Notes

PENEMS: SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-(1-AZOLYL) DERIVATIVES

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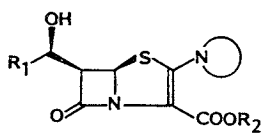
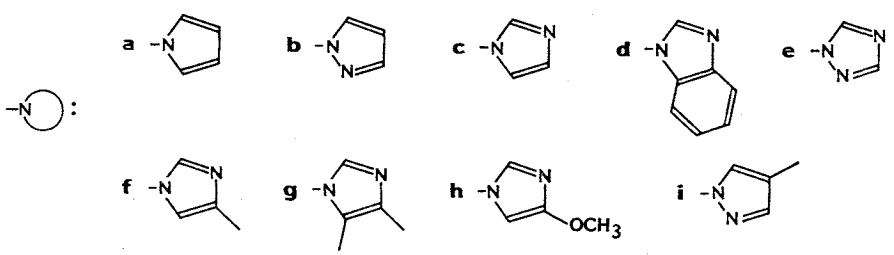
Since the disclosure of the first penem synthesis by WOODWARD[1], many research groups have prepared variously substituted penems, including derivatives bearing hetero-substituents at C-2. Whereas the vast majority of these have been sulfur derivatives[2~6], analogous to the naturally occurring thienamycin and a few 2-oxy-substituted penems have been synthesized[7], no nitrogen derivatives have yet† been described. In continuation of our studies in the 2-(heterocyclyl)alkyl series[8,9], we decided to concentrate on penems **1** and **2**, featuring an azole heterocycle directly linked to the penem nucleus through a ring nitrogen (Scheme 1).

In contrast to their unreactive dialkylamino homologues††, the azolyl-dithiocarbamates **7** proved to be good substrates for the Wittig ring closure. Depending on the nature of the heterocycle, these key compounds **7** were arrived at by different pathways (Scheme 2). The 4-acetoxyazetidinone **3**[10] was reacted with potassium 1-pyrrolyldithiocarbamate **4a**[11] (1.5 equiv, ethanol, 1 hour, room temp) to afford a 4:1 mixture of the *trans*-(3*S*,4*R*)-dithiocarbamate **5a** (70% yield): IR (CH_2Cl_2) 3410, 1780 cm^{-1}; NMR ($CDCl_3$) δ 0.11 (6H, s, $2CH_3$), 0.93 (9H, s, $3CH_3$), 3.48 (1H, m, CH), 4.05 (2H, ABX, CH_2), 5.57 (1H, d, CH), 6.37 (2H, m, 2CH), 6.67 (1H, br s, NH), 7.64 (2H, m, 2CH) and its *cis* homologue (19% yield), which was separated by chromatography (SiO_2, toluene - EtOAc, 95:5). With potassium 1-pyrazoledithiocarbamate **4b**[12] only the *trans* substituted (3*S*,4*R*)-azetidinone **5b** could be isolated (76% yield) from the reaction mixture. The classical three-

Scheme 1.



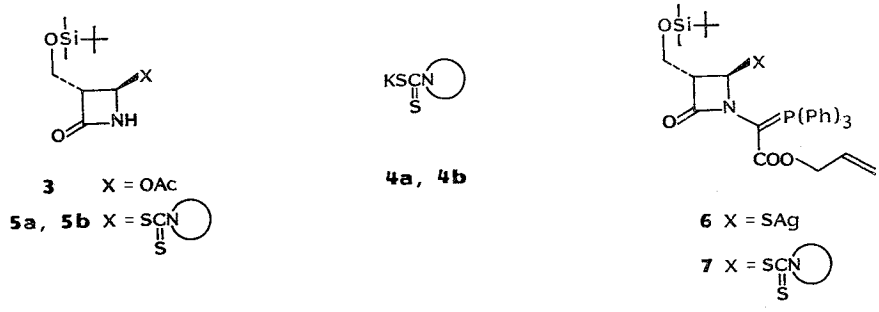
1 $R_1 = H$
2 $R_1 = CH_3$



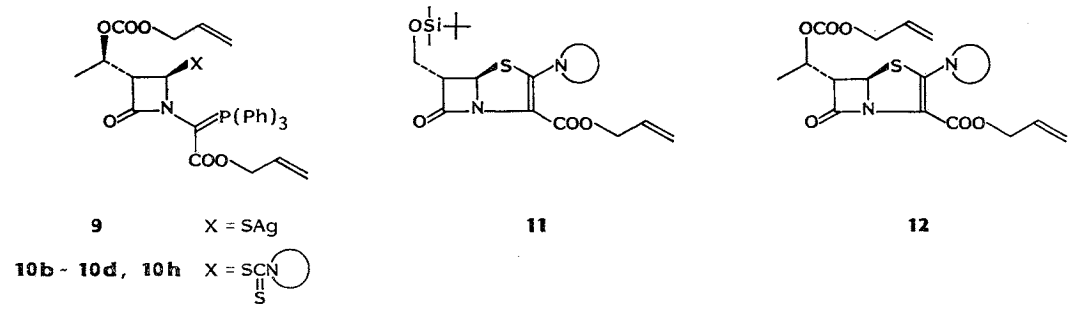
† A similar work was reported[19] during the publication procedure for this article. For the patent literature *cf.* refs 20 and 21.

†† HOLICK, W. & C. D. WEIS: Unpublished results.

Scheme 2.



