THE OXIDATION OF CHIRAL 2-THIAZOLINES AND THIAZOLIDINE-2-THIONES

by

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I, David Philip Armstrong hereby certify that this thesis has been composed by myself, that it is a record of my own work, and that it has not been accepted in partial or complete fulfilment of any other degree.

Signed Date 25/6/90

I was admitted to the Faculty of Science of the University of St Andrews under Ordinance General No. 12 on October 1st 1985 and as a candidate for the degree of Ph.D. on October 1st 1986.

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Abstract

Chiral 2-thiazolines with a variety of substituents at the 2- and 4-positions have been prepared starting from readily available enantiomerically pure aminoalcohols *via* intermediate 2-oxazolines or N-acylamino alcohols. The behaviour of these 2-thiazolines towards oxidation has been investigated in detail. Stable 2-thiazoline N-oxides, a previously unknown class of compounds, are formed with two oxidising agents: peroxytrifluoroacetic acid and dinitrogen tetroxide. A large number of other oxidising agents give mixtures of some or all of 2-thiazoline S,S-dioxides, aromatised thiazoles and both N-acylaminodisulphides and sulphonic acids apparently derived from initial hydrolytic ring-opening to the N-acylaminothiols followed by further oxidation. Conditions have not yet been developed to obtain the desired S,S-dioxides in pure form.

Potential applications of the 2-thiazoline N-oxides in asymmetric synthesis have been investigated. The compounds surprisingly do not undergo 1,3-dipolar cycloaddition with a wide variety of dipolarophiles. They do however transfer oxygen both to neutral acceptors such as styrene and to organolithium species such as LDA and phenyllithium. Other anions have given disappointing results but the use of the N-oxides as a chiral OH^+ source merits further investigation.

A number of chiral thiazolidine-2-thiones have also been prepared from chiral aminoalcohols. Conditions have been developed

for the efficient direct oxidation of these to the corresponding thiazolidin-2-one S,S-dioxides. A preliminary study of the thermal decomposition of one example showed this to proceed by a concerted fragmentation to give SO_2, an alkene and an isocyanate. This may be due in part to the bulky groups present at positions 3 and 4, and the prospects for elimination of only SO_2 to give β-lactams in cases with less bulky or interconnected groups look bright.

CONTENTS

Experimental

Discussion

Page No

INTRODUCTION

Oxidation of Monocyclic Five-membered Ring Heterocycles Containing Nitrogen and Sulphur

The behaviour of five-membered ring heterocycles containing both nitrogen and sulphur towards oxidation forms a complex picture. For the aromatic heterocycles oxidation can potentially occur either on nitrogen or sulphur. For partly saturated systems we can also get dehydrogenation to an aromatic form and in addition there are many other possible modes of reaction including oxidative coupling via an activated ring carbon, oxidation accompanied by hydrolysis and replacement of sulphur by oxygen.

In the following review the oxidation of heterocyclic compounds containing only carbon, nitrogen and sulphur in the five-membered ring is considered and for reasons of space the coverage is confined to monocyclic systems.

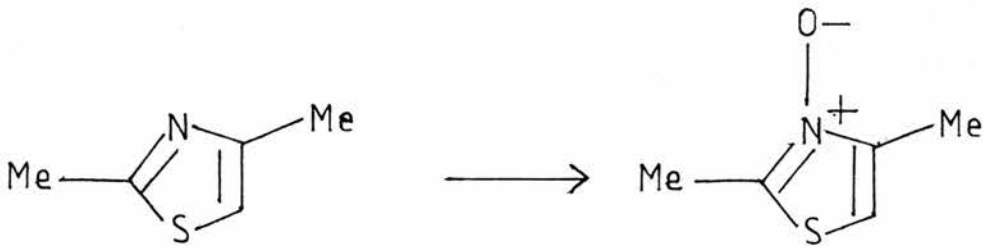
A. Thiazole derived ring systems

1. Thiazoles

Two principal modes of oxidation are known for the thiazoles: oxidation on nitrogen using peroxyacids to form thiazole N-oxides and sensitised photooxygenation to form bridged peroxy adducts which undergo fragmentation.

a. N-Oxidation

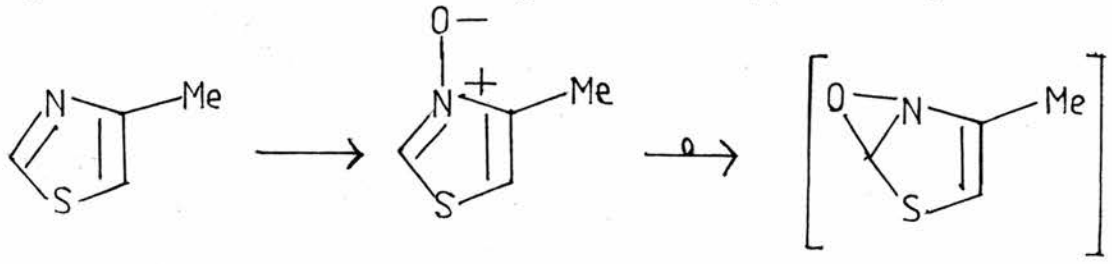
The first successful oxidation of this relatively resistant ring system was carried out by Ochiai in 1947[1]. He obtained 2,4-dimethylthiazole 3-oxide (2) by treating the thiazole (1) with hydrogen peroxide in acetic acid. The same reaction was subsequently



(1) (2)

reported both with peroxyacetic acid[2] and with monoperoxyphthalic acid[3]. When the 2-unsubstituted substrate 4-methylthiazole (3) was used the N-oxide (4) was only formed in low yield and its formation was accompanied by extensive ring-decomposition to produce ammonium sulphate[4]. This was attributed to the facile isomerisation

of (4) to the 2-hydroxythiazole (5) which is then susceptible to further oxidation. Ring decomposition to give sulphuric acid was also used to explain the formation of the sulphate salt of (2) in low yield



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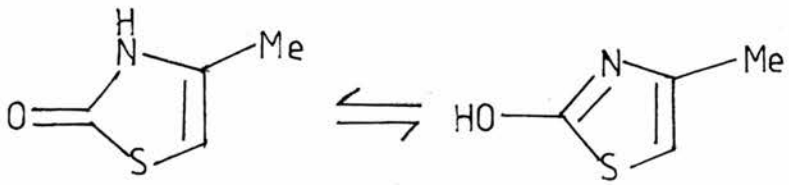

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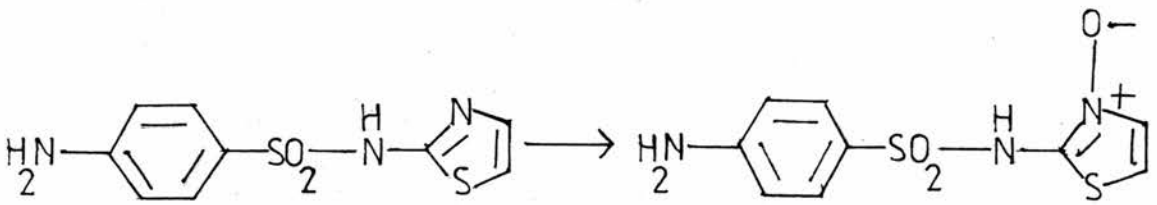
on prolonged oxidation of (1) with peroxyacetic acid[2]. The 2-unsubstituted thiazole N-oxides are relatively unstable, vacuum distillation of (4) leading to decomposition probably by autoxidation. Oxidation of 2-sulphanilylaminothiazole (6) occurs readily with hydrogen peroxide in acetic acid at 70°C to give exclusively the N-oxide (7)[5].



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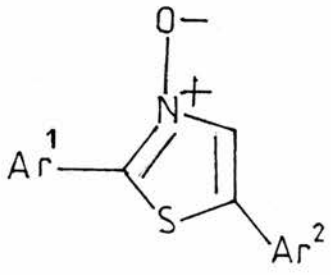
Monoperoxymaleic acid has been used to convert a series of 2,5-diarylthiazoles to the corresponding N-oxides (8) at 0°C over several days[6]. The occurrence of oxidation on nitrogen as opposed to sulphur was clear from the strong N-oxide absorption at 1210cm^{-1} in the i.r. spectra of the products as well as their ready deoxygenation back to



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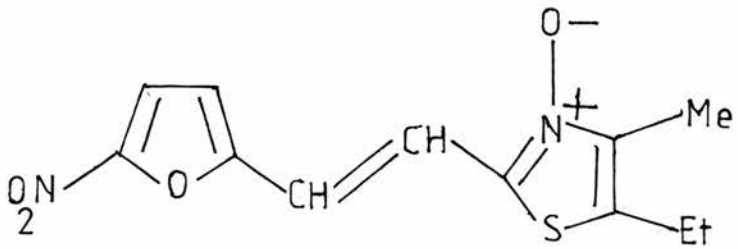
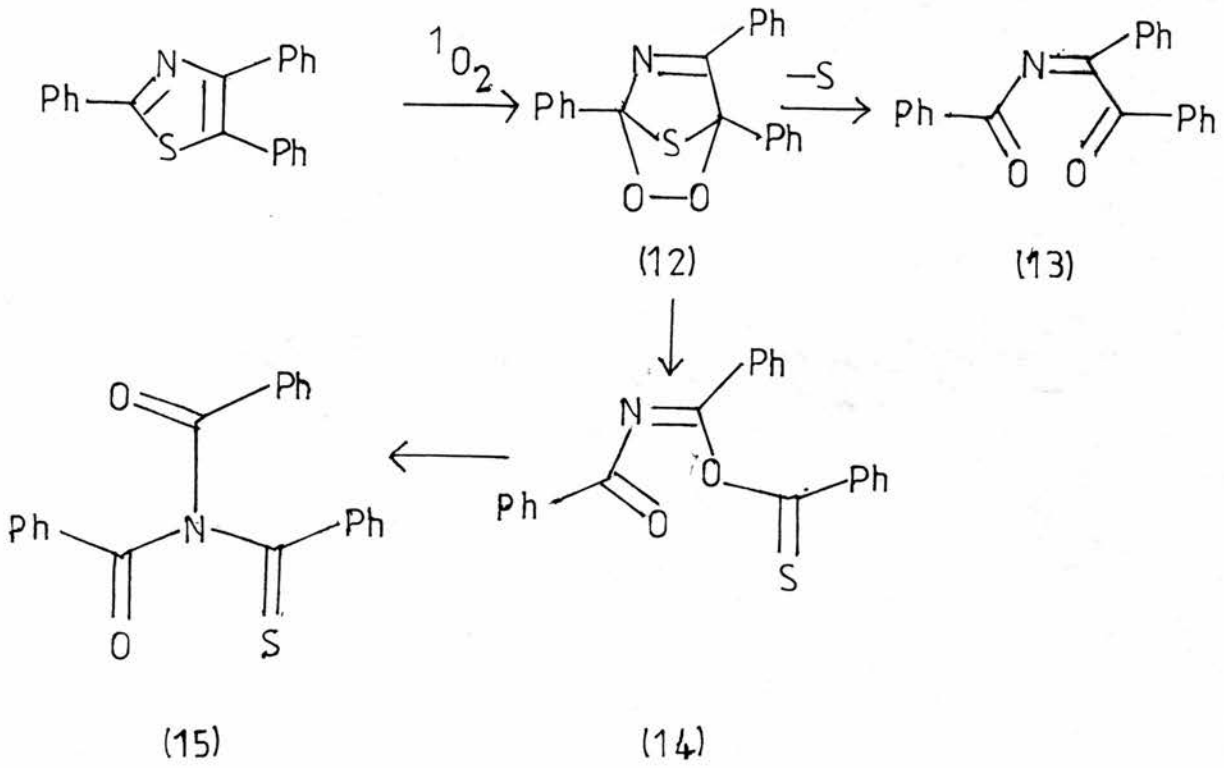


(9)

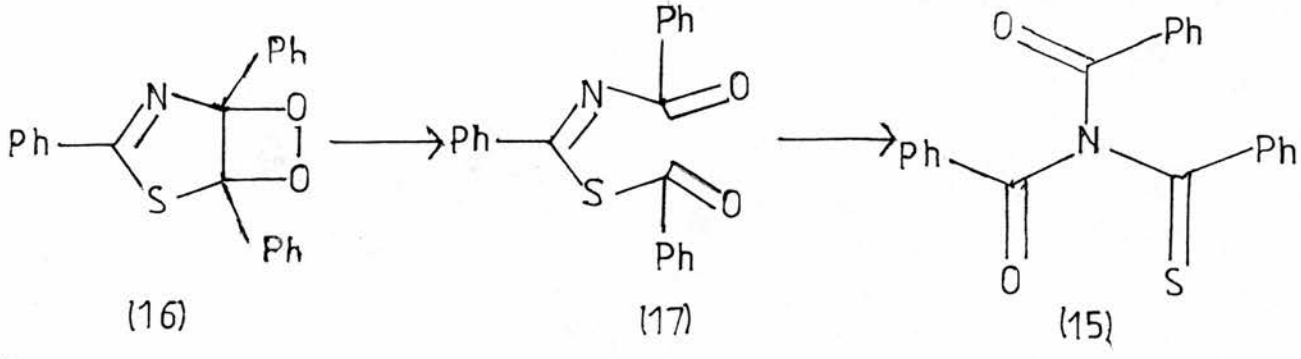
the thiazoles with PCl_3. A series of complex trisubstituted thiazole N-oxides such as (9) were formed in good yield from the corresponding thiazoles with peroxyacetic acid[7].

b. Sensitised Photooxygenation

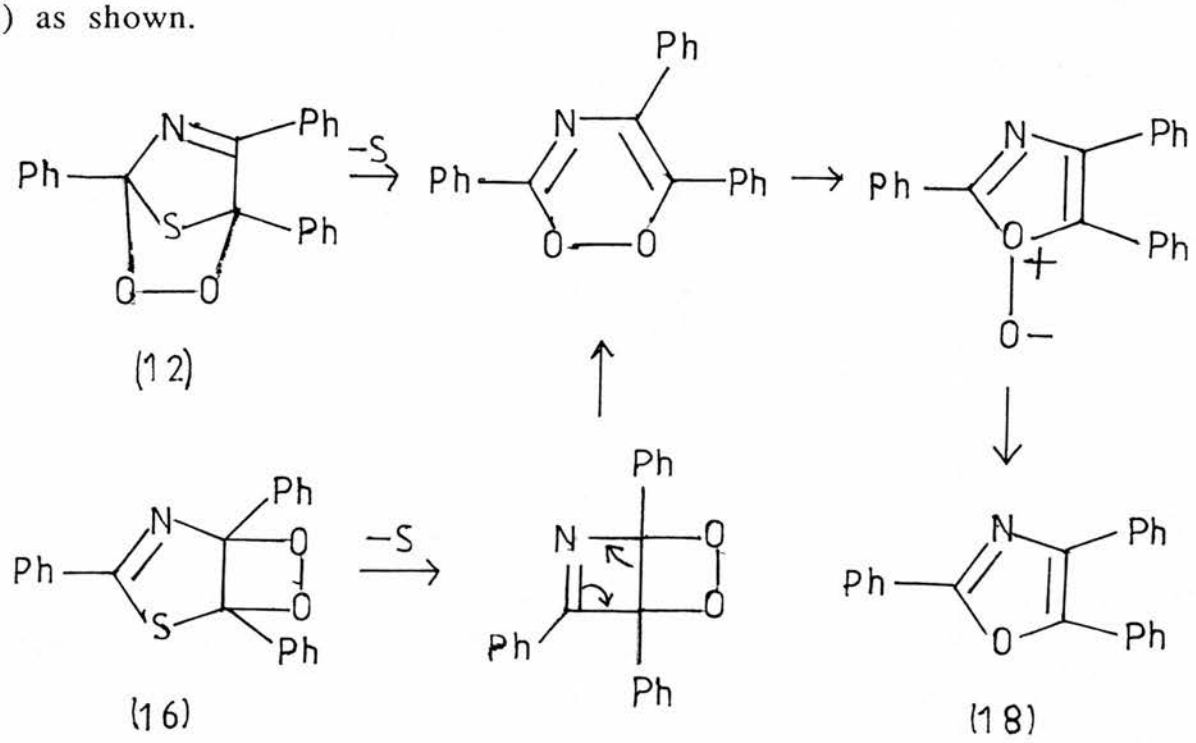
When thiazoles are subjected to photolysis in the presence of oxygen and a photosensitiser a variety of deep-seated rearrangements occur yielding mainly acyclic products. In every case however the reactions begin by cyclo-addition of singlet oxygen to the thiazole either in a 1,4-sense to give (12) or 1,2 to give (16). Thus photooxygenation of 2,4,5-triphenylthiazole in methanol with rose bengal gives benzil and benzamide by photochemical extrusion of



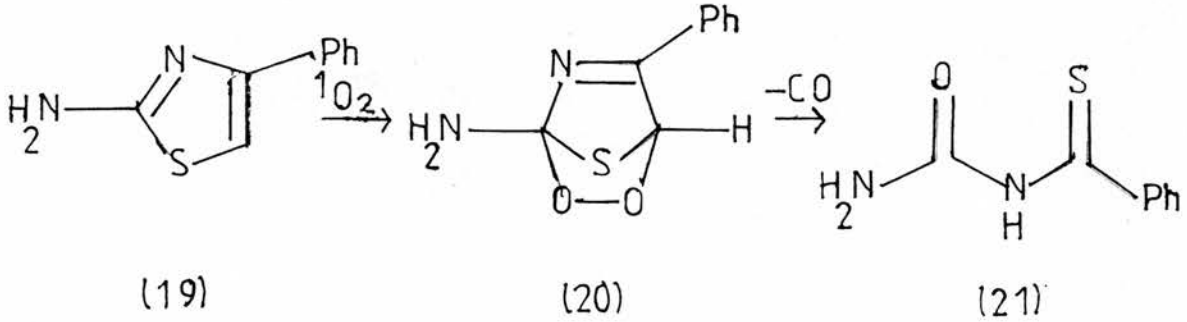
sulphur from (12) to give imine (13) which is then hydrolysed[8]. If the reaction is instead carried out in chloroform with methylene blue the product is dibenzoyl(thiobenzoyl)amine (15). This may be formed either by an alternative rearrangement of (12) to (14) which then gives (15) as shown, or from the isomeric oxygen adduct (16) by rearrangement first to (17) and then to (15)[8].



Re-examination of these reactions confirmed the formation of benzil and benzamide in methanol but also revealed a low yield of the corresponding oxazole (18)[9]. In chloroform this was reported to be the only product. Its formation can be rationalised either from (12) or (16) as shown.

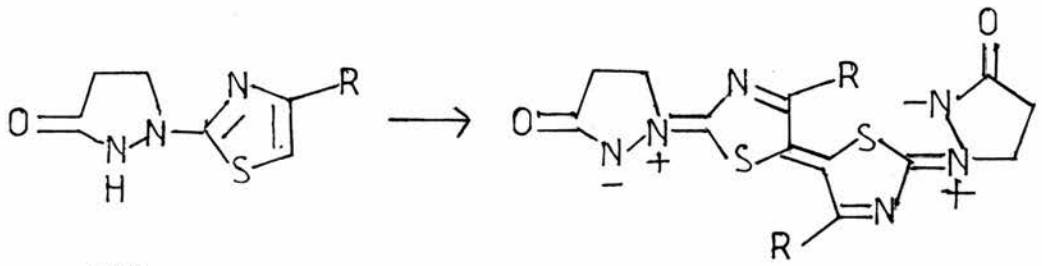


In the case of 2-amino-4-phenylthiazole (19) photooxygenation in chloroform with methylene blue gives thiobenzoylurea (21) by a mechanism involving loss of the 5-carbon atom as CO from the initial adduct (20)[10].



c. Other oxidations

An unusual type of oxidation is observed on treatment of thiazoles (22) with sodium periodate. The bis-azomethine imines (23) are formed in high yield[11].



(22) (23)

2. Thiazolines

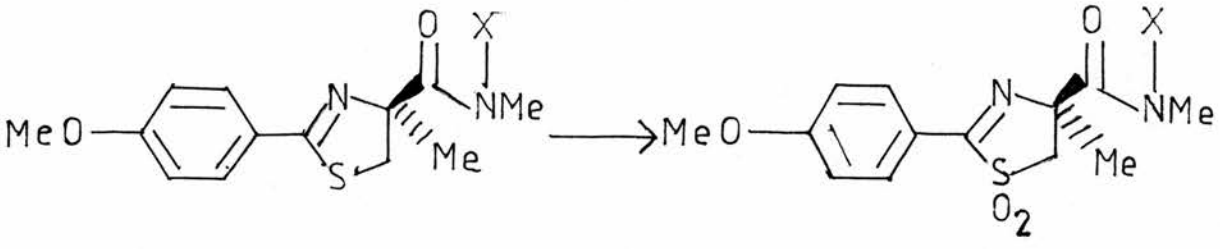
Two main oxidation reactions are known for thiazolines: oxidation on sulphur using peroxyacids, permanganate or atmospheric oxygen and dehydrogenation using a variety of reagents including potassium ferricyanide and elemental sulphur. Photo-oxidation on carbon also occurs but is a less common reaction. Hydrolytic ring opening followed by oxidation with bromine water to give sulphonic acids has also been reported. It is particularly interesting in relation to the present work that no example of the N-oxidation of a 2-thiazoline appears to have been reported previously.

Thiazoline has different isomeric forms due to the variation in the position of the double bond. The oxidation of the ring system is considered according to the type of oxidation as well as the nature of the isomer involved.

a. S-Oxidation

(i) 2-Thiazolines

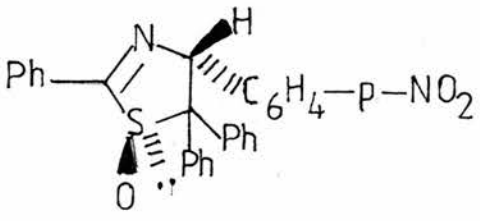
The first succesful S-oxidation was carried out by Scott in 1976[12]. He obtained a 2-thiazoline 1,1-dioxide (25) by treating the 2-thiazoline (24) with two equivalents of m-chloroperoxybenzoic acid in dichloromethane. The same reagent (one equivalent) was subsequently used by Bonini to give a diastereomeric mixture of *anti*



(24) (25)

X = $-OSO_2C_6H_4-p-NO_2$

and *syn* sulphoxides (26 and 27) from the corresponding 2-thiazoline[13].



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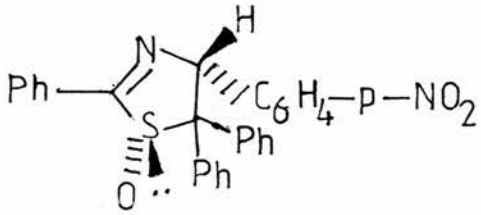
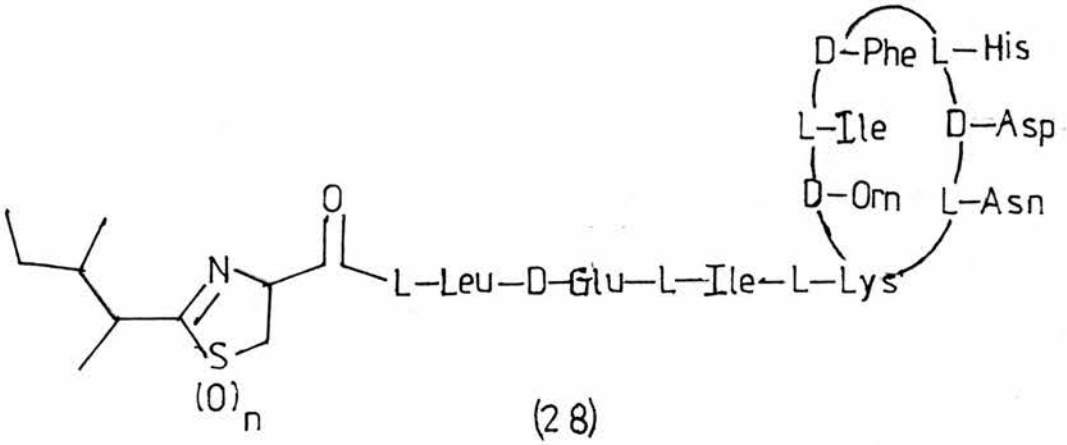


(27)

Sodium periodate and potassium permanganate have also been used to oxidise the 2-thiazoline ring in Bacitracin A(28, n=0) to the sulphoxide (28, n=1) and sulphone (28, n=2) respectively at 0-5°C in an acetic acid/water buffer system maintained at pH6[14].



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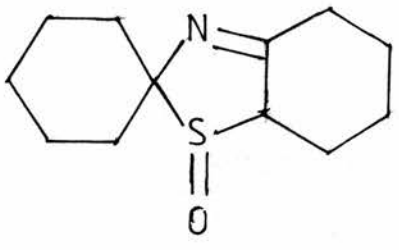
(ii) 3-Thiazolines

A series of complex trisubstituted 3-thiazoline 1-oxides such as (29) have been formed in moderate yield by treating the 3-thiazolines with molecular oxygen at room temperature[15].



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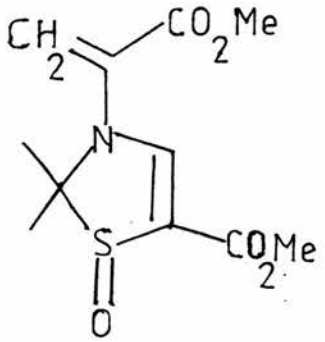
(iii) 4-Thiazolines

A 4-thiazoline 1-oxide (30) was formed from the corresponding

4-thiazoline using one equivalent of m-chloroperoxybenzoic acid in dichloromethane at -78°C[16,17]. The sulphoxide was unstable on



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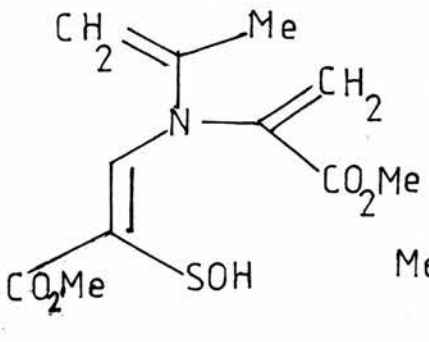

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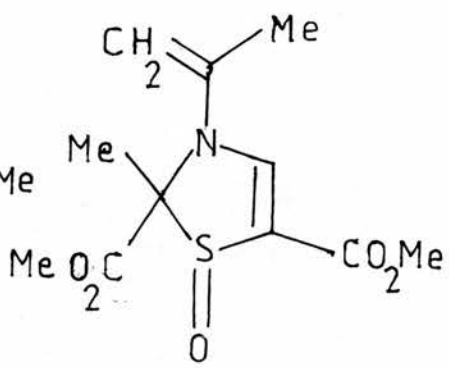


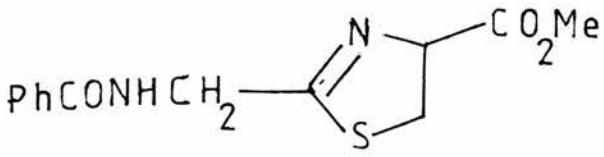
(32)

heating in boiling benzene, undergoing a rearrangement via the sulphenic acid (31) to the 4-thiazoline (32).

(b) Dehydrogenation

(i) 2-Thiazolines

Manganese dioxide was first used in 1966 to effect dehydrogenation of (33) to the corresponding thiazole[18]. More

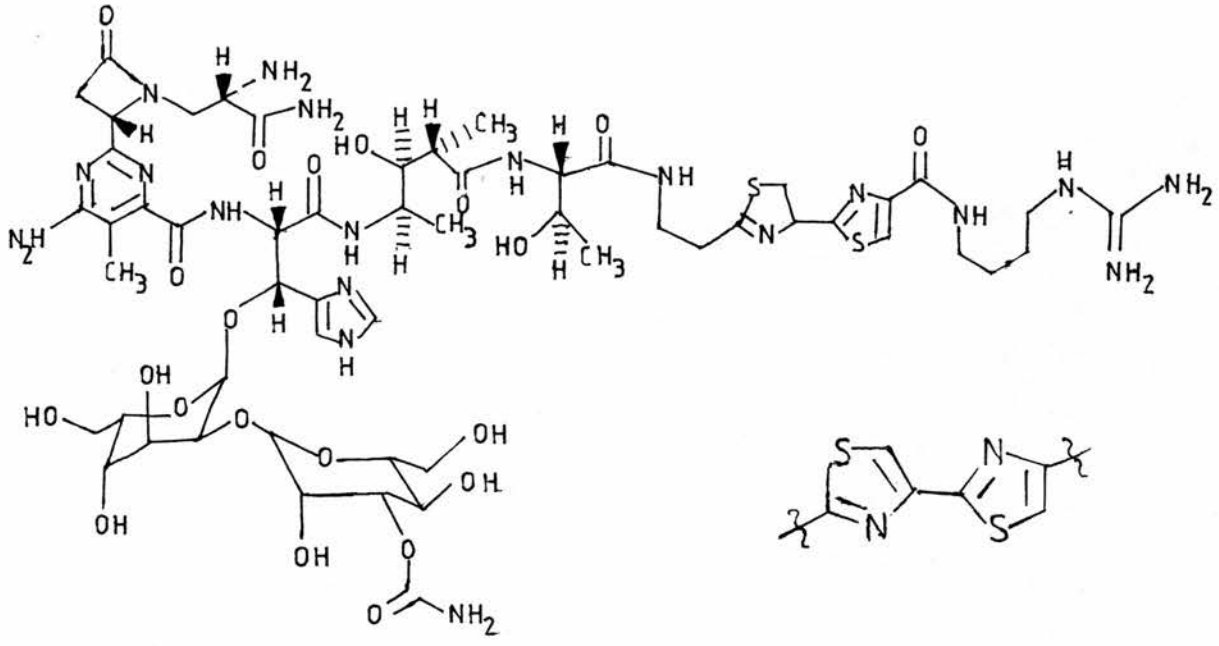


(33)

recently nickel peroxide has been widely used due to its greater oxidising power, giving rise to more efficient conversions. A wide range of 2,4-disubstituted 2-thiazolines such as (34) have been oxidised to the corresponding thiazoles (35), demonstrating the versatility of this reagent[19-21]. In addition the mild, selective

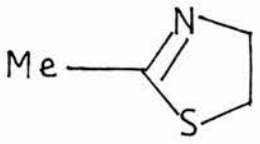
(34) (35)

nature of nickel peroxide is apparent from its smooth conversion of phleomycin A_2 (36) to the antitumour antibiotic bleomycin A_2 (37) without any reaction of the complex side-chains[20].



(36) (37)

The vapour phase oxidation of 2-methyl-2-thiazoline (38) at 340-395°C using a vanadium-molybdenum oxide catalyst gave thiazole (39), 2-methylthiazole (40), thiazole-2-carboxaldehyde (41) and 2-thiazoline-2-carboxaldehyde (42)[22].



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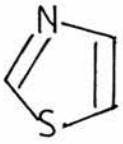

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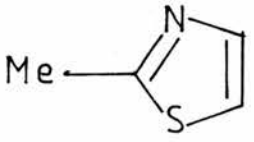

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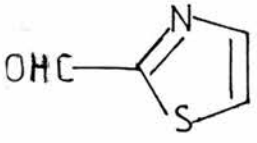

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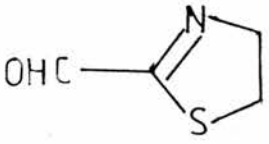

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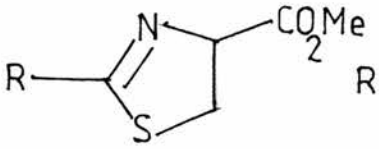
Potassium ferricyanide in aqueous alkaline solution was used to oxidise a series of 2-substituted-2-thiazolines (43)[23]. In addition to the thiazoles, (44), a range of side products were formed by ring



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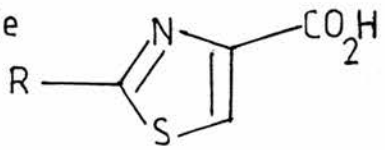

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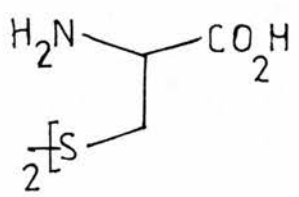
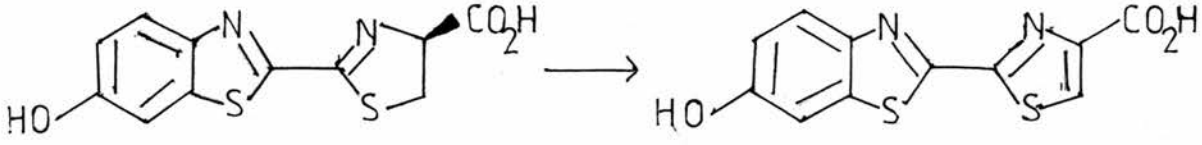


(45)

opening and further oxidation to the disulphide. The degree of hydrolysis was dependent upon the nature of the 2-substituent, the electron withdrawing phenyl group giving the smoothest reaction to the thiazole and the methyl and hydrogen groups yielding increasing amounts of cystine (45).

In the naturally occurring example Firefly luciferin (46) desaturation occurs readily to the dehydroluciferin (47) with the same reagent[24].

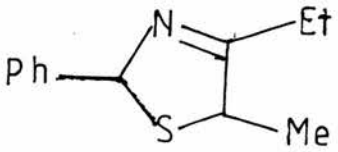


(46) (47)

Atmospheric oxidation under alkaline conditions also gives (47)[25].

(ii) 3-Thiazolines

Sulphur has been highly effective in dehydrogenating a series of 2,4,5-trisubstituted 3-thiazolines such as (48) to the corresponding thiazoles (49) with liberation of hydrogen sulphide on heating to 125-135°C[26,27] .



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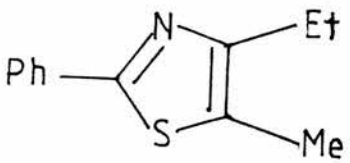
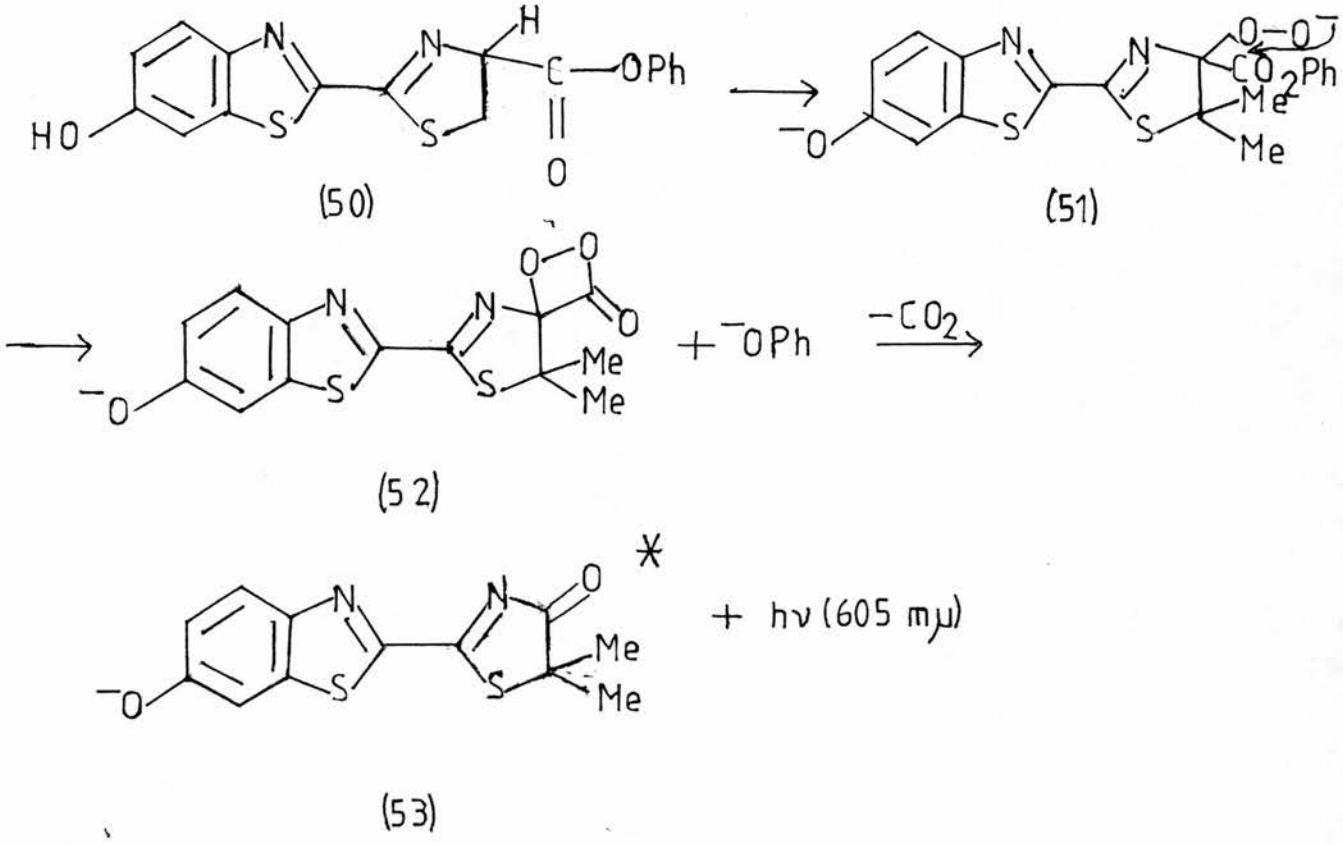


(49)

Transition metal oxidising agents such as ferric chloride, potassium ferricyanide and potassium dichromate at 70°C are successful but less effective under similar circumstances[26,27].

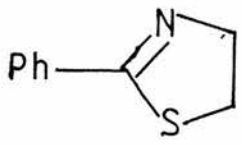
(c) Photo-oxidation

An unusual type of oxidation was observed on investigating chemiluminescence in the North American firefly. The 5,5-dimethyl analogue of Luciferin (50) in dimethyl sulphoxide reacted by photo-oxidation in the presence of a base, guanidine carbonate to give brilliant red luminescence[28]. This was attributed to the formation of an electronically excited carbonyl derivative (53) via decomposition of a four membered cyclic peroxide intermediate (52)[29,30].



(d) Hydrolytic ring opening

In a very early study, 2-phenylthiazoline (54) was oxidised with bromine water in dilute hydrochloric acid and found to give N-benzoyltaurine (56), formed by hydrolytic ring opening and subsequent oxidation of the N-acylthiol (55) to the sulphonic acid (56)[31]. Deacylation of benzoyltaurine (56) in fuming hydrochloric acid to the free aminosulphonic acid and benzoic acid together with analysis of the silver salt provided evidence for the structure.



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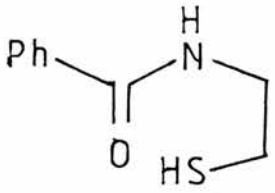

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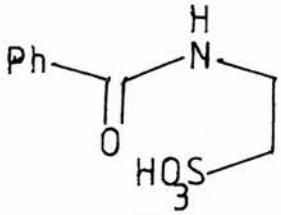
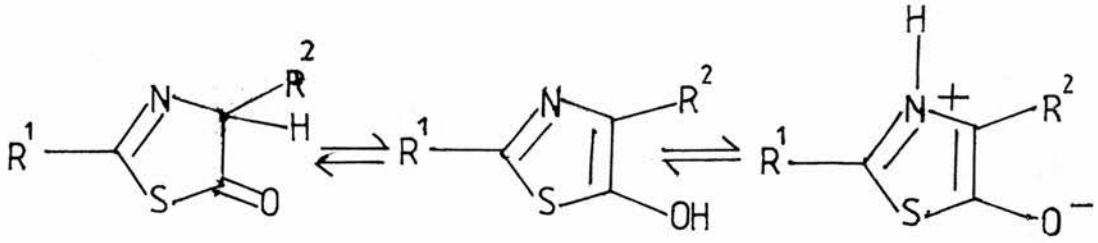


(56)

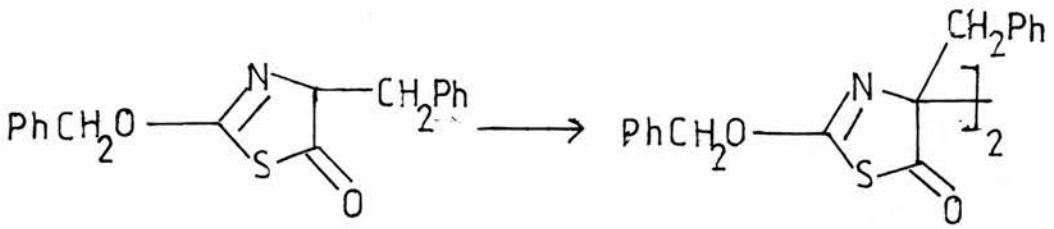
3. 2-Thiazolin-5-ones

The oxidation reactions of 2-thiazolin-5-ones (57) form a separate class as the parent ring system can exist in three tautomeric forms (57), (58) and (59). The enol (58) and mesoionic forms (59) in



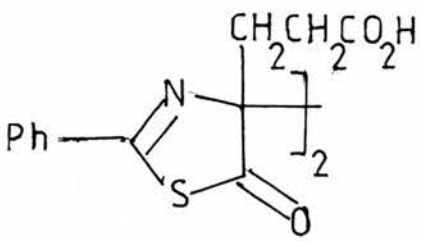
(57) (58) (59)

the equilibrium are favoured by polar solvents whereas strong bases can be used to induce the enolate to form[32]. The enolates of various 4-substituted- 2-benzyloxy-2-thiazolin-5-ones such as (60) have been oxidatively dimerised in the presence of iodine and triethylamine to give mixtures of meso and (±) diastereoisomeric forms (61)[33]. The same reaction has been found to proceed stereoselectively with the 4-phenyl derivative[33].



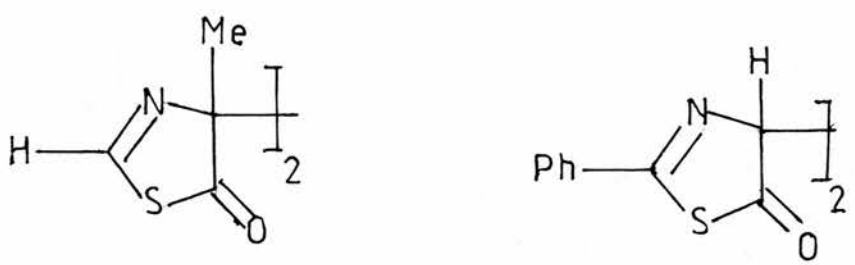
(60) (61)

Aeration in aqueous dioxan has likewise given a 4,4'-bis (2-thiazolin-5-one) (62)[34,35].



(62)

Photo-oxidation was observed to give the dehydro-dimers (63)[36] and (64)[34] in dioxan and dichloromethane respectively.

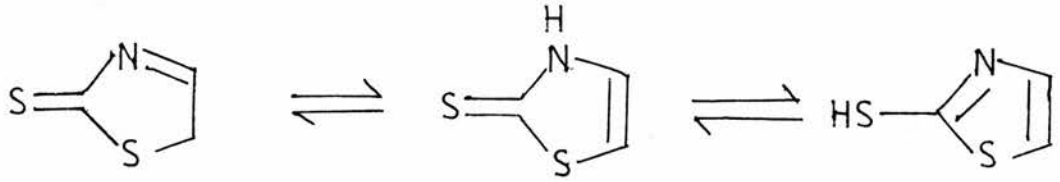


(63) (64)

A mechanism was postulated involving peroxides generated by photo-oxygenation of the solvent[37].

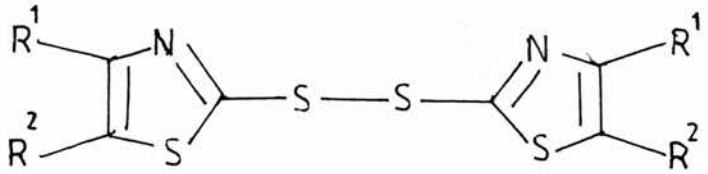
4. 4-Thiazoline-2-thiones

4-Thiazoline-2-thione also exists in a tautomeric equilibrium in which the thione (65) is the predominant form in neutral solution. The major oxidation reactions involve the nucleophilic reactivity of the exocyclic sulphur atom[32].



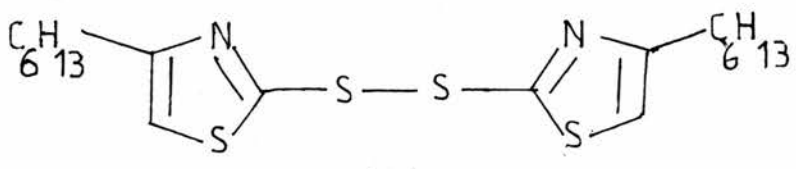
(65)

Mild reagents such as iodine[38] in the presence of base (15% sodium hydroxide) and ammonium persulphate[39] in aqueous solution have given the disulphides (66) and (67) from the corresponding 4-thiazoline-2-thiones.



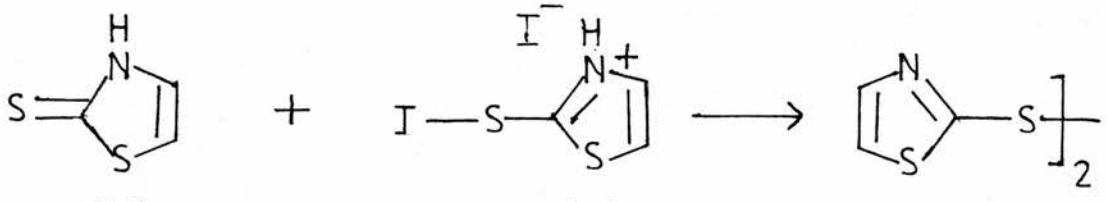
(66) $R^1 = CH_2SO_2Et$, $R^2 = H$ (67) $R^1 = R^2 = Me$

Various disulphides such as (68) have also been obtained on oxidation with hydrogen peroxide in neutral solution[40].



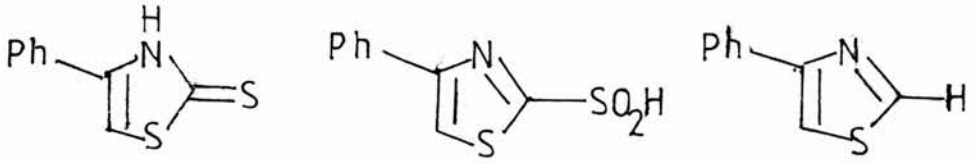
(68)

A mechanism for these reactions involving the attack of the nucleophilic exocyclic sulphur of (69) on the electrophilic exocyclic sulphur of (70) has been suggested[32].



(69) (70)

In an acidic medium such as dilute sulphuric acid, however, using 2 equivalents of hydrogen peroxide, the unstable sulphinic acid (72) has been formed from (71), losing sulphur dioxide to give a good yield of 2-unsubstituted thiazole (73)[41,42].

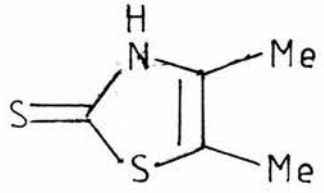


(71) (72) (73)

These 2-unsubstituted thiazoles have also been obtained in high yield as perchlorate salts using 3 equivalents of hydrogen peroxide in acetic acid, reaction of (74) for example giving (75)[43].

(74) (75)

Dinitrogen tetraoxide (1.5 equivalent) in chloroform gives the more highly oxidised sulphonic acid (77) from (76)[39].



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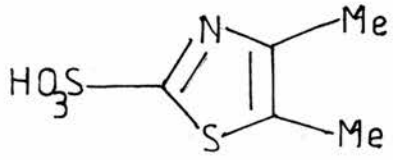
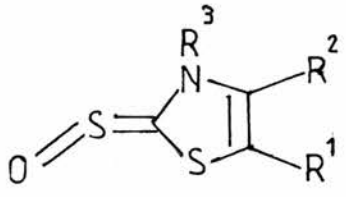


(77)

A final route of oxidation of the 4-thiazoline-2-thiones is the replacement of the exocyclic sulphur atom by oxygen. This is thought to proceed by S-oxidation to sulphine (78) which loses sulphur from a transient oxathiirane[44]. In this way 4-thiazoline-2-thiones may be converted to the corresponding 4-thiazolin-2-ones such as (79) and (80) in the presence of mercury (II) acetate in acetic acid at 50°C[45] or using hydrogen peroxide under basic conditions (10% potassium hydroxide) at 80°C[46].



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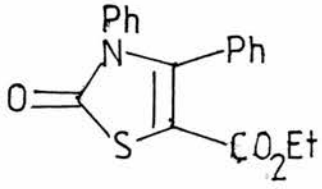

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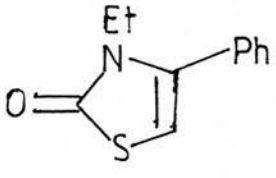


(80)

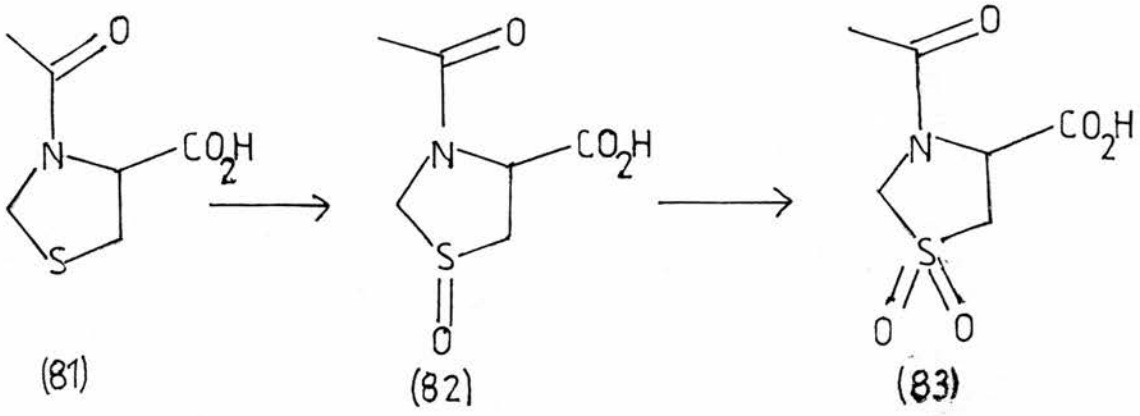
5. Thiazolidines

Thiazolidines undergo oxidation in several different ways. S-oxidation to the sulphoxide or the sulphone occurs readily with

peroxyacids, sodium periodate or permanganate in the case of N-protected thiazolidines. Disulphides or sulphonic acids are formed when the ring system is unprotected in the presence of hydrogen peroxide, iodine or bromine water. Dehydrogenation with D-amino acid oxidase yields 3-thiazolines while lead tetraacetate, photo-oxidation or peroxybenzoic acid oxidise the ring carbon atoms.

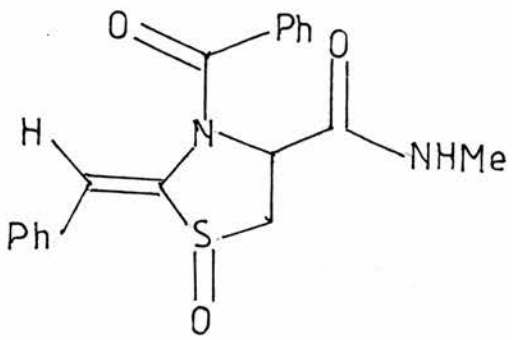
(a) S-oxidation

The first successful S-oxidation was reported in 1937 by Clarke and Ratner[47]. They obtained both the sulphoxide (82) and the sulphone (83) of 3-acetylthiazolidine-4-carboxylic acid (81) using one or two equivalents of hydrogen peroxide in acetone or acetic acid. The same reactions were subsequently repeated with peroxyacetic acid in acetonitrile in moderate yield[48].

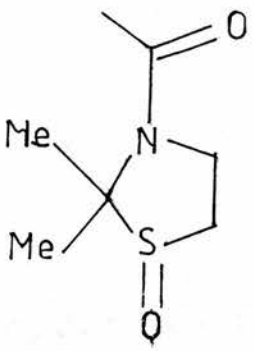


(81) (82) (83)

m-Chloroperoxybenzoic acid (1 equivalent) in dichloromethane was used to obtain 3-acylthiazolidine1-oxides (84)[49] and (85)[50] in very high yield.

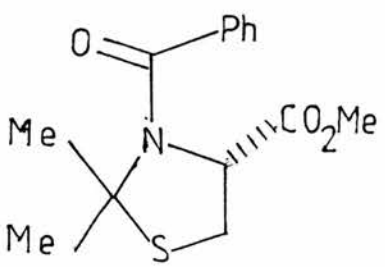


(84)



(85)

Recent work has concentrated on the oxidation of thiazolidines under the influence of one or more chiral centres. Ando and Huang[51] have thoroughly investigated 1,2 and 1,3-asymmetric induction in the formation of sulphoxides from (86), (87), (88) and (89), using m-chloroperoxybenzoic acid, sodium periodate and the Sharpless reagent[52].



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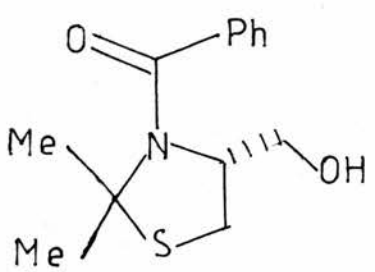
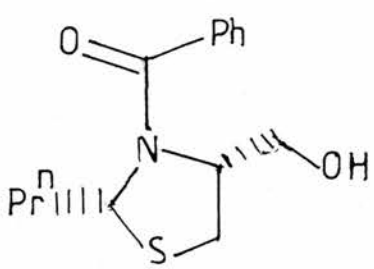


(87)



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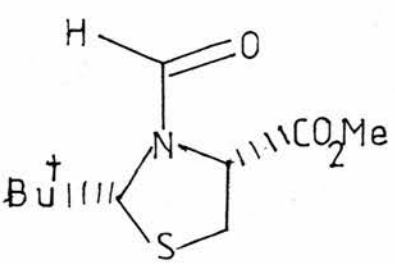
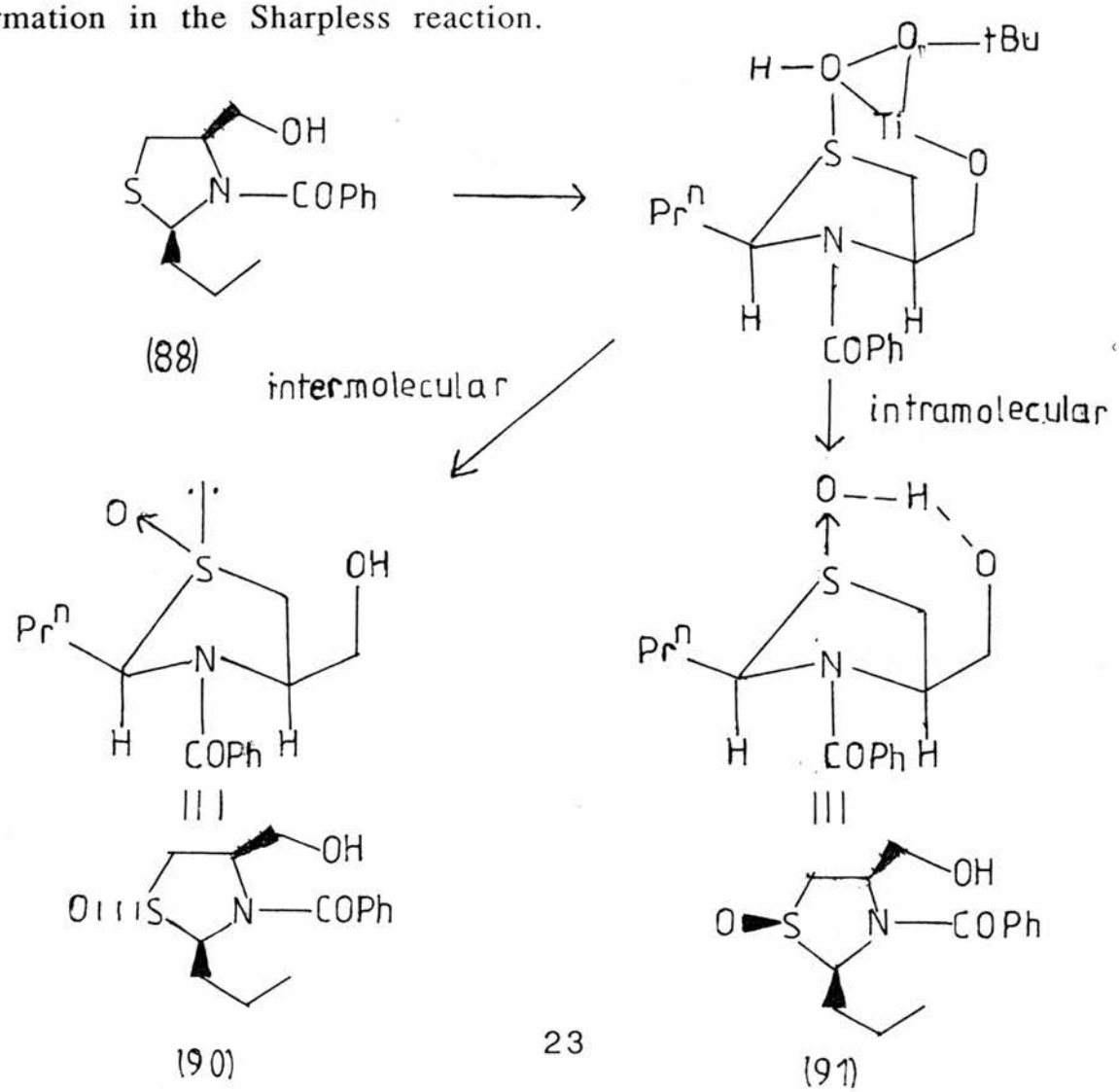


(89)

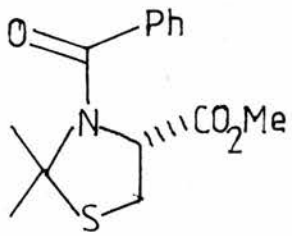
They have found that (89) is exclusively oxidised to the *trans* -sulphoxide solely under the influence of the C-2 centre with all three

reagents. Compound (87) is oxidised stereospecifically to the *cis* -sulphoxide by the Sharpless reagent in contrast to (86) suggesting binding of the titanium complex to the hydroxyl group as the major influence.

