PEPTIDES BASED UPON α-AMINO SULPHINIC ACIDS

This thesis has been has been submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Technology

by

Michael Singh, B. Sc. (UMIST)

1990

January 1990

DECLARATION

I declare that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification at this or any other University or any Institute of Learning.

DEDICATION

I wish to dedicate this thesis to my family.

CONTENTS

PREFACE

The work described in this thesis was carried out in the Department of Organic Chemistry at the University of Manchester Institute of Science and Technology, between October 1986 and September 1989. In addition three months were spent in the Chemical Research Laboratories at the Wellcome Research Laboratories, Langley Park, Beckenham, Kent.

I would like to thank my supervisor, Professor Richard J. Stoodley, for his continual guidance and encouragement throughout the period of this research. In addition , I would like to thank my industrial supervisor, Dr. S. R. Challand, and members of the Wellcome Foundation for many useful and helpful discussions.

I wish to thank Mr. A. Crompton for determination of mass spectra, Mr. K. Walking for the determination of i. r. and u. v. spectra, Mr. C. Evans and Mr. F. Skinkis for measurement of high field n.m.r. spectra, Dr. R. Perry for determination of elemental compositions, and Mr. A. Schofield for valuble technical assistance. My thanks are also due to Eileen Clare and past and present members of Professor Stoodley's research group.

In addition I would like to thank Salim Valera, Mohammed Riaz, Sashi Momin, Arshed Hussain, Marki, Cameron, Shaheed, Ashutosh Sharma, Zuliqur Ali, Mike Matthews, Pasha, GT , Latif, Farid, and Sarfraz for many moments of much welcomed encouragement and helpfulness.

I am grateful to the Science and Engineering Research Council and the Wellcome Foundation for financial sponsorship under the C. A. S. E. scheme.

MICHAEL SINGH

ABSTRACT

Some synthetic approaches to peptides based upon α-amino sulphinic acids have been examined. Such peptide surrogates are designed to mimic the natural α-amino carboxylic acids and, as such, may be of potential chemotherapeutic value.

Protected forms of the dipeptide analogue, glycyl-α-amino-methanesulphinic acid, were prepared by application of β-elimination reactions of 4-methoxycarbonylthiazolidine 1,1-dioxides. Removal of the acrylate chain was achieved using Barton's procedure. tert-ButylN-(N-methyl-N-trifluoroacetylglycyl)aminomethanesulphinate, methyl N-(benzyloxycarbonylglycyl)aminomethane-sulphinate and tert-butyl-N-(benzyloxycarbonylglycyl)aminomethanesulphinate were obtained in this way. The last-cited compound was further transformed into N-(benzyloxycarbonylglycyl)aminomethanesulphinic acid potassium salt, by sequential reaction with formic acid and potassium 2-ethylhexanoate.

Similarly, the dipeptide analogue N-(benzyloxycarbonylglycyl)-aminomethyl-methylsulphone was prepared in a five-stage synthesis from glycine.

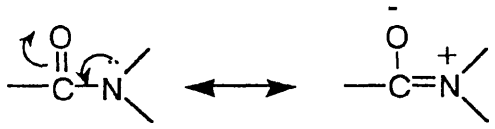
Various substituted piperazines were prepared in a five-stage synthesis from glycine and (6R)-2,5-dioxo-8-thia-1,4-diazabicyclo[4.3.0]-nonane 8,8-dioxide was obtained on oxidation of the bicycle formed on dephthaloylation of methyl (4R)-3-(α-phthalimido)acetylthiazolidine-4-carboxylate with hydrazine hydrate.

INTRODUCTION

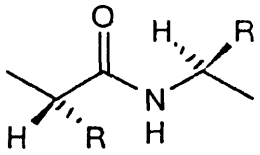
1) GENERAL INTRODUCTION

A peptide is an amide formed from two or more amino acids. The amide link between an α-amino group of one amino acid and the carboxyl group of another amino acid is called a peptide bond. Depending upon the number of amino acid units in the molecule, a peptide may be referred to as a dipeptide (two units), a tripeptide (three units), and so forth. A polypeptide is a peptide with a large number of amino acid residues. By convention, a polyamide with fewer than fifty amino acid residues is classified as a peptide, while a larger polyamide is considered a protein.

The amide bond in peptides has some double bond character due to partial overlap of the lone pair electrons of the nitrogen with the p-orbitals of the carbonyl group.



Because of the double bond character of this peptide bond, rotation of groups around this bond is somewhat restricted, and the atoms attached to the carbonyl group and to the nitrogen all lie in the same plane. X-Ray analysis shows that the amino acid side chains around the plane of the peptide bond are in a trans-type of relationship. This stereochemistry minimizes steric hindrance between the side chains.

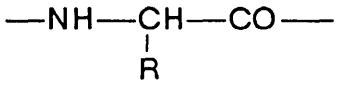


Peptides, which display a central role in metabolism, display a broad spectrum of biological activity, ranging from antibiotic activity to hormonal activity. Over five hundred peptide antibiotics are known[1] of varying molecular complexity; many contain unusual or modified α-amino carboxylic acids.

2) AMIDE BOND REPLACEMENTS

The search for surrogates (isosteres) of amide bonds in peptides has produced a range of new structural types designed to mimic the natural functional group.[2] Isosteres are defined as " atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical,"[3] and the subject of peptide bond isosteres has been well reviewed.[4,5]

The backbone of peptides (1) is composed of three repeating elements : the amide nitrogen, the α-carbon, and the amide carbonyl.



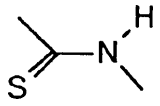
(1)

Isosteric replacement of these elements can be classed into two types : those that retain the amide bond geometry and those that lose it.

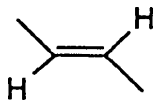
i) Replacements with Retention of Amide Bond Geometry

Examples of these surrogates include inversion of the stereochemistry of the α-carbon. This substitution has been widely used in obtaining compounds with improved biological properties, increased resistance to enzymic degradation and altered conformational properties.[2]

Other examples include the endothiono variant **(2)**, first achieved in 1973,[6] and the alkene surrogate **(3)**.[7] The bond lengths of the alkene entity are essentially equal to the normal amide unit in peptides.

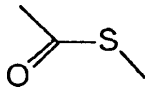


(2)

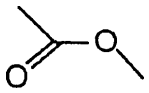


(3)

Substitution of the amide nitrogen by sulphur and oxygen to afford the thioester **(4)** and the ester **(5)** surrogates are well known.[8]

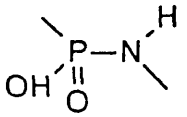


(4)

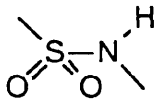


(5)

Peptide analogues bearing the phosphonamidate unit **(6)** were designed as carboxypeptidase A inhibitors.[9]



(6)

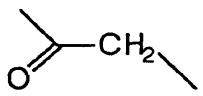


(7)

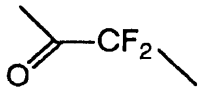
Sulphonamide analogues **(7)** have also been prepared.[10]

ii) <u>Replacements with Non-retention of Amide Bond Geometry</u>

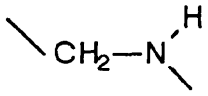
Examples of this type include the substitution of the amide nitrogen by a methylene or difluoromethylene group, to produce a ketone **(8)** or a ketodifluoromethylene unit **(9)**, and the replacement of the carbonyl group by a methylene unit, to give the amino surrogate **(10)**.[11]



(8)

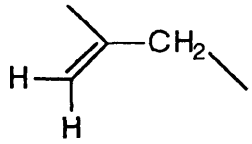


(9)



(10)

The ketone moieties in and (8) and (9) can duplicate the hydrogen bond acceptor properties, but not the rigidity, of the amide bond. The modification using the unit (11) preserves the π-character of the carbonyl group while altering its polarity and acceptor characteristics.

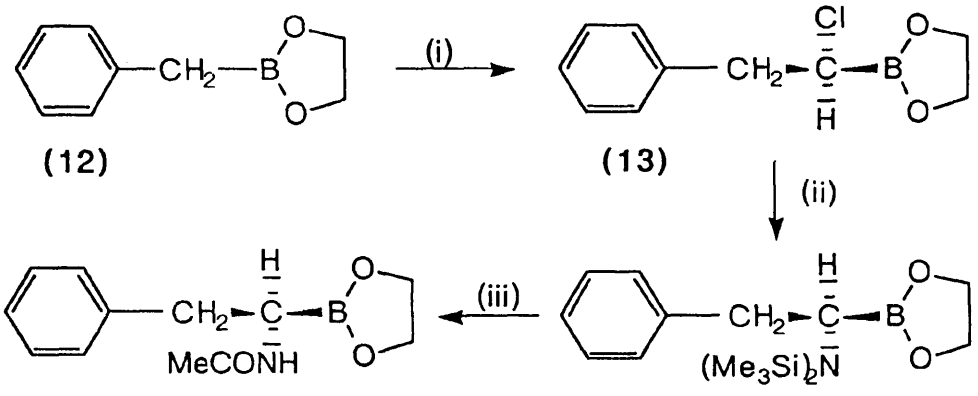


(11)

3) TERMINAL CARBOXY REPLACEMENTS

i) α-Amino Boronic Acids

The boronate analogue of N-acetyl-L-phenylalanine (15) has been synthesised by the route outlined in Scheme 1.[12]



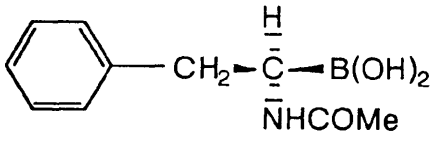
(12) (13) (14) (15)

Scheme 1

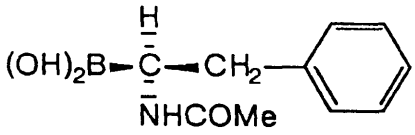
Reagents : (i) $LiCHCl_2$, (ii) $LiN(SiMe_3)_2$, (iii) $Ac_2O/AcOH$

Homologation of ethylene glycol benzylboronate **(12)** by (dichloromethyl)lithium afforded 1-chloro-2-phenylethaneboronate **(13)**. Reaction of the highly hindered nucleophile lithiohexamethyldisilazane with compound **(13)** gave, via a boron assisted displacement, the silylated amino boronic ester **(14)**. Treatment of compound **(14)** with acetic anhydride and acetic acid afforded the ethylene glycol 1-acetamido-2-phenylethaneboronate **(15)**.

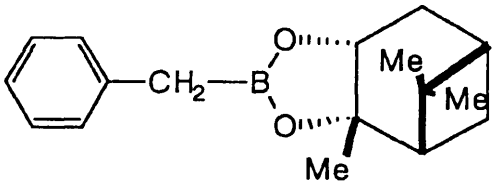
The separate enantiomers of 1-acetamido-2-phenylethaneboronic acid **(16a)** and **(16b)** have been obtained. Thus, optically pure (+)-pinanediol benzylboronate **(17)** was homologated to compound **(18)** [by (dichloromethyl)lithium] which, on immediate treatment with lithiohexamethyldisilazane followed by acetic anhydride and acetic acid, afforded (+)-pinanediol (R)-1-acetamido-2-phenylethaneboronate **(19)**. Cleavage of this pinanediol ester **(19)** with boron trichloride gave (R)-1-acetamido-2-phenylethaneboronic acid **(16a)**. The (S)-enantiomer was similarly obtained.



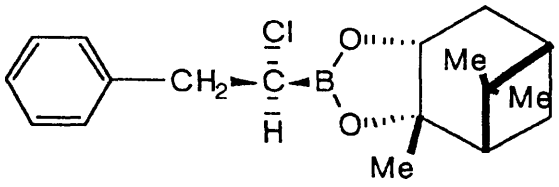
(16a)



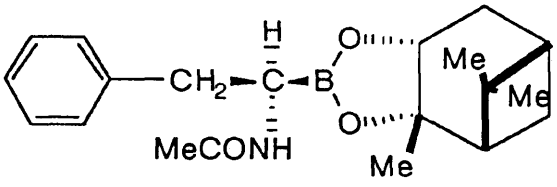
(16b)



(17)



(18)



(19)

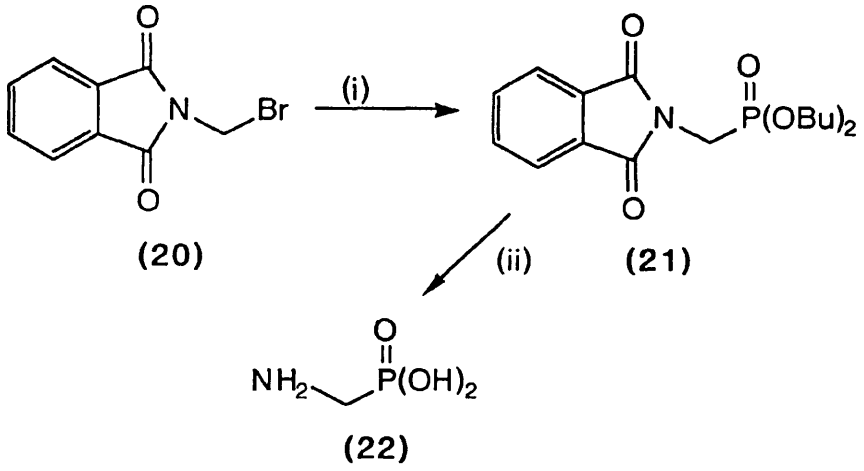
Compound **(16a)** was found to be a potent competitive inhibitor of chymotrypsin. Alkylated amino boronic acid derivatives of types $R_2NCH_2B(OR')_2$ and $R_3N^+CH_2B(OR')_2$ have also been described.[13,14]

ii) α-Amino Phosphonic Acids

a) Phosphorylation of Amino Compounds

α-Aminoalkyl phosphonic acids **(22)** can be prepared by the introduction of a phosphonic grouping into an organic amine by the Arbuzov and Michaelis-Becker reactions. Thus sodium dibutyl phosphite reacts with the bromomethylphthalimide **(20)** to afford, after hydrolysis of the resulting

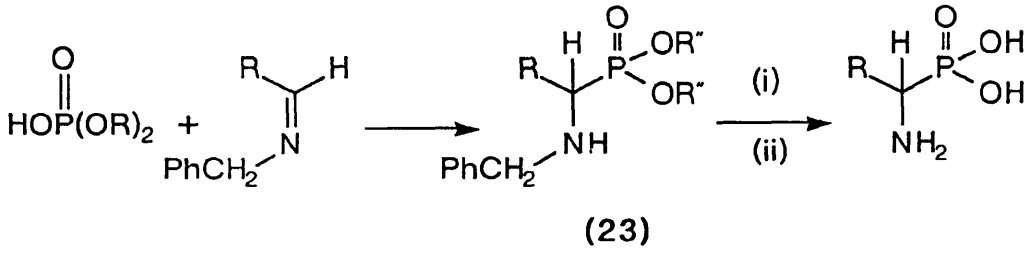
phthalimidomethylphosphonic ester **(21)**, α-aminomethane phosphonic acid **(22)** (Scheme 2).[15]



Scheme 2

Reagents : (i) $(BuO)_2PONa$, (ii) NaOH

The reaction of acid phosphites with aldimines based on benzylamine affords adducts of type **(23)**; removal of the protecting groups affords α-aminoalkane phosphonic acids (Scheme 3).

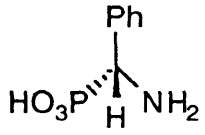


(23)

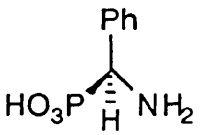
Scheme 3

Reagents : (i) Pd/C-H_2 (ii) H_3O^+

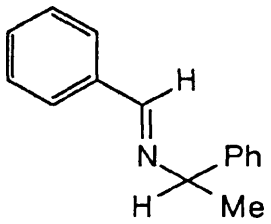
The synthesis of the phenylglycine analogue enantiomers **(24)** and **(25)** was reported by Gilmore and McBride,[16] by employing an asymmetric addition reaction of diethyl phosphite to the chiral imine **(26)** [formed from PhCHO and $PhCH(Me)NH_2$], followed by acidic hydrolysis and hydrogenolysis.



(24)



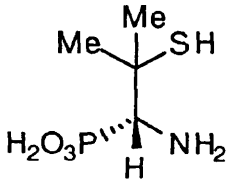
(25)



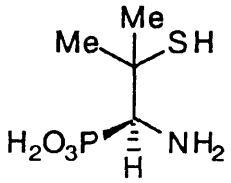
(26)

The imine **(26)** was formed from (S)-(-)-α-methylbenzylamine, and the derived analogue **(24)** showed $[\alpha]_D$ +18.1° (NaOH); when (R)-(+)-α-methyl-benzylamine was used, the analogue **(25)** showed $[\alpha]_D$ -18.1° (NaOH).

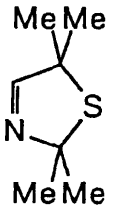
Hope et al.[17] have achieved the synthesis of the penicillamine analogue enantiomers **(27)** and **(28)**, by the addition of the cyclic imine **(29)** to the chiral cyclic phosphite **(30)**. Separation of the 2:1 mixture of diastereoisomers **(31)** and **(32)** followed by acidic hydrolysis furnished the separate enantiomers **(27)** and **(28)**.



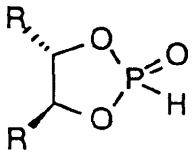
(27)



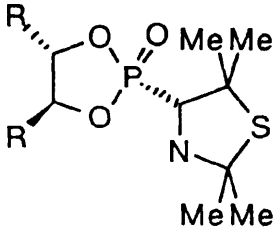
(28)



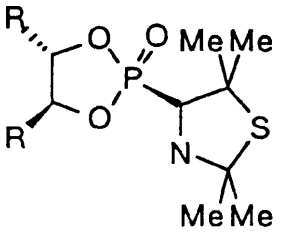
(29)



(30)

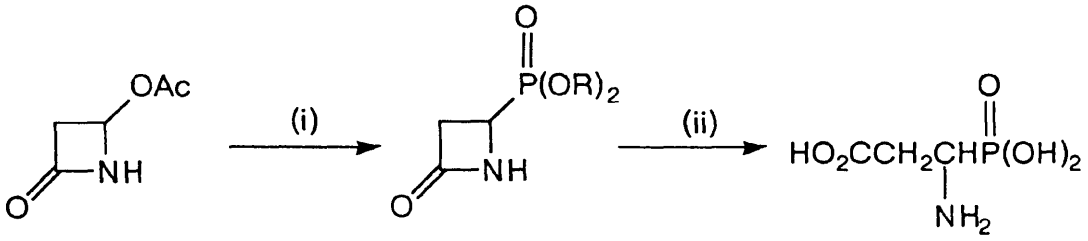


(31)



(32)

The phosphonic analogue of aspartic acid **(35)** has been obtained by acidic hydrolysis of 2-oxoazetidin-4-yl phosphonate **(34)** [formed on reaction of 4-acetoxyazetidin-2-one **(33)** with phosphites] (Scheme 4). [18-20]



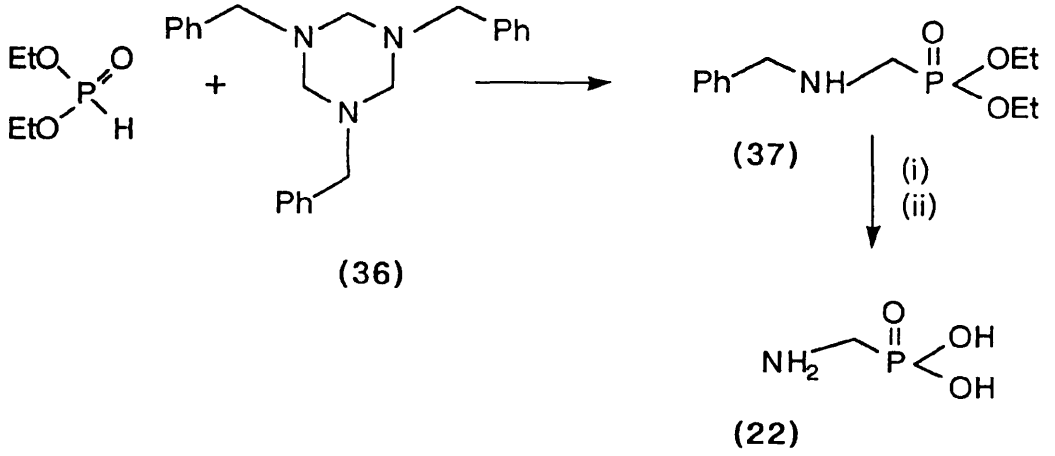
(33) (34) (35)

Scheme 4

Reagents : (i) $P(OR)_3$, (ii) H_3O^+

N-Substituted α-amino phosphonic acids, e.g. **(37)**, have been obtained from hexahydrotriazines, e.g. **(36)**, on reaction with acid

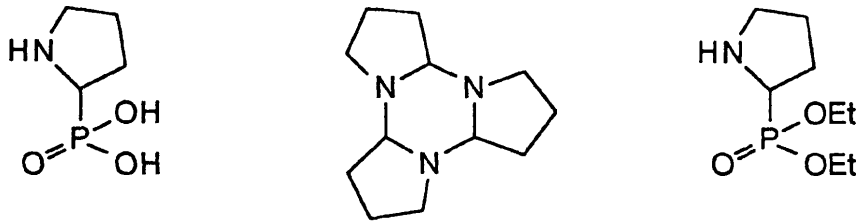
phosphites; deprotection affords α-amino phosphonic acids, e.g. (22) (Scheme 5). [21,22]



Scheme 5

Reagents : (i) H_2/Pd (ii) H_3O^+

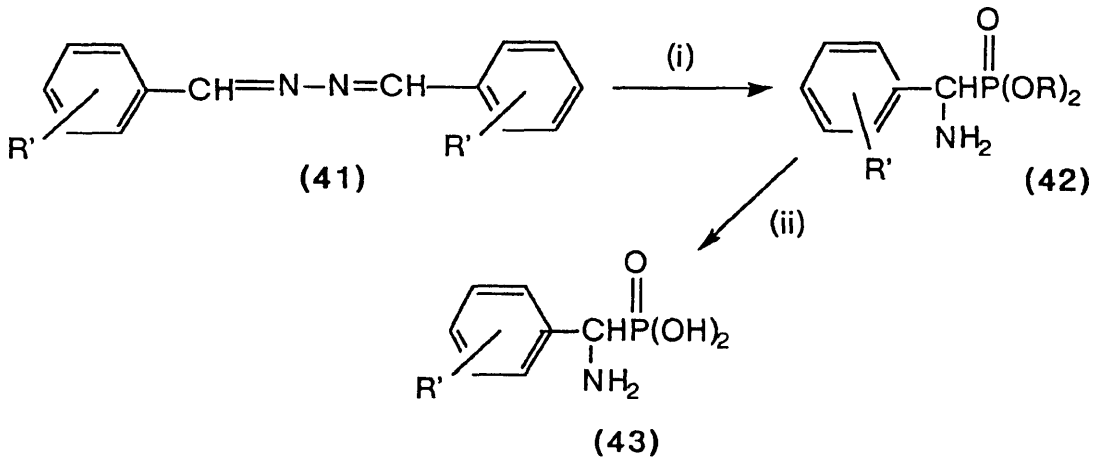
The proline analogue (38) was prepared from the reaction of diethyl phosphite with 1-pyrroline trimer (39), followed by hydrolysis of the resulting ester (40).[22]



(38) (39) (40)

α-Amino phosphonic acids can also be obtained from aldazines by phosphorylation and reductive cleavage of the nitrogen-nitrogen bond. Two equivalents of dialkyl phosphite react with aryl aldazines (41) to afford

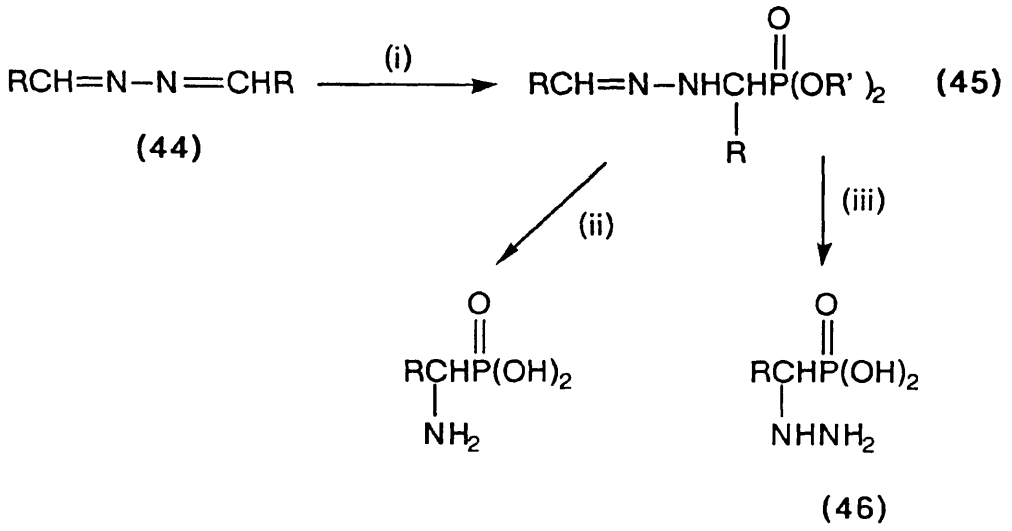
adducts **(42)** which are reduced by the excess dialkyl phophite to esters of α-aminobenzyl phosphonic acids **(43)**. [23-26]



Scheme 6

Reagents : (i) $(RO)_2P(O)H$, $(RO)_2P(O)Na$ (ii) H_3O^+

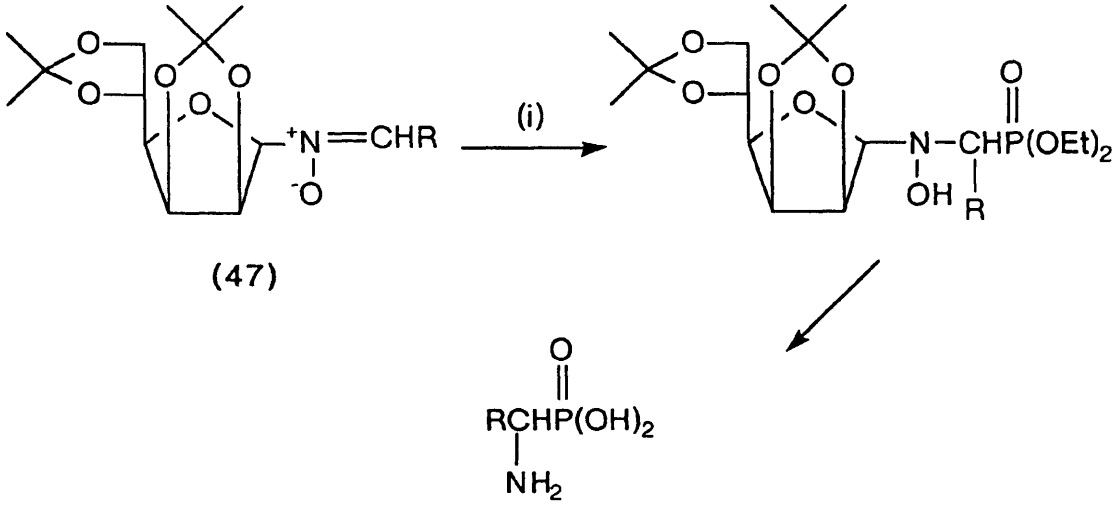
Aliphatic aldazines **(44)** only form monoadducts **(45)** with dialkyl phosphites; they afford α-hydrazino phosphonic acids **(46)** upon acidic hydrolysis[27] and α-amino phosphonic acids upon hydrogenation on Raney nickel[27-28] (Scheme7).



Scheme 7

Reagents : (i) $(RO)_2P(O)H$, $(RO)_2P(O)Na$, (ii) H_2/Ni, H_3O^+, (iii) 6M HCl

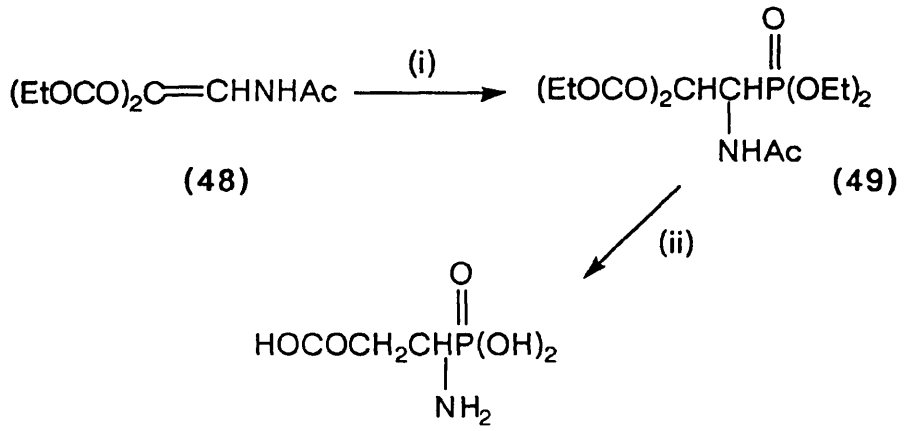
Asymmetric syntheses of (+)-phosphonic analogues of serine, valine, and alanine[29] have been achieved by phosphorylation of N-glycosylnitrones **(47)** with dialkyl phosphites (Scheme 8).



Scheme 8

Reagents : (i) $(RO)_2P(O)H$

The phosphonic analogue of aspartic acid **(35)** has been obtained by the Michael addition of dialkyl phosphite with acetamidomethylenemalonate **(48)** and subsequent hydrolysis and decarboxylation of the adduct **(49)** (Scheme 9).[30]

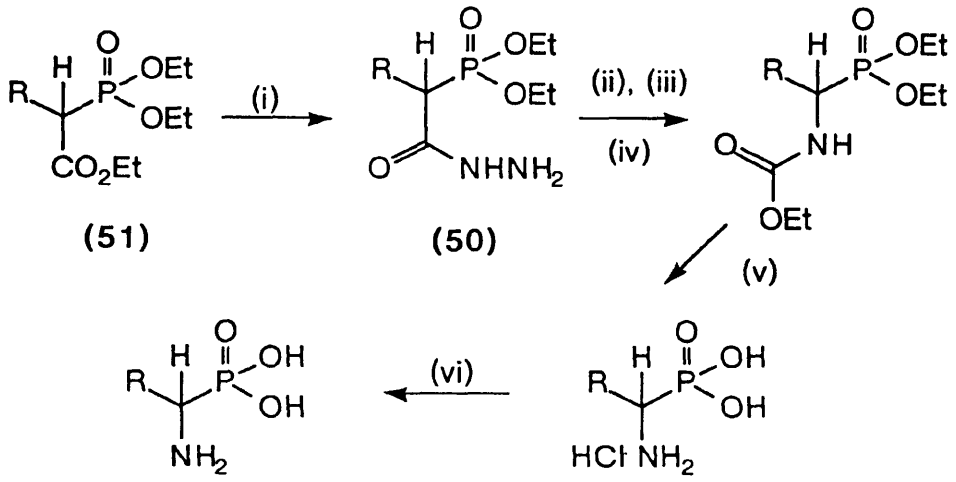


Scheme 9

Reagents : (i) $(EtO)_2P(O)H$, $(EtO)_2P(O)Na$, (ii) H_3O^+

b) Amination of Substituted Phosphonic Acids

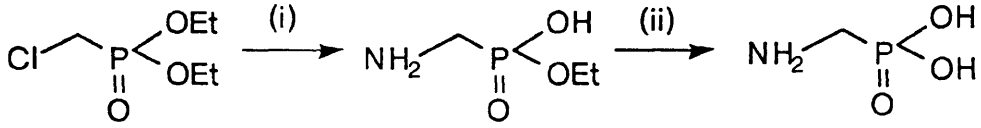
An alternative synthetic approach to α-amino phosphonic acids involves Curtius degradation of phosphonohydrazides **(50)** [prepared from phosphonoacetates **(51)**], followed by hydrolysis (Scheme 10).[31]



Scheme 10

Reagents : (i) NH_2NH_2, (ii) HNO_2, (iii) Δ, (iv) EtOH, (v) HCl, (vi) propylene oxide

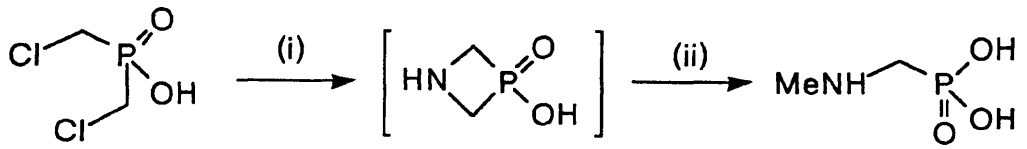
The replacement by an amino group of the halogen in a halogenoalkyl phosphonic acid has also been described (Scheme 11).[32-33]



Scheme 11

Reagents : (i) NH_3/H_2O, (ii) H_3O^+

Reaction of di(chloromethyl)phosphinic acid **(52)** with ammonia affords N-methylaminomethane phosphonic acid **(54)** via the azaphosphetidine oxide ring intermediate **(53)**, which is cleaved by water at the P-C bond (Scheme 12).[34]

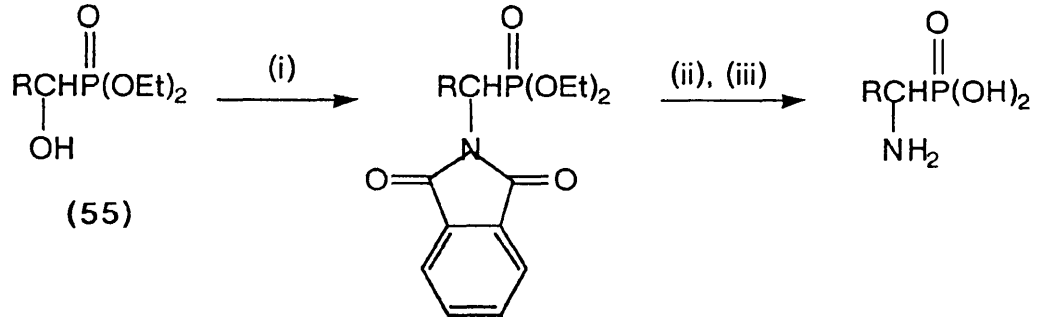


(52) (53) (54)

Scheme 12

Reagents : (i) NH_3/H_2O, 155 °C, (ii) H_2O

The hydroxy group in α-hydroxy phosphonic acid esters **(55)** is substituted by the phthalimido group by using the Mitsunobu reaction (Scheme 13).



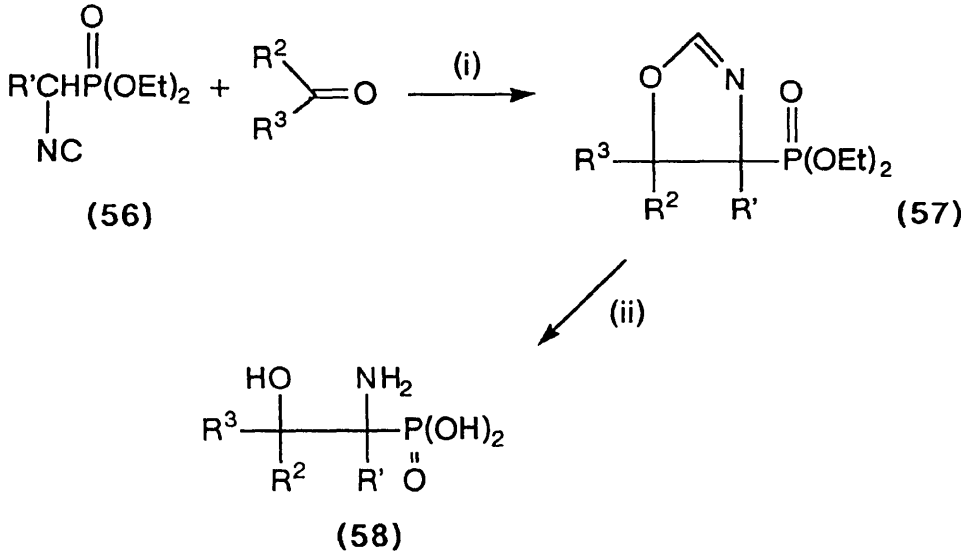
(55)

Scheme 13

Reagents : (i) phthalimide, triphenylphosphine, DEAD, (ii) N_2H_4, (iii) H_3O^+

α-Hydroxy phosphonates and phthalimide react in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD), followed by dephthaloylation with hydrazine, to afford α-amino phosphonic acids.[35]

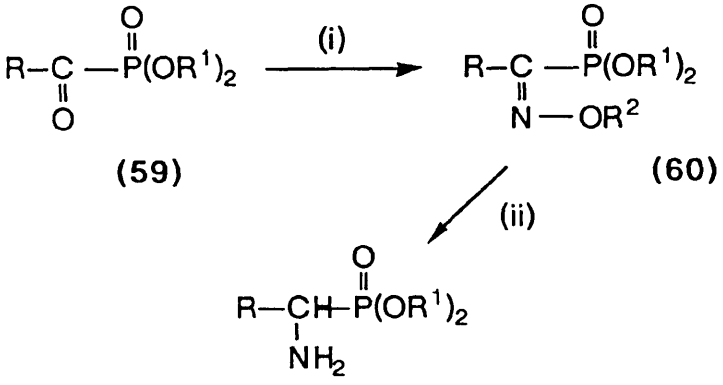
Phosphonic analogues of serines **(58)** can be obtained from oxazolinylphosphonates **(57)** [formed from addition of carbonyl compounds to isocyanomethylphosphonates **(56)**] (Scheme 14).[36]



Scheme 14

Reagents : (i) Cu_2O (ii) H_3O^+

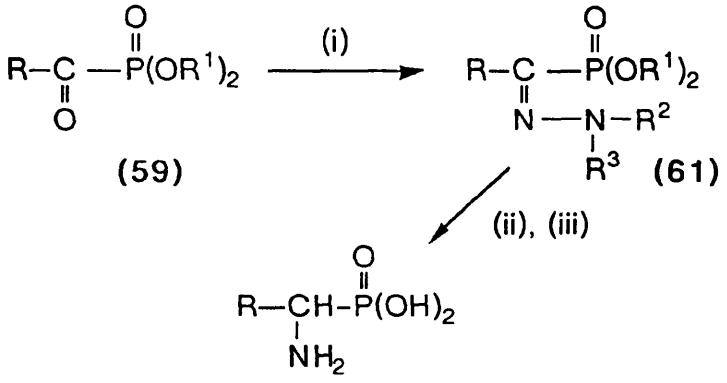
A synthesis of various α-amino phosphonic acids is based on the conversion of α-oxoalkyl phosphonates **(59)** into oximes **(60)** followed by reduction (H_2, Ra-Ni) (Scheme 15).[37-41]



Scheme 15

Reagents : (i) NH_2OR^2, (ii) [H]

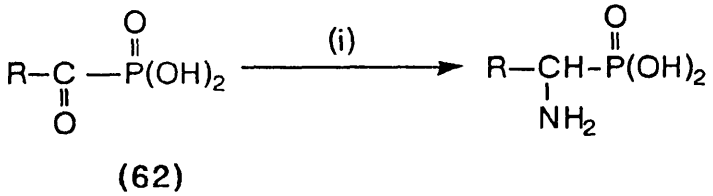
α-Amino phosphonic acids are also obtained from α-oxophosphonates **(59)** by way of hydrazones **(61)** (Scheme 16).[42-43]



Scheme 16

Reagents : (i) $NH_2NR^2R^3$, (ii) [H], (iii) H_3O^+

α-Oxophosphonic acids **(62)** can also be converted directly into α-amino phosphonic acids on reaction with ammonia and sodium tetrahydroborate (Scheme 17).[44]

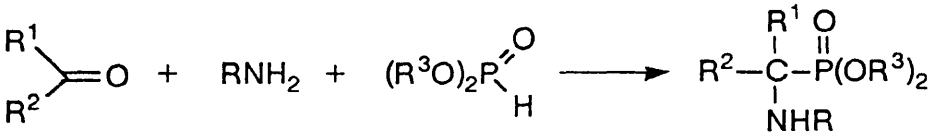


Scheme 17

Reagents : (i) NH_3, $NaBH_4$, H_2O or EtOH

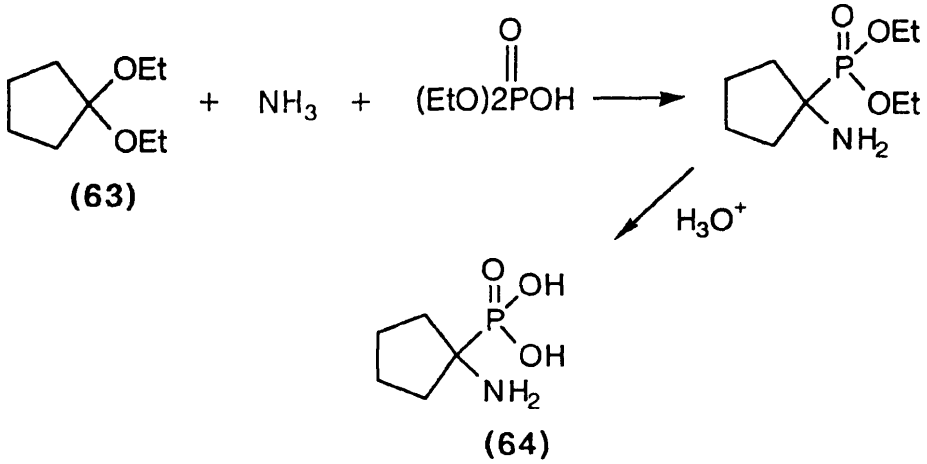
c) Condensation of Dialkyl Phosphites and their Analogues with Amines and Aldehydes or Ketones

Kabachnik and co-workers[45-50] and independently Fields[51] showed that the interaction of ammonia (or an amine), a carbonyl compound, and a dialkyl phosphite leads to the formation of an α-amino phosphonic ester (Kabachnik-Fields reaction).

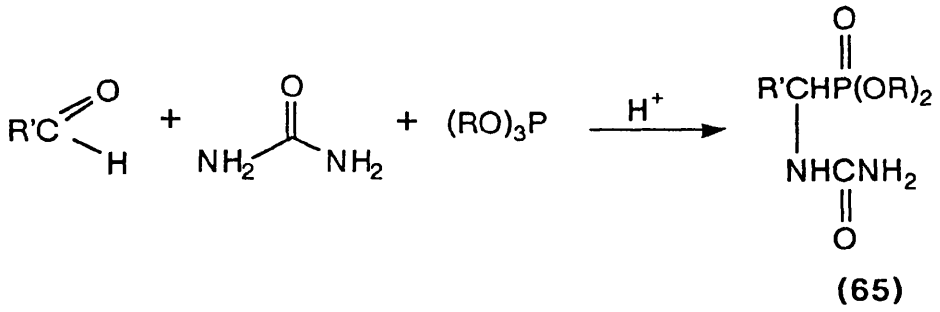


The free α-amino phosphonic acid is then liberated upon hydrolysis. This method of synthesis is general, and most of the common α-amino phosphonic acids are accessible using this approach.

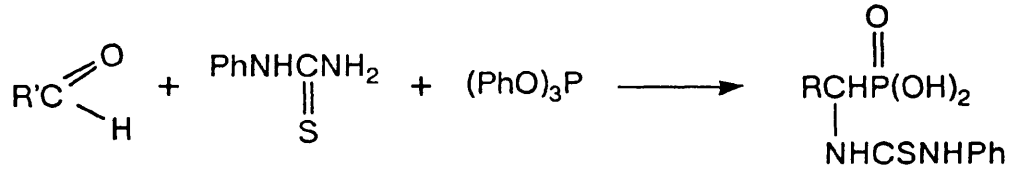
The phosphonic analogue of cycloleucine **(64)** was obtained by the reaction of the diethylacetal of cyclopentanone **(63)**, diethyl phosphite and ammonia followed by hydrolysis.[22]



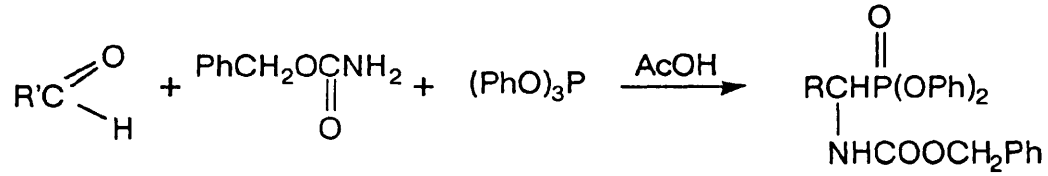
Aldehydes, phosphites and ureas, thioureas or carbamates react to give α-ureidoalkylphosphonic acids **(65)**, α-thioureidoalkylphosphonic acids **(66)**,[52-55] or α-carbamidoalkylphosphonic acids **(67)**.[56-57] Compounds **(65)-(67)** can be readily deprotected to give α-aminoalkylphosphonic acids.



(65)

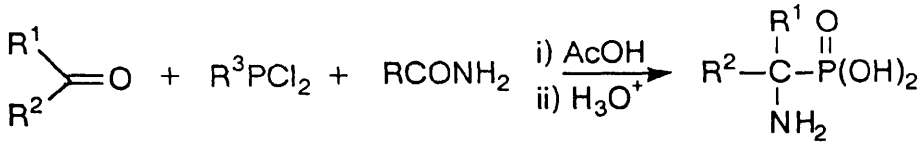


(66)



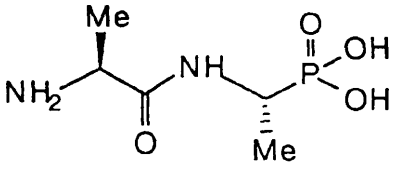
(67)

Reaction of a carbonyl compound, phosphorus trichloride [or an alkyl (aryl) dichlorophosphine], and an amide in acetic acid, followed by hydrolysis, affords α-amino phosphonic acids.[58]

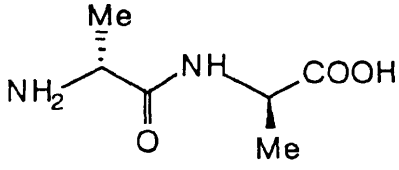


R^3 = Cl, Alkyl, Aryl

The dipeptide analogue L-alanyl-L-aminoethane phosphonic acid **(68)** (alaphosphalin) has been prepared;[59] it is reported to inhibit the growth of certain bacteria in vitro and in vivo in animals.[60]Alaphosphalin **(68)** was found to be more effective against Gram-negative than Gram-positive bacteria. This antibacterial activity is believed to be due to its close structural resemblance to the dipeptide, D-alanyl-D-alanine **(69)**, the terminal feature of the various peptides from which bacteria build their cell walls.

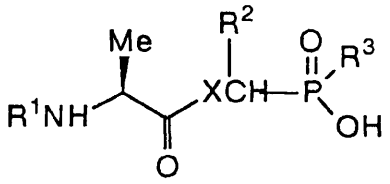


(68)



(69)

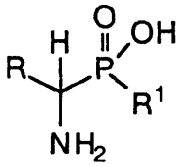
Phosphonodipetide variants of alaphosphalin **(68)** have also been described.[61]



R^1	R^2	R^3	X	C*
Me	Me	OH	NH	L
Me	H	OH	NH	-
AcO	Me	OH	NH	L
HCO	Me	OH	NH	L
H	CH_2Cl	OH	NH	DL
H	CH_2OH	OH	NH	L
H	CH_2OH	OH	NH	D
H	$(CH_2)_2CO_2H$	OH	NH	L
H	$(CH_2)_2CO_2H$	OH	NH	D
H	Me	OMe	NH	L
H	H	Me	NH	-
H	H	OH	$NHCH_2$	-
H	H	OH	O	-
H	H	OH	NMe	-
H	Me	OH	NHNH	DL

iii) α-Amino Phosphinic Acids

Two types of α-amino phosphinic acids can exist : α-amino phosphonous acids **(70a)** and α-amino phosphinic acids **(70b)**. α-Amino phosphonous acids can be oxidised to α-amino phosphinic acids with bromine water or mercury(II) chloride.[62]

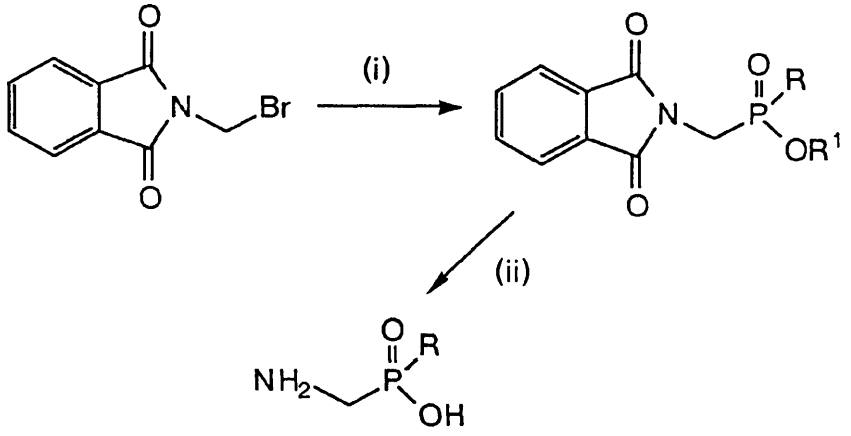


a; $R^1 = H$
b; R^1 = Alkyl, Aryl

(70)

a) Phosphorylation of Amino Compounds

α-Amino phosphinic acids can be obtained by the use of the Arbuzov and Michaelis-Becker reactions, i.e. reaction of bromoalkylphthalimides with dialkyl phosphonites followed by hydrolysis (Scheme 18).[63]

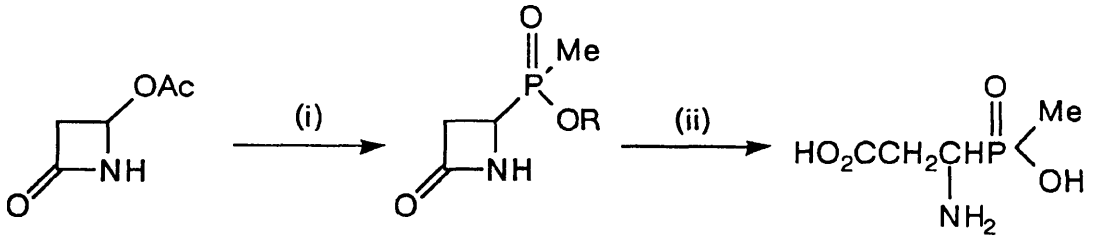


Scheme 18

Reagents : (i) $RP(OR^{1)}{}_2$ (ii) H_3O^+

Esters of α-ureido phosphinic acids can be obtained by heating aldehydes, ureas, and phosphonites; thioureas can also be employed in place of ureas.

4-Acetoxyazetidin-2-one **(33)** reacts with phosphonites to afford 2-oxoazetidin-4-yl phosphinates **(71)** which, upon acidic hydrolysis, afford the phosphinic analogue of aspartic acid **(72)** (Scheme 19).[18-20]

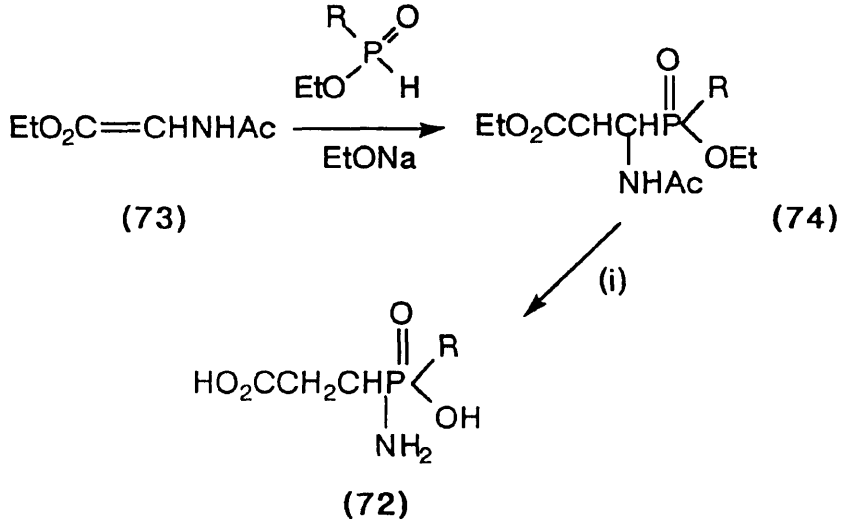


(33) (71) (72)

Scheme 19

Reagents : (i) $MeP(OR)_2$, (ii) H_3O^+

Phosphinic analogues of aspartic acid **(72)** have also been obtained by the Michael addition of acid phosphonites to acetamidomethylenemalonate **(73)** with subsequent hydrolysis and decarboxylation of the adducts **(74)** (Scheme 20).[64]



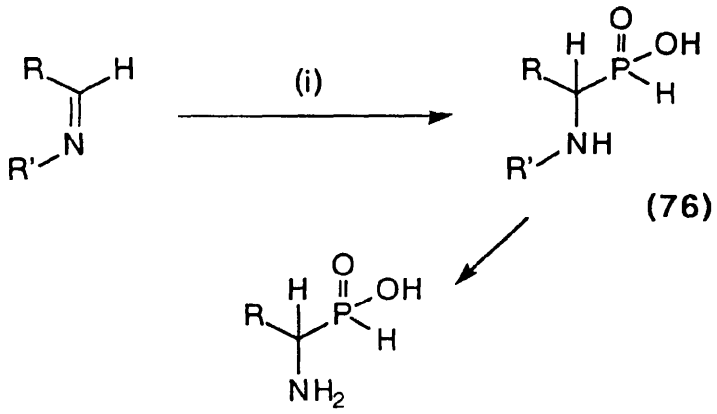
(73) (74) (72)

Scheme 20

Reagents : (i) H_3O^+

The esterification of the carboxy groups in these compounds with subsequent ammonolyis leads to the formation of the asparagine analogue.

