SYNTHESIS OF NEW OXAPENAMS AND CARBAPENAMS

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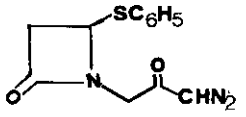
Abstract - Diazoketones derived from 4-thioazetidinon-1-yl-acetic acids, on metal-catalysed decomposition, gave either carbapenams and/or oxapenams depending upon the nature of the substituent present on the thio function. Synthesis of a novel oxapenam carboxylic acid 16 which exhibited potent β-lactamase inhibitory properties comparable to clavulanic acid is described.

Copper-catalysed decomposition of some monocyclic azetidinone diazoketones possessing either an arylthio group or an alkylthio group at position-4 was recently reported by Oida, Yoshida and Ohki[1]. They observed the formation of 2-arylthiomethylene oxapenam 3 in the former case and an oxocepham 4 in the latter instance. Recently we reported[2] the formation of a mixture of carbapenams 6 and 7 and an oxapenam 8 in



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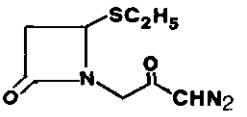

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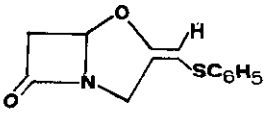

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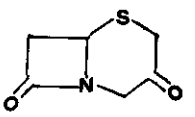

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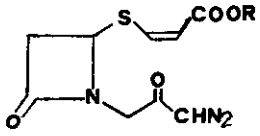

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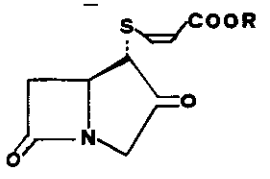

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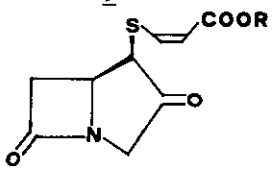

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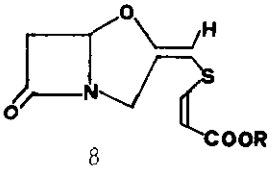


8

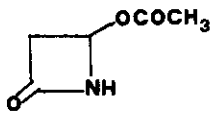
R = p-nitrobenzyl

the decomposition of diazoketone 5. We would now like to present some of the results with monocyclic azetidinone diazoketones possessing different mercaptan substituents at position-4.

β-MERCAPTOACRYLATE GROUP

Employing the procedures described earlier[2] for the synthesis of compound 5, diazoketone 13 was prepared in four steps starting from azetidinone 9. Thus treatment of 9 with cis-β-carboallyloxyvinylisothiuronium chloride[3] in the presence of aqueous NaOH yielded the mercaptoazetidinone 10, which on alkylation followed by hydrolysis afforded the free acid 12. The mixed anhydride, prepared from the free acid 12, gave the diazoketone 13 on treatment with diazomethane.

As with compound 5, diazoketone 13 on copper (II) acetylacetonate catalysed decomposition gave oxapenam 14; IR(CH_2Cl_2): 1765, 1695 and 1645 cm^{-1}; NMR($CDCl_3$): 3.08 (1H, dd, J = 0.5 and 17 Hz), 3.49 (1H, ddd, J = 0.8, 2.5 and 17 Hz), 3.72 (1H, ddd, J = 0.8, 1.8 and 16 Hz), 4.67 (1H, dd, J = 1.8 and 16 Hz), 4.68 (2H, m), 5.18-5.50 (2H, m), 5.61 (1H, dd, J = 0.5 and 2.5 Hz), 5.70 (1H, t, J = 1.8 Hz), 5.70-6.22 (1H, m), 5.93 (1H, d, J = 10 Hz), and 7.02 (1H, d, J = 10 Hz) ppm; and a diastereomeric mixture of 2-ketocarbapenams 15 in 52 % and 20 % yield respectively. Hydrogenolytic cleavage of the p-nitrobenzyl group from compound 8 with 10 %



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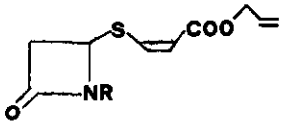
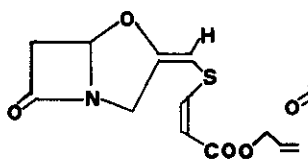


10 R = H

11 R = CH_2COOCH_3

12 R = CH_2COOH

13 R = CH_2COCHN_2



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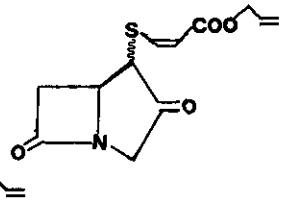
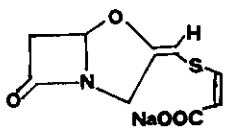


