APPLICATIONS OF 1,3,4-OXATHIAZOL-2-ONES

IN HETEROCYCLIC SYNTHESIS

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ABSTRACT

The synthesis of 5-(*o*-acyloxyphenyl)- and 5-(*o*-acylamidophenyl)-1,3,4-oxathiazol-2-ones is described. Two routes were developed to the former class of compounds the preferred one involving acylation of 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one. Of such compounds, those having alkyne components in the *ortho*-substituents give rise respectively to the novel chromeno[4,3-*c*]isothiazole and isothiazolo[4,3-*c*]quinoline ring systems on thermal decarboxylation of the oxathiazolone and intramolecular 1,3-dipolar cycloaddition of the resulting nitrile sulphide. In a similar fashion acrylate, fumarate and cinnamate esters of 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one give the same chromeno[4,3-*c*]isothiazole system. In the case of the cinnamate esters this is accompanied by nitrile, chromeno[4,3-*b*]quinoline and aminochromene by-products. The mechanism of this reaction is discussed in depth with reference to the results of a number of associated reactions.

o-Hydroxybenzonitrile sulphide, generated by thermolysis of 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one undergoes 1,3-dipolar cycloaddition with dimethyl acetylene-dicarboxylate yielding methyl 4-oxo-4*H*-chromeno[4,3-*c*]-isothiazole-3-carboxylate. From this the parent ring system, 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole is obtained by hydrolysis and decarboxylation. These products are also formed from 5-(*o*-acetoxyphenyl)-1,3,4-oxathiazol-2-one by hydrolysis of the initial adduct with dimethyl

acetylenedicarboxylate. 5-(*o*-Acetamidophenyl)-1,3,4-oxathiazol-2-one undergoes an analogous reaction sequence leading ultimately to the parent isothiazolo[4,3-*c*]-quinolin-4(5*H*)-one. The cycloadditions of *o*-hydroxy- and *o*-acetoxy-benzonitrile sulphides with ethyl cyano-formate, ethyl propiolate and diethyl fumarate are described as is the reaction of *o*-acetamidobenzonitrile sulphide with ethyl cyanoformate.

The reactions of diazo compounds with an oxathiazolone lead to thiocarbonyl derivatives and nitrile, accompanied in one example by a 1,4,3-oxathiazine system of a new type.

Triphenylphosphine removes sulphur from an oxathiazolone under mild conditions yielding triphenylphosphine sulphide and nitrile with loss of carbon dioxide.

Acknowledgements

I would like to thank especially Dr. R. Michael Paton for his invaluable supervision, guidance and patience over the last few years. Many other members of the Chemistry Department, both staff and students, are also thanked for their advice and assistance, in particular the inmates and associates of Lab.29 during 1982-1984 where such an enjoyable atmosphere was created. Finally, I thank the S.E.R.C. for providing maintenance and funding for my studentship.

Post-graduate Lectures

The following post-graduate lecture courses were attended during 1982-1985.

Silicon in Organic Synthesis (E.W. Colvin), 5 lectures.
The Chemistry of the Photographic Process (Kodak), 5 lectures.
1,3-Dipolar Intermediates in Heterocyclic Synthesis (R.M. Paton, J.T. Sharp), 5 lectures.
Synthetic Strategy (R. Ramage), 5 lectures.
Current Topics in Organic Chemistry (various lecturers), 15 lectures.
Departmental seminars, three years attendance.

Declaration

I declare that the research presented in this thesis is entirely my own work (except in two instances noted in the text) which was carried out in Edinburgh between September 1982 and August 1985.

CONTENTS

THE TRIPTYCH

A quest is but a game which holds the mind
Thralled by the action, with the goal forgot
And everything adventured in the means.
Here we shall voyage out. Was ever given
So insignificant a terminus
For roads so splendidly beset with hope-
Such opportunity of crowded hours
On ways so self-absorbing and so great
With fascination and discovery,
But yet with dark uncertainty and doubt?

