SOME NEW REACTIONS IN ORGANIC SYNTHESIS

by

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Acknowledgements.

This thesis is a record of research work carried out in the Department of Molecular Sciences at the University of Warwick, during the period from October 1969 to September 1972. It has been presented for no other degree, and is believed to be wholly original except where due reference is made.

I should like to thank Professor V.M.Clark and Dr.T.J.Kemp for making the laboratories of the Department available, and all the other members of the Department who made the three years so satisfying.

I acknowledge a maintenance grant from the Science Research Council in conjunction with Pfizer, Sandwich, Kent. I am grateful to the latter for providing facilities for two most enjoyable summers of experience in industrial research, and especially to Dr. Michael Tute who supervised my work there.

I am extremely grateful to Dr.N.W.Alcock for the patience and understanding he showed in giving a humble organic chemist such a valuable insight into X-ray crystallographic and computing techniques. Without him, the structure of 'Hornone' would still be a mystery.

But my deepest debt of gratitude is to Dr. Bernard Golding - my long-suffering supervisor. The value of his continual stream of ideas and helpful advice is surpassed only by the enthusiasm and consideration that he offers to his students, both in and out of the laboratory. It can only be hoped that this thesis reflects just a few of these qualities.

Abstract.

The first part of this thesis is concerned with work towards the total synthesis of β-lactam antibiotics, and a second part deals with two topics arising from the author's contribution to research on cobaloximes being conducted in these laboratories.

The introduction to β-lactam antibiotics describes characteristics related to their biological action and synthesis. Published synthetic methods are discussed as routes to analogues of penicillins and cephalosporins, particularly those in which sulphur is replaced by oxygen. Synthesis of such an oxa-penam by photocyclisation of an α-diazoamide is described in chapter 2.

Attempts to synthesise more stable oxa-penams are the subjects of chapters 3 and 4. Formation of the C5-C6 bond of an oxa-penam by radical-induced cyclisation of N-acyloxazolidines was not achieved photochemically, or chemically with azo-bis-isobutyronitrile or nickel peroxide. The former two sets of conditions initiated oxidation of the oxazolidine ring, and azo-bis-isobutyronitrile also effected a characteristic cleavage of peptide derivatives. Nickel peroxide caused trimerisation of some amides and an ester of cyanoacetic acid to derivatives of 1,2,3-tricyanocyclopropane.

Reaction of acyl chlorides and triethylamine with 2-oxazolines did not give β-lactams. 1:1 Adducts of acyl chlorides and oxazolines were identified as reaction intermediates, and the products analysed in the particular case of phthalimidoacetyl chloride.

Chapter 5 describes the reactions of vicinal diols with hydrogen bromide in acetic acid. Certain such diols are converted rapidly and stereospecifically to vicinal acetoxybromides *via* an intermediate 2-methyl-1,3-dioxolan-2-ylium ion formed by 'front-side' participation. Applicability and limitations of this reaction as applied to a range of acyclic and cyclic diols is discussed.

In the final chapter, the product of a degradation of alkylcobaloximes by acetic anhydride in pyridine is proved to be a derivative of imidazo[1,2-a]pyridine by chemical methods and single crystal X-ray analysis. Limited studies on the reaction mechanism and its relation to coenzyme B_{12} action are discussed.

CONTENTS

GENERAL LAYOUT AND EXPERIMENTAL DETAILS.

The division of this dissertation into chapters corresponds to sections of differing practical approach, and an individual experimental section has been appended to each chapter. The diagrams, figures, schemes and tables are numbered separately for each chapter, but the references run in continuous sequence throughout the whole work, and are complete through to August 31, 1972.

The following are details of the experimental methods used.

Melting points (m.p).

Determined in open capillary tubes in an Electrothermal apparatus, and not corrected.

Infra-red spectra (i.r).

Recorded on a Perkin-Elmer 257 grating spectrophotometer, with the compounds as nujol mulls between sodium chloride plates, or as 1% solutions in the solvent indicated, in 0.2mm path length cells with sodium chloride windows. The position of an absorption is given in wave numbers (cm^{-1}), followed by an indication of its intensity:-

vw - very weak m - medium vs - very strong.
w - weak s - strong

This may be followed by one of the qualifications (br) - broad, or (sh) - shoulder.

In most cases, only significant absorptions at wave numbers higher than 1500 cm^{-1} are given.

^{1}H-Nuclear magnetic resonance spectra (n.m.r).

Taken on a Perkin-Elmer R12 spectrometer at 60 MHz, in 5mm diameter sample tubes in the solvent indicated. Sodium 3-(trimethylsilyl)-propanesulphonate was used as internal reference in aqueous solvents, otherwise tetramethylsilane was used. The probe temperature was 37°. The chemical shifts of resonances are given in τ units relative to the internal standard at τ10.0, followed by:-

multiplicity: s singlet; d doublet; t triplet; q quartet; sx sextuplet; m multiplet; br broad, unresolved resonance; dd double doublet.

the spin-coupling constant (J Hz) where appropriate;

the integral value of the resonance (nH).

Where indicated by the suffix 100MHz, spectra were taken on a Varian HA-100 spectrometer at 100MHz by the Physicochemical Measurements Unit, Harwell.

Ultra-violet spectra (u.v).

Recorded on a Pye-Unicam SP 800 spectrometer in methanol solution in quartz cells with 1cm path length. (MeOH/HCl) Prefixes the spectrum observed on adding 2 drops of aqueous concentrated hydrochloric acid to the methanolic solution (3ml). The absorption maxima are given in nanometers (nm) followed by the molar extinction coefficient (ε). A further qualification may be added: br - broad, or sh - shoulder

Mass spectra (m.s).

Measured on an AEI MS 902 spectrometer by the University of Hull Mass Spectrometry Service. For the majority of compounds peaks of intensity >10% of the base peak (B) having m/e greater than the base peak only are recorded. For each peak, the m/e value is followed in brackets by the intensity as a percentage of the base peak intensity. Where a high resolution measurement has been made on the ion, the molecular formula giving the best fit is then given within square brackets. Finally an interpretation of the derivation of the ion may be given, and where a breakdown is supported by an appropriate metastable peak it is marked *. The molecular ion is signified by (M).

In special cases where the identification of the compound is open to question, or where the spectrum is characteristic but not fully explained, the fragmentation pattern is given in full, including all ions with intensity >10% of the base peak intensity and any others thought significant.

Elemental analyses.

Combustion analyses were performed at the Microanalytical Laboratory of Dr.F.B. Strauss, Oxford. The molecular formula is given first, accompanied by the calculated elemental composition. The analytical figures are quoted directly below the latter.

Optical rotations.

Measured with a Bendix-NPL Automatic Polarimeter type 143, calibrated frequently with a freshly prepared standard sucrose solution ($[\alpha]_D$ +66.5°). The sample cell used had a 1cm path length. The values recorded are the specific rotations $[\alpha]_D^t$ at the sodium

D line (λ 589nm) and temperature t°C, followed in brackets by the solvent and concentration (c) in g/100ml.

The limitations of the sample cell size and scale full scale deflection forbade direct measurement of neat liquids having $\alpha_D > 10.0°$, and compounds outside this range were diluted with pure racemic material accurately by weight, and the true values for the rotation calculated accordingly.

Refractive index (n_D^t).

Measured on a Hilger-Watts refractometer at temperature t°C.

Density (d).

Measured by weighing the volume discharged from a 100µl microsyringe on a Mettler 5-figure balance, and calibrating with distilled water.

Thin layer chromatography (t.l.c).

T.l.c analysis was on plates prepared from Machery, Nagel and Co. silica gel G/UV_{254} (with fluorescent indicator) developed in the solvents indicated;

a) plates of 0.25mm thickness with standard 10cm elution path;

b) microscope slides of 0.15mm thickness, prepared by spreading (this procedure is immeasurably superior to dipping with respect to resolution and consistency of results).

Spots were detected by examination of the plates under u.v light (254nm) and/or by exposure to iodine vapour. Compounds containing N-H groups were conveniently detected as black spots by spraying with 1% t-butyl hypochlorite solution in cyclohexane, heating for 3 minutes at 100°, cooling, and spraying with 2% starch/potassium iodide solution.[89]

Preparative layer chromatography (p.l.c).

On plates of 0.5mm or 0.75mm thickness prepared from Merck silica gel PF_{254}. Compounds were extracted from the silica gel with redistilled acetone, the extracts evaporated, and the residue dissolved in dichloromethane, filtered and evaporated.

Column chromatography.

a) On Fisons silica gel (for chromatography) 100-200 mesh, using an absorbent : mixture ratio of approximately 50:1.

b) Small scale (100mg) separations and purifications on

Machery, Nagel and Co. silica gel N (for t.l.c) in a glass sinter funnel subject to gentle suction (similar absorbent : mixture ratio as above).

Gas-liquid chromatography (g.l.c).

Performed on a Honeywell F and M Dual Column apparatus with columns as indicated - 2' SE30, 6' E301 or 6' Carbowax. The injector was at c. 260°, and the detector at c. 280°.

This machine was also used for small scale preparative work. Larger scale preparative g.l.c was performed on an Aerograph 'Autoprep' A-700 apparatus.

Solvents and reagents.

These were of reagent grade unless otherwise stated, and all solvents for routine use were redistilled before use. Solvents used in spectroscopy were of the appropriate grade.

Abbreviations.

Abbreviations not explained above or in the text are those approved by the Chemical Society (except for use of c. = circa).

For clarity in some instances, common reagents are designated by their chemical formulae, and these are self-evident.

Chapter 1
SOME ASPECTS OF PENICILLIN CHEMISTRY.

1i. The β-lactam antibiotics.

The bacteriocidal action of extracts from the fungus Penicillium notatum was first reported in 1929 by Fleming, who also observed that the extracts had no effect when injected into mice. He did not then go on to perform the third, and now obvious, experiment of injecting the extracts into mice previously infected with the bacteria, because he did not think it was worth the trouble. The extracts were unstable, and the contemporary thinking, particularly in the Innoculation Department of St. Mary's Hospital, London, where Fleming worked, favoured immunological techniques and rejected the idea of a relatively simple chemical substance specifically active against pathogens and without effect on the host. Florey and Chain began the reinvestigation of Fleming's work in 1938, and the impetus of the Second World War promoted penicillin as the progenitor of the Antibiotic Era.

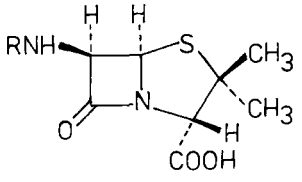
The β-lactam structure (I) for penicillin was demonstrated by chemical means and the use of i.r spectroscopy (1943), and was confirmed by X-ray analysis (1949). A limited range of new penicillin could be produced by addition of specific nutrients to the fermentation medium, the most important being addition of phenoxyacetic acid to give penicillin V (I, R = $PhOCH_2CO$). However, in 1961 the parent 6-aminopenicillanic acid (I, R = H) - 6APA - became commercially available by enzymatic deacylation of the natural penicillin G (I, R = $PhCH_2CO$), opening the field of semi-synthetic penicillins.[1]

Two antibiotic substances were isolated from Cephalosporia spp. - the group of steroids cephalosporin P, and penicillin N (I, R = D-α-aminoadipyl) (1948). Reinvestigation (1956) of the latter fraction revealed a new β-lactam antibiotic cephalosporin C, whose structure was shown to be (II), proved by X-ray analysis of the sodium salt (1961).

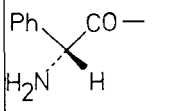
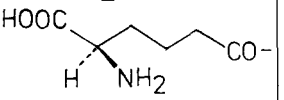
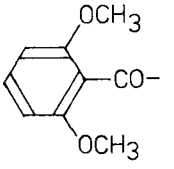
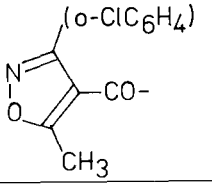
Cephalosporin C is less susceptible to acid and to β-lactamase enzymes than penicillins, and is less potent but has a broader spectrum of biological activity. The side chain of natural ceph-

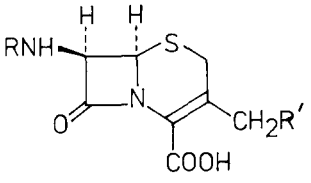
alosporin C cannot be removed enzymatically because of its polarity, but can be more easily removed chemically than in the more labile penicillins, giving 7-aminocephalosporanic acid (II, R = H) - 7ACA. Medically important cephalosporins have both modified C7-side chains and modified 3-methyl groups.[2]

A third group of β-lactam antibiotics has recently been isolated[3] from streptomycetes - the cephamycins (III). These are cephalosporins with a 7-α-methoxy substituent and novel 3-methyl substituents. They show activity against Gram-negative bacteria equal to or greater than that of cephalosporin C.

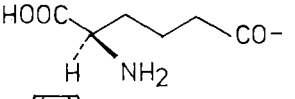
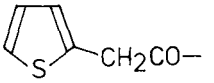
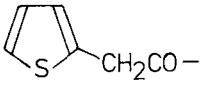
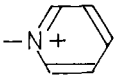


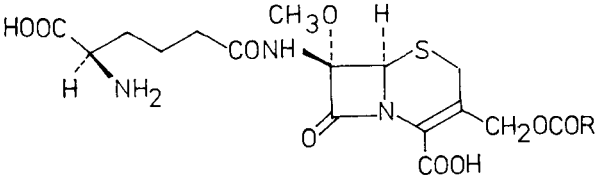
(I)

	R		R
6APA	H		
penicillin G	$PhCH_2CO-$	Ampicillin	
penicillin V	$PhOCH_2CO-$		
penicillin N		Methicillin	
Cloxacillin			

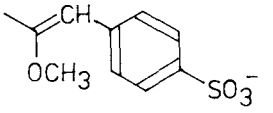
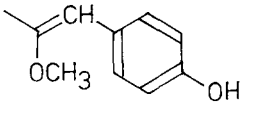


(II)

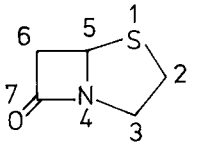
	R	R'
7ACA	H	OAc
cephalosporin C		OAc
Cephalothin		OAc
Cephaloridine		



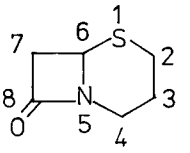
(III)

	R
cephamycin	CH_3
cephamycin A	
cephamycin B	
cephamycin C	NH_2

The penicillin nucleus is derived from 1-aza-4-thiabicyclo-[3.2.0]heptan-7-one (IV), and that of the cephalosporins from 1-aza-5-thiabicyclo[4.2.0]octan-8-one (V). Nomenclature now standard[4,5] gives these basic bicyclic nuclei the trivial names 'penam' and 'cepham' respectively, with numbering as shown. α- and β- are used to denote substituents below and above the molecular plane respectively, consistent with their use in steroid chemistry.



(IV)



(V)

Penicillin G and the semi-synthetic penicillins maintain a dominant position in the treatment of bacteria-caused diseases, being highly active against Gram-positive strains, although less active against Gram-negative bacteria, and they are by far the least toxic of all the antibiotics. Table I compares the activity of some penicillins and cephalosporins with those of other antibiotics against Gram-positive and Gram-negative bacteria, and those producing β-lactamase enzymes (summarised from ref.1a).

table I. Minimum Inhibitory Concentrations (μg/ml)

antibiotic	Staph.Oxford (Gram +)	Salm.typhi (Gram -)	penicillinase producing
penicillin G	0.02	2.5	5 - 125
Ampicillin	0.05	1.25	
Methicillin	0.6 - 1.25		1.25 - 2.5
Cloxacillin	0.05 - 0.25		0.25 - 0.5
chloramphenicol	2.5	2.5	
tetracycline	0.25	2.5	
cephalosporin C	60 - 125	60 - 125	60 - 125
Cephalothin	0.3 - 0.6		0.3 - 0.6

lii. Chemistry of penicillins and cephalosporins related to their syntheses.

The chemical studies that led to the elucidation of the structure of the natural penicillins were summarised in 1949[6] along with details of unsuccessful synthetic attempts. Much of this original chemistry stemmed from the ease of cleavage of the amide bond of the β-lactam. β-Lactams had been relatively little studied, and the known monocyclic β-lactams were quite stable. Fusion to the thiazolidine ring in the penicillins causes the bridgehead nitrogen atom to be non-planar, reducing resonance in the amide bond, as shown by increase in the i.r frequency of the carbonyl absorption from c. 1740 cm^{-1} in monocyclic β-lactams to 1770-1780 cm^{-1} in penicillins (summarised in ref.7). Nucleophiles readily open the β-lactam ring to give derivatives of penicilloic acid.

In the natural penicillins, the 6-acylamino side chain facilitates acid cleavage of the β-lactam via the isomeric oxazolone structure (scheme 1):

- at pH 4 β-elimination in an oxazolone intermediate opens the thiazolidine ring to give penicillenic acid;

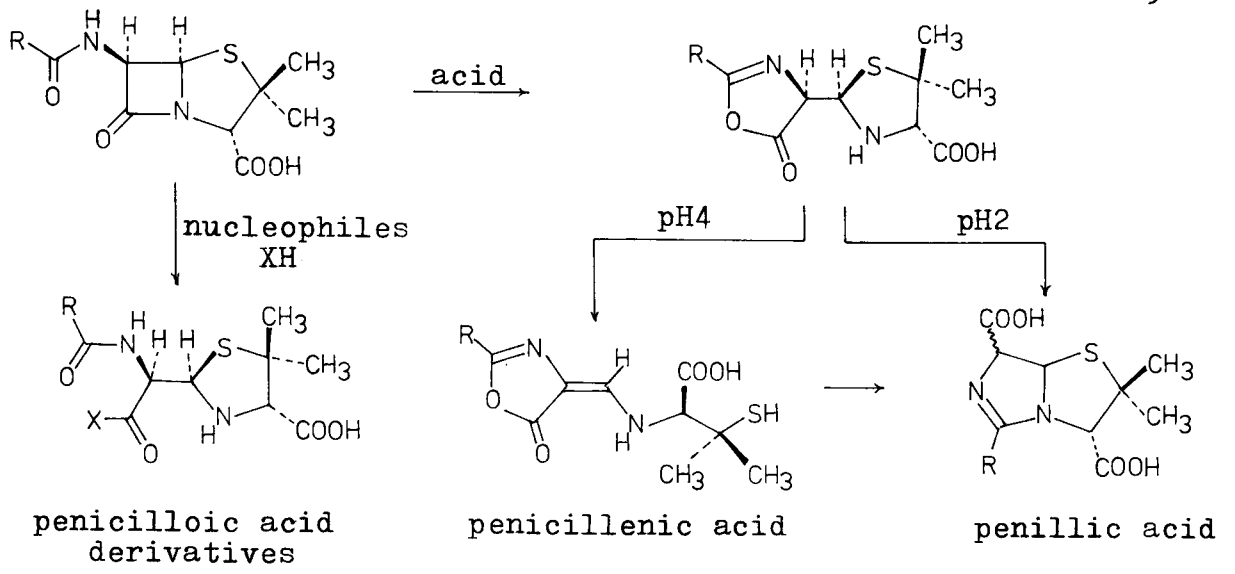
- at pH 2 recyclisation of penicillenic acid gives penillic acid;

- dilute mineral acid gives penicilloic acid, and may further degrade the more labile, deacylated thiazolidine ring on warming.

Incorporation of electron-withdrawing groups into the C6-acylamino side chain thus reduces the tendency towards oxazolone formation and gives penicillins more resistant to acid cleavage and hence more suitable for oral administration (e.g penicillin V, I R = $PhOCH_2CO$).

In cephalosporins, the i.r frequency of the β-lactam carbonyl is marginally lower than that in the penicillins (1765-1775 cm^{-1})[7] but still much higher than that in monocyclic β-lactams. Cephalosporin C is less susceptible than penicillins to nucleophiles - it can be recrystallised from methanol - and also to acid - it is stable at pH 3, and was discovered as a biologically active component of Cephalosporia fermentations after removal of activity due to penicillins by mild acid hydrolysis.

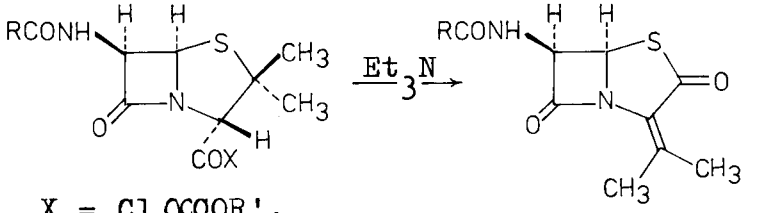
A number of factors must be considered in explaining these



scheme 1.

properties. A six-membered ring is more flexible than a five-membered, and fusion to a β-lactam should not cause such a distortion from planarity at the bridgehead nitrogen atom. However, the Δ^3-unsaturation in the dihydrothiazine ring of cephalosporins reduces the flexibility, and X-ray studies[7] have shown the deviation from planarity around nitrogen to be 0.40Å in penicillin G, and 0.24Å in cephaloridine (c.f 0.56Å in Me_3N). In Δ^2-cephalosporins the bridgehead nitrogen is virtually planar.

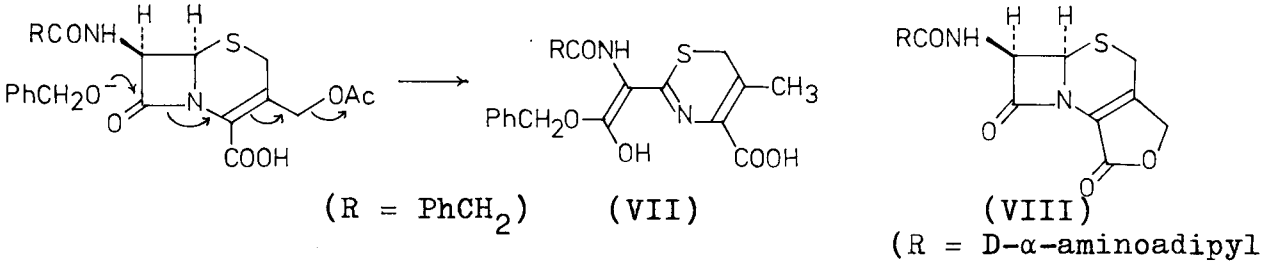
The bond lengths show that, despite this non-planarity, the nitrogen lone-pair electrons are involved in both enamine and amide resonance in Δ^3-cephalosporins, and this is confirmed by their u.v absorption at 260nm, which is that calculated for an enamine-enamide system with appropriate increments for the various substituents.[8]



However, the anhydropenicillins[9] (VI) have both a 5-membered ring fused to the β-lactam and a bridgehead nitrogen atom in an enamine-enamide situation. The i.r frequency of the β-lactam

carbonyl is c. 1810 cm^{-1}, but the anhydropenicillins are remarkably stable to nucleophilic attack, being recovered unchanged from boiling in alcohols or from the melt. Studies of the basic hydrolysis of acetanilides have suggested that increase in basicity of the amidic nitrogen atom increases the rate of hydrolysis, and the stability of anhydropenicillins has been ascribed to a decrease in the basicity of the bridgehead nitrogen due to extensive delocalisation into the exocyclic enamine system and presumably into the C2-carbonyl function.[9]

An additional factor peculiar to the cephalosporins is the 3-acetoxymethyl group. The acetoxy group, conjugated with the carboxyl substituent at C4, is susceptible to S_N1 substitution, and can assist in concerted cleavage of the β-lactam, e.g by benzylate anion giving (VII).[10] The desacetoxy compound is more resistant, while in Δ^2-cephalosporins acetoxy displacement is four times slower, and the β-lactam very much more stable (no reaction with hydroxylamine). Deacetylation of cephalosporin C is accompanied by conversion to the lactone, cephalosporin C_c (VIII).



(R = $PhCH_2$) (VII) (VIII)
(R = D-α-aminoadipyl

A final point is that in addition to the u.v maximum at 260nm, Δ^3-cephalosporins show a second absorption, generally weak but seen as a negative Cotton effect in the circular dichroism spectrum at 230nm. This has been attributed[8] to homoconjugation between the 3,4-double bond and the β-lactam carbonyl. This maximum is markedly increased in intensity and shows a bathochromic shift in the cephamycins due to the methoxy substituent adjacent to the β-lactam carbonyl.

The reactivity of the β-lactam in these antibiotics is an important feature of their biological activity - see below - and clearly is the result of many interacting molecular characteristics, not all reflected by the i.r frequency of the β-lactam carbonyl.

Stereochemistry.

Three of the four tetrahedral centres of the penicillin nucleus are chiral. The cephalosporins have two chiral centres, but also a double bond in the dihydrothiazine ring that is specifically in the 3,4-position. This is the more stable arrangement in the free acid, but Δ^2-unsaturation is favoured in most esters.

Configuration at C6(7).

In both penicillins and cephalosporins the side chain at C6 and C7 respectively has the endo-configuration. This would be expected to suffer unfavourable interactions with the sulphur atom in both molecules, and also with the endo-2-methyl group in the penicillins. After silylation of the acylamino-side chain in the natural penicillins, treatment with mild base allows epimerisation at C6 and formation of an equilibrium mixture containing predominantly the 6-exo-epimer (4:1).[11] With other C6(7)-substituents in penicillins (cephalosporins) - e.g phthalimido[12] - epimerisation often gives wholly the unnatural configuration.

The carboxyl group.

Both penicillins and cephalosporins have a free carboxyl group that must generally be protected during syntheses and manipulations of the nuclei. Deprotection must not violate the intact nuclei, and this generally excludes acidic or basic hydrolysis. Catalytic hydrogenation may also be complicated by the presence of sulphur in the molecules. 2,2,2-Trichloroethyl esters have been much used, and are converted to the free acids with zinc and acetic acid. In the cephalosporin series, setting the lactone cephalosporin C_c (VIII) as synthetic target provides for protection of the carboxyl-group and localisation of the double bond.

liii. The mode of action of penicillins and cephalosporins.

Fleming originally observed that staphylococci exposed to penicillin underwent lysis, and it was found that penicillin was only effective during active growth phase. Park[13] showed that sub-inhibitory doses of penicillin caused accumulation of uridine-diphospho-N-acetylmuramic acid and peptide derivatives thereof. These were suggested to be intermediates in cell-wall biosynthesis.

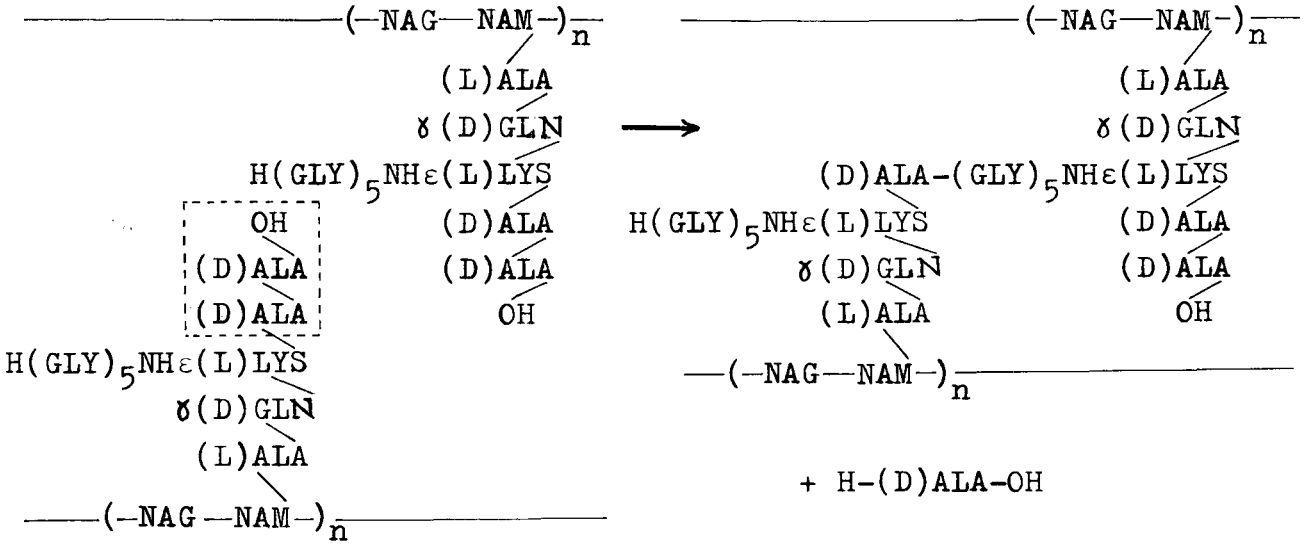
Subsequently the mucopeptide component of the bacterial cell wall was identified as linear strands of alternating N-acetyl-glucosamine (NAG) and N-acetylmuramic acid (NAM), cross-linked by peptide chains.[14] Soluble linear polymer is formed inside the cell membrane with the carboxyl groups of the NAM units attached to the N-terminal of a short peptide carrying a free amino group and C-terminal D-alanyl-D-alanine dipeptide. This linear polymer is transported outside the cell, where the terminal D-alanine of a peptide chain is removed and replaced by the free amino group of a peptide attached to an adjacent linear chain. Repetition of this step gives an insoluble, cross-linked polymer[15] (scheme II).

Strominger[16] has shown that after pulse-labelling cells of S.aureus with ^{14}C-glycine and breaking up the mucopeptide with N-acetylmuramidase (hydrolysing only the glycosidic linkages) the label is distributed over oligomers of varying size according to the differing degrees of cross-linking of the linear chains. If the cells are exposed to penicillin after labelling, on analysis the radioactivity is confined to the lowest molecular weight fragments - i.e penicillin inhibits the cross-linking at some stage.

Formation of the linear polymer is not affected by penicillin. Particulate preparations from Escherichia coli provided with uridinediphospho-NAG and with NAM-pentapeptide labelled with ^{14}C-D-alanine can produce labelled insoluble polymer with liberation of ^{14}C-D-alanine into the medium. In the presence of penicillin, only labelled soluble polymer is formed, and no ^{14}C-D-alanine is liberated.

Strominger concluded that penicillin inhibits the final cross-linking step in cell wall biosynthesis, and showed that the antibiotic resembles a particular configuration of the D-alanyl-D-alanine terminus of the peptide chains prior to this step[17] (fig.1). The β-lactam corresponds to the peptide bond, and he suggested that

scheme II. Final stages of formation of mucopeptide in S.aureus.[15]



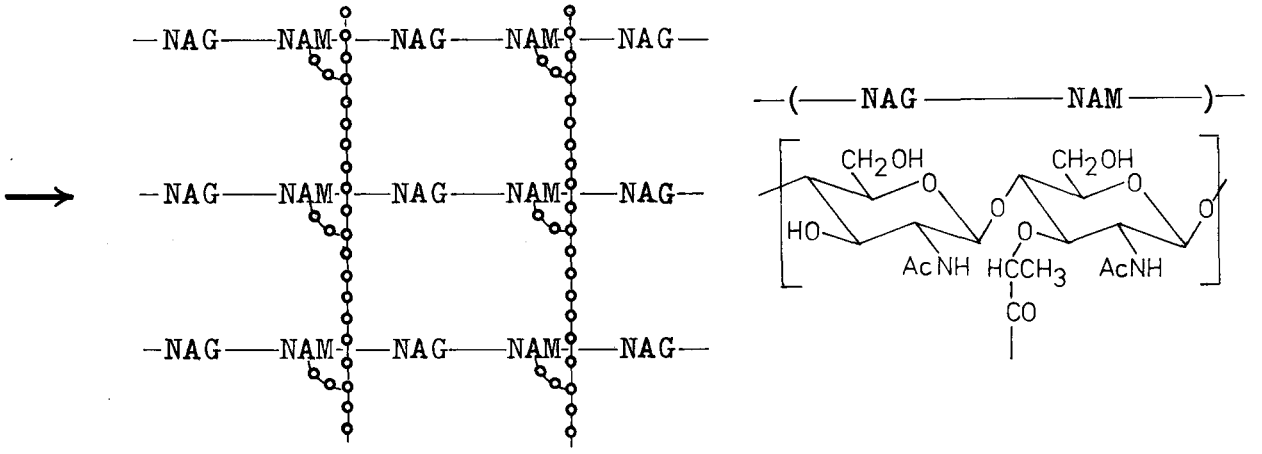
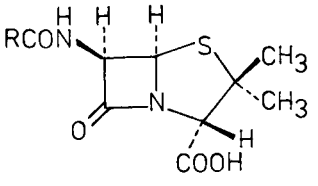
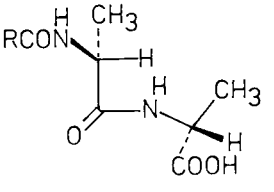


fig.1



penicillin



RCO-(D)ALA-(D)ALA-OH

penicillin acts as an antimetabolite of the transpeptidase enzyme, and the β-lactam irreversibly acylates the active site. ^{35}S-Penicillin, once bound to the bacteria, cannot be removed by washing,[18] but can be removed by alkali as the penicilloate.[19]

Recently it has been suggested that the rigid penicillin molecule more closely resembles the D-alanyl-D-alanine unit if the peptide bond of the latter is twisted through about 45° from the normal planar configuration.[20] Such a twist may be a key step in the enzymatic cleavage of the peptide bond, destroying the amide resonance present in the planar configuration. As such, it would constitute a major component of the binding energy for the substrate, and binding of the already twisted penicillin molecule would lack this energy requirement, and hence be that much more favourable (estimated 10-17kcal/mole).

The exact mode and extent of cross-linking in the cell wall varies in different bacteria. In S.aureus (scheme II), linked to the NAM unit is the pentapeptide L-alanine-D-glutamine-L-lysine-D-alanine-D-alanine, and a pentaglycine chain is attached to the lysine ε-amino group. Cross-linking joins the penultimate D-alanine of one peptide to the terminal glycine of another. Other Gram-positive strains may lack the pentaglycine unit, but cross-linking is extensive. In Gram-negative bacteria, cross-linking is restricted to one link per peptide chain, and the mucopeptide is a relatively minor component of the cell wall compared with layers of lipoprotein and lipopolysaccharide.

Hence penicillins generally show low activity against Gram-negative strains. Activity is increased by polar C6-side chains - e.g Ampicillin (I, R = D-α-aminophenylacetyl). This feature may reduce accumulation of the antibiotic in the lipoid outer cell wall, and accounts for the higher activity of cephalosporin C against Gram-negative bacteria (table I).

Another consideration in penicillin therapy is that some bacterial strains are resistant to the drug because they produce a β-lactamase enzyme. Semi-synthetic penicillins with bulky side chains show increased activity against these bacteria - e.g Methicillin (I, R = 2,6-dimethoxybenzoyl) induces the β-lactamase of Gram-positive bacteria, but is less than one hundred times as rapidly destroyed as is penicillin G; however, it is equally susceptible

to the β-lactamases of some Gram-negative strains, and has a narrower antibiotic spectrum compared with penicillin G. A more effective example of this type is Cloxacillin (I, R = 3-(o-chlorophenyl)-5-methyl-4-isoxazolyl) (table I).

Cephalosporin C was discovered by its greater resistance to acid and to purified β-lactamase than penicillin N, and while its activity is much lower than that of penicillin G, it is proportionately more effective against Gram-negative bacteria. The former properties are due to the nucleus, the latter to the polar C7-side chain. Two semi-synthetic cephalosporins are in clinical use - Cephalothin (II, R = (2-thiophenyl)acetyl, R' = OAc) and Cephaloridine (II, R = (2-thiophenyl)acetyl, R' = 1-pyridinium) - and both have much higher activity than cephalosporin C against Gram-positive bacteria, but still retain the insensitivity to β-lactamases and show useful activity against some Gram-negative strains (table I).

Observations similar to those made on the natural penicillins have confirmed that the semi-synthetic penicillins and cephalosporins have a similar mode of action.

liv. Structural modifications.

Semi-synthetic penicillins have massively increased the applicability of the natural antibiotics, but the possibility that modifications to the nucleus might provide new antibiotics is a tempting prospect. Discovery of the cephalosporins and cephamycins confirmed the existence of such a possibility, but there are no synthetic β-lactam antibiotics yet in clinical use.

a) Biological activity requires an intact β-lactam. Monocyclic β-lactams are inactive, and the bicyclic structure of penicillins and cephalosporins both activates the β-lactam to nucleophilic attack and gives it the correct orientation relative to other substituents. Homo-penicillin analogues with γ-lactams are inactive,[21] and increase in the i.r frequency of the β-lactam carbonyl has been correlated with increasing biopotency in some cephalosporins (summarised in ref.7).

b) The natural 6-(S)- and 5-(R)- configuration of penicillins

seems to be necessary, as both 6-epi-[11] and 5-epi-penicillins[22b] are biologically inactive.

c) A C6(7)-acylamino-substituent is required for maximum antibiotic effect. 6APA shows only low activity, and this is little increased by replacement of the 6-amino group by other substituents[1a] (configuration not specified, however).

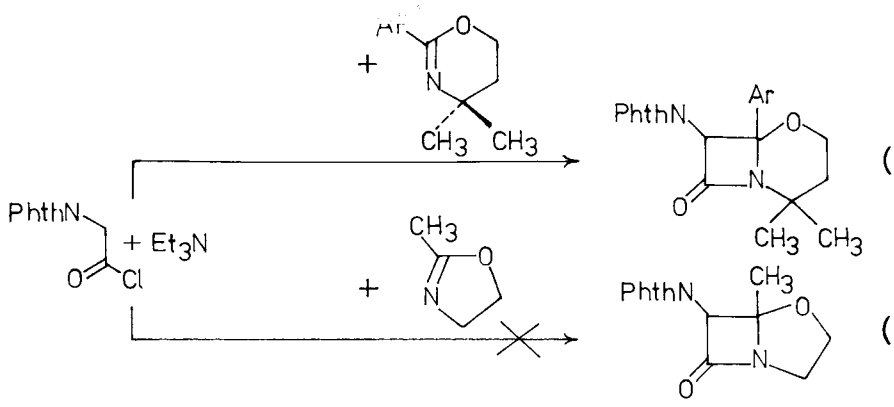
d) A free carboxyl group is probably required by penicillins. Esters and amides are less active, and the extent of hydrolysis is uncertain. However, the cephalosporin lactone - cephalosporin C_c - (VIII) - shows appreciable activity.[2b]

The orientation of the carboxyl group is important. Penicillin V synthesised from DL-penicillamine had only half the activity of that synthesised from D-penicillamine.[23] Although there might seem little resemblance in structure around the carboxyl groups in penicillins and cephalosporins, certain conformations of each are quite analogous.[20]

e) An alternative to the β-lactam has not been found, although a conceivable candidate is suggested in this work (chapter 4). Within the above limitations, the only possible variations on the structure of the natural β-lactam antibiotics are in the ring fused to the β-lactam. Oxidation of the sulphur to the more bulky and polar sulphoxide or sulphone greatly reduces biological activity of penicillins and cephalosporins.[1a,2b] However, desmethyl penicillins showed activity,[24] and appropriate β-lactams fused to a wide range of sulphur-containing 6-membered rings have been shown to possess antibiotic activity by the CIBA-Geigy group.[25]

An obvious variation would seem to be the replacement of sulphur by oxygen. The only comments in the literature on such derivatives are that reaction of phthalimidoacetyl chloride and triethylamine with 2-aryl-5,6-dihydro-1,3-oxazines gave O-cephams (e.g IX), but with 2-methyl-2-oxazoline did not give an oxa-penam (X) - see chapter 4.

While investigating new synthetic routes to penicillins, we have been particularly concerned with the possibility of producing nuclear analogues with oxygen replacing sulphur - referred



(IX) refs.143,144.

(X) ref.145

to as oxa-penams in this work.

Monocyclic oxazolidines are markedly less stable than the analogous thiazolidines.[26] The former are in equilibrium with the acyclic Schiff bases, but this is prevented by acylation - N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine is stable to 10 hours reflux in 10% methanolic sulphuric acid (chapter 4).

Oxygen is less sterically demanding than sulphur, and in an oxygen-containing penicillin analogue the interaction with an endo-C6-substituent would be reduced. This could lead to increased folding of the molecule - further decreasing the resonance in the β-lactam amide - and possibly to increased stability of endo-substitution at C6. The existence of an oxa-penam is demonstrated in chapter 2, and the i.r spectrum shows a high frequency carbonyl absorption (1790 cm^{-1}), although the substitution at C5,C6 is probably trans.

f) In the analogy between penicillins and the D-alanyl-D-alanine dipeptide (fig.1), the C5-C6 bond in the penicillins corresponds to the C-H bond in the penultimate D-alanyl unit, not to the C-CH_3 bond, which might be thought a closer similarity. Since 6-epi-penicillins are biologically inactive, this correspondence cannot be reversed, and Strominger hence prophesied that penicillins (cephalosporins) with 6(7)-α-methyl substituents should show increased activity, being even closer analogues. The recently discovered cephamycins with 7-α-methoxy substituents showed activity against Gram-negative bacteria equal to or greater than that of cephalosporin C.

7-α-Methoxy-Cephalothin and 6-α-methoxypenicillin G have been synthesised from 7ACA and 6APA respectively.[27] The former showed activity similar to that of Cephalothin, but the latter was

less active than penicillin G. 6-α-Alkylpenicillins have also been synthesised by alkylation of the C6-anion of benzylidene-aminopenicillanates,[28] but 6-α-methylpenicillin G had less than 16% of the activity of penicillin G, and a narrower antibiotic spectrum.

These results are disappointing. They may cast doubts on the proposed mechanism of action, although the C6(7)-substituents may adversely affect some other facet of antibiotic activity - e.g translocation - thus masking any advantage at the active site.

A successful antibiotic must overcome many barriers, and all must be considered when attempting structural modifications.

1v. Total synthesis of β-lactam antibiotics.

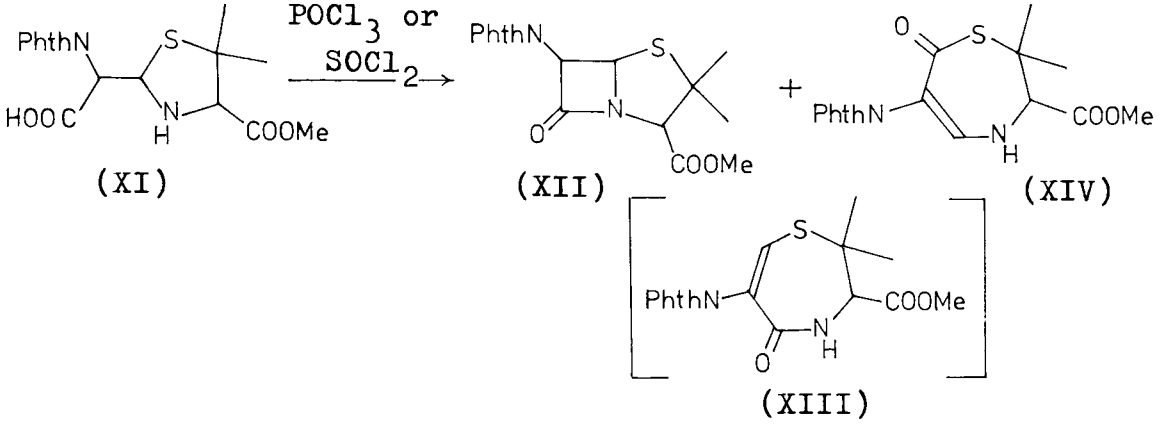
The relatively small, deceptively simple penicillin molecule is the most fiendish concatenation of functionality known. The definition of almost every atomic centre presents a synthetic problem of greater or lesser magnitude. There have been four main approaches to the total synthesis[21] of penicillins, cephalosporins and analogues. Three of these - due to Sheehan, Lowe and Bose - involve fusion of a β-lactam onto the second heterocycle, but the Woodward cephalosporin synthesis produced an intermediate already containing the β-lactam and sulphur moieties, from which a variety of bicyclic β-lactam structures could be derived.

A. Sheehan's method.

The only successful total synthesis of a natural penicillin involved cyclisation of a 2-(2-thiazolidinyl)-acetic acid derivative. It is a classic example of the use of protecting groups whose removal is compatible with the final structure. The final step in formation of the nucleus does not generate a chiral centre, and the stereochemistry can be resolved with the less labile acyclic and monocyclic precursors. However, formation of the β-lactam amide bond had previously employed 'dangerously' acidic reagents, and was impossible by any method in acylaminopenicilloic acids where oxazolone formation was preferred (as was found in the original penicillin work[6]).

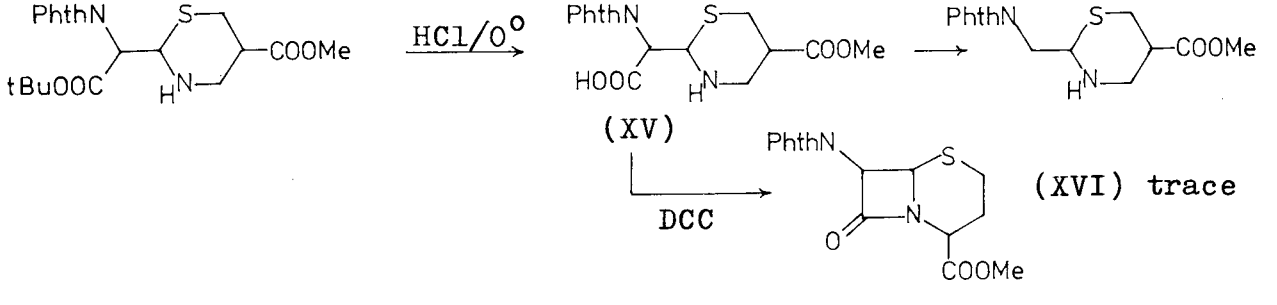
Phthalimidopenicilloic acid (XI) of unnatural configuration could be cyclised to the penam (XII) with thionyl chloride or with

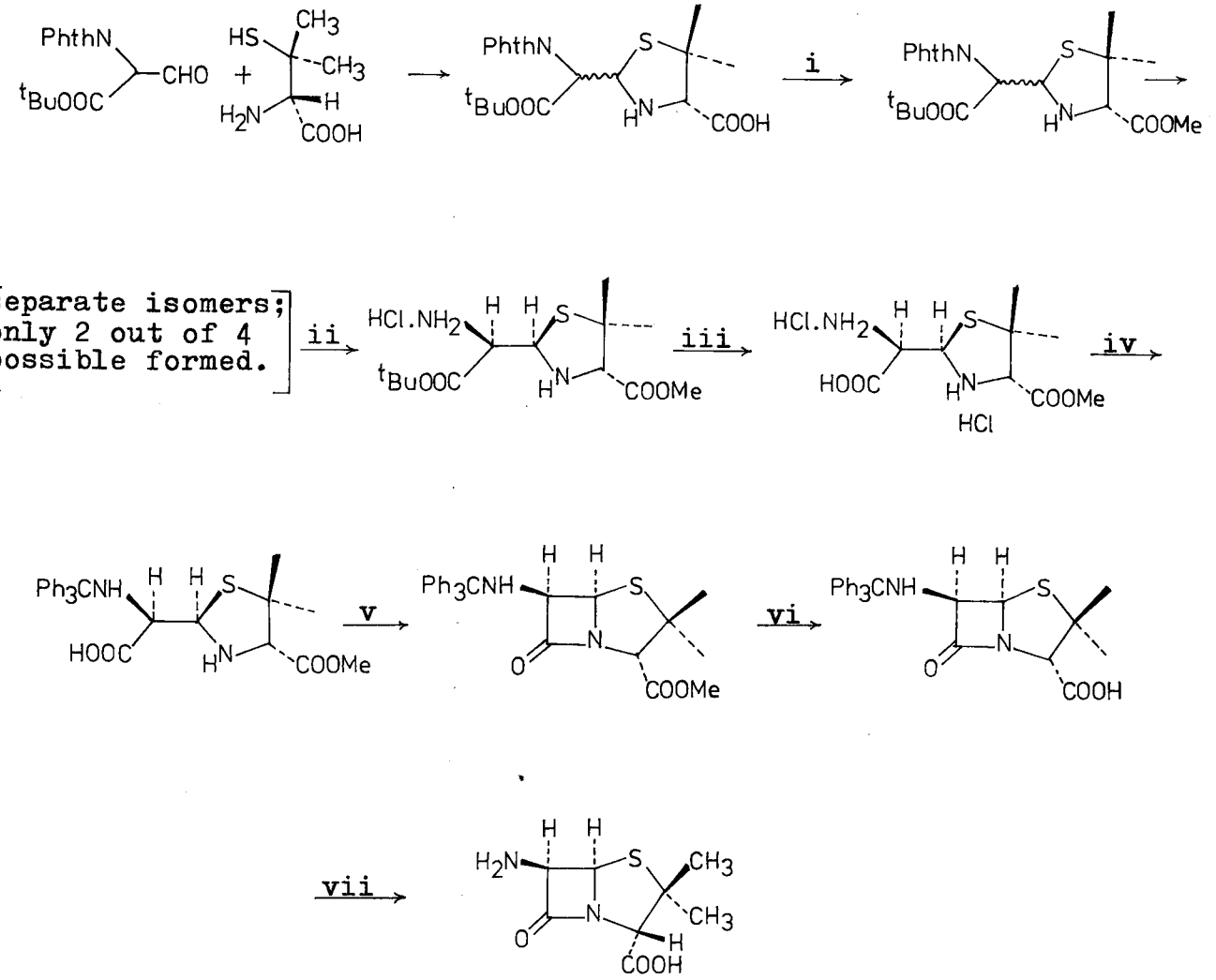
phosphorus oxychloride.[29] Oxazolone formation was precluded, but removal of the phthaloyl N-protecting group by hydrazinolysis also destroyed the nucleus. Moreover, with the monocyclic precursor of natural configuration, the acidic cyclisation reagents caused conversion to a tetrahydrothiazepinone, isomeric with XII, and originally formulated as (XIII), although more recent work suggests it probably had structure (XIV).[30,31]



The successful route[32] (scheme III) replaced the phthaloyl N-protecting group for the final stages by trityl, and used mild, non-acidic carbodiimide reagents for ring-closure. The bulky trityl group probably also favoured the cyclisation, and permitted subsequent preferential saponification of the 3-methoxycarbonyl group of the penam without destroying the β-lactam, although hydrogenolysis of the benzyl ester was the preferred method. 2N HCl in isopropyl alcohol removed the trityl group without undue β-lactam cleavage (44% yield) to give 6APA, almost before the first conclusive reports of its identification in Penicillium fermentations.

This route is in theory applicable to an infinite range of bicyclic β-lactams. However, during attempted synthesis of the dihydrocephalosporanate (XVI), Sheehan[33] found that the 2-(tetrahydro-1,3-thiazin-2-yl)-acetic acid precursor (XV) decarboxylated on purification.



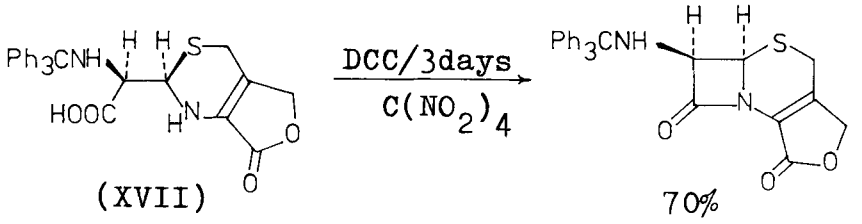


scheme III. Total synthesis of 6-aminopenicillanic acid.[32]

Reagents: i) CH_2N_2; ii) N_2H_4, HCl; iii) anhydrous HCl/0°; iv) Ph_3Cl, Et_2NH; v) $(CH_3)_2CH-N=C=N-CH(CH_3)_2$; vi) leq.NaOH, leq.$H_3O^+$; vii) HCl/iPrOH.

(PhthN = phthalimido)

Heymès, Amiard and Nominé[34] encountered another problem implied earlier in connection with cephalosporin chemistry - the lower basicity of the nitrogen atom of the dihydrothiazine ring, but by careful definition of conditions they managed to induce cyclisation of a cephalosporin C_c precursor (XVII) in good yield.



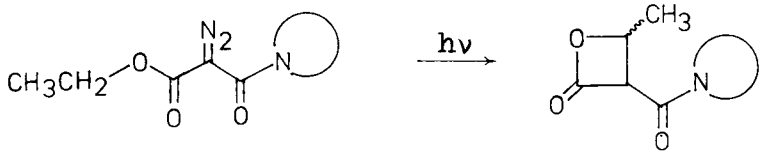
(XVII) 70%

From our experience with oxa-penams (chapter 2), the 2-(2-oxazolidinyl)-acetic acid precursor to a cyclisation by this route would probably be rather labile, and readily give a tetrahydro-oxazepinone, analogous to XIV.

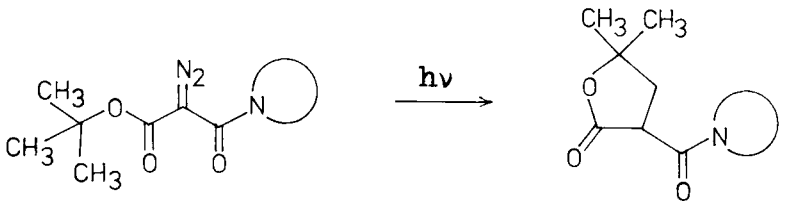
B. Lowe's method.

The synthetic approach originally demonstrated by Corey and Felix[35] but only put to effective use by Lowe,[36] involves the alternative C5-C6 cyclisation (penam numbering) of the β-lactam onto the other heterocycle. Photolysis of an α-diazoamide generates a carbene, which, at high dilution, will insert intramolecularly into a suitably disposed C-H bond. The conditions are mild and convenient, and the great contribution of Lowe was the realisation of a facile route to suitable α-diazoamides and appropriate modification of the cyclisation products. α-(Alkoxycarbonyl)diazoamides are readily prepared by acylation of an appropriate heterocycle with a malonic acid half ester and base-catalysed diazo-exchange between the resulting alkyl malonyl amide and p-toluenesulphonyl azide, e.g.[37]

There are three potential drawbacks to this method.
i) The α-(alkoxycarbonyl)diazoamides are easy to synthesise, but provide for an alternative cyclisation to that desired, leading to formation of β-lactones (XVIII) from ethoxycarbonyl and δ-lactones (XIX) from t-butoxycarbonyl derivatives.

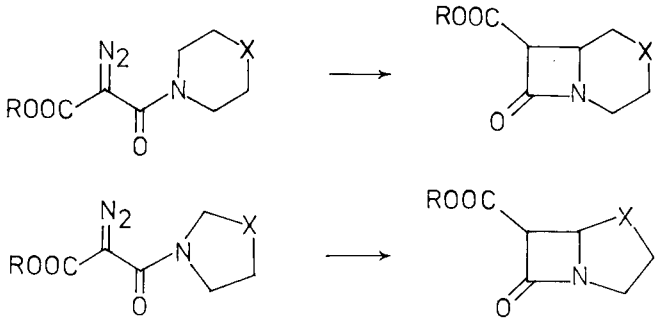


(XVIII)



(XIX)

β-Lactam formation is the favoured reaction of α-(alkoxycarbonyl)diazoamides derived from 6-membered heterocycles - piperidines and tetrahydro-1,4-thiazines. Those derived from pyrroloidines give only lactones, but insertion into the more labile C2-H bond of thiazolidines gives penams.



X = CH_2, S

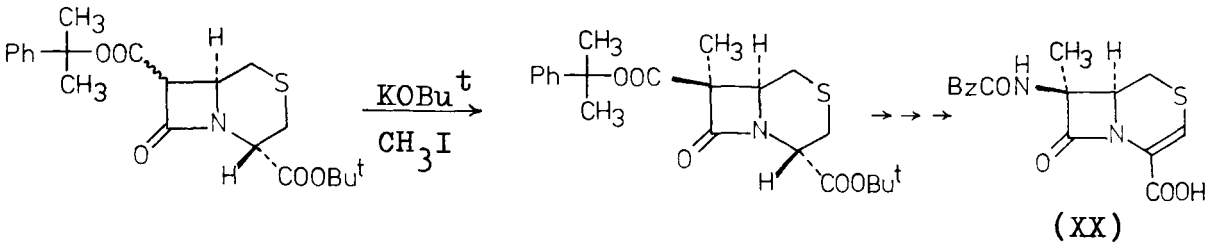
X = S
X ≠ CH_2

ii) Cyclisation gives a penam or cepham analogue with C6-or C7-alkoxycarbonyl substituent. Lowe converts these to acylamino groups by a sequence (e.g scheme IV) based on a Curtius rearrangement. Many steps are required, but all proceed in good yield and purification of intermediates is not necessary.

$$^{t}BuOOC- \xrightarrow{i} HOOC- \xrightarrow{ii} {}^{t}BuOOC.NH.NH.OC- \xrightarrow{i} H_2N.NH.OC-$$
$$\xrightarrow{iii} N_3.OC- \xrightarrow{iv} OCN- \xrightarrow{v} {}^{t}BuO.OC.HN- \xrightarrow{i} H_2N- \xrightarrow{vi} RCO.NH-$$

scheme IV. Reagents: i) TFA; ii) $^{t}BuOOC.NH.NH_2$/DCC; iii) HONO iv) heat in benzene; v) $^{t}BuOH$; vi) RCOCl.

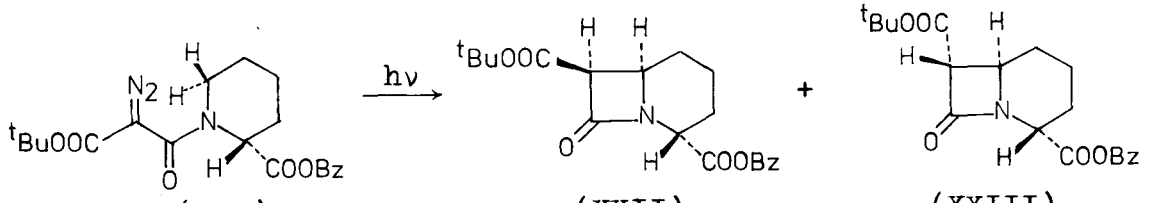
However, an advantage of the alkyloxycarbonyl group is that it allows alkylation of the adjacent carbon atom in the cyclisation product prior to modification of the side chain. This has been realised in the synthesis of a 7-α-methylcephalosporin analogue (XX).[38] Alkylation occurred exclusively at the less-hindered α-face regardless of configuration at C7 of the cyclisation product.



(XX)

iii) The cyclisation produces two new chiral centres, and a trans-arrangement of substituents on the new bond is favoured. Corey[35] obtained only a 5,6-trans-penam, but Lowe showed that both cis- and trans-isomers could be formed.

A chiral centre at one of the carbon atoms adjacent to the amidic nitrogen controls the stereochemistry of carbene insertion at the other carbon atom adjacent to the nitrogen. Cyclisation of the α-(t-butoxycarbonyl)diazoamide derived from benzyl piperidine-2-(R)-carboxylate (XXI) occurred exclusively at the least hindered C-H bond, giving only one pair of diastereomers (XXII and XXIII) with correct (R)-configuration at C6 (cepham numbering). A similar result is seen in the example above. This technique also secures the trans-arrangement of the carboxyl group and the β-lactam found in the natural penicillins.



(XXI) (XXII) (XXIII)

Application of this route to the synthesis of an oxa-penam is described in chapter 2, although modification of the 6-ethoxy-carbonyl substituent was not possible.

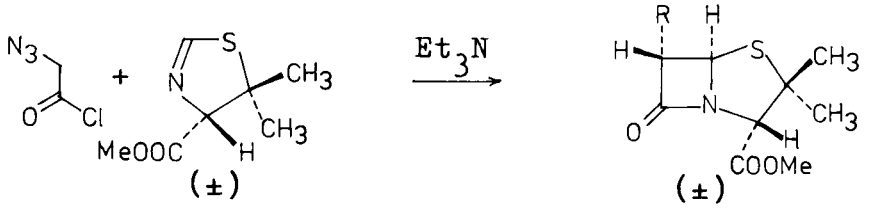
C. Bose's method.

Cycloaddition of azidoacetyl chloride and triethylamine onto a heterocyclic imine is a modification of a long-known route to β-lactams, and is discussed in detail in chapter 4. A wide range of bicyclic β-lactams has been produced by this method, and the azido group can be catalytically reduced to an amino function, although this may be complicated in the presence of sulphur.

The method suffers from being rather discriminating over substituents on the imine component - proceeding best with aryl substituents - and from the lack of stereochemical control.

Thus addition of triethylamine to a mixture of azidoacetyl chloride and methyl DL-5,5-dimethyl-2-thiazoline-4-carboxylate gave the bicyclic β-lactam (XXIV) in only 5-8% yield. Hydrogenation with excess Adam's catalyst converted XXIV to the 6-aminopenicillanate (XXV), and this was acylated with phenoxyacetyl chloride to give (XXVI) in 17% yield from XXIV.

N.m.r spectroscopy showed that H5 and H6 in the product XXVI were exclusively trans. Similarity of the spectrum of XXIV with that of methyl 6-α-chloropenicillanate suggested that in XXIV H3 and H5 were also trans, and the product XXVI was described as 6-epi-penicillin V methyl ester.[39]



(XXIV) R = N_3

(XXV) R = NH_2

(XXVI) R = $PhOCH_2CONH$

Although this is not a very efficient method, its applicability to the synthesis of an oxa-penam was investigated because of the ready availability of ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (chapter 4). No β-lactams were obtained.

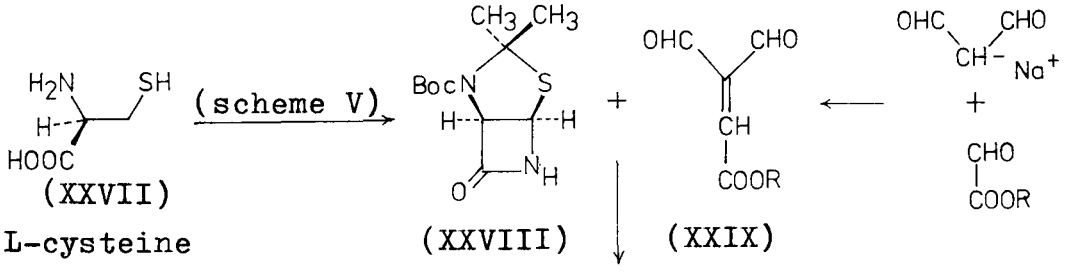
D. Woodward's method.

The Woodward cephalosporin synthesis[40a] differs fundamentally from the preceding three methods in constructing the β-lactam first, with both the chiral centres of cephalosporins already defined, and then cyclising the second heterocycle onto this.

The sequence (scheme V) has biogenetic origins in that the (S)-configuration at C7 of the product is derived from that at the α-carbon atom of L-cysteine (XXVII). The nitrogen and sulphur of the latter are jointly protected by conversion to a thiazolidine, and the nitrogen is acylated with phosgene, reaction with t-butanol

then giving the N-(t-butoxycarbonyl) (Boc) derivative. The methylene group adjacent to sulphur can be functionalised stereospecifically by heating with excess dimethyl azodicarboxylate. Subsequently free radical acetylation with lead tetra-acetate[40b] or bromination with trichloro-bromomethane[40c] have been used. These derivatives are subject to a series of stereospecific reactions to give an amino group cis to the esterified carboxyl group. Cyclisation with tri-(isobutyl)aluminium gives a stable cis-fused β-lactam-thiazolidine (XXVIII) - c.f penicillin, which is also a cis-fused β-lactam-thiazolidine, but with bridgehead nitrogen.

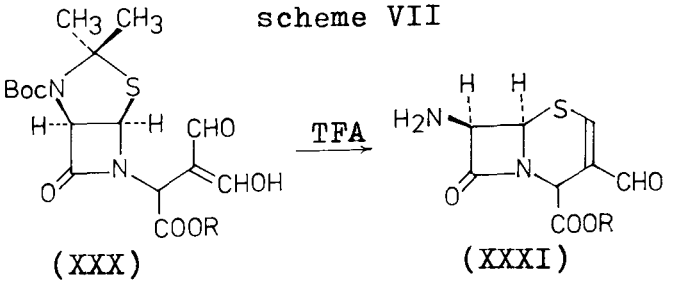
The β-lactam nitrogen in XXVIII, although amidic, is sufficiently nucleophilic to react with glyoxylic acid derivatives. In the original synthesis[40a] (scheme VII), XXVIII underwent Michael addition to the highly electrophilic α,β-unsaturated dialdehyde ester (XXIX) derived from 2,2,2-trichloroethyl glyoxylate and malondialdehyde. Treatment of the resulting adduct (XXX) with trifluoroacetic acid (TFA) removed the t-butoxycarbonyl and isopropylidene N,S-protecting groups, and also caused cyclisation through sulphur to give the dihydro-1,3-thiazine moiety of a cephem ester (XXXI). XXXI was converted to both Cephalothin and cephalosporin C.



Boc = $^{t}BuOOC-$

R = $Cl_3C.CH_2$

scheme VII



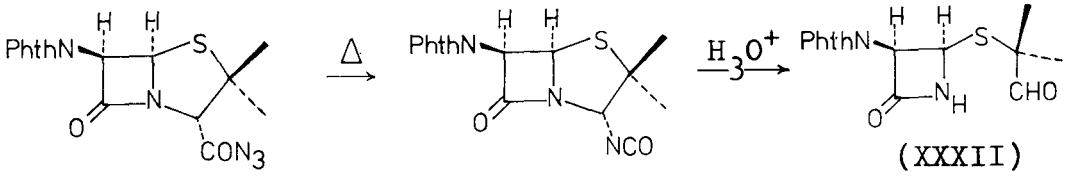
It would be extremely interesting to synthesise an oxa-analogue of XXVIII from L-serine, and to investigate its potential in synthesis of oxa-cephams and maybe oxa-penams.

lvi. Partial synthesis of β-lactam antibiotics.

Natural penicillin has now become so cheap that contemporary research has neglected the total synthesis approach in favour of developing new degradations of the penicillin nucleus that leave the β-lactam and its substitution pattern intact and with suitable 'handles' for elaborating new bicyclic β-lactam antibiotics. Mostly the sulphur substitution is retained, and this excludes such derivatives as direct precursors to oxa-analogues, but a recent report has described a product with potential in this field.

a) An example of the former type of degradation is the conversion of 6APA to the intermediate XXVIII of the Woodward cephalosporin synthesis.[41] This is described here for completeness - and for its aesthetic appeal - and also because it has made XXVIII so readily available that many transformations of this intermediate have been devised which might be applicable to an oxa-analogue derived by total synthesis from L-serine.

The sequence is based on a cleavage of the thiazolidine ring of penicillins originally discovered by Sheehan and Brandt.[42] Acid hydrolysis of the isocyanate derived from Curtius rearrangement of 6-phthalimidopenicillanyl azide gives the aldehyde (XXXII).

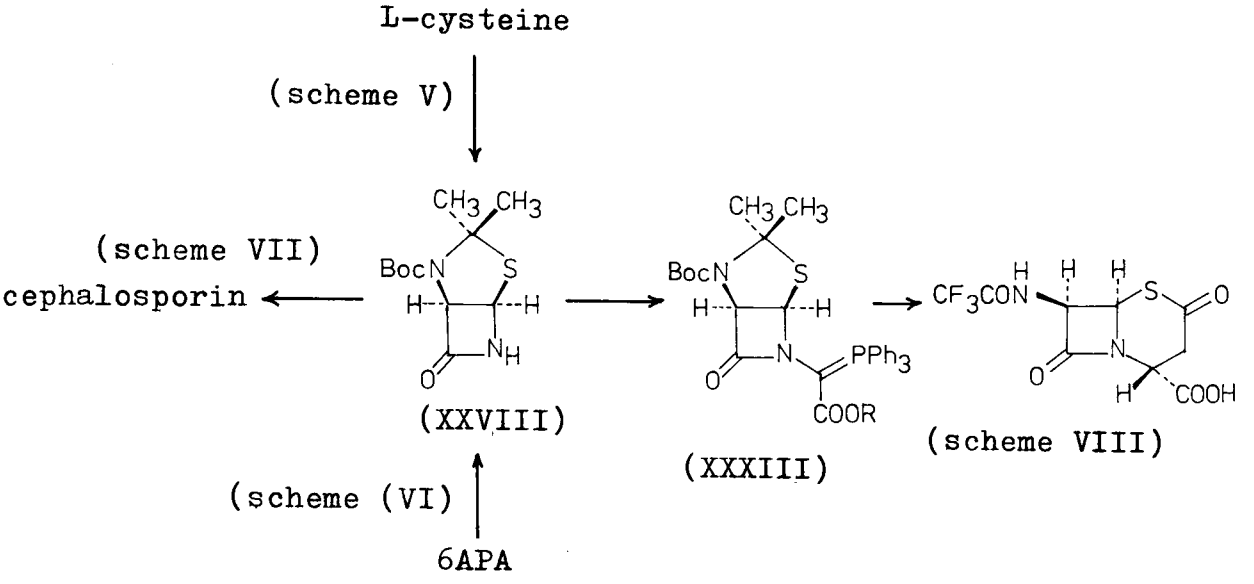


(XXXII)

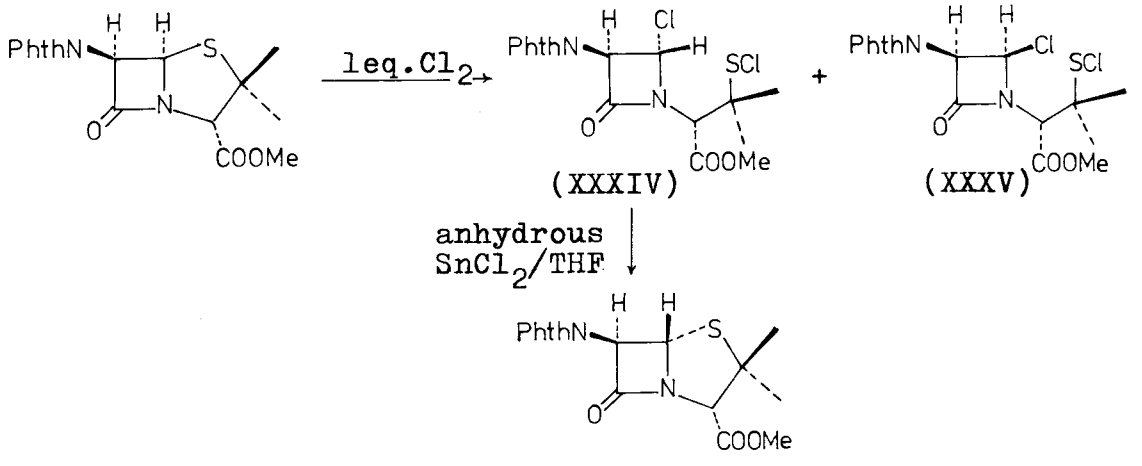
The CIBA group adapted this for application to acid-labile penicillins. Modification of the acyclic half of the thioether of the analogue of XXXII from 6-(t-butoxycarbonylamino)penicillanic acid allowed cyclisation to give XXVIII in which the gem-dimethyl group was derived from that in the original penicillanic acid[41] (scheme VI).

Many new β-lactam antibiotics have been produced from XXVIII,[25] the majority by reaction with a derivative of glyoxylic acid (c.f cephalosporin synthesis above), and conversion of the resulting carbinolamide to a phosphorane (e.g XXXIII). The latter possess the carboxyl group common to penicillins and cephalosporins,

and are more flexible precursors than XXVIII. A simple example of the general type of procedure is shown in scheme VIII.[25]



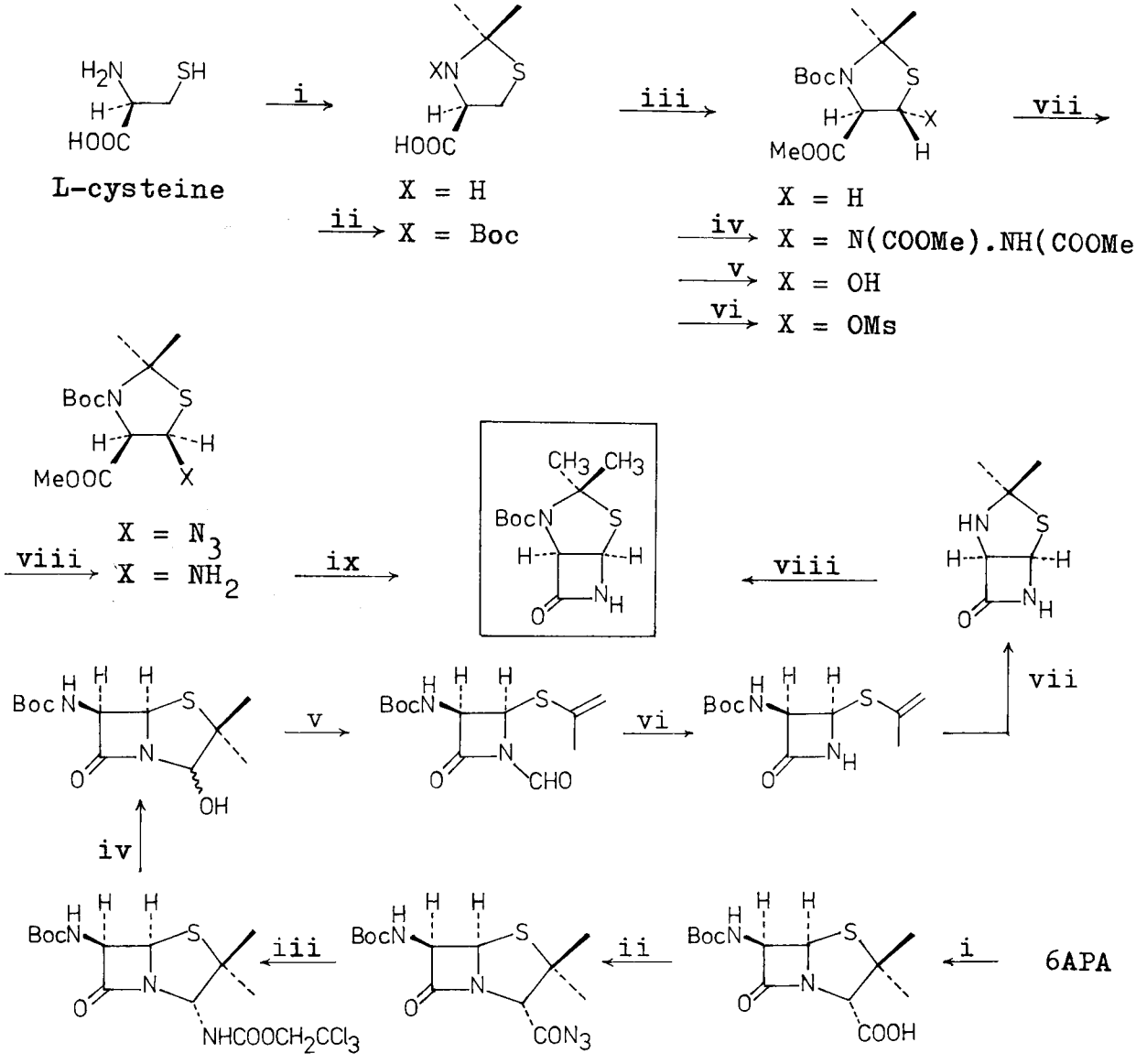
b) Reaction of methyl 6-phthalimidopenicillanate with 1 equivalent of chlorine gives epimeric 4-chloroazetidin-2-ones (XXXIV) and (XXXV).[22a] This reaction is only in its infancy as yet, and the only reported reaction is recyclisation to the C5-epimers of the starting penicillin.[22b]



If the sulphur in the chloro-β-lactams XXXIV and XXXV could be replaced by an oxygen anion, this could provide precursors to an oxa-penam or oxa-cepham.

scheme V.[40a]

Reagents: i) $(CH_3)_2CO$; ii) $COCl_2$, t-BuOH; iii) CH_2N_2; iv) excess $(=NCOOMe)_2$/105°; v) $Pb(OAc)_4$, NaOAc/MeOH; vi) MsCl/pyridine; vii) NaN_3; viii) Al/Hg, MeOH/-15°; ix) $(iBu)_3Al$.

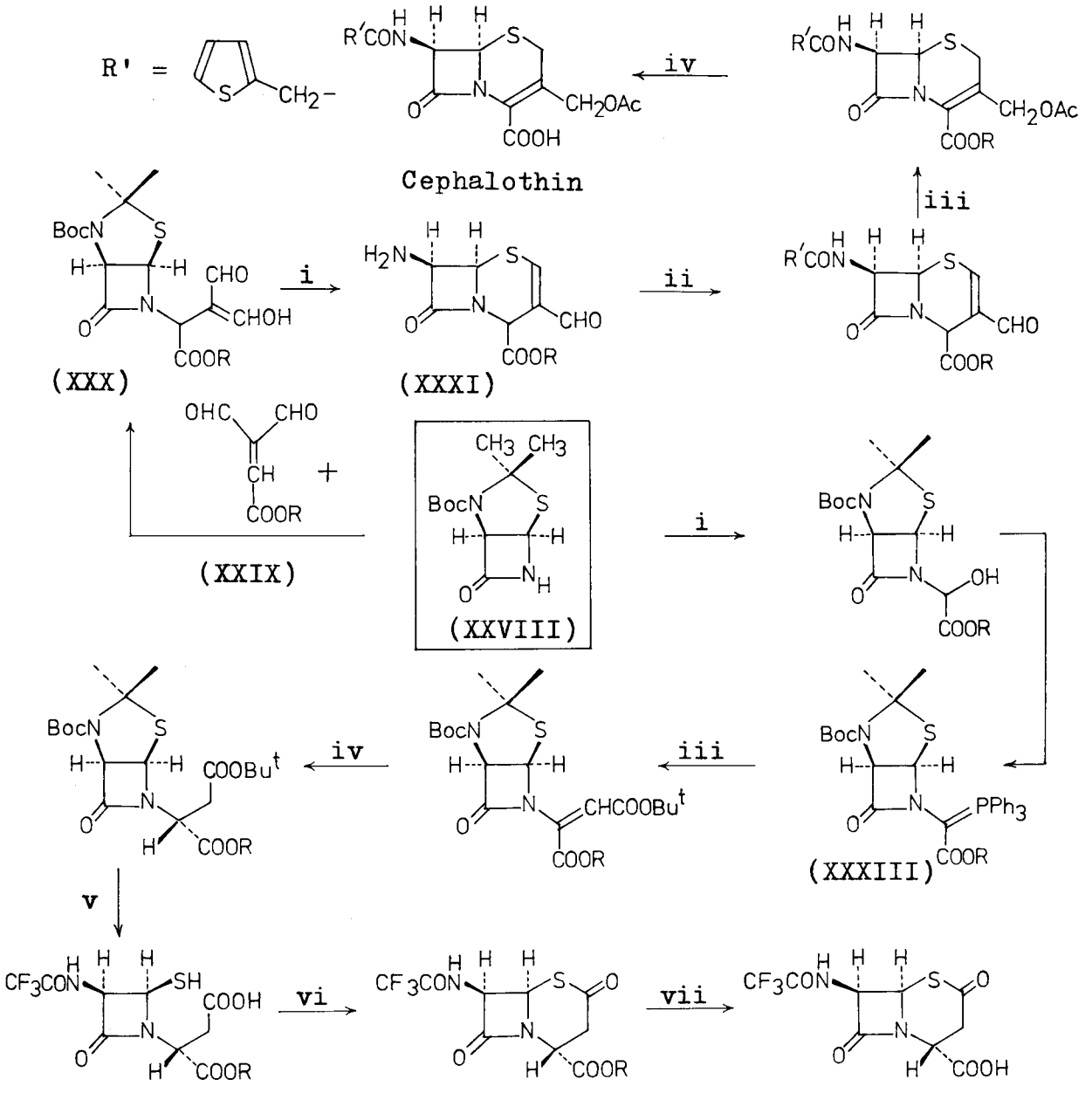


Reagents: i) ^tBuOCOF; ii) ClCOOEt/Et_3N; NaN_3; iii) heat in benzene + CCl_3CH_2OH; iv) Zn/HOAc; v) $Pb(OAc)_4$/benzene/hν; heat 90°/17hr; vi) NH_4OH; vii) TFA; viii) $COCl_2$, ^tBuOH.

scheme VI.[41]

scheme VII[40a]

Reagents: i) TFA; ii) R'COCl; iii) B_2H_6; Ac_2O/pyridine; iv) Zn/HOAc. (R = CH_2CCl_3)



Reagents: i) ROOC.CHO; ii) $SOCl_2$/pyridine; PPh_3/pyridine; iii) $^tBuOOC.CHO$; iv) $Co(CO)_4H$; v) TFA; $(CF_3CO)_2O$; vi) Ac_2O; vii) Zn/HOAc. (R = CH_2CCl_3).

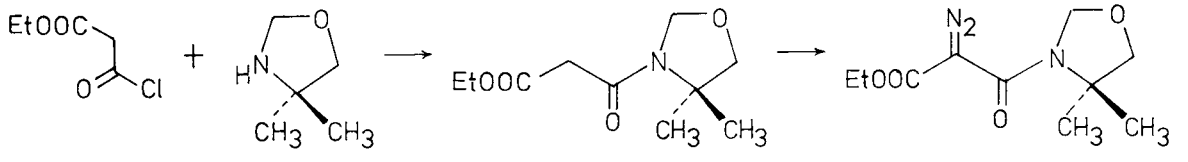
scheme VIII[25]

Chapter 2
SYNTHESIS AND SOME PROPERTIES OF AN OXA-PENAM.

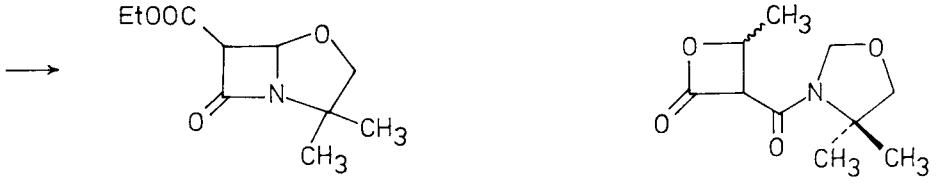
As a route to bicyclic β-lactams under the mildest of conditions, the photocyclisation of α-diazoamides[36] was considered to be a good test for the existence of an oxa-penam. Carbene insertion into the C2-H bond of an oxazolidine should be facile.

A number of N-acyl-4,4-dimethyloxazolidines had already been synthesised (chapter 3), and N-ethoxycarbonylacetyl-4,4-dimethyloxazolidine (I) was easily prepared from the oxazolidine and ethyl malonyl chloride. Diazo-exchange (p-toluenesulphonyl azide/Et_3N/CH_3CN) gave the corresponding α-diazoamide (II) as low melting point yellow needles. Attempts at diazo-exchange reactions with derivatives of cyanoacetic acid gave rapid reaction resulting in mixtures of several highly-coloured products.

Photolysis of α-diazoamide II in dilute solution in carbon tetrachloride (100mg/12ml) under nitrogen in Pyrex tubes strapped to the water-cooled probe of a medium pressure mercury u.v lamp was monitored by i.r spectroscopy. The diazo band (2135 cm^{-1}) disappeared completely within 2 hours, and bands at 1790 and 1737 cm^{-1} replaced the starting ester (1712 cm^{-1}) and amide (1630 cm^{-1}) carbonyl absorptions. The spectrum was that expected for the oxa-penam (III) - 1-aza-4-oxa-2,2-dimethyl-6-ethoxycarbonyl-bicyclo[3.2.0]heptan-7-one, but penam numbering is used throughout.



(I) (II)



(III) (IV)

The i.r absorption at 1790 cm^{-1} was assigned to the β-lactam of III. It was not due to the β-lactone carbonyl of the alternative cyclisation product (IV) as shown by the subsequent chemical transformations. Such β-lactones absorb at c. 1810 cm^{-1} (ref.43) and a very weak shoulder was in fact present at 1820 cm^{-1} in the spectrum of the reaction mixture, along with a weak amide carbonyl absorption at 1670 cm^{-1}.

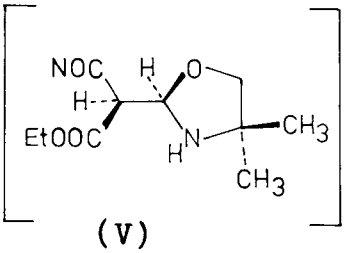
On addition of one mole equivalent of benzylamine to the dilute solution after photolysis was complete, reaction was rapid, as judged from the i.r spectrum, and compound (VI) was isolated by p.l.c in 60% yield. Compound VI is clearly derived from oxa-penam III by nucleophilic attack at the β-lactam and eliminative fragmentation of the oxazolidine ring.

Reaction of III with methanol was very much slower. A photolysis mixture was evaporated <u>in vacuo</u> to 0.5ml. The i.r spectrum was unchanged, and the reaction with 1.5 mole equivalents of methanol was monitored by n.m.r spectroscopy. Integration of the signal at τ4.69 (see below) showed that 50% of oxa-penam III was still present after 18 hours at room temperature, and 20% after a further hour at 60°. After 2 hours at 60°, the acyclic diester (VII) was isolated by p.l.c in 50% yield.

