STUDIES ON THE SYNTHESIS OF CARBAPENEM ANTIBIOTICS. STEREOSELECTIVE SYNTHESIS OF A POTENTIAL INTERMEDIATE FOR 6-AMIDOCARBAPENEM ANTIBIOTICS

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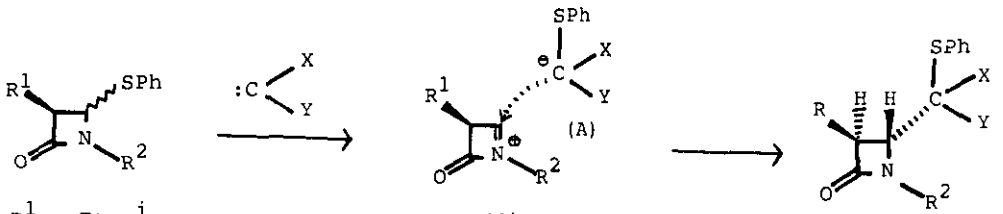
Abstract —— Stereoselective carbon-introducing reaction at the C_4 position of an azetidinone has been achieved by the application of an intramolecular carbene reaction as a key step.

We have recently published the new carbon-introducing reaction at the C_4 position of an azetidinone[1] by employing carbene reaction as shown in chart 1.

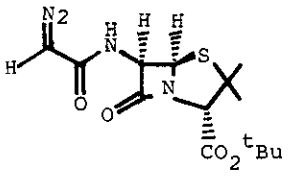
Chart 1



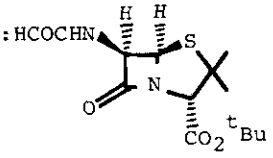
The stereochemistry between the C_3 and C_4 positions of the product in the above reaction was deduced to be trans, on the basis of its nmr data. This stereoselectivity was rationalized by assuming that the nucleophile (A) attacked from the less hindered side to the intermediate (B). In the course of our studies on the syntheses of carbapenem antibiotics, we have been interested

in the synthesis of 6-amidocarbapenem antibiotics[2] with the stereochemistry of cis relationship between the C_3 and C_4 positions of an azetidinone. For the above purpose, we have decided to apply an intramolecular carbene approach to the penicillin derivative by assuming the possibility of carbon introduction at the C_4 position with desired chirality. Although an intramolecular carbene reaction for penicillin derivative (1) was attempted by Sandoz group[3] very recently, they could not obtain a desired carbon-introduced product, but the cycloheptatriene (3) arising from the reaction of the carbene (2) with benzene used as solvent. We here wish to report our own results.

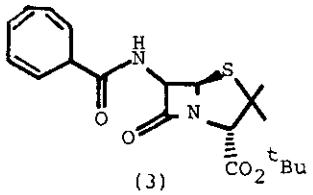
Chart 2



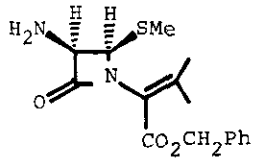
(1)



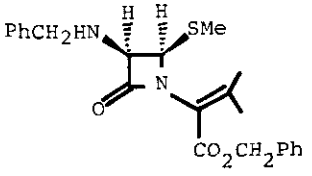
(2)



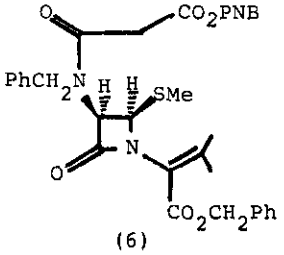
(3)



(4)



(5)



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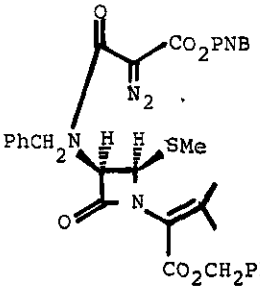
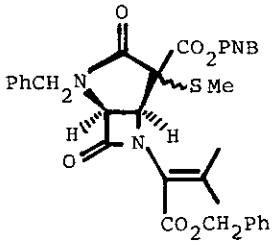