A general method for the synthesis of α-amino phosphonous acids involves the addition of hypophosphorous acid **(75)** to imines with subsequent removal of the nitrogen substituent from the adducts **(76)** (Scheme 21).[62]

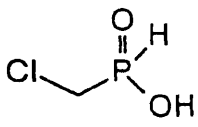


Scheme 21

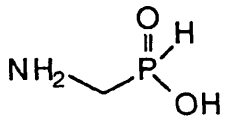
Reagents : (i) $(HO)_2PH$ (75)

b) Amination of Substituted Phosphinic Acids

Aminomethane phosphonous acid **(78)** has been obtained from reaction of chloromethane phosphonous acid **(77)** with ammonia.[65]



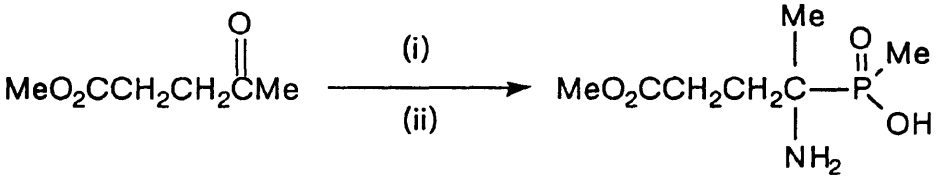
(77)



(78)

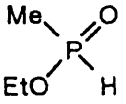
c) The Kabachnik-Fields Reaction

α-Amino phosphinic acids have been obtained by the Kabachnik-Fields reaction - the interaction of phosphonites, a carbonyl compound, and ammonia. The phosphinic analogue of α-methylglutaric acid **(79)** was obtained in this way (Scheme 22).

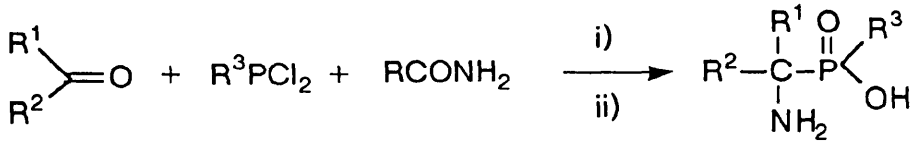


(79)

Scheme 22

Reagents : (i)  , (ii) H_3O^+

Tervalent phosphorous compounds have also found application in the synthesis of α-amino phosphinic acids. The reaction of a carbonyl compound, an alkyl(aryl)dichlorophosphine, and a compound containing an amide group interact in acetic acid, followed by acidic hydrolysis and liberation of the free amino acid to afford α-amino phosphinic acids **(80)** (Scheme 23).



(80)

Scheme 23

Reagents : (i) AcOH, (ii) H_3O^+

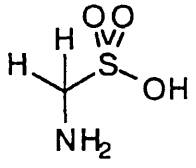
iv) α-Amino Sulphonic Acids

The biological activity of α-amino sulphonic acids was recognised as long ago as 1941 by McIlwain,[66] in which in vitro studies with strains of Proteus and Staphylococcus showed growth inhibition upon the addition of α-amino sulphonic acids. α-Amino sulphonic acids and several peptide derivatives containing a terminal sulphonic acid group have also been shown to cause a transient growth inhibition of Escherischia coli and Proteus vulgaris.[67] The α-amino sulphonic acid **(81)** was found to display enkephalin-like activity.[68-69]

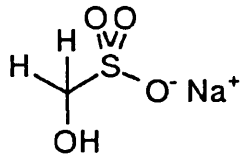
L-Tyrosyl-D-norLeucyl-Glycyl-L-Phenylalanyl-X **(81)**

X ; L-α-amino pentane sulphonic acid

α-Amino sulphonic acid analogues of the α-amino carboxylic acids have been known for some time. Thus the glycine analogue **(82)** was prepared by the reaction of sodium bisulphite and formaldehyde to afford the sodium α-hydroxymethanesulphonate **(83)** which, on reaction with ammonia and consequent acidification, afforded the free acid **(82)**.[70]



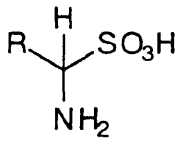
(82)



(83)

McIlwain, in 1941[71], introduced a general method of synthesis of α-amino sulphonic acids by passing sulphur dioxide into a solution of ammonium hydroxide and an aldehyde. Acidification then afforded the α-amino sulphonic acid.

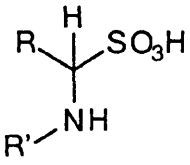
Backer and Mielder[72] modified this synthesis to prepare the analogues **(84a-d)** by the reaction of ammonia with sodium bisulphite and the corresponding aldehyde.



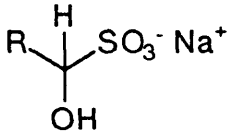
(84)

a ; R = Me
b ; R = Ph
c ; R = p-$NO_2C_6H_4$
d ; R = p-$MeOC_6H_4$

The N-alkyl-α-amino sulphonic acids **(85a-e)**, were prepared by the reaction of aldehyde-bisulphite addition compounds **(86)** with primary amines or ammonia.[73]



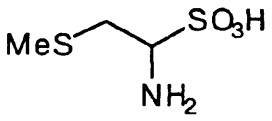
(85)



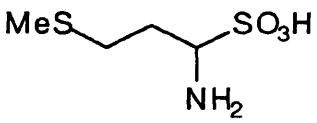
(86)

a ; R = $CHMe_2$, R' = H
b ; R = $CHMe_2$, R' = Ph
c ; R = Ph, R' = Ph
d ; R = Ph, R' = H
e ; R = $PhCH_2$, R' = H

The cysteine and methionine analogues **(87)** and **(88)** were readily prepared by the reaction of 1-amino-2-(methylthio)ethane and 1-amino-3-(methylthio)propane with sulphur dioxide in diethyl ether.[74]



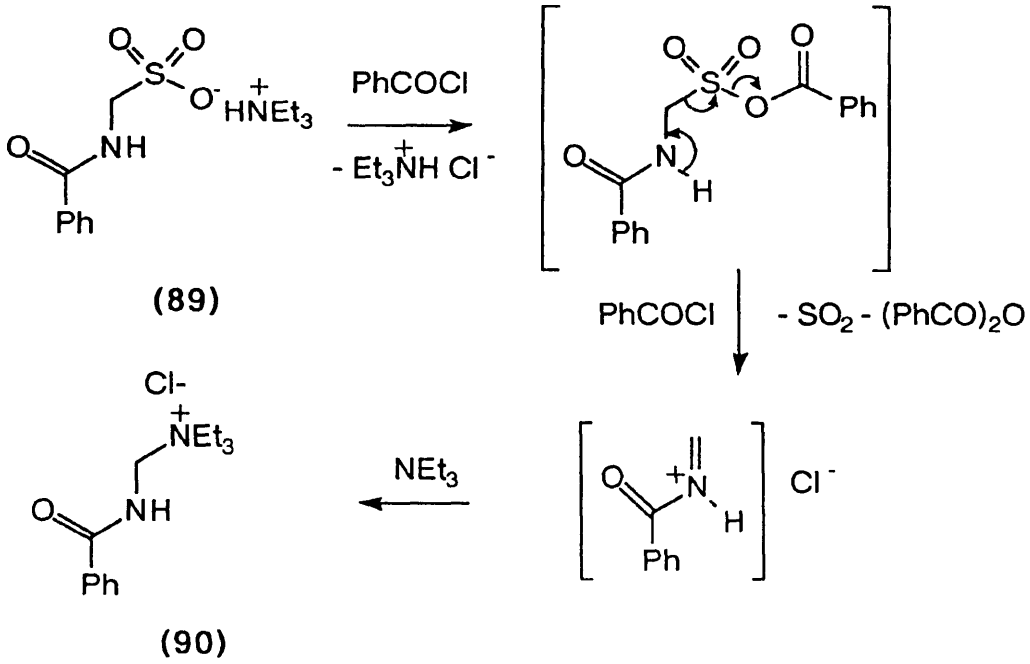
(87)



(88)

The preparation of peptide analogues containing sulphonamide linkages has largely been unsuccessful. Most methods have involved activation of the acid towards amide bond formation and treatment with an amino acid.

An explanation for this failure was proposed by Portughese;[75] monoacylation of compound **(82)** with benzoyl chloride in the presence of an excess of triethylamine afforded the salt **(89)** which, in the presence of two further molar equivalents of benzoyl chloride, underwent desulphonylation to give the salt **(90)**, benzoic anhydride, and sulphur dioxide.

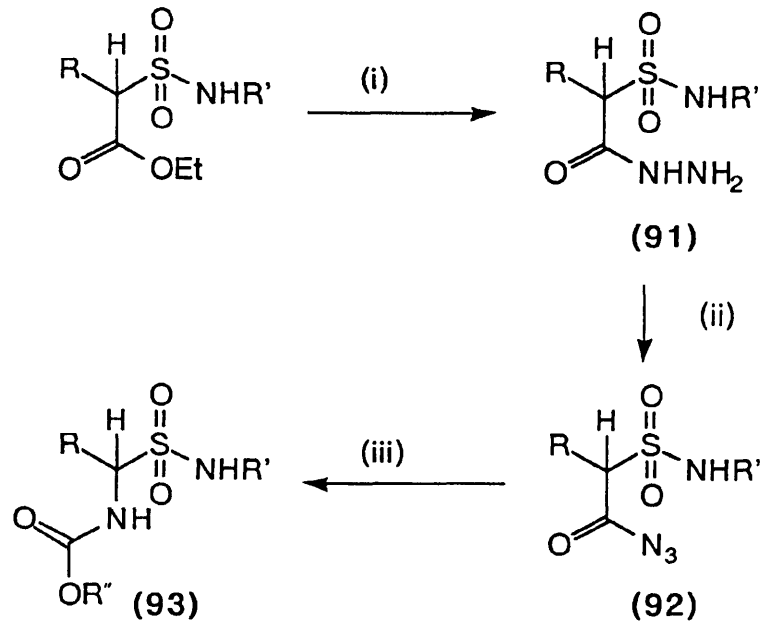


(89)

(90)

The desulphonylation is presumed to occur by mixed anhydride formation at sulphonate which enhances the leaving capability of the sulphur group.

However, Curtius rearrangement of the derivative **(91)** did lead to α-amino sulphonamide derivatives. In this way, simple urethanes of type **(93)** were prepared (Scheme 24).[10]



(91)

(92)

(93)

a : R = H, R' = H, R" = Et

b : R = H, R' = $CH(Me)CO_2CH_2Ph$, R" = Et

Scheme 24

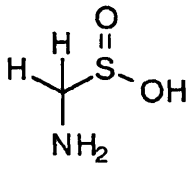
Reagents : (i) NH_2NH_2, (ii) HNO_2, (iii) Δ, R"OH

v) α-Amino Sulphinic Acids

Until recently little work had been done on α-amino sulphinic acids. In D. Barrett's Ph. D. Thesis, University of Newcastle Upon Tyne, several routes to α-amino sulphinic acids were examined. A brief survey of the work done on α-amino sulphinic acids, dipeptide derivatives based on α-amino sulphinic acids and approaches to α-substituted α-amino sulphinic acids, before and in the Ph. D. thesis will now be presented.

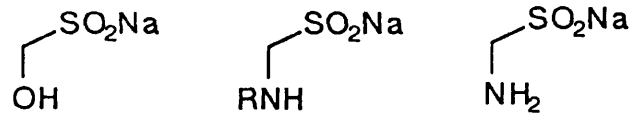
1) Reaction of Rongalite and Ammonia

The sodium salt of α-aminomethanesulphinic acid **(94)** has been claimed in patents but no evidence has been forwarded in support of the proposed structure.[76]



(94)

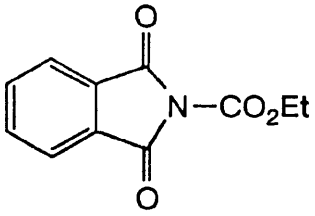
It is reported that formaldehyde reacts with zinc dithionite, then sodium carbonate[77] to afford sodium α-hydroxymethanesulphinate (Rongalite) **(95)**, which then then reacts with amines in water at 60 °C to afford the N-substituted α-aminomethanesulphinate salts **(96)**. However, when rongalite was reacted with an excess of concentrated ammonia solution at 60-65 °C, the crude evaporated product was shown to comprise a 2:1:1 mixture of materials on the basis of 220 MHz ^{1}H n.m.r. spectroscopy.



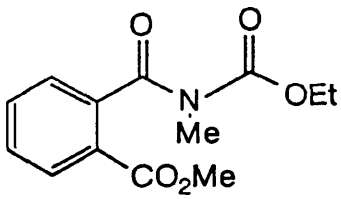
(95) **(96)** **(97)**

Proof that one of the components was the hoped-for salt **(97)** was obtained by treatment of the crude product with ethoxycarbonylphthalimide **(98)** (an established phthaloylating reagent for α-amino carboxylic acids)[78], followed by diazomethane. The resultant two-component mixture was shown to comprise the ester **(99)** (24%) [presumed to arise by hydrolysis of the reagent **(98)** under the reaction conditions followed by methylation with

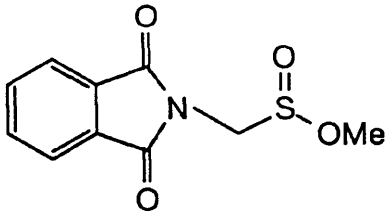
CH_2N_2] and the sulphinate ester **(100)** (10%). Clearly, the isolation of compound **(100)** confirmed that the salt **(97)** was a component of the mixture generated by the reaction of rongalite with ammonia.



(98)

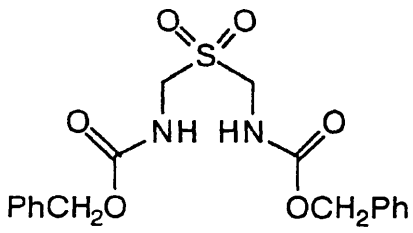


(99)

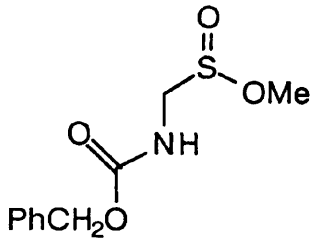


(100)

Further evidence for the presence of the salt **(97)** in the mixture was obtained by treatment with benzyloxycarbonyloxysuccinimide[79] in methanol. Immediate esterification of the crude acidic product with diazomethane afforded a two-component mixture. The minor component was considered to be the symmetrical sulphone **(101)** (11%). The major product was considered to be the urethane **(102)** (26%).

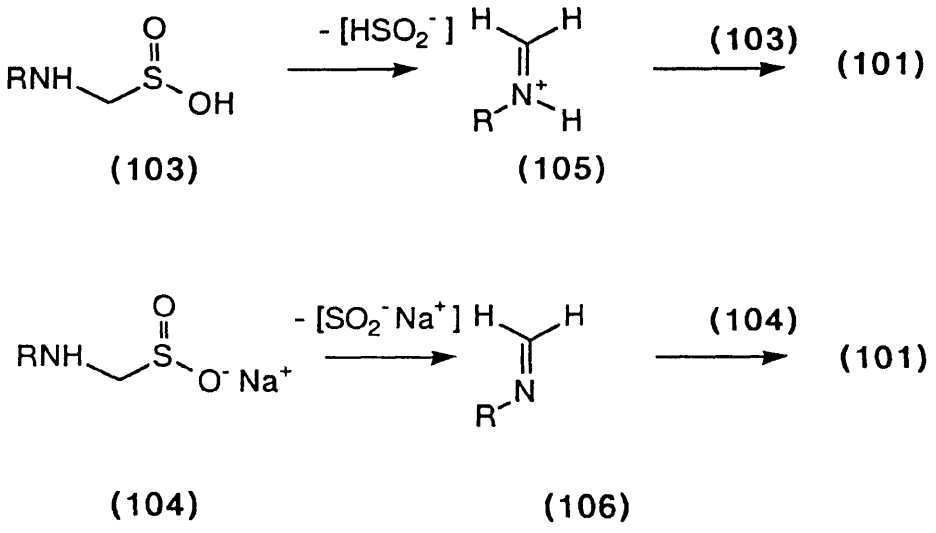


(101)



(102)

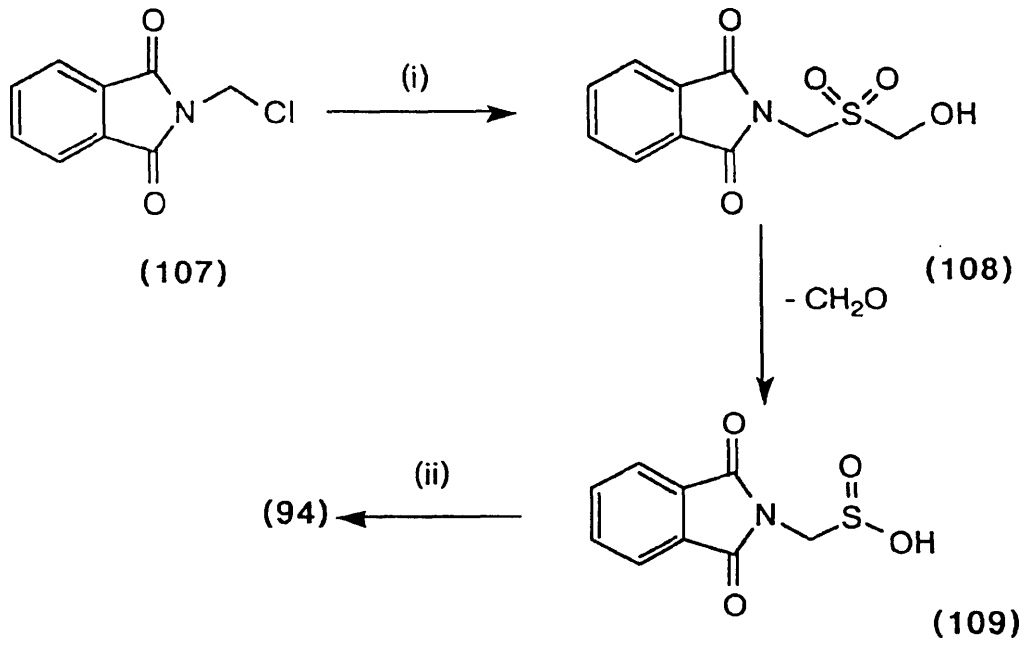
The formation of the symmetrical sulphone (101) was explained by decomposition of the sulphinic acid (103) [or its salt (104)] in acidic or basic solution, leading to the intermediate (105) or (106) which was then intercepted by another molecule of the acid (103) [or its salt (104)] by S-alkylation (Scheme 25).



Scheme 25

Since the attempt to convert rongalite (95) into the α-amino sulphinate (94) was less than satisfactory, attention was turned to another method for obtaining the salt (97).

It was hoped to prepare the sulphinic acid (94), via the intermediate α-hydroxysulphone (108), as shown in Scheme 26. Unfortunately, when the chloride (107) and rongalite (95) were reacted together, there was no evidence for the formation of the sulphinic acid (109).



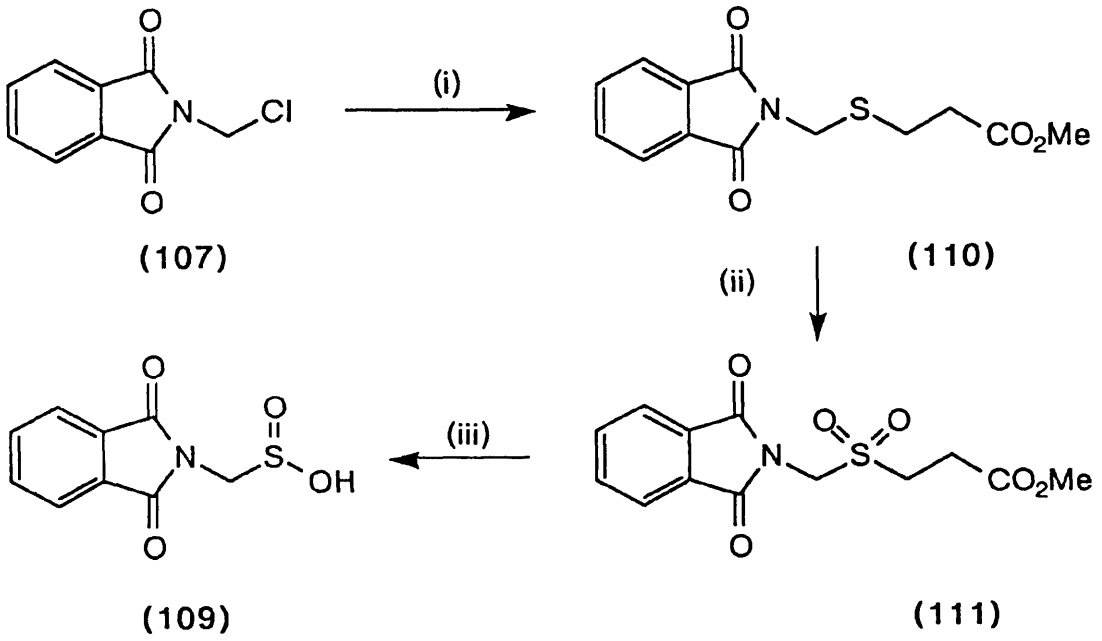
Scheme 26

Reagents : (i) rongalite **(95)**, (ii) NH_2NH_2

2) From α-Amino Acids and Methyl Mercaptoacetate

a) α-Amino Sulphinic Acids

In recognising the ease of generation of sulphinic acids by β-elimination reactions under basic conditions,[80-82] the possibility of preparing the sulphinic acid **(109)** by the route shown in Scheme 27 was considered.



(107) (110) (111) (109)

Scheme 27

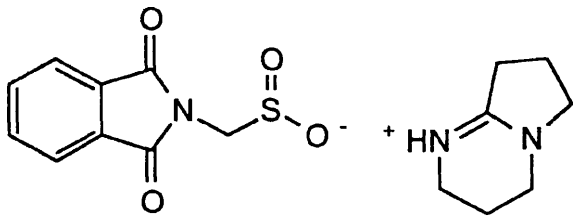
Reagents : (i) $HSCH_2CH_2CO_2Me$, (ii) $KMnO_4$, (iii) DBN

Chloromethylphthalimide reacted with methyl 3-mercaptopropionate[83] in the presence of triethylamine to afford the sulphide **(110)** in 89% yield; the last-cited compound was readily transformed into the sulphone **(111)**, with potassium permanganate in aqueous acetic acid, in 86% yield. The sulphone **(111)** then reacted with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) followed by an acidic work-up to afford the sulphinic acid **(109)** in 58% yield (Scheme 27.)

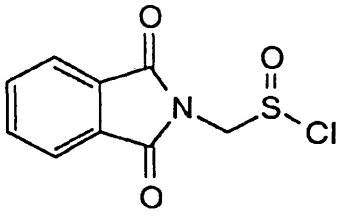
In the preparation of the sulphinic acid **(109)**, according to Scheme 27, crude yields were generally in the range 40-70%. In view of the importance of this step, since it generates the α-amino sulphinic acid moiety, it was decided to examine the reaction of the sulphone **(111)** with DBN in more detail.

b) α-Amino Sulphinamide Derivatives

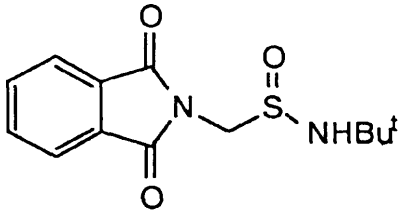
Perrone and Stoodley[84] have demonstrated that DBN salts of sulphinic acids, derived from penicillinate 1,1-dioxides, are converted into sulphinyl chlorides upon treatment with thionyl chloride. In the hope that the DBN- salt (112) would be converted into the sulphinyl chloride (113), the sulphone (111) was treated sequentially with DBN and thionyl chloride. tert-Butylamine was then added to the reaction mixture and the sulphinamide (114) was obtained in 28% yield. This was the first example of an α-amino sulphinamide derivative.



(112)



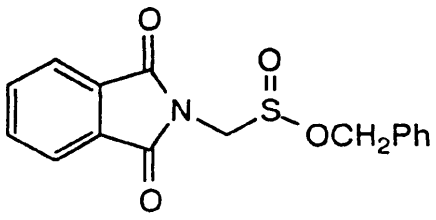
(113)



(114)

Clearly, the sulphinyl chloride (113) had been generated in situ from the DBN salt (112). The low overall yield supports the notion that the salt (112) may be participating in other processes leading to water-soluble products. When the sulphone (111) was treated sequentially with DBN and benzyl chloroformate, the benzyl sulphinate (115) was obtained in 40% yield.

In an attempt to trap the DBN salt **(112)** as it was formed, the sulphone **(111)** was treated with benzyl chloroformate then DBN; work-up returned the starting sulphone **(111)** in 70% yield. From these observations, it is clear that the DBN salt **(112)** could not be trapped quantitatively.

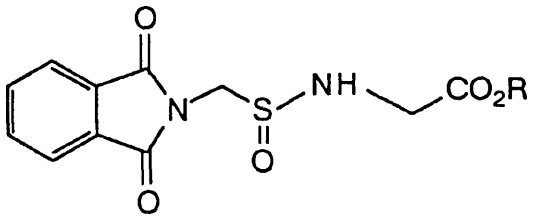


(115)

Proof for the formation of the sulphinic acid **(109)** was obtained by the reaction of the freshly regenerated acid in ethyl acetate solution with diazomethane to afford the methyl ester **(100)** [in 38% overall yield from **(111)**].

When the sulphinic acid **(109)** was briefly exposed to thionyl chloride, a quantitative yield of the sulphinyl chloride **(113)** was obtained. This sulphinyl chloride reacted with an excess of tert-butylamine to afford the sulphinamide **(114)** in 40% yield.

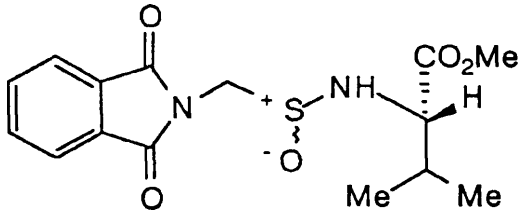
With a view to obtaining a dipeptide sulphinamide derivative, the reaction of compound **(113)** with glycine derivatives was investigated. Unfortunately, when the chloride **(113)** was treated with ethyl glycinate and with benzyl glycinate there was no evidence for the formation of the sulphinamides **(116a)** and **(116b)**. Evidently, the acylation of glycine derivatives by the chloride **(113)** was not suitable for the synthesis of the sulphinamides **(116a)** and **(116b)**.



(116)

a ; R = Et, b ; R = CH_2Ph

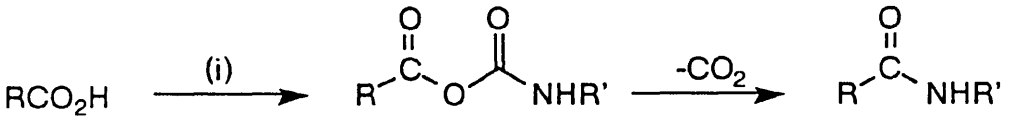
However, the sulphinyl chloride (113) reacted with L-valine methyl ester to produce the dipeptide derivative (117) in 48% yield, as a 2:1 mixture of diastereoisomers.



(117)

The isolation of the dipeptide derivative (117) clearly showed that such compounds were not intrinsically unstable and attention was therefore turned to examining alternative methods of construction of sulphinamide links with a view to obtaining the derivatives (116a) and (116b).

Initially, the methods which were tried in order to couple the sulphinic acids and the amines, all failed. These included a dicyclohexylcarbodiimide (DCC) mediated coupling and a 1,1-carbonyldiimidazole (CDI) coupling method. Then a recent method,[85] used for the synthesis of amides from carboxylic acids and isocyanates in the presence of a base, was tried (Scheme 28).

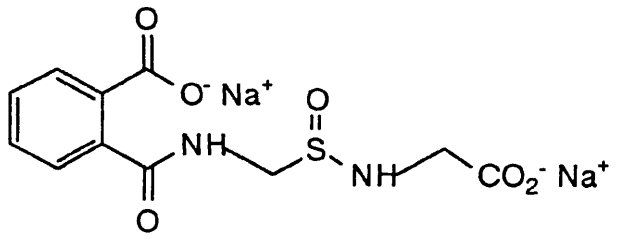


Scheme 28

Reagents : (i) R'NCO

When a benzene solution of the sulphinic acid **(109)** and triethylamine was heated with ethyl isocyanatoacetate under reflux, and the product purified by silica-gel chromatography, the dipeptide sulphinamide derivative **(116a)** was obtained in 29% yield. This clearly established that when the amino group is diacylated there are no problems regarding instability.

With a view to obtaining a monoacylated derivative, the reaction of compound **(116a)** with sodium hydroxide was next examined. With two molar equivalents of sodium hydroxide, the sulphinamide **(116a)** afforded the disodium salt **(118)** in 96% yield.

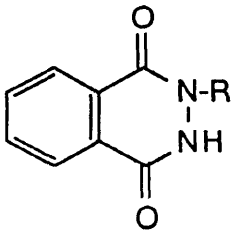


(118)

The isolation of this dipeptide clearly established the stability of monoacylated dipeptide derivatives. Having demonstrated the feasibility of preparing protected dipeptide derivatives containing internal

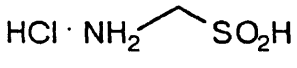
aminomethanesulphinic acid moieties and protected α-amino sulphinic acids, attention was turned to the removal of the phthaloyl-protecting group. The sulphinic acid **(109)** was selected for study since it would serve as a model compound for the removal of the phthaloyl group from the dipeptide derivative **(116a)**.

Classically, removal of the phthaloyl group from α-amino acids and peptides has been achieved using the Ing-Manske procedure[86], involving reaction with hydrazine followed by digestion with dilute acid. When an ethanolic solution of the sulphinic acid **(109)** was treated with hydrazine hydrate and then with dilute hydrochloric acid, the expected side-product, phthalhydrazide **(119a)** was recovered in 53% yield.



(119)

a : R = H,
b : R = Me

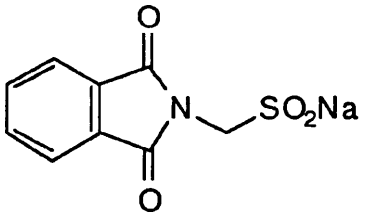


(120)

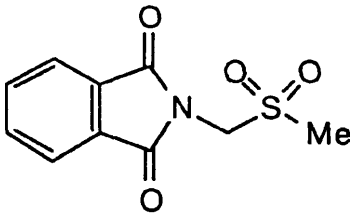
Unfortunately, there was no evidence for the anticipated hydrochloride **(120)**. Anticipating that it was possible that acidic conditions were proving destructive to the sulphinic acid **(109)**, the removal of the phthaloyl group from the salt **(121)** was next investigated. If successful, the sodium salt **(97)** would result, a compound known to be stable and isolable. In addition, methylhydrazine was selected in place of hydrazine because it is more nucleophilic and because the cleavage product, methylphthalhydrazide **(119b)**, possesses a less-acidic hydrogen preventing the formation of a salt between the amine and the side product.[87-88]Such salt formation

necessitates the acidic work-up in the Ing-Manske reaction.[86] The sulphinic acid **(109)** was reacted with sodium hydrogen carbonate in aqueous acetone to afford the salt **(121)** in 60% yield as a yellow solid. Proof that the salt was formed came by its conversion into the methyl sulphone **(122)** upon treatment with iodomethane in DMF.

Unfortunately, when the sodium salt **(121)** was treated with methylhydrazine, evaporation yielded only a mixture of unidentified materials.

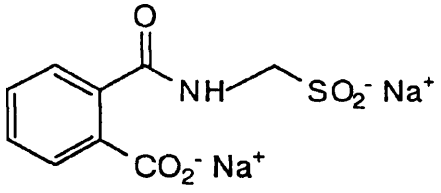


(121)

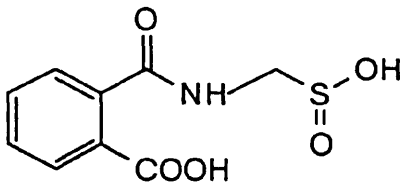


(122)

The sulphinic acid **(109)** reacted with two molar equivalents of sodium hydroxide in water to afford an essentially quantitative yield of the disodium salt **(123)**. Acidification of this salt **(123)** was achieved using Amberlite IR 120 (H^+) ion-exchange resin in water, to afford the diacid **(124)** in 75% yield.



(123)

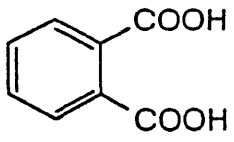


(124)

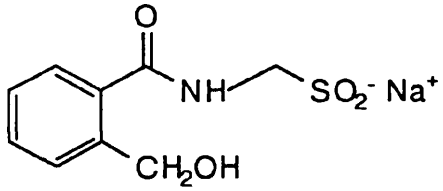
The acid **(124)** reacted with dilute hydrochloric acid under reflux to afford phthalic acid **(125)** in 85% isolated yield. This clearly indicated that the acyl group had been removed from the acid **(124)**. Examination of the

filtrate from the reaction revealed the presence of a white solid, which was not the anticipated hydrochloride **(120)** and remained unidentified.

A recent method for the removal of the phthaloyl group has been published by Ganem.[89] It involves the sodium borohydride reduction of a phthalimide to an alcohol, followed by acid-catalysed cyclisation to phthalide and the free amine. However, attempts to convert the sodium salt **(121)** into the salt **(126)** were unsuccessful.

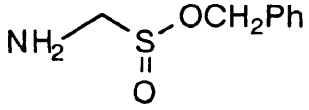


(125)



(126)

Since conditions for removal of the phthaloyl group from the sulphinic acid **(109)** or the salt **(121)** were not conducive to the isolation of the acid **(120)** or the salt **(97)**, attention then turned to the removal of the phthaloyl group from the benzyl sulphinate **(115)** in the hope that the free amine **(127)** would be more stable.

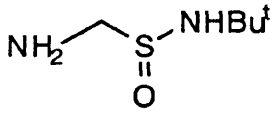


(127)

When the sulphinate **(115)** was treated with methylhydrazine, an impure sample of methylphthalhydrazide **(119b)** was precipitated and a gas was evolved. A complex mixture of compounds was present in the filtrate. Clearly, the phthaloyl group of compound **(115)** had been removed but the

product was unstable; it was presumed that the evolved gas was sulphur dioxide.

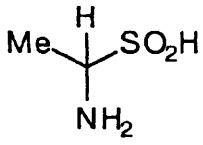
The reaction of the sulphinamide **(114)** with methylhydrazine was then examined. As with the sulphinate **(115)**, an impure sample of methylphthalhydrazide was precipitated and a gas was evolved; a complex mixture of materials was present in the filtrate. Again the phthaloyl group had been removed but the product **(128)** was unstable under the reaction conditions.



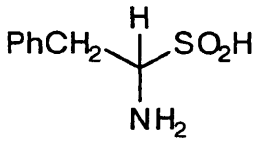
(128)

c) <u>α-Substituted α-Amino Sulphinic Acids</u>

The synthesis of the α-aminoethanesulphinic acid **(129)** (alanine analogue) and the α-aminobenzylsulphinic acid **(130)** (phenylalanine analogue) was examined.

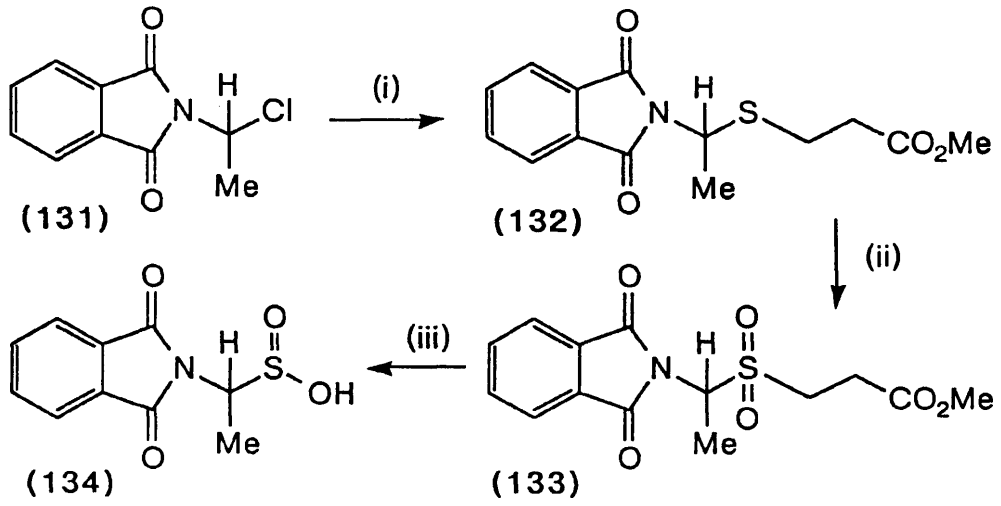


(129)



(130)

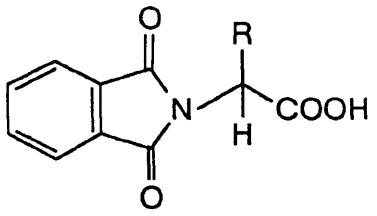
The preparation of the sulphinic acid **(134)** was effected by the route shown in Scheme 29.



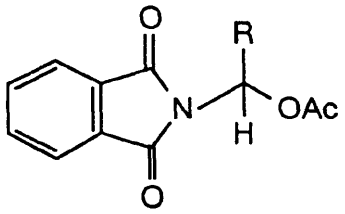
Scheme 29

Reagents : (i) $HS(CH_2)_2CO_2Me$, (ii) $KMnO_4$, (iii) DBN/H^+

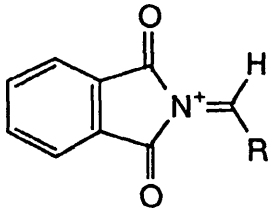
Phthaloyl α-amino carboxylic acids are readily available;[90] hence, the route to α-chloroalkylphthalimides of type **(138)** was considered. It was envisaged that the phthaloyl α-amino carboxylic acids of type **(135)** could be transformed into acetates of type **(136)**,which, in turn, could afford chlorides of type **(138)** via interception of intermediates of type **(137)** by chloride ions.



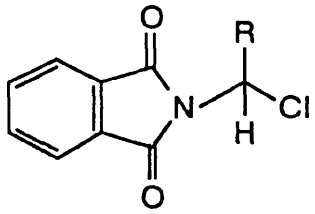
(135)



(136)

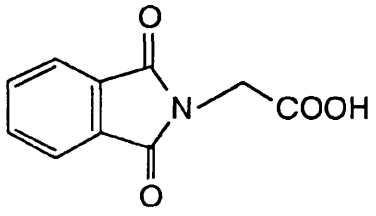


(137)

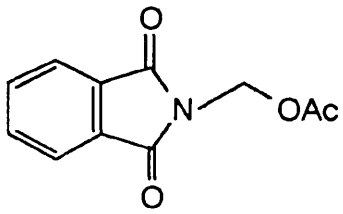


(138)

In a model study, N-phthaloylglycine **(139)** was found to react with lead(IV) acetate in the presence of pyridine[91] to afford the acetate **(140)**.[78] The acetate was then treated with thionyl chloride in the hope of obtaining the chloride **(107)**, but no reaction was observed. However, it was found that the addition of boron trifluoride etherate to the thionyl chloride solution afforded the chloride **(107)** in quantitative yield.

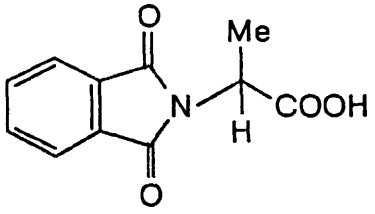


(139)

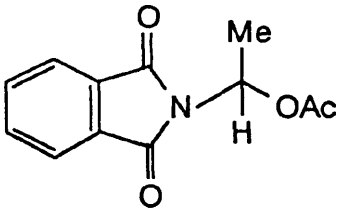


(140)

When the acid **(141)** was treated with lead(IV) acetate and pyridine, the acetate **(142)** was obtained (42%); it reacted with thionyl chloride to give the chloride **(131)** (76%). The addition of boron trifluoride etherate to the last-cited reaction accelerated the formation of the chloride **(131)** but, upon work-up, decomposition occurred.



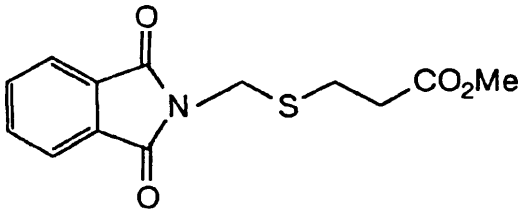
(141)



(142)

Since boron trifluoride etherate was able to remove the acetoxy group from acetates of type **(136)** to afford intermediates of type **(137)**, the possibility of using a thiol as a nucleophile to intercept the intermediate **(137)** was examined.

Reaction of the acetate **(140)** with methyl 3-mercaptopropionate and boron trifluoride etherate afforded the sulphide **(143)** (80%).

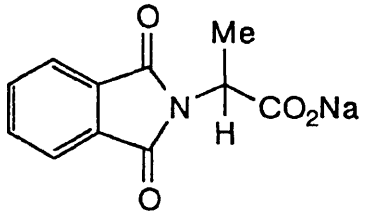


(143)

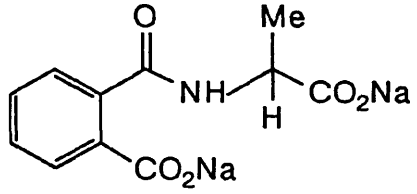
Similarly, reaction of the acetate **(142)** with methyl 3-mercaptopropionate and boron trifluoride etherate afforded the required sulphide **(132)** which, upon immediate oxidation with potassium permanganate in aqueous acetic acid, afforded the sulphone **(133)** in 85% yield.

As indicated in Scheme 29, the sulphone **(133)** was treated with DBN followed by an acidic work-up to afford the sulphinic acid **(134)**. The isolation of this sulphinic acid **(134)** clearly demonstrated that, when the amino functionality is phthaloylated, no instability problems arise.

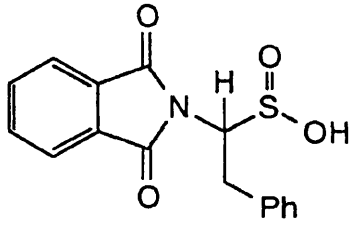
Treatment of the sulphinic acid **(134)** with sodium hydrogen carbonate in aqueous acetone afforded the salt **(144)**. The sulphinic acid **(134)** was also treated with two molar equivalents of sodium hydroxide in water to afford the monoacylated disodium salt **(145)**. Again, the successful preparation of this salt clearly demonstrates the stability of such as a species. This suggested that, if appropriate nitrogen protection was selected, it would be possible to prepare the sulphinic acid **(129)**.



(144)

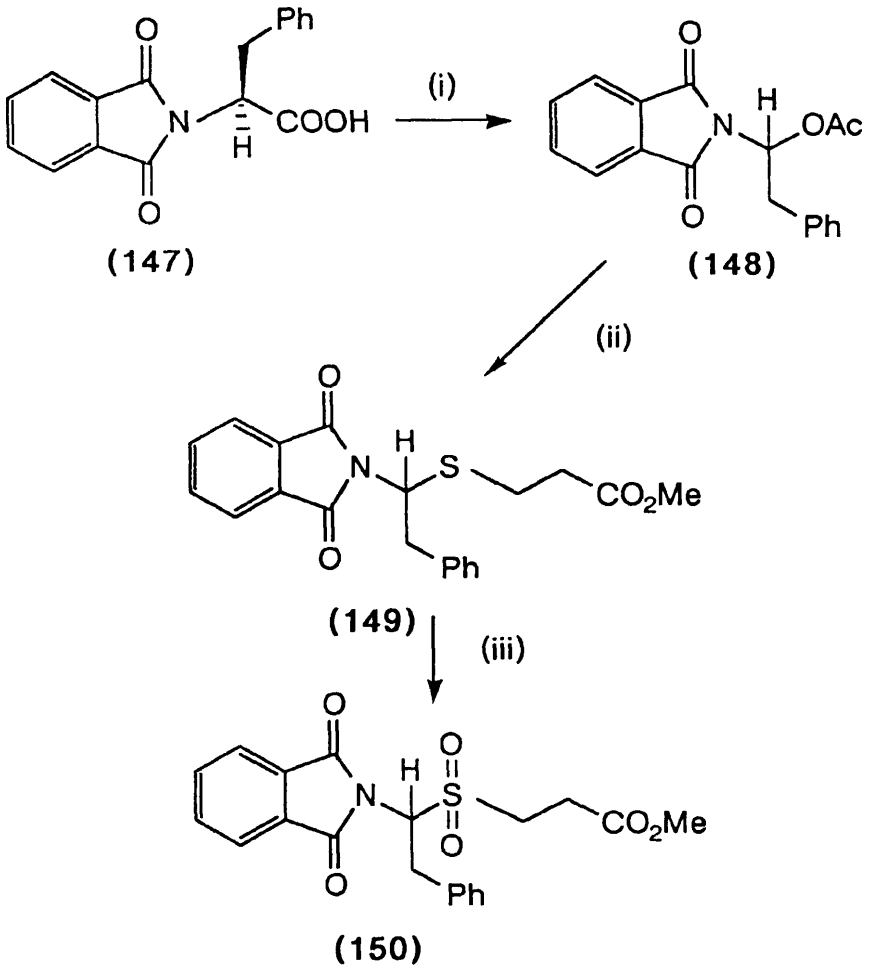


(145)



(146)

Attention was then turned to the preparation of the sulphinic acid **(146)**. It was planned to adopt a similar methodology to that used in the preparation of the α-(phthalimido)ethane sulphinic acid **(109)**. Scheme 30 outlines the route taken to prepare the sulphone **(150)**.

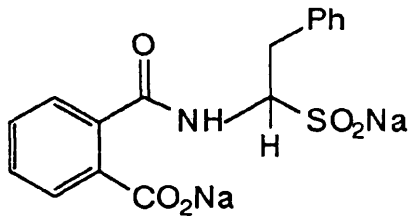


Scheme 30

Reagents : (i) $Pb(OAc)_4$, (ii) $HS(CH_2)_2CO_2Me$, $BF_3{\cdot}Et_2O$, (iii) $KMnO_4$

The Billman and Harting fusion-hydrolysis method[90] was used to prepare N-phthaloyl-L-phenylalanine, which was then reacted with lead(IV) acetate containing pyridine to afford the acetate **(148)** (63%). Compound **(148)**, on reaction with methyl 3-mercaptopropionate and boron trifluoride etherate, gave the sulphide **(149)** (93%). Oxidation of the sulphide **(149)** with potassium permanganate then afforded the sulphone **(150)** (81%). Treatment of the sulphone **(150)** with DBN followed by an acidic work-up gave the required sulphinic acid **(146)** in 61% yield.

The sulphinic acid **(146)** was reacted with sodium hydroxide in aqueous THF to afford the monoacylated salt **(151)** in 80% yield. Clearly, the isolation of this salt implied that the α-benzylamino sulphinic acid **(130)** was stable when the amino group was monoacylated and the acid was present as a salt.

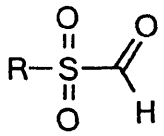


(151)

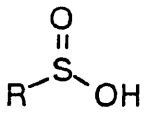
3) From L-Cysteine or D-Penicillamine and Aldehydes

a) Thiazoline Route

The feasibility of generating the sulphinic acid group on a preformed dipeptide backbone was examined. It was considered that sulphonyl formates of type **(152)** might fragment to sulphinic acids of type **(153)** and carbon monoxide under mild conditions.



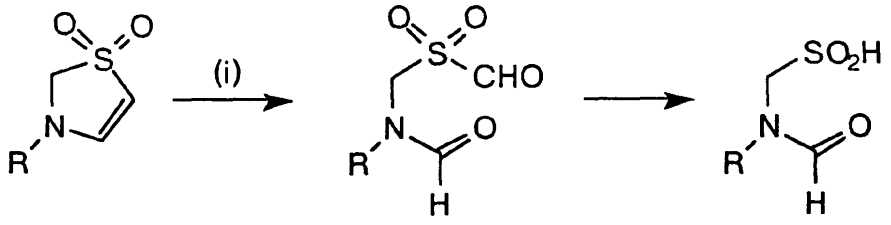
(152)



(153)

Accordingly, the possibility of converting 4-thiazolidine 1,1-dioxides of type **(154)** into sulphinic acids of type **(156)** via formates of type **(155)** was

considered. The selection of the R group as a protected glycine unit would furnish, after deprotection, a dipeptide (Scheme 31).



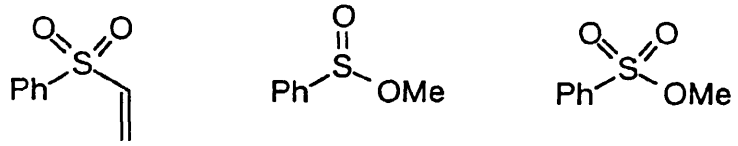
(154) **(155)** **(156)**

R = $PhCH_2OCO$

Scheme 31

Reagents : (i) O_3, - 78 °C, Me_2S

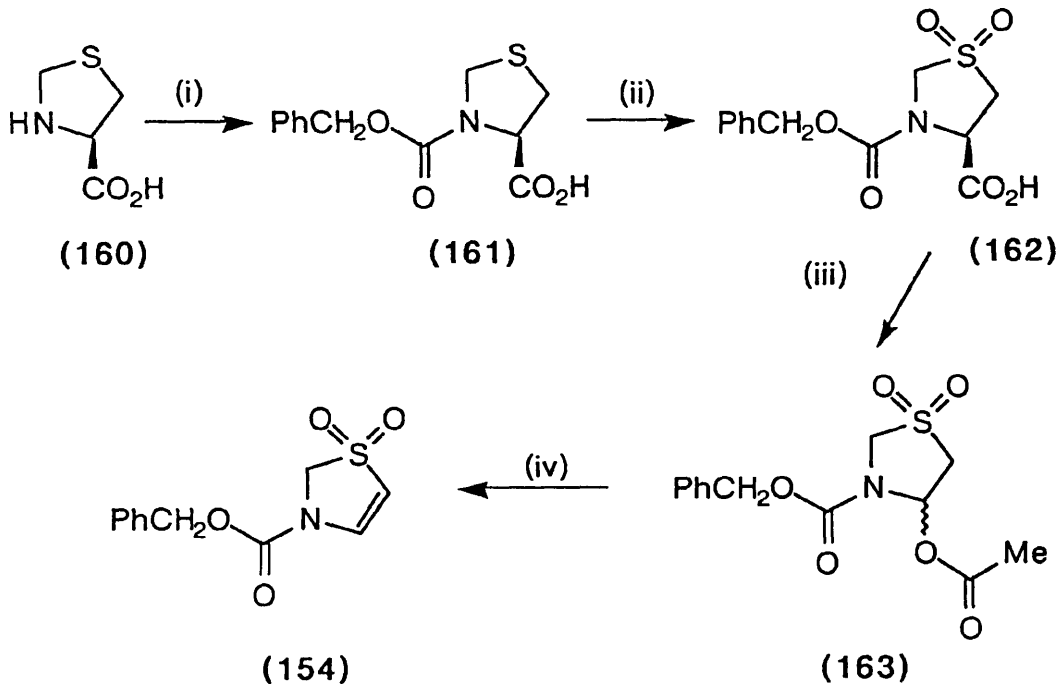
It was decided to examine the feasibility of the key decarbonylation step upon the model compound, phenyl vinyl sulphone **(157)**. Thus, treatment of this compound **(157)** with ozone in dry dichloromethane at -78 °C, followed by a reductive work-up with dimethyl sulphide, afforded an acidic material, which was treated with an excess of diazomethane. The product was found to be a 2:1 mixture of methyl benzenesulphinate **(158)** and methyl benzenesulphonate **(159)**.



(157) **(158)** **(159)**

The formation of some of the sulphinic acid in this reaction directed attention to the preparation of the thiazoline **(154)**

Compound **(154)** would be prepared by the route outlined in Scheme 32. The key reaction step would be the oxidative decarboxylation of the carboxylic acid **(162)**.



Scheme 32

Reagents : (i) $PhCH_2OCOCl$, (ii) $KMnO_4$, (iii) $Pb(OAc)_4$, (iv) DBU

The urethane **(161)** was easily prepared from the thiazolidine **(160)**[93] in 80% yield as an oil. Oxidation of compound **(161)** to the sulphone **(162)** was best achieved by using potassium permanganate; in this way, compound **(162)** was obtained in 55% yield.

Treatment of the carboxylic acid **(162)** with lead(IV) acetate, according to the conditions of Corey and Casanova,[91] afforded a syrupy 4:1 mixture of the acetate **(163)** and the thiazoline **(154)**. Exposure of this mixture to 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) in deuteriochloroform

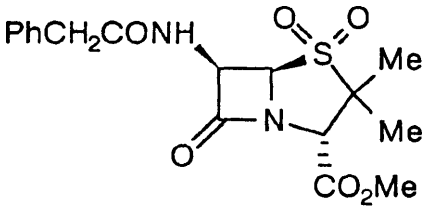
smoothly transformed the acetate **(163)** into the thiazolidine **(154)**, which was isolated in 60% yield as a white solid.

With compound **(154)** in hand, attention was turned to effecting the transformation shown in Scheme 31. However, only limited success was achieved in preparing sulphinic acids from the thiazoline **(154)**.

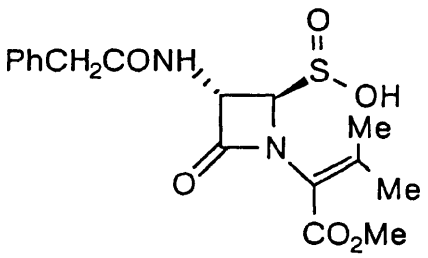
b) Thiazolidine Route

i) α-Amino Sulphinic Acids

An extension of the β-elimination methodology, developed by Mahmoud for the preparation of the sodium salt **(97)**,[81] was next examined. Pant[80] has shown that penicillinate 1,1-dioxides, e.g. **(164)**, undergo epimerisation and β-elimination in the presence of DBN, to afford substituted α-amino sulphinic acids, e.g. **(165)**.



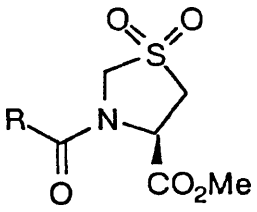
(164)



(165)

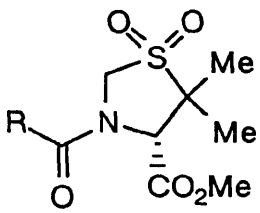
Mahmoud[81] has extended the β-elimination reaction to thiazolidine sulphones of type **(166)** and **(167)** derived from L-cysteine and D-penicillamine, respectively. In the former series, only the thiazolidines **(166c-e)** gave rise to the sulphinic acids **(168c-e)** as isolable entities. In the latter series, the thiazolidines **(167a-c)** afforded the sulphinic acids **(169a-c)**, although the N-formyl derivative **(169a)** was unstable at room

temperature. The isolation of sulphinic acids of type **(168)** and **(169)** appears to be a function of the electron-withdrawing capabilities of the nitrogen substitutent and the presence of substitution on the double bond.



