CHEMICAL STUDIES OF

SOME 6-DIAZOPENICILLANIC ESTERS

A thesis submitted in fulfilment

of the Conditions for the

Degree of Doctor of Philosophy

by

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LONDON

March 1982

For Mum and for John

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Acknowledgements

I wish to express my most sincere appreciation to Dr. S.A. Matlin for his invaluable advice and encouragement throughout the duration of this work.

Thanks are also due to the staff at the University, in particular Dr. A.G. Osborne for his assistance and advice concerning n.m.r. spectra, and Mr. P. Hemming for his efficient elemental analysis service.

For their assistance and friendship I would like also to thank [redacted]

Finally, I am grateful to both Pfizer for their financial backing during my studies, and to [redacted] for her conscientious typing of this thesis.

Abstract

The main aim of the studies undertaken was to introduce carbon substituents at the 6-position of the penicillin nucleus, by means of the reactions of 6-diazopenicillanates with a variety of nucleophiles, including heterocycles. For this reason, the examples of such C-6 substitution already in the literature were reviewed, as well as the reactions of diazocompounds with heterocycles.

The syntheses of penicillanic esters as starting materials for the reactions were carried out according to the literature methods, incorporating either the p-nitrobenzyl or pivoyloxymethyl groups for protection of the acid function.

Reaction of p-nitrobenzyl 6-diazopenicillanate with diborane gave p-nitrobenzyl penicillanate but with tributylborane afforded only the rearranged thiazepine. In the case of the latter, several attemptswere made to trap, isolate or identify the proposed enol-borinate intermediate, but without success. Extensive H.P.L.C. was employed for rapid analysis of product mixtures.

With furans, 6-diazopenicillanates were shown to undergo cyclopropanation, ring-opening and ring-expansion reactions, and a new mechanism for formation of the products via ylid intermediates was proposed. Support for this theory was obtained from a variety of control reactions. Although the corresponding reactions of 6-diazopenicillanates with pyrroles proved unsuccessful, novel substituted penicillins were obtained from the reactions with 3,4-dimethylthiophene and N-methylindole. Assignments of the stereochemistries of these adducts were made with the aid of n.O.e. difference spectroscopy.

The reaction of p-nitrobenzyl 6-diazopenicillanate with 1-cyclohexenyloxytrimethylsilane produced the cyclopropane adduct as required, but the analogous reaction with 1-phenyl, 1-trimethylsilyloxyethene afforded no substituted penicillins. Cyclopropanes were produced in the reaction of p-nitrobenzyl 6-diazopenicillanate with methyl acrylate. Reaction with allyl acetate gave both allyloxythiazepine and a doubly-substituted penicillanate, the structure of which has still to be confirmed. With ^{t}butylisonitrile, complexation between reagent and catalyst was thought to be the reason for lack of reaction with the carbenoid of the penicillin.

H.P.L.C. was applied to the analysis and isolation of substituted penicillins. Product mixtures which were inseparable by preparative T.L.C. were successfully resolved by preparative H.P.L.C., and rapidly-occurring reactions successfully monitored by analytical H.P.L.C.

Abbreviations

POM	=	pivoyloxymethyl
PNB	=	p-nitrobenzyl
Trityl	=	Ph_3C
Pyr	=	Pyridine
H.P.L.C.	=	High Performance Liquid Chromatography
T.L.C.	=	Thin Layer Chromatography

Section 1 Literature Review

Chapter 1 Some Developments in the Chemistry of β-Lactam Antibiotics

1.1 The History of β-lactam antibiotics

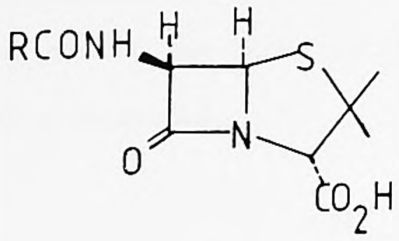
β-lactam antibiotics, first discovered more than 50 years ago by Alexander Fleming, are considered to be the most important chemotherapeutic agents and are the most widely prescribed antibiotics used in medicine[1]. Even so, they have two major drawbacks, in that not all bacteria are susceptible to β-lactam antibiotics and many can produce enzymes to inactivate them[2].

The discovery of penicillin at St. Mary's Hospital, London by Fleming occurred by chance when a plate seeded with staphylococci in the laboratory had been accidentally contaminated with Penicillium notatum. It appears that, initially, conditions were favourable for the Penicillium mould which therefore grew and began to produce penicillin without rapid growth of the bacteria. Conditions then changed to warmer temperatures, so that the growth of the staphylococci accelerated, with lysis occurring in close proximity to the mould.

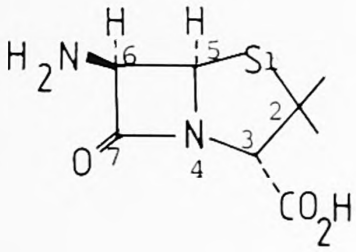
Although Fleming had described the antibacterial activity of the penicillin and had shown that it was non-toxic to man, he did not exploit its great potential. The demonstration of the chemotherapeutic power of penicillins, first in animals and then in man, was made twelve years later by Florey and Chain at Oxford.

In 1943, Abraham *et al*.[3] proposed the β-lactam structure (1) which met both support, notably from R.B. Woodward, and also

powerful opposition. It was not accepted generally until 1945 when Crowfoot and Low accomplished an X-ray crystallographic analysis.

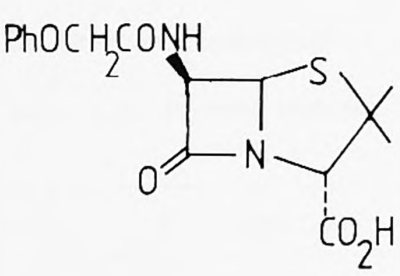


(1)



(2)

Although the total synthesis of 6-aminopenicillanic acid (6-APA)(2) was reported in 1958 by Wolstenholme and O'Connor[4], and that of penicillin V(3) in 1959 by Sheehan[5], penicillins were not readily available until shortly after, when Batchelor et al[6] found the existence of 6-APA in penicillin fermentations.



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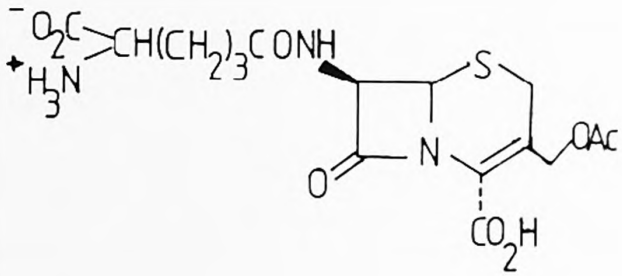
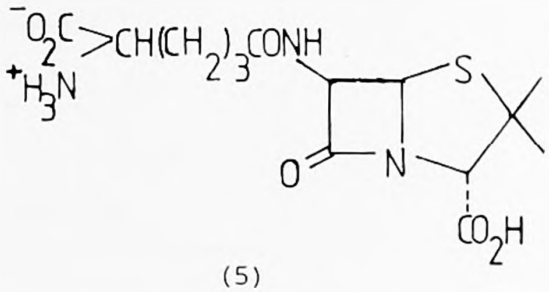


(4)

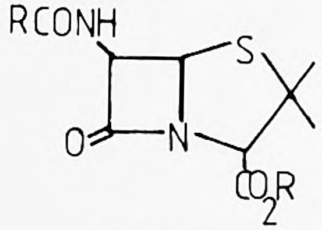
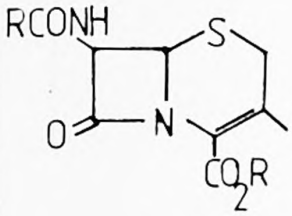
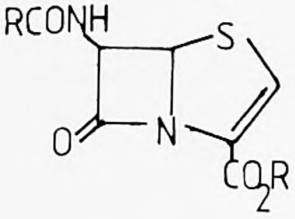
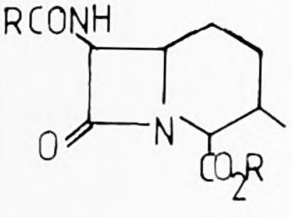
In 1945, Brotzu isolated Cephalosporium acremonium from sewage waste[7]. Its metabolic products were subsequently shown to possess antibacterial activity against a range of bacteria. This activity was found to be due to three antibiotics, the first of which was cephalosporin C (4), discovered in 1953 by Newton and Abraham[8]. Its structure was proposed in 1959 and confirmed shortly afterwards by X-ray crystallographic analysis[9],

and its total synthesis was completed in 1966 by Woodward and co-workers[10]. Although low in activity, cephalosporin C showed resistance to hydrolysis by β-lactamases - the enzymes produced by the bacteria to inactivate the antibiotic. Penicillin N(5) was one of the other antibiotics isolated from the same metabolic products.



(5)

Since the cephalosporin group of antibiotics are costlier to produce and yet are often clinically more useful than the penicillins due to their broader spectrum of activity and increased resistance to β-lactamases, it was a prime objective of chemical studies at this time to convert the penam nucleus into the cephem system (Table 1).

4, 5-systems	4, 6-systems
 Penam	 Cephem
 Penem	 Carbacepham

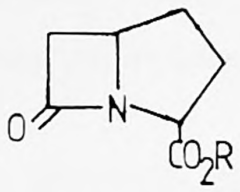
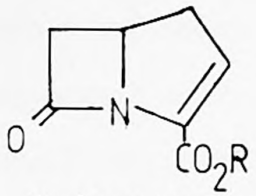
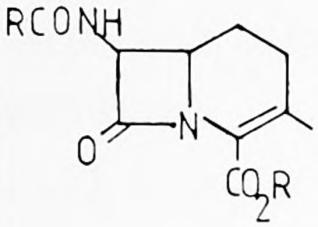
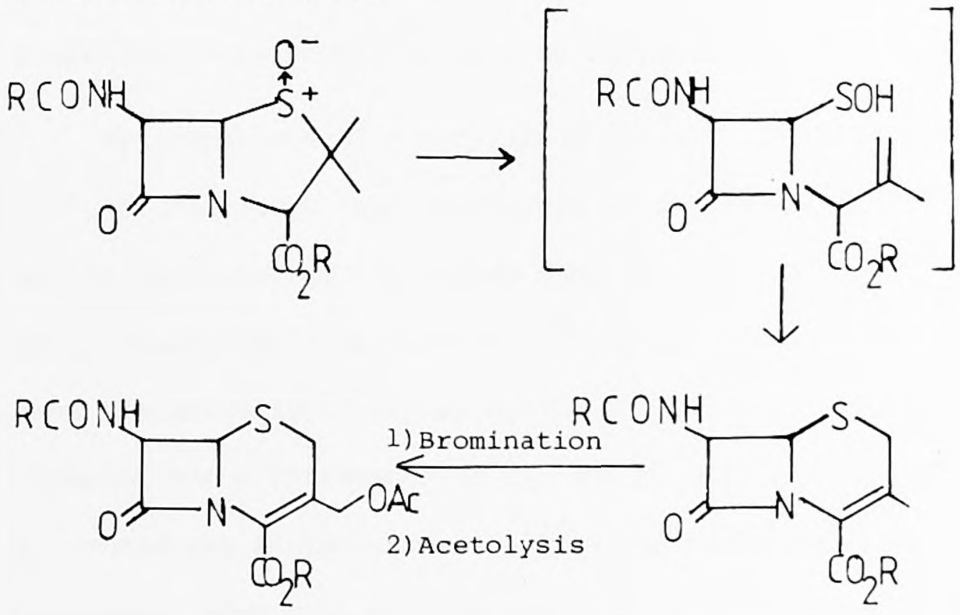
4,5-systems	4,6-systems
 Carbapenam  Carbapenem	 Carbacephem

Table 1: The nomenclature of Penicillins and Cephalosporins

Such a transformation requires oxidation of the methyl groups of the penicillin and an expansion of the thiazolidine ring. The route employed by Morin and co-workers[11] involved an intermediate sulphenic acid from which the deacetoxycephalosporin was obtained (Scheme 1).



Scheme 1

The Morin reaction is extremely general for penicillin sulphoxides. Alternatively, several other methods for converting penicillins into ceph-3-ems have been reported[12-17].

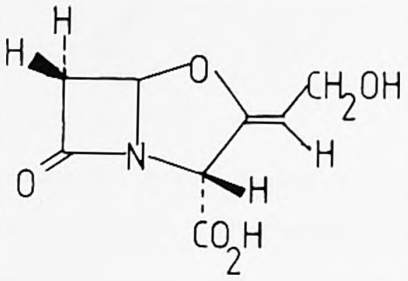
1.2 Structure, Activity and Reactions of Penicillins & Cephalosporins

Once 6-aminopenicillanic acid (6-APA) and 7-amino-cephalosporanic acid (7-ACA) were readily available, many more substituted penicillins and cephalosporins were produced, with the aim of discovering new, active antibiotics.

Methicillin (2,6-dimethoxyphenylpenicillin) was both highly active and highly resistant to β-lactamases, but unfortunately was acid labile, rendering it unsuitable for oral administration. This prompted further work which led to the discovery of two derivatives; oxacillin and cloxacillin, which possessed the same favourable characteristics but were stable to acid hydrolysis.

By comparison of penicillin N (5) with cephalosporin C(4), it was shown that resistance to β-lactamases was due to the chemistry of the cephem ring and not the N-acyl side chain which they both possess. However, it was also shown that the activity of cephalosporin C could be increased by changing the substituents in the N-acyl side chain. Thus a whole new series of penicillins and cephalosporins was produced; some with a broad spectrum of activity, others more specific.

Then in 1976 came the discoveries of clavulanic acid (6) and thienamycin (7)[18,19].



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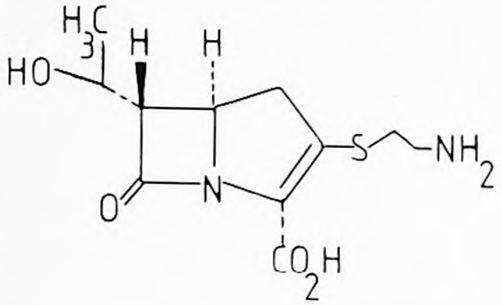
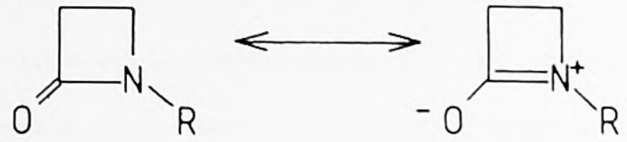


(7)

Clavulanic acid, a β-lactamase inhibitor but with only low antibacterial activity, was unusual in that it contained a β-lactam ring fused to an oxazolidine ring with no side chain at C-6. The discovery of thienamycin was a major breakthrough as it was shown to possess a broad spectrum of activity and resistance to many β-lactamases. It has unparalleled activity against Pseudomonas species. It is most likely that it owes its high activity to its unstable β-lactam ring, as it has been shown by Woodward et al.[20] that the less stable the β-lactam ring, the more active the antibiotic. He pointed out that the position of the nitrogen at the bridgehead between the 4- and 5-membered rings of the penicillin would suppress normal

amide resonance (Figure 1), and this would account for the high reactivity of the penicillin nucleus.



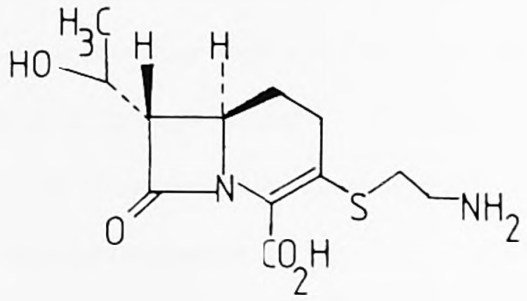
(1) (2)

Figure 1: Amide Resonance in β-lactams; (1) longer, weaker C-N bond and (2) change in hybridization of N from sp^3 to sp^2

In the cephalosporin system, the strain is less, but nevertheless the β-lactam nitrogen is still not coplanar with its 3 adjacent atoms - a principal requirement for maximization of this type of charge delocalization - and again amide resonance is suppressed. High reactivity of the β-lactam ring may be correlated with the ability to inactivate penicillin-sensitive enzymes in the bacterial membrane. Steric factors are obviously important and may influence the ability of the antibiotic to combine with the active centre of a sensitive enzyme and also its ability to penetrate the cell wall.

Thienamycin differs from the classical penicillins and cephalosporins most notably by the incorporation of the novel carbapenem nucleus and the unusual hydroxyethyl and cysteamine side chains. Also, the protons in thienamycin at C-5 and C-6 differ from the usual cis geometry, being trans. In such a structure, the β-lactam amide bond would be expected to be highly active due to both ring strain and electronic effects. In fact, stability studies have revealed that thienamycin is relatively unstable in concentrated aqueous solutions suitable

for therapeutic use, proving an obvious disadvantage. In order to more fully understand the factors which are responsible for this instability, and in the hope of obtaining a clinically useful antibiotic, Saltzmann et al.[21] proposed to synthesize an analogue which would incorporate all the essential functionality of thienamycin in a less strained ring system i.e. the homothienamycin (8).



(8)

As anticipated, the chemical stability was vastly superior to that of thienamycin. However, its biological activity was disappointing, giving only low levels of activity against even highly susceptible bacterial species. Thus, it appears that the exceptional biological activity of thienamycin is due mainly to the presence of the highly reactive carbapenem nucleus.

After the initial isolation of thienamycin, several additional natural products containing the carbapenem nucleus were found, all of which may be regarded as derivatives of thienamycin. While all of these natural products possess considerable antibacterial activity, thienamycin is the most potent natural antibiotic. The trans R configuration found in thienamycin itself appears to be optimal for both potency and

β-lactamase resistance. The N-acetylated natural products all possessed reduced antipseudomonal activity.

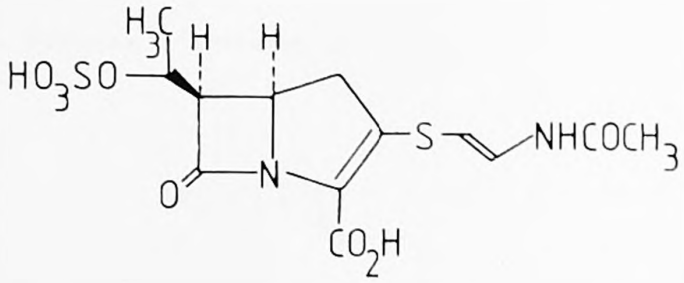
Synthesis of a series of thienamycin derivatives made it possible to assess the effect of the various structural features on its remarkable biological activity[22]. Carbapen-2-em-3-carboxylic acid possessed considerable potency of the same order of magnitude of activity as clinicially used penicillins. The potency was enhanced by replacement of the 2-proton with a phenyl group. However, neither of these two modified thienamycins showed resistance to β-lactamases or antipseudomonal activity. Addition of the 6α-(1R-hydroxyethyl) side chain not only enhanced the potency of the carbapenem nucleus, but was also responsible for β-lactamase stability. The incorporation of the cysteamine side chain caused 2 to 3-fold enhancement over the decysteamine derivative and the Δ^1-isomer of thienamycin was almost devoid of activity, showing the necessity for the Δ^2-double bond. The incorporation of an additional basic function at C-2 maximized anti-pseudomonal activity.

Hence the potency of thienamycin was seen to be due to the carbapenem-3-carboxylic acid while the 6α-(1R-hydroxyethyl) function conferred β-lactamase stability and further enhanced activity.

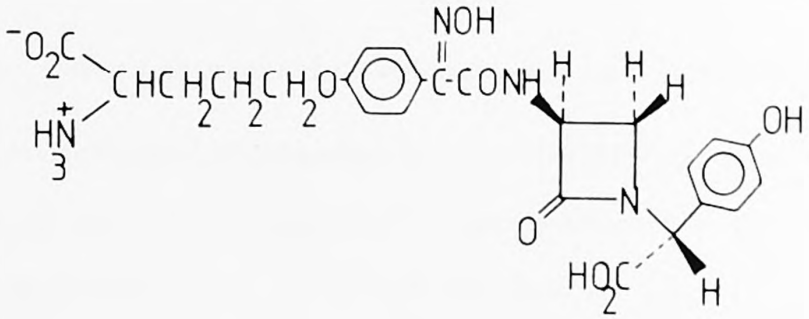
Gorman and Ryan discussed several factors, in addition to that of enzyme inhibition, which are involved in the suppression of bacterial growth by β-lactam antibiotics[23].

The total synthesis of thienamycin was achieved by Johnston *et al.* in 1978[24].

Olivanic acid (9), which is closely-related to thienamycin structurally, was another major discovery of this time[25], together with nocardicin A (10)[26,27].



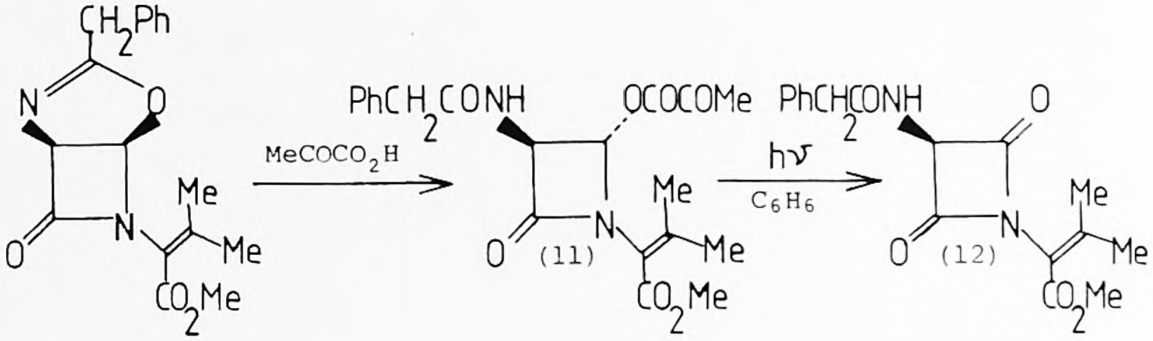
(9)



(10)

Nocardicin A is unusual in containing an unfused β-lactam ring as well as a novel side chain. This, too, has a broad spectrum of activity but is particularly active against Gram-ve bacteria.

Hence the Nocardicins revealed that appropriate monocyclic azetidinones could display significant antibacterial activity. The total synthesis of nocardicin A was achieved by Koppel et al. in 1978[28]. Subsequently, as part of a programme aimed at the synthesis of monocyclic derivatives incorporating an electronically-activated β-lactam linkage, Kaura and Stoodley[29] have been interested in the preparation of azetidine-2,4-diones(12) from compounds such as (11), utilizing the method of Binkley for conversion of esters into ketones[30] (Scheme 2).



Scheme 2

However, their antibacterial activity was not discussed.

The discovery of thienamycin in 1976 triggered a complete revival in penicillin research. New methods for the introduction of carbon substituents at C-6 of the penicillin nucleus were investigated as a means of preparing thienamycin-related compounds.

Interest in 6-alkyl-penicillins actually dates from Strominger's theory, proposed in 1965[31], in which he described the action of penicillin. Several reactions are involved in the final stages of cell wall synthesis, including closure of the glycine bridges by transpeptidation, thus linking the two glycopeptides. This step is of special interest because it is the probable site of

penicillin action. Closure of the bridge results in the loss of the terminal D-alanine residue, providing energy for the transpeptidation (Figure 2).

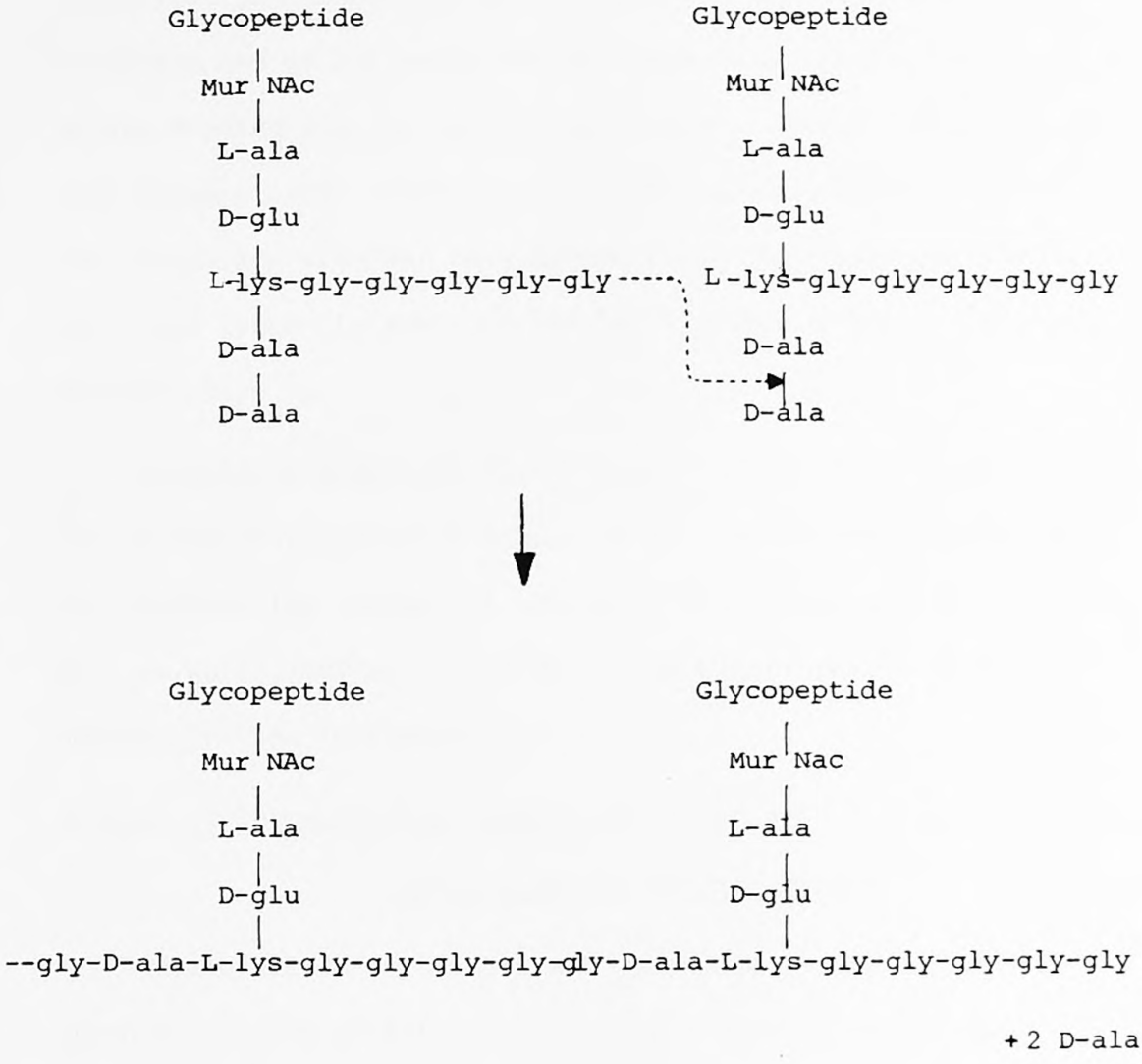


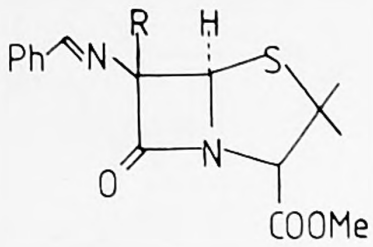
Figure 2 : Closure of the Glycine Bridges by Transpeptidation

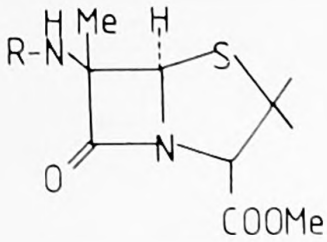
Each glycopeptide ends in two D-alanine residues prior to cross-linking. Penicillin can be viewed as a dipeptide almost identical to one conformation of D-alanine-D-alanine, even though one of the carbons in pencillin has the L-configuration. Strominger postulated that penicillin has the conformation in which the D-alanyl-D-alanine end of the pentapeptide fragment is fixed to the substrate binding site of the transpeptidase. The penicillin therefore becomes irreversibly bound to the transpeptidase in place of the D-alanyl-D-alanine, thus inactivating the enzyme and inhibiting the final cross-linkage. A similar hypothesis was proposed by Wise and Park[32].

Strominger suggested that introduction of a methyl group at C-6 of the penicillin may result in an even closer resemblance to the glycopeptide substrate, and hence might enhance its effectiveness as an antibacterial agent. Thus the search for 6-alkyl penicillins was initiated.

1.3 Methods of Incorporating Carbon Substituents at C-6 of the Penicillins and C-7 of the Cephalosporins

Subsequent to Strominger's suggestions, Bohme and co-workers[33] synthesized both 6-methylpenicillin and 7-methylcephalosporin to examine their activity as antibiotics. Treatment of N-benzylidene 6-APA methyl ester (13) with sodium hydride and methyl iodide afforded the 6-methyl derivatives (14) and (15) in 90 and 5% yields respectively, as a result of preferential methylation at the sterically-less hindered α-face.





(13) R = α-H

(14) R = α-CH_3

(15) R = β-CH_3

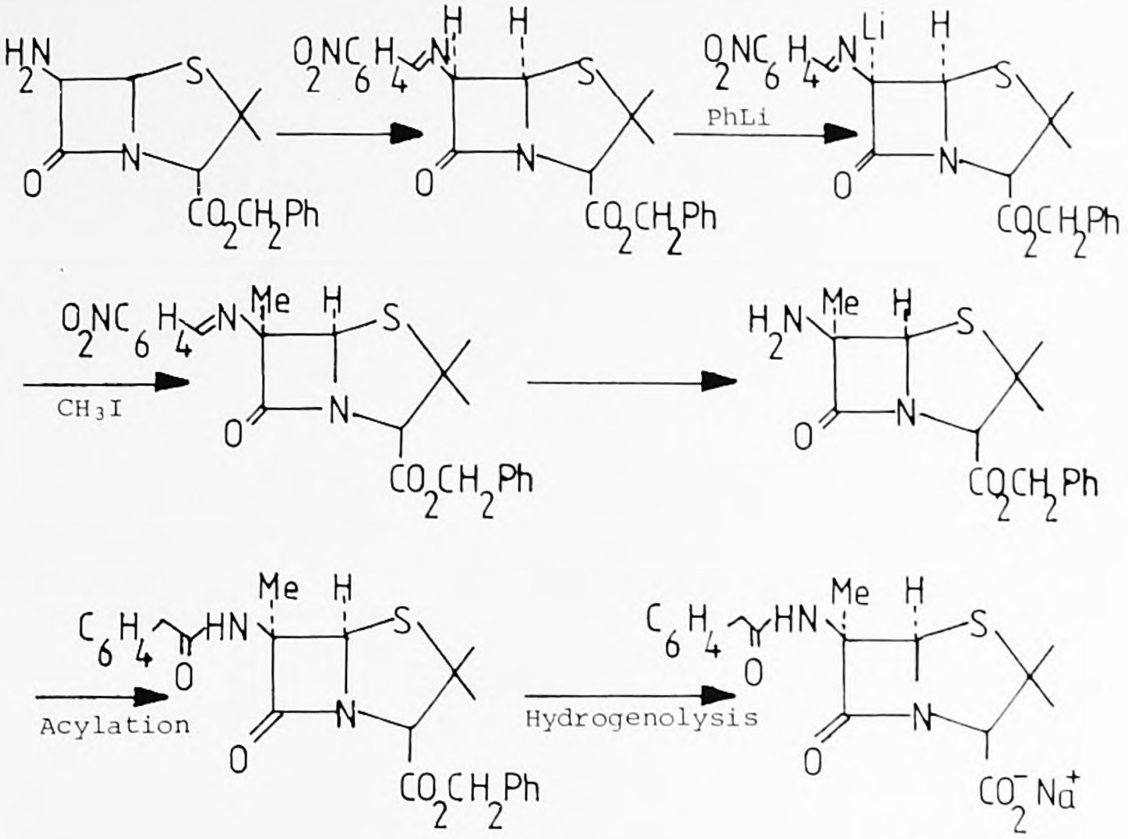
(16) R =H,α-Me at C-6

(17) R =C(=O)CH_2Ph,α-Me at C-6

(18) R =C(=O)CH_2Ph,β-Me at C-6

Hydrolysis of (14) produced (16) in almost quantitative yield. Acylation of (16) gave the desired 6α-methyl-6-phenylacetimido-penicillanic acid methyl ester (17) in high yield. The 6β-isomer (18) was prepared by first hydrolysing the mother liquors from (14) followed by acylation, affording (18) in poor yield. The corresponding cephalosporins have been prepared in a similar manner. Surprisingly, both 6-methylpenicillanic acid and 7-methylcephalosporanic acid were inactive.

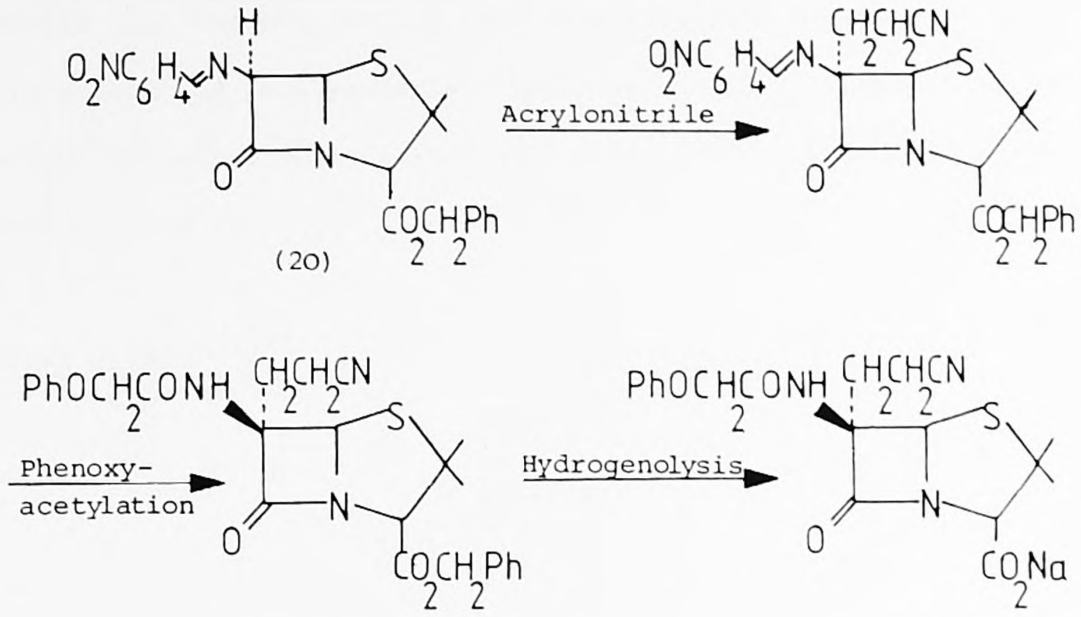
In 1972, following along this theme, Firestone et al.[34] described the preparations of further 6-alkyl penicillanates and 7-alkylcephalosporinates by the procedure depicted in Scheme 3, with the initial formation of the Schiff base from 6-APA. 6-α-methyl (19) and ethyl penicillin G and the corresponding cephalosporins, prepared as their sodium salts by the following method, all showed appreciable antibacterial activity.



(19)

Scheme 3

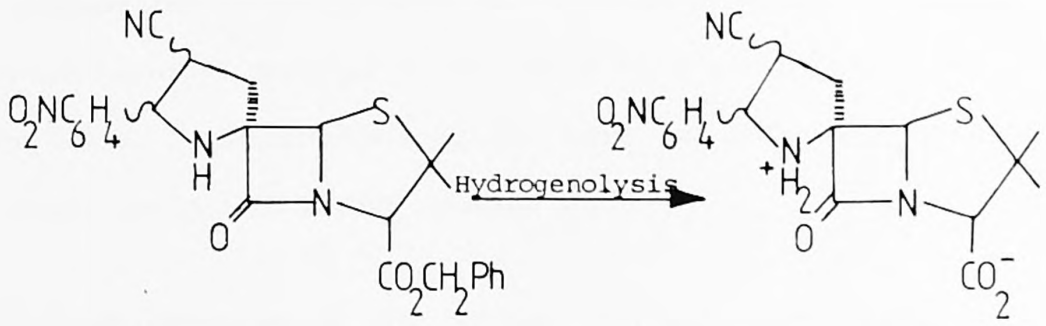
Rasmusson et al.[35] in 1973 made further use of the knowledge that a reactive nucleophilic site could be generated at C-6 and C-7 of the penicillins and cephalosporins respectively by base treatment of the nitrobenzaldehyde Schiff's bases of 6-APA and 7-ACA esters[34,36,37]. The nucleophilic centre could be induced to undergo alkylation or aldol condensation to give the corresponding unsubstituted or monosubstituted alkyl derivatives. Rasmusson reported the preparation of additional 6-substituted penicillins in which the side chain contained a carbon atom in a more highly oxidized state (Scheme 4).



(20)

Scheme 4

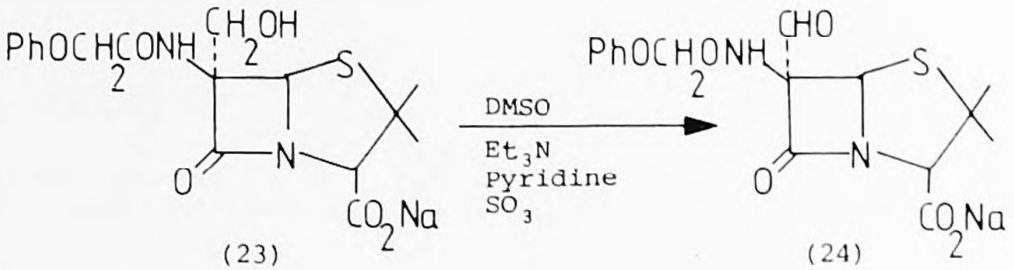
The spiro-pyrrolidine (21) was also isolated during the purification of the above products. On hydrogenolysis, (21) afforded the zwitterion (22).



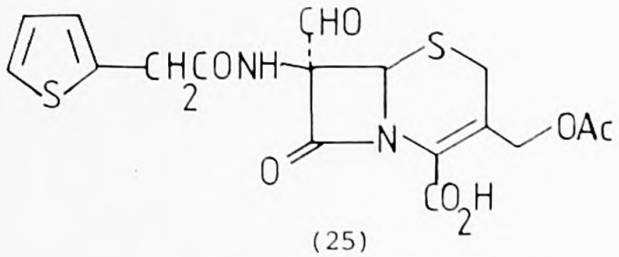
(21) (22)

As 6-methoxypenicillins and 7-methoxycephalosporins showed interesting antibiotic activity, Rasmusson et al. attempted to prepare other substituted penicillins in which the new C-6 substituent was electron-withdrawing. The alcohols

obtained via aldol condensation of formaldehyde[36] and acetaldehyde with the Schiff base (20) were converted to the corresponding formyl- and acetyl- derivatives. For example, oxidation of the 6-hydroxy-methyl penicillin V (23) with DMSO afforded 6-formyl penicillin V (24)



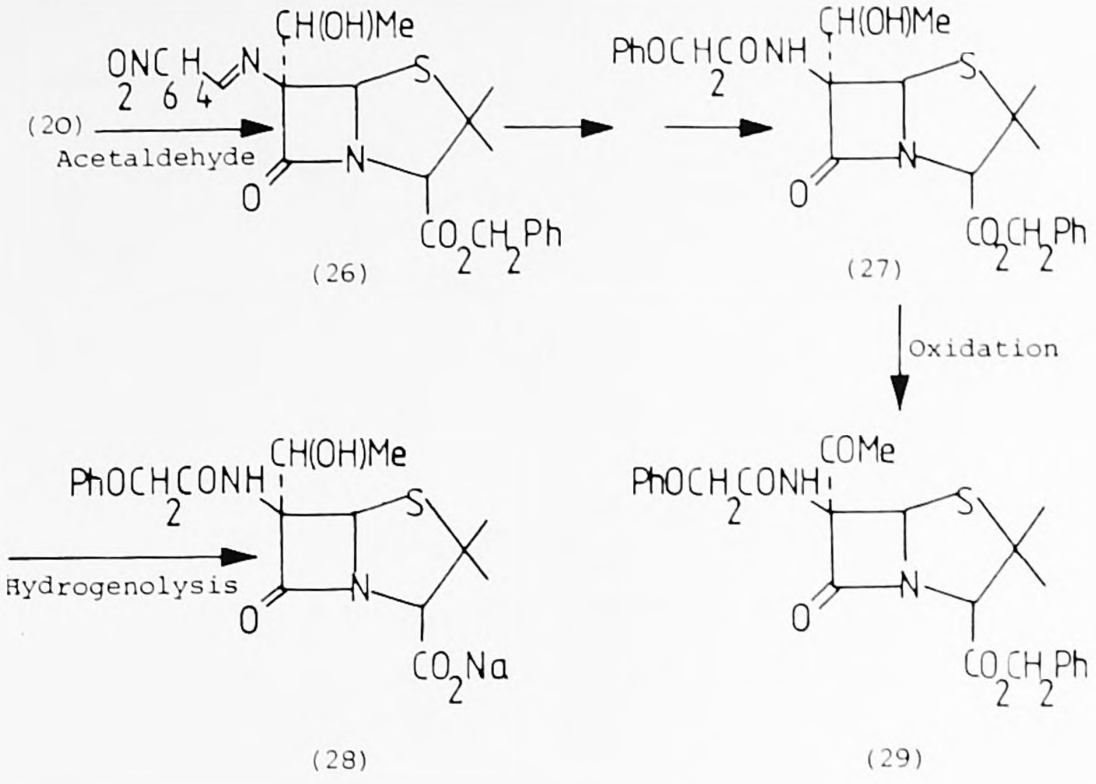
(23) (24)



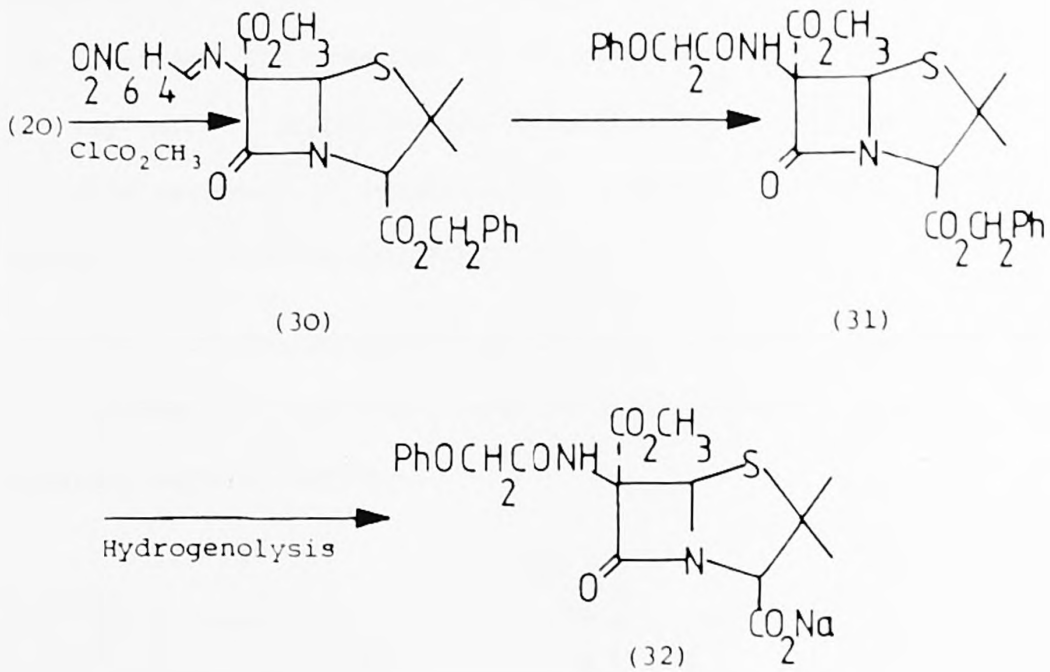
(25)

The analogous product (25) was prepared in the same manner. Condensation of Schiff base (20) with acetaldehyde afforded the α-hydroxyethyl derivative (26) which in two steps was converted to (27). Hydrogenolysis of (27) gave sodium 6α-(α-hydroxyethyl) penicillin V (28) (Scheme 5).

Although oxidation of (28) failed, (27) was quantitatively oxidized to (29), which liberated the free acid on hydrogenolysis. Reaction of (20) with methylchloroformate yielded (30) which was subsequently converted to (31). (31) was converted by hydrogenolysis to (32) (Scheme 6).



Scheme 5

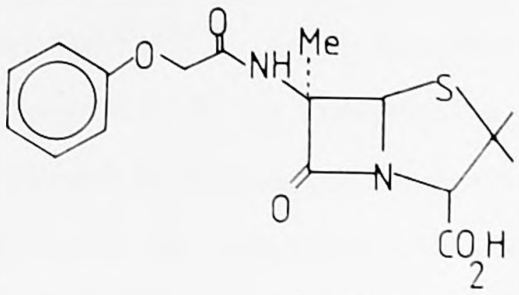


Scheme 6

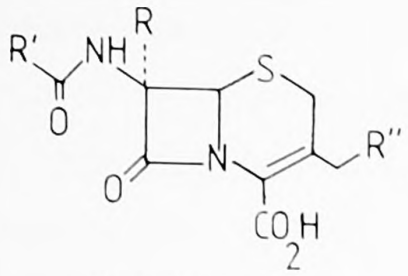
The final products all possessed some antibacterial activity, providing some evidence in support of Strominger's theory.

Also in 1973, Bohme et al.[38] prepared structures (33), (34),

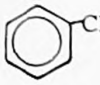
(35) and (36) which all proved to be less active than their unsubstituted parent.



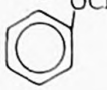
(33)



(34) (35) (36)

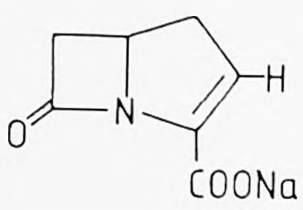
(34) R = CH_3, R' =  , R" = H

(35) R = CH_3, R' =  , R" = H

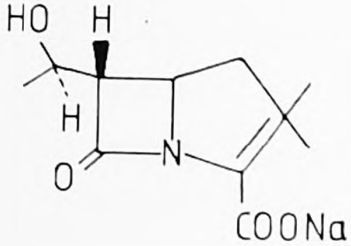
(36) R = CH_3, R' =  , R" = OAc

Since the biological activity in such antibiotics is attributed to enzymatically-catalysed nucleophilic attack on the β-lactam, the presence of the methyl group at C-6 and C-7 may tend to stabilize the β-lactam, hence causing the observed decrease in antibacterial activity. Steric interaction could also be involved.

Cama and Christensen[39] synthesized the thienamycin derivatives (37) and (38), both of which showed activity against certain bacteria.

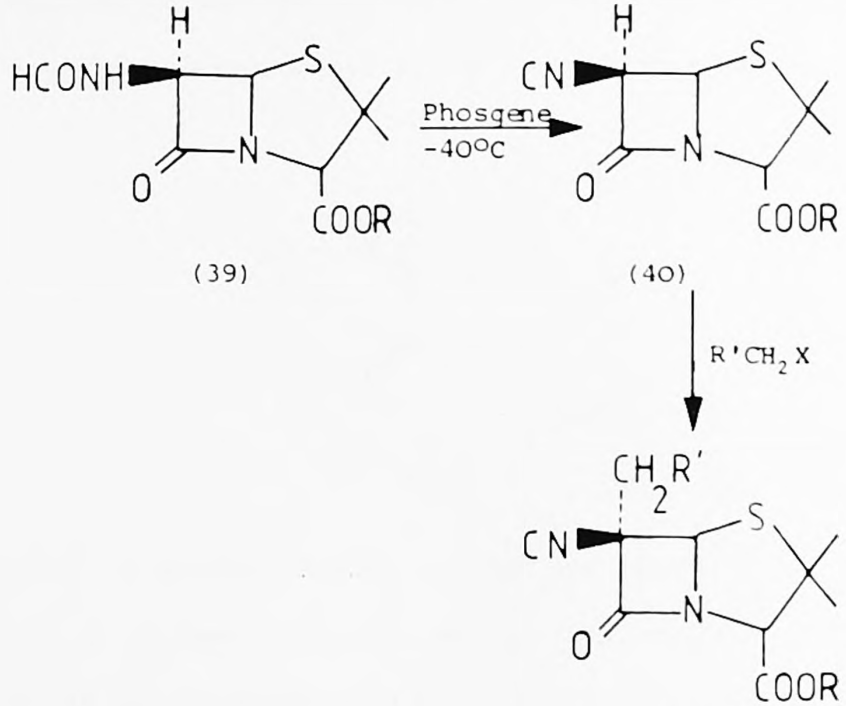


(37)



(38)

Based on the activating influence of the isocyanide group, several 6α-substituted penicillins were prepared by Bentley and Clayton[40]. As in the previous examples, the reactions proceeded with the intermediate formation of the C-6 anion, followed by nucleophilic substitution. Initially, treatment of benzyl 6β-formylpenicillanate (39) with phosgene at -40°C in the presence of a tertiary base afforded benzyl 6-isocyano-penicillanate (40). By heating the isocyanide (40) with reactive alkyl halides in dimethylformamide and potassium carbonate as base, substitution occurred readily, yielding (41) (42) and (43) (Scheme 7).



(39) (40)

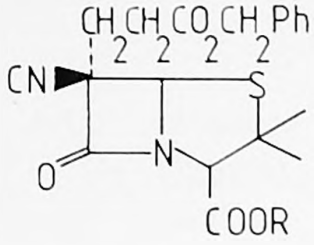
(41) R' = Ph

(42) R' = CO_2Me

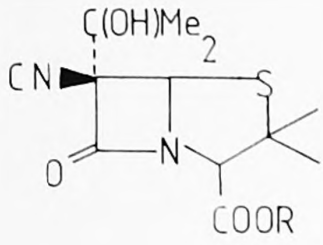
(43) R' = COPh

Scheme 7

Similarly, reaction with benzylacrylate gave the Michael addition product (44) and reaction with acetone afforded (45).

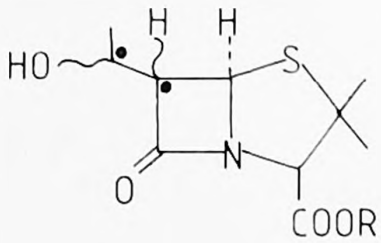


(44)



(45)

In 1977, DiNinno et al.[41] prepared the hybrid of thienamycin (46). The stereochemistry of thienamycin was unknown at this time. Introduction of the hydroxyethyl function at C-6 could lead to four possible stereoisomers at the designated centres.



(46)

Generally, β-hydroxycarbonyl systems are generated by the use of an aldol or Reformatsky reaction, but few examples of the required penicillin and cephalosporin enolates had appeared in the literature (Figure 3).

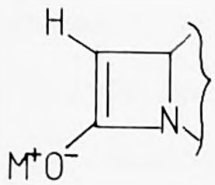
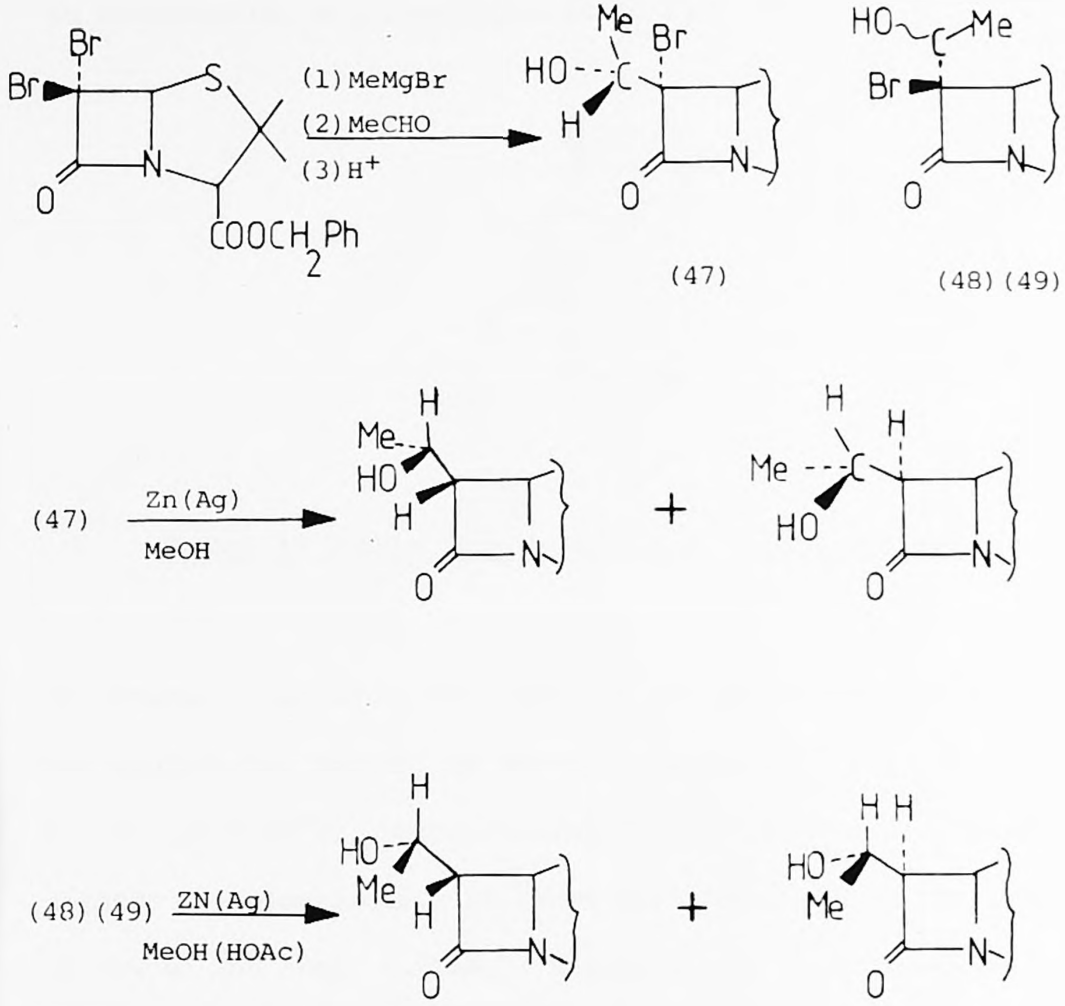


Figure 3: Structure of the Metal Enolate

However, work by Sheehan et al.[42,43] did give some evidence for enolate formation, and so this method of metal-halogen exchange was utilized in the formation of the four possible stereoisomers of the thienamycin-related species (Scheme 8).



Scheme 8

Similarly, the cephalosporin derivatives bearing the hydroxyethyl function at C-7 were produced. In the above reactions, only one of the two possible 6β-hydroxyalkylpenicillanate diastereoisomers could be detected. This was rationalized on the grounds of steric hindrance of substrate approach to the more sterically

hindered face of the penicillanate with concomitant coordination of the aldehyde carbonyl oxygen atom to the metal of the enolate. Molecular models show a severe steric interaction of the aldehyde R_1 group with the thiazolidine ring and the C-2β-Me group when it occupied the position depicted in Figure 4.

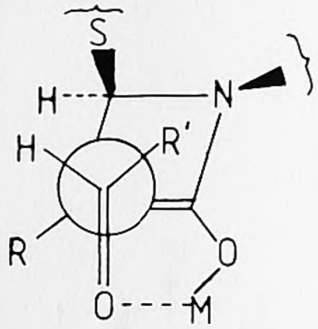
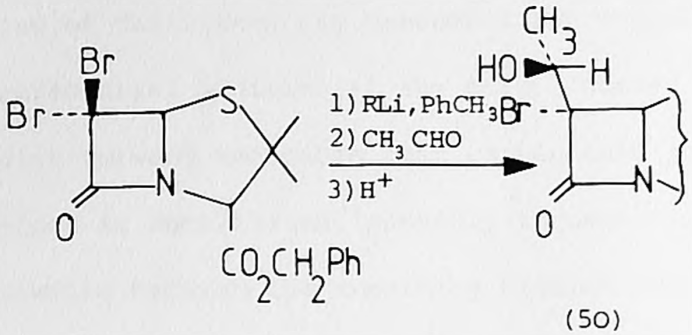


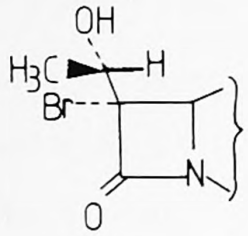
Figure 4: Steric Interaction in the Metal Enolate

In general, control of the required stereochemistry at C-6 of the penicillins and C-7 of the cephalosporins[44] has proved to be a major problem[45]. Hence a considerable amount is known about methods of epimerisation at these positions, and of the properties of the 6- and 7-epi series. Almost all of these compounds are devoid of antibiotic activity. Aimetti et al.[46] had independently obtained similar results to those of DiNinno et al.[41] but in addition demonstrated the marked influence of the solvent and the metal cation on the reaction. Reaction of benzyl 6,6-dibromopenicillanate with sec or tert butyl lithium in toluene at -78°C, followed by condensation of the anion with acetaldehyde gave, in 89% yield, a mixture of the isomers (50) to (53). Isomers (50) and (51) were isolated separately in the ratio 26:1. The diastereomeric pair (52) and (53) were an inseparable equicomponent

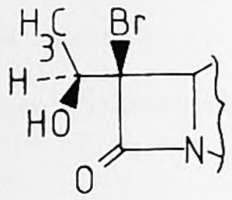
mixture comprising 60% of the total yield.



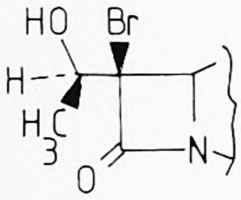
(50)



(51)



(52)



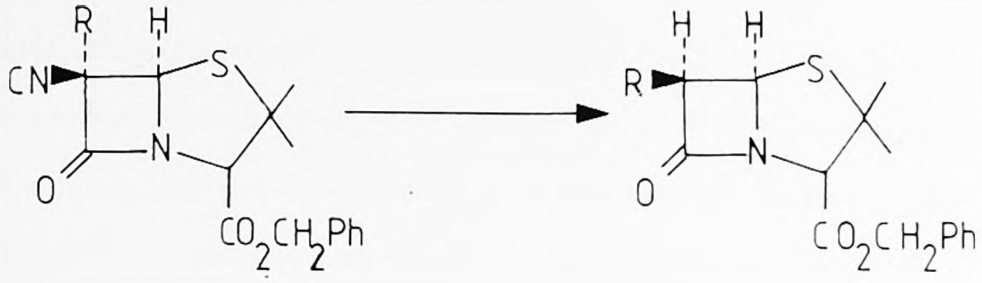
(53)

Aldolization in toluene produced an α to β ratio of 6:4 compared to the corresponding ratio of 1:4 produced in THF, indicating that solvent plays an integral rôle in the stereotopic formation of the C-C bond.

