Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2793–2796

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 2-ALKOXY PENEMS

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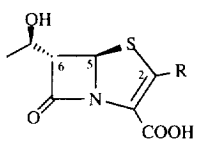
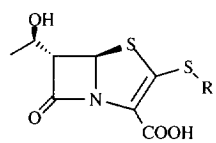
Received 10 July 1998; accepted 28 August 1998

Abstract: The phosphite mediated Oxalimide cyclization reaction was extended to 4-dithiocarbonates of N-oxalyl-2-azetidinones to synthesize 2-alkoxy penems **3**. In general, the *in vitro* antibacterial potency of compounds **3** was weak compared to the highly potent 2-alkylthiopenems **2**.

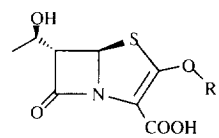
Penems **1** were the subject of intense synthetic studies by several research groups during the 1980s in view of their potential clinical use as potent broad spectrum antibacterial agents. From our laboratories, such investigations led to the identification of the two potent alkylthiopenems **2** as candidates for clinical development as broad spectrum antibacterials.[1] We report here the synthesis and antibacterial activity of 2-alkoxy penems **3**, which include the oxa analogs of **2**.



1

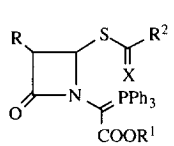


2a, R = -CH_2CH_3 (Sch 29482)
2b, R = -$CH_2CH_2OCONH_2$ (Sch 34343)

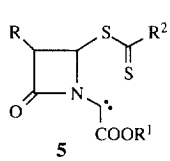


3

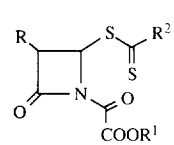
The Woodward penem synthetic methodology that utilizes the cyclization of phosphorane intermediates **4** has been used extensively in penem research. However, this methodology is not applicable to dithiocarbonates **4** (R^2 = O-alkyl, X = S) to generate 2-alkoxy penems **3** and consequently prior literature reports have described multistep reaction sequences for synthesizing these compounds.[2] The oxalimide cyclization reaction, which proceeds via carbene intermediates **5**, generated from oxalimides **6** by trialkylphosphites, is a convenient method to prepare 2-alkylthiopenems[3] and 2-alkylpenems[4a] from appropriate intermediates **6**, and 3-heterosubstituted iso-cephems and iso-oxacephems from intermediates **7**.[4b] We have found that the oxalimide reaction is also a simple and convenient method to synthesize the 2-oxapenems **3** described herein (Scheme 1).[5]



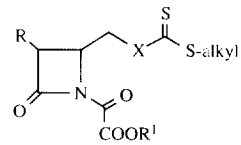
4, R^2 = alkyl, aryl, S-alkyl
X = S, O



5



6, R^2 = S-alkyl, alkyl, O-alkyl



7, X = S,O

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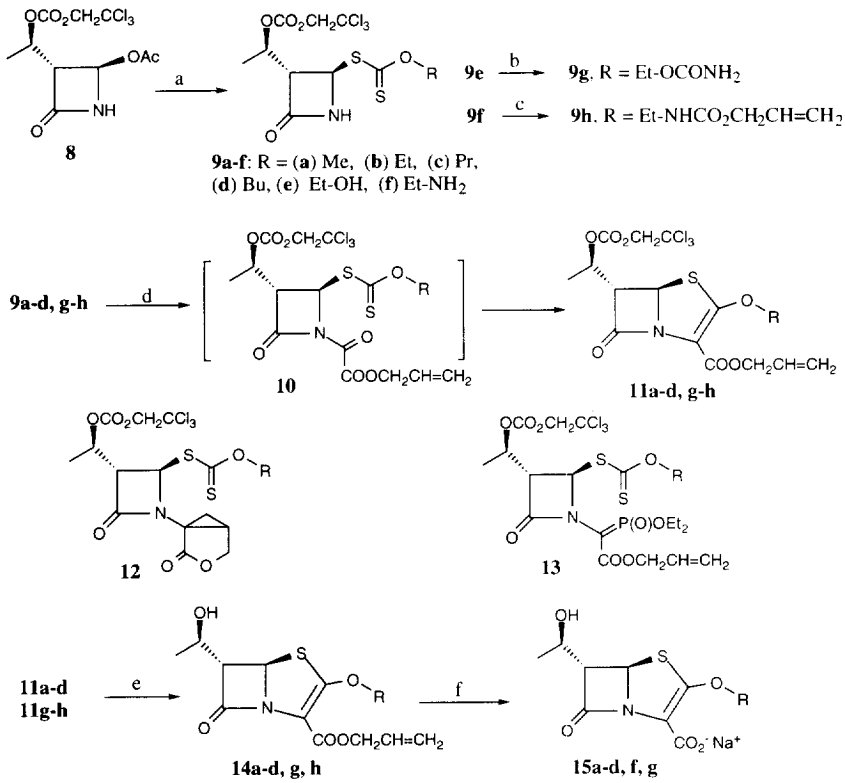
PII: S0960-894X(98)00502-2

