New Reactions of 2-Alkylthiopenems

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The conversion of 2-alkylthiopenems into the 2-thioxopenam, 2-oxopenam, 2-*O*-alkylpenem, and into the 2-unsubstituted penem, and the reactivity of 2-alkylthiopenems to various types of chlorinating agents is described.

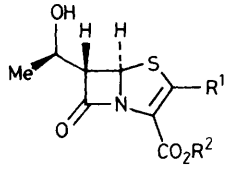
6-(1-Hydroxyethyl)-2-alkylthiopenems such as Sch 29482[1a,b] [allyl ester (**1**)] are potent antibacterial agents and can also serve as intermediates to related structures; oxidation with *m*-chloroperbenzoic acid (mCPBA) is known to provide epimeric sulphoxides (**2**), which react with RSH–Pr_2^iNEt to generate new 2-alkylthiopenems.[2] The 'thione' (**6**) has also proved[3a,b,c] to be a versatile intermediate for 2-thiopenems, and we now report the conversion of (**1**) into (**6**), its 2-oxo analogue (**8**), and the 2-unsubstituted compound (**3**).

The sulphoxide (**2**) was rapidly reduced with zinc–aqueous acetic acid in tetrahydrofuran (THF) to the chiral 2-unsubstituted compound (**3**), the derived acid (**4**) being spectroscopically identical with the racemic material described previously.[4] Although treatment of (**2**) with hydrogen sulphide and a tertiary amine[2] gave only traces of 'thione', (**6**), a 60% yield was secured on reaction of (**2**) with sodium hydrosulphide (2 equiv.) in aqueous acetonitrile, providing an alternative route to this useful substance.

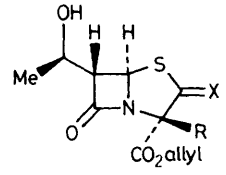
When (**1**) was oxidised with sodium hypochlorite in buffered (KH_2PO_4) aqueous acetonitrile at 0—5 °C, sulphoxide (**2**) was the dominant product, but the reaction took quite a different course in a two-phase system of aqueous methylene chloride or aqueous ethyl acetate under similar buffered conditions, giving a new product, identified spectroscopically as the 2-oxo-3-chloro compound (**7**) [i.r. (film) 1795, 1770, 1730 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 5.95 (1H, m), 5.47 (1H, d, *J* 2.0 Hz, β-lactam), 5.5—5.1 (2H, m), 4.75 (2H, m), 4.3 (1H, m), 3.63 (1H, dd, *J* 6, 2 Hz, β-lactam), 2.2 (1H, s, exch. D_2O), 1.34 (3H, d, *J* 7 Hz); $M^+ + 1$ (fast atom bombardment) *m/z* 306, $M^+ + 1 - H_2O$ 288, $M^+ - Cl$ 270]. This substance was unstable, but could be isolated in 30—40% yield by flash silica gel chromatography. Experiments with (**2**) established that the sulphoxide is not an intermediate to (**7**), although it was a minor co-product. The formation of (**7**) in the biphasic system may be rationalized by two competing pathways for the initial chlorination step, as shown in Scheme 1; alternative possibilities such as conversion of the cationic species (A) into (B) or of an alternative chlorinating agent (Cl_2O ?) cannot be discounted.

Reduction of (**7**) with either zinc–acetic acid in THF, or triphenylphosphine in aqueous methylene chloride readily gave the 2-oxopenam (**8**), which could be prepared in 55% yield from (**1**) by omitting the purification of (**7**). Compound (**8**) was also a somewhat sensitive, non-crystalline substance whose structure followed from spectroscopic data [i.r. (CH_2Cl_2) 1790, 1755, 1720 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$) 5.9 (1H, m), 5.55 (1H, d, *J* 1.5 Hz, β-lactam), 5.5—5.2 (2H, m), 5.05 (1H, s), 4.7 (2H, m), 4.32 (1H, m), 3.62 (1H, dd, *J* 6, 1.5 Hz, β-lactam), 2.8 (1H, exh. D_2O), and 1.37 (3H, d, *J* 7 Hz)]. Further confirmation of its structure followed from conversion into the known 2-methoxypenem (**5**)[5] by reaction with diazomethane.

