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β-LACTAMS: RETROSPECT AND PROSPECT

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Abstract—Interest in β-lactams as a class was prompted by the discovery of penicillin and cephalosporin, and this interest continues unabated because of the therapeutic importance of β-lactam antibiotics and recent finding of new naturally occurring β-lactams. As a result of vigorous research, a vast literature has accumulated over the years, and the chemistry of β-lactams continues to be a blossoming field. In this article, an attempt has been made to evaluate critically this prolific development, and the chemistry of β-lactams is presented in an integrated form and in its proper perspective under the following headings.

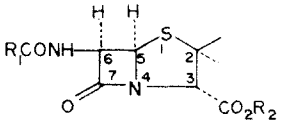
A. INTRODUCTION

β-Lactams are 4-membered cyclic amides derived from 3-amino propanoic acids. Though the first member was synthesised by Staudinger[1] in 1907, the β-lactams as a class acquired importance since the discovery of penicillin[2] which contains a β-lactam unit as an essential

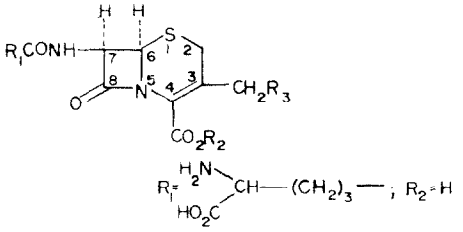
structural feature of its molecule. The importance of penicillin lies in its capacious potency against several bacteria. It should be mentioned that researches on penicillin played a very important role in the development of organic chemistry and related branches of science, and the whole gamut of refined preparative methods, discovery of new reagents and techniques, and the use of some of the esoteric physical methods as diagnostic tools have widened the horizon of organic chemistry. The novelty of β-lactam structure, the ensemble of diverse reactions and rearrangements[3] of β-lactam antibiotics,[4-6] the challenge posed by the drug resistance in several susceptible bacteria and consequent need for improving the therapeutic value[7-9] of the available β-lactam antibiotics have been responsible for the abiding interest in this class of compounds, and recent discovery of several naturally occurring β-lactams has rekindled this interest. Commercial production[10,11] of β-lactam antibiotics has been improved by studying the genetics of penicillin formation.[12,13]

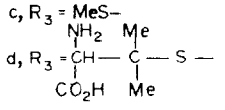
I. Natural β-lactams

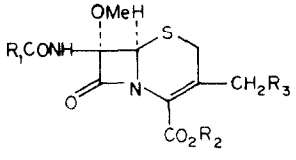
Discovery of penicillin **1** was followed by the isolation of cephalosporin C $\mathbf{2}_a$[14] which resembles the former in its stereospecific bicyclic disposition of the molecule. Recently, deacetoxy cephalosporin C $\mathbf{2}_b$,[15,16] 3-alkylthiomethyl cephalosporins $\mathbf{2}_c$[17] and $\mathbf{2}_d$,[18] and cephamycins **3**[19-23] have been added to the list. Another fused bicyclic β-lactam system with an oxazolidine ring, namely clavulanic acid $\mathbf{4}_a$,[24] and its isomer isoclavulanic acid $\mathbf{4}_b$[25] was reported. Monocyclic β-lactams, such as steroidal alkaloids pachystermine A $\mathbf{5}_a$[26] and pachyster-



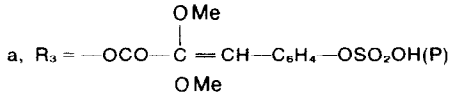
(1) $R_1 = PhCH_2$, $PhOCH_2$ etc.
$R_2 = H$

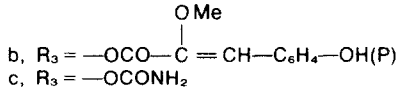


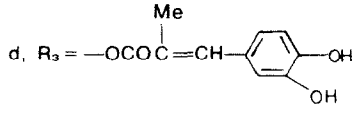
(2) a, R_3 = ACO—
b, R_3 = H
c, R_3 = MeS—
d, R_3 = 

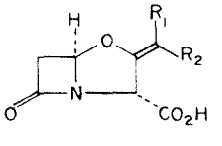


(3) $R_1 = HO_2C-CH(NH_2)-(CH_2)_3-$; $R_2 = H$

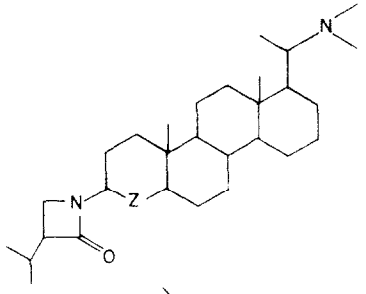
a, R_3 = 

b, R_3 = 
c, $R_3 = -OCONH_2$

d, R_3 = 



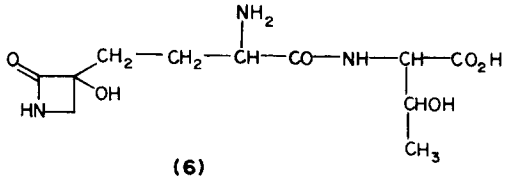
(4) a, $R_1 = -CH_2OH$; $R_2 = H$
b, $R_1 = H$; $R_2 = -CH_2OH$



(5) a, Z = >CO
b, Z = >CHOH

mine B $\mathbf{5}_b$,[26] wild-fire toxin **6**,[27] bleomycins **7**,[28–30] and nocardicins **8**[31] were recently discovered. Thus, the occurrence of β-lactams in Nature seems to be not unusual, and it is likely that many more naturally occurring β-lactams will be isolated in future.

in the case of fused β-lactams having no bridge head nitrogen atom, and in those having no hetero atom at position 1 or alterations in the position of the hetero atom of the non β-lactam ring. This discrepency can be removed by adopting a new system in which fused



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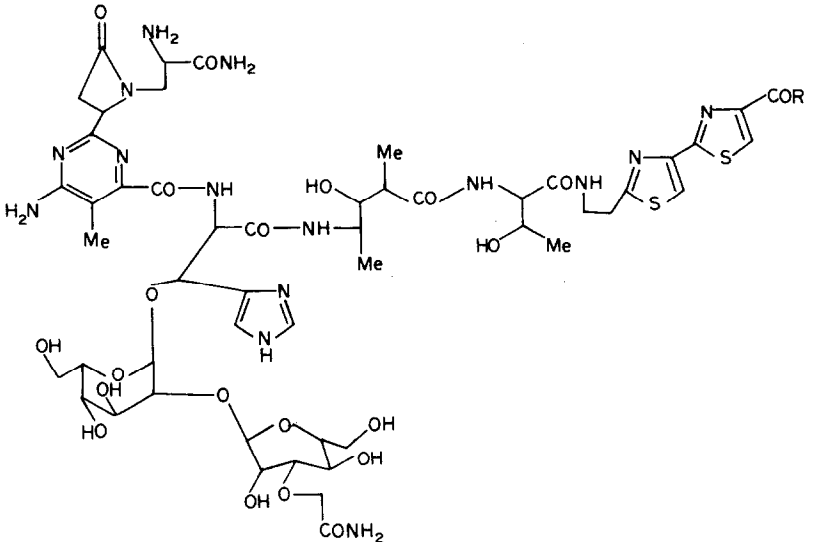
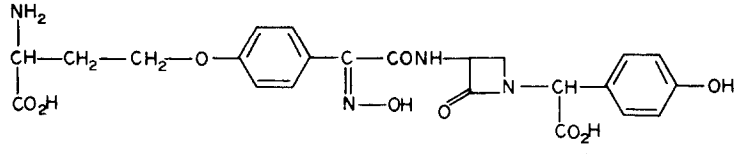


(7) a, R = —NH—$(CH_2)_3$—$\overset{\oplus}{S}Me_2\overset{\ominus}{X}$

b, R = —NH—$(CH_2)_4$—NH—C(=NH)—NH_2

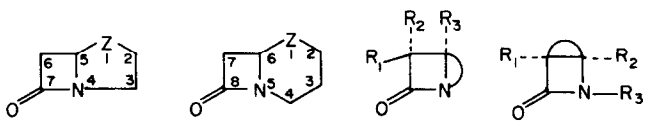


(8) *Syn-* and *anti-*

II. Nomenclature

In the literature, monocyclic β-lactams are usually referred to as azetidin-2-ones or 2-oxoazetidines, based on the nomenclature of the parent heterocycle, azetidine. However, the trivial names "penam" for the fused β-lactam $\mathbf{9}_a$, and "cepham" for the bicyclic system $\mathbf{10}_a$ gained currency.[32] Similarly, the terms 0-penam, 0-cepham, azapenam, and azacepham were coined for the bicyclic β-lactams $\mathbf{9}_b$, $\mathbf{10}_b$, $\mathbf{9}_c$, and $\mathbf{10}_c$ respectively. This trivial system of nomenclature is inadequate, especially

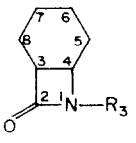
β-lactams **11** and **12** may be called "Alkanam" and "isoalkanam" respectively. Thus, β-lactams containing 7, 8 and 9 atoms in the bicyclic system **11** may be given generic names, heptanam, octanam, nonanam and so on, using the corresponding Latin roots. The numbering system as shown in $\mathbf{9}_d$ and $\mathbf{10}_d$ is in conformity with the convention followed in the case of penam-cepham nomenclature. Thus, the conventional penam will be termed as 1-thiaheptanam, and cepham as 1-thiaoctanam according to this system. Similarly, the fused β-lactams



(9) a, Z = S
b, Z = O
c, Z = NH
d, Z = CH_2

(10) (11) (12)

of the type **12** may be termed as isoheptanam, isoctanam, isononanam and so on, depending on the number of atoms in the bicyclic system. The numbering of ring atoms in this case may be the one used for azatidin-2-ones, and it is shown in **13**.



(13)

A bicyclic β-lactam containing a double bond in the ring system may be given the corresponding generic name derived from the collective name "Alkenam" or "Isoalkenam", depending on the mode of fusion of the rings. For stereo description of the molecule, the terms "α" and "β", denoting the configuration of the substituents, which may be below or above the plane of the β-lactam ring, may be used as in the case of steroids.

It should be mentioned that a similar trivial nomenclature for fused β-lactams was proposed recently.[33]

B. BIOSYNTHESIS

Of all the naturally occurring β-lactams, only the biosynthesis of penicillin and cephalosporin has been investigated, and this was recently reviewed.[34,35] Different penicillins with a variety of side-chains were obtained by the addition of suitable side-chain precursors to the fermentations with *Penicillium* species. Recently, a new biosynthetic penicillin, namely 6D-[2-amino-2-carboxy ethylthio]-acetamido penicillanic acid was isolated in the fermentations of a mutant of *Cephalosporium acremonium*.[36] However, no cephalosporin with side-chains other than D-α-aminoadipoyl group was obtained from the *Cephalosporium* species, and this fact has not yet been rationalised.

6-Aminopenicillanic acid (6-APA), formed in fermentations of *P. chrysogenum*, to which no side-chain precursor had been added, appeared to be an intermediate in penicillin biosynthesis.[37] Several enzymes were reported to catalyse the formation of a penicillin from 6-APA. It was also observed that bacterial penicillin acylases cause the reversible hydrolysis of benzylpenicillin to 6-APA, and the transfer of a phenylacetyl group from phenylacetylglycine to 6-APA.[38,39] Recently, enzymic N-deacylation of benzyl- and phenoxymethyl penicillin tetrazoles was reported.[40]

The discovery of penicillin N, which has a (D-α-aminoadipoyl) side-chain, in the fermentations of a strain of *C. acremonium*,[41] and the isolation of the tripeptide δ-(α-aminoadipyl) cysteimyl valine from the mycelium of *P. chrysogenum*,[42] led to the suggestion that penicillin N was a precursor of natural penicillins with non-polar side-chains. It was found that DL-α-aminoadipic acid stimulated the production of benzylpenicillin, but L-lysine inhibited it, and this finding is consistent with the view that α-aminoadipic acid is essential in the biosynthesis of benzylpenicillin.[43]

The role of penicillin N as a precursor of penicillin was contested by the discovery of isopenicillin N in *P. chrysogenum*, which has a δ-(L-α-aminoadipoyl) side-chain,[44,45] and the subsequent finding of δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine in *C. acremonium*.[46] It was found that addition of either 6-APA or synthetic isopenicillin N to a crude extract of *P. chrysogenum* enhanced the incorporation of ^{14}C from [^{14}C] phenylacetyl CoA into benzylpenicillin.[47,48] Recently, tritium-labelled penicillin N, isopenicillin N, and 6-APA were synthesised.[49] It was found that tritium was incorporated into solvent-soluble penicillin from isopenicillin N and 6-APA, having tritium in the 2β-methyl group, when the labelled compounds were incubated with a crude extract of *P. chrysogenum*. It is noteworthy that no incorporation of tritium into solvent-soluble penicillin was found on incubation of these extracts with penicillin N. This result indicates that the isopenicillin N is a substrate for an acyl-transferase enzyme.[50] It remains to be established whether the free 6-APA is actually formed on the pathway from isopenicillin N to penicillins or 6-APA is formed but not free from enzyme complex.

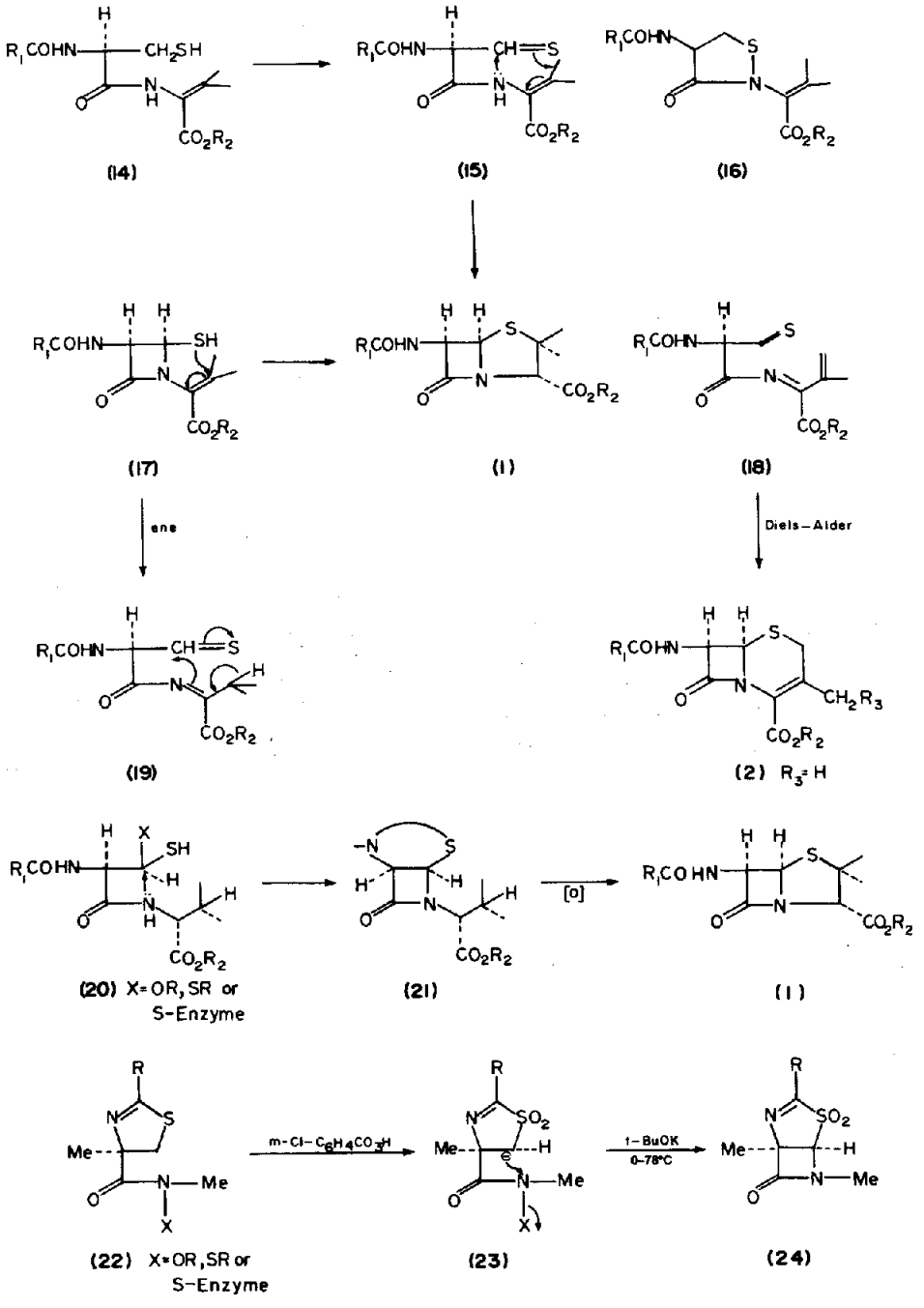
The mode of formation of the β-lactam ring in the biosynthetic pathway of β-lactam antibiotics was investigated by several workers.[51] As already indicated, the tripeptide δ-(L-aminoadipoyl)-L-cysteinyl-D-valine was considered as a precursor, and its transformation was supposed to involve oxidative ring closure. Attempts by Baldwin *et al.*[52] to oxidise the cysteinyl thiol function to thioaldehyde, in a number of cysteinyl peptides, afforded peptide derivatives containing the isothiazolidinone moiety. On the basis of facile formation of such compounds, it was suggested that biological conversion of isothiazolidinones **16**, derived from cysteinyl valine and cysteinyl dehydrovaline peptides, into thioaldehyde **15** could be a plausible pathway in the formation of β-lactam ring in penicillin and cephalosporin.

The thioaldehyde **19** by "ene" reaction would provide the thiol **17**, which on Michael addition can give penicillins, as is already known in the literature.[53] The process was claimed to be in complete stereochemical accord with experiment conducted with chiral ^{13}C-valine as a precursor to penicillin V.[54] Similarly, an isothiazolidinone from cysteinyl dehydrovaline peptide could afford the thioaldehyde **18**, which on Diels–Alder reaction can give a cephalosporin **2**.[52] Recently, incorporation of (2*S*, 3*R*)-[4,4,4-(H-2)3]-valine and (2*S*, 3*S*)-[4,4,4-(H-2)3]-valine in β-lactam antibiotics was achieved.[55] Similarly, (Me_2-$2H_6$)-DL-valine was incorporated into penicillin V, and on the basis of the mass spectrum of the methyl ester, the retention of all the six deuterium atoms in the biosynthetic product was confirmed.[56] Feeding of L-(α-2H)- and L-(α-3H)-cysteine to *P. chrysogenum* afforded (6-2H)- and (6-3H)-penicillin G. This finding rules out the involvement of α,β-dehydrocysteine residue in the biosynthetic pathway.[57]

It should be mentioned that the thioaldehyde system **15** was recently synthesised chemically, but it failed to produce β-lactam antibiotics when tested *in vitro*.[58]

A new biogenetic model **21** which might be formed by the nucleophilic attack of amide nitrogen in **20** on the sp^2 carbon of a thioaldehyde or its sp^3 receptor equivalent, was recently proposed.[59,60]

Another pathway of β-lactam formation could be oxidation at amide nitrogen followed by nucleophilic displacement by an anion generated at the β-carbon of the cysteine moiety. This proposition is supported by the cyclisation of the model peptide hydroxamate **22** to the thiosubstituted β-lactam **24**, in which the stereochemical fate of the cysteinyl β-protons is similar to the one observed in the biosynthesis of β-lactam antibiotics.[61] The oxidised peptides in the form of hydroxamic acids are known to occur in nature, however, the involvement



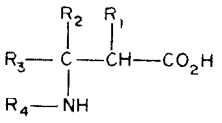
of such hydroxamates as biosynthetic intermediate of β-lactam antibiotics remains to be established.

