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NEW SYNTHESIS OF PENEMS *VIA* A REDUCTIVE CYCLIZATION REACTION OF OXALIMIDES WITH TRIALKYL PHOSPHITE(1)

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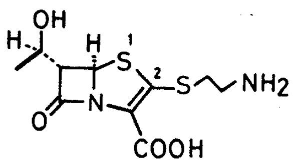
Treatment of the oxalimide 5 with triethyl phosphite formed the penem 3 and the triethoxyphosphonium ylide 7, presumably *via* the common carbene intermediate 10. Prolonged heating of 7 afforded 3 and its C-5 epimer. Similar reaction of the oxalimide 13 with trimethyl phosphite gave only the ylide 14, which was further heated to cyclize to the penem 15.

KEYWORDS ——— antibiotic; penem; N-oxalylazetidinone; carbene intermediate; reductive cyclization; thienamycin analog

In a preceding paper,(2) we reported synthesis of a series of 2-(alkylthio)penems ("1-thiathienamycin" 1 and related compounds) which were shown to possess potent broad-spectrum antibacterial activities. Although their activities were somewhat lower than that of thienamycin, their chemical and biological stabilities seemed to be superior to those of the natural antibiotic. We are especially interested in the penem 1 because of its remarkable antimicrobial potency and spectral breadth including anti-*Pseudomonas* activity. The key reaction used in the previous synthesis was an intramolecular Wittig reaction of the phosphorane 2 to the penem ester 3 which had been developed by Woodward *et al.*(3) This cyclization reaction required rather higher temperature and longer time, and under these conditions the product 3 underwent C-5 epimerization to give some undesired *cis* isomer.(2,4) In addition, synthesis of the phosphorane 2 from the trithiocarbonate 4 by the conventional Woodward procedure took several days for the sequence to be completed. Consequently, a more efficient and practical route to penems was required.(5) We report here a new synthesis of penems *via* a reductive cyclization of oxalimides with trialkyl phosphite.



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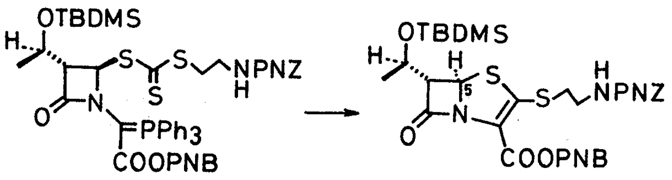
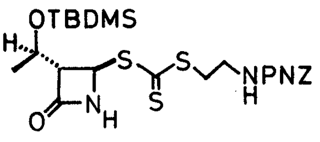


2 3

TBDMS: *tert*-butyldimethylsilyl
PNZ: *p*-nitrobenzyloxycarbonyl
PNB: *p*-nitrobenzyl

Very recently, a Schering research group has independently reported a new penem synthesis6) using the same methodology as described in the present paper.1)

First we anticipated that the trithiocarbonate ester group of the oxalimide **5** would react with triethyl phosphite to form the triethoxyphosphonium ylide **6** according to the precedent7) and **6** would in turn cyclize to give the penem **3** by an intramolecular Wittig reaction.8) The oxalimide **5** was prepared in 77% yield by reaction of **4**2) with *p*-nitrobenzyloxyoxalyl chloride9) (2 eq) and diisopropylethylamine (2 eq) in methylene chloride at -15°C followed by aqueous work-up and purification by silica gel chromatography. Treatment of **5** with triethyl phosphite (5 eq) in toluene at 80°C for 1 h gave the desired penem **3**2) (29%) and the phosphonium ylide **7** (43%) after silica gel chromatography. There was no formation of the *cis* penem. In contrast to the phosphorane **2**, the ylide **7** was susceptible to hydrolysis, especially in the presence of acid [*p*-TsOH (trace), tetrahydrofuran-H_2O (3 : 1), room temperature, 15 min], to give the reduced product **8** (87%).10)



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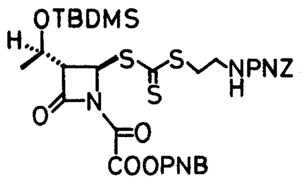

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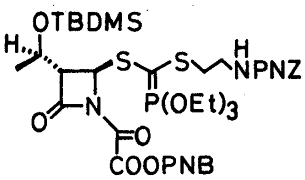

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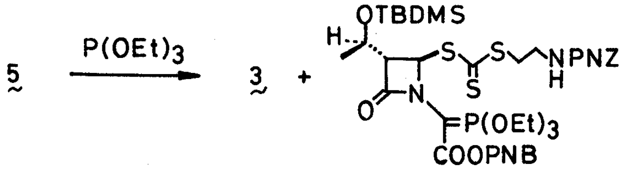

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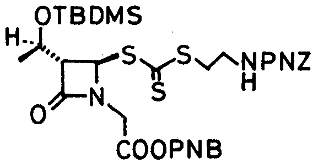

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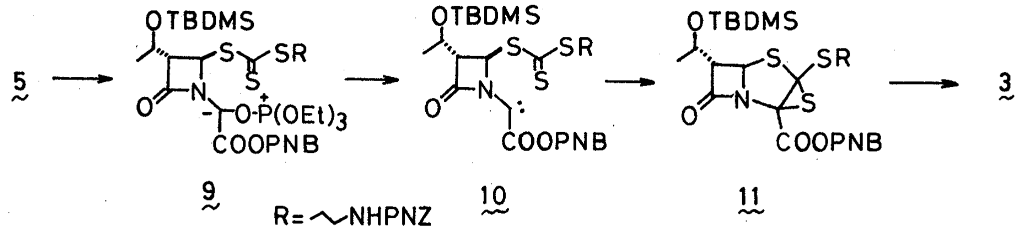
Involvement of the ylide **6** or **7** as intermediates in the formation of **3** under the above reaction conditions was excluded by the following data. The trithiocarbonate **8** was further treated with triethyl phosphite, but the thiocarbonate ester group was inactive to this reagent. No formation of ylides such as **6** was detectable. The ylide **7** was found to be stable on heating at 80°C for a few hours. These facts indicated that the penem **3** was not formed *via* the intermediate **6** or **7**. However it is worth noting that cyclization of the ylide **7** proceeded slowly at 85°C over a period of 60 h to give a mixture of **3** and its C-5 epimer in a 3.5 : 1 ratio in 65% yield, and the reaction was markedly accelerated by raising the reaction temperature to 125°C to afford the same epimeric mixture of penems (the reaction was completed in 3 h).

