Synthetic Approaches to Nuclearly-Modified Cephalosporin Antibiotics

THESIS

presented to the University of Glasgow
in part fulfilment of the requirements
for the degree of Doctor of Philosophy

by

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1977

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To my wife, Rosemary

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During the course of my work in these laboratories a number of research workers have contributed to creating an intellectually and socially stimulating atmosphere in which to work; specifically Drs. J. O'Donnell, B. Hamill, D. MacDougall, H. Mackie, and Messrs. D. Picken, I. Forbes, and D. Anderson who have given freely of advice and friendship and to them I am indebted.

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I should also like to thank Professor G.W. Kirby for extending his hospitality to allow me to undertake this work in the University of Glasgow Chemistry Department.

SUMMARY

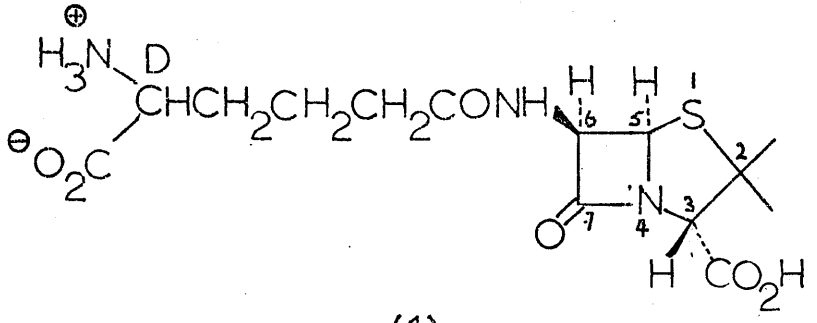
Synthetic routes to a 1-hydroxy-1-carbacephem (1), by structure-activity considerations an analogue of potential antibiotic activity, are described.

Synthesis of a substituted pyridine for reduction to a cyclic enamine and subsequent annellation to a β-lactam were not successful.

An acyclic imine precursor of (1) was prepared but did not yield a β-lactam by an established annellation procedure.

Approaches to a cyclic amine potentially convertible into (1) are described.

CONTENTS



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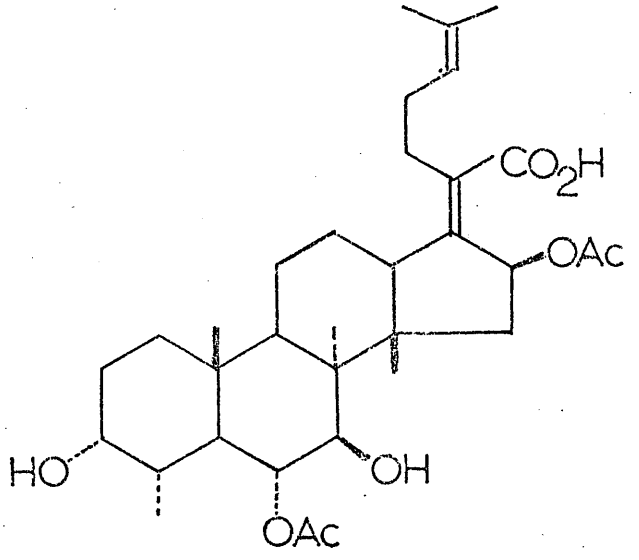

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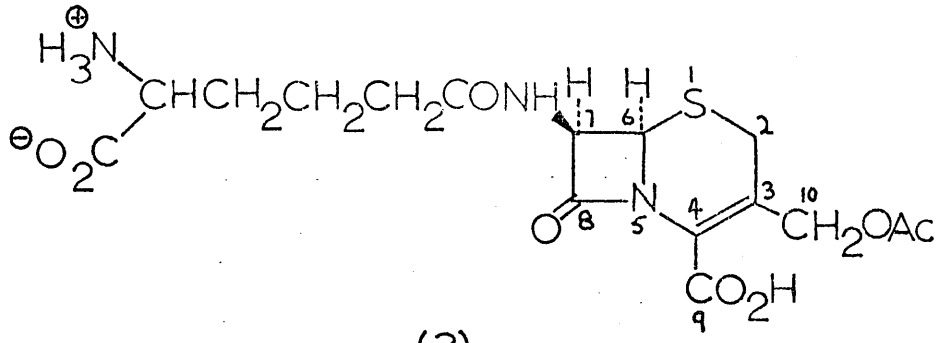
INTRODUCTION

From relatively inauspicious beginnings, the cephalosporin group of antibiotics has grown in importance as a potent weapon in the armoury of chemical substances employed in chemotherapeutics. Following the discovery of the penicillins at Oxford and the demonstration of their antibacterial properties,[1] a search was initiated for other antibiotic-producing organisms. A publication in 1948 in a little circulated journal, 'The Works of the Institute of Hygiene of Cagliari', hailed the entry of the cephalosporins on to the antibiotic scene. Guiseppe Brotzu, considering that the process of self-purification of sewage wastes might be due to bacterial antagonism, examined the microbial extracts of sea water at a sewage outlet in Sardinia. From these he was able to isolate and culture a species of fungus similar to Cephalosporium acremonium, the filtrates of which showed considerable bacteriocidal properties. Isolation of the active principles of the cultures proved beyond the limited resources of Brotzu and investigations were transferred to Oxford.

There, extensive work involving advanced separation techniques and degradative chemistry revealed three major active species:[2] penicillin N (1), a penicillin with the novel D-α-aminoadipyl side chain, which was responsible for the biological activity observed by Brotzu; cephalosporin P (2), a steroidal antibiotic of limited activity; and cephalosporin C, a novel β-lactam



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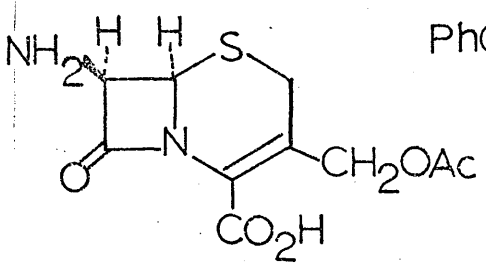

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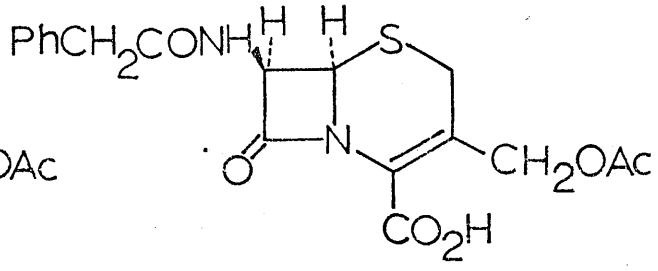

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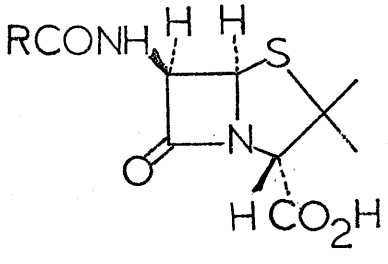

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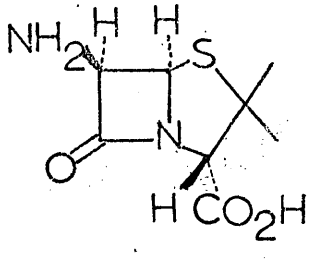

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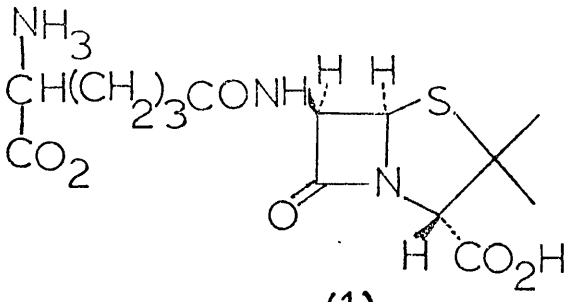
again exhibiting limited bacteriological potency. Despite its low activity, cephalosporin C aroused considerable excitement due to its resistance to cleavage by the enzyme penicillinase, a β-lactamase produced by penicillin-resistant bacteria. The structure (3) of this new antibiotic was ultimately established as a result of chemical elucidation[3] and X-ray analysis,[4] when it became evident that, since penicillin N also contained the D-α-aminoadipyl side chain, β-lactamase resistance was due to the novel ring system, a fused β-lactam-dihydrothiazine. Furthermore, careful hydrolysis of cephalosporin C to 7-aminocephalosporanic acid (7-ACA) (4) and acylation to the N-phenylacetyl derivative (5) gave a new antibiotic with greatly enhanced activity.

Thus, a decade after the original discovery by Brotzu, the cephalosporin ring system or cephem had been added to the penicillin system or penam as the parent of a second family of β-lactam antibiotics, although it was yet another ten years before they became established products in medicine. It is with the chemistry and biochemistry of these antibiotics that this review is concerned.

1. Occurrence and Structural Types

Until five years ago only penicillins (6), 6-aminopenicillanic acid (6-APA) (7) and cephalosporin C (3) were obtained from a relatively few micro-organisms; the penicillins from Penicillium chrysogenum, cephalosporin C



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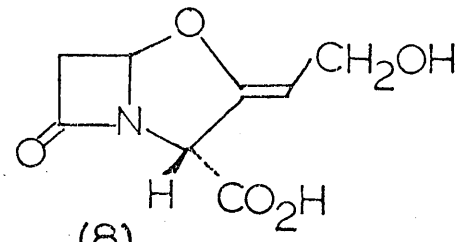

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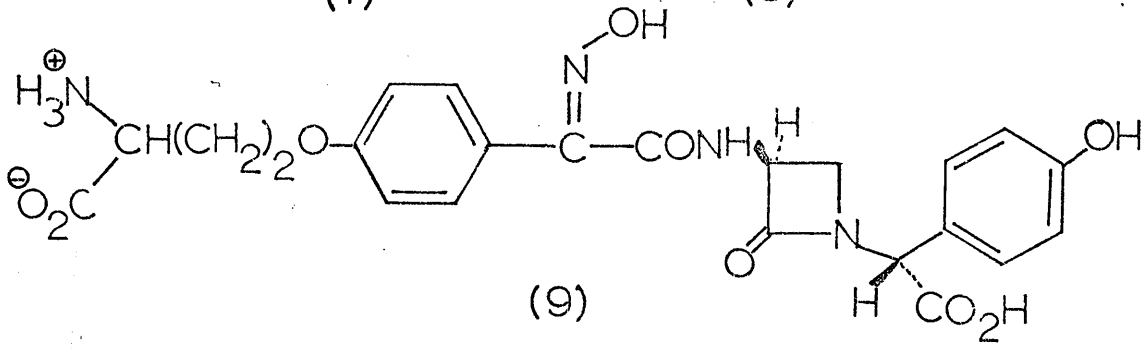

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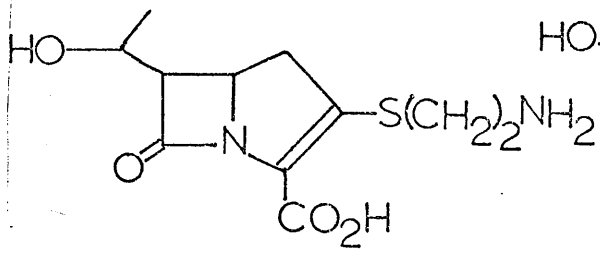

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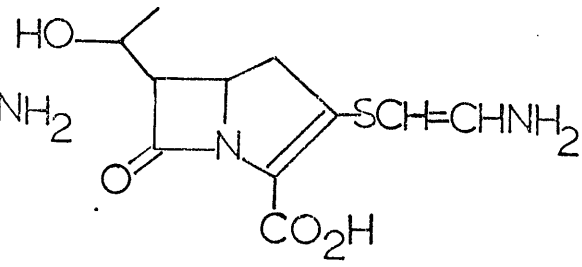

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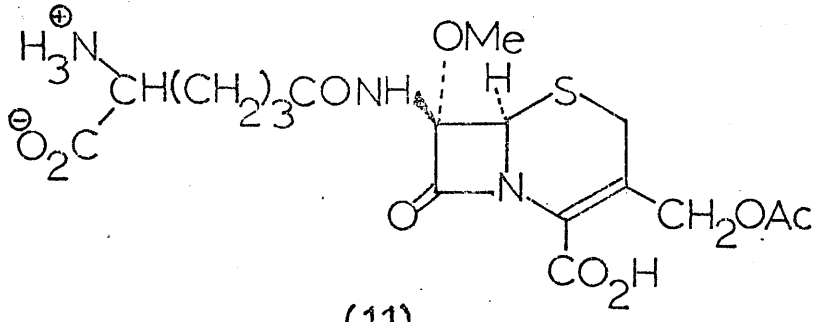

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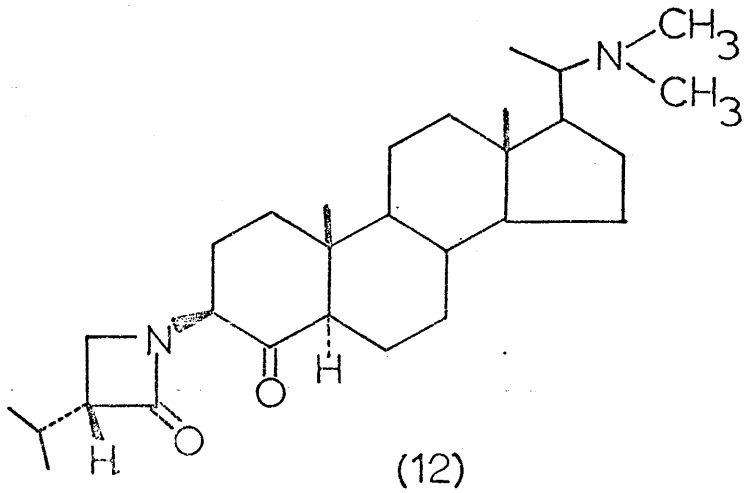
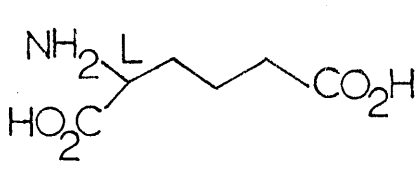


(12)

and penicillin N (1) from Cephalosporium acremonium. This situation altered dramatically with the discovery of other β-lactam containing compounds from Streptomyces and related Nocardia species. A feature of some of these substances is the lack of a fused sulphur-containing ring yet each exhibits biological activity; clavulanic acid (8)[5] is a powerful β-lactamase inhibitor; nocardicin A (9) and related compounds[6] and thienamycin (10a)[7a] are antibiotics; the recently isolated[7b] derivatives of olivanic acid (10b) combine these two features of biological activity. The diversity of structure and departure from the penam and cephem ring systems without loss of biological potency will certainly stimulate considerable research into more deep-seated modifications to the two basic ring systems. Also isolated from Streptomyces was the highly active 7-methoxycephem (11),[8] a member of the cephamycins.

The β-lactam antibiotics, detected because of their biological activity, represent only a sample of the naturally occurring β-lactam compounds; biosynthesis of these compounds now appears to be more widespread than was at first thought. For example, steroidal β-lactams such as (12) have been isolated[9] from the higher plant Pachysandra terminalis; these are not antibiotics. If β-lactams are produced by organisms for their attendant biological activity, then it is reasonable to predict the discovery of further members of the family with an even greater variety of structure.

Commercial production of clinically useful cephalo-



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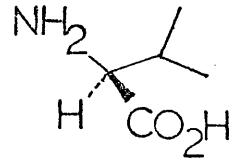

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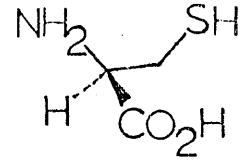

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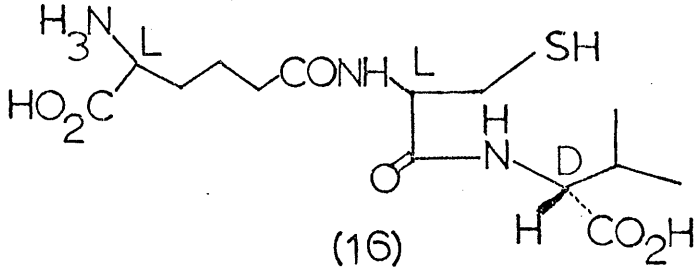

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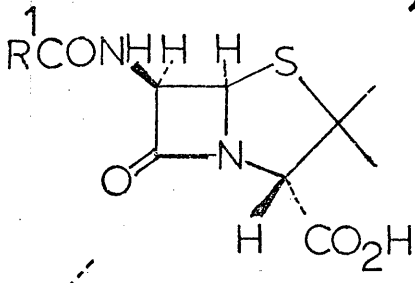
P. chrysogenum

C. acremonium, Streptomyces spp



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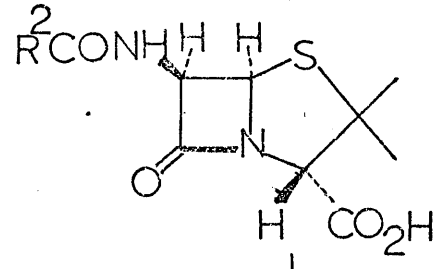

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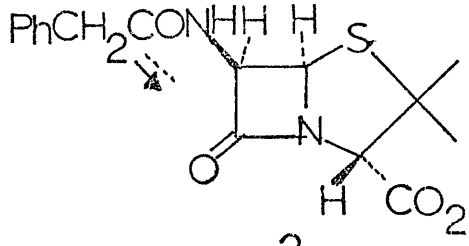
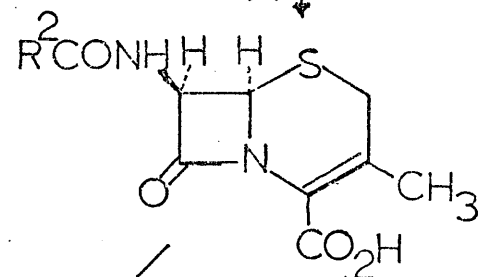
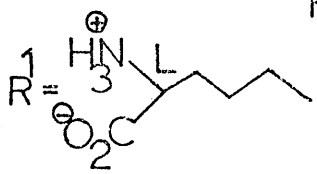
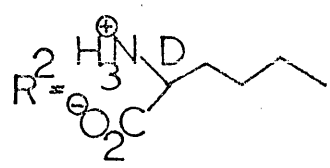
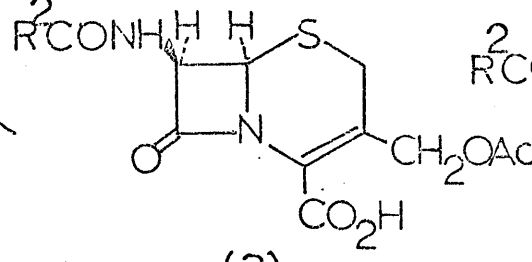
6-APA











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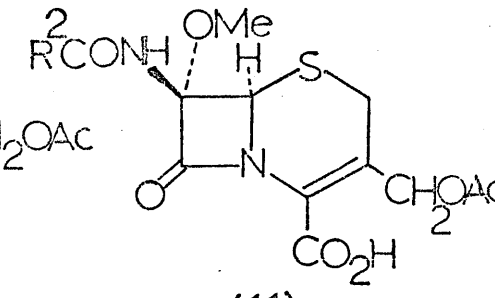

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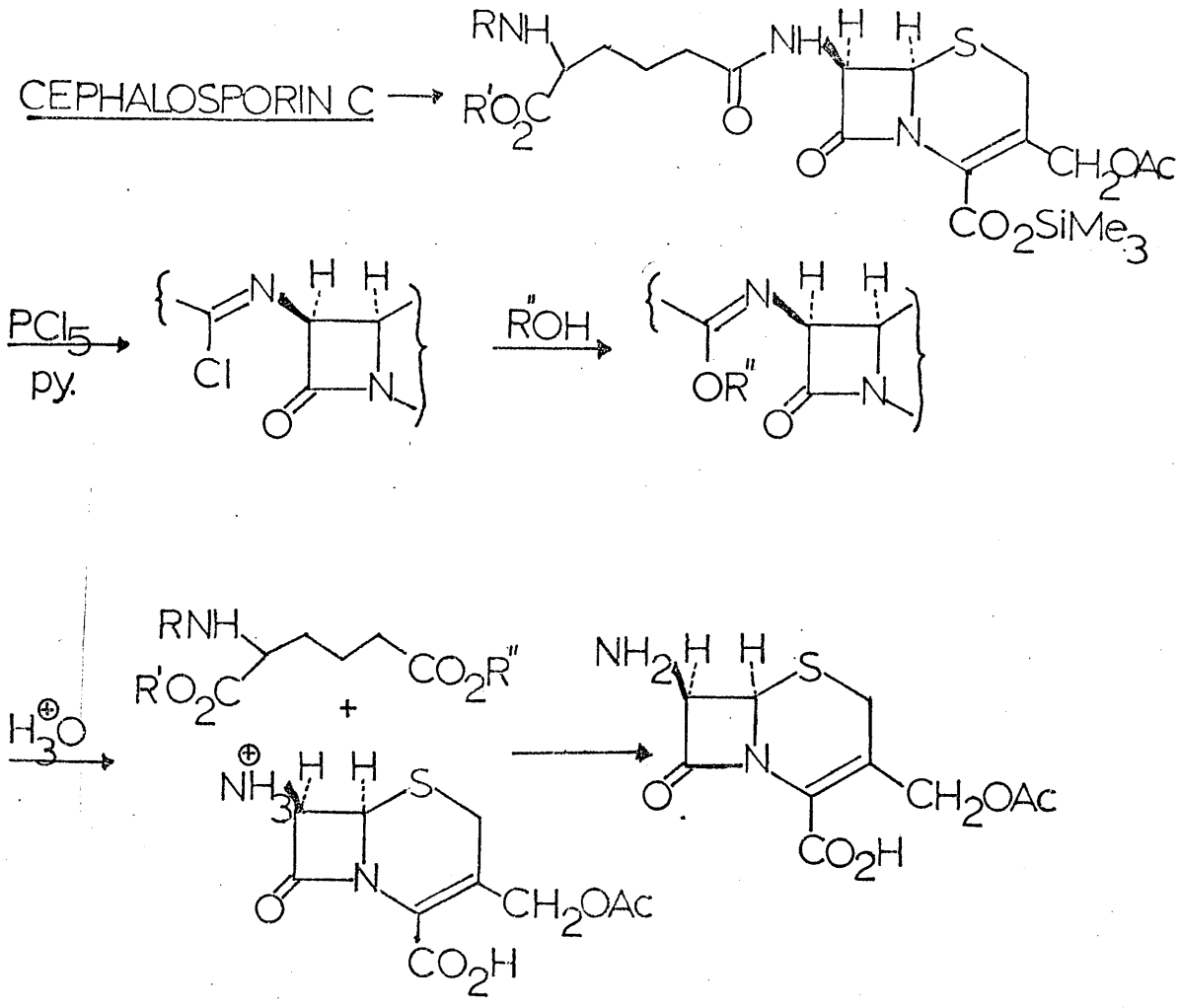
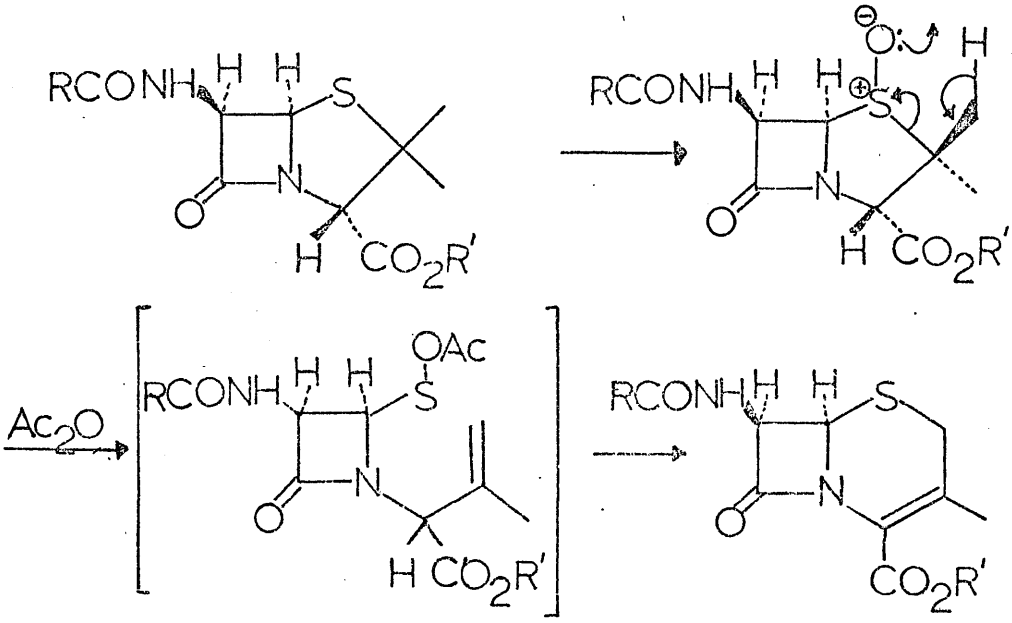
SCHEME 3



SCHEME 1



SCHEME 2

sporins relies heavily on fermentation techniques to produce cephalosporin C from which 7-aminocephalosporanic acid (4) can be prepared chemically[10] (Scheme 1); acylation then provides a range of valuable cephalosporin antibiotics.[9] The low yield of cultured cephalosporin C, and the inability to introduce a range of acyl side chains during culture, stimulated research into routes to 7-ACA from the more readily available penicillin nucleus. Such transformations (Scheme 2) have now been achieved[11] and constitute a further important commercial source of cephalosporin antibiotics.[12]

2. Biosynthesis of the Penicillins and Cephalosporins

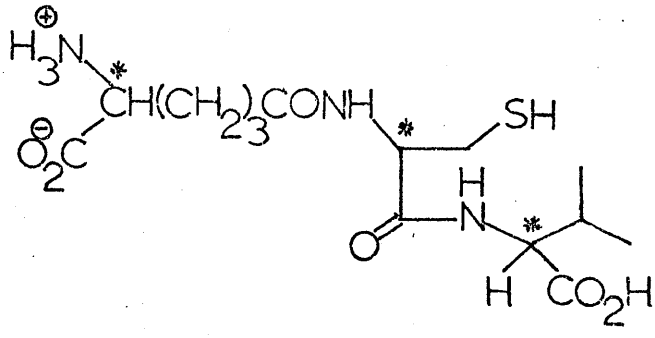
Early investigations established L-valine (13), L-cysteine (14) and L-α-aminoadipic acid (15) as essential precursors of the penicillins and cephalosporins. In the course of biosynthesis two configurational inversions take place; L-valine becomes a D-penicillamine fragment, and, in penicillin N and all the isolated cephalosporins, the α-aminoadipyl side chain is in the D-configuration.

In 1960, Arnstein isolated[14] from *Penicillium chrysogenum* the tripeptide δ-(α-aminodipyl) cysteinyl-valine (16) of undefined chirality. This so-called Arnstein tripeptide could, by further bond connections (Scheme 3), give rise to the penicillins and cephalosporins. Subsequently, this same tripeptide was isolated from the mycelium of *Cephalosporium acremonium* and its configur-

TABLE I

3 H LABELLED COMPOUND ADDED	INCORPORATION OF LABEL
L L D (∝- C labelled)	+
L L D (methyl labelled)	+
L L L (methyl labelled)	-
D L D (methyl labelled)	-
6 A P A	-
L Valine (methyl labelled)	-

Diastereoisomers of the tripeptide intermediate are indicated by LLD, LLL, DLD referring in order to the chiral centres in (16).

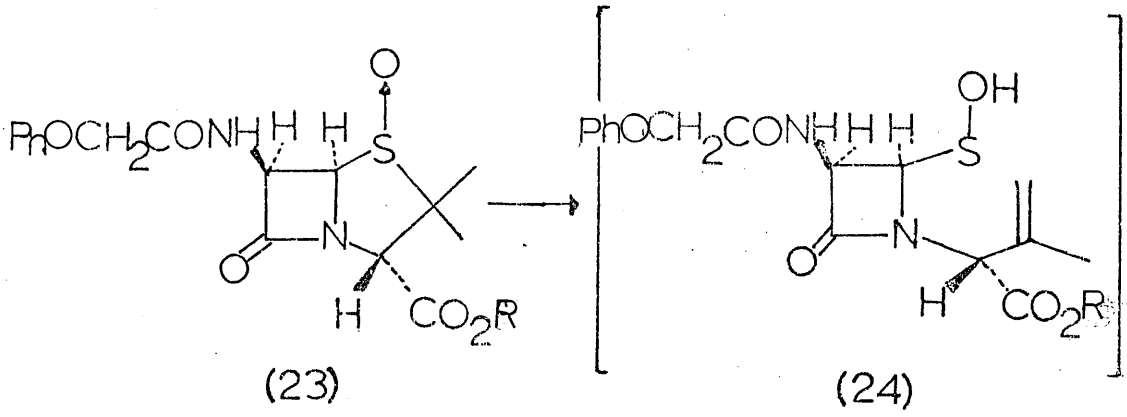


(16)

ation assigned[15] as LLD δ-(α-aminoadipyl) cysteinylvaline a configuration also assigned[16] to the tripeptide isolated by Arnstein.

Biosynthetic studies investigating this postulate have been hampered until recently by the fact that mycelial cells fail to incorporate all but the simplest precursors. Abraham has described[17] the use of cell free systems which have largely overcome these considerable difficulties and allowed incorporation studies of key intermediates to be undertaken. Several tritium labelled precursors were fed and the degree of incorporation of the radioactive label into penicillin N, the only β-lactam produced by the system, observed. These experiments (Table 1) unequivocally demonstrated the intermediacy of the LLD-tripeptide in penicillin N biosynthesis. The failure to observe incorporation of the DLD-tripeptide indicates that epimerisation of the α-aminoadipyl side chain occurs at a stage subsequent to tripeptide formation. Feeding studies with labelled isopenicillin N, penicillin N and 6-APA have demonstrated the intermediacy of both isopenicillin N and 6-APA but not penicillin N in the biosynthesis of benzyl penicillin in Penicillium chrysogenum (Scheme 3). These experiments show that most of the proposed transformations (Scheme 3) can occur in cell-free systems and that the LLD-tripeptide (16) is indeed the progenitor of both penicillins and cephalosporins.

The mode of cyclisation of the tripeptide (16) has been the subject of considerable speculation and scrutiny, an αβ dehydrocysteinyl-αβ-dehydrovalinyl intermediate



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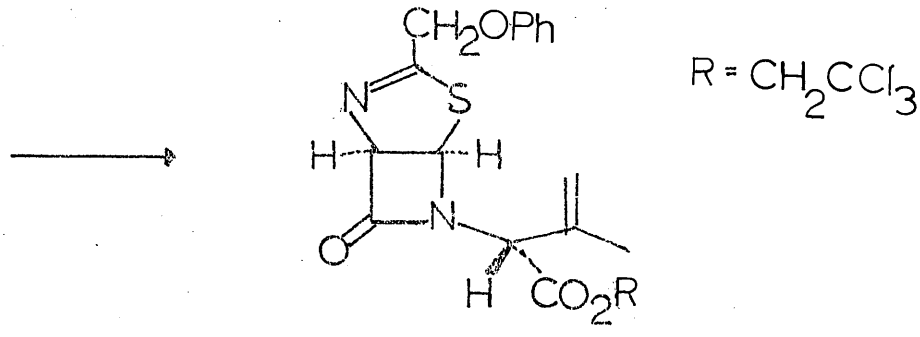
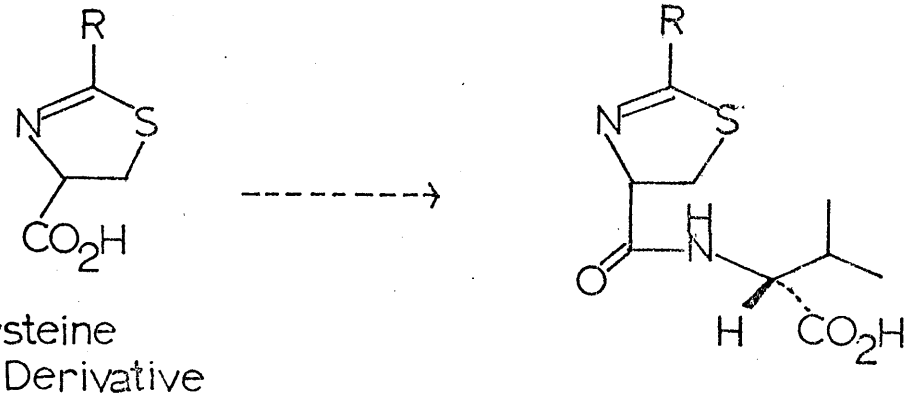


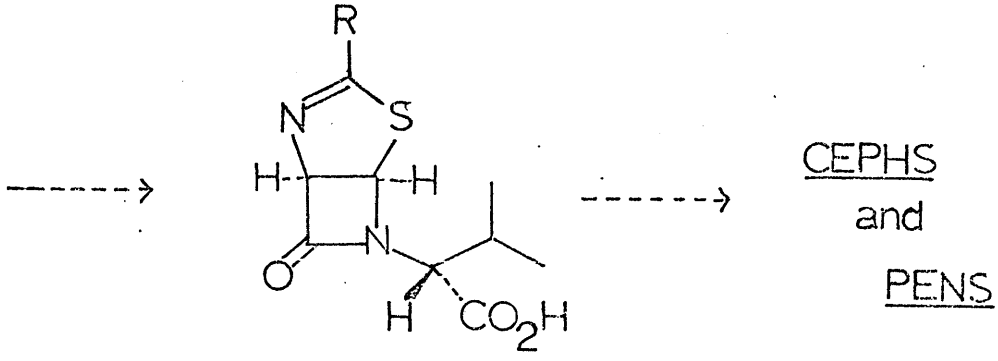
$R = CH_2CCl_3$

(25)

SCHEME 6

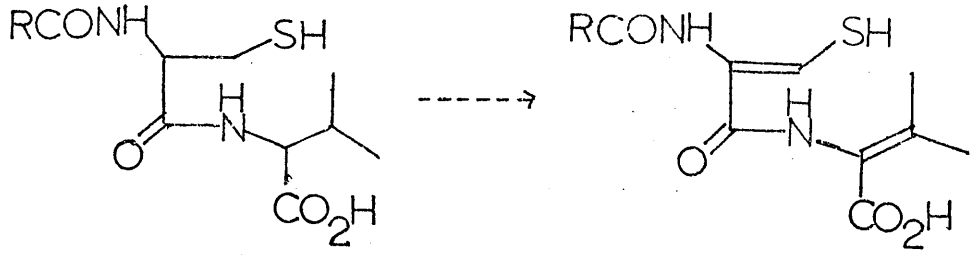


Cysteine Derivative



CEPHS and PENS

SCHEME 7



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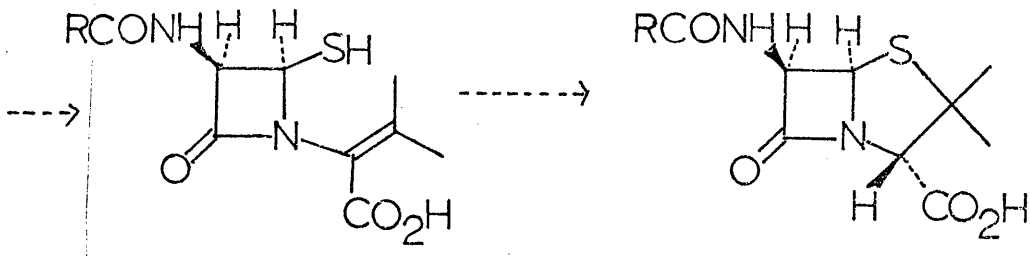

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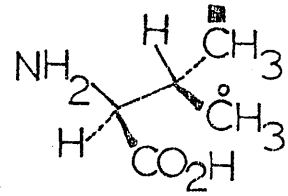

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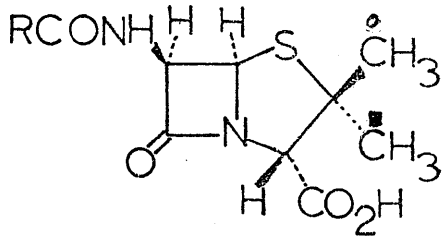

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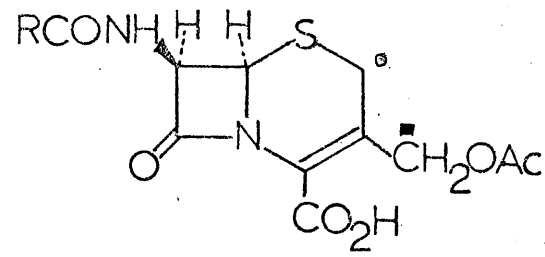


(22)

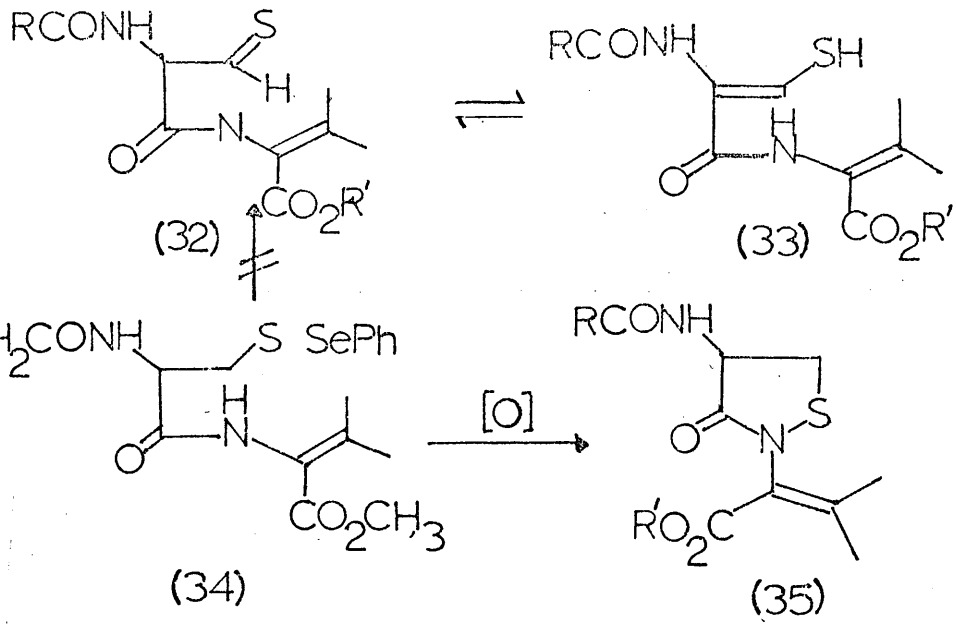
SCHEME 5

such as (19) being considered a possibility (Scheme 4). Involvement of an $\alpha\beta$-dehydrovaline in the cyclisation has recently been disproved; the labelled tripeptide produced by Cephalosporium acremonium in the presence of L-[2,3-^{3}H]-valine retained tritium at C-3 of the valine residue but the C-2 tritium was absent.[18] Bycroft has demonstrated[19,20] that $\alpha\beta$-dehydrocysteines are not involved in the biosynthesis of penicillins, by feeding L-[α-^{2}H]- and L-[α-^{3}H]-cysteine to Penicillium chrysogenum and observing incorporation of labels into the 6-position of the penicillin G produced.

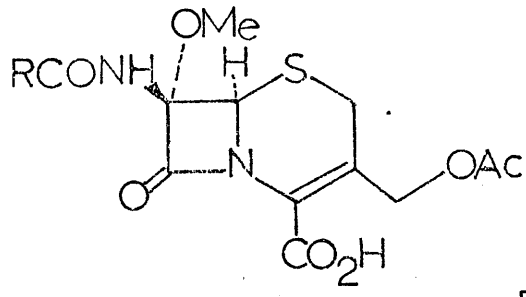
Attempts to obtain further information about the mechanism of cyclisation have employed "chiral" valine (20) to monitor the stereochemical course of cyclisation. 1,2-Bond formation in penicillins was found to proceed prochirally, giving rise to a single penicillin[21] (21); in cephalosporins 1,2-bond formation was again stereospecific,[22] giving rise to a single labelled species (22) (Scheme 5).

