∼D are as shown in Table II or the Mitsunobu route.

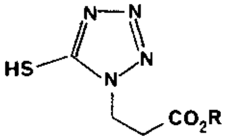
Other obvious pathways to compounds I entailed the displacement with the heterocyclic thiol of either a halo or an acetoxy group, in analogy with methodologies routinary in the cephalosporin field. However, reaction of MMT sodium salt with the acetate 10a[16] under a variety of conditions gave, if any, only a trace amount of the desired penem Ia, ß-lactam opening occurring first. Acetoacetates have been claimed to undergo easier displacement by nucleophiles than acetates,[17] but reaction of MMT on 10b (from 5c and diketene) or on the sodium salt 10c (from 10b by hydrogenolysis) was equally unrewarding. On the other hand, halomethylpenems proved to be reactive species, though plagued by stability problems. Compound 10d could be obtained by treatment of 5c with PPh_3/CCl_4 (24 h, r.t.), while 10e, accompanied by a consistent amount of 4-allyloxycarbonyl-5-chloromethylthiazole, was secured from reaction of 5e with $SOCl_2$ (pyr; CH_2Cl_2-40°C) they both survived rapid flash-chromatography, but yields were low and irreproducible. Better results were obtained from



10

a $R^1 = H$, $R^2 = OCOCH_3$, $R^3 = Na$
b $R^1 = CO_2pNB$, $R^2 = OCOCH_2COCH_3$, $R^3 = pNB$
c $R^1 = H$, $R^2 = OCOCH_2COCH_3$, $R^3 = Na$
d $R^1 = CO_2pNB$, $R^2 = Cl$, $R^3 = pNB$
e $R^1 = TBDMS$, $R^2 = Cl$, $R^3 = CH_2CH{=}CH_2$
f $R^1 = R^2 = H$, $R^3 = K$
g $R^1 = CO_2pNB$, $R^2 = OSO_2CH_3$, $R^3 = pNB$
h $R^1 = TBDMS$, $R^2 = OSO_2C_6H_4\text{-}pCH_3$, $R^3 = CH_2CH{=}CH_2$

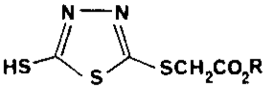
halomethylpenems generated under milder conditions: in particular from the carbinols through a new application of the Mitsunobu reaction,[18] from 4-haloacetylthioazetidinones by a low-temperature Wittig condensation,[19] from 3-bromomethyl-2-thiacephems by ring-contraction[20] with PPh_3 at -40°C.On balance, however, the mesylate and Mitsunobu approaches remained the most satisfactory routes to penems I. Mesylates, e.g. 10g, although unstable upon storage, could easily be reacted in situ and proved more handy than the corresponding tosylates, e.g. 10h. The Mitsunobu procedure turned out particularly appealing when we found that a modification in the order of addition, originally suggested by Volante[21] for the synthesis of thioesters, minimizes by-products and base-catalyzed side-reactions in this particular thioether synthesis.[22] According to this methodology, diethyl azodicarboxylate and PPh_3 were first allowed to form a crystalline complex (THF, 30 min,r.t.), which then immediately reacted at 0°C when added to a THF solution of the carbinol 5 and the heterocyclic thiol. The functionalities present on some heterocyclic thiols had to be taken into account. The reaction of 8c to give the iminophosphorane 8d in the presence of excess Mitsunobu reagent is a singular example,[23] although in the instance the free amino group could be restored by mild acidic hydrolysis (THF-HOAc-H_2O 3:1:1, overnight). Acid hydroxy groups had to be protected before condensation; in order to avoid any unnecessary lenghtening of the synthetic sequence, allyl and silyl protecting groups were chosen for the purpose. Thus, the tetrazolylpropionic acid 11a was protected as its allyl ester 11b, (neat allyl alcohol, cat. 37% aq.HCl), while the thiadiazole derivative 12a was protected as the tert-butyldiphenylsilyl ester 12b (TBDPS chloride, NEt_3; THF). The difference in acidity between the two isomeric triazinones 13a and 14[25] was reflected by their need for protection: the less acidic isomer 14 readily reacted as such, while the strongly acidic hydroxyl group of 13a had to be protected as its silyl ether 13b. This last compound suffered desilylation upon attempted mesylate displacement, but could be condensed either with 5b or 5e under the previously reported Mitsunobu conditions.



11

a R= H

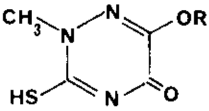
b R= $CH_2CH=CH_2$



12

a R= H

b R=TBDPS



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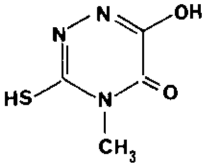
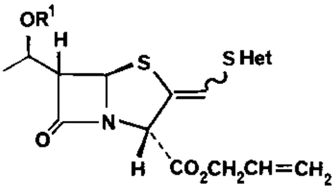


14

A major problem in the preparation of thiomethylpenems I, II was their propensity to undergo equilibration to thiomethylenepenams III, IV. Shift of the double bond between the endo and the exo position following base treatment was first observed by Woodward,[26] and it has since found some utility for the synthesis of thia-analogs of clavulanic acid,[27] for 2-oxopenam intermediates[28] and also for obtaining 2-alkylpenems from alkylidenepenams[29] in cases where, owing to the lack of conjugation, the latter are the thermodynamically less stable isomers. For heterocyclylthiomethylpenem esters I the endo-exo equilibrium lies somewhere in the proximity of 30:70, and this proportion is even more unfavourable for the alkylthio analogs II, so that the success of the synthesis was largely dependent on the kinetic factor, i.e. on the ingenuity exerted in avoiding prolonged basic conditions during the exchange-deprotection sequence. The synthesis of Ic is illustrative. Condensation of 5e with 1-(2-dimethylaminoethyl)tetrazole-5-thiol (mesylate route) and quenching with HOAc afforded a 1:1 mixture of the endo/exo products, 8e and 15a. In the presence of a large excess of acetic acid, this mixture underwent desilylation (TBAF, THF overnight) without significant change in the isomer ratio, and then the desired intermediate 9e could be separated from the