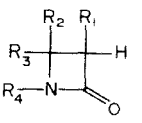
C. CONSTRUCTION OF β-LACTAM RING

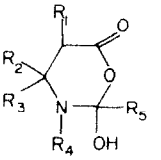
There are diverse synthetic routes to β-lactams,[62–66] and in principle the 4-membered heterocycle could be constructed by the formation of one, two, three or all four bonds of the ring system during the process of cyclisation. Except for the last one all the possibilities have been realised, an account of which is given below.

I. Cyclisation of suitable acyclic compounds

1. *Cyclisation of 3-aminopropanoic acid derivatives* (N–C_2 *bond formation*). The direct cyclisation of 3-aminopropanoic acids by simple heating fails to give β-lactams, due to deamination through β-elimination. Recently, Stezhko *et al.*[67] prepared the parent compound by heating 3-aminopropanoic acid in DMSO at 150°C. Generally, cyclisation of **25** is facilitated by reagents, such as acetic anhydride, acetyl chloride, phosphorus trichloride, and the thionyl chloride, and N-acylated β-amino acids themselves are easily converted into β-lactams in good yields, on heating. This has been explained on the assumption that an intermediary hydroxylactone **27** is formed during the reaction which engenders the conversion into β-lactam.[63] N-Benzoyl-β-amino acid **28** was reported to give β-lactam, on treatment with acetic-anhydride, but recently the product was found to be oxazine-6-one **30**.[68]



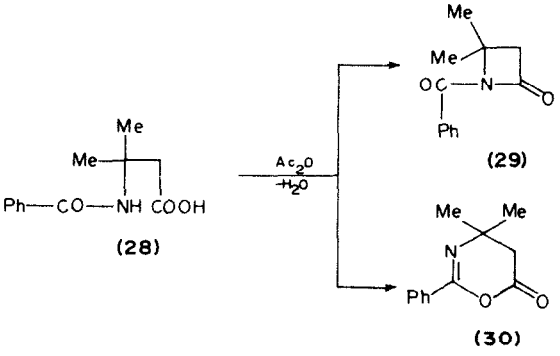




(25) a, $R_1 = R_2 = R_3 = R_4$ = alkyl or aryl
b, R_1 = alkyl; $R_2 = R_3$ = aryl; R_4 = PhCO
c, $R_1 = R_2 = R_4$ = aryl; R_3 = H

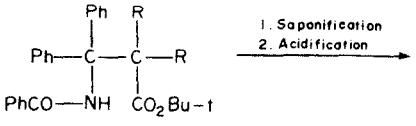
(26) a
c

(27)



(28) **(29)** **(30)**

Five 1,3,4-triarylazetidin-2-ones **26**$_c$ were prepared by treating **25**$_c$ with benzenesulphonylchloride and alkali.[69] Recently, saponification of 2,2-disubstituted-3-benzamido propanoic acid esters **31** was found to give β-lactams besides the acid derivatives.[70] The cyclisation is possibly initiated by removal of the amidic proton, followed by Dieckmann reaction.



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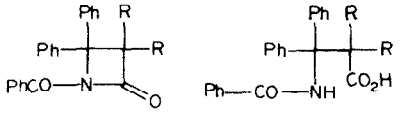
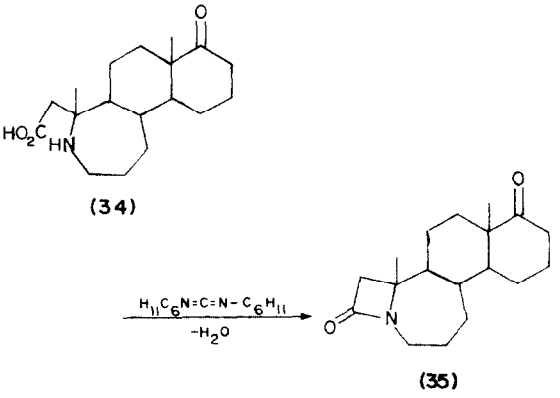


(32) **(33)**

Bicyclic β-lactams, such as penicillins,[71,72] cephalosporin analogues[73,74] and the compound **35**[75] were synthesised by this method, using carbodiimides as cyclising agents. It is noteworthy that the effectiveness

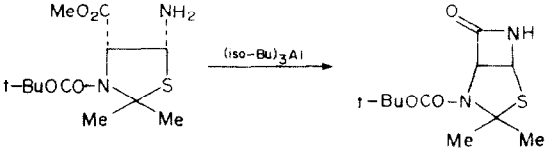


(34) **(35)**

of carbodiimides and other peptide-forming reagents has not been explored for the construction of monocyclic β-lactam ring.

β-Amino acids were also cyclised by converting the carboxylic function into acid chloride followed by treatment with a base, such as triethylamine, N,N-dimethylaniline, and dry ammonia. The yields varied from 30 to 80%, and this method afforded N-unsubstituted-, and bicyclic β-lactams.[65] This route is rather circuitous, and is often accompanied by epimerisation, as in the case of the cephalosporin analogue.[73]

Cyclisation of β-amino acid esters was effected with Grignard reagents,[65,76,77] and by this method N-unsubstituted-,[78] and optically active azetidin-2-ones[65] were also synthesized. Triisobutylaluminium was used for cyclising compound **36** to the bicyclic β-lactam **37** which is a key intermediate for the synthesis of cephalosporin and other β-lactam antibiotics.[79]



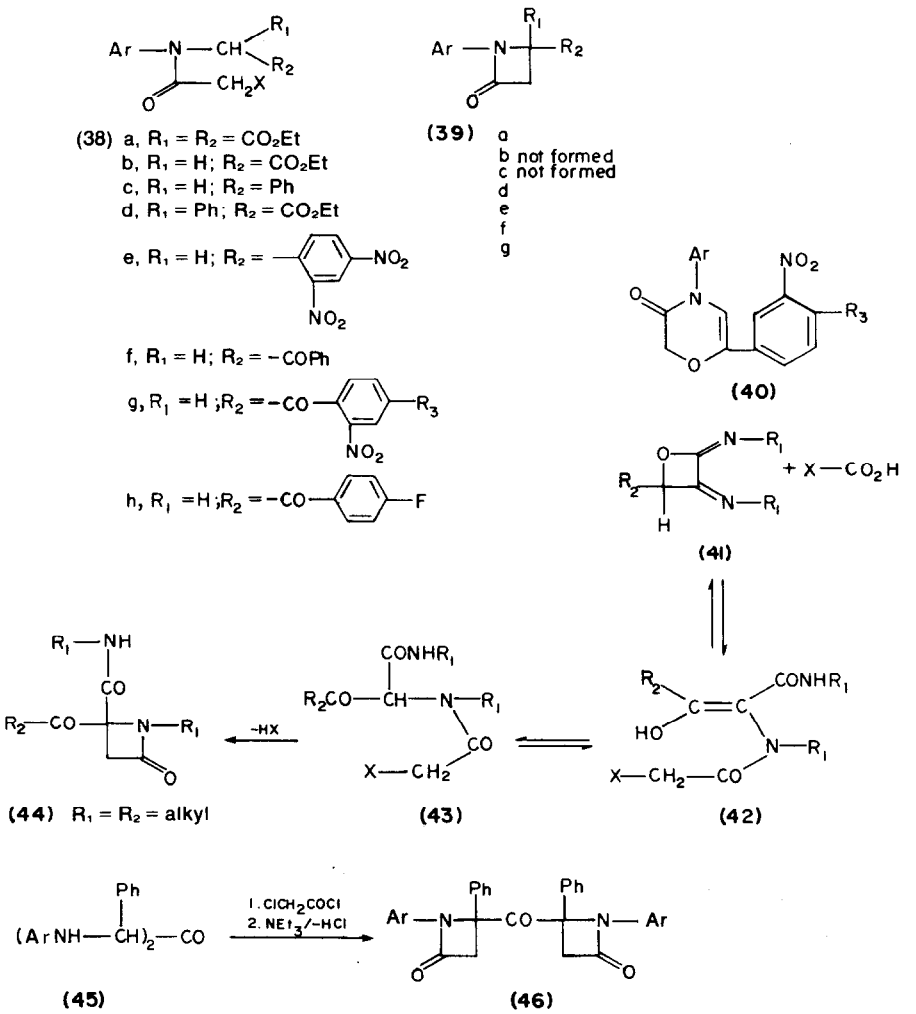
(36) **(37)**

Ring closure of β-aminocarboxamide was reported, but the azetidin-2-one structure was not supported by the necessary spectral data.[80]

2. *Cyclisation of halo acid amides by dehydrohalogenation (formation of the* C_3–C_4, *and* N–C_4 *bonds by ring closure).* The α-haloacetanilidomalonate **38**$_a$, on treatment with a mild base cyclised to β-lactam **39**$_a$ through dehydrohalogenation.[81] This method can yield 3-substituted β-lactams by using suitable α-halo acid amides,[82] and saponification and decarboxylation of the carboxylic group would afford 3,4-*cis-trans*-isomers of the corresponding β-lactams.

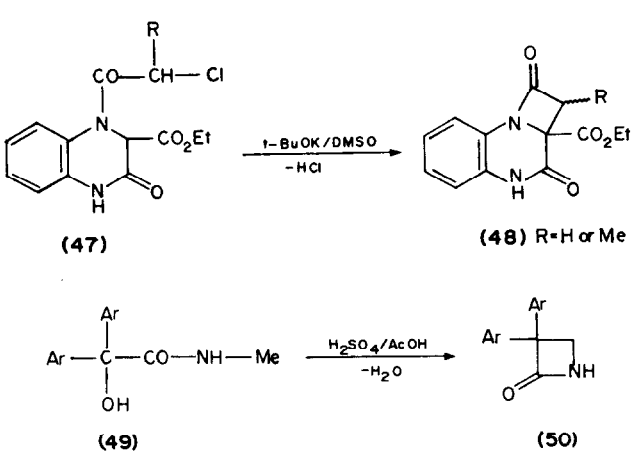
On examining the activating influence of groups R_1 and R_2 in the compound **38**, it was found that compounds **38**$_b$ and **38**$_c$ do not cyclise under the influence of triethylamine or sodium alkoxide. In most of the cases, presence of two electronegative groups is essential for activation of the methine hydrogen in the compound **38**. However, a single strong electron withdrawing group also ensures cyclisation.[65] It is noteworthy that cyclisation of **38**$_g$ afforded the dihydro 1,4-oxazine **40** or the β-lactam **39**$_g$ or both depending on the aryl substituent.[83] The oxazine derivative is obviously obtained by the nucleophilic displacement of the halogen atom by the enolic oxygen, and any factor that will stabilise the enolic form of the ketone **38**$_g$ will enhance the formation of the oxazine.

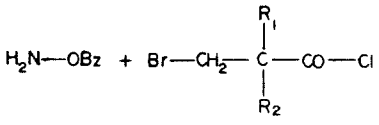
This method was successfully employed to convert bis-imino-oxetanes **41** and α-halocarboxylic acids into β-lactams **44**.[84] Similarly, compounds **46**[85] and **48**[86] were



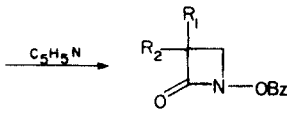
prepared. This route to β-lactam is unsuccessful in the case of N-unsubstituted β-lactams, and the conformation of the α-haloacid amides seems to be important for the cyclisation. Recently, synthesis of β-lactams **50** by dehydration of hydroxy amides **49** was reported, and it envisages the formation of the C_3–C_4 bond.[87] The scope of this conversion remains unexplored.

Knunyants *et al.* synthesised β-lactams *via* N–C_4 bond formation through dehydrohalogenation of 3-halopropanamides in the presence of strong bases, such as potassium or sodium amide, potassium tertiary butoxide, etc.[65] Recently, lithium or sodium carbonate in paraffin oil was used for such cyclisation.[88] Also, β-bromo acid chlorides and an alkoxy amine were reported to give β-lactams **52** in the presence of pyridine,[89] and it is likely that the reaction is initiated by N-alkylation, followed by N–C_2 bond formation. This method is applicable for the synthesis of different types of β-lactams, and the substitution at the nitrogen atom does not affect cyclisation. Usually, α,β-unsaturated acid amides are obtained as



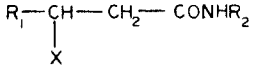


(51)



(52)

side products in this reaction, and it is unlikely that they isomerise to the corresponding β-lactams through intramolecular Michael addition. The reaction may be supposed to involve abstraction of the amidic proton, followed by an intramolecular nucleophilic substitution.



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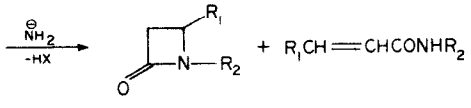
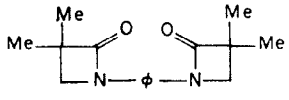
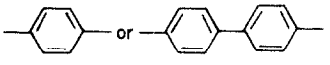


(54) (55)

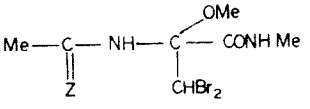
Recently, bis-compounds **56** were synthesised by this method.[90]



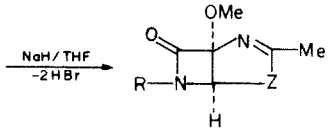
(56) ϕ = $-CH_2-CH_2-$,



Also, the synthesis of bicyclic β-lactams **58** by double cyclisation of **57** with sodium hydride in THF was reported recently.[91] The compound **58b** was converted into C_6 α-methoxypenicillin and C_7 α-methoxy cephalosporin derivatives.



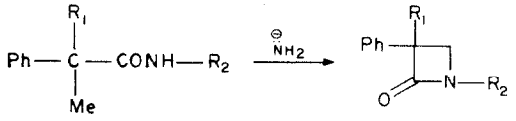
(57) Z = O or S



(58) a, R=Me CO_2Me

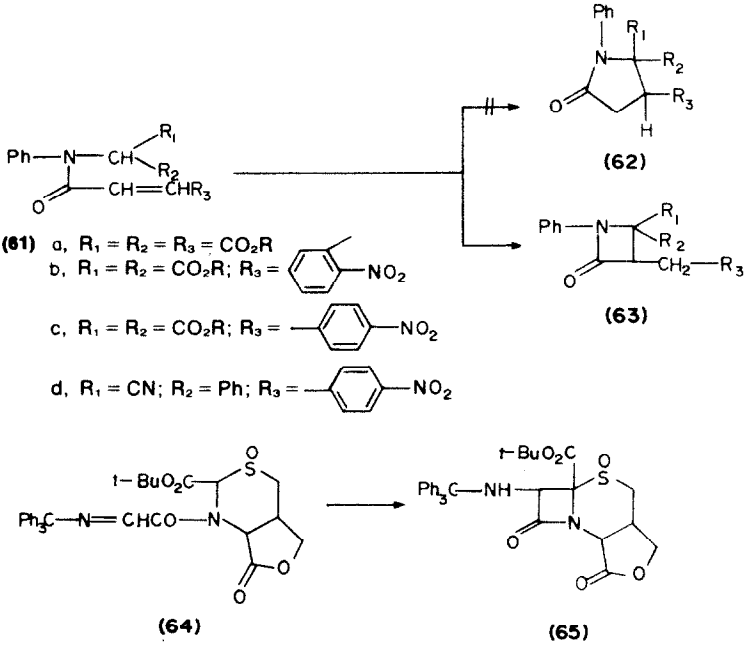
b, R=Me_2C=C−; Z=S

Cyclisation of amides **59** by sodium amide to β-lactams **60** may be considered to be a modified version of this reaction.[92]



(59) (60)

3. *Cyclisation through intramolecular Michael addition.* Acrylamides of the type **61** underwent intramolecular Michael addition under the influence of a suitable base.[93] Piperidine was found suitable, but it also catalysed the retro Michael addition. The presence of a strong electron withdrawing group is essential in the β-position of the acrylic acid part. Similarly, two electronegative groups R_1 and R_2 in **61** are essential for the cyclisation.[93] Recently, the imine **64** was converted into the bicyclic β-lactam **65** through intramolecular Michael



(61) a, $R_1 = R_2 = R_3 = CO_2R$

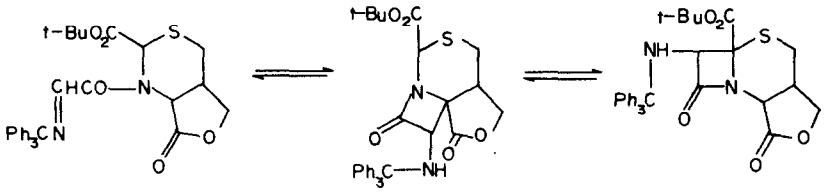
b, $R_1 = R_2 = CO_2R$; R_3 = $-C_6H_4-NO_2$

c, $R_1 = R_2 = CO_2R$; R_3 = $-C_6H_4-NO_2$

d, R_1 = CN; R_2 = Ph; R_3 = $-C_6H_4-NO_2$

(62) (63)

(64) (65)

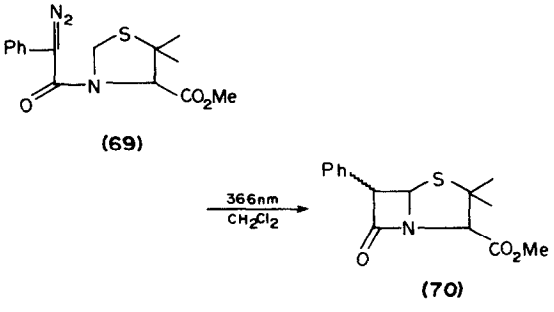


(66) (67) (68)

addition.[94] Similarly, the compound **67** was obtained which isomerised to **68**.

It is noteworthy that the reaction of unsymmetrical hydrazines and α,β-unsaturated carboxylic acid derivatives were reported to give β-lactams, however, the spectral data are incompatible with the proposed structures.[95]

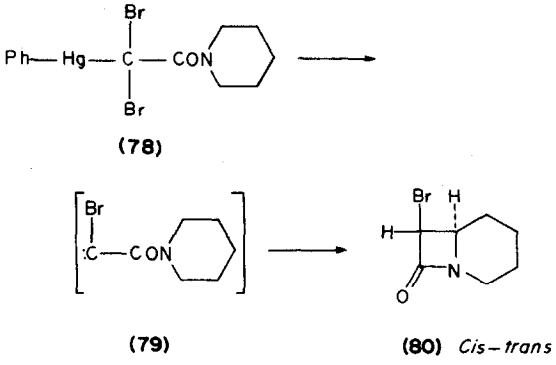
4. *Annulation through carbene insertion.* Photolysis of the diazoamide **69** gave the annulated β-lactam **70** via the corresponding intermediary carbene.[96] This method was extended to the synthesis of several bicyclic β-lactams, containing a carboxylic function α to the β-lactam carbonyl group, which was later converted into amino group through Curtius reaction.[5]



(69) (70)

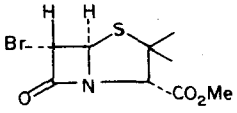
A similar photolysis of **71** in methanol gave in good yields the β-lactam **77**, besides the γ-lactam **74** and other products derived from the intermediary carbene.[97] It appears that the conformation of the carbene generated is favourable for the intramolecular insertion. The scope of this method for the synthesis of different azetidin-2-ones has not been explored.