In case of (88), oxidation using m-chloroperoxybenzoic acid gave exclusively the *trans* -sulphoxide (90) whereas with the Sharpless reagent a mixture of 3:1 in favour of *cis* -sulphoxide (91) was obtained. The influence of the C-2 centre predominated in the former and the C-4 centre in the latter case. A competing intermolecular reaction to the *trans* -sulphoxide (90) involving the n-propyl group at the C-2 centre was postulated to explain the *trans* -sulphoxide formation in the Sharpless reaction.



Diastereoisomeric sulphoxides have also been obtained with little selectivity from thiazolidines (92)[53], (93)[54] and (94)[55] using m-chloroperoxybenzoic acid in the former case and sodium periodate in the latter two cases.



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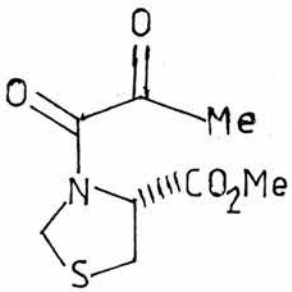
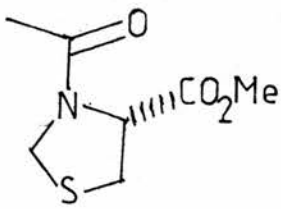


(93)

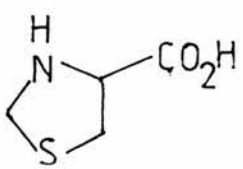


(94)

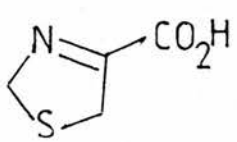
Potassium permanganate was used to convert the mixture obtained from (93) to the sulphone[54].

(b) Dehydrogenation

Only one example of this type of oxidation has been reported. The D-isomer of thiazolidine-4-carboxylic acid (95) was used as a substrate for hog kidney D-amino acid oxidase resulting in its conversion to the 3-thiazoline-4-carboxylic acid (96) using oxygen in a phosphate buffer system at pH8.3[56].



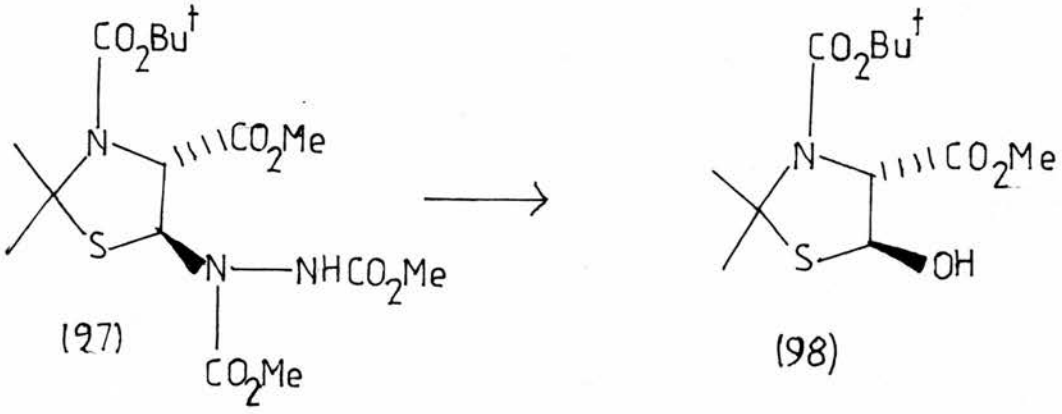
(95)



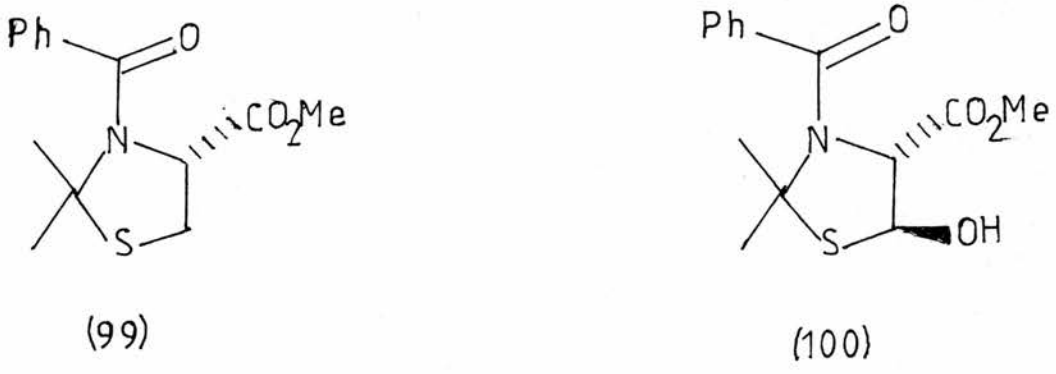
(96)

(c) Oxidation at the ring carbon atoms

The earliest example of this type of reaction was reported in 1966 by Woodward in his classic synthesis of Cephalosporin C[57]. He oxidised the thiazolidine (97) to give the trans-5-hydroxy derivative (98) using two equivalents of lead tetraacetate in boiling benzene.

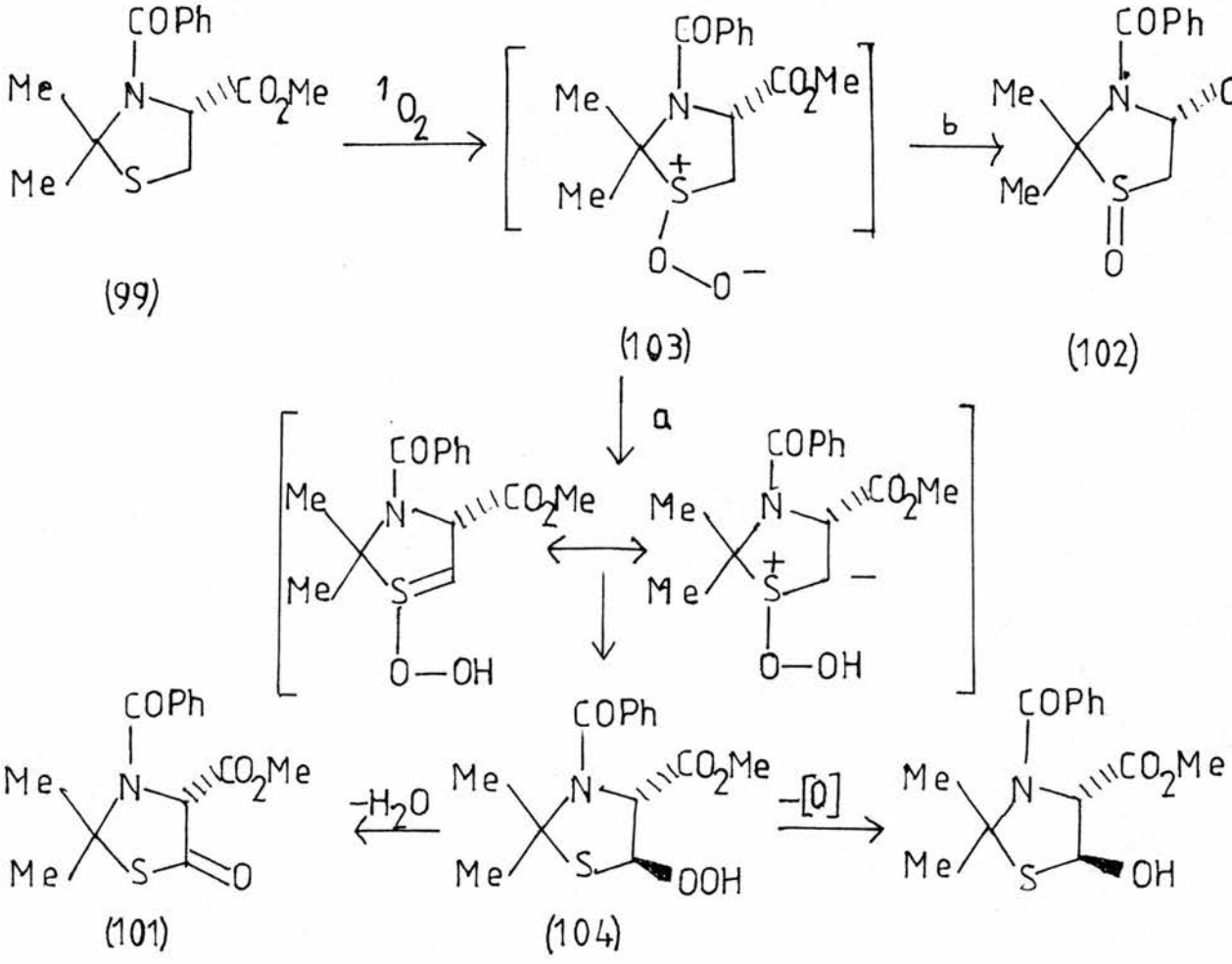


In 1984 Ando prepared 5-(R)-hydroxy derivatives of 3-acyl-2,2-dimethyl-4(R)-substituted thiazolidines (99) by photo-oxidation[58].



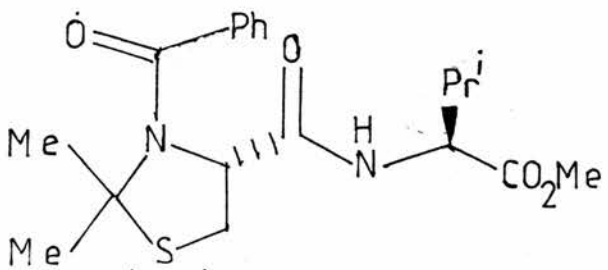
He found that the reaction gave exclusively the 5-(R)-hydroxy product (100) in very high yield on irradiation in tetrahydrofuran with tetraphenylporphyrin as the sensitiser. However in acetonitrile-dimethylsulphoxide, with methylene blue as the sensitiser, two minor

byproducts were formed: the ketone (101) and the sulphoxide (102). He proposed a mechanism involving a Pummerer type rearrangement of a persulphoxide (103) via abstraction of an α-proton (path a) in competition with the sulphoxidation (path b).



The main evidence for the perhydroxy from (104) was the quantitative conversion of added triphenylphosphine or dimethyl sulphide to their respective oxides. Later studies showed that protic solvents such as methanol altered the reaction course by suppressing the proton abstraction to give mainly (102)[59].

A further example of this unusual type of reaction, is the oxidation of (105) to 5-benzoyloxy-2-thiazolidine (106) using perbenzoic acid in carbon tetrachloride at 70°C[60].



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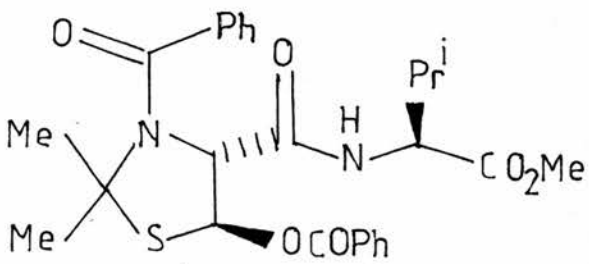
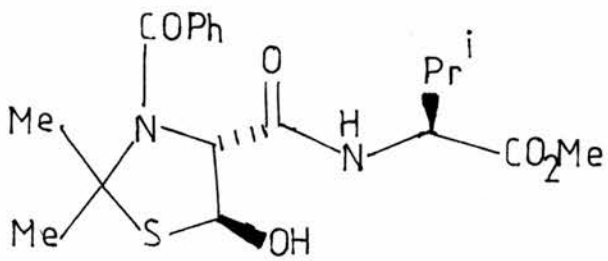


(106)

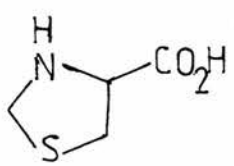
Hydrolysis of the 5-benzoate to the 5-hydroxythiazolidine (107) occurred on heating in aqueous dioxan at 125°C.



(107)

(d) Ring opening

The disulphide (109) was obtained almost quantitatively on oxidation of thiazolidine-4-carboxylic acid (108) with one equivalent of hydrogen peroxide or iodine[47]. Increased concentrations, such as six equivalents of bromine water, give the more highly oxidised sulphonic acid (110)[47].



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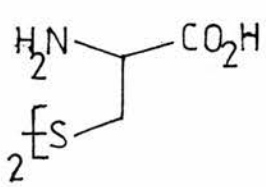

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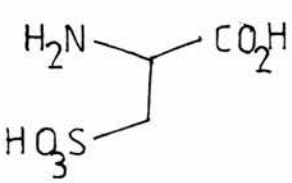


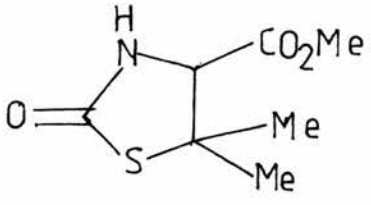
(110)

6. Thiazolidine-2-thiones

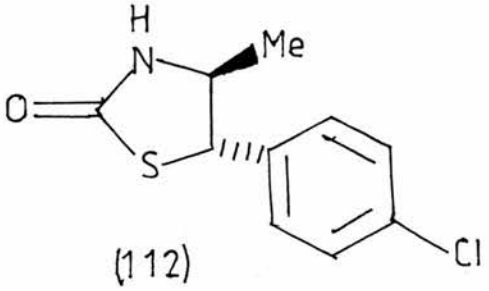
Thiazolidine-2-thiones are able to undergo two types of oxidation: oxidation of the exocyclic sulphur to either the ketone via the sulphine or the disulphide and under more forcing conditions, oxidation of the heterocyclic sulphur to the sulphone. The more facile thione oxidation will be outlined first.

(a) Thione oxidation

Hydrogen peroxide in a basic medium of aqueous potassium hydroxide[61] or methanolic sodium methoxide[62] results in conversion of the corresponding thiones to thiazolidin-2-ones (111) and (112), respectively.



(111)

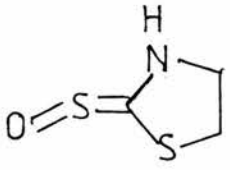


(112)

Both the reactions proceed via the sulphine. This was shown by Walter who isolated an iron (III) complex of the sulphine (113) on adding an aqueous solution of iron (III) chloride to the reaction mixture[63].

Potassium permanganate has also been used to prepare a similar thiazolidin-2-one (114) from the thione under basic conditions with aqueous potassium hydroxide as the solvent[64].

Mercuric oxide in boiling acetic acid has effected oxidation of the corresponding 3-substituted thiazolidine-2-thiones in two instances to give (115)[65] and (116)[66] in high yield.



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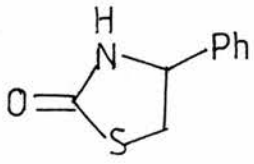
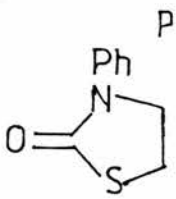


(114)



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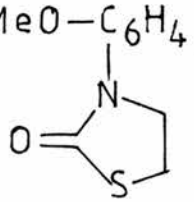
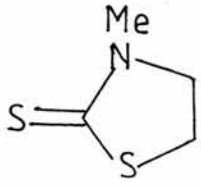


(116)

A more novel and interesting reagent is propylene oxide[67]. A catalytic amount of triethylamine is required in the reaction of (117) which occurs at 170°-180°C in a sealed tube to give 3-methylthiazolidin-2-one (118) in high yield.



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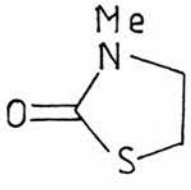
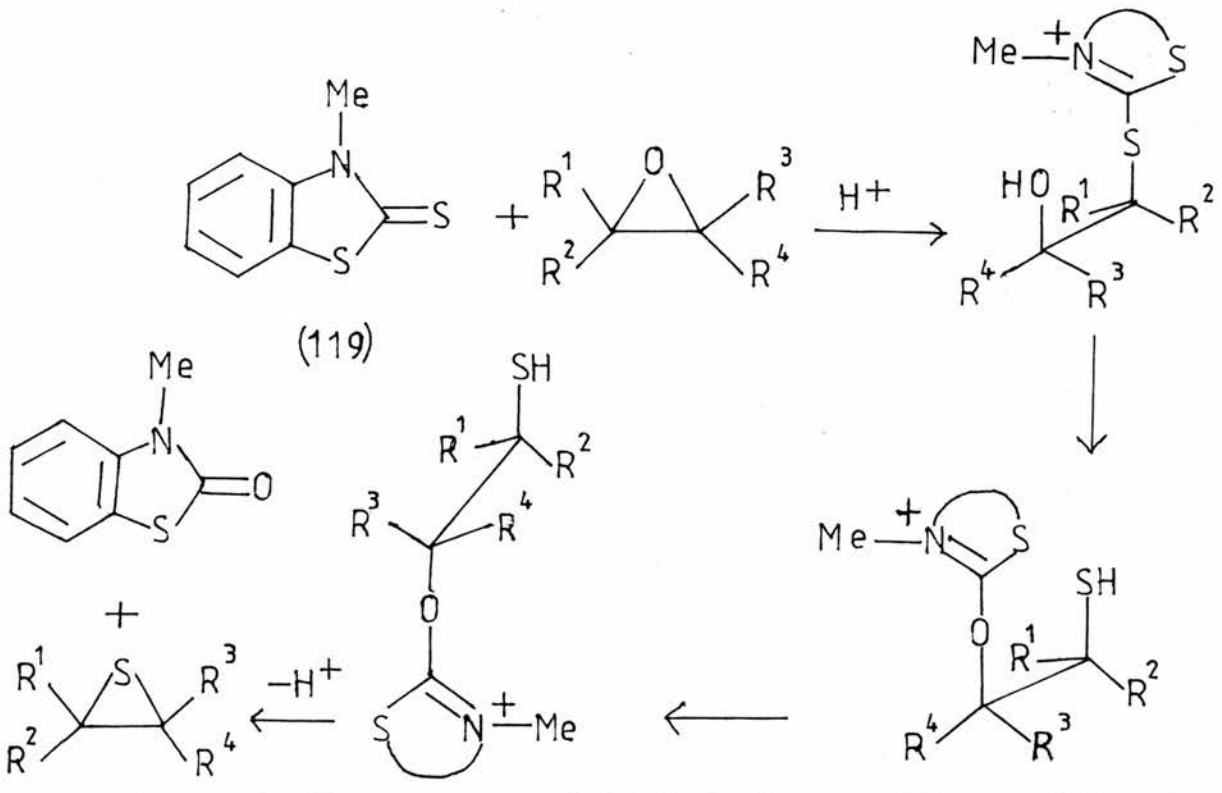


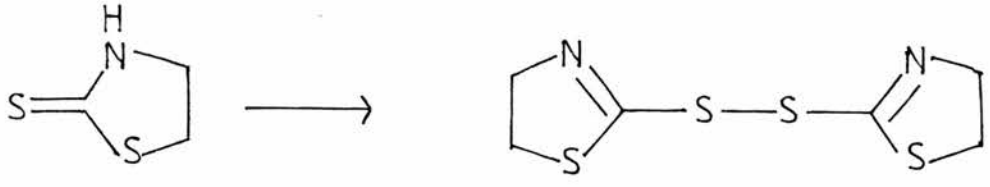
(118)

A mechanism has been outlined in the case of the benzothiazole-2-thione analogue (119) with a trifluoroacetic acid catalyst[68].



(119)

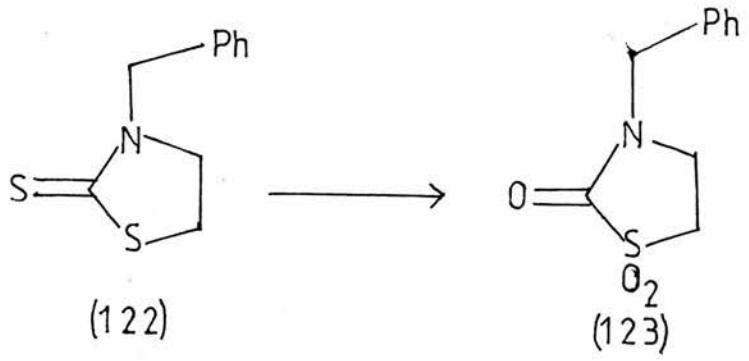
Iodine in the presence of triethylamine provides an interesting disulphide product (121) in good yield from the thiazolidine-2-thione (120)[69].



(120) (121)

(b) Heterocyclic sulphur oxidation

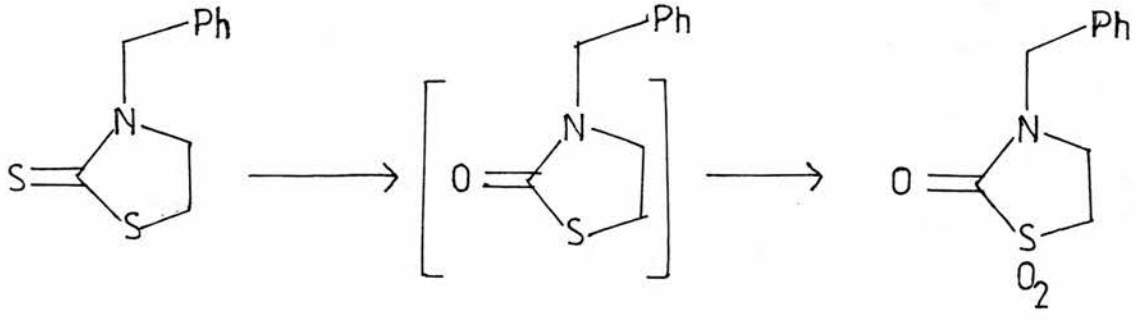
Gaul and Fremuth[70] in 1961 oxidised a range of 3-substituted thiazolidine-2-thiones such as (122) to the corresponding thiazolidin-2-one 1,1-dioxides (123), using six equivalents of



(122) (123)

hydrogen peroxide in acetic acid at 70°C in high yield. This new class of cyclic sulphone was identified by the strong ketone and sulphone absorptions at 1710-1740 cm^{-1} and 1310-1320/1130-1135 cm^{-1} respectively in the infra-red spectra of the products, as well as by the net addition of oxygen in the elemental analysis.

A two stage mechanism was suggested involving the intermediate formation of the thiazolidinone (124), due to the rapidity with which the sulphur separated, coupled with what appeared to be a much slower second stage to the thiazolidin-2-one 1,1-dioxide (123).



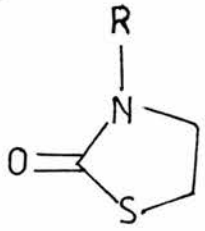
(122) (124) (123)

7. Thiazolidin-2-ones

One main type of oxidation has been reported for the thiazolidin-2-one: oxidation on the heterocyclic sulphur atom to give either the cyclic sulphoxide or sulphone.

Examples of thiazolidin-2-one oxidation are rare and only two reports have appeared on the subject.

Oxidation of (125) with m-chloroperoxybenzoic acid in dichloromethane at 0-5°C gave the cyclic sulphoxide (126) (one equivalent) or the cyclic sulphone (127) (two equivalents)[71].



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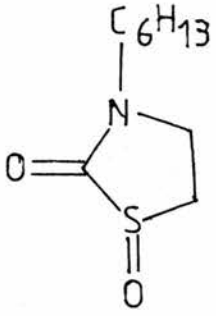

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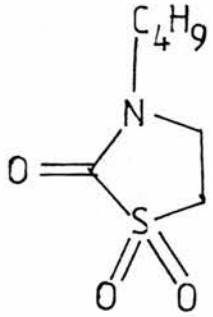
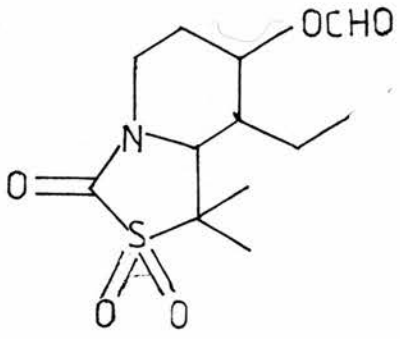


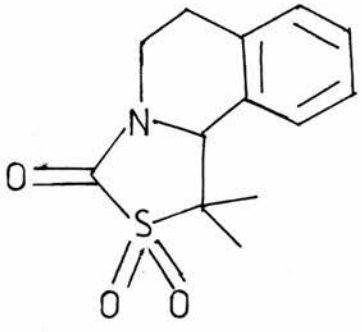
(127)

The same reagent in chloroform provided the bicyclic 1,1-dioxide (128) from the corresponding thiazolidinone in very high yield using



(128)

3 equivalents at room temperature[72]. Two closely related bicyclic thiazolidin-2-ones also undergo oxidation on sulphur. Oxidation with peroxyformic acid using twenty-five equivalents occurred readily at room temperature to give exclusively the 1,1-dioxides (129) and (130)[72].



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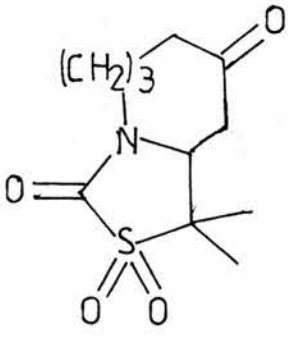


(130)

8. Thiazolidin-4-ones

The oxidation of thiazolidin-4-ones has been much studied and has been reviewed in depth by Brown[73] in 1961 and briefly again in 1979 by Newkome[74].

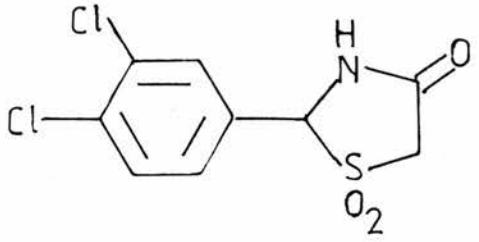
S-oxidation to the 1-oxide or 1,1-dioxide is the principal mode of oxidation. Peroxyacetic acid, in the presence or absence of acetic anhydride gives both S-oxides by varying the quantity of reagent.

Selective oxidation to the sulphoxide is possible with sodium periodate, hydrogen peroxide or chloramine - T. Stronger reagents such as potassium permanganate and chromium trioxide give the sulphone. Hydrogen peroxide catalysed by ammonium molybdate also gives the sulphone.

Photo-oxidation is a minor reaction yielding dimeric species. Ring destruction occurs with drastic conditions such as 6M nitric acid.

(a) S-oxidation

Potassium permanganate has been widely used to obtain the sulphone. Several examples of both 2- and 3-substituted halophenyl derivatives such as (131)[75], (132)[76], (133)[77], (134)[78] and (135)[79]



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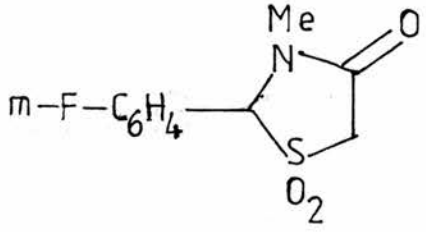

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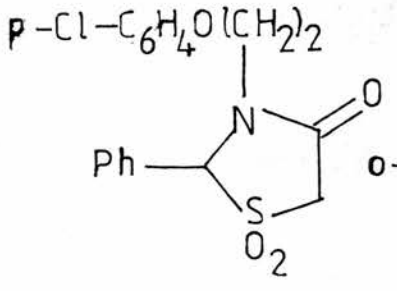

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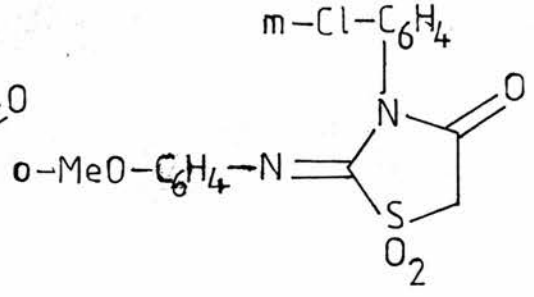

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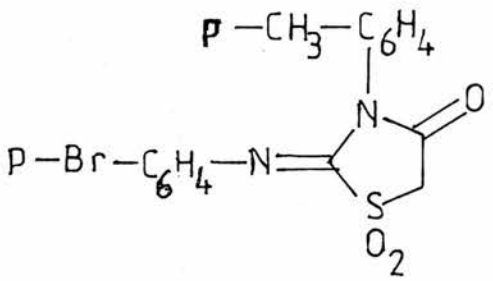

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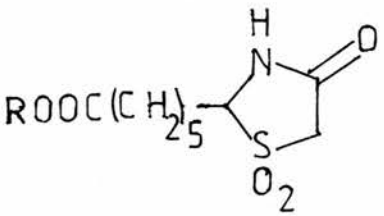

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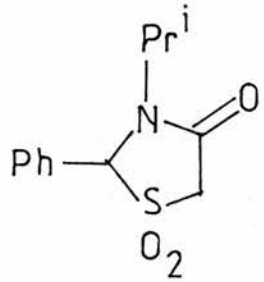
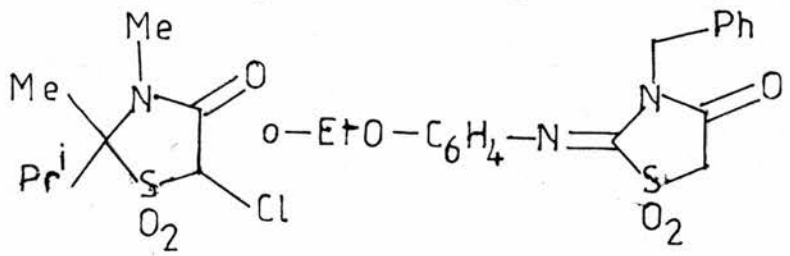


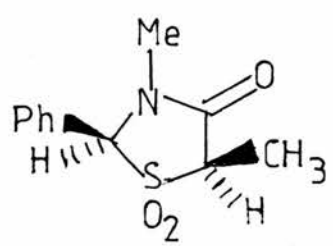
(137)

have been formed from the corresponding thiazolidinones and investigated for fungicidal activity. Other 2- and 3-substituted derivatives such as (136)[80], (137)[81], (138)[82], (139)[83] and (140)[84] have also been obtained using the same reagent (two equivalents) at



(138)

(139)



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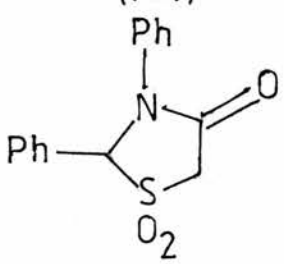
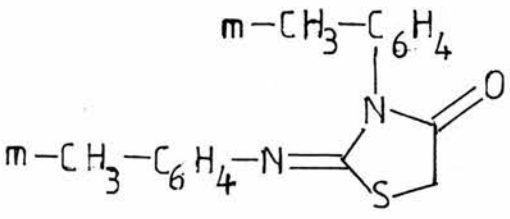


(141)

room temperature in acetic acid/water. Compound (141) has been synthesised with sodium permanganate in acetic acid/water/dioxan at room temperature[85].

The sulphone (142) has been formed using chromium trioxide[86].

Peroxyacetic acid (two equivalents) at room temperature has given the sulphone (136)[80]. The formation of the sulphone (143) requires an elevated temperature of 100°C due to the deactivation of



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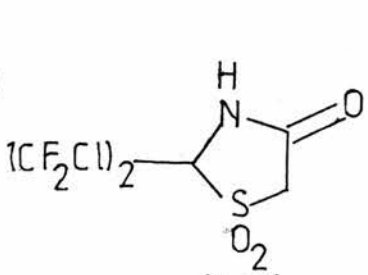
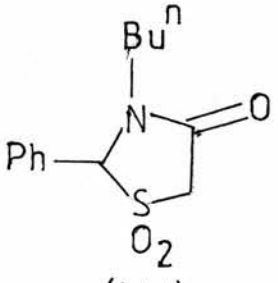


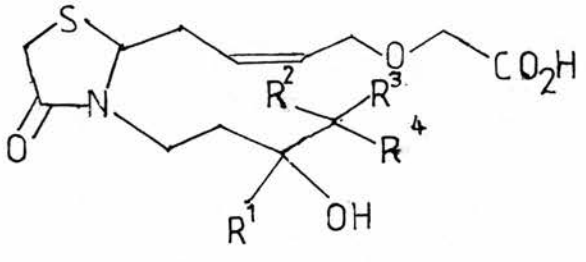
(143)



(144)

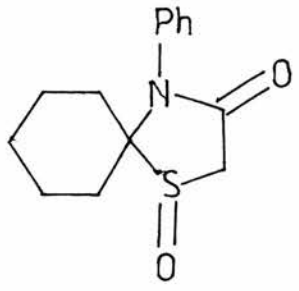
the sulphur atom by the electron withdrawing trihaloalkyl groups[87]. Peroxyacetic acid and acetic anhydride at 60°C, has been used to obtain the sulphone (144) from the corresponding thiazolidin-4-one[88].

Hydrogen peroxide in ethanol or acetic acid in the presence of an ammonium molybdate catalyst at 0-30°C was used to obtain the sulphone of a molecule (145) which had prostaglandin-like biological activity[89].



(145)

Various sulphoxides such as (146) were synthesised using peroxyacetic acid (1.15 equivalents) at 0-5°C in high yield[90].



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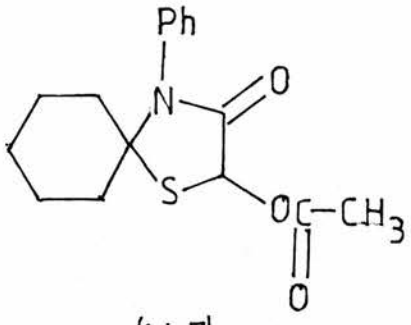
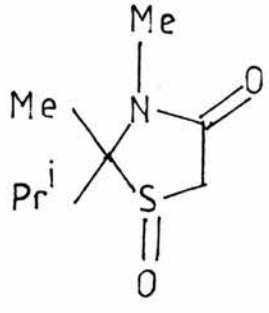


(147)

The Pummerer products such as (147) were obtained using either acetic anhydride or trifluoroacetic anhydride as the electrophile.

Sulphoxide (148) was likewise obtained with peroxyacetic acid[82].



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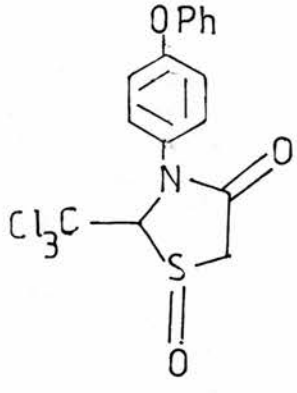
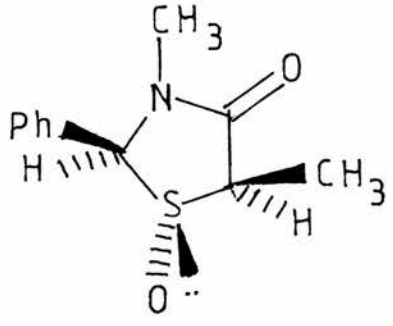


(149)

Addition of acetic anhydride and a temperature of 55°C were necessary to give the 1-oxide (149) in high yield, the harsher conditions being required due to the deactivating effect of the trichloroalkyl group[91].

Diastereoisomeric sulphoxides (150) and (151) were prepared in low yield using sodium periodate (one equivalent) in aqueous



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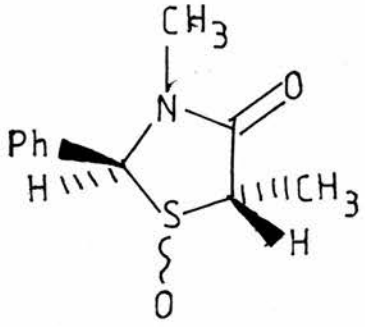
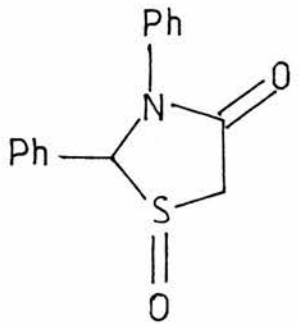


(151)

methanol at 0°C[84]. X-ray crystallography confirmed the structure (150) of the *cis*- sulphoxide. The sulphoxide of prostaglandin analogue (145) was likewise prepared with sodium periodate[89].

A more interesting reaction involves the action of chloramine-T to form the 1-oxides (152) and (153)[92]. The reaction proceeds in dioxan/water at the temperature of a hot water bath to give a 50% yield, via a complex mechanism[93].



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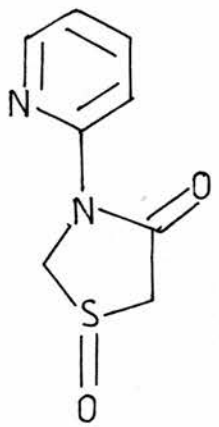
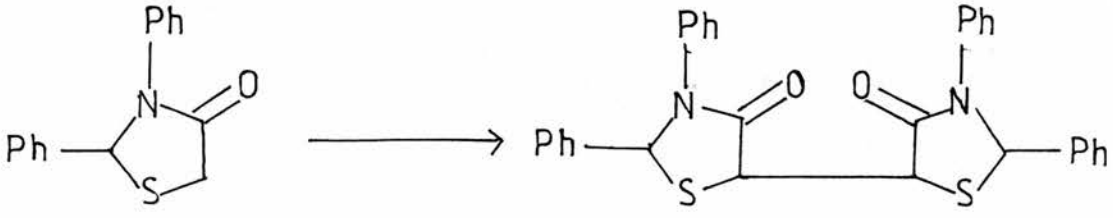


(153)

(b) Photo-oxidation

Photo-oxidation of 2,3-diphenylthiazolidin-4-one (154) in dichloromethane gives the dimeric 4,4'-bisthiazolidin-2-one (155) due to the nucleophilicity of the C-5 atom in its enol form[94].



(154) (155)

(c) Ring destruction

Early oxidation studies in 1953 showed that 6N nitric acid oxidised (136) in a steam bath to give a mixture of adipic, oxalic and pimelic acids[80]. The sulphur was oxidised to sulphate and the nitrogen lost as ammonia, with evolution of carbon dioxide.

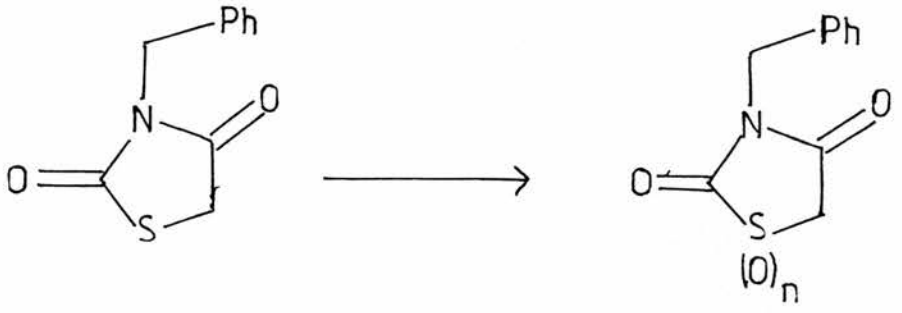
9. Thiazolidine-2,4-diones and Thiazolidine-2-thione-4-ones

Oxidation reactions of these two closely related ring systems are considered together. S-oxidation to the sulphoxide or to the sulphone

occurs with m-chloroperoxybenzoic acid or potassium permanganate. Further oxidation of the ring carbon atoms to the trione via an enol intermediate has been achieved using selenium dioxide. Ring opening to give N-acyl sulphonic acids has occurred using an excess of hydrogen peroxide. Oxidative dimerisation involving selenium dioxide and a base catalyst is also known.

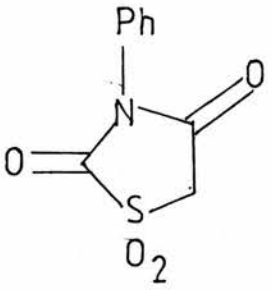
In 1986 Hanefeld and Jalili oxidised thiazolidine-2,4-diones such as (156) with m-chloroperoxybenzoic acid to give the 1-oxide (157, n=1) (1.5 equivalent), and the 1,1-dioxide (157, n=2) (2.5 equivalent, 60°C)[95].

The sulphone (158) was obtained with potassium permanganate in acetic acid/water at 0°C in very high yield[96].

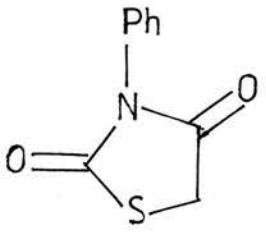


(156) (157)

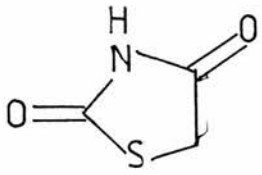
The selenium dioxide oxidation of compound (159) as well as the N-unsubstituted analogue (160) was investigated in an attempt to introduce a third oxo-group into the thiazole ring[97]. Oxidation was only successful in the unsubstituted case (160) to give the



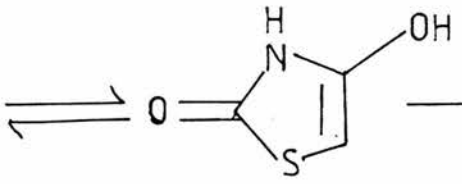
(158)



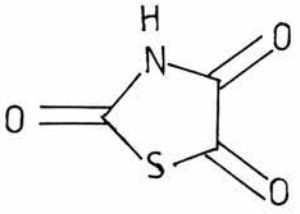
(159)



(160)



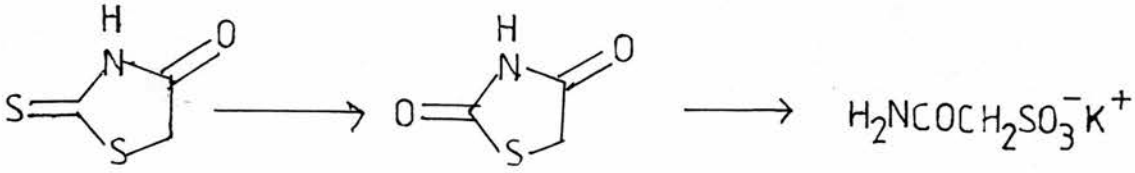
(161)



(162)

thiazolidine-2,4,5- trione. Compound (159) failed to react suggesting that the oxidation occurred on the enol form (161), and that the presence of the aromatic nucleus on the nitrogen atom in (159) was sufficient to prevent enolisation by a small negative inductive effect.

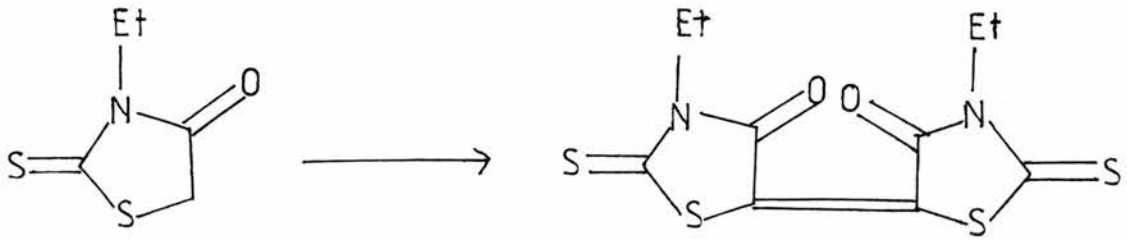
Hydrogen peroxide (4-5 equivalents) was required to convert the 2-thione function in rhodanine (163) to the 2-one (160) in an aqueous solution of 1M barium hydroxide[98].



(163) (160) (164)

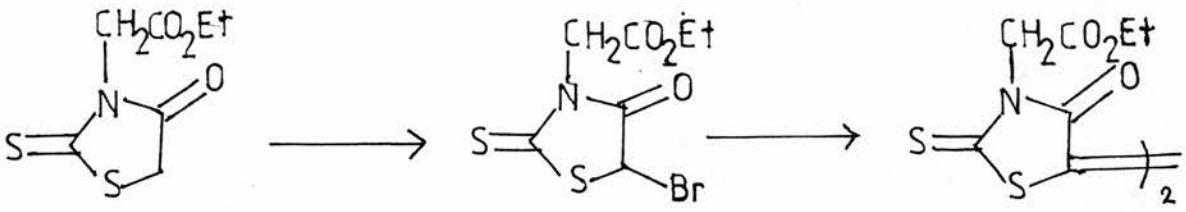
Further hydrogen peroxide oxidation in the presence of 2 moles of potassium carbonate gave the ring opened sulphoacetamide (164). In all these reactions the exocyclic sulphur atom was lost as sulphate anion.

A novel and interesting oxidation involves the dimerisation of 3-ethylthiazolidine-2-thione-4-one (165) at the C-5 position on treatment with selenium dioxide in the presence of a tertiary amine catalyst[99].



(165) (166)

A similar transformation has been reported in which (167) was oxidised by one equivalent of bromine to give (168), followed by base induced dimerisation using triethylamine at room temperature to give (169)[100].



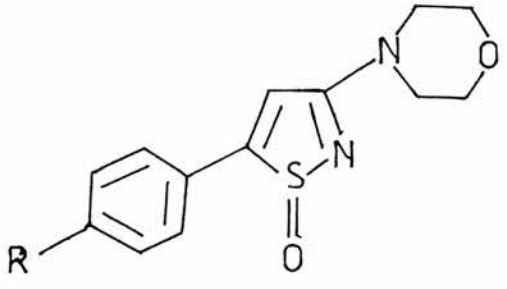
(167) (168) (169)

B. Isothiazole derived ring systems

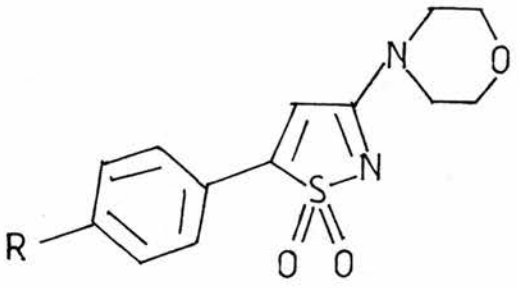
1. Isothiazoles

The major reaction of isothiazoles is S-oxidation to the 1-oxide or 1,1-dioxide. Only two successful S-oxidations of this relatively inert parent ring have been reported[101].

Bruno and Purrello in 1966 synthesised both the sulphoxides (170) and the sulphones (171)[102]. Nitric acid in acetic acid or sulphuric acid gave the intermediate sulphoxides (170) which could then be further oxidised using peroxyacetic acid to the sulphones (171). A one step oxidation to the sulphones (171) could be achieved using peroxyacetic acid.

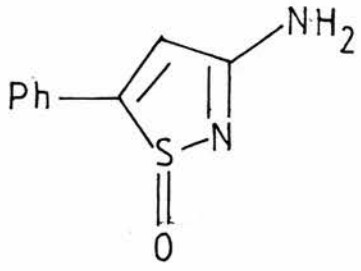


(170) R = H, NO_2



(171) R = H, NO_2

Wooldridge[103] in 1972 used a very powerful peroxyacid, peroxysulphuric acid to prepare 3-amino-5-phenylisothiazole 1-oxide (172).

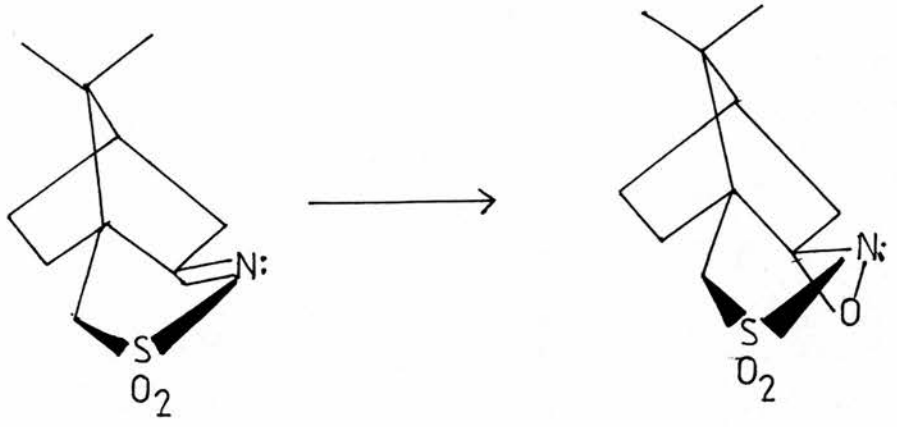


(172)

The main evidence for the S-oxide structure was the strong infra-red band at 1040 cm^{-1} due to the S=O stretch.

2. 2-Isothiazolines

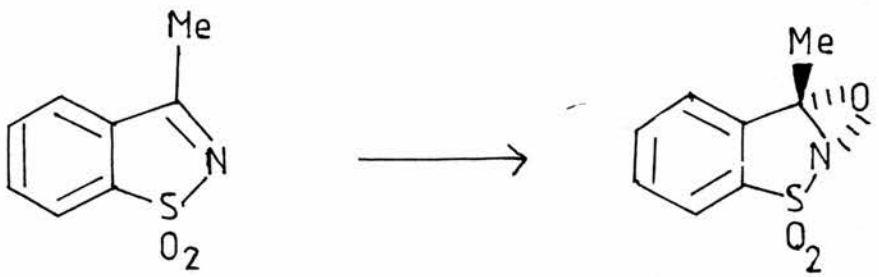
Epoxidation of a 2-isothiazoline 1,1-dioxide (173) has been described using potassium peroxymonosulphate/18-crown-6 in benzene/water to give exclusively the (+)-(2R,8aS)-oxaziridine (174) in almost quantitative yield due to steric hindrance involving the camphor ring[104].



(173) (174)

3. Benzisothiazoles

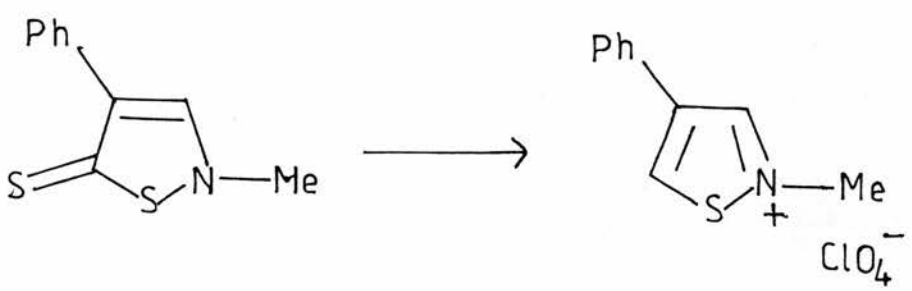
Benzisothiazole 1,1-dioxide (175) behaves in the same way as a 2-isothiazoline dioxide in its reactivity, undergoing epoxidation to the sulphonyl oxaziridine (176) with one equivalent of m-chloroperoxybenzoic acid in chloroform in very high yield[105].



(175) (176)

4. 3-Isothiazoline-5-thiones

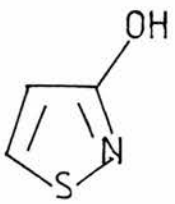
3-Isothiazoline-5-thiones such as (177) undergo reaction with three equivalents of peroxyacetic acid to give isothiazolium salts (178) on addition of 70% perchloric acid[43]. The ring system is reduced, but the exocyclic sulphur atom is oxidised and eliminated as a sulphate.



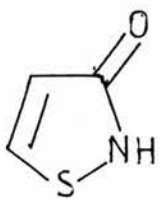
(177) (178)

5. 4-Isothiazolin-3-ones

The tautomeric equilibrium existing in the 4-isothiazolin-3-one system has been investigated in detail by Chan, Crow and Gosney[106]. The 3-hydroxy form (179) predominates in non-polar solvents with an increasing contribution from the 3-keto form (180) in solvents of higher polarity.



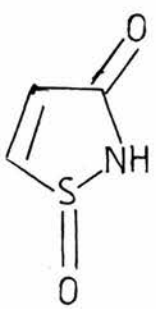
(179)



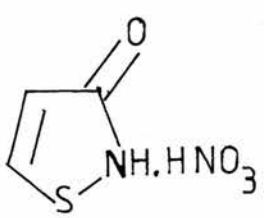
(180)

Substituted examples such as the 5-methyl analogue exhibit similar lactim-lactam tautomerism.

Lewis prepared the first example of an unsubstituted 4-isothiazoline- 1-oxide (181) in 1971 from the parent ring (180) using either nitric acid, dinitrogen tetroxide or chromic acid[107]. In the nitric acid oxidation an intermediate nitrate salt (182) was isolated and subsequently thermally decomposed (at 80°C) to (181).

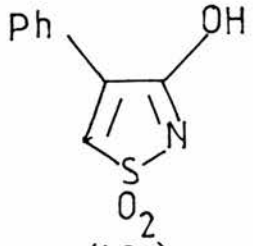


(181)

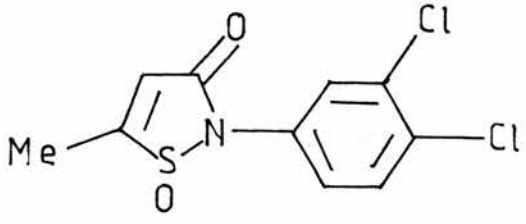


(182)

Peroxyacetic acid at 90°C has also been used to obtain the 3-hydroxy-4-phenyl-isothiazole 1,1-dioxide (183)[108].



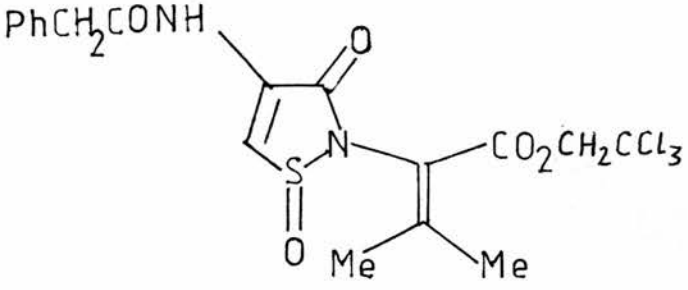
(183)



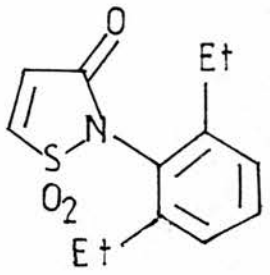
(184)

Several examples of 2-substituted 4-isothiazolin-3-ones have been investigated. m-Chloroperoxybenzoic acid was used by Lewis in 1971 to obtain both the 1-oxide (184) and the corresponding 1,1-dioxide by varying the quantity of the reagent from one to two equivalents[107].

Kamiya has synthesised a number of complex substituted 1-oxides such as (185) using the same reagent[109,110]. The sulphone



(185)

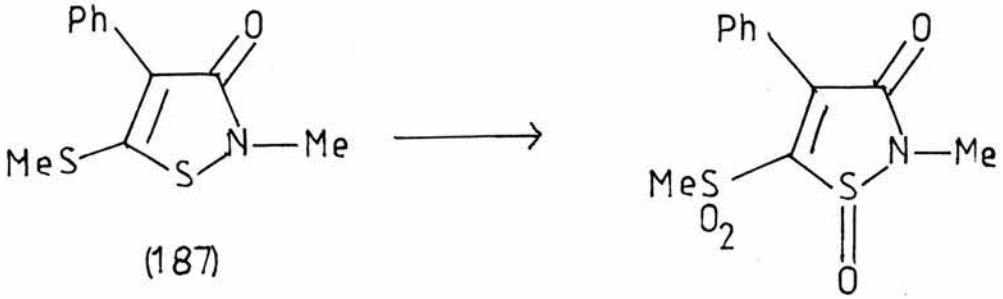


(186)

(186) has also been obtained by oxidation in high yield and is reported to show fungicidal activity[111].