Thus, displacement of the C_4-acetoxy of **8**[6] with various xanthates (ROCSS$^-$ Na$^+$) derived from the corresponding alcohols provided the C_4-dithiocarbonates **9a–f** (58–66%). Dithiocarbonates **9e–f** were functionalized (**9e**, OH to $OCONH_2$) or protected (**9f**, NH_2 to $NH\text{-}CO_2CH_2CH{=}CH_2$) to afford **9g–h**. The dithiocarbonates **9a–d** and **g–h** were converted (acylation with allyloxalyl chloride) to the oxalimides **10**.

Scheme 1[a]



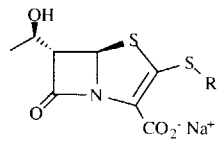
[a]Reagents and conditions: (a) ROH/1 N NaOH (1 equiv.)/CS_2 /THF/rt. (b) NaCNO/CF_3COOH (1.1 equiv.)/CH_2Cl_2/rt. (c) $ClC(O)OCH_2CH{=}CH_2$/Et_3N/CH_2Cl_2. (d) i. $Cl(CO)CO_2CH_2CH{=}CH_2$/*i*-Pr_2NEt/$CaCO_3$/CH_2Cl_2/0 °C. ii. $CHCl_3$/$P(OEt)_3$ (1 equiv.)-syringe pump addition/reflux 17 h/chromat. (e) Zn dust/THF-50% AcOH-10% H_2O/-15 °C/chromat. (f) for **14a–d,g**: Sodium 2-Et-hexanoate (1 equiv.)/$Pd(PPh_3)_4$ (cat)/PPh_3/EtOAc, rt; for **14h**: pyridinium formate/$Pd(PPh_3)_4$ (cat)/PPh_3/CH_2Cl_2, rt.

which without purification were treated with triethylphosphite (slow addition) in refluxing chloroform to afford after chromatography the desired protected 2-alkoxypenems **11a–d** and **11g–h** (30–40%). The expected competing products of the oxalimide cyclization,[3] cyclopropanes **12** and phosphoranes **13**, were formed in low yields in all of these cyclization reactions. Removal of the trichloroetoxycarbonyl protective groups (zinc dust/dil. acetic acid) afforded **14a–d,g,h**. Allylester exchange[7] mediated by Pd^0 for **14a–d,g** provided the 2-alkoxypenems **15a–d,g** as their sodium salts; palladium^0 mediated allyl deprotection under reductive conditions[8] was used for the deprotection of **14f** to **15f**.[10]

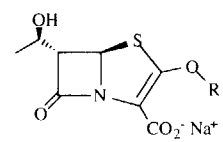
Table 1. GRAM-POSITIVE *IN VITRO* ANTIBACTERIAL ACTIVITY OF 2-ALKOXY PENEMS*

Entry Number	Geometric Mean MICs in μg/mL (*number of strains*)			GRAM-POSITIVE Geometric Mean MICs μg/mL
	B. subtilis	*Staphyl.*	*E. faecalis.*	
15a	1.41 (2)	1.51 (21)	32.0 (4)	3.20 (28)
15b	1.0 (2)	3.12 (28)	64.0 (2)	2.80 (31)
15c	1.0 (1)	1.66 (22)	32.0 (4)	2.44 (28)
15d	1.0 (1)	1.51 (22)	32.0 (4)	2.26 (28)
15f	8.0 (1)	27.43 (18)	45.26 (2)	27.34 (22)
15g	1.0 (1)	1.57 (17)	64.0 (2)	2.07 (21)
2a				0.10 **
2b				0.20 **
2c				0.20 **

* Mueller–Hinton agar, 24 h; ** Data from ref. 1



2a, R = -Et
2b, R = -Et-OCONH$_2$
2c, R = -Et-NH$_2$



15a, R = -Me **15d**, R = -Bu
15b, R = -Et **15g**, R = -Et-OCONH$_2$
15c, R = -Pr **15f**, R = -Et-NH$_2$

