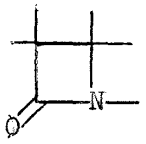
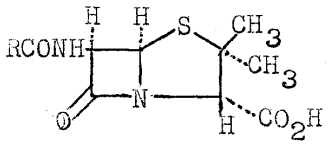
INTRODUCTION

The four membered heterocyclic system, known as β-lactam or 2-azetidinone (I) has acquired importance since the discovery of penicillin[1] (II). Interest in this class of heterocycle continues unabated because of isolation of new β-lactam antibiotics from time to time, such as cephalosporin[2] (III), clavulanic acid[3] (IV) and complex antibiotic family bleomycins[4] etc. More recently thienamycin[5] (V), an exceptionally potent broad spectrum antibiotic and nocardicins[6] A and B, two novel biologically active monocyclic β-lactam antibiotics have been discovered.



(I)



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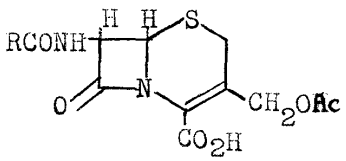

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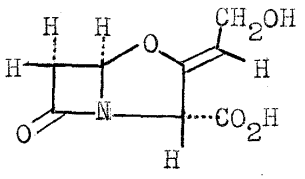

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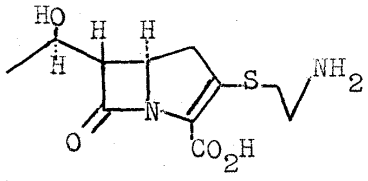
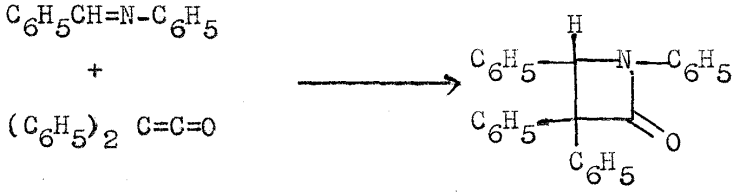


(V)

Most of these β-lactam antibiotics have deceptively

simple structure. Yet in many cases the structures are unique and synthetically challenging because the β-lactam rings in most cases are fragile under many reaction conditions. It undergoes scission in presence of nucleophilic reagents and is also prone to molecular rearrangements.

The earliest claims to compounds containing β-lactam moeity from workers like Mayor, Einhorn and others[7-11], were not adequately substantiated. Staudinger[12] in 1907 synthesised the first authentic β-lactam (VI) by reacting benzalaniline with diphenyl ketene.



(VI)

Since then a great deal of work has been devoted to the development of these lower cyclic amides, particularly by the workers of the Anglo-American program on penicillin. Complete reviews upto 1947 are available in "The Chemistry of Penicillin"[1] and "Antibiotics"[13]. King[14] has given a full account of all published work on the subject till 1948 in his famous Tilden memorial lecture. A review of literature by Sheehan and Corey[15] contains different synthetic routes developed upto 1952.

In recent year many reviews on the synthesis[16-19], reactions[20,21] and chemistry of β-lactam antibiotics[22,23] have appeared in literature.

The wealth of data thus compiled shows a marked difference between the chemical and physical properties of the β-lactams and those of the lactams of larger ring size and open chain amides. As a result, most of the synthetic routes to higher cyclic amides failed to lead to β-lactam. Consequently, new and unique methods had to be devised for their synthesis[24,25].

The various methods developed for the synthesis of β-lactams can be summarised as follows :

(i) The Ketene-Imine reaction. A ketene, either pre-synthesised or made in situ, is added to compounds with a C=N moeity.

(ii) Cycloaddition of Isocyanate to Olefins.

(iii) Cyclisation of β-Amino acids.

(iv) Cyclisation of β-Halo-amides.

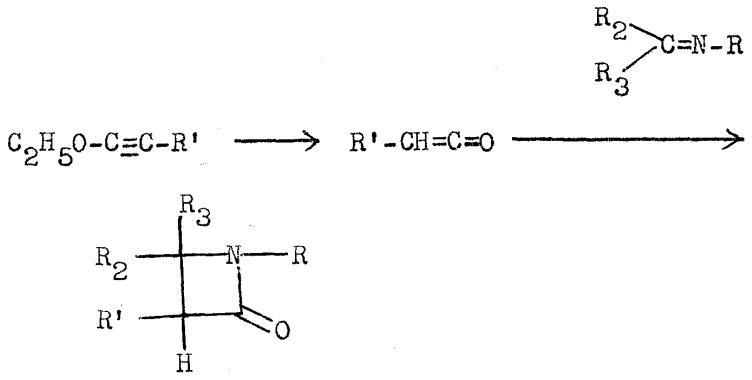
(v) Photolysis of α-Diazo compounds.

(vi) Miscelleneous synthesis.

Cycloaddition of Ketene to Imine remains a popular route to β-lactams forming C_2-N and C_3 - C_4