15

Pd/C in methanol yielded the free acid, which upon treatment with one equivalent of $NaHCO_3$ solution, followed by chromatography on LiChroprep RP-18 (Merck) using water as an eluent afforded the sodium salt 16; IR(KBr): 1780, 1655 and 1600 cm^{-1}; in 33 % yield. Deprotection[4] of the allyl group in compound 14 using sodium 2-ethylhexanoate, Pd-$(PPh_3)_4$ and triphenylphosphine in CH_2Cl_2 gave a much better yield (76 %) of compound 16. Under the above conditions, we also obtained in trace amounts an isomeric compound, IR(KBr): 1785, 1655 and 1600 cm^{-1}, for which structure 17 was assigned on the basis of the following NMR data.



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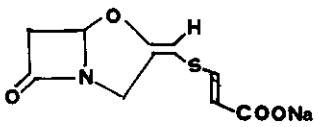
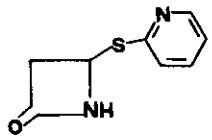


17

Compound-16 NMR(D_2O)	Compound-17 NMR(D_2O)
3.14 (1H, dd, J = 0.7 and 17 Hz)	3.19 (1H, dd, J = 0.7 and 17 Hz)
3.58 (1H, ddd, J = 1, 2.7 and 17 Hz)	3.62 (1H, ddd, J = 1, 2.7 and 17 Hz)
3.73 (1H, ddd, J = 1, 2 and 16 Hz)	3.84 (1H, ddd, J = 1, 2 and 16 Hz)
4.68 (1H, dd, J = 2 and 16 Hz)	4.71 (1H, dd, J = 2 and 16 Hz)
5.73 (1H, dd, J = 0.7 and 2.7 Hz)	5.75 (1H, dd, J = 0.7 and 2.7 Hz)
5.78 (1H, t, J = 2 Hz)	5.62 (1H, t, J = 2 Hz)
5.86 (1H, d, J = 10 Hz)	5.84 (1H, d, J = 15 Hz)
6.77 (1H, d, J = 10 Hz)	7.26 (1H, d, J = 15 Hz) ppm.

THIA-HETEROCYCLES

With the intention of investigating the effect of the thia-heterocycles at position-4 on the reaction course during the decomposition of monocyclic diazoketones, we initially attempted the alkylation of examples 18 and 19 using methyl bromoacetate. Under the above conditions only the thioalkylated products, (pyridine-2-yl)-thioacetic acid methyl ester and (benzothiazol-2-yl)-thioacetic acid methyl ester were isolated in quantitative yields. This prompted us to look for an alternative method for the preparation of compounds 22-26. Methyl 4-chlorazetidinone-1-yl-acetate 21 was discovered to be a useful precursor to these derivatives. Chlorinolysis of the azetidinone 20[1] gave the desired intermediate 21 in quantitative yield, which upon treatment with various heterocyclic thiols in the presence of finely powdered KOH and tetrabutylammonium bromide in dry THF resulted in the formation of the mercaptoazetidinones in good yields. Hence, compounds 22-26[6] were prepared by this way (Table-1).



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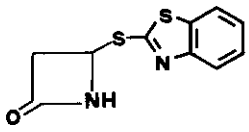

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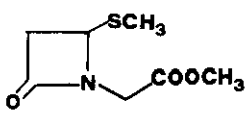

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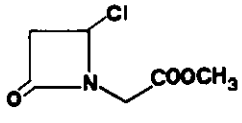

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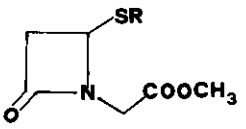
Table-1 Spectral and analytical data of compounds 22-26