Then let us go, and we, on other seas,
Perhaps shall share the secret which they knew,
The old adventurers, and was their meed.
Then let us play, and we perhaps shall crush
Into a glorious day their months and years,
So to gain recompense where is no prize.
For this compelling triptych, grandly shown
Like a new country ready to be searched,
Offers rich booty on its hidden ways,
Where searching may disclose reality
And in the doing earn its own reward.

From: "BRENVA" by T. Graham Brown, 1944

1. INTRODUCTION

Foreword

The concept of the 1,3-dipole has been with us for twenty-five years[1]. In this time the characteristic 1,3-dipolar cycloaddition reaction has been developed into an invaluable tool in heterocyclic synthesis. The scope and advantages of this reaction are now widely appreciated and its theoretical basis well understood. In view of this only a brief introduction to this theory is considered necessary, especially since the publication of Padwa's excellent volumes entitled "1,3-Dipolar Cycloaddition Chemistry".[2]

Nitrile sulphides, however, are one of the least well known classes of 1,3-dipole and require a more detailed introduction. This is effected firstly in Section 1.1 where theoretical aspects of 1,3-dipoles are discussed briefly using nitrile sulphides as examples. Secondly, the chemistry of nitrile sulphides is discussed in more detail in Sections 1.3 and 1.4.

The remaining sections deal with intramolecular 1,3-dipolar cycloaddition reactions and 1,3,4-oxathiazol-2-ones (Sections 1.2 and 1.5 respectively); both topics are considered pertinent to the present work. Section 1.2 is intended to emphasise those aspects peculiar to the intramolecular reaction rather than provide a general review of its scope.

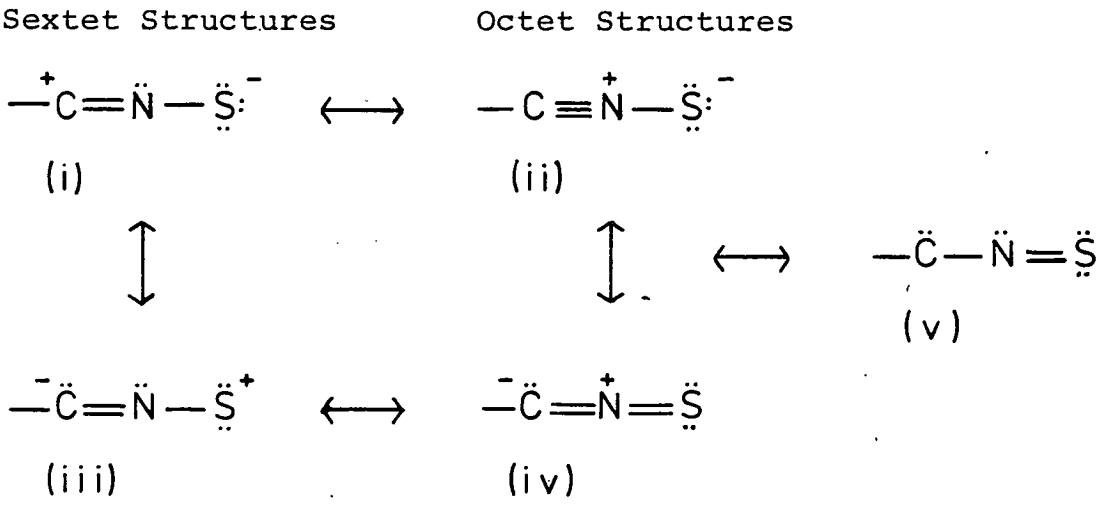
1.1 1,3-DIPOLES

1.1.1 Structure

A 1,3-dipole may be defined[3] as a system a-b-c in which *a* has an electron sextet, *i.e.* an incomplete valence shell, and carries a formal positive charge; and *c* is a negatively charged centre having a free electron pair. 1,3-Dipoles are stabilised by an unshared pair of electrons at atom *b* relieving the electron deficiency at *a* and giving an octet structure as shown below.

In the nitrile sulphide the lone pair of the nitrogen atom provides this stabilisation. This can be seen in the resonance structures (i)-(iv) (Scheme 1) which, together with the carbenic structure (v), are generally used to represent the dipole.