Since zinc ions accommodate ligands to form complexes more readily than either magnesium or lithium[47], and since stereochemical control of aldol-type condensation by zinc enolates is well precedented[48], the behaviour of zinc enolates in this reaction was also investigated. Reduction of the dibromopenicillanate in toluene at -78°C with sec-or tert-butyllithium followed by addition of a concentrated solution of anhydrous zinc chloride in THF and acetaldehyde produced benzyl 6-α-bromopenicillanate and one single aldol product, which proved

to have the structure (52) each in approximately 40% yield. Predominant addition to the hindered β-face was surprising in view of the literature precedent for α-addition[33,34,36,40,49,50]. Preferential addition at the more hindered β-face in the more polar solvent indicates that carbanionic localization on the β-face is facilitated, possibly through elimination of steric crowding between the remaining bromine atom and the β-methyl group. Absence of addition to the β-face in the presence of zinc suggests that a zinc-carbon bond on the more hindered β-face might be rendered less reactive to aldolization, either due to steric factors or through interaction with the lone pair on the adjacent sulphur atom.

A high degree of stereoselectivity was also demonstrated in the reduction of 6α-alkyl-6β-isocyanopenicillanates to 6β-alkylpenicillins using tri-n-butyl tin hydride[51]. Although reduction of isocyanides by trialkyl tin hydrides had not been widely studied, it had been reported that benzyl isocyanide was reduced to toluene by tri-n-butyl tin hydride[52]. Since 6α-alkyl-6β-isocyanopenicillins are readily available by alkylation of 6-isocyanopenicillins[40], the reduction of these compounds as a possible route to 6-alkylpenicillins was studied. 6α-benzyl-, 6α-(1-hydroxy-1-methyl ethyl) -, 6α-methoxycarbonylmethyl-, and 6α-(2-methoxycarbonyl ethyl) - 6β-isocyanopenicillins (54,55, 56,57) were prepared according to the literature method and were treated with tri-n-butyl tin hydride[53] to afford 6β-alkylpenicillins (58,59,60,61).



(54) R = $PhCH_2$

(55) R = Me_2CHOH

(56) R = MeO_2C-CH_2

(57) R = $MeO_2C-CH_2CH_2$

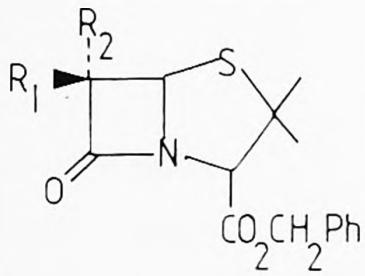
(58) R = $PhCH_2$

(59) R = Me_2CHOH

(60) R = MeO_2C-CH_2

(61) R = $MeO_2-C-CH_2-CH_2$

Similarly, the reduction of a 6α/6β mixture of the 6-iso-cyano-penicillins (62,63) afforded benzylpenicillanate (64).



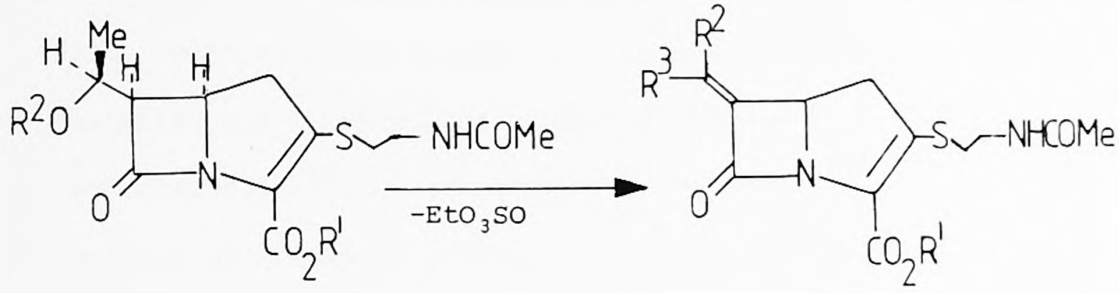
(62) R_1 = H, R_2 = NC

(63) R_1 = NC, R_2 = H

(64) R_1 = R_2 = H

The products were assigned as β-substituents on the basis of the H_5-H_6 coupling, which was 4.4Hz in each case, indicating cis protons[54]. The high stereoselectivity of reduction of the 6α-alkyl-6β-isocyanopenicillins (54-57) was initially surprising. The stereochemistry-determining step probably involved the transfer of a hydrogen atom from a molecule of tri-n- butyl tin hydride to the less hindered α-face of the penicillin radical to give the 6β-alkyl product. This stereoselectivity is analogous to the selectivity of alkylation of C-6 penicillin anions[33,34]. A preparation of C-6 substituted β-lactams based on the olivanic

acid series was reported by Corbett and Eglington[55]. The ethyl sulphate p-nitrobenzyl carboxylate (66) was prepared from the corresponding disodium salt (65) by esterification. Elimination of the sulphate group gave rise to the useful intermediates (67) and (68). Hydride reduction of the ethylidene group in (67) gave predominantly the trans β-lactam (69), together with a small proportion of the cis isomer (70) (9:1). In contrast to the hydride reduction, catalytic hydrogenation of the 6-ethylidene derivatives gave predominantly the cis-6-ethyl isomer(cis:trans=4:1).

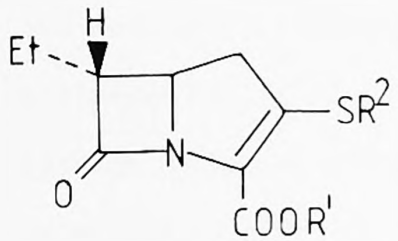


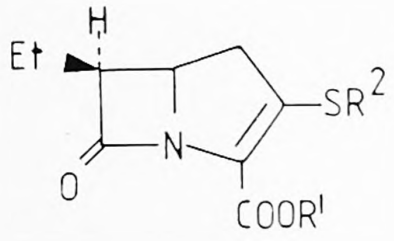
(65) R^1 = Na, R^2 = NaO_3S

(66) R^1 = PNB, R^2 = EtO_3S

(67) R^1 = PNB, R^2 = Me, R^3 =H

(68) R^1 = PNB, R^2 = H, R^3 =Me





(69) R^1 = PNB, R^2 = $CH_2CH_2NHCOMe$

(70) R^1 = PNB, R^2 = $CH_2CH_2NHCOMe$

(71) R^1 = H, R^2 = CH=CHNHCOMe

(72) R^1 = H, R^2 = $CH_2CH_2NHCOMe$

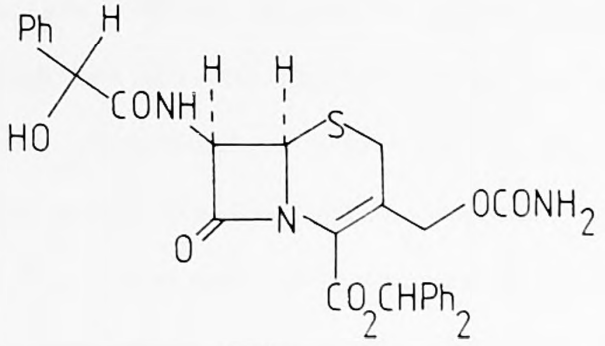
(73) R^1 = H, R^2 = $CH_2CH_2NHCOMe$

(74) R^1 = H, R^2 = CH=CHNHCOMe

In order to obtain samples bearing the free acid for testing, the four isomers (71)-(74) were prepared bearing the p-methoxycarbonyl-

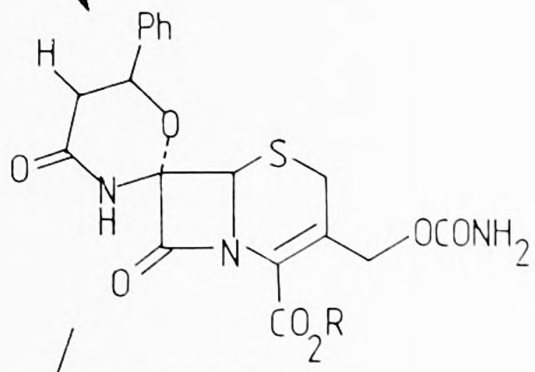
benzyl protecting group, which could be readily removed by electrochemical means. Cleavage was effected by reduction at a mercury cathode. All four derivatives showed a high level of antibacterial activity.

Many reports of spiro-structures generated at C-6 and C-7 to form, overall, tricyclic structures have appeared in the literature. Such spiro-substitution has been of considerable interest due to virucidal properties of the 6-spiropyrroline[56]. Baldwin has reported the general synthesis of α-methoxyamides by generation of an acylimine followed by addition of methanol to the highly reactive functionality[57]. The possibility of intercepting such an acylimine intermediate with an internal nucleophile prompted Koppel and Koehler to investigate the reaction of (75) in a similar manner[58]. Treatment of (75) with lithium methoxide afforded (77a) which was deprotected to give the free acid (77b), and was subsequently shown to possess biological activity.



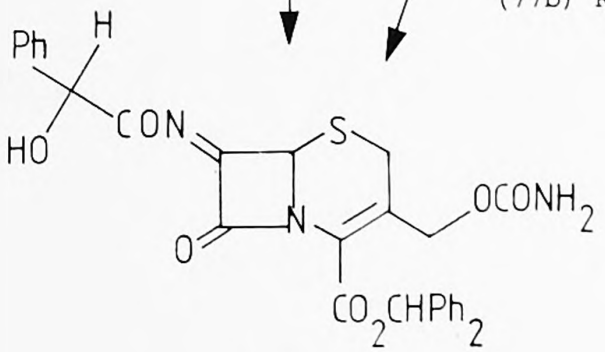
(75)

LiOMe



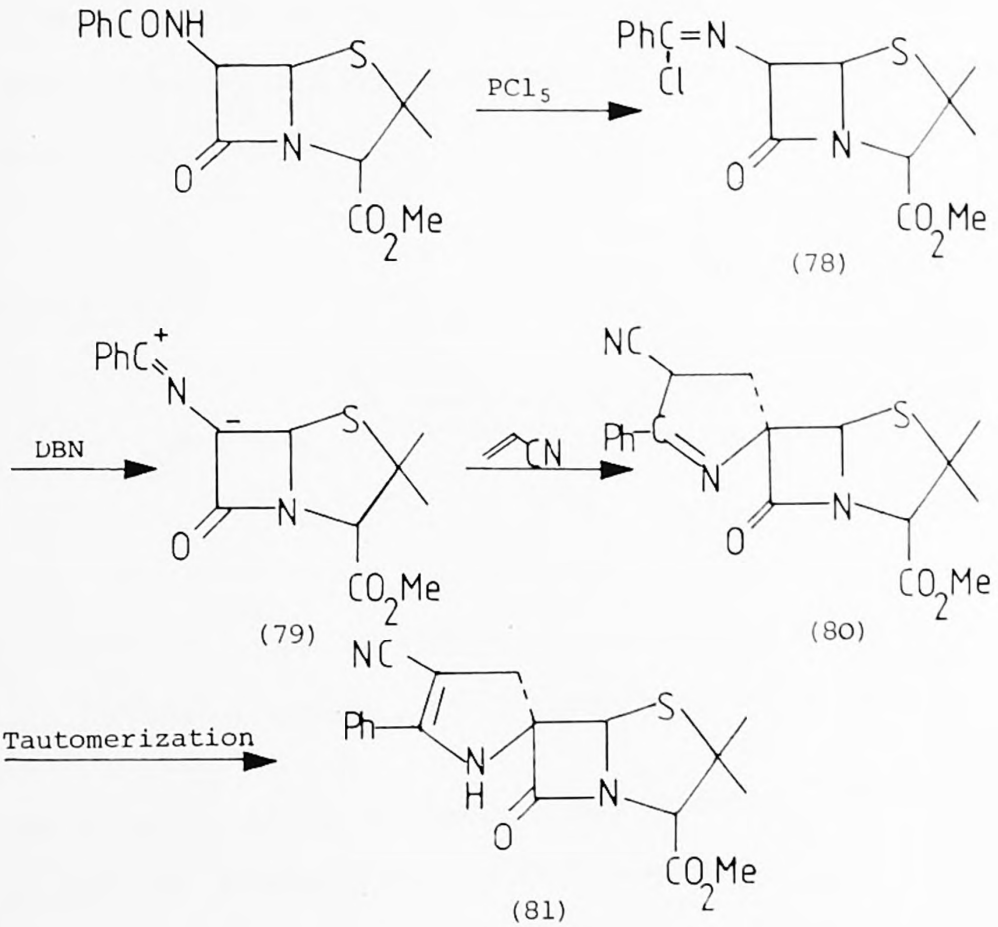
(77a) R=$CHPh_2$

(77b) R=H

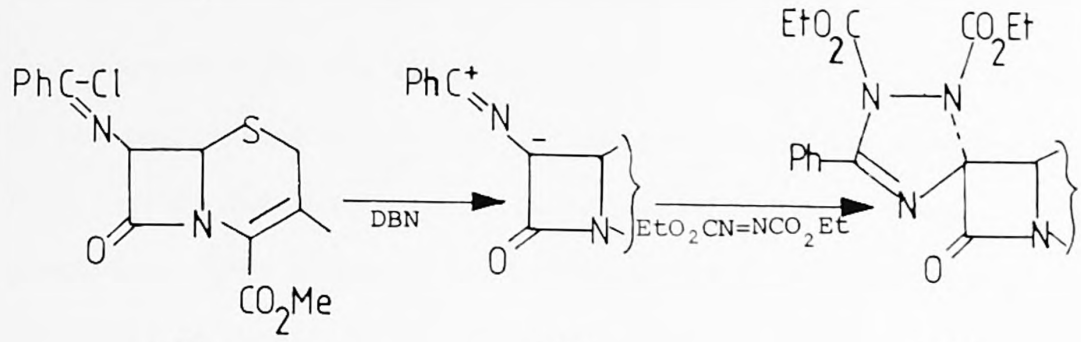


(76)

In 1976, Hirai et al.[59] reported a tricyclic penicillin structure formed by means of a 1,3-dipolar addition. The 1,3-dipolar intermediate (79) was generated by base treatment of (78). Suitable dipolarophiles for the addition were acrylonitrile and methyl acrylate. Treatment of (79) with the dipolarophile afforded the tricyclic structure (80) which underwent tautomerization to (81) (Scheme 9). The same sequence was followed with the cephalosporins, whereby (82), on treatment with base such as DBN, afforded (83) which was subsequently reacted with the dipolarophile to yield the spiro-cephalosporanate (84)(Scheme 10).



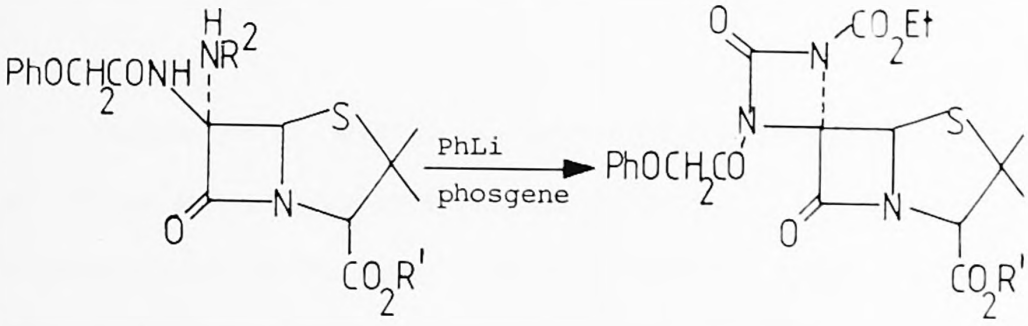
Scheme 9



(82) (83) (84)

Scheme 10

From the 6,6-disubstituted penams (85) and (86), Bremner, Campbell and Johnson reported the production of the spiro-1, 3-azetidin-2-one structures (87) and (88)[60]. Neither of these possessed signifcant activity as antibiotics following their deprotection.



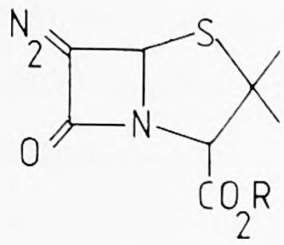
(85) R^1 = Me, R^2 = CO_2Et (87) R^1 = Me

(86) R^1 = CH_2CCl_3, R^2 = CO_2Et (88) R^1 = CH_2CCl_3

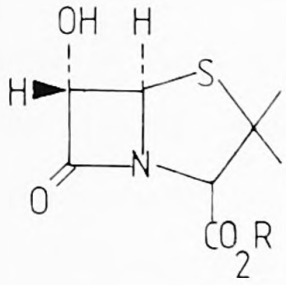
The formation of the spiropyrrolidine structure (21) by Rasmusson et al.[35] was discussed earlier in Chapter 1.3.

1.4 Introduction of C-6 Substituents via 6-Diazopenicillanate and 6-Oxopenicillanate Esters

Generation of the diazo group from the amine function at C-6 of the penicillins and C-7 of the cephalosporins has provided a facile route for the introduction of substituents at these positions. The formation of 6-diazopenicillanates (89) will be discussed in detail in the following chapter.



(89)

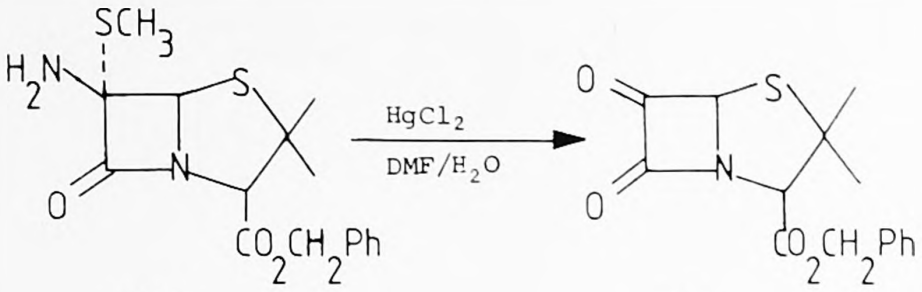


(90)

Sheehan et al. exploited the use of 6-diazopenicillanates as convenient precursors in the preparation of a wide range of 6-substituted penicillins. In 1972, Sheehan hydrolysed a 6-diazopenicillanate ester in aqueous acetone with perchloric acid to give a 60% yield of 6α-hydroxypenicillanate (90, $R=CH_2CCl_3$) which was isolated from the reaction mixture by crystallization.

Sheehan developed synthetic procedures for the conversion of both 6-hydroxypenicillanate and 6-diazopenicillanate into 6-oxopenicillanate (91)[61,62] which was known to be a useful intermediate for the synthesis of novel β-lactam antibiotics. A third synthesis for the preparation of 6-oxopenicillanate (91)

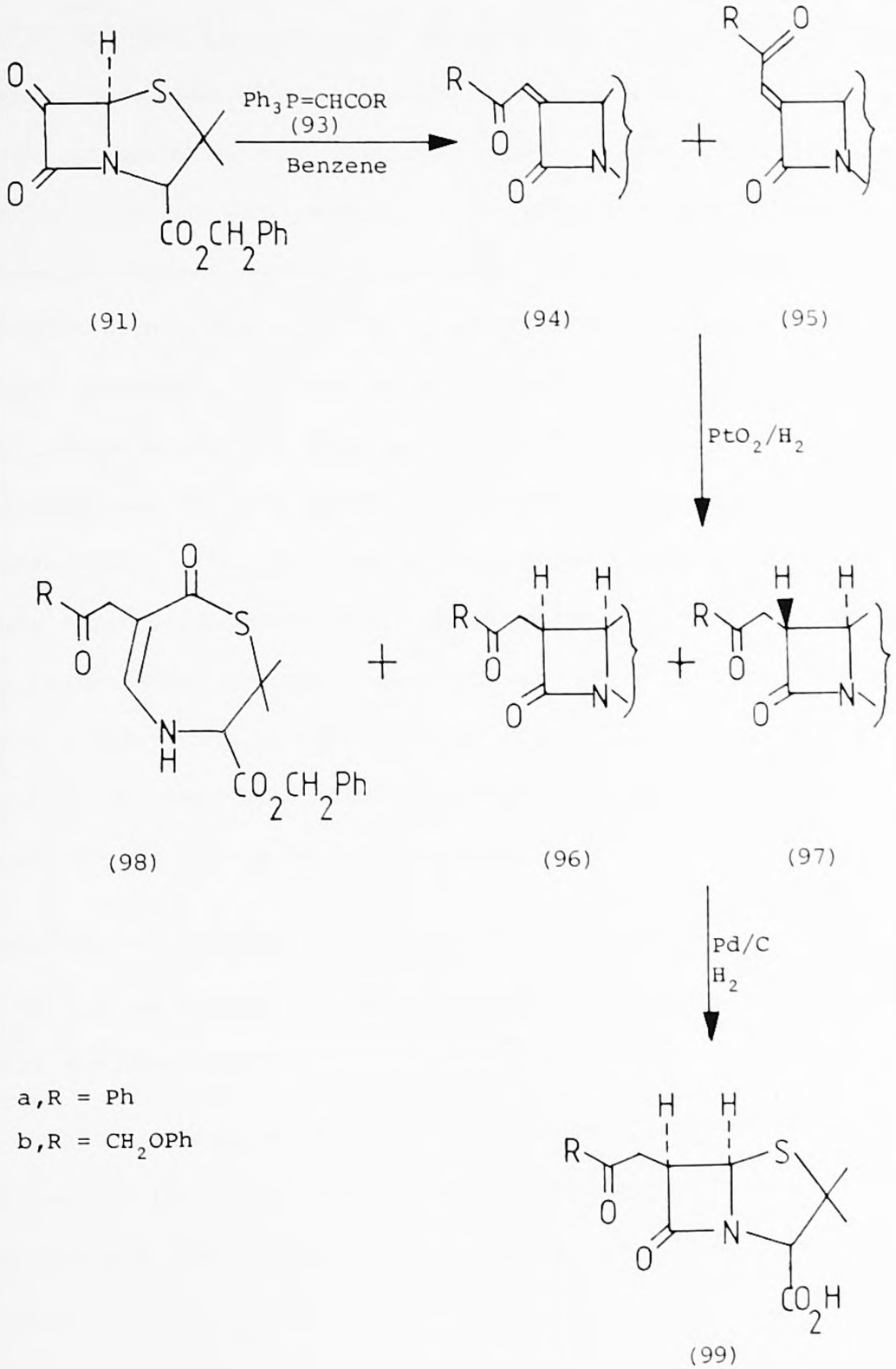
was reported by Jen, Frazee and Hoover[63], and involved oxidation of (92) by treatment with mercuric chloride in DMF (Scheme 11).



(92) (91)

Scheme 11

This method was also successfully employed in the conversion of the cephalosporanate analogue of (92) into the corresponding 7-oxocephalosporanate. Benzyl 6-oxopenicillanate was utilized by Sheehan and Lo[42] in the preparation of various analogues of pencillin V. The readily available benzoylmethylene-triphenylphosporane (93a) was allowed to react with benzyl 6-oxopenicillanate in refluxing benzene to give, after chromatography, a mixture of isomers of benzyl benzoylmethylene penicillanate (94a)(95a) (Scheme 12).



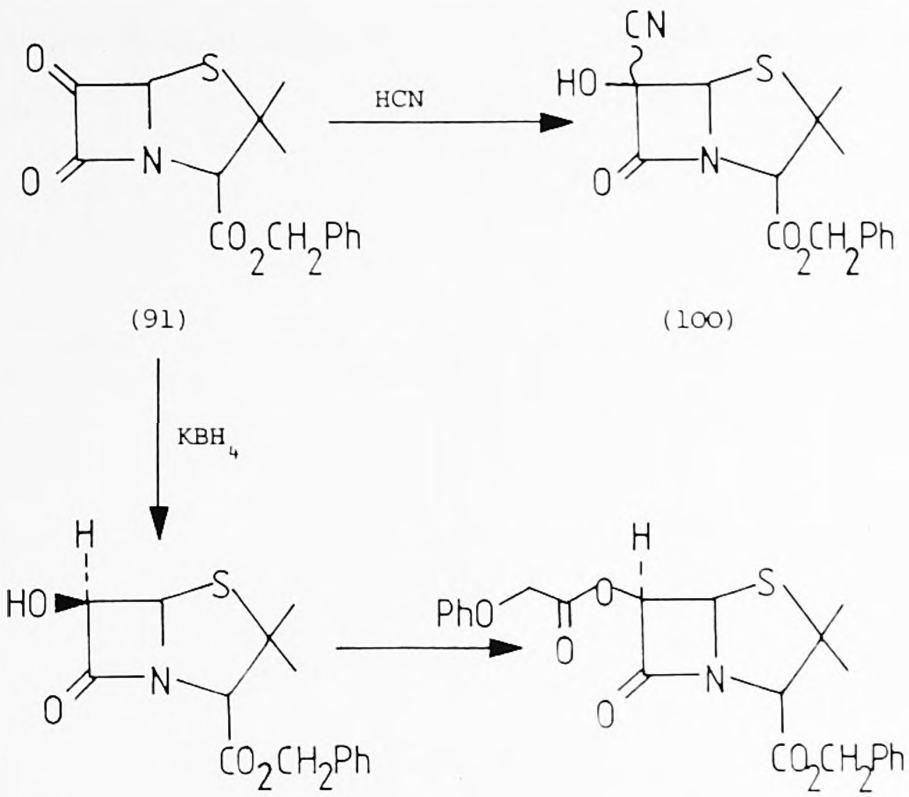
(91) (94) (95) (98) (96) (97) (99)

Scheme 12

Hydrogenation of this isomeric mixture in the presence of platinum oxide afforded two fractions, one of which contained cis-and trans-benzyl benzoylmethylpenicillanate (96a) and (97a), while the other fraction contained the rearranged product (98a). A similar reaction involving the condensation of benzyl6-oxopenicillanate with phenoxyacetylmethylenetriphenylphosporane (93b) followed by hydrogenation with platinum oxide/H_2 afforded the cis and trans isomers (96b) and (97b). Further hydrogenation in the presence of palladium on charcoal gave rise to the free acid (99b) which, on testing, was shown to possess antibiotic activity and penicillanase resistance. The synthesis of 6β-phenoxyacetoxypenicillanic acid from benzyl 6-oxopenicillanate was also reported by Sheehan and Lo[61], in which benzyl 6α-hydroxypenicillanate (90, R=CH_2Ph) was prepared from 6-APA by the method of Hauser and Sigg[64]. Oxidation of (90) to (91) followed by immediate reaction with liquid hydrogen cyanide produced the crystalline cyanohydrin (100)

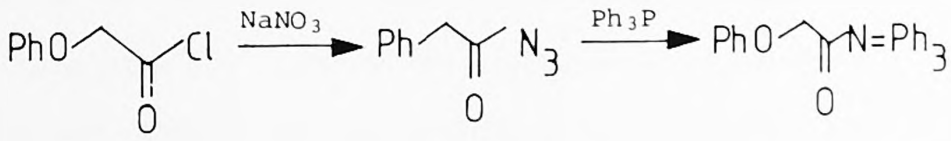
Reduction of the ketone (91) with potassium borohydride afforded the 6β-isomer (101) which was phenoxyacetylated to give the ester (102).

In an analogous reaction, Sheehan used the ketone(91) to prepare the N-acyl imine (104) by condensation with the phosphorane (103) which, in turn, was prepared from its azide (Scheme 13).



(91) (100)

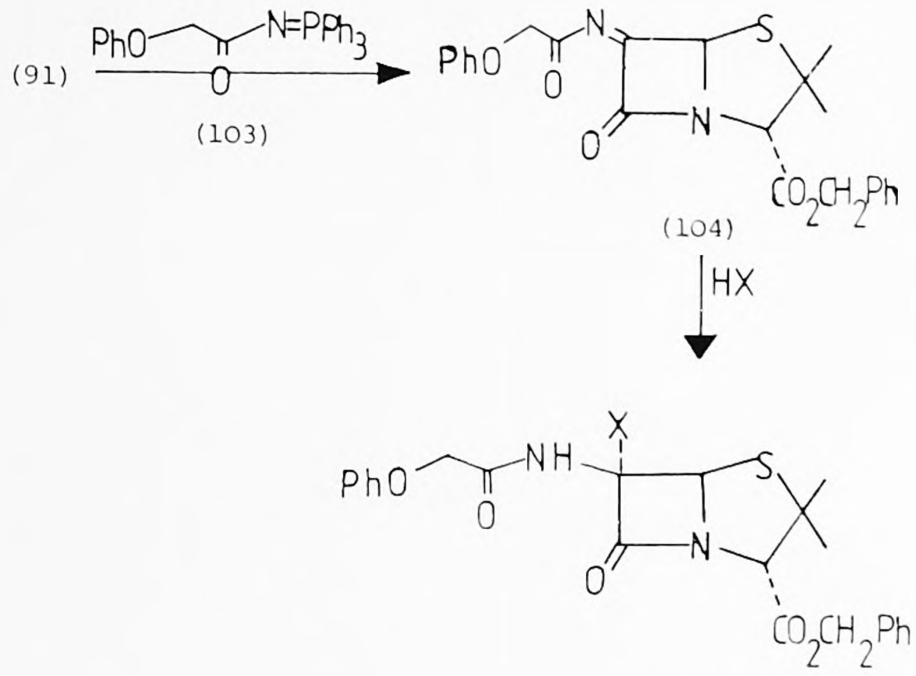
(101) (102)



(103)

Scheme 13

Addition of methanol or hydrogen cyanide to the imine gave the substituted penicillins (105). In both cases, addition occurred from the less-sterically hindered side to give the α-substituted products.

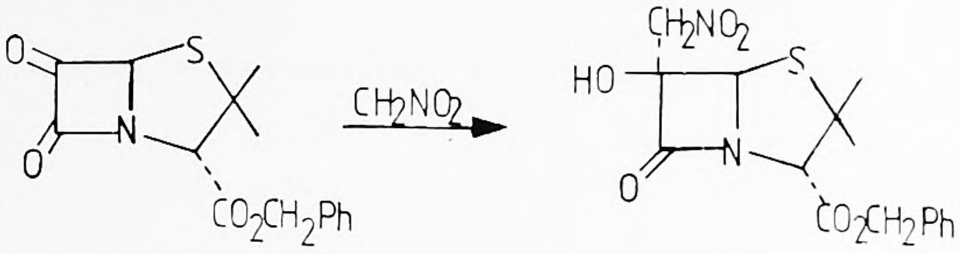


(105a) X = OMe

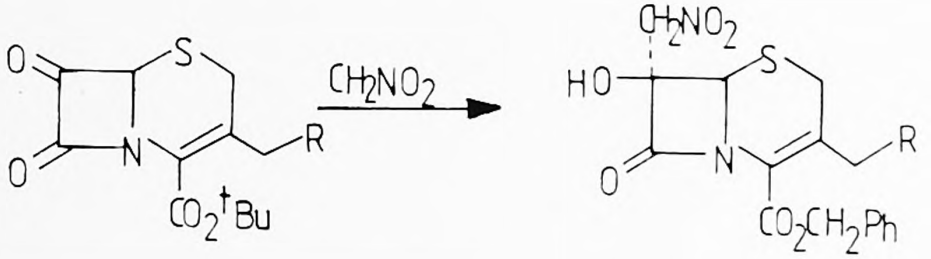
(105b) X = CN

Both 6α-methoxy- and 6α-cyano-6β-phenoxyacetamido-penicillanic acids showed weak antibacterial activities. Chandrasekaran and co-workers[65] utilized 6-oxopenicillanate and 7-oxocephalosporanate in the condensation with nitromethane and potassium tert-butoxide at $0^{\circ}C$ to produce the α-nitromethyl compounds (106)(107) and (108). The two nitroalcohols (106) and (107) were subsequently converted into nitroolefins (109) and (110) by reaction with mesylchloride and triethylamine at $-40^{\circ}C$. Catalytic hydrogenation using tris (triphenylphosphine) rhodium chloride afforded the reduced compounds (111)(112) and (113).

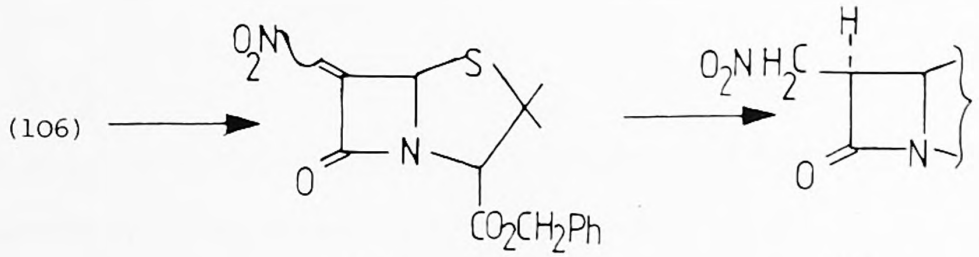
Compounds (112) and (113) were also obtained by $NaBH_4$ reduction of (110) (Scheme 14).



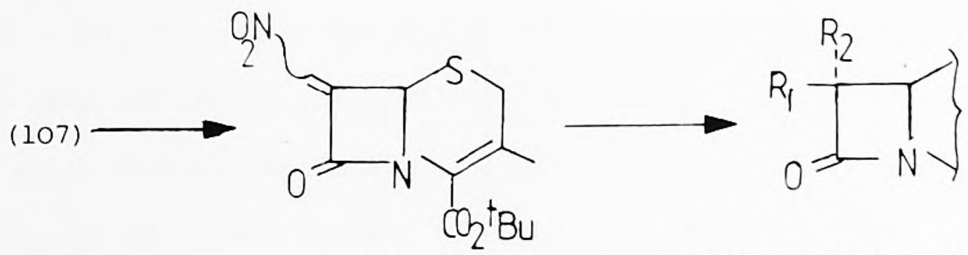
(106)



(107) R=H, (108) R=OAc



(109) (111)



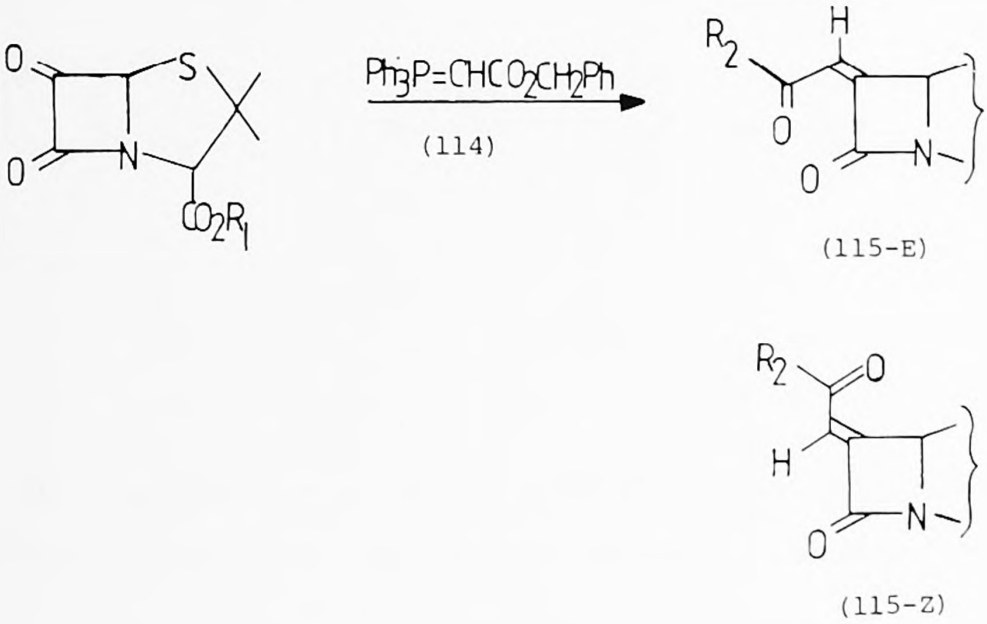
(110)

(112) R_1=H, R_2= CH_2NO_2

(113) R_1=CH_2NO_2, R_2= H

Scheme 14

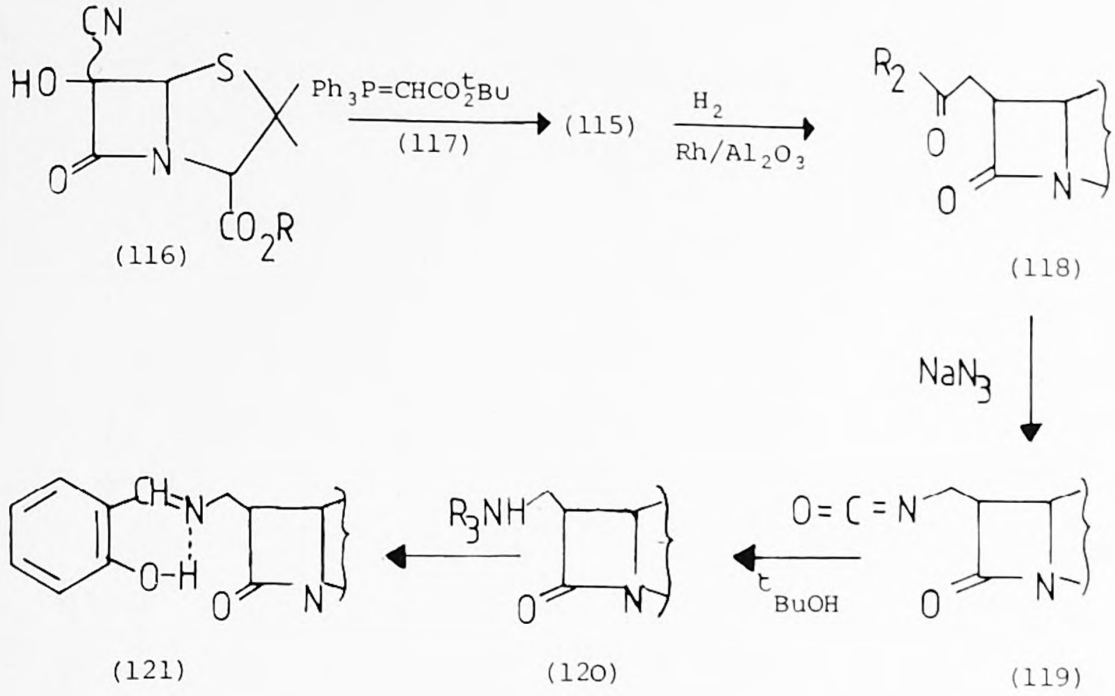
Compound (107) was deprotected and converted to its sodium salt, which was subsequently shown to possess only low antibacterial activity. In 1977, Sheehan et al.[62] reported the Wittig reaction of 6-oxopenicillanate with the ylid (114), affording the E and Z isomers of (115) (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) (Scheme 15). The major isomer, as expected, was the less-hindered Z-structure.



Scheme 15

Addition of hydrogen cyanide to 6-oxopenicillanate afforded the cyanohydrin (116) which, on reaction with the ylid (117) again yielded (115) (R_1 = CH_2Ph, R_2 = O^tBu). Hydrogenation of (115) (R_1 = CH_2CCl_3, R_2 = OCH_2Ph) in the presence of rhodium on alumina gave one isomer of (118). Treatment of (118) with sodium azide caused rearrangement to (119), which, in turn, was treated with tert-butyl alcohol to yield (120, R_3 = COO^tBu). (120) reacted with salicylaldehyde, affording the Schiff base

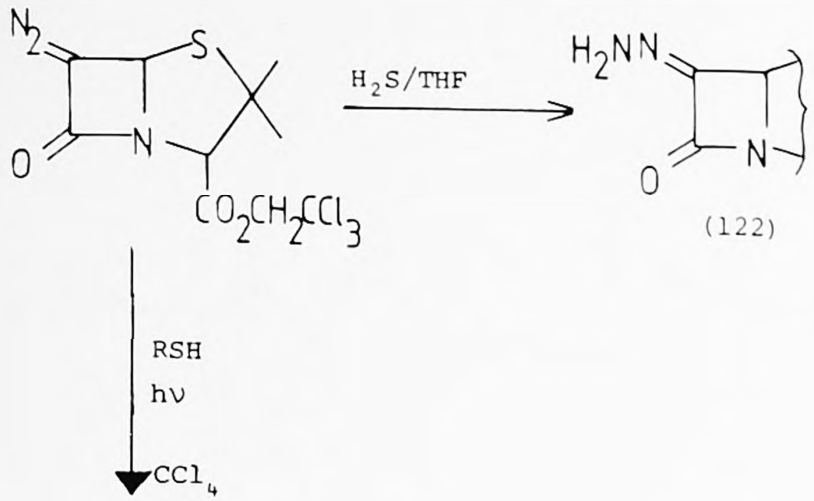
(121) on deprotection (Scheme 16).



Scheme 16

All compounds were tested for antibacterial activity, but only the C-6 carbon analogues of (118) showed any activity.

The stereoselective conversion of 6-diazopenicillanates to analogues in which the side chain nitrogen was replaced by a sulphur atom was described by Sheehan, Commous and Lo[66] in 1977. Treatment of a THF solution of 6-diazopenicillanate with hydrogen sulphide afforded 66% yield of the hydrazone (122), whereas a mixture of 6-diazopenicillanate and an excess of either thiobenzoic acid, phenylthiolacetic acid or phenoxythiolacetic acid, on irradiation in carbon tetrachloride, gave the cis thiol esters (123)(125) and (127) together with small quantities of the corresponding trans isomers (124)(126) and (128) (Scheme 17).



(123) R = PhCO (124)

(125) R = $PhCH_2CO$ (126)

(127) R = $PhOCH_2CO$ (128)

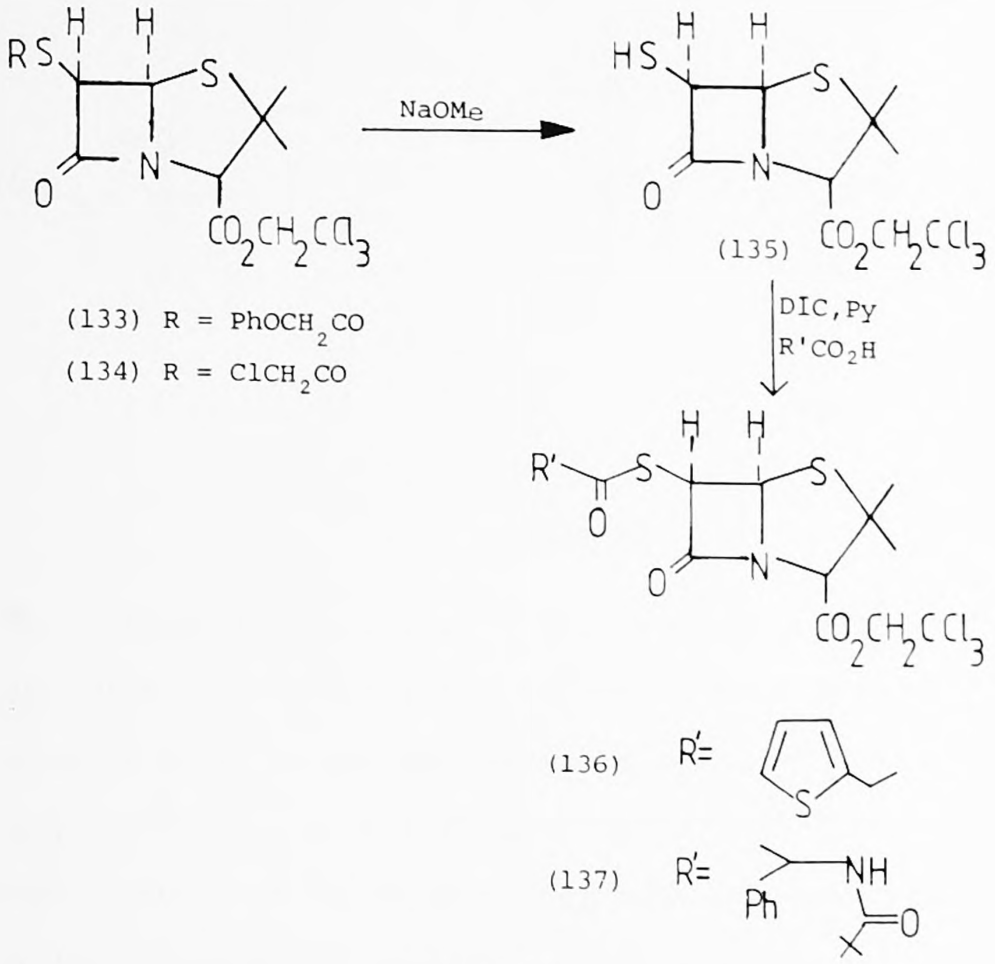
(129) R = Ph (130)

(131) R = $PhCH_2$ (132)

Scheme 17

The stereochemistry at C-6 was assigned on the basis of the coupling between the C-5 and C-6 protons on the β-lactam ring. Irradiation of 6-diazopenicillanate in thiophenol gave a mixture of sulphides (129) and (130), and similarly, irradiation with benzylmercaptan gave (131) and (132). In each case the cis isomer was the most abundant, and this was attributed to attack by the sulphur on the nitrogen of the diazo moiety forming an azo intermediate in which the β-lactam protons were cis. Loss of nitrogen with retention of configuration led to the desired product with the cis stereochemistry. Reaction of (133) and

(134) with sodium methoxide followed by acylation afforded the thiol esters (136) and (137) via the mercaptan (135) (Scheme 18).



(133) R = $PhOCH_2CO$

(134) R = $ClCH_2CO$

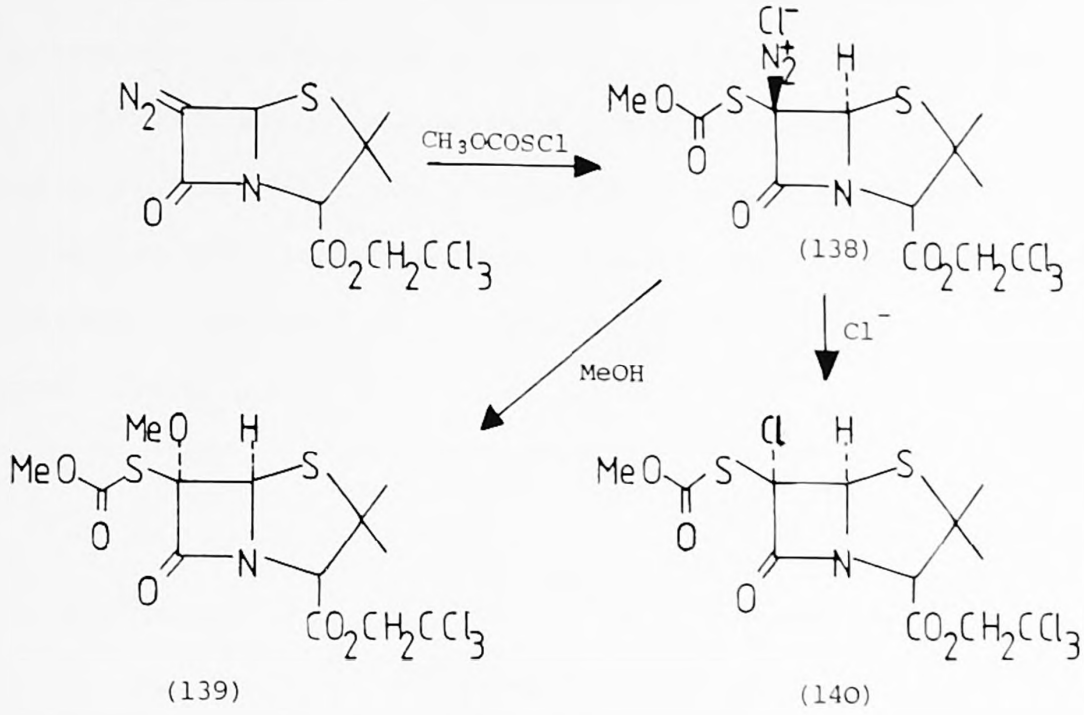
(135)

(136) R'=

(137) R'=

Scheme 18

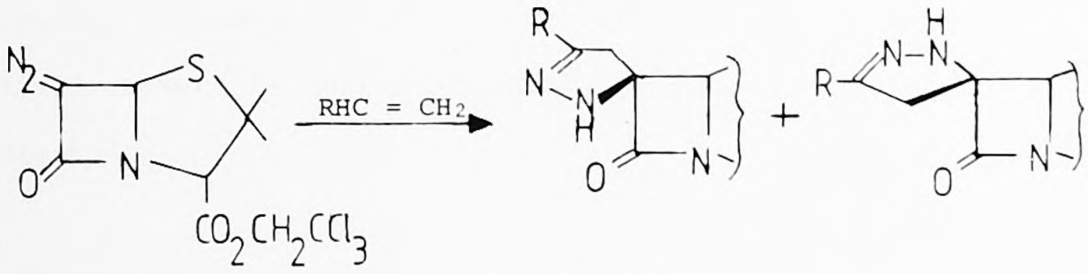
The reactions of 6-diazopenicillanate with sulphenyl chlorides were also reported by Sheehan[67]. In the presence of methanol, 6-diazopenicillanate reacted with carbomethoxysulphenyl chloride to produce the 6α-methoxythiol penicillanate(139) together with a small amount of the 6α-chloro ester (140).



Scheme 19

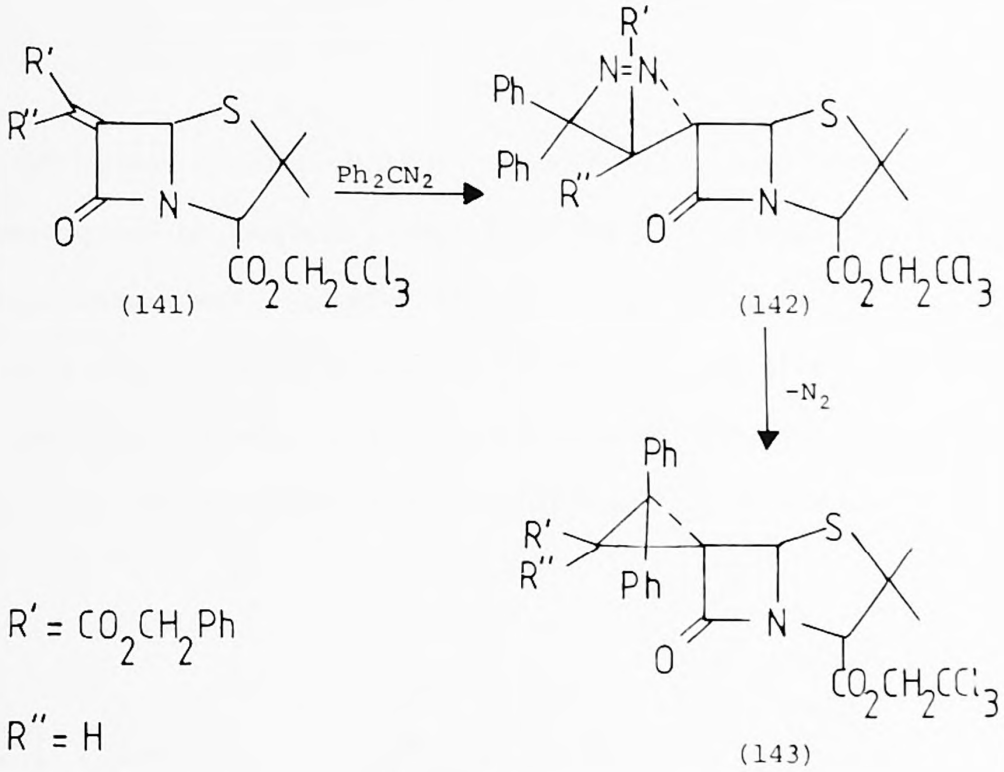
The proposed mechanism involved the initial formation of a diazonium intermediate (138), followed by addition of methanol or chloride ion to the less-hindered α-face of the β-lactam with simultaneous loss of nitrogen (Scheme 19). Similar results were obtained for the corresponding cephalosporin series.

In the reactions with olefins[50], 6-diazopenicillanate underwent 1,3-dipolar additions to give isomeric spiropyrazolines, with preferential addition occurring at the least-hindered α-side (Scheme 20).



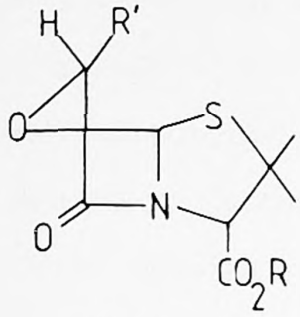
Scheme 20

Spiropyrazolines were also produced when the dipolarophile was incorporated at C-6 of the penicillin molecule. Hence reaction of (141) with diphenyldiazomethane afforded a single isomer of the pyrazoline (142), with the considerable steric interaction preventing formation of the other isomer. Pyrolysis of (142) resulted in evolution of nitrogen to give the spirocyclopropane (143) (Scheme 21).



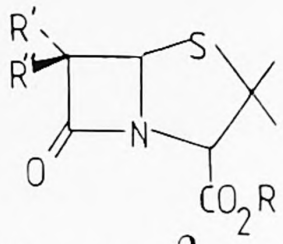
Scheme 21

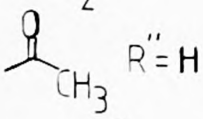
Reaction of 6-diazopenicillanate with acetaldehyde afforded compounds (144), (145)(146) and (147). (145) and (146) were rapidly converted to (147) during chromatography. At reduced temperatures, the sole products of the reaction were the epoxides.

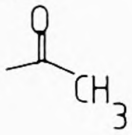


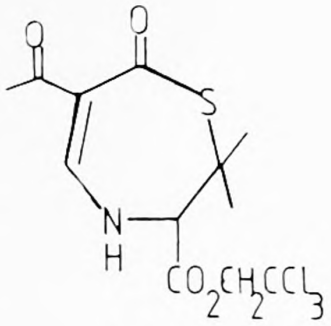
(144)

$R' = CH_3$



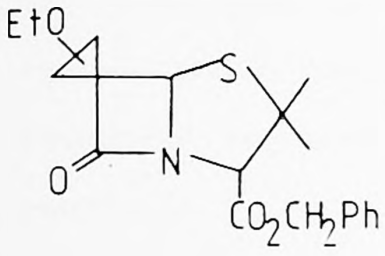
(145) $R' =$  $R'' = H$

(146) $R' = H$ $R'' =$ 

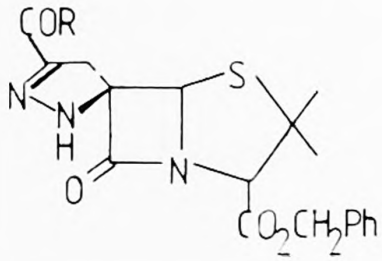


(147)

The reactions of olefins with 6-diazopenicillanate were also investigated by Campbell, Harcus and Ray[68]. Benzyl 6-diazopenicillanate was reacted with ethyl vinyl ether in the presence of $Cu(acac)_2$ to yield a mixture of the four possible isomers of the ethoxy-substituted spirocyclopropane (148a-d). The four analogous cyclopropanes were also obtained in the cephem series.

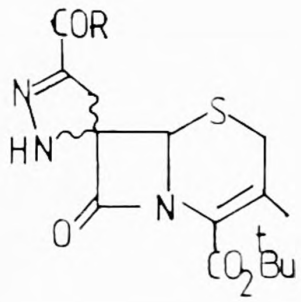


(148a-d)



(149) R = OMe

(150) $R = NH_2$



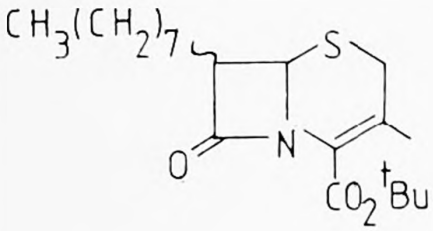
(151)

However, reaction of 6-diazopenicillanate with methylacrylate and acrylamide each gave one single pyrazoline isomer (149) and (150) respectively, with or without catalyst, as a result

of a 1,3-dipolar addition. It appeared that the initial 1, 3-cycloaddition afforded 1-pyrazolines which then gave the corresponding 2-pyrazolines by prototropic rearrangement. Extrusion of nitrogen to produce the cyclopropanes did not occur. In the reaction of methyl acrylate with 6-diazoceph-3-em, two spiro-pyrazolines were produced which were isomeric at C-7 (151).

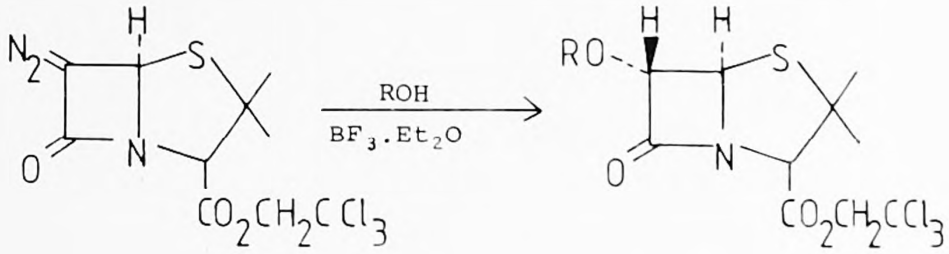
It is possible that the formation of the cyclopropane isomers (148a-d) occurred as a result of rapid extrusion of nitrogen from the corresponding pyrazoline structures. This would account for the difference in products observed between the two sets of reactions.

C-7-alkylated cephalosporanates were produced by Wiering and Wynberg in 1977 to determine the effect on biological activity[69]. To introduce the side chain at C-7, they utilized the reaction of trialkylboranes with diazoesters previously demonstrated by Hooz and Linke on diazoamides[70]. The reaction of 7-diazocephem with trioctylborane gave rise to the alkylated species (152). Other trialkylboranes proved to be equally successful (see Chapter 4 for a full discussion of these reactions).



(152)

The Lewis-catalysed reactions of 6-diazopenicillanate with alcohols, thiols and related compounds as a direct route to 6-oxy- and 6-thiopenicillanates were reported by Giddings et al. in 1978[71]. The addition of $BF_3.Et_2O$ to a solution of 6-diazopenicillanate and an alcohol led to the formation of the corresponding 6α-alkoxy penicillanate (153)(Scheme 22).

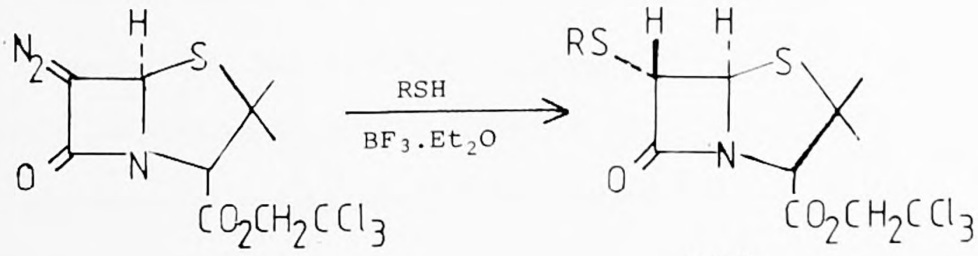


R=Me-
^{t}Bu-
$PhCH_2$-
$PhCH_2CO$-

(153)

Scheme 22

In this manner, 6α-methoxy, ^{t}butoxy, and benzyloxypenicillanates were obtained. Under the same conditions, 6-diazopenicillanate also reacted with phenylacetic acid to give the 6α-phenylacetoxypenicillanate (153; R = $PhCH_2CO$). In excess thiol, 6-diazopenicillanate reacted to form the corresponding 6α-alkylthiopenicillanate (154, R = $PhCH_2$, Me_2CHCH, Et-)(Scheme 23).

