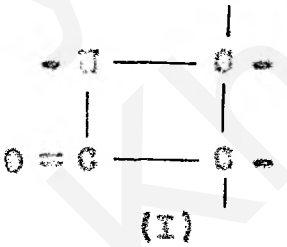
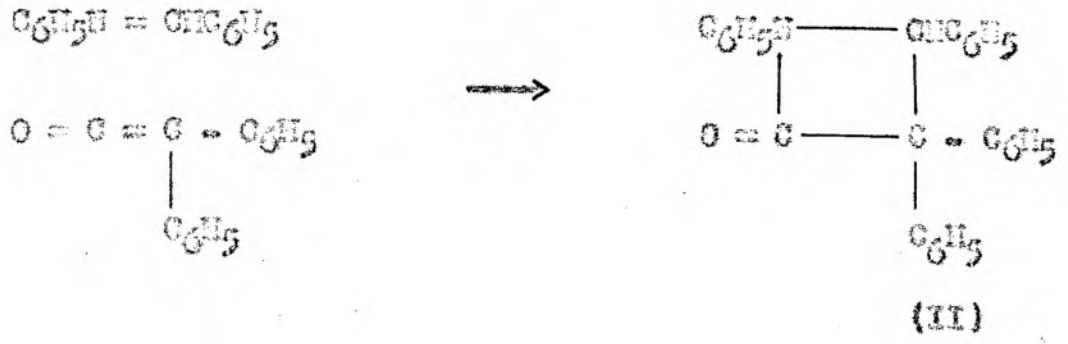
Introduction

The four membered heterocyclic ring compounds containing the amide function I, are commonly known as β- lactams. These smallest cyclic amides possess physical and chemical properties that diverge sharply, partially as a result of ring strain, from those of cyclic amides and lactams of greater ring size. The simple β- lactams are unusually susceptible to reactions involving the carbonyl group and generally undergo facile ring cleavage. The conventional methods of lactam syntheses fail in the formation of β- lactams, which has necessitated the development of special and unique method for their synthesis.



(I)

Staudinger[1] synthesised the first β- lactam in 1907, and definitely established it to be 1,3,3,4-tetra-phenyl-2-azetidinone II, by allowing benzalaniline to react with diphenyl ketene.



(II)

This lactam cyclic amide became the subject of intensive and extensive investigations both in U.K. and in U.S.A. during the last world war, when it was shown to be the active ring system of penicillins.

Prior to Staudinger's work, a few other workers[2,3,4,5,6] claimed the β- lactam structure for their compounds. In most of the cases their claims were either incorrect or the evidences put forward in support of the structures were inadequate.

Fotn and Norbol[7] proposed a β- lactam structure IV for the reaction product that was obtained by refluxing compound III in aniline for two hours. Here also their claims have not been substantiated.

(III) (IV)

The survey of the literature concerning β- lactams and their derivatives that have been proposed upto 1947 have been fully reviewed in "The Chemistry of Penicillin"[8] and "Antibiotics"[9], published in England. Later King[10] has reviewed all the work published till the end of 1946 in his Hilton memorial lecture for 1949. The work done till 1952 has been reviewed by Sheehan and Corey[11], in "Organic Reactions - Vol. 9", in the chapter entitled "The Synthesis of β- Lactams".

The methods developed until the end of 1947 for synthesising β - lactams can be divided into four groups.

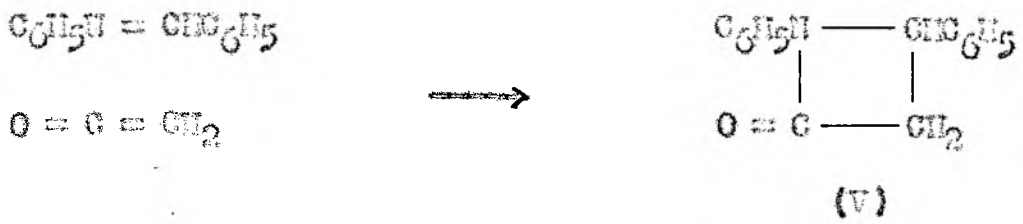
(i) Addition of ketene to >C = N - bonds.

(ii) Cyclization of β- amino and β - acyl-amino acids.

(iii) Cyclization of β- amino esters by the action of Grignard reagents.

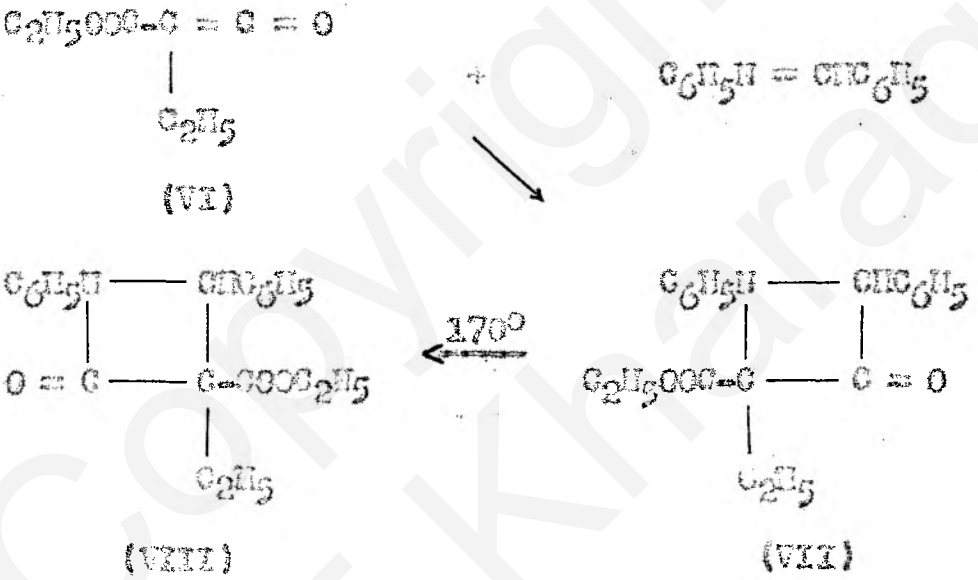
(iv) Action of α- halo esters and zinc on Shiff's bases.

Staudinger[12] and coworkers proposed a number of β- lactams by the direct combination of ketenes and imines. 1,4-Diphenyl-2-azetidinone V was prepared from ketene and benzalaniline.