Peroxyacetic acid at 90°C has been used to obtain the 1-oxide

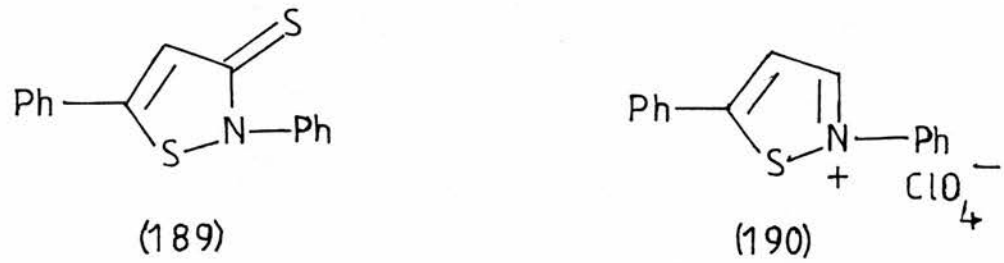
(188) from the isothiazolin-3-one (187) with concomittant oxidation of the less resistant exocyclic methylthio group to the sulphone[108].



(187) (188)

6. 4-Isothiazoline-3-thiones

This class of ring system undergoes a similar oxidation to the 3-isothiazoline-5-thiones giving for example, the isothiazolium salt (190) on treatment of (189) with peroxyacetic acid and perchloric acid[43].

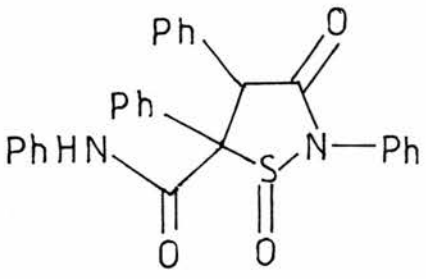


(189) (190)

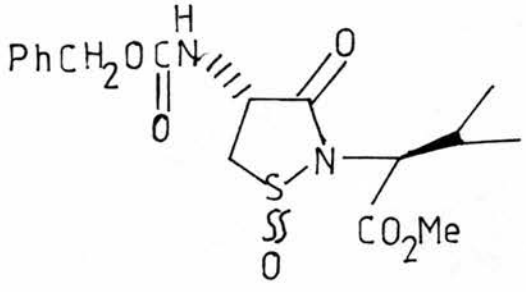
7. Isothiazolidines

Very few examples of isothiazolidine 1-oxides or 1,1-dioxides synthesised by direct ring oxidation have been reported, despite the important pharmacological activities of various sultams[112]. The major route has involved base induced ring closure of sulphonamides[113].

Isothiazolidin-3-one 1-oxides such as (191) have been prepared by oxidation using one-equivalent m-chloroperoxybenzoic acid at room temperature[114].



(191)



(192)

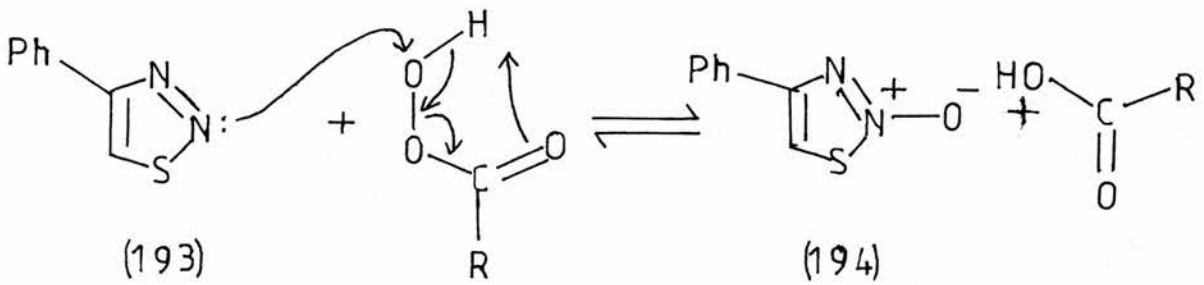
A mixture of isomeric sulphoxides (192) has been converted into the corresponding sulphone with the same peroxyacid[115].

C. Thiadiazole ring systems

1. 1,2,3-Thiadiazoles

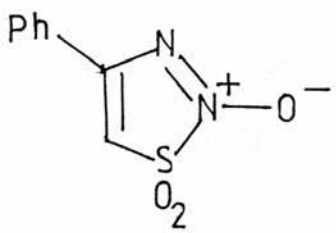
The oxidative properties of this heterocyclic system have only recently been investigated. Reaction with one equivalent of peroxyacetic acid at 50°C or m-chloroperoxybenzoic acid resulted in

the formation of 1,2,3-thiadiazole 2-oxide (194) in an equilibrium involving the starting heterocycle (193)[116].



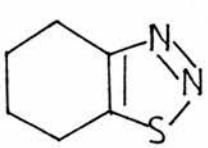
(193) (194)

Further oxidation in the presence of excess peroxyacetic acid led to a mixture of the 2-oxide (194) and the 1,1,2-trioxide (195).

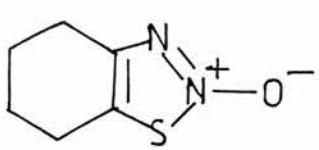


(195)

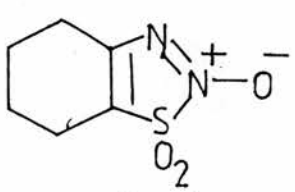
A similar reaction was also observed, in the action of peroxyacetic acid on various cycloalkeno-1,2,3-thiadiazoles such as



(196)



(197)

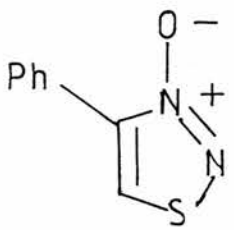


(198)

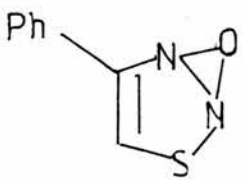
(196)[117]. A mixture of the 2-oxide (197) and 1,1,2-trioxide (198) was formed. The yields of the 2-oxide were considerably higher than

before, but it still gave a very low recovery of the trioxide (198) on further oxidation.

Later work confirmed the structure of both the 2-oxide (194) and the 1,1,2-trioxide (195). The 2-oxide (194) was photolysed to give the 3-oxide (199) <u>via</u> an oxadiaziridine intermediate (200)[118]. The



(199)

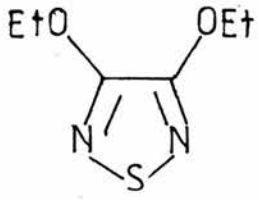


(200)

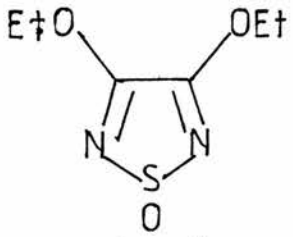
crystal structure of the 3-oxide (199) gave positive proof of its identity along with the earlier infra-red and elemental analytical data[119]. Thus the 2-oxide structure (194) could also be assigned.

2. <u>1,2,5-Thiadiazoles</u>

The first example of oxidation to a 1,2,5-thiadiazole 1-oxide was reported in 1981 by Karady[120]. Previous syntheses of S-oxides were <u>via</u> condensation reactions[121]. Karady used one equivalent of m-chloroperoxybenzoic acid to give the sulphoxide (202) from (201)[120].

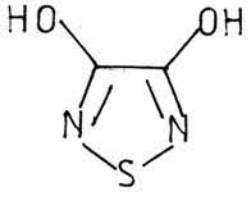


(201)

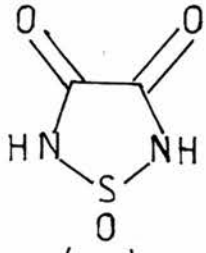


(202)

A more complex oxidation occurred using 2,3-dicyano-5,6-dichloroquinone (DDQ) in dioxan at 0°C in the conversion of 3,4-dihydroxy- 1,2,5-thiadiazole (203) to the 1-oxide (204) in almost quantitative



(203)



(204)

yield[122]. The tautomeric equilibrium was shifted over to favour the non- aromatic keto-form (204) by the sulphur becoming pyramidal on oxidation[120].

3. 1,3,4-Thiadiazolines

A variety of oxidation reactions are known for 1,3,4-thiadiazolines. S-oxidation to the sulphoxide or sulphone occurs with monoperoxyphthalic acid, m-chloroperoxybenzoic acid, peroxyacetic acid and potassium permanganate. Dehydrogenation to the fully aromatic ring is effected with peroxyacetic acid, potassium

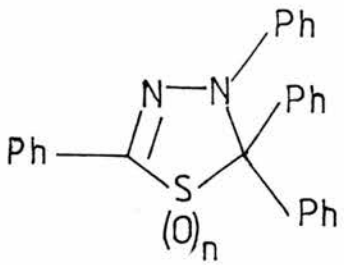
permanganate and ferric chloride.

1,3,4-Thiadiazolines have different isomeric forms. These will be considered under the type of oxidation.

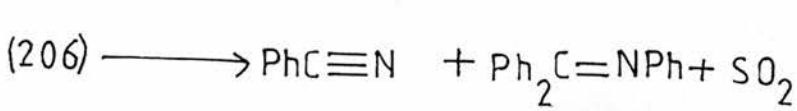
(a) S-oxidation

(i) Δ^2-1,3,4-Thiadiazolines

Up to the 1970's the major method for the synthesis of 1,3,4-thiadiazoline 1,1-dioxides was the Staudinger-Pfenninger reaction involving diazo compounds and sulphur dioxide[123-5]. In 1973 monoperoxyphthalic acid at room temperature was used to obtain both the 1-oxide (205) and the 1,1-dioxide (206)[126].



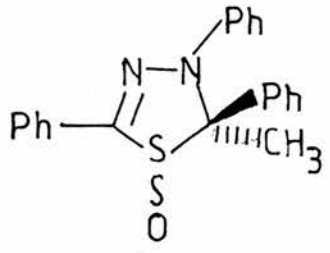
(205) n=1
(206) n=2



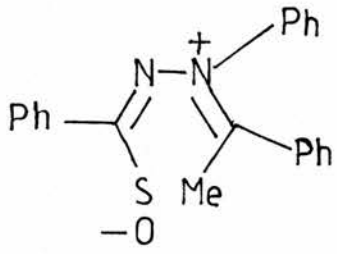
(207)

The 1,1-dioxide (203) structure was proved by thermolysis to benzonitrile and imine (207) by extrusion of sulphur dioxide.

Diastereoisomeric sulphoxides (208) in an E:Z ratio of 1:2 were obtained on treating the corresponding thiadiazoline with m-chloroperoxybenzoic acid at room temperature[126,127]. The change to a 2:3 ratio on gentle warming indicated a ring opening-ring closure mechanism via (209).

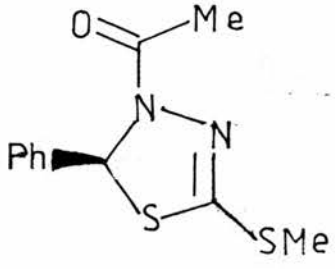


(208)



(209)

Oxidation with m-chloroperoxybenzoic acid generally gives the sulphoxide resulting from oxidation on the least hindered side of the molecule[128-130] a point illustrated by the conversion of (210) to



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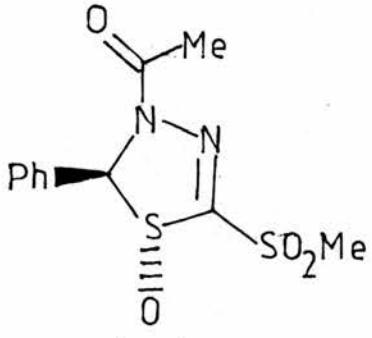


(211)

sulphoxide (211)[131,132]. With potassium permanganate full oxidation to the 1,1-dioxide occurs accompanied in both cases by oxidation of the thioether side-chain[131].

(ii) Δ^3-1,3,4-Thiadiazolines

In 1972 Barton and co-workers converted the Δ^3-1,3,4-thiadiazoline (212) first to the 1-oxide (213, n=1) and then

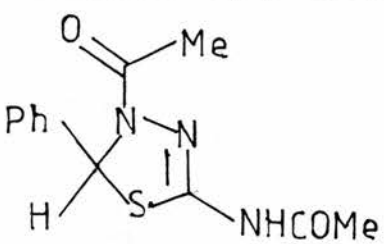
into the 1,1-dioxide (213, n=2) using peroxyacetic acid at room temperature in quantitative yield[133]. Subsequent elimination of N_2 and SO_2 provided a useful route for the construction of sterically crowded alkenes.

(212) (213)

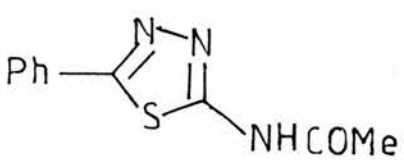
(b) Dehydrogenation

(i) Δ^2-1,3,4-Thiadiazolines

Potassium permanganate in acetic acid has been used to oxidise the 1,3,4-thiadiazoline (214) to the corresponding thiadiazole (215)[131,134]. This was said to occur via deacylation of the intermediate 1,3,4-thiadiazoline 1-oxide (216).



(214)



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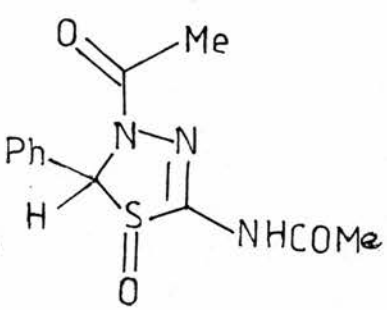
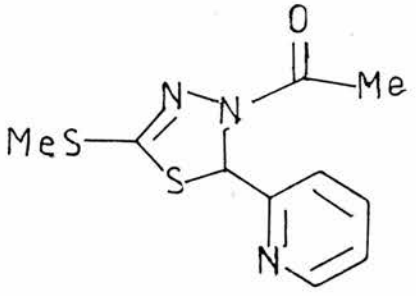


(216)

An alternative reagent was ferric chloride in water at 100°C in the case of the 2-amino derivative of (214)[134].

A related reaction is the aromatisation of the 1,3,4-thiadiazoline



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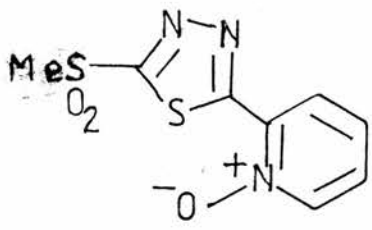


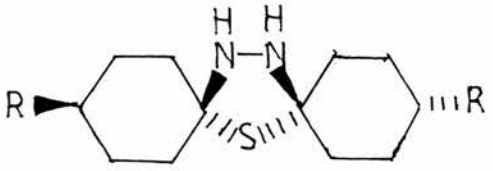
(218)

(217) with concomittant oxidation of the methylthio group and pyridine ring, to give (218) using an excess of peroxyacetic acid at 90°C[135].

4. 1,3,4Thiadiazolidines

The main oxidation reaction is dehydrogenation resulting in an unsaturated ring at the 3-position.

Lead tetraacetate[133,136], dichlorodicyanobenzoquinone[133] and manganese dioxide[136] have been used at 0°C up to room temperature to oxidise the 2,5-bis(cyclohexylidene)-1,3,4-thiadiazolidines (219) to the Δ^3-thiadiazolines (220) in very high yield.

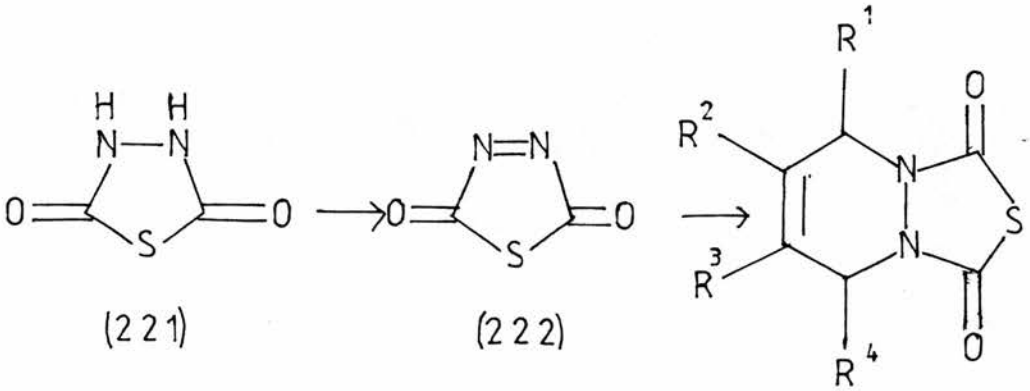


(219) R=H, OCH_2Ph

(220)

1,3,4-thiadiazolidine-2,5-dione (221) undergoes convertion to the Δ^3-thiadiazoline 2,5-dione (222) a powerful but unstable

dienophile which can then be trapped at low temperatures to give a Diels Alder adduct (223). Lead tetraacetate[137,138], t-butyl hypochlorite[138] and cupric chloride[138] at -78°C or 0°C have been used in this conversion.

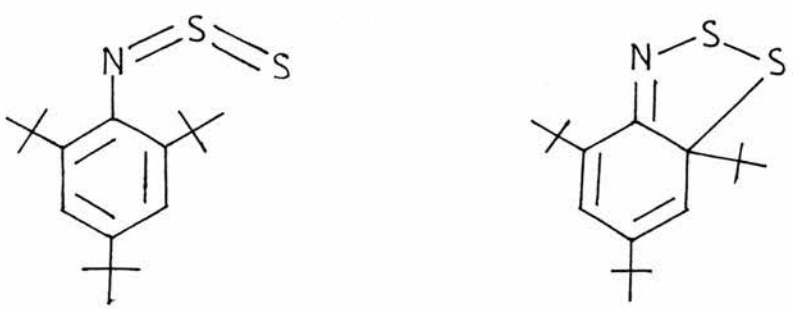


(221) (222) (223)

D. Dithiazole ring systems

1. Δ^3-1,2,3-Dithiazolines

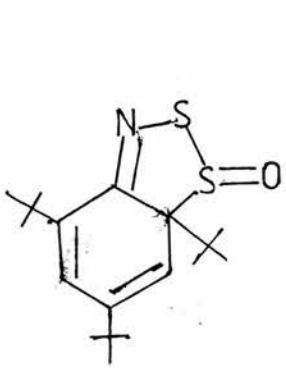
The first example of a 1,2,3-dithiazoline S-oxide was reported by Inamoto in 1979, while investigating the stable thiosulphinylamino compound (224) of which heterocycle (225) is a valence isomer[139].



(224) (225)

Treatment of the latter with a deficiency of m-chloroperoxybenzoic acid in dichloromethane at 40°C gave 2 major products (226), (227) together with (228) as a very minor product.

The structure of the new thiosulphinate (226) was determined by X-ray crystallography. The identity of (227) was established by spectral data and by alkaline hydrolysis giving (229)[140,141]. The



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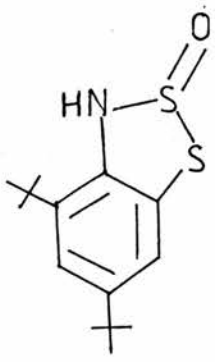

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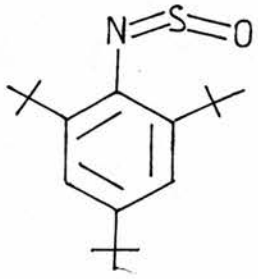

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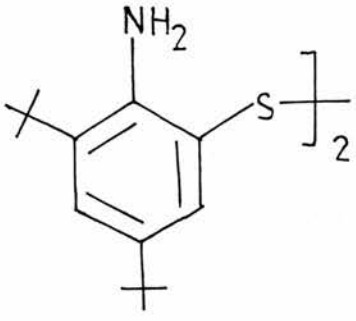

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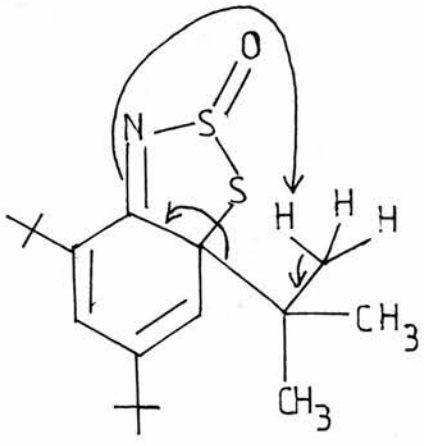


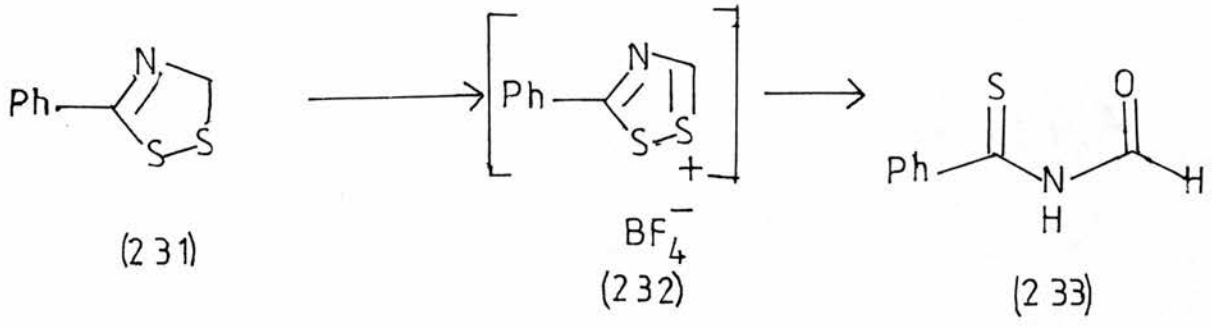
(230)

N-sulphinyl-aniline (228) was compared with the authentic sample obtained by the reaction of 2,4,6-tri-t-butylaniline and thionyl chloride.

They proposed the formation of (227) through (230), which was unstable under the reactions conditions to fast retro-ene type decomposition.

2. Δ^4-1,2,4-Dithiazolines

A novel reaction was reported by Böhne and Ahrens in 1974, involving the use of trityl-tetrafluoroborate ($(C_6H_5)_3\ C^{\oplus}\ BF_4^{\ominus}$) as a hydride abstractor in the conversion of a Δ^4-1,2,4-dithiazoline (231) into a 1,2,4-dithiazolylium salt (232). Hydrolysis yielded N-formylthiobenzamide (233)[142].



The structure of (232) was ascertained by the singlet at 9.06 ppm in ^1H n.m.r. (CF_3CO_2D) and confirmed by the correct elemental analysis and molecular ion peak in the mass spectrum.

The Δ^4-1,2,4-dithiazoline-3-thione (234) has been oxidised to the corresponding Δ^4-1,2,4-dithiazolin-3-one (235) using potassium permanganate[143], mercury (II), acetate[144,145], peroxyacetic acid[146] and chlorine[146] at room temperature.

(234) (235)

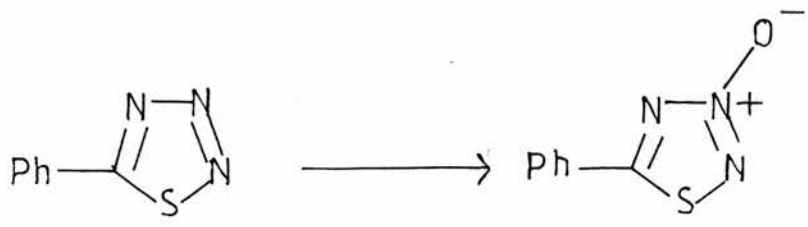
A more unusual reagent, benzonitrile oxide was used by Huisgen to give the ketone (235) in 60-70% yield[147]. In none of these cases was there any oxidation of the ring sulphur atoms.

E. Thiatriazole ring systems

1. 1,2,3,4-Thiatriazoles

The first example of a 1,2,3,4-thiatriazole 3-oxide a new class of heteroaromatic N-oxide was reported by Holm and co-workers in 1975[148].

Thiatriazoles with an aromatic substituent in the 5-position were shown to be extremely stable towards oxidising reagents. Thus 5-phenyl-1,2,3,4-thiatriazole (237) was not attacked by chlorine, nitric acid, hydrogen peroxide or peroxyformic acid[149]. However a solid was obtained which proved to be the thermally stable 5-phenyl-1,2,3,4-thiatriazole-3-oxide (238) by the action of peroxytrifluoroacetic acid at room temperature[148].

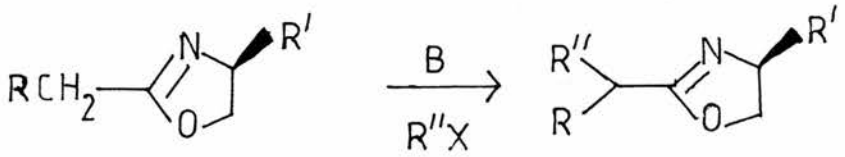


(237) (238)

Oxidation took place slowly and competed with acid catalysed decomposition of the starting material to benzonitrile, nitrogen and sulphur[150]. This resulted in a relatively low yield of 15%. The main technique used in the structural assignment of the oxide was mass spectroscopy. Fragmentation patterns of both (238) and 2-^{15}N labelled (238) upon electron impact pointed to the 3-oxide structure. The infra-red spectrum did not distinguish between an N-oxide or S-oxide since the absorption band observed at 1011 cm^{-1} could be due to either. The frequency of the band, if due to an N-oxide, was close to that of aliphatic amine oxides. This suggested less N-0 double bond character than expected for a heteroaromatic N-oxide. E.S.C.A. measurements[148] indicated N-oxidation as opposed to S-oxidation and ruled out N-oxidation at position 4. The chemical properties were investigated. Hexachlorodisilane, a potent deoxygenation reagent gave the starting thiatriazole (237). However the oxygen was released much more slowly than in the case of pyridine N-oxide[151].

Programme of Research

Meyers has used 4-chiral 2-oxazolines widely in asymmetric synthesis[152]. Diastereoselective alkylation reactions on the 2-substituent of the oxazoline (239) have given, after removal of the chiral auxiliary (C-4 and C-5 in the ring), a wide range of chiral acids, esters, lactones and alcohols such as (240). Similarly



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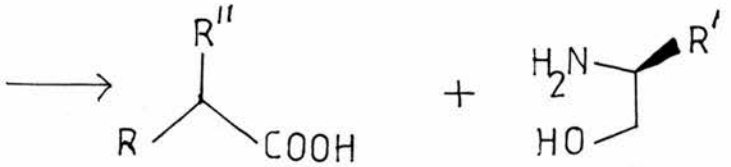
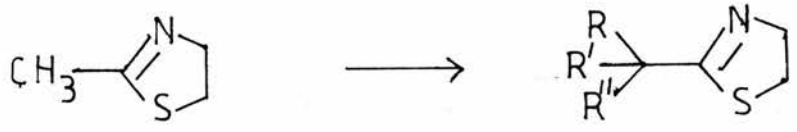


(240)

achiral 2-substituted-2-thiazolines (241) undergo alkylation reactions on the 2-substituent[153]. Reduction of the ring system using aluminium amalgam and cleavage using mercury (II) chloride gives the trialkyl aldehyde (242).



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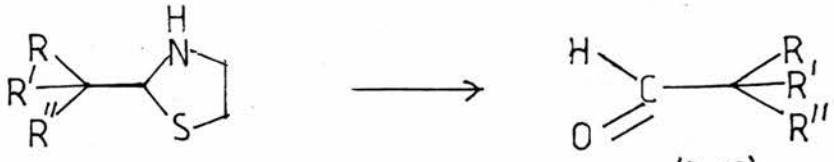
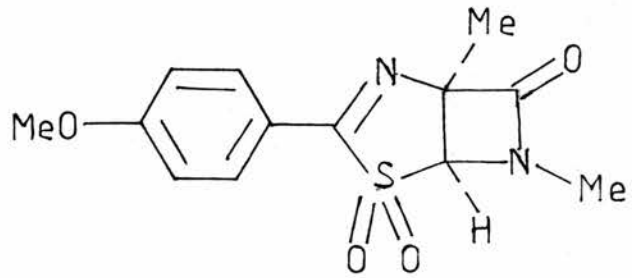


(242)

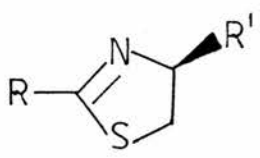
In 1976 Scott and coworkers reported the oxidation of the 2-thiazoline (24) using m-chloroperoxybenzoic acid to the 2-thiazoline

1,1-dioxide (25)[12]. The α-sulphonyl anion was subsequently formed and the thiosubstituted β-lactam ring obtained (243) on nucleophilic displacement of the sulphonate anion. The initial aim of the project was



(243)

to investigate the reactivity of a range of chiral 2-thiazolines (244) with a varied substitution pattern at the 2- and 4-positions, towards oxidation with a view to obtaining the corresponding thiazoline 1,1-dioxides (245). On deprotonation the α-sulphonyl anion formed could undergo diastereoselective alkylation at the 5-position, induced by the adjacent



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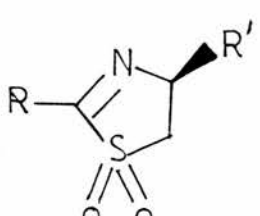

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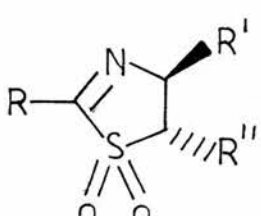
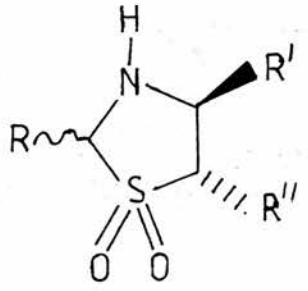


(246)

centre. Reduction of the alkylated thiazoline 1,1-dioxide (246) by aluminium amalgam would then give the thiazolidine 1,1-dioxide (247)

with some degree of asymmetric induction at the C-2 position[153]. The previously unreported stereospecific extrusion of sulphur dioxide via



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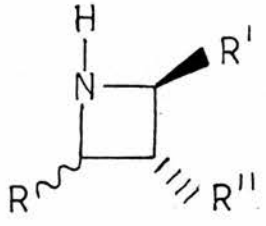
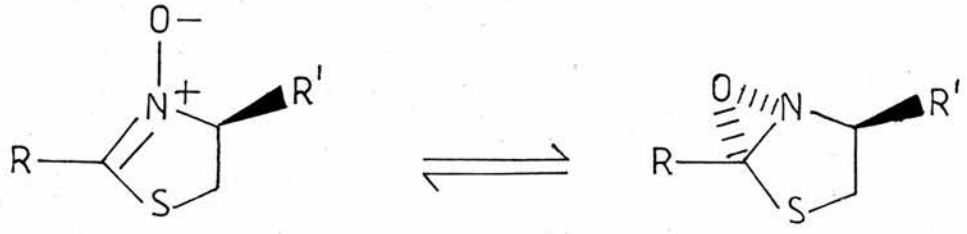


(248)

flash vacuum pyrolysis of this new ring system could give a chiral azetidine (248) containing three contiguous chiral centres.

Stronger oxidising reagents than m-chloroperoxybenzoic acid such as peroxytrifluoroacetic acid may result in the formation of the novel thiazoline N-oxide (249) or its isomeric oxaziridine form (250) depending upon the substituent effect at the C-2 position. The potentially

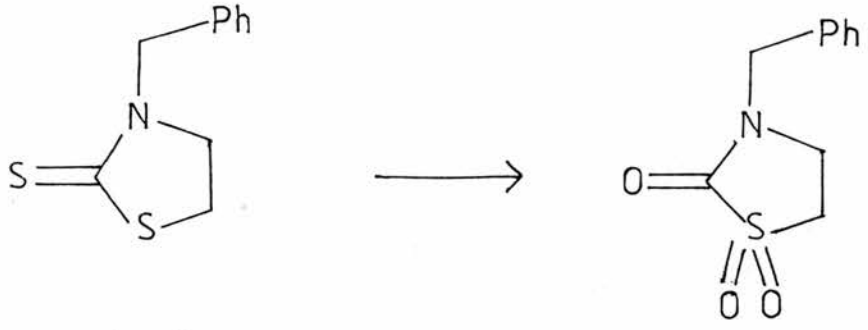


(249) (250)

weak nitrogen-oxygen bond (c.f. N-sulphonyloxaziridines[154]) in the nitrone-oxaziridine system could open the way to asymmetric oxygen

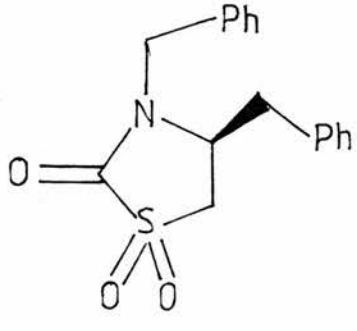
transfer reactions with a wide range of substrates including neutral acceptors (alkenes, amines, sulphides) and lithium anions as potential OH^+ synthons. The ability of cyclic nitrones such as oxazoline N-oxides[155] and pyrroline N-oxides[156] to serve as 4π-addends in cycloaddition reactions with an array of dipolarophiles might provide access to chiral bicyclic ring systems containing several stereocentres.

In 1961, Gaul and Fremuth reported the oxidation of N-protected thiazolidine-2-thiones such as (122) to the corresponding thiazolidine-2-one 1,1-dioxides (123)[70]. Synthesis of the oxidised ring



(122) (123)

system with a larger chiral side chain such as (251) could allow diastereoselective alkylation reactions at the C-5 position, after deprotonation to form the α-sulphonyl anion.



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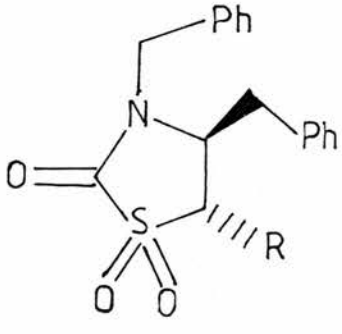

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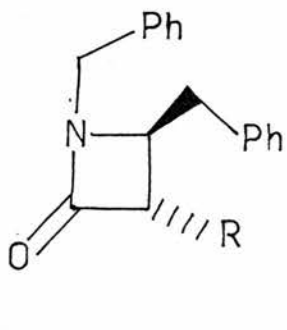


(253)

The previously uninvestigated pyrolytic removal of sulphur dioxide from the alkylated thiazolidin-2-one 1,1-dioxide (252) might produce a stable chiral β-lactam (253) with two contiguous chiral centres. An alternative approach via photochemical extrusion could give the same N-protected β-lactam[84].

EXPERIMENTAL

A. Symbols and Abbreviations

mmol - millimoles

M - mol dm^{-3}

h,min - hours,minutes

g.c. - gas liquid chromatography

g.c.m.s. - gas chromatography-mass spectroscopy

t.l.c. - thin layer chromatography

i.r. - infrared spectroscopy

ν - wave number

λ - wave length

n.m.r. - nuclear magnetic resonance spectroscopy

δ - chemical shift

J - spin-spin coupling constant

s,d,t,q,m - singlet, doublet, triplet, quartet, multiplet

m.s. - mass spectroscopy

c.i.m.s. - chemical ionisation mass spectroscopy

m/z - mass to charge ratio

M^+ - mass of molecular ion

f.v.p. - flash vacuum pyrolysis

m.p. - melting point

b.p. - boiling point

B. Instrumentation and General Techniques

1. N.m.r. spectroscopy

a. ^{1}H n.m.r.

Routine spectra were obtained at 60MHz on a Varian EM 360 spectrometer. Spectra of new compounds were obtained at 80 MHz on a Bruker WP 80 and high resolution spectra were obtained at 300 MHz on a Bruker AM 300 spectrometer, both operated by Mrs M Smith.

b. ^{13}C n.m.r.

Earlier spectra were obtained at 20MHz on a Varian CFT 20 spectrometer and later spectra were obtained at 75MHz on a Bruker AM 300 spectrometer operated by Mrs M Smith. For all spectra, unless otherwise stated, solutions are in deuteriochloroform and chemical shifts are expressed in parts per million to high frequency of tetramethylsilane.

2. Infrared spectroscopy

Spectra were obtained on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. Solids were run as nujol mulls and liquids as thin films, both on sodium chloride plates. Solution spectra were run in chloroform or dichloromethane using matched sodium chloride cells of path length 0.1mm. Spectra were calibrated with the polystyrene peak at $1603cm^{-1}$.

3. Ultraviolet spectroscopy

Spectra were obtained on a Pye-Unicam SP8 150 ultraviolet/visible spectrophotometer using a solution in ethanol.

4. Mass spectroscopy

Earlier mass spectra and accurate mass measurements were obtained on an A.E.I. MS-902 instrument and later mass spectra were obtained on a Finnigan Incos 50 mass spectrometer, both operated by Mr C Millar. Chemical ionisation mass spectra were obtained at ICI Pharmaceuticals Division.

5. Gas chromatography - mass spectroscopy

Gas chromatography - mass spectroscopy studies were carried out on a Hewlett-Packard 5890 A gas chromatograph coupled to a Finnigan Incos 50 mass spectrometer operated by Mr C Millar.

6. Elemental analyses

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba 1106 elemental analyser operated by Mrs S Smith.

7. Melting points

Routine melting points were determined using an Electrothermal melting point apparatus while melting points of new

compounds were determined on a Reichert hot-stage microscope.

8. Optical rotations

These were determined on an Optical Activity AA 1000 polarimeter.

9. Gas liquid chromatography

A Pye Unicam PU4500 chromatograph with flame ionisation detector was used with nitrogen as the carried gas and a 2m × 4.5mm glass column. The column used was 2% neopentylglycolsuccinate (NPGS) on Chromosorb W (80-100 mesh).

10. Thin layer chromatography

This was carried out using 0.2mm layers of silica (Merck, Kieselgel $60F_{254}$) or alumina (Merck, Alumina $60F_{254}$) on aluminium sheets. The components were observed under ultraviolet light or by their reaction with iodine vapour.

11. Preparative thin layer chromatography

This was carried out using 1.0mm layers of silica (Merck, Kieselgel 60-80 mesh), containing 0.5% Woelm fluorescent green indicator, on glass plates. The components were observed under ultraviolet light or by their reaction with iodine vapour. The bands

were scraped off and the products removed from the support by soaking with dichloromethane for 3h.

12. Column chromatography

This was carried out using Fisons silica gel for chromatography (60-120 mesh) or Fisons aluminium oxide for chromatography (100-250 mesh).

13. Drying and evaporation of organic solutions

Organic solutions were dried by standing over anhydrous magnesium sulphate for several hours and were evaporated under reduced pressure on a rotating evaporator.

14. Photochemical reactions

The lamp used was a 125W medium pressure water cooled mercury lamp supplied by Engelhard Hanovia Lamps, Slough, Bucks. Reactions were carried out by attaching a quartz tube containing the reaction mixture to the side of the reactor well.

15. Drying and purification of solvents

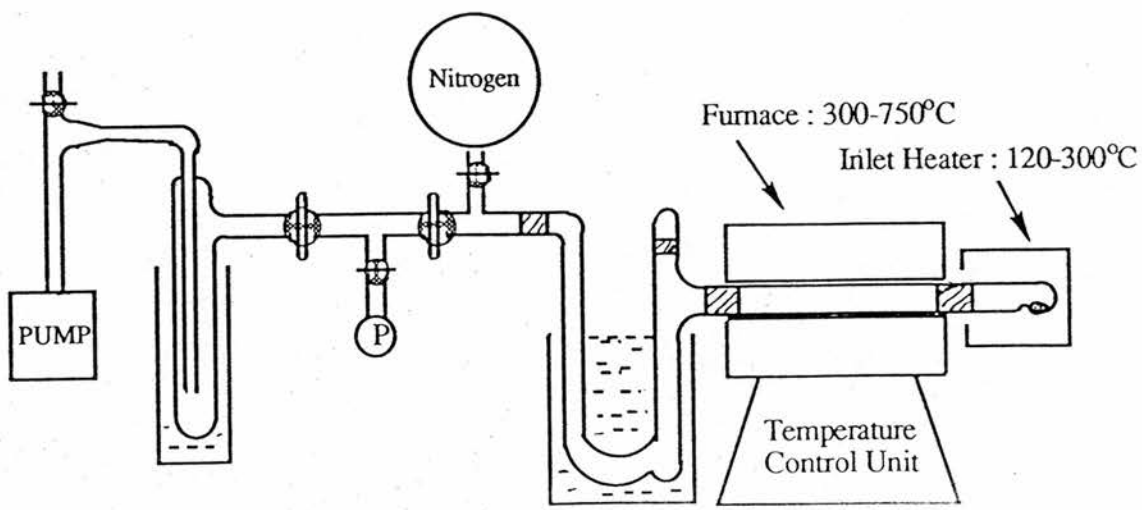
Commercially available solvents were used without further purification unless otherwise indicated. Where pure methanol, acetone or chloroform were required the commercial Analytical

Reagent (AR) grade solvents were used. Dry acetonitrile was prepared by storing over freshly activated molecular sieves. Dry ether and dry tetrahydrofuran were prepared by preliminary drying using sodium wire and then distillation from potassium benzophenone ketyl. Dry dichloromethane was distilled from phosphorus pentoxide and stored over molecular sieves. Dry N,N-dimethylformamide was prepared by distillation under an atmosphere of nitrogen and stored over molecular sieves. "Petroleum ether" refers to light petroleum, the redistilled 40-60°C boiling fraction being used for chromatography.

16. Flash vacuum pyrolysis

The apparatus used was based on the design of W D Crow, Australian National University. A similar set up is illustrated in a recent monograph by Brown[157].

The essential features of the apparatus are shown in the diagram below. The sample was volatilised from a horizontal inlet tube, heated in



a Büchi Kugelrohr oven, through a 30 × 2.5 cm silica tube. This was heated at temperatures in the range of 500-650°C by a Stanton Redcroft laboratory tube furnace LM 8100, the temperature being measured by a Pt|Pt-13% Rh thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2}-10^{-3} torr by an Edwards Model E2M5 high capacity rotatory oil pump, the pressure being measured by a Pirani gauge situated between the trap and the pump. Under these conditions the contact time in the hot zone was estimated to be in the range 1-10 ms.

Small scale pyrolses were generally carried out using 50-100 mg of material. After the pyrolysis the system was isolated from the pump and filled with nitrogen gas. The product was dissolved out of the trap in deuteriochloroform and analysed directly by n.m.r.. Yields were estimated by adding 5-10 mg of solvent such as dichloromethane and comparing the n.m.r. integrals.

C. Preparation of the 2-Thiazolines

1. Preparation of the amino alcohols

a. Preparation of 2-(S)-amino-3-methylbutan-1-ol

The method used was based on that of Meyers[158]. S-Valine (30.0g, 252 mmol) was added to a stirred suspension of lithium aluminium hydride (14.3g, 376 mmol) in dry tetrahydrofuran (500 ml) under nitrogen. After heating under reflux for 120h, finely ground sodium sulphate decahydrate (37.1g, 121 mmol) was added at 0°C to destroy the excess lithium aluminium hydride. The salts were filtered off and washed with ether (900 ml).

Evaporation of the filtrate gave a yellow liquid (20.3g) which was Kugelrohr distilled using a dry-ice acetone cooled collection bulb to give 2-(S)-amino-3-methylbutan-1-ol (14.9g, 57%) as a colourless liquid b.p. 64°C (oven temperature) at 3.0 torr (lit.[159] b.p. 55-57°C at 2.0 torr)

b. Preparation of 2-(S)-amino-3-phenylpropan-1-ol

This was prepared by a modification of the method of Meyers[160].

Thionyl chloride (95 ml, 154.9g, 1300 mmol) was added to a stirred suspension of S-phenylalanine (100.0g, 606 mmol) in A.R. methanol (500 ml) at 0°C over twenty minutes. Evaporation, of the solvent followed by removal of the remaining traces of thionyl

chloride under 1 torr gave a colourless solid. Washing the solid with ether (500 ml) gave the methyl ester hydrochloride (129.3g, 99%) as colourless crystals.

A solution of the methyl ester hydrochloride (86.6g, 401 mmol) in 50% aqueous ethanol (750 ml) was added slowly to a solution of sodium borohydride (75.7g, 200 mmol) in 50% aqueous ethanol (750 ml) at 0°C. After heating under reflux for 146h, the ethanol was evaporated off. 2M Sodium hydroxide (300 ml) was added to dissolve the borate salts. Extraction using ethyl acetate (150 ml × 5), followed by drying and evaporation gave 2-(S)-amino-3-phenylpropan-1-ol (45.8g, 76%) as colourless crystals, m.p. 89-91°C (lit[160] 89-91°C); $[\alpha]_D^{25}$-25.2° (c 1.6, EtOH) (lit[160] $[\alpha]_D^{25}$-24.2° (c 1.5, EtOH)).

2. Preparation of ethyl iminoacetate hydrochloride

This was prepared in 63% yield by the method of Dox[161] as colourless hygroscopic crystals, m.p. 103-104°C (lit.[161] 107-108°C).

3. Preparation of the 2-oxazolines

a. Preparation of 4-(S)-isopropyl-2-methyl-2-oxazoline and 4-(S)-benzyl-2-methyl-2-oxazoline

These were prepared using the general method of Meyers[162]. A solution of the amino alcohol (167 mmol) in dichloromethane (150 ml) was added to a stirred solution of ethyl iminoacetate

hydrochloride (29.4g, 235 mmol) in dichloromethane (400 ml) at 0°C. After stirring for 76h at room temperature, the solution was washed with water (150 ml × 2). The aqueous layer was extracted with dichloromethane (150 ml) and the combined organic layer dried and evaporated at room temperature to give a deep red liquid/yellow oil. Kugelrohr distillation gave 4-(S)-isopropyl-2-methyl-2-oxazoline (13.8g, 65%) as a colourless liquid, b.p. 62-63°C (oven temperature) at 3.0 torr.

4-(S)-Benzyl-2-methyl-2-oxazoline (20.4g, 70%) was similarly obtained as a colourless liquid, b.p. 96°C (oven temperature) at 0.02 torr.

4-(S)-isopropyl-2-methyl-2-oxazoline

(Found : C, 65.9; H, 10.45; N, 11.0. $C_7H_{13}NO$ requires C, 66.1; H, 10.3; N, 11.0%); $[\alpha]_D^{25}$ - 94.2° (c 1.0, $CHCl_3$); ν_{max} 1720, 1520, 1490, 1430, 1390, 1340, 1320, 1280, 1030, 950, 850 and 720 cm^{-1}; δ_H (80 MHz) 4.4-3.9 (3H,m), 2.00(3H, d, J2Hz), 1.75 (1H, septet of d, J8,2Hz), 1.00 (3H, d, J8Hz) and 0.90 (3H, d, J8Hz); δ_c (20 MHz) 164.3(s), 72.5(t), 70.2(d), 32.8(d), 18.8(q), 18.3(q) and 13.8(q); m/z 127 (M^+, 21%), 112 (4), 97 (6), 84 (100), 70 (12) and 56 (95).

4-(S)-benzyl-2-methyl-2-oxazoline

(Found: C, 75.4; H, 7.5; N, 8.0; M^+, 175.0999. Calc. for $C_{11}H_{13}NO$ C, 72.3; H, 7.4; N, 9.35%; M^+, 175.0997); $[\alpha]_D^{25}$ - 48.9° (c 2.95, $CHCl_3$)

(lit.[163] $[\alpha]_D$ - 50.7 (c 2.83, $CHCl_3$)); ν_{max} 1670, 1450, 1390, 1230, 980 and 700 cm^{-1}; δ_H (80 MHz) 7.4 (5H, s), 4.6-4.2 (1H, m), 4.20 (1H, half of AB pattern of d, J_{AB} 8, J_{AX} 8Hz), 4.00 (1H, half of AB pattern of d, J_{AB} 8, J_{BX} 8Hz), 3.10 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 2.70 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz) and 1.95 (3H, d, J1Hz); δ_c (20 MHz) 164.9 (s), 138.1 (s), 129.2 (2C,d), 128.5 (2C,d), 126.4 (d), 71.8 (t), 67.4 (d), 41.8 (t) and 13.8 (q); m/z 176 (M^++1, 11%), 175 (M^+, 31), 172 (11), 152 (9), 145 (26), 130 (19), 117 (33), 103 (39) and 91 (100).

b. Preparation of 4-(S)-benzyl-2-phenyl-2-oxazoline

Phosphorus pentoxide (3.5g, 24.6 mmol) was added to a stirred suspension of 2-(S)-benzoylamino-3-phenylpropan-1-ol [see 4b] (2.0g, 13.2 mmol) in dry toluene (70 ml). After heating under reflux for 18h, the toluene was decanted. The solid residue was taken up in dichloromethane and washed with saturated aqueous sodium carbonate solution (× 2). Drying and evaporation of the organic layer gave a light brown oil (0.91g, 49%). This was Kugelrohr distilled to give 4-(S)-benzyl-2-phenyl-2-oxazoline as a colourless liquid (0.59g, 32%) b.p. 221°C (oven temperature) at 0.5 torr. (Found: C, 81.6; H, 6.15; N, 6.55; M^+, 237.1174. $C_{16}H_{15}NO$ requires C, 81.0; H, 6.4; N, 5.9%;

M^+, 237.1154); $[\alpha]_D^{25}$ - 12.2° (c 1.53, $CHCl_3$); ν_{max} 1640 (C=N), 1600, 1580, 1490, 1450, 1360, 1280, 1080, 1060, 1020, 960, 780 and 690 cm^{-1}; δ_H (80 MHz) 8.0-7.9 (2H, m), 7.5-7.4 (3H, m), 7.00 (5H, s), 4.75-4.45 (q of d, J8, 6Hz), 4.35 (1H, half of AB pattern of d, J_{AB} 8, J_{AX} 8Hz), 4.10 (1H, half of AB pattern of d, J_{AB} 8, J_{BX} 8Hz), 3.25 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz) and 2.70 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz); δ_c (20 MHz) 163.8 (s), 138.0 (s), 131.2 (s), 129.3 (2C,d), 128.5 (2C,d), 128.3 (4C,d), 127.9 (d), 126.5 (d), 71.8 (t), 67.9 (d) and 41.8 (t); m/z 237 (M^+, 21%), 209 (17), 196 (9), 160 (15), 146 (100), 128 (32) and 121 (70).

c. Preparation of 4-(R)-ethyl-2-phenyl-2-oxazoline

Trimethylorthobenzoate (10.2g, 56.2 mmol) and 2-(R)-aminobutan -1-ol (5.00g, 56.2 mmol) were distilled at a temperature of 170°C for 3 hours. Column chromatography on silica then gave the orthoester (hexane/ether (1:8), R_F 0.3) and 4-(R)-ethyl-2-phenyl-2-oxazoline (hexane/ether (1:1), R_F 0.5) as a colourless liquid (0.37g, 4%). δ_H (80 MHz) 8.0-7.9 (2H, m), 7.5-7.3 (3H, m), 4.45 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 7Hz), 4.3-4.2 (1H, m), 4.05 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 7Hz), 1.9-1.7 (1H, m),

1.65 (1H, q of d, J7, 7Hz) and 1.00 (3H, t, J 7Hz).

4. Preparation of the 2-(S)-benzoylamino alcohols

a. Preparations of 2-(S)-benzoylamino-3-methylbutan-1-ol and 2-(R)-benzoylaminobutan-1-ol

A modification of the method of Ireland was used[164]. A solution of benzoyl chloride (39.2 ml, 47.4g, 338 mmol) in dichloromethane (150 ml) was added to a solution of triethylamine (34.1g, 375 mmol) and the amino alcohol (338 mmol) in dichloromethane (150 ml) at room temperature. After stirring for 20h, t.l.c. (SiO_2, ethyl acetate) showed only the amide to be present. Washing the solution with water (× 2), 2M hydrochloric acid and water, followed by drying and evaporation gave the crude product (80%). Recrystallisation using hexane/ethyl acetate 3:1 (× 3) gave 2-(S)- benzoylamino-3-methylbutan-1-ol as colourless crystals (31.5g, 45%) m.p. 107-108°C. Likewise 2-(R)-benzoylaminobutan-1-ol was obtained as colourless crystals (39.2g, 60%) m.p. 93-94°C.

2-(S)-benzoylamino-3-methylbutan-1-ol

(Found: C, 69.6; H, 8.5; N, 6.7. $C_{12}H_{17}NO_2$ requires C, 69.55; H, 8.25; N 6.75%); $[\alpha]_D^{25}$ - 29.8° (c 2.5, MeOH); ν_{max} 3700-3100 (br, OH), 3440 (NH), 1640 (C=0), 1600, 1520, 1480, 1220, 1070 and 700 cm^{-1}; δ_H (80 MHz) 7.8 (2H, m), 7.5 (3H, m), 6.6-6.2 (1H, br s), 4.1-3.9 (1H,

m), 3.8 (2H, m), 2.8-2.6 (1H, br s), 2.00 (1H, octet, J 8Hz), 1.05 (3H, d, J 8Hz) and 1.00 (3H, d, J 8Hz); δ_c (75 MHz) 166.4 (s), 134.5 (s), 131.3 (d), 128.4 (2C,d), 127.0 (2C,d), 62.7 (d), 57.3 (t), 29.0 (d), 19.5 (q) and 19.2 (q); m/z 207 (M^+, 1%), 176 (34), 164 (1), 122 (9), 105 (100) and 77 (48).

2-(R)-benzoylaminobutan-1-ol

(Found: C, 68.6; H, 8.05; N, 7.25. $C_{11}H_{15}NO_2$ requires C, 68.35; H, 7.8; N, 7.25%); $[\alpha]_D^{25}$ + 26.3° (c 1.8, MeOH); ν_{max} ($CHCl_3$) 3700-3100 (br, OH), 3440 (NH), 1640 (C=O), 1520, 1480, 1290, 1220, 1080, 1040 and 700 cm^{-1}. δ_H (80 MHz) 7.7 (2H, m), 7.4 (3H, m), 6.9-6.5 (1H, br d), 4.2-3.8 (1H, m), 3.70 (2H, d, J 6Hz), 3.5 (1H, br s), 1.9-1.4 (2H, m) and 0.90 (3H, t, J 6Hz); δ_c (75.5 MHz) 166.4 (s), 134.4 (s), 131.4 (d), 128.4 (2C, d), 127.0 (2C, d), 64.3 (d), 53.5 (t), 24.2 (t) and 10.6 (q); m/z 194 (M^++1, 2%), 193 (M^+,1), 162 (35), 122 (11), 105 (100), 77 (57) and 51 (18).

b. Preparation of 2-(S)-benzoylamino-3-phenylpropan-1-ol

The reaction was identical to that used with the previous benzoylamino alcohols. The precipitate obtained was filtered, washed with water (× 3) to remove the triethylamine hydrochloride, and dried (80°C, 10 torr, 5h) to give 2-(S)-benzoylamino-3-phenylpropan-1-ol (71.5g, 83%) as colourless crystals m.p. 174-175°C. (Found: C, 75.3; H,

6.7; N, 5.5. $C_{16}H_{17}NO_2$ requires C, 75.3; H, 6.7; N, 5.5%); $[\alpha]_D^{25}$ - 85.1° (c 2.2, MeOH), ν_{max} 3700-2300 (br OH), 3300 (NH), 1630 (C=O), 1540, 1460, 1330, 1080, 1050, 1030 and 700 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 8.15 (1H, d, J 8Hz), 7.9-7.7 (2H, m), 7.5-7.4 (3H, m), 7.25 (5H, s), 5.85 (1H, t, J 6Hz), 4.4-4.0 (1H, m), 3.50 (2H, t, J, 6Hz), 3.00 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz) and 2.85 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz); δ_c (20 MHz, CD_3SOCD_3) 166.0 (s), 139.1 (s), 134.6 (s), 130.6 (d), 128.8 (2C, d), 127.8 (4C, d), 126.9 (2C, d), 125.6 (d), 62.7 (t), 53.0 (d) and 36.3 (t); m/z 255 (M^+, 12%), 224 (31), 164 (100), 144 (51), 134 (26) and 122 (42).

c. Preparation of 2-(S)-trimethylacetylamino-3-methylbutan-1-ol and 2-(S)-trimethylacetylamino-3-phenylpropan-1-ol

A solution of trimethylacetyl chloride (25.6 ml, 25.1g, 208.7 mmol), triethylamine (32.1 ml, 23.3g, 230.3 mmol) and the amino alcohol (208.7 mmol) in dichloromethane was stirred for 18h. The work up was identical to that used for 2-(S)-benzoylamino-3-methylbutan-1-ol. The orange solids obtained were recrystallised using hexane (× 3) to give 2-(S)-trimethylacetylamino-3-methylbutan-1-ol as colourless prisms (10.1g, 25%) mp. 65-66°C and 2-(S)-trimethylacetylamino-3-phenylpropan-1-ol as colourless crystals (24.0, 49%) mp. 75-76°C.

2-(S)-trimethylacetylamino-3-methylbutan-1-ol

(Found : C, 64.3; H, 11.5; N, 7.5. $C_{10}H_{21}NO_2$ requires C, 64.3; H, 11.5; N, 7.5%); $[\alpha]_D^{25}$ - 33.6° (c 1.8, MeOH); ν_{max} ($CHCl_3$) 3700-3100 (br OH), 3440 (NH), 1640 (C=0), 1580, 1520, 1480, 1220, 1070 and 700 cm^{-1}; δ_H (300 MHz) 6.2 (1H, br d, J 8Hz), 4.3 (1H, br s), 3.7-3.5 (3H, m), 1.95 (1H, octet, J 8Hz), 1.20 (9H, s), 1.00 (3H, d, J 8Hz) and 0.90 (3H, d, J 8Hz); δ_c (75 MHz) 179.1 (s), 62.8 (d), 56.4 (t), 38.8 (s), 28.8 (d), 27.6 (3C, q), 19.6 (q) and 18.9 (q); m/z 187 (M^+, 4%), 169 (2), 156 (57), 144 (15), 102 (19), 85 (29), 72 (25) and 57 (100).