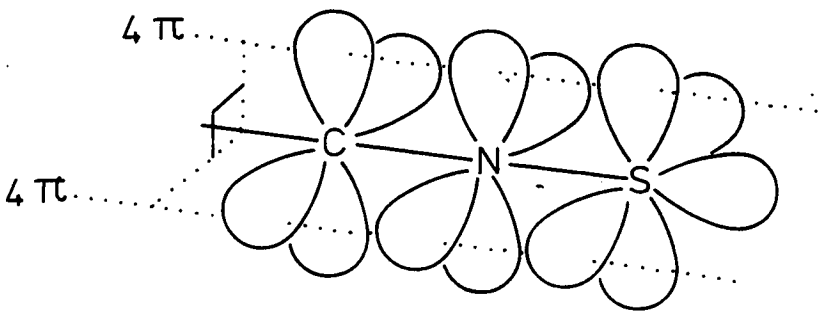
Scheme 1



In terms of formal charges the 1,3-dipoles are ambivalent, the charges at either end being interchangeable as shown by the sextet structures (i) and (iii). Similar structures can be drawn for the whole class of nitrilium betaines ($RC\equiv\overset{+}{N}-\overset{-}{X}$; $X=CR_2$, NR, O, S) of which nitrile sulphide is a member and also for the related diazonium betaines ($N\equiv\overset{+}{N}-\overset{-}{X}$; $X=CR_2$, NR, O).[4]

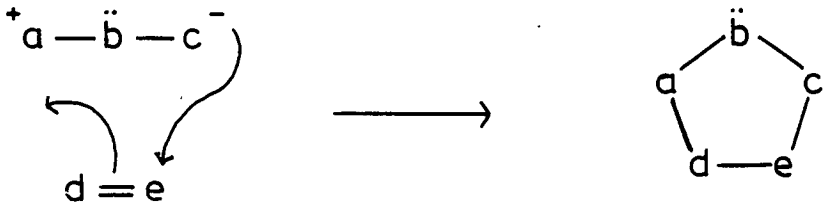
Nitrilium and diazonium betaines are known collectively as the propargyl-allenyl type 1,3-dipoles from the distribution of π-bonds in the two octet structures (ii) and (iv). They are mostly linear[5] and possess an additional π-bond in the plane perpendicular (orthogonal) to the set of molecular orbitals (MO's) of the heteroallyl anion containing the four π-electrons particular to the 1,3-dipolar nature of the species. In the case of the linear species nitrous oxide, nitrile oxide and, by analogy, nitrile sulphide it should be noted that there are two equivalent sets of four π-electrons[6] as shown in Figure 1.

Figure 1



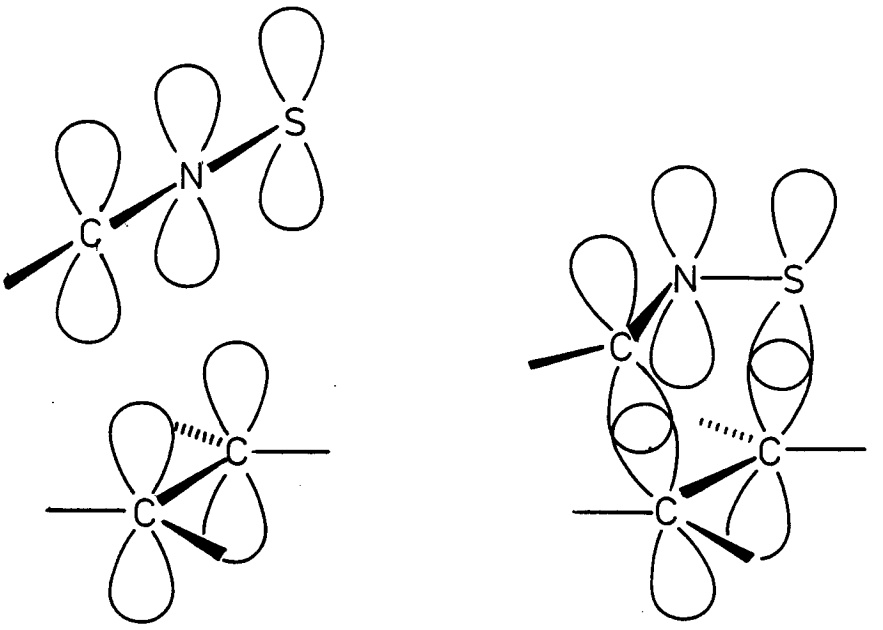
1.1.2 1,3-Dipolar Cycloaddition Reactions