Formation of the penem **3** accompanied by the ylide **7** in the early stage of the reaction of the oxalimide **5** and triethyl phosphite can be explained by another pathway involving a carbene intermediate. The oxalimido carbonyl group of **5** is supposed to be highly activated by both the azetidinone ring and the ester group, and reacts with triethyl phosphite to form the adduct **9** which would decompose to the carbene **10** by removal of triethyl phosphate. The carbene **10** cyclizes by an intramolecular addition to the carbothioyl group to form an episulfide **11** which would be easily desulfurized by excess triethyl phosphite to the penem **3**. The carbene **10** also reacts



with triethyl phosphite to give the phosphonium ylide 7. Based on the same mechanism, Schering chemists recommend a slow addition of triethyl phosphite to oxalimides in order to diminish the formation of ylides such as 7 and to obtain optimum yield of penems.[6] The present method for penem synthesis is simpler and more practical than the previous one using the conventional phosphorane cyclization. Trimethyl or triisopropyl phosphite instead of triethyl phosphite was also effective for the cyclization of oxalimides.

Next, we were interested in applying this methodology to the synthesis of 2-alkylpenems which were first synthesized by Woodward *et al.*[3] *via* their triphenylphosphorane cyclization reaction. The synthesis starting from the azetidinone 12 is described below as a typical example.

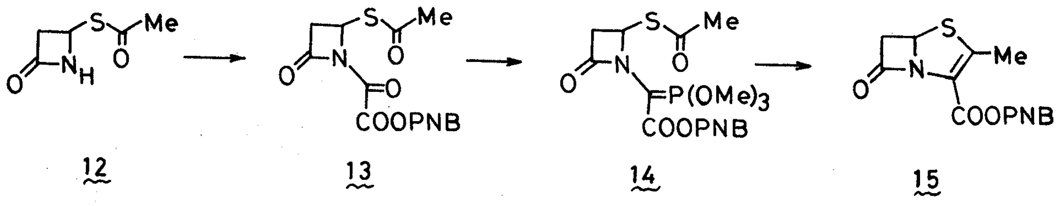


TABLE I. IR and NMR Data of Azetidinone Derivatives

Compd.	IR cm^{-1} (state or solvent)	NMR δ[a] (CDCl$_3$)
5	3440, 1815, 1760, 1725 (CHCl$_3$)	0.00 & 0.10 (3H each, s), 0.83 (9H, s), 1.23 (3H, d, 6(, 3.3-3.8 (5H, m), 4.40 (1H, m), 5.16 (2H, s), 5.40 (2H, s), ∿5.4 (1H, br), 6.72 (1H, d, 3.5)
7	3400, 1752, 1722, 1636 (CHCl$_3$)	0.00 & 0.08 (6H, s), 0.82 (9H, s), 1.25 (3H, d, overlapped with OEt absorption), 1.32 (9H, t, 7), 2.9-3.8 (5H, m), 3.8-4.5 (7H, m), 5.18 (4H, s), ∿5.3 (1H, br), 6.20 (1H, br)
8	3420, 1770, 1725 (CHCl$_3$)	0.03 & 0.07 (3H each, s), 0.86 (9H, s), 1.25 (3H, d, 6), 3.0-3.8 (4H, m), 3.29 (1H, dd, 6.5, 2.5), 3.85 (1H, d, 17), 4.23 (1H, d, 17), 4.25 (1H, m), 5.15 & 5.21 (2H each, s), 5.98 (1H, d, 2.5)
13	1803, 1747, 1718, 1702 (Nujol)	2.31 (3H, s), 3.21 (1H, dd, 18, 4), 3.76 (1H, dd, 18, 6), 5.39 (2H, s), 5.71 (1H, dd, 6, 4)
14	1760, 1695, 1640 (CHCl$_3$)	2.30 (3H, s), 2.85 (1H, m), 3.40 (1H, m), 3.85 (9H, d, 12), 5.22 (2H, s), 5.50 (1H, m)
15	1793, 1708 (Nujol)	2.40 (3H, s), 3.48 (1H, dd, 16, 2), 3.81 (1H, dd, 16, 3.5), 5.25 (1H, d, 14), 5.49 (1H, d, 14), 5.69 (1H, dd, 3.5, 2)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. Absorptions of aromatic protons of the *p*-nitrobenzyl group(s) at δ 7.4-8.3 are not given in the table. The abbreviations used are as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet; br, broad.

Oxalimide 13, mp 117-118°C, obtained from 12 in 85% yield in a manner similar to the one described above, was heated at 65°C with trimethyl phosphite to give the trimethoxyphosphonium ylide 14 which was unstable to silica gel chromatography. In contrast to the reaction of 5, the cyclized product 15 was not formed in this step probably due to lower reactivity of the carbonyl group of the thiolester to the possible intermediate carbene. The crude ylide 14 was further heated in toluene at 105°C for 20 h to provide the desired penem 15, mp 132-135°C (lit.[3b] mp 130-132°C), in 48% yield based on 13.

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