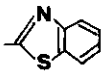
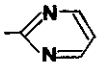
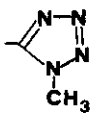
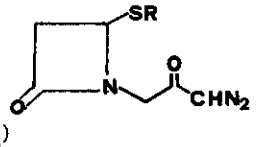
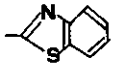
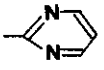
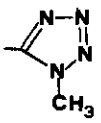
Compd.	R	Yield (%)	IR(CH_2Cl_2)	NMR($CDCl_3$)
22 (foam)		82	1775, 1750	3.12(1H,dd,J=2.5,15), 3.64(1H,dd,J=5,15 Hz), 3.77(3H,s),3.96(1H,d,J=18 Hz),4.38(1H,d, J=18 Hz), 5.92(1H,dd,J=2.5,5 Hz) and 7.18-7.90(4H,m) ppm.
23 (oil)		70	1765, 1745	3.03(1H,dd,J=2.5,17 Hz), 3.30-4.40(7H,m), 3.78(3H,s), 5.71(1H,dd,J=2.5,5 Hz) ppm.
24 (oil)		62	1765, 1740	3.08(1H,dd,J=2.5,15 Hz), 3.56(1H,dd,J=5.15 Hz), 3.78(3H,s), 3.80(1H,d,J=18 Hz), 4.32(1H,d, J=18 Hz), 5.81(1H,dd,J=2.5,5 Hz) and 6.99-8.36(4H,m) ppm.
25 (oil)		69	1760 1745	3.14(1H,dd,J=2.5,16 Hz), 3.64(1H,dd,J=5,16 Hz), 3.76(1H,d,J=18 Hz), 3.85(3H,s), 4.40(1H,d, J=18 Hz), 5.85(1H,dd,J=2.5,5 Hz), 7.12(1H,t, J=5 Hz) and 8.56(2H,d,J=5 Hz)ppm.
26 (oil)		67	1775, 1745	3.18(1H,dd,J=2.5,17 Hz), 3.74(1H,dd,J=5,17 Hz), 3.80(3H,s), 4.00(3H,s), 4.03(1H,d,J=18 Hz), 4.36(1H,d,J=18 Hz) and 5.83(1H,dd,J=2.5, 5 Hz) ppm.

Table-2 Spectral and analytical data of compounds 27-31

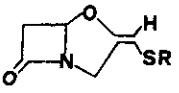


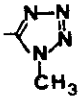
Compd.	mp	R	IR(CH_2Cl_2)	NMR($CDCl_3$)
27*	169-70°C		2060, 1770, 1650	3.28(1H,dd,2.5,17 Hz), 3.72(1H,dd,J=5,17 Hz), 3.94(1H,d,J=18 Hz), 4.33(1H,d,J=18 Hz), 5.86(1H,dd,J=2.5,5 Hz), 6.19(1H,s) and 7.40-8.16(4H,m) ppm.
28	oil		2060, 1765, 1640	3.08(1H,dd,J=2.5,17 Hz), 3.30-3.75(3H,m), 3.90(1H,d,J=18 Hz), 4.05-4.35(3H,m), 5.50(1H,s), 5.72(1H,dd,J=2.5,5 Hz) ppm.
29	oil		2065,1765, 1645	3.12(1H,dd,2.5,17 Hz), 3.56(1H,dd,J=5,17 Hz), 3.85(1H,d,J=18 Hz), 4.32(1H,d,J=18 Hz), 5.64(1H,s), 5.90(1H,dd,J=2.5,5 Hz) and 6.96-8.38(4H,m) ppm.
30	oil		2060, 1760, 1640	(not recorded)
31	foam		2060, 1765, 1645	3.20(1H,dd,J=2.5,17 Hz), 3.78(1H,dd,J=5,17 Hz), 4.00(3H,s), 4.10(1H,d,J=18 Hz), 4.31(1H,d, J=18 Hz), 5.38(1H,s) and 5.76(1H,dd,J=2.5,5 Hz) ppm.

*NMR in DMSO

The preparation of the diazoketones 27-31 (Table-2) from the corresponding azetidinones 22-26 was performed using the conditions mentioned earlier. Thermal decomposition of the diazoketones 27-31 in benzene containing a catalytic amount of copper (II) acetylacetonate gave the respective oxapenams 32-36 (Table-3). However, no other products were isolated from these reactions. In the NMR spectra (Table-4)

Table-3

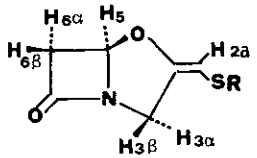


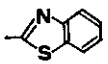
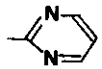
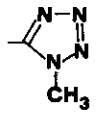
Compd	mp	R	Reaction time (hrs)	Yield (%)	IR(CH_2Cl_2)
32	143-45°		5	58	1795 and 1640 cm^{-1}
33	oil		5	15	1795 and 1645 cm^{-1}
34	95-96°C		4	15	1795 and 1645 cm^{-1}
35	oil		4	20	1795 and 1645 cm^{-1}
36	oil		1	17	1795 and 1645 cm^{-1}

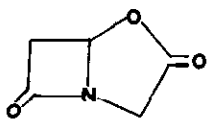
of the oxapenams 32-36 the vinylic proton absorbed in the region 5.69-5.92 ppm indicating that the double bond in all the examples has the E-geometry. These chemical shifts are in good agreement[1] with those reported for the vinylic proton in phenylthiomethyleneoxapenam[7].