The characteristic cycloaddition reaction of 1,3-dipoles involves the combination of a set of heteroallyl anion MO's containing four π-electrons with two π-electrons from a π-orbital of a multiply bonded system, the dipolarophile. The product of this [3+2→5]cycloaddition is a five membered heterocycle as shown below.



The mechanism of the cycloaddition is now generally accepted as a concerted process as first suggested by Huisgen,[7] where the two new σ-bonds are formed simultaneously although not necessarily in a synchronous manner. It is thermally allowed by the Woodward-Hoffmann rules[8] and involves a two plane orientation complex[9] as shown in Figure 2. The dipole must bend as shown, on going from the orientation complex, (i), to the transition state, (ii). There is now a considerable body of evidence for this process whereas the alternative two step mechanism, proposed by Firestone[10] and involving a biradical intermediate, is less widely accepted.

Figure 2



(i) (ii)

1.1.3 Frontier Molecular Orbital Theory

Acceptance of a concerted mechanism of 1,3-dipolar cycloaddition has allowed frontier molecular orbital (FMO) theory and molecular orbital perturbation theory to be used to rationalise the effects of substituents on reactivity and regioselectivity.[11,12]

At a simple qualitative level the findings can be summarised as follows: in forming the transition state the interaction of the FMOs gives an energy gain inversely