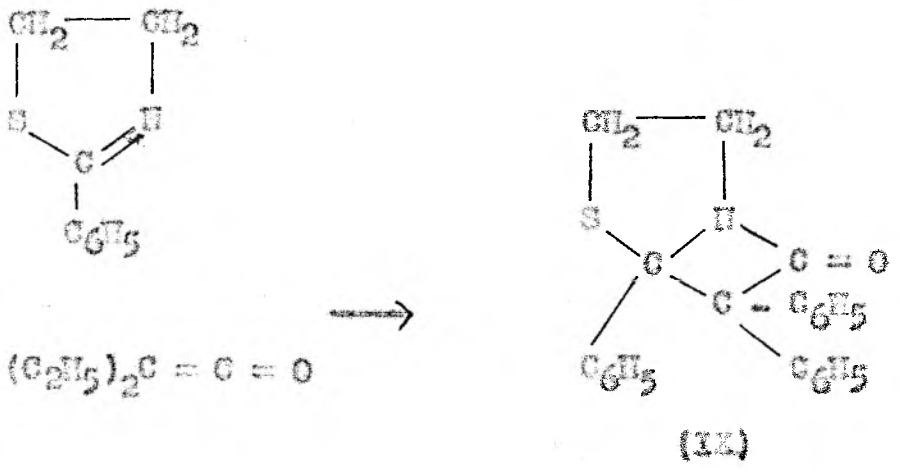
(V)

The method does not seem to be a general one as compound VII was obtained by reacting ethyl carboethoxy ketene VI with benzalaniline. However it rearranged to β- lactam VIII on heating to 170°.



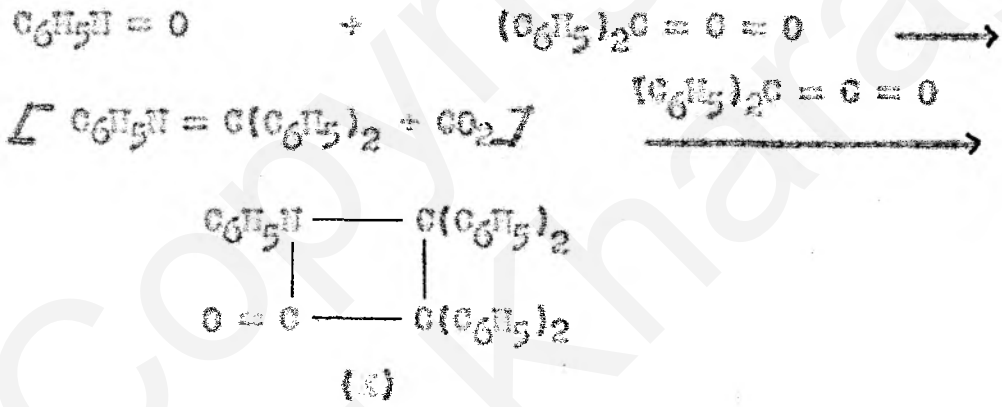
(VIII) (VII)

This method was successfully used during the penicillin synthesis program for making three thiozolidine β- lactams of which I is an example[1].



(XI)

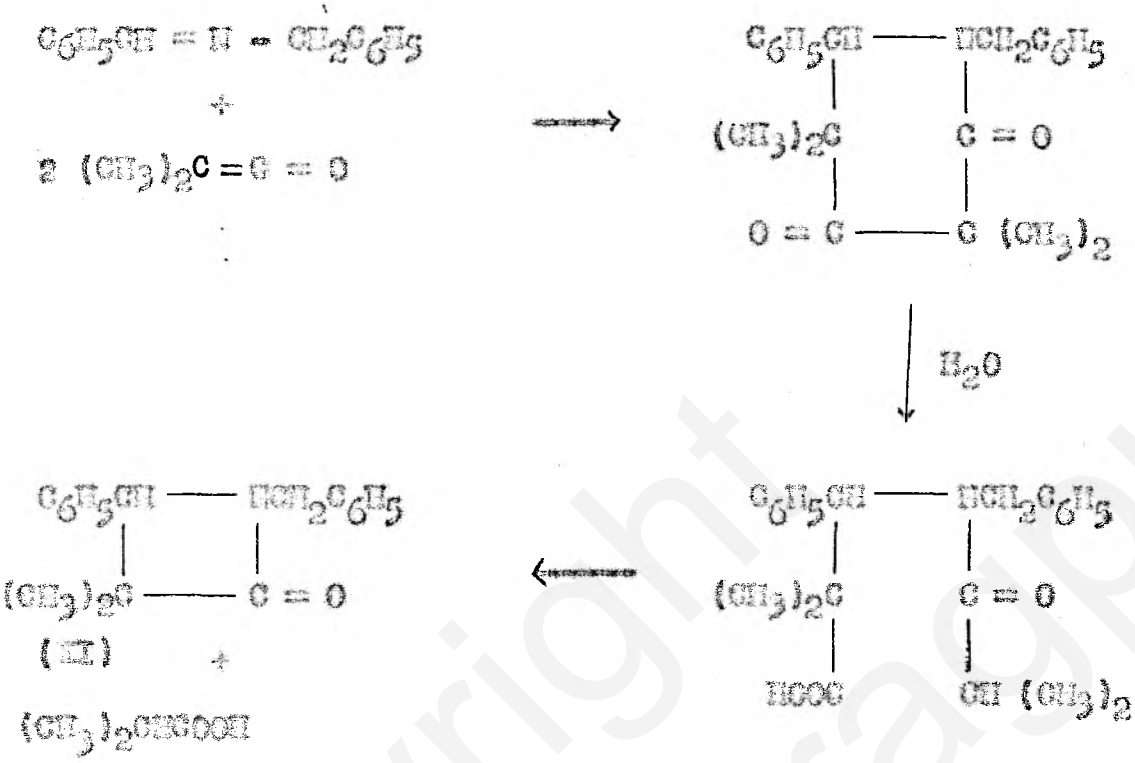
Staudinger and Jelagin[14] have synthesised 1,3,3,4,4-penta-phenyl-2-azetidinone XI, by reacting two moles of diphenyl ketone with one mole of nitrosobenzene.



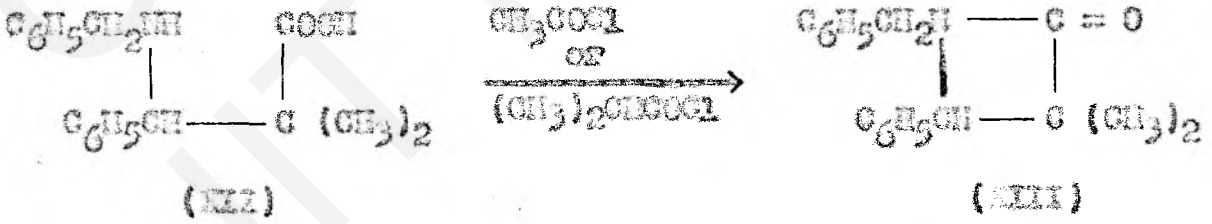
(X)

Staudinger and his Coworkers[15] have further shown that piperidinediones obtained from two moles of ketone and one mole of some of the compounds containing $>C=N-$ bond, could be easily hydrolysed to N-acyl-β-amino acids, which when heated are converted to β-lactams. The sequence of reactions for the synthesis of compound XI

is as follows.



They have also shown that certain β- amino acids with suitable structures such as XII can be cyclized to β- lactam XIII by refluxing them with an acid chloride.



The above cyclization process was modified during the penicillin synthesis programme by the Pfizer[16] group.

