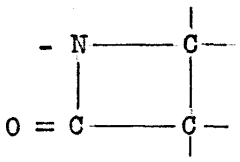
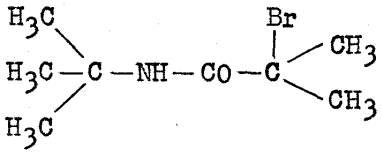
INTRODUCTION

Till recently the four membered heterocyclic ring compounds were considered to be the smallest cyclic systems that were capable of accommodating the amide function. These azetidin-2-ones are commonly known as "β-lactams" (I). Sheehan[1] has reported in a recent communication the synthesis of an α-lactam, 1-t-butyl-3,3-dimethyl aziridinone (III) by dehydrobromination of 2-bromo-N-t-butyl-2-methyl propionamide (II) with potassium t-butoxide.

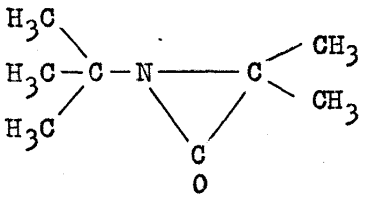


I



II

$KOC(CH_3)_3$



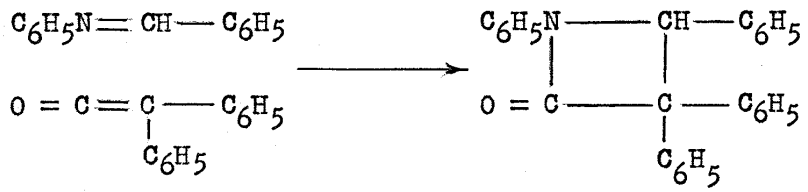
III

The fused β-lactam-thiazolidine structure of penicillin has greatly accelerated the interest of chemists in the hitherto limited field of lower cyclic amides with particular reference to β-lactams. This interest was further renewed by the finding that the antibiotic cephalosporin-c also

contains the β -lactam ring[2], as well by the discovery that some members of this family show interesting physiological activity[3]. It has been recently demonstrated that the β -lactams are also useful as monomers for the preparation of polyamides[4].

The physical and chemical properties of these compounds diverge sharply, partially as a result of ring strain, from those of acyclic amides and lactams of greater ring size. As these cyclic amides are unusually susceptible to reactions involving the carbonyl group, the conventional methods of lactam syntheses fail in the formation of β -lactams and some special and unique methods were developed to build up these compounds.[5,6]

The first β -lactam (IV) was synthesised by Staudinger[7] in 1907 by allowing benzalaniline to react with diphenyl ketene.



IV

Earlier to this work of Staudinger few others[8-13] 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 this field. Since then the chemistry of these lower cyclic amides became the subject of intensive and extensive investigation, both in U.S.A. and in U.K.; and a wealth of data was obtained on both the monocyclic β-lactams and the bicyclic β-lactams (fused with thiazoline 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"[14] published in U.S.A. and "Antibiotics"[15] published in England. Subsequently King[16] has presented an account of all the work published till the end of 1948 in his famous Tilden memorial lecture. Sheehan and Corey[17] have summed up all the work done till 1952 in their chapter entitled " The Synthesis of β-lactams" in Organic Reactions, Volume IX, p.388.

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

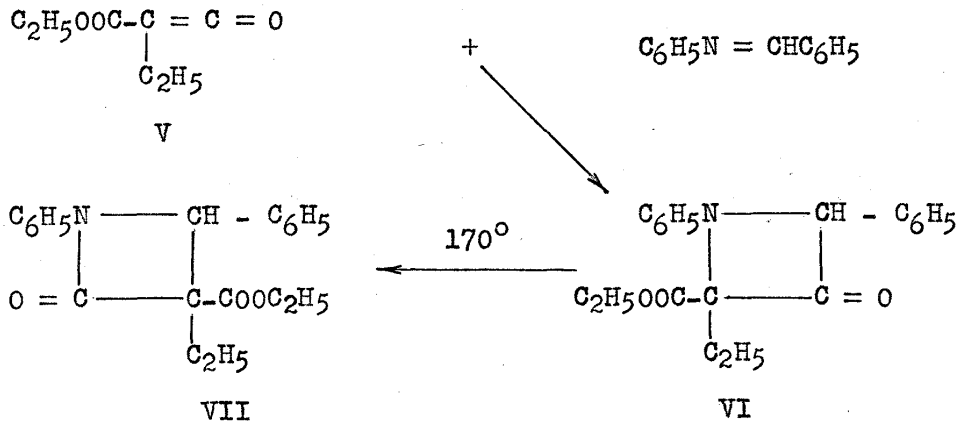
i) Addition of ketene to compounds containing $\rangle C = N -$ bonds.

ii) The cyclisation of β-amino acid esters to β-lactams[18] by means of Grignard's reagents.