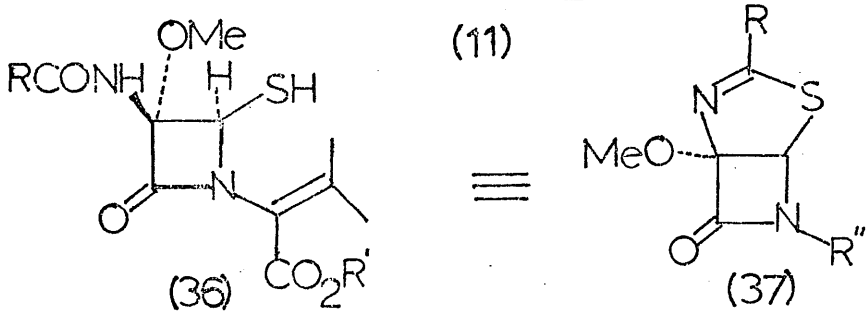
3. Biogenetically Patterned Cyclisation Studies

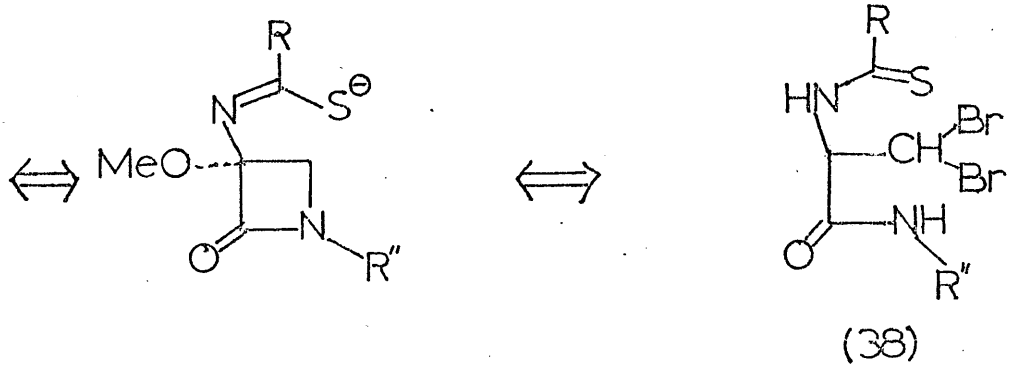
The thiazoline azetidinone (25) was obtained[23] by reductive intramolecular trapping of the reactive sulphenic acid (24) produced in the thermolysis of the penicillin sulphoxide (23) (Scheme 6). Cooper later proposed[24] this thiazoline azetidinone, with its N-$\alpha\beta$-dehydrovalinyl group, as a possible intermediate in the biosynthesis of penicillins and cephalosporins (Scheme 7). Indeed, mild



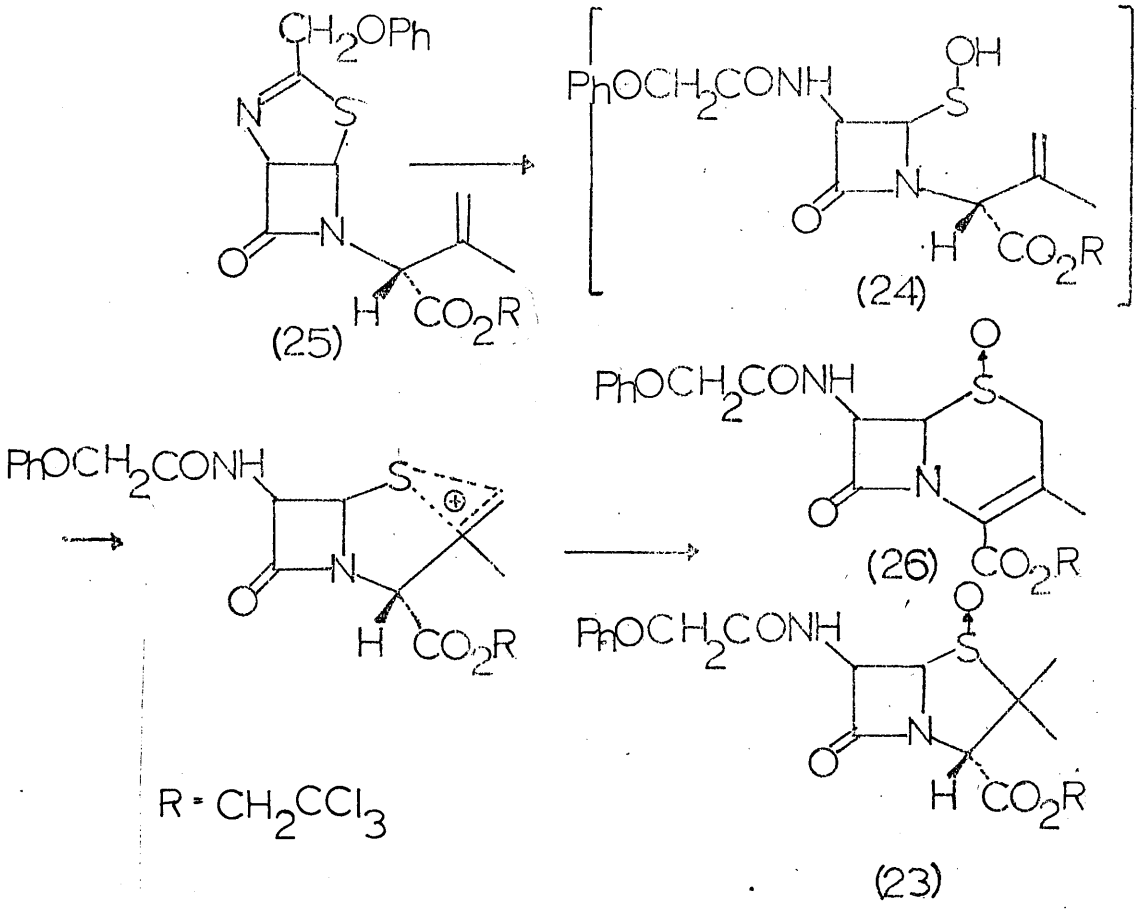
SCHEME 10



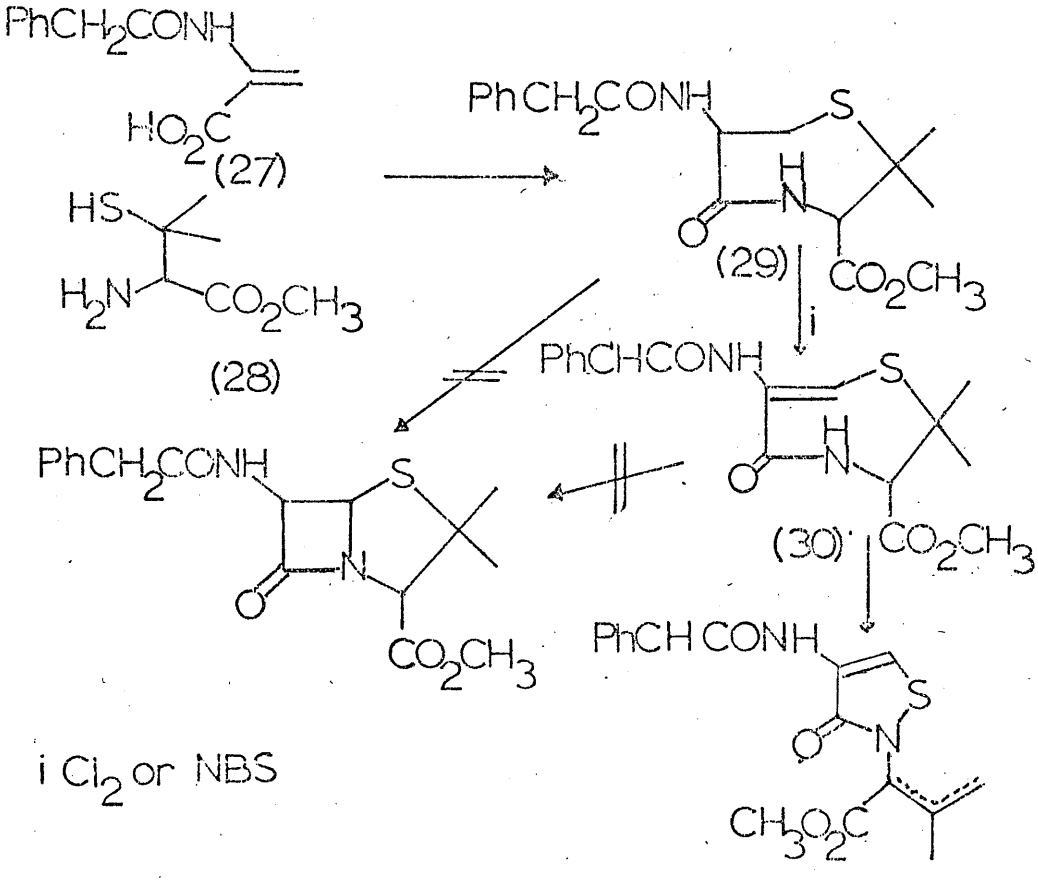




SCHEME 11



SCHEME 8



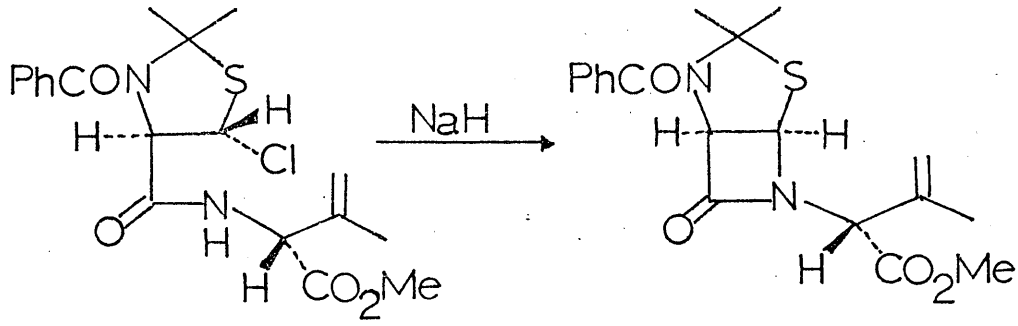
SCHEME 9

oxidation of (25) with peracid afforded a mixture containing the penam- (23) and the cephem- (26) sulphoxides, which presumably arose by cyclisation of the sulphenic acid (24) followed by rapid further oxidation (Scheme 8).

In contrast to such 1,2 bond formation, chemical formation of the 4,5 bond has proved much more difficult. Leonard prepared[25] the seven-membered lactam (29) from α-phenylacetamidoacrylic acid (27) and penicillamine methyl ester (28), but the anticipated oxidative cyclisation of (29) was not observed; rather, dehydrochlorination took place yielding (30) which further rearranged to an isomeric mixture of 3-isothiazolones (31).

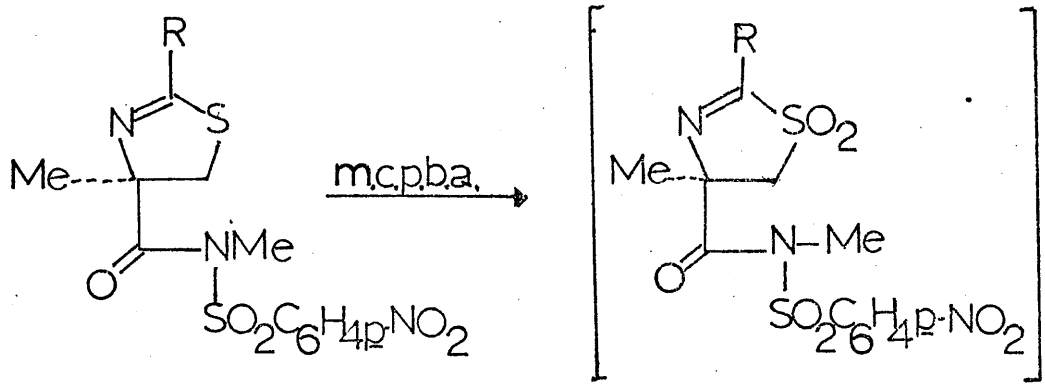
The thioaldehyde (32) and its enol (33) have attracted considerable attention as species thought likely to undergo spontaneous cyclisation to the β-lactam thiazolidine ring system. Baldwin[26] approached the thioaldehyde *via* the selenide (34), which on oxidation gave not (32) but the isothiazolidine (35) (Scheme 10). Scott also prepared[27] the thioaldehyde and related compounds, but was unable to convert any to β-lactams *in vitro*.

Kishi, in an elegant and ambitious synthetic study,[28] chose to construct ring systems with a methoxy group at the penam 6- or cephem 7-position, i.e., a cephamycin (11), reasoning that a substituent on the potential β-lactam ring would increase the tendency towards cyclisation. The basic route proposed is outlined in Scheme 11. The thiazoline (37), by analogy with Cooper's earlier work,[23] was considered to be the synthetic equivalent of (36); cyclisation of the dibromide (38) should yield (37),

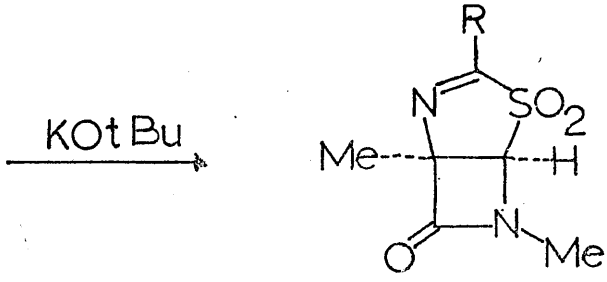


(45) (46)

SCHEME 13

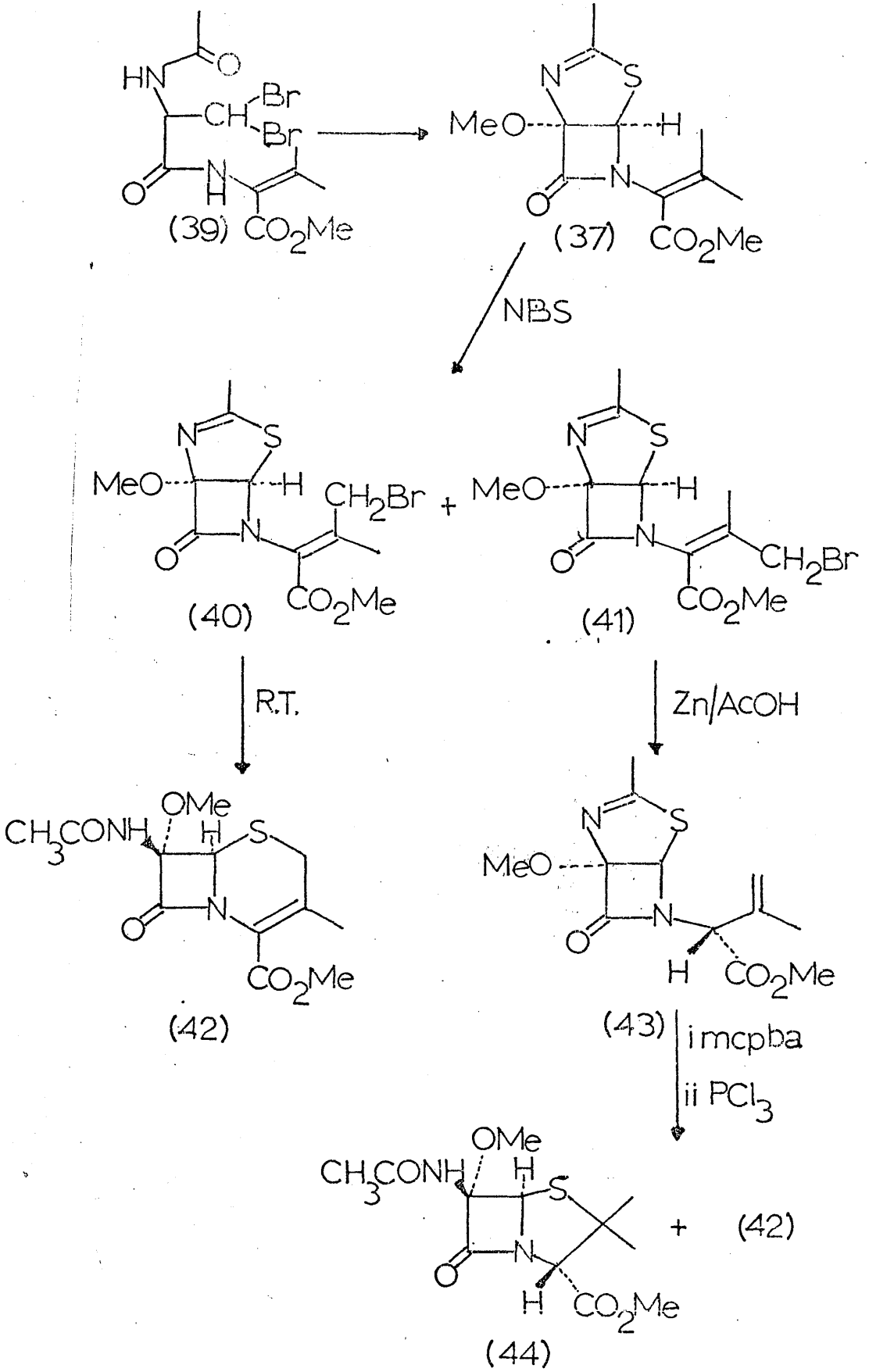


(47)



(48)

SCHEME 14


HN
O
CH
Br
Br
N
H
O
(39) CO2Me
N
S
MeO
H
O
N
(37) CO2Me
NBS
MeO
CH2Br
(40)
CO2Me
+
MeO
CH2Br
(41)
CO2Me
R.T.
Zn/AcOH
CH3CONH
OMe
H
S
N
O
CO2Me
(42)
MeO
N
S
O
N
H
CO2Me
(43)
i mcpba
ii PCl3
CH3CONH
OMe
H
S
N
O
H
CO2Me
(44)
+
(42)

SCHEME 12

the relative stereochemistry at the two epimeric centres being defined by the necessary cis ring fusion. The double cyclisation of the dibromide (38) to the thiazolidine β-lactam was achieved in one step from (39) (Scheme 12). 1,2-Bond formation was effected by bromination of (37) to give the isomeric bromides (40) and (41) the former affording the cephem (42) spontaneously. Reduction of the bromides (40) and (41) gave a mixture of alkenes from which (43) was separated and treated with peracid;[23] reduction of the sulphoxides so produced gave both the penam (44) and the cephem (42) (Scheme 12).

More recently, two complementary approaches to 4,5-bond formation have been reported. Baldwin prepared[29] the chloro-amide (45) which on treatment with base cyclised to the thiazoline (46) (Scheme 13), from which a penam was obtained. Indeed, application of this methodology led to the first chiral synthesis of benzyl penicillin.[30] Scott[31] adopted the alternative approach involving nucleophilic displacement on nitrogen; the thiazolidine sulphone (47) formed the β-lactam (48) on treatment with base (Scheme 14).

A number of these purported biomimetic syntheses were published prior to the biosynthetic studies which excluded the intermediacy of α,β-dehydrocysteine and α,β-dehydrovaline precursors. However, the more recent work proposes plausible cyclisation studies, which remain to be investigated in vivo.

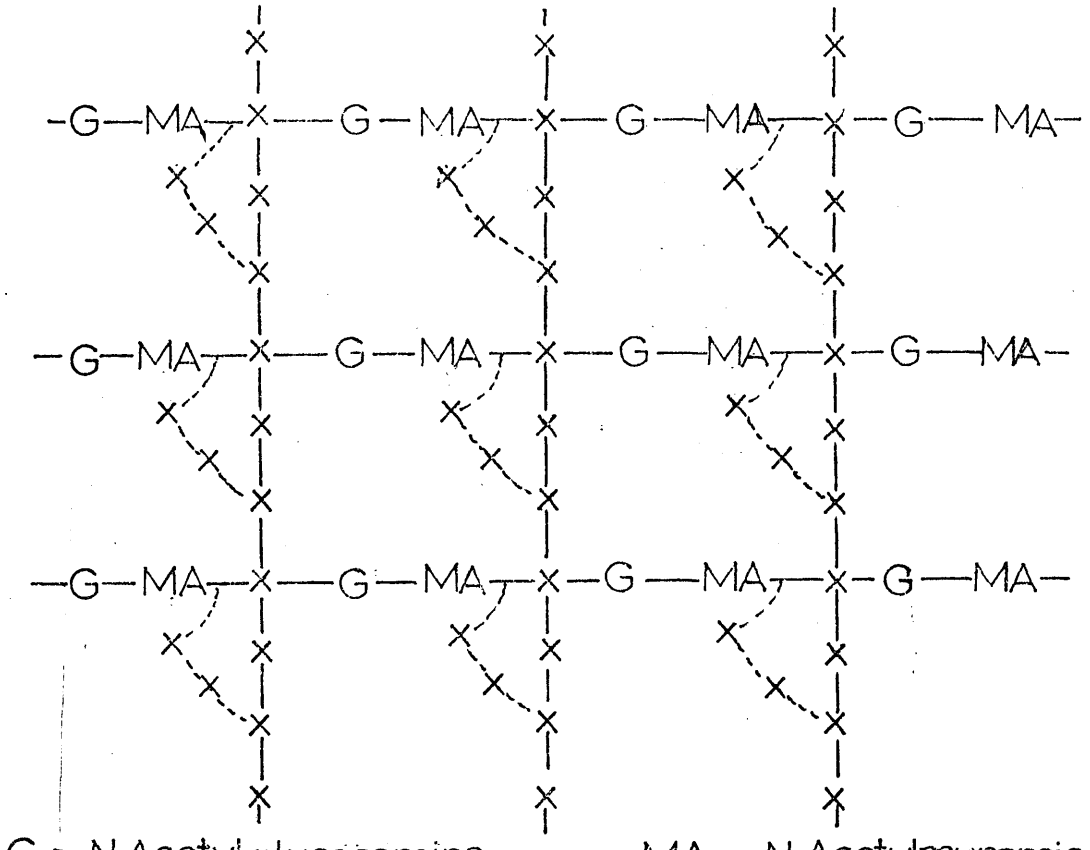
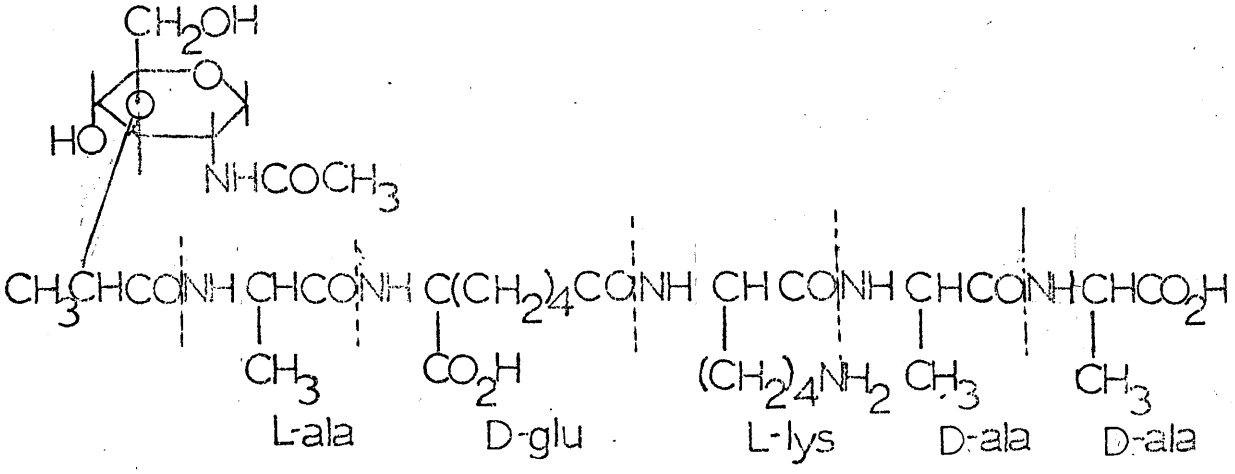

G = N-Acetylglucosamine
MA = N-Acetylmuramic acid
X = Amino acid units

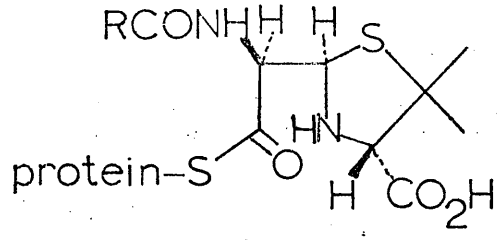
FIGURE 1


L-ala
D-glu
L-lys
D-ala
D-ala

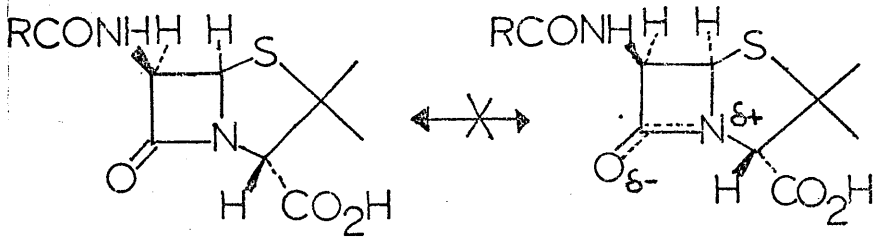
4. Mode of Action of β-Lactam Antibiotics.[32]

It is now well established that β-lactams interfere with bacterial cell wall synthesis, causing ultimate cell rupture. A close examination of bacterial cell walls reveals a considerable diversity of structure; the bacteria themselves are broadly classified according to their reaction to the Gram stain, as either Gram-negative or Gram-positive. This classification has greater significance than a mere practical staining reaction, as it reflects the nature of the cell wall structure. Gram-positive cell walls are simple structures with two main layers, of teichoic acid and murein, of about equal thickness. The murein is a tough fibrous layer providing strength and shape to the cell, enabling it to withstand osmotic pressure differences. Gram-negative bacteria, which are generally the more harmful to humans, have a complex multilayered cell wall, with a murein layer again providing rigidity. Biosynthesis of the murein layer is blocked in both cases by β-lactam antibiotics, thus fatally reducing the ability of the cell wall to withstand its internal osmotic pressure.

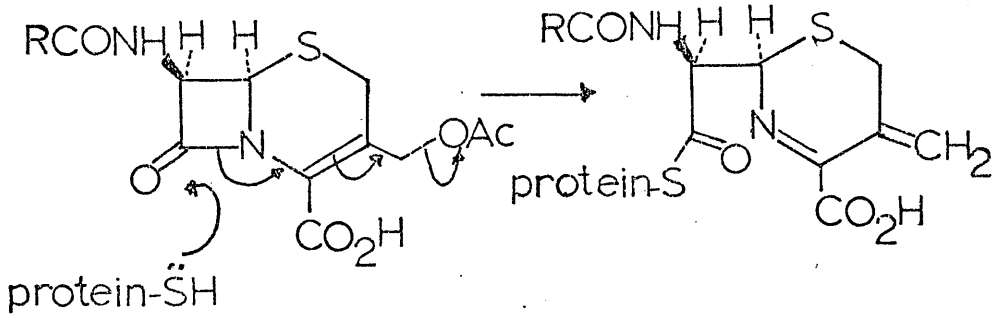
The structure of murein varies from species to species but its general form is that of a series of linear chains of amino sugars cross-linked by chains of amino acids (Figure 1). The synthesis of murein is a four stage process.[33] In the first three stages, which occur inside the cell, nucleotide pentapeptide units (49) are joined to form a linear polysacharide polymer and



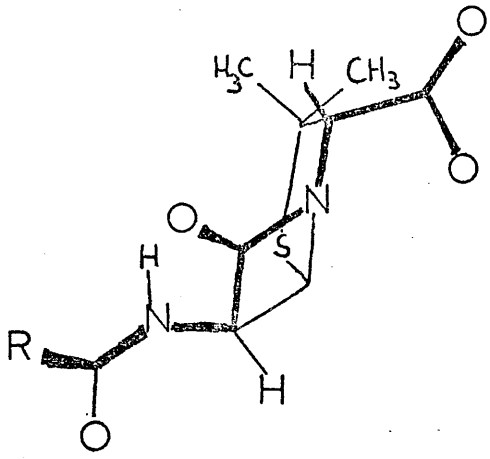
(50)



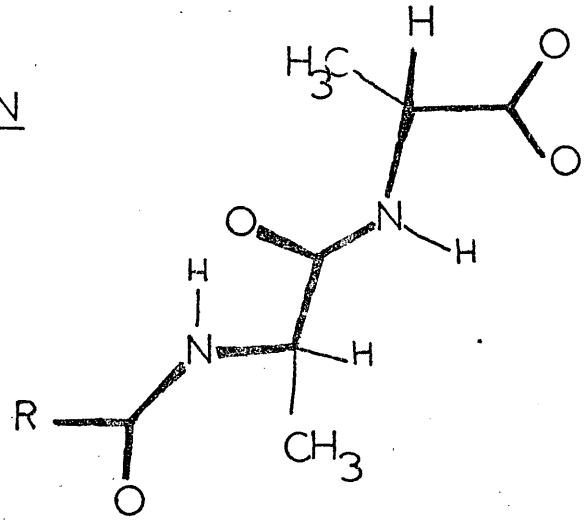
SCHEME 16



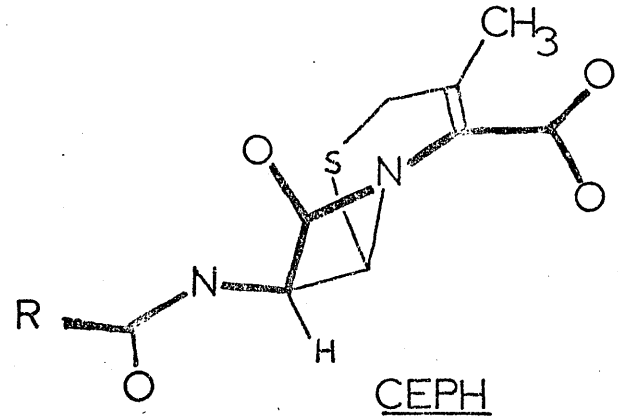
SCHEME 17



PEN

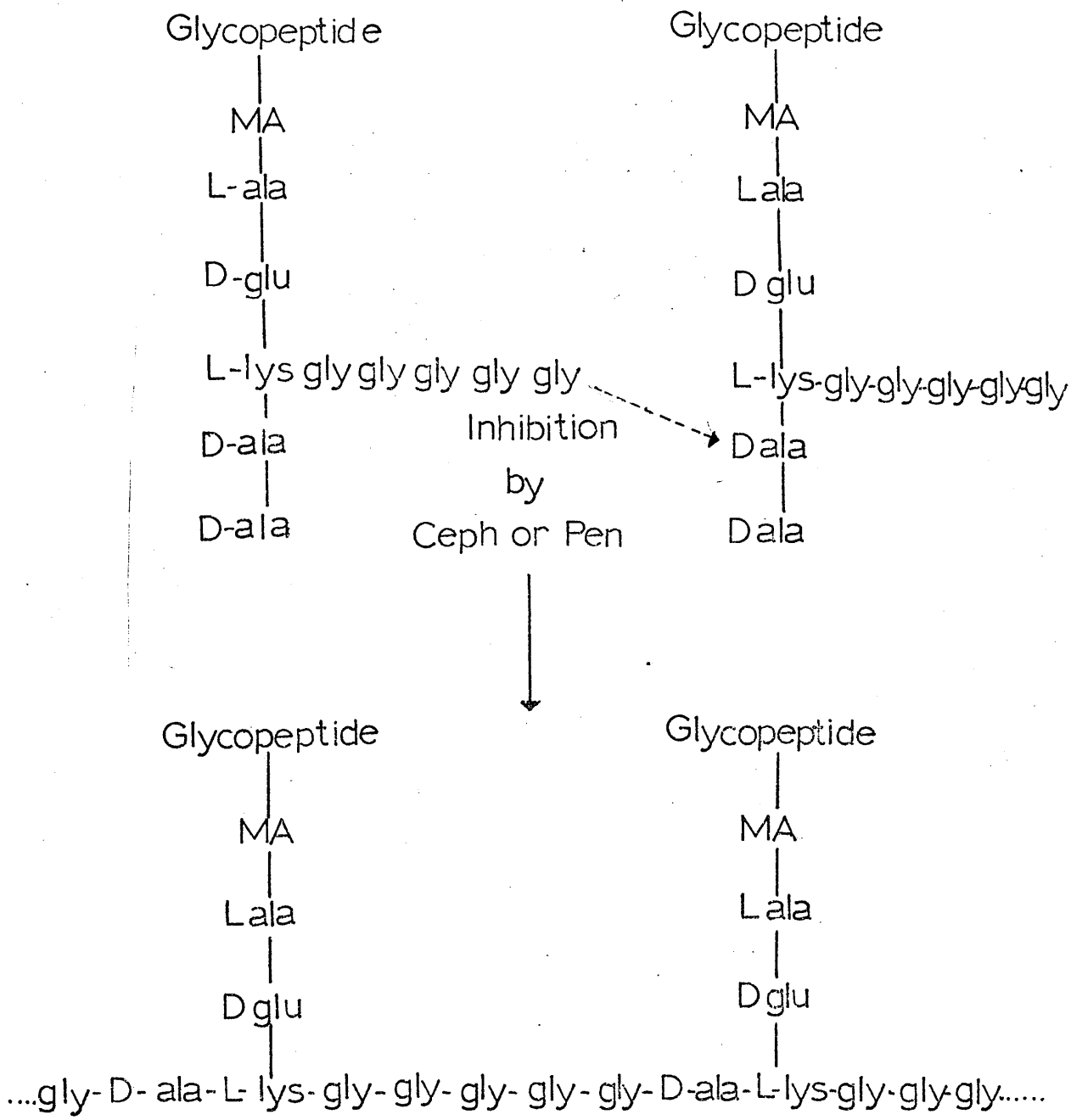


D-ala-D-ala



CEPH

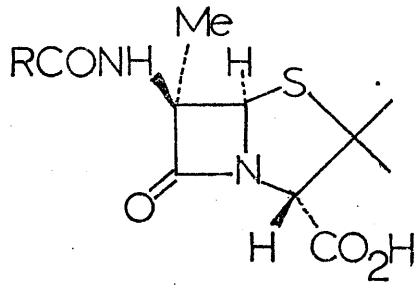
FIGURE 2


Glycopeptide
MA
L-ala
D-glu
L-lys gly gly gly gly gly
D-ala
D-ala
Inhibition
by
Ceph or Pen
Glycopeptide
MA
Lala
Dglu
L-lys-gly-gly-gly-gly-gly
Dala
Dala
Glycopeptide
MA
Lala
Dglu
Glycopeptide
MA
Lala
Dglu
....gly-D-ala-L-lys-gly-gly-gly-gly-gly-D-ala-L-lys-gly-gly-gly.....

SCHEME 15

pentaglycyl units added as branches to the amino acid chains. The final stage is cross-linking of the peptide chains, to impart the necessary strength to the murein, in an enzyme-mediated transpeptidation between the pentaglycyl side chains and a terminal D-alanyl-D-alanine residue to another peptide chain; D-alanine is eliminated and a new peptide bond is formed (Scheme 15).

In 1965, Tipper and Strominger,[34] recognising the basic similarity in the three dimensional structures of β-lactams and a D-alanyl-D-alanine unit (Figure 2) suggested that the transpeptidase enzyme involved in the cross-linking process may falsely recognise the antibiotic as the terminal D-alanyl-D-alanine unit, resulting in irreversible acylation and consequent deactivation, by the β-lactam moiety. It has been postulated that reaction of the enzyme with penicillins proceeds by thiol attack on the β-lactam to give the thioester (50). The degree of strain in penicillins, as indicated by the position of the carbonyl infrared stretching frequency, has been correlated with biological activity.[35] Increased acylating ability of penicillins compared with monocyclic β-lactams is directly attributable to steric inhibition to resonance induced by the fused five-membered ring, which prohibits adoption of the planar configuration necessary for full orbital overlap (Scheme 16). In the cephalosporins, ring strain induced by the fused six-membered ring is less; structure activity correlations have indicated activation by the Δ^3 double bond[36,37] (Scheme 17). Indeed, in the absence of a Δ^3 double bond,



(52)

biological activity is lost.[38]

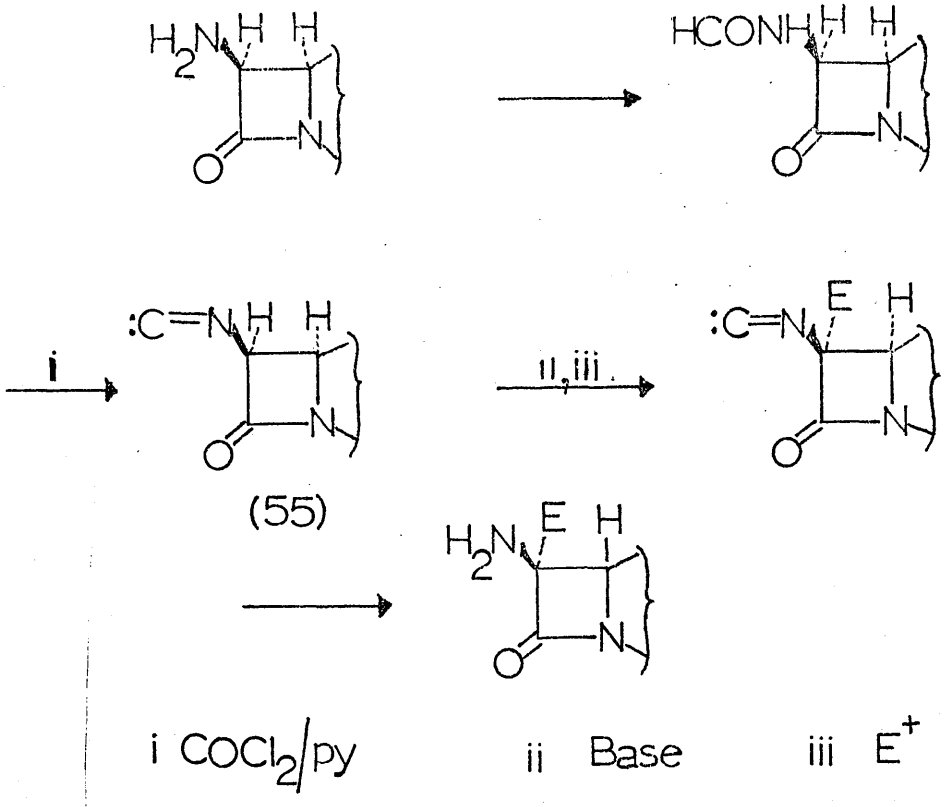
This mode of action has an additional major beneficial consequence. Animal cells do not have similar cell wall construction to bacteria, and hence do not have similar biosynthetic pathways which can be interrupted by β-lactam antibiotics. This discrimination between bacteria and their hosts means that the β-lactam antibiotics have a very low inherent mammalian toxicity level.

5. Partial Syntheses of Penams and Cephems

The β-lactam antibiotics have been subjected to intense chemical scrutiny. It is beyond the scope of this review to consider any but a few of the more important reactions used to modify the basic ring structures in an attempt to improve or alter the biological properties of the parent compound.

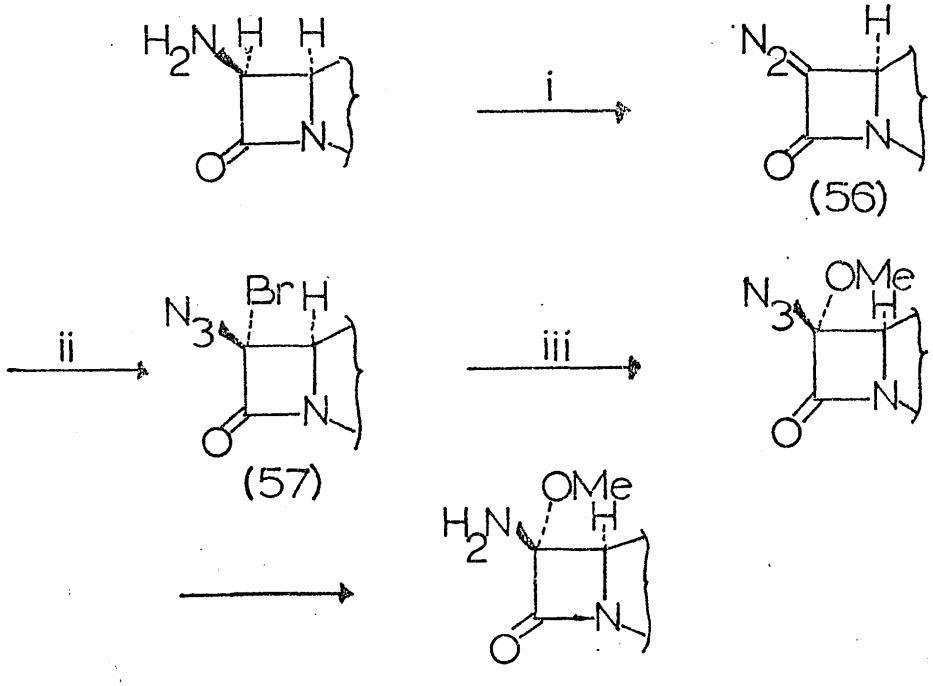
Early activity in penicillin research concentrated on modifications to the N-acyl side chain. However, the discovery of cephalosporin C, and the consequent realisation that antibacterial activity was a property which could be exhibited by ring systems other than penam, stimulated chemists to make more far-reaching changes in the basic framework of these β-lactams.

The parallel drawn by Tipper and Strominger between the penam framework and a D-alanyl-D-alanine unit suggested[39] that introduction of a 6-α-methyl group, to give the penam (52), would result in an even closer structural correlation with the dipeptide and consequently higher



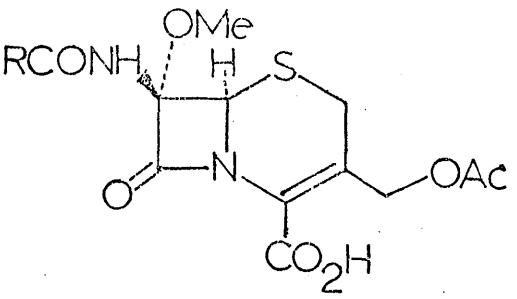
i $COCl_2$/py ii Base iii E^+

SCHEME 20



i $NaNO_2$/HCl ii BrN_3 iii $AgBF_4$/MeOH

SCHEME 21



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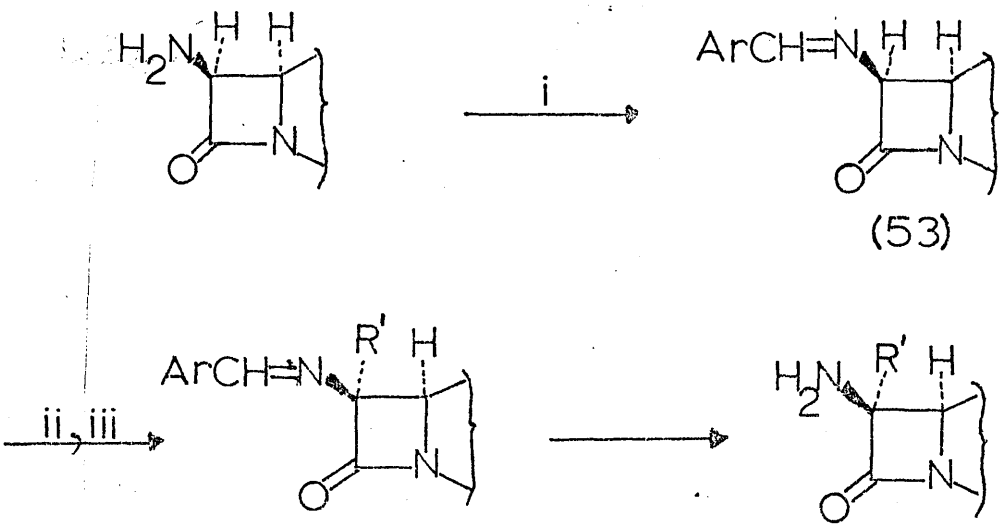
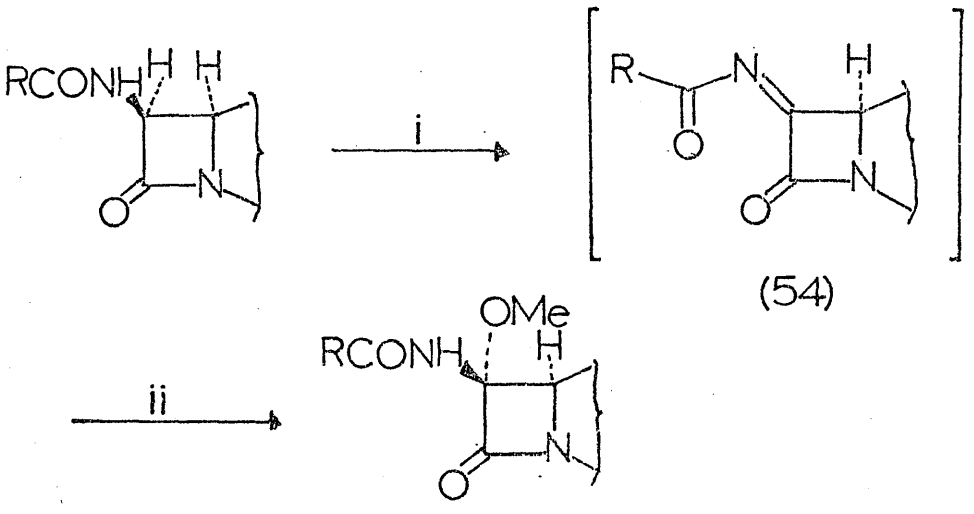


i $pNO_2C_6H_4CHO$ ii NaH or PhLi iii RX

SCHEME 18



i LiOMe, t-BuOCl ii MeOH

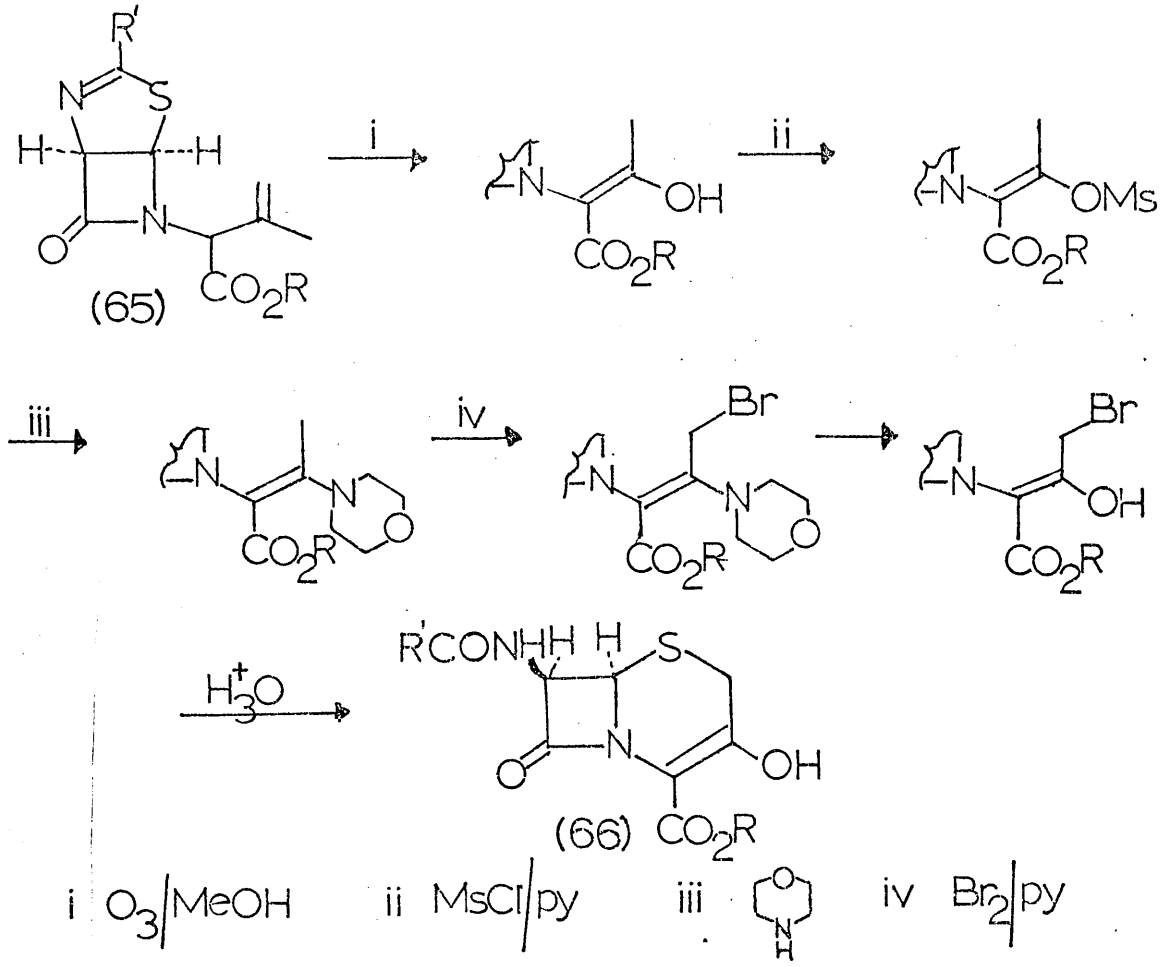
SCHEME 19

activity. This postulate was further strengthened by the isolation[8] of 7-α-methoxycephems, the cephamycins (11).