2-(S)-trimethylacetylamino-3-phenylpropan-1-ol

(Found : C, 71.3; H, 9.2.; N, 5.9. $C_{14}H_{21}NO_2$ requires C, 71.45; H, 9.0; N, 5.95%); $[\alpha]_D^{25}$ - 16.4 (c 1.8, MeOH); ν_{max} ($CHCl_3$) 3700-3100 (br OH), 3460 (NH), 1640 (C=0), 1510, 1370, 1200, 1090, 1040, 730 and 670 cm^{-1}; δ_H (80 MHz) 7.25 (5H, s), 6.1-5.9 (1H, br d, J 7Hz), 4.4-4.0 (1H, m), 3.8 (1H, br s), 3.60 (2H, d, J 5Hz), 2.95 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 7 Hz), 2.80 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8 Hz) and 1.10 (9H, s); δ_c (75 MHz) 179.2 (d), 63.7 (d), 52.5(t), 38.7 (s), 36.7 (t) and 27.4 (3C, q); m/z 235 (M^+, 4%), 204 (6), 144 (32), 120 (12), 102 (16), 91 (26), 85 (28), 60 (18) and 57 (100).

5. Preparation of the 2-thiazolines

a. Preparation of 4-(S)-isopropyl-2-methyl-2-thiazoline and 4-(S)-benzyl-2-methyl-2-thiazoline

Phosphorus pentasulphide (40.1g, 181 mmol) was added to a solution of the oxazoline (109 mmol) in dichloromethane (400 ml). After heating under reflux with vigorous stirring for 138h, the suspension was filtered and the filtrate washed with 2M sodium hydroxide (110 ml × 3) to remove unreacted phosphorus pentasulphide. The organic layer was washed with water (100 ml × 2), dried and evaporated to give a brown liquid. Kugelrohr distillation (× 2) gave 4-(S)-isopropyl-2-methyl-2- thiazoline (6.4g, 41%) as a volatile colourless liquid, b.p. 95°C (oven temperature) at 7 torr. Likewise 4-(S)-benzyl-2-methyl-2-thiazoline (10.2g, 49%) was obtained as a volatile colourless liquid, b.p. 233°C (oven temperature) at 2 torr.

4-(S)-isopropyl-2-methyl-2-thiazoline

(Found : C, 57.2; H, 9.15; N, 9.7. M^+, 143.0759. $C_7H_{13}NS$ requires C, 58.7; H, 9.15; N, 9.8%; M^+, 143.0769); $[\alpha]_D^{25}$ - 72.1° (c, 1.20, CH_2Cl_2); ν_{max} 1650, 1470, 1440, 1380, 1160 and 960 cm^{-1}; δ_H (80 MHz) 4.4-4.0 (1H, m), 3.25 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 8Hz), 3.05 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 9Hz), 2.20 (3H, d, J

2Hz), 2.00 (1H, m), 1.05 (3H, d, J8Hz) and 0.95 (3H, d, J 8Hz); δ_c (20 MHz) 164.9 (s), 8.39 (d), 36.4 (t), 33.0 (d), 20.3 (q), 19.6 (q) and 18.8 (q); m/z 143 (M^+, 44%), 100 (100), 87 (27), 82 (22) and 69 (37).

4-(S)-benzyl-2-methyl-2-thiazoline

(Found : C, 66.6; H, 6.6; N, 8.9. M^+, 191.0777. $C_{11}H_{13}NS$ requires C, 69.1; H, 6.85; N, 7.3%; M^+, 191.0767); $[\alpha]_D^{25}$ - 95.4° (c 1.15, CH_2Cl_2); ν_{max} 1630, 1490, 1450, 1435, 1370, 1160, 745 and 700 cm^{-1}; δ_H (80 MHz) 7.4 (5H, s), 5.0-4.5 (1H, m), 3.30 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 8Hz), 3.10 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 2.70 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 9Hz) and 2.20 (3H, d, J 2Hz); δ_c (20 MHz) 165.8 (s), 138.5 (s), 129.2 (2C,d), 128.5 (2C, d), 126.4 (d), 78.4 (d), 40.5 (t), 38.5 (t) and 20.4 (q); m/z 191 (M^+, 9%), 144 (2), 117 (19), 115 (7), 104 (8), 102 (8) and 92 (19).

b. Preparation of 4-(S)-isopropyl-2-phenyl-2-thiazoline, 4-(S)-benzyl-2-phenyl-2-thiazoline and 4-(R)-ethyl-2-phenyl-2-thiazoline

A solution of the chiral 2-benzoylamino alcohol (48.4 mmol) in dichloromethane (250 ml) was vigorously stirred while phosphorus pentasulphide (81.1 mmol) was added. After heating under reflux for

42h, t.l.c. (SiO_2, ether) showed no starting material to be present. Filtration of the solid, extraction with 2M sodium hydroxide (50 ml) to remove unreacted phosphorus pentasulphide, followed by washing with water (50 ml), drying and evaporation gave an orange oil. This was Kugelrohr distilled (× 2) to give 4-(S)-isopropyl-2-phenyl-2-thiazoline as a colourless liquid (4.6g, 46%), b.p. 176°C (oven temperature) at 1.3 torr. Likewise 4-(S)-benzyl-2-phenyl-2-thiazoline was obtained as a yellow liquid (8.8g, 72%), b.p. 220°C (oven temperature) at 0.1 torr. Similarly 4-(R)-ethyl-2-phenyl-2-thiazoline was prepared as a colourless liquid (8.9g, 96%) b.p. 92-93°C (oven temperature) at 0.4 torr.

4-(S)-isopropyl-2-phenyl-2-thiazoline

(Found : C, 70.3; H, 7.6; N, 8.6. M^+, 205.0942. $C_{12}H_{15}NS$ requires C, 70.2; H, 7.35; N, 6.8%; M^+, 205.0925); $[\alpha]_D^{25}$ - 62.2° (c 1.16, $CHCl_3$); ν_{max} (neat) 1600, 1575, 1470, 1450, 1250, 1020, 940, 770 and 650 cm^{-1}; δ_H (80 MHz) 7.8 (2H, m), 7.4 (3H, m), 4.45 (t of d, J 8,6 Hz), 3.40 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 8Hz), 3.15 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 8Hz), 2.10 (1H, octet, J 6Hz), 1.1 (3H, d, J 8Hz), and 1.0 (3H, d, J 8Hz); δ_c (20 MHz) 165.9 (s), 133.8 (s), 130.8 (d), 128.3 (4C, d), 84.2 (d), 35.5 (t), 33.4 (d), 19.8 (q) and 19.1 (q); m/z 206 (M^++1, 5%), 205 (M^+, 21), 162 (100), 144 (26) and 122 (14).

4-(S)-benzyl-2-phenyl-2-thiazoline

(Found : C, 75.2; H, 5.95; N, 6.7. M^+, 253.0957; $C_{16}H_{15}NS$ requires C, 75.85; H, 5.97; N, 5.53%; M^+, 253.0925); $[\alpha]_D^{25}$ - 52.5° (c 1.12, CH_2Cl_2); ν_{max} 1600, 1570, 1490, 1450, 1310, 1250, 1030, 940, 770, 750 and 700 cm^{-1}; δ_H (80 MHz) 7.9-7.8 (2H, m), 7.4-7.3 (3H, m), 7.15 (5H, s), 5.1-4.7 (1H, m), 3.30 (1H, half of AB pattern of d, J_{Ab} 10, J_{AX}8Hz), 3.15 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 8Hz), 3.30 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 5Hz) and 2.85 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 9Hz); δ_c (20 MHz) 167.0 (s), 138.4 (s), 133.2 (s), 131.0 (d), 129.2 (2C, d), 128.3 (6C, d), 126.3 (d), 78.4 (d), 40.3 (t) and 37.1 (t); m/z 254 (M^++1, 6%), 253 (M^+,4), 206 (6), 162 (100), 135 (7), 121 (50), 115 (30) and 104 (47).

4-(R)-ethyl-2-phenyl-2-thiazoline

(Found : C, 69.2; H, 6.8; N, 7.1. $C_{11}H_{13}NS$ requires C, 69.1; H, 6.9; 7.1%); $[\alpha]_D^{25}$ + 55.9° (c 0.8, $CHCl_3$), ν_{max} 1600, 1490, 1450, 1320, 1250, 990, 960, 940, 720 and 640 cm^{-1}; δ_H (200 MHz) 7.8 (2H, m), 7.4 (3H, m), 4.60 (1H, m), 3.50 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 8Hz), 3.10 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 8Hz), 1.90 (1H, m), 1.75 (1H, m) and 1.10 (3H, t, J 8Hz); δ_c (75.5 MHz) 166.6 (s), 133.9 (s),

131.5 (2C, d), 130.3 (2C, d), 126.9 (d), 79.7 (d), 36.1 (t), 28.6 (t) and 11.5 (q); m/z 191 (M^+, 42%), 162 (100), 145 (10), 130 (31) and 122 (12).

c. Preparation of 2-t-butyl-4-(S)-isopropyl-2-thiazoline and 4-(S)-benzyl-2-t-butyl-2-thiazoline

Phosphorus pentasulphide (20.0g, 90.1 mmol) was added to a vigorously stirred solution of the 2-(S)-trimethylacetylamino alcohol (67.9 mmol) in dichloromethane (250 ml). After heating under reflux for 51h, t.l.c. (SiO_2, ether) showed no starting material to be present. The solution was washed with 2M sodium hydroxide (50 ml) to remove unreacted phosphorus pentasulphide. After washing with water (50 ml), drying and evaporation gave a brown oil. Kugelrohr distillation (× 2) gave 2-t-butyl-4-(S)-isopropyl-2-thiazoline as a colourless liquid (4.33g, 60%), b.p. 164°C (oven temperature) at 1.4 torr. Likewise 4-(S)- benzyl-2-t-butyl-2-thiazoline was obtained as a colourless liquid (9.3g, 59%) b.p. 172°C (oven temperature) at 1.0 torr.

2-t-butyl-4(S)-isopropyl-2-thiazoline

(Found : C, 62.45; H, 10.2; N, 8.65. M^+ 233.1212. $C_{10}H_{19}NS$ requires C, 64.8; H, 10.3; N, 7.55%; M^+, 233.1238); ν_{max} 1620, 1460, 1360, 1250, 1030 and 970 cm^{-1}; δ_H 4.30 (1H, t of d, J 9, 6Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 9Hz), 3.00 (1H, half of AB

pattern of d, J_{AB} 11, J_{BX} 9Hz), 2.00 (1H, octet, J 6Hz), 1.25 (9H, s), 1.00 (3H, d, J 6Hz) and 0.90 (3H, d, J 6Hz); δ_c (20 MHz) 177.4 (s), 83.3 (d), 37.9 (s), 34.8 (t), 33.0 (d), 29.3 (3C, q), 19.3 (q) and 18.6 (q); m/z 185 (M^+, 85%), 143 (100), 124 (20) and 102 (15).

4-(S)-benzyl-2-t-butyl-2-thiazoline

(Found : C, 71.35; H, 8.25; N, 6.7. $C_{14}H_{19}NS$ requires C, 72.05; H, 8.2; N, 6.0%); $[\alpha]_D^{25}$ - 59.7° (c 2.0, $CHCl_3$); ν_{max} 1620 (C=N), 1450, 1360, 1040, 990, 740 and 650 cm^{-1}; δ_H 7.25 (5H, s), 4.9-4.6 (1H, m), 3.10 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 5 Hz), 2.75 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 6Hz), 3.10 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 5Hz), 2.95 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 5Hz) and 1.25 (9H, s); δ_c (20 MHz) 178.5 (s), 138.5 (s), 129.3 (2C, d), 128.2 (2C, d), 126.2 (d), 77.9 (d), 40.1 (t), 37.7 (s), 36.8 (t) and 29.2 (3C, q); m/z 234 (M^++1, 5%), 233 (M^+, 20), 142 (100) and 126 (60).

d. Attempted preparation of 4-(R)-ethyl-2-phenyl-2-thiazoline

Phosphorus pentasulphide (21.0g, 94.6 mmol) was added to a vigorously stirred solution of 2-(R)-benzoylaminobutan-1-ol (16.0g, 83.7 mmol) in 1, 2-dichlorothane (250 ml) at room temperature. After heating under reflux for 70h, the solution was dried over anhydrous sodium carbonate to remove excess phosphorus pentasulphide.

Evaporation gave a brown oil. Kugelrohr distillation (× 2) gave a pale yellow liquid (9.4g), b.p. 210°C (oven temperature) at 0.6 torr, which crystallised out. Recrystallisation using ethyl acetate gave 2-(R)-thiobenzoylamino- 1-butyldisulphide as colourless needles (6.1g, 33%) m.p. 109-111°C. (Found : C, 57.85; H, 6.2; N, 6.1. $C_{22}H_{28}N_2S_4$ requires C, 58.9; H, 6.3; N, 6.3%); $[\alpha]_D^{25}$ + 41.0° (c 2.1, MeOH); ν_{max} 3400 (NH), 1600, 1400, 1380, 1300, 1260, 1220, 960, 920, 880, 780 and 700 cm^{-1}; δ_H 13.0-12.9 (1H, br s), 8.5-8.3 (4H, m), 7.8-7.5 (6H, m), 5.2-4.8 (2H, m), 3.90 (2H, half of AB pattern of d, J_{AB}12, J_{AX} 9Hz), 3.45 (2H, half of AB pattern of d, J_{AB} 12, J_{BX} 7Hz), 2.5-1.8 (4H, m) and 1.10 (6H, t, J 7Hz); δ_c (75 MHz) 185.0 (s), 136.6 (s), 130.8 (2C, d), 129.7 (2C, d), 125.4 (d), 69.6 (d), 34.9 (t), 26.1 (t) and 9.5 (q).

D. N-Oxidation of 2-thiazolines

1. Oxidation of 4-(S)-isopropyl-2-methyl-2-thiazoline

a. Reaction with nitrogen dioxide

A modification of the method of Horner was used[165]. A solution of 4-(S)-isopropyl-2-methyl-2-thiazoline (0.40g, 2.8 mmol) in dichloromethane (25 ml) was added to a stirred solution of nitrogen dioxide (0.77g, 8.4 mmol) in dichloromethane (50 ml) at room temperature. After stirring for 2h, evaporation gave 4-(S)-isopropyl-2- methyl-2-thiazoline 3-oxide as a red oil (0.51g,

43%) which had identical spectroscopic properties to that obtained in part b (see below).

b. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (1.0 ml, 1.1g, 9 mmol) was added dropwise to trifluoroacetic acid anhydride (10.0 ml, 14.8g, 70 mmol) at 0°C with stirring. A solution of 4-(S)-isopropyl-2-methyl-2-thiazoline (0.5g, 3.5 mmol) in dichloromethane (10 ml) at 0°C was added. After stirring for 4h at 0°C t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed no starting material to be present. Evaporation gave a brown liquid which was Kugelrohr distilled to give 4-(S)-isopropyl-2-methyl-2-thiazoline 3-oxide as a yellow liquid (0.35g, 63%) b.p. 126°C (oven temperature) at 0.5 torr. δ_H (80 MHz) 4.8-4.4 (1H, m), 3.80 (1H, half of AB pattern of d, J_{AB}12, J_{AX} 10Hz), 3.50 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.65 (3H, s), 2.10 (1H, octet, J 7Hz), 1.05 (3H, d, J 7Hz) and 1.00 (3H, d, J 7Hz); δ_c 193.8 (s), 73.3 (d), 34.0 (t), 31.7 (d), 17.9 (q), 17.8 (q) and 17.0 (q); m/z 160 (M^++1, 61%), 159 (M^+,7), 143 (23), 128 (100), 118 (28), 114 (67) and 100 (72).

2. Oxidation of 4-(S)-benzyl-2-methyl-2-thiazoline

a. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (1.0 ml, 1.1g, 9.0 mmol) was added

dropwise to trifluoroacetic acid anhydride (10.0 ml, 14.8g, 70 mmol) at 0°C with stirring. A solution of 4-(S)-benzyl-2-methyl-2-thiazoline (0.67g, 3.5 mmol) in dichloromethane (15 ml) was added. After stirring for 2h at 0°C, the solution was left to warm up to room temperature overnight. T.l.c. (SiO_2, ether) showed no starting material to be present. Evaporation, followed by Kugelrohr distillation gave 4-(S)-benzyl-2-methyl -2-thiazoline 3-oxide (0.23g, 34%) as a brown oil b.p. 167°C (oven temperature) at 0.3 torr, δ_H 7.6-7.1 (5H, m), 5.25-4.85 (1H, m), 3.65 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 9Hz), 3.40 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 6Hz), 3.25 (1H, half of AB pattern of d, J_{AB}14, J_{AX}5Hz), 3.10 (1H, half of AB pattern of d, J_{AB} 14, J_{BX}8Hz) and 2.60 (3H, d, J 1Hz); δ_c (75 MHz) 191.6 (s), 133.9 (s), 129.4 (2C, d), 129.3 (2C, d), 127.9 (d), 68.4 (d), 38.6 (t), 35.9 (t) and 18.1 (q); m/z 191 (M^+-O, 9%), 144 (2), 117 (19), 115 (7), 104 (8), 101 (9) and 92 (19).

3. Oxidation of 4-(S)-isopropyl-2-phenyl-2-thiazoline

a. Reaction with nitrogen dioxide

A solution of nitrogen dioxide (1.74g, 14.6 mmol) in dichloromethane (20 ml) was added to a stirred solution of 4-(S)-isopropyl- 2-phenyl-2-thiazoline (1.00g, 4.88 mmol) in dichloromethane (20 ml) at room temperature. After stirring for 20h,

evaporation gave a yellow oil (1.3g). Column chromatography on silica gel gave the thiazoline as a yellow oil (0.15g) using petroleum ether/ether (1:1) as the solvent. 4-(S)-Isopropyl-2-phenyl-2-thiazoline 3-oxide was obtained as a yellow oil (0.32g, 30%) with 10% methanol in ethyl acetate. δ_H (80 MHz) 8.2-8.0 (2H, m), 7.7-7.3 (3H, m), 5.2-4.9 (1H, m), 3.85 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 10Hz), 3.50 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.40 (1H, octet, J 8Hz), 1.10 (3H, d, J 8Hz), and 1.05 (3H, d, J 8Hz); m/z 206 (M^++1-O, 5%), 205 (M^+-O, 21), 162 (100), 144 (26) and 122 (14).

b. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (0.46 ml, 0.51g, 4.1 mmol) was added dropwise to trifluoroacetic acid anhydride (6.8 ml, 10.1g, 47.7 mmol) at 0°C with stirring. A solution of 4-(S)-isopropyl-2-phenyl -2-thiazoline (0.50g, 1.46 mmol) in dichloromethane (10 ml) at 0°C was added. After stirring for 4h at 0°C, and at room temperature for a further 10h, t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed material more polar than the starting material to be present. Evaporation gave 4-(S)-isopropyl-2- phenyl-2-thiazoline 3-oxide as an orange liquid. δ_H 8.0-7.4 (5H, m), 5.0-4.7 (1H, m), 3.90 (1H, half of overlapping AB pattern of d, J_{AB} 12, J_{AX} 10Hz), 3.60 (1H, half of overlapping AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.40 (1H, octet, J 8Hz), 1.10 (3H, d, J

8Hz) and 1.05 (3H, d, J 8Hz).

4. Oxidation of 4-(S)-benzyl-2-phenyl-2-thiazoline

a. Reaction with nitrogen dioxide

A solution of nitrogen dioxide (4.23g, 45.9 mmol) in dichloromethane (30 ml) was added to a stirred solution of 4-(S)-benzyl-2-phenyl-2- thiazoline (3.00g, 11.85 mmol) in dichloromethane (30 ml) at room temperature. After stirring for 18h, evaporation gave an orange oil (3.12g). ^{1}H n.m.r. showed oxidation of the starting material. Column chromatography on silica gave the thiazoline as a yellow oil (70 mg) with ether as the eluant. Two fractions were obtained using 25% methanol in ethyl acetate as the solvent: the thiazoline (2.20g) as an orange oil at R_F 0.7 and 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide as an orange oil (0.65g, 21%) at R_F 0.0. The thiazoline 3-oxide had identical spectroscopic properties to that obtained in b. below.

b. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (4.56 ml, 5.04g, 41.1 mmol) was added dropwise to trifluoroacetic acid anhydride (4.56 ml, 6.8g, 320 mmol) at 0°C with stirring. A solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (4.0g, 15.8 mmol) in dichloromethane (10 ml) at 0°C was added

dropwise.

After stirring for 4h at 0°C, and for a further 40h at room temperature t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed material more polar than the starting material to be present. Evaporation, followed by column chromatography on silica gave 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide as an orange oil (2.5g, 59%) with 15% methanol in ethyl acetate as the eluant. δ_H 8.0-7.8 (2H, m), 7.6-7.2 (3H, m), 7.20 (5H, s), 5.3-4.9 (1H, m), 3.50 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 8Hz), 3.30 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 5Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 4Hz) and 3.00 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz); δ_c (20 MHz) 183.1 (s), 135.5 (2C, s), 129.6 (4C, d), 129.5 (2C,d), 129.1 (2C, d), 127.4 (2C, d), 70.9 (d), 38.8 (t) and 35.4 (t); m/z 254 (M^++1, 6%), 253 (M^+, 4), 206 (6), 162 (100), 135 (7), 121 (50), 115 (30) and 104 (47).

5. Oxidation of 4-(R)-ethyl-2-phenyl-2-thiazoline

a. Reaction with nitrogen dioxide

A modification of the method of Horner was used[165]. A solution of nitrogen dioxide (25.0g, 543 mmol) in dichloromethane (60 ml) was added to a stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (4.0g, 20.9 mmol) in dichloromethane (90 ml) at room temperature. After stirring for 20h, evaporation at 25°C gave a greenish-yellow oil.

Washing with hexane/dichloromethane (3:1) gave 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide as a yellow oil (2.4g, 55%). Evaporation of the solution gave a yellow sticky solid which was washed with ether to give a white solid (0.41g). ^1H n.m.r., infra-red spectroscopy and t.l.c (SiO_2, ethyl acetate, R_F 0.6) indicated the presence of benzoic acid. The thiazoline 3-oxide was stored at -30°C over a period of 2-3 months. δ_H (300 MHz) 8.1-7.9 (3H, m), 7.6-7.3 (2H, m), 5.00 (1H, m), 3.90 (1H, half of AB pattern of d, J_{AB}12, J_{AX} 8Hz), 3.50 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.10 (1H, m), 1.90 (1H, m) and 1.00 (3H, t, J 8Hz); δ_c (75 MHz) 187.4 (s), 136.9 (s), 130.3 (2C, d), 130.2 (2C, d), 128.6 (d), 69.2 (d), 35.6 (t), 26.2 (t) and 9.5 (q); m/z 191 (M^+, 42%), 162 (100), 145 (10), 130 (31) and 122 (12).

b. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (4.47 ml, 40.0 mmol) was added dropwise to trifluoroacetic acid anhydride (44.7 ml, 66.3g, 314 mmol) at 0°C with stirring. A solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (3.0g, 15.7 mmol) in dichloromethane (50 ml) at 0°C was added. The solution was left to warm up to room temperature for 2h. T.l.c. (SiO_2, hexane/ether 1:1) showed material more polar than the starting material. Evaporation at 25°C gave an orange oil (5.5g). ^1H n.m.r. showed the presence of 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide

plus an excess residue of trifluoroacetic acid. Rotatory evaporation using a dry-ice condenser under a vacuum of 1 torr at 25°C over 2h was only partially successful at removing the residual trifluoroacetic acid suggesting binding in the form of an ionic complex to the N-oxide. Column chromatography on silica using hexane/ether/triethylamine (20:3:1)) (900 ml) to remove the excess trifluoroacetic acid, gave 4-(R)-ethyl-2-phenyl-2-thiazoline as a colourless liquid (2.18g).

6. Oxidation of 2-t-butyl-4-(S)-isopropyl-2-thiazoline

a. Reaction with peroxytrifluoroacetic acid

30% hydrogen peroxide (0.46 ml, 0.51g, 4.1 mmol) was added dropwise to trifluoroacetic acid anhydride (6.8 ml, 10.1g, 47.7 mmol) at 0°C with stirring. A solution of 2-butyl-4-(S)-isopropyl-2-thiazoline (0.30g, 1.62 mmol) in dichloromethane (20 ml) at 0°C was added. The solution was left to warm up to room temperature over 18h. T.l.c. (SiO_2, petroleum ether/ether (1:1)) showed material more polar than the starting material to be present. Evaporation gave 2-t-butyl-4-(S) -isopropyl-2-thiazoline 3-oxide as an orange liquid (0.42g). δ_H (80 MHz) 5.0-4.6 (1H, m), 3.80 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 10Hz), 3.45 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 6Hz), 2.5-2.0 (1H, m), 1.40 (9H, s), 1.05 (3H, d, J 7Hz) and 1.00 (3H, d, J 7Hz), δ_c (75 MHz) 205.5 (s), 73.0 (d), 31.4 (s), 31.1 (t), 28.8 (3C, q), 17.8 (q) and 15.8 (q);

c.i.m.s. m/z 186 (M^++1-O, 100%), 170 (12), 156 (5), 142 (7), 119 (4), 102 (5), 86 (6), 72 (4) and 58 (8); m/z 186 (M^++1-O, 14%), 185 (M^+-O, 22), 170 (12), 156 (3), 142 (100), 126 (18), 102 (28), 87 (18), 69 (52) and 57 (43).

E. S-Oxidation, ring-opening with oxidation and aromatisation of 2-thiazolines

1. Oxidation of 4-(S)-isopropyl-2-methyl-2-thiazoline

a. Reaction with potassium monopersulphate

Potassium monopersulphate (5.1g, 8.3 mmol) was added to a stirred solution of 4-(S)-isopropyl-2-methyl-2-thiazoline (1.1g, 7.7 mmol) in 50% aqueous tetrahydrofuran (250 ml) at room temperature. After stirring for 45h, t.l.c. (SiO_2, ether) showed no starting materials to be present. The yellow suspension was partitioned using ether (100 ml). The aqueous layer was extracted with ether (100 ml) and ethyl acetate (100 ml). Drying and evaporation gave 2-(S)-acetylamino-3-methyl-1- butyldisulphide as yellow crystals (0.30g, 20%). δ_H (80 MHz) (CD_3SOCD_3) 6.2-5.9 (2H, br s), 4.1-4.0 (2H, m), 2.90 (4H, d, J 6Hz), 2.1-1.8 (2H, m), 2.00 (6H, s), 0.90 (6H, d, J 9Hz) and 0.85 (6H, d, J 9Hz); m/z 320 (M^+, 25%), 305 (21), 160 (16), 144 (24) and 128 (32).

2. Oxidation of 4-(S)-benzyl-2-methyl-2-thiazoline

a. Reaction with potassium monopersulphate

A solution of potassium monopersulphate (23.9g, 39 mmol) in water (200 ml) was added dropwise to a stirred solution of 4-(S)-benzyl-2- methyl-2-thiazoline (5.0g, 26 mmol) in tetrahydrofuron (100 ml) at 0°C. After stirring for 114h, the white suspension was partitioned using ether (250 ml). The aqueous layer was further extracted with ether (250 ml) and ethyl acetate (250 ml × 2). Drying and evaporation gave a white solid (2.3g) which was recrystallised using hexane/ethyl acetate (1:2) to give 2-(S)-acetylamino-3-phenyl-1-propyldisulphide (1.3g, 24%) as colourless crystals m.p. 160-162°C. (Found : C, 63.0; H, 6.85; N, 6.6. $C_{22}H_{28}N_2O_2S_2$ requires C, 63.45; H, 6.8; N, 6.7%); $[\alpha]_D^{25}$ - 45.3 (c 0.8, MeOH); ν_{max} 3300 (NH), 1710, 1630 (C=0), 1520, 740 and 700 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 7.8 (2H, d, J 6Hz), 7.2 (10H, s), 4.3-3.9 (2H, m), 2.9-2.7 (8H, m) and 1.75 (6H, s); δ_c (20 MHz, CD_3SOCD_3) 168.9 (2C, s), 138.4 (2C, s), 129.1 (4C, d), 128.1 (4C, d), 126.1 (2C, d), 49.7 (2C, d), 42.9 (2C, t), 38.9 (2C, t) and 22.6 (2C, q); m/z 325 (M^+-CH_2Ph, 17%), 210 (21), 208 (21), 192 (28), 176 (52), 162 (34) and 150 (100).

b. Reaction with m-chloroperoxybenzoic acid

m-chloroperoxybenzoic acid (3.5g, 20.3 mmol) was added to a

solution of 4-(S)-benzyl-2-methyl-2-thiazoline (1.6g, 8.4 mmol) in ether (350 ml) at -71°C with stirring. After stirring for 2h, the solution was allowed to warm up to room temperature over 41h. The solution was washed with saturated aqueous sodium carbonate solution (50 ml × 6) and water (100 ml). Drying and evaporation of the solution gave a yellow oil. ^1H n.m.r. showed thiazoline plus a new compound in the ratio of 3:5 (using the methyl group). Column chromatography (SiO_2, petroleum ether/ether (1:1)) gave S-(2-(S)-acetylamino-3-phenylpropyl) m-chlorothiobenzoate as colourless crystals (0.73g, 25%) with R_F 0.20. ν_{max} 3320 (NH), 1690 (C=0), 1640 (C=0), 1530, 1130, 960, 760 and 600 cm^{-1}; δ_H (80 MHz) 7.75-7.30 (4H, m), 7.30 (5H, s), 6.6-6.4 (1H, br d, J 6Hz), 4.7-4.2 (1H, m), 3.10 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 6Hz)), 3.05 (2H, d, J 6Hz), 2.90 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), and 2.30 (3H, s); δ_C (20 MHz) 169.9 (s), 165.8 (s), 136.9 (s), 134.6 (s), 131.4 (s), 130.2 (2C, d), 129.3 (2C, d), 128.6 (2C, d), 127.4 (d), 124.8 (2C, d), 52.2 (d), 40.2 (t), 32.3 (t) and 30.5 (q); m/z 258 and 256 (35, 100%, M^+ - CH_2Ph), 216 and 214 (12, 35), 208 (25), 158 and 156 (15, 45).

3. Oxidation of 4-(S)-isopropyl-2-phenyl-2-thiazoline

a. Reaction with one equivalent of peroxyacetic acid

Anhydrous sodium carbonate (1.99g, 21.6 mmol) was added to a stirred solution of 4-(S)-isopropyl-2-phenyl-2-thiazoline (1.0g, 4.87 mmol) in dichloromethane (25 ml) at room temperature. 35% peroxyacetic acid (0.99g, 5.36 mmol) was added slowly. After stirring for 20h, filtration and evaporation gave a mixture of 4-(S)-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide and 2-(S)-benzoylamino-3-methylbutane-1-sulphonic acid as yellow crystals (0.24g), (ratio 1:1 by N-methyne proton). Flash chromatography on silica using ether as the eluant gave 4-(S)-isopropyl-2-phenyl-2-thiazoline 1,1-dioxide as colourless crystals m.p. 183-185°C (55 mg, 5%). (Found : C, 58.8; H, 6.6; N, 5.4. $C_{12}H_{15}NO_2S$ requires C, 60.7; H, 6.4; N, 5.8%); δ_H (80 MHz) 8.2-8.0 (2H, m), 7.6-7.2 (3H, m), 4.95 (1H, q, J 7Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 5Hz), 2.60 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 7Hz), 2.00 (1H, octet, J 7Hz), 1.10 (3H, d, J 7Hz) and 0.95 (3H, d, J 7Hz); δ_c (20 MHz) 161.6 (s), 132.5 (s), 129.0 (2C, d), 128.2 (2C, d), 126.6 (d), 67.0 (d), 49.1 (t), 33.3 (d), 18.5 (q) and 18.2 (q); c.i.m.s. m/z 238 (M^++1, 16%), 237 (M^+,2), 135 (15), 104 (42), 70 (100) and 55 (39).

b. Reaction with one equivalent of 2-benzenesulphonyl-3-phenyloxaziridine

2-Benzenesulphonyl-3-phenyloxaziridine was prepared in 78% yield by the method of Davis[166] as colourless crystals m.p. 94-96°C (lit. m.p.[166] 96-98°C).

A solution of 2-benzenesulphonyl-3-phenyloxaziridine (0.70g, 2.68 mmol) in dichloromethane (20 ml) was added to a solution of 4-(S)- isopropyl-2-phenyl-2-thiazoline (0.50g, 2.44 mmol) in dichloromethane (20 ml) at room temperature. After stirring for 65h, evaporation gave a yellow oil. Washing with ether to remove the oxaziridine gave yellow crystals (0.29g). ^{1}H n.m.r. showed 4-(S)-isopropyl-2-phenyl-2-thiazoline 1,1 dioxide and 2-(S)-benzoylamino-3-methylbutanesulphonic acid to be present in a 1:1 ratio (using the N-methyne proton).

c. Reaction with three equivalents of peroxyacetic acid

Anhydrous sodium carbonate (4.62g, 49.9 mmol) was added to a solution of 4-(S)-isopropyl-2-phenyl-2-thiazoline (1.00g, 4.86 mmol) in dichloromethane (25 ml) with stirring at room temperature. 35% peroxyacetic acid (3.17g, 14.6 mmol) was added slowly. After stirring for 18h, filtration and evaporation gave colourless crystals (0.57g). Recrystallisation using ether/acetonitrile (1:1) gave 2-(S)-benzoylamino-3-methylbutanesulphonic acid as colourless

prisms (0.38g, 28%) m.p. 178-180°C. (Found : C, 53.2; H, 6.3; N, 5.1. $C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.2; N, 5.2%); $[\alpha]_D^{25}$ + 26.6° (c 0.84, MeOH); ν_{max} 3700-2100 (br OH), 3340 (NH), 1650 (C=0), 1540, 1250, 1100, 1030, 990, 880, 780, 720 and 690 cm^{-1}; δ_H (80 MHz) 8.45 (1H, br d, J 8Hz), 8.3 (1H, br s), 8.2-8.0 (2H, m), 7.6-7.4 (3H, m), 4.3 (1H, q, J 6Hz), 3.30 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 3.00 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 6Hz), 2.10 (1H, octet, J 6Hz), 1.10 (3H, d, J 6Hz) and 1.00 (3H, d, J 6Hz); δ_c (20 MHz, CD_3SOCD_3) 166.3 (s), 135.4 (s), 131.1 (d), 128.4 (2C, d), 127.4 (2C, d), 51.8 (d), 39.2 (t), 31.3 (d), 18.9 (q) and 18.5 (q); c.i.m.s. m/z 271 (M^+, 1%), 270 (M^+-1, 20%), 256 (15), 238 (17), 224 (67), 208 (70), 190 (100), 176 (10), 139 (78), 122 (56), 104 (24), 86 (22) and 72 (22).

d. Conversion of the products from the one equivalent peroxyacetic acid reaction to the product from the three equivalent peroxyacetic acid reaction.

Anhydrous sodium carbonate (1.00g, 10.7 mmol) was added to a stirred solution of 4-(S)-isopropyl-2-phenyl-2-thiazoline 1,1 dioxide and 2-(S)-benzoylamino-3-methylbutanesulphonic acid (1:1 ratio) (0.24g) in dichloromethane (25 ml) at room temperature. 35% peroxyacetic acid (0.47g, 2.18 mmol) was added slowly. After stirring for 48h, filtration and evaporation gave colourless crystals (150 mg).

^1H n.m.r. showed only 2-(S)-benzoylamino-3-methylbutanesulphonic acid to be present.

4. Oxidation of 4-(S)-benzyl-2-phenyl-2-thiazoline

a. Reaction with one equivalent of peroxyacetic acid

Anhydrous sodium carbonate (0.50g, 5.3 mmol) was added to a solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (0.30g, 1.19 mmol) in dichloromethane (20 ml) with stirring at room temperature. 35% peroxyacetic acid (0.26, 1.20 mmol) was added slowly. After stirring for 20h, filtration and evaporation gave a mixture of 4-(S)-benzyl-2-phenyl-2-thiazoline 1,1-dioxide and 2-(S)-benzoylamino-3-phenylpropane- sulphonic acid as a yellow oil (0.35g) (ratio 1:1 by N-methyne proton). δ_H (80 MHz), 8.5 (1H, br d, J 8Hz), 8.3 (1H, br s), 8.2-8.0 (4H, m), 7.6-7.4 (6H, m), 7.30 (5H, s), 7.25 (5H, s), 5.40 (1H, quintet, J 6Hz), 5.0-4.6 (1H, m) and 3.5-2.5 (8H, complex m).

b. Reaction with three equivalents of peroxyacetic acid

Anhydrous sodium carbonate (4.8g, 50.8 mmol) was added to a solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (12.8g, 5.04 mmol) in dichloromethane (20 ml) with stirring at room temperature. 35% peroxyacetic acid (3.2g, 14.7 mmol) was added slowly. After stirring for 20h, filtration and evaporation gave 2-(S)-benzoylamino-3-

phenylpropanesulphonic acid as colourless prisms (0.60g, 37%). (Found : C, 58.5; H, 5.3; N, 4.2. $C_{16}H_{17}NO_4S$ requires C, 60.2; H, 5.4; N, 4.4%); δ_H (80 MHz), 8.5 (1H, br d, J 8Hz), 8.3 (1H, br s), 8.2-8.0 (2H, m), 7.6-7.4 (3H, m), 7.30 (5H, s), 4.9-4.6 (1H, m), 3.40 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 3.25 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 7Hz), 2.95 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz) and 3.00 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 9Hz); δ_c (20 MHz, CD_3SOCD_3) 165.8 (s), 138.9 (s), 134.9 (s), 131.1 (d), 129.4 (2C, d), 128.2 (4C, d), 127.1 (2C, d), 126.1 (d), 53.7 (d), 48.6 (t) and 39.4 (t); c.i.m.s. m/z 337 ($M^+ + NH_4$, 5%), 320 ($M^+ + 1$), 302 (12), 272 (52), 254 (46), 238 (100), 180 (6), 162 (8), 146 (12), 122 (44), 105 (27) and 91 (10).

c. Conversion of the products from the one equivalent peroxyacetic acid reaction to the product from the three equivalents peroxyacetic acid reaction

Anhydrous sodium carbonate (0.9g, 9.8 mmol) was added to a stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 1,1-dioxide and 2-(S)-benzoylamino-3-phenylpropanesulphonic acid (1:1 ratio) (0.30g) in dichloromethane (25 ml) at room temperature. 35% peroxyacetic acid (0.45g, 2.10 mmol) was added slowly. After stirring for 20h, evaporation gave colourless crystals (0.21g). ^1H n.m.r. showed only 2-(S)- benzoylamino-3-phenylpropanesulphonic acid to be present.

d. Reaction with m-chloroperoxybenzoic acid

m-Chloroperoxybenzoic acid (2.88g, 14.4 mmol) was added to a stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (1.20g, 4.76 mmol) in dichloromethane (100 ml) at room temperature. After stirring for 44h, the insoluble white solid (0.80g) was filtered off. Recrystallisation using ether/acetonitrile (1:1) gave 2-(S)-benzoylamino-3-phenyl- propanesulphonic acid as colourless prisms (0.80g, 53%) m.p. 211-212°C. (Found : C, 58.75; H, 5.15; N, 4.15. M^+, 320.0975. $C_{16}H_{17}NO_4S$ requires C, 60.2; H, 5.4; N, 4.4%; M^+, 320.0956); $[\alpha]_D^{25}$ - 40.0° (c 0.37, MeOH); ν_{max} 3600-2400 (br OH), 3300 (NH), 1710 (C=0), 1650, 1250, 1100, 1010 and 710 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 8.55 (1H, br d, J 8Hz), 8.3 (1H, br s), 7.9-7.7 (2H, m), 7.6-7.4 (3H, m), 7.30 (5H, s), 4.6-4.3 (1H, m), 3.20 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 3.00 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 6Hz), 2.90 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz) and 2.80 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 6Hz); δ_c (20 MHz, CD_3SOCD_3) 165.8 (s), 139.0 (s), 134.9 (s), 131.1 (d), 129.4 (2C, d), 128.3 (4C, d), 127.2 (2C, d), 126.1 (d), 53.7 (d), 48.7 (t) and 39.4 (t).

e. Reaction with t-butyl hydroperoxide

A solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (0.40g, 1.58 mmol) in dichloromethane (40 ml) was stirred while a solution of t-butyl hydroperoxide (3.30M, 1 ml, 3.30 mmol) in dichloromethane was added slowly. After stirring for 35h at room temperature, evaporation gave a green oil (0.63g). ^1H n.m.r. showed the presence of 4-benzyl-2-phenyl- thiazole and another new product in a ratio of 2:5. Washing with dry ether gave a pale green solid. Extraction using boiling ethyl acetate gave product A as pale green crystals (0.20g) on evaporation. The insoluble yellow oil (40 mg) product B remained behind. Product A could be 2-(S)- benzoylamino-3-phenylpropanesulphonic acid. Product B is difficult to identify.

Product A ν_{max} 3600-2300 (br OH), 3300 (NH), 1720 (C=0), 1640, 1530, 1310, 1150, 1100, 1010 and 680 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 8.35 (1H, br d, J 8Hz), 7.9-7.6 (2H, m), 7.6-7.4 (3H, m), 7.25 (5H, s), 4.9-4.6 (1H, br s), 4.6-4.2 (1H, m) and 3.2-2.6 (4H, m); δ_c (75 MHz, CD_3SOCD_3) 166.0 (S), 138.4 (s), 134.6 (s), 130.9 (d), 129.0 (2C, d), 128.0 (4C, d), 127.1 (2C, d), 126.0 (d), 54.7 (d), 50.4 (t) and 39.7 (t); c.i.m.s. m/z 318 (6%), 302 (6), 286 (12), 272 (25), 254 (72), 238 (95), 162 (55), 122 (100), 105 (42) and 91 (15).

Product B δ_H (300 MHz, CD_3SOCD_3) 7.9-7.7 (2H, m), 7.6-7.4 (3H, m), 7.3-7.1 (5H, m), 5.00 (1H, quintet, J 8Hz), 3.60 (1H, half of AB pattern

of d, J_{AB} 12, J_{AX} 8Hz), 3.30 (1H, half of AB pattern of d, J_{AB} 12, J_{BX}8Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 8Hz) and 2.75 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz); δ_c (75 MHz, CD_3SOCD_3) 165.9 (s), 137.2 (s), 133.3 (s), 129.4 (2C, d), 128.5 (2C, d), 128.1 (2C, d), 126.8 (2C, d), 126.5 (d), 125.9 (d), 73.9 (d), 52.6 (t) and 48.8 (t).

f. Reaction with potassium permanganate using phase transfer conditions

A modification of the method of Gokel was used[167]. Benzyltriethylammoniun chloride (0.10g, 0.43 mmol) was added to a vigorously stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline (0.50g, 1.98 mmol) in dichloromethane (25 ml). A solution of potassium permanganate (0.63g, 3.96 mmol) in water (50 ml) was added. After stirring for 12h, the mixture was filtered to remove manganese dioxide and the two phases were separated. The aqueous layer was extracted with dichloromethane (× 2). The combined organic phase was extracted with 1M aqueous hydrazine dihydrochloride (50 ml) (to reduce any remaining manganese salts) and washed with brine (50 ml) and dried. After evaporation a yellow oil (0.38g) was obtained. ^1H n.m.r. showed thiazoline and 4-benzyl-2-phenylthiazole in a ratio of 1:2 (using the benzyl methylene protons). δ_H (80 MHz) 8.0-7.8 (2H, m), 7.5-7.3 (3H, m),

7.30 (5H, s), 6.70 (1H, t, J 1Hz) and 4.20 (2H, d, J 1Hz).

5. Oxidation of 4-(R)-ethyl-2-phenyl-2-thiazoline

a. Reaction with one equivalent of peroxyacetic acid

35% peroxyacetic acid (1.16g, 5.34 mmol) was added slowly to a stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (1.00g, 5.24 mmol) in dichloromethane (25 ml) over anhydrous sodium carbonate (1.00g, 10.8 mmol). After stirring at room temperature for 22h, filtration, followed by drying and evaporation gave a green oil (1.15g). Flash chromatography on silica gave three main fractions: 4-(R)-ethyl-2- phenyl-2-thiazoline as a colourless liquid (40 mg) using hexane/ether (4:1) as the eluant (R_F 0.8); a green oil (540 mg), a mixture of three unknown products by ^{13}C n.m.r., using ethyl acetate as the solvent (R_F 0.40); and 4-(R)-ethyl-2-phenyl-2-thiazoline 1,1-dioxide as a yellow oil (90 mg) using ethyl acetate as the eluant (R_F 0.30). The sulphone later gave yellow prisms (20 mg) m.p. 158-160°C. (Found : C, 58.75; H, 6.15; N, 5.5; M^+-O, 207.0704; $C_{11}H_{13}NO_2S$ requires C, 59.15; H, 5.85; N, 6.25%. M^+-O, 207.0718); $[\alpha]_D^{25}$ - 10.9° (c 0.5, $CHCl_3$); ν_{max} ($CHCl_3$), 1730, 1650, 1620, 1580, 1520, 1490, 1460, 1450, 1320, 1250, 1050, 1030, 980, 950, 920, 780 and 690 cm^{-1}; δ_H (300 MHz) 8.1-8.0 (2H, m), 7.5-7.4 (3H, m), 5.00 (1H, quintet, J 6Hz), 3.35 (1H, half of AB pattern of d, J_{AB}14, J_{AX} 6Hz), 2.60

(1H, half of AB pattern of d, J_{AB} 14, J_{BX} 6Hz), 1.90 (1H, m), 1.80 (1H, m) and 1.10 (3H, t, J 6Hz); δ_c (75 MHz) 168.6 (s), 132.7 (2C, d), 130.5 (s), 130.3 (2C, d), 129.8 (d), 78.5 (d), 57.1 (t), 28.8 (t) and 11.5 (q); m/z 208 (M^++1-O, 10%) 207 (M^+-O,9) 191 (2), 162 (17), 151 (6), 130 (8), 104 (100), 77 (80) and 55 (72).

b. Reaction with three equivalents peroxyacetic acid

35% peroxyacetic acid (3.44g, 15.9 mmol) was added to a vigorously stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (1.0g, 5.3 mmol) in dichloromethane (40 ml) over anhydrous sodium carbonate (3.6g, 34 mmol) at room temperature. After stirring for 18h, filtration and evaporation gave colourless crystals (0.64g). ^1H n.m.r. showed two products to be present in a ratio of 18:13 (using the ring methyne protons). Recrystallisation using dry acetonitrile/dry ether (1:1) failed. Washing with dichloromethane and filtering gave 2-(R)-benzoylaminobutanesulphonic acid as colourless crystals (0.21g) m.p. 160-162°C. (Found : C, 51.1; H, 5.95; N, 5.45. $C_{11}H_{15}NO_4S$ requires C, 51.35; H, 5.85; N, 5.45%); $[\alpha]_D^{25}$ + 31.2 (c 0.9, MeOH); ν_{max} 3300 (NH), 1630 (C=0), 1520, 1300, 1180, 1060, 870, 840, 730 and 700 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 8.40 (1H, br d, J 7Hz), 7.9-7.7 (2H, m), 7.6-7.4 (3H, m), 6.0-5.7 (1H, br s), 4.4-4.0 (1H, m), 3.00 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 9Hz), 2.70 (1H, half of AB pattern of d,

J_{AB}12, J_{BX} 5Hz), 1.8-1.4 (2H, m) and 0.85 (3H, t, J 6Hz); δ_c (75 MHz, CD_3SOCD_3) 165.8 (s), 135.1 (s), 128.4 (2C, d), 127.1 (2C, d), 126.9 (d), 63.1 (d), 46.2 (t), 27.3 (t) and 10.2 (q); m/z 258 (M^++1, 17%), 257 (M^+,4), 229 (11), 176 (51), 162 (62), 146 (100) and 130 (81).

c. Reaction with t-butylhydroperoxide

A solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (2.00g, 10.5 mmol) in dichloromethane (100 ml) was stirred while a solution of t-butyl hydroperoxide (3.60 M, 6.1 ml, 22.0 mmol) in dichloromethane was added slowly. After stirring at room temperature for 90h, the insoluble colourless crystals (120 mg) were filtered. Recrystallisation using acetonitrile/ether (2:1) gave 2-(R)-benzoylamino-1-butyldisulphide as colourless prisms (65 mg) m.p. 186-188°C. Evaporation of the solution gave a yellow oil (2.1g) which partially crystallised out. 1.1g of the oil was cooled at 0°C to obtain further crystals which were washed with hot hexane/ethyl acetate (1:2). Filtration of the colourless crystals (350 mg), followed by recrystallisation (× 2) using acetonitrile/ether (1:1) gave a product which could be 2-(R)-benzoylaminobutane-1-sulphonic acid as slightly impure colourless crystals (170 mg). Preparative t.l.c. on 200 mg of the oil using hexane/ether (6:1) as the eluant gave 4-ethyl-2-phenylthiazole as a colourless liquid (60 mg) at R_F 0.56.

2-(R)-benzoylamino-1-butyldisulphide (Found : C, 62.0; H, 6.6; N, 6.6. $C_{22}H_{28}N_2O_2S_2$ requires C, 63.4; H, 6.8; N, 6.7%); $[\alpha]_D^{25}$ - 37.1° (c 1.0, MeOH); ν_{max} 3300 (NH), 1640 (C=0), 1530, 1310, 1250, 1180, 1150, 1120, 1080, 1030 and 700 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3), 8.2 (2H, d, J 7Hz), 8.0-7.8 (4H, m), 7.6-7.3 (6H, m), 4.1 (2H, quintet, J 7Hz), 2.95 (4H, d, J 7Hz), 1.8-1.4 (4H, m) and 0.90 (6H, t, 7Hz); δ_c (75 MHz, CD_3SOCD_3) 166.1 (2C, s), 134.7 (2C, s), 130.9 (2C, d), 128.0 (4C, d), 127.1 (4C, d), 50.3 (2C, d), 43.2 (2C, t), 26.4 (2C, q) and 10.3 (2C, q); m/z 417 (M^++1, 13%), 416 (M^+,5), 387 (9), 370 (12), 295 (29), 241 (15), 208 (52), 189 (81), 176 (40) and 162 (100).

4-ethyl-2-phenylthiazole

ν_{max} ($CHCl_3$) 1810, 1790, 1730, 1650, 1600, 1520, 1450, 1380, 1250, 1100 and 1000 cm^{-1}; δ_H (80 MHz) 8.1-7.8 (2H, m), 7.6-7.3 (3H, m), 6.90 (1H, t, J 1Hz), 2.85 (2H, q of d, J 8, 1Hz) and 1.35 (3H, t, J 8Hz); δ_c (75 MHz) 167.6 (s), 160.2 (s), 133.7 (s), 129.8 (d), 128.9 (2C, d), 126.5 (2C, d), 112.1 (d), 25.0 (t) and 13.4 (q); m/z 189 (M^+, 38%), 188 (M^+-1, 100), 174 (25), 161 (25), 142 (12), 121 (25), 104 (23), 85 (49), 77 (15), 71 (47) and 45 (41).

2-(R)-benzoylaminobutane-1-sulphonic acid

ν_{max} 3600-2100 (br OH), 3300 (NH), 1630 (C=0), 1340, 1300, 1230, 1150, 1050, 850, 770, 710 and 680 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3)

8.0-7.8 (2H, m), 7.8-7.5 (3H, m), 4.75 (1H, quintet, J 8Hz), 3.80 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 8Hz), 3.40 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.0-1.6 (2H, m) and 1.05 (3H, t, J 8Hz); m/z 257 (M^+,11%), 228 (15), 208 (90), 192 (100), 176 (81), 162 (51) and 152 (42).

d. Reaction with hydrogen peroxide

30% hydrogen peroxide (0.74 ml, 6.60 mmol) was added to a stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (0.30g, 3.14 mmol) in acetone at room temperature. After stirring for 20h, t.l.c. (SiO_2, hexane/ ether 1:1) showed the reaction had gone to completion. The insoluble colourless crystals (30 mg) were filtered. ^1H n.m.r., i.r. and m.s. showed 2-(R)-benzoylamino-1-butyldisulphide to be present. Evaporation at 25°C, gave a yellow oil (0.26g). ^1H n.m.r. showed the presence of 4-ethyl-2-phenylthiazole and a product which could be 2-(R)-benzoylaminobutane-1 -sulphonic acid in a ratio of 1:1 (using the ethyl methylene protons).

e. Reaction with tetrabutylammonium periodate

A modification of the method of Santaniello was used[168]. Tetrabutylammonium periodate (1.36g, 3.14 mmol) was added to a stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (0.30g, 1.57 mmol) in 1,2-dichloroethane (40 ml) at room temperature. After

heating under reflux for 90h, t.l.c. (SiO_2, hexane/ether 1:1) showed the reaction had gone to completion. Evaporating the solution to dryness, adding ether to remove the periodate, and then filtering the solid and evaporation gave an orange oil (0.27g). ^1H n.m.r. showed the presence of 4-ethyl-2-phenyl -thiazole and a product which could be 2-(R)-benzoylaminobutane- 1-sulphonic acid in a ratio of 1:1 (using the ethyl methylene protons).

f. Reaction with peroxyacetimidic acid

A modification of the method of Lumb was used[169]. 30% hydrogen peroxide (0.37 ml, 3.30 mmol) was added dropwise to acetonitrile (20 ml) with stirring. After stirring for ten minutes, a solution of 4-(R)-ethyl-2- phenyl-2-thiazoline (0.30g, 1.57 mmol) in acetonitrile (15 ml) was added. On stirring for a further 40h, t.l.c. (SiO_2 hexane/ether (1:1)) showed the reaction had gone to completion. Evaporation of the solution and addition of ether, gave insoluble colourless crystals (40 mg) which were filtered. ^1H n.m.r., i.r. and m.s. showed 2-(R)-benzoylamino-1-butyldisulphide to be present. Evaporation of the ether solution at 25°C, gave a yellow oil (0.34g). ^1H n.m.r. showed the presence of 4-ethyl-2-phenylthiazole and a product which could be 2-(R)-benzoylaminobutane-1-sulphonic acid present in a ratio of 1:1 (using the ethyl methylene protons).

g. Reaction with peroxyformic acid

30% hydrogen peroxide (2.5 ml, 22.0 mmol) was added to formic acid (10 ml) at room temperature with stirring. A solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (2.00g, 10.5 mmol) in formic acid (10 ml) was added. After stirring for 40h and evaporation at 25°C, most of the remaining formic acid was removed over sodium hydroxide pellets in vacuo. Flash chromatography (1.00g) on silica gave three main fractions: 4-ethyl-2-phenylthiazole as a yellow liquid (25 mg) using petroleum ether/ether (1:1) as the eluant (R_F 0.8); thiazoline and 2-(R)-benzoylamino-1-butyldisulphide in a ratio of 2:1 as a yellow liquid (90 mg) using ether as the solvent (R_F 0.80) and a mixture of two products (in a ratio of 1:1) as a colourless solid (130 mg) using ethyl acetate/isopropanol (3:1) as the solvent (R_F 0.70, 0.00). Washing the solid with isopropanol gave 2-(R)-benzoylamino-1-butyldisulphide as colourless insoluble crystals (50 mg).

h. Reaction with potassium permanganate using phase transfer conditions.

A modification of the method of Gokel was used[167]. Benzyltriethylammonium chloride (0.10g, 0.43 mmol) was added to a vigorously stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline (0.50g, 2.62 mmol) in dichloromethane (25 ml). A solution of

potassium permanganate (0.83g, 5.24 mmol) in water (50 ml) was added. After stirring for 12h, the mixture was filtered to remove the manganese dioxide. The two phases were separated, and the aqueous layer was extracted with dichloromethane (× 2). The combined organic phase was extracted with 1M aqueous hydrazine dihydrochloride (50 ml) (to reduce any remaining manganese salts) and washed with brine (50 ml) and dried. After evaporation a yellow oil was obtained (0.34g). ^{1}H n.m.r. showed the presence of thiazoline and 4-ethyl-2-phenylthiazole in a ratio of 1:1 (using the ethyl methylene protons).