15

a R^1= TBDMS, Het= C

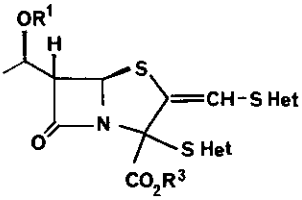
b R^1= H, Het= C

c R^1= TBDMS, Het= D

d R^1= H, Het= D

e (Z isomer), R^1= H,. Het= B

f (E isomer), R^1= H, Het= B



16

a R^1= TBDMS, R^3= $CH_2CH=CH_2$, Het= K

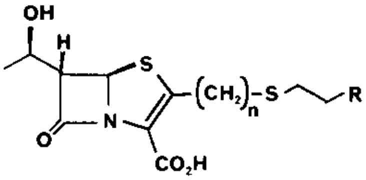
b R^1= H, R^3= Na, Het= K

slower-running exo-isomer 15b by chromatography on silanized silica. By using HOAc instead of sodium ethylhexanoate, deallylation of 9e with the Pd-PPh_3 complex furnished an inseparable 3:2 mixture of Ic and IIIc (as the internal salts); under the usual conditions the sodium salt of the latter was exclusively obtained. In this instance, and whenever penams III were the predominant final products, it proved difficult to revert the exo form into the equilibrium mixture in acceptable yields, presumably owing to the limited intrinsic stability of compounds I. Nevertheless, direct evidence of a reversible equilibrium being at work was often apparent in protected intermediates when the two forms happened to be easily differentiated by chromatography; for example on separate desilylation of pure 8f and 15c the same mixture (ca. 1:1) of isomers 9f, 15d was obtained.

Alkylidenepenams arising from base-catalyzed isomerization of penems are expected to possess the more stable configuration at the centres involved in the equilibration, i.e. to be S at C-3 and Z at the exo double bond. Indeed, a single isomer had always been found in previous works[26,29] and assigned this structure. In one instance, however, we were able to detect by nmr spectroscopy the presence of a minor component (1:9), 15f, accompanying the major compound, 15e; they were considered, respectively, as the E, Z alkene isomers of the 8R, 6S, 5R, 3S form. Although the relative assignment was made by inference,[30] the high deshielding experienced by the C-3 protons in both compounds, and the minimal mutual difference ($\Delta\delta = 0.07$ ppm), ruled out an alternative interpretation in terms of a diastereomeric relationship at C-3.[31]

Another unusual alkylidenepenam structure was detected in the reaction mixture from 5e and 2-mercapto-5-methyl-1,3,4-thiadiazole (mesylate route); it manifestly incorporated two elements of the heterocyclic thiol and on the basis of analytical and spectral data was formulated as 16a.[33] This material, as well as any other alkylidenepenam that could be isolated reasonably free ($\leqslant 5\%$) from its penem isomer, was conventionally deprotected, and the obtained salts (16b, IIIc-h; Table III) were assayed for antimicrobial activity (Table IV).