Another similar method is the synthesis of bicyclic β-lactams through metal-induced carbene reaction. Thus, a mixture of two isomeric bromo-substituted β-lactams **80** were obtained by the thermal decomposition of the mercury compound **78**.[98] Recently, fused α-halo-β-



(78) (79) (80) *Cis–trans*

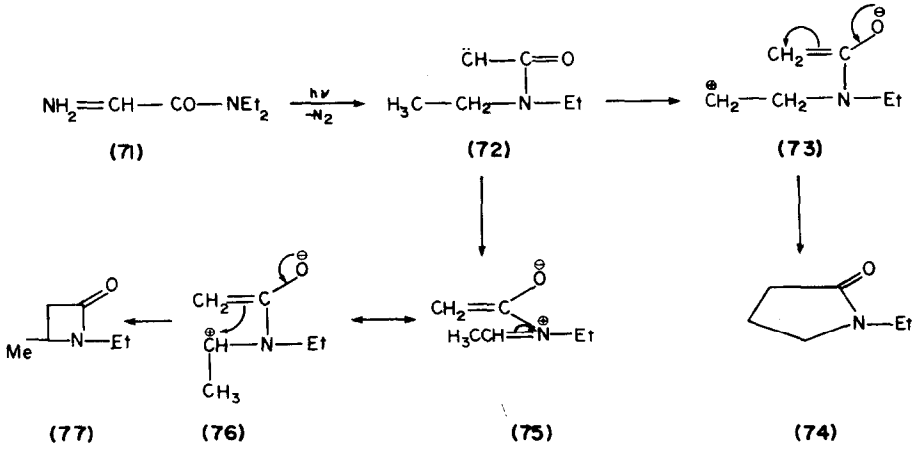
lactams were synthesised by the thermal decomposition of diethylthallium dihaloamides.[99] This method was extended to the synthesis of (+) methyl 6-bromopenicillanate **81**.[100,101] It is noteworthy that the substitution of the halogen atom by a phthalimide group in the compound **80** was recently achieved,[102] but such substitution is not general.



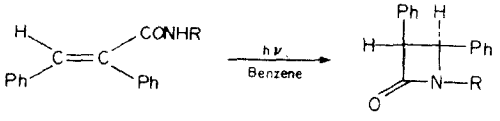
(81)

5. *Photochemical isomerisation of α-keto-, and α,β-unsaturated acid amides.* Irradiation of *cis*-α-phenylcinnamides **82** in degassed benzene afforded *cis*- and *trans*-β-lactams, the former being in better yields.[103] Recently, N-benzylacryl- and crotonamides were isomerised to the corresponding β-lactams.[104]

Irradiation of α-keto acid amides **84** afforded the corresponding bicyclic β-lactams **85** in low yields, besides non β-lactam compounds as major products.[105] Slightly better yields were obtained in the case of **87**.[106] It would

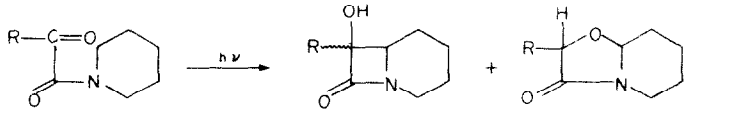


(71) (72) (73) (77) (76) (75) (74)



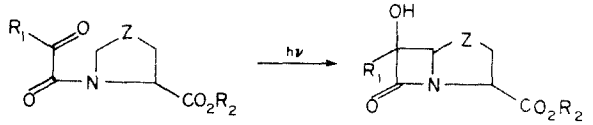
(82) a, R = H
b, R = Ph

(83) *Cis–trans–*



(84) a, R = Ph
b, R = Me

(85) (86) *Cis–trans–*



(87) Z = S, SO, or SO_2
R_1 = H or Ph
R_2 = Me or Et

(88)

be worth trying to explore cyclisation of α-keto acid amides in which a carbanion at the carbon atom α to the amidic nitrogen can easily be generated. The hydroxy β-lactams are potentially important, and only a few such compounds are known which were obtained by manipulation of preformed β-lactams through a circuitous route.

II. Cycloaddition reactions

Cycloaddition reactions of heterocumulenes[107] have been widely used for the synthesis of different types of β-lactams. This method is quite convenient, as the reactants are easily available and the reaction proceeds smoothly under mild condition, affording the product in good yields.

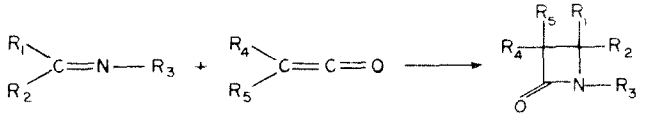
1. *Addition on imines (simultaneous formation of* $N–C_2$ *and* $C_3–C_4$ *bonds).* The first β-lactam was prepared by the ketene-imine interaction. Usually, ketenes are generated *in situ* by dehydrohalogenation of suitable acetylchlorides in the presence of a tertiary base. Also, photolysis and thermal decomposition of diazoketones were employed for generating ketenes, which were trapped by imines to give β-lactams. Thermal fragmentation of acetylenic ethers to aldoketenes was also reported.

The choice of ketene precursor is important, because it gives β-lactams with a suitable group at the carbon atom α to the β-lactam carbonyl function.[65]

The structural requirements of the imines are difficult to define due to the inconsistency in the results obtained from different procedures. Imidoylchlorides, O-alkyloximes, and phenyl hydrazones did not give azetidin-2-ones. Recently, addition of diphenyl ketene on acyl hydrazones is reported to give β-lactams. Imines, such as **89**$_a$ and **89**$_b$ gave β-lactams **91**$_a$ and **91**$_b$, on treatment with diphenyl- and dimethylketenes respectively.[65] Recently, tert-butyl-cyanoketene with iminoether gave β-lactam **91**$_c$.[108] Diphenyl ketene with imines **79**$_d$ gave β-lactams **91**$_d$, but their reactivity and yields varied considerably with change in the substituent in the aromatic ring.[109] Conjugated diimines,[110,111] and carbodiimides[65] also gave β-lactams with suitable ketenes.

A variation of this reaction is addition of substituted acetic acid derivatives to imines in the presence of a tertiary base. Thus, many acid chlorides, anhydrides, and mixed anhydrides[112] give β-lactams when added to suitable imines. Recently, substituted acetic acids, in the presence of phosphorus oxychlorides, gave β-lactams, on treatment with imines.[113]

This reaction is wide in scope, and it is useful for the synthesis of simple, bicyclic, and spirocyclic β-lactams. It should be mentioned that the addition of acid chlorides on 2-methyl-Δ^2-oxazoline[114] and thiazoline[115] failed to give the corresponding β-lactam. Similarly, β-lactams could not be obtained with Δ^1-pyrrolines,[116] possibly due to isomerisation of the imine into the corresponding

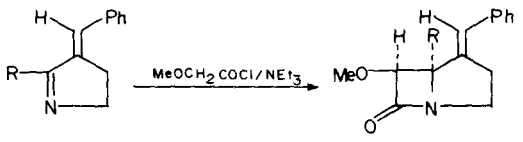


(89) (90) (91)

a: R_1 =  ; R_2 = H; R_3 = Ph; R_4 = R_5 = Me or Ph

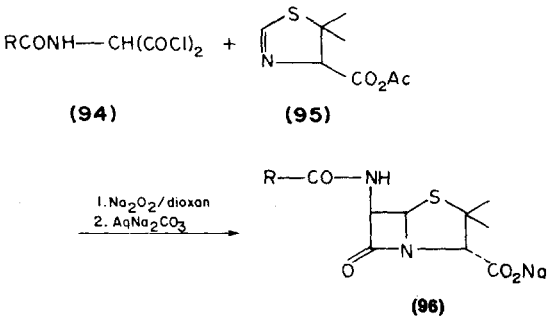
b: R_1 = Ph; R_2 = MeS—; R_3 = Ph; R_4 = R_5 = Me or Ph
c: R_1 = H; R_2 = —OMe; R_3 = t-Bu = R_4; R_5 = CN
d: R_1 = p-Me_2N—C_6H_4—, p-$MeOC_6H_4$—, etc; R_2 = H;
R_3 = Ph, p-$MeOC_6H_4$—, p-Cl—C_6H_4—, etc.; R_4 = R_5 = Ph

enamine.[117] When such an isomerisation was ruled out, as in **92**, addition of acid chloride afforded the bicyclic β-lactam **93**.[118]



(92) (93)

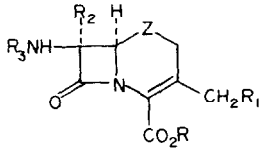
Also, the addition of acid chlorides on several thiazoline derivatives gave penicillin analogues.[32] Recently, a one-step synthesis of penicillin was achieved by this reaction.[119] Though with Δ^2, 1,3-imidazoline and suitable acid chlorides the corresponding β-lactams were obtained, the products were found to be very unstable.[120]



(94) (95) (96)

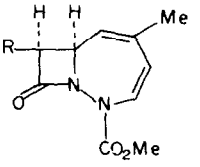
This reaction has not been properly explored in the case of the oxazoline system.

The addition of acid chlorides on compounds in which imino group is a part of 6- or 7-membered ring was successful. Thus, addition of suitable acid chlorides to Δ^2-thiazine[32,121,122] and Δ^2-pyrimidine[120] systems afforded the corresponding cephalosporin analogues.[32,121,122] Recently, novel bicyclic β-lactams **97** were constructed by manipulating preformed azetidin-2-one derivatives which were synthesised by addition of acid chlorides to imines.[123–125] However, the compounds **98**,[126] and **99**[127,128] were obtained directly by this method. The addition of acid chlorides or ketenes on compounds

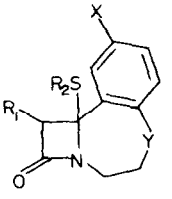


(97)

Z = CH_2, O, NH, NMe, NMe, NCO_2CH_2Ph, NCH_2Ph, NCHO;
R = Na, H, CH_2Ph, $CHPh_2$
R_1 = OAc, OH, O_2CNH_2, 1,3,4-thiadiazol-2-ylthio;
R_2 = H, OMe, SMe;
R_3 = H, 2-thienylacetyl, $H_2N-\underset{Ph}{CH}-CO$

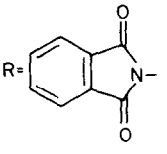


(98)



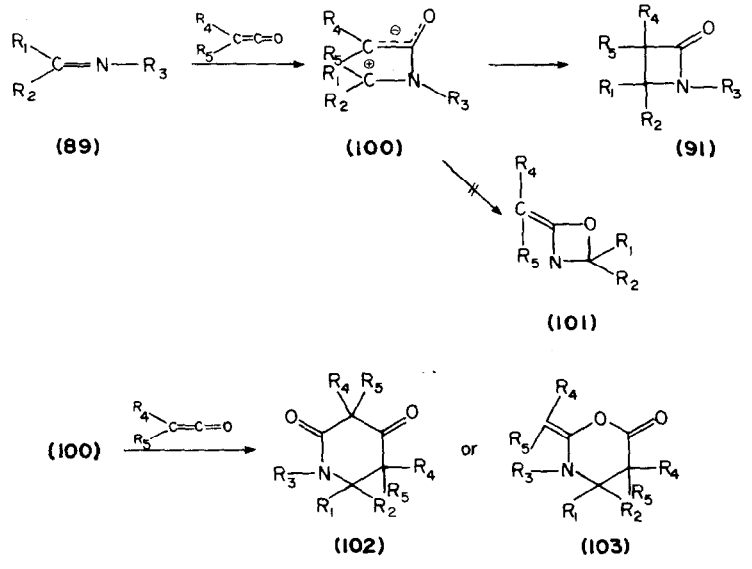
(99)

R_1 = OMe or N_3
R_2 = Me, Et or i-Pr
X = H or Cl
Y = O or S



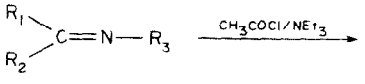
with an imino group as a part of a heteroaromatic system failed to give β-lactam.

The interaction of acid chlorides and imines may follow two routes. When the acid chloride is added to an imine solution containing a tertiary base, apparently a ketene is generated which may add to the imine in a concerted fashion to give the β-lactam or it may generate an ambident species **100** which can stabilise itself by ring closure and formation of **91** or it may further react with a second ketene-molecule to give a 6-membered ring 2:1 adduct **102** or **103**.



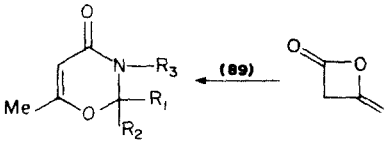
(89) (100) (91) (101) (102) (103)

It should be emphasised that the course of the reaction is governed by the nature of the substituents in the reacting species. The reactivity of the ketenes vary considerably from one member to another, and in some cases the ketene dimer is first formed which then reacts with the imine to give the 6-membered heterocycle.[129] For example, addition of acetyl chloride on imines in the presence of triethylamine afforded **105**, which was also obtained by the direct interaction of ketene dimer **104** and the imine.[130] Similarly, an electron donating group on the imino carbon atom may stabilise the ambident species **100**, and thus exposing it to the attack of another ketene-molecule. The rate of addition of the reagents and the concentration of the solution also influence the product yields.



(89)

e, R_1 = Ph; R_2 = H; R_3 = $PhCH_2$
f, R_1 = Ph; R_2 = H; R_3 = Ph
g, R_1 = R_2 = Me; R_3 = Ph
h, R_1 = R_2 = Me; R_3 = p-O_2N—C_6H_4—

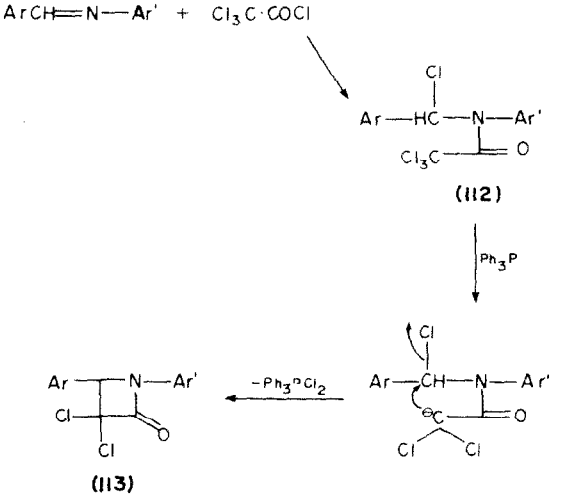


(105) (104)

It is noteworthy that the adduct from benzylideneaniline and acetic anhydride gave 1,4-diphenylazetidin-2-one, on heating at 210°C in diphenylmethane or diphenyl silane.[131] Earlier, 3,3-dichloroazetidin-2-ones were obtained when dichloroaceticanhydride and Schiff bases were kept together overnight.[132,133]

The addition of acid chloride to an imine may give an immonium chloride, which may undergo dehydrohalogenation in the presence of a tertiary base to afford a β-lactam. Thus, the interaction of benzylidinetryptamine **106** with an acid chloride generated an intermediate salt **107** which cyclised to the β-lactam **111** by dehydrohalogenation in the presence of triethylamine. Formation of a β-carboline **110**,[134] besides the β-lactam **111**, justifies the formulation of the proposed mechanism. Intermolecular trapping of the immonium salts of the type **108** with suitable nucleophiles would be worth trying.

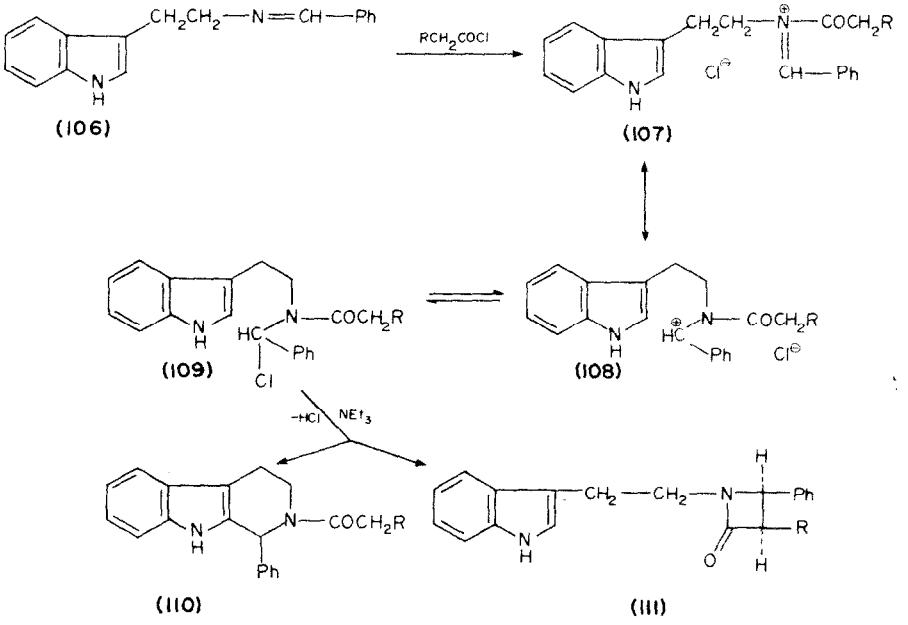
Recently, addition of trichloroacetyl chloride to a Schiff base afforded an adduct **112** which with triphenylphosphine gave β-lactam **113**.[135]



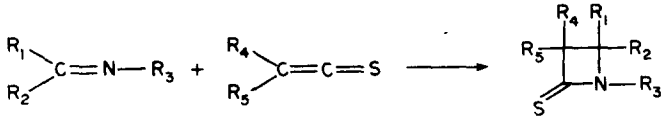
(112) (113)

It should be mentioned that reaction of acid chlorides or ketenes and imines give both *cis*- and *trans*-isomers. A certain amount of steric control on the product of this reaction can be exercised by changing the sequence of addition of the reactants, however, the nature of substituents in the reactants also influences the course of the reaction.[134]

Recently, thioketenes **114** were successfully added to imines to give β-thiolactams **115** and it was found that



(106) (107) (109) (108) (110) (111)

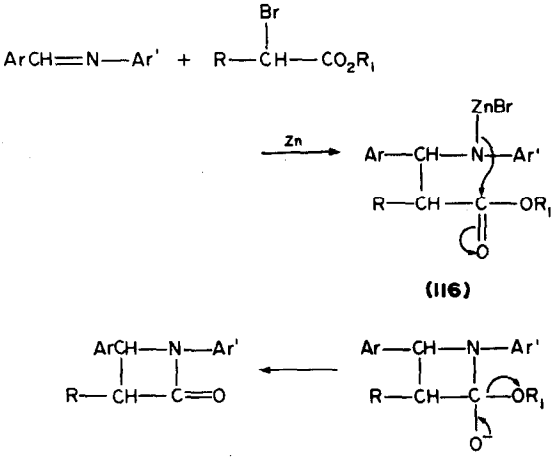


(89) (114) (115)

unsymmetrically substituted thioketenes are poorly stereoselective.[136]

The addition of mesoionic oxazolones[137,138] or 4-alkylazlactones[139] to imines afforded β-lactams. Also, phenylmalonic acid with dicyclohexylcarbodiimide in methylene chloride, carbon tetrachloride or nitrobenzene gave the corresponding 4-iminoazetidin-2-one as the principal product.[140] The mechanism involved in these transformations may be similar to that of the ketene-imine reaction.

Several β-lactams were synthesised by the interaction of imines and α-bromoacid esters in the presence of zinc, which envisages formation of C_3–C_4 and N–C_2 bonds.[65] Both stereoisomers are obtained in this reaction, and the *cis*/*trans*- ratio of the β-lactams formed

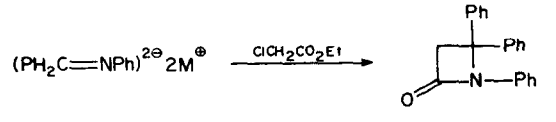


(116)

(117) *cis-trans*-
R = alkyl or aryl;
Ar = aryl, ferrocenyl or tricarbonyl maganese cyclopentadienyl
Ar' = aryl.

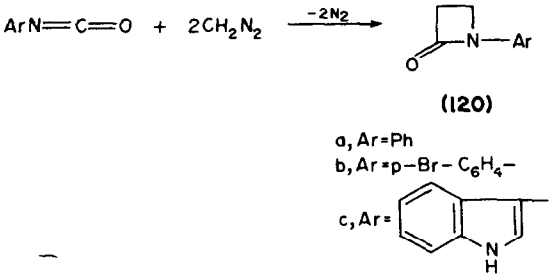
depends on the nature of the substituent R and R_1 in the ester and also on the nature of the solvent. It was found that increased polarity of the solvent favoured formation of the *cis*-β-lactam. This reaction seems to have not been tried for the construction of fused bicyclic and spirocyclic β-lactams. It is noteworthy that this method was employed for the synthesis of β-lactams bearing a ferrocene moiety and a tricarbonyl manganese cyclopentadienyl group.