The above procedure was repeated except using 18-crown-6 (0.050g, 0.20 mmol) as the catalyst. ^{1}H n.m.r. of the yellow oil (0.29g) showed the presence of 4-ethyl-2-phenylthiazole and thiazoline in a ratio of 2:1 (using the ethyl methylene protons).

i. Reaction with nickel peroxide

The method of Meyers was used[21]. A solution of 4-(R)-ethyl-2-phenyl-2- thiazoline (3.8g, 19.9 mmol) in A.R. chloroform (50 ml) was shaken vigorously with freshly prepared nickel peroxide (10.5g, activity 2.95 mequiv O_2/g by liberated iodine titration) for 70h. Filtration, followed by evaporation gave an orange liquid (4.1g). ^{1}H n.m.r. showed the presence of 4-(R)-ethyl-2-phenyl-2-thiazoline and 4-ethyl-2-phenyl-thiazole in a

ratio of 7:1 (using the ethyl methylene protons).

j. Preparation of 2-(R)-benzoylamino-1-chlorobutane

(i) A solution of 2-(R)-benzoylaminobutan-1-ol (2.00g, 10.4 mmol) and triethylamine (2.16 ml, 1.57g, 15.5 mmol) in 1,2-dichloroethane (50 ml) was stirred at room temperature while a solution of methanesulphonyl chloride (1.20 ml, 1.77g, 15.5 mmol) in 1,2 dichloroethane (50 ml) was added. After heating under reflux for 20h, t.l.c. (SiO_2, ether) showed a new product to be present (R_F 0.80). The solution was washed with water (× 3), dried and evaporated to give light brown crystals (1.4g). Recrystallisation using hexane/ethyl acetate (3:1) gave 2-(R)-benzoylamino-1-chlorobutane as colourless needles (0.9g, 41%) m.p. 96-99°C. (Found: C, 62.7; H, 6.6; N, 6.65. $C_{11}H_{14}ClNO$ requires C, 62.4; H, 6.65; N, 6.6%); $[\alpha]_D^{25}$ +44.4° (c 0.9, $CHCl_3$); ν_{max} (CH_2Cl_2) 3440 (NH), 1660 (C=0), 1510, 1490, 1460, 1440, 1350, 1290, 1150, 1070, 1030 and 800 cm^{-1}; δ_H (300 MHz), 7.8-7.7 (2H, m), 7.6-7.4 (3H, m), 6.4 (1H, br d, J 8Hz), 4.4-4.3 (1H, m), 3.80 (1H, half of AB pattern of d, J_{AB} 8, J_{AX} 4Hz), 3.75 (1H, half of AB pattern of d, J_{AB} 8, J_{BX} 2Hz), 1.80-1.65 (2H, m) and 1.00 (3H, t, J 6Hz); δ_c (75 MHz) 167.2 (s), 134.4 (s), 131.6 (d), 128.6 (2C, d), 127.0 (2C, d), 51.3 (d), 47.8 (t), 25.0 (t) and 10.4 (q); c.i.m.s. m/z 214 (M^++1, 32%), 212 (M^+-1, 100), 176 (32), 162 (5), 122 (3), 105 (25), 94 (3) and 58 (6).

(ii) A modification of the method of Snyder was used[170]. Triphenylphosphine (13.6g, 52.0 mmol) was added to a stirred solution of 2-(R)-benzoylaminobutan-1-ol (10.0g, 51.8 mmol) in carbon tetrachloride (200 ml). After stirring for 30 minutes at room temperature, t.l.c. (SiO_2, ether) showed the presence of a new product (R_F 0.8) plus triphenylphosphine oxide (R_F 0.15). Evaporation gave a yellow oil. ^{1}Hn.m.r. showed 2-(R)-benzoylamino-1-chlorobutane and triphenylphosphine oxide to be present. Column chromatography on silica gave 2-(R)-benzoylamino-1-chlorobutane as colourless crystals (4.5g, 41%) using ether as the eluant (R_F 0.8). ^{1}H n.m.r. confirmed the product as identical to the previous reaction.

k. Preparation of 2-(R)-benzoylaminobutane-1-thiol

A modification of the method of Mundy was used[171]. 2-(R)-benzoylamino-1-chlorobutane (1.00g, 4.73 mmol) was heated under reflux with sodium sulphide nonahydrate (3.40g, 14.2 mmol) in 1:1 ethanol/water (50 ml) for 44h. T.l.c. (SiO_2, petroleum ether/ether (1:1)) showed a new product to be present (R_F 0.70). Evaporation of the ethanol and extraction of the water layer with dichloromethane (× 3) gave colourless crystals (0.64g). Recrystallisation using hexane/ethyl acetate (3:1) gave 2-(R)-benzoylaminobutane-1-thiol as colourless prisms (0.42g, 43%) m.p. 89-91°C. (Found: C, 67.9; H, 8.0; N,

7.2. M^+, 209.0893. $C_{11}H_{15}NOS$ requires C, 63.1; H, 7.2; N, 6.7%; M^+, 209.0874); $[\alpha]_D^{25}$ + 41.1° (C 0.9, $CHCl_3$); ν_{max} 3600-2400 (br), 3280 (NH), 1640 (C=0), 1530, 1330, 1300, 1260, 1150, 1100, 1050, 800 and 700 cm^{-1}; δ_H (80 MHz) 7.9-7.7 (2H, m), 7.6-7.3 (3H, m), 6.5-6.2 (1H, br s), 4.2-3.9 (1H, m), 3.85 (1H, half of AB pattern of d, J_{AB}12, J_{AX}4Hz), 3.80 (1H, half of AB pattern of d, J_{AB} 12, J_{BX}5Hz), 2.6-2.3 (1H, br s), 1.9-1.5 (2H, m) and 1.00 (3H, t, J 8Hz); δ_c (75 MHz) 168.3 (s), 134.5 (s), 131.6 (d), 128.6 (2C, d), 127.0 (2C, d), 65.1 (d), 53.7 (t), 24.4 (t) and 10.7 (q); m/z 209 (M^+,5%), 208 (26), 176 (28), 162 (18), 122 (10), 105 (100) and 77 (46).

l. Preparation of 2-(R)-benzoylamino-1-butyldisulphide

A modification of the method of Friedländer was used[172]. Sulphur (S_8) (0.54g, 2.10 mmol) was added to melted sodium sulphide nonahydrate (1.64g, 6.84 mmol) to form disodium disulphide. A solution of 2-(R)-benzoylamino-1-chlorobutane (1.00g, 4.73 mmol) in ethanol (50 ml) was added with stirring at room temperature. After stirring for 20h, t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed a new product to be present at R_F 0.80. The ethanol was evaporated and water was added. Extraction using dichloromethane, followed by drying and evaporation gave yellow crystals (0.73g). Recrystallisation

using ethyl acetate/isopropanol (2:1) gave 2-(R)-benzoylamino -1-butyldisulphide as colourless prisms (0.49g, 50%) m.p. 145-147°C. ν_{max} (nujol), 3280 (NH), 1630 (C=0), 1530, 1370, 1310, 1250, 1080, 1020, 780 and 690 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 8.35 (2H, br d, J 8Hz), 8.0-7.8 (4H, m), 7.6-7.4 (6H, m), 4.4-4.1 (2H, m), 3.40 (2H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 3.15 (2H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz), 1.9-1.5 (4H, m), 1.00 (6H, t, J 7Hz); δ_c (75 MHz, CD_3SOCD_3) 166.2 (2C, s), 134.6 (2C, s), 131.0 (2C, d), 128.1 (4C, d), 127.1 (4C, d), 50.3 (2C, d), 43.8 (2C, t), 26.2 (2C, t) and 10.3 (2C, q); m/z 417 (M^++1, 6%), 416 (M^+,1), 364 (3), 314 (3), 295 (24), 277 (18), 256 (40), 224 (24), 208 (72), 192 (32) and 180 (14).

6. Oxidation of 2-t-butyl-4(S)-isopropyl-2-thiazoline

a. Reaction with three equivalents of peroxyacetic acid

Anhydrous sodium carbonate (2.0g, 21.4 mmol) was added to a solution of 2-t-butyl-4-(S)-isopropyl-2-thiazoline (0.30g, 1.62 mmol) in dichloromethane (25 ml) with vigorous stirring at room temperature. 35% peroxyacetic acid (1.05g, 4.84 mmol) was added slowly. After stirring for 18h, filtration and evaporation gave 3-methyl-2-(S)-trimethylacetylamino butanesulphonic acid as colourless prisms (0.24g, 96%) m.p. 150-152°C. (Found : C, 46.9; H, 8.1; N, 5.4; M^+, 252.1289. $C_{10}H_{20}NO_4S$ requires C, 47.8; H, 7.9; N, 5.5%; M^+,

252.1269); $[\alpha]_D^{25}$ + 18.7 (c 0.5, MeOH); ν_{max} 3700-2100 (br OH), 3340 (NH), 1620 (C=0), 1540, 1230, 1100, 1040, 810 and 800 cm^{-1}; δ_H (80 MHz), 8. 4(1H, br d, J 8Hz), 8.3 (1H, br s), 4.05 (1H, q, 7Hz), 3.15 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 7Hz), 2.80 (1H, half of AB pattern of d, J_{AB} 14, J_{BX}7Hz), 2.00 (1H, octet, J 7Hz), 1.40 (9H, s), 1.00 (3H, d, J 7Hz) and 0.95 (3H, d, J 7Hz); δ_c (20 MHz, CD_3SOCD_3), 176.8 (s), 51.8 (d), 50.9 (t), 37.5 (s), 30.9 (d), 27.6 (3C, q), 19.1 (q) and 18.5 (q); c.i.m.s. m/z 269 (M^++NH_4, 100%), 252 (M^++1, 56), 251 (M^+,5), 234 (8), 204 (6), 170 (75), 156 (18), 128 (20), 119 (12), 102 (14), 86 (16) and 57 (3); m/z 252 (M^++1, 100%), 251 (M^+,6), 234 (8), 208 (10), 170 (28), 128 (26), 102 (24), 85 (44), 69 (25) and 57 (84).

7. Oxidation of 4-(S)-benzyl-2-t-butyl-2-thiazoline

a. Reaction with three equivalents of peroxyacetic acid

Anhydrous sodium carbonate (4.2g, 44.9 mmol) was added to a solution of 4-(S)-benzyl-2-t-butyl-2-thiazoline (1.00g, 4.29 mmol) in dichloromethane (30 ml) with vigorous stirring at room temperature. 35% Peroxyacetic acid (2.77g, 12.8 mmol) was added slowly. After stirring for 17h, filtration and evaporation gave 2-(S)-trimethylacetyl amino-3-phenylpropanesulphonic acid as colourless crystals (0.61g, 48%). ν_{max} (CH_2Cl_2) 3700-2100 (br OH), 3440 (NH), 1650 (C=0), 1510,

1370, 1320, 1220, 1120, 1030, 920 and 800 cm^{-1}; δ_H (80 MHz) 8.3 (1H, br d, J 8Hz), 8.2 (1H, br s), 7.25 (5H, s), 4.6-4.4 (1H, m), 3.20 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 6Hz), 2.80 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 10Hz), 3.00 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 7Hz), 2.75 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 9Hz), and 1.40 (9H, s); m/z 299 (M^+, 21%), 284 (32), 266 (35), 250 (71), 218 (82), 208 (65), 204 (51), 160 (100) and 142 (79).

F. Reactions of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide

1. Oxygen transfer reactions to neutral acceptors

A solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.12 mmol) in toluene (30 ml) was heated under reflux for 18h. Evaporation gave a brown oil (0.34g). ^{1}Hn.m.r. showed the thiazoline to be present implying thermal loss of oxygen.

a. Reaction with styrene

Freshly distilled styrene (1.0g, 16.2 mmol) was added to a stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.40g, 1.48 mmol) in toluene (25 ml) at room temperature. After heating under reflux for 70h, evaporation at 60°C gave a brown oil (0.55g). Preparative t.l.c. (250 mg) on silica using petroleum ether/ether (1:1)

as the eluant gave four main fractions. Fraction 1 was a yellow oil (40 mg) eluted at R_F 0.85. G.c.m.s. at 70-200°C showed the presence of carbon-carbon coupling products, for example 1,3-diphenylbut-1-ene and benzaldehyde. ^1H n.m.r. showed a mixture of three to four products to be present. Fraction 2 was a colourless oil (20 mg) eluted at R_F 0.45. ^1H n.m.r. showed benzaldehyde to be present. Fraction 3 was a colourless liquid (19 mg) eluted at RF 0.20. ^1H n.m.r. showed 1-phenylethanol to be present. G.c.m.s. at 70-120°C and G.c. at 120°C confirmed the presence of 1-phenylethanol. Fraction 4 was a yellow oil (18 mg) eluted at R_F 0.00. ^1Hn.m.r. showed thiazoline 3-oxide to be present. The optical rotation of the 1-phenylethanol was measured as $[\alpha]_D^{25}$ + 0.7° (c 1.17, hexane). The value indicated a 1.7% enantiomeric excess[173].

b. Control reaction for styrene

A solution of freshly distilled styrene (1.0g, 16.2 mmol) in toluene was heated under reflux for 120h. Evaporation at 60°C, gave a colourless oil (1.1g). ^1H n.m.r. showed styrene epoxide, benzaldehyde, benzyl alcohol, a primary alcohol and polymerised material to be present. G.c.m.s. at 80-160°C indicated styrene epoxide, benzaldehyde and carbon-carbon coupling products to be present.

c. Attempted reaction with cyclohexene

A stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.35g, 1.38 mmol) in cyclohexene (30 ml) was heated under reflux for 70h. Evaporation at 25°C gave an orange oil (2.1g). ^{1}H n.m.r. showed the thiazoline plus a cyclohexene derived product to be present. Kugelrohr distillation gave a colourless liquid (80 mg) b.p. 168°C (oven temperature) at 0.3 torr. ^{1}H n.m.r. and ^{13}C n.m.r. showed cyclohexanol, cyclohexene and aromatic products to be present. G.c. at 130°C indicated a complex mixture of several different products to be present. G.c.m.s. at 80-100°C pointed to 1,2-cyclohexanediol and bi-2-cyclohexen-1-yl.

d. Control reaction for cyclohexene

A sample of cyclohexene (30 ml) was heated under reflux for 70h. Evaporation gave a colourless oil/solid (1.3g). ^{1}H n.m.r. showed no cyclohexene epoxide to be present. G.c. at 100-170°C showed several products to be present. G.c.m.s. at 100-170°C indicated 1,2-cyclohexanediol and bi-2-cyclohexen-1-yl to be present.

e. Preparation of cyclohexene epoxide

A modification of the method of Paquette was used[174]. m-Chloroperoxybenzoic acid (6.34g, 66.8 mmol) was added to a stirred solution of cyclohexene (5.0g, 60.8 mmol) in dichloromethane solution

(250 ml) at room temperature. After stirring for 20h, the solution was extracted with saturated aqueous sodium carbonate solution (× 4). Washing with water (× 2), followed by drying and evaporation gave a white solid (0.70g). ^1H n.m.r. showed cyclohexene epoxide and cyclohexene in a ratio of 12:1 (using the epoxide and olefinic protons) plus m-chlorobenzoic acid/m-chloroperoxybenzoic acid. δ_H (300 MHz) 3.1 (2H, s), 1.9 (2H, m), 1.8 (2H, m), 1.4 (2H, m) and 1.3 (2H, m).

f. Reaction with hexene

A stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.35g, 1.38 mmol) in hex-1-ene (30 ml) was heated under reflux for 150h. Evaporation at 25°C gave a brown oil (0.80g). ^1H n.m.r. showed hexene type signals and signals for the thiazoline/thiazoline 3-oxide to be present. G.c.m.s. at 80-180°C indicated an isomer of $C_{16}H_{30}$ and benzoic acid to be present (from the decomposition of the thiazoline 3-oxide).

g. Control reaction for hexene

Hex-1-ene (30 ml) was heated under reflux for 140h open to the atmosphere. Evaporation gave a colourless liquid plus some white solid. G.c. at 80°C showed several different products to be present. G.c.m.s. at 60-200°C showed only carbon-carbon coupling products to be present.

h. Preparation of hexene epoxide

Anhydrous sodium carbonate (17.0g, 160 mmol) was added to a vigorously stirred solution of hex-1-ene (3.88 ml, 2.61g, 31 mmol) in dichloromethane (100 ml) at room temperature. A solution of 35% peroxyacetic acid (6.52 ml, 7.37g, 34.4 mmol) was added dropwise. After stirring for 27h, the sodium carbonate was filtered off. Evaporation at 25°C gave hexene epoxide as a colourless liquid (1.45g, 48%) b.p. 118-120°C (lit.[175] 118-120°C).

i. Attempted reaction with thioanisole

Thioanisole (0.22g, 0.20 ml) was added to a stirred solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.38g, 1.50 mmol) in toluene (20 ml) at room temperature. After heating under reflux for 90h, evaporation at 60°C gave a brown oil (0.55g). ^{1}Hn.m.r. showed thiazoline 3-oxide and thioanisole to be present.

2. Oxygen transfer reactions to lithium anions

a. Reaction with lithium diisopropylamide

A solution of butyl lithium in hexane (0.88 ml, 0.14g, 2.20 mmol) was added to a stirred solution of diisopropylamine (0.31 ml, 0.22g, 2.20 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. After stirring for 15 minutes, a solution of 4-(S)-benzyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.01 mmol) in dry

tetrahydrofuran (10 ml) was added at -70°C. After stirring for a further 30 minutes and allowing to warm up to room temperature over 20h, saturated aqueous ammonium chloride was added. Extraction with dichloromethane (× 2), followed by drying and evaporation gave a brown oil (0.37g). ^{1}H n.m.r. showed thiazoline and diisopropylhydroxylamine in a ratio of 1:2 (using the phenyl protons and the isopropyl protons).

b. Preparation of diisopropylhydroxylamine

A modification of the method of Denney was used[176].

(i) A solution of benzoyl peroxide (3.60g, 15.0 mmol) in dry ether (100 ml) was added to a stirred solution of diisopropylamine (4.15 ml, 3.00g, 30.0 mmol) in dry ether (20 ml) at room temperature. After heating under reflux for 15h, the solution was washed with 0.35M aqueous sodium carbonate (200 ml) and then water. Drying and evaporation gave 0-benzoyl-N,N-diisopropylhydroxylamine as colourless crystals. (2.0g, 65%) (^{1}H n.m.r.)

(ii) The product from (i) (2.0g, 9.5 mmol) was dissolved in dry ether (100 ml). Sodium ethoxide (1.00g, 14.5 mmol) in absolute ethanol (50 ml) (made from 0.34g sodium metal plus ethanol) was added slowly. After stirring at room temperature for 46h and washing with water (50 ml × 2), oxalic acid (2.50, 27.3 mmol) in ether

(50 ml) was added to the organic layer, to precipitate the hydroxylamine as its oxalate. The oxalate was filtered, washed with ether, and stirred with aqueous sodium carbonate for 4h. The aqueous layer was extracted with ethyl acetate and the combined layers were dried. Evaporation, followed by Kugelrohr distillation gave diisopropylhydroxylamine as a colourless liquid (0.67, 60%) (^{1}H n.m.r.).

G. Reactions of 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide

1. Attempted 1,3-dipolar cycloaddition reactions of the N-oxide

a. Reaction with acrylonitrile

A modification of the method of Ashburn was used[155]. A solution of acrylonitrile (0.11 ml, 0.085g, 1.60 mmol) in dichloromethane (5 ml) was added to a stirred solution of 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.45 mmol) in dichloromethane (10 ml). After stirring for 20h, evaporation gave a yellow oil (0.35g). ^{1}H n.m.r. showed thiazoline 3-oxide plus small amounts of acrylonitrile to be present.

The reaction was repeated as above except using 1,2-dichloroethane (30 ml) and heating under reflux for 4h. Evaporation gave an orange oil. ^{1}H n.m.r. showed a complex product mixture to be present.

b. Reaction with ethyl vinyl ether

The reaction was identical to a. at room temperature. After stirring for 23h, evaporation gave a brown oil (0.35g). ^{1}H n.m.r. showed the presence of thiazoline 3-oxide.

c. Reaction with methyl acrylete

The reaction was identical to a. using 1,2-dichloroethane and heating under reflux for 6h. Evaporation gave a yellow oil (0.31g). ^{1}H n.m.r. showed thiazoline 3-oxide and small amounts of methyl acrylate to be present.

d. Reaction with dimethyl fumarate

Seven equivalents of dimethyl fumarate and heating under reflux with 1,2-dichloroethane were the conditions used. After 120h, evaporation gave yellow crystals. Ether was used to remove the excess dipolarophile. ^{1}H n.m.r. showed thiazoline 3-oxide plus dimethyl fumarate to be present.

e. Reaction with dimethyl acetylene dicarboxylate

The reaction was identical to a. except toluene was used as the solvent. After heating under reflux for 6h, evaporation gave an orange liquid (0.55g). Preparative t.l.c. (150 mg) on silica using ether as the eluant gave colourless crystals (30 mg). ^{1}H n.m.r., ^{13}C n.m.r.

and i.r., g.c. (180°C) and g.c.m.s. (80-180°C) showed benzoic acid to be present.

f. Reaction with ethyl propiolate

The reaction was identical to a. using 1,2-dichloroethane and heating under reflux for 70h. Evaporation gave a brown oil (0.40g). ^{1}H n.m.r. showed the presence of thiazoline 3-oxide and ethyl propiolate.

g. Reaction with phenylacetylene

The reaction was identical to a. except toluene was used as the solvent. After heating under reflux for 6h, evaporation gave a red liquid (0.52g). ^{1}H n.m.r. showed thiazoline 3-oxide and phenylacetylene to be present.

h. Reaction with phenyl isocyanate

The reaction was identical to a. at room temperature. After stirring for 22h, evaporation gave a brown oil (0.43g). ^{1}H n.m.r. showed thiazoline and excess aromatic peaks derived from the dipolarophile to be present. Washing the oil with dry ether, to remove the thiazoline gave a red crystalline solid (130 mg). Recrystallisation in ether gave an orange solid. ^{1}Hn.m.r. showed only the presence of aromatic peaks. G.c.m.s. at 60-200°C showed the presence of phenyl

isocyanate, diphenylurea (derived from phenyl isocyanate), aniline, thiazoline and benzoic acid (from the decomposition of the thiazoline 3-oxide). There was no indication of azobenzene formed from the decomposition of a possible cycloadduct in either ^1H n.m.r. or g.c.m.s.

i. Reaction with phenyl isothiocyanate

This was carried out by a modified literature method[177]. Four equivalents and heating under reflux with toluene as the solvent were the conditions used. After 20h, evaporation gave a red liquid. ^1H n.m.r. showed the presence of thiazoline 3-oxide plus excess aromatic peaks due to the dipolarophile.

j. Reaction with 4-phenyl-1,2,4-triazoline-3,5-dione

The reaction was identical to a. using 1,2-dichloroethane and heating under reflux for 3h. Evaporation gave a brown solid (0.69g). ^1H n.m.r. showed thiazoline and excess aromatic peaks derived from the dipolarophile to be present. Recrystallisation (0.25g) using ethyl acetate/ isopropanol 1:2 gave an orange solid (0.11g). ^1H n.m.r. showed the presence of aromatic peaks. M.s. failed to identify the product. Preparative t.l.c. (0.30g) on silica using acetonitrile as the eluant gave two main fractions containing aromatic peaks (^1H n.m.r.). G.c.m.s. failed to identify either of the two fractions.

2. Oxygen transfer reactions to lithium anions

a. Reaction with phenyl lithium

A solution of 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.45 mmol) in dry tetrahydrofuran (20 ml) was added to a stirred solution of 1.7M phenyl lithium in hexane (2.0 ml, 3.4 mmol) in dry tetrahydrofuran (10 ml) at room temperature under nitrogen. After stirring for 60h, water was added. The aqueous layer was extracted with ether (× 2). The ether layer was then discarded and the aqueous layer was acidified. After further extraction wtih ether, a brown oil (130 mg) was obtained on evaporation. A distinctive aromatic smell was present. ^{1}H n.m.r. and i.r. indicated the presence of phenol. Addition of neutral 1% iron (III) chloride solution to an aqueous solution of the phenol gave a positive purple colouration.

b. Reaction with phenylethynyl lithium

A solution of butyl lithium in hexane (0.88 ml, 2.18 mmol) was added to a stirred solution of phenylacetylene (0.24 ml, 2.18 mmol) in dry tetrahydrofuran (10 ml) at -70°C under nitrogen. After stirring for 30 minutes, a solution of 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.45 mmol) in dry tetrahydrofuran (10 ml) was added. After 10 minutes the solution was allowed to warm up to room temperature over 20h. Adding saturated aqueous ammonium chloride, followed by extracting with dichloromethane (× 2) and

evaporation, gave a red oil (0.55g). ^1H n.m.r. showed thiazoline and aromatic peaks derived from phenylacetylene to be present. Preparative t.l.c. on silica using hexane/ ether (4:1) as the eluant gave four fractions: an aromatic product (^1H n.m.r.) as a colourless oil (25 mg) at R_F 0.85; thiazoline (^1H n.m.r.) as a colourless yellow liquid (30 mg) at R_F 0.65; thiazoline plus an acetylene derived product (^1H n.m.r.) as a yellow liquid (25 mg) at R_F 0.50 and phenylacetylene (^1H n.m.r.) as a brown liquid (10 mg) at R_F 0.20. G.c.m.s. at 60-200°C of the first fraction indicated 1-phenylnaphthalene and bis-(phenylethynyl) ether to be present. G.c.m.s. at 60-200°C of the third fraction indicated thiazoline to be present.

The water layer was evaporated and the inorganic salts were extracted using dichloromethane. Drying the solution, followed by evaporation gave a colourless solid. ^1H n.m.r., i.r. and m.s. showed benzoic acid to be present. T.l.c. (SiO_2, ethyl acetate) confirmed this result by comparison with the authentic material (R_F 0.6).

c. Reaction with 2-lithiocyclohexanone

A solution of butyl lithium in hexane (0.88 ml, 2.18 mmol) was added to a stirred solution of diisopropylamine (0.33 ml, 2.18 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. After stirring for 15 minutes, a solution of cyclohexanone (0.21g, 0.22 ml, 2.18 mmol) in

dry tetrahydrofuran (10 ml) was added at -70°C. Stirring for a further 30 minutes allowed the temperature sensitive anion to form. 4-(R)-ethyl-2- phenyl-2-thiazoline 3-oxide (0.30g, 1.45 mmol) was then added. After a further 20h (-70°C up to room temperature), saturated aqueous ammonium chloride was added. Extraction using dichloromethane (× 2) followed by drying and evaporation gave an orange oil (0.52g). ^{1}H n.m.r. showed the presence of thiazoline and diisopropylhydroxylamine formed in a competing oxygen transfer reaction with lithium diisopropylamide. A small amount of diisopropylhydroxylamine was insoluble in the dichloromethane solution and was filtered as colourless crystals (25 mg).

Evaporation of the water layer and extraction using dichloromethane (× 3) gave diisopropylhydroxylamine, on drying and evaporation, as colourless crystals (20 mg). ^{1}H n.m.r. of the remaining salt showed no cyclohexanone derived products to be present.

The above reaction was repeated except at room temperature to facilitate the formation of the cyclohexanone lithium enolate anion. The crude reaction gave an identical result. The water layer extracts showed diisopropylhydroxylamine as before and ^{1}H n.m.r. of the lithium salt gave no further evidence of a cyclohexanone derived product, suggesting loss of the cyclohexanone on rotatory evaporation.

d. Reaction with 4,4-dimethyl-2-lithiomethyl-2-oxazoline

A solution of butyl lithium in hexane (0.88 ml, 2.18 mmol) was added to a stirred solution of diisopropylamine (0.33 ml, 2.18 mmol) in dry tetrahydrofuran (10 ml) under nitrogen. After stirring for 15 minutes, a solution of 2,4,4-trimethyl-2-oxazoline (0.19g, 0.21 ml, 1.45 mmol) in dry tetrahydrofuran (10 ml) was added at -70°C. Stirring for 30 minutes allowed the temperature sensitive anion to form. 4-(R)-ethyl-2-phenyl-2-thiazoline 3-oxide (0.30g, 1.45 mmol), was then added. After stirring for 20h (0°C up to room temperature), saturated aqueous ammonium chloride was added. Extraction with dichloromethane followed by drying and evaporation gave orange crystals (0.42g). ^{1}Hn.m.r. showed thiazoline and diisopropylhydroxylamine to be present.

Evaporation of the water layer and extraction using dichloromethane (× 3) gave diisopropylhydroxylamine, on drying and evaporation, as colourless crystals (50 mg) (^{1}H n.m.r.). ^{1}H n.m.r. of the remaining salts showed no oxazoline derived product to be present.

The above reaction was repeated except at room temperature to facilitate the formation of the oxazoline lithium anion. The crude reaction gave the same result. The water layer extracts showed diisopropylhydroxylamine as before and ^{1}H n.m.r. of the lithium salts gave no further evidence of an oxazoline-type product, indicating loss of the volatile oxazoline on rotatory evaporation.

H. Oxidation of 4-(S)-isopropyl-2-methyl-2-oxazoline

a. Reaction with m-chloroperoxybenzoic acid

A modification of the method of Ashburn was used[155]. A solution of m-chloroperoxybenzoic acid (9.0g, 5.21 mmol) in dichloromethane (150 ml) was added to a stirred solution of 4-(S)-isopropyl-2-methyl-2- oxazoline (4.20g, 3.31 mmol) in dichloromethane (200 ml). After stirring for 1-2h a blue-green colour appeared, which subsequently faded. After 17h, t.l.c. (SiO_2, ether/hexane (2:1)) showed a new product to be present at R_F 0.8 (oxazoline R_F 0.9). Extraction with saturated aqueous sodium carbonate solution (× 6), followed by washing with water, drying and evaporation gave a yellow liquid (4.0g). ^1H n.m.r. showed *E*-2-(S)-azo-3 -methyl-1-butyl acetate N,N'-dioxide and both *E*- and *Z*-2- hydroxyimino-3-methyl-1-butyl acetates in a ratio of 6:2:1. Chromatrography on silica gel using 3.0g of the crude product gave two main fractions: *E*- and *Z*-2-hydroxyimino-3-methyl-1-butyl acetate as a colourless liquid (0.21g) using hexane/ether (4:1) (600 ml) as the eluant at R_F 0.70 and *E*-2-(S)-azo-3-methyl-1-butyl acetate N,N'-dioxide as a yellow liquid (2.3g, 43%) using hexane/ether (1:1) (500 ml) as the eluant at RF 0.80. Kugelrohr distillation (0.50g) of the purified nitroso-dimer gave *E* - and *Z*-2-hydroxyimino-3-methyl-1-butyl acetate as a colourless liquid

(0.32g) b.p. 195°C (oven temperature) at 0.9 torr. Warming a solution of the purified nitroso-dimer (200 mg) in toluene (10 ml) at 100-110°C resulted in conversion to the nitroso-monomer as indicated by a colour change from yellow to blue. Ultraviolet spectroscopy showed no definite λ_{max} shift to lower wavenumber due to *E*-*Z* conversion of the nitroso-dimer. Leaving the purified nitroso- dimer to stand for 3 months resulted in decomposition to both *E*- and *Z*-oximes.

E-2-(S)-azo-3-methyl-1-butyl acetate N,N'-dioxide

(Found: C, 54.75; H, 8.35; N, 8.75; M^+, 318.1803. $C_{14}H_{26}N_2O_6$ requires C, 52.8; H, 8.25; N, 8.8%; M^+, 318.1791); $[\alpha]_D^{25}$-9.0° (c 1.6, $CHCl_3$); ν_{max} 1750 (C=0), 1470, 1440, 1380, 1370, 1230, 1200, 1130, 1040 and 840 cm^{-1}; λ_{max} (EtOH) 205 n.m. (log ε5.02), 292 n.m. (log ε5.00); δ_H (80 MHz) 5.45 (2H, d of t, J 8, 4Hz), 4.60 (2H, half of AB pattern of d, J_{AB} 12, J_{AX} 4Hz), 4.30 (2H, half of AB pattern of d, J_{AB}12, J_{BX} 8Hz), 2.30 (2H, octet, J 8Hz), 2.00 (6H, s), 1.05 (6H, d, J 6Hz), and 0.95 (6H, d, J 8Hz); δ_c (75 MHz) 170.2 (s), 70.7 (d), 61.6 (t), 26.2 (q), 20.5 (d), 19.5 (q) and 16.4 (q); c.i.m.s. m/z 319 (M^++1, 22%), 318 (M^+,3), 298 (17), 228 (5), 217 (3), 188 (3), 177 (55), 160 (100), 139 (15), 129 (32), 118 (4), 100 (7) and 69 (8); m/z 319 (M^++1, 5%), 318 (M^+,2), 298 (6), 228 (8), 184 (3), 160 (3), 139 (50), 129 (27), 118 (12),

100 (38), 90 (7) and 69 (90).

E- and *Z*-2-hydroxyimino-3-methyl-1-butyl acetate

(Found: C, 53.0; H, 8.5; N, 8.75. $C_7H_{13}NO_3$ requires C, 52,8; H, 8.25; N, 8.8%); ν_{max} 3700-2500 (br OH), 1750 (C=0), 1650 (C=N), 1450, 1370, 1220, 1050, 950 and 750 cm^{-1}; m/z 159 (M^+, 3%), 139 (2), 129 (2), 99 (53), 84 (8), 69 (80) and 43 (83).

E-2-hydroxyimino-3-methyl-1-butyl acetate

δ_H (80 MHz) 10.2-9.5 (1H, br s), 4.70 (2H, s), 3.40 (1H, septet, J 8Hz), 2.08 (3H, s), 1.10 (3H, d, J 8Hz) and 1.10 (3H, d, J 8Hz); δ_c (75 MHz) 170.7 (s), 159.5 (s), 62.3 (t), 25.9 (q), 20.8 (d), 19.9 (q) and 19.9 (q);

Z-2-hydroxyimino-3-methyl-1-butyl acetate

δ_H (80 MHz) 10.2-9.5 (1H, br s), 5.00 (2H, s), 2.65 (1H, septet, J 8Hz), 2.10 (3H, s), 1.10 (3H, d, J 8Hz) and 1.10 (3H, d, J 8Hz); δ_c (75 MHz) 170.7 (s), 160.4 (s), 58.0 (t), 30.6 (q), 20.8 (d), 19.9 (q) and 18.6 (q).

b. Reaction with nitrogen dioxide

Nitrogen dioxide (16.4g, 35.6 mmol) in dichloromethane (50 ml) was added to a stirred solution of 4-(S)-isopropyl-2-methyl-2-oxazoline (3.0g, 23.6 mmol) in dichloromethane (50 ml) at 0°C.

On leaving to warm up to room temperature for 20h, evaporation gave a pale green liquid (3.4g). ^{1}Hn.m.r. showed a mixture of products and no starting material to be present. Kugelrohr distillation (0.50g) gave a colourless liquid b.p. 162°C (oven temperature) at 8 torr. ^{1}H n.m.r. showed 3-methyl-2-(S)-nitrato-1-butyl acetate plus substantial minor components to be present. Flash chromatography on silica gel using 1.0g of crude product gave one main fraction, 3-methyl-2-(S)-nitrato-1-butyl acetate (plus 2 minor components) as a pale yellow liquid (0.37g) using petroleum ether/ether (2:1) (1200 ml) as the eluant at R_F 0.30. Preparative t.l.c. on silica using petroleum ether/ether (2:1), failed to resolve the mixture. (Found: M^++1, 192.0856. $C_7H_{13}NO_5$ requires M^++1, 192.0872). δ_H (80 MHz) 5.25-4.95 (1H,m), 4.40 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 3Hz), 4.10 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 8Hz), 2.05 (3H, s), 2.05 (1H, octet, J 8Hz), 1.05 (3H, d, J 8Hz) and 1.03 (3H, d, J 8Hz); δ_C (75 MHz) 170.0 (s), 84.9 (d), 61.9 (t), 28.4 (q), 20.1 (d), 17.8 (q) and 17.4 (q); c.i.m.s. m/z 209 (M^++NH_4, 85%), 192 (M^++1, 17), 191 (M^+, 100) and 129 (30); m/z 192 (M^++1, 25%), 132 (12), 129 (53), 114 (34), 85 (43), 69 (62) and 43 (100).

I. Preparation of 3-unsubstituted thiazolidine-2-thiones

1. Preparation of 4-(S)-isopropylthiazolidine-2-thione

a. A modification of the method of Roth was used[178]. Carbon disulphide (44.3g, 35.4 ml, 0.583 mmol) was added with stirring to a suspension of 2-(S)-amino-3-methylbutan-1-ol (12.0g, 117 mmol) in 5.5% sodium hydroxide (200 ml), at room temperature. After stirring for 40h, the solution was extracted with dichloromethane. Drying and evaporation gave a red oil (6.1g). ^{13}C n.m.r. showed 4-(S)-isopropyloxazolidine-2- thione to be present. δ_C (20 MHz) 189.3 (s), 73.5 (t), 62.3 (d), 32.0 (d), 17.8 (2C,q).

b. Phosphorus pentasulphide (12.0g, 339 mmol) was added to a solution of the above product (6.1g) in toluene (100 ml) with stirring. After heating under reflux for 20h, filtration and evaporation gave a red oil. Chromatography on silica using petroleum ether/ether (1:1) gave an orange oil which crystallised on standing. Washing the crystals with ether several times gave 4-(S)-isopropylthiazolidine-2-thione as colourless needles (2.1g, 3.4%) m.p. 66-67°C (lit.[179] m.p. 67-68°C).

2. Preparation of 4-(S)-benzylthiazolidine-2-thione

a. Preparation of 4-(S)-benzyloxazolidin-2-one

A modification of the method of Newman was used[180]. Potassium t-butoxide (0.5g, 4.5 mmol) was added to a stirred suspension of 2-(S)-amino-2-phenylpropan-1-ol (6.1g, 40 mmol) in diethyl carbonate (85.0 ml, 82.7g, 700 mmol) at room temperature. Distillation using a fractionating column gave a few mls of ethanol (b.p. 78-80°C) and then an azeotrope of ethanol/diethyl carbonate for 90 minutes, until a temperature of 124°C was reached. Evaporation of the diethyl carbonate gave an orange oil. Crystallisation using ether gave 4-(S)-benzyloxazolidin-2-one (5.0g, 94%) as colourless crystals, m.p. 85-87°C (lit.[180] m.p. 87-88.5°C). δ_H (80 MHz) 7.5-7.0 (5H, m), 6.1-5.8 (1H, br s), 4.5-4.0 (3H, m) and 2.85 (2H, d, J 6Hz); δ_C (20 MHz) 159.9 (s), 136.2 (s), 129.1 (2C, d), 128.7 (2C, d), 126.9 (d), 69.3 (t), 53.5 (d) and 41.0 (t).

b. Preparation of 4-(S)-benzylthiazolidine-2-thione

Phosphorus pentasulphide (5.0g, 22.6 mmol) was added to a hot solution of 4-(S)-benzyl-oxazolidin-2-one (1.0g, 5.2 mmol) in toluene (100 ml) with stirring. After heating under reflux for 24h, t.l.c. (SiO_2, ether) showed no starting material to be present. Column chromatography on silica (to remove unreacted phosphorus pentasulphide) using 10% petroleum ether in ether as the eluant gave

4-(S)-benzyl-thiazolidine-2-thione as an orange oil (0.58g, 49%) at R_F 0.3.

c. 4-(S)-benzylthiazolidine-2-thione and 4-(S)-benzyl-oxazolidine-2-thione

A modification of the method of Roth was used[178]. Carbon disulphide (16.0 ml, 20.0g, 264 mmol) was added with stirring to a suspension of 2-(S)-amino-3-phenylpropan-1-ol (8.0g, 52 mmol) in 5.5% sodium hydroxide (150 ml) at room temperature. After stirring for 18h, extraction with dichloromethane, followed by drying and evaporation gave colourless crystals (4.0g). ^{13}C.n.m.r. showed both 4-(S)-benzylthiazolidine-2-thione and 4-(S)-benzyloxazolidine-2-thione to be present. 4-(S)-benzyloxazolidine-2-thione: δ_H (80 MHz) 8.1-7.9 (1H, br s), 7.4-7.0 (5H, m), 4.7-4.1 (3H, m) and 2.85 (2H, d, J, 6Hz); δ_c (20 MHz) 189.1 (s), 135.3 (s), 128.9 (2C,d), 127.7 (2C, d), 127.2 (d), 74.6 (t), 57.6 (d) and 40.1 (t).

d. Complete conversion to 4-(S)-benzylthiazolidine-2-thione

Phosphorus pentasulphide (20.0g, 90.4 mmol) was added to a solution of the above product (4.0g) in toluene (200 ml) with stirring. After heating under reflux for 48h, filtration and evaporation gave a red oil. Column chromatography on silica using petroleum ether/ether

(1:1) gave one main fraction at R_F 0.7, a red solid (2.7g). Recrystallisation using hexane/ethyl acetate (5:1) gave 4-(S)-benzylthiazolidine-2-thione as red needles (1.9g, 18%) m.p. 79-80°C. (Found: C, 57.4; H, 5.3; N, 6.65. $C_{10}H_{11}NS_2$ requires C, 57.4; H, 5.3; N, 6.7%); $[\alpha]_D^{25}$ - 112.2° (c 1.7; $CHCl_3$); ν_{max} ($CHCl_3$) 3480 (NH), 1470, 1290, 1250, 1220, 1140, 1040, 1010, 960 and 600 cm^{-1}; δ_H (300 MHz) 8.4 (1H, br s) 7.4-7.2 (3H, m), 7.2-7.1 (2H, m), 4.45 (1H, quintet, J 10Hz), 3.45 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 10 Hz), 3.25 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 10Hz), 3.02 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 10Hz) and 2.95 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 10Hz); δ_c (75 MHz) 200.5 (s), 135.7 (s), 129.1 (2C, d), 128.7 (2C, d), 127.3 (d), 65.1 (d), 39.7 (t) and 37.9 (t); m/z 209 (M^+, 40%), 182 (12), 167 (15), 146 (14), 132 (12), 119 (27) and 118 (20).

J. Preparation of 3-substituted thiazolidine-2-thiones

1. Preparation of 3,4-(S)-dibenzylthiazolidine-2-thione

a. Preparation of 3,4-(S)-dibenzyloxazolidin-2-one

A modification of the method of Kaneko was used[181]. 40% Potassium hydroxide (30 ml) was added to 2-(S)-benzylamino-3-phenylpropan-1-ol (2.00g, 8.28 mmol). After stirring for 30 minutes, a 1.93 M solution of phosgene (1.64g, 16.5 mmol) in toluene

(9.0 ml) was added slowly. After stirring vigorously for 20h, the toluene layer was separated. Extraction of the water layer using dichloromethane (× 3) gave, after evaporation, a yellow oil (2.9g). ^1H n.m.r. showed 3,4-(S)-dibenzyloxazolidin-2-one to be present. Flash chromatography on silica gave three fractions: a ring opened product (?) as a white oil (120 mg) using petroleum ether/ether (4:1) as the eluant (R_F 0.4); 3,4-(S)-dibenzyloxazolidin-2-one as a colourless oil (350 mg) using ether as the solvent (R_F 0.6) and 4-(S)-benzyloxazolidin-2-one as a yellow liquid (210 mg) using ether/ethyl acetate (1:1) as the eluant (R_F 0.7). (Found: M^+ 267.1278. $C_{17}H_{17}NO_2$ requires 267.1259); ν_{max} ($CHCl_3$) 1740 (C=0), 1450, 1420, 1260, 1240, 1180, 1160, 1090, 1070 and 1030 cm^{-1}; δ_H (300 MHz) 7.5-7.1 (8H, m), 7.05 (2H, m), 4.90 (1H, half of AB pattern, J_{AB} 16Hz), 4.15 (1H, half of AB pattern, J_{AB} 16Hz), 4.15 (1H, half of AB pattern of d, J_{AB} 8, J_{AX} 6 Hz), 4.00 (1H, half of AB pattern of d, J_{AB} 8, J_{BX} 6Hz), 3.70 (1H, m), 3.10 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 4Hz) and 2.65 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz); δ_c (75 MHz) 158.4 (s), 135.8 (s), 135.5 (s), 129.0 (3C, d), 128.9 (3C, d), 128.2 (2C, d), 128.0 (d), 127.2 (d), 67.0 (t), 55.3 (d), 46.5 (t) and 38.5 (t); m/z 268 (M^++1, 5%), 267 (M^+,3), 176 (48) and 91 (100).

b. Preparation of 3,4-(S)-dibenzylthiazolidine-2-thione

(i) Preparation of 2-(S)-benzylidene-amino-3-phenylpropan-1-ol

A modification of the method of Freifelder was used[182]. Benzaldehyde (20.0g, 189 mmol) was added to a stirred suspension of 2-(S)-amino-3-phenyl-propan-1-ol (28.6g, 189 mmol) in toluene (250 ml) at room temperature. After heating under reflux for 1h using a Dean-Stark separator, evaporation gave a light brown solid. Recrystallisation using ethyl acetate (300 ml) and hexane (50 ml) gave 2-(S)-benzylideneamino-3-phenylpropan-1-ol as colourless prisms (29.0g, 64%) m.p. 78-80°C. (Found: C, 80.1; H, 7.2; N, 5.8. $C_{16}H_{17}NO$ requires C, 80.0; H, 7.1; N, 5.8%); $[\alpha]_D^{25}$ - 215.6° (c 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3600-2700 (br OH), 1640 (C=N), 1490, 1450, 1380, 1220, 1030 and 700 cm^{-1}; δ_H (80 MHz) 8.0 (1H, s), 7.75-7.5 (2H, m), 7.5-7.3 (3H, m), 7.2 (5H, s), 3.85 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 6Hz), 3.70 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 4Hz), 3.7-3.4 (1H, m), 3.00 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 5Hz), 2.80 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz) and 2.2 (1H, br s); δ_c (20 MHz) 162.4 (d), 138.6 (s), 135.6 (s), 130.6 (d), 129.6 (2C, d), 128.4 (2C, d), 128.2 (4C, d), 126.0 (d), 74.4 (d), 65.6 (t) and 38.9 (t); m/z 208 (M^+ - CH_2OH, 16%), 148 (M^+ - CH_2Ph, 100), 130 (25), 128 (65) and 127 (70).

(ii) Preparation of 2-(S)-benzylamino-3-phenylpropan-1-ol

Hydrogen gas (2.345 l, 104.5 mmol) was absorbed into a stirred solution of 2-(S)-benzylideneamino-3-phenylpropan-1-ol (25.0g, 103 mmol) in ethyl acetate in the presence of a 10% palladium/charcoal catalyst (4.0g). Filtration and evaporation gave a yellow oil (24.0g, 95%) which crystallised out. Recrystallisation with hexane/ethyl acetate (5:1) gave 2-(S)-benzylamino-3-phenylpropan-1-ol as colourless prisms (17.0g, 71%) m.p. 124-126°C. (Found: C, 79.6; H, 7.95; N, 5.75. $C_{16}H_{19}NO$ requires C, 79.65; H, 7.95; N, 5.8%); $[\alpha]_D^{25}$ -49.8° (c 2.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3700-2400 (br OH), 1640 (C=N), 1490, 1450, 1400, 1220, 1110, 1030, 910 and 700 cm^{-1}; δ_H (80 MHz) 7.25 (10H, s), 3.9-3.6 (1H, m), 3.80 (2H, s), 3.60 (1H, half of AB pattern of d, J_{AB} 10, J_{AX} 4Hz), 3.40 (1H, half of AB pattern of d, J_{AB} 10, J_{BX} 5Hz), 2.90 (1H, half of AB pattern of d, J_{AB} 8, J_{AX} 4Hz), 2.80 (1H, br s) and 2.70 (1H, half of AB pattern of d, J_{AB} 8, J_{BX} 4Hz); δ_c (20 MHz) 139.9 (s), 138.8 (s), 129.2 (2C, d), 128.4 (4C, d), 128.0 (2C, d), 127.0 (d), 126.2 (d), 62.6 (t), 59.7 (d), 51.1 (t) and 37.8 (t); m/z 242 (M^++1, 7%), 241 (M^+,5), 210 (42) and 150 (100).

(iii) Preparation of 3,4-(S)-dibenzylthiazolidine-2-thione

A modification of the method of Roth was used[178]. A solution of 2-(S)-benzylamino-3-phenylpropan-1-ol (24.0g, 99.5 mmol) in 5.5% sodium hydroxide (300 ml) was stirred at room temperature while

carbon disulphide (20.0g, 16.0 ml, 328.5 mmol) was added slowly. After stirring for 24h, extraction using dichloromethane (100 ml), was followed by washing with water (500 ml), drying and evaporation to give a pale brown solid (21.2g). Recrystallisation using hexane/ethyl acetate (3:1) gave 3,4-(S)-dibenzylthiazolidine-2-thione as colourless needles (15.9g, 53%) m.p. 137-139°C. (Found: C, 68.4; H, 5.55; N, 4.65. $C_{17}H_{17}NS_2$ requires C, 68.2; H, 5.7; N, 4.7%); $[\alpha]_D^{25}$ - 25.8° (c 1.60, CH_2Cl_2); ν_{max} ($CHCl_3$) 1490, 1450, 1420, 1350, 1300, 1220, 1170, 1080, 1030, 920 and 700 cm^{-1}; δ_H (200 MHz) 7.5-7.2 (8H, m), 7.1 (2H, m), 5.85 (1H, half of AB pattern, J_{AB} 16Hz), 4.30-4.15 (1H, m), 4.20 (1H, half of AB pattern, J_{AB} 16Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 8Hz), 3.15 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 5Hz), 2.88 (1H, half of AB pattern of d, J_{AB} 12, J_{BX} 10Hz) and 2.85 (1H, half of AB pattern of d, J_{AB} 14, J_{BX}10Hz); δ_c (75 MHz) 196.7 (s), 135.9 (s), 135.4 (s), 129.1 (2C,d), 129.0 (2C,d), 128.9 (2C,d), 128.2 (d), 128.0 (2C, d), 127.2 (d), 67.5 (d), 50.7 (t), 36.3 (t) and 32.2 (t); m/z 299 (M^+, 42%), 208 (100), 148 (92) and 117 (31).

2. Preparation of 3-benzyl-4-(S)-isopropylthiazolidine-2-thione

a. Preparation of 2-(S)-benzylideneamino-3-methylbutan-1-ol

Benzaldehyde (15.5g, 146 mmol) was added to a stirred solution of 2-(S)-amino-3-methylbutan-1-ol (15.0g, 146 mmol) in toluene (250 ml) at room temperature. After heating under reflux for 1h using a Dean-Stark separator, evaporation gave a yellow solid (17.4g). Recrystallisation using hexane/ethyl acetate (5:1) gave 2-(S)-benzylideneamino-3-methylbutan-1-ol as colourless needles (13.0g, 46%) m.p. 71-72°C. (Found: C, 75.25; H, 9.05; N, 7.32. $C_{12}H_{17}NO$ requires C, 75.35; H, 8.95; N, 7.32%); $[\alpha]_D^{25}$ - 83.3° (c 0.30, $CHCl_3$); ν_{max} ($CHCl_3$) 3700-2400 (brOH), 1640 (C=N), 1470, 1450, 1380, 1260, 1220, 1060 and 1020 cm^{-1}; δ_H (80 MHz) 8.20 (1H, s), 7.7-7.6 (2H, m), 7.6-7.3 (3H, m), 3.8 (2H, m), 3.2-2.8 (1H, m), 1.90 (1H, octet, J 7Hz), 0.95 (3H, d, J 7Hz) and 0.90 (3H, d, J 7Hz); δ_C (20 MHz) 161.7 (d), 136.0 (s), 130.4 (d), 128.4 (4C, d), 79.2 (d), 64.1 (t), 30.0 (d), 19.7 (q) and 19.2 (q); m/z 190 (M^++1, 5%), 189 (M^+, 2), 170 (100), 158 (70) and 130 (25).

b. Preparation of 2-(S)-benzylamino-3-methylbutan-1-ol

Hydrogen gas (1.761 l, 78.6 mmol) was absorbed into a stirred solution of 2-(S)-benzylideneamino-3-methylbutan-1-ol (14.9g, 78.1 mmol) in ethyl acetate (150 ml) in the presence of a 10%

palladium/charcoal catalyst (3.0g). Filtration and evaporation gave an orange liquid (13.8g). Kugelrohr distillation gave 2-(S)-benzylamino-3-methylbutan-1-ol as a colourless liquid (11.5g, 76%) b.p. 106-108°C (oven temperature) at 0.4 torr (lit.[183] b.p. 103-107°C at 0.2 torr).

c. Preparation of 3-benzyl-4-(S)-isopropylthiazolidine-2-thione

A modification of the method of Roth was used[178]. A solution of 2-(S)-benzylamino-3-methylbutan-1-ol (4.6g, 23.8 mmol) in 5.5% sodium hydroxide (100 ml) was stirred at room temperature while carbon disulphide (9.8 ml, 5.5g, 71.6 mmol) was added slowly. After stirring for 20h, extraction with dichloromethane (× 3), followed by washing with water, drying and evaporation gave a brown oil. This was Kugelrohr distilled to given an orange liquid (1.3g, 22%) b.p. 234°C (oven temperature) at 0.1 torr. Washing with hexane gave colourless crystals which were recrystallised using dry tetrahydrofuran (20 ml) and hexane (80 ml) to give 3-benzyl-4-(S)-isopropylthiazolidine-2-thione as colourless needles (0.40g, 7%) m.p. 77-78°C. (Found: C, 62.25; H, 6.9; N, 5.6. $C_{13}H_{17}NS_2$ requires C, 62.1; H, 6.82; N, 5.55%); $[\alpha]_D^{25}$ - 143.1° (c 0.50, $CHCl_3$); ν_{max} (CH_2Cl_2) 1460, 1450, 1330, 1240, 1220, 1200, 1180, 1130, 1040, 990 and 960 cm^{-1}; δ_H (80 MHz) 7.40 (5H, s), 6.00 (1H, half of AB pattern, J_{AB} 16Hz), 4.20 (1H, half of AB

pattern, J_{AB} 16Hz), 4.05 (1H, d of t, J 6, 4Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 11, J_{AX} 9Hz), 3.05 (1H, half of AB pattern of d, J_{AB} 11, J_{BX} 6Hz), 2.30 (1H, d of septets, J 7, 4Hz) and 0.95 (3H, d, J 7Hz) and 0.90 (3H, d, J 7Hz); δ_c (20 MHz) 197.4 (s), 135.1 (s), 128.7 (2C, d), 127.8 (3C, d), 71.0 (d), 50.0 (t), 28.9 (d), 26.9 (t), 18.6 (q) and 14.7 (q); m/z 251 (M^+, 100%), 208 (15), 188 (24) and 148 (82).

K. Oxidation of 3,4-(S)-dibenzylthiazolidine-2-thione

a. Reaction with peroxyacetic acid

A modification of the method of Gaul was used[70]. 30% Hydrogen peroxide (12.4 ml, 109 mmol) was added to a stirred solution of 3,4-(S)- dibenzylthiazolidine-2-thione (5.0g, 16.7 mmol) in glacial acetic acid (125 ml) at 70°C. After stirring for 3h at 70°C, the solution was left to cool to room temperature over 4h to give a small crop of crystals. Chilling the solution at 0°C for 12h gave 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide (0.95g) as colourless crystals. Evaporation of the acetic acid at 25°C under 1 torr gave an orange oil. Washing the oil with petroleum ether/ether, followed by decanting and evaporating the resulting solution gave an orange liquid. Chilling at 0°C produced a second crop of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide as colourless crystals (0.31g), [combined yield 24%].

b. Reaction with peroxytrifluoroacetic acid

A solution of 3,4-(S)-dibenzylthiazolidine-2-thione (0.50g, 1.67 mmol) in trifluoroacetic acid (15 ml) was stirred at room temperature while 30% hydrogen peroxide (1.24 ml, 1.36g, 11.2 mmol) was added dropwise. After stirring for 16h at room temperature, evaporation at 25°C gave a brown oil (0.63g). Preparative t.l.c. (100 mg) on silica using ethyl acetate as the eluant gave two identical fractions: an orange oil (17 mg) at R_F 0.90 and an orange liquid (12 mg) at R_F 0.50. ^1H n.m.r. showed 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide to be present.

c. Reaction with potassium permanganate

A modification of the method of Stoodley was used[184]. A solution of potassium permanganate (6.0g, 37.9 mmol) in water (150 ml) was added slowly to a stirred solution of 3,4-(S)-dibenzylthiazolidine-2-thione (5.0g, 16.7 mmol) in acetic acid (250 ml) at room temperature. After stirring for 18h, the brown solution was decolourised using 30% hydrogen peroxide. The acetic acid was removed at 25°C under 1 torr. After redissolving the oil in dichloromethane, drying and evaporation gave an orange oil (4.1g). Medium pressure liquid chromatography on silica gave two main fractions: 3,4-(S)-dibenzylthiazolidin-2-one as colourless prisms (220 mg) m.p. 70-71°C using hexane/ether (1:1) (800 ml) as the eluant (R_F

0.40) and 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide as colourless needles (250 mg) m.p. 143-144°C using ether (800 ml) as the eluant (R_F 0.18).