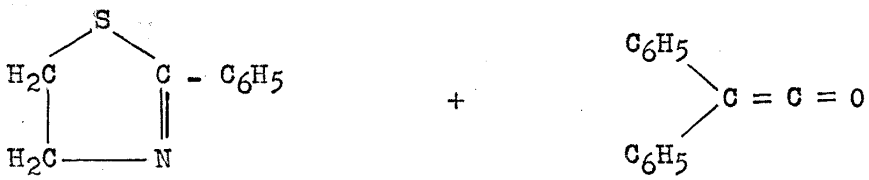
iii) Cyclisation of β-amino and β-acylamino acids.

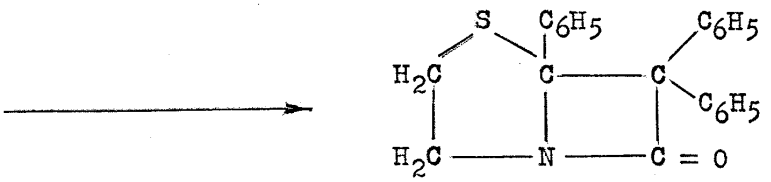
iv) Action of α-haloketones and zinc on Schiff's bases.

A number of β-lactams have been prepared by Staudinger and co-workers[19] by the direct 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 β-lactam (VII) on heating to 170°C.



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





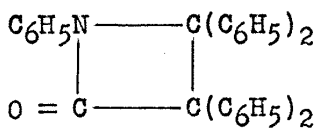
VIII

A synthesis of 1, 3, 3, 4, 4 - pentaphenyl azetidin-2-one (X) by reacting two moles of diphenyl ketene with one mole of nitrosobenzene 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 reacts with another mole of the ketene to give the β - lactam (X).

$$C_6H_5N = O \quad + \quad (C_6H_5)_2C = C = O \longrightarrow$$

$$[\ C_6H_5N = C(C_6H_5)_2 + CO_2\ ] \xrightarrow{(C_6H_5)_2C = C = O}$$

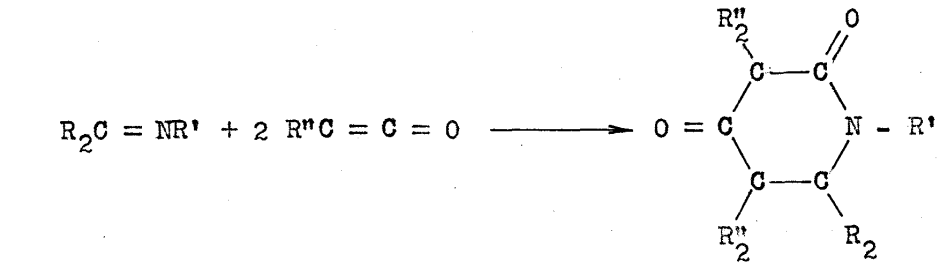
IX



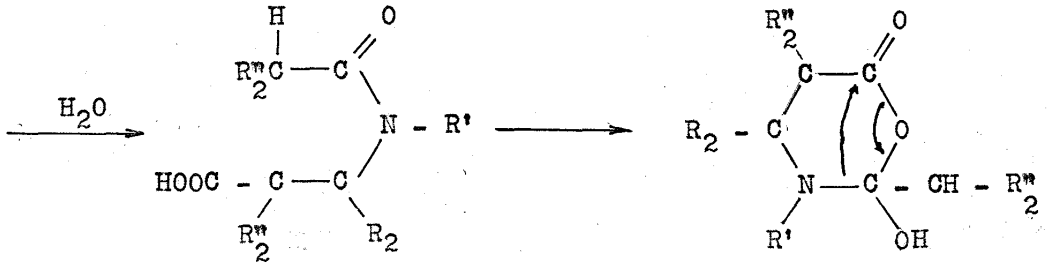
X

Staudinger has shown that hydrolysis of piperidine diones (XI), obtained from two moles of a ketene and one mole of an imine, proceeds readily and yields the β -acylamino

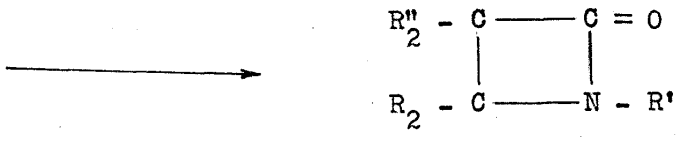
acids (XII) which can be cyclised to β-lactams (XIII) according to the following scheme :



XI



XII



XIII

This method has been successfully extended for the synthesis of certain fused β-lactam-thiazolidines such as (XIV)[22].