163. (+)-(5*R*,6*S*)-2-(1′-Aminoalkyl)-6-(hydroxyalkyl)penem-3-carboxylic Acids

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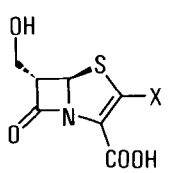
In continuation of our work on penem antibiotics, novel chiral (5*R*,6*S*)-2-(1′-aminoalkyl)-6-(hydroxyalkyl)-derivatives **1** have been synthesized by two essentially different strategies. Whereas the starting materials for **1a–f**, azetidinones **2** and **5**, were obtained from chiral building blocks (6-aminopenicillanic acid and L-threonine, resp.), the one for **1g**, azetidinone **9**, was derived from racemic 4-acetoxyazetidinone and, as chiral auxiliary, (2*R*)-2-mercaptopropan-1-ol. The 2-aminomethyl derivatives **1a** (CGP 30779) and **1f** (CGP 31608) proved the most potent compounds in the antibacterial tests *in vitro* and showed a well-balanced spectrum of activity by comparison with that of established β-lactams.

Introduction. – The penems, which were initially considered insufficiently stable to exert any notable antibacterial activity [1], reached a high level of development by the end of their first decade [2–5]. In general, they are active against a broad spectrum of bacteria, excluding, however, *Pseudomonas aeruginosa*. Knowing that the older rules governing substituent requirements that apply to penicillins and cephalosporins are inoperative, and that antipseudomonal activity seems to be related – at least in the structurally close carbapenem series – to the presence of a basic substituent [6], we decided to assess the



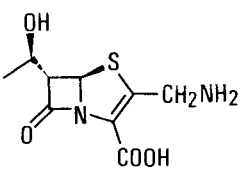
1a X = CH_2NH_2

b X = $CH(CH_3)NH_2$ (*S*)

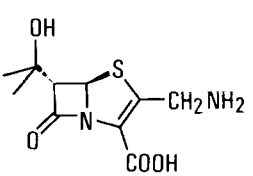
c X = $CH(CH_3)NH_2$ (*R*)

d X = $CH(C_3H_7)NH_2$ (*S*)

e X = CH_2NHCH_3



1f

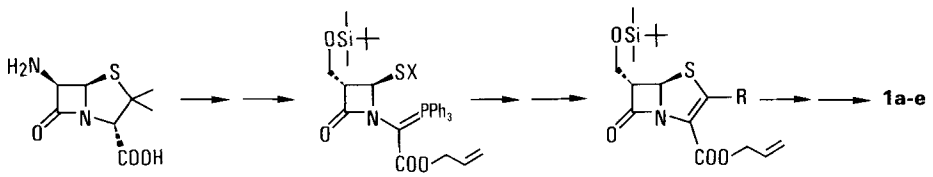


1g

minimal structural requirements for this activity in the 2-(aminoalkyl) series. The C(6) substituent was limited to the hydroxymethyl, (1*R*)-1-hydroxyethyl and 1-hydroxy-1-methylethyl groups first found in the isolated natural carbapenem derivatives [6] and attached to the *β*-lactam in a *trans*-configuration with respect to the condensed dihydrothiazole ring. These penems **1a–g** were synthesized by two essentially different strategies.

Synthesis. – For penems **1a–e**, the final (5*R*,6*S*)-configuration was attained by synthesis starting from 6-aminopenicillanic acid *(Scheme 1)*. An intermediate silver (3*S*,4*R*)-

Scheme 1



6-aminopenicillanic acid **2** : X = Ag **4a-e**

3a-e : X = COR

a R= CH_2NH–AOC AOC = COO

b R= $CH(CH_3)NH$–AOC (*S*)

c R= $CH(CH_3)NH$–AOC (*R*)

d R= $CH(C_3H_7)NH$–AOC (*S*)

e R= $CH_2N(CH_3)$–AOC

Table 1. *Typical Reaction Conditions and Chemical Yields for the Syntheses of* **1a–g**