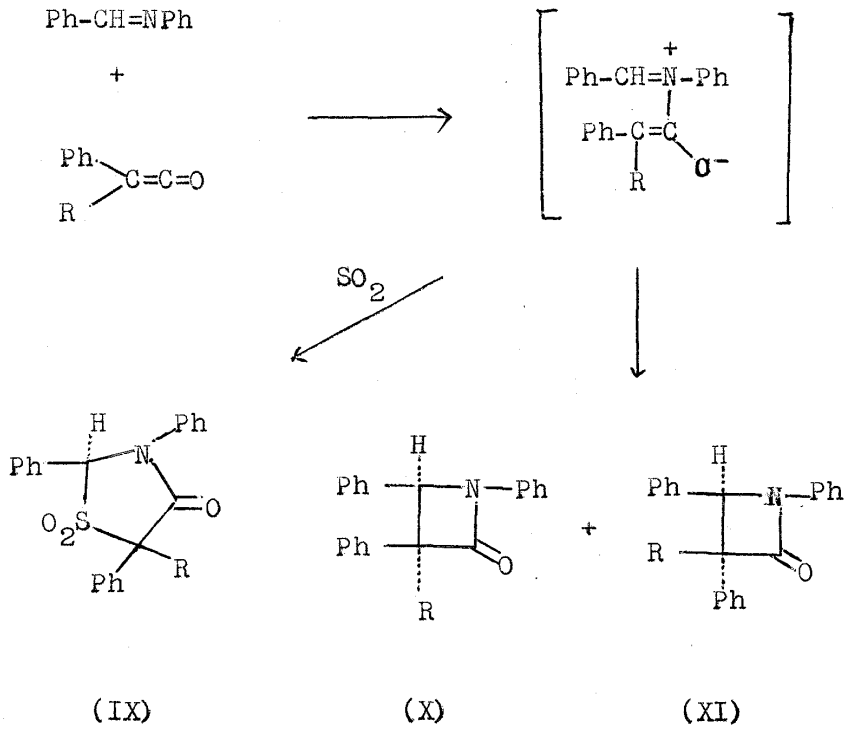
bonds simultaneously. Various β-lactams have been synthesised using structurally different Ketenes[15,16] and imines. The structural requirements of imines are difficult to define because of the lack of consistency in the results obtained from different procedures. Phenylhydrazine, imidoyl-chloride and O-alkyloximes do not give 2-azetidinones[26,27]. The method however has been successfully employed for the synthesis of monocyclic[16], polycyclic[18] and even spiro-β-lactams[28].

A synthetic ketene may be employed in this reaction or the ketene may be generated in situ by dehydrohalogenation of substituted acetyl chlorides in presence of base such as triethylamine, pyridine etc. Ketene obtained on photolysis[29] or thermolysis[30] of diazoketones have also been employed for the synthesis of 2-azetidinones. Leusen and Arens[31] have shown that at elevated temperature acetylenic ethers react with inines via ketene intermediate to form β-lactams (VII).



(VII)

Both cis- and trans- β-lactams have been isolated from the interaction of acid chloride and immine in presence of base[32,33]. The mechanism is presumed to involve in situ formation of ketene which immediately reacts with the imine to give the dipolar intermediate (VIII). Good evidence for the intermediate has been obtained by the isolation of the adduct[34] (IX) from the reaction of imine with ketene in liquid sulphur dioxide. The proposed mechanism, involving step-wise addition, may theoretically lead to both cis- and trans-β-lactam (X,XI).

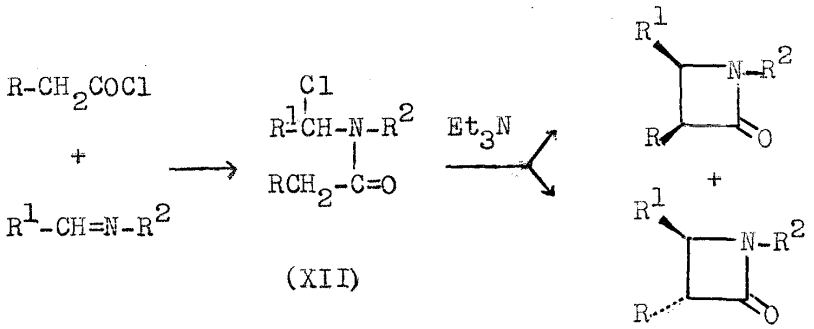


(IX) (X) (XI)

The amount of cis- β-lactam[35] (X) formed increased with the bulk of the ketene substituent R- and this has been interpreted in terms of dipolar intermediate (VIII). The effect of changing aromatic substitution in the imine on the stereochemistry of the product has also been investigated[36] in an attempt to find systems which give a high proportion of cis- β-lactams.

A certain amount of steric control can also be exercised on the products of this reaction by changing the experimental conditions[37]. Thus addition of acid chloride to a mixture of imine and triethylamine generally gave more cis- than trans- product. The major product obtained when triethylamine was added to a mixture of imine and acid chloride, was the trans isomer.

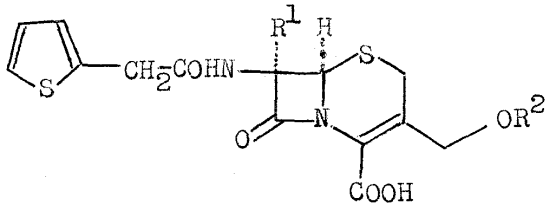
In the absence of triethylamine, however the reaction of acid chloride with imine lead to the reversible formation of the amide[38], (XII) followed by ring closure. The mode of ring closure depends on the conditions used.



(XII)

The acid chlorides that have been used for β-lactam synthesis include dichloracetyl chloride[39], cyanoacetyl chloride[40], phenylcyanoacetyl chloride[41], methoxyacetyl chloride[37], substituted-malonyl chloride[42], azido-acetyl chloride[37], azidopropionyl chloride[32], phthalimidoacetyl chloride[43] succinimidoacetyl chloride[44] and few heterocyclic-substituted acetyl chlorides[45].

Phthalimiodoacetyl chloride and azidoacetyl chloride, however, have been extensively used since they provide a convenient pathway to a suitably situated amino function. This method has been successfully employed for the synthesis of penicillin derivatives[46] and cephalosporin analogues[47]. Such useful antibiotics as Cephalothin[48] (XIII) and Cefoxitin[49] (XIV) are now totally synthetic products.

