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A NEW METHOD FOR THE SYNTHESIS OF α-AMINO-β-LACTAMS

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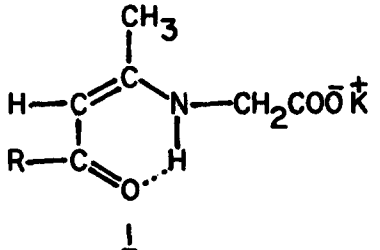
Presence of an α-amido side chain on a cis β-lactam is an essential feature for the antibacterial activity of the Penicillins and Cephalosporins. Several years ago Sheehan[1] demonstrated the use of phthalimidoacetyl chloride for the formation of phthalimido-β-lactams where phthalimido group serves as the progenitor of the amino- or amido function. Later, Bose and associates[2] demonstrated the use of azidoacetyl chloride for making α-azido-β-lactams. The azido group could then be reduced to an amino function. An alternative to this was then reported by these workers[3] mentioning the use of benzyloxycarbonylglycyl chloride for the preparation of α-amido-β-lactams. However, the yields of the products in many cases were reported to be in the range of 10-20% only.

During the course of our investigations towards β-lactam antibiotics, we have explored a new and convenient method for the synthesis of α-amino-β-lactams. An α-acylamino acid when converted into the corresponding chloride, always tends to form the azalactone. So, direct synthesis of α-amido-β-lactams from imines is not possible. We, therefore, planned to use the enamine derivative (1) of an amino acid. Glycine on condensation[4] with a β-dicarbonyl compound leads to a product of high stability due to hydrogen bonding. We have been successful in using this enamine derivative of the amino acid for the annelation of imines to the corresponding β-lactams through our recently developed $POCl_3$ method.[5]



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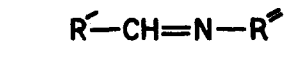
(a) R = OC_2H_5

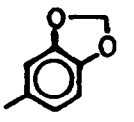
(b) R = CH_3

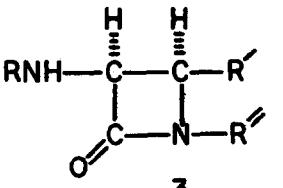


2

(a) R′ = C_6H_5 ; R″ = C_6H_5

(b) R′ = p-$CH_3OC_6H_4$; R″ = p-$CH_3C_6H_4$

(c) R′ =  ; R″ = p-$CH_3C_6H_4$



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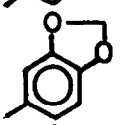
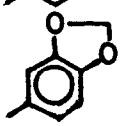
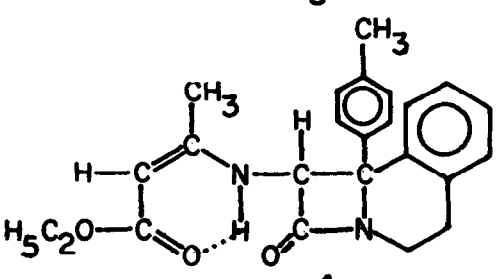
	R	R′	R″
(a)	$-C(CH_3)=CHCOOC_2H_5$	C_6H_5	C_6H_5
(b)	H	C_6H_5	C_6H_5
(c)	$-C(CH_3)=CHCOOC_2H_5$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
(d)	H	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
(e)	$PhOCH_2CO$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$
(f)	$-C(CH_3)=CHCOOC_2H_5$		p-$CH_3C_6H_4$
(g)	H		p-$CH_3C_6H_4$
(h)	$PhOCH_2CO$		p-$CH_3C_6H_4$
(i)	$-C(CH_3)=CHCOCH_3$	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$



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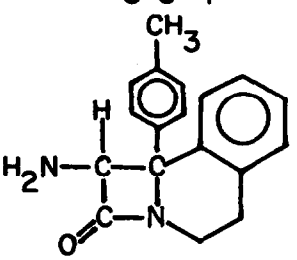

5

One step synthesis of 3-enamino-2-azetidinone (3a) was achieved by the reaction of $POCl_3$ on a mixture of the potassium salt (1a) and the imine (2a) in the presence of triethylamine. Thus the reaction is carried out by the slow addition of $POCl_3$ (one mole) to a mixture of one mole each of the potassium salt and the imine alongwith two moles of triethylamine in dichloromethane. Obviously there is no need of making any acid chloride or mixed anhydride of the acid component. Moreover, the yields of the products are in the range of 35 to 45% or higher. Similarly the enamido-β-lactams (3c) and (3f) could be obtained from the salt (1a) and imines (2b) and (2c) respectively. We were also successful in reacting (1b) with (2b) to obtain (3i) in 35% yield. In all of these cases we obtained the cis stereochemistry of the β-lactams as shown by the NMR spectrum. The C_4-H appeared as a doublet in the range of τ4.85-5.02 with the required cis coupling (J=5-6 H_z).

Further confirmation of their structures as well as cis stereochemistry became apparent by converting them into the corresponding 3-amino- or 3-amido-β-lactams. The β-dicarbonyl function in (3a, 3c, 3f and 3i) was easily cleaved by stirring the compounds in a mixture of ethanol-HCl (2:1) at room temperature. Thus (3a) gave (3b) in high yield and was found identical to the one already reported.[2] The α-amino-β-lactam (3d) obtained after removing the protecting group from (3c) or (3i) was acylated with phenoxyacetyl chloride to give phenoxyacetamido-β-lactam (3e). The compound (3e) is identical in all respects to the compound synthesised earlier[6] having a cis stereochemistry of H-3 and H-4.

This method was also successful in synthesising the bicyclic systems. The cepham (4) was obtained from the corresponding 3,4-dihydroisoquinoline[7] and (1a) in 45% yield. Its structure was confirmed by IR and NMR spectra. Treatment of (4) with HCl in ethanol easily converted this compound into the α-amino-cepham (5). The cepham (5) obtained by this method was identical with one prepared through the azidoacetyl chloride method.[8] By using different N-protected amino acids the present method should result in the stereospecific synthesis of a variety of new β-lactams.

All the new compounds reported in this communication showed satisfactory elemental and spectral analysis.

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