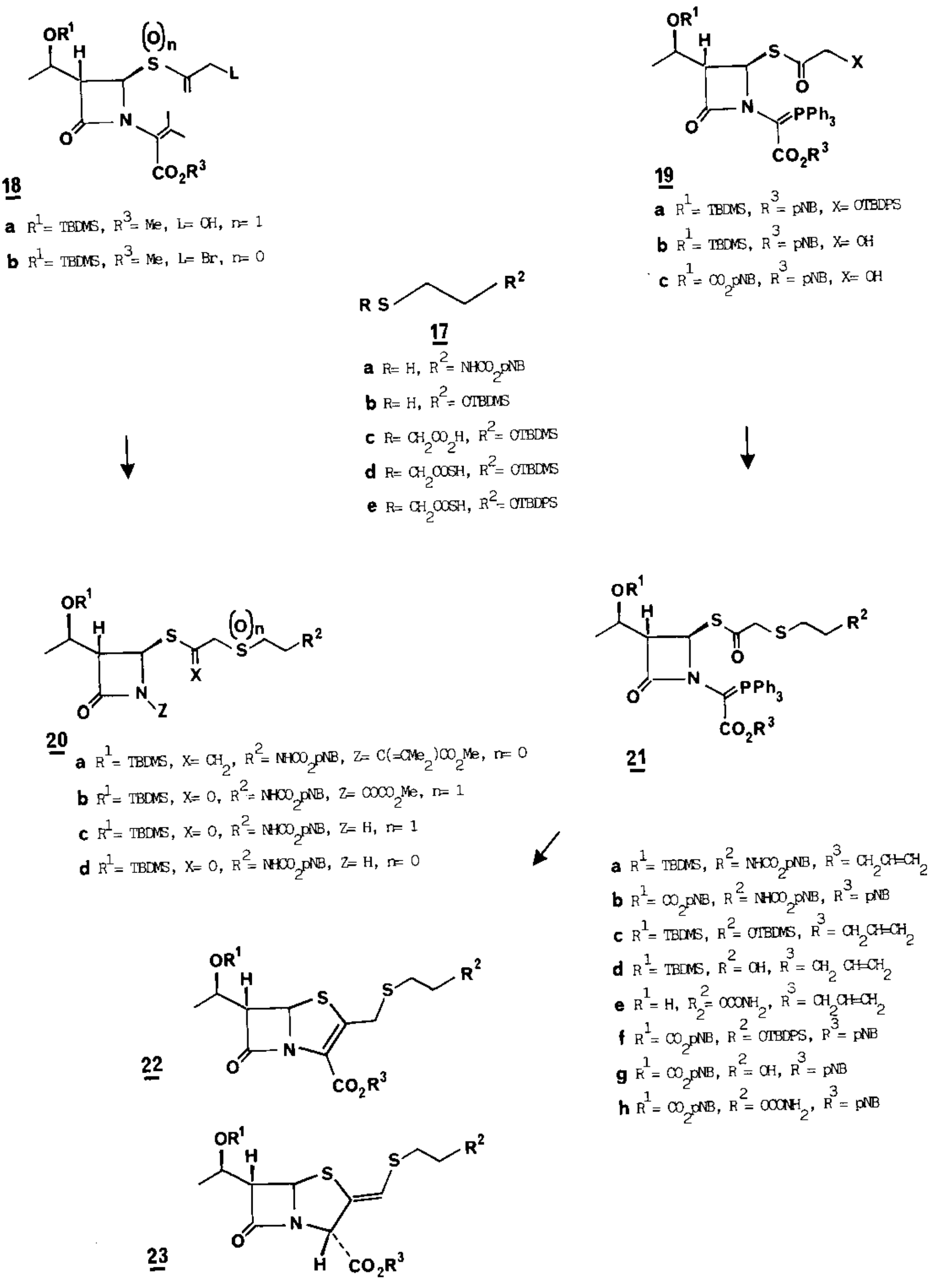
While the heterocyclylthiomethylpenems I are reminiscent of cephalosporins, the alkylthiomethyl analogs II offer different reasons for interest. In particular, compound IIa bears strict relationships with thienamycin and its penem counterpart, Sankyo's "1-thiathienamycin", Va.[34] Compound IIb carries the carbamoyloxy functionality characterizing Farmitalia Carlo Erba's FCE 22101,[11] and is the 2-homolog of another 1-thiathienamycin derivative, Vb, the new Schering's candidate (Sch34343).[35]



II a n= 1, R= NH_2
II b n= 1, R= $OCONH_2$
V a n= 0, R= NH_2
V b n= 0, R= $OCONH_2$

For the synthesis of compounds II the hydroxymethylpenem approach proved of very limited value, owing to the weak acidity of alkylthiols and to the sensitiveness of penems towards nucleophiles. Thus, the mesylate from 5e did not react in the presence of triethylamine with the protected

