STUDIES IN THE CHEMISTRY OF PENICILLIN

A thesis presented by

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in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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ABSTRACT

The thesis is in two parts.

Part I

The recent literature concerning penicillin and cephalosporin derivatives is briefly reviewed.

The sulphenic acid intermediates formed on heating penicillin sulphoxides have been trapped with toluene-p-sulphinic acid to form the corresponding thiosulphonate S-esters. These esters were reacted with nucleophiles, such as the anion of diethyl malonate, to produce the corresponding sulphides. The sulphenic acids were also trapped with isopropenyl n-butyl ether and the resulting sulphides hydrolysed to the corresponding β-ketosulphides. These trapped products are potentially useful intermediates in the synthesis of new bicyclic β-lactam structures.

Sulphenic acid trapping reactions have been carried out with Penicillin G sulphoxide acid, using various hydrazides as the carboxylic acid protecting group. Attempted cyclisation of the trapped products, *via* reactions such as bromination and ozonolysis of the nitrogen attached side-chain, proved unsuccessful because of intramolecular cyclisation of the hydrazide protecting groups, or because of enolisation of the ozonolysis products.

Part II

The chemistry of diimide is briefly reviewed.

The reducing power of NN'-dihydrobenzo(c)cinnoline, a very mild reducing agent, has been examined. The reducing power of other dihydro-aromatic systems, such as benzimidazolines and benzothiazolines, was also investigated. These compounds were found to be less powerful than NN'-dihydrobenzo(c)cinnoline.

ACKNOWLEDGEMENTS

I wish to thank Professor Sir D.H.R. Barton, F.R.S. for the privilege of working under his guidance, Dr. P.G. Sammes for the encouragement and useful suggestions he made during the first two years' work, and Dr. R.D. Allan, who read the proofs of this thesis.

I also wish to thank the staff of the Chemistry Department for their essential analytical, spectral and technical services, and my fellow workers in the Hofmann Laboratory for their advice and co-operation.

Final acknowledgements are due to the Science Research Council for the award of a research studentship.

To my Parents, Eileen and Margaret.

"I feel I'm knocking on heaven's door."

Bob Dylan,

1973.

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PART I

REVIEW

1. Introduction

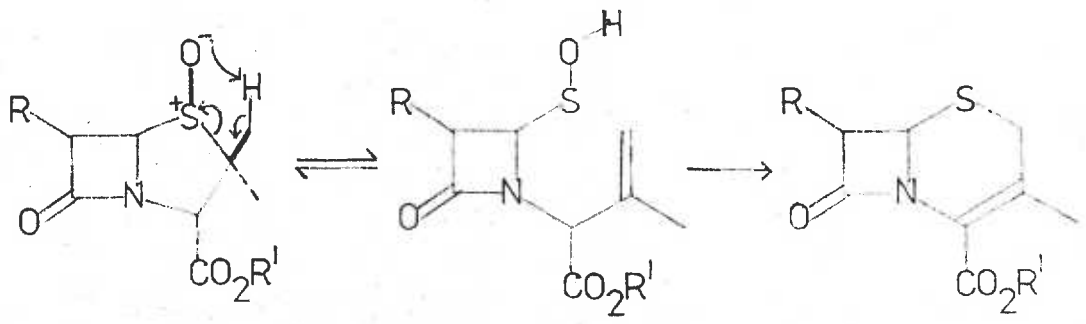
Although there are many different types of penicillin and cephalosporin antibiotics available on the market the spate of publications related to their chemistry still continues. The aim is to develop new antibiotics which are resistant to β-lactamases and show greater biological activity. The following review covers the advances which have been made from the beginning of 1973 to the present time. The chemistry of the β-lactam antibiotics has been excellently reviewed up to this point.[1,2]

The main topics reported are; penicillin chemistry, including the rearrangement of penicillin sulphoxides and methods of conversion into cephalosporins; cephalosporin chemistry, including methods of altering the dihydrothiazine ring moiety and reactions at position 6(7) of the penam (cephem) nucleus, including both substitution and epimerisation reactions.

2. Penicillin Chemistry

2.1 Sulphoxide rearrangements

The sulphenic acid (2) has been postulated as an intermediate in the thermal rearrangements of penicillin sulphoxide (1), but until very recently compounds with this reactive function have only been known as transient species.



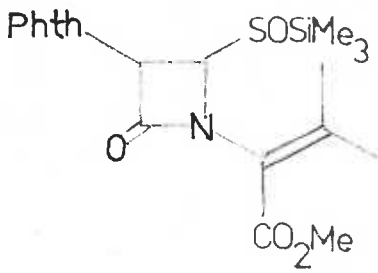
(1) (2) (3)

1a R = phthalimido(phth) R' = Me

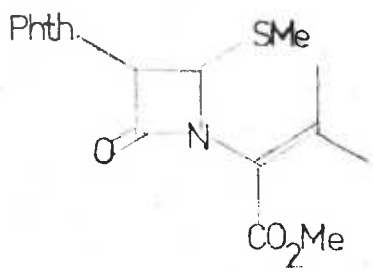
2a R = phth R' = Me

3 R = phth R' = Me

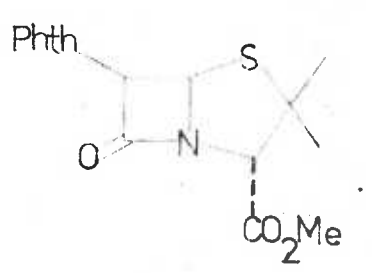
Recent work by Chou *et al.*,[3] has enabled the sulphenic acid (2a) to be isolated in a crystalline form, by refluxing the sulphoxide ester (1a) in ethyl acetate for 10 min. and evaporating to dryness. The sulphenic acid (2a) was isolated along with the starting material. Several reactions were carried out to demonstrate the reactive nature of the sulphenic acid (2a). Indeed a 50% conversion to the sulphoxide (1a) was obtained on heating for 3 hours in chloroform solution. Ring closure to the cephalosporin derivative (3) occurred upon treatment with methane sulphonic acid in benzene-dimethylacetamide. On refluxing the sulphoxide (1a) in benzene, in the presence of excess trimethyl silyl chloride, the trimethyl silyl ester (4) is obtained after conjugation of the side chain with triethylamine.[4] Reduction with trimethyl phosphite gives the methyl sulphide (5) together with the penam (6).



(4)



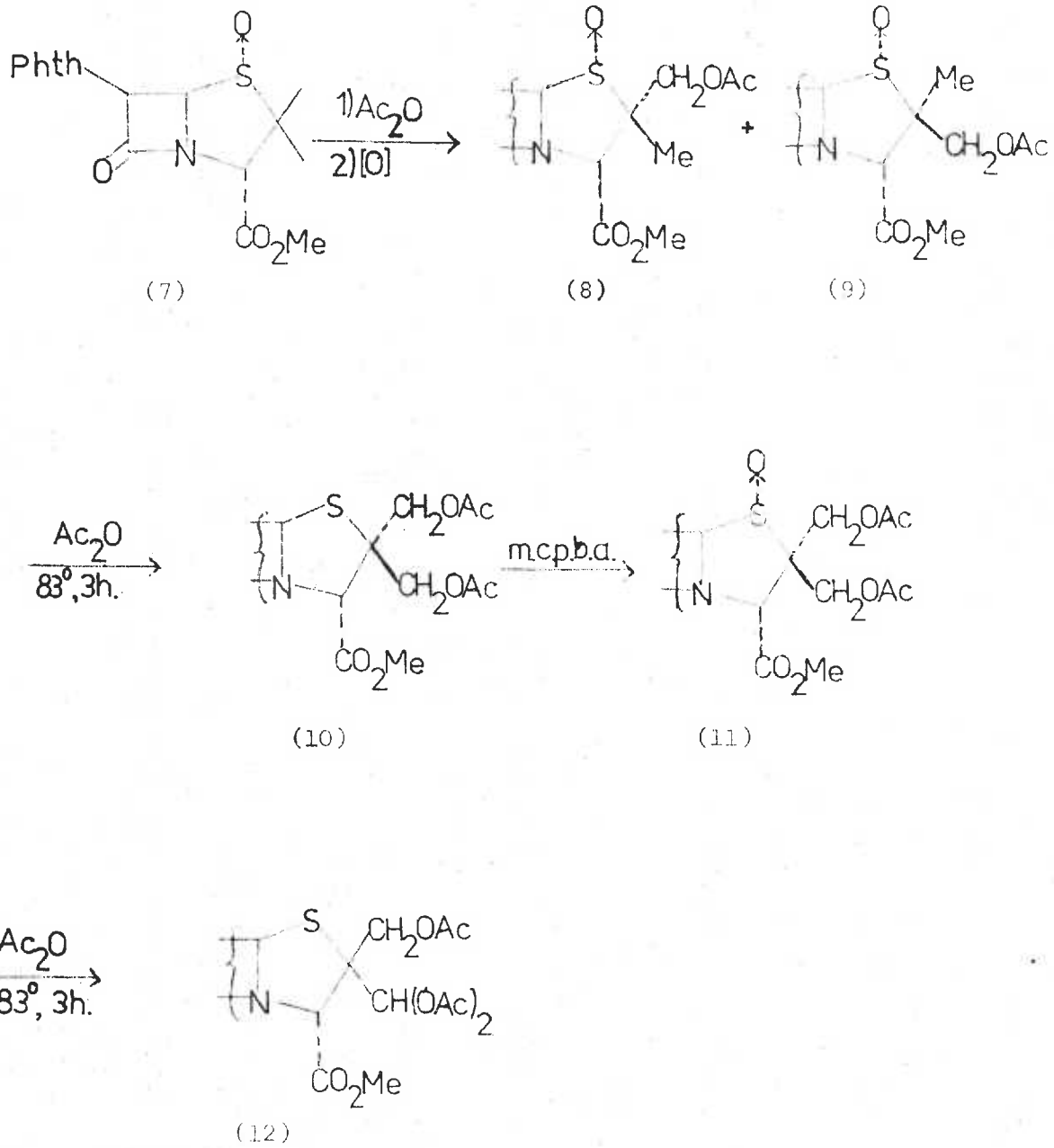
(5)



(6)

The rearrangement of penicillin sulphoxide esters with acetic anhydride was reported by Morin *et al.*[5] Further work on this rearrangement has been carried out[6] and it was found that on multiple rearrangement

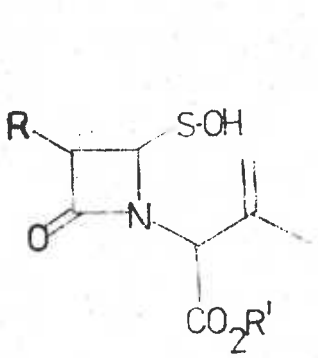
of methyl 6β-phthalimido penicillanate sulphoxide (7), 2-C-bisacetoxy-methyl(10) and 2-C-triacetoxymethyl(12) penicillin derivatives are formed. The results are summarised in Scheme 1.



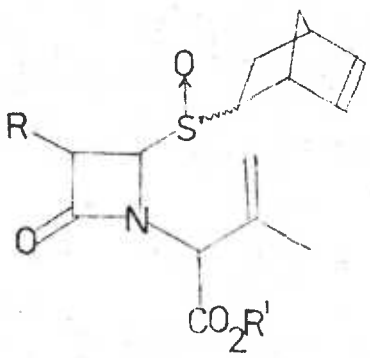
Scheme 1

This rearrangement of compound (7) is not completely stereoselective. The reasons for this have been discussed.[2]

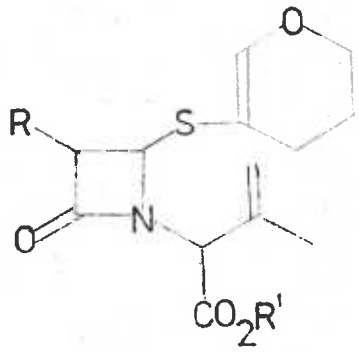
Results of reactions trapping the sulphenic acids with olefins and acetylenes[7,8] and with thiols[9] have been reported. Norbornadiene, diketen and dimethyl acetylene dicarboxylate react with the sulphenic acid (13) by addition, thus norbornadiene yields the sulphoxide (14), whereas vinyl ethers react by substitution. Thus dihydropyran yields the sulphide (15).



(13)

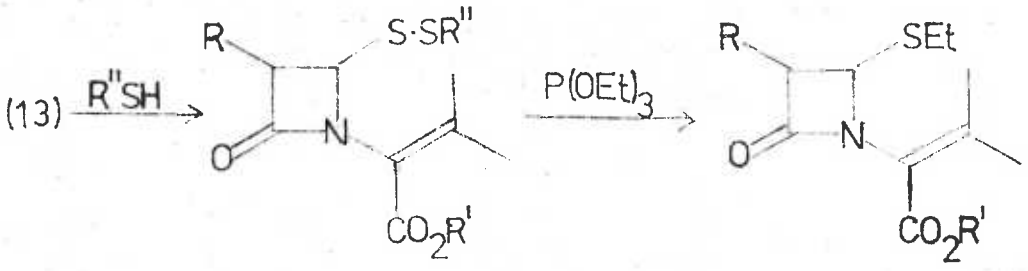


(14)



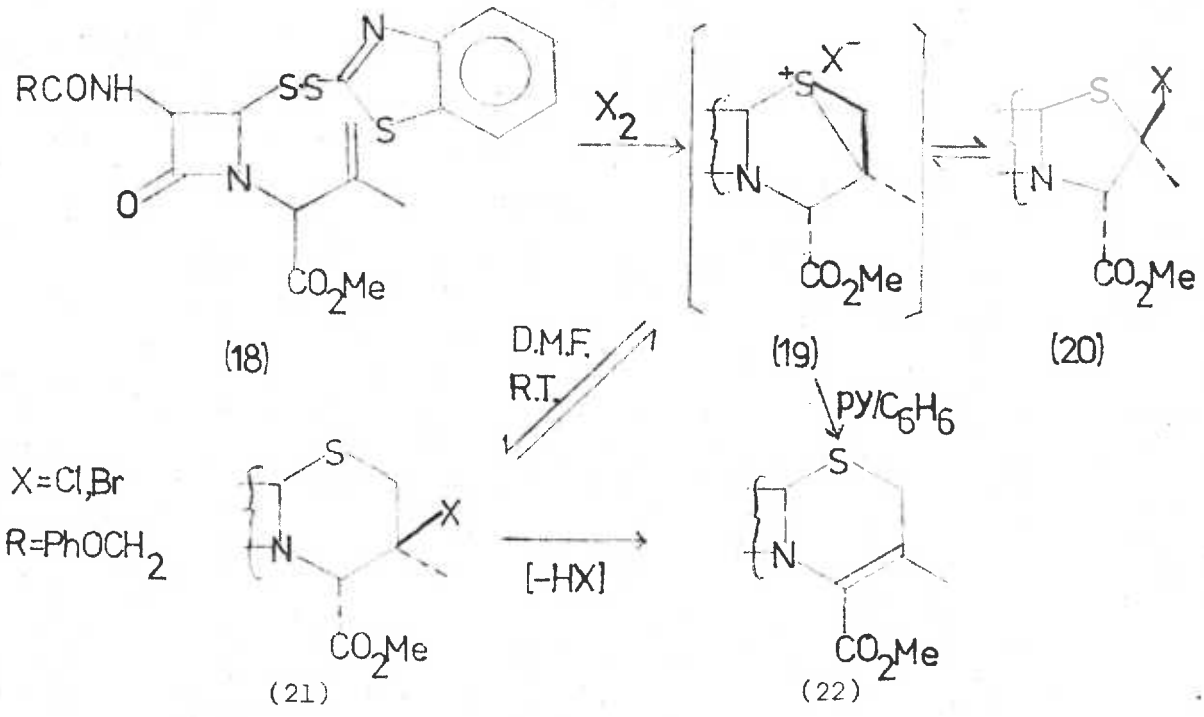
(15)

Thiols produce the corresponding disulphides (16) which in turn can be reacted with trialkyl phosphites to produce the corresponding sulphides (17), the alkyl residue arising from the phosphite reagent.

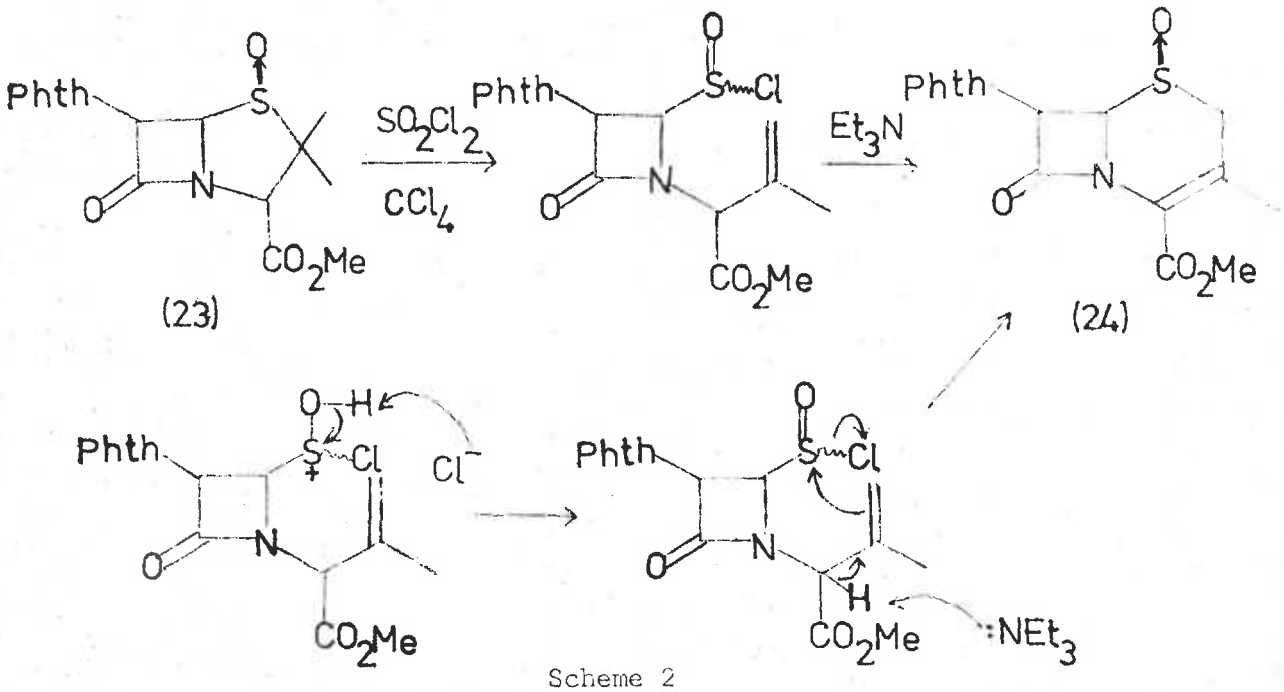


(16) (17)

With aliphatic thiols the resulting nitrogen substituent is isolated as the αβ-unsaturated isomer only, whereas with acidic thiols it is isolated as the βγ-unsaturated isomer. The latter are key intermediates for preparing 2-halomethyl penam and cepham derivatives. Thus the disulphide (18) gives the 2-halomethyl penicillin (20) by halogenation.[10] On standing in dimethylformamide overnight the 3β-halogenocepham derivative (21) is formed quantitatively, which can in turn be dehydrohalogenated to produce the cephem derivative (22). This rearrangement involves initial formation of the episulphonium ion (19).

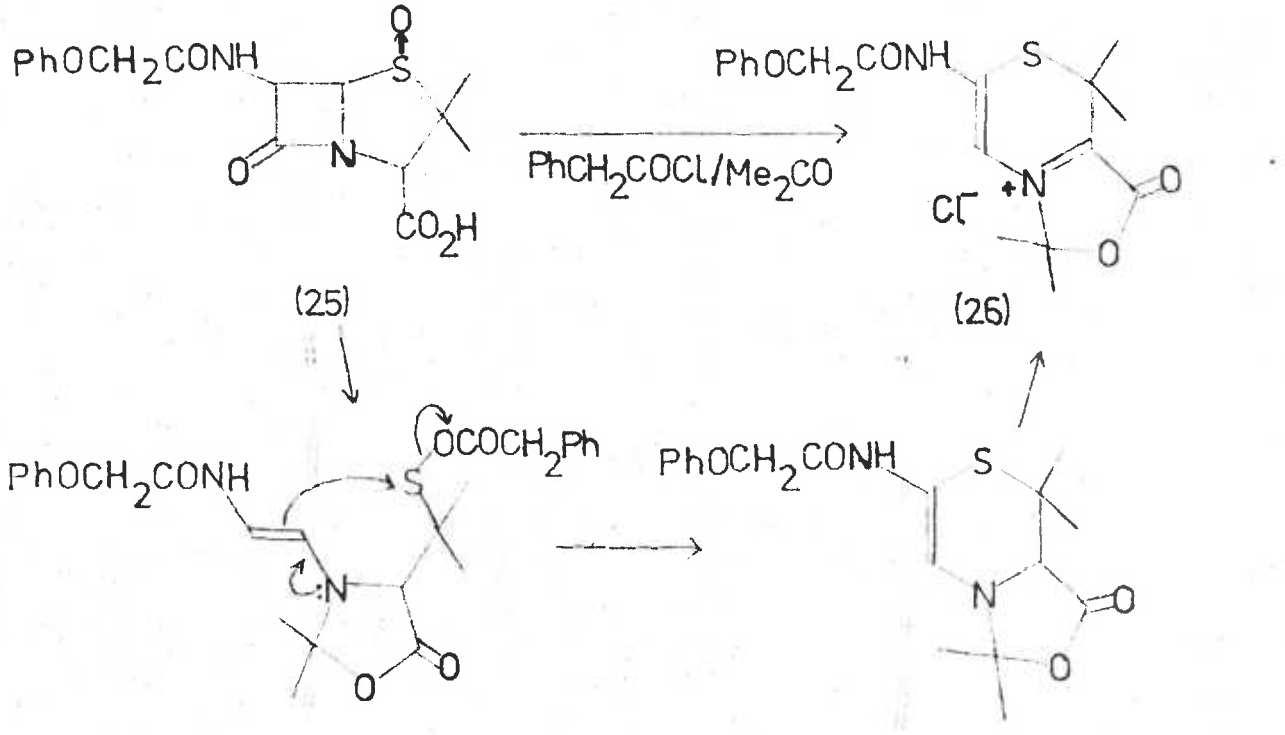


Another method of converting penicillins into cephalosporins *via* halogenation was reported by Kukolja *et al.*[11] This makes use of the nucleophilic character of the sulphur atom in the intermediate sulphenic acid. Thus penicillin (23) was converted to cephalosporin (24). The reaction is summarised in Scheme 2, and presumably goes by the mechanism shown, since no evidence of sulphine formation was found.



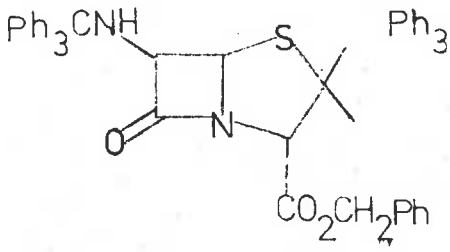
Scheme 2

An unusual reaction occurs on treating penicillin V β-sulphoxide (25) with phenyl acetyl chloride in acetone, at room temperature.[12] The product was structurally characterised as the 2H-1,4-thiazinium chloride (26) following X-ray crystallographic study. The reaction involves S-C(5) bond cleavage, and probably goes by the mechanism shown.

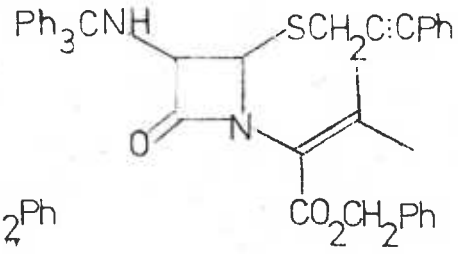


2.2. Other reactions

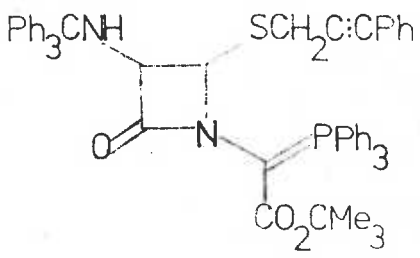
A novel conversion of penicillin into cephalosporins has been reported by Nayler.[13] Treatment of benzyl 6β-triphenylmethylamino penicillanate (27) with 3-phenylprop-2-ynyl bromide yields the 3-phenyl-prop-2-ynyl thioazetidinone (28). This compound is then converted, in several steps, into the phosphorane (29), which is hydrated to the ketone (30) by refluxing in neat piperidine. This ketone is converted by refluxing in dioxan, into the cephem (31), which is then converted into 3-benzyl-7β-(2-thienylacetamido) ceph-3-em-4carboxylic acid. (32) This new antibiotic had similar activity to its isostere cephaloridine (33) against gram-positive bacteria but was less active against gram-negative organisms.



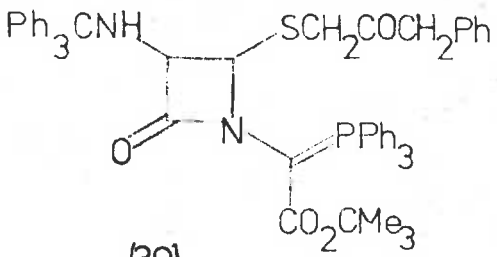
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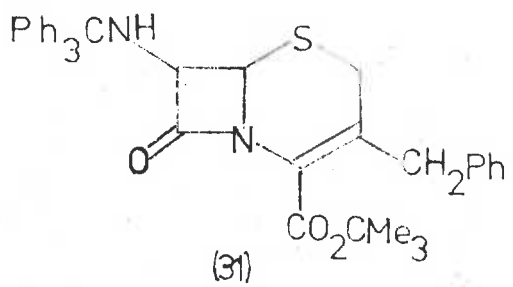
(28)



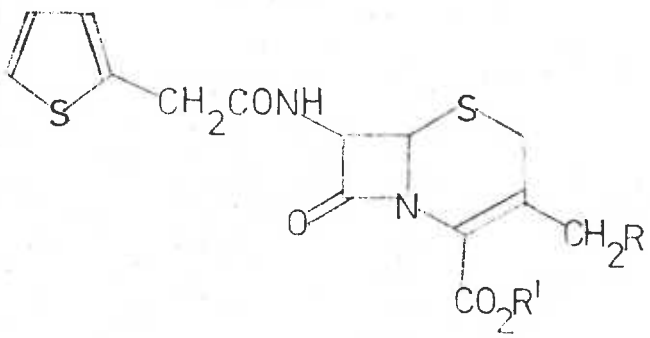
(29)



(30)



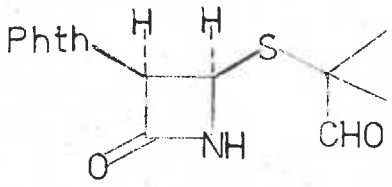
(31)



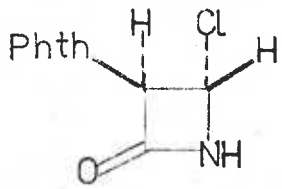
(32) R = Ph,R'=H.

(33) R = pyridinium, R' = Na

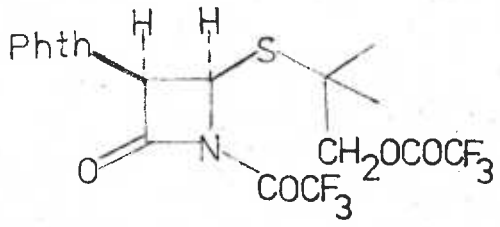
It has already been reported that chlorination of the penicillin nucleus involves cleavage of the 1,5-bond.[14] Some related chlorination experiments have been carried out by Sheehan and co-workers.[15] Chlorination of the aldehyde (34) produced the chloro compound (35), whereas, chlorination of the ester (36) produces the sulphenyl chloride (37).



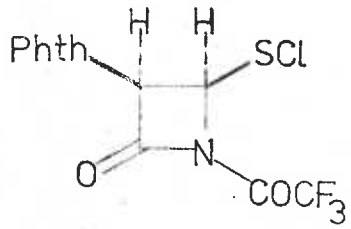
(34)



(35)



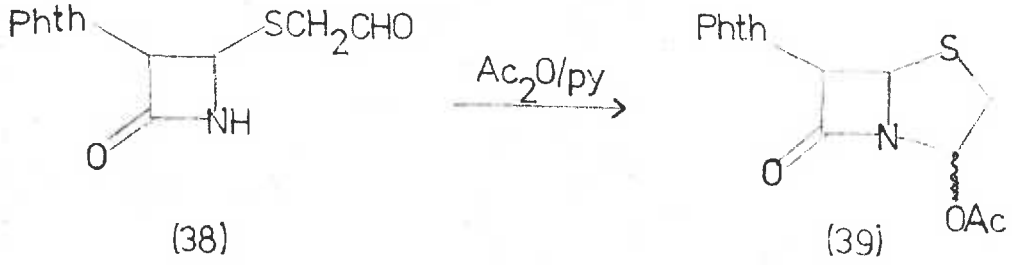
(36)



(37)

The chloro compounds (35) and (37) are potentially useful intermediates in the reconstruction of modified cepham and penam systems. Indeed, reaction of compound (37) with ethylvinyl ether produces the

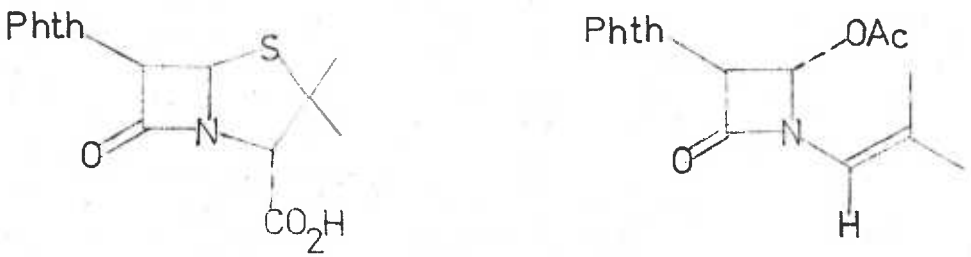
aldehyde (38), which on reaction with acetic anhydride affords the acetate (39).[16]



(38) (39)

Compound (35) has been used to produce alkyloxy-2-and acyloxy-2-azetidinones.[17]

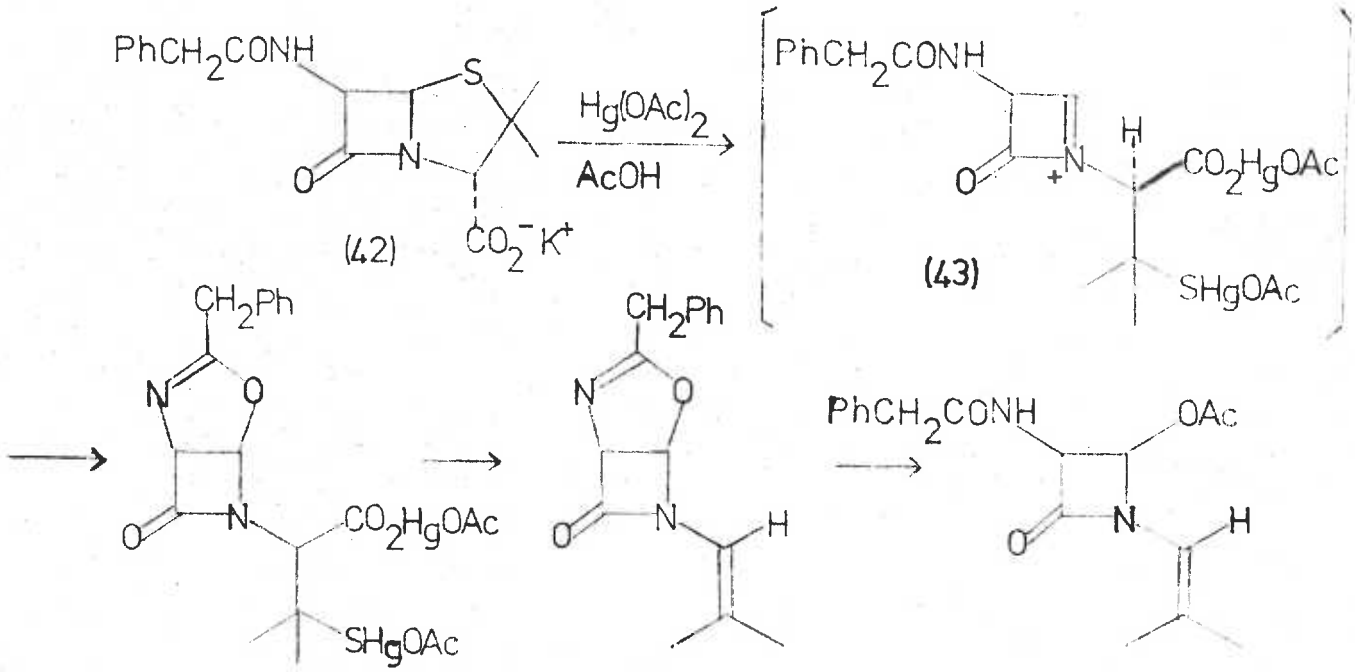
Selective cleavage of the 1,5-bond of penicillanic acid derivatives without loss of the sulphur atom has only been carried out by chlorination.[14] However, Stoodley *et al.*, in an attempt to induce a direct oxidative decarboxylation and a concomitant cleavage of the 3,4-bond studied the reactions of penicillanic acid derivatives with mercury (II) acetate.[18] On treatment of 6β-phthalimidopenicillanic acid (40) with mercury (II) acetate in acetic acid, at 85°, extrusion of sulphur took place affording compound (41).



(40) (41)

A more detailed investigation of the reaction[19] on potassium benzyl penicillanate (42) showed that the degradation initially involves 1,5-bond cleavage, producing the intermediate cation (43), which

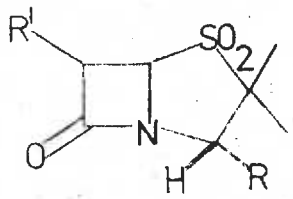
then affords the oxazoline (44). In turn this is converted to the oxazoline (45), which, on heating to 85°, eventually forms the acetate (46).



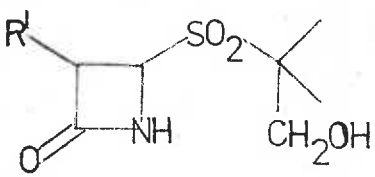
(44) (45) (46)

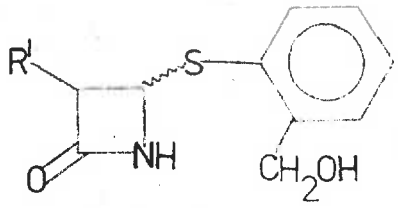
The oxazoline (45) can also be opened by other reagents such as alcohols and acids.[20]

A new method of cleaving the thiazolidine ring of the penam nucleus, whilst leaving the β-lactam ring intact has been reported.[21] Thus penicillin V sulphone (47) was converted to the isocyanate (48). Hydrolysis of the isocyanate afforded the masked aldehyde (49) which was reduced to the alcohol (50) with sodium borohydride. Reaction of the alcohol with O-mercaptobenzyl alcohol, in the presence of triethylamine, gave a 1:1 mixture of cis and trans azetidinones (51). Oxidation of (51) with dimethyl sulphoxide and dicyclohexyl carbodiimide[22] gave the tricyclic cephalosporanic compound (52), which was shown to be biologically active.



(50)





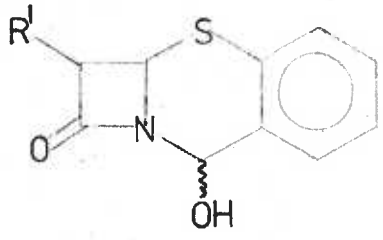
(51)

47 R = CO_2H R' = $PhOCH_2CONH$

48 R = NCO

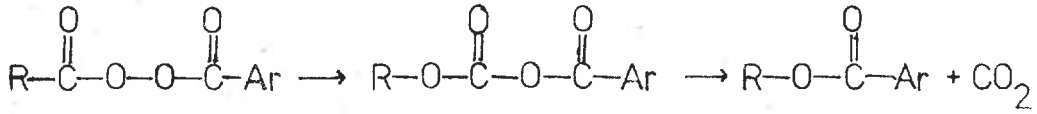
49 R = OH

DMSO
DCC



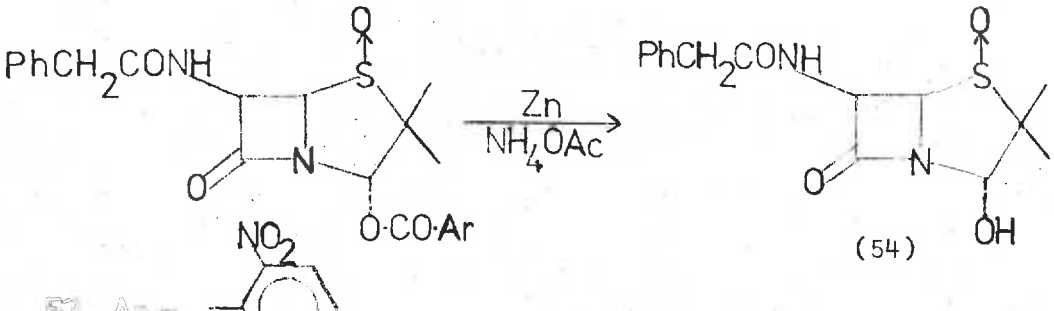
(52)

A new route to alcohols of type (49) has been described.[23] This employs decarboxylative rearrangement of alkanoyl-aroyl peroxides, as shown in Scheme 3.



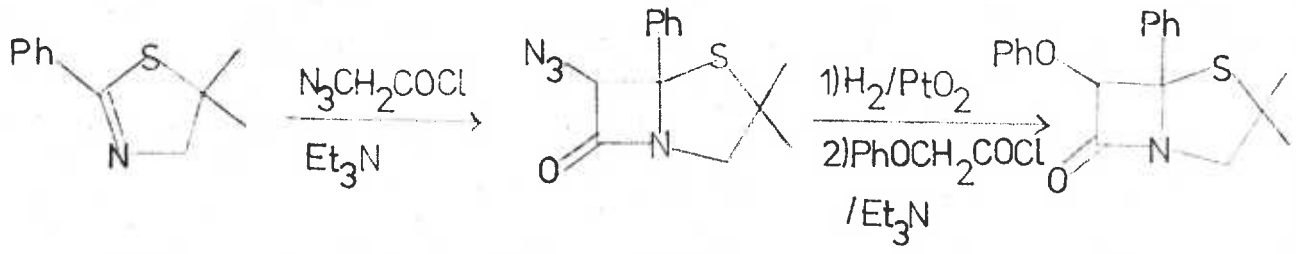
Scheme 3

Use of o-nitrobenzoic acid gives an ester of type (53), which on mild reduction produces the alcohol (54)



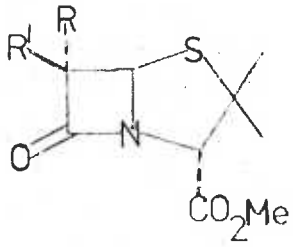
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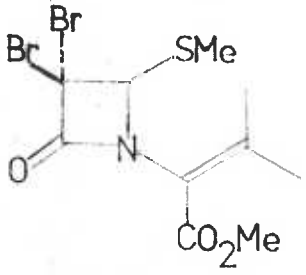
An unusual reaction of some 6-azido penams has been reported[24]. The 6-azido penam (56), formed by reaction of thiazoline (55) with azidoacetyl chloride in the presence of triethylamine, was reduced with hydrogen on platinum oxide and then treated with phenoxyacetyl chloride in the presence of triethylamine. The resulting product was (57). Thus, the amino compound formed by reduction of (56) undergoes β-lactam ring scission to the thiazoline (55).[25]



(55) (56) (57)

Methyl penicillanate (58) [26] and its 6α-bromo (59) and 6,6-dibromo derivatives (60) [27] are readily prepared from 6β-amino penicillanic acid and constitute convenient model compounds for studying the chemistry of the penam system without the complications which may arise from the presence of the 6β-acylamino group. The action of methyl iodide with strong anhydrous base on both (58) and (59) leads to 3-methylation and cleavage of both thiazolidine and β-lactam rings, but with (60) the β-lactam system remains intact the product being the azetidinone (61).[28] Some further reactions of (61) were reported.