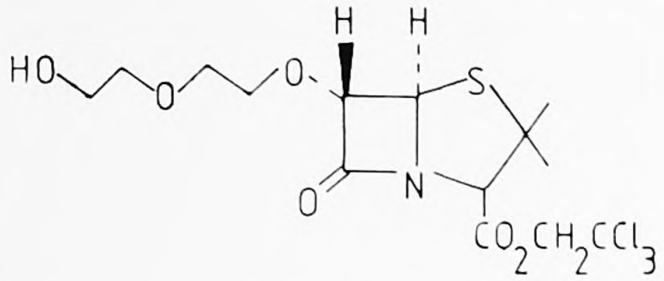


(154)

R=$PhCH_2$-
Me_2CHCH-
Et-

Scheme 23

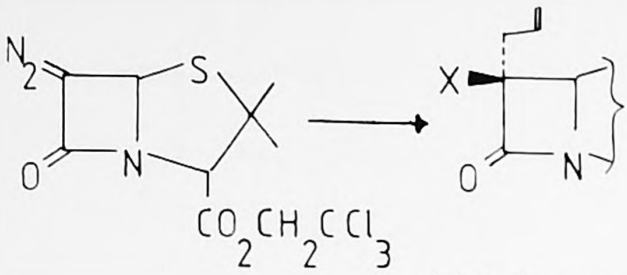
Decomposition of the diazoester in dioxan resulted in the formation of a dioxan cleavage product (155), and similarly, reaction with diethylether resulted in cleavage to form (153, R = Et).



(155)

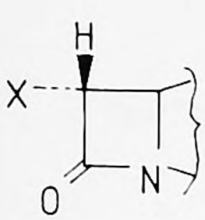
Two mechanisms have been proposed for the above $BF_3.Et_2O$ - catalysed reactions. Either the $BF_3.Et_2O$ coordinates with the alcohol or thiol which then protonates the 6-diazo-penicillanate, or, alternatively, the $BF_3.Et_2O$ coordinates with the 6-diazopenicillanate so making it more electrophilic and more susceptible to nucleophilic attack.

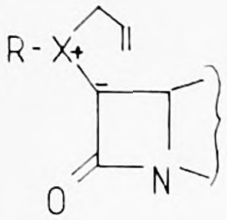
As an extension to this work, Giddings et al.investigated the reactions of 6-diazopenicillanates with allylic sulphides, selenides and bromides[72], producing various 6-substituted penicillanates via a [2,3] sigmatropic rearrangement. The work complemented the reactions of Campbell et al.[68] and was directly related to Baldwin's report on [2,3] sigmatropic rearrangements of 6-alkylaminopenicillanates[73]. Initially, reaction of 6-diazopenicillanate phenylallylsulphide in the presence of $BF_3.Et_2O$ gave rise to three products (156)(157) and (160).

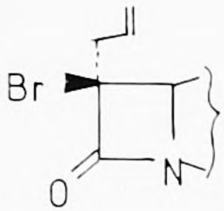


(156) X = PhS (157) X = PhS

(158) X = MeS (159) X = MeS





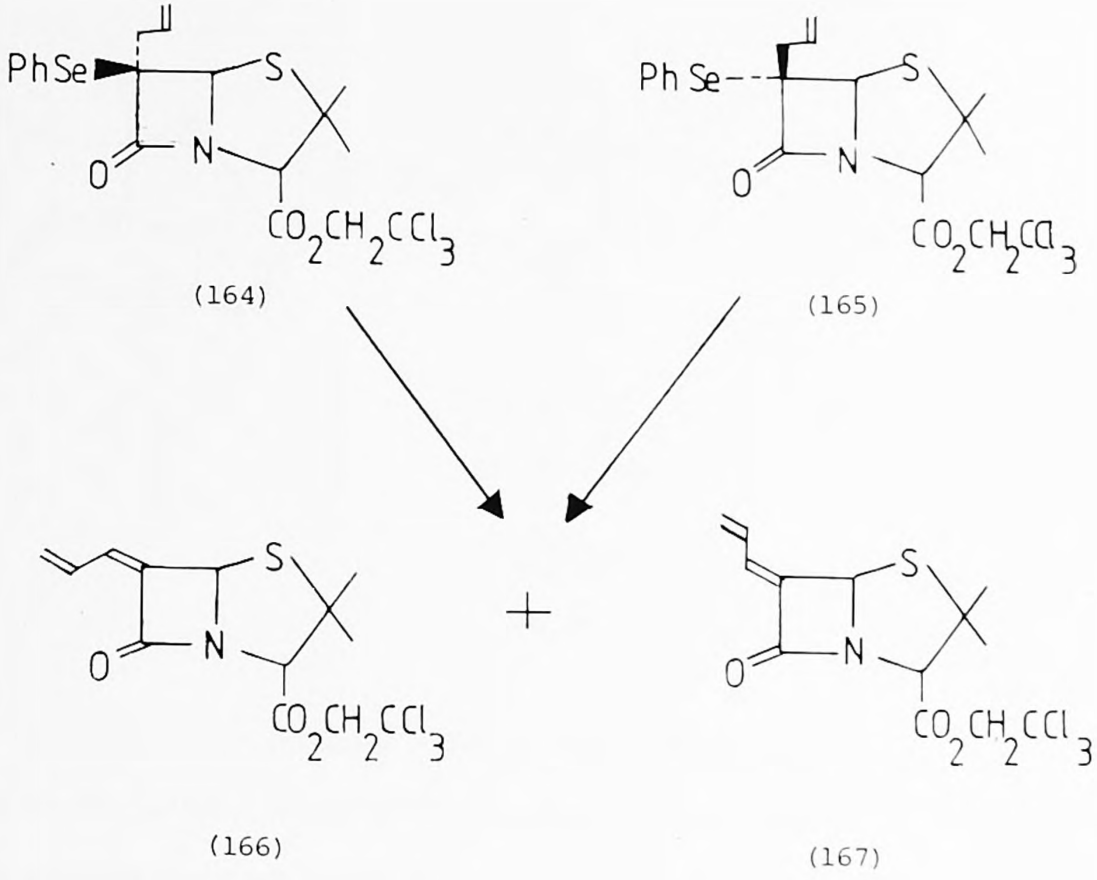


(160) X = PhS (162) (163)

(161) X = MeS

Similarly, reaction with methyl allyl sulphide afforded (158) (159) and (161). By using $Cu(acac)_2$ in place of $BF_3.Et_2O$, the 6α-monosubstituted products were avoided. The mechanism proceeded via an intermediate ylid (162).

The reaction of 6-diazopenicillanate with allyl bromide in the presence of $Cu(acac)_2$ afforded 6α-allyl-6β-bromopenicillanate (163). Treatment of 6-allyl-6-phenylselenylpenicillanates (164) (165) with m-chloroperoxybenzoic acid resulted in the rapid formation of the dienes (166) and (167). Both selenides gave the same dienes in approximately the same 2:1 ratio (Scheme 24).

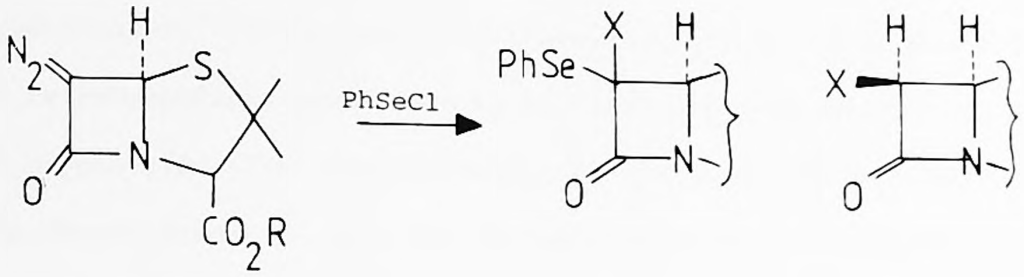


(164) (165)

(166) (167)

Scheme 24

The preparation of several 6-phenylselenylpenicillanates and their subsequent reduction by tri-n-butyl tin hydride to give novel 6β-substituted penicillanates was also described by Giddings and co-workers[74]. It was shown that 6-diazopenicillanate reacted rapidly with phenyl selenyl chloride to give the corresponding 6-chloro-6-phenylselenylpenicillanates (168) in high yield. Only one isomer was produced, which, by mechanistic consideration, was supposed to bear the phenylselenyl group in the 6β-position. The similar reaction of 6-diazopenicillanate with diphenylselenide, in the presence of $BF_3.Et_2O$ catalyst, afforded the corresponding 6,6-bis(phenylselenyl)penicillanate (169).



(168) X = Cl

(169) X = PhSe

R = CH_2CCl_3 or CH_2Ph

(170) X = Cl

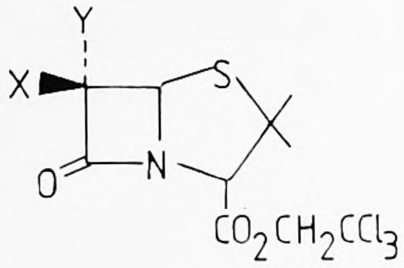
(171) X = PhSe

R = CH_2Ph

In contrast, the analogous reaction with phenyl selenyl bromide was unsuccessful, as the products could not be isolated from the complex reaction mixture.

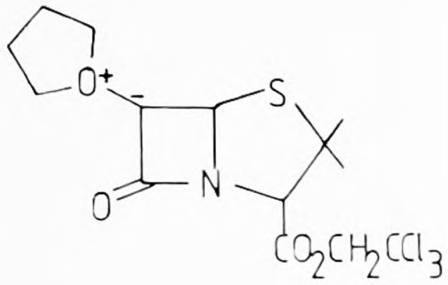
The reductions of the esters (168)(169) bearing the trichloroethyl group were complicated by competing reduction of the protecting group. However, reduction of benzyl 6-phenylselenylpencillanates (168)(169) using tri-n-butyl tin hydride in the presence of a catalytic amount of azobisisobutyronitrile led to the formation of one product in each case, (170) and (171) respectively. Both reductions were highly stereoselective, producing only the 6β-isomers. The preparation of 6-phenylselenylpenicillanate by direct reaction of 6-diazopenicillanate with phenyl selenol in dichloromethane, in the presence of $BF_3.Et_2O$, led to a single isomer, (172), which was subsequently identified as the 6α-isomer. However, when a mixture of dichloromethane and tetrahydrofuran was used as the reaction

solvent, a mixture containing both the 6α- and 6β-phenylselenyl-penicillanates (172)(173) was obtained, in which the β-isomer(173) predominated. The inverted stereoselectivity in the presence of tetrahydrofuran may be due to its participation in the reaction. An oxygen ylid (174) could possibly be involved, which reacts with the phenyl selenol to give the 6β-phenylselenylpenicillanate (173).



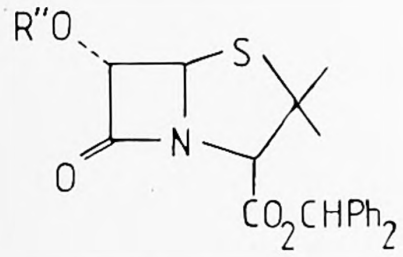
(172) X = H, Y = PhSe

(173) X = PhSe, Y=H



(174)

Closely-related studies on the reactions of 6-diazopenicillanate with alcohols were reported by Matlin and Chan[75], in which benzhydryl 6-diazopenicillanate decomposed in ethanol by $Cu(acac)_2$ catalysis to produce a mixture of the 6α-ethoxypenicillanate (175) and the ethoxythiazepine (176) in the ratio 1:1.5.

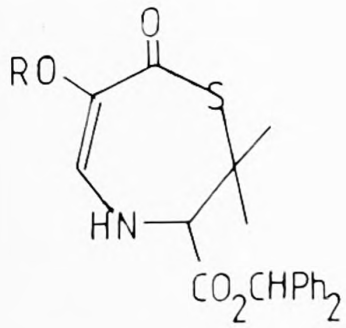


(175) R" = Et

(177) R" = ^{t}Bu

(178) R" = $PhCH_2$

(179) R" = Me



(176) R = Et

Although the corresponding thiazepine was the major product in each case, the synthesis of butoxy- and benzyloxypenicillanates (177) and (178) were achieved in the same manner. The same result was obtained when the reactions were repeated in the presence of rhodium acetate catalyst. Use of $BF_3.Et_2O$ to catalyse the analogous reaction between 6-diazopenicillanate and methanol resulted in the formation of 70% of the 6α-methoxy-penicillanate (179) with no detection of the thiazepine. TsOH as catalyst also produced a high yield of the substituted penicillanate.

Section 1

Chapter 2 : The Reactions of Diazo Compounds with Heterocycles

2.1 Introduction

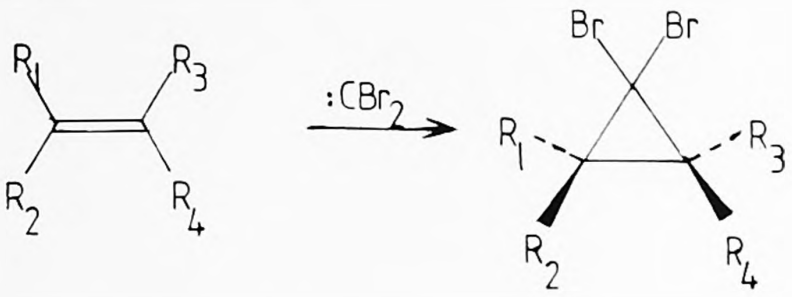
The reactions of diazo compounds by catalytic decomposition to give the carbene or carbenoid (in which the carbene complexes to the metal of the catalyst) are a well-documented area of organic chemistry[76,77]. Ethyl diazoacetate, $N_2=CHCO_2Et$, for example, has been used for more than seventy years for the preparation of cyclopropane carboxylic esters through addition to olefins[78]. This important method of synthesis of cyclopropanes has been extended to other unsaturated systems such as allenes, acetylenes and aromatic compounds.

Skell[76d] pointed out the similarity in structure between the singlet carbene and a carbonium ion (Figure 1).

Singlet carbene Carbonium ion

Figure 1

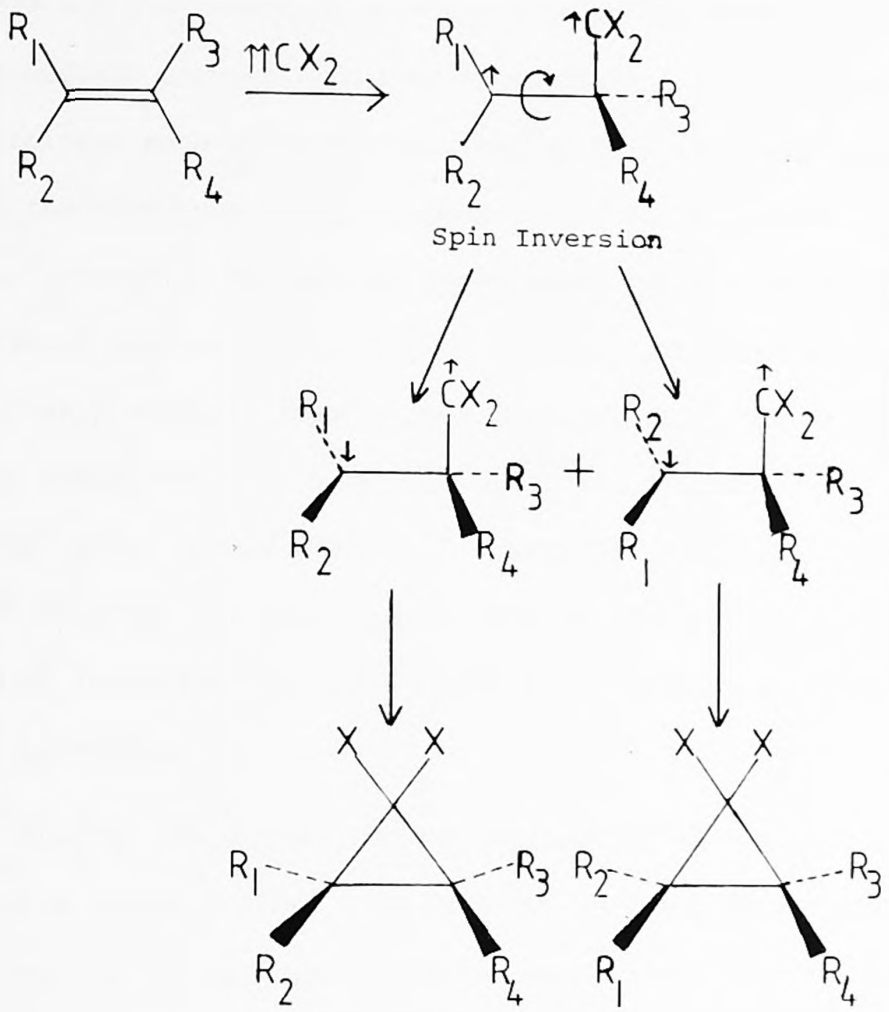
In the reaction involving the addition of dibromocarbene to olefins, dibromocarbene was seen to act as an electrophile, leading to stereospecific cycloaddition in which the stereochemistry of the olefin was retained in the cyclopropane (Scheme 1).



Scheme 1

Skell rationalized this observation by pointing out that a singlet carbene could add to an olefin in a concerted manner, since the two new σ-bonds of the cyclopropane could be formed without changing the spin of any of the electrons involved. On the other hand, for a triplet carbene, the cycloaddition should go through a triplet diradical intermediate. Before this diradical can close to a cyclopropane, there must be an inversion of spin of one of the electrons. If the free rotation about the C-C bonds of the diradical is faster than the spin inversion, then the stereochemistry of the original olefin will not be retained in the cyclopropanes (Scheme 2).

There are many carbenes which do not add stereospecifically to olefins, and it has been possible to correlate stereospecific addition with carbenes in a singlet state, and non-stereospecific addition with triplet carbenes, by use of the Skell Theory.



Scheme 2

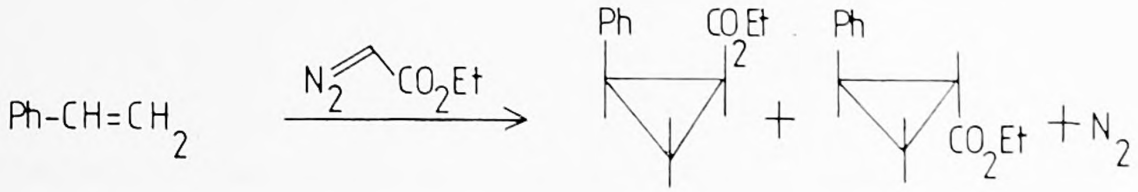
The use of copper and its salts for the catalytic decomposition of diazo compounds has been thoroughly investigated[76,77,79-82]. Surprisingly, little is known concerning the mechanism of the processes involved and what is generally known tends to be oversimplified[83-85], or neglects reasonable alternative explanations[76,84,85]. However, some light has been shed on the subject by Wulfman et al.[86] The reactions of olefins with diazocompounds in the presence of a

metal catalyst can lead to three possible products; cyclopropanes, dimers and C-H insertion products, due to the formation of an intermediate carbene or carbenoid species. Surprisingly, no pyrazolines such as those described by Sheehan[50] and Campbell[68] from the reactions of 6-diazopenicillanates with olefins have been observed. Perhaps the pyrazolines are the initial products, but rapid extrusion of nitrogen leads to cyclopropane formation. This was previously seen to be a possibility in the reaction between 6-diazopenicillanate with ethyl vinyl ether to afford the ethoxy cyclopropanes (Chapter 1) (148a-d). The presence of an electron-releasing substitutent such as the ethoxy group could lead to immediate expulsion of nitrogen, whereby no pyrazolines were identified.

Wulfman found that product distibution is a function of catalyst concentration. He proposed at least three possible pathways to cyclopropane formation alone. Two involve a single common intermediate which is formed before product partitioning between C-H insertion and cyclopropanation and involves a single molecule of catalyst. The third process involves two molecules of catalyst and therefore requires higher catalyst concentrations. There exists only a small probability that some processes are occurring by dissociation of an intermediate to a free carbene. It appears much more probable that the carbene binds to the metal of the catalyst, affording a carbenoid complex.

Paulissen et al.[87] have reported evidence in support of this probable coordination mechanism in their studies of the palladium-catalysed cyclopropanation of olefins. By investigating the

model system A, using palladium dichloride, rhodium trichloride and tris(triphenylphosphine) rhodium (1) chloride, the palladium catalysts were shown to give striking rate enhancement as compared to the other catalysts.



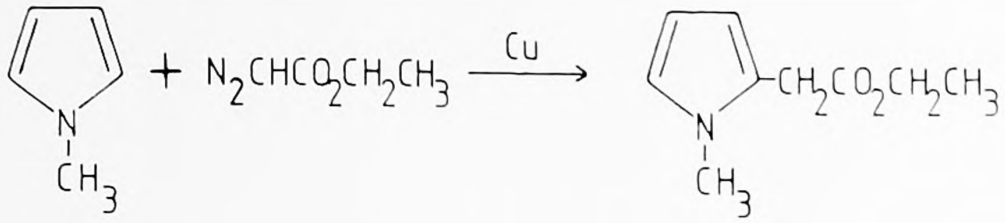
System A: Reaction of Ethyl Diazoacetate with Styrene in the presence of a) $PdCl_2$ b) $RhCl_3$ c) $Rh(PPh_3)_3Cl$.

This rate enhancement, together with the influence of ligands on the stereochemistry, point towards formation of a coordination complex. Similar suggestions that the reactions of diazoalkanes with olefins to produce cyclopropanes proceed through a soluble metal-carbene complex had also been made by Moser[83]. It therefore is dangerous to generalise on the mechanism involved in the reactions between diazocompounds and olefins, as each proceeds by its own pathway, dependent on various factors such as catalyst and catalyst concentration, all of which have some influence on the mechanism. Many reports have appeared in the literature concerning the reactions of diazocompounds with heterocycles, proceeding via metal-carbene complexes, or initiated by the action of heat or light.

2.2 The Reactions of Diazocompounds with Pyrroles

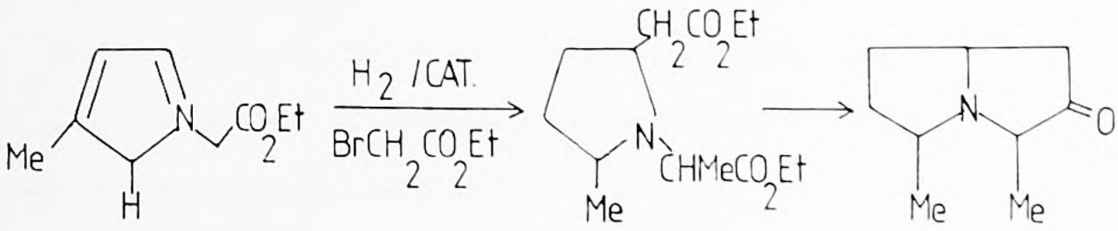
Nenitzescu and Solomonica[88] reported the reaction between 1-methylpyrrole and diazoacetic ester as long ago as 1931. This reaction was then utilized by Sohl and Shriner in 1933 in their synthesis of ethylhomogrinate[89] in an attempt to investigate the structure of cuscohygrine. The product of the reaction was

1-methyl-2-pyrrylacetic ester (1).



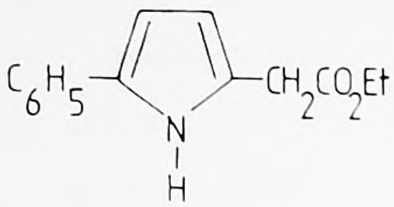
(1)

Similarly, Clemo and Metcalf[90], in an attempt to synthesize 5, 5'-dimethyldi(1,2) pyrrolidine (3), a lupin alkaloid, produced (2) initially by the method of Sohl and Shriner[89].



(2) (3)

In 1944, Blicke and co-workers[91] prepared a series of acids, and esters containing phenylpyrryl nuclei. Among the variety of methods employed was that involving attack on the pyrrole ring by carbenic species. For example, ethyl 2-(5-phenyl)-pyrrylacetate (4) was produced by the reaction of ethyl diazoacetate with 2-phenylpyrrole. Similarly, ethyl-2-(3-phenyl-5-methyl)-pyrrylacetate (5) was prepared by the action of ethyl diazoacetate on 3-phenyl-5-methyl pyrrole. Copper powder or copper bronze were employed as catalysts.



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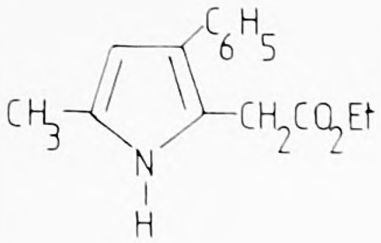
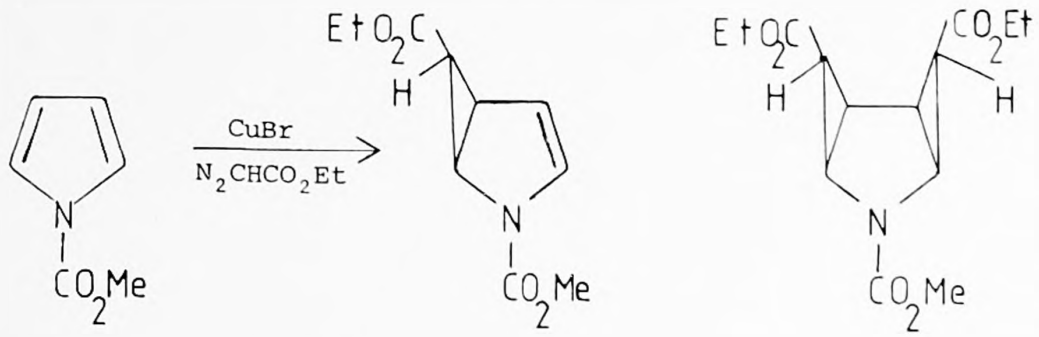


(5)

In 1958, Badger, Christie, Rodda and Pryke[92] reported the reaction of ethyl diazoacetate with naphthalene and its heterocyclic analogues. With polycyclic aromatic hydrocarbons, the addition of ethyl diazoacetate to carbon-carbon double bonds to form the cyclopropane derivative occurs at the bond having the greatest bond order[93,94]. Previously, only a few attempts had been made to apply this reaction to heterocyclic systems, although the reaction with thiophene had been studied and was known to produce a cyclopropane adduct[95]. On the other hand, pyrrole has been shown to undergo substitution to give, after hydrolysis, 2-pyrrylacetic acid[96]. Badger had heated indole, 1-methylindole, thionaphthene and benzofuran with ethyl diazoacetate; and the resulting esters were distilled and hydrolysed to the corresponding acids. The acidic product from the reaction employing indole was identified as 3-indolylacetic acid. No cyclopropane was isolated, which was surprising but confirmed the findings of previous workers[97,98]. Substitution therefore was shown to occur at the 3-position, whereas it had been at the 2-position in pyrroles. Fowler reported the first carbene or

carbenoid addition to a pyrrole derivative, thus providing the first known synthesis of the 2-azabicyclo-[3,1,0] hex-3-ene ring system (2,3 homopyrrole)[99]. The crude reaction products were a complex mixture, from which the mono- and bis-adducts (6) and (7) were isolated in 14% and 5% yields respectively.

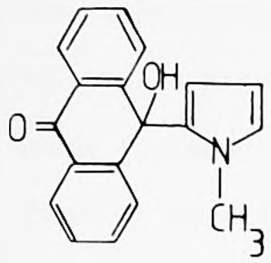


(6) (7)

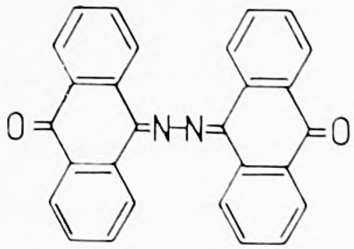
The presence of the electron-withdrawing methoxycarbonyl group could be responsible for the change in mode of action of these pyrroles. (6) could be converted into (7) in 10% yield by decomposition of ethyl diazoacetate in the presence of (6) using copper (1) bromide. Although not confirmed, the ethoxycarbonyl group in (6) would be predicted to occupy the exo-position since this is the stereochemistry of the main adduct from the addition of ethyl diazoacetate to cyclopentadiene[100]. However, the configuration of the ethoxycarbonyl groups in (7) could not be assigned with certainty.

The preference for N-substituted pyrroles to undergo substitution at the 2-position was demonstrated again in 1971 by Cauquis et al.[101] in the reaction between diazoanthraquinone and N-methyl pyrrole. The products of the reaction, induced

by irradiation, were the hydroxyanthraquinone (8), the azine (9) and the bianthronyl compound (10).



(8)



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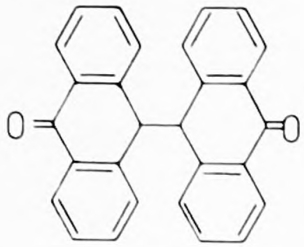
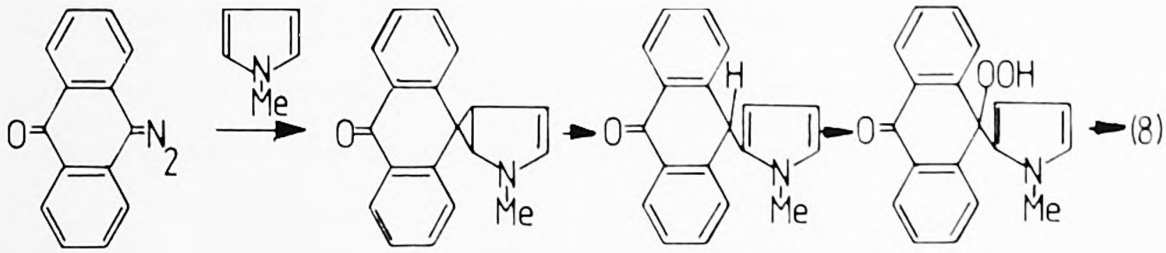


(10)

Formation of (8) is thought to occur as a result of auto-oxidation of (12) during chromatographic purification procedures, to yield the hydroperoxide (13), which, as a result



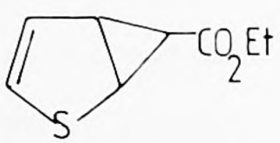
(11) (12) (13)

of its instability, decomposes to the hydroxyanthraquinone (8). Structure (12) is thought to form from a cyclopropane intermediate (11), which undergoes ring opening to furnish the substituted anthraquinone. Alternatively, (12) may be formed as a result of nucleophilic attack by the pyrrole on the carbene. Either

way, the normal pattern of 2-substitution was observed.

2.3 The Reactions of Diazocompounds with Thiophenes

The reactions of sulphur heterocycles with carbenes have been thoroughly investigated. Steinkopf and Angestad-Jensen[95] in 1922 reported that thermolysis of ethyl diazoacetate in thiophene yielded the cyclopropane adduct (14). Photolysis was shown to give the same result by Schenck and Steinmetz[103] many years later.



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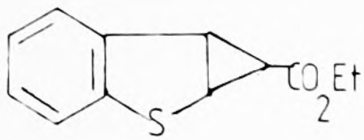
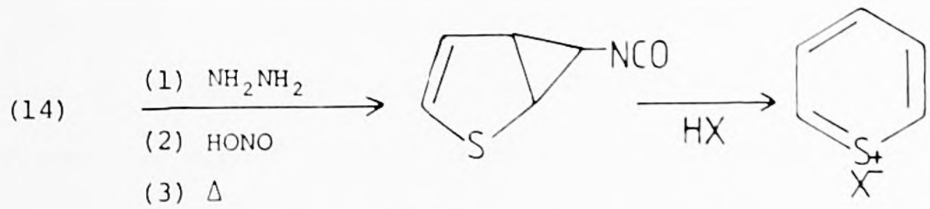


(15)

Rearrangement of (14) afforded ethyl-3-thiopheneacetate. Pettit[104] confirmed the structure of (14) and effected its conversion to the thiapyrylium cation (Scheme 3).

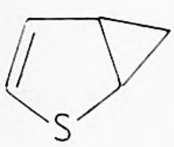


Scheme 3

Photolysis, thermolysis and metal catalysis of diazomethane or ethyl diazoacetate result in addition to the π system of thiophene

to form bicyclic products. However, copper catalysed decomposition of diazoacetone in thiophene afforded α-(2-thienyl)acetone[105].

Badger et al.[94] in 1958 showed that thionaphthene, unlike its nitrogen counterpart, reacted with ethyl diazoacetate to yield the cyclopropane (15). As previously mentioned, the indole analogue had formed no cyclopropane, but instead had undergone substitution at the characteristic 3-position. Again cyclopropanation was shown to be the favoured pathway for thiophene reactions in the reactions between diazomethane and thiophene, in which the major product was 2-thiabicyclo[3.1.0]hex-3-ene (16) and between ethyl diazoacetate and thiophene, from which the major product was ethyl 2-thia-bicyclo-[3.1.0]hex-3-ene-6-carboxylate (17)[106].



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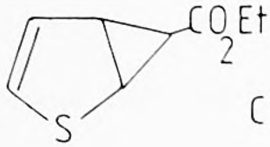

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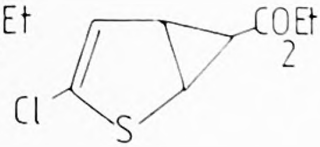

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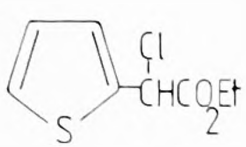
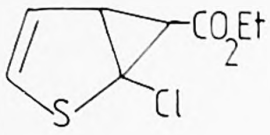


(19)

Carbenic reactions of substituted thiophenes and furans with diazomethane and diazoesters were studied by Jackson[107] in order to investigate the directive effects of substitutents on the heterocycle. Repeating the above reactions of thiophene with diazomethane and ethyl diazoacetate yielded the same products (16) and (17) respectively whether by thermolytic, photolytic or catalytic methods. Thermolysis of ethyl diazoacetate in 2-chlorothiophene furnished 3-chloro-2-thiabicyclo [3.1.0]hex-

3-ene-6-carboxylate (18) and ethylα-chloro-2-thiophenacetate (19) in poor yield. But although the yields were low, the effect of the chlorine was obvious. None of (20) was detected, which indicates



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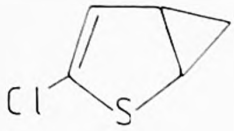

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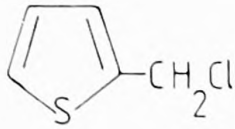
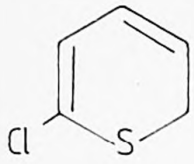


(22)

that if it is formed, it isomerised to (19), the insertion product, very readily. Hence there was a 2:1 preference for the mode of carbene attack which avoided direct reaction with the chlorine substituent. The effect was even more pronounced when the reaction was repeated catalytically as the adduct formation occurred only at the unsubstituted position of the thiophene ring. The difference in results of thermolysis and catalysis indicated that the catalytic intermediate possesses reduced carbenoid character since no insertion products were observed.

Reaction of diazomethane and 2-chloro-thiophene afforded both the adduct (21) and the insertion product (22). Steric and electronic factors favour (21) to (22). It was claimed that, on standing, (22) rearranged to the thiopyran (23), although evidence was by no means conclusive. The decomposition of diazomethane by CuCl in 2-methylthiophene resulted in a 2:1

mixture of (24) and (25). Again, steric and electronic factors made (24) the more favourable adduct. As expected, the reaction of methyldiazoacetate with 2,5-dimethylthiophene in the presence of CuCl yielded (26), and similarly, the reaction with diazomethane afforded (27).



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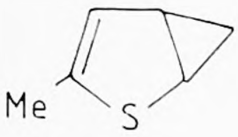

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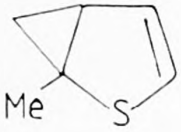

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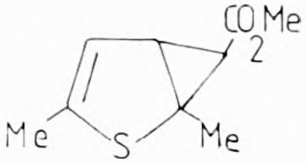
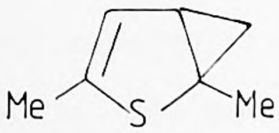


(26)

To confirm that steric hindrance favoured the unsubstituted face of thiophene, 2-tert-butylthiophene was reacted with diazomethane, from which only one isomer, (28), was produced. Finally, Jackson showed that the reaction between 2,5-dichlorothiophene and diazomethane in the presence of CuCl formed no cyclopropane. Instead, the product was 5-chloro-2-chloromethylthiophene(29), presumably forming by a mechanism similar to that by which (19) was produced.

Extensive work has been carried out on the reactions of sulphur heterocycles to form sulphonium ylids. In 1969, Ando et al.[108] reported the formation of (30) by the catalysed decomposition of diacetyldiazomethane in 4-t-butylthiacyclohexane. Ando complemented these results by studying the reactions of carbenes with cyclic



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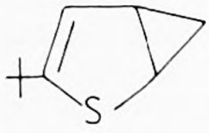

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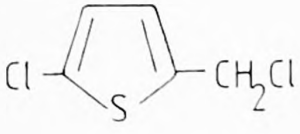

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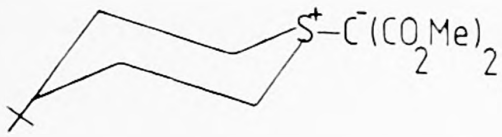

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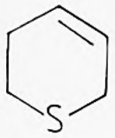

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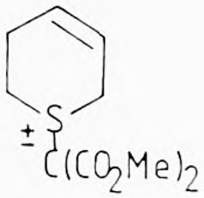

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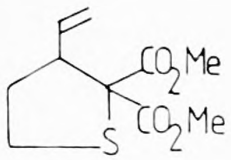
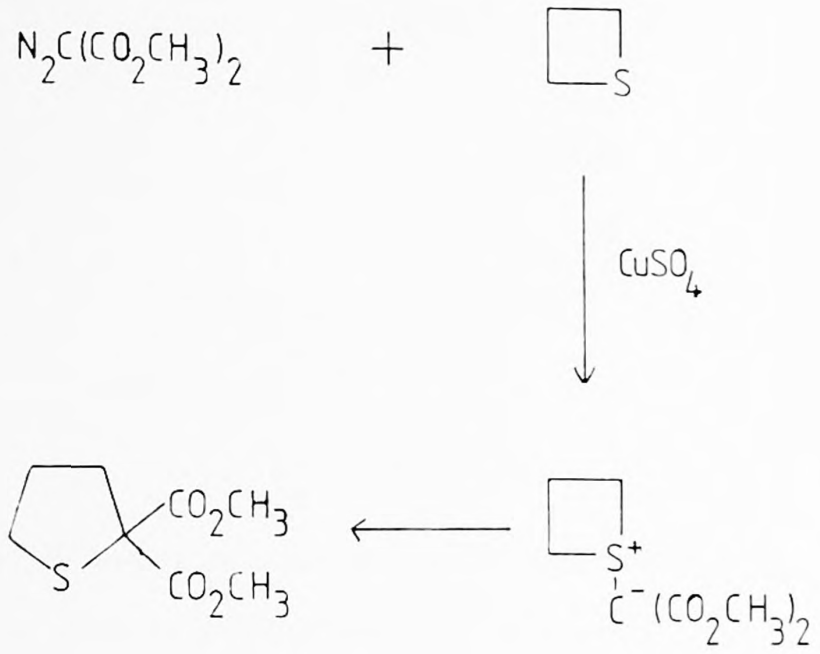


(33)

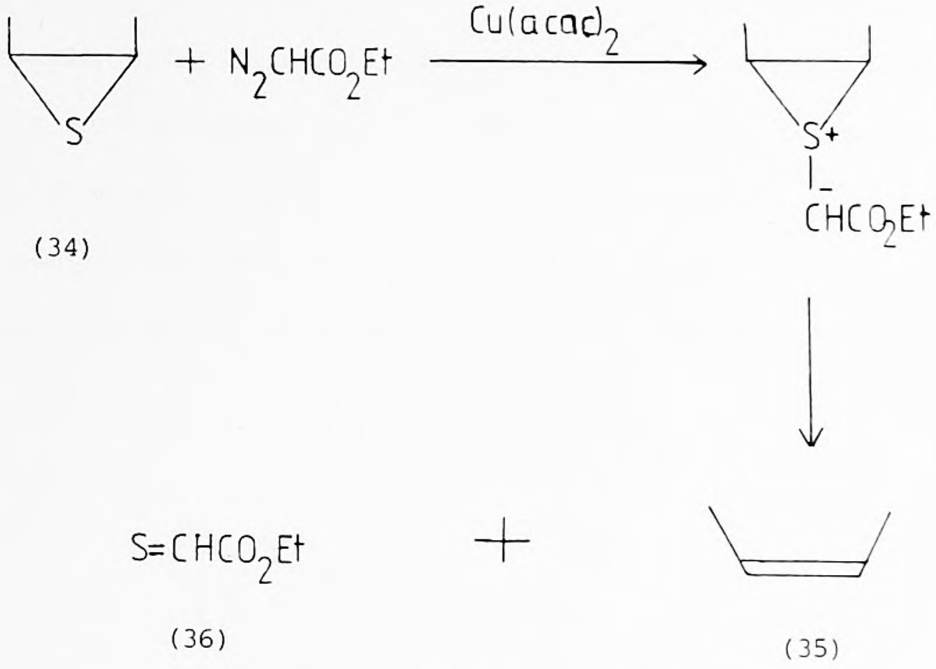
allyl sulphides[109], work also carried out by Appleton and co-workers[110]. Photolysis of dimethyl diazomalonate in Δ^3-dihydrothiopyran (31) afforded the sulphonium ylid (32), which was sufficiently stable for isolation but rearranged on heating to (33). Open chain allylic sulphides gave rise to unstable sulphonium ylids which rearranged at room temperature and hence could not be isolated. Catalysis using $CuSO_4$ produced ylids in improved yields compared to photolysis. The electrophilic carbene formed by both processes attacked the non-bonding electron pairs in sulphur to form the ylid. The isolation of stable sulphonium ylids is direct evidence for involvement of ylids in the reactions of carbenes with compounds containing hetero-atoms, even when no intermediate ylid has been isolated. For example, in the reaction between dimethyl diazomalonate with saturated cyclic sulphides, the corresponding sulphonium ylids were obtained as stable solids when initiation was by irradiation[111]. On the other hand, copper catalysed thermal reaction of diazomalonate in thietane gave the insertion product of the carbene

into the C-S bond. The ring-expanded product was probably formed through the facile rearrangement of the intermediate sulphonium ylid[109] (Scheme 4).



Scheme 4

An intermediate sulphonium ylid was also suggested in the reaction between the episulphide (34) and ethyl diazoacetate, in which the cis-olefin (35) was formed (Scheme 5). The ylid appeared to decompose stereospecifically by fragmentation into the olefin and the thioglyoxalic ester (36).



Scheme 5

In contrast to Ando's results, Kaiser[112] observed no carbene insertion or sulphonium ylid formation, but only cyclopropanation. In more recent studies, Parham[113,114] also observed the formation of cyclopropanes as major reaction products in the reaction of dichlorocarbene with several vinyl sulphides. The difference in behaviour was attributed to the difference in nucleophilicity of the double bond related to sulphur, since vinyl sulphides are known to be electron rich olefins due to the M effect of the sulphur atom.

The recent report by Hubert and co-workers[115] that rhodium (11) carboxylates catalyse carbene insertion of bismethoxycarbonyl-carbenes into olefinic systems prompted Gillespie et al.[116] to examine this type of catalyst. They employed rhodium (11) acetate in the reactions between dimethyl diazomalonate and substituted and unsubstituted thiophenes. The ylid (37) was

produced quantitatively from the reaction of dimethyl diazomalonate with thiophene, employing rhodium (11) acetate as catalyst. The same reaction had previously been attempted using conventional catalysts such as copper (1) chloride, but the diazo group underwent decomposition extremely slowly. It is interesting to note the stereochemistry of the ylid (37) (Figure 2). The molecule has an approximate mirror plane with the sulphur atom pyramidal as

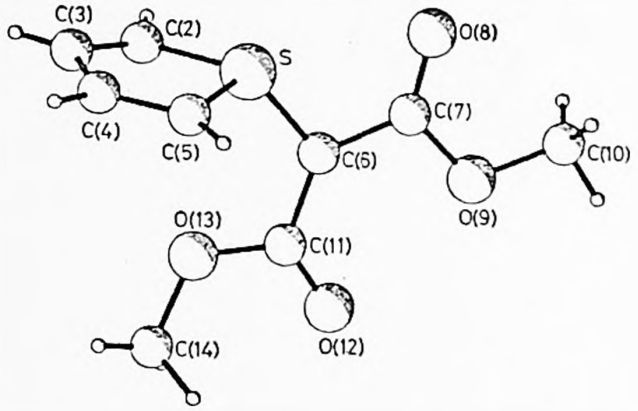
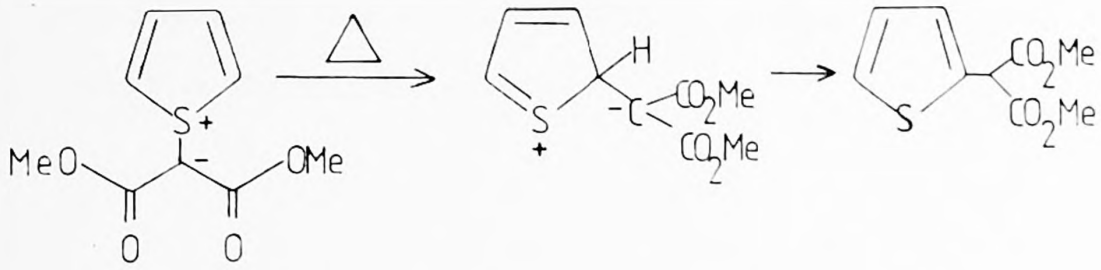


Figure 2 : The Structure of the Ylid (37)

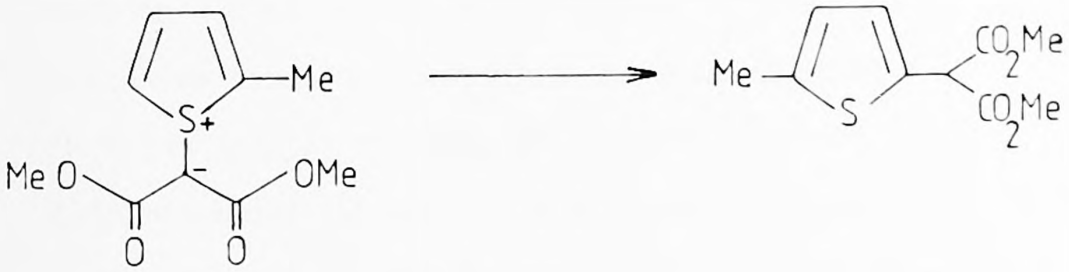
expected. The ylid bond is significantly shorter than the C-S bonds in the thiophene ring, and there is greater localization of double bonds than in thiophene itself, reflecting the shift of electron density from the ring to the malonate group. Surprisingly, the molecule is not planar. Thiophenes bearing electron-withdrawing substituents such as acetyl and cyano groups failed to produce ylids, but other systems capable of stabilizing ylid structures did not form thiophenium ylids either. For example, ethyldiazoacetate, ethyl diazoacetoacetate and diazoacetophenone

gave rise to the corresponding cyclopropanes with no evidence for ylid formation. Thus, it appears that fairly stringent electronic demands are necessary for stabilization of the ylid structure in the system. In further studies, Gillespie et al.[117] identified the thermal rearrangement of the ylids to thiophene esters. On heating (37) in thiophene, decomposition occurred to afford one major product (38).



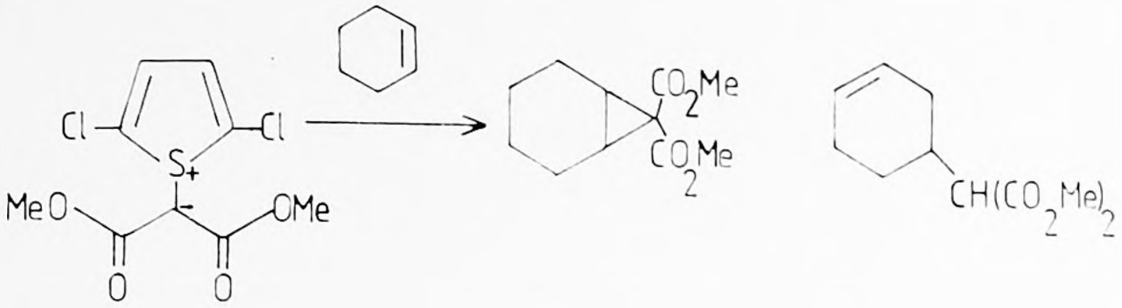
(37) (38)

This thermal rearrangement of thiophenium ylids appears to be general. For instance, on refluxing (39) in 2-methylthiophene, rearrangement to the malonate (40) occurred in 95% yield.



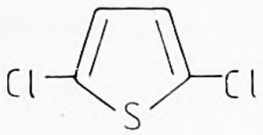
(39) (40)

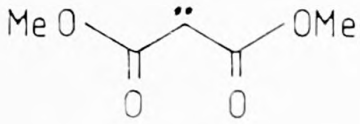
When heated in cyclohexene, (41) gave both the cyclopropane (42) and the carbene insertion product (43), confirming the dissociation



(41) (42) (43)

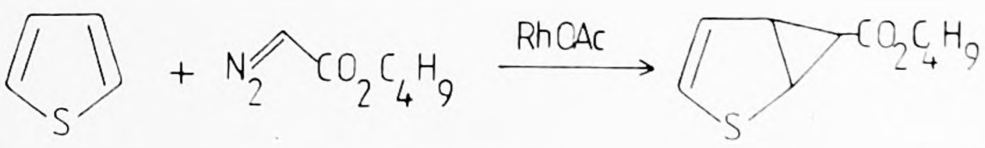
of (41) into dichlorothiophene (44) and the carbene (45). [It should be noted that a trace of rhodium catalyst was probably present in the reaction mixture].



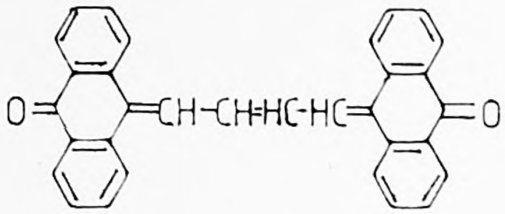


(44) (45)

The ylid (37) therefore provides a convenient source of bis-methoxycarbonylcarbene (45) which can undergo reaction with a variety of olefins such as cyclohexene to yield the corresponding cyclopropanes and malonates in excellent yields[118]. Gillespie et al.[119] demonstrated the effectiveness of the rhodium acetate catalyst and its superiority over copper catalysts in the reaction between thiophene and n-butyl diazoacetate (Scheme 6).



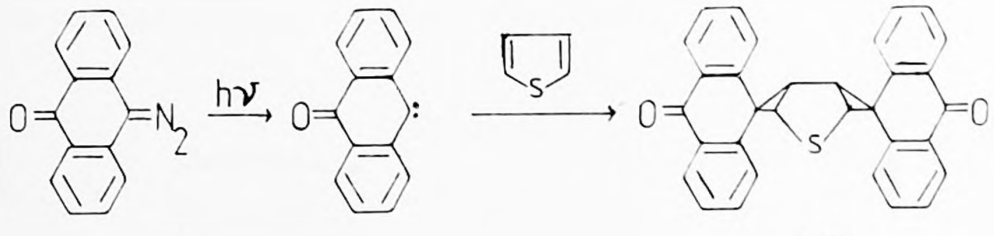
Scheme 6



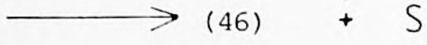
(46)

n-Butyl-2-thiabicylo[3.1.0]hex-3-ene-6-carboxylate was formed in 71% yield when RhOAc was employed, but only 17% using copper(1)chloride.

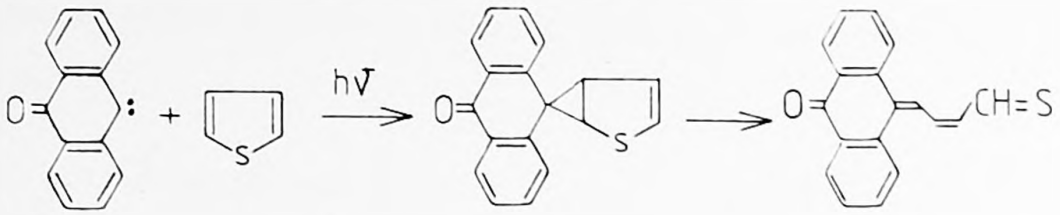
In the previous section, the reactions of pyrroles with diazoanthraquinone as reported by Cauquis et al. were discussed[101]. The same author also reports the reactions of thiophene with diazoanthraquinone by photolysis[101], but none of the three products (9), (10), (46) of the reaction contained thiophene. Products (9) and (10) were also produced in the pyrrole reaction, and their mechanism of formation was described in a preceding paper[102]. Compound (46) is thought to be formed either via a bis-cyclopropane (47) (Scheme 7), or via a dienyl thioaldehyde (48) (Scheme 8).



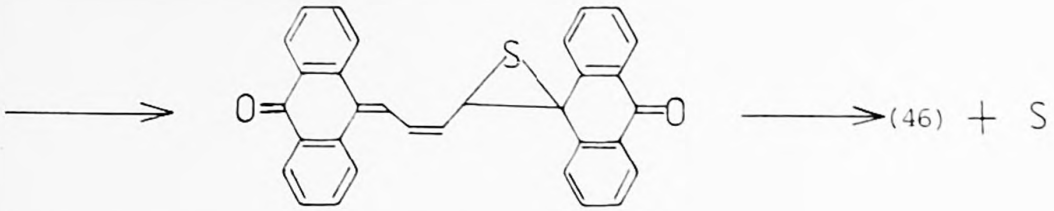
(47)



Scheme 7



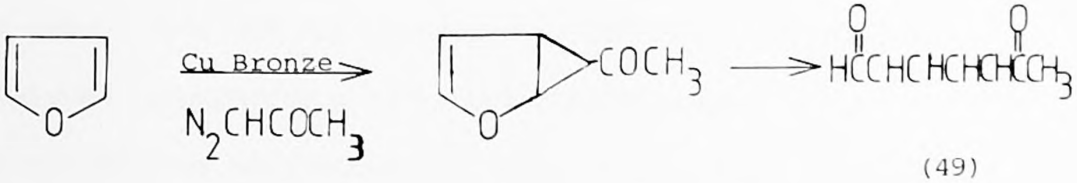
(48)



Scheme 8

2.4 The Reactions of Diazocompounds with Furans

There have been numerous reports of furan, 2-methylfuran and 2,5-dimethylfuran reacting with a variety of diazocompounds. Sorm and Novak[120,121] decomposed diazoacetone with copper bronze in furan to give a ring opened conjugated aldehyde - ketone (49) (Scheme 9).

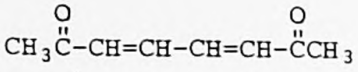


(49)

Scheme 9

2-methylfuran and 2,5-dimethylfuran reacted to yield (50) and (51) respectively. Similarly,ethyl diazoacetate with

copper bronze in 2-methylfuran also gave a ring-opened product (52).



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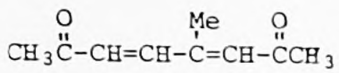
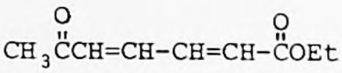


(51)



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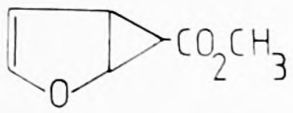
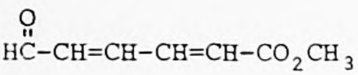


(53)

The products (49)-(52) are assumed to arise from intermediate bicyclic adducts. Photolysis of methyl diazoacetate in furan yields the bicyclic adduct (53), methyl 2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate, which is sufficiently stable to allow isolation[103,106]. The action of heat on this cyclopropane derivative causes ring opening to the dienal, methyl-5-formyl trans, cis, 2,4-pentadienoate (54)



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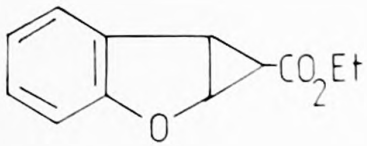
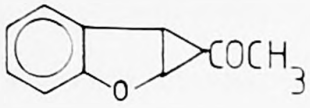


(55)

The adduct (54) was also prepared by Jackson[107] by the copper-catalysed decomposition of methyl diazoacetate in furan.
The reaction of benzofuran with ethyldiazoacetate to furnish the cyclopropane (55) was demonstrated by Badger et al. in 1958[92]. Similarly, with diazoacetone, benzofuran affords the cyclopropane (56)[105], and with dichlorocarbene yields (57)[122]. Although (57)

was not isolated, its existence was confirmed by hydrolysis to (59), probably via (58).



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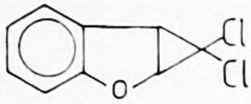

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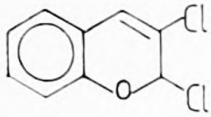
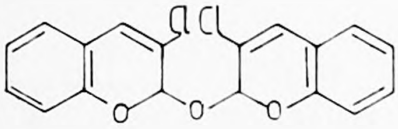


(58)

Decomposition of diazomethane in furan afforded the bicylic adduct (60)[123]. By photolysis, diazomethane in furan also



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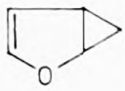

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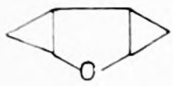
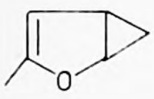


(61)

(62)

gave (61). With 2-methylfuran, copper catalysed decomposition of diazomethane afforded 30% of 1-methyl-2-oxabicyclo[3.1.0]hex-3-ene(62), 20% of 3-methyl-2-oxabicyclo[3.1.0]hex-3-ene(63) and 7% of 1-methyl-2-oxatricyclo[4.1.0.0]heptane (64)[124]. But with



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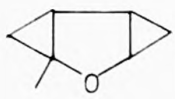

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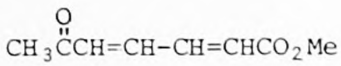
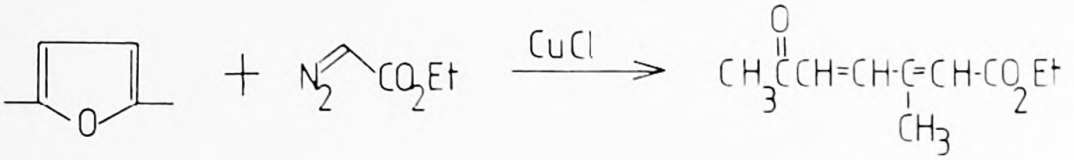


(65)

methyl diazoacetate, 2-methylfuran formed only the dienoate (65), presumed to result from ring-opening of a cyclopropane intermediate. Generally, the 2,3-double bond of the furan remains in the cis conformation on ring opening to form the dienal, unless

it is converted to the thermally-stable trans isomer by, for example, excessive heat.