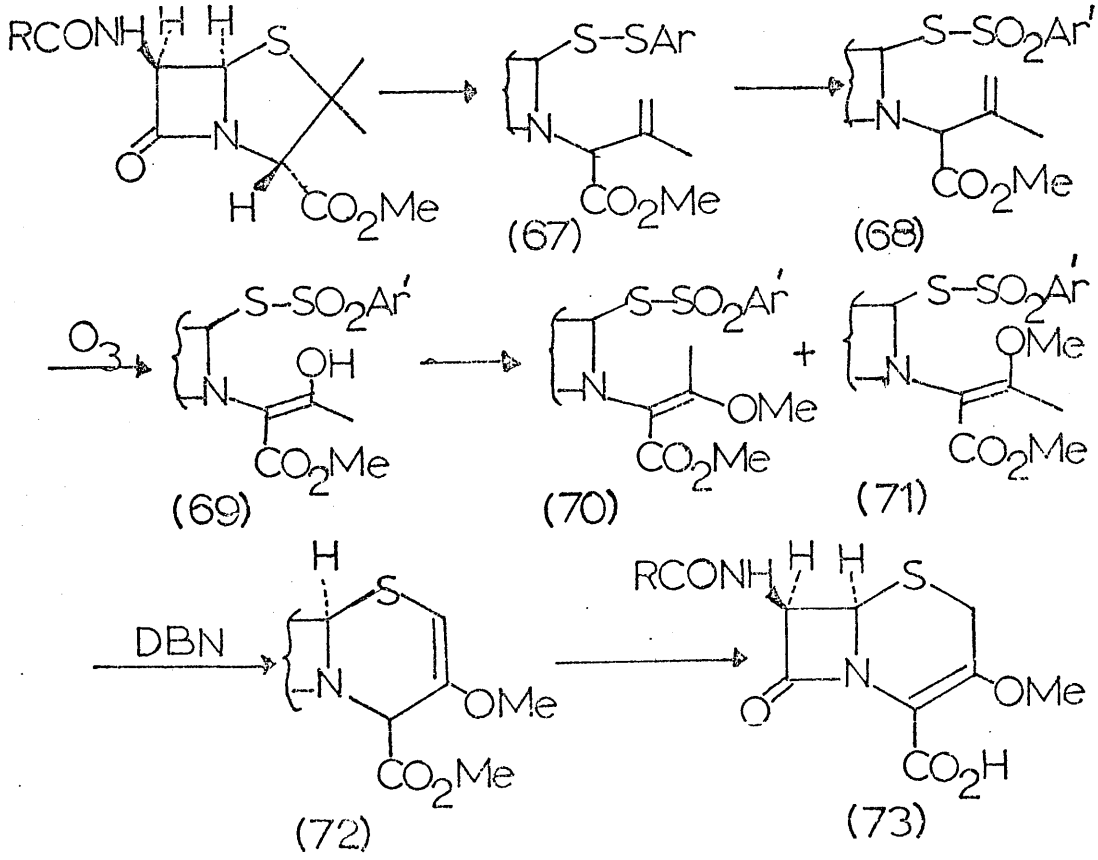
Activation of the 6(7-)-position towards substitution has been achieved by judicious modification of the adjacent amine function. Aryl imines[40](53), acyl imines[41] (54) and isocyanides[42](55) have all found extensive use (Schemes 18,19,and 20) in preparing the cephamycins and other analogues of penams and cephems, including the 6-α-methylpenams and 7-α-methylcephems, both of which were suprisingly less active than the parent compounds.[40] In addition to substitution, these methods allow epimerisation, a process frequently required in synthetic schemes where the unnatural, inactive trans-substituted β-lactam ring is produced.

An essentially different approach to the synthesis of 6(7-)-methoxy-penams and cephems was adopted by Christensen,[43] who treated the known diazo-β-lactams (56) with bromonium azide to give (57); displacement of the bromine by methoxyl, with retention of configuration, was followed by reduction of the azide and subsequent acylation (Scheme 21).

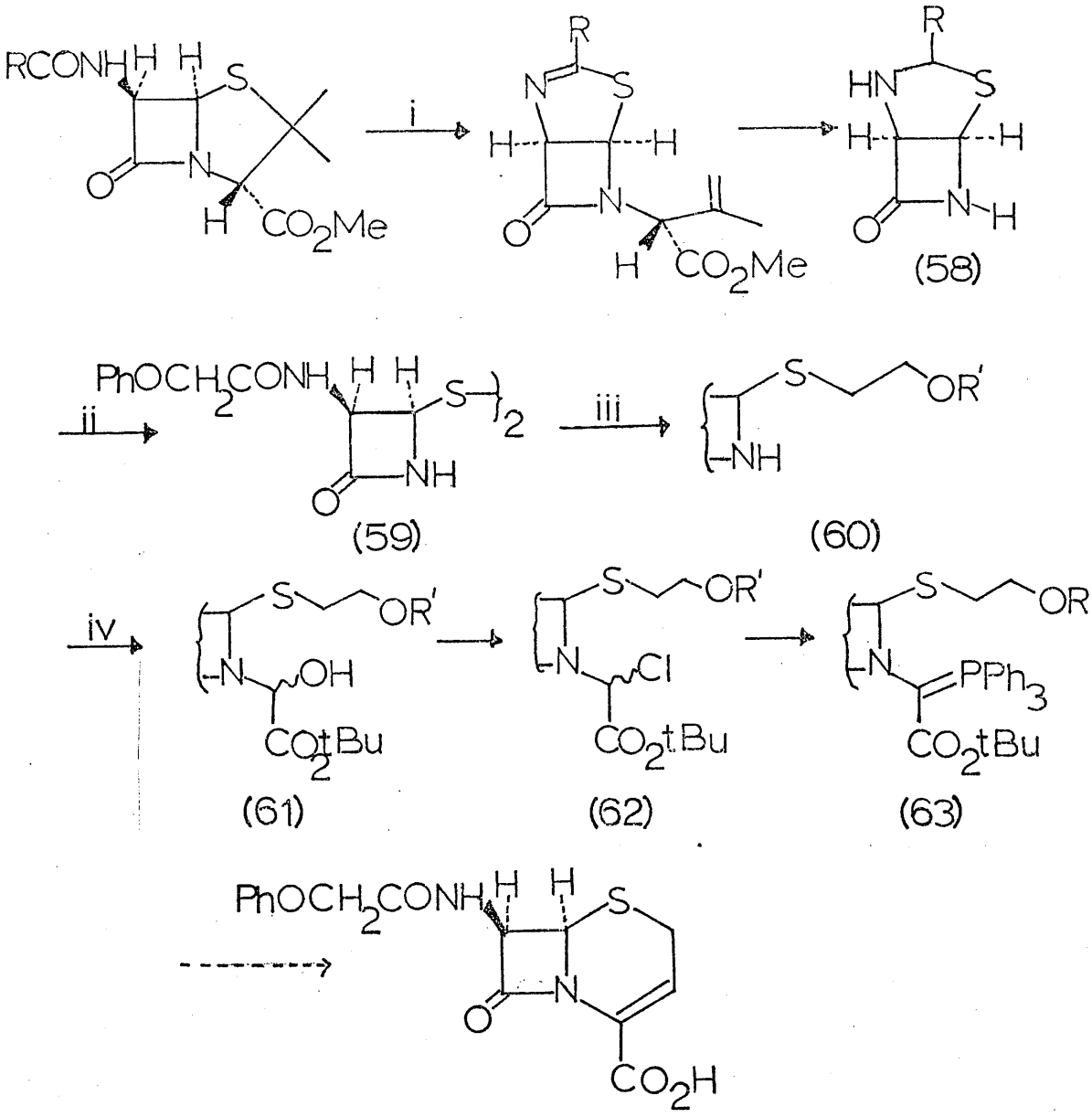
The ready availability and low cost of penicillins have made them extremely attractive as a source of the basic framework of cephems and considerable effort has been expended in this direction. These approaches, simple in their conception - cleavage of the penam thiazolidine ring and building of a new fused six-membered ring - are frequently more difficult in their execution due to the extreme sensitivity of the intermediates



SCHEME 23



SCHEME 24


RCONH
H
H
S
N
O
H
CO2Me
i
R
N
S
H
H
N
O
H
CO2Me
(58)
HN
S
H
H
N
H
O
PhOCH2CONH
H
H
S
2
NH
O
(59)
ii
iii
S
OR'
NH
(60)
iv
OH
CO2tBu
(61)
Cl
(62)
PPh3
OR
(63)
PhOCH2CONH
(64)
i (MeO)3P
ii I2/H2O, PhOCH2COCl
iii H+, protect
iv
CHO
CO2tBu

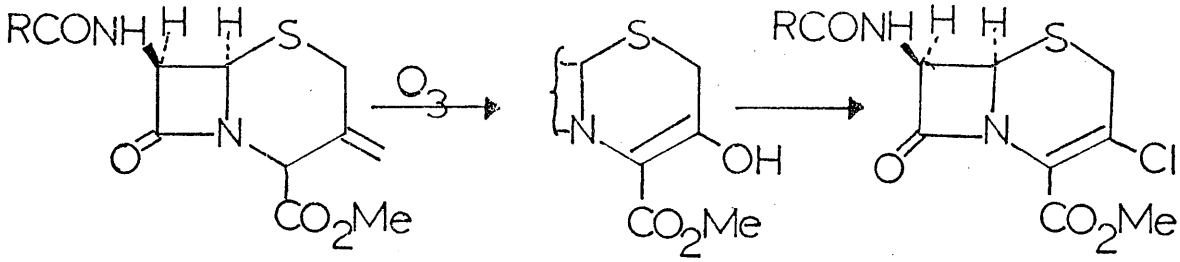
SCHEME 22

involved.

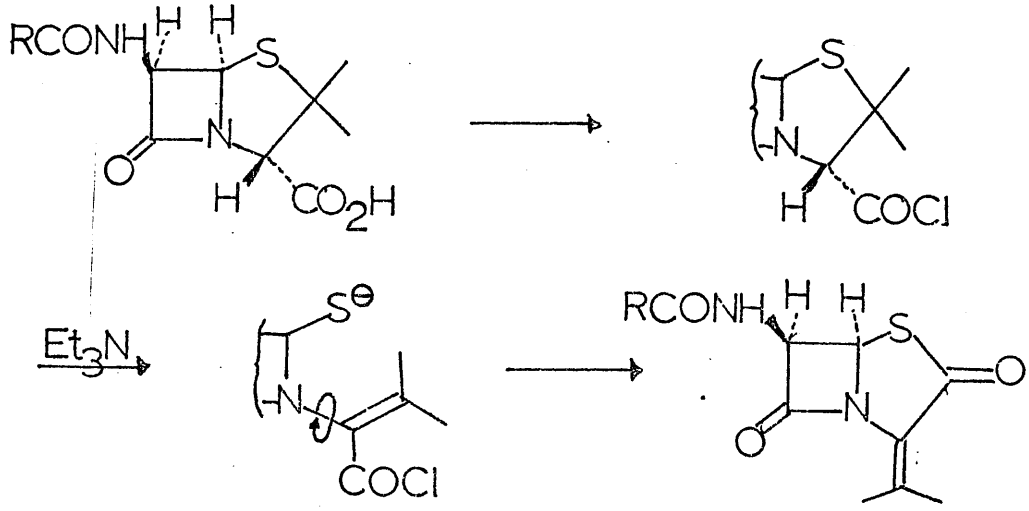
The thermal rearrangement of penicillin sulphoxides and the trapping of the reactive intermediate sulphenic acid as a thiazolidine-β-lactam has already been described (p.4). These penicillin-derived compounds provide excellent starting points for syntheses of a range of cephem analogues: two examples have been selected.

The thiazolidine (58) was oxidised to the disulphide (59) and converted into the protected alcohol (60). In a general annelation procedure developed by Woodward,[44] (60) was condensed with t-butyl glyoxylate to give an epimeric mixture of hydroxyamides (61); treatment with thionyl chloride afforded the corresponding chlorides (62) which were readily converted into the phosphorane (63). Intramolecular Wittig cyclisation with an aldehyde function derived from the protected alcohol led[45] to the 3-cephem (64) (Scheme 22).

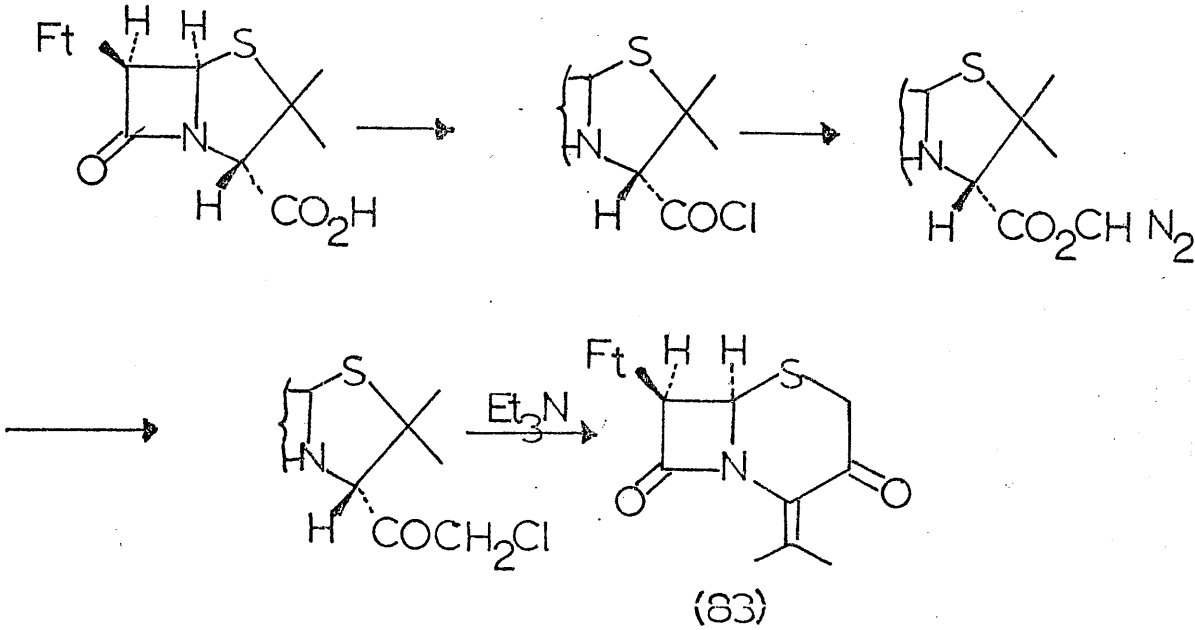
In a very efficient one-pot process (Scheme 23) the thiazolidine (65) was converted[46] into the 3-hydroxycephem (66). There has been considerable interest in such 3-oxycephems following the discovery that the 3-methoxycephems (73) are potent antibiotics.[47] Woodward executed[48] their synthesis from a sulphenic acid, produced on thermolysis of a penam sulphoxide and trapped as the disulphide (67). Ozonolysis of the derived sulphone (68) afforded the enol (69) which was converted into the mixture of enol ethers (70) and (71) both of which underwent base-induced cyclisation to the Δ^2-cephem (72); subsequent isomerisation of the double bond gave the



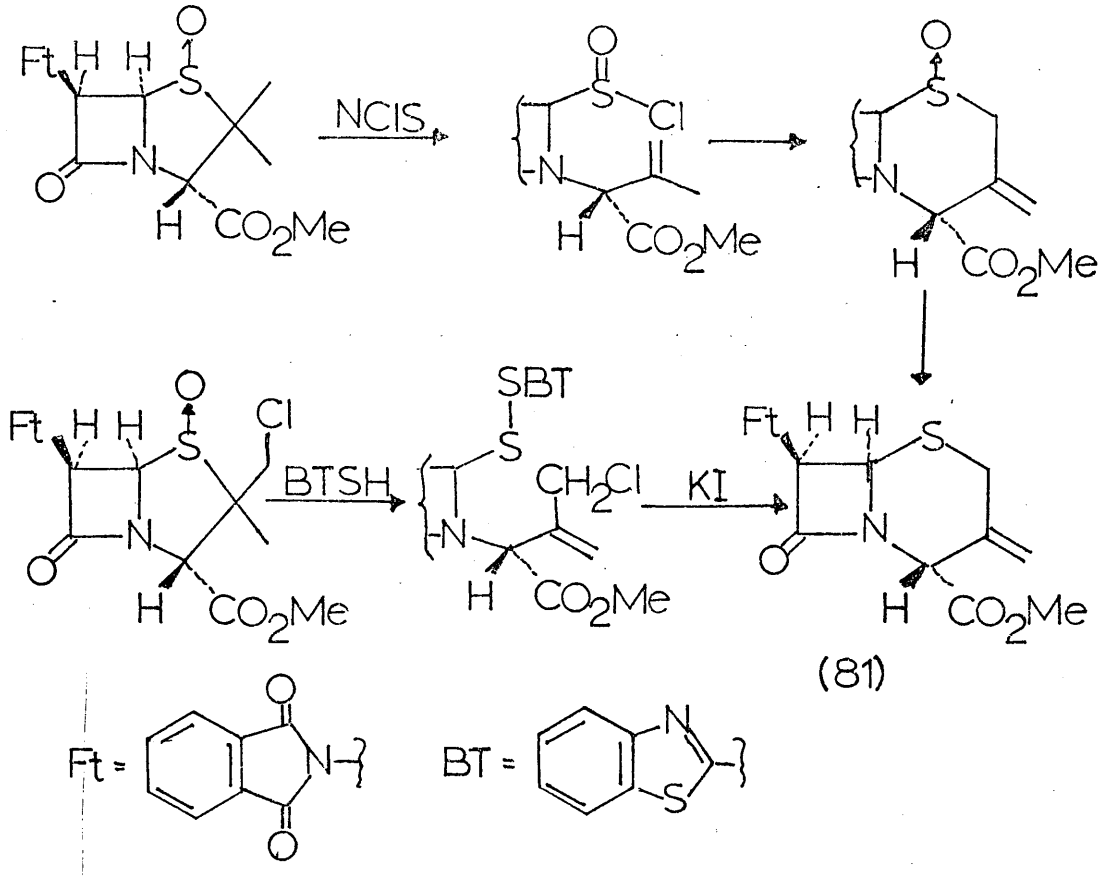
SCHEME 29



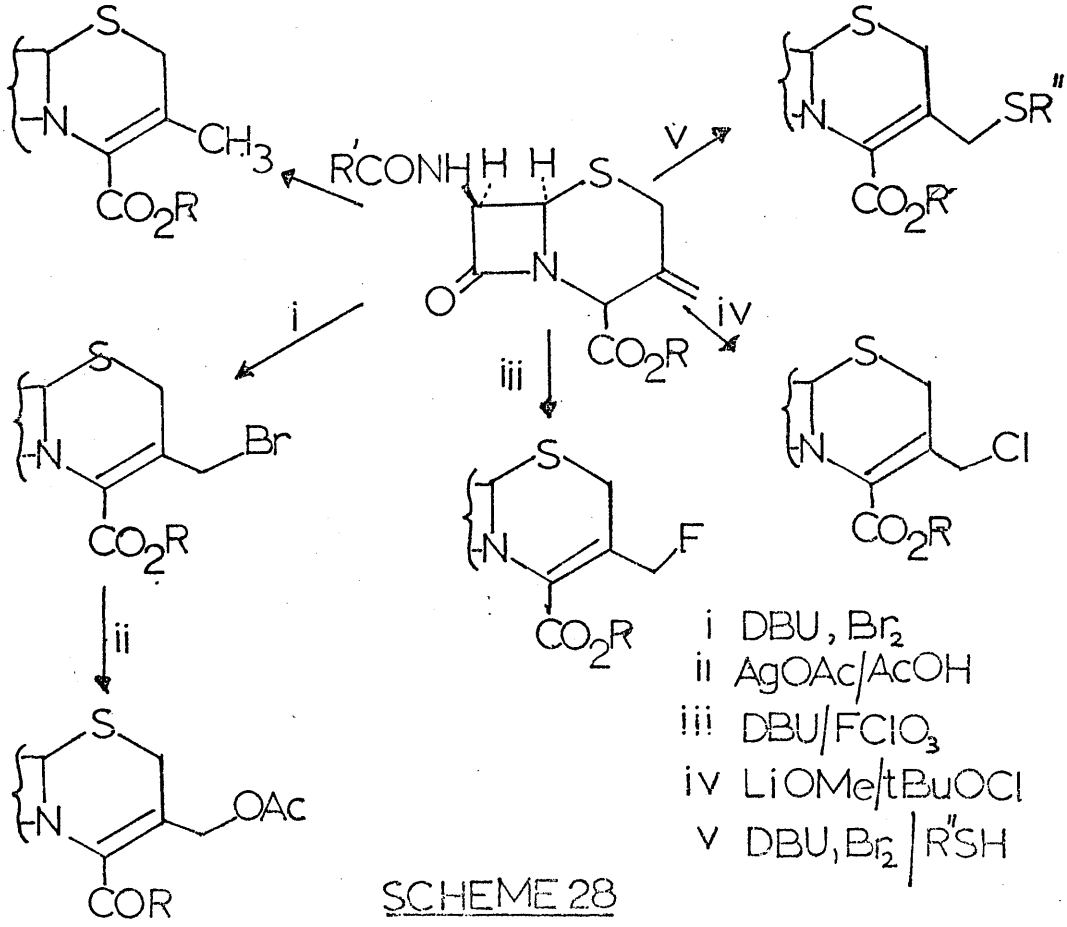
SCHEME 30



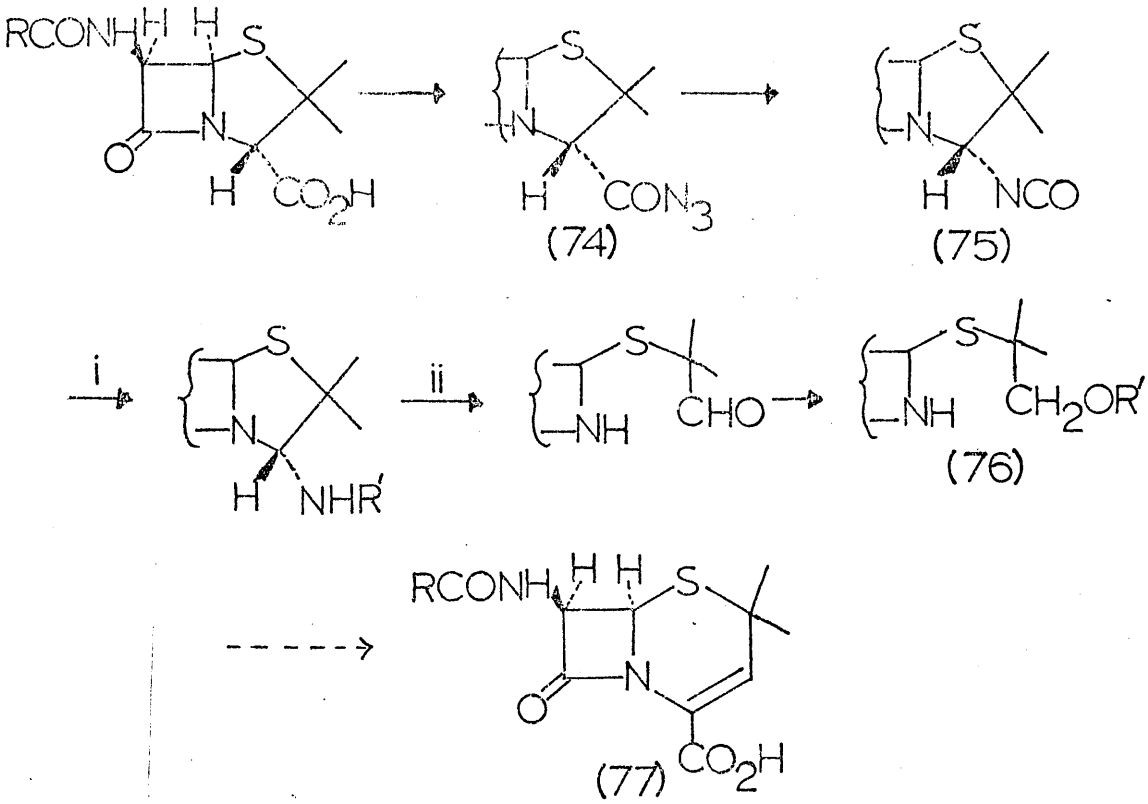
SCHEME 31



SCHEME 27 .

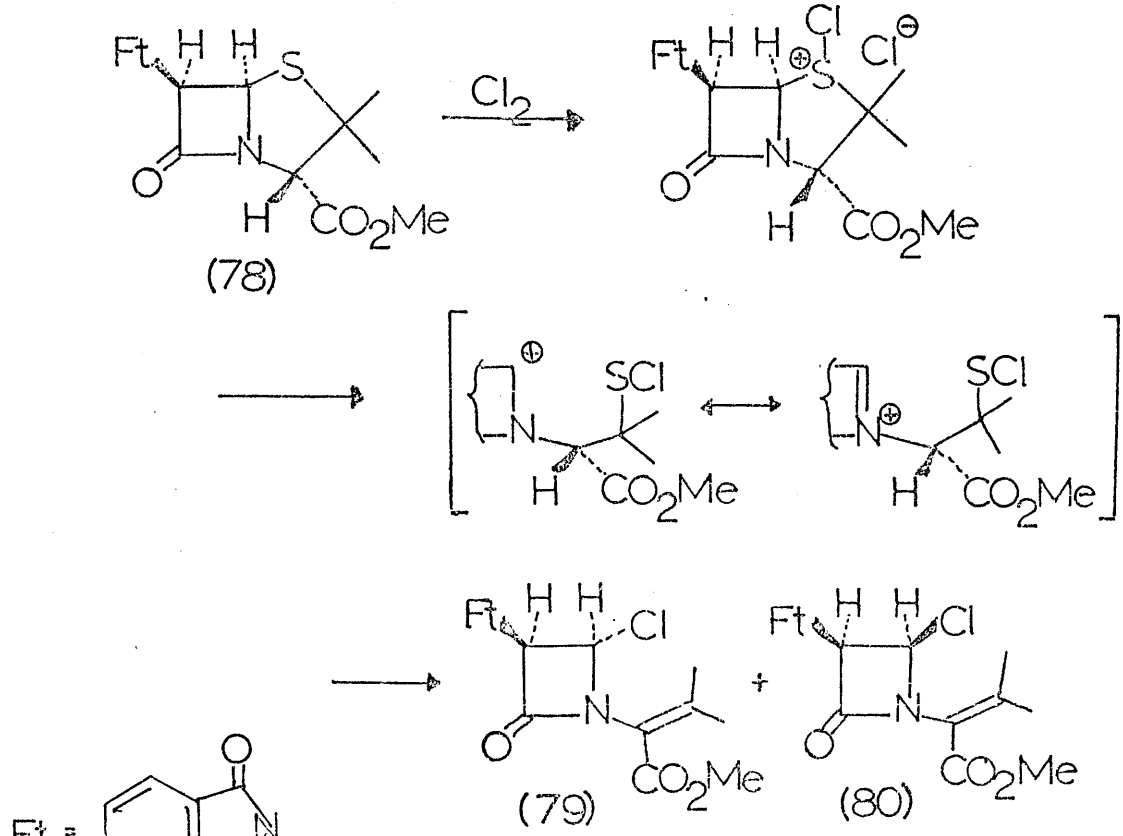


SCHEME 28



i CCl_3CH_2OH ii Zn/AcOH $R' = CO_2CH_2CCl_3$

SCHEME 25



SCHEME 26

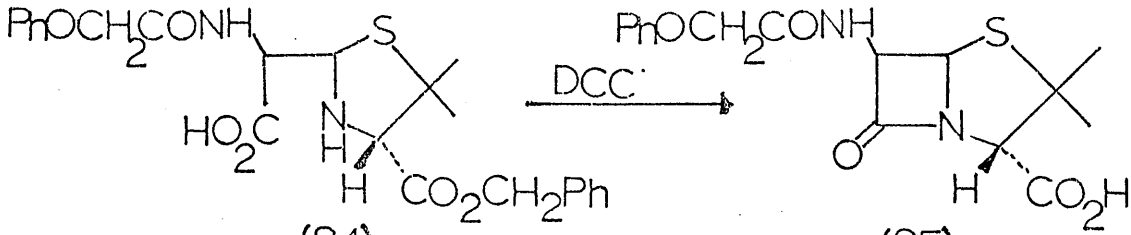
Δ^3-cephem (73) (Scheme 24).

Cleavage of the 3,4-bond of a penam was effected[49] by Curtius rearrangement of the acid azide (74) to the isocyanate (75) which was smoothly converted to the protected alcohol (76); application of the annelation procedure already described[44] led to the cephem (77) (Scheme 25).

In an example of 1,5-bond scission, Kukolja[50] developed a controlled cleavage of (78), (Scheme 26), to afford the potentially useful chloro β-lactams (79) and (80).

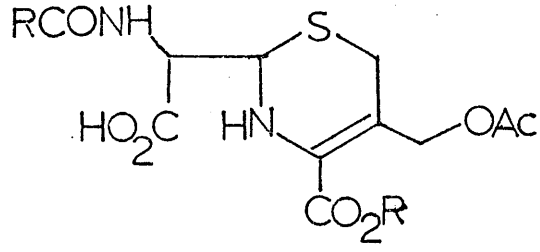
3-Exomethylenecephams (81), conveniently prepared[51,52] from penicillin sulphoxides (Scheme 27), have proven valuable intermediates in the preparation of a range of modified cephalosporins. They provide a versatile route to a range of C-10 substituted cephems (Scheme 28)[53,54] in addition to allowing entry into the 3-methoxy- and 3-chlorocephems (Scheme 29).[55]

A more deep-seated rearrangement of the penam skeleton (Scheme 30) produced[56] the apparently promising intermediates (82), although little or no direct success has been achieved using them. In 1970, Stoodley[57] reported a clever extension of this so-called anhydropenicillin rearrangement to produce the 6-membered ring analogue (83) (Scheme 31), but again this has apparently not led to biologically useful derivatives.

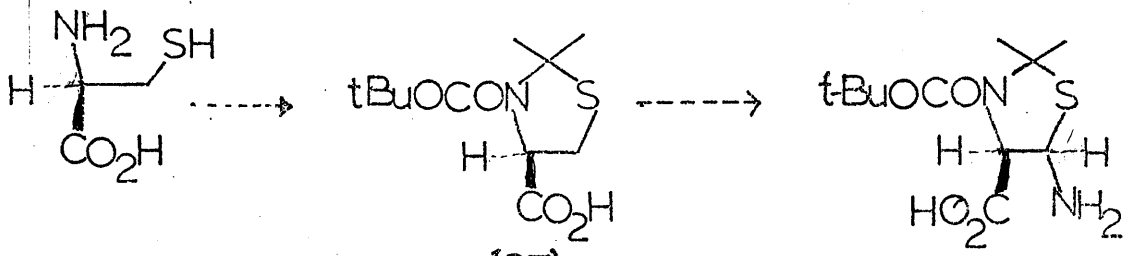


(84) (85)

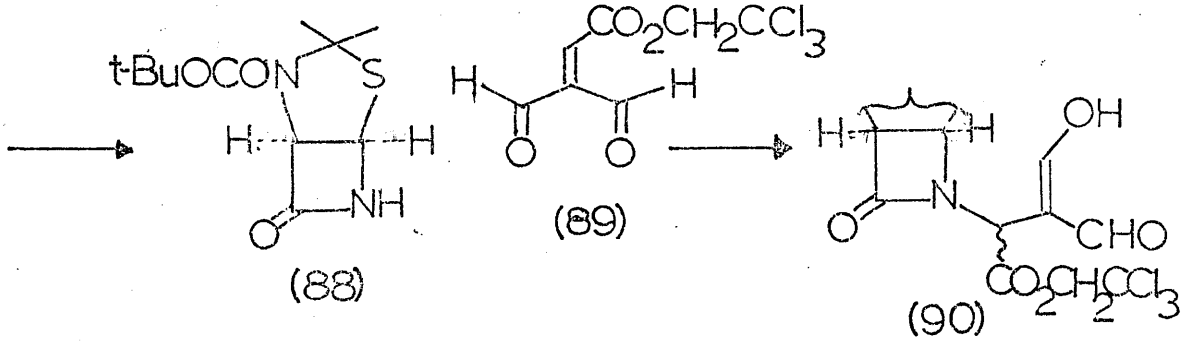
SCHEME 32



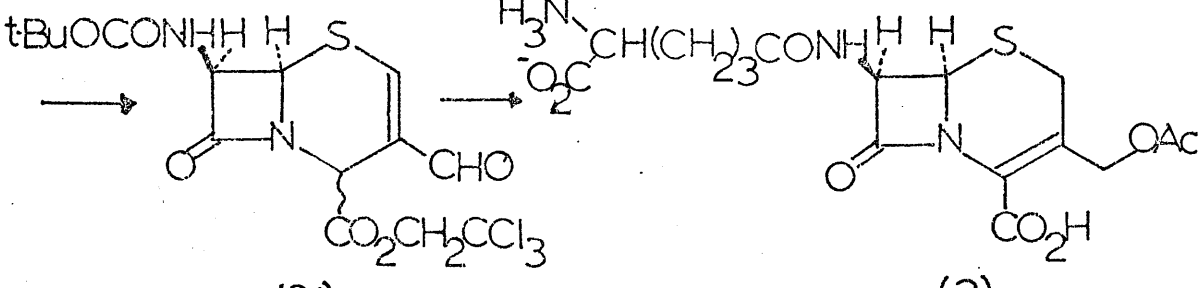
(86)



(87)



(88) (89) (90)



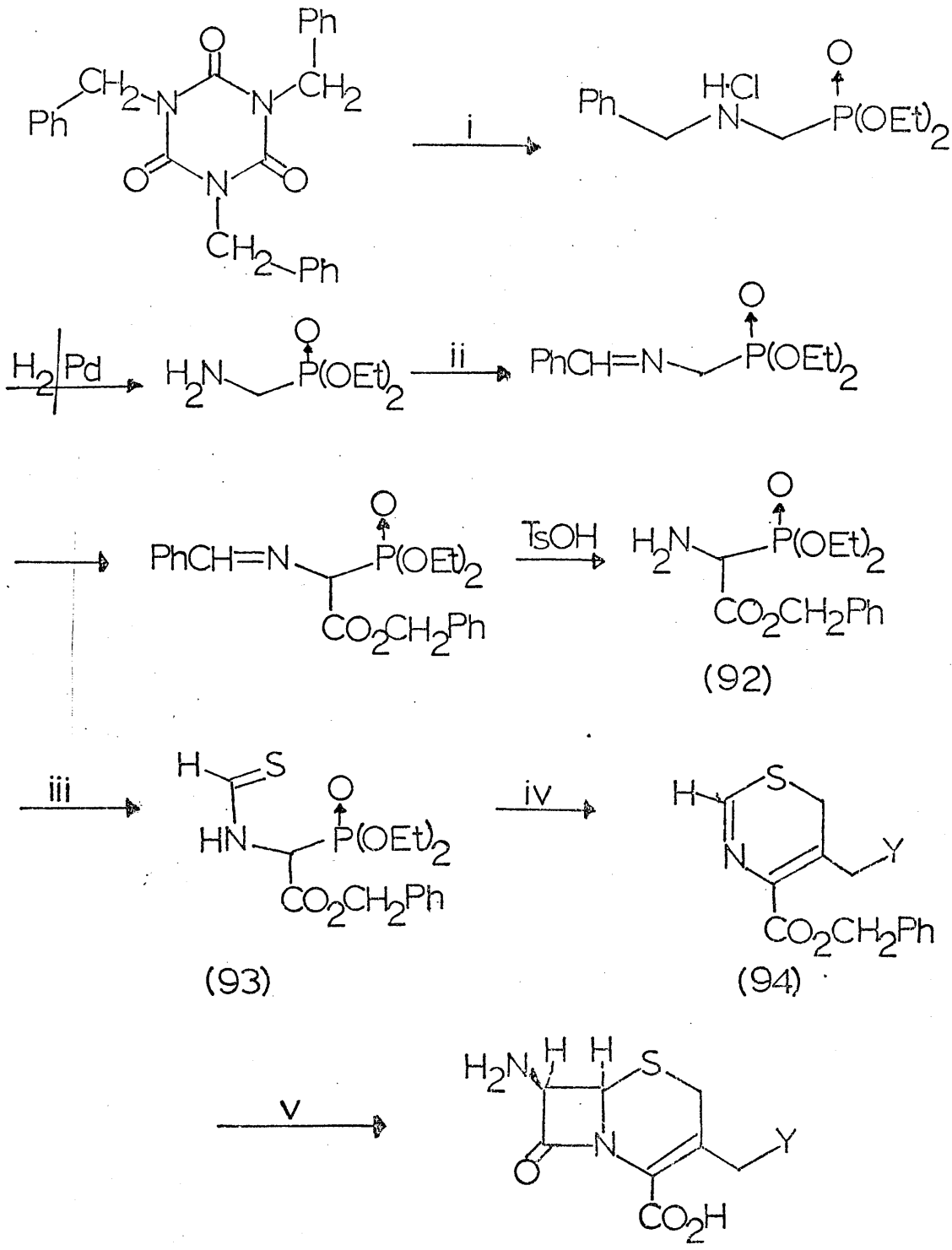
(91) (3)

SCHEME 33

6. Total Synthesis of Penams and Cephams

Five years after the structure elucidation of cephalosporin C, Woodward reported[58] the first stereocontrolled total synthesis. Sheehan,[59] in a total synthesis of penicillin V (85) carried out some years earlier, had employed a route involving late introduction of the sensitive β-lactam moiety by carbodiimide-mediated cyclisation of the β-amino acid (84) (Scheme 32). Woodward, however, was forced to adopt an entirely different approach since the key β-amino acid (86), obtained by acid hydrolysis of the cephem, proved to be even less stable than the earlier system. Accordingly, the β-lactam ring was created first, even though this then required a very sensitive functionality to survive subsequent synthetic operations. This bold strategy was not without reward in versatility, permitting as it does a variety of fused β-lactams to be constructed from a common intermediate.

L-(+)-Cysteine was protected in the form of the thiazolidine (87); ingenious introduction of an amine group at C-3 provided the functionality for cyclisation to the β-lactam thiazolidine (88). This key substance now contained most of the basic functionality and stereochemistry present in the cephem ring system, merely requiring condensation of the β-lactam nitrogen with the dialdehyde (89) to provide the remaining carbon atoms and functionality of the six-membered ring. Acid treatment of the thiazolidine (90) induced cyclisation to the amino



i $(EtO)_2POH$ ii PhCHO iii HCSOEt

iv $ClCH_2COCHY$ v 1 N_3CH_2COCl/Et_3N 2 Red^n

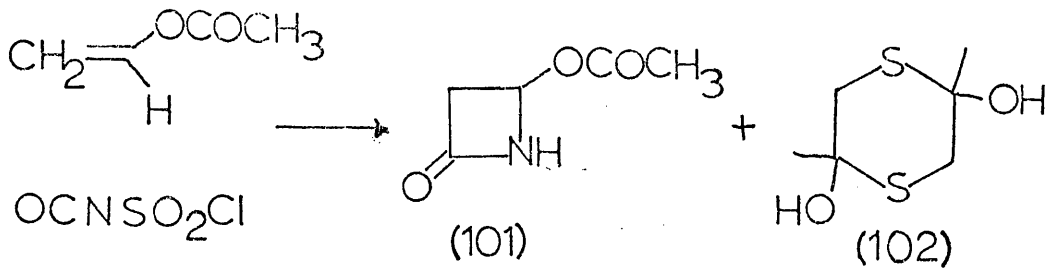
Y = H or OAc

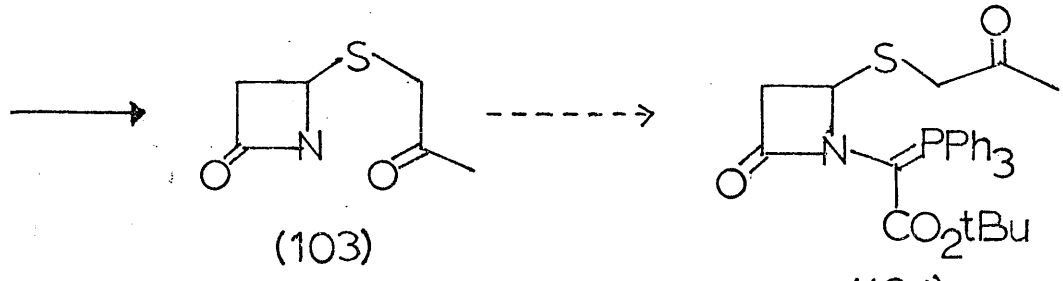
SCHEME 34

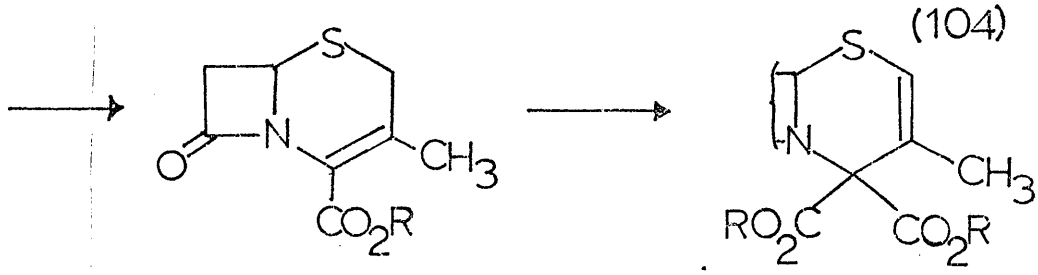
aldehyde (91) and thence to cephalosporin C (Scheme 33).