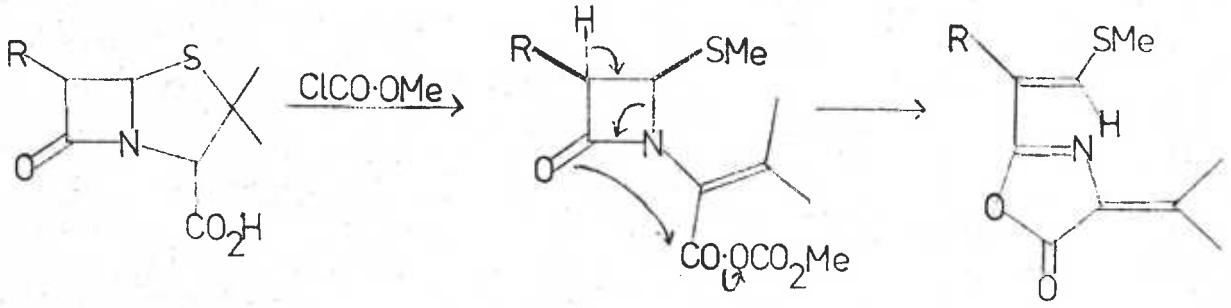
58. R = R' = H

59. R = Br, R' = H

60. R = R' = Br

(61)

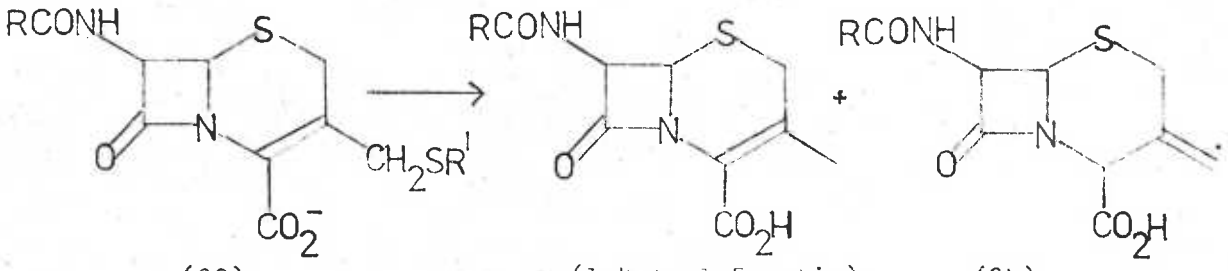
The product from the interesting rearrangement of penicillins with methyl chloroformate has been shown to have the structure (62) by total stereospecific synthesis.[29]



R = $PhCH_2CONH$ (62)

3. Cephalosporin Chemistry

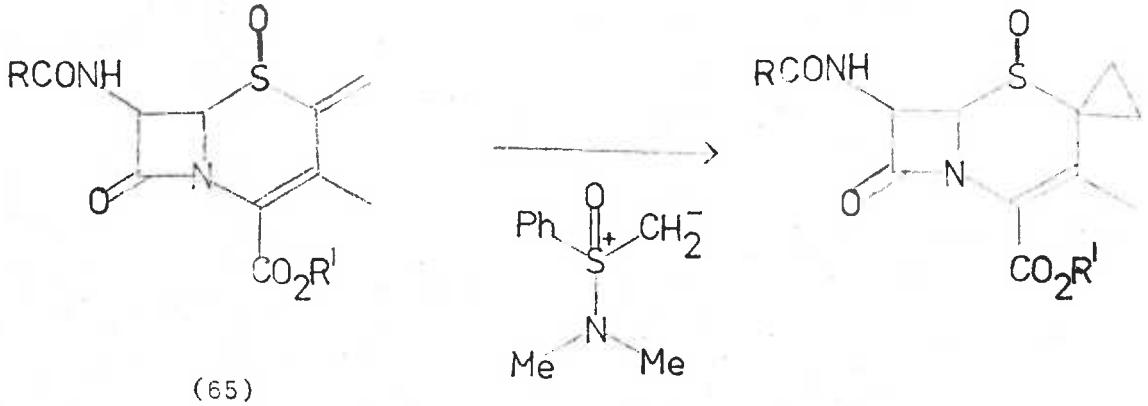
It has been shown that cephalosporanic acids (63), in which the acetoxy group is displaced by sulphur nucleophiles (*e.g.* thiourea, thiobenzoic acid) are reduced to 3-methylene cephams[30] (64) by catalytic hydrogenation . These compounds are also produced by reduction with zinc dust in a mixture of formic acid and dimethyl formamide.



(63) (1:4 to 1:5 ratio) (64)

3-methylene cephams (64) are also produced by electrochemical reduction of cephalosporanic acids (63) under mild conditions.[31]

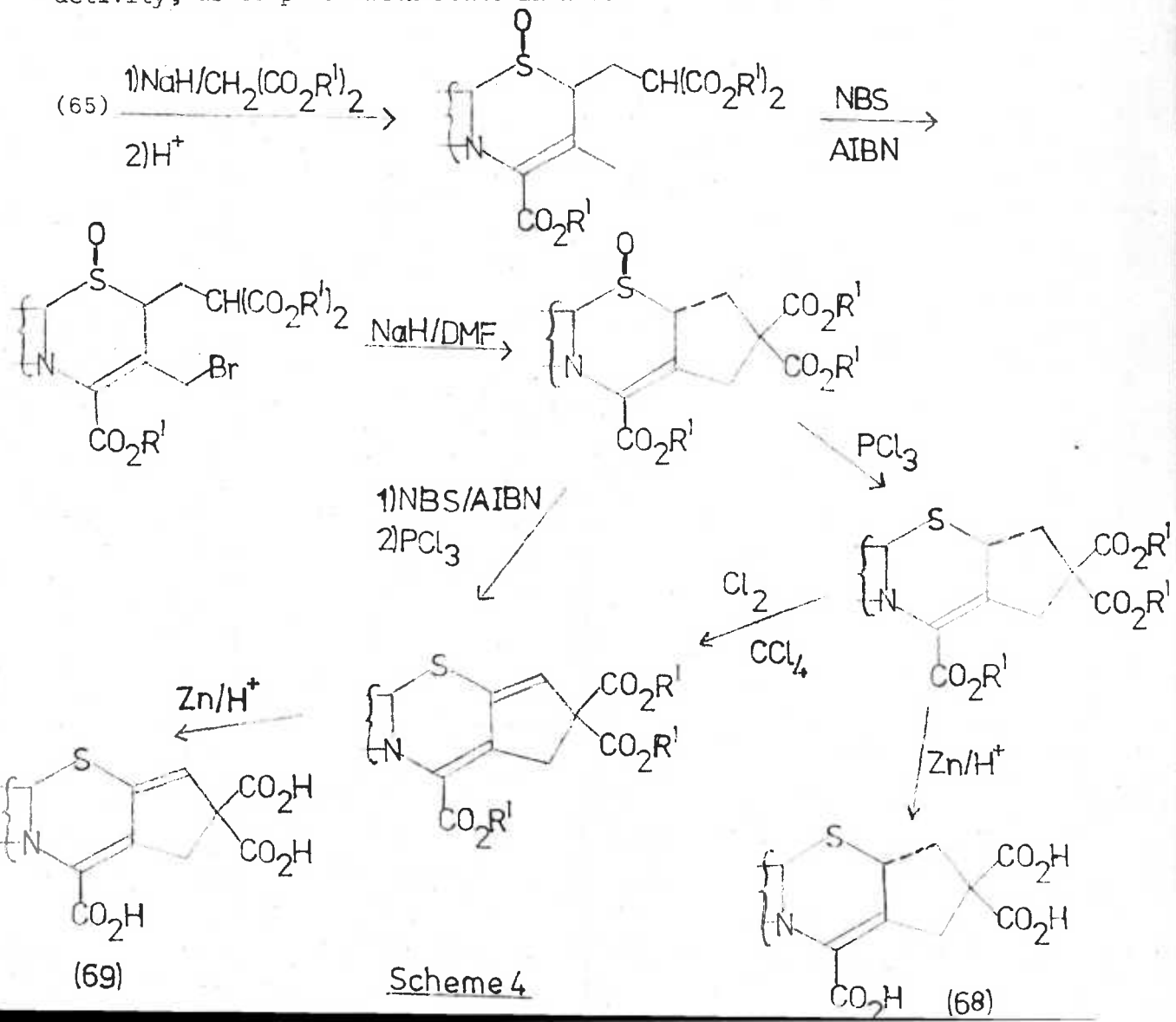
Two noteworthy reactions using the 2-methylene cephem derivative (65) have been reported. In the first, reaction with the methyleneating agent (66) produces the spiro cyclopropyl derivative (67).[32]



(65) (66) (67)

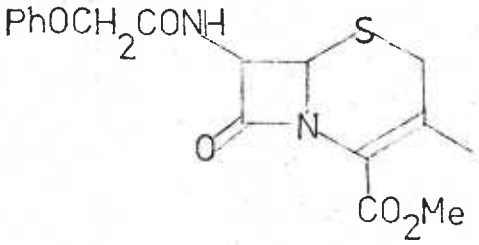
R = $PhOCH_2$, R' = CH_2CCl_3

In the second, manipulation of (65) gives rise to the tricyclic cephalosporanic derivatives (68) and (69).[33] The procedure is summarised in Scheme 4. Both (68) and (69) showed reduced biological activity, as compared with Penicillin V.

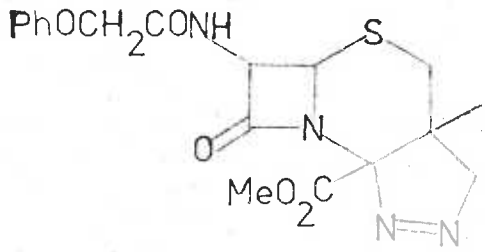


Scheme 4

Other tricyclic cephalosporanic compounds (71) have been prepared by the cycloaddition of diazomethane to 3-cephem esters (70).[34] No addition takes place with 2-cephem derivatives.

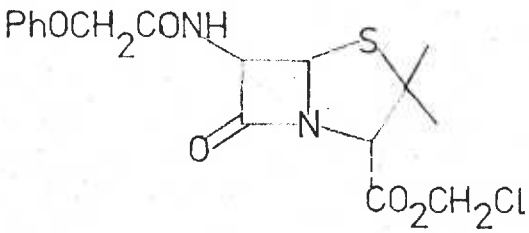


(70)

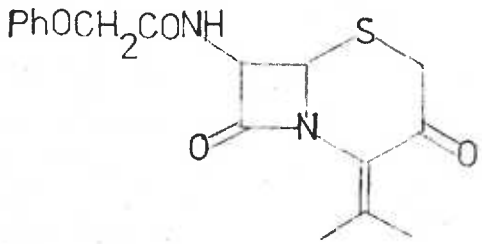


(71)

Stoodley and coworkers have reported that base-promoted ring enlargement of penicillanoyl halogenomethanes (*e.g.* (72)) gives cepham derivatives (*e.g.* (73)).[35] They hoped that the latter derivatives could be converted into penicillin and cephalosporin analogues. They have made several attempts to cleave the 4,5-bond of the cepham (73)[36] but have met with no success as yet.

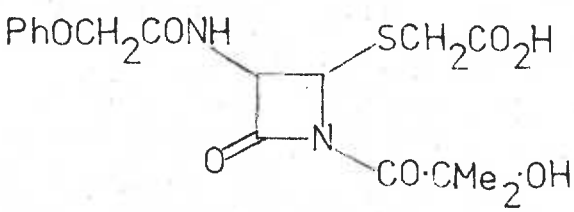


(72)



(73)

One interesting reaction which resulted from the above studies was the oxidation of (73) to the azetidinone (74) by potassium permanganate.



(74)

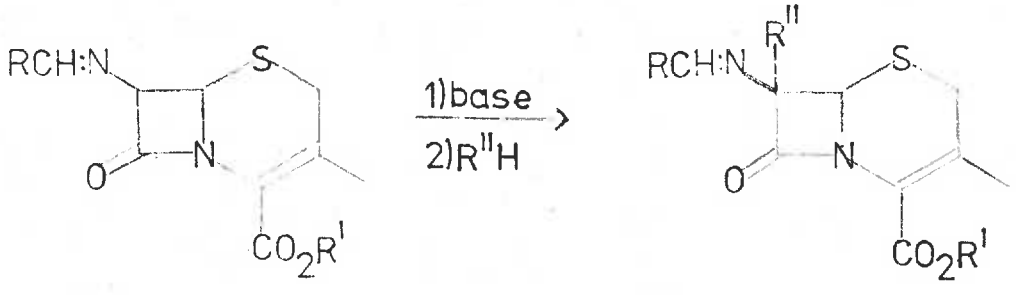
This reaction results from initial hydroxylation of the cepham double bond, followed by oxidative 3,4-bond cleavage. The derivative (74) is of potential value in the synthesis of β-lactam antibiotics if the acyl group on the β-lactam nitrogen can be replaced by hydrogen. Attempts to carry out this transformation have so far proven unsuccessful.[37]

4. Reactions at position 6 (7) of the penam (cephem) nucleus

4.1. Substitution reactions

Much effort has recently been thrown into introducing the methoxy, as well as other, functions into the normal penam and cepham systems. This is so, since 7α-methoxylated cephalosporins have been shown to be resistant to attack by β-lactamases and to have a wide spectrum of antimicrobial activity.

The most commonly used method of introducing a substituent at the 6 (7) position of the penam (cephem) nucleus is by base treatment of a Schiff base (75). This generates a reactive nucleophilic site which then undergoes alkylation or aldol condensation giving rise to the corresponding substituted derivatives (76).



(75) (76)

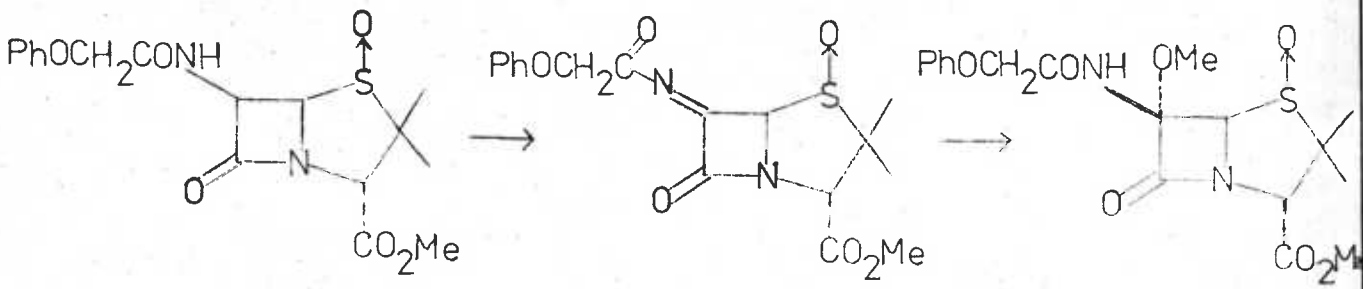
R = NO_2—C$_6$H$_4$—

R = Ph

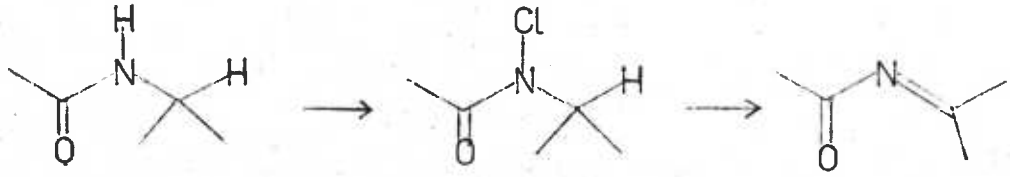
R'' = OMe, SMe, I, Me, CH_2CH,CN, CH_2OH, CHOHMe, COMe, CO_2Me, CO_2Na.

The substituents listed above have been introduced using this technique, and are generally introduced in the α-orientation[38-41] as shown.

Despite all the varied substituents introduced at this position, none of the products possess the activity associated with the introduction of the methoxy group. This has meant that renewed efforts have been made to find better ways of introducing the methoxy function. Baldwin and coworkers[42] utilised t-butyl hypochlorite in methanol containing sodium borate buffer, at 0°, for the introduction of the methoxyl group into the 6-position of penam (77). This reaction involves formation of the acylimine intermediate (78), *via* the N-chloro compound (79).



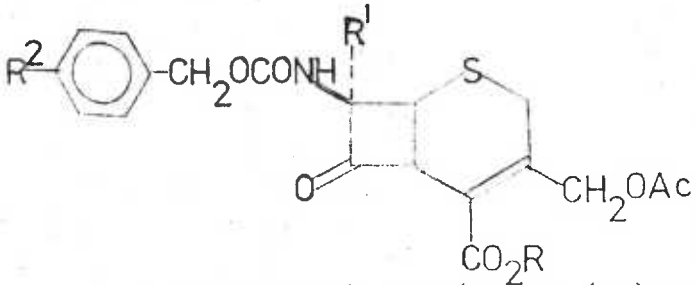
(77) (78)



(79)

This technique has been modified by Christensen[43] and Koppel[44], to involve low temperature formation of the anions of 7β-amido cephalosporins and 6β-amidopenicillins, oxidation of these by t-butyl hypochlorite, base elimination to acylimines followed by alcohol addition, all in one reaction vessel, to give the required alkoxy compounds. The technique has been further modified by Lunn and Mason[45] to provide a facile

synthesis of the 7α-methoxyamino nucleus, which can be acylated at will. Their process involves oxidation of p-nitrobenzyl carbamates (80).

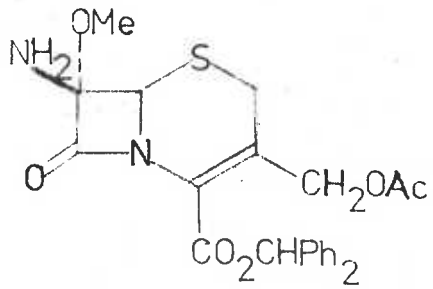


80. R = Ph_2CH R' = H; R^2 = NO_2

81. R = Ph_2CH; R' = OMe; R^2 = NO_2

82. R = Ph_2CH; R' = OMe; R^2 = NH_2

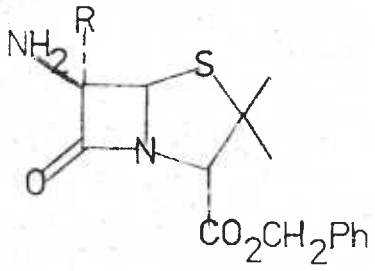
Methoxylation of (80) to (81) was carried out using the method of Koppel.[44] Trimethyl phosphite was added prior to allowing the reaction mixture to warm up, thus preventing overoxidation by excess t-butyl hypochlorite. The methoxy compound (81) was hydrogenated in methanol-tetrahydrofuran, using 5% palladium-on-charcoal as catalyst, to form an unstable product, probably the amine (82). Pure 7α-methoxy-7β-amino cephalosporanic acid benzhydryl ester (83) was obtained by stirring the crude hydrogenation product with an equal weight of Merck silica gel (< 200 mesh). Compound (83) can be acylated by reaction with acid chlorides and pyridine in cold chloroform, and the benzhydryl protecting group removed with trifluoroacetic acid, thus providing the required 7α-methoxy cephalosporins.



(83)

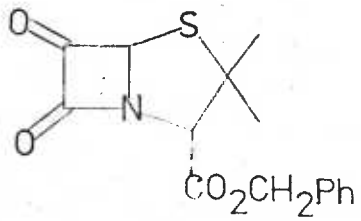
Other methods for introduction of the methoxy function have been utilised. One involves the diazotisation of 7β-amino cephalosporins and 6β-amino penicillins, and subsequent treatment of the diazocompounds with haloazides and then methanol.[46] Various workers have also employed the solvolysis of halo and methyl thio substituted compounds with some success.[38,39,47,48] Thus, on treatment with mercury (II)

chloride in methanol-pyridine, the methylthio compound (84) is converted into the methoxy compound (85).[38] On treatment of compound (84) with mercury (II) chloride in aqueous dimethylformamide the α-keto-β-lactam (86), a potentially useful penicillin derivative, is formed.



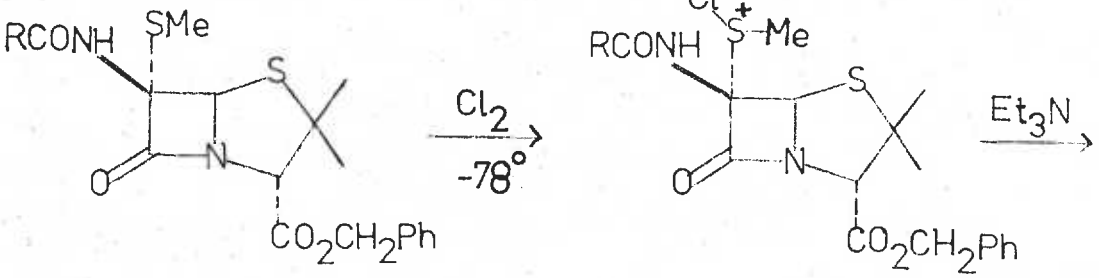
84. R = SMe

85. R = OMe

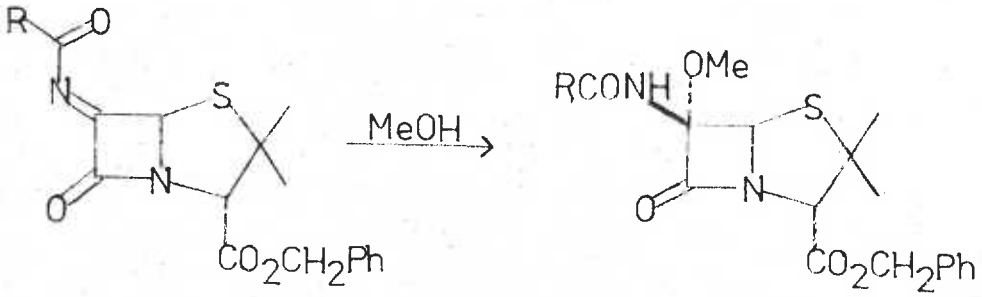


(86)

Exchange of the methylthio groups in acylated derivatives of compound (84) does not occur with mercury (II) chloride. In these cases a more vigorous treatment is necessary. Selective chlorination gives the chlorosulphonium chloride (87) which, on treatment with triethylamine in methanol, produces the methoxy compound (89), *via* the acylimine intermediate (88).[47]



(87)

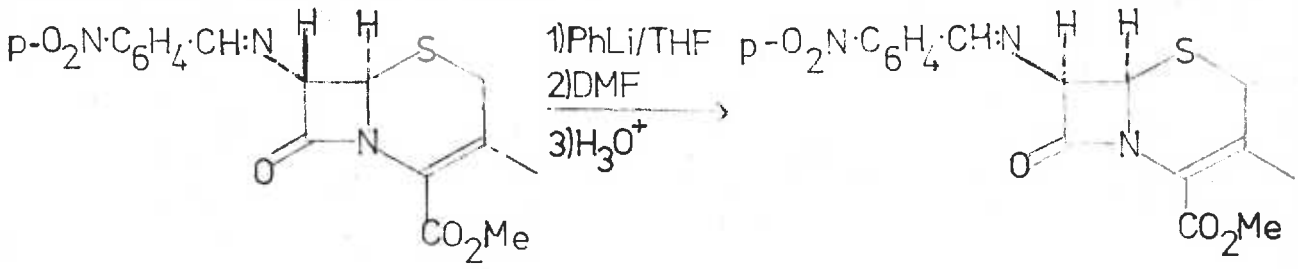


(88) (89)

Benzyl 6-isocyanopenicillanate has also been utilised in the preparation of 6α-substituted penicillins.[49]

4.2. Epimerisation

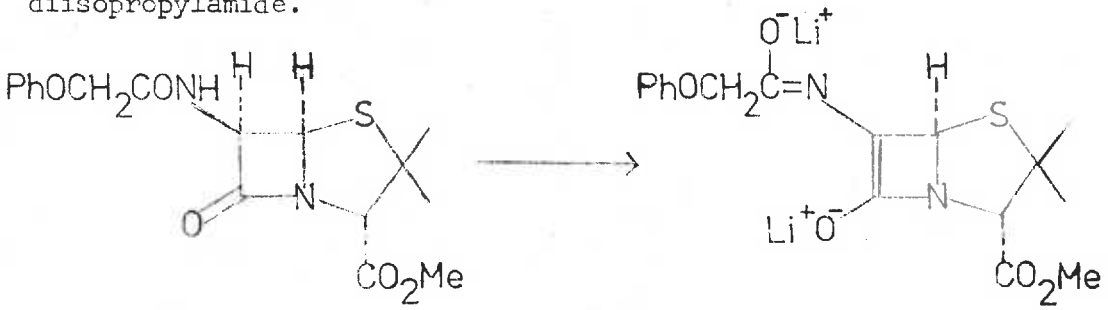
6α-Aminopenicillins and 7α-amino cephalosporins can be epimerised to their β-epimers by treatment of their p-nitrobenzaldehyde Schiff bases with phenyl lithium, followed by protonation under kinetically controlled conditions,[50] *e.g.* (90) to (91).



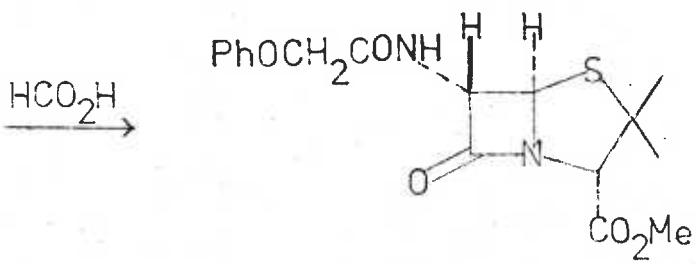
(90) (91)

[+ 33% of (90)]

Direct C-6 epimerisation of penicillin V methyl ester (92) can be carried out *via* the vicinal dianion (93) formed on treatment with lithium diisopropylamide.[51]

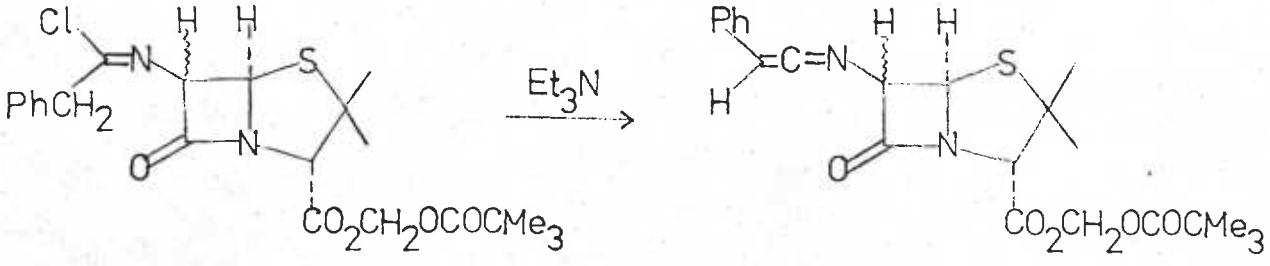


(92) (93)



[+ 20% of (92)]

Carroll and coworkers[52], in work related to the chemistry of penicillin imino chlorides, found that the imino chloride (94) of penicillin G pivaloyl oxymethyl ester undergoes rapid and nearly complete epimerisation to (95) prior to dehydrochlorination by triethylamine. Thus, epimeric ketenimine (96) results as the major product.



94. H - cis

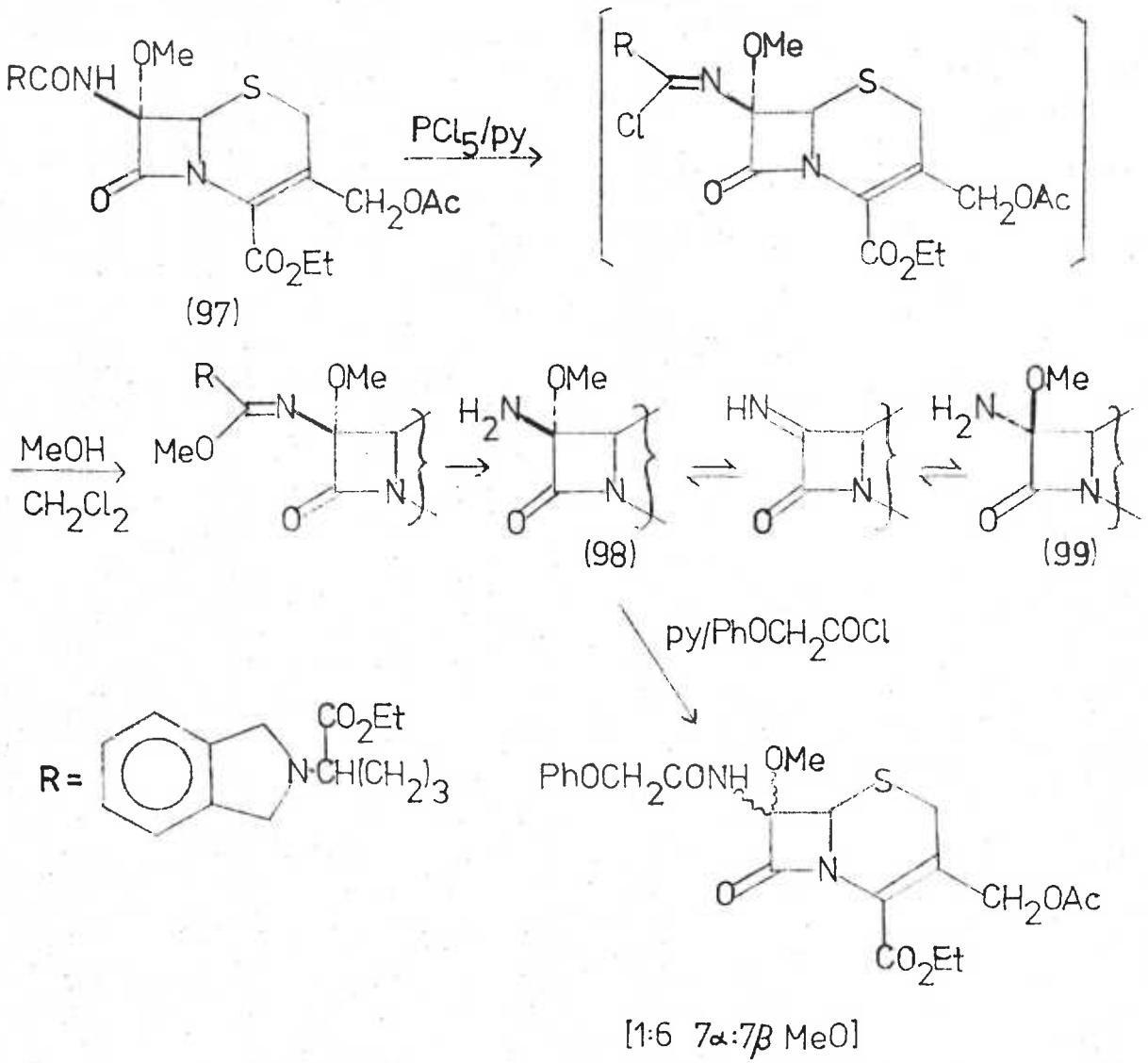
95. H - trans

96. H - trans

Vlietinck and coworkers[53] have reported a method for the epimerisation of penicillin with a secondary amide side chain. The method is based on N-silylation of the amide group with silyl exchange reagents, such as NO-bis(trimethyl silyl) acetamide, followed by treatment with an organic base.

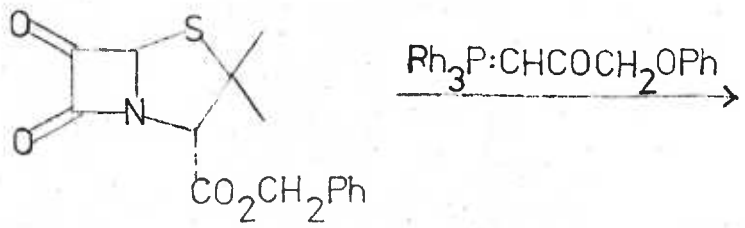
4.3. Other reactions

The cleavage of 7α-methoxy cephalosporin C derivatives (97) with phosphorus pentachloride produces a mixture of the α- and β-methoxyamino compounds (98) and (99) respectively.[54] This suggests that following methoxyamine formation an equilibrium is established. The results are summarised in Scheme 5.

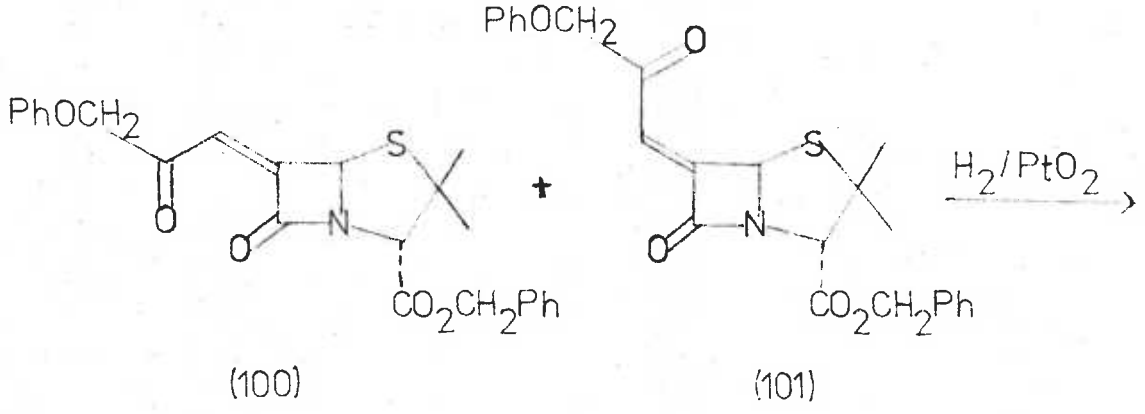


Scheme 5

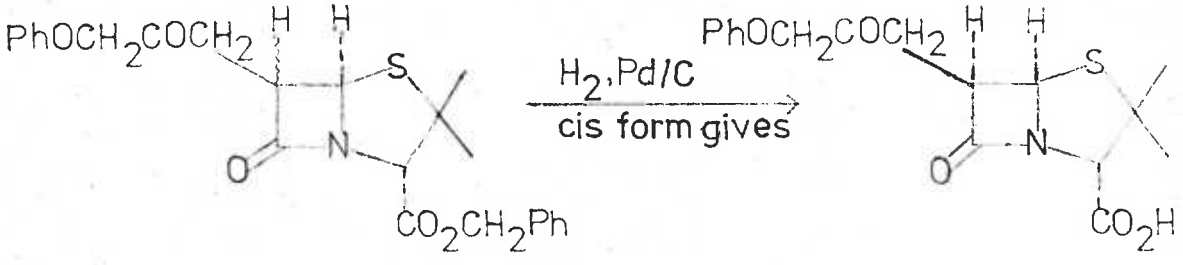
The α-keto-β-lactam (86) referred to above has been prepared by Lo and Sheehan.[55] They used (86) in a Wittig reaction with phenoxyacetyl methylene triphenylphosphorane, thus producing the olefins (100) and (101) which gave the new ketone (102) on reduction, as a mixture of cis and trans isomers (4:1).



(86)



(100) (101)



(102) (103)

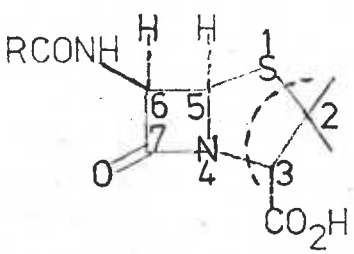
The acid (103), formed by removal of the benzyl group in (102), showed considerable antibacterial activity and was also resistant to some β-lactamases.

PART I

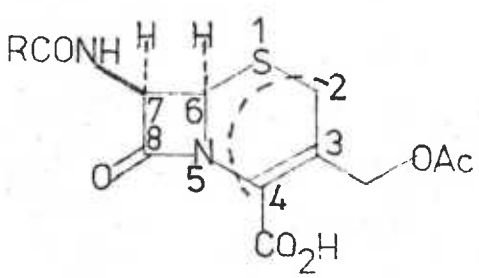
DISCUSSION OF RESULTS

1. Introduction

Penicillins are obtained by fermentation in very high yield at low cost, making their derivatives into potentially useful raw materials for further chemical transformations. Indeed, they have been used as precursors for the synthesis of the related antibiotics, the cephalosporins.[57] This approach has the advantage over total synthesis in that the nitrogen and sulphur substituents are already attached to the β-lactam in the desired stereochemical configuration. This fact is borne out on studying the parent penam (1) and cephem (2) systems. The structures have the identical β-lactam grouping, to the left, and the same C_5 isoprenoid-like unit, to the right of the dotted lines in (1) and (2). The systems differ in that the cephalosporins have a higher oxidation level than the penicillins and a different substitution pattern on the C_5-unit.



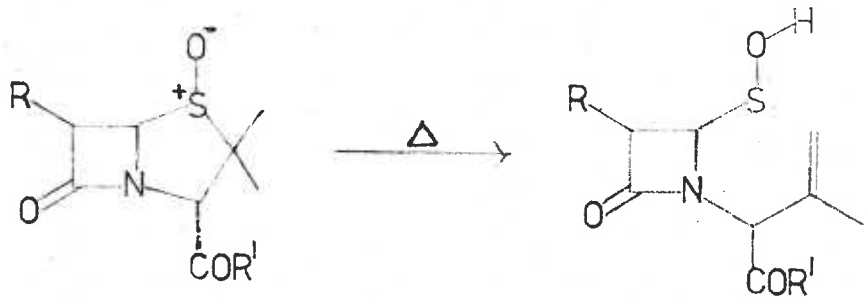
(1)



(2)

In order to convert the penam into the cephem, or other related systems, chemically two approaches can be readily conceived, both requiring modification of the thiazolidine ring without any concomitant change of the sensitive β-lactam function. Firstly, the thiazolidine ring could be opened and the C_5 carbon chain on the β-lactam nitrogen cleaved off, to be replaced with a new carbon framework of the desired substitution pattern. The second approach involves selective oxidation of the two methyl groups and ring expansion of the thiazolidine ring.

It was proposed to make use of this second approach by carrying out trapping reactions on the sulphenic acid (4) formed on heating the penicillin sulphoxide[5] (3), followed by modification of the substituents attached to the sulphur and to the β-lactam nitrogen, and recyclisation. It was hoped that this approach would produce new and biologically active cephalosporins.