3,4-(S)-dibenzylthiazolidin-2-one

(Found: C, 72.2; H, 6.3; N, 4.8. $C_{17}H_{17}NOS$ requires C, 72.1; H, 6.0; N, 4.95%); $[\alpha]_D^{25}$ + 11.8° (c 0.9, $CHCl_3$); ν_{max} ($CHCl_3$) 1650, 1490, 1450, 1440, 1400, 1350, 1200, 1080, 1030, 970 and 930 cm^{-1}; δ_H (300 MHz) 7.4-7.2 (8H, m), 7.1 (2H, m), 5.10 (1H, half of AB pattern, J_{AB} 16Hz), 4.00 (1H, half of AB pattern, J_{AB} 16Hz), 3.80 (1H, m), 3.20-3.05 (2H, m), 2.95 (1H, half of AB pattern of d, J_{AB} 12, J 4Hz) and 2.80 (1H, half of AB pattern of d, J_{AB} 12, J 8Hz); δ_c (75 MHz) 171.8 (s), 136.4 (s), 136.3 (s), 192.2 (2C, d), 128.7 (2C, d), 128.6 (2C, d), 128.0 (2C, d), 127.9 (d), 127.1 (d), 59.5 (d), 46.7 (t), 37.3 (t) and 30.4 (t); c.i.m.s. m/z 301 (M^++NH_4, 2%), 284 (M^++1, 100), 192 (46), 108 (7), 91 (65) and 65 (7); m/z 284 (M^++1, 12%), 283 (M^+, 2), 192 (60), 91 (100) and 65 (13).

3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide

(Found: C, 65.0; H, 5.4; N, 4.4. $C_{17}H_{17}NO_3S$ requires C, 64.7; H, 5.4; N, 4.4%); $[\alpha]_D^{25}$ - 22.6° (c 0.7, $CHCl_3$); ν_{max} ($CHCl_3$) 1730 (C=0), 1490, 1450, 1420, 1330, 1220, 1140 and 700 cm^{-1}; δ_H (300 MHz)

7.5-7.3 (8H, m), 7.1 (2H, m), 5.15 (1H, half of AB pattern, J_{AB} 16Hz), 4.20 (1H, half of AB pattern, J_{AB} 16Hz), 3.90 (1H, m), 3.30 (1H, half of AB pattern of d, J_{AB} 16, J_{AX} 6Hz), 3.20 (1H, half of AB pattern of d, J_{AB} 12, J_{AX} 4Hz), 3.05 (1H, half of AB pattern of d, J_{AB} 12, J_{BX}8Hz) and 2.85 (1H, half of AB pattern of d, J_{AB} 16, J_{BX} 10Hz); δ_c (75 MHz) 159.5 (s), 134.7 (s), 133.2 (s), 129.4 (2C, d), 129.3 (2C, d), 129.2 (2C, d), 129.0 (d), 128.5 (2C, d), 127.8 (d), 51.7 (d), 47.9 (t), 47.4 (t) and 38.1 (t); δ_s (23 MHz, $CDCl_3$) -49.5 ($W_{1/2}$ = 131Hz); c.i.m.s. m/z 333 (M^++NH_4, 73%), 316 (M^++1, 26), 301 (11), 285 (333-SO, 78), 269 (333-SO_2, 32), 268 (316-SO, 56), 252 (316-SO_2, 100), 224 (20), 211 (20), 194 (12), 177 (7), 160 (10), 153 (22), 134 (24), 108 (28) and 91 (10); m/z 316 (M^++1, 1%), 251 (M^+-SO_2, 7), 192 (8), 176 (19), 160 (28), 134 (12), 118 (38), 91 (100) and 65 (17).

d. Reaction with nitrogen dioxide

A solution of nitrogen dioxide (1.8g, 39 mmol) in dichloromethane (20 ml) was added to a stirred solution of 3,4-(S)-dibenzyl-thiazolidine-2 -thione (0.30g, 1.00 mmol) in dichloromethane (50 ml) at room temperature. After stirring for 70h, evaporation of the brown solution gave an orange oil (0.42g). ^{1}Hn.m.r. showed 3,4-(S)-dibenzylthiazolidin- 2-one to be present. T.l.c. (SiO_2,

ether/hexane (1:1)) using the authentic material as a comparison verified the result (R_F 0.50).

e. Reaction with m-chloroperoxybenzoic acid

A solution of 3,4-(S)-dibenzylthiazolidine-2-thione (1.0g, 3.35 mmol) in 1,2-dichloroethane (50 ml) was stirred at room temperature while m-chloroperoxybenzoic acid (2.40g, 13.8 mmol) was added. After stirring for 40h, t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed no starting material to be present. Extraction using saturated aqueous sodium carbonate solution (× 3), followed by washing with water, drying and evaporation, gave a yellow oil (750 mg). Column chromatography on silica using petroleum ether/ether (3:1) as the eluant gave two main fractions: product **A** a colourless solid (220 mg) and product **B** a ring opened product as a yellow oil (150 mg). The identity of products **A** and **B** is outlined in the discussion.

Product A. δ_H (80 MHz) 8.0-7.9 (2H, m), 7.5-7.4 (3H, m), 7.30 (5H, s), 4.75-4.50 (1H, m), 4.40 (1H, half of AB pattern of d, J_{AB} 18, J_{AX} 11Hz), 4.10 (1H, half of AB pattern of d, J_{AB} 18, J_{BX} 10Hz), 3.25 (1H, half of AB pattern of d, J_{AB} 14, J_{AX} 4Hz) and 2.75 (1H, half of AB pattern of d, J_{AB} 14, J_{BX} 8Hz).

Product B. δ_H (80 MHz) 8.35 (1H, s), 8.20 (1H, s), 7.35 (10H, s), 7.3-7.0 (10H, s), 4.70 (2H, half of AB pattern, J_{AB} 14Hz), 4.20 (2H, half of AB pattern, J_{AB} 14Hz), 4.0-3.5 (2H, m) and 3.1-2.5 (8H, m); c.i.m.s. m/z 286 (M^++1, 92%), 268 (12), 238 (9), 210 (3), 194 (37), 176 (6), 166 (10), 150 (5), 136 (13), 117 (7), 91 (100), 76 (7) and 65 (10).

f. Reaction with peroxyacetic acid over base

35% peroxyacetic acid (1.46g, 6.72 mmol) was added to a stirred solution of 3,4-(S)-dibenzylthiazolidine-2-thione (0.25g, 0.84 mmol) in 1,2-dichloroethane (30 ml) over anhydrous sodium carbonate (2.1g, 20.1 mmol). After heating under reflux for 18h, t.l.c. (SiO_2, petroleum ether/ether (1:1)) showed no starting material to be present. Filtering the solution, followed by drying and evaporation gave a yellow solid (0.14g). Preparative t.l.c. (SiO_2, petroleum ether/ether (1:1)) on silica gel gave a product equivalent to **A** in the m-chloroperoxybenzoic acid reaction, as colourless crystals (30 mg) at R_F 0.45.

L. Reactions of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide

1. F.V.P. of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide

Flash vacuum pyrolysis of the title compound (50.0 mg, 600°C, 4.8×10^{-2} torr, inlet 130°C) gave two fractions: a yellow oil in the sidearm of the trap and a colourless solid in the main part of the trap.

^{1}H n.m.r. showed the first fraction to be benzaldehyde and the second fraction to be a mixture of benzylisocyanate (6.1 mg, 10%), allylbenzene (8.5 mg, 7.6%) and bibenzyl (6.9 mg, 22.6%). G.c.m.s. at 60-200°C of the colourless solid indicated allylbenzene and bibenzyl to be present. G.c. at 100°C showed benzylisocyanate to be present.

2. Photolysis of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide

A solution of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide (0.20g, 0.64 mmol) in A.R. acetone was irradiated for 48h. Filtration of the insoluble colourless crystals gave a product whose identity is discussed in the discussion and whose spectra are given below (60 mg). The remaining solution was evaporated to give a yellow oil (150 mg). The oil was washed with ether to give a colourless solid (55 mg). Chilling the ether solution at 0°C gave a second crop of colourless solid (25 mg). ^{1}Hn.m.r. showed both crops to be 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide.

The solution was evaporated to dryness to give a yellow solid. ^{1}Hn.m.r. showed a mixture of 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide and a new product which could not be properly identified.

(Found: C, 64.7; H, 5.4; N, 4.4%). ν_{max} 3700-2200 (br OH), 1250, 1210, 1160, 1130, 1020, 960, 770, 740 and 700 cm^{-1}; δ_H (80 MHz, CD_3SOCD_3) 9.4-9.2 (1H, br s), 9.2-9.0 (1H, br s), 7.6-7.4 (5H, m), 7.4-7.2 (5H, m), 4.5-4.2 (2H, m), 3.7 (1H, m), 3.40 (1H, half of AB pattern of d,

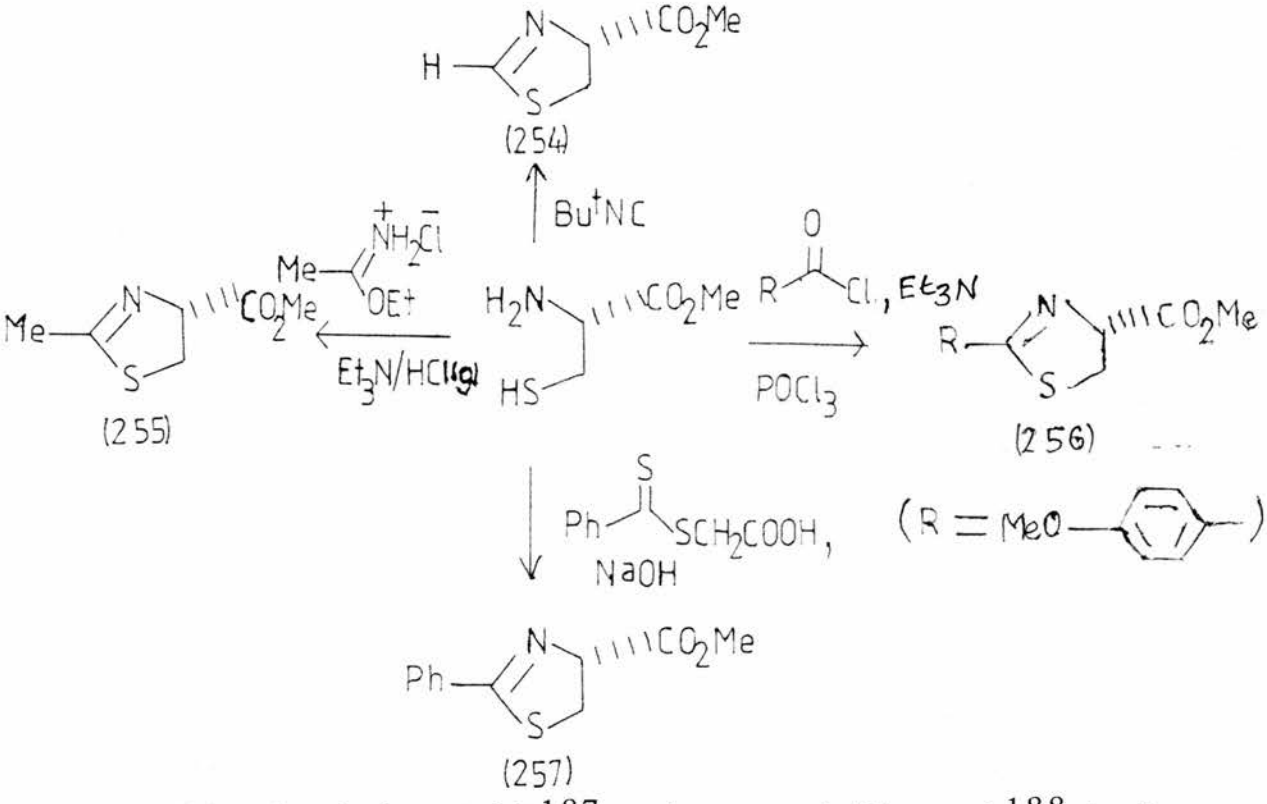
J_{AB} 20, J_{AX} 15Hz), 3.00 (1H, half of AB pattern of d, J_{AB} 20, J_{BX} 10Hz), 2.90 (1H, half of AB pattern of d, J_{AB} 15, J_{AX} 10Hz) and 2.70 (1H, half of AB pattern of d, J_{AB} 15, J_{BX} 5Hz); δ_c (75 MHz, CD_3SOCD_3) 136.0 (s), 132.0 (s), 129.5 (2C, d), 129.4 (2C, d), 129.0 (d), 128.9 (2C, d), 128.7 (2C, d), 127.0 (d), 56.7 (d), 49.0 (t), 47.8 (t) and 35.3 (t); m/z 304, 268, 244, 222, 214, 194 and 179.

DISCUSSION

A. Preparation of the Chiral 2-Thiazolines

1. The synthetic background

Comprehensive reviews on the preparation of the 2-thiazoline heterocycle have been published by Loudon in 1957[185] and Metzger in 1984[186]. The main precursor to chiral 2-thiazolines in the literature is the thiol-containing amino-acid cysteine. This reacts

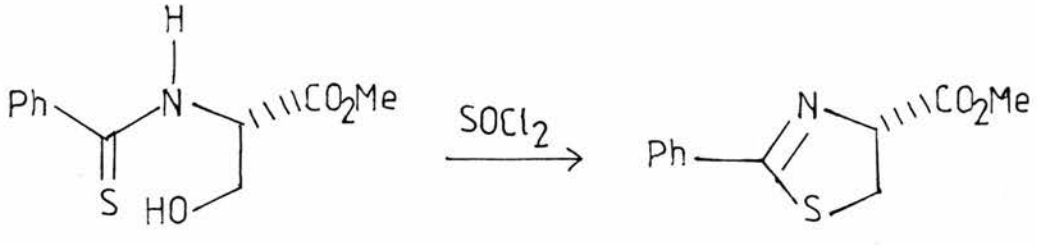


directly with t-butyl isocyanide[187] and an acetimidate salt[188] in the presence of triethylamine to give the parent 2-thiazoline (254) and the 2-methyl-2-thiazoline (255) respectively. Alternatively cysteine can react with the amino functional group via an initial base induced acylation[189] or by a base induced thioacylation[190] step, followed by a dehydration process ($POCl_3$) or a neutralisation ($-H_2S$) to give the

2-p-methoxyphenyl-2-thiazoline (256) and the 2-phenyl-2-thiazoline (257) respectively.

These reactions demonstrate the forcing reaction conditions, such as high temperature and strongly basic or alkaline media needed to synthesise 2-thiazolines. The stability of a range of 2-thiazolines involving varied substitution at the 2-position between the heteroatoms has thus been established with both electron–withdrawing and electron–donating groups.

The hydroxyl-containing amino-acid serine, in the form of the N-thiobenzoylserine methyl ester (258), reacts with thionyl chloride to produce an intermediate chlorosulphinic ester. A slow cyclisation step involving the reaction of further thionyl chloride results in the hydrochloride salt which is neutralised by sodium hydrogencarbonate solution to give the 2-phenyl-2-thiazoline (257)[191].

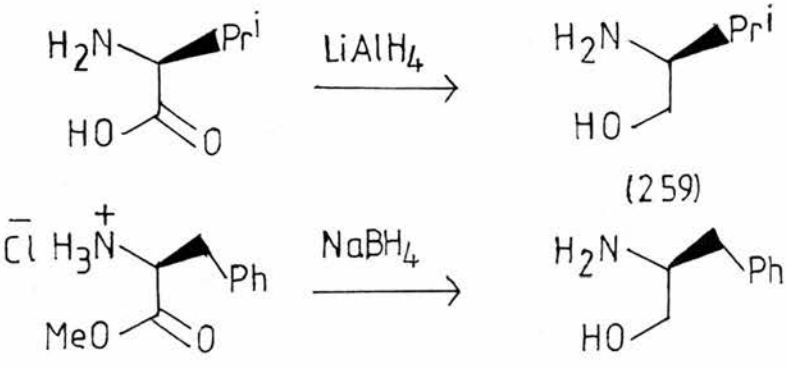


(258) (257)

The final method of synthesis involves the transformation of the reactive 2-oxazoline heterocycle using phosphorus pentasulphide with replacement of the α-heteroatom to give the 2-thiazoline and is unpublished work[192].

2. Preparation of the chiral amino-alcohols

Standard reduction procedures were used to prepare the amino-alcohols, 2-(S)-amino-3-methylbutan-1-ol (259) and 2-(S)-amino-3-phenylpropan-1-ol (260). The reaction of the dipolar amino-acid S-valine with the strong reducing reagent, lithium aluminium hydride[158] and the reaction of the activated methyl ester hydrochloride salt of S-phenylalanine with sodium borohydride[160], a weak hydride source gave the desired amino-alcohols in good yield.



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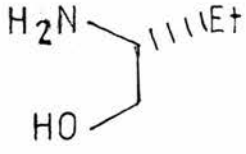
(260)

The commercially available 2-(R)-amino butan-1-ol (261) was available on a large scale for subsequent use.



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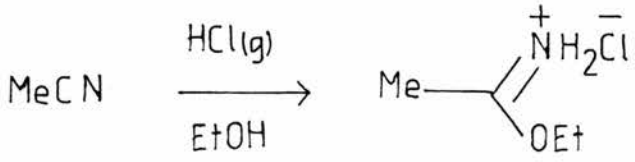
3. Preparation of the chiral 2-thiazolines

a) 2-Methyl-2-thiazolines

The 2-methyl-2-oxazolines were prepared as precursors to the 2-methyl-2-thiazolines by a standard method of synthesis[162]. The moisture sensitive imidate salt (262) was formed by the Pinner reaction, where dry hydrogen chloride gas reacts with a combination of dry acetonitrile and dry ethanol[161].



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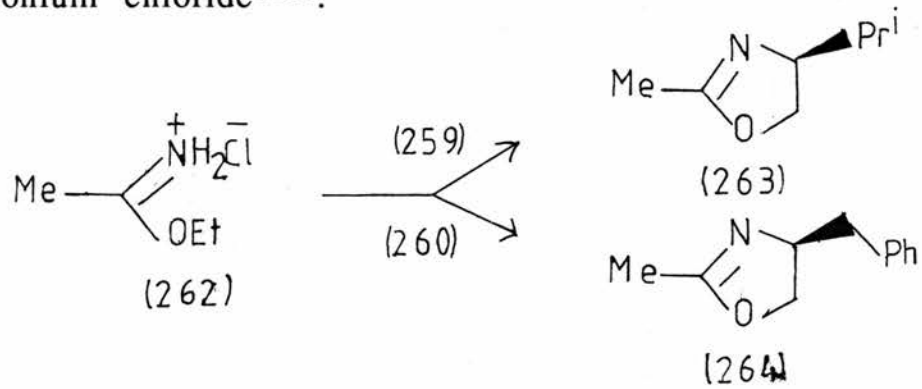
The acetimidate salt react with the amino-alcohols to give the 2-methyl-2-oxazolines (263) and (264) after elimination of ethanol and ammonium chloride[162].

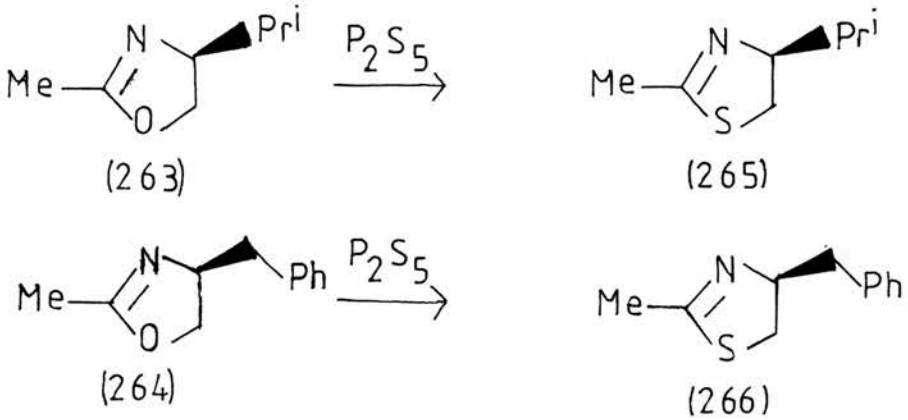


(262) (263) (264)

The 2-oxazolines were volatile, hygroscopic liquids showing all the expected analytical and spectral properties including ν_{max} (C=N) at 1720 and 1670 cm^{-1}[193]. Retention of configuration was assumed in the reaction.

Although the 2-oxazolines are extremely versatile templates which can be used as chiral auxiliaries as is shown in two extensive reviews on this subject[194,195], the heterocyclic transformation to a 2-thiazoline has not yet been published[192].

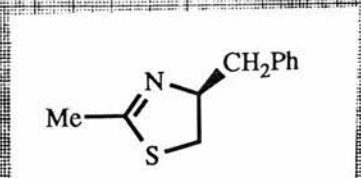
The reaction of the 2-methyl-2-oxazolines with phosphorus pentasulphide gave the 2-methyl-2-thiazolines (265) and (266) as volatile hygroscopic liquids.



The lowering of the frequency of the IR ν_{max} (C=N) by 70 and 40cm^{-1} respectively in going to the 2-thiazolines can be explained by the higher atomic weight of the sulphur atom damping the oscillation of the attached carbon-nitrogen double bond. The movement of the n.m.r. signals of H-5 and C-5 in the 2-oxazoline to a lower frequency in the 2-thiazoline reflects the increase in charge density at the atom in each case as a result of the decreased inductive effect of the electronegative heteroatom. The ^{1}Hn.m.r. spectra of the 2-oxazoline (264) and the 2-thiazoline (266) are shown for a comparison on page 162.

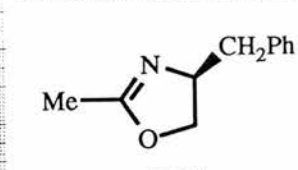
The important features in a mechanistic approach to the reaction

80 MHz ^{1}H n.m.r. spectrum of thiazoline (**266**)



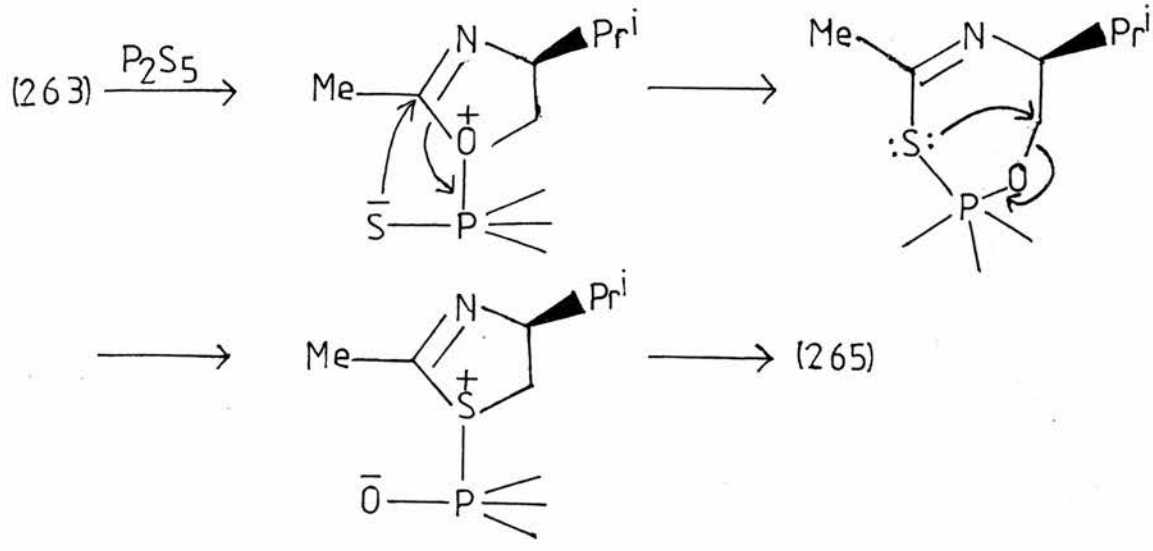
(**266**)

80 MHz ^{1}H n.m.r. spectrum of oxazoline (**264**)



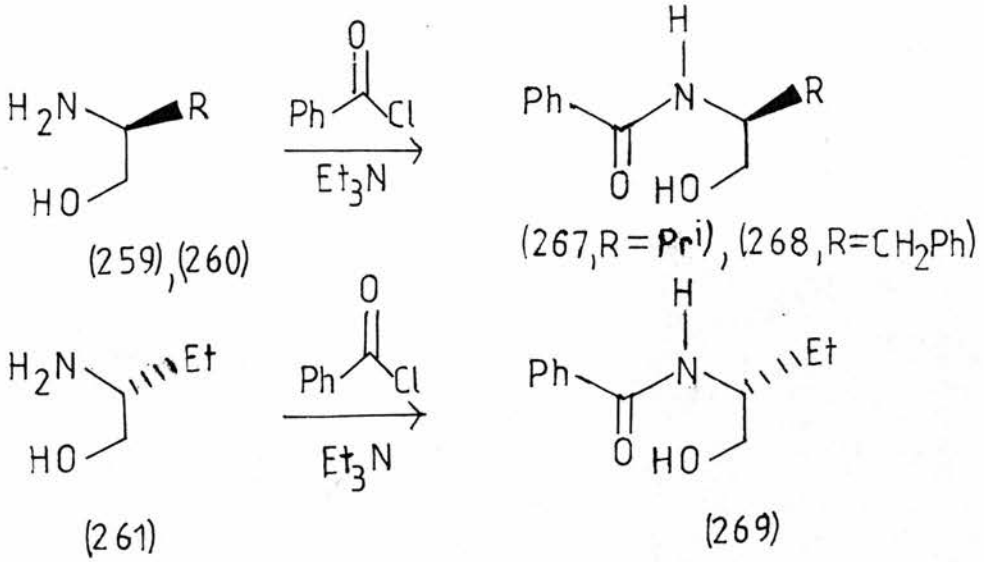
(**264**)

are the larger C-S-C bond angle and hence the lower ring strain in the 2-thiazoline and the greater affinity of phosphorus for oxygen and hence the ease of expulsion of the highly stable phosphorus oxide.



b) 2-Phenyl-2-thiazolines

As early as 1935, a variety of N-acylated amino-alcohols were reported to undergo ring closure reactions with phosphorus pentoxide and phosphorus pentasulphide to give the achiral 2-oxazolines and 2-thiazolines[196]. In these case the precursors were prepared by heating equimolar quantities of the carboxylic acid and amino alcohol. In the present work it proved more convenient to treat the amino alcohols with benzoyl chloride and triethylamine giving the products (267), (268) and (269)[164].



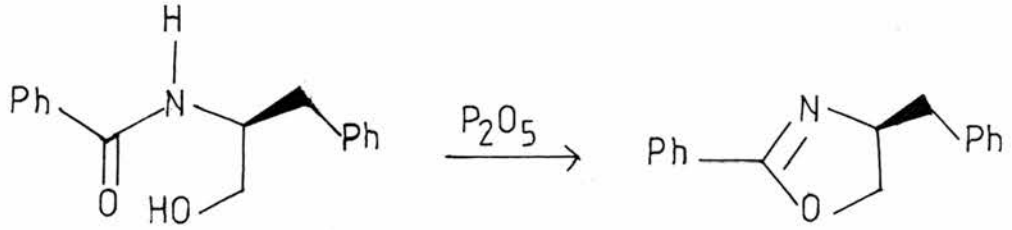
(259), (260)

(267, R = Pr^i), (268, R = CH_2Ph)

(261)

(269)

Phosphorus pentoxide was effective as a dehydrating reagent in the conversion of (268, R = CH_2Ph) to the desired 2-oxazoline (270) by an updated literature procedure[197].



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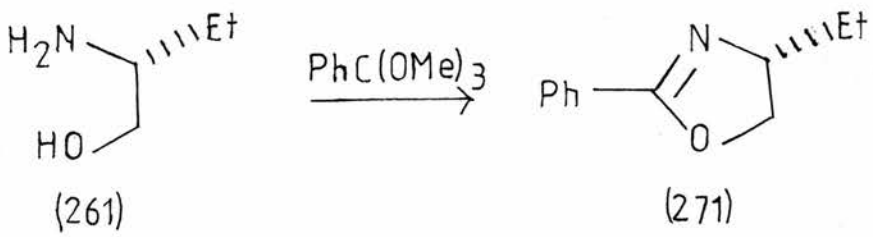
(270)

The value of the IR ν_{max} (C=N) at 1640 cm^{-1} indicated no apparent delocalisation of the carbon-nitrogen double bond by the electron withdrawing phenyl substituent in comparison with the parent 2-oxazoline (ν_{max} (C=N), 1630 cm^{-1})[198]. The two AB patterns of doublets in the proton n.m.r. spectrum indicated the non-equivalence of the methylene protons both in the 2-oxazoline heterocycle and in the benzyl side chain.

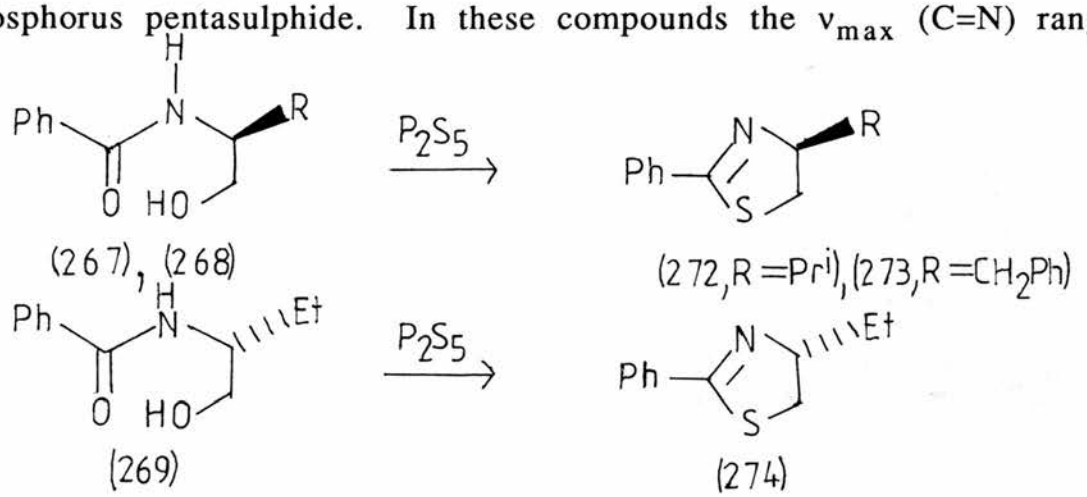
The condensation of the amino alcohol (261) and trimethylorthobenzoate[199] by distillation gave a low recovery of the

2-oxazoline (271).



(261) (271)

The three N-benzoyl-2-amino alcohols all yielded the 2-thiazolines (272, R = Pr^i; 273, R = CH_2Ph), (274) under the influence of phosphorus pentasulphide. In these compounds the ν_{max} (C=N) range

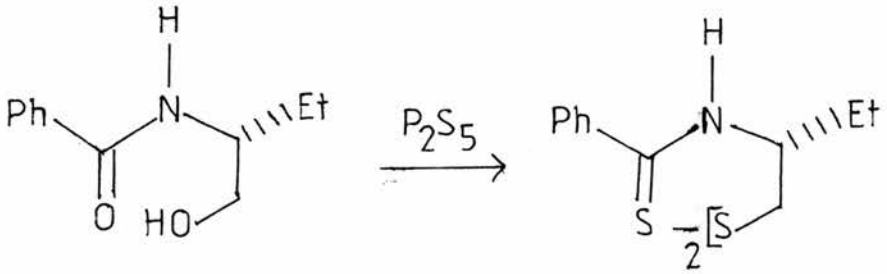


from 1650 to 1630 cm^{-1} (cf. literature values of 1640-1560 cm^{-1}[200]) indicated little change from the 2-oxazoline (270). The 4-proton n.m.r. signal occured at 5.1-4.0 ppm in each of the three 2-thiazolines. The heterocyclic methylene protons in the 2-thiazoline (273, R = CH_2Ph) can be clearly identified by a comparison with the 2-oxazoline (270) thus distinguishing them from the exocyclic benzyl methylene protons in each case.

The ^{13}C n.m.r. values at the C-2 position are in good agreement with a literature study on 4-methyl-2-substituted-2-thiazolines[201]. A proposal for the mechanism of this reaction has been outlined in

detail by Roggero and Metzger[202].

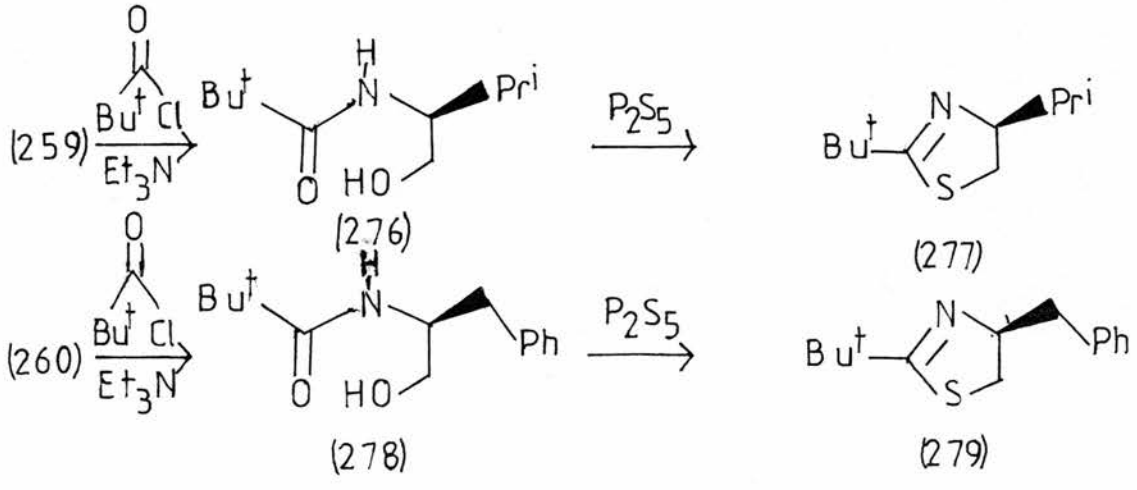
An alternative method involved heating the hydroxyalkylamide (269) at a higher temperature with phosphorus pentasulphide and neutralising the acidic residue using dried sodium carbonate[203]. This led to the isolation of the N-benzoylaminoalkyldisulphide (275) as a by-product presumably derived from oxidation of a thiol intermediate at an immediate stage before ring closure.



(269) (275)

c) 2-t-Butyl-2-thiazoline

The preparation of the 2-t-butyl-2-thiazolines (277) and (279) *via* the hydroxyalkylamides (276) and (278) was achieved from the amino alcohols using identical reagents to those used for the 2-phenyl-2-thiazolines.



(276) (277)

(278) (279)

d) The attempted preparation of 2-p-methoxyphenyl-2-thiazolines

In the introduction, the formation of a stable 2-thiazoline 1,1-dioxide (25) with a p-methoxyphenyl 2-substituent was described[12]. An attempted preparation of the 2-thiazoline precursor via a synthetic method using the amino alcohol (259), triethylamine and p-anisoyl chloride led to acylation on the amino and hydroxyl functions suggesting the necessity of a hydroxyl protecting group[164].

B. Oxidation of the Chiral 2-Thiazolines

1. The Synthetic Background

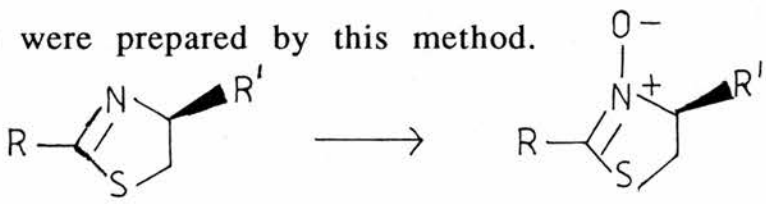
In the introduction a variety of oxidation processes involving achiral 2-thiazolines were described including, S-oxidation, aromatisation and hydrolytic ring opening. In the S-oxidation by m-CPBA the stabilisation of the heterocyclic isothioamide moiety by delocalisation of the charge density through a conjugating substituent, either phenyl[13] or p-methoxyphenyl[12], at the 2-position is apparent.

The instability of the heterocycles is shown in acid or basic media by the hydrolytic ring opening reactions in the presence of 6M bromine water/dilute hydrochloric acid[31] or in potassium

ferricyanide/aqueous alkaline solution[23]. This suggests the necessity of having neutral or mild conditions in the present oxidation reactions. The formation of thiazole byproducts in the oxidation reactions is also possible due to the stability of the aromatic ring and a number of reagents can effect this process.

2. N-oxidation of the chiral 2-thiazolines

In situ generation of peroxytrifluoroacetic acid by addition of 30% hydrogen peroxide to excess trifluoroacetic acid anhydride provided anhydrous conditions for the formation of the previously unknown 2-thiazoline 3-oxides. A total of six examples: the 2-methyl-2-thiazoline 3-oxides (280) and (281), the 2-phenyl-2-thiazoline 3-oxides (282), (283) and (285), and the 2-t-butyl-2-thiazoline 3-oxide (284) were prepared by this method.



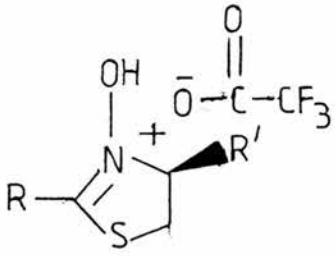
R	R′	
Me	Pr^i	(280)
Me	CH_2Ph	(281)
Ph	Pr^i	(282)
Ph	CH_2Ph	(283)
Bu^t	Pr^i	(284)

(274) (285)

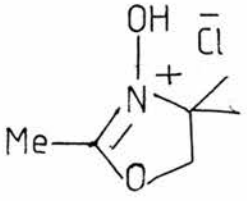
The 2-methyl-2-thiazoline 3-oxides were stable to distillation at high temperatures whereas the 2-phenyl-2-thiazoline 3-oxides eliminated oxygen thermally in boiling toluene to regenerate the

starting 2-thiazoline. Cleavage of the weak nitrogen-oxygen bond in the 2-phenyl-2-thiazoline 3-oxide occurred readily under both acidic and basic conditions: silica gel chromatography in the absence or presence of triethylamine and stirring in dichloromethane over solid anhydrous sodium carbonate.

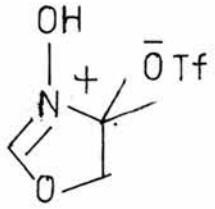
The residual trifluoroacetic acid on chromatography or distillation suggested that a complex (286) may have formed somewhat similar to those reported for the 2-oxazoline 3-oxides (287)[204] and (288)[205].



(286)

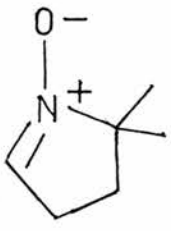


(287)

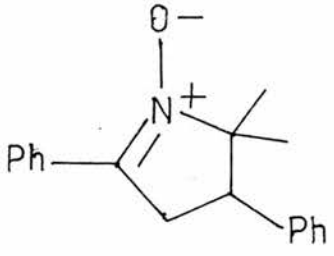


(288)

In contrast to pyrroline 1-oxides with hydrogen or phenyl 2-substituents (289)[206] and (290)[207], irradiation of (285) in a suitable solvent, acetone, did not result in conversion to the oxaziridine isomeric form.



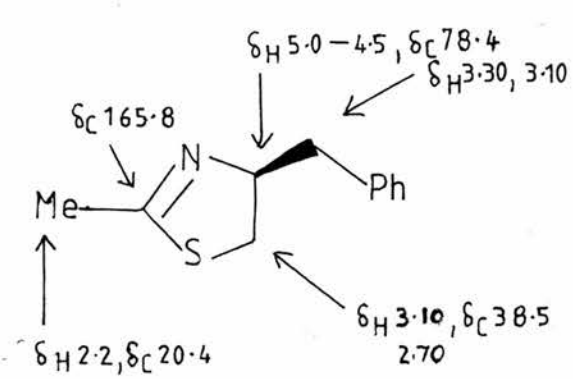
(289)

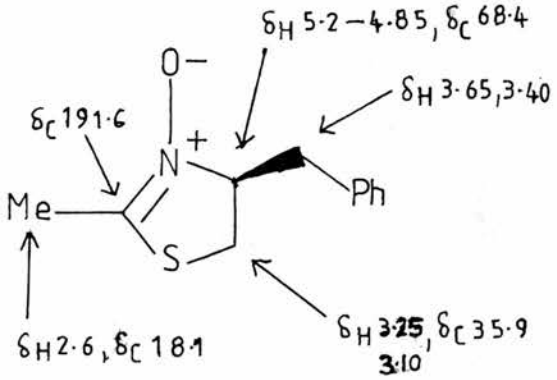


(290)

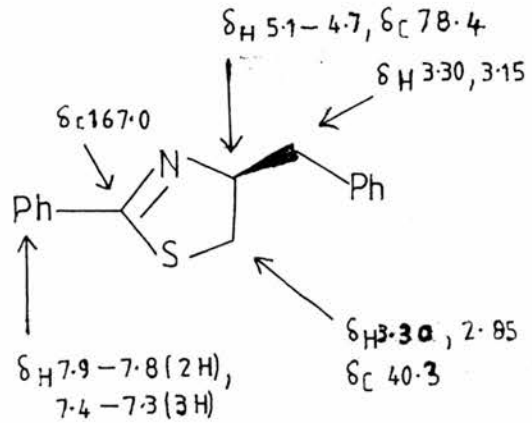
The main evidence for the structure of the 2-thiazoline 3-oxides was obtained from the proton and carbon n.m.r. spectra which are

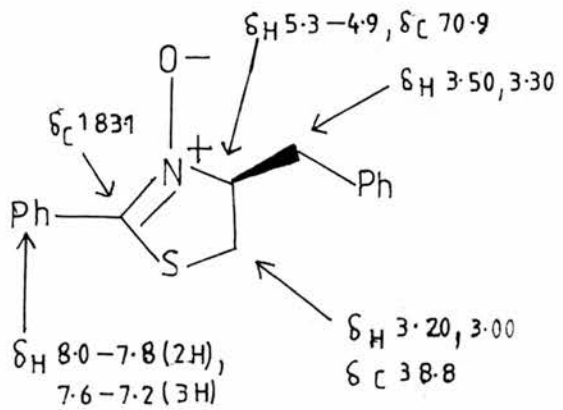
shown below for (281), (283) and (284), and the corresponding 2-thiazolines.



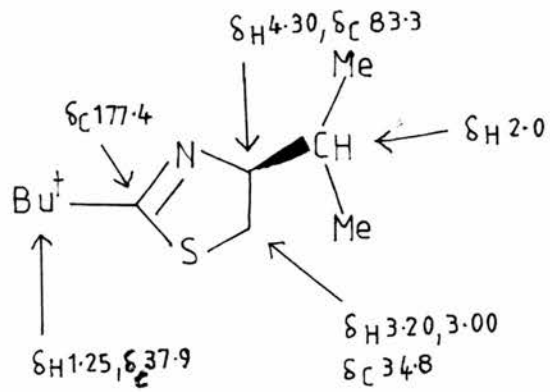


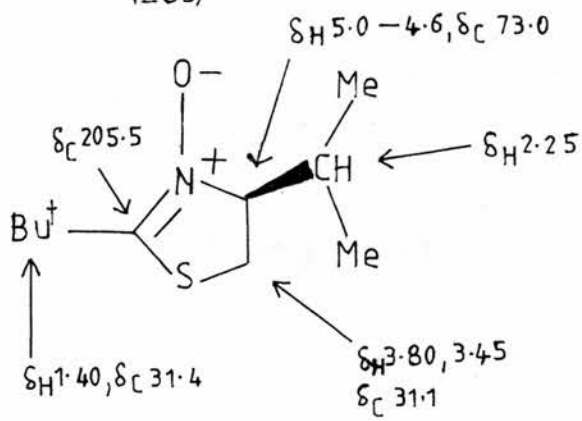
(281)





(283)





(284)

The anisotropic and inductive magnetic influences of the highly polar N-oxide functional group and hence the position of oxidation on the nitrogen atom is clearly indicated by the changes in the chemical shift of the ring protons and the neighbouring exocyclic substituent in a comparison between the 2-thiazoline 3-oxide structure and the 2-thiazoline. In all three cases the H-4 proton is at a higher frequency in the oxidised product. The H-5 protons resonate at a higher frequency for both protons in all three cases with the proton (below the ring plane) of lowest frequency undergoing a significant change. The methyl (281) and the three methyl groups in the t-butyl group (284) are at a higher frequency. The two other phenyl hydrogen atoms in (283) which are syn to the nitrone oxygen function resonate at a higher frequency a phenomenon which has literature precedent in the case of fused tricyclic nitrones[208]. However the key change is at the benzyl methylene protons where both protons resonate at a higher frequency in (281) and (283) and at the isopropyl methyne proton in (284) where the resonance frequency is higher. This indicates the likelihood of N-oxidation as opposed to S-oxidation because the position of the side chain is at carbon atom 4 in the heterocycle.

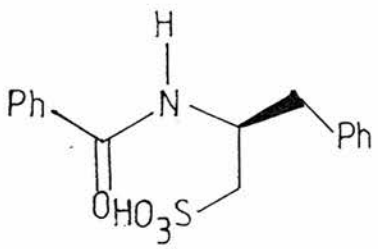
The ^{13}C spectrum is more important in determining the oxide structure as the effects are transmitted through the ring carbon structure and do not depend upon spatial/orientational factors. The most significant changes are at the C-2 carbon atom in all three cases

which move to a higher frequency suggesting the influence of an adjacent nitrone functional group through an inductive effect which also extends along the carbon chain to polarise the C-atoms at C-4, C-5 and C(Bu^t) in (284) and C(Me) in (281) in an opposite direction, to lower frequency. This indicates N-oxidation instead of S-oxidation.

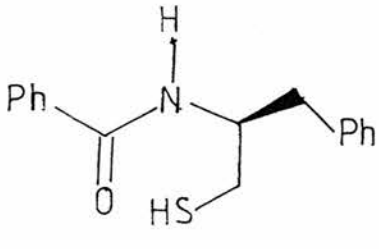
An additional feature of interest is a long-range coupling constant of 1Hz between the methyl group and the C-4 hydrogen atom in (281), which has literature precedent in the case of cyclic nitrones[209].

In all three cases the mass spectrum indicated ring retention as shown clearly by the identical fragmentation patterns of both the 2-thiazoline and the 2-thiazoline 3-oxide[237]. The nitrogen-oxygen bond is only stable in (280) in the mass spectrometer (cf. 1-pyroline 1-oxides[210] and 2-oxazline 3-oxides[211]) while for all the other N-oxides only an M^+-16 peak is observed.

A second reagent, nitrogen dioxide, was found to oxidise a similar range of 2-thiazolines to the 2-thiazoline 3-oxides (281), (282), (283) and (285). The oxidation of sulphides to sulphoxides using nitrogen dioxide is well known but oxidation on the nitrogen atom has been less frequently reported[212]. The mechanism of the reaction involves the regeneration of radicals in the form of dinitrogen trioxide which are liberated on initial attack by the reagent[213]. Byproducts in the reaction of (283) included hydrolysis and S-oxidised products such as benzoic acid and N-benzoylaminoalkylsulphonic acid (291). The



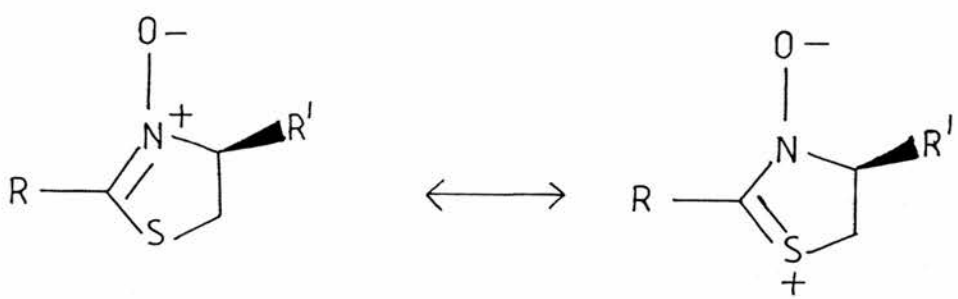
(291)



(292)

sulphonic acid product can be envisaged as arising from acidic hydrolysis to (292) which undergoes oxidation of the free thiol to the sulphonic acid, via a thionitrite[214].

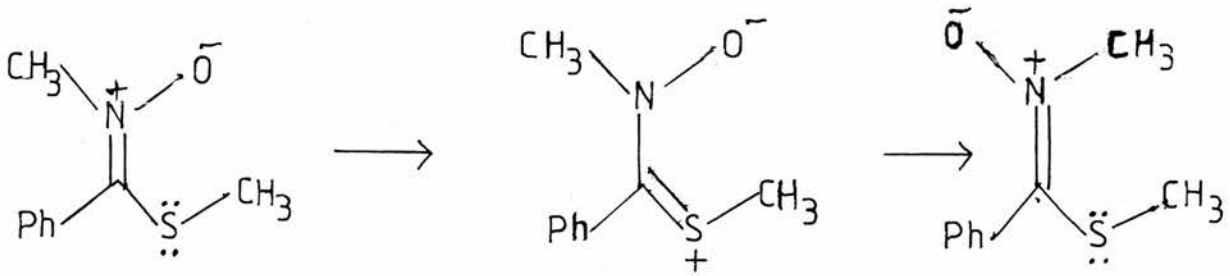
The 2-thiazoline 3-oxides formed with NO_2 had identical spectroscopic properties to the peroxytrifluoroacetic acid reaction products. Further oxidation did not occur in either reaction in spite of the excess concentrations of reagents present. The 2-thiazoline N-oxides can be viewed as a delocalised structure with a contribution from a form (293) with a localised positive charge on the sulphur atom which would hinder mixed oxidation products on both N and S atoms.



(293)

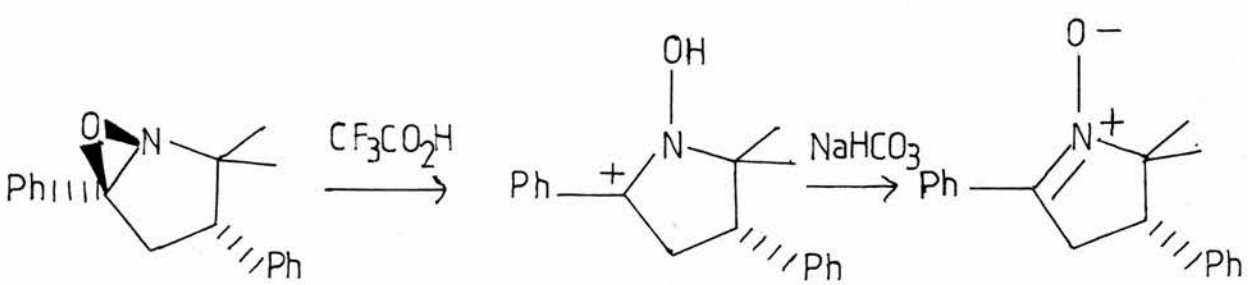
The structure (293) is similar to an acyclic intermediate (294) required to explain the interconversion of the stabilised thioimidate

N-oxide conformers (295a and 295b) in which an electronic interaction occurs between the non-bonded electron pair on the sulphur and the C=N group[215].



(295a) (294) (295b)

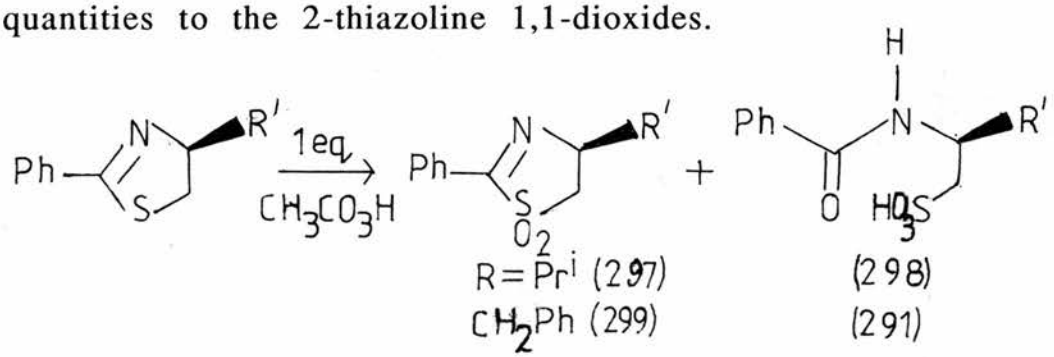
An interesting point is the absence of a stable oxaziridine tautomeric form in the acidic medium in both reactions (cf. the oxaziridines of 2-oxazoline 3-oxides[204] which are discussed on p.194). Acid catalysed isomerisation occurs for the oxaziridine of 1-pyrroline 1-oxide (296) to the cyclic nitrone (290) with trifluoroacetic acid[207].



(296) (290)

3. S-oxidation of the chiral 2-thiazolines

35% Peroxyacetic acid was added to the chiral 2-thiazolines in the presence of a base, anhydrous sodium carbonate, to reduce the nucleophilic potential of the reduced peracid on any oxidised product. This gave the chiral 2-phenyl-2-thiazoline 1,1-dioxides (297), (299) and (300). In addition to the unoxidised chiral 2-thiazolines which were eluted on chromatography the N-benzoylaminoalkylsulphonic acids (298), (291) and (301) were detected in the ^1H n.m.r. spectra in equal quantities to the 2-thiazoline 1,1-dioxides.



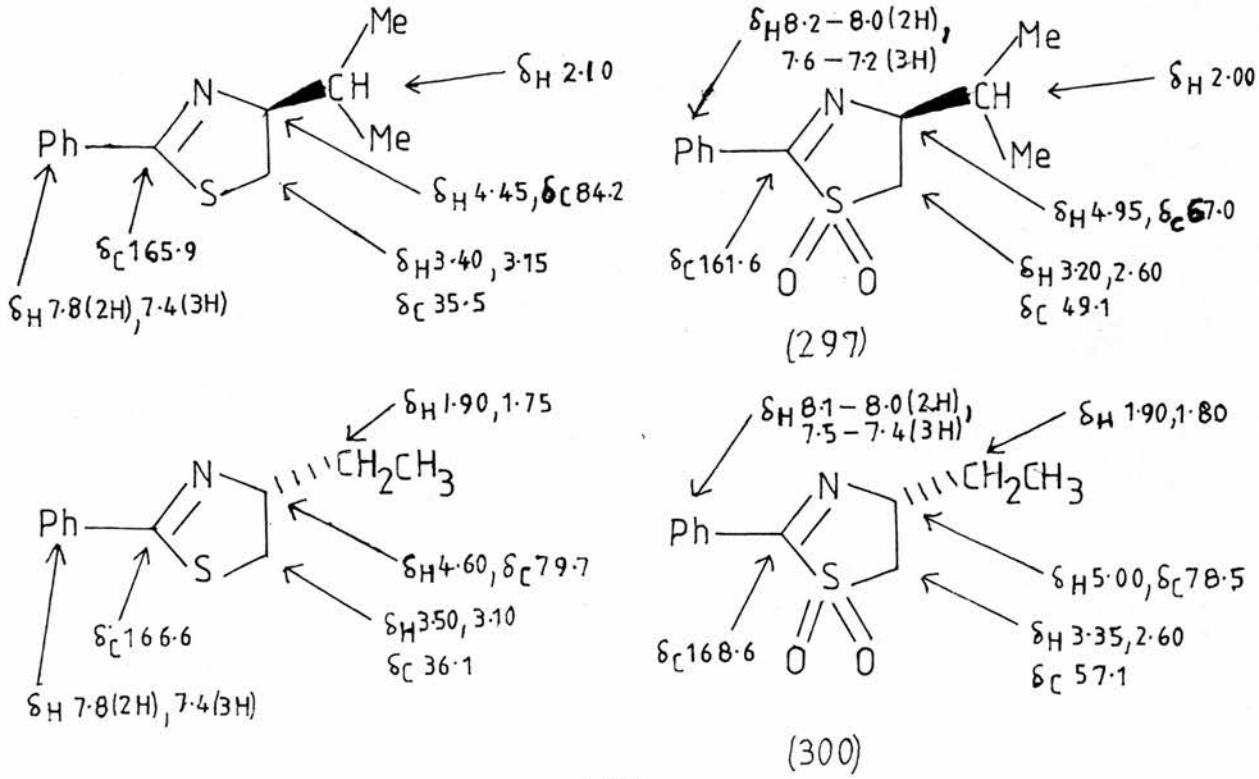
An identical product mixture was isolated from the reaction of the chiral 2-thiazoline (272 , R = Pr^i) with 2-benzenesulphonyl-3-phenyl-oxaziridine[216].

The 2-thiazoline 1,1-dioxides are thermally stable at 140°C under a pressure of 5×10^{-3} torr. but do not readily sublime. Acidic reagents such as silica result in decomposition of the heterocycle.

The most significant spectroscopic evidence is in the chemical ionisation mass spectrum of (297) and in the electron impact mass spectrum of (300). In both cases a fragmentation pattern involving loss of benzonitrile (104 mass units) and an alkene (70 or 55 mass units) can be seen, produced by extrusion of sulphur dioxide from the parent ions 237 or 223. The parent ion is only seen in (297) and not in (300) where an M^+-0 peak appears due to the lesser sensitivity of the electron impact technique.

The infra-red spectrum of (300) indicated that the carbon-nitrogen bond in conjugation with a sulphone functional group will vibrate at a shift of 130 cm^{-1} to a higher frequency than in the 2-thiazoline (274) (cf. Scott[12], 1700 cm^{-1}).

The data for the proton and carbon spectra are shown in a tabulated form below.