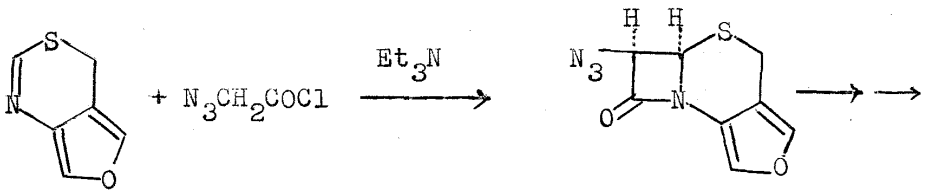


(XIII) R^1=H, R^2=AC

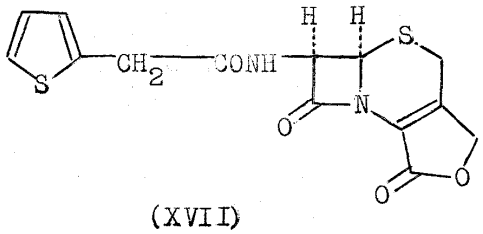
(XIV) R^1=OMe, R^2=$CONH_2$

A novel and totally synthetic route to (±) desacetylcephalothin lactone[50] (XVII) has been recently reported. The key step in the synthetic route was

reaction of azidoacetyl chloride/triethylamine with 4-H-furo-(3,4-d)-1,3-thiazine (XV) to give the furo-(3,4)-cepham (XVI).

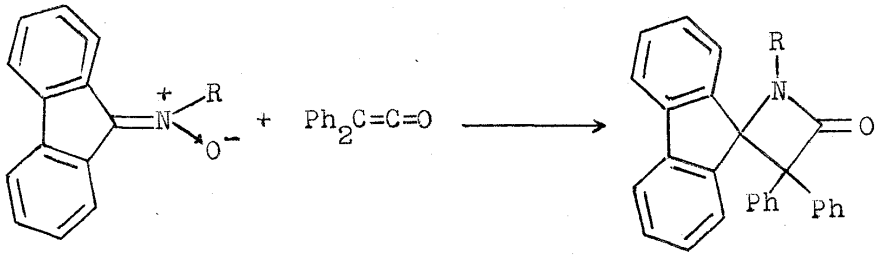


(XV) (XVI)



(XVII)

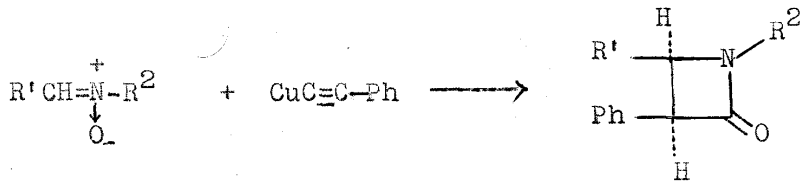
Recently two novel routes to β-lactams from nitrones have been reported. Diphenyl ketene reacts with a variety of N-alkylnitrones (XVII) to give 2-azetidinones (XIX) as one of the products. It is thought that nitrones undergo initial



(XVIII) (XIX)

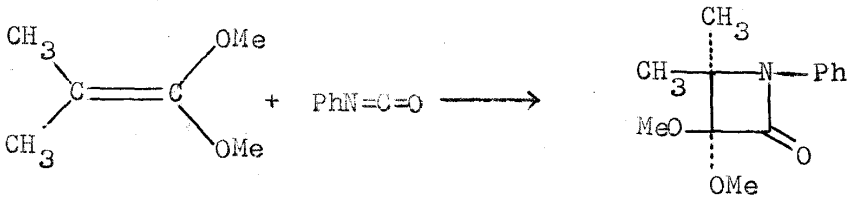
deoxygenation to imines necessary for the β-lactam synthesis[51].

A stereospecific route to β-lactams, which appears to be the first example of exclusive formation of cis 2-azetidinone (XXI), utilises the reaction of copper (I) phenylacetylide with nitrones[52] (XX).



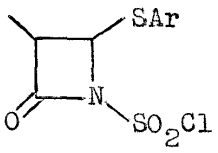
(XX) (XXI)

Cycloaddition of isocyanate to olefins is also a versatile method for the synthesis of 2-azetidinones. The addition of trichloroacetyl isocyanate to dienes[53], phenyl isocyanate to dienes[54] and enamines[55], and p-nitrophenyl isocyanate to styrene[56] lead to the formation of 2-azetidinone derivatives. Various aryl, aroyl and arene sulfonyl isocyanate have been reacted with alkenes[57] and vinyl ethers[58] to give β-lactam derivatives. Aryl-isocyanate[59] however have been found to react only with activated olefins such as (XXII) to form β-lactams (XXIII).

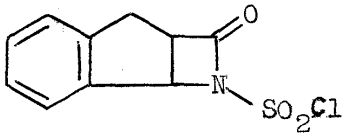


(XXII) (XXIII)

The highly reactive N-chlorosulphonyl-isocyanate has been extensively used in cycloaddition reactions with alkenes. Thus reactions of CSI with vinylthioethers[60] and with indene[61] give the N-chlorosulphonyl β-lactams (XXIV) and (XXV) respectively.

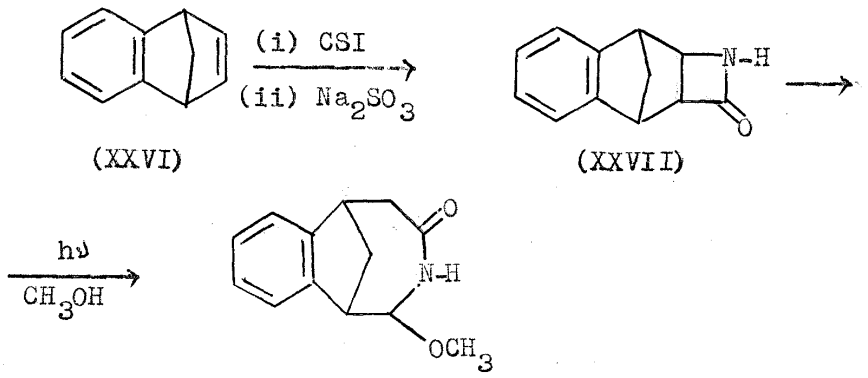


(XXIV)



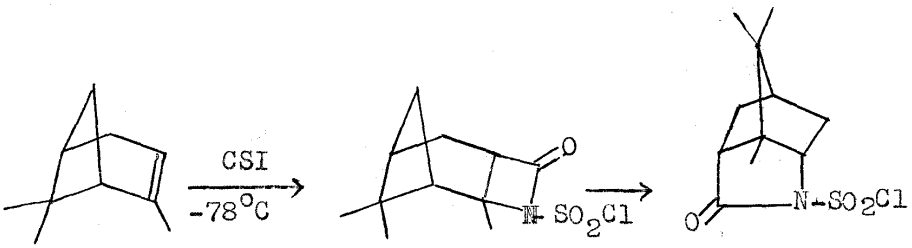
(XXV)

Some of the β-lactams prepared by this method have been subjected to interesting rearrangements. The reaction of (XXVI) with CSI followed by sodium sulphite gives β-lactam (XXVII) which can undergo photoinduced ring expansion to (XXVIII) in methanol.



