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PENEMS. I. NOVEL SYNTHESIS OF ANTIBACTERIAL PENEM COMPOUNDS UTILIZING 1,3-DITHIOLANE DERIVATIVES

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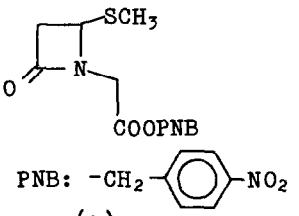
Summary: A novel penem synthesis utilizing 1,3-dithiolane or 1,3-dithiane derivatives allowed us to synthesize a number of new antibacterial penem compounds.

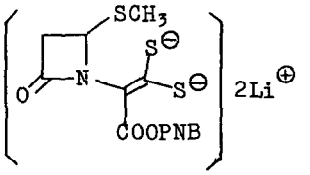
The discovery of thienamycin[1], a broad spectrum β-lactam antibiotic, provoked considerable interest in the synthesis of carbapenem or penem compounds. From the viewpoint of molecular modification, penem derivatives were of particular interest to us, since the thienamycin analog in which the C_1-methylene group of thienamycin is replaced by sulfur has been demonstrated to be more stable and retain the intrinsic activity of the carbapenem antibiotic.[2] We considered the unique synthesis of new penem derivatives, some of which are inaccessible by the most reliable method utilizing an intramolecular Wittig reaction. This paper reports the novel synthetic route to a variety of penem derivatives by way of azetidinone derivatives possessing 1,3-dithiolane or 1,3-dithiane moiety.

p-Nitrobenzyl (±)-4-methylthio-2-oxoazetidin-1-ylacetate(1)[3] was treated with 2 mole-equivalent of lithium hexamethyldisilazide in tetrahydrofuran(THF) at -78°C followed by the action of carbon disulfide[4] to form possibly the dithiolate anion(2). The intermediate anion was, without isolation, allowed to react with α-bromoacetone in THF to yield the 4-hydroxy-1,3-dithiolane derivative(3)[5] in excellent yield. Based on the NMR spectrum, the dithiolane derivative was assumed to be a mixture of geometrical isomers, but was not separated by chromatography. The methylthio group of 3 was displaced by a chlorine atom with an equimolar amount of chlorine or sulfuryl chloride in methylene chloride at 0°C and the resulting 4-chloro azetidinone derivative(4) was treated with excess triethylamine in methylene chloride at room temperature to obtain the penem derivative(5).[6] This reaction proceeded smoothly with the C_5-S bond formation of the penem nucleus together with the C-S bond cleavage of the dithiolane ring concertedly or in two steps. The removal of the p-nitrobenzyl group was carried out by catalytic hydrogenolysis over 10% Pd-C in phosphate buffer(pH=7.1) and the sodium salt(6)[7] was isolated through a column packed with Mitsubishi Daiya-ion CHP20P.

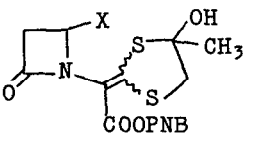


PNB: $-CH_2-C_6H_4-NO_2$

(1)

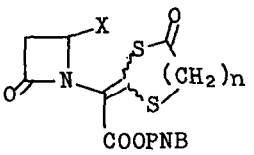


(2)



(3) X= SCH_3

(4) X= Cl

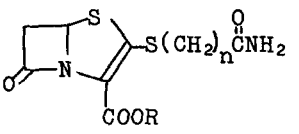


(7) X= SCH_3, n=1

(8) X= Cl, n=1

(11) X= SCH_3, n=2

(12) X= Cl, n=2

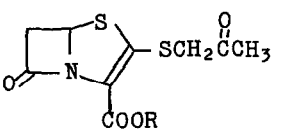


(9) R=PNB, n=1

(10) R= Na, n=1

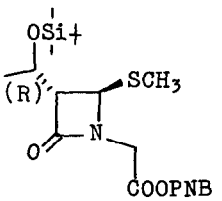
(13) R=PNB, n=2

(14) R= Na, n=2

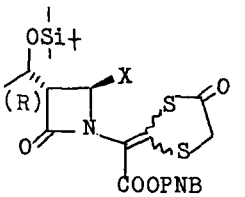


(5) R=PNB

(6) R= Na

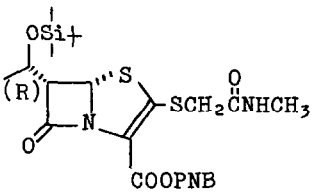


(15)