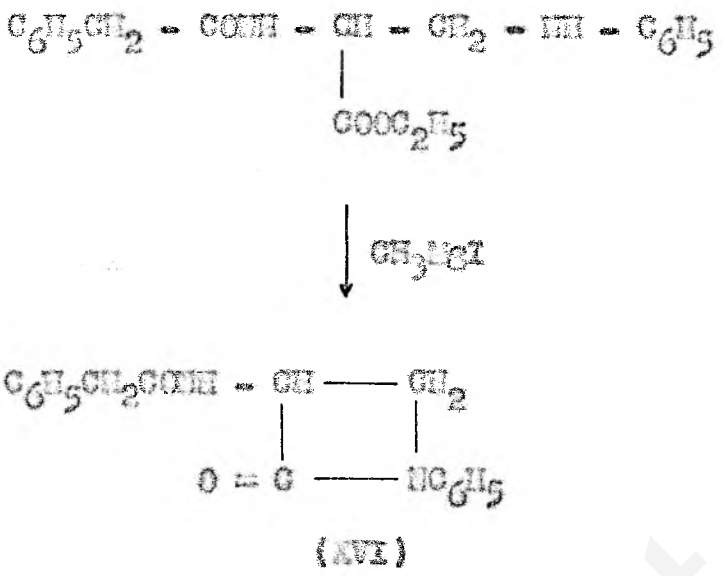
They prepared 1,4-diphenyl-2-azetidinone XIV from β-phenyl-β′-anilino propionic acid by refluxing it with phosphorous trichloride.

(XIV)

Brockpot[17] developed a method for the preparation of β-lactams which entails the cyclisation of β-amino-esters with Calgonol reagent. This method was used by the Indian[18] group for the synthesis of 1,3-diphenyl-2-azetidinone XV, from ethyl-β-anilino-α-phenyl-propionate with ethyl-magnesium bromide.

(XV)

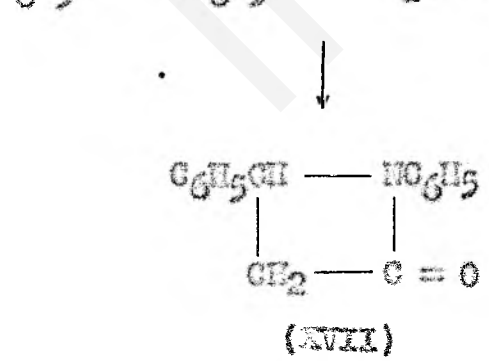
The Horak[19] group utilised this method for the preparation of β-lactam XVI containing acyl-amino group.



(XVI)

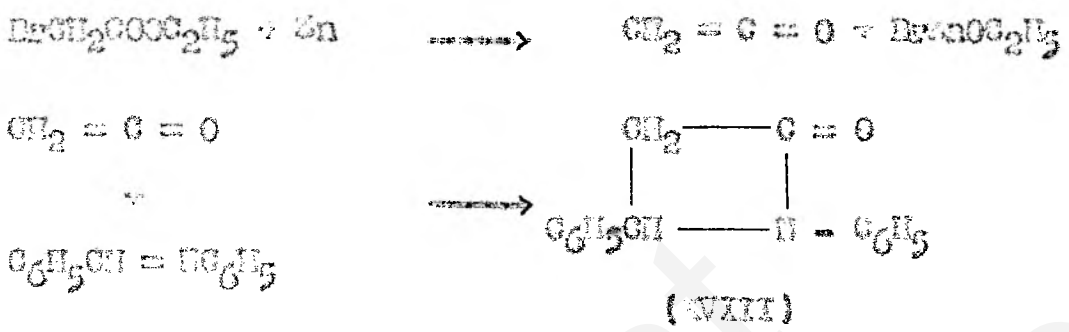
The method was also successfully applied by Molloy and Molloy[20] in the synthesis of N-allyl-β-lactams.

Gilman and Speeter[21] reported a new method for the preparation of β-lactams which depended on the action of α-halo-ester and zinc on Schiff's bases. Their synthesis of 1,4-diphenyl-2-azetidinone XVII in 85% yield from benzalaniline, ethyl-bromoacetate and zinc is an example.



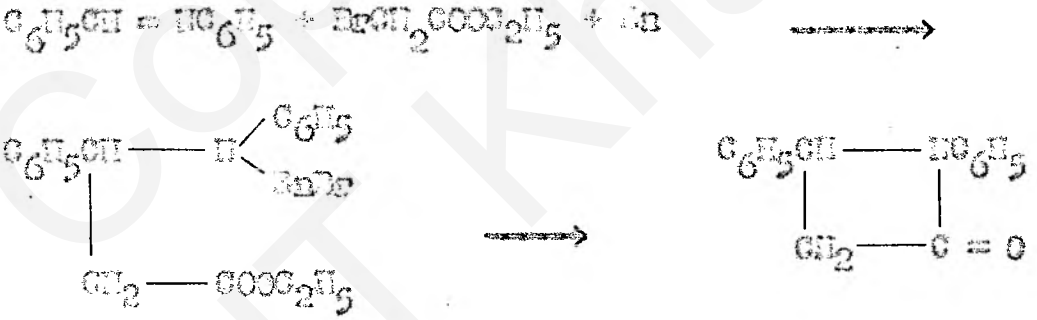
(XVII)

It is possible that zinc and ethyl bromoacetate produce a ketene which adds to benzalaniline to give the β- lactam XVIII according to the following scheme.



(XVIII)

Alternately it may be a true Reformatsky type reaction going through an organo-metallic intermediate. The ring closure then would be analogous to that of Brodigan's method.



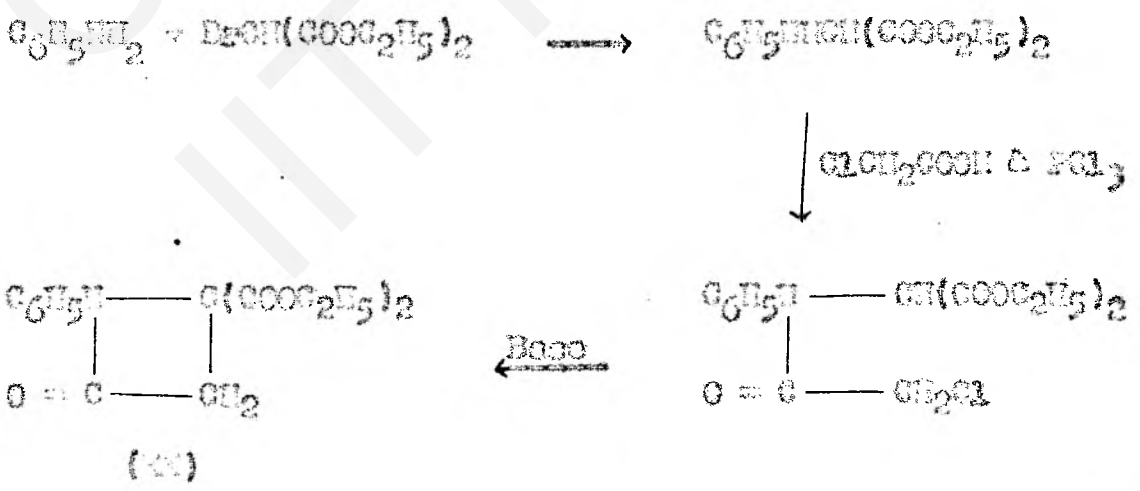
Staudinger and Ruzicka[22] have synthesized β- lactam NH_2 by the action of diazomethane on phenylisocyanate. The method, though novel, does not seem to be a general one, as it fails with α-naphthyl, p-nitrophenyl and

benzyl isocyanates.