Recently, benzophenone anil was reduced to dianion **118** with alkali metals which reacted with ethyl-chloroacetate to give β-lactam **119** as one of the products.[141] Apparently, the reaction involves formation of C_3–C_4 and N–C_2 bonds.



(118) (119)

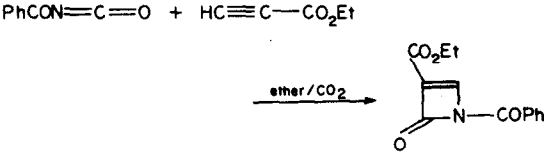
2. *Reaction of isocyanates (simultaneous formation of C_2–C_3 and N–C_4 bonds).* Diazomethane was found to give β-lactams **120** when treated with phenyl- and p-bromophenylisocyanates.[63] Recently, indolyl-3-isocyanate reacted similarly.[142] This reaction is not a general one. Also, addition of other diazoalkanes on isocyanates have not been reported.



(120)

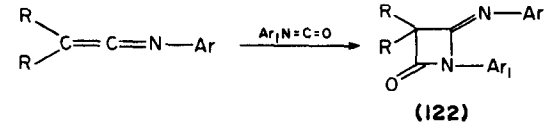
a, Ar=Ph
b, Ar=p-Br-C_6H_4-
c, Ar=

Addition of isocyanates have been tried on several olefins, and it was found that less reactive isocyanates require reactive olefins to produce β-lactams.[66] For example, phenylisocyanate and phenyl isothiocyanate failed to add on methylacrylate and methylcinnamate.[143] However, benzoyl isocyanate with carbethoxy acetylene in ether under carbon dioxide gave **121** in 32% yield.[144]



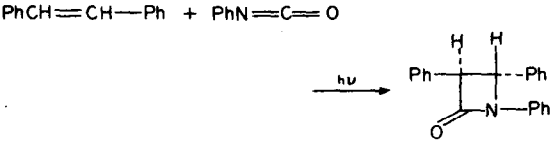
(121)

It is noteworthy that arylisocyanates added successfully to ketenimines to give 4-iminoazetidin-2-ones **122**.[145]



(122)

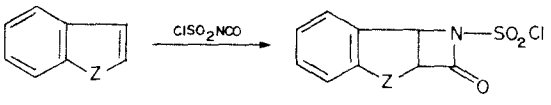
Recently, photocycloaddition of *cis*- and *trans*-stilbene to phenylisocyanate has been reported.[146]



(123)

Olefins, such as ketene acetals and enamines react with phenyl isocyanate to give β-lactams in good yields, however, the products, especially those derived from enamines, are highly unstable.[65]

Reactive isocyanates[144b] give β-lactams with ordinary olefins, though the reaction cannot be said to be a general one. Chlorosulphonylisocyanate was found to be highly reactive and it forms monocyclic, bicyclic and spirocyclic β-lactams with suitable olefins.[65] Recently, polyisoprene[147] was converted into compound with β-lactam units by using this reaction. Also, novel bicyclic β-lactams, such as **125**$_a$[148] and **125**$_b$[149] were recently obtained by addition of isocyanate to **124**$_a$ and **124**$_b$ respectively. Recently, this reaction was extended to the synthesis of an annulene bearing a β-lactam ring.[150]



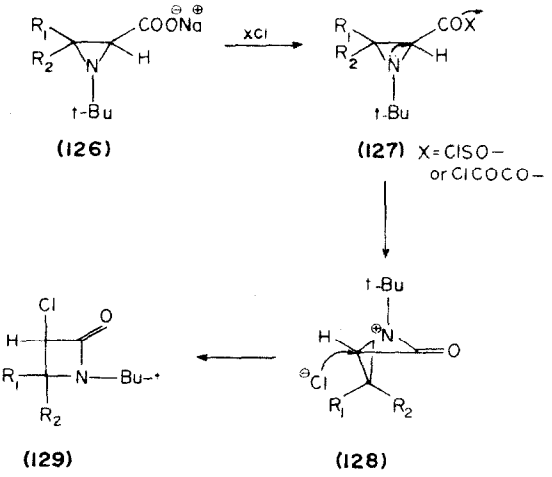
(124) a, Z=CH_2
b, Z=Me_2Si **(125)** a
b

This method cannot be used directly for the synthesis of bicyclic β-lactams with a bridge-head nitrogen atom. However, this reaction is important for synthesising N-unsubstituted β-lactams.

From the various examples of this (2 + 2)cycloaddition reaction reported in the literature, it appears that the reaction mechanism is dependent on the nature of the reactants, and it may not be always a concerted reaction strictly according to Woodward–Hoffmann rule. Moriconi *et al.* have proposed a pseudo-concerted reaction mechanism in the case of cycloaddition of chlorosulphonylisocyanate.[150]

III. *Conversion of ring compounds into β-lactams*

1. *Ring expansion of 3-membered rings.* The aziridine **126** in the presence of thionylchloride or oxalylchloride rearranges to β-lactam **129** in benzene, possibly via a mixed anhydride which undergoes ring expansion. The conversion is stereospecific and yields are good.[151]

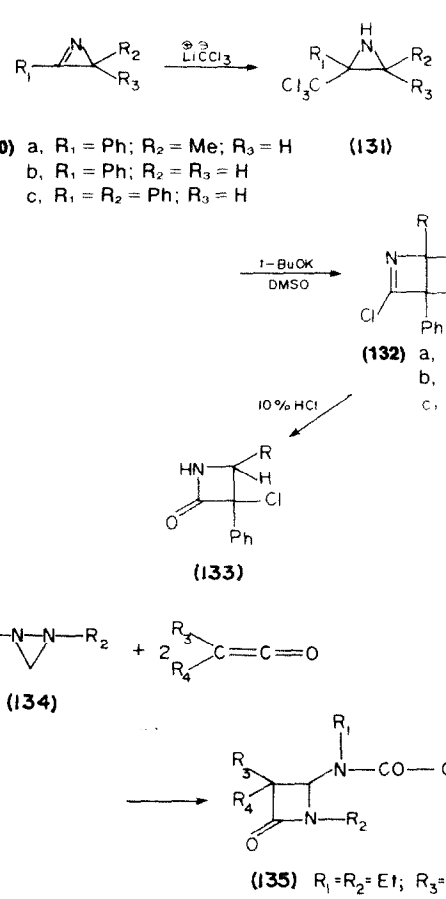


(126) **(127)** X=ClSO– or ClCOCO–

(129) **(128)**

Recently, the reaction of azirine and carbene was used in the synthesis of β-lactam. Thus, addition of trichloromethide ions to several azirines, followed by base-catalysed ring closure of the intermediate gave azetines which were converted into the corresponding β-lactam **133**. The nature of substituents in the azirine ring influences the course of the reaction.[152]

Diaziridines **134** reacted with ketenes to give β-lactam **135**, and the reaction possibly follows ketene-imine type interaction.[153]



(130) a, R_1 = Ph; R_2 = Me; R_3 = H
b, R_1 = Ph; R_2 = R_3 = H
c, R_1 = R_2 = Ph; R_3 = H

(131)

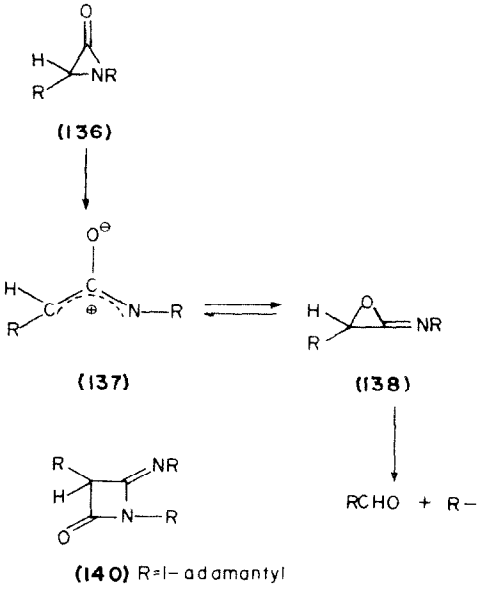
(132) a, R = Me
b, R = H
c, R = Ph

(133)

(134)

(135) R_1=R_2=Et; R_3=R_4=Ph

A new expansion of an α-lactam to a β-lactam system was reported. Thus, thermal fragmentation of **136** produced isocyanide **139**, besides other products, which on cycloaddition to either **137** or its rearranged product **138** gave the corresponding β-lactam **140** which was characterised by degradation and alternative synthesis.[154] In view of the drastic conditions involved, this route does not seem to be a general one.



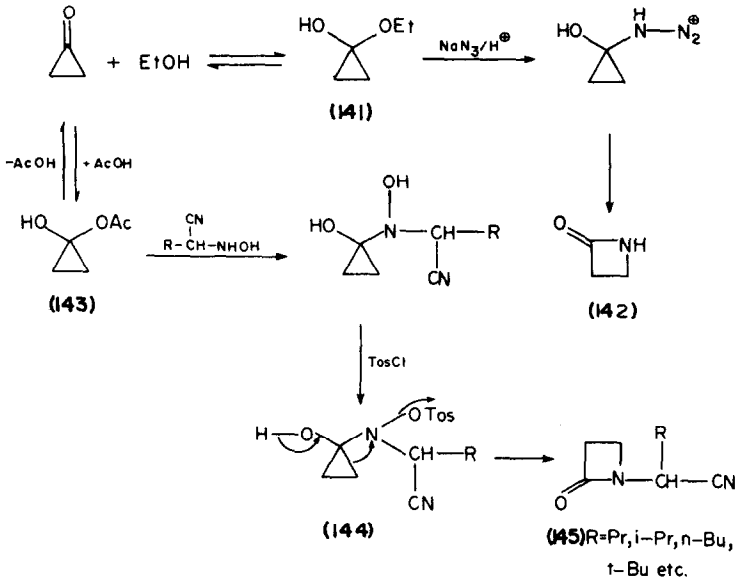
(136)

(137) **(138)**

(140) R=1-adamantyl **(139)**

Cycloalkanones are known to undergo ring expansion to lactams by Schmidt reaction or Beckmann rearrangement. It was found that cyclopropanone hemiacetal with sodium azide in acetone at pH 5.5 ($KH_2PO_4^-$/NaOH buffer) gave azetidin-2-one **142** in 21% yield.[155]

Similarly, the compound **143**, on treatment with hydroxylamine, followed by subsequent tosylation afforded β-lactams **145**.[156] Recently, cyclopropanone with aminoacid esters was converted into β-lactams by similar ring expansion.[157]

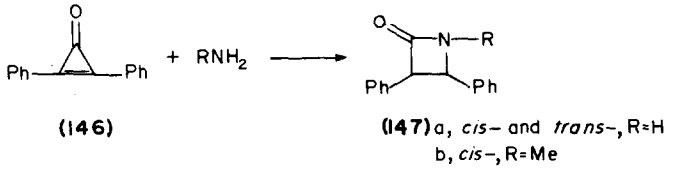


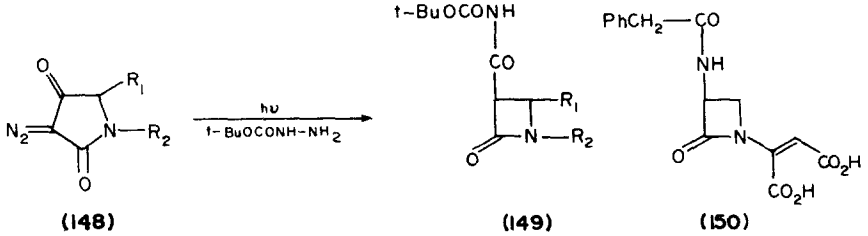
It is noteworthy that diphenylcyclopropenone **146** with ammonia or methylamine at room temperature gave azetidin-2-ones **147**.[158]

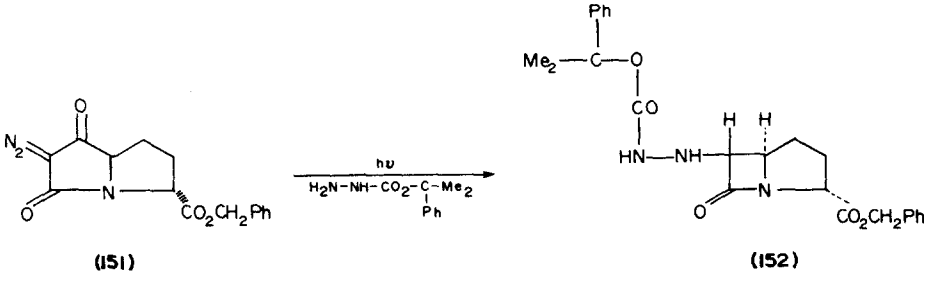
Synthesis of β-lactams by ring expansion of 3-membered ring does not seem to have any special advantage, except in limited cases, and this method is still in an exploratory stage.

2. *Ringcontraction of 5-membered rings.* Photolytic Wolf rearrangement of 3-diazopyrrolidine-2,4-diones **148**, in the presence of *tert*-butylcarbazate, afforded β-lactams **149**.[159,160] Recently, this method was extended to the synthesis of azetidin-2-one **150**, which was found to be inactive.[161] The fused system **151** under similar conditions produced **152**, which was found to be highly unstable.[162]

This method offers a new route to the synthesis of β-lactams, bearing a carboxyl group on the α-position of the lactam carbonyl function, which is amenable to further modification. The difficulty of achieving steric control has raised some doubt about its usefulness.[163]

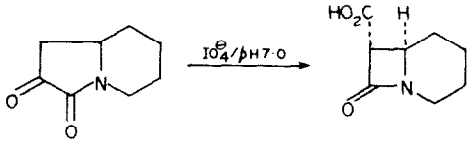






However, the interconversion of the stereoisomers is possible through facile epimerisation, and the inherent disadvantage of this method regarding stereospecifity can be thus rectified.

Reagent induced ring contraction has been reported recently.[5] For example, the compound **153** was converted into **154** by oxidation with periodate, and this reaction has been extended to several mono and bicyclic β-lactams.[164]



(153) (154)

Photolytic ring contraction of pyrazolidin-3-one systems was reported recently.[95,165] This method has been extended to the synthesis of a novel system **158**, from the compound **157**,[165] and other bicyclic and spirocyclic β-lactams.[166] Treatment of pyrazolidinones **159** successively with base and glyme, mercury(II) oxide and 2,4,6-trimethylbenzenesulphonylhydroxyl amine gave β-lactams **160**.[167]

There are other ring contraction reactions in which β-lactams were obtained as minor products. For example the compound **161** rearranged to N-acylated β-lactams **162** or the compound **163**, depending on their substituents.[168] Similarly, compounds **164** with dialkyl acylphosphonates in the presence of triethylamine afforded **165** and/or β-lactam **166**, the yield being low.[169]

Earlier, conversion of anthralium salts **167** into compounds of the type **170** by nucleophiles was found to proceed via unstable β-lactams **169**. Also, similar β-lactams were obtained by photolysis of **171**.[65]

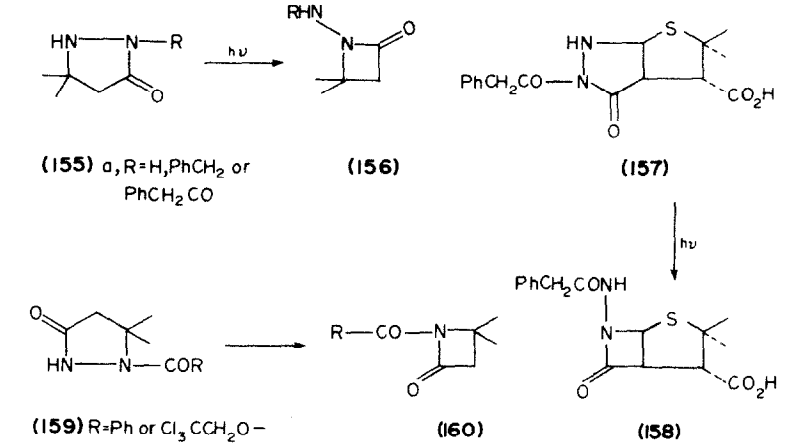
Recently, a new β-lactam synthesis was achieved by thermolysis of **175**.[170] Also, some 1,2-thiazolidin-3-ones **178** were found to give β-lactams **179** in poor yield, when desulphurised with Raney nickel.[171]

3. *Conversion of azetidine derivatives into azetidin-2-ones.* Perfluoroisobutene gave with benzylidine aniline under drastic conditions, the azetidine **181** which on hydrolysis afforded the corresponding β-lactam **182**.[65] The scope of this reaction has not been investigated.

In another method, the compound **183** was treated with imines and the resulting azetidinylidene ammonium salt afforded β-lactams **187**, on hydrolysis.[172]

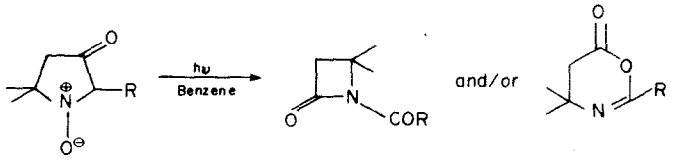
Recently, oxygenation of azetidine dianions **189** afforded β-lactams **192**.[173]

Conversion of azetidines into the corresponding

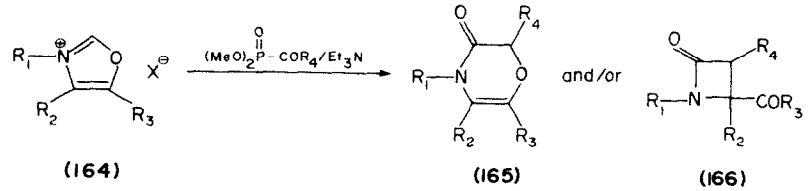


(155) a, R=H, $PhCH_2$ or $PhCH_2CO$ (156) (157)

(159) R=Ph or Cl_3CCH_2O- (160) (158)



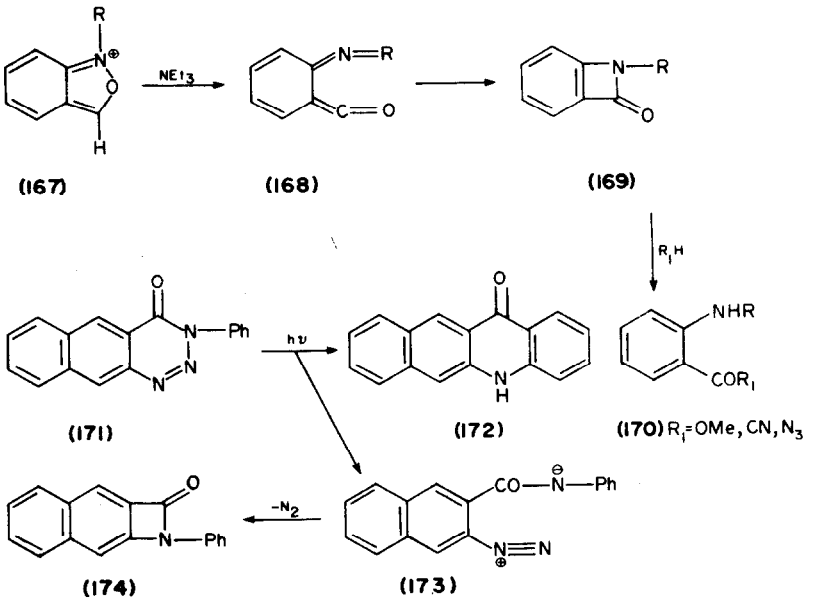
(161) (162) (163)