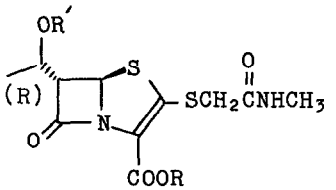


(16) X= SCH_3

(17) X= Cl



(18)



(19) R=PNB, R´= Si+

(20) R=PNB, R´= H

(21) R= Na, R´= H

Similarly the dithiolate anion 2 reacted with bromoacetyl bromide in THF to afford the 4-oxo-1,3-dithiolane derivative(7)[8] in good yield. After treatment with chlorine or sulfuryl chloride, the 4-chloro derivative(8) was allowed to react with excess ammonia in methylene chloride at 0°C. The resultant penem derivative(9)[9] was subjected to catalytic hydrogenolysis to give the sodium salt(10).[10]

The dithiolate anion 2 when treated with 2-bromopropionyl chloride yielded the 4-oxo-1,3-dithiane derivative(11) in 44% yield. Following the conversion of 11 into 12, the corresponding penem derivative(13) was obtained by treatment of 12 with excess ammonia in methylene chloride and led to the sodium salt(14).

(3S,4R)-3-[(R)-1-tert-Butyldimethylsilyloxyethyl]-4-methylthio-2-oxoazetidine(15)[3] was similarly converted into the corresponding 4-oxo-1,3-dithiolane derivative(16) in 47% yield. Chlorination of 16 to give the trans 4-chloro derivative(17) and subsequent cyclization using methylamine in methylene chloride-methanol gave rise to the cis penem (18)[11] in 80% yield. Heating a toluene solution of 18 and a small amount of hydroquinone at 125°C for 4 hr under nitrogen gave an equilibrating 1:2 mixture[2] of the cis and the trans isomers(18 and 19)[12] which were separated by column chromatography. The t-butyldimethylsilyl group of 19 was removed by treating with excess tetrabutylammonium fluoride and acetic acid in THF for 52 hr at room temperature. The hydroxyethyl derivative(20)[13] was converted into the sodium salt (21)[14] as described for 6.

This synthetic method enabled us to synthesize numerous penem derivatives which will be reported elsewhere. The following paper will describe the preparation of an alternative valuable intermediate for penem synthesis.

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References and Notes

1) J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Curie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, and J. Birnbaum, J. Antibiot., 32, 1(1979).

2) S. Oida, Recent Advances in the Chemistry of β-Lactam Antibiotics, 2nd International Symposium, ed. by G. I. Gregory, Chem. Soc., Spec. Publ., No.38, 330(1980); T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara, and E. Ohki, Chem. Pharm. Bull., 29, 3158(1981).

3) The starting materials(1 and 15) were prepared in the following three steps: i) p-nitrobenzyl glyoxylate,4-methylthio-2-oxoazetidine derivative/benzene; ii) $SOCl_2$-2,6-lutidine/THF; iii) $NaBH_3CN$/HMPA.

4) K. Hirai in our laboratories has attempted the reaction of 1 with CS_2 in the presence of one mole-equivalent of the base for other purpose.

5) Compound 3, purified by preparative TLC(benzene-AcOEt), a foam; NMR($CDCl_3$)δ: 1.89(3H, s, CH_3), 2.16, 2.18(3H, 2xs, SCH_3), 2.84-3.78(4H, m, 2xC_3-H, SCH_2), 4.20(1H, b, OH), 5.07(1H, m, C_4-H), 5.23(2H, s, OCH_2), 7.50, 8.18 (4H, A_2B_2, J=8.5 Hz, arom. H); IR($CHCl_3$): 3420, 1760, 1700 cm^{-1}.

6) Compound 5, purified by preparative TLC($CHCl_3$-MeOH=100:1), a powder; MS m/e: 394(M^+). NMR(DMSO-d_6)δ: 2.12(3H, s, CH_3), 3.41(1H, dd, J=16.0, 2.0 Hz, C_6-H), 3.75(1H, dd, J=16.0, 4.0 Hz, C_6-H), 4.04(2H, s, SCH_2), 5.26(2H, bs, OCH_2), 5.66(1H, dd, J=4.0, 2.0 Hz, C_5-H), 7.59, 8.14(4H, A_2B_2, J=9.0 Hz, arom. H); IR($CHCl_3$): 1805, 1720, 1700 cm^{-1}.

7) Compound 6, freeze-dried, a powder; NMR(D_2O)δ: 2.34(3H, s, CH_3), 3.52(1H, dd-like, J=17.5 Hz, C_6-H), 3.79(1H, dd, J=17.5, 4.0 Hz, C_6-H), 5.72(1H, dd-like, C_5-H); IR(KBr): 1765, 1707, 1590 cm^{-1}; UV(H_2O): 249.5, 321.6 nm.