(XI c)

Shoohan and Rose[23] have described a simple method for the synthesis of β- lactams. The amide linkage is first established by chloroacetylation of a substituted anthranilic ester, which is then followed by a base-catalysed ring closure. The exact nature of the basic reagent is not important since a number of bases have been successfully used in the ring closure.

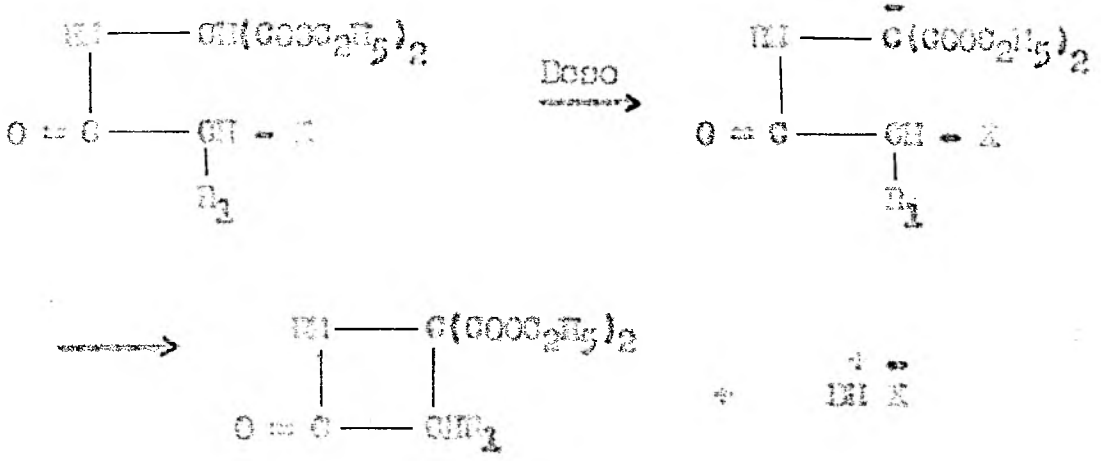
The preparation of 1-phenyl-4,4'-dicarbethoxy-2-azetidinone XI can be illustrated by the following sequence of reactions :



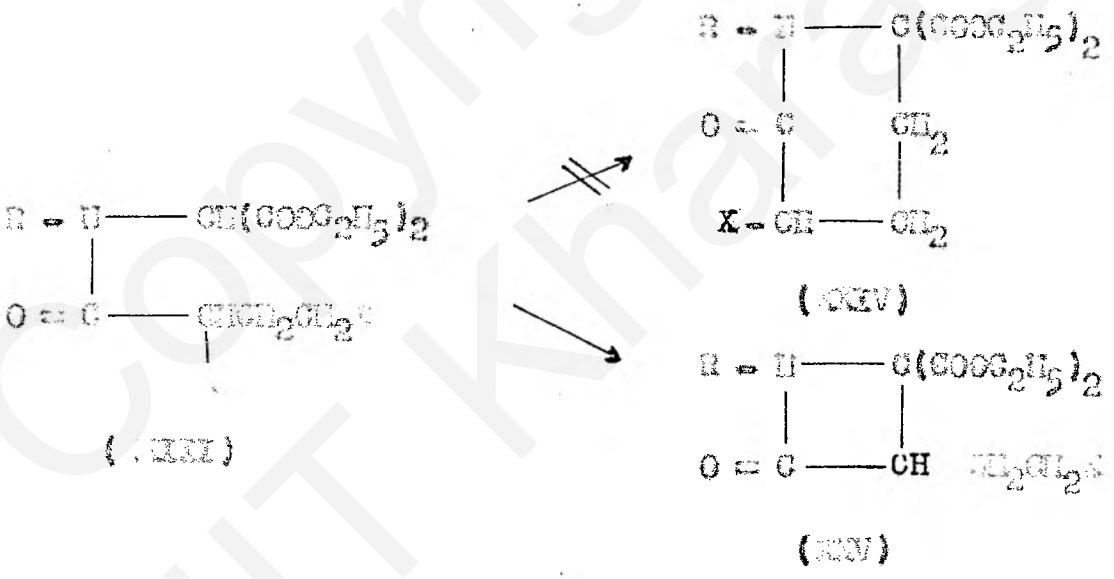
Shoshan and Bose[24] have further shown that the method could be successfully applied to compounds containing non-aromatic substituents on the amide nitrogen. The method although efficient is restricted to the preparation of β- lactams possessing one or two carbonyl functions at the position four. However, it is interesting to note that no dimeric or linear condensation products are formed.

Bose, Ghosh Hazarika and Bhattacharjee[25] have studied the effect of the activation of the methine hydrogen by various electronegative groups in effecting the cyclisation of L-halo-acetamido-malonic esters XII, to β- lactams XIII.

Their findings are that the compounds, in which the methine hydrogen is activated by groups other than two ester groups failed to cyclise in presence of triethylamine or sodium alkoxide. They postulated the formation of carbanion as an intermediate for the synthesis of β- lactams.



Dese and Ronbo[25] have subsequently shown that given equal opportunities, the cyclisation of α,γ-dibromo-acyl-aminoalcohols to XIII leads exclusively to β-lactam XV and not to δ-lactam XIV.



They have also supported the mechanism of cyclisation put forward by the earlier workers[25].

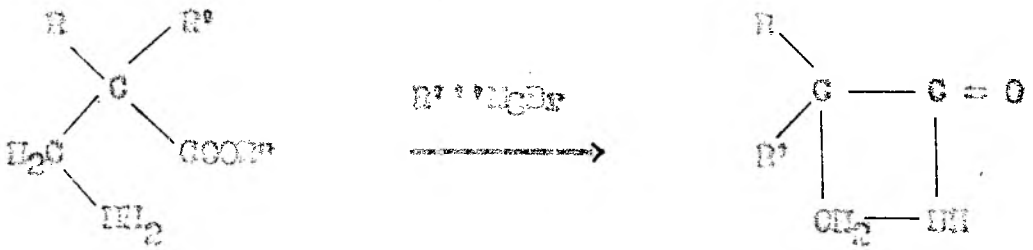
In 1956 Bolley, Fitzpatrick and Porter[27] synthesised N-unsubstituted β- lactam (XVI) in low yield from L and DL-asparagin by cyclisation in phosphate buffer (pH 6.7) at 100° for 24 hours.