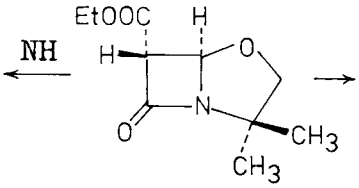
An optimistic attempt at chromatography of oxa-penam III gave only the half ester (VIII).

The i.r spectrum of a dilute photolysis reaction mixture was unchanged after standing at 0° for 12 hours, but after 36 hours at room temperature showed complete disappearance of the β-lactam band. T.l.c indicated a number of compounds to be present, but the only one isolated in significant amount (20%) was highly crystalline, and assigned the 2,3,4,7-tetrahydro-1,4-oxazepin-7-one structure (X) on the basis of its i.r and n.m.r spectra. However, the mass spectrum suggested that the compound was a dimer, presumably (XI) (M^+ at m/e 426, B at m/e 214; for X, $C_{10}H_{15}NO_4$ requires M = 213).

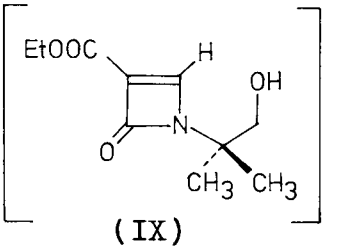
Addition of one mole equivalent of triethylamine to the photolysis reaction mixture caused no change in the i.r spectrum after 20 minutes at room temperature.



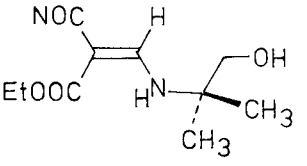
(V)



5,6-trans-(III)



(IX)

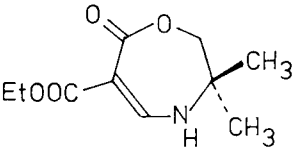


(probable configuration)

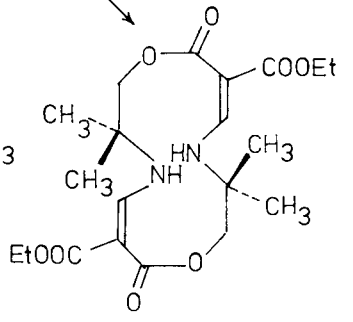
(VI) N = $NH.CH_2Ph$

(VII) N = OCH_3

(VIII) N = OH



(X)



(XI)

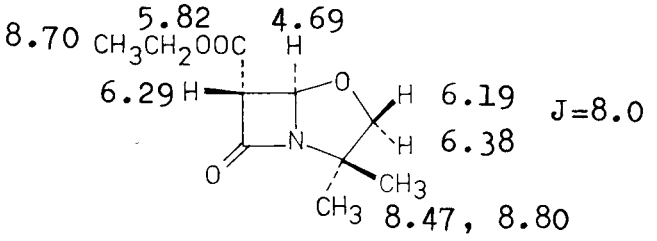
The major product of irradiation of the α-diazoamide II is certainly the oxa-penam III, probably formed in about 60% yield. The n.m.r spectrum of the reaction mixture, evaporated in vacuo to 0.5ml, was studied in detail, but the assignments are still somewhat speculative. The prominent features are an AB quartet (J=8.0Hz, component doublets centred at τ6.19 and τ6.38), assigned to the ring methylene protons of III, and a doublet (J=1.0Hz) at τ4.69. The latter is assigned to H5 of III (c.f C2-H_2 of N-acyloxazolidines at c. τ5.0 (chapter 3)), and the low coupling constant indicates trans-configuration of H5 and H6.[44] Assuming this assignment is correct, this single proton signal integrates for 55% of the total mixture, suggesting that the oxa-penam product has almost exclusively the 5,6-trans-configuration.

The AB quartet covers a doublet (J=1.0) at τ6.29. Double irradiation of the doublet at τ4.69 converted that at τ6.29 into a sharp singlet, and the latter is hence assigned to H6 (c.f chemical shifts for similar examples in ref. 43).

The doublet splitting of the H5 resonance at τ4.69 is barely defined at 60MHz compared with that of the signal at τ6.29 due to H6. This is probably the result of long-range 'W-coupling' of H5 with the cis-ring methylene proton at C2, and, in agreement with this, one of the doublets of the AB quartet (that to higher

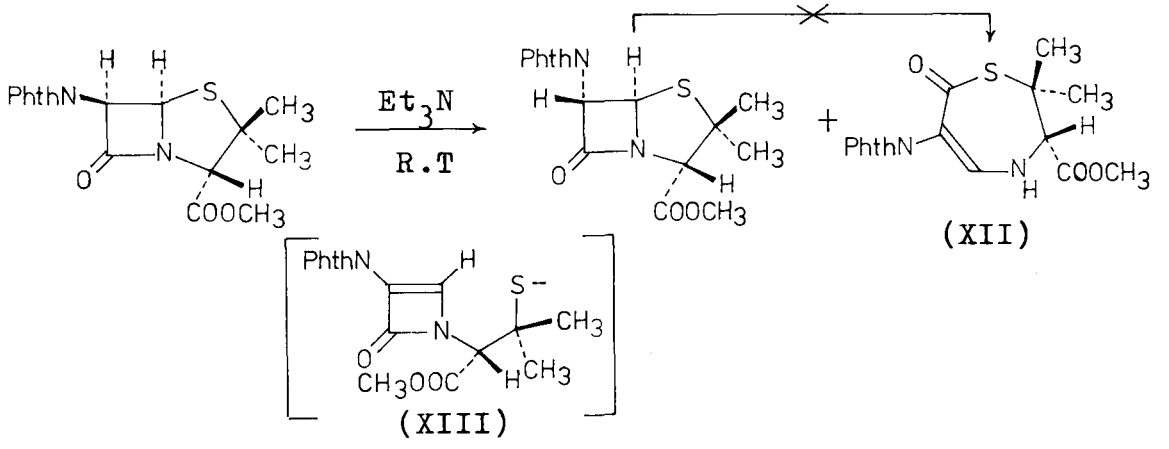
field) is appreciably broader than the other. A similar effect is clearly seen in the spectra of 2-substituted-N-acyl-4,4-dimethyl-oxazolidines (chapter 4, e.g fig 7).

Singlets at τ8.47 and τ8.80 integrate correctly for the C3-methyl groups of III, and the major triplet (τ8.70) and quartet (τ5.82) correspond to the ethyl ester grouping.



n.m.r data for 5,6-trans-(III) ($\tau(CCl_4)$).

Formation of the oxazepinone X or dimer XI presumably proceeds via the monocyclic enol (IX). Treatment of certain penicillin esters with triethylamine causes epimerisation at C6 and formation of thiazepinones, e.g (XII)[45]. The latter, and possibly the former, involves the ene-thiolate (XIII) formed by β-elimination, which can only occur when H6 and sulphur are in trans-anti-trans relationship, as in the natural epimer. The 6-epi-penicillanate only gives the thiazepinone under forcing conditions.

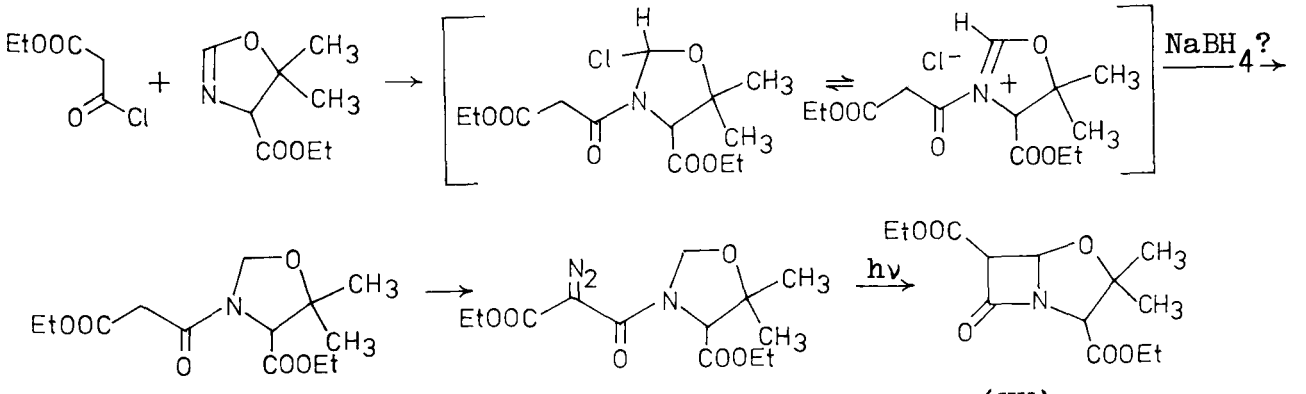


It is difficult to see why the enol IX from oxa-penam III should react intermolecularly. In the penicillanates the gem-dimethyl group adjacent to sulphur could favour cyclisation of the ene-

thiolate XIII and disfavour an intermolecular reaction. Molecular weight data in some,[46] but not all reports, exclude the possibility of the thiazepinones, e.g XII, in fact being dimers analogous to XI. The 14-membered ring of dimer XI would not seem a particularly favourable product, especially under the dilute conditions of the transformation. The high crystallinity of the product (m.p 209°) also argues against structure XI, and an independent molecular weight determination is awaited before confirming structure X or XI.

The conversion of oxa-penam III to the enol IX must be autocatalysed or caused by some basic species in the crude reaction mixture. If III has the 5,6-trans-configuration, this cannot involve a concerted β-elimination, and must occur by an E_1 mechanism, favoured by the acidic H6-proton, α- to two carbonyl groups. 2-Substituted-N-acyloxazolidines in which such a fragmentation is not available are rather stable (chapter 4), and it may be that the susceptibility of oxa-penam III to opening of the oxazolidine ring is an example of the instability of 6-alkoxycarbonylpenams in general. An oxa-penam with different 6-substitution making H6 less acidic might be very much more stable to oxazolidine cleavage while retaining the highly reactive β-lactam as in III.

It is hoped to prepare the thia-analogue of III, and also to make an oxa-penam (XV) with penicillin-like substitution via the α-diazo derivative of ethyl N-ethoxycarbonylacetyl-5,5-dimethyl-oxazolidine-4-carboxylate (XIV). The latter should be available by reduction of the adduct of ethyl malonyl chloride and ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (chapter 4). Direct comparisons could then be made to establish the significance of the 6-ethoxy-carbonyl substituent in III.



(XIV) (XV)

Reaction of nucleophiles with oxa-penam III presumably proceeds by initial attack at the β-lactam carbonyl carbon to give derivatives of the oxa-penicilloic acid analogue (V). If the reaction involved the monocyclic enol IX then, at least in the slow reaction with methanol, the alternative transformation to X or XI would be expected to be a competing reaction. However, none of the alternative product was observed in these reaction mixtures. The oxa-penicilloic acid derivatives V were also not observed, and free rotation about their C5-C6 bond would allow the ensuing elimination to be stereospecifically trans-anti-trans. The configuration about the double bond in the products VI-VIII would then be determined by the relative configuration at C5 and C6 in the starting material III.

The n.m.r spectrum of the ethyl, methyl diester VII showed two groups of signals for both ester groups ($COOC\underline{H}_3$ at τ6.27 and τ6.35, ratio 55:45; $COOC\underline{H}_2CH_3$ at τ5.79 and τ5.87, and $COOCH_2C\underline{H}_3$ at τ8.69 and τ8.75, higher field signals stronger than lower field). It was first thought that this indicated a 55:45 mixture of the two double bond isomers of VII - i.e a 55:45 cis/trans or trans/cis ratio in III. However, III has predominantly, if not exclusively, the 5,6-trans-configuration, and the above features of the n.m.r spectrum of VII must be due to restricted rotation around the ROOC-C= bonds. Spectra of VI and VIII showed only one set of signals for the ethyl ester grouping even before crystallisation.

EXPERIMENTAL.

Ethyl malonyl chloride.

The literature preparations of ethyl malonyl chloride (reaction of malonic acid half ethyl ester with phthaloyl chloride,[47] or short exposure of the half ester or its salt to thionyl chloride[48] were not found to be satisfactory.

The reaction of malonic acid half ethyl ester with freshly-distilled thionyl chloride (1.2 mole equivalents) at 60-70° was followed by n.m.r spectroscopy of samples of the neat reaction mixture, and was not complete until after 1.5 hours. After 2 hours, fractionation of the mixture gave ethyl malonyl chloride (72%), b.p 60°/8mm.

N-Ethoxycarbonylacetyl-4,4-dimethyloxazolidine (I).

A solution of ethyl malonyl chloride (3.74g, 24.8mM) in dry dichloromethane (25ml) was added dropwise to a stirred, ice-cooled mixture of 4,4-dimethyloxazolidine (2.1g, 21mM) and sodium carbonate (3.0g, 29mM) in dichloromethane (20ml). The resulting mixture was stirred at room temperature for 1 hour, refluxed for 15 minutes, and then filtered. The filtrate was washed with 5% citric acid solution and water before drying and evaporating to give 3.70g (85%) of an oil that was quite pure by t.l.c and n.m.r.

Attempted distillation caused extensive decomposition with a small pure sample at 116°/0.1mm. The crude product could be purified by chromatography on silica gel in benzene and 5% and 10% EtOAc/benzene, but was subsequently found to be pure enough for use in the next step.

i.r (film) 2980w,2940w,2865w,1740s,1660s cm^{-1}.

n.m.r (CCl_4) τ8.55 (s,6H) 6.26 (s,2H)
8.73 (t,J=7.0,3H) 5.83 (q,J=7.0,2H)
6.81 (s,2H) 5.01 (s,2H)

N-(Ethoxycarbonyl)diazoacetyl-4,4-dimethyloxazolidine (II).

To the crude reaction product from above (2.15g, 10mM if pure) in acetonitrile (15ml) was added triethylamine (1.1g, 11mM) and p-toluenesulphonyl azide[49] (2.0g, 11mM), and the mixture left at room temperature for 24 hours. The reaction mixture was then

evaporated on a rotary evaporator, and the residue treated with 5N NaOH solution (4ml) and extracted with ether. The extracts, dried and evaporated, gave a yellow oil (2.5g). Chromatography on silica gel in benzene and 5% EtOAc/benzene gave unreacted p-toluenesulphonyl azide in the first fractions, and the product as a golden yellow oil (1.54g, 64%) that crystallised on storing in the refrigerator.

The material was unchanged after 6 months in a stoppered vial at 0°C.

m.p 30°.

i.r (CCl_4) 2975m,2935w,2895w,2845w,2135s,1710s,1630s cm^{-1}.

n.m.r (CCl_4) τ8.71 (t,J=7.0,3H) 5.73 (q,J=7.0,2H)
8.47 (s,6H) 4.98 (s,2H)
6.23 (s,2H)

u.v (MeOH) 212nm (ε14,420) 366nm (ε627)
255nm (ε10,200)

m.s m/e 226(1.8) (M-15), 213(2.3) (M-28), 196(4.5), 183(14), 141(18), 123(18), 114(27), 100(B).

$C_{10}H_{15}N_3O_4$ C49.78, H6.27, N17.42% (241.24)
found C50.42, H6.24, N14.97% (nitrogen deficient.)

Formation and reactions of 1-aza-4-oxa-2,2-dimethyl-6-ethoxycarbonyl-bicyclo[3.2.0]heptan-7-one (III).

Conditions for photocyclisation of the α-diazoamide II to oxa-penam III were described in the text, as were details of the reactions of III. The products were isolated by p.l.c, using multiple development with EtOAc/benzene 1:1, and all recrystallised well from petrol (60-80°).

N-(3-(2-(1-Hydroxy-2-methylpropyl)amino)-2-ethoxycarbonylacryloyl)-N-benzylamine (VI).

m.p 87-88°

i.r (CH_2Cl_2) 3605w,3420w,3315m,1660vs,1640vs,1590s,1530s cm^{-1}.

n.m.r ($CDCl_3$) τ8.73 (t,J=7.0) ┐ total 9H 5.49 (d,J=6.0,2H)
8.72 (s) ┘ 2.68 (s,5H)
7.27 (br,1H) 1.87 (d,J=14.0,1H)
6.56 (s,2H) 0.78 (br,1H)
5.82 (q,J=7.0,2H) -0.66 (d,J=14.0,1H) br

u.v (MeOH) 231nm (ε14,925)
285nm (ε29,850)

m.s m/e 320(19) [$C_{17}H_{24}N_2O_4$](M), 289(35), 243(9) (289-46*), 214(24), 182(62) (289-101*), 149(32), 148(37), 142(11), 106(19), 91(29), 77(17), 57(13), 44(19), 28(B).

$C_{17}H_{24}N_2O_4$ C63.73, H7.55, N8.74%
found C64.12, H7.56, N8.57%

Methyl 3-(2-(1-hydroxy-2-methylpropyl)amino)-2-ethoxycarbonylacrylate (VII).

m.p 86-88°

i.r (CH_2Cl_2) 3610m,3420w(br),3255w,3180w(br),1697s,1670s,1655s, 1608s cm^{-1}.

n.m.r ($CDCl_3$) τ8.75 (t,J=7.0) and 8.69 (t,J=7.0) ┐
8.69 (s) ├ total 9H
6.83 (br,1H)
6.50 (s,2H) br
6.35 (s) and 6.27 (s) ratio 45:55, total 3H.
5.87 (q,J=7.0) and 5.79 (q,J=7.0) total 2H
1.88 (d,J=14.7,1H)
0.45 (d,J=14.7,1H) br

u.v (MeOH) 226nm (ε11,480)
281nm (ε21,050)

m.s m/e 245(17) (M), 214(45), 182(45), 168(55), 136(18), 128(12), 110(11), 82(21), 68(25), 55(23), 53(20), 45(25), 43(20), 42(40), 41(30), 31(95), 29(B).

$C_{11}H_{19}NO_5$ C53.86, H7.81, N5.71%
found C54.15, H7.76, N5.80%

3-(2-(1-Hydroxy-2-methylpropyl)amino)-2-ethoxycarbonylacrylic acid (VIII).

m.p 104°

i.r (CH_2Cl_2) 3610m,3500-3000w,1688s,1603s cm^{-1}.

n.m.r ($CDCl_3$) τ8.68 (t,J=7.0) ┐
8.65 (s) ├ total 9H
6.45 (s,2H) br
5.74 (q,J=7.0,2H)
1.89 (d,J=15.0,1H)
-0.11 (br,1H)

2,3,4,7-Tetrahydro-3,3-dimethyl-6-ethoxycarbonyl-1,4-oxazepin-7-one (X), or dimer (XI).

m.p 209°.

i.r (CH_2Cl_2) 3260w,1708s,1658s,1607s cm^{-1}.

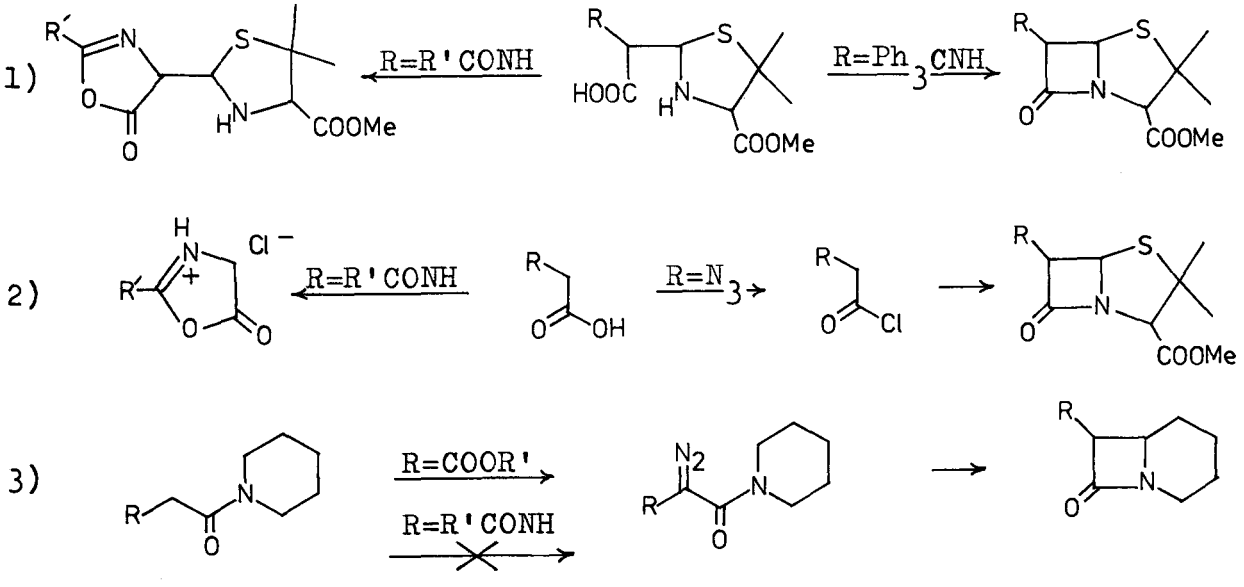
n.m.r ($CDCl_3$) τ8.65 (t,J=7.0) ┐
8.60 (s) ┘ total 9H
5.90 (s) ┐
5.72 (q,J=7.0) ┘ total 4H
1.44 (d,J=14.0,1H)
0.64 (d,J=14.0,1H)

u.v (MeOH) 222nm (ε12,000) 290nm (ε8,480) sh
273nm (ε19,600)

m.s m/e 426(43) [$C_{20}H_{30}N_2O_8$], 396(32), 395(20), 381(17), 380(11), 214(B), 183(70), 182(90), 168(33), 142(47), 110(43), 82(50), 58(70), 55(77).

Chapter 3
SOME NOVEL OXIDATIONS

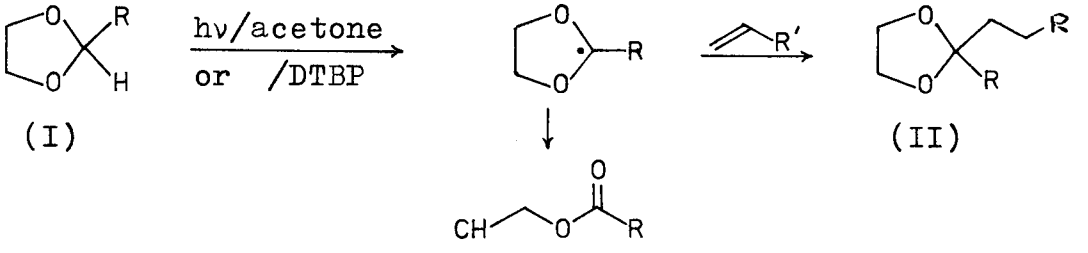
The major problem in any synthetic route to penicillins relying on fusion of a β-lactam onto a preformed thiazolidine has been the seeming incompatability of techniques for ring closure and a suitable side chain at C6. Formation of the β-lactam amide bond as in Sheehan's route (1) is not possible with an acylamino function at C6 as this provides for competing oxazolone formation, and for the same reason α-acylamino-acyl chlorides and ketenes cannot be made for the type of cycloaddition used by Bose (2). The particular contribution of these authors has been the development of substituents compatible with the chosen method of ring closure, and capable of modification to an acylamino group at C6. Photocyclisation of α-diazoamides would possibly not be complicated by the presence of a preformed acylamino substituent, but here the problem is the synthesis of the precursor α-diazoamides (3). α-Alkoxycarbonyl-α-diazoamides are readily prepared from the alkyl malonyl amides by base-catalysed diazo-exchange, and after cyclisation the alkoxycarbonyl group can be converted to an acylamino side chain by a many-step process that is apparently high yielding and not nearly so cumbersome as it appears.



There is obviously a need for a route to penicillins in which the potential acylamino side chain does not have to be heavily disguised. The Woodward cephalosporin synthesis used the sulphur substituent on the prospective β-lactam to assist in protection of the amino substituent (and vice versa), and these were together deprotected after formation of the monocyclic β-lactam.

However, we proposed a route to penams or cephams that actually required the presence of an acylamino side chain to succeed.

The C2-atom of cyclic 1,3-acetals readily loses a hydrogen radical to form a radical stabilised by the two adjacent heteroatoms. Mixtures of dioxolans (I) and olefins are converted to the 2-alkyldioxolans (II) in the presence of photoexcited acetone[50] or thermally decomposing di-t-butyl peroxide (DTBP)[51]. The radical initiator abstracts a hydrogen from C2 of the dioxolan, and the resultant radical is captured by the olefine, and lesser yields of products formed via radical formation at C4(5) may also be formed[52]. In the absence of olefin, ring-opening to give acyclic ethyl esters (III) occurs[53].

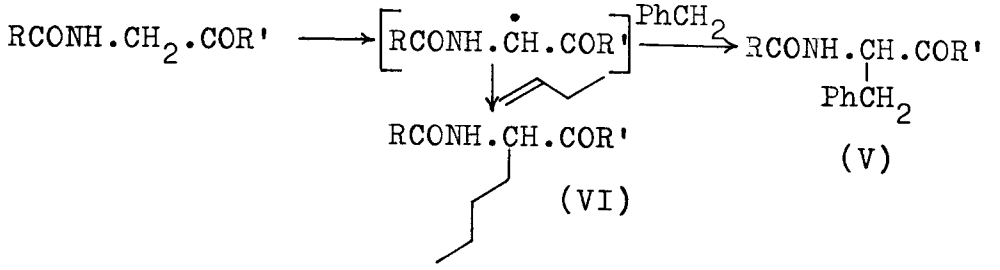


(I) (II) (III)

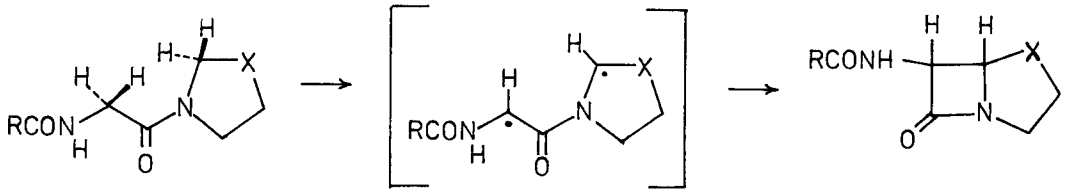
C2 in oxazolidines, and especially thiazolidines, should provide an equally good potential radical centre.

Elad has reported considerable success in photochemical modification of glycine-containing peptides. A radical initiator abstracts a hydrogen radical from the glycine α-methylene group, and the resultant peptide radical (IV) can react with benzyl radicals or butene to convert the glycyl residue to a

phenylalanyl (V) or nor-leucyl (VI) residue respectively. u.v irradiation of acetone[54] and decomposition of DTBP induced by α-diketones in the presence of visible light[55] have been used to provide the hydrogen abstraction agents in these reactions.



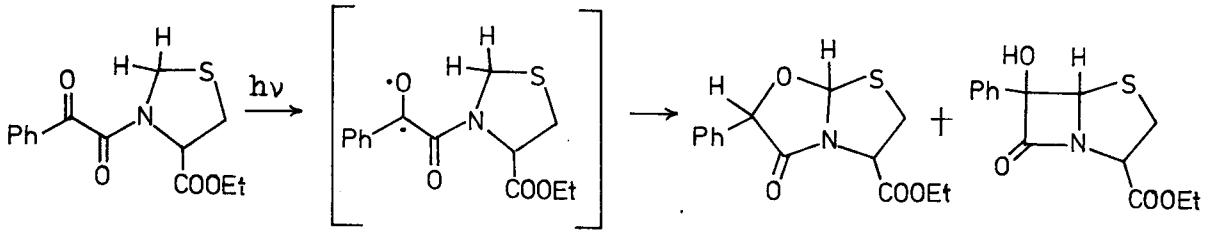
Combination of the foregoing experimental observations provides a potential route to penams and oxa-penams via intramolecular reaction of a biradical derived from an N-(N'-acyl-glycyl)-thiazolidine or oxazolidine (VII).



(VII) X = S, O

Such a reaction requires the generation of a biradical; but the photochemical conversion of glycyl to phenylalanyl residues above requires the simultaneous production of the peptide and benzyl radicals in close proximity, and then intermolecular reaction of the two radicals, whereas closure of the penam precursor would be intramolecular. The proposed cyclisation would result in loss of amide resonance present in the acyclic precursor VII, but a similar situation does not prevent cyclisation of the carbenes derived by photolysis of α-diazoamides.

The only reported route to penams via a radical reaction is the photochemical cyclisation of an N-(phenylglyoxalyl)-thiazolidine (VIII)[56]. Photoexcitation of the α-carbonyl group provided the hydrogen abstraction agent and the centre with which the resultant 2-thiazolidinyl radical could react. Cyclisation through oxygen gave (IX) (22%) and through carbon gave the 6-hydroxypenam (X) (8%).



(VIII) (IX) (X)

This reaction provides something of a precedent for the proposed cyclisation, and also shows that such products are stable under u.v irradiation. The authors did not specify the stereochemistry of the product X, and these routes to penams, generating two asymmetric centres, would probably give the unnatural isomers for reasons discussed in chapter 1. Useful amounts of the natural isomers might be produced, especially in the case of oxa-penams where interaction of an endo-C6-substituent with oxygen is less than with sulphur.

A number of N-acyloxazolidines were prepared as possible precursors to oxa-penams, and three methods were investigated in attempts to induce the desired oxidative ring closure:

i) photosensitised oxidation analagous to Elad's work, using a) u.v. irradiation and acetone,
and b) induced decomposition of DTBP by biacetyl under visible irradiation.

ii) chemical initiation by thermally decomposing azo-bis-isobutyronitrile (ABIN).

iii) oxidation by nickel peroxide (NiPO), a powerful oxidising agent[57], known to act by radical mechanisms. Biradical formation might be facilitated by reaction on the reagent surface.

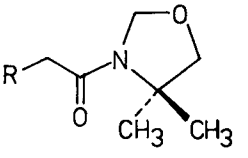
The reaction hoped for has not been achieved. The above predictions were verified in that products derived from both of the postulated radical centres were obtained, and the fears confirmed that the difficulty of forming a biradical and/or the energy increase on cyclisation might prevent the reaction.

Preparation of precursors.

The parent oxazolidine readily trimerises on attempted formation from ethanolamine and formaldehyde,[58] but oxazolidines with C4 fully substituted are more stable. 4,4-Dimethyloxazolidine was readily prepared, and was selected as precursor to a model oxapenam. While stabilising the heterocycle, the gem-dimethyl substituent adjacent to nitrogen also hindered N-acylation. The latter could not be achieved using N,N'-dicyclohexylcarbodiimide (DCC) as coupling agent, but use of the acyl chlorides was successful.

N-Chloroacetyl-4,4-dimethyloxazolidine (XIb) provided a route to (XId) via (XIc), and to (XIe) and (XIf) by direct displacement of chlorine. The N-(N'-trifluoroacetyl-aminoacetyl) derivative (XIg) was prepared from N-trifluoroacetylglycyl chloride and the oxazolidine. Thus a range of N-acetyl-4,4-dimethyloxazolidines (XI) was prepared, having α-acetyl substituents designed to stabilise a radical centre at the α-carbon atom of the N-acetyl group.

XIa	R =	H
b		Cl
c		NH_2
d		PhCONH
e		CN
f		I
g		CF_3CONH

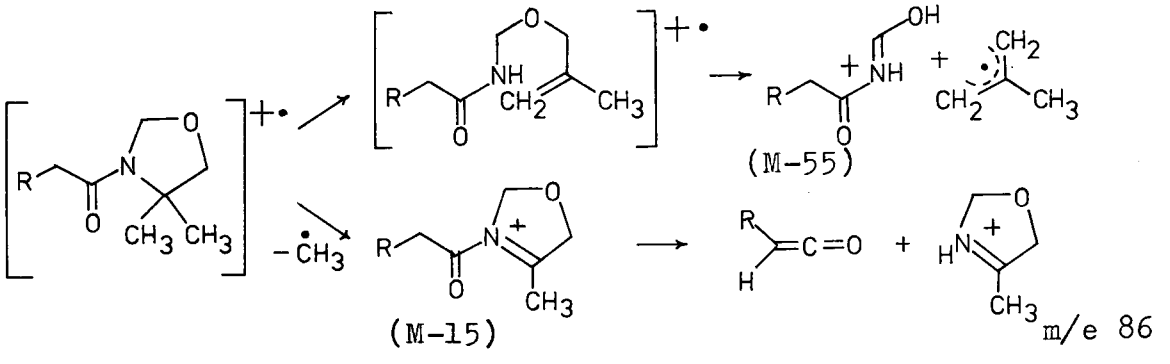


(XI)

These N-acyl-4,4-dimethyloxazolidines XI were characterised in the n.m.r spectra by a sharp singlet resonance (2H) at c. τ5.0 due to the protons at C2 of the oxazolidine ring (useful in checking reaction mixtures for the presence of starting material).

The i.r spectra showed a conspicuous absorption at c. 2870 cm^{-1}, presumably due to the C2-H bond stretch.

The mass spectra typically showed loss of a methyl allyl radical from the molecular ion (M-55), and/or loss of one methyl radical and then elimination of a ketene to give an ion at m/e 86.



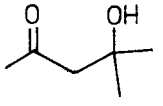
(M-55)

(M-15)

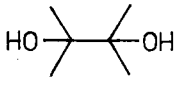
m/e 86

3i. PHOTOCHEMICAL OXIDATIONS.

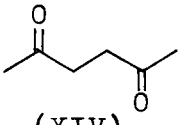
Initial experiments were performed by irradiating the N-acyl-4,4-dimethyloxazolidines in dilute solution in acetone in a Pyrex or quartz vessel with a medium pressure mercury lamp. Large amounts of polymeric material derived from the acetone were obtained. In a separate run without the substrate, after 90 hours the three main products, accounting for over 80% of the total, were diacetone alcohol (XII) (12%), pinacol (XIII) (30%) and acetonyl acetone (XIV) (42.5%), in order of increasing retention time on the g.l.c column used to separate the mixture (6ft E301 column at 120°; detector at 280°; injection at 260°). The products were identified by their i.r and n.m.r spectra and comparison with authentic samples.



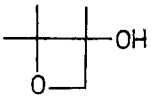
(XII)



(XIII)



(XIV)



(XV)

No reliable work seemed to have been done on this fundamental topic, but a report appeared[59] which found after only 4 hours irradiation, four major products making up 40% of the total. They were XII (12%), XIII (12%), XIV (25%) and 50% of 2,2,3-trimethyl-3-hydroxyoxetane (XV). Reexamination of the n.m.r spectra of our reaction mixtures suggested that not more than 10% of this oxetane was present, and no other component of even this magnitude appeared on g.l.c analysis. This may have been due to decomposition on the column, and the lesser amount observed in the reaction mixture may have been due to the longer irradiation time causing decomposition, perhaps by reversion to acetone.

Subsequent experiments were performed in dry t-butanol as solvent, and the following reaction conditions are typical.

a) 1mM substrate
2ml acetone
3ml t-butanol

The mixtures were deoxygenated by bubbling nitrogen through for 10 minutes, and sealed under nitrogen in Pyrex tubes which were strapped to the water-cooled Pyrex probe of a 200W Hanovia medium pressure mercury u.v lamp, and irradiated for 60 hours.

The reactions were followed by i.r spectroscopy and by t.l.c and products were isolated by p.l.c and characterised so that quantitative measurements could be made from the n.m.r spectra of the crude reaction mixtures.

A small amount of acetone polymer was formed, but did not complicate isolation of the products.

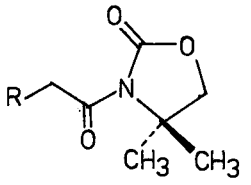
b) 0.5mM substrate
0.5ml freshly-distilled biacetyl (c. 5.6mM)
0.5ml DTBP (c. 3.4mM)
10ml t-butanol

The mixtures were made up as in (a) and the Pyrex reaction flasks were half-immersed in a large water bath at room temperature, and irradiated with a single flood lamp for 24 hours.

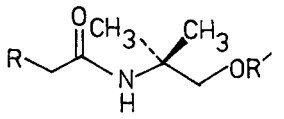
The products observed (table I) were the N-acyloxazolidin-2-ones (XVI), N-acyl-2-amino-2-methylpropanols (XVIII) and their O-formates (XVII). That the compounds XVII were the formyl esters and not the N-formyl-isomers was shown by their n.m.r spectra. The singlet resonance at c. τ5.7 was as expected for $C\underline{H}_2OCOR$, c.f $C\underline{H}_2OH$ at c. τ6.3, and exchange of the N$\underline{H}$ proton for deuterium in the presence of D_2O was measurably slow, c.f exchange of O$\underline{H}$ should be very rapid.

The products XVIII could have arisen by hydrolysis of the formyl esters XVII during work-up, but an alternative source could be the N-formyl-isomers of XVII. The latter, as N,N-diacyl-amines might be relatively unstable, and these alternative products of ring cleavage were not observed as such.

In table I, in absence of a clarification of the origin of products XVIII, the acyclic products XVII and XVIII have been entered under the one heading.



(XVI)



(XVII) R' = CHO
(XVIII) R' = H

table I. Photosensitised oxidation of N-acyl-4,4-dimethyl-oxazolidines. Percentages of products obtained.

starting compound XI R =	products		
	s.m	XVI	XVII
	conditions (a)		
H	0	0	100
PhCONH	70	12	18
CN	19	39	42
CN*	64	12	24
I	100	0	0
CF_3CONH	0	40	60
	conditions (b)		
H	0	0	100
PhCONH**	0	10	60
CN	40	0	60
I	100	0	0
CF_3CONH	0	0	100

* deoxygenated for 30 minutes.

** small amounts of N-formylbenzamide detected.

Clearly the products are those expected in the presence of oxygen. The above deoxygenation procedure was sufficient to completely alter the course of reactions with ABIN (section 3ii), but for rigorous exclusion of the possibility of forming β-lactams by this route the above experiments should be repeated after

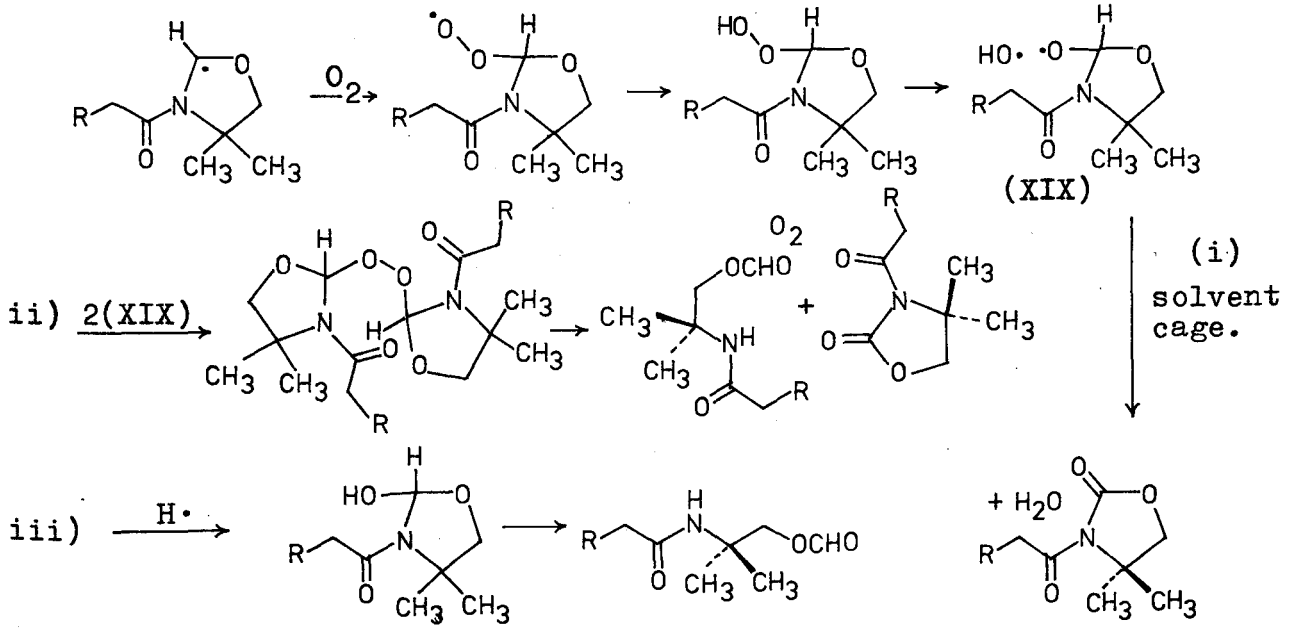
degassing by several freeze-thaw cycles under vacuum. However, N-iodoacetyl-4,4-dimethyloxazolidine XIf gave no reaction under either set of conditions - no oxidation and no cyclisation. Also in the second run with the cyanoacetyl derivative XIe, after deoxygenating for 30 minutes the only effect was increased recovery of starting material. These observations suggest that in these cases no alternative to the reaction with oxygen was available.

Mechanisms of reaction.

Formation of the formyl esters XVII is formally a two electron oxidation, while formation of the N-acyloxazolidin-2-ones XVI is a four electron oxidation. Thus the former cannot be derived from the latter, and presumably not vice versa, ring opening being irreversible. In all cases more of the acyclic products were formed, the predominance being particularly marked under the conditions (b).

a) u.v irradiation.

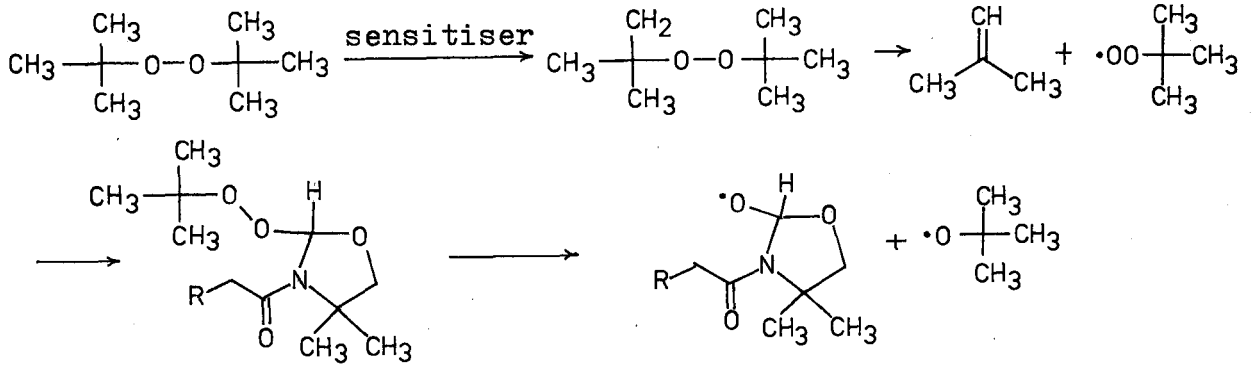
Hydrogen abstraction from C2 of the N-acyloxazolidine by photoexcited acetone would be followed by capture of the radical by oxygen, the resulting peroxy radical abstracting a hydrogen atom from acetone or a product of its photolysis, or from another molecule of substrate. Homolytic fission of the hydroperoxide thus formed would give the N-acyloxazolidin-2-yloxy radical (XIX) that could generate both products XVI and XVII by termination reactions (i) and (ii), or the formyl ester XVII by further hydrogen abstraction from the solvent or substrate (iii).



b) photosensitised DTBP

Decomposition of di-t-butyl peroxide is generally considered[60] to give t-butoxy radicals by O-O bond fission, and these could initiate the reactions described above. Biacetyl might prove a better hydrogen radical source in the reaction medium, leading to a predominance of pathway (iii).

However, the apparent facility of these latter reactions tempts a further speculation that the source of the oxidation is not molecular oxygen. Sensitised decomposition of DTBP could alternatively involve abstraction of hydrogen by the sensitiser and fragmentation of the peroxide to isobutene and a t-butylperoxy radical. Reaction of the latter with an oxazolidin-2-yl radical and homolysis of the mixed peroxide would produce the N-acyloxazolidin-2-yloxy radical XIX and a t-butoxy radical. Such a scheme would be analogous to the mechanism proposed for the conversion of dioxolans to vicinal diol monoesters by thermally decomposing t-butyl hydroperoxide.[61] The radical initiator species in that case is more certainly a t-butylperoxy rather than a t-butoxy radical.

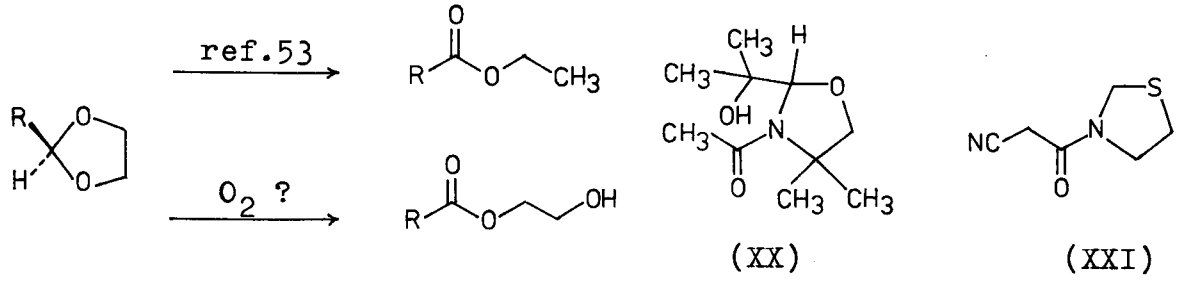


(XIX)

Small amounts of N-formylbenzamide were obtained from the reaction of N-(N'-benzoylaminoacetyl)-4,4-dimethyloxazolidine XId. This product must have been derived from oxidation at C2' of the N-acyl group - the other predicted radical centre in the oxa-penam precursor. Formation of this compound is discussed below in the section dealing with ABIN-initiated reactions, in which it is the major product.

The necessity for deoxygenation is not mentioned in literature reports of similar experiments. We repeated Elad's experiments using N-acetyl-(N'-glycylvaline) ethyl ester with toluene under conditions (b).[55] Without initial deoxygenation, only benzoic acid was obtained, but after deoxygenation as above, a 20% yield of N-acetyl-(N'-phenylalanylvaline) ethyl ester (by comparison with authentic material) was obtained, along with 3 mole % of bibenzyl and no benzoic acid. Increasing the concentration of the reactants increased the yield of bibenzyl but reduced the yield of modified peptide.

Similarly the irradiation of dioxolans in the presence of acetone is reported to give ethyl esters,[53] with no mention of deoxygenation. In the presence of oxygen, the products would be expected to be the mono-esters of ethane-1,2-diol.

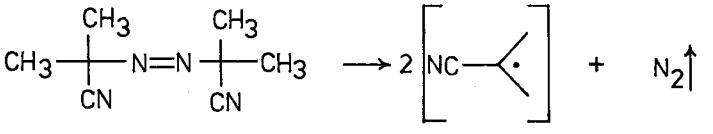


Following the failure to achieve an intramolecular cyclisation by these methods, an analogous intermolecular reaction was attempted. N-Acetylglycine ethyl ester and N-acetyl-4,4-dimethyloxazolidine XIa were irradiated together under conditions (a) and (b) In both cases the former was recovered unchanged, and the oxazolidine derivative was converted to the corresponding acyclic formyl ester (XVII, R = H). In the reaction under conditions (a), 10% of an adduct (XX) of the oxazolidine and acetone was obtained.

U.v irradiation of N-cyanoacetylthiazolidine (XXI) under conditions (a) gave a rapid reaction to form a brown mixture with a strong thiol odour and undissolved matter present. Continued irradiation gave no further change, and separation of the mixture gave largely recovered starting material and less than 5% of three products showing N-H absorption in their i.r spectra. Presumably ring degradation had occurred, obscuring further irradiation.

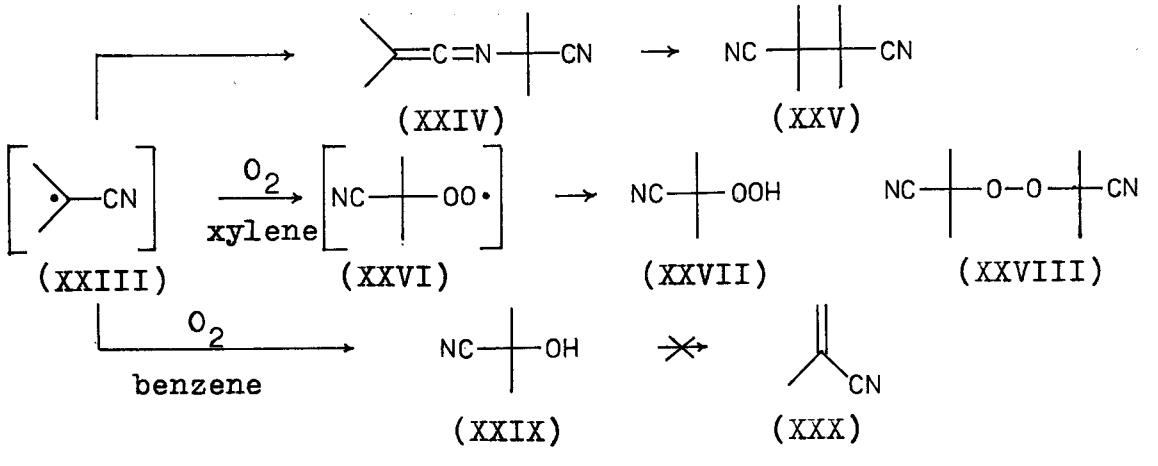
3ii. OXIDATIONS INITIATED BY AZO-BIS-ISOBUTYRONITRILE (ABIN).

Azo-bis-isobutyronitrile (ABIN) (XXII) undergoes first order decomposition to 2-cyano-2-propyl radicals (XXIII) with a half-life of about 20 hours at 60° and 5 hours at 70° [62], and hence was considered as a possible candidate for a radical initiator under suitably mild conditions - relatively low temperatures, in a range of inert solvents and with absence of interfering by-products.



(XXII) (XXIII)

The ambident 2-cyano-2-propyl radicals XXIII are highly stabilised and quite unreactive. It has been shown[63] that they recombine to form the kinetic product - 2-cyano-2-aminopropane dimethylketenimine (XXIV) (DKI) - which isomerises to the thermodynamic product - tetramethyl-succinodinitrile (XXV) (TMSN). The conversion proceeds by a radical mechanism at a rate similar to that of decomposition of ABIN, but the rate of isomerisation is doubled in the presence of oxygen. This latter effect is destroyed by addition of antioxidants, and hence is not a direct effect of oxygen but may be due to induced decomposition of DKI by some radical species only formed in the presence of oxygen, e.g the 2-cyanopropyl-2-peroxy radical (XXVI)[63]. Thus decomposition of ABIN in xylene under oxygen gives rise to 2-cyanopropyl-2-hydroperoxide (XXVII)[64,65], and a recent report claims to have isolated di-(2-cyano-2-propyl)-peroxide (XXVIII) in 4-5% yield[66].



(XXIV) (XXV)

(XXIII) (XXVI) (XXVII) (XXVIII)

(XXIX) (XXX)

We performed blank experiments in the absence of substrate by heating ABIN in benzene at 65° for 60 hours. If the solution was initially deoxygenated merely by bubbling nitrogen through for 10 minutes and the decomposition carried out under nitrogen, evaporation of the reaction mixture gave a residue showing a strong absorption in the i.r spectrum at 2019 and a weak doublet at 2241, 2220 cm^{-1}. This residue was hence a mixture of mainly DKI with some starting material and TMSN. A similar reaction performed with a slow stream of dry oxygen bubbled in, or vigorously stirred in air, gave a residue containing little or no DKI, as judged from the i.r spectrum. Following this latter reaction in benzene by n.m.r spectroscopy showed disappearance of the singlet due to the methyl protons of the starting ABIN, and appearance of two new singlets slightly upfield (τ8.89 and 9.10 in benzene), in ratio c. 3:1. Peak enhancement showed that the weaker, higher field signal corresponded to the methyl protons of TMSN, and that the signal to lower field was isochronous with that due to the methyl protons of 2-cyano-propan-2-ol (XXIX). Distillation of the reaction mixture removed most of the benzene and gave a final fraction containing XXIX with some benzene (XXIX was identified by comparison of i.r and n.m.r spectra with those of authentic material - it decomposes on g.l.c). Evaporation and chromatography of the reaction mixture gave only about 25% of TMSN, and small amounts of 2-cyanopropan-2-ol and other products (the boiling point of XXIX is 82°/23mm, and hence it would be mostly removed on a rotary evaporator[67]).

Iodometric titration for peroxides, as described for 2-cyanopropyl-2-hydroperoxide in ref. 65 showed negligible amounts present in the reaction mixtures (4% and 6% in absence and presence of substrates (below) respectively).

The first fractions eluted from the chromatography column, in benzene, contained 2-3 mole % of biphenyl from reactions performed in the presence of oxygen. None was obtained from the reactions under nitrogen.

Talât-Erben claimed[64], on rather sketchy chemical evidence, that while 2-cyanopropyl-2-hydroperoxide XXVII was

a major product of thermal decomposition of ABIN under oxygen in xylene, decomposition in benzene gave 80 mole % of 2-cyano-propan-2-ol XXIX and some TMSN. There was no mention of biphenyl formation, although this is noted cursorily in ref. 66.

In xylene, initially formed 2-cyanopropyl-2-peroxy radicals XXVI can remove a hydrogen atom from solvent molecules and form the hydroperoxide XXVII and methyl-benzaldehyde, observed as a side product[64]. In the absence of such a hydrogen source, e.g in benzene, it was suggested that the peroxide XXVIII was formed which decomposed to 2-cyanopropan-2-ol XXIX. But the peroxide XXVIII has now been shown to be stable below 120° [66], and in any case this still does not explain the origin of the hydrogen atom required for formation of XXIX.

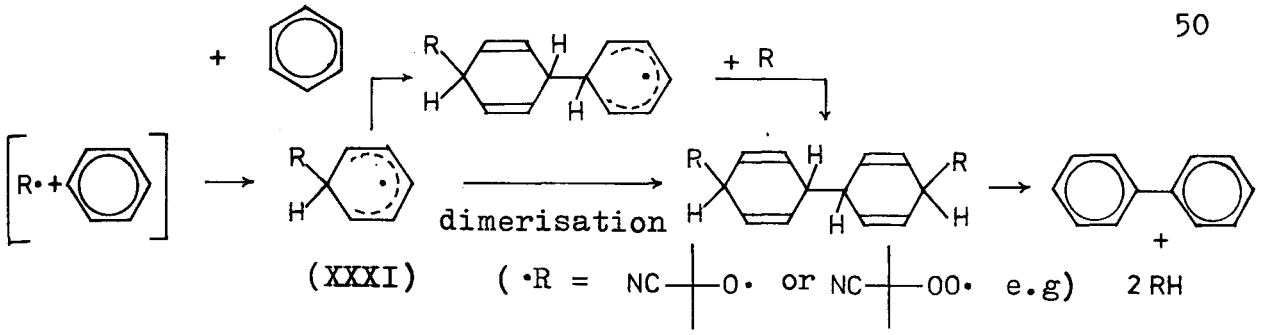
Abstraction of hydrogen from another 2-cyano-2-propyl radical XXIII would give rise to methylacrylonitrile (XXX) which has been observed as a minor product of ABIN decompositions but was not observed in our experiments as judged from the n.m.r spectra (ref. 68 gives n.m.r data for most of the products of ABIN decomposition). Indeed no other major products could be detected in our, or, apparently in Talât-Erben's experiments

Biphenyl is formed, but not in sufficient amount to account for formation of all the 2-cyanopropan-2-ol XXIX. The relative bond energies[69]:

Ar-H	100.5kcal/mole
ROO-H	90
RO-H	104

make it unlikely that phenyl radicals are formed in sufficient concentration by direct hydrogen abstraction, and a more probable mechanism is formulated by analogy with that proposed by Schuster[70] for biphenyl formation from photochemically-excited ketone triplets.

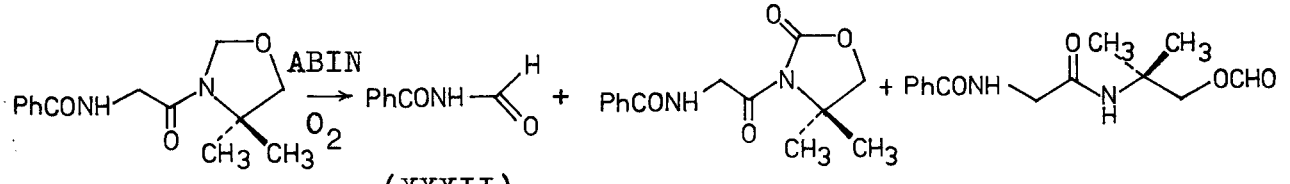
2-Cyanopropyl-2-peroxy radicals XXVI are electron-poor and should form complexes with electron-rich aromatic compounds. Such complexes have been invoked to explain the capture of radicals XXVI by antioxidants[71]. Capture of such a radical by benzene could give rise to a cyclohexadienyl radical (XXXI) and dimerisation and rearomatisation of this species would give biphenyl and the formal product of hydrogen abstraction by the radical.



The mode of thermal decomposition of ABIN in benzene has not been satisfactorily elucidated, and explanations of oxidations initiated by this reagent can only be speculative.

Reaction of amino acid derivatives with ABIN.

N-(N'-Benzoylaminoacetyl)-4,4-dimethyloxazolidine XId was treated with decomposing ABIN (2 mole equivalents) in benzene solution for 60 hours at 65°. Under nitrogen, after deoxygenation as above, the substrate was completely recovered, but when the reaction mixture was stirred in air XId was completely converted to the corresponding N-acyloxazolidin-2-one XVI (R = PhCONH) and the acyclic N-acyl-2-amino-2-methylpropanol formyl ester XVII (R = PhCONH), and also to N-formylbenzamide (XXXII) (50%). In all experiments with ABIN conducted under oxygen in benzene, 2-3 mole % of biphenyl was obtained.



(XId) (XXXII) (XVI) (XVII)

Formation of the oxazolidin-2-one and acyclic oxidation products has been discussed above, but the N-formylbenzamide XXXII must have arisen via hydrogen abstraction from the methylene group of the N-benzoylglycyl moiety. The resultant radical centre may recapture a hydrogen radical more readily than does the oxazolidin-2-yl radical, and hence the former is destroyed in the photochemical reaction media where hydrogen radicals are available, but not in the ABIN-initiated reactions in benzene.

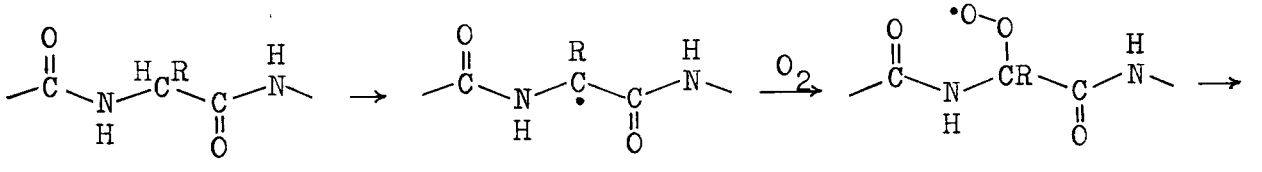
As a means of achieving the desired cyclisation to an oxa-penam, ABIN initiation is clearly of no value. In the absence of oxygen the 2-cyano-2-propyl radicals XXIII are probably too unreactive to abstract hydrogen radicals from the substrate, or

at any rate do not cause cyclisation of the desired biradical. In the presence of oxygen, a more reactive species, presumably the 2-cyanopropyl-2-peroxy radical XXVI is formed, and this can generate both the requisite radical centres, but these then react with the oxygen present.

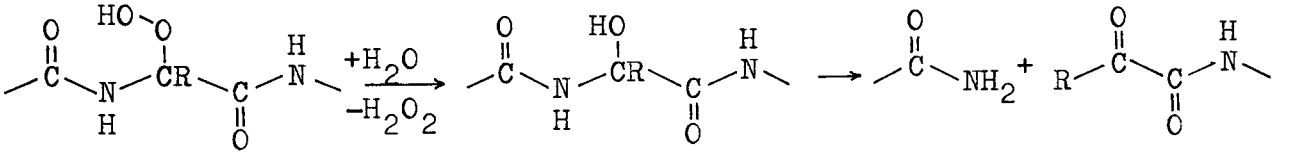
Formation of N-formylbenzamide XXXII.

Radical-induced oxidation of peptides has been much studied in relation to radiation damage of proteins and photolytic degradation of fibres.

Products have generally been formulated as carbonyl compounds and amides, formed by fission of the NH-CHR.CO bond. Thus Meybeck[72] subjected fibrous proteins in oxygenated aqueous solution to u.v irradiation, and estimated the extent and localisation of degradation by hydrolysis, followed by chromatography of the product α-keto acids as their 2,4-dinitrophenylhydrazones. Reaction was assumed to proceed via a peptide radical IV that was captured by oxygen, the resulting peroxy radical abstracting a hydrogen radical from the solvent or an adjacent peptide chain. The hydroperoxide formed could react with water in the reaction medium or on work-up to give an amide and α-keto acid. Only glyoxylic acid - derived from glycyl radicals IV (R = H) - and much smaller amounts of pyruvic acid - derived from alanyl radicals IV (R = CH_3) - were obtained, and the authors suggested that the more bulky substituents of the higher amino acids hindered planarity and hence maximum stabilisation of the peptide radical IV.



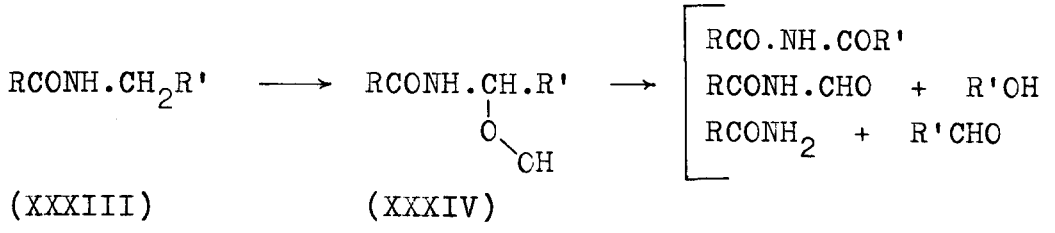
(IV)



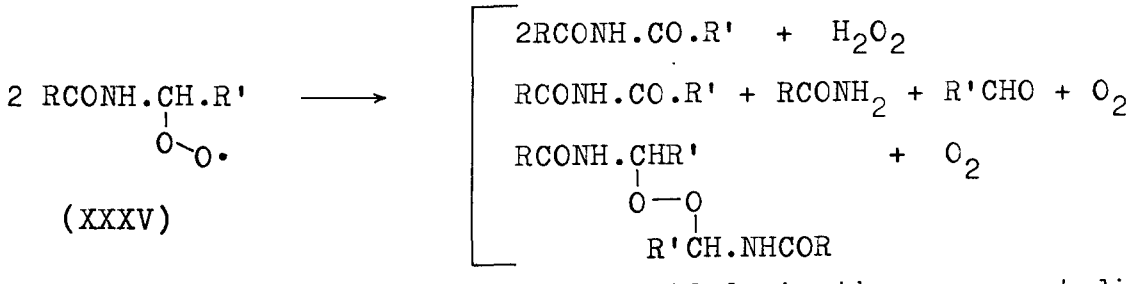
(R = H, CH_3 only)

Amides and glyoxylic acid were the main products observed from aerial oxidation of tetraglycine-nickel(II) complexes, catalysed by the metal[73].

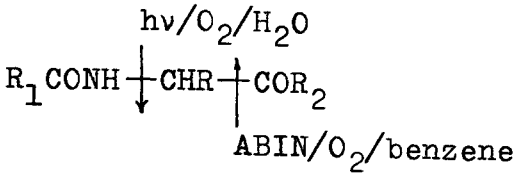
In contrast to these peptide oxidations conducted in aqueous media, our reactions were carried out under anhydrous, aprotic conditions, and more closely resemble the systems used by Sagar[74] to study the autoxidation of N-alkylamides (XXXIII) in relation to the degradation of Nylon. The products of oxidation in organic solvents initiated thermally, photochemically or chemically, were N-acylamides, N-formylamides and amides, and the hydroperoxides (XXXIV) postulated as intermediates were isolated and shown to decompose to similar product mixtures.



Thermal autoxidation proceeded with long kinetic chain length, and, on the basis of the low consumption of added α-naphthol (a radical scavenger) heterolysis and rearrangement of the hydroperoxides XXXIV was proposed. Reactions at lower temperatures (less than 75°) initiated chemically or photochemically had shorter chain lengths, the products being principally those of quadratic termination of peroxy radicals (XXXV) within solvent cages.



A number of acylated amino acid derivatives were studied To find the generality of the oxidation initiated by ABIN resulting in predominant NH.CHR-CO bond cleavage. The results are shown in table II.



substrate	%s.m	Products, % of total
N-(N'-benzoylaminoacetyl)-4,4-dimethyloxazolidine XId	0	PhCONH.CHO 50% XVI (R=PhCONH) 25 XVII (R=PHCONH) 25
PhCO-GLY-OEt	40	PhCONH.CHO 40 $PhCONH_2$ 20
PhCO-(DL)ALA-OEt	80	$PhCONH.CO.CH_3$ 20
PhCO-(DL)LEU-OEt	100	
PhCO-(DL)VAL-OEt	76	PhCONH.CHO 10 $PhCONH_2$ 10
PhCO-(L)PHE-OMe	75	PhCONH.CHO 20 $PhCONH_2$ 5 PhCOOH trace
CH_3CO-GLY-OEt	60	$CH_3CONH.CHO$ + CH_3CONH_2 40
PhCO-GLY-GLY-OEt	40	PhCONH.CHO 40 $PhCONH_2$ 15
PhCO-GLY-(DL)LEU-OEt	50	PhCONH.CHO 40 $PhCONH_2$ 10
PhCO-(DL)LEU-GLY-OEt	80	no -CONHCHO in n.m.r

table II. Reactions with 1mM substrate stirred in air at
2mM ABIN 65° for 60 hours.
8ml benzene

Products isolated by p.l.c or column chromatography; quantitative data from recovery and n.m.r spectra.

The effect of varying the molar ratio of ABIN : substrate was studied with N-benzoylglycine ethyl ester, the extent of reaction being determined by the proportion of N-formylbenzamide shown by the n.m.r spectrum of the reaction mixture after evaporation.

s.m = $PhCONH.CH_2.COOEt$

molar ratio ABIN/s.m	%PhCONH.CHO
0.1	3%
0.5	15
1.0	35
2.0	50
3.0	50

The role of the ABIN is not catalytic, and the reaction only goes to 50% conversion with 2 or more molar equivalents of ABIN. Auto-inhibition of amide oxidation was observed by Sagar.[74]

Table II shows that derivatives of N-benzoylglycine gave predominantly N-formylbenzamide with some benzamide. The former can decompose to the latter on work-up, and the latter is difficult to estimate from the n.m.r spectrum of the reaction mixture, so it is not certain whether benzamide is a primary product or not. Allowing for at least some being derived from N-formylbenzamide, the amount formed during the reactions can at most be quite small. N-Acetylglycine ethyl ester gave N-formylacetamide, as estimated from the n.m.r spectrum of the crude reaction product, although only acetamide was actually isolated. However, this is not a general reaction for N-acyl derivatives of glycine as N-benzoyl(N'-leucylglycine) ethyl ester gave less than 20% reaction, and no N-formyl proton resonance was observed in the n.m.r spectrum.

In agreement with the results of Meybeck[72] concerning the ease of formation of the peptide radical IV, it was found that N-benzoylalanine ethyl ester (XXXVI) gave a much lower yield of N-acetylbenzamide (XXXVII) compared with the yield of N-formylbenzamide from N-benzoylglycine ethyl ester, and that N-benzoylleucine ethyl ester (XXXVIII) did not react.

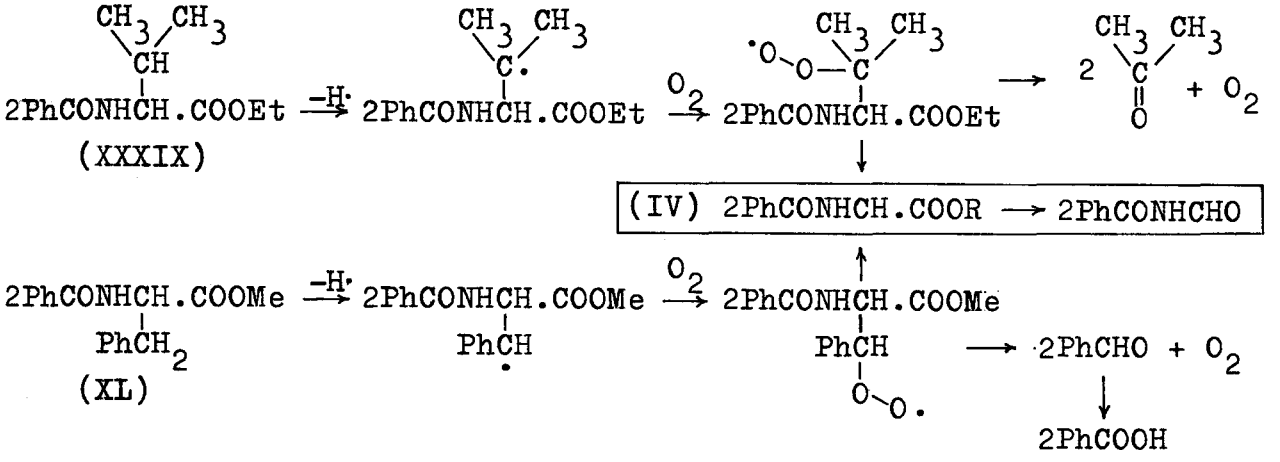
$PhCONH.CHR.COOEt \longrightarrow PhCONH.CRO$

$R = H \longrightarrow$ XXXII $R = H$

XXXVI $R = CH_3 \longrightarrow$ XXXVII $R = CH_3$

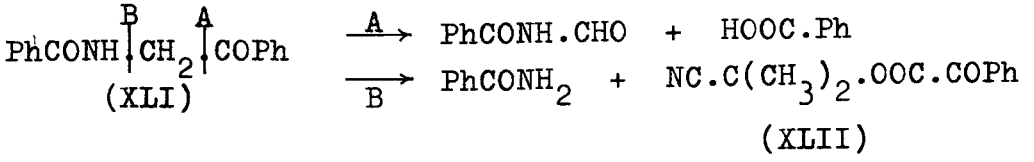
XXXVIII $R = CH_2.CH(CH_3)_2 \not\longrightarrow$

However, reaction of both N-benzoylvaline ethyl ester (XXXIX) and N-benzoylphenylalanine methyl ester (XL) with ABIN surprisingly gave N-formylbenzamide. Both these substrates possess a second site for radical formation - a tertiary and a benzylic carbon atom respectively - and attack at these centres presumably leads to side chain cleavage. Benzoic acid was detected in the product from the oxidation of XL.



Unfortunately in none of these experiments could the other fragment from the oxidation be isolated. Even using N-benzoyl-(N'-glycylleucine) ethyl ester no identifiable fragments were found. It was proved that neither leucine ethyl ester nor the derived diketopiperazine were present, by comparison with authentic samples.

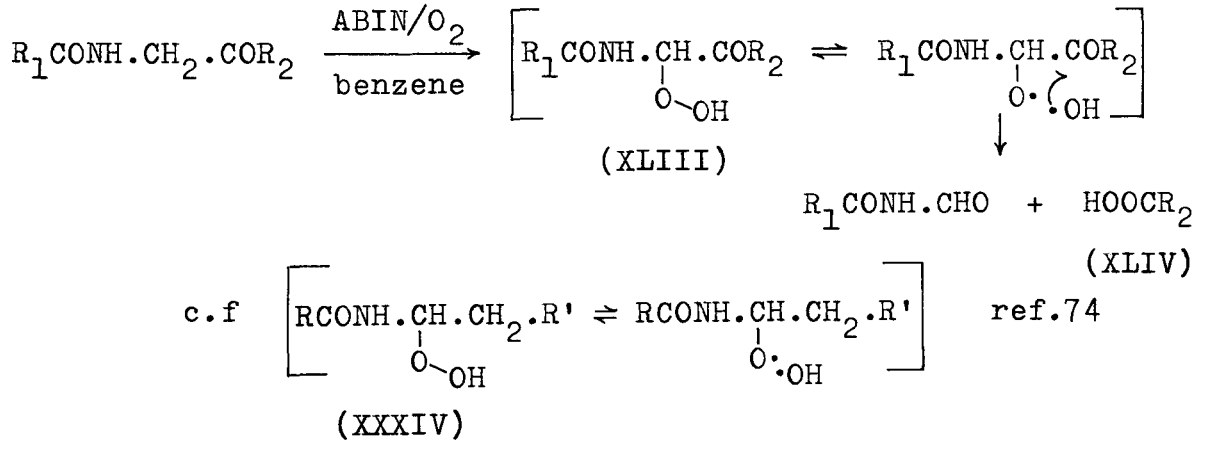
Accordingly, a closely analagous substrate - α-benzoylaminoacetophenone (XLI) - was specially designed to provide evidence of the other reaction products. Reaction with ABIN under oxygen proceeded better than with any of the other substrates to give mostly N-formylbenzamide (32%) and benzoic acid (34%), with some benzamide (20%) and the 2-cyano-2-propyl ester of phenylglyoxylic acid (XLII) (10%), with 20% recovered XLI. The yields of the products do not agree exactly, but it seems reasonable to pair them off as products of two alternative modes of cleavage:



The sketchy evidence available does, however, provide a basis for some tenable mechanistic hypotheses for these reactions.

The reactions with ABIN described here differ from most peptide oxidations studied previously in being performed under anhydrous, aprotic conditions. The significant difference between the peptide derivatives and the N-alkylamide substrates studied by Sagar under similar conditions, is the presence in the former of a carbonyl group adjacent to the initially formed radical centre. This would be expected to increase the lability of the hydrogen atom removed, and to assist in the stabilisation of the radical centre once formed. It may also be responsible for the predominance of the particular mode of cleavage observed in the ABIN-initiated oxidation of peptides.

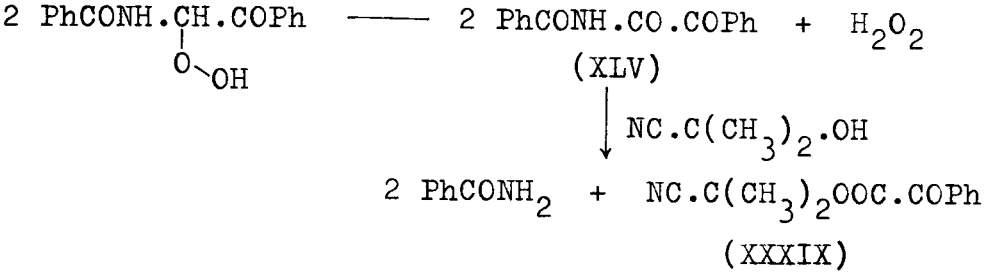
Sagar proposed that homolysis of the hydroperoxides XXXIV formed as intermediates in autoxidation of N-alkylamides XXXIII was suppressed by radical recombination within solvent cages. Analogous intermediates (XLIII) in the peptide oxidations possess an alternative mode of recombination after homolysis, leading to cleavage in the manner observed.



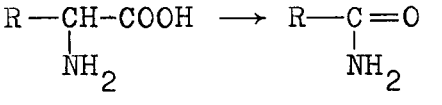
Oxidation of glycyl esters would then give monoesters of carbonic acid (XLIV, e.g R_2 = OEt), and of glycyl-peptide esters would give N-carboxylamino acid esters (XLIV, R_2 = NH.CHR.COOR'). Decarboxylation of the latter should give amino acid esters, which, however, were not observed.

From the result of the experiment with α-benzoylaminoacetophenone XLI, benzamide may be a primary product from the alternative mode of cleavage rather than a secondary derivative from the N-formyl-

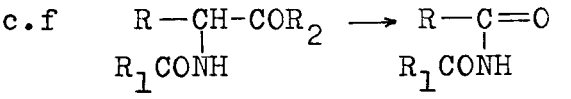
benzamide. Major products of the autoxidation of N-alkylamides are N-acylamides,[74] and analogous products of the peptide oxidations would be N-glyoxalylamides - e.g XLV from XLI, and reaction of XLV with 2-cyanopropan-2-ol could give benzamide and the observed phenylglyoxylic acid ester XXXIX.



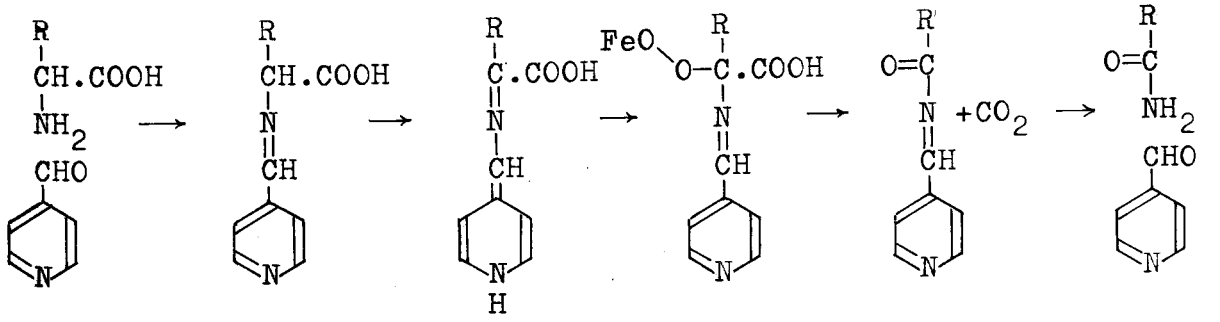
It is surprising that there seem to be no other reports of peptide oxidations performed under non-aqueous conditions, when apparently a different mode of cleavage predominates compared with that customarily observed in aqueous systems. Furthermore, this type of degradation has been observed in biological systems, where amides (XLVII) have been shown to be derived by decarboxylation of α-amino acids (XLVI) without transfer of the amino group.[75]



(XLVI) (XLVII)



The mechanism proposed for the enzymic process involves reaction of XLVI with pyridoxal to form the Schiff base, followed by deprotonation at the α-carbon atom and oxidation by perferryl iron.(scheme I). Radical mechanisms were not considered, but the above work may provide chemical evidence that such reactions could cause the transformations observed in the biological system.



scheme I

3iii. OXIDATIONS WITH NICKEL PEROXIDE (NiPO)[76]

Nickel peroxide (NiPO) was prepared from nickel sulphate and alkaline sodium hypochlorite, and standardised iodometrically[77]. In the original reference activities as high as 3.2mg atom oxygen/g were quoted. A sample having activity 2.8mg atom oxygen/g was obtained on the first run, and after five months in a reagent bottle on the bench the activity had not fallen below 2.7mg atom oxygen/g. This batch was used in all the experiments described here, except in that indicated when a second batch was used, prepared from reagents from the same bottles, but having activity only 2.3mg atom oxygen/g. It is reported that the activity of NiPO is affected by the water content[78].

Warming benzene solutions of the N-acyl-4,4-dimethyl-oxazolidines XI with stoichiometric excesses of NiPO had no effect, except in the case of the N-cyanoacetyl derivative XIe. On adding the NiPO slowly to a stirred solution of XIe in benzene at room temperature there was an exothermic reaction and the mixture became coloured. At least two equivalents of NiPO were required before t.l.c analysis showed that no starting material remained. After stirring for a further 10 minutes, filtration and evaporation gave 69% of a coloured oil that crystallised from carbon tetrachloride. Sublimation at 200°/0.03mm to remove traces of nickel salts, and recrystallisation from carbon tetrachloride gave 42.5% of colourless crystals, whose spectroscopic and analytical data were consistent only with the trimeric, cyclopropane structure (XLVIII). ($C_{24}H_{30}N_6O_6$ requires C57.82, H6.07, N16.86%, M = 498; found C57.94, H6.16, N16.89%, M(mass spectrum) = 498, M(osmometric) = 520).

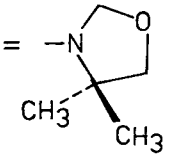
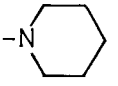
The crystallisation liquors from XLVIII were resolved on p.l.c into a large number of coloured bands with strong u.v absorption spectra, presumably unsaturated polymers. The trimer XLVIII moved well ahead of the coloured bands on t.l.c, and was easily detected by its bluish fluorescence under u.v light.

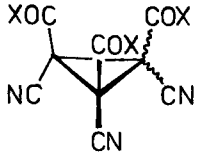
The generality of the reaction was investigated by examining the effect of NiPO on N-cyanoacetylpiperidine (XLIX)

N-cyanoacetyl-N,N-diethylamine (L) and ethyl cyanoacetate (LI). In the former two cases the products were isolated on p.l.c, the major components always appearing as colourless bands well ahead of the coloured polymeric material. The trimeric product from the reaction of NiPO and ethyl cyanoacetate seemed to be unstable on silica gel, and was isolated by crystallisation and sublimation.

The products described all had the molecular formula corresponding to $(\text{monomer} - 2H)_n$ as indicated by analytical and/or n.m.r data. The value of n in the formula was determined from the mass spectrum, and from the presence or absence of a u.v absorption spectrum for the alkene dimers and cyclopropane trimers respectively.

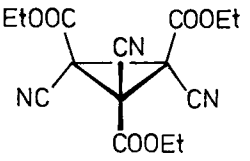
$X.CO.CH_2.CN$

(XIe) X =  ; (XLIX) X =  ; (L) X = $N(Et)_2$; (LI) X = OEt

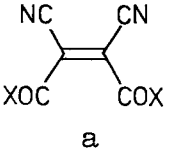


(XLVIII) X = 4,4-dimethyl-oxazolidin-3-yl

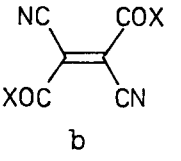
(LII) X = piperidino



(LIII)



a



b

(LIV) X = piperidino

(LV) X = diethylamino

Trimers of the cyclopropane type were also obtained from N-cyanoacetylpiperidine (trimer LII) and from ethyl cyanoacetate (trimer LIII). The latter compound has previously been prepared from ethyl 2-bromo-2-cyanoacetate and certain bases - the sodium salt of ethyl cyanoacetate,[79,80] o-nitrophenoxide ion[81] and the CCl_3^- anion from the thermal decomposition of sodium trichloroacetate.[82]

The melting point and spectral data of our product LIII were identical with those reported,[83] and, while the literature routes are no less ambiguous than ours, these independent conclusions support our structural assignment for this, and, by inference, for the other trimers obtained.

The triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate LIII has the trans-configuration shown above, like the

products of the methods already in the literature. The n.m.r spectrum of LIII shows two quartets (τ5.47 and τ5.55, $C\underline{H}_2CH_3$) and two triplets (τ8.55 and τ8.60, $CH_2C\underline{H}_3$) in a 1:2 ratio. The n.m.r spectrum of the original trimer XLVIII from N-cyanoacetyl-4,4-dimethyloxazolidine XIe is complicated by restricted rotation about the N-CO bonds, and is not readily explicable even on cooling to -50°. Both methylene groups of the oxazolidine rings give rise to two signals in approximately 2:1 ratio, and it is expected that XLVIII has the trans-configuration also. Resonances from the trimer LII are all broad due to the conformational mobility of the piperidine rings.

Using the more active NiPO, N-cyanoacetylpiperidine gave a dimer (10%, m.p 196°) in addition to the trimer LII (10%). With the less active NiPO, reaction was extremely slow, starting material only disappearing after 7 days at 60°, and none of the trimer LII was formed. Two isomeric dimers (LIVa and LIVb) (4% m.p 94°, and 8% m.p 196°) were isolated by p.l.c and fractional crystallisation.

The configurations of these two dimers cannot be assigned unambiguously from the melting point and spectral data. The conspicuous differences are in their melting points (A m.p 94°, B m.p 196°) and relative polarity (A is preferentially extracted into warm petrol, and has slightly higher R_f on t.l.c on silica gel in $CHCl_3$; this difference was not enhanced by use of silver nitrate impregnated silica gel). In their i.r spectra, A has a weak C≡N stretch band at 2225 cm^{-1} (CH_2Cl_2) while B has virtually no absorption here, and the C=O stretch band of A is at marginally lower frequency (1659 cm^{-1}) relative to that of B (1661 cm^{-1}). The u.v absorption of A is stronger and at longer wavelength (286nm (ε3,800)) compared with that of B (265nm (ε2,700)).

Felton and Orr[111] discussed the i.r spectra of olefins carrying carbonyl and/or cyano substituents, relevant considerations being the greater electronegativity of the cyano compared with the carbonyl group, the electrostatic interaction of cis-cyano substituents, and the steric interactions inhibiting planarity of cis-carbonyl groups.

Kudo[84] reported an assignment of configuration to diethyl 1,2-dicyanoethylene-1,2-dicarboxylate (trans) by supposedly un-

ambiguous chemical means, giving full spectral data, but no consistent conclusions can be reached concerning the configurations of the two dimers LIV.