2,5-dimethylfuran reacted with ethyl diazoacetate in the presence of copper (1) chloride affording the dienone (66), whereas with diazomethane, both the cyclopropane (67) and the dienone (68) were produced[107].



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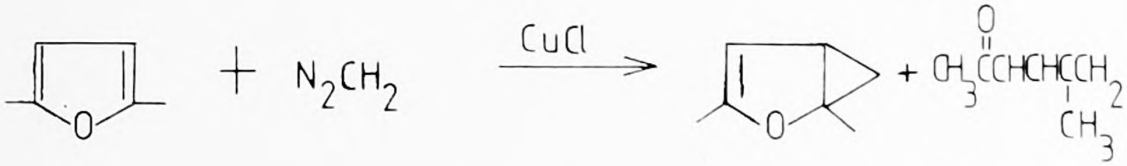
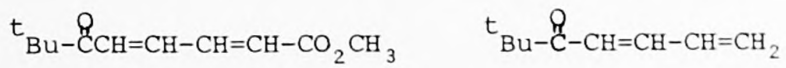


(67) (68)

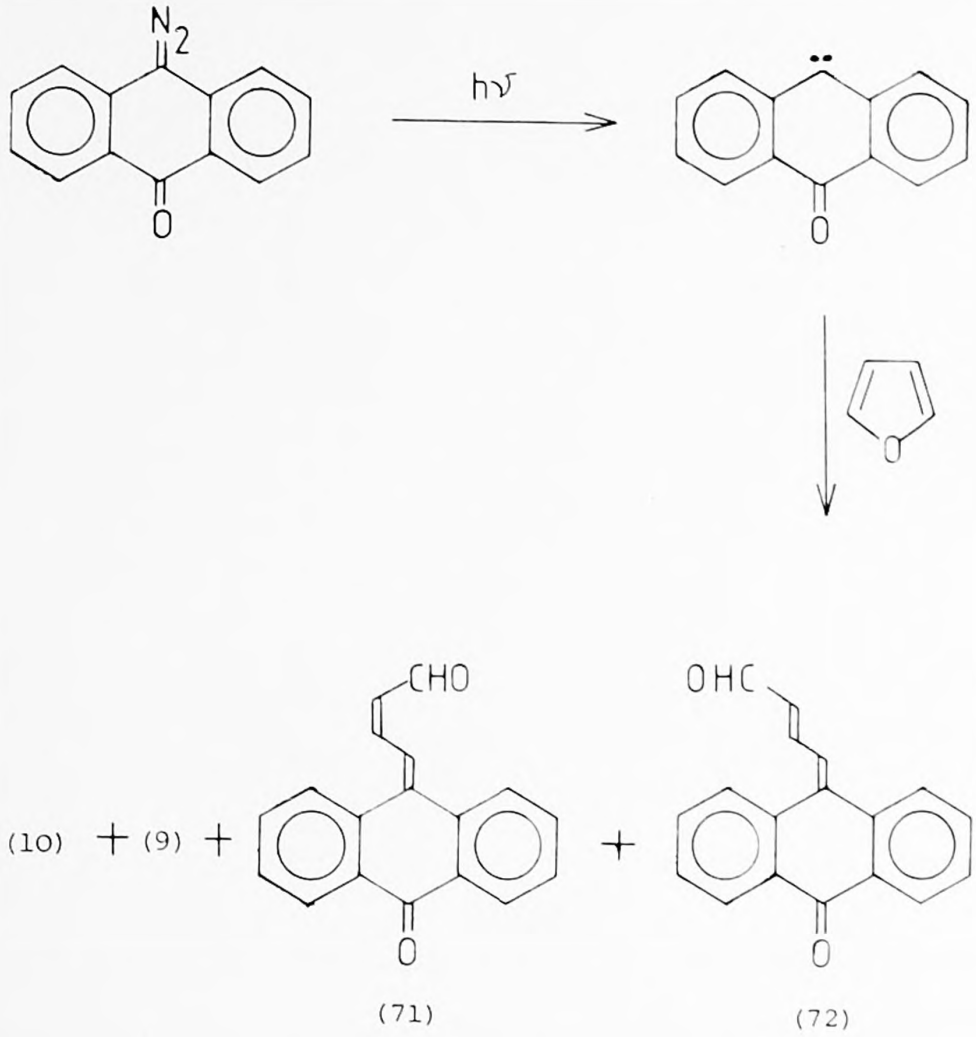
^{t}Butylfuran afforded only the ring-opened products (69) and (70) on catalytic reaction with methyl diazoacetate and diazomethane respectively.



(69)

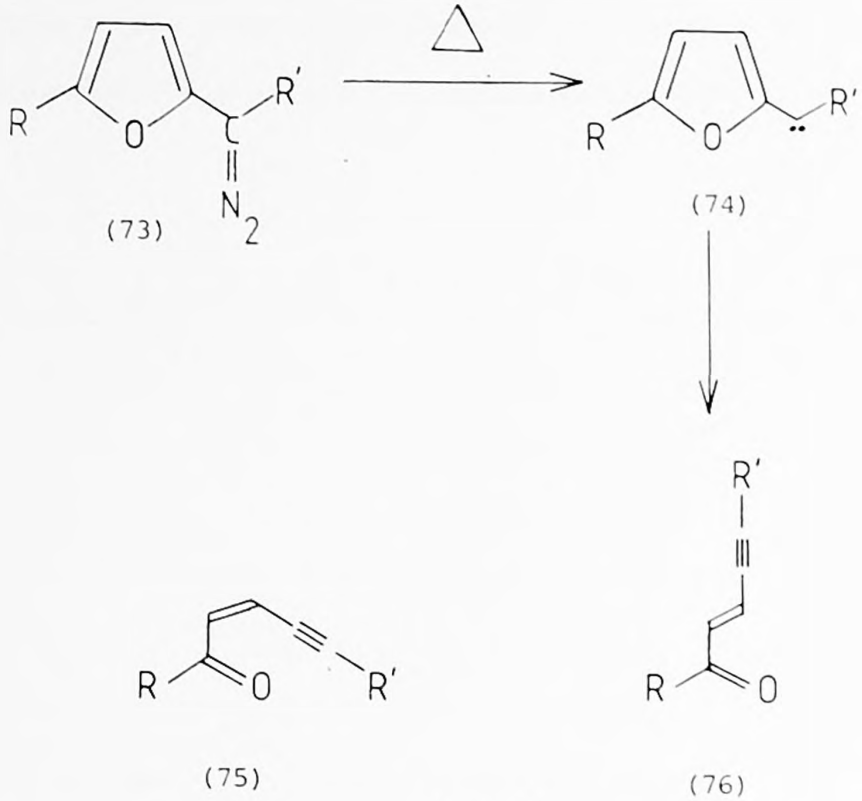
(70)

As seen in both the pyrrole and the thiophene photolytic reactions with diazoanthraquinone, several products were produced. In the furan case[102], the major products were the isomers (71) and (72) which constituted 53% of the total yield (Scheme 10).



Scheme 10

Hoffman and Shechter[125] reported the thermolysis of 1-diazo-1-(2-furyl)alkanes (73) to generate the furfurylidenes (74) which, being unstable, rearranged to the corresponding aldehydes or ketones (75)(76) (Scheme 11).

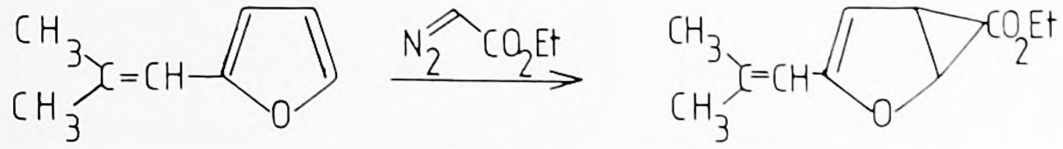


Scheme 11

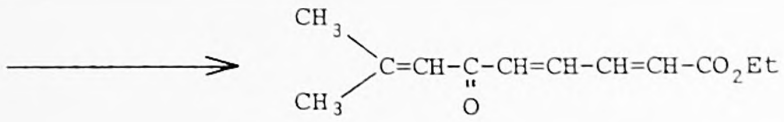
As seen previously, the double bond in the ring-opened product will generally be cis, and therefore partial rearrangement must occur to afford the mixture of cis and trans products. This is supported by the ready conversion of the cis isomer into the trans at elevated temperatures.

The reaction of alkenylfurans with ethyl diazoacetate was investigated by Nefedov and co-workers in 1977[126]. Whereas alkenylarenes such as vinylbenzene and vinylnaphthalene react with ethyldiazoacetate with exclusive formation of cyclopropane derivatives, the alkenylfurans undergo ring opening to yield the corresponding esters, presumably via a cyclopropane intermediate. For example, 2-isobutenyl furan (77) reacts with ethyl diazoacetate, furnishing the ester (78) (Scheme 12). In contrast

2-vinylfuran and substituted vinlyfurans react with ethyl diazoacetate to yield the corresponding cyclopropanecarboxylic esters. An example is the reaction of 2-methyl-5-vinylfuran (79) with ethyl diazoacetate to afford the cyclopropanes (80).

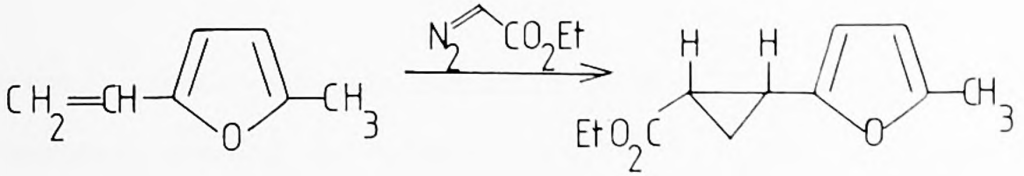


(77)

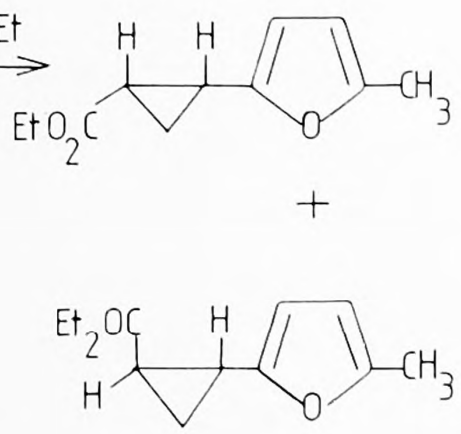


(78)

Scheme 12



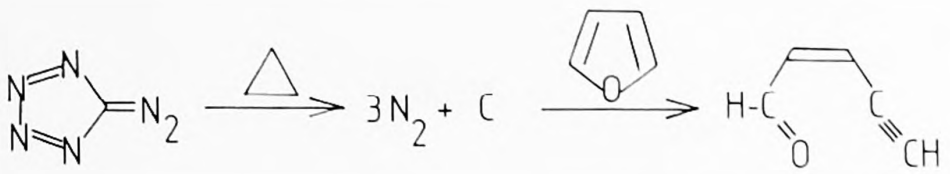
(79)



(80)

The difference in behaviour is due to steric interaction in (77) preventing attack on the vinyl group by the carbene. Attack therefore occurs on the furan ring. In (79), however, the vinyl group is no longer sterically hindered and there is no longer a free α-position on the furan ring, hence attack at this bond occurs preferentially.

The reaction of carbon atoms with furan was discussed by Dyer and Shevlin[127], pyrolysis of 5-diazotetrazole in the presence of gaseous furan affording cis-2-penten-4-ynal (81) (Scheme 13). As the unsaturated aldehyde (81) has previously been obtained in the rearrangement of the 2-furfurylcarbene (82) (Scheme 14), the formation of (81) could be rationalized by proposing a C-H insertion reaction followed by rearrangement.

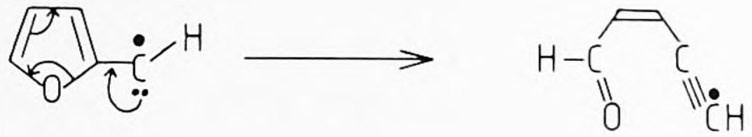


(81)

Scheme 13

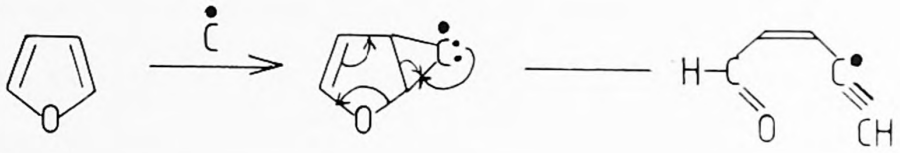
However, atomic carbon is selective in its C-H insertions and invariably prefers the weakest C-H bond[128]. Since vinyl C-H bonds are rather strong and other sites are available for reaction, it seems unlikely that a C-H insertion by atomic carbon provides the major pathway in this system. An alternate mode of attack is initial carbon addition to a vinylic bond of the furan, generating a cyclopropylidene intermediate (83). The intermediacy of cyclopropylidenes in the reactions of carbon

with simple alkenes has been well-documented[129] and it appears to be the more probable route to formation of (81). The cyclopropylidene rearranges to afford the 2-penten-4-ynal as depicted in Scheme 15.



(82) (81a)

Scheme 14



(81b)

Scheme 15

The mechanism was investigated by means of ^{13}C labelling experiments, as each pathway would generate an aldehyde bearing the labelled carbon atom or a different position (Schemes 14, 15). It was found that the aldehyde so formed was 83% labelled at C_4, indicating that the major route of the reaction was via the cyclopropylidene, with only a small amount of (81) forming from C-H insertion.

Section 2

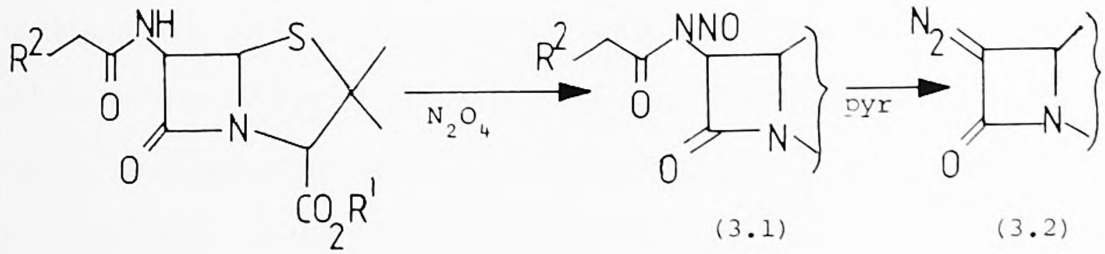
Chapter 3

Synthesis of 6-Diazopenicillanic Esters

3.1 Introduction

Various methods for the synthesis of 6-diazopenicillanates and 7-diazocephalosporanates have been described in the literature. The first, by Cignarella et al. in 1962[130], reported the diazotization of 6-APA at 0-2°C by treatment with sodium nitrite and hydrochloric or hydrobromic acid. However, the 6-diazopenicillanic acid was not isolated, but instead converted directly to the corresponding 6-chloro and 6-bromopenicillanic acids. Similar examples describing the substitution of the amino group of an amino acid or amino alcohol through a diazotization in hydrohalogenic acid have been reported[131-134].

In 1967, Hauser and Sigg[64] developed a route for the conversion of 6-amido penicillanates into their N-nitrosamides by treatment with N_2O_4. Subsequent treatment with pyridine afforded 6-diazopenicillanate (3.2) in poor yield (Scheme 1).



(3.1) (3.2)

Scheme 1

The preparation of benzhydryl 7-diazocephalosporanate was reported in 1972 by Cama et al.[37] A two-phase system was developed in which the p-toluene sulphonic acid salt of benzhydryl 7-amino-cephalosporanate in dichloromethane was diazotized by an aqueous nitrous acid solution. The presence of the two phases prevented undue exposure of the 7-diazocephalosporanate to the acid solution, thus minimizing the risk of decomposition by hydrolysis. The same method of diazotization was also adopted by Wiering and Wynberg in their studies of the reactions of 7-diazocephalosporanates with trialkylboranes[69].

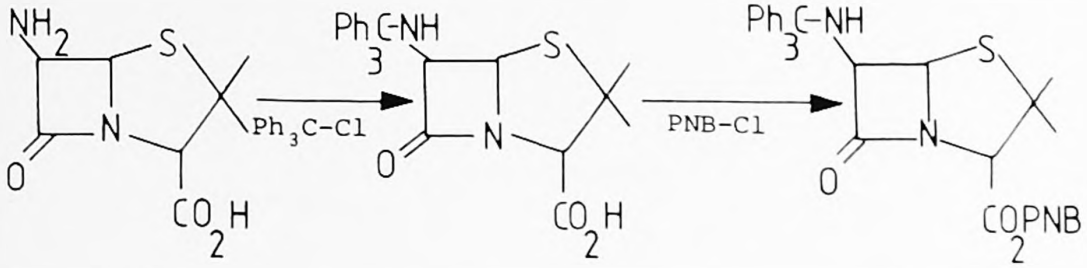
Slight modifications to the method of Hauser and Sigg were implemented by Sheehan and co-workers[135] in 1974, enabling the isolation of β,β,β-trichloroethyl 6-diazopenicillanate as a yellow crystalline solid. The nitrosamide (3.1), prepared by the method of Hauser and Sigg, was refluxed with pyridine in dichloromethane for three hours, producing a brown syrup, which, on recrystallization from carbon tetrachloride, afforded β,β,β-trichloroethyl 6-diazo-penicillanate in 72% yield.

In 1978, Sheehan applied Cama's two phase synthesis of 7-diazo-cephalosporanates to the conversion of benzhydryl 6-aminopenicillanate to its diazo derivative. Nitrous acid was generated in the aqueous phase by the action of perchloric acid on sodium nitrite. Once again, decomposition of the diazo compound was minimized by avoiding prolonged contact with the acid, leading to the formation of benzhydryl 6-diazopenicillanate in high yield.

3.2 P-Nitrobenzyl 6-aminopenicillanate (3.6).

6-APA(3.3) is a convenient starting material for the synthesis of 6-diazopenicillanate as it is produced commercially by large scale fermentation. Prior to conversion of 6-APA to 6-diazopenicillanic acid, the acid function requires protection in order to avoid acid-catalysed decomposition of the diazo group, and to avoid acid involvement in subsequent reactions. The use of the p-nitrobenzyl (PNB) group for acid protection[136] has several practical advantages. For example, it causes many 6-substituted penicillins to exist as solids rather than oils, thus facilitating handling; it provides a strong chromophore for U.V. detection; it gives a substantial increase in molecular weight; it introduces readily-recognizable peaks in the n.m.r. spectra; and it requires only mild conditions for its removal. Its one major drawback is the necessity to protect the amine function prior to introduction of the p-nitrobenzyl group as p-nitrobenzyl halides readily react with both amines and acids in the presence of base.

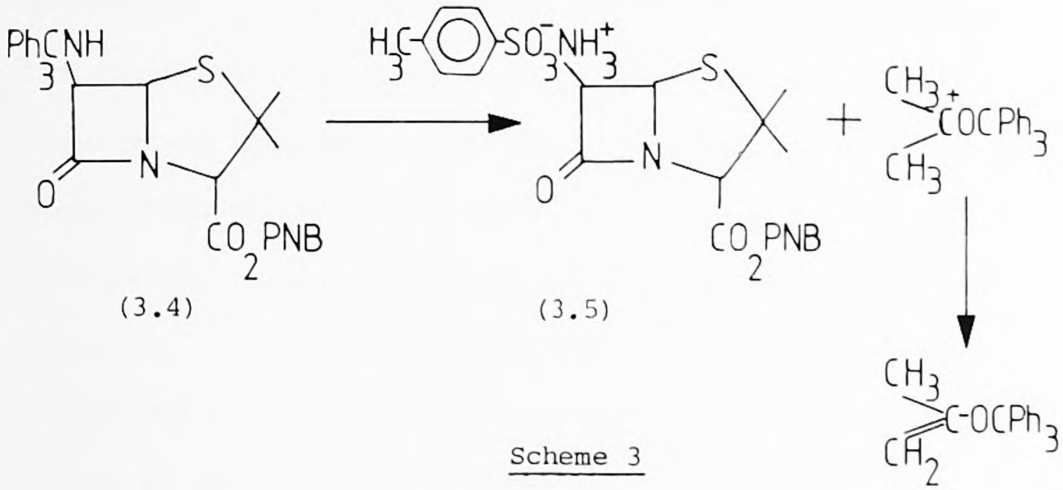
Hence the initial reaction of 6-APA with triphenylmethyl chloride (trityl chloride) to protect the amine was carried out. Although the trityl group has also been used for the protection of acids[137], in this case it reacted solely with the amine due to the stronger nucleophilic nature of the latter. This left the acid group available for reaction with p-nitrobenzyl chloride, thus affording the doubly-protected penicillin (3.4) (Scheme 2).



(3.3) (3.4)

Scheme 2

Removal of the trityl group involved a straight-forward reaction in which the ester (3.4) was stirred in acetone with p-toluene sulphonic acid (tosic acid) to generate the tosic acid salt of the amine (3.5) (Scheme 3).



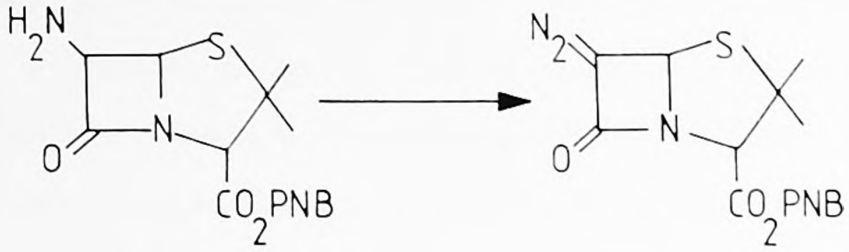
(3.4) (3.5)

Scheme 3

The salt so formed is extremely stable and can be stored indefinitely.

3.3 P-Nitrobenzyl 6-diazopenicillanate (3.7)

P-Nitrobenzyl 6-aminopenicillanate(3.6) was converted to the corresponding diazo compound(3.7) by the method of Sheehan and Commons[67].



(3.6) (3.7)

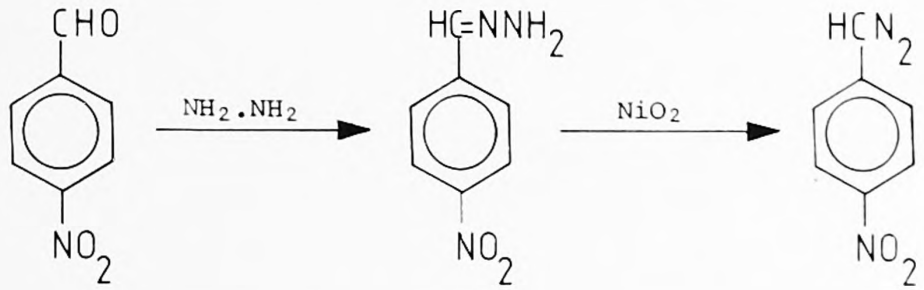
This involved dissolving the amine (3.6) in water together with sodium nitrite and perchloric acid, and partitioning the solution so formed with dichloromethane. The sodium nitrite and perchloric acid reacted to produce nitrous acid, which brought about the diazotization. Once formed, the 6-diazopenicillanate (3.7) transferred into the organic phase, preventing subsequent decomposition by the acid. Prior removal of the tosic acid was unnecessary, due to liberation of the free amine in the aqueous solution. The 6-diazopenicillanate afforded by the above reaction was produced cleanly in 90-95% yield and therefore required no purification prior to use. It can be stored for fairly long periods at -20°C without significant decomposition.

Slight modifications to the above procedure at a later date enabled the formation of the 6-diazopenicillanate in a fraction of the time in equally good yield[138].

3.4 Alternative Procedure for Synthesis of p-Nitrobenzyl 6-aminopenicillanate

The necessary protection of the amine function prior to introduction of the p-nitrobenzyl group had proved tedious, and

a new method for the protection was consequently attempted. It was hoped that 6-APA would react directly with p-nitrobenzyldiazomethane (3.9) to afford the required acid-protected penicillin (3.6) in a one-step reaction. The synthesis of p-nitrobenzyldiazomethane was reasonably straightforward, involving the reaction of p-nitrobenzaldehyde with hydrazine hydrate to yield the hydrazone (3.8)[139]. Oxidation of the hydrazone with nickel peroxide[140] led to formation of the required p-nitrobenzyl diazomethane (3.9).



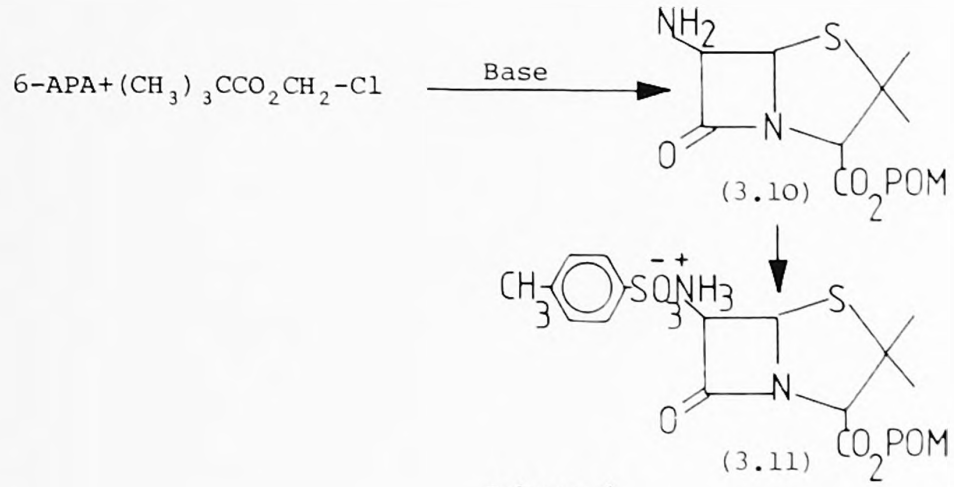
(3.8) (3.9)

Unfortunately, the reaction of p-nitrobenzyldiazomethane (3.9) with 6-APA was extremely slow, and resulted in a final yield of only 8.1%. Such a low yield was obviously impractical, and the original synthesis therefore had to be adhered to.

3.5 Pivoyloxymethyl 6-aminopenicillanate, Tosic Acid Salt(3.11).

The introduction of the pivoyloxymethyl group (POM)[141] for protection of the acid function of the penicillin has two important advantages over the use of the p-nitrobenzyl group. Firstly, it requires no deprotection prior to bacteriological testing, as the free acid is liberated in the biological system. Secondly, no

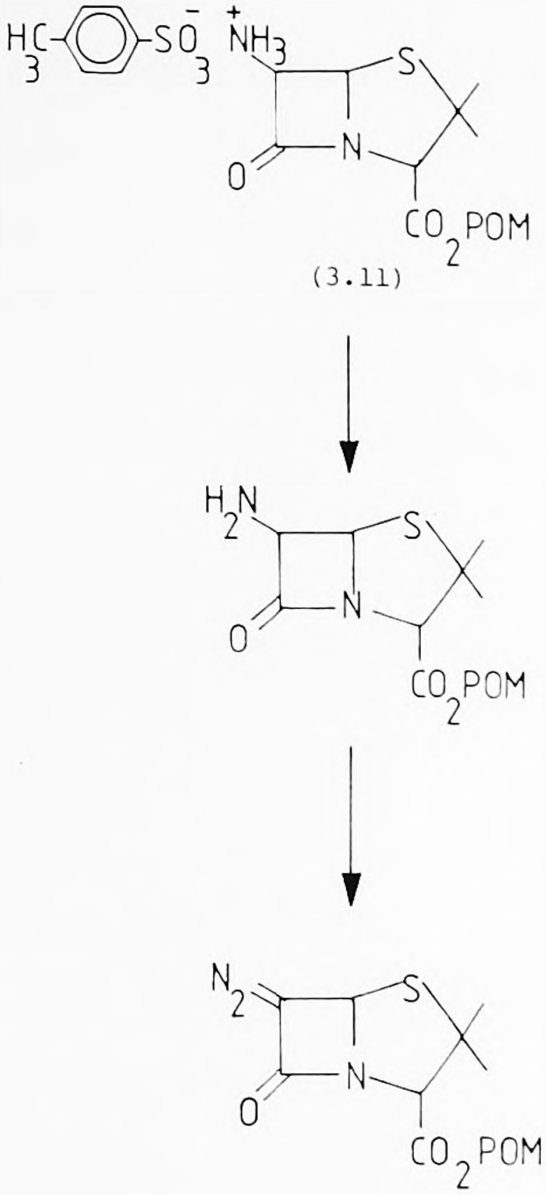
amine protection is needed as the pivoyloxymethyl chloride reacts solely with the acid, enabling the synthesis of the pivoyloxymethyl ester (3.11) in two facile steps. Initially, the 6-APA is reacted with pivoyloxymethyl chloride in the presence of base, affording the amine (3.10), which, on stirring with p-toluene sulphonic acid, crystallizes out as the corresponing salt (3.11) (Scheme 4).



Scheme 4

3.6 Pivoyloxymethyl 6-diazopenicillanate (3.12)

In exactly the same manner in which the p-nitrobenzyl 6-aminopenicillanate was converted to the corresponding diazo derivative, the pivoyloxymethyl ester (3.11) was diazotized to give pivoyloxymethyl 6-diazopenicillanate (3.12). The p-toluene sulphonic acid salt of the amine (3.11) was stirred with sodium nitrite and either perchloric acid or p-toluene sulphonic acid in an aqueous solution partitioned with dichloromethane. As the product formed, it transferred to the organic phase, enabling isolation of the ester (3.12) in yields comparable to those of the corresponding p-nitrobenzyl ester (Scheme 5).



(3.11)

(3.12)

Scheme 5

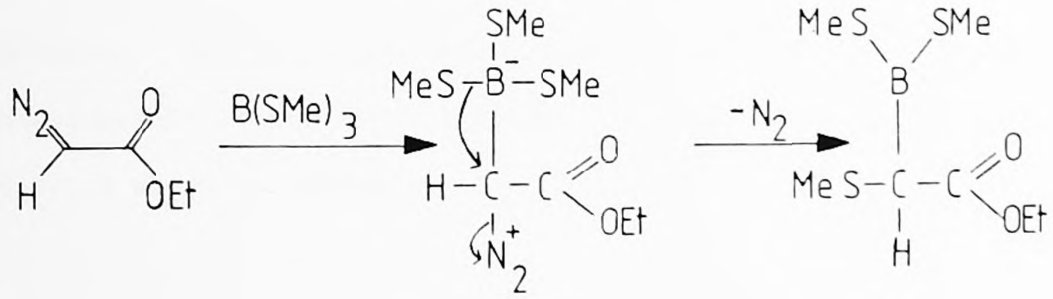
Section 2

Chapter 4

The Reactions of p-Nitrobenzyl 6-diazopenicillanate with Boranes

4.1 Introduction

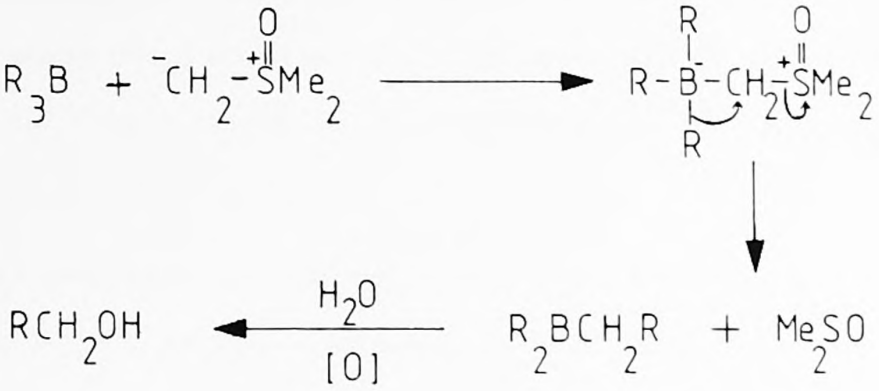
It has been known for some time that certain boron compounds will induce polymerisation in simple diazoalkanes such as diazomethane[142,143]. Gutshe and Kinoshita[144] have shown that trimethyl thioborate reacts with α-diazocarbonyl compounds to produce thioethers (Scheme 1), although yields were poor and numerous by-products were also formed. It was suggested that the substituents around the diazomethyl group were crucial in diverting the reaction away from polymerisation.



(28%)

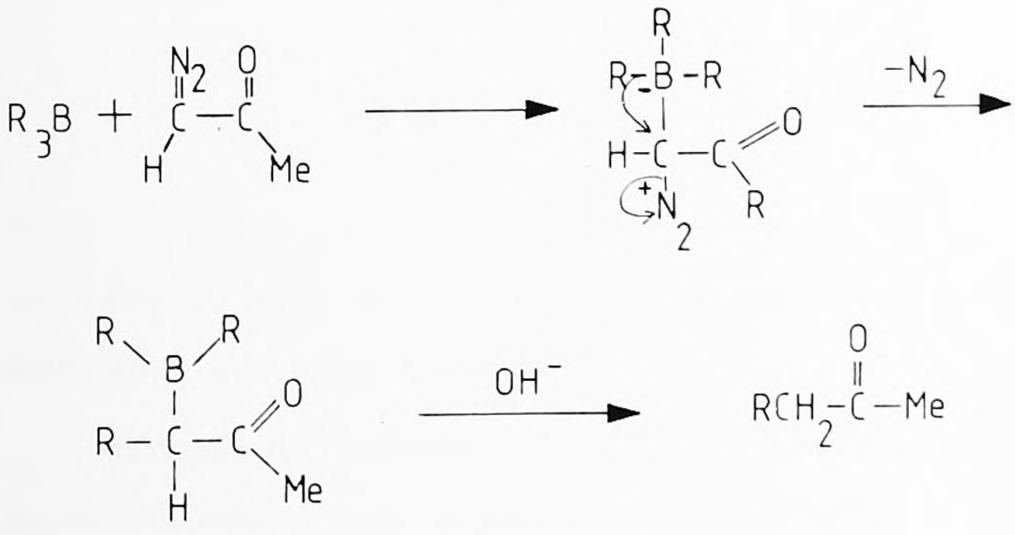
Scheme 1

It has been established that trialkylboranes will react, in general, with ylids and carbanions to give homolagated boranes from which alcohols can be obtained. For example, the reaction with dimethyl-oxosulphonium methylide[145,146] is depicted in Scheme 2.



Scheme 2

In the light of these observations, Hooz and co-workers[147-150] examined the reactions of α-diazocarbonyl compounds with trialkylboranes. The reactions with α-diazoacetone provided three-carbon-homologated ketones in good yield. The mechanism proposed by Hooz is shown in Scheme 3.

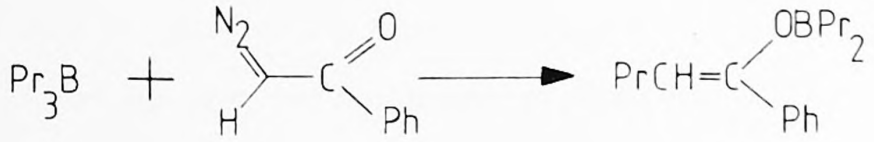


(4.1)

Scheme 3

It was shown that similar reactions of alkylboranes with α-diazoacetonitrile and with ethyl diazoacetate could be used for high yield syntheses of homologated nitriles and esters, respectively, and the reaction between an alkylborane and α-diazoacetophenone gave the corresponding alkyl phenyl ketone. The reaction could be extended to the synthesis of α-deuterio-carbonyls[149] by carrying out the hydrolysis of the intermediate boron derivative with D_2O.

The proposed intermediate (4.1) in Hooz's mechanism (Scheme 3) is a borane. However, in 1970, Pasto and Wojkowski[151] studied the reaction between tri-n-propylborane and α-diazo-acetophenone. They were able to isolate the intermediate by evaporation of the THF solvent and found that it was not a β-ketoborane, but an enol borinate (4.2) of unspecified stereo-chemistry.

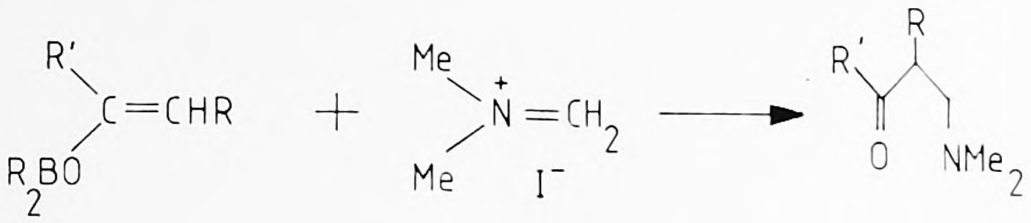


(4.2)

Brown[152] has modified the Hooz reaction by using a dialkyl-chloroborane, which greatly improves the yields when transfer of bulky alkyl groups is required.

Utilizing the knowledge that an intermediate enol borinate is formed, Hooz[153] later developed a modified Mannich reaction in which the enol borinate is trapped with an iminium salt

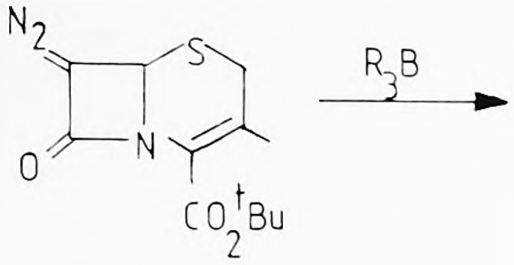
Scheme 4). This is particularly effective for the case of unsymmetrical ketones, where the Mannich reaction usually gives isomeric mixtures.



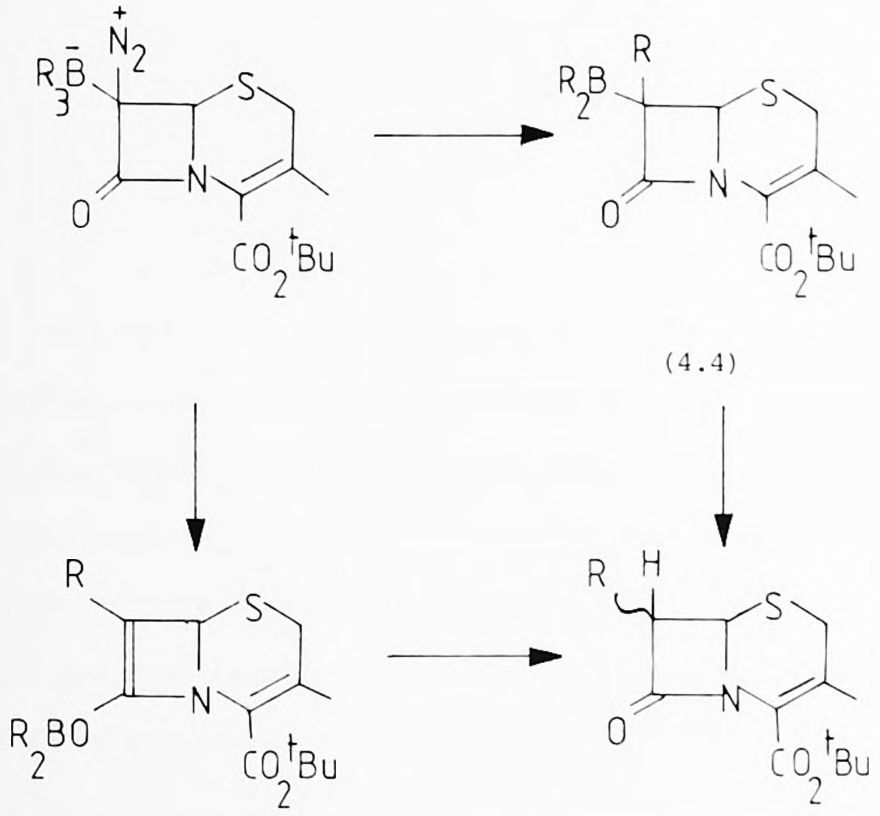
Scheme 4

In 1976, Wiering and Wynberg[69] reported the reaction of alkylboranes with a 7-diazocephalosporanate (4.3). The reactions were carried out at -40° to -80°C in the presence of 1-5 equivalents of water in THF, conditions which appeared to be crucial to success. The 7-alkylcephalosporanates formed were assumed to arise by the in situ hydrolysis of either an intermediate borane (4.4) or the alternative enol borinate (4.5) (Scheme 5).

Recent work by Masamune and Mori[154] has greatly clarified the picture and has also led to useful new synthetic applications. It was shown that the enol-borinate formed by the reaction of a trialkylborane with a simple α-diazocarbonyl compound is predominantly the E-isomer (4.6) and that this can be conveniently converted into the Z-isomer (4.7) by the action of a catalytic amount of lithium phenoxide or pyridine in benzene. A series of isomeric enol-borinates was prepared and the stereochemistry of addition of various aldehydes in a directed aldol-type condensation was investigated. In general, it was found that Z-isomers gave erythro aldol products and E-isomers gave threo



(4.3)

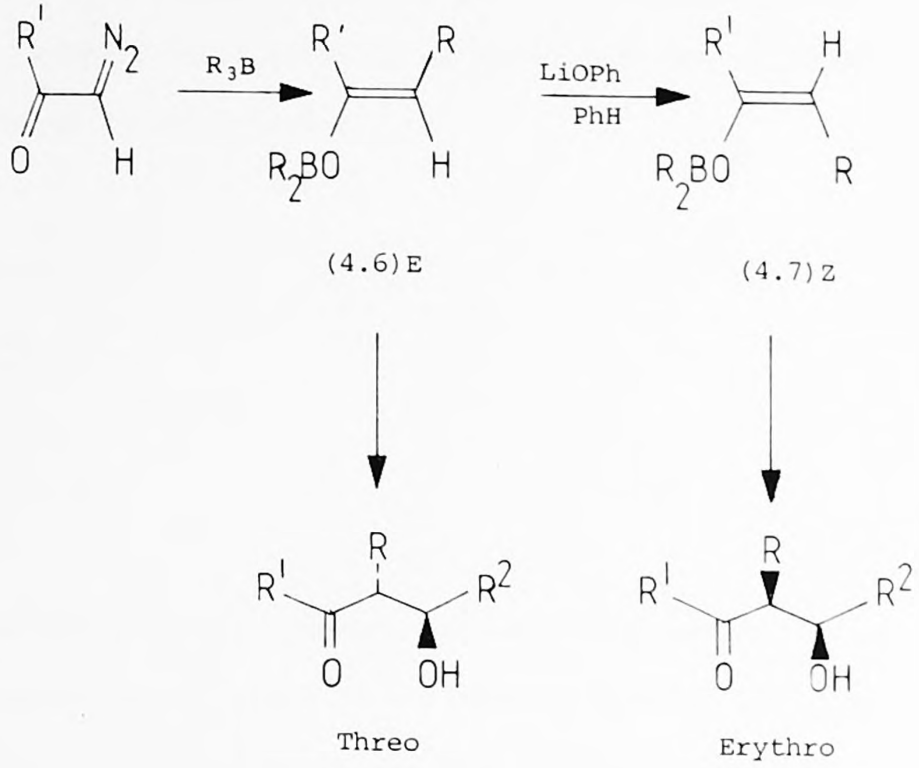


(4.4)

(4.5)

Scheme 5

aldol products (Scheme 6).



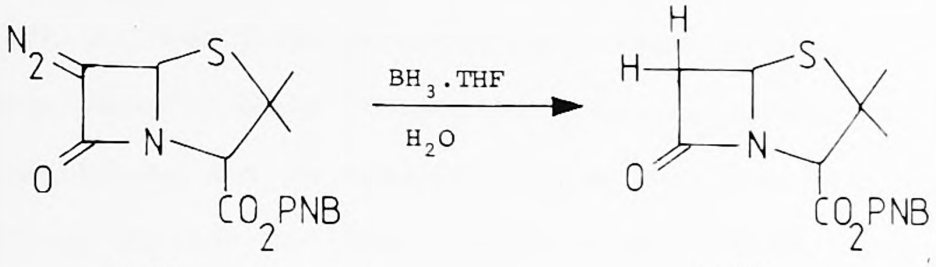
Scheme 6

In the light of the studies reported in the literature, it was decided to investigate the reactions of alkylboranes with 6-diazopenicillanic esters. It was hoped that in this way it would be possible to introduce 6-alkyl substituents in place of the 6-amino group, and also that the trapping by aldol condensation of any enol borinate intermediate formed in such a reaction might lead to a new synthesis of 6-(α-hydroxylalkyl) derivatives.

4.2 Reaction of p-Nitrobenzyl 6-diazopenicillanate with borane-THF

Using the experimental procedure described by Wiering and Wynberg[69], p-nitrobenzyl 6-diazopenicillanate (4.8) was reacted with diborane in THF containing a small amount of water. It was

found that a large excess of diborane had to be used to obtain complete reaction of the diazo compound. p-Nitrobenzyl penicillanate (4.9) was formed in 60% yield. After chromatographic work-up, several other products were isolated, none of which contained an intact β-lactam ring.



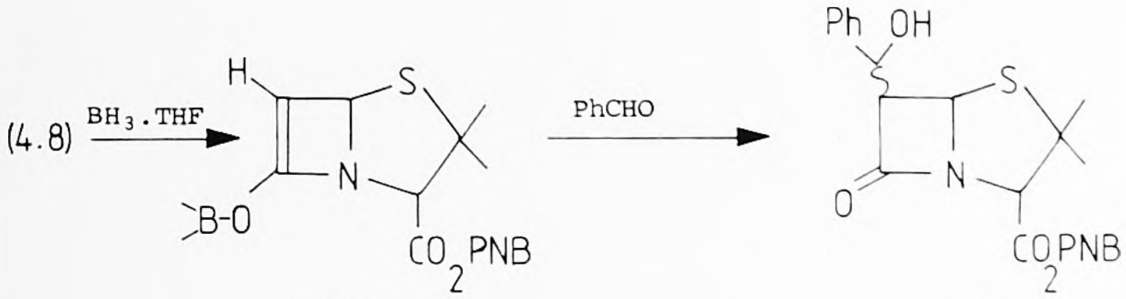
(4.8) (4.9)

This reaction provides a convenient method for the conversion of 6-aminopenicillanic esters to the corresponding penicillanic esters and an alternative to the more cumbersome literature procedure[155].

The formation of p-nitrobenzyl penicillanate (4.9), as expected in this reaction, was encouraging evidence in support of an intermediate boron derivative being formed and trapped by the water which was present. A further reaction between the diazo ester (4.8) and diborane was then carried out under anhydrous conditions, with addition of water at a later stage. The penicillanic ester (4.9) was produced in lower yield (30%), indicating that the intermediate boron compound is not very stable and requires rapid trapping before undergoing decomposition. These results are consistent with the observations of Wiering and Wynberg[69].

It was hoped to trap any intermediate enol borinate (4.10)

present in the reaction mixture by means of an aldol condensation (Scheme 7). Benzaldehyde was selected for this purpose. Because of the indications of instability of the intermediate boron derivative, initial attempts were made to carry out the reaction of the diazo compound (4.8) with diborane in the presence of benzaldehyde. However, apart from some p-nitrobenzyl penicillanate (4.9), no other β-lactam-containing products were formed. A large amount of benzyl alcohol was obtained, as well as recovered benzaldehyde, and the presence of these materials hampered the work-up and made the identification of by-products difficult.

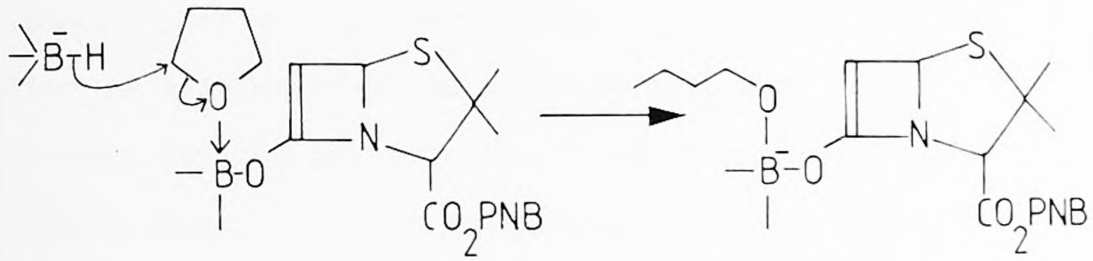


(4.10) (4.11)

Scheme 7

It was therefore decided to modify the reaction by first adding diborane to the diazo compound (4.8) in dry THF, then evaporating to dryness and adding benzaldehyde in dichloromethane. It was hoped that this would avoid the presence of excess reducing agent and simplify work-up. After evaporation of a solution of diazo compound (4.8) and borane-THF, an n.m.r. spectrum of the vacuum-dried residue showed the presence of a butyl compound in great quantity. The multiplets at 0.92, 1.44 and 3.84 δ compared well with the literature values for the alkyl chain in n-butanol (0.93, 1.5, 3.66 δ)[156], but no hydroxyl proton was observed. It

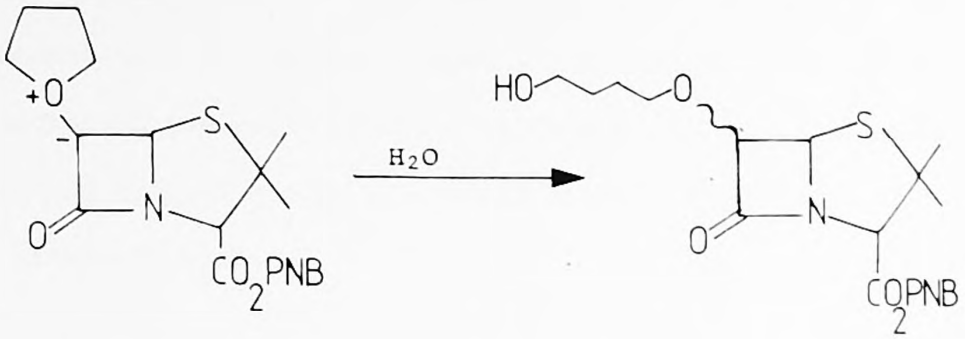
was then recognised that the product was a butyl borate ester[157], which was presumably formed by ring-opening of the THF. Since borane-THF is normally stable, this reaction must be occurring as a result of an increase in electron demand by the boron atom in a THF complex. It is proposed that this reaction is occurring via an intermediate enol-borinate complex (4.12), where electron withdrawal from the boron by the enolate group makes the boron more electron deficient and thereby activates a complexed THF molecule towards hydride attack (Scheme 8).



(4.12)

Scheme 8

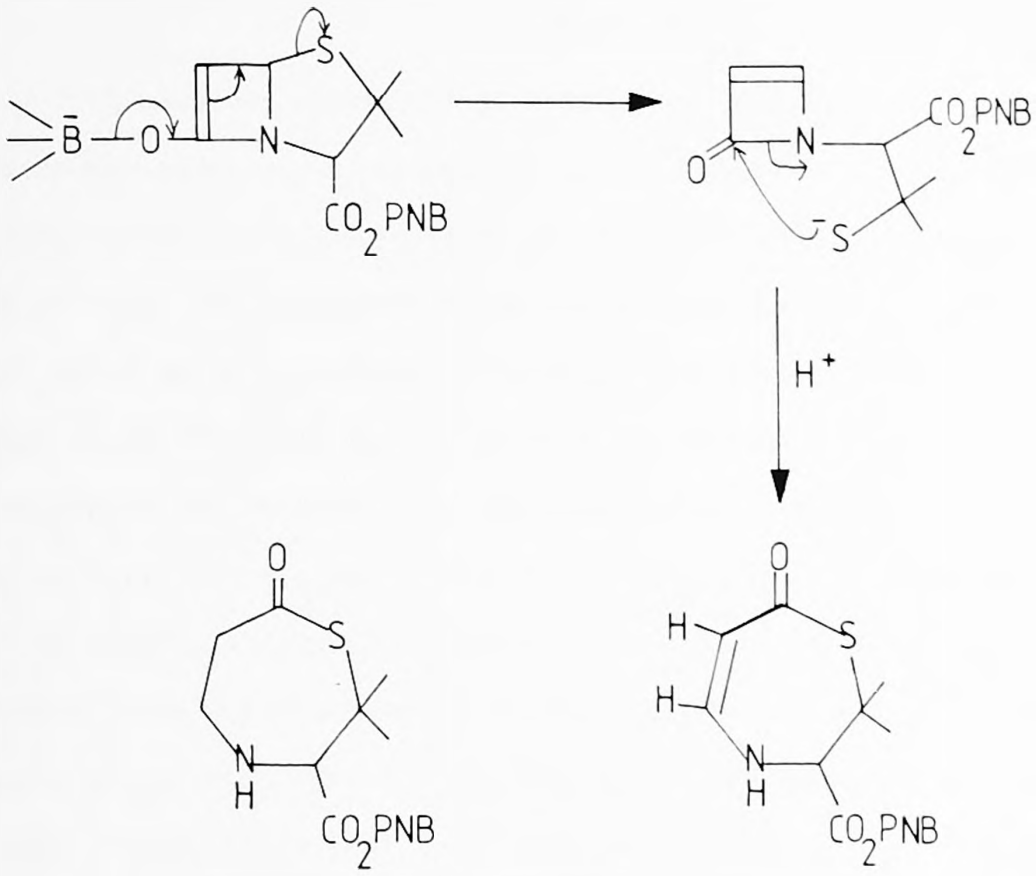
This type of reaction has not been previously reported in the literature, although Thomas et al.[72], during an investigation of BF_3- mediated reactions of diazopenicillanates, isolated isomeric 6-(4-hydroxybutoxy) penicillanates in low yield. They suggested that these were formed by adventitious hydrolysis of an intermediate oxonium ylid involving the solvent THF (Scheme 9).



Scheme 9

After subsequent addition of benzaldehyde to the dried product of the reaction of borane with the diazo ester (4.8), the aldol product (4.11) could not be detected and TLC both before and after the addition of the benzaldehyde indicated that most of the final reaction products were already present before the aldehyde addition. Apart from p-nitrobenzyl penicillanate (4.9), another product was obtained which was tentatively assigned as the thiazepine (4.13) on the basis of its spectral data. The IR spectrum showed stretches at 3,400 cm^{-1} and at 1735 cm^{-1} corresponding to the N-H group and the carbonyl of the α,β-unsaturated thiolactone, and the n.m.r. spectrum showed low field multiplets between 6 and 7.5 δ characteristic of vinyl protons. In addition, the mass spectrum gave a maximum m/e value of 338, corresponding to a further reduction of the thiazepine to (4.14), although no peak at m/e 336 for the molecular ion was observed. Its formation presumably results from collapse of the unstable enol borinate intermediate (Scheme 10). This mechanism is consistent with several other known cases[75] in which the build-up of anionic character at C-6 in a penicillin derivative

results in expulsion of the neighbouring sulphur atom at C-5 and rearrangement to a thiazepine. Some p-nitrobenzyl alcohol was also detected in the crude reaction mixture by n.m.r., indicating that reducing hydride groups were still present in the intermediate after evaporation.



(4.14) (4.13)

Scheme 10

In summary, the reaction of the 6-diazopenicillanate ester with diborane appears to involve hydride transfer to C-6, and formation of an unstable enol borinate intermediate. The latter may undergo protonation at C-6 leading to the penicillanate ester, or re-

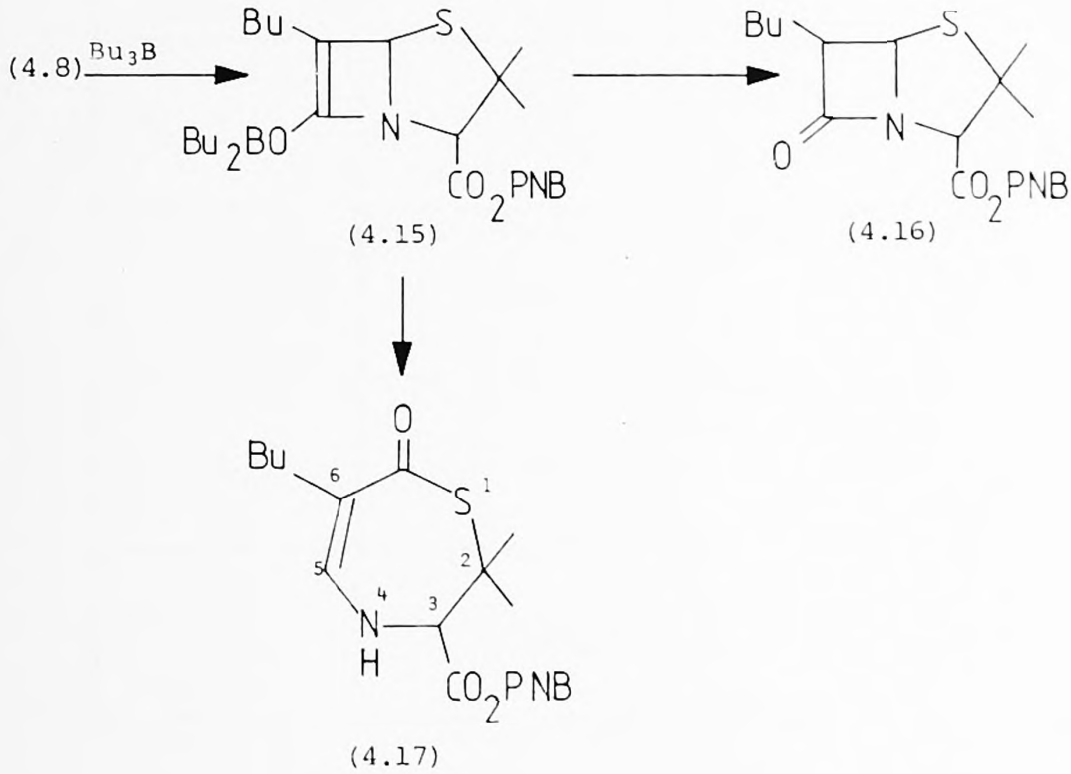
arrangement to the thiazepine, depending on the reaction conditions. The reducing environment of the reaction medium tends to complicate the outcome, especially on attempting to trap the enol borinate by reaction with an aldehyde.

Attention was then turned to the reaction of the 6-diazopenicillanate with a non-reducing trialkylborane.

4.3 Reaction of p-Nitrobenzyl 6-diazopenicillanate with tributylborane

Following the conditions of Wiering and Wynberg, tributylborane was added under nitrogen to p-nitrobenzyl 6-diazopenicillanate in THF containing a trace of water, at -65°C. After a few minutes, the reaction mixture was allowed to warm to -45°C and worked up with addition of hydrogen peroxide. An n.m.r. spectrum of the crude product mixture showed evidence for the presence of the enol borinate intermediate (4.15) [δ 3.40(q, 2H, CH_2 at C_6), 4.60 (s, 1H, H-3), 5.80 (s, 1H, H-5)], although no 6-butyl penicillanate (4.16) could be detected. However, the major product was the butyl thiazepine (4.17), and in fact, after purification (TLC) this was the only product isolated, in 60-70% yield. (n.m.r. δ 4.46(d, 1H, J=6Hz, H-3), 5.76 (m, 1H, N-H), 6.83(d, 1H, J=7.5Hz, H-5)). Thus, if the enol borinate intermediate or the 6-butyl penicillanate had been produced, then either the yield was too low to allow isolation, or conversion to the thiazepine had occurred during chromatography. The latter of these appears the more probable. A mechanism which accounts for the observations is shown in Scheme 11 and involves alkylation by the tributylborane to give an enol-borinate intermediate

(4.15) which may either rearrange to butyl thiazepine (4.17) or undergo protonation, giving 6-butyl penicillanate (4.16). Alkyl substitution should tend to destabilize anionic charge at C-6 and hence it would be expected that more rearrangement would occur for the butyl-substituted intermediate (4.15) than for the unsubstituted one (4.10), as observed.