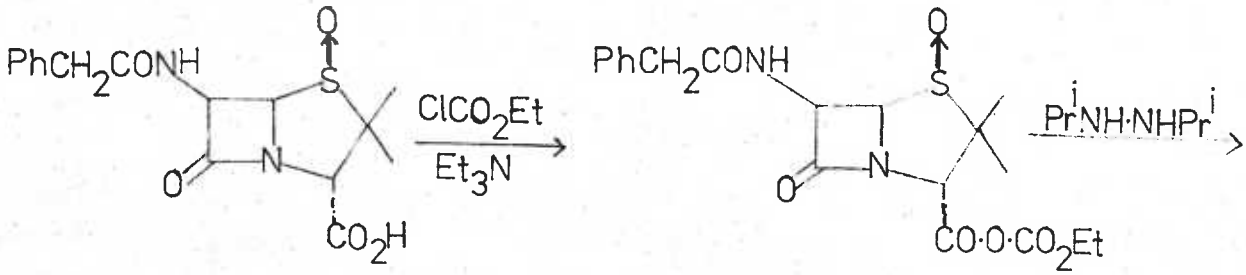
(3) (4)

2. Trapping with toluene-p-sulphinic acid

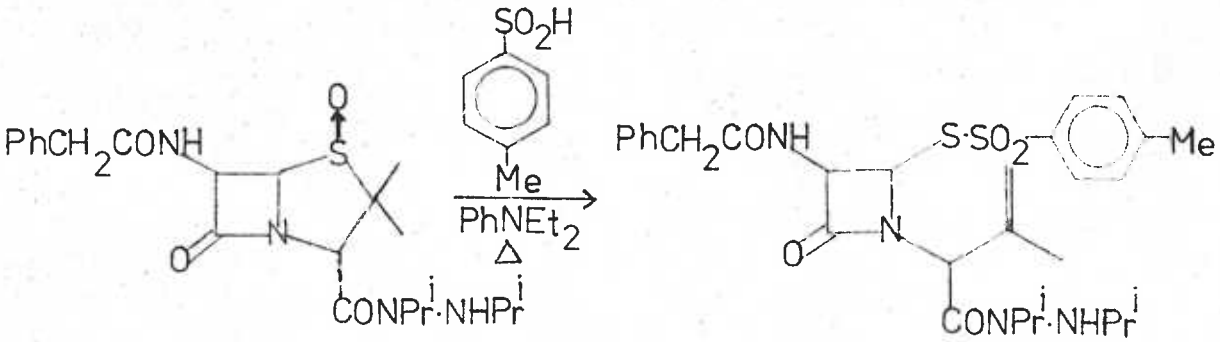
2.1. Penicillin sulphoxide hydrazides

a) Halogenation

It has been shown by Barton and coworkers[58] that NN^1-di-isopropyl-hydrazine is a useful reagent for the protection of carboxylic acids. The derived hydrazides can be reconverted by selective oxidation, with, for example, lead tetra-acetate, into the parent acids in very high yield. Use was made of this protecting group in the initial reactions carried out.[59] The NN^1-di-isopropylhydrazide (7) was formed from (IS)-6β-phenylacetamidopenicillanic acid 1-oxide (5) *via* the mixed anhydride (6) formed by reaction with ethyl chloroformate in the presence of triethylamine[58]. The sulphenic acid from the hydrazide (7) was trapped with toluene-p-sulphinic acid, in the presence of NN-diethylaniline, to give the desired thiosulphonate (8).[59]

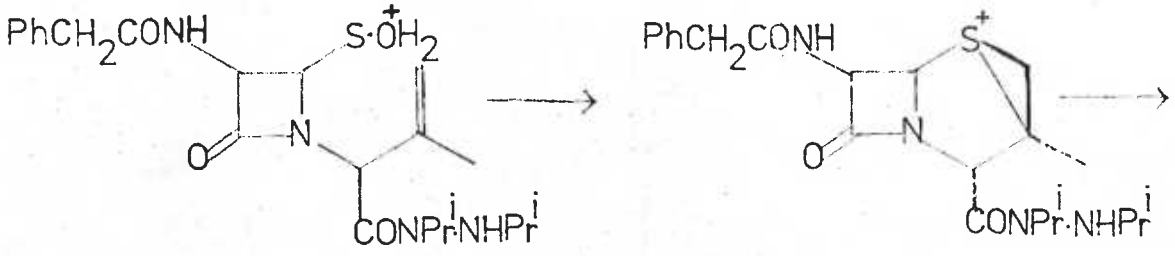


(5) (6)

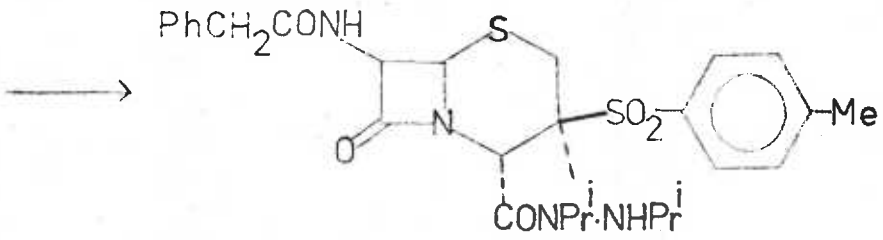


(7) (8)

The thiosulphonate (8), resulting from the sulphenic acid (9) functioning as an electrophile towards the sulphinic acid, was separated by column chromatography, in 70% yield. The cephalosporin derivative (10a) was formed as a by-product, resulting from the attack of toluene-p-sulphinic acid on the intermediate sulphonium ion (10) formed by intramolecular nucleophilic attack of the protonated sulphenic acid (9) by the olefinic linkage.

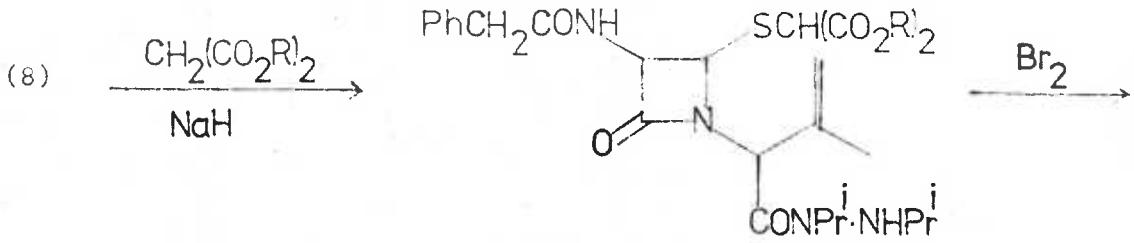


(9) (10)



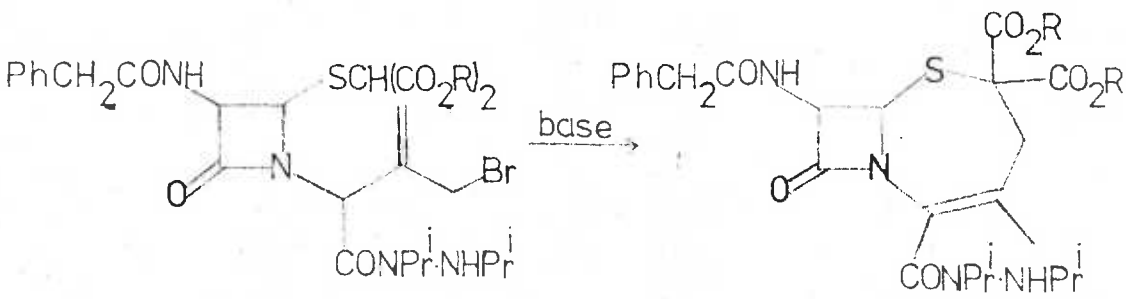
(10a)

It was hoped that the thiosulphonate (8) could be converted into the cyclic compound (13) by initial displacement of the sulphinate by the anion of di-t-butyl malonate, followed by allylic bromination and treatment with base.



R = t-Bu

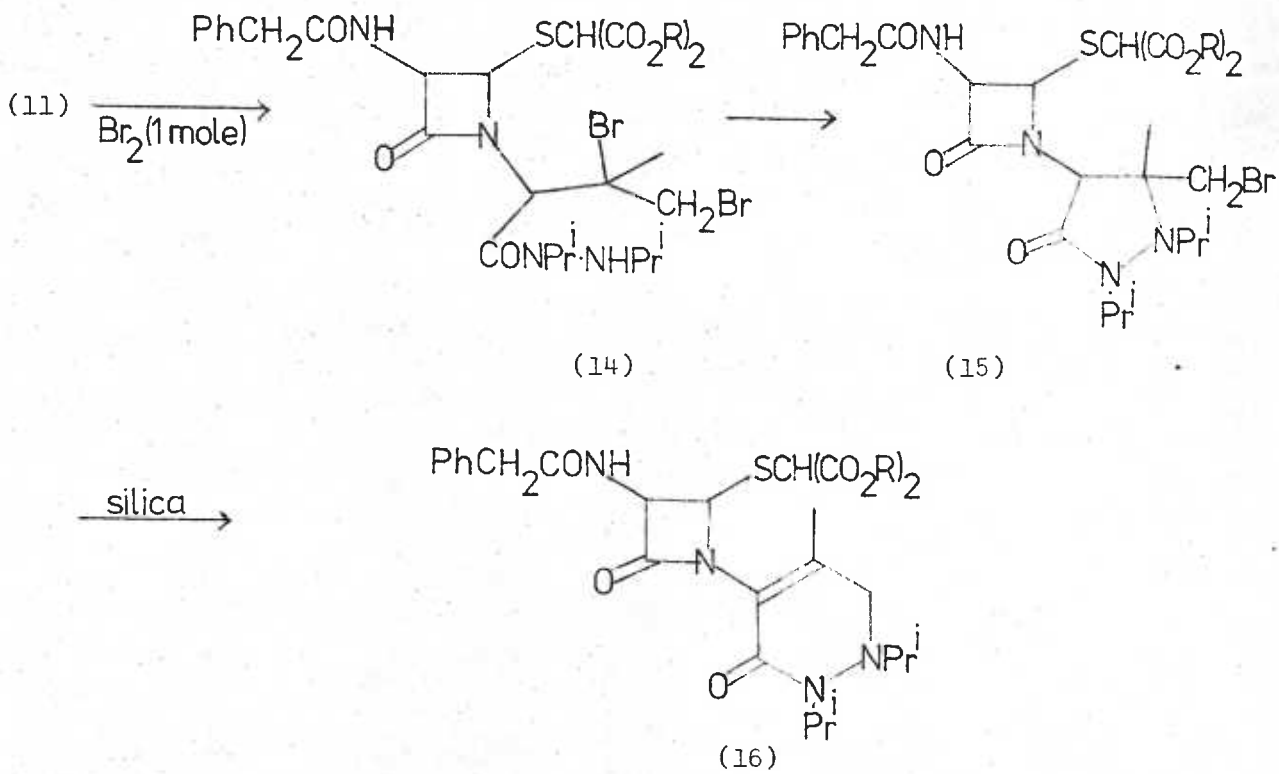
(11)



(12) (13)

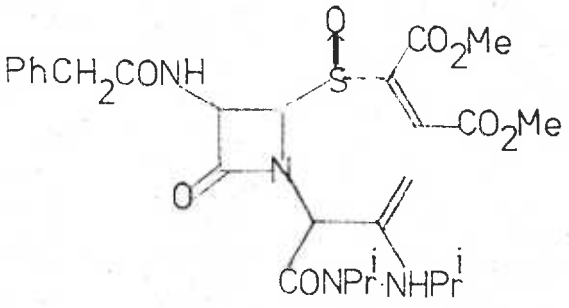
Compound (8) was reacted with di-t-butyl sodiomalonate in dry benzene, to afford compound (11). Compound (11) was treated with

bromine(1equiv.) in carbon tetrachloride, in the presence of toluene-p-sulphonic acid (1 equiv.). The nuclear magnetic resonance (n.m.r.) spectrum of the crude product showed that there were no olefinic protons and that there was no methyl on a double bond. It also indicated the presence of a new methylene function. Thus, bromine had added to the double bond to afford compound (14). An attempt was made to purify the brominated compound by preparative layer chromatography (p.l.c.). However, the n.m.r. spectrum of the compound removed from the silica gel showed the disappearance of a methine signal, the shift of a methylene signal and the appearance of a signal due to a methyl on a double bond. A sample of this compound was sent for mass spectral analysis and showed a parent ion of molecular weight 644. This corresponds to the molecular weight of compound (16), indicating that the hydrazide part of the molecule had cyclised and that the molecule did not contain bromine. The complete interpretation of the results is shown in Scheme 1.

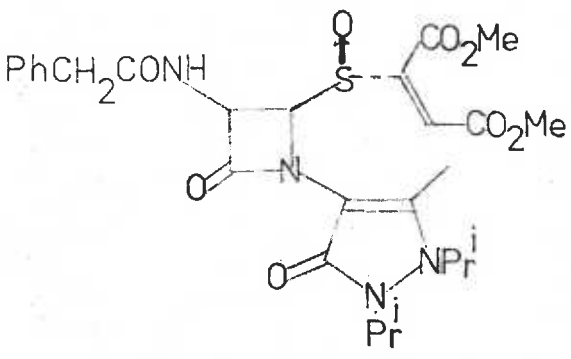


Scheme 1

Thus, it appears that the initial dibromo compound (14) cyclises to (15) before chromatography and rearranges to (16), with loss of hydrogen bromide, on the silica. The infra-red (i.r.) spectrum of compound (16) shows hydrazide carbonyl absorption at 1630 cm^{-1}, whereas the relevant absorption in compound (11) appears at 1680 cm^{-1}. This is indicative of the αβ-unsaturation in (16). Compound (16) was also obtained when the thiosulphonate (8) was brominated, treated with di-t-butyl sodiomalonate and the product separated by p.l.c. The problem of cyclisation of the N,N^1-di-isopropylhydrazide has been reported before.[60] Thus, on ozonolysis of compound (17), resulting from trapping of (7) with dimethyl acetylenedicarboxylate, the sole product is the pyrazolinone (18).

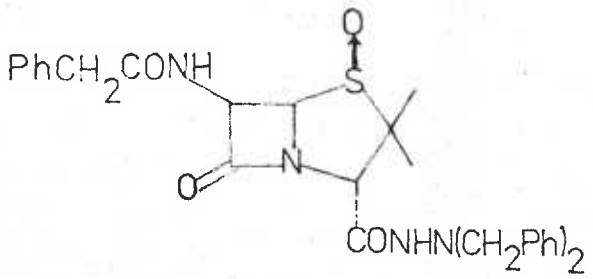


(17)



(18)

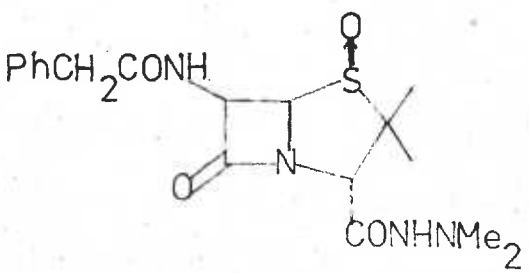
In the light of the results obtained using the NN^1-disubstituted hydrazine, it was thought that if an NN-disubstituted hydrazine was used as the prctecting group the desired cyclisation would take place, in preference to the cyclisation of the hydrazide. Thus, the crystalline NN-dibenzylhydrazide (19) was prepared, in the same manner as the NN^1-di-isopropylhydrazide (7).



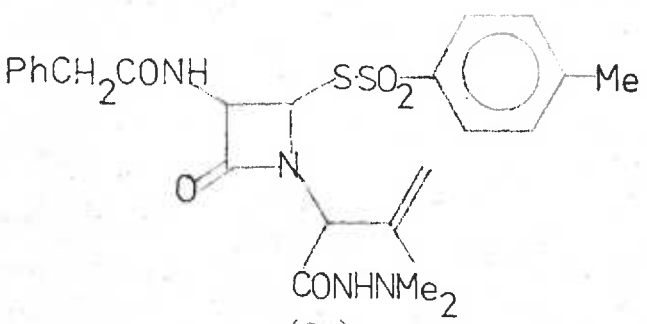
(19)

A trapping of (19) with toluene-p-sulphinic acid was carried out. It was found to proceed very slowly. Indeed, after 12h. a number of products had formed (t.l.c.) and the crude reaction mixture showed only weak β-lactam absorption (i.r.). An oxidation of (19) with lead tetraacetate [58] was carried out, in dichloromethane, but only about 15% of sulphoxide acid was regenerated. Norman has reported that on reaction of dibenzylhydrazine derivatives with lead tetraacetate, several products are formed. [61] These results show that NN-dibenzylhydrazine is not suitable as a protecting group.

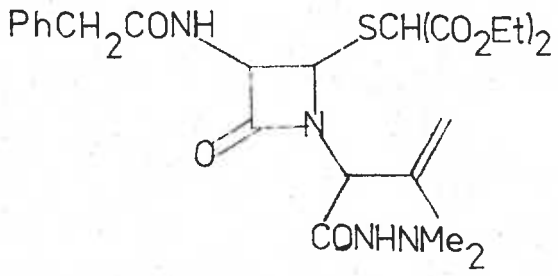
Attention was switched to the use of NN-dimethylhydrazine as the protecting group. The NN-dimethylhydrazide (20) was prepared as an oil, by the usual method, and was purified by precipitation from light petroleum. The trapping of (20) with toluene-p-sulphinic acid was carried out, and the desired product (21) separated by column chromatography. Compound (21) was then reacted with diethyl sodiomalonate in dry benzene, to afford compound (22).



(20)

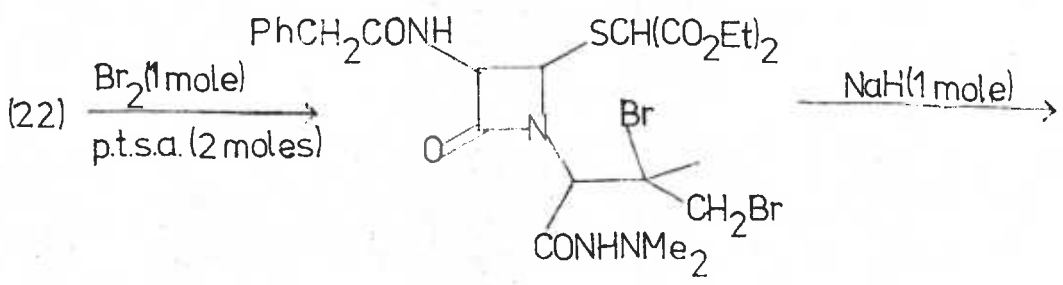


(21)

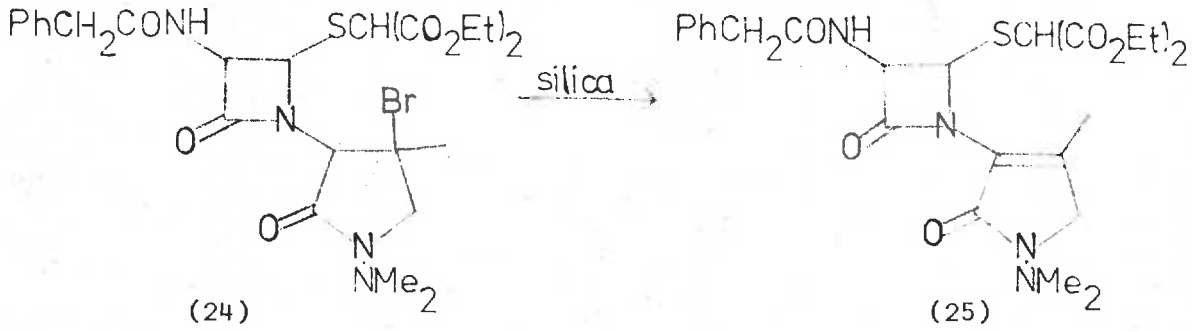


(22)

Attempts were made to brominate compound (22) using bromine in dichloromethane. The initial results indicated that the hydrazide part of the molecule was being attacked. However, on reaction with bromine (1 mole) in the presence of toluene-p-sulphonic acid bromination of the double bond took place to afford compound (23). The crude bromination product was treated with sodium hydride in dimethyl-formamide. Reaction was complete in about 4.5 hours, and a new β-lactam containing compound was formed (n.m.r. and i.r.). The n.m.r. spectrum of this compound showed a shift in the signal assigned to the $\underline{CH_2}Br$ resonance in (23), indicating that cyclisation might have taken place. The product was separated by p.l.c. The n.m.r. spectrum of the isolated compound showed the presence of a new signal which was assigned to a methyl on a double bond. It is postulated that on base treatment of (23) the hydrazide cyclised to afford the monobromo compound (24) which then eliminated hydrogen bromide on the silica to yield compound (25). The interpretation of these results is shown in Scheme 2.



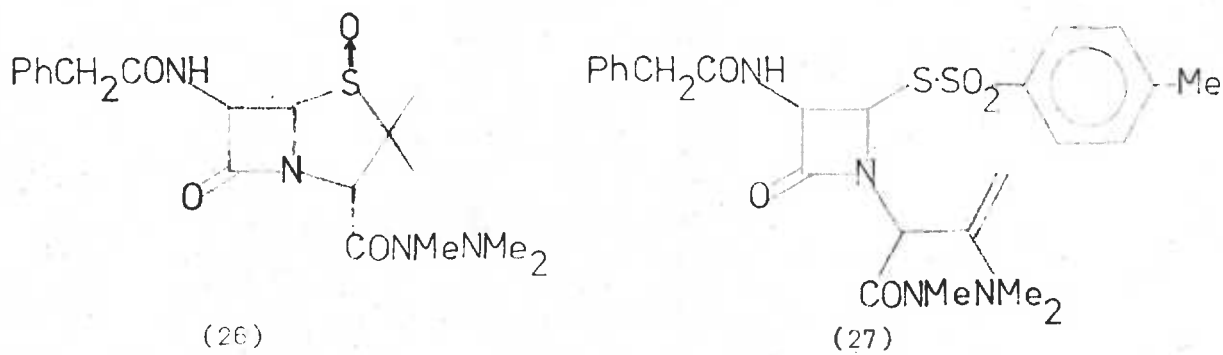
(23)



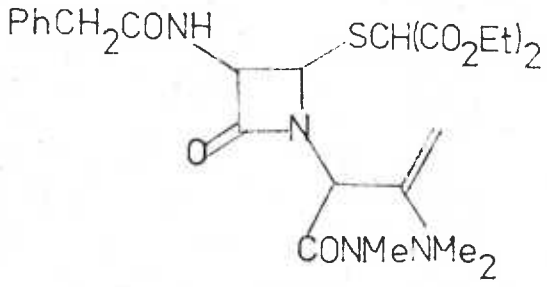
(24) (25)

Scheme 2

The reaction of the dibromo compound (23) with sodium hydride was also carried out in dioxan. Reaction was complete in 2.5 hours and the same result was observed. The isolated product showed a molecular ion of 532 in its mass spectrum which is consistent with the proposed structure (25). This result is comparable to that obtained using NN^1-di-isopropylhydrazide and indicated that an NNN^1-trisubstituted hydrazine would have to be used as the protecting group. Thus, the crystalline trimethyl hydrazide (26) was prepared and trapped with toluene-p-sulphinic acid[59] to afford compound (27). The product was purified by precipitation from light petroleum. Compound (27) was reacted with diethyl sodiomalonate to afford compound (28).



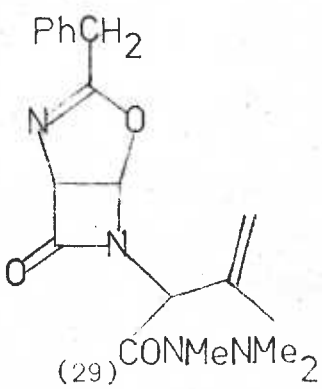
(26) (27)



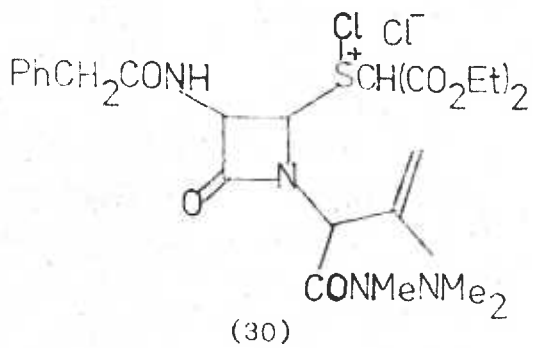
(28)

Compound (28) was treated with bromine, in dichloromethane, in the presence of toluene-p-sulphonic acid, calcium carbonate or propylene oxide. However, in each case, no β-lactam compound was present after work-up (i.r.). Compound (28) was also reacted with N-bromosuccinimide, in chlorobenzene. The two major products were separated by p.l.c. One of these was non β-lactam and the n.m.r. spectrum of the other showed that the hydrazide side chain had been attacked, and that bromination did not take place in the desired fashion.

Compound (28) was treated with chlorine, in carbon tetrachloride/dichloromethane, at 0°. A new β-lactam containing compound was formed (n.m.r.) and was separated by p.l.c. The n.m.r. spectrum of the isolated compound showed the presence of two β-lactam doublets and the absence of the diethyl malonate function. The i.r. spectrum also showed the absence of the malonate ester carbonyl absorption. Hence, the oxazoline structure (29) was assigned to this compound.[62] The n.m.r. spectrum was in complete accord with this structure. The reaction probably proceeds *via* the chlorosulphonium chloride (30).

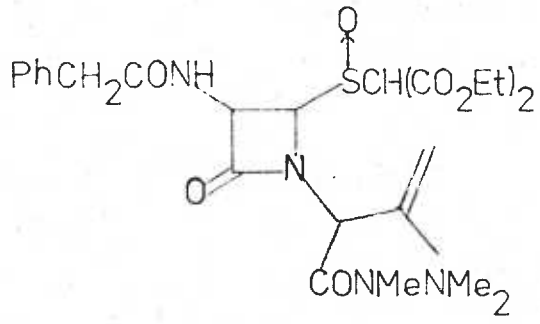


(29)



(30)

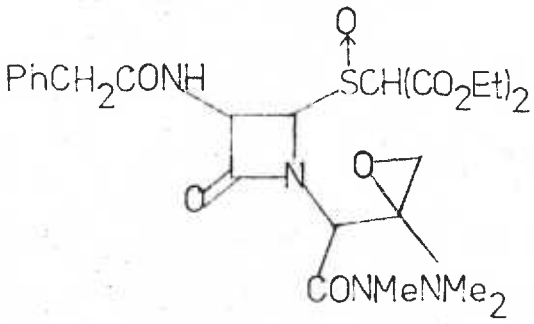
It was thought that bromination of the sulphoxide (31) might prove more fruitful. Thus, compound (28) was oxidised with m-chloroperbenzoic acid (1 equiv.) to afford the desired sulphoxide (31).[63] However, after bromination with bromine in dichloromethane no β-lactam remained (i.r., n.m.r.).



(31)

b) epoxidation

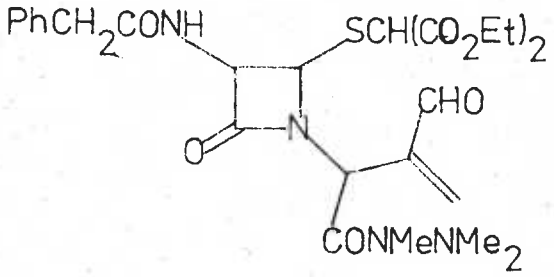
Compound (28) was reacted with m-chloroperbenzoic acid (2 equiv.) in the hope that the double bond would be epoxidised to give compound (32), which could then be cyclised on treatment with base. All the peracid had reacted inside 24 hours at 0°C (starch-iodide paper). The products were separated by p.l.c. The only product which showed strong β-lactam absorption (i.r.) was the sulphoxide (31). Spectra (i.r., n.m.r.) of the other products showed that very little β-lactam was present, and also that the malonate part of the substrate had been attacked.



(32)

c) Selenium dioxide oxidation

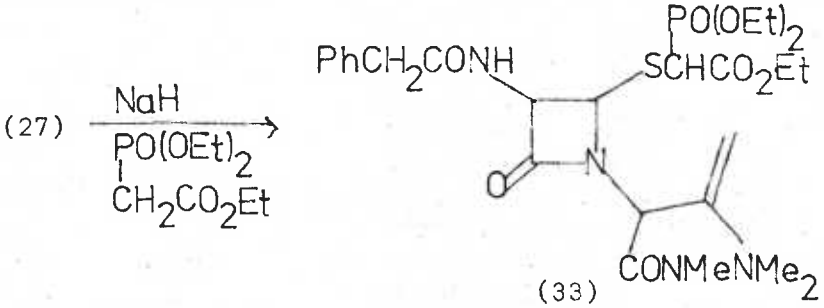
As an alternative way of functionalising the isopentenoyl side chain, attempts were made to carry out allylic oxidation of the thiosulphonate (8) in the NN^1-di-isopropylhydrazide series, and of the diethyl malonate derivative (28) in the trimethylhydrazide series, using selenium dioxide in the hope of producing the aldehyde (32a). Reactions were carried out in both acetic acid and dioxan. All the reactions produced complex mixtures with no product in reasonable yield.



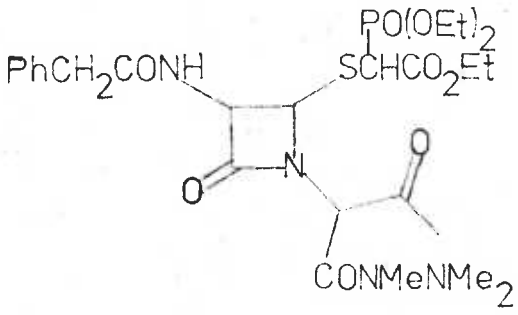
(32a)

d) Ozonolysis

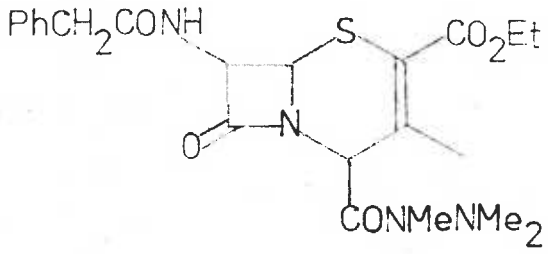
It was proposed that triethyl phosphonoacetate[64] would be a useful compound to produce intermediates such as (34) with the objective of cyclising to compound (35). Hence, compound (27) was reacted with sodium hydride/triethyl phosphonoacetate, in benzene. A smooth displacement reaction ensued to afford compound (33). This compound was then ozonised, in dichloromethane at -78°, to produce the ketone (34) in good yield. An attempt was made to cyclise this ketone, to compound (35), using Triton B in dimethyl formamide. However, there was no sign of any reaction (t.l.c., n.m.r.) even after heating at 60° for 4 hours.



(33)

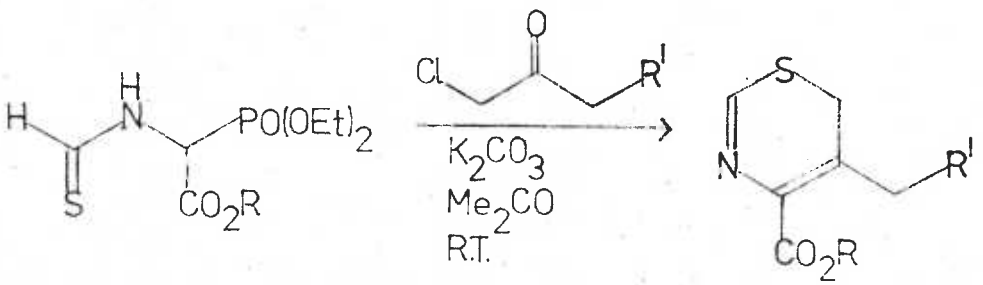


(34)



(35)

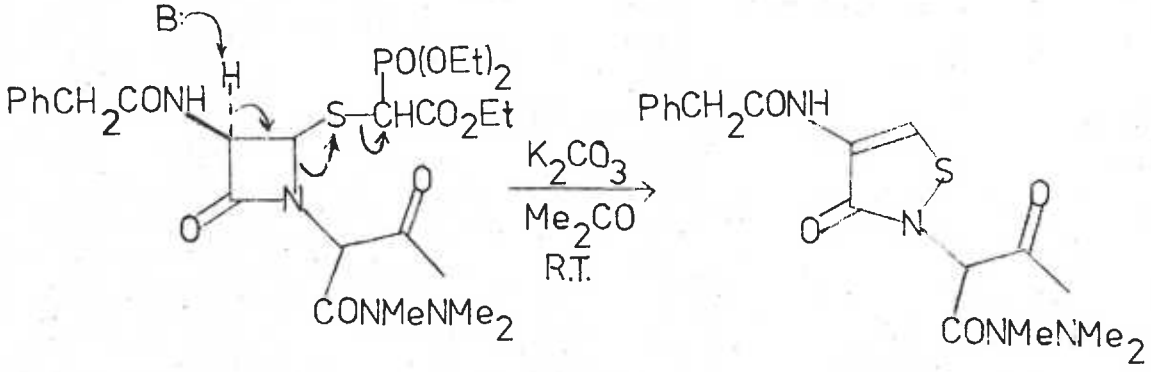
While surveying recent literature, a paper was found on the total synthesis of β-lactam antibiotics, in which use was made of the phosphonoacetate derivative (36) in forming the dihydrothiazine derivative (37)[56].



(36)

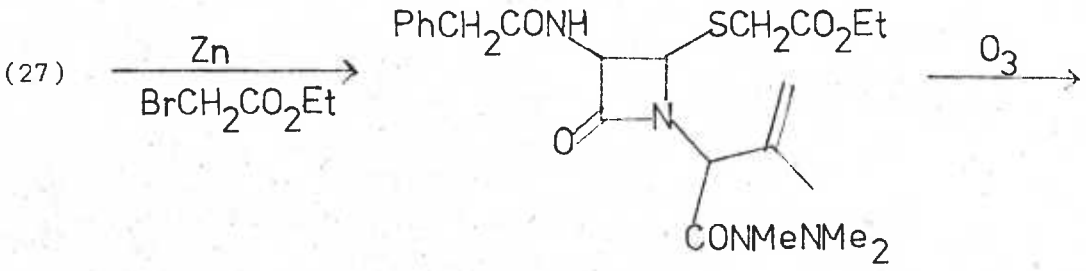
(37)

An attempt was made to cyclise the phosphonoacetate derivative (34) using the same method as in the above case. A sample of compound (34) was stirred vigorously, with excess potassium carbonate, in dry acetone, at room temperature. The product formed was separated by p.l.c. It contained no β-lactam (i.r.) and was shown to be the isothiazolone derivative (38) (n.m.r.).[62]

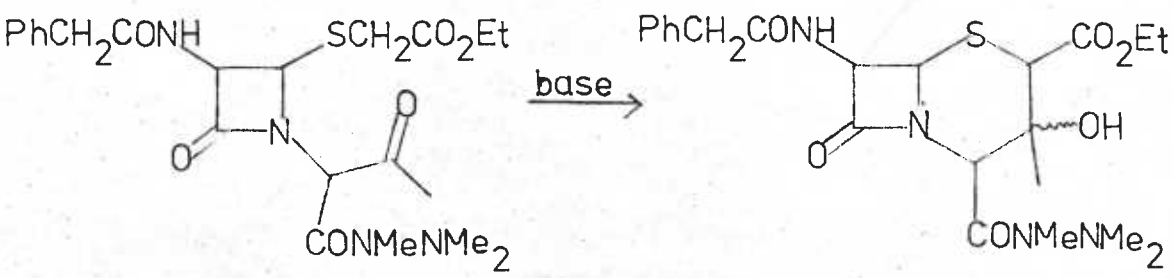


(34) (38)

Attempts were made to displace the sulphinate in compound (27) by a Reformatsky type reaction, using zinc and ethyl bromoacetate to produce compound (39). This could be ozonised to compound (40) which could then be cyclised to give the cephalosporin derivative (41).

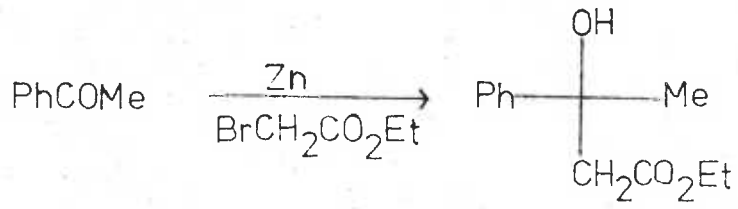


(39)



(40) (41)

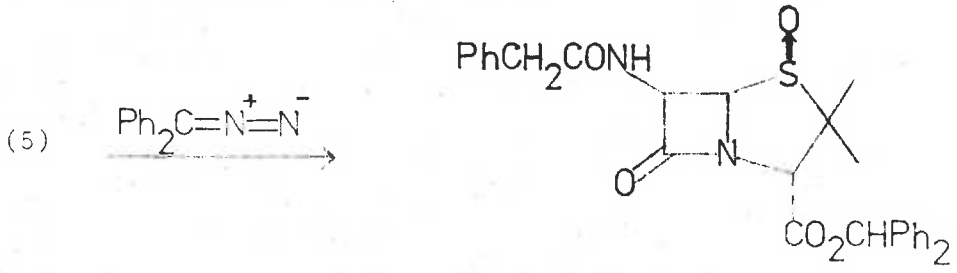
Initial attempts to form compound (39) were unsuccessful, so a standard reaction, using acetophenone,[65] was carried out. This reaction went smoothly, producing compound (42) in good yields. The penicillin reaction was repeated using the same conditions but was again unsuccessful.



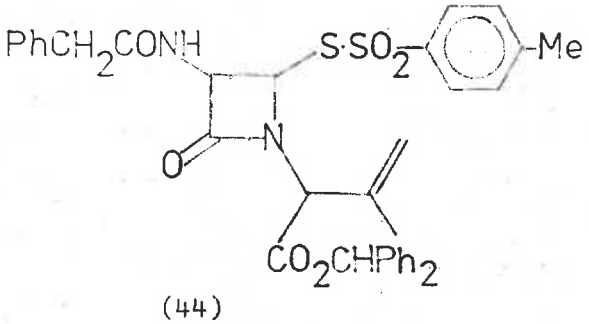
(42)

2.2. Penicillin sulphoxide benzhydryl ester

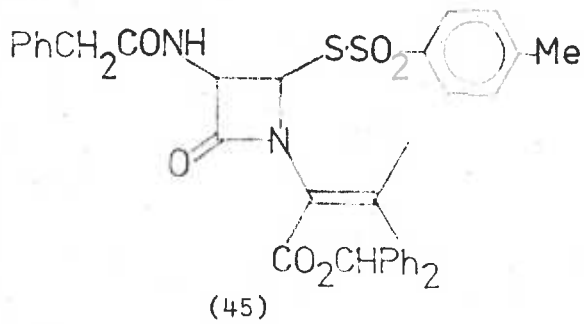
The benzhydryl ester (43) was prepared from penicillin sulphoxide acid (5) by reaction with diphenyl diazomethane[66]. This ester was then trapped with toluene-p-sulphinic acid, using the normal procedure, to afford the thiosulphonate (44).