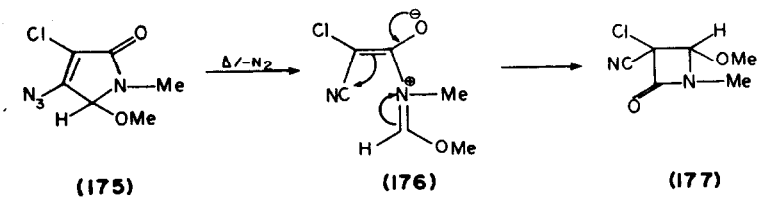


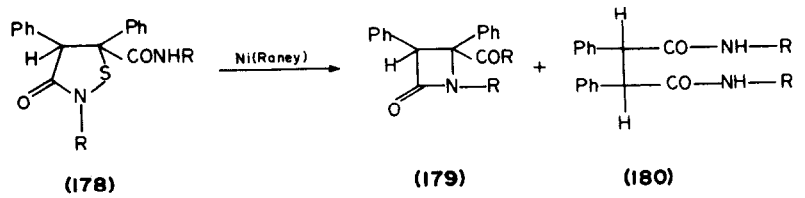
(164)

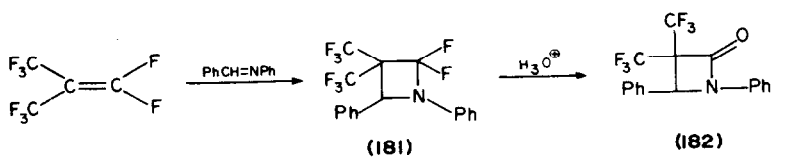
	R_1	R_2	R_3	X
a,	$PhCH_2$	H	Ph	Cl
b,	Me	H	Ph	Cl
c,	Me	Me	Ph	I
d,	Me	Ph	Ph	I
e,	Me	Ph	Me	I

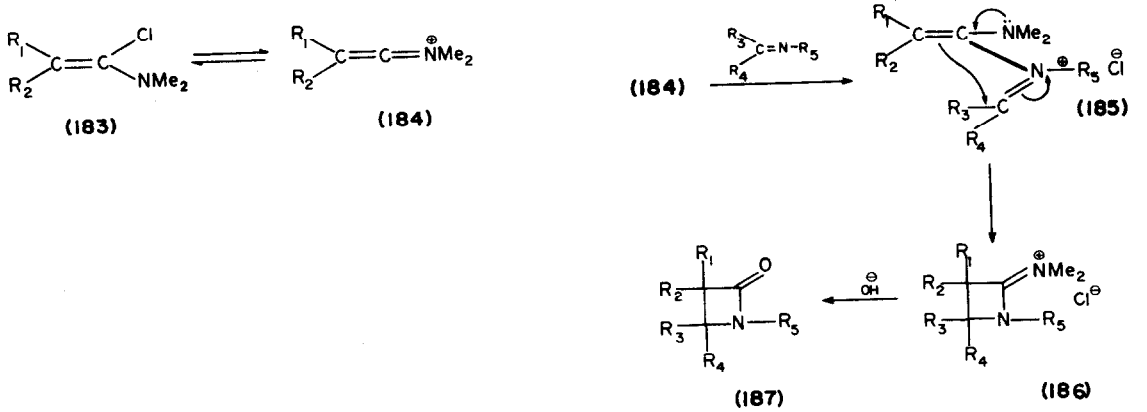
(165) (166)

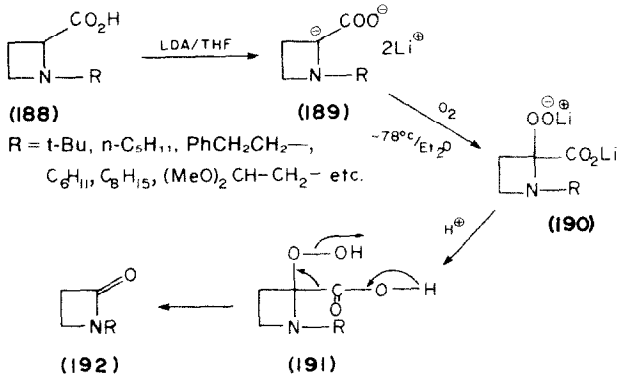

NEt3
(167)
(168)
(169)
R1H
hν
(171)
(172)
(170) R1=OMe, CN, N3
-N2
(174)
(173)


Δ/-N2
(175)
(176)
(177)


Ni(Raney)
(178)
(179)
(180)


PhCH=NPh
H3O⊕
(181)
(182)


(183)
(184)
(184)
(185)
(186)
(187)
R1 = Me, H; R2 = H, Me3C;
R3 = Ph, PhCH2S; R4 = H, Ph;
R5 = Me, Ph, CMe3



azetidin-2-ones does not seem to be of any special advantage.

IV. *Miscellaneous syntheses*

1. *Passerini reaction.* The reaction of carbonyl compounds with 3-aminopropanoic acids, followed by treatment with a suitable isocyanide afforded β-lactam derivatives. This is an extension of the Passerini reaction, and it was useful for the preparation of monocyclic and bicyclic β-lactams **194** and **196** respectively. The reaction envisages formation of a cyclic compound **193** which on transannular acyl migration gave the β-lactam **194**. It is noteworthy that the configuration of the newly formed asymmetric center in the penicillin analogue **196** is predetermined by the steric disposition of the reacting molecule.[174]

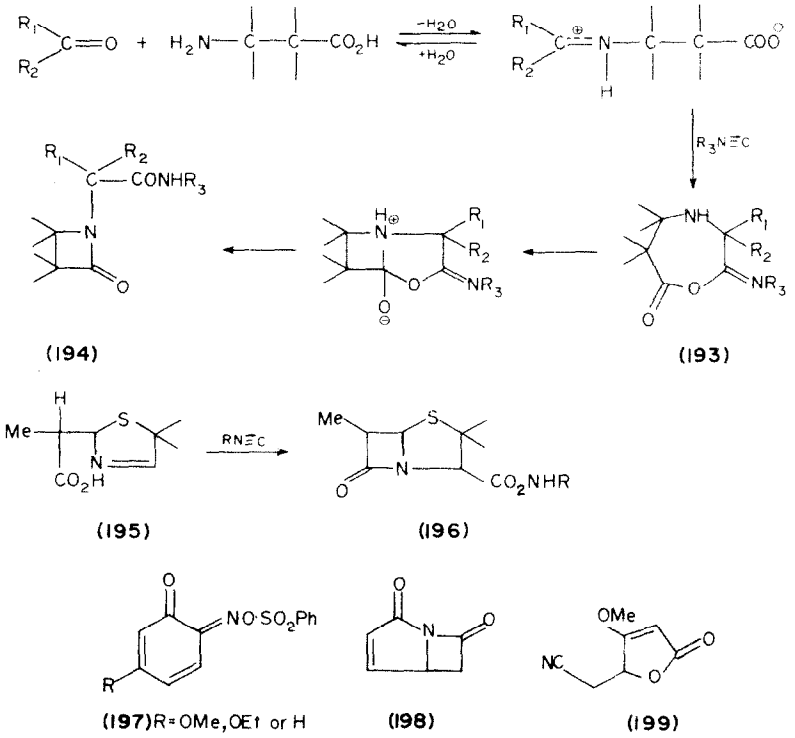
2. *Rearrangement reactions.* There are several cycloadducts which undergo thermal or photochemical fragmentation, generating ketenes and imines which recombine to give β-lactams. This method is of limited use because of the drastic conditions involved, and possible side reactions.[65]

Beckmann rearrangement of O-sulfonyloximes **197** was reported to give novel β-lactams **198**, but recently the revised structure **199** has been proposed.[175]

D. REACTIONS OF PENICILLIN, CEPHALOSPORIN AND OTHER β-LACTAMS

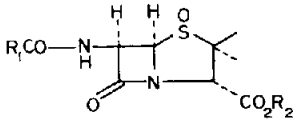
I. *Conversion of preformed β-lactams into β-lactam derivatives*

1. *Cleavage of the 1,2-bond in penicillins and cephalosporins.* The skeletal rearrangement of penicillin-1-oxide to cephalosporin is of practical importance since it offers a method for the facile conversion of easily available penicillins into cephalosporins which are biologically more active.[3,5,176] In such a transformation, as in some other reactions of penicillin, it is necessary to protect the carboxylic function to avoid decarboxylation. Recently, benzyl-penicillin-1-oxide was reported to undergo rearrangement without decarboxylation, and the yield was about 37–61%. This finding is important because it eliminates the protection-deprotection steps.[177] Usually, benzyl, nitrobenzyl, trichloroethyl, *tert*-butyl, methyl, dichlorodimethyl silane and N,N'-diisopropylhydrazine are used as protecting groups.[176] Recently, pentachlorophenyl moiety was used for this

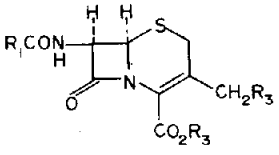


purpose.[178] Also, oxidation of a hydrazone in the presence of a suitable penicillin or cephalosporin in an organic or aqueous organic solvent with a trace of iodine afforded the corresponding ester.[179,180] It should be mentioned that tributylstannyl ester of penicillin has been used in the 6-N-deacylation of penicillin, but its protecting usefulness under various conditions has not been reported.[181] Similar is the case with penicillin thiol esters.[182] Penicillin-1-oxide is obtained by oxidation of penicillin with various oxidising agents.[5] Recently, peracetic acid afforded in good yields the sulphoxides of penicillin G, penicillin V,[183] and chloromethyl penicillin.[184] Also, irradiation of penicillin or cephalosporin in the presence of air and methylene blue was reported to give the corresponding R-isomer of the sulphoxide. It should be mentioned that reagents and reaction conditions can influence the formation of one of the sulphoxide isomers.[5] Also, it depends, in some cases, on whether penicillin or its ester is used.[185]

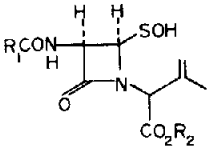
The penicillin-1-oxide **200** undergoes facile ring expansion to deacetoxy cephalosporin under the influence of different catalysts,[176] and the reaction involves cleavage of the 1,2-bond in penicillin, generating a sulphenic acid **201** which has been trapped by various reagents.[5,176,186] Recently, this sulphenic acid was used in the synthesis of (β-methyl-H-3) benzyl penicillin.[187] It should be mentioned that various other products are obtained along with the cephalosporin derivative. The reaction proceeds smoothly and the presence of a C_6-substituent is not a deterrent to the ring expansion. Also the steric integrity is maintained.



(200)

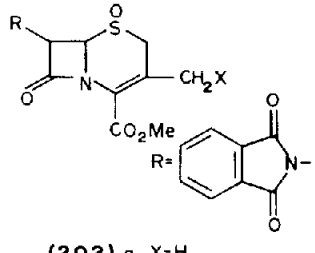


(2) R_3=H

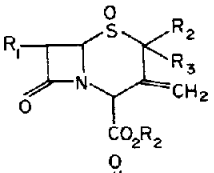


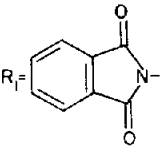
(201)

Recently, phthalimido penicillin-1-oxide was converted with N-bromosuccinimide into the corresponding sulphenylbromide, in high yields, and subsequently into cephalosporin-1-oxide **202**$_a$.[188] Also, the compound **202**$_b$, obtained in this reaction was converted into **202**$_c$. Similarly, other N-chlorohalogenating agents,[189] such as N-chlorosuccinimide,[190] N-chloro-N-methyl-p-tosylamide, and N-chlorophthalimide, were used in inert solvents like toluene, carbontetrachloride or ethylenechloride. It is noteworthy that some of the sulphenylchlorides with tin(IV) chloride afforded 3-methylenecephalosporin-1-oxides **203**[190] which are key intermediates for the preparation of 3-hydroxy- and 3-chlorocephalosporins.[191–193] The sulphoxide can be deoxygenated by treating with phosphorous tribromide.[190]

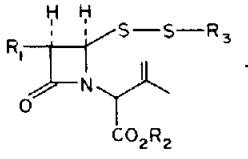


(202) a, X=H
b, X=Br; c, X=OAc.

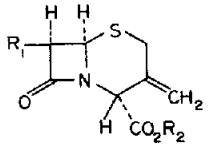


(203) R_1=  ; R_2=Me
or p-$O_2N-C_6H_4-CH_2$; R_3=H or D

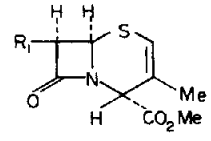
As already mentioned, sulphenic acid obtained from penicillin-1-oxide can be easily trapped to give useful intermediates. Thus, the compound **204**$_a$ gave 3-methylenecephalosporin **205** and Δ^2-cephalosporin **206** on irradiation.[194] Also, the disulphide **204**$_b$ was converted into novel thioxo-β-lactams **208**.[195] It is noteworthy that a similar thione was obtained from **209** on thermolysis.[196]



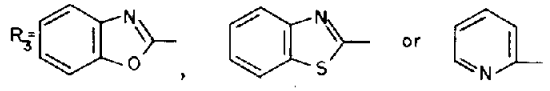
(204)a, R_1=$PhCH_2CONH$; R_2=Me

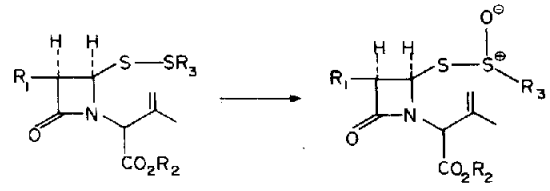


(205)

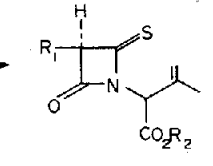


(206)

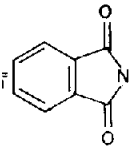


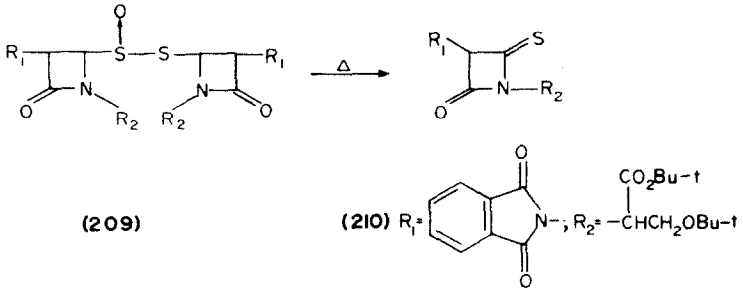


(207)



(208)

(204) b, R_1=  ; R_2=Me; R_3=n-C_5H_{11}



(209) (210) R_1 = ; R_2 = $-CHCH_2OBu\text{-}t$ ($CO_2Bu\text{-}t$)

Penicillin sulphones were recently found to undergo cleavage of the 1,2-bond.[197,198]

2-Ethoxycephalosporin-1-β-oxide **211**$_c$ was found to be thermally unstable, and was easily converted into isothiazolones **212** and the β-lactam derivative **213** under varying reaction conditions. Also, 2-ethoxycephalosporin **211**$_b$, on treatment with *tert*-butylhypochlorite, gave the oxazoline azetidinone **216**$_a$.[199]

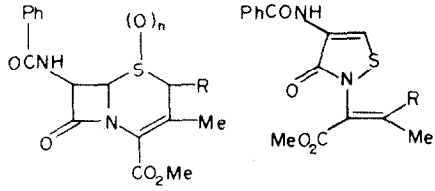
It is noteworthy that deacetoxycephalosporanate (*S*)-1-oxide 2-anion afforded Michael adduct with acrylonitrile. Pummerer reactions with alkoxy chloroformates, and it underwent diazoexchange with tosyl azide. However the (*R*)-sulphoxide under similar condition gave only the Michael adduct with acrylonitrile at the C_4 position.[200]

6α-Phenoxyacetamido penicillanate was converted into **220**, on reacting with chloroamine T or dichloroiodobenzene. Similarly, the 6β-isomer **1** gave **219**, and it was found that reactivities of 6α- and 6β-isomers differ, and the reaction involved cleavage of the 1,5-bond in penicillin.[201]

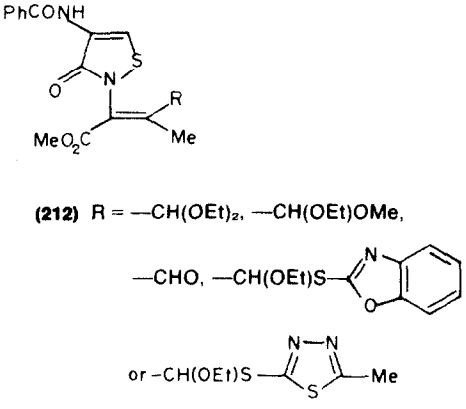
Penicillin-1-oxide **221**, bearing a 6-thioamido function, rearranges to **225**, which can also be obtained by treating the disulphide **204**$_c$ with phosphorus pentasulphide.[202,203]

Phosphorus pentasulphide in pyridine and methylenechloride conveniently deoxygenated penicillin and cephalosporin sulphoxides.[204] The disulphide **204**$_c$ was used in the preparation of iodo derivatives of cephalosporin **226** and penicillin **227**.[205]

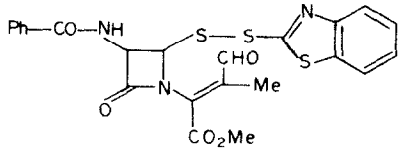
The 1,2-bond cleavage of suitable penicillins by alkyl-



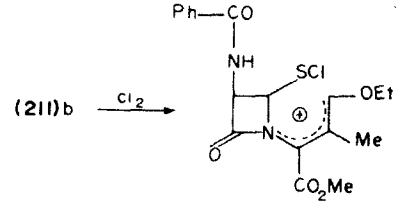
(211) a, n = 0; R = H
b, n = 0; R = OEt
c, n = 1; R = OEt



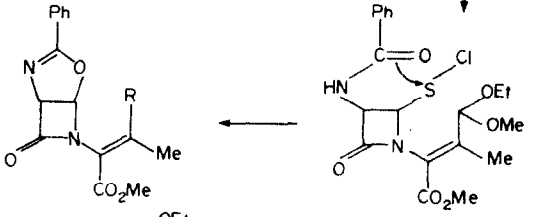
(212) R = —CH(OEt)$_2$, —CH(OEt)OMe, —CHO, —CH(OEt)S— or —CH(OEt)S—



(213)