Reaction of N-cyanoacetyl-N,N-diethylamine with the more active NiPO gave only a dimer (LV). This was obtained crystalline, although t.l.c evidence and a rather broad C≡N absorption in the i.r spectrum suggest that it could possibly contain both the isomers LVa and LVb. The n.m.r spectrum shows two triplets ($CH_2\underline{CH}_3$) and the quartet ($\underline{CH}_2CH_3$) is broad, but these may be due to different rotamers rather than to different isomers.

table III. Yields and conditions for reactions of NiPO with the compounds $X.CO.CH_2.CN$.

	$X.CO.CH_2.CN$, X =	conditions	trimer %	dimer %
XIe	4,4-dimethyl-oxazolidin-3-yl	2 mole equiv NiPO/ 5 min/room temp.	42.5%	-
XLIX	piperidino	3 mole equiv NiPO/ 30 min/room temp.	10%	10%
XLIX	piperidino	3 mole equiv NiPO*/ 7 days/60°	-	4 + 8%
L	diethylamino	3 mole equiv NiPO/ 30 min/room temp.	-	14%
LI	ethoxy	3 mole equiv NiPO/ 0° - room temp/2 hr.	6%	-

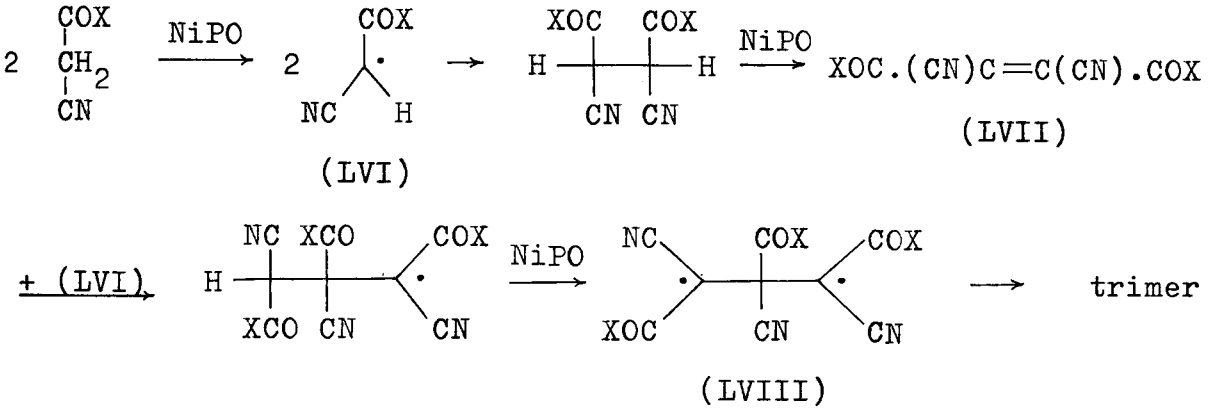
(1 mole equiv NiPO indicates use of that quantity of nickel peroxide giving 1 g.atom oxygen/mole of substrate. NiPO had activity 2.8 mg.atom oxygen/g, NiPO* had activity 2.3 mg.atom oxygen/g. Benzene was used as solvent in all reactions.)

Mechanism of reaction.

The only related observations in the literature are that heating neat ethyl cyanoacetate with selenium dioxide gave diethyl 1,2-dicyanoethylene-1,2-dicarboxylate (probably the trans-isomer) and recovered starting material,[80] and that treatment of

phenylacetonitrile with NiPO gave meso-2,3-diphenylsuccinodinitrile, cis- and trans-dicyanostilbenes and poly-(phenylcyanomethylene).[85] Radical intermediates have been detected by e.s.r spectroscopy during many reactions of NiPO,[57] and the latter reaction is considered to be initiated by hydrogen abstraction from the phenylacetonitrile. Two of the resulting PhĊHCN radicals couple to give 2,3-diphenylsuccinodinitrile which has been demonstrated to undergo further oxidation to dicyanostilbenes. Addition of a PhĊHCN radical to the latter could initiate polymerisation.

Formation of cyclopropane trimers has not been reported in analogous systems, but could occur by a similar mechanism, involving addition of the primary radical (LVI) to an alkene dimer (LVII) with further hydrogen abstraction by the reagent followed by cyclisation of the biradical (LVIII).



The electron-withdrawing cyano and carboxyl substituents are required to stabilise radical intermediates and provide a highly electrophilic alkene precursor LVII to trimer formation. Thus treatment of N-cyanoacetyl-4,4-dimethyloxazolidine XIe with NiPO in ethyl vinyl ether (a nucleophilic olefin) and benzene (1:2) gave only the trimer XLVIII and no adduct of the alkene and oxazolidine derivative.

Similar criteria probably control the formation of triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate by anionic routes as in the literature methods, and also the properties reported for this compound. It readily forms a radical anion, and is very susceptible to basic hydrolysis,[86] decarboxylation, and formation of an acyclic propenide anion.[83] Hence isolation of this compound was not possible by chromatography (see above). The unusual

electronic properties of LIII might also explain the bluish fluorescence exhibited by all the trimers on t.l.c plates under u.v light.

Two features of the reaction are not so easily explained:

i) The different substrates show differing propensities towards formation of trimers and dimers. N-Cyanoacetyl-4,4-dimethyloxazolidine XIe gives a very much higher yield of trimer compared with N-cyanoacetylpiperidine XLIX, e.g, which might be thought quite similar on steric and electronic grounds

Formation of dimers only with the NiPO of lower activity is not an unreasonable observation if these are intermediates to trimer formation.

ii) In all the reactions, stoichiometric excesses of NiPO were used, but the residue filtered off after the reaction showed little or no remaining available oxygen. Use of less than the indicated amounts resulted in disproportionately low yields.

EXPERIMENTAL.

A. Preparation of starting materials.

Ai. 4,4-Dimethyloxazolidine and N-acyl derivatives (XI).

4,4-Dimethyloxazolidine.

Slightly more than an equimolar quantity of paraformaldehyde was added slowly to 2-amino-2-methylpropanol, and the mixture stood at room temperature overnight. The product was distilled at 120-135° (lit.[87] 124-125°/750mm). Yield 90%, 96% pure by g.l.c (6'E301/100°).

i.r (film) 3300m(br),2970s,2940m,2880s,1465m,1387m,1370m,1280w, 1240w,1188m,1104m(sh),1085s,1023s,980w,891s,855m,790wcm^{-1}

N-Acetyl-4,4-dimethyloxazolidine (XIa).

Acetyl chloride (4.30g, 55mM) in dry dichloromethane (20ml) was added dropwise to a cooled, stirred suspension of Na_2CO_3 (7.5g, 75mM) in a solution of 4,4-dimethyloxazolidine (5.05g, 50mM) in dry dichloromethane (30ml). The mixture was allowed to reach room temperature over 15 minutes, and then refluxed for 15 minutes. It was then filtered, and the filtrate washed twice with water, dried and evaporated, and the residue distilled at 65-67°/1.0mm (5.7g, 80%).

i.r (film) 2970m,2940m,2870w,1650s cm^{-1}.

n.m.r ($CDCl_3$) τ8.52 (s,6H)
8.05 (s) and 7.86 (s) (total 3H, ratio 75:25)
6.24 (s,2H)
5.05 (s) and 4.92 (s) (total 2H, ratio 70:30)

m.s m/e 143(16) (M), 128(8), 100(22), 88(65), 86(91), 43(B).

N-Chloroacetyl-4,4-dimethyloxazolidine (XIb).

Method as for XIa, using 1.1 mole equivalents of chloroacetyl chloride. The product (85%) was an oil that formed waxy crystals on seeding or storing in the refrigerator.

i.r ($CHCl_2$) 2930w,2861m,1662s cm^{-1}.

n.m.r ($CDCl_3$) τ8.58 (s,6H)
6.20 (s,2H)
6.08 (s,2H)
4.92 (s,2H)

N-Aminoacetyl-4,4-dimethyloxazolidine (XIc).

Treatment of XIb with .880 ammonia gave two products as shown by t.l.c, neither corresponding to the desired XIc.

The chloroacetyl derivative XIb (30g, 170mM) was dissolved in a little dichloromethane (20ml) and stirred with liquid ammonia (c.200ml) under a dry-ice condenser for 10 hours. The ammonia was then allowed to boil off over 20 hours, ammoniun chloride (9.1g, 100%) filtered off, washing through with dichloromethane, the filtrate evaporated, and the product distilled at 81-83°/0.03mm (14.1g, 52%) with appreciable amounts of a more volatile component and involatile residue.

i.r (film) 3380m(br),2980m,2940m,2870w,1650s cm^{-1}

n.m.r ($CDCl_3$) τ8.51 (s,6H)
8.35 (s,2H; exchanges with D_2O)
6.75 (s,2H;br)
5.04 (s,2H)

$C_7H_{14}N_2O_2$ C53.14, H8.92, N17.73%
found C53.73, H8.95, N17.76%

N-(N'-Benzoylaminoacetyl)-4,4-dimethyloxazolidine (XId).

XIc was benzoylated under Schotten-Baumann conditions with 1.2 mole equivalents of benzoyl chloride and 1.4 mole equivalents of N NaOH, to give crude crystalline XId (88%), recrystallised from ether.

m.p 92°

i.r (CH_2Cl_2) 3418m,2870w,1650s(d),1605w,1580w,1510m cm^{-1}

n.m.r ($CDCl_3$) τ8.48 (s,6H)
6.20 (s,2H)
5.92 (d,2H; collapses to s in D_2O over 36 hours)
4.96 (s,2H)
2.56 (m,4H; 3H in D_2O after 36 hours)
2.10 (m,2H)

m.s m/e 262(4) $[C_{14}H_{18}N_2O_3]$, 207(20), 162(21), 141(16), 134(19), 105(B).

$C_{14}H_{18}N_2O_3$ C64.10, H6.92, N10.68%
found C64.56, H7.10, N11.05%

N-Cyanoacetyl-4,4-dimethyloxazolidine (XIe).

A solution of the chloroacetyl derivative XIb (3.56g, 20mM) in dry D.M.F (20ml) was added dropwise to a stirred suspension of dried sodium cyanide (3g, 60mM) in dry D.M.F (30ml) at 60-70°, and heating and stirring continued for 1 hour. The mixture was filtered, washing through with chloroform, and the filtrate extracted with several small portions of water. Then solvents were distilled off from the organic phase to give a coloured semi-crystalline mass. This was washed with a little ether, and recrystallised five times from dichloromethane/petrol (1.44g, 43%).

m.p 86°

i.r (CH_2Cl_2) 2941w,2875m,2265w,1670s cm^{-1}

n.m.r ($CDCl_3$) τ8.50 (s,6H)
6.55 (s,2H)
6.20 (s,2H)
4.98 (s,2H)

u.v (MeOH) end absorption only.

m.s m/e 168(14) $[C_8H_{12}N_2O_2]$, 153(57), 141(11), 138(10), 113(48), 86(B).

$C_8H_{12}N_2O_2$ C57.10, H7.19, N16.68%
found C57.03, H7.19, N16.71%

N-Iodoacetyl-4,4-dimethyloxazolidine (XIf).

N-Chloroacetyl-4,4-dimethyloxazolidine XIb (6.03g, 34mM) was dissolved in dry acetone (30ml) and refluxed with dried sodium iodide (10.1g, 68mM) for 3 hours. The mixture was filtered, and the filtrate evaporated, taken up in dichloromethane, washed twice with water, and evaporated to give an orange oil (8.3g), 95% pure by g.l.c (2' SE30/150°) and containing no starting material. This was distilled at 84°/0.03mm to give a similar orange oil (6.5g, 72%), 96% pure by g.l.c.

i.r (CH_2Cl_2) 2960m, 2930w,2860w,1655s cm^{-1}.

n.m.r ($CDCl_3$) τ8.58 (s,6H)
6.42 (s,2H)
6.22 (s,2H)
4.99 (s,2H)

m.s m/e 269(52) $[C_7H_{12}INO_2]$, 254(67), 169(43), 142(B)

N-(N'-Trifluoroacetyl-aminoacetyl)-4,4-dimethyloxazolidine (XIg).

N-Trifluoroacetylglycine was prepared in 60% yield from glycine and 1.2 mole equivalents of trifluoroacetic anhydride in trifluoroacetic acid. Two crystallisations from benzene and sublimation at 100°/0.05mm gave white crystals, m.p 115° (lit.[88] 120°).

i.r (nujol) 3315s,3110w,3000-2300w,1700s,1560s cm^{-1}.

N-Trifluoroacetylglycyl chloride was prepared by refluxing the acid in benzene with 1.2 mole equivalents of freshly distilled thionyl chloride and one drop of D.M.F for 15 minutes. The mixture was filtered and evaporated to a yellow oil (95%).

i.r (film) 3310m,3100w,1800s,1715s,1545m cm^{-1}.

4,4-Dimethyloxazolidine (0.85g, 8.5mM) was acylated with the crude N-trifluoroacetylglycyl chloride (1.82g, 9.6mM) as described for XIa. The crude product (1.3g) was recrystallised three times from ether/petrol, m.p 98° (0.85g, 40%).

i.r (CH_2Cl_2) 3377m,2880w,1725s,1663s,1525m cm^{-1}.

n.m.r ($CDCl_3$) τ8.47 (s,6H)
6.18 (s,2H)
6.05 (d,2H, collapses to s with D_2O immediately)
4.98 (s,2H)
2.40 (br,1H,disappears with D_2O)

m.s m/e 254(45) (M), 199(B).

Detection of these and subsequent trifluoroacetyl derivatives on t.l.c proved difficult. Iodine and u.v were negative, and t-butyl hypochlorite/starch-KI treatment[89] was not very satisfactory. The best method was short exposure to ammonia fumes, and then spraying with ninhydrin and heating, giving pink spots.

Aii. Thiazolidine and N-acyl derivatives.

Thiazolidine hydrochloride was prepared in 89% yield from 2-mercaptoethylamine hydrochloride and aqueous formalin,[90] and the free base liberated with aqueous K_2CO_3 and extracted into ether.(85%)

i.r (film) 3280m(br),2940m,2870m,1440m,1322w,1260w,1230m,1171m, 1110m,930s,840s(br) cm^{-1}.

n.m.r (CCl_4) τ8.38 (s,1H)
6.8 - 7.4 (A_2B_2m,4H)
5.97 (s,2H)

N-Chloroacetylthiazolidine

The thiazolidine was acylated by the procedure used for XIa with 1.1 mole equivalents of chloroacetyl chloride, to give an oil (85%) with appropriate spectral data, that was used crude in the next step.

i.r (film) 2940m,2875w,1652s,790m cm^{-1}.

n.m.r ($CDCl_3$) τ6.86 (t,J=6.0,2H;br)
6.17 (t,J=6.0,2H)
5.90 (s,2H)
5.40 (s,2H)

N-Cyanoacetylthiazolidine (XXI).

A solution of the crude N-chloroacetylthiazolidine (1.65g, 10mM) in dry D.M.F (15ml) was added dropwise to a stirred suspension of dried sodium cyanide (1.5g, 30mM) in dry D.M.F (20ml) at 60°, and heating continued for 1 hour. Evaporation after filtration gave a red oil that was extracted with portions of boiling ether. On cooling, the combined extracts gave plate-like crystals m.p 59°. Two further recrystallisations from ether gave m.p 61° (0.42g, 27%).

i.r (CH_2Cl_2) 2935w,2878w,2275w,1670s cm^{-1}

n.m.r ($CDCl_3$) τ6.98 (t,J=6.0,2H)
6.26 (t,J=6.0,2H)
6.49 (s,2H)
5.55 (s,2H)

m.s m/e 156(100) (M).

$C_6H_8N_2OS$ C46.13, H5.16, N17.93%
found C46.40, H5.10, N17.70%

Aiii. Amino acid derivatives.

N-Benzoylamino acids were prepared by Schotten-Baumann benzoylation of the amino acids.

The better procedure for preparing N-benzoylamino acid esters from the amino acids was by esterification and then

benzoylation, rather than vice versa. Amino acid ester hydrochlorides were prepared by saturating a solution of the amino acid in the appropriate alcohol with dry hydrogen chloride and standing overnight at 0°.[91]

The amino acid ester hydrochlorides were benzoylated with benzoyl chloride in a two phase system of chloroform and aqueous Na_2CO_3[95].

Peptides were prepared using dicyclohexylcarbodiimide (DCC). 1 Mole equivalent of triethylamine was added to a stirred suspension of the amino acid ester hydrochloride in dry dichloromethane. After 5 minutes 1.2 mole equivalents of DCC dissolved in the minimum quantity of dichloromethane was added, followed by 1 mole equivalent of the N-protected amino acid also dissolved in the minimum quantity of dichloromethane. After stirring for 3 hours at room temperature, one drop of acetic acid was added, dicyclohexylurea filtered off, and the filtrate washed with saturated Na_2CO_3 solution, water, dilute HCl, and water, and then dried, evaporated and recrystallised.

Products were identified by their melting points and/or analyses. All compounds gave molecular ions in the mass spectra in agreement with their molecular formulae.(table IV).

Aiv. Materials for reactions with ABIN (section 3ii).

Azo-bis-isobutyronitrile (ABIN) was used as supplied. It was stored at 0°, and the melting point (101-103°decomp.) was checked frequently.

Tetramethylsuccinonitrile (TMSN) was prepared by refluxing ABIN in benzene for 48 hours under nitrogen, and recrystallising several times from methanol, m.p 168°[102].

2-Cyanopropan-2-ol (XXIX) was prepared by treatment of the bisulphite addition compound of acetone with aqueous potassium cyanide[67]. The crude product had appropriate spectral data, and attempted distillation only caused decomposition to

compound	m.p	lit. m.p	C%	H%	N%	lit. ref.
PhCO-GLY-OEt	60°	60.5°				93
PhCO-(DL)ALA-OEt(XXXVI)	73°	76-7°				94
PhCO-(DL)VAL-OEt(XXXIX)	66-8°	65-8°				95
PhCO-(L)PHE-OMe (XL)	82°	83.6-84.6°	72.06 71.83	6.05 6.13	4.94 4.34	96
PhCO-(DL)LEU-OEt (XXXVIII)	76-7°	73-5°	68.41 68.45	8.04 7.68	5.32 5.35	97
CH_3CO-GLY-OEt	48°	48°				98
PhCO-GLY-GLY-OEt	117°	117°	59.08 59.40	6.10 6.30	1.60 10.60	99
PhCO-GLY-(DL)LEU-OEt	75-7°	oil	63.73 64.06	7.55 7.69	8.74 8.64	100
PhCO-(DL)LEU-GLY-OEt	146°	145-146°	63.73 63.50	7.55 7.73	8.74 8.60	101
CH_3CO-GLY-(DL)VAL-OEt	83°		54.08 54.12	8.25 8.18	10.47 11.64	
CH_3CO-(L)PHE-(DL)VALOEt	163-164°		64.65 64.90	7.84 7.86	8.38 8.59	

table IV. Amino acid derivatives - melting points and analytical data (calculated analysis given first, then observed)

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acetone. XXIX decomposed to acetone on g.l.c (6'E301/80°; injection 250°; detector 260°).

i.r (film) 3420s(br),2995m,2225w,1460w,1375m,1190s,1150m(sh),975m, 875w cm^{-1}.

n.m.r (CCl_4) τ8.43 (s,6H) (benzene) τ8.64 (s,6H)
5.75 (br,1H) 5.60 (br,1H)

α-Benzoylaminoacetophenone (XLI) was prepared by nitrosation of acetophenone[103] (25%), reduction of the nitroso-acetophenone with stannous chloride[104] (70%) and benzoylation of the aminoacetophenone hydrochloride with benzoyl chloride in glacial acetic acid[105] (65%, m.p 126°, lit. 124°).

i.r (CH_2Cl_2) 3420w,1690m,1660s,1598w,1580w,1515s cm^{-1}.

n.m.r ($CDCl_3$) τ5.04 (d,J=4.3,2H)
2.50 (m,7H) and 2.05 (m,4H)
$C_{15}H_{13}NO_2$ C75.30, H5.48, N5.85%
found C75.60, H5.42, N5.84%

Av. Materials for reactions with NiPO (section 3iii).

N-Cyanoacetylpiperidine (XLIX) was prepared from ethyl cyanoacetate and piperidine,[106] m.p 86-87°(benzene), lit. 88°(water).
i.r (CH_2Cl_2) 2250w,1675s cm^{-1}.

Ethyl cyanoacetate did not react with 4,4-dimethyloxazolidine. With excess diethylamine, only 20% of N-cyanoacetyl-N,N-diethylamine (L) was formed after several days at room temperature.

Cyanoacetyl chloride.

Cyanoacetic acid and thionyl chloride form a black tar on warming; the literature route[107] requires 2.5 mole equivalents of phosphorus pentachloride. The following procedure was found satisfactory.

Phosphorus pentachloride (15g, 75mM) was added in small portions to a stirred, cooled solution of cyanoacetic acid (4.25g, 50mM) (dried under vacuum over P_2O_5) in sodium-dried ether (40ml). The mixture was stirred at room temperature for 4 hours, when most of the solid had gone into solution. The ether was distilled off at atmospheric pressure, and the product at 32-35°/0.15mm (3.45g, 67%).

Cyanoacetyl chloride decomposes within 8 days, even at 0°.

N-Cyanoacetyl-N,N-diethylamine (L).

Diethylamine was acylated with a slight excess of cyanoacetyl chloride, according to the procedure for XIa. The product (65%) was a non-crystallisable red oil, and the colour was not removed by distillation (108°/0.25mm) or by chromatography (silica gel/$CHCl_3$).
i.r (CH_2Cl_2) 2255w,1657s cm^{-1}.
n.m.r ($CDCl_3$) τ8.75 (t,J=7.0,3H) and 8.85 (t,J=7.0,3H)
6.57 (q,J=7.0,2H) and 6.62 (q,J=7.0,2H)
6.36 (s,2H)
m.s m/e 140(8)$[C_7H_{12}N_2O]$, 125(12), 100(13), 72(25), 58(B).

B. Characterisation of the reaction products.

Bi. Products from photochemical oxidations (section 3i).

N-(N'-Benzoylaminoacetyl)-4,4-dimethyloxazolidin-2-one (XVI, R = PhCONH)
m.p 110.5°
i.r (CH_2Cl_2) 3435w,1775vs,1705s,1660vs,1605w,1580w,1510s cm^{-1}.
n.m.r ($CDCl_3$) τ8.39 (s,6H) 2.95 (br,1H)
5.90 (s,2H) 2.52 (m,3H)
5.23 (d,J=5.3,2H) 2.11 (m,2H)
m.s m/e 276(23) $[C_{14}H_{16}N_2O_4]$(M), 171(9), 161(7), 116(19), 105(B).

N-(N'-Benzoylaminoacetyl)-2-amino-2-methylpropanol-O-formate (XVII, R = PhCONH)
oil
i.r (CH_2Cl_2) 3420m,3320m(br),1720s,1670s,1650vs,1603w,1578m,1510s cm^{-1}.
n.m.r ($CDCl_3$) τ8.60 (s,6H)
5.84 (d,J=5.3,2H; collapse to singlet with D_2O)
5.62 (s,2H)
2.98 (br,1H)
2.50 (m,3H) and 2.10 (m,2H)
1.90 (s,1H)

N-(N'-Benzoylaminoacetyl)-2-amino-2-methylpropanol (XVIII, R = PhCONH)
oil
i.r (CH_2Cl_2) 3500-3300w(br),3420m,3320m,1650s(br),1603w,1578w, 1510s cm^{-1}
n.m.r ($CDCl_3$) τ8.66 (s,6H) 3.13 (br,1H)
6.36 (s,2H) 2.50 (m,3H)
5.80 (d,J=5.3,2H) 2.10 (m,2H)
m.s m/e 219(7) ($M-CH_2OH$), 105(B).

N-Cyanoacetyl-4,4-dimethyloxazolidin-2-one (XVI, R = CN)
m.p 80° (ether/petrol)
i.r (CH_2Cl_2) 2954w,2280w,1777s,1717s cm^{-1}.
n.m.r ($CDCl_3$) τ8.40 (s,6H)
5.94 (s,4H)
m.s m/e 182(2.4) $[C_8H_{10}N_2O_3]$(M), 167(12), 100(B).

2-(Cyanoacetylamino)-2-methylpropanol-O-formate (XVII, R = CN).

oil.

i.r (CH_2Cl_2) 3420m,2250w,1725s,1690s,1520m cm^{-1}.

n.m.r ($CDCl_3$) τ8.60 (s,6H) 2.70 (br,1H)
6.66 (s,2H) 1.90 (s,1H)
5.69 (s,2H)

2-(Cyanoacetylamino)-2-methylpropanol (XVIII, R = CN).

oil.

i.r (CH_2Cl_2) 3410m,3300w(br),2250w,1680s,1520m cm^{-1}.

n.m.r ($CDCl_3$) τ8.65 (s,6H) 6.85 (br,1H)
6.62 (s,2H) 3.75 (br,1H)
6.37 (s,2H)

m.s m/e 157(0.6)$[C_7H_{13}N_2O_2]$ (M+1), 141(2.1)$[C_6H_9N_2O_2]$ ($M-CH_3$), 125(B).

N-(N'-Trifluoroacetyl-aminoacetyl)-2-amino-2-methylpropanol-O-formate (XVII, R = CF_3CONH).

oil.

i.r (CH_2Cl_2) 3420m,3375m,1725s,1690s,1522m cm^{-1}.

n.m.r ($CDCl_3$) τ8.59 (s,6H) 3.78 (br,1H)
6.00 (d,J=5.0,2H) 1.89 (s,1H)
5.66 (s,2H)

m.s m/e 211(88) ($M-CH_2OCHO$), 58(B).

2-Acetylamino-2-methylpropanol-O-formate (XVII, R = H).

oil.

i.r (CH_2Cl_2) 3445m,1725s,1678m,1508m cm^{-1}.

n.m.r ($CDCl_3$) τ8.64 (s,6H) 3.83 (br,1H)
7.95 (s,3H) 1.85 (s,1H)
5.65 (s,2H)

N-Acetyl-2-(2-(2-hydroxypropyl))-4,4-dimethyloxazolidine (XX).

m.p 85° (needles from petrol).

i.r (CH_2Cl_2) 3300m(br),1610s cm^{-1}.

n.m.r ($CDCl_3$) τ8.87 (s,3H) and 8.72 (s,3H)
8.50 (s,6H) 6.33 (d,1H) ┐ AB,J=9.0Hz
7.75 (s,3H) 6.09 (d,1H) ┘
4.75 (s,1H)

m.s m/e 202(1.6) (M+1), 186(1.6) [$C_9H_{16}NO_3$] (M-CH_3), 143(20), 142(58) (M-$(CH_3)_2COH$), 100(B).

Bii. Products from reactions with ABIN (section 3ii).

N-Formylbenzamide (XXXII).

m.p 112° (lit.[92] 112-113°)

i.r (CH_2Cl_2) 3400m,3260w,1729s,1688s,1603w,1582w,1500m cm^{-1}.

n.m.r ($CDCl_3$) τ2.36 (m,3H) and 1.99 (m,2H)
0.58 (d,J=10.0,1H)
0.00 (br,1H)

m.s m/e 149(11) [$C_8H_7NO_2$] (M), 121(45), 105(B).

The characteristic doublet at τ0.58 in the n.m.r spectrum is very useful for detecting and estimating N-formylbenzamide in reaction mixtures.

N-Acetylbenzamide (XXXVII).

m.p 111° (lit.[108] 117°)

i.r (CH_2Cl_2) 3400m,1720s,1700s,1603m,1583w,1502m cm^{-1}.

n.m.r ($CDCl_3$) τ7.38 (s,3H)
2.35 (m,3H) and 2.15 (m,2H)
1.00 (br,1H)

m.s m/e 163(37) [$C_9H_9NO_2$] (M), 105(B).

2-Cyano-2-propyl phenylglyoxylate (XLII).

oil

i.r (CCl_4) 2950w,1750w,1692s,1595m cm^{-1}.
also, inter alia, 1190s,1177s,1138s,1100m(sh) cm^{-1}.

n.m.r (CCl_4) τ8.11 (s,6H)
2.50 (m,3H) and 1.95 (m,2H)

m.s m/e 189(6), 122(20), 105(B).

The spectral data for this compound closely resemble those expected for 2-cyano-2-propyl benzoate, except for the C=O absorption at 1692 cm^{-1} (c.f methyl phenylglyoxylate, synthesised unambiguously from phenylglyoxylic acid and diazomethane: ν_m(film) 1735s, 1689s,1592m,1575w cm^{-1}).

2-Cyano-2-propyl benzoate.

2-Cyanopropan-2-ol (0.85g, 10mM) and benzoyl chloride (1.54g 11mM) were mixed in pyridine (1ml). After a vigorously exothermic reaction, water (6ml) was added, and the mixture extracted twice with ether (10ml). The extracts were washed with small portions of N HCl until free of pyridine, and evaporated (1.8g). T.l.c showed several products, but g.l.c showed a single major product and this was collected (6' E301/150°), giving a total of 30mg from two 60μl injections. The product crystallised on cooling, and was recrystallised from petrol at -80°.

m.p 39.5°

i.r (CCl_4) 1735s,1600w cm^{-1}.
and, inter alia, 1155s,1102s(sh) cm^{-1}.

n.m.r (CCl_4) τ8.11 (s,6H)
2.50 (m,3H) and 1.95 (m,2H)

m.s m/e 189(18) (M), 122(35) ($M-CH_2C(CH_3)_2CN$), 105(B).

$C_{11}H_{11}NO_2$ C69.82, H5.86, N7.40%
found C70.23, H5.94, N7.47%

The i.r spectrum of 2-cyano-2-propyl benzoate lacks the absorption at 1692 cm^{-1} of the phenylglyoxylate analogue (XLII) and is different in the fingerprint region. The n.m.r and mass spectra are identical. α-Carbonyl esters are known to decarbonylate readily, and this probably occurs in the mass spectrometer inlet, so that the spectrum observed for XLII is in reality that of 2-cyano-2-propyl benzoate. Independent synthesis of XLII was attempted.

Phenylglyoxylic acid (reagent grade 95% pure, 3.0g, 19mM) and freshly distilled thionyl chloride (2.6g, 22mM) were heated together for 3 hours at 100° (ref.109). The product was distilled at 31-35°/0.2mm (1.93g), and had an i.r spectrum similar to that of benzoyl chloride, with only a medium intensity band at 1690 cm^{-1}.

This product (0.85g) was mixed with 2-cyanopropan-2-ol (0.425g, 5mM) in pyridine (3ml), and after a mildly exothermic reaction was worked up as above (1.0g). G.l.c analysis showed a major peak corresponding to 2-cyano-2-propyl benzoate, and a minor component with longer retention time. The latter was collected, and its i.r spectrum was identical with that of XLII.

The available values for the boiling point of phenylglyoxylyl

chloride are thus 212° (91°/9.5mm),[109] 260° (125°/9mm)[110] and 210-220° (31-35°/0.2mm) (this work), corrected to 760mm. The boiling point of benzoyl chloride is 198° (56°/4mm) and most probably the method of ref.109 causes extensive decarbonylation.

Biii. Products of the reactions with NiPO (section 3iii).

1,2,3-Tricyano-1,2,3-tri-(4,4-dimethyl-3-oxazolidinecarbonyl)cyclopropane (XLVIII).

m.p 235° (CCl_4); sublimed at 200°/0.03mm.

i.r (nujol) 2260vw,1690s cm^{-1}.

(CH_2Cl_2) 2880m,1690s cm^{-1}.

n.m.r 100MHz ($CDCl_3$) τ8.45 (s), 8.48 (s), 8.505 (s) — total 18H; peak height ratios 142:135:117.

6.16 (s), 6.14 (s) — total 6H; intensity ratio c. 2:1.

4.73 (s), 4.71 (s) — total 6H; intensity ratio c. 2:1.

at -50°, three pairs of signals, each pair in c. 2:1 ratio:-

τ8.46, 8.42 (18H)

6.09, 6.06 (6H)

4.73, 4.68 (6H)

u.v (MeOH) end absorption only.

m.s m/e 498(0.21) (M), 398(11), 327(6) (398-71*), 298(4), 272(12) (327-55*), 271(46), 254(14) (298-44), 241(7), 200(15), 199(60) (271-72*), 170(21), 167(21), 166(B) (241-75*)

osmometric molecular weight ($CHCl_3$) 520.

$C_{24}H_{30}N_6O_6$ C57.82, H6.07, N16.86% (M = 498.5)

found C57.94, H6.16, N16.89%

1,2,3-Tricyano-1,2,3-tri-(1-piperidinecarbonyl)cyclopropane (LII).

m.p 237.5° (benzene/petrol).

i.r (CH_2Cl_2) 2940s,2860s,2239w,1670s cm^{-1}.

n.m.r ($CDCl_3$) τ8.35 (m,18H) br

6.1-6.35 (m,12H)

u.v (MeOH) end absorption only.

m.s m/e 450(0.26) (M), 338(10), 255(30), 150(32), 112(84), 84(B).

1,2-Dicyano-1,2-di-(1-piperidinecarbonyl)ethylene.(LIV).

A) m.p 94° (petrol)
i.r (CH_2Cl_2) 2950m,2865m,2225w,1659s,1440s,1365w,1302w,1198m, 1123m,1015m,991m,951w,850m cm^{-1}.
u.v (MeOH) 286nm (ε3,800)
m.s m/e 300(8)$[C_{16}H_{20}N_4O_2]$ (M), 217(5), 216(8), 84(B).

B) m.p 196° (benzene)
i.r (CH_2Cl_2) 2950m,2865m,1661s,1440s,1365w,1302w,1230m,1141w, 1121w,1011m,951w,850w cm^{-1}.
u.v (MeOH) 265nm (ε2,700)
m.s m/e 300(5) (M), 217(13), 216(10), 84(B).

cis and/or trans-1,2-Dicyanoethylene-1,2-di-(N,N-diethylcarboxamide) (LV).
m.p 68-69° (ether)
i.r (CH_2Cl_2) 2220vw,1660s cm^{-1}.
n.m.r ($CDCl_3$) τ8.86 (t,J=7.0,6H) and 8.69 (t,J=7.0,6H) 6.60 (q,J=7.0,8H) br
u.v (MeOH) 283nm (ε8,060)
m.s m/e 276(7)$[C_{14}H_{20}N_4O_2]$ (M), 261(11) (276-15*), 205(17), 204(71) 176(12) (204-28*), 148(12) (176-28*), 72(B).

trans-Triethyl 1,2,3-tricyanocyclopropane-1,2,3-tricarboxylate (LIII).
m.p 119.5° (lit.[83] 119-120°)
i.r (CH_2Cl_2) 2250vw,1760s cm^{-1} (lit.[83] 2257vw,1761 cm^{-1}).
n.m.r ($CDCl_3$) τ8.60 (t,J=7.0,6H) and 8.55 (t,J=7.0,3H) 5.55 (q,J=7.0,4H) and 5.47 (q,J=7.0,2H)
u.v (MeOH) end absorption only.
m.s m/e 333(7)$[C_{15}H_{15}N_3O_6]$ (M), 288(23), 260(23), 216(25) (260-44*) 206(23), 205(35), 189(23), 187(31), 161(59), 160(22), 99(59), 86(50), 29(B).

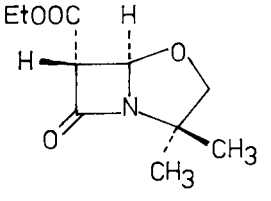
Chapter 4
THE REACTIONS OF ACYL CHLORIDES WITH 2-OXAZOLINES.

In chapter 2, synthesis of the oxa-penam (I) was described. The oxazolidine ring of I proved to be rather labile, and it was suggested that this is due, at least in part, to the electron-withdrawing substituent at C6. The latter, however, is essential for the synthesis of the α-diazoamide precursor to I, and production of an oxa-penam without such a substituent requires an alternative method.

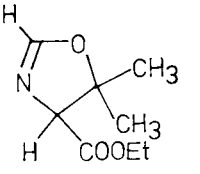
A facile route to 2-unsubstituted-2-oxazolines has been reported,[112] and ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (II)[113] was seen to be particularly interesting as a precursor to an oxa-penam with natural penicillin-type substitution.

We have investigated the reaction of acyl chlorides and triethylamine with the imino function of II and of other oxazolines, by analogy with the route to bicyclic β-lactams pioneered by Sheehan and developed by Bose (chapter 1). An oxa-penam with 6-azido substitution, e.g., could be very much more stable than I with its 6-ethoxycarbonyl substituent, and might even permit catalytic reduction of the azido to an amino function.

Oxa-penams were not obtained by these methods, but the alternative reactions in specific cases were investigated, and observations pertinent to the reactions in general recorded.



(I)

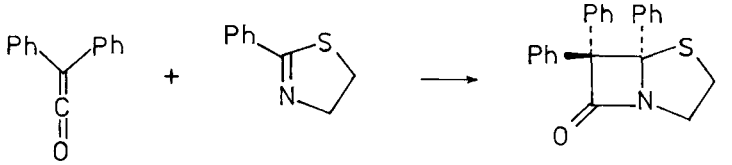


(II)

Some of the material in this chapter was given in a short talk to the Heterocyclic Section of the Annual Conference of the Chemical Society, Manchester, April 1972.

CYCLOADDITIONS TO IMINES AS ROUTES TO β-LACTAMS.

Reaction of ketoketenes with imines provided the first genuine β-lactams,[114] and the reaction proceeds in high yield with Schiff bases derived from aromatic amines and aldehydes. In the original penicillin studies[6] the adduct (III) from diphenylketene and 2-phenylthiazoline provided vital spectral data for the structural elucidation, but a variety of ketenes failed to react with 2-unsubstituted thiazolines.

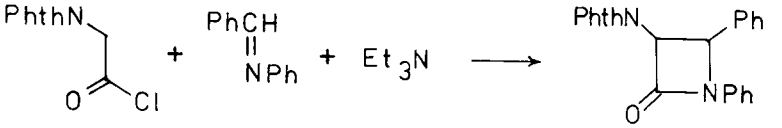


(III)

The reaction is also limited by the nature of the ketene. A 6-monosubstituted penicillin requires use of an aldoketene, and these polymerise readily. In the original penicillin work[6] it was realised that such an aldoketene would have to be generated *in situ*, but phenylacetylcarbamoyl-diazomethane with silver oxide - a potential source of the unknown phenylacetylamino-ketene - in the presence of methyl 5,5-dimethyl-2-thiazoline-4-carboxylate gave a mixture of products devoid of antibiotic activity. Since then the reaction of diazoacetophenone with silver oxide has been used successfully to generate phenylketene *in situ* by a Wolff rearrangement.[115]

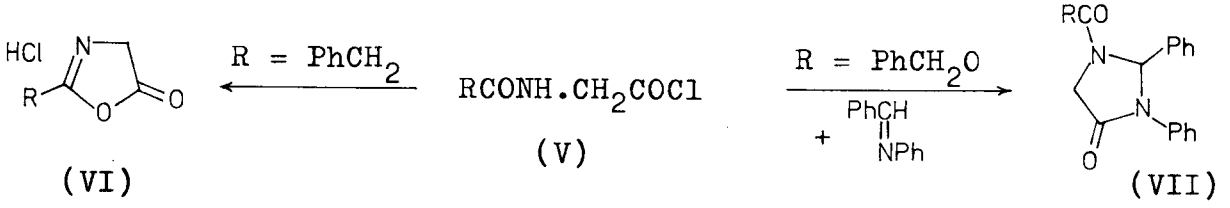
Other sources of aldoketenes include α-bromoacyl bromides with zinc,[116] and acyl halides with a tertiary amine. The former has been used in cycloadditions to aldehydes to form β-lactones, but only the latter has been used in reaction with imines to give β-lactams.

The reaction was introduced by Sheehan.[117] Reaction of phthalimidoacetyl chloride with benzylideneaniline and triethylamine in benzene at room temperature gave the β-lactam (IV) in 50% yield. The phthalimido group could be converted to an amino function by hydrazinolysis, and the 3-amino-1,4-diphenylazetidin-2-one reacylated.



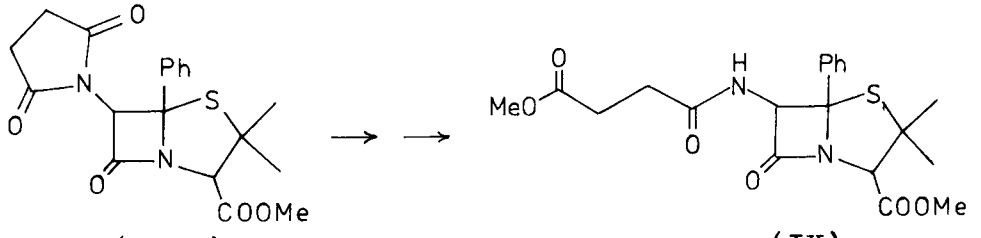
(IV)

Application of the reaction to 2-thiazolines was limited to those with 2-aryl or 2-carboxy substituents[118], and also by the lability of the derived fused β-lactam to hydrazine. Amino-acyl chlorides in which the amino nitrogen is not fully substituted (V) could not be used in the reaction. In many such cases the acyl chloride probably exists as the hydrochloride of the oxazol-5-one (azlactone) (VI), and addition of base merely liberates the free heterocycle. Where azlactonisation is impossible, reaction through the amino nitrogen occurs in the cycloaddition reaction[119] e.g to (VII).



(VI) (V) (VII)

Some of these problems have been overcome. Sheehan[120,122] utilised a principle recently classified as 'latent functionality'[121]. He replaced the phthalimido group in the above reactions with the succinimido group. The adduct (VIII) with 2-phenyl-5,5-dimethyl-2-thiazoline-4-carboxylate was reacted with mild base and then diazomethane, when this protecting group was converted into a β-methoxycarbonyl-acylamino side chain in the 5-phenylpenicillin (IX)[120]. Other heterocyclic protecting groups were devised to give a phenylacetamido group on deprotection[122].



(VIII) (IX)

More recently Bose and Manhas have developed the use of azidoacetyl chloride in the reaction with imines and triethylamine[123]. The azido group can be catalytically hydrogenated to an amino function, but this may be complicated in adducts containing sulphur. Nevertheless, a number of penicillin analogues have been produced including 6-epi-penicillin V methyl ester[39].

THE MECHANISM OF CYCLOADDITIONS TO IMINES.

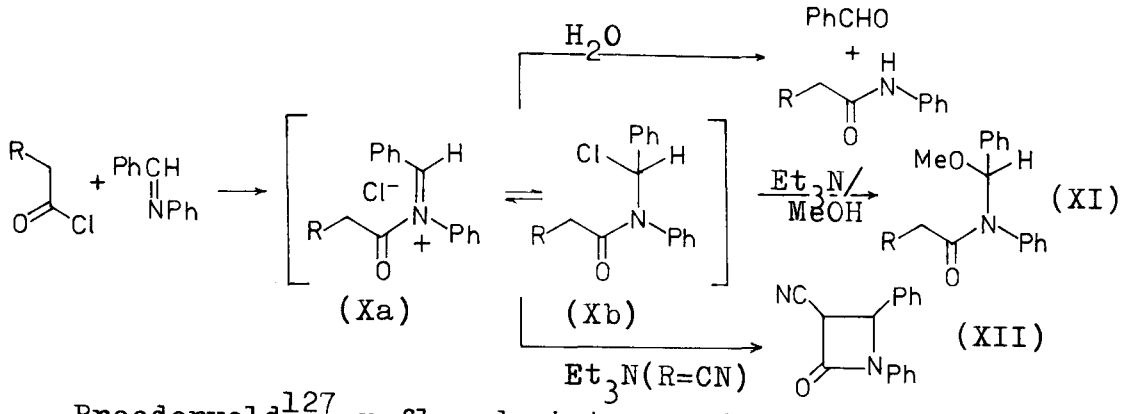
1) Adducts of acyl chlorides and imines.

In subsequent studies of these cycloadditions to imines, all too often distinction has not been made between those reactions employing ketenes and those using an acyl chloride and tertiary base. Only diphenyl- and dimethyl- ketene are readily available as such, although several other ketenes, including the parent can be regenerated from the corresponding dimers.

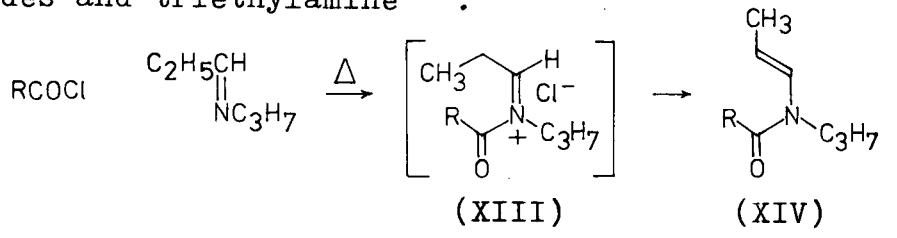
The majority of other ketenes are derived in situ from the acyl chloride and tertiary amine. Two reaction procedures are possible:

A. addition of the acyl chloride to a mixture of the imine and tertiary base;
B. addition of triethylamine to a mixture of the imine and acyl chloride.

1:1 Adducts of acyl chlorides and imines have been known since 1914[124], when a crystalline product was obtained on mixing equimolar amounts of benzoyl chloride and benzylideneaniline. This product gave benzaldehyde and N-benzoylaniline on exposure to moisture. More recently, Böhme has isolated similar adducts - some crystalline, some distillable oils - to which he assigned the ionic N-acylimmonium chloride (e.g Xa) and/or the covalent α-chloro-N-acylamine (e.g Xb) structures[125]. These hydrolysed readily, and reacted with triethylamine and methanol to give α-acylamino methyl ethers (e.g XI). The adduct between cyanoacetyl chloride and benzylideneaniline (X, R = CN) cyclised to the β-lactam (XII) on treatment with triethylamine[126].



Breederveld[127] refluxed mixtures of propylidenepropylamine and acyl chlorides with triethylamine to obtain 1-(N-acylpropylamino)-1-propene (XIV) by elimination of HCl from a proposed intermediate N-acylimmonium chloride (XIII), c.f Xa, and a similar reaction has been observed between lactim ethers, acyl chlorides and triethylamine[128].

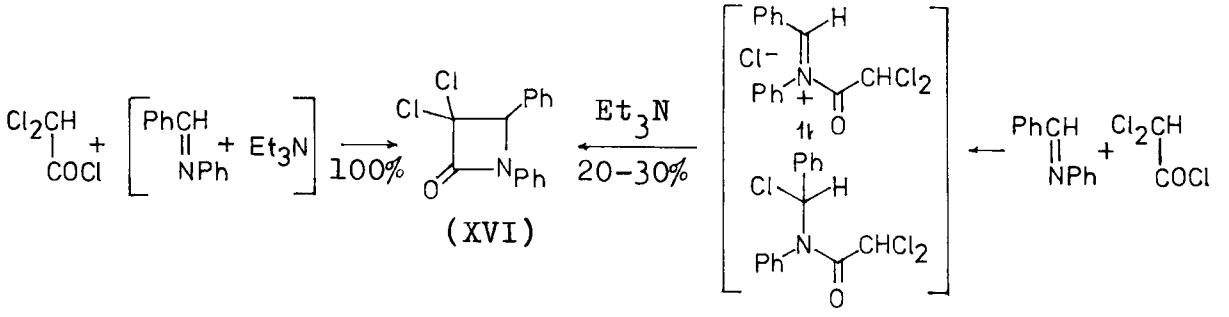


Spectroscopic evidence for at least partially covalent adducts (c.f Xb) of acyl chlorides and imines has been reported by Bose[129] and by Nelson[130]. The resonance of the benzylic proton in benzylideneaniline shifted upfield on addition of acetyl chloride, excluding formation of an ionic product, and suggesting formation of the covalent adduct (XV).[129]

$$CH_3COCl + \underset{\tau 1.62}{PhC\underline{H}{=}NPh} \longrightarrow \underset{\tau 2.10}{PhC\underline{H}(Cl)\text{-}N(Ph)COCH_3} \quad (XV)$$

Thus reaction procedure B above probably does not involve a ketene, but is the reaction of the tertiary amine with the adduct of acyl chloride and imine. Depending upon the relative rates of formation of the latter adduct and the corresponding ketene, procedure A could proceed *via* the same pathway or *via* a ketene and its reaction with the imine. Duran and Ghosez[131] reacted dichloroacetyl chloride with benzylideneaniline and triethylamine (procedure A) to obtain the corresponding 3,3-dichloro-

1,4-diphenylazetidin-2-one (XVI) in quantitative yield. They isolated the acyl chloride-imine adduct (XVII) and reacted it with triethylamine to obtain the β-lactam XVI in only 20-30% yield (c.f procedure B). Furthermore, on mixing the acyl chloride and triethylamine, precipitation of triethylammonium chloride was virtually instantaneous even at -50°, and the authors concluded that, in this case, reaction procedure A involved a ketene intermediate.

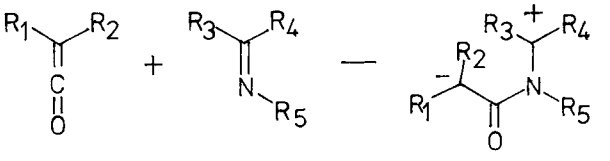


(XVI)

(XVII)

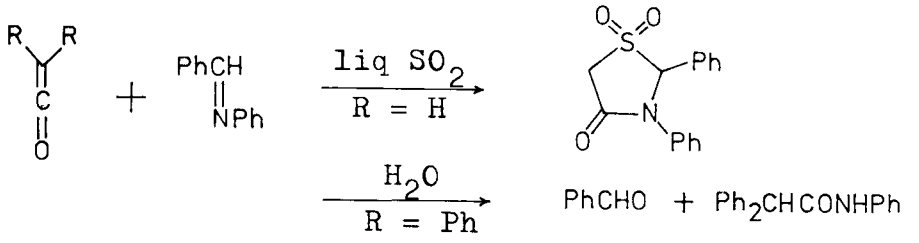
2) Cyclisation reactions.

The reaction of ketenes with imines could proceed by a concerted $[{}_2\pi_a + {}_2\pi_s]$ cycloaddition, or by a two step ionic or radical mechanism. While cycloaddition to olefins is probably concerted in at least some cases, that to imines is certainly a two-step process, as evidenced by a) trapping of the ionic intermediate, b) formation of 2:1 as well as 1:1 adducts, and c) the lack of stereospecificity (ref. 132). The ketene and imine form a 1:1, 1,4-dipolar adduct (XVIII) which can close to form a β-lactam, for example.



(XVIII)

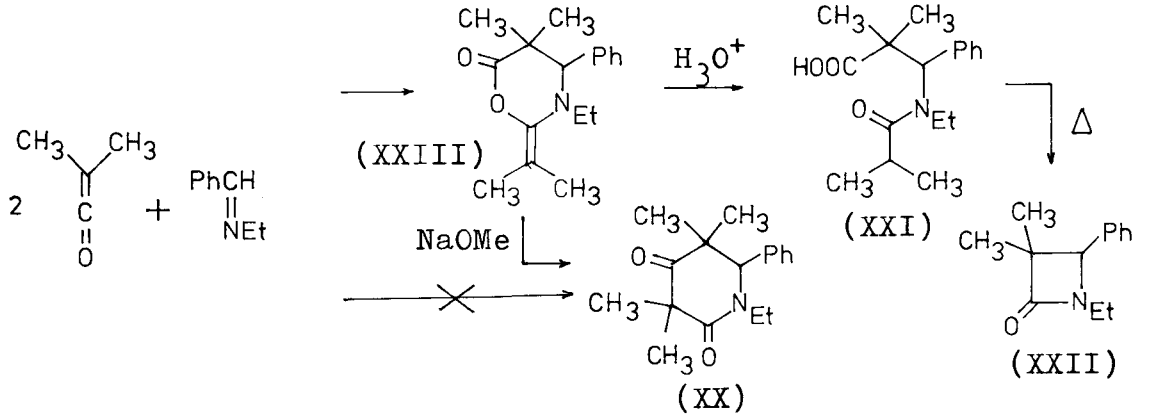
a) When ketene is reacted with benzylideneaniline in liquid sulphur dioxide, the initial 1,4-dipolar adduct is captured by the solvent to give 2,3-diphenylthiazolidin-4-one dioxide (XIX).[133] Kagan and Luche stopped the reaction of diphenylketene and benzylideneaniline with water to obtain benzaldehyde and diphenylacetanilide.[134]



Substituting either of the aromatic rings of the imine with p-methoxy groups caused a 2.3 times rate increase.[134] A concerted cycloaddition would not be affected by such a substitution.

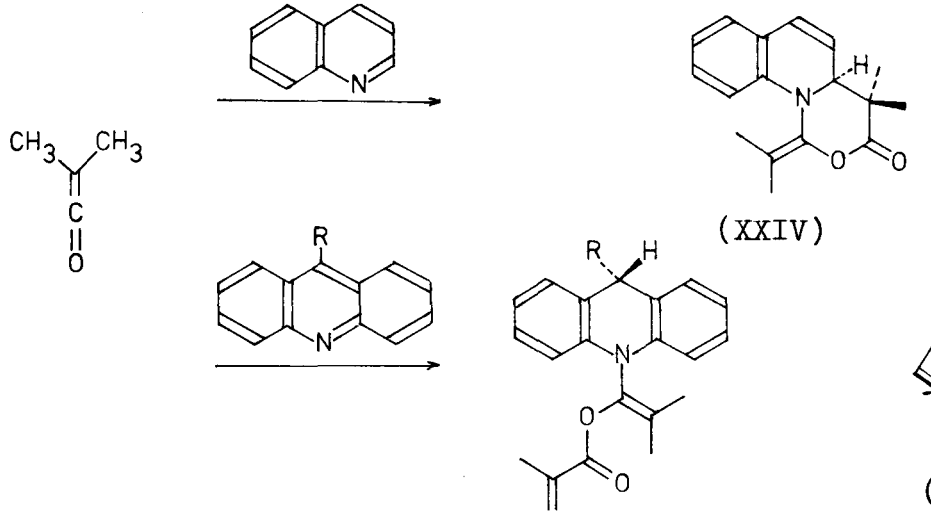
b) Formation of 2:1 adducts in the reactions of ketenes with imines was recognised by Staudinger. He assigned these the symmetric piperidin-2,4-dione structure (e.g XX). On hydrolysis they gave β-acylaminoacids (e.g XXI) that could be cyclised to β-lactams by heating (e.g XXII). This procedure was used to generate 5-phenyl-6,6-dimethylpenam from dimethylketene and 2-phenylthiazoline in the original penicillin work.[6]

The facile hydrolysis of the 2:1 adducts is not explained by the piperidin-2,4-dione structure, and it is surprising that the latter went unchallenged until 1965 when it was replaced by the asymmetric tetrahydro-1,3-oxazin-6-one structure (e.g XXIII). Specifically, dimethylketene and benzylidene-ethylamine gave a 2:1 adduct XXIII, the n.m.r spectrum of which at once showed the presence of two vinylic methyl groups. As a vinyl ester it was easily hydrolysed, and with catalytic sodium methoxide gave the piperidin-2,4-dione XX, providing conclusive proof of the error of the original assignment.[135,136]

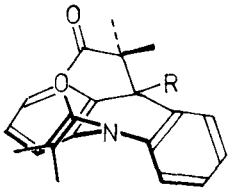


Other 2:1 adducts have been obtained with heterocyclic imines where formation of β-lactams or tetrahydro-1,3-oxazin-6-ones would lead to greater loss of aromaticity. Reaction of dimethylketene with quinoline or isoquinoline gives 2:1 adducts of the

latter type (e.g XXIV),[137] but the 2:1 adduct with phenanthridine has the acyclic structure (XXV, R = H). Reaction with 9-methylphenanthridine gave an analogous acyclic adduct (XXV, R = CH_3), and also the bridged compound (XXVI).[138]



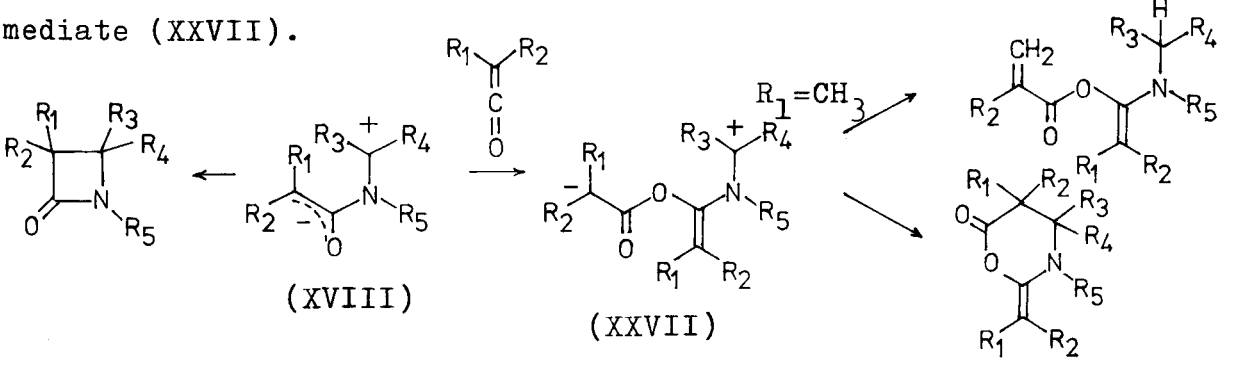
(XXIV)



(XXVI, R = CH_3)

(XXV, R = H,CH_3)

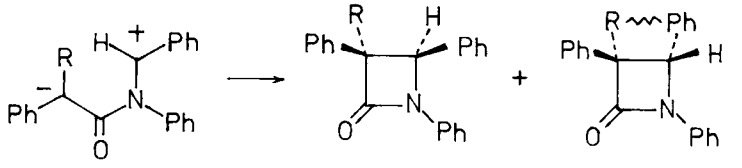
All these adducts are cited as evidence for a 1,4-dipolar intermediate XVIII in the reaction of ketenes with imines. This can close to form a β-lactam, or react with a second molecule of the ketene. The bridged adduct XXVI is merely a vinylogue of the tetrahydro-1,3-oxazin-6-one type of 2:1 adduct, and the acyclic isomer XXV is formed by hydride transfer, from the common intermediate (XXVII).



(XVIII)

(XXVII)

c) The stereochemistry of β-lactam formation has been interpreted in terms of the 1,4-dipolar intermediate XVIII. Aldoketenes (acyl chloride + triethylamine) with benzylideneaniline (c.f XVIIIa, R = H) give exclusively <u>trans</u>-β-lactams, while phenylketoketenes (via all three routes) give mixtures of <u>cis</u>- and <u>trans</u>-β-lactams, the proportion of the <u>cis</u>-component increasing with increasing steric bulk of the ketene substituent (R in XVIIIa).[139]



(XVIIIa) cis trans

In one of the few real acknowledgements of specific reaction conditions, Bose[123] claimed that the reaction of azidoacetyl chloride, benzylideneaniline and triethylamine gives the trans-β-lactam by procedure A, and the cis- by procedure B. No explanation was offered, and we found that performing the Sheehan reaction between phthalimidoacetyl chloride, benzylideneaniline and triethylamine in benzene gave the cis- and trans-β-lactams (IV) (30:70) in 50% yield by procedure A, and the same mixture in 30% yield by procedure B, here accompanied by hydrolysis products - benzaldehyde and phthalimidoacetanilide. In the latter procedure there is a delay before addition of the triethylamine during which water can react with the acyl chloride-imine adduct, while in procedure A successive steps in the reaction - whatever they may be - proceed without delay.

Formation of the 1,4-dipolar adduct XVIII of ketenes and imines has been well established.

The reaction between imines and acyl chlorides in the presence of a tertiary base under conditions A may proceed via ketene formation. Under conditions B, and possibly under conditions A, a 1:1 acyl chloride-imine adduct is formed.

If this adduct is in equilibrium with its components, the tertiary base could react with the small amount of acyl chloride present to form a ketene, and hence the 1,4-dipolar ketene-imine adduct.

Direct elimination of HCl from the acyl chloride-imine adduct could generate the same 1,4-dipolar intermediate as in ketene reactions.

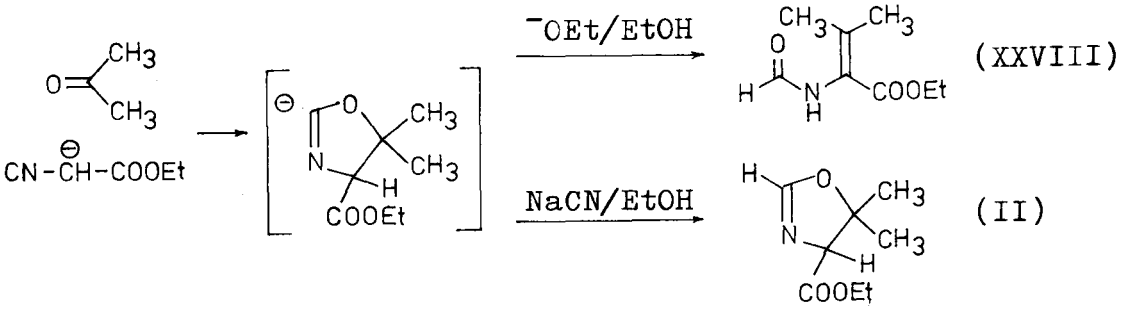
α-Elimination of HCl from the adduct of an acyl chloride and imine of an aldehyde could generate a carbenoid intermediate, which could insert into the C2-H bond of the N-acyl group forming a β-lactam.

The point is that the adducts of acyl chlorides and imines undoubtedly have a chemistry of their own, and may or may not give rise to ketene-type intermediates according to the specific example. The adducts of acyl chlorides and 2-oxazolines, for instance show some unusual reactions. All too often in product and stereochemistry studies, reactions of imines with ketenes, and with acyl chlorides and tertiary base under conditions A and B have been grouped together with no explicit rationale.

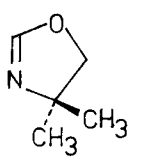
ATTEMPTED SYNTHESES OF OXA-PENAMS.

Synthesis of an oxa-penam by a ketene-type cycloaddition requires a 2-oxazoline as imino component. The oxazolines and oxazolidines are markedly less stable than their sulphur analogues,[26] and the 2-unsubstituted derivatives are particularly hard to come by. Prior to this work, Schöllkopf had published the synthesis of 2-unsubstituted oxazolines from the α-carbanions of isonitriles by reaction with carbonyl compounds[112]. Use of ethyl isocyanoacetate and acetone should then give ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate, the oxygen analogue of the 5-membered ring of the penicillin nucleus.

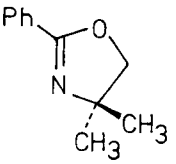
Using sodium ethoxide or sodium hydride as base in this reaction gave the crystalline α-formylaminoacrylate ester (XXVIII) as Schöllkopf later reported.[158] Schöllkopf subsequently[113] showed that sodium cyanide in ethanol was sufficiently basic to catalyse the initial cyclisation, but not basic enough to labilise the proton α- to the ester group and cause the rearrangement to XXVIII. The desired oxazoline II was obtained in 50% yield by using a 50% excess of acetone.



The 2-unsubstituted (XXIX) and 2-phenyl- (XXX) 4,4-dimethyl-2-oxazolines were prepared from 2-amino-2-methylpropanol and formic[140] and benzoic[141] acids respectively.



(XXIX)



(XXX)

With rigorous exclusion of water from the reactions, and working at high dilutions - 1mM scale in 75ml - in dichloromethane, reaction of the Schöllkopf oxazoline II or 4,4-dimethyloxazoline XXIX with phthalimidoacetyl chloride or azidoacetyl chloride and triethylamine failed to give any β-lactam, as judged from the i.r spectra of the reaction mixtures, under the following conditions:

i) addition of the acyl chloride to an equimolar mixture of the oxazoline and triethylamine at room temperature or at -80° (procedure A);

ii) addition of triethylamine to a mixture of the acyl chloride and oxazoline at room temperature or at -80° (procedure B);

ii)) dropwise addition of triethylamine to azidoacetyl chloride at -80° under nitrogen, and transfer of the solution of the ketene (?) at -80° under nitrogen pressure to a solution of the Schöllkopf oxazoline II at -80°.

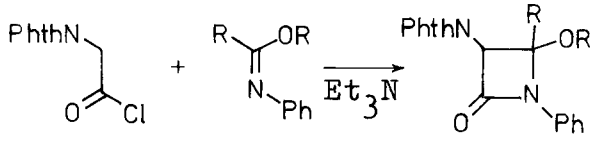
It was noted above that the course of these ketene-type cycloadditions was very dependent upon the nature of the reactants.

Sheehan stated that phthalimidoacetyl chloride and triethylamine gave β-lactams when reacted with thiazolines having 2-aryl or 2-methoxycarbonyl substituents, but not with 2-unsubstituted, 2-chloro- or 2-thio-thiazolines[118]. Bose obtained fused β-lactams in good yield with azidoacetyl chloride, triethylamine and 2-arylthiazolines, but only in 8% yield from methyl 5,5-dimethyl-2-thiazoline-4-carboxylate.[39]

2-oxazolines are cyclic imino-ethers. Acyclic N-phenylimino-ethers (XXXI)(and thioethers), with the imino carbon bearing a phenyl group (XXXI, R = Ph) or hydrogen (XXXI, R = H) gave

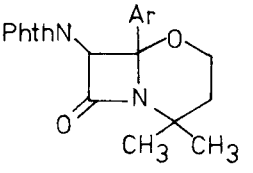
monocyclic β-lactams (XXXII) with phthalimidoacetyl chloride and triethylamine (procedures A and B) in 50-70% and 30% yields respectively[142]. The product 3-phthalimido-4-alkoxy-azetidin-2-ones XXXII were extracted into boiling ethanol, deprotected with hydrazine and reacylated. The same authors[143], as well as Sheehan[144], obtained 6-aryl-O-cephams (e.g XXXIII) in c. 60% yield from 2-aryl-5,6-dihydro-1,3-oxazines with phthalimidoacetyl chloride and triethylamine, and these could be deprotected and reacylated.

Thus imino-ethers are not unknown as components in these cycloadditions. An oxa-penam 'monohydrate' (!) was reported from 2-methyloxazoline, phthalimidoacetyl chloride and triethylamine, but this was promptly shown to be the expected N-phthalimidoacetylethanolamine-O-acetate (XXXIV)[145].

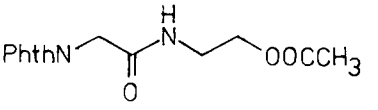


(XXXI) (XXXII)

(R = H,Ph)



(XXXIII)



(XXXIV)

ADDUCTS OF ACYL CHLORIDES AND 2-OXAZOLINES.

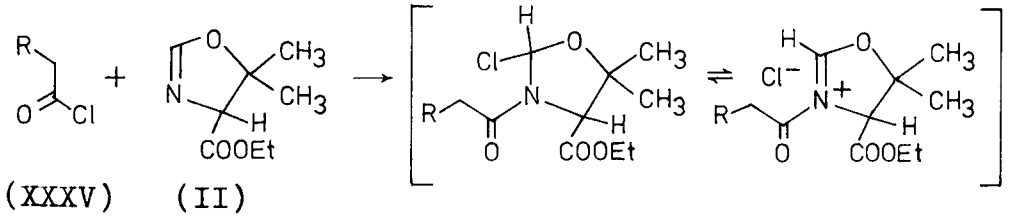
i) N.m.r spectra.

On mixing the Schöllkopf oxazoline II with substituted acetyl chlorides (XXXV, R = H, Cl, N_3, COOEt or phthalimido (PhthN)) in $CDCl_3$ in an n.m.r sample tube, the resultant n.m.r spectra show basically two sets of signals in each case. The major set corresponds to that expected for the N-acyl-2-chloroöxazolidine (XXXVI), by comparison with the spectra of corresponding amides and of other 2-substituted-N-acyloxazolidines obtained in this work. Particularly noticeable is a sharp 1H singlet at c. τ2.4 corresponding to the methine proton at C2 of the heterocyclic ring. The other set of signals is assigned to the N-acyloxazolinium chloride (XXXVII). The protons attached to the ring substituents resonate at positions similar to those in the trifluoroacetate salt of the oxazoline II, appreciably downfield from those in

the covalent tautomer XXXVI. The C2-H resonance appears as a broad hump between τ0-1 (c.f τ1.30 in the trifluoroacetate of II). Table I shows the τ values of the signals assigned to the covalent XXXVI and ionic XXXVII forms of the different adducts.

When the acyl chlorides and oxazoline II are mixed in the less polar solvent carbon tetrachloride, similar n.m.r spectra are observed, but with an increased proportion of the covalent form XXXVI, as might be expected if the two species are in equilibrium. Table III compares the percentages of the covalent tautomers XXXVI in the two solvents.

As an illustration, mixing chloroacetyl chloride XXXV (R = Cl) with the Schöllkopf oxazoline II in carbon tetrachloride gives rise to only one set of signals in the n.m.r spectrum, assigned to the covalent species XXXVI (R = Cl), while in $CDCl_3$ the covalent XXXVI : ionic XXXVII ratio is 3:1. These two spectra are shown in figs. 1 and 2 respectively.



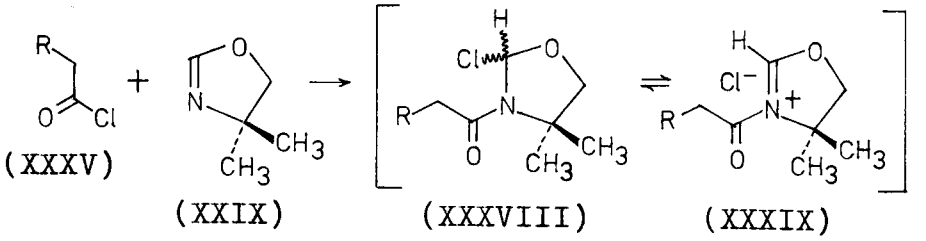
(XXXV) (II) (XXXVI) (XXXVII)

On mixing the above acyl chlorides and 4,4-dimethyl-oxazoline XXIX in carbon tetrachloride, a white precipitate is formed. On mixing the acyl chlorides XXXV (R = H, Cl, N_3, and PhthN) with the oxazoline XXIX in $CDCl_3$ two sets of signals are observed in the n.m.r spectrum, and assigned to the covalent (XXXVIII) and ionic (XXXIX) tautomers of a 1:1 adduct on exactly the same principles as above, and the percentages of the covalent forms XXXVIII are recorded in table III. Again C2-H in the covalent form resonates at c. τ2.4 while that of the ionic form gives a broad signal to lower field. Fig.3 shows the n.m.r spectrum (100MHz) of an equimolar mixture of chloroacetyl chloride XXXV (R = Cl) and 4,4-dimethyl-oxazoline XXIX in $CDCl_3$.

However, with 4,4-dimethyloxazoline XXIX, ethyl malonyl chloride XXXV (R = EtOOC) gives an n.m.r spectrum (fig.4) that, on the previous assignments, indicates predominance of the ionic

form XXXIX (R = EtOOC). C2-H resonates as a sharp singlet at τ0.43, and there are two very small singlets at τ2.30 and 2.40, i.e in the region expected for the C2-H resonance of the covalent form XXXVIII (R = EtOOC).

Table II shows the τ values of the signals assigned to the covalent XXXVIII and ionic XXXIX tautomers of the adducts of acyl chlorides and oxazoline XXIX.



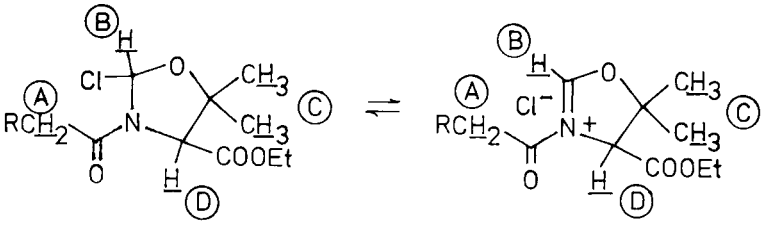
(XXXV) (XXIX) (XXXVIII) (XXXIX)

The reactions of acyl chlorides with the two oxazolines II and XXIX seem to be very rapid at room temperature. However, on mixing the acyl chlorides with 2-phenyl-4,4-dimethyloxazoline XXX no reaction occurs - as judged by the n.m.r and i.r spectra and subsequent chemical reactions - even on refluxing for several hours in dichloromethane.

Presumably electrophilic attack on the nitrogen atom of an oxazoline can occur in the plane of the ring - blocked by the phenyl group in XXX - or perpendicular to the ring - blocked by the gem-dimethyl substituent at C4 in XXX (and in XXIX). The steric effect of the latter was also noticed in attempts to acylate 4,4-dimethyloxazolidine (chapter 3), where the nitrogen lone pair electrons are perpendicular to the mean ring plane.

There was no reaction, as judged by n.m.r spectroscopy, between 4,4-dimethyloxazoline XXIX and trimethylsilyl chloride over 48 hours at 37°.

These observations extend those of the authors mentioned above who characterised definite intermediates in the reactions of acyl chlorides with acyclic imines. We made no attempt to isolate the adducts of acyl chlorides and oxazolines, although a preliminary report has appeared of full characterisation of N-acyloxazolinium fluoroborates produced by cyclisation of 2-N,N-diacylaminoethyl chlorides with silver fluoroborate.[146]

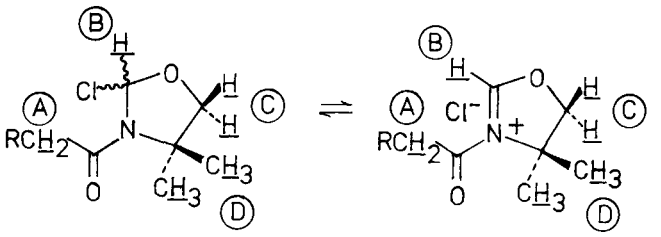


XXXVI (cov) XXXVII (ion)

RCH_2COCl R	CH_2	A cov	A ion	B cov	B ion	C cov	C ion	D cov	D ion	%cov
Ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (II)					1.30		8.17 8.39		5.20	
				3.20		8.50 8.70		5.78		
H		7.80	7.34	2.41	0.41	8.29 8.55	8.22 8.43	5.53	5.10	81
		7.75	7.34	2.51		8.30 8.59	8.20 8.50	5.68	5.03	93
Cl		5.64	5.44	2.40	0.80	8.28 8.53	8.19 8.41	5.48	5.11	75
		5.67		2.33		8.29 8.58		5.55		100
N_3		5.80	5.63	2.49	0.60	8.31 8.36	8.22 8.42	5.49	5.10	74
	5.71	5.84	5.63	2.45		8.29 8.55	8.17 8.42	5.53	5.01	87
EtOOC	6.13	6.30	6.11	2.44	0.62	8.30 8.55	8.18 8.42	5.52	5.10	74
		6.33	6.09	2.35	0.50	8.29 8.53	8.10 8.41	5.74	4.83	88
PhthN ($CDCl_3$ only)	5.13	(5.22)	(5.13)	2.22	0.72	8.27 8.52	8.19 8.43	(5.46)	(5.13)	75

table I. Adducts of acyl chlorides (RCH_2COCl) with ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (II). τ values assigned to the covalent XXXVI (cov) and ionic XXXVII (ion) species. Values in $CDCl_3$ are given first for each derivative, then values in CCl_4.

Adducts with cyanoacetyl chloride ($NCCH_2COCl$) and benzoyl chloride were also investigated, but the spectra are so far uninterpretable.



XXXVIII (cov) XXXIX (ion)

RCH_2COCl R	CH_2	A cov	A ion	B cov	B ion	C cov	C ion	D cov	D ion	%cov
4,4-dimethyl-2-oxazoline (XXIX)				3.28	1.52	6.12	5.19	8.71	8.36	
H	7.35	7.56	7.32	2.08	0.35	5.67	5.24	8.42	8.32	65
Cl		5.80	5.43	2.43	0.78	5.72	5.33	8.42	8.33	78
N_3		5.86	5.62	2.48	0.85	5.77	5.34	8.42	8.34	73
EtOOC	6.13		6.08		0.51		5.23		8.31	mostly ion?
PhthN	5.13	5.31	5.15	2.29	0.83	5.78	5.40	8.46	8.35	71

table II. Adducts of acyl chlorides (RCH_2COCl) with 4,4-dimethyl-2-oxazoline (XXIX). τ values in $CDCl_3$ solvent assigned to the covalent XXXVIII (cov) and ionic XXXIX (ion) species.

RCH_2COCl R	(II) $CDCl_3$	(II) CCl_4	(XXIX) $CDCl_3$
H	81%	93%	65%
Cl	75	100	78
N_3	74	87	73
EtOOC	74	88	mostly ionic?
PhthN	75		71

table III. Adducts of acyl chlorides and ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate (II) and 4,4-dimethyl-2-oxazoline (XXIX). Percentages of the covalent species XXXVI and XXXVIII, from n.m.r spectra.

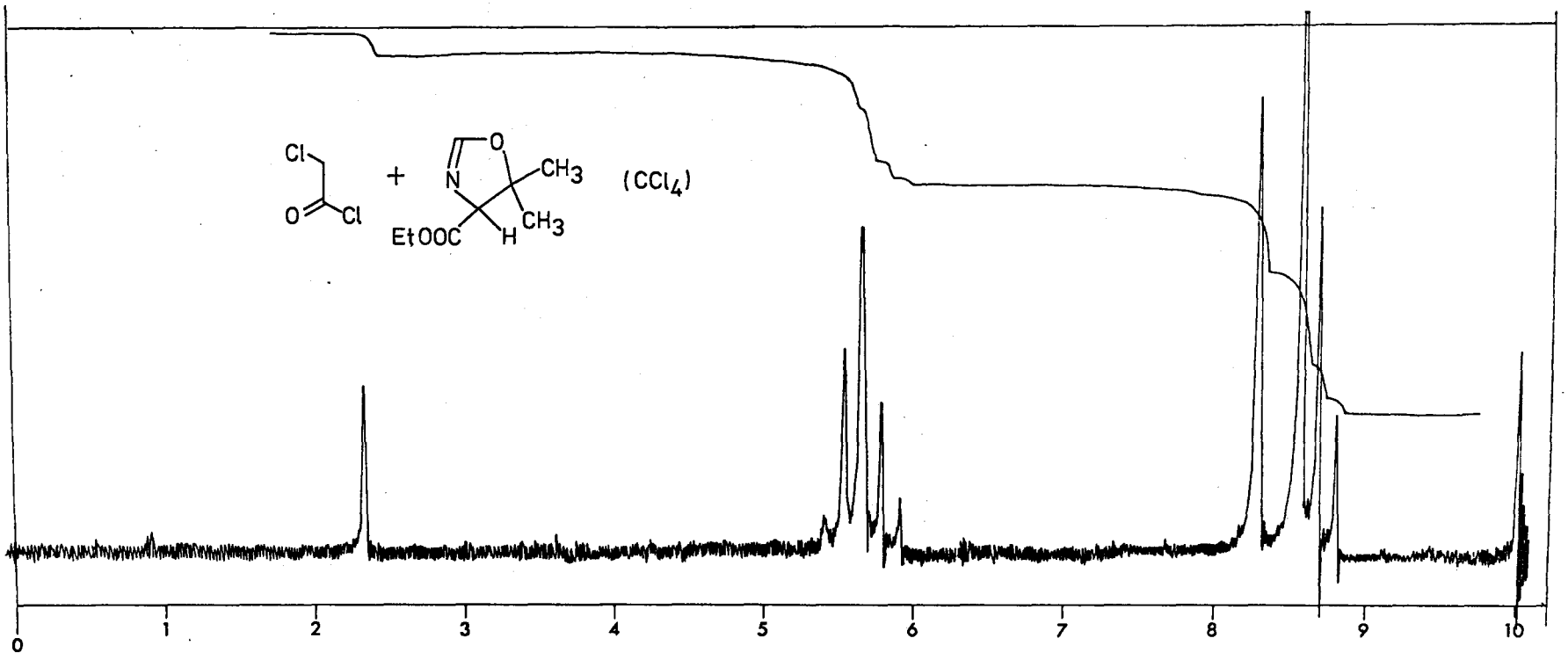


fig.1. 60 MHz (CCl_4) n.m.r spectrum of an equimolar mixture of chloroacetyl chloride and ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate.

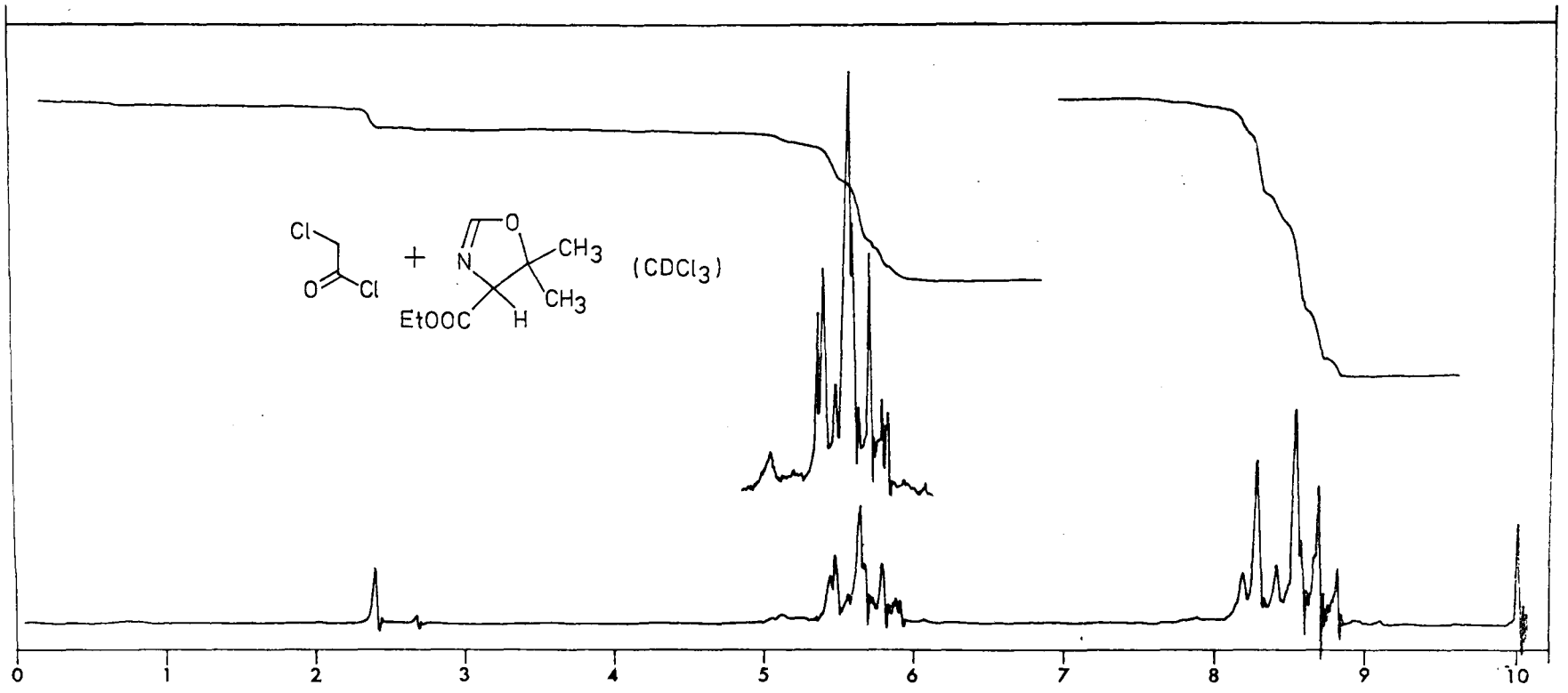


fig.2. 60 MHz ($CDCl_3$) n.m.r spectrum of an equimolar mixture of chloroacetyl chloride and ethyl 5,5-dimethyl-2-oxazoline-4-carboxylate.