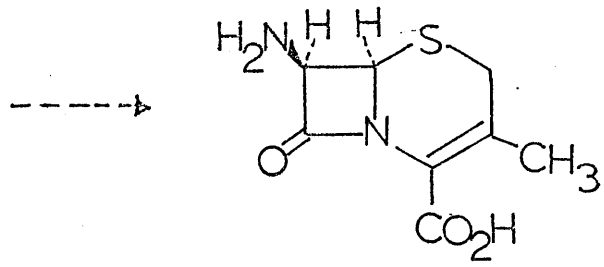
From an academic point of view, the synthetic challenge of β-lactam antibiotics lies not in stereochemical considerations - penams have three and cephems two asymmetric centres - but in the diversity of functionality confined within a relatively compact molecular framework. Current objectives in designing synthetic routes to the β-lactam antibiotics do not include competition with the relatively efficient fermentation methods for the obtention of penicillins, but do with the inefficient microbial methods for the production of cephems. Such synthetic approaches follow two distinct philosophies: utilisation of penicillins as precursors to cephems, and total syntheses. The commercial viability of such approaches has led to extensive investigation of modified ring systems in the quest for greater antibacterial potency.

(a) Merck Syntheses.- The overall strategy relies upon a process developed by Bose,[60] in which cycloaddition of a ketene or its precursor and an imine creates the β-lactam ring and provides an entry into a range of cephems. In a synthesis[61] of the 7-amino cephems (95) (Scheme 34) the aminomethylphosphonate (92) was converted into the thioformimidate (93). Condensation with a 1-chloro-2-alkanone and Emmons cyclisation afforded the imine (94). Annelation with azidoacetyl chloride and triethylamine followed by reduction and epimerisation at C-7 led to the 7-aminocephems (95). The necessity for epimerisation at C-7 can be avoided by use of chloroacetyl chloride/

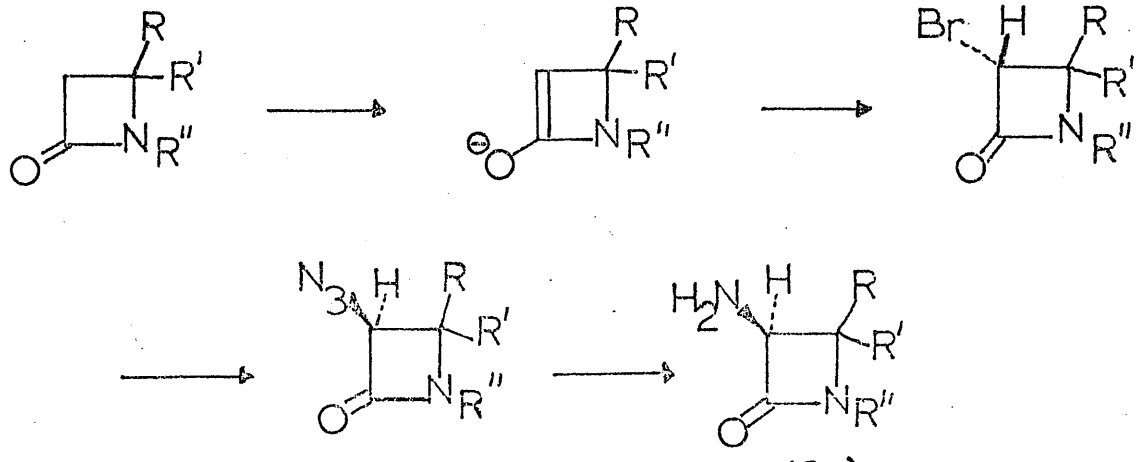




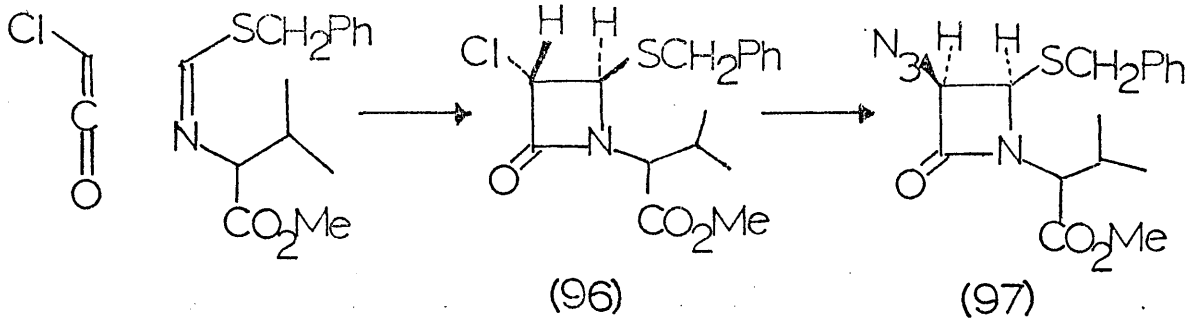




SCHEME 38

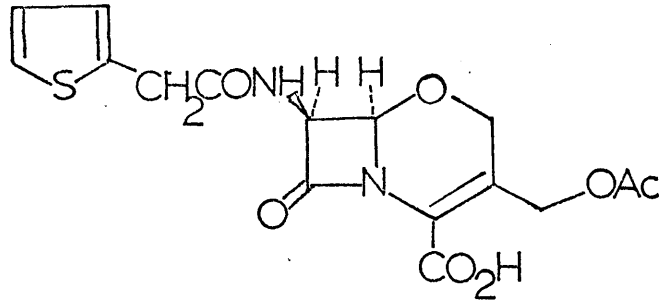


SCHEME 39



(96) (97)

SCHEME 35



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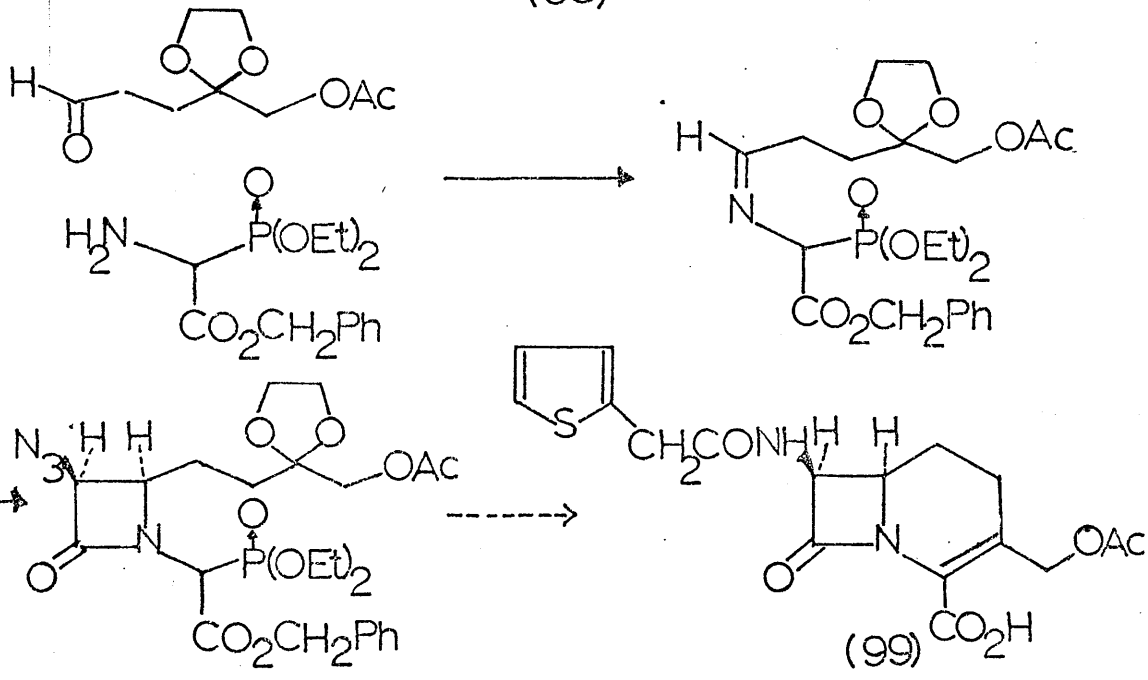
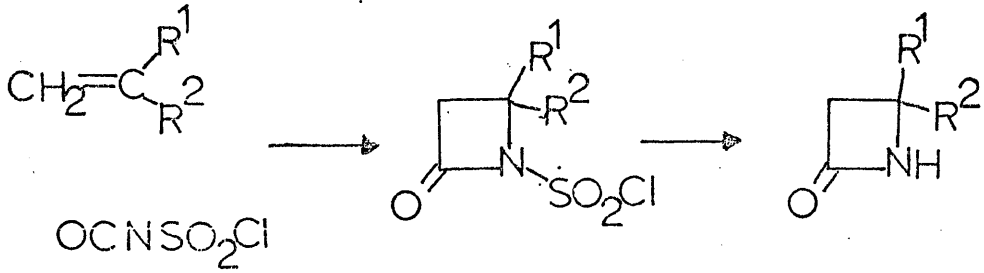


(99)

SCHEME 36



(100)

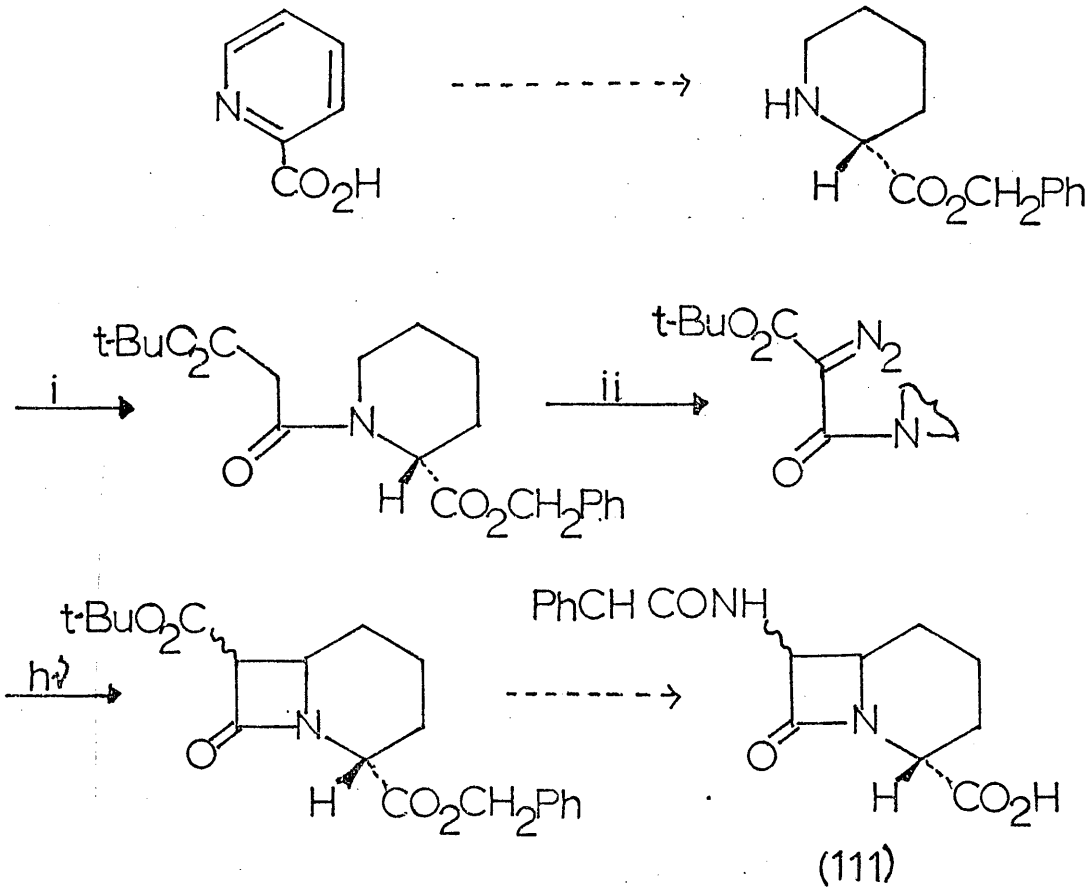
SCHEME 37

triethylamine,[62,63] which gives the trans-chloroazetidinone (96); this, on treatment with sodium azide, yields the required cis-azidoazetidinone (97) (Scheme 35).

This basic methodology has been extended by Christensen to the synthesis of a number of nuclearly modified cephems such as 1-oxacephalothin (98)[64] and 1-carbacephalothin (99)[65] (Scheme 36) both of which are active antibiotics.

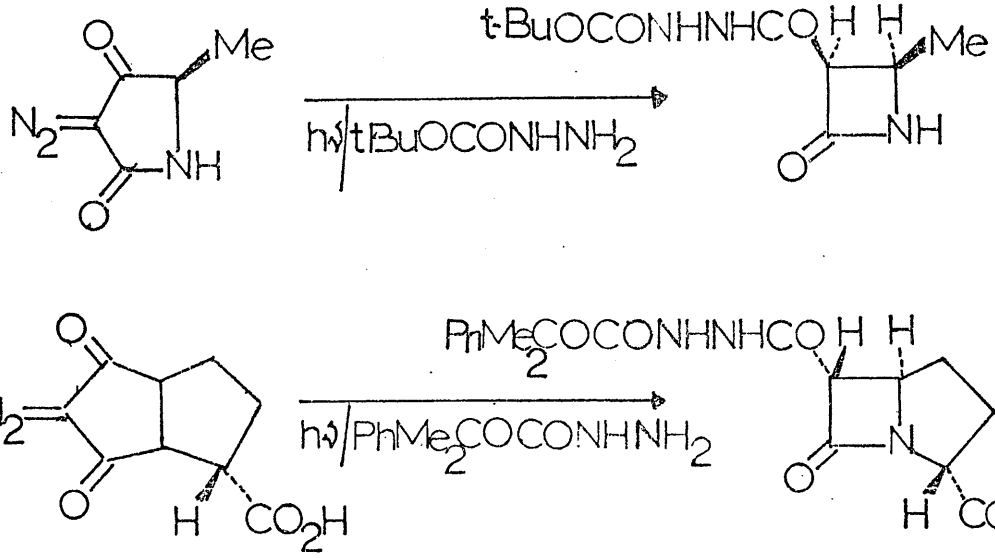
(b) Hoechst Syntheses.[66]- The discovery by Graf[67] that N-chlorosulphonyl isocyanate (100) reacted with alkenes to produce β-lactams after hydrolysis (Scheme 37) stimulated an investigation of the potential of this β-lactam forming reaction in the synthesis of cephems. This resulted in a synthetic procedure which could be applied to a range of cephem nuclei (Scheme 38).[68] Treatment of the β-lactam (101) with the dimer (102) resulted in substitution of the acetate group of (101) without cleaving the β-lactam. The keto-β-lactam (103) was converted by Woodward's method[44] to the phosphonium ylid (104) and thence to the 3-cephem (105). Introduction of the 7-amino function presented some difficulty. Monocyclic β-lactams had been shown[69] to deprotonate at the 3-position in strong base and could subsequently be converted to the 3-amino-β-lactam (107) (Scheme 39). Application of this procedure to the bicyclic system resulted in deprotonation of the six-membered ring; this was readily obviated by conversion to the diester (106).

(c) Smith, Kline and French Synthesis.- A recent synthetic approach uses a modification[70] of the Bose annelation

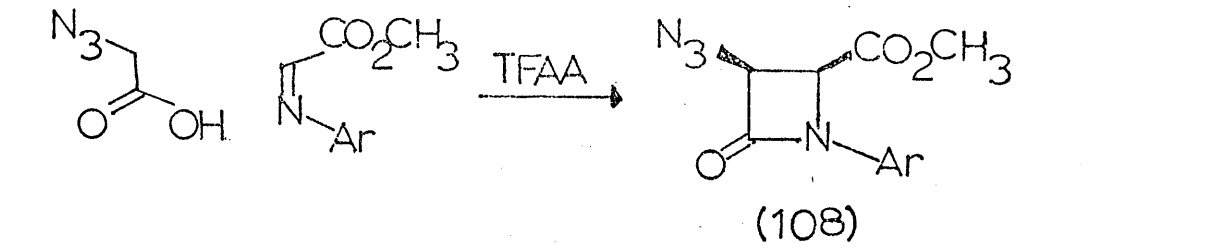


i $tBuCO_2CH_2CO_2H$/DCC ii p $MeC_6H_4SO_2N_3$/Et_2NH

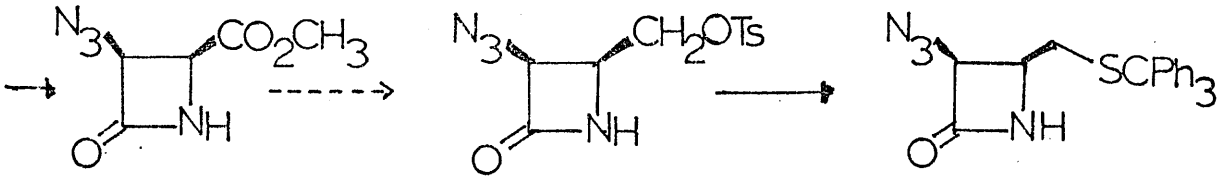
SCHEME 42

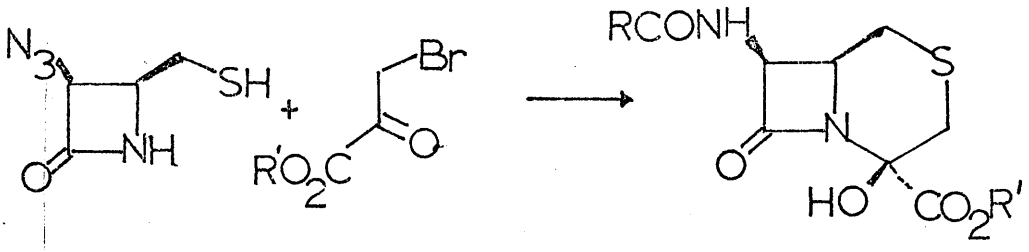


SCHEME 43

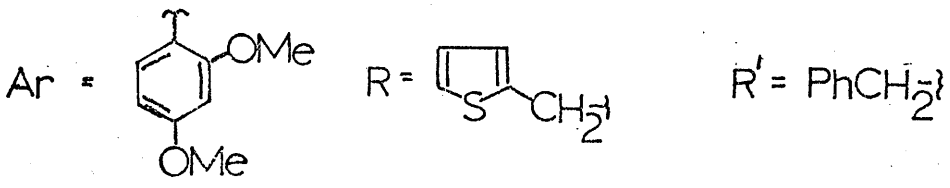


(108)

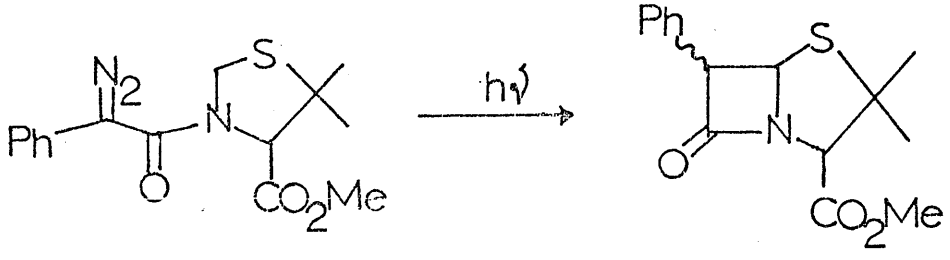




(109)



SCHEME 40



110

SCHEME 41

procedure to form the monocyclic β-lactam (108).[71] This versatile intermediate has been used in a synthesis[72] (Scheme 40) of the cephem (109), which shows enhanced activity against gram-negative bacteria.

(d) Lowe Syntheses. - This approach to β-lactam formation rests on the earlier observation[73,74] that α-diazoketones such as (110) are photolysed to carbene intermediates, which insert into the C-H bond adjacent to the amide nitrogen, forming β-lactams (Scheme 41). Lowe has extended this concept to provide a general route to a range of modified cephems and the more inaccessible penams.[75] The approach is typified by the synthesis of the biologically inactive cepham analogue (111),[76] (Scheme 42).

To overcome the problem of lack of stereospecificity of the insertion reaction, the Oxford group,[77] and independently Stork,[78] made use of the Wolff rearrangement of diazodiketones (Scheme 43). Ring contraction proceeded stereoselectively, giving rise to the kinetic product.

This review is but a brief summary of the current awareness in the penicillin and cephalosporin fields. For more detailed accounts the reader is directed to the appended general bibliography.

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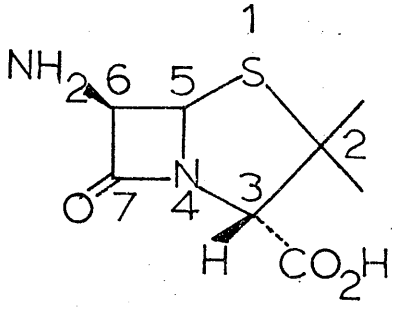

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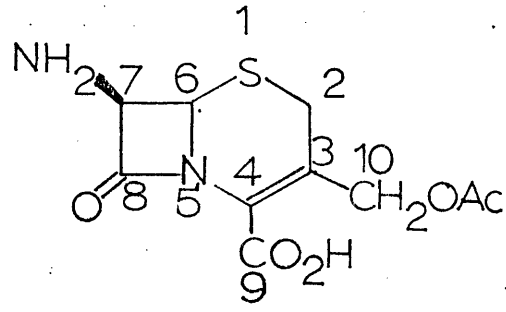
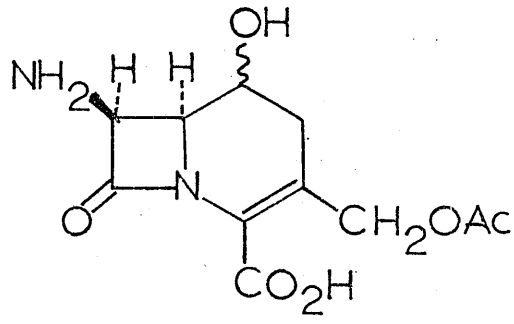


3-cephem

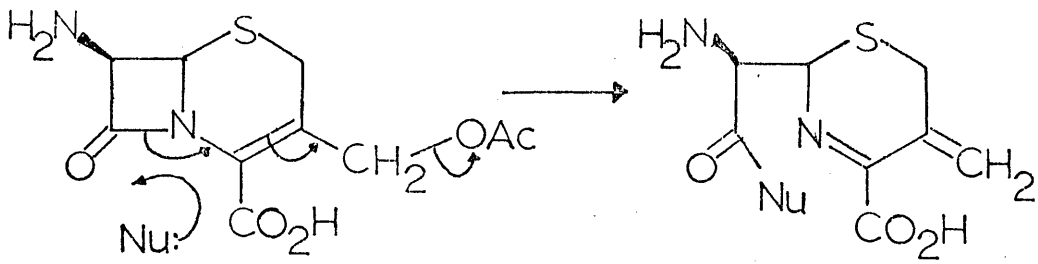


(1)

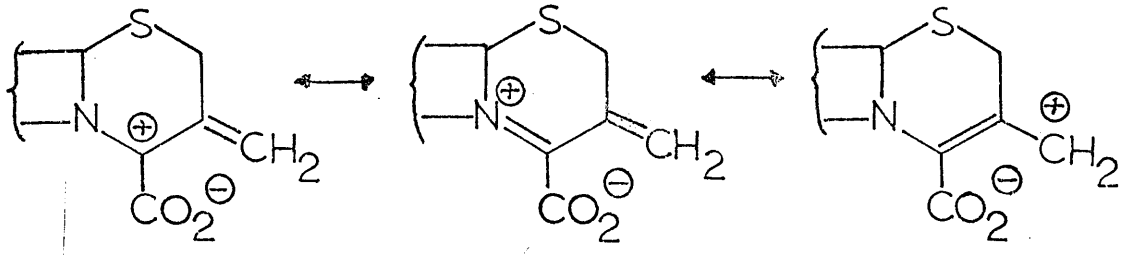
DISCUSSION

The purpose of this research has been to investigate potential synthetic routes to the nuclearly-modified cephalosporin (1). The rationale for the considerable effort which has been expended on total and partial synthesis of cephalosporin analogues is threefold: such compounds may not only mimic the parent antibiotic, but may also show enhanced, or a different range of, activity; making modifications to a structure of known activity and observing the resulting changes provides insight into structure-activity relationships; finally, as in all such synthetic problems, there should be a significant yield of knowledge about new and existing synthetic methods.

The exact mode of action of cephalosporin, and related penicillin antibiotics, at the molecular level, is inadequately understood. In 1965, Tipper and Strominger[1] suggested that peptidoglycan transpeptidase, the enzyme involved in the transpeptidation of a glycine terminus and a D-alanyl-D-alanine pentapeptide in the final stage of cell-wall construction, falsely recognises penicillins and cephalosporins as the cell-wall D-alanyl-D-alanine unit, resulting in irreversible acylation and hence deactivation of the transpeptidase by the β-lactam function. The biological activity of the cephalosporins has been directly linked with the chemical reactivity of the β-lactam ring. The observation that chemical reactivity diminishes and biological activity is lost when the Δ^3-double bond is reduced[2a] or replaced by a Δ^2-double bond,[2b]



SCHEME 1



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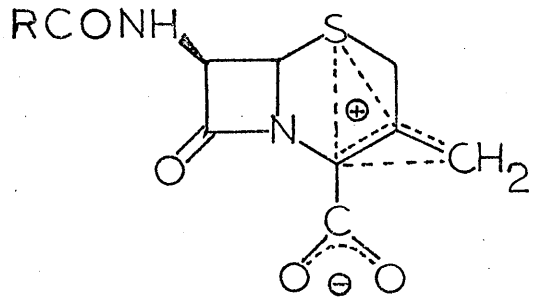

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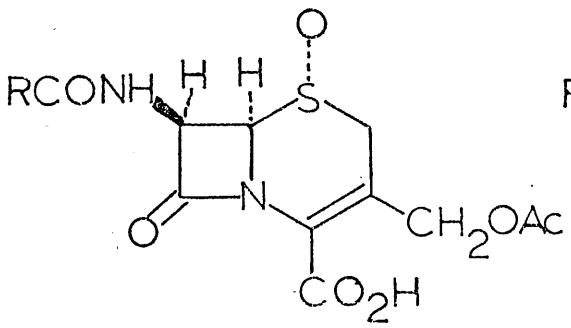
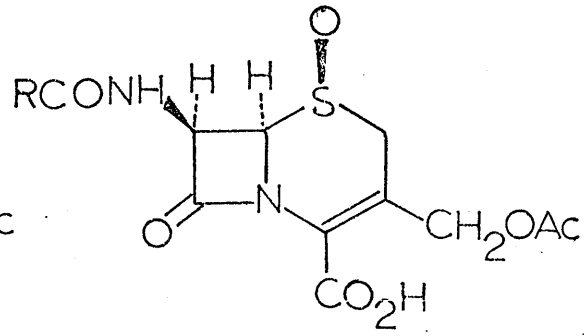


(6)

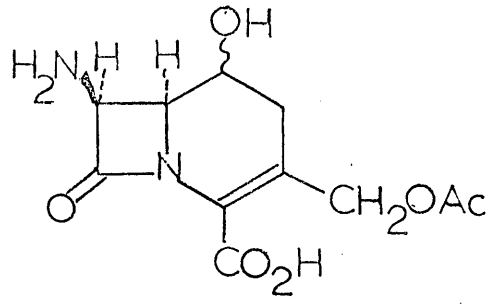


(7)

can be attributed to participation of the Δ^3-double bond in elimination of the acetoxy group as shown in Scheme 1.

Cocker[3] and Taylor[4] on investigating the nucleophilic displacement of a variety of leaving groups at C-10 concluded that stabilisation of the transition state leading to the allylic dipolar carbonium ion (2) is increased by the resonance structures (3) and (4). The sulphur atom is implicated also in a transannular interaction, stabilising the transition state (5). As expected, oxidation of the sulphur to the 1-sulphoxide resulted in a decrease in the rate of displacement,[44] due to the residual lone pair of electrons occupying a hybrid orbital with increased s character and consequently decreased potential for orbital overlap.

A recent disclosure in the patent literature reports[5] that the cephalosporin (R)-sulphoxide (6) shows a wide range of antibacterial activity, while the cephalosporin (S)-sulphoxide (7) is inactive when isolated in pure form (oxidation with peracids normally gives a mixture of (R)- and (S)-sulphoxides, the inactive (S) epimer greatly predominating due to hydrogen bonding between the oxidant and the 7-amino substituent; this led to early suggestions of a lack of activity in the cephalosporin sulphoxides). Clearly an alternative mechanism of transition state stabilisation must be operating which does not involve orbital overlap of the residual lone pair of electrons on sulphur. N.m.r. experiments[6] have shown that as a consequence of the anisotropy of the sulphoxide bond (8) and the orientation of the sulphur lone pair of



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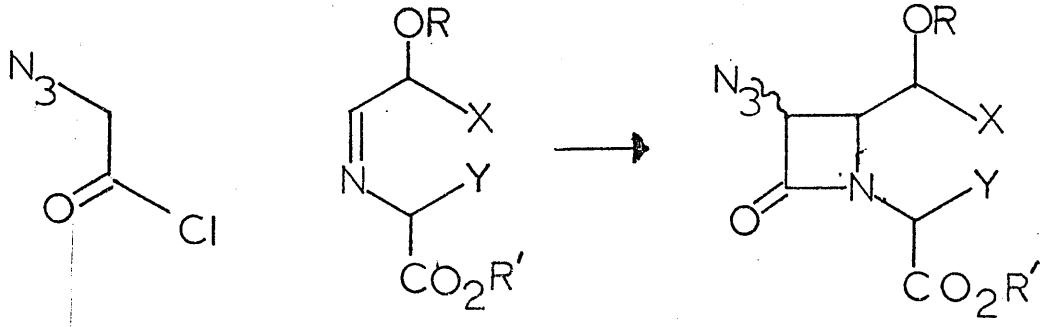
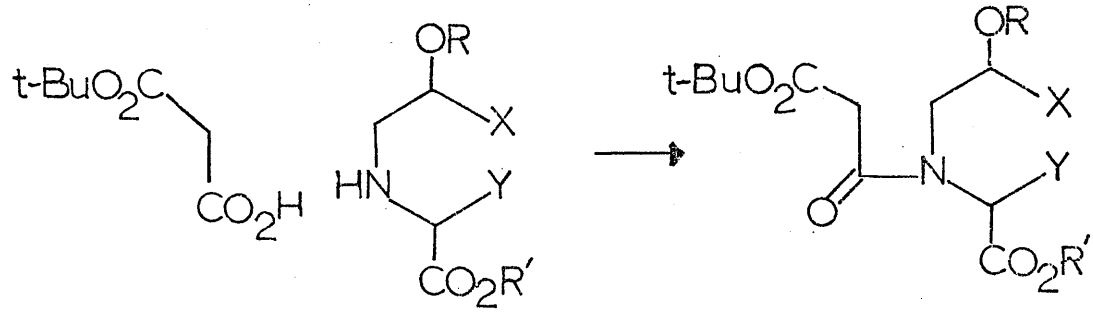
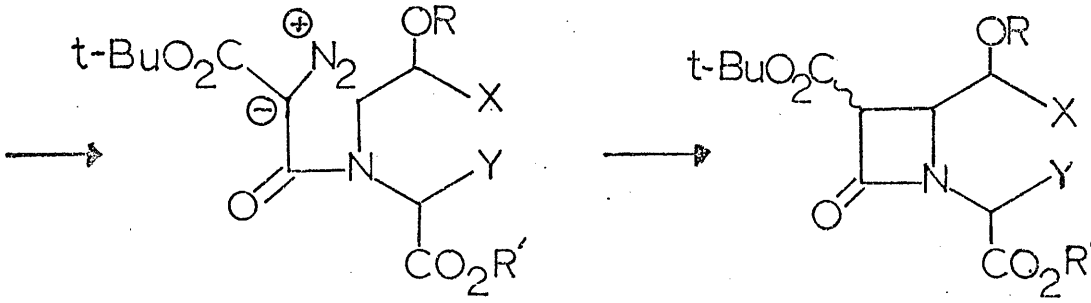
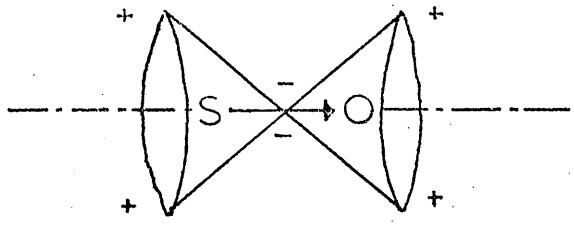


SCHEME 2





SCHEME 3



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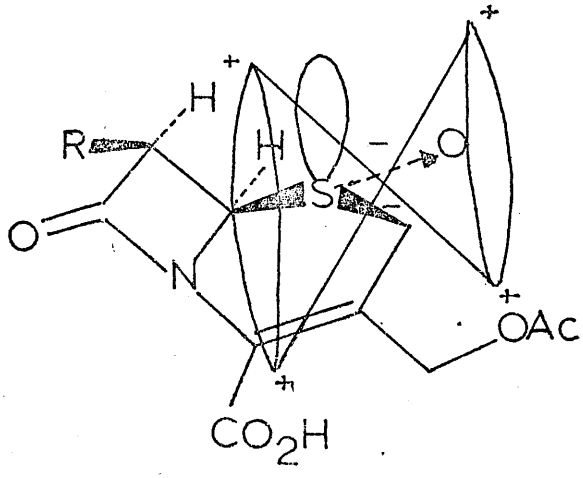

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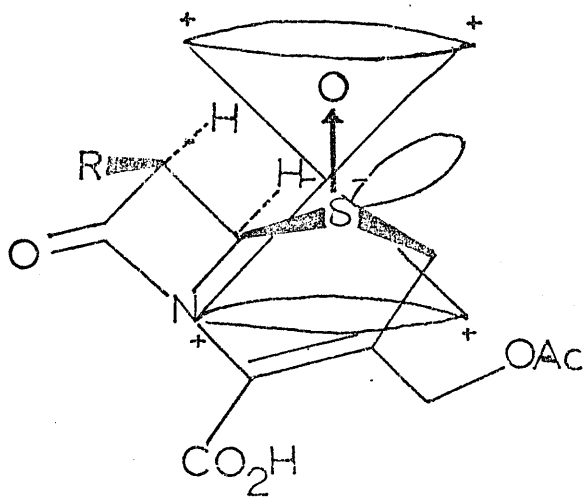


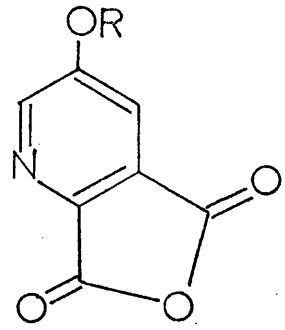
(10)

electrons, the magnetic environment around carbons C-3 and C-4 is opposite in the two isomers (shielding in the (R)-sulphoxide (9), deshielding in the (S)-sulphoxide (10)). It is conceivable that the electronic environment at C-3 and C-4 in the (R) isomer is such that activation of the β-lactam function occurs by stabilisation of the transition state, while in the (S) isomer deactivation results.

Speculation upon a modification of the cephalosporin nucleus likely to impart enhanced biological activity suggested that a 1-hydroxy-1-carbacephem (1) might exhibit the desired properties. The 1-hydroxyl group, by virtue of its lone pairs of electrons on oxygen and hydrogen bonding ability, may provide sufficient stabilisation of a polarised transition state to confer the desired enhancement of antibiotic potency.

In a projected β-lactam synthesis the pivotal question concerns the most suitable sequence of events, particularly the stage of introduction of the β-lactam ring. A common approach is late introduction due to the reactivity of the β-lactam and in the synthetic studies described here this philosophy was adopted. Two methods of introducing the β-lactam ring were considered, using either azidoacetylchloride/triethylamine, as developed by Bose[7] and used by Christensen[8,9] to advantage (Scheme 2), or a carbene insertion route in the photodecomposition of a diazo compound (Scheme 3).[10]

In the first approach, x and y are fragments suitably functionalised to allow construction of the six-



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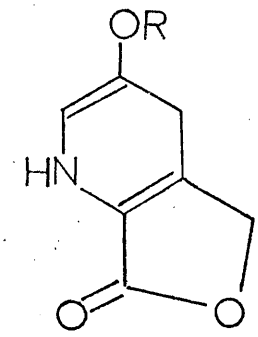

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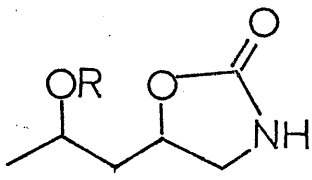

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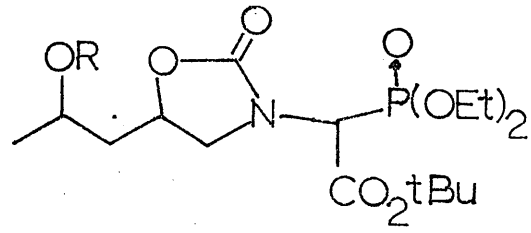

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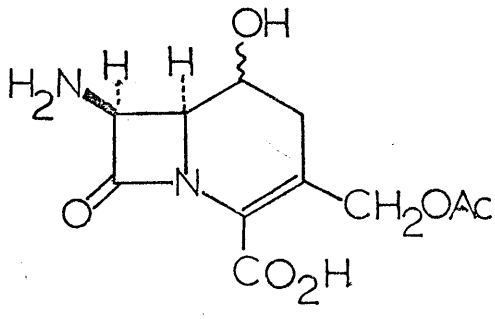

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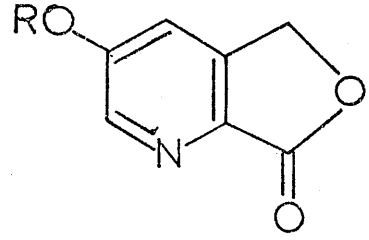


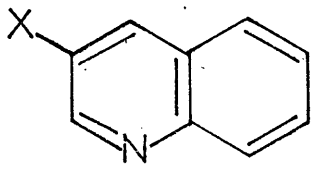
(15)

membered ring after introduction of the β-lactam. In the second method two approaches were thought worthy of consideration. Reduction of a suitably substituted pyridine (11) will give the bisenamine (12) which should couple with mono-t-butyl malonic acid as previously described.[10] Alternatively, the oxazolidone (13) is potentially convertible into the phosphonate (14) by a modification of Woodward's method[11] and thence, via a cyclic enamine to (1). Each of these approaches is discussed in detail in the following chapters.

1. Pyridine Approaches

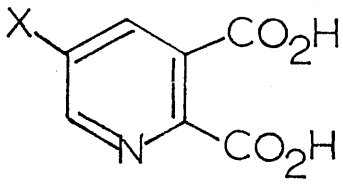
A variety of reduction techniques are available which might be applied to a pyridine such as (15) converting it to the crucial bisenamine (12) in this approach to the target cephalosporin. Eisner[12] has reported the successful use of sodium borohydride in the 1,4-reduction of a variety of substituted pyridines while catalytic hydrogenation has been employed in the reduction of nicotinic acid derivatives.[13] Of considerable interest and utility is the platinum-catalysed addition of trimethylsilane to a substituted pyridine, offering, by manipulation of reaction conditions, selective reduction of the pyridine nucleus.[14] Thus construction of a suitable pyridine such as (15) became the primary synthetic target.

Oxidation of quinolines with acidic hydrogen peroxide[15] or with alkaline potassium permanganate[16] is reported to yield the corresponding pyridine-2.3-dicarb-

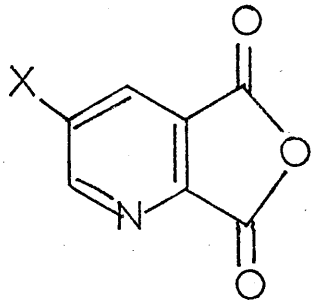


(16) X = NO_2

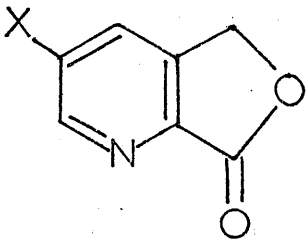
(17) X = Br



(18) X = Br



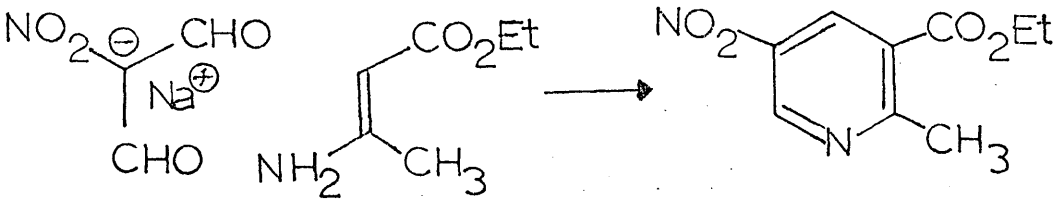
(19) X = Br



SCHEME 4

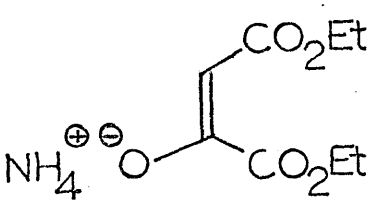
oxylic acids. The proposed route utilising such oxidations is outlined in (Scheme 4). The readily available 3-nitro-[17] and 3-bromo-[18] quinolines (16) and (17) provide substituents which can, at a suitable stage, be easily converted into a hydroxyl function in free or protected form. In the reduction of the anhydride it was anticipated that by careful selection of the reducing agent[19] and reaction conditions, selective reduction in the manner illustrated would be possible, the two carbonyl groups differing electronically by virtue of their positions relative to the pyridine nitrogen. However, a considerable range of reaction conditions and isolation techniques failed to provide an efficient or reproducible conversion of either quinoline into the corresponding diacid. For example, in the most successful procedure, a 16% yield of 5-bromopyridine-2,3-dicarboxylic acid (18) was obtained by oxidation of 3-bromoquinoline using hydrogen peroxide in the presence of copper sulphate; the diacid was isolated from the intermediate copper salt by treatment with hydrogen sulphide. In a pilot conversion, this diacid afforded the corresponding anhydride (19) in 14% yield. All attempts to repeat the oxidation and provide more material to allow rigorous purification and characterisation of products were unsuccessful.

The failure to develop an adequate oxidation procedure led to consideration of methods of constructing the desired pyridine *via* suitably substituted fragments. Fanta has reported[20] a synthesis of ethyl 2-methyl-5-nitropyridine-3-carboxylate (22) by the reaction of sodium



(20) (21) (22)

(23) (24)



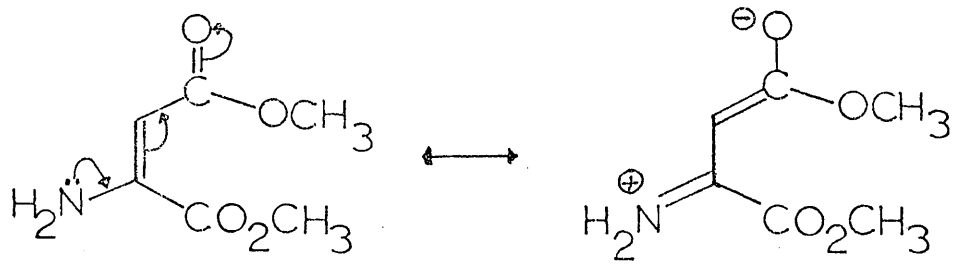
(25)

nitromalondialdehyde (20) with ethyl 3-aminobut-2-enoate (21). This method is potentially susceptible to modification by variation of the substituents on both the enamine and the malondialdehyde; use of diethyl 2-aminofumarate (23) in this cyclisation should lead directly to the diethyl ester of 5-nitropyridine-2,3-dicarboxylic acid.