(43)

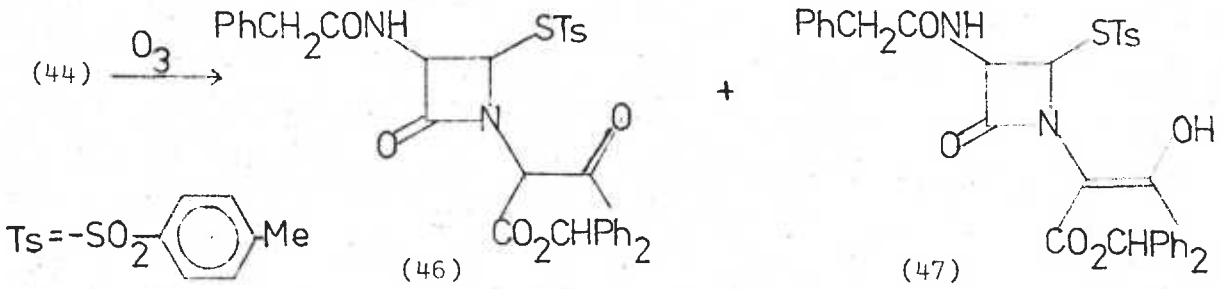


(44)

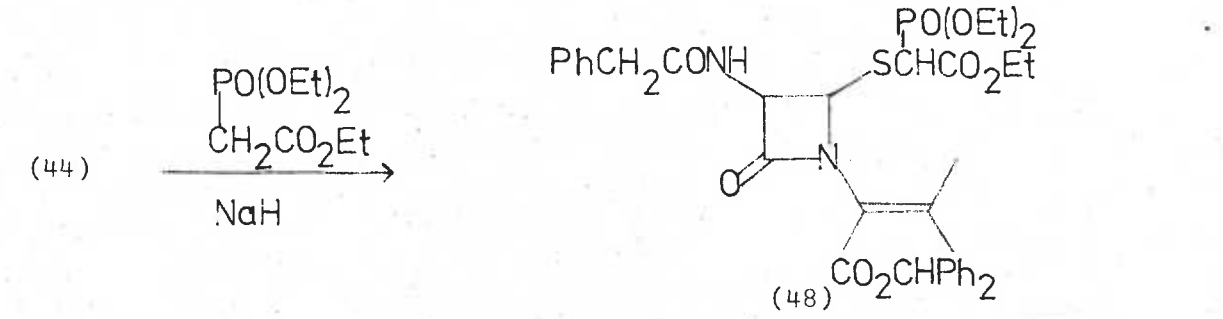


(45)

The trapping reaction was carried out in benzene, toluene and dioxan and followed by t.l.c. Reaction in benzene was very slow, very little product having formed after 5 hours. Trapping in toluene was complete after 5 hours. Trapping in dioxan was complete after 4.5 hours. The product (44) was separated by p.l.c. in 50% yield, and can be isomerised into the αβ-unsaturated ester (45) on treatment with triethylamine. Compound (44) was ozonised, in dichloromethane, at -78°. The n.m.r. spectrum of the crude product indicated that a mixture of the ketone (46) and the enol (47) had been obtained. On attempted separation by p.l.c. all of the ketone (46) enolised. Repeated ozonolyses of compound (44) produced the same mixtures.



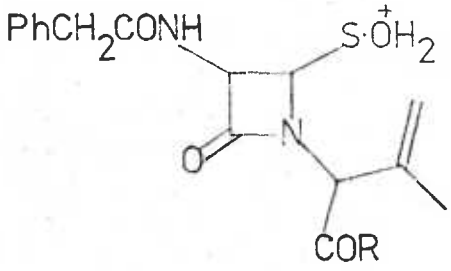
Compound (44) was treated with sodium hydride/triethyl phosphonoacetate, in dry benzene. A smooth displacement reaction ensued, yielding compound (48), which is the αβ-unsaturated ester and not the desired βγ-unsaturated product.



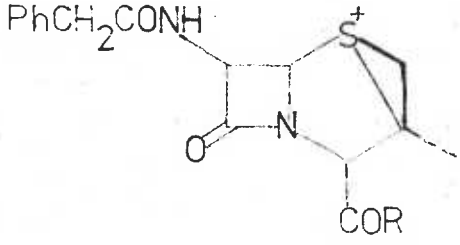
These results show that the ester (44) conjugates much more readily than desired.

3. Trapping with isopropenyl n-butyl ether

As stated in section 2.1. the by-product in the trapping of penicillin sulphoxide NN[1]-di-isopropylhydrazide (7) is formed by attack on the intermediate sulphonium ion (10). This sulphonium ion is formed by the nucleophilic attack of the olefin on to the protonated sulphenic acid intermediate (9).

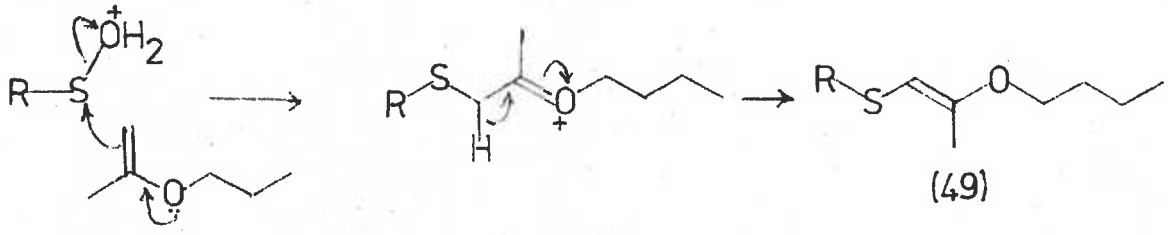


(9)



(10)

It has been shown that other, more nucleophilic, double bonds can compete successfully with the intramolecular process for displacement of OH_2 from the sulphur.[7] Having had no success in forming the desired bicyclic products after trapping with toluene p-sulphinic acid, it was decided that trapping with isopropenyl n-butyl ether would prove more profitable, since the trapped product (49) can be hydrolysed to the ß-ketosulphide (50). It was then hoped to be able to make use of the acidity of the methylene protons in the α-position to the carbonyl function in carrying out the desired cyclisation reactions.



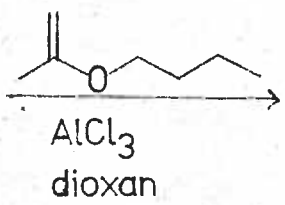
H^+/H_2O → $R.SCH_2COCH_3$

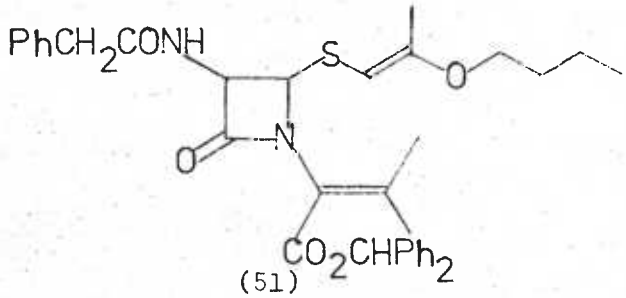
(50)

3.1. Penicillin sulphoxide benzhydryl ester

The first trapping to be carried out with isopropenyl n-butyl ether was that of the benzhydryl ester (43). The reaction was carried out in dioxan, using aluminium chloride as catalyst, and was complete in 4.5 hours. The β-lactam containing product was separated by p.l.c. and was found to be the αβ-unsaturated ester (51) (n.m.r.).

(43)



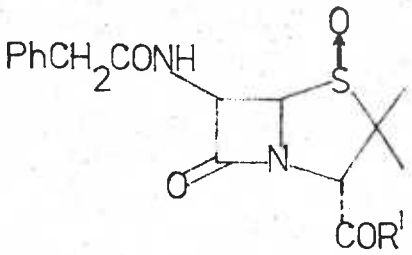


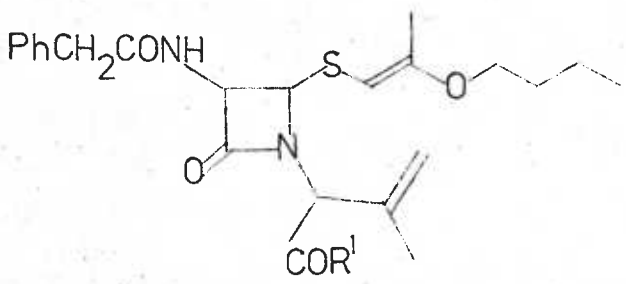
(51)

This result again shows that the benzhydryl ester conjugates much more readily than desired. Therefore, no further work was carried out in this series.

3.2. Penicillin sulphoxide hydrazides

Trappings of both the N^1N^1-diisopropylhydrazide (52) and the trimethylhydrazide (26) with isopropenyl n-butyl ether were carried out. The trapping in the trimethyl series is a very clean one, producing compound (53) which was hydrolysed *in situ*, using aqueous phosphoric acid, to produce the ketone (56) in 75% yield.



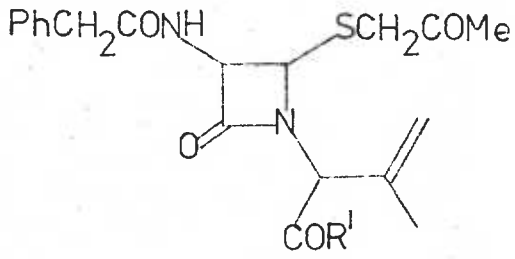


26. R' = $-NMeNMe_2$

52. R' = $-NHNPr^i_2$

53. R' = $-NMeNMe_2$

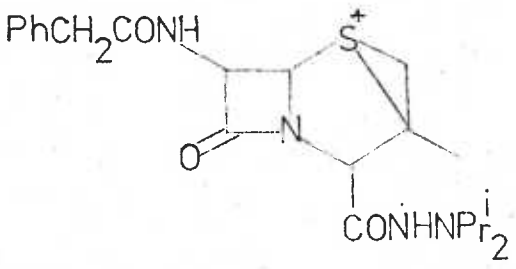
54. R' = $-NHNPr^i_2$



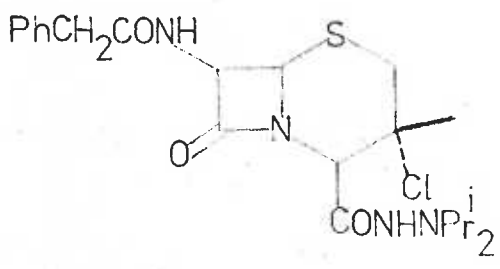
55. R' = -NMeNMe$_2$

56. R' = -NHNPr$^i_2$

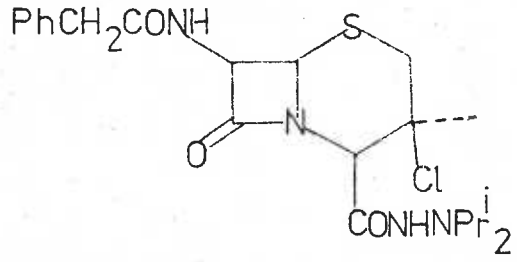
The trapping in the NN-di-isopropyl series is not so clean. The crude product (54) was hydrolysed *in situ* and the resulting ketone (56) separated by column chromatography in 40% yield. At least three other products were removed from the column. Only two of these compounds were β-lactam containing. These compounds were very similar in polarity. The n.m.r. spectrum of the mixture showed only one methyl resonance, at 8.35τ, apart from the isopropyl methyls. It also shows two doublets at 7.45 and 7.23 (J = 14 Hz) and 5.79 and 5.56τ respectively. The mixture was sent for mass spectral analysis. The mass spectrum showed molecular ions at 466 and 468 indicating that the compounds were the 3-chloro cephalosporin derivatives (58) and (59). These could result from attack on the sulphonium ion intermediate (57) by chloride ion from the aluminium chloride catalyst.



(57)



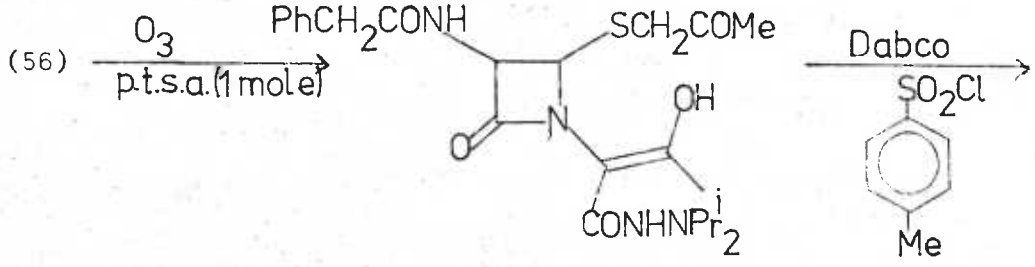
(58)



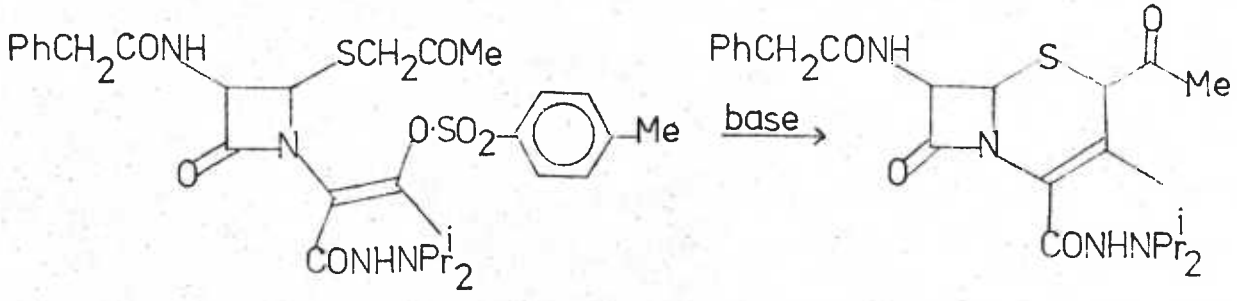
(59)

One isomer of the 3-chloro cephalosporin derivative was formed in the trapping of the trimethyl hydrazide, but in smaller quantity.[67]

The ketone (56) was ozonised, in the presence of toluene p-sulphonic acid (1 mole) to give the enol (60). This compound was reacted with toluene p-sulphonyl chloride and 1,4-diazobicyclo[2.2.2]octane in tetrahydrofuran, to give the enol-tosylate (61).



(60)

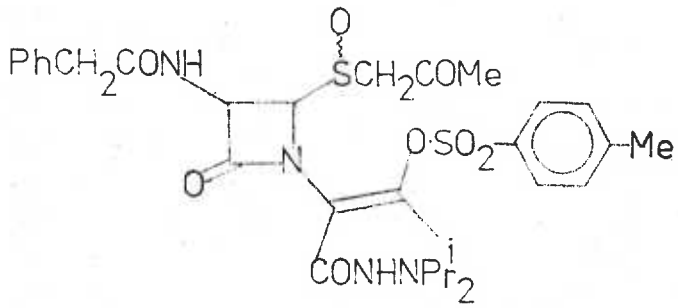


(61) (62)

Attempts were made to cyclise the enol-tosylate (61) to the desacetoxy cephalosporin derivative (62). These attempts were made using sodium hydride, Dabco and Triton B respectively, in various solvents including

benzene, dioxan and hexamethylphosphoramide (HMPA). All were unsuccessful, the result being that either starting material was recovered or β-lactam was destroyed.

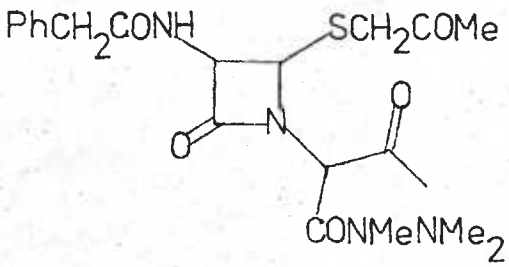
At this stage it was proposed that if the sulphide in compound (61) was converted to the sulphoxide, the cyclisation might be facilitated. Thus, compound (61) was oxidised with m-chloroperbenzoic acid in dichloromethane to produce two compounds. These were assigned as either two sulphoxide isomers (63) or one sulphoxide plus sulphone.



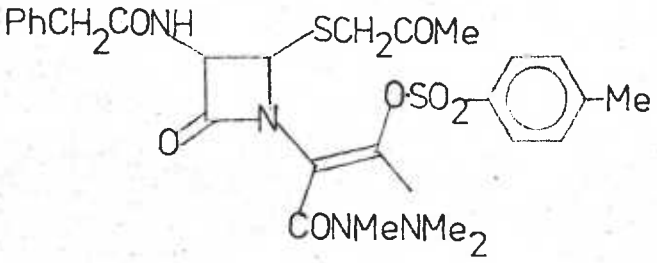
(63)

The crude oxidation product was treated with Triton B in HMPA, at room temperature, but this resulted in complete destruction of β-lactam (i.r.).

The ketone (55) was ozonised to give the diketone (64). Attempts were made to form the enol-tosylate (65) of compound (64), but none were successful. Compound (64) was treated with p-toluene sulphonyl chloride in the presence of sodium hydride, DBN and Dabco respectively, in various solvents, including benzene, tetrahydrofuran and HMPA. In all cases, the reaction was either too slow, or destruction of β-lactam took place. Similar results were found when attempts were made to form the enol mesylate of compound (64), the reaction, if indeed there was any, being very slow.

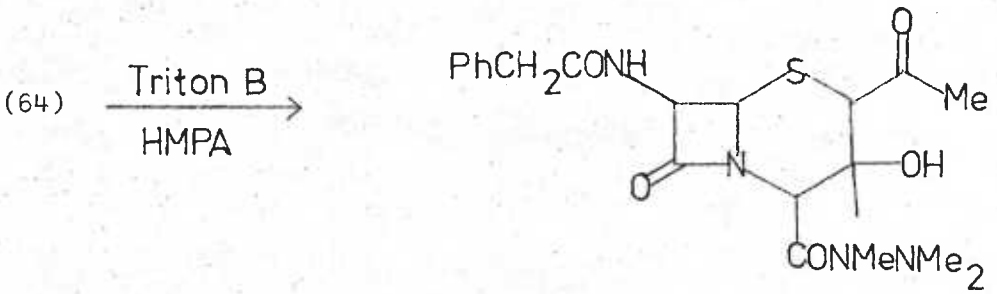


(64)



(65)

It has been shown, by another worker at Imperial College,[67] that on treatment with Triton B in HMPA the diketone (64) cyclises to give the desacetoxy cephalosporin derivative (66).



(66)

Since an efficient way of removing the trimethyl-hydrazine protecting group from penicillin compounds has not yet been found it would be useful if the compound analogous to (66) is formed in the N^1N^1-di-isopropylhydrazide series, since the N,N-di-isopropylhydrazine protecting group can be efficiently removed. Thus, compound (60) was treated with Triton B in HMPT. However, no cyclisation took place.

4. Conclusions

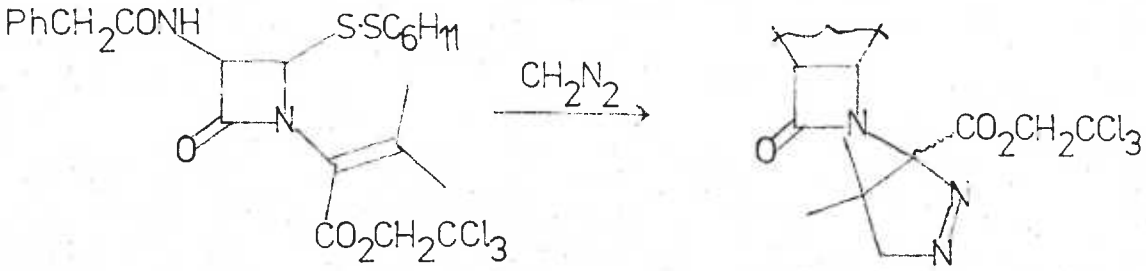
The sulphenic acids derived by heating penicillin sulphoxides react with toluene-p-sulphinic acid to form the corresponding thiosulphonate

S-esters. The esters react with stabilised carbanions to form the corresponding sulphides, liberating the anion of toluene-p-sulphinic acid. These sulphides were considered to be potentially useful intermediates in the synthesis of bicyclic β-lactam structures. Attempts to carry out the desired cyclisation proved unsuccessful.

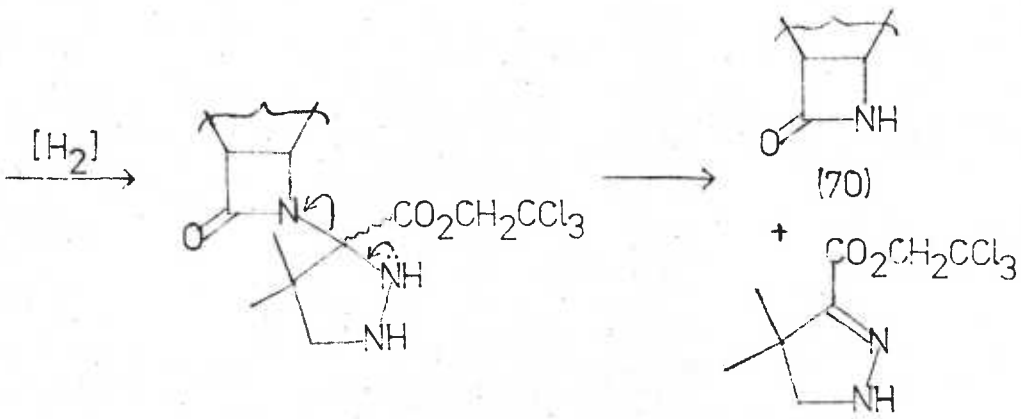
The products from reaction of the sulphonic acids with isopropenyl n-butyl ether can be hydrolysed to the corresponding β-ketosulphides. Attempts to synthesise bicyclic β-lactam structures using these β-ketosulphides proved unsuccessful. However, further work with these compounds should produce novel bicyclic β-lactam structures as potential antibiotics.

5. Removal of isopentenoyl side chain *via* pyrazolines

It has recently been reported [9] that the nitrogen substituent in the disulphide (67) can be removed by reacting it with diazomethane, to give the pyrazoline (68), followed by reduction of the pyrazoline (68) with a mild reducing agent such as chromium (II) acetate or NN[1]-dihydrobenzo(c)cinnoline. These reductions liberate both the β-lactam fragment (70) and the corresponding pyrazoline(71), *via* the pyrazolidine (69). In order that the liberated pyrazoline could be fully characterised, the authentic pyrazoline (71) was prepared by addition of diazomethane across trichloroethyl ββ-dimethylacrylate.



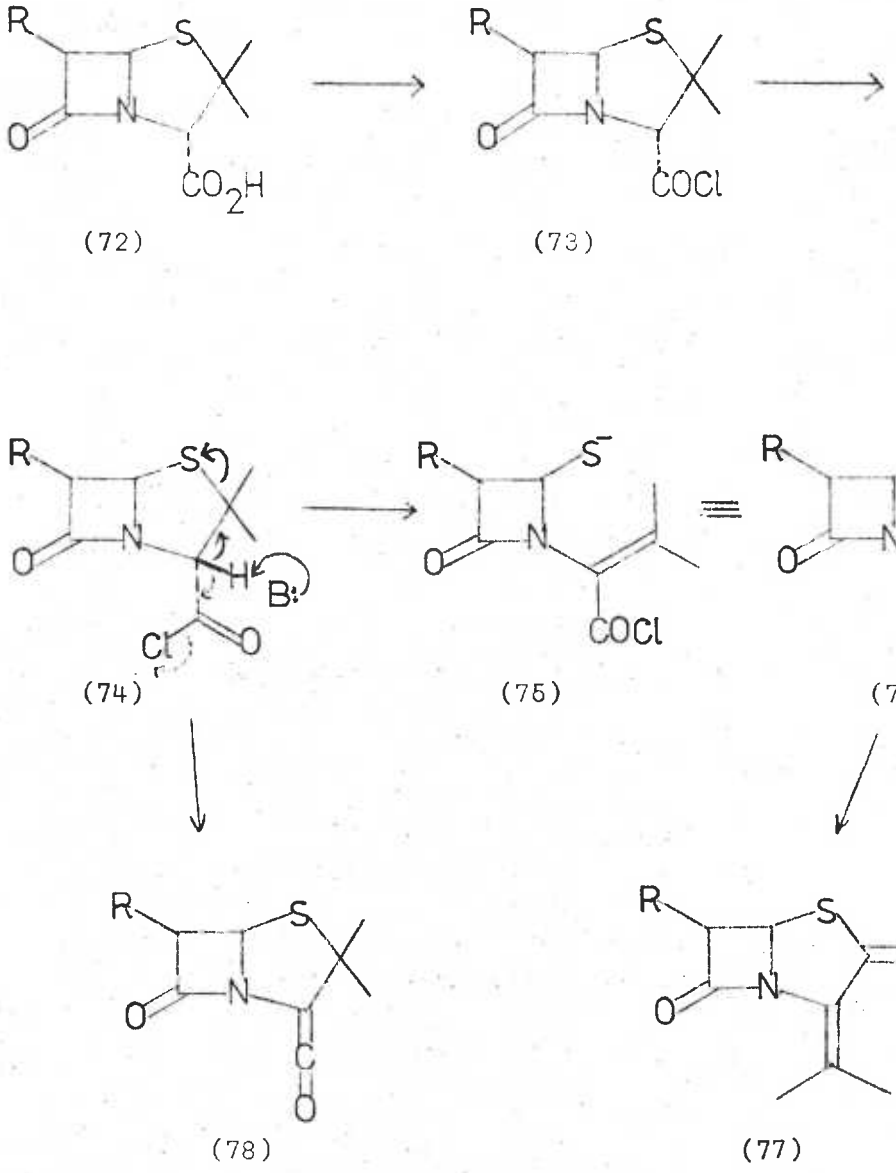
(67) (68)



(69) (71)

6. Anhydropenicillin rearrangement

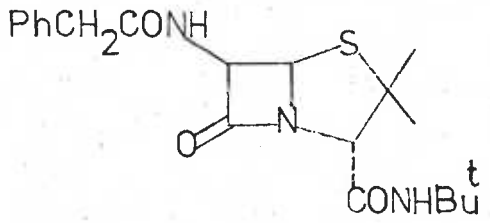
Wolfe and co-workers[68] found that treatment of the acid chloride, or mixed anhydride of a penicillanic acid (*e.g.* 73) with a base induces a striking transformation into a new compound, identified as an anhydropenicillin (77). This rearrangement is assumed to proceed *via* opening of the thiazolidine ring to the anion (75), followed by rotation about the nitrogen-carbon bond to the conformer (76) and recyclisation to the thialactone (77), as shown in Scheme 3.



R = $PhCH_2CONH$

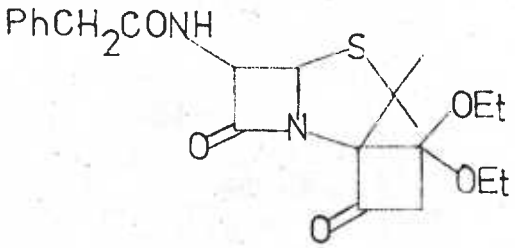
Scheme 3

It was proposed that the rearrangement could proceed *via* the ketene (78). Hence, it was decided to try to prove the presence of the ketene intermediate by trapping it *in situ*. If this experiment was successful it would mean that substituents could be introduced into the 3-position of the thiazolidine ring very readily. (1S)-6β-Phenylacetamidopenicillanic acid (72) was converted into its acid chloride (73) by reaction with thionyl chloride, in chloroform solution, at low temperature, under nitrogen. The formation of the acid chloride (73) was monitored by infra-red spectroscopy, the carbonyl stretch of the carboxylate anion (1620 cm^{-1}) disappearing as the acid chloride (1780 cm^{-1}) was formed. The formation of the acid chloride was proven by reacting it with t-butylamine to form the corresponding t-butylamide (79).



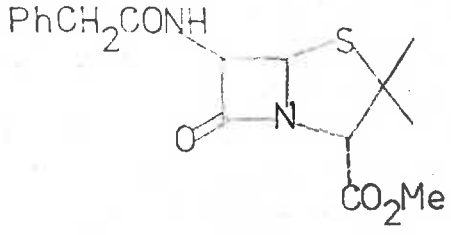
(79)

In one experiment the solution of the acid chloride was basified with triethylamine. The infra-red spectrum of the mixture, taken 15 min. after basification showed a peak at 2050 cm^{-1}, which was assigned as a ketene carbonyl absorption. Thus, 1,1-diethoxyethylene was added, in the hope that the trapped ketene product (80) would be produced.[69] However, t.l.c. results indicated that the only product formed was the anhydropenicillin (77).



(80)

In a second experiment, an attempt was made to trap the ketene intermediate with deuterium oxide. After the addition of triethylamine to the acid chloride solution, the mixture was allowed to warm up to 0°. Deuterium oxide was then added, in excess, and the mixture stirred vigorously for 20 min. T.l.c. indicated that about 20% anhydropenicillin had formed from the acid chloride. The mixture was then worked up and the acid fraction recovered by diluting the reaction mixture with ethyl acetate, extracting with dilute sodium bicarbonate solution, acidifying with phosphoric acid and extracting the acid solution. A sample of this acid fraction was esterified, using diazomethane, and purified by p.l.c. to give the methyl ester (81). The mass spectrum of the isolated product was identical to that of the authentic methyl ester (81), thus showing that no detectable amount of deuterium had been incorporated in the 3-position.



(81)

These results indicate that the anhydropenicillin rearrangement does not go *via* a ketene intermediate.

PART I

EXPERIMENTAL

I.R. spectra were recorded with a Unicam SP 200 spectrometer, the phase employed being indicated in the text. U.V. spectra were recorded with a Unicam SP 800 spectrometer, for ethanolic solutions. Mass spectra were determined with an A.E.I. MS9 machine. ^{1}H n.m.r. spectra were recorded with Varian T60 or HA 100 instruments, for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Rotations were carried out on a Perkin-Elmer 141 polarimeter for solutions in chloroform. Reactions were monitored by t.l.c. on Merck Kieselgel GF_{254} nach Stahl. Preparative thin layer chromatography (p.l.c.) was carried out on 1 mm thick Merck Kieselgel GF_{254} nach Stahl plates, with the solvents indicated. Column chromatography was carried out on Merck Kieselgel 60. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Light petroleum refers to the fraction of boiling range 60-80°. All solutions were dried over anhydrous sodium sulphate.

(1S)-6ß-Phenylacetamidopenicillanic acid 1-oxide was kindly supplied by Glaxo Research LTD.

(1S)-N-6β-Phenylacetamidopenicillanoyl-NN'-di-isopropylhydrazine S-oxide (7)

6β-Phenylacetamidopenicillanic acid 1-oxide (5) (3.5g, 10 m mole) was dissolved in dry tetrahydrofuran (50 ml) and magnetically stirred at -20°, under nitrogen. Ethyl chloroformate (1.2g, 10 m mole) was added followed by triethylamine (1g, 10 m mole) and the mixture stirred for 1 h. NN'-Di-isopropylhydrazine (1.01g, 12 m mole) was then added and stirring continued for a further 20 min. The mixture was then poured into ethyl acetate (100 ml), washed with 5% v/v phosphoric acid (2 x 50 ml), dilute bicarbonate (2 x 30 ml) and brine (25 ml), dried and evaporated to dryness. The crude product in benzene (5 ml) was precipitated from light petroleum (100 ml). Crystallisation from benzene afforded the sulphoxide hydrazide (7) (3.54g, 77%) as white needles, m.p. 158-160°, $[\alpha]_D^{25}$ + 111° (c 1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3500 and 3380 (NH), 1785 (β-lactam) and 1685 cm^{-1} (amide), τ 2.8 (5H,s,Ph), 2.95 (1H,d,J8Hz,NH), 4.1 (1H,dd,J4 and 8Hz,H-6), 4.33(1H,s,H-3), 5.05 (1H,d,J4Hz,H-5), 5.9 (1H,m,$CONCHMe_2$), 6.42 (2H,s,CH_2Ph) and 6.82 (1H,m,$NCHMe_2$) (Found: C,58.9; H,7.0; N,12.4; S, 7.1. $C_{22}H_{32}N_4O_4S$ requires C, 58.9; H, 7.2; N, 12.5; S, 7.1%).

Trapping of the NN'-di-isopropylhydrazide (7) with toluene-p-sulphinic acid

The hydrazide (7) (5.0g, 11 m mole) in dry benzene (80 ml) was heated with toluene-p-sulphinic acid (8.0g, 50 m mole) and diethylaniline (25 ml, 20 m mole) at reflux for 1.5 h. The solution was cooled, diluted with ethylacetate (100 ml) and washed with 15% v/v phosphoric acid (2 x 30 ml), dilute bicarbonate (30 ml) and brine (30 ml). The organic extract was evaporated to small bulk in vacuo and the residue precipitated from hot light petroleum several times. The residual oil was then chromatographed to give two products.

The first compound, eluted with benzene, was recrystallised from benzene-cyclohexane to give (3S,4S,6R,7R)-4-(NN'-di-isopropylhydrazinocarbonyl)-3-methyl-7-phenylacetamido-3-(p-tolylsulphonyl)cepham (10a) (1.3g, 20%) as white needles, m.p. 178-179°, $[\alpha]_D^{25}$ + 49° (c 1.4 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3450 and 3350 (NH), 1775 (β-lactam), 1690 (amide), 1660, 1520, 1330 and 1155 (SO_2) cm^{-1}, τ 2.3 (2H,d,Ar), 2.8 (7H,m,Ar), 3.7 (1H,s), 4.3-4.6 (2H,β-lactam), 5.9 (1H,m,C<u>H</u>Me$_2$), 6.2br (1H,s), 6.45 (2H,s,C<u>H</u>$_2$Ph), 6.68br (2H,s), 6.75 (1H,m,CONC<u>H</u>), 7.6 (3H,s,Ar<u>Me</u>), 8.35 (3H,s,Me) and 8.8-9.2 (12H,m,2 x <u>Me</u>$_2$CH) (Found: C,59.2; H, 6.4; N, 9.6; S, 11.0. $C_{19}H_{38}N_4O_5S_2$ requires C,59.4; H,6.5; N,9.55; S,10.9%).

The second compound, eluted with benzene-ethyl acetate mixtures, was crystallised from benzene-cyclohexane to yield (3R,4R)-1-[(1R)-NN'-di-isopropylhydrazinocarbonyl-2-methylprop-2-enyl]-3-phenylacetamido-4-(p-tolylsulphonylthio)azetidin-2-one (8). (4.5g, 70%) as a colourless foam, $[\alpha]_D^{25}$ -117° (c 1.5 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3450 and 3350 (NH), 1770 (β-lactam), 1690 and 1600 (amide) and 1340 and 1150 cm^{-1} (SO_2), τ 2.4 (2H,m,Ar), 2.7 (7H,m,Ar), 3.4 (1H,d,J8Hz,NH), 4.2 (1H,d,J5Hz,H-4), 4.7 br (1H,s), 4.95 (1H,dd,J5 and 8Hz, H-3), 5.35 br (s) and 5.6 br (s) (2H, c=C<u>H</u>$_2$), 5.9 (1H,m,CON<u>H</u>), 6.2-6.9 (4H,m), 7.6 (3H,s,Ar<u>Me</u>), 8.25 (3H,s, MeC=C) and 8.6-9.2 (12H,m,2x<u>Me</u>$_2$CH). A sample was precipitated from dioxan for analysis. (Found: C, 58.9; H,6.5; N,9.0; S, 10.4. $C_{29}H_{38}N_4O_5S_2$, $0.5C_4H_8O_2$ requires C,59.0; H,6.7; N,8.9; S,10.2%).

<u>Reaction of the thiosulphonate (8) of the NN'-di-isopropylhydrazide with di-t-butyl sodiomalonate</u>

Sodium hydride (0.173g, 4 m mole) was stirred in dry benzene (8 ml) under nitrogen, at room temperature. Di-t-butyl malonate (0.864g, 4 m mole) was added and stirring continued until evolution of hydrogen ceased. The hydrazide (8) (1.17g, 2 m mole) in dry benzene (3 ml) was added and the mixture stirred for a further 20 min. The reaction mixture was

then acidified with 5% v/v phosphoric acid and extracted with ethyl acetate (2 x 25 ml). The extract was washed with dilute bicarbonate (2 x 20 ml) and water (15 ml), dried and the solvent removed in vacuo to afford a pale yellow oil. The oil was separated by p.l.c. (1:9, ethylacetate:benzene) to give (3R,4R)-4-[(bis-t-butoxy-carbonyl) methylthio]-1-[(1R)-2-methyl-1-NN'-di-isopropylhydrazino-carbonylprop-2-enyl]-3-phenylacetamidoazetidin-2-one (11). (0.85g, 70%) as a white foam, $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1720 (ester) and 1660 cm^{-1} (amide), τ 2.7 (5H,s,Ph), 4.3 (1H,d,J4Hz,H-4), 4.5 (2H,m), 5.02 and 5.1 (2H,C=CH_2), 5.9 (1H,s,SCH), 6.38 (2H,s,CH_2Ph), 8.15 (3H,s,MeC=C), 8.6 (18H,s,6xMe) and 8.6-9.2 (12H,m,4xMe).

Reaction of the di-t-butyl malonate derivative (11) with bromine

A solution of bromine (0.064g, 0.4 m mole) in dry carbon tetrachloride (1 ml) was added dropwise, over 10 min, to a stirred solution of the hydrazide (11) (0.129g, 0.2 m mole) and dry toluene-p-sulphonic acid (0.034g, 0.2 m mole) in dry carbon tetrachloride (3 ml), at room temperature. The solution was stirred for 15 min. after completion of the addition and then diluted with ethyl acetate (50 ml), washed with dilute bicarbonate (15 ml) and brine (15 ml) and dried. The solvent was removed, in vacuo, to give the monobromo-compound (15) (0.13g, 90%) as a pale-yellow foam. $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1770 (β-lactam), 1720 (ester) and 1680 cm^{-1} (amide), τ 2.78 (5H,s,Ph), 4.44 (1H,d,J4Hz,H-4), 4.74 (1H,dd,J4 and 8Hz, H-3), 5.35 (1H,s), 5.78 (1H,s,SCH), 6.36-6.78 (6H,m,CH_2Ph,CH_2Br, 2xCHMe_2), 8.55 (18H,s,2xMe_3C) and 8.68-8.98 (15H,m, 5xMe).

An attempt was made to purify the brominated compound (15) by p.l.c. (1:9, ethyl acetate:benzene), but on the silica gel the compound was transformed to compound (16) which was obtained as a white foam.

$\nu_{max.}$ ($CHCl_3$) 3450 (NH), 1760 (β-lactam), 1720 (ester), 1670 and 1630 cm^{-1} (amide), τ 2.7 (5H,s,Ph), 4.2 (1H,d,J4Hz, H-4), 4.8 (1H,dd,J4 and 9Hz,H-3), 5.86 (1H,s,SCH), 6.32 (2H,s,CH_2Ph), 6.4 (2H,s,CH_2), 8.0 (3H,s,MeC=C), 8.5 (18H,s,2xMe_3C) and 8.68-9.0 (12H,m,2xMe_2CH), $\lambda_{max.}$ 251 nm (ε2380). Mass measurement: M^+ 644.

(1S)-N-6β-Phenylacetamidopenicillanoyl-N'N'-dibenzylhydrazine S-Oxide (19)

The mixed anhydride from the sulphoxide acid (5) (3.5g) and ethyl chloroformate (1 ml) in tetrahydrofuran (50 ml) was treated with NN-dibenzylhydrazine (2.4g) at -20°. The mixture was stirred for 20 min, diluted with ethyl acetate (100 ml), washed with 5% v/v phosphoric acid (2 x 30 ml), dilute bicarbonate (2 x 30 ml) and brine (30 ml), dried, and evaporated, in vacuo, to give a white solid. Crystallisation from benzene-ethyl acetate (1:1) afforded the sulphoxide hydrazide (19) (3.8g, 75%) as white needles, m.p. 174-176°. $\nu_{max.}$ ($CHCl_3$) 3420 (NH), 1800 (β-lactam) and 1690 cm^{-1} (amide),τ 2.68 (15H,d,Ar), 4.2 (1H,dd,J4 and 8Hz, H-6), 5.2 (1H,d,J4Hz,H-5), 5.76 (1H,s,H-3), 6.0 (4H,s,2xNCH_2Ph), 6.46 (2H,s,CH_2Ph), 8.58 (3H,s,Me) and 9.42 (3H,s,Me).