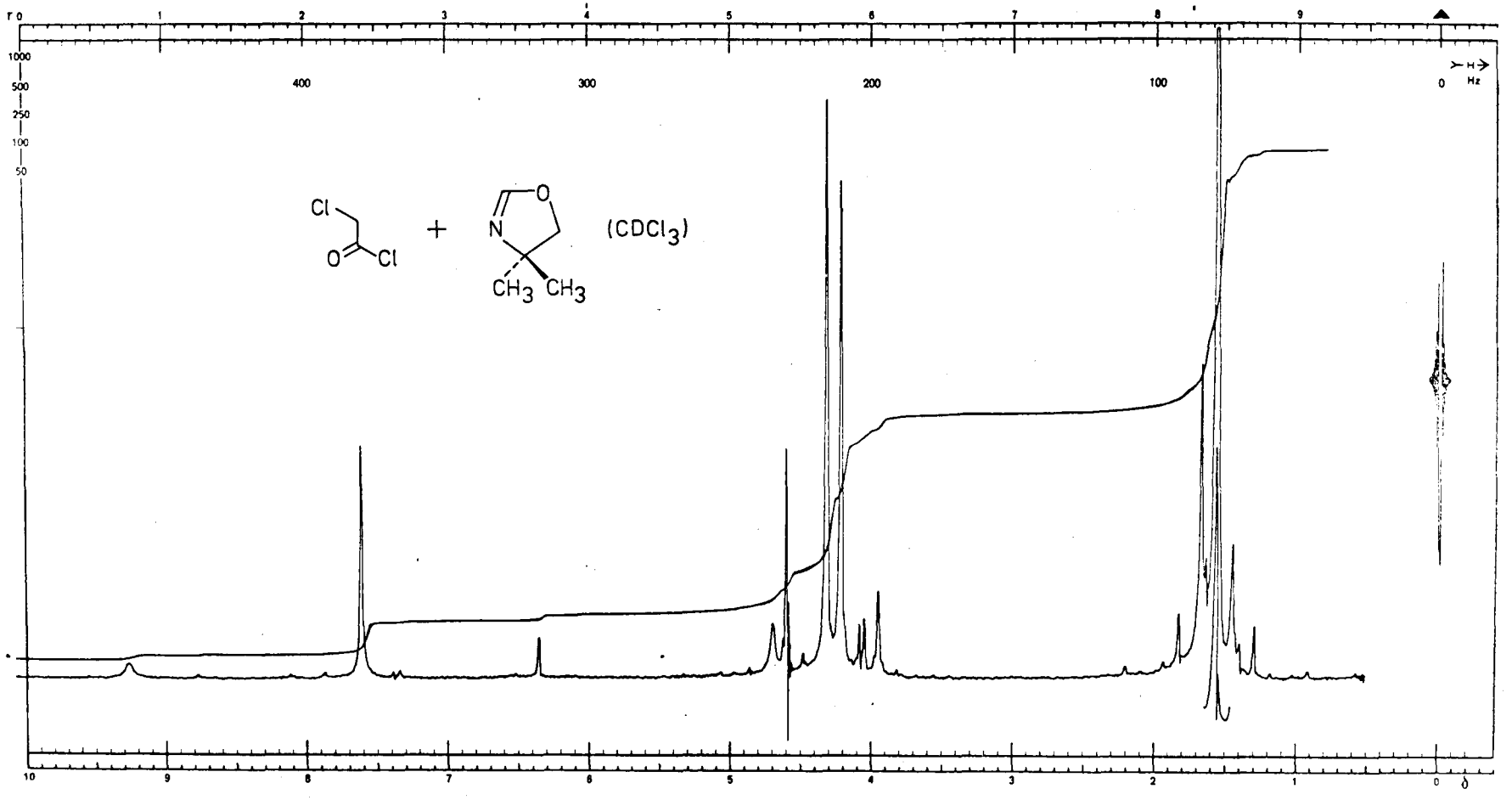


fig.3. 100 MHz ($CDCl_3$) n.m.r spectrum of an equimolar mixture of chloroacetyl chloride and 4,4-dimethyl-2-oxazoline.

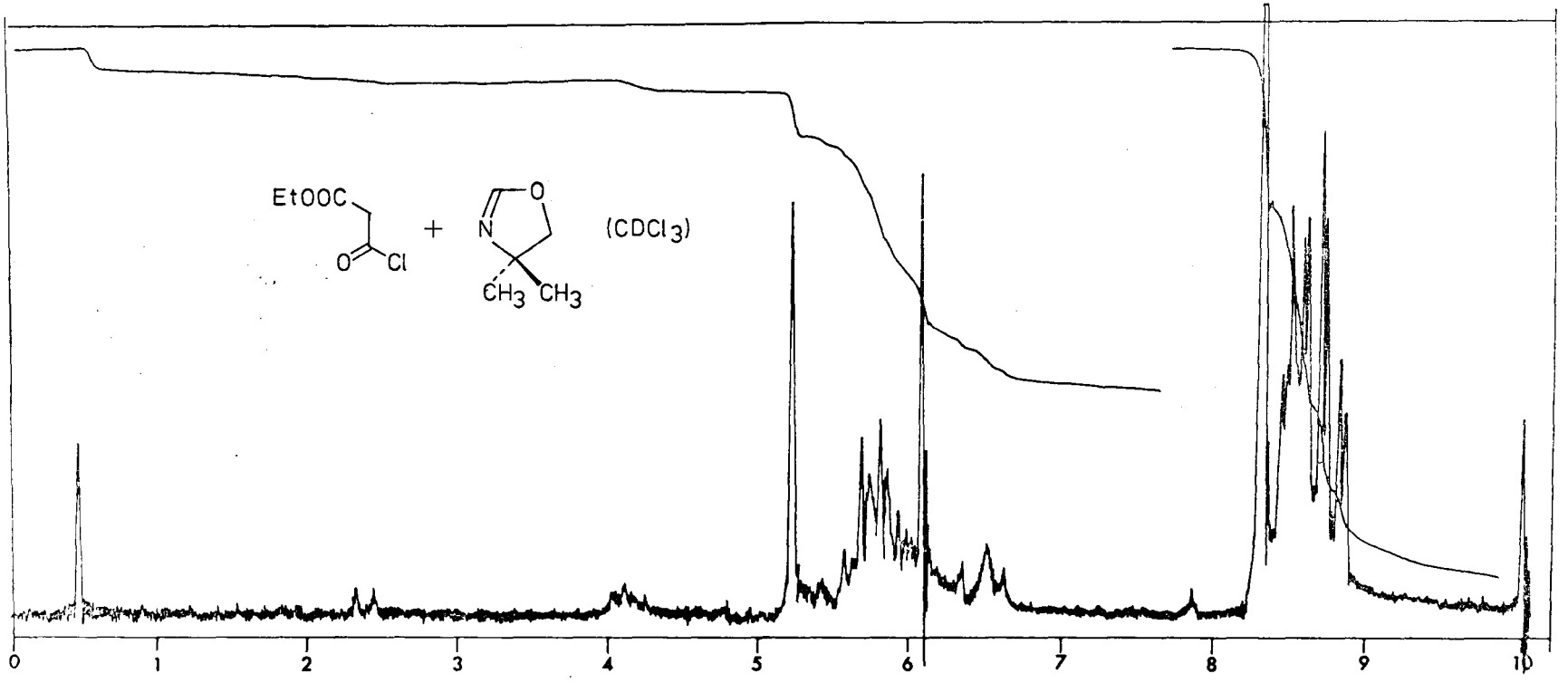
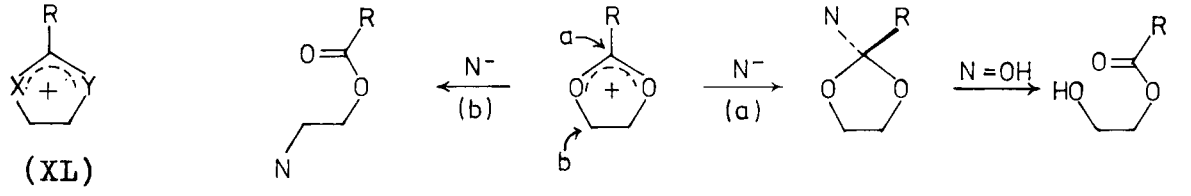


fig.4. 60 MHz ($CDCl_3$) n.m.r spectrum of an equimolar mixture of ethyl malonyl chloride and 4,4-dimethyl-2-oxazoline.

i) Chemical reactions.

Oxazolinium salts are members of the group of 5- or 6-embered heterocyclic cations (e.g XL), the best known of which s the 1,3-dioxolan-2-ylium ('acetoxonium') ion (XL, X=Y=O). Re-lacing one of the oxygen atoms in the latter by an imino group ives the more stable oxazolinium ion (XL, X=NH, Y=O), and while oth have been implicated as intermediates in reaction mechanisms, ,3-dioxolanylium ions have only relatively recently been isolated s their fluoroborate or hexachloroantimonate salts, while oxazol-nes have long been characterised as their picrates or, in some ases, even as their hydrochlorides.[147]



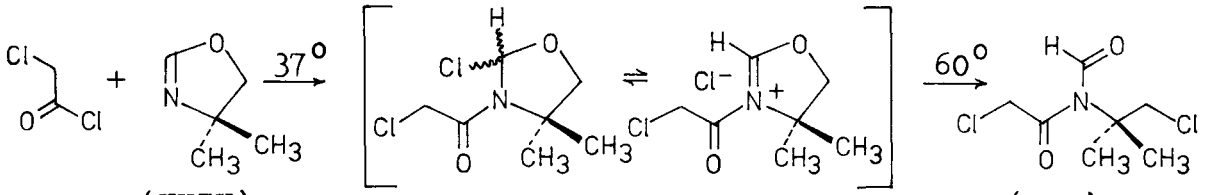
XL (X=Y=O)

The heterocyclic cations XL are ambident electrophiles, eacting at the 2-position (lowest electron density) with strong ucleophiles to give the product of kinetic control (pathway a), nd with weaker nucleophiles at the 4(5)-position to give the hermodynamic product (pathway b).

Thus the 1,3-dioxolanylium ion reacts with water at the -position, prototropy giving the vicinal diol monoester, and with romide ion at the 4(5)-position to give the vicinal acyloxybromide chapter 5). The ease of the latter reaction gives rise to a val-able synthetic method, but, by contrast, the oxazolinium[147] and -acyloxazolinium cations are clearly relatively stable to attack y chloride ion at C4(5) at room temperature. Oxazolinium chlorides re more stable than the 2-chloroöxazolidines,[147] but N-acylation ould be expected to reduce the stability of the former, and the esults above show that the predominant tautomer at equilibrium is ery dependent upon detailed changes in substitution.

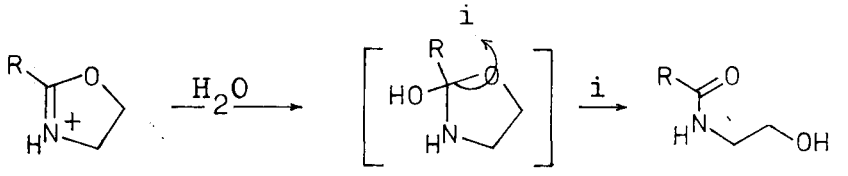
The only other analogous studies of such derivatives have nvolved heating 2-oxazolines with acyl chlorides, when the thermo-ynamic product is obtained - the 2-(diacylamino)-ethyl chloride

derivative.[148] On heating to 60°, the n.m.r spectrum of a mixture f chloroacetyl chloride and 4,4-dimethyloxazoline XXIX (c.f fig.3) s that expected for N-chloroacetyl-N-formyl-2-amino-2-methylpropyl ıloride (XLI), although this derivative has only been characterised pectroscopically.

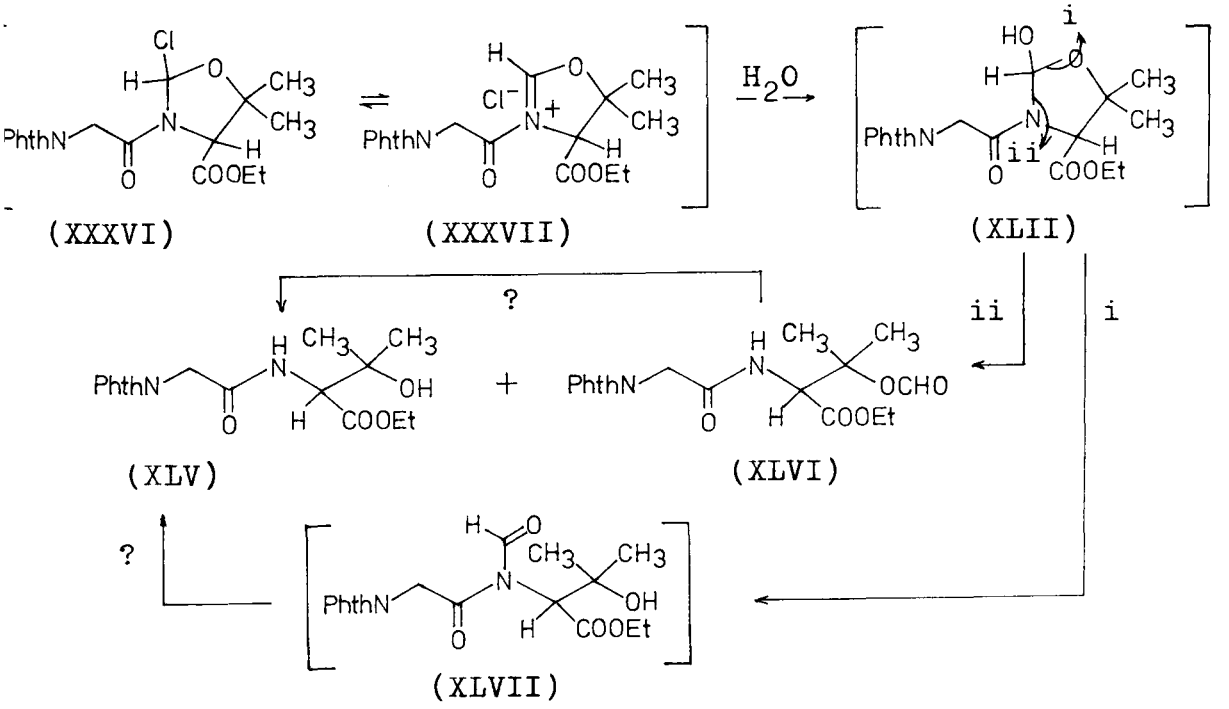


(XXIX) XXXVIII (R=Cl) XXXIX (XLI)

The adducts of acyl chlorides and oxazolines are very ısceptible to hydrolysis, especially in the presence of triethyl- nine, giving the products of kinetic control, e.g (XLII), removed rom the equilibrium by irreversible prototropy. Oxazolinium salts XLIII) give N-acylethanolamine derivatives (XLIV) on hydrolysis[147] y bond breaking towards the more electronegative oxygen (pathway i).



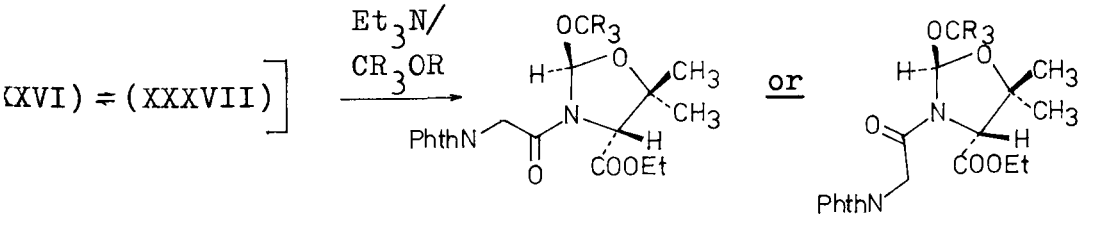
(XLIII) (XLIV)



(XXXVI) (XXXVII) (XLII) (XLV) (XLVI) (XLVII)

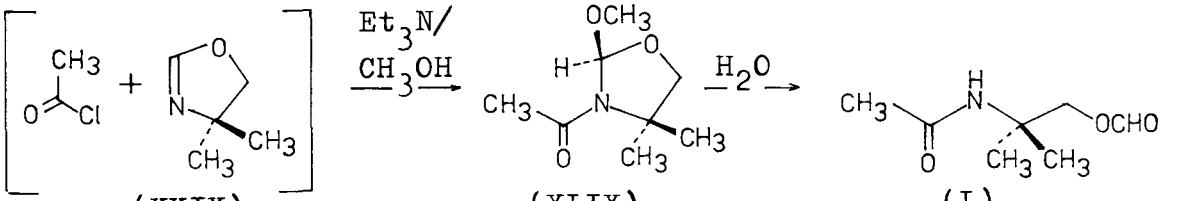
Acylation at nitrogen should favour the alternative cleavage athway ii), and reaction of the mixture of the Schöllkopf azoline II and phthalimidoacetyl chloride with water or an equi-lar mixture of water and triethylamine gives the N-acylethanolamine rivative (XLV) and its O-formate (XLVI), the latter predominating atios 17:83 and 27:73 respectively). The former product XLV could ise by deformylation of the latter XLVI, but this O-formate seems ite stable, and an equally possible source is via deformylation the N-acyl-N-formylethanolamine derivative (XLVII) - the product the alternative ring cleavage (pathway i).

When a mixture of an acyl chloride and oxazoline is treated th an equimolar mixture of triethylamine and methanol, the only oduct is the corresponding N-acyl-2-methoxyoxazolidine (e.g XLVIII, = ^{1}H). Crystalline compounds were fully characterised using thalimidoacetyl chloride and both the Schöllkopf oxazoline II and 4-dimethyloxazoline XXIX. Using the latter oxazoline and acetyl loride, the n.m.r spectrum of the reaction mixture corresponded that expected for N-acetyl-2-methoxy-4,4-dimethyloxazolidine LIX), but on exposure to air this hydrolysed completely to the yclic N-acetyl-2-amino-2-methylpropanol-O-formate (L) within 24 irs.



(XLVIIIa) (XLVIIIb)

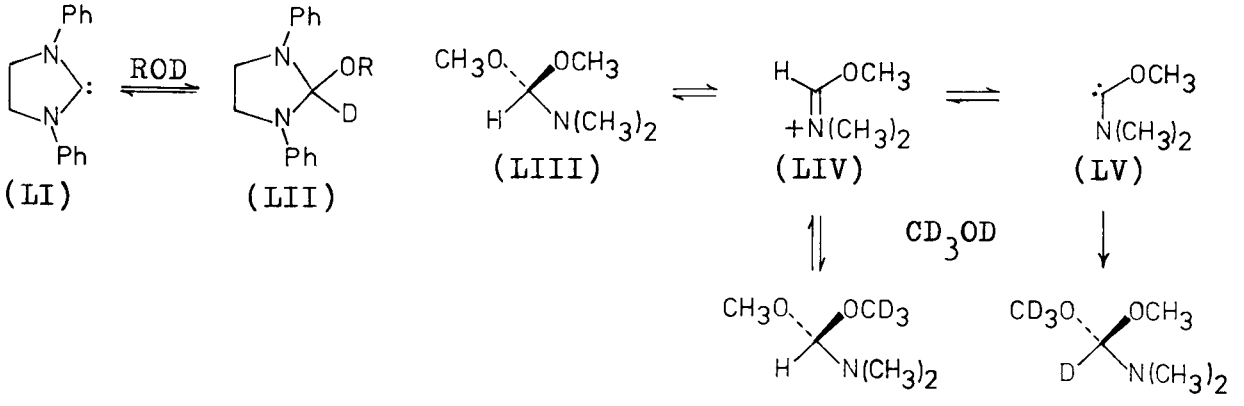
(one enantiomer of one of the two possible diastereomeric pairs shown)



(XXIX) (XLIX) (L)

(one enantiomer) shown

The N-acyl-2-methoxyoxazolidines (e.g XLVIII) are the products of nucleophilic attack by methoxide ion *via* path a on the ambident N-acyloxazolinium ion (XL, X=NCOR, Y=O). In view of later findings, it was also considered that elimination of HCl from the latter could give a carbenoid centre at C2 of the oxazolidine ring, and this could insert into the O-H bond of methanol. Such a nucleophilic carbene would be analogous to the diaminocarbene (LI) studied by Wanzlick,[149] which reacts with alcohols to give 1,3-diphenyl-2-alkoxyimidazolidine (LII). Dimethylformamide dimethylacetal (LIII), closely resembling the structure of the N-acyl-2-methoxyoxazolidines (e.g XLVIII), has been shown to undergo exchange of both the methoxy groups and the methine proton in $^{2}H_{4}$-methanol solution.[150] This was explained by ready formation of the highly stabilised carbonium ion (LIV) and carbene (LV) intermediates. Exchange of the methoxy groups (via LIV) was faster than exchange of the methine proton (via LV).



However, reaction of the adduct of phthalimidoacetyl chloride and the Schöllkopf oxazoline II with an equimolar mixture of triethylamine and $^{2}H_{4}$-methanol gave the corresponding N-acyl-2-methoxyoxazolidine (XLVIII, R = ^{2}H) with the 2-methoxy group wholly deuterated, but the 2-hydrogen wholly protium, as far as could be judged from the n.m.r spectrum of the crude reaction product.

Attack on the N-acyloxazolinium ion by methoxide ion must thus be much faster than carbene formation, as was found for dimethylformamide dimethylacetal LIII. The N-acyl-2-methoxy-oxazolidines (e.g XLVIII) are generally much more stable (e.g to

hydrolysis) than LIII because the N-acylation in the former reduces the stability of cationic reaction intermediates, although the N-acyl-2-chloroöxazolidines (e.g XXXVI and XXXVIII) are of comparable reactivity to LIII.

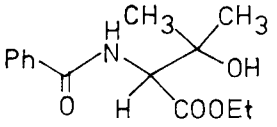
iii) Further considerations of the n.m.r spectra of the adducts of acyl chlorides and oxazolines.

It is thought that the simple explanation described so far is basically correct - that acyl chlorides and oxazolines (e.g II and XXIX) form 1:1 adducts that can exist as N-acyl-2-chloroöxazolidines (e.g XXXVI and XXXVIII) and as N-acyloxazolinium chlorides (XXXVII and XXXIX) in equilibrium. The i.r spectra of the mixtures are not much help as all show a broad carbonyl band at c. 1690 cm^{-1}. The chemical results are those expected, and the reaction with triethylamine and methanol shows that the heterocycle has not been cleaved in the adducts, as occurs in the only other reactions of acyl chlorides and oxazolines reported.[148] While N-acyl-2-methoxyoxazolidines were only fully characterised for derivatives of phthalimidoacetyl chloride, the similarities of the n.m.r spectra are thought to indicate comparable situations in the other adducts.

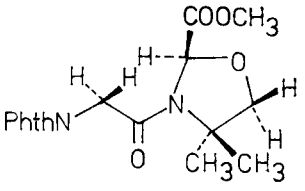
However, the detailed structure of the acyl chloride-oxazoline adducts is still very much open to question.

a) The spectra observed on mixing benzoyl chloride with either oxazoline II or XXIX cannot be fully interpreted, and are not discussed further here. Aqueous work-up with acid of the adduct with oxazoline II gave ethyl 2-benzoylamino-3-methyl-3-hydroxy-butyrate (LVI).

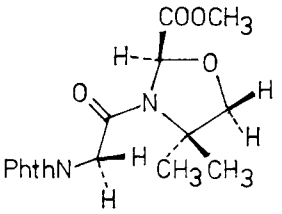
b) The n.m.r spectrum of N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine (LVII) obtained later in this work shows all signals as unresolved multiplets at room temperature. On cooling to -20^{o} two sets of signals are seen, corresponding to the two rotamers about the N-CO bond (LVIIa and LVIIb). The C2-$\underline{H}$ proton gives rise to two singlet resonances. By virtue of the monosubstitution at C2, the phthalimido-$C\underline{H}_2$ and also the ring -$C\underline{H}_2$- protons are non-equivalent, and each methylene group gives rise to two AB quartets corresponding to the two planar rotamers. Similarly, the C4-methyl groups are non-equivalent in each rotamer, and give rise to two pairs of singlets (fig.5).



(LVI)



(LVIIa)

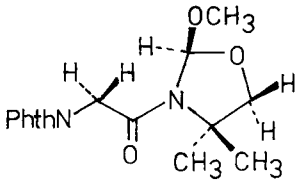


(LVIIb)

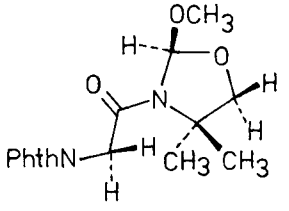
((R)-enantiomer only shown here)

On warming to +60°, rotation about the N-CO bond in LVII becomes rapid on the n.m.r time scale. The phthalimido-C<u>H</u>$_2$ resonance collapses to a singlet. A single resonance is seen for C2-<u>H</u>, a single AB quartet for the ring methylene protons, and one pair of singlets for the non-equivalent methyl groups at C4 (fig.6).

The n.m.r spectrum of N-phthalimidoacetyl-2-methoxy-4,4-dimethyloxazolidine (LVIII) at 37° shows a singlet for C2-<u>H</u>, a single AB quartet for the ring methylene protons, and two singlets for the methyl groups at C4. But the phthalimido-C<u>H</u>$_2$ protons give rise to a single AB quartet, so that this spectrum does not correspond to that of LVII at +60° - i.e free rotation about the N-CO bond - but is that of one single planar rotamer about this bond (LVIIIa <u>or</u> LVIIIb) (fig.7).



(LVIIIa)



(LVIIIb)

((S)-enantiomer only shown here)

By contrast, in the n.m.r spectra of the adducts of acyl chlorides - e.g chloroacetyl chloride (fig.3) - and 4,4-dimethyl-oxazoline XXIX, the signals for the C<u>H</u>$_2$ of the acyl group, for the ring methylene protons and for the C4-methyl groups (6H) assigned to the N-acyl-2-chloroöxazolidine tautomer XXXVIII are all singlets. In structure XXXVIII the ring methylene protons and the methyl

groups at C4 must be non-equivalent, but in no case are separate signals seen. The C$\underline{H}_2$-protons of the acyl group might or might not be non-equivalent according to the magnitude of the barrier to rotation about the N-CO bond.

The n.m.r spectrum of ethyl N-phthalimidoacetyl-2-methoxy-5,5-dimethyloxazolidine-4-carboxylate (XLVIII, R = ^{1}H) also shows a single planar rotamer (XLVIIIa or XLVIIIb) at 37°. With the asymmetry at C4, two diastereomeric epimers are possible at C2. In the spectrum of the crude reaction product, two singlet resonances are just resolved for C2-$\underline{H}$, although one of the epimers (enantiomeric pair) is obtained preferentially on recrystallisation.

This should be compared with the n.m.r spectra of adducts of the Schöllkopf oxazoline II and acyl chlorides - e.g chloroacetyl chloride (figs. 1 and 2). In the set of signals corresponding to the covalent tautomer XXXVI, C2-$\underline{H}$ resonates as a sharp singlet, although the C5-methyl groups retain their non-equivalence due to the asymmetry at C4.

c) The downfield shift of the resonance due to C$\underline{H}$-Cl relative to that for C$\underline{H}$-OMe should not be great (Shoolery's Effective Shielding Constants (σ^{eff}) for -Cl = 2.53ppm, and for C$\underline{H}$-OR = 2.36ppm[151]). The C2-$\underline{H}$ resonance in the spectra of the N-acyl-2-methoxyoxazolidines (e.g XLVIII and LVIII) is at c. τ3.8, but the resonance assigned to C2-$\underline{H}$ of the N-acyl-2-chloroöxazolidines (XXXVI and XXXVIII) is at c. τ2.4.

Scheme 1 is an attempt to account for the n.m.r spectra of the adducts of acyl chlorides and the oxazolines II and XXIX, and in particular to explain the lack of non-equivalence and the low field resonance of C2-$\underline{H}$ in the set of signals assigned to the covalent N-acyl-2-chloroöxazolidine tautomers XXXVI and XXXVIII. It is suggested that there is an appreciable barrier to free rotation about the N-CO bond in the adducts, and that at ambient temperature interconversion between the two planar rotamers A and B (adducts with 4,4-dimethyloxazoline shown for example in scheme 1) is slow on the n.m.r time scale. In one of the rotamers, for example rotamer A in scheme 1, there is rapid equilibration between the two C2-epimers of the covalent tautomer (XXXVIIIa and XXXVIIIa') $\underline{via}$ the

ionic tautomer (XXXIXa), resulting in substituents rendered non-equivalent by asymmetry at C2 becoming equivalent - the ring methylene protons, the C4-methyl groups, and the two protons of the acyl $C\underline{H}_2$-group. The resonance due to C2-$\underline{H}$ is a singlet at a position in between that expected for the covalent tautomers XXXVIIIa and XXXVIIIa' (c. τ3.6) and that predicted for the ionic species XXXIXa (c. τ1.0).

In most of the examples studied, this rotamer predominates (table III) giving rise to the set of signals previously assigned to the 'covalent tautomer' (tables I and II).

In the alternative planar rotamer (B in scheme 1) - the minor component in most cases - the ionic-covalent equilibrium is slow, and separate sets of signals should be seen for the two tautomers (XXXVIIIb and XXXIXb), the intensity of each set depending upon the position of the equilibrium. In most of the examples investigated, the ionic form XXXIXb of rotamer B seems to be favoured, giving rise to the set of signals previously assigned to the 'ionic tautomer' (tables I and II). In some spectra (e.g fig.3), however, a small singlet at c. τ3.6 is present, and this may be due to C2-$\underline{H}$ of the covalent form XXXVIIIb of rotamer B.

Which rotamer is in fact A and which is B is obviously wide open to speculation. N-phthalimidoacetyl-2-methoxy-4,4-dimethyl oxazolidine LVIII exists as one planar rotamer at 37°, but replacement of the 2-methoxy group by the more bulky methoxycarbonyl group in LVII causes both planar rotamers to be populated. This suggests that the exclusive rotamer of LVIII is that shown as LVIIIa, and in LVII the corresponding rotamer LVIIa is less favoured due to steric interaction between the acyl side chain and the more bulky substituent at C2. By analogy, the favoured planar rotamer of the acyl chloride-oxazoline adducts could be that shown as rotamer A in scheme 1.

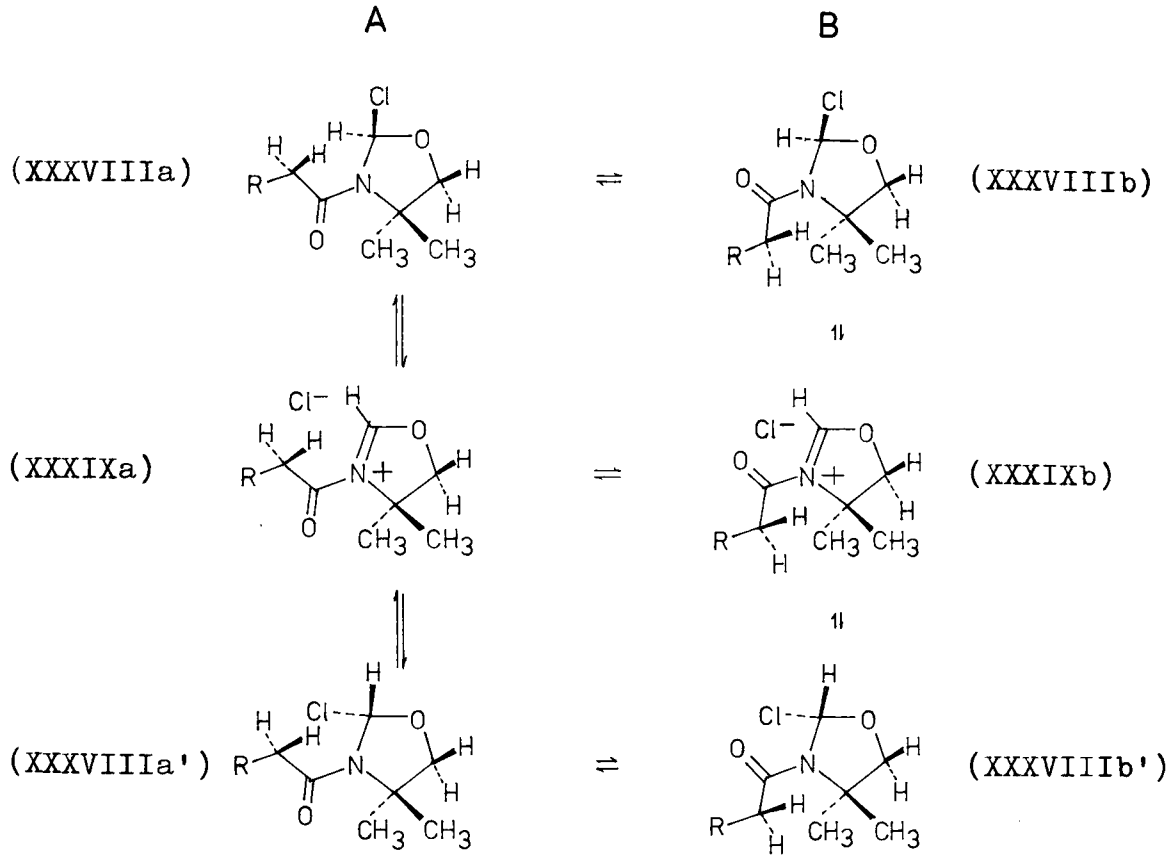
In the minor rotamer B, the ionic form XXXIXb could be stabilised by electrostatic interaction between the positive charge at C2 and the negative oxygen end of the acyl group carbonyl dipole.

Apart from the adducts of benzoyl chloride, there are other exceptions to the general pattern described so far. The n.m.r spectrum of an equimolar mixture of cyanoacetyl chloride and the

Schöllkopf oxazoline II in $CDCl_3$ (precipitation occurred in CCl_4) s more complex, including a small singlet at τ2.4 and singlets at .50 and 0.70 (ratios 16:42:42; total 1H). These may be due to a fferent balance in the equilibria in scheme 1, although the sing- t at τ1.50 could be due to the N-CHO proton of a ring-opened oduct (c.f τ1.275 in XLI).

If scheme 1 is correct, then lowering the temperature will crease the rates of interconversion; signals that are singlets in e n.m.r spectrum by virtue of these exchange processes should oaden, and maybe separate out into individual resonances. In the m.r spectrum of the mixture of chloroacetyl chloride and 4,4-di- thyloxazoline XXIX (c.f fig.3) at -60°, all signals are broad cept for the hump at low field which sharpens significantly. The oadening cannot then be due to general loss of resolution. The sitions of most of the signals also change relative to one another lowering the temperature also alters the equilibrium concentrat- ns, and no conclusions have yet been reached over the significance the spectrum observed. On rewarming to ambient temperature, the arting spectrum (fig.3) is regained.

Scheme 1 has been formulated mainly to show that some con- derable refinement is necessary of the basic interpretation of e n.m.r spectra of the adducts of acyl chlorides and oxazolines. is not merely of academic interest, as a phenomenon such as that esented in scheme 1 would be highly relevant to the subsequent actions of the adducts. Rotamer B in scheme 1, for instance, would markedly unsuited for cyclisation to a β-lactam.



A. Rapid epimerisation at C2; the predominant rotamer in most cases; gives signals assigned to 'covalent tautomer'.

B. Slow covalent-ionic equilibrium; ionic predominates in most cases; gives signals assigned to 'ionic tautomer'.

ıeme 1. Suggested detailed structures of adducts of acyl chlorides (RCH_2COCl) and oxazoline (XXIX).

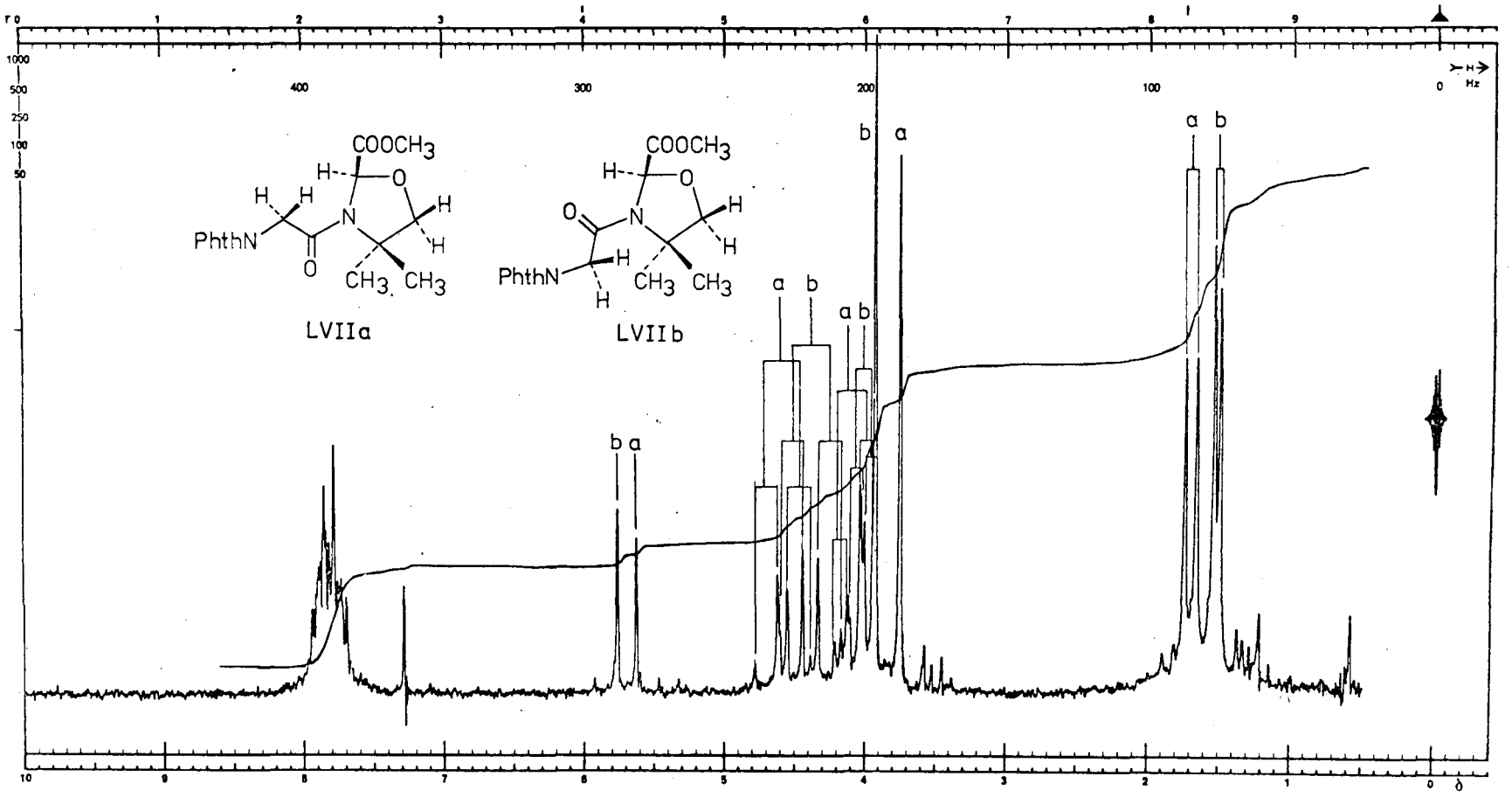


fig.5. 100 MHz ($CDCl_3$) n.m.r spectrum of N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine (LVII) at -20°C ((R)-enantiomer only inset).

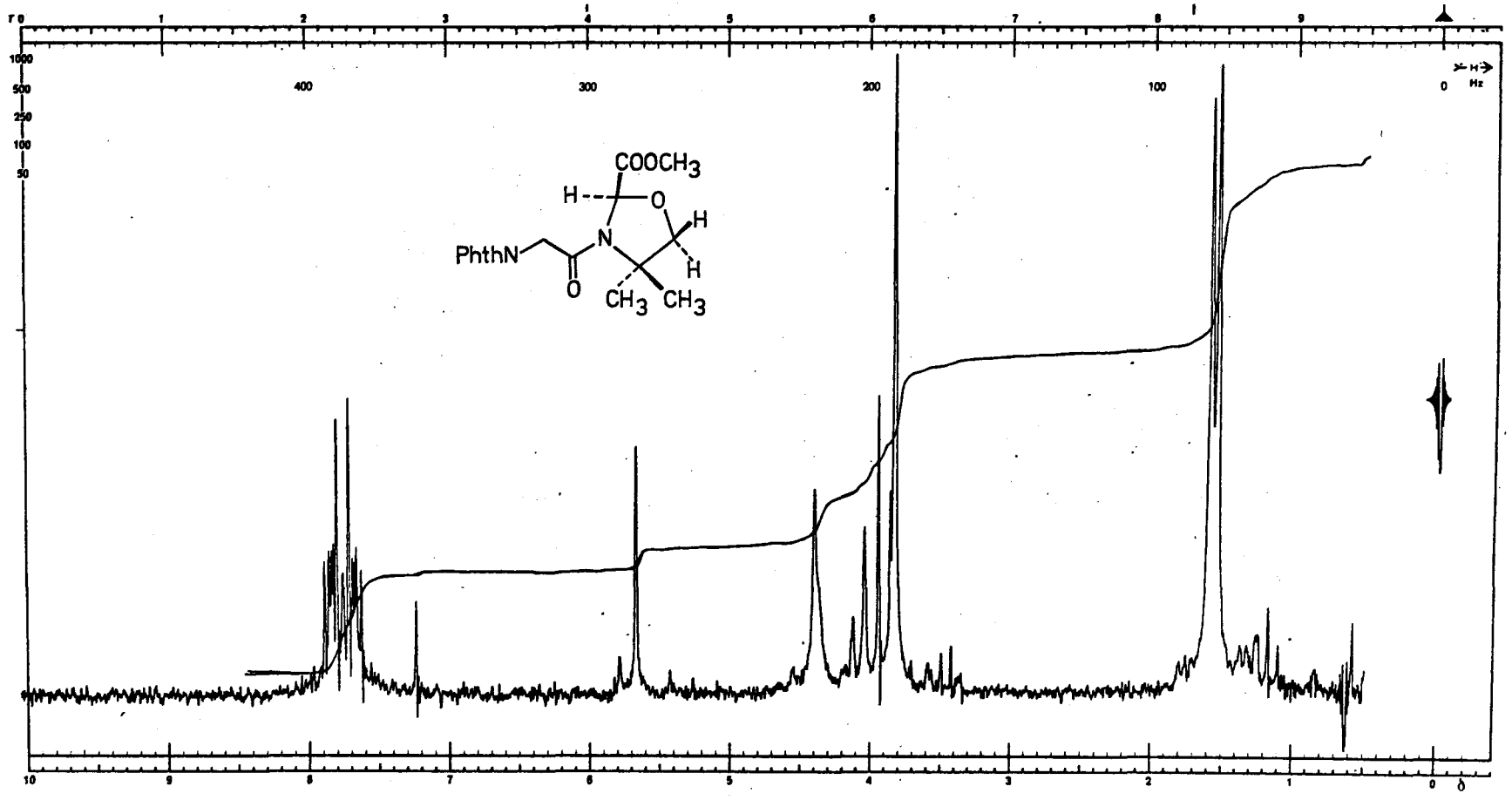


fig.6. 100 MHz ($CDCl_3$) n.m.r spectrum of N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine (LVII) at +60°C ((R)-enantiomer only inset).

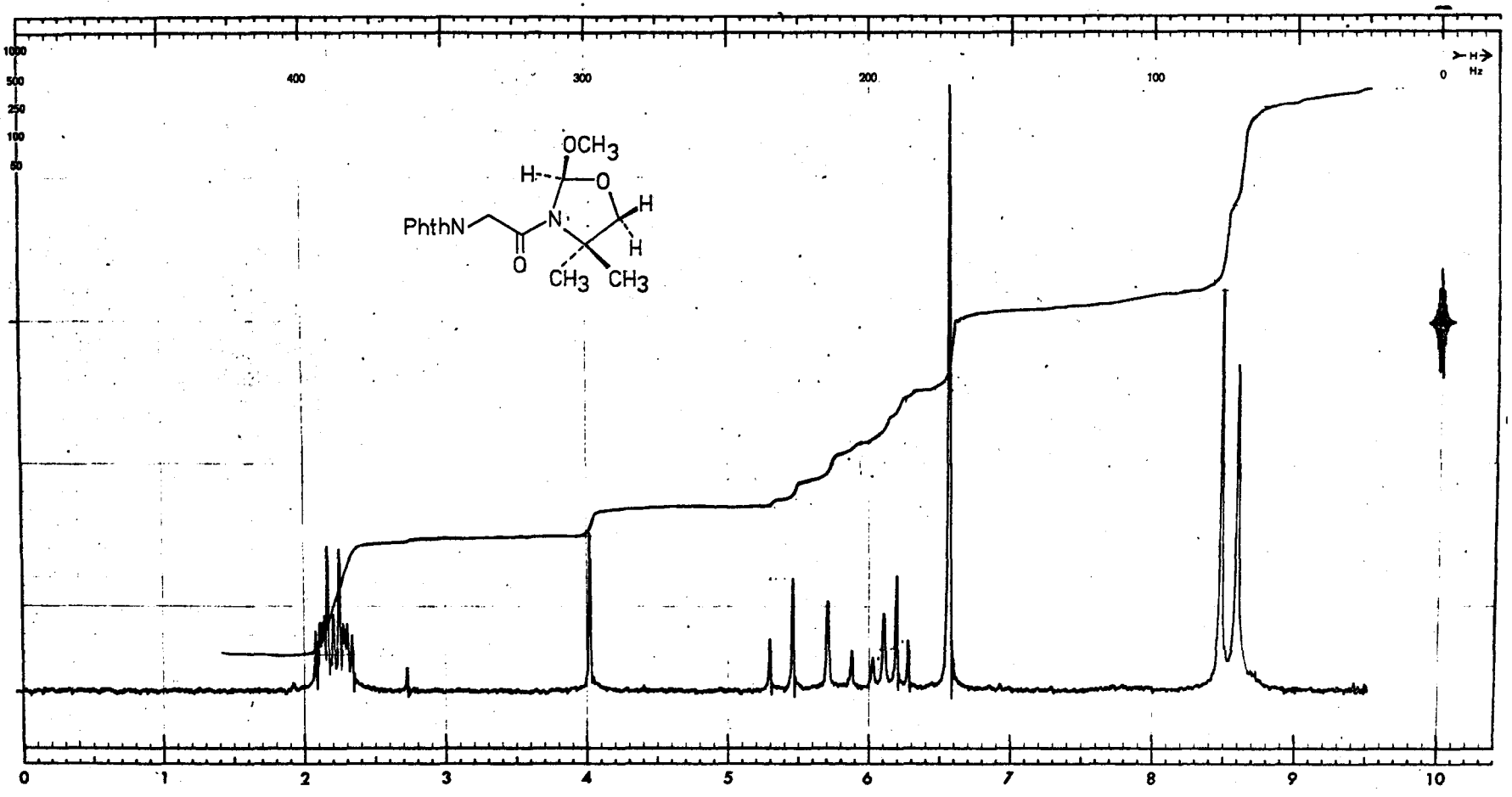


fig.7. 100 MHz ($CDCl_3$) n.m.r spectrum of N-phthalimidoacetyl-2-methoxy-4,4-dimethyloxazolidine (LVIII) ((S)-enantiomer only inset).

THE REACTIONS OF THE ADDUCTS OF ACYL CHLORIDES AND OXAZOLINES WITH TRIETHYLAMINE.

Dropwise addition of 1 mole equivalent of triethylamine at high dilution in dichloromethane at room temperature to a dilute solution of phthalimidoacetyl chloride and (a) the Schöllkopf oxazoline II and (b) 4,4-dimethyloxazoline XXIX gave in both cases a product virtually homogenous on t.l.c in several solvent systems, with R_f's markedly lower than those of the corresponding N-phthalimidoacetyl-2-methoxyoxazolidines XLVIII and LVIII. Numerous attempts at chromatography failed to isolate truly crystalline products in either case.

On standing, a concentrated solution in dichloromethane of reaction mixture (b) yielded 10 mole % of a crystalline compound m.p 221°, which was shown to be a 2:1 adduct (LIX) of the hypothetical phthalimidoketene and the oxazoline XXIX, by analysis and mass spectrum. A further small crop of less pure material could be obtained by addition of ether to the mother liquors, and the n.m.r spectrum of the remainder showed complete absence of LIX, although t.l.c showed a major component with similar R_f. This second compound was isolated (16 mole %) and shown to be a 1:2 adduct (LX) of the ketene and oxazoline.

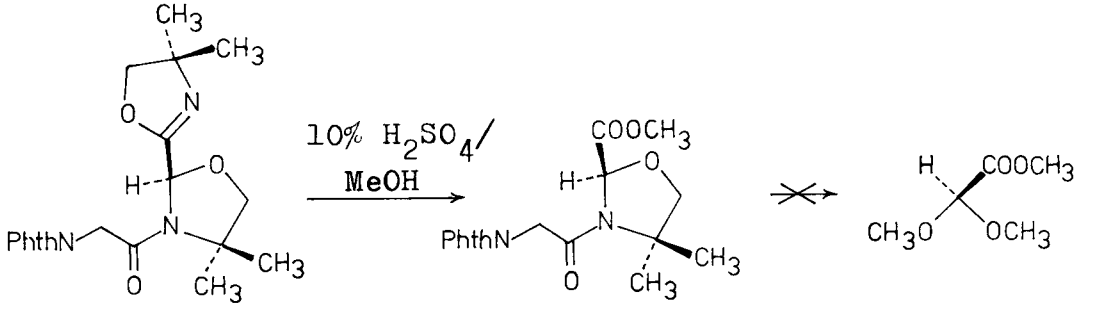
The above results were obtained with a 1:1:1 ratio of oxazoline:acyl chloride:triethylamine. When an equimolar mixture of phthalimidoacetyl chloride and the oxazoline XXIX was treated with an equimolar mixture of triethylamine and oxazoline XXIX, the n.m.r spectrum of the reaction mixture showed complete absence of the 2:1 adduct LIX and 52 mole % of pure 1:2 adduct LX was isolated. When two mole equivalents of phthalimidoacetyl chloride were mixed with the oxazoline XXIX, the i.r spectrum suggested that the excess acyl chloride did not react with the 1:1 adduct of acyl chloride and oxazoline, and addition of two mole equivalents of triethylamine gave 28 mole % of the crystalline 2:1 adduct LIX. The residues contained a small amount of LX, and 30 mole % of insoluble matter was obtained, probably ketene polymer, indicating that the available acyl chloride in this reaction was in fact less than two mole equivalents.

Reaction mixture (a) derived from the Schöllkopf oxazoline II gave an analogous 2:1 adduct (LXI) on crystallisation from benzene, but a 1:2 adduct could not be detected and the crystallisation liquors seemed to contain a number of compounds with similar R_f's on t.l.c. As above, using two mole equivalents of the acyl chloride and triethylamine increased the yield of LXI.

Near quantitative yields of triethylammonium chloride were obtained in all the reactions.

i) Structure of the 1:2 adduct LX.

The 1:2 adduct of phthalimidoketene and 4,4-dimethyloxazoline XXIX is N-phthalimidoacetyl-2-(4,4-dimethyloxazolin-2-yl)-4,4-dimethyloxazolidine. The n.m.r spectrum shows the two different ring structures. The methylene protons and the two methyl groups at C4 of the oxazoline portion give rise to two singlets (2H and 6H), but in the 2-substituted oxazolidine moiety they resonate as an AB quartet (2H) and two 3H singlets respectively. C2-H in the latter gives a sharp singlet at τ4.09. As in the N-phthalimidoacetyl-2-methoxyoxazolidines XLVIII and LVIII, apparently only a single N-CO rotamer is present at room temperature, the phthalimido-CH_2 protons resonating as a single AB quartet.



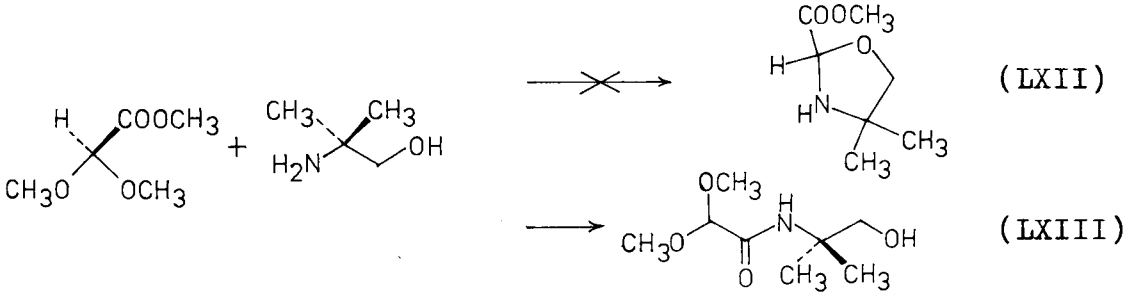
(LX) (LVII) ((R)-enantiomers shown)

Meyers has developed the 2-(4,4-dimethyloxazolinyl) group as a carboxylic acid protecting group[152], regenerating the carboxylate ester by refluxing the derivative with 10% alcoholic sulphuric acid. It was predicted that similar treatment of the 1:2 adduct LX would degrade both the oxazoline and oxazolidine rings. However, after refluxing for 12 hours in 10%

methanolic sulphuric acid, none of the expected methyl glyoxylate dimethylacetal was formed by LX, as shown by comparison with an authentic sample. The product, separated from a small amount of methyl phthalimidoacetate by p.l.c, was the N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine LVII, which crystallised slowly on standing when pure. The oxazoline ring of LX was degraded as expected, but LVII is stable to acid. The 2-methoxycarbonyl substituent in LVII would reduce the tendency to form a carbonium ion at C2, this latter being the initial product of cleavage of the oxazolidine ring by acid.

The n.m.r spectrum of LVII was discussed earlier (page 102) and is a classic example of hindered rotation about the amide N-CO bond. At $+60^{\circ}$ rotation is rapid on the n.m.r time scale, but at -20° the two planar rotamers are 'frozen' out. On the basis of deshielding by nearby carbonyl groups the two sets of signals can be assigned to their specific rotamers. LVIIa and LVIIb are present in a 55:65 ratio.

An attempt to synthesise 2-methoxycarbonyl-4,4-dimethyloxazolidine (LXII) from methyl glyoxylate dimethylacetal and 2-amino-2-methylpropanol with catalytic p-toluenesulphonic acid gave only 2-(2,2-dimethoxyacetylamino)-2-methylpropanol (LXIII).



The 1:2 adduct LX may be derived by attack of the 4,4-dimethyloxazolin-2-yl anion, present in the presence of triethylamine in low concentration, on the N-phthalimidoacetyl-4,4-dimethyloxazolinium cation. In the reactions with 1:1:1 ratio of reactants, formation of the 2:1 adduct LIX must release free oxazoline that reacts to form LX.

No 1:2 adduct was obtained from the reactions with the Schöllkopf oxazoline II, and no 'crossed' adduct was obtained by adding a mixture of II and triethylamine to an equimolar mixture

of phthalimidoacetyl chloride and 4,4-dimethyloxazoline XXIX. The inverse reaction was not attempted. Maybe steric factors limit the reactivity of the 2-anion of oxazoline II, or perhaps deprotonation of II occurs preferentially from C4, α- to the ester group (c.f the strict limitation on basicity in the preparation of II compared with the preparation of simpler oxazolines by the isonitrile route; even so, oxazoline II is stable in CCl_4 solution with one equivalent of triethylamine for at least 7 days at room temperature).

ii) Structure of the 2:1 adducts LIX and LXI.

The n.m.r spectrum of the 2:1 adduct LIX derived from 4,4-dimethyloxazoline XXIX showed, in addition to two different phthalimido multiplets (total 8H), singlet resonances for the gem-dimethyl (6H), ring methylene (2H) and phthalimido-$C\underline{H}_2$-CO- (2H) protons, and a 1H singlet at τ2.79. The i.r spectrum showed the very strong and the weaker bands at 1725 and 1775 cm^{-1} respectively, due to the phthalimido groups. There was also a very weak absorption at 1640 cm^{-1}, and a pronounced shoulder at 1790 cm^{-1} on the higher frequency phthalimido band. Comparison of the spectrum of LIX with those of known phthalimidoacetyl amides and esters at standard dilutions (two phthalimido groups in LIX) suggested that the higher frequency phthalimido absorption was stronger than normal in the spectrum of LIX - i.e that it masked a second carbonyl band.

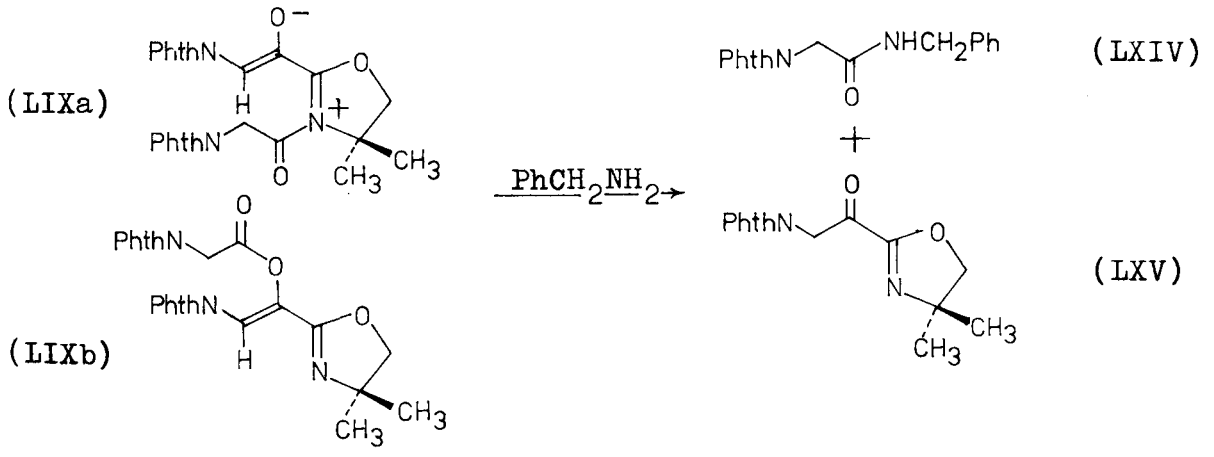
The 2:1 adduct LXI from the Schöllkopf oxazoline II has an i.r spectrum almost identical with that of LIX, except for the presence of a shoulder at 1740 cm^{-1} on the stronger phthalimido band, due to the ester carbonyl. The n.m.r spectrum of LXI shows the signals expected for an analogue of LIX, including those from two non-equivalent phthalimido groups, and also a 1H singlet at τ2.72.

On addition of a slight excess of benzylamine to a dichloromethane solution of the 2:1 adduct LIX, an equimolar mixture of N-phthalimidoacetyl-N-benzylamine (LXIV) (by comparison with authentic material) and 2-phthalimidoacetyl-4,4-dimethyl-oxazoline (LXV) (identified by full spectral data and chemical

transformations described below) was formed. Methyl phthalimidoacetate and the same ketone LXV were formed much more slowly with methanol (57% conversion of 0.03mM LIX with 0.15mM methanol in 0.35ml $CDCl_3$ after 14 hours at 37°).

If the crude reaction product from the reaction of equimolar quantities of phthalimidoacetyl chloride, oxazoline XXIX and triethylamine was treated with benzylamine to remove the 2:1 adduct LIX, then isolation of the 1:2 adduct LX was made easier.

The 2:1 adduct LXI derived from oxazoline II also reacted with benzylamine and methanol to give the corresponding derivatives of phthalimidoacetic acid, but the other product analogous to LXV decomposed during chromatography and was only characterised in the n.m.r spectrum (LXVII).



Two candidate structures for the 2:1 adduct LIX are suggested by this evidence - the 1,4-dipolar compound (LIXa), and the vinyl ester (LIXb). Analogous derivatives (LXIa) and (LXIb) follow as possible structures for the 2:1 adduct from oxazoline II.

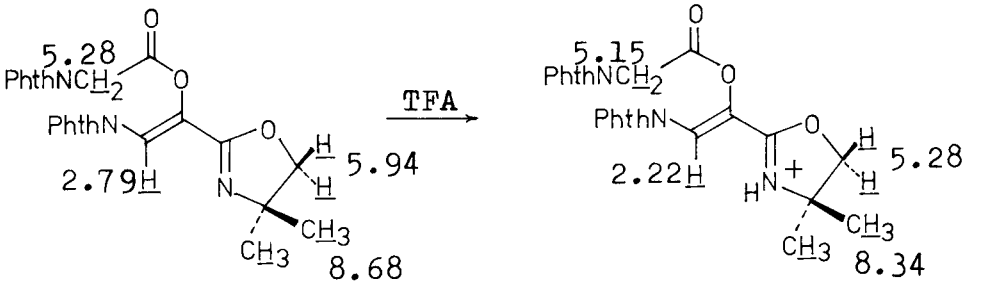
Both LIXa and LIXb would be expected to give the observed products with benzylamine, and to have a low-field vinylic 1H singlet in the n.m.r spectrum. The i.r absorptions of phthalimidoacetate esters are typically c. 10 cm^{-1} higher than normal (methyl ester ν_m 1755 cm^{-1}) and 1780-1790 cm^{-1} would not be an unreasonable value for the vinyl ester carbonyl absorption of LIXb. However, if the nitrogen atom in the dipolar structure LIXa bears appreciable positive charge, as is suggested by the rapid aminolysis, then the amide carbonyl absorption might appear at similarly high frequency

(c.f 1,2-diphenyl-5-oxopyrrolinium perchlorate, ν_m1825 cm^{-1}).[153]

The dipolar structure LIXa was initially favoured for the 2:1 adduct because of the general insolubility of the compound, its low R_f on t.l.c (R_f 0.3 on silica gel in ethyl acetate/benzene, c.f R_f 0.6 for the corresponding N-acyl-2-methoxyoxazolidine XLVIII), its high melting point and the extreme difficulty of removing solvent from the crystals. These properties are paralleled by those of the other 2:1 adduct LXI, except for the melting point (150-160°; LXI is presumably an enantiomeric mixture).

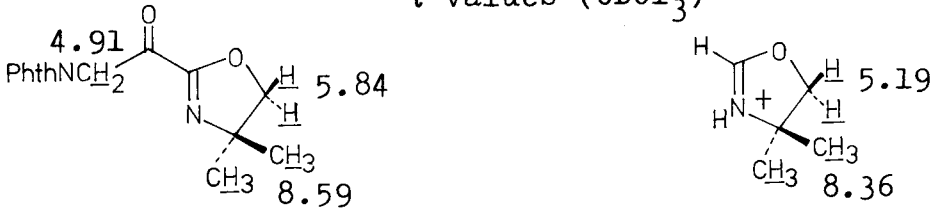
Currently the vinyl ester structure LIXb is favoured. The positions of the resonances corresponding to the C4-methyl groups and the methylene protons of the oxazoline ring of LIX are very similar to those of the derived 2-phthalimidoacetyl-4,4-dimethyloxazoline LXV. In the presence of excess trifluoroacetic acid (T.F.A) these signals of LIX shift downfield to positions similar to those of the same protons in the spectrum of the trifluoroacetate of 4,4-dimethyloxazoline (LXVI) - note the large shift of the ring methylene protons resonance. The vinylic proton of the 2:1 adduct LIX also resonates at lower field.

(LIXb)



τ values ($CDCl_3$)

(LXV)

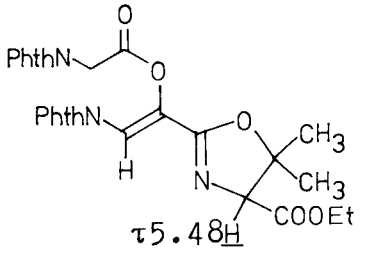


(LXVI)

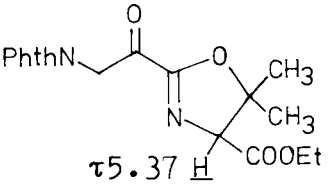
These observations would fit the vinyl ester structure LIXb and its N-protonation in T.F.A. It could also be argued

that O-protonation of the dipolar structure LIXa would give a similar oxazolinium ion. But the n.m.r spectrum of LIX, in which the positions of the resonances due to protons on ring substituents closely resemble those in the spectrum of LXV, suggests there is no charge on the ring before protonation, whereas appreciable charge on nitrogen is required to explain the high frequency carbonyl absorption, and the rapid reaction with benzylamine.

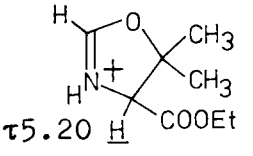
In the 2:1 adduct LXI derived from the Schöllkopf oxazoline II there are an ester group and a methine hydrogen attached to the carbon atom adjacent to the ring nitrogen. The ester carbonyl absorption in the i.r spectrum of LXI is a shoulder at 1740 cm^{-1}, whereas any positive charge on nitrogen would be expected to raise this to higher frequency. The methine proton at C4 of LXI resonates at τ5.48. This is comparable to the signal for the same proton in the derived ethyl 2-phthalimidoacetyl-5,5-dimethyloxazoline-4-carboxylate LXVII (τ5.37), but appreciably upfield from that in the spectrum of the trifluoroacetate of the oxazoline II (LXVIII) (τ5.20).



(LXIb)



(LXVII)



(LXVIII)

These observations count against any charge on the oxazoline ring in LXI, i.e against the dipolar structure LXIa.

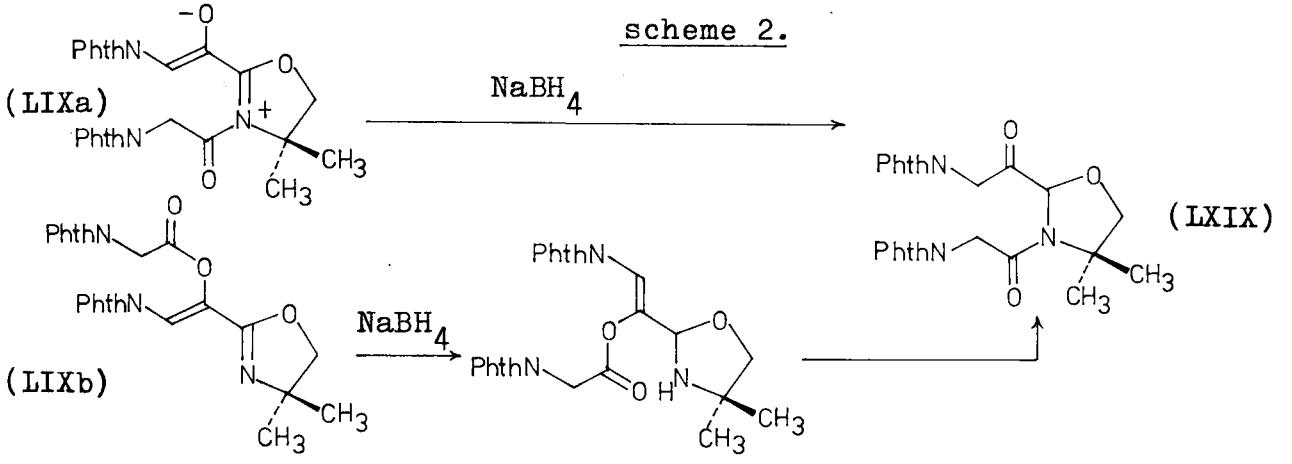
iii) Unsuccessful attempts at structural elucidation.

a) The 2:1 adduct LIX did not react with methyl iodide in refluxing dioxan. The dipolar structure LIXa would be expected to methylate readily on oxygen, and the vinyl ester LIXb on the oxazoline nitrogen. Reduction of such methylated products should provide clearly distinguishable oxazolidine derivatives.

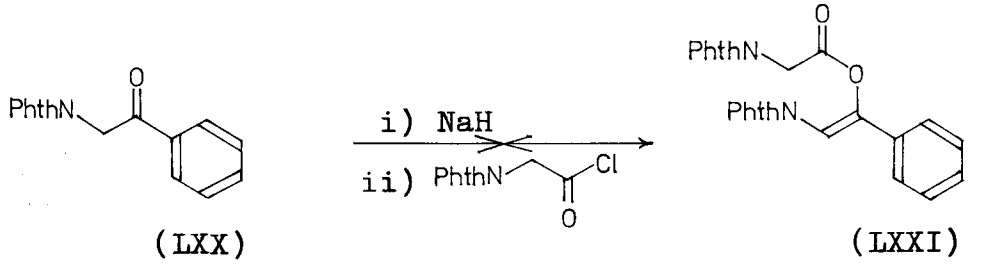
b) The 2:1 adduct LIX was reacted with sodium borohydride in an attempt to convert the dipolar structure LIXa to 2,3-di-(phthalimidoacetyl)-4,4-dimethyloxazolidine (LXIX). There was no reaction with one equivalent of borohydride in dioxan; reaction occurred with a large excess, but no products were identified.

Even if the desired product LXIX had been obtained, it could equally well have arisen by reduction of the oxazoline portion of the vinyl ester structure LIXb, followed by intra- or intermolecular transacylation of the resulting oxazolidine (scheme 2).

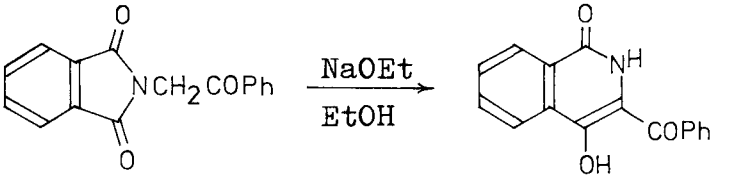
scheme 2.



c) An attempt was made to synthesise a model compound (LXXI) of the vinyl ester structures LIXb and LXIb, by reacting the anion from phthalimidoacetyl-benzene (LXX) with phthalimidoacetyl chloride. Addition of sodium hydride to phthalimidoacetyl-benzene LXX in diglyme caused an immediate deep red colouration, which did not disappear on addition of the acyl chloride. The only significant product, isolated by p.l.c, showed spectral properties expected of the desired product of O-acylation LXXI - a high frequency i.r carbonyl band concealed under the higher frequency phthalimido band, and a 1H singlet proton resonance at τ3.30. The compound even reacted with benzylamine over about 30 minutes, but neither the expected N-phthalimidoacetyl-N-benzylamine LXIV nor phthalimidoacetyl-benzene LXX was formed.



The reactions were only done on a small preliminary scale, and neither the mystery compound nor the products of its reaction with benzylamine were further characterised. It is known that the anion of phthalimidoacetyl-benzene LXX can react by cleavage of the phthalimide ring, e.g to (LXXII)[154], and probably something similar happened here, although the n.m.r spectrum indicates two phthalimido groups in the original product.

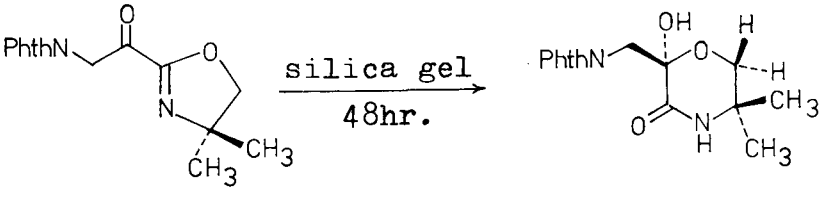


(LXX) (LXXII) (ref. 154)

iv) Chemical studies of 2-phthalimidoacetyl-4,4-dimethyloxazoline (LXV).

The 2-phthalimidoacetyl-4,4-dimethyloxazoline LXV formed by reaction of the 2:1 adduct LIX with nucleophiles was isolated by column chromatography. During a subsequent experiment this compound was left for 48 hours on a silica gel p.l.c plate, and on recovery was found to have hydrolysed and recyclised to 2-hydroxy-2-phthalimidomethyl-5,5-dimethyl-1,4-morpholin-3-one (LXXIII). This was characterised by a very distinctive AB pattern of the ring methylene proton resonances, indicative of the cyclic structure.

The analogous compound LXVII from the 2:1 adduct LXI decomposes on chromatography to more polar products that were not identified.



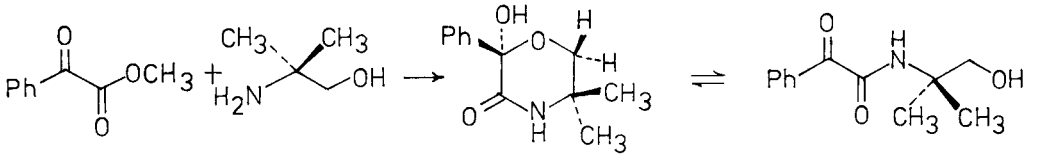
(LXV) (LXXIII) ((R)-enantiomer shown)

It has been reported that reaction of phenylglyoxylic acid esters with 2-amino-2-methylpropanol gives an analogous

2-phenyl-2-hydroxy-5,5-dimethyl-1,4-morpholin-3-one (LXXIV), that is cyclic (LXXIVa) in the solid state, as judged by the i.r spectrum of a KBr disc preparation, but which tautomerises to the acyclic glyoxylic acid amide (LXXIVb) on standing in methanolic solution, as judged from the u.v spectrum.[155]

We obtained the same compound independently. It is only soluble in $CDCl_3$ on warming, when the resultant n.m.r spectrum shows only the acyclic tautomer LXXIVb. The compound is more soluble in $^2H_4$-methanol, when the n.m.r spectrum is that of the cyclic form LXXIVa, with an AB pattern for the ring methylene protons identical to that in the spectrum of LXXIII. Over 70 minutes at 37°, LXXIVa was converted to an equilibrium mixture of cyclic LXXIVa : acyclic LXXIVb ratio 71:29. The i.r spectrum of LXXIV in dichloromethane taken immediately shows the cyclic structure LXXIVa (no amide II band, $\nu_{C=O}$1675 cm^{-1}), but after standing overnight shows the acyclic form LXXIVb (amide II band at 1515 cm^{-1}, $\nu_{C=O}$1668 cm^{-1})

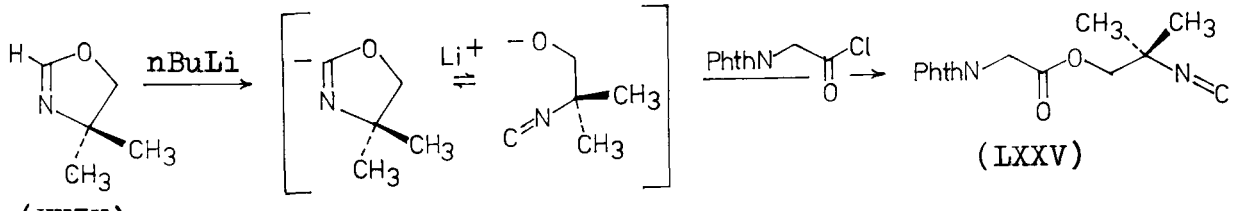
LXXIII existed solely in the cyclic form under all the conditions described above.



(LXXIVa) (LXXIVb)

((R)-enantiomer shown)

2-Acyloxazolines like LXV have not been described before, except for an isolated report of 2-benzoyloxazoline.[156] Attempted synthesis of LXV from the anion of 4,4-dimethyloxazoline[152] and phthalimidoacetyl chloride gave only the odourless, crystalline 2-isocyano-2-methylpropyl phthalimidoacetate (LXXV) by reaction of the acyl chloride with the acyclic tautomer of the 4,4-dimethyl-oxazolin-2-yl anion.



(XXIX) (LXXV)

v) Reaction mechanisms.

Similar product mixtures were obtained from the reactions of phthalimidoacetyl chloride, triethylamine and the oxazolines II and XXIX under both conditions A and conditions B (see page 81). Procedure B certainly generates the corresponding 1:1 acyl chloride-oxazoline adducts, and this result could indicate that, in these cases, procedure A also involves these intermediates rather than phthalimidoketene, at least in the initial stages.

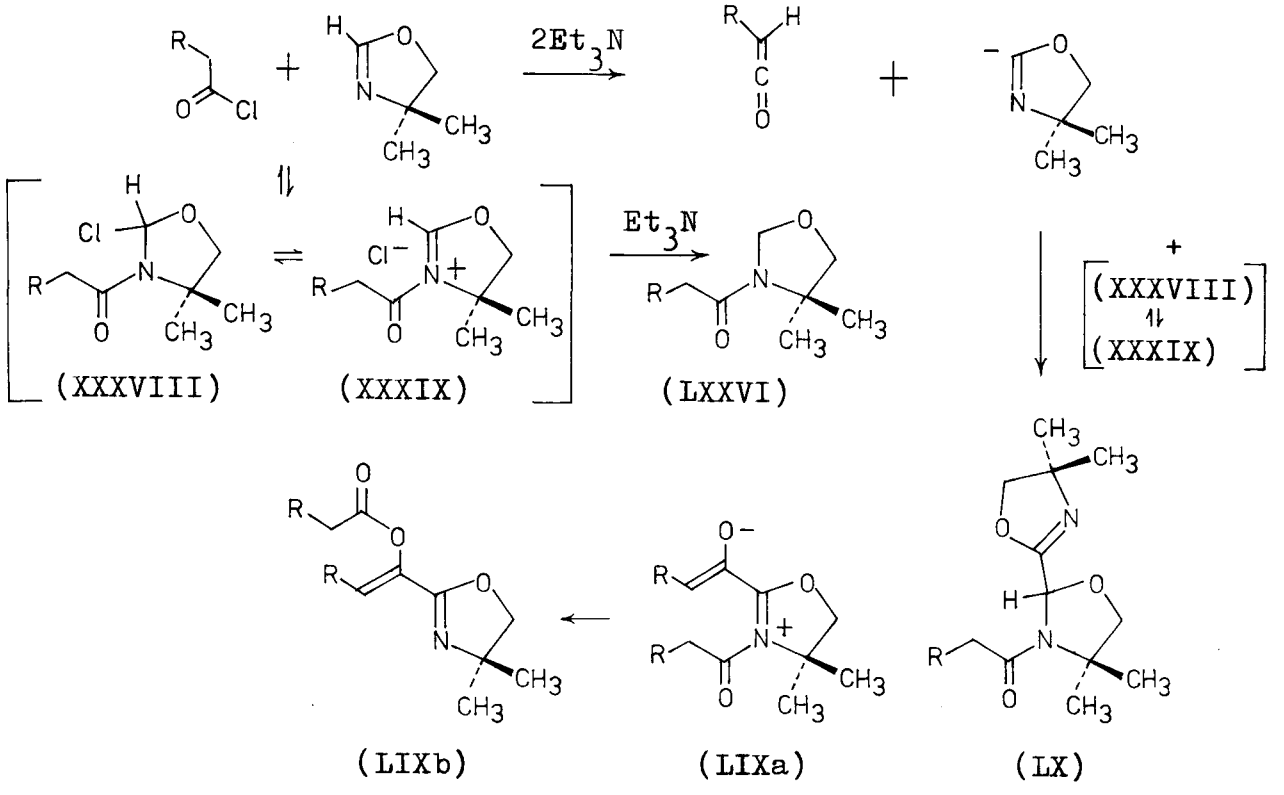
The products are novel for this type of reaction. The only tenable mechanism for formation of the 2:1 adducts LIX and LXI is via reaction of the nucleophilic carbene (e.g LXXVI) with a mole of phthalimidoketene. The carbene LXXVI can be derived from the acyl chloride-oxazoline adduct by elimination of HCl. The phthalimidoketene must be formed from the small amount of acyl chloride in equilibrium with the acyl chloride-oxazoline adduct by the action of triethylamine, and this would liberate a mole of free oxazoline that could react to form a 1:2 adduct LX.

Carbene LXXVI could also be derived from a 1,4-dipolar ketene-oxazoline adduct by intramolecular proton shift.

The reaction of a carbene with a ketene has not been proposed before, and would lead to the dipolar 2:1 adduct, e.g LIXa, which could undergo intra- or intermolecular transacylation to the vinyl ester structure LIXb. As such, LIXa and LIXb are almost tautomeric. (Scheme 3 outlines the mechanisms proposed for the reaction of phthalimidoacetyl chloride and 4,4-dimethyloxazoline with triethylamine, as example.)

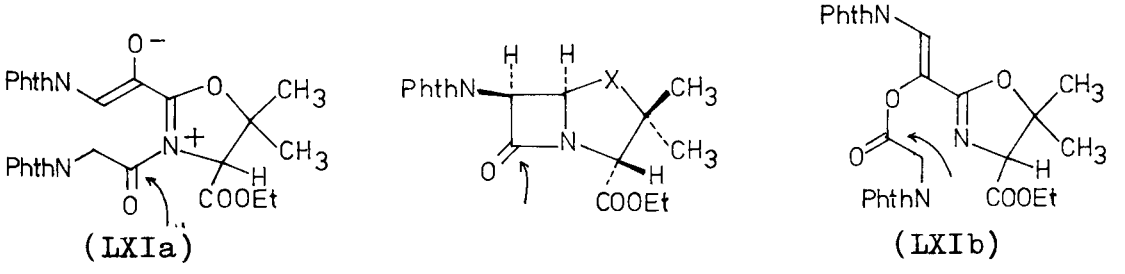
Formation of the nucleophilic carbene LXXVI from the N-acyl-oxazolinium ion must be slow, as shown by the absence of deuterium at C2-H in the N-acyl-2-($^2H_3$-methoxy)-oxazolidine (XLVIII, R = ^2H) product of the reaction of the acyl chloride-oxazoline adduct with triethylamine and $^2H_4$-methanol. β-Lactam formation from the acyl chloride-oxazoline adduct could occur by deprotonation at C2' of the N-acyl group and cyclisation onto the oxazolinium ion, or by intramolecular insertion of the carbene LXXVI into the C2'-H bond of the N-acyl group. The potential bicyclic products have been shown to exist (chapter 2), and there must be some considerable factor preventing their formation here and allowing the generation and rather odd intermolecular reaction of carbene LXXVI, even in very dilute

solution. The reason is probably to be found in the detailed conformational and electronic properties of the adducts of acyl chlorides and oxazolines.



scheme 3. (R = PhthN)

It is also interesting that the 2:1 adducts LIX and LXI react rapidly with benzylamine. Both the suggested structures LXIa and LXIb can assume conformations in which the active carbonyl group is adjacent to the nitrogen of the 5-membered heterocycle, and provide potential alternatives to the β-lactam of the desired oxapenam.



vi) Generality of the reactions.

Preliminary attempts only have been made to obtain other 2:1 adducts analogous to LIX and LXI without the phthalimido grouping which dominates the i.r spectrum. Reaction of a mixture of two mole equivalents of azidoacetyl chloride and one of 4,4-dimethyloxazoline with two mole equivalents of triethylamine gave only one significant product that is probably a 2:1 adduct having yet another structure. It does not react with benzylamine, and the available spectral and chemical data are given in the following Experimental section, along with a possible structure.

EXPERIMENTAL.

1) Solvents and triethylamine.

Benzene and ether were tried as reaction solvents, but dichloromethane was found the most convenient, being easy to dry and purify, and a good solvent for the compounds encountered. Reagent grade dichloromethane was predried over calcium sulphate and redistilled from phosphorus pentoxide under nitrogen.[162] It was stored in brown bottles under nitrogen, and withdrawn with a syringe as required.

Ether, benzene, chloroform (containing 2% ethanol as stabiliser) and ethyl acetate for extractions and chromatography were reagent grade redistilled before use.

Triethylamine was reagent grade redistilled from sodium-lead alloy and stored in a brown bottle over a few pieces of sodium alloy in the dry box.

2) Acyl chlorides.

Acetyl chloride, benzoyl chloride and chloroacetyl chloride were obtained commercially and redistilled within 7 days before use.

Preparation of ethyl malonyl chloride was described in chapter 2, and that of cyanoacetyl chloride in chapter 3.

Azidoacetyl chloride.

Ethyl azidoacetate was obtained in 90% yield by refluxing ethyl chloroacetate with a slight excess of sodium azide in 2% ethanol/water for at least 4 hours; this was converted to azidoacetic acid by stirring vigorously with one equivalent of aqueous KOH for 1 hour, and extracting into ether.[157]

The crude azidoacetic acid was not distilled (it may explode[157]) but stirred with 1.5 mole equivalents of freshly distilled thionyl chloride overnight. The n.m.r spectrum of the neat reaction mixture indicated complete conversion to azidoacetyl chloride, and the product was fractionally distilled to give 72% from ethyl azidoacetate, b.p 57-59°/30mm.[159]

It was stored in a stoppered vial in the refrigerator at 0° and slowly turned brown over several months, although spectroscopic properties were unchanged.

i.r (film) 2115s,1795s cm^{-1}.

n.m.r (CCl_4) τ5.71 (s)

Phthalimidoacetyl chloride.

Phthalimidoacetic acid was prepared by fusing an equimolar mixture of glycine and phthalic anhydride at 185° for 15 minutes, cooling and recrystallising from hot water (96%, m.p 185°).

The acid was refluxed for 45 minutes with 2.5 mole equivalents of freshly distilled thionyl chloride, then evaporated on a rotary evaporator, and the residue recrystallised twice from benzene/petrol (70%, m.p 84-85°).[160]

i.r (CH_2Cl_2) 1802s,1778s,1727vs,1700m(sh),1610w cm^{-1}.

n.m.r ($CDCl_3$) τ5.12 (s,2H) (c.f phthalimidoacetic acid τ5.44)
2.07 (m,4H)

This product was unchanged in melting point and spectroscopic properties after storing for 6 months in a dessicator over silica gel under vacuum.

3) Oxazolines.

4,4-Dimethyloxazoline (XXIX) and 2-phenyl-4,4-dimethyloxazoline (XXX) were prepared from freshly distilled 2-amino-2-methylpropanol and formic acid[140] and benzoic acid[141] respectively. XXIX was difficult to fractionate and only obtained in 30% yield. XXX was distilled at 75-80°/1mm in 64% yield, leaving a yellow viscous residue.