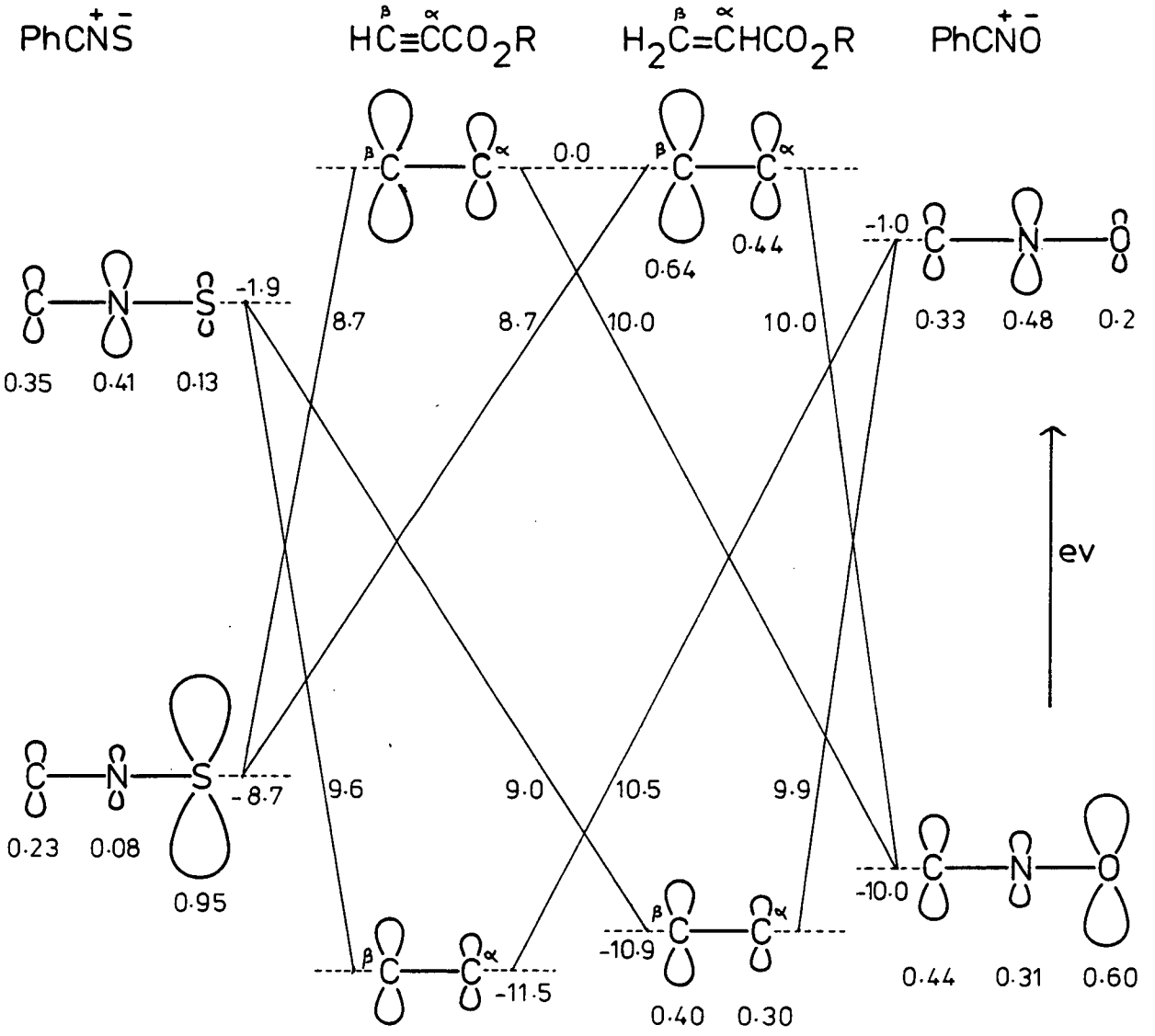
proportional to the energy difference between the FMOs, and directly proportional to the square of the extent of orbital overlap at a given separation of the reacting species. This means that reactions will be favoured between highest occupied (HO) MO and lowest unoccupied (LU) MO pairs that are closest in energy and in the orientation for which the largest atomic orbital (AO) coefficients on one reactant overlap with the largest on the other.

The HOMO and LUMO energy levels and the AO coefficients have been calculated for benzonitrile sulphide by Saunders *et al.*[13] and are shown in Figure 3 where a comparison is made with benzonitrile oxide. It will be seen that the HOMO and LUMO energy levels are compressed with respect to benzonitrile oxide and lie roughly midway between the corresponding energy levels for the electron deficient dipolarophiles propiolate and acrylate esters.

Thus, with respect to these particular dipolarophiles, nitrile sulphides can be considered members of the type II class of Sustmann;[15,16] that is, both sets of HOMO-LUMO interactions must be considered in explaining regiochemistry. The observed isomer ratios for the reaction of arenenitrile sulphides with acrylate and propiolate esters support the theoretical predictions; some experimental results are presented in Table 1.

Consideration of the size of AO coefficients of the HOMO-LUMO pairs (Figure 3) shows that the 4-carboxylate product in these reactions is the result of the dipole HOMO-dipolarophile LUMO interaction and the 5-carboxylate product

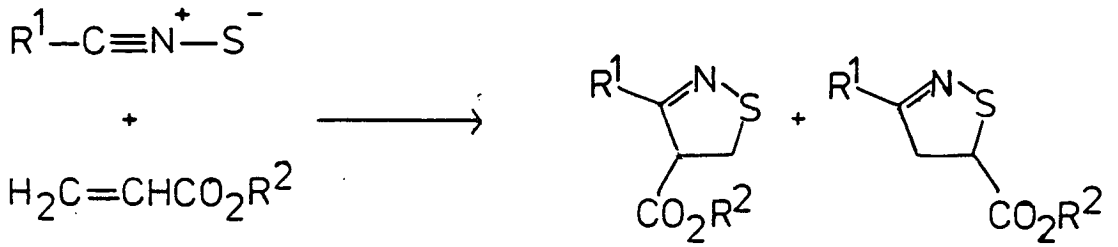
Figure 3 FMO Energies and AO Coefficients for Benzonitrile Oxide, Benzonitrile Sulphide and Propiolate and Acrylate Esters