(1S)-N-6β-Phenylacetamidopenicillanoyl-N'N'-dimethylhydrazine S-Oxide (20)

The mixed anhydride from the sulphoxide acid (5) (7.0g) and ethyl chloroformate (2 ml) in tetrahydrofuran (50 ml) was treated with NN-dimethylhydrazine (1.2g) at -20°. The mixture was stirred for 20 min, diluted with ethylacetate (100 ml), washed with 5% v/v phosphoric acid (2x30 ml), dilute bicarbonate (2x30 ml) and brine (30 ml), dried, and evaporated to small volume, in vacuo. The crude product was precipitated from light petroleum to afford the sulphoxide hydrazide (20) (5.6g, 70%) as an amorphous solid. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1780 (β-lactam) and 1680 cm^{-1} (amide), τ 2.72 (5H,s,Ph), 4.0 (1H,dd,J4 and 8Hz,H-6), 5.05 (1H,d,J4Hz,H-5), 5.56 (1H,s,H-3), 6.42 (2H,s,CH_2Ph), 7.4 (6H,s,NMe_2), 8.20 (3H,s,Me) and 8.8 (3H,s,Me).

Trapping of the N'N'-dimethylhydrazide (20) with toluene-p-sulphinic acid

The hydrazide (20) (10g) in a mixture of dry THF (75 ml) and dry dioxan (175 ml) was heated with toluene-p-sulphinic acid (10 g) and diethylaniline (35 ml) at reflux for 7½h. The reaction mixture was worked up in the usual manner to give, after column chromatography using benzene-ethyl acetate mixtures, (3R,4R)-1-[(1R)-2-methyl-1-(N'N'-dimethylhydrazinocarbonyl) prop-2-enyl]-3-phenylacetamido-4-(p-tolylsulphonylthio) azetidin-2-one (21) (8g, 60%) as a pale yellow foam. $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH), 1770 (β-lactam) and 1680 cm^{-1} (amide), τ 2.20 (2H,d,Ar), 2.83 (8H,m,Ar), 4.53 (1H,d,J4Hz,H-4), 4.7-5.3 (2H,m,H-3+NH), 5.25 (2H,s,$\underline{CH_2}$=C), 6.06 (1H,s), 6.43 (2H,s,Ph$\underline{CH_2}$), 7.53 (6H,s,$\underline{NMe_2}$), 7.56 (3H,s,Ar$\underline{Me}$) and 8.23 (3H,s,MeC=C).

Reaction of the thiosulphonate of the N'N'-dimethyl hydrazide (21) with diethyl sodiomalonate

A solution of the hydrazide (21) (0.59g, 1.5 m mole) in dry benzene (15 ml) was added to a freshly prepared solution of diethyl sodiomalonate (0.37g, 3 m mole) in benzene (15 ml) with stirring at room temperature. After 15 min. the solution was acidified with 5% v/v phosphoric acid and then extracted with ethyl acetate (2 x 50 ml). The extract was washed with dilute bicarbonate (2 x 25 ml) and water (25 ml) dried and evaporated in vacuo, to afford a pale-yellow oil. The oil was then chromatographed using benzene-ethylacetate mixtures, to give (3R,4R)-4-[(bisethoxycarbonyl) methylthio]-1-[(1R)-2-methyl-1-N'N'-dimethyl-hydrazinocarbonylprop-2-enyl]-3-phenylacetamidoazetidin-2-one (22) (450 mg, 80%) which was crystallised from ethyl acetate as white needles, m.p. 138-141°, $[\alpha]_D^{20}$ - 71° (c 1.1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH), 1760 (β-lactam), 1740 (ester) and 1680 cm^{-1} (amides), τ 2.73 (5H,s,Ph), 4.6 (1H,d,J4Hz,H-4), 4.93 (2H,s,CH_2=C), 5.23 (1H,dd,J4 and 8Hz,H-3), 5.55-6.0 (6H,m), 6.33 (2H,s,Ph$\underline{CH_2}$),

7.43 (6H,s,$\underline{NMe}_2$), 8.08 (3H,s,Me), 8.73 (6H,t,2 x $\underline{MeCH}_2$) (Found: C, 56.2; H,6.2; N,10.2; S, 6.2. $C_{25}H_{34}N_4O_7S$ requires C,56.2; H,6.4; N,10.5; S,6.0%).

Reaction of the diethyl malonate derivative (22) with bromine

A solution of bromine (0.06g, 0.375 m mole) in dry dichloromethane (1 ml) was added dropwise, over 10 min, to a stirred solution of the hydrazide (22) (0.16g, 0.3 m mole) and dry toluene-p-sulphonic acid (0.105g, 0.6 m mole) in dry dichloromethane (3 ml), at room temperature. The reaction mixture was stirred for a further 15 min. and then diluted with ethyl acetate (20 ml), washed with dilute bicarbonate (10 ml) and brine (10 ml) and dried. The solvent was removed, in vacuo, to give the dibromo-compound (23) (0.19g, 95%) as a yellow foam. $\nu_{max.}$ ($CHCl_3$) 3430 and 3280 (NH), 1770 (β-lactam), 1740 (ester) and 1670 cm^{-1} (amide), τ 2.74 (5H,s,Ph), 4.5 (1H,d,J4Hz, H-4), 5.2-6.12 (7H,m), 6.32 (2H,s,$\underline{CH}_2Ph$), 7.43 (6H,s,$\underline{NMe}_2$), 7.82 (3H,s,Me) and 8.7 (6H,t,2x$\underline{MeCH}_2$).

Reaction of the dibromo-compound (23) with sodium hydride

The dibromo-compound (23) (0.14g, 0.2 m mole) was stirred with sodium hydride (0.005g, 0.2 m mole) in dry dioxan (3 ml), under nitrogen, at room temperature. The reaction was monitored by t.l.c. and was complete in 2.5h. The reaction mixture was then acidified with 5% v/v phosphoric acid and extracted with ethyl acetate (2x10 ml). The extract was washed with water (10 ml), dried and evaporated, in vacuo, to give a pale yellow oil. The oil was separated by p.l.c. (1:20, ethanol: ethyl acetate) to afford compound (25) (0.032g, 30%) as an amorphous solid. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1800 (β-lactam), 1730 (ester) and 1690 cm^{-1} (amide), τ 2.68 (5H,s,Ph), 3.9 (1H,dd,J4 and 8Hz,H-3), 5.05 (1H,d,J4Hz,H-4), 5.4-6.2 (5H,m),6.4(2H,s,$\underline{CH}_2Ph$), 7.3 (2H,s,$\underline{CH}_2$), 7.4 (6H,s,$\underline{NMe}_2$), 8.28 (3H,s,$\underline{Me}C=C$) and 8.8 (6H,m,2x$\underline{MeCH}_2$), $\lambda_{max.}$ 257 nm (ε2210). Mass measurement: M^+ 532.

(1S)-N-6β-Phenylacetamidopenicillanoyl-NN'N'-trimethylhydrazine S-oxide (26)

The mixed anhydride from the sulphoxide acid (5) (31g) and ethyl chloroformate (10g) in dry tetrahydrofuran (300 ml) was treated with trimethylhydrazine (6.7g) at -20°. The mixture was stirred for 20 min, diluted with ethyl acetate (500 ml), washed with 5% v/v phosphoric acid (2x50 ml) dilute bicarbonate (2x50 ml) and brine (50 ml) dried and evaporated in vacuo. The crude product was crystallised from chloroform to give the sulphoxide hydrazide (26) (24g, 51%), as a mono solvate, m.p. 76-82° (loss of solvent), $[\alpha]_D^{20}$ - 140° (C 2.0 in $CHCl_3$), $\nu_{max.}$ 3400 (NH), 1780 (β-lactam), 1680 (amide) and 1510 cm^{-1}, τ 2.75 (5H,s,Ph), 2.80 (1H,d,J10Hz,NH), 4.05 (1H,dd,J4 and 10Hz,H-6), 4.40 (1H,s,H-3), 4.98 (1H,d,J4Hz,H-5), 6.42 (2H,s,$\underline{CH_2}$Ph), 7.07 (3H,s,NMe_2), 7.42 (6H,s,NMe_2), 8.35 (3H,s,Me) and 8.75 (3H,s,Me) (Found: C, 45.5; H,5.1; Cl, 20.5; N, 10.6; S, 6.1. $C_{19}H_{26}N_4O_4S$, $CHCl_3$ requires C, 45.7; H,5.2; Cl, 20.2; N, 10.7; S, 6.1%).

Trapping of the NN'N'-trimethylhydrazide (26) with toluene-p-sulphinic acid

The hydrazide (26) (5g) in a mixture of dry THF (30 ml) and dry dioxan (70 ml) was heated with toluene-p-sulphinic acid (8.0g) and diethylaniline (25 ml) at reflux for 1.25h. The reaction mixture was worked up in the usual manner to give, after column chromatography, using benzene-ethylacetate mixtures, (3R,4R)-1-[(1R)-2-methyl-1-(NN'N'-trimethylhydrazinocarbonyl)prop-2-enyl]-3-phenyl-acetamido-4-(p-tolyl-sulphonylthio)azetidin-2-one (27) (4.6g, 70%). The product was crystallised from ethyl acetate as white needles, m.p. 143-145°, $[\alpha]_D^{25}$ -186° (C 1.0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 and 3350 (NH), 1775 (β-lactam), 1680 and 1670 (amide) and 1340 and 1150 cm^{-1} (SO_2), τ 2.05-2.85 (9H,m,Ar), 3.38 (1H,d, J8Hz,NH), 4.0 (1H,d,J4Hz, H-4), 4.50 (1H,s), 4.80 (1H,dd,J4 and 8Hz, H-3), 5.10 br(s) and 5.28 br(s) (2H,CH_2=C), 6.25 (2H,s,Ph$\underline{CH_2}$), 7.0 (3H,s,CON$\underline{Me}$),

7.35 and 7.38 (6H,NMe_2) and 8.0 (3H,s,MeC=C). (Found: C, 57.5; H,5.9; N, 10.4; S, 11.9. $C_{26}H_{32}N_4O_5S_2$ requires C, 57.35; H, 5.9; N, 10.3; S, 11.8%).

Reaction of the thiosulphonate (27) of the NN'N'-trimethylhydrazide with diethyl sodiomalonate

A solution of the hydrazide (27) (0.60g, 1.1 m mole) in dry benzene (15 ml) was added to a freshly prepared solution of diethyl sodiomalonate (0.37g, 2.2 m mole) in benzene (15 ml) with stirring at room temperature. After 15 min. the solution was acidified with 5% v/v phosphoric acid and then extracted with ethyl acetate (2 x 50 ml). The extract was washed with dilute bicarbonate (2 x 25 ml) and water (25 ml) dried and evaporated in vacuo, to afford a pale yellow oil. The oil was then chromatographed using benzene-ethylacetate mixtures to give (3R,4R)-4-[(bisethoxycarbonyl) methylthio]-1-[(1R)-2-methyl-1-NN'N'-trimethyl-hydrazinocarbonylprop-2-enyl]-3-phenyl acetamidoazetidin-2-one (28) (475 mg, 80%) which was crystallised from ethyl acetate, as white needles m.p. 146-148°, $[\alpha]_D^{20}$ -117° (C 1.0 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1765 (β-lactam), 1720 (ester), 1690 and 1680 (amide), τ 2.7 (5H,s,Ph), 3.21 (1H,d,J8Hz,NH), 4.25 (1H,d,J4Hz,H-4), 4.44 br (1H,s), 4.58 (1H,dd,J4 and 8Hz, H-3), 4.95 and 5.05 (2H,CH_2=C), 5.65 (1H,s), 5.85 (4H,q,J7Hz,2x$\underline{CH_2}$Me), 6.40 (2H,s,Ph$\underline{CH_2}$), 7.15 (3H,s,CON$\underline{Me}$) 7.5 and 7.6 (6H,2xN$\underline{Me}$), 8.08 (3H,s) and 8.80 (6H,t, J7Hz,2x$\underline{Me}CH_2$) (Found: C, 57.1; H, 6.5; N, 9.95; S, 5.9. $C_{26}H_{36}N_4O_7S$ requires C, 56.9; H, 6.6; N, 10.2; S, 5.8%).

Reaction of the diethyl malonate derivative (28) with chlorine

A solution of chlorine (0.044g, 0.6 m mole) in dry carbon tetrachloride (1 ml) was added to a stirred solution of the hydrazide (28) (0.165g, 0.3 m mole) and dry toluene-p-sulphonic acid (0.104g, 0.6 m mole) in dry dichloromethane (3 ml), at room temperature. The solution was stirred

for 20 min, diluted with ethylacetate (20 ml), washed with dilute bicarbonate (5 ml) and brine (5 ml) and dried. The solvent was removed, in vacuo, to afford a colourless oil which was purified by p.l.c. (ethyl acetate) to give the oxazoline (29) (0.053g, 50%) as a white foam. $\nu_{max.}$ ($CHCl_3$) 1765 (β-lactam) and 1660 cm^{-1} (amide), τ 2.68 (5H,s,Ph), 3.7 (1H,d,J3Hz), 4.65 (1H,s), 4.88 (1H,d,J3Hz), 5.13 (2H,s,CH_2=C), 6.35 (2H,s,CH_2Ph), 7.15 (3H,s,CONMe), 7.5 (3H,s,Me), 7.61 (3H,s,Me) and 8.49 (3H,s,MeC=C).

Reaction of the diethyl malonate derivative (28) with m-chloroperbenzoic acid

m-Chloroperbenzoic acid (0.24g of 70%, 1 m mole) was added to a stirred solution of the hydrazide (28) (0.548g, 1 m mole) and dry toluene-p-sulphonic acid (0.172g, 1 m mole) in dichloromethane (20 ml) at 0°. T.l.c. results showed that reaction was complete after 1.75 h. The reaction mixture was then diluted with chloroform (30 ml), washed with dilute bicarbonate (2x10 ml) and brine (10 ml) dried, and evaporated, in vacuo, to afford a white foam. The crude product was purified by p.l.c. (1:3, chloroform:ethylacetate) to give the desired sulphoxide (31) (0.23g, 40%) as a white foam. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1775 (β-lactam), 1730 (ester) and 1665 cm^{-1} (amide), τ 2.76 (5H,s,Ph), 3.94 (1H,dd,J4 and Hz,H-3), 4.36 (1H,d,J4Hz, H-4), 4.49 (1H,s), 4.86 (1H,s,HC=C), 5.0 (1H,s,HC=C), 5.26 (1H,s,SCH), 5.48-5.96 (4H,m,2xCH_2Me), 7.14 (3H,s,Me), 7.46 (3H,s,Me), 7.56 (3H,s,Me), 8.02 (3H,s,MeC=C), 8.66 (3H,t,J8Hz,MeCH_2) and 8.68 (3H,t,J8Hz,MeCH_2).

Reaction of the thiosulphonate (27) of the NN'N'-trimethylhydrazide with sodium hydride/triethyl phosphonacetate

Sodium hydride (0.13g, 3m mole) was stirred with triethyl phosphonoacetate (0.67g, 3 m mole) in dry benzene (5 ml), under nitrogen, until evolution

of hydrogen ceased. A solution of the hydrazide (27) (0.82g, 1.5 m mole) in dry benzene (5 ml) was added and t.l.c. results showed that the displacement was complete after 5 min. The mixture was acidified with 5% v/v phosphoric acid and extracted with ethyl acetate (20 ml). The organic layer was washed with dilute bicarbonate (10 ml) and brine (10 ml), dried and evaporated, in vacuo, to afford a colourless oil. The oil was subjected to column chromatography, using benzene-ethylacetate mixtures, to afford compound (33) (0.60g, 65%) as a colourless oil. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1730 (ester) and 1660 cm^{-1} (amide), τ 2.8 (5H,s,Ph), 4.2-4.92 (3H,m), 4.92-5.28 (2H,m,$\underline{CH_2}$=), 5.52-6.2 (7H,m,3x$\underline{CH_2}$Me + S$\underline{CH}$), 6.36 (2H,s,$\underline{CH_2}$Ph), 7.14 (3H,s,CON$\underline{Me}$), 7.52 (3H,s,Me), 7.6 (3H,s,Me), 8.05 (3H,s,MeC=), and 8.47-8.92 (9H,m,3x$\underline{Me}CH_2$).

Ozonolysis of the triethylphosphonoacetate derivative (33)

Ozone was passed through a solution of the hydrazide (33) (0.3g) and dry toluene-p-sulphonic acid (0.02g) in dry dichloromethane (15 ml), at -78°, the reaction being monitored by t.l.c. After 1.25 h, when all the starting material had reacted, the mixture was poured into chloroform (25 ml) and washed with a solution of potassium iodide (1g) and sodium thiosulphate (1g) in water (5 ml) and then with brine (5 ml) dilute bicarbonate (5 ml) and brine (5 ml), dried and evaporated, in vacuo, to produce a colourless oil. The oil was subjected to column chromatography, using chloroform-ethylacetate mixtures, to afford compound (34) (0.25g, 80%) as a colourless gum. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1720 (ester) and 1670 cm^{-1} (amide), τ 2.68 (5H,s,Ph), 4.1-5.2 (3H,m), 5.4-6.2 (7H,m,3x$\underline{Me}CH_2$,+ S$\underline{CH}$), 6.34 (2H,s,$\underline{CH_2}$Ph), 7.12 (3H,s,CON$\underline{Me}$), 7.48 (3H,s,$\underline{Me}$CO), 7.6 (3H,s,Me), 7.68 (3H,s,Me) and 8.42-8.92 (9H,m,3x$\underline{Me}CH_2$).

Reaction of the triethylphosphonoacetate derivative (34) with potassium carbonate

A solution of the hydrazide (34) (0.062g, 0.1 m mole) in dry acetone (5 ml) was stirred vigorously with potassium carbonate (0.04g, 0.3 m mole), at room temperature and under nitrogen. After 36 h. the mixture was filtered and the filtrate diluted with ethyl acetate (60 ml) and washed with 15% v/v phosphoric acid (10 ml) and brine (10 ml). The dried solution was evaporated, in vacuo, and subjected to p.l.c. (1:19, ethanol:ethyl acetate) to afford the isothiazolone (38) (0.033g, 35%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1680 and 1660 cm^{-1} (amide), τ 2.1 (1H,s,HC=C), 2.67 (5H,s,Ph), 6.35 (2H,s,$\underline{CH_2}$Ph), 7.1 (3H,s,CONMe), 7.40 (3H,s,Me), 7.55 (3H,s,MeCO) and 7.74 (3H,s,Me).

Benzhydryl-6-phenylacetamidopenicillanate-1β-oxide (43)

A solution of diphenyldiazomethane (1.15g, 6 m mole) in anhydrous ether (20 ml) was added to a stirred suspension of sulphoxide acid (5) (2.1g, 6 m mole) in ethyl acetate (30 ml) at room temperature. After 36 h. the mixture was washed with dilute bicarbonate (10 ml) and brine (10 ml) dried and evaporated, in vacuo, to give a pale yellow oil. The oil was crystallised from acetone/light petroleum to afford the sulphoxide ester (43) (1.86g, 60%) as white needles, m.p. 174-176°. $\nu_{max.}$ ($CHCl_3$) 3420 (NH), 1800 (β-lactam), 1750 (ester) and 1680 cm^{-1} (amide), τ 2.7 (15H,s,Ar), 3.04 (1H,s,$\underline{CH}Ph_2$), 4.0 (1H,dd,J4 and 8Hz,H-6), 5.1 (1H,d,J4Hz,H-5), 5.28 (1H,s,H-3), 6.44 (2H,s,$\underline{CH_2}$Ph), 8.37 (3H,s,Me) and 9.15 (3H,s,Me).

Trapping of the benzhydryl ester (43) with toluene-p-sulphinic acid

The ester (43) (5.16g, 10 m mole) in dry dioxan (80 ml) was heated with toluene-p-sulphinic acid (3.2g, 18 m mole) and diethylaniline (5.5 ml, 36 m mole) at reflux for 4.5 h. The reaction mixture was worked up in the usual way to give, after column chromatography, using chloroform-ethyl acetate mixtures, the thiosulphonate (44) (3.9g, 60%) as a white foam. $\nu_{max.}$ ($CHCl_3$) 3440 (NH), 1770 (β-lactam), 1735 (ester) and 1680 cm^{-1} (amide), τ 2.78 (19H,s,Ar), 3.2 (1H,s,$\underline{CH}Ph_2$), 4.3 (1H,d,J4Hz,H-4), 4.9-5.3 (3H,m,H_2C=, H-6), 5.63 (1H,s), 6.5 (2H,s,$\underline{CH_2}Ph$), 7.68 (3H,s,Ar$\underline{Me}$) and 8.28 (3H,s,$\underline{Me}$C=C).

The product (44), in benzene solution (5 ml), was isomerised to the αβ-unsaturated ester (45) on treatment with triethylamine (1 ml). $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1770 (β-lactam), 1720 (ester) and 1680 cm^{-1} (amide), τ 2.7 (19H,m,Ar), 3.17 (1H,s,$\underline{CH}Ph_2$), 4.28 (1H,d,J4Hz,H-4), 5.18 (1H,dd,J4 and 8Hz,H-3), 6.4 (2H,s,$\underline{CH_2}Ph$), 7.7 (3H,s,Ar$\underline{Me}$), 8.0 (3H,s,$\underline{Me}$C=C) and 8.05 (3H,s,$\underline{Me}$C=C).

Ozonolysis of the thiosulphonate (44)

Ozone was passed through a solution of the ester (44) (0.33g) in dichloromethane (15 ml), at -78°, the reaction being monitored by t.l.c. After 20 min, when all the substrate had reacted, the solution was diluted with dichloromethane (20 ml) and washed with a solution of potassium iodide (1g) and sodium thiosulphate (1g) in water (8 ml), then with brine (10 ml) and dried. The solvent was removed in vacuo to produce a colourless foam. The n.m.r. spectrum of the foam showed it to be a 9:1 mixture of the ketone (46) and the enol (47). The crude product was subjected to column chromatography, using dichloromethane-chloroform mixtures, to afford the enol (47) (260 mg, 80%) as a white foam.

$\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1770 (β-lactam) and 1670 cm^{-1} (amide), τ 2.7 (19H,m,Ar), 3.2 (1H,s,$\underline{CH}Ph_2$), 5.21 (1H,dd,J4 and 8Hz,H-3), 6.34 (1H,d,J4Hz,H-4), 6.46 (2H,s,$\underline{CH_2}Ph$), 7.69 (3H,s,Ar$\underline{Me}$) and 8.04 (3H,s,MeC=C), $\lambda_{max.}$ 260 nm (ε7500).

Reaction of the thiosulphonate (44) with sodium hydride/triethyl phosphonoacetate

Sodium hydride (0.084g of 50%, 2 m mole) was stirred with triethyl phosphonoacetate (0.45g, 2 m mole) in dry benzene (5 ml), under nitrogen, at room temperature, until evolution of hydrogen ceased. A solution of the ester (44) (0.654g, 1 m mole) in dry benzene (5 ml) was added and t.l.c. results showed that the displacement was complete after 5 min. The mixture was acidified with 5% v/v phosphoric acid and extracted with ethyl acetate (20 ml). The organic layer was washed with dilute bicarbonate (10 ml) and brine (10 ml), dried and evaporated, in vacuo, to afford a colourless oil. The oil was purified by column chromatography, using benzene-ethyl acetate mixtures, to afford the αβ-unsaturated ester (48) (0.42g, 60%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1720 (ester) and 1680 cm^{-1} (amide), τ 2.7 (15H,s,Ar), 2.9 (1H,s,$\underline{CH}Ph_2$), 4.5 (1H,d,J4Hz,H-4), 4.85 (1H,dd,J4 and 8Hz,H-3), 5.6-6.2 (7H,m,3x$\underline{CH_2}$Me + S$\underline{CH}$), 6.34 (2H,s,$\underline{CH_2}Ph$), 7.74 (3H,s,MeC=), 7.9 (3H,s,MeC=) and 8.5-9.0 (9H,m,3x$\underline{Me}CH_2$).

Trapping of the benzhydryl ester (43) with isopropenyl n-butyl ether

The ester (43) (2.0g, 4 m mole) in dry dioxan (10 ml) was heated with isopropenyl n-butyl ether (2.0g, 17 m mole), in the presence of aluminium chloride (50 mg), at reflux for 4.5 h. The reaction mixture was then concentrated, in vacuo, to afford a yellow foam which was taken up into benzene solution (5 ml) and precipitated twice from light petroleum to give, after separation by p.l.c. (1:4, ethylacetate:benzene)

compound (51) (1.0g, 40%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam), 1720 (ester) and 1680 cm^{-1} (amide). τ 2.7 (15H,s,Ar), 3.05 (1H,s,$\underline{CH}Ph_2$), 4.58 (1H,dd,J4 and 8Hz, H-3), 5.0 (1H,d,J4Hz,H-4), 5.52 (1H,s,HC=), 6.36 (2H,s,$\underline{CH_2}Ph$), 6.6 (2H,m,$\underline{CH_2}O$), 7.75 (3H,s,Me), 8.0 (3H,s,$\underline{Me}C=C$), 8.2 (3H,s,$\underline{Me}C=C$), 8.3-8.9 (4H,m,2xCH_2), and 9.07 (3H,m,Me).

Trapping of the NN'N'-trimethylhydrazide (26) with isopropenyl n-butyl ether

The hydrazide (3.0g, 6 m mole) in a mixture of dry tetrahydrofuran (12 ml) and dry dioxan (60 ml) was heated with isopropenyl n-butyl ether (10 ml, 90 m mole), in the presence of aluminium chloride (50 mg), at reflux for 3 h. An aliquot (5 ml) of the reaction mixture was removed, diluted with ethyl acetate (15 ml), washed with dilute bicarbonate (5 ml) and brine (5 ml) and dried. The solvent was removed, in vacuo, to afford compound (53) as a yellow foam. $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam) and 1670 cm^{-1} (amide), τ 2.76 (5H,s,Ph), 4.44-4.6 (3H,m), 4.8 (1H,d,J4Hz, H-4), 5.0 (1H,s,$\underline{HC}=C$), 5.08 (1H,s,$\underline{HC}=C$), 5.5 (1H,s,$\underline{S}>=$), 6.3-6.7 (4H,m,$\underline{CH_2}Ph$, $\underline{CH_2}O$), 7.2 (3H,s,CON$\underline{Me}$), 7.54 (3H,s,N$\underline{Me}$), 7.64 (3H,s,N$\underline{Me}$), 8.1 (6H,d, 2x$\underline{Me}C=C$), 8.34-8.9 (4H,m,2x$\underline{CH_2}$) and 8.9-9.2 (3H,m,Me).

The remainder of the reaction mixture was acidified with 20% v/v phosphoric acid (25 ml) and allowed to stand overnight (14 h) at room temperature. The mixture was then diluted with ethyl acetate (250 ml), washed with brine (25 ml), dilute bicarbonate (2x50 ml) and brine (50 ml), dried and evaporated, in vacuo, to afford a yellow oil. This oil was subjected to column chromatography, using chloroform-ethyl acetate mixtures, to give the β-ketosulphide (55) (2.2g, 80%) as a pale yellow foam. $[\alpha]_D^{21}$ -137° (C 1 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1760 (β-lactam) and 1660 cm^{-1} (amide), τ 2.78 (5H,s,Ph), 4.54-4.74 (3H,m), 5.0 (1H,s,$\underline{HC}=C$), 5.1 (1H,s,$\underline{HC}=C$), 6.44 (2H,s,$\underline{CH_2}Ph$), 6.8 (2H,s,$\underline{CH_2}CO$),

7.18 (3H,s,CONMe), 7.54 (3H,s,NMe), 7.6 (3H,s,NMe), 7.92 (3H,s,MeCO) and 8.1 (3H,s,MeC=C) (Found: C, 59.1; H, 6.9; N, 12.6; S, 7.4. $C_{22}H_{30}N_4O_4S$ requires C, 59.2; H, 6.8; N, 12.6; S, 7.2%).

Ozonolysis of the β-ketosulphide (55)

Ozone was passed through a solution of the β-ketosulphide (55) (0.45g, 1 m mole) and dry toluene-p-sulphonic acid (0.018g, 0.1 m mole) in dry dichloromethane (15 ml) at -78°, the reaction being monitored by t.l.c. After 30 min, when all the substrate had reacted, the mixture was diluted with dichloromethane (20 ml), washed with a solution of potassium iodide (1g) and sodium thiosulphate (1g) in water (8 ml) and then with dilute bicarbonate (10 ml) and water (10 ml) and dried. The solvent was evaporated, in vacuo, to afford the diketo-compound (64) (0.36g, 80%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1780 (β-lactam), 1720 (ketone) and 1680 cm^{-1} amide), τ 2.75 (5H,s,Ph), 4.3-4.9 (3H,m), 6.4 (2H,s,CH_2Ph), 6.68 (2H,s,CH_2CO), 7.14 (3H,s,CONMe), 7.5 (3H,s,NMe), 7.63 (3H,s,COMe), 7.7 (3H,s,NMe) and 7.88 (3H,s,$MeCOCH_2$).

(1S)-N-6β-Phenylacetamidopenicillanoyl-N'N'-di-isopropylhydrazine S-oxide (52)

The mixed anhydride from the sulphoxide acid (35g) and ethyl chloroformate (10.9 ml) in dry tetrahydrofuran (300 ml) was treated with NN-di-isopropylhydrazine (11.6g) at -20°. The mixture was stirred for 20 min, diluted with ethyl acetate (500 ml), washed with 5% v/v phosphoric acid (2x75 ml), dilute bicarbonate (2x75 ml) and brine (50 ml), dried, and evaporated, in vacuo, to give a pale yellow solid. Crystallisation from ethyl acetate afforded the sulphoxide hydrazide (52) (26g, 55%) as pale yellow needles, m.p. 176-178°, $|\alpha|_D^{21}$ +200° (C 2 in $CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1780 (β-lactam) and 1680 cm^{-1} (amide), τ 2.78 (5H,s,Ph), 4.0

(1H,dd,J4 and 8Hz, H-6), 5.14 (1H,d,J4Hz,H-5), 5.46 (1H,s,H-3), 6.44 (2H,s,$\underline{CH_2}$Ph), 6.7 (2H,m,2x$\underline{CH}Me_2$), 8.22 (3H,s,Me), 8.78 (3H,s,Me) and 8.9 and 9.02 (12H,d,2x$\underline{Me_2}$CH) (Found: C, 58.9; H, 7.1; N, 12.4; S, 7.1. $C_{22}H_{32}N_4O_4S$ requires C, 58.9; H,7.2; N, 12.5; S, 7.1%).

Trapping of the N'N'-di-isopropylhydrazide (52) with isopropenyl n-butyl ether

The hydrazide (52) (2.5g) in a mixture of dry tetrahydrofuran (20 ml) and dry dioxan (80 ml) was heated with isopropenyl n-butyl ether (10 ml), in the presence of aluminium chloride (50 mg), at reflux for 7.5 h. The solution was then cooled, acidified with 20% v/v phosphoric acid (15 ml) and allowed to stand overnight (14 h) at room temperature. The mixture was then diluted with ethyl acetate (200 ml), washed with brine (2x50 ml), dilute bicarbonate (2x30 ml) and brine (50 ml), dried, and evaporated, in vacuo, to afford a yellow oil. The oil was then chromatographed to give three products.

The first two compounds, eluted with chloroform, were very similar in polarity and were inseparable by crystallisation. These compounds were crystallised from chloroform to give a mixture of the chloro-compounds (58) and (59) (0.29g, 12%), $\nu_{max.}$ ($CHCl_3$) 3450 and 3300 (NH), 1760 (β-lactam) and 1680 cm^{-1} (amide), τ 2.6 (5H,s,Ph), 4.3 (1H,m,H-7), 4.75 (1H,m,H-6), 5.2 (1H,s,H-4), 5.65 (1H,d,J14Hz), 6.3 (2H,s,$\underline{CH_2}$Ph), 6.8 (2H,m,2x$\underline{CH}Me_2$), 7.3 (1H,d,J14Hz), 8.02 (3H,s,Me) and 8.9 and 9.04 (12H,d,2x$\underline{Me_2}$CH). Mass measurement: M^+ 466, 468.

The third compound, eluted with ethyl acetate, was the β-ketosulphide (56) (1.25g, 45%) and was obtained as a pale yellow foam. $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH), 1755 (β-lactam) and 1680 cm^{-1} (amide), τ 2.74 (5H,s,Ph), 4.72-5.18 (5H,m), 6.38 (2H,s,$\underline{CH_2}$Ph), 6.46-7.26 (4H,m,$\underline{CH_2}$CO, 2x$\underline{CH}Me_2$), 7.86 (3H,s,$\underline{Me}$CO), 8.12 (3H,s,$\underline{Me}$C=C) and 8.78-9.26 (12H,d,2x$\underline{Me_2}$CH). Mass measurement: M^+ 488, (M^+-CH_3) 473, (M^+-C_3H_6O) 430, (M^+-C_3H_6OS) 398.

Ozonolysis of the β-ketosulphide (56)

Ozone was passed through a solution of the β-ketosulphide (56) (0.31g, 0.6 m mole) and dry toluene p-sulphonic acid (0.11g, 0.6 m mole) in dichloromethane (15 ml) at -78°, the reaction being monitored by t.l.c. After 20 min, when all the substrate had reacted, the mixture was diluted with dichloromethane (20 ml), washed with a solution of potassium iodide (1g) and sodium thiosulphate (1g) in water (8 ml), and then with dilute bicarbonate (10 ml) and water (10 ml) and dried. The solvent was evaporated, in vacuo, to afford compound (60) (0.25g, 80%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3350 (NH), 1780 (β-lactam), 1680 and 1630 cm^{-1} (amide), τ 2.75 (5H,s,Ph), 5.05 (1H,d,J4Hz,H-4), 5.32 (1H,dd,J4 and 8Hz,H-3), 6.38 (2H,s,$\underline{CH_2}$Ph), 6.6-7.2 (2H,m,2x$\underline{CHMe_2}$), 6.85 (2H,s,$\underline{CH_2}$CO), 7.85 (3H,s,$\underline{Me}$CO), 8.08 (3H,s,$\underline{Me}$ $\overset{OH}{C}$ =C) and 8.95 and 9.05 (12H,d,2x$\underline{Me_2}$CH), $\lambda_{max.}$ 260 nm (ε7500).

Reaction of the Ozonised product (60) with toluene-p-sulphonyl chloride

Diazabicyclooctane (0.079g, 0.75 m mole) was added to a stirred solution of the enol (60) (0.25g, 0.5 m mole) and toluene-p-sulphonyl chloride (0.18g, 1 m mole) in dry tetrahydrofuran (8 ml), at room temperature, the reaction being monitored by t.l.c. After 20 min, when all the substrate had reacted, the mixture was filtered, the filtrate diluted with ethyl acetate (25 ml), washed with 15% v/v phosphoric acid (10 ml) and brine (10 ml) and dried. The solvent was evaporated, in vacuo, to afford a pale yellow oil. The oil was chromatographed, using benzene-ethyl acetate mixtures, to give the enol-tosylate (61)(0.19g, 60%) as a pale yellow foam. $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH), 1770 (β-lactam) and 1680 cm^{-1} (amide), τ 2.12 (2H,d,Ar), 2.75 (7H,s,Ar), 4.63 (1H,d,J4Hz,H-4), 4.98 (1H,dd,J4 and 8Hz, H-3), 6.38 (2H,s,$\underline{CH_2}$Ph), 6.6 (2H,s,$\underline{CH_2}$CO), 6.6-7.2 (2H,m,2x$\underline{CHMe_2}$), 7.54 (3H,s,Ar$\underline{Me}$), 7.85 (6H,d,$\underline{Me}$C=C,$\underline{Me}$CO) and 8.7 and 9.3 (12H,d,2x$\underline{Me_2}$CH).

Reaction of the enol-tosylate (61) with m-chloroperbenzoic acid

m-Chloroperbenzoic acid (0.045g of 80%, 0.2 m mole) in dichloromethane solution (3 ml) was added dropwise, over 10 min, to a solution of the enol-tosylate (61) (0.13g, 0.2 m mole) in dichloromethane (5 ml) at -10°. T.l.c. showed that oxidation was complete after 20 min, all the starting material having reacted. The mixture was then diluted with dichloromethane (20 ml), washed with dilute bicarbonate (3x10 ml) and brine (10 ml) and dried. The solvent was removed to afford a mixture of sulphoxides (63) (0.10g, 80%) as a colourless foam. $\nu_{max.}$ ($CHCl_3$) 3400 and 3300 (NH), 1770 (β-lactam) and 1680 cm^{-1} (amide), τ 2.1 (2H,d,Ar), 2.68 (7H,s,Ar), 4.08 (1H,dd,J4 and 8Hz,H-3), 4.48 (1H,d,J4Hz,H-4), 5.76-6.16 (2H,m,$\underline{CH_2}CO$), 6.38 (2H,s,$\underline{CH_2}Ph$), 6.6-7.08 (2H,m,2x$\underline{CH}Me_2$), 7.53 (3H,s,Ar$\underline{Me}$), 7.74-7.84 (6H,d,$\underline{Me}CO$,$\underline{Me}C=C$) and 8.6 and 9.28 (12H,d,2xMe_2CH).

2,2,2-Trichloroethyl 4,4-dimethyl-Δ^2-pyrazoline-3-carboxylate (71)

An excess of diazomethane in ether was kept with ββ-tri-chloroethyl ββ-dimethylacrylate for 1 week, at 0-5°. P.l.c. (1:9, ethyl acetate: benzene) afforded the pyrazoline (71) as a white solid. Crystallisation from cyclohexane afforded the product as clear prisms, m.p. 146-148°, $\nu_{max.}$ ($CHCl_3$) 1715 (ester), 1550, 1340 and 1105 cm^{-1}, $\lambda_{max.}$ 298 mm (ε12,000), τ 5.16 (2H,s), 6.52 (2H,s) and 8.68 (6H,s) (Found: C, 35.0; H, 4.1; N, 10.3. $C_8H_{11}Cl_3N_2O$ requires C, 35.1; H, 4.05; N, 10.2%).

6β-Phenylacetamidopenicillanoyl-t-butylamide (79)

The N-ethylpiperidinium salt of 6β-phenylacetamidopenicillanic acid (72) (1.79g, 4m mole) in dry, ethanol-free chloroform (30 ml) was cooled to -50°, under nitrogen, and thionyl chloride (0.48g, 4 m mol3) added.

After stirring for 1 h, t-butylamine (0.58g, 8 m mole) was added and the pH of the mixture adjusted to 8 with triethylamine. The mixture was then stirred for 1 h at -5°, diluted with ethyl acetate (30 ml), washed with 5% v/v phosphoric acid (15 ml) dilute bicarbonate (10 ml) and brine (10 ml), dried and evaporated, in vacuo, to yield the amide (79) (1.25g, 78%) which was recrystallised from benzene as white needles, m.p. 139-140°, $\nu_{max.}$ ($CHCl_3$) 3400 (NH), 1780 (β-lactam) and 1680 cm^{-1} (amide), τ 2.89 (5H,s,Ph), 4.44 (1H,dd,J4 and 8Hz,H-6), 4.74 (1H,d,J4Hz, H-5), 5.98 (1H,s,H-3), 6.42 (2H,s,CH_2Ph), 8.44 (3H,s,Me), 8.54 (3H,s,Me) and 8.68 (9H,s,3xMe).

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PART II

REVIEW

1. Introduction

In spite of the advanced state of azo-chemistry the question of the existence of the parent compound, diimide, remained unanswered until a few years ago, although the first attempts to detect it date back to the last century.[1] Actually, it exists as a transient intermediate and cannot be isolated under normal conditions. It is more stable at lower temperatures, however, and was first detected in the solid state in 1955 by Dows, Pimentel, and Whittle,[2] and in 1958 by Foner and Hudson[3] as one of the products in the electrical decomposition of hydrazine and hydrazoic acid, under reduced pressure.