Ethyl 5,5-dimethyloxazoline-4-carboxylate (II).

Ethyl isocyanoacetate was prepared from N-formylglycine ethyl ester and phosgene in dichloromethane.[161]

i.r (film) 2990m,2170s,1760s cm^{-1}.

On storing at 0° this compound goes quite brown, but the i.r spectrum is unchanged, and it can be redistilled almost quantitatively before use (85-87°/14mm).

Sodium cyanide was ground in a mortar and dried for 4 hours at 100°/2mm. Ethanol was dried over preheated molecular seives, but was not redistilled.

A mixture of ethyl isocyanoacetate (13.6g, 120mM) and acetone (13ml, 180mM) dissolved in ethanol (30ml) was added dropwise to a stirred suspension of sodium cyanide (0.5g, 10mM) in ethanol (30ml) at room temperature over about 30 minutes. The resulting orange mixture was then refluxed for 1 hour and evaporated on the rotary evaporator. The residue was dissolved in carbon tetrachloride (100ml), cooled in ice, and filtered, washing through with carbon tetrachloride. The filtrate was evaporated to give an oil (19.7g), which was distilled at 0.55mm. The first fraction(2.52g, $< 60^{\circ}$) contained II and c. 15% of starting isocyanide (g.l.c 2'E301/70°). The next two fractions (3.06g, 60-64°, and 7.02g, 64°) were pure II by i.r, n.m.r, and g.l.c. (10.08g, 50%). The residue contained some N-formylglycine ethyl ester (b.p 67-70°/0.02mm).

The product was stored in the refrigerator in a stoppered vial and was unchanged after 12 months. It also showed no change in CCl_4 solution in the presence of 1 mole equivalent of triethylamine.

n_D^{23} 1.4390 d^{23} 1.082 g/ml.

i.r (film) 2985m,2945w,1748s,1735s(sh),1628s cm^{-1}.

n.m.r (CCl_4) τ8.70 (t,J=7.0)┐
8.70 (s) ┘ total 6H
8.50 (s,3H)
5.80 (q,J=7.0,2H)
5.78 (d,J=1.0,1H)
3.20 (d,J=1.0,1H)

Ethyl 2-formylamino-3,3-dimethylacrylate (XXVIII).

Freshly prepared and standardised 1.0N sodium ethoxide in ethanol (5ml, 5mM) was added dropwise to a stirred solution of ethyl isocyanoacetate (0.565g, 5mM) and acetone (0.73ml, 10mM) in dry ethanol (5ml), and the mixture stirred for 3 hours at room temperature. The mixture was then evaporated, dissolved in ether (15ml), washed with water, dried and evaporated to a crystalline mass. Recrystallisation from ether/petrol gave white needles (0.17g, 20%) m.p 78.5°. The residues were not worked up further.

i.r (nujol) 3240m(br),1715s,1665s,1630s,1530m cm^{-1}.

n.m.r ($CDCl_3$) τ8.70 (t,J=7.0,3H)
8.12 (s) and 8.02 (s) total 3H, ratio 22:12.
7.80 (s) and 7.86 (s) total 3H, not completely resolved at 60 MHz.
5.74 (q,J=7.0,2H)
2.72 (br, 1H)
2.09 (s,br), 1.89 (s,br), and 1.77 (d,J=1.0, sharp) total 1H, ratio 3:2:7.

$C_8H_{13}NO_3$ C56.11, H7.65, N8.18%
found C56.48, H7.66, N8.16%

4) Recording n.m.r spectra of acyl chloride-oxazoline adducts.

All liquid compounds were transferred by microsyringes through serum caps. c. 0.5mM of the oxazoline was syringed into an n.m.r sample tube, followed by 0.5ml of the appropriate solvent ($CDCl_3$ or CCl_4). An equimolar quantity of the acyl chloride was added from a syringe slowly down the side of the tube, the reactants mixed by partially inverting the tube, and the spectrum recorded immediately.

The spectra in several examples were found unchanged after 4 hours at 37°.

Table 4 is a list of some of the compounds used, their molecular weights and the volumes (μl) of 1mM.

	mol.wt.	vol.1mM
Ethyl 5,5-dimethyloxazoline-4-carboxylate (II)	171	158μl
4,4-dimethyloxazoline (XXIX)	99	103
CH_3COCl	78.5	71
N_3CH_2COCl	119.5	87
$EtOOCCH_2COCl$	150.5	124
PhCOCl	140.5	107
Et_3N	101	139

table 4.

Phthalimidoacetyl chloride is a crystalline solid, stable over at least 6 months in a dessicator under vacuum. It was handled by weighing out rapidly into a sample vial, which was then fitted with a serum cap. The appropriate amount of solvent was added with a syringe, and the solution withdrawn with the same syringe and transferred to the reaction.

N-Chloroacetyl-N-formyl-2-amino-2-methylpropyl chloride.(XLI).

On warming to 60°, the spectrum of a mixture of chloroacetyl chloride and 4,4-dimethyloxazoline changed to that expected for the acyclic derivative XLI.

100MHz $\tau(CDCl_3)$ 8.395 (s, 6H)
6.085 (s,2H)
5.420 (s,2H)
1.275 (s,1H)

5) Reactions of acyl chloride-oxazoline adducts with triethylamine.

The general procedure was to flame out a 2-necked 100ml flask fitted with reflux condenser, nitrogen bubbler and magnetic stirrer follower, under a rapid stream of dry nitrogen. The apparatus was allowed to cool under nitrogen, and the flow rate of the latter reduced. 1mM of the oxazoline was syringed into the flask, and 1mM of each reactant weighed out or syringed into separate sample vials fitted with serum caps. 10ml of dry dichloromethane was syringed into each, and the solutions transferred to the reaction vessel by syringe as appropriate.

Reactions were followed by withdrawing aliquots (c. 0.5ml) for solution i.r spectra or t.l.c analysis.

The reactions were worked up by evaporation on the rotary evaporator. The residue was dissolved in benzene and filtered through a weighed sinter to remove triethylammonium chloride(Et_3NHCl) (m.p 260°, very soluble in water) which was weighed. The filtrate was evaporated and worked up by crystallisation or chromatography.

Great difficulty was experienced over intrusion of moisture in early experiments - the triethylamine and its handling may have been the culprits - but using the above procedure, reactions were invariably completely free of acyclic hydrolysis products

(no O-CHO singlet at c. τ2.0 in the n.m.r spectrum). Data for the hydrolysis products - derivatives of N-acylethanolamine and its O-formate - obtained as by-products in these reactions are given in section 8.

Three examples are described in some detail as typical of the reaction procedure.

N-Phthalimidoacetyl-2-methoxy-4,4-dimethyloxazolidine (LVIII).

4,4-Dimethyloxazoline (103μl, 1mM) was syringed into the dried reaction flask, followed by dry dichloromethane (10ml). Phthalimidoacetyl chloride (224mg,μlmM) was quickly weighed into a dry sample vial fitted with a serum cap. Dichloromethane (10ml) was syringed into the vial, and the solution withdrawn into the syringe and transferred dropwise to the stirred solution of the oxazoline over about 3 minutes.

Triethylamine (139μl, 1mM) was syringed into a dried sample vial in the dry box. The vial was fitted with a serum cap and removed from the dry box. Dichloromethane (10ml) was added, followed by spectroscopic grade methanol (40μl, 1mM). This mixture was added from a syringe to the stirred acyl chloride-oxazoline mixture dropwise over about 15 minutes. The reaction was stirred for 10 minutes at room temperature, although t.l.c indicated that reaction was almost immediate, giving a single product, R_f0.6 in EtOAc/benzene 1:1.

The mixture was evaporated on a rotary evaporator, dissolved in benzene (c.25ml) and filtered through a weighed sinter, washing through with small portions of benzene and sucking the white crystalline residue - $Et_3N.HCl$ - dry (130mg, 96%). The filtrate was evaporated, and crystallised from benzene/petrol (226mg, 71%) m.p 152-155°. The analytical sample was crystallised twice from carbon tetrachloride, m.p 156°.

i.r (CH_2Cl_2) 1775w,1720vs,1680s cm^{-1}.

n.m.r ($CDCl_3$) τ8.56 (s,3H) and 8.47 (s,3H) (100 MHz, fig.7)

6.24 (d,1H, sharp) ┐
6.065(d,1H, less sharp) ┘ AB, J=8.0

5.71 (d,1H) ┐
5.53 (d,1H) ┘ AB, J=16.7

3.93 (s,1H) 6.52 (s,3H)

2.09 (m,4H)

m.s m/e 287(14) ($M-OCH_3$), 188(15), 161(45), 160(B).

$C_{16}H_{18}N_2O_5$ C60.37, H5.70, N8.80%
found C60.20, H5.56, N8.63%

Ethyl N-phthalimidoacetyl-2-methoxy-5,5-dimethyloxazolidine-4-carboxylate (XLVIII, R = H).

As for LVIII, using ethyl 5,5-dimethyloxazoline-4-carboxylate II (158µl, 1mM). The n.m.r spectrum of the crude product (400mg) showed two $OC\underline{H}_3$ signals, just resolvable at 60MHz (ratio 5:1), but after one crystallisation (benzene/petrol) only one signal (120mg, 30%)

m.p 156°

i.r (CH_2Cl_2) 1776w,1740s(sh),1720vs,1688s cm^{-1}.

n.m.r ($CDCl_3$) τ8.74 (t,J=7.0,3H)
8.67 (s,3H) and 8.42 (s,3H)
6.48 (s,3H)
5.76 (q,J=7.0,2H)
5.58 (s,1H)
5.59 (d,1H) and 5.22 (d,1H) AB, J = 16.7
3.78 (s,1H)
2.10 (m,4H)

m.s m/e 390(0.12) (M), 359(7) ($M-OCH_3$)$[C_{18}H_{19}N_2O_6]$, 257(24), 188(13), 172(11), 161(24), 160(B).

$C_{19}H_{22}N_2O_7$ C58.45, H5.68, N7.18%
found C57.85, H5.49, N6.97%

Ethyl N-phthalimidoacetyl-2-($^2H_3$-methoxy)-5,5-dimethyloxazolidine-4-carboxylate (XLVIII, R = ^2H).

As for XLVIII (R = H), using $^2H_4$-methanol (45µl, 1mM). The crude product showed two C2-$\underline{H}$ signals (ratio 2:1, total 1H) in the n.m.r spectrum, and no $OC\underline{H}_3$ (415mg). One crystallisation from benzene/petrol gave 115mg, n.m.r spectrum identical to that of XLVIII (R = H), except for absence of $OC\underline{H}_3$ singlet at τ6.48.

m.p 159-160°

i.r (CH_2Cl_2) 2260vw,2220w,2070w cm^{-1} ┐
m.s m/e 393(0.06) (M), 378(0.08) ($M-CH_3$), ├ otherwise same as XLVIII (R = H)
375(0.08) ($M-C^2H_3$), ┘

$C_{19}H_{19}N_2O_7{}^2H_3$ mol.wt = 393.41
calcd. for $C_{19}H_{22}N_2O_7$ with mol.wt 393.41: C58.01, H5.64, N7.12%
found C57.97, H5.61, N7.06%

N-Acetyl-2-methoxy-4,4-dimethyloxazolidine (XLIX).

The above reaction, using 4,4-dimethyloxazoline (103μl,1mM), acetyl chloride (71μl, 1mM), triethylamine (139μl, 1mM) and methanol (40μl, 1mM) gave a crude product, 2 spots on t.l.c (R_f's 0.2 and 0.7 in EtOAc/benzene 1:1) and the n.m.r spectrum showed 60% of XLIX and 40% N-acetyl-2-amino-2-methylpropanol-O-formate (L). After 24 hours exposure to air, the n.m.r spectrum of the product showed only L.

n.m.r ($CDCl_3$)	(XLIX)	(L)
	τ8.61 (s,3H) and 8,50 (s,3H)	τ8.66 (s,6H)
	8.01 (s,3H)	8.06 (s,3H)
	6.66 (s,3H)	5.64 (s,2H)
	6.30 (d,1H) ┐AB, J=8.3	3.74 (br,1H)
	6.10 (d,1H) ┘	1.87 (s,1H)
	4.27 (s,1H)	

2:1 Adduct (LIX).

Phthalimidoacetyl chloride (447mg, 2mM) was added to 4,4-dimethyloxazoline (103μl, 1mM) in dichloromethane (2 x 10ml) as described above.

i.r (CH_2Cl_2) 1802m,1775w,1725s,1685m,1640vw cm^{-1}.

Triethylamine (278μl, 2mM) was measured out as described, dissolved in dichloromethane (10ml), and added dropwise from a syringe to the stirred mixture over about 15 minutes. After stirring for a further 15 minutes at room temperature, the mixture was evaporated, dissolved in benzene and filtered. The residue from this filtration was washed with water, removing $Et_3N.HCl$ (270mg, 100%) and leaving insoluble polymeric (?) matter (70mg).

The filtrate was evaporated. The n.m.r spectrum showed the ratio of 2:1 adduct LIX : 1:2 adduct LX to be 5:2 by integration of the singlet resonances at τ2.79 and τ4.09 respectively. The mixture was extracted with ether (four 20ml portions).

The material insoluble in ether (160mg) contained no LX (by n.m.r). It was dissolved in the minimum amount of dichloro-

methane (c. 2ml) and stood for 12 hours to give colourless crystals (50mg) of m.p 219-221°.

The material soluble in ether (230mg) contained LIX : LX in ratio 57:43 (by n.m.r). Dissolving in the minimum of dichloromethane and standing gave crystals (35mg) m.p 219°. All the residues were combined, dissolved in a little dichloromethane, and small portions of ether added to get several small crops of crystals, (total 47mg) m.p 210-219°. Total yield of LIX 132mg (0.28mM), and yield of LX (by n.m.r) 0.16mM.

The analytical sample was recrystallised once from dichloromethane, m.p 221°.

i.r (CH_2Cl_2) 1790w(sh),1777m,1720vs,1680w,1640w cm^{-1}.

n.m.r ($CDCl_3$) τ8.68 (s,6H)
5.93 (s,2H)
5.29 (s,2H)
2.79 (s,1H)
2.16 and 2.25 (m,8H)

m.s m/e 473(4) (M), 286(18), 285(61) (M-PhthNCH$_2$CO), 271(6) (286-15*), 258(2) (285-27*),187(13) (285-98*), 161(22), 160(B) (187-27*),133(14) (161-28*),132(17) (187-55*), 105(11), 104(33), 78(28), 77(30), 76(30), 51(13), 50(17).

$C_{25}H_{19}N_3O_7$ C63.42, H4.05, N8.88%
found C63.80, H3.95, N8.62%

1:2 Adduct (LX).

By the general procedure phthalimidoacetyl chloride (224mg, 1mM) in dichloromethane (10ml) was added to 4,4-dimethyloxazoline (103μl, 1mM) in dichloromethane (10ml), followed by a mixture of triethylamine (139μl, 1mM) and 4,4-dimethyloxazoline (103μl, 1mM) in dichloromethane (10ml). The mixture was evaporated, dissolved in benzene and filtered to give $Et_3N.HCl$ (130mg, 95%). The filtrate was evaporated, and the n.m.r spectrum showed no LIX (no signal at τ2.79). It was extracted with ether (four portions of 20ml). The n.m.r spectrum of the ether-soluble fraction (300mg) showed almost pure LX. It was purified by p.l.c (two 100cm x 20cm x 0.5mm plates, developed twice in EtOAc/benzene 1:1) to give material that crystallised on adding ether (105mg; 60% recovery gives 175mg).

The ether-insoluble fraction (100mg) was purified on a

short silica gel column (5g) with benzene and 15% EtOAc/benzene to give LX (24mg). Total yield of crude LX was thus 199mg (0.52mM). This product was crystalline, but very difficult to recrystallise and free from traces of the acyclic N-acylethanolamine-O-formate derivative (section 8). The analytical sample was obtained by low temperature recrystallisation from ether, m.p 130°.

i.r (CH_2Cl_2) 1773w,1720vs,1672s cm^{-1}.

n.m.r ($CDCl_3$) τ8.62 (s,6H)
8.50 (s,3H) and 8.43 (s,3H)
5.89 (s,2H)
6.12 (d,1H) and 5.84 (d,1H) AB, J=8.0
5.73 (d,1H) and 5.44 (d,1H) AB J=16.0
4.09 (s,1H)
2.24 (m,4H)

m.s m/e 385(14) (M), 330(4) (M-55), 287(11) (M-98), 259(14), 258(47), 245(26), 225(20), 197(43), 188(14), 183(17), 161(47), 160(B).

$C_{20}H_{23}N_3O_5$ C62.32, H6.02, N10.90%
found C61.38, H5.94, N10.67%

Using the above reactants in a 1:1:1 ratio gave 333mg after removal of $Et_3N.HCl$ (126mg, 93%). Recrystallisation from dichloromethane gave LIX (42mg, 0.089mM). The residue (230mg) showed little LIX, and was purified on a silica gel column, eluting LX with 15% EtOAc/benzene (62mg, 0.16mM). LIX and LX both have R_f0.3 on t.l.c in EtOAc/benzene 1:1, but on a column LX is eluted with 15% and LIX with 25% EtOAc/benzene.

2:1 Adduct (LXI)

Procedure as for LIX, using ethyl 5,5-dimethyloxazoline-4-carboxylate II (158μl, 1mM). The evaporated reaction mixture, dissolved in benzene and filtered, gave insoluble solid (290mg) that was mostly soluble in water (theoretical $Et_3N.HCl$ 273mg), but on attempting to crystallise the filtrate from benzene/petrol, small amounts of fluffy white matter, probably polymeric, were repeatedly obtained. The total filtrate (560mg) was purified twice on p.l.c (developing three times with EtOAc/benzene 1:1) to give finally 250mg of apparently pure LXI, that was crystallised by dissolving in the

minimum of benzene at room temperature, then adding petrol until just cloudy, scratching to induce crystallisation, and standing at room temperature for 6 hours (130mg, 0.24mM) m.p 160° (softens 140°).

i.r (CH_2Cl_2) 1790w(sh),1775m,1735s(sh),1723vs,1680w(sh),1630w cm^{-1}.

n.m.r ($CDCl_3$) τ8.74 (t,J=7.0,3H)
8.63 (s,3H) and 8.42 (s,3H)
5.77 (q,J=7.0,2H)
5.48 (s,1H)
5.28 (s,2H)
2.72 (s,1H)
2.23 (m) and 2.14 (m) total 8H.

m.s m/e 545(8) $[C_{28}H_{23}N_3O_9]$ (M), 518(1.1), 473(9), 360(26), 359(B), 312(11), 286(11), 285(38), 243(11), 201(26), 188(13), 187(17), 161(30), 160(B), 133(13), 104(38), 100(11), 77(19), 76(21), 70(17), 43(11).

$C_{28}H_{23}N_3O_9$ C61.65, H4.25, N7.70%
C61.33, H4.43, N7.63%

The n.m.r spectra of crude reaction products in this series showed no signals in the τ4.0 region belonging to a 1:2 adduct analogous to LX.

Reaction with azidoacetyl chloride and 4,4-dimethyloxazoline.

Azidoacetyl chloride (174μl, 2mM) in dichloromethane (10ml) was added to 4,4-dimethyloxazoline (103μl, 1mM) in dichloromethane (10ml). Triethylamine (278μl, 2mM) was then added to the mixture, dissolved in dichloromethane (10ml) according to the general method. The brown mixture was evaporated, dissolved in benzene and the solution filtered to give a dark solid (255mg) that was mostly soluble in water, leaving a small amount of black oil. The filtrate was evaporated, and the residue (240mg) showed a major product on t.l.c (R_f0.8 in 20% EtOAc/benzene, R_f0.5 in $CHCl_3$ - i.e much less polar than the products with phthalimidoacetyl chloride). The n.m.r spectrum showed 80% of the major product - by comparison with the spectrum of the pure material below - and 20% of the N-acylethanolamine-O-formate hydrolysis product (section 8).

In the original experiment, this major product was isolated on p.l.c - not very successfully because it is not detected on u.v

fluorescent plates. It is probably best isolated, and was subsequently purified, on a silica gel column, eluting with benzene and 5% and 10% EtOAc/benzene. N-Azidoacetyl-2-amino-2-methylpropanol-O-formate is eluted much later with 20% EtOAc/benzene. The major product was an oil with the following spectral properties:

i.r (CH_2Cl_2) 2118vs,1675s(sh),1662s cm^{-1}.

n.m.r ($CDCl_3$) τ8.52 (s,3H) 5.94 (s,2H)
8.41 (s,3H) 4.08 (s,1H) rather broad.
6.10 (s,2H)

u.v (MeOH) strong end absorption only.

m.s m/e 183(4) $[C_7H_{11}N_4O_2]$, 181(4) $[C_7H_9N_4O_2]$, 153(26), 125(13), 111(19), 99(12), 98(18), 84(43), 81(79), 69(43), 57(25), 56(39), 55(86), 43(43), 42(57), 41(71), 40(24), 28(B).

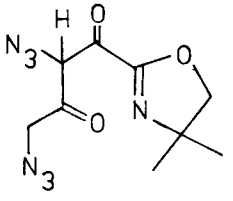
A 1:1 adduct of azidoketene and 4,4-dimethyloxazoline would have molecular weight 182 ($C_7H_{10}N_4O_2$), a 2:1 adduct 265 ($C_9H_{11}N_7O_3$); then the two peaks at highest m/e in the mass spectrum would correspond to (265 - $N_3C.CO$) and (265 - $N_3CH_2.CO$). The stoichiometry of the n.m.r spectrum indicates a 2:1 adduct, but different from the type obtained with phthalimidoacetyl chloride (LIX). There was no reaction with 1.5 mole equivalents of benzylamine over 3 days at 37° in $CDCl_3$, as judged by the n.m.r spectrum.

The C-acyl analogue (LXXVII) of the vinyl ester structure LIXb was first suggested as a possible structure for this new 2:1 adduct, the 1H resonance at τ4.08 in the n.m.r spectrum being due to C2-H of the 1,3-dicarbonyl system. However, this single proton showed no exchange with D_2O over 48 hours at 37°, conditions under which the analogous proton in acetylacetone was 75% exchanged with deuterium.

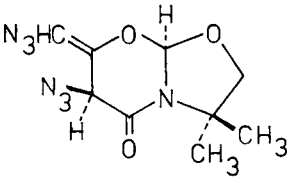
On refluxing the compound (10mg) in 10% sulphuric acid in dioxan/water for 1 hour and extracting the acidic, the neutralised, and the basified solutions separately with dichloromethane, only from the first was any material recovered, and this was azidoacetic acid (3mg) identified by its i.r spectrum. This result is not inconsistent with the oxazolo[2,3-b]dihydro-1,3-oxazin-4-one structure (LXXIX), derived from (LXXVIII). The latter has been recognised as a possible type of 2:1 adduct from ketene additions to imines, although never actually observed.[163] The single proton would then be that attached to the bridgehead carbon atom in LXXIX,

c.f C2-H in the N-acyl-2-methoxyoxazolidines (e.g XLVIII and LVIII) resonating at c. τ3.8.

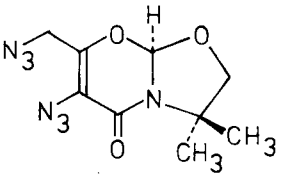
One difficulty in any structure proposition is that in this new 2:1 adduct the methyl groups at C4 of the oxazolidine ring are non-equivalent, while the methylene protons of the ring are (fortuitously?) equivalent in the n.m.r spectrum.



(LXXVII)



(LXXVIII)



(LXXIX)

6) Reactions of the 2:1 adducts (LIX and LXI) and of the 1:2 adduct (LX).

Reaction of LIX with benzylamine.

The 2:1 adduct LIX (70mg, 0.15mM) was dissolved in dichloromethane (4ml) and benzylamine (20μl, 0.2mM) added. t.l.c after 5 minutes showed only two new spots (5% MeOH/$CHCl_3$, R_f's 0.6 and 0.3) or a long streak (EtOAc/benzene 1:1). The mixture was evaporated (90mg) and chromatographed on a short silica gel column (5g) in chloroform and 1% and 2% methanol/chloroform. The first fraction was pure LXV (12mg,28%), the second was mainly LXIV, and the third pure LXIV (total 51mg). A further 10mg of unidentified materials was eluted.

Subsequent repetition of the experiment in an n.m.r sample tube showed that reaction was complete within 4 minutes at 37°, and that equimolar amounts of LXIV and LXV were the only products.

2-Phthalimidoacetyl-4,4-dimethyloxazoline (LXV).

m.p 148° (benzene/petrol)

i.r (CH_2Cl_2) 1775w,1722vs,1631w cm^{-1}.

n.m.r ($CDCl_3$) τ8.59 (s,6H) 4.91 (s,2H)
5.84 (s,2H) 2.08 (m,4H)

m.s m/e 286(53)[$C_{15}H_{14}N_2O_4$], 271(6) (M-15*), 258(1) (M-28*), 161(15), 160(B).

N-Phthalimidoacetyl-N-benzylamine (LXIV)

Surprisingly this compound has not been reported before.

Sodium carbonate (200mg, 2mM) was added to a solution of benzylamine (107mg, 1mM) in dry dichloromethane (5ml). The mixture was cooled in ice, and a solution of phthalimidoacetyl chloride (224mg, 1mM) in dichloromethane (5ml) added dropwise with stirring. After stirring for 30 minutes at room temperature. the suspension was filtered, and the filtrate washed with small portions of saturated Na_2CO_3 solution, N HCl, and water, and then dried and evaporated. The residue was recrystallised from methanol. m.p 221° (t.l.c R_f0.3 in 5% MeOH/$CHCl_3$, streaks in EtOAc/benzene 1:1).

i.r (CH_2Cl_2) 3425w,1775m,1720vs,1700s(sh),1615m cm^{-1}.

n.m.r ($CDCl_3$) τ5.67 (s,2H) 2.76 (s,5H)
5.58 (d,J=5.0,2H) 2.25 (m,4H)
3.90 (br,1H)

m.s m/e 294(2.1) (M), 43(B).

$C_{17}H_{14}N_2O_3$ C69.37, H4.80, N9.52%
found C69.62, H4.87, N9.47%

Reaction of LXI with benzylamine.

Following the reaction by n.m.r spectroscopy showed that the 2:1 adduct LXI reacted rapidly with 1.5 mole equivalents of benzylamine, to give equimolar amounts of LXIV and ethyl 2-phthalimidoacetyl-5,5-dimethyloxazoline-4-carboxylate (LXVII) analogous to LXV. After 10 hours at 37°, the n.m.r spectrum showed appreciable decomposition of LXVII, and attempted isolation on p.l.c gave only LXIV and small amounts of several other products.

Ethyl 2-phthalimidoacetyl-5,5-dimethyloxazoline-4-carboxylate (LXVII).

n.m.r ($CDCl_3$) from mixture; note characteristic PhthN-$C\underline{H}_2$ signal
τ8.63 (s,3H) and 8.39 (s,3H) at τ4.93.
5.37 (s,1H) 4.93 (s,2H) *inter alia*.

Reaction of the 2:1 adducts LIX and LXI with methanol and ethanol.

By n.m.r spectroscopy it was shown that with 5.4 mole equivalents of methanol in 0.5ml of $CDCl_3$, LIX (14mg, 0.030mM)

was 80% converted to a mixture of LXV and methyl phthalimidoacetate after 27.5 hours at 37°.

Reaction of LXI was much slower, giving only 24% reaction after 67 hours at 37° with 5.8 mole equivalents of ethanol.

Methyl phthalimidoacetate

From phthalimidoacetyl chloride and methanol.

m.p 114° (lit.[164] 113°)

i.r (CH_2Cl_2) 1776w,1755m,1726vs,1605w cm^{-1}.

n.m.r ($CDCl_3$) τ6.21 (s,3H) 2.13 (m,4H)
5.52 (s,2H)

2-Hydroxy-2-phthalimidomethyl-5,5-dimethyl-1,4-morpholin-3-one (LXXIII).

The 2:1 adduct LIX (34mg, 0.072mM) was dissolved in dry dichloromethane (3ml), spectroscopic methanol (40μl, 1mM) added, and the mixture stood for 24 hours at room temperature. The mixture was evaporated and separated on p.l.c (developed three times with 2% MeOH/$CHCl_3$) to give only two bands corresponding to methyl phthalimidoacetate and LXV.

The plate was left on the bench for 48 hours, when the band corresponding to LXV was extracted, giving crystalline LXXIII (16mg, 0.053mM) R_f0.15 in 5% MeOH/$CHCl_3$.

m.p 148° (benzene)

i.r (CH_2Cl_2) 3370m,3500-3270w,1775m,1706vs,1680s cm^{-1}.

n.m.r ($CDCl_3$) τ8.82 (s,3H) and 8.66 (s,3H)
6.58 (d,1H) and 6.00 (d,1H) AB, J = 12.0
5.78 (s,2H)
3.65 (br,1H)
2.16 (m,4H)

m.s m/e 304(1) (M), 287(1.7) (M-17), 273(20) ($C_{14}H_{13}N_2O_4$)
(M-CH_2OH), 162(17), 161(B), 160(53).

Reaction of the 1:2 adduct (LX) with H_2SO_4/methanol.

The 1:2 adduct LX (36mg,0.093mM) was dissolved in methanol (2ml), concentrated sulphuric acid (0.2ml) added, and the mixture refluxed for 12 hours. Water (6ml) was added, and solid sodium

carbonate added until there was no further effervescence. Extraction with ether gave 29mg, separated on p.l.c (developed three times with dichloromethane) into two bands only. Extraction of the first gave methyl phthalimidoacetate (4.5mg) and of the second N-phthalimidoacetyl-2-methoxycarbonyl-4,4-dimethyloxazolidine LVII (14mg, 0.04mM) as an oil that crystallised slowly on standing.

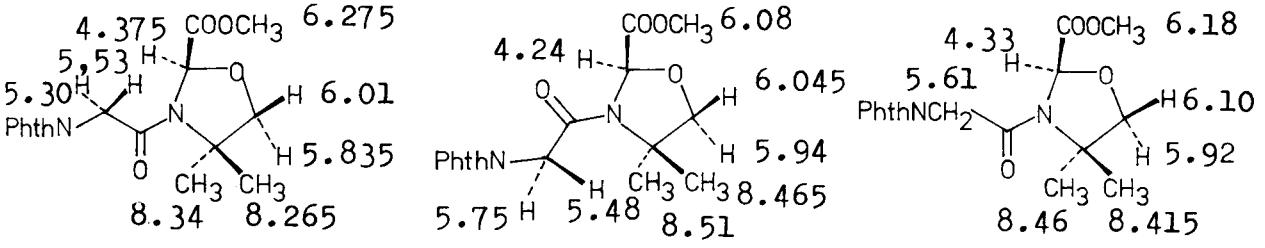
i.r (CH_2Cl_2) 1778m,1750s,1725vs,1675s,1657s cm^{-1}.

m.s m/e 346(0.19) (M), 287(31) (M-COOMe), 188(9), 163(63), 100(37) (287-187*), 88(15) (OHC.COOMe), 73(26) (88-CH_3*), 43(B).

n.m.r 100MHz ($CDCl_3$) all signals unresolved at room temperature.

-20° (fig.5) $+60^{\circ}$(fig.6)

46% (LVIIa) 54% (LVIIb)



AB coupling constants: C5 ring methylene protons J = 9.0Hz
C2' acyl group methylene protons J = 16.0Hz

Signals are assigned on the basis of intensities and deshielding by carbonyl groups. The resonance for the ring methylene proton cis to C2-H is broader due to W-coupling.

7) Model compounds.

2-Methyl-2-isocyanopropyl phthalimidoacetate (LXXV).

Commercial 15% n-butyllithium in hexane was standardised by double titration[165] and found to contain 1.58mM/ml. Tetrahydrofuran (THF) was refluxed over lithium aluminium hydride and distilled and stored under nitrogen.

A 2-necked 100ml flask was flamed out under nitrogen and cooled. 4,4-Dimethyloxazoline (103μl, 1mM) was syringed in, followed by T.H.F (10ml), and the solution cooled to -80°. n-Butyllithium in hexane (634μl, 1mM) was added dropwise from a syringe over c. 5 minutes, and after stirring at -80° for 10 minutes, phthalimido-acetyl chloride (224mg, 1mM) was transferred from a vial in T.H.F (10ml), and added dropwise to the reaction mixture over c. 10 minutes. The mixture was allowed to come to room temperature over 30 minutes, and then evaporated to give a residue that was dissolved in water and extracted with ether. The extracts dried and evaporated gave an oil (200mg) that was fairly homogenous on t.l.c (R_f0.7 in EtOAc/benzene 1:1), and crystallised from warm petrol (80mg, m.p 95° - the residues were not worked up further). The analytical sample was recrystallised twice more from petrol, m.p 96.5°.

A similar result was obtained when the experiment was performed at room temperature in T.H.F, or at -80° in ether.

i.r (CH_2Cl_2) 2135m,1776m,1758s,1723vs cm^{-1}.

n.m.r ($CDCl_3$) τ8.55 (t,J=1.6,6H) 5.46 (s,2H)
5.85 (t,J=1.5,2H) 2.14 (m,4H)

note coupling of hydrogen to nitrogen through three bonds characteristic of isonitriles[166].

m.s m/e 286(6) (M), 260(2) (M-NC), 188(13), 186(20), 161(15), 160(B).

$C_{15}H_{14}N_2O_4$ C62.93, H4.93, N9.79%
found C62.84, H4.99, N9.79%

2-Hydroxy-2-phenyl-5,5-dimethyl-1,4-morpholin-3-one (LXXIV)[155].

Diazomethane in ether was added to a cold solution of phenylglyoxylic acid (300mg, 2mM) in ether (10ml) until there was no further effervescence and a yellow colour persisted. After 30 minutes at room temperature the solution was washed with water, dried and evaporated to give methyl phenylglyoxylate (220mg, 1.34mM).

i.r (film) 1735s,1690s,1592m,1575w cm^{-1}.

The product was mixed with freshly distilled 2-amino-2-methylpropanol (119mg, 1.34mM) and stood overnight at room temperature to give a semi-crystalline mass. This was washed with ether to give a white solid that on t.l.c in EtOAc/benzene 1:1 showed one spot R_f0.2, and in 5% MeOH/$CHCl_3$ two spots R_f's 0.2 and 0.4.

Chromatography on silica gel in chloroform gave a near quantitative yield of identical material. It was recrystallised from benzene, m.p 121.5° (lit.[155] 122°).

	cyclic (LXXIVa)	acyclic (LXXIVb)*
i.r	(CH_2Cl_2) 3545w,3365w,1673s cm^{-1}	(CH_2Cl_2) 3365m,1668s,1595w, 1615m cm^{-1}.
n.m.r	($^2H_4$-MeOH) τ8.77 (s,3H)	($CDCl_3$) τ8.61 (s,6H)
	8.57 (s,3H)	6.52 (br,1H)
	6.43 (d,1H) ┐ AB,J=12.0	6.32 (s,2H)
	5.87 (d,1H) ┘	2.50 (m,3H)
	2.74 (m,3H) 2.40 (m,2H)	1.74 (m,2H)

*acyclic tautomer is 2-(phenylglyoxaloyl-amino)-2-methylpropanol.

Reaction of phthalimidoacetyl-benzene with sodium hydride and phthalimidoacetyl chloride.

Phthalimidoacetyl-benzene (ω-phthalimidoacetophenone) was best prepared from potassium phthalimide and phenacyl bromide.[167]

50% Sodium hydride dispersion in mineral oil (100mg, 2mM) was weighed out into a dry flask, dry diglyme (2ml) added, and the flask purged with nitrogen. Phthalimidoacetyl-benzene (265mg, 1mM) dissolved in diglyme (2ml) was added dropwise. The solution turned red. After 15 minutes stirring at room temperature, phthalimidoacetyl chloride (224mg, 1mM) in diglyme (1ml) was added dropwise. There was a slight reduction in the red colour. After 15 minutes water (10ml) was added, the mixture neutralised with N HCl, and extracted with ether. The extracts were dried and evaporated to give a residue that was separated on p.l.c (EtOAc/benzene 1:1) and the main band (R_f0.4) extracted to give an oil (30mg), pure on t.l.c with the following spectral data:-

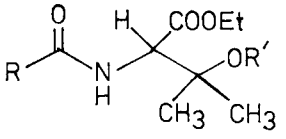
i.r (CH_2Cl_2) 1772m,1722vs,1595vw cm^{-1}.

n.m.r ($CDCl_3$) τ5.34 (s,2H)
3.30 (s,1H)
2.7-1.9 (m,11H)

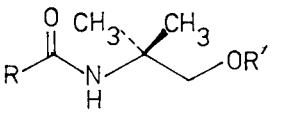
The compound reacted completely with 2 mole equivalents of benzylamine in $CDCl_3$ over about 30 minutes, but the n.m.r spectrum showed neither N-phthalimidoacetyl-N-benzylamine nor phthalimidoacetyl-benzene.

8) Hydrolysis products of the adducts of acyl chlorides and oxazolines.

Hydrolysis of the acyl chloride-oxazoline adducts leads to the corresponding derivatives of N-acylethanolamine (LXXX and LXXXI R' = H) and their O-formates (LXXX and LXXXI, R' = CHO). These were also obtained as side products in earlier reactions with triethylamine. Three such compounds were crystalline and fully characterised, and spectral data for other examples are given to make possible their detection in reaction mixtures.



(LXXX)



(LXXXI)

i) Benzoyl chloride + ethyl 5,5-dimethyloxazoline-4-carboxylate.

a. Ethyl 2-benzoylamino-3-hydroxy-3-methylbutyrate (LVI; LXXX, R = Ph, R' = H)

m.p 85° (petrol)

i.r (CH_2Cl_2) 3575m(br),3430m,1725s,1664s,1508m cm^{-1}.

n.m.r ($CDCl_3$) τ8.71 (t,J=7.0) ┐ total 9H 5.80 (q,J=7.0,2H)
8.66 (s) ┘ 5.29 (d,J=9.0,1H)
6.71 (br,1H) 2.6 (m,4H), 2.15 (m,2H)

m.s m/e 250(3) $[C_{13}H_{16}NO_4]$ $(M-CH_3)$, 220(5), 207(77), 192(17), 161(B).

$C_{14}H_{19}NO_4$ C63.38, H7.22, N5.28%
found C63.16, H7.15, N5.44%

b. Ethyl 2-benzoylamino-3-hydroxy-3-methylbutyrate-O-formate (LXXX, R = Ph, R' = CHO).

n.m.r ($CDCl_3$) τ8.69 (t,J=7.0,3H) 4.85 (d,J=9.3,1H)
8.32 (s,3H) and 8.24 (s,3H) 3.3 (br,1H)
5.71 (q,J=7.0,2H) 2.4 (m,3H), 1.9 (m.3H).

ii) Phthalimidoacetyl chloride + ethyl 5,5-dimethyloxazoline-4-carboxylate.

a. Ethyl N-phthalimidoacetyl-2-amino-3-hydroxy-3-methylbutyrate (XLV; LXXX, R = PhthN.CH_2, R' = H).

m.p 141-142° (benzene)

i.r (CH_2Cl_2) 3540w(br),3505w,1776m,1720vs(br),1505m cm^{-1}.

n.m.r ($CDCl_3$) τ8.72 (t,J=7.0,3H) 5.50 (s,2H)
8.70 (s,6H) 5.43 (d,J=9.6,1H)
7.08 (br,1H) 2.85 (br,1H)
5.75 (q,J=7.0,2H) 2.18 (m,4H)

m.s m/e 333(2) (M), 290(4), 257(12), 244(67) (290-46*), 187(14), 161(47), 160(B).

$C_{17}H_{20}N_2O_6$ C58.61, H5.79, N8.04%
found C58.68, H5.79, N7.66%

b. Ethyl N-phthalimidoacetyl-2-amino-3-hydroxy-3-methylbutyrate-O-formate (XLVI; LXXX, R = PhthN.CH_2, R' = CHO).

n.m.r ($CDCl_3$) τ8.72 (t,J=7.0,3H) 5.09 (d,J=9.6,1H)
8.42 (s,3H) and 8.34 (s,3H) 2.72 (br,1H)
5.78 (q,J=7.0,2H) 2.16 (m,4H)
5.52 (s,2H) 2.04 (s,1H)

iii) Phthalimidoacetyl chloride + 4,4-dimethyloxazoline.

N-Phthalimidoacetyl-2-amino-2-methylpropanol-O-formate (LXXXI, R = $PhthNCH_2$, R' = CHO)

m.p 202° decomp. (benzene)

i.r (CH_2Cl_2) 3415w,1773w,1718vs,1700s(sh),1610w cm^{-1}.

n.m.r ($CDCl_3$) τ8.63 (s,6H) 2.20 (m,4H)
5.72 (s,4H) 1.91 (s,1H)
3.95 (br,1H)

m.s m/e 303(3) (M), 258(6) (M-45*), 245(44), 243(44), 227(11), 188(12), 161(50), 160(B).

$C_{15}H_{16}N_2O_5$ C59.20, H5.30, N9.21%
found C58.99, H5.30, N9.09%

iv) Azidoacetyl chloride + 4,4-dimethyloxazoline.

N-Azidoacetyl-2-amino-2-methylpropanol-O-formate (LXXXI, R = N_3CH_2, R' = CHO)

n.m.r ($CDCl_3$) τ8.61 (s,6H) 3.75 (br,1H)
6.11 (s,2H) 1.88 (s,1H)
5.66 (s,2H)

Chapter 5.
REACTIONS OF VICINAL DIOLS WITH HYDROGEN BROMIDE IN ACETIC ACID.

A brief note on cobaloxime chemistry.

Alkyl(base)cobaloximes (I) are bis(dimethylglyoximate) complexes of cobalt with an alkyl group and Lewis base as axial ligands. They have been much studied as model compounds for coenzyme B_{12} - 5'-deoxyadenosyl-(5,6-dimethylbenzimidazolyl)-cobinamide - which they resemble in many of their chemical properties[168]. In both classes of compounds the cobalt is coordinated through nitrogen in a strong, essentially planar ligand field that is required to stabilise the axial cobalt-carbon bond.

Most coenzyme B_{12}-dependent enzymes catalyse a rearrangement involving exchange of hydrogen and an alkyl, acyl or electronegative group X on adjacent carbon atoms in the substrate (scheme I)

The most extensively studied system has been diol-dehydrase (scheme I, X = Y = OH). Hydrogen transfer is stereospecific, but not intramolecular, although there is no exchange with solvent. The substrate hydrogen atom rapidly equilibrates with the two hydrogens on C5' of the coenzyme before one of the three equivalent hydrogens is transferred to the product[169].

A tentative mechanism has been proposed for coenzyme B_{12}-catalysed reactions[169] (scheme II). There is initial alkyl-metal exchange forming a new σ-bond between cobalt and C1 of the substrate, the migrating hydrogen being transferred to C5' of the deoxyadenosyl fragment. The key step is then migration of cobalt from C1 to C2 of the substrate, and the reverse migration of the group X. Reversal of the initial alkyl-cobalt cleavage completes one cycle. It is likely that the enzyme is important in activating the coenzyme for the cobalt-carbon bond cleavages, possibly causing distortion of the corrin ligand and reversible dissociation of one nitrogen coordinated to the metal, giving rise to a coordinatively unsaturated complex.

There are no satisfactory chemical model systems for the initial and final alkyl-metal exchange reactions. It was suggested

that the intermediate step in scheme II - migration of cobalt from C1 to C2 of the substrate - might occur *via* a π-complex of metal and substrate (e.g (II))[170], and recently such σ⇌π rearrangements have been demonstrated in cobaloximes[171].

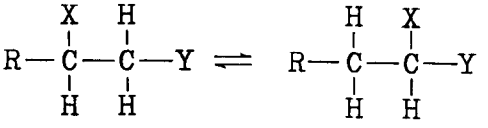
2-Acetoxyalkyl(pyridine)cobaloximes solvolyse at rates comparable to that of trityl acetate[172]. Methanolysis of 2-acetoxy-2-$^{2}H_{2}$-ethyl(pyridine)cobaloxime (III) gave 2-methoxyethyl(pyridine) cobaloxime in which the doubly-deuterium-labelled methylene group was equally distributed between C1 and C2 of the alkyl ligand (IV and V). No species with singly labelled methylene groups were detected, eliminating the possibility that the result was due to hydrogen/deuterium exchange, and a symmetrical π-complex intermediate (c.f II) was proposed for the solvolyses. Furthermore, alcoholysis in benzyl alcohol of (S)-(+)-2-acetoxypropyl(pyridine) cobaloxime (VI) gave (S)-(+)-2-benzyloxypropyl(pyridine)cobaloxime (VII) with complete retention of configuration, showing the magnitude of the interaction between metal and ligand in the π-complex.

A similar σ⇌π rearrangement has been evoked to explain the isomerisation of 1- and 2-cyanoethylcobaloximes[173], and Dolphin has demonstrated randomisation of the label during methanolysis of 2-acetoxy-2-^{13}C-ethyl(pyridine)cobaloxime[174], complementing the first part of the work from our laboratory.

Arising from the preparation of the ligands for the chiral cobaloximes used in the solvolysis studies above, a versatile new synthetic method has been developed, and is described in this chapter.

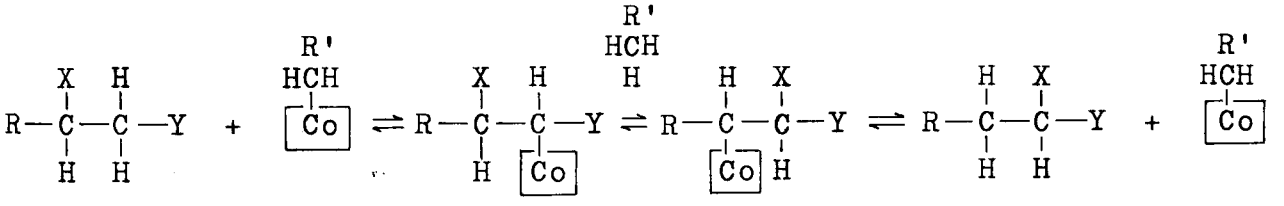
A novel degradation of cobaloximes was encountered during cobaloxime solvolysis studies, and the elucidation of the structure of the product and preliminary studies on its mechanism of formation are the subject of chapter 6. This degradation involves interaction of the axial and equatorial ligands of the cobaloxime, and is probably initiated by partial disruption of the equatorial ligand system leading to cleavage of the cobalt-carbon bond. As such, it may have a bearing on the alkyl-metal exchange processes postulated for coenzyme B_{12}-catalysed reactions.

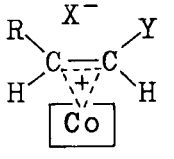
scheme I. Reactions catalysed by coenzyme B_{12}-dependent enzymes.



	R	X	Y
glutamate mutase	H	COOH	$CH(NH_2)COOH$
methylmalonyl-coenzyme A mutase	COOH	CO.SCoA	H
ethanolamine deaminase	H	NH_2	OH
dioldehydrase	CH_3	OH	OH
	CH_2OH	OH	OH
β-lysine mutase	COOH	NH_2	$(CH_2)_2CH_2NH_2$

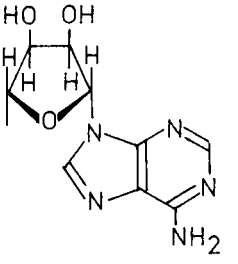
scheme II. A suggested mechanism of action for coenzyme B_{12}.

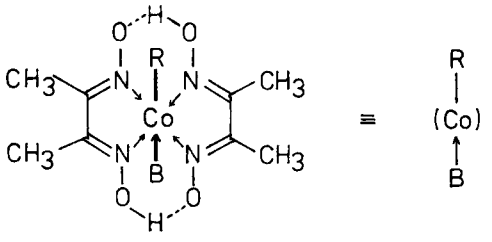




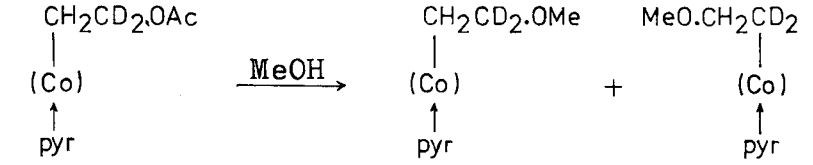
(II)


= cobalamin

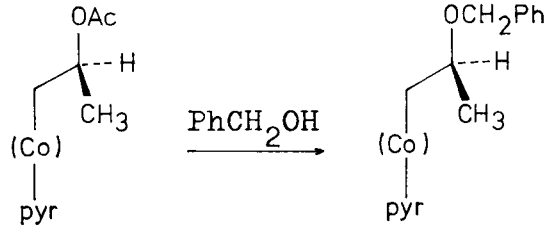
R' = 



(I)



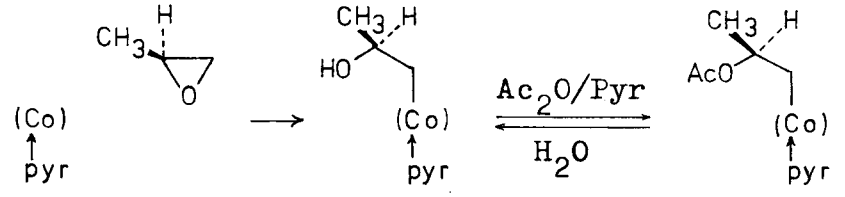
(III) (IV) (V)



(VI) (VII)

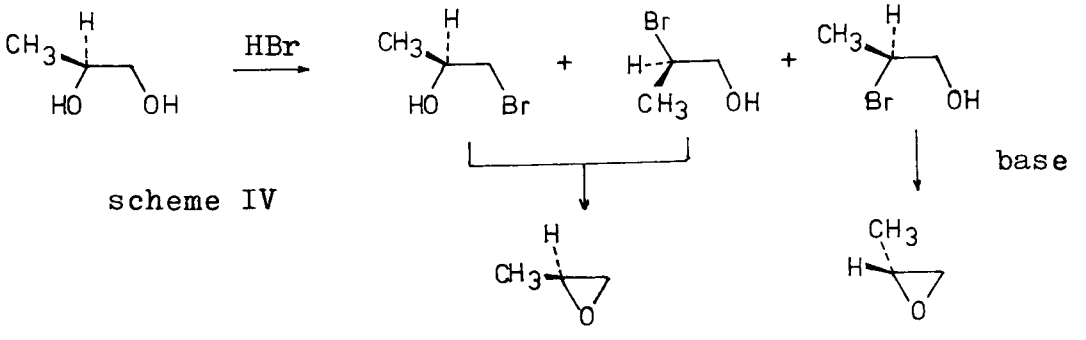
The rapid solvolysis of 2-acetoxyalkyl(pyridine)cobaloximes illustrates the special stability of a carbonium ion β- to cobalt[172]. A measure of the degree of interaction between the metal and/or the equatorial ligand and such a carbonium ion would be the degree of retention of configuration in the product of solvolysis of a 2-acetoxyalkylcobaloxime chiral at the 2-acetoxyalkyl centre.

It was proposed to use 2-acetoxypropyl(pyridine)cobaloxime in such a study. Alkylation of reduced (pyridine)cobaloxime with chiral propylene oxide would provide 2-hydroxypropyl(pyridine)-cobaloxime of known configuration. This could be acetylated with retention, and the product hydrolysed to regenerate the 2-hydroxy-propyl(pyridine)cobaloxime whose optical activity could be compared with that of the starting material (scheme III, (S)- configuration shown).



scheme III

The literature route to chiral propylene oxide[175] (scheme IV) requires heating optically active propane-1,2-diol ((S)-configuration shown) with anhydrous or fuming hydrogen bromide to give a mixture of 1-bromo-2-propanol and 2-bromopropanol. The latter is formed in amounts up to 50% of the product, depending upon the temperature, and its formation is accompanied by 59% inversion, 41% retention of configuration at C2 - i.e 82% racem-isation[176]. Presumably formation of 1-bromo-2-propanol leaves the chiral carbon atom unaffected. Reaction of the mixture of bromo-propanols with base then leads to propylene oxide of doubtful optical purity.

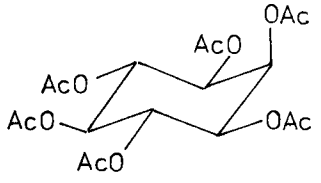


scheme IV

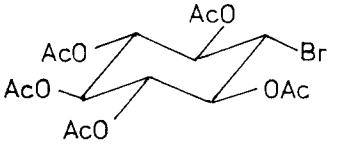
Such a reaction leaves much to be desired.

A new route to chiral propylene oxide.

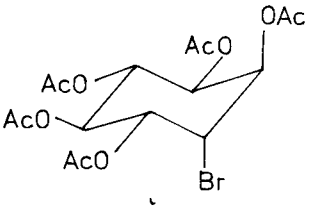
Hydrogen bromide in glacial acetic acid is a brominating agent popular in carbohydrate chemistry. Generally the hydroxylic substrate is acetylated and then heated with the reagent. McCasland bubbled hydrogen bromide through a solution of myoinositol hexa-acetate (VIII) in glacial acetic acid at reflux for 24 hours to obtain a 5% yield of meso-(1,3,5)-6-bromoquercitol (IX) and 38% of d,l-(1,2,4)-6-bromoquercitol (X) (probable configuration at C6 shown)[177].



(VIII)

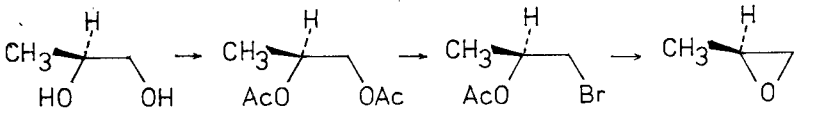


(IX)



(X)

It was anticipated that this reagent, under carefully defined conditions, might react with chiral propane-1,2-diol to acetylate both the hydroxyl groups (with retention) and then substitute the (supposed) more accessible primary acetoxy group by bromine. The resulting 1-bromo-2-acetoxypropane could be cyclised by base to give propylene oxide with retained configuration at C2 (scheme V, (S)-configuration shown). An added bonus would be that the 1-bromo-2-acetoxypropane could be used to synthesise the required 2-acetoxypropyl(pyridine)cobaloxime directly.



scheme V

Preliminary studies by S.Sakrikar with racemic material showed that reaction of propane-1,2-diol with a slight excess of a commercial saturated solution of hydrogen bromide in glacial acetic acid (HBr/acetic acid) did indeed give predominantly 1-bromo-2-acetoxypropane, but with appreciable amounts of 1,2-diacetoxypropane that could not be removed by simple distillation

(10% still remained in the best fraction after one distillation). He further found that the mixture could be converted to propylene oxide. Using the anion of a high boiling alcohol as base (e.g potassium amyloxide) the product (b.p 35°) could be distilled directly from the reaction mixture, free of solvent (b.p 125°) or impurities from the starting material (b.p of diacetate 190°/762mm).

Before using chiral material it was desirable to investigate further and to optimise the conditions for this reaction sequence, and it became apparent that a general reaction of considerable theoretical interest and practical importance was involved.

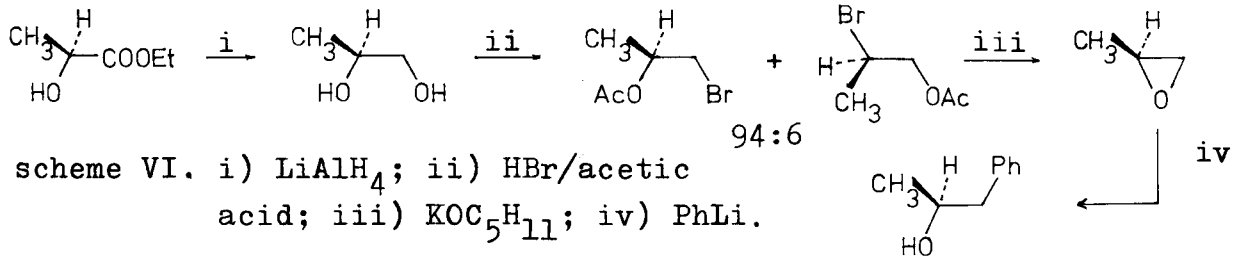
i) Having determined the exact concentration of the HBr/acetic acid by titration, it was soon established that use of a higher HBr:diol ratio reduced formation of side products. Reaction with 2 mole equivalents of HBr/acetic acid per mole of propane-1,2-diol for 30 minutes at 37° gave a crude product in almost quantitative yield containing 94% (by g.l.c) 1,2-acetoxybromopropane, with no diacetate or monoacetate, and this could be purified by a single distillation. Reaction of propane-1,2-diol with 1 mole equivalent of HBr/acetic acid for 30 minutes at 37° gave a mixture of the corresponding acetoxybromide (53%), diacetate (21%) and monoacetate (26%).

ii) The reaction was extremely rapid. At 37°, n.m.r spectroscopy of the reaction of propane-1,2-diol with 3 mole equivalents of HBr/acetic acid, performed in the sample tube, showed that after 3 minutes only 20% of the starting diol remained, and the reaction was essentially complete after 8 minutes.

iii) Both the crude and the redistilled 1,2-acetoxybromopropane were in fact mixtures of 1-bromo-2-acetoxypropane (94%) and 1-acetoxy-2-bromopropane (6%). Substitution by bromide ion at C2 to give the latter product would be expected to proceed with considerable S_N1 character, and hence racemisation (c.f the action of fuming HBr on propane-1,2-diol described above). However, the propylene oxide obtained from the mixture of isomeric acetoxy-

bromopropanes derived from optically pure (S)-(+)-propane-1,2-diol was optically pure (S)-(-)-propylene oxide by comparison of the sign[176] and magnitude of its optical rotation with the best literature values. Furthermore, reaction of this product with phenyl lithium gave (S)-(+)-1-phenyl-2-propanol in near quantitative yield and of ⩾98% optical purity by comparison of the magnitude of its optical rotation with those of the (R)- and (S)-enantiomers obtained by classical resolution by Kenyon[178].

Thus substitution by bromide ion at C2 must occur stereospecifically with inversion, since conversion of 1-acetoxy-2-bromopropane to propylene oxide involves a second inversion at C2 - i.e overall retention, and the product has the same configuration as that derived <u>via</u> 1-bromo-2-acetoxypropane (scheme VI).



scheme VI. i) $LiAlH_4$; ii) HBr/acetic acid; iii) KOC_5H_{11}; iv) PhLi.

Optically active propane-1,2-diol has been previously prepared by yeast reductase reduction of hydroxyacetone[179], giving the (R)-(-)-enantiomer. (S)-(+)-propane-1,2-diol is conveniently prepared by lithium aluminium hydride reduction of (S)-(-)-ethyl lactate, which is available in kilogram quantities from Fluka A.G. An 81% yield of the crude diol was obtained when the product was isolated by continuous extraction with dichloromethane.

Reaction of this diol with 3 mole equivalents of HBr/acetic acid at room temperature for 30 minutes was followed by quenching with water, neutralisation with solid sodium carbonate, and extraction into ether. Evaporation and distillation gave 89% of the 'pure mixture' of isomeric acetoxybromopropanes. Dropwise addition of exactly one equivalent of potassium amyloxide in amyl alcohol to this product caused rapid precipitation of potassium bromide, and (S)-(-)-propylene oxide was then distilled out directly and collected in an efficiently cooled condenser and receiver.

This illustrates the convenience of the reaction sequence,

and of those described subsequently. It is anticipated that the undistilled 1,2-acetoxybromopropane mixture (95%) should give at least as good a yield of propylene oxide provided the correct amount of base is used.

Having optimised this particular example, the wider implications of the reaction of HBr/acetic acid with vicinal diols were considered worthy of further study. The reaction of simple alcohols was compared with that of corresponding diols, and the stereochemistry of the latter was investigated. The effect of a limited range of substituents on the diols was determined.

Characteristics of the reaction of vicinal diols with HBr/acetic acid.

Reactions of butan-1-ol, butan-2-ol and cyclohexanol with 3 mole equivalents of HBr/acetic acid (4.2mM HBr per gram of reagent) were followed by n.m.r spectroscopy, products being compared by n.m.r and g.l.c with authentic samples. Initial acetylation followed by bromination was observed. Under these conditions, acetic acid is in excess (equation 1) and acetylation showed pseudo first order kinetics well through the half-life.

$$\underset{1}{ROH} + \underset{3}{HBr} + \underset{7.86 \text{ mole equivalent}}{HOAc} \xrightarrow{k_1} ROAc + H_2O + HBr \xrightarrow{k_2} RBr + HOAc + H_2O \quad \text{(eqn.1}$$

$$\text{for acetylation} \quad \ln[ROH] \sim -k_1[HOAc]t = -k'_{Ac}.t$$

Table I shows the pseudo first order rate constants for acetylation ($k'_{Ac} = k_1[HOAc]$) and hence the half-times for acetylation ($t_{\frac{1}{2}Ac} = \ln 2/k'_{Ac}$), and also the half-times for the subsequent bromination ($t_{\frac{1}{2}Br}$) estimated graphically.

The derived true rate constants (k_1) agreed well with those obtained using only 1.5 mole equivalents of HBr/acetic acid, when pseudo first order kinetics were still followed reasonably well up to the half-time of acetylation. However, under the latter conditions bromination proceeded to only about 70-80% completion where it was complete with 3 mole equivalents of HBr/acetic acid.

Acetylation of the primary acyclic alcohol was 12 times

more rapid than that of the secondary, and the acetylation of cyclohexanol was about 2/3 of the latter rate. Subsequent bromination was much slower in all cases, but four times more rapid for the secondary alcohol than for the primary, indicating considerable S_N1 character in the former case.

A series of vicinal diols was studied under the above reaction conditions - 3 mole equivalents of HBr/acetic acid per mole of diol (not per -OH group). Reactions were followed by n.m.r spectroscopy of the reaction mixtures, and n.m.r and g.l.c analysis of samples worked up at intervals (quenched with water, neutralised and extracted into ether). Products were identified spectroscopically and where possible by comparison with authentic samples.

The results for diols related to the three alcohols in table I are shown in table II. $t_{\frac{1}{2}Ac}$ Is the half-time for disappearance of starting diol; $t_{\frac{1}{2}Br}$ is the half-time for appearance of the corresponding acetoxybromide.

The results must be interpreted with care.

i) On electronic grounds, a neighbouring hydroxy- or acetoxy- substituent would be expected to decrease the rate of acid-catalysed esterification and of S_N1 substitution, but to favour S_N2 substitution at the vicinal carbon atom. Thus bromination of diol acetates might be predominantly S_N2 where it is S_N1 in corresponding alcohol acetates.

ii) The acetylation of diols as measured in table II - by the rate of disappearance of starting material, is, as will be shown below, in most cases equal to the conversion of -OH to OAc. This will be more rapid than the acetylation of alcohols due to a statistical factor (= 2 for symmetrical diols):

for alcohol with 1 -OH group: rate $= k'_{Ac}[\text{alcohol}]$.

for diol with 2 -OH groups, rate of conversion of -OH to -OAc

$$= k'_{Ac}[\text{diol}] + k'_{Ac}[\text{diol}].$$

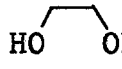
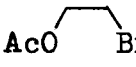
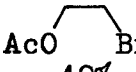
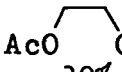
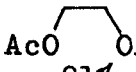
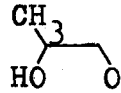
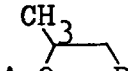
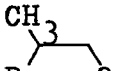
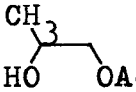
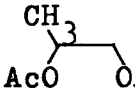
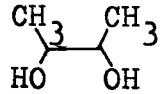
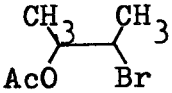
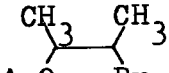
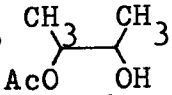
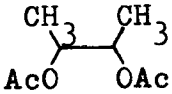
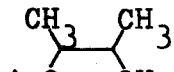
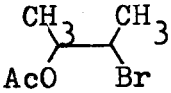
in tables I and II, $[\text{alcohol}] = [\text{diol}]$.

In the case of trans-cyclohexane-1,2-diol, the rate of disappearance of starting material is not equal to the rate of conversion of -OH to -OAc, as this compound is converted via the

table I. Reaction of alcohols with HBr/acetic acid at 37°.

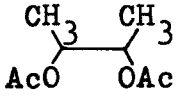
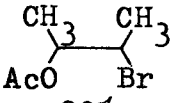
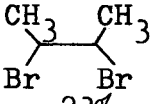
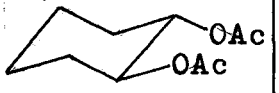
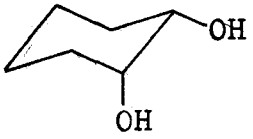
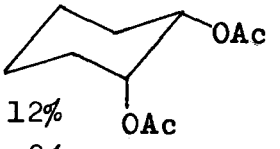
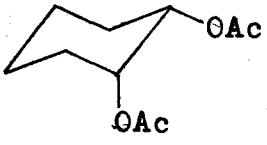
alcohol	mole equiv HBr	$k'_{Ac} \times 10^4$ sec^{-1}	$t_{\frac{1}{2}Ac}$ min	$t_{\frac{1}{2}Br}$ hr
butan-1-ol	1.5	39.8	2.9	36
	3.0	47.6	2.4	14.5
butan-2-ol	1.5	3.36	36.3	9
	3.0	3.98	29.0	3.4
cyclohexanol	3.0	2.99	38.6	3.9

table II. Reaction of some diols with HBr/acetic acid at 37°

diol	mole equ HBr	$t_{\frac{1}{2}Ac}$	$t_{\frac{1}{2}Br}$	time	products
	3			16 min	
	1			13 hr	 49%  30%  21%
	3			8 min	 94 :  6
	2			30 min	"
	1			30 min	acetoxy bromide 53%  26%  21%
	3	6.6 min	16.25 min	90 min	
	2			90 min	 90%  10%  trace
	1			90 min	40% 44% 16%
	3			16 min	

continued...

table II (continued)

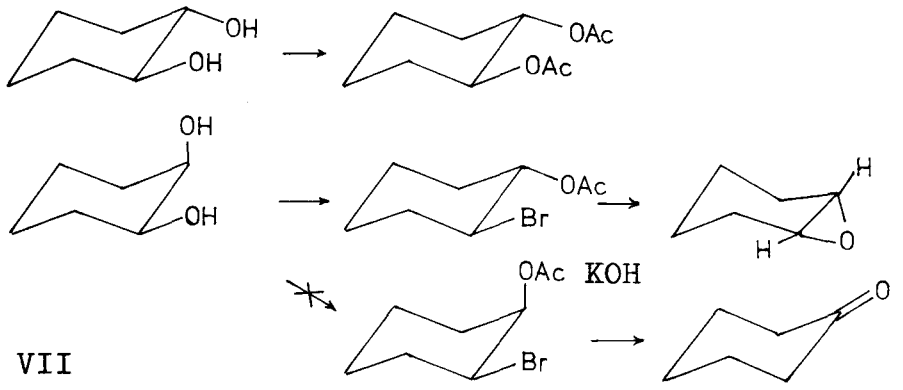
diol	mole eq HBr	$t_{\frac{1}{2}}$Ac	$t_{\frac{1}{2}}$Br	time	products
	3		5 hr	14 hr	 90%
	3+ $\frac{1}{2}H_2O$		4 hr	12.5 hr	90%
	3			8 day	 77% 23%
	3	5.21 min		6 day	 
	3			7 day	
	3				
	3	6.75 min	11.5 min	90 min	 88%  12%
	3.5			90 min	92% 8%
	4			90 min	100%
	3		6.1 hr	20 hr	
	3+ $\frac{1}{2}H_2O$		5.5 hr	20 hr	

monoacetate to the diacetate. Assuming that the rate of the second acetylation is equal to or less than the rate of the first, then initially the rate of disappearance of starting diol will be approximately equal to the rate of conversion of -OH to -OAc.

iii) For derivatives of cyclohexane, steric factors must be considered. In the trans-1,2-diol both hydroxyl groups will be equatorial, while in the cis-1,2-diol and cyclohexanol each hydroxyl group will be alternating to a greater or lesser extent between axial and equatorial orientation.

Nevertheless, it is clear that acyclic vicinal diols and cis-cyclohexane-1,2-diol react very much more rapidly with HBr/acetic acid than would be expected. In most cases disappearance of starting material is faster than for corresponding alcohols, but the remarkable feature is the rate of bromination. The products are the vicinal acetoxybromides, and subsequent conversion to the dibromide is negligibly slow. An α-bromo substituent retards the second displacement, and the reaction mixture at that stage contains a mole of water and only 2 mole equivalents of HBr (equation 1).

After 2 hours at 37° with 3 mole equivalents of HBr/acetic acid, trans-cyclohexane-1,2-diol gave 88% of trans-1,2-diacetoxy-cyclohexane and 12% of trans-2-acetoxycyclohexanol, with no acetoxy-bromide or dibromocyclohexane even after a further 6 days. cis-Cyclohexane-1,2-diol under the same conditions rapidly gave 2-acetoxy cyclohexylbromide, and the exclusive trans-configuration of this was shown by its reaction with methanolic potassium hydroxide. Analysis by g.l.c of the crude reaction product showed only 1,2-epoxy cyclohexane. There was no cyclohexanone - the expected product from the action of alkali on the cis-acetoxybromide[180] - and no starting material (scheme VII). The latter is an important point as the conversion of the cis-acetoxybromide to cyclohexanone is relatively sluggish, and the absence of cyclohexanone is not by itself sufficient proof of the absence of the cis-acetoxybromide. Use of potassium in methanol to ensure complete reaction degraded the 1,2-epoxycyclohexane to trans-2-methoxycyclohexanol, identified by comparison (i.r and g.l.c) with authentic material derived by reaction of the epoxide with methanolic sulphuric acid.[181]



scheme VII

Aqueous work up and analysis by g.l.c of aliquots from the reactions of butane-2,3-diol* and cis-cyclohexane-1,2-diol with 3 mole equivalents of HBr/acetic acid showed the corresponding monoacetates to be apparent intermediates in the conversion of diol to acetoxybromide (diagrams 1 and 2). The diacetates only appeared in small amounts (≤10%) relatively late in the reaction. 2-Acetoxybutan-3-ol was converted to 2-acetoxy-3-bromobutane even more rapidly than was butane-2,3-diol under the same conditions ($t_{\frac{1}{2}Br}$ for diol 16 minutes, reaction of monoacetate complete within 16 minutes), and both reacted faster than 2,3-diacetoxybutane ($t_{\frac{1}{2}Br}$ c. 12 hours).

However, no signals from the diol monoacetates were observed in the n.m.r spectra of the actual reaction mixtures. Instead, low field signals at c. τ4-5 were observed to appear rapidly and disappear as formation of acetoxybromide was complete. Reaction of ethane-, propane-, and 1-phenylethane-1,2-diols with HBr/acetic acid was too rapid for analogous signals to be observed, and no such signals were seen during the reaction of trans-cyclohexane-1,2-diol, which does not give an acetoxybromide.

From the above evidence, it is proposed that the conversion of vicinal diols to vicinal acetoxybromides by HBr/acetic acid proceeds via 2-methyl-1,3-dioxolan-2-ylium ions (XI) formed by front-side participation of a neighbouring acetoxy group, and giving rise to the transient low field n.m.r signals from the

* the butane-2,3-diol used throughout this work was a commercial mixture of diastereomers.

Aqueous work-up and analysis by g.l.c of aliquots from the reactions at 37° of 3 mole equivalents of HBr/acetic acid with:

fig.1. Butane-2,3-diol.

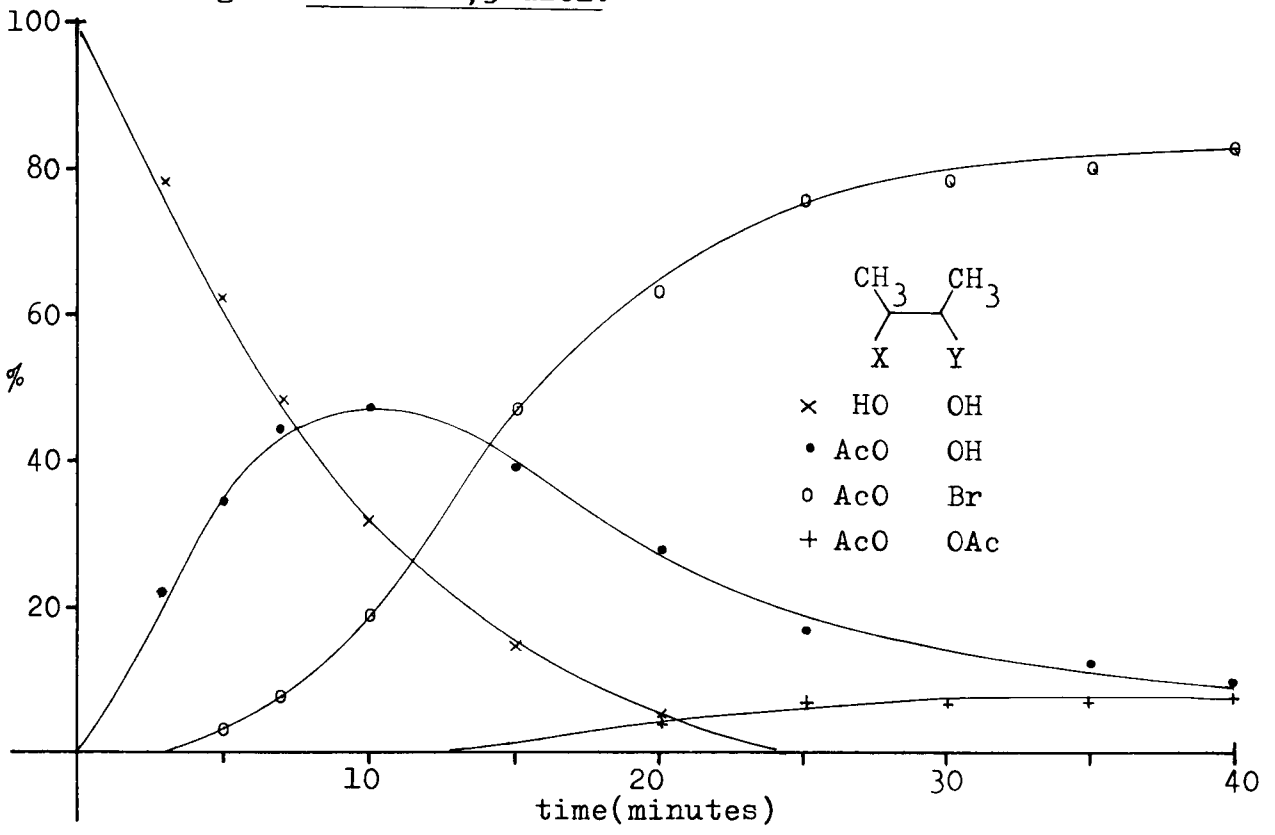
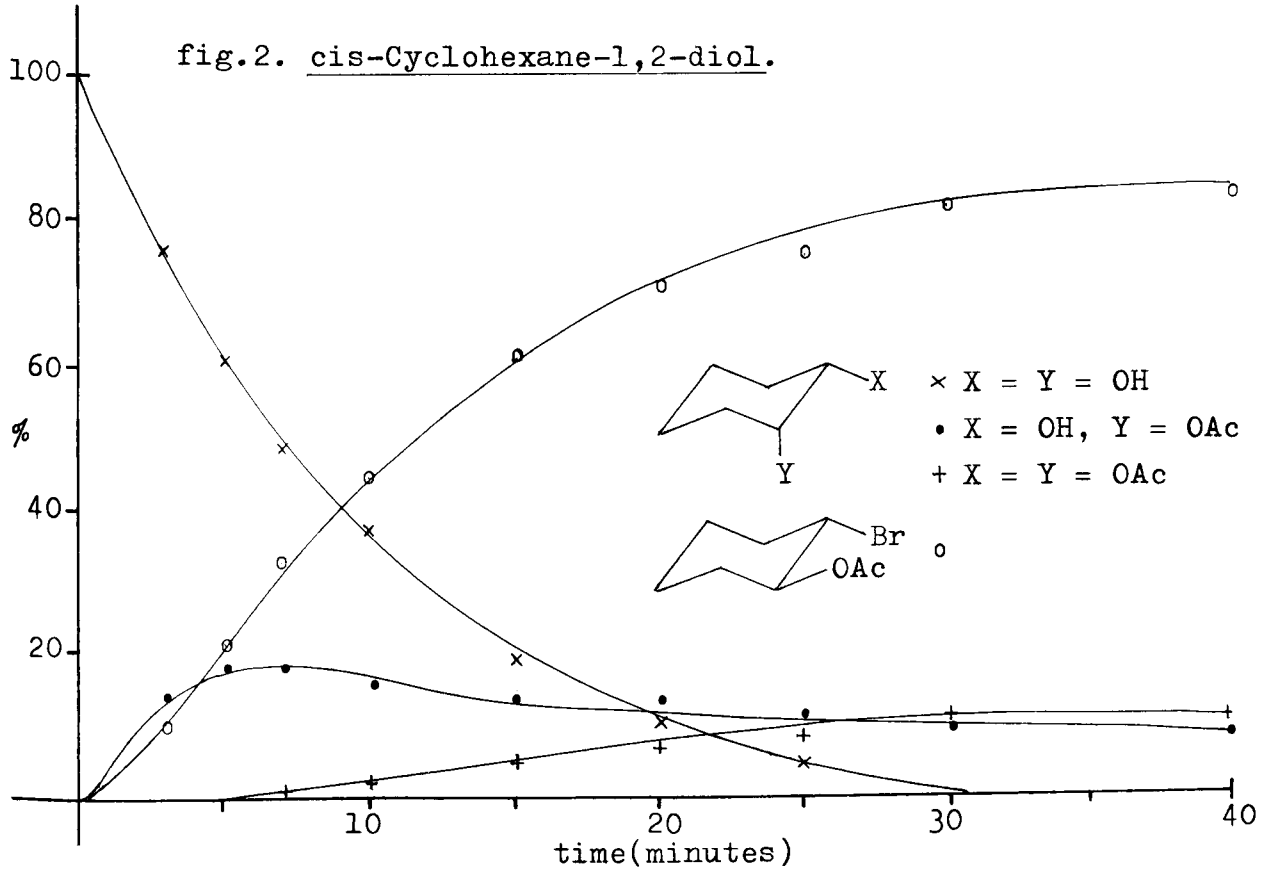
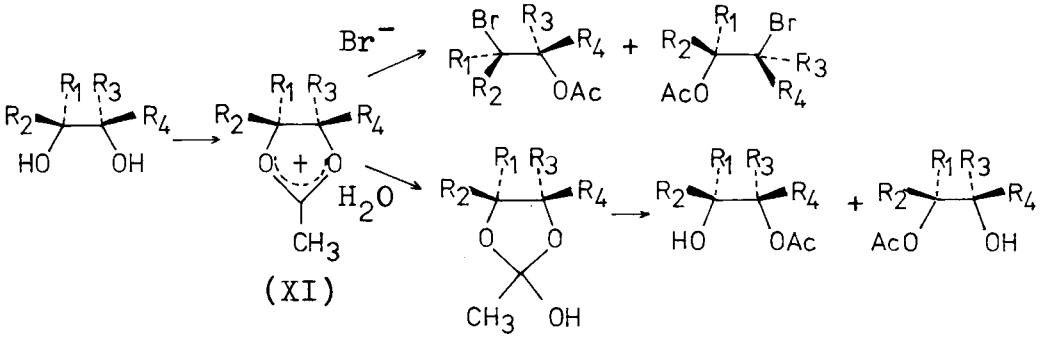


fig.2. cis-Cyclohexane-1,2-diol.



reaction mixtures, The dioxolanylium ions are captured by bromide ion at C4(5) with inversion to give the vicinal acetoxy-bromide, or during aqueous work-up they react with water to give monoacetates with the same configuration as the starting diols (scheme VIII). These are known reactions of isolated dioxolanylium ions.



scheme VIII

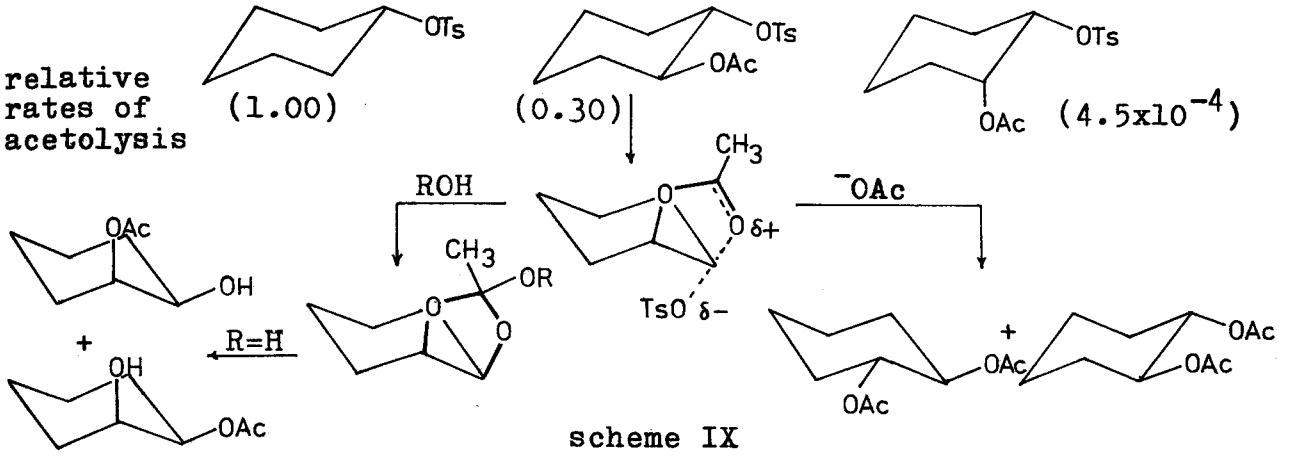
1,3-Dioxolan-2-ylium ions.[147]

Winstein originally formulated 'acetoxonium' ions as intermediates in reactions at centres with neighbouring acetoxy groups. The latter could participate in (a) a trans-sense, as in the solvolysis of vicinal acetoxytosylates, or (b) a cis-sense, which was necessary to explain the stereochemistry of the conversion of vicinal diacetates to dibromides with fuming hydrobromic acid.

(a) The acetolysis of trans-2-acetoxycyclohexyl-p-toluene-sulphonate proceeds with retention of configuration,[182] and 670 times faster than that of the cis-isomer (the latter solvolyses very much slower than the parent cyclohexyl p-toluenesulphonate because of the inductive effect of the adjacent acetoxy group, but this is almost completely countered by the anchimeric effect in the trans-isomer).[183] The solvolysis of the trans-isomer is still first order, agreeing with a rate determining step in which neighbouring group participation lowers the energy of the transition state for substitution (scheme IX).

The symmetry of the transition state was further shown by the observation that optically active trans-2-acetoxycyclohexyl p-toluenesulphonate gave racemic trans-1,2-diacetoxycyclohexane. Solvolysis in wet acetic acid gave mostly cis-2-acetoxycyclohexanol (i.e inversion). Attack by water at the 2-position of

the dioxolanylium ion intermediate gave a cyclic ortho-ester that isomerised to the more stable diol monoacetate. If ethanol was added to the solvolysis reaction, the ortho-ester formed could be isolated[184].

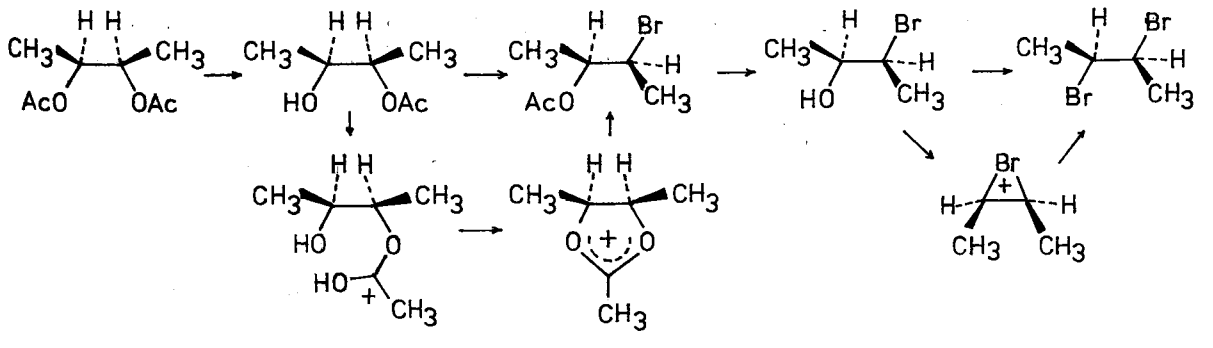


scheme IX

Similar retention of configuration was found in the solvolyses of threo- and erythro-2-acetoxy-3-bromobutanes[185].