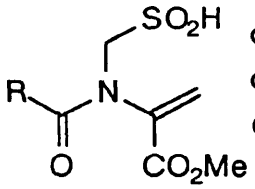
(166)

a : R = H
b : R = Me
c : R = CF_3
d : R = $PhCH_2O$
e : R = Bu^tO



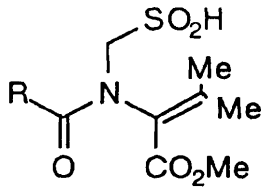
(167)

a : R = H
b : R = Me
c : R = CF_3



c : R = CF_3
d : R = $PhCH_2O$
e : R = Bu^tO

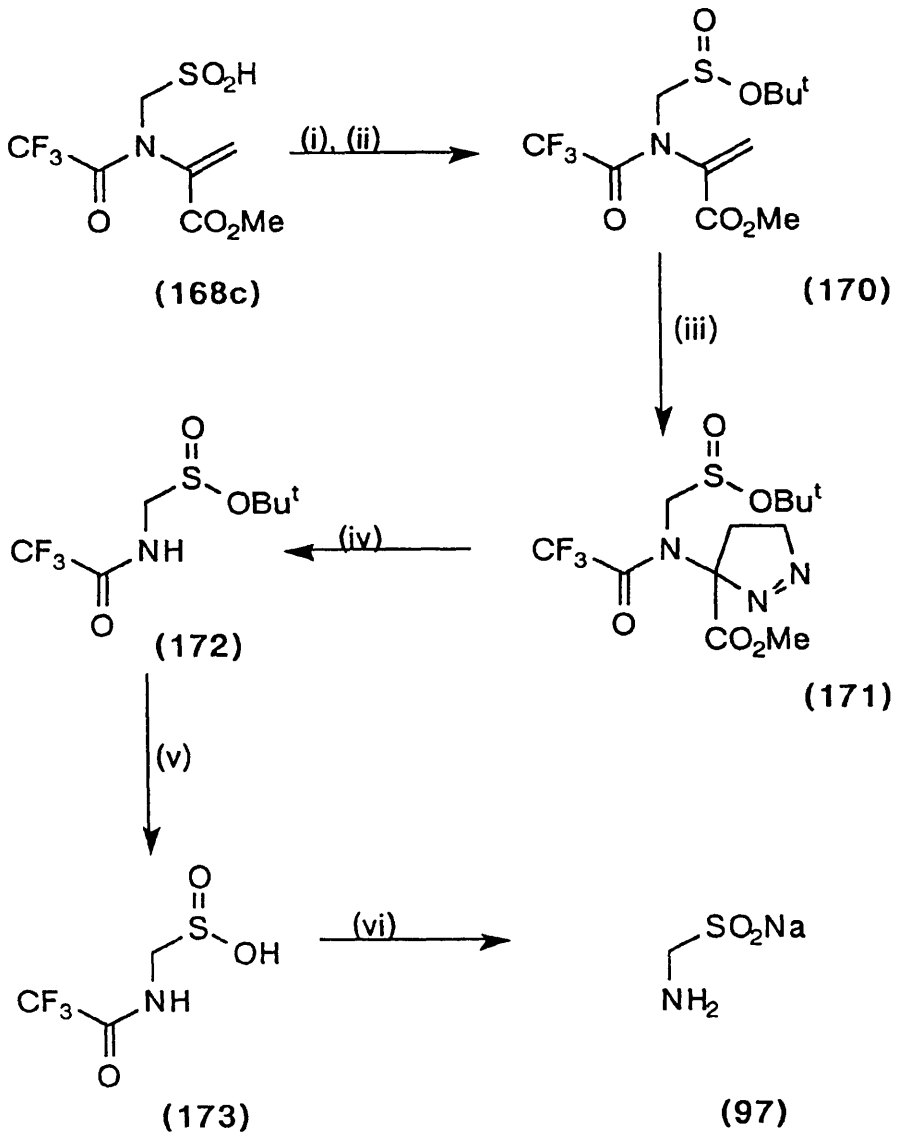
(168)



a : R = H
b : R = Me
c : R = CF_3

(169)

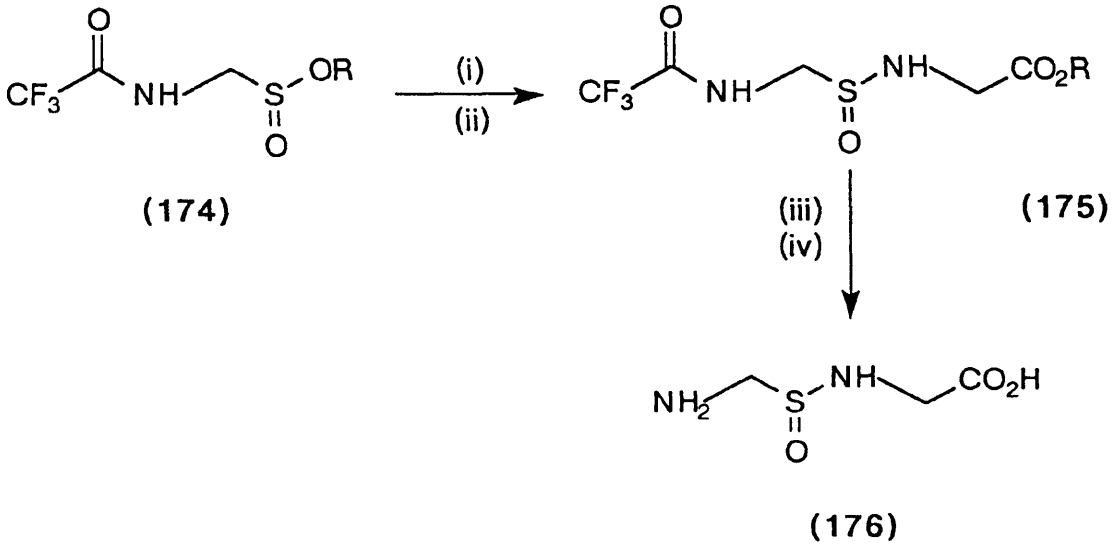
In certain cases, the sulphinic acids were further transformed. Thus, the trifluoroacetyl derivative **(168c)** was converted into sodium α-aminomethanesulphinate **(97)** by the route shown in Scheme 33.



Scheme 33

Reagents : (i) $SOCl_2$, (ii) ^tBuOH, (iii) CH_2N_2, (iv) Zn / AcOH, (v) CF_3CO_2H, (vi) NaOH.

Attention was turned to the synthesis of the alternative dipeptide **(176)** containing a terminal glycine and internal α-aminomethanesulphinic acid moiety. The ready availability of the trifluoroacetylated sulphinate ester **(172)** prompted an investigation of the route shown in Scheme 34.

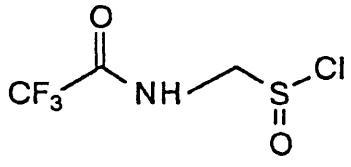


(174) (175) (176)

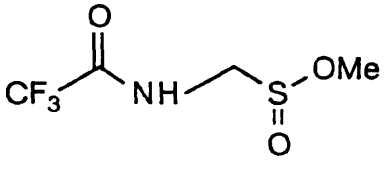
Scheme 34

Reagents : (i) $SOCl_2$, (ii) $NH_2CH_2CO_2R$, (iii) H^+, (iv) OH^-

It was planned to couple an ester of type **(174)** with a glycine derivative to afford a dipeptide derivative of type **(175)**. Removal of the protecting groups would then furnish the dipeptide **(176)**. The sulphinate ester **(172)**, prepared according to the route shown in Scheme 33, was quantitatively converted into the sulphinyl chloride **(177)** upon exposure to thionyl chloride. Proof for the formation of compound **(177)** was obtained by its reaction with methanol, which afforded the methyl ester **(178)** (82%).

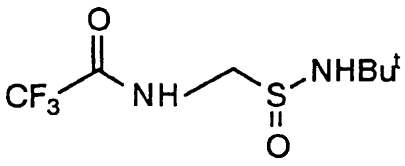


(177)

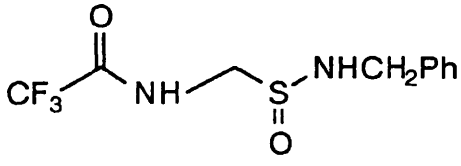


(178)

The reaction of the sulphinyl chloride **(177)** with amines was next examined. When the chloride **(177)** was treated with an excess of tert-butylamine, very little material was recovered on work-up and there was no evidence for the formation of the sulphinamide **(179)**. Similarly, when the chloride **(177)** was treated with benzylamine-triethylamine, there was no evidence for the production of the sulphinamide **(180)**.



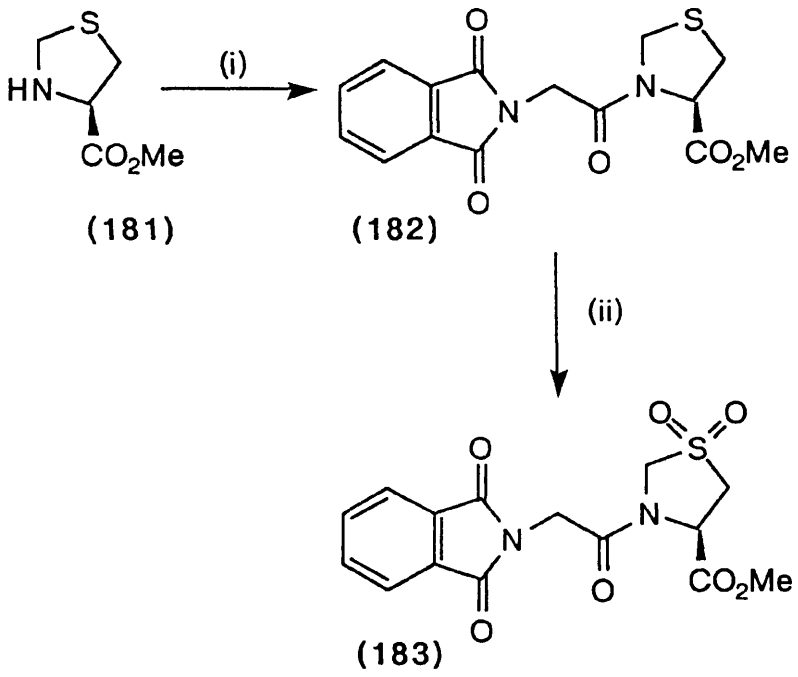
(179)



(180)

ii) Dipeptides Based Upon α-Amino Sulphinic Acids

The overall yield of compound **(97)** (Scheme 33) was poor (3% over 10 steps) so attention was turned to Scheme 35, which outlines the route envisaged to prepare the sulphone **(183)**. The methyl ester **(181)** was prepared from the thiazolidine-4-carboxylic acid **(160)**[92-93] in 72% yield. It was then reacted with phthaloylglycyl chloride[94] in dichloromethane containing triethylamine to give the sulphide **(182)** in 73% yield. The sulphone **(183)** was obtained in 76% yield, by oxidation of compound **(182)** with potassium permanganate in aqueous acetic acid.

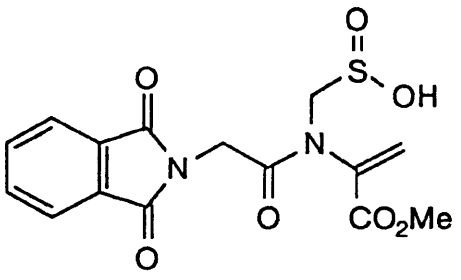


Scheme 35

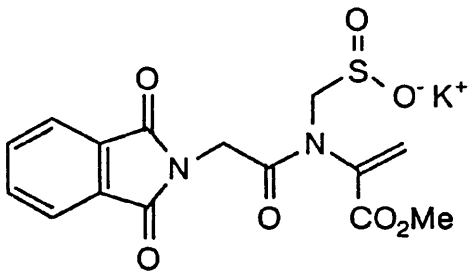
Reagents : (i) phthaloylglycyl chloride, (ii) $KMnO_4$ / AcOH

Having obtained the sulphone **(183)**, attention was then turned to performing the key β-elimination step. When compound **(183)** was treated with DBN, acidic work-up furnished the sulphinic acid **(184)** in 43% yield. The transformation of the sulphinic acid **(184)** into a dipeptide requires the removal of the acrylate portion and the phthalimido protecting group. However, in view of the modest yield of the sulphinic acid **(184)** and the importance of the β-elimination as the key reaction step, the behaviour of the sulphone **(183)** towards potassium tert-butoxide in THF at -78 °C was examined. The potassium salt **(185)** was produced and it reacted with iodomethane to give the methyl sulphone **(186)** in 71% yield.

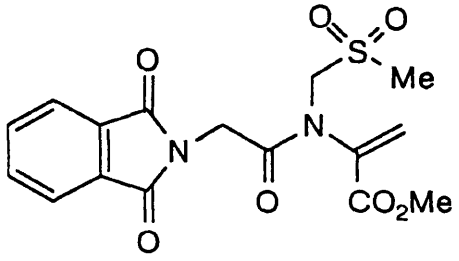
Unfortunately, no characterisable material was obtained when the salt was treated with Amberlite IR 120 (H^+) ion-exchange resin.



(184)

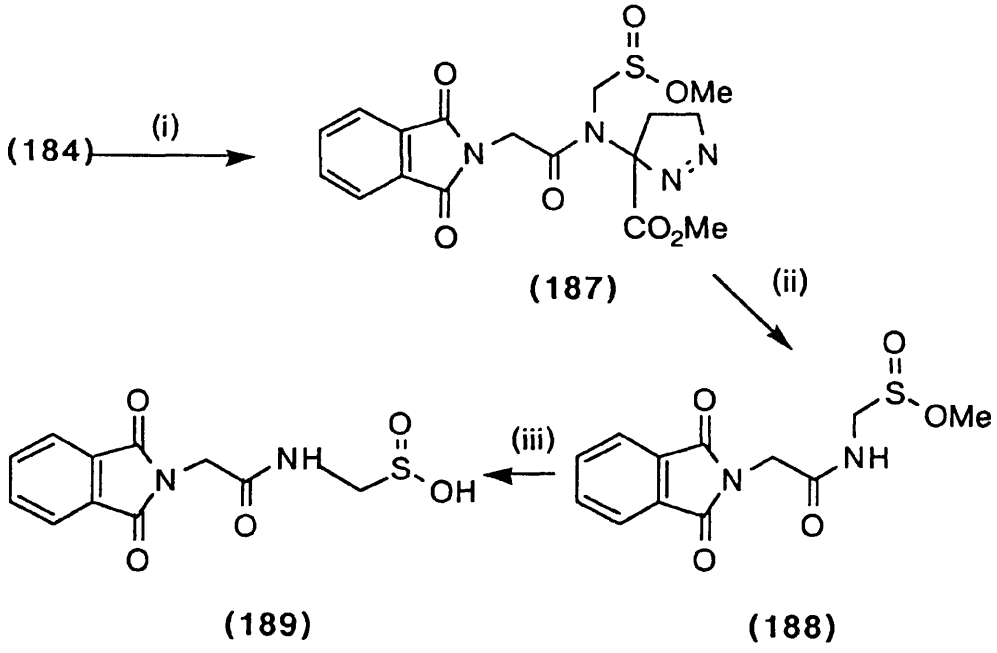


(185)



(186)

Reasoning that the unmasking of the amino group should be a late step in the synthesis, attention was then turned to the removal of the acrylate moiety of compound **(184)**. Accordingly, the feasibility of the route shown in Scheme 36 was next examined.



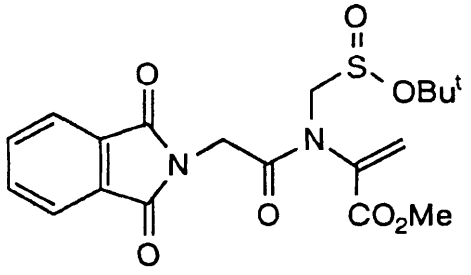
(189) (188)

Scheme 36

Reagents : (i) CH_2N_2, (ii) Zn / AcOH, (iii) H^+

Compound **(184)** reacted with an excess of diazomethane to afford the pyrazoline **(187)** in 61 % yield. When this pyrazoline was treated with zinc in aqueous acetic acid, an intractable mixture of products was obtained, with no evidence for the dipeptide derivative **(188)**.

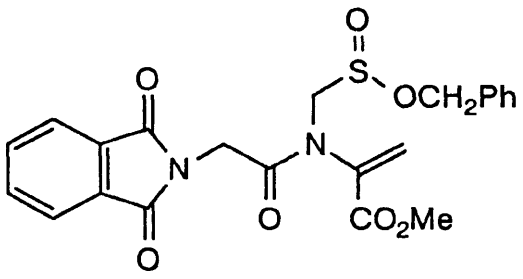
The failure to isolate the ester **(188)** prompted an examination of other protecting groups for the sulphinic acid moiety of compound **(184)**. Attempts to prepare the tert-butyl ester **(190)** from the reaction of the sulphinic acid **(184)** with thionyl chloride-tert butyl alcohol were unsuccessful. The ester did result, however, when the potassium salt **(185)** was treated sequentially with oxalyl chloride-tert butyl alcohol; compound **(190)** was obtained in 54% yield. Unfortunately, the reaction proved to be capricious and useful quantities of the ester **(190)** could not subsequently be obtained.



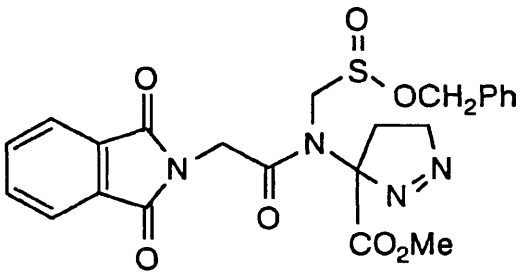
(190)

Mixed anhydrides react with alcohols to form esters. The reaction of the potassium salt **(185)** with ethyl chloroformate-tert-butyl alcohol was investigated but, unfortunately, intractable mixtures of products were obtained.

However, when the sulphone **(183)** was treated sequentially with DBN then benzyl chloroformate, the benzyl sulphinate **(191)** was obtained in 53% yield. Compound **(191)** reacted smoothly with diazomethane to afford the Δ^1-pyrazoline **(192)** in essentially quantitative yield.

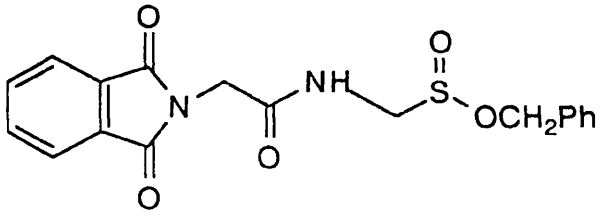


(191)

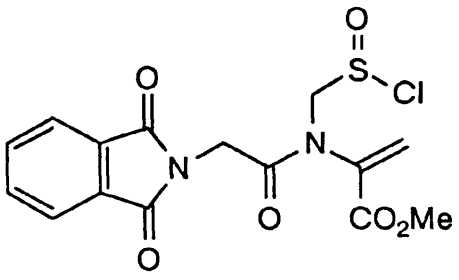


(192)

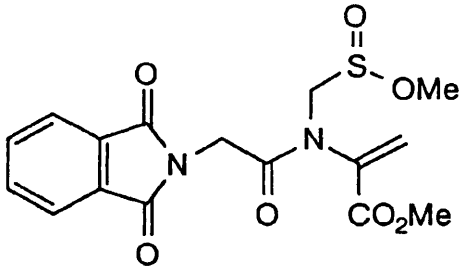
The pyrazoline **(192)** also underwent reaction with zinc in aqueous acetic acid-acetone to afford the dipeptide derivative **(193)** in 24% yield. Earlier work at Newcastle had established that penicillinate-derived sulphinate esters could be converted into the corresponding sulphinyl chlorides by treatment with thionyl chloride.[84] The sulphinate **(191)** was slowly converted into the sulphinyl chloride **(194)** by reaction with thionyl chloride. As hoped, the sulphinyl chloride **(194)** reacted with tert-butyl alcohol to afford the tert-butyl ester **(190)** (69%) and with methanol to afford the methyl ester **(195)** (55%).



(193)



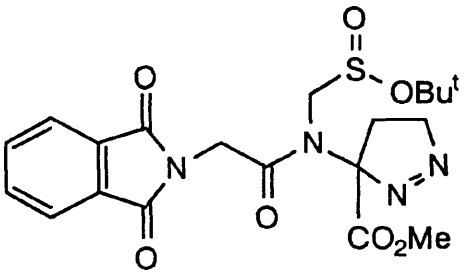
(194)



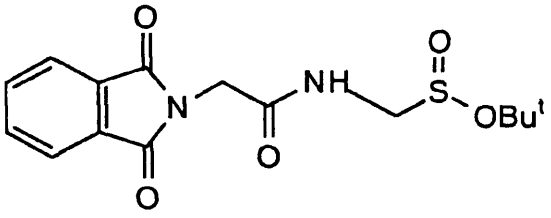
(195)

Having discovered a reliable route to the tert-butyl ester **(190)**, attention was turned to the removal of the acrylate portion. Compound **(190)** was converted into the Δ^1-pyrazoline **(196)** by the action of diazomethane in 84% yield. This pyrazoline **(196)** was then treated with zinc in aqueous acetic acid-acetone to afford a mixture of the dipeptide derivative **(197)** (26%) and the carbinol **(198)** (30%).

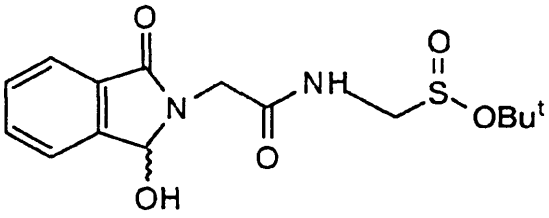
Proof for the structure of the carbinol **(198)** came from its conversion into the acetate **(199)**, upon reaction with acetic anhydride-pyridine-4-dimethylaminopyridine (DMAP). The compound **(199)** was obtained as a 1:1 mixture of diastereoisomers in 66% yield.



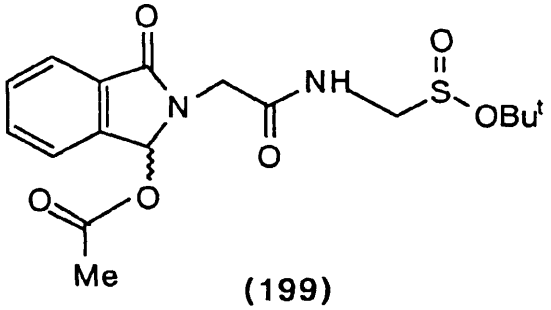
(196)



(197)



(198)



(199)

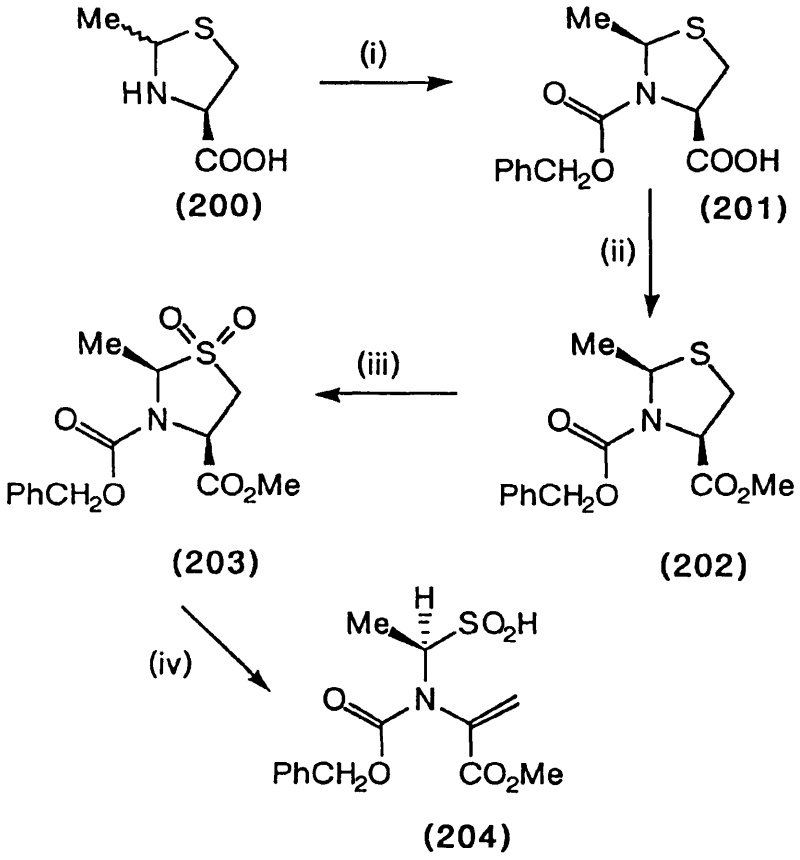
The carbinol **(198)** was presumed to arise by over-reduction of the imide **(197)** and this occurred to a significant extent even with short reaction times. So it was considered worthwhile to examine means of converting the alcohol **(198)** into the imide **(197)**.

Chromium(VI)-based oxidising agents are well known for the oxidation of secondary alcohols to ketones,[95] and the carbinol **(198)** was smoothly converted into the imide **(197)** (71%) upon exposure to pyridinium dichromate in dichloromethane.

Attention was finally turned to the removal of the tert-butyl group from compound **(197)** in the hope of obtaining compound **(189)**. Perrone and Stoodley[84] have used trifluoroacetic acid for removing the tert-butyl group from penicillinate-derived sulphinate esters. Exposure of the ester **(197)** to trifluoroacetic acid in deuteriochloroform afforded a new volatile tert-butyl containing material; however, work-up did not give the sulphinic acid **(189)**. Seemingly, compound **(189)** was unstable to the acidic conditions.

iii) α-Substituted α-Amino Sulphinic Acids

The synthesis of α-aminoethanesulphinic acid **(129)** (alanine analogue) and the α-aminobenzyl sulphinic acid **(130)** (phenylalanine analogue) was examined. The sulphinic acid **(204)** had been prepared by Mahmoud[81] previously from the reaction of DBN with the sulphone **(203)** followed by an acidic work-up (Scheme 37).

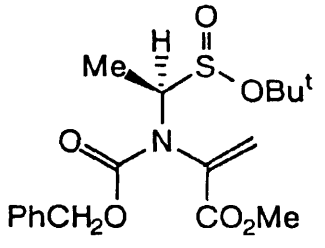


Scheme 37

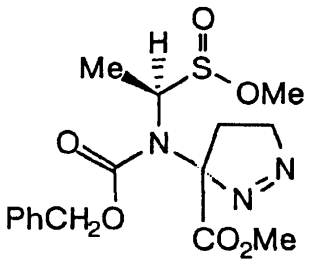
Reagents : (i) $PhCH_2OCOCl$, (ii) CH_2N_2, (iii) $KMnO_4$, (iv) DBN/H^+

Acylations of thiazolidine derivatives are known to be cis-selective,[96] so the absolute stereochemistry of the acid **(201)** was assigned (2R,4R). The methyl ester **(202)** was obtained in 95% yield by esterification of the acid **(201)** with diazomethane; ^{1}H n.m.r. spectroscopy of compound **(202)** showed that only one diastereoisomer was present. The sulphone **(203)** was obtained in 62% yield by the reaction of the sulphide **(202)** with potassium permanganate in aqueous acetic acid; the 300 MHz ^{1}H n.m.r. spectrum (CD_3SOCD_3, 373 K) of the sulphone **(203)** indicated that it was a single isomer.

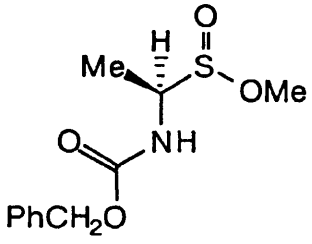
Reaction of the sulphone **(203)** with DBU followed by an acidic work-up afforded the sulphinic acid **(204)** in 69% yield. Attempts to convert the sulphinic acid **(204)** into the tert-butyl ester **(205)** by treatment with thionyl chloride then tert-butyl alcohol failed. However, the pyrazoline **(206)** was obtained by the reaction of the sulphinic acid **(204)** with an excess of diazomethane. Unfortunately, attempts to convert the pyrazoline **(206)** into the ester **(207)** by employing Barton's reducing conditions (Zn, HOAc, H_2O)[97] were unsuccessful.



(205)

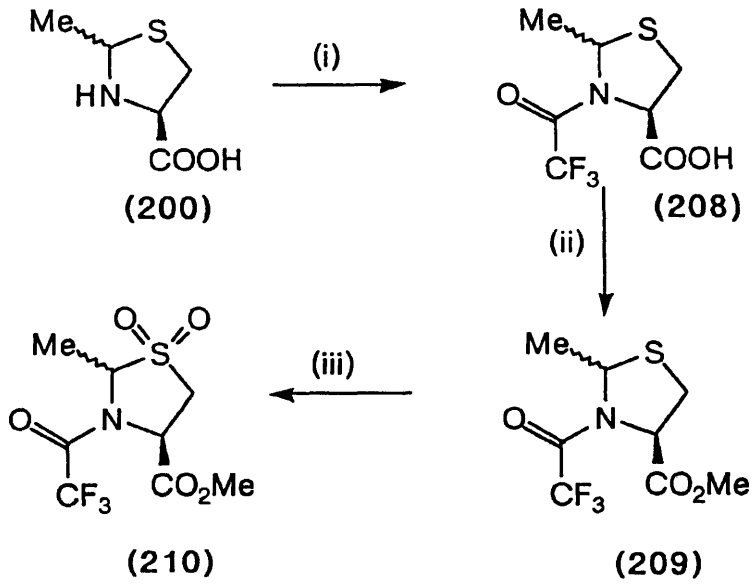


(206)



(207)

It was suggested that, if appropriate nitrogen protection was selected, it would be possible to prepare the sulphinic acid **(129)**. With this in mind, the preparation of the sulphone **(210)** was investigated (Scheme 38).



Scheme 38

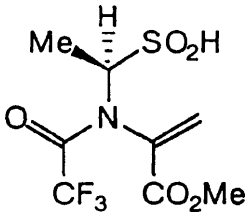
Reagents : (i) $(CF_3CO)_2O$, (ii) CH_2N_2 or MeI/Et_3N, (iii) $KMnO_4$

300 MHz ^1H N.m.r. spectroscopy clearly showed that compound **(208)** was a 1:1 mixture of diastereoisomers. Evidently, acylation of the thiazolidine **(200)** employing trifluoroacetic anhydride has proceeded non-stereoselectively.

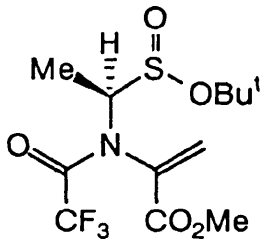
Oxidation of the sulphide **(209)** afforded the sulphone **(210)**, as a 1:1 mixture of diastereoisomers on the basis of 300 MHz ^1H n.m.r. spectroscopy. However, crystallisation of the crude sulphone **(210)** afforded a single diastereoisomer; the mother liquors from the crystallisation showed a 3.5:1 mixture of diastereoisomers. The optical rotation {$[\alpha]_D$ -22 ° ($CHCl_3$)} of the diastereomically pure sulphone **(210)** was similar to that of compound **(202)** {$[\alpha]_D$ -37 ° ($CHCl_3$)} suggesting that compound **(209)** possessed the (2R,4R) stereochemistry.

The sulphone **(210)** underwent reaction with DBN to afford, after an acidic work-up, the sulphinic acid **(211)**. Synthesis of the alanine analogue

(129) from the sulphinic acid (211) requires removal of the acrylate portion. When compound (211) was treated with thionyl chloride then tert-butyl alcohol, there was no evidence for the formation of the tert-butyl ester (212). It would appear that α-substitution was not compatible with esterification using the aforecited conditions.

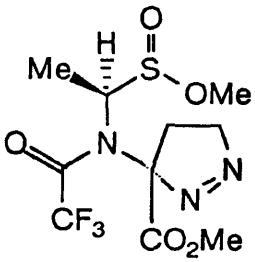


(211)

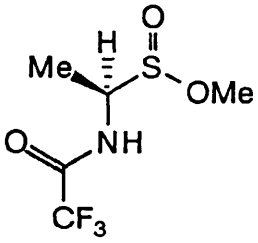


(212)

However, the pyrazoline (213) was obtained by the reaction of the sulphinic acid (211) with an excess of ethereal diazomethane. When the pyrazoline (213) was subjected to Barton's reducing conditions[97] (Zn, HOAc, H_2O), the sulphinate (214) was isolated which was shown by 300 MHz ^1H n.m.r. spectroscopy to exist as a 1:1 mixture of diastereoisomers. The optical rotation {$[\alpha]_D$ +150 ° ($CHCl_3$)} clearly indicated that racemisation had not occurred as a result of the (210) → (214) transformation; this suggested that the absolute configuration at C2 in the sulphone (209), considered to be (2R), was preserved to give the ester (214).

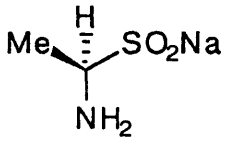


(213)

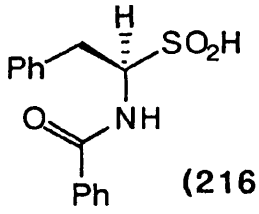


(214)

Finally, reaction of this ester **(214)** with two molar equivalents of sodium hydroxide in water afforded a 1:1 mixture of (R)-(-)-sodium α-aminoethanesulphinate **(215)** and sodium trifluoroacetate. The optical rotation {$[\alpha]_D$ -28 ° (H_2O)} of the mixture clearly showed that racemisation had not occurred [the rotation was calculated on the basis that **(215)** comprised 50 % of the product].

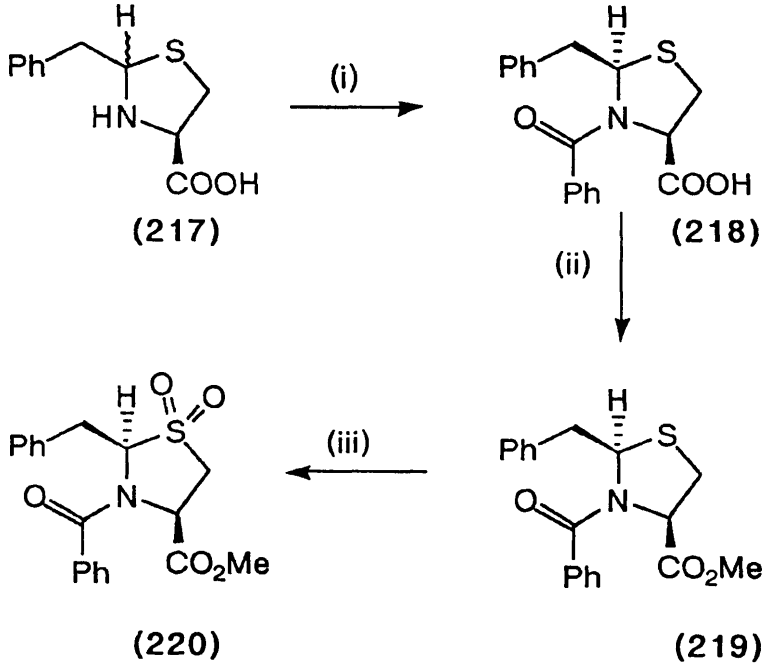


(215)



(216)

The preparation of the phenylalanine analogue **(216)** was also examined The thiazolidine sulphone **(220)** was prepared as shown in Scheme 39.



(217) **(218)** **(219)** **(220)**

Scheme 39

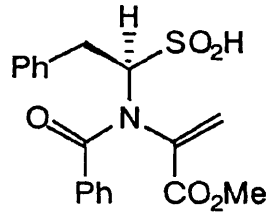
Reagents : (i)PhCOCl, (ii) MeOH/HCl, (iii) $KMnO_4$

Reaction of L-cysteine and phenylacetaldehyde afforded the thiazolidine **(217)** (60%) which, on the basis of 300 MHz ^1H n.m.r. spectroscopy, was present as a 1:1 mixture of diastereoisomers.

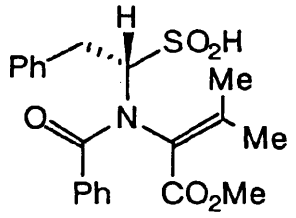
Reaction of this thiazolidine **(217)** with benzoyl chloride in aqueous sodium hydroxide afforded the thiazolidine sulphide **(218)** (96%) which, on the basis of 300 MHz ^1H n.m.r. spectroscopy, existed as a single diastereoisomer.

Clearly, the acylation of compound **(217)** with benzoyl chloride had proceeded stereoselectively. The absolute configuration was assigned as (2R, 4R), on the basis of analogy to compound **(209)**.

The sulphone **(220)** was a single diastereoisomer. However, the reaction of this compound with DBN followed by an acidic work-up failed to afford the sulphinic acid **(221)**, even though ^1H n.m.r. spectroscopy showed signals attributable to the olefinic protons during the course of the reaction.



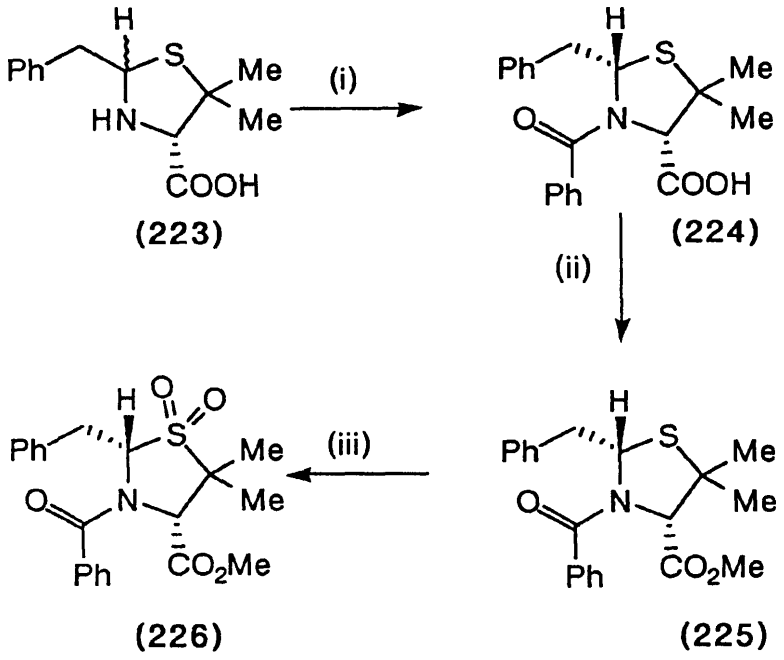
(221)



(222)

The failure to isolate the sulphinic acid **(221)** then turned attention to the preparation of the sulphinic acid **(222)**. It was hoped that gem-dimethyl substitution of the acrylate portion of the sulphinic acid **(222)** would lead to

stability in the structure. The sulphone **(226)** was obtained by the route shown in Scheme 40.



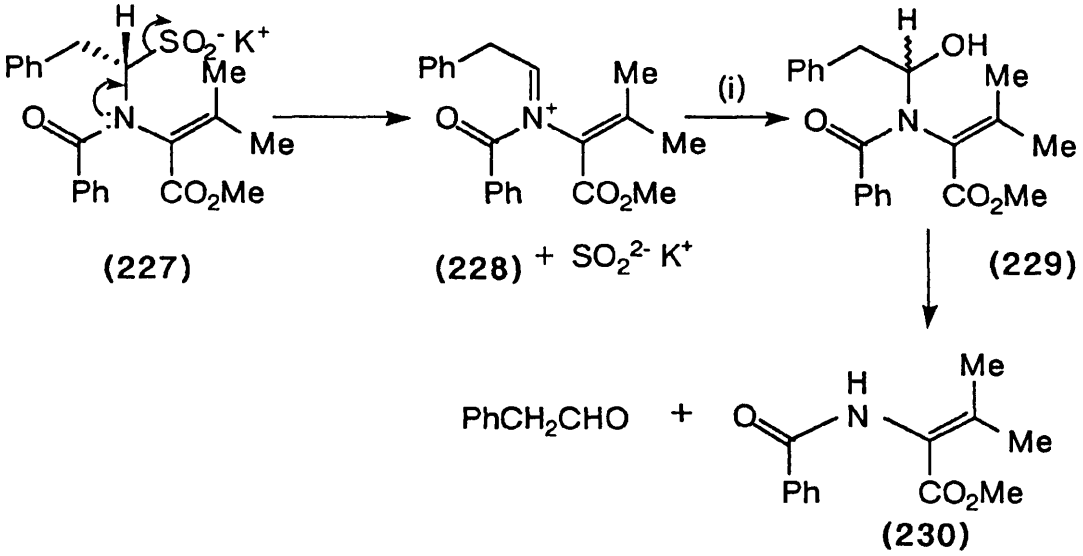
Scheme 40

Reagents : (i) PhCOCl, (ii) CH_2N_2, (iii) $KMnO_4$

The sequential reaction of D-penicillamine with phenylacetaldehyde, benzoyl chloride, and diazomethane afforded the thiazolidine sulphide **(225)** (24%). 300 MHz ^1H N.m.r. spectroscopy clearly showed the sulphide **(225)** was present as a single diastereoisomer. The sulphone **(226)** was then obtained in 51% yield by oxidation of the sulphide **(225)**; again, on the basis of ^1H n.m.r. spectroscopy, it was a single diastereoisomer.

It was assumed that the acylations were cis-stereoselective; hence the absolute configuration of compounds **(225)** and **(226)** was assigned as (2S,4S).

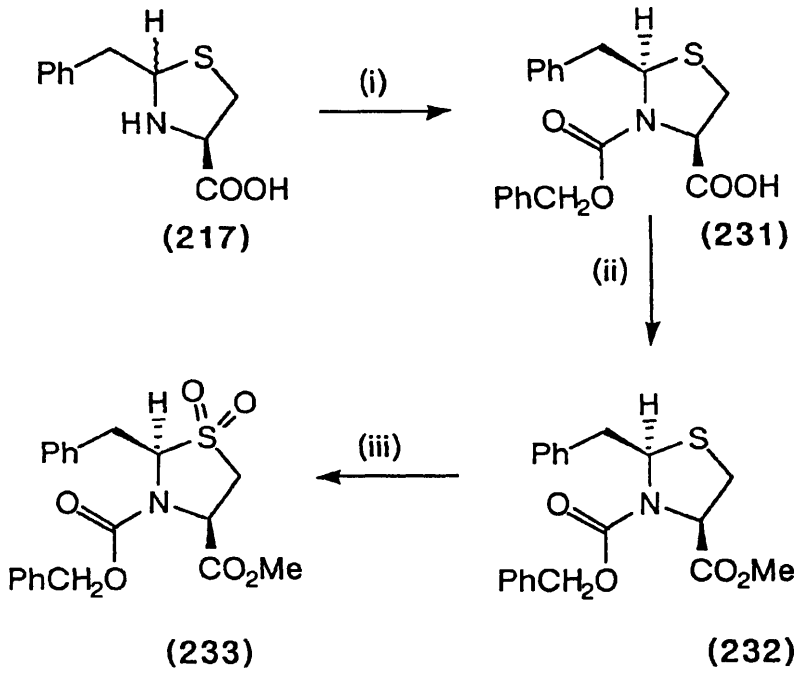
With the sulphone **(226)** in hand, the key β-elimination step was attempted. The reaction of the sulphone **(226)** with DBN followed by an acidic work-up did not furnish the sulphinic acid **(222)**. Reaction of the thiazolidine **(226)** with potassium tert-butoxide afforded a complex mixture of products, from which was isolated the enamide **(230)**. This was presumed to have formed by the route outlined in Scheme 41.



Scheme 41

Reagents : (i) H_2O

It was decided to investigate the effect of the benzyloxycarbonyl group on the stability of the sulphinic acids.[81] The sulphone **(233)** was obtained by the route outlined in Scheme 42.

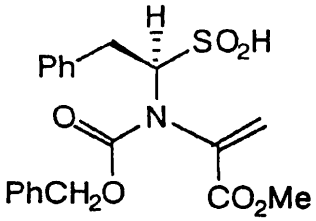


Scheme 42

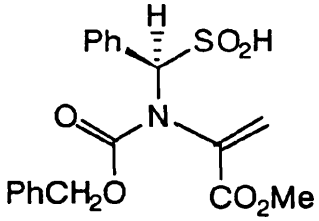
Reagents : (i) $PhCH_2OCOCl$, (ii) CH_2N_2, (iii) $KMnO_4$

On the basis of 300 MHz ^1H n.m.r. spectroscopy, the sulphone **(233)** existed as a single diastereoisomer. Its absolute stereochemistry at C2 was assigned (R) on the basis of the close similarity of its n.m.r. chemical shifts to those of the sulphone **(220)**, and on the geminal and vicinal coupling constants.

The key β-elimination reaction of the sulphone **(233)**, using DBN followed by an acidic work-up, did not give the sulphinic acid **(234)**. Clearly, the benzyloxycarbonyl group was not compatible with the isolation of the sulphinic acid **(234)** but it was for the sulphinic acid **(204)**. It was decided to investigate the possibility of isolating the sulphinic acid **(235)**.

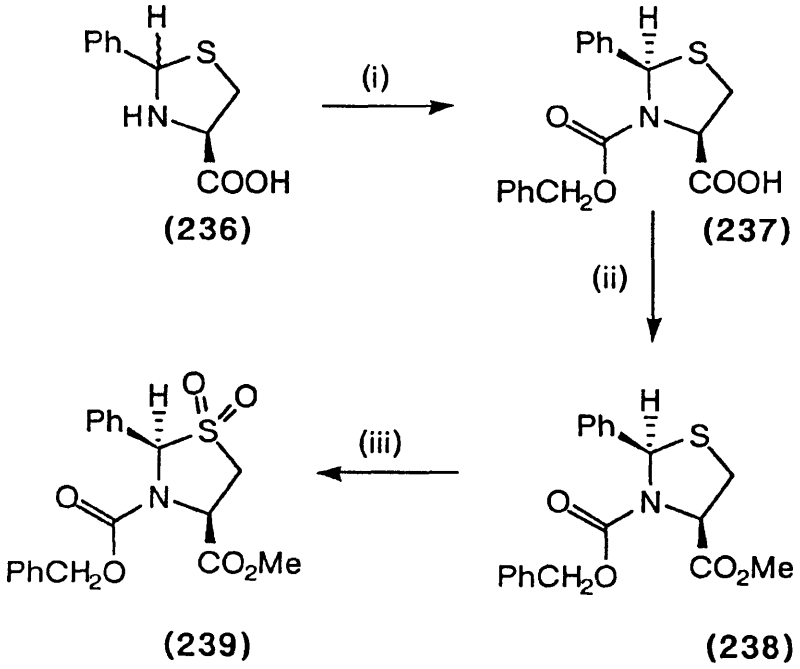


(234)



(235)

The route outlined in Scheme 43 shows the preparation of the sulphinic acid precursor **(239)**. L-Cysteine hydrochloride and benzaldehyde were reacted to afford the thiazolidine **(236)** (90%) which, on the basis of 300 MHz ^{1}H n.m.r. spectroscopy, was a 1:1 mixture of diastereoisomers. Sequential reaction of the thiazolidine **(236)** with benzyl chloroformate, diazomethane, and potassium permanganate afforded the sulphone **(239)** (38% yield) which, on the basis of 300 MHz ^{1}H n.m.r. spectroscopy, was present as a single diastereoisomer and was assigned the absolute configuration (2R, 4R), on the basis of analogy with the sulphones **(220)** and **(233)**.



(236) (237) (238) (239)

Scheme 43

Reagents : (i) $PhCH_2OCOCl$, (ii) CH_2N_2, (iii) $KMnO_4$

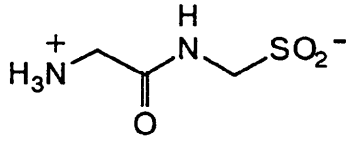
Reaction of the sulphone **(239)** with DBN in deuteriochloroform showed evidence for the formation of olefinic protons, but an acidic work-up did not afford the sulphinic acid **(235)**. Evidently, the reaction or work-up conditions were destructive to the sulphinic acid **(235)**.

DISCUSSION

1. Approaches to the Glycyl-α-aminomethanesulphinic Acid and Related Dipeptide Derivatives

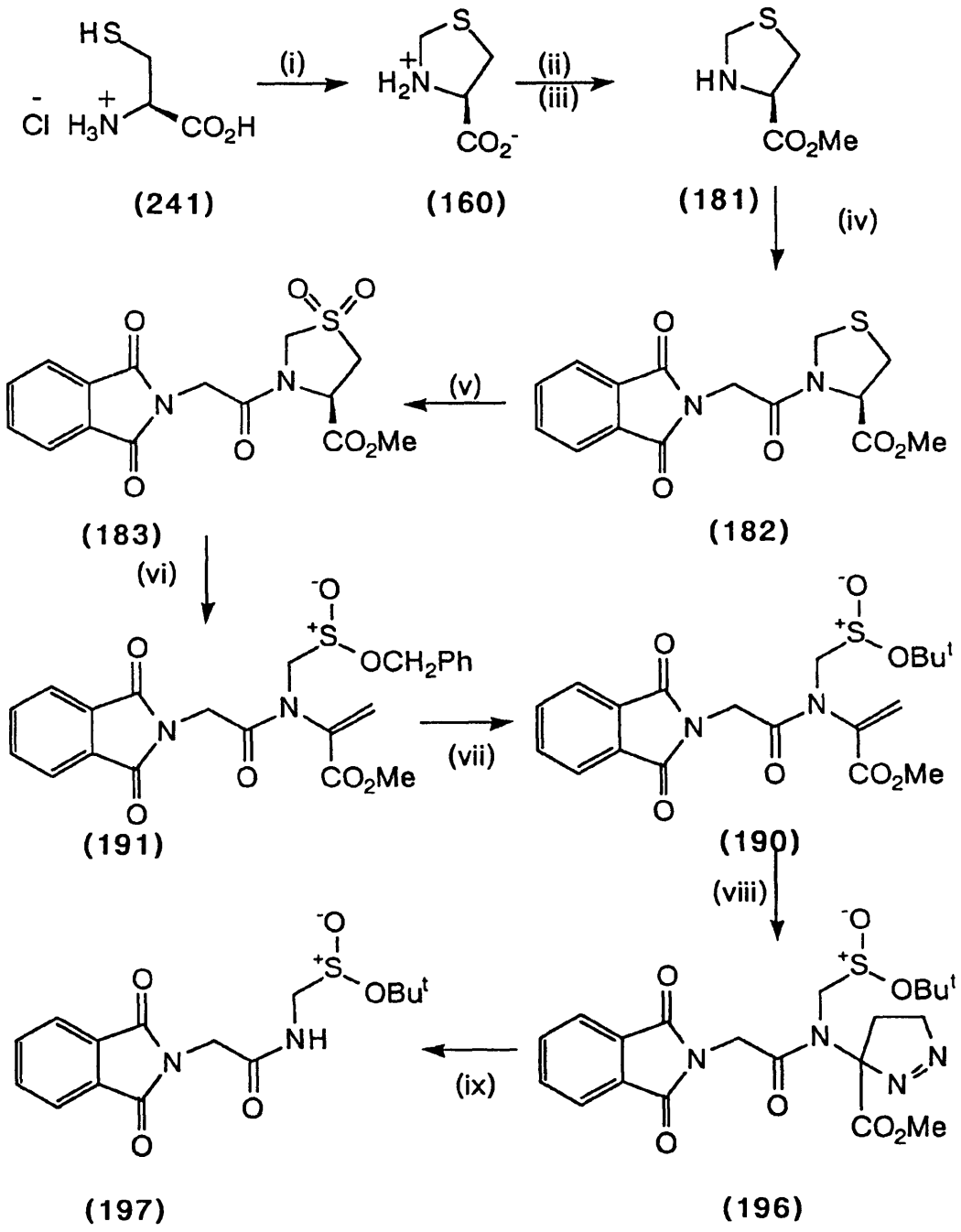
α-Amino sulphinic acids are isosteres of natural α-amino carboxylic acids and so they may be of potential chemotherapeutic value. α-Amino acid analogues in which the carboxy moiety has been replaced by other acidic moieties, e.g. α-amino phosphonic acids, α-amino phosphinic acids, and α-amino sulphonic acids, have been widely studied. However, little work has been done relating to α-amino sulphinic acids.

The aim of the investigation is to construct simple peptide analogues in which the carboxy terminus is replaced by a sulphinic acid moiety, and it was decided that efforts should focus upon the derivation of the glycyl-glycine analogue **(240)**.



(240)

In previous work,[98] compound **(197)** - a protected form of the dipeptide analogue **(240)**, had been prepared. Scheme 44 outlines the synthetic sequence employed.

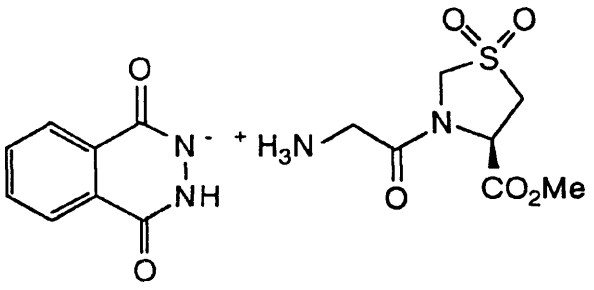


Scheme 44

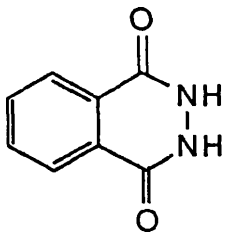
Reagents : (i) HCHO, pyridine, (ii) MeOH / HCl, (iii) Na_2CO_3, (iv) phthaloylglycyl chloride / Et_3N, (v) $KMnO_4$ / HOAc, (vi) DBN, $ClCO_2CH_2Ph$, (vii) $SOCl_2$, Bu^tOH, (viii) CH_2N_2, (ix) Zn / HOAc

Since attempts to remove the phthalimido group from compound **(197)** were unsuccessful, it was necessary to bring forward the deprotection step. Initially, the sulphone **(183)** was selected for study. The sequence outlined in Scheme 44 was used to prepare the sulphone **(183)**. Thus treatment of L-cysteine hydrochloride **(241)** with aqueous formaldehyde followed by pyridine gave, after recrystallisation, the thiazolidine acid **(160)**[93] in 65% yield (Exp.1). The last-cited compound **(160)** reacted with methanolic hydrogen chloride under reflux to give, following neutralisation with sodium carbonate, the methyl ester **(181)**[93] as a clear oil in 73% yield (Exp.2) (D.Barrett quotes 72%). In dichloromethane solution in the presence of triethylamine, the thiazolidine **(181)** underwent acylation with phthaloylglycyl chloride to give the amide **(182)**[98] in 73% yield after recrystallisation (Exp.3) (D. Barrettquotes 73%). Oxidation of the thiazolidine **(182)** to the 1,1-dioxide **(183)**[98] was achieved in 62% yield after recrystallisation by the action of potassium permanganate in aqueous acetic acid (Exp.4) (D. Barrett quotes 76%).