Scheme 11

The influence of reaction conditions on the course of the reaction was then examined. The fate of the intermediate (4.15) might be expected to depend on temperature and on the presence of water, as in Wiering and Wynberg's study, and might also be influenced by the presence of a base which could affect proton transfer

processes, as in Ramsey and Stoodley's studies of the epimerisation and rearrangement of 6-aminopenicillanate derivatives[158]. Five sets of conditions were therefore selected for study, as shown in Table 4.1

System No.	Conditions	Temperature
1	WET	$-65^{o}C$
2	DRY	$-65^{o}C$
3	WET	$0^{o}C$
4	DRY	$0^{o}C$
5	DRY/Et_3N	$-65^{o}C$

Table 4.1

The Conditions employed in each of the 5 systems

To be able to follow closely the course of each reaction, it was decided to establish an H.P.L.C. method for the quantitative analysis of thiazepine formed in each system shown in Table 1. After trials with several potential candidates, p-nitrobenzyl alcohol was selected as a suitable internal standard which had an appropriate

chromophore and a convenient retention time. For calibration, six solutions were prepared each containing known quantities of butyl thiazepine (4.17) and p-nitrobenzyl alcohol. The resulting peak area ratios were plotted against mole ratios to give the calibration graph shown in Figure 4.1. With the aid of this graph, it was now possible to determine the absolute yield of butyl thiazepine produced in any set of reaction conditions simply by adding a known amount of p-nitrobenzyl alcohol to the reaction solution and measuring the H.P.L.C. peak areas for the mixture.

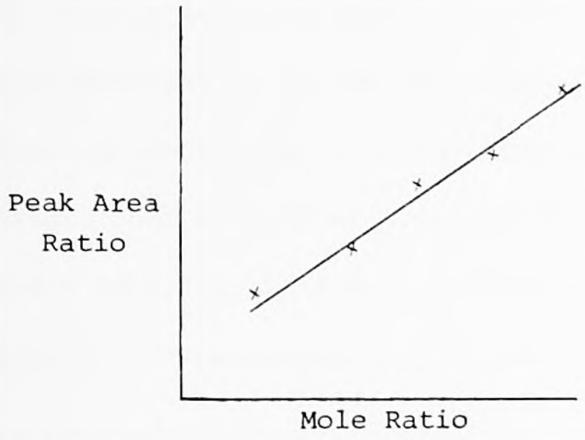


Figure 4.1

Calibration Graph of Peak Area Ratio Against Mole Ratio

Reactions were then performed according to each of the sets of conditions, systems 1-5, shown in Table 4.1. Surprisingly, when H.P.L.C. analyses were performed shortly after mixing the reagents, none of the five systems showed thiazepine, but each showed instead a peak of shorter, but somewhat varying retention time. A second injection of each reaction solution was then performed after a further 10 minutes and this now revealed butyl thiazepine (4.17) as the sole product in each of systems 1-4. However, system 5

did not show any thiazepine at this point and in fact the shorter-retained peak persisted over a period of several weeks.

The reaction conditions of systems 1-4 were repeated several times, on each occasion the reaction being closely followed by frequent H.P.L.C. injections commencing a few seconds after mixing. It became apparent that the peak of shorter retention time than butyl thiazepine appeared very rapidly after mixing the reagents: that its retention time, even for a given solution, varied unpredictably from one injection to the next: that the eventual disappearance of this peak was unpredictable and did not correlate in any obvious way with temperature or moisture content, and that its disappearance coincided exactly with the sudden appearance of the final product, the butyl thiazepine (4.17). It should be emphasised that throughout these studies, injections of stock solutions of butyl thiazepine at intervals gave consistently sharp peaks of reproducible retention time.

The explanation which is proposed to account for these unusual observations is as follows: on mixing the reagents the butyl borinate intermediate (4.15) is formed rapidly and persists for a few minutes in solution. It is then transformed into butyl thiazepine (4.17). The factor which triggers this transformation is not clear (but is possibly due to a trace of adventitious acid), although once started it occurs very rapidly and cleanly. When solutions containing the intermediate (4.15) are injected onto the silica H.P.L.C. column, the enol borinate travels some distance down the column and suddenly and rapidly transforms into the more polar butyl thiazepine (4.17) which then completes its passage

through the column. This explanation would account for the somewhat erratic retention times of the HPLC peaks observed.

Efforts were made to characterise the postulated intermediate enol borinate. Preparative T.L.C. of crude reaction mixtures containing the intermediate compound led only to the isolation of butyl thiazepine, of which the R_f on the preparative plates varied erratically in accordance with the HPLC observations above. An attempt to observe the intermediate by n.m.r. was made by carrying out the reaction of tributylborane with p-nitrobenzyl 6-diazopenicillanate in $CDCl_3$. However, this change of solvent and the fact that the reaction temperature used was $0^{o}C$ rather than $-65^{o}C$ to avoid freezing of the solvent proved unhelpful: the disappearance of 6-diazopenicillanate coincided exactly with the appearance of butyl thiazepine in the n.m.r. spectrum, and no signals for an intermediate could be detected.

It was recognised that the rôle of solvation was critical, but unfortunately, the requisite deuterated THF was unavailable. A new reaction was carried out in THF and the solution gradually concentrated under vacuum, with frequent H.P.L.C., sampling and comparisons with a standard solution of butyl thiazepine. This study revealed that the intermediate would survive until a very late stage in the concentration procedure, but rearranged rapidly on being stripped of the last traces of THF. In the light of these results, a concentrated THF solution containing the intermediate (H.P.L.C. evidence) was partitioned between water and $CDCl_3$. The n.m.r. spectrum of this solution was partially masked

by the large quantity of THF which extracted into the organic phase, but a singlet was visible at δ 6.7 which did not correspond to any peak in the butyl thiazepine, and which could be due to H-5 of an enol borinate. The $CDCl_3$ solution was gradually concentrated and further n.m.r. spectra taken at intervals, with the following results:

a) at 50% of original volume: the singlet at δ 6.7 was still present, with no evidence for the butyl thiazepine.

b) at 25% of original volume: as in (a)

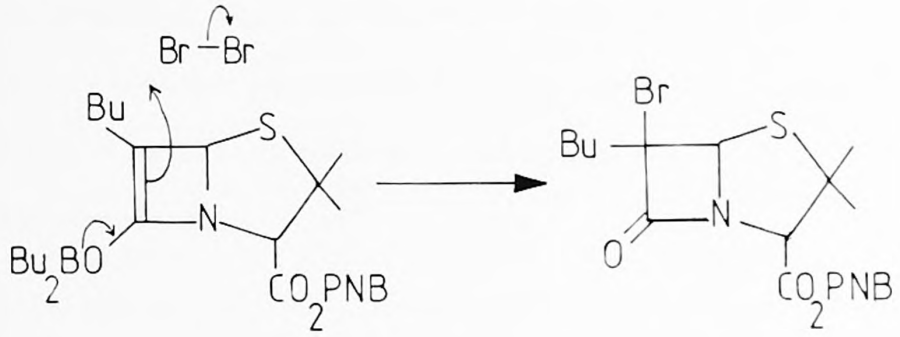
c) with complete evaporation and re-addition of fresh $CDCl_3$: only thiazepine was now present.

It seems apparent that the enol borinate intermediate receives stabilization from the THF molecules coordinating to the boron, and rearranges rapidly once separated (either by evaporation or chromatography) from the THF. This view explains the considerably increased stabilization observed in the presence of triethylamine, since the latter will coordinate more strongly than THF to the electron-deficient boron. This consideration led to the attempt to isolate an Et_3N-stabilized enol borinate by evaporation of a THF solution. Once again the intermediate persisted, as shown by HPLC, until a late stage in the concentration process, but did not survive evaporation to dryness.

Since attempts at the physical isolation of the postulated enol borinate intermediate proved unsuccessful, attention was

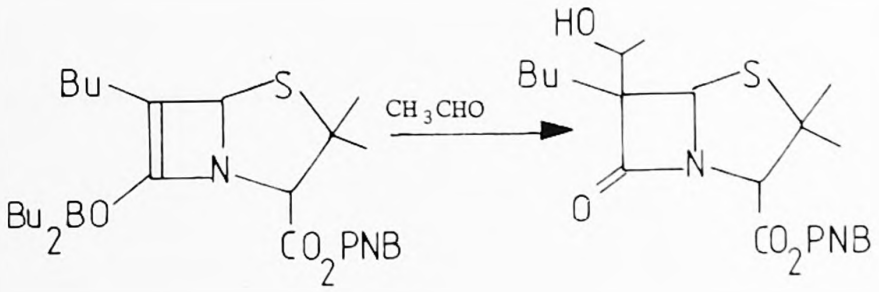
turned to its chemical manipulation by means of added trapping agents. Three different methods were used in an effort to capture the enol borinate and prevent its rearrangement to butyl thiazepine:

a) Addition of bromine was carried out in the hope of effecting an electrophilic substitution of the enolate (Scheme 12). However, there were no identifiable products of this reaction.



Scheme 12

b) Condensation with acetaldehyde was attempted in an effort to obtain an aldol condensation (Scheme 13) , but none of the desired product could be detected. Instead, the main product was again butyl thiazepine.



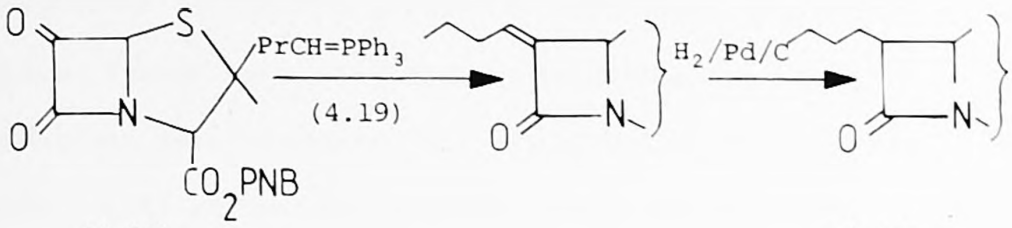
Scheme 13

c) Acetic acid addition to the reaction mixture was examined in the hope that rapid proton transfer to the intermediate might lead to butyl penicillanate rather than butyl thiazepine. However, no 6-butyl penicillanate could be isolated.

4.4 Attempted Synthesis of p-nitrobenzyl 6-butyl penicillanate

In the study of the reaction of 6-diazopenicillanate with tributyl-borane, there was no evidence for the production of 6-butyl penicillanate under any of the conditions examined. It was felt that it would be helpful to prepare an authentic sample of the 6-butyl penicillanate by an independent route, so that its n.m.r., H.P.L.C. behaviour and stability could be accurately assessed.

Initially, p-nitrobenzyl 6-diazopenicillanate was converted to the 6-oxopenicillanate (4.18)[62]. Purification of the latter proved extremely difficult, since it was found to decompose during chromatography. Eventually, therefore, the ketone (4.18) was used in crude form for a reaction with butylidene triphenyl-phosphorane (4.19) (Scheme 14). Again, the crude products were found to be extremely difficult to purify, and were therefore hydrogenated at once over 10% Pd/C. None of the required product (4.20) could be isolated, although several modifications in the overall procedure were tried.

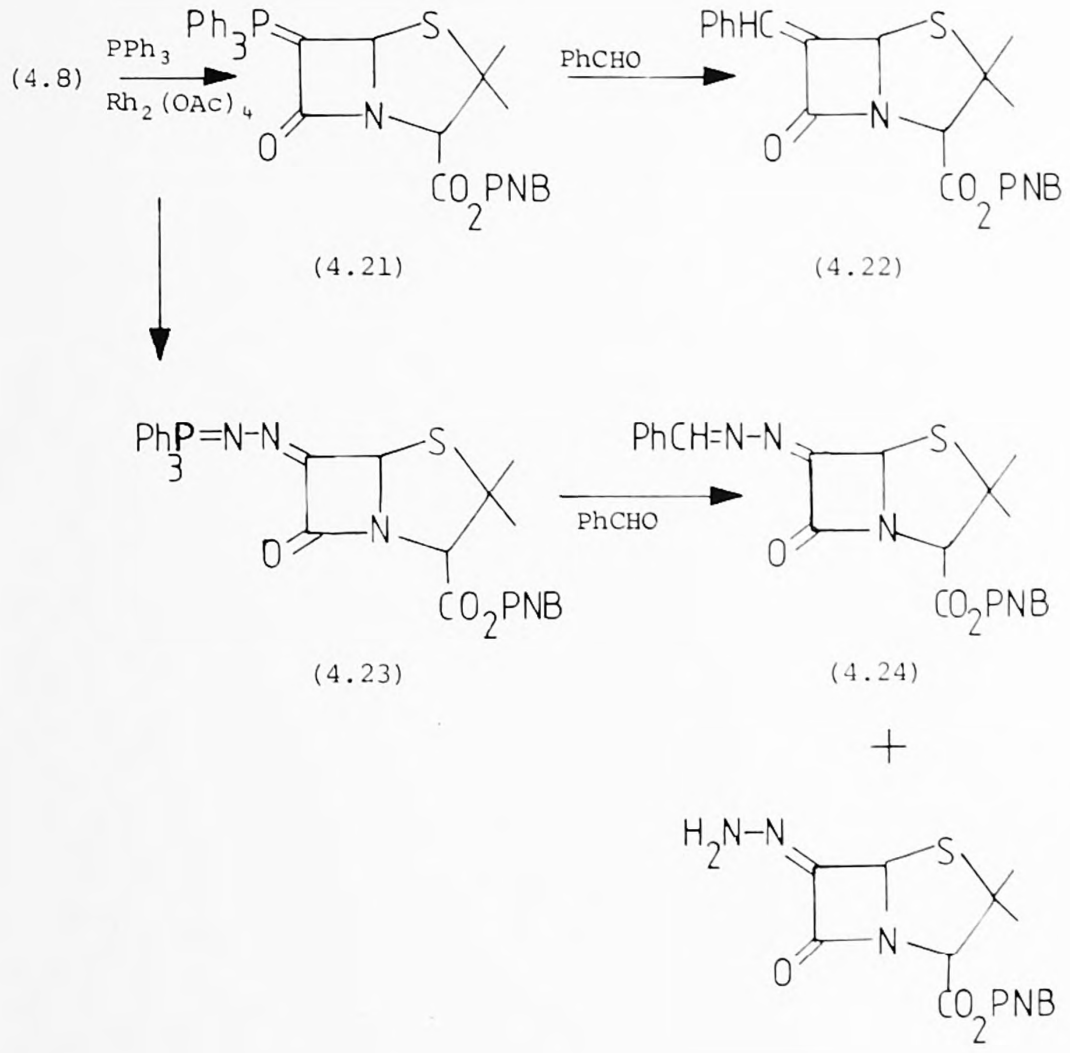


(4.18) (4.20)

Scheme 14

An alternative to this route was considered, which avoided involvement of the 6-oxopenicillanate and butylidene phosphorane, both of which are difficult to handle. If the phosphorane (4.21) could be prepared, it should be relatively stable, because of the carbonyl group adjacent to the ylid, and should be capable of condensing with an aldehyde to give the Wittig product. Nucleophilic displacement of a 6-halogeno substituent by phosphorus would not be an appropriate approach to the phosphonium salt, and hence ylid, in a bicyclic β-lactam. However, ylids can also be formed by carbenoid reaction with a phosphine. Consequently, the reaction of 6-diazopenicillanate with triphenylphosphine in the presence of rhodium acetate was investigated. It was hoped that rhodium catalysis would result in the loss of nitrogen from the diazo compound and trapping of the metallocarbenoid with phosphorus. Since the desired ylid intermediate (4.21) might be of limited stability, it was attempted to trap it without isolation, by immediate addition of an aldehyde. Benzaldehyde was selected for initial study as a convenient model. Unfortunately, the product of this reaction was not the desired benzylidine penicillanate (4.22),

but the yellow azine (4.24). This indicated that the phosphazine (4.23) rather than the ylid (4.21) was being formed (Scheme 15). A number of variations in reaction conditions were attempted, but all reactions afforded the azine (4.24) as the main product, and no Wittig product (4.22). In addition to the yellow azine, a white solid was also produced in some reactions, the spectra suggesting it to be the hydrazone (4.25)



Scheme 15

The presence of the phosphazine (4.23) as a stable intermediate prior to the addition of benzaldehyde was shown by n.m.r. Attempts to remove nitrogen thermally[159] from the phosphazine in order to convert it to the ylid (4.21) proved unsuccessful. Refluxing in a variety of solvents with increasing boiling points led eventually to destruction of the β-lactam ring. At this point, no further attempts to synthesize 6-butyl penicillanate were made.

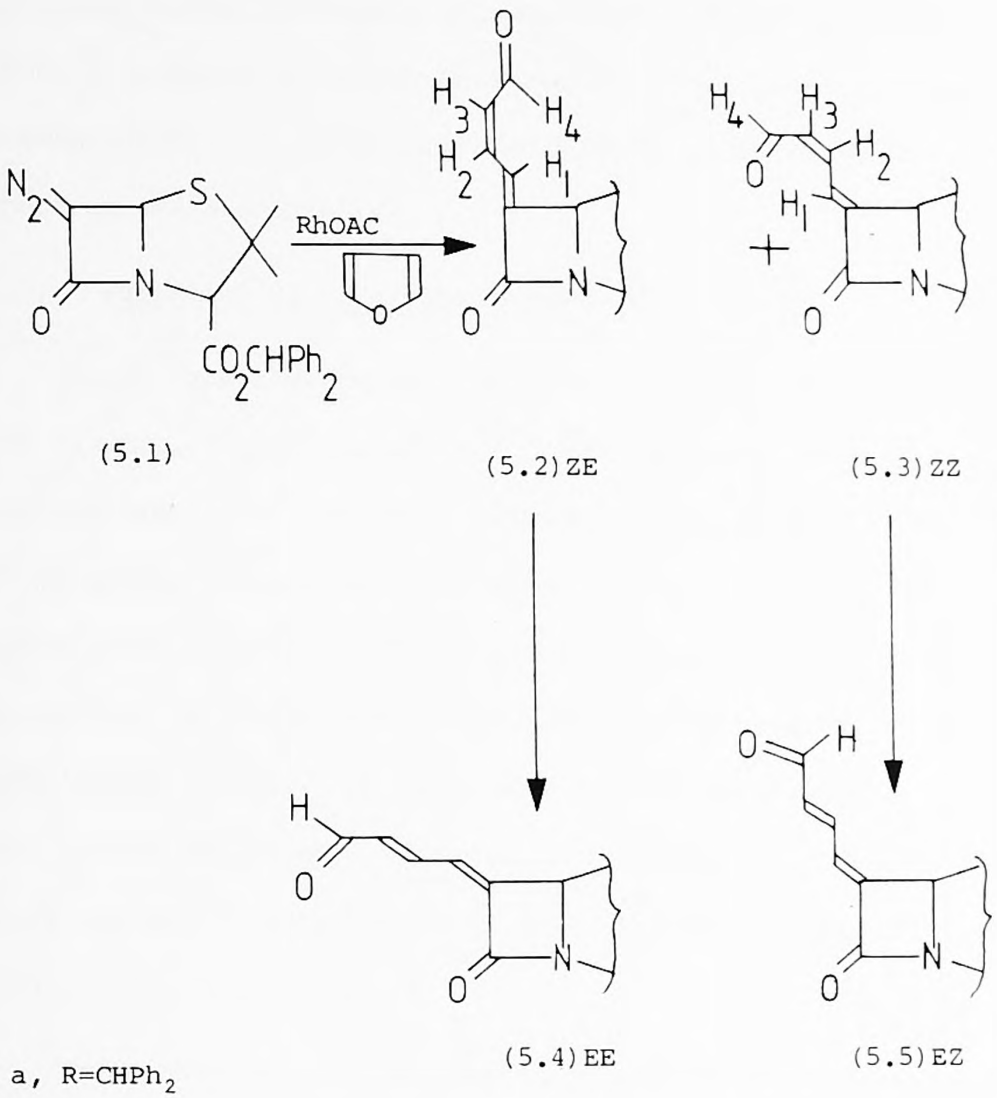
Section 2

Chapter 5 : The Reactions between 6-Diazopenicillanates and Furans

5.1 Introduction

In general, diazo compounds react with furans to form both cyclopropanes and ring opened products. Substitution at the 2-and 3-positions as observed for pyrroles and indoles respectively, is rare, if, indeed, it occurs at all. Thiophenes, under the correct conditions, form stable sulphonium ylids, and although oxonium ylids are known, they are less stable and tend to rearrange[74,75].

The recent paper concerning the reaction of benzhydryl 6-diazopenicillanate with furan[160] reports the quantitative production of the dienal isomers (5.2a)(5.3a)by rhodium acetate catalysis. The initial product ratio was a 2:1 mixture of the ZE:ZZ isomers, but isomerization occurred during chromatographic separation to afford the EE and EZ isomers also (5.4a)(5.5a)(Scheme 1).



a, R=$CHPh_2$

b, R=PNB

c, R=POM

Scheme 1

It was felt that the above reaction held potential for further investigations and consequently, several developments were examined.

5.2 Variation of Protecting Group

The literature reaction of 6-diazopenicillanate with furan utilized the benzhydryl group for protection of the acid. Similar reactions in which the diazopenicillanic

acid was protected by a) the p-nitrobenzyl group and b) the pivoyloxymethyl group, were subsequently attempted and were shown to proceed in equally good yields. The isomer ratios, determined by the characteristic aldehyde peaks in the n.m.r. spectrum, were unaffected.

5.3. Variation of Furan Concentration

In the previous cases, the furan had acted as both reagent and solvent, thus being present in the reaction mixtures in large excess. By employing dichloromethane as solvent and reducing the concentration of furan to 1,2,5 and 10 molar equivalents in each of four systems, it was found that 5 molar equivalents of furan afforded the same yield of products as a much larger excess. Satisfactory results could also be obtained for 2 molar equivalents of furan, but in reactions where the scale was small, this amount of furan proved difficult to handle owing to its volatility.

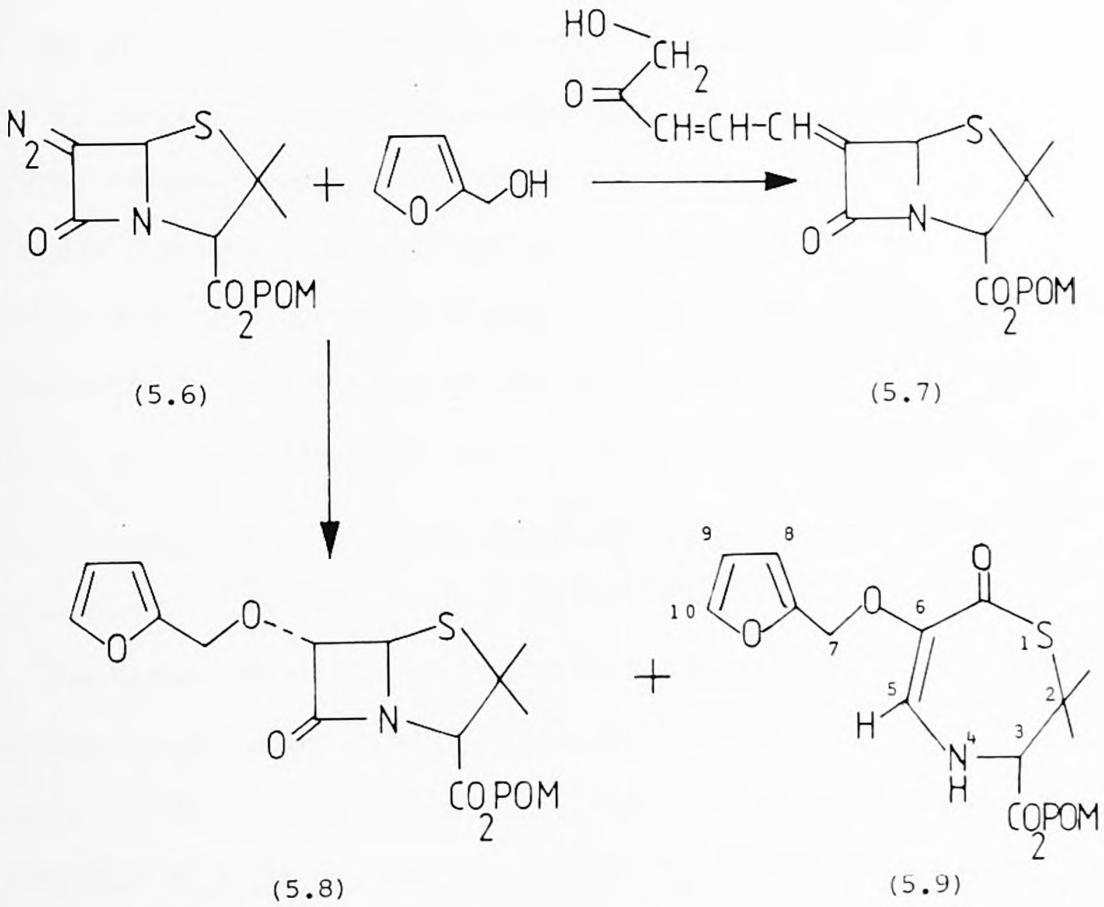
These observations are important for two reasons. Firstly, reduction in the amount of furan used means less waste of reagent and improved economy. Secondly, in the planned studies of substitution effects in this reaction, some of the furan derivatives would be very high boiling and their presence in large excess would hinder work-up.

5.4 Reaction of Pivoyloxymethyl 6-diazopenicillanate with furfuryl alcohol

Matlin and Chan[75] have shown that simple alcohols react with 6-diazopenicillanates to give a mixture of 6α-alkoxypenicillanate and alkoxythiazepine products, the latter arising by

rearrangement of an intermediate oxonium ylid. The product distribution was found to depend on alcohol structure, with methanol giving mainly 6α-methoxypenicillanate and benzyl alcohol giving virtually complete rearrangement to benzyloxy-thiazepine.

It was therefore of interest to examine the behaviour of furfuryl alcohol, where competition for attack on the ring and on the side-chain hydroxyl group might be expected. Thus, three possible products (5.7-5.9) would be anticipated for this reaction (Scheme 2).



Scheme 2

A five-fold excess of furfuryl alcohol in dichloromethane was used (since this alcohol is high boiling and inconvenient to use as the solvent), being reacted with pivoyloxymethyl 6-diazopenicillanate (5.6) in the presence of rhodium acetate. On chromatographic work-up, none of the dienone (5.7) nor of the furfuryloxypenicillanate (5.8) could be detected, only the thiazepine (5.9) being isolated. The thiazepine was recognised by its characteristic ^{1}H n.m.r. spectrum, which included doublets for the olefinic proton (H-5) and for the proton α to the ester (H-3), both of these protons coupling to the N-H group which appeared as a multiplet.

The result obtained indicates that the side-chain hydroxyl group in furfuryl alcohol is considerably more reactive than the ring towards electrophilic carbenoid species derived from the diazo compound (5.6) and rhodium acetate. Evidently, the reaction then proceeds through rearrangement of the oxonium ylid intermediate to give the thiazepine (5.9) rather than by a proton transfer process which would lead to the alkoxypenicillin (5.8).

5.5 The Reaction of p-Nitrobenzyl 6-diazopenicillanate with Diethyl 3, 4- furandicarboxylate

The 6-diazopenicillanate was stirred with rhodium acetate in the presence of excess diethyl 3,4- furandicarboxylate. In contrast to the reaction with furan, there was no rapid evolution of nitrogen from the solution and even after 2 hours some diazopenicillanate was still present, shown by its characteristic stretch in the IR spectrum. After 3 hours, however, total decomposition of the diazo group had occurred, and so the reaction mixture was investigated. Separation of the products by

chromatography afforded no 6-substituted penicillins and it was evident that no reaction had occurred between the two reagents. This difference in activity between diethyl 3,4-furandicarboxylate and furan is probably due to electronic factors, as the ethoxycarbonyl groups are strongly deactivating.

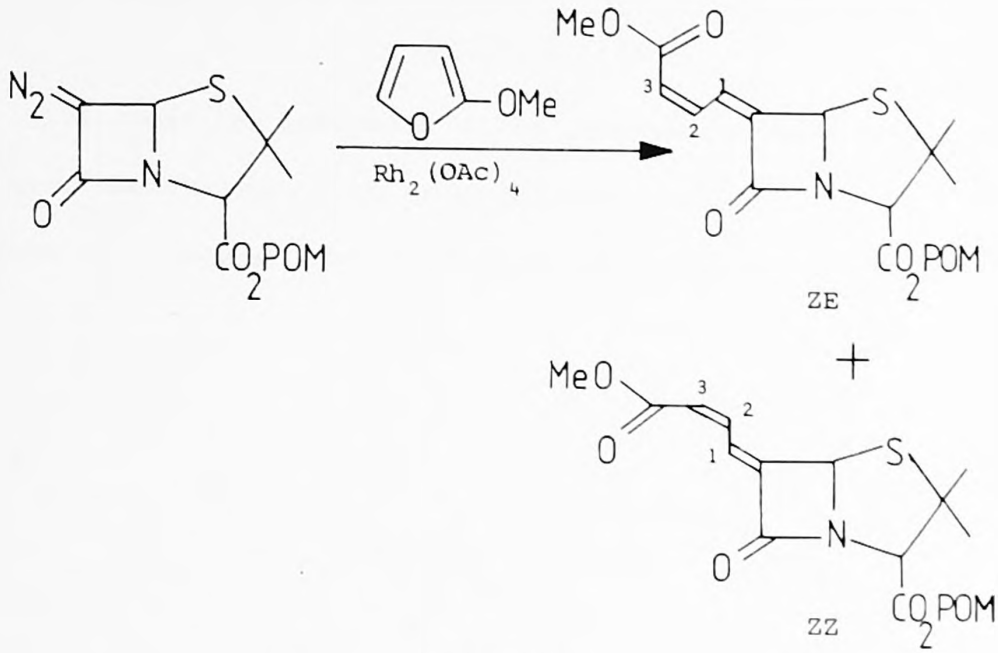
5.6 The Reaction of Pivoyloxymethyl 6-diazopenicillanate with Methyl 2-furoate

The diazopenicillanate was decomposed by rhodium acetate in the presence of a five-fold excess of methyl 2-furoate. Although the rate of decomposition was rapid, no identifiable products could be isolated from the complex reaction mixture. The reaction was repeated several times, and the products carefully separated by repeated chromatography on silica plates. On each occasion, no furan-substituted penicillins could be detected. It appears that the methoxycarbonyl group is too deactivating, withdrawing electron density from the furan nucleus and decreasing the nucleophilic nature of the ring.

5.7 The Reaction of Pivoyloxymethyl 6-diazopenicillanate with 2-Methoxyfuran

Incorporation of electron withdrawing groups onto the furan nucleus has caused complete deactivation of the furan, with the disappointing result of no reaction. In contrast, 2-methoxyfuran should possess increased nucleophilicity due to the incorporation of the electron releasing methoxy substituent, although it may still, being a fairly bulky group, have some steric effects. The reaction between 2-methoxyfuran and the 6-diazopenicillanate proceeded with the rapid evolution of nitrogen and total loss of the diazo group within 1 hour. The product mixture was separated

by preparative T.L.C. on silica, affording two isomers of the diene (5.10) (Scheme 3).



Scheme 3 (5.10)

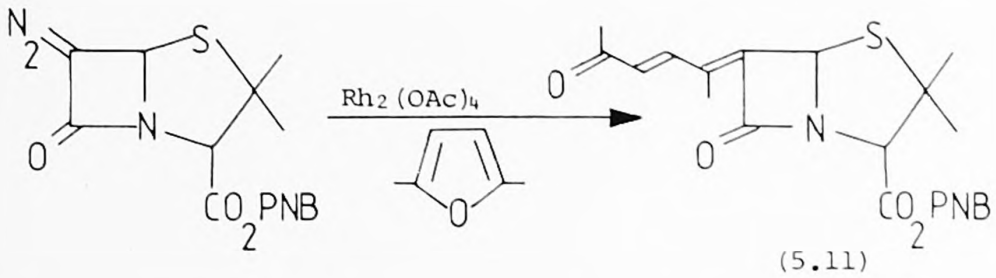
As no aldehydic peaks were present in the n.m.r. spectra, it was concluded that attack had occurred solely at the side of the furan bearing no substituent. The two isomers were due to two configurations about the double bond adjacent to the penicillin nucleus being possible. The configuration about the remaining double bond, as expected, was cis in both cases, having been derived directly from the furan ring. The ratio of ZE to ZZ isomers was 5:1.

The combined yield of both isomers after several purifications amounted to 26%. Comparing the yield of this reaction with the almost quantitative yield in the parent furan reaction, it can be seen that a large decrease in yield of products has occurred in the methoxyfuran case. This may be due to steric hindrance

and/or to excessive reactivity of the strongly activated furan leading to side reactions and to possible competing interaction of the side-chain ether oxygen with the carbenoid.

5.8 The Reaction of p-Nitrobenzyl 6-diazopenicillanate with 2,5-Dimethylfuran

This reaction proceeded in the presence of rhodium acetate to give the dienone (5.11), as described in Scheme 4. However, the final yield of (5.11) was a mere 2.5%.



(5.11)

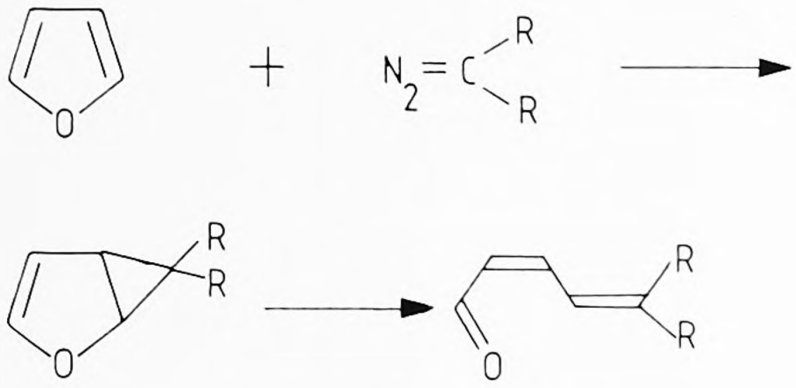
Scheme 4

The crude reaction mixture was extremely complex, and repeated chromatography was necessary in order to isolate any of the required product. Preparative H.P.L.C. had to be employed finally to obtain a pure sample (see Chapter 8). It is therefore probable that the initial yield of the dienone was substantially greater than 2.5%, but was reduced by mechanical losses as well as some decomposition during the chromatographic procedures. Clearly, however, the yield is substantially lower than in the case of furan, and it is apparent that substituent groups at the 2- and 5- positions, even when activating in

electronic character, have a pronounced steric effect.

5.9 Mechanistic Study of Reactions with Furans

The literature reports of reactions of diazo compounds with furans, leading to dienals and dienones, have all suggested that the reactions proceed via cyclopropanation and ring opening (Scheme 5). The evidence for this has been that on some occasions cyclopropanes (5.12) have been isolated from the reaction mixtures and these have been shown to undergo thermal ring opening to diene derivatives at elevated temperatures.

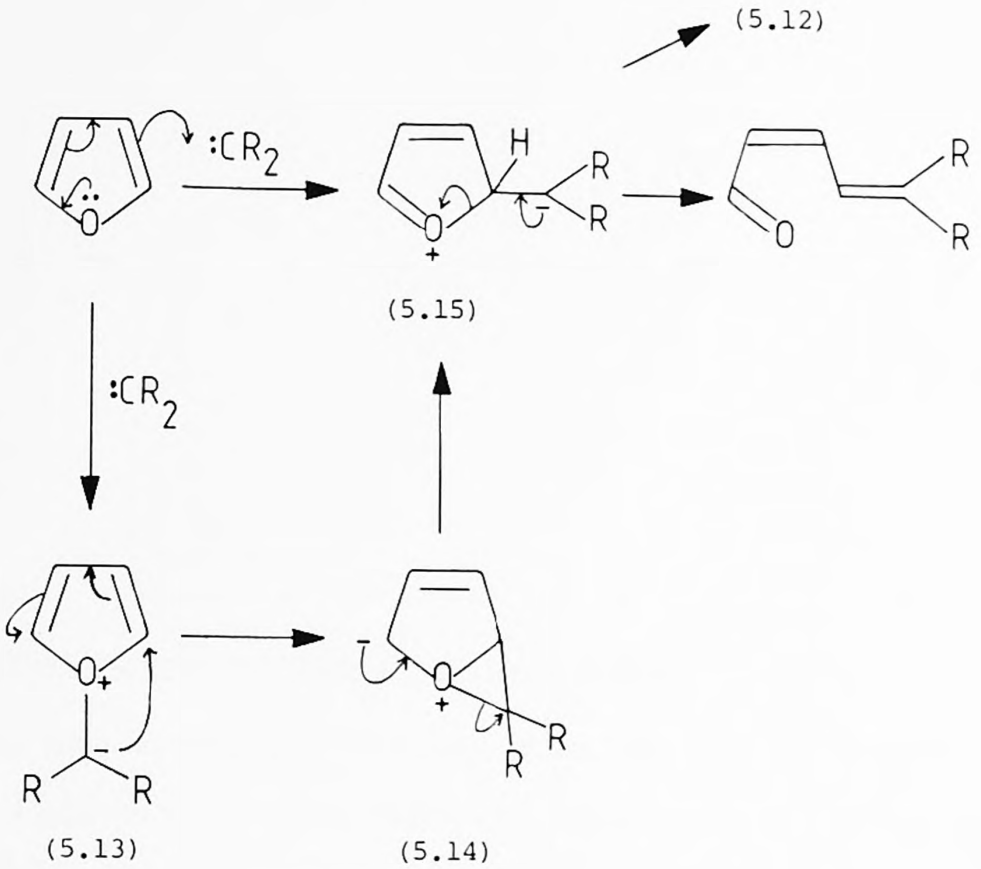


(5.12)

(Scheme 5)

This evidence is by no means conclusive and examination of the results of our own reactions has led us to consider an alternative possibility, in which the α-substituted furan intermediate (5.15) is formed, either by direct electrophilic attack on the α-carbon of furan, or via the rearrangement of an oxonium ylid (5.13) (Scheme 6). The latter intermediate would be consistent with the known behaviour of saturated compounds containing oxygen, which do give oxonium ylids. For the present, to simplify the discussion, it will be assumed that the ylid (5.13) is a precursor to (5.15). Although the zwitterion (5.15) could

now ring close to give the intermediate cyclopropane (5.12) proposed in the literature, a simple ring opening could produce the observed dienals directly (Scheme 6).



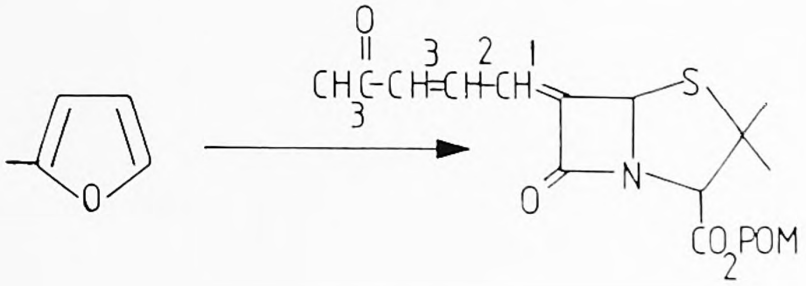
Scheme 6

In order to explore this alternative mechanistic scheme, the following reactions were studied.

a) Reaction of 6-diazopenicillanate with 2-methylfuran

The rhodium catalysed reaction of the pivoyloxymethyl diazoester (5.6) with 2-methylfuran led exclusively to two isomers of the methyl ketone (5.16)(Z/E, Z/Z). There was no evidence, either from n.m.r. or from the chromatographic work-up, for formation

of aldehydes. Thus, it is evident that the presence of the 2-methyl group completely blocks reaction on the substituted side of the furan ring. This observation is also consistent with the very poor yield of ring-opened adduct obtained in the case of 2, 5-dimethylfuran (Section 5.8).

(5.6) 

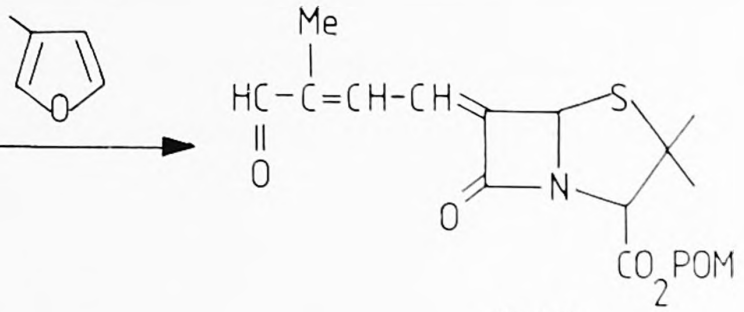
(5.16)

b) Reaction of 6-diazopenicillanate with 3-methylfuran

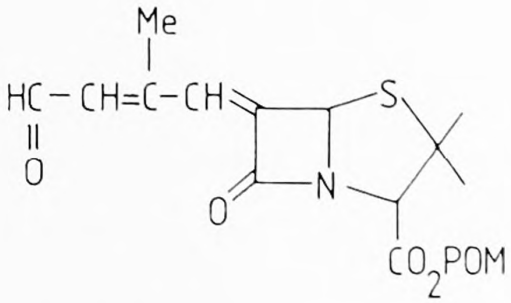
The rhodium catalysed reaction, under the usual conditions, led to a mixture of products which was partially separated into two fractions by preparative T.L.C. In one fraction there was a single proton visible in the aldehyde region of the n.m.r. spectrum and this was observed to be a singlet. This is consistent with the product (5.17) bearing a methyl group α to the aldehyde function. The second chromatographic fraction showed two sets of aldehydic doublets, indicating a mixture of the isomers (5.18) and (5.19) bearing β-methyl groups. In view of the complexity of the aldehyde region in this mixture, it cannot be stated with certainty that there was no further aldehyde singlet buried under the doublets, which would represent a

second isomer of the α-methyl product (5.17). It will be assumed that this is not the case. Integration of the signals for the aldehyde singlet and for the aldehyde doublets in the n.m.r. spectrum of the total crude product mixture showed that the α-methyl and the β-methyl types of product were present in the ratio 60:40.

(5.6)



(5.17)



(5.18) ZE

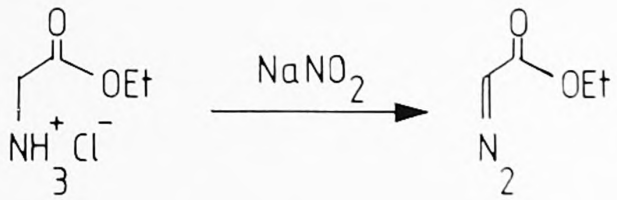
(5.19) ZZ

This result provides evidence contradictory to the cyclopropanation mechanism. It is apparent that a 2-methyl group blocks attack on the substituted side. If this were a steric effect preventing cyclopropanation of the 2,3-bond, it should be equally present for the case of a 3-methyl substituent.

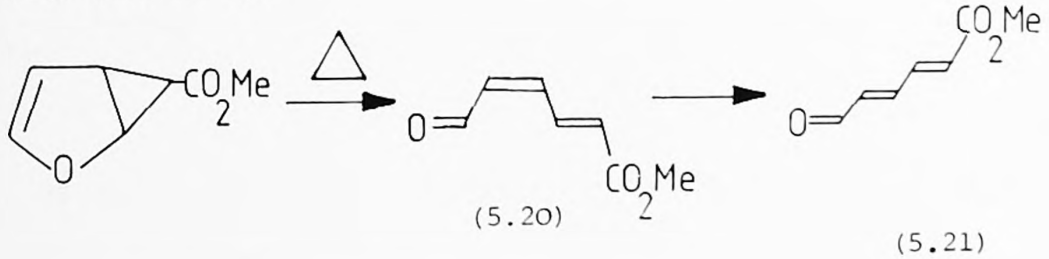
However, if the mechanism proceeds through oxonium ylid formation and rearrangement to an α-substituted furan intermediate (Scheme 6), attack should be very sensitive to the presence of a 2-methyl group, but much less so to a 3-methyl group.

c) Reaction of Ethyl Diazoacetate with Furan

In order to further explore the mechanism of these reactions, the literature reports on the reaction of ethyl diazoacetate with furan were reinvestigated in detail. Ethyl diazoacetate was prepared from ethyl glycinate hydrochloride according to the method of La Forge et al.[161], and obtained as a yellow liquid.



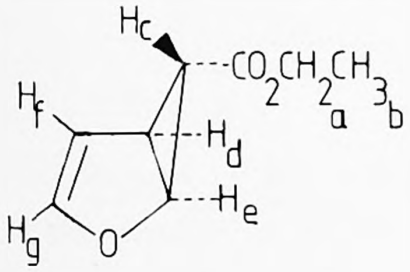
Jackson has reported that methyl diazoacetate reacts with furan, either by copper catalysis or photochemically, to give the cyclopropane adduct[107]. Schenck and Steinmetz also obtained the cyclopropane from the reaction of methyl diazoacetate[106], and claimed that on heating to 150°C it rearranged to the cis-trans-dienal (5.20), which further rearranged to the trans-trans isomer (5.21) (Scheme 7).



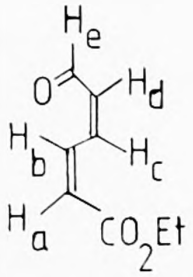
(5.20) (5.21)

Scheme 7

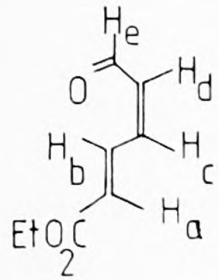
The addition of ethyl diazoacetate to furan was investigated, using both copper acetylacetonate and rhodium acetate as catalysts in separate experiments. In each case, the product mixture was examined closely by H.P.L.C. and n.m.r., which revealed no significant differences in products from the two catalysts. Both gave a mixture of three products, which were separated and individually characterized as the cyclopropane (5.22) and the isomeric dienals (5.23) and (5.24), in the ratio 6:1:1. There was, however, a substantial difference in the rate of reaction for the two catalysts, as revealed by monitoring the diazo band by IR, the rhodium acetate giving complete loss of diazoester in 1 hour, whereas the copper acetylacetonate took 24 hours. Although all three of the reaction products had previously been synthesized[106], no n.m.r. data had been obtained due to n.m.r. spectroscopy being in its infancy at that time. U.V. had been the only previous guide to the configuration of the isomers. However, n.m.r. is a necessity for accurate assignment and differentiation between the isomers.



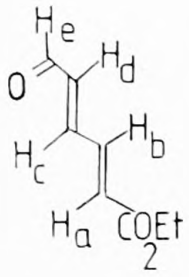
(5.22)



(5.23)



(5.24)



(5.25)

From the n.m.r. spectrum of the cyclopropane (5.22), the 3Hz and 1Hz coupling constants between H_c/H_d and H_c/H_e respectively are typical of trans couplings, thus indicating that the carboxyethyl group occupies the position exo to the furan ring, as predicted on stereochemical grounds. By comparison of the assignments of the dienals prepared by Matlin and Chan[160], it was possible to determine that the stereochemistry about the double bond adjacent to the aldehyde group was cis in each of (5.23) and (5.24). The original assignments had been made by use of the "Tobey-Simon Rules", for estimation of the chemical shift of a proton attached to a double bond. This cis configuration was as expected considering that the bonds were derived directly from the furan ring. The stereochemistry of the second double bond was rather more difficult to assign. Figure 1 illustrates the splitting pattern obtained for the protons H_a - H_e in the n.m.r. spectrum of (5.23).

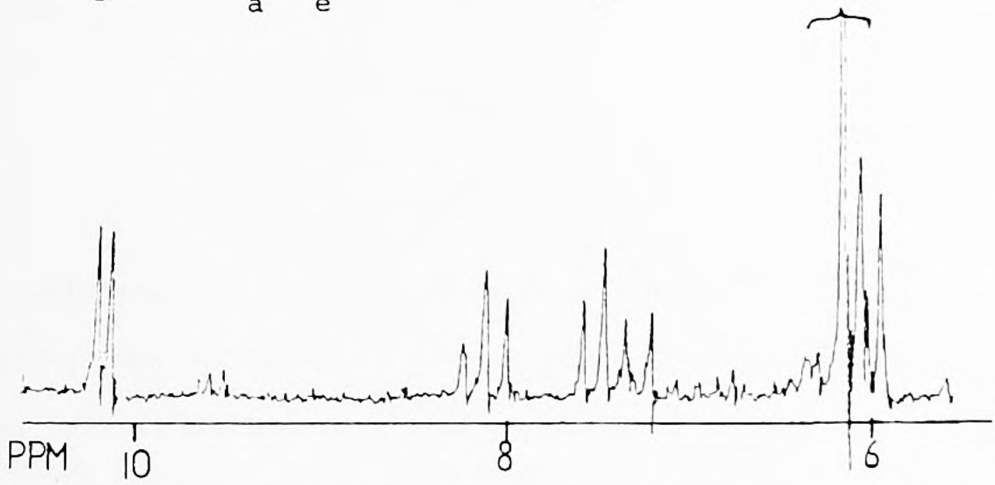


Figure 1: The splitting pattern of protons H_a - H_e in (5.23)

The doublet at 10.26δ represents the aldehydic proton H_e. By irradiation, the signal at 6.24δ, due to proton H_d, causes collapse of the aldehydic doublet to a singlet, as expected, in a decoupling experiment. The occurrence of H_d as an apparent singlet was surprising, as coupling to neighbouring protons H_e and H_c

should cause a more complicated pattern. Irradiation of the aldehydic doublet was shown to cause sharpening of the signal, verifying that it was, indeed, H_d. Protons H_b and H_c had very similar splitting patterns, both occurring as triplets rather than the expected doublets of doublets, due to overlap of signals and the couplings between H_d/H_c, H_c/H_b and H_b/H_a being equal. From the amount of information available, it was not possible to distinguish between the triplets of H_c and H_b.

As H_b and H_c give equal patterns, and as it is known that H_c is cis to H_d, then because the coupling between H_b and H_c is equal to the coupling between H_c and H_d, then H_b and H_c must be vicinal[162]. Similarly, the coupling between H_a and H_b must be cis also, as it is equal to the vicinal coupling between H_b and H_c. These assignments have been based on the fact[162] that

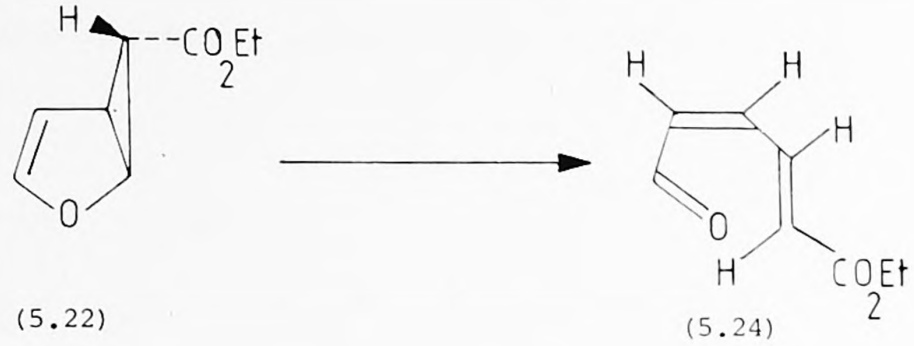
$$J_{cis} = J_{vic}$$

$$J_{trans} > J_{vic}$$

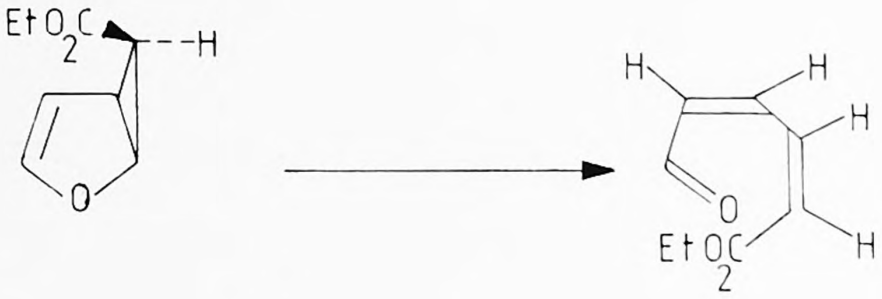
The assignment of (5.24) was much more straightforward, as the coupling constant between H_a and H_b could be measured. This being 15.5Hz, the olefinic bond was assigned as trans. Also, $J_{trans} > J_{vic}$ as predicted. Hence (5.24) was assigned as the cis-trans isomer, which is in agreement with the assignment of (5.23) as the cis-cis isomer.

If the cyclopropanes were intermediates in dienal formation, then the cis-trans isomer would arise from the cyclopropane with the ethoxycarbonyl group in the exo position, and the cis-cis isomer from the cyclopropane with the ethoxycarbonyl group in

the endo position (Scheme 8)



(5.22) (5.24)



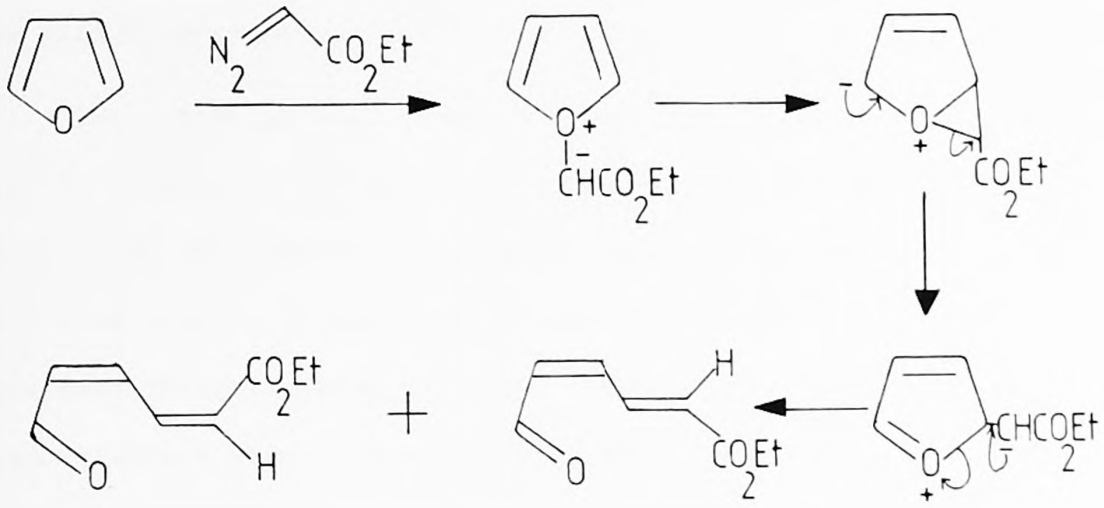
(5.23)

Scheme 8

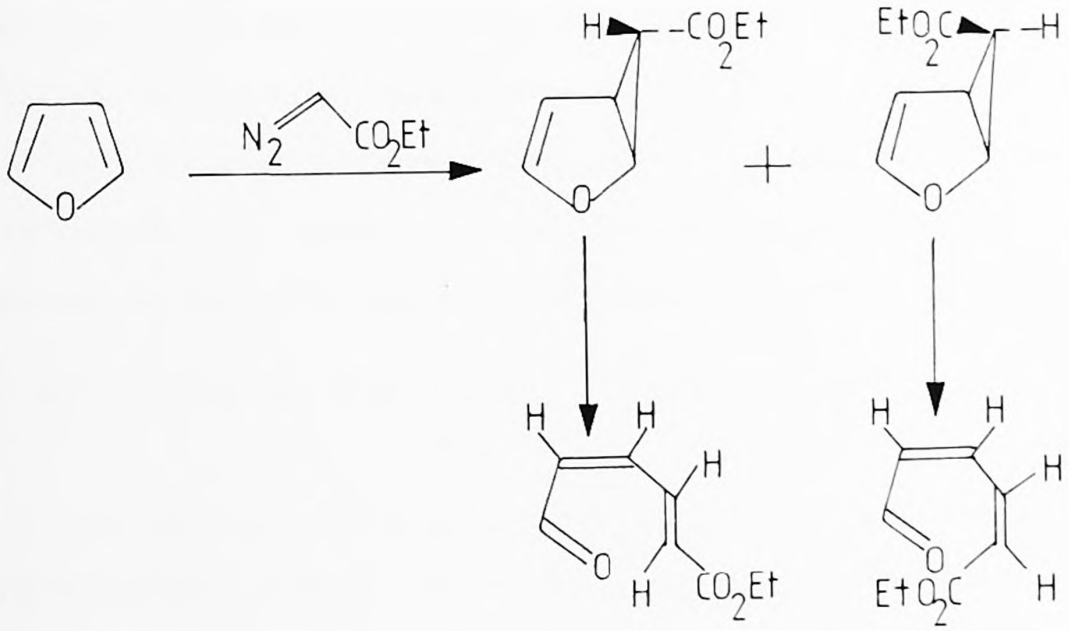
Stirring of the exo-cyclopropane (5.22) in the presence of rhodium acetate was subsequently attempted in order to effect ring opening to the cis-trans dienal (5.24), which would be expected to occur if the cyclopropane was an intermediate in its formation. However, no ring opening was observed. It therefore appears unlikely that (5.24) is derived from the cyclopropane.

To verify that the cis-trans isomer was not occurring as a result of isomerization of the cis-cis isomer, (5.23) was stirred in the presence of rhodium acetate, but no isomerization was observed. Cyclopropanation does not therefore appear to be the intermediate step in the production of the dienals. Also, the cis-cis isomer (5.23) and the cis-trans isomer (5.24)

occurred in the ratio 1:1. On considering both ylid and cyclopropane mechanisms (Schemes 9 and 10 respectively), this becomes further evidence in support of ylid formation.



Scheme 9



Scheme 10

From Scheme 9, both dienals are equally probable, whereas from Scheme 10, the cis-trans isomer appears to be the most likely, having arisen from the sterically less-hindered and therefore preferred cyclopropane. Formation of equal quantities of each dienal therefore favours the mechanism depicted in Scheme 9 via an ylid intermediate.

The action of heat on the cyclopropane (5.22), according to the literature[106], should effect ring opening to give a mixture of dienal isomers. Repeating this reaction, however, afforded only the trans-trans dienal (5.25), which is obviously the most thermally stable isomer. None of the cis-cis or cis-trans isomers were isolated, but it would be unlikely for these isomers to be stable to temperatures of 150°C, even if they had been the initial products of ring opening.