(XXVI) (XXVII) (XXVIII)

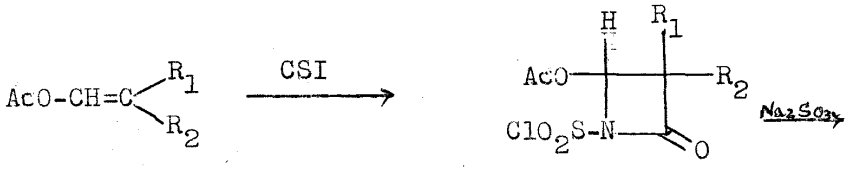
∝-Pinen reacts with CSI to give initially the β-lactam (XXIX), which overnight at room temperature readily rearranges to γ-lactam[63] (XXX).



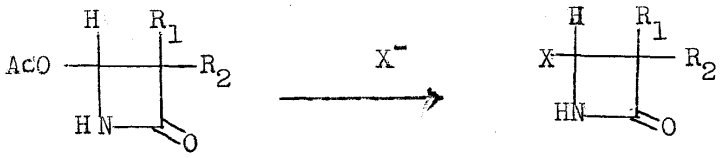
(XXIX) (XXX)

Vinyl ester (XXXI) undergo cycloaddition reaction with CSI to form 4-acyloxy-2-azetidinone derivative[64] (XXXII). The synthetic importance of this reaction arises from the fact that the acyloxy group can be readily replaced by variety of nucleophiles such as RSO_2^-, N_3^-,

RO^-, and RS^- to form corresponding 2-azetidinones derivatives (XXXIV). The displacement occur with recemization[65].

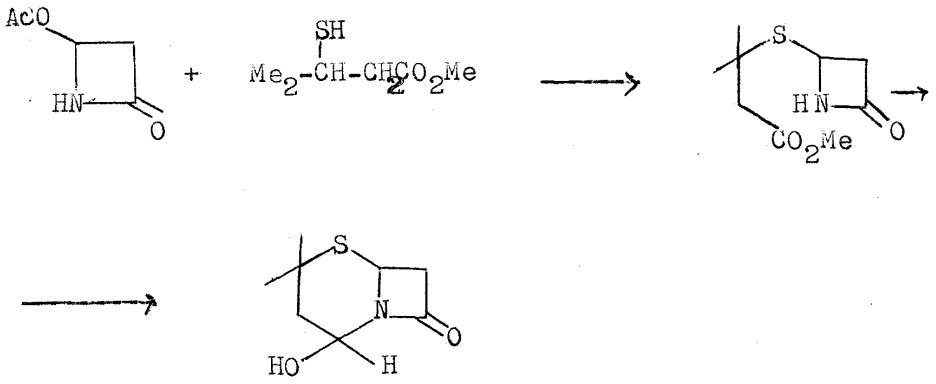


(XXXI) (XXXII)



(XXXIII) (XXXIV)

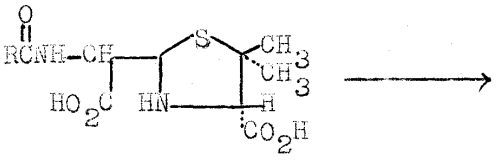
Recently this reaction has been extended to synthesis of bicyclic system[66] (XXXV).



(XXXV)

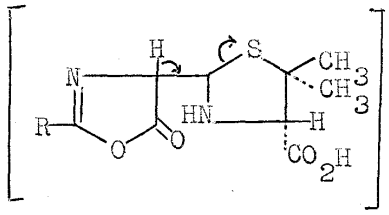
In principle the β-lactam synthesis can be accomplished by the formation of one, two, three or all four bonds of the ring during the cyclisation step. Of these four possibilities all but last have been realised. Also of the routes to β-lactam in which only one bond is formed during cyclisation, the formation of C_2 - C_3 bond has yet to be achieved.

Though β-amino-acids readily undergo cyclisation to β-lactams in presence of acetic anhydride[67], acetyl chloride[68], thionyl chloride[69], phosphorous trichloride[67] etc., all attempts to synthesize penicillin by cyclodehydrohalogenation of suitable β-amino acid derivatives failed because of azlactonization followed rearrangement to penicillenic acid (XXXVI).

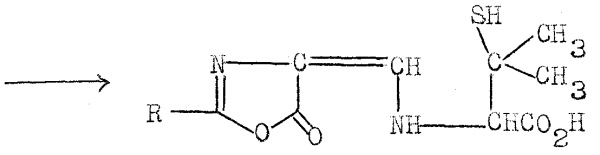


Penicillanic acid

(XXXVI)

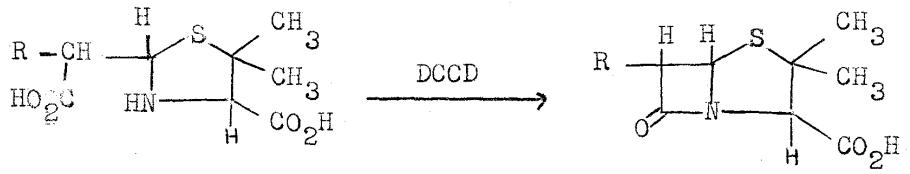


Thizolidine-Oxazolone Structure



(XXXVII)

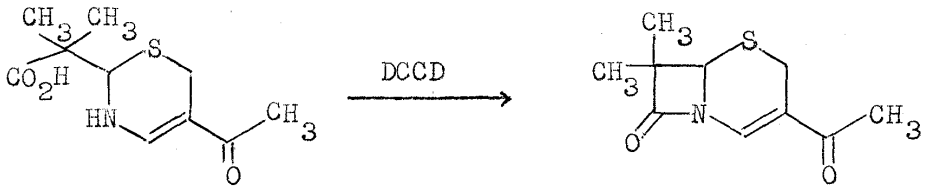
The difficulty was overcome by Sheehan and coworkers[70] by carrying out cyclodehydration of suitable β-amino acids with carbodiimides.