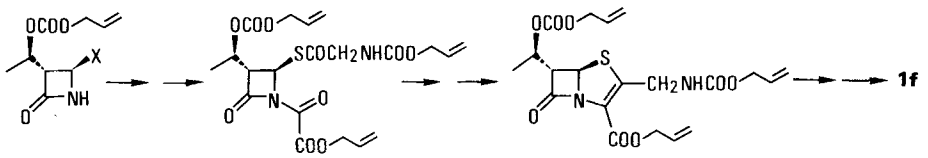
Conversion[a])	Conditions	Yield [%]
2 → **3a**[b])	AOC-Gly-Cl, pyridine, CH_2Cl_2, 0°, 30 min	63
3a → **4a**[b])	Toluene, reflux, 1.5 h	96
4a → **1a**[b])	a) Bu_4NF, AcOH, THF , r.t., 3 h	59
	b) Bu_3SnH, $(PPH_3)_4Pd$[c]), THF, r.t., 30 min	58
5 → **6**	$NaSCOCH_2NH$–AOC, CH_2Cl_2/H_2O, pH 11.8, 0°, 1 h	65
6 → **7**	AOC–COCl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, −15°, 20 min	90
13 → **14**	AOC–COCl, $(i\text{-}Pr)_2EtN$, CH_2Cl_2, −15°, 20 min	82
7 → **8**	$P(OEt)_3$, dioxane, 100°, 6 h	45
9 → **10**	$LiN(i\text{-}Pr)_2$, THF, −70°; acetone, 45 min	83
10 → **11**	*m*-ClC_6H_4COOH, CH_2Cl_2, −20 → 0°, 45 min	93.5
11 → **12**	$AcOH/H_2O$, 120°, 2.5 h	52
12 → **13**	$NaSCOCH_2NH$–AOC, acetone/H_2O, pH 8, 10°, 35 min	50
14 → **15**	$P(i\text{-}PrO)_3$, 16 h, r.t.; dioxane, 10 h, 100°	97
15 → **1g**	Dimedone, $(PPh_3)_4Pd$[c]), THF. r.t., 3 h	55

[a]) Spectroscopic data are in full agreement with the proposed structures.
[b]) **3b–e, 4b–e,** and **1b–e,** respectively, were synthesized by analogy.
[c]) Catalyst.

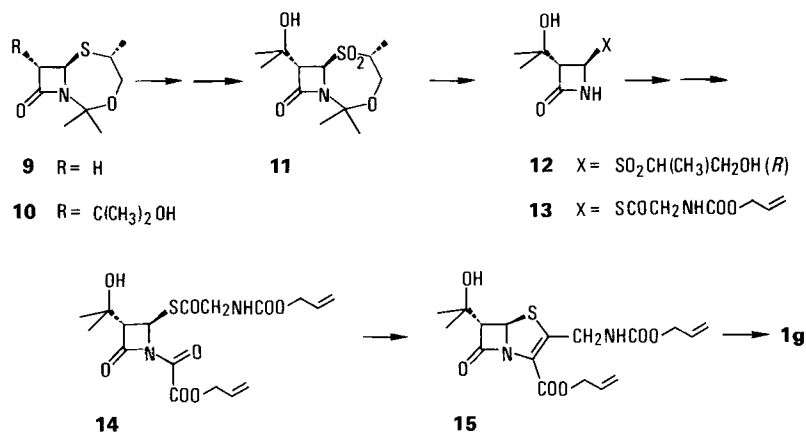
thiolate **2** [7] was acylated with various *N*-(allyloxycarbonyl)-protected α-amino-acid chlorides to provide the phosphoranes **3a–e**. The latter were converted *via* the standard *Wittig* reaction first described by *Woodward* [1] to penems **4a–e**. Initial deprotection of the OH group, followed by simultaneous deprotection of the NH_2 and COOH groups by way of a modified Pd-catalysed transallylation [8] yielded penems **1a–e** (reaction conditions and chemical yields are summarized in *Table 1*).

The homologous ((1′*R*)-hydroxyethyl)penem **1f** was synthesized in several steps from L-threonine by way of the (3*S*,4*R*)-azetidinone **5** [9] *(Scheme 2)*. Substitution of the AcO group of **5** with sodium α-[*N*-(allyloxycarbonyl)amino]thioacetate with overall retention of configuration at C(4) gave the azetidinone **6**, which was converted by analogy with published procedures [10] *via* the oxamide **7** to the penem **8** and, after deprotection, to **1f**[1]).