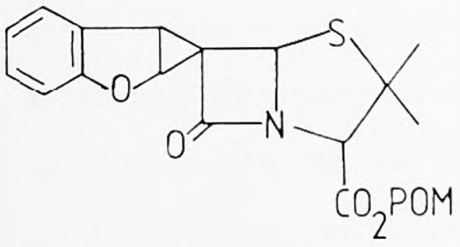
The formation of the trans-trans isomer appears to suggest that the cyclopropane could be an intermediate in the thermal reaction between ethyl diazoacetate and furan, with ring opening being followed by isomerization of the initially formed cis-cis and cis-trans isomers. It is therefore probable that the thermal and catalytic decompositions occur by different pathways.

d) The Reaction of Pivoyloxymethyl 6-diazopenicillanate and Benzofuran

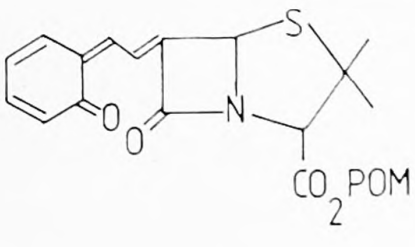
The reaction between pivoyloxymethyl 6-diazopenicillanate and benzofuran could provide further interesting information as to the mechanism of this series of reactions, as ring-opening to the analogous dienone (5.27) would involve the destruction of the aromaticity of the adjacent benzene ring and would therefore

be less likely to occur. Also, the product would be very closely related to the series of compounds known as o-quinone methides (5.28) which have been thoroughly investigated in recent years and are known to be relatively unstable species[163]. Therefore, unless some new rearrangement is undergone, the most likely product of the reaction would be the cyclopropane (5.26).

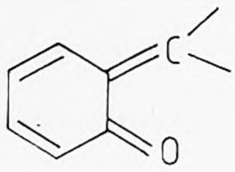
The reaction between pivoyloxymethyl 6-diazopenicillanate and benzofuran was initiated by the presence of 1% rhodium acetate catalyst and began with the immediate and rapid evolution of nitrogen. Within only ten minutes the reaction had reached completion, and separation of the products by chromatography afforded one major component in 10-15% yield as a yellow oil. The remaining material was a complex mixture from which no further substituted penicillins were isolated. There was no evidence for the formation of the cyclopropane (5.26), and the purified product proved, on close examination, to be the new spiro penicillin derivative (5.31). This showed both β-lactam and ester carbonyl stretches in the IR spectrum, but no carbonyl absorptions below 1745 cm^{-1}. This ruled out the possibility that the product was an o-quinone methide such as (5.29,5.30) as it would have a carbonyl stretch in the 1600-1650 cm^{-1} region[163,164].



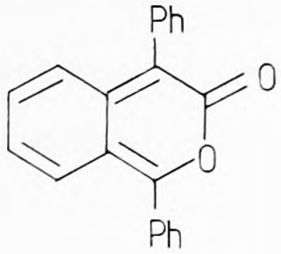
(5.26)



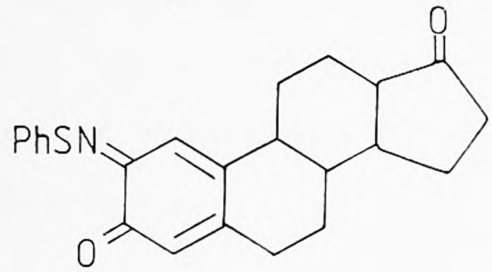
(5.27)



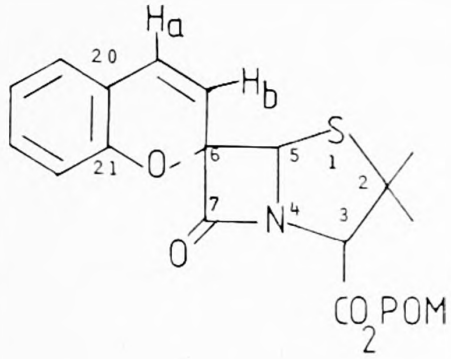
(5.28)



(5.29)



(5.30)



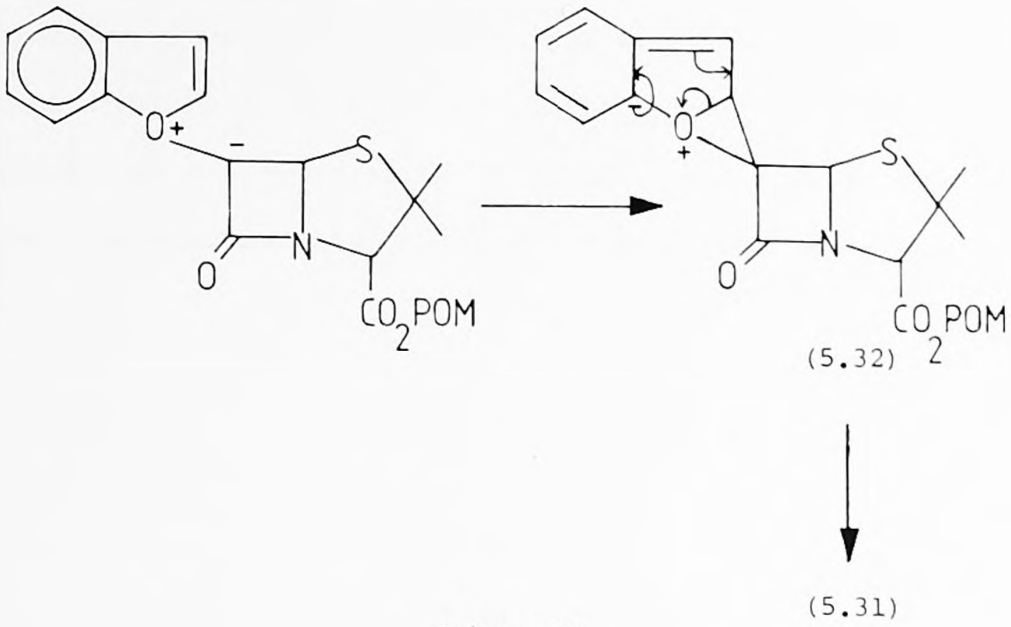
(5.31)

The ^{1}H n.m.r. spectrum of the product revealed it to have six olefinic hydrogens and no cyclopropane hydrogens, excluding the possibility of the cyclopropane (5.26). In addition the ^{13}C n.m.r. spectrum showed the presence of six vinylic carbons which were doublets in the proton-coupled spectrum (all with coupling constants of about 170Hz, typical of olefinic C-H coupling). The stereochemistry about C-6 of the product (5.31) was assigned by an n.O.e. difference experiment. In n.O.e. difference spectroscopy, a control spectrum without n.O.e. is subtracted from the spectrum with n.O.e. so that only differences in the spectrum should appear. This overcomes the limited scope of traditional n.O.e. experiments due to the need to resolve the

signal to be observed. Also, with traditional n.O.e. experiments, the minimum observable effect using conventional integration is ~5%, whereas in n.O.e. difference spectra, effects are observable at levels well below 1%. On irradiating a particular proton, the n.O.e. difference spectrum will only show intensity changes for other protons close to it.

Irradiation of the 2β-methyl group in (5.31) gave an n.O.e. effect on the vinylic doublet H_b and also on H-3. This result shows that the stereochemistry at C-6 is as shown, with the oxygen attached to the α-face and the vinylic protons H_a and H_b occupying the β-face.

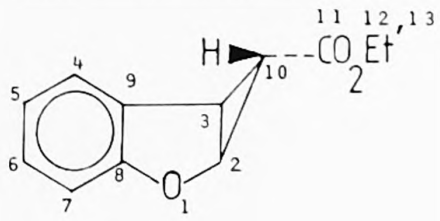
The observed formation of the spiro adduct (5.31) provides further evidence for the proposed reaction mechanism. If the cyclopropane (5.26) was an intermediate, it is difficult to see any direct way in which it would rearrange to (5.31). At best, it might be undergoing ring opening to the conjugated ketone (5.27), which could then recyclize by a 6π electrocyclic process to give (5.31). In contrast, the mechanism involving ylid formation (Scheme 11) provides an intermediate (5.32) which can cleave an internal bond and give the observed product (5.31) directly, without involving either cyclopropane or polyenone intermediates.



Scheme 11

e) Reaction of Ethyl Diazoacetate with Benzofuran

As a test of the above argument, the rhodium-catalysed reaction of ethyl diazoacetate with benzofuran was examined. The thermal reaction had previously been shown[94] to give the cyclopropane (5.33) and this was isolated as the sole product from the rhodium-catalysed process. By comparing the splitting patterns on the n.m.r. spectrum of this product with those of the cyclopropane formed in the reaction of ethyl diazoacetate with furan, it appeared that, as expected, the carboxy-ethyl group occupied the position exo to the ring.



(5.33)

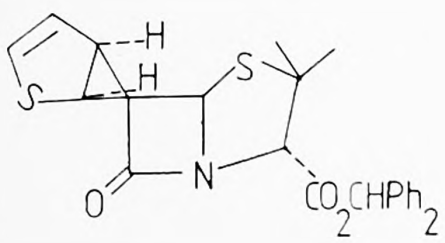
The cyclopropyl ester (5.33) was stable to prolonged contact with rhodium acetate and was stable thermally up to 150°C. At higher temperatures, it decomposed to afford a complex mixture of products, in which no evidence could be found for either _o_-quinone methides or for ring expanded benzopyrans. This result suggests that the cyclopropanation product is not an intermediate in the ring expansion reaction with the diazopenicillanate.

Section 2

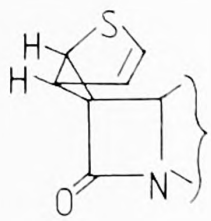
Chapter 6: The Reactions of 6-Diazopenicillanates with Sulphur and Nitrogen Heterocycles

6.1 Introduction

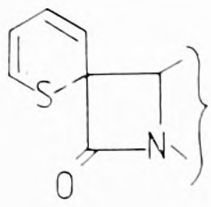
6-Diazopenicillanates, with only a few exceptions, react with furans and substituted furans to give ring-opened dienals and dienones. However, the catalysed reaction between benzhydryl 6-diazopenicillanate and thiophene was recently reported to afford the cycloaddition products (6.1)(6.2) together with the 2H-thiopyran (6.3)[165]. Product differences were observed between the reactions when conducted in the presence of rhodium acetate and copper acetylacetonate. Catalysis by rhodium acetate afforded the single cyclopropane adduct (6.1) and the thiopyran (6.3) in the ratio 2:1. With copper acetylacetonate, only a mixture of the two 2-thiabicyclo[3.1.0]hex-3-enes(6.1) and (6.2) was observed in the ratio 1:1, with no evidence for the ring-expanded product (6.3).



(6.1)



(6.2)



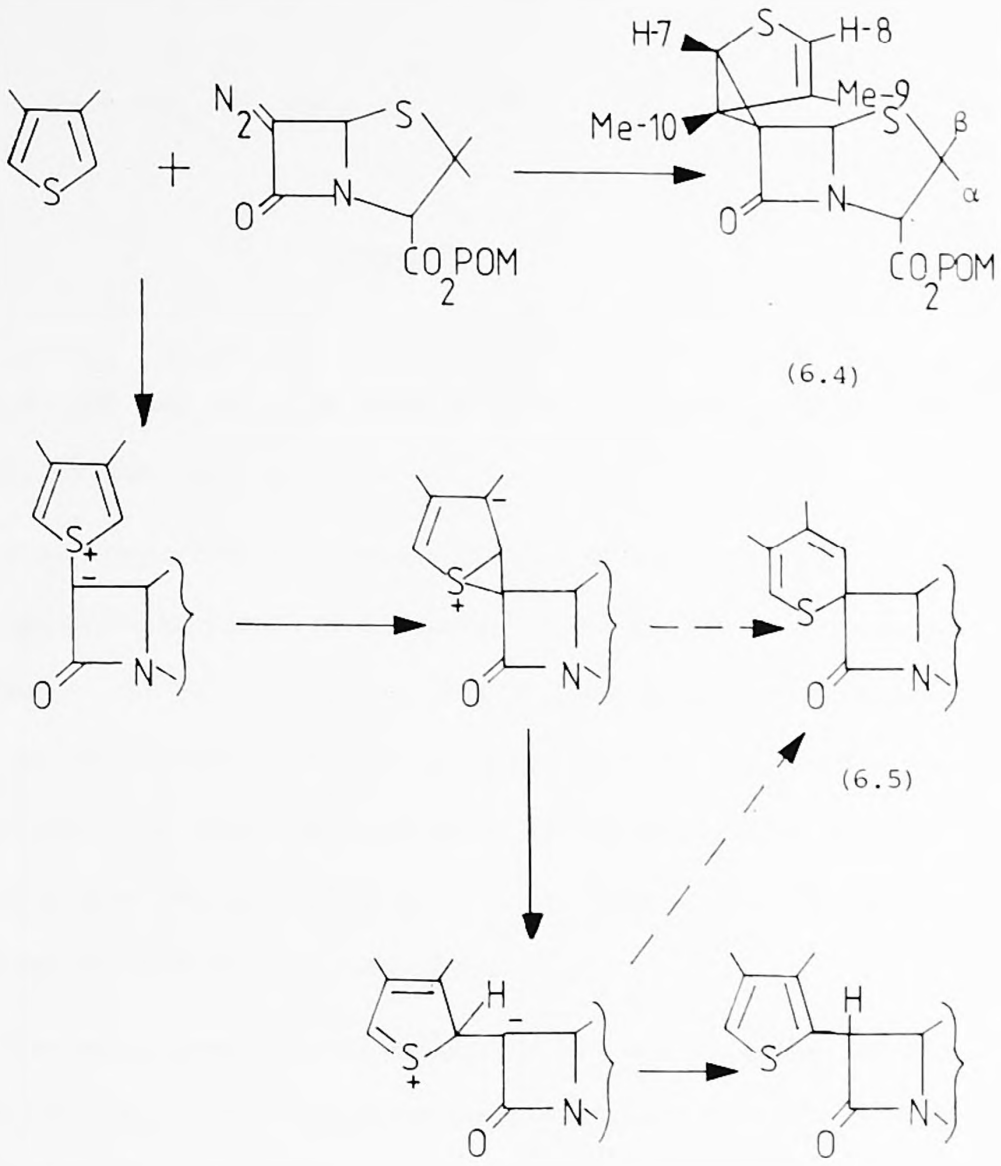
(6.3)

Although cyclopropanation is the normal mode of reaction of thiophenes, this is believed to be the first known production of a 2H-thiopyran during their reactions with diazoesters.

6.2 The Reaction of Pivoyloxymethyl 6-diazopenicillanate with 3,4-Dimethylthiophene: Results and Discussion

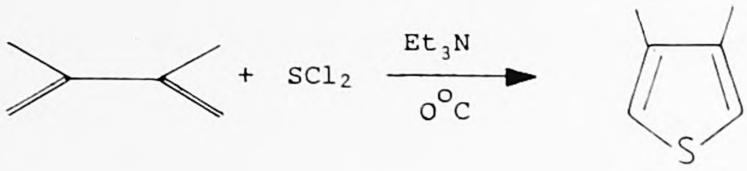
The reaction discussed in Chapter 5 between pivoyloxymethyl 6-diazopenicillanate and 2-methylfuran was shown to furnish products in which attack on the furan ring by the carbenoid took place exclusively at the unsubstituted side of the ring. Similarly, Jackson showed [107b] that the catalysed reaction between 2-chlorothiophene and ethyl diazoacetateled to attack solely at the unhindered side of the thiophene, to yield the cyclopropane adduct (Chapter 2, 18).

On the basis of these observations, it was expected that the presence of the methyl groups on the thiophene ring in the reaction of pivoyloxymethyl 6-diazopenicillanate with 3,4-dimethylthiophene would block cyclopropanation, either wholly or partially, leading to preferential formation of the 2H-thiopyran (6.5) and/or the substitution product (6.6)(Scheme 1).



Scheme 1

3,4-dimethylthiophene was prepared prior to the reaction by modifying the method of Brandsma et al.[166]. 2,3-Dimethyl-buta-1, 3-diene was reacted with sulphur dichloride in the presence of triethylamine (to remove HCl) and the crude products were distilled to obtain 3,4-dimethylthiophene as a pure liquid (Scheme 2). The structure of the product was confirmed by its n.m.r. spectrum



Scheme 2

which showed two singlets corresponding to the vinyl and methyl protons in the ratio 1:3.

Pivoyloxymethyl 6-diazopenicillanate was decomposed at 20°C in a two-fold excess of 3,4-dimethylthiophene by 2% rhodium acetate catalyst. An I.R. spectrum after 2 hours showed total decomposition of the diazo group, and separation of the complex product mixture into its components by chromatography surprisingly afforded only the cyclopropane (6.4). None of the 2H-thiopyran (6.5) or the adduct (6.6) was isolated.

The assignment of the product as the cyclopropane was based on the ^{1}H n.m.r. spectrum which showed a sharp singlet for H-5, signifying a doubly-substituted carbon at the 6-position and therefor discounting (6.6) as a possibility. The thiopyran (6.5) was also discounted owing to the presence of only one vinylic proton. The signal assigned to the cyclopropyl proton H-7 occurred as a very fine doublet of doublets at 3.44δ due to small couplings to H-5 and H-8. This was verified by a decoupling experiment in which irradiation of H-7 caused H-5 to collapse from a fine doublet to a singlet, and H-8 to collapse from a doublet of doublets to a doublet.

Irradiation of H-8 at 5.7δ caused H-7 to sharpen to a fine

doublet and the methyl group at C-9 to collapse from a doublet to a singlet. The C-10 methyl group at 1.63δ was not coupled, as expected.

An n.O.e. difference spectrum provided evidence supporting the configuration of (6.4) in which the sulphur atom occupied the position above the plane of the β-lactam. This was shown by irradiating the 2β-methyl group of the penicillin at 1.58δ, giving an n.O.e. on H-7 only. Also, irradiating the C-9 methyl gave an n.O.e. on H-5, confirming that the methyl groups lie below the plane of the β-lactam, and indicating that the C-9 methyl group is very close to H-5 in space, as depicted in (6.4). No n.O.e. on H-5 on irradiation of the C-10 methyl confirmed this.

The cyclopropane adduct was produced in a very low yield, which was as predicted on account of steric hindrance by the methyl groups. It is probable that the absence of (6.5) and (6.6) was due to destabilization of the intermediate by the electron-releasing methyl groups (Scheme 1).

6.3 The Reactions of p-Nitrobenzyl 6-diazopenicillanate with Pyrroles: Results and Discussion

The reactions of diazoesters with pyrroles have been less thoroughly investigated in the literature than the corresponding reactions with furans and thiophenes. In general, however, the 2-position of the pyrrole tends to be the preferred site of attack by electrophiles.

The reaction between p-nitrobenzyl 6-diazopenicillanate and pyrrole was initially conducted at room temperature in the

presence of copper acetylacetonate and rhodium acetate catalysts. The reactions proceeded extremely rapidly to yield complex mixtures of reaction products. Several chromatographic purifications afforded no pyrrole-substituted penicillins. Repeating the reactions at -35°C gave the same result.

Similarly, p-nitrobenzyl 6-diazopenicillanate reacted with both N-methylpyrrole and N-phenylpyrrole to afford large numbers of unidentifiable products which were unstable to chromatography and consequently proved extremely difficult to separate.

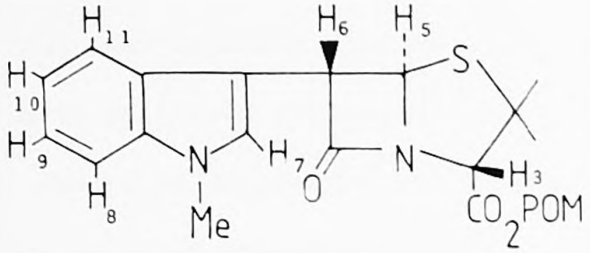
6.4 The Reaction of Pivoyloxymethyl 6-diazopenicillanate with N-Methylindole: Results and Discussion

The absence of substituted penicillins from the complex product mixtures of the reactions between 6-diazopenicillanates and pyrroles suggested that the pyrroles were too reactive to be of any synthetic value.

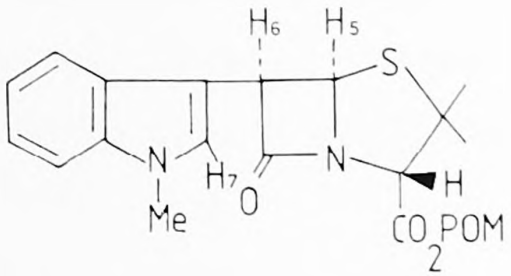
Indoles, however, are generally less reactive than pyrroles due to the fused aromatic ring withdrawing electrons from the pyrrole ring. They should therefore prove sufficiently deactivated to avoid the occurrence of such a large number of side-reactions and afford less complicated product mixtures. In general, indoles react with electrophiles to undergo β-substitution.

The reaction of pivoyloxymethyl 6-diazopenicillanate with N-methylindole was conducted in the presence of rhodium acetate catalyst. The rate of evolution of nitrogen from the solution, which marked the decomposition of the diazo group, was notably slower than in the reactions with pyrroles, and proceeded at a steady rate. Even so, an I.R. spectrum of the reaction mixture

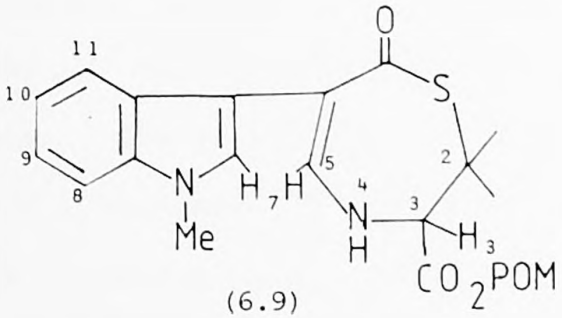
after only 15 minutes indicated that the reaction had reached completion. Separation of the products by chromatography afforded two indole-substituted penicillins (6.7) and (6.8) together with the rearranged product (6.9). Compounds (6.7) and (6.8) were extremely closely-running on silica T.L.C. plates and had to be separated by preparative H.P.L.C. (see Chapter 8).



(6.7)



(6.8)



(6.9)

The yields were difficult to assess due to partial loss of the isomers (6.7) and (6.8) during H.P.L.C. peak shaving, but amounted to approximately 33% in total, in the ratio 1:1:1. The products were identified on the basis of their ^{1}H n.m.r. spectra.

In (6.7) and (6.8), substitution was shown to have occurred at the β-position in the indole by the loss of the n.m.r. signal for the proton at that position. The spectrum of (6.7) showed a pair of doublets for H_5 and H_6 with a coupling constant of 1.5Hz, characteristic of trans coupling and signifying α-substitution at C-6. Similarly, in (6.8), H_5 and H_6 both appeared as doublets, but in this case the coupling constant was 4Hz, indicating cis protons and therefore 6β-substitution.

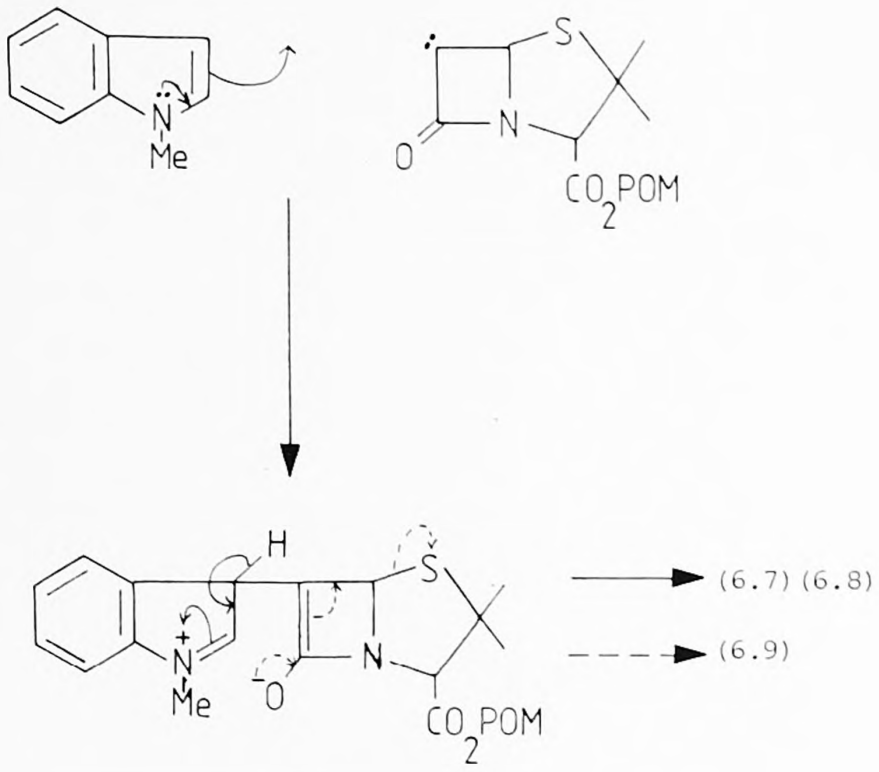
The rearrangement product (6.9) was assigned by its characteristic splitting pattern in its ^1H n.m.r. spectrum. Coupling of H_3 and H_5 to the proton on the nitrogen atom resulted in a doublet at 4.52δ corresponding to H_3 and a low field doublet at 7.09δ corresponding to H_5. The N-H proton was an ill-defined multiplet occurring at 5.80δ, which, on irradiation, caused the collapse of the H_3 and H_5 doublets to two individual singlets. As with (6.7) and (6.8), the disappearance of the proton at 6.45δ on the pyrrole ring indicated β-substitution.

Further evidence for the thiazepine (6.9) was obtained from its I.R. spectrum, which possessed no carbonyl absorption at 1780 cm^{-1} and therefore confirmed the rearrangement of the β-lactam. The new thiolactone carbonyl stretch appeared at 1735 cm^{-1}, alongside the stretch at 1750 cm^{-1} of the carbonyl of the protecting group. A second new band at 1625 cm^{-1}, characteristic of an unsaturated thiolactone, was also present.

Both elemental analysis and a molecular ion at 444 in the mass spectrum were in agreement with the proposed structure.

It is likely that these products are derived from direct

electrophilic substitution of the pyrrole ring by the carbenoid (Scheme 3), as the dipolar intermediate so formed would be stabilized by electron donation from the nitrogen into the ring, and electron withdrawal towards the oxygen from the C-6 carbanion.



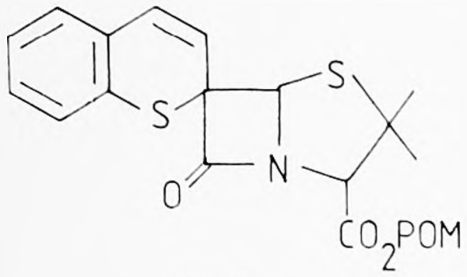
Scheme 3

The same intermediate which gives rise to (6.7) and (6.8) can undergo an alternative reaction in which the C-6 anion forces expulsion of the thiolate anion, leading to rearrangement to the thiazepine (6.9).

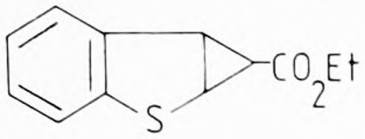
6.5 The Reaction of p-Nitrobenzyl 6-diazopenicillanate with thionaphthene: Results and Discussion

The formation of ring-expanded products in the reaction of 6-diazopenicillanate with thiophene and benzofuran prompted

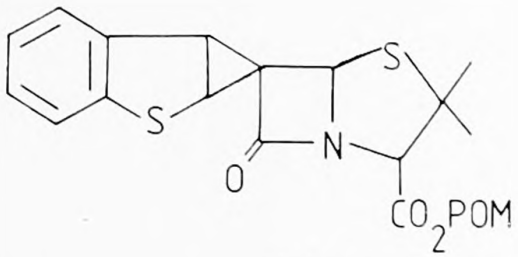
the examination of the analogous reaction with thionaphthene, in the hope of producing the corresponding 2H-thiopyran (6.12). The reaction of ethyl diazoacetate with thionaphthene has been previously described by Badger et al.[92] to afford the cyclopropane adduct (6.13). The benzothiopyran (6.12) and the cyclopropane (6.14) were therefore the anticipated products.



(6.12)



(6.13)



(6.14)

Pivoyloxymethyl 6-diazopenicillanate was decomposed in the presence of a two-fold excess of thionaphthene at room temperature using rhodium acetate catalysis. On completion, the solvent was removed and the products separated by chromatography affording no substituted penicillins. Repeating the reaction at lower temperatures gave the same results. The presence of the aromatic ring could be responsible for causing deactivation of the thiophene, whereby preventing its reaction with the electrophilic penicillanate.

6.6. The Reaction of Pivoyloxymethyl 6-diazopenicillanate with Pyridine: Results and Discussion

Whereas pyrroles react with electrophiles to undergo α-substitution, pyridine requires severe conditions for electrophilic substitution to occur, owing to the instability of the intermediates involved, caused by electron withdrawal by the nitrogen atom (Figures 1,2).

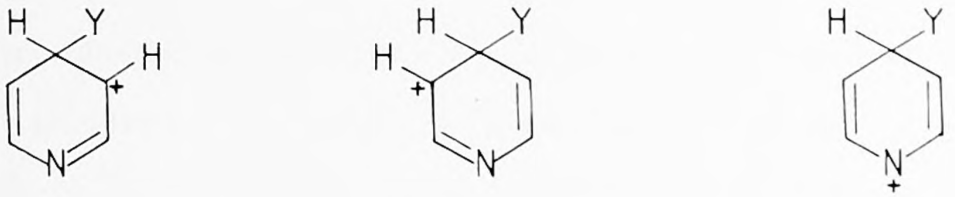


Figure 1 : Electrophilic Substitution at the 4-position

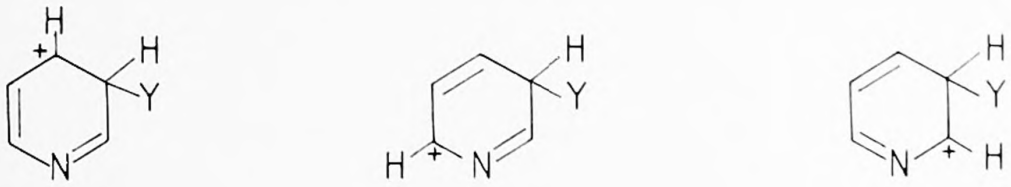
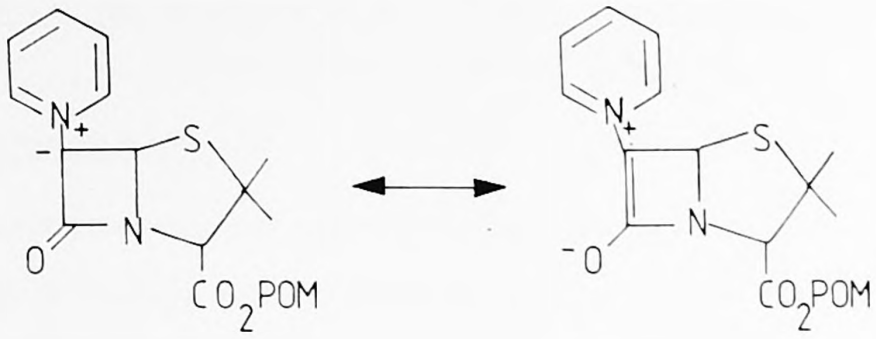


Figure 2 : Electrophilic Substitution at the 3-position

The reaction between pyridine and 6-diazopenicillanate would therefore not result in substitution. However, the ability of the nitrogen to donate electrons, and the ability of the carbonyl group α to C-6 to stabilize a negative charge may allow the formation of the ylid (6.15).

Pivoyloxymethyl 6-diazopenicillanate was subsequently decomposed in a large excess of pyridine in an attempt to obtain evidence for the formation of (6.15).



(6.15)

Copper bronze was employed as catalyst to avoid complexing to the pyridine. On completion of the reaction, chromatographic work-up of the large number of components afforded no identifiable products.

Section 2

Chapter 7: The Reactions of 6-Diazopenicillanates with Miscellaneous Unsaturated Systems

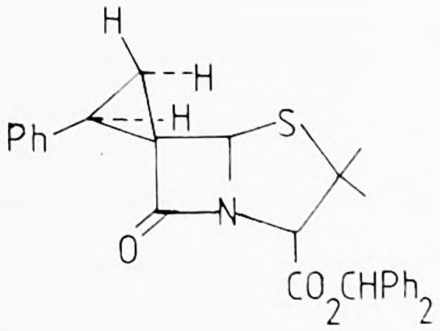
7.1 Introduction

Since carbenes and carbenoids are electrophilic reagents, they react readily with unsaturated systems such as alkenes and alkynes to form the corresponding cyclopropanes and cyclopropenes[76a]. The presence of alkyl substituents increases the nucleophilic character of the unsaturated system, as does the presence of a heteroatom adjacent to the double or triple bond. Thus alkenes and alkynes bearing alkyl substituents, together with enol ethers, enamines and vinylicesters make excellent carbene traps. Similarly, the stability of carbenes is somewhat dependent on the substituents, as demonstrated by the relative selectivities of the dihalogeno-carbenes, in which $:CF_2 > :CCl_2 > :CBr_2$. The greater stability of $:CF_2$ is due to its increased electron delocalization. Steric factors also govern the selectivity of carbenes for different olefins and acetylenes. For example, the effect of successive α-methylation on the addition of dichlorocarbene to 1-butene is illustrated by the following relative rates: $EtCH=CH_2$, 1; $^{i}PrCH=CH_2$, 0.43; $^{t}BuCH=CH_2$, 0.029.

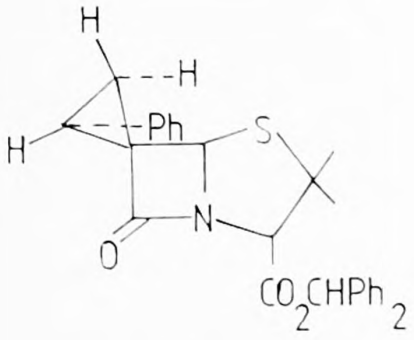
The addition of carbenes and carbenoids to unsaturated systems is a versatile method for the synthesis of cyclopropanes and cyclopropenes, and consequently, a large number of these compounds has been prepared in this manner.

The decomposition of benzhydryl 6-diazopenicillanate by $Cu(acac)_2$ catalysis in the presence of styrene and cyclohexene to afford the

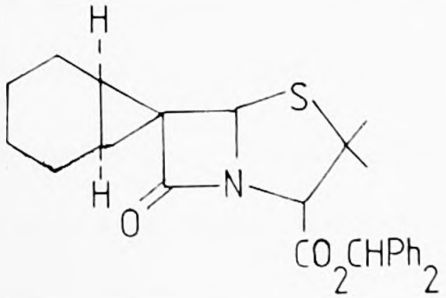
corresponding cyclopropanes (7.1) and (7.2) has recently been described by Chan[165]. The isomers of (7.2) were directly analogous to cyclopropanes previously synthesized by Moser[83] by the catalysed decomposition of ethyl diazoacetate in cyclohexene, affording the exo and endo cyclopropanes (7.3) together with a trace amount of the insertion product (7.4). Similarly, the reaction of ethyl diazoacetate with styrene, reported by both Moser[83] and Paulissen[87], gave rise to the corresponding isomeric cyclopropanes (7.5).



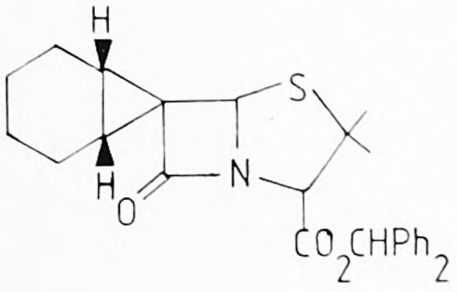
(7.1a)



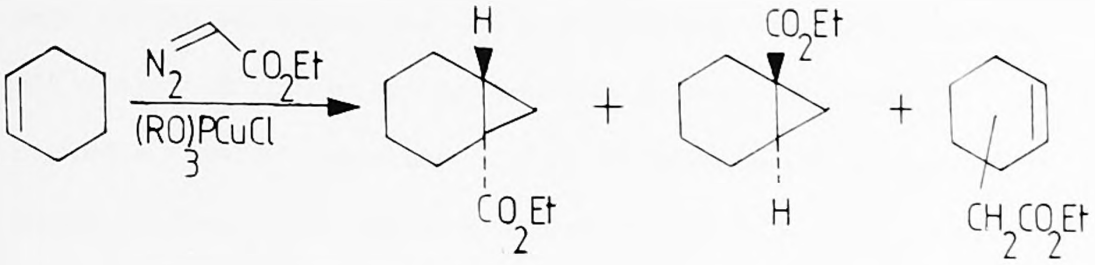
(7.1b)



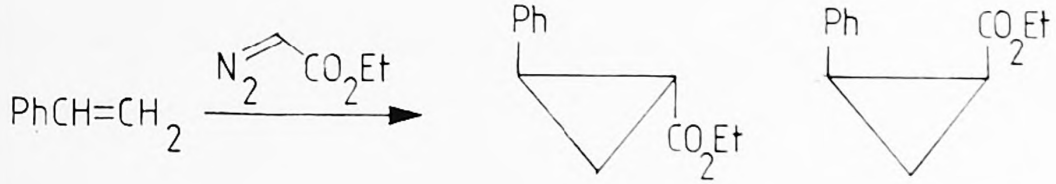
(7.2a)



(7.2b)



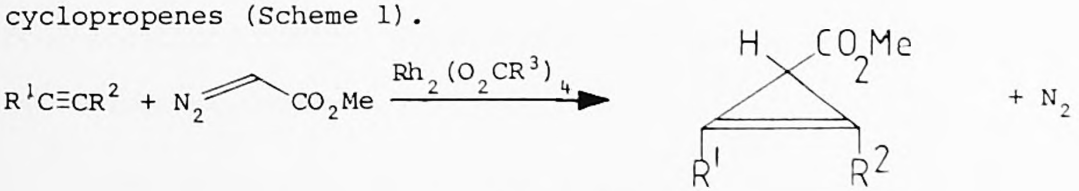
(7.3a) (7.3b) (7.4)



(7.5a) (7.5b)

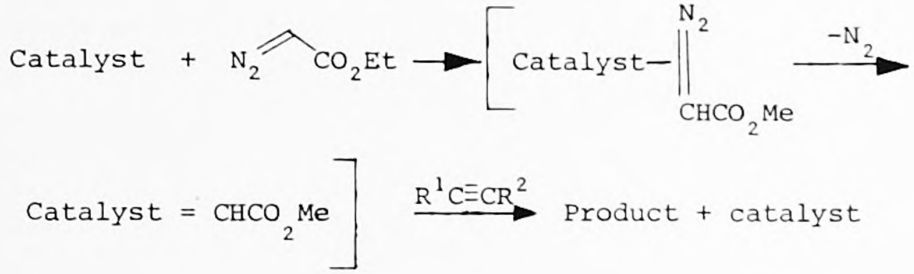
The reaction between 6-diazopenicillanate and ethyl vinyl ether proceeded in the presence of $Cu(acac)_2$, to afford the cyclopropanated penicillanates. However, with methyl acrylate, no loss of nitrogen occurred, thus forming the 5-membered spiropyrazoline structures discussed in Chapter 1[68]. In comparison, Sheehan's report on the reaction of 6-diazopenicillanate with dipolarophiles discussed the sole formation of pyrazolines[50].

In the presence of rhodium carboxylate, acetylenes were observed to react with methyl diazoacetate, affording substituted cyclopropenes (Scheme 1).



Scheme 1

Although steric hindrance of the substituents on the triple bond of the acetylene did not significantly influence the overall yields of the cyclopropenes, the presence of polar groups caused a drastic reduction. With regards to the mechanism, it seems unlikely that the reaction proceeded with simultaneous coordination of starting materials to the catalyst, due to the availability of only one vacant coordination site. More likely is an intermediate such as that depicted in Scheme 2, in which only the diazo compound is bound to the catalyst at the intermediate stage.



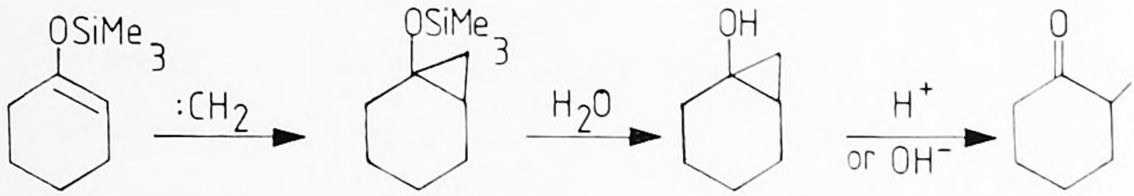
Scheme 2

7.2 The Reaction of p-Nitrobenzyl 6-diazopenicillanate with 1-Cyclohexenyloxytrimethylsilane : Results and Discussion

The reactions outlined above indicate that spirocyclopropyl penicillanates can be obtained by the metal-catalysed reactions of olefins with 6-diazopenicillanates. It was hoped to extend the synthetic utility of this type of reaction by the use of a functionalized olefin which could subsequently be transformed into other structures.

Cyclopropanols, which have a versatile chemistry involving ring opening[167], appeared attractive targets. In principle, the

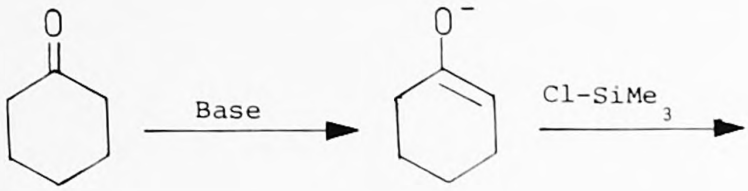
ethoxy-cyclopropanes (Chapter 1, 148a-d) reported by Campbell et al.[68] might be regarded as cyclopropanol precursors, but in practice, the cleavage of the ethyl ether function without destruction of the β-lactam ring would be difficult. However, work in the literature indicates that trimethylsilyl enol ethers are also readily cyclopropanated and are easily cleaved to cyclopropanols, which can then be ring-opened to α-substituted ketones (e.g. Scheme 3).



(7.6)

Scheme 3

These considerations led us to examine the cyclopropanation of trimethylsilyloxy cyclohexene (7.6) with a 6-diazopenicillanate ester. The silyl enol ether (7.6) was prepared by adapting the method described by House et al.[168]. Cyclohexanone and chlorotrimethylsilane were refluxed for 11 hours with triethylamine, using a ratio of reagents of 5:6:12 respectively. Distillation of the crude products using a Vigreux column afforded the required cyclohexene (7.6) as a pure, colourless liquid (Scheme 4).

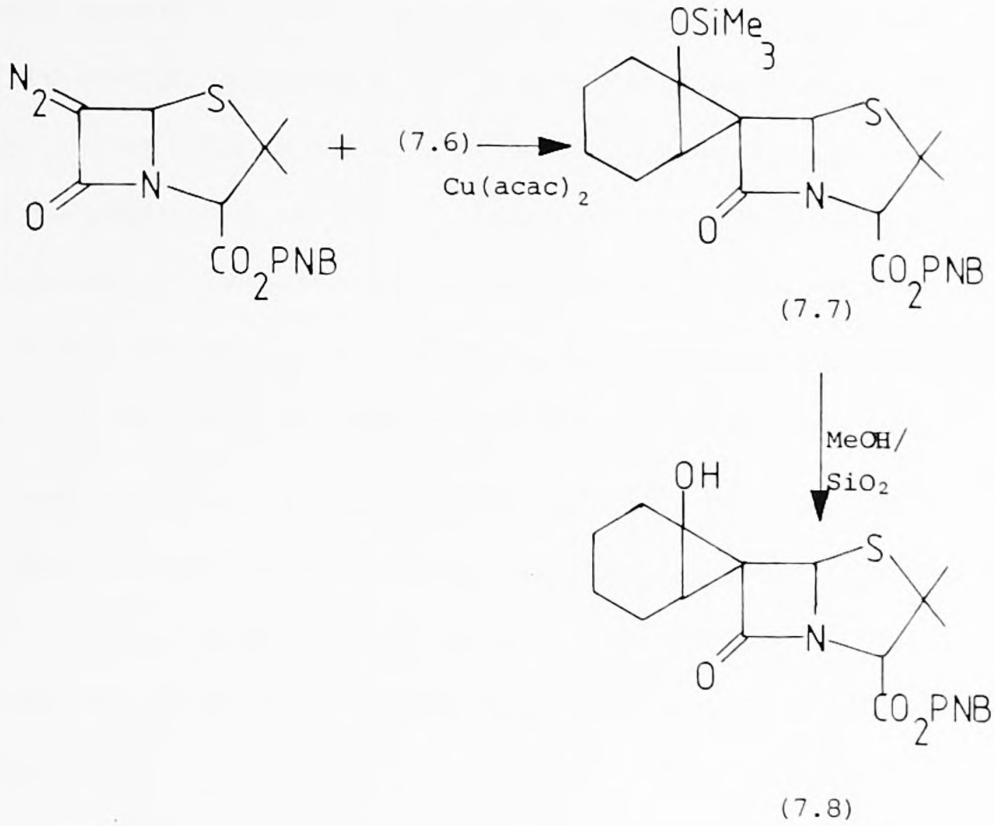


(7.6)

Scheme 4

Subsequently, p-nitrobenzyl 6-diazopenicillanate was decomposed in the presence of the silyl enol ether (7.6) by means of 5% $Cu(acac)_2$ catalyst at $0^{o}C$. Total decomposition of the diazo group was shown to have occurred within 4.5 hours by loss of the characteristic stretch in the I.R. spectrum at 2090 cm^{-1}, affording structure (7.7).

The addition of a suspension of silica in methanol to the product mixture in dichloromethane, followed by stirring of the solution for 2 hours, resulted in replacement of the trimethylsilyloxy group in (7.7) by the hydroxy group (7.8, Scheme 5). Several chromatographic separations were necessary for the isolation of compound (7.8) in poor yield.



Scheme 5

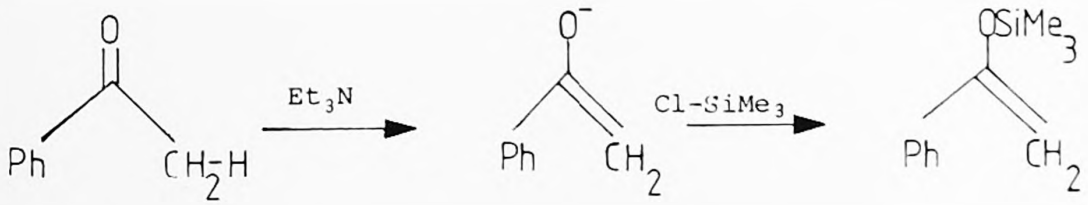
The exchange of the trimethylsilyloxy group for the alcohol was indicated by both loss of the strong trimethylsilyl signal at 0.12δ in the n.m.r. spectrum and the corresponding appearance of the fairly broad alcohol stretch at 3400 cm^{-1} in the I.R. spectrum. There was substantial evidence for the formation of structure (7.8) from its spectra. For instance, the presence of the OH stretch at 3,400 cm^{-1}, the aliphatic C-H at 2980 cm^{-1}, the β-lactam carbonyl at 1780 cm^{-1}, and the ester carbonyl at 1750 cm^{-1} in the I.R. spectrum were all consistent with (7.8) being the structure of the isolated material. In addition, the n.m.r. spectrum showed a singlet for the C-5 proton at 5.92δ, indicating disubstitution at the 6-position, with one substituent

being electron withdrawing. The presence of the cyclohexane protons between 0.70 and 1.94δ, and the appearance of an ill-defined doublet of doublets at 0.84δ corresponding to a cyclopropyl proton with an electron-withdrawing group on the α-carbon were all supportive of (7.8). Owing to the inadequate quantity of material, it was not possible to obtain a sample of sufficient purity for microanalysis. However, a mass spectrum produced a peak on the position required for the molecular ion of (7.8).

The poor yield of the required cyclopropane (7.8), which was 2% after repeated chromatographic separations, meant that the reaction was of little synthetic use, and consequently, no further reactions on the cyclopropane to give ring opening were attempted.

7.3 The Reaction of p-Nitrobenzyl 6-diazopenicillanate with 1-Phenyltrimethylsilyloxyethene (7.9): Results and Discussion

As in the previous reaction, the trimethylsilyloxyethene (7.9) was prepared according to the method of House and co-workers[168], in which acetophenone was refluxed with chlorotrimethylsilane and triethylamine, employing DMF as solvent (Scheme 6).

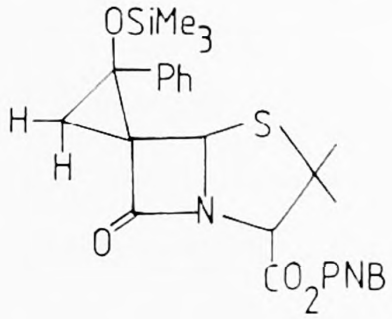


(7.9)

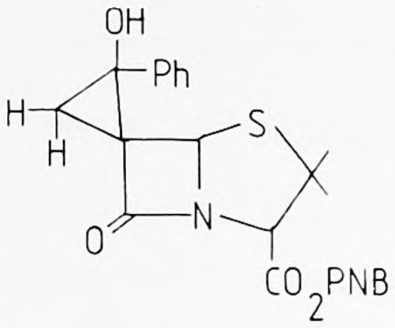
Scheme 6

However, the synthesis of the acetophenone derivative (7.9) required a much longer refluxing period than that of the analogous cyclohexanone derivative (7.6). Following extensive washing of the reaction mixture with sodium bicarbonate solution, ice-cold 1.5M hydrochloric acid and further sodium bicarbonate solution, an orange, impure material was obtained, containing a mixture of unreacted acetophenone and the trimethylsilyloxyethene (7.9). Several distillations through a Vigreux column were necessary in order to obtain a sample of silyl enol ether free from contamination by starting material, due to the small separation of boiling points of the two liquids under reduced pressure. Once this was achieved, 6-diazopenicillanate was catalytically decomposed in a solution of the 1-phenyltrimethylsilyloxyethene (7.9) in dichloromethane. However, in contrast to the previously described reaction with 1-cyclohexenyloxytrimethylsilane (7.6), none of the analogous products (7.10) (7.11) or (7.12) were formed. In fact, the products of the reaction were a complex mixture from which no identifiable compounds could be isolated.

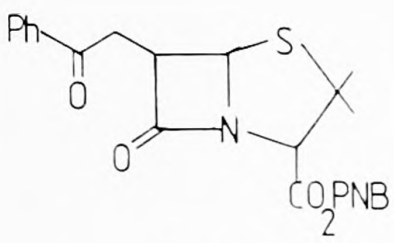
Steric interactions involving the bulky trimethylsilyloxy and phenyl groups during the formation of all three products was the most likely reason for the failure of the reaction.



(7.10)



(7.11)

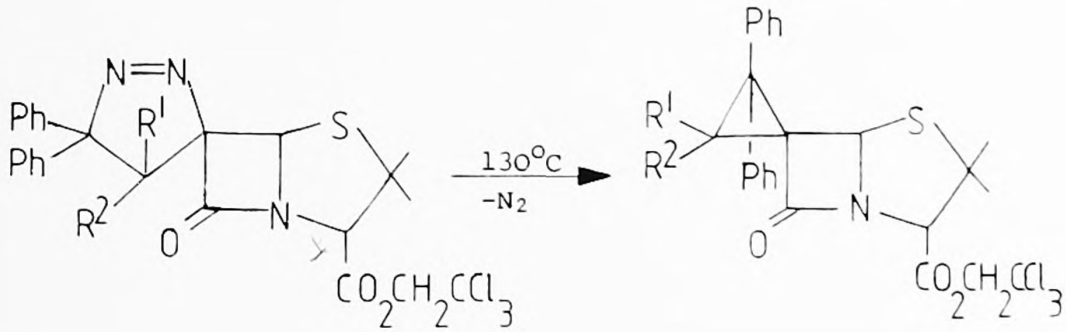


(7.12)

7.4 Formation of the Spiropyrazolines (7.17, 7.18) and the Subsequent Action of Heat

7.4.1 Introduction

The Δ^1-pyrazolines formed by Sheehan et al.(7.13, 7.14)[50] were seen to undergo ready evolution of nitrogen on pyrolysis to produce the corresponding cyclopropanes (7.15, 7.16) (Scheme 7).



(7.13) $R^1 = CO_2CH_2Ph$, $R^2 = H$ (7.15) $R^1 = CO_2CH_2Ph$, $R^2 = H$

(7.14) $R^1 = H$, $R^2 = CO_2CH_2Ph$ (7.16) $R^1 = H$, $R^2 = CO_2CH_2Ph$

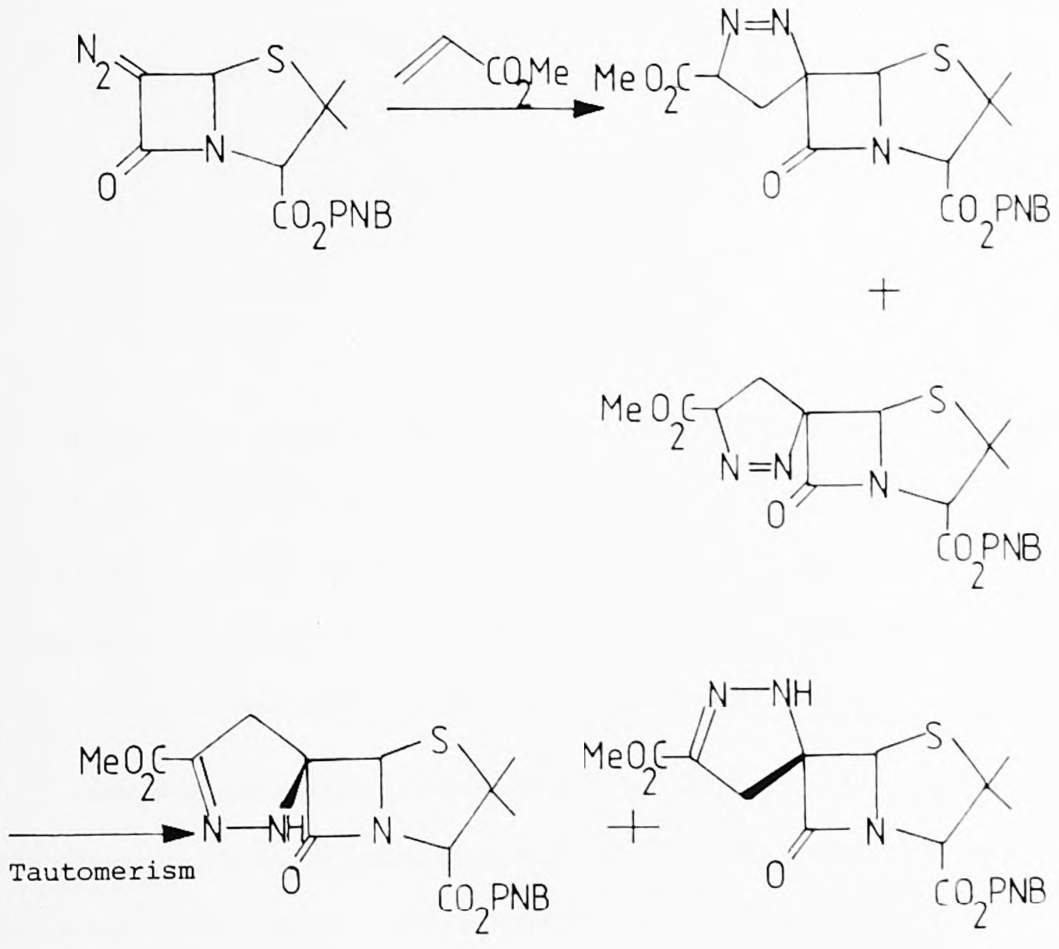
Scheme 7

It would therefore be of interest to examine the analogous Δ^2-pyrazoline prepared by Campbell et al.[68] to observe whether this could also extrude is nitrogen, on heating, to afford the

corresponding cyclopropane. The method employed by Campbell for the preparation of pyrazolines was adopted.

7.4.2 Results and Discussion

p-Nitrobenzyl 6-diazopenicillanate was stirred in dichloromethane with methyl acrylate for 22 hours in the absence of catalyst. Although Campbell had reported formation of one isomer only, (7.17), in 75% yield, in this instance there was strong evidence in support of a second isomer (7.18) produced in the ratio 5.5:1 (7.17:7.18) in a total yield of 71% (Scheme 8).

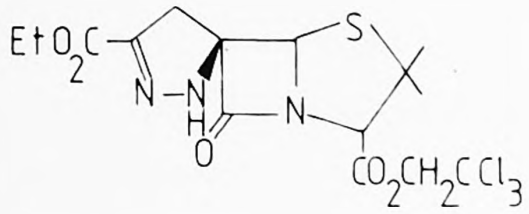


(7.17) (7.18)

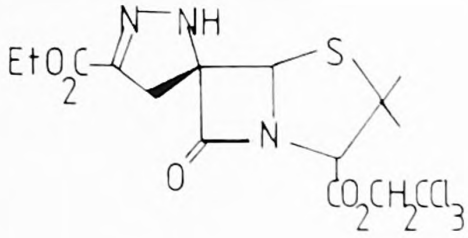
Scheme 8

It was unlikely that the observed difference in products was caused by the substitution of Campbell's benzyl protecting group for the p-nitrobenzyl group.

The preferred mode of addition was, as expected, from the sterically less hindered α-face. These results are consistent with those of Sheehan in which two isomers (7.19) and (7.20) were produced in the reaction of 6-diazopenicillanate with ethyl acrylate, with (7.19) again being the major isomer, forming in the ratio 6:1 (7.19:7.20).



(7.19)



(7.20)

As in Sheehan's report, the major dissimilarity between the spectra of the two isomers was a divergence in the n.m.r. signals of the gem dimethyl groups of the minor isomer. There was also a simultaneous convergence of the doublet of doublets representing the $-CH_2$ group in the pyrazoline ring of the same isomer.