Scheme 3.



step sequence of the phosphorane synthesis[13~15] led to the precursors **7a**, **7b** for the Wittig cyclization reaction. This sequence was unsuitable for the imidazolyl homologue **7c**.

An alternative pathway was based on the acylation of the key silver thiolate **6**[16] with thiocarbonyldiimidazole (2 equiv, CH_2Cl_2, 2.5 hours, 0°C) to give phosphorane **7c** (65% yield): IR(CH_2Cl_2) 1750, 1615 cm^{-1}. Derivatives **7b**, **7d~7f** were obtained analogously through the reaction of **6** with thiocarbonyl-dipyrazole[17], -dibenzimidazole[17] and di-(4-methyl)imidazole†. Phosphorane **7c** proved to be a suitable substrate for azole exchange reactions, as shown by the conversion **7c**→**7b**, **7e~7i**. It reacted, for instance, with 4-methylpyrazole (3 equiv, DMF, 18 hours, room temp) to give phosphorane **7i** (87% yield).

The 3-(1′-*R*-hydroxyethyl)phosphoranes **10b**, **10d**, **10h** were synthesized through a similar reaction from phosphorane **10c**, which was obtained from silver thiolate **9**[18] and thiocarbonyldiimidazole (Scheme 3).

The penems **11a~11i** and **12b~12d**, **12h** are formed in the Wittig reaction of their corresponding phosphoranes **7** and **10**. [For example **10c**→**12c** (toluene, 18 hours, reflux; 77% yield): IR (CH_2Cl_2) 1795, 1742, 1715, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (3H, d, CH_3), 4.02 (1H, m, CH), 4.62~4.75 (4H, m, $2CH_2$), 5.1~5.4 (5H, m, $2CH_2$+CH), 5.71 (1H, d, CH), 5.82~6 (2H, m, 2CH), 7.14 (1H, s, CH), 7.23 (1H, s, CH), 7.85 (1H, s, CH)].

Finally, all penems were deprotected to the title compounds (Table 1) by standard deblocking procedures[8,9]. For penems **11**, the cleavage of the *tert*-butyldimethylsilylether with tetrabutylammonium fluoride and acetic acid was followed by a deblocking of the carboxyl group and, if present of the amino group through a Pd°-catalyzed transallylation reaction. [For example **11c**→**1c** (1.2 equiv (n-Bu)$_3$SnH, THF, 0.5 hour, −10°C; 55% yield): UV $\lambda_{max}^{H_2O}$ nm 310, NMR (D_2O) δ 4.0 (2H, m, CH_2), 4.2 (1H, m, CH), 5.78 (1H, d, CH), 7.08 (1H, d, CH), 7.33 (1H, d, CH), 7.93 (1H, s, CH)].

The *in vitro* antimicrobial activity of the new penems **1** and **2** against a selection of representative Gram-positive and Gram-negative bacteria is listed in Table 1. In direct comparison, the imidazole derivatives proved to be the most active compounds (**1c** vs. **1a**, **1b**, **1d**, **1e**), and in this

† Prepared by analogy with procedures reported in ref 17.

Table 1. *In vitro* antibacterial activity of various 2-(1-azolyl)penems **1** and **2**.

Penem (R_2=Na)	MIC (μg/ml)							
	S.a. 10B	S.a. 2999 i^+p^+	S.p. Aronson	E.c. 205	E.c. 205 R^+TEM	M.m. 2359	P.a. ATCC 12055	B.f. LO1
1a	0.5	1	0.2	2	4	4	>128	0.5
1b	0.5	1	0.1	2	2	4	128	0.1
1c	0.1	0.2	0.05	1	1	4	128	0.05
1d	0.1	0.2	0.01	1	8	8	>128	0.5
1e	0.2	0.5	0.1	2	2	8	128	0.2
1f	0.05	0.1	0.02	1	1	2	>128	0.05
1g	0.05	0.1	0.01	0.2	0.5	1	>64	0.2
1h	0.1	0.2	0.02	1	1	2	>128	0.1
1i	0.2	0.5	0.05	1	2	4	>64	0.1
2b	0.1	0.1	0.05	1	1	2	64	0.1
2c	0.01	0.05	0.01	0.5	0.5	1	64	0.01
2d	0.05	0.05	0.01	4	4	2	>64	1
2h	0.05	0.05	0.02	1	1	2	>128	0.05

Abbreviations: S.a.: *Staphylococcus aureus*, S.p.: *Streptococcus pyogenes*, E.c.: *Escherichia coli*, M.m.: *Morganella morganii*, P.a.: *Pseudomonas aeruginosa*, B.f.: *Bacteroides fragilis*.

series the 4,5-dimethylimidazolyl penem **1g** exhibited the greatest antibacterial potency. As observed in other penem series[8,9,17], exchange of the 6-hydroxymethyl for a 1'-*R*-hydroxyethyl group afforded a perceptible gain in activity, mainly against Gram-positive strains.

Finally, a high level of antibacterial potency against Gram-positive strains and anaerobes and lack of a significant activity against *Pseudomonas aeruginosa* were characteristic properties of the whole series.

Preliminary *in vivo* results indicated that penems **1** and **2** possess good therapeutic efficacy in the treatment of experimental infections in mice. For instance, ED_{50} values of 4.9 and 0.7 (cumulative dose; mg/kg) were determined following subcutaneous administration of **1c** and **2c** respectively to mice infected with *Staphylococcus aureus* 10B.

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