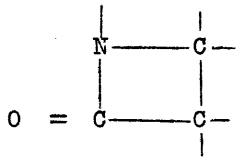
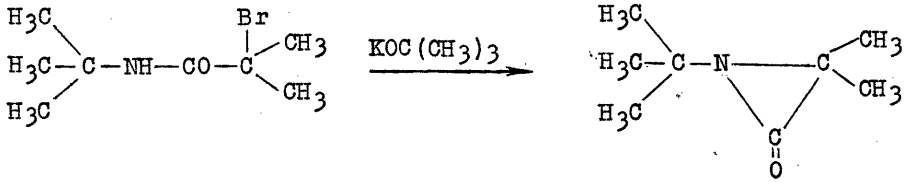
INTRODUCTION

Four membered heterocyclic ring compounds (I) containing an amide function are commonly known as β -lactams.



I

Till recently these azetidin-2-ones were thought to be the smallest cyclic systems capable of accommodating an amide function. Sheehan[1] has reported the synthesis of an α -lactam, 1-t-butyl-3-3-dimethyl aziridinone (III) by the dehydrobromination of 2-bromo-N-t-butyl-2-methyl propionamide (II) with potassium t-butoxide. A number of α-lactams have since been prepared[2,3] and their properties studied.[4,5]



II III

The presence of the β -lactam ring :

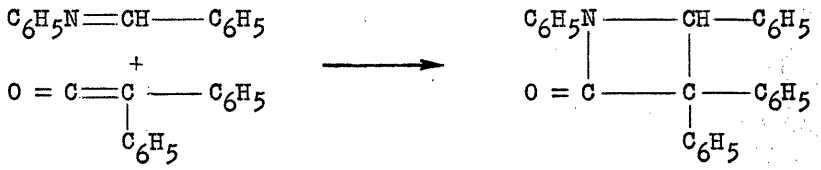
(i) as the active moiety in penicillin,

(ii) a constituent of the antibiotic cephalosporin-c[6],

(iii) a constituent of the major steroidal alkaloid of Pachysandra terminalis[7]

and its utility as a monomer in polyamide formation, renewed the interest of chemists in the field of these lower cyclic amides.

These four membered heterocyclic ring compounds were virtually unknown until Staudinger[8] synthesised the first β-lactam in 1907 and definitely established it to be 1, 3, 3, 4-tetra-phenyl-azetidin-2-one (IV) by allowing benzalaniline to react with diphenyl ketene.



IV

Earlier to this work of Staudinger few others[9-14] have assigned β-lactam structure to their compounds but their claims were not adequately substantiated.

From the time Staudinger synthesised the first β-lactam to the discovery of the presence of this ring system in penicillin, there was but sporadic interest in the field. When the potential utility of penicillin in the treatment of infected war wounds or as a prophylactic agent became obvious, the chemistry of these lower cyclic amides became the subject of intensive and extensive investigation both in U.K. and U.S.A. and valuable information was obtained on both the monocyclic β-lactams and the bicyclic β-lactams (fused with the thiazolidine ring).

The literature concerning β-lactams and the list of compounds that have been prepared upto 1947, have been fully reviewed in the monographs entitled "The Chemistry of Penicillin"[15] published in U.S.A. and "Antibiotics"[16] published in England. Subsequently King[17] has presented an account of all the work published till the end of 1948 in his famous Tilden memorial lecture. Sheehan and Corey[18] have summed up all the work done till 1952 in their chapter entitled "The synthesis of β-lactams" in Organic Reactions Vol. IX.

The various methods that have been developed till the end of 1947 for the synthesis of β-lactams can be summarised as follows:

(i) addition of ketenes to compounds containing $>C=N-$ bonds,

(ii) the cyclisation of β-amino acid esters to β-lactams by means of Grignard reagents,

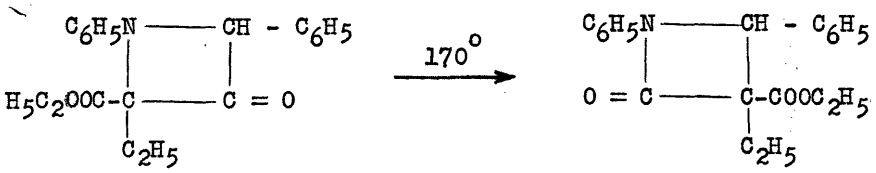
(iii) cyclisation of β-amino and β-acylamino acids, and

(iv) action of α-haloketones and zinc on Schiffs bases.

A number of β-lactams have been prepared by Staudinger and coworkers[19] by the combination of ketenes and imines. This method does not seem to be a general one as the compound (V) when reacted with benzalaniline gave the product (VI) instead of the β-lactam (VII). However, it rearranged to the desired compound on heating to 170°C.

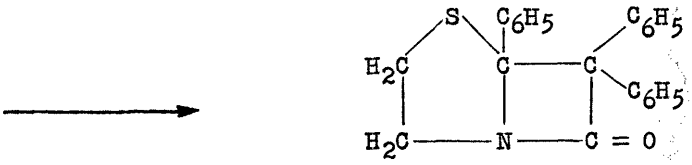
$$H_5C_2OOC - \underset{\underset{C_2H_5}{|}}{C} = C = O \quad + \quad C_6H_5N = CHC_6H_5 \longrightarrow$$

V



VI VII

This method was successfully employed during the penicillin synthesis programme for making thiazolidine β -lactams of which (VIII) is an example.[20]



VIII

A synthesis of 1, 3, 3, 4, 4-pentaphenyl azetidin-2-one (X) by reacting two moles of diphenyl ketene with one mole of nitroso-benzene was reported by Staudinger and Jelagin.[21] The formation of (IX) as an intermediate from one mole of the ketene and one mole of nitrosobenzene was suggested, and this then reacted with another mole of ketene to give the β -lactam (X).