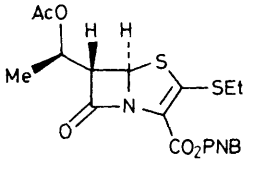
Reaction of the fully protected penem (**9**) with chlorine (2.1 equiv.) in dry methylene chloride at −70 °C for 0.5 h, followed by removal of the volatile material *in vacuo* gave a highly sensitive, bicyclic β-lactam. Spectral data suggested the trichloro compound (**10**) [i.r. ($CHCl_3$) 1795, 1740 cm^{-1};



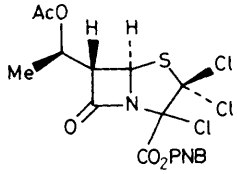
(**1**); R^1 = SEt, R^2 = allyl
(**2**); R^1 = S(O)Et, R^2 = allyl
(**3**); R^1 = H, R^2 = allyl
(**4**); R^1 = R^2 = H
(**5**); R^1 = OMe, R^2 = allyl



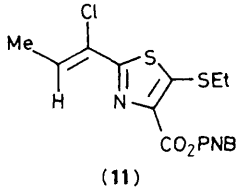
(**6**); X = S, R = H
(**7**); X = O, R = Cl (or 3-epimer)
(**8**); X = O, R = H



(**9**)

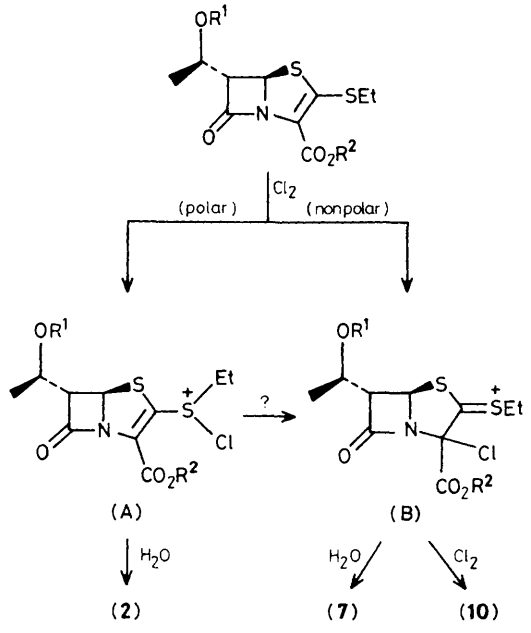


(**10**)



(**11**)

PNB = *p*-$O_2NC_6H_4CH_2$



Scheme 1

^{1}H n.m.r. δ ($CDCl_3$) 8.25 (2H, br. d, *J* 10 Hz), 7.6 (2H, br. d, *J* 10 Hz), 5.5 (2H, s, $-CH_2O-$), 5.4 (1H, d, *J* 1.5 Hz, β-lactam), 5.3 (1H, m), 3.75 (1H, dd, *J* 6, 1.5 Hz, β-lactam), 2.05 (3H, s), 1.4 (3H, d, *J* 6 Hz); M^+ (chemical ionisation, C.I.) 496–498 (3-chlorine pattern)]. Attempts to effect reduction of (**10**) to a 2-chloro or 2-unsubstituted penem led to destruction of the β-lactam. Chlorination of (**9**) with sulphuryl chloride in methylene chloride at −20 °C in the presence of anhydrous calcium carbonate for 3 h led to a crystalline non-β-lactam substance (**11**), having the ethylthio group intact [m.p. 136—138 °C; i.r. ($CHCl_3$) 1720, 1700 cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$) 8.25 (2H, d, *J* 10 Hz), 7.7 (2H, d, *J* 10 Hz), 7.05 (1H, q, *J* 7.5 Hz), 5.5 (2H, s), 3.1 (2H, q, *J* 8 Hz), 2.1 (3H, d, *J* 7.5 Hz), 1.42 (3H, t, *J* 8 Hz); M^+ (C.I.) 398, M^+- 136, 262 (base peak)].

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