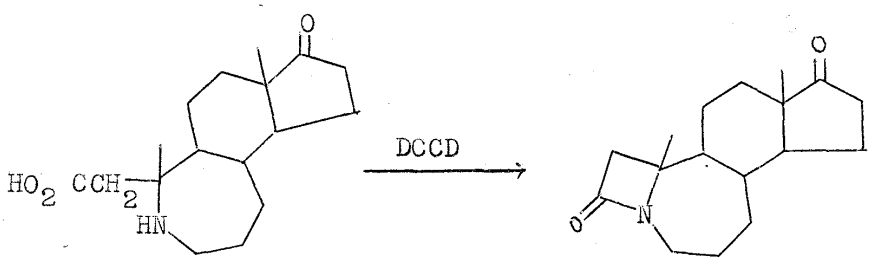
(XXXVIII) (XXXIX)

These workers have successfully extended this method for the synthesis of 6-aminopenicillanic acid which has resulted in the introduction of many synthetic and semi-synthetic penicillins in medicine.

Many other polycyclic β-lactams such as cephalosporin analog[71] (XL), steroidal β-lactam[72] (XLI) etc. have also been successfuly prepared by this novel route.

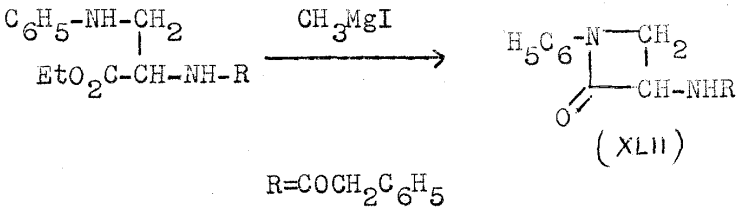


(XL)



(XLI)

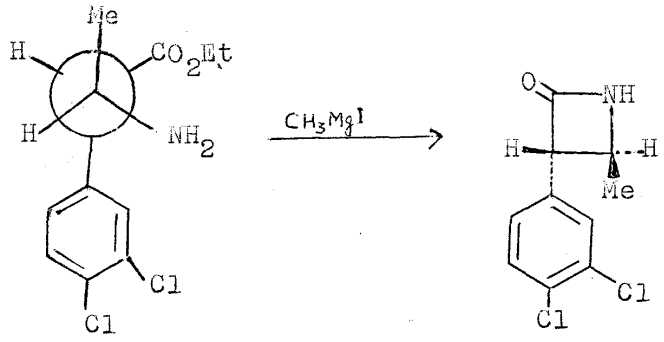
Breckpot[73] synthesis of β-lactams involves the cyclisation of β-amino esters using Grignard reagents. This method was applied with success by Pfizer group[74] for the synthesis of 1,3-diphenyl-2-azetidinone and by the Merk group[75] for the synthesis the following acylamino β-lactam (XLII).



(XLII)

R=$COCH_2C_6H_5$

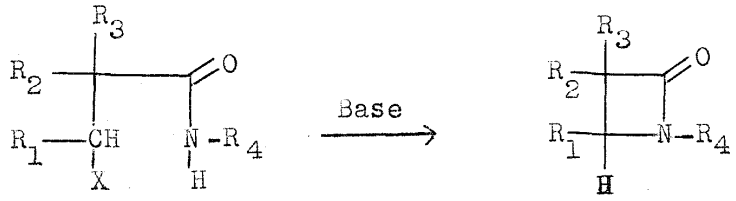
The stereochemistry of cyclisation of β-amino esters with organometallic reagents has recently been investigated. The threo form of the ester (XLIII) gives the azetidinone where as the erythro form does not react[76].



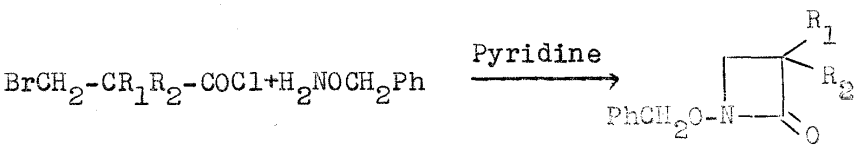
(XLIII) (XLIV)

Of the routes to β-lactam in which one bond is formed during cyclisation, the formation of N -C_4 bond has been achieved by cyclodehydrohalogenation of β-halo-amides. This intramolecular displacement of halogen by amide nitrogen has been carried out in presence of such bases as sodium hydride[77], potassium t-butoxide[78], alkali metal amides in liquid ammonia[79], lithium carbonate[80], amines in dimethyl formamide[81] etc.

Knunyant[82] et al have reported the synthesis of large number of β-lactams using alkali metal in liquid ammonia.

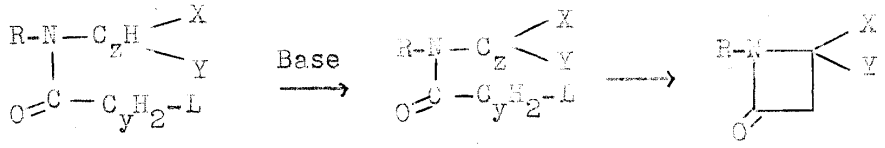


It has however been shown that the cyclisation could be brought about by weaker bases using higher temperature[83]. The synthesis of 1-alkoxy-2-azetidinone (XLV) was carried out in presence of pyridine[84].