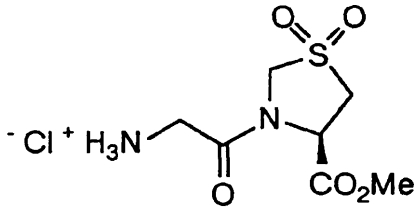
Initially, the Ing-Manske[86] procedure was examined in the hope of converting the phthalimido derivative **(183)** into the amine salt **(242)**. Thus, compound **(183)** was heated in methanol with hydrazine hydrate (1 mol. equiv.) and, after 1.5 h, an insoluble material was removed by filtration (Exp.5). On the basis of i.r. and ^{1}H n.m.r. spectroscopy, the insoluble material was considered to be mainly phthalhydrazide **(119a)** together with some starting material. Evaporation of the filtrate and heating the residue with 2M-hydrochloric acid deposited a further crop of the phthalhydrazide **(119a)**, but there was no sign of the hydrochloride **(243)** on the basis of ^{1}H n.m.r. spectroscopy.



(242)



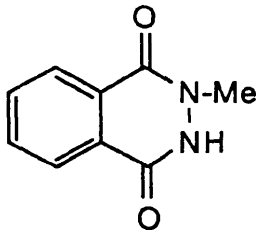
(119a)



(243)

Evidently, the phthaloyl group of the sulphone **(183)** had been removed by hydrazinolysis. To determine whether the failure to isolate the amine hydrochloride **(243)** was due to its acid lability, a different work-up procedure was examined. When the residue was partitioned between sodium hydrogen carbonate solution and ethyl acetate, no material was isolated from the organic layer. Furthermore, a complex mixture of products was formed when the residue was treated with acetyl chloride.

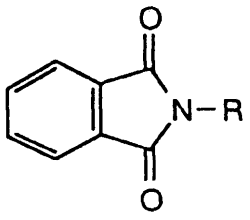
Methylhydrazine has advantages over hydrazine as a reagent for liberating amines from phthalimido derivatives. Thus, it is more reactive (due to the increased nucleophilicity of the methylamino moiety). Moreover, the cleavage product, N-methylphthalhydrazide **(119b)**, has a less acidic hydrogen; salt formation with the liberated amine is therefore not a complication.



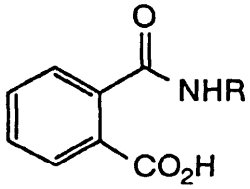
(119b)

In tetrahydrofuran (THF) at room temperature, the phthalimido derivative (183) slowly reacted with methylhydrazine with the deposition of a white precipitate, identified as N-methylphthalhydrazide (119b) (Exp.6). Disappointingly, the residue, obtained by evaporation of the filtrate, was shown to be a complex mixture of products on the basis of t.l.c. and ^{1}H n.m.r. spectroscopy.

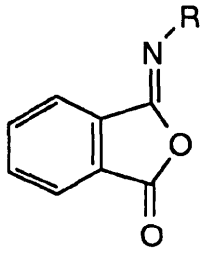
Among alternative methods for the removal of the phthaloyl group, that developed by Kukolja[88] is of some appeal. It involves converting a phthalimido derivative of type (244) into an isoimide of type (246) by way of a phthalimidic acid of type (245). Isoimides of type (246) are much more susceptible to hydrazinolysis than the related phthalimido derivatives of type (244).



(244)



(245)

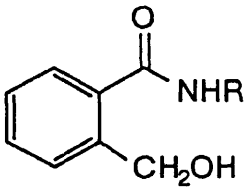


(246)

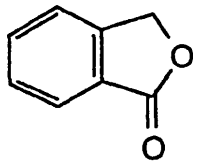
The phthalimido derivative (183) reacted rapidly with sodium hydroxide (1 mol equiv.) to give a water-soluble product which, on the basis of i.r. spectroscopy, no longer contained the phthalimido moiety. However,

300 MHz ^{1}H n.m.r. spectroscopy indicated that the material was a complex mixture.

Ganem[89] has reported that sodium borohydride in aqueous propan-2-ol converts phthalimido derivatives of type **(244)** into alcohols of type **(247)** which react with hot acetic acid to liberate the corresponding amines and the lactone **(248)**.



(247)



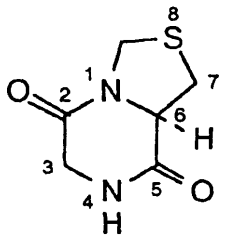
(248)

The sulphone **(183)** reacted with sodium borohydride (4 mol equiv.) in aqueous propan-2-ol / water (6:1) to give, after filtration and concentration of the filtrate, a white solid. Following addition of methanol, acidification [addition of Amberlite 120 (H^+)] and evaporation, a straw-coloured solid was isolated which lacked the phthalimido entity but which contained a mixture of components by ^{1}H n.m.r. spectroscopy.

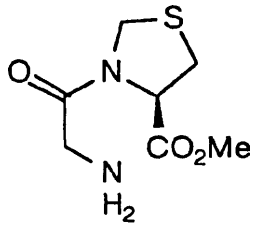
In view of the lack of success in deriving compound **(243)** or its free base, from the sulphone **(183)**, it was decided to attempt to remove the phthalimido group from compound **(182)**. The phthalimido derivative reacted in methanol with hydrazine hydrate (1 mol equiv.) to deposit phthalhydrazide **(119a)** in 68% yield. Evaporation of the filtrate gave a white solid which was purified by flash silica-gel chromatography and recrystallisation from hot propan-2-ol; the product was considered to be the bicycle **(249)** (76% yield) (Exp.7). Evidently, the amine **(250)** is produced and undergoes a spontaneous cyclocondensation to give the bicycle **(249)**.

In accord with the proposed structure, compound **(249)** displayed in its 300 MHz ^{1}H n.m.r. spectrum (CD_3SOCD_3) a broad one-proton triplet at δ 4.30 (separation 8 Hz), for the 6-hydrogen atom and a broad one-proton singlet at δ 8.30, for the amide proton. I.r. absorptions were present at 1 680 and 1 650 cm^{-1} for the two amide carbonyl groups and the mass spectrum of compound **(249)** displayed a peak at m/z 172, attributable to the molecular ion. Additionally, elemental analysis and high-resolution mass spectrometry established the molecular formula as $C_6H_8N_2O_2S$.

The bicycle **(249)** was also prepared by the action of methylhydrazine upon the sulphide **(182)** (Exp.8); it was obtained in 62% yield after purification by silica-gel chromatography. The i.r. and 300 MHz ^{1}H n.m.r. spectroscopic properties of the material were identical with those of the compound obtained in Experiment 7.

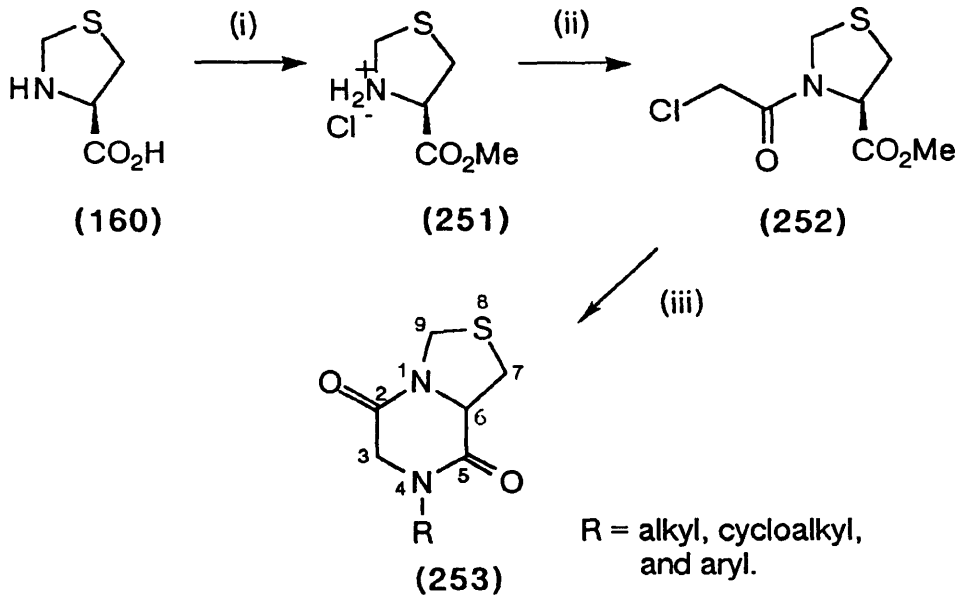


(249)



(250)

Thiazolidinopiperazine-2,5-diones of type **(253)** have been reported in recent work[99]; Scheme 45 outlines the route that was used. Interestingly, almost all of these compounds **(253)** exhibited weak central nervous activity. However some of them were significantly neurosedative; others gave positive responses in antidepressant activity tests.

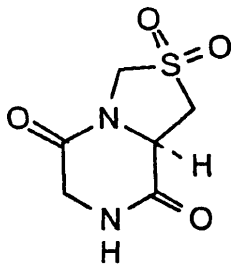


Scheme 45

Reagents : (i) $SOCl_2$ / MeOH, (ii) chloroacetyl chloride, NEt_3 (iii) RNH_2

Oxidation of this bicycle **(249)** to the sulphone **(254)** was next investigated. Initially, the action of potassium permanganate in aqueous acetic acid was examined. However, after work-up, no product was isolated in the organic layer.

Suspecting that the product **(254)** was lost in the aqueous work-up, an alternative oxidation procedure was then examined, which involved the use of m-chloroperoxybenzoic acid (m-CPBA) in dichloromethane. Evaporation of the aqueous layer and recrystallisation of the product from hot water gave a white solid (88% by mass) which contained the sulphone **(254)** and an impurity (Exp.9).

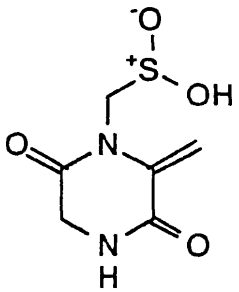


(254)

A better oxidant for the conversion of the sulphide **(249)** into the sulphone **(254)** was hydrogen peroxide in formic acid. This reagent gave a quantitative conversion of the sulphide **(249)** into the sulphone **(254)** following recrystallisation (Exp.10).

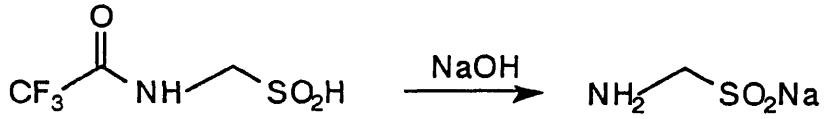
The spectroscopic properties of compound **(254)** were in accord with the proposed structure; in particular, the 300 MHz ^1H n.m.r. spectrum showed a broad one-proton singlet at δ 8.51 for the amide proton which disappeared on addition of deuterium oxide. Compound **(254)** displayed an i.r. absorption at 1 680 cm^{-1} for the amide carbonyl group and also its elemental composition was consistent with the formula $C_6H_8N_2O_4S$.

Disappointingly, the sulphone **(254)** failed to give the sulphinic acid **(255)** on treatment with DBN.



(255)

Due to the lack of success in the removal of the phthaloyl group, it was decided to change the nature of the amino-protecting group. Previously,[81] Mahmoud had successfully used the trifluoroacetyl group for the protection of the amino functionality in obtaining sodium α-aminomethanesulphinate **(97)** from the sulphinic acid **(173)**. In view of this, it was decided to carry out the sequence depicted in Scheme 46.

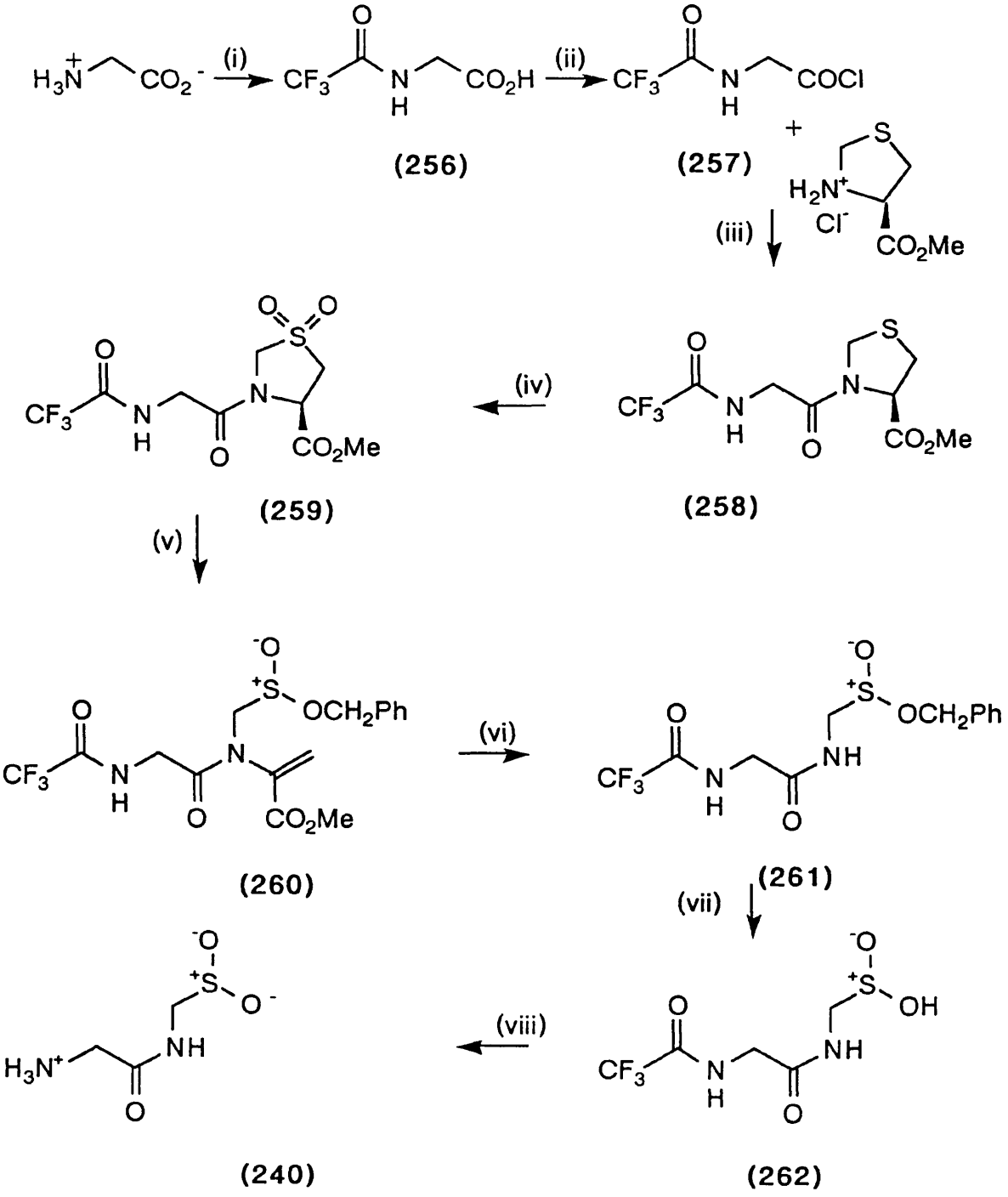


(173) **(97)**

N-Trifluoroacetylglycine **(256)**[100] was prepared in quantitative yield by adding trifluoroacetic anhydride to glycine (with cooling) and then heating the mixture at 80 °C (Exp.11). When refluxed with an excess of thionyl chloride, the last-cited compound was converted into the acid chloride **(257)** (Exp.12), which reacted with the thiazolidine **(251)** in dichloromethane in the presence of triethylamine to give the amide **(258)** (75% yield after recrystallisation) (Exp.13). On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(258)** existed as a 2:1 mixture of rotamers in deuteriodimethyl sulphoxide solution.

Its 300 MHz ^{1}H n.m.r. spectrum, featured two-singlets at δ 3.65 and 3.75 (2 and 1 H, respectively), for the ester protons. The ^{1}H n.m.r. spectrum was also run at 423 K, at which temperature coalescence of the rotameric forms was complete and a significantly simplified spectrum resulted. I.r. absorptions were present at 1 745, 1 715, and 1 650 cm^{-1}, for the ester, trifluoroacetyl, and amide carbonyl groups, respectively. Whilst the mass spectrum of compound **(258)** did not display a molecular ion, it did show a peak at m/z 301, attributable to the MH^+ ion. Additionally, compound **(258)**

displayed an elemental analysis consistent with the formula $C_9H_{11}F_3N_2O_4S$.

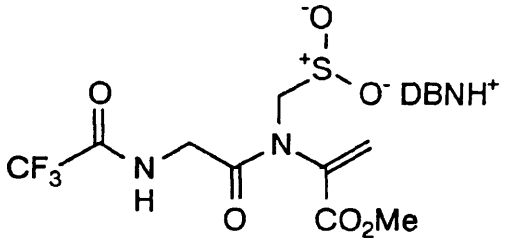


Scheme 46

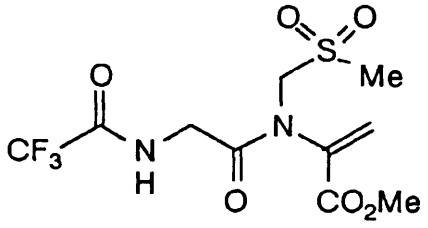
Reagents : (i) $(CF_3CO)_2O$, (ii) $SOCl_2$, (iii) Et_3N, (iv) $KMnO_4$/HOAc, (v) DBN, $ClCO_2CH_2Ph$, (vi) CH_2N_2, Zn/HOAc, (vii) $SOCl_2$, H_2O, (viii) NaOH/H^+

The thiazolidine **(258)** was converted into the 1,1-dioxide **(259)** (69% yield after recrystallisation) by the action of potassium permanganate in aqueous acetic acid (Exp.14). On the basis of 300 MHz ^1H n.m.r. spectroscopy, compound **(259)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution. Its ^1H n.m.r. spectrum featured two-singlets at δ 3.86 and 3.92 (2.25 and 0.75 H, respectively) for the ester protons. Compound **(259)** showed i.r. absorptions at 1 755, 1 725, and 1 670 cm^{-1}, for the ester, trifluoroacetyl, and amide carbonyl groups, respectively. Whilst the mass spectrum did not display a molecular ion, it did show a peak at m/z 333, attributable to the MH^+ ion. Compound **(259)** displayed a microanalysis consistent with the formula $C_9H_{11}F_3N_2O_6S$.

Disappointingly, attempts to induce the β-elimination reaction with the sulphone **(259)** failed to provide any evidence for the formation of the sulphinate **(263)**. Thus, when the reaction was monitored by ^1H n.m.r. spectroscopy, no acrylate protons were detectable even after using an excess of DBN or extended reaction times.

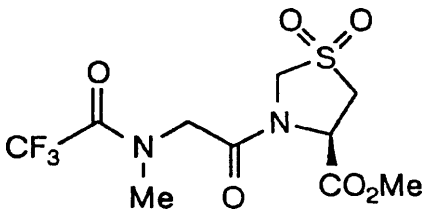


(263)

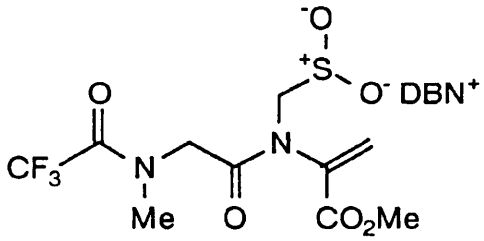


(264)

In earlier work, it was established that sulphinates related to **(263)** could be intercepted with iodomethane to give methyl sulphones.[98] Accordingly, the thiazolidine **(259)** was reacted with DBN in dichloromethane followed by iodomethane. Work-up and purification of the product by silica-gel chromatography gave a material (71% yield after recrystallisation) that was tentatively considered to be the N-methyl derivative **(265)** (Exp.15), rather than compound **(264)**.

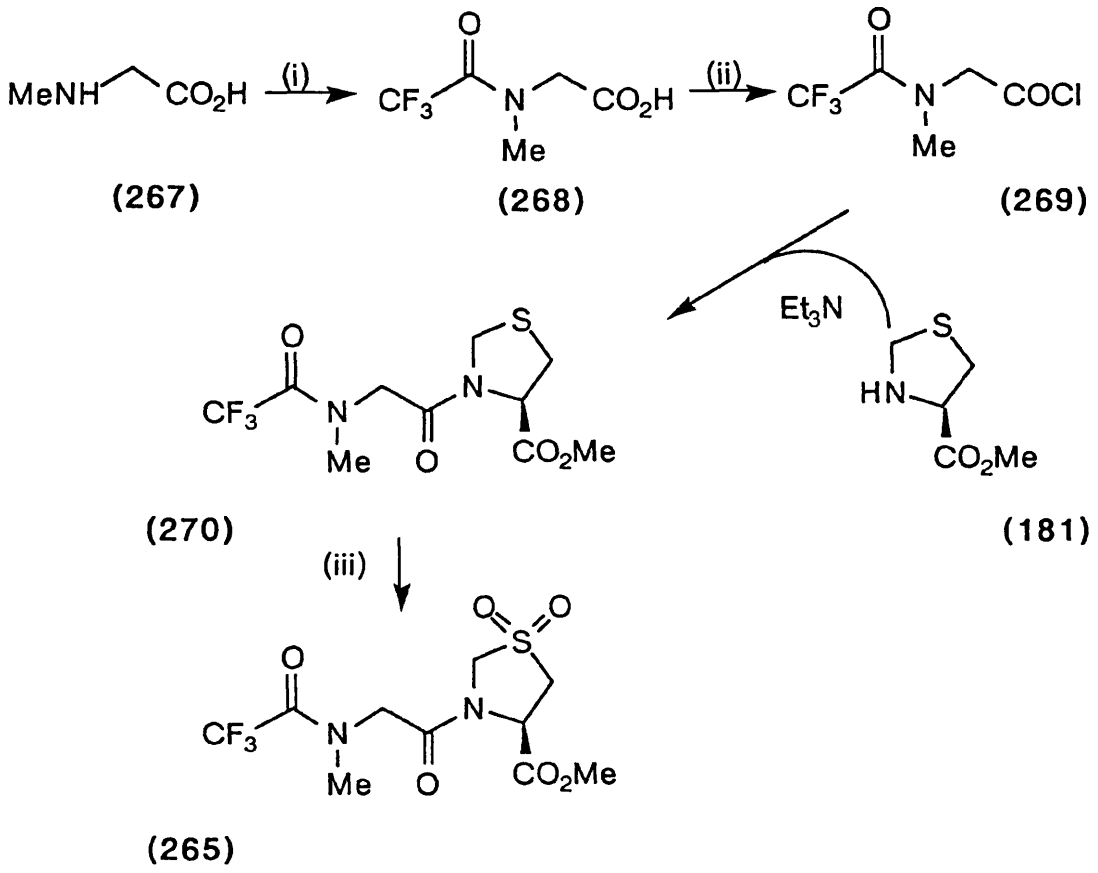


(265)



(266)

Attempts to induce a β-elimination of this compound **(265)**, by the action of DBN, failed to provide any evidence for the formation of the sulphinate **(266)**. Consequently, doubts were raised concerning the proposed structure **(265)**. An unambiguous synthesis of the sulphone **(265)** was therefore undertaken using the route outlined in Scheme 47.



Scheme 47

Reagents : (i) $(CF_3CO)_2O$ / CF_3CO_2H, (ii) $SOCl_2$, (iii) $KMnO_4$ / HOAc

N-Methyl-N-trifluoroacetylglycine **(268)**[101] was prepared (36% yield after distillation) (Exp.16) by adding trifluoroacetic anhydride to a cooled solution of sarcosine **(267)** in trifluoroacetic acid and then stirring the mixture at -20 °C for 16 h.

When refluxed with an excess of thionyl chloride, the acid **(268)** was converted into the acid chloride **(269)**, which reacted in dichloromethane with the thiazolidine methyl ester **(181)** in the presence of triethylamine to give the amide **(270)** (89% yield) (Exp.17 a), as a clear oil. On the basis of ^1H n.m.r. spectroscopy, compound **(270)** existed as a 2:1 mixture of rotamers in deuteriochloroform solution, its 300 MHz ^1H n.m.r. spectrum

featuring two-singlets at δ 3.73 and 3.80 (2 and 1 H, respectively) for the ester protons. I.r. absorptions were present at 1 745, 1 700, and 1 670 cm^{-1}, for the ester, trifluoroacetyl, and amide carbonyl groups, respectively. Although the mass spectrum of compound **(270)** did not contain a molecular ion, it did show a peak at m/z 315, attributable to the MH^+ ion. Compound **(270)** displayed an elemental analysis consistent with the formula $C_{10}H_{11}F_3N_2O_4S$.

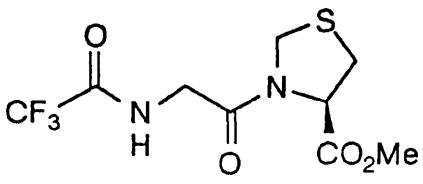
The sulphide **(270)** was also prepared by sequential treatment of the acid **(268)** in dichloromethane with dicyclohexylcarbodiimide (DCCI)[102] and the methyl ester **(181)**. The sulphide **(270)** was isolated in 93% yield (Exp.17 b) and was found to be identical with the material obtained in Experiment 17a by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

The sulphide **(270)** was then oxidized to the sulphone **(265)** (78% yield after recrystallisation) (Exp.18a), by the action of potassium permanganate in aqueous acetic acid. On the basis of its 300 MHz ^1H n.m.r. spectrum, compound **(265)** existed as a 4:1 mixture of rotamers in deuteriochloroform solution; the ^1H n.m.r. spectrum featured two-three proton multiplets at δ 3.23-3.35 and 3.74-3.94 for the N-methyl and methyl ester protons, respectively. I.r. absorptions were present at 1 750 (ester) and 1700br cm^{-1} (trifluoroacetyl and amide). The mass spectrum contained a peak at m/z 384, attributable to the MNH_4^+ ion. Compound **(265)** displayed an elemental analysis consistent with the formula $C_{10}H_{13}F_3N_2O_6S$.

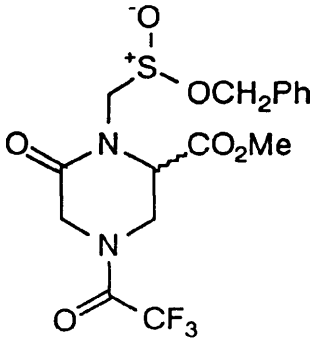
The oxidation of compound **(270)** with potassium hydrogen persulphate ($KHSO_5$), commercially sold as "Oxone" was also examined.[103-104] This is an excellent reagent for the oxidation of sulphides to sulphones in the presence of other common functional groups. The reaction in aqueous methanol, afforded the sulphone **(265)** in 90% yield (Exp.18b) as a crystalline white solid which was found to be identical with the material obtained in Experiment 18a by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

The ^1H n.m.r. spectrum of compound **(265)** was not the same as that for the product obtained from the reaction of the sulphone **(259)** with DBN-iodomethane. In contrast to the ^1H n.m.r. spectrum of the sulphone **(265)**, the ^1H n.m.r. spectrum (CD_3SOCD_3, 438 K) of the product of Exp.15, featured two three-proton singlets at δ 3.00 and 3.73, two one-proton doublets at δ 3.94br, and 4.49br, one two-proton AB q at δ 4.33, two one-proton doublets at δ 4.62 and 5.11, and a one proton doublet at δ 4.80.

Originally, it was proposed that, due to the acidity of its amide proton, compound **(259)** had reacted with DBN followed by iodomethane to give the methyl sulphone **(265)**. However, with the elimination of this structure **(265)**, an alternative pathway was implicated. Moreover, the failure to convert the sulphide **(258)** into the N-methyl sulphide **(270)** by the sequential action of DBN-iodomethane reinforced this requirement.



(258)

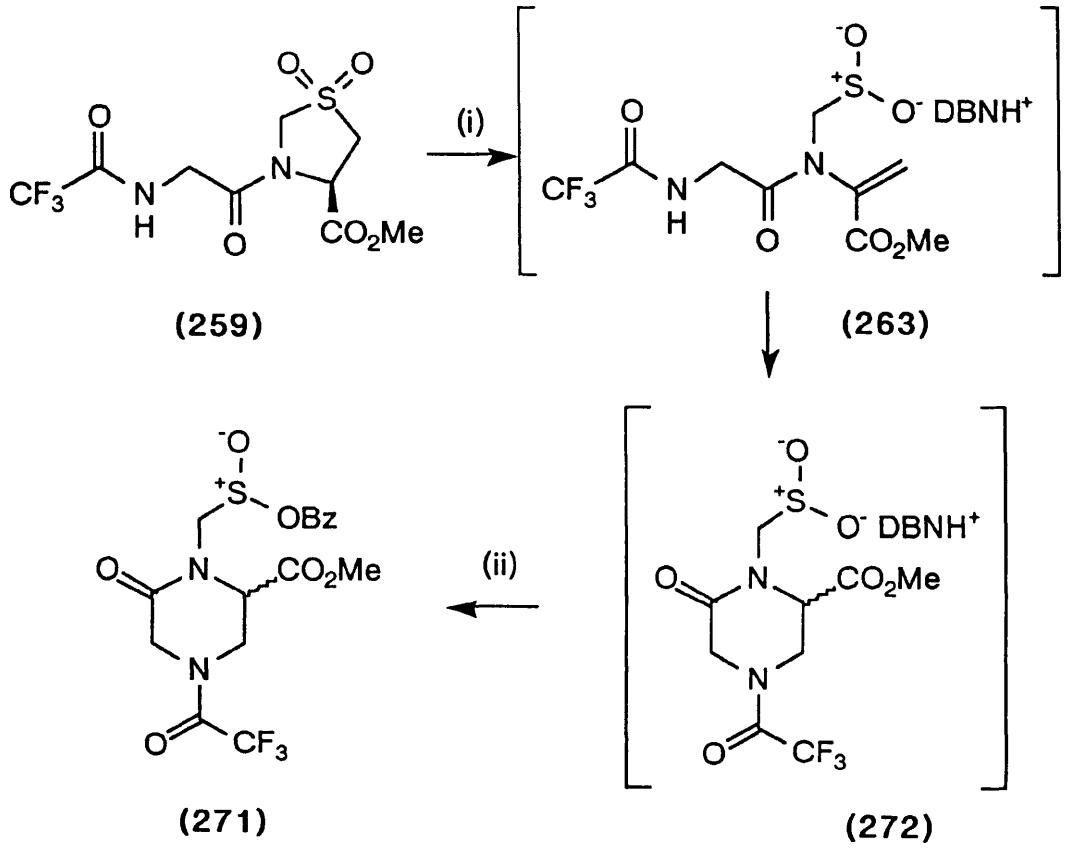


(271)

Sequential treatment of the sulphone **(259)** with DBN and benzyl chloroformate led to a material which was considered to be the substituted piperazine **(271)** (70% yield after purification by SiO_2 chromatography) (Exp.19). In accord with the proposed structure, compound **(271)** displayed in its 300 MHz ^1H n.m.r. spectrum five singlets at δ 3.58, 3.62, 3.63, 3.66, and 3.70, together integrating for three protons, for the ester group. I.r. absorptions were present at 1 747, 1 695, and 1 681 cm^{-1}, for the ester,

trifluoroacetyl, and amide carbonyl groups, respectively. Although the mass spectrum did not display a molecular ion, it did show a peak at m/z 384, attributable to the MNH_4^+ ion; Additionally, compound **(271)** displayed an elemental analysis consistent with the formula $C_{10}H_{13}F_3N_2O_6$.

Compound **(271)** is thought to arise from the sulphone **(259)** by a DBN-induced β-elimination to give the acrylate intermediate **(263)** which, by the nature of the nucleophilic amide nitrogen, undergoes a spontaneous intramolecular Michael addition to the pyrazine intermediate **(272)**, which then rapidly reacts with benzyl chloroformate to give the product **(271)** (Scheme 48).

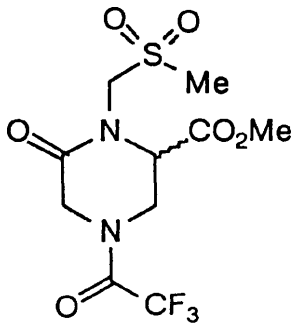


(259) **(263)** **(271)** **(272)**

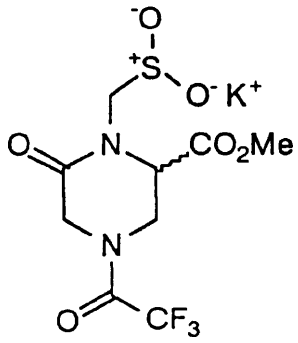
Scheme 48

Reagents : (i) DBN, (ii) $PhCH_2OCOCl$

By analogy, the product of the reaction of the sulphone **(259)** with DBN-iodomethane was considered to be the substituted piperazine **(273)**. This explains why no evidence was found for the appearance of acrylate protons [expected for the sulphinate **(263)**], when the reaction was monitored by ^{1}H n.m.r. spectroscopy.



(273)



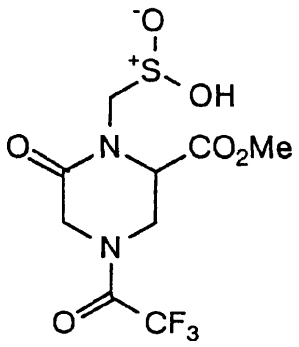
(274)

In previous work,[82,98] potassium tert-butoxide had been used as a base for inducing β-eliminations. The behaviour of the sulphone **(259)** towards this reagent was therefore examined. When the sulphone **(259)** was treated with the freshly resublimed base in THF at -78 °C, work-up by evaporation afforded a pale-yellow solid considered to be the potassium salt **(274)** (Exp.20), which existed as a 1.5:1 mixture of rotamers in deuteriodimethyl sulphoxide solution. In accord with the proposed structure, compound **(274)** showed in its 300 MHz ^{1}H n.m.r. spectrum two singlets at δ 3.64 and 3.68 (1.2 and 1.8 H, respectively), for the ester protons. Additionally, compound **(274)** showed i.r. absorptions at 1 754, 1700, and 1 657 cm^{-1}, for the ester, trifluoroacetyl, and amide carbonyl groups, respectively.

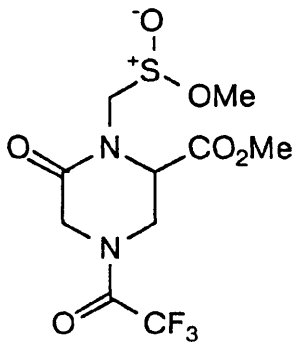
Proof for the proposed structure of the potassium salt was produced by treating the salt **(274)** with iodomethane in DMF. The S-alkylation of sulphinate salts by iodomethane is well established,[105] and the sole product

isolated was the substituted piperazine **(273)** (62% yield after recrystallisation) as a white solid (Exp.21). The spectroscopic properties of this solid were identical with those of the compound obtained in Experiment 15, which was produced by the reaction of the sulphone **(259)** with DBN followed by iodomethane.

Reaction of the salt **(274)** in methanol with an excess of Amberlite IR 120 (H^+) ion-exchange resin afforded, after evaporation, a white solid considered to be the sulphinic acid **(275)** (100% recovery) (Exp.22). In accord with its proposed structure, compound **(275)** displayed in its mass spectrum a peak at m/z 332 attributable to the molecular ion and a peak at m/z 268, attributable to the loss of sulphur dioxide from the molecular ion. The i.r. spectrum displayed absorptions at 1 750, 1 700, and 1 682 cm^{-1}, for the ester, trifluoroacetyl and amide carbonyl groups, respectively. However, its 300 MHz ^1H n.m.r. spectrum was complex suggesting that the sample had decomposed. (The spectrum was not recorded on freshly prepared material.)



(275)



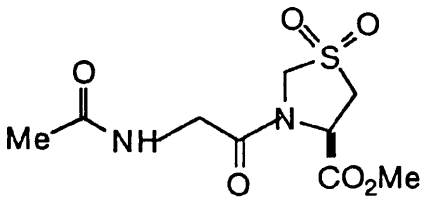
(276)

Further proof that the sulphinic acid **(275)** was formed was obtained from the reaction of the freshly generated material with an excess of diazomethane in diethyl ether. Work-up yielded the methyl sulphinate **(276)** [(17% yield from the salt **(274)** after SiO_2 chromatography)] as a microanalytically pure white foam (Exp.23). The 300 MHz ^1H n.m.r. spectrum

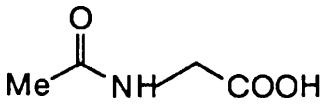
of compound **(276)** displayed two singlets at δ 3.77 and 3.78 (1.5 H each), for the methyl sulphinate protons and showed i.r. absorptions at 1 750 (ester carbonyl) and 1 745 cm^{-1} (trifluoroacetyl and amide carbonyl). The mass spectrum showed a peak at m/z 346, attributable to the molecular ion. Compound **(276)** displayed an elemental analysis consistent with the formula $C_{10}H_{13}F_3N_2O_6S$.

To recap, the sulphone **(259)**, on sequential reaction with DBN and benzyl chloroformate, gave the substituted pyrazine **(271)**. This compound was thought to arise from the intermediate **(263)** by an intramolecular Michael addition caused by the nucleophilic nature of the amide nitrogen. In order to further investigate this reaction, it was decided to study the behaviour of the sulphone **(277)** towards β-elimination. A synthesis of the sulphone **(277)** was therefore undertaken.

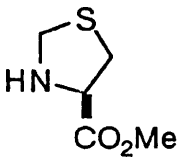
Aceturic acid **(278)** was treated sequentially in aqueous DMF with DCCI and the thiazolidine methyl ester **(181)**; however, work-up afforded a complex mixture of products. Similarly, aceturic acid **(278)** failed to yield the acid chloride **(279)** on reaction with thionyl chloride. Presumably, activation of the carboxyl moiety of aceturic acid **(278)** is followed by oxazolidinone formation which then leads to a mixture of products.



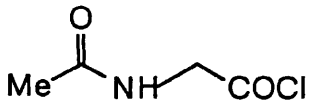
(277)



(278)

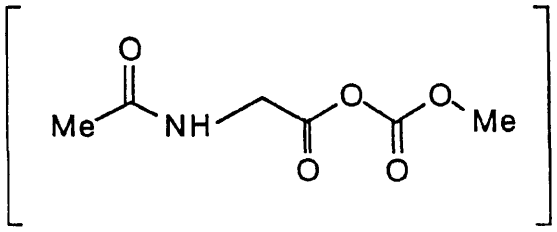


(181)

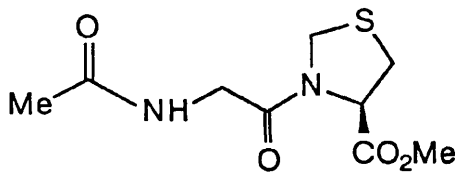


(279)

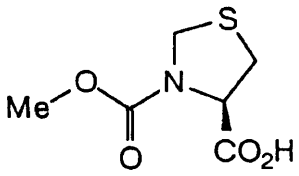
It was envisaged that the triethylamine salt of the acid **(278)** would react with methyl chloroformate to yield a mixed anhydride **(280)**, which might then react with the thiazolidine **(181)** to afford the required sulphide **(281)**. However, sequential treatment of aceturic acid **(278)** in DMF with triethylamine, methyl chloroformate, and the thiazolidine methyl ester **(181)**, gave the sulphide **(282)** in 30% yield after work-up and silica-gel chromatography (Exp.24). In accord with the presence of a 1:1 mixture of rotamers, compound **(282)** displayed in its 300 MHz ^{1}H n.m.r. spectrum, a six-proton multiplet at δ 3.60-3.73 for the methoxycarbonyl and methyl ester protons. I.r. absorptions at 1 760 and 1 715 cm^{-1} for the ester and urethane carbonyl groups, respectively, were present. Additionally, the mass spectrum displayed a peak at m/z 205, attributable to the molecular ion.



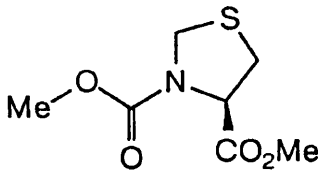
(280)



(281)



(283)

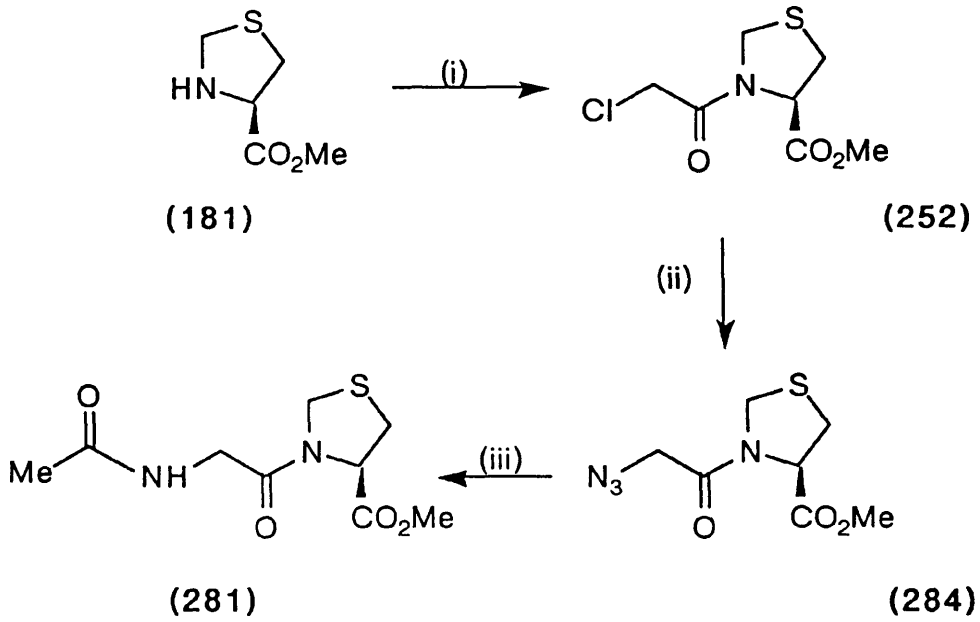


(282)

Further structural proof was obtained by an independent synthesis of compound **(282)**. Thus, the acid **(160)** was reacted with methyl chloroformate in ice-cooled sodium hydroxide solution to afford the urethane **(283)** in 87% yield as an oil (Exp.25). The 300 MHz ^{1}H n.m.r. spectrum of compound **(283)** displayed a three-proton singlet at δ 3.75, for the methoxycarbonyl protons, and a broad one-proton singlet at δ 7.94, for the carboxyl proton. I.r. absorptions were present at 1 715br cm^{-1}, for the acid and urethane carbonyl group. The mass spectrum of compound **(283)** showed a peak at m/z 191, attributable to the molecular ion.

Esterification of the acid **(283)** was achieved by treatment in dichloromethane with an excess of ethereal diazomethane to afford the methyl ester **(282)** in 79% yield as a microanalytically pure oil (Exp.26). The spectroscopic properties were identical with those of the compound **(282)** obtained in Experiment 24.

It was hoped that compound **(281)** would be obtained by the route outlined in Scheme 49.



Scheme 49

Reagents : (i) $ClCH_2COCl$ / NEt_3, (ii) NaN_3, (iii) Zn / Ac_2O

When the thiazolidine methyl ester **(181)** was treated in dichloromethane with chloroacetyl chloride and triethylamine, the thiazolidine sulphide **(252)** was produced in 93% yield after recrystallisation (Exp.27)[99] (literature quotes 86%). On the basis of 300 MHz ^1H n.m.r. spectroscopy, compound **(252)** existed as a 2:1 mixture of rotamers in

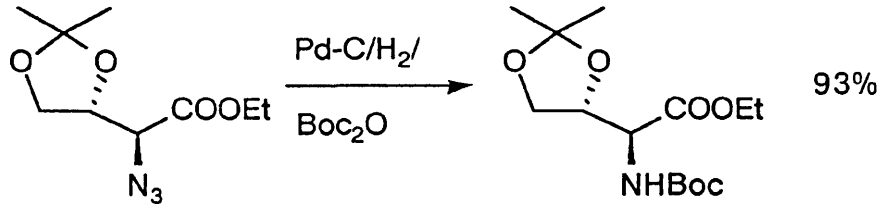
deuteriochloroform solution; the spectrum displayed two singlets at δ 3.81 and 3.85 (2 and 1 H, respectively), for the ester protons. I.r. absorptions were present at 1 755 (ester carbonyl), and 1 680, and 1 665 cm^{-1} (amide carbonyl) and the mass spectrum displayed a peak at m/z 224, attributable to the MH^+ ion. Additionally, compound **(252)** displayed an elemental analysis consistent with the formula $C_7H_{10}ClNO_3S$.

Treatment of the chloride **(252)** with sodium azide in boiling aqueous ethanol gave the azido compound **(284)** (80% yield after SiO_2 chromatography) (Exp.28). The last-cited material also existed as a 2:1 mixture of rotamers in deuteriochloroform solution, the spectrum of compound **(284)** displaying two singlets at δ 3.78 and 3.81 (2 and 1 H, respectively), for the ester protons. I.r. absorptions were present at 2 110, 1 750, and 1 670 cm^{-1}, for the azido, ester carbonyl, and amide carbonyl groups, respectively. Compound **(284)** did not display a molecular ion in its mass spectrum, but it did display a peak at m/z 202, attributable to the loss of molecular nitrogen from the molecular ion. Additionally, compound **(284)** displayed a microanalysis consistent with the formula $C_7H_{10}N_4O_3S$.

When the azido sulphide **(284)** was treated with activated zinc in an acetic acid-acetic anhydride mixture, a vigorous reaction was observed and work-up followed by silica-gel chromatography afforded the required sulphide **(281)** (36% yield) (Exp.29a). In accord with the presence of a 2:1 mixture of rotamers, compound **(281)** displayed in its 300 MHz ^1H n.m.r. spectrum a three-proton singlet at δ 2.00, for the N-acetyl protons, and two singlets at δ 3.71 and 3.76 (2 and 1 H, respectively), for the ester protons. I.r. absorptions were present at 1 750 and 1 660 cm^{-1}, for the ester and amide carbonyl groups, respectively. Compound **(281)** also displayed in its mass spectrum, a peak at m/z 247, attributable to the MH^+ ion; additionally, compound **(281)** displayed an elemental analysis consistent with the constitution $C_9H_{14}N_2O_4S$.

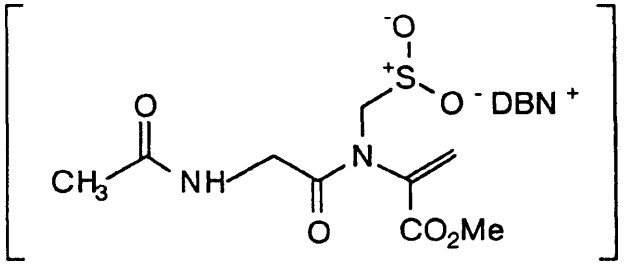
However, attempts to obtain useful quantities of the thiazolidine **(281)** by this procedure proved to be fruitless. The capricious nature of this reaction was indicated by the formation of intractable mixtures of products from various subsequent runs.

A recent publication described a one-pot transformation of an azido group into a N-tert-butoxycarbonyl group by catalytic hydrogenation.[106]



Gratifyingly, the azido sulphide **(281)** was obtained in reasonable yield upon reaction of the sulphide **(284)** in ethyl acetate with acetic anhydride, hydrogen, and 10% palladium on charcoal (Exp.29b). Its spectroscopic properties were identical with those of the material obtained in Experiment 29a.

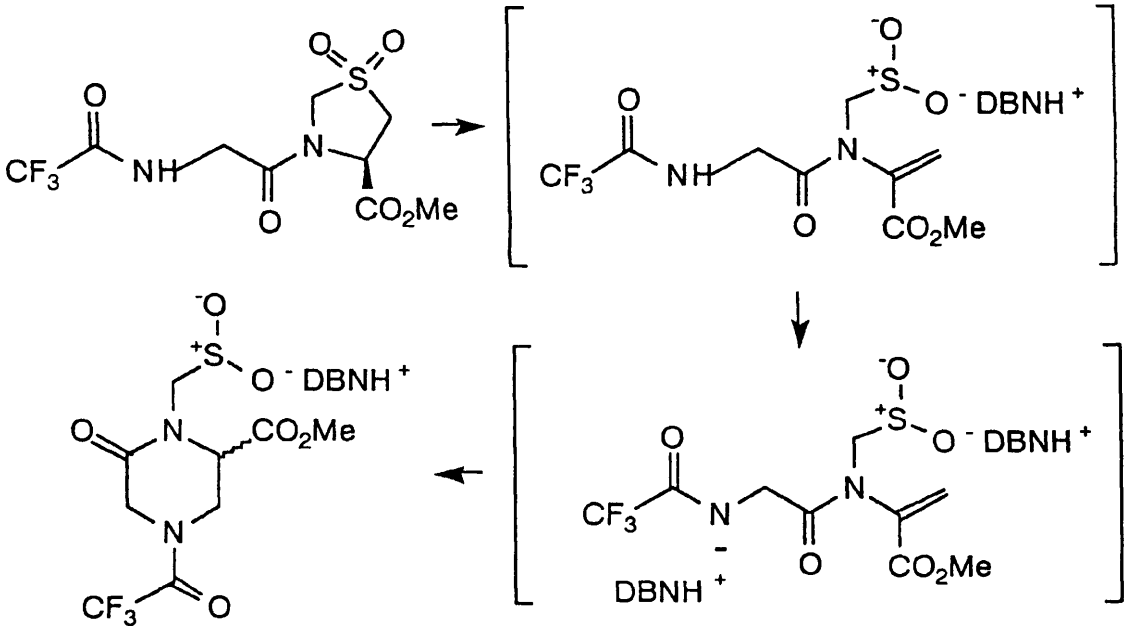
Oxidation of the sulphide **(281)** was performed by the action of "Oxone" in aqueous methanol, which gave the sulphone **(277)** (27% yield after recrystallisation) (Exp.30). On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(277)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution. Compound **(277)** showed in its 300 MHz ^{1}H n.m.r. spectrum a three-proton singlet at δ 2.06, for the N-acetyl methyl protons, and two-singlets at δ 3.83 and 3.88 (2.25 and 0.75 H, respectively), for the ester protons. I.r. absorptions were present at 1 750 (ester carbonyl) and 1 700-1 650 cm^{-1} (amide and urethane carbonyl). Compound **(277)** displayed in its mass spectrum a peak at m / z 279, attributable to the MH^+ ion.



(285)

Having obtained the sulphone (277), attention was then turned to the key β-elimination step. When compound (277) was treated sequentially with DBN and methyl chloroformate in deuteriochloroform, ^{1}H n.m.r. spectroscopy indicated the rapid disappearance of the starting material and work-up furnished an oil which, on the basis of 60 MHz ^{1}H n.m.r. spectroscopy, contained signals for the acrylate, methyl carboxylate, and methyl sulphinate ester groups. Clearly, the DBN-salt (285) was implicated in this reaction.

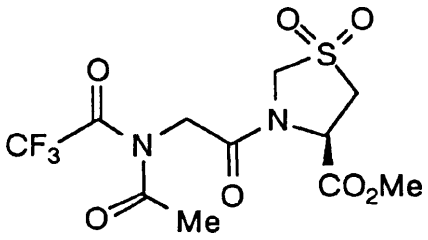
The aforecited finding re-focusses attention upon the mechanism of the reaction between the sulphone (259) and DBN. The most probable mechanism would appear to be the one indicated in Scheme 50.



Scheme 50

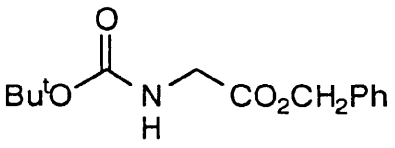
It was expected that acylation or silylation of the amide nitrogen in the precursor **(259)** would prevent this unwanted addition. In work performed by Inch and Fletcher,[107] acetylation of an amide nitrogen was performed by using isopropenyl acetate and a catalytic amount of toluene-p-sulphonic acid.

By this method, it was hoped to convert the sulphone (259) into the diacylated compound (286); disappointingly, no reaction was observed.

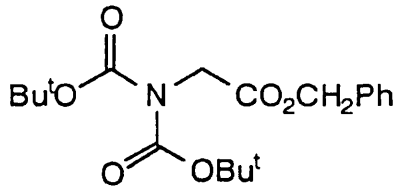


(286)

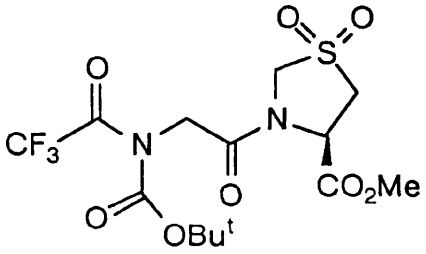
Grehn and Ragnarsson[108] described a method to acylate the urethane moiety in compound (287), using di-tert-butyl dicarbonate $[Boc)_2O]$ and 4-dimethylaminopyridine (DMAP) in acetonitrile to afford the N,N-diacyl compound (288) in high yield. Unfortunately, the sulphone (259) failed to afford the diacylated sulphone (289) with these reagents.



(287)



(288)

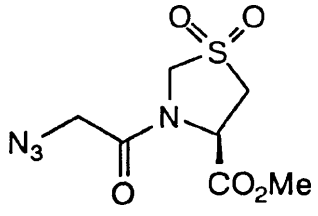


(289)

Primary and secondary amides are normally readily silylated at the nitrogen;[109] however, the sulphone **(259)** failed to react with tert-butyldimethylsilyl triflate in the presence of triethylamine.

At this point, it was considered that the azido group could be used as a masked form of the amino function. Unveiling of the azido group to the amine functionality was expected to be readily accomplished under reductive conditions.