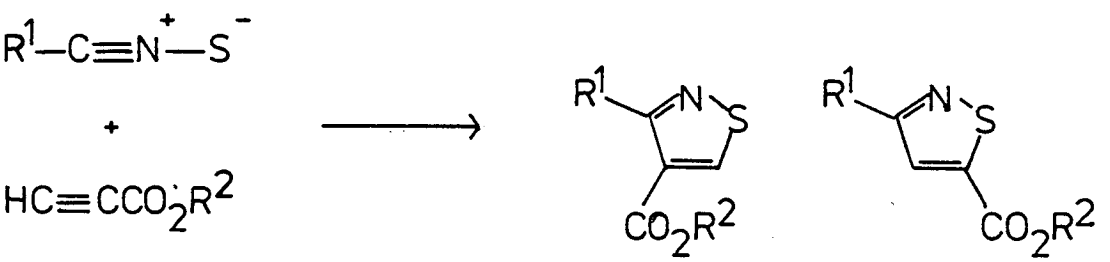
Footnote: Relative FMO energies and dipole AO coefficients calculated by Saunders et al.[13], acrylate AO coefficients by Bastide[14], both using CNDO/2 calculations. Propiolate AO coefficients unavailable but assumed similar to acrylate.

is the result of the dipole LUMO-dipolarophile HOMO interaction. The ratios of 4- to 5-carboxylate products show that both dipole HOMO and dipole LUMO control is in operation. For both dipolarophiles the extent of dipole HOMO control is much greater with benzonitrile sulphide than in the corresponding reaction with benzonitrile oxide, for which 5-carboxylate esters are the predominant products.[22,23]

Table 1 4- to 5-Carboxylate Ratios for the Reaction of some Nitrile Sulphides with Propiolate and Acrylate Esters



R^1	4-/5-Ratio	Reference
4-ClC_6H_4-	0.31	17
4-$MeOC_6H_4$-	0.35	18

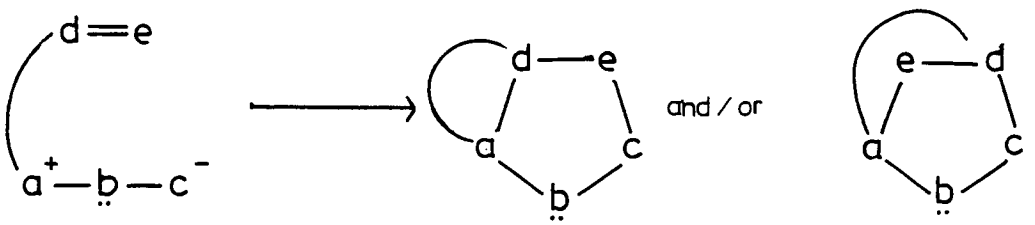


R^1	4-/5-Ratio	Reference
Ph-	1.0	19,20
4-$MeOC_6H_4$-	1.3	21

1.2 INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTIONS

1.2.1 Introduction

A 1,3-dipole bearing a functional group which is able to act as a dipolarophile may react by an intramolecular cycloaddition.



Such reactions have been reported for most of the known types of 1,3-dipoles and have been used extensively in the synthesis of fused ring heterocycles. The area has been reviewed by Padwa[24,25] and by Oppolzer.[26]

There are a number of special features of intramolecular 1,3-dipolar cycloadditions relevant to the present work. These are discussed in the following sections using examples drawn from the most recent review[25] unless otherwise indicated.