(XLV)

Sheehan and Bose[85,86] made a major break-through in the synthesis of substituted β-lactams by cyclisation of α-haloacylaminomalonic esters(XLVI). The reaction appears to be general for N-substituted-aminomalonic esters N-acylated with α-halo-acids and the yields obtained are invariably high[86]. It is however restricted to the preparation of β-lactams possessing one or two electron withdrawing functions at C_z to provide necessary carbanionic centre for committing nucleophilic displacement on C_y possessing the leaving group.



(XLVI) (XLVII) (XLVIII)

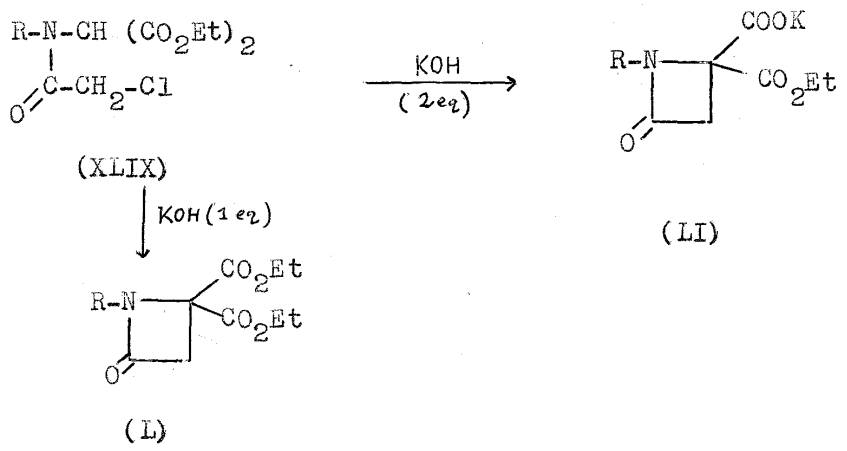
R=Aryl, L=Halogen, X=Y=CO_2Et ; X=COPh, Y=H

X=Ph , Y=CO_2Et etc.

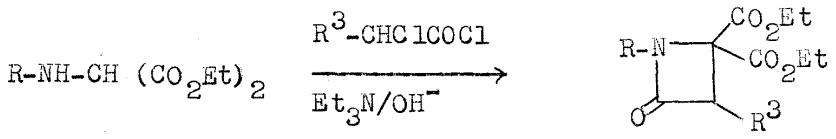
This method has been widely used for the synthesis of large number of β-lactams and also their ring homologs viz. γ- and δ-lactams[87].

The nature of basic reagents depends upon the activation exerted by group X and Y.

Extending the Sheehan and Bose synthesis, Chatterjee[88a-i] et al. were able to cyclise to amidomalonate (XLIX) to the lactams (L) with one equivalent of base in about 10 min. and to the corresponding monoacids (LI) with an excess of potassium hydroxide in one hour.

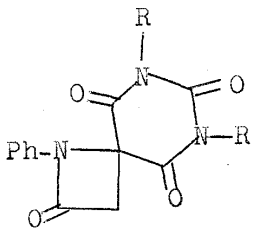


A substituted aminomalonate (LII) can be converted to β-lactam (LIII) in one step, by reacting with appropriate haloacetyl halide and excess of triethylamine at room temperature for three days or alcoholic potassium hydroxide in 10 minutes[89].

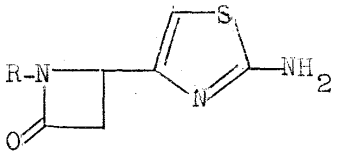


(LII) (LIII)

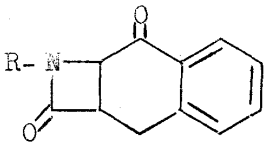
This versatile method has been extended for the synthesis of a number of interesting β-lactams such as spirobarbirate[90](LIV), thiazoline derivative[91] (LV) and polycyclic β-lactam[92] (LVI).



(LIV)



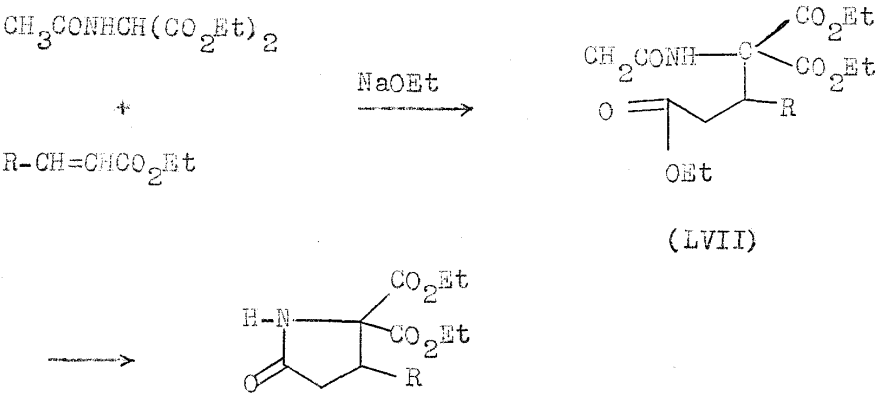
(LV)



(LVI)

Cocolas and Hartung[93] have shown that glutamic ester derivatives (LVII) obtained by Michael addition of ethyl acetamidomalonate to β-substituted acrylic esters

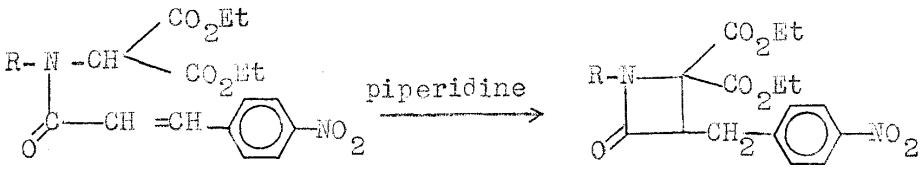
undergo cyclisation to γ-lactam (LVIII) in moderate to good yield.



