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7-OXO-2-THIA-1-AZABICYCLO[3.2.0]HEPT-3-ENE, A REVISED STRUCTURE FOR PENEMS SYNTHESIZED VIA OXIDATIVE ADDITION MEDIATED BY COPPER(I)

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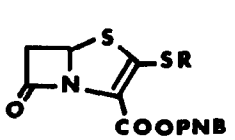
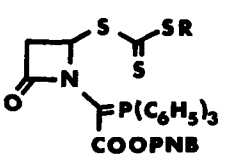
Summary: The structure for the fused β-lactam obtained by treatment of the secolactam 3 with base in the presence of Cu(I)-ion is not the penem 1 (R=CH_3), but the isopenem 4 on the basis of X-ray analysis.

In our preceding paper,[1] it was reported that 2-(alkylthio)penem-3-carboxylates (1) were synthesized from phosphoranes 2 by an intramolecular Wittig reaction developed by Woodward and his group[2] and penem-3-carboxylic acids derived from 1 exhibited marked antibacterial activities against gram(+) and (-)bacteria. During the course of this study, DiNinno et al[3] reported that the secolactam 3 was converted into the p-nitrobenzyl 2-(methylthio)penem-3-carboxylate (1, R=CH_3) via Cu(I)-mediated oxidative addition brought about by treatment with lithium diisopropylamide in the presence of CuI-PBu_3. However, the reported data for 1 (R=CH_3) showed marked discrepancies with our sample[4] synthesized by cyclization of 2 (R=CH_3). In order to investigate the reason for the differences, we followed their procedure and obtained the sample reported for 1, which



1



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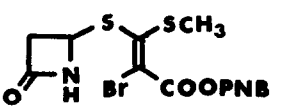

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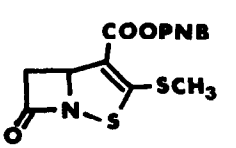


4

PNB = p-nitrobenzyl

was submitted to X-ray crystallographic analysis. The result was that its structure was not a penem 1 but an isopenem 4 with the β-lactam fused to an isothiazoline ring. Crystal data: $C_{13}H_{12}O_5N_2S_2$, Mw=352.4, monoclinic, space group $P2_1/c$, a=11.280(2), b=10.119 (2), c=13.869(2)Å, β =105.02(6)° , Dcalc.=1.53g/cm^3. The phases were solved using MULTAN[5] and the first stage of the E-map yielded the well resolved structure 4 as shown in the Figure 1. All atomic species were determined by temperature factors and electron densities. The final R-value was 7.5%.

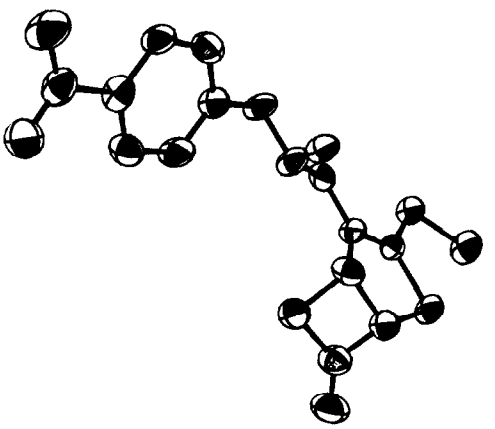
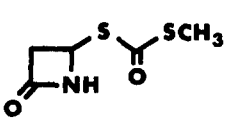


Figure 1. ORTEP view of 4

It is of interest to note that the Cu(I)-mediated cyclization of 3 seems to proceed under C-S bond cleavage to give the azetidinone and dithiomalonate moieties which recombine to form the isothiazoline ring.[6]

References and Notes

1) S. Oida, A. Yoshida, T. Hayashi, N. Takeda, T. Nishimura, and E. Ohki, J. Antibiotics, in press.
2) I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, J. Am. Chem. Soc., 100, 8214 (1978) and references cited therein.
3) F. DiNinno, E. V. Linek, and B. G. Christensen, J. Am. Chem. Soc., 101, 2210 (1979).
4) mp 165-166°, IR(KBr) 1800, 1683 cm^{-1}; UV λ_{max}(dioxane) 260 nm (ε 16400), 338.5 nm (ε 10900); NMR δ($CDCl_3$) 2.54 (3H, s), 3.51 (1H, dd, J=16, 2 Hz), 3.84 (1H, dd, J=16, 3.5 Hz), 5.24 (1H, d, J=14 Hz), 5.47 (1H, d, J=14 Hz), 5.73 (1H, dd, J=3.5, 2 Hz), 7.62 (2H, d, J=9 Hz), 8.23 (2H, d, J=9 Hz).
5) G. Germain, P. Main, and M. M. Wolfson, Acta Cryst. 1971, A27, 368.
6) The structure of 3 was verified by ozonization of 3 to give an azetidinone dithiocarbonate 5 : oil, IR ($CHCl_3$) 3425, 1785, 1640 cm^{-1}; NMR δ($CDCl_3$+D_2O) 2.46 (3H, s), 2.95 (1H, dd, J=16, 2.5 Hz), 3.48 (1H, dd, J=16, 5.5 Hz), 5.40 (1H, dd, J=5.5, 2.5 Hz).



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