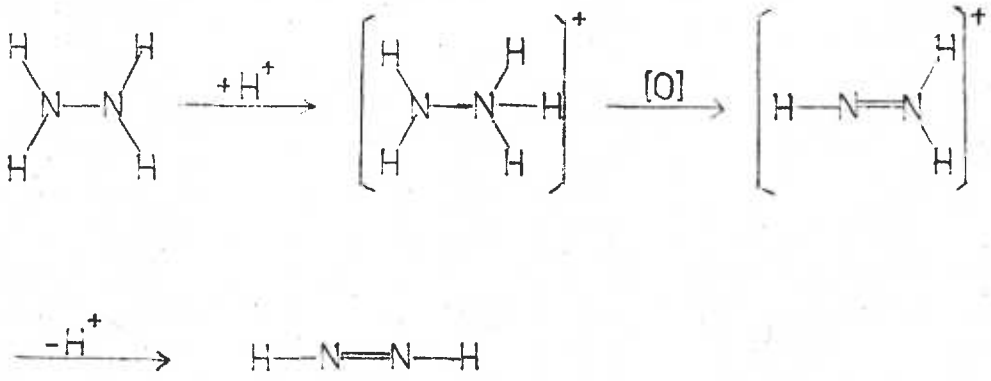
The existence of diimide has now been confirmed chemically: In the Wolff-Kishner reduction of long-chain keto-carboxylic acids, having a double bond in the ω-position, hydrogenation of the double bond is observed as soon as the hydrazone is formed. This side reaction can be completely suppressed by the exclusion of atmospheric oxygen, showing that hydrogenation of the double bond is not caused by hydrazine itself, but by an oxidation product of hydrazine.[4] The stoichiometry of this redox reaction, the stereochemistry of the hydrogenation, and the discovery that the olefinic double bond is also hydrogenated by decomposing benzenesulphonyl hydrazide or azodicarboxylate, led to the conclusion that the hydrogenating agent is diimide.[5,6] This conclusion was reached almost simultaneously by Corey[7], van Tamelen[8] and Aylward[9]. Since then the chemistry of diimide has become well known and its selectivity (both functional and stereo) makes diimide reduction a useful alternative to catalytic hydrogenation.

2. Sources of Diimide

Since the instability of diimide precludes its isolation, the procedures for reduction with diimide involve generation of the reagent

in situ. The most common of these procedures are listed below:

a) From hydrazine. Hydrazine (1) yields diimide in the presence of oxidising agents such as atmospheric oxygen,[6,7,9] peroxides (especially with traces of CuII), mercuric oxide[6], NN-dichloro-toluene sulphonamide[5] and particularly Chloramine T[5] and hexacyanoferrate III.[6] Audrieth and Ogg[10] postulated that the oxidations proceed *via* an acid catalysed process, as shown in Scheme 1.



Scheme 1

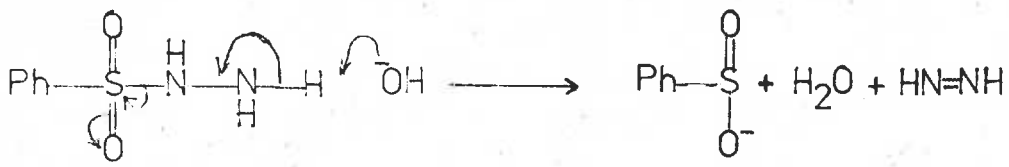
b) From azodicarboxylate salts. Azodicarboxylate (2)[6,7,8] decomposes to give diimide and carbon dioxide, as shown in Scheme 2. It has been shown that the decomposition reaction is subject to general acid catalysis[11]. This method has found some use in preparative work.[6,7,8,12,13,14]

$$\underset{(2)}{{}^{-}O_2C\text{-}N{=}N\text{-}CO_2^{-}} + 2H^{+} \rightarrow 2CO_2 + HN{=}NH$$

Scheme 2

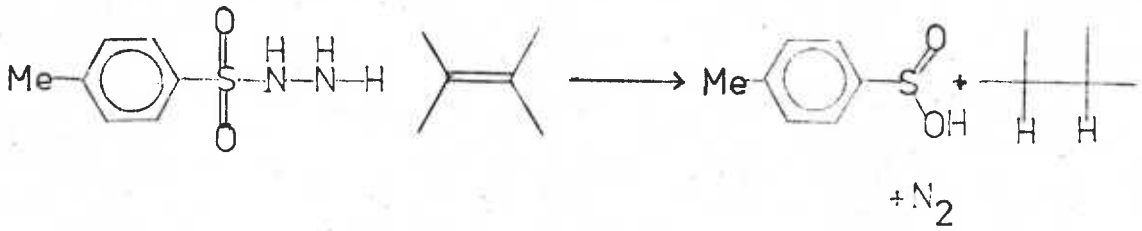
c) From azenesulphonyl hydrazides. When benzenesulphonyl hydrazide (3) is decomposed[6,15,16,17,18] with sodium hydroxide in the presence of olefins, using boiling glycol monomethyl ether as the solvent, reduction

of the latter occurs in high yields.



(3)

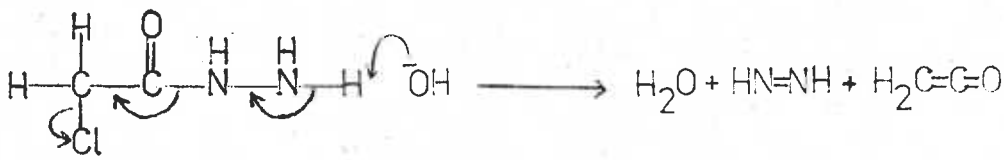
p-Toluenesulphonyl hydrazide (4), in boiling diglyme, behaves similarly towards olefins.[16]



(4)

Diimide can also be obtained from m-,p- and o-nitrobenzenesulphonyl hydrazides[18], at a rate suitable for preparative use, at about 75, 50 and 25°C respectively.

d) From chloroacetyl hydrazide. The hydrochloride of chloroacetyl hydrazide (5) decomposes in alkaline medium rapidly[19], at 0°, as shown in Scheme 3.



(5)

Scheme 3

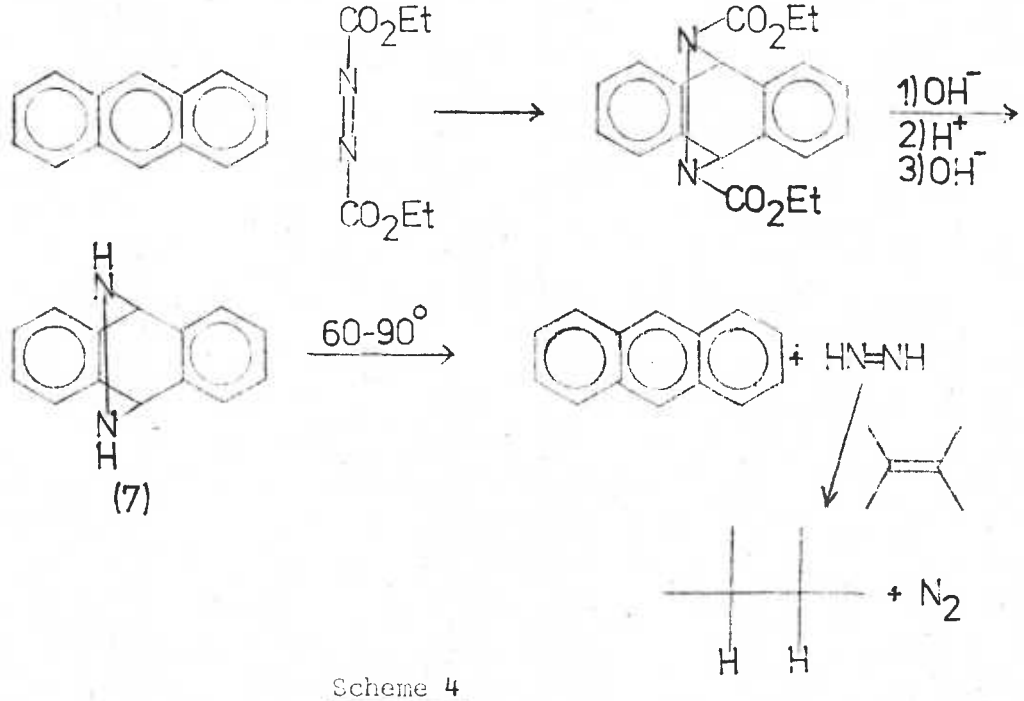
In the absence of olefin, the diimide undergoes disproportionation to nitrogen and hydrazine. The hydrazine then reacts with the ketene to give acetylhydrazide (6), which can be isolated.

$$2HN{=}NH \rightarrow N_2 + H_2N{-}NH_2$$

$$\xrightarrow{H_2C{=}C{=}O} MeCO{-}NH{-}NH_2$$

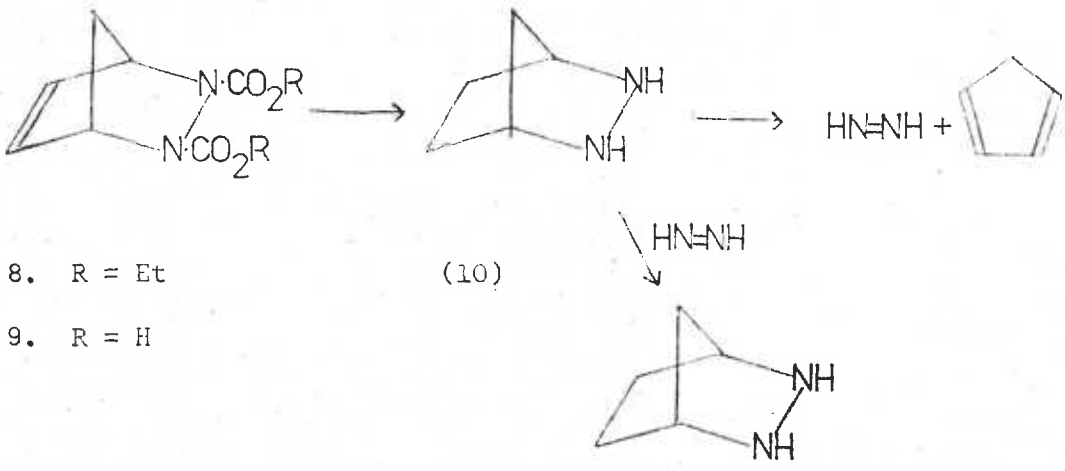
(6)

e) From anthracene-9,10-bisimine. In order to avoid use of acid or basic media when generating diimide, Corey and Mock[20] devised a method whereby the reagent could be formed by heating anthracene-9,10-bisimine (7) together with the olefin in refluxing ethanol. The procedure is shown in Scheme 4.



Scheme 4

f) From cyclopentene-3,5-bisimine. When the diene adduct (8) undergoes mild hydrolysis the free carboxylic acid (9) cannot be isolated.[21] The expected decarboxylation product (10) undergoes a retro-diene reaction, and the resulting diimide is consumed in hydrogenation reactions, for instance with formation of (11).[22]

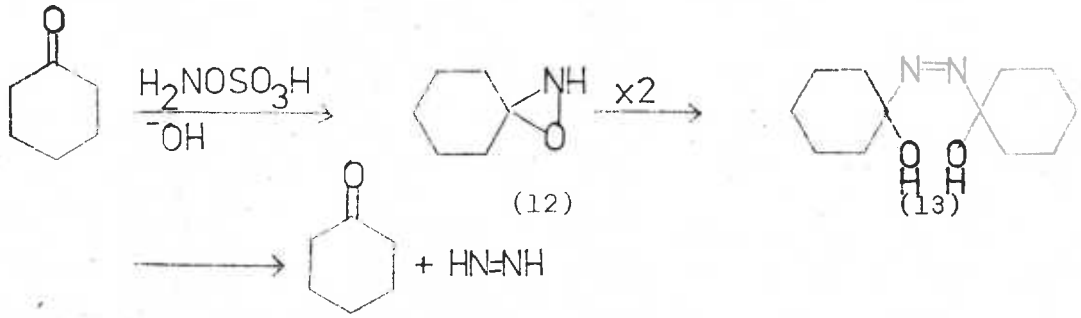


8. R = Et (10)

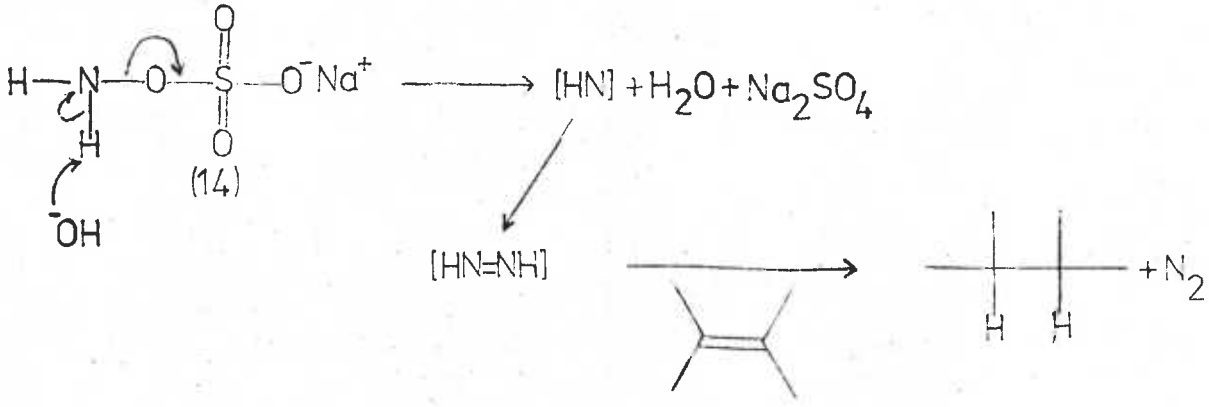
9. R = H

(11)

g) From 1,1'-dihydroxyazocyclohexane. Cyclohexanone and hydroxylamine-O-sulphonic acid react at 10°C, *via* (12), to form the crystalline 1,1'-dihydroxyazocyclohexane (13) which liberates diimide even at room temperature.[23,24]



h) From hydroxylamine-O-sulphonic acid. Simple olefins, such as ethylene, cyclohexene and fumaric acid are hydrogenated by hydroxylamine-O-sulphonic acid (14) in aqueous or methanolic alkali.[25] Yields are of the order of 40%. The reaction is believed to proceed through the formation of "nitrene"[26] which dimerises to diimide, as shown in Scheme 5.



Scheme 5

k) From chloramine. The alkaline cleavage of chloramine (15)[25] follows a course similar to that of (14).

$$\underset{(15)}{NH_2Cl} + NaOH \longrightarrow NaCl + H_2O + [HN] \longrightarrow [HN{=}NH]$$

This reaction has been applied to the reduction of olefins. Thus, undecylenic acid is reduced to undecanoic acid, in 80% yield, in the presence of four moles of chloramine and alkali.

All the above methods for hydrogenating multiple bonds, although, versatile, have the common disadvantage of requiring large excesses of reagent with respect to the amount of substrate. This is a result of the competing reaction whereby diimide undergoes disproportionation.

3. Hydrogenation with diimide

3.1. Selectivity

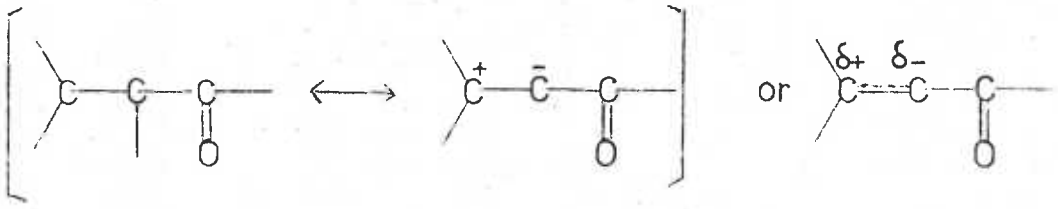
The ease with which diimide reacts with multiple bonds is influenced by the electrical nature of the substituents on the bond. As a general rule, multiple bonds that are symmetrical with regard to electronic distribution are more reactive than multiple bonds in which the electrons of the bond are polarised.[28,29,30] For example, symmetrical multiple bonds such as C=C, C≡C and N=N are reduced much more readily by diimide than are unsymmetrical bonds such as C=N, C≡N, C=O, S=O and C-S. This pronounced difference permits selective hydrogenations. Since even the labile disulphide bond remains intact, allyl disulphide (16) can be smoothly hydrogenated to give n-propyl disulphide (17) in quantitative yields.[13] This reaction cannot be performed in any other way.

$$CH_2{=}CH_2{-}CH_2{-}S{-}S{-}CH_2{-}CH{=}CH_2 \xrightarrow{HN=NH} CH_3CH_2CH_2S{-}SCH_2CH_2CH_3$$

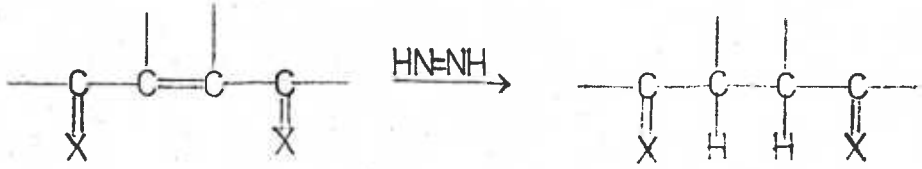
(16) (17)

Vinyl groups on chlorins and porphyrins[31,32] have been reduced to ethyl groups by diimide (generated from hydrazine) without disturbing the other multiple bonds of these systems. Although conjugated systems have not been studied in detail, it is known that aromatic nuclei are stable to diimide, whereas conjugated dienes are reduced, since attempts to trap diimide by Diels-Alder interception with cyclopentadiene resulted in the formation of cyclopentene and cyclopentane.[6,7]

If the stability of polar multiple bonds toward diimide is in fact due to their polarity, then it would be expected that α,β-unsaturated carbonyl compounds, for example, would be somewhat less reactive toward diimide due to the polarity of the double bond:

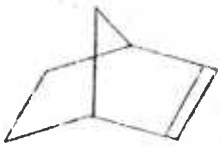
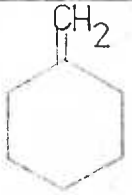
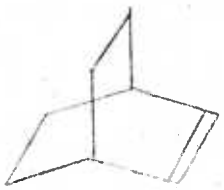
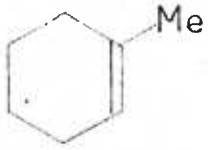
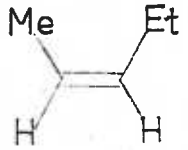
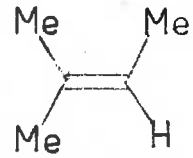


On the other hand, multiple bonds which are flanked on both sides by the same polar groups should themselves be non-polar and hence easily reduced by diimide. This has been demonstrated by Corey[12] and van Tamelen.[33]

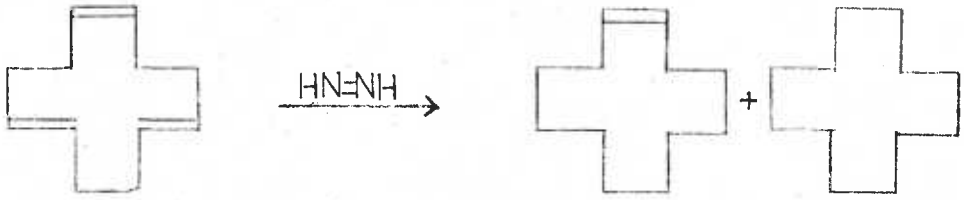


The reactivity of diimide with olefins is also influenced by the number and nature of alkyl substituents present. It has been shown that trans olefins are hydrogenated 3-10 times faster than cis-olefins, and that the rate of hydrogenation decreases rapidly with increasing number of substituents on the double bond.[34,35,36] These reactivity differences have been attributed to differences in strain (torsional, bond angle and eclipsing) in the various olefins, with the more strained olefins reacting more rapidly.[35] The relative rates of reaction of a number of olefins with diimide[35] are summarised in Table 1.

Table 1

Olefin	Relative rate	Olefin	Relative rate
	$4{\cdot}5 \times 10^{2}$		3·3
	29		0·11
	1		2·65
	15·5		0·28
		$Me(CH_2)_2CH{=}CH_2$	20·2
		$Me(CH_2)_2\overset{Me}{\overset{\vert}{C}}{=}CH_2$	2·04

The rigidity of the ring of cis, trans, trans-1,5,9-cyclododecatriene (18) produces large differences in the conformations of the possible transition states for the diimide reaction, so that specific hydrogenation of the trans double bonds is possible.[37] Such a marked selectivity is not observed with acyclic olefins.

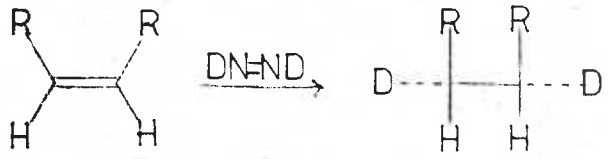


(18) 95 : 5

In addition to high functional specificity, diimide possesses other advantages over metal catalysed hydrogenation. For example, diimide reduction gives no migration or cis-trans isomerisation of double bonds as occurs in some catalytic processes.[9] Also deutero-diimide is an excellent way of introducing deuterium across a multiple bond,[12] since there is no danger of deuterium-hydrogen exchange in other parts of the molecule, which often occurs in metal catalysed reactions.[33] It has also been demonstrated that diimide can be used to reduce the C=O bond of aromatic aldehydes and ketones,[30,38] but reduces the carbonyl function of aliphatic aldehydes and ketones slowly if at all.

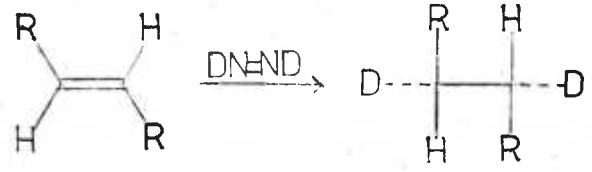
3.2. Stereochemistry

The fact that diimide reduction proceeds with cis-addition across the multiple bond has been determined by infra-red analysis,[5,6] by gas chromatography[5] and by isotopic labelling experiments.[12] Examples of the latter experiments are shown in Scheme 6.



Cis meso (97% yield)

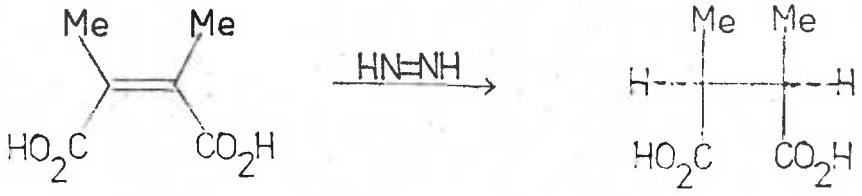
R=CH_2OH; CO_2H



Trans dl (97% yield)

Scheme 6

Symmetrical cis-tetrasubstituted olefins are hydrogenated to the meso-derivatives, indicating cis-addition of hydrogen. For example, dimethyl maleic acid (19) is reduced to meso-2,3-dimethyl succinic acid (20).



cis (19) meso (20)

Acetylenic linkages are converted to cis-olefins, without any trans-olefin being produced at all[6,12,25]. For example phenyl propiolic acid (21) is reduced to cis-cinnamic acid (22). Some fully saturated

product is produced in these cases, even if the system is deficient in diimide.



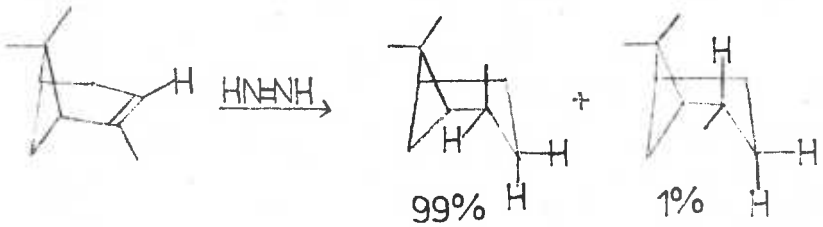
(21) (22)

As in the case of catalytic hydrogenation, addition of hydrogen from diimide usually occurs from the less hindered side of an unsymmetrical olefin.[33] A comparison of products produced by diimide reduction and by catalytic hydrogenation is shown in Table 2.

Table 2

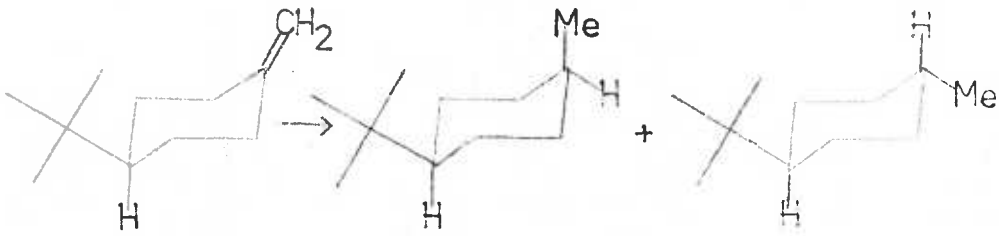
Olefin reduced	Product % cis:trans	Catalytic reduction (H_2/Pt) Product % cis:trans
α-pinene	99:1	93:7
2,3-dimethylcyclohexene	24:76	71:29
2-methylmethylenecyclohexane	61:39	68:32
4-t-butylmethylenecyclohexane	49:51	83:17
2-norbornene-2,3-dicarboxylic acid	92(endo):8(exo)	75(endo):25(exo)

Where bulk effects are large, reduction is subject to steric approach control. However, when steric effects are moderate, there is less stereochemical discrimination, although the stability of the product still does not govern the course of the reaction. This stereochemical control is shown especially in the case of α-pinene (23) which reacts with diimide to give a 99% yield of cis-pinane (24) which has the methyl group in the least favourable position.[33]



(23) (24)

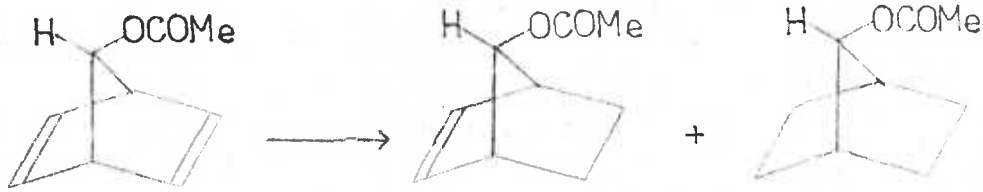
An interesting result is shown with 4-t-butylmethylenecyclohexane (25) since even though the approach is equally hindered from each direction the more and less stable products, (27) and (26) respectively, are formed in approximately equal amounts.[33]



(25) cis (49%) trans (51%)

(26) (27)

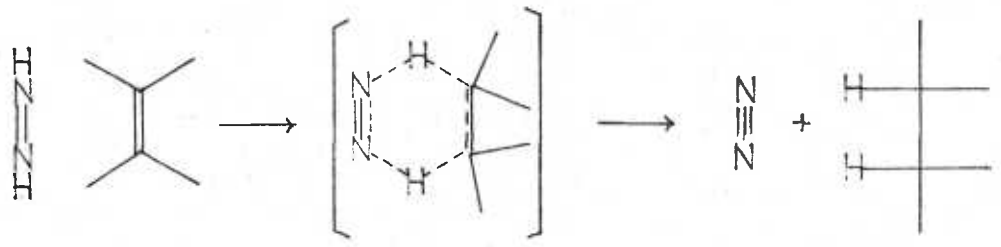
Another interesting result is shown in the partial reduction of norbornadiene derivatives such as (28), with an electronegative substituent at C-7.[39] In these cases it was clear that reduction was occurring from an exo direction at the more sterically hindered carbon-carbon double bond.



(28) 65% 35%

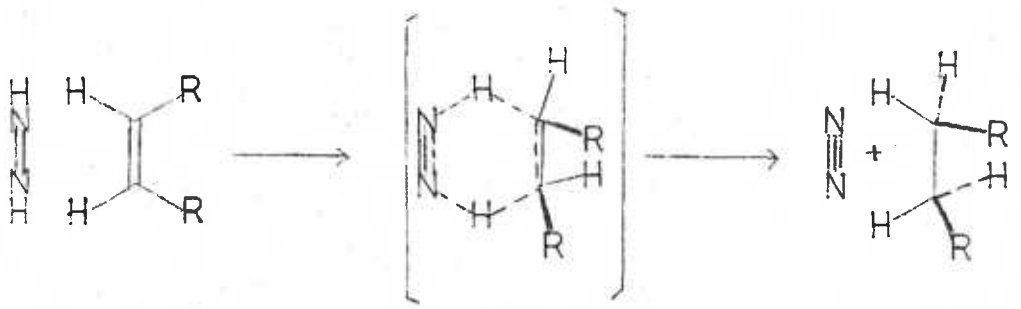
3.3. Mechanism

Reductions with diimide are believed to proceed through the cyclic process[6,12,13] shown in Scheme 7.

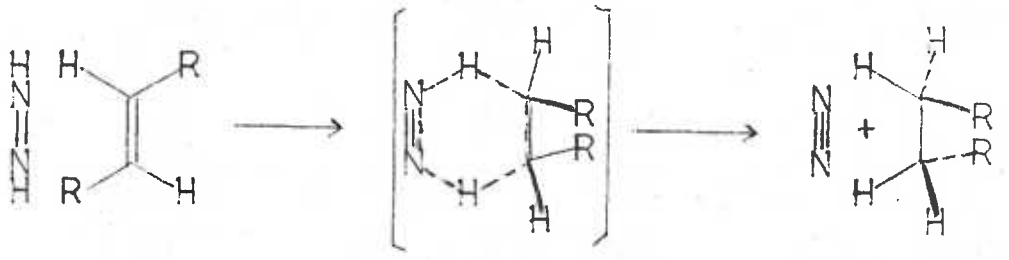


Scheme 7

This mechanism is in agreement with the observed cis-addition of hydrogen across multiple bonds. Since the addition of deutero-diimide across cis and trans olefins results almost exclusively in meso and dl products respectively, there is little likelihood of a step-wise addition of hydrogen. The mechanism agrees with the observation that the rate of reduction, as measured by the yield of product, decreases with increasing substitution about the multiple bond due to steric crowding in the transition state. Furthermore, the transition state should be more cluttered for cis than for trans olefins, as shown in Scheme 8, thereby raising the activation energy.[40] This theory is supported by the observed faster rate of hydrogenation of trans-olefins over that of cis-olefins.



cis

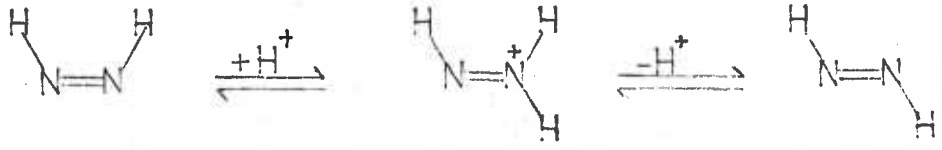


trans

Scheme 8

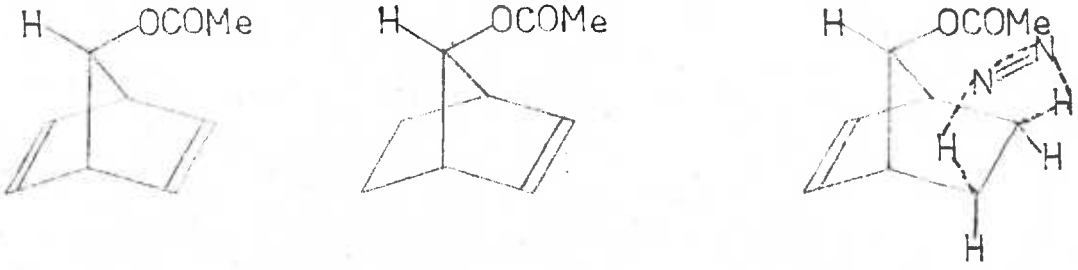
Under ordinary conditions, hydrogenation of multiple bonds using substituted hydrazines, such as phenyl or hydroxyethyl hydrazine have been unsuccessful.[9] The substituted diimides thus formed as intermediates could not be expected to react with multiple bonds according to the above mechanism. Conductometric studies have shown that the reduction step is non-ionic.[9] Moreover, p-substituents of cinnamic acid have no effect on the rate of hydrogenation of the double bond. Thus, electronic interaction between the aromatic moiety and the reaction centre is weak, which is understandable if the transition state is weakly polar.[40] The stability of polar multiple bonds toward diimide may be due in part to the higher activation energy required to form the correspondingly more polar transition state complex.[13]

A point of interest concerning the concerted mechanism shown, in Scheme 7, is that the process requires the cis form of diimide (29). In practice, an excess of the diimide precursors is often used for the reduction of carbon-carbon multiple bonds to allow for loss of part of the diimide formed by concurrent disproportionation. Consequently, it is difficult to determine what fraction of the diimide generated is potentially useful as a reductant for multiple bonds. It is possible that mixtures of cis and trans-diimide, (29) and (30) respectively, are produced and that only the cis isomer functions as a reducing agent. Alternatively, the cis and trans forms may be rapidly equilibrated by the reversible protonation[41] shown below, or by thermal isomerisation[42].



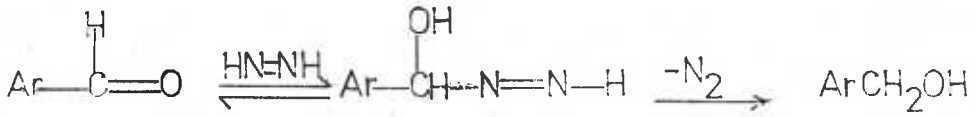
(29) (30)

Two points are worthy of note when discussing the mechanism of the reductions. Firstly that in the reduction of the norbornadiene derivative (28) the expected product, (31), was not produced. This indicates that the transition state (32) for transfer of hydrogen atoms from diimide to the double bond can be stabilised by electrostatic interaction with a suitably located substituent.[39]



(28) (31) (32)

The second point worthy of note is that the reduction of aromatic aldehydes and ketones,[30,38] rather than reflecting diminished polarity of the carbonyl group because of conjugation with an aromatic ring, is occurring by a different mechanism. The diimide serves as a nucleophile which adds reversibly to the carbonyl group to form the hydroxy diazene (33). This diazene intermediate could then decompose, with loss of nitrogen, to form the alcohol product (34), by a process analagous to the decomposition of other alkyl diazenes.[43] The nucleophilic addition of diimide to form (33) is analogous to the known addition of alkyl diazenes to aldehydes to form hydroxyalkylazo compounds.[44]



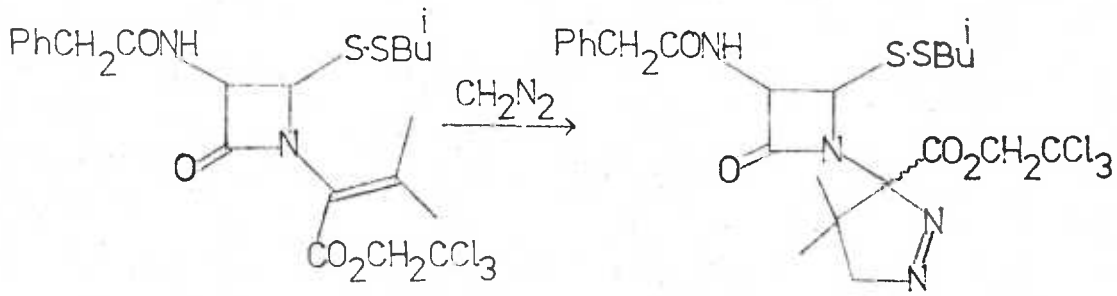
(33) (34)

PART II

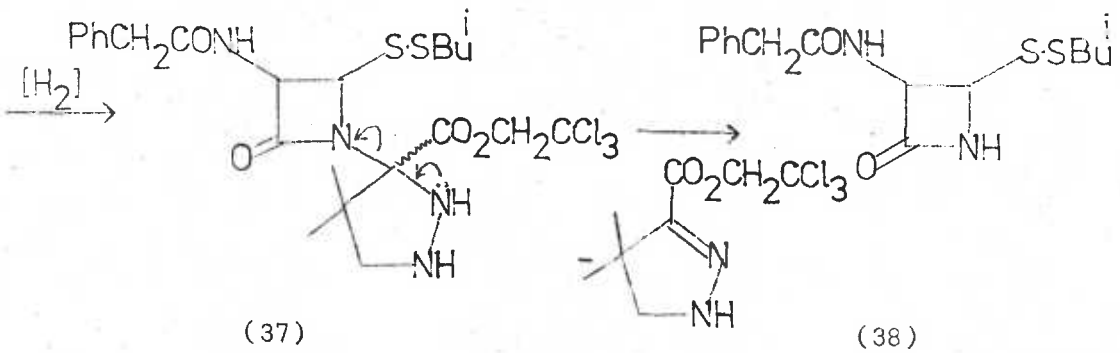
DISCUSSION OF RESULTS

1. Introduction

As stated in Part I, one way of carrying out penicillin transformations is to remove the N-attached isopentenoyl side-chain in the sulphenic acid trapped products, such as (35), giving the free N-H compounds which can then be further functionalised before recyclisation. As reported,[45] this was accomplished by reacting the trapped product, for instance the disulphide (35), with diazomethane to give an epimeric mixture of pyrazolines (36), which, when treated with a mild reducing agent, afforded the pyrazolidine (37). This immediately collapsed to give the desired β-lactam derivative (38).

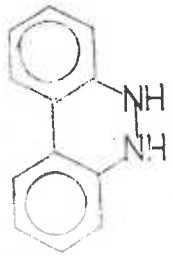


(35) (36)

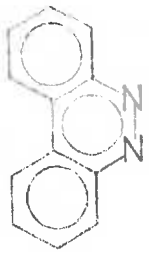


(37) (38)

Several reducing agents were used to form the pyrazolidine (37). One of these was the novel reducing agent NN'-dihydrobenzo(c)-cinnoline (39). This compound shows a strong tendency to aromatise to benzo(c) cinnoline (40), by donation of two hydrogen atoms to a suitable substrate.



(39)



(40)

Having shown that this dihydro-compound is sufficiently mild to reduce a pyrazoline selectively in the presence of a disulphide bond without destroying the β-lactam function, it was decided to examine its reducing power since selective reducing agents can be of great value in synthetic chemistry. Several other systems were also examined in an attempt to discover a new, synthetically useful, selective reducing agent.

2. NN'-Dihydrobenzo(c)cinnoline

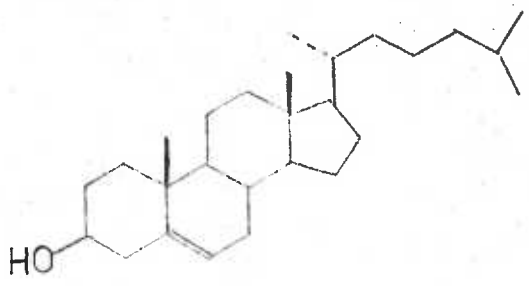
Benzo(c)cinnoline (40) was prepared by reducing 22'-dinitrodiphenyl with lithium aluminium hydride.[46] Further reduction to the monohydrochloride of NN'-dihydrobenzo(c)cinnoline (39) was achieved using zinc/hydrochloric acid.[47] This reagent was used in one of two ways:- By removing the aqueous acid solution from the precipitated hydrochloride by pipette, diluting with ethanol, neutralising with triethylamine and then adding an ethanolic solution of the substrate. Or, alternatively, by filtering off the precipitated hydrochloride, drying it *in vacuo*, neutralising a stirred suspension of the dried reagent in dry benzene or dichloromethane with triethylamine, and then adding a solution of the substrate in the same solvent. The latter method was used when water or alcohol sensitive substrates were present.

