A NEW SYNTHESIS OF CARBAPENAMS THROUGH THE FORMATION OF THE 1,5-BOND AS A FINAL STEP

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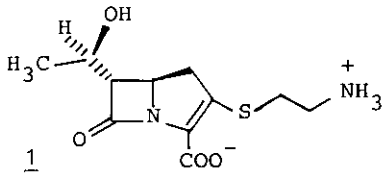
Abstract: Synthetic methods for the preparation of the racemic carbapenems 12 and 13 and an oxapenam 16 starting from diazoketone 11 are described.

Thienamycin[1] (1) and PA 31088-IV[2] (2) along with other examples[3] belonging to the carbapenem family of antibiotics isolated from various species of Streptomyces illustrate the diverse structural variations that are possible, even in natural sources without affecting the remarkable antibacterial activity of these compounds.



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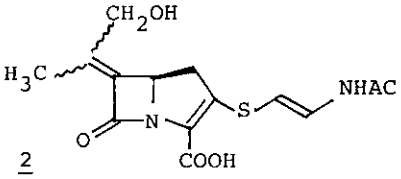

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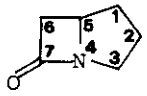

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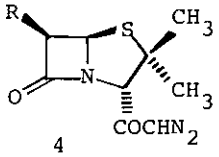
There are three main synthetic routes described in the literature for the construction of carbapenem ring system (3). Two of these three approaches utilise the intramolecular Wittig reaction for the formation of either the 2,3-bond[4] or the 1,2-bond[5] in the final step. The third involves the formation of the 3,4-bond by carbene insertion[6]. We report in this communication an alternative method for the construction of the above bicyclic ring system through the formation of the 1,5-bond.

Development of our present approach was stimulated by the literature observation[7] that the copper (II) catalysed decomposition of penicillin-derived diazoketones (4) resulted in the formation of tricyclic ketones (5) through the insertion of carbene between sulphur and C_5. We were interested in the scope of



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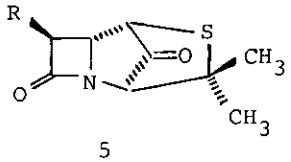

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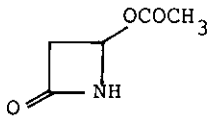
this reaction and investigated the reactivity of several diazoketones derived from the monocyclic 4-thioazetidin-2-one-1-yl acetic acid derivative.

Recently Oida and co-workers[8] reported the synthesis of oxapenam derivatives from these monocyclic diazoketones. We indepently obtained similar products with our diazoketones, but at least in one instance we were successful in isolating the desired carbapenam derivative and this constitutes the subject matter for the present communication.

The novel diazoketone 11 which yielded carbapenem derivatives 12 and 13 was synthesised in four steps starting from azedidinone (6)[9]. Treatment of compound (6) with isothiuronium chloride[10] 7 in the presence of aqueous sodium hydroxide yielded the thioazetidinone 8 in the 60 % yield.



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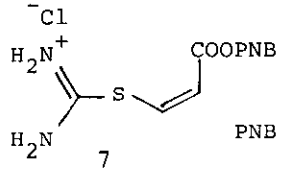

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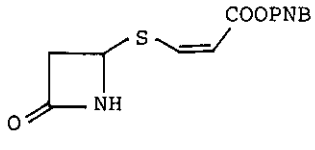
PNB = P-Nitrobenzyl



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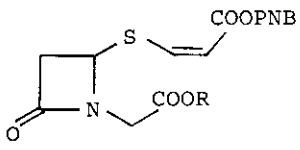
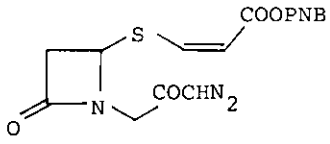


9 R = CH_3

10 R = H



11

Compound 8: mp 129-31° C (recrystallised from CH_2Cl_2/ether); IR: (CH_2Cl_2) 3405, 1780, 1700, 1520 and 1355 cm^{-1}; NMR ($CDCl_3$/DMSO), 2.80-3.05 (1H, m), 3.35-3.63 (1H, m), 4.98 (1H, dd, J = 2.5, 5 Hz), 5.30 (2H, s), 6.10 (1H, d, J = 10 Hz), 7.44 (1H, d, J = 10 Hz), 7.60 (2H, d, J = 10 Hz), 8.24 (2H, d, J = 10 Hz), 8.50 (1H, br) ppm.

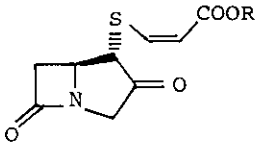
Alkylation[12] of compound 8 was carried out methyl bromoacetate using finely powdered KOH and tetrahytylammonium bromide in dry tetrahydrofuran to give the methyl ester 9 in 52 % yield. Compound 9: mp 98-100° C (recrystallised from CH_2Cl_2/ether); IR: (CH_2Cl_2) 1770, 1745, 1700, 1520, 1350 cm^{-1}; NMR ($CDCl_3$) 3.20 (1H, dd, J = 16, 2.5 Hz), 3.64 (1H, dd, J = 16, 5.5 Hz), 3.78 (3H, s), 3.92 (1H, d, J = 20 Hz), 4.35 (1H, d, J = 20 Hz), 5.20 (1H, dd,

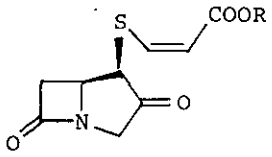
J = 2.5,5.5Hz), 5.30 (2H, s), 6.12 (1H, d, J = 10 Hz), 7.24 (1H, d, J = 10 Hz), 7.58 (2H, d, J = 9 Hz), 8.24 (2H, d, J = 9 Hz) ppm.