(LVII)

(LVIII)

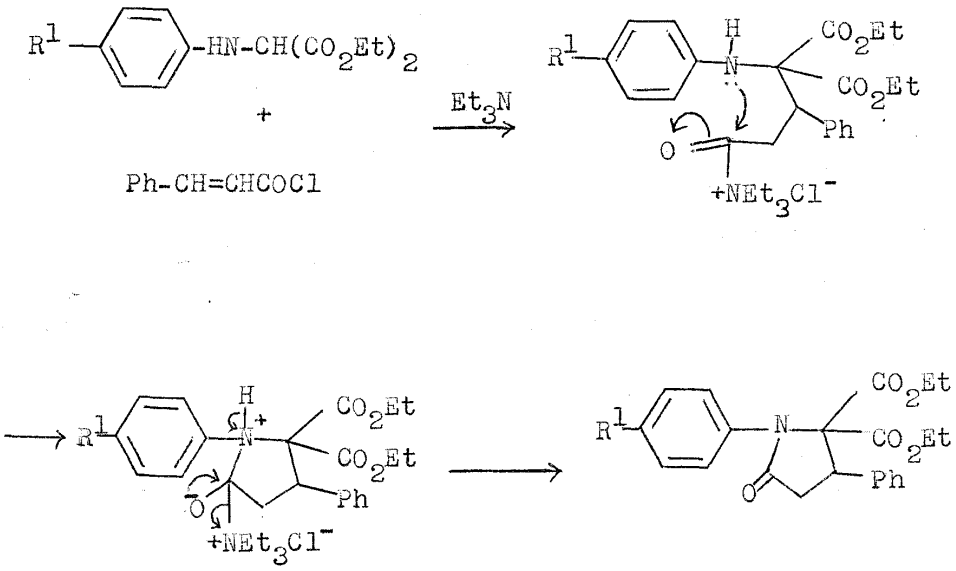
Recently Bose and coworker[94] have reported the isolation of one β-lactam derivative (LX) from a suitable acrylamide (LIX) via. intramolecular Michael addition under influence of piperidine.



(LIX) (LX)

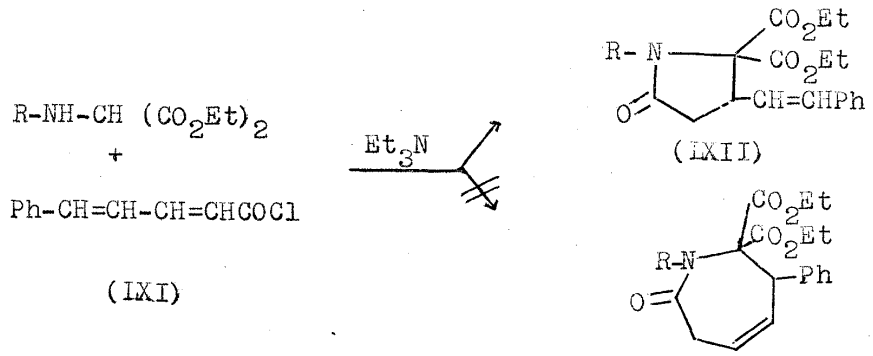
Extensive work on intramolecular Michael addition leading to lactam formation has been carried out by

Chatterjee and Sahu[95]. They have subsequently developed an unique route to γ-lactams involving inter-molecular Michael addition followed by intramolecular amidification. This method has been shown to be very general in applicability and yields are invariably high, and also this appears to be the only instance when an acylhalide has been used as a Michael acceptor.

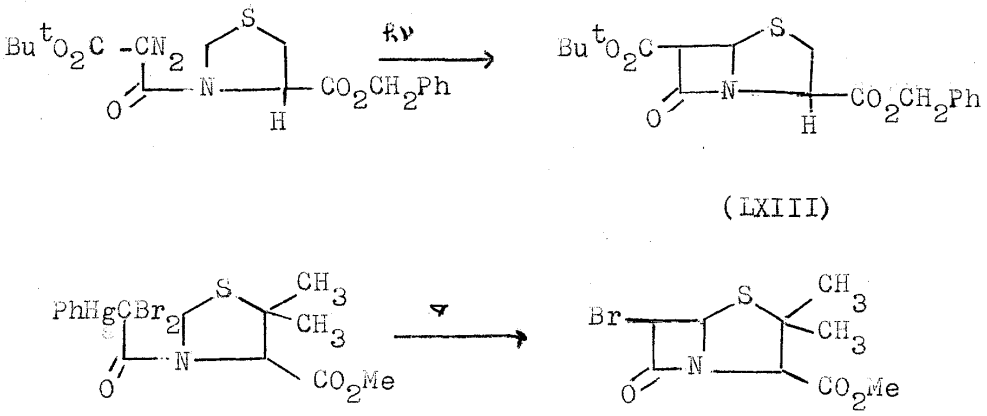


R^1 = H, CH_3, Cl, Br, NO_2, CO_2Et

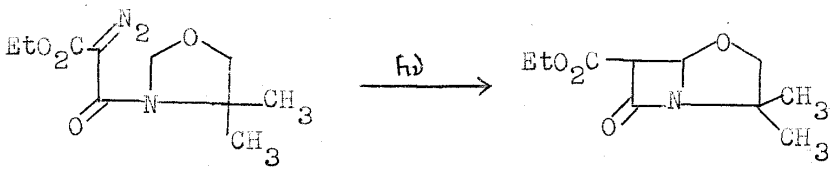
It is interesting to note here that when β-styrylacrylolyl chloride was used as Michael acceptor, the product was a five membered rather than a seven membered cyclic amide.



Photolysis of diazo-compounds as well as thermolysis of certain mercury derivatives are known methods of carbene generation. Both these methods have been utilized for the synthesis of penam derivatives[96,97] (LXII, LXIV).