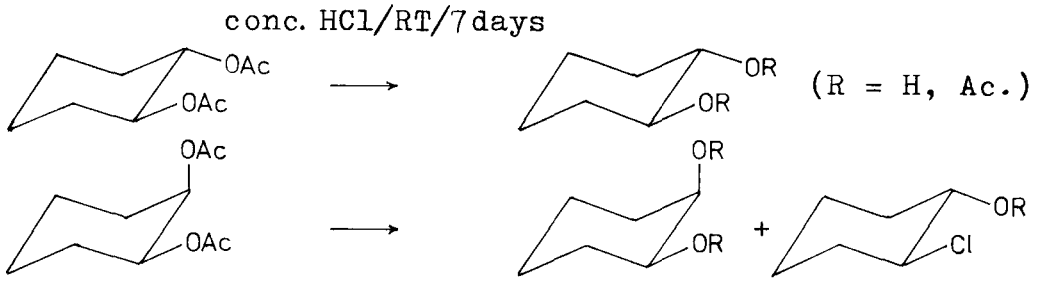
(b)By contrast, heating d,l- or meso-2,3-diacetoxybutane in fuming aqueous hydrobromic acid - strongly acidic conditions- gave stereospecifically meso- or d,l-2,3-dibromobutane respectively. Winstein traced the reaction pathway by synthesising possible intermediates and subjecting them to the reaction conditions[186].

Stepwise hydrolysis and substitution occurred. 2-Hydroxy-3-bromobutane gave the 2,3-dibromide of same configuration, and the overall inversion was due to the 2-acetoxy-3-hydroxybutane→2-acetoxy-3-bromobutane step. Winstein proposed that the former conversion involved a bromonium ion intermediate (trans-neighbouring group effect), and the latter a 'cis'-dioxolanylium ion formed from the protonated 2-acetoxy-3-hydroxybutane (scheme X).



scheme X

The 'cis'-nature of this participation was further shown by heating the isomeric 1,2-diacetoxycyclohexanes with concentrated HCl. The trans-isomer gave only hydrolysis products, while cis-1,2-diacetoxycyclohexane gave in addition trans-2-chlorocyclohexanol and its acetate[187] (scheme XI).



scheme XI

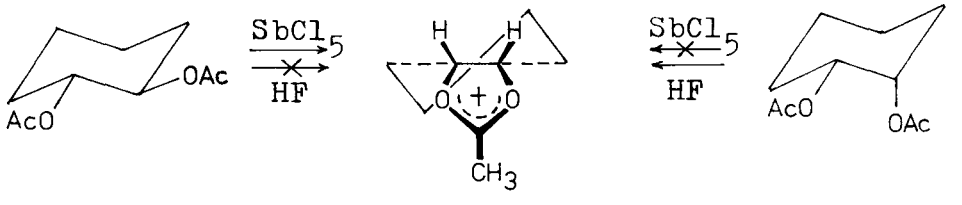
Dioxolanylium ions have been prepared and isolated as salts of non-nucleophilic anions, and Winstein's mechanistic conclusion verified by a study of their properties.

There are three routes for their formation - from cyclic acetal precursors[188], and, by analogy with the above reactions, from acyclic precursors by (a) trans-and (b) cis-cyclisations.

(a) Vicinal acyloxy- halides, acetates and ethers are cyclised by strong Lewis acids that form non-nucleophilic anions, in media of low nucleophilicity[189].

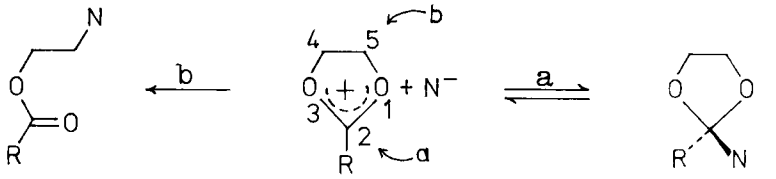
(b) Vicinal diesters can be cyclised in a strong protic acid, non-nucleophilic medium, e.g hydrogen fluoride, and the dioxolanylium ions isolated as their fluoroborates by addition of fluoroboric acid[190]. Diol monoesters have been cyclised in concentrated sulphuric or fluorosulphonic acids[191], and diols in acetic anhydride/perchloric acid/ethyl acetate.[192]

Thus trans-1,2-diacetoxycyclohexane is converted to the cis-4,5-tetramethylene-2-methyl-1,3-dioxolan-2-ylium ion by antimony pentachloride, but the cis-isomer does not react[189]. The same cation is obtained on dissolving cis-1,2-diacetoxycyclohexane in liquid hydrogen fluoride, while the trans-isomer does not react[190](scheme XII).



scheme XII

Dioxolanylium ions are highly reactive ambident electrophiles[193]. Strong nucleophiles (OH^-, OR^-, CN^-) react at C2 - the position of lowest electron density - to give the product of kinetic control. With weaker nucleophiles (Br^-, OAc^-, Cl^-) attack at C2 does not cause such a decrease in energy, and equilibrium is set up between the kinetic product and the cation. Under these equilibrium conditions the more stable thermodynamic product formed by attack at C4(5) and extensive bond reorganisation can form. (Alternatively C2 may be thought of as a hard acid site, C4(5) as a soft acid) (scheme XIII).



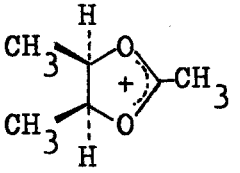
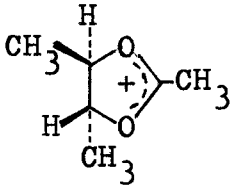
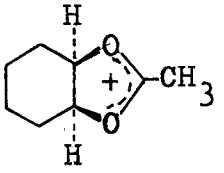
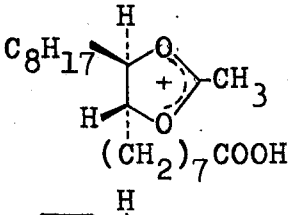
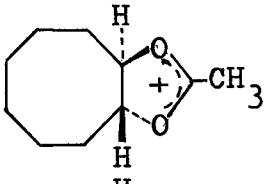
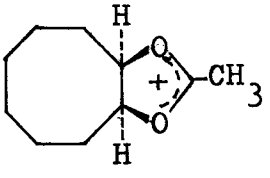
scheme XIII

Winstein isolated the cis-4,5-tetramethylene-2-methyl-1,3-dioxolanylium ion he had implicated in his earlier studies, and showed that it did react with water to give cis-2-acetoxycyclohexanol derived from the kinetic product, and with potassium acetate to give trans-1,2-diacetoxycyclohexane, the thermodynamic product, by exclusive 'backside attack' at C4(5)[194].

The n.m.r spectra of a number of dioxolanylium ions have been reported[147], and the position of the resonances of the methine protons of the fluoroborate of the cis-4,5-tetramethylene-2-methyl-1,3-dioxolanylium ion in glacial acetic acid agrees well with that o the transient signal observed during the reaction of cis-cyclohexane 1,2-diol with HBr/acetic acid. The 3H singlet (τ7.10) for the C2-methyl group of the dioxolanylium ion can also be seen if care is taken that it is not submerged under side bands from the acetic acid solvent signal.

n.m.r Spectra of other dioxolanylium ions observed during this work (table III) have not been reported, but are comparable to similar examples. The butane-2,3-diol used was a mixture of diastereomers - probably predominantly threo because the derived mixture of diacetates was partially crystalline at room temperature (m.p of diacetates: threo 41.0-41.5°, erythro 2.5-3.0° [186]). Transient signals during the reaction of this diol with HBr/acetic acid

tableIII.N.m.r data for 2-methyl-1,3-dioxolanylium ions compared with that for corresponding diols and acetoxybromides in HBr/acetic acid (τ values);

	dioxolanylium ion		diol	acetoxy-bromide	
	CHO	CH_3	CHOH	CHOAc	CHBr
a 	3.98	7.10	5.72	5.02	5.65
a 	4.45	7.10	"	"	"
	4.08	7.10	5.85	5.30	6.07
lit.[194] BF_4^-	4.23	7.23			
	4.45	7.15	5.90	4.90	5.75
	4.22	7.10	5.72		
	4.10	7.10	5.66	4.85	5.61

a assignments deduced from mixture of diastereomers (see text).

appeared at τ3.98 and τ4.45 in ratio 36:64. The stronger higher field resonance corresponds with that observed during the reaction of threo-9,10-dihydroxyoctadecanoic acid (τ4.45), and that to lower field with that due to the cis(i.e erythro)-4,5-tetramethylene 2-methyl-1,3-dioxolanylium ion (τ4.08).

Further studies of the reactions of diols with HBr/acetic acid.

The reactions of HBr/acetic acid with a range of diols and their derivatives have been investigated, and the further results are listed in table IV. In table V are compared the positions of the n.m.r signals in 3 mole equivalents of HBr/acetic acid for protons adjacent to -OH, -OAc and -Br in some of the compounds cited in this work. The resonances due to CH-OAc and CH-Br protons are in similar positions to those in more conventional n.m.r solvents, but the CH-OH proton resonances are often to lower field due to protonation in HBr/acetic acid.

The reactions are discussed according to their illustration of features of the general reaction described so far.

i) Kinetics of formation of the dioxolanylium ions.

When following the reactions of HBr/acetic acid with diols that form dioxolanylium ions by n.m.r spectroscopy of the reaction performed in the n.m.r sample tube, the diol monoacetate is never observed. This is especially well seen in the slower reactions - e.g that of threo-9,10-dihydroxyoctadecanoic acid - where the build up of the signal from the methine protons of the dioxolanylium ion matches the decrease in the signal from the methine protons (CH-OH) of the starting diol, and only later do signals due to CH-OAc protons appear, parallelled exactly by the appearance of signals due to CH-Br protons as the dioxolanylium ion is converted to acetoxybromide. The positions of the resonances due to CH-OH and CH-Br protons are generally similar in HBr/acetic acid (table V), and in the faster reactions where the steps of the reaction occur simultaneously, it may be difficult to ascertain whether the increase in CH-OAc signals is exactly matched by the increase in CH-Br, i.e that there is no -CH(OAc)-CH(OH)- species present. However, when 2-acetoxy-3-hydroxy-butane is dissolved in 3 mole equivalents of HBr/acetic acid, the

table IV. Further reactions with HBr/acetic acid at 37°.

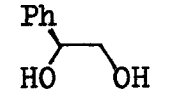
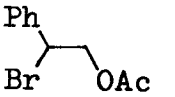
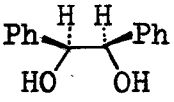
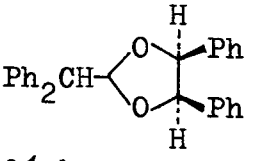
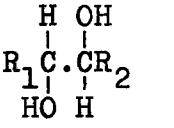
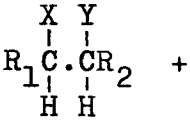
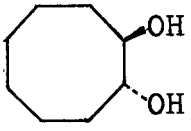
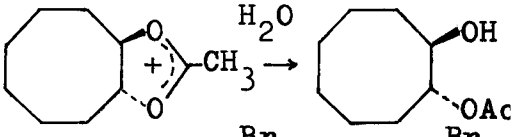
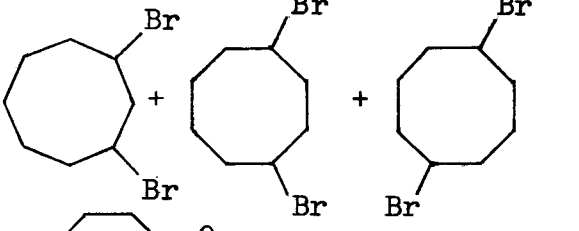
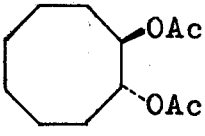
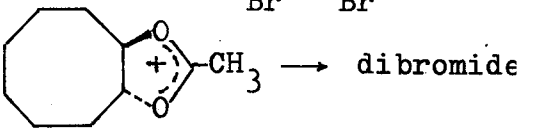
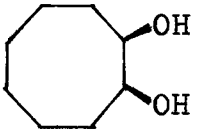
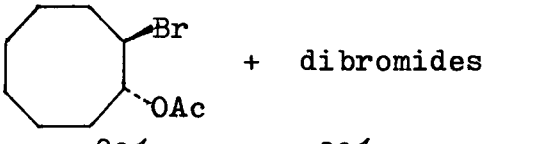
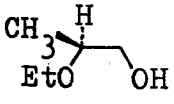
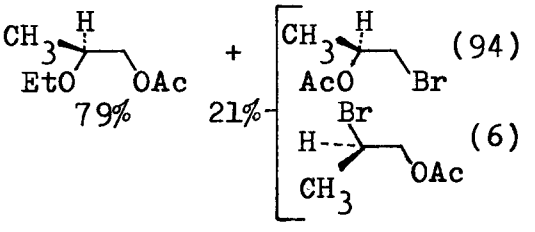
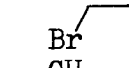
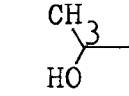
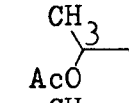
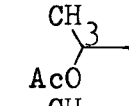
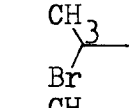
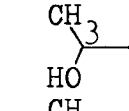
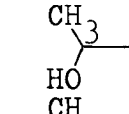
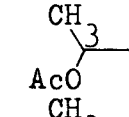
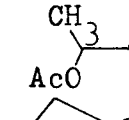
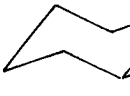
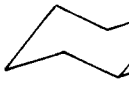
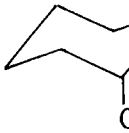
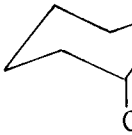
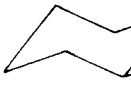
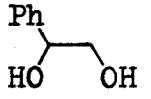
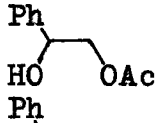
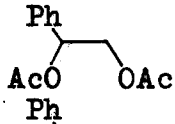
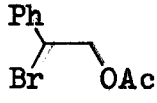
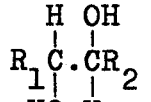
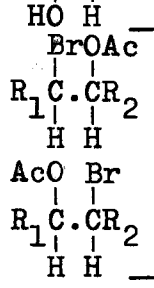
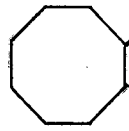
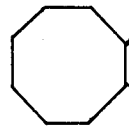
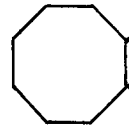
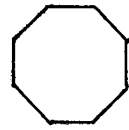
substrate	mole equ. HBr	$t_{\frac{1}{2}}Ac$	$t_{\frac{1}{2}}Br$	time	products
	3			15 min	 62% at 3min, 79% at 7min, 85% at 10min.
	3			2 min	solidifies,  30% by n.m.r
	3	30 min	43 min	110 min	 X = Br, Y = OAc + X = OAc, Y = Br
	3	9.1 min		45 min	
	3			6hr 60°	
					 dibromide
	3	9.1 min	17 hr	140 hr	 + dibromides 80% 20%
n-BuOMe	3	28 min		150 min	93.5% (BuOAc + MeBr) + 6.5% (BuBr + MeOAc)
	1.5			8 day	 (94) (6)

table V. N.m.r spectra (τ values) in HBr/acetic acid and other solvents

compound	3 mole equiv. HBr/acetic acid			CCl_4(b), $CDCl_3$(c), or neat(d).			
	CHOH	CHOAc	CHBr	CHOH	CHOAc	CHBr	other signals, et
1-butyl	5.92	5.85	6.51				
2-butyl	5.53	5.08	5.80				
cyclohexyl	5.61	5.19	5.65				
		5.49[a]	6.32[a]		[b]5.59[a]	6.46[a]	J = 6.0
	6.14[a] 5.73						
					[d]5.84[a] 4.87		
		4.95	6.47[a]		[b]4.98	6.57[a]	CH_3 8.66 d,J=5.0
		5.73[a]	5.73		[b]c5.8[a]	c5.8	CH_3 8.30 d,J=6.0
	5.72			[b]6.60 [e]6.44			CH_3 [e]9.02,9.00,d J=5.5; OH 5.7 5.55, d,J=4.0
				[b]6.25	5.18		CH_3 8.88, 8.83 d,J=6.5
		5.00					
		5.02	5.65		[b]5.10	5.81	CH_3COAc 8.71 CH_3CBr 8.36
	6.00			[c]6.00			
		5.20			[b]5.30		
	5.85			[c]6.20			
		5.91					
		5.30	6.07		[b]5.18	6.07	

continued...

table V. (continued)

compound	3 mole equiv. HBr/acetic acid			CCl_4(b), $CDCl_3$(c), neat(d)			
	CHOH	CHOAc	CHBr	CHOH	CHOAc	CHBr	other signals, e
	5.85[a] 4.78						
				[b]5.24	5.97 5.95		J = 4.7, 6.0
					[b]5.83 5.81 4.10		J = 4.7,6.0
		5.35	4.75		[b]5.57	4.98	J = 6.7, 7.0
	5.90						
		4.90	5.75		[c]5.12	6.00	
	5.72						
		4.88					
	5.66						
		4.85	5.61		[b]4.88	5.78	

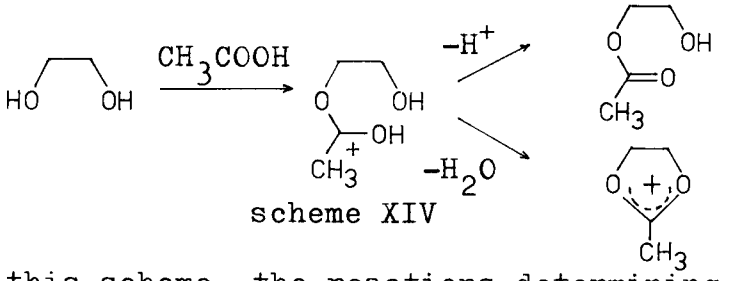
[a] methylene CH_2 ; [e] minor signal

$R_1 = CH_3(CH_2)_7-$; $R_2 = -(CH_2)_7COOH$.

only signals seen in the n.m.r spectrum are those from the dioxolanylium ions (mixture of diastereomers) and the acetoxybromides. This contrasts with the results obtained using hydrogen fluoride, where Pederson[195] claims that the conversion of diol monoacetates to dioxolanylium ions is observably slow.

The vicinal diacetates are converted to acetoxybromides in HBr/acetic acid, but much more slowly than the corresponding diols (table II), and are presumably not intermediates in the reaction of the latter.

The rate determining step in the conversion of diols to dioxolanylium ions in HBr/acetic acid is thus probably formation of the protonated monoacetate followed by rapid cyclisation, or, where this is impossible - e.g with trans-cyclohexane-1,2-diol and the alcohols - by deprotonation to give the monoacetate (scheme XIV).

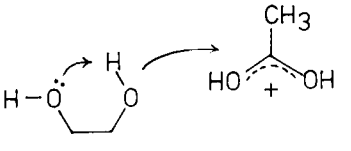


scheme XIV

In this scheme, the reactions determining the rates of disappearance of alcohols and diols are identical, but even allowing for a statistical factor, the rates of disappearance of diols are typically over twice those for the corresponding alcohols (tables I and II). Moreover, the rate of disappearance of trans-cyclohexane-1,2-diol - which does not form a dioxolanylium ion - is marginally faster than that of the cis-isomer which does form a dioxolanylium ion.

It is suggested that intramolecular general base catalysis is responsible for the rate enhancement of acetylation of vicinal diols (scheme XV). This would not be subject to the steric constraints attending dioxolanylium ion formation (see below) and could occur equally well in trans- and in cis-cyclohexane-1,2-diol. The faster acetylation of the former may be due to both hydroxyl groups having equatorial orientation compared with one equatorial and one axial in the cis-isomer.

scheme XV



This rate enhancement requires further study. The effect depicted in scheme XV should also occur in vicinal methoxy-alcohols, but attempts to verify this were thwarted by the discovery that HBr/acetic acid is an excellent reagent for ether cleavage at room temperature (c.f ref. 196). The reactions observed were those of the parent diols, accompanied by liberation of methyl bromide. Previous attempts to correlate acetylation rates with hydrogen bonding, as measured by the i.r spectrum, have been inconclusive[197]. Circumstances in dilute carbon tetrachloride solution probably bear little relation to those in an acetylation medium, e,g HBr/acetic acid.

It should also be pointed out that on mixing liquid alcohols and diols with HBr/acetic acid there is a slight exotherm, and this might cast doubt on any kinetic results subsequently obtained. However, the results in this work were derived graphically, and the graphs showed no irregularities at the origin in these cases (fig.1). The cyclohexane-1,2-diols are both crystalline, and a graphical correction of c. 1 minute had to be applied to allow for mixing not being instantaneous. In these cases no exotherm was detectable.

Acetylation is subject to steric hindrance in both alcohols and diols - e.g reaction of propane-1,2-diol probably proceeds via the protonated 1-acetoxy-2-propanol rather than its isomer. Conversion of the cyclooctane-1,2-diols and of threo-9,10-dihydroxy-octadecanoic acid is much slower than cyclohexane-1,2-diols and butane-2,3-diol e.g presumably because of the longer more flexible substituents on the hydroxylic carbon atoms in the former diols.

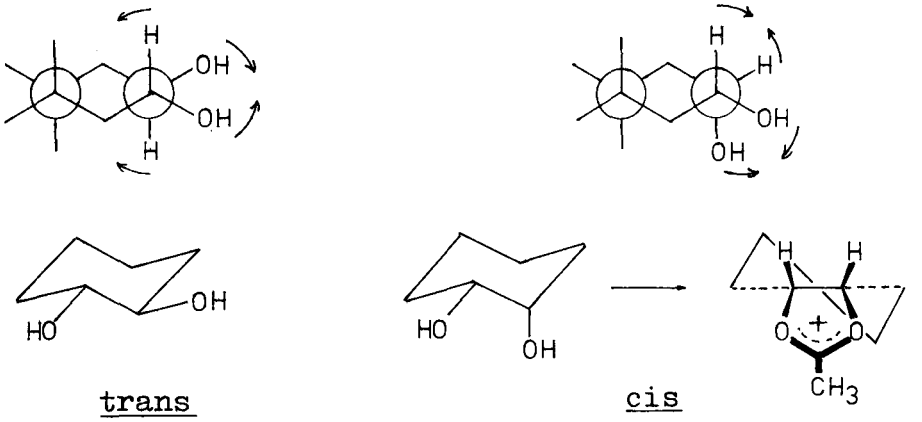
ii) Stereochemistry of formation of the dioxolanylium ions.

All the acyclic vicinal diols studied so far have given vicinal acetoxybromides more rapidly than would be expected for simple substitution, and, even where they have not actually been detected, it is assumed that dioxolanylium ions are intermediates in the reactions. From the stereochemical outcome of the reaction of (S)-(+)-propane-1,2-diol with HBr/acetic acid, assuming attack by bromide ion on the intermediate occurs with inversion, it can be deduced that the dioxolanylium ion is formed specifically by 'front-side' participation (schemes VI and VIII).

Of the two cyclohexane-1,2-diols, only the cis-isomer

forms an acetoxybromide, and this is exclusively the trans-isomer (scheme VII). Formation of a dioxolanylium ion by 'back-side' participation is apparently not merely less favourable, but is impossible in HBr/acetic acid, because the trans-1,2-diacetoxycyclohexane is quite inert for 7 days at 37° in the presence of 3 mole equivalents of HBr/acetic acid.

In both the cyclohexane-1,2-diol molecules the distance between the hydroxyl oxygens is the same. The charged, 5-membered dioxolanylium ring tends to be planar, and eclipsing of the hydroxyl oxygens of trans-cyclohexane-1,2-diol leads to unacceptable buckling of the cyclohexane ring and inward movement of the methine hydrogen atoms, whereas this same process in the cis-isomer only causes flattening of the cyclohexane ring towards the half-chair conformation (scheme XVI). These results parallel the greater ease of ketal formation by cis-cyclohexane-1,2-diol compared with the trans-isomer[198].



trans cis

scheme XVI

However, it is probable that the 5-membered ring is more strained in the dioxolanylium ion derived from cis-cyclohexane-1,2-diol than in that derived from an acyclic diol. Fig. 1 shows that in the reaction of butane-2,3-diol with 3 mole equivalents of HBr/acetic acid at 37°, the proportion of the dioxolanylium ion, as measured by the proportion of the monoacetate formed on aqueous work-up, rises to a maximum of 48% after about 9 minutes, and that $t_{\frac{1}{2}Br}$ is 16.25 minutes. In the reaction of cis-cyclohexane-1,2-diol (fig. 2), the proportion of dioxolanylium ion only reaches a maximum of 19% (after 7.0 minutes) and the ion is much more susceptible

to attack by bromide ion ($t_{\frac{1}{2}Br}$ 11.5 minutes).

The cyclooctane ring is much more flexible than the cyclohexane, and both the cis- and the trans-cyclooctane-1,2-diols form dioxolanylium ions - distinguishable in the n.m.r spectra - and at remarkably similar rates ($t_{\frac{1}{2}}$ 8.9 minutes, complete within 40 minutes

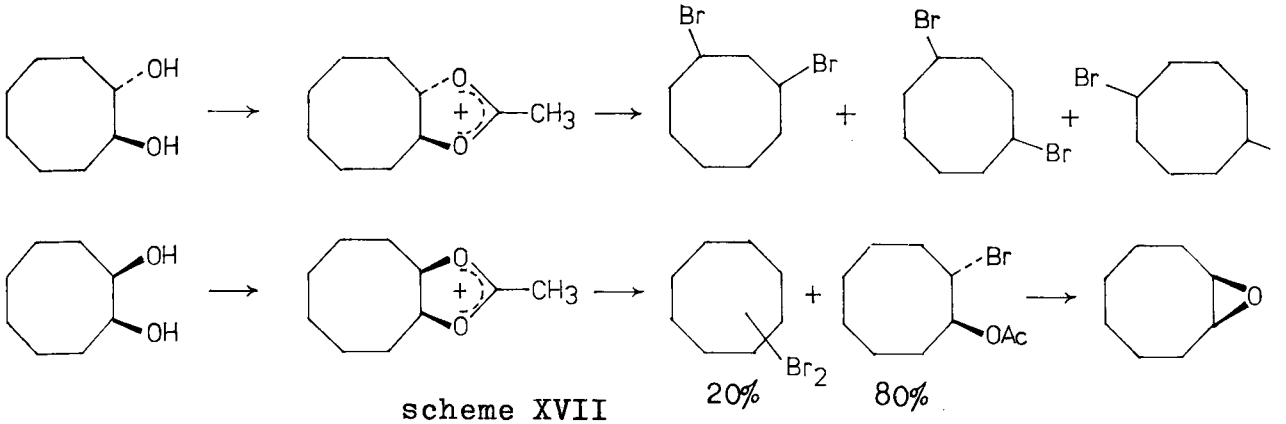
The results of the reactions of the cis- and trans-cycloheptane-1,2-diols with HBr/acetic acid are awaited with interest.

iii) Stereochemistry of acetoxybromide formation.

Capture of the dioxolanylium ion intermediates by bromide ion has been shown to be stereospecific (with inversion) and regioselective (at the least hindered of the two possible carbon atoms) in the propane-1,2-diol and cis-cyclohexane-1,2-diol series. It is expected that these results will apply to all primary and secondary vicinal diols with alkyl substituents. meso-Butane-2,3-diol (99.8% sterically pure) is now on hand (we thank Bayer A.G for this generous gift) and it is hoped to convert this via the threo-acetoxybromide to cis-2,3-epoxybutane, and to check the stereochemical purity with chiral n.m.r shift reagents[199].

Both cis- and trans-cyclooctane-1,2-diol are converted to dioxolanylium ions by HBr/acetic acid, but models of these show 'backside' attack is hindered by the hexamethylene substituent in both these, especially in the trans-case. Conversely, these ions are susceptible to transannular hydrogen shifts, and that derived from the trans-diol is slowly converted (75% in 8 days at 37°, complete within 6 hours at 70°) to a mixture of the 1,3-, 1,4- and 1,5-dibromocyclooctanes (ratio 1:2:1, stereochemistry not determined There is no 1,2-substituted product (scheme XVII). This parallels the solvolysis in formic acid of trans-1,2-epoxycyclooctane which gives mainly trans-cyclooctane-1,4-diol, with some of the trans-1,3-diol and products of skeletal rearrangement[200].

The cis-4,5-hexamethylene-2-methyl-1,3-dioxolanylium ion is converted more rapidly ($t_{\frac{1}{2}}$ 17 hours, complete after 140 hours at 37°) to 80% of trans-1-acetoxy-2-bromocyclooctane and 20% of a mixture of dibromides - mainly the 1,4- but including some of the 1,2-isomer. The trans-configuration of the acetoxybromide was proved by near quantitative conversion to cis-1,2-epoxycyclooctane (comparison with an authentic sample) by methanolic KOH (scheme XVII).



scheme XVII

These results emphasise the absolute stereospecificity of the final step in the sequence of reactions of these diols with HBr/acetic acid. When 'backside' attack is blocked, no leakage *via* 'front-side' attack occurs, as shown by the absence of 1,2-substituted products from *trans*-cyclooctane-1,2-diol.

Treatment of 1-phenylethane-1,2-diol with 3 mole equivalents of HBr/acetic acid gives complete conversion within 20 minutes to 1-phenyl-1-bromo-2-acetoxyethane - i.e bromide ion attacks regiospecifically at the benzylic carbon atom. However, reaction of the acetoxybromide from optically pure (R)-(-)-1-phenylethane-1,2-diol with base gives (R)-(+)-styrene oxide of only 88% optical purity, checked by conversion to (R)-(+)-1,2-diphenylethanol with phenyl lithium (separated chromatographically from *trans*-stilbene, and its optical rotation measured before recrystallisation).

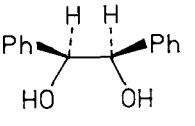
Both S_N1 and S_N2 substitution are favoured at a benzylic carbon atom. Thus it is possible that the reaction of 1-phenylethane-1,2-diol with HBr/acetic acid involves initial acetylation of the primary hydroxyl group and formation of the 4-phenyl-2-methyl-1,3-dioxolanylium ion by front-side participation, in the 'usual' way. Subsequently incipient carbonium ion formation at the benzylic carbon atom leads to attack by bromide ion exclusively at this centre, mostly by 'backside' attack, but with some leakage *via* an S_N1 process, and hence loss of steric integrity.

In the reaction of styrene with acetyl hypobromite, an intermediate bromonium ion is captured by acetate ion exclusively at the benzylic carbon to give 1-phenyl-1-acetoxy-2-bromoethane,[201] the exact inverse of the reaction of 1-phenylethane-1,2-diol with HBr/acetic acid. The same authors report that this product equil-

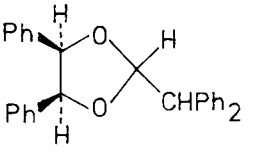
ibrates with the isomeric acetoxybromide on distillation, ratio c. 1:1. Our product was not distilled, but this result contrasts with those obtained with the acetoxybromopropanes where either equilibration does not occur, or the equilibrium is markedly in favour of the 1-bromo-2-acetoxypropane isomer (94:6). If equilibration does occur in the latter compounds then it must be stereospecific, proceeding via dioxolanylium ions formed by 'backside' participation.

It is significant that there are no reported examples of isolated 4(5)-aryl-dioxolanylium ions. There are two reports of 5-phenyloxazolinium ions[202] (oxazolinium ions are generally much more stable than dioxolanylium ions) and one of a 4-vinyl-2-phenyl-dioxolanylium ion[203]. The latter undergoes substitution by acetate ion at both the primary C5 and secondary, allylic, C4 positions - a similar but less marked effect to that observed for the 4-phenyl-2-methyl-1,3-dioxolanylium ion above.

meso-1,2-Diphenylethane-1,2-diol (XI) dissolves in 3 mole equivalents of HBr/acetic acid, but after 2 minutes at 37° the mixture sets solid. The resulting product complex is similar to that obtained by the action of concentrated sulphuric acid or of phosphorus pentoxide on XI, including cis-4,5-diphenyl-2-diphenylmethyl-1,3-dioxolan (XII)[204]. The latter is derived by benzylic acid-type rearrangement of one molecule of diol XI to diphenylacetaldehyde and reaction with a second molecule of unrearranged XI.



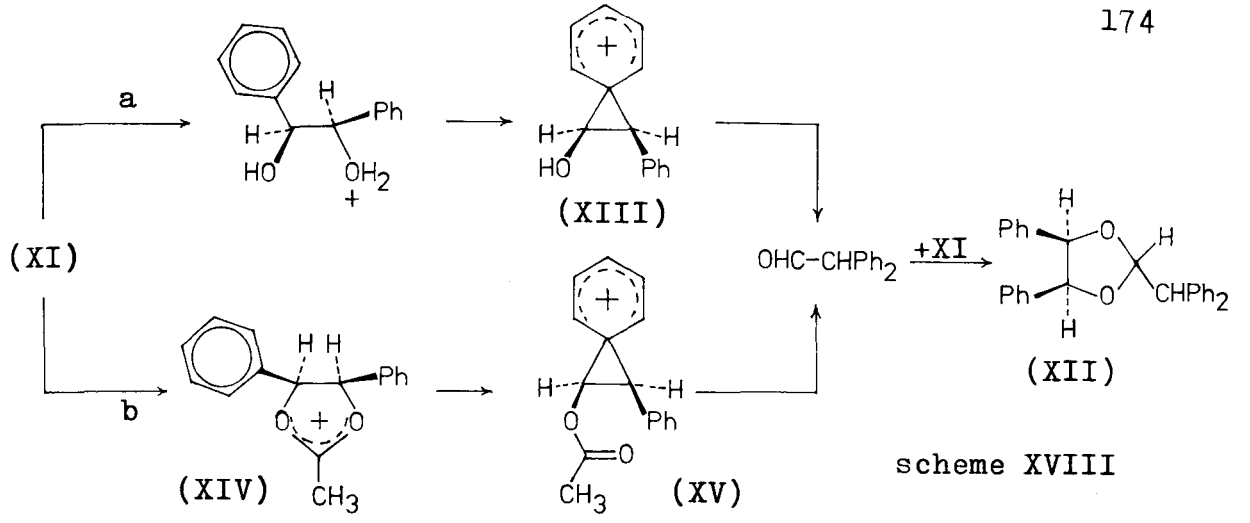
(XI)



(XII)

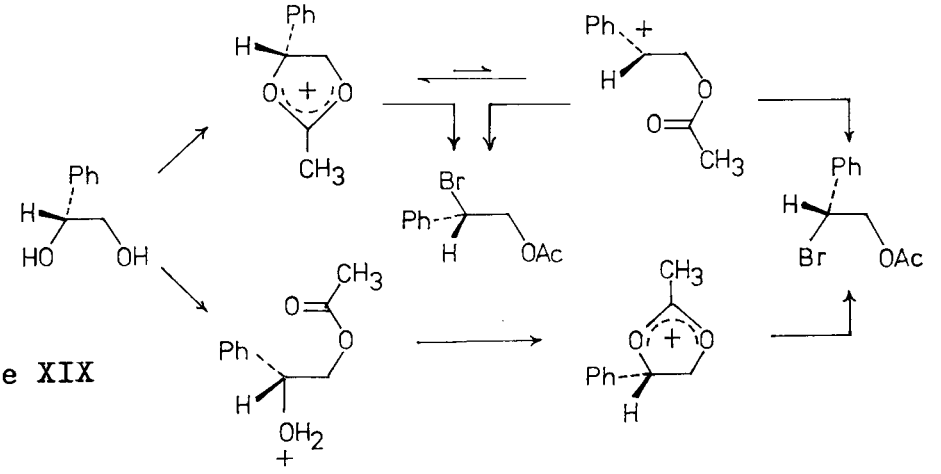
In the reaction of XI in HBr/acetic acid, the rearrangement may be simply an acid catalysed effect via phenonium ion (XIII) (path a), but might well occur after initial formation of the cis-4,5-diphenyl-2-methyl-1,3-dioxolanylium ion (XIV) via phenonium ion (XV) (scheme XVIII).

Path b in scheme XVIII would be a further illustration of the lability of a dioxolanylium ion with one or more aryl substituents at C4(5), offered as an explanation of the partial



scheme XVIII

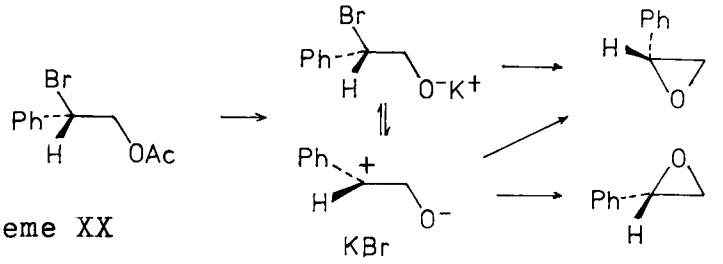
racemisation that occurs during conversion of (R)-(-)-1-phenylethane-1,2-diol to (R)-(+)-styrene oxide via the acetoxybromide. By analogy with path a of scheme XVIII, which is initiated by acid-catalysed formation of a benzylic carbonium ion with anchimeric (trans-) assistance from the vicinal phenyl group, it could be postulated that 1-phenyl-2-acetoxyethanol could be converted to the 4-phenyl-2-methyl-1,3-dioxolanylium ion by backside participation, the acetoxy group assisting in formation of the benzylic carbonium ion following protonation of the hydroxyl group at C1. Stereospecific attack by bromide ion on this would give the acetoxybromide enantiomeric to that derived from the dioxolanylium ion formed by front-side participation in the 'usual' way in HBr/acetic acid. These ideas are summarised in scheme XIX.



scheme XIX

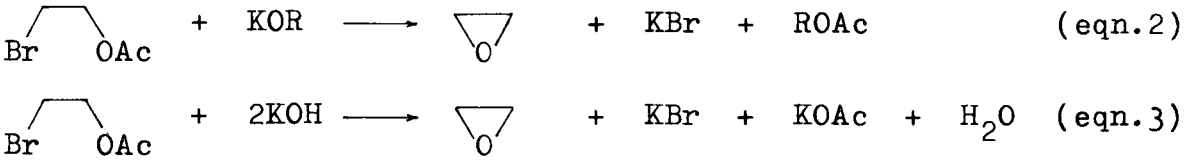
Yet a third possible explanation of the phenomenon under discussion is that the racemisation actually occurs during conversion of the 1-phenyl-1-bromo-2-acetoxyethane to styrene oxide. The negative charge of the intermediate alkoxide would further stabilise

the incipient benzylic carbonium ion, and the ensuing cyclisation might not be so stereospecific (scheme XX).



scheme XX

This latter cyclisation has produced one anomaly that was only discovered after completion of the experiments, and may be related to the above observations. Conversion of an acetoxybromide to an epoxide requires 1 mole equivalent of alkoxide as base (equation 2), but 2 mole equivalents of potassium hydroxide (equation 3).



(eqn.2)

(eqn.3)

Forgetting this basic fact, only one equivalent of KOH/methanol was used to generate styrene oxide, although this step was performed correctly in all the other series. However, two separate experiments with racemic and chiral material gave near quantitative yields of styrene oxide (see Experimental section), and this mystery remains unexplained.

iv) The rôle of diacetates.

Figs. 1 and 2 illustrate the course of the reactions of butane-2,3-diol and cis-cyclohexane-1,2-diol respectively with 3 mole equivalents of HBr/acetic acid at 37°. In both these, small amounts of the corresponding diacetates (≤10%) appear towards the end of the period under investigation (c. 45 minutes). When these same reactions were performed on a preparative scale and left for longer periods, e.g butane-2,3-diol with 3 mole equivalents of HBr/acetic acid at 37° for 90 minutes, the products were the pure acetoxybromides.

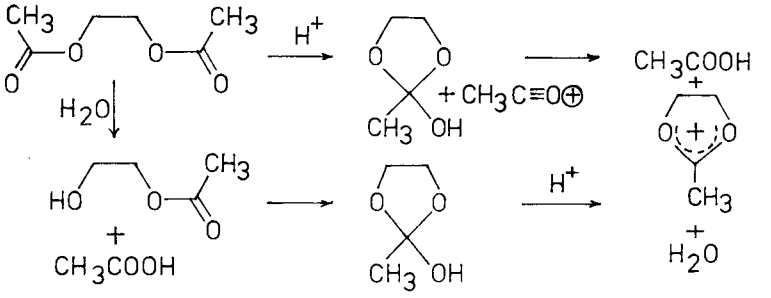
As the reaction of a diol with HBr/acetic acid proceeds,

the concentration of bromide and the acidity of the medium fall, and in the later stages presumably some of the protonated monoacetate does not cyclise to dioxolanylium ion but is converted to the diacetate. This diacetate can apparently be then converted to acetoxybromide, and the question remains whether this provides a potential source of loss of stereospecificity.

Conversion of a secondary acetate to bromide is predominantly S_N1 in character (table I), and this would be retarded by an adjacent (electron-withdrawing) acetoxy group. The experimental investigations on this topic so far show that conversion of a vicinal diacetate to vicinal acetoxybromide by HBr/acetic acid can, and possibly can only, proceed *via* a dioxolanylium ion formed by front-side participation. Thus 3 mole equivalents of HBr/acetic acid converts 2,3-diacetoxybutane and *cis*-1,2-diacetoxycyclohexane to the 2,3-butane- and *trans*-1,2-cyclohexane-acetoxybromides respectively, with respective half-times of 5.0 and 6.1 hours, although it is known that nucleophilic substitution in derivatives of cyclohexane is very much slower than in acyclic analogues[205]. *trans*-1,2-Diacetoxycyclohexane is quite inert in 3 mole equivalents of HBr/acetic acid at 37°; this cannot form a dioxolanylium ion by front-side participation, but it is also possible that backside S_N2 attack on the equatorial acetoxy groups is blocked here.

N.m.r signals from the corresponding dioxolanylium ions were not observed during the reactions of 2,3-diacetoxybutane or *cis*-1,2-diacetoxycyclohexane - clearly the rate of their formation from the diacetates is much slower than the rate of attack by bromide ions on the dioxolanylium ions. However, in the presence of 3 mole equivalents of HBr/acetic acid *trans*-1,2-diacetoxycyclooctane is converted to the *trans*-4,5-hexamethylene-2-methyl-1,3-dioxolanylium ion (appropriate signals seen in the n.m.r spectrum) and this decomposes over a similar period as occurs in the reaction of *trans*-cyclooctane-1,2-diol. Preliminary examination suggests that the product mixture is the same in both cases - i.e absence of 1,2-substituted derivatives - and this would provide conclusive proof that simple nucleophilic substitution of vicinal diacetates by bromide ion in HBr/acetic acid does not occur, only reactions *via* dioxolanylium ions formed by front-side participation.

Conversion of vicinal diacetates to dioxolanylium ions in HBr/acetic acid parallels the same reaction in hydrogen fluoride observed by Pedersen[190]. In the absence of water, the reaction must proceed via formation of an acylium ion and cyclic ortho-ester. However, table II shows that the reactions of 2,3-diacetoxy-butane and cis-1,2-diacetoxycyclohexane with 3 mole equivalents of HBr/acetic acid proceeded faster when 0.5 mole equivalents of water was added. This must permit hydrolysis of the diacetate to the monoacetate which cyclises immediately to the dioxolanylium ion, the whole process - hydrolysis and cyclisation - being faster than the cyclisation under anhydrous conditions (scheme XXI).



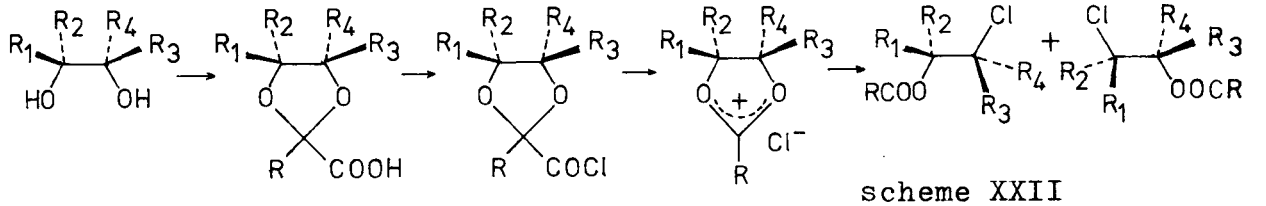
scheme XXI

Conversion of vicinal acetoxybromides to dibromides is also very slow (2,3-diacetoxybutane in 3 mole equivalents of HBr/acetic acid showed only 23% conversion after 8 days at 37°). Displacement of an isolated secondary acetate by bromide is predominantly S_N1 in character (table I), and this is retarded by the neighbouring bromine substituent for the same electronic reasons as an adjacent acetoxy group. An illustration of this is the fact that the products of the decomposition of the dioxolanylium ion from trans-cyclooctane-1,2-diol, formed by transannular hydrogen shifts are initially the 1,3-, 1,4- and 1,5-acetoxybromides, but these are then completely converted to the corresponding dibromides within the time scale of the reaction (c. 8 days at 37°), in contrast to the 1,2-acetoxybromide formed from the cis-diol.

Synthetic applications of the reaction of vicinal diols with HBr/acetic acid.

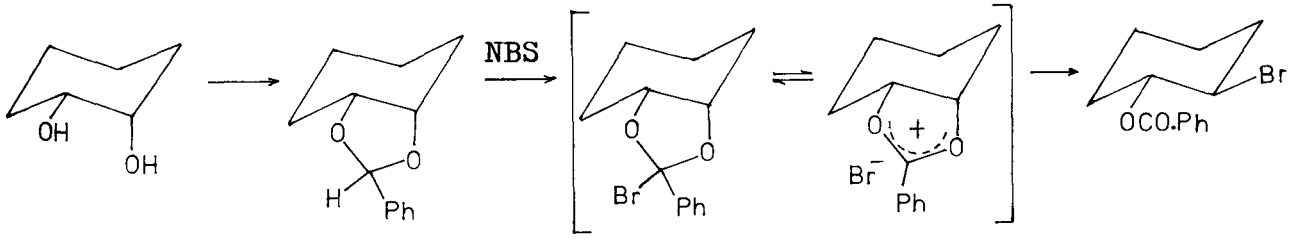
The one-step, stereospecific conversion of vicinal diols to vicinal acetoxybromides by HBr/acetic acid at room temperature is a reaction of great potential in synthetic organic chemistry. It certainly compares favourably with two existing procedures for achieving similar conversions, both involving more than one step, but both probably proceeding via dioxolanylium ion intermediates.

In Newman's procedure[206], derived from an earlier observation[207], the diol is reacted with an α-keto acid to give the dioxolan-2-carboxylic acid. This is converted to the corresponding acyl chloride by phosphorus pentachloride at -60°, and, on warming, this decarboxylates to give the dioxolanylium ion that is captured stereospecifically by the liberated chloride ion to give the vicinal chloroester (scheme XXII).



scheme XXII

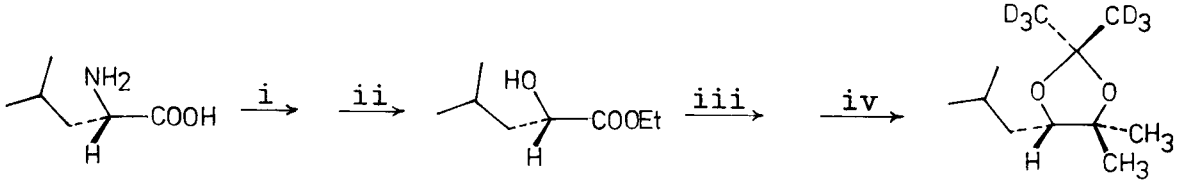
The other method[208] is to react the 0,0'-benzylidene acetal of the diol with N-bromosuccinimide (NBS) in refluxing carbon tetrachloride. Free-radical substitution gives a 2-bromo-2-phenyl-dioxolan, which isomerises via the 2-phenyl-1,3-dioxolanylium ion to the acyclic vicinal bromobenzoate (scheme XXIII).



scheme XXIII

This reaction has been much used in carbohydrate chemistry by Hanessian[209].

The starting diols can be derived by stereospecific hydroxylation of olefins - stereospecifically cis by hydrogen peroxide in anhydrous t-butanol with osmium tetroxide as catalyst, and stereospecifically trans by performic acid (see Experimental section). Chiral 1,2-diols are available by reduction of α-hydroxy acids or their esters, the acids being relatively convenient to resolve. The possibility of devising a general route from α-amino acids is being considered, and has been described recently for (S)-(-)-leucine[210] (scheme XXIV).



scheme XXIV. i) HNO_2; ii) EtOH/HCl; iii) CH_3MgBr; iv) $(CD_3)_2CO$/pTsOH.

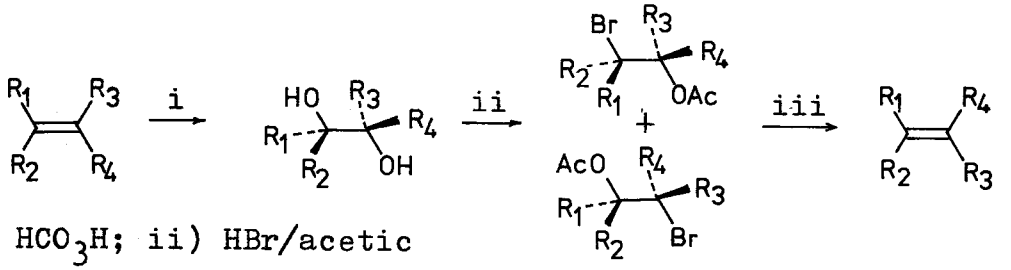
Some cyclic vicinal diols can be prepared by acyloin condensation and subsequent reduction.

All acyclic and some cyclic primary and secondary vicinal diols with alkyl substituents are converted rapidly and stereospecifically to the corresponding acetoxybromides. Some stereospecificity may be lost with mono-aryl substituted diols, and the reaction failed with a diol susceptible to acid-catalysed rearrangement. Whether the rearrangement occurred merely on exposure to the acidic reagent or within the generated dioxolanylium ion is uncertain. It would be interesting to determine whether the two alternative methods for production of the dioxolanylium ion described above are applicable to meso-1,2-diphenylethane-1,2-diol.

The product acetoxybromides have been used for alkylation of cobaloximes[171] and for production of chiral epoxides. They are readily converted to olefins by warming with zinc in ethanol, but the elimination is non-stereospecific, as has already been reported by House.[211] Oleic acid (cis-9-octadecenoic acid) was converted to threo-9,10-dihydroxyoctadecanoic acid by performic acid, and this was reacted with 3 mole equivalents of HBr/acetic acid overnight at room temperature to give a mixture (presumably) of erythro-9,10-acetoxybromides. Refluxing with zinc in ethanol gave a crystalline product, m.p 36°, from which pure elaidic acid (trans-9-octadecenoic

acid) m.p 43-44° was obtained by repeated recrystallisation from ethanol, but in only 12% yield (under equilibrating conditions the ratio of elaidic : oleic acids is 67:33[212]).

If a stereospecific trans-elimination of the acetoxy-bromides could be devised, a convenient route for olefin inversion would be via 'trans'-hydroxylation, conversion to the 'cis'-acetoxy-bromide with HBr/acetic acid, and final 'trans'-elimination (scheme XXV).



i) HCO_3H; ii) HBr/acetic acid; iii) ?

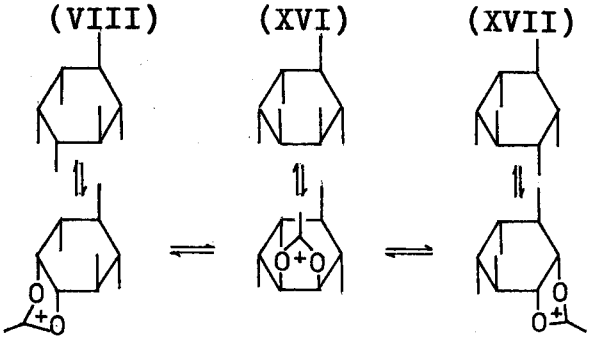
scheme XXV

An 'interesting' report by Blomquist[213] on a route to trans-cyclodecene starts by reduction of sebacoin to a cyclodecane-1,2-diol, m.p 135-138°. Comparison with Prelog's results later[214] shows this to be the cis-diol (m.p cis 140°, trans 54°). This diol was refluxed in acetic acid with hydrogen bromide bubbled through for 3.5 hours, to give 65% of a vicinal acetoxybromide, expected to have the trans-configuration from our results. Refluxing this acetoxybromide in methanol with zinc and zinc chloride then gave a 68% yield of trans-cyclodecene, identical with a sample prepared by pyrolysis of cyclodecyl-trimethylammonium iodide.

This result requires a stereospecific and cis-elimination from the acetoxybromide, both of which characteristics are difficult to explain. It is hoped to make a systematic study of the reactions of medium ring diols with HBr/acetic acid.

We have also investigated the reaction of HBr/acetic acid with some polyhydroxy compounds. There are numerous such reactions reported in the literature, but generally under extreme conditions and without any rationale - for instance the work of McCasland[177] mentioned at the beginning of this chapter. It will be noticed that the 6-bromoquercitols IX and X obtained from myoinositol hexaacetate VIII are those expected from the only dioxolanylium ion that can be formed by 'front-side' participation.

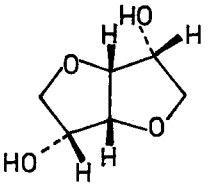
Furthermore, cyclitol peracetates with adjacent cis- and trans-acetoxy groups equilibrate on heating in glacial acetic acid containing 1.5% concentrated sulphuric acid.[215] A dioxolanylium ion is formed by front-side participation, and equilibrates via rear-side participation; e.g myoinositol hexaacetate VIII equilibrates with the hexaacetates of (±)- (XVI) and muco- (XVII) inositol after 12 days reflux.(scheme XXVI).



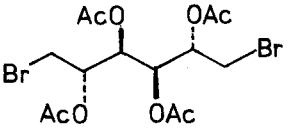
scheme XXVI

Considering the very rapid reaction of vicinal diols with HBr/acetic acid at room temperature, it was expected that myoinositol would react first at the two cis-hydroxyl groups to give the two acetoxybromides IX and X only. However, peracetylation of the reaction mixture gave only myoinositol hexaacetate, with no bromine incorporation.

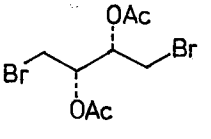
Reaction of HBr/acetic acid with the acyclic polyol mannitol was rapid, but gave a mixture of products with no bromine incorporation, as evidenced by n.m.r spectroscopy and the weight of material recovered. It is thought that cyclisation to form anhydromannitols (e.g XVIII) may have occurred, rather than the expected formation of 1,6-dibromo-2,3,4,5-tetraacetoxyhexane (XIX).



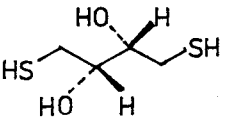
(XVIII)



(XIX)



(XX)



(XXI)

XIX was reported in 10% yield from mannitol hexaacetate and 7 mole equivalents of HBr/acetic acid after 9 months (!) at room temperature.[216] The failure of these polyols to react with HBr/acetic acid is under investigation as some interesting compounds would then be available. XIX has anticancer properties, and 1,4-dibromo-2,3-acetoxybutane (XX) is a precursor to Cleland's reagent (dithiothreitol XXI).

EXPERIMENTAL.

This experimental section is subdivided as follows:

1) starting materials and standard samples;
2) kinetic experiments;
3) product analyses;
4) preparative procedures.

1) Starting materials and standard samples.

The alcohols - butan-1-ol, butan-2-ol and cyclohexanol - and also ethane-1,2-diol, (±)-propane-1,2-diol and butane-2,3-diol were obtained commercially and redistilled once before use. The butane-2,3-diol was a mixture of diastereomers, probably mostly the threo-isomer (see text).

The commercial saturated solution of hydrogen bromide in glacial acetic acid was supplied as approximately 48% w/v, density approximately 1.4g/ml. It was kept in the refrigerator and only opened when necessary. Titrations at roughly 3 monthly intervals showed no significant loss of bromide ion. No extra precautions were taken to exclude moisture. Two titrations for bromide ion were employed:

a) a sample of the HBr/acetic acid solution (c. 0.3-0.4g) was weighed accurately into a slight excess of N NaOH solution (c. 6ml). The mixture was made neutral to litmus with 2N HNO_3, and titrated against 0.1N silver nitrate solution with potassium chromate as indicator.

b) to the mixture of HBr/acetic acid and N NaOH as above was added ferric ammonium sulphate solution (1ml), then 4N HNO_3 (10ml) and c. 0.1N potassium thiocyanate solution (0.1-0.2ml), and the mixture titrated against 0.1N silver nitrate solution to the disappearance of the red colour[217].

Both procedures showed the commercial material to contain 4.2mM HBr/g solution (for density 1.4g/ml this corresponds to 47.5% w/v).

Analysers of the acetoxybromide derived from propane-1,2-diol claimed that c. 10% of the halide present was in fact chloride. However, similar analyses were obtained for this product following

use of HBr/acetic acid prepared from bromine redistilled from caesium bromide and redistilled Analar glacial acetic acid.

Alcohol acetates and diol diacetates were obtained by addition of a drop of concentrated sulphuric acid to a mixture of the alcohol or diol and a slight excess of acetic anhydride. After standing at room temperature for 2 hours, the mixture was quenched with water, neutralised with solid sodium carbonate and extracted with ether. The extracts were dried and evaporated to give remarkably pure product which could be redistilled.

2-Acetoxy-3-butanol was prepared by the same procedure from butane-2,3-diol and 1 mole equivalent of acetic anhydride, and the mixture of diol, monoacetate and diacetate separated on preparative g.l.c (20' E301/150°).

Products were identified spectroscopically (table V) and their purity checked by g.l.c and t.l.c.

cis- and trans-Cyclohexane-1,2-diols were prepared from cyclohexene with anhydrous hydrogen peroxide in t-butanol with osmium tetroxide catalyst[218], and hydrogen peroxide in formic acid[219] respectively.

The cis-diol was best purified from adipic acid formed by over oxidation, by sublimation (100-111°/11mm) and recrystallisation from ethyl acetate (yield 20% m.p 98°). Yield of the trans-diol was 67% m.p 103-104°.

1,2-Epoxycyclohexane was prepared in 72% crude yield from cyclohexene and a slight excess of m-chlorperbenzoic acid in dichloromethane, and was used as such for a standard comparison and for conversion to trans-2-methoxycyclohexanol.($\tau(CCl_4)$ 7.00 C<u>H</u>-O; i.r (film) very characteristic, D.M.S catalogue No. 9413) trans-2-Methoxycyclohexanol[181].

Crude 1,2-epoxycyclohexane (1.2g, 13.4mM) was dissolved in dry methanol (14ml), concentrated sulphuric acid (2 drops) added and the mixture stood overnight at room temperature. G.l.c analysis indicated absence of starting material. The mixture was quenched with water (30ml) and neutralised with a little solid sodium carbonate, and extracted with ether. The extracts were

washed twice with a little water, dried and evaporated to give trans-2-methoxycyclohexanol (1.30g, 75%) pure on g.l.c (6'E301/100° n_D^{20} 1.4604 (lit.[181] n_D^{25} 1.4586).

i.r (film) 3420s(br),2935s,2860s,2825m,1452m,1190m,1098s,995m, 910m,845m cm^{-1}.

trans-Cyclooctane-1,2-diol was prepared from cyclooctene and hydrogen peroxide in formic acid, and purified via distillation of the isopropylidene ketal and column chromatography (silica gel/ 1% $MeOH/CHCl_3$) of the diol obtained on hydrolysis of the ketal[220].

cis-Cyclooctane-1,2-diol was prepared in 4% yield by reaction of cyclooctene with anhydrous hydrogen peroxide in t-butanol with osmium tetroxide as catalyst[220]. After evaporation the reaction mixture was sublimed at 100°/0.5mm with the cold finger cooled by acetone/dry-ice, and the resulting crystals recrystallised from ethyl acetate, m.p 77-78° (lit.[220] 76-79°).

cis-1,2-Epoxycyclooctane.

Cyclooctene (1.10g, 10mM) was dissolved in dry dichloromethane (20ml), cooled in ice and stirred, and m-chlorperbenzoic acid (2.0g, 10mM if 85%) added in portions. After stirring 4 hours at room temperature, the mixture was filtered, washing through with dichloromethane, and the filtrate washed several times with saturated sodium carbonate solution (effervescence!) until neutral. The organic layer was dried and evaporated to give product (1.23g) quite pure on g.l.c (6'E301/120°) and t.l.c (benzene), m.p 40-50°.

Purification was best by short path distillation onto a cold finger either at 140°/atmospheric pressure or, better, 100-110°/110mm, these conditions being fairly critical (b.p 180°). Yield 0.78g (62%) m.p 54° (very sharp) (lit.[220] 52.5-56.5°).

trans-1,2-Dibromocyclooctane was prepared from cyclooctene and bromine in carbon tetrachloride, and the product distilled at 76-80°/0.035mm (80%). It was pure on t.l.c (petrol), but partiall reverted to cyclooctene on g.l.c (2'SE30/150°).

N.m.r data on this compound given below.

meso-1,2-Diphenylethane-1,2-diol (meso-hydrobenzoin) was prepared from benzil and sodium borohydride by the excellent procedure of Fieser[221].

2) Kinetic experiments.

a) following experiments by n.m.r spectroscopy.

b) analysis of aliquots by g.l.c and n.m.r.

a) Experiments were run on approximately 0.5-1.0mM scale in n.m.r sample tubes at the temperature of the preheater (37°). For liquid substrates, a suitable volume of HBr/acetic acid was transferred to the stoppered n.m.r sample tube and weighed. The calculated amount of substrate was added from a microsyringe, the reactants mixed at room temperature, and the sample tube placed in the preheater or probe of the spectrometer.

For crystalline diols, the compound was weighed out in the sample tube and the calculated amount of HBr/acetic acid weighed out directly into the tube, added from a Pasteur pipette.

No special procedures were used for rigorous exclusion of moisture, but operations were performed as quickly as possible without undue exposure of the reagents to the atmosphere.

Nor were reactants accurately thermostatted before mixing. As pointed out in the text, mixing of alcohols and diols, particularly the latter, causes a slight exotherm on the scale involved here. This may bring the temperature up to about 37° from room temperature, but could also be a source of inaccuracy in subsequent kinetic measurements. No irregularities were observed in graphical plots, and it is difficult to see how this factor can easily be overcome, but it should be further checked. For instance, the acetylation of diols is roughly twice as fast as that of alcohols, and only a 10° rise in temperature is required to double the rate of the average chemical reaction.

b) Reactions set up as in (a) were run in stoppered sample vials in a constant temperature bath at 37° on approximately 5mM scale. Aliquots containing c. 0.5mM of substrate (c.0.25ml for reactions with 3 mole equivalents of HBr/acetic acid) were withdrawn at

appropriate intervals with a pipette, and transferred into cold water (5ml). The mixtures were neutralised with solid sodium carbonate and extracted with ether (4 portions of 10ml). The extracts were combined, dried and evaporated on the rotary evaporator. It was important to neutralise the quenched sample as soon as possible as the aqueous acidic medium was found to be quite efficient at acetate hydrolysis.

Ethane- and propane-1,2-diols are not extracted completely from water by ether, but it was established that the other diols and products were extracted satisfactorily by the above procedure.

Most of the relevant n.m.r data is given in tables III and V. G.l.c analyses used 6' E301 and Carbowax columns to check both product identities and quantitative analyses by n.m.r. The reaction mixtures from butane-2,3-diol and cis-cyclohexane-1,2-diol could not be satisfactorily analysed by n.m.r spectroscopy because of variability of and obscuring of the OH resonances. The graphs (figs. 1 and 2) were drawn from g.l.c results (6'E301/130°). Calibration with pure materials showed that in both series, peak areas had to be multiplied by 2.4, 1.0, 1.0, and 0.67 for diol, monoacetate, acetoxybromide and diacetate respectively to convert to molar ratios. Slight variations in running conditions sometimes caused acetoxybromides to give broad multiplet humps on g.l.c analysis due to decomposition.

3) Product analyses.

The result of the reactions of HBr/acetic acid studied are given in tables I, II and IV, and the n.m.r signals used to identify products of typical cases of the general reaction are given in tables III and V. In this section, details of further transformations and analyses of anomalous reactions are given.

Conversion of trans-1-acetoxy-2-bromocyclohexane to 1,2-epoxycyclohexane.

The crude acetoxybromide (76mg, 0.346mM) was dissolved in dry methanol (0.4ml) and 2.93N KOH in methanol (236µl, 0.692mM) added from a microsyringe dropwise with shaking. Potassium bromide

was precipitated after the addition of the first two drops. When addition was complete, t.l.c analysis ($CHCl_3$) showed no starting material, just a faint spot (R_f0.5) corresponding to the epoxide, most having evaporated (b.p 130°). G.l.c analyses (6'E301 at 100° and at 130°) showed only methanol and 1,2-epoxycylohexane, with no cyclohexanone or acetoxybromide, these observations being confirmed by coinjections.

A disturbing anomaly is that after addition of about half of the total amount of KOH/methanol, g.l.c analysis showed no starting acetoxybromide, although this was clearly present on t.l.c. A similar observation was made with trans-1-acetoxy-2-bromocyclo-8ctane.

Reactions of trans-1,2-cyclo8ctanediol with HBr/acetic acid.

i) trans-Cyclo8ctane-1,2-diol (80mg, 0.556mM) was dissolved in HBr/acetic acid (0.398g, 1.668mM) and stood for 10 hours at room temperature. Aqueous work-up as above (2(b)) gave trans-2-acetoxycyclo8ctanol (100mg, 97%), pure on t.l.c (20% EtOAc/benzene), and identified by its n.m.r spectrum:

$\tau(CCl_4)$	8.38 (m,12H)	6.30 (m,1H)	C<u>H</u>-OH
	8.00 (s,3H)	5.30 (m,1H)	C<u>H</u>-OAc
	7.03 (s,1H,br) O<u>H</u>		

ii) trans-Cyclo8ctane-1,2-diol (93mg, 0.645mM) was dissolved in HBr/acetic acid (0.461g, 1.935mM) and heated for 6 hours at 60°, after which the n.m.r spectrum showed complete absence of the trans-4,5-hexamethylene-2-methyl-1,3-dioxolanylium ion. Aqueous work-up as above (2(b)) gave 130mg of pale brown oil that contained three highly non-polar components only, just resolvable by careful t.l.c (R_f c. 0.4 in petrol).

The product mixtures from three such experiments were combined and separated by column chromatography (silica gel, eluting with petrol) and overlapping fractions rechromatographed, to give the three components in approximately 1:2:1 ratio, identified as the 1,3-, 1,4-, and 1,5-dibromides of cyclo8ctane respectively (in order of decreasing R_f on t.l.c)

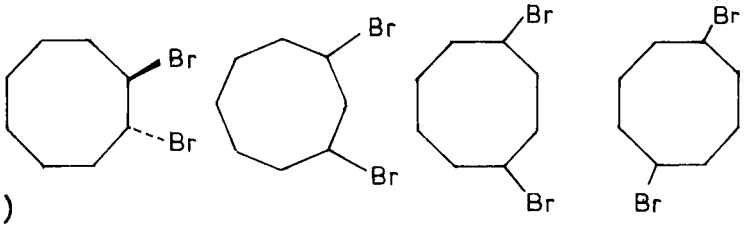
The i.r spectra were not characteristic, but all had similar mass spectra.

e.g for cyclooctane-1,5-dibromide:-

m/e 191(2.4), 189(4.8), 187(2.4) corresponding to loss of ^{79}Br and ^{81}Br from $C_8H_{14}{}^{81}Br_2$, $C_8H_{14}{}^{81}Br^{79}Br$, and $C_8H_{14}{}^{79}Br_2$ species; strong base peak at m/e 109 ($C_8H_{13}^+$).

The three products were distinguishable by their behaviour on t.l.c (petrol) where R_f 1,3- >1,4- >1,5-, and also R_f 1,3- > trans-1,2-dibromocyclooctane, prepared independently.

The n.m.r spectra were also characteristic. The C<u>H</u>-Br proton resonances move progressively upfield as the distance apart of the bromine substituents increases. Also the relative integrals corresponding to C<u>H</u>$_2$-CBr (τ7.8) and CH$_2$-C<u>H</u>$_2$-CH$_2$ (τ8.35) distinguish 1,3-, 1,2-, and 1,4- or 1,5- substitution. The 1,3-dibromocyclooctane shows a distinctive 2H triplet resonance (J = 5.5) at τ7.36.



n.m.r (CCl_4)

	τ5.45	τ5.53	τ5.63	τ5.72	(m,2H,C<u>H</u>-Br)
τ7.8 (m)	4H	4H	8H	8H	C<u>H</u>$_2$-CBr
τ8.35 (m)	8H	6H	4H	4H	C<u>H</u>$_2$-CH$_2$
		τ7.36			(t,J=5.5,2H)

<u>Reaction of cis-cyclooctane-1,2-diol with HBr/acetic acid.</u>

<u>cis</u>-Cyclooctane-1,2-diol (77mg, 0.535mM) was reacted with HBr/acetic acid (0.401g, 1.605mM) for 140 hours at 37°, after which time the n.m.r spectrum showed absence of the <u>cis</u>-4,5-hexamethylene-2-methyl-1,3-dioxolanylium ion. The product was quenched in water, neutralised, extracted into ether, and the extracts dried and evaporated to give an oil (122mg). This was chromatographed on silica gel (5g). Petrol eluted a mixture of cyclooctane-dibromides (18mg), shown by comparison with the samples from above on t.l.c to be a mixture of 1,2-, 1,3-, 1,4- and 1,5 dibromides, mainly the 1,4- isomer. Elution was continued with 5%, 10% and 15% benzene in petrol, when pure <u>trans</u>-1-acetoxy-2-bromocyclooctane (95mg) was obtained. (t.l.c in $CHCl_3$, n.m.r see table V)

Conversion of trans-1-acetoxy-2-bromocyclooctane to cis-1,2-epoxycyclooctane.

The crude trans-1-acetoxy-2-bromocyclooctane from the chromatography described above (37mg, 0.148mM) was dissolved in dry methanol (0.1ml), and 2.93N KOH/MeOH (101µl, 0.296mM) was added dropwise from a microsyringe with shaking. After standing for 10 minutes at room temperature, water (3ml) was added, and the mixture extracted with ether. The extracts were dried and evaporated to give colourless crystalline cis-1,2-epoxycyclooctane (16mg, 88%) identical with the authentic material on t.l.c and by its i.r spectrum, both showing clearly the absence of acetoxybromide.

Reaction of meso-1,2-diphenylethane-1,2-diol with HBr/acetic acid.

meso-1,2-Diphenylethane-1,2-diol (187mg, 0.874mM) was reacted with HBr/acetic acid (0.625g, 2.62mM). At 37° the solid all dissolved after 45 seconds, but after 2 minutes the mixture set to a white solid. After 10 minutes at 37°, water was added, the mixture neutralised, and extracted with dichloromethane, leaving voluminous white material soluble in neither solvent. The dichloromethane extract was evaporated and shown to be a mixture of many products by n.m.r spectroscopy and t.l.c (variety of solvents), although the presence of cis-4,5-diphenyl-2-diphenylmethyl-1,3-dioxolan (XII) in about 30% of the total was detected by comparison of the n.m.r spectrum with that of a standard sample (below), and its presence was verified on t.l.c (R_f 0.7 EtOAc/benzene 1:1).

cis-4,5-Diphenyl-2-diphenylmethyl-1,3-dioxolan (XII)[204].

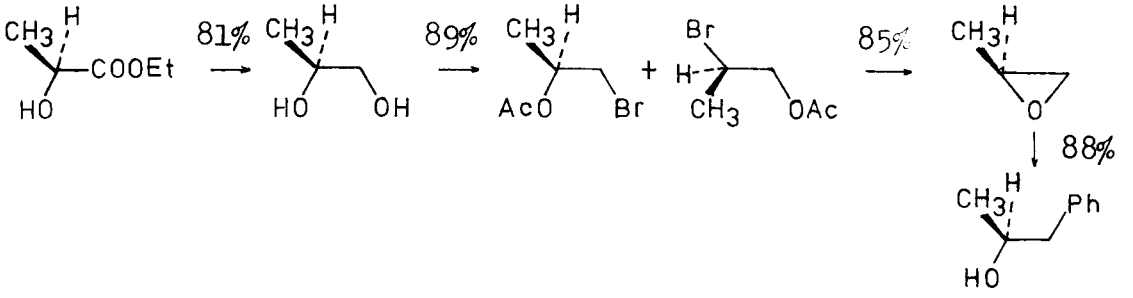
meso-1,2-Diphenylethane-1,2-diol (440mg, 2mM) and phosphorus pentoxide (207mg) were heated together in a test tube over a bunsen burner, when they melted together in an exothermic reaction. After standing for 15 minutes, water was added, and the mixture extracted with ether. The extract was dried and evaporated, and the residue recrystallised three times from ethanol (120mg, 30%) m.p 129° (lit.[204] 130-132°).

n.m.r ($CDCl_3$) τ5.32 (d,J=4.0,1H) 3.15 (m,10H)
4.67 (s,2H) 2.60 (m,10H)
4.22 (d,J=4.0,1H)

m.s m/e 391(0.8) (M+1), 286(6), 225(28), 197(13), 180(B).

4) Preparative procedures.

A new route to chiral propylene oxide.



(S)-(-)-Ethyl lactate is readily available in kilogram quantities from Fluka A.G, and was used as supplied. A redistilled sample had $[\alpha]_D^{26}$ -13.9° (neat), d^{26} 1.044, as compared with a sample prepared from Sigma (S)-(+)-lactic acid by refluxing with excess ethanol and a catalytic amount of concentrated sulphuric acid and subsequent azeotropic distillation, having $[\alpha]_D^{26}$ -14.6° (neat). The literature shows a wide range of values for the optical rotation of ethyl lactate, probably due to the presence of ethers having high rotations - e.g the dimer, 2,5-dimethyl-1,4-dioxan-3,6-dione, has $[\alpha]_D$ -298° (benzene, c 1.17).[222] Kenyon gives a range of values for the rotation in ref. 223.

(S)-(+)-Propane-1,2-diol.

(S)-(-)-Ethyl lactate (33g, 0.28M) was dissolved in dry ether (150ml) and added dropwise to a stirred suspension of lithium aluminium hydride (10.8g, 0.284M) in dry ether (200ml) under nitrogen at such a rate as to maintain steady reflux (approximately 30 minutes). The mixture was stirred at room temperature for 3 hours, and then a slight excess of water (25ml) added carefully, and stirring continued for a further 1.5 hours. The mixture was filtered, and the solid washed well with ether and dichloromethane. The filtrate was dried and evaporated to give 5g of product (23%).

2N sulphuric acid was added to the solid until the milky suspension was just acidic, and this was then subject to continuous extraction with twice the volume of dichloromethane (c. 150ml). After 117 hours this gave a combined yield of 17.2g (81%) of g.l.c pure material, which was distilled at 93°/18mm (15.0g, 71%).

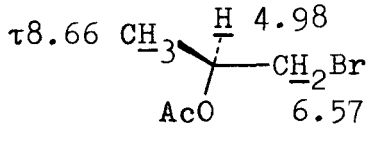
d^{25} 1.038g/ml
$[\alpha]_D^{25}$ +16.28° (neat); $[\alpha]_D^{20}$ +20.7° (H_2O, c 7.5).

highest literature value for optical rotation, for (R)-(-)- isomer from yeast reductase reduction of hydroxyacetone[179], $[\alpha]_D^{26}$ -15.9° (neat).

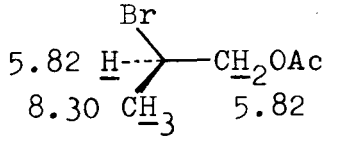
Acetoxy-bromopropane.

HBr/acetic acid (71g, 0.3M) was added to (S)-(+)-propane-1,2-diol (7.6g, 0.1M) with stirring and ice-cooling over about 5 minutes. After stirring at room temperature for 30 minutes, water (200ml) was added, and the mixture was neutralised with solid sodium carbonate. The neutral solution was extracted with ether (3 portions of 150ml), and the extracts combined, dried and evaporated. The residue (18g) was 94% pure on g.l.c (6'E301/100°), and was distilled, collecting the major fraction at 57°/11mm (16.0g, 89%) which was pure by g.l.c.
d^{26} 1.429g/ml; n_D^{20} 1.4481.
$[\alpha]_D^{26}$ -9.46° (neat); $[\alpha]_D^{23}$ -13.55° ($CHCl_3$, c 5.8).

the n.m.r spectrum (CCl_4) shows 94% 1-bromo-2-acetoxypropane (XXII)
6% 1-acetoxy-2-bromopropane (XXIII)



(XXII)



(XXIII)

A satisfactory analysis was not obtained for this product. Sample 1 was prepared from the commercial HBr/acetic acid and twice redistilled; samples 2 and 3 were prepared from HBr/acetic acid made from bromine redistilled from caesium bromide (to remove chlorine[162]) and 'Analar' glacial acetic acid.

$C_5H_9BrO_2$	C33.17, H5.01, Br44.14%	
sample 1	C33.20, H5.48%	Strauss, Oxford.
	C33.69, H5.23, Br40.86%	Bernhard, Germany.
	C33.58, H5.16, Br40.98, Cl 5.08%	Pfizer, Kent.
sample 2	C33.58, H5.07, Br41.50, Cl 7.3%	Pfizer, Kent.
sample 3	C33.64, H5.09, Br43.80, Cl 7.9%	Pfizer, Kent.

(S)-(-)-1,2-Epoxypropane.

0.86N Potassium amyloxide (59.1ml, 50mM) was added dropwise to a stirred solution of the redistilled mixture of acetoxybromopropanes (9.05g, 50mM) in amyl alcohol (20ml) at room temperature over about 20 minutes. Potassium bromide was precipitated after addition of the first few drops, and when addition was complete, the mixture was warmed to about 100°, and the epoxypropane distilled out through a 10cm Vigreux column with efficiently cooled condenser and receiver (2.47g, 85%) b.p 35°. This material was pure by g.l.c (6'E301/50°) which showed absence of any amyl alcohol.

solvent	conc.	$[\alpha]_D^{22}$	lit.[224] $[\alpha]_D^{20}$ (c=5).
$CHCl_3$	5.04	- 8.21	+ 8.5
CCl_4	5.83	-18.55	+18.7
ether	5.69	-16.6	+17.0
EtOH	5.61	- 8.56	+ 7.9
neat			+12.53
			for (R)-(+)-isomer.

Dropwise addition of 2 mole equivalents of 2.8N NaOH to the acetoxybromopropane mixture in dioxan/water 1:1 resulted in the mixture rapidly becoming homogenous, and when addition was complete, the propylene oxide could be distilled out in 55% yield. Eliel[225] used NaOH in ethane-1,2-diol (b.p 190°) to convert dl-2-hydroxybutane-3-(p-toluenesulphonate) to cis-2,3-epoxybutane (b.p 60°) with direct distillation of the product from the reaction mixture.

(S)-(+)-1-Phenyl-propan-2-ol.

(S)-(-)-1,2-Epoxypropane (3.37ml, 50mM) was added dropwise from a syringe to a stirred, ice-cooled 1.0N ethereal solution of phenyl lithium (50ml, 50mM) under nitrogen at such a rate that reaction was just detectable - about 40 minutes. At room temperature the mixture refluxed. Stirring was continued at room temperature. In one run the mixture rapidly became cloudy and almost set solid, in another run this did not occur until 2 hours after addition was complete.

After 4 hours, water was added to dissolve the solid (25ml),

the ether layer removed, and the aqueous solution extracted with two more portions (50ml) of ether. The combined extracts were washed once with a little water, dried and evaporated. The residue (7.0g) was distilled at 103-104°/17mm to give 6.1g (88%) of (S)-(+)-1-phenyl-propan-2-ol, pure by g.l.c (6'E301/130°).

n_D^{27} 1.5181 (lit.[178] n_D^{20} 1.5190)

solvent	conc.	$[\alpha]_D^{25}$	lit. $[\alpha]_D^{25}$	$[\alpha]_D^{20}$
neat		+25.6	-27.70	
ether	5.12	+20.5	-20.20	
EtOH	4.55	+16.5		+17.0
$CHCl_3$	4.76	+39.2		+41.2

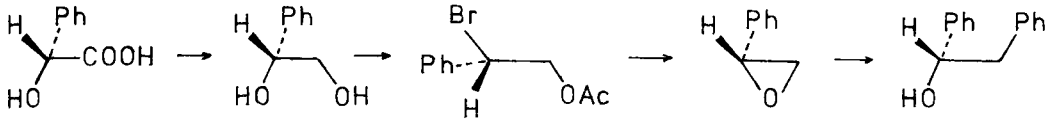
The highest literature value for the optical rotation is for the (R)-(-)- isomer[178]. The values for the (S)-(+)- isomer given are derived by appropriate correction of values given by the same author[226] for a sample having a rotation of slightly lower magnitude ($[\alpha]_D^{20}$ +26.24° (neat)).

n.m.r ($CDCl_3$) τ8.82 (d,J=6.0,3H) 6.02 (sx,1H)
8.01 (s,1H) 2.72 (s,5H)
7.31 (d,J=6.5,2H)

$C_9H_{12}O$ C79.37, H8.88%
found C79.06, H8.81%

Reaction of propylene oxide with ethereal methyl lithium under a variety of conditions gave complex product mixtures containing ⩾20% of the expected butan-2-ol. Addition of organometallic reagents to epoxides is generally complicated by polymerisation, and 1-phenyl-propan-2-ol was obtained in 60% yield by the action of phenylmagnesium bromide on propylene oxide[227].

Preparation of (R)-(+)-Styrene oxide.



O.P 88%

(R)-(-)-Mandelic acid was supplied by Koch-Light.
$[\alpha]_D^{26}$ -157.0° (lit.[228] $[\alpha]_D^{18}$ +157.5° (H_2O, c 3.5) for (S)-(+)-isomer)
(H_2O, c 3.15)

Reduction of (R)-(-)-mandelic acid with 1.2 mole equivalents of lithium aluminium hydride in dry ether gave only 43% of (R)-(-)-1-phenylethane-1,2-diol after 4 hours reflux. It is anticipated that the ester would give a better yield.

(R)-(-)-1-Phenylethane-1,2-diol.

(R)-(-)-Mandelic acid (7.6g, 50mM) dissolved in dry ether (150ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.0g, 53mM) in dry ether (50ml) under nitrogen. The mixture was refluxed under nitrogen for 4 hours, and then water (4.5ml) added carefully, and stirring continued for 30 minutes. Then the mixture was filtered, washing through well with ether, and the filtrate dried and evaporated to give (R)-(-)-1-phenylethane-1,2-diol (3.0g, 43%). The residue from filtration was made acid with 2N sulphuric acid, and the milky suspension extracted with ether (4 portions of 75ml). The combined extracts were dried and evaporated to give quite pure (R)-(-)-mandelic acid (4.5g, 57%) that was recycled in a second reduction.

The (R)-(-)-1-phenylethane-1,2-diol was recrystallised once from benzene/petrol, m.p 65° (lit.[229] 65-66°)
$[\alpha]_D^{26}$ -40.4° (H_2O, c 3.34) (lit.[229] $[\alpha]_D^{20}$ +40.6° (H_2O, c 3.23) for (S)-(+)- isomer).

(S)-(+)-1-Bromo-1-phenyl-2-acetoxyethane.

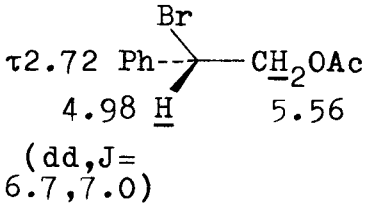
Cold HBr/acetic acid (12.4g, 52.2mM) was added dropwise to (R)-(-)-1-phenylethane-1,2-diol (2.4g, 17.4mM) over about 5

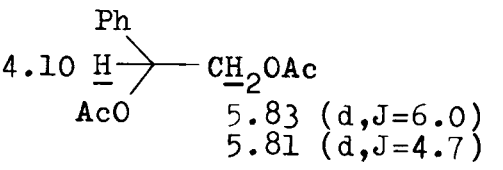
minutes, and the mixture stirred at room temperature for 40 minutes. Water (25ml) was added, and the solution neutralised with sodium carbonate, and extracted with ether (3 portions of 30ml). The combined extracts were dried and evaporated to give (S)-(+)-1-bromo-1-phenyl-2-acetoxyethane (3.93g, 93%).

d^{25} 1.415g/ml.

$[\alpha]_D^{25}$ +93.5° (CCl_4,c 5.63).

This product was not distilled. The isomeric homogeneity was established by comparison of the n.m.r spectrum (CCl_4) with that of (±)-1-phenyl-1,2-diacetoxyethane. The former showed no resonance due to a Ph-C<u>H</u>-OAc proton.