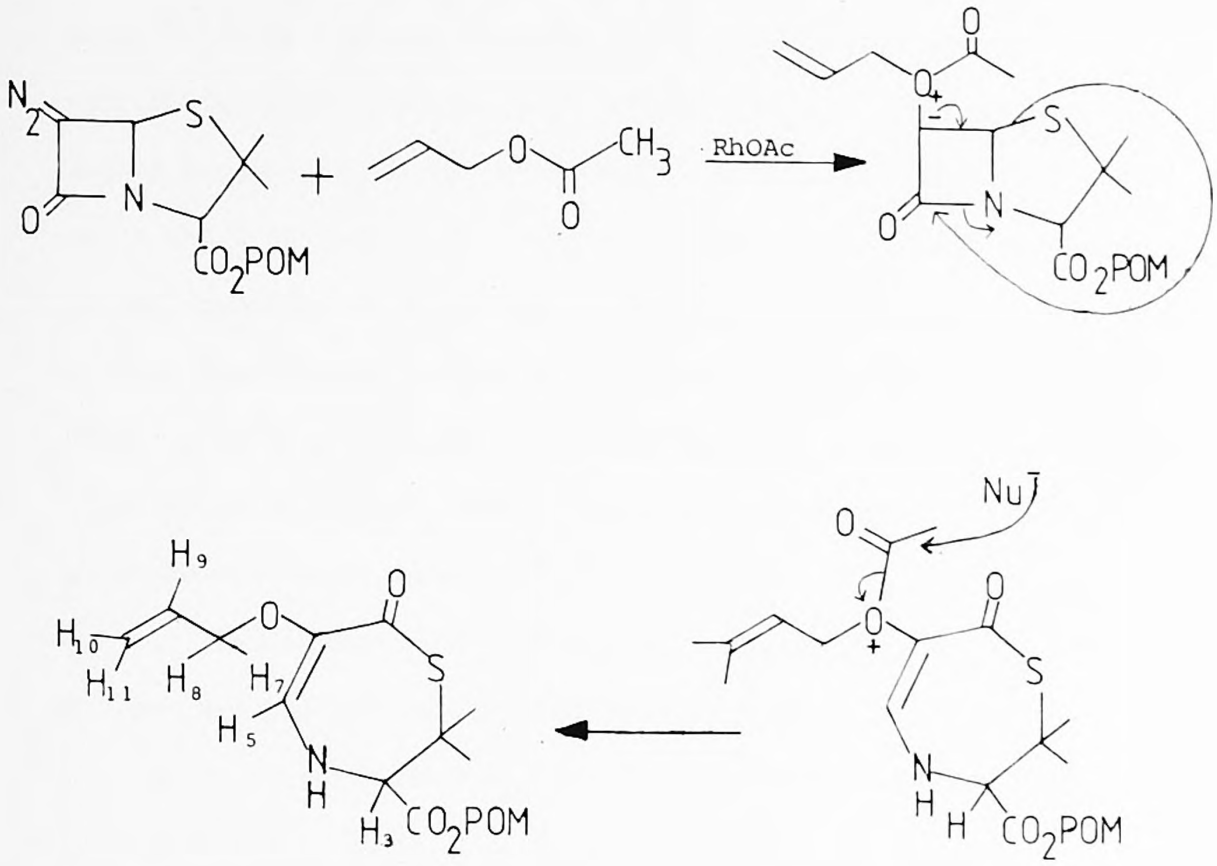
Heating the major isomer (7.17) to 120°C caused no loss of nitrogen. Stronger heating eventually led to breakdown of the β-lactam. Evidently, re-tautomerisation of the Δ^2- to Δ^1-pyrazoline and nitrogen loss is not a practical possibility for the penicillanate derivative.

7.5 The Reaction of Pivoyloxymethyl 6-diazopenicillanate with Allyl acetate: Results and Discussion.

The production of oxonium ylids during the reactions of 6-diazopenicillanates with both furans and alcohols has been shown to be a strong possibility[75,169]. It is therefore likely that reactions occurring between 6-diazopenicillanates and compounds possessing a carbonyl function could similarly proceed with initial formation of an ylid by donation of the lone pair of electrons from the oxygen of the carbonyl onto the electron-deficient carbenoid at C-6 of the penicillin, following decomposition of the diazo group.

This likelihood was investigated by means of the reaction of pivoyloxymethyl 6-diazopenicillanate with allyl acetate. While there were other possible modes of reaction of the allyl acetate with the carbenoid, this compound was selected with the aim of forming a single C-C bond at C-6 as in (7.22a) via ylid formation, followed by an electrocyclic rearrangement (Scheme 10). Rhodium acetate was employed as catalyst and a large excess of allyl acetate provided both solvent and reagent. The reaction was monitored by I.R.. When complete decomposition of the diazo group had occurred, the products were isolated by preparative T.L.C., affording the rearrangement product (7.21) in 13% yield. No substituted penicillins were isolated. Presumably, formation of (7.21) had resulted from attack at the carbenoid by the oxygen atom of the allyloxy functionality, giving rise to the C-6 anion. This, as seen in several previous examples, had caused ring opening followed by rearrangement to the familiar thiazepine

structure (Scheme 9).



Scheme 9

Matlin and Chan[75] observed the analogous allyloxy thiazepine as the major product of the reaction between benzhydryl 6-diazo-penicillanate and allyl alcohol. Confirmation of the structure of (7.21) was obtained by means of a D_2O exchange experiment which resulted in the complete disappearance of the N-H multiplet and collapse of the H-5 and H-3 doublets to singlets.

The recent report by Anciaux et al.[170] claimed rhodium trifluoroacetate to be a more efficient catalyst than rhodium acetate for carbenoid reactions. The reaction was therefore repeated in the presence of rhodium trifluoroacetate in a further attempt

to form the carbonyl ylid. Preparative T.L.C. of the product mixture again gave (7.21), in 10% yield. However, the major product of the reaction, formed in 13% yield, was a doubly-substituted penicillanate whose 360MHz ^{1}H n.m.r. spectrum showed singlets at δ1.48 and 1.55 (2α- and 2β- methyls), 4.55 (H-3) and 5.67 (H-5). The $-CH_2$ of the protecting group appeared as two doublets, δ5.72 and 5.83. For the substituents at C-6, signals were observed at δ1.95(s,3H,$COCH_3$), 1.85(dd,H-7_A,J=14Hz, 6Hz), 2.13(dd,H-7_B,J=14Hz,10Hz), 4.27(dd,H-9_A,J=12Hz,4Hz), 4.65 (dd,H-9_B,J=12Hz,2.7Hz), and 5.00(m,H-8). Decoupling experiments gave the following results:

a) Irradiation of H-8 caused the doublets of doublets for H-7 and H-9 protons to collapse to doublets.

b) Irradiation of H-9_A caused simplification of the H-8 multiplet and collapse of H-9_B to a doublet.

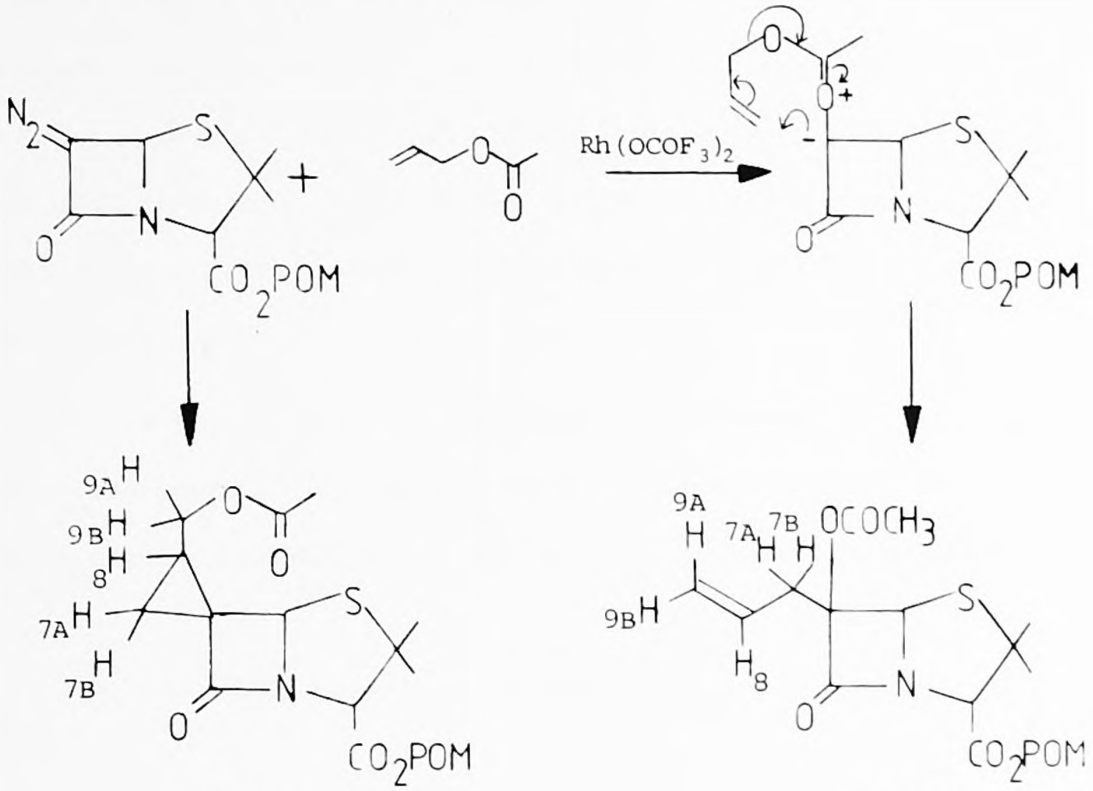
c) Irradiation of H-9_B similarly simplified H-8 and reduced H-9_A to a doublet.

d) Irradiation of each of H-7_A and H-7_B caused the other to collapse to a doublet and also caused H-8 to simplify.

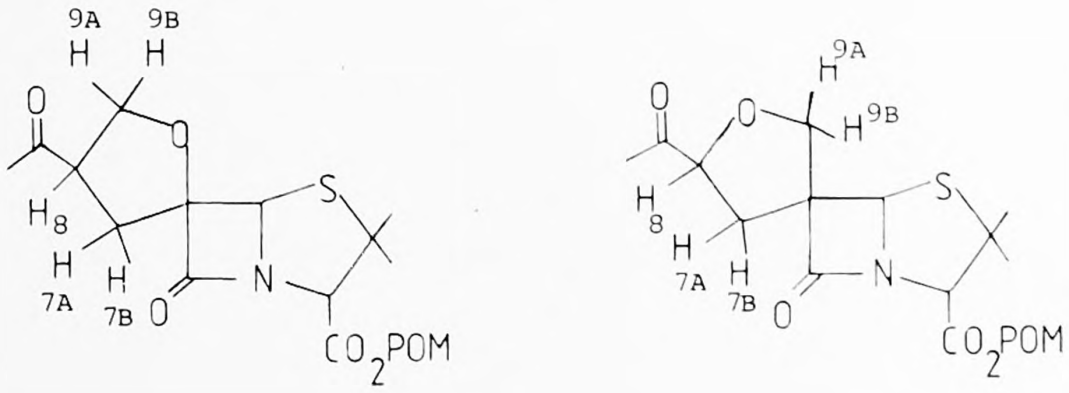
The mass spectrum showed m/e 413.1442 (M^+, $C_{19}H_{27}NO_7S$) and the I.R. showed a shoulder below 1740cm^{-1} and a stretch at 3060cm^{-1}.

Several structures were considered for this product. The 6-allyl-6-acetoxypenicillanate (7.22a) is untenable because of the large H-9_A to H-9_B coupling observed. The cyclopropane (7.22b) was ruled out because of the observed couplings and the low field positions of H-7 and H-8 protons. The 3-acetyl-tetrahydrofuran (7.22c) would not show a sufficiently low field chemical shift

for H-8. The isomeric 2-acetyl-tetrahydrofuran (7.22d) appears to provide the best fit to the n.m.r. data but it is not easy to rationalise the formation of such a structure under the reaction conditions. Further work on this compound will be required in order to clarify its structure.



(7.22b) (7.22a)



(7.22c) (7.22d)

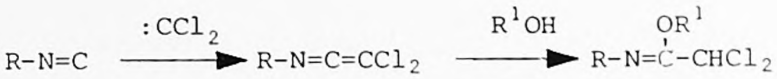
Scheme 10

7.6 The Reaction of Pivoyloxymethyl 6-Diazopenicillanate with ^{t}Butyl Isonitrile

7.6.1 Introduction

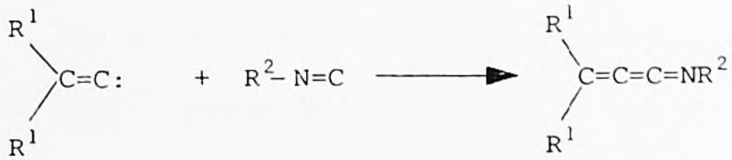
As previously mentioned, carbenes generally react with olefins to produce the corresponding cyclopropanes[76a]. In contrast, carbenes undergo nucleophilic attack by isocyanides to give, by α-addition, N-substituted ketenimines[171]. For example, with dichlorocarbene, isocyanides initially produce the ketenimines (7.23), which rapidly undergo hydrolysis to afford the corresponding imidates (7.24)(Scheme 11).

The analogous reactions of alkylidene carbenes (7.25) with isocyanides were recently reported by Stang and Bjork[172] to afford the heterocumulenes (7.26)in a similar manner (Scheme 12).



(7.23) (7.24)

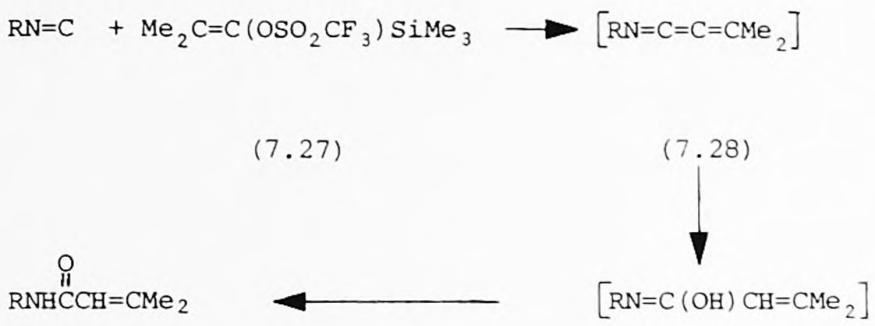
Scheme 11.



(7.25) (7.26)

Scheme 12.

More specifically, ethyl-, phenyl-, and 2-ethyl-5-methylphenyl isocyanides were reacted with the alkylidene carbene (7.25), generated from silylvinyltrifluoromethanesulphonate (7.27) via phase transfer procedures, using stoichiometric amounts of benzyltrioctyl ammonium chloride as the phase transfer agent. The appropriately N-substituted acrylamides (7.29) were the sole products of the reaction, having arisen from the hydrolysis of the alkadienylideneimine intermediate (7.28) (Scheme 13).

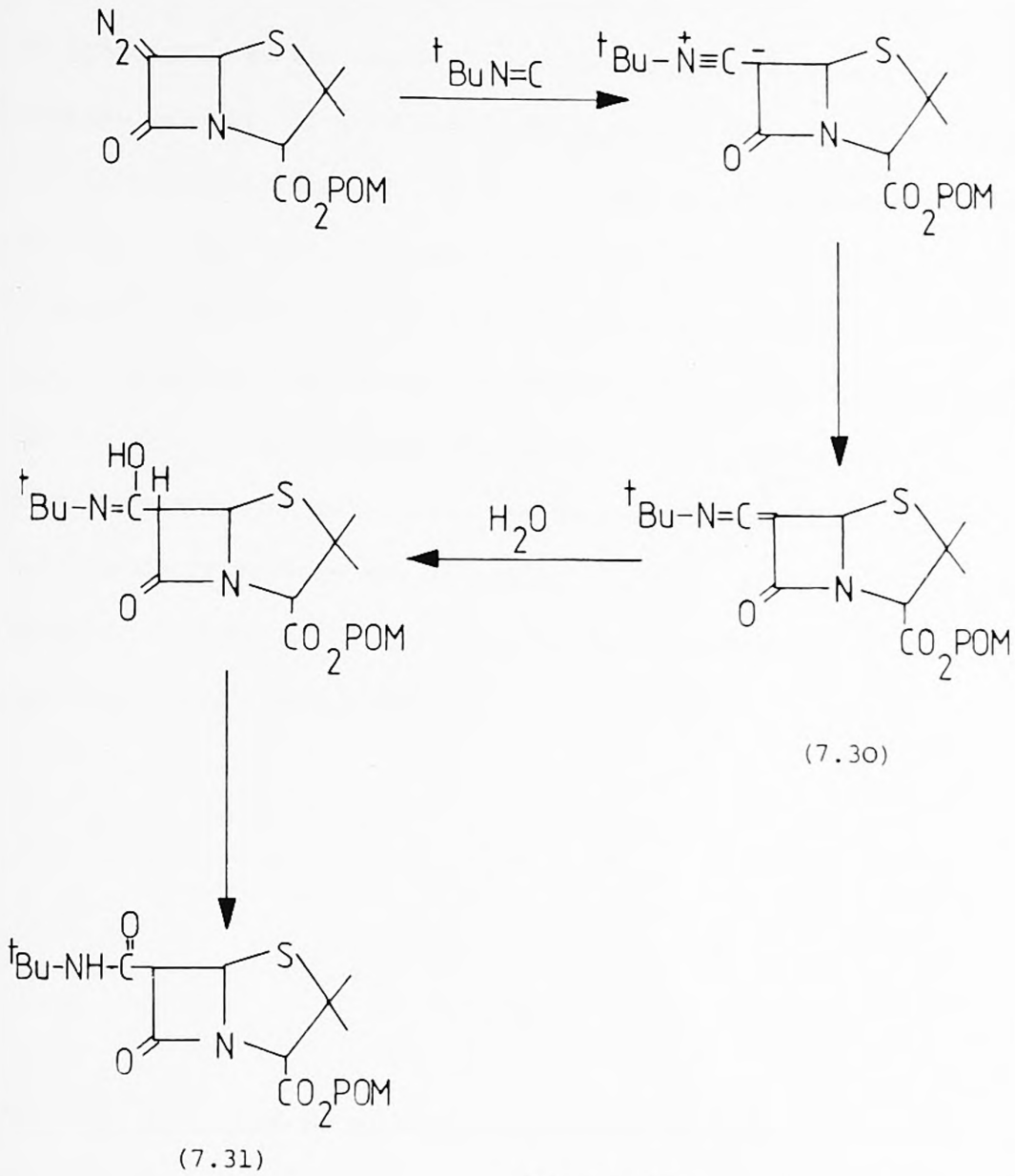


(7.29)

Scheme 13.

7.6.2 Results and Discussion

The reaction between pivoyloxymethyl 6-diazopenicillanate and ^{t}butyl isocyanide was expected to afford the amide (7.31) by hydrolysis of the initially formed ketenimine (7.30) (Scheme 14).

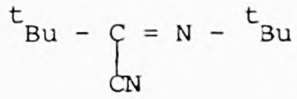


Scheme 14

In theory, reduction of the amide function in (7.31) would provide a convenient route for the synthesis of a versatile intermediate, the further reaction of which could lead to a series of novel substituted penicillins.

6-Diazopenicillanate was stirred in $CDCl_3$ with $Rh_2(OAc)_4$ and two molar equivalents of ^{t}butyl isocyanide at 0°C. The choice of $CDCl_3$ as solvent enabled an n.m.r. spectrum of the

reaction mixture to be run prior to any work-up procedure, in order that formation of the ketenimine (7.30) could be observed, as hydrolysis to the amide (7.31) was expected to occur on contact with silica during chromatography. However, the n.m.r. and subsequently the I.R. spectra showed no identifiable products. Instead, a new band, in addition to the isocyanide stretch at 2140 cm^{-1}, appeared in the I.R. spectrum at 2180 cm^{-1}. The n.m.r. spectrum discounted the possibility of this new band being due to any ketenimine, and therefore it was supposed that it must have appeared as a result of self-condensation of the ^{t}butyl-isocyanide to produce the structure (7.32). Such 'dimers' were isolated by Saegusa[173] from the $BF_3.Et_2O$ catalysed reaction with tertiary alkyl isocyanides.



(7.32)

However, there was no evidence for (7.32) in this case, as n.m.r. showed a symmetric molecule, while a mass spectrum showed only peaks corresponding to the monomer. The dimer (7.32) would not be expected to produce the same monomeric peak in the mass spectrum, and it was therefore discounted as a possibility. One theory for the failure of the reaction was that coordination of the isocyanide to the rhodium acetate catalyst resulted in its inactivation, but the same result was obtained on changing the catalyst to each of copper acetylacetonate, copper butanoate and copper acetate.

Varying the concentration of the catalyst was also shown to give the same result, no substituted penicillins being produced.

Section 2

Chapter 8 The Use of HPLC in the Isolation and Quantitative Analysis of Protected Penicillins and Related Compounds

8.1 Introduction

As in the majority of synthetic organic chemistry projects, chromatographic techniques have been used extensively in examination of the products of the reactions of 6-diazopenicillanates described in the foregoing chapters. However, the most widely used of these techniques, i.e. classical 'open column' chromatography and analytical and preparative thin layer chromatography, often proved inadequate. This was due to three major reasons;

(a) the instability of a large number of the products,

(b) reaction product mixtures were frequently very complex and

(c) these product mixtures often contained very closely related or isomeric compounds which consequently were difficult to separate.

High Performance Liquid Chromatography, H.P.L.C., was used to overcome these problems. The basic system involved pumping of the eluant at high pressure with a regular, pulse-free flow, through a tightly packed bed of very small (usually 5μm, spherical) particles of adsorbent in a stainless steel column. The eluant was monitored, as it emerged from the column, by a modified U.V. spectrophotometer.

The main advantage of H.P.L.C. over the classical liquid chromatographic techniques is its 'efficiency', i.e. much less band-spreading occurs per retention volume. Band-spreading

generally takes place as a result of diffusion, inefficient mass transfer and poor bed packing during liquid chromatography. Of these, diffusion is only important at very low flow rates. Mass transfer of solute molecules from the stationary phase (adsorbent) to the mobile phase (eluant) is greatly enhanced in H.P.L.C. by the use of very small particles. Also, bed packing is much improved as a result of high pressure slurry-packing techniques and very narrow size ranges of often spherical particles.

Because the solutes are eluted in much narrower zones, these zones are easier to separate and thus analysis times can be vastly reduced. Analysis times are also shortened by pumping the eluant through the column at high pressures. Typically, dichloromethane can be pumped through a 250mm x 5mm column of 5μm silica particles at ca. 1000 p.s.i. to give a flow rate of $2ml.min^{-1}$. Coupled with the fact that the whole process takes place in a closed, air-free system, the short analysis time is a significant factor in the prevention of decomposition of labile reaction products. The other principal advantage of the efficiency of the chromatography is that the separation of the various components of a reaction mixture is less dependent on finding a highly selective solvent system and therefore the time taken in method development is minimized.

H.P.L.C. was utilized in both analytical and preparative modes. Analytically, quantification was carried out by use of peak heights or areas recorded from the post-column U.V. detector. The ratio of reaction products to one another could generally be determined by direct comparison of peak areas, with U.V. detection

at 254nm, as this provided a satisfactory absorbance. At this wavelength, the U.V. absorbance of each product would frequently be due entirely to the presence of the protecting group, and would therefore be the same for each component. In other cases, the U.V. absorbances would be almost identical due to the close similarity of the groups introduced at the 6-position of the penicillin molecule.

For absolute quantification of any product, peak areas must be compared with peak areas of a standard solution of a pure sample of that product. Here it was not necessary to combine the use of such standard solutions with an internal standard, since with the use of a valve injector, the exact same volume could be injected each time. Such quantification is invaluable in the study of a reaction under various conditions, since it overcomes the necessity to isolate each reaction product every time.

When the sample load on an analytical H.P.L.C. column is increased, efficiency is lost. However, the scale of the reactions under investigation (usually 100-200 mg) was such that preparative separation of the products was possible on an analytical H.P.L.C. column (250 x 5mm) by use of as high a load as possible while still maintaining base-line separation, and making repeated injections. Although it would have been possible to utilize a larger column, the cost of the quantity of 5µm silica particles necessary for packing would have been prohibitive. Alternatively, a large column packed with 20µm particles could have been used, as carried out elsewhere[165a],

but which would suffer from two major drawbacks. Firstly, the same separations would not have been achieved without the use of an inordinately large column or without resorting to extensive 'peak shaving' or recycling. Secondly, additional method development would have had to be carried out over and above the analytical method development.

The majority of the work described in the literature in the HPLC of penicillins[174] involved the use of the reverse-phase mode, in which the eluant or mobile phase was aqueous, with an organic modifier, and in which the stationary phase was a hydrophobic alkyl-modified silica. Mostly the work has been carried out by biochemists on penicillins in their unprotected form and which have consequently been quite polar. Such polar molecules are especially suited to reverse phase H.P.L.C., which was first developed as a solution to the problem of peak asymmetry in the straight-phase, i.e. polar adsorbent, non-polar eluant. However, the penicillins used here were much less polar than those in the literature examples, and therefore straight-phase HPLC on silica microparticles could be used. This was very important since many of the reaction products of this study were unstable and would have possibly decomposed in the aqueous mobile phases. Also, it is well established[175] that in the separation of very closely related compounds with only minute electrostatic and steric differences, a non-aqueous chromatographic system can be much more highly selective. For these reasons, straight phase HPLC on silica was the method chosen rather than the more commonly used reverse-phase mode.

8.2, The Use of Analytical H.P.L.C. in the Reaction of 6-Diazopenicillanate with 3,4-Dimethylthiophene

On several occasions in which separation of product mixtures was effected by preparative thin layer chromatography, the degree of purity of the individual components was investigated by analytical H.P.L.C. For example, following the reaction between 6-diazopenicillanate and 3,4-dimethylthiophene, preparative thin layer chromatography of the crude products afforded five fractions on elution with dichloromethane/acetonitrile (95:5). The n.m.r. spectrum of fraction 3 indicated the formation of a 1:1 adduct, and subsequent re-examination by analytical H.P.L.C. confirmed the presence of one single pure compound. A variety of mobile phases of gradually decreasing polarity were investigated, all of which showed only one component to be present in the solution. Optimum retention time and peak shape were achieved by elution using a mixture of dichloromethane/hexane/acetonitrile (21:77.5:1.5) (Figure 1).

Figure 1 The investigation of product purity by the use of analytical H.P.L.C.

8.3 Investigation of the Product Ratios of the Reaction between Ethyl Diazoacetate and Furan by means of Analytical HPLC

Analytical HPLC was successfully employed to compare and contrast the products of the reactions of ethyl diazoacetate with furan, in the presenc of rhodium acetate and copper acetylacetonate catalysts respectively. Following completion of each reaction, an injection of a sample of reaction mixture into the HPLC system, with the subsequent comparison of chromatograms, indicated very little difference between the products of the two reactions. Furthermore, as the reactions had been conducted on the same scale, injection of equal volumes of each solution showed comparable quantities of the major product (Figure 2). The tedious work-up procedures of the two reactions were thus avoided by the use of HPLC.

Figure 2a) The reaction of ethyl diazoacetate with furan using rhodium acetate as catalyst

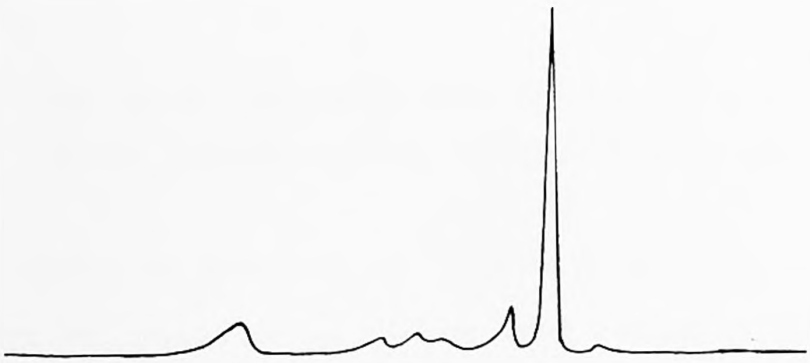


Figure 2b) The reaction of ethyl diazoacetate with furan using copper acetylacetonate as catalyst

8.4 The Examination of the Products of the Reaction of 6-Diazopenicillanate with N-Methylpyrrole by Use of Analytical HPLC.

During the reactions of 6-diazopenicillanate with N-methylpyrrole and the parent pyrrole, repeated attempts to isolate and identify individual components of the reaction mixtures by preparative thin layer chromatography had continually failed, owing to the decomposition of the products of an already complex mixture at some stage in the procedure. Separation of the products was therefore attempted by means of H.P.L.C. An analytical injection of a sample of the crude reaction mixture from the decomposition of 6-diazopenicillanate in N-methylpyrrole,, using a mobile phase of dichloromethane/acetonitrile (95:5), indicated the presence of at least nineteen closely-running components (Figure 3). Attempts were made to collect the two major constituents of the complex mixture by repeated injections onto the analytical column, using the maximum loading possible without loss of separation. However, subsequent re-examination of these two fractions showed that some decomposition had occurred by the appearance of new peaks in the chromatogram. Decomposition, whether on or off the silica column, was occurring too rapidly to allow any isolation of pure materials, even by use of HPLC, and consequently, no positive identifications could be made.

8.5 The Use of Preparative HPLC for Separation of the Products of the Reaction between 6-Diazopenicillanate and N-Methylindole

Again, by increasing the loading of material onto the analytical column to the maximum level without serious loss of base-line separation, semi-preparative separations could be obtained

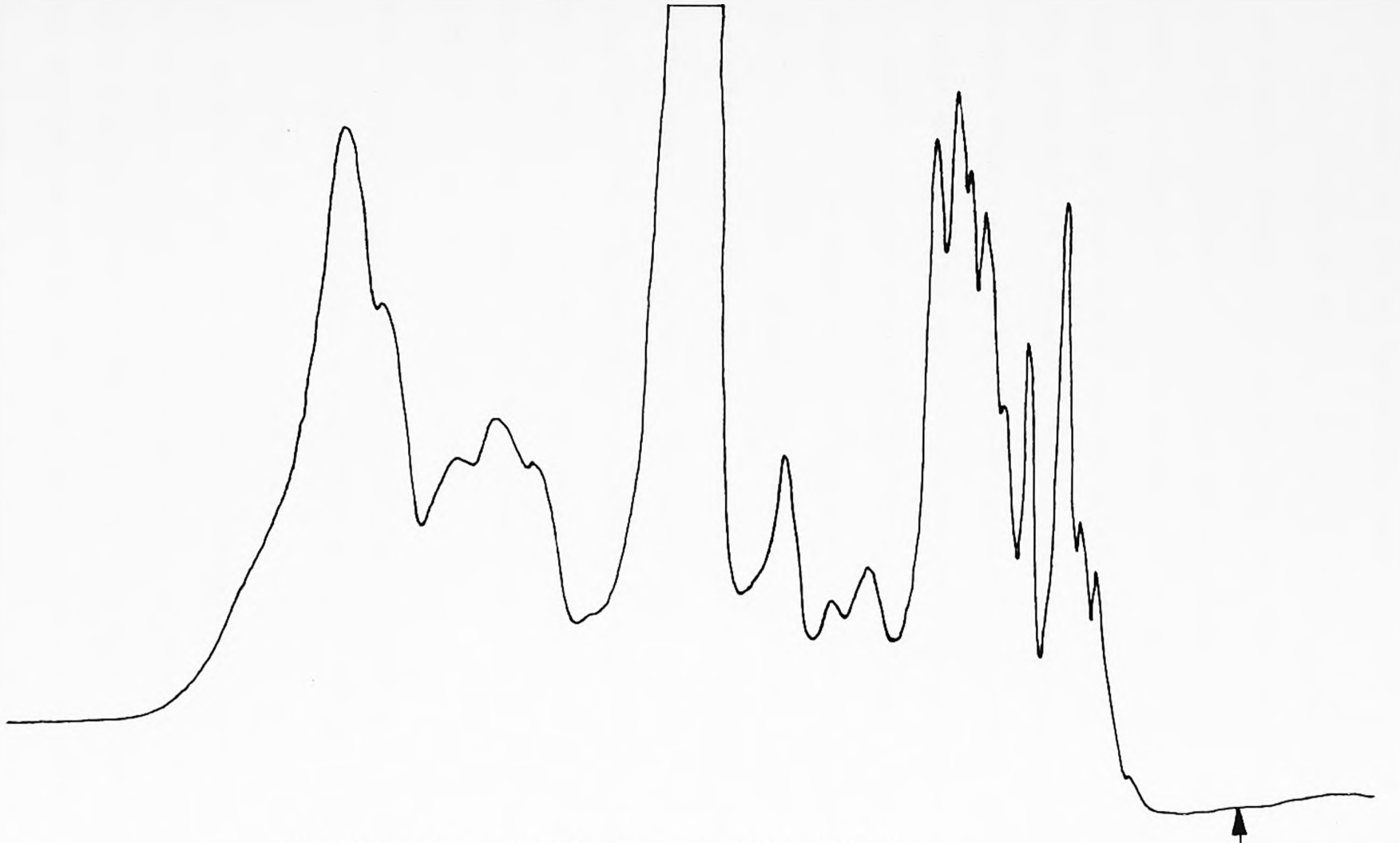


Figure 3: The crude products of the reaction of 6-diazopenicillanate with N-methylpyrrole.

with no need for further method development.

The products of the reaction between 6-diazopenicillanate and N-methyl indole were initially separated into five fractions by means of preparative thin layer chromatography. The n.m.r. spectrum of fraction 2 showed the presence of two closely-related compounds, although only 1 spot was apparent on T.L.C. Analytical HPLC confirmed the presence of two components but separation was minimal (Figure 4). Several solvent systems were examined in an attempt to resolve the two products, and base-line separation was eventually achieved using dichloromethane/hexane/acetonitrile (43:56:1) (Figure 5). As expected, some resolution was lost on increasing the quantity of injected material for the preparative run (Figure 6), resulting in each compound being contaminated with a small quantity of the other. Reinjection of each sample afforded one component completely free from contamination, whereas the second component could not be isolated without the presence of a trace of the first. Identification, however, was not seriously affected by this small amount of contaminant.

8.6. Purification of the Products of the Reaction of 6-Diazopenicillanate with 2,5-Dimethylfuran by Preparative HPLC

Further preparative HPLC was necessary for the separation of the products of the reaction between 6-diazopenicillanate and 2,5-dimethylfuran. Initial separation by preparative thin layer chromatography afforded 6 fractions, only one of which contained any substituted penicillins. An n.m.r. spectrum showed that the fraction was not homogeneous, despite the appearance of only 1 spot on reanalysis by TLC. Analytical HPLC identified five closely-

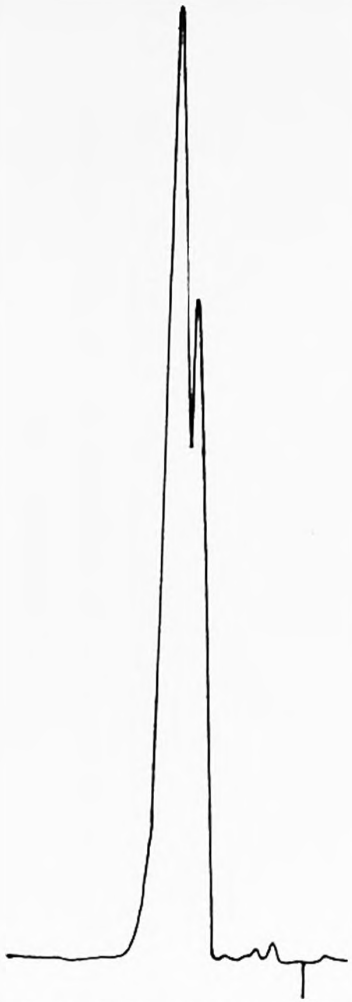


Figure 4: The identification of 2 closely-running components

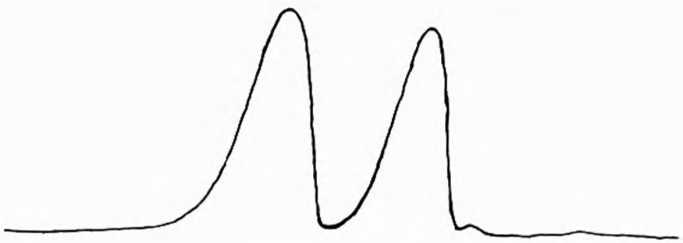


Figure 5: Achievement of satisfactory base-line separation

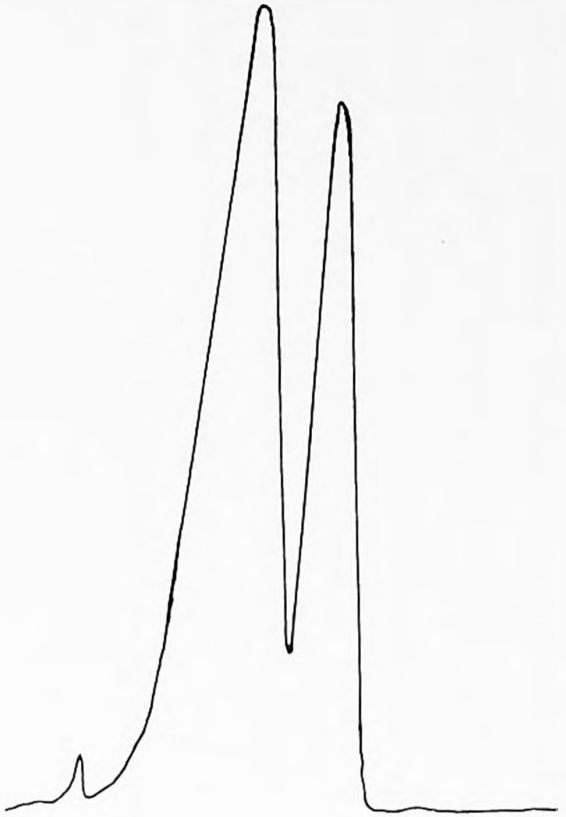


Figure 6: Partial loss of resolution on increasing sample load

running components , (Figure 7), which were isolated from the analytical column on a semi-preparative scale as in the previous cases. A mixture of dichloromethane/acetonitrile (97:3) provided a convenient mobile phase. Compound (5.11), the final yield of which was a mere 2.5%, was isolated sufficiently pure to enable characterization, although partial loss of resolution on increasing the sample load had been incurred.

Figure 7: The identification of 5 closely running components

8.7 Use of Analytical HPLC to investigate the nature of the Intermediate of the Reaction between 6-Diazopenicillanate and Tributylborane

The ability of the HPLC system to produce rapid results

proved invaluable during the reaction which took place between 6-diazopenicillanate and tributylborane. Repeated injections of the reaction mixture containing the proposed enol-borinate intermediate (4.15) afforded irreproducible results, in which the peak corresponding to the intermediate possessed a different retention time on each injection (Figure 8). It was suggested in Chapter 4 that this difference was due to the length of time the intermediate survived on the silica column. The addition of triethylamine to the reaction mixture prior to any work-up procedure was seen to have a stabilizing effect on the intermediate, thus providing a reproducible peak and preventing formation of the rearrangement product (4.17) (Figure 9).

8.8 Conclusions

The examples on the preceding pages demonstrate a few of the broad range of ways in which H.P.L.C. may be utilized. Several other reactions were also successfully investigated by means of H.P.L.C.

The techniques of analytical and preparative H.P.L.C. will clearly play a major rôle in the future development of β-lactam chemistry, and also of many other areas of organic chemistry.

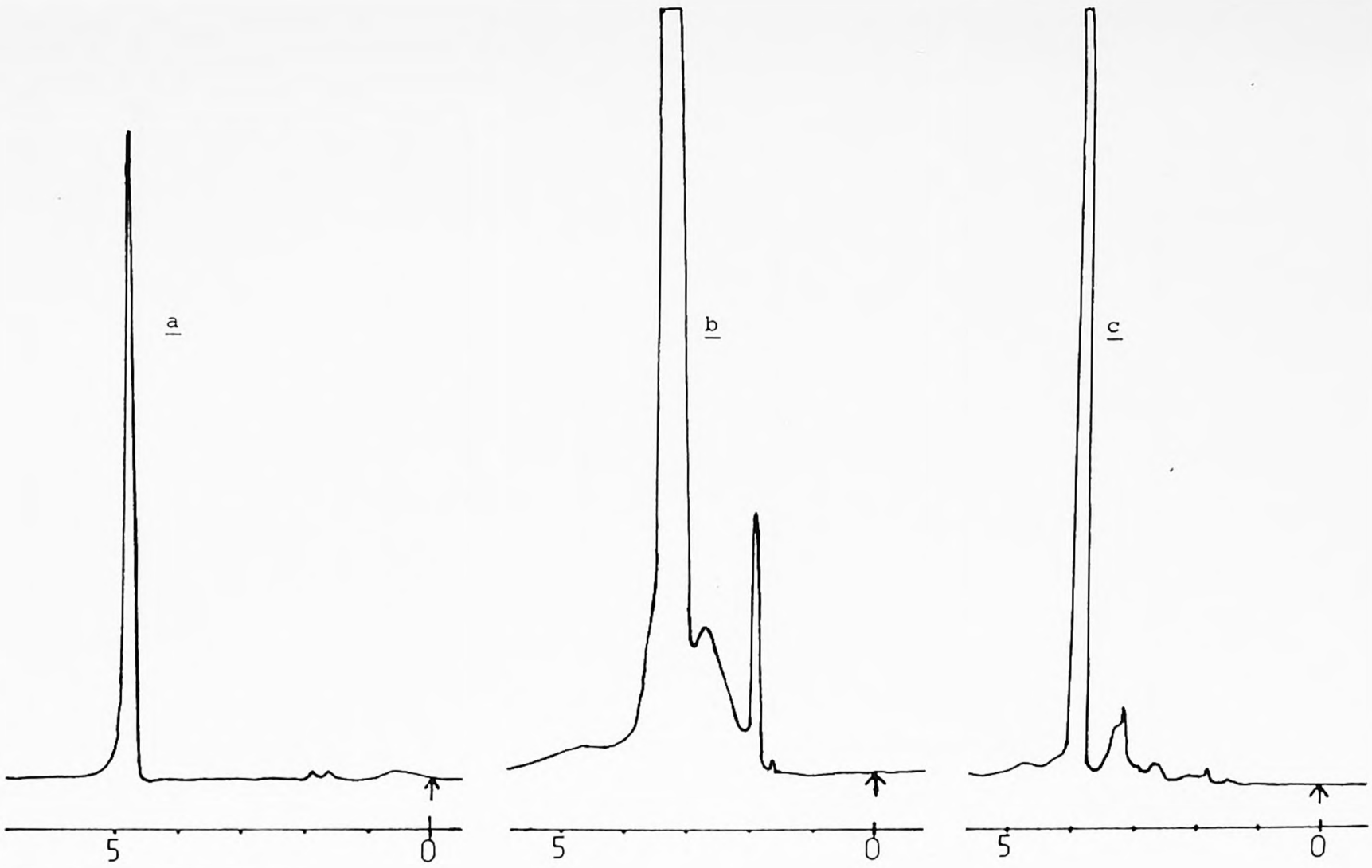


Figure 8: Injection of

a) standard thiazepine solution

b) crude reaction products

c) crude reaction products (repeat)

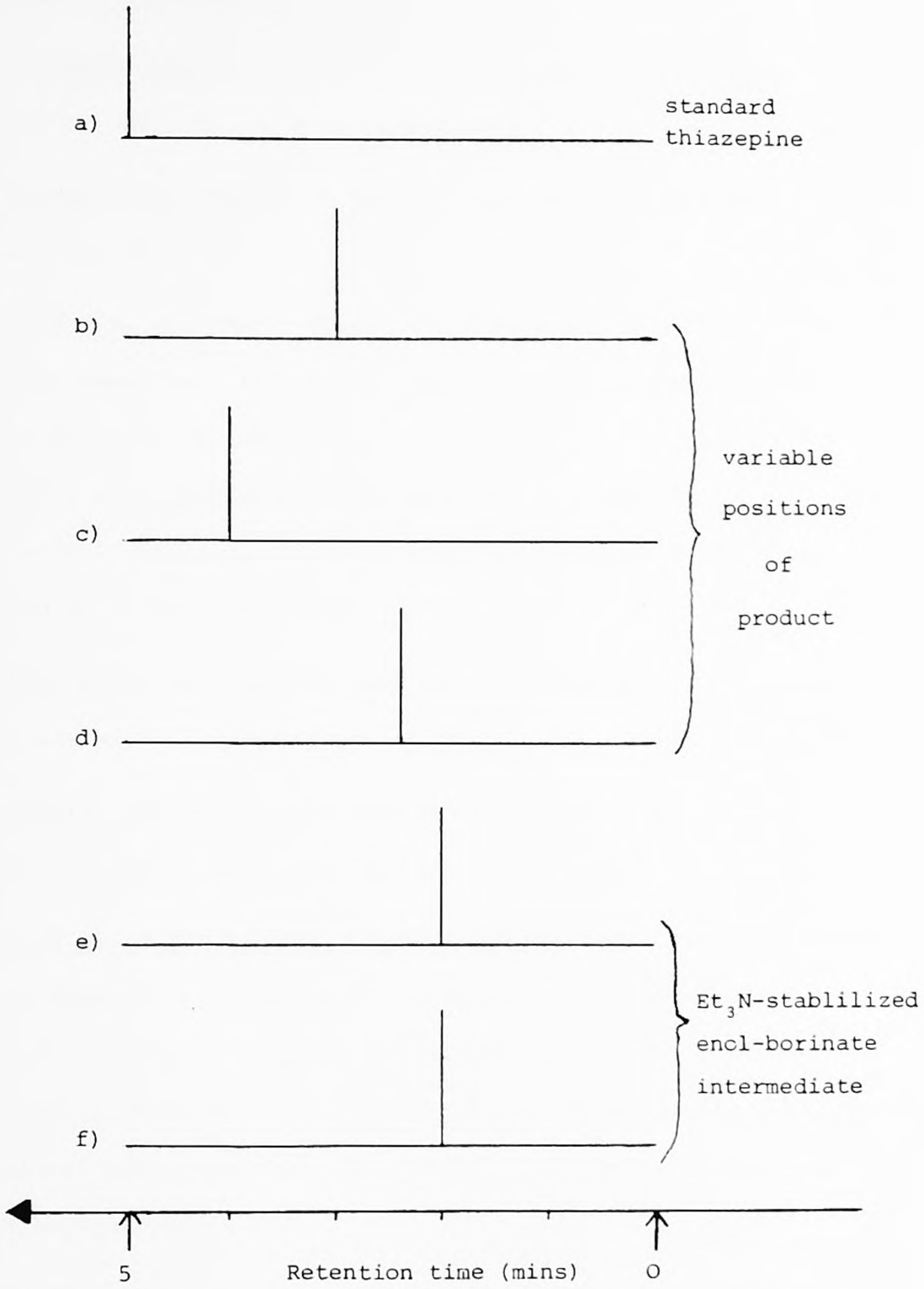


Figure 9: The diagrammatic representation of the variation in the retention time of the intermediate

Section 2

Chapter 9 : Experimental

GENERAL EXPERIMENTAL DETAILS

INFRARED SPECTRA:- These were recorded on a Perkin-Elmer 157G, 457 or 599 Infrared Spectrophotometer.

ULTRA-VIOLET SPECTRA:- Spectra were recorded on a Perkin-Elmer 402 instrument.

^{1}H N.M.R. SPECTRA:- Spectra were recorded on a Jeol 100MHz continuous wave instrument, unless otherwise stated, using TMS as an internal standard.

^{13}C N.M.R. SPECTRA:- These were run on a Jeol FX60 instrument, as $CDCl_3$ solutions containing TMS as an internal standard, and D_2O as an external lock.

MASS SPECTRA:- Spectra were recorded on a Kratos MS30 Mass Spectrometer, operating at an ionization voltage of 70 or 20 eV.

MELTING POINTS:- These were determined on a Koffler hot-stage melting point apparatus, and are uncorrected.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY:- This was carried out by means of a Waters 6000 A pump, a Cecil variable wavelength U.V. detector, a Linseis Strip-chart recorder and a Rheodyne 7125 valve injector. Columns were stainless steel, packed with either Lichrosorb Si60 10μ irregular particles, or Hypersil 5μ spherical particles.

SOLVENTS FOR H.P.L.C.:- These were either H.P.L.C. grade or were distilled prior to use.

PREPARATIVE T.L.C. PLATES:- 5 plates measuring 20cm x 20cm were coated with a slurry of silica (130g, Merck Silica Gel $^{60}GF_{254}$) in water (240ml), to produce a film of silica of 1mm thickness. The plates were allowed to stand at room temperature for 1 hour before activation at 120°C in an oven overnight.

Section 2

Chapter 9

Experimental

p-Nitrobenzyl 6-aminopenicillanate, tosic acid salt (3.5)

(i) Protection of NH_2 group using Trityl Chloride[137]. 6-APA (21g, 0.0972 moles), triethylamine (31g) and $CHCl_3$ (500 ml) were stirred for 10 minutes until the 6-APA had dissolved. Trityl chloride (32g) was added to the mixture and stirring continued at room temperature for 17 hours. The solvent was removed under reduced pressure and the product was partitioned between ether (400 ml) and water (400 ml). The trityl 6-APA dissolved in the aqueous phase due to the presence of the base. The layers were separated and the ether layer washed with water (400 ml). The two aqueous phases were combined and acidified with 5N HCl to pH 4 while stirring at $0^{o}C$. The product was rapidly extracted into ether (400 ml), dried ($MgSO_4$) and evaporated to give a yellow foam in 64% yield.

I.R. ($CHCl_3$) ν_{max} 3,400-2800 cm^{-1} (OH), 1780 cm^{-1} (β-lactam C=O), 1730 cm^{-1} (acid C=O).

(ii) Protection of acid function using p-nitrobenzyl chloride[136]. Trityl 6-APA (28.5g, 0.062 moles), triethylamine (6.28g, 0.062 moles) and p-nitrobenzyl chloride (10.63g, 0.062 moles) were stirred in DMF (200 ml) for 24 hours. The solvent was removed under reduced pressure until 40% of the original volume remained. This was dissolved in ethyl acetate (150 ml) and partitioned with water (150 ml). The triethylamine hydrogen chloride dissolved in the

aqueous phase, while the product extracted into the ethyl acetate. The layers were separated, and the ethyl acetate solution dried ($MgSO_4$) and concentrated to 25% of its volume. The product (3.4) crystallized out as a white solid, which was recrystallized from ethyl acetate. Yield = 50%;

M.pt 176°C;

I.R. ($CHCl_3$) $\nu_{max.}$ 1520 cm^{-1}, 1345 cm^{-1}, 850 cm^{-1} (NO_2)

(iii) Removal of the Trityl Group. The doubly-protected ester (3.4) (18.4g, 0.0311 moles) was stirred in analar acetone (150 ml) and to this solution was added toluene sulphonic acid (5.9g, 0.0311 moles). The mixture was stirred at room temperature for 1 hour, after which the solvent was removed under reduced pressure. The products were taken up in a small amount of chloroform and precipitated out of solution with petroleum ether. The brown solid so formed was stirred at 0°C in ethyl acetate until the p-nitrobenzyl 6-APA crystallized out as its tosyl salt (3.5). Yield - 34%.

M.pt = 145°C.

I.R. ($CHCl_3$) $\nu_{max.}$ = 3,400 cm^{-1} (-NH); 3,000-2,900 cm^{-1}(C-H); 2,700–2,600 cm^{-1} (NH_3^+); 1790 cm^{-1} (β-lactam C=O); 1750 cm^{-1} (ester C=O); 1600 cm^{-1}(NH); 1520 cm^{-1} (NO_2); 13500^{-1}(NO_2): 850 (NO_2)

N.m.r. ($CDCl_3$) δ 1.30 (s,3H, CH_3); 1.44 (s,3H,CH_3); 2.32 (s,3H,CH_3), 4.52 (s,1H,H-3); 5.06(d,1H,J=4Hz, H-5), 5.24 (s,2H,-CH_2); 5.46 (d,1H,J=4Hz, H-6); 7.10(d,2H,J27.5Hz, tosyl), 7.50(d,2H,J=7.5Hz,benzyl); 7.76(d,2H,J=7.5Hz,tosyl); 8.19 (d,2H,J=7.5Hz,benzyl).

p-Nitrobenzyl 6-diazopenicillanate (3.7)[67]

Method 1

The tosic acid salt of p-nitrobenzyl 6-aminopencillanate (3.5) can be used without initial removal of the tosic acid group, due to liberation of the free amine in the aqueous medium.

The salt (3.5) (0.1988 g, 3.801×10^{-4} moles) was dissolved in ice-cold water (20 ml) and partitioned with dichloromethane (20 ml). To this mixture were added $NaNO_2$ (0.0603 g, 8.7423×10^{-4} moles) and $HClO_4$ (7.6 ml, 0.1M, 7.6×10^{-4} moles). The solution was stirred over an ice bath for 2 hours. The organic phase was separated, washed with ice-cold NaCl solution (20 ml), and dried ($MgSO_4$). Evaporation of solvent afforded a yellow oil which crystallized on standing, and which was recrystallized from CH_2Cl_2/ petroleum ether at $-50^{o}C$, giving pure (3.7) in 90% yield. M.pt = $39-42^{o}C$.

I.R. (CHC_3) $\nu_{max.}$ = 2080 cm^{-1} (diazo group); 1780 cm^{-1} (β-lactam C=O); 1747 cm^{-1} (ester C=O).

N.m.r. ($CDCl_3$) δ 1.40 (s,3H,Me), 1.64(s,3H,Me), 4.43 (s,1H,H-3), 5.25(s,2H,$-CH_2$), 6.14 (s,1H,H-5), 7.56 (d,2H,J=7.5Hz, aromatic), 8.19 (d,2H,J=7.5Hz, aromatic).

Method 2

The tosic acid salt (3.5), (2g, 5.5 248 $\times 10^{-3}$ moles) was dissolved in ice-cold water (150 ml) and partitioned with ice-cold CH_2Cl_2 (100 ml). The mixture was stirred rapidly over an ice bath while $NaNO_2$ (4.4g) and p-toluene sulphonic acid (1g) were added. Stirring was continued for 8 minutes, then the organic layer was separated and washed with ice-cold NaCl solution (100 ml). After drying, the CH_2Cl_2 was removed under reduced pressure to afford the yellow 6-diazopenicillanate (3.7) which was characterised as above. Yield = 90%.

p-Nitrobenzyl hydrazone (3.8)[139]. Hydrazine hydrate (20g) was cooled and stirred over an ice bath, and to this was added p-nitrobenzaldehyde (30.2g). The temperature was maintained at 40°C once the addition was complete. The reaction was followed by T.L.C, and when over, the solution was extracted with ether (30 ml), dried briefly over pulverized KOH and evaporated under reduced pressure. The solid so formed was recrystallized from ethanol. M.pt = 134°C (Lit.134°C).

p-Nitrobenzyldiazomethane (3.9)[140]. Oxidation of p-nitrobenzylhydrazone (3.8) was attempted using HgO, Ag_2O and NiO_2. Of these only the NiO_2 gave reasonable results.

p-Nitrobenzylhydrazone (0.5g) was dissolved in dichloromethane (100 ml) and added over 15 minutes to NiO_2 (2g, 8 equivalents) in dichloromethane (30 ml). The solution was stirred at room temperature for 9 hours, after which an I.R. spectrum showed a strong diazo stretch at 2060 cm^{-1}, as reported in the literature[140], which showed that oxidation had occurred.

p-Nitrobenzyl 6-aminopenicillanate(3.6) 6-APA (0.648 g, 0.003 moles) together with p-nitrobenzyldiazomethane (0.49g, 0.003 moles) were stirred over an ice-bath in dichloromethane (100 ml) and methanol (33 ml). The reaction was monitored by T.L.C. After stirring overnight, no further diazo group remained and the solvent was then removed under reduced pressure, and the products separated by preparative T.L.C. Elution with chloroform afforded 8 bands of which band 7 was the required protected penicillin (3.6).

Yield = 8.1%.

I.R. ($CHCl_3$) $\nu_{max.}$ 3350 cm^{-1} (NH), 1770 cm^{-1} (β-lactam C=O),

1745 cm^{-1} (ester C=O).

N.m.r. ($CDCl_3$) δ 1.46 (s,3H,CH_3), 1.65(s,3H,CH_3), 4.48(s,1H,H-3), 4.61 (d,1H, J=4Hz, H-5), 5.30 (s,2H,-CH_2-), 5.52 (d,1H, J=4Hz,H-6), 7.54 (d,2H, J=8Hz, aromatic), 8.25 (d,2H, J=8Hz, aromatic).

Pivoyloxymethyl 6-aminopenicillanate (3.10)[141]. 6-APA (10g) was stirred in DMF (80 ml) at 50°C with triethylamine (10 ml) for 20 minutes until dissolved. To this solution was added pivoyloxymethylchloride (14 ml) and the mixture was stirred for a further 4 hours at 45°C. Ethyl acetate (100 ml) was added to dilute the solution and to bring about the precipitation of the triethylamine hydrochloride which formed as a by-product, and which was subsequently filtered off. The solution was washed (3 x 100 ml H_2O) to remove any further triethylamine hydrochloride, dried ($MgSO_4$) and evaporated to 50% of its volume under reduced pressure. A solution of ethyl acetate (100 ml) containing p-toluene sulphonic acid (8.8g) was added with stirring, causing precipitation of the product in the form of its tosic acid salt (3.11). This was filtered and washed with ethyl acetate followed by ether,affording a pure white solid in 81% yield. M.pt = 150-151°C (Lit. mpt 150-1°C).

I.R. ($CHCl_3$) $\nu_{max.}$ 2700-2600 cm^{-1} (NH_3^+), 1750 cm^{-1} (broad,β-lactam and ester carbonyls), 1680 cm^{-1}protecting group carbonyl).

N.m.r. ($CDCl_3$) δ 1.22(s,9H,^tBu), 1.21(s,3H,CH_3), 1.28(s,3H,CH_3) 2.36 (s,3H,CH_3), 4.48 (s,1H,H-3), 5.00 (d,1H, J=3Hz, H-5), 5.40 (d,1H,J = 3Hz, H-6), 5.79 (dd,2H,-$\underline{CH_2}$-), 7.15(d,2H, J=7.5Hz, aromatic), 7.78 (d,2H,J=7.5Hz, aromatic).

Pivoyloxymethyl 6-diazopenicillanate (3.12). Pivoyloxymethyl 6-aminopenicillanate tosic acid salt (3.11) (1g) was stirred in H_2O

(75 ml) and partitioned with CH_2Cl_2 (50 ml). The solution was stirred vigorously over an ice-bath. To the solution were added $NaNO_2$ (2.2g) and p-toluene sulphonic acid (0.5g). After 8 minutes, the stirring was stopped and the organic phase separated, washed with ice-cold NaCl solution, dried ($MgSO_4$) and evaporated. The yellow foam so produced was approximately 95% pure from its n.m.r. spectrum. Yield = 94%.

I.R. ($CHCl_3$) $\nu_{max.}$ 2960-2880 cm^{-1} (C-H), 2080 cm^{-1} (diazo group), 1780-1973 cm^{-1} (broad, β-lactam and ester carbonyls).