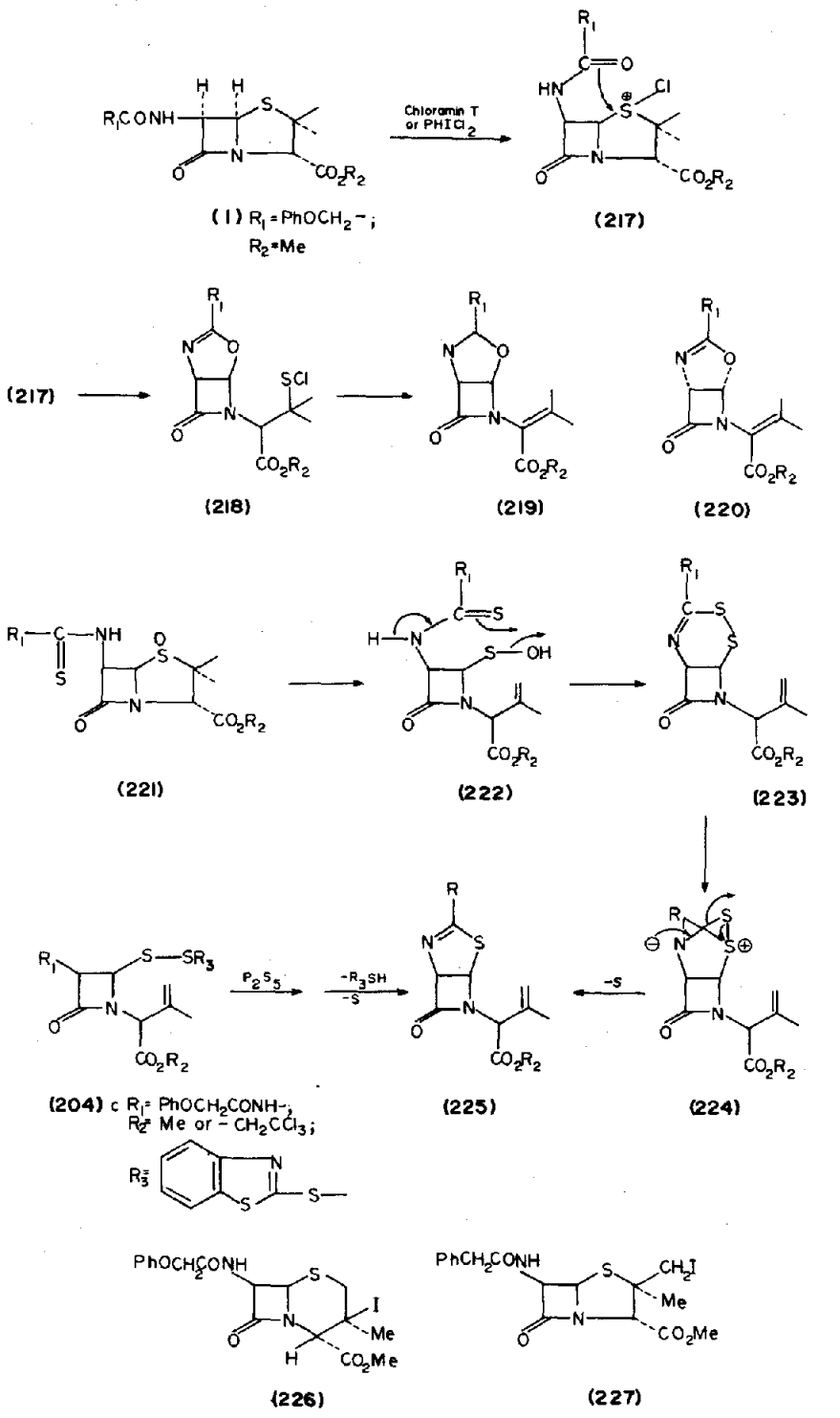


(214)



(215)

(216) a, R = —CH(OEt)(OMe); b, R = —CHO

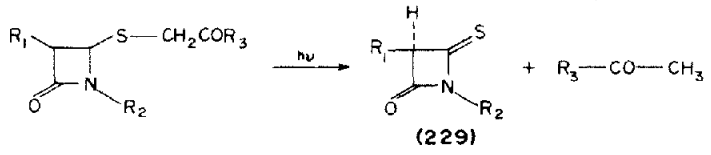


halides in the presence of a strong base results in the formation of azetidin-2-ones, known in the literature as secopenicillins.[5,176] Recently, trimethyloxoniumtetrafluoroborate was used as an alkylating agent, and sulphonium salts were isolated as intermediary products.[206] Also, reaction of carbenes and penicillins afforded secopenicillins.[176] It should be mentioned that a direct synthesis of such compounds is possible by the addition of suitable acid chlorides to thioimidates in the presence of a tertiary base.[207]

Secopenicillins are important intermediates,[208–210] and their manipulation afforded cephalosporins and other novel β-lactam derivatives. For example, the secopenicillins **228** were converted into **229**.[211] The compound $\mathbf{229_b}$ isomerised to $\mathbf{229_a}$, on treatment with triethylamine, and finally the penicillin **230** was obtained.

Recently, the secopenicillin $\mathbf{231_d}$ was converted into a novel tricyclic β-lactam **232**.[212]

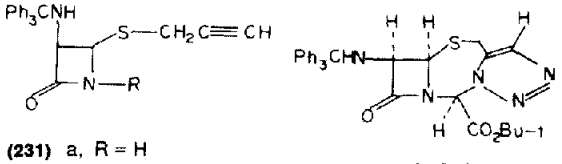
The cephalosporin **2**, on treatment with a carbene formed a sulphonium ylid, which rearranged to penicillin



(228) R_1 = Ph_3CNH, $PhOCH_2CONH$ or CH_3CONH; R_3 = Ph or Me

a, R_2 = $-C(CO_2R)=CMe_2$

b, R_2 = $-CH(CO_2R)-CH=CH-Me$ (R = Me or $PhCH_2$)



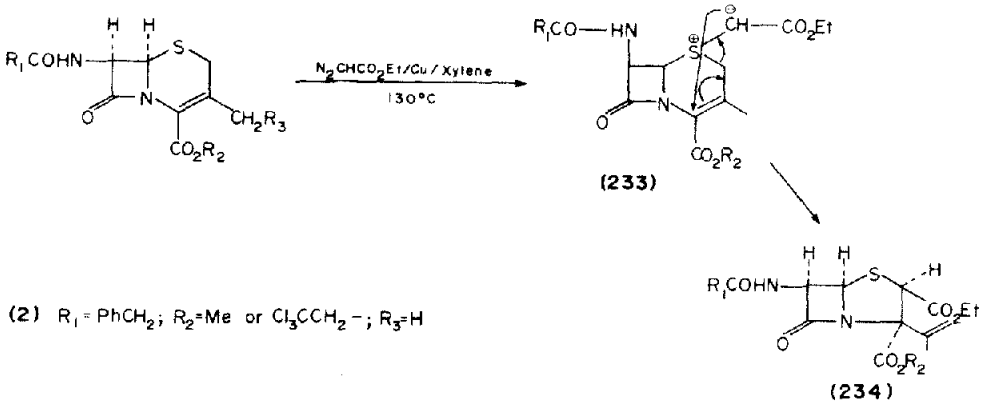
(231) a, R = H
b, R = —CHOH—CO_2Bu-t
c, R = —CHCl—CO_2Bu-t
d, R = —CHN_3—CO_2Bu-t

(232)

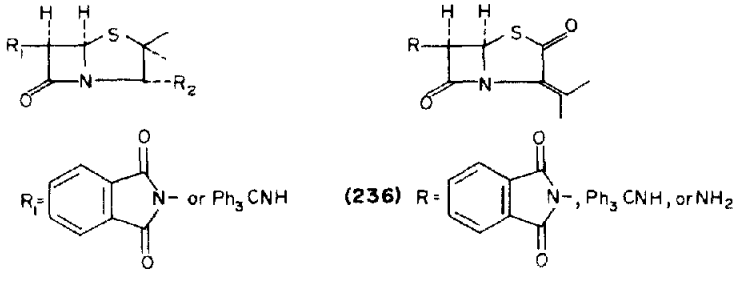
234 via cleavage of the 1,2-bond and subsequent 2,3-sigmatropic change.[176]

Penicillanic acid chloride and anhydride in the presence of triethylamine undergo cleavage of the 1,2-bond with formation of thiolactone **236**, called anhydropenicillin, in 20% yield.[5] Recently, 6-tritylaminopenicillanic acid with chlorosulphonylisocyanate in methylnitrile, containing triethylamine, gave the corresponding tritylaminoanhydropenicillin in 45% yields, which was detritylated with p-toluenesulphonic acid in acetone.[213] The compound **235**$_d$ afforded **237**.[3] Anhydropenicillins are quite stable and reagents, such as selenium dioxide and lead(IV) acetate failed to oxidise allylic methyl groups.

2. *Formation of 1-unsubstituted azetidin-2-ones and N-substitution.* The cleavage of the 3,4-bond in penicillin

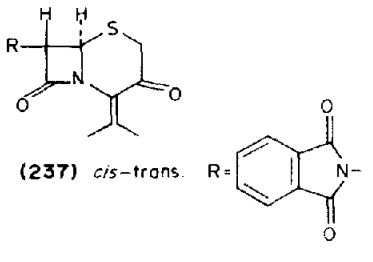


(2) R_1 = $PhCH_2$; R_2 = Me or Cl_3CCH_2—; R_3 = H



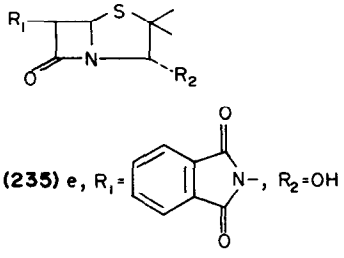
(235) a, R_2 = CO_2H
b, R_2 = COCl
c, R_2 = $COOCOOR_3$
d, R_2 = $COCH_2Cl$

(236) R = N—, Ph_3CNH, or NH_2



(237) *cis*–*trans*. R =

gave a N-unsubstituted azetidinone.[3,176] This was achieved by converting phthalimidopenicillanic acid into its azide which on Curtius reaction and subsequent hydrolysis gave the amidol **235**$_e$ which can exist as the azetidin-2-one **238**. Recently, a simplified Curtius reaction was reported in which an equimolecular mixture of the carboxylic acid, diphenylphosphorazidate and triethylamine was refluxed in the presence of a hydroxyl compound to give the corresponding carbamate **235**$_g$.[214]



(238)

(235) e, R_1 = , R_2 = OH

f, R_1 = $PhCH_2CONH$, or $PhOCH_2CONH$;
R_2 = $-CO_2(PhO)_2P(OH)N_3$

g, R_1 = $PhCH_2CONH-$ or $PhOCH_2CONH$; R_2 = $-NHCO_2R$

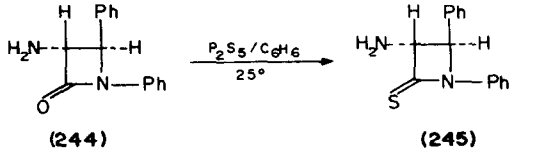
Alternatively, penicillin-1-oxide **200** was converted into amidol ester **239** which on reductive cleavage with sodium borohydride gave **240**.[215]

Similarly, deprotection of the ring nitrogen atom, bearing suitable groups, in monocyclic β-lactams is also possible and it has been discussed elsewhere.[176]

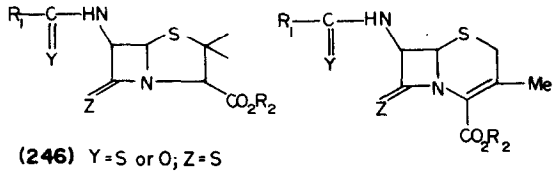
1-Unsubstituted azetidin-2-ones undergo facile N-substitution with various groups.[176] Recently, N-acetylation and N-hydroxymethylation of the azetidin-2-one **238** using Grignard reagent under mild condition was reported.[216]

N-Unsubstituted β-lactams having a suitable functionality at the C-4 atom can be converted into novel bicyclic and tricyclic β-lactams.

3. *Conversion of β-lactams into β-thiolactams.* The first β-thiolactam **245** was obtained by treating azetidin-2-one **244** with phosphorus pentasulphide.[217] Recently, β-thiolactam analogues of penicillin **246** and cephalosporin **247** were obtained in low yields by treating the corresponding β-lactam antibiotics with boron sulphide.[218] It is noteworthy that β-thiolactam antibiotics exhibited lower antibacterial activity.



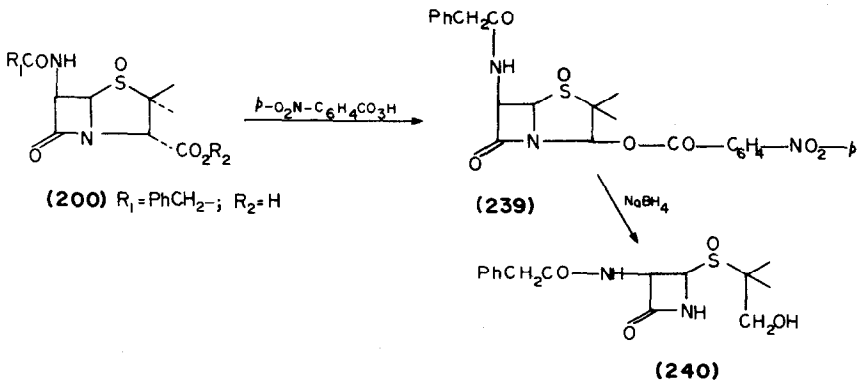
(244) (245)



(246) Y = S or O; Z = S
R_1 = $PhOCH_2-$ or $PhCH_2-$;
R_2 = H or $Cl_3C{\cdot}CH_2-$

(247)

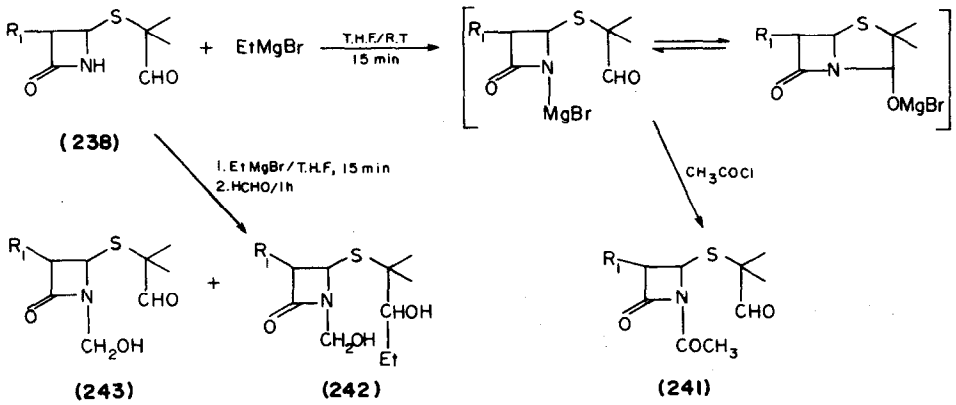
4. *Formation and reactions of amino function at the carbon atom α to the β-lactam carbonyl group.* N-Deacylation of penicillin and cephalosporin can be achieved enzymatically[219] or chemically[176] under mild condition. Recently, N-deacylation of 7α-methoxy cephalosporin C was effected by converting the 7-amido function into an imidoyl chloride, followed by treatment



(200) R_1 = $PhCH_2-$; R_2 = H

(239)

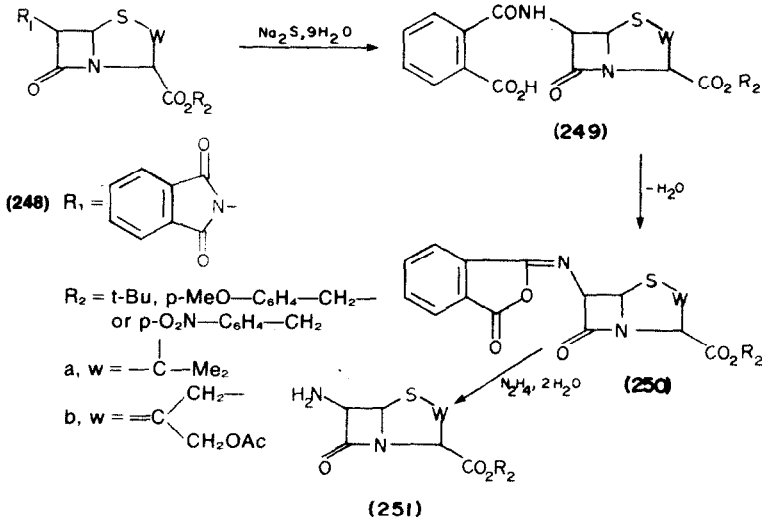
(240)



(238)

(243) (242) (241)

with methanol and water at 0°C. It is noteworthy that the 7β-methoxy isomer failed to undergo similar N-deacylation.[220] Dephthaloylation of several phthalimido-β-lactams have been effected by hydrazinolysis,[176] but the choice of solvent and reaction temperature is important in this case as otherwise the β-lactam ring may be ruptured.[221] Recently, N-dephthaloylation ofphthalimido penicillin and cephalosporin was achieved by treating phthalimido compounds **248** with sodium sulphide and subsequently with ethyl chloroformate/triethylamine, trifluoroacetic anhydride or carbodiimide to give the iminolactone **250** which undergoes facile hydrazinolysis without affecting the β-lactam ring.[222]



Azido-β-lactams serve as progenitors of the corresponding amino derivatives and the conversion is effected by catalytic hydrogenation.[32] Nickel, palladium, platinum and platinum oxide usually serve as catalysts. However, the presence of a sulphur moiety or a carbon-carbon double bond in the β-lactam molecule may cause desulphurisation or complete reduction which may not be desirable. Lindlar catalyst seems to have not been applied in azide—primary-amine transformation in β-lactams, and this catalyst may be of use in selective reduction of the azide group. Recently, ammonium sulphide was used to reduce a β-lactam azide.[223]

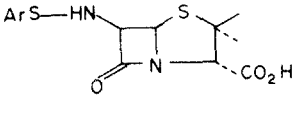
The carboxylic acid function has been converted into an amino group[5,176] via Curtius reaction in many β-lactam derivatives. It should be emphasised that the β-lactam in this case should be sufficiently stable so as to withstand the conversion process.

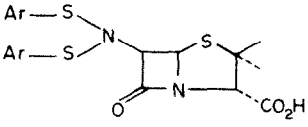
Recently, 3-isocyanoazetidin-2-one was converted into the corresponding amino compound by treating with *p*-toluenesulphonic acid hydrate.[224]

The amino group gives all the usual reactions of a primary amine,[176] and the availability of 6-aminopenicillanate and 7-aminocephalosporanate has ensured the preparation of a large number of semisynthetic β-lactam antibiotics[5,225] with improved biological activity. Normally, the amino function is acylated under mild condition. Transacylation of penicillin and cephalosporin is now possible,[176,226] and this process is of practical importance. In some cases, the side-chain amide was converted into a thioamide function by treating the suitable penicillin with phosphorus pentachloride and subsequently with hydrogen sulphide.[227] Recently, penicillin sulphenamides **252** and **253** were prepared by the interaction of a suitable sulphenyl chloride and 6-APA.[228]

Deamination in penicillin and cephalosporin was achieved recently, and this has been discussed elsewhere.[176]

5. *Epimerisation and substitution at the carbon atom α to the β-lactam carbonyl group.* The biological activity of penicillins and cephalosporins is due to the 5,6-*cis*- and 6,7-*cis* stereodisposition of their respective molecules. It is now possible to convert the non-active *trans*-isomers into the corresponding active *cis*-isomers under the influence of a base.[229,230] Such a transformation

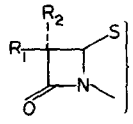




depends on the electro-negativity of C-6 and C-7 substituents in penicillin and cephalosporin respectively, and also on the basicity of the catalysing base.[3] Recently, penicillin-1-oxide[231] and penicillin-1,1-dioxide[197,198] were found to epimerise in the presence of a base. The process of epimerisation[5,176] is of practical importance, and it has enabled to prepare several novel penicillin and cephalosporin analogues with the desired stereochemistry.

Epimerisation and incorporation of deuterium at the C-6 atom in penicillin indicated the lability of the C-6 hydrogen atom, and this property has been used in C-6 and C-7 substitution reactions of penicillin and cephalosporin respectively.[5,176] Usually, the aromatic aldimines **254** are used, and diverse moieties such as alkyl, cyanoalkyl, hydroxyalkyl, alkoxy and alkylthio groups have been introduced. The reaction has been variously modified. Recently, the compound **257** was

(254) R = p-O_2N—C_6H_4—CH=N—, or PhCH=N— (255)

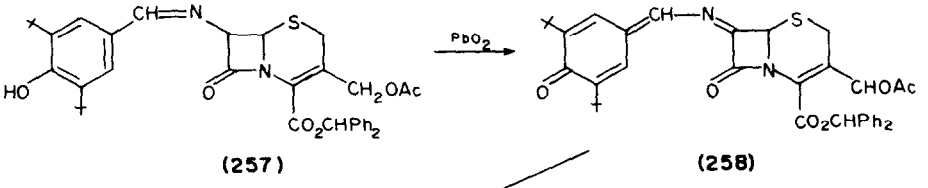


(256) R_1 = ArCH=N—, NH_2, $PhCH_2CONH$— etc.; R_2 = Me, MeO, MeS, etc.