1.2.2 Effect of Dipole-Dipolarophile Linkage

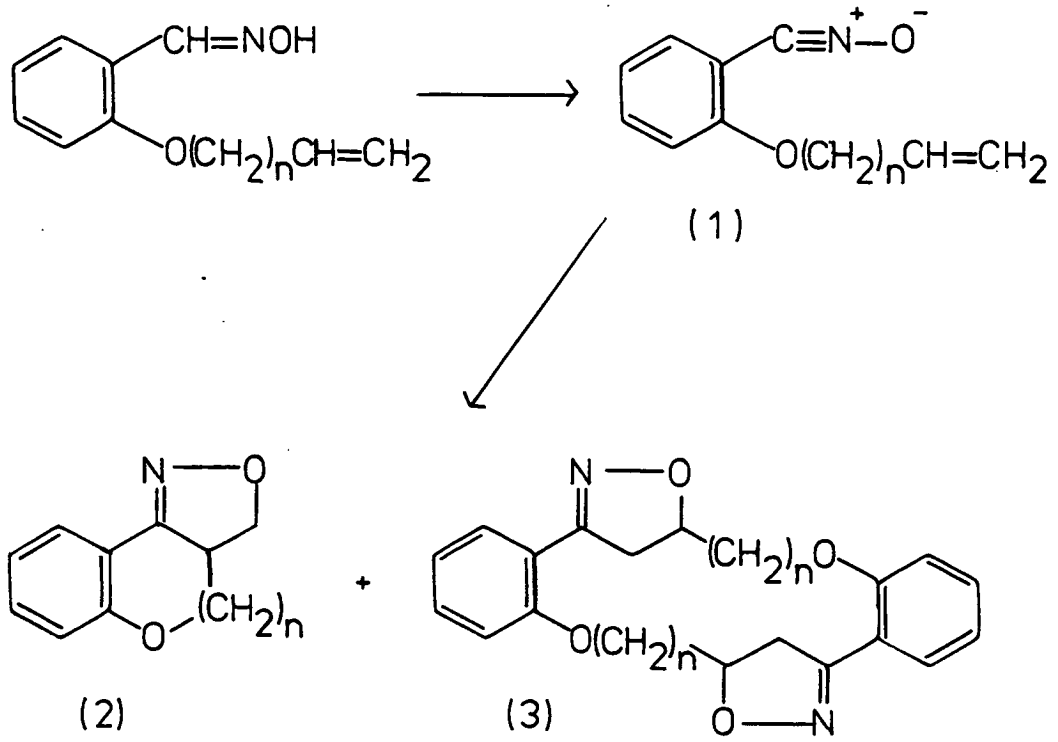
The course of the reaction, and the products, may depend strongly on the nature of the linkage between dipole and dipolarophile and often differ from those observed for similar intermolecular reactions. This property has been exploited in some cases to give a high degree of selectivity of products.

Some examples follow which illustrate these effects.

2-Allyloxybenzonitrile oxide (1a), generated *in situ*, undergoes an intramolecular 1,3-dipolar cycloaddition giving the chromenoisoxazoline (2a) shown in Scheme 2.[27] The regiochemistry of cycloaddition, giving a 3,4-substituted isoxazoline, is opposite to that favoured in corresponding intermolecular reactions where 3,5-substituted products dominate.

The formation of the 3,4-substituted product shows that geometric factors in the dipole-dipolarophile linkage can force a reaction to occur in a different manner to that normally observed. By comparison, in reactions of higher homologues, (1, b-d; Scheme 2) the yield of product (2) is decreased and the dimer (3) with the favoured regiochemistry is preferred.

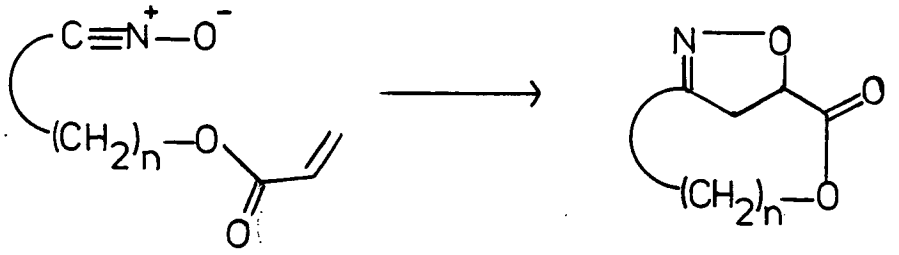
Scheme 2



(1)	n	Yield, %	
		(2)	(3)
a	1	42	0
b	2	17	2
c	3	0	13
d	4	0	19

However, with a more active dipolarophile and sufficient chain length a 3,5-substituted isoxazoline is formed by an intramolecular cycloaddition in high yield (Scheme 3).