SCHEME II



18

a R^1= TBDMS, R^3= Me, L= OH, n= 1

b R^1= TBDMS, R^3= Me, L= Br, n= 0

19

a R^1= TBDMS, R^3= pNB, X= OTBDPS

b R^1= TBDMS, R^3= pNB, X= OH

c R^1= CO_2pNB, R^3= pNB, X= OH

17

a R= H, R^2= $NHCO_2$pNB

b R= H, R^2= OTBDMS

c R= CH_2CO_2H, R^2= OTBDMS

d R= CH_2COSH, R^2= OTBDMS

e R= CH_2COSH, R^2= OTBDPS

20

a R^1= TBDMS, X= CH_2, R^2= $NHCO_2$pNB, Z= C(=CMe_2)CO_2Me, n= 0

b R^1= TBDMS, X= O, R^2= $NHCO_2$pNB, Z= $COCO_2$Me, n= 1

c R^1= TBDMS, X= O, R^2= $NHCO_2$pNB, Z= H, n= 1

d R^1= TBDMS, X= O, R^2= $NHCO_2$pNB, Z= H, n= 0

21

a R^1= TBDMS, R^2= $NHCO_2$pNB, R^3= $CH_2CH{=}CH_2$

b R^1= CO_2pNB, R^2= $NHCO_2$pNB, R^3= pNB

c R^1= TBDMS, R^2= OTBDMS, R^3= $CH_2CH{=}CH_2$

d R^1= TBDMS, R^2= OH, R^3= CH_2 $CH{=}CH_2$

e R^1= H, R_2^2= $OCONH_2$, R^3= $CH_2CH{=}CH_2$

f R^1= CO_2pNB, R^2= OTBDPS, R^3= pNB

g R^1= CO_2pNB, R^2= OH, R^3= pNB

h R^1= CO_2pNB, R^2= $OCONH_2$, R^3= pNB

22

23

cysteamine 17a, while reaction with the lithium salt of the latter (from the thiol and BuLi) resulted in ß-lactam opening. Similarly, the carbinol 5e was decomposed by treatment with PBu_3-Et_2S_2 (with PPh_3 no reaction occurred), and condensation of 5e with 17a under Mitsunobu-Volante conditions gave a mixture of penem 22a and penam 23a in moderate yields. We therefore resorted to the preparation of azetidinyl thioesters already incorporating the desired functionality. Following an original Farmitalia route,[36] the 1,2-secopenicillanate 18a, obtained by trapping a penicillin-derived sulphenic acid with propargyl alcohol, was converted into the bromo-sulphide 18b; this monocyclic ß-lactam, different from the activated hydroxymethylpenems, could be easily thiolated with the lithium salt of 17a to give 20a (Scheme II). Although the key N-unsubstituted azetidinone 20d was eventually obtained from the latter by sequential ozonolysis to 20b (80%), methanolysis on silica to 20c (30%) and sulphoxide reduction (PBr_3, DMF-CH_2Cl_2, 90%), any attempt to convert this compound or its oxalimido precursor 20b into a triphenyl or triethoxyphosphoranylidene intermediate met with unexpected failure. Phosphoranes 19 proved better suited than azetidinones 20 for the derivation of penem IIa. Thus 19b and 19c, easily obtained from the silylated parents, e.g. 19a,[37] were activated either as the mesylates or the bromides and reacted with the protected cysteamine 17a (lithium salt). Thermal cyclization of 21b, followed by catalytic hydrogenation of the resulting tris-protected penem 22b, finally afforded a sample of the desired 2-homo-1-thiathienamycin IIa. Similarly, we considered the phosphorane 21c as a suitable precursor for our second target in this series, IIb. The required thioacid 17d was synthesized from 2-mercaptoethanol by sequential monosilylation (TBDMS chloride/imidazole; DMF, overnight, quantitative), alkylation with chloroacetic acid ($KOBu^t$ 2 mol eq.; EtOH, 2 h, 95%), activation[38] of the resulting acid 17c as the chloride (oxalyl chloride/NEt_3; CH_2Cl_2, -15°C) and in situ treatment with H_2S in the presence of a further amount of NEt_3 (30 min; 20%).[39] Reaction of said thioacid with the acetoxyazetidinone 2a, followed by the conventional phosphorane build-up sequence, uneventfully yielded 21c and thence 22c after brief heating in refluxing toluene. Although penem 22d could be gained virtually uncontaminated from the exomethylene isomer 23d by selective unmasking of the primary alcohol under mild acidic conditions (THF/HOAc/H_2O 2:1:1; 40 h, 80%),[40] the particular propensity of alkylthiomethylpenems to undergo double bond migration was apparent in the cleavage of the secondary silyl ether ($Bu_4NF.3H_2O$, HOAc-THF) on the adduct from 22d and trichloroacetyl isocyanate, whereupon the alkylidenepenam 23e and thence the sodium salt IVb were exclusively obtained.

The final adjustment of the synthetic sequence embodied a non-isomerative deblocking of protecting groups and the use of a more stable thioacid. Substitution of the TBDPS group for TBDMS in the route leading to 17d from 2-mercaptoethanol conveniently afforded 17e, which was then allowed to react with azetidinone 2b and conventionally processed to the phosphorane 21f. Reversal of the cyclization-desilylation previously exploited[41] gave 21g and thence the penem carbinol 22g, uncontaminated by any penam isomer. Reaction of the latter with trichloroacetyl isocyanate (CH_2Cl_2, -20 °C) followed by cleavage of the intermediate urethane (MeOH/SiO_2 230-400 Mesh; EtOAc, 5 h) afforded the carbamate 22h and finally, after deblocking of the pNB groups (Fe/NH_4Cl; THF-H_2O, 1 h), penem IIb was secured.