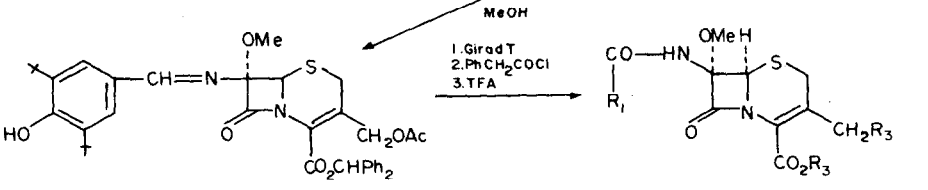
oxidised with lead(II) oxide to give **258** which afforded a cephamycin derivative on further manipulation.[232] This method has been extended to the synthesis of other C-7 substituted cephalosporins.

Earlier, C-6 substituted penicillins **262** were obtained by converting 6-oxopenicillin **260** into **261** and subsequent addition of methanol or hydrogen cyanide.[233]

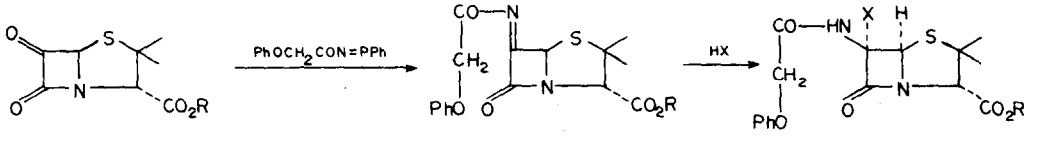
In another approach, cephalosporins **263** were converted into their respective iminochlorides **264** which on treatment with a base gave the key intermediate **265**, via 1,4-elimination, which with a methoxide anion afforded **266** and subsequently 7α-methoxy-cephalosporin with trifluoroacetic acid and water.[234] It is noteworthy that the reactivity of the imine **265** depended on the substituent R_1, and when R_1 was phenyl or alkyl the ketenimine **266** was obtained. When R_1 was halogen, thienyl, PhS-, MeS- or $MeSO_2$-, the imino-ethers **267** were isolated which



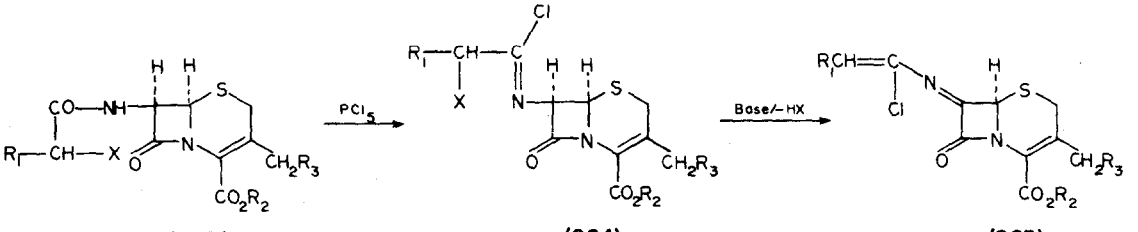
(257) (258)



(259) (3) e, R_1 = $PhCH_2$—; R_2 = H; R_3 = —OAc

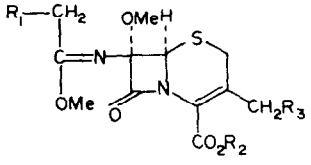


(260) R = $PhCH_2$ (261) (262) X = O Me or CN; R = $PhCH_2$ or H

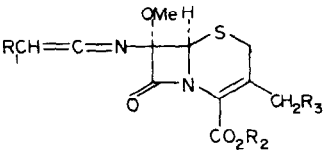


R_1 = Ph or Cl; R_2 = H, Me, Ph_2CH, or p-C_6H_4CO—CH_2—; R_3 = H or AcO—; X = Cl or Br

(263) (264) (265)



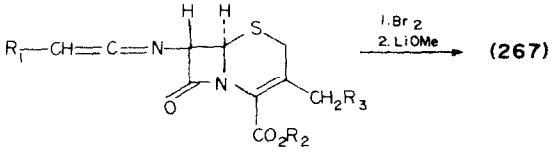
(267) R_1 = Ph or Cl; R_2 = H, Me, p-Br—$C_6H_4COCH_2$—; R_3 = H or AcO—



(266) R_1 = Ph; R_2 = Me or Ph_2CH; R_3 = H

were converted into **266** by treating with an excess of trimethylchlorosilane and one equivalent of quinoline, in chloroform at room temperature for 12 h, and finally with water. The acyl part with a γ-halo α,β-unsaturation under similar condition underwent 1,6-elimination, and the resultant compound was converted into C-7 methoxy derivative. The yields were high. Similar methoxylation was effective also in penicillin.[234]

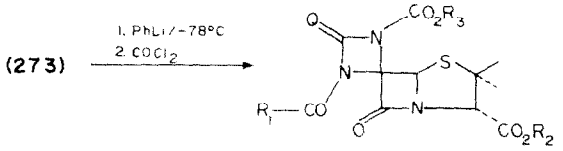
Cephalosporin iminochloride **264**, in which X is hydrogen, on treatment with a base, gave **268** which on reacting with bromine and subsequent treatment with lithium methoxide gave **267** which is a progenitor of 7-methoxy cephalosporin.[235]



(268)

It is noteworthy that iminochlorides **270**, on treatment with a strong organic base, generated a 1,3-dipolar intermediate which reacted with several dipolarophiles, such as acrylonitrile, methylacrylate, dimethyl acetylenedicarboxylate, diethyl azo dicarboxylate, chloral, and phenylisothiocyanate, to give spiro compounds **272**.[236]

Recently, penicillin esters were found to give **273**, with N-chloro-N-sodiourethane in methylnitrile at room temperature, which were converted into cephalosporin derivatives **274** via the corresponding sulphoxide.[237]



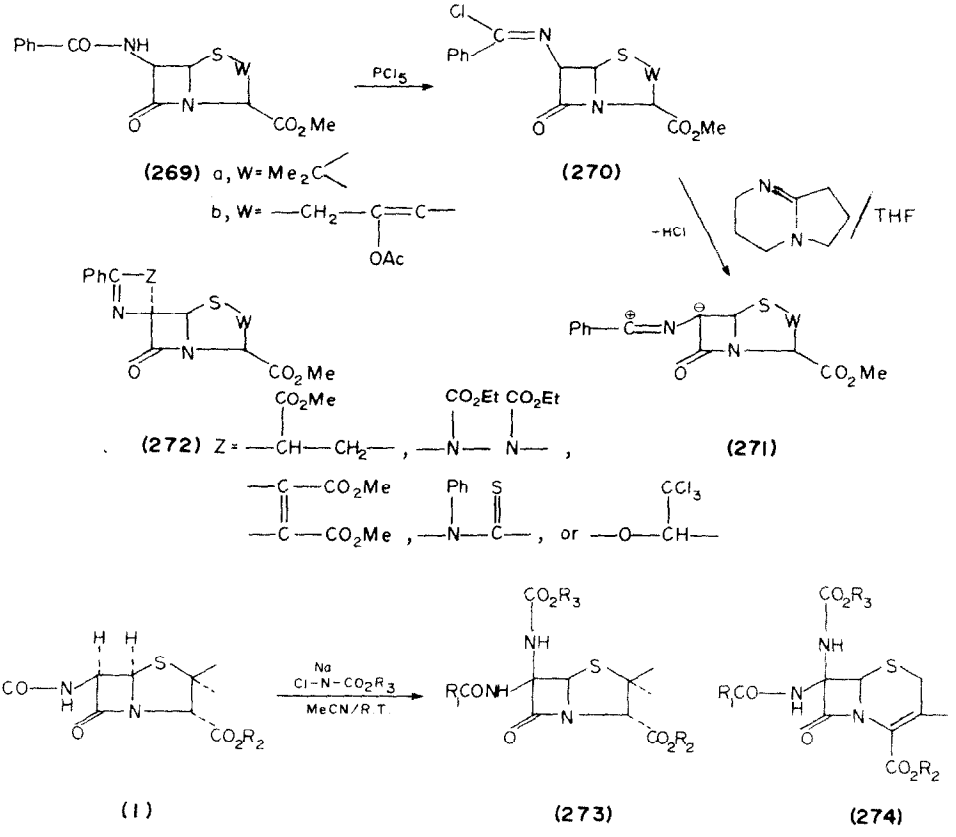
(275)

Recently, the compound **273** was converted into a novel spiro compound **275** with phosgene.[238]

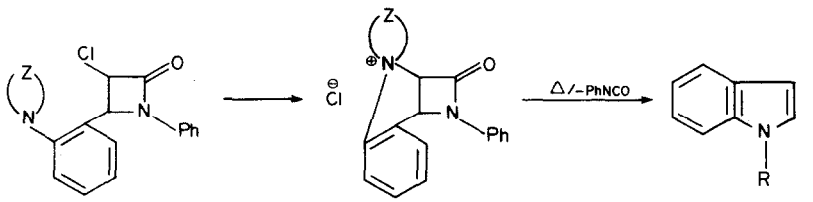
As already mentioned, β-lactams with a C-α halogen atom were synthesised by various workers with a view to convert the halogen function into an amino group. Such a conversion was found difficult, possibly due to the vulnerability of the β-lactam ring. Recently, 3-chloro-azetidin-2-one **276** was found to undergo intramolecular cyclisation to give **277** which on thermolysis afforded a novel indole system **278**.[239]

1-Alkyl- and 1-aryl β-lactams, on treatment with a powerful base at low temperature, generated a C-3 carbanion which was used for the preparation of 3-alkyl-, hydroxyalkyl-, acyl- and nitroazetidin-2-ones.[176]

6. *Reactions at the C-4 atom in azetidin-2-ones.* Removal of sulphur in penicillin and 4-thioazetidin-2-ones was achieved by reductive desulphurisation,[176] and chlorinolysis.[176,240,241] The reaction products serve as useful intermediates. It is noteworthy that the 4-thioazetidin-2-one **238** gave 1,4-azetin-2-one **279** under mild conditions which was converted into the thiol **280** on heating with hydrogen sulphide in an organic solvent.[242] Michael reaction with **279** has not been explored, and it is likely that the compound **279** may serve as an useful intermediate for constructing biolo-



R_1 = $PhOCH_2$; R_2 = Me or CCl_3CH_2—; R_3 = Et or CCl_3CH_2.



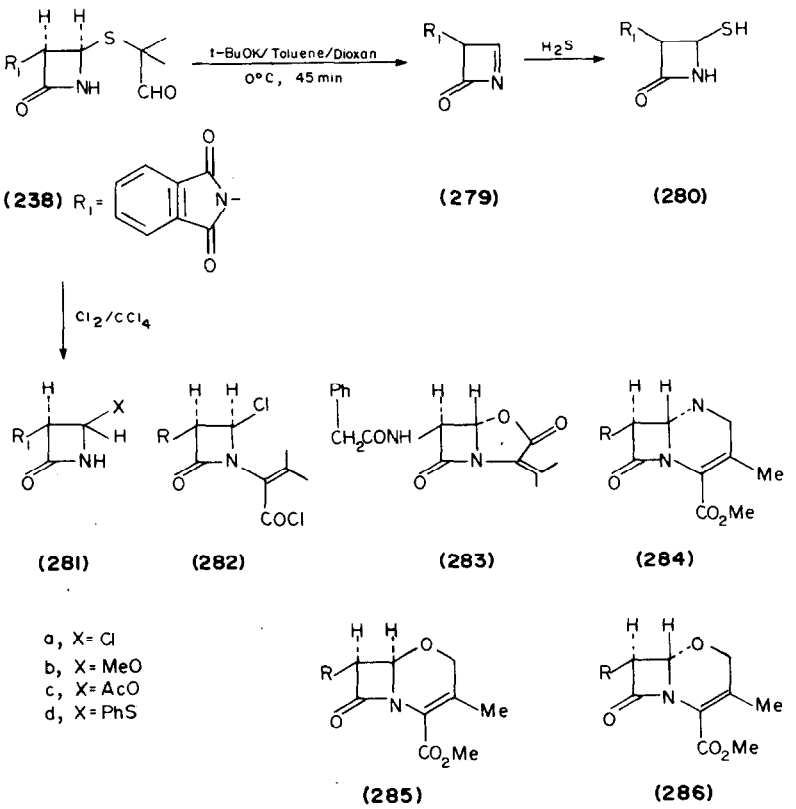
(276) (277) (278)

Z = Me_2, $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_6$ etc.

R = $(CH_2)_4Cl$, $(CH_2)_5Cl$, $(CH_2)_6Cl$, $(CH_2)_5OH$ etc.

gically active β-lactams. Chlorinolysis of **238** afforded 4-chloroazetidin-2-one **281**$_a$ in which chloro group is highly reactive, possibly due to the vicinal nitrogen atom, and it was converted into **281**$_{b-d}$.[243] Recently, the 4-chloroazetidin-2-one **282** obtained by chlorinolysis of anhydro penicillin was converted into **283**,[244] **284**,[244] **285**,[245] **286**[245] by suitable manipulation.

modification.[176] For example, the β-lactam **287**$_a$ gave the haloketone **287**$_c$, via the corresponding diazoketone **287**$_b$, which was converted into aminothiazole **288** with thiourea. The haloketone **287**$_c$ could be useful for the synthesis of β-lactams bearing other heterocycles at the C-4 atom. Also, it would be worthwhile to explore annulation of the diazo carbon atom with the 1-aryl group via



(238) (279) (280)

(281) (282) (283) (284)

a, X = Cl
b, X = MeO
c, X = AcO
d, X = PhS

(285) (286)

Also, the (±)-2-spirocyclopentano-bis-norpenicillin system was obtained by chlorinolysis of suitable penicillin followed by manipulation of the resultant compound.[246] Recently, cleavage of the 1,5-bond in penicillin was achieved by treatment with chloramine.[147]

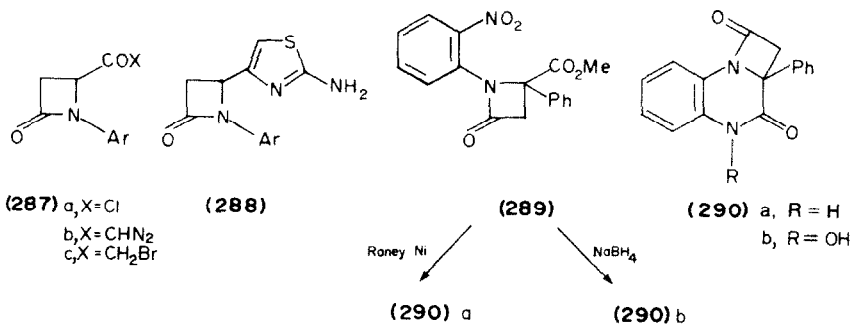
It is noteworthy that C-4 acetoxy group is also easily replaceable with a suitable mercaptan, and this facile displacement was used for the synthesis of cephalosporin analogues.[248] A similar replacement of C-4 sulphone group by a suitable mercaptan has also been reported.[49]

Another important functionality at the C-4 atom of azetidin-2-ones is carboxylic group which is amenable to a carbene insertion. Recently, 4-carbethoxyazetidin-2-one **289** on reduction, gave **290**$_a$ or **290**$_b$ depending on the reducing agent.[86]

Thus, functional groups, at the C-4 position in azetidin-2-ones, which are amenable to suitable modification, could be profitably utilised for the construction of novel β-lactams.

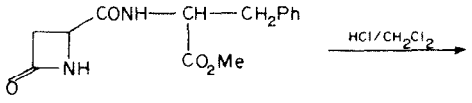
II. *Opening of the β-lactam ring*

The various bonds in β-lactam can undergo cleavage to give an acyclic system which may further undergo transformation resulting into rearranged cyclic products or fragmentation of the molecule.[176]



1. *Cleavage of the β-lactam bond.* The β-lactam bond undergoes rupture in the presence of an alkali, acid and β-lactamase, yielding 3-amino propanoic acids. By selective degradation the natural β-lactams could afford useful amino acids.

In the presence of dry hydrogen chloride, a β-amino acid chloride hydrochloride is generated. For example, the compound **291** gave **292**, on treatment with hydrogen chloride in methylene chloride.[250] Similarly, the β-lactam may be cleaved by amines.[176]



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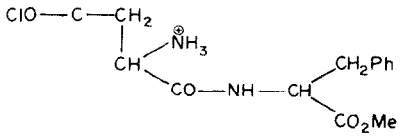
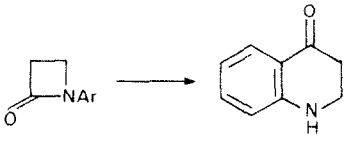


(292)

These reactions may have application in peptide synthesis. If a β-lactam contains an amino function or its progenitor at a suitable position, an intramolecular aminolysis may be achieved which would yield an appropriate heterocycle. Recently, the compound **293** was converted into **294** and other cyclic compounds.[251] When a 3-chloro substituent was present, the propionamide formed during aminolysis reacted further to give an aziridine carboxamide. Thus, the compound **295** with piperidine gave **296** in excellent yields.[253]

β-Lactams are also capable of polymerisation, and especially 1-unsubstituted azetidin-2-ones have been useful monomers.[176]

Intramolecular N–C transacylation of 1-phenylazetidin-2-one **120**$_a$ by photolysis[176] or trifluoroacetic acid[254] gave tetrahydroquinolin-4-one **297**. Thus, with suitable substitution in the 1-aryl ring, different quinolinones can be synthesised. Thermal transformation of 4-iminoazetidin-2-ones **298** into 2-aminopyridines is another example.[255]



(120) a (297)

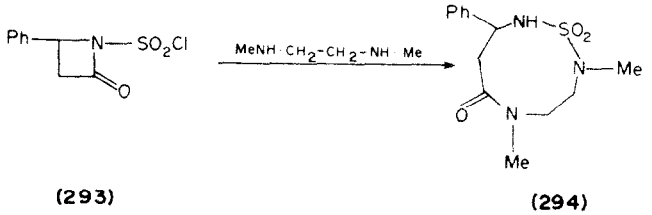
The penicillin diazoketone **235**$_e$, on irradiation in aqueous dioxan, followed by methylation with diazomethane gave a bicyclic ketone **305** and methyl ester of homopenicillanic acid.[256] Recently, it was found that copper-catalysed decomposition of the diazoketone in an aprotic solvent afforded a novel tricyclic β-lactam **308**.[257]

This reaction is reminiscent of the carbene-induced secopenicillin formation, with the difference that it is intramolecular and it involves cleavage of the 1,5-bond in penicillin.