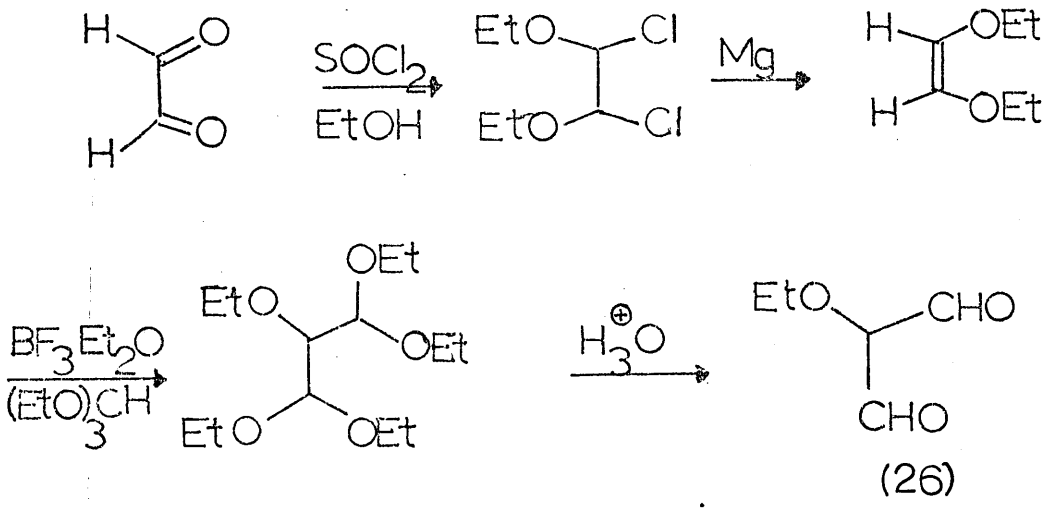
At 0°C in ether saturated with dry ammonia[20] ethyl oxalacetate (24) formed a white low melting solid which failed to undergo cyclisation with sodium nitromalondialdehyde, starting materials being returned unchanged. However, diethyl 2-aminofumarate is reported to be a stable, distillable liquid,[21] while the solid obtained from the ether solution melted with decomposition, with accompanying evolution of ammonia, at room temperature. It seems likely that the unstable ammonium salt (25) had formed under these reaction conditions.

2-Aminofumarates may be prepared in two ways; either by the action of ammonia on ethyl oxalacetate in the presence of ammonium nitrate in refluxing toluene,[21] or by treatment of dimethyl acetylenedicarboxylate with ammonia in ether at 0°C.[22] Typically an 85% yield of dimethyl 2-aminofumarate was obtained by the latter method. Both Z and E alkene isomers are formed, and may be isolated, but distillation of the total crude product results in thermal isomerisation of the E to the Z isomer.

Attempts to cyclise dimethyl 2-aminofumarate with sodium nitromalondialdehyde in aqueous solution and in refluxing ethanol were singularly unsuccessful. The only reaction noted after several days of refluxing in ethanol



SCHEME 5



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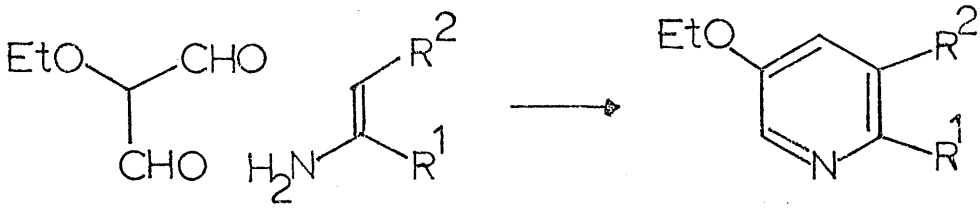
SCHEME 6

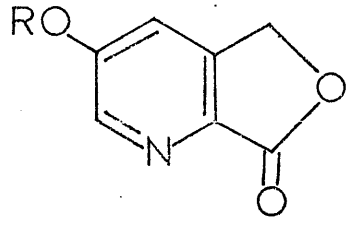


(27) $R^1 = CO_2Me$, $R^2 = Me$

(28) $R^1 = Me$, $R^2 = CO_2Et$

(29) $R^1 = Me$, $R^2 = CO_2Et$

(30) $R^1 = CO_2Me$, $R^2 = Me$

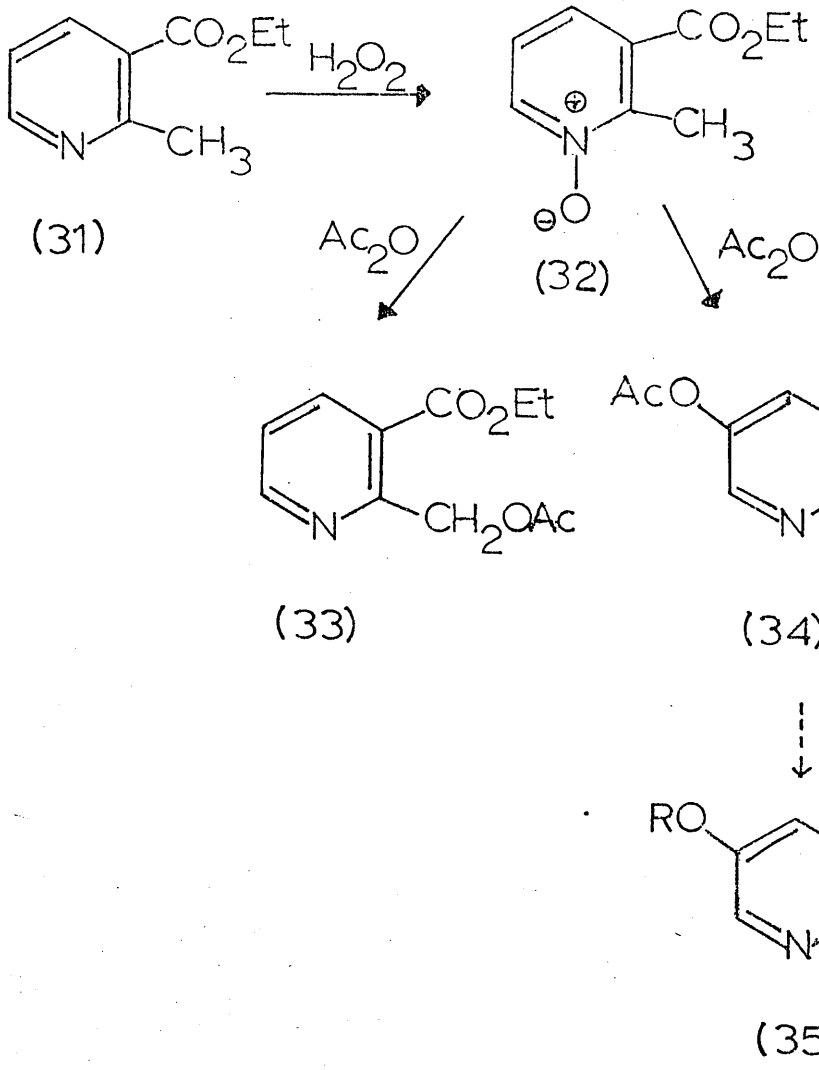


(15)

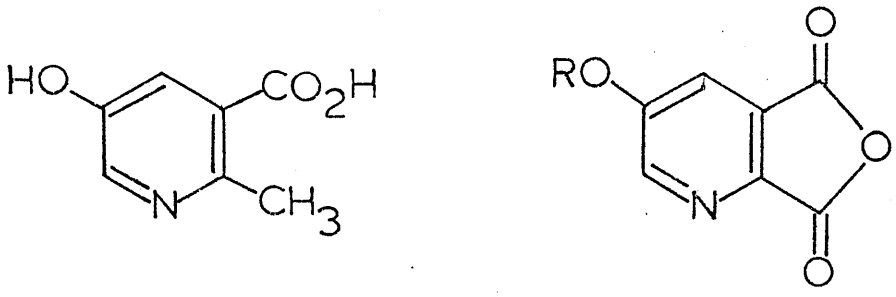
was conversion of the α-methyl ester to the corresponding α-ethyl ether. The fact that only one ester group is exchanged is a consequence of the mesomeric delocalisation of the nitrogen lone pair of electrons into the α-ester carbonyl group rendering it less susceptible to nucleophilic attack (Scheme 5).

Ethoxymalondialdehyde (26) can be prepared in the four step process[23,24,25] outlined in Scheme 6 and has the particular advantage that condensation with suitable enamines should lead directly to pyridines with an oxygen function at the 5-position. The 2-and 3-aminobut-2-enoates (27) and (28) were selected since the respective products (30) and (29) should be capable of conversion into the lactone (15). Ethyl 3-aminobut-2-enoate is reported[20] to be granular white solid, produced by the action of ammonia on a solution of ethyl acetoacetate in ether at 0°C. However the white solid produced by this method failed to undergo the desired cyclisation. As was found in the earlier case with ethyl 2-aminofumarate, ethyl 3-aminobut-2-enoate is a stable distillable liquid, prepared by passing gaseous ammonia through neat ethyl acetoacetate.[26] Numerous attempts, under a range of conditions, failed to induce cyclisation of this authentic enamine with ethoxy malondialdehyde. In each case complex mixtures resulted from which no substituted pyridine (29) could be isolated.

Although 2-aminobut-2-enoates are unreported in the literature the preparation of methyl 2-aminobut-2-enoate was approached in a manner analogous to that already


CO2Et
H2O2
CH3
N
(31)
Ac2O
(32)
Ac2O
CH2OAc
(33)
AcO
(34)
RO
O
(35)

SCHEME 7

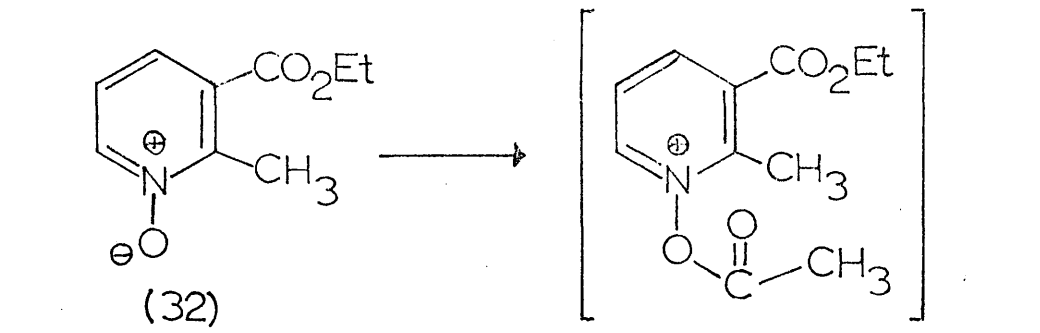

HO
CO2H
CH3
N
(36)
RO
O
(11)

employed. 2-Oxobutanoic acid was converted into its methyl ester with diazomethane in ether, then, without purification, treated with ammonia. High vacuum distillation of the resulting gummy oil afforded a deep red viscous liquid, the n.m.r. spectrum of which exhibited a variety of resonances attributable to protons in a saturated environment, suggesting extensive polymerisation.

The N-oxide (32) rearranges[27] in acetic anhydride to form two products; the 2-acetoxymethylpyridine (33) in 60% yield and the 5-acetoxypyridine (34) in 15-18% yield. The low yield of this process precludes its direct use in a synthetic scheme, but nonetheless it is interesting in that the lactone (35) derived from (34) is one of the isomeric lactones which will result from reduction of the anhydride (11).

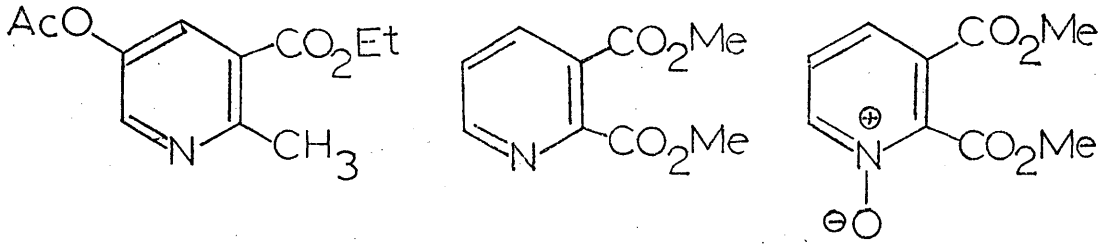
Ethyl 2-methylpyridine-3-carboxylate (31) was readily prepared by the cyclisation[28] of ethyl 3-aminobut-2-enoate with propynal.[29] The N-oxide (32) prepared by treatment with hydrogen peroxide in glacial acetic acid, was not characterised but was treated directly with acetic anhydride at 90°C to afford a yellow oil, distinguishable from the starting material by boiling point difference and by a broadened carbonyl stretching frequency, and other differences in i.r. spectrum. This material, after hydrolysis in aqueous hydrochloric acid, failed to precipitate any of the amphoteric hydroxypyridine (36) at pH 3.[27]

The mechanism of this rearrangement has been the

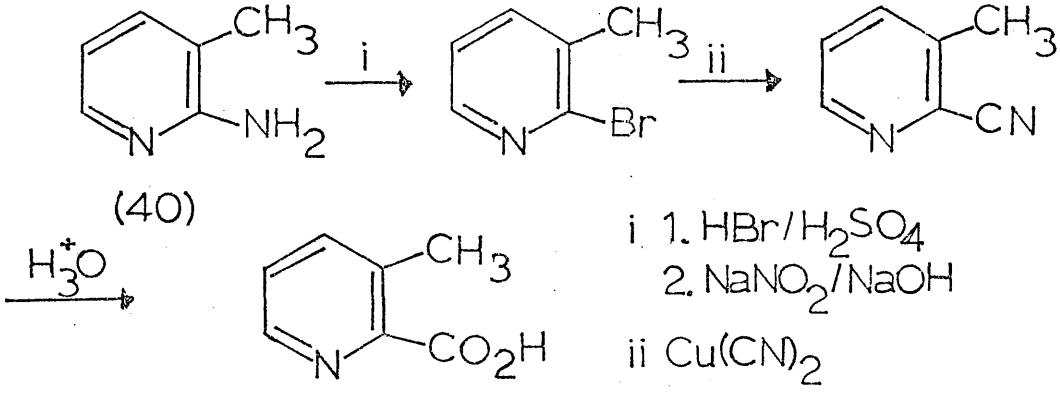


(32) (37) (33)

SCHEME 8



(34) (38) (39)

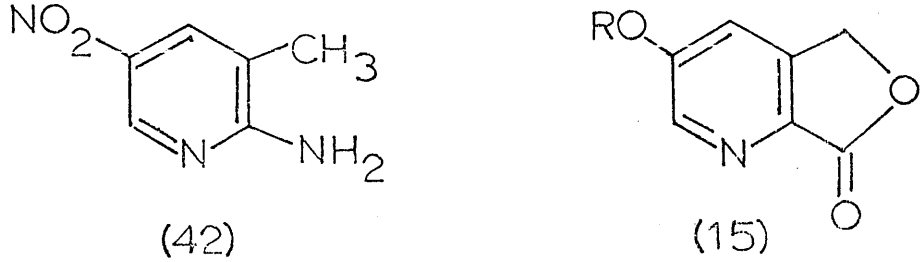


(40) (41)

i 1. HBr/H_2SO_4
2. $NaNO_2/NaOH$

ii $Cu(CN)_2$

SCHEME 9

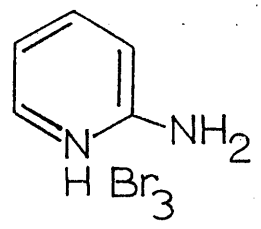


(42) (15)

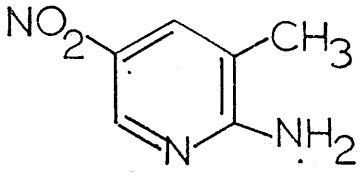
subject of considerable investigation. It has been established that the acetoxymethyl product arises solely from the intramolecular decomposition of the N-acetoxy intermediate (37).[30,31] The presence of radicals in the reaction mixture has been detected[30] and, although not leading to the major product as was first suggested,[32] may account for the ring substituted product (34). These observations suggested that if the decomposition of the N-acetoxypyridine by the intramolecular rearrangement shown in Scheme 8 were eliminated then the mechanistic pathway leading to ring substituted products may become dominant. Dimethyl pyridine-2,3-dicarboxylate (38) was chosen for investigation, being easily prepared[33] and potentially convertible to the key pyridine lactone (15).

The dimethyl ester (38) on oxidation with hydrogen peroxide in glacial acetic acid[27,34] afforded the N-oxide (39) in 50% yield. This was subjected to the conditions required to effect rearrangement but was recovered unchanged. At temperatures greater than 90°C, extensive decomposition occurred and no discrete product could be isolated.

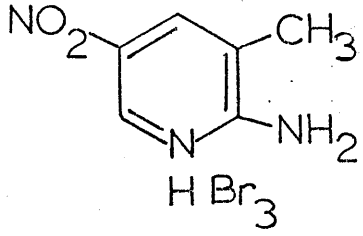
2-Amino-3-methylpyridine (40) can be transformed[35] into 3-methylpyridine-2-carboxylic acid (41) by the procedure outlined in Scheme 9. This process combined with the observation that 2-amino-3-methylpyridine can be nitrated specifically and in high yield at the 5-position,[36,37] suggested a route to 3-methyl-5-nitropyridine-2-carboxylic acid (42), a potential precursor of the lactone (15). Bromination of 2-amino and 4-aminopyridines



(43)



(44)

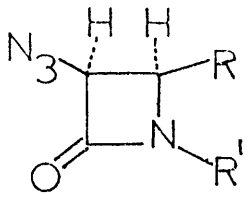


(45)

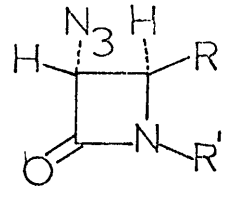
by a normal Sandmeyer reaction gives unsatisfactory yields of the bromide unless modifications[38] to the procedure are made. This is a consequence of inductive destablisation of the diazonium ion by the pyridine nitrogen causing decomposition of the salt prior to reaction. This problem can be overcome by diazotisation of a preformed pyridinium hydrobromide perbromide (43), probably involving trapping of the reactive intermediate in a solvent cage.

The nitropyridine (44), prepared by conventional nitration,[36] on treatment with hydrobromic acid in concentrated sulphuric acid, followed by bromine, formed a labile orange crystalline solid presumed to be the salt (45). Careful diazotisation with sodium nitrite solution at -10°C, followed by gentle warming afforded, after chromatography, a pale yellow solid in extremely low yield. The i.r. spectrum of this material indicated loss of the 2-amino function by the absence of the twin N-H stretches at 3450 cm^{-1} and 3310 cm^{-1} in the starting material; the n.m.r. showed an AB quartet in the aromatic region characteristic of a 2,3,5-trisubstituted pyridine.

All attempts to repeat this procedure failed to produce isolable quantities of the desired 2-bromopyridine, the major and unidentified product being of a polar nature. The difficulties experienced in this reaction may be due to electron withdrawal by the nitro group <u>para</u> to the amine function further destabilising an already unstable and reactive diazonium ion.



(46)



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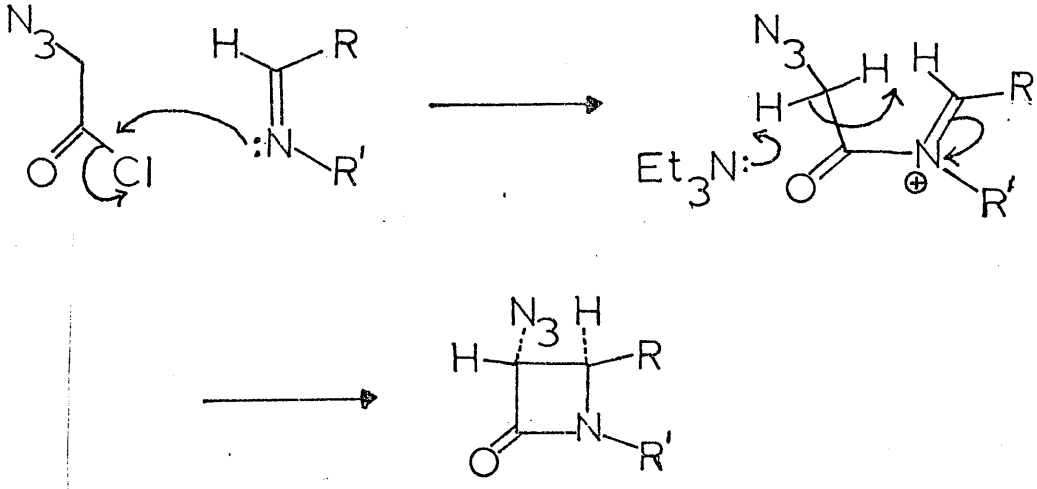
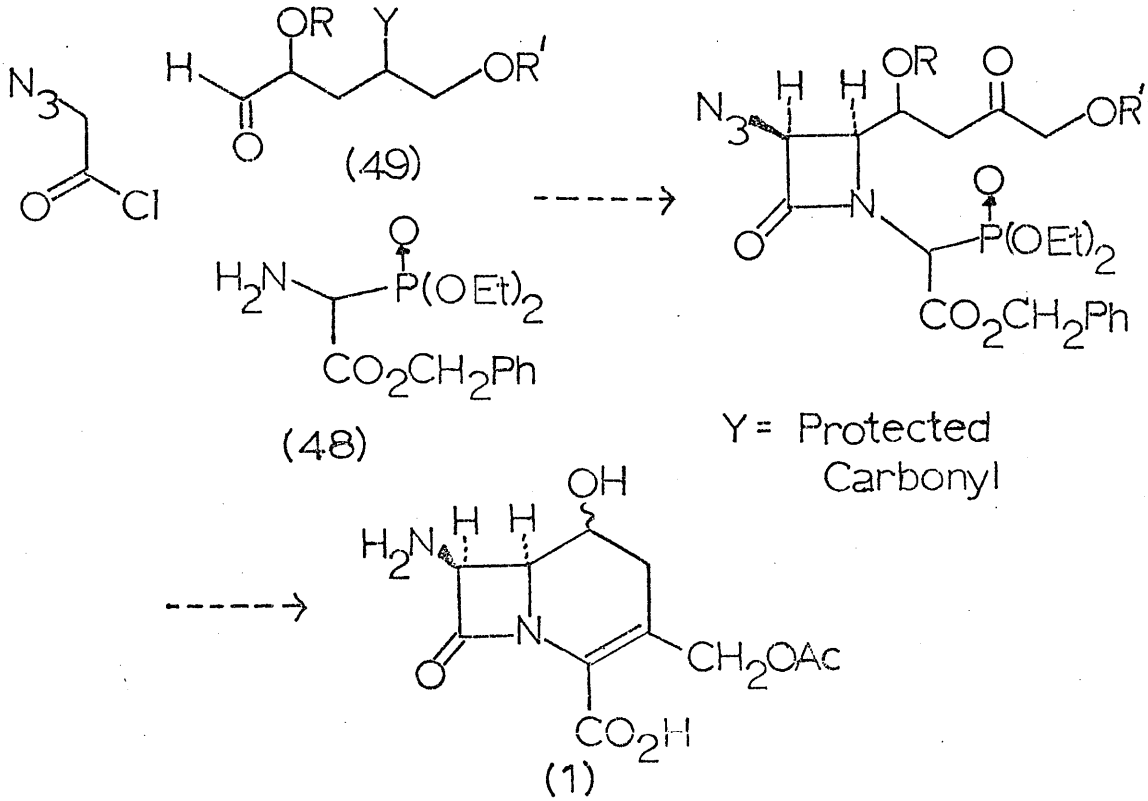


SCHEME 10



(48)

(49)

(1)

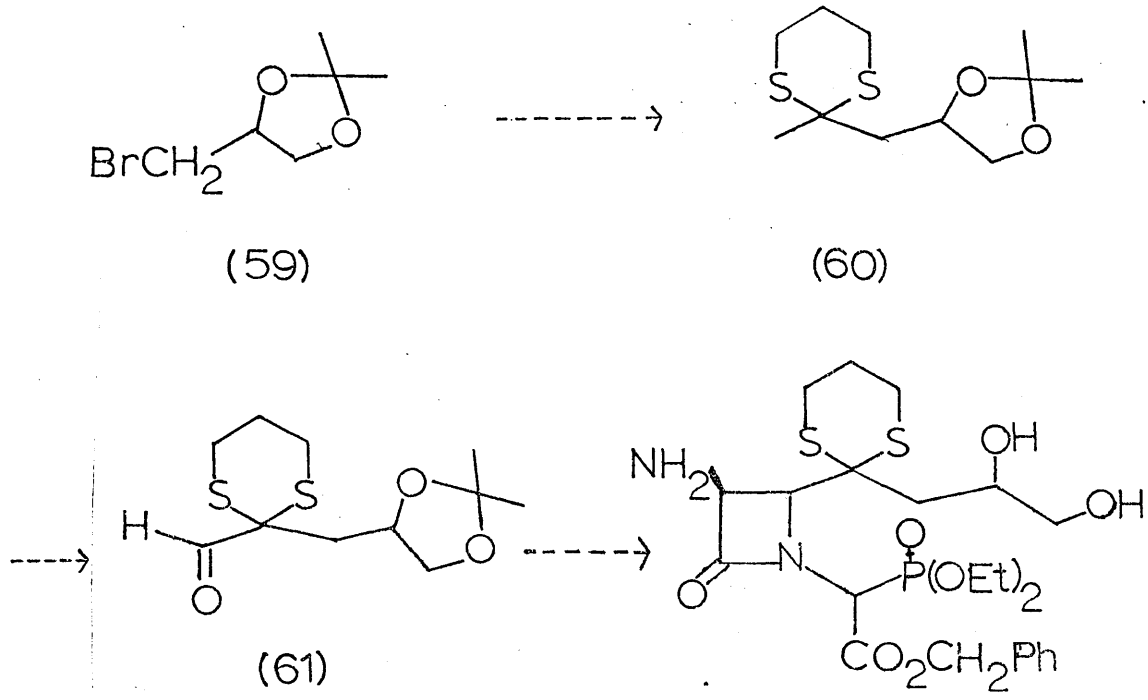
SCHEME 11

2. Iminophosphonate Approaches

Imines react with a variety of ketenes and ketene precursors to provide a general synthetic route to substituted β-lactams.[39] In particular, azidoacetylchloride in the presence of triethylamine[7] has proved invaluable in the preparation of amino-substituted β-lactams, and thence the clinically useful 6- and 7-N-acyl penicillins and cephalosporins. Stereochemical control in this cyclisation is dependent on the sequence of addition of the reagents, two different mechanisms being operable. Addition of the acid chloride to the imine and triethylamine results predominantly in the biologically active cis-isomer (46); a concerted [2+2] cycloaddition between azidoketene and the imine explains the observed stereochemistry. Addition of triethylamine to the acid chloride/imine mixture leads to the trans-isomer (47); here cyclisation probably proceeds in a stepwise manner (Scheme 10).

Application of this general method has led to elegant syntheses of cephalosporin analogues, using imines prepared from the aminomethylphosphonate (48) and suitably substituted aldehydes.[8,9,40] Following this approach, a 1-hydroxy-1-carbacephem (1) could be constructed as depicted in Scheme 11.

A number of routes to the target aldehyde (49) were investigated; the challenge in a synthesis of this fragment arises not only from the differing oxidation levels of the functional groups on the five carbon chain of (49)



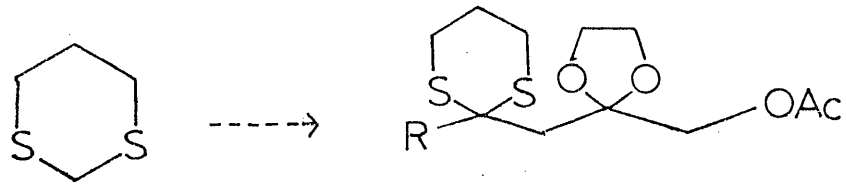
(59) (60)

(61)

(62)

(63)

SCHEME 14

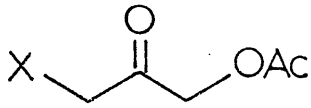


(50)

(51) R = H

(52) R = CHO

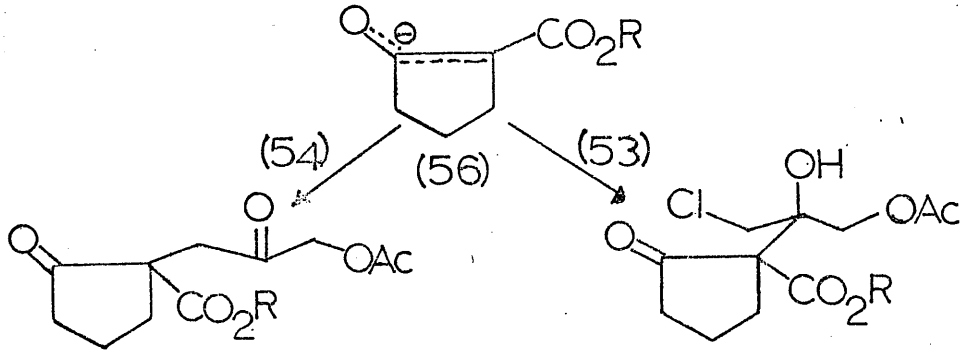
SCHEME 12



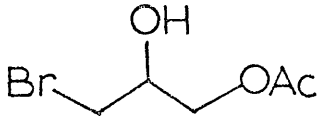
(53) X = Cl

(54) X = I

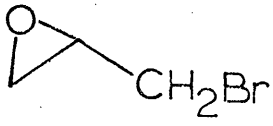
(55) X = Br



SCHEME 13



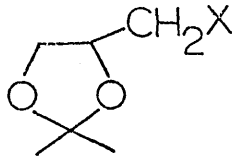
(57)



(58)

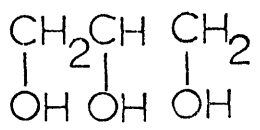
but also from the need for their selective chemical manipulation. An initial approach proposed the use of 1,3-dithiane (50) to provide C-2 of the pentanal; sequential alkylation with 1-chloro-3-acetoxypropanone (53) followed by formylation of the derived anion, would allow introduction of the remaining carbon atoms in appropriately functionalised form (52) (Scheme 12). The ketone (53) was readily prepared from 1,3-dichloropropanone,[41,42] but failed to condense with the 1,3-dithiane anion. This reaction was not pursued further in light of the reported[41] reactions of the 1-chloro- and 1-iodo-3-acetoxypropanones with the enolate anion (56) (Scheme 13). The chloroketone (53) was converted[42] into the corresponding iodoketone (54), which on reaction with the 1,3-dithiane anion gave complex mixtures from which the only identifiable component was 1,3-dithiane. It is possible that the 1,3-dithiane anion is acting as a base rather than as a nucleophile, abstracting an α-proton and perhaps inducing Favorski rearrangement[43] of (54). In order to complete the series, several unsuccessful attempts were made to prepare 1-bromo-3-acetoxypropanone (55) by oxidation of the corresponding propanol (57) obtained in turn by treatment of 1,2-epoxy-3-bromopropane (58) with sodium acetate/iron(III) chloride.[41]

Condensation of the bromide (59) with the 1,3-dithiane anion should provide (60), formylation of which would afford the aldehyde (61). Here, the acetonide, would provide protection to the primary secondary diol (64) destined[44] to become the acetoxy-ketone (63) required



(64) X=OH

(65) X=OTs



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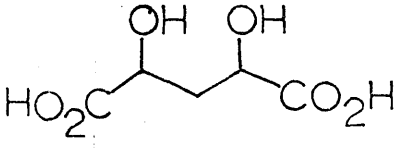

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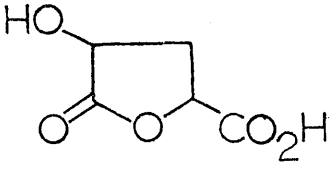
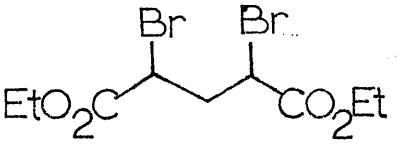


(68)



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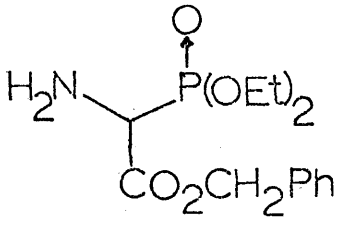

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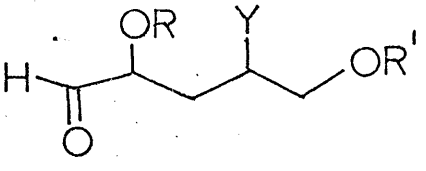
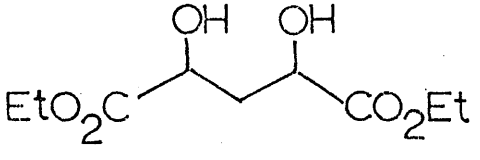
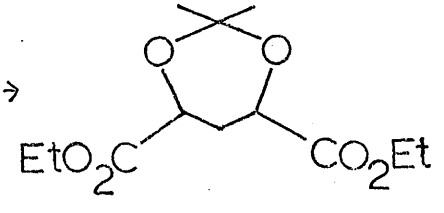
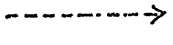


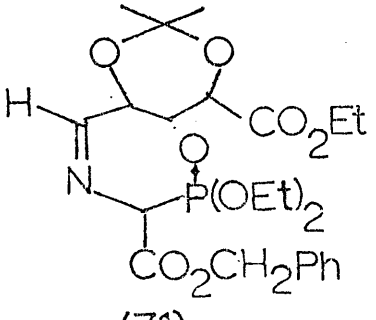
(49) Y=Protected C=O



(70)







(71)

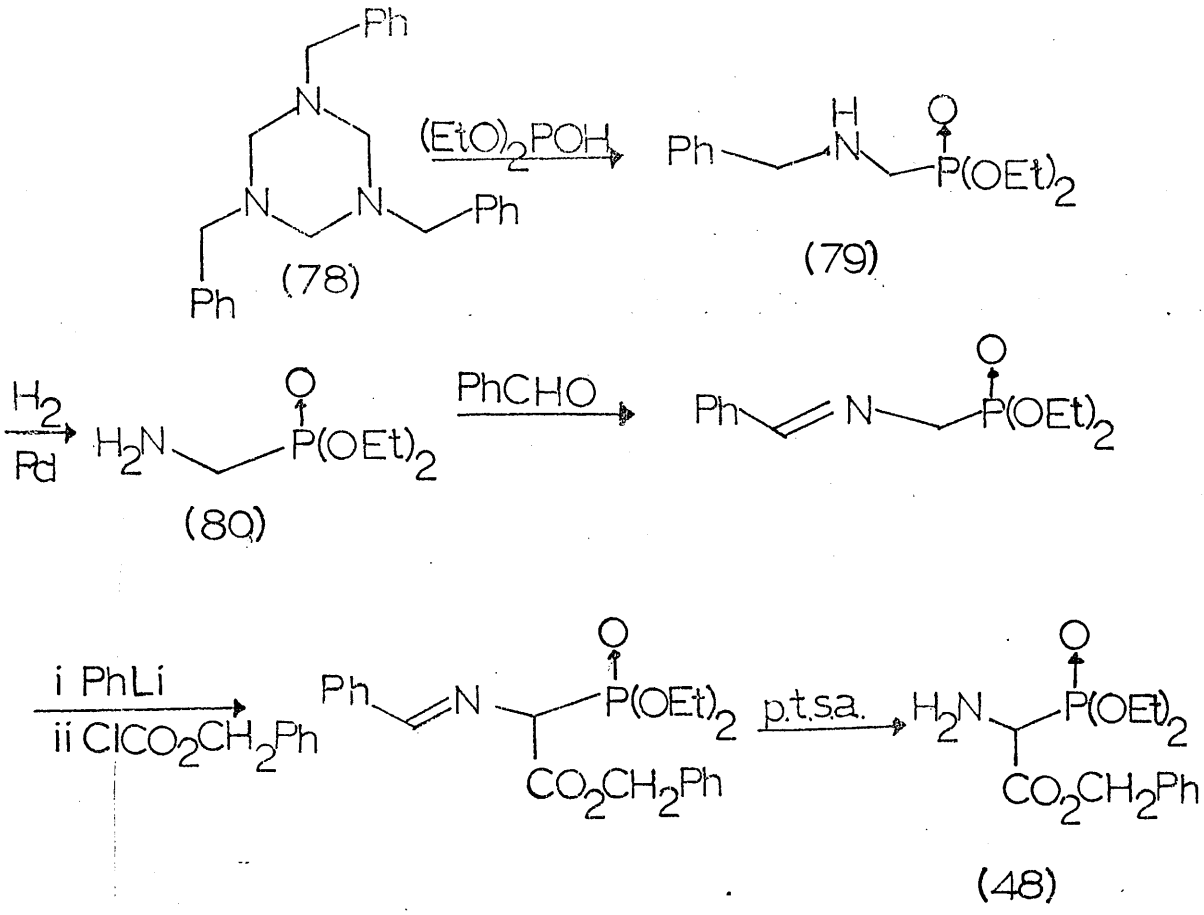
SCHEME 15

for Emmons cyclisation (Scheme 14).

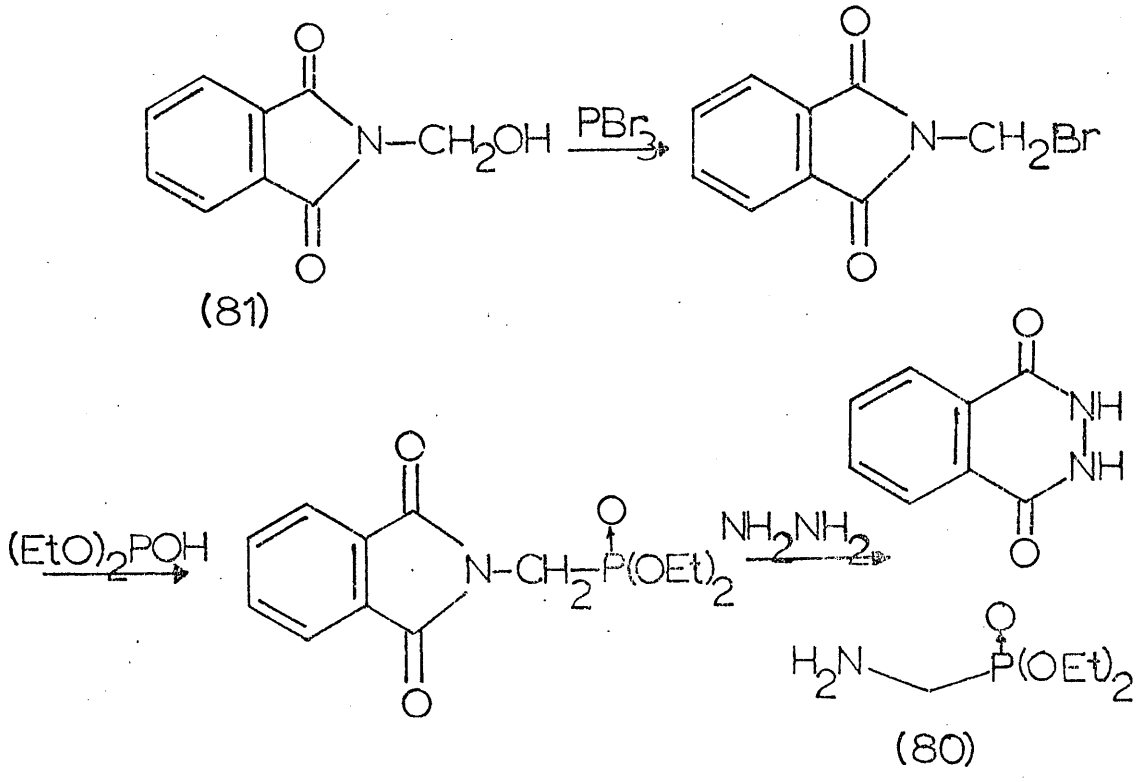
The acetonide alcohol (64) was readily prepared[45] from glycerol (66) and converted into the bromide *via* the tosylate (65).[46,47] Repeated attempts to effect condensation of this bromide with the 1,3-dithiane anion met with consistent failure; low reactivity of ∝-halo-ketals in displacement reactions have been reported.[48]

Ingold has reported[49] the preparation of the dihydroxy-acid (67) and the derived lactone (68) by hydrolysis of the dibromide (69). The carbon skeleton of (67) is functionalised at the same positions as the key aldehyde (49) and by appropriate functional group manipulation could be useful for condensation with the phosphonate (48). The ∝∝-dibromo-ester (69) was prepared[49] from glutaric acid by photochemical bromination of the diacid chloride, followed by quenching with ethanol prior to work-up. Careful hydrolysis of (69) in buffered solution failed to produce any of the dihydroxy-ester (70), considered to be a more useful target than the corresponding diacid, since selective reduction of one of the ester groups would provide the necessary aldehyde for the preparation of the imine (71) (Scheme 15).