(XVI)

The details of the method[28] for the synthesis of another N-unsubstituted β- lactam by the following scheme are not available.

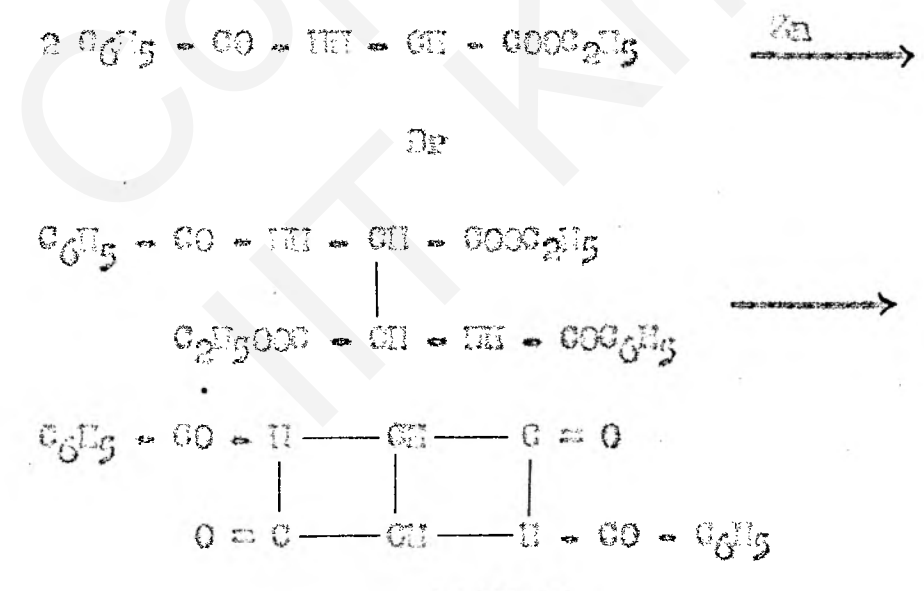
Behrs[29] has also reported the synthesis of

N-unsubstituted β-lactam (XVII), using Brockpot's method[17].



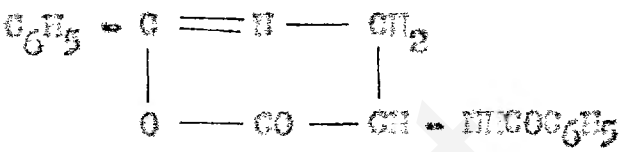
(XVII)

Chosh and Bose[30] tried to synthesise compounds in which two β-lactam rings are fused together, in order to compare the chemical, physical and biological properties of these diverse type of compounds with those of penicillin and desthiopenicillin. Their scheme of work is given below.



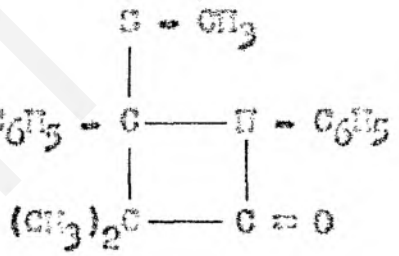
(XVIII)

In the course of their investigations however, they did not get the desired product. The reaction of zinc on ethyl α-Bromo hippurate led to the formation of a compound to which they tentatively assigned the structure XXX.



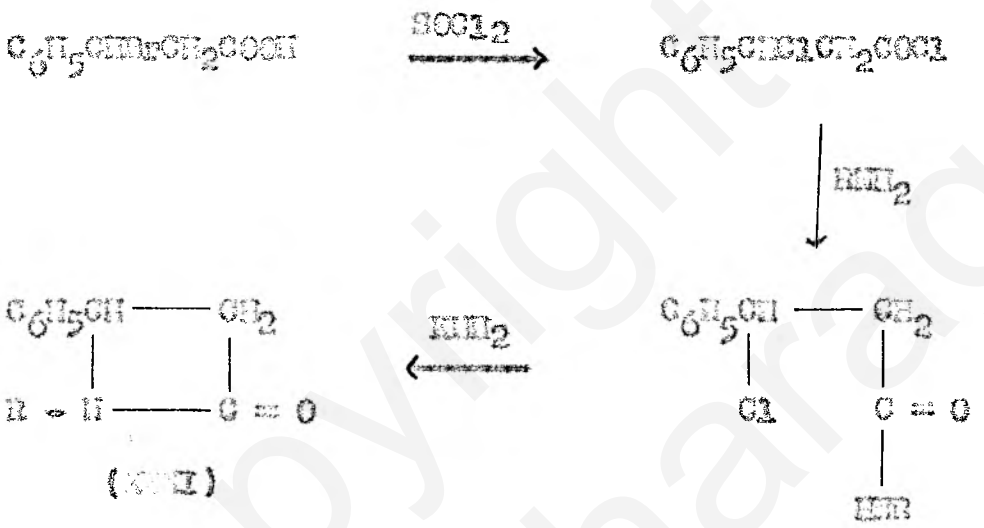
(XXX)

Holley and Holley[31] prepared β- lactam XXX with sulphur substituent in the desired position for studies relating to the reactivity of benzyl penicillin towards alkali.

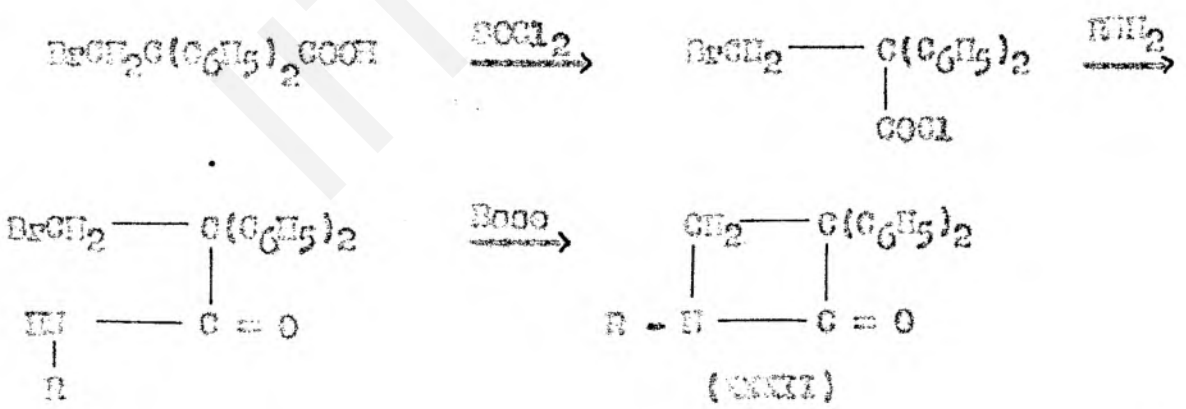


(XXX)

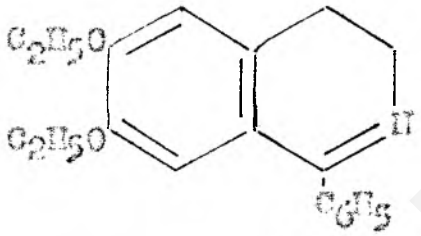
Baumgarten and Canborgan[32] prepared β- lactam from amides of β-halo-carboxylic acids. Refluxing phenyl bromopropionic acid with thionyl chloride gave acyl halide. Treatment of acyl halide with 2 moles of amine in ether with cooling gave amide, which cyclised to β- lactam with in presence of NH_2 or $NaNH_2$ in liquid ammonia.