Table I - Spectral data of key intermediates

Compd.	ir (ν max, cm^{-1})[1]	^{1}H nmr (δ , ppm)[2]
1a[3]	3500-2600,1750br	4.70 and 5.25(each 2H,s), 7.47 and 8.15(each 2H,d,8Hz)
1b	-	4.75,4.80,5.25(each 2H,s), 7.47 and 8.15(each 2H,d,8Hz)
1c	3380,2550,1755,1710sh, 1605	-
1d	2600,1700	1.1(9H,s), 4.1(2H,s), 4.6(1H,br s), 7.1-7.9(10H,m)
3a	3250br,1760br,1695	0.08(6H,s), 0.89(9H,s), 1.21(3H,d), 3.22(1H,dd,2.5 and 3Hz), 4.26(1H,m), 4.82 and 5.34(each 2H,s), 5.38(1H,d), 6.52(1H,br s)
3b	3410,1780,1750,1690 ($CHCl_3$)	1.1(9H,s), 1.5(3H,d), 3.45(1H,dd,2 and 6.5Hz), 4.2(2H,s), 5.1 (1H,m), 5.2(2H,s), 5.25(1H,d), 6.7br(1H,s)
4b	1795,1755,1710,1605 (CCl_4)	0.08(6H,s), 0.84(9H,s), 1.26(3H,d), 3.80(1H,dd,1.8 and 3.5Hz), 4.27(1H,m), 5.30 and 5.40(each 2H,ABq, 16Hz), 5.31(2H,s), 5.67 (1H,d)
4c	-	0.08(6H,s), 0.9,1.06 and 1.08(each 9H,s), 1.39(3H,d), 3.75(1H, dd), 4.24(1H,m), 4.73(2H,s), 5.60(1H,d), 7.2-7.9(20H,m)
5b	1790,1710,1660	0.08(6H,s), 0.88 and 1.1(each 9H,s), 1.24(3H,d), 3.50(1H,t), 3.77(1H,dd,1.5 and 5Hz), 4.24(1H,m), 4.42(2H,d), 5.63(1H,d)
5c[3]	1795,1755,1710	1.51(3H,d,6.5Hz), 3.55(1H,br s), 3.97(1H,dd,2 and 8Hz), 4.68 (2H,s), 5.19(1H,m), 5.25-5.45(4H,m), 5.65(1H,d)
5d	-	1.13(9H,s), 1.36(3H,d), 3.76(1H,dd,1.8 and 6.5Hz), 4.18(1H,m), 4.52(2H,s), 5.57(1H,d), 7.2-7.9(10H,m)
5e	1790,1690,1570	0.06(6H,s), 0.97(9H,s), 1.22(3H,d), 3.69(1H,dd,1.5 and 4.5Hz), 3.8(1H,br s), 4.21(1H,m), 4.62(2H,s), 4.66(2H,m), 5.21 and 5.34 (each 1H,m), 5.56(1H,d), 5.87(1H,m)
6	1785,1710,1255($CHCl_3$)	0.06(6H,s), 0.90(9H,s), 1.26(3H,d), 3.73(1H,dd,1.5 and 5Hz), 4.22(1H,m), 4.67(2H,s), 5.59(1H,d)
7	-	1.30(3H,d,6.8Hz), 3.88(1H,dd,1.5 and 6.3Hz), 4.23(1H,m), 4.63 (2H,ABq,14.5Hz), 5.62(1H,d) (in D_2O)
8c[3]	3340,1785,1700,1640	0.06(6H,s), 0.9(9H,s), 1.26(3H,d), 3.72(1H,dd,2 and 4.5Hz), 4.20(1H,m), 5.13-5.50(2H,m), 5.70(1H,m), 5.59(1H,d), 5.80-6.20 (1H,m), 6.42(1H,s), 6.70(2H,br s)
8f	1790,1705,1570	0.06(6H,s), 0.88(9H,s), 1.2(3H,d,6.5Hz), 3.64(1H,dd,1.5 and 6.5Hz), 4.25(1H,m), 4.67(2H,s), 4.7(2H,m), 5.2-5.5(2H,m), 5.51 (1H,d), 5.6-6.2(1H,m), 8.2-8.5(3H,m)
9b	-	1.13(9H,s), 1.34(3H,d,6Hz), 3.82(1H,dd,1.5 and 6Hz), 3.85(3H, s), 4.19(1H,m), 4.6(2H,ABq,14Hz), 5.61(1H,d),7.24-7.83(10H,m)
9c[3]	3400,1785,1710,1620 ($CHCl_3$)	1.24(3H,d), 3.71(1H,dd,1.6 and 6.2Hz), 4.30(1H,m), 4.59 and 4.78(2H,each d,14.8Hz), 5.58(1H,d), 6.29(1H,s)
9d[3]	3400,1780,1700($CHCl_3$)	3.68(1H,dd,1.7 and 6.5Hz), 4.45 and 4.64(2H,each d,14.6Hz), 5.54 (1H,d), 5.77(1H,s)
10b	1795,1750,1720,1605, 1580	1.52(3H,d,6.5Hz), 2.31(3H,s), 3.59(2H,s), 4.06(1H,dd,2 and 6.5 Hz), 5.04-5.70(5H,m), 5.51(2H,s), 5.73(1H,d)
10d	-	1.50(3H,d), 4.00(1H,dd,2 and 7Hz), 4.75(2H,ABq,13.5Hz), 5.20(1H, m), 5.26(2H,s), 5.35(2H,ABq,14Hz), 5.68(1H,d)

Table I - Continued

10e	1785,1700($CHCl_3$)	0.08(6H,s), 0.90(9H,s), 1.26(3H,d,6.5Hz), 3.73(1H,dd, 2 and 5Hz), 4.2(1H,m), 4.70(2H,s), 4.81(2H,ABq,14.5Hz), 5.35 and 5.5(each 1H,m), 5.65(1H,d), 5.6-6.2(1H,m)
10g[3]	1795,1710,1360,1180	1.51(3H,d,7Hz), 3.09(3H,s), 4.02(1H,dd,2 and 7.5Hz), 5.16(1H,m), 5.25(2H,s), 5.28(2H,ABq,17 Hz), 5.39(2H, ABq,15Hz), 5.71(1H,d), 7.50 and 7.60(each 2H,d,8Hz), 8.20(4H,d)
10h[3]	1775,1700,1580,1370,1180(KBr)	0.08(6H,s), 0.90(9H,s), 1.25(3H,d,6Hz), 2.48(3H,s), 3.65(1H,dd,1.8 and 4Hz), 4.25(1H,m), 4.65(2H,m), 5.2-5.5(2H,m), 5.28(2H,ABq,15Hz), 5.6-6.1(1H,m), 7.35 and 7.80(each 2H,d,16Hz)
11b	-	3.04 and 4.60(each 2H,t), 4.63(2H,m), 5.15-5.45(2H,m), 5.70-6.10(1H,m) (in $CDCl_3+D_2O$)
13b[3]	1700,1585,1300(KBr)	1.10(9H,s), 3.40(3H,s), 7.0-7.7(10H, m), 9.9(1H,br s)
15c	1785,1745,1505	0.08(6H,s), 0.90(9H,s), 1.28(3H,d,6.5Hz), 3.40(1H,dd, 1.8 and 4.5Hz), 4.25(1H,m), 4.65(2H,m), 5.1-5.5(2H,m), 5.42(1H,s), 5.48(1H,d), 5.6-6.2(1H,m), 6.95(1H,d,1.2Hz), 8.2-8.5(3H,m)
15e	-	3.46(1H,dd,1.6 and 6.7Hz), 5.48(1H,d,1.6Hz), 5.56 (1H, d,1.2Hz), 6.31(1H,s), 7.01(1H,d,1.2Hz)
15f	-	3.48(1H,dd,1.6 and 6.5Hz), 5.47(1H,d,1.6Hz), 5.63(1H, d,1.2Hz), 6.29(1H,s), 6.84(1H,d,1.2Hz)
16a[3]	1790,1745	0.08(6H,s), 0.85(6H,s), 1.20(3H,d,6Hz), 2.71(6H,s), 3.42 (1H,dd,1.5 and 4Hz), 4.2(1H,m), 4.55(2H,m), 5.1-5.3(2H, m), 5.40(1H,d,1.5Hz), 5.82(1H,s)
17b	2960,2920,2850,2570,1535,1520	0.06(6H,s), 0.90(9H,s), 1.50(1H,t,8Hz), 2.58(1H,dq,6.5 and 8Hz), 3.80(2H,t,6.5Hz)
17c	-	0.08(6H,s), 0.90(9H,s), 2.8(2H,t,6.5Hz), 3.34(2H,s), 3.83(2H,t)
17e	2860,2570,1695,1585,1460 ($CHCl_3$)	1.1(9H,s), 2.75(2H,t,6.5Hz), 3.40(2H,s), 3.85(2H,t), 5.1(1H,br s), 7.2-7.8(10H,m)
20a	-	0.08(6H,s), 0.9(9H,s), 1.30(3H,d), 2.00 and 2.22(each 3H,s), 2.60(2H,t,6Hz), 3.30(5H,m), 3.71(3H,s), 4.27 (1H,m), 5.17(2H,s), 5.25(2H,m), 5.42(1H,d,2.5Hz)
20c[3]	-	0.06(6H,s), 0.9(9H,s), 1.20(3H,d,6Hz), 3.0-3.3(3H,m), 3.7-4.0(4H,m), 4.2(1H,m), 5.18(2H,s), 5.33(1H,d,2Hz), 5.85 and 6.9(each 1H,br s)
20d[3]	-	0.06(6H,s), 0.88(9H,s), 1.20(3H,d,6.5Hz), 2.75(2H,t), 3.15-3.50(5H,m), 4.2(1H,m), 5.13(2H,s), 5.23(1H,d,2Hz), 5.8 and 7.05(each 1H,br s)
22d	1785,1700,1310($CHCl_3$)	0.08(6H,s), 0.88(9H,s), 1.27(3H,d,6.5Hz), 2.05(1H,br), 2.76 and 3.75(each 2H,t,6Hz), 3.8-4.4(4H,m), 4.70(2H,m), 5.1-5.4(2H,m), 5.55(1H,d,1.8Hz), 5.5-6.0(1H,m)
22g	1790,1750,1710($CHCl_3$)	1.50(3H,d,6.5Hz), 2.73 and 3.73(each 2H,t,6Hz), 3.85-4.10(3H,m), 5.1-5.4(5H,m), 5.60(1H,d,1.5Hz)
22h	3540,3430,1790,1735br,1605,1580	1.50(3H,d,6.5Hz), 2.78(2H,t,6Hz), 3.9-4.3(5H,m), 5.0 (2H,br s), 5.18(1H,m), 5.30(4H,m), 5.65(1H,d,1.8Hz)