Table 2. GRAM-NEGATIVE *IN VITRO* ANTIBACTERIAL ACTIVITY OF 2-ALKOXY PENEMS*

Entry Number	Geometric Mean MICs in μg/mL (*number of strains*)								GRAM-NEGATIVE Geometric Mean MICs μg/mL
	E. coli	*Enterobacter*	*Klebsiella*	*Morganella*	*Providencia*	*Salmonella*	*Sarcinea lut.*	*Serratia*	
15a	10.44 (13)	24.25 (5)	8.98 (12)	45.26 (2)	39.40 (10)	6.96 (5)	2.0 (1)	29.63 (9)	16.60 (56)
15b	6.82 (13)	≥24.25 (5)	5.04 (12)	45.26 (2)	39.40 (10)	4.60 (5)	1.0 (1)	≥22.63 (8)	12.13 (55)
15c	14.38 (13)	≥73.52 (5)	20.16 (12)	64.0 (2)	≥64.0 (9)	10.56 (5)	1.0 (1)	≥87.09 (9)	31.60 (55)
15d	≥25.85 (13)	≥128.0 (5)	≥32 (12)	≥90.51 (2)	≥80.64 (9)	≥36.76 (5)	1.0 (1)	≥128 (9)	52.98 (55)
15f	≥128.0 (11)	≥128.0 (3)	≥128.0 (10)	≥128.0 (1)	≥128.0 (5)	≥128.0 (3)	32.0 (1)	≥128 (4)	≥128.0 (37)
15g	6.62 (11)	10.08 (3)	4.92 (10)	16.0 (1)	27.86 (5)	4.0 (3)	0.50 (1)	16.0 (4)	8.30 (37)
2a									0.70 **
2b									0.50 **
2c									3.60 **

* Mueller–Hinton agar, 24 h; ** Data from ref. 1

The *in vitro* antibacterial activity of the 2-alkoxy penems is summarized in Tables 1 and 2. Methodology for determining the minimum inhibitory concentrations (MIC values) has been described previously.[9] In general, the 2-alkoxy penems have modest activity against gram-positive organisms and weak activity against gram-negative organisms. The gram-negative activity decreases when the alkyl group is larger than ethyl (e.g., **15b** to **15c** and **15d**). An amino substituent on the ethyl group has a deleterious effect on the gram-negagtive activity (**15f** vs. **15b**). When compared to the C_2-alkylthio series (**2a-c**), the 2-alkoxypenems are approximately 10x less active against gram-positive organisms and 20x less active against gram-negative organisms.

In summary, the oxalimide cyclization reaction has been applied for the synthesis of a selected series of 2-alkoxy penems. The compounds were found to be weak antibacterial agents when compared to the corresponding 2-alkylthio penems, thereby demonstrating the importance of C_2-sulfur atom for antibacterial potency in penems.

Acknowledments: The authors thank the Analytical Services Department for obtaining spectroscopic data on the compounds, and Dr. A. Cacciapouti for compilation of test data.

Refereces and notes:

1. *For a review on penem antibiotics see* McCombie, S. W.; Ganguly, A. K. *Med. Res. Rev.* **1988**, *8*, 393.
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10. All new compounds gave mass spectral and spectroscopic data in agreement with their assigned structures. Data on selected compounds: **9c**: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.02 (t, 3H, *J* = 6 Hz), 1.50 (d, 3H, *J* = 6 Hz), 1.79 (q, 2H, *J* = 6 Hz), 3.40 (dd, 1H, *J* = 2, 4 Hz), 4.58 (t, 2H, *J* = 6 Hz), 4.80 (s, 2H), 5.27 (m,1H), 5.50 (d,1H, *J* = 2 Hz). **11b**: white crystals from EtOAc/hexane, mp 84-85 °C; $[\alpha]_D$+167° ($CHCl_3$, c 0.3); λ_{max} (MeOH) 310 mμ (ε 9000), 275 mμ (ε 6000), 206 mμ (ε 7400); IR ($CHCl_3$) 1798, 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.44 (t, 3H, *J* = 6 Hz), 1.54 (t, 3H, *J* = 6 Hz), 3.87 (dd, 1H, *J* = 1.5, 9 Hz), 4.22 (q, 2H), 4.70 (m, 3H), 4.77 (s, 2H), 5.25 (m,2H), 5.60 (d, 1H, *J* = 1.5 Hz), 5.90 (m, 1H), **14c**: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.98 (t, 3H, *J* = 7 Hz), 1.34 (d, 3H, *J* = 6 Hz), 3.64 (dd, 1H, *J* = 1.7, 7 Hz), 4.1 (m, 3H), 4.67 (m,2H), 5.30 (m, 2H), 5.57 (d, 1H, *J* = 1.7 Hz), 5.93 (m, 1H).**15d**: ^{1}H NMR (D_2O, 80 MHz) δ 0.90 (t, 3H, *J* = 6 Hz), 1.30 (d, 2H, *J* = 6 Hz), 3.79 (dd, 1H, *J* = 1.5, 6 Hz), 4.12 (m, 3H), 5.57 (d, 1H, *J* = 1.5 Hz). **15g**: ^{1}H NMR (D_2O, 80 MHz) δ 3.90 (dd, 1H, *J* = 1.5, 6 Hz), 5.67 (d, 1H, *J* = 1.5 Hz).