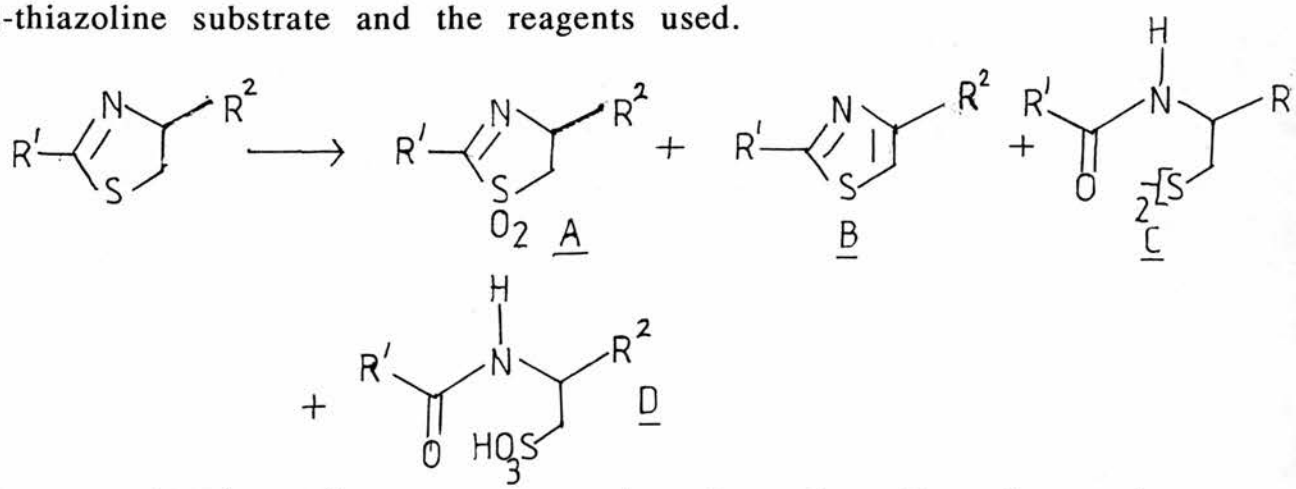
In the proton spectrum the most notable features indicating ring retention (coupling patterns are retained) and oxidation in the heterocycle are the movement to a higher frequency of the H-4 proton, the wide 'splitting' or differentiation of the H-5 proton below the ring plane and that above the ring plane due to the anisotropic effect of the oxidised functional group and the higher (resonance) frequency of the two ortho phenyl hydrogen atoms compared with the meta and para-phenyl hydrogen atoms.

The most important contrast to the N-oxide oxidation is the small change in the C-2 atom on oxidation suggesting oxidation on the S-atom. The substantial chemical shift change to a higher frequency at the C-5 position on oxidation is due to the inductive effect of the adjacent sulphone functional group.

The small change at the C-2 atom on S-oxidation is likely to be due to the opposite competing effects of the conjugative delocalisation of the carbon-nitrogen double bond through a *mesomeric* effect of the adjacent sulphone functional group and the inductive effect of the sulphone functional group. In contrast, the 2-thiazoline 3-oxides may be viewed as a nitrone and a partially delocalised structure (293) which is stabilised to a greater extent in the electron-releasing 2-methyl- and 2-t-butyl-2-thiazoline 3-oxides than in the electron-withdrawing 2-phenyl-2-thiazoline 3-oxides resulting in a more substantial shift change at the C-2 atom on N-oxidation.

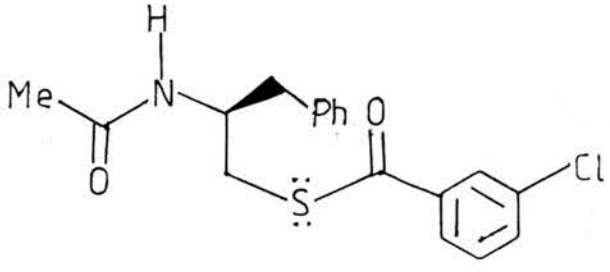
4. Oxidation of the chiral 2-thiazolines to ring-opened acyclic products or aromatised products

The reactions are shown below in a tabulated form to emphasise the distribution of products in terms of the substituents in the 2-thiazoline substrate and the reagents used.



starting material	R^1	R^2	reagent	A	B	C	D	other products
(266)	Me	CH_2Ph	$KHSO_5$			(304)		
(266)	Me	CH_2Ph	m-CPBA					(305)
(272)	Ph	Pr^i	1eqCH_3CO_3H	(297)			(298)	
(272)	Ph	Pr^i	3eqCH_3CO_3H				(298)	
(273)	Ph	CH_2Ph	1eqCH_3CO_3H	(299)			(291)	
(273)	Ph	CH_2Ph	3eqCH_3CO_3H				(291)	
(273)	Ph	CH_2Ph	m-CPBA				(291)	
(273)	Ph	CH_2Ph	Bu^tOOH		(306)		(291)?	1 unidentified product
(273)	Ph	CH_2Ph	$KMnO_4$/BTEAC		(306)			
(274)	Ph	Et	1eqCH_3CO_3H	(300)				1 unidentified product
(274)	Ph	Et	3eqCH_3CO_3H				(301)	1 unidentified product
(274)	Ph	Et	HCO_3H		(307)	(308)		1 unidentified product

(274)	Ph	Et	H_2O_2	(307)	(308)	(301)?
(274)	Ph	Et	Bu^tOOH	(307)	(308)	(301)?
(274)	Ph	Et	$CH_3C(=NH)(O\text{-}OH)$	(307)	(308)	(301)?
(274)	Ph	Et	Bu_4NIO_4	(307)		(301)?
(274)	Ph	Et	$KMnO_4$/BTEAC	(307)		
(274)	Ph	Et	$KMnO_4$/ 18-CROWN-6	(307)		
(274)	Ph	Et	Ni_2O_3	(307)		
(277)	Bu^t	Pr^i	1/3eqCH_3CO_3H			(309)
(279)	Bu^t	CH_2Ph	1/3eqCH_3CO_3H			(310)



(305)

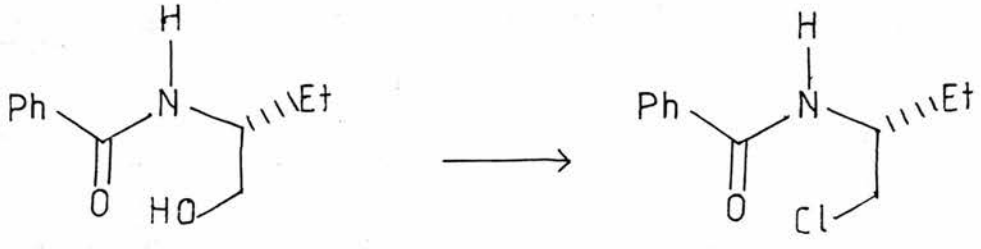
The acyclic nature of the structures for (304), (291) and (309) is clearly shown by the patterns in the proton n.m.r. spectra. In (30 4) an overlapping pattern at 2.0-2.7 ppm due to the benzyl methylene and S-methylene protons is apparent. The broad doublet at 7.8ppm (NH) is due to the presence of two isomers formed by the slow rotation of the amide carbon-nitrogen bond (cis-trans isomerism) on the n.m.r. time scale. In (291) the acidic groups are easily identified at 8.55 ppm (d) and at 8.3 ppm (brs) but the benzyl

methylene and S-methylene protons are in the form of an AB pattern of doublets due to hindrance in rotation caused by the bulky N-benzoyl group. In (309) a similar situation occurs in the S-methylene protons due to the bulky N-trimethyl acetyl group.

The structure of the thiazole (307) was confirmed by the high intensity molecular ion peak in the mass spectrum resulting from the aromatic character of the ring[217], a ^{13}Cn.m.r. signal comparison with 4-ethylthiazole[218] and an IR comparison with 2-phenylthiazole[219].

A route to the authentic compounds for the disulphide (308) and the sulphonic acid (301) was investigated. The formation of a precursor with a good leaving group such as a mesylate or a chloride from the hydroxyalkylamide was envisaged, followed by replacement of the leaving group with a nucleophilic sulphur source such as sodium sulphide.

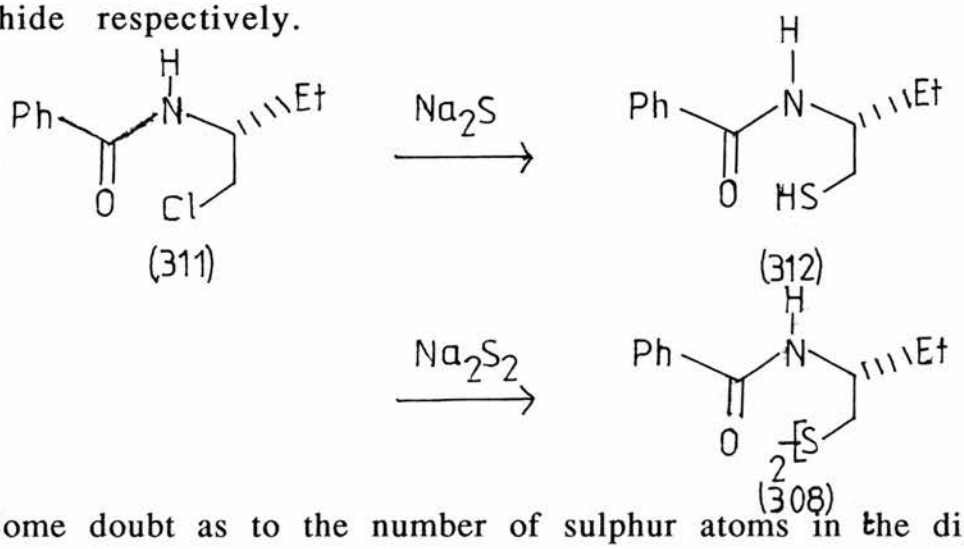
The chloride (311) was produced by reaction with either mesyl chloride and triethylamine in boiling 1,2-dichloro ethane[220] or the triphenylphosphine-carbon tetrachloride reagent[221]. The chloride is formed from the mesyl group by a clean bimolecular displacement



(269) (311)

reaction and is well known particularly with added lithium chloride 222.

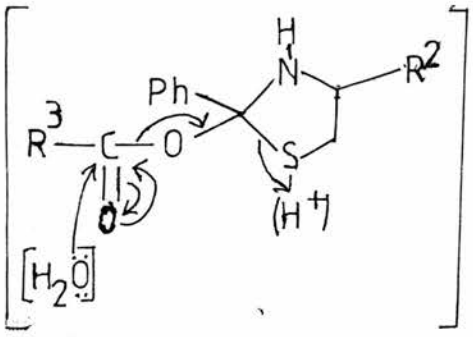
The thiol (312) and disulphide (308) were prepared by reaction of the chloride with sodium sulphide nonahydrate and disodium disulphide respectively.



Some doubt as to the number of sulphur atoms in the disulphide (308) remains as aliphatic polysulphides can be formed under similar reaction conditions[223].

The oxidation of the thiol (312) to the sulphonic acid (301) with four equivalents of m-CPBA using boiling 1,2-dichloroethane resulted in a complex reaction mixture.

The N-acylated oxidation products (308) and (301) can be rationalised by the formation of the thiazolidine intermediates (313) or (314) through attack of the 2-thiazoline or its dioxide (A) by a nucleophilic peroxyacid or acid, thus releasing the ring strain due to the carbon-nitrogen double bond. The tetrahedral intermediate breaks down by a rearrangement induced via a hydrolysis reaction of the acyl group to give the N-acyl derivatives with the free thiol (315) or



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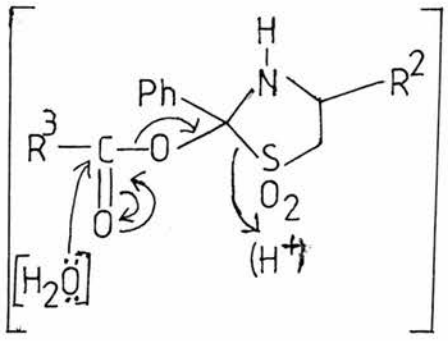
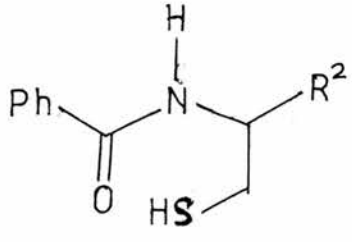


(314)

sulphinic acid groups (316) which can further oxidise to the disulphide (308) or the sulphonic acid (301). Evidence for the intermediate (314)



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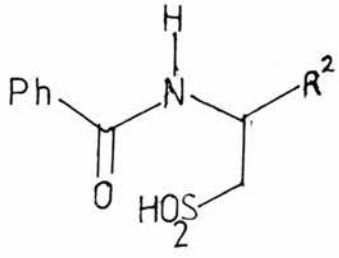


(316)

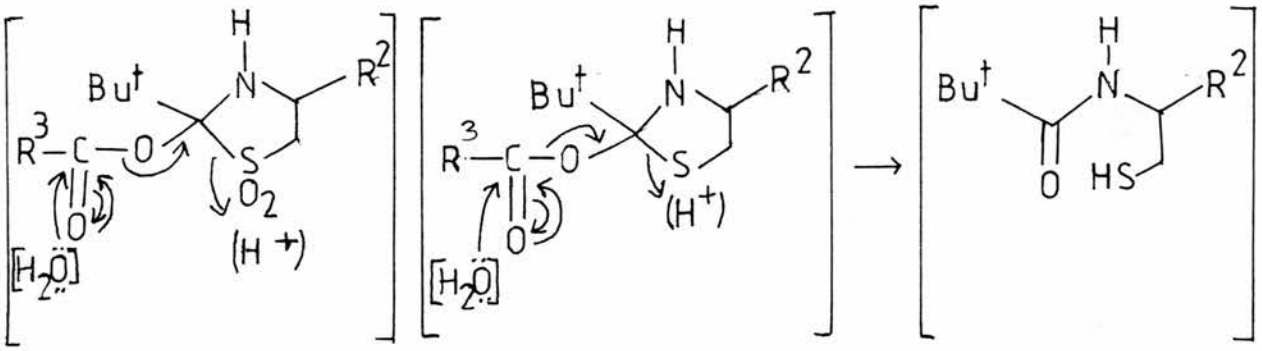
is the conversion of the 2-thiazoline 1,1-dioxides (297) and (299) to the N-benzoylalkylsulphonic acids (298) and (291) using an excess of two equivalents peroxyacetic acid.

The more sterically hindered peroxyacids such as m-CPBA react through a similar reaction pathway via (314). An increased concentration of the peroxyacid is required to induce S-oxidation on the S-atom of the 2-thiazoline and in the subsequent nucleophilic attack on the 2-thiazoline 1,1-dioxide (299). The increased bulk of the R^3 group does not appear to slow the reaction through the formation of the intermediate (314) as the 2-thiazoline 1,1-dioxide is not isolated.

Instead the hydrolysis reaction is increased by the electron withdrawing-effect of the aromatic ring in the acyl substituent.

In the peroxyformic acid oxidation reaction, the smaller size of the R^3 group (H atom) compared with the longer chain peroxyacids, is likely to increase the rate of the step involving nucleophilic attack to give the intermediate (314).

In the peroxyacetic acid oxidation of the 2-t-butyl-2-thiazolines (277) and (279) there is no direct evidence for the 2-thiazoline 1,1-dioxide as a stable intermediate but the ease of oxidation of the 2-thiazoline by both one equivalent or three equivalents of reagent suggests a reaction through an intermediate such as (317) rather than through (318) and (319) to the N-acyl alkylsulphonic acids (309) and (310). The electron-releasing t-butyl group will accelerate the hydrolysis reaction after the intermediate (317) is formed, relative to

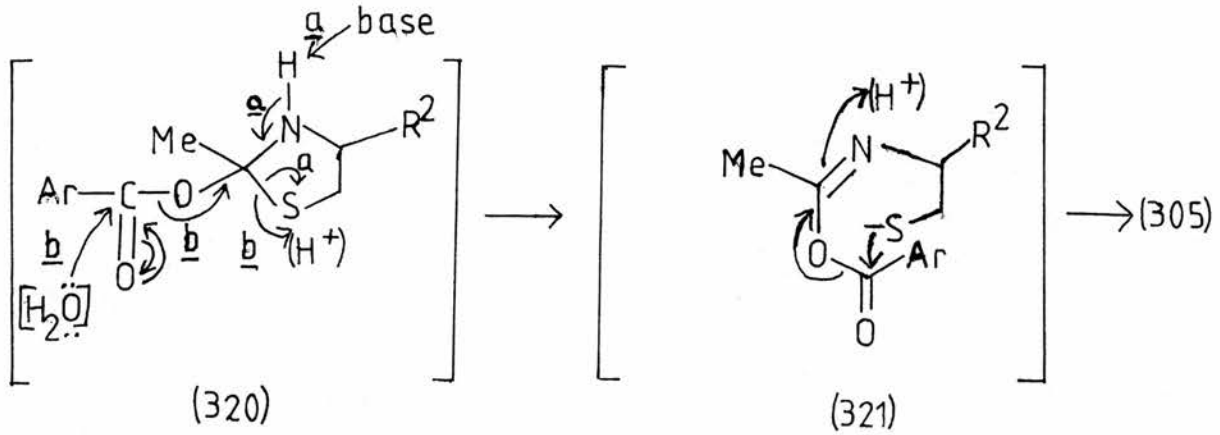


(317) (318) (319)

the electron-withdrawing phenyl group due to the ease of expulsion of the sulphinyl leaving group from the ring.

In the case of the 2-methyl-2-thiazoline (266) reaction with

m-CPBA the electron-releasing methyl group favours the formation of the intermediate (320) at lower concentrations of oxidising reagent than with the 2-phenyl substituent. The deprotonation of the free



amino function in the thiazolidine intermediate (320) by a base is followed by the intramolecular acylation of the free thiol anion via a seven-membered transition state in (321). A hydrolysis product such as (304) which could be obtained via pathway (b) is not isolated.

In the oxidation reaction of the 2-phenyl-2-thiazoline (274) by peroxyformic acid, the decreased steric effects in the acyl group in the peroxyacid and in the 4-ethyl side chain in the substrate are important in the approach of the reagent and the electronic effect in the thiazole, stabilisation by aromatisation, is important in product formation.

In the potassium permanganate oxidation, 18-crown-6 appears to be more efficient as the phase transfer catalyst compared with BTEAC[224]. The 2-thiazoline with the 4-(R)-ethyl side chain is more reactive than that with the bulkier 4-(S)-benzyl side chain. Potassium permanganate is likely to react via a cyclic complex[225]. The

1,2,3-triazoles have been formed in a phase transfer $KMnO_4$ reaction by oxidation of 1,2,3-triazolines[226].

The mechanistic details of the oxidation by non-stoichiometric oxides such as nickel peroxide are still to be clarified. A proposal involves the hydrogen abstraction from the substrate by the oxidant and formation of OH radicals which undergo further reaction[227]. The formation of OH radicals may be involved in both hydrogen peroxide and t-butyl hydroperoxide oxidations[228,229].

The reactive species in the aceto-nitrile/hydrogen peroxide reaction has been established as the peroxycarboximidic acid[230]. It can act as an ^{+}OH source or potentially as the anion ($R\text{-}\overset{\overset{NH}{\|}}{C}\text{—}OO^{-}$) exhibiting both electrophilic and nucleophilic character[231].

C. Reactions of the 2-Thiazoline 3-oxides

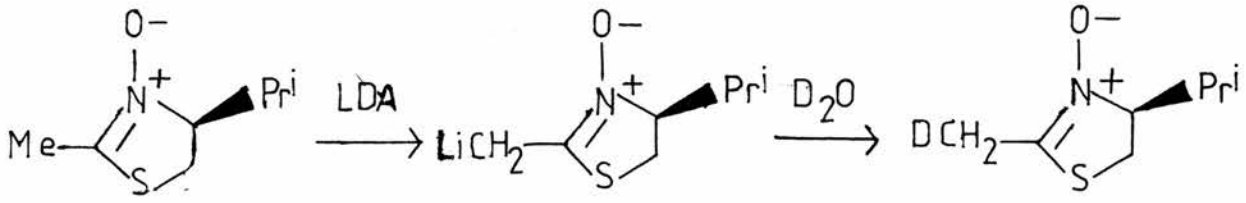
1. 4-(S)-Isopropyl-2-methyl-2-thiazoline 3-oxide

a) Deuteriation

Treatment of the 2-thiazoline oxide with a base such as lithium diisopropylamide at -70°C, followed by deuteriation using deuterium oxide, should establish the position of oxidation in the molecule.

The LDA reaction of (280) produced a stable lithiomethyl derivative (322) which became deuteriated with D_2O and indicated N-oxidation in (323). The 2-methyl group is activated by the nitrone

functional group towards lithiation.



(280) (322) (323)

b) Attempted further oxidation

Treatment of the 2-thiazoline oxide with 2.5 equivalents of m-CPBA, should indicate the position of oxidation in the original oxide and whether mixed oxidation products on both heteroatoms are possible. The deoxygenation of (280) during the base extraction (aqueous sodium carbonate) suggested that the N-oxide was indeed the original structure (cf. 2-phenyl-2-thiazoline 3-oxides), as the 2-phenyl-2-thiazoline 1,1-dioxides are not sensitive to this base. Further oxidation of the 2-thiazoline 3-oxide did not in fact occur due to deactivation of the sulphur electrons by the nitrone functional group. Attack at the activated C-2 position to give ring-opened products did not occur either cf. 1-pyrroline 1-oxide[232] and 2-oxazoline 3-oxides (which is discussed in a later section). Oxidative deoxygenation is an alternative possibility which occurs when N-oxides such as quinoline 1-oxide is treated with peroxyacetic acid[233].

c) Attempted 1,3-dipolar cycloaddition reactions

1-Pyrroline 1-oxides[234] and 2-oxazoline 3-oxides[155] are very reactive 1,3-dipoles, the rate of reactivity increasing with the change from an α-carbon atom to an α-oxygen heteroatom[155]. It would be interesting to investigate the analogue with an α-sulphur heteroatom to determine the relative reactivities of the related N-oxidised heterocycles towards a range of dipolarophiles. A particularly useful feature of the new 2-thiazoline 3-oxides is the chiral centre at the C-4 position which could influence the orientation and stereospecificity of the reaction with sp^2 hybridised carbon-based dipolarophiles to give enantiomerically pure products cf. 2-oxazoline 3-oxides[155].

The reactions of (280) with dimethyl acetylene dicarboxylate, maleic anhydride and phenyl acetylene gave unreacted starting materials at 40°C and 70°C using chlorinated polar solvents.

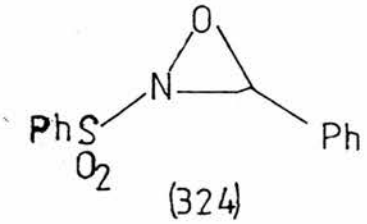
2. 2-Phenyl-2-thiazoline 3-oxides

a) Oxygen transfer reactions

The thermal properties of the nitrogen-oxygen bond in the 2-thiazoline 3-oxide (283) were investigated by heating in boiling toluene. The bond surprisingly cleaved, with loss of oxygen to give the 2-thiazoline. The previous 2-methyl-2-thiazoline 3-oxide was thermally stable at 150°C on distillation. An explanation may lie in

the electron-withdrawing nature of the 2-phenyl group and the weakening of the bond in the nitrone through a conjugative effect.

This property of the 2-thiazoline 3-oxides could be used to deliver oxygen directly to a variety of substrates, as has already been investigated with N-sulphonyl oxaziridines (324)[216], N-methyl morpholine N-oxide (325)[235] and oxoammonium chloride (326)[236].



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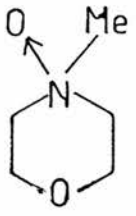

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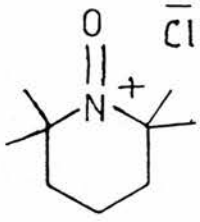


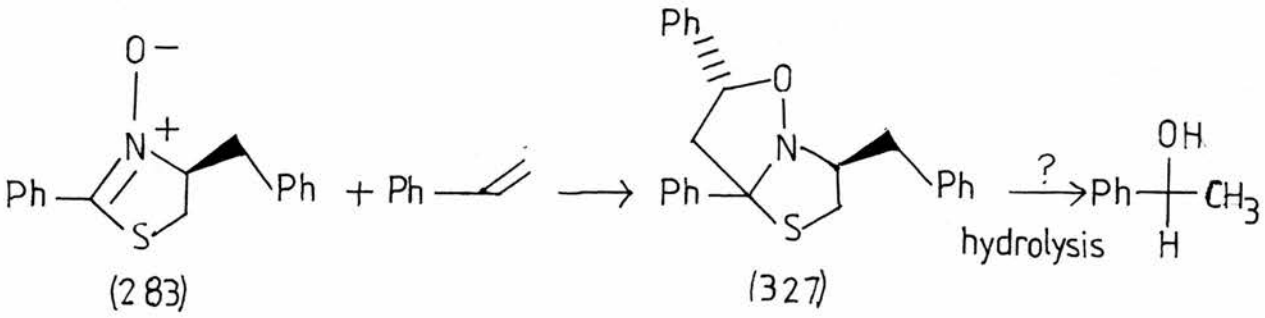
(326)

In addition there is a possible asymmetric aspect to the oxidations which are shown below in a tabulated form.

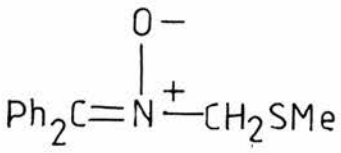
(i) Oxygen transfer reactions of (283) to neutral acceptors

substrate	products in N-oxide reaction	control reaction (heating without N-oxide)
styrene	1-phenylethanol, (273) carbon-carbon coupling products	styrene epoxide, benzylalcohol, a primary alcohol, polymers
cyclohexene	cyclohexanol, (273) 1,2-cyclohexane diol bi-2-cyclohexen -1-yl	1,2-cyclohexane diol bi-2-cyclohexen-1-yl
hexene	(273) carbon-carbon coupling products	carbon-carbon coupling products
thioanisole	no reaction	none

Styrene is an asymmetric neutral acceptor with a phenyl substituent in conjugation with an alkene double bond. The main product of the reaction is 1-phenylethanol with a low optical rotation formed *via* a net hydration of the alkene. This might possibly involve hydrolysis of an adduct such as (327) but the mechanism is unclear



(283) (327)



(328)

because styrene is found not to undergo cycloaddition reactions with nitrones (328) of similar reactivity[237].

The styrene epoxide is only produced in the control reaction as a result of atmospheric oxidation.

Cyclohexene has an advantage in that it does not extensively polymerise and should give a better quantitative measure of oxidation. Cyclohexanol is the only product present in the 2-thiazoline 3-oxide reaction. However since the g.c. trace was very complex, other minor products could remain undetected. Cyclohexene can readily oxidise to cyclohexanol. Hex-1-ene is an asymmetric analogue of cyclohexene. The reaction was not very informative as only polymerised products

were detected.

In both the cyclohexene and hex-1-ene reactions the epoxides were not present as shown by ^{1}H n.m.r. spectroscopy and a comparison with the authentic samples.

Previously sulphides have been oxidised using pyridine N-oxide[238], aza-aromatic N-oxides[239] and particularly asymmetrically using chloroperoxidase[240] and modified Sharpless reagents[241,242]. In the last reaction methyl arylsulphides were chosen and this suggested thioanisole as a suitable substrate. Thioanisole was unreactive towards the 2-thiazoline 3-oxide (285) even on prolonged heating.

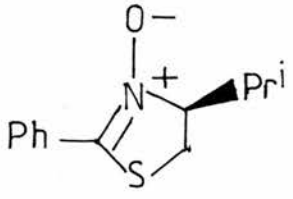
The 2-phenyl-2-thiazoline 3-oxide with a 4-(R)-ethyl side chain (285) did not transfer oxygen on heating in toluene due to the thermal stability of the nitrogen-oxygen bond.

(ii) Oxygen transfer reactions to lithium anions

Lithium anions have been oxygenated using a variety of reagents which include t-butyl perbenzoate[243], bis (trimethylsilyl) peroxide[244], molybdenum peroxide[245], dibenzyl peroxydicarbonate[246] and camphorylsulphonyl oxaziridines[247]. Chirality has been induced in the hydroxylated lithium enolate product by an asymmetrically substituted heterocycle, in an adjacent part of the substrate, in the two most recently published

examples[246,247].

The 2-phenyl-2-thiazoline 3-oxide (285) has the ability to act as a chiral reagent where the substrate possesses acidic hydrogen atoms in a prochiral environment. A number of simple substrates and those which can be stabilised via potential resonance forms on lithiation are shown in the table below.



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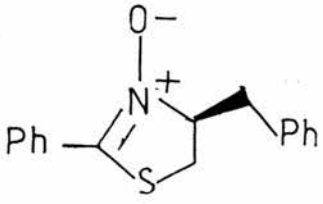

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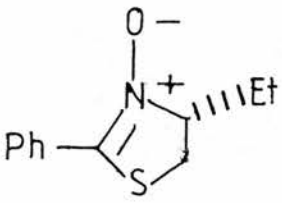


(285)

Reagent	Substrate	Product
(282)	PhLi	PhOH
(285)	PhLi	PhOH
(283)	LDA	Pr^i_2NOH
(285)	PhC ≡ CH, PhLi	$(PhC{\equiv}C)_2O$
(285)	cyclohexanone, LDA	Pr^i_2NOH
(285)	2,4,4-trimethyloxazoline, LDA	Pr^i_2NOH

The 2-thiazoline 3-oxides (282) and (285) reacted with phenyl lithium in dry tetrahydrofuran at R.T. to give phenol on aqueous work up.

In the reactions of the 2-thiazoline 3-oxides (283) and (285),

with lithium diisopropylamide as the lithium species at -70°C, diisopropylhydroxylamine is isolated as the oxidised species, formed by rearrangement of the intermediate diisopropylamine N-oxide. The cyclohexanone and 2,4,4-trimethyl-2-oxazoline are lithiated to the lithium enolate and azaenolate respectively[248].

In the process one mole of diisopropylamine is generated and it appears that this has a greater affinity for oxygen than the anions. Thus the expected 2-hydroxycyclohexanone and 2-hydroxymethyloxazoline are not formed and the reactions instead give diisopropylhydroxylamine, whose identity was proved by comparison with an authentic sample[249].

In the reaction of the 2-thiazoline 3-oxide (285) with phenylethynyl lithium, the potential product was an acetylenic alcohol which is known to be unstable to a rearrangement involving a hydrogen shift to the ketene[250]. In general, functionalised acetylenes such as acetylenic esters either carboxylate, sulphonate or phosphate are unknown[251]. Phenylacetylene requires a more reactive, less sterically hindered base such as phenyl lithium at 0°C, to form phenylethynyl lithium. The only product on reaction with (285) was bis(phenylethynyl) ether which might be a byproduct of an oxidative coupling reaction.

b) Attempted 1,3-dipolar cycloaddition reactions

The nitrone with a 2-methyl electron-releasing substituent had been shown to be unreactive towards cycloaddition reactions. The 2-phenyl substituted nitrones have a flat planar ring which is conjugated to the nitrone functional group and might therefore be expected to exhibit a greater reactivity towards dipolarophiles due to its electron-withdrawing effect increasing the positive charge at the carbon end of the 1,3-dipole. In addition the smaller ethyl side chain may reduce steric hindrance in the reaction at the site of the potential 1,3-dipolar cycloaddition.

The new 1,3-dipole (285) from the nitrogen dioxide reaction was reacted with dimethyl acetylenedicarboxylate, phenyl acetylene, ethylpropiolate, acrylonitrile, methyl acrylate, dimethyl fumarate, phenyl isocyanate, phenyl isothiocyanate and 1-phenyl-1,3,4-triazoline-2,5-dione[252]. However in no case did the expected cycloaddition actually take place.

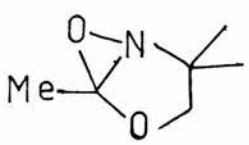
In the phenyl isothiocyanate reaction and the 1-phenyl-1,3,4-triazoline-2,5-dione reaction unidentified aromatic products were isolated. In the former case, the product was shown beyond reasonable doubt not to be azobenzene[253] which might have been produced in an elimination reaction from the cycloadduct. Benzoic acid was isolated from the dimethyl acetylene dicarboxylate reaction due to decomposition of the 1,3-dipole on heating. The phenyl

isocyanate reaction gave a complex mixture of decomposition products.

The lack of reactivity as a 1,3-dipole shown by the 2-thiazoline 3-oxides suggests the possibility of deactivation of the positive centre of the 1,3-dipole at the C-2 position by back polarisation of the electron density from the π-orbitals on the sulphur atom. The back polarisability of the double bond and in particular the positive charge at the carbon atom often determines the reactivity of nitrones[254] and is known in 1-pyrroline 1-oxides[255] and 2-oxazoline 3-oxides[155].

D. The Attempted Preparation of Alternative 1,3-Dipoles for Cycloaddition Reactions

It is reported in the literature that 2-oxazoline 3-oxides are more reactive as 1,3-dipoles than the 1-pyrroline 1-oxides[155]. Examples have been reported of 2-methyl or 2-alkyl substituted 2-oxazoline oxaziridines (329)[155], (330)[256,257] and (331)[258] prepared as a result of direct oxidation of the heterocycles with one equivalent of m-CPBA.



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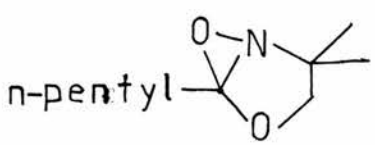

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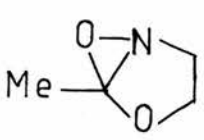
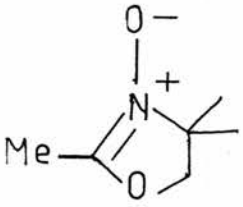


(331)

The nitrones (332)[155] and (333)[257], obtained on silica gel isomerisation of these oxaziridines are also mentioned. Chiral



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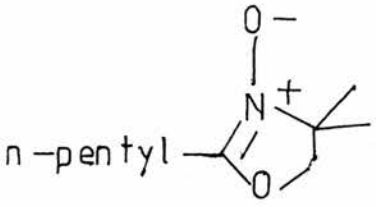

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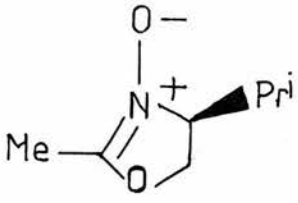
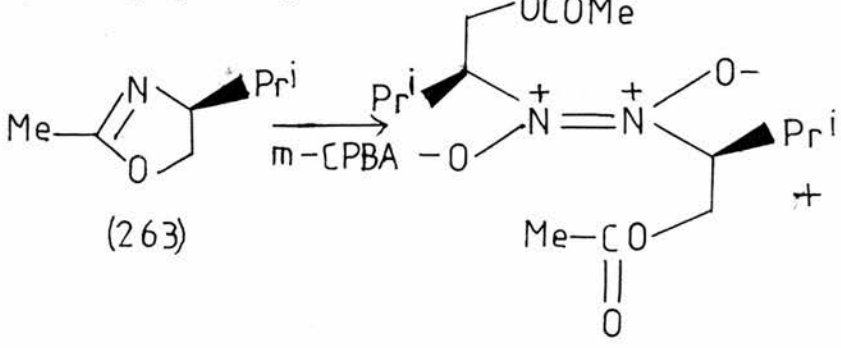


(334)

2-oxazoline 3-oxides such as (334) might be excellent *chiral* 1,3-dipoles.

Unfortunately however reaction of 1.5 equivalents of m-CPBA with 4-(S)-isopropyl-2-methyl-2-oxazoline gave the nitroso-dimer (335) together with the E- and Z-oximes (336) and (337). These types of ring-opened products, formed as a result of further oxidation of the



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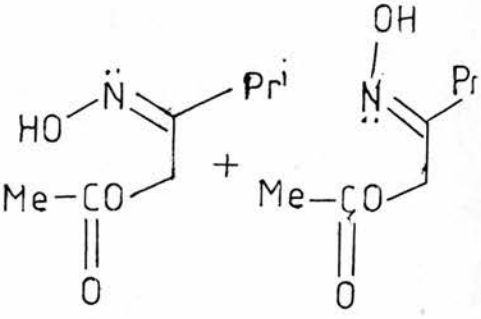
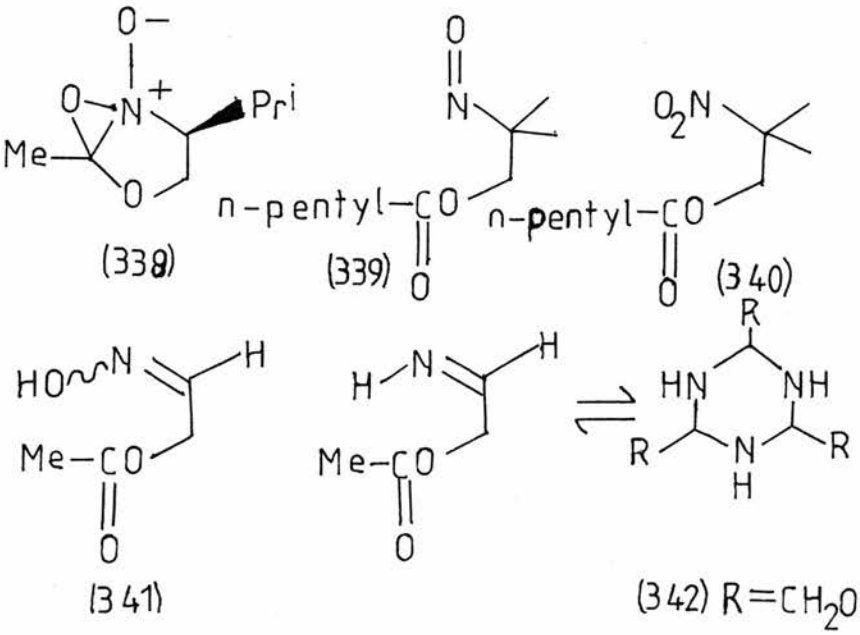


(335) (336) (337)

oxaziridine via an oxaziridine N-oxide intermediate (338)[258,259] (cf. 1-pyrroline 1-oxides[232]) have also been observed in the oxidation of (330) and (331) where excess quantities of reagent lead to the nitroso (339)[257] and nitro-esters (340)[257] or the oxime (341)[258] and imine trimer (342)[258].



(338) (339) (340)

(341) (342) R=CH_2OCOCH_3

The key factor in product formation is the number of abstractable hydrogen atoms at the C-4 position which determines the formation of the isomeric oximes instead of the nitroso-compounds or the more highly oxidised nitro-compounds. The formation of C-nitroso-dimers instead of nitro-compounds in peracid media is usually only favoured in dilute solution[260]. Isomerisation of nitroso-compounds[261] or heating nitroso-dimers results in the formation of oximes[262].

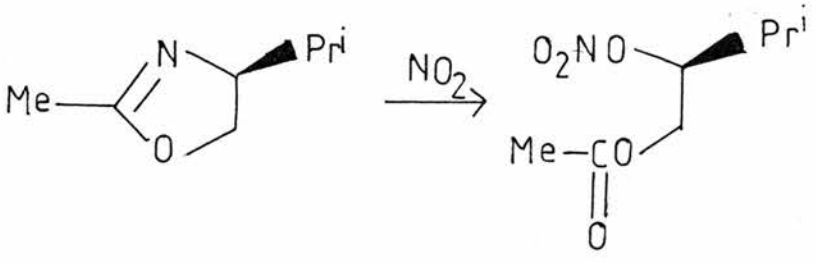
Ultra-violet spectroscopy failed to distinguish between the E and Z-dimers which is normally possible due to the lowering of the λ_{max} from the E-dimer to the Z-dimer[263,264]. Steric hindrance in the nitroso-dimer (335) due to the large 'R' groups is likely to favour the E-structure.

The chemical ionisation mass spectrum of the nitroso-dimer (335) indicated the dimeric molecular ion peak at 318 and characteristic fragmentation patterns due to the expulsion of the nitroso-radical[265]

at 298. The distinctive signals in the ^{1}H and ^{13}C n.m.r. spectra corresponding to the position adjacent to the azo dioxide function occur at 5.45 ppm and 70.7 (d) ppm as in literature examples[266].

In the spectra of the E and Z-oximes (336) and (337) the increased stability and so higher proportion of the E-form compared with the Z-form was observed from the integral in the ^{1}H n.m.r. spectrum and the peak height in the ^{13}C n.m.r. spectrum. The deshielding of the hydroxyl function on a carbon atom through space has been reported in half cage molecules[267] and resembles the changes at the methyl group from (336) to (337).

The reaction of the 2-oxazoline (263) with nitrogen dioxide gave an unexpected product which may be the nitrato-ester (343).



(263) (343)

The mechanism might be envisaged as an insertion of an additional oxygen between the carbon-nitrogen bond in a nitro-ester. Oxidation in this manner is a novel process. Nitrate-esters are normally the oxidation product of nitrite-esters in nitrogen pentoxide reactions[268].

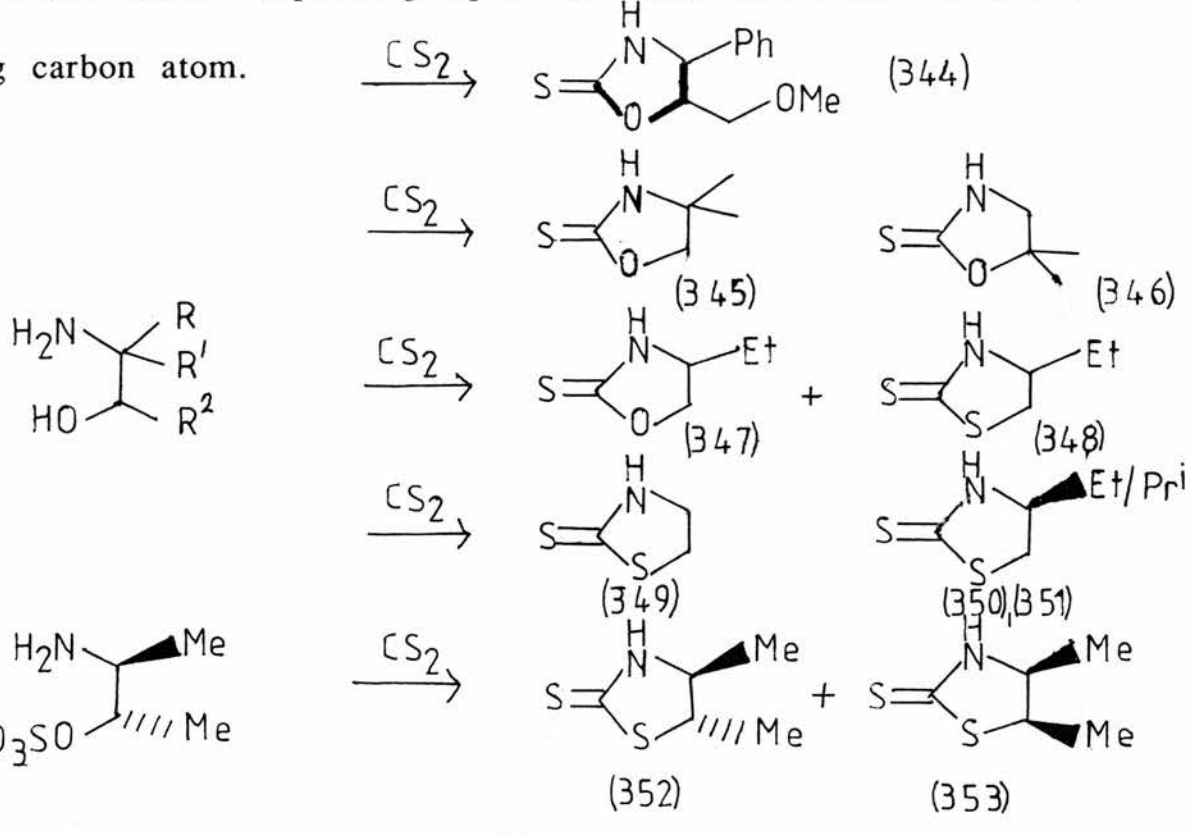
The main evidence for the three oxygen atoms on the nitrogen atom is the base peak at 129 mass units in the chemical ionisation mass spectrum due to a secondary radical formed by α-fission on fragmentation of the nitrato-group from the parent ion 191.

E. The Preparation and Oxidation of Thiazolidine-2-thiones

1. Preparation of 3-unsubstituted thiazolidine-2-thiones

a) The synthetic background

The preparation of thiazolidin-2-thiones has been described in a comprehensive review on thiazolidines by Metzger[186]. The main route to thiazolidine-2-thiones is via cyclisation of amino alcohols using carbon disulphide to give either the oxazolidine-2-thione or the thiazolidine-2-thione depending upon the substitution at the amino bearing carbon atom.



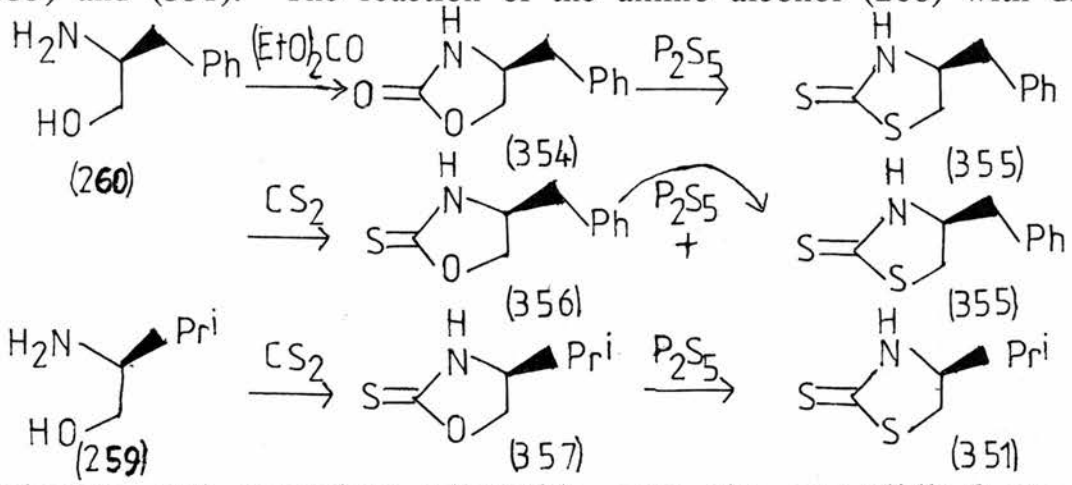
The oxazolidine-2-thione (345) is formed via a dithiocarbamate salt in alcoholic alkali with evolution of hydrogen sulphide on heating[269]. The oxazolidine-2-thione (346) is produced by the same method[269] presumably through the dithiocarbamate on heating or via an accelerated xanthate ester in the *aprotic solvent*, dimethyl sulphoxide in the presence of powdered potassium hydroxide[270]. The mixture of the oxazolidine-2-thione (347) and the thiazolidine-2-thione (348) is produced in an *alcoholic* solvent with alkali present via the dithiocarbamate or the dithiocarbamate/xanthate ester[271]. The amino alcohol, ethanolamine reacts when heated in *alcoholic* alkali via the dithiocarbamate/xanthate ester to give only the thiazolidine-2-thione (349)[272]. Asymmetric examples involving the formation of a chiral thiazolidine-2-thione (350) and (351)[273] in *alcoholic* alkali and the formation of a chiral oxazolidine-2-thione (344) with a sterically hindered hydroxyl bearing carbon atom in dry dimethylformamide[274] have been reported.

An alternative method is via the aminoalkyl-hydrogen sulphates which react in alkaline media in the presence of xanthanates to give the diastereoisomeric thiazolidine-2-thiones (352) and (353)[275].

b) Preparation of 3-unsubstituted thiazolidine-2-thiones

Two routes were used to prepare the chiral thiazolidine-2-thiones

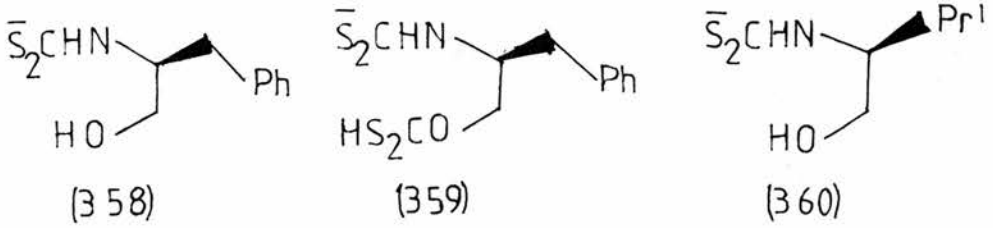
(355) and (351). The reaction of the amino alcohol (260) with diethyl



carbonate and potassium t-butoxide gave the oxazolidin-2-one (354) which was converted into the thiazolidine-2-thione using phosphorus pentasulphide. Alternatively the amino alcohols (259) and (260) were reacted with carbon disulphide in *alkali* to form the oxazolidine-2-thione (356) and the thiazolidine-2-thione (355) or the oxazolidine-2-thione (357). Phosphorus pentasulphide completed the conversion of these to the thiazolidine-2-thiones (355) and (351).

An interesting feature of the ^{13}C n.m.r. spectrum in (355) is the very high thiocarbonyl carbon atom shift at 200.5 ppm, which will be seen again.

The mechanisms of formation of (356) and (357) or (355) are consistent with literature precedent, involving the dithiocarbamates (358) and (360) or the xanthate ester/dithiocarbamate (359)[269,276].



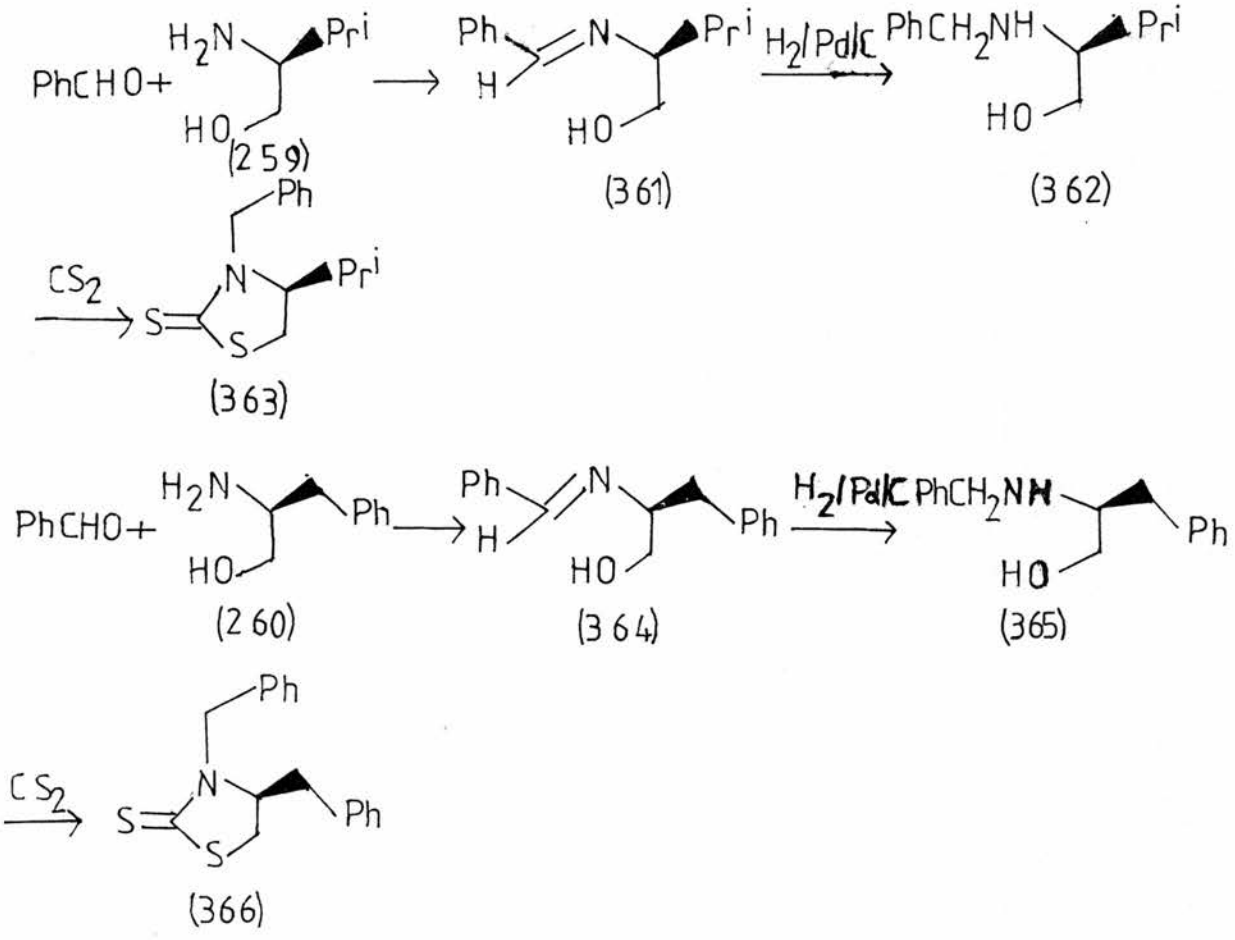
2. Preparation of 3-substituted thiazolidine-2-thiones

In view of the later oxidation studies which showed ring opening in the presence of base (see page 205), it was decided to synthesise thiazolidine-2-thiones with an N-benzyl protecting group which would reduce the nucleophilicity of the nitrogen atom by steric hindrance and avoid the tautomeric proton exchange in the thioamide function[70].

Various attempts at direct alkylation of the thiazolidine-2-thione (355) and the oxazolidin-2-one (354) involving phase transfer methods, benzyl chloride and bases of differing strengths were unsuccessful.

N-benzylation of the amino alcohol and direct incorporation into the heterocycle via a carbon disulphide cyclisation step seemed a more effective target route[70]. The use of imine intermediates (361) and (364) and subsequent catalytic hydrogenation appeared to be a more favourable method than direct N-benzylation using benzyl chloride and sodium carbonate as in the literature for (362)[277].

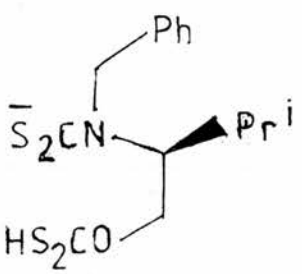
The formation of the heterocyclic 3-benzylthiazolidine-2-thiones (363) and (366) proceeded from the N-benzyl amino alcohols (362) and (365) via a cyclisation reaction involving carbon disulphide in an *alkaline* medium. The ^{13}C n.m.r. spectra in both heterocycles indicated thiocarbonyl groups at 196.7(s) ppm and 197.4(s) ppm and carbon



atoms adjacent to sulphur at 50.7(t) ppm and 50.0(t) ppm. A distinctive feature of the ^{1}H n.m.r. spectrum of (366) was the widely spaced AB pattern at 5.85 and 4.20 which is due to the anisotropic effect of the thiocarbonyl group on the N-benzyl protons which are conformationally locked by the C-benzyl protons. This gear effect in which the two large alkyl groups are interlocking is due to the inherent disymmetry of the alkyl groups which implies a strong conformational correlation between unbounded groups in 3,4-dialkylthiazolidine-2-thiones [278,279]. The absolute configuration

at the 3-position is unknown.

The mechanistic pathway in the carbon disulphide reaction is directed through the dithiocarbamate/xanthate ester intermediates (367) and (368) by the steric hindrance of the N-benzyl group which equilibrates the rate of attack at the normally faster amino function relative to the rate of attack at the hydroxyl function in both carbon disulphide steps.



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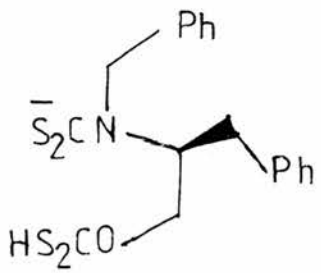
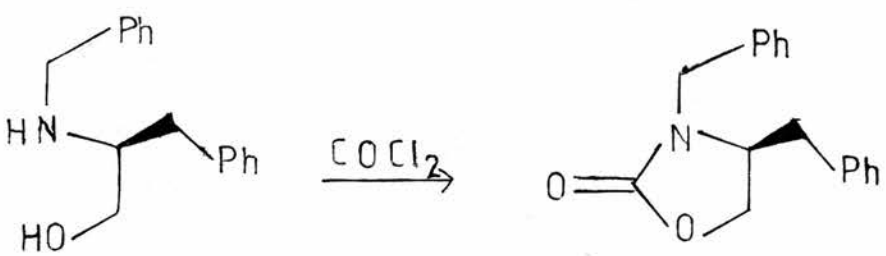


(368)

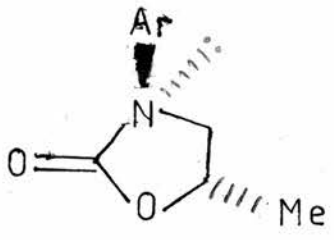
The oxazolidin-2-one (369) with an N-benzyl protecting group was synthesised by a literature procedure using phosgene and potassium hydroxide [180]. This enabled a spectral comparison with the thiazolidin-2-one (375). Examples of



(365) (369)

oxazolidin-2-ones which are diastereomeric due to the configuration at the 2-position are known (370) and (371) [280]. In the

oxazolidin -2-one (369)



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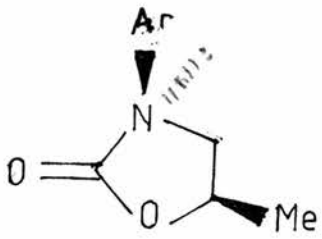


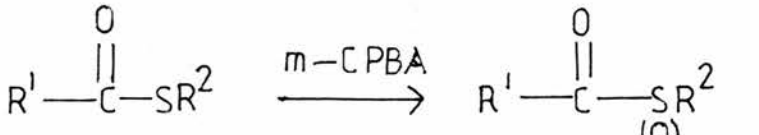
(371)

the absolute configuration at the 3-position is unknown.