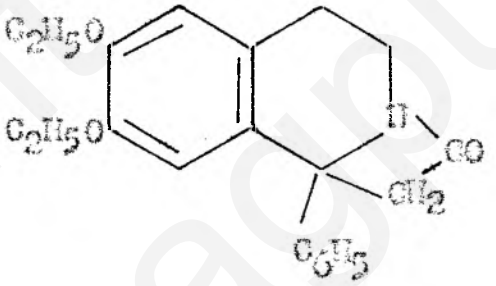
In further communication[33] they have reported the synthesis of 3,3'-diphenylazetidin-2-one XXIII.



Gardent[34] has assigned structure XXIV to one of the products obtained by the action of trioxymethylene on 1-phenyl-6,7-diethoxy-dihydroisoquinoline XXIII in acetic anhydride. The compound results from the fixation of a molecule of acetic acid on the double bond of 1,2-position of dihydroisoquinoline, followed by internal condensation.

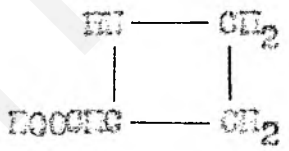


(XXIII)



(XXIV)

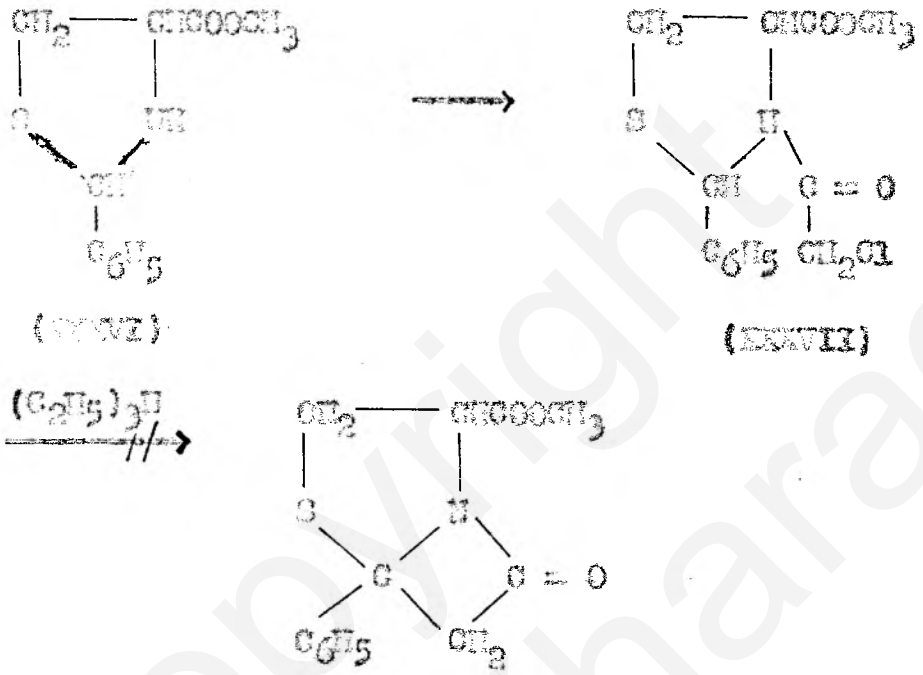
Besides naturally occuring β-lactams in penicillins, Fowden[35] has reported the isolation of a new relative, 2-carboxyazetidine XXV from natural sources (Convallaria majalis).



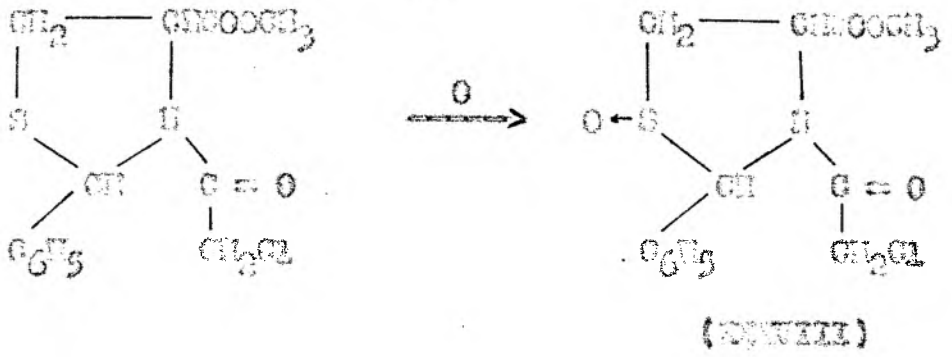
(XXV)

In 1952 Chouhan and Dodd[36] tried to extend their

method[23,24] for the synthesis of fused thiazolidino-β-lactam. 2-Phenyl-3-chloroacetyl-4-carbomethoxy thiazolidine XXVII obtained by reacting chloroacetic anhydride with 2-phenyl-4-carbomethoxy-thiazolidine XXVI could not be cyclised with triethylamine.



In order to effect the cyclisation of XXVII, they tried to convert it to a sulfone, but got a sulfoxide XXVIII instead, which did not cyclise with triethylamine when refluxed in dioxane.



(XVIII)

They also carried on reactions with 2-carboxy-thiocolidine (since the methoxyl group could be activated by the carboxy function and perhaps also by the sulphur atom) without any success.

Sheehan and coworkers in a series of papers[37-40] have described the preparation of a number of penicillin analogs. In these experiments, they avoided the possibility of azlactone formation by the incorporation of phthaloyl blocking group. In one communication, they have described the use of benzyl sulfonyl blocking group in penicillinate synthesis.