Table I - Continued

23e	3540,3420,1780,1730,1580($CHCl_3$)	1.37(3H,d,6.5Hz), 2.98 and 4.60(each 2H,t), 3.77 (1H, dd,1.8 and 6Hz), 4.1(1H,m), 4.67(2H,m), 5.15(1H,m), 5.30-5.45(3H,m), 5.5-6.0(1H,m), 6.20(1H,d,1Hz)

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1) Film unless otherwise stated; 2) in $CDCl_3$ unless otherwise stated; 3) additional data: 1a: mp 97-98° (isopropyl ether); 5c: $[\alpha]_D$ +66°(1% $CHCl_3$), λ_{max} (CH_2Cl_2) 269 (ε = 17,000) and 323 nm (ε = 6,800); 8c: λ_{max} ($CHCl_3$) 256 (17,613), 275 (sh), 330 (sh) nm; 9c: MS(FD) m/Z 435; 9d: MS(FD) m/Z 695; 10g: MS(FD) m/Z 637; 10h: mp 102-104°; 13b: mp 135° (ethyl ether), λ_{max} ($CHCl_3$) 276 nm (ε = 20,820); 16a: MS(FD) m/Z 643; 20c: MS(FD) m/Z 574, 516; 20d: MS(FD) m/Z 558, 500.

Table II - Spectral data of thiomethylpenems I, II

Compd.[1]	R[2]	ir (KBr) ν_{max} (cm^{-1})	uv (H_2O) λ_{max} (nm)	^1H nmr (D_2O)[3] δ (ppm)
Ia*	A	1760,1620	315(ε =5,900)	3.87(1H,dd,1.4 and 5Hz), 4.10(3H,s), 4.40 (2H,ABq,16Hz), 5.59(1H,d).
Ib	B	3500-3150,1760, 1625,1570	262(ε =11,200), 299(ε =10,200)	3.77(1H,dd,1.8 and 6.5Hz), 4.55(2H,br s), 5.50(1H,d), 6.50(1H,s)
Ic**	C	3600-3200,1765, 1630,1370	263,315	2.93(3H,s), 3.73(2H,t), 3.88(1H,dd,1.8 and 4.5Hz), 4.57(2H,ABq), 4.90(2H,t), 5.64(1H, d)
Id	D	1760,1600,1570	250(ε =10,344), 319(ε =8,682)	3.74(1H,dd,1.5 and 5Hz), 4.58(2H,s), 5.41 (1H,d), 8.37,8.51 and 8.62(each 1H)
Ie	E	1760,1610	245,306	3.80(1H,dd,1.4 and 5Hz), 4.37(2H,ABq,14Hz), 5.54(1H,d), 8.34(1H,s)
If	F	1765,1610,1560	299	3.85(1H,dd,1.8 and 7Hz), 4.00(2H,s), 4.59 (2H,s), 5.60(1H,d)
Ig	G	1760,1600br	315	3.78(3H,s), 3.83(1H,dd,1.4 and 6Hz), 4.07 and 4.31(2H,each d,14Hz), 5.56(1H,d), 7.05 and 7.27(2H,each d,1.3Hz)
Ih	H	-	261,314	3.82(1H,dd,1.5 and 6Hz), 4.42(2H,ABq,14.4 Hz), 5.53(1H,d)
Ii	I	1760,1600,1570	260,316	1.42(3H,t,5.6Hz), 3.77(1H,dd,1.6 and 5.6Hz), 4.17(2H,q), 4.20 and 4.43(2H,each d,14Hz), 5.52(1H,d), 8.55(1H,s)
Ij*	J	3420,2960,2920, 1760,1640,1605	241(ε =15,340) 302(ε =11,466)	3.67(3H,s), 3.84(1H,dd,1.6 and 5.9Hz), 4.61 (2H,ABq,14.5Hz), 5.57(1H,d)
Ik	K	1765,1625,1570	-	2.70(3H,s), 3.80(1H,dd), 4.55(2H,ABq), 5.55 (1H,d)
Il	L	1765,1620,1570, 1550,1520,1490, 1255	251,326	3.77(1H,dd), 3.97(3H,s), 4.60(2H,ABq), 5.55 (1H,d), 7.8-8.0(2H,m)