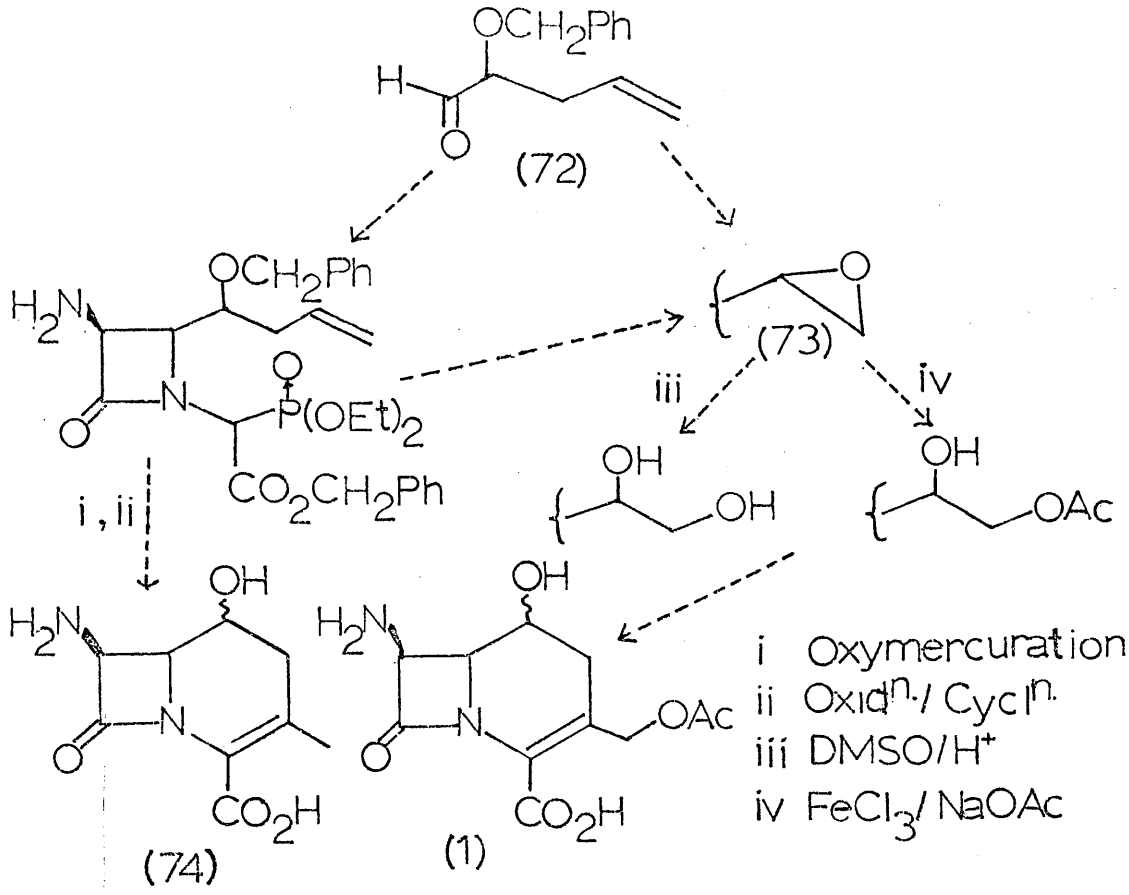
The failure of the preceding approaches to the problem suggested incorporation of a functional group in the aldehyde fragment which would allow introduction of one or more oxygen functions at a later stage. To this end the aldehyde (72) was chosen, the terminal double bond providing versatility of choice in subsequent reactions required to introduce the necessary functionality. The



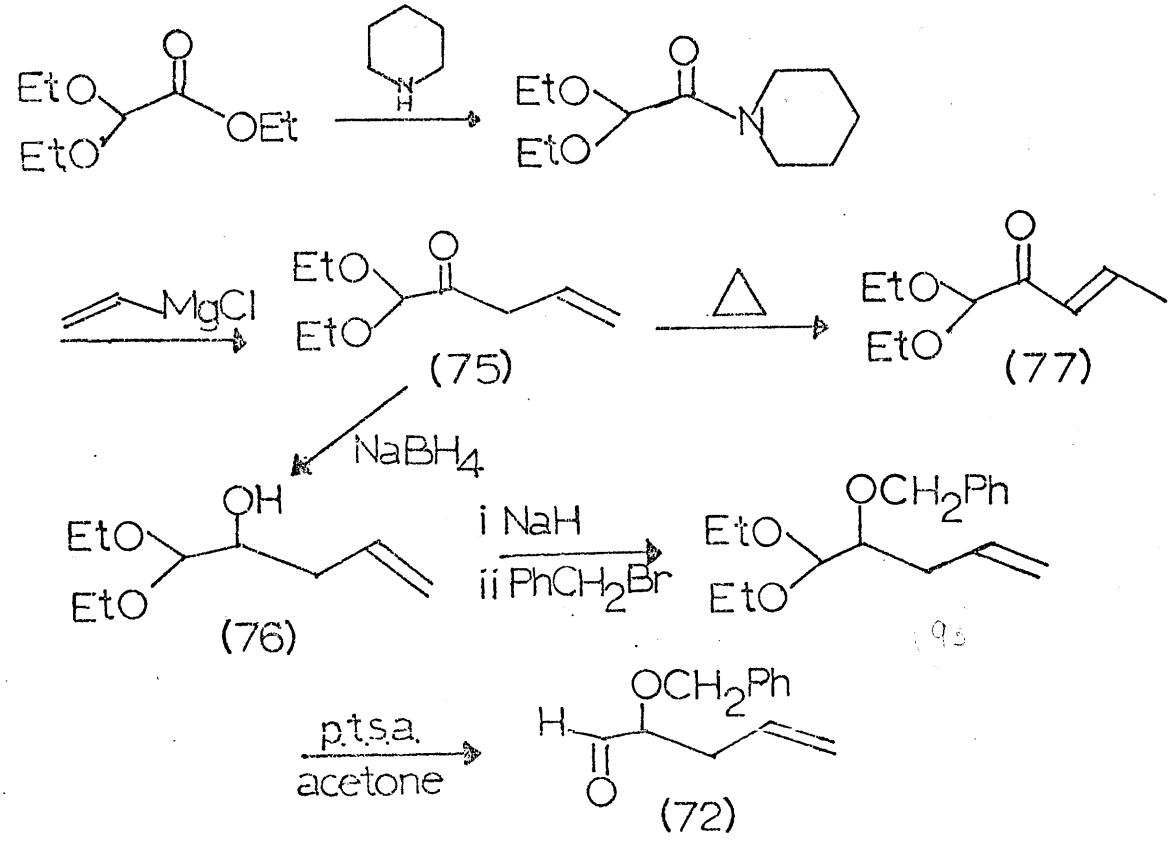
SCHEME 18



SCHEME 19



SCHEME 16



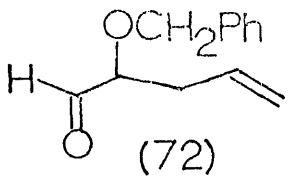
SCHEME 17

oxymercuration procedure developed by Brown,[50,51] or hydride reduction[52] of the epoxide (73) would introduce the carbonyl group necessary for cyclisation of the six-membered ring present in the 10-desacetoxy-1-carbacephem (74) while a potential route to the acetoxymethyl analogue (1) would involve nucleophilic opening of the epoxide (73) (Scheme 16).

The aldehyde (72) was readily prepared as outlined[53] in Scheme 17. A difficulty encountered in this route was facile migration of the terminal double bond in (75) to the isomeric conjugated enone (77), a problem easily circumvented by direct reduction of the crude ketone (75) to the alcohol (76).

The aminomethylphosphonate (48) has been synthesised[54] by the route shown (Scheme 18). Conversion of the triazine (78), prepared[55] from benzylamine and formaldehyde, into the amine (79) proved difficult in our hands; isolation of (79) either as the free amine or its hydrochloride was quite unsatisfactory and an alternative approach was sought. The aminomethylphosphonate (80) was synthesised[56] in three steps from N-hydroxymethylphthalimide[57] (Scheme 19), and was then smoothly converted into (48) as shown in Scheme 18, lithium isopropycyclohexylamide being found superior to phenyl lithium as base.

A virtually quantitative yield of the unstable imine (82) was obtained by mixing equimolar amounts of the aldehyde (72) and the amine (48) and removing the water produced. Disappointingly, this imine failed to undergo cyclisation in the desired manner with azidoacetyl-



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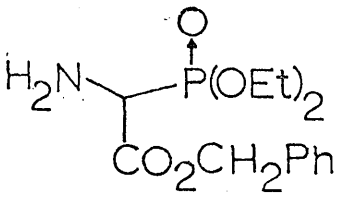

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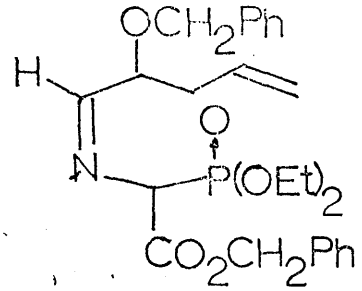

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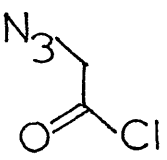

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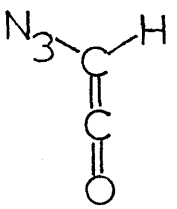

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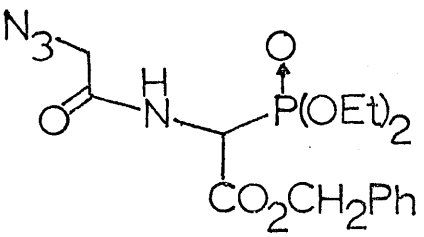

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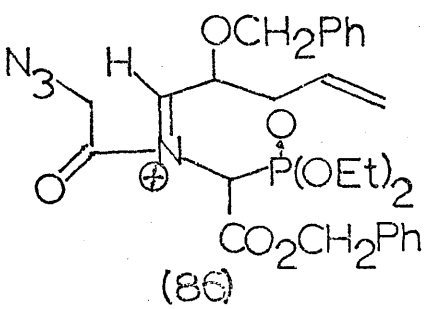

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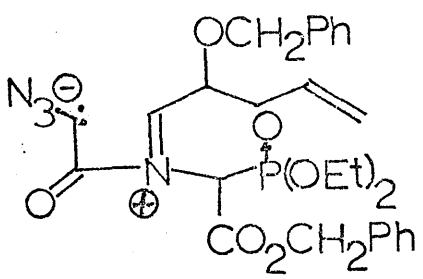

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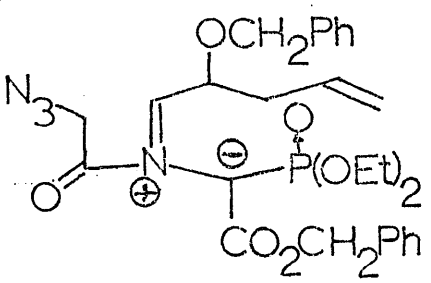
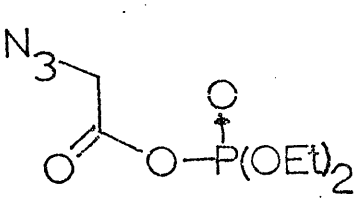


(88)

SCHEME 20

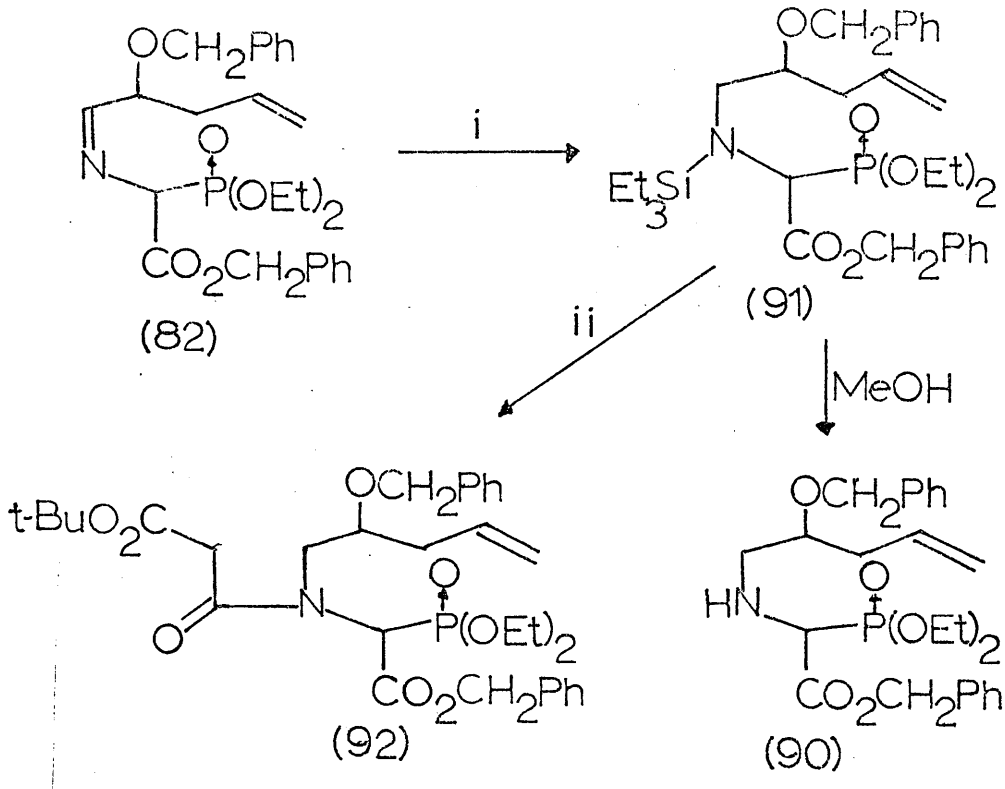


(89)

chloride (83)[58,59]/triethylamine[7] under a wide variety of conditions, which ranged from preformation of azidoketene (84) through to conditions expected to favour the stepwise cyclisation. In a similar case, without an aromatic substituent or heteroatom α to the imine carbon, Christensen[40] indicated considerable difficulty in achieving cyclisation. In the present example the only products isolated were the acylated amine (85) and starting aldehyde (72).

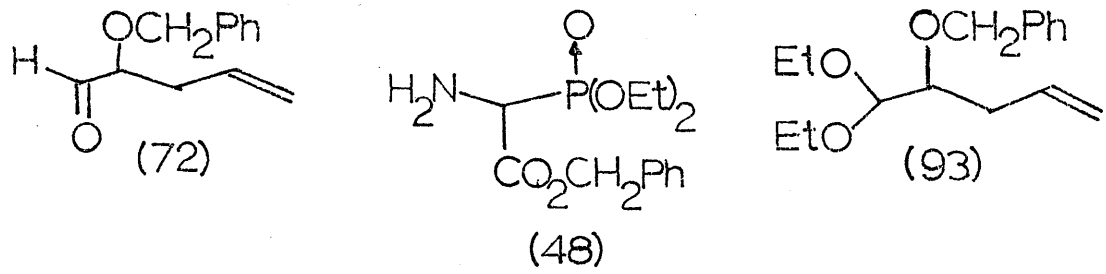
In view of the care taken to ensure scrupulously anhydrous conditions it is unlikely that hydrolysis of the imine followed by acylation of the liberated amine led to formation of (85). More likely is hydrolysis, on work-up, of an intermediate adduct of the imine (82) and azidoacetylchloride (83) or azidoketene (84). In these reactions the initially formed adducts (86) and (87) may undergo either abstraction of the more acidic proton H_A or proton transfer respectively forming the ylid (88), rather than abstraction of the proton α to the azido group and subsequent cyclisation. This ylid (88) will be in a thermodynamic well on the reaction co-ordinate, and the driving force for cyclisation is lost. On work-up, protonation of (88) will reform the reactive iminium ion (86) which will immediately cleave to the amide (85) and the aldehyde (72).

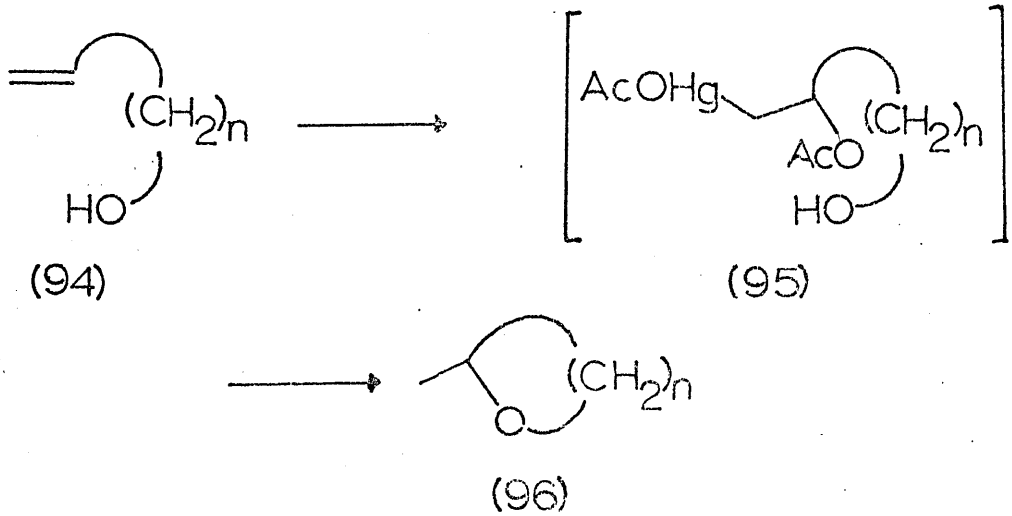
Use of the phosphonate ester (89), prepared <u>in situ</u> from azidoacetic acid and diethyl chlorophosphite[60] in the presence of triethylamine,[61] resulted in exclusive formation of the amide (85). Attempts to effect the



i $Et_3SiH/PdCl_2$ ii $t\text{-}BuO_2CCH_2COCl$

SCHEME 21





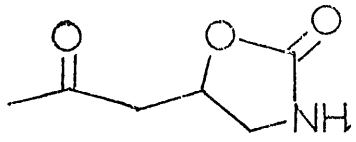
SCHEME 22

cyclisation with dichloroacetylchloride/triethylamine were equally unsuccessful.

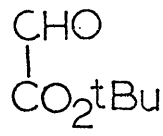
Faced with failure at such a late stage, it was only sensible to consider means of salvaging something from this approach. Attention was focused on an alternative mode of construction of the β-lactam ring *via* an amine by the procedure developed by Lowe[10] and described earlier. Two routes to the required secondary amine (90) were contemplated. Reduction of the imine (82) under extremely mild conditions with triethylsilane[62] and palladium(II) chloride as catalyst led to extensive decomposition. A potential advantage of this particular reduction technique is that the initial N-triethylsilane (91) if it had been produced could have been converted into the amine (90) or the amide (92) (Scheme 21).

Conversion of the aldehyde moiety in (72) into a good leaving group such as a tosylate, and condensation with the aminomethylphosphonate (48) should produce the secondary amine (90). Before undertaking this, it was decided to explore the oxymercuration step. Oxymercuration of the acetal (93) gave inconsistent results, the products of reaction remaining unidentified. Brown has reported[63] that in the oxymercuration of alkenes such as (94) the oxygen function intramolecularly traps the intermediate acetoxymercurinium cation (95), leading to cyclic ether (96) (Scheme 22). It is possible that one of the acetal oxygens in (93) is trapping the intermediate cation in an analogous way, leading initially to cyclic products.

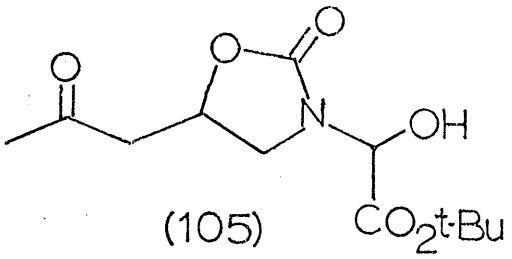
The failure of this crucial step in the sequence



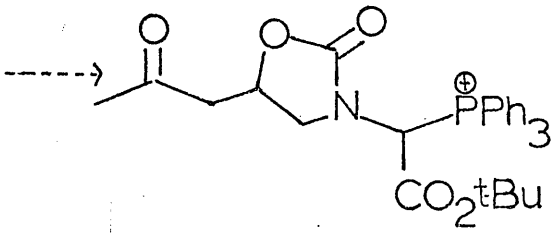
(103)

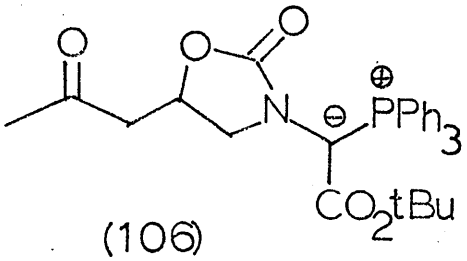


(104)



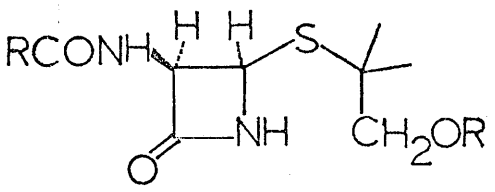
(105)

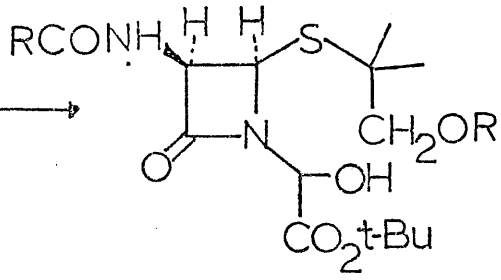


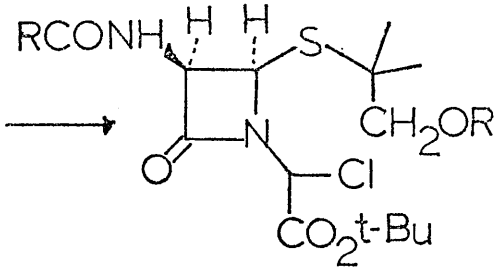


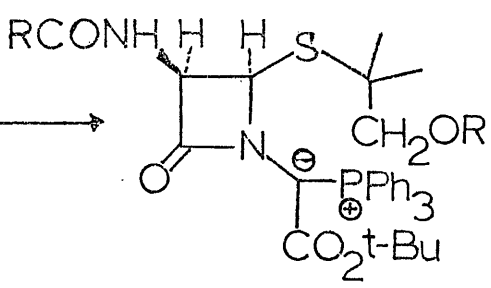
(106)

SCHEME 25

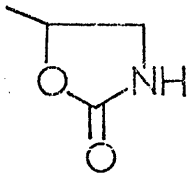




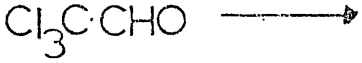




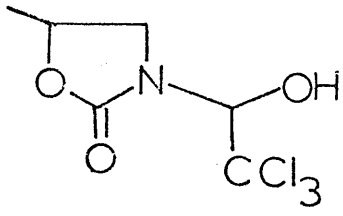
SCHEME 26



(107)

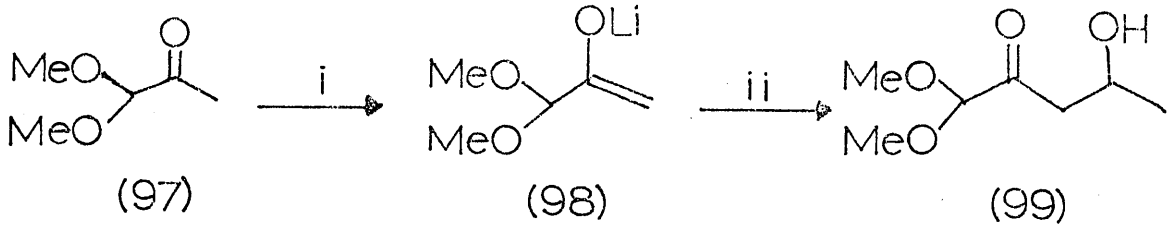


(108)



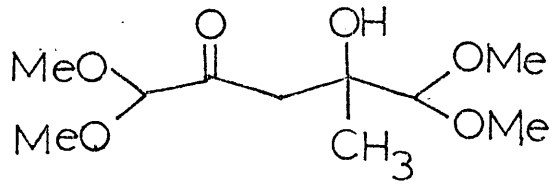
(109)

SCHEME 27

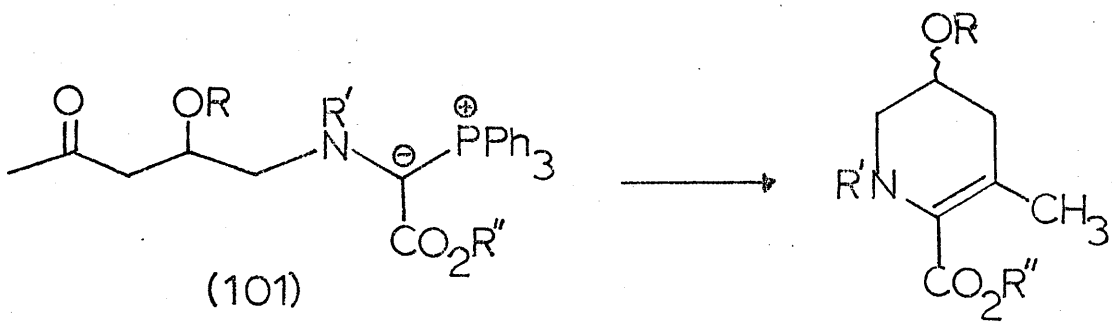


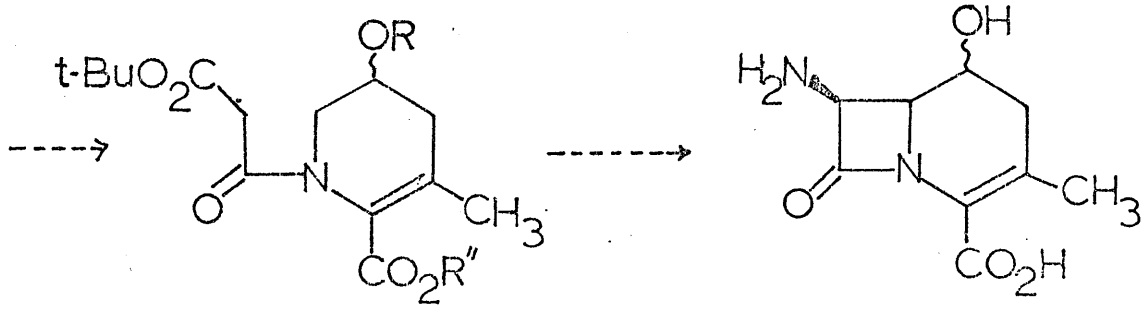
i iPr_2NLi ii CH_3CHO

SCHEME 23



(100)





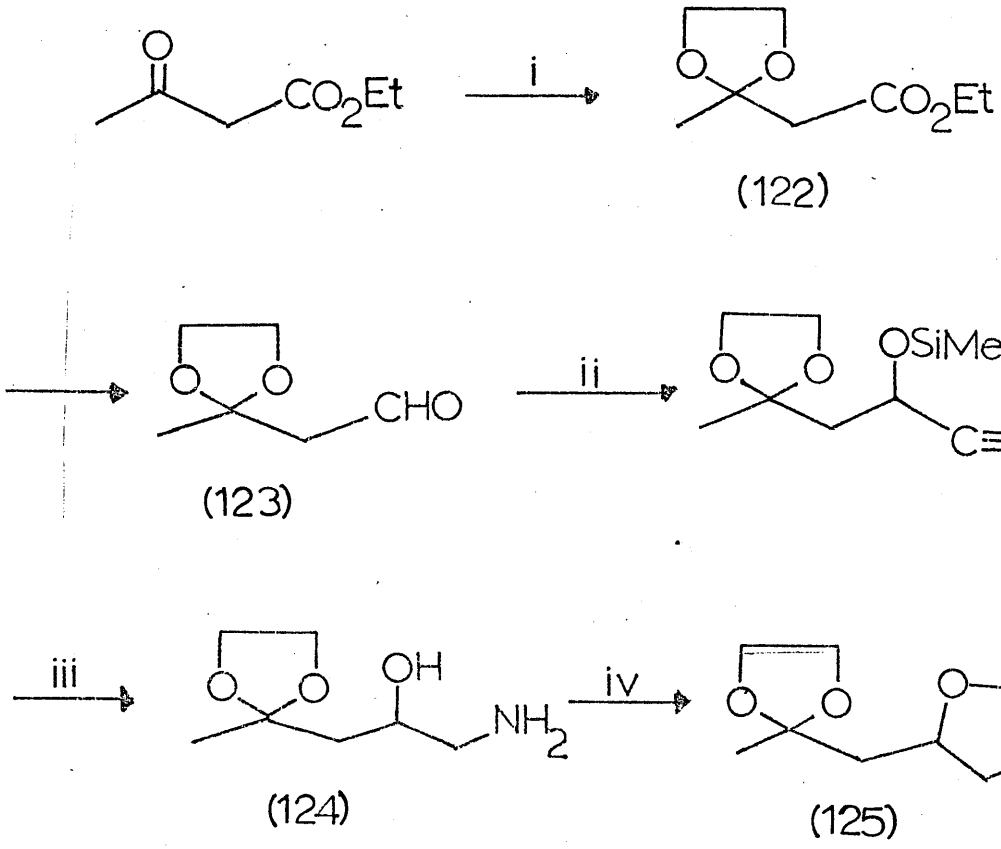
SCHEME 24

prompted an investigation of a potentially direct route to the acetal alcohol (99). Stork[64] has described the use of lithio-enolates to perform directed aldol condensations a and it was hoped that the enolate (98) would condense with acetaldehyde to give (99). However, this reaction afforded complex mixtures from which (99) was not readily obtainable; the major contaminant appeared to be (100), arising from self condensation of (97) (Scheme 23).

3. Oxazolidone Approaches

The cyclic enamine (102) should be capable of transformation into (74) employing the annelation procedure developed by Lowe.[7] (Scheme 24). The enamine (102) could be obtained by an intramolecular Wittig reaction of (101). Here, the need for protection of both the amine and hydroxyl functions could be satisfied by the oxazolidone (106), a ring system which can be cleaved by hydrolysis,[65,66] or metal hydride reduction.[67] By a modification of Woodward's procedure[11] it should then be possible to prepare the alcohol (105) and thence the ylid (106) from the oxazolidone (103), by condensation with t-butyl glyoxylate (104)[68] (Scheme 25).

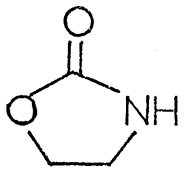
A sequence of transformations (Scheme 26) had already been reported[11] but it was felt necessary to confirm that an oxazolidone would react in an equivalent manner. There was some analogy for believing that this would be the case; the oxazolidone (107) is reported[69] to react with trichloroethanal (108) to give the alcohol (109) (Scheme 27).



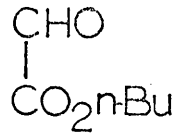
i $\square_{OH}^{OH}$/p.t.s.a. ii Me_3SiCN iii Red^n

iv ClCOCl

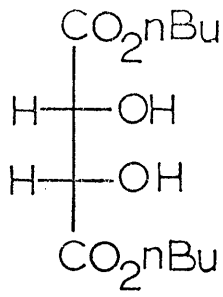
SCHEME 28



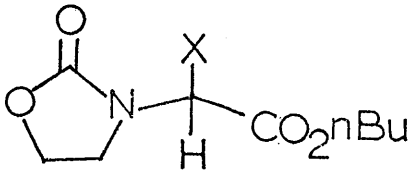
(110)



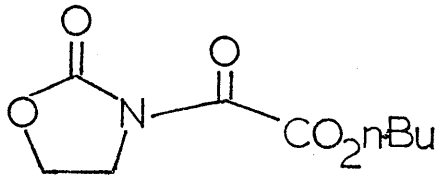
(111)



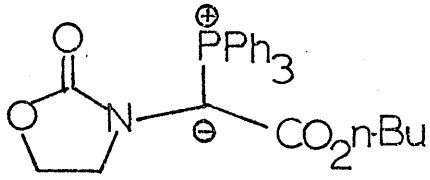
(112)



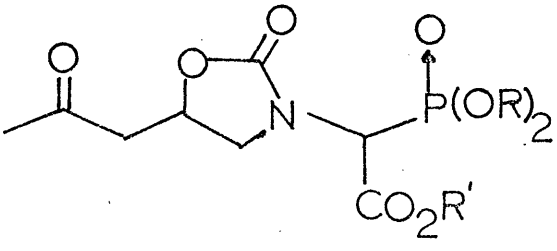
(113) X = OH
(114) X = OAc
(116) X = Cl
(117) X = Br



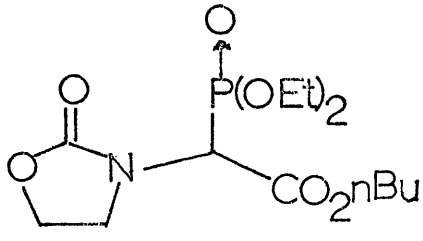
(115)



(118)



(119)

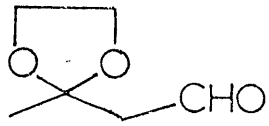


(120)

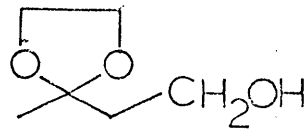
2-Oxazolidone (110) and n-butyl glyoxylate (111), readily prepared from dibutyl L-tartrate (112) by oxidation with lead(IV) acetate,[70] were heated together neat at 90°C to give the alcohol (113). Conversion into the acetate (114) and oxidation to the ketone (115) confirmed this structure. Attempts to prepare and isolate the chloride (116) employing thionyl chloride[11] or triphenyl phosphine/carbon tetrachloride[71] proved futile, as did attempts to prepare the ylid (118) directly without isolation of the reactive halide. This disappointing failure led to two ultimately successful modifications requiring no revision of the overall strategy.

Ring closure can be achieved by an Emmons reaction[72] of the phosphonate (119). However, all attempts to convert the model alcohol (113) into the phosphonate (120) via the chloride (116) in a one-pot process were frustrated. The second modification of the published procedure involved the intermediacy of the more reactive bromide (117) prepared by treatment of the alcohol with phosphorus tribromide in benzene. Without isolation, the bromide reacted in an Arbusov manner[73] with trimethyl phosphite to yield the phosphonate (120) in good yield.

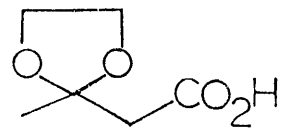
Model studies successfully completed, potential routes to the oxazolidone (125) were then investigated. β-Amino alcohols yield oxazolidones directly on treatment with phosgene.[74] The amino alcohol (124) was conceived as arising[75,76] from the aldehyde (123) (Scheme 28). Ethyl 3-oxobutyrate (121) can be converted to the ketal (123);[77] reduction of the ester should lead to (123).



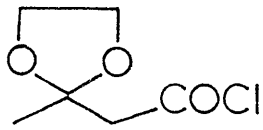
(123)



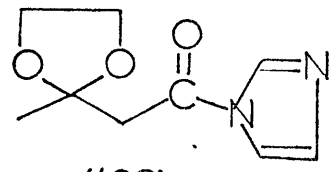
(126)



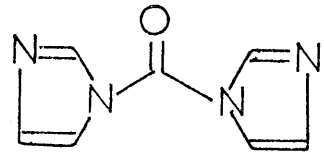
(127)



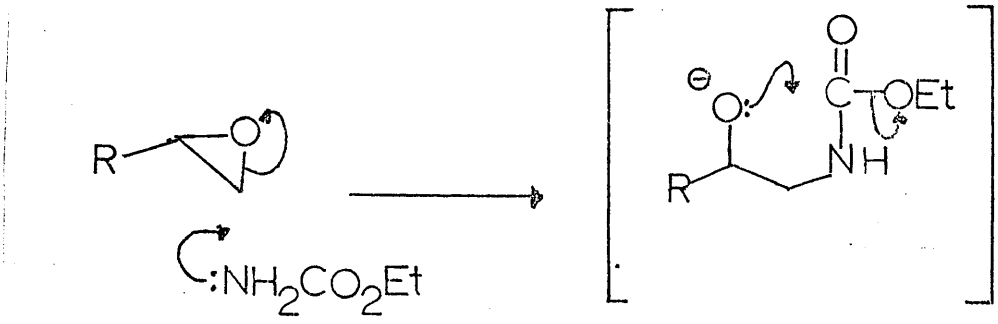
(128)



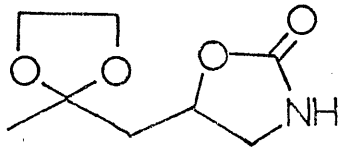
(129)



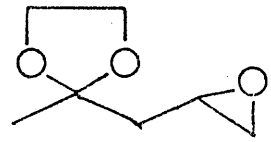
(130)



SCHEME 29



(125)

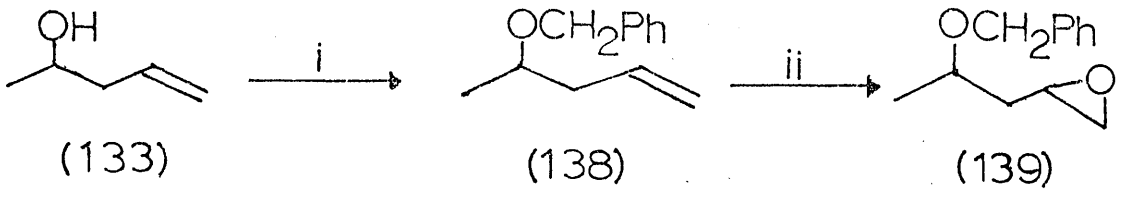


(131)

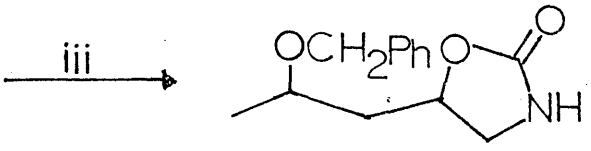
Reduction of (122) with lithium aluminium hydride in ether afforded the primary alcohol (126) in almost quantitative yield. Oxidation of (126) with pyridinium chlorochromate[78] or Collins reagent[79] failed to produce isolable quantities of the aldehyde (123). Physical changes as these reactions proceeded indicated some degree of oxidation, and n.m.r. spectra of crude reaction mixtures indicated significant quantities of an aldehyde as evidenced by a singlet resonance at $\delta 9.3$.

Acids can be converted into aldehydes by the reduction of the corresponding chlorides[80] or imidazolides.[81] Attempts to prepare the acid chloride (128) from the acid (127), obtained by hydrolysis of (122), were unsuccessful, so the alternative reduction procedure was adopted. The imidazolide (129) was prepared <u>in situ</u> by treatment of (127) with one equivalent of N,N'-carbonyldiimidazole (130). Reduction with two equivalents of lithium aluminium hydride and n.m.r. analysis of the crude reaction mixtures again revealed the presence of an aldehyde which was not isolable, in addition to some alcohol (126) produced by over-reduction. The aldehyde is obviously unstable, decomposing, possibly by acetal exchange, to give intractable mixtures.

An alternative route to oxazolidones is the nucleophilic opening of an oxirane with ethyl carbamate in the presence of triethylamine[82] (Scheme 29). A synthesis of the oxazolidone (125) by this route would require the oxirane (131); the routes investigated to this target are outlined in Scheme 30. Treatment of the conjugated enone



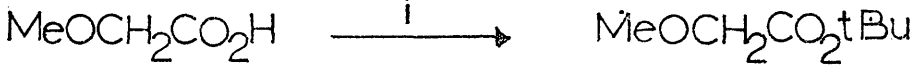
(133) (138) (139)

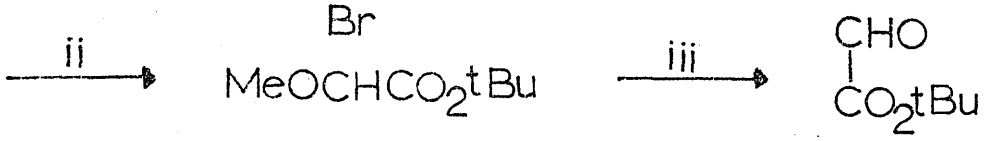


(140)

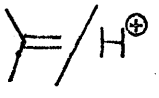
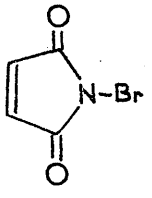
i 1. NaH 2. $PhCH_2Br$ ii Peracid iii NH_2CO_2Et

SCHEME 31

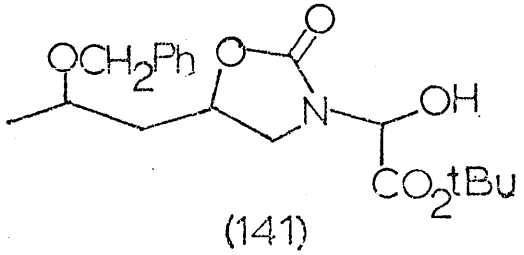




(104)

i  ii  iii $H_2O/NaHCO_3$

SCHEME 32



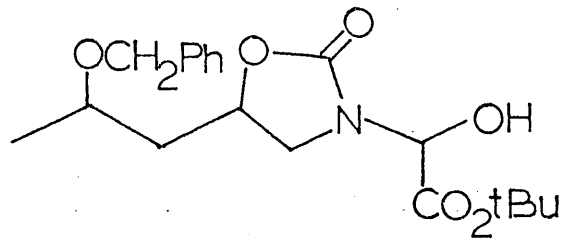
(141)

enone (132) with ethylene glycol and p-toluene sulphonic acid failed to result, to any appreciable extent, in the expected migration of the double bond to the terminal position. The isomeric mixture of alkenes (135) and (136) was inseparable and remained so on conversion to the oxiranes (137) and (131). Accordingly, the terminal alkene alcohol (133) was carefully oxidised to the ketone (134), which without purification, was treated with ethylene glycol in the catalytic presence of p-toluene sulphonic acid. Undesired conjugation of the double bond occurred resulting in inseparable mixtures of alkenes, and subsequently oxiranes, albeit in differing proportions from the earlier sequence.

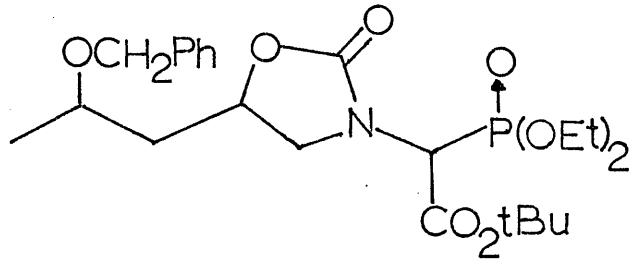
To circumvent this problem, the benzyl ether (138) was prepared from (133). This alteration merely necessitated the addition to the sequence of hydrogenolytic cleavage of the benzyl ether and oxidation prior to Emmons cyclisation.

Epoxidation of (138) with sodium carbonate buffered trifluoroperacetic acid[83] was successful but unreliable, frequently resulting in polymerisation. This difficulty was obviated, and reliability conferred, by the use of permaleic acid[84] as epoxidising agent. Treatment of the resulting oxirane (139) with ethyl carbamate/triethylamine furnished the oxazolidone (140) in very satisfactory yield (Scheme 31).

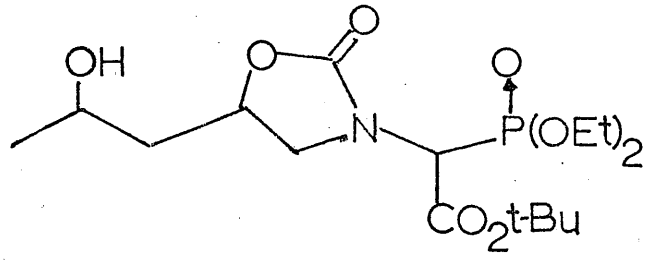
t-Butyl glyoxylate (104), obtained[85] from methoxy acetic acid (Scheme 32), condensed with (140) as expected to give the alcohol (141). Preparation of the phosphonate



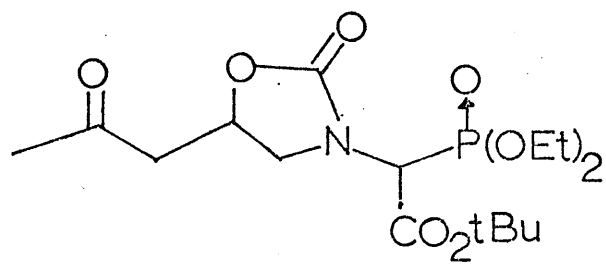
(141)



(142)



(143)



(144)

(142) from (141) was accomplished by the method developed for the model compounds with exception that, in the preparation of the intermediate bromide, triethylamine was added to preclude acid-catalysed decomposition of the t-butyl ester.

Hydrogenolysis of the benzyl ether (142) afforded the alcohol (143). Attempted oxidation of this alcohol to the ketone (144) has, to date, been unsuccessful. Oxidations with pyridinium chlorochromate[78] and Collins reagent[79] gave crude reaction mixtures which indicated the formation of a ketone. However, preparative t.l.c. of this material gave unidentifiable products not apparent in the crude mixture. Time did not permit the finding of a solution to this oxidation problem, which is undoubtably minor in nature.

This total project, having now reached a most significant stage of development, will continue in other hands, hopefully to completion.

EXPERIMENTAL

EXPERIMENTAL - CONTENTS

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GENERAL EXPERIMENTAL AND ABBREVIATIONS

Melting points are uncorrected and were determined on a Kofler hot stage apparatus. Microanalyses were obtained by Mrs. Harkness and her staff. Mass spectra were recorded by Mr. A. Ritchie on A.E.I. - G.E.C./ MS 12 and A.E.I. - G.E.C./ MS 902 mass spectrometers. Routine i.r. spectra were recorded on a Perkin Elmer 225 grating spectrophotometer and were liquid film unless otherwise stated. Routine n.m.r. were recorded on a Varian T 60 and high resolution n.m.r. spectra were recorded by Mr. J. Gall on a Varian HA 100 spectrometer, with tetramethyl silane as internal standard in both cases.

Kieselgel G (Merck) was used for preparative thin layer chromatography. Analytical t.l.c. plates were stained with iodine vapour and/or ceric ammonium sulphate followed by heating to approximately 150 ^{o}C.

All dilute mineral acids were 6N aqueous unless otherwise stated. Light petroleum refers to the fraction boiling in the range 40-60 ^{o}C. All organic solutions were dried, unless otherwise noted, over anhydrous magnesium sulphate.