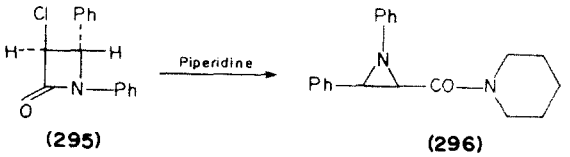
1-Substituted β-lactams undergo reductive cleavage with lithiumaluminium hydride to give 3-alkyl- or aryl-aminopropanol.[176]

2. *Cleavage of the 2,3-bond in azetidin-2-ones.* 1-Haloazetidin-2-ones **309** undergo photolyti or thermolytic cleavage to give isocyanates **310** capable of undergoing secondary cyclisation under suitable condition.[258] Similarly, 3-azidoazetidin-2-one **312**, on refluxing in diglyme, underwent ring expansion through 2,3-bond cleavage.[259]

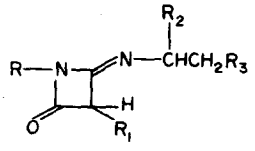
3. *Cleavage of 3,4- and 5,6-bonds, respectively in azetidin-2-ones and penicillins.* Rearrangement of peni-



(293) (294)



(295) (296)



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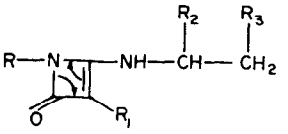
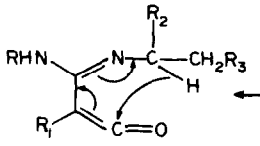


(299)

180–190°C



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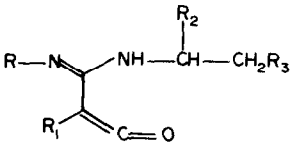

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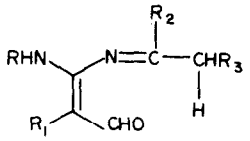

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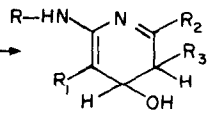
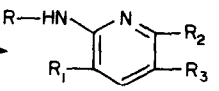


(303)

$-H_2O$



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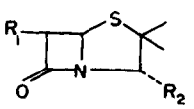
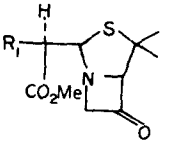
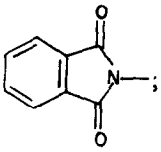
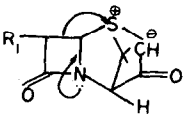


1. hν/$-N_2$
2. CH_2N_2



(235)e R_1 =  ; R_2 = —$COCHN_2$ (305)

$-N_2$



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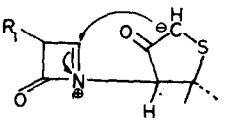
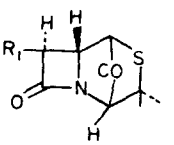
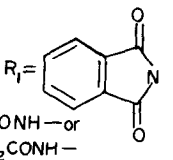
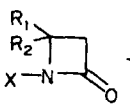


(307)

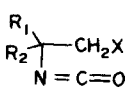


(308) R_1 = 

$PhCH_2CONH$— or $PhO—CH_2CONH$—

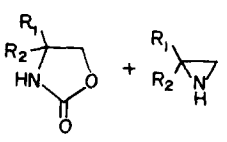


(309) X=Cl or Br

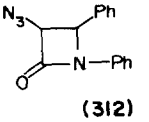


(310)

1. Aq.HCl
2. $OH^{\ominus}$

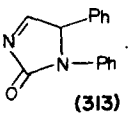


(311)

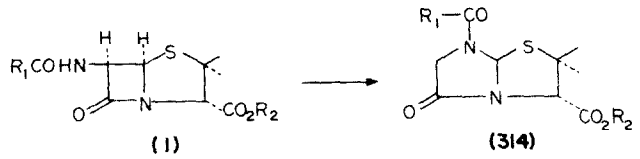


(312)

Δ/diglyme
$-N_2$



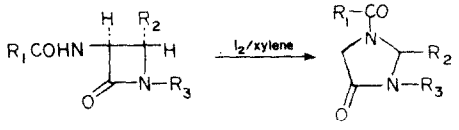
(313)



(1) (314)

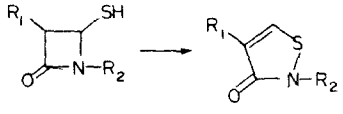
cillin to penillonic acid **314** involves cleavage of the 5,6-bond.[2] Similar bond cleavage was recently observed in penicillin-1-oxides.[260]

Cleavage of the 3,4-bond in 3-acylamino-1,4-diphenylazetidin-2-ones **315** and concomitant rearrangement afforded imidazolidinones **316** and other products. It is noteworthy that substituents and the stereodisposition of the molecule influenced the proportion of the products.[176]

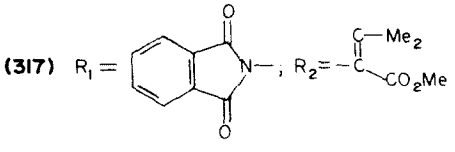


(315) R_1, R_2, R_3=Aryl (316)

4. *Cleavage of the 1,4-bond in azetidin-2-ones and collapse of the bridge in bicyclic β-lactams.* β-Lactams bearing a C-4 hetero atom are unstable and easily undergo 1,4-bond cleavage.[176,223,261-263] For example, the 4-mercapto azetidin-2-one **317** changes to isothiazolinone **318** in 40% yield, on treatment with dimethyl sulphoxide.[264]



(318)



(317)

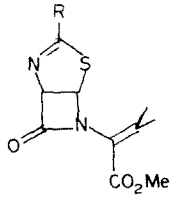
Isomerisation of 1,4-diarylazetidin-2-ones in cold sulphuric acid gives the corresponding 3,4-dihydro-4-arylquinolin-2-ones **320**.[176] It is noteworthy that 1-aryl-3-chloroazetidin-2-ones **319b** in polyphosphoric acid at higher temperature changed to 3-arylquinolin-2-ones **321** as a result of elimination of hydrogen chloride and aryl migration.[265]

The conversion of 1,4-divinylazetidin-2-ones **322** into **323** and **324** through Cope rearrangement also involved cleavage of the 1,4-bond.[176]

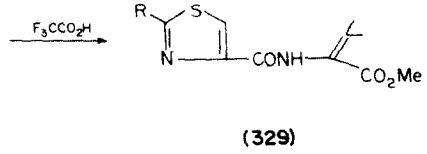
N-Benzyl-β-lactams rearranged to γ-lactams when treated with lithium diisopropylamide.[176] Similarly, 4-chloromethylazetidin-2-one **325** underwent ring expansion on treatment with aqueous potassiumhydroxide.[266]

It is noteworthy that several 4-phenylazetidin-2-ones gave 3-phenyl-propanoic acid amides, on hydrogenolysis via cleavage of the 1,4-bond, possibly due to their benzylamine-like nature.[176]

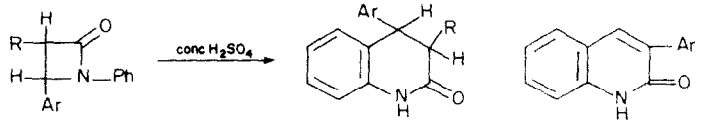
Recently, the bicyclic β-lactam **328** was converted into the thiazole derivative **329** with trifluoroacetic acid.[267,268]



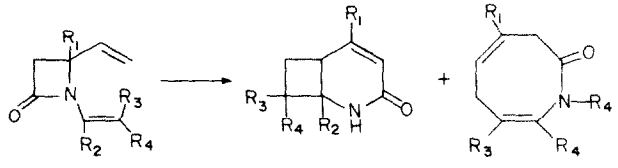
(328) R=$PhCH_2$ or Ph



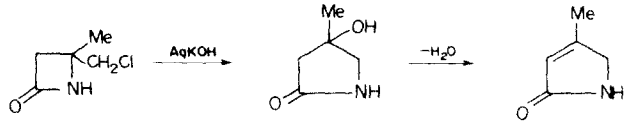
(329)



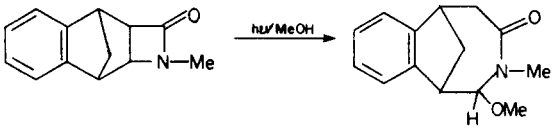
(319)a, R=H
b, R=Cl (320) (321)



(322) (323) (324)

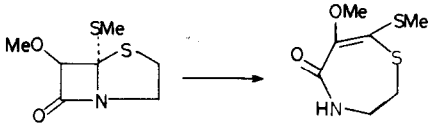


(325) (326) (327)



(330) (331)

On the other hand the compound **330**, on photolysis rearranged to **331**.[269] Similarly, the compound **332** rearranged to a large ring heterocycle **333** with the collapse of the bridge, and this reaction is potentially important.[127]



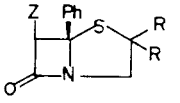
(332) (333)

III. *Miscellaneous reactions*

1. *Fragmentation of β-lactams.* Monocyclic β-lactams on photolysis or thermolysis breaks up into ketenes and imines or alkenes and isocyanates, depending on the substituent present in the molecule and which ever fragmentation is energetically profitable.[176] This process is essentially a case of retrocycloaddition. Reagent-induced fragmentation leads to diverse products, depending on the substituents and reagents used.

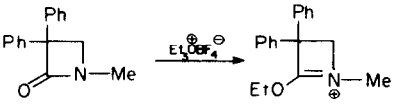
Fragmentation of penicillin[270] and cephalosporin[271] occurred, on treatment with trifluoroacetic acid, the fragments being amido ketene, and Δ^2-thiazoline and Δ^2-1,3-thiazine derivatives respectively. Sometimes, the fragments formed as primary products may undergo secondary reactions. For example, the β-lactam **334**, on retro Michael reaction, gave **335** and subsequently **338** and **339**.[272]

Recently, enzyme-catalysed fragmentation of benzylpenicillin was reported.[273,274] It is noteworthy that the azido group in β-lactam **340**$_a$, on reduction with Adam's catalyst and subsequent acylation with phenoxyacetylchloride and triethylamine afforded the 6-phenoxy compound **340**$_c$.[275] Such an unusual result may be explained only on the assumption that the 6-amino compound **340**$_b$ undergoes fragmentation and generates a Δ^2-thiazoline, which then reacts with phenoxyacetylchloride and triethylamine in the usual way.

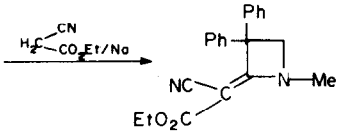


(340) R = H or Me
a, Z = N_3
b, Z = NH_2
c, Z = PhO

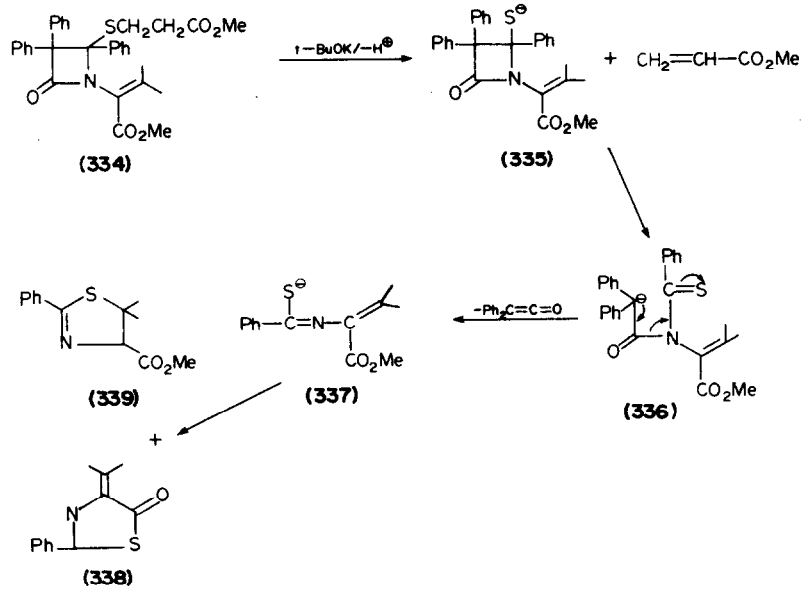
2. *Conversion of β-lactams into lactim ethers and azetidines.* 1-Unsubstituted azetidin-2-ones were converted into lactim ethers by O-alkylation and also by treating with trimethyloxonium fluoroborate.[176] It is noteworthy that vapour phase pyrolysis of 2-alkoxy-1-azetines brings about an electrocyclic ring opening analogous to the opening of cyclobutenes to butadienes.[276] Recently, 1-methyl-3,3-diphenylazetidin-2-one **341** gave with triethyloxoniumfluoroborate the compound **342** which on reaction with ethylcyanoacetate and sodium afforded **343** in 41% yield.[176] This reaction is potentially important and may be useful for the conversion of 1-substituted azetidin-2-ones into the corresponding azetidines.



(341) (342)



(343)

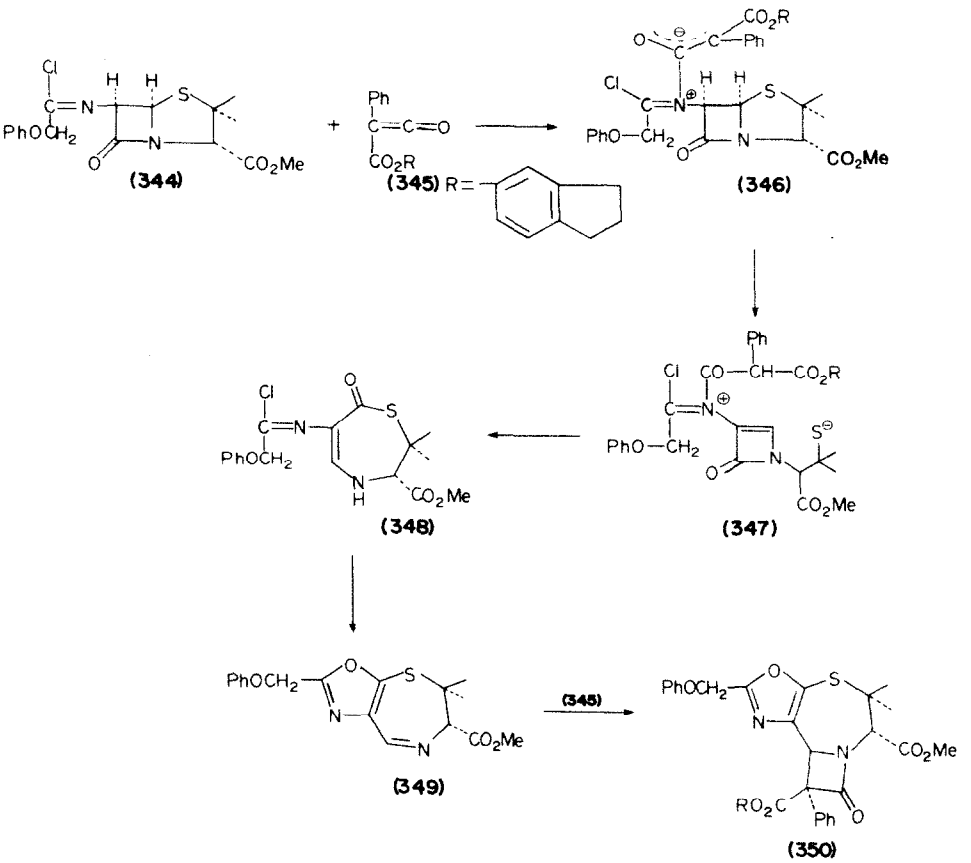


(334) (335) (336) (337) (338) (339)

The 1-unsubstituted β-lactams undergo facile reduction to azetidines, on treatment with lithiumaluminiumhydride, and diborane. The nature of solvent influences the reaction, and often reductive cleavage takes place, as in the case of 1-substituted β-lactams.[176]

3. *Transformation of penicillin derivatives into a novel tricyclic β-lactam.* As already mentioned, skeletal rearrangement of penicillin leads to different products. Recently, a novel tricyclic β-lactam **350** was obtained by the interaction of phenyl-5-indanyloxy carbonyl ketene **345** and iminochloride of penicillin V. The reaction is supposed to involve the oxazole derivative **345**, which is obtained by the cleavage of the 1,5- and β-lactam bonds in penicillin.[277] It is noteworthy that the imino bond of the oxazole moiety is not attacked by the ketene.

β-lactamase inhibitors.[288] In the last category, the acyl part carries a basic or acidic function. Recently, in a series of cephalosporins having C-7 side-chains, derived from 2-[(2,2,2-trifluoroethyl)thio]- or 2-(cyanomethylthio)acetic acid, it was found that the oxidation state of the side-chain sulphur atom from sulphide to sulphoxide/sulphone affected the activity of the antibiotic.[289] Similarly, some bis-cephalosporins were also found active.[290,291] It should be mentioned that other side-chains present in penicillins and cephalosporins also affect the activity directly or indirectly. For example, the carboxylic function when in the form of an ester or a less soluble salt behave differently. Similarly, replacement of the 3-actetoxy function in cephalosporin by other moieties affects the activity. Thus, suitable alteration in

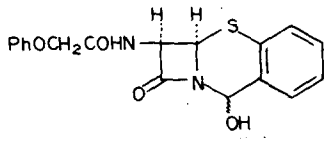


4. *Biological activity.* As already mentioned, penicillins and cephalosporins are active against several bacteria, and the main thrust of research in the field of β-lactam antibiotics has been to improve their therapeutic value.[278] As a result, the number of new penicillins[279] and cephalosporins[280–287] has been multiplying with the years. Generally, the activity of these antibiotics requires stereospecific fused bicyclic β-lactam disposition of the molecule, which in concert with the amido side-chain controls the nature and degree of the activity. Thus, the biologically active penicillins and cephalosporins can be classified under three groups. In the first group, the acyl functions are derived from alkyl, aryl, heteroaryl or aralkyl acids. To the second group belong those in which the acyl function enhances the activity by virtue of its steric factor. Recently, β-lactam antibiotics with an acyl group bearing a ferrocenyl moiety was found to exhibit high antibiotic activity and some of them are potent

the molecule of penicillin and cephalosporin widened the scope of these antibiotics and a large number of broad-spectrum antibacterial agents of this group are now available.[278]

The precise relationship of the structure and activity cannot be defined when the large number of biologically active penicillin and cephalosporin analogues are taken into consideration. For example, replacement of the sulphur atom of the thiazine part in cephalosporin by oxygen atom, methylene and amino groups did not denude the molecule of its antibacterial property.[8,123,124] Also, some cephalosporin-1-oxides were reported active.[292] Similarly, the tricyclic amidol **351**, in which the thiazolidine nucleus of penicillin is absent, exhibited activity against *S. aureus*.[293] It is noteworthy that cephalosporin, in which the C-4 carboxylic function was replaced by an acrylate moiety, was found inactive.[294]

Recently, 6β - (hexahydro - 1 - H - azepin - 1 - yl)-



(351)

methyleneamino penicillanic acid, called mecillinam, which does not carry the 6-amido side-chain, exhibited high level of activity.[295–297] Also, penicillin systems in which the amido function was replaced by phenoxy acetoxy and benzoylmethyl groups retained activity notwithstanding a major change in the penicillin molecule.[298] Similarly, the naturally occurring β-lactam clavulanic acid 4_a[24,299–301] and its isomer isoclavulanic acid 4_b[25,302] derivatives were found to act as β-lactamase inhibitors and bactericides.

As already mentioned, several monocyclic β-lactam antibiotics were found in nature. In recent years, a number of azetidin-2-ones were found to exhibit antibacterial property,[303–306] and the activity is not stereospecific.[307] Also, some 3-acylated amino azetidin-2-ones are potentially useful lactamase inhibitors.[308,309]

Considering such structural diversity, it is likely that the structure-activity relationship in β-lactam antibiotics is not so rigid and their mode of action may be flexible. β-Lactam antibiotics are known to interfere with the synthesis of bacterial cell wall by blocking transpeptidase, and this has been reviewed recently.[310,311]

It is important in this connection to consider the role of the enzyme β-lactamase which is secreted by several bacteria and which brings about rupture of the β-lactam bond, causing deactivation of several β-lactam antibiotics. Recently, various aspects of this enzyme were reviewed.[312–314] Resistance to β-lactam antibiotics by bacteria due to their β-lactamase continues to be a challenge to medicinal chemists. Recently a resistant gonococcus was found to produce this enzyme.[315,316] Though reduced penicillin sensitivity in *Neisseria gonorrhoeae* has been reported to have no connection with enzymic deactivation,[317] this aspect needs further investigation.

Compounds which are by themselves not antibacterials may potentiate a conventional drug if they act as β-lactamase inhibitors. Besides, combination of different β-lactam anbitiotics often gives better results. Recently, synergy produced by combination of β-lactam antibiotics was reviewed.[318–322]

Some azetidin-2-one derivatives also exhibited harbicidal activity.[323] Besides several β-lactams possess antiinflammatory property[324,325] and CNS activity.[326] It is likely that many more important biological activity will be exhibited by new naturally occurring or synthetic β-lactams.

E. CONCLUDING REMARKS

The chemistry of β-lactams is still a blossoming field. Their utility lies in their potent biological activity and their usefulness as synthons. The numerous methods for the synthesis of β-lactams as also their diverse reactions offer an enormous scope, and judicious application is necessary to obtain the desired result.

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