Table II - Continued

Im	M	3420,3300,3180, 1765,1620,1560	320	3.92(1H,dd), 4.42(2H,s), 5.64(1H,d)
In	N	2250,1765,1615	259,316	3.23(2H,t), 3.84(1H,dd,1.4 and 6.0Hz), 4.54 (2H,ABq,14.2Hz), 4.8(2H,t), 5.58(1H,d)
Io*	O	3420,1760,1700, 1610,1580	304(ε =8,600)	-
Ip*	P	3600-3200,1765, 1580,1390	315	-
Iq*	Q	1765,1605,1570	239(ε =18,930), 312(ε =9,074)	4.06(1H,dd,1.5 and 6.1Hz), 4.70 and 5.00 (2H,each d,12Hz), 5.64(1H,d), 7.72 and 8.42 (2H,each d,9.6Hz)
IIa*	$CH_2CH_2NH_2$	3420,1770,1610	308	2.83 and 3.24(each 2H,t,6.7Hz), 3.88(1H,dd, 1.4 and 6.3Hz), 4.01(2H,ABq,14.7Hz), 5.64 (1H,d)
IIb*	$CH_2CH_2OCONH_2$	3600-3200,1765, 1610,1570	310	-

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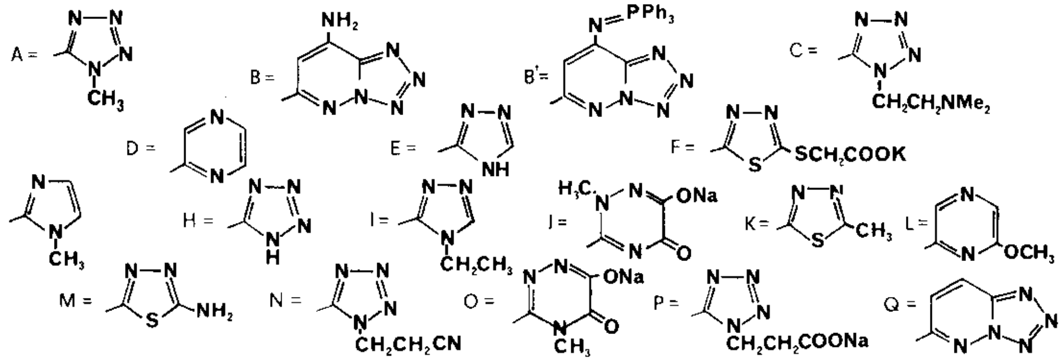
1) Potassium salt unless otherwise indicated: *) Na^+ salt; **) inner salt.

2)



3) Data relative to H_5, H_6, 2-CH_2 and R protons; HOD at 4.81 ppm as internal standard.

Table III - Spectral data of thiomethylenepenams III, IV, 16b

Compd.[1]	R[2]	ir (KBr) ν_{max} (cm^{-1})	uv (H_2O) λ_{max} (nm)	^{1}H nmr (D_2O)[3] δ (ppm)
IIIc*	C	1760,1610	-	2.63(6H,s), 3.35(2H,t), 3.58(1H,dd,1.5 and 7Hz), 5.00(2H,t), 5.40(1H,d,1Hz), 5.47(1H, d,1.5Hz), 6.44(1H,d,1Hz)
IIId	D	1760,1610	267(ε =7,814), 326(ε =4,787)	3.55(1H,dd,1.3 and 5Hz), 5.43(2H,m), 6.65 (1H,d,1Hz), 8.3-8.6(3H,m)

Table III - Continued

IIIh	H	1755,1610	260(ε =9,897)	3.58(1H,dd,1.5 and 6.2Hz), 5.37(1H,d,1.1 Hz), 5.44(1H,d,1.5Hz), 6.24(1H,d,1.1Hz)
IIIo*	O	1765,1700, 1625,1580	278(ε =10,586)	-
IIIq*	Q	1765,1620	263,344	3.58(1H,dd,1.5 and 6.2Hz), 5.47(1H,d,1.5 Hz), 5.51 and 6.80(each 1H,d,1Hz), 7.48 and 8.21(each 1H,d,9.5Hz)
IVb	$CH_2CH_2OCONH_2$	1760,1705, 1605	256	3.12(2H,t,6Hz), 3.58(1H,dd,1.5 and 6Hz), 4.30(2H,t), 5.30(1H,d,1Hz), 5.45(1H,d,1.5 Hz), 6.38(1H,d)
16b	-	1770,1640, 1630	286(ε =8,377)	2.72(6H,s), 3.71(1H,dd,2 and 6Hz), 5.52 (1H,d), 5.76(1H,s)

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1), 2) See footnotes 1, 2, Table II.