Oxidation of the thiazolidine **(284)** with potassium permanganate in aqueous acetic acid gave the sulphone **(290)** but in variable yields. In view of this, the use of an alternative oxidant was investigated. The sulphide **(284)** reacted with m-CPBA in dichloromethane to give the sulphone **(290)** in 67% yield (after SiO_2 chromatography) as a white solid (Exp.31a). The sulphone **(290)** existed as a 4:1 mixture of rotamers in deuteriochloroform solution, the spectrum displaying two-singlets at δ 3.82 and 3.88 (2.4 and 0.6 H respectively), for the ester protons. I.r. absorptions were present at 2 105, 1 750, and 1 685 cm^{-1}, for the azido, ester carbonyl, and amide carbonyl groups, respectively. Compound **(290)** did not display a molecular ion in its mass spectrum, but it did show a peak at m/z 263, attributable to the MH^+ ion. Additionally, compound **(290)** displayed a microanalysis consistent with the formula $C_7H_{10}N_4O_5S$.

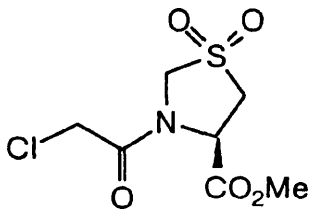


(290)

The sulphone **(290)** was also obtained by the oxidation of the sulphide **(284)** with "Oxone" in aqueous methanol, in 84% yield (Exp.31b).

It was envisaged that the sulphone **(290)** would also be obtained from the chloro ketone **(252)**, by oxidation followed by reaction with sodium azide. The sulphide **(252)** was converted into the 1,1-dioxide **(291)** (91% yield after recrytallisation) (Exp.32a) by the use of potassium permanganate in aqueous acetic acid. On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(291)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution, the spectrum displaying two-singlets at δ 3.84 and 3.90 (2.25 and 0.75 H, respectively), for the ester protons. I.r. absorptions were present at 1 770 (ester carbonyl), and 1 695, and 1 685 cm^{-1} (amide carbonyl). Compound **(291)** displayed an elemental analysis consistent with the constitution $C_7H_{10}ClNO_5S$.

"Oxone" also reacted with the sulphide **(252)** in aqueous methanol to afford the sulphone **(291)** in 86% yield (Exp.32b) as a crystalline white solid. The material was found to be identical with that obtained in Experiment 32a by m.p. and 300 MHz ^{1}H n.m.r. spectroscopy.

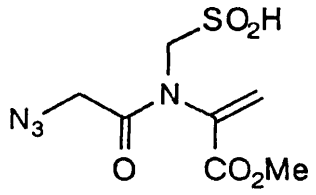


(291)

Disappointingly, the chloro ketone **(291)** failed to give the azido ketone **(290)** in a clean and efficient manner, when treated with sodium azide in aqueous ethanol.

Having obtained the sulphone **(290)**, attention was turned to performing the key β-elimination step. When compound **(290)** was treated with DBN in deuteriochloroform solution, ^{1}H n.m.r. spectroscopy indicated the disappearance of the starting material but no acrylate protons were

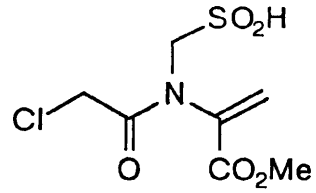
detectable. Acidic work-up did not furnish the sulphinic acid (292); in addition, recovery of the starting material could not be achieved.



(292)

When the sulphone (290) was treated with DBN followed by iodomethane in dichloromethane, work-up yielded a red-brown oil which was shown to be a complex mixture of products. No acrylate protons were observed in the ^1H n.m.r. spectrum. A similar result was observed in the reaction of the sulphone (290) with DBN followed by benzyl chloroformate.

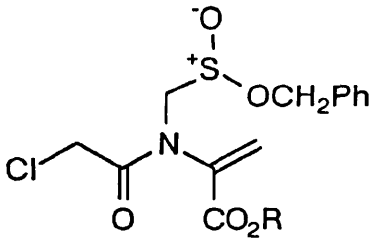
At this stage, it was decided to investigate the β-elimination reaction of the sulphone (291). Disappointingly, attempts to isolate the sulphinic acid (293) from the reaction of the sulphone (291) with DBN in dichloromethane were unrewarding.



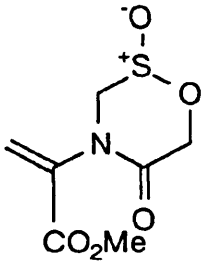
(293)

When the sulphone (291) was treated sequentially with DBN and benzyl chloroformate, work-up and purification of the product by silica-gel chromatography led to the isolation of two components in very poor yield (Exp.33). On the basis of 300 MHz ^1H n.m.r. spectroscopy, the first-eluted

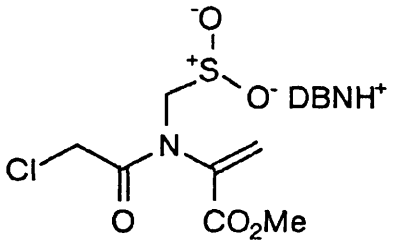
material was considered to be an acrylate of type **(294)** (the methyl ester signal was very small). The second-eluted material was tentatively considered to be the compound **(295)** or **(296)**. ^1H n.m.r. spectroscopy suggested that the second-eluted material was most likely compound **(295)**.



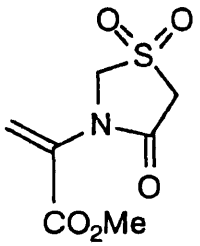
(294)



(295)



(297)



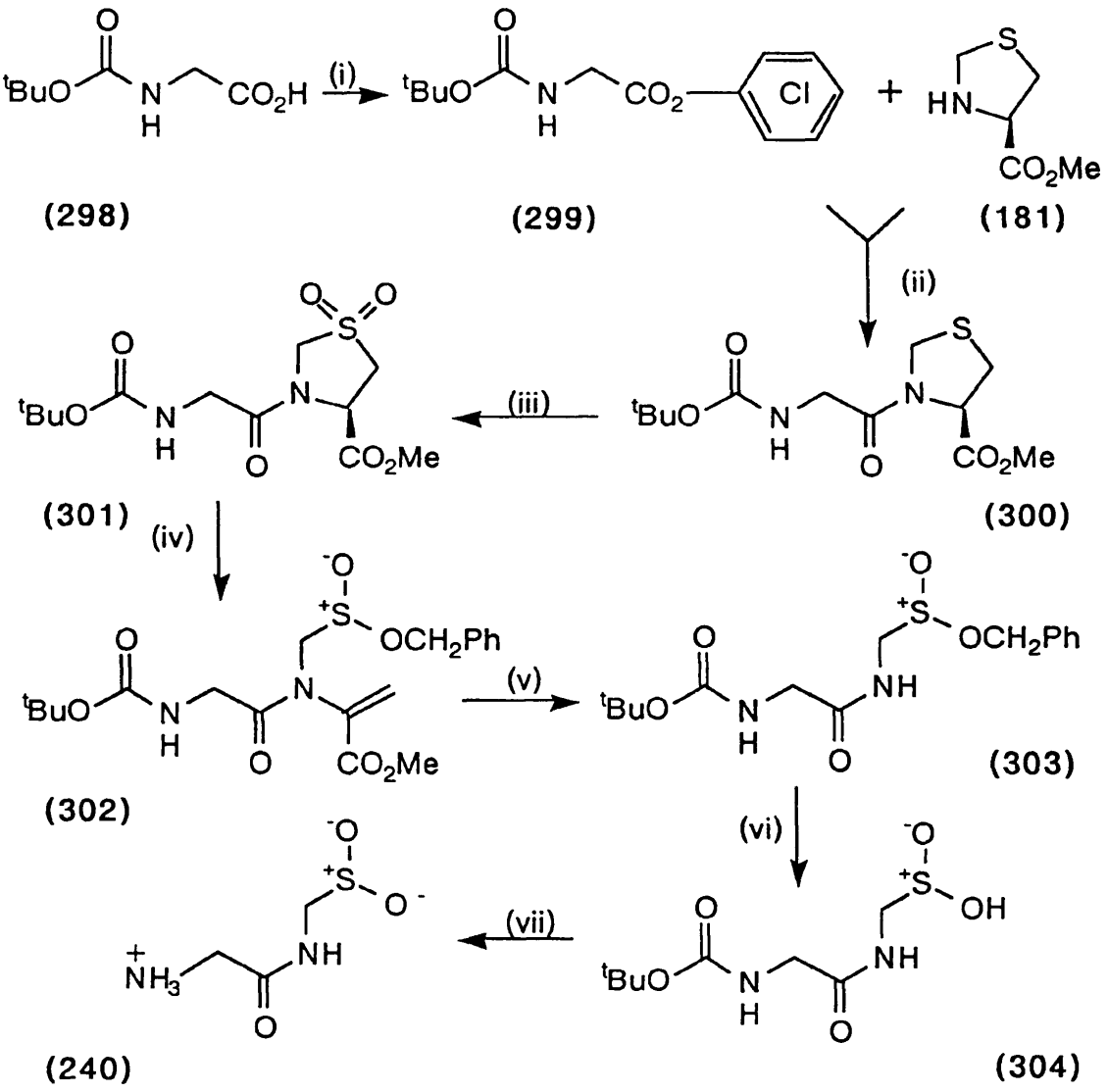
(296)

Compounds **(295)** or **(296)** are thought to arise by the intramolecular displacement of the halogen by the sulphinate group, from the intermediate compound **(297)**.

Due to the lack of success in obtaining the sulphinic acid **(293)**, it was proposed that an alternative way of inhibiting the intramolecular Michael addition would be to incorporate a steric constraint at the nucleophilic site. Therefore, it was decided to attempt to carry out the sequence depicted in Scheme 51.

N-tert-Butoxycarbonylglycine pentachlorophenyl ester **(29)**[110] was prepared in 64% yield by reacting N-tert-butoxycarbonylglycine **(298)** in

dichloromethane with pentachlorophenol followed by DCCI (Exp.34). The activated ester **(299)** did not react with the thiazolidine methyl ester **(181)** in dichloromethane in the presence of triethylamine. However, the addition of a catalytic amount of DMAP led to the sulphide **(300)** (28% yield after SiO_2 chromatography) (Exp.35).



Scheme 51

Reagents : (i) DCCI/ pentachlorophenol, (ii) NEt_3, (iii) $KMnO_4$ / HOAc, (iv) DBN / $ClCO_2CH_2Ph$, (v) CH_2N_2 / Zn, H^+, (vi) $SOCl_2$ / H_2O, (vii) H^+

In view of the poor yield of this reaction and the importance of compound **(300)** in the proposed synthesis, alternative routes to the sulphide **(300)** were examined.

The use of an agent to effect the coupling of the acid **(298)** and the amine **(181)** was next investigated. An example of such an agent, commonly used in peptide chemistry, is N,N'-carbonyldiimidazole (CDI). The easily aminolysed acylated imidazoles are intermediates. The acid **(298)** was treated in THF with CDI followed by the thiazolidine methyl ester **(181)** to give the corresponding sulphide **(300)** in 35% yield (Exp.36a).

Another method, which has been used for coupling amines and carboxylic acids in peptide chemistry, involves a mixed anhydride intermediate. The acid **(298)** was treated with ethyl chloroformate in the presence of triethylamine followed by the thiazolidine methyl ester **(181)** to afford the sulphide **(300)** in 59% yield after silica-gel chromatography (Exp.36 b).

In accord with the proposed structure, compound **(300)** showed in its 300 MHz ^{1}H n.m.r. spectrum, a nine-proton multiplet at δ 1.42-1.69 and the presence of a 2:1 mixture of rotamers for the tert-butyl protons and two-singlets at δ 3.75 and 3.82 (2 and 1 H, respectively) for the ester protons. I.r. absorptions were present at 1 750, 1 715, and 1 670 cm^{-1}, for the ester, urethane, and amide carbonyl groups, respectively. The mass spectrum displayed a peak at m/z 304, attributable to the molecular ion and compound **(300)** showed an elemental analysis consistent with the constitution $C_{12}H_{20}N_2O_5S$.

An improvement in the synthesis of the sulphide **(30)** was achieved by the use of the DCCI. The acid **(298)** was treated in dichloromethane with DCCI followed by the thiazolidine methyl ester **(181)** to give the sulphide **(300)** as a white solid in 98% yield after work-up (Exp.36c).

Having obtained the sulphide **(300)** in good yield, attention was turned to its oxidation to the sulphone **(301)**. Initially, the sulphide **(300)** was treated with potassium permanganate in aqueous acetic acid at 0 °C to yield the sulphone **(301)**. However, it was necessary to subject the product to column chromatography to remove an impurity and the yield of the sulphone **(301)** was only 30% (on a 4 mmol scale) (Exp.37a).

A number of alternative oxidants were examined. The sulphone **(301)** was obtained from the sulphide **(300)** by the action of m-CPBA (62% yield on a 1 mmol scale) following silica-gel chromatography and recrystallisation (Exp.37 b). Unfortunately, attempts to operate the reaction on a larger scale resulted in a much reduced yield of the sulphone **(301)**.

The sulphide **(300)** was reacted with"Oxone" to afford the sulphone **(301)** (62% yield on a 6.5 mmol scale following recrystallisation) (Exp.37 c), but again yields were poor on a larger scale. 300 MHz ^{1}H N.m.r. spectroscopy indicated that the sulphone **(301)** existed as a 5:1 mixture of rotamers in deuteriochloroform solution, due to restricted rotation about the amide bond, the spectrum showing a nine-proton singlet at δ 1.48, for the tert-butyl protons and two singlets at δ 3.82 and 3.88 (2.5 and 0.5 H, respectively) for the methyl ester protons. I.r. absorptions were present at 1 744, 1 701, and 1 676 cm^{-1} for the ester, urethane, and amide carbonyl groups, respectively. The mass spectrum of compound **(301)** showed a peak at m/z 354, attributable to the MNH_4^+ ion. The sulphone **(301)** displayed an elemental analysis consistent with the formula $C_{12}H_{20}N_2O_7S$.

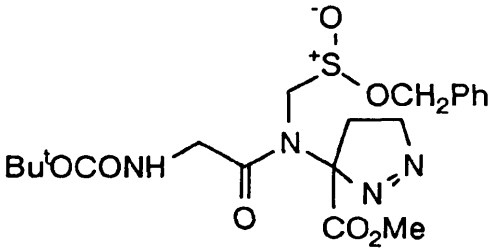
Suspecting that the low yield of the sulphone **(301)** on the larger scale may have been due to the use of an aqueous alcoholic solvent, the behaviour of tetra-n-butylammonium oxone (TBA-OX)[111] in dichloromethane was investigated. TBA-OX, which was readily prepared from "Oxone" and tetra-n-butylammonium hydrogen sulphate, did not show any significant

improvement, the sulphone (301) being isolated in 30 % yield on a 12 mmol scale (Exp.37 d).

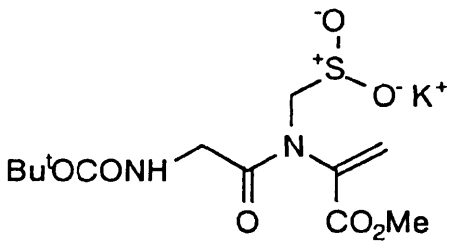
Finally, the use of peroxyacetic acid was examined for the oxidation of the sulphide (300) to the sulphone (301). The oxidant yielded the sulphone (301) in a modest 44% yield on a 5 mmol scale, following flash silica-gel chromatography and recrystallisation (Exp.37 e).

Having examined various oxidative methods for obtaining the sulphone (301) from the sulphide (300), attention was turned to performing the key β-elimination step on compound (301).

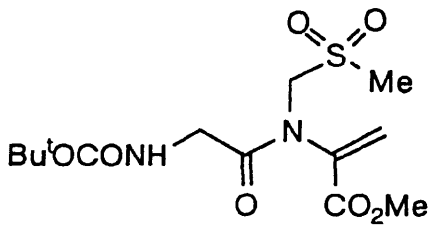
The sulphone (301) was treated sequentially with DBN and benzyl chloroformate. Work-up furnished the desired acrylate (302) as an analytically pure white foam; disappointingly, the yield was only 26% after purification by silica-gel chromatography (Exp.38). In accord with its proposed structure, compound (302) showed in its 300 MHz ^{1}H n.m.r. spectrum two one-proton singlets at δ 5.88 and 6.38, for the olefinic protons; i.r. also showed an i.r. absorption at 1 654 cm^{-1} for the olefinic group.



(305)



(306)



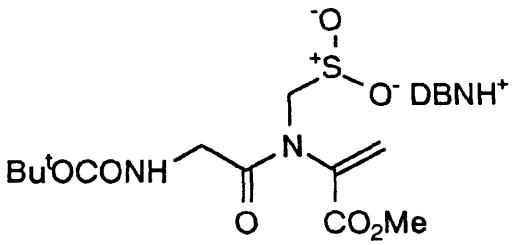
(307)

Reaction of the acrylate **(302)** in dichloromethane with an excess of ethereal diazomethane afforded, after evaporation, the pyrazoline **(305)**; crystallisation of the crude product furnished a single diastereoisomer of the pyrazoline **(305)** in 91% yield (Exp.39). In accord with the assignment, the ^{1}H n.m.r. spectrum of compound **(305)** displayed features consistent with a single isomer being present; in particular, a three-proton singlet was present at δ 3.72 for the methyl ester group. Compound **(305)** also displayed an elemental analysis consistent with the formula $C_{20}H_{28}N_4O_7S$.

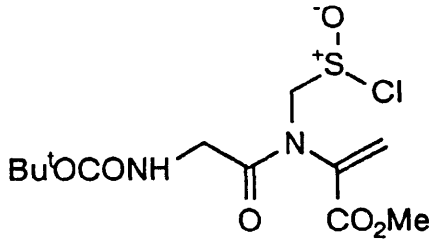
The behaviour of the sulphone **(301)** towards potassium tert-butoxide was next examined . The sulphone **(301)** afforded a yellow solid, considered to be the potassium salt **(306)** (90% yield), upon treatment with the freshly resublimed base in THF at -78 °C (Exp.40). The 300 MHz ^{1}H n.m.r. spectrum of this compound **(306)** was complex and the material failed to give an exceptable elemental analysis.

Proof for the proposed structure of the salt **(306)** was obtained by treatment of the material with iodomethane in DMF. The sole product isolated was the methyl sulphone **(307)** (28% yield after SiO_2 chromatography) (Exp.41). Its spectroscopic properties matched those of a compound produced by the reaction of the sulphone **(301)** with DBN followed by iodomethane (Exp.42) (21% yield after SiO_2 chromatography). In accord with the proposed structure, compound **(307)** displayed in its 300 MHz ^{1}H n.m.r. spectrum, two one-proton singlets at δ 6.25 and 6.62 for the olefinic protons. Additionally, compound **(307)** displayed an elemental analysis consistent with the constitution $C_{13}H_{22}N_2O_7S$.

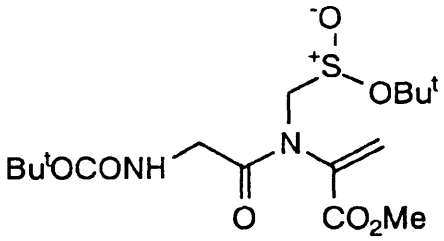
It was hoped that the sulphinates **(306)** or **(308)** would react with thionyl chloride (or oxalyl chloride) to afford the sulphinyl chloride **(309)**, which would then yield the sulphinate ester **(310)** upon reaction with tert-butyl alcohol.



(308)



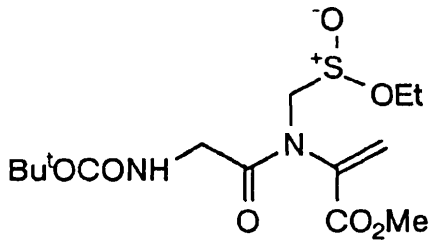
(309)



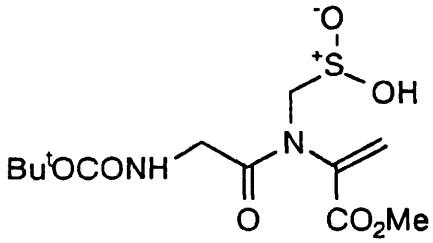
(310)

Sequential treatment of the sulphone **(301)** with DBN, thionyl chloride, and tert-butyl alcohol failed to yield the acrylate **(310)**. The ester **(310)** was formed, however, when the sulphone **(301)** in THF was treated sequentially with potassium tert-butoxide, oxalyl chloride, and tert-butyl alcohol (Exp.43); compound **(310)** was obtained in 47% yield after SiO_2 chromatography) as a clear oil. 300 MHz ^1H N.m.r. spectroscopy revealed the presence of two one-proton singlets at δ 6.21 and 6.60 for the acrylate protons and two nine-proton singlets at δ 4.05 and 4.15 for the tert-butyl protons. Unfortunately, attempts to repeat the preparation proved to be fruitless.

Sulphinate esters can be prepared by the reaction of sulphinate salts with alkyl chloroformates.[112-113]However, the reaction between the salt **(306)** and ethyl chloroformate failed to yield the sulphinate ester **(311)**. Additionally, when the sulphone **(301)** was treated with DBN followed by an acidic work-up, it failed to produce the sulphinic acid **(312)**.



(311)



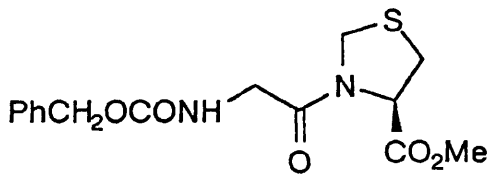
(312)

Due to the lack of success in performing the key β-elimination step on the sulphone **(301)**, it was hoped that a change in the nature of the amino protecting group would improve matters.

It was decided to examine the benzyloxycarbonyl (Z) group as the amino protecting group. The Z- group should enhance the ability of the sulphone to undergo β - elimination, due to its increased electron-withdrawing properties. In addition, due to the increased acid-stability of the Z-group, the oxidation step to the sulphone from the sulphide should be improved.

The sulphide **(313)** was prepared in quantitative yield by treating N-benzyloxycarbonylglycine **(314)** in dichloromethane with DCCI followed by the thiazolidine methyl ester **(181)** (Exp.44). On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(313)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution, displaying two singlets at δ 3.75 and 3.78 (2.25 and 0.75 H, respectively), for the ester protons. The ^{1}H n.m.r. spectrum was also run at higher temperatures, coalescence of the rotameric forms being virtually complete at 373 K and resulting in a significant simplification of the spectrum. The spectrum reverted back to its original form when the temperature was reduced back to 303 K. I.r. absorptions were present at 1 724 (ester and urethane carbonyl) and 1 664 cm^{-1} (amide carbonyl). The mass spectrum displayed a peak at m/z 338, attributable to the molecular

ion and compound **(313)** displayed an elemental analysis consistent with the formula $C_{15}H_{18}N_2O_5S$.



(313)

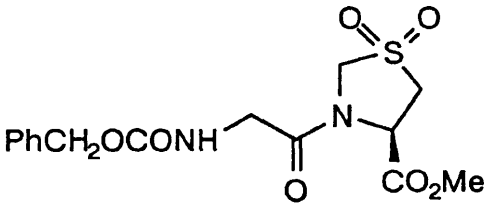
(314)

Oxidation of compound **(313)** to the sulphone **(315)** was performed in aqueous methanol by the action of "Oxone", which gave the sulphone **(315)** (90% yield after recrystallisation) (Exp.45).

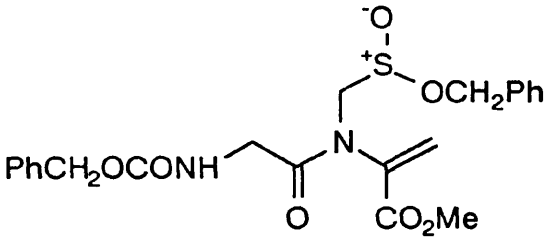
On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(315)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution, the spectrum displaying two-singlets at δ 3.68 and 3.72 (2.25 and 0.75 H, respectively), for the ester protons. I.r. absorptions were present at 1 751, 1 720, and 1 682 cm^{-1}, for the ester, urethane, and amide carbonyl groups, respectively. The mass spectrum displayed a peak at m/z 370, attributable to the molecular ion. Compound **(315)** displayed an elemental analysis consistent with the formula $C_{15}H_{18}N_2O_7S$.

Having obtained the sulphone **(315)** in good yield, attention was turned to performing the key β-elimination step. When compound **(315)** was treated with DBN in dichloromethane, followed by benzyl chloroformate, work-up afforded the benzyl sulphinate **(316)** in 18% yield as a white foam (Exp.46). The spectroscopic properties of compound **(316)** were in accord with the proposed structure. In particular, ^{1}H n.m.r. spectroscopy revealed the presence of a three-proton singlet at δ 3.72, for the ester protons, and two one-proton singlets at δ 5.97 and 6.49, for the olefinic protons. Additionally,

i.r. absorptions were present at 1 728 (ester and urethane carbonyl),1 690 (amide carbonyl), and 1 630 cm^{-1} (olefinic).

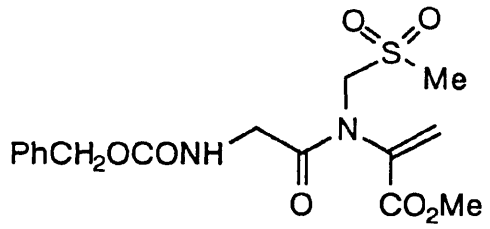


(315)

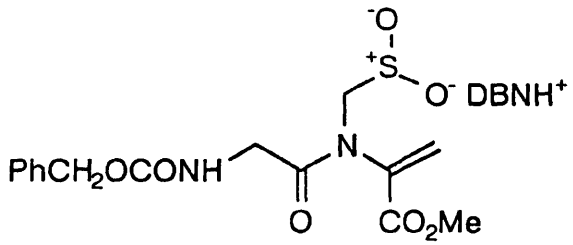


(316)

The poor yield of compound **(316)** was disappointing. However, sequential treatment of the sulphone **(315)** with DBN and iodomethane afforded the methyl sulphone **(317)** in good yield (77% after purification by SiO_2 chromatography) (Exp.47). The spectroscopic properties of compound **(317)** were in accord with the proposed structure. In particular, the ^1H n.m.r. spectrum displayed two three-proton singlets at δ 2.88 and 3.79, for the S-methyl and methyl ester protons, respectively, and two one-proton singlets at δ 6.25 and 6.50, for the olefinic protons. Additionally, i.r. absorptions were present at 1 742, 1 726, and 1 676 cm^{-1}, for the ester, urethane, and amide carbonyl groups, respectively.



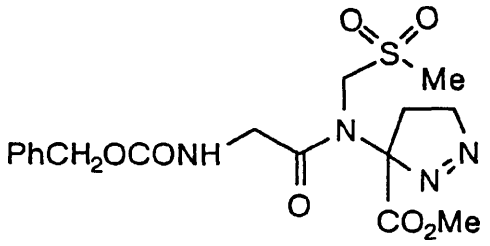
(317)



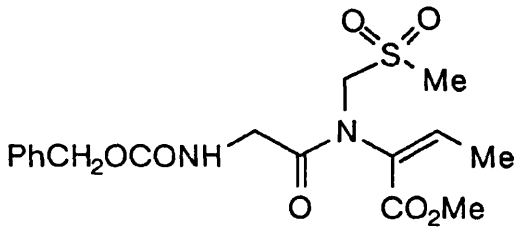
(318)

Experiments 46 and 47 indicate that the β-elimination step of the sulphone **(315)** with DBN to form the intermediate DBN salt **(318)** is a good one; clearly, it is the reaction of this DBN salt **(318)** with benzyl chloroformate which is responsible for the poor yield of compound **(316)** in Experiment 46.

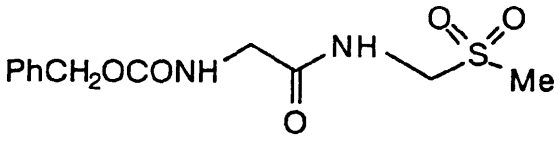
The acrylate **(317)** was reacted in dichloromethane with an excess of ethereal diazomethane to afford the pyrazoline **(319)** as a white crystalline solid in quantitative yield (Exp. 48). The 300 MHz ^{1}H n.m.r. spectrum (CD_3SOCD_3) of this compound was complex at 20 °C but a reasonable spectrum was obtained at 50 °C. At ca. 80 °C, elimination of nitrogen occurred; signals at δ 6.91 and 2.25 for the olefinic and methyl protons, respectively, were considered diagnostic evidence for the but-2-enoate product **(320)** (Exp. 49). Compound **(319)** also diplayed i.r. absorptions at 1 745, 1 725, and 1 680 cm^{-1}, for the ester, urethane, and amide carbonyl groups, respectively; its mass spectrum featured a peak at m/z 427, attributable to the MH^+ ion.



(319)



(320)

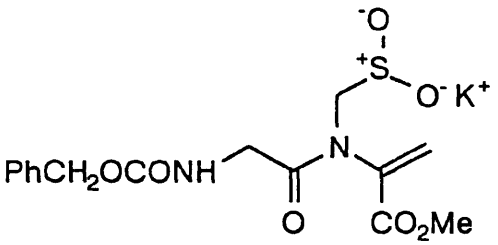


(321)

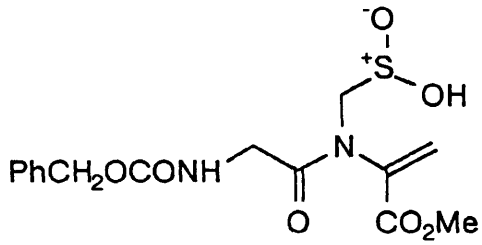
Removal of the pyrazoline group was effected by subjecting compound **(319)** to Barton's reducing conditions (Zn / $MeCO_2H$,/ H_2O, 0 °C). This afforded, after work-up, the dipeptide derivative **(321)** as a white solid (54% yield after recrystallisation) (Exp.50). Its 300 MHz ^1H n.m.r. spectrum displayed a three-proton singlet at δ 2.89, for the S-methyl protons, and two two-proton doublets (J 6 and 6.5 Hz) at δ 3.83 and 4.63, for the methylene protons of the NCH_2CO and NCH_2S groups, respectively. Additionally, compound **(321)** displayed i.r. absorptions at 1 690 and 1 660 cm^{-1}, for the urethane and amide carbonyl groups, respectively. The mass spectrum displayed a peak at m/z 301, attributable to the MH^+ ion. Compound **(321)** also showed an elemental analysis consistent with the formula $C_{12}H_{16}N_2O_5S$.

The behaviour of the sulphone **(315)** towards potassium tert-butoxide was next examined. The sulphone **(315)** afforded a yellow solid (92% yield), which was considered to be the potassium salt **(322)**, upon treatment with the base in THF at -78 °C (Exp.51).

When the salt was treated with Amberlite IR 120 (H^+) ion-exchange resin, work-up by evaporation afforded a pale-yellow solid considered to be the sulphinic acid **(323)** (92 % yield) (Exp.52). In accord with its proposed structure, compound **(323)** displayed in its mass spectrum a peak at m/z 370, attributable to the molecular ion, and a peak at m/z 306, attributable to the loss of sulphur dioxide from the molecular ion. However, its 300 MHz ^1H n.m.r. spectrum was complex suggesting that the sample was unstable.



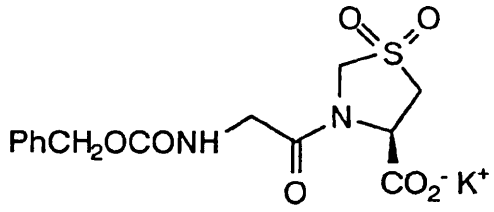
(322)



(323)

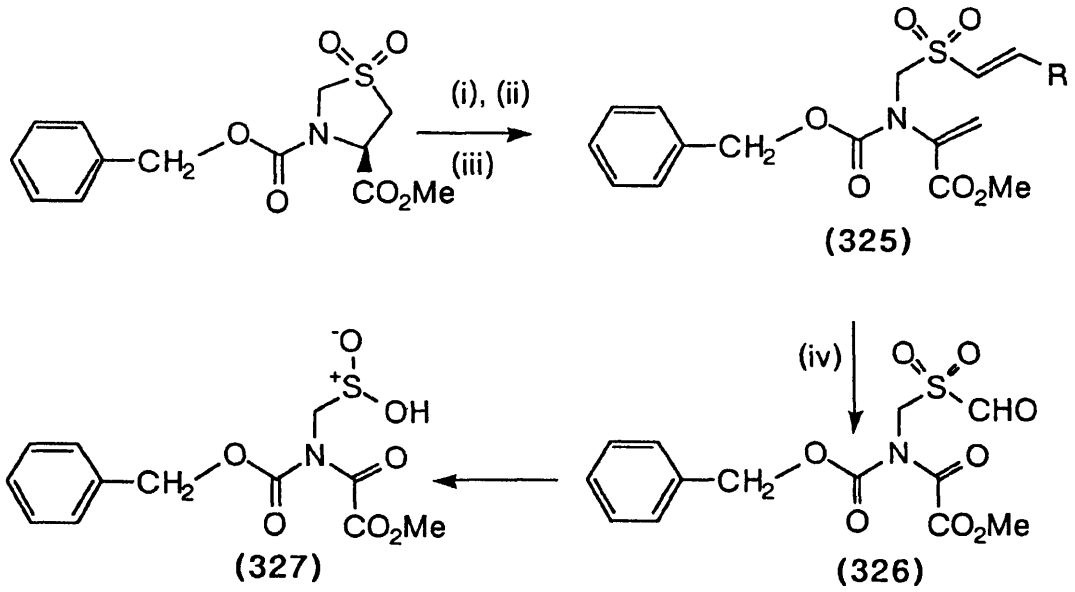
Evidence for the proposed structure of the salt (322) was obtained by treatment of compound (322) with iodomethane in DMF. A product was isolated from this reaction after silica-gel chromatography (Exp.53) which, on the basis of 300 MHz ^{1}H n.m.r. spectroscopy, was a 1:1 mixture of the thiazolidine sulphone (315) and the methylated material (317).

The sulphone (315) presumably arose from the methylation of the salt (324) which must have been present in the salt (322). Evidently, β-elimination of the sulphone (315) by potassium tert-butoxide was incomplete and some hydrolysis of the ester functionality in the sulphone (315) had occurred to give the salt (324) (probably induced by KOH in KOBu^t).



(324)

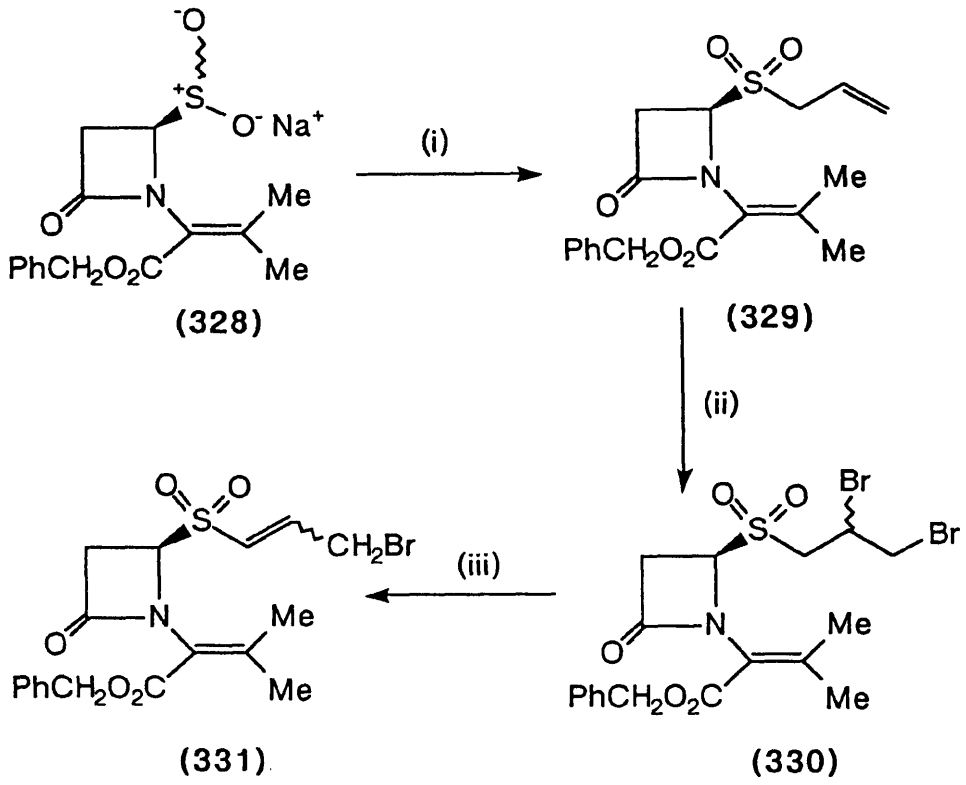
It was decided to examine methods for effecting the conversion of the sulphone **(166d)** into a vinyl sulphone of type **(325)**. It was considered that ozonolysis of the vinyl sulphone would afford a sulphonyl formate of type **(326)** which, it was anticipated, would be an unstable entity and would fragment to a sulphinic acid of type **(327)** and carbon monoxide under mild conditions (Scheme 52).



Scheme 52

Reagents : (i) DBN, CH_2=$CHCH_2Br$, (ii) Br_2, (iii) NEt_3, (iv) O_3, - 78 °C

In earlier work[114](Scheme 53), it was shown that the salt **(328)** reacted with allyl bromide to give the allyl sulphone **(329)**. The dibromide **(330)** was then obtained by treatment of the allyl sulphone **(329)** with bromine. The dibromide **(330)**, on reaction with triethylamine, gave the vinyl sulphone **(331)**, as a mixture of diastereoisomers.



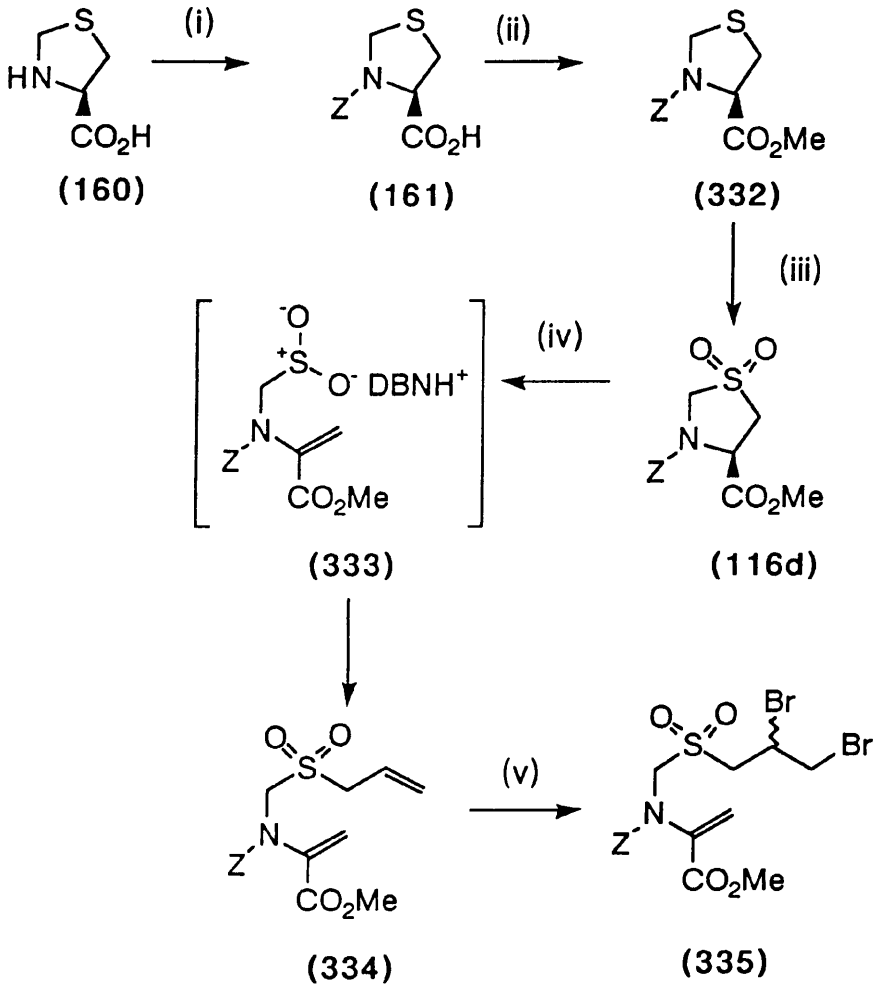
Scheme 53

Reagents: (i) CH_2=$CHCH_2Br$ / DMF, (ii) Br_2, (iii) Et_3N

Consequently, it was planned to examine the transformation of the thiazolidine carboxylic acid **(160)** into the allyl sulphone **(334)** by a route similar to that outlined in Scheme 53.

The acid **(160)** reacted with benzyl chloroformate in ice-cooled sodium hydroxide solution to afford the urethane **(161)** in 71% yield as an a oil (Exp.54). The ^1H n.m.r. spectrum of the product was in agreement with that reported.[81] Esterification of the acid **(161)** was achieved in dichloromethane by treatment with an excess of ethereal diazomethane to afford the methyl ester **(332)** in 81% yield as an oil (Exp.55). Oxidation of the sulphide **(332)** to the sulphone **(116d)** in 77% yield was performed using " Oxone " in aqueous methanol (Exp.56). The analytical and

spectroscopic properties of compound **(116d)** were in agreement with those of an authentic sample.[81]



Scheme 54

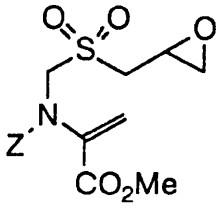
Reagents : (i) BzOCOCl / NaOH, (ii) CH_2N_2, (iii) "Oxone", (iv) DBN / CH_2=$CHCH_2Br$, (v) Br_2

The sulphone **(116d)** was treated sequentially with DBN and allyl bromide in DMF to afford the allyl sulphone **(334)** in 73% yield (after SiO_2 chromatography) as a microanalytically pure oil (Exp.57). The analytical and

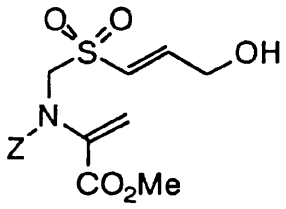
spectroscopic properties were in full accord with the proposed structure. The 300 MHz ^{1}H n.m.r. spectrum ($CDCl_3$) of the allyl sulphone **(334)** displayed broadening at ambient temperature due to restricted rotation about the urethane bond. However, at 100 °C, the spectrum (CD_3SOCD_3) showed considerable sharpening and simplification. I.r. absorptions were present at 1 730 (ester and urethane carbonyl) and 1 640 cm^{-1} (olefinic). The mass spectrum of compound **(334)** displayed a peak at m/z 354, attributable to the MH^+ ion.

However, when the allyl sulphone **(334)** was treated with bromine in dichloromethane, a mixture of products was observed due to the non-selective attack of the bromine at the allyl and the acrylate double bonds.

It was hoped that selective epoxidation of the allyl group of the sulphone **(334)** could be achieved by the use of m-CPBA, and that the resultant epoxide **(336)** could be transformed into the vinyl sulphone **(337)** on reaction with triethylamine. However, efforts to effect the epoxidation of the sulphone **(334)** by the use of m-CPBA were unsuccessful, even when refluxing conditions in dichloromethane were employed.



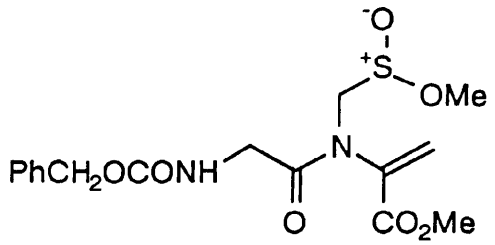
(336)



(337)

Previously, the sulphone **(315)** was treated with DBN in dichloromethane, followed by benzyl chloroformate to afford the benzyl sulphinate **(316)** in 18% yield. The poor yield of this sulphinate prompted an investigation of the use of an alternative chloroformate.

The sulphone **(315)** in dichloromethane was sequentially treated with DBN and methyl chloroformate, to give the methyl sulphinate ester **(338)** in a modest 33% yield, as a white solid (after SiO_2 chromatography and recrystallisation) (Exp. 58). On the basis of 300 MHz ^1H n.m.r. spectroscopy, compound **(338)** existed as a 3:1 mixture of rotamers in deuteriochloroform solution, the spectrum displaying two-three proton singlets at δ 3.79 and 3.84, for the methyl carboxylate and sulphinate esters, respectively, and two-one proton multiplets at δ 6.19-6.33 and 6.62-6.69, for the olefinic protons. Additionally compound **(338)** displayed i.r. absorptions at 1 730 (ester and urethane carbonyl), 1 690 (amide carbonyl), and 1 640 cm^{-1}(olefinic).



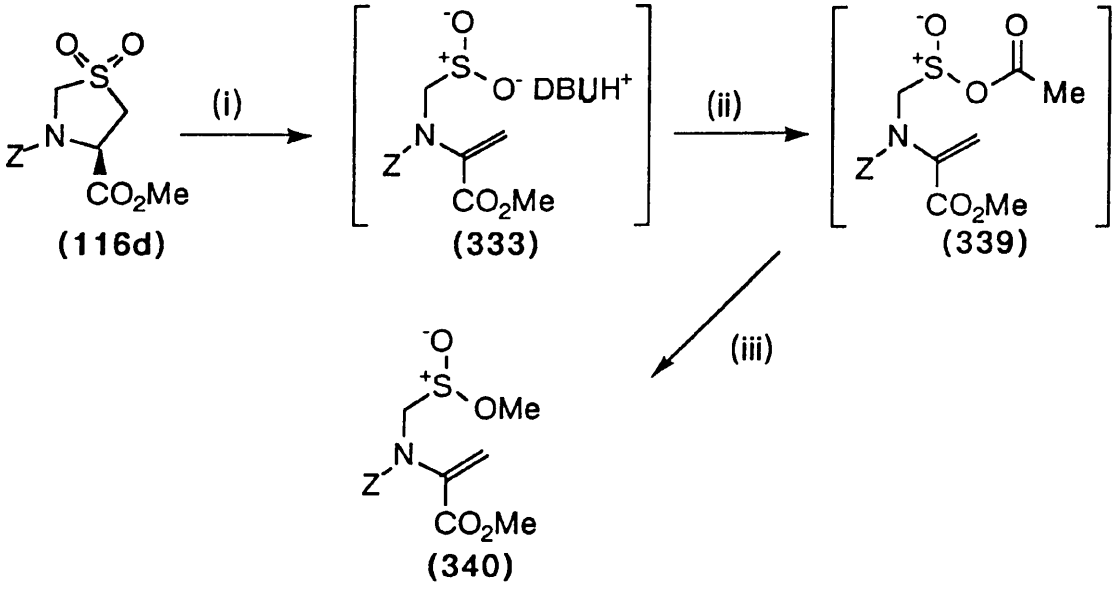
(338)

In an attempt to increase the yield of the sulphinate ester **(338)**, it was decided to investigate the use of alternative anhydride intermediates. The sulphone **(116d)** was selected as a model compound for this examination.

It was shown that the sulphone **(116d)**, on sequential treatment in dichloromethane with DBU, acetyl chloride (-78 °C) and an excess of methanol, gave an excellent yield of the methyl sulphinate **(340)** (75% yield) as a clear oil, following purification by silica-gel chromatography (Exp. 59). In accord with the proposed structure, compound **(340)** displayed in its 300 MHz ^1H n.m.r. spectrum, two three-proton singlets at δ 3.58 and 3.80 for

the methyl carboxylate and methyl sulphinate ester protons, respectively, and two one-proton singlets at δ 5.85 and 6.19 for the olefinic protons. Additionally, i.r. absorptions at 1 730 (ester and amide carbonyl) and 1 640 cm^{-1} (olefinic) were present and the mass spectrum displayed a peak at m/z 328, attributable to the MH^+ ion.

Presumably, the sulphinate salt **(333)** is initially formed and reacts with acetyl chloride to give the mixed anhydride **(339)** which is then attacked by methanol, selectively at sulphur, to afford the methyl sulphinate **(340)** (Scheme 55).



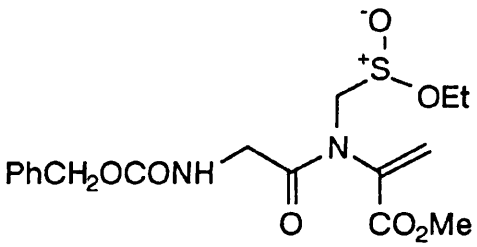
Scheme 55

Reagents : (i) DBU, (ii) MeCOCl, - 78 °C, (iii) MeOH

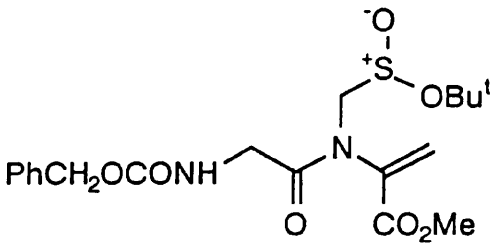
Having established a method for the conversion of sulphones into sulphinate esters (in a one-pot reaction) in good yield, this procedure was then extended to the sulphone **(315)**. When the sulphone **(315)** in dry

dichloromethane was treated sequentially with DBU, acetyl chloride at -78 °C, and methanol, the methyl sulphinate **(338)** was obtained in 77% yield (after SiO_2 chromatography) as a white solid (Exp.60). This compound was found to be identical with the material obtained in Experiment 58 by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

Similarly, the sulphinate esters **(341)** and **(342)** were obtained from the sulphone **(315)** by sequential treatment with DBU, acetyl chloride, and ethanol and with DBU, acetyl chloride, and tert-butyl alcohol, respectively. The esters **(341)** and **(342)** were obtained in 40 and 36 % yields (Exp. 61 and 62), respectively, and their analytical and spectroscopic properties were in accord with the proposed structures.



(341)



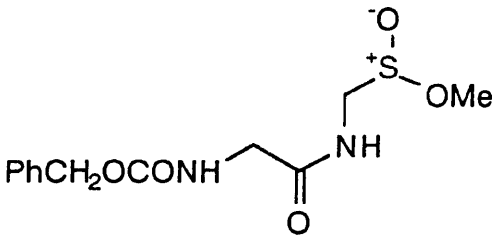
(342)

Compound **(341)** displayed in its 300 MHz ^1H n.m.r. spectrum two one-proton singlets at δ 6.11 and 6.66, due to the olefinic protons, and showed i.r. absorptions at 1 730 (ester and urethane carbonyl), 1 690 (amide carbonyl), and 1 640 cm^{-1} (olefinic). The mass spectrum showed a peak at m/z 399, attributable to the MH^+ ion. Additionally, compound **(341)** displayed an elemental analysis consistent with the constitution $C_{17}H_{22}N_2O_7S$.

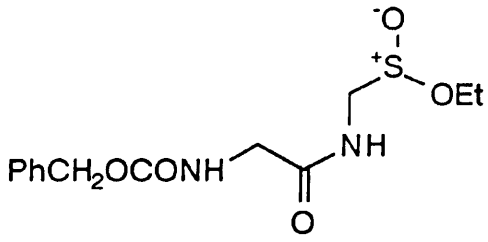
Compound **(342)** displayed in its 300 MHz ^1H n.m.r. spectrum a nine-proton singlet at δ 1.45, for the tert-butyl group, and two one-proton singlets at δ 6.25 and 6.63, for the olefinic protons. Its i.r. spectrum featured

absorptions at 1 730 (ester and urethane carbonyl), 1 690 (amide carbonyl), and 1 640 cm^{-1} (olefinic). The mass spectrum showed a peak at m/z 427, attributable to the MH^+ ion. Additionally, compound **(342)** displayed an elemental analysis consistent with the constitution $C_{19}H_{26}N_2O_7S.CHCl_3$.

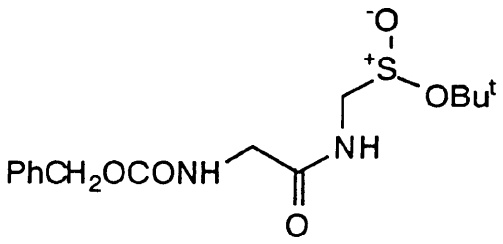
The transformation of compounds **(338)**, **(341)** and **(342)** into the dipeptide derivatives **(343)**, **(344)** and **(345)** requires the removal of the acrylate portions. Attention was therefore turned to the conversion of the acrylate **(342)** into the protected dipeptide compound **(345)**.



(343)



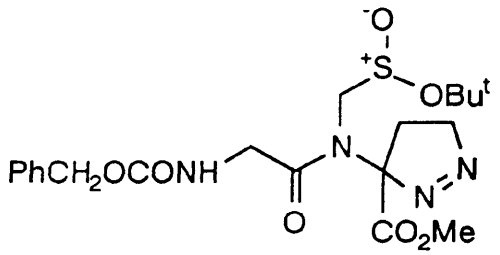
(344)



(345)

The acrylate **(342)** was reacted with an excess of ethereal diazomethane to afford the Δ^1-pyrazoline **(346)** as a single diastereoisomer in 95% yield (after recrystallisation) as a white solid (Exp. 63.) The ^1H n.m.r. spectrum of compound **(346)** displayed a nine-proton

singlet at δ 1.36 for the tert-butyl group and a three-proton singlet at δ 3.66 for the methyl ester group. I.r. absorptions were present at 1 745, 1 730, and 1 680 cm^{-1}, for the ester, urethane, and the amide carbonyl groups. The mass spectrum of compound **(346)** showed a peak at m/z 469, attributable to the MH+ ion and a peak at m/z 347, attributable to the loss of the SO_2Bu^t group from the molecular ion. Additionally, compound **(346)** displayed an elemental analysis consistent with the formula $C_{20}H_{28}N_4O_7S$.

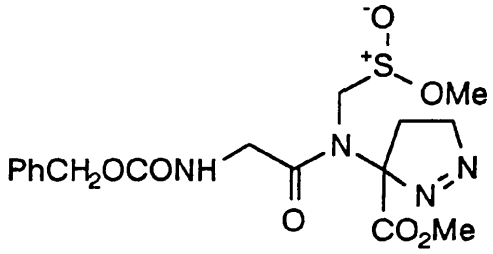


(346)

The pyrazoline **(346)** reacted with zinc in aqueous acetic acid-acetone at 0 °C to afford the dipeptide derivative **(345)** in 90% yield as a microanalytically pure foam (Exp. 64). In accord with the proposed structure, compound **(345)** displayed i.r. absorptions at 1 730 and 1 695 cm^{-1} for the urethane and amide carbonyl groups, respectively. ^1H N.m.r. spectroscopy established that the sulphinate moiety was intact, the spectrum displaying a three-proton multiplet at δ 3.77-4.40 and a one proton double doublet at δ 5.37 (J 15 and 7 Hz), for the methylene protons NCH_2CO and NCH_2S. The mass spectrum did not display a molecular ion; however, it did show a peak at m/z 343, attributable to the MH^+ ion and a peak at m/z 221, attributable to the loss of the SO_2Bu^t group from the molecular ion.