<u>(R)-(+)-Styrene oxide.</u>

3.43N KOH in methanol (6.34ml, 21.7mM) was added dropwise to a stirred solution of (S)-(+)-1-bromo-1-phenyl-2-acetoxyethane (5.3g, 21.7mM) in methanol (5ml) at room temperature. After stirring for 30 minutes, the precipitated potassium bromide was dissolved in water (20ml), and the mixture extracted with ether (4 portions of 25ml). The combined extracts were washed once with a little water, dried and evaporated. The residue (2.3g, 89%) was pure (R)-(+)-styrene oxide by g.l.c (6'E301/130°), and was distilled at 83-84°/17mm (2.03g, 79%).

d^{26} 1.060g/ml.

$[\alpha]_D^{26}$ +27.3° (neat). The highest value in the literature is $[\alpha]_D$ +35.2° (neat),[230] according to which the above material is 88.8% optically pure.

Chiral styrene oxide has previously been prepared by conversion of chiral 1-phenylethane-1,2-diol to the primary p-toluenesulphonate, and treatment of this with base.[225] Optical purity depends upon exclusive tosylation of the primary hydroxyl group.

(R)-(+)-1,2-Diphenylethanol

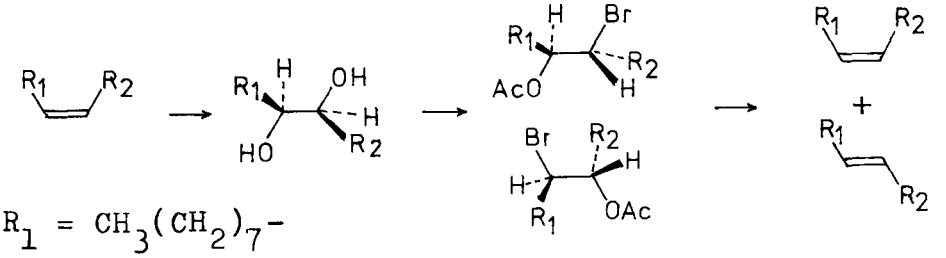
0.54M Phenyl lithium in ether (3.71ml, 2mM) was added dropwise from a syringe to a stirred solution of (R)-(+)-styrene oxide (0.24g, 2mM) in dry ether (2ml) under nitrogen, with ice cooling. After stirring for 4 hours at room temperature, water (6ml) was added, the ether layer removed, and the aqueous solution extracted three times with ether (15ml). The extracts dried and evaporated gave 0.37g that was chromatographed on a short silica gel column. Benzene eluted 17mg of trans-styrene (identified by comparison of its n.m.r spectrum with that of authentic material), and 5% ethyl acetate/benzene eluted (R)-(+)-1,2-diphenylethanol (70mg) m.p 58°, pure on t.l.c ($CHCl_3$), and 105mg of slightly less pure material.

The pure fraction had $[\alpha]_D^{25}$ +40.7° (EtOH, c 4.73). The highest value in the literature is $[\alpha]_D^{25}$ +52.8° (EtOH, c 5),[231] from which the optical purity of the above material is 88.5%.

Low temperature recrystallisation from ether/petrol gave needles, m.p 63°, $[\alpha]_D^{21}$ +40.8° (EtOH, c 4.5), (lit.[231] m.p 67°)

n.m.r (CCl_4) τ7.62 (s,1H) 2.95 (s,5H)
7.12 (d,J=7.0,2H) 2.87 (s,5H)
5.40 (t,J=7.0,1H)

Conversion of Oleic acid to Elaidic acid.



$R_1 = CH_3(CH_2)_7-$

$R_2 = -(CH_2)_7COOH$

Commercial oleic acid (cis-9-octadecenoic acid) containing at most 83% of oleic acid (by g.l.c of the methyl ester) was converted as described[232] by hydrogen peroxide in formic acid to threo-9,10-dihydroxyoctadecanoic acid, m.p 92.5-93.5°, in 20% yield, based on pure starting material, after six recrystallisations

from ethanol. Several less pure fractions were obtained that were not purified further.

erythro-9,10-Acetoxybromooctadecanoic acid.

threo-9,10-Dihydroxyoctadecanoic acid (1.58g, 5mM) was treated with cold HBr/acetic acid (3.75g, 15mM), and the mixture stirred at room temperature overnight. Water (5ml) was added, and the aqueous layer decanted from the oily product. This was repeated five times, and the product then dried at 0.05mm for 3 hours to give 1.93g (91%) of an oil, pure on t.l.c (5% MeOH/$CHCl_3$), and by n.m.r (table V).

i.r (film) 3400-3200m,1741s,1711s cm^{-1}.

(c.f diol ν_m (nujol) 3300s,3250s,1722m,1702s cm^{-1})

cis- and trans-9-Octadecenoic acids.

The total erythro-9,10-acetoxybromooctadecanoic acid product from above (1.93g) was dissolved in ethanol (20ml) and refluxed for 1 hour with zinc dust (0.65g, 10mM). Water (100ml) was added to the cooled mixture after decanting from the zinc residues, and the white crystalline solid filtered off (1.2g, 85% based on diol) m.p 38°. The i.r spectrum of this material showed complete absence of the acetoxy carbonyl band at 1741 cm^{-1}.

T.l.c on 10% silver nitrate-impregnated silica gel failed to resolve the mixture in a variety of solvent systems (e.g 5% MeOH/$CHCl_3$, EtOAc). Three recrystallisations from ethanol gave 0.17g (12%) m.p 44°, with 0.22g of m.p 40° and 0.6g of oily residues.

Literature m.p oleic acid (cis) 16°

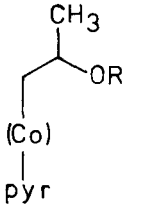
elaidic acid (trans) 44-45° (ref.212)

Chapter 6
A NOVEL DEGRADATION PRODUCT OF COBALOXIMES[233]

The problem and a trial solution.

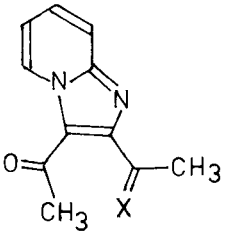
Although 2-acetoxypropyl(pyridine)cobaloxime (II) is now more directly prepared (chapter 5), the original route used to this compound was via acetylation of 2-hydroxypropyl(pyridine)cobaloxime (I), itself prepared from cobaltous chloride and dimethylglyoxime (D.M.G) in sodium hydroxide and pyridine, with sodium borohydride and propylene oxide.

It was claimed that acetylation of I in a 10 molar excess of acetic anhydride in pyridine proceeded well when performed under nitrogen, but that under air or oxygen after 24 hours very little cobaloxime material was present. The n.m.r spectrum of the crude reaction product in this latter case showed a conspicuous doublet with allylic splitting at τ0.31, and the compound responsible, now known to have structure (III), was isolated with great difficulty due to its relative instability. The key step in the isolation of III was sublimation at c. 100°/0.001mm.



(I) R = H

(II) R = CO.CH_3



(III) X = NO.$COCH_3$

(IV) X = NOH

(XV) X = $(NO_2)_2$

The compound III contained no cobalt, and analysed for $C_{13}H_{13}N_3O_3$. Apart from the remarkable low field doublet, the n.m.r spectrum (fig.1) of III showed three other resonances in the aromatic region with a very characteristic splitting pattern, and these four protons were assigned to the protons of a mono-substituted pyridine ring. The only other signals were singlet resonances due to three methyl groups. The i.r spectrum showed two carbonyl absorptions at 1775 and 1640 cm^{-1}.

Compound III was easily deacetylated to give compound IV m.p 190°, this conversion being one of the causes of the instability

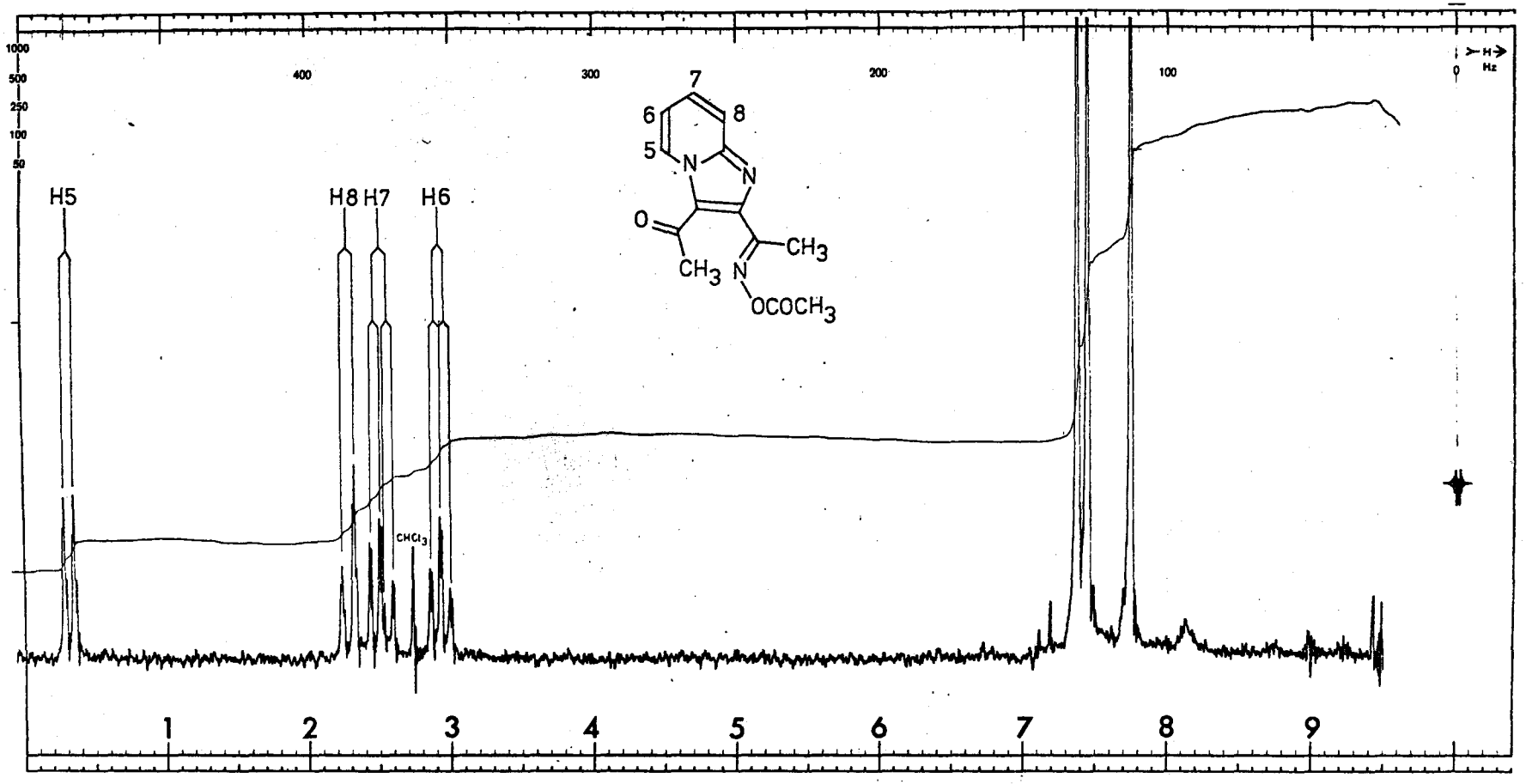


fig.1. 100 MHz ($CDCl_3$) n.m.r spectrum of 2-(1-(E)-acetoxyiminoethyl)-3-acetyl-imidazo[1,2-a]pyridine (III).

of III. Compound IV had spectral data very similar to that of III, except for the absence of the band at 1775 cm^{-1} in the i.r spectrum, and the presence of free and intermolecularly hydrogen-bonded O-H absorptions at 3583 (sharp) and 3320 (broad, concentration dependent) cm^{-1}. The n.m.r spectrum of IV showed loss of one of the methyl singlets, and gain of a broad 1H resonance at τ0.70.

The mass spectrum of III showed loss of ketene from the molecular ion (m/e 259 - 217) corresponding to deacetylation of III to IV (molecular ion m/e 217). Thereafter the mass spectra of III and IV were identical, showing loss of OH and each of the two methyl groups, and with strong peaks at m/e 105 ($C_6H_5N_2^+$ by accurate mass measurement).

From this data, it was proposed that the cobaloxime decomposition product III was formally derived by oxidation of a mole each of pyridine, D.M.G, and acetic anhydride (equation 1).

$$\underset{\text{pyridine}}{C_5H_5N} + \underset{\text{D.M.G}}{C_4H_8N_2O_2} + \underset{\substack{\text{acetic}\\\text{anhydride}}}{C_4H_6O_3} + \text{'O'} \longrightarrow \underset{\text{(III)}}{C_{13}H_{13}N_3O_3} + 3H_2O$$

$$\downarrow \; -CH_3COOH \; +H_2O$$

$$\underset{\text{(IV)}}{C_{11}H_{11}N_3O_2}$$

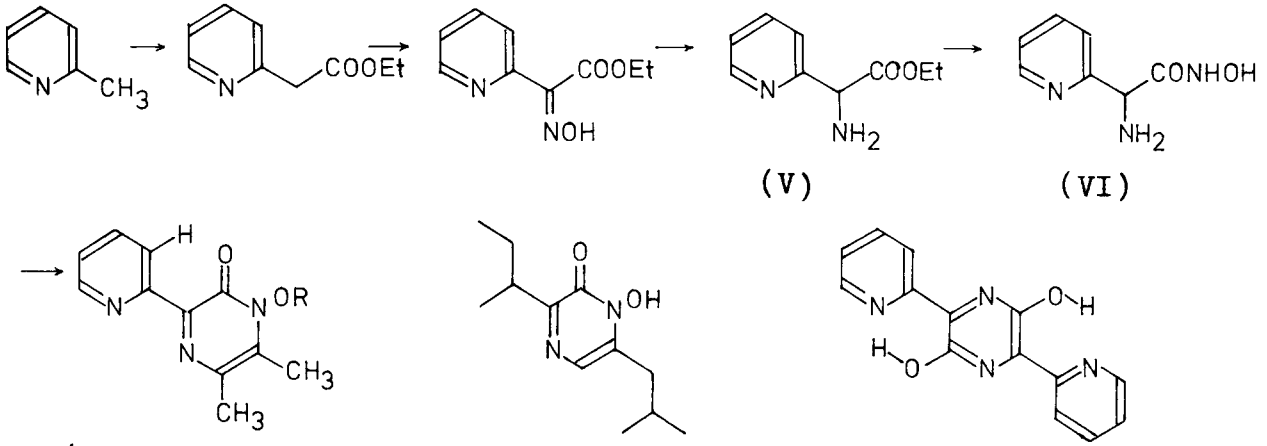
equation 1.

Bubbling oxygen through a mixture of the three components in equation 1 in the presence or absence of cobaltous acetate did not give any III, only dimethylglyoxime di-O-acetate.

The labile acetate group of III was attributed to the presence of an -N-OAc group on the basis of its i.r frequency, this being converted to -N-OH in IV. IV gave a red colour on addition to methanolic ferric chloride solution, and the cyclic hydroxamic acid structure (VIIa) was proposed for IV, and hence the structure (VIII) for III. These structures contain the components suggested above in unrearranged form, with a methyl group of an acetate unit having suffered the oxidation required in equation 1. The low field doublet resonance in the n.m.r spectra of III and IV was assigned to H3 of the 2-substituted pyridine ring. Conjugation between the two aromatic rings in VIIa and VIII might be expected to cause restricted

rotation about the pyridine-pyrazinone bond. In the favoured planar rotamers, H3 would experience deshielding by two aromatic systems, and in the particular rotamer shown would also be deshielded by the peri-carbonyl group.

The results described so far were obtained by Dr. U. Horn, the remainder by the present author. It was anticipated that compound VIIa could be independently synthesised by conversion of the known[234] ethyl 2-(2-pyridyl)-2-aminoacetate (V) to its hydroxamic acid (VI), and cyclisation of this with biacetyl to give VIIa. This compound would also be of interest as an analogue of the powerful but toxic antibiotic aspergillic acid (IX)[235].



(V) (VI)

(VIIa) R = H
(VIII) R = $COCH_3$

(IX) (X)

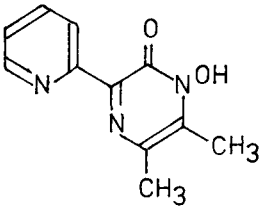
Conversion of the α-amino ester V to the hydroxamic acid VI proved troublesome at first, but was successful using hydroxylamine in aqueous alkali[236]. Attempted recrystallisation of VI from hot water caused rapid conversion to the red dimeric 2,5-dihydroxypyrazine (X). VI reacted readily with biacetyl to give compound VII.

However, the cyclic hydroxamic acid VIIa showed none of the characteristics of the deacetylated cobaloxime degradation product IV.

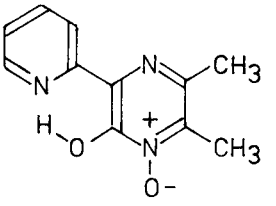
VII was a high melting point (263°) yellow crystalline solid, insoluble in most solvents except for boiling water from which it crystallised as its monohydrate. It was soluble in dilute sodium bicarbonate solution and gave an intense red colouration with ferric chloride solution - both characteristics of hydroxamic

acids. IV was not soluble in bicarbonate, although soluble in sodium hydroxide solution, and the colouration it gave with ferric chloride was found really to be insignificant in comparison. Hydroxamic acid VIIa showed no low field signal in the n.m.r spectrum (Na_2CO_3/D_2O), and the absence of a strong carbonyl band in the i.r spectrum suggested it exists as the 2-hydroxypyrazine-1-oxide tautomer (VIIb). The compound is subsequently referred to as VII.

The only resemblance to IV shown by VII was a strong peak at m/e 105 in its mass spectrum, although the major breakdown of VII involved extrusion of CO and loss of CH_3CN fragments.



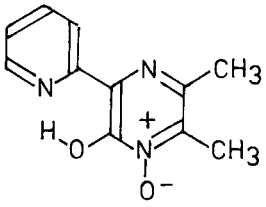
(VIIa)



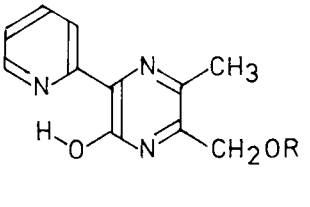
(VIIb)

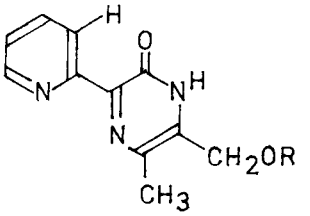
Both the free acid VII and its sodium salt were inert to a wide range of acetylating agents. This was perhaps not surprising as O-acylhydroxamic acids are known acyl-transfer agents[235].

VII did react with hot acetic anhydride, and was rapidly converted to 2-hydroxy-3-(2-pyridyl)-5-methyl-6-acetoxymethyl-pyrazine (XI), a reaction characteristic of 2-methyl heterocyclic N-oxides[237]. XI is isomeric with cobaloxime degradation product III, and, like III, is easily deacetylated, giving the hydroxymethyl analogue (XII), isomeric with IV and VII.



(VII)





(XI) R = $COCH_3$

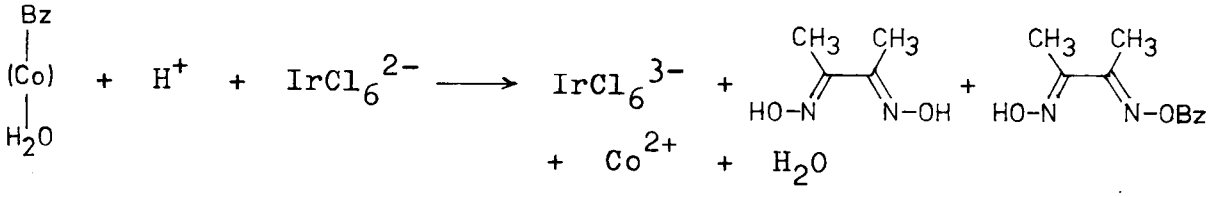
(XII) R = H

A further paradox is that in both XI and XII, although not in VII , H3 of the pyridine ring is markedly deshielded, being

isochronous with H6 (c. τ1.4) in the n.m.r spectrum in $CDCl_3$ (c.f H6 at τ1.43, H3 at τ2.12 in the spectrum of VII in Na_2CO_3/D_2O). This is presumably due to the effect of the peri-carbonyl group in the keto tautomer of the 2-hydroxypyrazines in $CDCl_3$ - exactly the effect predicted for the model compound VII to explain the low field doublet in the spectra of III and IV.

Further chemistry of VII and its derivatives and their relation to aspergillic acid is discussed in a separate section at the end of the chapter.

Despite this initial failure to solve the problem, the cobaloxime degradation product III was considered worthy of further study. No such reaction of cobaloximes, involving axial and equatorial ligands had been described, although recently Halpern reported such a reaction with hexachloroiridate-(IV) ion[238] (equation 2).



In our reaction the axial alkyl group apparently was not incorporated into the product, and it was possible that the interaction of the equatorial ligands and axial base lead to cobalt-carbon bond cleavage, a process similar to that postulated to occur during reactions catalysed by coenzyme B_{12} (see introduction to chapter 5). In the case of the cobaloxime, however, these events initiated further degradation of the complex.

The further studies involved:

i) improvement of the isolation procedure of III and IV;
ii) further conventional spectroscopic studies;
iii) chemical studies;
iv) examination of model compounds;
v) determination of the structure of IV by X-ray crystallography;
vi) a limited investigation of the reaction mechanism.

i) Isolation of III and IV.

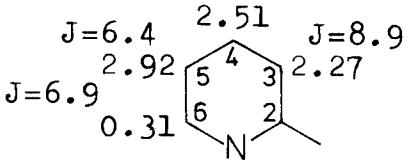
In the original isolation of III, much material was lost due to its instability. It was apparent that this mainly involved deacetylation to IV, which, in contrast, was shown to be remarkably stable (stable to refluxing in N acid or alkali for 4 hours). In a subsequent preparation on 10mM starting cobaloxime scale, the reaction was followed by n.m.r spectroscopy and run for longer - 9 days at room temperature. The mixture was then evaporated on a vacuum pump and dissolved in dichloromethane, and the solution filtered through silica gel. The filtrate was evaporated and sublimed at 100°/0.001mm to give a mixture of III and dimethylglyoxime di-O-acetate, free of inorganic material. This total mixture was deacetylated with sodium in methanol and neutralised with aqueous acid to give IV and dimethylglyoxime. The former was extracted into dichloromethane, and the latter filtered off. Evaporation of the extracts gave a 30% yield of crystalline IV almost pure by t.l.c, and this recrystallised beautifully from ethyl acetate. Subsequent studies were mostly performed on IV.

It was later found that running the reaction for 48 hours at 60° gave comparable yields. Using up to 1mM of starting cobaloxime, the crude dichloromethane extract from the reaction could be rapidly chromatographed on silica gel under suction without undue decomposition of III. Dimethylglyoxime di-O-acetate was eluted with dichloromethane, and then III with dichloromethane/chloroform (containing 2% ethanol) 1:1. The product III was pure on t.l.c, but coloured, and was finally purified by sublimation, a satisfactory system for recrystallisation not being found.

ii) Further spectroscopic data.

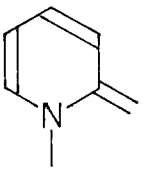
a) The preliminary attempts at structure elucidation assigned the distinctive low field resonance in the n.m.r spectra of III and IV to H3 of a 2-substituted pyridine ring. However, it was clear that if this was correct, then the doublet resonance at τ2.27 due to H6 was shifted appreciably upfield from its usual position in pyridine derivatives at c. τ1.4. Based on the original assignment, the coupling constants J_{34}= 6.9 and J_{56}= 8.9 Hz would be the inverse of the pattern in typical pyridine derivatives -

(e.g in pyridine itself, J_{34}= 7.5 and J_{56}= 5.5 Hz). Hence the low field doublet in the spectra of III and IV was reassigned to H6 as in (XIII). The coupling constants J_{34} and J_{56} are then both higher than in simple substituted pyridines, suggesting the bond localisation pattern in a 2-pyridone-type structure (XIV).[239]



τ($CDCl_3$)

(XIII)



(XIV)

b) The n.m.r spectrum of IV dissolved in NaOD showed a general upfield shift of all resonances, and rapid disappearance of the lower field methyl resonance - half time 1.3 minutes at 37°. $^2H_4$-IV was prepared in near quantitative yield by dissolving IV in NaOD, neutralising with DCl in D_2O and extracting into dichloromethane. At the time, it was thought that this was an unprecedentedly facile exchange, indicating conjugation of that methyl group with positive charge. IV was certainly not ionic, and this was interpreted as indicating a mesoionic structure for IV. The methyl protons of acetophenone oxime showed no measurable exchange within 2 hours under the same conditions.

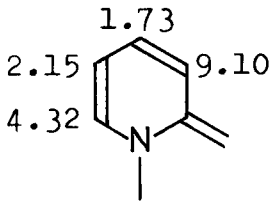
However, a recent paper[240] reported that in NaOD only the protons of the methyl group α- to the carbonyl group in butane-2,3-dione monoxime exchanged. This was verified, and under the same conditions as used for IV the half time for exchange at 37° was 3 minutes - definitely slower, but of a similar order of magnitude to the rate for IV.

c) Lanthanide n.m.r 'shift reagents' have recently come into vogue as tools in structural elucidation.[241] The n.m.r spectrum of an equimolar mixture of IV and tris(dipivalomethanato)-europium ($Eu(DPM)_3$) in $CDCl_3$ showed large downfield shifts of the non-exchangeable methyl resonance and the H3 doublet, appreciable shifts of the exchangeable methyl resonance and H6 doublet, and small shifts for the resonances due to H4 and H5 of the pyridine ring (table I).

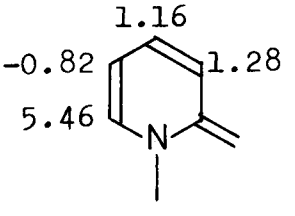
table I. N.m.r shifts in the presence of $Eu(DPM)_3$.

	$\tau(CDCl_3)$	$\tau(CDCl_3$ + 1:1 $Eu(DPM)_3)$	$\Delta\tau$	Δ_{Eu}ppm
i) compound (IV)				
s, 3H	7.56	-2.41	9.97	9.97
s, 3H (exchange in NaOD)	7.45	1.76	5.69	5.69
t, J+J' = 13.5, 1H	2.95	0.8	2.15	2.15
dd, J = 6.7,8.9, 1H	2.53	0.8	1.73	1.73
d, J = 8.9, 1H	2.23	-6.87	9.10	9.10
d, J = 6.7, 1H	0.32	-4.00	4.32	4.32
		$\tau(CDCl_3$ + 1:2 $Eu(DPM)_3)$		
ii) compound (XV)				
s, 3H	7.35	6.62	0.70	1.40
s, 3H	7.30	5.35	1.95	3.90
dd, J = 11.3,7.0 1H	2.69	2.11	0.58	1.16
d, J = 11.3, 1H	2.29	1.65	0.64	1.28
t, J+J' = 14.0, 1H	2.17	2.58	-0.41	-0.82
d, J = 6.7, 1H	1.09	-1.64	2.73	5.46

Δ_{Eu}ppm

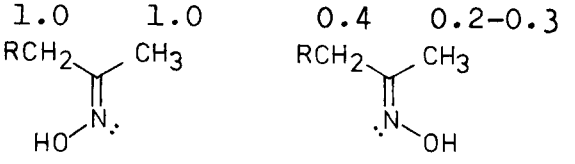


(IV)



(XV)

The shifts of the resonances in the presence of $Eu(DPM)_3$ are most informatively given in terms of Δ_{Eu}ppm, which is the magnitude of the downfield shift that would be observed in the presence of an equimolar amount of the shift reagent, assuming that the size of the shift is directly proportional to the concentration of the reagent relative to the substrate. Then the shifts of the methyl resonances of IV are not as large as those expected for isolated $\underline{CH}_3.CO$ systems - e.g for the methyl resonance in the spectrum of acetophenone, Δ_{Eu} was found to be 14.4ppm. However, the larger shift shown by the two methyl resonances of IV would fit with data reported for aliphatic methyl ketoximes[242] shown below (shifts in ppm for 1:36 shift reagent : substrate ratio).

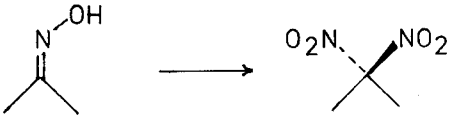


(anti) (syn)

Δ_{Eu} for the syn methyl group is 7.2-10.8 ppm, compared with 9.97 ppm observed for the non-exchangeable methyl group in IV.

iii) Chemical studies.

a) It was proposed to try some classical oxidative degradation procedures on IV. However, on adding IV to concentrated nitric acid, it dissolved over a few minutes with evolution of brown fumes, and was quantitatively converted to a new compound (XV) m.p 177°. This compound was assigned a gem-dinitro grouping, having a very strong i.r band at 1580 cm^{-1}, and showing ready loss of NO_2 twice in the mass spectrum. The molecular ion (m/e 278) and analysis ($C_{11}H_{10}N_4O_5$) agreed with the conversion:



This is a known reaction, but does not generally proceed in good yield because of the forcing conditions required.[243]

The n.m.r spectrum of XV showed resonances due to the two methyl groups slightly downfield from those in IV (τ7.56 and τ7.45 in IV, τ7.35 and τ7.30 in XV). Conversion of acetophenone oxime to the gem-dinitro derivative was shown to cause the methyl resonance to shift downfield from τ7.52 to τ7.41. This latter conversion was also achieved with concentrated nitric acid, but the dinitro derivative was accompanied by an equal amount of a second product that seems to be the result of cyclisation onto the aromatic ring, but has not been conclusively identified.

The most significant spectral differences between IV and the new compound XV were that in the n.m.r spectra the low field doublet due to H6 in IV was shifted upfield to τ1.09 in XV, and in the i.r spectra the carbonyl band at 1640 cm^{-1} in the spectrum of IV was at higher frequency (1656 cm^{-1}) in that of XV.

Compound XV did not show the mutual increase in solubility in $CDCl_3$ with $Eu(DPM)_3$ shift reagent that was observed with IV, and the shifts observed in the resultant n.m.r spectrum were small. Only the doublet due to H6 of the postulated pyridine ring of XV showed a shift slightly greater in XV than that for the corresponding resonance of IV. The triplet resonance due to H5 of XV was shifted upfield. Such upfield shifts with $Eu(DPM)_3$ have been attributed to:

- contact shifts of opposite sign to that of pseudocontact shifts[244];

- negative contribution from the angular term in the full pseudocontact shift equation:-[245]

$$\nu_i \quad \alpha \quad (3\cos^2\chi_i - 1)/d^3$$

where χ_i is the angle ∠coordinating site-Eu-H_i
and $3\cos^2\chi_i < 1$ for $54.7^\circ < \chi_i < 125.3^\circ$.

Table I compares the shifts with $Eu(DPM)_3$ observed with compounds IV and XV.

The small shifts observed for nitro compounds in general, compared with the large shifts for oximes has lead to the conclusion that the lanthanide shift reagents coordinate to nitrogen rather than to oxygen in the latter.[246] This would also fit with the finding above that resonances due to methyl groups syn to an oxime -OH group show smaller shifts than those anti to the -OH.

b) The presence of an oxime group in IV had been established by the conversion of IV to XV, and the shift reagent data on IV suggested that this was a syn methyl ketoxime. The possible existence of a CH_3CO-grouping in IV was inferred from the n.m.r and i.r spectra. With sodium hypochlorite and potassium iodide in alkaline solution, IV gave iodoform but only in about 20% yield, where the yield from butan-2-one was checked to be quantitative. All of IV was consumed, and a yellow compound could be isolated in minute yield by chromatography. This was soluble in chloroform but had m.p > 330°. The i.r spectrum showed a new carbonyl band at 1735 cm^{-1} as well as that at 1640 cm^{-1}, and the mass spectrum had a strong base peak at m/e 44 (CO_2^+), suggesting a carboxylic acid product from the iodoform reaction. However, this clearly did not fit the assignment of the carbonyl absorption at 1640 cm^{-1} to a CH_3CO-grouping in IV.

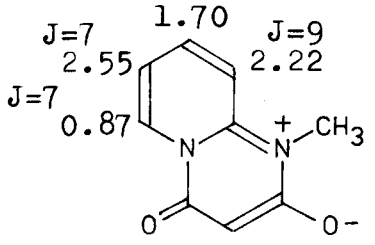
Acetophenone oxime gives the iodoform reaction with difficulty, so the complex result with IV is perhaps not so surprising now the true structure is known.

c) It was recognised that there were two methyl groups in compound IV, derived from two methyl groups of dimethylglyoxime and one of an acetate unit. By repeating the cobaloxime degradation with benzoic anhydride it was hoped to determine whether or not a phenyl analogue of III was formed. The production of such a compound would have indicated that it was one of the methyl groups of the dimethylglyoxime that suffered the oxidation, and not that derived from the acetic anhydride.

No compound having a low field doublet in the n.m.r spectrum analogous to that of III was formed by the reaction of 2-acetoxypropyl(pyridine)cobaloxime with benzoic anhydride in pyridine, indicating that oxidation of the methyl group of the acetate component occurred in the formation of III (see equation 1). It was realised that this result could also have been a consequence of the lower acylating power of benzoic anhydride compared with acetic anhydride, and this seems the only tenable explanation for this misleading result.

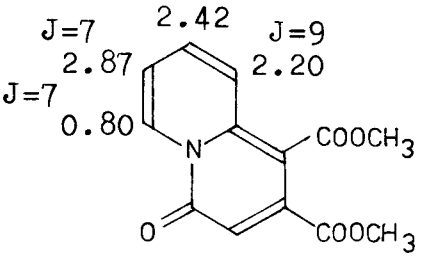
iv) Examination of model compounds.

Potts[247] reported n.m.r data for the fused pyridine compounds (XVI) and (XVII) as shown below:



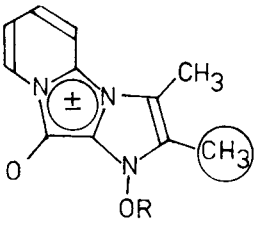
$\tau(^2H_6\text{-DMSO})$

(XVI)



$\tau(CDCl_3)$

(XVII)

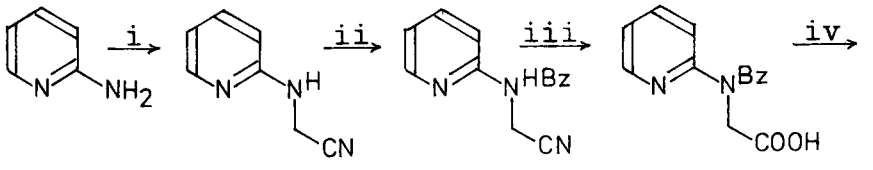


(XVIII)

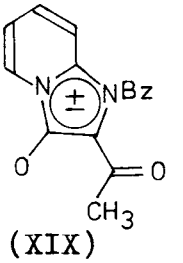
The coupling constants between the pyridine protons are similar to those in III and IV, and both XVI and XVII show deshielding of the α- proton of the pyridine ring moiety. Presumably this is due to the anisotropy of the carbonyl group attached to the pyridine nitrogen atom. Accordingly, the mesoionic structure (XVIII) was suggested for III (XVIII, R = $COCH_3$) and IV (XVIII, R = H).

Structure XVIII could be derived from pyridine, dimethylglyoxime and acetic anhydride, and the hydrogens of the ringed methyl group might be expected to exchange rapidly in base, being conjugated to that nitrogen of the mesoionic ring which bears partial positive charge.

In the light of the later finding of the reaction of IV with concentrated nitric acid, structure XVIII would not be viable, but the mesoionic anhydro(3-hydroxyimidazo[1,2-a]pyridinium hydroxide) (XIX) was prepared by a known route[248] to test the above explanation for the low field doublet in the n.m.r spectra of III and IV.



reagents: i. $HCHO/NaHSO_3/NaCN$; ii. $BzCl(=PhCH_2Cl)$
iii. NaOH; iv. Ac_2O.



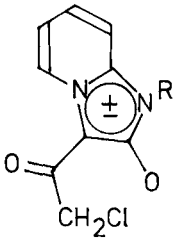
(XIX)

The α- proton of the pyridine ring component of XIX resonated at τ1.60 ($CDCl_3$), although the splitting pattern of

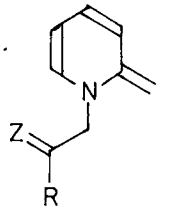
the signals from the four pyridine protons closely resembled the distinctive pattern in the spectra of III and IV.

A paper by Anderson and Friedman[249] then appeared, reporting that they had also found a compound with a highly deshielded pyridine α- proton. Similarly they had examined and rejected XIX as a model compound, but had then gone on to produce a new series of model compounds (XX) from 2-(substituted-amino)-pyridines, chloroacetic acid and chloroacetic anhydride, In the compounds XX, the pyridine α- proton resonated at c. τ0.0.

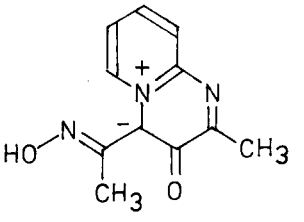
Two examples of XX were prepared (XX, R = CH_3 and R = CH_2Ph) in high yields by modification of the brief experimental details given. Their described properties were verified, but the n.m.r spectral pattern due to the pyridine protons, the u.v. spectra and the mass spectra showed no resemblances to the corresponding spectra of III and IV. The deshielding effect of the peri-carbonyl group was found to be quite well documented in the literature,[250] and was recognised in design of the initial trial structure VII for IV.



(XX)



(XXI)



(XXII)

The spectral and chemical data available at this stage were comprehensive and well-defined, but their explanation lacked both of these qualities.

i) The components of the cobaloxime degradation product III were almost certainly pyridine, dimethylglyoxime and acetic anhydride, with a 2-electron oxidation involved in their combination.

ii) The partial structure (XXI) fitted the n.m.r data. In XXI, =Z could be =O or =NOH, and R might or might not be CH_3

iii) Structure XXI (Z = NOH) explained why the low field doublet in the n.m.r spectrum of IV moved upfield on conversion to XV (c.f XXI Z = $(NO_2)_2$). If XXI (Z = NOH) was correct, probably R = CH_3

iv) Structure XXI (Z = O, R = CH_3) might have explained the exchange of the protons of one of the methyl groups of IV in base,

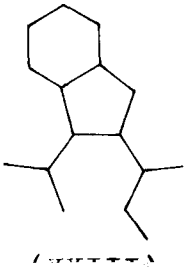
but would have been expected to give the normal iodoform reaction, and did not explain the absence of the deshielding effect in XV.

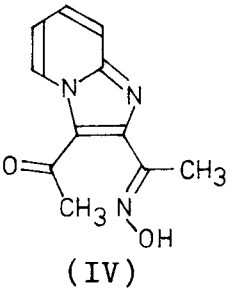
The final structure suggested for IV was (XXII). This incorporates most of the ascribed features, except that the two halves of the dimethylglyoxime component have become separated by a rearrangement at some stage during the formation. Such a novel mesoionic system might be very stable - one canonical resonance structure is that of a pyridinium ylid with the negative charge further stabilised by carbonyl and oximino groupings. In the same resonance structure the ring methyl group is conjugated to the nitrogen atom bearing positive charge, and would be expected to show rapid proton exchange in base. The deshielding effect would be due to the oximino group, analogous to, but not quite so effective as, the deshielding by the carbonyl group in XX. Conversion of the oximino grouping in IV to the dinitro grouping in XV would remove the deshielding effect.

v) Determination of the structure of IV by X-ray crystallography.

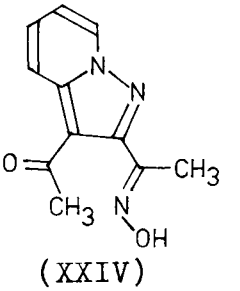
It was apparent that elucidation of the structures of III and IV by traditional methods was unlikely, and any proposed structure could only be proved correct by independent synthesis or X-ray analysis. The latter was performed under the supervision of Dr. N.W. Alcock.

The solution was obtained by direct methods, and the Fourier map showed 16 peaks corresponding to the 16 non-hydrogen atoms of the molecular framework (XXIII), from which could be derived either of the two structures IV and (XXIV). The orientation of the carbonyl group was defined by the relative intensities of the peaks on the Fourier map corresponding to carbon and oxygen and the respective bond lengths, and also by the positioning of the hydrogen atoms of the methyl group at a later stage of refinement.





(IV)



(XXIV)

The pyrazo[2,3-a]pyridine structure XXIV was excluded on the basis of intensity and temperature factor data which defined conclusively the position of the bridgehead nitrogen atom. Structure XXIV would not fit the interpretation of the n.m.r spectrum of IV where the deshielded proton is the α- proton of the pyridine ring.

A difference Fourier map gave the positions of all the 11 hydrogen atoms, but these were not further refined. The final R-value was 0.089.

The structures of the O-acetate III and the dinitro-derivative XV follow clearly from that defined for IV - 2-(1-(E)-hydroxyiminoethyl)-3-acetyl-imidazo[1,2-a]pyridine - and the spectral and chemical data can now be correlated with these structures.

a) The predicted component molecules - pyridine, dimethylglyoxime and acetic anhydride - can be clearly visualised in III in unrearranged form, the oxidation having occurred at one of the dimethylglyoxime methyl groups. The cobaloxime alkyl ligand is not incorporated in III.

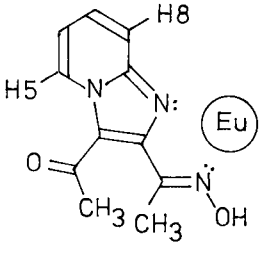
b) The bicyclic ring system in IV is planar with the 3-acetyl group almost in this plane ($\varnothing = 12.4^{\circ}$) but the 2-(1-(E)-hydroxyiminoethyl) substituent twisted 60.0° out of this plane. The deshielding of H5 in III and IV is due to the peri-carbonyl group.[250] The rotamer observed in the crystalline state is presumably not the exclusive configuration in $CDCl_3$, but there will be restricted rotation about the CH_3CO-C bond due to conjugation with the 10e hetero-aromatic system, and the rotamer shown may be favoured over the alternative planar rotamer on steric grounds.

The reduced deshielding of H5 in the dinitro derivative XV is not so immediately apparent, and was probably the most misleading factor in the previous attempts at structural elucidation. However, the greater bulk of the 2-(1,1-dinitroethyl) substituent in XV could make the planar orientation of the 3-acetyl group much less favourable than in III or IV, and this is corroborated by the shift to higher frequency of the carbonyl stretching frequency in XV (1656 cm^{-1}) relative to that in III and IV (1640 cm^{-1}), indicating less conjugation of the carbonyl group with the aromatic system in XV.

The splitting pattern of the pyridine ring proton resonances is similar to that reported for other imidazo[1,2-a]-pyridines.[239]

c) The changes in the n.m.r spectra of IV and XV observed in the presence of $Eu(DPM)_3$ (table 1) provided no conclusive structural information, except for suggesting the presence of a methyl ketoxime moiety in IV, but can be interpreted in the knowledge of the actual structures.

IV has two sites for complexation with the europium. The stronger coordination would be through the nitrogen of the 2-(1-(E)-oximinoethyl) substituent and N1 of the ring system, causing a shift of the non-exchangeable methyl resonance as expected for that syn to an oxime -OH, but also a large shift of the doublet resonance due to H8. Coordination to the oxygen of the 3-acetyl group may be sterically hindered, the acetyl (exchangeable) methyl group and H5 being shifted appreciably but less than might be expected for such a ketone.



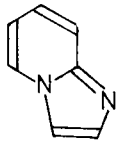
(IV)

The shift reagent does not complex with nitro groups[246], and hence in the n.m.r spectrum of XV with $Eu(DPM)_3$ only the acetyl methyl group and H5 have their resonance positions appreciably shifted.

d) The u.v spectral data - so often valuable in the identification of heterocyclic compounds - does not seem to show any conspicuous features for the recognition of imidazo[1,2-a]-pyridines.(table II).

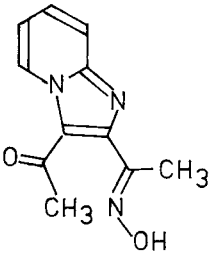
Similarly the mass spectra provide little structural information, other than confirming the presence of the two nitro groups in XV.

table II. u.v spectra of some imidazo[1,2-a]pyridines.



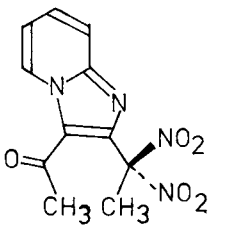
$\lambda_m$nm	ε_m
221	28,400
226	23,600
278	3,920
298	3,400

(EtOH)
ref. 251



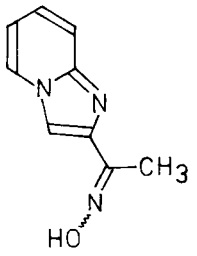
$\lambda_m$nm	ε_m
219	16,800sh
227	17,350
252	25,000
299	7,230sh
311	7,510br

(MeOH)



$\lambda_m$nm	ε_m
219	21,600
248	12,030
254	10,190sh
302	5,560sh
318	5,710
330	5,090

(MeOH)



$\lambda_m$nm	ε_m
234	30,850
278	4,000sh
288	4,270sh
306	5,240sh
315	5,580
328	4,090sh

(MeOH)

vi)Studies on the mechanism of the reaction.

a) The mechanism of oxidation.

When the reaction of 2-hydroxypropyl(pyridine)cobaloxime I with a 10 molar excess of acetic anhydride in pyridine was followed by n.m.r spectroscopy of aliquots worked up at intervals, it was observed that conversion to the 2-acetoxypropyl derivative II was at least 90% complete after 13 hours at room temperature, and that the signals due to II slowly disappeared to be replaced by those of III and dimethylglyoxime di-O-acetate. Dr. Horn claimed good yields of III after 32 hours at room temperature, but it was found that the cobaloxime was not completely degraded until after at least 7 days at room temperature.

Although cobaloximes are known to form complexes with oxygen[252], it was very difficult to incorporate molecular oxygen into a mechanistic scheme for formation of III. Assuming that the metal was converted to cobaltous(II) acetate during the degradation of the cobaloxime (cobalt(III)), then it underwent a one electron reduction and was a potential source of oxidation.

It was rigorously shown that the cobaloxime degradation to III was not oxygen-dependent by following parallel oxygenated and degassed runs by n.m.r spectroscopy, and quantitative analysis of the products from reactions degassed and sealed in a vial. Similarly the degradation was found not to require light. Strong irradiation of the reaction mixture with visible light caused a significant reduction in the yield of III, presumably due to alternative decomposition routes. Test experiments were performed with c. 0.3mM 2-hydroxypropyl(pyridine)cobaloxime and run for 48 hours at 60°. The resulting black mixtures were evaporated under high vacuum at room temperature or below, and the products analysed by chromatography as described in section (i). Yields of III were consistently about 0.27 mole, accompanied by 0.7-1.0 mole of dimethylglyoxime di-O-acetate per mole of cobaloxime (table IV).

Reexamination of Dr. Horn's experiments showed that his reactions under nitrogen had been worked up after 24-32 hours - when conversion of I to II was complete but little degradation to III had occurred -by quenching with water and extracting into dichloromethane. By contrast, after running for a similar time, the experiments under oxygen had been evaporated on a rotary

evaporator with the bath at 50° for 4-5 hours - ideal conditions for the degradation of II to III to take place.

Conversion of a cobaloxime (cobalt(III)) to cobaltous acetate (cobalt(II)) is a one electron oxidation. Formation of III from pyridine, dimethylglyoxime and acetic anhydride is a two electron oxidation (equation 1). Thus presumably two molecules of cobaloxime are required to form one of III, and the 27% molar yields of III are in fact 54% of the theoretical maximum. If formation of a molecule of III involves conversion of cobalt(III) to cobalt(I) and its reoxidation to stable cobalt(II), then it is surprising that oxygen has no effect since cobalt(I) species are generally very susceptible to oxygen. Preferential reoxidation by a second cobalt(III) species must involve a very specific interaction during the actual formation of compound III rather than 'at random' afterwards.

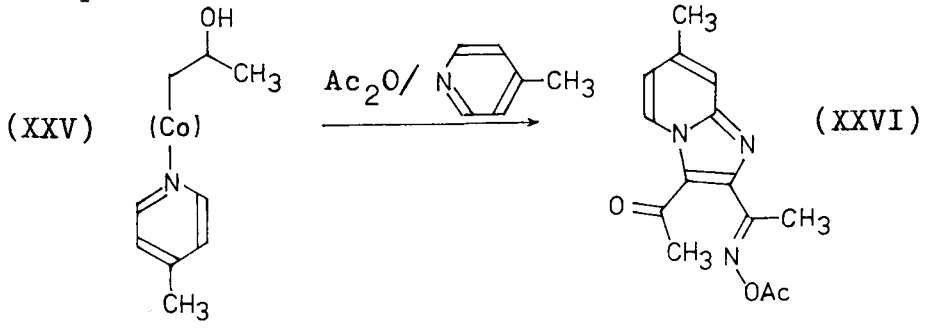
i.e $2Co(III) \longrightarrow 2Co(II) + \text{compound III}$

and not $Co(III) \longrightarrow Co(I) + \text{compound III}$

$Co(I) \xrightarrow{Co(III)\ \text{or}\ O_2} Co(II)$

b) Rôle of the axial base.

When 2-hydroxypropyl(4-methylpyridine)cobaloxime (XXV) was reacted with acetic anhydride in 4-methylpyridine for 48 hours at 60°, a 16% yield of the expected homologue (XXVI) of III was obtained. This was only characterised spectroscopically using material pure on t.l.c but coloured.



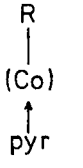
c) Rôle of the second axial ligand.

2-hydroxyethyl(pyridine)cobaloxime (XXVII) and methyl-(pyridine)cobaloxime (XXVIII) both gave III with acetic anhydride and pyridine, but in lower yield and after prolonged reaction times

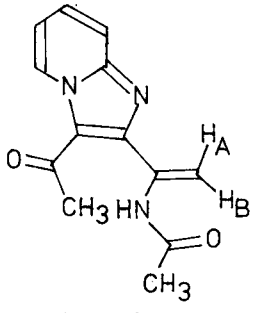
relative to the results with 2-hydroxypropyl(pyridine)cobaloxime I. The former cobaloxime XXVII showed very little III after 11 days at room temperature, a 16% yield of III being isolated after a further 7 days at 60°.

The reaction mixture with methyl(pyridine)cobaloxime (XXVIII) turned scarlet within 1 hour - a characteristic colour seen during generation of cobalt(I) species during cobaloxime syntheses. The n.m.r spectra of aliquots from this reaction showed that the signal due to the cobaloxime-$C\underline{H}_3$ disappeared after 3 days, but that formation of III continued until after 7 days at room temperature. After 7 days at 60° a 14% yield of III was isolated, accompanied by only 16% of dimethylglyoxime di-O-acetate. Further elution of the column in this case gave a new compound (XXX) in about 5% yield. The structure of XXX was determined by i.r, n.m.r and mass spectral data, including an accurate mass measurement on the molecular ion.

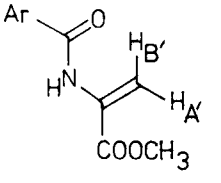
XXX was subsequently isolated in a similar yield from a run with 2-hydroxyethyl(pyridine)cobaloxime XXVII. It has not been sought in reactions with 2-hydroxypropyl(pyridine)cobaloxime I, but extended reaction times in this case reduced the yield of III to about 20% (after 6 days at 60°). XXX is an analogue of III formed by reduction, and the initial results might suggest that it is formed from III - rather than in addition to III - by some reducing species in the reaction mixture after the initial degradation of the cobaloxime to III.



(XXVII) R = CH_2CH_2OH
(XXVIII) R = CH_3
(XXIX) R = Br



(XXX)



(XXXI)

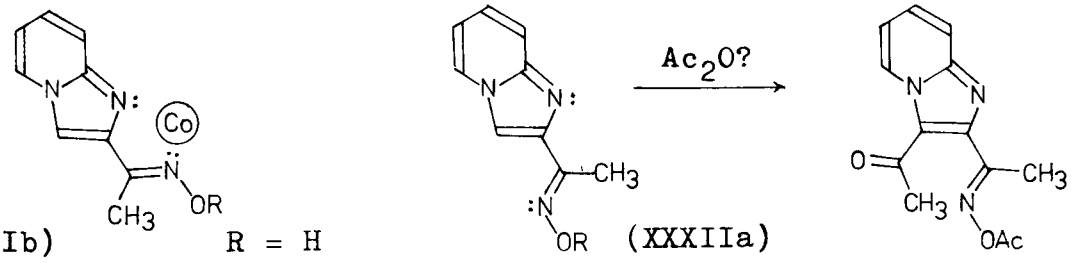
Bromo(pyridine)cobaloxime (XXIX) gave no III, only dimethylglyoxime di-O-acetate even after prolonged reaction.

In the i.r spectrum of XXX the 3-acetyl carbonyl band is at slightly lower frequency (1638 cm^{-1}) than that in the spectrum

of III (1640 cm^{-1}), although in the n.m.r spectrum of XXX $\underline{H}5$ resonates at τ0.47 - to slightly higher field compared with that in the spectrum of III (τ0.31). Like the 2-(1-(E)-hydroxyiminoethyl) group of IV, the enamide substituent at C2 of XXX is expected to be planar, but probably twisted out of the plane of the heteroaromatic ring system to allow the acetyl group at C3 to be approximately in this latter plane. The vinylic protons of XXX are not coupled to one another, but are widely separated in chemical shift (τ4.98 and τ3.61), and the lower field vinylic proton resonance is assigned to $\underline{H}_B$, deshielded by the acetamido-carbonyl group. The resonance due to $\underline{H}_B$ is a singlet while that due to $\underline{H}_A$ is a doublet (J = 1.0Hz) which collapses to a singlet on double irradiation at the position of the N-$\underline{H}$ resonance or on deuterium exchange of the N-$\underline{H}$ proton. Only the proton $\underline{H}_A$ can couple with the N-$\underline{H}$ proton by long-range 'W-coupling'. An exactly similar example (XXXI) was reported recently[253] ($\underline{H}_A$, τ4.1 (d,J=1.5Hz); $\underline{H}_B$, τ3.45 (s)).

d) A possible intermediate.

Imidazo[1,2-a]pyridines undergo electrophilic substitution readily at the 3-position.[254] Hence the primary product of the cobaloxime degradation may be 2-(1-(E)-acetoxyiminoethyl)-imidazo[1,2-a]-pyridine (XXXIII) which reacts with acetic anhydride to give III.

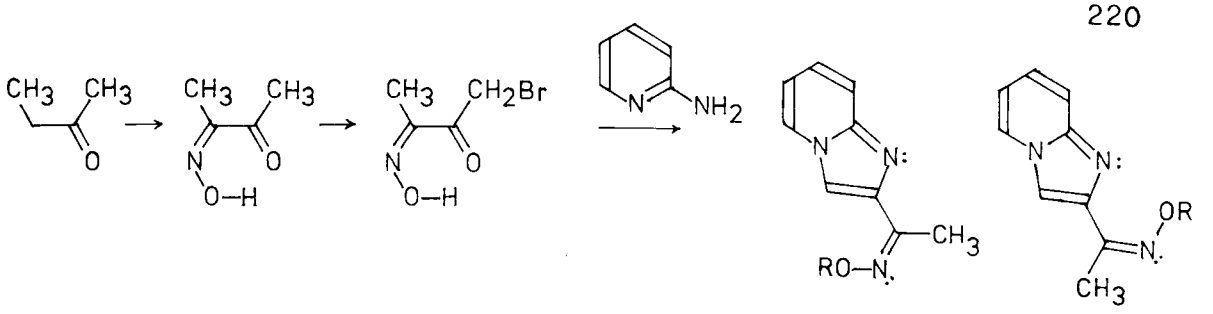


(XXXIIb) R = H (XXXIIa)

(XXXIIIb) R = $COCH_3$ (XXXIIIa) (III)

2-Aminopyridine and 1-bromo-3-hydroxyiminobutan-2-one reacted smoothly to give a compound thought to be (XXXII). However, its derivation from 3-hydroxyiminobutan-2-one prepared by nitrosation of butan-2-one probably means that the methyl group and oxime-OH have the anti-configuration in this series, i.e the product obtained was 2-(1-(Z)-hydroxyiminoethyl)-imidazo[1,2-a]pyridine (XXXIV).

Reaction of XXXIV with acetic anhydride and pyridine in the presence or absence of cobaltous acetate gave only the O-acetate (XXXV) - making three compounds in addition to IV with the formula $C_{11}H_{11}N_3O_2$ isolated during this work!



R = H (XXXIVa) (XXXIVb)

R = $COCH_3$ (XXXVa) (XXXVb)

The failure of XXXIV to acetylate at C3 under the conditions of the cobaloxime degradation may exclude such a compound as an intermediate in the reaction. However, it is quite possible that XXXIII could be activated to electrophilic attack by coordination to cobalt as in XXXIIIb, this being impossible in the isomeric compound XXXVb. Compound XXXV should be acetylated at C3 by acetyl chloride in the presence of aluminium chloride, and the identity or otherwise of the product with III would clarify these results.

e) A reaction mechanism.

With the results available, any reaction scheme proposed will of necessity be hypothetical.

The cobalt is probably the oxidising agent in the formation of III from alkylcobaloximes, and may be responsible for correct orientation of at least some of the reaction components. One axial ligand does not appear in the product III, but its nature is not irrelevant. The 2-acetoxypropylcobaloximes are very much more rapidly converted to III than are the other alkylcobaloximes studied, and bromo(pyridine)cobaloxime did not give III.

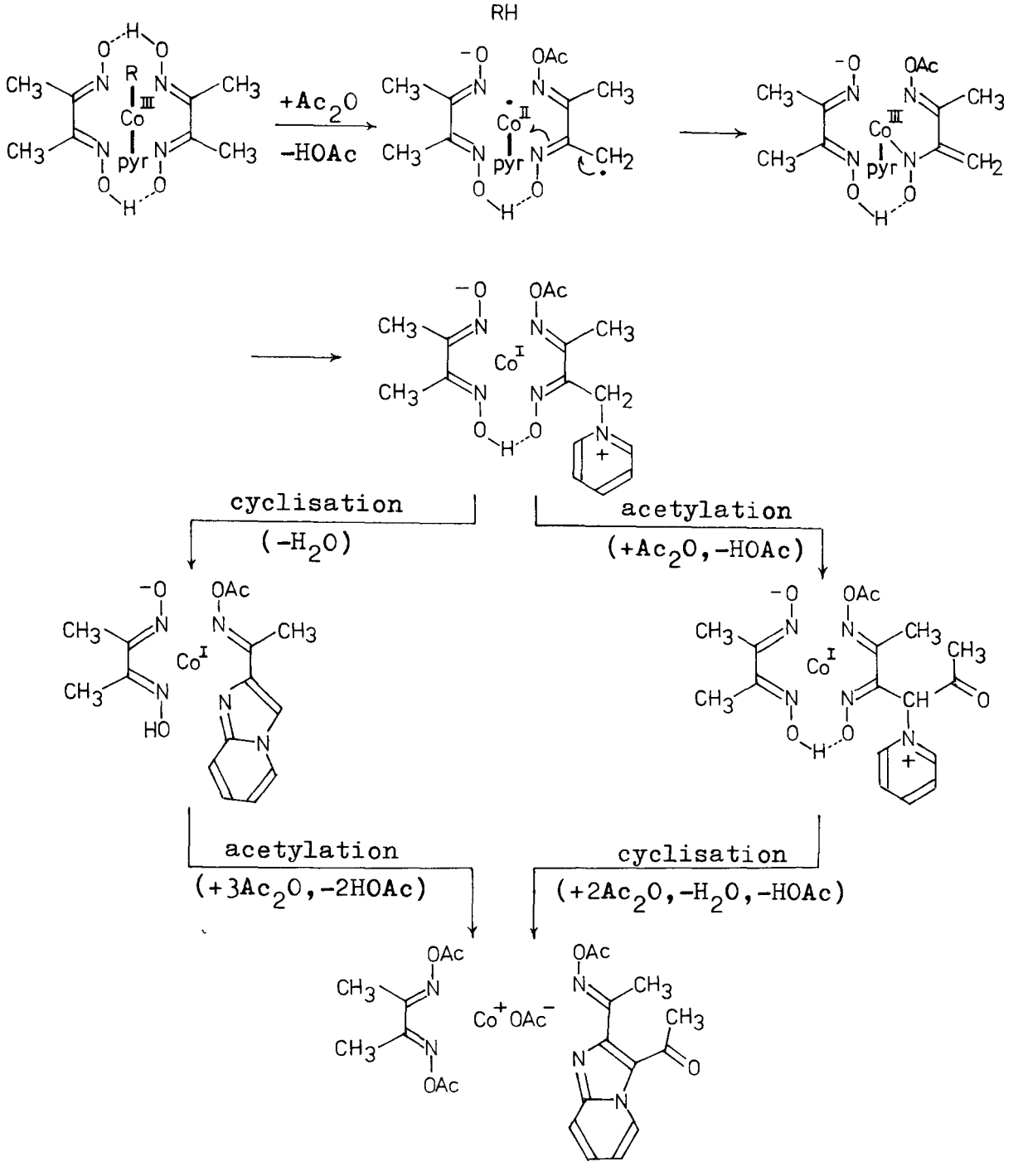
An important step in the degradation, and possibly the one diverting the reaction to formation of III rather than simple fragmentation to cobaltous acetate and dimethylglyoxime di-O-acetate, must be activation of one of the methyl groups of the dimethylglyoxime moiety destined to be incorporated into III. In scheme 1 O-acetylation of the cobaloxime dimethylglyoximate ligand disrupts the equatorial ligand system leading to homolytic cobalt-carbon bond cleavage, and hydrogen abstraction from the equatorial ligand by the departing alkyl radical. Nucleophilic attack by pyridine with concomitant reduction of cobalt(III) to cobalt(I) could be followed by cyclisation to the coordinated 2-(1-hydroxyiminoethyl)-imidazo[1,2-a]pyridine (c.f XXXIIIb) suggested above, which is

acetylated at C3. Alternatively acetylation could precede cyclisation via a pyridinium ylid.

The failure, real or apparent, of benzoic anhydride to give a phenyl analogue of III by reaction with cobaloximes might be due to its lower acylating power. It was also not too soluble in the reaction medium, and benzoyl chloride might produce the desired result.

A mechanism for reactions catalysed by coenzyme B_{12} has been proposed[169] (see introduction to chapter 5). One of the two essential steps in this scheme is cobalt-alkyl bond cleavage and reformation, and it was suggested that this was controlled by the enzyme through the ligand system of the coenzyme. The cobaloxime degradation described here may provide a chemical analogy for cobalt-carbon bond cleavage controlled through the equatorial ligand system.

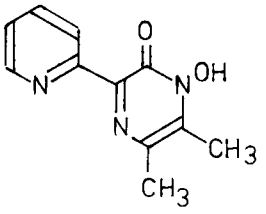
SCHEME I.



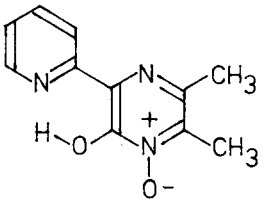
(III)

$$\begin{matrix} R \\ | \\ (Co) \\ | \\ pyr \end{matrix} + 5Ac_2O \longrightarrow (III) + DMG\text{-}diOAc + Co^{+}OAc^{-} + RH + 5HOAc$$

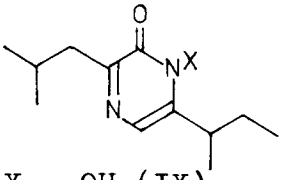
Chemistry of 'cyclic hydroxamic acid' (VII) - comparison with aspergillic acid (IX).



(VIIa)

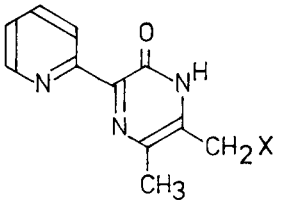


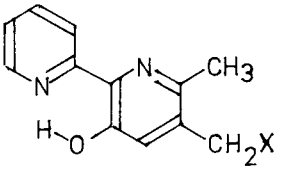
(VIIb)



X = OH (IX)
X = H (XXXVII)

The structure of VII was proven by its method of formation, its spectral data, and also by its reduction to the 2-hydroxypyrazine (XXXVI). This was obtained in only 12% yield by refluxing for 12 hours with zinc and acetic acid, and in 32% after 4 hours with zinc and acetic acid at room temperature. In the original structural elucidation of aspergillic acid IX, Dutcher found that treatment with zinc and acetic acid gave tetrahydro-desoxyaspergillic acid, but hydriodic acid gave desoxyaspergillic acid (XXXVII).[255] Refluxing VII with phosphorus and iodine in acetic acid gave the desoxy derivative XXXVI in 66% yield.





X = H	(XXXVIa)	(XXXVIb)
X = $OCOCH_3$	(Xa)	(Xb)
X = OH	(XIa)	(XIb)

Acetic anhydride converted VII to the 2-hydroxy-6-acetoxymethylpyrazine XI as described earlier. This was assumed to be the 6-acetoxymethyl rather than the 5-acetoxymethyl isomer by analogy with results reported in the literature, where pyrazine-1-oxides with 2- and/or 6-methyl substituents, but not those with 3- and/or 5-methyl groups, react with acetic anhydride to give acetoxymethylpyrazines.[256] However, XI was obtained in only 50% yield from VII, and a number of other compounds were present. Deacetylation of XI in methanolic potassium hydroxide proceeded rapidly and in good yield to XII.

The three derivatives XI, XII and XXXVI were all very similar compounds - pale yellow crystals from petrol, m.p approximately 120° - and quite different from the parent compound VII - yellow crystals insoluble in most solvents, m.p 263°. The i.r spectra of the former three compounds did not show much resemblance to that of VII, but still lacked a strong carbonyl absorption. In the n.m.r spectrum of XI there was a broad 1H absorption at τ-4.46, suggesting a hydrogen-bonded O<u>H</u> rather than an amide N<u>H</u> proton. The enolic form is probably favoured in all the four compounds - c.f VIIb, XIb, XIIb, and XXXVIb - by the possibility of hydrogen bonding of the hydroxyl group to the pyridine nitrogen atom.

In the absence of other factors, 2-hydroxypyridine and its N-oxide are thought to exist predominantly in the keto form, and the pyrazine derivatives likewise.[257] Thus aspergillic acid IX and desoxyaspergillic acid XXXVII probably exist as the keto tautomers, and their u.v spectra do not resemble those of the analogues VII and XXXVI respectively (table III). It is difficult to determine the effect of the 3-(2-pyridyl) substituent in the latter two compounds on their u.v spectra.

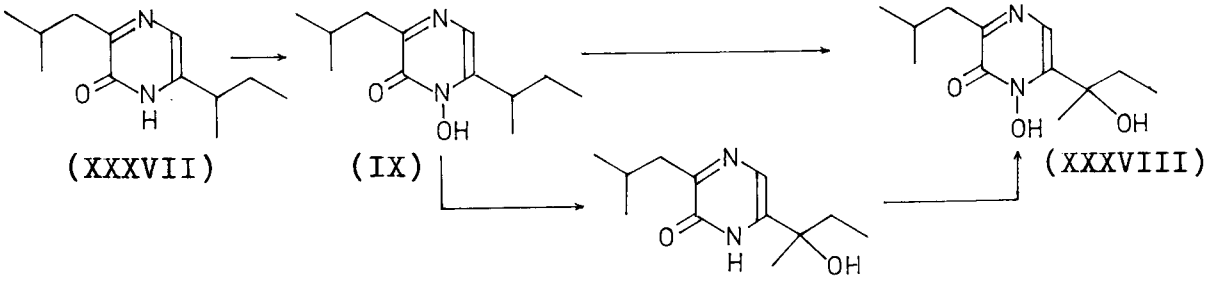
table III. <u>u.v data for aspergillic acid derivatives and analogues</u>.

aspergillic acid (IX)		(VII)		desoxy aspergillic acid (XXXVII)		(XXXVI)	
$\lambda_m$nm	ε_m	$\lambda_m$nm	ε_m	$\lambda_m$nm	ε_m	$\lambda_m$nm	ε_m
234	6,500	232	15,900	228	7,000		
		256	9,000sh			244	10,770
328	8,300			325	8,400	340	19,970
		372	11,000				
		433	2,290sh				
ref. 258 (EtOH)		(MeOH)		ref. 258 (EtOH)		(MeOH)	

However, in the n.m.r spectra ($CDCl_3$) of the three derivatives XI, XII and XXXVI, <u>H</u>3 of the pyridine ring is deshielded so that it resonates at c. τ1.4, in a position similar to <u>H</u>6. This effect is not observed in VII (<u>H</u>3 at τ2.12, <u>H</u>6 at τ1.43) although the solvent is, of necessity, different (Na_2CO_3/D_2O). This specific deshielding of <u>H</u>3 must be due to the <u>peri</u>-carbonyl group of the keto form (c.f XIa, XIIa, XXXVIa).

It is also of interest that the action of acetic anhydride on aspergillic acid has not been reported. However, hydroxyaspergillic acid has been isolated from the same fungus and shown to have the structure (XXXVIII).[259] This is analogous to the compound XII obtained from the aspergillic acid analogue VII and acetic anhydride and subsequent deacetylation. The latter step has been shown to proceed readily in our compounds, and Dutcher reported that neither hydroxyaspergillic acid nor its desoxy derivative could be acetylated under normal conditions for a secondary alcohol. Biosynthetic studies have shown that desoxyaspergillic acid XXXVII is a precursor of aspergillic acid IX,[260] and that aspergillic acid is a precursor of hydroxyaspergillic acid.[261] Thus the fungus is capable of oxidising certain 2-hydroxypyrazines to their 1-oxides. Although aspergillic acid could be converted to hydroxyaspergillic acid by a direct hydroxylation of the side chain (path A), our results show the chemical possibility of converting an aspergillic acid analogue VII to a desoxy derivative XII with an oxygen function specifically at the 1-position of the 2-alkyl substituent. Thus aspergillic acid could be converted to the desoxy-hydroxyaspergillic acid by an analogous process, and this then oxidised (path B).

The chemical reaction of 2-alkyl heterocyclic 1-oxides with acetic anhydride is thought to proceed by acylation of the N-O function, and rearrangement <u>via</u> an ion pair[237] - a process quite feasible in biological systems



EXPERIMENTAL.

1) Isolation of III and IV, and also XXVI and XXX.
2) Reactions of IV - conversion to XV.
3) Synthesis of possible intermediates XXXIV and XXXV.
4) Model mesoionic compounds XIX and XX.
5) Hydroxamic acid VII and its derivatives.
6) X-ray crystallographic data on IV.

1) Isolation of III.

2-Hydroxypropyl(pyridine)cobaloxime (158mg, 0.37mM) was dissolved with warming in dry pyridine (1.4ml) and redistilled acetic anhydride (0.4ml) added. The mixture, in a stoppered test tube, was heated in an oil bath at 60° for 48 hours.

The black mixture was evaporated under high vacuum at room temperature or below (2 hours). The residue was dissolved in chloroform (containing 2% ethanol) (25ml) and shaken with silica gel N (for t.l.c) (1g), and then filtered to give a pale brown filtrate. The black residue was washed with more chloroform (total c. 60ml). Further washing with ethyl acetate gave very little more material containing none of the desired products.

The chloroform washings were combined and evaporated. The residue (118mg) was chromatographed on silica gel N (4g) under suction. Elution with dichloromethane gave white crystalline dimethylglyoxime di-O-acetate (81mg, 0.41mM), and then with 25% and 50% chloroform in dichloromethane gave III (25mg, 0.097mM) as coloured crystals, pure on t.l.c (R_f0.4 in 5% MeOH/$CHCl_3$; R_f0.3 in EtOAc/benzene 1:1). This material could be sublimed (100°/0.001mm) to obtain white crystals.

Using this procedure, good agreement was obtained between the results of parallel experiments, and table IV shows the results of experiments done under this method of analysis to determine the effects on the reaction of a) the presence or absence of oxygen;
b) the nature of the cobaloxime.
c) The effect of light on the degradation to III was determined by quantitative analysis by n.m.r spectroscopy of aliquots from appropriate reaction mixtures run at room temperature.

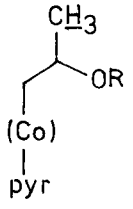
table IV. Experiments to determine the effect on the cobaloxime degradation of a) the presence or absence of oxygen;
b) the nature of the cobaloxime component.

	temp	time	mole % D.M.G di-OAc	mole % (III)
i) 2-hydroxypropyl(pyridine)cobaloxime.				
O_2 bubbled through, in daylight	60°	48hr	70	29
sealed in air, in daylight	60°	48hr	83	29
sealed in air, in dark	60°	48hr	93	19.
degassed in Schlenk tube, in daylight	60°	48hr	107	26
degassed in a sealed vial, in daylight	60°	48hr	108	27
sealed in air, irradiated by a flood lamp	60°	48hr	93	12
ii) 2-hydroxyethyl(pyridine)cobaloxime.				
sealed in air, in daylight (by n.m.r)	R.T	11 day	tr	tr
	60°	144 hr	74	16
iii) Methyl(pyridine)cobaloxime				
sealed in air, in daylight	60°	144 hr	16	14
iv) Bromo(pyridine)cobaloxime	R.T	212 hr	50	0
	60°	144 hr	60	0
v) 2-hydroxypropyl(4-methylpyridine)-cobaloxime	60°	48hr	77	16 (XXVI)

R.T = room temperature; D.M.G di-OAc = dimethylglyoxime di-O-acetate.
tr = trace;

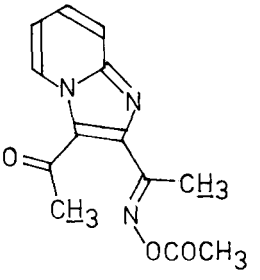
c) 2-Hydroxypropyl(pyridine)cobaloxime (0.427g, 1mM) was dissolved with warming in pyridine (4ml) in a stoppered test tube, and acetic anhydride (1ml) added. The mixture was stood at room temperature, and at intervals aliquots (0.5ml) were withdrawn, evaporated under high vacuum at room temperature (20 minutes), dissolved in dichloromethane and filtered through a Celite pad. The filtrate was evaporated and dissolved in $CDCl_3$ (0.4ml) and the n.m.r spectrum taken.

Ratios of starting material, product III and dimethylglyoxime di-O-acetate were estimated by integration of the signals shown below at the positions as they occurred in the spectrum of the mixtures.



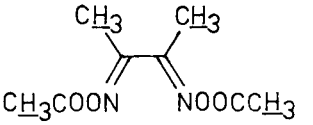
τ8.92 (d,J=6.0,3H)

(s.m)



τ7.46 (s)
7.42 (s)
(III)

total 6H



τ7.78 (s)
7.76 (s)
from III 7.79 (s)

total 12H + 3H from III

mixture A - in daylight.

mixture B - wrapped in aluminium foil.

Table V shows the analyses at intervals. There is no significant difference in the reactions in daylight (A) and in the dark (B) up to c. 50% conversion. These results also give a good idea of the time scale of the degradation at room temperature.

	24hr		38hr		48hr		72hr		144hr	
	A	B	A	B	A	B	A	B	A	B
s.m	72%		58%	60%	55%	55%	38%	38%		14%
D.M.G di-O-OAc	13		23	17	20	19	27	24		34
(III)	15		19	23	25	26	35	38		52

table V.

Larger scale preparation of IV.

2-Hydroxypropyl(pyridine)cobaloxime (3.63g, 8.5mM) was dissolved with warming in dry pyridine (30ml) and redistilled acetic anhydride (9ml, 90mM) added. The mixture was stirred at room temperature with exclusion of moisture, and the reaction monitored by withdrawing aliquots (0.5ml) at intervals, evaporating and examining their n.m.r spectra ($CDCl_3$). Formation of 2-acetoxypropyl(pyridine)cobaloxime was 90% complete after 13 hours.

After 9 days the mixture, less 6 aliquots (10%), was evaporated (0.05mm), and the residue dissolved in ethyl acetate and the evaporation repeated. The residue was filtered through silica gel after dissolving in dichloromethane, and the total dichloromethane washings evaporated to give 1.28g of a mixture of III and dimethylglyoxime di-O-acetate. Washing the residue with ethyl acetate gave 0.080g of dark oil containing a little III, but which could not be purified further. No alkyl cobaloxime was present.

The oily dichloromethane eluate was sublimed ($100^{\circ}/0.001$mm) to give white crystals (0.825g). This was added to a solution of sodium (0.23g, 10mM) in methanol (20ml). T.l.c (5% MeOH/$CHCl_3$) showed immediate conversion of III (R_f0.4) to IV (R_f0.2). After standing overnight, the solution was evaporated, and water and N HCl added until the mixture was exactly neutral to litmus. IV was extracted into dichloromethane (3 portions of 30ml), dimethylglyoxime was insoluble in water or dichloromethane. The extracts dried and evaporated gave white crystalline IV (0.50g, 2.3mM), and recrystallisation from hot ethyl acetate gave colourless plates (0.30g) m.p 190°, and a second crop (0.10g) m.p 189°.

(III) 2-(1-(E)-acetoxyiminoethyl)-3-acetyl-imidazo[1,2-a]pyridine.
(data from sample isolated by Dr. Horn by p.l.c, sublimation and recrystallisation from carbon disulphide)

m.p 112°

i.r ($CHCl_3$) 1775s,1640s cm^{-1}.

n.m.r 100MHz ($CDCl_3$) τ7.73 (s,3H)
(fig.1) 7.43 (s,3H)
7.36 (s,3H)

(continued...

τ2.92 (dd, $J_{56}+J_{67}$=13.5, 1H) H6
2.51 (dd, J_{67}+6.5, J_{78}=8.9, 1H) H7
2.27 (d, J_{78}=8.9, 1H) H8
0.31 (d, J_{56}=6.9, 1H) H5

m.s m/e 259(11) $[C_{13}H_{13}N_3O_3]$ (M), 217(26) $[C_{11}H_{11}N_3O_2]$, 201(35), 200(B) $[C_{11}H_{10}N_3O]$ (217-OH*), 186(19) $[C_{10}H_8N_3O]$ (201-CH_3), 185(17) $[C_{10}H_7N_3O]$ (200-CH_3), 170(32) $[C_9H_4N_3O]$ (185-CH_3), 158(12), 145(21), 144(26), 143(18), 105(47) $[C_6H_5N_2]$, 90(14), 79(21), 78(62) (105-27*), 60(18), 51(15) (78-27*), 45(18), 43(50).

$C_{13}H_{13}N_3O_3$ C60.22, H5.05, N16.21%
found C60.03, H4.84, N16.56%

(IV) 2-(1-(E)-hydroxyiminoethyl)-3-acetyl-imidazo[1,2-a]pyridine.

m.p 190°

i.r ($CHCl_3$) 3585m, 3320m(br), 1640s cm^{-1}.

n.m.r ($CDCl_3$) similar to that of III except for absence of signal at τ7.73, and gain of signal at τ0.70 (br,1H)

u.v (MeOH) 219nm (ε16,800)sh (MeOH/HCl) 210nm (ε16,630)
227nm (ε17,350) 246.5nm (ε20,650)
252nm (ε25,000) 282nm (ε9,110)
299nm (ε7,230)sh
311nm (ε7,510)br

m.s similar to that of III except for molecular ion; given in detail for comparison with deuterated compound below.
m/e 218(14), 217(B) $[C_{11}H_{11}N_3O_2]$ (M), 202(19), 201(18), 200(90) (217-17*), 185(10) (217-32*), 174(7) (217-43*), 170(10), 158(8) (200-42*), 145(14), 144(22), 143(14) (202-59*), 105(73), 90(74), 79(33), 78(78) (105-27*), 51(18) (78-27*), 43(24).

molecular weight: osmomometric ($CHCl_3$) 221.

$^2H_4$-(IV).2-(1-(E)-$^2H_1$-hydroxyiminoethyl))-3-($^2H_3$-acetyl)-imidazo-[1,2-a]pyridine.

IV (40mg, 0.18mM) was dissolved in 1.94N NaOD (1ml) for 10 minutes, neutralised with DCl in D_2O, and extracted into dichloromethane. The extracts dried and evaporated gave 40mg crystalline material, m.p 190°.

i.r (CH_2Cl_2) 3555m,3300-2800w,1635s cm^{-1}.

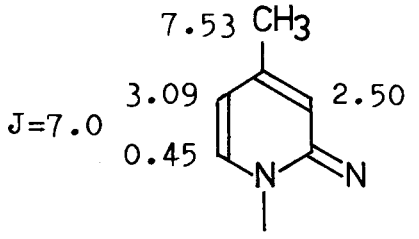
n.m.r ($CDCl_3$) identical to that of IV except for complete absence of the lower field $C\underline{H}_3$ singlet (τ7.45) and the broad 1H resonance (τ0.70). The higher field $C\underline{H}_3$ singlet remains (τ7.56).

m.s m/e 221(16), 220(46), 204(20), 203(60), 202(20), 188(12), 170(18), 146(16), 145(18), 144(26), 107(12), 106(30), 105(60), 80(16), 79(32), 78(B).

$C_{11}{}^1H_7{}^2H_4N_3O_2$ requires M = 221.

(XXVI) 2-(1-(E)-acetoxyiminoethyl)-3-acetyl-7-methyl-imidazo[1,2-a]pyridine.

n.m.r ($CDCl_3$) τ7.86 (s,3H) 3.09 (d,J_{65}=7.0,1H) H6
7.53 (s,3H) 2.50 (s,1H) br H8
7.39 (s,3H) 0.45 (d,J_{56}=7.0,1H) H5
7.36 (s,3H)



(XXX) 2-(1-acetylaminovinyl)-3-acetyl-imidazo[1,2-a]pyridine.

After reactions of 2-hydroxyethyl(pyridine)cobaloxime and of methyl(pyridine)cobaloxime with acetic anhydride in pyridine, for 7 days at 60°, and isolation of dimethylglyoxime di-O-acetate and III as described above, further elution of the column with chloroform gave approximately 5% of XXX. On t.l.c in EtOAc/benzene 1:1 XXX had the same R_f as IV (R_f0.2), but in 5% MeOH/$CHCl_3$ XXX had a slightly lower R_f. The sample of XXX for mass spectral analysis was purified by p.l.c (developed 4 times in 5% MeOH/$CHCl_3$), m.p 184°.

i.r (CH_2Cl_2) 3420m,1690s,1638s,1485s,cm^{-1}.

n.m.r ($CDCl_3$) τ7.86 (s,3H) 3.00 (t,$J_{56}+J_{67}$=14.0,1H) H6
7.35 (s,3H) 2.45 (m,2H) H7,H8
4.98 (d,J=1.0,1H) 2.05 (br,1H)
3.61 (s,1H) 0.47 (d,J_{56}=6.7,1H) H5

m.s m/e 243(69)[$C_{13}H_{13}N_3O_2$](M), 228(20), 200(B) (243-43*), 186(20) (228-42*), 158(10), 144(11), 118(11), 79(13), 78(37), 51(13), 43(41).

The doublet at τ4.98 in the n.m.r spectrum of XXX llapsed to a singlet on double irradiation with H_2 at τ2.05, after shaking for 10 minutes the solution in $CDCl_3$ with 2 drops D_2O, which also caused disappearance of the broad 1H signal τ2.05.

Reactions of IV.

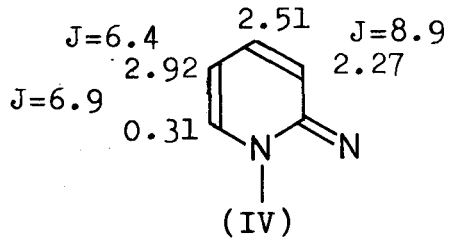
V) 2-(1,1-dinitroethyl)-3-acetyl-imidazo [1,2-a] pyridine.

The deacetylated cobaloxime degradation product IV (43mg, 2mM) was added to concentrated nitric acid (2ml). It dissolved th the evolution of brown fumes. After 10 minutes at room temp-ature water (5ml) was added, and the pale yellow solid (31mg) ltered off. This was homogenous on t.l.c (R_f0.6 in 5% MeOH/$CHCl_3$); further 10mg of slightly less pure material was extracted from e acid solution into dichloromethane.