3) Data refer to H_3, H_5, H_6, vinyl and R protons; HOD at 4.81 ppm as internal standard.

Table IV - Antibacterial in vitro activities[1,2] of selected penems and penams

Compd.	R^3	S.a.S.	S.p.	E.c.	K.a.+
Ia	A	0.01	0.01	0.12	0.35
IIa	$CH_2CH_2NH_2$	0.08	0.02	2	5.7
IIb	$CH_2CH_2OCONH_2$	0.04	0.008	2.8	8
IVb	$CH_2CH_2OCONH_2$	0.05	0.17	32	32
Ic	C	0.3	0.008	1	1
IIIc	C	0.5	0.12	8	8
Id	D	0.01	0.008	8	22.6
IIId	D	0.25	0.5	32	32
Ih	H	0.17	0.06	0.5	0.5
IIIh	H	2	1.4	8	8
Io	O	0.03	0.01	4	1.4
IIIo	O	0.06	0.016	8	5.7
Iq	Q	0.004	0.002	2	5.7
IIIq	Q	0.5	0.25	32	32
16b	-	32	4	32	32
10f	-	0.38	0.09	3.1	3.1

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1) MIC values are given in μg/ml, and were determined in Isosensitest broth.

2) Organisms included in this Table are: S.a.S., Staphylococcus aureus Smith; S.p., Streptococcus pyogenes C203; E.c., Escherichia coli G; K.a. +, Klebsiella aerogenes 1082 E (producer of chromosomally mediated ß-lactamase).

3) Heterocycles A, C, D, H, O, Q are as indicated in Table II.

Table IV shows the minimal inhibitory concentration (MIC) values against four significative bacterial strains for the functionalized alkylthiomethyl penems **IIa**, **IIb**, and for a representative of the heterocyclylthiomethyl family,[42] the methyltetrazole product **Ia**; the 2-(unsubstituted methyl) penem **10f** was taken as a reference standard. These data are striking when compared to the early report by Bristol-Myers[1,43] on 6-unsubstituted penems, which in median activity against Gram-negative bacteria favoured the 2-methylthiomethyl product over the 2-methyl reference, and the latter over the tetrazolylthiomethyl analogue by a total factor of over 60. Instead, and in line with our original working hypothesis, our data suggest that the tetrazolylthio substituent, similarly to the acetoxy and carbamoyloxy groups, plays a definite role in contributing to good antibacterial performance (**Ia** vs. **10f**). These incongruities, and unexpected losses of activity occasionally found for a few entries **I**, may hint at a subtle interplay between intrinsic activity and stability factors, which in the 6-unsubstituted series might have become particularly severe. A peculiar source of instability common to all the thiomethylpenems might be envisaged in the possibility of equilibration into the exo form under the conditions of antimicrobial testing.[44] Conversely, on such hypothesis one could surmise that the activity observed for thioalkylidenepenams **III**, **IV** be the result of a slight proportion of the penem form arising from equilibration, if not already present in the sample. Table IV does indeed show that the potency ratio within each penem-penam couple is rather evenly distributed accross the whole spectrum,[45] even when, as for **IIIo**, the penam form apparently exhibits a remarkable level of antimicrobial activity.

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33. We regard this product as the result of a thiolation at the active C-3 methine of the exo form.

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35. S.R. Norrby and M. Johnnson, *Antimicrob. Agents Chemother.*, 1985, **27**, 128.

36. M. Foglio, C. Battistini, F. Zarini, C. Scarafile, and G. Franceschi, *Heterocycles*, 1983, **20**, 1491.

37. Selective cleavage of TBDPS vs. TBDMS ether (TBAF-3H_2O; THF-HOAc, 30 min) in compound **19a** is noteworthy, and should be related to the presence of the ß-carbonyl group.

38. Every attempt to activate the acids **17e**, **17h** through their mixed anhydrides with ethyl chlorocarbonate resulted in the formation of the corresponding ethyl ester. Mixed carboxylic-carbonic anhydrides usually require some particular catalysis (dimethylaminopyridine) in order to collapse into the esters: S. Kim, Y.C. Kim, and J.I. Lee, *Tetrahedron Lett.*, 1982, **24**, 3365.

39. Low yields in thioacid **17d** were mainly due to competing desilylation.

40. Desilylation under the usual conditions (TBAF) predominantly gave the exo form **23d**.

41. Direct heating of **21f** gave penem **22f** but, different from the TBDMS analogue **22c**, this silyl ether was unaffected by acidic conditions compatible with the penem structure.

42. For a more detailed account on the antibacterial activity of heterocyclylthiomethylpenems, see G. Franceschi, M. Alpegiani, A. Bedeschi, M. Foglio, E. Perrone, G. Meinardi, S. Grasso, and I. de Carneri, *J. Antibiotics*,1984, **37**, 685.

43. J. Banville, P. Belleau, P. Dextraze, J.L. Douglas, F. Leitner, A. Martel, M. Menard, R. Saintonge, and Y. Ueda, "Syntheses and Structure-Activity Relationships in the Penem Series". Presented at the 182nd ACS National Meeting, New York, 1981.

44. Analysis of additional "2-CH_2X" penem structures wherein the double bond is locked in the endo position will be the subject of a forthcoming paper.

45. A low order of intrinsic activity, limited to Gram-positive species, might be proper of alkylidenepenams.[29,32]

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