The removal of the acrylate group from the methyl sulphinate **(338)** was also examined. The acrylate **(338)**, on reaction with an excess of

diazomethane, afforded a white solid which was mainly the Δ^1-pyrazoline **(347)**. Purification of the material by silica-gel chromatography afforded the Δ^1-pyrazoline **(347)** as a white solid in 77% yield (Exp. 65). In accord with the proposed structure, compound **(347)** displayed a microanalysis consistent with the constitution $C_{17}H_{22}N_4O_7S$. The ^1H n.m.r. spectrum of the pyrazoline **(347)** supported the contention that the cycloadduct was obtained as a single diastereoisomer, displaying two three-proton singlets at δ 3.75 and 3.83, for the sulphinate and methyl ester groups . I.r. absorptions were present at 1 750, 1 730, and 1 680 cm^{-1}, for the ester, urethane, and amide carbonyl group, respectively. Additionally, the mass spectrum displayed a peak at m/z 427, attributable to the MH^+ ion.

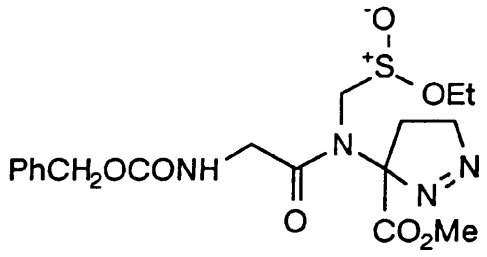


(347)

When the pyrazoline **(347)** was subjected to Barton's reducing conditions (Zn / $MeCO_2H$ / H_2O, 0 °C), work-up afforded a mixture of two products (ca. 74% by mass). Purification by silica-gel chromatography afforded the dipeptide derivative **(343)** as a white powder in 46% yield (Exp. 66). In accord with its structure, compound **(343)** displayed an elemental analysis consistent with the formula $C_{12}H_{16}N_2O_5S$. I.r. absorptions were present at 1 695 and 1 670 cm^{-1}, for the urethane and amide carbonyl groups, respectively. The 300 MHz ^1H n.m.r. spectrum displayed a three-proton multiplet at δ 3.80-4.24 for the NCH_2CO and NCHHS protons and a one-proton double-doublet (J 7 and 13 Hz) at δ 4.40

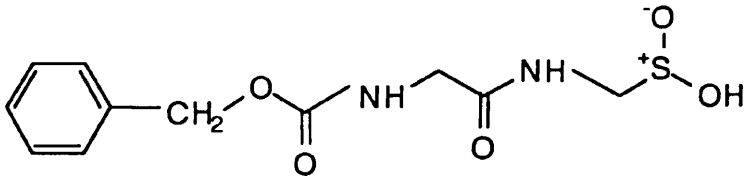
for the NCHHS proton. The mass spectrum displayed a peak at m / z 301, attributable to the MH$^+$ ion.

The acrylate **(341)**, on reaction with an excess of ethereal diazomethane, afforded the Δ^1-pyrazoline **(348)** as a brittle white foam in quantitative yield (Exp. 67); ^{1}H N.m.r. spectroscopy established that the pyrazoline was present as a single diastereoisomer; in particular, the spectrum featured a three-proton singlet at δ 3.74 for the methyl ester group. Compound **(348)** also displayed i.r. absorptions at 1 745, 1 730, and 1 680 cm^{-1}, for the ester, urethane, and amide carbonyl group respectively. The mass spectrum showed a peak at m/z 441, attributable to the MH$^+$ ion. Compound **(348)** displayed an elemental analysis consistent with the formula $C_{18}H_{24}N_4O_7S$.



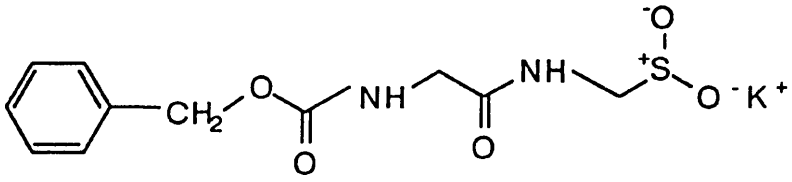
(348)

Perrone and Stoodley[84] have used trifluoroacetic acid for the removal of tert-butyl groups from penicillinate-derived sulphinate esters. Exposure of the ester **(345)** to neat trifluoroacetic acid in deuteriochloroform afforded a new volatile tert-butyl-containing material; however, work-up did not give the sulphinic acid **(349)**. Seemingly, compound **(349)** was unstable to the acidic conditions.



(349)

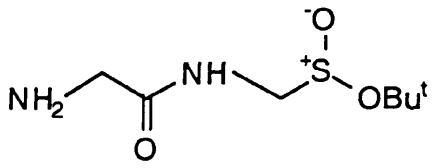
Similarly, exposure of the ester (342) to formic acid in deuteriochloroform, showed removal of the tert-butyl group, but no evidence for the sulphinic acid (323) was found. However, treatment of the dipeptide derivative (345) with neat formic acid, followed by evaporation of the excess formic acid and consequent treatment of the recrystallised residue with potassium-2-ethylhexanoate in ethyl acetate-diethyl ether caused the precipitation of a white solid. This was separated by centrifugation and identified as the potassium salt (350) (47% yield) (Exp.68). In accord with the proposed structure, compound (350) displayed in its 300 MHz ^{1}H n.m.r. spectrum, two two-proton multiplets at δ 3.75-3.86 and 3.95-4.03, for the two methylene protons. It also showed an elemental analysis consistent with the formula $C_{11}H_{13}KN_2O_5S$.



(350)

Additonal structural proof was obtained by treating the salt (350) with iodomethane in DMF to afford the methyl sulphone (321) (53% yield) (Exp.69), which was found to be identical with the material isolated in Experiment 50 by m.p. and ^{1}H n.m.r. spectroscopy.

It was decided to attempt to remove the Z-group from the dipeptide derivative **(345)** in the hope of obtaining compound **(351)**. A number of methods are available for the cleavage of the Z-group, the most common of which is catalytic hydrogenation.[115]



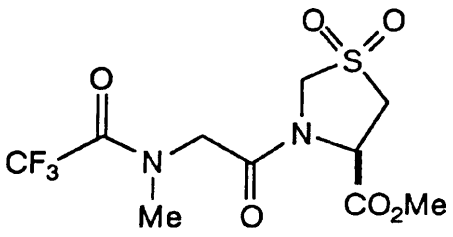
(351)

Unfortunately, when the dipeptide derivative **(345)** was subjected to catalytic hydrogenation using 10% palladium on charcoal, no reaction was observed and full recovery of the starting dipeptide **(345)** was achieved. It was suspected that the sulphinate moiety of compound **(345)** was poisoning the palladium catayst.

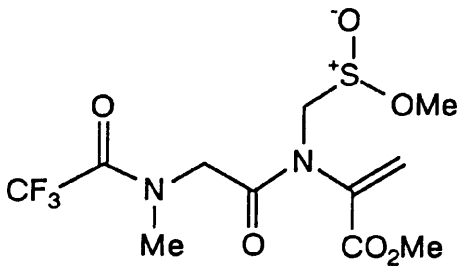
It was shown by Meienhofer and Kuromizu[116] that, when ammonia is used as a solvent in catalytic hydrogenations, cysteine or methionine units in a peptide do not poison the catalyst. However, when compound **(345)** was subjected to catalytic hydrogenation using ammonia as a solvent, no cleavage of the Z-group was observed and recovery of the starting material was achieved.

The removal of the Z-group from the potassium salt **(350)** was also investigated, using catalytic hydrogenation. However, no cleavage of the Z-group was observed.

Although the sulphone **(265)** had been previously obtained, its β-elimination reaction had not been very successful. It was therefore decided to investigate the sequential reaction of the sulphone **(265)** with DBU, acetyl chloride, and methanol in the hope of obtaining the sulphinate ester **(352)** in improved yield.



(265)

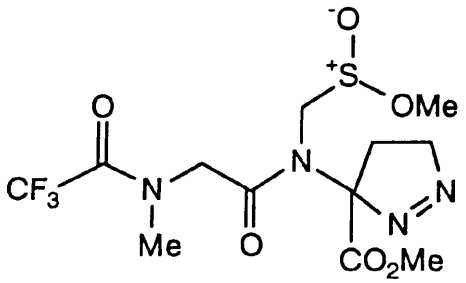


(352)

The reaction of the sulphone **(265)** with DBU and acetyl chloride at -78 °C followed by an excess of methanol led to the required acrylate **(352)** in 67% yield (after SiO_2 chromatography and recrystallisation) as a white solid (Exp. 70). 300 MHz ^1H n.m.r. spectroscopy indicated that the acrylate existed as a 4:1 mixture of rotamers in deuteriochloroform solution, due to restricted rotation about the amide bond, the spectrum showing a singlet and a multiplet at δ 3.09 and 3.18-3.24 (0.6 and 2.4 H, respectively), for the N-methyl protons, and two-three proton singlets at δ 3.81 and 3.88, for the methyl carboxylate and methyl sulphinate protons; in addition, a one-proton singlet and a one-proton multiplet were present at δ 6.25 and 6.60-6.75, for the olefinic protons. I.r. absorptions were observed at 1 730 (ester carbonyl), 1 700 (trifluoroacetyl and amide carbonyl), and 1 640 cm^{-1} (olefinic). Although the mass spectrum did not display a molecular ion, a peak at m/z 361 was observed and attributed to the MH^+ ion. Additionally, compound **(352)** displayed an elemental analysis consistent with the constitution $C_{11}H_{15}F_3N_2O_6S$.

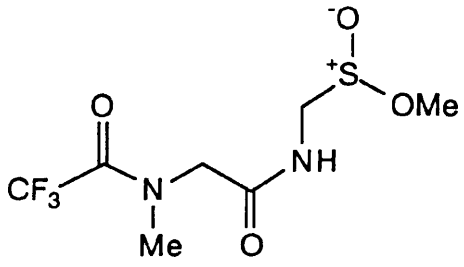
Reaction of the acrylate **(352)** with an excess of ethereal diazomethane afforded the Δ^1-pyrazoline **(353)** as a white solid in 95% yield (Exp.71). The ^1H n.m.r spectrum displayed two three-proton signals at δ 3.60-3.71 and 3.74-3.83, which were attributed to the methyl ester and sulphinate ester protons. I.r. absorptions were present at 1 750 (ester carbonyl) and 1 700br cm^{-1} (trifluoroacetyl and amide carbonyl)

and the mass spectrum displayed a peak at m/z 420, attributable to the MNH_4^+ ion. Additionally, compound **(353)** displayed an elemental analysis consistent with the formula $C_{12}H_{17}F_3N_4O_6S$.



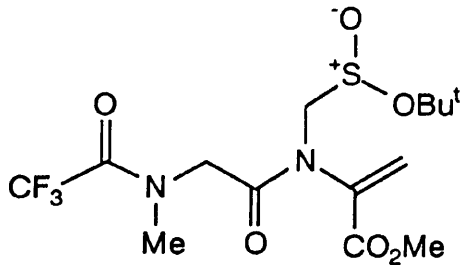
(353)

When the pyrazoline **(353)** was subjected to Barton's reducing conditions (Zn / $MeCO_2H$ /H_2O, 0 °C), work-up afforded a mixture of components, which on the basis of 300 MHz ^1H n.m.r. spectroscopy, did contain the dipeptide derivative **(354)** (Exp. 72). The ^1H n.m.r. spectrum displayed a three proton multiplet at δ 3.09-3.35, for the N-methyl group, and a three proton doublet (J 3.5 Hz) at δ 3.83, for the methyl sulphinate protons.

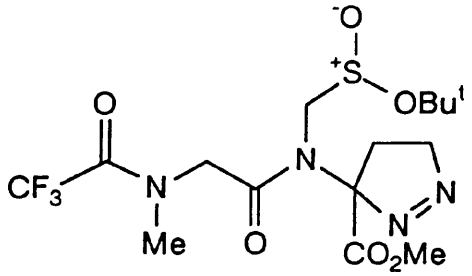


(354)

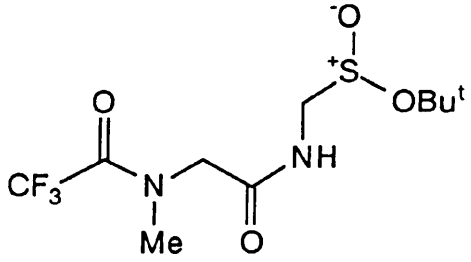
The observation that this reaction gave a mixture of products raised a concern about the stability of the methyl sulphinate ester. With this in mind, it was decided to examine the ease of removal of the acrylate moiety from the tert-butyl sulphinate ester **(355)**.



(355)



(356)



(357)

The sulphone **(265)**, on sequential reaction with DBN, acetyl chloride (-78 °C), and an excess of tert-butyl alcohol, gave the required acrylate **(355)** (60% yield) as a clear oil, following purification by silica-gel chromatography(Exp.73). In accord with the proposed structure, compound **(355)** displayed in its 300 MHz ^{1}H n.m.r. spectrum, a nine-proton singlet at δ 1.45, for the tert-butyl protons, a three-proton singlet at δ 3.86, for the methyl ester protons, and a one-proton singlet and a one-proton multiplet at δ 6.30 and 6.56-6.69, for the olefinic protons. I.r. absorptions were present at 1 735 (ester carbonyl), 1 705br (trifluoroacetyl and amide carbonyl), and 1 640 cm^{-1} (olefinic). Additionally, compound **(355)** displayed a peak at m/z 403, attributable to the MH^+ ion, and an elemental analysis consistent with the formula $C_{14}H_{21}F_3N_2O_6S$.

The acrylate **(355)** was reacted with an excess of ethereal diazomethane to afford the Δ^1-pyrazoline **(356)** as a single diastereoisomer

in 96% yield (after recrystallisation) as a white solid (Exp.74). In accord with the assignment, the ^{1}H n.m.r. spectrum displayed one nine-proton and two-three proton singlets at δ 1.48, 3.24, and 3.76, for the tert-butyl, N-methyl, and methyl ester protons, respectively. I.r. absorptions were present at 1 755 (ester carbonyl) and 1 710-1 680br cm^{-1} (trifluoroacetyl and amide carbonyl) and the mass spectrum displayed a peak at m/z 445, attributable to the MH^+ ion. Additionally, compound **(356)** displayed an elemental analysis consistent with the formula $C_{15}H_{23}F_3N_4O_6S$.

When the pyrazoline **(356)** was reacted with zinc in aqueous acetic acid-acetone at 0 °C, work-up afforded the dipeptide derivative **(357)** in 80% yield as a microanalytically pure syrup (Exp.75). The spectroscopic properties were in full agreement with the proposed structure. On the basis of 300 MHz ^{1}H n.m.r. spectroscopy, compound **(357)** existed as a 4:1 ratio of rotamers in deuteriochloroform solution, the spectrum displaying a nine-proton singlet at δ 1.44, for the tert-butyl protons, and two-singlet signals at δ 3.10 and 3.24 (0.6 and 2.4 H, respectively) for the N-methyl protons. Compound **(357)** displayed an i.r. absorption at 1 700 cm^{-1}, for the trifluoroacetyl and amide carbonyl group. The mass spectrum featured a peak at m/z 319, attributable to the MH^+ ion. Additionally, compound **(357)** displayed an elemental analysis consistent with the constitution $C_{10}H_{17}F_3N_2O_4S$.

Previously, the reaction of compound **(291)** with DBN followed by benzyl chloroformate had led, after work-up, to a very low recovery of material. The sequential reaction of the sulphone **(291)** with DBN, acetyl chloride, and methanol was investigated in the hope of improving the yield of the hoped-for product. Gratifyingly, the acrylate **(358)** was isolated, following purification by silica-gel chromatography, as a clear oil in 43% yield (Exp.76). In accord with the proposed structure, compound **(358)** displayed in its 300 MHz ^{1}H n.m.r. spectrum a three-proton singlet at δ 3.80, for the methyl ester

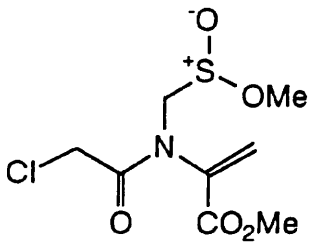
decided to change the methyl sulphinate protecting group for a tert-butyl sulphinate ester.

The chloro ketone sulphone **(291)** reacted with DBN, acetyl chloride, and tert-butyl alcohol to give, after work-up, silica-gel fractionation, and recrystallisation, the desired acrylate compound **(359)** as a white solid in 45% yield (Exp.77). In accord with the proposed structure, the 300 MHz ^1H n.m.r. spectrum of compound **(359)** displayed a nine and a three-proton singlet at δ 1.46 and 3.85, for the tert-butyl and methyl ester protons, respectively. I.r. absorptions were present at 1 725, 1 675, and 1 635 cm^{-1}, for the ester carbonyl, amide carbonyl, and the olefinic groups. The mass spectrum displayed a peak at m/z 312, attributable to the MH^+ ion. Compound **(359)** displayed an elemental analysis consistent with the formula $C_{11}H_8ClNO_5S$.

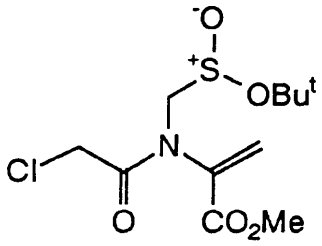
The acrylate **(359)** reacted with an excess of ethereal diazomethane to afford after purification by silica-gel chromatography the Δ^1-pyrazoline **(360)** as a single isomer in 97% yield as a clear oil (Exp.78). In accord with the assignment the ^1H n.m.r. spectrum of compound **(360)** displayed a three-proton signal at δ 3.72-3.77, for the methyl ester protons. I.r. absorptions were present at 1 745 and 1 665 cm^{-1}, for the ester and amide carbonyl groups, respectively. Additionally the mass spectrum showed a peak at m/z 232, attributable to the loss of the SO_2Bu^t group from the molecular ion.

Unfortunately, removal of the pyrazoline group from compound **(360)**, employing Barton's reducing conditions, led to a mixture of components. However, 300 MHz ^1H n.m.r. spectroscopy suggested that compond **(361)** was present in the mixture; no attempt was made to isolate the material **(361)**, due to the small quantity available (Exp.79).

protons, and a three-proton multiplet at δ 3.85-3.90, for the methyl sulphinate ester protons. I.r. absorptions were present at 1 730, 1 690, and 1 635 cm^{-1}, for the ester carbonyl, amide carbonyl, and the olefinic groups, respectively. The mass spectrum of compound **(358)** showed a peak at m/z 270, attributable to the $(M-2)H^+$ ion. Compound **(358)** displayed an elemental analysis consistent with the formula $C_8H_{10}ClNO_5S$.



(358)



(359)

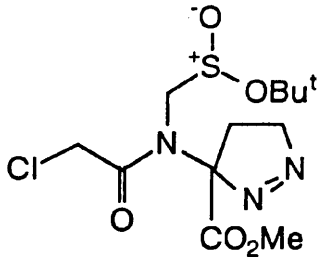
However, when the acrylate **(358)** was reacted with an excess of ethereal diazomethane, work-up afforded a mixture of products. Due to the lack of success in removing the acrylate moiety of compound **(358)**, it was decided to change the methyl sulphinate protecting group for a tert-butyl sulphinate ester.

The chloro ketone sulphone **(291)** reacted with DBN, acetyl chloride, and tert-butyl alcohol to give, after work-up, silica-gel fractionation, and recrystallisation, the desired acrylate compound **(359)** as a white solid in 45% yield (Exp.77). In accord with the proposed structure, the 300 MHz ^1H n.m.r. spectrum of compound **(359)** displayed a nine and a three-proton singlet at δ 1.46 and 3.85, for the tert-butyl and methyl ester protons, respectively. I.r. absorptions were present at 1 725, 1 675, and 1 635 cm^{-1}, for the ester carbonyl, amide carbonyl, and the olefinic groups. The mass spectrum displayed a peak at m/z 312, attributable to the MH^+ ion.

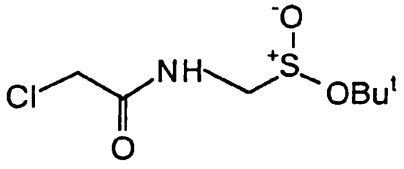
Compound **(359)** displayed an elemental analysis consistent with the formula $C_{11}H_8ClNO_5S$.

The acrylate **(359)** reacted with an excess of ethereal diazomethane to afford after purification by silica-gel chromatography the Δ^1-pyrazoline **(360)** as a single isomer in 97% yield as a clear oil (Exp.78). In accord with the assignment the ^1H n.m.r. spectrum of compound **(360)** displayed a three-proton signal at δ 3.72-3.77, for the methyl ester protons. I.r. absorptions were present at 1 745 and 1 665 cm^{-1}, for the ester and amide carbonyl groups, respectively. Additionally the mass spectrum showed a peak at m/z 232, attributable to the loss of the SO_2Bu^t group from the molecular ion.

Unfortunately, removal of the pyrazoline group from compound **(360)**, employing Barton's reducing conditions, led to a mixture of components. However, 300 MHz ^1H n.m.r. spectroscopy suggested that compound **(361)** was present in the mixture; no attempt was made to isolate the material **(361)**, due to the small quantity available (Exp.79).



(360)



(361)

Final Comments

The work described in this section has examined some approaches to dipeptides containing an α-aminomethanesulphinic acid moiety. Construction of the backbone framework of atoms was achieved and it was clear that the dipeptide analogue **(240)** could be isolated when the amino group was protected by the Z-group and the acid was present as the potassium salt.

However, further work is required to effect the removal of the Z-group from the potassium salt **(350)**, but the prospect of preparing other substituted dipeptides containing substituted α-amino sulphinic acids appears to be good.

EXPERIMENTAL

General Experimental Details

Melting points were determined using a Buchi 512 melting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature (20-25 °C) with a Thorn-Automation-NPL automatic polarimeter, type 243. Infra-red (i.r.) spectra were recorded using a Unicam S.P. 200 or a Perkin-Elmer 783 spectrometer : solids as potassium bromide discs, syrups and oils as natural films between sodium chloride or caesium iodide plates. Ultra-violet (u.v.) spectra were determined using either a Cary 118 spectrometer or a Perkin-Elmer lambda 15 u.v. / vis. spectrophotometer. Mass spectra were recorded using either an A. E. I. MS9 or a Kratos MS45 spectrometer.

^{1}H Nuclear magnetic resonance (n.m.r.) spectra were measured at 60 MHz using a Varian EM360, at 220 MHz using a Perkin-Elmer R34, and at 300 MHz using a Brucker AC300 E or a Varian XL 300 spectrometer. Tetramethylsilane was used as the internal standard for spectra run in deuteriochloroform and deuteriodimethyl sulphoxide. 3-(Trimethylsilyl)propanesulphonic acid sodium salt was used as the internal stanard for spectra run in deuterium oxide.

Microanalyses were performed with a Carlo-Erba Instrumentazione Model 1106 analyser.

Solvents were dried in the following manner: dichloromethane was distilled from calcium hydride; light petroleum and hexane were distilled from sodium wire; diethyl ether and tetrahydrofuran (THF) were predried over sodium wire before being distilled from benzophenone ketyl; triethylamine was distilled from calcium hydride and stored over potassium hydroxide pellets; N,N-dimethylforamide (DMF) was distilled from calcium hydride at reduced pressure (ca. 1 mm of Hg) and stored over activated 4 A molecular sieves; pyridine was distilled from potassium hydroxide and

stored over 4 A molecular sieves; methanol and acetone (Analar grade) were stored over activated 4 A molecular sieves.

Diazomethane was prepared by treatment of an ethereal solution of N-methyl-N-nitroso-p-toluenesulphonamide ('Diazald') with sodium hydroxide; it was stored in ethereal solution at -20 °C. All reactions involving air-sensitive reagents were performed under an atmosphere of dry nitrogen or argon.

The term 'evaporation' refers to solvent removal on a Buchi rotatory evaporator at water-pump pressure at 30-40 °C for solvents boiling at or below 80 °C at atmospheric pressure or at ca. 1 mm of Hg at 20-40 °C (for higher boiling solvents), followed by evacuation of the flask at ca. 0.1 mm of Hg for 0.25-2 h.

Column chromatography was performed using Merck Kieselgel 60 H silica gel, under reduced pressure (water pump). Thin layer chromatography (t.l.c.) was carried out using Merck t.l.c. plastic sheets of silica gel (60 F_{254}), precoated to 0.2 mm thickness. The plates were examined firstly under u. v. light and then developed using an aqueous potassium permanganate aerosol spray.

Unless stated, all yields refer to purified compounds: solids by chromatography and/or recrystallisation, syrups and oils by chromatography.

Experiment 1

Reaction of L-Cysteine Hydrochloride **(241)** with Formaldehyde

L-Cysteine hydrochloride **(241)** (63.31 g, 0.402 mmol) was dissolved in water (200 cm^3) and the solution was treated with 40% formaldehyde solution (46 cm^3) and left to stand overnight at room temperature. On addition of pyridine (53 cm^3), crystals appeared which, on filtration and recrystallisation from hot water, afforded (4R)-thiazolidine-4-carboxylic acid **(160)** (35.3 g, 65%) as white powdery crystals;

m.p. 196 °C (with decomp.) (lit.,[93] 196-197 °C),

$\nu_{max.}$ (KBr) inter alia 3 450br ($^{+}NH_2$) and 1 630 cm^{-1} (CO_2^-).

Experiment 2.

Reaction of the Acid **(160)** with Methanolic Hydrogen Chloride

The acid **(160)** (9.78 g, 66.5 mmol) was heated under reflux in saturated methanolic hydrogen chloride (65 cm^3) for 2 h. Evaporation to a small volume followed by addition of diethyl ether (20 cm^3) caused precipitation of the methyl ester hydrochloride. This crude hydrochloride was dissolved in water (20 cm^3) and treated with an excess of sodium carbonate. The solution was extracted with diethyl ether (x2) and the dried ($MgSO_4$) ethereal extracts evaporated to yield methyl (4R)-thiazolidine-4-carboxylate **(181)** (9.91 g, 73 %) as a clear oil ;[93]

$\nu_{max.}$ (film) inter alia 1 740 cm^{-1} (ester C=O),

δ (220 MHz, $CDCl_3$) 2.88 (1 H, dd, J 10 and 8 Hz, 5-H), 3.25 (1 H, dd, J 10 and 7 Hz, 5-H), 3.79 (3 H, s, CO_2Me), 3.88 (1 H, t, separation 8 Hz, 4-H), and 4.12 and 4.37 (each 1 H, d, J 10 Hz, 2-H_2) .

Experiment 3

Reaction of N-Phthaloylglycyl Chloride with the Methyl Ester **(181)**

N-Phthaloylglycine (14.36 g, 70 mmol) and thionyl chloride (85 cm^3) were heated under reflux for 2 h. Evaporation of the excess thionyl chloride yielded phthaloylglycyl chloride (15.67 g, 100%) which was dissolved in dry dichloromethane (50 cm^3). The solution was cooled to 0 °C and treated with the methyl ester **(181)** (10.3 g, 70 mmol) followed by a solution of triethylamine (7.07 g, 70 mmol) in dichloromethane (50 cm^3) added over 5 min. After stirring for 2 h, work-up [by dilution with CH_2Cl_2 (150 cm^3) and washing sequentially with dilute HCl, saturated $NaHCO_3$ solution and brine, followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from $CHCl_3$-EtOH] afforded methyl (4R)-3-(α-phthalimido)acetylthiazolidine-4-carboxylate **(182)** (17.08 g, 73%), existing as a 3:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 170 °C (lit.,[98] 170-172 °C),

$\nu_{max.}$ (KBr) inter alia 1 780 and 1 715 (imide C=O), 1 710 (ester C=O), and 1 655 cm^{-1} (amide C=O),

δ (220 MHz, $CDCl_3$) 3.30 (2 H, m, 5-H), 3.74 and 3.98 (2.25 H and 0.75 H, each s, CO_2Me), 4.37-4.79 (3 H, m, 2-H and NCH_2CO), 4.99br (0.25

H, d, separation 5 Hz, 4-H), 5.12 (0.75 H, dd, J 7 and 4 Hz, 4-H), and 7.71-7.74 and 7.84-7.88 (each 2 H, m, C_6H_4).

Experiment 4

Reaction of the Sulphide **(182)** with Potassium Permanganate

The sulphide **(182)** (15.6 g, 41.7 mmol) was dissolved in 80% acetic acid (300 cm^3) and treated dropwise with potassium permanganate (14.8 g, 93.4 mmol) in water (150 cm^3) at 0 °C over 1 h. After a further 1 h, the colour was discharged with aqueous hydrogen peroxide. Work-up [by dilution with EtOAc, sequential washing with saturated $NaHCO_3$ solution, brine and water, followed by evaporation of the dried ($MgSO_4$) organic extract and recrystallisation of the residue from $CHCl_3$-EtOH] afforded (4R)-4-methoxycarbonyl-3-(α-phthalimido)acetylthiazolidine 1,1-dioxide **(183)** (10.65 g, 62%), existing as a 2:1 mixture of rotamers in deuteriodimethyl sulphoxide solution ;

m.p. 182 °C (lit.,[98] 182-184 °C),

$\nu_{max.}$ (KBr) inter alia 1 770 and 1 710 (imide C=O), 1 720 (ester C=O), and 1 675 cm^{-1} (amide C=O),

δ (300 MHz, CD_3SOCD_3) 3.63 (0.66 H, dd, J 13.6 and 4.4 Hz, 5-H), 3.71 and 3.84 (2 and 1 H, each s, CO_2Me), 3.79-4.03 (1.33 H, m, 5-H), 4.23 and 4.82 (each 0.33 H, d, J 12 Hz, 2-H), 4.89 and 5.28 (each 0.66 H, d, J 12 Hz, 2-H), 4.53 and 4.91 (each 0.33 H, d, J 17 Hz, NCH_2CO), 4.64 and 4.75 (each 0.66 H, d, J 17 Hz, NCH_2CO), and 5.20 (0.66 H, dd, J 9.4 and 4.4 Hz, 4-H), 5.80 (0.33 H, d, separation 7 Hz, 4-H), and 7.84-7.91 (4 H, m, C_6H_4).

Experiment 5

Reaction of the Phthalimido Derivative **(183)** with Hydrazine

Hydrazine hydrate (0.135 g, 2.7 mmol) was added to a suspension of compound **(183)** (0.968 g, 2.7 mmol) in methanol (15 cm^3) and the mixture heated under reflux. After 1.5 h, the mixture was filtered to give a white solid (0.366 g) which was predominately phthalhydrazide **(119a)** (i.r. and ^1H n.m.r. spectroscopy) together with unreacted starting material. Evaporation of the filtrate left a yellow solid, a portion of which (0.041 g) was heated at 50 °C with 2M-hydrochloric acid (25 cm^3). On cooling the solution deposited crystals of phthalhydrazide **(119a)** (0.016 g). The residue, obtained on evaporation of the filtrate, did not contain the hydrochloride **(243)** on the basis of ^1H n.m.r. spectroscopy.

Experiment 6

Reaction of the Sulphone **(183)** with Methylhydrazine

To a solution of the sulphone **(183)** (0.051 g, 0.14 mmol) in THF (5 cm^3) was added methylhydrazine (0.011 g, 0.24 mmol) in THF (5 cm^3). After 67 h, the white solid which had precipitated (0.010 g, 25 %) was collected by filtration. It was identified as N-methylphthalhydrazide **(119b)** (m.p. and i.r. spectroscopy). Evaporation of the filtrate left a yellow syrup (0.066 g) which comprised a complex mixture of components (t.l.c. and ^1H n.m.r. spectroscopy).

Experiment 7

Conversion of the Thiazolidine **(182)** into the Bicycle **(249)**

A suspension of the sulphide **(182)** (6.18 g, 18.5 mmol) in methanol (25 cm^3) was treated with hydrazine (1.0 cm^3, 21 mmol) and the mixture heated to reflux. After 1.5 h, evaporation of the mixture left a white solid. Purification by silica-gel chromatography (EtOAc, gradient elution) and recrystallisation of the product from hot propan-2-ol gave (6R)-8-thia-1,4-diazabicyclo[4.3.0.]nona-2,5-dione **(249)** (2.42 g, 76%) ;

m.p. 186-189 °C,

$[\alpha]_D^{22}$ - 104 ° (1 % in Me_2SO),

$\nu_{max.}$ (KBr) inter alia 1 680 (amide C=O) and 1 650 cm^{-1} (amide C=O),

$\lambda_{max.}$ [EtOH / H_2O (1:1)] 261 (ε 160) and 296 nm (220),

δ (300 MHz, CD_3SOCD_3) 3.13 (1 H, dd, J 12 and 9 Hz, 7-H), 3.25-3.45 (ca. 9 H, m, 7-H_2 and H_2O), 3.68 (1 H, dd, J 17 and 4 Hz, 3-H), 4.03 (1 H, dd, J 17 and 2 Hz, 3-H), 4.30 and 4.74 (each 1 H, d, J 10 Hz, 9-H_2), 4.30br (1 H, apparent t, separation 8 Hz, 6-H), and 8.30br (1 H, s, CONH) [addition of D_2O caused the signal at 3.25-3.45 to simplify to a dd (1 H, J 12 and 7 Hz) centered at 3.29],

m/z (c.i., NH_3) 174 (MH_2^+, 13%), 173 (MH^+, 72%), and 172 (M^+, 100%).

Found : C, 42.0; H, 4.5; N, 16.0; S, 19.0. $C_6H_8N_2O_2S$ requires C, 41.9; H, 4.7; N, 16.3; S, 18.6 %.

Experiment 8

Reaction of the Sulphide **(182)** with Methylhydrazine

The sulphide **(182)** (0.254 g, 0.76 mmol) was dissolved in chloroform (5 cm^3) and the solution treated with methylhydrazine (2 drops). After 12 h, the white solid which had precipitated was collected by filtration. Purification of the white solid by flash silica-gel chromatography (EtOAc, gradient elution) afforded a white solid (0.031 g, 62% yield) which was identified as compound **(249)** (m.p. and 300 MHz ^1H n.m.r. spectroscopy).

Experiment 9

Reaction of the Sulphide **(249)** with m-CPBA

The sulphide **(249)** (0.080 g, 0.46 mmol) was suspended in dry dichloromethane (2 cm^3) and the suspension was treated dropwise with m-CPBA (0.210 g, 1.2 mmol) dissolved in dry dichloromethane (4 cm^3). After stirring overnight, work-up [by dilution with CH_2Cl_2, washing with H_2O, followed by evaporation of the aqueous layer and recrystallisation of the residue from hot H_2O] afforded a white solid (0.070 g) which contained the sulphone **(254)**.

Experiment 10

Reaction of the Sulphide **(249)** with Hydrogen Peroxide

The sulphide **(249)** (0.626 g, 3.6 mmol) was dissolved in formic acid (2 cm^3) and the solution treated dropwise with 30 % hydrogen peroxide (2.23 cm^3, 21.9 mmol) at 0 °C over a period of 5 min. After stirring overnight, excess reagents and solvents were removed by evaporation under reduced pressure. Purification of the residue by recrystallisation from hot water afforded (6R)-2,5-dioxo-8-thia-1,4-diazabicyclo[4.3.0]nonane 8,8-dioxide **(254)** (0.742 g, 100 %) as a white soild ;

m.p. > 250 °C,

$[\alpha]_D^{22}$ - 100 ° (1 % in Me_2SO),

$\nu_{max.}$ (KBr) inter alia 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (H_2O) 261 and 291 nm (sample not completely soluble),

δ (300 MHz, CD_3SOCD_3) 3.63-3.83 (3 H, m, 7-H_2 and 3-H), 4.12 (1 H, d, J 17 Hz, 3-H), 4.42 and 4.88 (each 1 H, d, J 12 Hz, 9-H_2), 4.93 (1 H, t, separation 4 Hz, 6-H), and 8.51br (1 H, s, NH) (addition of D_2O caused the signal at 8.51 to disappear),

m / z (c.i., NH_3) inter alia 272 (43 %), 238 (69 %), 154 (80 %), 136 (65 %), and 19 (100 %).

Found : C, 35.1; H, 3.7; N, 13.6; S, 15.7. $C_6H_8N_2O_4S$ requires C, 35.3; H, 3.9; N, 13.7; S, 15.4 %.

Experiment 11

Reaction of Trifluoroacetic Anhydride with Glycine

Trifluoroacetic anhydride (1.62 cm^3, 26.75 mmol) was added to dried glycine (2.01 g, 26.8 mmol) which had been cooled in an ice-salt mixture. This mixture was then heated slowly to 80 °C and, after the first vigorous reaction had ceased, it was allowed to cool. The product was placed under a high vacuum, to remove traces of unreacted anhydride, to give a quantitative yield of N-trifluoroacetylglycine **(256)**. A portion of the crude product was sublimed at 90 °C/0.05 mm Hg ;

m.p. 114 °C, (lit., 116 °C),[100]

$\nu_{max.}$ (KBr) inter alia 1 710 cm^{-1} (carboxy and amide C=O),

δ (300 MHz, CD_3SOCD_3) 3.88 (2 H, d, J 6 Hz, $NHCH_2CO$), 9.77 (1 H, t, J 6 Hz, CONH), and 12.45br (1 H, s, CO_2H).

Experiment 12

Reaction of N-Trifluoroacetylglycine **(256)** with Thionyl Chloride

Crude N-trifluoroacetylglycine **(256)** (4.32 g, 27.5 mmol) was refluxed with an excess of thionyl chloride (35.6 cm^3) for a period of 2 h, then stirred at room temperature for a further 1.5 h. The excess thionyl chloride was

evaporated off to give N-trifluoroacetylglycyl chloride **(257)** (4.46 g, 92%) which was used immediately in the following reaction.

Experiment 13

Conversion of N-Trifluoroacetylglycyl Chloride **(257)** into the Thiazolidine **(258)**

N-Trifluoroacetylglycyl chloride **(257)** (4.46 g, 25.4 mmol) was dissolved in dry dichloromethane (20 cm^3) and the solution cooled to 0 °C by using an ice-salt mixture.This solution was then treated with the thiazolidine methyl ester **(181)** (3.698 g, 27.8 mmol) dissolved in dichloromethane (5 cm^3) followed by a solution of triethylamine (3.54 cm^3, 25.4 mmol) in dry dichloromethane (10 cm^3 added over 5 min.) After stirring overnight, work-up [by dilution with EtOAc (50 cm^3) and washing sequentially with 10% HCl, saturated $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from $CHCl_3$-light petroleum] afforded methyl (4R)-3-(N-trifluoroacetylglycyl)thiazolidine-4-carboxylate **(258)** (5.638 g, 75%), as a light orange solid which existed as a 2:1 mixture of rotamers in deuteriodimethyl sulphoxide solution ;

m.p. 94 °C,

$[\alpha]_D^{24}$ - 91 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 1 745 (ester C=O), 1 715 (trifluoroacetyl C=O), and 1 650 cm^{-1} (amide C=O),

δ (300 MHz, CD_3SOCD_3) 3.14 (0.66 H, dd, J 3.5 and 12 Hz, 5-H of major rotamer), 3.32-3.42 (1.33 H, m, 5-H_2 of both rotamers), 3.65 and 3.75 (2 and 1 H, each s, CO_2Me), 3.87 (0.33 H, dd, J 6 and 17 Hz, NCHHCO of minor rotamer), 4.12 (0.66 H, dd, J 6 and 17 Hz, NCHHCO of major rotamer), 4.23-4.32 (1 H, m, NCHHCO of both rotamers), 4.34 and 4.62 (each 0.33 H, d, J 9.5 Hz, 2-H_2 of minor rotamer), 4.64 and 4.80 (each 0.66 H, d, J 8.5 Hz, 2-H_2 of major rotamer), 4.89 (0.66 H, dd, J 3.5 and 7.5 Hz, 4-H of major rotamer), 5.34 (0.33 H, dd, J 2 and 6 Hz, 4-H of minor rotamer), and 9.65-975 (1 H, m, NH),

δ (300 MHz, CD_3SOCD_3, 423 K) 3.27 (1 H, dd, J 11 and 3 Hz, 5-H), 3.40 (1 H, dd, J 11 and 7 Hz, 5-H), 3.72 (3 H, s, CO_2Me), 4.13 (2 H, d, J 5 Hz, $NHCH_2CO$), 4.52 and 4.80 (each 1 H, d, J 9 Hz, 2-H_2), 5.10 (1 H, dd, J 7 and 3 Hz, 4-H), and 9.0br (1 H, m, NH),

m / z (c.i., NH_3) inter alia 301 (MH^+, 11 %) and 88 (100 %).

Found : C, 36.0; H, 3.7; F, 19.0; N, 9.1; S, 11.1. $C_9H_{11}F_3N_2O_4S$ requires C, 36.0; H, 3.7; F, 19.0; N, 9.3; S, 10.7 %.

Experiment 14

Conversion of the Sulphide **(258)** into the Sulphone **(259)** by Potassium Permanganate

The sulphide **(258)** (1.031 g, 3.44 mmol) was dissolved in 80% acetic acid (20 cm^3) and the solution was treated dropwise with potassium permanganate (1.090 g, 6.90 mmol) in water (15 cm^3) at 0 °C over 1 h. After

a further 1 h, the colour was discharged with aqueous hydrogen peroxide. Work-up [by dilution with EtOAc, sequential washing with saturated $NaHCO_3$, brine and H_2O, followed by evaporation of the dried ($MgSO_4$) organic extract and recrystallisation of the residue from $CHCl_3$-light-petroleum] afforded (4R)-4-methoxycarbonyl-3-(N-trifluoroacetylglycyl)-thiazolidine 1,1-dioxide **(259)** (0.784 g, 69 % yield), existing as a 3:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 54 °C,

$[\alpha]_D^{25}$ -68 ° (1.05 % in Me_2SO),

$\nu_{max.}$ (KBr) inter alia 1 755 (ester C=O),1 725br, and 1 670 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 3.58 (0.75 H, dd, J 5 and 14 Hz, 5-H of major rotamer), 3.64 (0.75 H, dd, J 8.5 and 14 Hz, 5-H of major rotamer), 3.74br (0.25 H, dd J 14 and 9 Hz, 5-H of minor rotamer), 3.82br (0.25 H, dd, J 14 and 4 Hz, 5-H of minor rotamer), 3.86 and 3.92 (2.25 and 0.75 H, each s, CO_2Me), 4.08-4.20 (1 H, m, NHCHHCO), 4.27-4.42 (1.25 H, m, NHCHHCO and 2-H of minor rotamer), 4.53 and 4.69 (each 0.75 H, d, J 11 Hz, 2-H_2), 5.00 (0.25 H, d, J 12 Hz, 2-H of minor rotamer), 5.13br (0.25 H, dd, J 8.5 and 3 Hz, 4-H of minor rotamer), 5.45 (0.75 H, dd, J 8.5 and 5 Hz, 4-H of major rotamer), and 7.32-7.43br (1 H, m, CONH),

m / z (c.i., NH_3) 333 (MH^+, 3%) and 56 (100%).

Found : C, 32.2; H, 3.2; F, 17.3; N, 8.2; S, 9.2. $C_9H_{11}F_3N_2O_6S$ requires C, 32.5; H, 3.3; F, 17.2; N, 8.4; S, 9.6 %.

Experiment 15

Reaction of the Sulphone **(259)** with DBN followed by Iodomethane

To a solution of the sulphone **(259)** (0.220g, 0.64 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (0.163 cm^3, 1.27 mmol) followed, after 0.5 h, by iodomethane (0.206 cm^3, 3.18 mmol). After stirring overnight, the mixture was diluted with ethyl acetate and washed sequentially with dilute sulphuric acid (x 3) and saturated aqueous sodium hydrogen carbonate (x 2). Evaporation of the dried ($MgSO_4$) organic layer afforded a yellow powder. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystallisation from chloroform-light petroleum afforded a white solid considered to be methyl 1-methylsulphonylmethyl-6-oxo-4-trifluoroacetylpiperazine-2-carboxylate **(273)** (0.16 g, 71%) ;

m.p. 146 °C,

$\nu_{max.}$ (KBr) inter alia 1 742 (ester C=O), 1 690 (amide C=O), and 1 676 cm^{-1} (amide C=O),

δ (300 MHz, CD_3SOCD_3, 438 K) 3.00 (3 H, s, NMe), 3.73 (3 H, s, CO_2Me), 3.94br and 4.49br (each 1 H, d, J 14 Hz, 5-H_2), 4.33 (2 H, AB q, J 19 Hz, separation of inner lines 8 Hz, NCH_2CO), 4.62 and 5.11 (each 1 H, d, J 14.5 Hz, 2-H_2), and 4.80 (1 H, dd, J 4 and 2 Hz, 4-H),

m / z (c.i., NH_3) inter alia 267 ($M^+ - CH_3O_2S$, 64 %) and 45 (100 %).

Found : C, 35.0; H, 4.0; F, 16.4; N, 7.9. $C_{10}H_{13}F_3N_2O_6S$ requires C, 34.7; H, 3.8; F, 16.5; N, 8.1 %.

Experiment 16

Reaction of Sarcosine **(267)** with Trifluoroacetic Anhydride

To a cooled solution (-10 °C) of sarcosine **(267)** (14.2 g, 190 mmol) in dry trifluoroacetic acid (60 cm^3) was added trifluoroacetic anhydride (25 cm^3, 209 mmol) over a period of 0.5 h. The mixture was then stirred at -20 °C for 16 h, and at room temperature for 1 h, after which excess reagent and solvent were removed by evaporation. The yellow residue was purified by vacuum distillation [b.p. 119-120 °C (1.1 mm of Hg)] yielding N-methyl-N-trifluoroacetylglycine **(268)** (12.65 g, 36%) as a white solid which existed as a 3:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 51-55 °C (lit.,[101] 54.5-55.5 °C),

$\nu_{max.}$ (KBr) inter alia 1 735 (acid C=O) and 1 695 cm^{-1} (amide C=O),

δ (220 MHz, $CDCl_3$) 3.17 and 3.20 (0.75 and 2.25 H, each s, Me), 4.26 and 4.30 (1.5 and 0.5 H, each s, NCH_2CO_2), and 11.6 (1 H, s, COOH).

Experiment 17

Preparation of the Thiazolidine **(270)**

(a) N-Methyl-N-trifluoroacetylglycine **(268)** (2.66 g, 14.4 mmol) and thionyl chloride (7.0 cm^3, 100 mmol) were heated under reflux for 1.5 h.

Evaporation of the excess thionyl chloride yielded N-methyl-N-trifluoroacetylglycyl chloride **(269)** (2.93 g, 100 %) which was dissolved in dry dichloromethane (20 cm^3). The solution was cooled to 0 °C and treated with the thiazolidine methyl ester **(181)** (2.117 g, 14.4 mmol) followed by a solution of triethylamine (1.45 g, 14.4 mmol) in dry dichloromethane (10 cm^3) added over 5 min. After stirring overnight, work-up [by dilution with EtOAc and washing sequentially with 10% HCl, saturated $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded methyl (4R)-3-(N-methyl-N-trifluoroacetyl)glycylthiazolidine-4-carboxylate **(270)** (4.02 g, 89%) as a pale-orange oil, existing as a 2:1 mixture of rotamers in deuteriochloroform solution ;

$[\alpha]_D^{21}$ -75 ° (0.97 % in CH_2Cl_2),

$\nu_{max.}$ (film) inter alia 1 745 (ester C=O), 1 700 (trifluoroacetyl C=O), and 1 670 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 3.05-3.50 (5 H, m, NMe and 5-H_2), 3.73 and 3.80 (2 and 1 H, each s, CO_2Me), 4.03-4.73 (4 H, m, NCH_2CO and 2-H_2), 4.93 and 5.07-5.13 (0.33 and 0.66 H, d (J 3 Hz) and m, 4-H),

m / z (c.i., NH_3) inter alia 332 (MNH_4^+, 31 %) and 315 (MH^+, 100%).

Found : C, 37.9; H, 4.4; N, 8.9; S, 10.5. $C_{10}H_{13}F_3N_2O_4$ requires C, 38.2; H, 4.1; N, 8.9; S, 10.2 %.

(b) The acid **(268)** (1.49 g, 8.05 mmol) was dissolved in dry dichloromethane at 0 °C, treated with DCCI (1.66 g, 8.05 mmol), and the resulting mixture was stirred for 0.25 h. To the solution was added the

thiazolidine methyl ester **(181)** (1.18 g, 8.03 mmol) and the mixture was allowed to stir at room temperature overnight. The insoluble N,N-dicyclohexylurea was filtered off and the filtrate concentrated and dissolved in ethyl acetate (10 cm^3). A second crop of the insoluble N,N-dicyclohexylurea was filtered off. Work-up of the filtrate [by washing sequentially with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded the thiazolidine **(270)** (2.34 g, 93 %) as a clear oil, which was identical with the material isolated in Exp.(17a) (i.r. and ^1H n.m.r. spectroscopy).

Experiment 18

Conversion of the Sulphide **(270)** into the Sulphone **(265)**

(a) The sulphide **(270)** (0.210 g, 0.67 mmol) was dissolved in 80% acetic acid (5 cm^3) and the solution was treated dropwise with potassium permanganate (0.216 g, 1.37 mmol) in water (15 cm^3) at 0 °C over 1 h. After leaving overnight, the colour was discharged with aqueous hydrogen peroxide. Work-up [by dilution with EtOAc, sequential washing with saturated aqueous $NaHCO_3$, brine and H_2O, followed by evaporation of the dried ($MgSO_4$) organic extract and recrystallisation of the residue from $CHCl_3$-light petroleum] afforded (4R)-4-methoxycarbonyl-3-(N-methyl-N-trifluoroacetylglycyl)thiazolidine 1,1-dioxide **(265)** (0.180 g, 78 %) existing, as a 4:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 60-65 °C,

$\nu_{max.}$ (KBr) inter alia 1 750 (ester C=O) and 1 700br cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) (for major rotamer) 3.23-3.35 (3 H, m, NMe), 3.50-3.63 (2 H, m, 5-H_2), 3.74-3.94 (3 H, m, CO_2Me), 4.15 and 4.26-4.39 (each 1 H, d (J 16 Hz) and m, NCH_2), 4.50 and 4.73 (each 1 H, d, J 11 Hz, 2-H_2), and 5.46 (1 H, dd, J 5 and 8 Hz, 4-H),

m/z (c.i., NH_3) 384 (MNH_4^+, 100 %).

Found : C, 34.4; H, 3.5; N, 8.0; S, 9.6. $C_{10}H_{13}F_3N_2O_6S$ requires C, 34.7; H, 3.8; N, 8.1; S, 9.2 %.

(b) The sulphide **(270)** (4.17 g, 13.28 mmol) was dissolved in a 1:1 mixture of methanol-water (50 cm^3) and the solution treated with "Oxone" (12.30 g, 20.03 mmol) over a period of 5 min. After stirring overnight, work-up [by dilution with EtOAc, sequential washing with H_2O (x 2) and brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded **(265)** (4.13 g, 90 %) as a white solid, identical with the material isolated in Exp. (18a) (i.r. and ^1H n.m.r. spectroscopy).

Experiment 19

Reaction of the Sulphone **(259)** with DBN followed by Benzyl Chloroformate

To a solution of the sulphone **(259)** (0.263 g, 0.76 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (0.194 cm^3, 1.15 mmol) followed, after 0.5 h, by benzyl chloroformate (0.338 cm^3, 2.3 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with dilute H_2SO_4 (x 2) and saturated $NaHCO_3$ (x 2), followed by

evaporation of the dried ($MgSO_4$) organic extract] afforded a brown oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded methyl 1-benzyloxysulphinylmethyl-6-oxo-4-trifluoroacetylpiperazine-2-carboxylate **(271)** (0.226 g, 70 %) as a clear oil, considered to be a 1:1 mixture of diastereoisomers each existing as a mixture of rotamers in deuteriodimethyl sulphoxide solution ;

$\nu_{max.}$ (KBr) inter alia 1 747 (ester C=O), 1 695 (trifluoroacetyl C=O), and 1 681 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 207 nm (ε 23 700),

δ (300 MHz, CD_3SOCD_3) 3.58, 3.62, 3.63, 3.66, and 3.70 (0.52, 0.46, 0.67, 0.83, and 0.52 H, respectively, each s, together CO_2Me), 3.85-5.25 (ca. 10.7 H, m), and 7.35-7.45 (5 H, m, Ph),

m / z (c.i., NH_3) inter alia 423 (MH^+, 4 %) and 91 (100 %).

Found : C, 45.2; H, 4.1; N, 6.3; S, 7.2. $C_{16}H_{17}F_3N_2O_6S$ requires C, 45.5; H, 4.0; N, 6.6; S, 7.6 %.

Experiment 20

Reaction of the Sulphone **(259)** with Potassium tert-Butoxide

The sulphone **(259)** (0.108 g, 0.33 mmol) was dissolved in dry THF (2 cm^3), the solution cooled to -78 °C and treated with freshly resublimed potassium tert-butoxide (0.039 g, 0.34 mmol). After 1.5 h, the mixture was allowed to warm up to room temperature. Evaporation of the solvent and

purification of the residue by recrystallisation from THF-chloroform afforded a white solid (0.119 g, 95 % yield) considered to be mainly the salt **(274)**, existing as a 1.5:1 mixture of rotamers in deuteriodimethyl sulphoxide solution ;

m.p. 88-92 °C,

$\nu_{max.}$ (KBr) inter alia 1 754 (ester C=O), 1 700 (trifluoroacetyl C=O), and 1 657 cm^{-1} (amide C=O),

$\lambda_{max.}$ (H_2O) 240 nm (ε 3 300),

δ (300 MHz, CD_3SOCD_3), inter alia 2.46 and 2.58 (0.4 and 0.6 H, each d, J 12 Hz, $NCHHSO_2$), 3.64 and 3.68 (1.2 and 1.8 H, each s, CO_2Me), 3.80-4.90 (ca. 6 H, m), 5.12-5.18 and 5.22-5.26 (0.4 and 0.6 H, each m, together 6-H),

m / z (c.i., NH_3) 364 (100 %).

Found : C, 27.0; H, 3.0; N, 6.7. $C_9H_{10}F_3KN_2O_6S$ requires C, 29.2; H, 2.7; N, 7.6 %.