Scheme 2



Scheme 3



The 6-(1′-hydroxy-1′-methylethyl)penem **1g** was prepared *(Scheme 3)* from the chiral bicyclic azetidinone **9** first synthesized by *Pfaendler* [12] from racemic 4-acetoxyazetidinone [13] and (2*R*)-2-mercaptopropan-1-ol [14] as chiral auxiliary. The generation of the enolate from the β-lactam **9** and subsequent quenching with acetone exclusively yielded the *trans*-configurated 1′-hydroxy-1′-methylethyl derivative **10**. Oxidation to the

[1]) For racemic **1f**, see [11].

Table 2. *Antibacterial Activity*[a]) *of 2-(1'-Aminoalkyl)-6-(hydroxyalkyl)penem-3-carboxylic Acids* **1a–g** in vitro (MIC; μg/ml) *Compared with that of Ampicillin, Ceftazidime, and Aztreonam*

Test organism	**1a** CGP 30779	**1b** CGP 31073	**1c** CGP 31221	**1d** CGP 32357	**1e** CGP 31461	**1f** CGP 31608	**1g** CGP 38602	Ampicillin	Ceftazidime	Aztreonam
Staphylococcus areus 10B	0.1	0.1	0.1	0.05	0.05	0.05	64	0.1	4	> 128
S. aureus 2999 i^+p^+	0.2	0.2	0.2	0.05	0.1	0.05	64	16	4	> 128
S. aureus A 124 (methicilin resistant)[b])	1	1	0.5	0.5	0.5	0.05	–	4	64	> 128
Streptococcus pyogenes Aronson	1	1	0.5	1	0.2	0.2	> 128	0.05	0.2	32
Neisseria meningitidis 1316	0.5	2	0.5	1	1	0.2	16	0.05	0.05	0.02
Haemophilus influenzae NCTC 4560	0.5	16	16	32	8	1	64	0.5	0.2	0.1
Escherichia coli 205	0.5	64	16	64	4	4	> 128	4	0.1	0.05
E. coli 205 R + TEM	1	64	32	64	8	4	–	> 128	0.1	0.05
Klebsiella pneumoniae 327	1	16	16	32	2	1	> 128	32	0.1	0.02
Enterobacter cloacae P 99	2	32	16	64	2	0.5	> 128	> 128	4	0.5
Morganella morganii 1518	2	64	128	> 64	> 32	2	> 128	> 128	4	0.1
Pseudomonas aeruginosa ATCC 12055	0.2	32	64	> 64	16	0.2	64	16	0.5	0.5
Clostridium perfringens[c])	8	32	16	64	16	1	> 128	0.25	0.06	32
Bacteroides fragilis L01[c])	1	4	4	16	2	0.5	> 128	32	16	64

[a]) Agar dilution method; DST Agar *Oxoid*, inoculum 10^6 CFU/ml.
[b]) MRSA: incubation at 30° for 48 h.
[c]) Anaerobic incubation.

sulfone **11** and acid-catalysed ring opening to the azetidinone **12** finally afforded the penem **1g**, after the previously described sequence (**12**→**13**→**14**→**15**→**1g**). It should be noted that protection of the tertiary OH group during the entire reaction sequence is unnecessary.

Antibacterial Activity. – The antibacterial activities of the 2-(1′-aminoalkyl) derivatives **1a–g** *in vitro* against selected Gram-positive and Gram-negative bacteria are listed in *Table 2*. Structural requirements relating to the C(6) and C(2) substituents are documented by a substantial loss of antibacterial activity caused by an additional CH_3 group α to the OH group or by a similar effect confined, however, to the Gram-negative strains, observed after the introduction of a branched side-chain at C(2) α to the amino group (**1b–d** *vs.* **1a**). The 2-aminomethyl penems **1a** (CGP 30 779) and **1f** (CGP 31 608) proved to be the most interesting compounds in the series; by comparison with established β-lactam antibiotics *(Table 2)*, they exhibit a well-balanced anti-bacterial spectrum, including activity against anaerobes and, especially, methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Preliminary results of studies *in vivo* indicate that they exert a good therapeutic effect against experimental infections in mice. The ED_{50}[2]) of penem **1f**, for instance, upon subcutaneous administration to mice infected with *Staphylococcus aureus 10B* or *Streptococcus pyogenes* ARONSON was 1.4 mg/kg (cumulative dose).

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