The zinc reduction and all subsequent reactions were carried out under oxygen-free nitrogen, since both NN'-dihydrobenzo(c)cinnoline (39) and its hydrochloride are rapidly oxidised by air.[47]

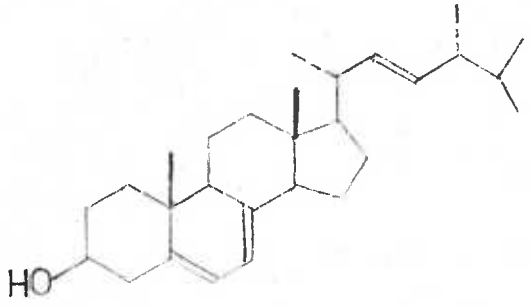
2.1. Scope of reduction

a) Carbon-carbon multiple bonds

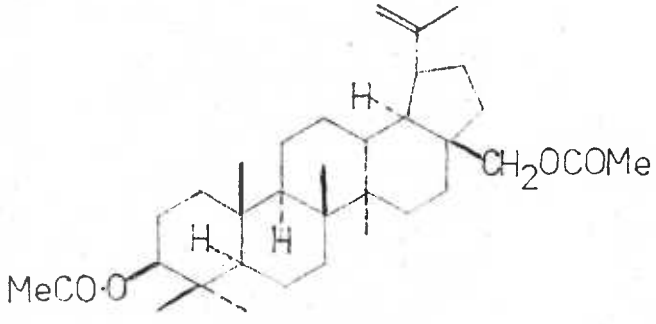
It was proposed that NN'-dihydrobenzo(c)cinnoline (39) might possess similar properties to those of diimide (see review). Exploratory experiments to find out the reducing power of the reagent were carried out by Dr. M.V. Taylor.[48] The reagent did not reduce the carbon-carbon double bonds in cholesterol (41) (monitoring by rotations), ergosterol (42) (n.m.r.) or betulin diacetate (43) (i.r.), in refluxing toluene.



(41)



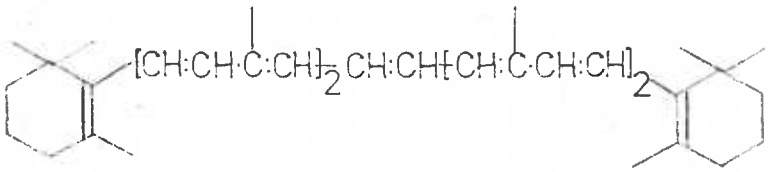
(42)



(43)

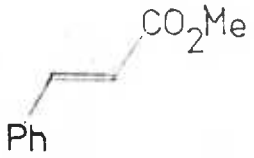
These initial experiments showed that NN'-dihydrobenzo(c)-cinnoline does not reduce exposed double bonds and must therefore be a considerably milder reagent than diimide which reduces cholesterol to some extent.[49]

In order to verify this result, attempts were made to reduce carbon-carbon double bonds in several other compounds. β-Carotene (44) was unaffected after stirring with excess reagent in dry benzene for 2 days at room temperature, as indicated by the unchanged ultra-violet absorbances at 464 and 493 nm, and by t.l.c. The fact that the reagent was still present was shown by adding some azobenzene to the reaction mixture, whereupon reduction to hydrazobenzene took place (see section 2.1b).

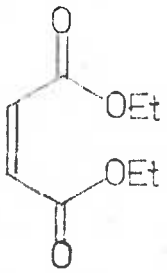


(44)

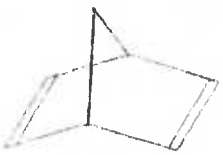
No reaction occurred with methyl cinnamate (45) (t.l.c., i.r., n.m.r.) diethyl maleate (46) (n.m.r.) or norbornadiene (47) (n.m.r.), even after refluxing in benzene.



(45)

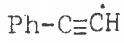


(46)



(47)

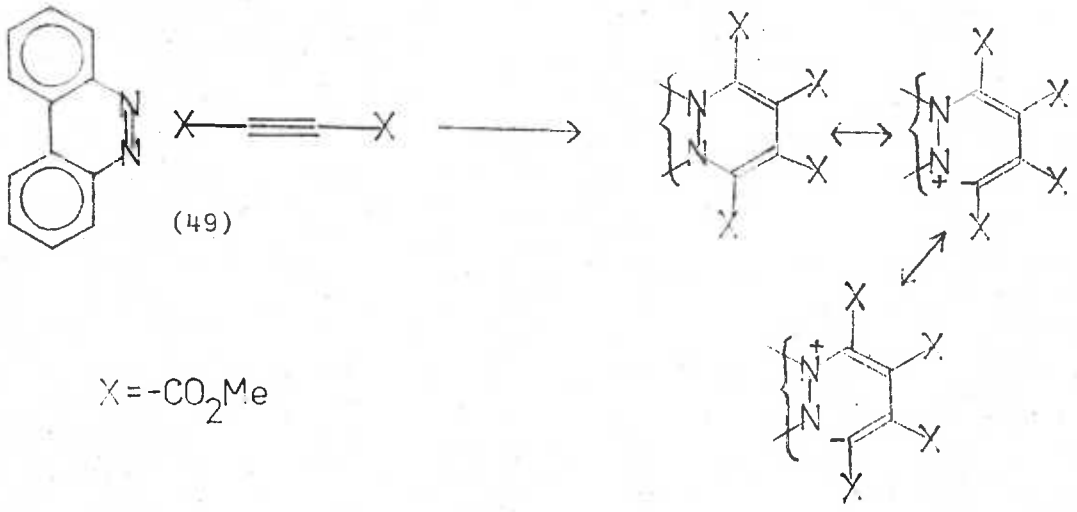
This verified the results of the initial experiments and showed that not even activated double bonds are reduced. The reagent does not reduce phenylacetylene (48) (n.m.r.). In all these cases, the reagent was washed out with dilute hydrochloric acid and the substrate recovered.



(48)

An interesting point to note here is that it has been reported that benzo(c)cinnoline adds to sufficiently activated acetylenic compounds,

such as dimethyl acetylenedicarboxylate (49), to form an adduct which is probably a resonance hybrid of the structures shown in Scheme 9.[50]



Scheme 9

b) Azo- and azoxy-compounds

The reagent was found to reduce azobenzene (50) to hydrazobenzene (51), in quantitative yield (t.l.c., u.v.) in benzene at room temperature inside 15 min. The product was isolated as its monobenzoylated derivative (52) in 80% yield.

Ph-N=N-Ph (50)

Ph-NH.NH-Ph (51)

Ph-NH-N(COPh)-Ph (52)

The reagent was also found to reduce azoxybenzene (53) to hydrazobenzene (51) in quantitative yield (t.l.c., u.v.) under the same conditions as above. The product was again isolated as its monobenzoylated derivative (52), in 60% yield.

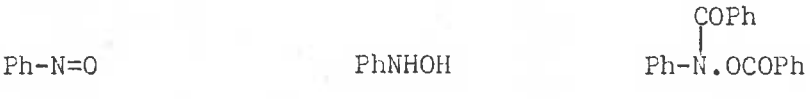
Ph-N(→O)=N-Ph

(53)

c) Nitro-and nitroso-compounds

Nitrosobenzene (54) was reduced to phenyl hydroxylamine (55) in

quantitative yield (t.l.c., u.v., i.r.). The product was isolated as its N,O-dibenzoylated derivative (56) in 75% yield.



Ph-N=O (54) PhNHOH (55) Ph-N(COPh).OCOPh (56)

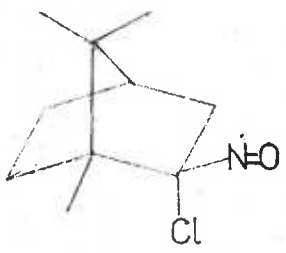
No reaction took place when phenylhydroxylamine was stirred with excess reagent. Nitrobenzene (57) was reduced to phenyl hydroxylamine, in quantitative yield (t.l.c., i.r.), which was again separated as its N,O-dibenzoylated derivative (56) in 70% yield.



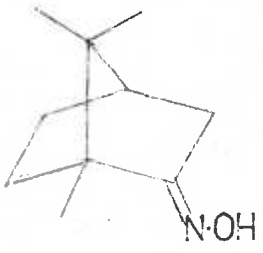
$PhNO_2$

(57)

Reductions of aliphatic nitro- and nitroso- compounds were also attempted. Chloronitrosocamphor[58] was reduced, in dichloromethane at room temperature. The product was shown to be camphor oxime (59) by comparison with an authentic sample, (t.l.c., i.r., n.m.r., m.p.).

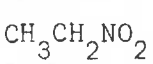


(58)



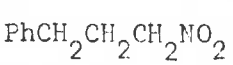
(59)

Neither nitroethane (60) (i.r.) nor 1-nitro-3-phenyl-propane (61) (i.r., t.l.c.) were reduced, even after refluxing in benzene.



$CH_3CH_2NO_2$

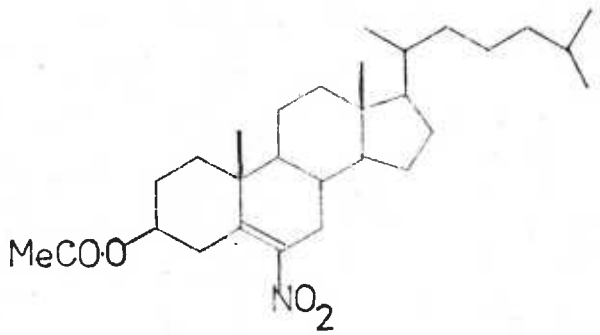
(60)



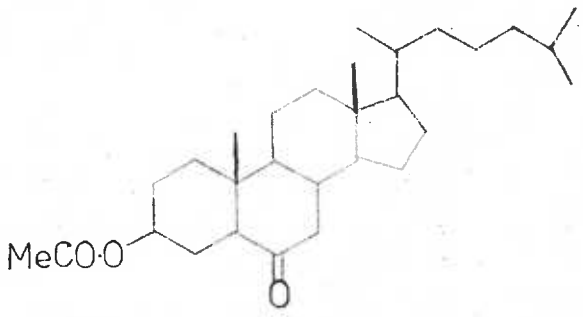
$PhCH_2CH_2CH_2NO_2$

(61)

6-Nitrocholesteryl acetate (62)[51] was reduced. The isolated product was shown to be 6-ketocholestanyl acetate (63),[52] after work-up that included washing with 6N hydrochloric acid followed by p.l.c. This was presumably formed *via* the 6-hydroxyimino derivative (93) (see section 2.2).



(62)



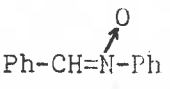
(63)

d) Schiff bases, nitrones and oximes

No reaction took place when benzylideneaniline (64) was stirred with excess reagent in benzene for 2 days at room temperature (t.l.c., n.m.r.). However, diphenyl nitrone (65) was reduced to benzylidene-aniline (64) and the product separated by column chromatography, in 35% yield.

Ph-CH=N-Ph

(64)

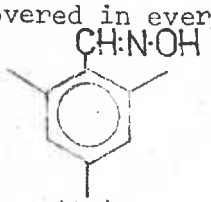


(65)

Attempts were made to reduce benzaldoxime (66), mesitaldehyde oxime (67) and camphor oxime (59). However, none of these compounds were reduced (t.l.c., n.m.r.), even after refluxing in benzene overnight, and the substrate was recovered in every case.

PhCH:N.OH

(66)



(67)

e) Aldehydes and ketones

Several attempts were made to reduce the carbonyl groups in both aliphatic and aromatic aldehydes and ketones. The reactions were followed by monitoring the carbonyl absorptions by infra-red spectroscopy. This showed that no reaction took place with benzaldehyde (68), benzophenone (69), octan-2-one (70), ethyl pyruvate (71) or valeraldehyde (72). The latter compound was recovered as its 2,4-dinitrophenylhydrazone derivative, whereas the other substrates were recovered in the free carbonyl form after washing out the reagent with hydrochloric acid.

$PhCHO$	$PhCOPh$	$MeCO(CH_2)_5Me$	$MeCOCO_2Et$
(68)	(69)	(70)	(71)

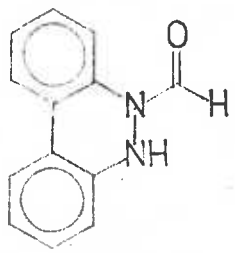
$Me(CH_2)_5CHO$

(72)

The NN'-dihydrobenzo(c)cinnoline reacted with both chloral (73) and trichloroethyl pyruvate (74). The products were separated by p.l.c. In the former case the product was shown to be the N-formyl compound (75) by n.m.r., i.r. and elemental analysis. In the latter case the product was shown to be the N-acetylformyl derivative (76) by n.m.r., i.r., and mass spectral analysis. These were not reduction products and their formation is discussed in section 2.2.

CCl_3CHO

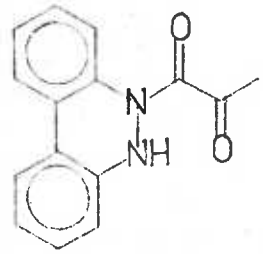
(73)



(75)

$MeCOCO_2CH_2CCl_3$

(74)



(76)

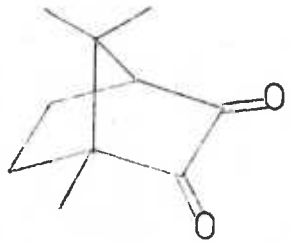
f) α-Diketones

Benzil (77) was reduced to benzoin (48), in quantitative yield (t.l.c.) in dichloromethane at room temperature. The product was isolated and was identical to the authentic compound.

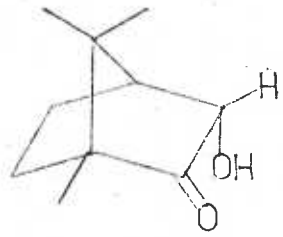
PhCOCOPh (77)

PhCH(OH)COPh (78)

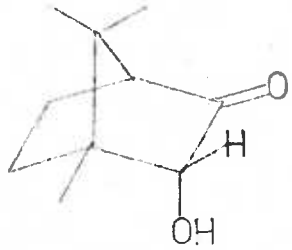
Camphor quinone (79), prepared by selenium dioxide oxidation[53] of (+)-Camphor, was reduced to give a 1:1 mixture of endo-3-hydroxycamphor (80) and endo-2-hydroxyepicamphor (81).



(79)

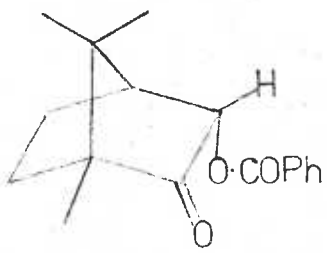


(80)

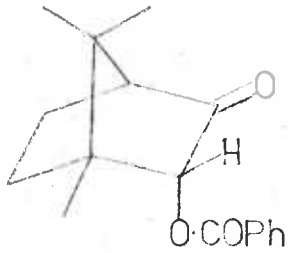


(81)

The mixture of products was benzoylated and the monobenzoyl compounds, (82) and (83), produced were separated by p.l.c. These products were identical to the derivatives obtained after reduction of camphor quinone with zinc/acetic acid,[54] which have been characterised in the literature.[55,56]



(82)



(83)

g) Quinones

p-Benzoquinone (84) was reduced to quinol (85) by reaction with the reagent, in benzene at room temperature. The product was separated by filtering the reaction mixture after 15 min, stirring the solid with ether, filtering the ethereal solution, drying and evaporating in vacuo. The product was identical to the authentic compound (85).

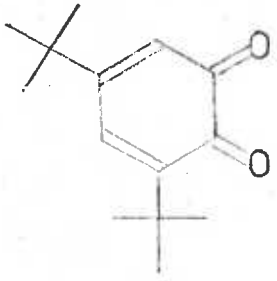


(84)

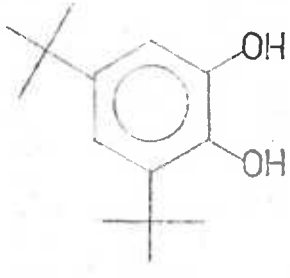


(85)

3,5-di-t-butyl-o-benzoquinone (86), prepared by silver oxide oxidation of 3,5-di-t-butylcatechol (87),[57] was cleanly reduced to 3,5-di-t-butylcatechol (87), in dichloromethane at room temperature.



(86)



(87)

The results of all the reported reactions are summarised in Table 1.

2.2. Reaction Mechanism

Several mechanisms for the reductions with NN'-dihydrobenzo(c)-cinnoline can be postulated. It was originally proposed that the reductions take place by the concerted mechanism shown in Scheme 10, as in the case of diimide reductions (see Review).

TABLE 1

Compound	Product	Monitored by:	Method
β-Carotene (44)	no reaction	t.l.c.,u.v.(463,493nm)	c
Methyl cinnamate (45)	no reaction	t.l.c.,n.m.r.(2.27,3.53τ)	b
Diethyl maleate (46)	no reaction	t.l.c.,n.m.r.(3.7τ)	b
Norbornadiene (47)	no reaction	n.m.r.(3.34τ)	b
Phenylacetylene (48)	no reaction	n.m.r.(6.95τ)	b
Azobenzene (50)	Hydrazobenzene (51)	t.l.c.,u.v.(247,291nm)	a
Azoxybenzene (53)	Hydrazobenzene (51)	t.l.c.,u.v.(247,291nm)	a
Nitrosobenzene (54)	Phenylhydroxylamine (55)	t.l.c.,i.r.(1510cm^{-1}), u.v.(281 nm)	a
Nitrobenzene (57)	Phenylhydroxylamine (55)	t.l.c.,i.r.(1550cm^{-1})	a
Chloronitrosocamphor (58)	Camphor oxime (59)	t.l.c.,i.r.(1565cm^{-1})	a
Nitroethane (60)	no reaction	i.r.(1550cm^{-1})	b
1-Nitro-3-phenylpropane (61)	no reaction	t.l.c.,i.r.(1560cm^{-1})	b
6-Nitrocholesteryl acetate (62)	6-ketocholestanyl acetate (63)	t.l.c.	a
Benzylideneaniline (64)	no reaction	t.l.c.	c
Diphenyl nitrone (65)	Benzylideneaniline (64)	t.l.c.	a
Benzaldoxime (66)	no reaction	t.l.c.,i.r.(3580cm^{-1}), n.m.r.(1.86τ)	b
Mesitaldehyde oxime (67)	no reaction	t.l.c.,n.m.r.(1.54τ)	b
Camphor oxime (59)	no reaction	t.l.c.,i.r.(3580cm^{-1})	b
Benzaldehyde (68)	no reaction	t.l.c.,i.r.(1710cm^{-1})	b
Benzophenone (69)	no reaction	t.l.c.,i.r.(1660cm^{-1})	b
Octan-2-one (70)	no reaction	t.l.c.,i.r.(1710cm^{-1})	b
Ethyl pyruvate (71)	no reaction	t.l.c.,i.r.(1730cm^{-1}), n.m.r.(7.55τ)	b
Valeraldehyde (72)	no reaction	t.l.c.,i.r.(1730cm^{-1})	a
Chloral (73)	N-formyl-NN'-dihydrobenzo(c)cinnoline (75)	t.l.c.,i.r.(1770cm^{-1})	a

Table 1 (continued)

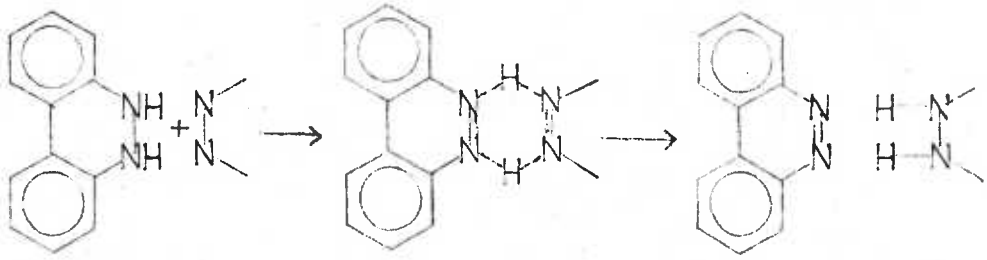
Compound	Product	Monitored by:	Method
Trichloroethyl-pyruvate (74)	N-acetylformyl-NN'-dihydrobenzo(c) cinnoline (76)	t.l.c.,i.r.(1745,1760 cm^{-1})	a
Benzil (77)	Benzoin (78)	t.l.c.,i.r.(1680 cm^{-1})	a
Camphorquinone (79)	endo-3-hydroxycamphor (80) endo-2-hydroxyepi-camphor (81)	t.l.c.,i.r.(1760,1775 cm^{-1})	a
p-Benzoquinone (84)	Quinol (85)	t.l.c.,i.r.(1665,1675 cm^{-1})	a
3,5-di-t-butyl-O-benzoquinone (86)	3,5,-di-t-butyl-catechol (87)	t.l.c.,i.r.(1670cm^{-1})	a

Method a: Carried out at room temperature in dry benzene or dichloromethane. See experimental section for work-up procedure.

Method b: Carried out in benzene, initially at room temperature, and then overnight at reflux. Substrate recovered by washing out the reagent with dilute hydrochloric acid.

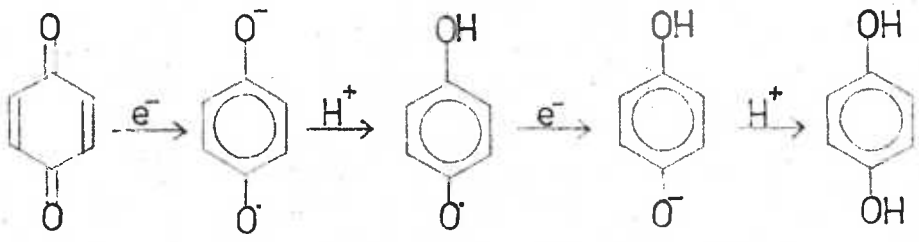
Method c: Carried out at room temperature in dry benzene or dichloromethane. Substrate not recovered.

N.B. In reactions which did not proceed, the presence of the reagent was shown by adding some azobenzene to the reaction mixture, whereupon reduction to hydrazobenzene took place.



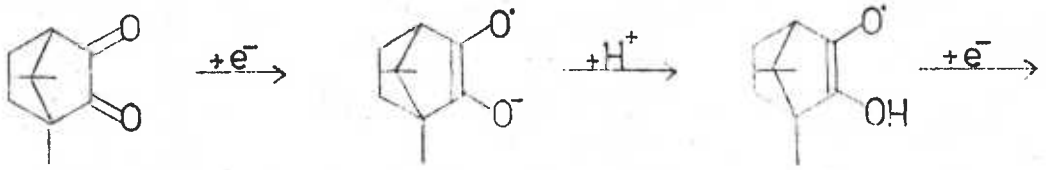
Scheme 10

However, since the reagent showed no signs of reducing even activated carbon-carbon multiple bonds it is unlikely whether this original proposal is correct. A more likely mechanism is one which involves electron transfer, as in the case of dissolving metal reductions. For instance, the reduction of p-benzoquinone could take place *via* the radical anion mechanism shown in Scheme 11.

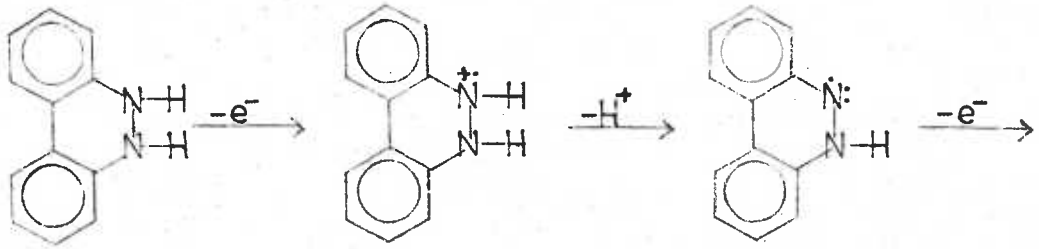


Scheme 11

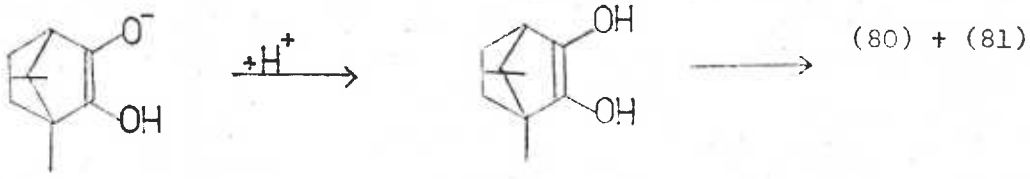
This sort of mechanism would also explain the production of the more stable endo- alcohols,[56] (80) and (81), on the reduction of camphorquinone (79), rather than the less stable exo- alcohols which are produced on hydride reduction.[56] The reduction probably proceeds *via* the dienolic compound (88) which then isomerises to the more stable products. The reaction mechanism is summarised in Scheme 12.



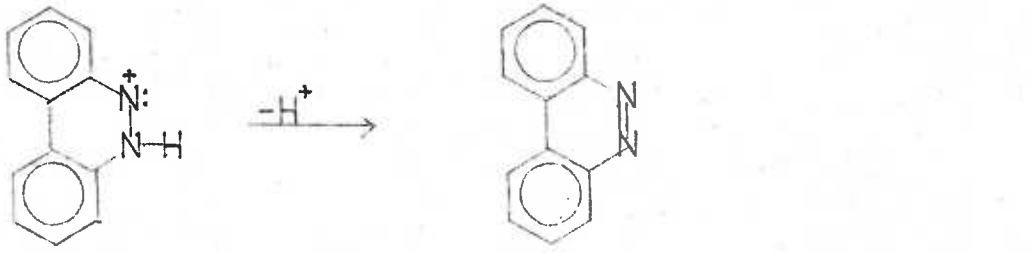
(79)



(39)



(88)

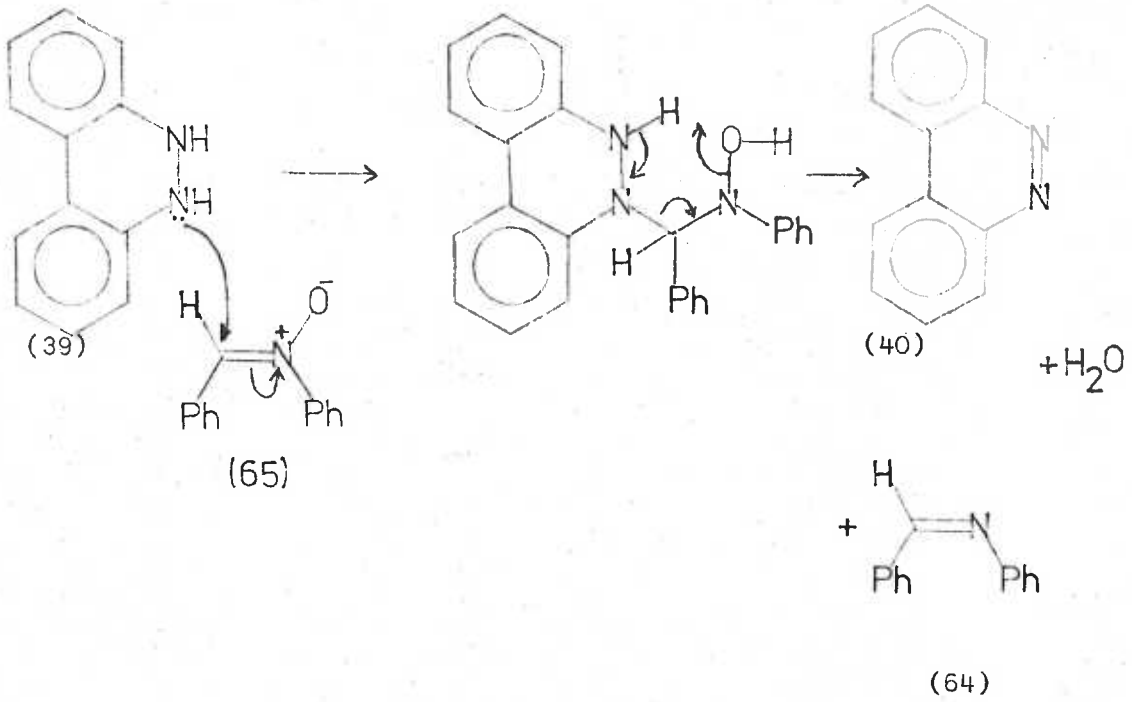


(40)

Scheme 12

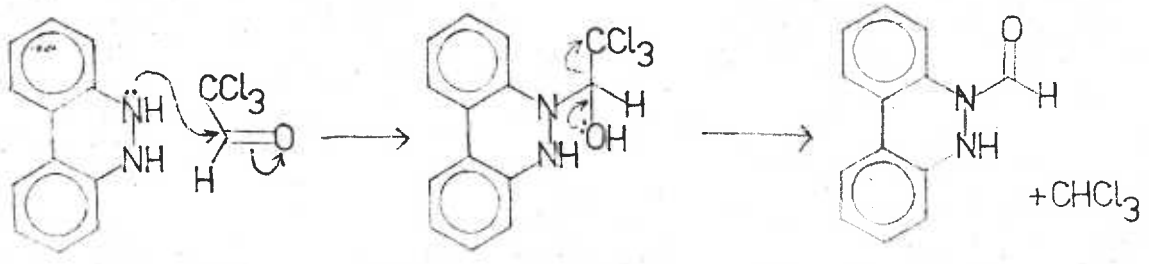
It has been shown that 1,2-dihydrobenzenes react with quinones in a two-step hydride ion transfer mechanism.[58] The transfer of two vicinal hydrogens in an electrocyclic reaction to the terminal point of an αβ-unsaturated carbonyl compound would involve 4π-electrons and is therefore

forbidden. The transfer of the hydrogens to the carbon and oxygen of the carbonyl group would be allowed, but is probably less favourable and would not compete with the two-step hydride ion transfer mechanism. This mechanism is conceivable in the case of NN'-dihydrobenzo(c)cinnoline. The mechanism which operates in the case of NN'-dihydrobenzo(c)cinnoline is probably dependent on the substrate.being reduced. Another mechanism can be proposed in the case of the reduction of diphenyl nitrone (65). This involves 1,3-addition to the nitrone, followed by elimination of benzo(c)-cinnoline and water, as shown in Scheme 12, to afford benzylidene-aniline (64).

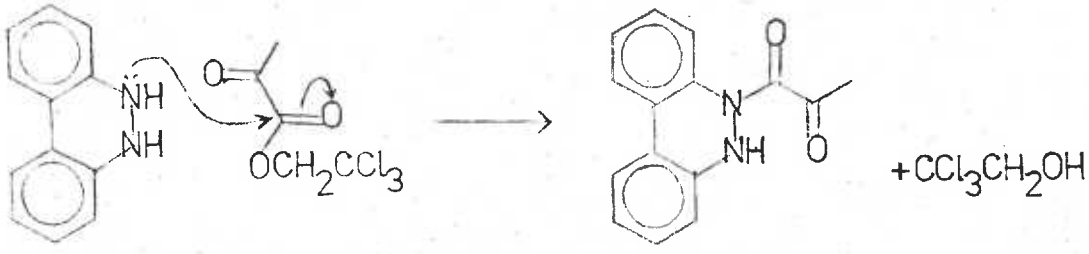


Scheme 12

In the case of more activated carbonyl groups, reduction does not take place. Instead, nucleophilic attack by the nitrogen in the reagent takes place. Thus, chloral (73) reacts to form the N-formyl compound (75), and trichloroethylpyruvate (74) reacts to form the N-acetylformyl derivative (76).

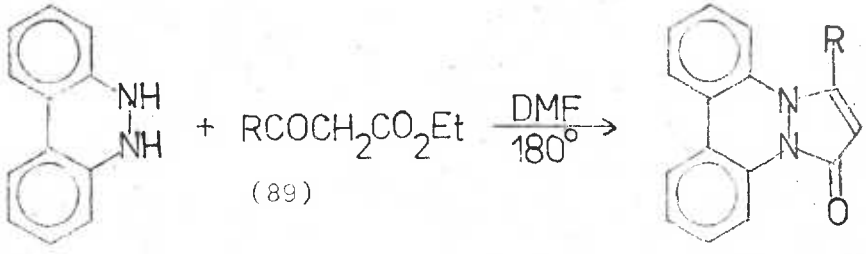


(73) (75)



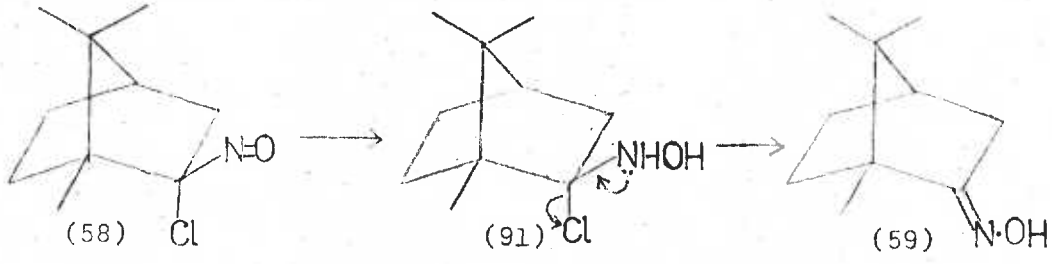
(74) (76)

Reactions involving nucleophilic attack by the nitrogen have been previously reported.[59] Thus, on reaction with β-ketoesters (89) substituted pyrazoline derivatives (90) are formed.



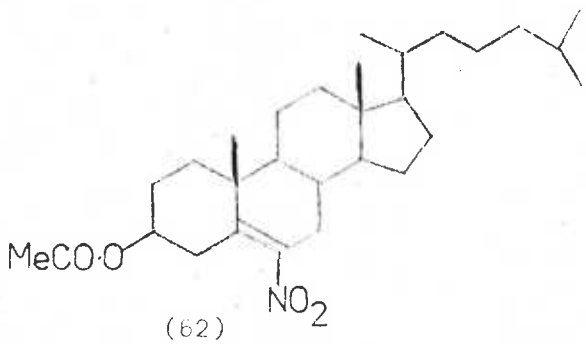
(89) (90)

As stated in the previous section, the product isolated in the reaction of chloronitrosocamphor (58) with NN'-dihydrobenzo(c)cinnoline is camphor oxime (59). This must arise from reduction to the hydroxylamino-compound (91), followed by elimination of hydrogen chloride to afford camphor oxime (59).

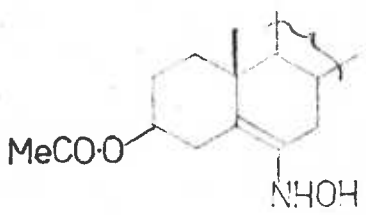


(58) (91) (59)

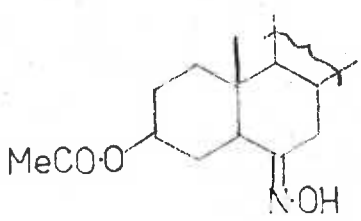
In the case of the reaction with 6-nitrocholesteryl acetate (62), the isolated product was shown to be 6-ketocholestanyl acetate (63). Thus, reduction probably proceeds *via* the hydroxylamino compound (92) to the hydroxyimino derivative (93) which is then hydrolysed to the ketone (63) on work-up.



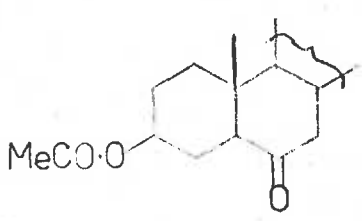
(62)



(92)



(93)

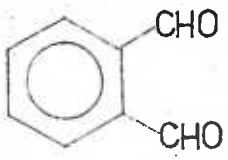


(63)

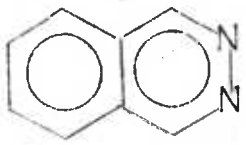
3. Pyridazine derivatives

Since NN'-dihydrobenzo(c)cinnoline had proven to be an extremely selective reducing agent an attempt was made to find another reducing agent which showed greater reducing power and would be of more use in synthetic chemistry. It was proposed that 1,2-dihydropyridazines,[60] *e.g.* (97), might possess the desired reducing properties since the resulting pyridazine system is a true aromatic system, thus providing the driving force for reductions to take place.

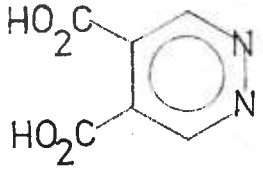
Phthalazine (95) was prepared by the reaction of o-phthalaldehyde (94) with hydrazine sulphate.[61] The phthalazine was then oxidised with alkaline potassium permanganate to afford 4,5-dicarboxypyridazine (96).[62]



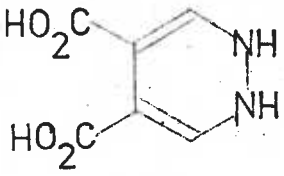
(94)



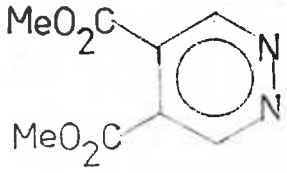
(95)



(96)



(97)



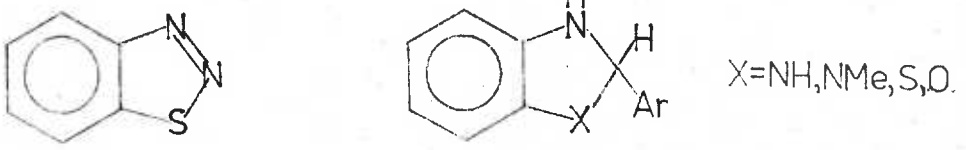
(98)

Attempts were made to reduce compound (96) to its dihydro derivative, 1,2-dihydro-4,5-dicarboxypyridazine (97). This reduction was attempted using zinc/acetic acid, zinc/hydrochloric acid and chromous acetate. In the latter case no reaction took place. In the two former cases, ultra-violet spectra of the reaction mixtures indicated that some reaction had taken place although the product was not identified. Instead, each reduction was repeated and some nitrosobenzene added to the reaction mixtures, after adjustment to pH8 with triethylamine. In both cases, ultra-violet spectra indicated that no reduction of nitrosobenzene took place. It is probable that the pyridazine was reduced to the tetrahydro- or hexahydro-derivative.[63] Negative results were also obtained when reduction of nitrosobenzene was attempted using zinc/aqueous acid reduction products of dimethyl pyridazine-4,5-dicarboxylate (98) [64] and phthalazine (95).

4. 2,3-Dihydro-1,2,3-benzothiadiazole

1,2,3-Benzothiadiazole (99) was prepared by diazotisation of o-aminobenzenethiol,[65] and an attempt was made to reduce it to the 2,3-dihydro compound using chromous acetate. This proved unsuccessful,

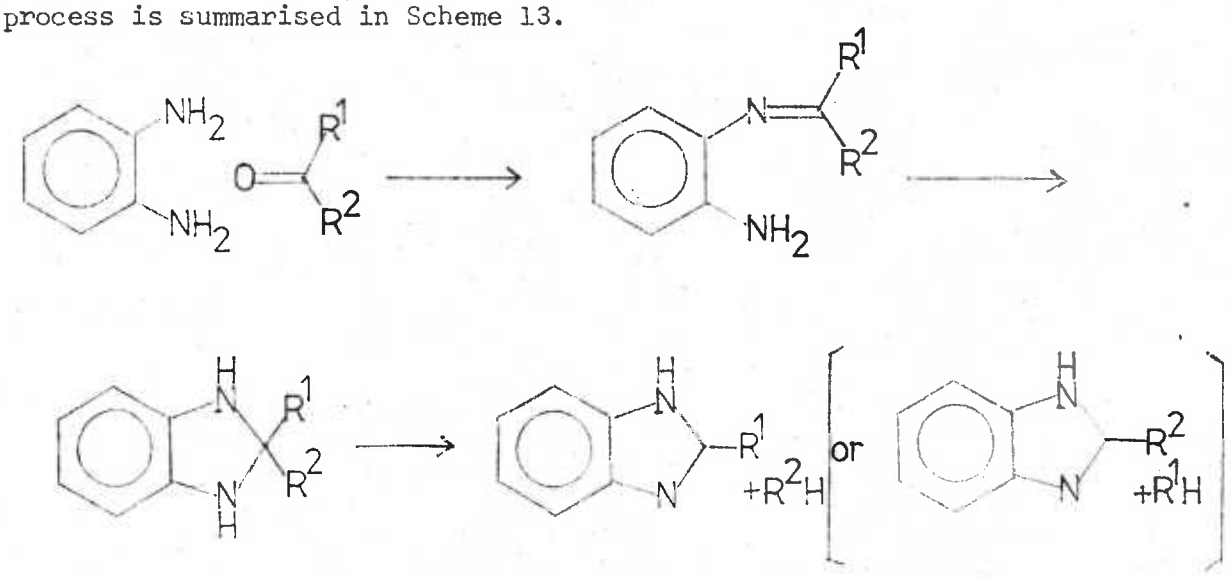
but no further experiments were carried out using this compound since the system (100) seemed more promising.