Ozonolysis of compound 32 in ethyl acetate yielded a novel 2-oxo-1-oxapenam 37; oil; IR(CH_2Cl_2): 1815 and 1800 cm^{-1}; NMR($CDCl_3$): 3.30 (1H, dd, J = 0.95 and 17.15 Hz), 3.55 (1H, 3 x d, J = 0.89, 1.13 and 17.44 Hz), 3.65 (1H, 4 x d, J = 0.2, 1.13, 2.97 and 17.15 Hz), 4.27 (1H, 3 x d, J = 0.2, 0.4 and 17.44 Hz)and 5.72 (1H, 4 x d, J = 0.4, 0.89, 0.95 and 2.97 Hz) ppm; ^{13}C NMR($CDCl_3$): 174.5 (CO), 172.5 (CO), 84.9(CH), 47.8 (CH_2) and 46.2 (CH_2) ppm. Compound 37 was volatile and unstable in protic solvents.

Table-4 H-NMR spectral data of compounds 32-36



Compound No	R	Chemical Shifts (ppm)						Coupling Constants (Hz)						
		2	3α	3β	5	6α	6β	2a,3α	2a,3β	3α,3β	3α,6α	5,6α	5,6β	6α,6β
32		5.82	3.80	4.78	5.71	3.50	3.12	2	2	16	1	2.5	0.6	17
33		5.85	3.78	4.75	5.68	3.49	3.11	2	2	16	1	2.5	0.7	16
34		5.84	3.75	4.72	5.67	3.49	3.11	2	2	16	1	2.5	0.7	16
35		5.92	3.74	4.70	5.67	3.49	3.12	2	2	16	1	2.5	0.5	17
36		5.69	3.90	4.80	5.71	3.52	3.10	2	2	16.2	1	2.7	0.8	16.6



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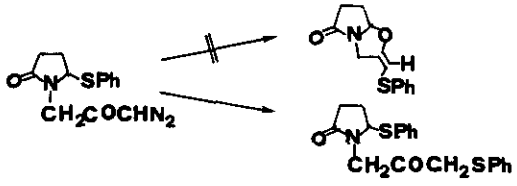
The formation of different bicyclic derivatives in the metal-catalysed decomposition of various 4-thio-substituted monocyclic azetidinones could be rationalised through a common S-ylid intermediate[1]. This may, depending on the nature of the substituent R, give rise to an array of products[8].

The oxapenam derivative 16 was found to be highly potent as a β-lactamase inhibitor compared to clavulanic acid[7]. Compounds 32-36 also inhibited several types of β-lactamases under the same in vitro screening.

ACKNOWLEDGEMENT: The authors are grateful to Messrs. K. Adlgasser and P. Kneussel for their excellent technical assistence and to Dr. G. Schulz and his co-workers for the interpretation and recording of the NMR spectra.

REFERENCES AND NOTES:

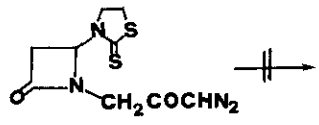
1. S.Oida, A. Yoshida and E. Ohki, Heterocycles, 1980, 14, 1999.
2. K.Prasad, G.Schulz, C.P.Mak, H.Hamberger and P.Stütz, Heterocycles, 1981, 16, 1305.
3. In contrast to the azetidinone diazoketones that are described in this communication, pyrrolidinone diazoketones failed to give any of the corresponding bicyclic products under the metal-catalysed thermal decomposition conditions. The only isolable product in low yield as the monocyclic derivative is shown below.



4. All the new compounds that are described in this communication showed the expected analytical and spectral properties.

5. P.D.Jeffrey and S.W.MaCombie, J.Org.Chem., 1982, 47, 587.

6. In the reaction of chloroazetidinone 21 with different heterocyclic thiols we obtained also the respective 4-N-substituted azetidinones as by-products. The diazoketone derived from one of these side-products failed to give any product on refluxing in benzene with copper (II) acetylacetonate.



7. Further corroboration for the geometry of this molecule has recently been established by X-ray analysis. The results pertaining to this study were conducted in this Institute and will appear in a future communication.

8. Different products that arise in these reactions as well as those that are formed with substituents such as thioacyl and thiobenzyl groups will be reported in a forthcoming communication.

9. T.T.Howarth, A.G.Brown and T.J.King, J.Chem.Soc.Chem.Commun., 1976, 266.

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