8) Compound 7, an oil; NMR($CDCl_3$)δ: 2.10(3H, s, SCH_3), 3.05(1H, dd, J=15.5, 3.5 Hz, C_3-H), 3.34(1H, dd, J=15.5, 5.0 Hz, C_3-H), 4.05(2H, s, SCH_2), 5.25 (1H, dd, J=5.0, 3.5 Hz, C_4-H), 5.35(2H, s, OCH_2), 7.60, 8.25(4H, A_2B_2, J= 9.5 Hz, arom. H); IR($CHCl_3$): 1765, 1725, 1703 cm^{-1}.

9) Compound 9, a powder; NMR(DMF-d_7)δ: 3.63(1H, dd, J=14.5, 2.0 Hz, C_6-H), 3.93 (2H, s, SCH_2), 3.98(1H, dd, J=14.5, 3.5 Hz, C_6-H), 5.40, 5.56(2H, AB-q, J= 14.0 Hz, OCH_2), 5.92(1H, dd, J=3.5, 2.0 Hz, C_5-H), 7.28(2H, bs, NH_2), 7.86, 8.34(4H, A_2B_2, J=9.0 Hz, arom. H); IR(KBr): 3370,3180,1785,1685, 1670 cm^{-1}.

10) Compound 10, a powder; NMR(D_2O)δ: 3.52(1H, dd, J=17.0, 2.0 Hz, C_6-H), 3.80 (1H, dd, J=17.0, 4.0 Hz, C_6-H), 5.75(1H, dd, J=4.0, 2.0 Hz, C_5-H), 3.71(2H, s, SCH_2); IR(KBr): 3400, 1760, 1668, 1580 cm^{-1}.

11) Compound 18, a powder; NMR($CDCl_3$)δ: 0.09(6H, s, $SiMe_2$), 0.80(9H, s, t-Bu), 1.36(3H, d, J=6.0 Hz, $CHCH_3$), 2.80(3H, d, J=5.0 Hz, NCH_3),3.70(2H,s, SCH_2), 3.88(1H, dd, J=4.0, 10.5 Hz, C_6-H), 4.1-4.6(1H, m, $CHCH_3$), 5.19, 5.49(2H, AB-q, J=14.5 Hz, OCH_2), 5.73(1H, d, J=4.0 Hz, C_5-H), 6.72(1H, bs, NH), 7.64, 8.25(4H, A_2B_2, J=8.5 Hz, arom. H); IR(KBr): 3300, 1785, 1700, 1680 cm^{-1}.

12) Compound 19, a powder; NMR($CDCl_3$)δ: 0.03, 0.06(6H, 2xs, $SiMe_2$), 0.80(9H, s, t-Bu), 1.19(3H, d, J=6.0 Hz, $CHCH_3$), 2.78(3H, d, J=5.0 Hz, NCH_3), 3.57(2H, s, SCH_2), 3.65(1H, dd, J=2.0, 4.0 Hz, C_6-H), 3.8-4.4(1H, m, C_5-H), 5.10 5.33(2H, AB-q, J=14.0 Hz, OCH_2), 5.58(1H, d, J=2.0 Hz, C_5-H), 6.52(1H, bs, NH), 7.50, 8.08(4H, A_2B_2, J=9.0 Hz, arom. H).

13) Compound 20, crystals; NMR(DMF-d_7)δ: 1.26(3H, d, J=6.0 Hz, CH_3CH), 2.69(3H, d, J=5.0 Hz, NCH_3), 3.43(1H, bs, OH), 3.83(1H, dd, J=2.0, 5.0 Hz, C_6-H), 3.84(2H, s, SCH_2), 3.6-4.2(1H, m, CH_3CH), 5.30(1H, bs, NH), 5.32, 5.50(2H, AB-q, J=14.0 Hz, OCH_2), 5.80(1H, d, J=2.0 Hz, C_5-H), 7.73, 8.19(4H, A_2B_2, J=9.0 Hz, arom. H); IR(KBr): 3430, 3300, 1768, 1685, 1653 cm^{-1}.

14) Compound, 21, a powder; NMR(D_2O)δ: 1.29(3H, d, J=7.0 Hz, CH_3CH), 2.79(3H, s, NCH_3), 3.70(2H, s, SCH_2), 3.91(1H, dd, J=1.5, 7.0 Hz, C_6-H), 4.24(1H, quintet, 7.0 Hz, CHOH), 5.69(1H, d, J=1.5 Hz, C_5-H).

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