(7)



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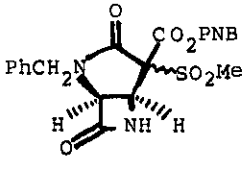

(9)

The requisite diazo-compound (7), a carbene precursor, was prepared as follows. The known azetidinone (4)[4] was treated with benzyl bromide in the presence of potassium carbonate in methylene chloride to afford the N-benzyl derivative (5), which was then acylated with the acid chloride, prepared from p-nitrobenzyl hydrogen malonate with oxalyl chloride, to yield the amide (6). The diazo exchange reaction of 6 with tosyl azide in the presence of triethylamine in acetonitrile gave the desired diazo compound (7). Though the carbene reaction was firstly attempted by decomposition of the diazo compound (7) in the presence of rhodium acetate, none of the desired product could be isolated[5]. But the carbon-introduced bicyclic compound (8)[6] was obtained in 72 % yield as a diastereomeric mixture (ca. 1 : 1), when the diazo compound (7) was subjected to photo-induced carbene reaction in carbon tetrachloride at 0 - 10 °C. The spectroscopic data of 8 were consisted with the structure 8. Finally, potassium permanganate oxidation[7] of 8 yielded the azetidinone 9[8] in 67 % yield.

Thus, we could achieve the introduction of carbon unit at the C_4 position of azetidinone with desired chirality, and the synthesis of 6-amidocarbapenem antibiotics along with this line is now under investigation in this laboratory.

ACKNOWLEDGEMENTS

We thank Mrs. T. Ogata, Mrs. A. Kumazawa, and Miss M. Moriki of Hoshi University for spectral measurements, microanalyses, and manuscript preparation.
This study was supported in part by a Grant-in-Aid for Scientific Research for the Sendai Institute of Heterocyclic Chemistry.

REFERENCES AND NOTES

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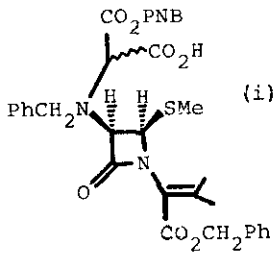
2. T. Kametani, A. Nakayama, H. Matsumoto, and T. Honda, Chem. and Pharm. Bull. (Tokyo), in press.
3. C. -P. Mak, K. Baumann, F. Mayerl, C. Mayerl, and H. Fliri, Heterocycles, 1982, 19, 1647.
4. E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, J. Chem. Soc. Perkin I, 1975, 562.
5. The product isolated from the reaction was tentatively assigned to be (i) arising from Wolff rearrangement of the carbene.



(i)

IR νmax ($CHCl_3$): 1790, 1724, 1695, 1626 (C=O), 1345 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 1.82 (3H, s, Me), 2.17 (3H, s, Me), 2.35 (3H, s, Me), 4.01 (0.5H, s, $CH(CO_2H)CO_2PNB$), 4.25 (0.5H, s, $-CH(CO_2H)CO_2PNB$); MS m/z 648 ($M^+ + 1$).

6. IR νmax ($CHCl_3$): 1778, 1710 (C=O), 1315 (NO_2) cm^{-1}; NMR ($CDCl_3$) δ 2.38 (3H, s, SMe), 4.03 (0.5H, d, J=3Hz, C_4-H), 4.12 (0.5H, d, J=3Hz, C_4-H).
7. Yield was not yet optimized.
8. IR νmax ($CHCl_3$): 3400 (NH), 1800, 1770, 1732 (C=O), 1350 (NO_2), 1320 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 2.98 (3H, s, SO_2Me), 3.92 (0.5H, d, J=3Hz, C_4-H), 4.01 (0.5H, d, J=3Hz, C_4-H); FDMS: m/e 474 ($M^+ + 1$); $[\alpha]_D$ -18.56° (C=0.73, $CDCl_3$).

Received, 15th August, 1983