N.m.r. ($CDCl_3$) δ 1.24(s,9H, ^tBu), 1.48(s,3H,CH_3), 1.65(s,3H,CH_3), 4.40 (s,1H,H-3), 5.81 (dd,2H,$-CH_2$), 6.19 (s,1H,H-5).

p-Nitrobenzyl penicillanate (4.9). A 100 ml three-necked flask fitted with 2 dropping funnels was flushed with dry, oxygen-free nitrogen. p-Nitrobenzyl 6-diazopenicillanate (0.274g, 0.8 mmol) was dissolved in freshly distilled, dry THF (20 ml) and placed in one dropping funnel. The reaction flask was charged with THF (10 ml), and a further solution of THF (20 ml) containing borane-THF etherate (1.6ml, 1M) was placed in the second dropping funnel. The apparatus was cooled to -65°C over a cardice/acetone bath. Water (50μl) was added to the dropping funnel containing the borane solution, and both solutions were added dropwise to the reaction flask over 5 minutes, whilst stirring. The temperature was maintained at -65°C for 1 hour, after which a T.L.C. showed that only unreacted diazo compound was present. The mixture was allowed to warm to -30°C and was maintained at this temperature for a further 2 hours. Again T.L.C. showed only unreacted starting material. Borane-THF was added (0.8 ml) but without effect. Addition of the borane solution was continued until 15 molar equivalents were

present (12 ml). The temperature was raised to -20°C, at which time bubbles of nitrogen began to evolve. Stirring was continued for a further 3 hours, followed by the addition of 50% aqueous THF (10 ml). The mixture was partitioned between water (50 ml) and diethyl ether (50 ml), and the ether layer separated, washed with 5% $NaHCO_3$ solution (2 x 50 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The mixture was separated by preparative T.L.C., using chloroform as eluant, and affording p-nitrobenzyl penicillanate (4.9) as a white solid in 60% yield.

M.pt = 139-141°C.

I.R. ($CHCl_3$): $\nu_{max.}$ 1760 cm^{-1} (β-lactam and ester carbonyls); 1600 (M); 1525 (M); 1350 (M).

N.m.r. ($CDCl_3$): δ 1.48 (s,3H,CH_3), 1.72(s,3H,CH_3), 3.16(dd,1H, J=1.5 and 17Hz, H-6β), 3.70(dd,1H, J=4 and 17Hz, H-6α),4.76(s,1H,H-3), 5.44(s,2H,$-CH_2-$, also dd,1H,J=1.5 and 4Hz), 7.76(d,2H,J=7Hz, aromatic), 8.44 (d,2H, J=7Hz, aromatic).

M/e 33.0737(M^+);

Elemental Analysis: Found C 53.09%,H 4.80%,N 7.75%.

Calculated C 53.57%,H 4.76%,N 8.33%

Attempted Aldol Condensation of Intermediate (4.10) with Benzaldehyde.

The apparatus was assembled as above and flushed with dry, oxygen-free nitrogen. p-Nitrobenzyl 6-diazopenicillanate (611mg, 1.66 mmol) was dissolved in freshly distilled THF (25 ml) and placed in one dropping funnel. The reaction flask was charged with THF (10 ml) and the apparatus cooled to -65°C over a cardice/acetone bath. Borane-THF (3.2 ml, 1M, 3.2 mmol) was dissolved in THF (25 ml) and placed in the other dropping funnel. The contents of both funnels were then added dropwise over 5 minutes into the reaction flask whilst

stirring. The flask was allowed to reach -20°C, and freshly distilled benzaldehyde (0.88g, 8.3 mmol) was added. Nitrogen began to evolve. The temperature was raised to 20°C, dichloromethane was added (50 ml) and the mixture washed with NaCl solution (3 x 25 ml). After drying ($MgSO_4$), the solvent was removed under reduced pressure, yielding a brown oil. The n.m.r. of this oil showed no aldol condensation product. p-Nitrobenzyl penicillanate (4.9) was present, together with what appeared to be structure (4.13) from its spectral data.

I.R. ($CHCl_3$) 3,400 cm^{-1} (NH); 1735 cm^{-1} (ester and thiolactone carbonyl);

N.m.r. ($CDCl_3$) δ 6-7.5 (m, vinyl protons).

M/e 336 (reduced form of molecular ion (4.14)).

Reaction of p-Nitrobenzyl 6-diazopenicillanate with Tributylborane

The apparatus was carefully dried and flushed with oxygen-free dry nitrogen. The reaction vessel, containing dry THF (15 ml) was cooled to -65°C over a cardice/acetone bath. With stirring, two solutions of a) p-nitrobenzyl 6-diazopenicillanate (0.4895g, 0.001352 moles) in THF (25 ml) and b) Bu_3B (2.7×10^{-3} moles of 1M solution in THF) in THF (25 ml) containing H_2O (0.1 ml) were added to the reaction vessel over 5 minutes. The temperature was raised to -45°C and 30% H_2O_2 (20 drops) was added. On reaching -15°C, the solution was washed with NaCl solution (50 ml) and diluted with dichloromethane (100 ml). After drying ($MgSO_4$), the solution was evaporated under reduced pressure and chromatographed on silica plates, affording the thiazepine (4.17) in 60% yield as a yellow oil.

I.R. (CHC_3) $\nu_{max.}$ 3,400-3,300 cm^{-1} (NH), 1735 cm^{-1} (ester C=O and

thiolactone C=O), 1625 cm^{-1} (unsaturated thiolactone).

N.m.r. ($CDCl_3$) δ 0.90, 1.39 (2m,9H,Bu), 1.48(s,3H,Me), 1.55 (s,3H,Me), 4.46 (d,1H, J= 6Hz), 5.39 (s,2H,$-CH_2-$),5.76(m,1H,N-H), 6.83 (d,1H, J=7.5Hz), 7.64 (d,2H, J=8Hz, aromatic), 8.32 (d,2H, J=8Hz,aromatic).

Elemental Analysis: Found C 58.05%, H6.42%, N 6.82%, Calculated C 58.15%, H 6.16%, N7.14%.

M/e 392 (M^+, 11.9%), 364 (49.8%), 335(0.5%, M^+-Bu), 256 (7.0%, M^+-PNB), 136 (27.6%, PNB), 82(100%).

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 264 nm, ε=1.3066 x 10^4; $\lambda_{max.}$ = 309 nm,ε=9.6548 x 10^3.

Reaction of Enol Borinate (4.15) with Bromine. At -65°C under nitrogen, p-nitrobenzyl 6-diazopenicillanate (0.1221g, 0.33 mmol) was stirred in dry THF (5 ml) and Bu_3B (0.67 ml of IM THF solution) was added. After stirring for 5 minutes, an H.P.L.C. injection showed the presence of the enol-borinate intermediate (4.15). Bromine (1.3509 mmol, 0.2161g, 0.07 ml) in THF (5 ml) was added, and after a further 5 minutes, a second H.P.L.C. injection showed new products which eluted at the solvent front. The reaction was stopped, washed with saturated NaCl solution (10 ml) and then H_2O (2 x 10 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The products were purified by preparative T.L.C. but none of the 6-bromo, 6-butylpenicillanate was present.

Reaction of Enol Borinate (4.15) with Acetaldehyde.p-Nitrobenzyl 6-diazopenicillanate (150 mg, 0.4144 mmol) was stirred in THF (5 ml) under nitrogen at -65°C. Bu_3B (0.8287 mmol, 0.82 ml IM THF solution) was added to the solution, and after 5 minutes, acet-

aldehyde (1.6574 mmol, 0.0729g) was also added. The solution was stirred for 10 minutes more, followed by an aqueous wash (2 x 10 ml). Drying ($MgSO_4$) and evaporation under reduced pressure afforded butyl thiazepine (4.17) as the major product.

Reaction of Enol Borinate (4.15) with Acetic Acid. p-Nitrobenzyl 6-diazopenicillanate (73mg, 0.2017 mmol) was stirred in THF (5 ml) at -65°C under a stream of nitrogen. Bu_3B (0.403 mmol, 0.4 ml IM THF solution) was added, and after stirring for 10 minutes, an H.P.L.C. injection showed the presence of the intermediate (4.15). Acetic acid (0.8068 mmol, 0.048g) was added to the solution and stirring continued for a further 15 minutes. The solution was neutralized with $NaHCO_3$ solution (2 x 10 ml), washed with H_2O (2 x 10 ml), dried ($MgSO_4$), and evaporated. Again, the only identifiable product was the thiazepine (4.17).

Attempted Synthesis of 6-Butylpenicillanate (4.16).

a) p-Nitrobenzyl 6-oxopenicillanate (4.18)[62]. p-Nitrobenzyl 6-diazopenicillanate (0.8g, 2.2099 mmol) was dissolved in dichloromethane (80 ml) and to this was added Ph_3P (0.579g, 2.2099 mmol). The solution was stirred at 0°C. To this solution was added a second solution containing $NaNO_2$ (0.76g) and trifluoroacetic acid (1.5g) in DMSO (40 ml). Stirring was continued for a further 1.75 hours. The solution was then washed extensively with H_2O, 5% $NaHCO_3$ solution and saturated NaCl solution. The organic phase was dried ($MgSO_4$) and evaporated to give (4.18).

I.R. ($CHCl_3$) $\nu_{max.}$ 1780 cm^{-1}, 1750 cm^{-1} (β-lactam carbonyls).

N.m.r. ($CDCl_3$) δ 4.96 (s,1H,H-3), 5.90(s,1H,H-5).

(b) Butyl Triphenylphosphonium Bromide. Ph_3P (8g) was refluxed with BuBr (5 ml) in dry DMF (60 ml) for 1 hour. The product crystallized out as a white solid, which was filtered and washed with ether. The n.m.r. spectrum compared well with that in the Aldrich n.m.r. library.

N.m.r. ($CDCl_3$) 0.26 (m,3H,CH_3-), 1.16(m,4H, -CH_2-CH_2-), 3.00 (m,2H,-CH_2-P), 7.39(m, 15H,Ph_3P-).

c) Butylidenetriphenylphosphorane (4.19) and addition of 6-oxo-penicillanate. The apparatus was oven-dried and flushed with dry nitrogen. Butyl triphenylphosphonium bromide (1.3007g, 0.326 mmol) was suspended in sodium-dried ether (10 ml), and, while stirring, BuLi (2 ml. 1.6M hexane solution, 3.26 mmol) was added. The solution was stirred at room temperature for 1.5 hours, turning first orange and then yellow. 6-Oxo-penicillanate (1.6320 mmol) was added, and stirring continued for a further 16 hours under a stream of nitrogen. The solvent was removed under reduced pressure and the products separated by preparative T.L.C. It was difficult to determine whether 6-butylidenepenicillanate had been produced and therefore the fraction most likely to be this material was subjected to hydrogenation. The fraction (43mg, 0.1128 mmol) was stirred in methanol (15 ml) containing palladium on charcoal catalyst (large excess). A volume of hydrogen was taken up (3.2 ml), but on running I.R. and n.m.r. spectra it was shown to have cleaved the p-nitrobenzyl protecting group. The C=C bond was still present, and hydrogenation was therefore continued, but without success. The reaction was repeated, but no t-butylpenicillanate could be produced.

Attempted Synthesis of Triphenylphosphonium ylid (4.21), and the Subsequent Addition of Benzaldehyde. Into a 3-necked flask fitted with a dropping funnel were placed Ph_3P (0.1848g, 0.7055 mmol), rhodium acetate (2%,2mg) and dry THF (30 ml). The system was flushed with nitrogen and stirred at -65°C over a cardice/acetone bath. 6-Diazopenicillanate(0.255g, 0.70552 mmol) was added dropwise into the reaction vessel from the dropping funnel as a solution in dry THF (20ml). After 1.5 hours, benzaldehyde (1.4 mmol, 0.1496g) in dry THF (5 ml) was added, and stirring was continued for 2 hours. The solvent was removed under reduced pressure and the mixture separated by preparative T.L.C. The major product was the azine (4.24), which formed as a yellow crystalline solid. M.pt 132-4°C.

I.R. ($CHCl_3$) $\nu_{max.}$ 2910 cm^{-1}, (C-H); 1780 cm^{-1},(β-lactam C=O); 1750 cm^{-1} (ester C=O).

N.m.r ($CDCl_3$) δ 1.40 (s,3H,Me), 1.58 (s,3H,Me), 4.64 (s,1H,H-3), 5.23 (s,2H,$-CH_2-$), 5.92 (s,1H,H-5), 7.42 (m,5H, aromatic), 7.98 (m,2H, aromatic), 8.16 (d,2H, aromatic), 8.46 (s,1H,Ph-C<u>H</u>=N).

M/e 452 (M^+),434, 407, 348(M^+-PhCHN), 295.

U.V. (CH_3CN) $\lambda_{max.}$ 223 nm, $\varepsilon = 1.26 \times 10^4$

$\lambda_{max.}$ 285 nm, $\varepsilon = 2.25 \times 10^4$

The reaction was repeated, but the solvent was removed prior to addition of benzaldehyde, affording the phosphazine (4.23). Attempts to remove the nitrogen and produce the ylid (4.21) were made by refluxing in CH_2Cl_2, THF and finally toluene, but all proved unsuccessful.

p-Nitrobenzyl 6-(4'-oxobut-2'-enylidene) penicillanates (5.2b) (5.3b). p-Nitrobenzyl 6-diazopenicillanate (127 mg) was stirred in furan (5 ml) with rhodium acetate catalyst (2mg). The reaction proceeded with the rapid evolution of nitrogen, and after 1.5 hours, T.L.C. showed that the reaction had reached completion. An n.m.r. spectrum of the crude products showed the formation of two isomeric dienals (5.2b)(5.3b) in almost quantitative yield.

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester carbonyls), 1680 cm^{-1} (aldehyde carbonyl).

N.m.r. ($CDCl_3$) δ 1.29(s,9H, ^tBu), 1.58(s,3H,Me), 1.66 (s,3H,Me), 4.71(s,1H,H-3), 5.94 (m,3H,H-5 and $-CH_2-$), 6.25, 6.52 (m,m,1-H,H_3), 7.39-7.80 (m,2H,H_1,H_2), 10.35, 10.40 (d,d,1H,H_4).

Pivoyloxymethyl 6-(4'-oxobut-2'-enylidene) pencillanates (5.2c) (5.3c). Pivoyloxymethyl 6-diazopenicillanate (110 mg) was stirred in furan (5 ml) in the presence of rhodium acetate catalyst (2mg). The reaction had reached completion after 100 minutes, shown by T.L.C. and I.R. An n.m.r. spectrum of the crude reaction mixture, following removal of the excess furan by evaporation, showed the formation of two isomeric dienals, which were separated by preparative T.L.C. with a solvent system of dichloromethane/ethyl acetate (95:5). The n.m.r. spectra showed them to be the Z/E and Z/Z dienals (5.2c)(5.3c) produced in the ratio 1.5:1. The total yield prior to separation was 90%.

(5.2c)(Z/E) I.R. ($CHCl_3$) $\nu_{max.}$ 1780 cm^{-1} (β-lactam C=O), 1750 cm^{-1} (ester C=O's), 1680 cm^{-1} (aldehyde C=O).

N.m.r. ($CDCl_3$) δ 1.23 (s,9H,$-CH_2-CO_2-^tBu$), 1.52 (s,3H,Me), 1.60 (s,3H,Me), 4.45 (s,1H,H-3), 5.77 (s,1H,H-5), 5.79(dd,2H,$-CH_2-$

$CO_2{}^tBu$,J=4.5,4.5Hz),6.08(dd,1H, J=7.5Hz, 7.5Hz, H_3), 7.20 (d,1H, J=13.5Hz,H_1), 7.56(dd, perturbed, 1H, J=13.5Hz, 7.5Hz, H_2), 10.4 (d,1H, J=7.5Hz,H_4).

M/e 381 (M^+, 5.63%), 222 (12%), 167 (11.2%), 138 (16.9%), 85(43.9%), 57(100%).

Elemental Analysis Found C.56.37%, H 6.16%, N 3.55%

Calculated C.56.68%, H 6.08%, N 3.67%

U.V. (CH_2Cl_2) $\lambda_{max.}$ 281nm, ε = 2.97 x 10^4

(5.3c)(Z/Z) I.R. ($CHCl_3$) $\nu_{max.}$ 1780 cm^{-1} (β-lactam C=O), 1760 cm^{-1} (ester C=O'S), 1680 cm^{-1} (aldehyde C=O).

N.m.r.($CDCl_3$) δ 1.25 (s,9H,^tBu), 1.53 (s,3H,Me), 1.60 (s,3H,Me), 4.56(s,1H,H-3), 5.84(m,3H,-CH_2-, H-5),6.18 (dd,1H, J=7.5Hz, 7.5Hz, H_3),6.80 (dd,perturbed, 1H, J=7.5Hz, 12Hz,H_2), 7.50(d,1H, J=12Hz, H_1), 10.12 (d,1H, J=7.5Hz, H_4).

M/e 381 (M^+,0.7%), 222(1.9%), 193(1.8%), 138 (1.3%), 85(13.7%), 57(100%).

Elemental Analysis Found C.56.69%, H.5.98% N 3.67%

Calculated C.56.68%, H.6.08% N 3.67%

U.V. (CH_2Cl_2) λ_{max} = 280 nm, ε = 2.97 x 10^4.

Reaction of Pivoyloxymethyl 6-diazopenicillanate with various concentrations of furan

a) 1 equivalent of furan Pivoyloxymethyl 6-diazopenicillanate (0.135g, 0.3959 mmol) was stirred in dichloromethane(2ml), and to this solution were added furan (0.0296g, .3959 mmol) and rhodium acetate catalyst (2mg). The reaction mixture was stirred at room temperature for 1 hour, after which T.L.C. showed that the reaction had reached completion. The solvent was removed under

reduced pressure, and although the I.R. and n.m.r. spectra of the crude products showed the formation of two new aldehyde isomers, as required, the integral of the n.m.r. spectrum showed that the aldehydes were responsible for only 30% of the yield of products.

b) 2 equivalents of furan. Pivoyloxymethyl 6-diazopenicillanate (150 mg, 0.4349 mmol.) was stirred with furan (59 mg, 0.8698 mmol,) and rhodium acetate (2 mg) in dichloromethane (2 ml) for 1 hour. The solvent was removed under reduced pressure, and an n.m.r. spectrum of the crude reaction products indicated a dienal yield of 80%.

c) 5 equivalents of furan. Pivoyloxymethyl 6-diazopenicillanate (57 mg, 0.167 mmol) was stirred with furan (57 mg, 0.836 mmol) and rhodium acetate (2 mg) in dichloromethane (2 ml). After stirring at room temperature for 1 hour an I.R. spectrum showed total loss of the diazo stretch, indicating completion of the reaction. Both solvent and excess furan were removed under reduced pressure, and an n.m.r. spectrum of the crude products showed an 83% yield of dienal isomers.

d) 10 equivalents of furan. Pivoyloxymethyl 6-diazopenicillanate (112 mg, 0.328 mmol) was stirred in dichloromethane (2 ml) with furan (200 mg, 3.28 mmol) in the presence of rhodium acetate catalyst (2mg). After 1 hour, the reaction was shown to have reached completion by the total absence of the diazo band in the I.R. spectrum. An n.m.r. spectrum showed that the dienals had been produced in 85-90% yield.

Furfuryloxythiazepine (5.9). Pivoyloxymethyl 6-diazopenicillanate (121 mg, 0.355 mmol) and furfuryl alcohol (103.3 mg, 1.0645 mmol) were stirred in the presence of rhodium acetate (3 mg) in dichloromethane (3 ml) for 45 minutes at room temperature. The solvent was removed under reduced pressure and the mixture was separated by preparative T.L.C., eluting with dichloromethane containing 5% ethyl acetate. The major product, the thiazepine (5.9), was isolated in 30% yield. No substituted penicillins were identified.

I.R. ($CHCl_3$) $\nu_{max.}$ 1750 cm^{-1} (ester and thiolactone C=O), 1630 cm^{-1} (unsaturated thiolactone).

N.m.r. ($CDCl_3$) δ 1.24 (s,9H, ^tBu), 1.44 (s,3H,Me), 1.47(s,3H,Me), 4.22 (d,1H,J=4.5Hz,H_3), 4.76 (s,2H,H_7), 5.36 (m,1H,N-H), 5.80 (dd,2H,J=4Hz, 4Hz, H_8H_9), 6.31(s,2H,-$CO_2\underline{CH_2}$-CO_2), 6.70 (d,1H,J=7.5Hz,H_5) 7.38 (s,1H,H_{10}).

M/e 411 (M^+, 0.14%), 274 (13.7%), 149 (25.7%), 98 (4.8%), 81 (10%)

Elemental Analysis : Found C.56.11%, H. 6.60%, N 3.42%

Calculated C.55.46% H. 6.12%, N 3.40%

U.V. (MeOH) $\lambda_{max.}$ 219 nm, $\varepsilon = 5.48 \times 10^3$; $\lambda_{max.}$ 213 nm, $\varepsilon = 3.65 \times 10^3$; $\lambda_{max.}$ 329 nm, $\varepsilon = 4.47 \times 10^3$

Pivoyloxymethyl 6-(3'-methoxycarbonylprop-2'-enylidene) penicillanate (5.10). 2-Methoxyfuran (82.5 mg, 0.838 mmol) and pivoyloxymethyl 6-diazopenicillanate (143 mg, 0.419 mmol) were stirred at 0^oC in dichloromethane (2 ml) with rhodium acetate catalyst (2 mg). After 1 hour, the reaction had reached completion and the products were separated, after removal of solvent under reduced pressure, by preparative T.L.C. Dichloromethane was employed as eluant, affording the dienone isomers (5.10), in 26% yield.

(5.10) Z,Z-isomer

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester C=O's), 1720 cm^{-1} (new ester C=O).

N.mr. ($CDCl_3$) δ 1.24 (s,9H ^tBu), 1.52 (s,3H,Me), 1.60 (s,3H,Me), 3.80 (s,3H,OMe), 4.60 (s,1H,H-3), 5.86 (m,3H,$-CH_2$ and H-5 overlapping), 6.08 (d,1H,J=12Hz,H_1), 6.52 (dd, perturbed, 1H,J=10.5Hz, 12Hz,H_2), 7.88 (d,1H,J=10.5Hz,H_3).

M/e 411.1333 (M^+, 1.7%), 380 (0.3%, M^+ -OMe), 252 (1.8%), 167 (4.7%), 119 (3.0%), 82 (100%), 57 (8.4%).

Elemental Analysis : Found C 55.59%,H 6.31% N 3.22%

Calculated C55.46%, H 6.12% N 3.40%

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 276 nm, ε = 3.25 x 10^4

Yield = 22%

(5.10) Z,E-isomer

I.R. ($CHCl_3$) $\lambda_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester C=O's), 1720 cm^{-1} (new ester C=O).

N.m.r. ($CDCl_3$) δ 1.30 (s,9H, ^tBu), 1.56 (s,3H,Me), 1.64(s,3H,Me), 3.84 (s,3H,OMe), 4.60 (s,1H,H-3), 5.86 (m,3H,$-CH_2$ and H-5 overlapping), 6.00 (d,1H, J=10.5Hz,H_1), 7.34 (dd,1H,J=10.5Hz, 10.5Hz,H_2) 7.72 (d,1H, J=10.5Hz,H_3).

M/e 411.1395 (M^+.7.6%), 252 (1.8%), 169 (7.4%), 168 (100%), 149 (10.4%),99 (18.4%), 95 (1.6%), 57(20.5%).

U.V. (MeOH) $\lambda_{max.}$ 274 nm, ε = 1.075 x 10^4.

Yield = 4%

p-Nitrobenzyl 6-(1'-methyl, 4'-acetylbut-2'-enylidene) penicillanate (5.11). p-Nitrobenzyl 6-diazopenicillanate (0.3468g, 0.958 mmol) was stirred at 0^oC for 2 hours with 2,5-dimethylfuran (0.0919g,0.958 mmol)

and rhodium acetate (2 mg) in dichloromethane (5 ml). T.L.C. showed complete decomposition of the diazopenicillanate, and the solvent was removed under reduced pressure. The products were separated by preparative T.L.C., eluting with dichloromethane/ethyl acetate (98:2). Chromatography had to be employed several times to obtain a reasonably pure sample of the required dienone (5.11). The final purification was effected by preparative H.P.L.C. on a silica column, eluting with dichloromethane/acetonitrile (97:3). No further substituted penicillins were isolated from the complex reaction mixture. Final yield = 2.5%.

I.R. ($CHCl_3$) 1760-1740 cm^{-1} (β-lactam and ester C=O's), 1690 cm^{-1} (ketone C=O).

N.m.r. ($CDCl_3$) δ 1.44 (s,3H,Me), 1.59 (s,3H,Me), 1.95 (s,3H, C=C$\underline{CH_3}$), 2.31 (s,3H,CH_3CO), 4.60 (s,1H,H-3), 5.34 (s,2H,-CH_2-), 5.79 (s,1H,H-5), 6.31 (d,1H, J=12Hz, $\underline{CH}$-C(CH_3)), 6.84 (d,1H, J=12Hz, $CH_3CO\underline{CH}$), 7.62 (d,2H, J=7.5Hz, aromatic) 8.32 (d,2H, J=7.5Hz, aromatic).

M/e 430.1179 (M^+, 5.6%), 387 (40.4%, M^+-CH_3C=O), 374 (0.2%, M^+-CH_3-COCH), 361 (M^+-CH_3COCH=CH), 294 (4.3%, M^+-PNB), 250 (2.2% M^+-CO_2PNB), 152 (100%), 96 (11.7% CH_3COCH=$CHCCH_3$), 46 (1.3%, NO_2).

U.V. (CH_2Cl_2) $\lambda_{max.}$ 273 nm, ε = 1.96 x 10^4.

Pivoyloxymethyl 6-(4'-acetylbut-2'enylidene) penicillanate (5.16).

Pivoyloxymethyl 6-diazopenicillanate (141mg, 0.4152 mmol) and 2-methylfuran (1.246 mmol, 0.1234ml) were stirred in dichloromethane (2ml). To this was added rhodium acetate (2 mg), and stirring was continued at room temperature for 3 hours, during which a steady rate of nitrogen evolution occurred. The reaction was shown to have reached

completion by the loss of the diazo stretch in the I.R. spectrum. The products were separated by preparative T.L.C., eluting with dichloromethane/ethyl acetate (90:10) and affording two isomers of the dienone (5.16). Further chromatography was necessary to obtain purer samples, and the final yield was 27%. The isomers were assigned as the Z,E and Z,Z. isomers by comparison with the unsubstituted dienals.

Z,E-isomer

I.R. ($CHCl_3$) $\nu_{max.}$ 1760 cm^{-1}(β-lactam and ester C=O's), 1690 cm^{-1} (new ketone C=O).

N.m.r. ($CDCl_3$) δ 1.25 (s,9H, ^tBu), 1.52 (s,3H,Me), 1.60 (s,3H,Me), 2.30 (s,3H, COMe), 4.59 (s,1H,H-3), 5.80 (s,1H,H-5), 5.89 (dd,2H, J=4.5Hz,4.5Hz,$-CH_2-$), 6.34(d,1H,J=11Hz, H^3), 7.20 (dd, perturbed, 1H, J=11Hz, 12Hz, H^2), 7.68 (d,1H, J=12Hz, H^1),

M/e 395.1384 (M^+, 0.1%), 168 (8.1%), 117 (1%), 99 (2.7%), 82 (100%), 57 (3.7%).

Elemental Analysis : Found C 56.48% H 6.55%, N 3.66%

Calculated C 57.71% H 6.37%, N 3.54%.

U.V. (MeOH) $\lambda_{max.}$ 278 nm, $\varepsilon = 3.623 \times 10^4$.

Z,Z-isomer

I.R. ($CHCl_3$) $\nu_{max.}$ 1770 cm^{-1}(β-lactam and ester C=O's), 1690 cm^{-1} (ketone).

N.m.r. ($CDCl_3$) δ 1.25 (s,9H, ^tBu), 1.53 (s,3H,Me), 1.60 (s,3H,Me), 2.32 (s,3H,COMe), 4.63 (s,1H,H-3), 5.90 (m,3H,$-CH_2-$ and H-5 overlapping), 6.30 (d,1H,J=12Hz, H^3), 6.89 (dd,1H, J=10.5Hz, 12Hz, H^2), 7.88 (d,1H, J=10.5Hz, H^1),

M/e 396 (M^+,^{13}C isotope, 0.2%), 395.1389 (M^+, 0.8%), 352 (0.7%),

236 (0.8%), 198 (0.7%), 183 (1.1%), 181 (1.4%), 168 (2.1%), 117 (2.5%), 82 (100%), 57 (4%).

Elemental Analysis : Found C.56.80%, H 6.42%,N 3.82%

Calculated C 57.71% H 6.37%,N 3.54%.

U.V. (MeOH) : $\lambda_{max.}$ 281 nm, ε = 3.43 x 10^4.

Pivoyloxymethyl 6-(2'-methyl,4'-oxobut-2'-enylidene) penicillanate and Pivoyloxymethyl 6-(3'-methyl,4'-oxobut-2'-enylidene) penicillanate (5.17) (5.18,5.19). 3-Methylfuran (0.30g, 3.758 mmol) and pivoyloxymethyl 6-diazopenicillanate (0.6408g, 1.8791 mmol) were stirred in dichloromethane (2 ml) together with rhodium acetate catalyst (3 mg). Nitrogen began to evolve immediately. The reaction had reached completion within 10 minutes, shown by the loss of diazo stretch and the formation of a new carbonyl stretch in the I.R. spectrum. The solvent was removed under reduced pressure and the mixture separated by preparative T.L.C., eluting with dichloromethane/ acetonitrile (98.5/1.5). Two fractions were isolated, one containing the single isomer (5.17) and the other containing a mixture of the two isomers (5.18,5.19). Further chromatography afforded separation of the isomers (5.18) and (5.19).

Isomer (5.17).

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester C=O's), 1680 cm^{-1} (aldehyde).

N.m.r.($CDCl_3$) δ 1.25 (s,9H, ^tBu), 1.55 (s,3H,Me), 1.62 (s,3H,Me), 1.98 (s,3H,COCMe), 4.60 (s,1H,H-3), 5.80(s,1H,H-5), 5.86 (dd,2H,J=4.5Hz, $-CH_2-$), 7.28 (d,1H,J=12Hz, vinylic), 7.68 (d,1H,J=12Hz, vinylic), 10.34 (S,1H,CHO).

M/e 396 (M^+, ^{13}C isotope, 0.6%). 395.1364 (M^+, 1.8%), 366 (0.5%),

236 (2.4%), 207 (1.7%), 181 (2.5%), 139 (4%), 122 (2.7%), 82 (100%), 57 (19.6%).

Elemental Analysis : Found C 58.60%, H 6.86%, N 3.40%

Calculated C 57.70%, H 6.37%, N 3.54%.

U.V. (CH_2Cl_2) $\lambda_{max.}$ 291 nm, $\varepsilon = 1.88 \times 10^4$.

Isomer (5.18).

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester C=O's 1670 cm^{-1} (aldehyde).

N.m.r. ($CDCl_3$) δ 1.25 (s,9H,^tBu), 1.53 (s,3H,Me), 1.64 (s,3H,Me), 2.13 (s,3H,CH=CMe), 4,66 (s,1H,H-3), 5.88 (dd,2H,J=4.5Hz,4.5Hz, $-CH_2-$), 5.96 (s,1H,H-5), 6.12(d,1H,J=8Hz, CHO-CH), 7.19 (s,1H,MeC-CH), 10.06 (d,1H,J=8Hz,CHO).

M/e 395.1496 (M^+,0.4%), 366 (0.2%), 252 (0.2%), 117 (1.3%), 116 (0.9%), 82 (100%), 57 (5.7%).

Elemental Analysis - The sample was insufficiently stable.

U.V. (CH_2Cl_2) $\lambda_{max.}$ 286 nm, $\varepsilon = 2.70 \times 10^4$.

Although isomer (5.19) was separated, a small amount of isomer (5.18) prevented a complete characterization. However, an I.R. and n.m.r. spectrum were obtained.

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester C=O's), 1670 cm^{-1} (aldehyde).

N.m.r. ($CDCl_3$) δ 1.25 (s,9H,^tBu), 1.53 (s,3H,Me), 1.64 (s,3H,Me), 2.13 (s,3H,Me),4.66 (s,1H,H-3),5.88 (dd,2H,J=4.5Hz, J=4.5Hz,$-CH_2-$), 5.96 (s,1H,H-5), 6.16(d,1H,J=8Hz,CHO-CH), 7.64 (s,1H,MeC-CH), 10.21 (d,1H,J=8Hz,CHO).

Ethyl diazoacetate

To a stirred solution of glycine ethyl ester hydrochloride (13.02g, 0.0933 moles) and NaOAc(65.1mg, 0.794 x 10^{-3} moles) in H_2O (15ml, 18°C) was added an ice cold solution of $NaNO_2$(9.77g, 0.142 moles) in H_2O (15ml), giving a yellow/green solution.Diethyl ether (10ml)(previously washed with conc. $CaCl_2$ to remove EtOH), was added to the mixture. To this stirred solution was added dropwise 10% H_2SO_4(1.55ml), and the mixture was stirred for 15 min.at 18°C. The mixture was separated and the ether layer poured immediately into excess 10% Na_2CO_3 solution, washed, and tested for neutrality. The ether layer was stored in an ice-cold flask while fresh diethyl ether (10ml) and 10% H_2SO_4(1.55ml) were added to the retained aqueous phase and stirring continued for 15 more minutes. The layers were separated and the ether fraction poured into excess 10% Na_2CO_3 solution, washed and combined with the previous ether layer. This organic fraction was washed (brine), dried and evaporated to yield a yellow liquid.

I.R. ($CHCl_3$) 2120 cm^{-1} diazo group.

N.m.r. ($CDCl_3$) δ 1.3 (t,3H), 4.24 (q,2H), 4.8 (s,1H).

Reactions between Ethyl diazoacetate and Furan using $Rh_2(OAc)_4$ and $Cu(acac)_2$

Ethyl diazoacetate (0.6g, 5.2631 x 10^{-3} moles) was divided equally between 2 flasks, and to each was added furan (3ml, 4.4 x 10^{-2} moles). To flask 1 was added rhodium acetate (2%, 6mgs), and to flask 2 was added copper acetylacetonate (2%, 6mgs). The rhodium acetate catalysed reaction began extremely rapidly with the evolution of nitrogen, and was consequently cooled to 0°C to reduce the reaction

rate. The reaction had reached completion within 1 hour, following which the solvent was removed under reduced pressure and an n.m.r. of the crude products was obtained.

With the copper-catalysed reaction, the diazo group was present for 24 hours, after which the solvent was removed under reduced pressure. An n.m.r. spectrum of the crude products showed the same pattern as obtained in the rhodium-catalysed reaction. The products of the two reactions were combined, and separated by chromatography on silica into the cyclopropane (5.22) and dienal isomers (5.23)(5.24). The three products were assigned on the basis of their n.m.r. spectra.(5.22):-

N.m.r. ($CDCl_3$) δ 0.99 (d,1H,J=3Hz,H_c),1.30 (t,3H,J=7.5Hz,H_a)
2.80 (quin,1H,H_d), 4.15 (q,2H,J=7.5Hz,H_b),
4.85 (d,1H,J=6Hz,H_e), 5.48(dd,1H,J=2Hz,3Hz,H_f)
6.41 (d,1H,J=2Hz,H_g).

Although there appeared to be no splitting between H_c and H_e, an expansion showed a very small splitting of ∿1Hz.

M/e 154(M^+).

(5.23)

I.R. ($CHCl_3$) $\nu_{max.}$ 1720 cm^{-1}(ester),1680 cm^{-1}(aldehyde).

N.m.r. ($CDCl_3$) δ 1.33 (t,3H,J=7.5Hz,CH_3), 4.25(q,2H,J=7.5Hz,$-CH_2-$),
6.06 (d,1H,J=8Hz,H_a), 6.21 (s,1H,H_d), 7.52 (dd,
severely perturbed, 1H,J=11Hz, 11Hz,H_c), 8.16(dd,
severelyperturbed,1H,J=11Hz, 11Hz,H_b).

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 272 nm.

M/e 154(M^+)

(5.24)

I.R. ($CHCl_3$) $\nu_{max.}$ 1720 cm^{-1}(ester), 1680 cm^{-1}(aldehyde).

N.m.r. ($CDCl_3$) δ 1.32(t,3H,J=7.5Hz,CH_3), 4.26(q,2H,J=7.5Hz,-CH_2-), 6.12(dd,severely perturbed ,1H,J=8Hz,H_d), 6.20(d,1H,J=15Hz, H_a), 7.00 (dd,severely perturbed,1H,J=11Hz, 13Hz,H_c), 8.08 (dd,1H, J=13Hz,15Hz,H_b),10.27(d,1H,J=8Hz,H_e).

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 272 nm.

M/e 154(M^+)

Action of heat on Ethyl 2-oxabicyclo[3.1.0]hex-3-ene-6-carboxylate (5.22).

The cyclopropane (50mgs) was dissolved in $CDCl_3$(0.5ml) and placed in an n.m.r. tube which was then sealed, and heated in a metal tube at 150°C for 2 hours. The tube was opened and an n.m.r. spectrum run, showing the trans -trans-dienal (5.25) in quantitative yield.

N.m.r. ($CDCl_3$) δ 1.36(t,3H,J=7.5Hz,CH_3), 4.28(q,2H,J=7.5Hz,-CH_2-), 6.36(m,severely pertured AB system, 2H,H_b,H_c), 7.08,7.50 (d,d,2H,J=12Hz,12Hz,H_d,H_e),9.62(d,1H, J=7.5Hz,H_a).

M/e 154(M^+)

U.V.(MeOH) $\lambda_{max.}$ = 265nm.

Reaction of Pivoyloxymethyl 6-diazopenicillanate with Benzofuran

Benzofuran (0.2422g, 2.0527 x 10^{-3} moles) and rhodium acetate (3mg) were stirred in CH_2Cl_2(4ml) at room temperature, and to this solution was added pivoyloxymethyl 6-diazopenicillanate (0.350g, 1.0263 x 10^{-3} moles). After 1 hour, the mixture was separated by chromatography on silica with an initial solvent system of CCl_4/CH_2Cl_2(40:60) to remove the unreacted benzofuran, followed by a gradual increase in CH_2Cl_2 concentration to resolve the products. The major product, the

pyran (5.31) was isolated as a bright yellow oil in 10-15% yield.

I.R. ($CHCl_3$) $\nu_{max.}$ 1780 cm^{-1}(β-lactam carbonyl),1750 cm^{-1}(ester)

n.m.r. ($CDCl_3$) δ 1.24(s,9H,^tBu), 1.52(s,3H,Me), 1.62(s,3H,Me), 4.55(s,1H,H-3), 5.56(s,1H,H-5),5.90 (dd,2H, J=2Hz,$-CH_2$), 5.95(d,1H,J=10Hz,H_b),6.76(d,1H, J=10Hz,H_a),6.87-7.24 (m,4H,aromatic).

M/e 431(M^+,14.5%), 244(4.1%), 176(11%), 175(10%). 130 (8.3%), 82(100%), 57(20.9%).

Elemental Analysis: Found C 69.98 H 6.21 N 3.08

Required C 61.24 H 5.84 N 3.25

U.V. (MeOH) $\lambda_{max.}$ = 226 nm ε = 3460

$\lambda_{max.}$ = 275 nm = 2500

^{13}C n.m.r.($CDCl_3$) ppm 25.9(Me), 26.9(^tBu), 32.9(Me), 63.8(C_2), 68.4(C_3), 79.9($\underline{C}H_2$), 115.9, 116.5 (vinylic), 122.4, 127.5 127.7, 130.3 (aromatic),152.2 (C=O), 166.4(C=O), 177.2 (C=O).

The quarternary carbons C_6, C_{20} and C_{21} were difficult to identify due to the high level of noise, but occurred in the region 91.5-142.8 ppm.

The proton coupled spectrum showed 6 doublets at 116(2d,J=170Hz), 123(d,J=170Hz), 128(2d,J=170Hz), 130(d,J=170Hz) each with a coupling constant characteristic of sp^2 hybridized carbons.

The stereochemistry at C-6 was determined by n.O.e. difference spectroscopy, as described in Chapter 5.

Ethyl 3,4-benzo-2-oxa-bicyclo[3.1.0]hex-3-ene-6-carboxylate (5.33).

Benzofuran (0.3000g, 2.5423×10^{-3} moles) was stirred in CH_2Cl_2 (1ml) with rhodium acetate (4mgs) at $0^{\circ}C$. To this solution was added ethyl diazoacetate (0.5796g, 5.0847×10^{-3} moles) dropwise over 2 hours. T.L.C. showed no reaction had occurred, and so the temperature was allowed to reach $20^{\circ}C$, and a further quantity of rhodium acetate (2mg) was added. After 1 hour, an I.R. spectrum showed complete decomposition of the diazo group. The reaction mixture was separated by preparative T.L.C. on silica, affording two main fractions, one of which was the unreacted benzofuran, and the other the cyclopropane adduct (5.33). Yield after purification = 40%.

I.R. ($CHCl_3$) $\nu_{max.}$ 2990-2900 cm^{-1} (C-H stretches), 1710 cm^{-1} (C=O).

N.m.r. ($CDCl_3$) δ 1.19(d,1H,H_3,J=3Hz), 1.25(t,3H,$-CH_3$,J=7Hz), 3.22(m,1H,H_4), 4.12(q,2H,$-CH_2-$, J=7Hz), 5.02(d,1H,H_5,J=6Hz), 6.76-7.36(m,4H,aromatic).

M/e 204(M^+,11.2%), 131(100%), 77(23.6%),51(10.7%).

$^{13}C(CDCl_3)$ ppm 14.3(C_{13}), 23.6(C_3 or C_{10}), 30.3(C_{10} or C_3),61.6(C_{12}) 67.2(C_2), 110.8(C_7), 121.5 (C_5 or C_4), 124.7(C_4 or C_5) 128.2(C_6),128.5(C_9), 159.8(C_8), 172.2(C_{11}).

3,4-Dimethylthiophene.[166] 2,3-Dimethyl-buta-1,3-diene (25g, 0.305 mole) in dichloromethane (50 ml) was stirred at $0^{\circ}C$ and to this was added an excess of sulphur dichloride (50g, 0.485 mole) dropwise. An excess of triethylamine was present to remove HCl as it was formed. The solution was stirred for 1 hour, and then washed with H_2O (2x50 ml). After drying (Na_2SO_4), the solvent was removed under reduced pressure

and the products distilled to give a clear liquid, which was re-dried (Na_2SO_4) and redistilled. B.pt. = 137-9°C. Yield= 12.5g, 37%.

N.m.r. ($CDCl_3$) δ 9.4 (s,2H,vinyls), 2.19 (s,6H,methyls).

Reaction of 3,4-Dimethylthiophene with Pivoyloxymethyl 6-diazopenicillanate. Pivoyloxymethyl 6-diazopenicillanate (0.7014g, 2mmol) was stirred with 3,4-dimethylthiophene (0.5g, 2 equivalents) in dichloromethane (5ml), and to this solution was added rhodium acetate (2%, 14mg) in dichloromethane (1ml). The solution was stirred at 20°C for 2 hours, and the solvent removed under reduced pressure. Purification of the products by preparative T.L.C. eluting with dichloromethane/acetonitrile (95:5) afforded (6.4) in 5% yield as an oil.

I.R. ($CHCl_3$) $\nu_{max.}$ 1790-1750 cm^{-1} (β-lactam and ester carbonyls), 1595 cm^{-1}(C=C).

N.m.r.($CDCl_3$)(360MHz) δ 1.24(s,9H,^tBu), 1.44(s,3H,α-Me), 1.58(s,3H,β-Me), 1.63(s,3H,C_{10}-Me), 1.90(s,3H,C_9-Me), 3.44(fine dd,1H,H-7),4.20(s,1H,H-3), 4.70(fine d,1H,H-5), 5.70(fine dd,1H,H-8).

M/e 425.1292 (M^+,7.0%), 266(6.1%), 170(12%), 169(56%), 124(53%), 82.9(73%),57(100%).

U.V. (CH_3CN) $\lambda_{max.}$ 231 nm, ε = 425
$\lambda_{max.}$ 250 nm, ε = 346

Reaction of Pivoyloxymethyl 6-diazopenicillanate with N-Methylindole.

A solution containing pivoyloxymethyl 6-diazopenicillanate (0.3138g, 0.902 mmol), N-methylindole (0.2411g, 1.8 mmol) and rhodium acetate (3 mg) in dichloromethane(3ml) was stirred for 15 minutes. An I.R. spectrum showed that the reaction had reached completion, and a T.L.C.

of the brown mixture showed several components. Separation by preparative T.L.C. using dichloromethane as eluant afforded two indole-substituted penicillanates (6.7),(6.8) as a mixture, together with the rearrangement product (6.9).

Total yield = 33%, approximate ratio = 1:1:1.

Compounds (6.7) and (6.8) were extremely difficult to separate, but separation was eventually achieved by means of preparative H.P.L.C. on a silica column with a solvent system comprising hexane /dichloromethane /acetonitrile (56:43:1). Some material was lost as a result of peak shaving.

(6.7)

I.R. ($CHCl_3$) $\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester carbonyls).

N.m.r. (360 MHz)($CDCl_3$) 1.22(s,9H,^tBu), 1.54(s,3H,Me), 1.72(s, 3H,Me), 3.78(s,3H,N-Me),4.65 (s,1H,H-3), 4.67(d,1H,H-6,J=1.5Hz), 5.39(d,1H,H-5,J=1.5Hz), 5.81, 5.88 (d,d,2H,$-CH_2-$, J=6Hz,6Hz), 7.06 (s,1H,H-7), 7.15(t,1H,J=7 Hz,H-10), 7.28(t,d,2H,J=7Hz,7Hz,H-9,H-11), 7.68 (d,1H,J=6Hz,H-8).

M/e 444.1714 (M^+,0.5%), 205 (0.7%), 172 (12.1%), 171(100%), 170(0.4%), 143 (5%), 142(0.4%) 115(0.5%), 69(0.7%).

U.V. (CH_3CN) $\lambda_{max.}$ = 225 nm,ε = 5.33 x 10^4; $\lambda_{max.}$ = 275 nm,ε = 3.3 x 10^4

(6.8)

I.R. ($CHCl_3$)$\nu_{max.}$ 1780-1750 cm^{-1} (β-lactam and ester carbonyls).

N.m.r. ($CDCl_3$) δ 1.22(s,9H,^tBu), 1.49(s,3H,Me), 1.62(s,3H,Me), 3.78(s,3H,N-Me), 4.45 (s,1H,H-3), 5.18(d,1H,J=4Hz,H-6), 5.74(d,1H, J=4Hz,H-5),5.78,5.92 (d,d,2H,J=6Hz,6Hz,CH_2), 7.12(t,1H,J=6Hz,H-10), 7.21(S,1H,H-7), 7.28(d,t,J=6Hz,H-9,H-11),7.42(d,1H,J=6Hz,H-8).

Elemental analysis : Found C 61.92% H 6.47% N 6.12%

Calculated C62.12% H 6.35% N 6.30%

M.pt = 119°-123°C

U.V. (CH_3CN) $\lambda_{max.}$ = 225 nm, $\varepsilon = 4.39 \times 10^4$

$\lambda_{max.}$ = 275 nm, $\varepsilon = 1.04 \times 10^4$

(6.9)

I.R. ($CHCl_3$) $\nu_{max.}$ 3400 cm^{-1}(N-H), 1750-1735 cm^{-1} (ester and thiolactone carbonyls), 1620 cm^{-1}(unsaturated thiolactone).

N.m.r. ($CDCl_3$) δ 1.23(s,9H ^{t}Bu), 1.50(s,3H,Me), 1.61(s,3H,Me), 3.74(s,3H,N-Me), 4.52(d,1H,J=7.0Hz,H-3) 5.80(m,1H,NH), 5.81,5.96 (d,d,2H,J=6Hz,6Hz,-CH_2-),7.04(s,1H,H-7), 7.09(d,d,2H,J=7.5Hz, 7.5Hz,H-5,H-11), 7.18,7.26(t,t,2H,H-9,H-10), 7.45(d,1H,J=7.5Hz, H-8).

M/e 444(M^+,5.6%), 178(16.0%), 84(74%), 82(100%).

U.V. (CH_3CN) $\lambda_{max.}$ = 231 nm, $\varepsilon = 7.86 \times 10^3$

$\lambda_{max.}$ = 274 nm, $\varepsilon = 5.89 \times 10^3$

1-Cyclohexenyloxytrimethylsilane(7.6)[168]. All reagents,solvents and glassware were carefully dried before use. Cyclohexanone (12.96ml, 0.125 moles) was dissolved in dimethylformamide (50ml), and to this solution were added triethylamine (41.74 ml, 0.3 moles) and chlorotrimethylsilane(19.01 ml, 0.15 moles). The mixture was refluxed for 11 hours, and filtered to remove triethylaminehydrochloride. The solution was diluted with 40°-60°C petroleum ether (100ml, immiscible), and washed with saturated sodium bicarbonate solution (3 x 150ml). The organic phase was rapidly washed with ice-cold hydrochloric acid solution (150 ml,1.5M) followed by an ice-cold sodium bicarbonate solution (150 ml). The solution was dried ($MgSO_4$) and evaporated at reduced pressure to yield a dark orange oil. Fractional distillation of the products through a Vigreux

column afforded the cyclohexene (7.6) as a colourless liquid.

b.pt 57-60°C, 18mm Hg. (lit.[168] 64-65°C, 15mm).

I.R.(film), $\nu_{max.}$ 2910 cm^{-1}(cyclic C-H stretches), 2840 cm^{-1}(CH_3), 1665 cm^{-1}(C=C), 1100 cm^{-1}(Si-O)

N.m.r. ($CDCl_3$) δ 0.15(s,9H,$SiMe_3$), 1.54, 1.94(m,m,8H,cyclohexane), 4.82(t,1H,vinyl).

Reaction of 1-Cyclohexenyloxytrimethylsilane (7.6) with p-Nitrobenzyl 6-diazopenicillanate. 6-Diazopenicillanate (0.6560g, 1.812 mmoles) was dissolved in dichloromethane (30ml). The solution was stirred at 0°C while cyclohexene (0.3080g, 1.812 mmoles) and copper acetylacetonate (5%, 0.0328g) were added. Stirring was continued for 4.5 hours, after which an I.R. spectrum showed that the diazo group was no longer present. Dry methanol (20ml) and T.L.C. grade silica (2g) were added to the reaction mixture, and stirring continued for a further 4 hours. The solution was filtered to remove the silica and evaporated under reduced pressure, yielding a dark brown oil, which was subsequently dissolved in chloroform (5ml) and precipitated with hexane (50 ml). The products were filtered, whereby the unreacted cyclohexene, soluble in hexane, was removed. The light brown solid was redissolved in chloroform and separated into its five individual components by preparative thin layer chromatography, using dichloromethane as eluant. The most polar fraction contained the required adduct (7.8) as a white solid. Yield = 14.1 mg, 2%, after purification.

M.pt 105-6°C.

I.R. ($CHCl_3$) $\nu_{max.}$ 3400 cm^{-1}(OH), 2980 cm^{-1}(cyclic CH), 1770 cm^{-1} (β-lactam carbonyl), 1750 cm^{-1}(ester carbonyl).

N.m.r. ($CDCl_3$) δ 0.70-1.94 series of multiplets including:

0.84(m,1H,H-7), 1.40(s,3H,Me), 1.56(s,3H,Me);
4.66(s,1H,H-3), 5.31(s,2H,$-CH_2CO_2PNB$),5.92(s,1H,
H-5), 7.58(d,2H,J=8Hz,PNB), 8.26(d,2H,J=8Hz,PNB).

M/e 432(M^+,0.4%), 295(0.3%), 180(0.2%,CO_2PNB),
136(3.9%,PNB), 100(0.1%, cyclohexanol).

1-Phenyl-1-trimethylsilyloxyethene (7.9)[168]. Acetophenone (20g, 0.1667 moles) was refluxed in DMF (60 ml) with trimethylsilyl chloride (0.3334 moles, 36.17g) and triethylamine (70ml, 0.5001 moles) for 46 hours. The triethylamine hydrochloride was filtered off and the filtrate diluted with petroleum ether (50ml). The solution was washed with $NaHCO_3$ solution (3 x 150ml) to remove the DMF. The organic phase was then washed with ice-cold 1.5M HCl followed by ice-cold $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated. The yellow liquid was fractionally distilled to give two fractions, the first of which was unreacted acetophenone (b.pt $_{12mm}$ 84-85°C), and the second the ethene (7.9) (b.pt $_{12mm}$ 93-94°C , lit.b.pt $_{12mm}$ 89-91°C). Further distillation was necessary in order to obtain a sample of product free from acetophenone. Yield = 20%.

I.R.(film) $\nu_{max.}$ 3100-2900cm^{-1}(aromatic and aliphatic CH), 1630cm^{-1}(C=C)
N.m.r. ($CDCl_3$) δ 0.24(s,9H,3Me), 4.44, 4.92 (d,d,2H,J=2Hz,2Hz,$=CH_2$)
7.25, 7.61(m,m,5H,Ph).

Reaction of p-Nitrobenzyl 6-diazopenicillanate with Methyl acrylate[68]. p-Nitrobenzyl 6-diazopenicillanate (0.2277g, 0.629mmol) was dissolved in dichloromethane (40ml) and methyl acrylate (0.0811g, 0.944mmol) was added. The solution was stirred for 22 hours out of light, and the solvent was removed under reduced pressure. The products were isolated by preparative T.L.C., eluting with dichloromethane/diethyl ether (9:1), giving rise to the pyrazolines (7.17) (7.18) in 59% and 11% yields respectively.

(7.17)

m.pt. 77-79°C.

I.R. ($CHCl_3$) $\nu_{max.}$ 3310 cm^{-1}(NH), 3010-2950 cm^{-1}(aromatic and aliphatic C-H), 1780 cm^{-1}(β-lactam C=O), 1745-1710 cm^{-1}(ester C=O's)

N.m.r. ($CDCl_3$) δ 1.44 (s,3H,Me), 1.55(s,3H,Me), 3.50 (q,2H,J=20Hz, $-CH_2-$), 3.88(s,3H,OMe), 4.55 (s,1H,H-3), 5.30,5.31(2s,3H,$-CH_2-$,H-5), 7.16(s,1H,N-H), 7.54(d,2H,J=8Hz, aromatic), 8.22(d,2H,J=8Hz,aromatic)

M/e 448(M^+)

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 274 nm

Elemental Analysis : Found C 50.86%, H 4.42%, N 12.42%

Calculated C 50.88%, H 4.50%, N 12.49%

(7.18)

m.pt 157-8°C

I.R. ($CHCl_3$) $\nu_{max.}$ 3320 cm^{-1}(N-H), 3010-2950 cm^{-1}(aromatic and aliphatic C-H),1780 cm^{-1}(β-lactam C=O),1745 cm^{-1}(ester C=O), 1710 cm^{-1}(ester C=O).

N.m.r. ($CDCl_3$) δ 1.47(s,3H,Me), 1.64(s,3H,Me), 3.5 (ill-defined dd,2H,$-CH_2$), 3.88 (s,3H,OMe), 4.60(s,1H,H-3), 5.32 (s,3H,$-CH_2-$,H-5), 7.07 (s,1H,N-H), 7.55(d,2H,J=8Hz, aromatic), 8.25(d,2H,J=8Hz, aromatic).

M/e 448(M^+).

U.V. (CH_2Cl_2) $\lambda_{max.}$ = 274 nm.

Elemental Analysis : Found C 50.73%, H 4.66%, N 12.36%

Calculated C 50.88%, H 4.50%, N 12.49%

Action of heat on spiropyrazoline (7.17). The spiropyrazoline (7.17)(50mg) was heated for 30 minutes in an oven at 120°C. I.R. and n.m.r. spectra of the material showed that no change had occurred.

Reaction of Pivoyloxymethyl 6-diazopenicillanate with Allyl acetate. Pivoyloxymethyl 6-diazopenicillanate (190mg, 05572 mmol) was stirred in allyl acetate (2ml) with rhodium acetate catalyst (2mg,1%). Bubbles of nitrogen began to evolve immediately. After 1 hour, an I.R. spectrum showed total decomposition of the diazo group had occurred, and the excess allyl acetate was removed under reduced pressure. The products were isolated by preparative T.L.C., eluting with dichloromethane/ethyl acetate (9:1), and giving (7.21) in 13% yield.

I.R. ($CHCl_3$) $\nu_{max.}$ 3460-3410 cm^{-1}(N-H), 1755 cm^{-1}(thiolactone and ester C=O's).

N.m.r. ($CDCl_3$)(360 MHz) δ,1.17(s,9H,^tBu), 1.39(s,3H,Me), 1.45(s,3H,Me), 4.21(m,3H,H-3,H-7,H-8), 5.12(m,1H,NH), 5.18(m,2H,H-10,H-11), 5.72, 5.86 (d,d,2H,-$\underline{CH_2}CO_2$), 5.92(m,1H,H-9), 6.94(d,1H,H-5,J=7Hz).

D_2O exchange caused the N-H signal at 5.12δ to disappear, and the doublets of H-3(4.21δ) and H-5(6.94δ) to collapse to singlets.

M/e 372 (M^+,^{13}C isotope, 3.33%), 371.1425(M^+, 12.55%), 274(25.7%), 244(18.4%), 160(17.1%), 82(38%), 57(100%).

U.V. (MeOH) $\lambda_{max.}$ 260 nm,ε = 2349.

$\lambda_{max.}$ 329 nm,ε = 2349.

Elemental Analysis : Found C 54.60%, H 6.92%, N 3.50%

Calculated C 54.97%, H 6.78%, N 3.77%

Reaction of Pivoyloxymethyl 6-diazopenicillanate with Allyl acetate using Rhodium trifluoroacetate. Pivoyloxymethyl 6-diazopenicillanate (352mg, 1.0322mmol) was stirred in allyl acetate (2ml) with rhodium trifluoroacetate (2%,7mg). The rate of reaction was much slower than the analogous reaction using rhodium acetate. After 16 hours,

an I.R. showed total decomposition of the diazo group, and the excess allyl acetate was evaporated under reduced pressure. The products were isolated by means of preparative T.L.C. using dichloromethane/ethyl acetate (9:1) as eluant, and eluting twice to obtain optimum separation. Compounds (7.21) and (7.22) were produced in 10% and 13% yields respectively.

(7.22)

I.R. ($CHCl_3$) $\nu_{max.}$ 3060 cm^{-1} (aliphatic C-H), 2995-2880 cm^{-1} (aliphatic C-H), 1790 cm^{-1} (β-lactam C=O), 1760-1740 cm^{-1} (ester C=O's).

N.m.r ($CDCl_3$) (360 MHz) δ 1.19(s,9H, ^tBu), 1.48(s,3H,Me), 1.55(s,3H,Me), 1.85(dd,1H,J=14Hz,6Hz,H-7_A), 1.95(s,3H,$\underline{CH_3}CO$),2.13(dd,1H,J=14Hz,10Hz, H-7_B),4.27(dd,1H,J=12Hz,4Hz,H-9_A), 4.55(s,1H,H-3),4.65(dd,1H,J=12Hz, 2.7Hz,H-9_B), 5.00(m,1H,J=2.7Hz,4Hz,10Hz,6Hz,H-8), 5.67(s,1H,H-5), 5.72,5.83(d,d,2H,-$\underline{CH_2}$-CO_2).

M/e 413.1442 (M^+, 1.53%), 339(1.2%), 326(2.1%), 274(3.8%), 225(4.6%), 212(9.4%), 175(10.3%), 139(19.1%), 57(100%).

U.V. (CH_3CN), $\lambda_{max.}$ = 224 nm, ε = 2,767

$\lambda_{max.}$ = 330 nm, ε = 248.

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