Experiment 21

Reaction of the Potassium Sulphinate **(274)** with Iodomethane

The potassium salt **(274)** (0.118 g, 0.32 mmol) was dissolved in dry DMF (2 cm^3) and treated with iodomethane (0.2 cm^3). After leaving overnight, work-up [by dilution with EtOAc and sequential washing with brine

(x 4) and H_2O followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from $CHCl_3$-light petroleum] afforded methyl 1-methylsulphonylmethyl-6-oxo-4-trifluoroacetylpiperazine-2-carboxylate **(273)** (0.069 g, 62 %) as a white solid. This compound was found to be identical with the material obtained in Experiment 15 (m.p. and i.r. and 300 ^1H n.m.r. spectroscopy).

Experiment 22

Conversion of the Sulphinate Salt **(274)** into the Sulphinic Acid **(275)**

The salt **(274)** (0.309 g, 0.84 mmol) was dissolved in methanol (10 cm^3) and treated with Amberlite IR 120 (H^+) ion-exchange resin until the solution turned acidic. The mixture was filtered and the resin thoroughly washed with methanol. The washings were concentrated and the procedure repeated once again. Evaporation of the washings gave a white solid, presumed to be the methyl 6-oxo-1-sulphinomethyl-4-trifluoroaceytlpiperazine-2-carboxylate **(275)** (0.276 g, 100 %), with the following properties (the ^1H n.m.r. spectrum, which was not recorded on a freshly prepared sample, was complex) ;

m.p. 80-85 °C (with decomp.),

$\nu_{max.}$ (KBr) inter alia 1 750 (ester C=O), 1 700 (trifluoroacetyl C=O), and 1 682sh cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 205 nm (ε 9 900),

m / z (c.i., NH_3) 350 (MNH_4^+, 17%), 332 (M^+, 1 %), 318 (49%), 272 (100 %), and 268 ($M^+ - SO_2$, 1%).

Experiment 23

Conversion of the Salt **(274)** into the Methyl Sulphinate **(276)**

The salt **(274)** (0.236 g, 0.64 mmol) was dissolved in methanol (5 cm^3) and treated with Amberlite IR 120 (H^+) ion-exchange resin until the solution was acidic. The mixture was filtered and the resin thoroughly washed with methanol. The washings were cooled to 0 °C, treated with an excess of ethereal diazomethane, and left to stand for 1h. Evaporation of the mixture afforded a clear oil. Purification of the residue by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl 1-methoxysulphinylmethyl-6-oxo-4-trifluoroacetylpiperazine-2-carboxylate **(276)** (0.037 g, 17 %) as a white foam, considered to be a 1:1 mixture of diastereoisomers ;

$\nu_{max.}$ (film) inter alia 1 750 (ester C=O) and 1 745br cm^{-1} (trifluoroacetyl and amide C=O),

δ (300 MHz, $CDCl_3$) 3.43 (0.25 H, dd, J 14 and 4 Hz, 5-H), 3.77 and 3.78 (each 1.5 H, s, together SOMe), 3.79-3.99 (ca. 5 H, m, CO_2Me and 5-H_2), 4.01 and 4.20 [(0.33 and 0.66 H, s and d (J 18 Hz)], respectively, together 3-H) , 4.40-4.56 (1 H, m, 3-H), 4.60 (0.66 H, d, J 19 Hz, NCHHS), 4.75-4.77 (1 H, m, NCHHS), 4.97 (0.33 H, dt, J , 2 and 14 Hz, NCHHS), and 5.58 (1 H, t, J 15 Hz, 6-H),

m / z (e.i.) 346 (M^+) and 314 (0.6 %).

Found : C, 34.4; H, 3.7; N, 7.8. $C_{10}H_{13}F_3N_2O_6S$ requires C, 34.7; H, 3.8; N, 8.1 %.

Experiment 24

Reaction of the Acid **(278)** with Triethylamine followed by Methyl Chloroformate followed by the Thiazolidine Methyl Ester **(181)**

Aceturic acid **(278)** (0.105 g, 0.905 mmol) was dissolved in dry DMF (5 cm^3) and the solution was cooled to 0 °C and treated with dry triethylamine (0.125 cm^3, 0.905 mmol) followed by methyl chloroformate (0.076 cm^3, 0.905 mmol) (dropwise addition). After stirring for 5 min, the mixture was treated with the thiazolidine methyl ester **(181)** (0.133 g, 0.905 mmol) and left to stir overnight. Work-up [by dilution with EtOAc, sequential washing with H_2O, 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic extracts] gave a clear oil. Purification of the oil by flash silica-gel chromatography afforded methyl (4R)-3-methoxycarbonylthiazolidine-4-carboxylate **(282)** (0.055 g, 30 %) as a clear oil, which existed as a 1:1 mixture of rotamers in deuteriochloroform solution ;

$[\alpha]_D$ -133 ° (0.48 % in CH_2Cl_2),

$\nu_{max.}$ (film) inter alia 1 760 (ester C=O) and 1 715 cm^{-1} (urethane C=O),

δ (300 MHz, $CDCl_3$) 3.11-3.31 (2 H, m, 5-H_2), 3.60-3.73 (6 H, m, 2 x OMe), 4.38 and 4.40 (each 0.5 H, d, J 10 Hz, 2-H), 4.52 and 4.63 (each 0.5 H, d, J 10 Hz, 2-H), and 4.78-4.83 and 4.85-4.90 (each 0.5 H, m, 4-H),

m / z (e.i.) inter alia 205 (M^+, 12 %) and 146 ($M^+ - C_2H_3O_2$, 100 %).

Experiment 25

Preparation of the Thiazolidine (283)

A solution of the acid (160) (1.78 g, 13.38 mmol) in 2 M-sodium hydroxide (6.72 cm^3, 13.38 mmol) was cooled to 0 °C and treated with methyl chloroformate (1.03 cm^3, 13.38 mmol) and 2M-sodium hydroxide (6.72 cm^3, 13.38 mmol) simultaneously over 10 min. The mixture was then extracted with diethyl ether (x 2) and the ethereal extracts discarded. Acidification and extraction with ethyl acetate, followed by evaporation of the dried ($MgSO_4$) organic layer afforded (4R)-3-methoxycarbonylthiazolidine-4-carboxylic acid **(283)** (2.21g, 87 % yield) as a clear oil ;

$\nu_{max.}$ (film) inter alia 1 715br cm^{-1} (acid and urethane C=O),

δ (300 MHz, $CDCl_3$) 3.30 (2 H, d, separation 4 Hz, 5-H_2), 3.75 (3 H, s, MeO), 4.43-4.75 (2 H, m, 2-H_2), 4.79-4.96 (1 H, m, 4-H), and 7.94br (1 H, s, CO_2H),

m / z (f.a.b.) inter alia 192 (MH^+, 70 %), 191 (M^+, 6 %), 146 (100 %), and 132 ($M^+ - C_2H_3O_2$, 15 %).

Found : C, 36.4; H, 4.8; N, 7.4; S, 16.0. $C_6H_9NO_4S$ requires C, 37.7; H, 4.7; N, 7.3; S, 16.8 %.

Experiment 26

Esterification of the Thiazolidine Acid **(283)**

A solution of the thiazolidine acid **(283)** (0.2 g, 1.05 mmol) in dichloromethane (10 cm^3) at 0 °C was treated with an excess of ethereal diazomethane. Evaporation afforded methyl (4R)-3-methyloxycarbonylthiazolidine-4-carboxylate **(282)** (0.17 g, 79 % yield) as a microanalytically homogeneous syrup, found to be identical with the material isolated in Exp.24;

Found : C, 41.1; H, 5.6; N, 7.1; S, 15.2. $C_7H_{11}NO_4S$ requires C, 41.0; H, 5.4; N, 6.8; S, 15.6 %.

Experiment 27

Reaction of Chloroacetyl Chloride with the Thiazolidine **(181)**

Chloroacetyl chloride (3.95 cm^3, 49.6 mmol) was dissolved in dry dichloromethane (10 cm^3) and the solution, cooled to 0 °C, was treated with the methyl ester **(181)** (7.29 g, 49.6 mmol) dissolved in dry dichloromethane (5 cm^3), followed by a solution of dry triethylamine (6.9 cm^3, 49.6 mmol) in dichloromethane (5 cm^3) (added over 5 min.). After stirring overnight, work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from $CHCl_3$-light petroleum] afforded methyl (4R)-3-(chloroacetylglycyl)thiazolidine-4-carboxylate **(252)** (10.28 g, 93% yield) as a light-brown solid, which existed as a 2:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 54-57 °C (lit.,[99] 60 °C),

$[\alpha]_D$ -137 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 1 755 (ester C=O), 1 680 and 1 665 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 283 nm (ε 90),

δ (300 MHz, $CDCl_3$) 3.23-3.56 (2 H, m, 5-H_2), 3.81 and 3.85 (2 and 1 H, each s, CO_2Me), 4.07 (0.66 H, s, $ClCH_2$ of minor rotamer), 4.16 (1.33 H, AB q, J 13 Hz, separation of inner lines 3 Hz, $ClCH_2$ of major rotamer), 4.58 and 4.80 (each 0.33 H, d, J 10 Hz, 2-H_2) of minor rotamer), 4.68 and 4.78 (each 0.66 H, d, J 8 Hz, 2-H_2 of major rotamer), 5.04br (0.33 H, apparent d, separation 6 Hz, 4-H of minor rotamer), and 5.14 (0.66 H, dd, J 7 and 4 Hz, 4-H of major rotamer),

m / z (c.i., NH_3) 241 (MNH_4^+, 7 %), 226 (M+2, 37 %), 225 (M+1, 9 %), and 224 (MH^+, 100 %).

Found : C, 37.4; H, 4.5; N, 6.3; S, 14.3. $C_7H_{10}ClNO_3S$ requires C, 37.6; H, 4.8; N, 6.3; S, 14.5 %.

Experiment 28

Reaction of the Chloro Ketone (252) with Sodium Azide

The sulphide (252) (5.29 g, 23.7 mmol) and sodium azide (1.539 g, 23.7 mmol) were refluxed in 50 % aqueous ethanol (20 cm^3) for a period of

24 h. Cooling and work-up [by dilution with EtOAc, and washing with brine (x 2), followed by evaporation of the dried ($MgSO_4$) organic extracts] afforded an orange oil which was purified by flash silica-gel chromatography (EtOAc-hexane, gradient elution) to yield methyl (4R)-3-(azidoacetylglycyl)thiazolidine-4-carboxylate **(284)** (4.34 g, 80%) as a clear pale-orange oil, which existed as a 2:1 mixture of rotamers in deuteriochloroform solution ;

$[\alpha]_D$ -126 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (film) inter alia 2 110 (N_3), 1 750 (ester C=O), and 1 670 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 272 nm (ε 75),

δ (300 MHz, $CDCl_3$) 3.19-3.49 (2 H, m, 5-H_2), 3.78 and 3.81 (2 and 1 H, each s, CO_2Me), 3.87 (0.66 H, AB q, J 16 Hz, separation of inner lines 10 Hz, N_3CH_2CO of minor rotamer), 3.98 (1.33 H, s, N_3CH_2CO of major rotamer), 4.53 (1.33 H, s, 2-H_2 of major rotamer), 4.57 and 4.79 (each 0.3 H, d, J 12 Hz, together 2-H_2 of minor rotamer), 4.76br (0.33 H, d, separation 6 Hz, 4-H of minor rotamer), and 5.16 (0.66 H, dd, J 6 and 4 Hz, 4-H of major rotamer),

m / z (c.i., NH_3) 231 (MH^+, 39 %), 203 ($MH^+ - N_2$), 202 ($M^+ - N_2$, 1 %), and 146 (100%).

Found : C, 36.5; H, 4.4; N, 24.0; S, 13.9. $C_7H_{10}N_4O_3S$ requires C, 36.5; H, 4.3; N, 24.3; S, 13.9 %.

Experiment 29

Conversion of the Sulphide (284) into the Thiazolidine (281)

(a) The azido sulphide **(284)** (0.33 g, 1.44 mmol), dissolved in an acetic anhydride (0.7 cm^3) / acetic acid (0.35 cm^3) mixture cooled to 0 °C, was treated with activated zinc (0.64 g, 2 mass equiv.) and the mixture stirred vigorously overnight. Work-up [by filtration through "Celite" and sequential washing with saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic extract] yielded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl (4R)-3-(N-acetylglycyl)thiazolidine-4-carboxylate **(281)** (0.128 g, 36%) as a clear oil, existing as a 2:1 mixture of rotamers in deuteriochloroform solution ;

$\nu_{max.}$ (film) inter alia 1 750 (ester C=O) and 1 660 cm^{-1}(amide C=O),

δ (300 MHz, $CDCl_3$) 2.00 (3 H, s, COMe), 3.13-3.51 (2 H, m, 5-H_2), 3.71 and 3.76 (2 and 1 H, each s, together CO_2Me), 3.77-4.23 (2 H, m, NCH_2CO), 4.54 (1.33 H, AB q, J 8 Hz, separation of inner lines 13.5 Hz, 2-H_2 of major rotamer), 4.58 (0.66 H, AB q, J 9.5 Hz, separation of inner lines 55 Hz, 2-H_2 of minor rotamer), 4.85 (0.33 H, apparent dd, 4-H of minor rotamer), 5.05 (0.66 H, dd, J 4 and 7 Hz, 4-H of major rotamer), 6.60br and 6.78br (0.66 H and 0.33 H, each s, together NH),

m / z (f.a.b.) 247 (MH^+, 80 %) and 148 (100 %).

Found : C, 43.2; H, 5.6; N, 11.0. $C_9H_{14}N_2O_4S$ requires C, 43.9; H, 5.7; N, 11.4 %.

(b) The azido sulphide **(284)** (0.75 g, 3.26 mmol) was dissolved in ethyl acetate (30 cm^3) and treated with acetic anhydride (1.5 cm^3) and 10% palladium on charcoal (2.26 g, 3 mass equiv.). The mixture was stirred under an atmosphere of hydrogen overnight when work-up [by filtration through "Celite" and evaporation of the filtrate] yielded a clear oil. The final traces of unreacted acetic anhydride were removed by evaporation under reduced pressure to afford **(281)** (0.744 g, 92%) as a clear oil, identical (t.l.c. and ^1H n.m.r. spectroscopy) with the sample prepared in the aforecited experiment.

Experiment 30

Reaction of the Sulphide **(281)** with "Oxone"

The sulphide **(281)** (0.46 g, 1.87 mmol) was dissolved in a 1:1 mixture of methanol-water (30 cm^3) and the solution treated with "Oxone" (1.78 g, 2.90 mmol) over a period of 5 min. After stirring overnight, work-up [by dilution with EtOAc, sequential washing with H_2O (x 2) and brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light-petroleum] afforded (4R)-4-methoxycarbonyl-3-(N-acetylglycyl)-thiazolidine 1,1-dioxide **(277)** (0.14 g, 27%) as a white solid, which existed as a 3:1 mixture of rotamers in deuteriochloroform solution ;

$\nu_{max.}$ (film) inter alia 1 750 (ester C=O) and 1 700-1 650 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 2.06 (3 H, s, COMe), 3.45-3.75 (2 H, m, 5-H_2), 3.83 and 3.88 (2.25 and 0.75 H, each s, together CO_2Me), 3.94-4.34 (2.25 H,

m, NCH_2CO and 2-H of minor rotamer), 4.59 (1.5 H, AB q, J 10.5 Hz, separation of inner lines 66 Hz, 2-H of major rotamer), 4.94 (0.25 H, d, J 12 Hz, 2-H of minor rotamer), 5.25 (0.25 H, apparent d, 4-H of minor rotamer), 5.42 (0.75 H, dd, J 6 and 7.5 Hz, 4-H of major rotamer), 6.43br and 6.50br (0.75 and 0.25 H, each s, together NH),

m / z (f.a.b.) 279 (MH^+, 53 %) and 136 (100 %).

Experiment 31

Conversion of the Sulphide **(284)** into the Sulphone **(290)**

(a) The sulphide **(284)** (1.11 g, 4.83 mmol) was dissolved in dry dichloromethane (30 cm^3) and stirred with m-CPBA (2.49 g, 14.5 mmol) at room temperature overnight. The mixture was then stirred vigorously with aqueous sodium sulphite solution for 0.25 h. Work-up [dilution with EtOAc, washing with aqueous $NaHCO_3$ (x 3), drying ($MgSO_4$) and evaporation] yielded a white solid. Purification by recrystallisation of the residue from chloroform-light petroleum yielded (4R)-3-azidoacetylglycyl-4-methoxycarbonylthiazolidine 1, 1-dioxide **(290)** (0.850 g, 67%) as a white solid, which was present as a 4:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 110-116 °C,

$[\alpha]_D$ -118 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 2 105 (N_3), 1 750 (ester C=O), and 1 685 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 211 (ε 2 700) and 279 nm (70),

δ (300 MHz, $CDCl_3$) 3.48-3.75 (2 H, m, 5-H_2), 3.82 and 3.88 (2.4 and 0.6 H, each s, CO_2Me), 3.98 (2 H, AB q, J 16 Hz, separation of inner lines 13 Hz, N_3CH_2CO), 4.27br and 4.97br (each 0.2 H, d, separation 12 Hz, 2-H_2 of minor rotamer), 4.48 and 4.62 (each 0.8 H, d, J 12 Hz, 2-H_2 of major rotamer), 5.06br (0.2 H, d, separation 6 Hz, 4-H of minor rotamer), and 5.47 (0.8 H, dd, J 8 and 5 Hz, 4-H of major rotamer),

m / z (c.i., NH_3) 280 (MNH_4^+, 100 %), 263 (MH^+, 27 %), 235 ($MH^+ - N_2$, 99%), 234 ($M^+ - N_2$, 0.2 %).

Found : C, 32.6; H, 3.7; N, 20.8; S, 12.0. $C_7H_{10}N_4O_5S$ requires C, 32.1; H, 3.8; N, 21.4; S, 12.2 %.

(b) The sulphide **(284)** (0.960 g, 4.18 mmol) was dissolved in a 1:1 mixture of methanol-water (30 cm^3) and the solution treated with "Oxone" (3.99 g, 6.50 mmol) over a period of 5 min. After stirring overnight, work-up [by dilution with EtOAc, sequential washing with H_2O (x 2) and brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded compound **(290)** (0.922 g, 84%), identical with the material isolated in Experiment 31a by m.p. and ^1H n.m.r. spectroscopy.

Experiment 32

Conversion of the Sulphide (252) into the Sulphone (291)

(a) The sulphide (252) (0.417 g, 1.87 mmol) was dissolved in 80% acetic acid (5 cm^3) and the solution treated dropwise with potassium permanganate (0.59 g, 3.73 mmol) in water (15 cm^3) at 0 °C over 1 h. After leaving overnight, the colour was discharged with aqueous hydrogen peroxide. Work-up [by dilution with EtOAc, sequential washing with saturated aqueous $NaHCO_3$, brine and H_2O, followed by evaporation of the dried ($MgSO_4$) organic extract and recrystallisation of the residue from $CHCl_3$-light petroleum] afforded (4R)-3-chloroacetylglycyl-4-methoxycarbonylthiazolidine 1,1-dioxide (291) (0.434 g, 91%) as a white solid, which was a 3:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 80-84 °C,

$[\alpha]_D$ -83 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 1 770 (ester C=O), and1 695 and 1 685 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 3.51-3.79 (2 H, m, 5-H_2), 3.84 and 3.90 (2.25 and 0.75 H, each s, CO_2Me), 4.12 (2 H, s, $ClCH_2CO$), 4.27br and 4.95br (each 0.25 H, d, separation 12 Hz, 2-H_2 of minor rotamer), 4.59 and 4.78 (each 0.75 H, d, J 11 Hz, 2-H_2 of major rotamer), 5.27br (0.25 H, apparent d, separation 7 Hz, 4-H of minor rotamer), and 5.44 (0.75 H, dd, J 8 and 5 Hz, 4-H of major rotamer),

m / z (c.i., NH_3) 275 and 273 (MNH_4^+, 44 and 100 %).

Found : C, 32.6; H, 3.9; N, 5.5; S, 12.2. $C_7H_{10}ClNO_5S$ requires C, 32.9; H, 3.9; N, 5.5; S, 12.5 %.

(b) The sulphide **(252)** (5.25 g, 23.54 mmol) was dissolved in a 1:1 mixture of methanol-water (50 cm^3) and the solution treated with "Oxone" (17.99 g, 29.31 mmol) over a period of 5 min. After stirring overnight, work-up [by dilution with EtOAc, sequential washing with H_2O (x 2) and brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded **(291)** (5.17 g, 86%), identical to the material isolated in Experiment 32b by m.p. and ^1H n.m.r. spectroscopy.

Experiment 33

Reaction of the Sulphone **(291)** with DBN followed by Benzyl Chloroformate

To a solution of the sulphone **(291)** (0.0597 g, 0.234 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (0.029 cm^3, 0.234 mmol) followed, after 0.5 h, by benzyl chloroformate (0.1 cm^3, 0.700 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with dilute H_2SO_4 (x 2) and saturated aqueous $NaHCO_3$ (x 2), followed by evaporation of the dried ($MgSO_4$) organic extract] afforded an orange oil (0.0932 g). Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded two components.

The first-eluted material, isolated as an oil (0.002 g), was considered to be an acrylate of type **(294)** ;

δ (300 MHz, $CDCl_3$) inter alia 4.46 and 4.84 (each 1 H, d, J 13 Hz, NCH_2SO_2), 4.73 (2 H, AB q, J 17 Hz, separation of inner lines 11 Hz, $ClCH_2CO$), 5.08 (2 H, AB q, J 11 Hz, separation of inner lines 20 Hz, OCH_2Ph), 5.58 and 5.96 (each 1 H, d, J 2 Hz, $C:CH_2$), and 7.24-7.36 (5 H, m, Ph).

The second-eluted material, isolated as an oil (0.003 g), was tentatively considered to be mainly compound **(295)** or **(296)** ;

δ (300 MHz, $CDCl_3$) inter alia 3.76 (3 H, s, CO_2Me), 4.08 and 4.84 (each 1 H, d, J 14 Hz, NCH_2SO), 4.50 and 4.83 (each 1 H, d, J 16 Hz, OCH_2CO), and 5.84 and 6.40 (each 1 H, d, J 1Hz, together $C:CH_2$).

Exp. 34

Conversion of N-tert-Butoxycarbonylglycine **(298)** into the Activated Ester **(299)**

N-tert-Butoxycarbonylglycine **(298)** (0.086 g, 0.49 mmol) was dissolved in dry dichloromethane (5 cm^3) and the solution treated with pentachlorophenol (0.132 g, 0.49 mmol) followed by DCCI (0.112 g, 0.54 mmol). The resulting mixture was stirred overnight at room temperature when the insoluble N,N-dicyclohexylurea was filtered off and the filtrate concentrated and dissolved in ethyl acetate (10 cm^3); a second crop of the insoluble N,N-dicyclohexylurea was filtered off. Work-up of the filtrate [washing sequentially with 10 % citric acid and H_2O, followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from hot MeOH] afforded pentachlorophenyl-N-tert-butoxycarbonylglycinate **(299)** (0.133 g, 64%) as a white solid ;

m. p. 134-136 °C (lit.,[110] 142 °C),

$\nu_{max.}$ (KBr) inter alia 1 785 (ester C=O), 1 710 and 1 690 cm^{-1} (urethane C=O),

δ (60 MHz, $CDCl_3$) 1.31 (9 H, s, CMe_3), 4.11 (2 H, d, J 6 Hz, NCH_2), and 5.13br (1 H, t, J 6 Hz, NH).

Experiment 35

Preparation of the Dipeptide Derivative (300)

The activated ester (299) (0.060g, 0.14 mmol) was dissolved in dry dichloromethane at 0 °C and to the solution was added the thiazolidine methyl ester (181) (0.02g, 0.15 mmol) dissolved in dry dichloromethane (10 cm^3) and a catalytic amount of DMAP. The resulting mixture was allowed to stir at room temperature overnight. Work-up [by dilution with EtOAc, sequential washing with 10% HCl, saturated aqueous $NaHCO_3$, followed by evaporation of the dried ($MgSO_4$) organic layer] yielded a clear oil (0.0704 g). Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded a slightly impure sample of the dipeptide derivative (300) (0.0121 g, 28%) as a clear oil. This compound was found to be identical with the material obtained in Experiment 36b by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

Experiment 36

Preparation of the Thiazolidine Sulphide **(300)**

(a) The acid **(298)** (0.129 g, 0.74 mmol) was dissolved in dry THF (10 cm^3) and the solution was treated sequentially with CDI (0.124 g, 0.74 mmol) and the thiazolidine methyl ester **(181)** (0.109 g, 0.74 mmol) at 0 °C. After leaving overnight, evaporation of the solvent and work-up [dilution with EtOAc, sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and H_2O, followed by evaporation of the dried ($MgSO_4$) organic layer] yielded a homogeneous clear oil considered to be the sulphide **(300)** (0.0785 g, 35%). This compound was found to be identical with the material obtained in Experiment 36b; by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

(b) The acid **(298)** (0.471 g, 2.69 mmol), dissolved in dry dichloromethane (10 cm^3), was treated dropwise with dry triethylamine (0.374 cm^3, 2.69 mmol) at 0 °C, followed by ethyl chloroformate (0.283 cm^3, 2.96 mmol); the thiazolidine methyl ester **(181)** (0.396 g, 2.69 mmol) was then added to the mixture. After stirring overnight, the mixture was diluted with ethyl acetate and washed sequentially with 10% hydrochloric acid and saturated aqueous sodium hydrogen carbonate. Evaporation of the dried ($MgSO_4$) organic layer yielded a clear oil (0.825 g) which was purified by silica-gel chromatography (EtOAc-hexane, gradient elution) to give methyl (4R)-3-(N-tert-butoxycarbonylglycyl)thiazolidine-4-carboxylate **(300)** (0.484 g, 59 %) as a clear oil which existed as a 2:1 mixture of rotamers in deuteriochloroform solution ;

$[\alpha]_D$ -82 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (film) inter alia 1 750 (ester C=O), 1 715 (urethane C=O), and 1 670 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 211 nm (ε 3 400),

δ (300 MHz, $CDCl_3$) 1.42-1.69 (9 H, m, CMe_3), 3.17-3.50 (2 H, m, 5-H_2), 3.75 and 3.82 (2 and 1 H, each s, CO_2Me), 3.93-4.16 (2 H, m, $NHCH_2CO$), 4.47-4.60 (2 H, m, 2-H_2), 4.74-4.81 (0.33 H, m, 4-H of minor rotamer), 5.11 (0.66 H, dd, J 6 and 4 Hz, 4-H of major rotamer), and 5.35br (1 H, s, NH),

m / z (c.i., NH_3) 306 ($(M+1)^+$, 1 %), 305 (MH^+, 8 %), 304 (M^+, 1 %), 249 ($MH_2^+ - C_4H_9$, 69 %), 248 ($MH^+ - C_4H_9$, 20 %), 247 ($M^+ - C_4H_9$, 2 %), and 205 ($MH_2^+ - C_5H_9O_2$, 100 %).

Found : C, 47.5; H, 6.9; N, 9.1; S, 10.1. $C_{12}H_{20}N_2O_5S$ requires C, 47.4; H, 6.6; N, 9.2; S, 10.5 %.

(c) The acid **(298)** (9.55 g, 54.51 mmol) was dissolved in dry dichloromethane (50 cm^3) at 0 °C and the solution was treated with DCCI (10.69 g, 54.51 mmol); the resulting mixture was stirred for 0.25 h. To the solution was added the thiazolidine methyl ester **(181)** (7.56 g, 51.41 mmol) and the mixture was allowed to stir at room temperature overnight. The insoluble N,N-dicyclohexylurea was filtered off and the filtrate concentrated and dissolved in ethyl acetate (50 cm^3); a second crop of the insoluble N,N-dicyclohexylurea was filtered off. Work-up of the filtrate by washing sequentially with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate and brine, followed by evaporation of the dried ($MgSO_4$) organic layer and recrystallisation of the residue from chloroform-light petroleum afforded **(300)** (16.17 g, 98%) as a white solid. This compound was found to be identical with the material obtained in Experiment 36b.

Exp.37

Conversion of the Sulphide **(300)** into the Sulphone **(301)**

(a) The sulphide **(300)** (1.31 g, 4.31 mmol) was dissolved in 80% acetic acid (5 cm^3) and the solution was treated dropwise with potassium permanganate (1.36 g, 8.61 mmol) in water (100 cm^3) at 0 °C over 1 h. After leaving for a further 1 h at room temperature, the colour was discharged with aqueous hydrogen peroxide. Work-up [by dilution with EtOAc, sequential washing with saturated aqueous $NaHCO_3$ and brine, followed by

evaporation of the dried ($MgSO_4$) organic extract, purification of the residue by SiO_2 chromatography (EtOAc-hexane, gradient elution), and recrystallisation from $CHCl_3$-light petroleum] afforded the sulphone **(301)** (0.429 g, 30%) as a white solid. This compound was found to be identical with the material obtained in Experiment 37c by m.p. and 300 MHz ^1H n.m.r. spectroscopy.

(b) The sulphide **(300)** (0.3187 g, 1.048 mmol) was dissolved in dry dichlorormethane (10 cm^3) and treated with m-CPBA (0.4553 g, 3.144 mmol). After stirring overnight, the mixture was stirred vigorously with saturated aqueous sodium sulphite for 0.5 h. Work-up [by dilution with EtOAc and washing with saturated aqueous $NaHCO_3$, followed by evaporation of the dried ($MgSO_4$) organic layer] yielded a white solid. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystallisation of the residue from chloroform-light petroleum afforded the sulphone **(301)** (0.2117 g, 62 % yield) as a white solid. This compound was found to be identical with the material obtained in Experiment 37c by m.p. and 300 MHz ^1H n.m.r. spectroscopy.

(c) The sulphide **(300)** (2.28 g, 7.50 mmol) was dissolved in a 1:1 mixture of methanol / water (30 cm^3) and stirred with "Oxone" (6.92 g, 11.27 mmol) at room temperature overnight. Work-up [by dilution with EtOAc and washing with brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded (4R)-4-methoxycarbonyl-3-(N-tert-butoxycarbonylglycyl)thiazolidine 1,1-dioxide **(301)** (1.55 g, 62%) as a white solid, existing as a 5:1 mixture of rotamers in deuteriochloroform solution ;

m.p. 66-70 °C,

$[\alpha]_D^{23}$ - 88 ° (1.2 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 1 744 (ester C=O), 1 701 (urethane C=O), and 1 676 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 209 nm (ε 2 300),

δ (300 MHz, $CDCl_3$) 1.48 (9 H, s, CMe_3), 3.50-3.76 (2 H, m, 5-H_2), 3.82 and 3.88 (each 2.5 and 0.5 H, s, CO_2Me), 3.89-4.24 (2 H, m, NCH_2CO), 4.25 (0.17 H, d, J 12 Hz, NCH_2S of minor rotamer), 4.55 (1.66 H, AB q, J 11 Hz, separation of inner lines 49 Hz, NCH_2S of major rotamer), 4.96 (0.17 H, d, J 12 Hz, NCH_2S of minor rotamer), 5.13-5.33 (1 H, m, NH), and 5.44 (1 H, dd, J 5.5 and 7.5 Hz, 4-H),

m / z (c.i., NH_3) 354 (MNH_4^+, 1.2 %) and 135 (100 %).

Found : C, 42.9; H, 6.2; N, 8.1; S, 9.1. $C_{12}H_{20}N_2O_7S$ requires C, 42.9; H, 5.9; N, 8.3; S, 9.5 %.

(d) The sulphide **(300)** (3.51 g, 11.55 mmol) was dissolved in dry dichlorormethane and stirred with TBA-OX[111] (14.85 g, 17.33 mmol) and sodium carbonate (1.22 g, 34.65 mmol) at room temperature overnight. Work-up [filtration and sequential washing of the filtrate with H_2O (x 3) and brine (x 2), followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded the sulphone **(301)** (1.17 g, 30%) as a white solid. This compound

was found to be identical with the material obtained in Experiment 37c by m.p. and 300 MHz ^{1}H n.m.r. spectroscopy.

(e) The sulphide **(300)** (1.60 g, 5.26 mmol) was stirred with 30% peroxyacetic acid (7 cm^3) at room temperature for 2 h. Work-up [vigorous stirring with saturated aqueous Na_2SO_3 for 0.5 h, sequential washing with saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic extract, purification of the residue by flash silica-gel chromatography, and recrystallisation from $CHCl_3$-light petroleum] afforded the sulphone **(301)** (0.70 g, 44%) as a white solid. This compound was found to be identical with the material obtained in Experiment 37c by i.r. and 300 MHz ^{1}H n.m.r. spectroscopy.

Experiment 38

Reaction of the Sulphone **(301)** with DBN followed by Benzyl Chloroformate

To a solution of the sulphone **(301)** (0.264 g, 0.788 mmol) in dry dichloromethane (5 cm^3) at 0 °C was added dropwise DBN (0.195 cm^3, 1.575 mmol) followed, after 0.5 h, by benzyl chloroformate (0.337 cm^3, 2.363 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with dilute HCl and saturated aqueous $NaHCO_3$, followed by evaporation of the dried ($MgSO_4$) organic extract] afforded an orange oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded methyl α-[N-(benzyloxysulphinylmethyl)-N-(tert-butoxycarbonylglycyl)aminoacrylate **(302)** (0.0872 g, 26%) as a white foam ;

$\nu_{max.}$ (film) inter alia 1 724 (ester and urethane C=O), 1 691 (amide C=O), and 1 654 cm^{-1} ($C=CH_2$),

δ (300 MHz, $CDCl_3$) 1.27 (9 H, s, CMe_3), 3.63 (3 H, s, CO_2Me), 3.69-4.03 (2 H, m, NCH_2CO), 4.15 and 4.50 (each 1 H, d, J 12 Hz,NCH_2S), 4.92 (2 H, AB q, J 12, separation of inner lines 4 Hz, $PhCH_2CO$), 5.34br (1 H, s, NH), 5.88 and 6.38 (each 1 H, s, together $C:CH_2$) and 7.17 (5 H, s, C_6H_5),

m / z (e.i.) inter alia 248 (29%), 146 (52%), and 57 (100%).

Found : C, 52.8; H, 6.1; N, 6.6. $C_{19}H_{26}N_2O_7S$ requires C, 53.5; H, 6.1; N, 6.6 %.

Experiment 39

Reaction of the Acrylate **(302)** with Diazomethane

A solution of the acrylate **(302)** (0.259 g, 0.609 mmol) in dry dichloromethane (15 cm^3) was cooled to 0 °C and the solution was treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and recrystallisation of the residue from chloroform-light petroleum afforded benzyl [N-(tert-butoxycarbonylglycyl)-N-(3-methoxycarbonyl-Δ^1-pyrazolin-3-yl]aminomethanesulphinate **(305)** (0.259 g, 91%) as a white solid ;

m.p. 90-95 °C (with softening at 30 °C),

$\nu_{max.}$ (KBr) inter alia 1 745 (ester C=O), 1 715 (urethane C=O), and 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 209 (ε 10 900) and 329 nm (300),

δ (300 MHz, $CDCl_3$) 1.40-1.48 (10 H, m, CMe_3 and $C\underline{H}HCH_2N$), 2.93-3.03 (1 H, m, $CH\underline{H}CH_2$), 3.72 (3 H, s, CO_2Me), 4.16-4.28, 4.40-4.58, and 4.62-4.77 (2, 2 and 1 H, each m, NCH_2S, $CH_2C\underline{H}_2N$, and $NHC\underline{H}HCO$), 4.90-5.14 (3 H, m, $OC\underline{H}_2Ph$ and $NHCH\underline{H}CO$), 5.20br (1 H, s, NH), and 7.29-7.44 (5 H, m, C_6H_5),

m / z (f.a.b.) 469 (MH^+, 2 %) and 307 (100 %).

Found : C, 51.0; H, 5.7; N, 11.6; S, 6.4. $C_{20}H_{28}N_4O_7S$ requires C, 51.3; H, 6.0; N, 12.0; S, 6.8 %.

Experiment 40

Reaction of the Sulphone **(301)** with Potassium tert-Butoxide

The sulphone **(301)** (0.449 g, 1.336 mmol) was dissolved in dry THF (10 cm^3) and the solution, cooled to -78 °C, was treated with freshly resublimed potassium tert-butoxide (0.150 g, 1.336 mmol). After 1 h, the mixture was allowed to warm up to room temperature. Evaporation of the solvent and purification of the residue by recrystallisation from acetone-light petroleum afforded a pale-yellow solid (0.450 g, 90%) considered to contain the salt **(306)** (the ^1H n.m.r. spectrum was complex) ;

m.p. 145-150 °C (with decomp.),

$\nu_{max.}$ (KBr) inter alia 1 703 (C=O) and 1 636 cm^{-1} ($C=CH_2$),

$\lambda_{max.}$ (EtOH) 210 nm (ε 4 020).

Experiment 41

Reaction of the Potassium Sulphinate **(306)** with Iodomethane

The potassium salt **(306)** (0.39 g, 1.04 mmol) was dissolved in dry DMF (1 cm^3) and treated with iodomethane (0.5 cm^3). After leaving overnight, the mixture was worked up [by dilution with EtOAc and sequential washing with brine (x 3) and H_2O, followed by evaporation of the dried ($MgSO_4$) organic layer] to afford an orange oil which was purified by silica-gel chromatography (EtOAc-hexane, gradient elution) to afford the acrylate **(307)** (0.102 g, 28%) as a colourless oil. This compound was found to be identical to the material obtained in Experiment 43 by i.r. and 300 MHz ^1H n.m.r. spectroscopy.

Experiment 42

Reaction of the Sulphone **(301)** with DBN followed by Iodomethane

To a solution of the sulphone **(301)** (0.29 g, 0.86 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (0.21 cm^3, 1.73 mmol) followed, after 0.25 h, by iodomethane (0.3 cm^3, 4.82 mmol). After stirring for 1 h, the mixture was diluted with ethyl acetate and washed sequentially with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium thiosulphate, and brine. Evaporation of the dried ($MgSO_4$) organic layer afforded a yellow oil which was purified by silica-gel chromatography (EtOAc-hexane, gradient elution) to yield methyl α-[N-(methylsulphonylmethyl)-N-(tert-

butoxycarbonylglycyl)aminoacrylate **(307)** (0.062 g, 21%) as a colourless oil ;

$\nu_{max.}$ (film) inter alia 1 717 (ester and urethane C=O), 1 688 (amide C=O) and 1 640 cm^{-1} ($C=CH_2$),

δ (300 MHz, $CDCl_3$) 1.39 (9 H, s, CMe_3), 2.90 (3 H, s, SO_2Me), 3.70-3.83 (4 H, m, CO_2Me and NCHHCO), 4.35-4.43 and 4.60-4.71 (0.5 and 1.5 H, both m, together NCHHCO and NCHHS), 5.11-5.43 (2 H, m, NCHHS and NH), 6.25 and 6.62 (each 1 H, both s, together $C:CH_2$).

Found : C, 44.5; H, 6.3; N, 7.7. $C_{13}H_{22}N_2O_7S$ requires C, 44.57; H, 6.28; N, 8.00 %.

Experiment 43

Reaction of the Sulphone **(301)** with Potassium tert-Butoxide followed by Oxalyl Chloride followed by tert -Butyl Alcohol

The sulphone **(301)** (0.1554 g, 0.4625 mmol) in dry THF (5 cm^3) was cooled to - 78 °C and the solution was treated with potassium tert-butoxide (0.052 g, 0.4634 mmol). After 0.5 h, the mixture was allowed to warm up to room temperature and treated with oxalyl chloride (0.2 cm^3, 2.293 mmol). The mixture was then allowed to stand for 1 h, cooled to - 23 °C, and treated with an excess of tert-butyl alcohol (3 cm^3) dropwise. After 0.5 h, work-up by evaporation afforded a pale-yellow oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded methyl α-[N-(tert-butoxycarbonylglycyl)-N-(tert-(butoxysulphinylmethyl)aminoacrylate **(310)** (0.0852 g, 47 %) as a clear oil ;

δ (300 MHz, $CDCl_3$) 1.40-1.44 (18 H, m, 2 x CMe_3), 3.73-4.06 (ca. 5.5 H, m, CO_2Me and NCH_2CO), 4.40-4.66 (2 H, m, NCH_2S), 5.30br (1 H, s, NH), 6.20 and 6.60 (each 1 H, each s, together $C:CH_2$).

Experiment 44

Preparation of the Thiazolidine Sulphide **(311)**

The acid **(314)** (1.06 g, 5.07 mmol), dissolved in dry dichloromethane at 0 °C, was treated with DCCI (1.06 g, 5.08 mmol) and the resulting mixture was stirred for 0.25 h. To the solution was added the thiazolidine methyl ester **(181)** (0.741 g, 5.04 mmol) and the mixture was allowed to stir at room temperature overnight. The insoluble N,N-dicyclohexylurea was filtered off and the filtrate concentrated and dissolved in ethyl acetate (10 cm^3); a second crop of the insoluble N,N-dicyclohexylurea was filtered off. Work-up of the filtrate [by washing sequentially with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded methyl (4R)-3-(N-benzyloxycarbonylglycyl)-thiazolidine-4-carboxylate **(311)** (1.72 g, 100%) as a colourless oil, which existed as a 3:1 mixture of rotamers in deuteriochloroform solution ;

$[\alpha]_D^{22}$ -109 ° (1.5 % in CH_2Cl_2),

$\nu_{max.}$ (film) inter alia 1 724 (ester and urethane C=O) and 1 664 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 216 (ε 2 200) and 257 nm (250),

δ (300 MHz, $CDCl_3$) 3.13-3.45 (2 H, m, 5-H_2), 3.75 and 3.78 (2.25 and 0.75 H, each s, CO_2Me), 3.87-423 (2 H, m, NCH_2CO), 4.47-4.60 (1.5 H, m, NCH_2S of major rotamer), 4.70-4.86 (0.75 H, m, NCH_2S and 4-H of minor rotamer) 5.05-5.40 (2.75 H, m, $PhCH_2CO$ of both rotamers and 4-H of major rotamer), 5.70br (1 H, s, NH), 7.20-7.50 (5 H, m, C_6H_5) (addition of D_2O caused the disappearance of the signal at 5.70 and a simplification of the signal at 3.87-4.23). The sample was run at 303 K, 333 K, 353 K and 373 K. Coalescence of the rotameric forms was virtually complete at 373 K and resulted in a significant simplification of the spectrum. The spectrum reverted back to its original form when the temperature was reduced back to 303 K.)

m / z (e.i.) 338 (M^+, 0.5 %) and 231 ($M^+ - C_7H_7O$, 1.5%).

Found : C, 53.3; H, 5.4; N, 8.3. $C_{15}H_{18}N_2O_5S$ requires C, 53.25; H, 5.33; N, 8.28 %.

Experiment 45

Oxidation of the Sulphide **(313)** to the Sulphone **(315)**

The sulphide **(313)** (3.07 g, 9.08 mmol) was dissolved in a 1:1 mixture of methanol-water (50 cm^3) and the solution treated with "Oxone" (9.20 g, 14.98 mmol) over a period of 5 min. After stirring overnight, work-up [by dilution with EtOAc, sequential washing with H_2O (x 2) and brine, followed by evaporation of the dried ($MgSO_4$) organic extract and purification of the residue by recrystallisation from $CHCl_3$-light petroleum] afforded (4R)-3-(N-benzyloxycarbonylglycyl)-4- methoxycarbonylthiazolidine 1,1-dioxide

(315) (3.02 g, 90%) as a white solid which, existed as a 3:1 mixture of rotamers in deuteriochloroform solution ;
m.p. 32-34 °C,

$[\alpha]_D^{22}$ -92 ° (1 % in CH_2Cl_2),

$\nu_{max.}$ (KBr) inter alia 1 751 (ester C=O), 1 720 (urethane C=O), and 1 682 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 251 (ε150), 257 (170), and 271 nm (1 100),

δ (300 MHz, $CDCl_3$) 3.33-3.61 (2 H, m, 5-H_2), 3.68 and 3.72 (2.25 and 0.75 H, each s, CO_2Me), 3.80-4.18 (2 H, m, NCH_2CO), 4.65 (1.5 H, AB q, J 11 Hz, separation of inner lines 46 Hz, NCH_2S of major rotamer), 4.76-4.97 (0.5 H, m, NCH_2S of minor rotamer), 5.04 (2 H, s, $PhCH_2CO$), 5.13-5.30 (1H, m, 4-H of both rotamers), 5.90br (1 H, s, NH), and 7.25-7.36 (5 H, m, C_6H_5),

m / z (e.i.) 370 (M^+, 18 %) and 263 ($M^+ - C_7H_7O$, 6 %).

Found : C, 48.1; H, 4.9; N, 7.3. $C_{15}H_{18}N_2O_7S$ requires C, 48.64; H, 4.87; N, 7.57 %.

Experiment 46

Reaction of the Sulphone **(315)** with DBN followed by Benzyl Chloroformate

To a solution of the sulphone **(315)** (2.01 g, 5.43 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (1.62 cm^3,

10.86 mmol) followed, after 0.25 h, by benzyl chloroformate (3.88 cm^3, 27.16 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic extract] afforded an orange oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded methyl α-[N-(benzyloxycarbonylglycyl)-N-(benzyloxysulphinylmethyl)amino]acrylate **(316)** (0.45 g, 18 %) as a white foam ;

$\nu_{max.}$ (film) inter alia 1 728 (ester and urethane C=O), 1 690 (amide C=O), and 1 630 cm^{-1} ($C=CH_2$),

$\lambda_{max.}$ (EtOH) 208 nm (ε 13 300),

δ (300 MHz, $CDCl_3$) 3.72 (3 H, s, CO_2Me), 3.82-3.98 (2 H, m, NCH_2CO), 4.22 and 4.62 (each 1 H, d, J 12 Hz, NCH_2S), 5.00 and 5.02 (each 2 H, s, together 2 x $PhCH_2CO$), 5.74br (1 H, apparent t, separation 2 Hz, NH), 5.97 and 6.49 (each 1 H, s, together $C:CH_2$) and 7.32 (10 H, m, 2 x Ph),

m / z (e.i.) inter alia 305 (56%), 204 (53%), 146 (85%), 114 (91%),and 91 (100%).

Found : C, 55.6; H, 5.4; N, 6.4. $C_{22}H_{24}N_2O_7S$ requires C, 57,39; H, 5.21;N, 6.08 %.

Experiment 47

Reaction of the Sulphone **(315)** with DBN followed by Iodomethane

To a solution of the sulphone **(315)** (1.00 g, 2.70 mmol) in dry dichloromethane (10 cm^3) at 0 °C was added dropwise DBN (0.8 cm^3, 5.40 mmol) followed, after 0.5 h, by iodomethane (0.84 cm^3, 13.5 mmol). After stirring overnight, the mixture was diluted with ethyl acetate and washed sequentially with 10% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium thiosulphate, and brine. Evaporation of the dried ($MgSO_4$) organic layer afforded a white solid, which was purified by flash silica-gel chromatography (EtOAc-hexane, gradient elution), and recrystallisation from $CHCl_3$-light petroleum gave methyl α-[N-(benzyloxycarbonylglycyl)-N-(methylsulphonylmethyl)-amino]acrylate **(317)** (0.80 g, 77%) as a white solid ;

m.p. 40-44 °C,

$\nu_{max.}$ (KBr) inter alia 1 742 (ester C=O), 1 726 (urethane C=O), and 1 676 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 2.88 (3 H, s, SO_2Me), 3.79 (3 H, s, CO_2Me), 3.90br (2 H, d, separation 5 Hz, NCH_2CO), 4.72 (2 H, s, NCH_2), 5.07 (2 H, s, $PhCH_2O$), 5.84br (1 H, apparent t, separation 5 Hz, NH), 6.25 and 6.50 (each 1 H, s, together $C=CH_2$), and 7.35br (5 H, s, C_6H_5),

m / z (e.i.) inter alia 305 (13%), 204 (21%), 114 (33%), and 91 ($C_7H_7^+$, 100%).

Found: C, 49.3; H, 5.3; N, 7.2. $C_{16}H_{20}N_2O_7S$ requires C, 50.00; H, 5.28; N, 7.29 %.

Experiment 48

Reaction of the Acrylate (317) with Diazomethane

A solution of the acrylate **(317)** (0.068 g, 0.177 mmol) in dry dichloromethane (10 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 3 h, and recrystallisation of the residue from chloroform-light petroleum afforded methyl 3-(N-benzyloxycarbonylglycyl-N-methylsulphonyl)amino-Δ^1-pyrazoline-3-carboxylate **(319)** (0.075 g, 100 %) as a white crystalline solid ;

m.p. 82-85 °C,

$\nu_{max.}$ (KBr) inter alia 1 745 (ester C=O), 1 725 (urethane C=O), and 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH 208 (ε 12 400) and 328 nm (250),

δ (300 MHz, CD_3SOCD_3, 323 K) 1.63-1.79 (1 H, m, C<u>H</u>HCH$_2$N), 2.89 (1 H, ddd, J 12, 9, and 3 Hz, CH<u>H</u>CH$_2$), 3.17 (3 H, s, SO_2Me), 3.70 (3 H, s, CO_2Me), 3.75-3.90 (2 H, m, NCH_2S), 4.25 and 4.40 (each 1 H, dd, J 17 and 5 Hz, NHC<u>H</u>$_2$CO), 4.60 -4.72 (1 H, m, CH$_2$C<u>H</u>HN), 5.03 -5.25 (3 H, m, PhC<u>H</u>$_2$O and CH$_2$CH<u>H</u>N), and 7.33-7.50 (5 H, m, Ph),

m / z (f.a.b.) 427 (<u>M</u>H$^+$, 4 %), 307 (60 %), and 136 (100 %).

Found : C, 44.0; H, 4.5; N, 11.1; S, 7.1. $C_{17}H_{22}N_4O_7S$ requires C, 47.9; H, 5.2; N, 13.1; S, 7.5 %.

Experiment 49

Thermolysis of the Pyrazoline **(319)**

The pyrazoline **(319)** was dissolved in deuteriodimethyl sulphoxide (0.5 cm3) and the sample heated from 273 K to 353 K, the 300 MHz ^1H n.m.r. spectrum clearly showed the disappearence of the pyrazoline **(319)** and the formation of a new material, considered to be the but-2-enoate compound **(320)**. It displayed the following property;

δ (300 MHz, CD_3SOCD_3, 353 K) inter alia 2.25 (3 H, d, J 7 Hz, C:CHMe), 3.03 (3 H, s, SMe), 3.82-3.86 (3 H, m, CO_2Me), 3.96 (2 H, d, J 6 Hz, NCH_2CO), 4.91 (2 H, s, NCH_2S), 5.18 (2 H, s, $PhCH_2$), 6.91 (1 H, dd, J 7 and 14 Hz, C:CHMe), 7.06br (1 H, s, NH), and 7.39-7.50 (5 H, m, $PhCH_2$),

Experiment 50

Reaction of the Pyrazoline **(319)** with Zinc

A solution of the pyrazoline **(319)** (1.62 g, 3.80 mmol) in 5:5:1 acetic acid-acetone-water (10 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (3.24 g, 2 mass equiv.) with vigorous stirring. After stirring overnight, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (X 3). The organic layer was dried ($MgSO_4$) and evaporated to yield a white powder. Purification by silica-gel

chromatography (EtOAc-hexane, gradient elution) afforded N-(benzyloxycarbonylglycyl)aminomethylmethylsulphone **(321)** (0.61g, 54%) as a white powder ;

m.p. 119 °C,

$\nu_{max.}$ (KBr) inter alia 1 690 (urethane C=O) and 1 660 cm^{-1} (amide C=O),

δ (300 MHz, CD_3SOCD_3) 2.89 (3 H, m, SO_2Me), 3.83 (2 H, d, J 6 Hz, NCH_2CO), 4.63 (2 H, d, J 6.5 Hz, NCH_2S), 5.14 (2 H, s, $PhCH_2$), 7.36-7.51 (5 H, m, $PhCH_2$), 7.70 (1 H, t, J 6 Hz, OCONH), and 9.19 (1 H, t, J 6.5 Hz, CH_2CONH),

m / z (f.a.b.) inter alia 301 (MH^+, 25 %) and 136 (100 %).

Found : C, 48.3; H, 5.6; N, 9.1; S, 10.6. $C_{12}H_{16}N_2O_5S$ requires C, 48.0; H, 5.3; N, 9.3; S, 10.7 %.

Experiment 51

Reaction of the Sulphone **(315)** with Potassium tert-Butoxide

The sulphone **(315)** (1.67 g, 4.51 mmol) was dissolved in dry THF (10 cm^3) and the solution, cooled to -78 °C, was treated with potassium tert-butoxide (0.56 g, 4.90 mmol). After 1.5 h, the mixture was allowed to warm up to room temperature. Evaporation of the solvent and purification of the residue by recrystallisation from acetone-chloroform afforded a yellow solid (1.69 g, 92%) considered to contain the salt **(322)** (the ^1H n.m.r. spectrum was complex) ;

m.p. 128-130 °C (decomp.),

$\nu_{max.}$ (KBr) inter alia 1 725br cm^{-1} (ester, urethane, and amide C=O).

Experiment 52

Conversion of the Salt (322) into the Sulphinic Acid (323)

The salt (322) (0.30 g, 0.74 mmol) was dissolved in methanol (2 cm^3) and the solution was treated with Amberlite IR 120 (H^+) ion-exchange resin until it turned acidic. The mixture was filtered and the resin thoroughly washed with water. The washings were concentrated and the procedure was repeated once again. Evaporation of the washings gave a pale-orange oil which was crystallised from chloroform-light petroleum to yield a pale orange solid, presumed to be the sulphinic acid (323) (0.25 g, 92 %), with the following properties (the ^1H n.m.r. spectrum was complex) ;

m.p. 30-35 °C (with decomp.),

$\nu_{max.}$ (KBr) inter alia 1 725br cm^{-1} (ester, urethane, and amide C=O),

$\lambda_{max.}$ (EtOH) 208 nm (ε 18 600),

m / z (e.i.) 370 (M^+, 2 %), 306 ($M^+ - SO_2$, 2 %), and 108 (100 %).