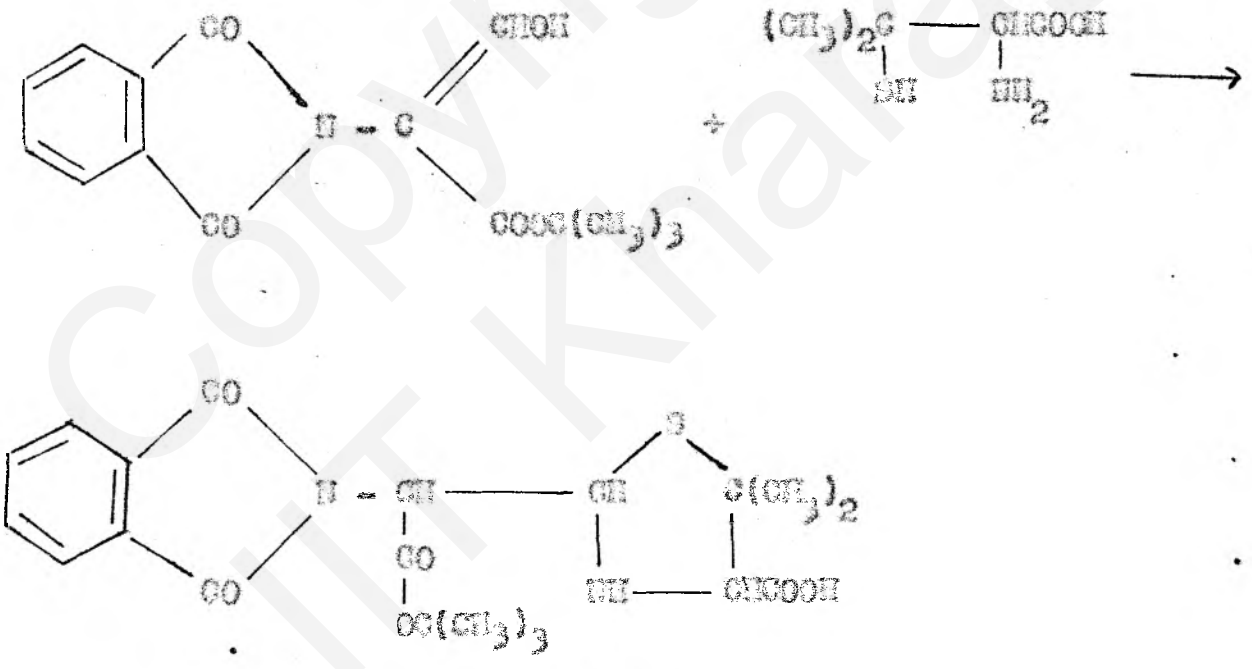
Sheehan's[41] latest achievement for the total synthesis of penicillin V depended on two factors arising out of unrelated researches. The first was the observation by Newell and Hargreaves[42] that phenoxy methyl penicillin is stable in cold solution and the second was the discovery made independently by Sheehan and Bose[43] and Khorana[44] that aliphatic carbodiimides can be used as a condensing agent

for the formation of the peptide bonds in the presence of water.

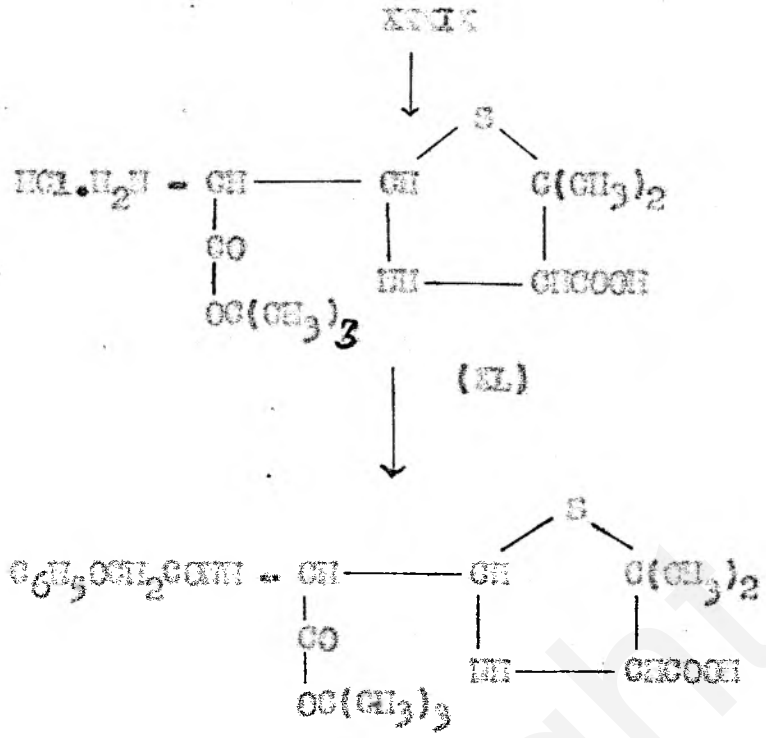
Condensation of D-penicillamine with t-butyl-phthalimido-malonaldehyde afforded the t-butyl-D-$\mathcal{L}$-4-carboxy-5,5'-dimethyl-$\mathcal{L}$-phthalimido-2-thiazolidine acetate XXIX.

Hydrazinolysis of XXIX followed by acidification with hydrochloric acid produced t-butyl-D-$\mathcal{L}$-4-carboxy-5,5'-dimethyl-$\mathcal{L}$-amino-2-thiazolidine acetate XL.

Phenoxy acetyl chloride and triethylamine converted XL to $\mathcal{L}$-t-butyl-D-$\mathcal{L}$-phenoxymethyl penicillocte XLI.



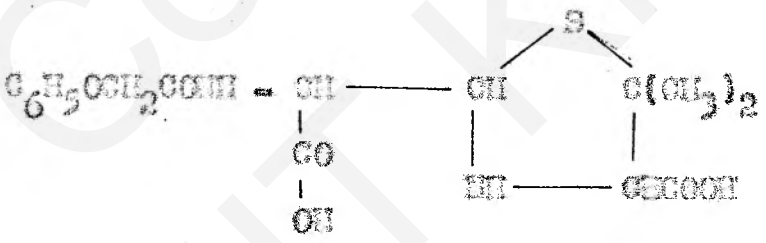
(XXIX)



(XL)

(XLI)

Cleavage of the t-butyl ester with dry hydrogen chloride followed by crystallisation led to 75 % of D- $\mathcal{L}$ -phenoxymethyl penicillinic acid hydrate' XLII.



(XLII)

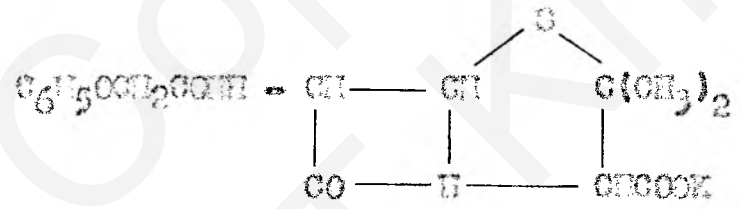
The structure of compound XLII was established by comparison of infra red spectra, optical rotation and

mixed melting point determination with a sample prepared by saponification of natural penicillin V.

Treatment with alkali and N,N'-dicyclohexylcarbodiimide in dioxane-water at room temperature cyclised XLII to the mono potassium salt in 10 to 12 % yield. By partition between methyl isobutyl ketone and pH 5.5 phosphate buffer, the totally synthetic crystalline potassium salt of penicillin V was isolated. The natural and synthetic potassium salts were shown to be identical by micro-biological assay, optical rotation, infra red spectra and mixed melting point determination.