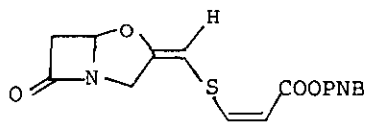
Hydrolysis[13] of the methyl ester 9 was achieved by treatment with 1 N sodium hydroxide solution and the free acid 10 was thus obtained in quantitative yield as an amorphous solid. Compound 10: IR (KBr) 3540, 1750, 1735, 1685, 1520 and 1340 cm^{-1}; NMR (DMSO) 3.04 (1H, dd, J = 16, 2.5 Hz), 3.46 (1H, dd, J = 16, 5 Hz), 3.68 (1H, d, J = 20 Hz), 4.08 (1H, d, J = 20 Hz), 5.22 (1H, dd, J = 2.5, 5 Hz), 5.32 (2H, s), 6.12 (1H, d, J = 10 Hz), 7.45-8.30 (5H, m) ppm.

Finally the diazoketone 11 was obtained in 73 % yield from the free acid 10 using triethylamine, isobutyl chloroformate and ethereal diazomethane in dry CH_2Cl_2. Compound 11: mp 102-104° C (recrystallised from CH_2Cl_2/ether); IR (CH_2Cl_2) 2060, 1765, 1700, 1645, 1520 and 1350 cm^{-1}; NMR ($CDCl_3$), 3.08 (1H, dd, J = 16, 2.5 Hz), 3.60 (1H, dd, J = 16, 5 Hz), 3.64 (1H, d, J = 19 Hz),4.24 (1H, d, J = 19 Hz), 5.22 (1H, dd, J=2.5,5 Hz), 5.30 (2H, s), 5.36 (1H,s), 6.30 (1H, d, J = 10 Hz), 7.26 (1H, d, J = 10 Hz), 7.56 (1H, d, J = 9 Hz), 8.24 (2H, d, J = 9 Hz) ppm.

Decomposition of the diazoketone 11 with a catalytic amount of copper (II) acetylacetonate in refluxing benzene afforded a racemic diastereomeric mixture of *carbapenam ketones* 12 and 13 (IR (CH_2Cl_2) 1775, 1700, 1570, 1520 and 1345 cm^{-1}) in 33 % yield in the ratio of 8:1 respectively. In addition to compounds 12 and 13, an oxapenam derivative 16 (52 % yield, mp 138-40°, recrystallised from CH_2Cl_2/ether, IR (CH_2Cl_2) 1795, 1695, 1645, 1560, 1520 and 1340 cm^{-1}) was also obtained in the above reaction.







12 R = PNB
14 R = Na

13 R = PNB
15 R = Na

16

Compound 12: NMR ($CDCl_3$) 3.13 (1H, dd, J = 16, 1.7 Hz), 3.41 (1H, dd, J = 18.5, 1.2 Hz), 3.44 (1H, dd, J = 7.6, 0.8 Hz), 3.72 (1H, ddd, J = 16, 5, 1.2 Hz), 3.84 (1H, ddd, J = 1.7, 5, 7.6 Hz), 4.23 (1H, dd, J = 18.5, 0.8 Hz), 5.28 (2H, s), 6.08 (1H, d, J = 10 Hz), 7.26 (1H, d, J = 10 Hz), 7.54 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz) ppm.

Compound 13: NMR ($CDCl_3$) 3.26 (1H, dd, J = 18.5, 1.2 Hz), 3.36 (1H, dd, J = 16, 1.7 Hz), 3.46 (1H, ddd, J = 16, 5, 1.2 Hz), 3.62 (1H, d, J = 6.5 Hz), 4.26 (1H, d, J = 18.5 Hz), 4.28 (1H, ddd, J = 1.7, 5, 6.5 Hz), 5.28 (2H, s), 6.10 (1H, d, J = 10 Hz), 7.28 (1H, d, J = 10 Hz), 7.54 (2H, d, J = 9 Hz), 8.22 (2H, d, J = 9 Hz) ppm.

Compound 16: NMR ($CDCl_3$): 3.13 (1H, dd, J = 17, 0.5 Hz), 3.57 (1H, ddd, J = 17, 2.5, 0.8 Hz), 3.82 (1H, ddd, J = 16, 1.8, 0.8 Hz), 4.68 (1H, dd, J = 16, 1.8 Hz), 5.30 (2H, s), 5.73 (1H, dd, J = 2.5, 0.5 Hz), 5.78 (1H, t, J = 1.8 Hz), 5.96 (1H, d, J = 10 Hz), 7.08 (1H, d, J = 10 Hz), 7.55 (2H, d, J = 9 Hz), 8.25(2H, d, J = 9 Hz) ppm.

Carbapenam carboxylates 14 and 15 were prepared by hydrogenolysis of the p-nitrobenzyl esters 12 and 13 using 10 % Pd/C and were found to be biologically inactive.

To our knowledge this is the first synthesis of a carbapenam involving the formation of the 1,5-bond as the ultimate step and extension of this method to the biologically active thienamycin analogues is in progress.

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References and Notes

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10. Compound 7 was prepared from p-nitrobenzyl propiolate and thiourea using conditions mentioned in ref. 11.

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12. Such alkylations were carried out earlier[8] using strong bases like sodium hydride.

13. We observed that methyl esters of type 9 could be hydrolysed quantitatively to the corresponding free acids at 0° C in a few minutes in the presence of 1·5 equivalents of sodium hydroxide solution. In contrast to our method Oida and co-workers[8] employed much more severe conditions (i.e., pyridine, lithium iodide, 3 hr heating at 110° C) for the hydrolysis of such esters.

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