Tetrahydrofuran was heated under reflux with lithium aluminium hydride and distilled prior to use. Pyridine was distilled from barium oxide and stored over Linde 4A molecular sieves.

Methylene chloride was dried by percolation through a column of alumina (Woelm, Grade I basic).

The following abbreviations and symbols have been used throughout this section:-

t.l.c.	thin layer chromatography
i.r.	infrared
n.m.r.	nuclear magnetic resonance
s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
b	broad
d d	double doublet
M^+	molecular ion

1. PYRIDINE APPROACHES

Sodium Nitromalondialdehyde Monohydrate (21)

This was prepared by the method of Fanta,[85] and was obtained as thermally labile pale tan needles.

3-Nitroquinoline (16)

This was prepared by the literature method,[17] m.p. 129-130° (lit. m.p. 127-128°)

$\nu_{max.}$ 1600, 1520, 1450, 800, 780, and 760 $cm.^{-1}$

Attempted Oxidation of 3-Nitroquinoline (16)

(a) With potassium permanganate.[16] - 3-Nitroquinoline (1.74 g, 10 mmol) was added to a solution of potassium permanganate (9.48 g, 60 mmol) and calcium carbonate (2.5 g, 25 mmol) in water (250 ml). The solution was stirred at room temperature for 18 h, when the water was evaporated in vacuo. The dark brown syrup was acidified with dilute nitric acid, and then neutralised with dilute aqueous sodium hydroxide solution. To this was added an excess of solid copper sulphate and the mixture warmed to 90 °C for 2 h. On cooling, no precipitation of copper salt was observed. This oxidation was repeated at 70 °C with identical results.

(b) With hydrogen peroxide. - This was carried out as described by Stix and Bulgatsch.[15] 3-Nitroquinoline (2.6 g, 15 mmol) afforded a copper salt (1.7 g) which

was added to aqueous sodium sulphide solution (2[illegible] ml, 10%) and stirred at 60 °C for 16 h. The mixture was filtered to remove a fine precipitate of copper sulphide, carefully acidified with concentrated sulphuric acid, and extracted with ethyl acetate. The extracts were dried and solvent removed in vacuo to yield a dark-brown oil, which on trituration with ether afforded a brown amorphous i.r. inactive solid.

Attempted Oxidation of 3-Bromoquinoline (17)

(a) With potassium permanganate. - The same reaction conditions and isolation procedure were employed as (a) above to obtain a copper salt as a pale blue solid (3.7 g), $\nu_{max.}$ 1650 $cm.^{-1}$ This material was added to aqueous sodium sulphide solution (48 ml, 10%) and stirred at 60 °C for 16 h. The mixture was filtered, and the filtrate carefully acidified with concentrated sulphuric acid. The fine precipitate which formed was collected but was not organic.

(b) With hydrogen peroxide. - The oxidation was carried out as in (b) above. 3-Bromoquinoline (6.6 g, 30 mmol) afforded a copper salt as a pale blue solid (8.2 g), $\nu_{max.}$ 1680 $cm.^{-1}$ Two methods of decomposition of this salt were investigated.

(i) The salt (2 g) was added to aqueous sodium sulphide solution (90 ml, 10%) and stirred for 16 h at

60 °C. The solution was filtered, and the filtrate acidified with concentrated sulphuric acid and the resulting precipitate collected (0.50 g); this material contained no carbonyl stretching frequency in the i.r.

(ii) The salt (3 g) was suspended in water (500 ml) in a 1 l three-necked flask equipped with a gas inlet tube projecting below the level of the liquid. Hydrogen sulphide was passed slowly through the vigorously stirred suspension at 60 °C. After 2.5 h the gas flow was stopped and the flask was set aside, open to the atmosphere, at 10 °C for 3 days. The mixture was filtered to remove the black precipitate of copper sulphide, the filtrate carefully acidified with concentrated sulphuric acid, and the water removed in vacuo with final benzene azeotroping to yield a yellow oil. This oil was taken up in water (20 ml) and extracted with ether (3 x 100 ml). The combined ethereal extracts were dried and solvent removed to yield a pale yellow solid (0.43 g, 16%) which crystallised from acetone as as amorphous powder, m.p. 138-142° (lit. m.p. 165°)

$\nu_{max.}^{Nujol}$ 3180, 1710, 1450, 1415, 1370, 1270, and 690 $cm.^{-1}$

The acid was characterised as its dimethyl ester:-

$\nu_{max.}$ 1740, 1725, 1290, 1130, and 1070 $cm.^{-1}$

$\delta (CDCl_3)$ 3.95 (3 H, s, OCH_3), 4.0 (3 H, s, OCH_3), and 8.3 and 8.8 (2 H, ABq, J_{AB} 2 Hz, ArH).

(Found: M^+, 273 and 275. $C_9H_8BrNO_4$ requires M, 273 and 275).

3-Bromopyridine-2,3-dicarboxylic Acid Anhydride (19)

A solution of 3-bromopyridine-2,3-dicarboxylic acid (200 mg, 8 mmol) and acetic anhydride (2 ml, 200 mmol), in xylene (5 ml) was heated under reflux for 4 h. The volatiles were removed under reduced pressure to furnish a pale yellow solid (25 mg, 14%) as an amorphous powder m.p. 120-124° (from ether at -78 °C) (lit. m.p. 134-136°)

$\nu_{max.}^{Nujol}$ 1770, 1450, 915, 730, and 710 $cm.^{-1}$

(Found: M^+, 227 and 229. $C_7H_2BrNO_3$ requires M, 227 and 229).

Attempted Preparation of Diethyl 5-Nitropyridine-2,3-dicarboxylate

Ethyl oxalacetate (3.8 g, 20 mmol) was dissolved in ether (20 ml) and gaseous ammonia, distilled from sodium, was passed through the solution at 0 °C, and the solid which formed was collected by filtration. At room temperature this material decomposed with accompanying evolution of ammonia. Accordingly it was used immediately without further characterisation.

This solid was added in one portion to a solution of sodium nitromalondialdehyde (1.6 g, 14 mmol) in water (10 ml) at 0 °C. The mixture was heated at 50 °C for 10 min and held at 40 °C for a further 20 min. T.l.c. examination of the reaction mixture showed that no product formation had occurred. Diethyl 2-aminofumarate is reported[21] to be a stable distillable liquid b.p. 155-157 ° at 16 mmHg. Clearly, the material obtained above

was not diethyl 2-aminofumarate.

Dimethyl 2-aminofumarate was prepared by the method of Huisgen,[22] and was obtained as a liquid, b.p. 110-120° at 15 mmHg (lit. b.p. 70-80° at 0.001 mmHg)

$\nu_{max.}$ 3480, 3320, 1735, 1680, 1620, 1290, and 780 $cm.^{-1}$

$\delta(CDCl_3)$ 3.7 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 5.55 (1 H, s, C=CH), and 6.2-6.8 (2 H, b s, NH_2).

(a) A solution of dimethyl 2-aminofumarate (0.3 g, 1.9 mmol) and sodium nitromalondialdehyde (0.25 g, 2.2 mmol) in water (15 ml) was heated under reflux, and the reaction course monitored by t.l.c. After 30 h, no reaction had occurred.

(b) A solution of dimethyl 2-aminofumarate (1.3 g, 7.6 mmol) and sodium nitromalondialdehyde (1.0 g, 8.6 mmol) in ethanol (40 ml, 95%) was heated under reflux. After 96 h, a change in the t.l.c. staining characteristics of the spot corresponding to dimethyl 2-aminofumarate was observed. The reaction mixture was concentrated *in vacuo*, the residue dissolved in water (25 ml) and extracted with ethyl acetate. The organic phase was dried and the solvent removed under reduced pressure. Preparative t.l.c. (developing solvent 20% ethyl acetate - light petroleum) afforded two compounds of R_f 0.41 and 0.65. The minor, more polar compound was unidentifiable, but was not aromatic; the major, less polar compound was

identified as methyl ethyl 2-aminofumarate

$\nu_{max.}$ 3480, 3320, 1720, 1670, 1620, 1290, and 775 $cm.^{-1}$

$\delta(CDCl_3)$ 1.3 (3 H, t, J Hz, $CO_2CH_2C\underline{H}_3$), 3.7 (3 H, s, CO_2CH_3), 4.3 (2 H, q, J 7 Hz, $CO_2C\underline{H}_2CH_3$), 5.5 (1 H, s, C=CH), and 6.1-6.8 (2 H, b s, NH_2).

1,2-Dichloro-1,2-diethoxyethane

This was prepared by the method of Baganz and Domaschke[23] and was obtained as a colourless liquid, b.p. 85° at 30 mmHg (lit. b.p. 79-82° at 12 mmHg)

$\nu_{max.}$ 2980, 1475, 1370, 1100, 1020, 720, and 670 $cm.^{-1}$

$\delta(CDCl_3)$ 1.3 (3 H, t, J 6 Hz, $CO_2CH_2C\underline{H}_3$), 1.29 (3 H, t, J 6 Hz, $OCH_2C\underline{H}_3$), 3.6-4.0 (4 H, m, 2 x $OC\underline{H}_2CH_3$), 5.5 (1 H, s, C=CH), 5.6 (1 H, s, C=CH).

1,2-Diethoxyethene

This was prepared by the published procedure,[24] and was obtained as a liquid b.p. 62° at 30 mmHg (lit. b.p. 132-134° at 760 mmHg); this was a 1:1 mixture of the Z and E isomers

$\nu_{max.}$ 1380, 1180, and 1100 $cm.^{-1}$

$\delta(CCl_4)$ 1.2 (3 H, t, J 7 Hz, $OCH_2C\underline{H}_3$), 1.23 (3 H, t, J 7 Hz, $OCH_2C\underline{H}_3$), 3.7 (2 H, q, J 7 Hz,

$OC\underline{H}_2CH_3$), 3.75 (2 H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 5.1 (1 H, s, C=CH), and 5.6 (1 H, s, C=CH).

1,1,2,3,3-Pentaethoxypropane

This was prepared by the published procedure,[86] b.p. 120-130° at 25 mmHg (lit. b.p. 88-89° at 2 mmHg)

$\delta(CCl_4)$ 1.1 (3 H, t, J 7 Hz, $OCH_2C\underline{H}_3$), 1.12 (12 H, t, J 7 Hz, 4 x $OCH_2C\underline{H}_3$), 3.1-3.8 11 H, m, 5 x $OC\underline{H}_2CH_3$ and $C\underline{H}CH(OCH_2CH_3)_2$, 4.25 2 H, d, J 5 Hz, 2 x $CHC\underline{H}(OCH_2CH_3)_2$

(Found: C, 58.9; H, 10.5. $C_{13}H_{28}O_5$ requires C, 59.05; H, 10.7%).

Ethoxymalondialdehyde (26)

This was prepared by a modification of the published procedure.[25] 1,1,2,3,3-Pentaethoxypropane (48 g, 0.18 mol) was added to a solution of concentrated hydrochloric acid (150 ml) in water (375 ml). The mixture was stirred for 4 h at 40 °C and for a further 3 days at room temperature. The now homogenous solution was continuously extracted with ether for 24 h, and the organic phase dried and evaporated in vacuo. Distillation of the resulting brown oil afforded a pale yellow oil, b.p. 110-114° at 0.15 mmHg (lit. b.p. 104° at 13 mmHg), which was a mixture of ethoxy malondialdehyde and its hydrate

$\nu_{max.}$ 3200, 1680(shoulder), 1630, 1210, and 1030 cm^{-1}

$\delta(CDCL_3)$ 8.95 (1 H, s, CHO)

This was further characterised by its reaction[87] with aniline to give 1-anilino-2-ethoxy-3-anilinoprop-2-ene, m.p. 227-229° (from ethanol) (lit. m.p. 225°) (Found: C, 55.35; H, 4.90; N, 7.35. $C_{17}H_{17}ClN_2O_5$ requires C, 55.60; H, 5.20; N, 7.60%).

Attempted Preparation of Ethyl 2-Methyl-5-ethoxypyridine-3-carboxylate (30)

Attempted preparation of ethyl 3-aminobut-2-enoate (28) as described by Fanta,[20] furnished a white granular solid, m.p. 55° (with decomposition and evolution of ammonia). This material did not undergo cyclisation with either sodium nitromalondialdehyde or propynal. Furthermore, ethyl 3-aminobut-2-enoate is elsewhere[26] reported to be a stable distillable liquid.

Ethyl 3-aminobut-2-enoate was successfully prepared by an alternative published procedure,[26] and was obtained as an oil, b.p. 108-109° at 25 mmHg (lit. b.p. 91-93° at 9 mmHg)

$\nu_{max.}$ 3440, 3340, 1670, 1620, 1280, 1160, and 790 $cm.^{-1}$

A solution of ethoxymalondialdehyde (290 mg, 2.5 mmol) and ethyl 3-aminobut-2-enoate (320 mg, 2.5 mmol) were heated at 50 °C for 3 h in water (2.5 ml). T.l.c. examination indicated consumption of starting materials and the formation of three products. The reaction

mixture was acidified with dilute hydrochloric acid and extracted with ether (3 x 25 ml); the ethereal extracts were discarded. The aqueous layer was basified with dilute aqueous sodium hydroxide solution and extracted with ether (3 x 25 ml). The ethereal extracts were dried and concentrated in vacuo. The crude product could not be identified, but was shown by its n.m.r. spectrum not to be aromatic.

In subsequent attempts the same quantities of reactants were used and the reaction conditions systematically altered as follows: a solution of the reactants in dried ethanol (5 ml) was heated under reflux for 4 h; a solution of the reactants and sodium (58 mg, 2.5 mmol) in dried ethanol (5 ml) was heated under reflux for 4 h; a solution of the reactants in water (5 ml) was heated under reflux for 4 h; the neat reactants were heated at 120 °C for 10 min.

T.l.c. examination of the reaction mixtures in each case revealed four products in approximately equal proportions. These mixtures were considered too complex for this method to provide a viable route to ethyl 2-methyl-5-methoxypyridine-3-carboxylate.

Attempted Preparation of Methyl 2-Aminobut-2-enoate (27)

2-Oxobutanoic acid (10 g, 98 mmol) was treated with an excess of diazomethane in ether and set aside for 16 h. Filtration and evaporation of solvent under reduced pressure afforded the methyl ester (8.2 g, 79%) which was

used without further purification.

Gaseous ammonia, distilled from sodium, was passed slowly through neat methyl 2-oxobutanoate (8.2 g, 70 mmol) at room temperature. After 3 h the liquid had become very viscous. Distillation of this material at 2 mmHg afforded a deep red viscous high-boiling polymeric material as indicated by a large concentration of resonances in the region 0.9-2.6 in the n.m.r. spectrum.

Ethyl 2-Methylpyridine-3-carboxylate (31)

Propynal was prepared by the method of Sauer,[29] and was then used in the preparation[28] of ethyl 2-methylpyridine-3-carboxylate, which was obtained as a pale yellow oil, b.p. 117° at 25 mmHg (lit. b.p. 55-60° at 0.1 mmHg)

$\nu_{max.}$ 1710, 1585, 1570, 1440, 1295, 1275, 1250, 1140, 1080, and 750 $cm.^{-1}$

δ ($CDCl_3$) 1.4 (3 H, t, J 7 Hz, $CO_2CH_2\underline{CH_3}$), 2.83 (3 H, s, $ArCH_3$), 4.35 (2 H, q, J 7 Hz, $CO_2\underline{CH_2}CH_3$), 7.15 (1 H, d d, J 8 Hz and 4 Hz, ArH), 8.15 (1 H, d d, J 8 Hz, ArH), and 8.50 (1 H, d d, J 4 Hz and 2 Hz, ArH).

Attempted Rearrangement of Ethyl 2-Methylpyridine-3-carboxylate N-oxide (32)

The oxidation of ethyl 2-methylpyridine-3-carboxylate was carried out as described by Rimek,[27] and, without

further purification the N-oxide was heated under reflux in acetic anhydride.[27] Distillation of the crude reaction product afforded a pale yellow liquid, b.p. 120° at 0.05 mmHg, with i.r. spectral characteristics different from those of starting N-oxide

$\nu_{max.}$(N-oxide) 1720, 1575, 1430, 1360, 1260, 1080, 1040, 1000, 830, and 750

$\nu_{max.}$(product) 1360, 1280, 1240, 1140, 1080, and 750 $cm.^{-1}$

This material was heated under reflux in dilute hydrochloric acid (25 ml, 25%) for 3 h. The solution was concentrated *in vacuo*, dissolved in water (10 ml) and the pH adjusted to pH3-4 with dilute aqueous sodium hydroxide solution; ethyl 3-methyl-5-hydroxypyridine-3-carboxylic acid did not precipitate. The aqueous solution was evaporated to dryness under reduced pressure and treated with diazomethane in ether. The solid residue, insoluble in ether did not react with diazomethane. This reaction was not investigated further.

Dimethyl Pyridine-2,3-dicarboxylate (38)

This was prepared by the method of Engler,[33] and was obtained as a pale yellow solid, m.p. 54-55° (lit. m.p. 53-54°)

$\delta(CCl_4)$ 3.9 (3 H, s, CO_2CH_3), 3.94 (3 H, s, CO_2CH_3), 7.4 (1 H, d d, J 8 Hz and 4 Hz, ArH), 8.15 (1 H, d d, J 8 Hz and 2 Hz, ArH), 8.7 (1 H, d d, J 4 Hz and 2 Hz, ArH).

Dimethyl Pyridine-2,3-dicarboxylate N-oxide (39)[27,34]

Dimethyl pyridine-2,3-dicarboxylate (1.8 g, 90 mmol) was dissolved in glacial acetic acid (4.5 ml), aqueous hydrogen peroxide solution (1.0 ml, 30%) was added and the solution heated at 80 °C for 8 h. At 2.5 h intervals two further portions of aqueous hydrogen peroxide solution (1.0 ml, 30%) were added. Volatiles were removed under reduced pressure to furnish dimethyl pyridine-2,3-dicarboxylate N-oxide (39) as a white solid (600 mg, 32%), m.p. 139-142° (from ethyl acetate) (lit. m.p. 141-142°) (Found: M^+, 211. $C_9H_9NO_5$ requires M, 211).

Attempted Rearrangement of Dimethyl Pyridine-2,3-dicarboxylate N-oxide (39)

(a) A solution of the N-oxide (39) (100 mg, 0.5 mmol) in acetic anhydride (10 ml) was heated to 90 °C with stirring for 4 h. T.l.c. examination showed that no reaction had occurred.

(b) A solution of the N-oxide (39) (100 mg, 0.5 mmol) and anhydrous sodium acetate (1.0 g. 12 mmol) in acetic anhydride was heated under reflux for 16 h. T.l.c. examination showed extensive decomposition.

(c) A solution of the N-oxide (39) (100 mg, 0.5 mmol) in acetic anhydride (1.5 ml) and acetic acid (1.0 ml) was heated under reflux for 16 h. T.l.c. examination again showed extensive decomposition.

2-Amino-3-methyl-5-nitropyridine (44)[36]

2-Amino-3-methylpyridine (2 g, 19 mmol) was dissolved, with stirring and cooling, in concentrated sulphuric acid (11 ml). To this was added concentrated nitric acid (1.3 ml) dropwise, over 15 min with stirring at 0 °C. Stirring was continued for a further 2 h, when the solution was poured on to ice water (20 ml). The resulting solution was basified with solid sodium carbonate and the precipitated solid collected by filtration and dried to give 2-amino-3-methyl-5-nitropyridine (2.2 g, 67%) as an amorphous powder, m.p. 255-257° (sealed tube) (lit. m.p. 255°)

$\nu_{max.}^{Nujol}$ 3450, 1650, 1460, 1340, and 1290 cm^{-1}

$\delta(d_6$ DMSO) 2.15 (3 H, s, $ArCH_3$), 7.3 (2 H, b s, $ArNH_2$), 8.0 (1 H, d, J 3 Hz, ArH), and 8.85 (1 H, d, J 3 Hz, ArH)

(Found: M^+, 153. $C_6H_7N_3O_2$ requires M, 153).

2-Bromo-3-methyl-5-nitropyridine

A solution of 2-amino-3-methyl-5-nitropyridine (1.0 g, 7 mmol) in aqueous hydrobromic acid (4.5 ml, 48%) was cooled to 0 °C, and concentrated sulphuric acid (1.5 ml) added dropwise. Bromine (1.2 ml, 3.84 g, 24 mmol) was then added dropwise, and the resulting orange slurry cooled to -10 °C in an ice/salt bath. A solution of sodium nitrite (3.5 g in 5 ml of H_2O) was added dropwise at such a rate as to avoid production of brown fumes. The mixture was then heated at 40 °C for 1 h,

when the evolution of gas had ceased. The solution was cooled to room temperature and 50% aqueous sodium hydroxide solution was added slowly until the colour of excess bromine had disappeared. An oily precipitate formed, which was extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were dried and the solvent removed under reduced pressure. Chromatography on alumina (Woelm, grade III basic) afforded 2-bromo-3-methyl-5-nitropyridine as a pale yellow solid, (110 mg, 7%), m.p. 54-56°

$\nu_{max.}^{Nujol}$ 1590, 1560, 1340, 1305, 1055, 800, and 795 $cm.^{-1}$

$\delta(CDCl_3)$ 2.55 (3 H, s, $ArCH_3$), and 8.35 and 9.1 (2 H, ABq, J_{AB} 3 Hz)

(Found: M^+, 216 and 218. $C_6H_5BrN_2O_2$ requires M, 216 and 218).

All attempts to repeat this preparation failed.

1-Chloro-3-acetoxypropan-2-ol

This was prepared by the method of Knoevenagel,[41] and was obtained as an oil, b.p. 110° at 10 mmHg (lit. b.p. 120-121° at 14 mmHg).

1-Chloro-3-acetoxypropanone (53)

A solution of 1-chloro-3-acetoxypropan-2-ol (13.5 g, 0.089 mol) in acetone (AnalaR, 200 ml) was treated at room temperature with Jones reagent (22.3 ml, 8N, 0.178 mol) and stirred for 16 h. Water (100 ml) was added and the aqueous solution extracted with ethyl acetate (2 x 100 ml). The combined extracts were washed with water (50 ml), brine (2 x 50 ml), dried, and the solvent removed under reduced pressure. Distillation afforded a colourless oil (1.2 g, 9%), b.p. 102-109° at 10 mmHg (lit.[42] b.p. 100-103° at 10 mmHg)

$\delta(CCl_4)$ 2.13 (3 H, s, $OCHCH_3$), 4.15 (2 H, s, CH_2Cl), and 4.85 (2 H, s, CH_2OCHCH_3).

An alternative published one-step route[42] from 1,3-dichloropropanone was subsequently adopted for this preparation.

Attempted Condensation of 1-Chloro-3-acetoxypropanone (53) with the 1,3-Dithiane Anion

A solution of 1,3-dithiane (0.48 g, 4 mmol) in tetrahydrofuran (15 ml) was cooled to -78 °C in an atmosphere of nitrogen and n-butyl lithium (1.9 ml, 2.2M in

hexane, 4.2 mmol) was added dropwise over 3 min. The solution was warmed to 40 °C and stirred for 3 h. The reaction mixture was again cooled to -78 °C and a solution of 1-chloro-3-acetoxypropanone (0.6 g, 4 mmol) in tetrahydrofuran (5 ml) was added dropwise over 10 min. The course of the reaction was monitored by t.l.c. After 4 h no reaction was observed. This reaction was not investigated further.

1-Iodo-3-acetoxypropanone (54)

This was prepared from 1-chloro-3-acetoxypropanone by the published procedure,[42] and was obtained as an oil, which was used without further purification

$\delta(CDCl_3)$ 2.15 (3 H, s, $OCHCH_3$), 3.9 (2 H, s, CH_2I), and 4.85 (2 H, s, CH_2OCOCH_3)

(Found: M^+, 242. $C_5H_7IO_3$ requires M, 242).

Attempted Condensation of 1-Iodo-3-acetoxypropanone with the 1,3-Dithiane Anion

A solution of 1,3-dithiane (0.48 g, 4 mmol) in tetrahydrofuran (15 ml) was cooled to -78 °C in an atmosphere of nitrogen and n-butyl lithium (1.9 ml, 2.2M in hexane, 4.2 mmol) was added dropwise over 3 min. The solution was warmed to -40 °C and stirred for 3 h. The reaction mixture was again cooled to -78 °C and a solution of 1-iodo-3-acetoxypropanone (0.96 g, 4 mmol) in tetrahydrofuran (5 ml) was added dropwise over 10 min.

The solution was maintained at -78 °C for 2 h and at -10 °C for 16 h. The reaction mixture was poured on to saturated aqueous ammonium chloride solution (10 ml) and extracted with ether. The ethereal extracts were dried and the solvent removed under reduced pressure to afford a dark brown oil. T.l.c. examination showed the presence of three components. Preparative t.l.c. (developing solvent 10% ethyl acetate-hexane) afforded three compounds; the two more polar materials were not identified; the least polar, and major isolated, material was identified as 1,3-dithiane. 1-Iodo-3-acetoxypropanone could not be detected in the reaction mixture.

1-Bromo-3-acetoxypropan-2-ol (57)

To a solution of anhydrous iron(III) chloride (0.5 g) in glacial acetic acid (7.1 ml) at 0 °C was added dropwise 1,2-epoxy-3-bromopropane (9.23 ml, 13.7 g, 0.1 mol). The reaction mixture was stirred at room temperature for 16 h. Anhydrous sodium acetate (0.75 g) was added and volatiles were removed under reduced pressure with final benzene azeotroping. The residue was taken up in ether (100 ml), extracted with saturated aqueous sodium carbonate (50 ml) and the organic layer dried over anhydrous sodium acetate. The solvent was removed under reduced pressure to give a yellow oil, which on distillation furnished 1-bromo-3-acetoxypropan-2-ol (7.2 g, 35%) b.p. 120-125° at 20 mmHg (lit. b.p. 100-110° at 2.5 mmHg)

$\delta(CDCl_3)$ 2.1 (3 H, s, $OCOCH_3$) and 3.2-4.2 (6 H, m).

Attempted Preparation of 1-Bromo-3-acetoxypropanone (55)

To a solution of 1-bromo-3-acetoxypropan-2-ol (15 g, 72 mmol) in acetone (AnalaR, 100 ml) was added an excess of Jones reagent (8N) and the solution stirred for 24 h at room temperature. Water (100 ml) was added and the solution extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with water (2 x 50 ml), brine (2 x 50 ml), dried, and the solvent removed under reduced pressure to afford a yellow oil. T.l.c. examination of the crude product showed three products inseparable by chromatography. Distillation of the crude product gave a major fraction, b.p. 80-85° at 2 mmHg, which contained only a small proportion of 1-bromo-3-acetoxypropanone, as indicated by n.m.r.

2,2-Dimethyl-4-bromomethyl-1,3-dioxolane (59)

2,2-Dimethyl-4-hydroxymethyl-1,3-dioxolane (64) was prepared by the published procedure,[45] and was obtained as a colourless liquid, b.p. 95-98° at 25 mmHg (lit. b.p. 86.5° at 13 mmHg).

This was converted[46] to the corresponding tosylate and thence[47] to the bromomethyl 1,3-dioxolane (59) which was obtained as a pale yellow oil, b.p. 58-60° at 10 mmHg (lit. b.p. 45° at 4 mmHg)

$\delta(CCl_4)$ 1.23 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 3.2 (2 H, m, CH_2CH_2Br), and 3.6-4.2 (3 H, m, CH_2O, CHO)

(Found: M^+, 194 and 196. $C_6H_{11}O_2Br$ requires M, 194, 196)

Attempted Condensation of 2,2-Dimethyl-4-bromomethyl-1,3-dioxolane and the 1,3-Dithiane Anion

(a) A solution of 1,3-dithiane (0.48 g, 4 mmol) in tetrahydrofuran (15 ml) was cooled to -78 °C in an atmosphere of dry nitrogen and n-butyl lithium (1.9 ml, 2.2M in hexane, 4.2 mmol) was added dropwise over 3 min. The solution was warmed to -40 °C and stirred for 2 h. The reaction mixture was again cooled to -78 °C and a solution of 2,2-dimethyl-4-bromomethyl-1,3-dioxolane (0.78 g, 4 mmol) in tetrahydrofuran (5 ml) was added dropwise. The course of the reaction was monitored by t.l.c. After 3 h at -78 °C, t.l.c. examination showed that no reaction had occurred. The reaction was allowed to warm to -10 °C and kept at this temperature for 20 h. T.l.c. examination again showed that no reaction had occurred.

(b) An identical procedure to (a) above was followed with the exception that after addition of the bromide the reaction mixture was maintained at -78 °C for 15 h and allowed to warm slowly to room temperature and left to stand for 2 days. T.l.c. examination showed that no reaction had occurred. The reaction mixture was poured on to saturated aqueous ammonium chloride solution (5 ml) and extracted with ether. The ethereal extracts were dried and concentrated *in vacuo*. Preparative t.l.c. (developing solvent 30% ethyl acetate-hexane) afforded as major product 1,3-dithiane (0.46 g, 96% recovery).

Attempted Preparation of Diethyl 2,4-Dihydroxyglutarate (70)

Diethyl 2,4-dibromoglutarate was prepared by the method of Ingold,[49] with the exception that the bromination was carried out using 2 x 60 watt tungsten light bulbs rather than an arc lamp. Diethyl 2,4-dibromoglutarate was obtained as a yellow liquid, b.p. 195-200° at 2 mmHg (lit. b.p. 174-175° at 21 mmHg)

$\delta(CCl_4)$ 1.3 (6 H, t, J 7 Hz, 2 x $CO_2CH_2C\underline{H}_3$), 2.6 (2 H, t, J 7 Hz, $CHC\underline{H}_2CH$), 4.3 (6 H, m, 2 x $CO_2C\underline{H}_2CH_3$ and $C\underline{H}CH_2C\underline{H}$)

(a) A solution of diethyl 2,4-dibromoglutarate (0.5 g, 1.5 mmol) in aqueous buffer solution (50 ml, pH 9) and acetone (30 ml) was stirred at room temperature for 2.5 days. T.l.c. examination showed that no reaction had occurred.

(b) A solution of dimethyl 2,4-dibromoglutarate (0.5 g, 1.5 mmol) in aqueous buffer solution (50 ml, pH 9) and acetone (30 ml) was heated under reflux for 30 min. T.l.c. examination showed that starting material had been consumed and a more polar unidentified material produced.

N-(Diethoxyacetyl)piperidine

This amide was prepared by the literature method,[53] and was obtained as a colourless oil, b.p. 92° at 0.2 mmHg

(lit. b.p. 87-90° at 0.12-0.15 mmHg).

$\delta(CDCl_3)$ 1.12 (6 H, t, J 6 Hz, 2 x $OCH_2\underline{CH_3}$) 1.55 (6 H, m, $-(CH_2)_3-$), 3.60 (8 H, m, 2 x $OC\underline{H_2}CH_3$ and CH_2NCH_2), and 4.95 (1 H, s, CH)

1,1-Diethoxypent-4-en-2-one (75)

This was prepared by an extension of a published procedure.[88] To a stirred solution of allyl magnesium chloride[89] [from magnesium (2.43 g, 0.1 mol) and allyl chloride (7.65 g, 0.1 mol)] in ether (100 ml) was added the above piperidide (11 g, 0.05 mol), dropwise over 30 min at 0 °C in an atmosphere of nitrogen. The solution was heated under reflux with stirring under nitrogen for 20 h. The reaction mixture was cooled to 0 °C and poured on to ice-cold saturated aqueous ammonium chloride solution (100 ml). The aqueous solution was extracted with ether (3 x 150 ml), the ethereal extracts dried over anhydrous sodium sulphate and the solvent removed under reduced pressure. Distillation afforded the ketone (75) as a colourless liquid (6.6 g, 76%), b.p. 45-46° at 1 mmHg.

$\delta(CDCl_3)$ 1.23 (6 H, t, J 7 Hz, 2 x $OCH_2\underline{CH_3}$), 3.5 (6 H, m, 2 x $OC\underline{H_2}CH_3$ and $COC\underline{H_2}$), 4.6 [1 H, s, $C\underline{H}(OCH_2CH_3)$], 5.1 (2 H, m, $C=CH_2$), and 5.9 (1 H, m, $\underline{H}C=CH_2$).

In a second run, distillation resulted in the formation of mixtures of 1,1-diethoxypent-4-en-2-one and

1,1-diethoxypent-3-en-2-one, as evidenced by the appearance of a resonance at 1.73 (3 H, d, J 5 Hz, C=CHC$\underline{H}_3$) and additional changes in the n.m.r. spectrum. These isomers were inseparable by chromatography and distillation. Accordingly, in subsequent preparations, the crude reaction product was carried on to the next stage without purification.

1,1-Diethoxypent-4-en-2-ol (76)

A solution of crude 1,1-diethoxypent-4-en-2-one (75) (42 g, 0.24 mol) in ethanol (100 ml, 95%) was added dropwise to a stirred solution of soldium borohydride (80 g, 2 mol) in water (300 ml). After 3 h at 0 °C the reaction mixture was poured on to water (300 ml) and extracted with ether (3 x 200 ml). The combined ethereal extracts were dried and concentrated under reduced pressure. Distillation afforded the alcohol (76) as a colourless liquid (18.7 g, 54% based on piperidide), b.p. 105-109° at 25 mmHg

$\delta(CDCl_3)$ 1.2 (6 H, t, J 7 Hz, 2 x $OCH_2C\underline{H}_3$), 2.3 (1 H, b s, exchanges with D_2O, OH), 3.6 (7 H, m, 2 x $OC\underline{H}_2CH_3$, CH_2CO, and $C\underline{H}OH$), 4.3 [1 H, d, J 2 Hz, $CH(OCH_2CH_3)_2$], 5.1 (2 H, m, $C=CH_2$), and (1 H, m, $\underline{H}C=CH_2$)

(Found: C, 62.2, H, 10.2. $C_9H_{18}O_3$ requires C, 62.05, H, 10.4%).

1,1-Diethoxy-2-benzyloxypent-4-ene (93)

To a solution of sodium hydride (3.6 g, 100%, 0.15 mol) in tetrahydrofuran (100 ml) in an atmosphere of nitrogen was added 1,1-diethoxypent-4-en-2-ol (76) (25 g, 0.14 mol), dropwise with stirring over 30 min at room temperature. The reaction mixture was stirred under reflux for 2 h, then cooled to 0 °C when benzyl bromide (25.7 g, 0.15 mol) was added dropwise with stirring over 30 min. The reaction mixture was heated under reflux for 3 h, cooled, and allowed to stand for 14 h. Ethanol was added dropwise to quench excess sodium hydride, and the solution poured on to water (150 ml). The aqueous solution was extracted with ether (3 x 300 ml), the combined ethereal extracts were washed with brine (2 x 100 ml), dried, and the solvent was removed under reduced pressure. Distillation of the residue afforded the benzyl ether (93) as a colourless liquid (30 g, 81%), b.p. 155-160° at 30 mmHg

$\nu_{max.}$ 1440, 1360, 1060, 905, 725, and 690 $cm.^{-1}$

$\delta(CDCl_3)$ 1.23 (6 H, t, J 8 Hz, 2 x $OCH_2\underline{CH}_3$), 2.4 (2 H, m, $\underline{CH}_2CH=CH_2$), 3.6 (5 H, m, 2 x $O\underline{CH}_2CH_3$ and $C\underline{H}OCH_2Ph$), 4.4 1 H, d, J 6 Hz, $C\underline{H}(OCH_2CH_3)_2$, 4.7 (2 H, s, OCH_2Ph), 4.9-5.3 (2 H, m, $C=CH_2$), 5.6-6.2 (1 H, m, $\underline{H}C=CH_2$), and 7.3 (5 H, m, Ph)

(Found: C, 72.75, H, 9.05. $C_{16}H_{24}O_3$ requires C, 72.70, H, 9.15%).

2-Benzyloxypent-4-en-1-al (72)

A solution of 1,1-diethoxy-2-benzyloxypent-4-ene (93) (15 g, 60 mmol) and p-toluenesulphonic acid (1 g) in acetone (AnalaR, 1.5 l) was heated under reflux for 24 h in an atmosphere of nitrogen. The solution was cooled and saturated aqueous sodium hydrogen carbonate solution (1 ml) was added. The solution was concentrated in vacuo, the residue taken up in ether (150 ml), dried, filtered and evaporated under reduced pressure to give a pale yellow oil. Column chromatography (eluting solvent ethyl acetate-hexane) on alumina (Woelm, grade IV basic) afforded the aldehyde (72) as a colourless liquid (7.3 g, 64%)

$\nu_{max.}$ 2705, 1740, 1045, 1455, 1060, 915, 740, and 700 $cm.^{-1}$.

$\delta(CDCl_3)$ 2.5 (2 H, m, $C\underline{H}_2CH=CH_2$), 3.84 (1 H, d t, J 6 Hz and 2 Hz, $C\underline{H}OCH_2Ph$), 4.64 (2 H, s, $C\underline{H}_2Ph$), 5.1 (2 H, m, $CH=C\underline{H}_2$), 5.9 (1 H, m, $C\underline{H}=CH_2$), and 7.4 (5 H, s, Ph).

(Found: m/e, 161. $C_{11}H_{13}O$ (M-CHO) requires 161).

Attempted Preparation of N-Benzylaminomethyl Diethyl Phosphonate (79)

1,3,5-Tribenzylhexahydro-s-triazine was prepared by a minor modification of the published procedure. Benzyl amine (40 g, 0.37 mol) was added to a vigorously stirred aqueous solution of formaldehyde (36 g, 40%, 0.36 mol) at

-5 °C. The reaction mixture was stirred at -5 °C for 2 h when a syrupy liquid had separated. This was extracted with ether (3 x 150 ml), and the combined ethereal extracts were dried over barium oxide for 48 h, filtered, evaporated under reduced pressure, and the residue distilled to afford a colourless viscous oil, b.p. 220-245° at 760 mmHg. This crystallised from ethanol at -10 °C to give 1,3,5-tribenzylhexahydro-s-triazine (21 g, 16%) as a white solid, m.p. 50° (lit.[91] m.p. 43°)

$\delta(CDCl_3)$ 3.4 (6 H, s, NCH_2N), 3.6 (6 H, s, $NC\underline{H}_2Ph$), and 7.19 (15 H, s, Ph).

A mixture of 1,3,5-tribenzylhexahydro-s-triazine (20 g, 0.056 mol) and diethyl phosphite (23.1 g, 0.166 mol) was heated for 2 h at 95 °C and left at room temperature for 15 h. Two methods of isolation of the product were investigated.

(a) The reaction mixture was taken up in ether and dry hydrogen chloride was passed through the solution until saturation. After 3 days at 4 °C, a gummy solid formed in the sealed flask. The supernatant liquid was decanted and the solid material transferred to a vacuum desiccator. After a further 3 days the material was still not crystalline. Attempts to hydrogenolyse this material, in 95% ethanol (250 ml) in the presence of 10% Pd/C catalyst (1 g), to give aminomethyl diethyl phosphonate (80) were unsuccessful.

(b) Distillation of the crude reaction mixture at

2 mmHg afforded only starting materials.

N-Bromomethyl Phthalimide

This was prepared from N-hydroxymethyl phthalimide (81) by the published procedure[56] and was obtained as a white crystalline solid, m.p. 148-149° (lit. m.p. 149-150°).

Aminomethyl Diethyl Phosphonate (80)

This was prepared by the method of Regitz,[57] and was obtained as a labile yellow oil which was used without purification

$\delta(CDCl_3)$ 1.36 (6 H, t, J 7 Hz, 2 x $OCH_2\underline{CH_3}$), 2.3 (2 H, b s, exchanges with D_2O, NH_2), 3.0 (2 H, d, J_{H-P} 11 Hz, $\underline{CH_2}NH_2$), and 4.3 (4 H, d q, J_{H-H} 7 Hz, J_{H-P} 8Hz, 2 x $O\underline{CH_2}CH_3$).

Benzyl Diethylphosphonato Amino Acetate (48)[54]

A solution of benzaldehyde (14.5 g, 0.14 mol) in benzene (200 ml) was added to a solution of aminomethyl diethyl phosphonate (23 g, 0.14 mol) in benzene (200 ml) with stirring at 0 °C. The reaction mixture was stirred for a further 1 h at 0 °C. The solution was concentrated in vacuo with final benzene azeotroping to remove water produced in the reaction and the residue distilled to give the benzaldehyde imine of aminomethyl diethyl

phosphonate as a pale yellow oil (14.5 g, 40%), b.p. 159-160° at 1 mmHg

$\delta(CDCl_3)$ 1.35 (6 H, t, J 7 Hz, 2 x $OCH_2\underline{CH}_3$), 3.9-4.4 6 H, m, 2 x $OC\underline{H}_2CH_3$ and $C\underline{H}_2PO(OEt)_2$, and 7.2-8.4 (6 H, m, Ph and N=C<u>H</u>).

This imine was acylated by a modification of the published procedure.[54] To a solution of isopropylcyclohexylamine (12.7 g, 90 mmol) in tetrahydrofuran (150 ml) at room temperature in an atmosphere of dry nitrogen was added n-butyl lithium (35 ml, 2.2M in hexane, 64 mmol). The solution was cooled to -78 °C and a solution of the benzaldehyde imine (8 g, 32 mmol) in tetrahydrofuran (10 ml) was added dropwise. The solution was stirred for 40 min, when a solution of benzyl chloroformate (13.0 g, 90 mmol) in tetrahydrofuran (10 ml) was added dropwise. The reaction mixture was stirred for a further 2 h at -78 °C, then allowed to warm slowly to room temperature and poured on to saturated aqueous ammonium chloride solution (100 ml). The aqueous solution was extracted with ether (2 x 200 ml) and the combined ethereal extracts washed with brine (50 ml), dried and concentrated under reduced pressure. Column chromatography (eluting solvent ethyl acetate - hexane) of the residue on alumina (Woelm, Grade V basic) afforded <u>the acylated amine</u> as a yellow oil (11.4 g, 30%)

$\nu_{max.}$ 1730, 1700, 1635, 1440, 1370, 1250, 1140, 1020, 960, 740, and 685 $cm.^{-1}$

$\delta(CDCl_3)$ 4.75 (1 H, d, J_{H-P} 20 Hz, C<u>H</u>PO), 5.3 (2 H, s, CH_2Ph), 7.1-7.9 (10 H, m, 2 x Ph), and

8.4 (1 H, d, J 5 Hz, CH=N).

To a solution of the acylated imine (350 mg, 0.9 mmol) in ether (50 ml) was added p-toluenesulphonic acid (350 mg, 1.8 mmol) and the mixture stirred at room temperature for 3 h, after which time a yellow oil had separated. The supernatant solution was decanted and the oil triturated with ether (2 x 15 ml). The residual oil was dissolved in saturated aqueous dipotassium hydrogen orthophosphate solution (10 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were dried, and concentrated in vacuo below 30 °C to give the amine (48) as a yellow oil (166 mg, 60%), which, due to its lability, was used immediately without further purification

$\delta(CDCl_3)$ 1.35 (6 H, t, J 7 Hz, 2 x OCH_2CH_3), 2.3 (2 H, b s, exchanges with D_2O, NH_2), 3.0 (2 H, d, J_{H-P} 10 Hz, CH_2PO), and 4.19 (4 H, m, 2 x OCH_2CH_3).