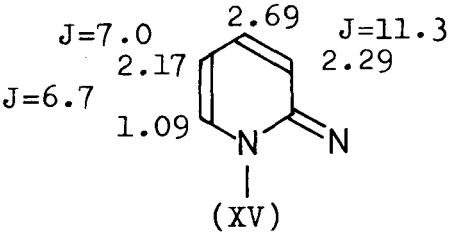
m.p 177° (plates from ether, needles from water)

i.r (CH_2Cl_2) 1656s,1580vs cm^{-1}.

n.m.r ($CDCl_3$) τ7.35 (s,3H) 2.69 (dd,J_{78}=11.3,J_{67}=7.0,1H) H7
7.30 (s,3H) 2.29 (d,J_{78}=11.3,1H) H8
2.17 (t,J_{56}+J_{67}=14.0,1H) H6
1.09 (d,J_{56}=6.7,1H) H5



(IV)



(XV)

u.v (MeOH) 218.5nm (ε21,600) 302nm (ε5,560)sh
248nm (ε12,030) 318nm (ε5,710)
254nm (ε10,190)sh 330nm (ε5,090)sh

m.s m/e 278(5) [$C_{11}H_{10}N_4O_5$] (M), 232(7) (M-NO_2), 217(4), 202(10), 201(8), 200(10), 188(11), 187(67), 186(B) [$C_{11}H_{10}N_2O$] (232-NO_2*), 185(33), 171(20) (278-107*), 157(21), 145(33) (187-42*), 143(27) (217-74*), 117(8), 105(13), 90(9) (117-27*), 79(15), 78(63).

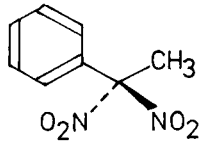
$C_{11}H_{10}N_4O_5$ C47.48, H3.62, N20.14%
found C47.56, H3.85, N19.78%

Reaction of acetophenone oxime with concentrated nitric acid.

As a comparison with the above conversion of IV to XV, acetophenone oxime was reacted with concentrated nitric acid. Two products were formed in roughly equal proportions. One of these is probably the expected dinitro derivative (XXXIX), but the other remains unidentified.

Acetophenone oxime (0.405g, 3mM) was dissolved in conc. HNO_3 (5ml). T.l.c indicated complete disappearance of starting material only after 6 hours at room temperature, or, in a later run, after 30 minutes at 60°. Water (20ml) was added, and the mixture extracted three times with ether (20ml). The extracts, dried and evaporated gave an oil (0.45g) that was two products on t.l.c (benzene/petrol 2:1 R_f0.5 (A), and R_f0.3 (B)). The mixture was separated on a silica gel column, putting the mixture on in petrol and eluting A with 20% benzene/petrol, B with 40-50% benzene/petrol. Combining fractions gave A (0.230g) pure on t.l.c, and B (0.200g) with a slight tail to the origin on t.l.c. B crystallised after 1 year and was unchanged on t.l.c.

It is proposed that A is 1-phenyl-1,1-dinitroethane (XXXIX).



(XXXIX)

A.

i.r (film) 1565vs,1500w,1452m,1390m,1355m,1322m,1265m,860m,822m, 720w,690m cm^{-1}.

n.m.r ($CDCl_3$) τ7.41 (s,3H)
2.42 (s,5H)

m.s m/e 150(29), 122(11) (150-28*), 120(16), 119(20), 117(16) (150-33*), 105(89), 104(42) (150-46*), 103(B), 91(18), 78(27), 77(82) (105-28*) (103-26*), 76(29).

($PhC(NO_2)_2CH_3$ requires M=196. Suggest $PhC(NO_2)CH_3$ = m/e 150; PhCN = m/e 103(B))

$C_8H_8N_2O_4$ C48.98, H4.11, N14.28% (196.16)
found C49.96, H4.03, N12.07%

i.r (film) 1684s,1668s,1610s,1585m(sh),1470w,1452m,1329m,1240m,
1222w(sh),1180w,925w,895m,794m,729m cm^{-1}.

n.m.r ($CDCl_3$) τ2.33 (m,2H)
2.07 (dd,J=7.7,J'=2.5,1H)
1.73 (dd,J=7.7,J'=2.5,1H)

m.s m/e 278(0.4), 195(0.9), 180(1.2), 150(4.5), 131(5.2), 122(6),
106(12), 105(B), 77(36) (105-28*).

ote the absence of a methyl group resonance in the n.m.r spectrum;
ssible reactions are nitration of the aromatic ring, Beckmann
arrangement or cyclisation onto the aromatic ring through the
thyl group).

action of IV with alkaline sodium hypochlorite and potassium iodide

IV (38mg, 0.18mM) was dissolved in 10% NaOH solution (1ml)
d 10% potassium iodide solution (1ml) added, followed by commercial
% sodium hypochlorite solution (2ml). Iodoform was precipitated.
dition of more hypochlorite seemed to cause further precipitation
til c. 8ml had been added. The iodoform (21mg, 0.0534mM) m.p 120°
s filtered off. T.l.c of the alkaline filtrate showed nothing in
variety of solvent systems, and similarly after acidification. On
reful neutralisation to pH 6-7, a yellow solid (8mg) could be
tracted into chloroform. Chromatography (silica gel/$CHCl_3$) gave
g of yellow crystals, m.p > 330°.

i.r (CH_2Cl_2) very broad weak absorption centred at 3000 cm^{-1},
1740s,1640s cm^{-1}.

m.s dominated by base peak at m/e 44; the only other significant
peaks were at m/e 229(3), 214(2), 203(2.5), 200(4).

Synthesis of possible intermediates XXXIV and XXXV.

XXIV) 2-(1-hydroxyiminoethyl)-imidazo[1,2-a]pyridine.

1-Bromo-3-hydroxyiminobutan-2-one[262] (0.90g, 5mM) dissolved
dry dioxan (5ml) was mixed with a solution of 2-aminopyridine
.47g, 5mM) in dioxan (5ml), and sodium bicarbonate (0.42g, 5mM)
dioxan (2ml) added. The mixture was heated at 100° until evolution

of carbon dioxide had ceased (c. 1.5 hours). Black insoluble matter was filtered off, and the filtrate evaporated. The residue was dissolved in chloroform (250ml) and washed with several small portions of water. The aqueous washings were extracted once with chloroform, and the combined chloroform extracts dried and evaporated to give a dirty white solid (0.50g) m.p 213°, quite pure on t.l.c (10% MeOH/$CHCl_3$, R_f0.3 identical to the starting 2-aminopyridine, but distinguished by t-BuOCl/starch-KI treatment for detecting N-H groups[89]).

Two recrystallisations from ethyl acetate gave colourless crystals (0.30g, 35%) m.p 215°.

i.r (nujol) 3400-2300m,1630w cm^{-1}.

n.m.r (NaOD) τ7.78 (s,3H)
3.30 (t,$J_{56}+J_{67}$=13.0,1H) H6
2.80 (m,2H) H7, H8
2.36 (s,1H) H3
1.98 (d,J_{56}=6.0,1H) H5

u.v (MeOH) 234nm (ε30,850) (MeOH/HCl) 226nm (ε20,610)
278nm (ε4,000)sh 276nm (ε8,920)
288nm (ε4,270)sh 288nm (ε11,910)sh
306nm (ε5,240)sh 295nm (ε12,670)
315nm (ε5,580) 306nm (ε8,920)sh
328nm (ε4,090)sh

m.s m/e 175(100) (M), 160(46)(175-15*), 158(10), 156(13), 145(28), 144(23), 143(35), 131(17) (158-29*), 118(18) (145-27*), 105(88) (160-55*) (131-26*), 90(16), 79(70), 78(97) (145-57*).

$C_9H_9N_3O$ C61.70, H5.18, N23.99%
found C61.02, H5.15, N24.02%

(XXXV) 2-(1-acetoxyiminoethyl)-imidazo[1,2-a]pyridine.

XXXIV (70mg, 0.4mM) was dissolved in dry pyridine (1.6ml) and redistilled acetic anhydride (0.4ml, 4mM) added. After 3 hours at room temperature the mixture was evaporated under high vacuum to give 83mg of crystalline XXXV. Three recrystallisations from benzene/petrol gave the analytical sample, m.p 131°.

i.r (CH_2Cl_2) 1763s,1635w,1611w cm^{-1}.

n.m.r ($CDCl_3$) τ7.75 (s,3H)
7.47 (s,3H)
3.20 (t,$J_{56}+J_{67}$=12.9,1H) H6
2.82 (dd,J_{67}=6.3,J_{78}=9.0,1H) H7
2.40 (d,J_{78}=9.0,1H) H8
1.91 (d,J_{56}=6.6,1H) H5
1.91 (s,1H) H3

m.s m/e 217(33) (M), 175(83), 144(46),143(42), 118(25), 105(60), 90(15), 79(50), 78(62), 60(42), 51(25), 45(56), 44(52), 43(B).

$C_{11}H_{11}N_3O_2$ C60.82, H5.10, N19.35%
found C60.90, H5.09, N19.35%

4) Model mesoionic compounds XIX and XX.

(XIX) Anhydro(1-benzyl-2-acetyl-3-hydroxyimidazo[1,2-a]pyridinium hydroxide).

This compound was prepared exactly as described[248] and found to have the following properties:

m.p 176-8° (lit.[248] 170-171°) yellow needles from benzene; slightly soluble in ether, benzene; soluble in $CHCl_3$ or methanol to give yellow-green fluorescent solution.

i.r (CH_2Cl_2) 1675s,1635w,1605s,1535m cm^{-1}.

n.m.r 100MHz ($CDCl_3$) τ7.35 (s,3H)
4.10 (s,2H)
3.09 (t,$J_{56}+J_{67}$=13.2,1H) H6
2.6-2.9 (m,6H) H8 + Ph
2.47 (dd,J_{67}=6.5,J_{78}=9.2,1H) H7
1.60 (d,J_{56}=6.7,1H) H5

u.v (MeOH) 209nm (ε19,300) 271nm (ε11,810)
262nm (ε14,100) 394nm (ε10,820)
no change in acid or alkali.

m.s m/e 266(32) (M), 197(16), 175(18), 108(48), 105(B), 95(33), 94(69), 91(56), 81(30), 80(41), 78(45).

$C_{16}H_{14}N_2O_2$ C72.16, H5.30, N10.52%
found C72.47, H5.39, N10.41%

X, R = CH_2Ph) Anhydro(1-benzyl-3-chloroacetyl-2-hydroxyimidazo-[1,2-a]pyridinium hydroxide).[249]

2-(Benzylamino)-pyridine (1.84g, 10mM) was dissolved in dry roxide-free dioxan (25ml) with chloroacetic anhydride (5.13g, 30mM) d chloroacetic acid (1.89g, 20mM), and refluxed for 2.5 hours. e cooled mixture was evaporated, and 10% sodium carbonate solution ded until basic. The mixture was extracted with dichloromethane portions of 40ml), and the extracts dried and evaporated to give brown oil (3.4g). This was purified on a short silica gel column 0g) under suction, eluting with chloroform. Combination of the best actions gave 2.6g (87%) that was recrystallised from benzene to ve pink crystals that turned brown on exposure to light (m.p 157°; t.[249] 154-155°). T.l.c in 5% MeOH/$CHCl_3$ R_f = R_f of starting material = 0.4; in 5% MeOH/$CHCl_3$+ 2 drops of HOAc, R_f0.7, R_f(s.m) 0.3.

Refluxing with only 2 mole equivalents of chloroacetic hydride for 2 hours gave only 50% conversion (by n.m.r).

i.r (CH_2Cl_2) 1670s,1598s,1510w cm^{-1}

m.s m/e 302(4.4) (^{37}Cl M), 300(11) (^{35}Cl M), 266(5), 251(18), 187(4), 91(B).

$C_{16}H_{13}N_2O_2Cl$ C63.88, H4.36, N9.32%

found C64.06, H4.57, N9.23%

X, R = CH_3) Anhydro(1-methyl-3-chloroacetyl-2-hydroxyimidazo[1,2-a]pyridinium hydroxide).

2-(Methylamino)-pyridine was best prepared from 2-bromo-ridine and aqueous methylamine, heated in a sealed tube for 4 urs at 150° (72%).[263]

The mesoionic derivative was prepared by refluxing the (methylamino)-pyridine with 3 mole equivalents of chloroacetic hydride and 2 mole equivalents of chloroacetic acid for 2 hours above. The product was insoluble in chloroform, cold ethanol and ld acetone, and the crude reaction product was recrystallised twice om hot acetone to give green crystals (85%) m.p 245°(dec.) (lit.[249] 234°)

i.r (CH_2Cl_2) 1665s,1635w,1593s,1520m cm^{-1}.

n.m.r 100MHz ($CDCl_3$) τ6.52 (s,3H) 2.375 (t,$J_{67}+J_{78}$=15.7,1H) H7

5.23 (s,2H) 0.015 (d,J =6.5,1H) H5

2.890 (d,J =8.0) — total 2H H8

2.850 (m) H6

5) Hydroxamic acid VII and its derivatives.

(VI) N-(2-(2-pyridyl)-2-aminoacetyl)-hydroxylamine.

Ethyl 2-(2-pyridyl)-2-aminoacetate (V) was prepared as described.[234] As an amino acid ester it is not particularly stable, and was distilled at as low a temperature as possible (75°/0.05mm), and stored in the deep freeze (-20°) where it was stable.

Ethyl 2-(2-pyridyl)-2-aminoacetate V (2.16g, 12mM) was mixed with a stirred solution of hydroxylamine hydrochloride (0.834g, 12mM) in 12.56N NaOH (2.1ml, 26.4mM) and water (2.4ml) at 0°. After 3 minutes at 0°, the mixture was exactly neutralised with cold conc. HCl as quickly as possible without letting the mixture warm too much, and then stored overnight at 0° to give 0.84g (42%) of crystalline hydroxamic acid VI. The mother liquors could be reacted with biacetyl to give a further 15% as the cyclic hydroxamic acid VII.

This is essentially the method of Safir and Williams[236] for α-amino hydroxamic acids in general. The product was only obtained crystalline by rigorously following the above procedure, and similar observations were made with glycine ethyl ester. If crystallisation did not occur, then addition of biacetyl to the solution gave the cyclised product VII in similar yield.

m.p turns red on warming, softens 112°, decomposes c. 135°.

i.r (nujol) 3350m,3250s(br),1665s,1590m(sh),1563s cm^{-1}.

(X) 3,6-di(2-pyridyl)-2,5-dihydroxypyrazine.

On attempting to recrystallise the hydroxamic acid VI from warm water, it turned red as it dimerised to X. This was recrystallised from methanol, and was orange in suspension in methanol, red after filtration, and turned deeper red on prolonged drying under vacuum. Successive analyses seemed to suggest water present (high hydrogen and oxygen). The mass spectrum of X was identical to that obtained from the hydroxamic acid VI which must dimerise in the spectrometer inlet. The spectrum shows extrusion of CO - characteristic of the 2(5)-hydroxypyrazines obtained during this work.

m.p softens 112°, decomposes c. 135°.

i.r (CH_2Cl_2) 3685w,3625w,3440m,3300-2700w,1645s,1620s,1600s,1590s 1565m,1550m(sh),1523s cm^{-1}

n.m.r ($CDCl_3$) pyridine ring protons only (+ N-H?); no other signal to τ -5.0.

u.v (MeOH) end abs.
254nm (ε6,700)
273nm (ε6,980)
370nm (ε12,750)
434nm (ε15,100)

(MeOH/HCl) end abs.
247nm (ε7,280)
413nm (16,900)

m.s m/e 266(1.5)$[C_{14}H_{10}N_4O_2]$(M), 239(18), 238(B) $C_{13}H_{10}N_4O$ (M-CO* 210(3.3) (238-28*), 209(7), 148(8), 106(42), 105(68), 79(83), 78(53).

$C_{14}H_{10}N_4O_2$ C63.15, H3.79, N21.04% (O 12.02%)
found C57.36, H4.66, N19.64% (O 18.34%) after 24 hours/2mm
C59.76, H4.56, N20.92% (O 14.76%) after 96 hours/2mm

'II) 2-hydroxy-3-(2-pyridyl)-5,6-dimethylpyrazine-1-oxide.

N-(2-(2-pyridyl)-2-aminoacetyl)-hydroxylamine VI (0.25g, 5mM) was dissolved in water (7ml) and biacetyl (0.2g, 2.3mM) added. ter a few minutes yellow needles formed, although scratching was metimes necessary (0.29g, 88%). Recrystallisation from hot water ve the bright yellow monohydrate, m.p 263°. The anhydrous compound s pale brown, obtained after drying for 4 hours at 80°/2mm.

i.r (nujol) 3340m(br),1720w,1635m,1590s cm^{-1}.

n.m.r (Na_2CO_3/D_2O) τ7.61 (s,3H)
7.54 (s,3H)
2.55 (dd,J_{45}=8.2,J_{56}=4.8, 1H) H5
2.06 (m,2H) H3,H4
1.35 (d,J_{65}=4.8,1H) H6

u.v (MeOH) 231.5nm (ε15,900)
256nm (ε9,000)sh
371.5nm (ε11,000)
430nm (ε2,000)sh
(solution yellow)

(MeOH/HCl) 223nm (ε10,580)
261.5nm (8,300)
416nm (ε19,000)
(solution fluorescent)
(MeOH/NaOH) solution colourless spectrum similar to neutral, bu for absence of shoulder at 430nm

m.s m/e 218(15), 217(B)$[C_{11}H_{11}N_3O_2]$(M), 202(13), 201(92), 200(4) (M-17*), 189(15), 173(35) (201-28*), 172(96) (200-28*) (189-17*) (173-1*), 131(13) (172-29*), 105(89) (131-26*), 79(96), 78(62) (105-27*).

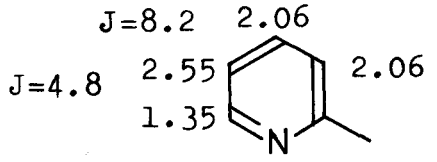
$C_{11}H_{11}N_3O_2 + H_2O$	C56.16, H5.57, N17.86%	
found	C56.68, H5.43, N17.96%	(dried RT/2mm/12hours.)
$C_{11}H_{11}N_3O_2$	C60.82, H5.10, N19.35%	
found	C60.76, H5.05, N19.19%	(dried 80°/2mm/4hours.)

(XXVI) 2-hydroxy-3-(2-pyridyl)-5,6-dimethylpyrazine.

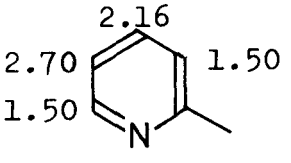
Anhydrous VII (25mg, 0.115mM) was dissolved in acetic acid 1.5ml), and red phosphorus (12mg) and iodine (4mg) added, and the ixture refluxed for 3 hours. Sodium bisulphite solution (5ml) was ided to the cooled mixture, and this was then extracted with ichloromethane (3 portions of 8ml). The extracts were dried and aporated, and the residue chromatographed on silica gel (3g) in $CHCl_3$ and 2%MeOH/$CHCl_3$, to give 15mg (66%) of crystalline product. ie analytical sample was recrystallised from 60-80 petrol.

m.p 118°

i.r (CH_2Cl_2) τ7.50 (s,6H)
2.70 (t,$J_{45}+J_{56}$=13.0,1H) H5
2.16 (t,$J_{34}+J_{45}$=15.3,1H) H4
1.50 (m,2H) H3,H6
-4.40 (br,1H)



(VII)
(Na_2CO_3/D_2O)



(XXXVI)
($CDCl_3$)

u.v (MeOH) 243.5nm (ε10,700)
340nm (ε19,970)

(MeOH/HCl) 221nm (10,300)
257.5nm (ε10,060)
413nm (ε21,180)

(MeOH/NaOH) 265nm (ε5,210)
367nm (ε19,970)

m.s m/e 202(18), 201(100) (M), 173(56) (201-28*), 172(83), 158(13)
119(14), 105(44).

$C_{11}H_{11}N_3O$	C65.67, H5.51, N20.88%
found	C65.34, H5.64, N21.18%

(XI) 2-hydroxy-3-(2-pyridyl)-5-methyl-6-acetoxymethylpyrazine.

The monohydrate of the cyclic hydroxamic acid VII (41mg, 0.175mM) was heated over a bunsen flame in acetic anhydride (1.5ml). After 1 minute the solution darkened, and was left to cool for 10 minutes. Water (8ml) was added, and the mixture neutralised with solid sodium bicarbonate. A yellow solid was extracted into dichloromethane, and the n.m.r spectrum of this showed several prominent $C\underline{H}_3$ resonances in addition to those of the isolated product. The mixture (40mg) was chromatographed on silica gel (3g) in $CHCl_3$ and 2% MeOH/$CHCl_3$ to give 22mg (49%) of pure crystalline XI. The analytical sample was recrystallised twice from 60-80 petrol,

m.p 118-123° (c.f m.p of deacetylated compound XII)

i.r (CH_2Cl_2) 3300-2300m,1740s,1595m,1585m,1560m cm^{-1}.

n.m.r ($CDCl_3$) τ7.87 (s,3H) 2.61 (dd,$J_{45}+J_{56}$=13.3,1H) $\underline{H}5$
7.44 (s,3H) 2.06 (dd,$J_{34}+J_{45}$=15.3,1H) $\underline{H}4$
4.81 (s,2H) 1.40 (m,2H) $\underline{H}3$, $\underline{H}6$
-4.60 (br,1H)

u.v (MeOH) 242.5nm (ε11,320)
340nm (ε16,720)

m.s m/e 259(25) (M), 218(40), 217(73), 202(18), 201(B), 188(25), 173(50), 172(85), 105(30).

$C_{13}H_{13}N_3O_3$ C60.22, H5.05, N16.21%
found C59.94, H5.07, N16.27%

(XII) 2-hydroxy-3-(2-pyridyl)-5-methyl-6-hydroxymethylpyrazine.

XI (23mg, 0.089mM) was dissolved in methanol (1ml) and 3.43N KOH in methanol (40μl, 0.137mM) added. T.l.c showed deacetylation was rapid (5% MeOH/$CHCl_3$ R_f(XI) = 0.8, R_f(XII) = 0.6). Water was added, the solution brought to pH7 with N HCl and the product extracted with dichloromethane (16mg, 85%) and recrystallised from 60-80 petrol, m.p 123°.

i.r (CH_2Cl_2) 3460m(br),2800-2100m,1598s,1590s(sh),1560m cm^{-1}.

n.m.r ($CDCl_3$) 100MHz τ7.54 (s,3H)
5.265 (s,2H)
2.60 (dd,J_{45}=7.6,J_{56}=5.0,1H) $\underline{H}5$
2.06 (t,$J_{34}+J_{45}$=15.5,1H) $\underline{H}4$
1.44 (d,J_{56}=5.0,1H) $\underline{H}6$
1.38 (d,J_{34}=7.8,1H) $\underline{H}3$
no other signal to τ-5.0

u.v (MeOH) 243nm (ε8,530) (MeOH/HCl) 223nm (ε7,420)
342nm (ε14,450) 257nm (ε7,540)
414nm (ε16,180)
(MeOH/NaOH) 234nm (ε7,150) (solution pale yellow when
253nm (ε5,560)sh neutral, fluorescent when
365nm (ε10,600) acidic, colourless when basic.)

m.s m/e 218(18), 217(90) $[C_{11}H_{11}N_3O_2]$ (M), 216(25), 202(22), 188(B) (217-29*), 172(50)(217-45*), 160(20), 131(20) (158-27*), 119(15) (160-41*) (172-53*), 105(84).

$C_{11}H_{11}N_3O_2$ C60.82, H5.10, N19.35%
found C60.29, H5.24, N19.21%

6) Determination of the crystal and molecular structure of (IV) by X-ray crystallography.

Crystals were chosen from the first crop from ethyl acetate obtained in the preparation of IV described in section 1.

Preliminary cell data was obtained on Weissenberg and precession cameras with Ni-filtered CuK_α radiation. The crystals were laths with c along their length and b across them. Their density was determined by flotation in diiodomethane/benzene solution.

crystal data: $C_{11}H_{11}N_3O_2$, M = 217.1. Orthorhombic.

a = 16.402(10) Å	D_M = 1.332g.cm^{-3}
b = 13.463(10) Å	D_X = 1.346g.cm^{-3}
c = 9.735(10) Å	Z = 8
V = 2149.7 A^3	F_{000} = 912

systematic absences: 0kl, k ≠ 2n (h00, h ≠ 2n)
h0l, l ≠ 2n (0k0, k ≠ 2n)
hk0, h ≠ 2n (00l, l ≠ 2n)
indicating space group Pbca.

Reflection data were collected on a Stoe-Weissenberg two circle diffractometer, using MoK_α radiation with graphite monochromator (λ = 0.71069Å), by ω-scan technique. Unit cell parameters were obtained from the reflecting positions of high angle reflections, with standard deviations estimated from the agreement of observed and calculated values.

1865 reflections were measured in 11 layers of the primary axis (c), and 439 reflections in 3 layers of the crossing axis (b), with check reflections measured every 30 reflections.

Lorentz and polarisation corrections were applied, assuming the monochromator to be ideally mosaic, and the intensities merged to give 1903 independent reflections. Of these, 546 had $I < 0.1\sigma(I)$, and were taken to have the limiting values of $0.1\sigma(I)$.

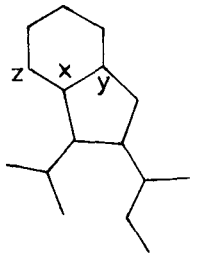
The intensities were converted to normalised structure factors and placed on an absolute scale. The program PHASER was used to solve the structure by direct methods.[264] In this procedure, as applied here, all the Σ_2 relationships were generated between the 366 reflections with $|E| > 1.3$, and sorted in order of descending

probability. The 60 strongest reflections ($|E| > 2.045$) were used as generators, with 3 origin-specifying reflections:

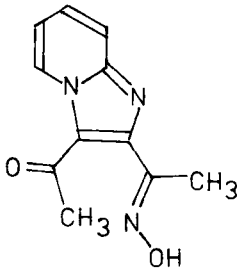
h	k	l	E
8	5	0	3.471
3	11	5	3.264
1	9	6	2.761

The remaining 57 phases were determined from the first encountered relationships. 5 Cycles to remove discrepant relationships resulted in 23 phases being changed from the values initially assigned. Further application of the Σ_2 relationships starting from these 60 generator phases allowed 247 new phases to be determined.

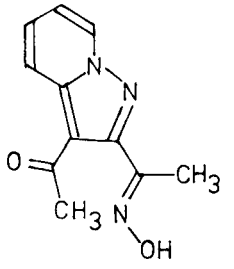
An E-map based on these phases showed 16 peaks corresponding to the 16 non-hydrogen atoms (XXIII). This molecular framework does not distinguish between the two alternative interpretations -(IV) and (XXIV).



(XXIII)



(IV)



(XXIV)

Further considerations show IV to be the correct structure.

i) The peak on the E-map due to the atom x is the most intense on the entire map.

ii) Initial refinement with all atoms as carbon atoms gave isotropic temperature factors (U):

atom x $U = 1.31 \times 10^{-2}$

atom y $U = 4.19 \times 10^{-2}$

atom z $U = 4.92 \times 10^{-2}$

iii) Structure XXIV would provide no explanation for the deshielding of the α-pyridine proton observed in the n.m.r spectrum. In structure IV, H5 would be deshielded by the peri-carbonyl group of the 3-acetyl substituent.

The orientation of the 3-acetyl group in IV was defined to be as shown by the intensity of the peak on the E-map corresponding

to oxygen, the relative lengths of the single and double bonds, and the siting of the methyl hydrogen atoms at a later stage of refinement.

Refinement.

The initial R factor for the 800 reflections with $I > 3.0\sigma(I)$ was 0.313. Two cycles of least squares refinement with isotropic thermal parameters for all atoms gave R = 0.189.

Further refinement used the 520 reflections with $I > 5.0\sigma(I)$. Two cycles reduced R to 0.130, and a difference Fourier map at this stage enabled the positions of all the 11 hydrogen atoms to be determined.

The final refinement was with anisotropic temperature factors for non-hydrogen atoms. Attempts to refine the positions of the hydrogen atoms gave unacceptable bond lengths and angles, and these atoms were therefore kept at the positions shown by the difference map.

The final R value was 0.089.

Table VI gives the coordinates of all the atoms, and table VII gives their temperature factors. Table VIII compares the observed and calculated structure factors.

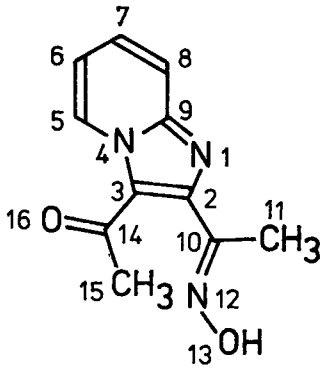
Fig.1 is a computer drawing of a molecule of IV viewed along the b axis, and figs. 2 and 3 respectively show the bond lengths and bond angles, excluding bonds to hydrogen.

Table IX lists the deviations of the non-hydrogen atoms from three least squares planes defined by (1) the 9 atoms of the heteroaromatic ring system, (2) the 4 atoms of the 3-acetyl substituent, and (3) the 5 atoms of the 2-(1-(E)-hydroxyiminoethyl) group, and also gives the equations of, and the angles between these planes.

Fig.4 shows the molecular packing arrangement of molecules within a unit cell, and table X gives the intermolecular distances less than 2.5A.

The planar heteroaromatic rings are arranged in stacks parallel to the a axis, with molecules of adjacent stacks situated in head-to-tail 'herring-bone' fashion. The main intermolecular interactions are between ring hydrogen atoms, although the =N-OH hydrogen and N(1) of the ring of adjacent molecules are sufficiently close for hydrogen bonding to occur.

table VI. Atomic coordinates, with standard deviations in brackets.



	x/a	y/b	z/c
C(2)	0.1511 (10)	-0.0968 (12)	0.1238 (17)
C(3)	0.1205 (10)	-0.0174 (12)	0.0475 (13)
C(5)	0.0431 (10)	0.1385 (12)	0.1124 (20)
C(6)	0.0134 (11)	0.1857 (12)	0.2193 (25)
C(7)	0.0247 (12)	0.1473 (15)	0.3485 (21)
C(8)	0.0633 (11)	0.0607 (13)	0.3802 (17)
C(9)	0.0934 (8)	0.0089 (11)	0.2630 (20)
C(10)	0.1951 (10)	-0.1878 (12)	0.0880 (15)
C(11)	0.2811 (9)	-0.2053 (12)	0.1470 (16)
C(14)	0.1266 (10)	-0.0017 (14)	-0.1035 (19)
C(15)	0.1839 (12)	-0.0643 (15)	-0.1863 (20)
N(1)	0.1353 (7)	-0.0762 (9)	0.2592 (16)
N(4)	0.0833 (8)	0.0489 (10)	0.1370 (15)
N(12)	0.1564 (7)	-0.2477 (12)	0.0084 (17)
O(13)	0.2039 (7)	-0.3313 (7)	-0.0186 (12)
O(16)	0.0848 (8)	0.0663 (11)	0.1522 (14)
H(5)	0.0221	0.1401	-0.0016
H(6)	-0.0229	0.2413	0.2403
H(7)	0.0143	0.1830	0.4380
H(8)	0.0679	0.0184	0.4821
H(111)	0.3167	-0.2000	-0.0500
H(112)	0.2500	-0.1800	0.2250
H(113)	0.3000	-0.2800	0.2250
H(13)	0.1706	-0.3634	-0.1097
H(151)	0.1667	-0.1200	-0.2000
H(152)	0.2333	-0.0600	-0.2000
H(153)	0.1750	-0.0200	-0.2500

ble VII. Anisotropic temperature factors ($10^3 u_{ij}$) for non-hydrogen atoms, with standard deviations in brackets. All hydrogen atoms were given isotropic temperature factors, U = 2.5 x 10^{-2} Å^2.

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
(2)	45 (11)	36 (10)	38 (11)	-3 (8)	26 (10)	-26 (9)
(3)	31 (9)	40 (9)	13 (8)	-6 (8)	-1 (7)	17 (8)
(5)	31 (10)	20 (10)	95 (16)	-2 (8)	-25 (12)	22 (10)
(6)	55 (14)	29 (10)	115 (19)	28 (10)	24 (14)	-9 (13)
(7)	68 (15)	57 (14)	68 (15)	-18 (11)	-19 (12)	24 (13)
(8)	80 (15)	32 (10)	40 (12)	-6 (10)	-37 (11)	16 (10)
(9)	-37 (9)	21 (8)	52 (12)	-13 (8)	11 (10)	5 (9)
(10)	3 (11)	50 (11)	19 (9)	-13 (9)	-7 (9)	15 (9)
(11)	39 (11)	80 (14)	38 (10)	21 (9)	7 (9)	3 (10)
(14)	31 (11)	62 (13)	68 (13)	-12 (10)	-1 (11)	19 (12)
(15)	72 (14)	53 (14)	88 (15)	4 (12)	31 (13)	16 (11)
(1)	30 (8)	32 (8)	80 (12)	15 (7)	23 (9)	5 (9)
(4)	39 (8)	43 (9)	40 (9)	-13 (8)	13 (8)	27 (8)
(12)	55 (9)	44 (8)	65 (11)	6 (8)	6 (10)	11 (8)
(13)	74 (9)	37 (7)	59 (8)	6 (6)	-17 (8)	-5 (7)
(16)	60 (9)	75 (11)	78 (10)	-2 (8)	-3 (9)	26 (9)

table VIII. Observed and calculated structure factors.
The columns are in the order l, $10F_o$, $10F_c$. Less-thans are indicated by *.

	0,0,L			1,1,L		9	149*	32	2	66*	64		2,18,L			3,7,L			4,2,L		2	96*	27
									3	98*	93										3	253	219
2	289	344	2	143	178		1,10,L		4	278	282	0	334	369	1	168	128	0	2181	2094	4	188	92
4	484	463	3	529	507				5	42*	37	1	87*	64	2	103*	152	1	893	889	5	134	31
6	170	135	4	148	199	1	122*	144	6	27*	34	2	196	197	3	49*	71	2	572	598	6	35*	168
8	442	501	5	243	239	2	198	197	7	161	136	3	105*	192	4	65*	13	3	57*	54	7	98*	191
10	25*	128	6	170	153	3	181	162	8	78*	13	4	161	152	5	31*	12	4	182	287	8	55*	48
			7	108*	84	4	28*	8	9	85*	46	5	178	141	6	93*	152	5	60*	28			
	0,2,L		8	77*	63	5	205	206	10	108*	8	6	97*	97	7	55*	16	6	206	288		4,11,L	
			9	104*	89	6	32*	24							8	148	147	7	113*	128			
0	1946	1057	10	27*	17	7	92*	92		2,9,L			2,14,L		9	36*	121	8	79*	63	0	335	353
1	228	258	11	27*	52	8	33*	38							10	36*	98	9	181*	98	1	131*	166
2	984	978				9	40*	88	0	25*	10		3,8,L					10	111*	188	2	71*	95
3	98*	230		1,2,L					1	114*	57	1	85*	50				11	28*	22	3	284	327
4	533	558					1,11,L		2	23*	65	2	119*	117							4	81*	68
5	338	338	1	166	116				3	114	85	3	82*	65	1	167	178		4,3,L		5	188	191
6	263	267	2	840	829	1	116*	14	4	559	544	4	30*	88	2	208	289				6	199	197
7	41*	16	3	581	596	2	30*	86	5	267	319	5	35*	27	3	146	187	0	1537	1598	7	138*	89
8	69*	52	4	316	340	3	27*	44	6	39*	192				4	26*	119	1	166	219	8	114*	87
9	98*	74	5	292	267	4	43*	9	7	223	210		2,15,L		5	184	204	2	684	738			
10	144	158	6	108	104	5	128*	45	8	96*	94				6	118*	188	3	185	176		4,12,L	
11	61*	5	7	130	97	6	178	163	9	130*	18	0	28*	33	7	27*	3	4	786	757			
			8	126*	149	7	29*	42	10	40*	20	1	86*	47	8	31*	19	5	317	295	0	239	249
	0,4,L		9	48*	8	8	103*	49				2	28*	24	9	90*	81	6	114*	138	1	27*	45
			10	26*	51					2,6,L		3	107*	108				7	24*	93	2	86*	51
0	387	398	11	27*	3		1,12,L									3,9,L		8	53*	177	3	26*	37
1	55*	37							0	103*	131		3,0,L					9	31*	29	4	61*	29
2	245	242		1,3,L		1	135	127	1	170	134				1	183	167	10	91*	98	5	98*	42
3	685	665				2	105*	110	2	419	414	2	588	574	2	26*	49				6	36*	128
4	481	461	1	511	477	3	107*	48	3	23*	68	4	391	448	3	182	176		4,4,L		7	66*	77
5	192	178	2	425	410	4	30*	9	4	124	71	6	158	241	4	28*	69						
6	49*	126	3	67*	12	5	80*	82	5	30*	92	8	142	156	5	59*	61	0	961	959		4,13,L	
7	42*	25	4	97*	87	6	69*	26	6	53*	9	10	102*	39	6	186	129	1	244	218			
8	40*	43	5	25*	45	7	95*	3	7	26*	96				7	64*	41	2	489	448	0	81*	48
9	13*	31	6	158	125				8	72*	2		3,1,L		8	112*	89	3	125	121	1	27*	23
10	11*	91	7	159	162		1,13,L		9	148*	37				9	157*	4	4	137	144	2	186*	118
			8	25*	51				10	33*	49	1	692	689				5	181*	186	3	98*	15
	0,5,L		9	118*	182	1	27*	32				2	78*	32		3,10,L		6	28*	7	4	225	217
			10	28*	55	2	80*	101		2,7,L		3	452	481				7	25*	3	5	126*	18
0	213	256				3	27*	49				4	206	220	1	64*	49	8	112*	11	6	35*	19
1	24*	68		1,4,L		4	74*	81	0	408	410	5	274	285	2	95*	138	9	34*	49			
2	398	408				5	82*	42	1	39*	39	6	77*	60	3	34*	129	10	31*	46		4,14,L	
3	299	305	1	193	138	6	55*	3	2	245	217	7	36*	24	4	75*	12						
4	170	185	2	23*	15				3	94*	22	8	92*	194	5	103*	139		4,5,L		0	27*	86
5	127*	153	3	486	458		1,14,L		4	111*	136	9	70*	48	6	138*	46				1	28*	32
6	251	231	4	103*	105				5	31*	11	10	27*	9	7	125*	49	0	482	468	2	45*	153
7	26*	178	5	349	318	1	27*	11	6	96*	116	11	28*	23	8	79*	21	1	270	272	3	128*	104
8	29*	116	6	249	231	2	29*	108	7	216	234							2	376	384	4	31*	147
9	34*	73	7	60*	16	3	27*	28	8	137*	282		3,2,L			3,11,L		3	289	248	5	37*	1
10	33*	36	8	178	170	4	31*	39	9	36*	29							4	179	188			
			9	30*	78	5	36*	40	10	46*	23	1	201	198	1	131	98	5	91*	116		4,15,L	
	0,6,L		10	76*	7							2	87*	69	2	112*	157	6	138*	128			
							1,15,L			2,8,L		3	705	707	3	26*	21	7	91*	69	0	79*	66
0	503	528		1,5,L								4	87*	108	4	29*	18	8	83*	93	1	183*	156
1	644	619				1	75*	39	0	161	165	5	128	105	5	315	309	9	138*	199	2	43*	68
2	400	378	1	102*	22	2	28*	47	1	93*	124	6	86*	24	6	35*	77	10	34*	43	3	28*	59
3	23*	88	2	187	214	3	27*	1	2	132	92	7	96*	21	7	30*	28						
4	239	248	3	123	94	4	30*	4	3	93*	73	8	83*	121	8	118*	19		4,6,L			5,0,L	
5	389	359	4	219	217				4	196	57	9	80*	49									
6	32*	89	5	28*	52		2,0,L		5	32*	14	10	50*	65		3,12,L		0	686	672	2	147	139
7	232	286	6	28*	62				6	106*	67	11	27*	7				1	143	149	4	237	238
8	80*	27	7	160	197	2	773	750	7	28*	21				1	82*	104	2	138	149	6	71*	41
9	138*	143	8	26*	26	4	492	522	8	108*	62		3,3,L		2	68*	87	3	239	289	8	181	164
10	58*	35	9	32*	30	6	137	114	9	38*	57				3	124	45	4	188*	91	10	121*	64
			10	31*	64	8	122	96	10	37*	43	1	661	709	4	39*	29	5	364	336			
	0,10,L					10	94*	76				2	101*	45	5	87*	88	6	273	287		5,1,L	
				1,6,L						2,9,L		3	212	220	6	119*	82	7	27*	114			
0	140	148					2,1,L					4	222	202	7	98*	33	8	152	178	1	774	758
1	218	205	1	313	307				0	118*	144	5	226	216				9	68*	67	2	245	221
2	173	160	2	77*	76	0	679	677	1	37*	40	6	242	218		3,13,L		10	96*	40	3	22*	19
3	25*	1	3	64*	14	1	911	920	2	337	312	7	22*	59							4	228	244
4	29*	93	4	184	141	2	599	610	3	200	176	8	46*	77	1	66*	19		4,7,L		5	173	198
5	34*	48	5	29*	49	3	105*	143	4	105*	142	9	30*	6	2	88*	125				6	143	135
6	349	372	6	29*	38	4	648	647	5	112*	133	10	29*	72	3	101*	58	0	521	480	7	261	259
7	121*	205	7	26*	90	5	414	430	6	210	229				4	30*	48	1	188	151	8	148	166
8	32*	117	8	88*	74	6	39*	26	7	79*	117		3,4,L		5	92*	11	2	42*	46	9	131*	144
9	119*	11	9	34*	26	7	195	188	8	148	70				6	36*	3	3	95*	20	10	36*	189
			10	141*	114	8	123*	58	9	40*	43	1	159	131				4	26*	38	11	113*	81
	0,12,L					9	182	256				2	166	195		3,14,L		5	214	182			
				1,7,L		10	48*	118		2,10,L		3	186	187				6	153	78		5,2,L	
0	293	346				11	27*	20				4	23*	26	1	144	157	7	146	184			
1	84*	123	1	24*	46				0	215	229	5	336	293	2	84*	88	8	31*	51	1	486	421
2	76*	43	2	47*	60		2,2,L		1	26*	21	6	82*	78	3	28*	15	9	37*	16	2	143	152
3	377	411	3	250	277				2	25*	10	7	123	163	4	30*	9	10	92*	33	3	147	131
4	313	300	4	71*	131	0	962	975	3	95*	82	8	103*	113	5	140*	28				4	57*	41
5	36*	192	5	227	267	1	1131	1184	4	405	447	9	129*	79					4,8,L		5	64*	121
6	34*	110	6	113*	99	2	579	683	5	83*	129	10	31*	31		3,15,L					6	87*	45
7	110*	15	7	89*	113	3	632	650	6	33*	16							0	369	329	7	59*	49
8	62*	87	8	71*	30	4	206	196	7	29*	32		3,5,L		1	78*	3	1	45*	116	8	78*	63
			9	48*	58	5	46*	59	8	32*	80				2	52*	9	2	260	223	9	26*	44
	0,14,L		10	36*	52	6	111*	108	9	41*	3	1	88*	25	3	28*	63	3	149	104	10	27*	29
						7	136	131				2	83*	120				4	141	159	11	28*	38
				1,8,L		8	97*	148		2,11,L		3	259	282		4,0,L		5	33*	29			
0	104*	144				9	120*	120				4	193	208				6	50*	94		5,3,L	
1	48*	124				10	27*	17	0	120*	94	5	279	277	0	1055	1033	7	162	158			
2	194	202	1	288	302	11	103*	23	1	117*	92	6	152	116	2	76*	84	8	31*	23	1	91*	79
3	166	151	2	59*	3				2	26*	68	7	168	195	4	189	116	9	38*	13	2	198	199
4	107*	110	3	78*	5				3	158	172	8	164	182	6	174	176				3	219	208
5	36*	18	4	116*	55		2,3,L		4	317	349	9	110*	58	8	161	128		4,9,L		4	49*	71
6	36*	99	5	32*	41				5	169	235	10	116*	44	10	86*	77				5	411	357
			6	161	145	0	318	280	6	123*	49							0	26*	78	6	28*	44
	0,16,L		7	157	149	1	27*	78	7	58*	28		3,6,L			4,1,L		1	57*	54	7	52*	223
			8	170	155	2	708	693	8	104*	51							2	77*	89	8	52*	35
0	136*	240	9	117*	62	3	412	404				1	138	139	0	2024	2048	3	34*	118	9	32*	30
1	65*	15	10	36*	51	4	388	393		2,12,L		2	23*	102	1	808	784	4	51*	26	10	92*	43
2	69*	87				5	254	218				3	467	467	2	542	527	5	240	269			
3	29*	5		1,9,L		6	304	297				4	24*	111	3	75*	43	6	95*	128		5,4,L	
4	59*	37				7	116	72	0	88*	124	5	38*	14	4	57*	48	7	132	32			
			1	68*	142	8	125	83	1	40*	61	6	38*	49	5	149	115	8	32*	78	1	161	173
	1,0,L		2	152	152	9	85*	167	2	162	126	7	152	139	6	127*	89	9	41*	61	2	195	197
			3	172	180	10	29*	25	3	127	123	8	139	112	7	85*	94				3	312	303
2	312	322	4	28*	170				4	47*	46	9	35*	64	8	115*	153		4,10,L		4	176	160
4	423	493	5	112*	178		2,4,L		5	184	140	10	79*	49	9	26*	78				5	97*	1
6	267	257	6	309	327				6	35*	31				10	97*	116	0	78*	141			
8	38*	33	7	28*	9	0	309	323	7	117*	33				11	47*	11	1	255	244			
10	26*	25	8	31*	123	1	880	872															

table VIII (cont.)

5,4,L		
6	286	250
7	68•	150
8	27•	11
9	36•	79
10	32•	16
5,5,L		
1	301	310
2	258	266
3	154	150
4	177	129
5	30•	25
6	30•	5
7	116•	145
8	28•	12
9	36•	75
10	65•	57
5,6,L		
1	84•	57
2	313	292
3	23•	60
4	112•	62
5	169	162
6	279	265
7	26•	57
8	121•	95
9	37•	90
10	126•	85
5,7,L		
1	212	200
2	30•	4
3	169	164
4	221	112
5	32•	2
6	256	288
7	90•	140
8	31•	158
9	153•	2
10	37•	53
5,8,L		
1	25•	37
2	114•	143
3	24•	67
4	129•	168
5	33•	7
6	199	177
7	28•	42
8	43•	138
9	39•	34
5,9,L		
1	128	112
2	144	98
3	25•	76
4	185	201
5	208	153
6	33•	133
7	59•	141
8	102•	71
9	40•	11
5,10,L		
1	85•	77
2	58•	30
3	25•	57
4	134	51
5	63•	66
6	33•	73
7	97•	28
8	82•	10
5,11,L		
1	60•	37
2	35•	24
3	149	185
4	86•	12
5	112•	21
6	65•	55
7	30•	36
5,12,L		
1	111•	66
2	127	130
3	34•	19
4	28•	86
5	81•	52
6	33•	60
7	31•	12
5,13,L		
1	108•	75
2	26•	28
3	27•	15
4	77•	64
5	37•	48
6	36•	146
5,14,L		
1	29•	46
2	68•	95

3	27•	21
4	68•	6
5,15,L		
1	29•	76
2	114•	43
6,0,L		
0	233	261
2	260	286
4	513	522
6	24•	40
8	25•	50
10	148	179
6,1,L		
0	615	632
1	158	138
2	467	442
3	576	558
4	234	262
5	276	248
6	60•	45
7	101•	172
8	80•	141
9	46•	95
10	80•	98
6,2,L		
0	1200	1224
1	107•	132
2	120	129
3	297	291
4	72•	41
5	95•	32
6	86•	105
7	190	200
8	175	163
9	26•	61
10	118•	33
6,3,L		
0	463	468
1	391	421
2	51•	22
3	126	108
4	92•	91
5	382	347
6	248	302
7	75•	141
8	118•	103
9	34•	19
10	33•	38
6,4,L		
0	456	438
1	374	387
2	404	381
3	22•	59
4	156	190
5	30•	63
6	112•	66
7	157	176
8	28•	99
9	177	191
10	74•	92
6,5,L		
0	281	282
1	241	230
2	334	366
3	23•	20
4	347	328
5	115•	122
6	30•	73
7	78•	190
8	29•	89
9	36•	96
10	35•	41
6,6,L		
0	24•	24
1	25•	1
2	68•	19
3	145	100
4	376	391
5	31•	12
6	32•	105
7	113•	112
8	77•	49
9	77•	57
10	44•	9
6,7,L		
0	268	270
1	369	349
2	166	187
3	92•	34
4	27•	51
5	204	193
6	31•	1
7	28•	48
8	54•	38
9	37•	62

6,8,L		
0	85•	103
1	25•	20
2	242	215
3	48•	6
4	307	302
5	33•	24
6	286	318
7	28•	40
8	108•	113
9	78•	2
6,9,L		
0	116•	108
1	95•	86
2	329	328
3	94•	151
4	113•	103
5	83•	29
6	81•	64
7	96•	8
8	85•	83
6,10,L		
0	27•	36
1	55•	115
2	96•	44
3	86•	91
4	289	319
5	34•	25
6	33•	16
7	41•	42
8	77•	29
6,11,L		
0	79•	58
1	109•	125
2	121	100
3	26•	19
4	85•	60
5	34•	43
6	108•	119
7	30•	67
6,12,L		
0	218	184
1	27•	27
2	77•	78
3	106•	14
4	30•	59
5	87•	53
6	72•	56
6,13,L		
0	70•	122
1	29•	90
2	27•	2
3	113•	139
4	30•	76
5	163•	181
6,14,L		
0	97•	168
1	68•	35
2	69•	6
3	78•	91
4	63•	24
6,15,L		
0	109•	145
1	29•	49
7,0,L		
2	140	141
4	86•	36
6	127	128
8	203	246
10	77•	15
7,1,L		
1	289	270
2	259	253
3	307	331
4	24•	74
5	25•	26
6	77•	60
7	56•	39
8	184	233
9	142•	88
10	109•	100
7,2,L		
1	118•	121
2	90•	98
3	445	464
4	188	200
5	114•	31
6	64•	101
7	79•	8
8	97•	39
9	71•	48
10	27•	47
7,3,L		

1	57•	38
2	23•	36
3	22•	74
4	91•	118
5	331	345
6	66•	35
7	177	220
8	29•	56
9	100•	2
10	34•	25
7,4,L		
1	187	207
2	23•	93
3	315	347
4	83•	140
5	193	159
6	30•	65
7	27•	132
8	36•	77
9	176	62
10	53•	89
7,5,L		
1	245	264
2	118	102
3	23•	56
4	53•	26
5	235	236
6	52•	37
7	26•	37
8	125•	15
9	114•	98
10	45•	26
7,6,L		
1	180	198
2	24•	57
3	134	95
4	95•	29
5	145•	177
6	31•	64
7	40•	7
8	164	197
9	159•	62
7,7,L		
1	114•	138
2	25•	51
3	104•	67
4	27•	77
5	179	122
6	93•	52
7	80•	59
8	151	134
9	39•	77
7,8,L		
1	142	149
2	26•	61
3	133	127
4	69•	61
5	33•	69
6	93•	75
7	91•	34
8	78•	22
9	98•	16
7,9,L		
1	113•	107
2	26•	115
3	253	282
4	43•	40
5	159	126
6	113•	63
7	29•	13
8	84•	59
7,10,L		
1	78•	161
2	174	155
3	43•	118
4	28•	94
5	159	77
6	94•	42
7	30•	82
8	91•	31
7,11,L		
1	142	176
2	70•	66
3	29•	49
4	29•	16
5	124•	24
6	35•	17
7	96•	28
7,12,L		
1	31•	16
2	27•	42
3	37•	32
4	80•	66
5	176	149
6	126•	64

7,13,L		
1	96•	58
2	28•	33
3	27•	92
4	129•	108
5	48•	119
7,14,L		
1	29•	56
2	27•	25
3	28•	14
8,0,L		
0	222	228
2	293	251
4	344	339
6	243	281
8	94•	98
10	89•	131
8,1,L		
0	243	198
1	198	192
2	84•	99
3	135	152
4	105•	63
5	264	252
6	128•	163
7	81•	44
8	76•	130
9	64•	17
10	27•	62
8,2,L		
0	206	205
1	195	232
2	414	389
3	99•	87
4	151	157
5	121•	14
6	209	228
7	87•	95
8	64•	101
9	94•	58
10	126•	8
8,3,L		
0	344	338
1	580	589
2	386	418
3	78•	16
4	252	233
5	111•	187
6	31•	86
7	134	119
8	53•	62
9	47•	160
10	35•	66
8,4,L		
0	321	304
1	649	633
2	252	293
3	24•	132
4	96•	98
5	162	151
6	108•	35
7	68•	89
8	158	73
9	102•	20
10	36•	22
8,5,L		
0	1116	1089
1	287	278
2	54•	1
3	98•	118
4	27•	47
5	33•	124
6	232	186
7	111•	147
8	145•	199
9	83•	44
8,6,L		
0	155	133
1	52•	74
2	115	53
3	25•	25
4	207	228
5	113•	21
6	61•	57
7	28•	40
8	133•	84
9	123•	137
8,7,L		
0	212	217
1	194	228
2	208	256
3	139	152
4	223	188
5	67•	171
6	128•	22
7	92•	63

8	33•	49
9	84•	64
8,8,L		
0	307	335
1	26•	87
2	169	215
3	126	139
4	249	286
5	100•	19
6	82•	22
7	29•	72
8	33•	12
8,9,L		
0	53•	48
1	79•	74
2	103•	79
3	179	198
4	275	262
5	90•	158
6	34•	60
7	30•	82
8	33•	31
8,10,L		
0	298	314
1	26•	22
2	26•	5
3	177	154
4	124•	122
5	35•	94
6	106•	18
7	30•	54
8,11,L		
0	69•	31
1	84•	38
2	60•	3
3	38•	5
4	30•	109
5	37•	101
6	66•	12
8,12,L		
0	171	190
1	118•	173
2	72•	103
3	56•	28
4	30•	47
5	165	91
6	37•	141
8,13,L		
0	61•	89
1	42•	5
2	27•	13
3	27•	157
4	80•	28
8,14,L		
0	29•	11
1	52•	13
2	28•	32
3	46•	35
9,0,L		
2	82•	46
4	82•	93
6	102	155
8	134•	159
10	88•	153
9,1,L		
1	90•	183
2	159	161
3	144	149
4	79•	106
5	120•	112
6	69•	2
7	86•	34
8	58•	88
9	66•	76
10	122•	68
9,2,L		
1	224	238
2	110•	134
3	129	51
4	65•	30
5	26•	44
6	77•	59
7	245	220
8	125•	6
9	72•	26
10	91•	68
9,3,L		
1	503	501
2	102•	43
3	23•	16
4	82•	6
5	164	180
6	127•	105

7	83•	130
8	92•	64
9	80•	61
10	187•	28
9,4,L		
1	196	224
2	163	177
3	279	292
4	47•	91
5	305	289
6	219	221
7	27•	18
8	76•	81
9	38•	1
9,5,L		
1	140	123
2	112•	155
3	67•	31
4	27•	12
5	43•	48
6	188	204
7	51•	97
8	92•	56
9	37•	22
9,6,L		
1	101•	40
2	276	318
3	25•	20
4	85•	20
5	32•	46
6	262	287
7	66•	91
8	98•	52
9	61•	8
9,7,L		
1	26•	57
2	25•	4
3	106•	11
4	29•	48
5	33•	49
6	33•	21
7	29•	18
8	32•	38
9	86•	78
9,8,L		
1	118•	114
2	26•	21
3	47•	67
4	118•	140
5	34•	183
6	57•	21
7	67•	18
8	82•	44
9,9,L		
1	27•	49
2	218	216
3	129	153
4	78•	26
5	63•	28
6	34•	3
7	30•	61
8	70•	28
9,10,L		
1	114•	28
2	26•	11
3	85•	60
4	144	77
5	143•	48
6	35•	34
7	123•	58
9,11,L		
1	61•	41
2	87•	8
3	69•	3
4	111•	144
5	38•	49
6	35•	114
9,12,L		
1	27•	7
2	92•	31
3	27•	53
4	30•	36
5	36•	38
9,13,L		
1	65•	13
2	27•	48
3	28•	45
4	31•	17
9,14,L		
1	30•	119
10,0,L		

0	298	276
2	84•	90
4	112•	65
6	121	93
8	75•	148
10	186•	90
10,1,L		
0	256	239
1	120	147
2	84•	19
3	202	194
4	27•	93
5	116•	214
6	126•	182
7	199	220
8	59•	21
9	27•	35
10,2,L		
0	107•	35
1	46•	56
2	40•	41
3	277	302
4	127	184
5	115•	18
6	173	151
7	102•	14
8	27•	7
9	27•	70
10,3,L		
0	517	541
1	225	212
2	114	82
3	69•	23
4	200	76
5	81•	76
6	59•	18
7	128•	165
8	153	148
9	138•	49
10,4,L		
0	170	208
1	188	178
2	278	272
3	108•	108
4	193	191
5	112•	23
6	101	178
7	44•	47
8	32•	27
9	106•	29
10,5,L		
0	489	533
1	228	243
2	105•	149
3	25•	5
4	230	219
5	117•	119
6	32•	5
7	100•	176
8	91•	135
9	41•	19
10,6,L		
0	565	581
1	90•	78
2	96•	98
3	228	139
4	242	225
5	32•	20
6	159	119
7	101•	16
8	176	156
9	40•	19
10,7,L		
0	134	129
1	27•	77
2	138	161
3	199	219
4	50•	29
5	162	176
6	160	184
7	29•	98
8	55•	35
10,8,L		
0	266	307
1	39•	37
2	186	195
3	29•	117
4	28•	153
5	82•	2
6	151•	192
7	30•	21
8	33•	35
10,9,L		
0	26•	10
1	138	108
2	79•	7
3	26•	80

table VIII (concl)

	10,9,L		8	33•	15		12,3,L		4	77•	47	3	82•	61	1	29•	4•		16,1,L			17,4,L	
									6	25•	24				2	39•	7						
4	76•	39		11,6,L		0	78•	44	8	111•	21		14,0,L		3	28•	48	0	106•	64	1	27•	41
5	34•	16				1	187	198										1	147	112	2	109•	31
6	188•	48	1	111•	125	2	71•	142		13,1,L		0	189	217		14,11,L		2	90•	102	3	74•	19
7	107•	21	2	26•	39	3	99•	99				2	67•	3				3	215	93	4	32•	14
			3	48•	25	4	93•	76	1	27•	57	4	244•	56	0	82•	75	4	27•	12			
	10,10,L		4	38•	23	5	149•	104	2	76•	2	6	709•	26	1	55•	56	5	76•	28		17,5,L	
			5	33•	77	6	128•	73	3	107•	148	8	844•	159				6	27•	91			
0	27•	155	6	72•	35	7	107•	42	4	26•	17					15,0,L					1	30•	119
1	27•	68	7	29•	37	8	94•	51	5	79•	76		14,2,L						16,2,L		2	55•	36
2	26•	18	8	116•	16				6	104•	13				2	88•	85				3	27•	35
3	26•	84					12,4,L		7	67•	102	0	186	214	4	89•	174	0	153	159	4	31•	32
4	98•	91		11,7,L					8	56•	64	1	83•	77	6	152•	116	1	107•	2			
5	35•	38				0	154	107				2	127•	86				2	99•	166		17,6,L	
6	165	122	1	27•	382	1	27•	36		13,2,L		3	95•	64		15,1,L		3	53•	38			
			2	32•	9	2	26•	98				4	89•	33				4	27•	15	1	28•	34
	10,11,L		3	204	249	3	26•	137	1	86•	1	5	164	158	1	26•	38	5	52•	82	2	28•	7
			4	40•	33	4	161	131	2	139	141	6	78•	21	2	138	66	6	106•	58	3	88•	75
0	27•	35	5	64•	36	5	34•	78	3	96•	61	7	136•	88	3	79•	7						
1	27•	54	6	34•	27	6	62•	28	4	99•	38	8	80•	19	4	29•	86		16,3,L			17,7,L	
2	129	124	7	30•	27	7	29•	38	5	78•	92				5	110•	68						
3	28•	48	8	34•	51	8	131•	180	6	189	197		14,2,L		6	90•	72	0	98•	8	1	188	145
4	66•	71							7	27•	47				7	89•	93	1	28•	24	2	86•	98
5	178	74		11,8,L			12,5,L		8	27•	8	0	65•	28				2	27•	31			
6	59•	23										1	134•	191		15,2,L		3	27•	29		18,0,L	
			1	89•	49	0	27•	3		13,3,L		2	65•	51				4	83•	80			
	10,12,L		2	151	139	1	356	305				3	91•	14	1	25•	5	5	36•	78	0	119•	194
			3	27•	109	2	63•	85	1	27•	38	4	125•	90	2	72•	59	6	149	188	2	113•	114
0	27•	58	4	29•	59	3	60•	48	2	188	810	5	72•	19	3	26•	38				4	38•	14
1	63•	72	5	142•	44	4	159	164	3	158	131	6	55•	72	4	81•	18		16,4,L				
2	27•	39	6	34•	69	5	43•	41	4	96•	93	7	82•	17	5	115•	75					18,1,L	
3	27•	13	7	30•	9	6	33•	73	5	34•	167				6	154•	126	0	43•	12			
4	134•	69				7	42•	141	6	39•	111		14,3,L		7	62•	36	1	28•	7	0	86•	48
				11,9,L		8	108•	8	7	29•	2							2	130	107	1	92•	82
	10,13,L								8	32•	37	0	114•	162		19,3,L		3	112•	77	2	85•	61
			1	132	162		12,6,L					1	101•	109				4	122•	176	3	128•	17
0	27•	76	2	26•	4					13,4,L		2	25•	42	1	97•	73	5	78•	66	4	88•	91
1	126•	51	3	151	155	0	333	319				3	92•	97	2	24•	32	6	36•	9			
2	27•	7	4	90•	32	1	221	247	1	141	152	4	117•	128	3	27•	68					18,2,L	
3	28•	22	5	39•	48	2	309	323	2	65•	119	5	35•	18	4	81•	48		16,5,L				
			6	37•	8	3	107•	164	3	37•	54	6	35•	128	5	139•	29				0	129•	188
	11,0,L		7	31•	56	4	120•	208	4	28•	32	7	101•	177	6	89•	18	8	133	99	1	46•	32
						5	35•	42	5	34•	180				7	31•	29	1	98•	14	2	124	108
2	24•	22		11,10,L		6	172	164	6	93•	146		14,4,L					2	28•	78	3	98•	4
4	181•	66				7	38•	6	7	106•	146					15,4,L		3	28•	48	4	97•	34
6	24•	62	1	96•	72	8	49•	9	8	34•	38	0	60•	27				4	73•	89			
8	91•	25	2	27•	40							1	64•	58	1	79•	105	5	37•	4		18,3,L	
			3	27•	78		12,7,L			13,5,L		2	88•	43	2	95•	99						
	11,1,L		4	30•	48							3	142	180	3	129	156		16,6,L		0	91•	102
			5	60•	56	0	143	133	1	197	289	4	134•	104	4	38•	1				1	36•	87
1	67•	14	6	39•	79	1	188	213	2	25•	18	5	82•	114	5	36•	17	0	27•	91	2	27•	2
2	138•	160				2	128•	172	3	53•	95	6	80•	66	6	36•	182	1	69•	31	3	41•	111
3	241	269		11,11,L		3	29•	31	4	29•	137	7	84•	46				2	153	186			
4	26•	51				4	70•	75	5	186	135					15,5,L		3	74•	8		18,4,L	
5	139•	121	1	28•	16	5	35•	29	6	134•	61		14,5,L					4	31•	76			
6	119•	107	2	92•	6	6	125•	17	7	30•	9				1	142	106	5	111•	111	0	28•	41
7	129	92	3	83•	35	7	30•	77				0	26•	81	2	85•	8				1	68•	42
8	31•	1	4	131•	36					13,6,L		1	72•	157	3	113•	108		16,7,L		2	30•	41
9	142•	98	5	123•	8		12,8,L					2	27•	139	4	29•	8				3	28•	98
									1	159	199	3	147	172	5	36•	62	8	28•	113			
	11,2,L			11,12,L		0	27•	110	2	26•	7	4	71•	123	6	36•	39	1	138	159		18,5,L	
						1	76•	30	3	51•	149	5	66•	60				2	28•	88			
1	98•	37	1	29•	39	2	68•	27	4	29•	47	6	34•	22		15,6,L		3	27•	26	0	28•	7
2	93•	184	2	141	87	3	119•	58	5	120•	65	7	31•	126				4	31•	27	1	29•	12
3	103•	112	3	28•	65	4	221	240	6	35•	2				1	156	159				2	28•	48
4	85•	120	4	56•	29	5	35•	66	7	49•	69		14,6,L		2	28•	158		16,8,L				
5	134•	117				6	35•	32							3	104•	63					18,6,L	
6	136•	148		11,13,L		7	114•	48		13,7,L		0	132•	194	4	30•	67	0	135	97			
7	26•	26							1	148	136	1	27•	18	5	137•	46	1	62•	72	0	41•	36
8	155•	162	1	35•	59		12,9,L		2	168	196	2	53•	45	6	36•	37	2	27•	69	1	28•	42
9	122•	121							3	26•	43	3	27•	127				3	95•	118			
				12,0,L		0	27•	19	4	99•	94	4	116•	56		15,7,L						19,0,L	
	11,3,L					1	88•	113	5	171	195	5	35•	56					16,9,L		2	27•	108
			0	24•	132	2	36•	84	6	34•	31	6	87•	69	1	28•	2						
1	25•	38	2	238	286	3	26•	63	7	31•	7				2	28•	21	0	74•	16			
2	131	110	4	25•	2	4	102•	101					14,7,L		3	55•	51	1	78•	86		19,1,L	
3	25•	26	6	101	203	5	36•	33		13,8,L					4	30•	43						
4	28•	20	8	26•	120	6	36•	98				0	358	380	5	36•	49		17,0,L		1	82•	88
5	32•	33							1	27•	51	1	110•	145							2	27•	35
6	33•	72		12,1,L			12,10,L		2	27•	12	2	65•	73		15,8,L		2	80•	143			
7	57•	129							3	27•	30	3	105•	52				4	102•	79		19,2,L	
8	32•	9	0	62•	80	0	72•	145	4	29•	10	4	64•	1	1	148	64						
9	39•	21	1	84•	65	1	43•	88	5	36•	33	5	57•	2	2	123	79		17,1,L		1	188•	36
			2	28•	78	2	96•	42	6	161	65	6	36•	26	3	27•	6				2	107•	17
	11,4,L		3	26•	25	3	70•	42							4	31•	39	1	27•	14			
			4	112•	147	4	76•	58		13,9,L			14,8,L					2	99•	56		19,3,L	
1	26•	13	5	82•	62	5	132•	13								15,9,L		3	143	121			
2	137	108	6	108•	44				1	116•	95	0	214	258				4	105•	9	1	101•	66
3	136	171	7	84•	84		12,11,L		2	26•	2	1	29•	105	1	95•	68	5	114•	72			
4	28•	14	8	111•	39				3	27•	9	2	27•	84	2	28•	18					20,0,L	
5	186	199	9	122•	17	0	71•	4	4	48•	11	3	27•	12	3	28•	19		17,2,L		0	27•	39
6	32•	67				1	80•	73	5	114•	12	4	30•	92									
7	29•	36		12,2,L		2	82•	34				5	80•	34		15,10,L		1	84•	46		20,1,L	
8	33•	123				3	83•	20		13,10,L								2	27•	33			
9	40•	49	0	88•	119	4	30•	77					14,9,L		1	59•	38	3	60•	29			
			1	96•	88				1	28•	37	0	28•	104		16,0,L		4	27•	18	0	29•	25
	11,5,L		2	136•	220		12,12,L		2	27•	8	1	28•	41				5	116•	184			
			3	118•	117				3	38•	37	2	47•	23	0	97•	61					20,2,L	
1	55•	10	4	171	154	0	44•	0	4	31•	61	3	28•	8	2	78•	114		17,3,L		0	29•	101
2	163	166	5	192	171	1	120•	113				4	90•	58	4	25•	29	1	58•	24			
3	53•	26	6	123•	96	2	27•	26		13,11,L					6	98•	181	2	70•	21			
4	93•	158	7	99•	42								14,10,L					3	115•	58			
5	34•	108	8	27•	103		13,0,L		1	29•	3							4	31•	79			
6	33•	74	9	118•	27				2	48•	60	0	78•	9				5	44•	49			
7	51•	62				2	111•	97															

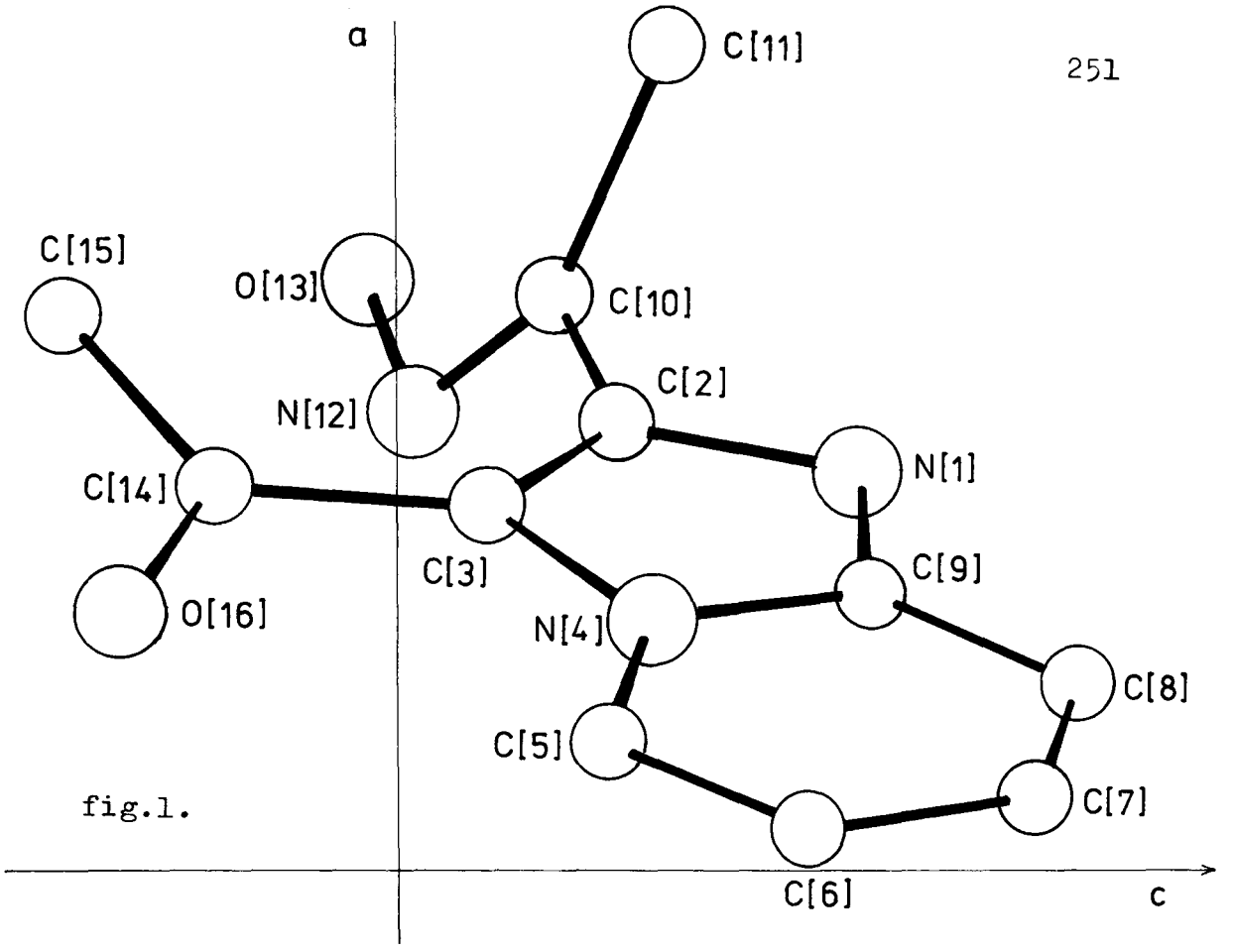


fig.1.

fig.2. Bond lengths (Å) and standard deviations in brackets. Bonds to hydrogen excluded.

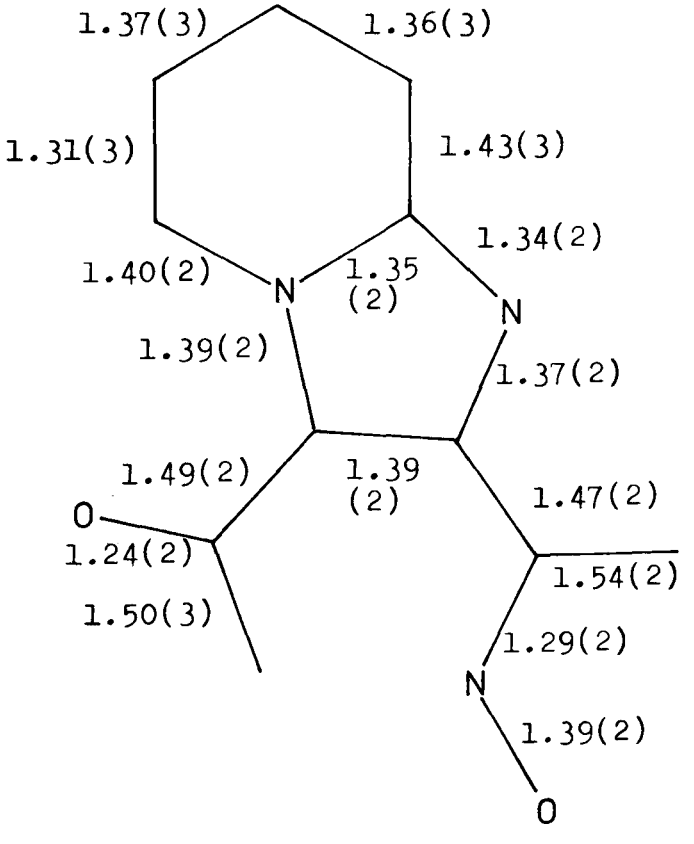


fig.3. Bond angles (°). Bonds to hydrogen excluded. Standard deviations in brackets.

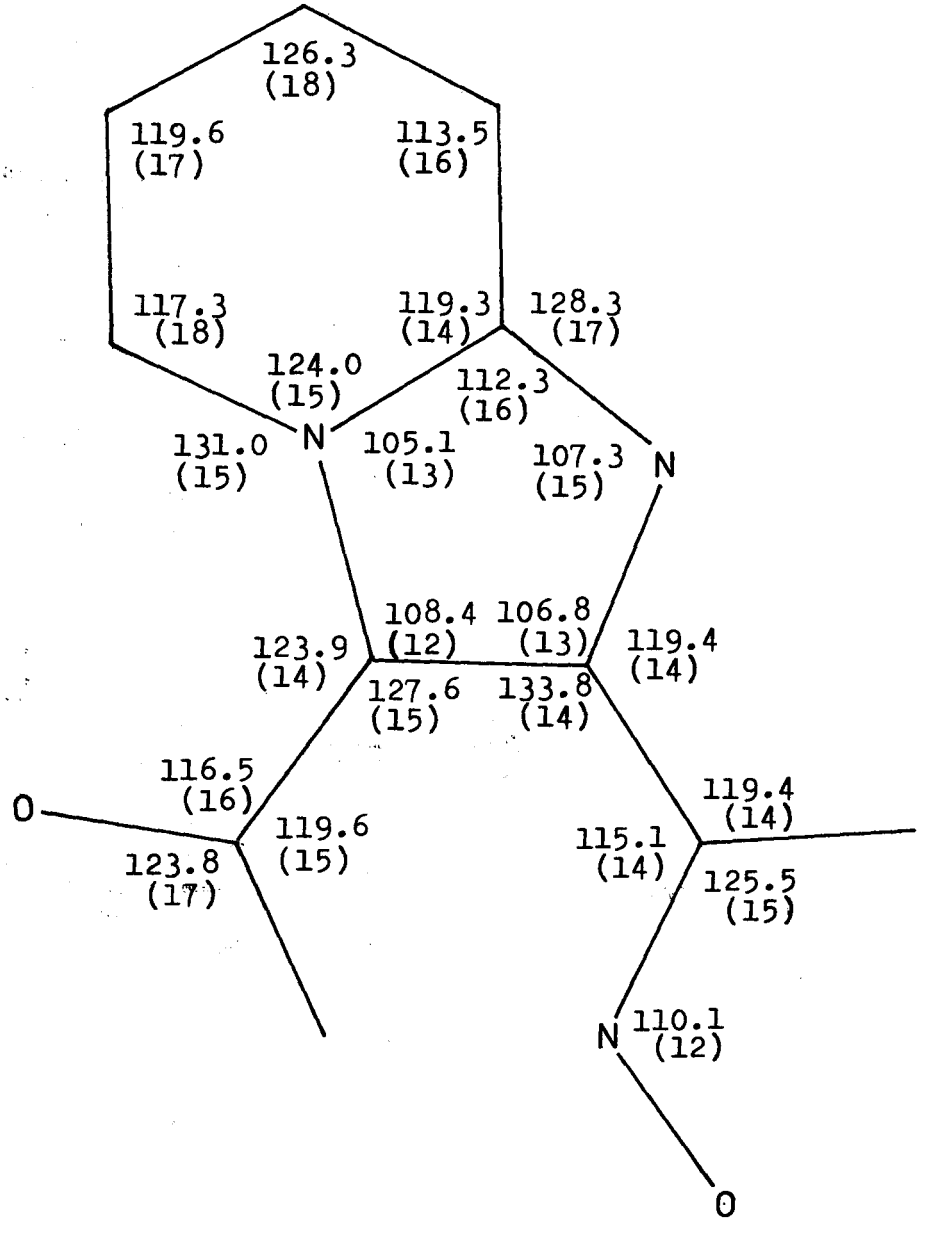
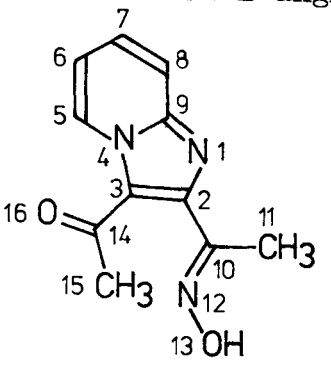


table IX. Least squares planes.

The deviations (Å) from the plane of the atoms defining the plane are given first, followed by the deviations of the other non-hydrogen atoms. σ Is the standard deviation of the defining atoms from the plane, and the equation of the plane is given in terms of orthogonal coordinates (Å). ϕ_{xy} Is the torsional angle between planes x and y.



plane 1 (9 atoms)		plane 2 (4 atoms)		plane 3 (5 atoms)	
C(2)	-0.016 Å	C(3)	0.004 Å	C(2)	0.000 Å
C(3)	0.012	C(14)	-0.013	C(10)	-0.003
C(5)	0.005	C(15)	0.004	C(11)	0.001
C(6)	-0.010	O(16)	0.005	N(12)	0.002
C(7)	0.004			O(13)	-0.001
C(8)	0.004	C(2)	-0.207		
C(9)	-0.014	C(5)	0.538	C(3)	-0.880
N(1)	0.013	C(6)	0.757	C(5)	-0.834
N(4)	0.002	C(7)	0.752	C(6)	-0.104
		C(8)	0.506	C(7)	1.060
C(10)	-0.026	C(9)	0.236	C(8)	1.586
C(11)	1.129	C(10)	-0.530	C(9)	0.802
C(14)	0.074	C(11)	0.450	C(14)	-2.186
C(15)	0.400	N(1)	-0.011	C(15)	-2.815
N(12)	-1.041	N(4)	0.274	N(1)	1.024
O(13)	-0.946	N(12)	-1.648	N(4)	-0.354
O(16)	-0.109	O(13)	0.124	O(16)	-2.710
σ = 0.0106		σ = 0.0087		σ = 0.0020	
0.0865X+0.4935Y +0.0879Z = 1.6227		0.7397X+0.6544Y +0.1567Z = 1.3763		-0.3975X-0.4579Y +0.7952Z = 0.5698	
		ϕ_{12} = 60.0°		ϕ_{13} = 12.4° ϕ_{23} = 62.0°	

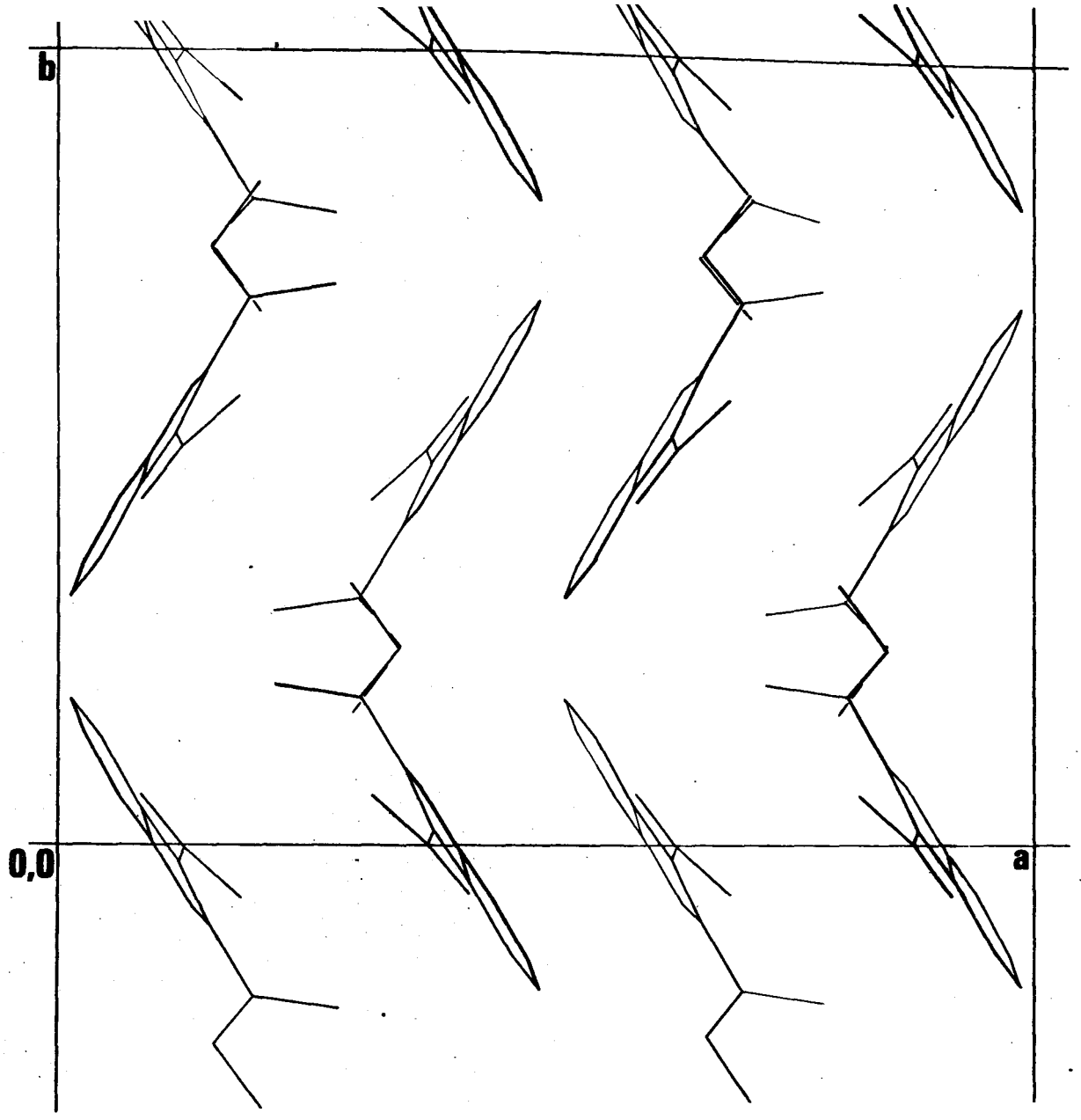


fig.4. One unit cell viewed down c.

table X. Intermolecular distances (A) less than 2.5A (translated atom second).

To molecule at (-x, -y, 1-z): H(8)-H(8) 2.31.

To molecule at (x, $\frac{1}{2}$-y, $\frac{1}{2}$+z): H(7)-H(5) 2.46.

To molecule at (x, $\frac{1}{2}$-y, z-$\frac{1}{2}$): H(5)-H(7) 2.46.

To molecule at (x, -$\frac{1}{2}$-y, $\frac{1}{2}$+z): H(112)-H(13) 2.15; N(1)-H(13) 1.62.

To molecule at (x, -$\frac{1}{2}$-y, z-$\frac{1}{2}$): H(13)-H(112) 2.15; H(13)-N(1) 1.62.

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