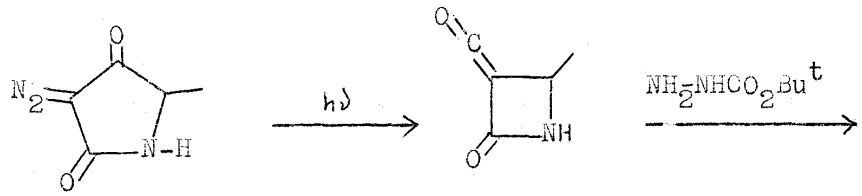


The Oxapenam[98] (LXVI) which is unusually susceptible to nucleophilic cleavage, has been prepared by photolysis of N-(ethoxycarbonyldiazoacetyl)-4,4-dimethyloxazolidine (LXV).

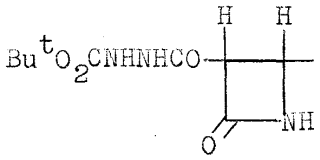


(LXV) (LXVI)

Photolytic Wolff rearrangement of the diazodione (LXVII) has been used in a new synthesis of β-lactams[99], the intermediate ketene (LXVIII) being trapped with t-butylcarbazate.

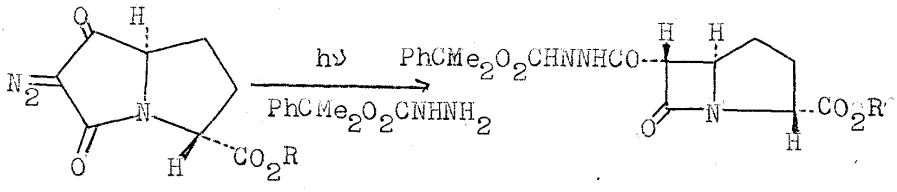


(LXVII) (LXVIII)



(LXIX)

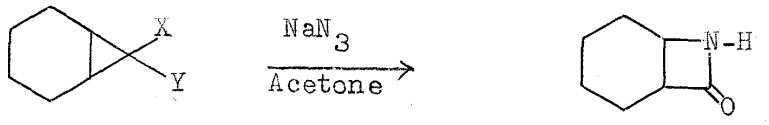
Similar reaction with bicyclic diazodione (LXX) gave carbpenam derivative[100] (LXXI).



(LXX) (LXXI)

The literature records a large number of miscellaneous methods used for the synthesis of β-lactams.

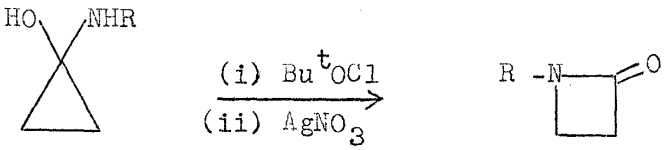
Norcarane derivative (LXXII) on treatment with sodium azide gave 2-azetidinone (LXXIII) in high yield[101].



(LXXII) (LXXIII)

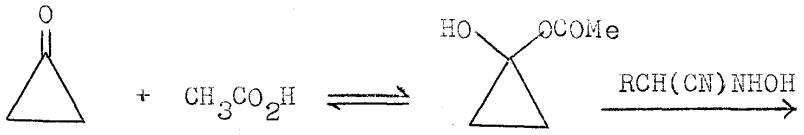
X, Y =  , -OH, -OMe

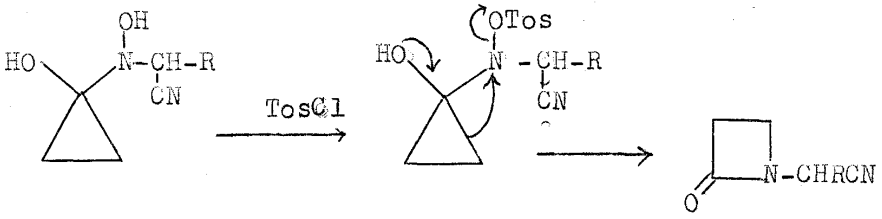
Carbinolamines (LXXIV), prepared in situ, have been ring expanded by sequential treatment with t-butyl hypochlorite and silver nitrate, to give 2-azetidinone[102](LXXV).



(LXXIV) (LXXV)

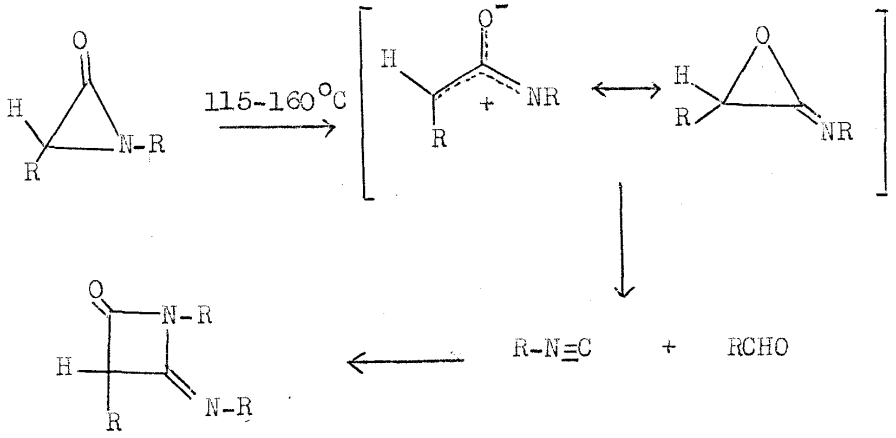
Tosylation of the hydroxylamine (LXXVI) prepared from cyclopropanone, results in smooth rearrangement to the β-lactams[103] (LXXVII).





(LXXVII)

∝-lactams can be converted to β-lactam on pyrolysis[104]. The mechanism is thought to involve formation of the isocyanide (LXXVIII) which adds to the ∝-lactam to give (LXXIX).



(LXXIX) R= 1-adamantyl

In view of the interesting physical, chemical and biological properties of β-lactams, tremendous academic and practical interest have been generated throughout the world on synthesis of β-lactams. It was decided to undertake the present investigation with the aim of synthesizing some novel compounds containing isolated and or fused β-lactams.