XLII

↓ 1. KOH (one equivalent)
↓ 2. $C_6H_{11}N=C=NC_6H_{11}$



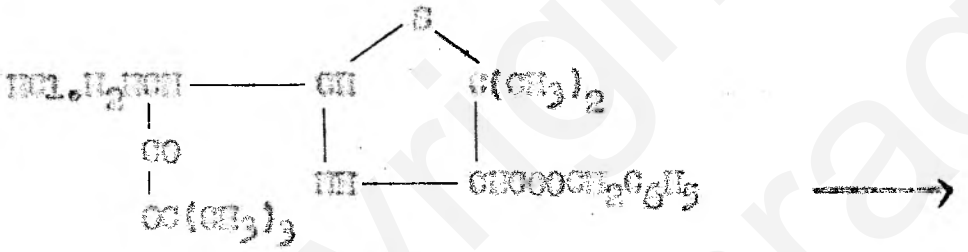
Penicillin V

(Potassium phenoxy methyl penicillinate).

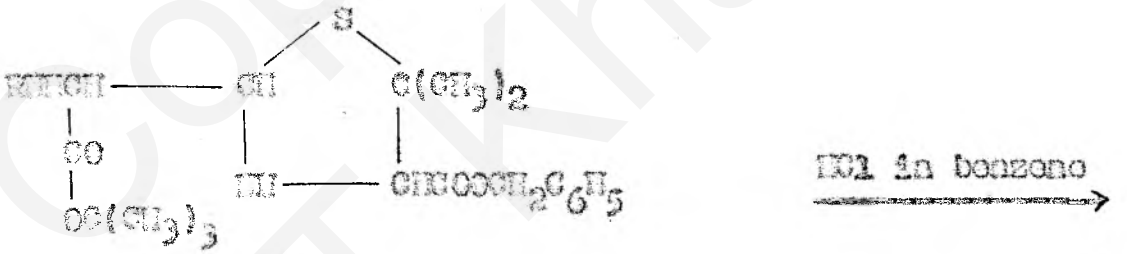
Dolhoffer, Shoehen and Abrams[45] synthesised new penicillin analogs in milligram quantity from the α-isomer of 6-butyl-4-carbobenzyloxy-5,5-dimethyl-α-

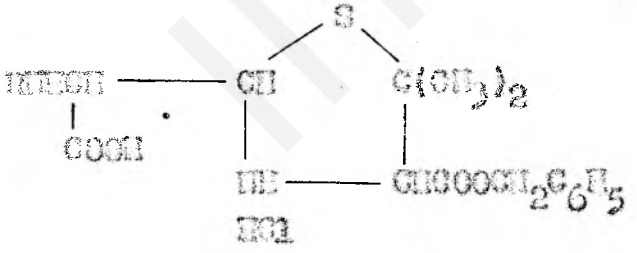
amino-2-thiazolidino acetate hydrochloride XLIII. It reacted with various chloroformates, sulfonyl chlorides, isocyanates, a carbonyl chloride, a sulphonyl chloride and dinitrofluorobenzene. Most of the reaction products underwent hydrohalogenolysis.

The β- lactam ring was formed with thionyl chloride. Catalytic hydrogenolysis of the benzyl ester yielded the new penicillin analogs, which were isolated as crystalline N-ethyl piperidine salts.



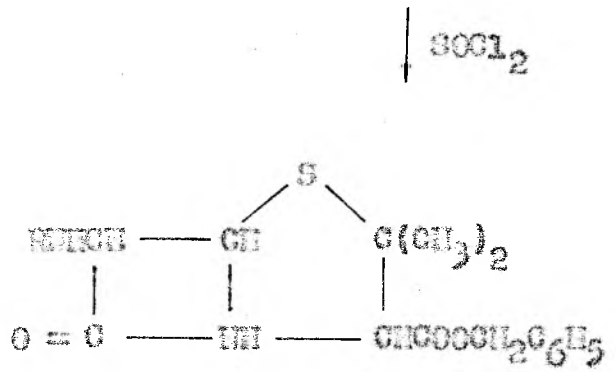
(XLIII)

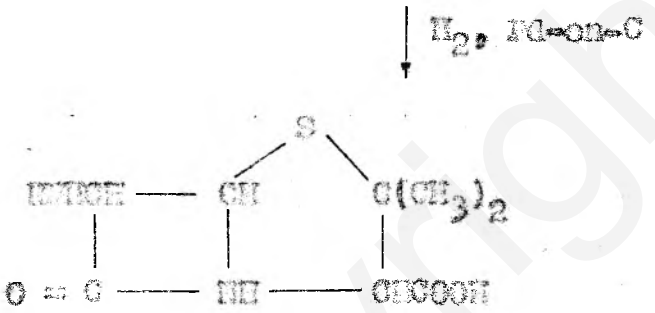




(XLIV)

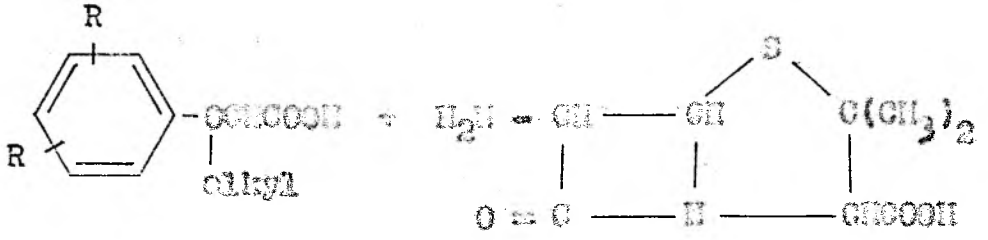
(XLIV)





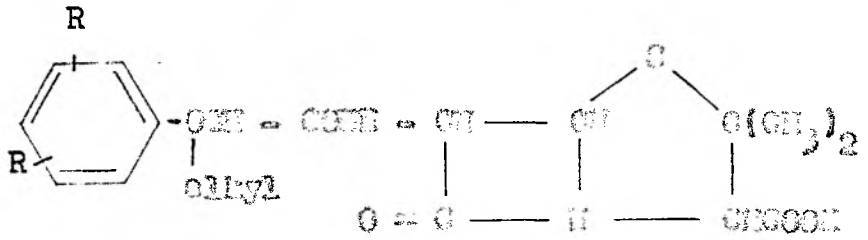
R = methyl sulfonyl, benzene sulfonyl, p-aminobenzene sulfonyl, p-chlorobenzene sulfonyl, phenoxy carbonyl etc.

New penicillins XLV have also been prepared by Y.G.Perron[46] and coworkers by the condensation of the α-aryloxyalkanoic acids with 6-amino-penicillinic acid, through the acid chloride or isobutyl chloroformate.



1. N-acylation

2. $C_2H_5CHCOOC_2H_5$
   |
   C_2H_5



(IV)

Instances have not been wanting in the field of medicinal chemistry, where compounds containing two or more physiologically active groups have potent chemotherapeutic properties.

It was therefore thought of interest to synthesize new series of compounds in which the β-lactam ring is associated with such active moieties as (i) thiocol, (ii) salicylic acid (iii) urea, and (iv) thiourea.