Preparation of the Key Imine (82)

Benzyl diethylphosphonato amino acetate (48) (500 mg, 1.6 mmol) and 2-benzyloxypent-4-en-1-al (72) (305 mg, 1.6 mmol) were mixed neat at room temperature, then cooled to 0 °C. After 1 h, the mixture was taken up in ether (50 ml) and dried with anhydrous magnesium sulphate to remove the water visibly produced in the reaction. Evaporation of the solvent at 30 °C under reduced pressure afforded the imine (82) (715 mg, 98%) as a yellow oil, which did

$\delta(CDCl_3)$ 1.12 (6 H, t, J 7 Hz, 2 x $OCH_2\underline{CH}_3$), 2.5 (2 H, b t, J 6 Hz, $\underline{CH}_2CH=CH_2$), 3.9-5.1 (8 H, m, 2 x $O\underline{CH}_2CH_3$, $CH=C\underline{H}_2$, $OC\underline{H}$, $C\underline{H}PO$), 5.3 (4 H, s, $PhC\underline{H}_2$), 7.38 (10 H, m, 2 x Ph), and 7.75 (1 H, d, J 6 Hz, N=CH).

Azidoacetic Acid[58]

This was prepared by the published procedure and was obtained as a colourless oil which due to its instability was used without purification.

Azidoacetyl Chloride[59]

This was prepared by the literature method,[59] and was obtained as a mobile colourless oil, b.p. 62-63° at 25 mmHg (lit. b.p. 55-60° at 18 mmHg)

$\nu_{max.}$ 2100, 1800, 1740, 1410, 1270, 1200, 900, 90 905, and 760 $cm.^{-1}$

Attempted β-Lactam Formation

(a) With azidoacetyl chloride/triethylamine - (i) To a solution of azidoacetyl chloride (25 mg, 0.2 mmol) and triethylamine (20 mg, 0.2 mmol) in ether (3 ml) was added a solution of the imine (82) (47 mg, 0.1 mmol) in ether (2 ml) with stirring under nitrogen at -78 °C. The reaction mixture was stirred at -78 °C for 30 min,

allowed to warm to room temperature and set aside for 16 h. The reaction mixture was partitioned between ether (50 ml) and water (10 ml) and the ethereal layer washed with brine, dried, and concentrated *in vacuo*. T.l.c. examination showed the presence of 2-benzyloxypent-4-en-1-al (72), amine (48), and a new product R_f 0.54 which was isolated by preparative t.l.c. (developing solvent 70% ethyl acetate - hexane) as a pale yellow oil (24 mg, 58%) which crystallised from ether as white needles, m.p. 91-92° This material was identified as the azidoacetamide (85).

This structural assignment was confirmed by preparation of the amide (85) by an alternative route. To a solution of azidoacetic acid (0.55 g, 8.0 mmol) in methylene chloride (5 ml), was added a solution of diethyl chlorophosphite[60] (1.25 g, 8.0 mmol) and triethylamine (0.8 g, 8.0 mmol) in methylene chloride (10 ml), dropwise over 15 min with stirring under nitrogen at room temperature. The reaction mixture was stirred for 30 min, when a solution of the amine (48) (1.8 g, 6.0 mmol) in methylene chloride (5 ml) was added. Stirring was continued for a further 4 h, then the methylene chloride solution was washed successively with dilute hydrochloric acid (2 x 5 ml), saturated aqueous sodium hydrogen carbonate solution (5 ml), brine (5 ml) and dried. Evaporation of solvent *in vacuo* afforded a yellow oil which crystallised from chloroform/hexane to give the amide (85) (1.63 g, 67%) m.p. 91-92°, identical to the material isolated above

$\nu_{max.}^{Nujol}$ 3220, 2100, 1740, 1685, 1450, 1370, and 1020 $cm.^{-1}$

$\delta(CDCl_3)$ 1.23 (3 H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.25 (3 H,

A	B	SOLVENT	MODE OF ADDITIONS	REACTION CONDITIONS & ADDITIVES	RESULT
1.5	1.5	CH_2Cl_2	(82)+A+ after 1 h B	Additions at R.T. in presence of Linde 4A mol. sieves and 1 equiv. silver acetate	2,3
1.5	1.5	CH_2Cl_2	(82)+A+ after 1 h B	Additions at R.T. in presence of Linde 4A mol. sieves and 1 equiv. silver heptafluoroborate	2,3
1.5	1.5	CH_2Cl_2	(82)+A+ after 1 h B	Additions at R.T. in presence of Linde 4A mol. sieves and 0.5 equiv. anhydrous lithium iodide	2,3
2	2	Et_2O	A+B sol$^{n.}$ filtered and added to (82)	Additions at -78 °C; 4 h -78 °C; 16 h R.T.	2,3

TABLE I - NOTES

A Azidoacetyl chloride (equivalents).

B Triethylamine (equivalents).

1 Acylated amine (85) isolated by preparative t.l.c.

2 T.l.c. examination showed only product to be acylated amine (85).

3 I.r. spectrum of crude reaction mixture showed no β-lactam carbonyl stretching frequency.

4 Unreacted aldehyde (72) detected by t.l.c.

TABLE I

1 equivalent of the imine (82) was treated with azidoacetyl chloride and triethylamine under the conditions described below. The crude reaction mixtures were partitioned between ether and water and the ethereal layer washed with brine, dried, and evaporated under reduced pressure.

A	B	SOLVENT	MODE OF ADDITION	REACTION CONDITIONS & ADDITIVES	RESULT
1	1	Et_2O	A+B+(82)	Additions at -78 °C; 2 h -78 °C; 16 h R.T.	1
1	1	Et_2O	A+B+(82)	Additions at -78 °C; 16 h R.T; Linde 4A mol. sieves	4
1	1	Et_2O	(82)+A+B	Additions at -78 °C; 16 h R.T; Linde 4A mol. sieves.	4
2	2	Et_2O	(82)+A+ after 30 min B	Additions at R.T; 1 h R.T.	1
1	1	CH_2Cl_2	(82)+A+ over 1 h B	Additions at 0 °C; 0.5 h 0 °C	2
1	1	Et_2O	A+B+(82)	Additions at 0 °C; 16 h R.T.	2,3
1	1	Et_2O	(82)+A+B	Additions at 0 °C; 16 h R.T.	2,3
1	2	CH_2Cl_2	(82)+A+ after 1 h B	Additions at R.T; 2 h R.T.	2,3

t, J 7 Hz, $OCH_2\underline{CH}_3$), 4.10 (2 H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 4.12 (4 H, q, J 7 Hz, $OC\underline{H}_2CH_3$), 4.02 (2 H, s, N_3CH_2), 5.2 (2 H, s, $PhC\underline{H}_2$), 5.2 [1 H, d, J 21 Hz, $C\underline{H}PO(OEt)_2$], and 7.4 (5 H, s, ArH)

(Found: C, 46.60; H, 5.55; N, 14.2. $C_{15}H_{21}N_4O_6P$ requires C, 46.90; H, 5.50; N,14.6%).

(ii) The reaction conditions and order of addition of the reagents were varied as summarised in Table I.

(iii) To test the conditions used for attempted β-lactam formation, the imine[90] from benzaldehyde and aniline was employed.

To a solution of benzalaniline (0.6 g, 3.3 mmol) and azidoacetyl chloride (0.4 g, 3.3 mmol) in methylene chloride at 0 °C was added triethylamine (0.3 g, 3.3 mmol) in methylene chloride (50 ml) dropwise over 15 min. After stirring at 0 °C for 0.5 h the reaction mixture was partitioned between ether (50 ml) and water (10 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution (10 ml), brine (10 ml) and dried. Evaporation of the solvent under reduced pressure afforded a dark brown oil from which two compounds were isolated by preparative t.l.c. (developing solvent 20% ethyl acetate - hexane). The more polar, minor material, obtained as an oil, was identified from its n.m.r. spectrum as aniline azidoacetate

$\delta(CDCl_3)$ 4.0 (2 H, s, N_3CH_2), 7.0-7.6 (5 H, m, ArH), and 8.1 (1 H, b s, CONH)

The less polar, major fraction was trans-1,2-diphenyl-

azetidinone, obtained as an oil (125 mg, 17%)

$\nu_{max.}$ 2200, 1760, and 1610 $cm.^{-1}$

$\delta(CDCl_3)$ 4.5 (1 H, d, J 2 Hz, PhC<u>H</u>), 4.8 (1 H, d, J 2 Hz, $N_3C\underline{H}$), 7.2 (5 H, s, ArH), and 7.4 (5 H, s, ArH).

(b) <u>With dichloroacetyl chloride/triethylamine</u>. - To a solution of the imine (82) (380 mg, 0.8 mmol) and triethylamine (100 mg, 1 mmol) in ether (5 ml) was added dichloroacetyl chloride (120 mg, 0.8 mmol) in ether (5 ml) dropwise with stirring at 0 °C in an atmosphere of nitrogen. The reaction mixture was stirred at 0 °C for 15 min and for 16 h at room temperature, when it was partitioned between ether (50 ml) and water (10 ml). The ethereal solution was washed with brine, dried, and concentrated <u>in vacuo</u>. T.l.c. examination showed that no reaction had occurred and that the major component in the mixture was 2-benzyloxypent-4-en-1-al (72).

(c) <u>With azidoacetic acid/diethyl chlorophosphite</u>.[61] - A solution of azidoacetic acid (55 mg, 0.8 mmol) and diethyl chlorophosphite[60] (125 mg, 0.8 mmol) in methylene chloride (15 ml) was stirred at room temperature in an atmosphere of nitrogen for 20 min. To this was added over 1 h a solution of the imine (82) (380 mg, 0.8 mmol) and triethylamine (161 mg, 1.6 mmol) in benzene (10 ml). After stirring for 16 h the reaction mixture was washed with water (10 ml), dried, and concentrated under reduced pressure. T.l.c. examination showed that the sole

product was the amide (85).

Attempted Reduction of the Imine (82)[62]

A solution of the imine (82) (390 mg, 0.81 mmol), triethylsilane (100 mg, 0.82 mmol) and a catalytic amount of palladium(II) chloride in benzene was stirred for 3 h at room temperature, after which time a black precipitate had formed. To this stirred solution was added, in one portion, a solution of acetyl chloride (0.09 ml, 70 mg, 0.82 mmol) in benzene (5 ml) and the solution stirred for a further 3 h at room temperature. The reaction mixture was suction-filtered through a pad of Celite and the filtrate concentrated under reduced pressure. T.l.c. examination of the crude product showed that extensive decomposition had occurred.

Attempted Oxymercuration of 1,1-Diethoxy-2-benzyloxypent-4-ene (93)

To a solution of mercury(II) acetate (1.3 g, 4 mmol) in aqueous tetrahydrofuran (50%, 40 ml) was added 1,1-diethoxy-2-benzyloxypent-4-ene (1 g, 3.7 mmol) with stirring at room temperature. Stirring was continued for 1 h after which the yellow colouration had been discharged. To this was added aqueous sodium hydroxide solution (3N, 20 ml) followed by a solution of sodium borohydride (0.5 g, 13 mmol) in aqueous sodium hydroxide solution (3N, 20 ml); an immediate precipitate of mercury

was formed. The solution was carefully decanted and the mercury washed with ether (100 ml). The combined organic extracts were separated, dried, and evaporated under reduced pressure. T.l.c. examination showed the formation of four products. The major and most polar product was obtained by preparative t.l.c. (developing solvent 30% ethyl acetate - hexane) as an oil (103 mg) the n.m.r. of which showed loss of the olefinic protons of the starting material and the appearance of a broad signal, δ2.2, which exchanged with D_2O.

This material was dissolved in acetic anhydride (10 ml) and pyridine (5 ml) and left at room temperature for 16 h. Concentration under reduced pressure and preparative t.l.c. (developing solvent 30% ethyl acetate - hexane) of the residue afforded a single compound. The n.m.r. spectrum of this material showed an acetate methyl as a singlet at 2.03 however the proton integration was not consistent with the proposed 1,1-diethoxy-2-benzyloxy-4-acetoxypentane. The mass spectrum of this material showed a parent ion at M^+, 207. ($C_{18}H_{28}O_5$ requires M, 324). This material was not further characterised.

The preparation was repeated varying the reaction time before addition of the reducing agent as follows: 10 min; 20 min; and 2 h. In each case t.l.c. examination showed three or more products present, none of which could be readily identified.

Attempted Preparation of 1,1-Dimethoxy-4-hydroxypentan-2-one (99)

This procedure is a modification of that of Stork.[64] To a solution of diisopropylamine (2 g, 26 mmol) in tetrahydrofuran (25 ml) was added n-butyl lithium (12.4 ml, 22M in hexane, 26 mmol) dropwise over 5 min with stirring at -78 °C in an atmosphere of nitrogen. To this was added a solution of 1,1-dimethoxypropanone (3 g, 25 mmol) in tetrahydrofuran (25 ml), dropwise with stirring over 1 h. After stirring for a further 2 h at -78 °C, acetaldehyde (1.4 ml, 1.1 g, 25 mmol) was added dropwise. After stirring for a further 15 min, a solution of glacial acetic acid (1.53 g, 26 mmol) in tetrahydrofuran (25 ml) was added in one portion, and the mixture allowed to warm to room temperature. The organic solution was partitioned between ether (100 ml) and water (25 ml) and the ethereal layer separated, washed with brine, dried, and concentrated *in vacuo*. T.l.c. examination showed the presence of three products in addition to 1,1-dimethoxypropanone. The major of these products was obtained as a pale yellow oil by preparative t.l.c. (developing solvent 60% ethyl acetate - light petroleum). This material was tentatively identified as a mixture of 1,1-dimethoxy-4-hydroxypentan-2-one and 1,1,5,5-tetramethoxy-4-methyl-4-hydroxypentan-2-one (100)

$\delta(CDCl_3)$ 1.20 (d, CH_3CHOH), 1.23 (s, CH_3COH), 3.42 (s, OCH_3), and 3.52 (s, OCH_3).

3. OXAZOLIDONE APPROACHES

n-Butyl Glyoxylate (111)

This was prepared by a modification of the published procedure.[70] To a vigorously stirred solution of di-n-butyl L-tartrate (62.5 g, 0.24 mol) in benzene (300 ml) was added lead tetraacetate (110 g, 0.25 mol) in portions over 30 min with intermittent cooling to maintain the reaction temperature below 30 °C. The solution was stirred for a further 1 h, suction filtered and the solids washed thoroughly with benzene. The combined filtrate and and washings were concentrated carefully at reduced pressure, and the residue distilled to afford a colourless liquid, b.p. 65-72° at 20 mmHg, still contaminated with acetic acid. It was dissolved in ether (100 ml), washed with saturated aqueous sodium hydrogen carbonate solution, dried, and the ether removed *in vacuo* to afford n-butyl glyoxylate as its hydrate (18.4 g, 51%), b.p. 73° at 25 mmHg (lit. b.p. 68-74° at 20 mmHg), which was used without further purification (attempts to obtain the free aldehyde by azeotroping with benzene failed)

$\delta(CCl_4)$ 1.95 (3 H, t, J 7 Hz, $CH_2C\underline{H}_3$), 1.1-1.9 (4 H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 4.2 (2 H, t, J 7 Hz, $OC\underline{H}_2CH_2$), and 5.2 (3 H, b s, sharpens to a singlet, 1 H, on addition of D_2O, 2 x O$\underline{H}$ and C$\underline{H}$OH).

Preparation of the 2-Oxazolidone - n-Butyl Glyoxylate Adduct (113)

A mixture of 2-oxazolidone (4.6 g, 53 mmol) and n-butyl glyoxylate hydrate (7.8 g, 53 mmol) was heated in a water bath at 95 °C for 2 h and left at room temperature for 15 h. Column chromatography of the crude reaction mixture on silica (eluting solvent ethyl acetate - hexane) afforded the alcohol (113) as a colourless oil (7 g, 61%)

$\nu_{max.}^{Nujol}$ 3400, 1775, 1740, 1490, 1440, 1250, 1070, 1030, 980, 950, 770, and 710 $cm.^{-1}$

$\delta(CDCl_3)$ 0.95 (3 H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.2-1.8 (4 H, m, $C\underline{H_2}C\underline{H_2}CH_3$), 3.4-4.6 (6 H, m, $OC\underline{H_2}C\underline{H_2}N$ and $OC\underline{H_2}$), 4.7 (1 H, b s, e exchanges with D_2O, OH), and 5.7 (1 H, b s, sharpens with D_2O, $\underline{H}CO$)

(Found: m/e, 216. $C_9H_{14}NO_5$ (M-H) requires 216).

Acetate of the Alcohol (113)

A solution of the alcohol (113) (0.5 g, 2.3 mmol) in acetic anhydride (5 ml) and pyridine (1 ml) was left at room temperature for 12 h. Volatiles were removed under reduced pressure with repeated azeotroping with toluene. Preparative t.l.c. (developing solvent 50% ethyl acetate - hexane) afforded the acetate (114) (0.42 g, 69%) as a pale yellow oil

$\delta(CDCl_3)$ 0.95 (3 H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.1-1.8 (4 H, m, $C\underline{H_2}C\underline{H_2}CH_3$), 2.15 (3 H, s, $OCOCH_3$), 3.4-4.5 (6 H, m, $OC\underline{H_2}C\underline{H_2}N$ and OCH_2) and 6.5

(1 H, s, $\underline{H}COCOCH_3$).

Preparation of the Ketone (115)

A solution of the alcohol (113) (250 mg, 1.2 mmol) in acetone (AnalaR, 20 ml) was treated with a slight excess of 8N Jones reagent at 0 °C. Water (20 ml) was added and the aqueous solution extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, washed with brine, dried, and concentrated in vacuo. Preparative t.l.c. (developing solvent 50% ethyl acetate - hexane) afforded the ketone (115) as a yellow oil (125 mg, 58%)

$\nu_{max.}$ OH absent

$\delta(CDCl_3)$ 0.95 (3 H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.1-1.8 (4 H, m, $C\underline{H_2}C\underline{H_2}CH_3$), and 3.8-4.6 (6 H, m, $OC\underline{H_2}C\underline{H_2}N$ and $OC\underline{H_2}$).

Attempted Preparation of the Ylid (118)

(a) To a stirred solution of the alcohol (113) (0.5 g, 2.3 mmol) and pyridine (0.2 ml, 0.19 g, 2.5 mmol) in benzene (15 ml) at 5 °C was added a solution of thionyl chloride (0.18 ml, 0.3 g, 2.5 mmol) in benzene (10 ml), dropwise. The solution was stirred at room temperature for 1 h, then filtered through Celite and the filtrate was concentrated in vacuo. Preparative t.l.c. (developing solvent 50% ethyl acetate - hexane) afforded, as sole

product, the starting alcohol (113).

The crude reaction mixture prepared as in (a) above and after filtration through Celite was added to a solution of triphenylphosphine (0.6 g, 2.3 mmol) in benzene (20 ml) and the solution stirred at room temperature. Periodic t.l.c. examination showed that after 4 days no reaction had occurred.

(b) A solution of the alcohol (113) (0.25 g, 1.15 mmol) and triphenylphosphine (0.3 g, 1.15 mmol, dried by azeotroping with benzene) in carbon tetrachloride (2 ml, dried over calcium chloride and distilled) was heated for 2 h at 70 °C, then stirred at room temperature for 12 h. The resulting heterogeneous solution was diluted with n-pentane (10 ml), the precipitated solid was removed by suction filtration and the filtrate was concentrated in vacuo. Preparative t.l.c. (developing solvent 50% ethyl acetate - hexane) afforded a white solid (100 mg) which was identified by t.l.c. as triphenylphosphine oxide; no other product was isolated.

Preparation of the Phosphonate (120).

(a) To a stirred solution of the alcohol (113) (0.5 g, 2.3 mmol) and pyridine (0.2 ml, 0.19 g, 2.5 mmol) in benzene (10 ml) was added dropwise a solution of thionyl chloride (0.18 ml, 0.3 g, 2.5 mmol) in benzene (10 ml) at 5 °C in an atmosphere of dry nitrogen. The solution was stirred at room temperature for 1 h, then

suction filtered. To the filtrate was added trimethyl phosphite (0.31 g, 0.25 mmol) and the solution heated under reflux for 3 h. After standing at room temperature for a further 12 h the volatiles were removed under reduced pressure. Preparative t.l.c. (developing solvent 20% ethyl acetate - hexane) afforded a product less polar than the starting material but this was not identifiable.

(b) A solution of the alcohol (113) (0.3 g, 1.4 mmol) and triphenylphosphine (500 mg, 1.9 mmol, dried by azeotroping with benzene) in carbon tetrachloride (15 ml, dried over calcium chloride and distilled) was heated at 50 °C for 3 h. The solution was concentrated in vacuo and the residue extracted with xylene (25 ml). To the resulting xylene solution was added trimethyl phosphite (260 mg, 2.1 mmol) and the solution heated under reflux for 3 h. Evaporation of the solvent under reduced pressure afforded an oil which was triturated with hexane. The hexane solution was concentrated in vacuo. T.l.c. examination of the crude product showed the presence of trimethyl phosphite, starting alcohol and triphenylphosphine oxide.

(c) A solution of the alcohol (113) (2.5 g, 11.5 mmol) and phosphorus tribromide (1.4 g, 5.1 mmol) in benzene (15 ml) was heated under reflux for 2 h. After cooling, the benzene solution was decanted from an oily precipitate which was washed with benzene (10 ml). The combined benzene extracts were added to trimethyl

phosphite (2.5 g, 20 mmol) and the resulting solution heated under reflux for 5 h. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica (eluting solvent chloroform) afforded the phosphonate (120) as a pale yellow oil (2.48 g, 70%)

$\nu_{max.}$ 2240, 1740, 1250, and 1025 cm^{-1}

$\delta(CDCl_3)$ 0.95 (3H, t, J 7 Hz, $CH_2\underline{CH_3}$), 1.3-1.8 (4 H, m, $C\underline{H_2}C\underline{H_2}CH_3$), 3.8-4.6 (12 H, m, $OC\underline{H_2}$, 2 x $OC\underline{H_3}$, $OC\underline{H_2}C\underline{H_2}N$), and 5.1 1 H, d, J_{H-P} 24 Hz, $C\underline{H}PO(OCH_3)_2$

(Found: M^+, 309. $C_{11}H_2NO_7P$ requires M, 309).

Ethylene Ketal (122) of Ethyl 3-Oxobutyrate

A solution of ethyl 3-oxobutyrate (30 g, 0.23 mol), ethylene glycol (16 g, 0.26 mol) and p-toluene sulphonic acid (0.1 g) in benzene (300 ml) was heated under reflux for 36 h using a Dean and Stark water separator. The benzene solution was cooled, washed with saturated aqueous sodium hydrogen carbonate solution, and the solvent removed under reduced pressure. Distillation of the residue afforded the ethylene ketal (122) as a colourless liquid, (27 g, 67%), b.p. 95-101° at 25 mmHg (lit. b.p.[77] 99.5-101° at 17-18 mmHg)

$\delta(CDCl_3)$ 1.25 (3 H, t, J 7 Hz, $OCH_2\underline{CH_3}$), 1.4 (3 H, s, CH_3), 2.5 (2 H, s, $C\underline{H_2}CO_2Et$), 3.85 (4 H, s, OCH_2CH_2O), and 4.05 (2 H, q, J 7 Hz, $OC\underline{H_2}CH_3$).

Ethylene Ketal (126) of 3-Oxobutan-1-ol

A solution of the ester (122) (12.2 g, 70 mmol) in ether (100 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.6 g, 42 mmol) in ether (100 ml). The solution was heated under reflux with stirring for 3 h, then cooled. Ethyl acetate was added dropwise to destroy excess hydride. Saturated aqueous sodium sulphate solution was added in small portions until the aluminium salts became granular, and the ethereal solution was decanted. The ether solution was concentrated *in vacuo* and the residue distilled to afford the alcohol (126) as a colourless liquid (7.5 g, 82%), b.p. 60-64° at 1 mmHg (lit. b.p.[92] 85-87° at 11 mmHg)

$\delta(CDCl_3)$ 1.3 (3 H, s, CH_3), 2.85 (2 H, t, J 6 Hz, $C\underline{H}_2CH_2OH$), 3.4-3.7 (3 H, b t, sharpens with D_2O to triplet, 2 H, 3.6, $CH_2O\underline{H}$), and 3.9 (4 H, s, OCH_2CH_2O).

Ethylene Ketal (127) of 3-Oxobutanoic Acid

This was prepared by the literature method,[93] and was obtained as a colourless liquid, b.p. 103-105° at 0.55 mmHg (lit. b.p. 95° at 0.3 mmHg)

$\delta(CDCl_3)$ 1.45 (3 H, s, CH_3), 2.60 (2 H, s, CH_2), 3.95 (4 H, s, $OC\underline{H}_2C\underline{H}_2O$), and 9.9 (1 H, s, exchanges with D_2O, CO_2H).

Attempted Preparation of the Ethylene Ketal (123) of 3-Oxobutanal.

(a) By oxidation of the alcohol (126) with pyridinium chlorochromate.[78] - A solution of the alcohol (126) (660 mg, 5 mmol) in methylene chloride (10 ml) was added in one portion to a vigorously stirred suspension of pyridinium chlorochromate (1.5 g, 7.5 mmol) and anhydrous sodium acetate (220 mg, 1.5 mmol) in methylene chloride (10 ml). After stirring at room temperature for 2 h, t.l.c. showed the formation of a product, R_f 0.69. Ether (25 ml) was added to the reaction mixture and the organic solution decanted and suction filtered through Celite. The filtrate was washed with saturated aqueous sodium hydrogen carbonate solution, saturated aqueous copper sulphate solution, water, and brine. The organic solution was dried and evaporated under reduced pressure to afford a yellow oil. N.m.r. investigation of this material showed an aldehydic proton, δ 9.3, as a broadened singlet, but preparative t.l.c. (developing solvent 30% ethyl acetate - light petroleum) resulted in extensive decomposition.

(b) By oxidation of the alcohol (126) with Collins reagent.[79] - To a solution of pyridine (9.5 g, 120 mmol) in methylene chloride (10 ml) was added chromium trioxide (6 g, 60 mmol, vacuum dried) in portions with stirring at 0 °C. To the resulting solution was added a solution of the alcohol (126) in methylene chloride (15 ml), in one

portion with stirring at 0 °C. After stirring for a further 1 h at 0 °C the supernatant solution was decanted from a black solid, which was thoroughly washed with methylene chloride (25 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution, saturated aqueous copper sulphate solution, dried, and concentrated in vacuo. The n.m.r. spectrum of the crude product showed an aldehydic proton at δ9.3. Preparative t.l.c. (developing solvent 30% ethyl acetate - light petroleum) again resulted in extensive decomposition.

(c) By reduction of the acid chloride (128). - Two procedures for the preparation of the acid chloride (128) were investigated.

(i) A solution of the acid (127) (0.5 g, 3.4 mmol), oxalyl chloride (0.32 ml, 0.48 g, 3.8 mmol) and anhydrous sodium hydrogen carbonate (0.32 g, 3.8 mmol) in benzene (15 ml) was stirred at room temperature, in the presence of presence of molecular sieves (Linde 4A). Aliquots (1 ml) were taken at intervals and treated with an excess of a solution of diethylamine in benzene. The solutions were washed with saturated aqueous sodium hydrogen carbonate solution, dried, and the solvent evaporated. After 3 h no reaction was observed.

(ii) A solution of the acid (127) (0.5 g, 3.4 mmol) and triphenylphosphine (0.9 g, 3.4 mmol) in carbon tetrachloride (1 ml) was heated with stirring at 70 °C in an atmosphere of nitrogen for 3 h after which time a white

precipitate had formed. On cooling, the solution was diluted with pentane (10 ml), filtered, and the filtrate concentrated in vacuo to afford a gummy solid (91 mg). The n.m.r. spectrum of this material showed it to be triphenylphosphine / triphenylphosphine oxide.

(d) By reduction of the imidazolide (129). - A solution of the acid (127) (1 g, 6.8 mmol) and N,N -carbonyldi-imidazole (1.1 g, 6.8 mmol) in ether (40 ml) was stirred at room temperature for 1 h. The reaction mixture was cooled to -20 °C and a suspension of lithium aluminium hydride (0.155 g, 4.1 mmol) in ether (20 ml) was added dropwise. Stirring was continued for a further 1 h, when ethyl acetate was added to quench excess hydride. Saturated aqueous sodium sulphate solution was added dropwise until the aluminium salts coagulated. The ethereal solution was filtered, concentrated under reduced pressure and extracted with hexane. The hexane extracts were concentrated in vacuo to afford a yellow oil, the n.m.r. spectrum of which showed an aldehydic proton at 9.3. T.l.c. examination of this product showed it to be predominantly the alcohol (126). The procedure above was repeated using tetrahydrofuran as solvent with identical results.

4-Oxopent-2-ene (132)

This was prepared by the published procedure[94] and was obtained as a colourless liquid, b.p. 120-122° at 760 mmHg (lit. b.p.[95] 121-122.5° at 76 mmHg)

$\delta(CDCl_3)$ 1.93 (3 H, d d, J 7 Hz and 2 Hz, $C\underline{H}_3CH=CH$), 5.9-6.3 (1 H, m, $CH_3CH=C\underline{H}$), 6.5-7.2 (1 H, m, $CH_3C\underline{H}=CH$).

4-Hydroxypent-1-ene (133)

This was prepared by the published procedure,[96] and was obtained as a colourless liquid, b.p. 117-118° at 760 mmHg (lit. b.p. 115-116° at 760 mmHg)

$\delta(CDCl_3)$ 1.1 (3 H, d, J 5 Hz, CH_3), 2.21 (2 H, d t, J 7 Hz and 2 Hz, CH_3), 3,2 (1 H, b s, exchanges with D_2O, OH), 3.4-4.0 (1 H, m, $C\underline{H}OH$), 4.9-5.3 (2 H, m, $CH=C\underline{H}_2$), 5.5-6.2 (1 H, m, $C\underline{H}=CH_2$).

4-Oxopent-1-ene (134)

A solution of 4-hydroxypent-1-ene (1 g, 12 mmol) in acetone (AnalaR, 10 ml) was treated until a slight excess of Jones reagent (8N) with stirring at 0 °C. The oxidation was complete in 1 h, when water (20 ml) was a added and the aqueous solution was extracted with ether (2 x 50 ml). The combined ethereal extracts were washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried, and the ether removed below 30 °C to furnish the ketone (134) as a pale yellow oil (500 mg, 50%). This was used in subsequent preparations without purification

$\delta(CDCl_3)$ 2.18 (3 H, s, CH_3CO), 3.15 (2 H, d, J 7 Hz,

CH_2), 4.8-5.3 (2 H, m, $CH=C\underline{H}_2$), and 5.6-6.3 (1 H, m, $C\underline{H}=CH_2$).

Attempted Preparation of the Ethylene Ketal (131) of 1,2-Epoxypentan-4-one

(a) A solution of 4-oxopent-2-ene (132) (5 g, 60 mmol), ethylene glycol (4.34 g, 70 mmol) and p-toluenesulphonic acid (20 mg) in benzene (50 ml) was heated under reflux for 36 h using a Dean and Stark water separator. The cooled reaction mixture was diluted with ether (50 ml), washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried over anhydrous sodium sulphate and carefully distilled using a Vigreux column. The n.m.r. spectrum of the major fraction, obtained as a colourless oil (2 g), b.p. 138-140° at 760 mmHg, showed it to be a mixture of the ethylene ketals of 4-oxopent-1-ene (136) and 4-oxopent-2-ene (135), the latter predominating

$\delta(CDCl_3)$ 1.22 (s, CH_3C), 1.34 (s, CH_3C), 1.7 (d, J 6 Hz, $C\underline{H}_3C=C$), 2.3 (d, $CH_2C=C$).

To a stirred suspension of this mixture (1.28 g, 10 mmol) and disodium hydrogen orthophosphate (2.84 g, 20 mmol) in methylene chloride at 0 °C was added m-chloroperbenzoic acid (2.23 g, 11 mmol). The solution was stirred at room temperature for 10 h, filtered and the solvent removed in vacuo. N.m.r. examination showed this material to be a mixture of the 2,3- and 1,2-epoxides, (137) and (131).

(b) A solution of crude 4-oxopent-1-ene (134) (10 g, 0.12 mol), ethylene glycol (7.2 g, 0.12 mol), and p-toluenesulphonic acid (10 mg) in benzene (100 ml) was heated under reflux for 24 h using a Dean and Stark water separator. The cooled reaction mixture was diluted with ether (100 ml), washed with saturated aqueous sodium hydrogen carbonate solution, brine, dried over anhydrous sodium sulphate and carefully distilled. The n.m.r. spectrum of the major fraction, obtained as a colourless oil, b.p. 110-115° at 760 mmHg, showed it to be a mixture of the ethylene ketals (136) and (135), in this case the former predominating.

The crude mixture was epoxidised as described above and afforded on preparative t.l.c. (developing solvent 20% ethyl acetate - hexane) a pale yellow oil, identified as a mixture of the two isomeric epoxides (131) and (137), the former predominating.

4-Benzyloxypent-1-ene (138)

To a stirred suspension of sodium hydride (9.0 g, 100%, 0.38 mol) in tetrahydrofuran (150 ml) was added 4-hydroxypent-1-ene (133) (30 g, 0.37 mol) dropwise over 30 min with stirring in an atmosphere of nitrogen. The mixture was heated under reflux for 2 h then cooled to 0 °C, when a solution of benzyl bromide (63.6 g, 0.37 mol) in tetrahydrofuran (30 ml) was added dropwise with stirring over 30 min. The mixture was heated under reflux for a further 2 h, then allowed to stand for 24 h at room

temperature. Ethanol was added dropwise to quench excess sodium hydride and the reaction mixture poured on to water (250 ml). The aqueous solution was extracted with ether (2 x 500 ml) and the combined organic extracts washed with brine, dried, and concentrated in vacuo. Distillation of the residue afforded the benzyl ether (138) as a colourless liquid, (43.8 g, 66%) b.p. 105-106° at 25 mmHg

$\nu_{max.}$ 3065, 3030, 1640, 1450, 1170, 1140, 1125, 1090, 1060, 1025, 910, 730, and 695 $cm.^{-1}$

$\delta(CDCl_3)$ 1.22 (3 H, d, J 6 Hz, CH_3), 2.35 (2 H, m, $C\underline{H}_2CH=CH_2$), 3.61 (1 H, q, J 6 Hz, CHO), 4.6 (2 H, s, CH_2Ph), 4.9-5.3 (2 H, m, $CH=C\underline{H}_2$), 5.6-6.2 (1 H, m, $C\underline{H}=CH_2$), and 7.39 (5 H, s, Ph)

(Found: C, 81.9; H, 9.3. $C_{12}H_{16}O$ requires C, 81.7; H, 9.2%).

1,2-Epoxy-4-benzyloxypentane (139)

(a) With trifluoroperacetic acid.[83] - To a stirred suspension of aqueous hydrogen peroxide solution (4.5 ml, 90%, 0.159 mol) in methylene chloride (45 ml) was added trifluoroacetic anhydride (25.2 ml, 34.9 g, 0.18 mol) dropwise over 10 min at 0 °C. The solution was stirred for a further 15 min at 0 °C, when anhydrous sodium carbonate (38.1 g, 0.45 mol) was added. To the resulting suspension was added a solution of 4-benzyloxypent-1-ene

(21 g, 0.12 mol) in methylene chloride (120 ml) dropwise over 30 min at room temperature with vigorous stirring. The mixture was heated under reflux for 30 min, by which time it showed a negative reaction to starch-iodide test paper. The mixture was cooled to 0 °C, suction-filtered through a glass sinter, and concentrated under reduced pressure. The residue was distilled to afford a mixture of the diastereoisomeric epoxides (139) as a colourless oil (15.8 g, 67%), b.p. 134° at 15 mmHg

$\nu_{max.}$ 1460, 1380, 1350, 1130, 1100, 1070, 1030, 910, 730, and 695 $cm.^{-1}$

$\delta(CDCl_3)$ 1.26 (3 H, d, J 6 Hz, CH_3), 1.28 (3 H, d, J 6 Hz, CH_3), 1.4-3.7 (12 H, m, 2 x $C\underline{H}_2C\underline{H}$ $C\underline{H}_2C\underline{H}OH$), 4.53 (4 H, b s, 2 x CH_2Ph), and 7.35 (10 H, s, 2 x Ph)

(Found: C, 74.9; H, 8.6. $C_{12}H_{16}O_2$ requires C, 74.9; H, 8.4%).

In subsequent runs, some polymerisation of the epoxide frequently occurred. Consequently the following alternative procedure was adopted.

(b) With permaleic acid.[84] - To a solution of aqueous hydrogen peroxide solution (2.02 g, 90%, 58 mmol) in methylene chloride maleic anhydride (7.46 g, 76 mmol, distilled) was added in one portion with stirring at 0 °C. The solution was stirred for a further 2 h, and a solution of 4-benzyloxypent-1-ene (7 g, 40 mmol) in methylene chloride was added dropwise at 0 °C. The solution was stirred at 0 °C for 4 h, filtered, and the

filtrate washed with saturated aqueous sodium hydrogen carbonate solution, brine, and dried. The solvent was removed under reduced pressure and the residue distilled to furnish the epoxide (139) (4.2 g, 55%).

Preparation of the Oxazolidone (140)

A mixture of the epoxide (139) (12 g, 63 mmol), ethyl carbamate (8 g, 85 mmol) and triethylamine (1.2 g) was heated for 5 h at 110° in a tube sealed with a Teflon valve. Column chromatography (eluting solvent ethyl acetate - hexane) of the crude reaction product on alumina (Woelm, Grade III acidic) afforded the oxazolidone (140) as a pale yellow oil (12.0 g, 81%)

$\nu_{max.}$ 3380, 1750, 1490, 1450, 1375, 1230, 1070 1030, 960, 740, and 705 $cm.^{-1}$

$\delta(CDCl_3)$ 1.22 (3 H, d, J 7 Hz, CH_3), 1.24 (3 H, d, J 7 Hz, CH_3), 1.6-2.1 (4 H, m, 2 x CH_2-$CHOCH_2Ph$), 3.0-4.2 (8 H, m, 2 x $OCHCH_2N$, 2 x $CHOCH_2Ph$), 4.48 (2 H, s, CH_2Ph), 4.52 (2 H, s, CH_2Ph), 6.35 (2 H, b s, 2 x NH), and 7.35 (10 H, s, 2 x Ph)

(Found: C, 66.1; H, 7.4; N, 5.75. $C_{13}H_{17}NO_3$ requires C, 66.4; H, 7.3; N, 5.95%).

t-Butyl Glyoxylate (104)

This was prepared by the literature[68] method and was obtained as a colourless oil, b.p. 76° at 30 mmHg

(lit. b.p. 59-61° at 20 mmHg), as a 1:2 mixture of the aldehyde (104) and its hydrate.

Preparation of the Oxazolidone - Aldehyde Adduct (141)

A mixture of the oxazolidone (140) (4 g, 17 mmol) and t-butyl glyoxylate (2.2 g, 17 mmol) were heated at 100 °C for 16 h in a tube sealed with a Teflon valve. Column chromatography (eluting solvent ethyl acetate - hexane) of the crude reaction product on silica afforded the alcohol (141) as a pale yellow oil (4.5 g, 70%)

$\nu_{max.}$ 3320, 1750, 1740, 1370, 1230, 1150, 1060, and 700 $cm.^{-1}$

$\delta(CDCl_3)$ 1.2 (3 H, m, CH_3), 1.5 9 H, s, $(CH_3)_3C$, 1.9 (2 H, m, $C\underline{H}_2CHOCH_2Ph$), 2.8-3.8 (4 H, m, $OC\underline{H}C\underline{H}_2N$, $C\underline{H}OCH_2Ph$), 4.5 (2 H, m, $C\underline{H}_2Ph$), 5.5 (1 H, s, CHOH), and 7.35 (5 H, s, Ph)

(Found: m/e 321. $C_{15}H_{19}NO_6$ $(M-C_4H_8)$ requires M, 321).

Preparation of the Phosphonate (142)

To a solution of the alcohol (141) (4.4 g, 12 mmol) and triethylamine (2.0 g, 20 mmol) in benzene (20 ml) was added a solution of phosphorus tribromide (1.6 g, 6 mmol) in benzene (15 ml) dropwise with stirring at 5 °C. The solution was heated under reflux for 2 h, cooled, filtered, and the filtered solids washed with benzene (40 ml). To the filtrate was added trimethyl phosphite (3.2 g, 26 mmol) and the solution heated under reflux for 5 h.

Volatiles were removed in vacuo. Column chromatography (eluting solvent ethyl acetate - hexane) on alumina (Woelm, Grade III, neutral) afforded the phosphonate (142) as a pale yellow oil (4.1 g, 78%)

$\nu_{max.}^{CHCl_3}$ 1760(shoulder), 1730, 1370, 1230, 1150, and 1060 $cm.^{-1}$

$\delta(CDCl_3)$ 1.62 [9 H, s, $(CH_3)_3C$], 3.8 (6 H, 3 x d, J_{H-P} 11 Hz, 2 x OMe), 5.0 (1 H, d, J_{H-P} 24 Hz, CHPO), 7.35 (5 H, s, Ph)

(Found: m/e, 401.12380. $C_{17}H_{24}O_8PN$ $(M-C_4H_8)$ requires 401.12392).

Preparation of the Alcohol (143)

A solution of the benzyl ether (142) (1.5 g, 3.4 mmol) in ethyl acetate (250 ml) in the presence of a catalytic amount of 10% Pd/C was stirred at room temperature for 5 days in an atmosphere of hydrogen. The solution was filtered and the solvent removed under reduced pressure. Column chromatography (eluting solvent ethyl acetate - hexane) of the residue on alumina (Woelm, Grade III,neutral) afforded the alcohol (143) as a colourless oil (0.6 g, 50%)

$\nu_{max.}^{CHCl_3}$ 3470, 1760(shoulder), 1735, 1370, 1250, 1150, 1040, and 850 $cm.^{-1}$

$\delta(CDCl_3)$ 1.23 (3 H, d, CH_3CHOH), 1.54 9 H, s, $(CH_3)_3C$, 2.5 (1 H, b s, exchanges with D_2O, OH), 4.82 (6 H, d d, J_{H-P} 11 Hz, 2 x OCH_3), 5.0 (1 H, d d, J_{H-P} 26 Hz, CHPO)

(Found: M^+, 367.13968. $C_{14}H_{25}NO_8P$ requires M, 367.13957).

Attempted Oxidation of the Alcohol (143)

(a) With Celite-supported[97] Collins reagent. - To a solution of pyridine (400 mg, 5 mmol) in methylene chloride (8 ml) at 0 °C was added chromium trioxide (260 mg, 1.7 mmol, dried in vacuo over phosphorus pentoxide). The solution was allowed to warm to room temperature over 1 h and Celite (660 mg) was added. To this slurry was added a solution of the alcohol (143) (150 mg, 0.4 mmol) in methylene chloride (2 ml), the mixture was stirred for 15 min and then sodium metabisulphite (600 mg) was added. A non-aqueous work-up[97] was employed. The reaction mixture was suction-filtered through Celite / anhydrous magnesium sulphate (50:50) with thorough washing of the filter cake with methylene chloride. The combined filtrate and washings were concentrated under reduced pressure to yield a dark brown oil, the n.m.r. spectrum of which showed a singlet at 2.2 attributable to a methyl ketone. T.l.c. examination of the product showed a single product of the same polarity as starting material but with markedly different staining characteristics. Preparative t.l.c. of the product (developing solvent 10% methanol - ethyl acetate) afforded a yellow oil which t.l.c. examination proved to be a mixture of two compounds neither of which could be identified.

(b) With pyridinium chlorochromate.[78] - To a suspension of pyridinium chlorochromate (180 mg, 0.8 mmol), and anhydrous sodium acetate (196 mg, 2.4 mmol) in methylene chloride (10 ml) was added a solution of the alcohol (150 mg, 0.4 mmol) in methylene chloride (2 ml). After stirring at room temperature for 1 h, the supernatant solution was decanted and the residual solids washed with ether. The combined organic solution was concentrated in vacuo to give a dark brown oil. Preparative t.l.c. (developing solvent 10% methanol - ethyl acetate) of this material gave the same mixture of products as (a) above.

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