(99) (100)

5. Benzimidazoline, Benzothiazoline and Benzoxazoline derivatives

After studying the Elderfield extrusion reaction[66], Scheme 13, it was proposed that if the right reagents were used in the reaction a novel selective reducing agent would be afforded. The basis of the reaction is that when 2,2-dialkylbenzimidazolines (101) are heated, one of the substituents is lost in combination with the hydrogen at the 3-position as a hydrocarbon, thus giving rise to the benzimidazole (102). When aromatic aldehydes are used in the formation of the benzimidazoline one gets preferential elimination of hydrogen and so such compounds should act as reducing agents if suitable substrates are present. The general process is summarised in Scheme 13.

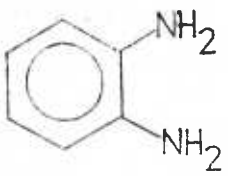


(101) (102)

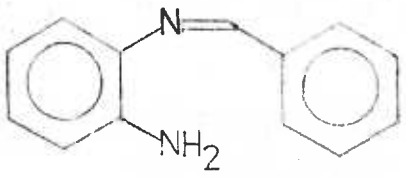
Scheme 13

These reactions also take place with benzothiazoline[67] and benzoxazoline[68] derivatives.

o-Phenylenediamine (103) was reacted with benzaldehyde (1 equiv.) in a minimal amount of ethanol, and the resulting Schiff base (104) filtered off and dried.[69] However, this compound decomposed on standing overnight in vacuo.

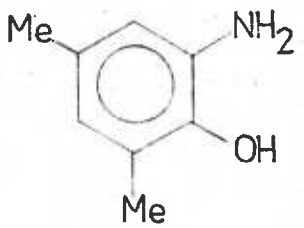


(103)

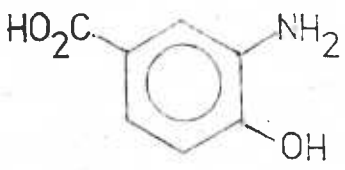


(104)

The reaction was repeated in ethanolic solution, under nitrogen at room temperature, and some nitrosobenzene (54) added to the stirred solution. Phenylhydroxylamine (55) was present within 30 min. (t.l.c.) and was isolated as its N,O-dibenzoyl derivative (56), in 25% yield. Reduction of nitrosobenzene to phenylhydroxylamine also took place when using o-aminobenzenethiol, under the same conditions. The product was again isolated as its N,O-dibenzoyl derivative (56), in 25% yield. Although reduction took place in the above cases the reactions were not very clean, and so it was decided to use substituted o-aminophenol derivatives to eliminate some of the side reactions. Both 6-amino-2,4-dimethylphenol (105) and 3-amino-4-hydroxybenzoic acid (106) were used in attempted reductions of nitrosobenzene, under the conditions used with o-phenylenediamine. Both gave negative results. Indeed, o-aminophenol itself gave no reduction.

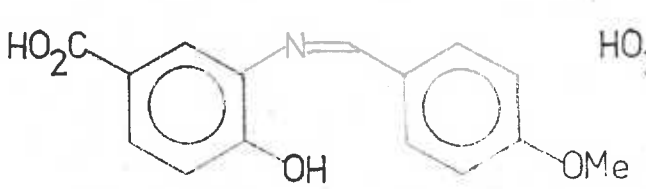


(105)

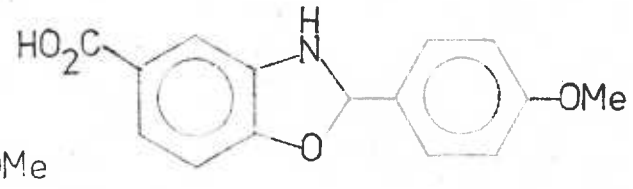


(106)

The reduction of nitrosobenzene was tried using compound (106) and anisaldehyde, in the hope that the p-methoxy function would assist the ring closure of the intermediate Schiff base (107). This was unsuccessful. Attempts were also made to see whether reduction would take place in the presence of an acid or base catalyst. There was no sign of any reaction when reduction of nitrosobenzene was attempted in the presence of triethylamine or toluene-p-sulphonic acid. The presence of the Schiff base intermediate (107) was shown in both cases, by n.m.r. Thus, once again, no cyclisation to the benzoxazoline derivative (108) had taken place.

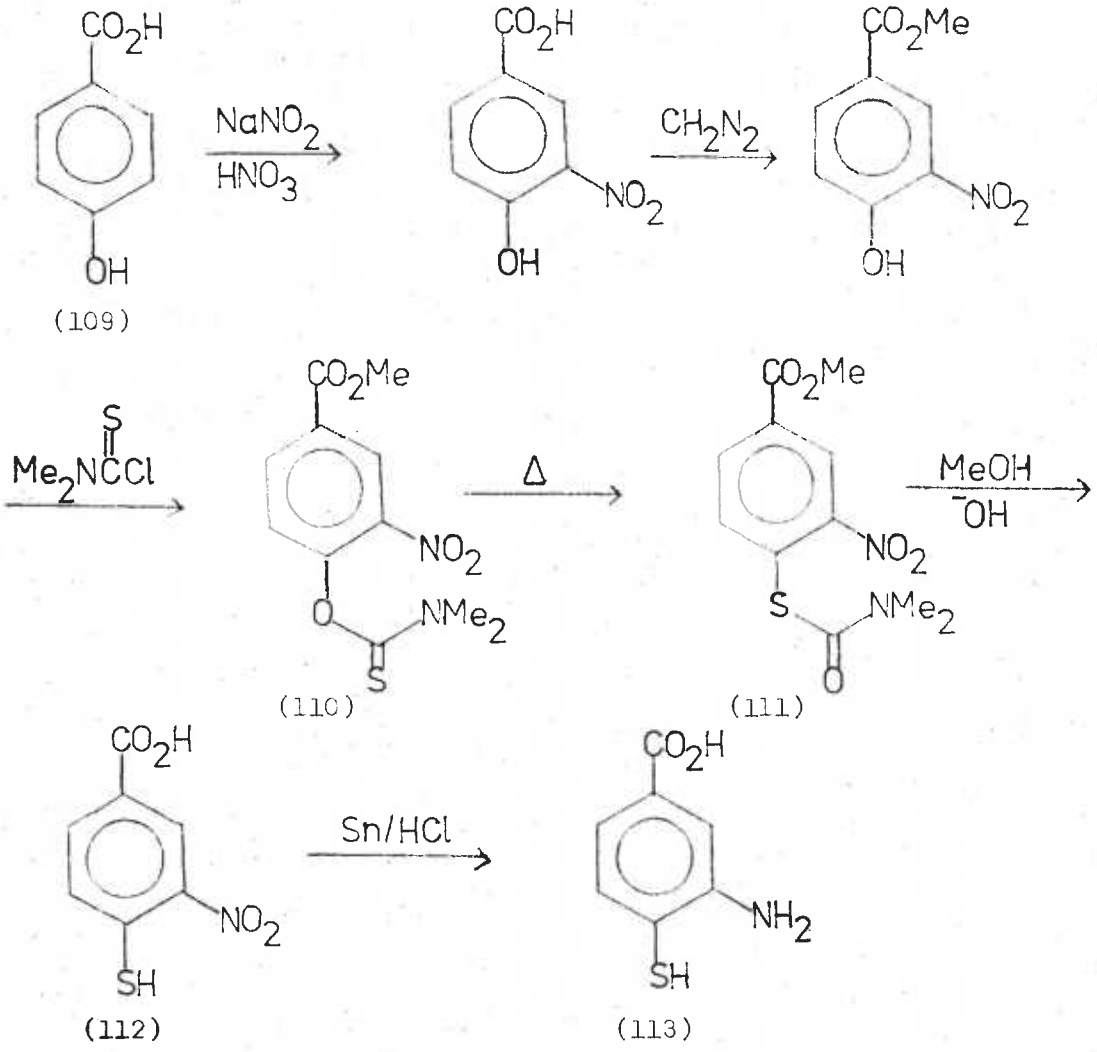


(107)



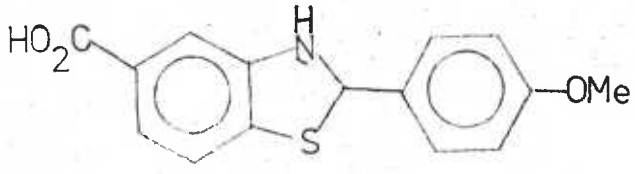
(108)

Since reductions using o-aminophenol derivatives proved abortive, attention was switched back to the use of derivatives of o-phenylenediamine and o-aminobenzenethiol. As stated previously, the reductions carried out using o-phenylenediamine and o-aminobenzenethiol were not very clean, and so it was decided to use substituted derivatives. It was also considered that the reducing agents would be of more use in synthetic chemistry if they had acid functions on them, thus making the work-up more convenient. Thus, 3-amino-4-mercaptobenzoic acid (113) was synthesised from p-hydroxybenzoic acid (109), as shown in Scheme 14. The hydroxy-function was converted into the mercapto-function *via* the O-aryldimethylthiocarbamate [70] (110). The reduction of the nitro group in compound (112) was carried out using tin/hydrochloric acid,[71] and the resulting amino-compound (113) separated as its hydrochloride.



Scheme 14

The benzothiazoline reagent (114) was prepared as follows:- Compound (113) was dissolved in a minimal amount of pyridine and anisaldehyde (1 equiv.) added.



(114)

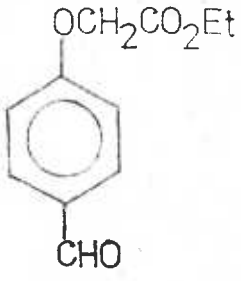
This reagent (114) reduced azobenzene (50) to hydrazobenzene (51) within 15 minutes (t.l.c.) and the product was isolated as its N-benzoyl derivative (52), in 60% yield. However, on attempting to isolate the hydrazobenzene

from another reduction reaction a mixture of azobenzene and hydrazobenzene was obtained. Some oxidation must have occurred during the work-up and the yield of hydrazobenzene was only 25% (u.v.). The reduction of nitrosobenzene was carried out under the same conditions giving phenylhydroxylamine which was isolated as its N,O-dibenzoyl derivative (56), in 40% yield. The reduction of methyl cinnamate (45) was also attempted but did not occur, the substrate being recovered.

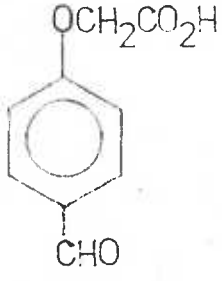
In order to save going through the six-step process to form the 3-amino-4-mercaptobenzoic acid (113) it was decided to use an aldehyde containing an acidic function in the formation of the intermediate Schiff base. Thus, 4-formylphenoxyacetic acid (117) was formed by reaction of the sodium salt of p-hydroxybenzaldehyde (115) with ethyl bromoacetate, followed by hydrolysis of the resulting ester (116) with aqueous sodium hydroxide.



(115)

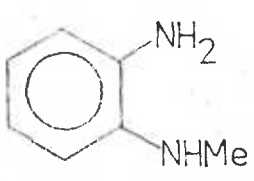


(116)

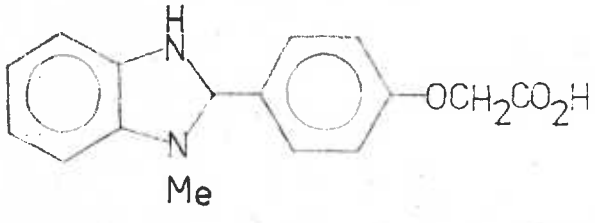


(117)

Several reductions were attempted using the benzimidazoline derivative (119) derived from o-methylaminoaniline (118) and 4-formylphenoxyacetic acid (117).



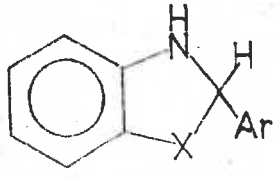
(118)



(119)

The general procedure was to add the substrate to a stirred solution of 4-formylphenoxyacetic acid (117), o-methylaminoaniline-dihydrochloride (118) (1 equiv.) and triethylamine (3 equiv.), under nitrogen at room temperature. 3,5-di-t-butyl-o-benzoquinone (86) was reduced quantitatively to 3,5-di-t-butylcatechol (87) (t.l.c.,i.r.) within 15 minutes. During work-up the reagent was removed by washing with dilute bicarbonate. p-Benzoquinone (84) was reduced quantitatively to quinol (t.l.c.,i.r.). T.l.c. results also showed that azobenzene (50) and nitrosobenzene (54) were reduced to hydrazobenzene (51) and phenylhydroxylamine (55) respectively. However, neither benzil (77) (t.l.c., i.r.), camphorquinone (79) (t.l.c.,i.r.), nitrobenzene (57) (t.l.c.,i.r.), diethyl maleate (46) (t.l.c.,n.m.r.), methyl cinnamate (45) (t.l.c.,n.m.r.), benzaldoxime (66) (t.l.c.,n.m.r.) nor phenylacetylene (48) (t.l.c.,n.m.r.) were reduced.

These results indicate that the benzimidazoline and benzothiazoline derivatives possess less reducing power than NN'-dihydrobenzo(c)cinnoline and thus no further experiments were carried out in this series. The conclusion is that the reducing power of compounds of the general formula (120) is too low to be synthetically useful.



X = NH,NMe,S,O.

(120)

PART II

EXPERIMENTAL

I.R. spectra were recorded with a Unicam SP200 spectrometer, the phase employed being indicated in the text. U.V. spectra were recorded with a Unicam SP 800 spectrometer for ethanolic solutions. Rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectra were determined with an A.E.I. MS9 machine. ^{1}H n.m.r. spectra were recorded with Varian T60 or HA100 instruments for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Reactions were monitored by t.l.c. on Merck Kieselgel G_{254} nach Stahl silica. Preparative thin layer chromatography (p.l.c.) was on 1 mm thick Merck Kieselgel G_{254} nach Stahl silica plates. Column chromatography was carried out on Merck Kieselgel 60. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

All solutions were dried over anhydrous sodium sulphate.

Benzo(c)cinnoline (39)

This is a modification of the method used by Badger.[46]

A fresh suspension of lithiumaluminium hydride (1.5g, 5 equiv.) in anhydrous ether (10 ml) was added dropwise, *via* pipette, over 1h to a stirred solution of 22'-dinitrodiphenyl (2.0g) in anhydrous benzene (22 ml), with cooling in an ice bath. The mixture was refluxed for 4h after the addition was complete and then allowed to cool to room temperature. Wet ether (8 ml) was slowly added to the reaction mixture, followed by ethyl acetate (8 ml) and water (8 ml). The inorganic material was filtered off and the organic layer extracted with 6N hydrochloric acid (4x25 ml). The acid solution was washed with ethyl acetate (25 ml). neutralised with sodium carbonate and then extracted with ethyl acetate (3x50 ml). The organic solution was dried and evaporated, in vacuo, to give a dark green solid which on crystallisation from benzene afforded the desired product (39) as yellow-green crystals (1.12g, 75%) m.p. 154-157° lit.[46] m.p.156°).

NN'-Dihydrobenzo(c)cinnoline (40)

This is a modification of the method used by Kuhne.[47]

Zinc dust (150 mg) was added to a stirred solution of benzo(c)cinnoline (100 mg) in 8% hydrochloric acid (5 ml), at 75-80° under a flow of oxygen-free (*via* copper chromite) nitrogen, over 30 min. The colour of the solution turned from dark green to pale green over this period and a white precipitate of NN'-dihydrobenzo(c)cinnoline (40) monohydrochloride had formed. Stirring was continued until all the zinc dust had reacted and then the mixture was cooled to 0°. The NN'-dihydrobenzo(c)cinnoline thus formed was used in the reduction reactions. The supernatant liquid was removed by pipette and the hydrochloride neutralised with triethylamine, or the product was filtered off, dried and then neutralised with triethylamine to give a yellow solution of NN'-dihydrobenzo(c)cinnoline in the desired solvent.

Reaction of β-carotene (44) with NN'-dihydrobenzo(c)cinnoline (40)

A solution of β-carotene (44) (0.05g, 0.1 m mole) and NN'-dihydrobenzo(c) cinnoline (0.14g, 0.75 m mole) in dry benzene (5 ml) (pH7.5) was allowed to stand, under nitrogen at room temperature. Both t.l.c. and u.v. (464,493 nm) indicated that there was no reaction, even after 2 days. After this period a sample of azobenzene was added to the mixture. T.l.c. results showed that reduction to hydrazobenzene took place, thus indicating that the reagent was still present.

Reaction of Azobenzene (50) with NN'-Dihydrobenzo(c)cinnoline

A solution of azobenzene (50) (0.1g, 0.55 m mole) and NN'-dihydrobenzo(c)cinnoline (0.11g, 0.60 m mole) in dry benzene (5 ml) (pH7.5) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c. and u.v. (247,291 nm). Reduction to hydrazobenzene (51) was complete after 0.5 h. Triethylamine (2 ml) and benzoyl chloride (0.3g, 2 m mole) were added and the mixture stirred overnight. It was then poured into ice-water (10 ml) and stirred for 1 h to hydrolyse the excess benzoyl chloride. The organic layer was separated and the aqueous layer extracted with ether (2x10 ml). The combined organic extracts were washed with 30% v/v phosphoric acid (5 ml), water (5 ml), dilute bicarbonate (2x5 ml) and water (5 ml), dried and evaporated, in vacuo, to afford a pale yellow oil. After separation by p.l.c. (1:9, ethylacetate: benzene) N-benzoylhydrazobenzene (52) was obtained and was crystallised from methanol as white needles (0.12g, 80%), m.p. 138-139° (lit.[72] m.p. 138-139°). $\nu_{max.}$ ($CHCl_3$)3350 (NH) and 1660 cm^{-1} (amide).

Reaction of Azoxybenzene (53) with NN'-Dihydrobenzo(c)cinnoline

The reaction was performed as in the case of azobenzene, using azoxybenzene (53) (0.1g, 0.5 m mole) and NN'-dihydrobenzo(c)cinnoline (0.2g, 1.1 m mole). Reduction to hydrazobenzene was complete in 1h.

The product was benzoylated and N-benzoylhydrazobenzene isolated by p.l.c. (1:9, ethylacetate=benzene) and crystallised from methanol as white needles (0.9g, 60%), m.p. 137-139° (lit.[72] m.p. 138-139°).

Reaction of Nitrosobenzene (54) with NN'-Dihydrobenzo(c)cinnoline

A solution of nitrosobenzene (54)(0.08g, 0.75 m mole) and NN'-dihydrobenzo(c)cinnoline (0.15g, 0.80 m mole) in dry benzene (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c., u.v., (281 nm) and i.r., (1510 cm^{-1}). Reduction to phenylhydroxylamine (55) was complete after 15 min. The product was benzoylated and N,O-dibenzoylphenylhydroxylamine (56) separated by p.l.c. (1:9, ethyl acetate:benzene) and crystallised from ethanol as white needles (0.18g, 75%) m.p. 118-119° (lit.[72] m.p. 121°).

Reaction of Nitrobenzene (57) with NN'-Dihydrobenzo(c)cinnoline

The reaction was performed as in the case of nitrosobenzene, using nitrobenzene (57) (0.062g, 0.5 m mole) and NN'-dihydrobenzo(c)cinnoline (0.36g, 2.0 m mole), and was followed by t.l.c., u.v. and i.r., (1550 cm^{-1}). Reduction to phenylhydroxylamine was complete in 1 h. The product was benzoylated and N,O-dibenzoylphenylhydroxylamine separated by p.l.c. (1:9, ethyl acetate:benzene) and crystallised from ethanol as white needles (0.10g, 70%) m.p. 119-120° (lit.[72] m.p. 121°).

Reaction of Chloronitrosocamphor (58) with NN'-Dihydrobenzo(c)cinnoline

A solution of chloronitrosocamphor[73] (58) (0.1g, 0.5 m mole) and NN'-dihydrobenzo(c)cinnoline (0.1g, 0.55 m mole) in ethanol (5 ml) was allowed to stand, under nitrogen at room temperature. The reaction was followed by t.l.c. and i.r. (1565 cm^{-1}) and was complete in 30 min. The reaction mixture was evaporated in vacuo and the product (59) separated by p.l.c. (1:2, ethylacetate:benzene) and crystallised from ethanol as white needles (0.07g, 75%) m.p. 116-117° (lit.[72] m.p. of camphor oxime (59) 118°) $[\alpha]_D^{20}$ - 40.5° (c 1 in EtOH), $\nu_{max.}$ ($CHCl_3$) 3580 (OH) and 1670 cm^{-1} (C=N).

Reaction of 6-Nitrocholesteryl acetate (62) with NN'-Dihydrobenzo(c)cinnoline

A solution of 6-nitrocholesteryl acetate [51](62) (0.19g, 0.4 m mole) and NN'-dihydrobenzo(c)cinnoline (270 mg, 1.5 m mole) in dry dichloromethane (5 ml) was allowed to stnad under nitrogen at room temperature. The reaction was monitored by t.l.c. and was complete in 2 h, a more polar compound being formed. The mixture was diluted with ether (25 ml), washed with water (10 ml), 6N hydrochloric acid (5x15 ml) and water (10 ml), dried and evaporated in vacuo to give a colourless oil. On leaving for 2 weeks at room temperature the oil crystallised. On recrystallisation from methanol 6-ketocholestanyl acetate (63) was obtained as white needles (0.085g, 50%) m.p. 129-130° (lit.[52] m.p.128°), $[\alpha]_D^{25}$ -13° (c 1 in $CHCl_3$) $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1} (ketone, ester). Mass measurement = M^+444.

Reaction of Diphenylnitrone (65) with NN'-Dihydrobenzo(c)cinnoline

A solution of diphenyl nitrone (65) (0.21g, 1.1 m mole) and NN'-dihydrobenzo(c)cinnoline (0.22g, 1.2 m mole) in dry benzene (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was monitored by t.l.c. and was complete in 1 h, a less polar compound being formed. The reaction mixture was evaporated in vacuo and the product separated by column chromatography, using benzene as eluent. Benzylidene-aniline (64) (0.07g, 35%) was separated and was crystallised from ethanol as pale yellow plates m.p. 47-48° (lit.[72] m.p. 48°) τ, 1.50 (1H,s,CH=N), 2.05 (2H,m,Ar), 2.35-3.0 (8H,m,Ar).

Reaction of Valeraldehyde (72) with NN'-Dihydrobenzo(c)cinnoline

A solution of valeraldehyde (72) (0.06g, 0.7 m mole) and NN'-dihydrobenzo(c)cinnoline (0.13g, 0.75 m mole) in ethanol (5 ml) was allowed to stand, under nitrogen, at room temperature. Both t.l.c. and i.r. (1730 cm^{-1}) showed that no reaction took place, even on leaving overnight. 2,4-Dinitrophenylhydrazine (0.14g, 0.7 m mole) was then added to the stirred solution

and the resulting 2,4-dinitrophenylhydrazone of valeraldehyde separated by column chromatography, using benzene as eluent, and crystallised from ethanol as red needles (0.15g, 80%) m.p. 96-97° (lit.[72] m.p. 98°).

Reaction of Chloral (73) with NN'-Dihydrobenzo(c)cinnoline

A solution of chloral (73) (0.12g, 0.8 m mole) and NN'-dihydrobenzo (c)cinnoline (0.15g, 0.85 m mole) in dry dichloromethane (5 ml) was allowed to stand under nitrogen at room temperature. The reaction was followed by t.l.c. and i.r. (1770 cm^{-1}) and was complete after 1.5 h, a more polar product being formed. The reaction mixture was evaporated in vacuo to give a pale yellow oil which was subjected to p.l.c. (chloroform) to afford N-formyl-NN'-dihydrobenzo(c)cinnoline (75). This was crystallised from chloroform as white needles (0.12g, 70%) m.p. 118-120°, $\nu_{max.}$ ($CHCl_3$) 3300 (NH) and 1690 and 1640 cm^{-1} (carbonyl), τ 1.66 (1H,d,J15Hz, CHO) and 2.0-3.4 (8H,m,Ar) (Found: C,74.1; H,4.9; N,13.2. $C_{13}H_{10}N_2O$ requires C,74.3; H,4.8; N,13.3%).

Reaction of 222-Trichloroethyl pyruvate (74) with NN'-Dihydrobenzo(c)cinnoline

The reaction was carried out as in the case of chloral, using 222-trichloroethyl pyruvate (74) (0.1g, 0.48 m mole) and NN'-dihydrobenzo (c)-cinnoline (0.1g, 0.55 m mole). The reaction was followed by t.l.c. and i.r. (1760, 1745 cm^{-1}) and was complete in 1 h, a more polar product being formed. The reaction mixture was evaporated in vacuo and the resulting yellow oil subjected to p.l.c. (chloroform) to afford N-acetyl-formyl-NN'-dihydrobenzo(c)cinnoline (76) as a pale yellow oil (0.09g, 70%). $\nu_{max.}$ ($CHCl_3$) 3260 (NH) and 1725 and 1680 cm^{-1} (carbonyl), τ 2.1-3.1 (8H,m,Ar) and 7.62 (3H,s,MeCo). Mass measurement: M^+252, (M^+-CH_2CO) 210, (M^+-CH_3COCO) 181.

Reaction of Benzil (77) with NN'-Dihydrobenzo(c)cinnoline

A solution of benzil (77) (0.06g, 0.28 m mole) and NN'-dihydrobenzo(c) cinnoline (0.11g, 0.60 m mole) in dry dichloromethane (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c. and was complete in 30 min. The mixture was diluted with ethyl acetate (25 ml) and washed with 6N hydrochloric acid (4x15 ml) and water (15 ml), dried and evaporated in vacuo to give benzoin (78) which was crystallised from ethanol as pale yellow needles (0.05g, 82%) m.p.136-137° (lit.[72] m.p. 137°).

Reaction of (+)-Camphorquinone (79) with NN'-Dihydrobenzo(c)cinnoline

A solution of (+)-camphorquinone[53](79) (0.20g, 1.2 m mole) and NN'-dihydrobenzo(c)cinnoline (0.23g, 1.3 m mole) in dry dichloromethane (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c. and i.r. (1775, 1760 cm^{-1}) and was complete in 1.5h. The mixture was diluted with ether (25 ml), washed with 6N hydrochloric acid (4x15 ml) and water (15 ml), dried and evaporated down to give a colourless oil. The n.m.r. spectrum of the oil indicated that two products had been obtained since it showed two new methine resonances at 5.78 (d,J4Hz) and 6.1 τ(bs) in the ratio 1:1, plus a new resonance at 6.38 τ(1H,s) which was assigned to the hydrogen in a hydroxyl group since it exchanged with deuterium oxide. The crude mixture was benzoylated, using pyridine and benzoyl chloride, and the two benzoylated products separated by p.l.c. (5:6, light petroleum:benzene). The more polar product was endo-2-hydroxyepicamphor benzoate (83) [56] and was crystallised from n-hexane as colourless plates (0.10g, 30%) m.p. 87-88° (lit.[56] 87.5-88°) $[\alpha]_D^{21}$ +487° (c 1 in $CHCl_3$) $\nu_{max.}$ ($CHCl_3$) 3520 (OH), 1760 (ketone) and 1725 cm^{-1} (ester), τ 2.05 (2H,m,Ar), 2.6 (3H,m,Ar), 4.65 br (1H,s,exo-2H), 7.4-8.6 (5H,m), 8.92 (3H,s,Me) and 8.98 (6H,s,2xMe).

The less polar product was endo-3-hydroxycamphor benzoate (82) [55] and was obtained as a colourless oil (0.10g, 30%) $[\alpha]_D^{21}$ +37.1°(c 1 in $CHCl_3$) $\nu_{max.}$ ($CHCl_3$) 3520 (OH), 1760 (ketone) and 1725 cm^{-1} (ester), τ 1.9 (2H,m,Ar), 2.5 (3H,m,Ar), 4.6 (1H,d,J4Hz,exo-3H), 7.42 (1H,s,CH), 8.2 (4H,m,2xCH_2), 8.92 (6H,s,2xMe) and 9.0 (3H,s,Me).

These products were identical to the derivatives obtained after reduction of camphorquinone (79) with zinc/acetic acid.[54]

Reaction of p-Benzoquinone (84) with NN'-Dihydrobenzo(c)cinnoline

A solution of p-benzoquinone (84) (0.06g, 0.056 m mole) and NN'-dihydrobenzo(c)cinnoline (0.12g, 0.67 m mole) in dry benzene (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c. and i.r., (1675, 1665 cm^{-1}). The reaction was complete in 1 min. and an off-white precipitate was formed. The mixture was filtered and the solid obtained stirred with ether (10 ml). After 5 min. the mixture was filtered. The filtrate was dried and evaporated in vacuo to afford quinol (85) as a pale-yellow solid which was crystallised from water as white needles (0.05g, 83%) m.p. 167-168° (lit.[72] m.p. 170°). $\nu_{max.}$ ($CHCl_3$) 3350 cm^{-1} (OH).

Reaction of 3,5-Di-t-butyl-o-benzoquinone (86) with NN'-Dihydrobenzo(c)cinnoline

A solution of 3,5-di-t-butyl-o-benzoquinone [57](86) (0.11g, 0.5 m mole) and NN'-dihydrobenzo(c)cinnoline (0.1g, 0.55 m mole) in dry dichloromethane (5 ml) was allowed to stand, under nitrogen, at room temperature. The reaction was followed by t.l.c. and i.r. (1670 cm^{-1}) and was complete in 1 min. The mixture was diluted with ether (25 ml) and washed with 6N hydrochloric acid (4x15 ml) and water (15 ml) dried and evaporated in vacuo to afford 3,5-di-t-butylcatechol (87) which was crystallised from ether as white needles (0.09g, 80%) m.p. 97-100° (lit.[72] m.p. 96-99°) $\nu_{max.}$ ($CHCl_3$) 3540 and 3280 cm^{-1} (OH).

Reaction of 4,5-Dicarboxypyridazine (96) with Zinc/hydrochloric acid, followed by attempted reduction of Nitrosobenzene

Zinc dust (0.15g) was added portionwise, over 15 min. to a stirred solution of 4,5-dicarboxypyridazine (96)[62] (0.05g) in 8% hydrochloric acid (8 ml), under nitrogen, at 70°. U.v. spectra showed changes in maxima from 262 and 215 nm to 245, 225 and 216 nm, showing that a reaction had taken place. The reaction mixture was stirred until all the zinc had reacted, filtered and the filtrate evaporated to about 0.5 ml, under vacuum. Dimethylformamide (5 ml) was added to the residue and the pH adjusted to 7.5 with triethylamine. Nitrosobenzene was added to the resulting solution which was then left under nitrogen for 24 h. U.v. spectra indicated that no reaction took place.

Reaction of o-Phenylenediamine (103) with Benzaldehyde, followed by reduction of Nitrosobenzene

Nitrosobenzene (0.04g, 0.4 m mole) was added to a stirred solution of o-phenylenediamine (103) (0.09g, 0.85 m mole) and benzaldehyde (0.09g, 0.85 m mole) in ethanol (5 ml), under nitrogen, at room temperature. T.l.c. showed that reduction to phenylhydroxylamine took place in 30 min. The reaction mixture was evaporated in vacuo and benzoylated using benzoyl chloride in pyridine. The resulting N,O-dibenzoylphenylhydroxylamine (56) was separated by p.l.c. (1:9, ethylacetate:benzene) and crystallised from ethanol as white needles (0.03g, 25%) m.p. 119-120° (lit.[72] m.p. 121°).

Reaction of 3-Amino-4-hydroxybenzoic acid (106) with Anisaldehyde

Anisaldehyde (0.068g, 0.5 m mole) was added to a stirred solution of 3-amino-4-hydroxybenzoic acid (0.076g, 0.5 m mole) in ethanol (3 ml) at room temperature. After 5 min the Schiff base (107) was deposited as a brown solid. $\nu_{max.}$ (nujol) 3350 (OH) and 1680 cm^{-1} (acid), τ 2.82 (1H,s,CH), 3.5 (2H,d,Ar), 3.8 (2H,m,Ar), 4.42 (3H,m,Ar) and 7.64 (3H,s,OMe).

O-4-Carbomethoxy-2-nitrophenyldimethylthiocarbamate (110)

Diazabicyclooctane (2.16g, 20 m mole) and dimethylthiocarbamoyl chloride[74] (1.80g, 15 m mole) were added to a solution of 4-hydroxy-3-nitromethyl benzoate (2g, 10 m mole) in dry dimethylformamide (8 ml). The resulting yellow suspension was stirred at 30°, under nitrogen, for 30 min. and then heated to 60° over 1 h. The reaction mixture was then allowed to cool down and diluted with ether (150 ml). The ethereal solution was washed with water (5x30 ml), dried and evaporated in vacuo to give the desired product (110) as a yellow solid which was crystallised from ethanol as yellow needles (1.8g, 60%), m.p. 86-90°, $\nu_{max.}$ ($CHCl_3$) 1730 (ester), 1680 (O-C=s) and 1540 cm^{-1} (NO_2), τ 2.13 (1H,d,J2Hz), 2.6 (1H,dd,J2 and 8Hz), 3.53 (1H,d,J8Hz), 6.85 (3H,s,OMe) and 7.4 (6H,d,NMe_2).

S-4-Carbomethoxy-2-nitrophenyldimethylthiocarbamate (111)

O-4-Carbomethoxy-2-nitrophenyldimethylthiocarbamate (110) (0.15g) was heated for 20 min at 150°, during which time it rearranged to the desired product (111) as a yellow gum. The gum solidified on standing and was recrystallised from ethanol as yellow needles (0.13g, 88%) m.p. 71-74°, $\nu_{max.}$ (nujol) 1720 (ester), 1660 (s-C=O) and 1540 cm^{-1} (NO_2), τ 2.3 (1H,d,J2Hz), 2.66 (1H,dd,J2 and 8Hz), 3.04 (1H,d,J8Hz), 6.85 (3H,s, OMe) and 7.72 (6H,s,NMe_2).

4-Mercapto-3-nitrobenzoic acid (112)

10% Sodium hydroxide solution (8 ml) was added to a solution of S-4-carbomethoxy-2-nitrophenyldimethylthiocarbamate (111) (1.30g, 4.5 m mole) in methanol (15 ml), under nitrogen. The resulting solution was heated to 50°, with stirring, over 1 h. The solution was stirred for 30 min. at this temperature, then cooled in an ice-bath and acidified with 6N hydrochloric acid. The desired product (112) was obtained as a yellow precipitate, which was filtered off and dried, in vacuo (0.69g, 80%) m.p. 295-300° (decomp.)

$\nu_{max.}$ (nujol) 2550 (SH), 1690 (COOH) and 1520 cm^{-1} (NO_2), τ 2.12 (1H,d, J2Hz), 2.88 (1H,dd,J2 and 8Hz) and 3.41 (1H,d,J8Hz).

3-Amino-4-mercaptobenzoic acid (113)

This is a modification of the method used by Dannley and Zazaris.[71]

4-Mercapto-3-nitrobenzoic acid (112) (1.5g) was stirred in ethanolic solution (15 ml). Tin (4g) was added and the mixture heated to 70°. Concentrated hydrochloric acid (6 ml) was then added dropwise, over 30 min. The mixture was stirred for a further 30 min. at 70°, the precipitated tin salts filtered off and the filtrate evaporated down to about 5 ml, in vacuo. The product was recrystallised from 1:1 methanol:hydrochloric acid. The tin salts precipitated first, followed by the desired product (113) as its pale yellow hydrochloride, (0.8g, 55%) m.p. 295-300° decomp. (lit.[71], 267-268°). $\nu_{max.}$ (nujol) 3500 (NH), 2550 (SH) and 1690 cm^{-1} (COOH). Mass measurement: M^+ 169.

Reaction of 3-amino-4-mercaptobenzoic acid (113) with Anisaldehyde, followed by reduction of Azobenzene

Anisaldehyde (0.1g, 0.75 m mole) was added to a solution of 3-amino-4-mercaptobenzoic acid (113) (0.15g, 0.75 m mole) in pyridine (2 ml). The mixture was stirred for 15 min. at room temperature, under nitrogen, and then diluted with benzene (10 ml). Azobenzene (0.1g, 0.55 m.mole) was added and the reaction followed by t.l.c. Reduction to hydrazobenzene took place in 30 min. The mixture was washed with 10% sodium hydroxide solution (2x5 ml) and water (5 ml) and then dried. The product was benzoylated using benzoyl chloride and the resulting N-benzoylhydrazobenzene (52) separated by p.l.c. (1:9, ethyl acetate:benzene) and crystallised from methanol as white needles (0.09g, 60%) m.p. 137-139° (lit.[72] m.p. 138-139°).

4-Formylphenoxyacetic acid (117)

Sodium hydride (0.96g, 40 m mole) was added, over 5 min, portionwise to a stirred solution of p-hydroxybenzaldehyde (115) (4.9g, 40 m mole) in dry THF (30 ml), under nitrogen, at room temperature. A grey precipitate was formed immediately. After the evolution of hydrogen ceased, ethyl bromoacetate (6.7g, 40 m mole) was added and stirring continued overnight. After this period, 10% sodium hydroxide solution (25 ml) was added, with caution, and stirring continued for 1 h. The resulting solution was concentrated to about 30 ml and acidified with glacial acetic acid. The off-white precipitate was filtered off and crystallised from aqueous acetic acid to give the desired product (117) as off-white leaflets (5.1g, 70%) m.p. 196-198° (lit.[72] m.p. 198°), τ 2.10(2H,d,J10Hz,Ar), 2.90 (2H,d,J10Hz,Ar) and 5.28 (2H,s,$\underline{CH_2}$).

Reaction of o-Methylaminoaniline (118) with 4-Formylphenoxyacetic acid (117) followed by reduction of 3,5-Di-t-butyl-o-benzoquinone (86)

3,5-Di-t-butyl-o-benzoquinone (86)[57] (0.05g, 0.24 m mole) was added to a stirred solution of 4-formylphenoxyacetic acid (117) (0.054g, 0.3 m mole), o-methylaminoaniline. dihydrochloride (118) (0.057g, 0.3 m mole) and triethylamine (0.09g, 0.9 m mole) in ethanol (5 ml) under nitrogen, at room temperature. The reaction was followed by t.l.c. and i.r. (1670 cm^{-1}) and was complete in 15 min. The reaction mixture was diluted with ether (25 ml), washed with dilute bicarbonate (2x15ml) and brine (15 ml), dried and evaporated in vacuo to give a pale yellow solid. On crystallisation from ether, 3,5-di-t-butyl-catechol (87) was obtained as white needles (0.038g, 75%) m.p. 96-98° (lit.[72] m.p. 96-99°) $\nu_{max.}$ ($CHCl_3$) 3540 and 3280 cm^{-1} (OH).

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