Experiment 53

Reaction of the Potassium Salt **(322)** with Iodomethane

The potassium salt **(322)** (0.081 g, 1.98 mmol) was dissolved in dry DMF (2 cm^3) and the solution was treated with iodomethane (1.5 cm^3). After leaving overnight, work-up [by dilution with EtOAc and sequential washing with brine (x 3), saturated aqueous $Na_2S_2O_3$, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a pale-yellow oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded a white foam (0.07 g), considered by 300 MHz ^1H n.m.r. spectroscopy to be a 1:1 mixture of compound **(317)** and the sulphone **(315)**, which displayed the following properties ;

$\nu_{max.}$ (film) inter alia 1 750 (ester C=O), 1 726 (urethane C=O), 1 686 (amide C=O), and 1 630 cm^{-1} ($C=CH_2$),

m / z (e.i.) inter alia 305 (39%), 204 (40%), 114 (66%), and 91 ($C_7H_7^+$, 100%).

Found : C, 50.6; H, 5.3; N, 6.9. $C_{16}H_{20}N_2O_7S$ requires C, 50.00; H, 5.21; N, 7.29 %.

Experiment 54

Preparation of the Thiazolidine (161)

A solution of the acid (160) (24.45 g, 183.83 mmol) in 2M-sodium hydroxide (92 cm^3, 184 mmol) was cooled to 0 °C and treated with benzyl chloroformate (26.25 cm^3) and 2 M-sodium hydroxide (92 cm^3, 184 mmol) simultaneously over 10 min. The mixture was then extracted with diethyl ether (x 2) and the ethereal extracts discarded. Acidification and extraction with ethyl acetate, followed by evaporation of the dried ($MgSO_4$) organic layer afforded (4R)-3-benzyloxycarbonylthiazolidine-4-carboxylic acid (161) (36.08 g, 74%) as a clear oil, found to be identical with the authentic material ;[81]

$\nu_{max.}$ (film) inter alia 3 500-3 200br (OH) and 1 711 cm^{-1} (acid and urethane C=O),

δ (300 MHz, $CDCl_3$) 3.23 (2 H, d, separation 4 Hz, 5-H_2), 4.34-5.03 (3 H, m, 2-H_2 and 4-H), 5.06-5.12 (2 H, s, PhCH_2), 7.13-7.47 (5 H, s, PhCH_2), and 10.76 (1 H, s, CO_2H).

Experiment 55

Preparation of the Thiazolidine Ester (332)

A solution of the thiazolidine acid (161) (1.30 g, 4.87 mmol) in dichloromethane (20 cm^3) at 0 °C was treated with an excess of ethereal diazomethane. Evaporation afforded methyl (4R)-3-benzyloxycarbonylthiazolidine-4-carboxylate (322) (1.18 g, 81%) as a

chromatographically homogeneous syrup, which existed as a 2:1 mixture of rotamers in deuteriochloroform solution, and was found to be identical with the authentic material ;[81]

$\nu_{max.}$ (film) inter alia 1 753 (ester C=O) and 1 709 cm^{-1} (urethane C=O),

δ (300 MHz, $CDCl_3$) 2.73-3.30 (2 H, m, 5-H_2), 3.56 and 3.65 (1 and 2 H, each s, CO_2Me), 4.13-4.96 (3 H, m, 2-H_2 and 4-H), 4.98-5.39 (2 H, m, $PhCH_2$), and 7.29-7.50 (5 H, s, $PhCH_2$),

m / z (e.i.) inter alia 281 (M^+ - $C_8H_7O_2$, 11%) and 91 ($C_7H_7^+$, base peak).

Found: C, 57.1; H, 5.5; N, 4.7. Calc. for $C_{13}H_{15}NO_4S$: C, 55.5; H, 5.3; N, 5.0%.

Experiment 56

Reaction of the Sulphide **(322)** with "Oxone"

To a solution of the sulphide **(322)** (2.52 g, 8.97 mmol) in 1:1 methanol / water (50 cm^3), was added "Oxone" (9.02 g, 14.69 mmol). After stirring overnight, work-up [by dilution with EtOAc and washing with brine (x 3), followed by evaporation of the dried ($MgSO_4$) organic layers] afforded (4R)-3-benzyloxycarbonyl-4-methoxycarbonylthiazolidine 1,1-dioxide **(116d)** (2.15 g, 77%) as a chromatographically homogeneous syrup, and was found to be identical with the authentic material ;[81]

$\nu_{max.}$ (film) inter alia 1 753 (ester C=O) and 1 718 cm^{-1} (urethane C=O),

δ (300 MHz, $CDCl_3$) 3.35-3.80 (5H, m, 5-H_2 and CO_2Me), 4.29 (1 H, d, J 11 Hz, NC<u>H</u>HS), 4.42-4.80 (1 H, m, NCH<u>H</u>S), 5.10-5.30 (3 H, m, PhC<u>H</u>$_2$ and 4-H), and 7.33 (5 H, m, C_6H_5).

<u>Experiment 57</u>

<u>Reaction of the Sulphone (116d) with DBN followed by Allyl Bromide</u>

To a solution of the sulphone **(116d)** (0.112 g, 0.359 mmol) in dry DMF (5 cm^3) was added dropwise DBN (0.089 cm^3, 0.359 mmol) followed, after 0.5 h, by allyl bromide (0.153 cm^3, 1.79 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with dilute HCl, saturated aqueous $NaHCO_3$, and brine, followed by evaporation of the dried ($MgSO_4$) organic extract] afforded the <u>methyl</u> α-[N-(<u>allylsulphonylmethyl</u>)-N-(<u>benzyloxycarbonyl</u>)]<u>aminoacrylate</u> **(334)** (0.913 g, 73%) as a clear oil ;

$\nu_{max.}$ (film) <u>inter alia</u> 1 730br (urethane and ester C=O) and 1 640 cm^{-1} (C=C),

$\lambda_{max.}$ (EtOH) 212 nm (ε 8 700),

δ (300 MHz, $CDCl_3$) 3.65br (3 H, s, CO_2Me), 3.80-3.94 (2 H, m, SC<u>H</u>$_2$CH), 4.73 (2H, s, NCH_2S), 5.16 (2 H, s, PhC<u>H</u>$_2$), 5.35-5.65 (2 H, m, CH:C<u>H</u>$_2$), 5.76-6.04 (1 H, m, C<u>H</u>:CH_2), 6.10 (1H, s, MeO_2CC:C<u>H</u>H), 6.35 (1 H, s, MeO_2CC:CH<u>H</u>), and 7.20-7.40 (5 H, m, C_6H_5),

δ (300 MHz, CD_3SOCD_3, 378 K) 3.80 (3 H, s, CO_2Me), 4.0 (2 H, d, J 7 Hz, SC<u>H</u>$_2$CH), 4.98 (2 H, s, NCH_2S), 5.24 (2 H, s, PHC<u>H</u>$_2$O), 5.45-5.58 (2 H, m, CH_2CH:C<u>H</u>$_2$), 5.84-6.02 (1 H, m, CH_2C<u>H</u>:CH_2), 6.17 (1 H, d,

J 1 Hz, $MeO_2CC:CHH$), 6.37 (1 H, d, J 1 Hz, $MeO_2CC:CHH$), and 7.40-7.50 (5 H, m, C_6H_5),

m / z (f.a.b.) inter alia 354 (MH^+, 30 %), 248 (60 %), 208 (80 %), and 91 (100 %).

Found : C, 54.7; H, 5.7; N, 4.0; S, 8.7. $C_{16}H_{19}NO_6S$ requires C,54,4; H, 5.4; N, 4.0; S, 9.1%.

Experiment 58

Reaction of the Sulphone **(315)** with DBN followed by Methyl Chloroformate

To a solution of the sulphone **(315)** (1.1203 g, 3.58 mmol) in dry dichloromethane (15 cm^3) at 0 °C was added DBN (0.78 cm^3, 7.158 mmol), followed, after 0.5 h, by methyl chloroformate (0.94 cm^3, 12.165 mmol). After stirring overnight, work-up [by dilution with EtOAc, sequential washing with dilute HCl, saturated aqueous $NaHCO_3$, and brine, followed by evaporation of the dried ($MgSO_4$) organic extracts] afforded an orange oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystallisation from dichloromethane-diethyl ether yielded [N-(benzyloxycarbonylglycyl)-N-(methoxysulphinylmethyl)amino]acrylate **(338)** (0.388 g, 33%) as a sticky white solid, which existed as a 3:1 mixture of rotamers in deuteriochloroform solution ;

$\nu_{max.}$ (film) inter alia 1 730 (ester and urethane C=O), 1 690 (amide C=O), and 1 640 cm^{-1} (C=C),

$\lambda_{max.}$(EtOH) 256 nm (ε 1 250),

δ (300 MHz, $CDCl_3$) 3.79 (3 H, s, CO_2Me), 3.84 (3 H, s, SO_2Me), 3.90-4.03 (2 H, m, NCH_2S), 4.15-4.68 (2 H, m, NCH_2CO), 5.11 (2 H, s, $PhCH_2$), 5.56br (1 H, s, NH), 6.19-6.33 (1 H, m, C:CHH), 6.62-6.69 (1H, m, C:CHH), and 7.30-7.38 (5H, m, C_6H_5).

Found : C, 50.2; H, 5.4; N, 7.3; S, 8.0. $C_{16}H_{20}N_2O_7S$ requires C, 50.5; H, 5.3; N, 7.4; S, 8.4 %.

Experiment 59

Reaction of the Sulphone **(116d)** with DBU followed by Acetyl Chloride followed by Methanol

The sulphone **(116d)** (0.231 g, 0.74 mmol) in dry dichloromethane (10 cm^3) was treated with DBU (0.110 cm^3, 0.74 mmol). After 0.25 h, the mixture was cooled to -20 °C and treated dropwise with acetyl chloride (0.053 cm^3, 0.74 mmol). After 0.5 h, the mixture was treated dropwise with an excess of methanol (5 cm^3) and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic extracts] afforded methyl [N-(benzyloxycarbonyl)-N-(α-methoxysulphinylmethyl)]-α-aminoacrylate **(340)** (0.180 g, 75%) as a clear oil ;

$\nu_{max.}$ (film) inter alia 1 730br (ester and amide C=O) and 1 640 cm^{-1} (C=C),

δ (300 MHz, $CDCl_3$) 3.58br (3 H, s, CO_2Me), 3.80 (3 H, s, SO_2Me), 4.14-4.30 and 4.41-4.70 (each 1 H, m, NCH_2S), 5.08-5.17 (2 H, m, $PhCH_2O$), 5.85 (1 H, s, C:CHH), 6.19br (1 H, s, C:CHH), and 7.23-7.38 (5 H, m, $PhCH_2$),

m / z (f.a.b.) 328 (MH^+, 11%), 248 ($M^+ - SO_2Me$, 5 %), and 91 ($C_7H_7^+$, 100 %).

Experiment 60

Reaction of the Sulphone (315) with DBU followed by Acetyl Chloride followed by Methanol

The sulphone **(315)** (0.318 g, 0.858 mmol) in dry dichloromethane (15 cm^3) was treated with DBU (0.129 cm^3, 0.858 mmol). After 0.5 h, the mixture was cooled to - 78 °C and treated dropwise with acetyl chloride (0.061 cm^3, 0.858 mmol). After 0.5 h, the mixture was treated dropwise with an excess of methanol (5 cm^3) and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) yielded methyl [N-(benzyloxycarbonylglycyl)-N-(methoxysulphinylmethyl)]-α-aminoacrylate **(338)** (0.25 g, 77%) as a white solid which was identical with the material obtained in Experiment 58 (i.r. and 300 MHz ^1H n.m.r. spectroscopy).

Experiment 61

Reaction of the Sulphone **(315)** with DBU followed by Acetyl Chloride followed by Ethanol

The sulphone **(315)** (1.26 g, 3.41 mmol) in dry dichloromethane (15 cm^3) was treated with DBU (0.509 cm^3, 3.41 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (0.242 cm^3, 3.41 mmol). After 0.5 h, the mixture was treated dropwise with an excess of ethanol and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded an oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl [N-(benzyloxycarbonylglycyl)-N-(ethoxysulphinylmethyl)]-α-aminoacrylate **(341)** (0.547 g, 40%) as a clear oil ;

$\nu_{max.}$ (film) inter alia 1 730 (ester and urethane C=O), 1 690 (amide C=O), and 1 640 cm^{-1} (C=C),

$\lambda_{max.}$ (EtOH) 250 (ε 56 700), 256 (49 700), 263 (40 600), and 266 (33 600),

δ (300 MHz, $CDCl_3$) 1.35 (3 H, t, J 7 Hz, CH_2Me), 3.84 (3 H, s, CO_2Me), 3.86-4.20 (5 H, m, NCHHCO, NCH_2S, and OCH_2Me), 4.65br (1 H, d, J 15 Hz, NCHHCO), 5.10 (2 H, s, $PhCH_2$), 5.54br (1 H, apparent t, separation 5 Hz, NH), 6.11 (1 H, s, C : CHH), 6.66 (1 H, s, C:CHH), and 7.30-7.40 (5 H, m, $PhCH_2$),

m / z (f.a.b) 399 (MH^+, 5 %).

Found : C, 51.0; H, 5.8; N, 6.7; S, 7.6. $C_{17}H_{22}N_2O_7S$ requires C, 51.3; H, 5.8; N, 7.0; S, 8.0 %.

Experiment 62

Reaction of the Sulphone (315) with DBU followed by Acetyl Chloride followed by tert-Butyl Alcohol

The sulphone (315) (5.47 g, 14.78 mmol) in dry dichloromethane (20 cm^3) was treated with DBU (2.211 cm^3, 14.75 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (1.051 cm^3, 14.78 mmol). After 0.5 h, the mixture was treated dropwise with an excess of tert-butyl alcohol (5 cm^3) and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$, and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a syrup. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystallisation of the product from chloroform-light petroleum afforded methyl [N-(benzyloxycarbonylglycyl)-N-(tert-butoxysulphinylmethyl)]-α-aminoacrylate (342) (as a $CHCl_3$ solvate) (2.26 g, 36%) as a white crystalline solid ;

m.p. 45-48 °C,

$\nu_{max.}$ (film) inter alia 1 730 (ester and urethane C=O), 1 690 (amide C=O), and 1 640 cm^{-1} (C=C),

$\lambda_{max.}$ (EtOH) 256 (ε 1 300), 263 (1 050), and 266 nm (850),

δ (300 MHz, $CDCl_3$) 1.45 (9 H, s, CMe_3), 3.84 (3 H, s, CO_2Me), 3.86-4.14 (3 H, m, NCH_2CO and NCHHS), 4.64 (1H, apparent d, separation 13 Hz, NCHHS), 5.11 (2 H, s, $PhCH_2$), 6.25 (1 H, s, C:CHH), 6.63 (1 H, s, C:CHH), and 7.33 (5 H, m, C_6H_5),

m / z (f.a.b.) 427 (MH^+, 25 %), 353 ($M^+ - C_4H_9O$, 15 %), and 91 (100 %).

Found : C, 44.3; H, 5.0; N, 5.2; S, 6.2. $C_{19}H_{26}N_2O_7S \cdot CHCl_3$ requires C, 44.0; H, 4.9; N, 5,1; S, 5.9.

Experiment 63

Reaction of the Acrylate (342) with Diazomethane

A solution of the acrylate **(342)** (0.0812 g, 0.191 mmol) in dry dichloromethane (15 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and recrystallisation of the residue from chloroform-light petroleum afforded tert-butyl [N-((benzyloxycarbonylglycyl)-N-(3-methoxycarbonyl-Δ'-pyrazolin-3-yl)]aminomethanesulphinate **(346)** (0.0848 g, 95 %) as a white solid ;

m.p. 72 °C (with softening at 33 °C),

$\nu_{max.}$ (KBr) inter alia 1 745 (ester C=O), 1 730 (urethane C=O), and 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 208 (ε 13 700), 211 (12 000), and 329 nm (350),

δ (300 MHz, $CDCl_3$) 1.36 (9 H, s, CMe_3), 1.44-1.55 (1 H, m, $CH_2C\underline{H}HC$), 2.93-3.09 (1 H, m, $CH_2CH\underline{H}C$), 3.66 (3 H, s, CO_2Me), 4.20-4.30 (3 H, m, NCH_2S and $NC\underline{H}HCO$), 4.56-4.66 (1 H, m, $CH_2C\underline{H}HN$), 4.80br (1 H, d, separation 17 Hz, $NHCH\underline{H}CO$), 4.93-5.10 (3 H, m, $CH_2CH\underline{H}N$ and $PhC\underline{H}_2O$), 5.45br (1 H, t, separation 5 Hz, $N\underline{H}CH_2$), and 7.24-7.38 (5 H, m, C_6H_5),

m/z (f.a.b.) 469 ($\underline{M}H^+$, 1 %), 347 ($\underline{M}^+ - SO_2Bu^t$, 1 %), and 91 ($C_7H_7^+$, 100 %).

Found : C, 51.0; H, 6.0; N, 11.7; S, 6.4. $C_{20}H_{28}N_4O_7S$ requires C, 51.3; H, 6.0; N, 12.0; S, 6.8 %.

Experiment 64

Reaction of the Pyrazoline **(346)** with Zinc

A solution of the pyrazoline **(346)** (2.48 g, 5.30 mmol) in 5:5:1 acetic acid-acetone-water (10 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (5.06 g, 2 mass equiv.) with vigorous stirring. After 4 h, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (x 3). The organic layer was dried ($MgSO_4$) and evaporated to yield tert-butyl N-(benzyloxycarbonylglycyl)aminomethanesulphinate **(345)** (1.63 g, 90%) as a white foamy solid that could not be crystallised ;

$\nu_{max.}$ (film) inter alia 1 730 (urethane C=O) and 1 695 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 257 (ε 13 600), 261 (11 600), 263 (11 720), 267 (10 300), and 305 nm (13 600),

δ (300 MHz, $CDCl_3$) 1.43 (9 H, s, CMe_3), 3.83-4.08 (3 H, m, NCH_2CO and NCHHS), 5.13 (2 H, s, $PhCH_2$), 5.37 (1 H, dd, J 15 and 7 Hz, NCHHS), 5.66br (1 H, apparent t, separation 5 Hz, OCONH), and 7.29-7.93 (6 H, m, CONH and $PhCH_2$),

m / z (f.a.b.) 343 (MH^+, 5 %), 287 (50 %), and 91 (100 %).

Found : C, 53.2; H, 6.6; N, 8.5; S, 8.9. $C_{15}H_{22}N_2O_5S$ requires C, 52.6; H, 6.4; N, 8.2; S, 9.3 %.

Experiment 65

Reaction of the Acrylate **(338)** with Diazomethane

A solution of the acrylate **(338)** (1.67 g, 4.35 mmol) in dry dichloromethane (10 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and purification of the residue by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystallisation of the product from chloroform-light petroleum afforded methyl [N-((benzyloxycarbonylglycyl)-N-(3-methoxycarbonyl- Δ^4-pyrazolin-3-yl)]aminomethanesulphinate **(347)** (1.35 g, 77%) as a white solid;

m.p. 80-83 °C (with softening at 28-30 °C),

$\nu_{max.}$ (KBr) inter alia 1 750 (ester C=O), 1 730 (urethane C=O), and 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 256 (ε 5 700), 263 (3 700), 266 (2 500), and 329 nm (3 300),

δ (300 MHz, $CDCl_3$) 0.74-0.80 (1 H, m, $CH_2C\underline{H}HC$), 3.04-3.10 (1 H, m, $CH_2CH\underline{H}C$), 3.75 and 3.83 (each 3 H, s, CO_2Me and SO_2Me), 4.20-4.50 (3 H, m, $NC\underline{H}HCO$ and NCH_2SO_2), 4.58-4.73 (1 H, m, $CH_2C\underline{H}HN$), 4.85 (1 H, d, J 15 Hz, $NCH\underline{H}CO$), and 5.00-5.15 (3 H, m, $CH_2CH\underline{H}N$ and $PhC\underline{H}_2O$), 5.50br (1 H, s, NH), and 7.30-7.40 (5 H, m, Ph),

m / z (f.a.b.) 427 ($\underline{M}H^+$, 5 %), 136 (90 %), and 91 (100 %).

Found : C, 47.6; H, 5.5; N, 13.3; S, 7.1. $C_{17}H_{22}N_4O_7S$ requires C, 47.9; H, 5.2; N, 13.1; S, 7.5 %.

Experiment 66

Reaction of the Pyrazoline **(347)** with Zinc

A solution of the pyrazoline **(347)** (0.42 g, 0.99 mmol) in 5:5:1 acetic acid-acetone-water (10 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (0.89 g, 2 mass equiv.) with vigorous stirring. After 12 h, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (x 3). The organic layer was dried ($MgSO_4$) and evaporated to afford a mixture of two products (ca. 74% by mass). Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded a white solid considered to be methyl N-(benzyloxycarbonylglycyl)aminomethanesulphinate **(343)** (0.136 g, 46%) ;

m.p. 54-57 °C,

$\nu_{max.}$ (KBr) inter alia 1 695 (urethane C=O) and 1 670 cm^{-1} (amide C=O),

λmax. (EtOH) 224 (ε 3 900), 256 (400), 263 (270), and 267 nm (170),

δ (300 MHz, $CDCl_3$) 3.75 (3 H, s, SO_2Me), 3.80-4.24 (3 H, m, NCH_2CO and NCHHS), 4.40 (1 H, dd, J 7 and 13 Hz, NCHHS), 5.07 (2 H, s, $PhCH_2$), 5.44br (1 H, m, OCONH), 7.05br (1 H, m, CONH), and 7.29 (5 H, m, $PhCH_2$),

m / z (f.a.b.) 301 (MH^+, 20 %) and 91 (100 %).

Found : C, 48.0; H, 5.3; N, 9.3; S, 10.3. $C_{12}H_{16}N_2O_5S$ requires C, 48.0; H, 5.2; N, 9.3; S, 10.7 %.

Experiment 67

Reaction of the Acrylate **(341)** with Diazomethane

A solution of the acrylate **(341)** (0.38 g, 0.955 mmol) in dry dichloromethane (5 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 2 h, and purification of the residue by recrystallisation from chloroform-light petroleum afforded ethyl [N-(benzyloxycarbonylglycyl)-N-(3-methoxycarbonyl-Δ^1-pyrazolin-3-yl)]-aminomethanesulphinate **(348)** (0.4 g, 100%) as a brittle white foam ;

$\nu_{max.}$ (film) inter alia 1 745 (ester C=O), 1 730 (urethane C=O), and 1 680 cm^{-1} (amide C=O),

$\lambda_{max.}$ (EtOH) 207 (ε 13 800), 256 (530), 263 (350), 266 (240), and 329 nm (340),

δ (300 MHz, $CDCl_3$) 1.35 (3 H, t, J 7 Hz, CH_2Me), 1.50-1.60 (1 H, m, $CHHCH_2N$), 3.05-3.15 (1 H, m, $CHHCH_2N$), 3.74 (3 H, s, CO_2 Me), 4.05-4.43 (5 H, m, OCH_2Me, NCH_2S, and $NHCHHCO$), 4.60-4.70 (1 H, m, CH_2CHHN), 4.86 (1 H, d, J 15 Hz, $NHCHHCO$), 5.00-5.18 (3 H, m, CH_2CHHN and $PhCH_2O$), 5.50br (1 H, t, J 5 Hz, NH), and 7.28-7.39 (5 H, m, $PhCH_2$),

m / z (f.a.b.) 441 (MH^+, 6 %), 247 (50 %), 136 (62 %), and 91 (100 %).

Found : C, 47.2; H, 5.3; N, 11.8; S, 6.4. $C_{18}H_{24}N_4O_7S$ requires C, 49.1; H, 5.5; N, 12.7; S, 7.3 %.

Experiment 68

Conversion of the Dipeptide Derivative **(345)** into the Salt **(350)**.

The dipeptide derivative **(345)** (0.129 g, 0.378 mmol) was dissolved in neat formic acid (0.5 cm^3) and the solution was left to stand at room temperature for 2 h, after which the excess formic acid was removed by evaporation under reduced pressure. The residue was recrystallised from ethyl acetate-light petroleum, redissolved in ethyl acetate, and treated dropwise with a solution of potassium 2-ethylhexanoate in diethyl ether, until no more precipitation occurred. The precipitate was centrifuged off and washed with diethyl ether (x 4), to afford a white solid, considered to be N-benzyloxycarbonylglycylaminomethanesulphinic acid potassium salt **(350)** (0.058 g, 47%) ;

$\nu_{max.}$ (KBr) inter alia 1 650-1 740 cm^{-1} (urethane and amide C=O),

δ (300 MHz, D_2O) 3.75-3.86 (2 H, m, NCH_2CO), 3.95-4.03 (ca. 2 H, m, NCH_2S), 5.25 (2 H, s, $PhCH_2$), and 7.51 (5 H, s, $PhCH_2$),

m / z (f.a.b.) inter alia 345 (100 %), 192 (98 %), and 64 (60 %).

Found : C, 40.7; H, 4.3; N, 8.5. $C_{11}H_{13}KN_2O_5S$ requires C, 40.7; H, 4.0; N, 8.6 %.

Experiment 69

Reaction of the Salt (350) with Iodomethane

The potassium salt **(350)** (0.051 g, 0.157 mmol) was dissolved in dry DMF (1 cm^3) and the solution was treated with an excess of iodomethane (0.1 cm^3). After leaving overnight, work-up [by dilution with EtOAc and sequential washing with brine (x 3), saturated aqueous $Na_2S_2O_3$, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded compound **(321)** (0.025 g, 53%) as a white solid, identical with the material isolated in Experiment 50 (m.p. and ^1H n.m.r. spectroscopy).

Experiment 70

Reaction of the Sulphone **(265)** with DBU followed by Acetyl Chloride followed by Methanol

The sulphone **(265)** (0.898 g, 2.594 mmol) in dry dichloromethane (10 cm^3) was treated with DBU (0.388 cm^3, 2.594 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (0.184 cm^3, 2.592 mmol). After 0.5 h, the mixture was treated with an excess of methanol (10 cm^3) dropwise and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl [N-(methoxysulphinyl)-N-(α-N-methyl-N-trifluoroacetylglycyl)]-α-aminoacrylate **(352)** (0.7077 g, 67%) as a white foam, which existed as a 4:1 mixture of rotamers ;

$\nu_{max.}$ (film) inter alia 1 730 (ester C=O), 1 700 (trifluoroacetyl and amide C=O), and 1 640 cm^{-1} (C=C),

$\lambda_{max.}$ (EtOH) 205 nm (ε 15 400),

δ (300 MHz, $CDCl_3$) 3.09 and 3.18-3.24 (0.6 and 2.4 H, s and m, NMe), 3.81 and 3.88 (each 3 H, s, 2 x OMe), 4.01-4.25 and 4.60-4.75 (3 and 1 H, each m, NCH_2CO and NCH_2S), 6.25 (1 H, s, C:C<u>H</u>H), and 6.63 and 6.65 (0.83 and 0.17 H, each s, C:CH<u>H</u>),

m / z (f.a.b.) 329 (50 %), 281 (M^+ - SO_2Me, 45%), 168 (98 %), and 140 (100 %).

Found : C, 36.8; H, 4.4; F, 15.6; N, 7.9; $C_{11}H_{15}F_3N_2O_6S$ requires C, 36.7; H, 4.2; F, 15.8; N, 7.8 % .

Experiment 71

Reaction of the Acrylate (352) with Diazomethane

A solution of the acrylate (352) (0.938 g, 2.61 mmol) in dry dichloromethane (20 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and purification of the residue by recrystallisation of the product from chloroform-light petroleum afforded methyl [N-(3-methoxycarbonyl-Δ^1-pyrazolin-3-yl)-N-(N-methyl-N-trifluoroacetylglycyl)]aminomethanesulphinate (353) (0.990 g, 95%) as a white solid ;

m.p. 68-71 °C (with softening at 45-50 °C),

$\nu_{max.}$ (KBr) inter alia 1 750 (ester C=O) and 1 700br cm^{-1} (trifluoroacetyl and amide C=O),

$\lambda_{max.}$ (EtOH) 209 (ε 10 800) and 329 nm (300),

δ (300 MHz, $CDCl_3$) 1.40-1.56 (1 H, m, $CHHCH_2$), 2.99-3.09 (1 H, m, $CHHCH_2$), 3.13-3.20 (3 H, m, NMe), 3.60-3.71 (3 H, m, CO_2Me),3.74-3.83 (3 H, m, SO_2Me), 3.94-4.46 (2 H, m, NCH_2CO), and 4.53-5.11 (4 H, m, NCH_2S and CH_2N_2),

m / z (c.i., NH_3) 420 (MNH_4^+, 4 %), 392 ($MNH_4^+ - N_2$, 50 %), and 343 ($M^+ - CH_3N_2O_2$, 100 %).

Found : C, 35.7; H, 4.3; F, 14.1; N, 13.6. $C_{12}H_{17}F_3N_4O_6S$ requires C, 35.8; H, 4.2; F, 14.2; N, 13.9 %.

Experiment 72

Reaction of the Pyrazoline (353) with Zinc

A solution of the pyrazoline (353) (0.114 g, 0.413 mmol) in 5:5:1 acetic acid-acetone-water (5 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (0.24 g, 2 mass equiv.). After stirring overnight, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (x 3). The organic layer was dried ($MgSO_4$) and evaporated to yield a clear oil (0.043 g) which was a mixture of two components on the basis of t. l. c. , but contained the required material,

methyl N-(N-methyl-N-trifluoroacetylglycyl)aminomethanesulphinate **(354)**, on the basis of 300 MHz ^{1}H n. m. r. spectroscopy ;

δ (300 MHz, $CDCl_3$) inter alia 3.09-3.35 (3 H, m, NMe), 3.83 (ca. 3 H, d, separation 3.5 Hz, SO_2Me), 4.02-4.15 (2 H, m, NCH_2CO), and 4.18-4.66 (2 H, m, NCH_2S),

Experiment 73

Reaction of the Sulphone **(265)** with DBU followed by Acetyl Chloride followed by tert-Butyl Alcohol

The sulphone **(265)** (1.40 g, 4.05 mmol) in dry dichloromethane (10 cm^3) was treated with DBU (0.609 cm^3, 4.05 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (0.290 cm^3, 4.08 mmol). After 0.5 h, the mixture was treated with an excess of tert-butyl alcohol (4 cm^3) dropwise and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl [N-(tert-butoxysulphinyl)-N-(α-N-methyl-N-trifluoroacetylglycyl)]-α-aminoacrylate **(355)** (0.969 g, 60% yield) as a clear oil ;

$\nu_{max.}$ (film) inter alia 1 735 (ester C=O), 1 705 (trifluoroacetyl and amide C=O), and 1 640 cm^{-1} (C=C),

δ (300 MHz, $CDCl_3$) 1.45 (9 H, s, CMe_3), 3.09 and 3.21 [0.75 and 2.25 H respectively, s and apparent d, separation 1.5Hz, together NMe], 3.86

(3 H, s, CO_2Me), 3.88-4.35 (3 H, m, NCH_2CO and NCHHS), 4.65br (1 H, apparent d, separation 12 Hz, NCHHS), 6.30br (1 H, s, C:CHH), and 6.56-6.69 (1 H, m, C:CHH),

m / z (f.a.b.) 403 (MH^+, 4 %) and 347 (5 %).

Found : C, 41.5; H, 5.3; N, 6.7; S, 7.6 . $C_{14}H_{21}F_3N_2O_6S$ requires C, 41.8; H, 5.2; N, 7.0; S, 8.0 % .

Experiment 74

Reaction of the Acrylate (355) with Diazomethane

A solution of the acrylate (355) (0.84 g, 2.09 mmol) in dry dichloromethane (10 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and purification of the residue by recrystallisation from chloroform-light petroleum afforded tert-butyl [N-(3-methoxycarbonyl-Δ^1-pyrazolin-3-yl)-N-(N-methyl-N-trifluoroacetylglycyl)]aminomethanesulphinate (356) (0.89 g, 96%) as a white solid ;

m.p. 53-56 °C (with softening at 36 °C),

$\nu_{max.}$ (KBr) inter alia 1 755 (ester C=O) and 1 710-1 680br cm^{-1} (trifluoroacetyl and amide C=O),

$\lambda_{max.}$ (EtOH) 329 nm (ε 350),

δ (300 MHz, $CDCl_3$) 1.48 (9 H, s, CMe_3), 1.58 (s, C<u>H</u>HCH_2 and H_2O), 2.98-3.14 (1 H, m, CH<u>H</u>CH_2), 3.24 (3 H, s, NMe), 3.76 (3 H, s, CO_2Me), 4.19-4.50 (2 H, m, NCH_2CO), 4.55-4.96 (3 H, m, NCH_2S and C<u>H</u>HN), and 5.00-5.98 (1 H, m, CH<u>H</u>N),

<u>m / z</u> (f.a.b.) 445 (<u>M</u>H^+, 10 %), 371 (<u>M</u>$^+$ - C_4H_9O, 9 %), 343 (<u>M</u>$^+$ - $C_4H_9N_2O$:, 58 %), and 140 (100 %).

Found : C, 40.2; H, 5.2; N, 12.3; S, 12.7. $C_{15}H_{23}F_3N_4O_6S$ requires C, 40.5; H, 5.2; N, 12.6; S, 12.8 %.

<u>Experiment 75</u>

<u>Reaction of the Pyrazoline</u> **(356)** <u>with Zinc</u>

A solution of the pyrazoline **(356)** (0.67 g, 1.51 mmol) in 5:5:1 acetic acid-acetone-water (10 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (1.44 g, 2 mass equiv.). After stirring overnight, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (x 3). The organic layer was dried ($MgSO_4$) and evaporated to yield tert-<u>butyl</u> N-(N-<u>methyl</u>-N-<u>trifluoroacetylglycyl)aminomethanesulphinate</u> **(357)** (0.421 g, 80 %) as a clear oil, which existed as a 4:1 mixture of rotamers in deuteriochloroform solution ;

$\nu_{max.}$ (film) <u>inter alia</u> 1 700 cm^{-1} (trifluoroacetyl and amide C=O),

δ (300 MHz, $CDCl_3$) 1.44 (9 H, s, CMe_3), 3.10 and 3.24 (0.6 and 2.4 H, both s, NMe), 3.89-4.04 (1 H, m, NC<u>H</u>HS), 4.09-4.22 (2 H, m, NCH_2CO),

4.30-4.46 (0.8 H, dd, J 7 and 12.5 Hz, NCHHS of major rotamer), 4.48-4.55 (0.2 H, dd, J 7 and 12.5 Hz, NCHHS of minor rotamer), 7.60 (0.8 H, apparent t, J 7 Hz, NH of major rotamer), and 7.84 (0.2 H, m, NH of minor rotamer),

m / z (f.a.b.) 319 (MH^+, 2 %), 245 ($M^+ - OBu^t$, 18 %), and 197 ($M^+ - SO_2Bu^t$, 10 %).

Found : C, 38.3; H, 5.6; N, 8.6; S, 9.4. $C_{10}H_{17}F_3N_2O_4S$ requires C, 37.7; H, 5.4; N, 8.8; S, 10.0 %.

Experiment 76

Reaction of the Sulphone **(291)** with DBU followed by Acetyl Chloride followed by Methanol

The sulphone **(291)** (0.6326g, 2.48 mmol) in dry dichloromethane (10 cm^3) was treated with DBU (0.37 cm^3, 2.47 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (0.176 cm^3, 2.48 mmol). After 0.5 h, the mixture was treated dropwise with an excess of methanol (10 cm^3) and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) afforded methyl α-[N-(chloroacetylglycyl)-N-(methoxysulphinylmethyl)]aminoacrylate **(358)** (0.2858 g, 43%) as a clear oil, which existed as a 6:1 mixture of rotamers in deuteriochloroform solution;

$\nu_{max.}$ (film) inter alia 1 730 (ester C=O), 1 690 (amide C=O), and 1 635 cm^{-1} (C=C),

δ (300 MHz, $CDCl_3$) 3.80 (3 H, s, CO_2Me), 3.85-3.90 (3 H, m, SO_2Me), 3.99-5.01 (4 H, m, NCH_2S and $ClCH_2CO$), 5.65 (0.14 H, d, J, 2.5 Hz, C:CHH of minor rotamer), 6.09 (0.14 H, d, J 2.5 Hz, C:CHH of minor rotamer), 6.16-6.40 (0.86 H, m, C:CHH of major rotamer), and 6.46-6.75 (0.86 H, m, C:CHH of major rotamer),

m / z (f.a.b.) inter alia 270 ($M+2H^+$, 1 %), 238 (M^+ - OMe, 7 %), 190 (M^+ - SO_2Me, 9 %), and 149 (100 %).

Found : C, 36.0; H, 4.5; N, 5.0; S, 11.5. $C_8H_{10}ClNO_5S$ requires C, 35.7; H, 4.5; N, 5.2; S, 11.9 %.

Experiment 77

Reaction of the Sulphone (291) with DBU followed by Acetyl Chloride followed by tert-Butyl Alcohol

The sulphone (291) (0.8823 g, 3.46 mmol) in dry dichloromethane (10 cm^3) was treated with DBU (0.518 cm^3, 3.46 mmol). After 0.25 h, the mixture was cooled to -78 °C and treated dropwise with acetyl chloride (0.246 cm^3, 3.46 mmol). After 0.5 h, the mixture was treated dropwise with an excess of tert-butyl alcohol (10 cm^3) and stirred at room temperature for 12 h. Work-up [by dilution with EtOAc and sequential washing with 10% HCl, saturated aqueous $NaHCO_3$ and brine, followed by evaporation of the dried ($MgSO_4$) organic layer] afforded a clear oil. Purification by silica-gel chromatography (EtOAc-hexane, gradient elution) and recrystalliastion from $CHCl_3$-light

petroleum afforded methyl α-[N-(chloroacetylglycyl)-N-(tert-butoxysulphinylmethyl)]aminoacrylate **(359)** (0.4821 g, 45%) as a white solid, which existed as a 8:1 mixture of rotamers ;

m.p 80-84 °C,

$\nu_{max.}$ (KBr) inter alia 1 725 (ester C=O), 1 675 (amide C=O), and 1 635 cm^{-1} (C=C),

δ (300 MHz, $CDCl_3$) 1.46 (9 H, s, CMe_3), 3.85 (3 H, s, CO_2Me), 3.91-4.22 and 4.54-4.94 (2.5 and 1.5 H, each m, NCH_2CO and NCH_2S), 5.73 (0.13 H, d, J 2.5 Hz, C:CHH of minor rotamer), 6.09 (0.13 H, d, J 2.5 Hz, C:CHH of minor rotamer), 6.26br (0.87 H, s, C:CHH of major rotamer), and 6.63br (0.87 H, s, C:CHH of major rotamer),

m / z (f.a.b.) inter alia 312 (MH^+, 3 %), 238 (M^+ - OBut, 40 %), 190 (M^+ - SO_2But, 20%), and 114 (100 %).

Found : C, 42.6; H, 6.0; N, 4.6. $C_{11}H_{18}ClNO_5S$ requires C, 42.4; H, 5.8; N, 4.5 %.

Experiment 78

Reaction of the Acrylate **(359)** with Diazomethane

A solution of the acrylate **(359)** (0.1977 g, 0.6357 mmol) in dry dichloromethane (10 cm^3) was cooled to 0 °C and treated with an excess of ethereal diazomethane. Evaporation, after 12 h, and purification of the residue by recrystallisation from chloroform-light petroleum afforded tert-butyl-[N-(chloroacetylglycyl)-N-(3-methoxycarbonyl-Δ^1-pyrazolin-3-yl)]-amino-methane-sulphinate **(360)** (0.2177 g, 97% yield) as a white foam ;

$\nu_{max.}$ (KBr) inter alia 1 745 (ester C=O) and 1 685 cm^{-1} (amide C=O),

δ (300 MHz, $CDCl_3$) 1.35-1.66 (10 H, m, CMe_3 and $CHHCH_2$), 3.13 (1 H, ddd, J 2, 8, and 13 Hz, $CHHCH_2$), 3.72-3.77 (3 H, m, CO_2Me), 4.06-4.72 (4 H, m, NCH_2S and $ClCH_2CO$), 4.83-4.96 (1 H, m, CH_2CHHN), and 5.07 (1 H, ddd, J 2, 9.5, and 18 Hz, CH_2CHHN),

m / z (f.a.b.) inter alia 232 ($M^+ - SO_2Bu^t$, 45 %) and 150 (100 %)

Experiment 79

Reaction of the Pyrazoline **(360)** with Zinc.

A solution of the pyrazoline **(360)** (0.216 g, 0.561 mmol) in 5:5:1 acetic acid-acetone-water (5 cm^3) was cooled to 0 °C and treated with unactivated zinc dust (0.49 g, 2 mass equiv.). After stirring overnight, the mixture was filtered, diluted with ethyl acetate, and washed with saturated aqueous sodium hydrogen carbonate (x 3). The organic layer was dried

($MgSO_4$) and evaporated to yield a clear oil (0.04 g) which was a mixture of two components on the basis of t. l. c. , but contained the required material ; tert-butyl N-(chloroacetylglycyl)aminomethanesulphinate **(361)** on the basis of 300 MHz ^1H n. m. r. spectroscopy ;

δ (300 MHz, $CDCl_3$) inter alia 1.34-1.42 (9 H, m, CMe_3), 3.63-3.86 (2 H, m, $ClCH_2CO$), 4.06 (1 H, d, J 1 Hz, NCHHS), and 4.19-4.23 (1 H, m, NCHHS).

INDEX TO EXPERIMENTS

BIBLIOGRAPHY

1. "Principles of Medicinal Chemistry" by William O. Foye, 2nd. ed. , Lea and Febiger (1981).

2. A. F. Spatola, in "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins", Ed. B. Weinstein, Marcel Dekker, 1983, Vol. 7, p 267.

3. H. Erlenmeyer, Bull. Soc. Chim. Biol. , 30, 792 (1948).

4. J. S. Morley, 'Medicinal Chemistry Advances, Proceedings of the 7th International Symposium on Medicinal Chemistry', Ed. F. G. De Las and S. Vega, Spain 1980, Pergamon Press, Oxford, 1981, p. 447.

5. J. S. Morley, Trends Pharm. Sci. , 463 (1980).

6. W. C. Jones Jr, J. J. Nestor Jr, and V. Duvigneaud, J. Am. Chem. Soc. , 95, 5677 (1973).

7. M. M. Hann, P. G. Sammes, P. D. Kenewell, and J. B. Taylor, J. Chem. Soc. Chem. Commun. , 234 (1980).

8. J. Rudinger, in "Drug Design", E. J. Ariens, Ed. , New York, Academic Press, 1971, Vol. 1, p. 319.

9. D. W. Christianson and W. N. Lipscomb, J. Am. Chem. Soc. , 110, 5560 (1988).

10. W. F. Gilmore and H. J. Lin, J. Org. Chem. , 43, 4534 (1978).

11. D. Hudson, R, Sharpe, and M. Szelke, Int. J. Peptide Protein Res. , 15, 122 (1980).

12. D. S. Matteson and M. S. Sadhu, J. Am. Chem. Soc. , 103, 5241 (1981).

13. R. N. Lindquist and A. C. Nguyen, J. Am. Chem. Soc. , 99, 6435 (1977).

14. D. S. Matteson and K. J. Arne, J. Am. Chem. Soc. , 100, 1325 (1978).

15. T. Rumpf and V. Chavane, Compt. rend. , 224, 919 (1947).

16. W. F. Gilmore and H. A. Mc Bride, J. Am. Chem. Soc. , 94, 4361 (1972).

17. I. Hoppe, U. Schollkopf, M. Nieger, and E. Egert, Angew. Chem. Int. Ed. Engl. , 24, 1067 (1985).

18. K. Clauss, D. Grimm, and G. Prossel, Annalen, 539 (1974).

19. M. M. Campbell and N. Carruthers, J. Chem. Soc. Chem. Commun. , 730 (1980).

20. M. M. Campbell, N. Carruthers, and S. J. Mickel, Tetrahedron, 38, 2513 (1982).

21. K. Issleib, K. P. Dopfer, and A. Balszuweit, Z. Chem. , 22, 215 (1982).

22. E. W. Petrillo and E. R. Spitzmiller, Tetrahedron Letters, 4929 (1979).

23. J. Rachon and C. Wasielewski, Z. Chem. , 13, 254 (1973).

24. J. Rachon and C. Wasielewski, Roczn. Chem. , 49, 397 (1975).

25. J. Rachon and C. Wasielewski, Tetrahedron Letters, 1609 (1978).

26. J. Rachon, C. Wasielewski, and K. Antczak, Z. Chem. , 19, 253 (1979).

27. J. Rachon and C. Wasielewski, Roczn. Chem. , 50, 477 (1976).

28. J. Rachon, C. Wasielewski, and M. Hoffmann, Chimia, 30, 187 (1976).

29. R.Huber, A. Knierzinger, J. P. Obrecht, and A. Vasella, Helv. Chim. Acta, 68, 1730 (1985).

30. M. Soroka and P. Masterlerz, Roczn. Chem. , 50, 661 (1976).

31. M. E. Chambers and A. F. Isbell, J. Org. Chem. , 29, 832 (1964).

32. M. I. Kabachnik and T. Ya. Medved, Izv. Akad. Nauk. SSSR. Otd. Khim. , 635 (1950).

33. M. I. Kabachnik and T. Ya. Medved', Izv. Akad. Nauk. SSSR. Otd. Khim. , 95 (1951).

34. L. Maier, J. Organomet. Chem. , 178, 157 (1979).

35. P. G. Baraldi, M. Guarneri, F. Moroder, G. P. Pollini, and D. Simoni, Synthesis, 653 (1982).

36. U. Schollkopf and T. Wintel, Synthesis, 1033 (1984).

37. K. D. Berlin, R. T. Claunch, and E. T. Gaudy, J. Org. Chem. , 33, 3090 (1968).

38. M. J. Stringer, J. A. Stock, and L. M. Cobb, Chem. Biol. Interactions, 9, 411 (1974).

39. K. D. Berlin, N. K. Roy, R. T. Claunch, D. Bude, J. Amer. Chem. Soc. , 90, 4494 (1968).

40. S. Asano, T. Kitahara, T. Ogawa, and M. Matsui, Agric. Biol. Chem. , 37, 1193 (1973).

41. W. Subotkowski, J. Kowalik, R. Tyka, and P. Mastalertz, Polish J. Chem. , 55, 853 (1981).

42. G. M. Kosalapoff, J. Amer. Chem. Soc. , 70, 1283 (1948).

43. Z. H. Kudzin and A. Kotynski, Synthesis, 1028 (1980).

44. R. M. Khomutov, T. I. Osipova, Yu. N. Zhukova, and I. A. Gandurina, Izv. Akad. Nauk. SSSR, Ser. Khim. , 2118 (1979).

45. M. I. Kabachnik and T. Ya. Medved', Dolk. Akad. Nauk. SSSR. , 83, 689 (1952).

46. M. I. Kabachnik and T. Ya. Medved', Dolk. Akad. Nauk. SSSR. , 84, 717 (1952).

47. M. I. Kabachnik and T. Ya. Medved', Izv. Akad. Nauk. SSSR. Otd. Khim. Nauk, 868 (1953).

48. M. I. Kabachnik and T. Ya. Medved', Izv. Akad. Nauk. SSSR. Otd. Khim. Nauk, 314 (1954).

49. M. I. Kabachnik and T. Ya. Medved', Izv. Akad. Nauk. SSSR. Otd. Khim. Nauk, 1024 (1954).

50. M. I. Kabachnik and T. Ya. Medved', Izv. Akad. Nauk. SSSR. Otd. Khim. Nauk, 1357 (1957).

51. E. K. Fields, J. Amer. Chem. Soc. , 74, 1528 (1952).

52. Z. H. Kudzin and W. J. Stec, Synthesis, 469 (1978).

53. Z. H. Kudzin and W. J. Stec, Synthesis, 1032 (1980).

54. C. C. Tam, K. L. Mattocks, and M. Tischer, Synthesis, 188 (1982).

55. Z. H. Kudzin, Synthesis, 643 (1981).

56. J. Oleksyszyn and R. Tyka, Tetrahedron Letters, 2823 (1977).

57. J. Oleksyszyn, L. Subotkowsa, and P. Mastalerz, Synthesis, 985 (1979).

58. J. Olekseszyn, R. Tyka, and P. Mastalerz, Synthesis, 479 (1978).

59. J. W. Huber and W. F. Gilmore, J. Med. Chem. , 18, 106 (1975).

60. J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. N. Lambert, L. J. Nisbet, and P. S. Ringrose, Nature, 272, 56 (1978).

61. W. H. Parsons, A. A. Patchett, H. G. Bull, W. R. Schoen, D. Taub, J. Davidson, P. L. Combs, J. P. Springer, H. Gadebusch, B. Weissberger, M. E. Valiant, T. N. Mellin, and R. B. Busch, J. Med. Chem. , 31, 1772 (1988).

62. E. K. Baylis, C. D. Campbell, and J. G. Dingwall, J. Chem. Soc. Perkin Trans. I, 2845 (1984).

63. I. C. Popoff, L. K. Huber, B. P. Block, P. D. Morton, and R. P. Riordan, J. Org. Chem. , 28, 2898 (1963).

64. M. Soroka and P. Masterlerz, Roczn. Chem. , 48, 1119 (1974).

65. US P.3160632 (1964); [Chem. Abs. , 62, 4053 (1965)].

66. H. M. McIlwain, Brit. J. Expt. Path. , 22, 148 (1941).

67. P. Moses, J. Mayer, and M. Franke, Bull. Research Council Israel, 9A, 46 (1960); [Chem. Abst. , 55, 3725h (1961)].

68. S. Balusz, A. Z. Ronai, J. I. Szekely, A. Turan, A. Juhasz, A. Patthy, E. Miglecz, and I. Berzetei, Febs. Letters. , 117, 308 (1980).

69. J. J. Stezzowski, E. Eckle, and S. Balusz, J. Chem. Soc. Chem. Commun. , 681 (1985).

70. R. Rehnel and H. Labhardt, Chem. Ber. , 38, 1069 (1905).

71. H. McIlwain, J. Chem. Soc. , 75 (1941).

72. H. J. Backer and H. Mulder, Rec. Trav. Chem. , 52, 454 (1933).

73. I. Neelakantan and W. H. Hartung, J. Org. Chem. , 24, 1943 (1959).

74. S. Jinachitra and A. J. Macleod, Tetrahedron, 35, 1315 (1979).

75. G. R. Moe, L. M. Sayre, and P. S. Portoghese, Tetrahedron Letters. , 537 (1981).

76. Japan 4 236 (1950) [Chem. Abst. , 46, 8810 (1952)];
Ger. 1 086 209 (1960) [Chem. Abst. , 55, 20447 (1961)];
Japan 35 415 (1974) [Chem. Abst. , 82, 150545 (1975)].

77. E. J. Muller, Melliand Textilber. , 30, 588 (1949).

78. G. H. L. Nefrens, Nature, 309 (1960).

79. M. Frankel, G. Gilon, D. Ladkany, and Y. Wolman, Tetrahedron Letters, 4765 (1966).

80. C. M. Pant, Ph. D. Thesis, University of Newcastle Upon Tyne (1976).

81. M. J. Mahmoud, Ph. D. Thesis,University of Newcastle Upon Tyne (1981).

82. J. Steele, Ph. D. Thesis,University of Newcastle Upon Tyne (1982).

83. C. P. Lo, J. Org. Chem ., 26, 3591 (1961).

84. E. Perrone and R. J. Stoodley, Unpublished results.

85. I. S. Blagbrough, N. E. Mackenzie, C. Ortiz, and A. I. Scott, Tetrahedron Letters., 1251, (1986).

86. H. R. Ing and R. H. F. Manske, J. Chem Soc ., 2348 (1926).

87. H. J. Barber and W. R. wragg, Nature (London) 158, 514 (1946).

88. S. Kukolja and S. R. Lambert, J. Am. Chem. Soc ., 97, 5582 (1975).

89. J. O. Osby, M. G. Martin, and B. Ganem, Tetrahedron Letters ., 2093 (1984).

90. J. H. Billman and W. F. Harting, J. Am. Chem. Soc. , 70, 1473 (1948).

91. J. Casanova and E. J. Corey, J. Am. Chem. Soc ., 85, 165 (1963).

92. M. P. Schubert, J. Biol. Chem . , 111, 671 (1935).

93. S. Ratner and H. T. Clarke, J. Am. Chem. Soc . , 59, 200 (1937).

94. S. Gabriel, Chem. Ber . , 40, 2648 (1907).

95. G. Piancatelli, A. Scettri, and M. D. Auria, Synthesis, 245 (1982).

96. R. Parthasarathy, B. Paul, and W.Korytnyk, J. Am. Chem. Soc. , 98, 6634 (1976).

97. D. H. R. Barton, D. G. T. Grieg, P. G. Sammes, and M. V. Taylor, J. Chem. Soc., Chem. Commun. , 845 (1971).

98. D. Barrett, Ph. D. Thesis,University of Newcastle Upon Tyne (1986).

99. N. Margoum, P. Tronche, P. Bastide, J. Bastide, and C. Rubat, Eur. J. Med. Chem.- Chim. Ther. , 19-5, 415 (1984).

100. F. Weygand and E. Osendes, Angew. Chem. , 64, 136 (1952).

101. H. C. J. Ottenheym, T. F. Spande and B. Witkop, J. Org. Chem. , 37, 3358 (1972).

102. G. P. Hess and J. C. Sheehan, J. Am. Chem. Soc. , 77, 1067 (1955).

103. R. J. Kennedy and A. M. Stock, J. Org. Chem. , 25, 1901 (1960).

104. B. M. Trost and D. P. Curran, Tetrahedron Letters,1287 (1981).

105. C. J. M. Stirling, Internat. J. Sulphur Chem. B. , 6, 277 (1971).

106. S. Saito, H. Nakajima, M. Inaba, and T. Moriwake, Tetrahedron Letters, 837 (1989).

107. T. D. Inch and H. Fletcher, Jr. , J. Org. Chem. , 31, 1815 (1966).

108. L. Grehn and V. Ragnarsson, Angew. Chem. Int. Ed. Engl. , 24, 310 (1984).

109. "Silicon in Organic Chemistry" by E. Colvin, p 316.

110. J. Kovacs, M. Q. Cepoint, C. A. Pupraz, G. N. Schimt, J. Org. Chem. , 32, 3696 (1967).

111. R. Braslau and B. M. Trost, J. Org. Chem. , 53, 532 (1988).

112. R. Otto and A. Rosing, Chem. Ber. , 2493 (1885).

113. R. Otto, Chem. Ber. , 2504 (1885).

114. J. A. Crompton, Ph. D. Thesis, University of Manchester (1987).

115. M. Bergmann and L. Zervas, Ber. , 65, 1192 (1932).

116. J. Meienhofer and K. Kuromizu, Tetrahedron Letters, 3259 (1974).