3. Oxidation of 3,4-(S)-dibenzylthiazolidine-2-thione

a) The synthetic background

The oxidation of thiazolidin-2-ones and thiazolidine-2-thiones was reviewed in the introduction. The related acyclic thiocarbonate O,S-diesters, dithiocarbonate S,S-diesters and the N,N-disubstituted thiocarbamate S-esters (372) have been oxidised by m-CPBA to give stable representatives of α-ketosulphoxides and α-ketosulphones (373)[281]. The stability of these compounds relies on the fact that R^1 is an electron-donating substituent. Earlier examples are

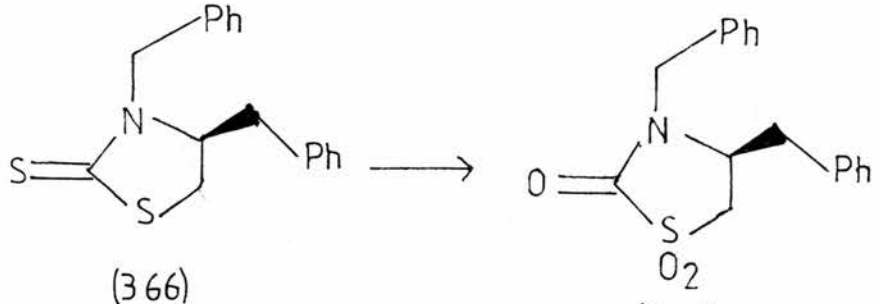


(372) $R' = OR, SR, NR_2$ (373) $n = 1, 2$

cited within the same reference and include oxidation using peroxyacetic acid, sodium periodate or ozone.

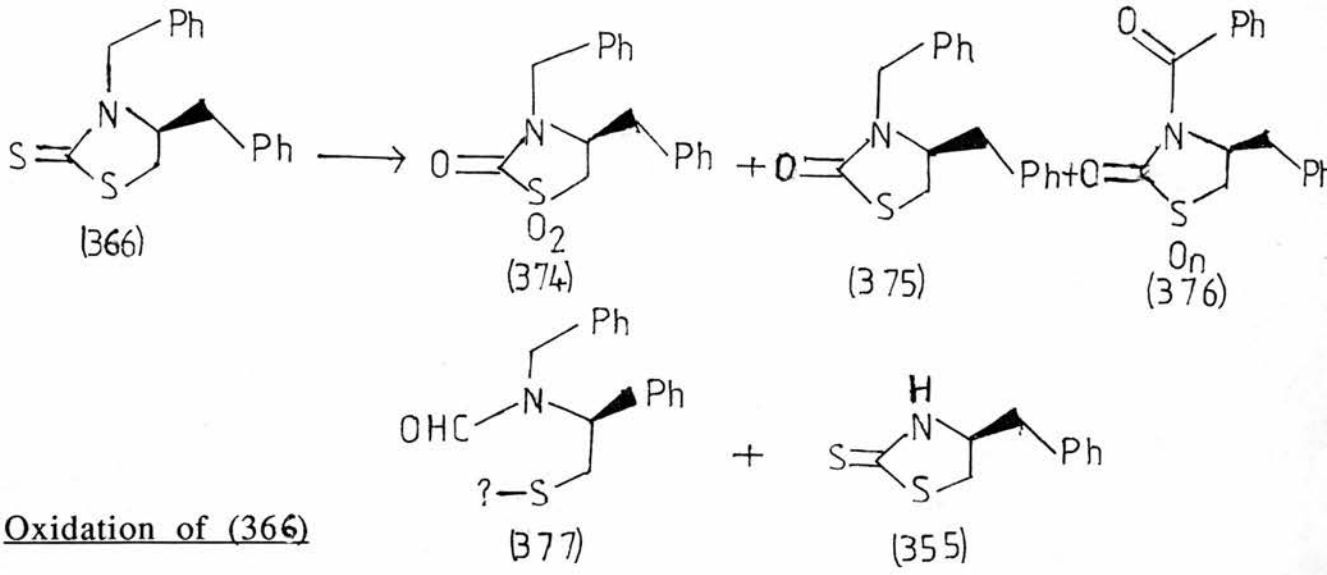
b) Oxidation reactions

Various attempts to oxidise the 3-unsubstituted thiazolidine-2-thiones (351) and (355) using several reagents led only to ring-opened products. Attention was therefore turned to the 3-substituted cases the main objective being to form the chiral 3,4-(S)-dibenzylthiazolidin-2-one 1,1-dioxide (374) by oxidation of 3,4-(S)-dibenzylthiazolidine-2-thione (366)



(366) (374)

In the tabulated reactions, the thiazolidin-2-one 1,1-dioxide (374) and the thiazolidin-2-one (375) have been isolated. The N-*benzyl*thiazolidin-2-one oxide (376) and the N-formylalkylthiol (377) or a higher S-oxidation state product e.g. a sulphonic acid are only suggested products on the basis of ^{1}H n.m.r. and chemical ionisation mass spectra.



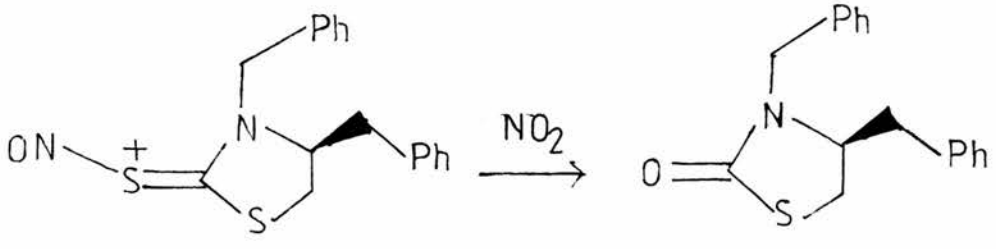
Oxidation of (366)

Reagent and conditions	Product
CH_3CO_3H, 70°C	(374) [+ (375)]
CF_3CO_3H, RT	(374)
$KMnO_4$, RT	(374) + (375)
$KMnO_4$, RT/BTEAC	(375)
NO_2, RT	(375)
m-CPBA (4equiv), 80°C, base workup	(376) + (377)
m-CPBA (3equiv), 80°C, base workup	(375) + (377)
CH_3CO_3H (1.5equiv), Na_2CO_3, 80°C	(355) + (377)
CH_3CO_3H (8equiv), Na_2CO_3, 80°C	(377)

The choice of the N-protecting group is shown to be important as the activated N-benzylic position can be oxidised to an N-benzoyl group or oxidatively cleaved via a hydrolysis mechanism[70]. The isolated intermediate ketone (375) demonstrates that the sulphur electrons are deactivated towards further oxidation to the dioxide (374) by the

electron–withdrawing ketone group. The peracetic acid, peroxy–trifluoro–acetic acid and potassium permanganate reactions indicate that forcing conditions are required in terms of high temperature, concentration of reagent and strength of reagent to obtain the dioxide (374).

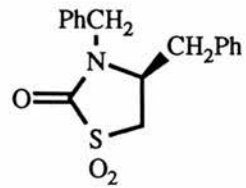
The mechanism of the nitrogen dioxide oxidation has been shown to proceed via an S-nitroso intermediate (378) by selective attack of the nitrosonium cation on the thione sulphur atom[282].



(378) (375)

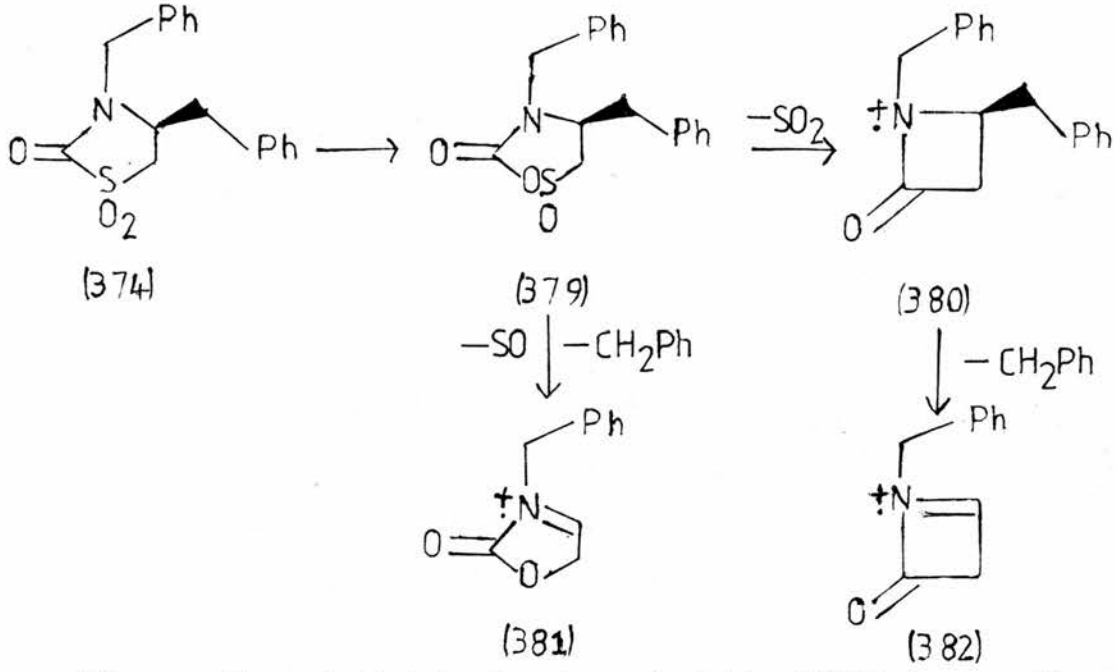
The spectra of the thiazolidine-2-one (375) and its dioxide (374) show some significant differences. In the infra-red spectrum the carbonyl absorption frequencies of 1650 and 1730 cm^{-1} respectively are in agreement with previously reported values and indicate the electron-withdrawing effect of the sulphone group[70]. The prominent pair of absorption bands at 1330 and 1140 cm^{-1} indicated the sulphone functional group. The shift of the carbonyl group in the ^{13}C n.m.r. spectrum from 159.5 ppm to 171.8 ppm indicated the electron-withdrawing effect of the sulphone group. The distinctive AB patterns in the ^{1}H n.m.r. spectra of both compounds were due to the N-benzylic protons as shown in the example of (374) on page 208.

300 MHz ^{1}H n.m.r. spectrum of thiazolidinone dioxide (**374**)



(**374**)

The chemical ionisation and electron impact mass spectra might be expected to provide a valuable guide to the pyrolysis behaviour in the fragmentation of the molecule. The chemical ionisation mass spectrum indicated loss of sulphur monoxide and sulphur dioxide from the parent molecular ion and the $M^+ + NH_4^+$ cation indicating a possible structure (379). The electron impact mass spectrum gave a weak M^+ but showed clearly, intermediates (380) at 251, (381) at 176 and (382) at 160.



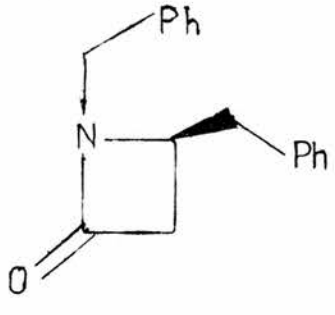
The cyclic sulphinic/carbamic anhydride (379) is an alternative structure to the thiazolidin -2-one 1,1-dioxide (374). Fortunately the two alternatives could be unambiguously distinguished by the use of ^{33}S n.m.r. The use of this technique in very similar systems has recently been reported[283] and relies on the fact that only sulphur in a symmetrical tetrahedral environment such as in (374) has a long enough relaxation time to be observed. More unsymmetrical

environments such as that in (379) lead to no observable signal. In the event the spectrum showed a strong and relatively sharp resonance at -49.5 ppm (wrt sulpholane) confirming that the compound is indeed (374) and that (379) is only formed by rearrangement in the mass spectrometer as already reported in several related systems[284-286].

F. Reactions of the Thiazolidin-2-one 1,1-dioxide

1. The Background

The objective of the thermal or photochemical extrusion reactions was to synthesise a chiral β-lactam such as (383) without racemisation of the stereogenic centre and then to experiment with possible diastereoselective alkylation of the thiazolidin-2-one 1,1-dioxide (374) which on extrusion could give (384) with retention of stereocnemistry.



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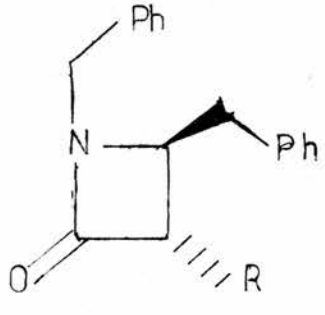
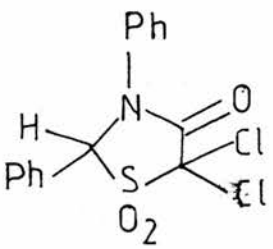


(384)

Flash vacuum pyrolysis provides a technique where a molecule can undergo a rapid extrusion reaction, at high temperatures under very low pressure minimising the side reactions compared to solution

reactions. Photochemical extrusion reactions can also produce strained or reactive structures in unreactive media at low temperatures when a photoactivating group is present in the substrate.

Thermal extrusion reactions of the thiazolidin-4-one 1,1-dioxide (385)[287] and the thiazolidin-2,4-dione 1,1-dioxide (386)[288] have given stable β-lactams.



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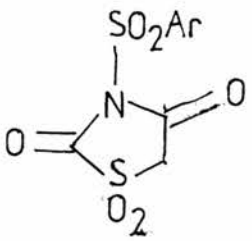

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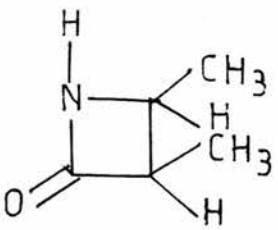
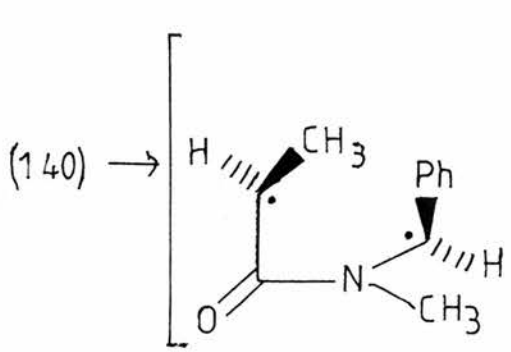


(387)

In contrast the β-lactams such as (387) break down to give an alkene and cyanuric acid at 600°C under 12mm in a stream of nitrogen with a contact time of two seconds[289].

The photochemical extrusion reactions of cis and trans-3,5-dimethyl-2-phenylthiazolidin-4-one 1,1-dioxides (140) have given mixtures of cis/trans β-lactams (390) via mechanisms involving the radical intermediate (388) or the ionic intermediate (389)[84].



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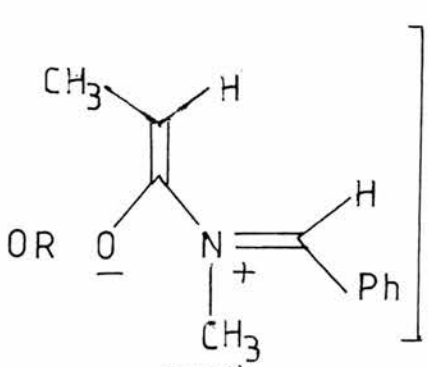

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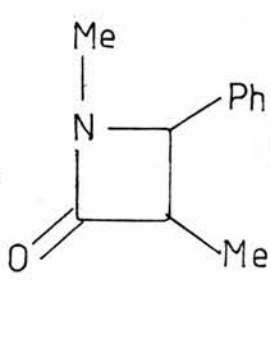
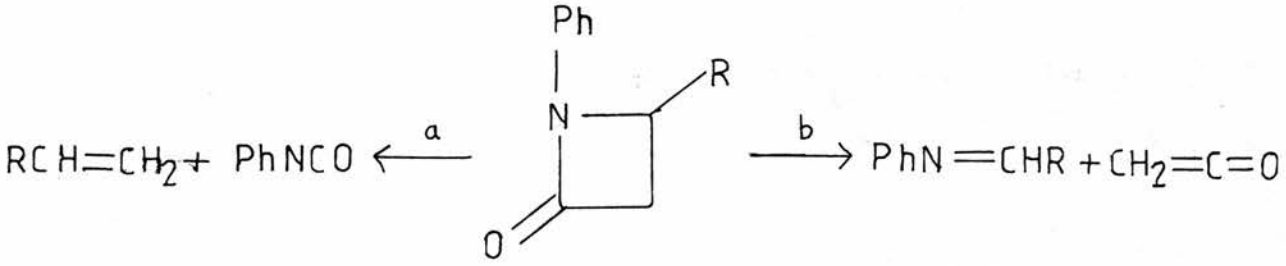


(390)

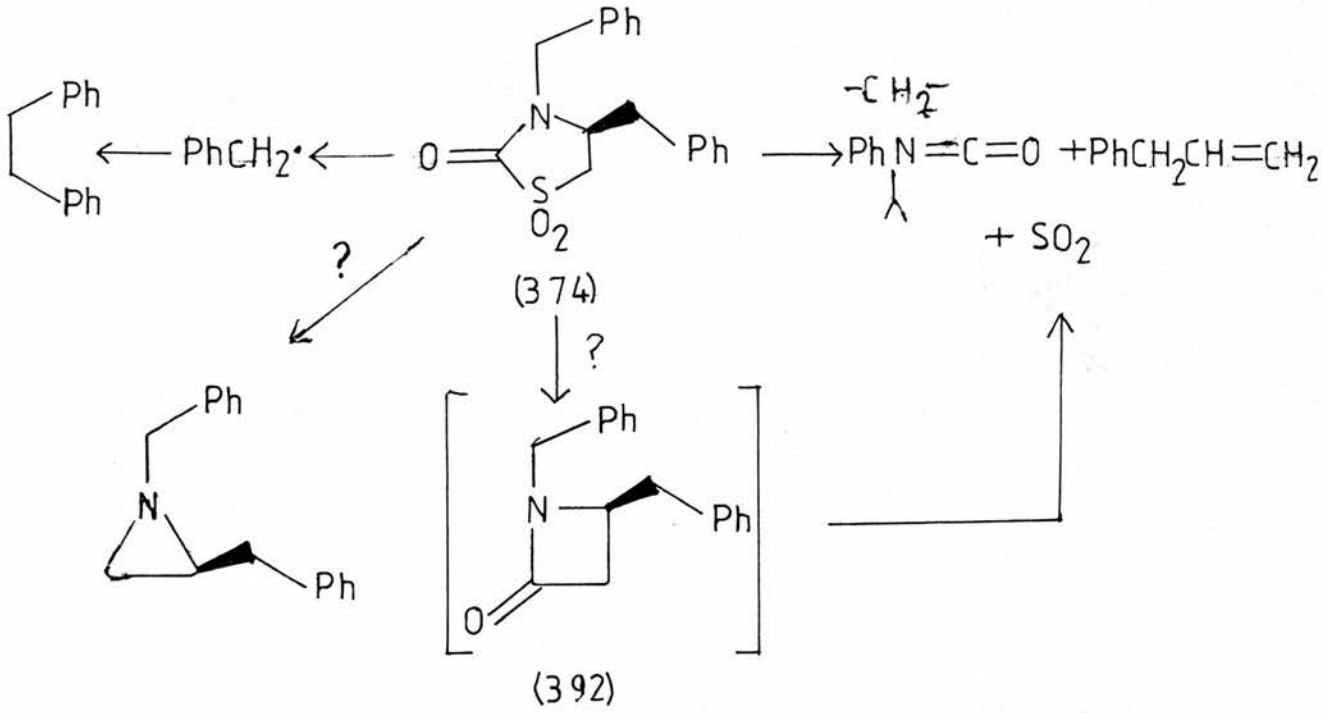
In the photolysis reaction of 4-substituted 1-phenylazetidin-2-ones (391), electron releasing groups in the 4-substituent give an isocyanate/olefin product distribution whereas electron-withdrawing groups give an azomethine/ketene product distribution[290].



(391)

2. Flash vacuum pyrolysis

The thiazolidin-2-one 1,1-dioxide (374) was reactive at 600°C under flash vacuum pyrolytic conditions, to give benzyl isocyanate,



(374)

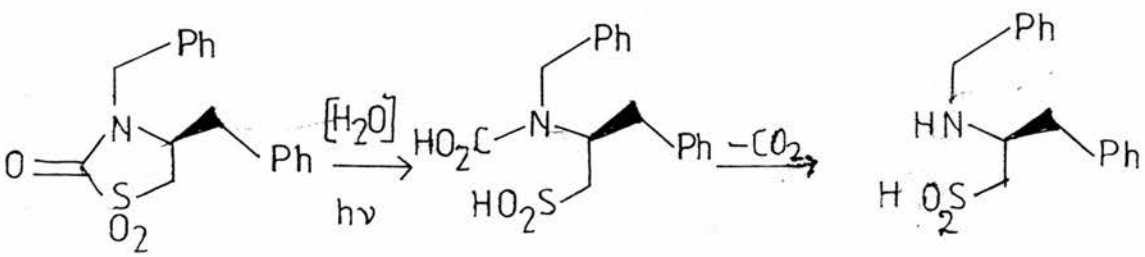
(392)

allylbenzene and bibenzyl as the main products. These are readily explained by the concerted electrocyclic fragmentation with loss of SO_2 to give the first two with competing fragmentation of the N-benzyl

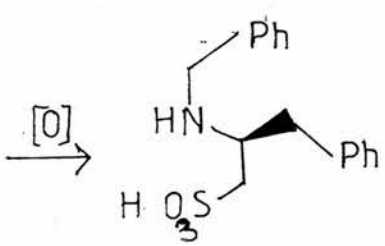
group to give benzyl radicals which then dimerise. It is of course possible that SO_2 extrusion does occur to give the β-lactam (392) but that under the conditions this is not stable and readily fragments further. A strong driving force for these processes is the steric hindrance between the two bulky benzyl groups which is relieved and by using thiazolidin-2-one dioxides with smaller or interconnected 3- and 4-substituents β-lactam formation may be more likely.

3. Photolytic extrusion reaction

The photochemical reaction in A.R. acetone at a distance of 70mm from the source gave a product which may be the aminoalkylsulphonic acid (395) or the sulphinic acid (394).



(374) (393) (394)



(395)

In the IR spectrum the carbonyl group was conspicuously absent in the region of 1800-1600 cm^{-1}. The two broad acidic peaks in the ^{1}H n.m.r. spectrum suggested acidic protons present in each of the functional groups. A 2D n.m.r. spectrum; carbon versus hydrogen, confirmed the basic framework of carbon and hydrogen atoms to be unchanged from the starting material. The mass spectrum showed only small fragments and the oxidation state of the nitrogen and sulphur atoms remains unknown. The formation of (395) may be explained by hydrolysis of a photoactivated starting material through a trace of water in the solvent to give the carbamic-sulphinic acid (393) which would readily decarboxylate to (394) which can possibly oxidise or disproportionate on isolation to give (395).

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Appendix

"Oxidation of Five-Membered Ring Heterocycles Containing N and S"

R.A. Aitken, D.P. Armstrong, and S.T.E. Mesher, Chapter 1 in*Progress in Heterocyclic Chemistry*, H. Suschitzky and E.F.V. Scriven eds., Vol. 2 Pergamon, 1990, pp 1-21, in the press.

CHAPTER 1

Oxidation of Five-Membered Ring Heterocycles Containing N and S

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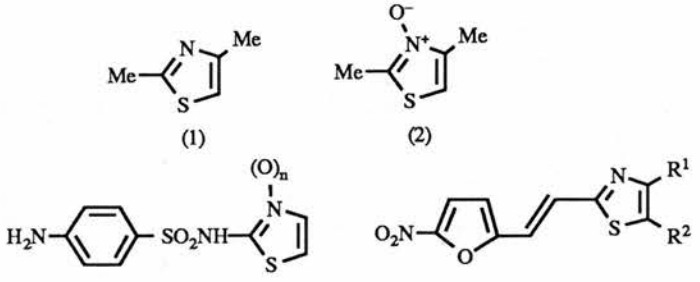
1.1 INTRODUCTION

Five-membered ring heterocycles containing both nitrogen and sulphur show an interesting pattern of reactivity towards various oxidising agents. The most important processes are formation of N- or S-oxides and, for partly saturated systems, dehydrogenation, but various ring-opening and oxidative coupling reactions have also been observed. In this article the most important reactions of five-membered ring heterocycles containing (only) N and S with oxidising agents are described.

1.2 THIAZOLE BASED SYSTEMS

1.2.1 Thiazoles

The first successful oxidation of this relatively resistant ring system was reported in 1947. Treatment of 2,4-dimethylthiazole (**1**) with hydrogen peroxide in acetic acid gave the N-oxide (**2**) in 60% yield [47JPJ34]. With thiazole itself the N-oxide was formed in low yield due to extensive ring cleavage. Monoperphthalic acid was also used to convert (**1**) to (**2**). Hydrogen peroxide in acetic acid readily converts sulphathiazole (**3**) to its N-oxide (**4**) [59AK225]. A number of 2,5-diarylthiazoles are readily oxidised to their N-oxides using monoperoxymaleic acid [77CPB3270] while, in studies on novel antibacterial

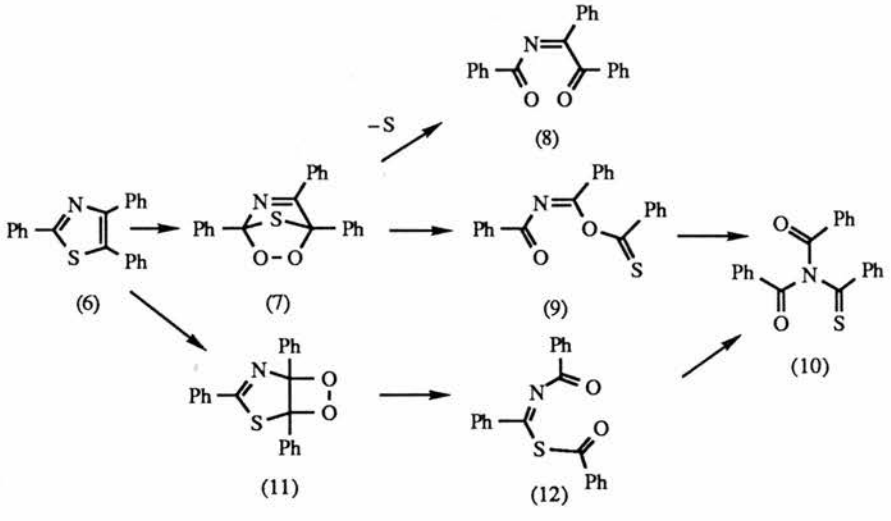


(1) (2)

(3) n=0
(4) n=1

(5)

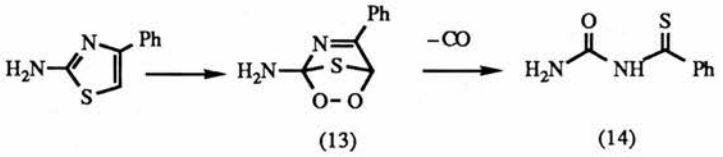
Photo sensitised oxidation of 2,4,5-triphenylthiazole (**6**) proceeds by initial cycloaddition of $^1O_2$ either in a 1,4-sense to give (**7**) or 1,2 to give (**11**). Irradiation with O_2 in MeOH in the presence of rose bengal gives benzamide and benzil which arise from extrusion of sulphur from (**7**) to give (**8**) which is then hydrolysed [69BCJ2973]. With methylene blue in $CHCl_3$ the main product is dibenzoyl(thiobenzoyl)amine (**10**). This may arise either from rearrangement of (**7**) to (**9**) followed by a 1,3-thiobenzoyl shift, or, alternatively, by cycloreversion of (**11**) to (**12**) followed by a 1,3-benzoyl shift. A later report confirmed the pathway in MeOH but reported the formation of 2,4,5-triphenyloxazole as a minor product and in $CHCl_3$ it was found to be the only



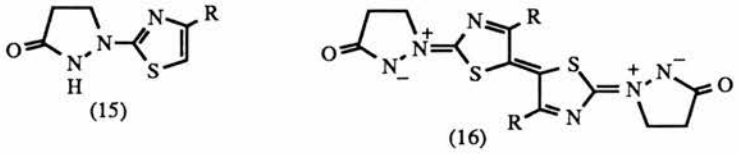
(6) (7) (8) (9) (10) (11) (12)

product [77HCA284]. Its formation is rationalised by loss of sulphur from either (**7**) or (**11**) followed by rearrangement to the oxazole O-oxide which is deoxygenated by $^1O_2$.

The photo-oxidation of 2-amino-4-phenylthiazole to thiobenzoylurea (**14**) with methylene blue in $CHCl_3$ involves loss of CO from in initial 1,4-adduct (**13**) [81IJC(B)870].



(13) (14)

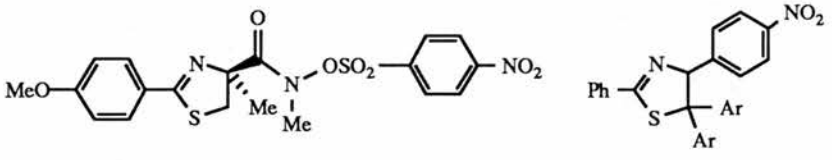


(15) (16)

Oxidative coupling occurs on treatment of thiazoles (**15**) with $NaIO_4$ to give bis-azomethine imines (**16**) [82JPR873].

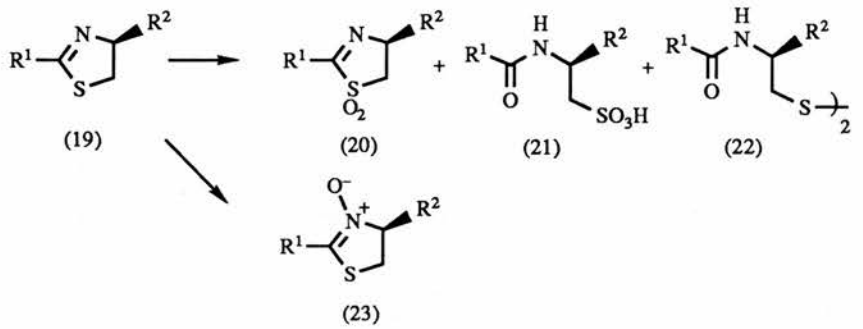
1.2.2 2-Thiazolines

MCPBA has been used to oxidise (**17**) to the corresponding S,S-dioxide [76TL1137] as well as (**18**) to a mixture of diastereomeric S-oxides [77G289]. The thiazoline ring of the N-terminal ThzIle residue of bacitracin A is oxidised to its S-oxide by $NaIO_4$ and to the S,S-dioxide by $KMnO_4$ [82JBI25].



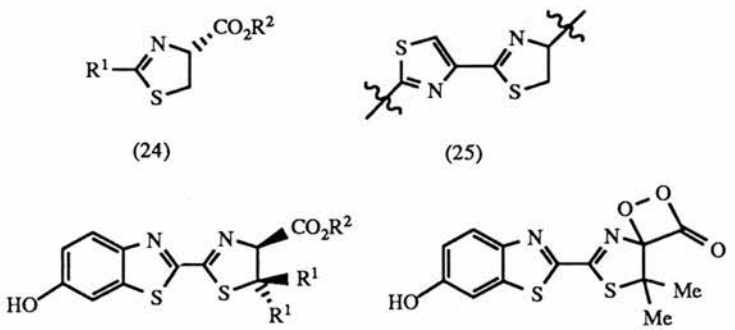
(17) (18)

In our own laboratory we have found that chiral thiazolines (**19**) are generally oxidised to mixtures of S,S-dioxide (**20**), sulphonic acid (**21**) and disulphide (**22**) with such reagents as MCPBA, peracetic acid, performic acid, $NaIO_4$ and $KMnO_4$. However the use of N_2O_4 or peroxytrifluoroacetic acid gives exclusively the previously unknown N-oxides (**23**) [90UP1]. An early report describes oxidation of 2-phenylthiazoline (**19**, R^1=Ph, R^2=H) to N-benzoyltaurine (**21**, R^1=Ph, R^2=H) using bromine water [1890CB157].



(19) (20) (21) (22) (23)

Various transition metal oxidants dehydrogenate 2-thiazolines to the corresponding thiazoles. Manganese dioxide is effective in oxidising thiazolines (**24**) in this way, a transformation also possible using phenanthraquinone [66JCS(C)1061]. Nickel peroxide is similarly effective in a wide range of examples [77JA8078] [78JOC1624] [79JOC497], including the thiazoylthiazoline moiety (**25**) in the anti tumour compound phleomycin A^2.



(24) (25) (26) (27)

Potassium ferricyanide in basic solution oxidises compounds of type (**24**) to the thiazoles although there is competing hydrolysis to give disulphides [68JCS(C)1526]. Basic solutions of firefly luciferin (**26**, R^1=R^2=H) are dehydrogenated by $K_3Fe(CN)_6$ as well as by atmospheric oxygen [63JA337]. Mercuric acetate in acetic acid has also been used for (**24**) [68JCS(C)1526].

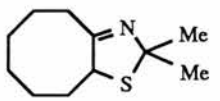
Products from the vapour phase oxidation of 2-methyl-2-thiazoline over a variety of mixed vanadium/molybdenum oxide catalysts include 2-methylthiazole, thiazole-2-carboxaldehyde and thiazole[82MI718].

Photo-oxidation of luciferin analogue (**26**, R^1=Me, R^2=Ph) in DMSO proceeds by addition of O_2 at C-4, displacement of PhO^- to give (**27**), which then loses CO_2 with luminescence to give the thiazolin-4-one [68CC22].

1.2.3 3-Thiazolines

Oxygen converts 3-thiazolines such as (**28**) and (**29**) to the corresponding S-oxides at room temperature [64LA(672)103].

A number of agents have been successfully used to bring about dehydrogenation of 3-thiazolines. Ferric chloride is effective for (**30**, R=H, Me, Et, Ph) [58LA(611)121]. For di- and trisubstituted examples such as (**31**)



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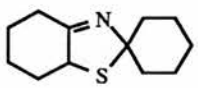

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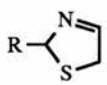

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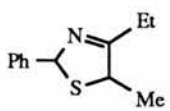

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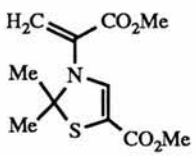


(32)

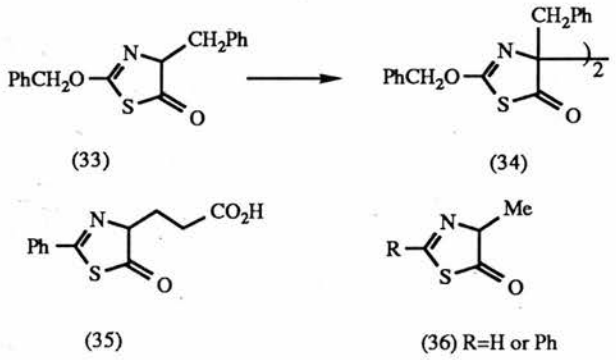
sulphur is most effective for conversion to the thiazoles while $FeCl_3$, hydrogen peroxide, potassium ferricyanide and potassium dichromate can all be used with somewhat lower yields [57LA(610)49].

1.2.4 4-Thiazolines

Treatment of (**32**) with one equivalent of MCPBA at –78°C affords the corresponding S-oxide [76JCS(P1)2540].

1.2.5 2-Thiazolin-5-ones

Oxidative coupling through the 4-position is the main mode of oxidation for these compounds. Thus treatment of (**33**) with iodine in the presence of triethylamine gives (**34**) [72MI29]. Aeration of (**35**) in aqueous dioxane gives the oxidised dimer in addition to α-ketoglutaric acid from hydrolysis [78TL2063], and photo-oxidation of (**36**) in CH_2Cl_2 also leads to dimerisation [87H1313] [80CL717].

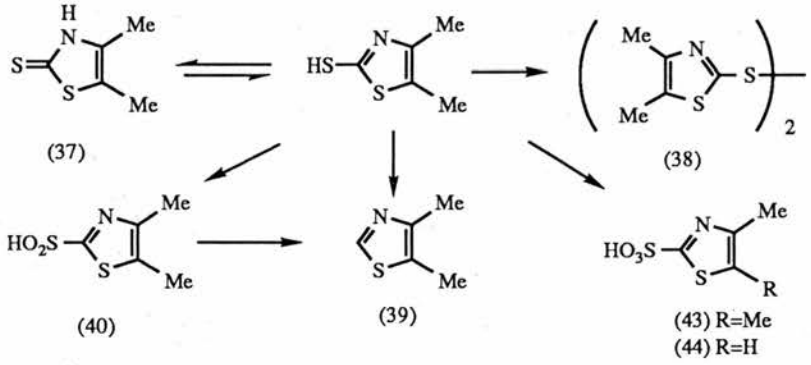


(33) (34)

(35) (36) R=H or Ph

1.2.6 4-Thiazoline-2-thiones

Many of the oxidation reactions of these compounds can be rationalised in terms of the 2-mercaptothiazole tautomer. Thus treatment of (**37**) with iodine [64JOC2148] or ammonium persulphate [49JOC1111] leads to the disulphide (**38**). This can also be obtained with H_2O_2 in neutral solution [41JOC764] [48JA3419] but under acidic conditions, as well as with nitric acid, sulphur is

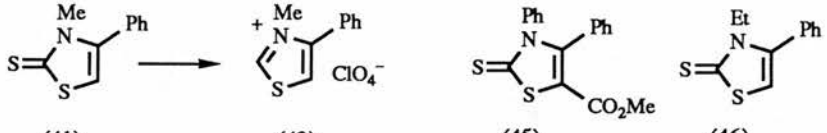


(37) (38)

(40) (39) (43) R=Me
(44) R=H

lost to give the thiazole (**39**) [49JOC1111] [41JOC764]. This reaction most likely occurs by oxidation to the sulphinic acid (**40**) which can be isolated as its sodium salt [50USP2509453] [50USP2509454] but decomposes with loss of SO_2 on acidification. With H_2O_2 in acetic acid, sulphur is also lost from (**41**) and the resulting thiazole can be isolated as its perchlorate (**42**) [74CJC3021]. Oxidation to thiazole-2-sulphonic acids is also possible as illustrated by the conversion of (**37**) to (**43**) with N_2O_4 [49JOC1111] and the formation of (**44**) from 4-methyl-4-thiazoline-2-thione with H_2O_2 under basic conditions [39JPJ43].

A final mode of oxidation of these compounds is the replacement of the exocyclic sulphur by oxygen. Both mercuric acetate [73BSF270] and



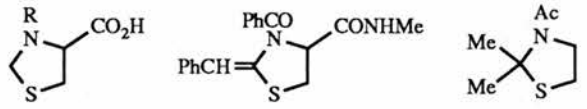
(41) (42) (45) (46)

H_2O_2/KOH [56JPJ1153] convert thiazolinethiones such as (**45**) and (**46**) to the corresponding thiazolinones.

Further examples of the different oxidation processes in this section are to be found in a review [76PS185].

1.2.7 Thiazolidines

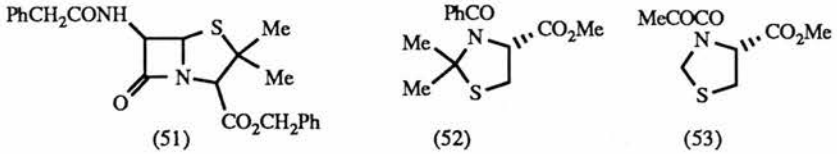
Thiazolidines, particularly those with a carboxylic acid function in the 4-position derived from cysteine, have been extensively studied with a variety of oxidising agents. As early as 1937 the oxidation of (**47**) to its S-oxide with H_2O_2 in acetone and to its S,S-dioxide with excess H_2O_2 in acetic acid was reported [37JA200]. With the non-acetylated derivative (**48**), on the other hand, H_2O_2 or iodine resulted in ring cleavage to cystine while bromine produced



(47) R=Ac
(48) R=H

(49) (50)

cysteic acid [37JA200]. Thiazolidine itself was similarly converted to a disulphide with iodine and a sulphonic acid with bromine. MCPBA has been used to obtain S-oxides from thiazolidines such as (**49**) [75JA5010] and (**50**) [78S744]. The penicillin derivative (**51**) is converted with peracetic acid to an S-oxide which can be further oxidised to the S,S-dioxide with $KMnO_4$



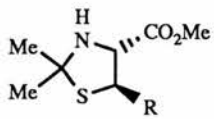
(51) (52) (53)

[50JOC815]. A detailed study of the stereoselectivity of S-oxide formation from substrates such as (**52**) using MCPBA, $NaIO_4$ and $Bu^tOOH/Ti(OPr^i)_4$ has

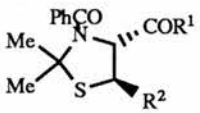
appeared [86TL3391]. The methyl ester of (**47**) is converted to its S-oxide using $NaIO_4$ [80BSB749] and the S-oxide of (**53**), obtained similarly, is further oxidised to the S,S-dioxide using $KMnO_4$ [73TL1103].

A single example of dehydrogenation of a thiazolidine to the 3-thiazoline is provided by the enzymatic reaction of (**48**) with D-amino acid oxidase [79MI252].

The final important mode of oxidation of this ring system is oxygenation at the 5-position. Lead tetra-acetate oxidation of (**54**) produced (**55**) as part of the first synthesis of cephalosporin C [66JA852].



(54) R=N(CO_2Me)NHCO_2Me
(55) R=OH

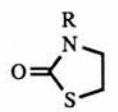


(56) R^1=OMe, R^2=H
(57) R^1=OMe, R^2=OH
(58) R^1=NHCH(Pr^i)CO_2Me, R^2=H
(59) R^1=NHCH(Pr^i)CO_2Me, R^2=OCOPh
(60) R^1=NHCH(Pr^i)CO_2Me, R^2=OH

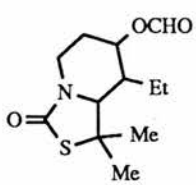
Photo-oxidation in THF in the presence of tetraphenylporphyrin results in conversion of (**56**) to (**57**). With methylene blue in DMSO this is accompanied by formation of the thiazolidin-5-one as well as the S-oxide of (**56**) [84TL4767] while in methanol the S-oxide is the sole product [85T2133]. Oxidation of (**58**) with perbenzoic acid at 70°C gives (**59**) which can be hydrolysed to (**60**) [77GEP2615621].

1.2.8 Thiazolidin-2-ones

A few cases of S-oxidation have been reported for this ring system. Thus MCPBA can be used to convert thiazolidinones such as (**61**) and (**62**) to either the S-oxide or the S,S-dioxide [81JAP87574] while for (**63**) peracetic acid



(61) R=n-C_6H_{13}
(62) R=Bu^n
(63) R=$CH_2CH_2CONH_2$



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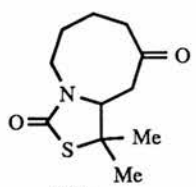


(65)

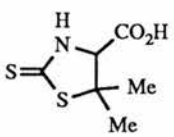
produces the S,S-dioxide [61JOC5103]. S,S-Dioxides are also formed on treatment of bicyclic thiazolidinones such as (**64**) with MCPBA and (**65**) with performic acid [85T2861].

1.2.9 Thiazolidin-4-ones

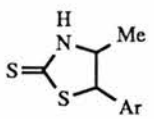
The oxidation of this ring system has been extensively studied and has been reviewed in detail elsewhere [61CRV463] [79AHC83]. Peracetic acid, sodium periodate and chloramine-T [81JHC633] have been used to form S-oxides, while $KMnO_4$, CrO_3 and excess peracetic acid give the S,S-dioxides.

1.2.10 Thiazolidine-2-thiones

The most facile oxidative process in this system is replacement of the exocyclic sulphur by oxygen. A variety of substrates such as (**66**) [49JCS2367] and (**67**) [83JAP5829775] are converted to the corresponding thiazolidinones



(66)



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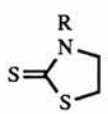
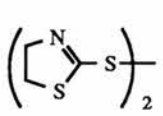


(68) R=p-MeO-C_6H_4-
(69) R=CH_2CH_2CN
(70) R=Me
(71) R=H

using H_2O_2 under basic conditions. The reactions involve initial S-oxidation to a sulphine, isolable as an iron complex [66LA(695)77], which cyclises to the oxathiirane and loses S. Mercuric acetate also brings about this oxidation of (**68**) [47HCA1336] and (**69**) [61JOC5106] as does the more unusual oxidant propylene oxide with (**70**) [70BCJ168]. In a process analogous to that for the 4-thiazoline-2-thiones (Section 1.2.6), iodine in the presence of triethylamine causes oxidative dimerisation of the parent thiazolidinethione (**71**) to (**72**) [80JCS(P1)665].

Further examples of these types of oxidation have been reviewed [76PS185].

A single paper describes the further oxidation of thiazolidine-2-thiones (**73**) to thiazolidinone S,S-dioxides using peracetic acid [61JOC5103].



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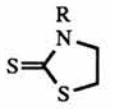

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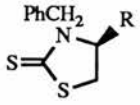


(74)

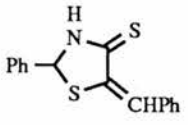
The rapid conversion to the thiazolidinone is apparently followed by slower oxidation of the ring S. In our own laboratory we have similarly obtained thiazolidinone S,S-dioxides from a variety of chiral 4-substituted thiones (**74**) [90UP2].

1.2.11 Thiazolidine-4-thiones

A single example of this type is provided by the conversion of (**75**) to the corresponding thiazolidinone using H_2O_2 [71KGS145].

1.2.12 Thiazolidine-2,4-diones and Thiazolidine-2-thione-4-ones

Thiazolidinedione (**76**) can be oxidised by MCPBA either to the S-oxide or the S,S-dioxide [86LA1787] and $KMnO_4$ converts (**77**) to its S,S-dioxide [79IJC(B)377]. Selenium dioxide introduces a third carbonyl group into (**78**) to produce the 2,4,5-trione [76S190].



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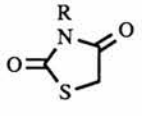
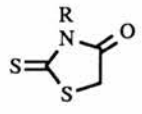
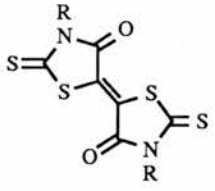


(76) R=CH_2Ph
(77) R=Ph
(78) R=H



(79) R=H
(80) R=Et
(81) R=CH_2CO_2Et



(82)

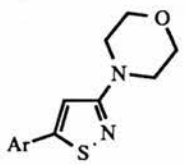
Rhodanine (**79**) is oxidised to the corresponding 2,4-dione by H_2O_2 in basic solution [38JPJ8] by way of an isolable sulphine [65LA(681)55] but with excess H_2O_2 ring opening gives sulphoacetamide.

Oxidative coupling to give (**82**) can be achieved for (**79**) and (**80**) using SeO_2 [57AG138] and for (**81**) using bromine in the presence of Et_3N [55JCS927].

1.3 ISOTHIAZOLE BASED SYSTEMS

1.3.1 Isothiazoles

Examples of isothiazole oxidation are rare. Nitric acid in either sulphuric or acetic acid converts compounds (**83**) to the S-oxides which are further oxidised



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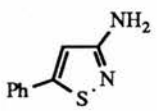
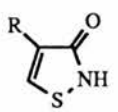


(84)

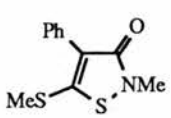
to S,S-dioxides by peracetic acid [66G1009]. Peroxysulphuric acid reacts with (**84**) to give the corresponding S-oxide [72JCS(P1)1247].

1.3.2 4-Isothiazolin-3-ones

The formation of S-oxides and S,S-dioxides has been reported. The parent ring system (**85**) as well as various substituted derivatives are converted to S-oxides with nitric acid, N_2O_4 or chromic acid, [71JHC591]. Peracetic acid



(85) R=H
(86) R=Ph



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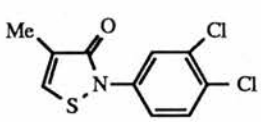

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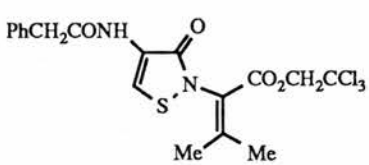

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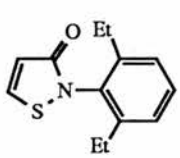


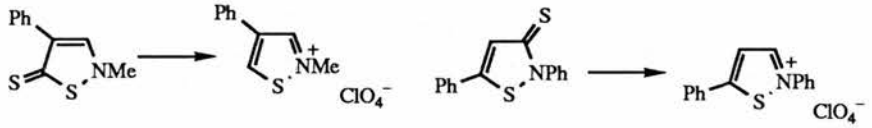
(90)

oxidises isothiazolinones such as (**86**) and (**87**) to the corresponding S,S-dioxides [77AJC1815]. MCPBA can be used to obtain either S-oxides or S,S-

dioxides in a variety of cases illustrated by (**88**) [71JHC591], (**89**) and (**90**) [75JA5020] [81JAP81573].

1.3.3 3-Isothiazoline-5-thiones and 4-Isothiazoline-3-thiones

In a process analogous to that observed for the 4-thiazoline-2-thiones (Section 1.2.6), treatment of compounds such as (**91**) and (**92**) with perchloric

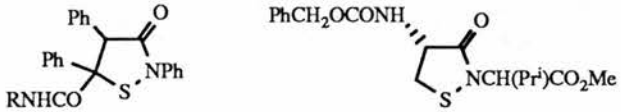


(91) (93) (92) (94)

acid results in loss of sulphur to give isothiazolium perchlorates (**93**) and (**94**) respectively [76PS185].

1.3.4 Isothiazolidin-3-ones

Although the S-oxides and S,S-dioxides of this ring system are well known they have generally been prepared by direct ring closure routes in the oxidised form. MCPBA has however been used to convert compounds such as (**95**) to their S-oxides [74JOC1210] and (**96**) to its S,S-dioxide [73TL5213].

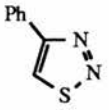


(95) (96)

1.4 THIADIAZOLE BASED SYSTEMS

1.4.1 1,2,3-Thiadiazoles

These compounds undergo both N and S-oxidation. Treatment of thiadiazoles such as (**97**) [72T5655] and (**98**) [75T637] with either MCPBA or peracetic acid first gives the 2-oxides. With excess peracetic acid these are further



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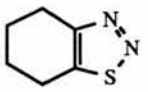


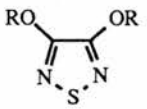
(98)

oxidised in low yield to the 1,1,2-trioxides. Upon photolysis the 2-oxide derived from (**97**) rearranged to the 3-oxide [75LA1257] whose X-ray structure unambiguously established the identity of the two isomers [78ZN(B)316].

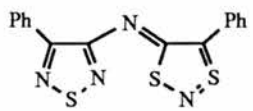
1.4.2 1,2,5-Thiadiazoles

The 3,4-diethoxythiadiazole (**99**) readily forms an S-oxide on treatment with MCPBA [81H1561]. For the dihydroxy compound (**100**) reaction with DDQ produces the S-oxide which is better regarded as the thiadiazolidinedione structure [690PP255].

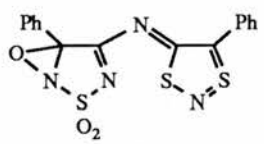
A fascinating recent example of this ring system is (**101**) which also contains a 1,3,2-dithiazole ring, thus allowing an internal comparison between



(99) R=Et
(100) R=H



(101)

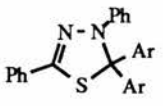


(102)

the oxidation behaviour of the two heterocycles [89CC1134]. All the oxidation occurs on the thiadiazole ring. Treatment with N_2O_4 at –20°C gives the S-oxide which is further oxidised to the S,S-dioxide with excess N_2O_4 at 20°C. Treatment of this with MCPBA then gives the trioxide (**102**) which can also be obtained directly from (**101**) with excess MCPBA.

1.4.3 Δ^2-1,3,4-Thiadiazolines

The highly substituted thiadiazolines (**103**) can be converted to S-oxides and S,S-dioxides with monoperphthalic acid [73T3569] or MCPBA [78JCS(P1)1218]. Where there is a hydrogen at the 5-position, as in (**104**) or (**105**), oxidation may be accompanied by N-deacylation to give the thiadiazoles. Thus while (**104**) gives an S-oxide (with concomitant oxidation of MeS to $MeSO_2$) on treatment with MCPBA [86JCS(P1)1357], the use of $KMnO_4$



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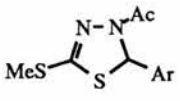

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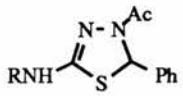
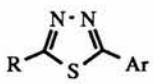


(105) R=H
(106) R=Ac



(107) R=$MeSO_2$
(108) R=NH_2, NHAc

[83JCS(P1)967] or peracetic acid [83JCS(P1)2957] gives mainly (**107**). Similarly reaction of (**106**) with MCPBA gives the S-oxide [82CC901], but with $KMnO_4$ the main product is (**108**) [83JCS(P1)967]. Conversion of (**105**) to (**108**) is possible using ferric chloride [80JOC1473].

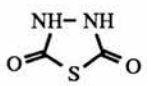
1.4.4 Δ^3-1,3,4-Thiadiazolines

Peracetic acid is effective in converting thiadiazoline (**109**) to both the S-oxide and the S,S-dioxide [72JCS(P1)305].

1.4.5 1,3,4-Thiadiazolidines

The main oxidative process in this system is dehydrogenation to Δ^3-1,3,4-thiadiazolines. Compound (**109**) and similar examples have been obtained

(109)



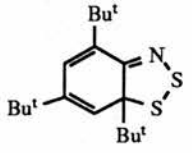
(110)

in this way from the corresponding thiadiazolidines using lead tetra-acetate, DDQ and MnO_2 [72JCS(P1)305] [78JCS(P1)45]. A further interesting oxidant used to prepare (**109**) and the parent thiadiazoline is diethyl azodicarboxylate [72JOC4045]. The thiadiazolidinedione (**110**) has been oxidised to the corresponding thiadiazolinedione, a highly reactive dienophile, using lead tetra-acetate, t-butyl hypochlorite, and cupric chloride [73JOC3622] [74JOC2951].

1.5 OTHER RING SYSTEMS

1.5.1 Δ^3-1,2,3-Dithiazolines

The unusually strained dithiazoline (**111**) is oxidised to a mixture of the 1-oxide, and the 2-oxide (**112**) which has lost one molecule of isobutene, by treatment with MCPBA [79BCJ3615].



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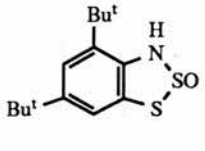

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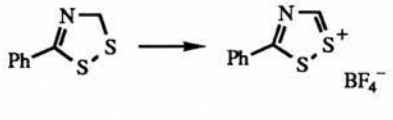


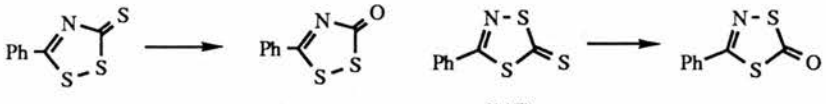
(113) (114)

1.5.2 Δ^4-1,2,4-Dithiazolines

The hydride abstraction from (**113**) to give dithiazolium salt (**114**) using trityl fluoroborate is formally an oxidation [74AP828].

1.5.3 Δ^4-1,2,4-Dithiazoline-3-thiones and Δ^4-1,3,4-Dithiazoline-5-thiones

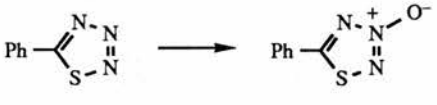
Replacement of the exocyclic sulphur atom by oxygen occurs on treatment with $KMnO_4$ [67TL1013], mercuric acetate [66BSF1183], peracetic acid and chlorine [70CJC2142] as exemplified by conversion of (**115**) to (**116**) and (**117**) to (**118**).



(115) (116) (117) (118)

1.5.4 1,2,3,4-Thiatriazoles

Although the thiatriazole (**119**) is very resistant to oxidation, being unaffected by chlorine, nitric acid, hydrogen peroxide or performic acid, it is



(119) (120)

converted to the 3-oxide (**120**) with peroxytrifluoroacetic acid [75T1783]. Although the yield is low due to competing fragmentation of (**119**), the product is stable [78JOC4816].

1.6 CONCLUSION

Five membered ring heterocycles containing N and S show a highly varied and interesting pattern of behaviour towards oxidation. While some systems have been investigated in detail and are well understood, many others have scarcely been examined and provide the opportunity for the discovery of many new useful reactions in the future.

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