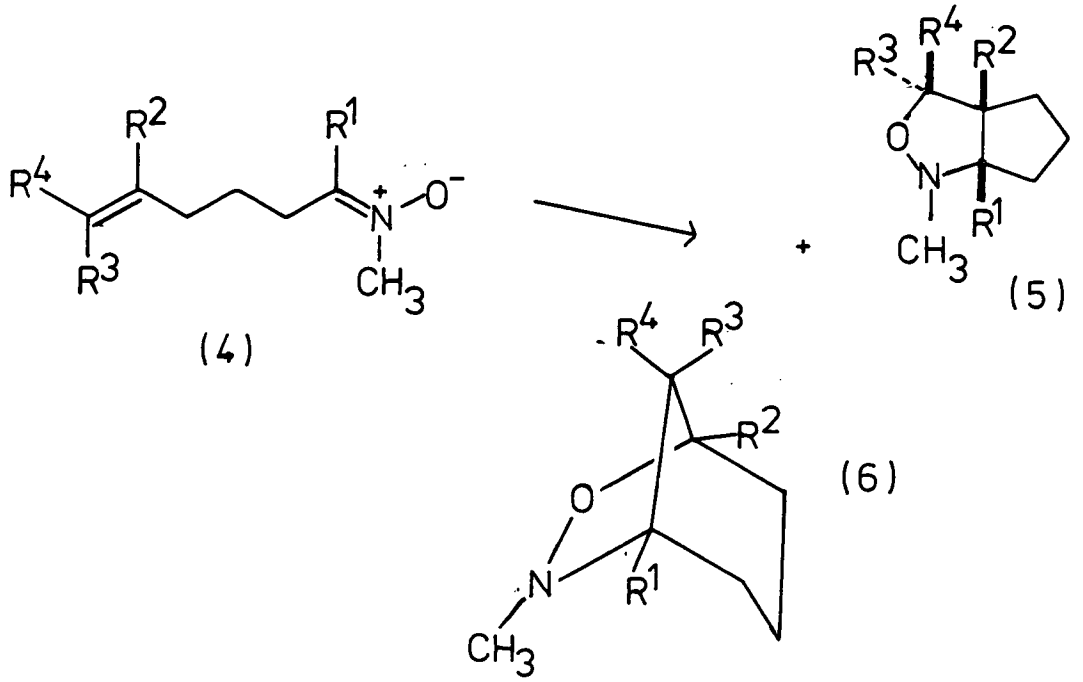
Scheme 3



n=8, 10, 11

In some circumstances both orientations of addition can be given. In the reaction of the nitrone (4) (Scheme 4), when $R^1=R^2=H$ only the fused bicyclo[3.3.0]octane (5) is formed, whereas for $R^1=R^2=CH_3$ both the fused system (5) and the bridged bicyclo[3.2.1]octane (6) are formed in approximately equal amounts. The suggested explanation is that methyl groups in these positions are strongly eclipsed in the transition state for the fused product allowing the formation of the bridged product to compete.

Scheme 4



Substituents in other positions may also have an influence over transition state geometry; an asymmetric group in the dipole-dipolarophile linkage can have a profound effect on the diastereoface selectivity of the cycloaddition.

Reaction of the nitrile oxide (8) (Scheme 5) generated by dehydration of the *Z*-nitroalkene (7) gave a high yield of a single isomer of isoxazoline (10), whereas the *E*-nitroalkene (11) gave a 1:3 mixture of the two cycloadducts (13), (14).[28] This was explained in terms of steric strain in the transition states leading to the various possible isomers. A severe methyl-methyl interaction is present in the transition state leading to isoxazoline (9), which is therefore not observed as a product.

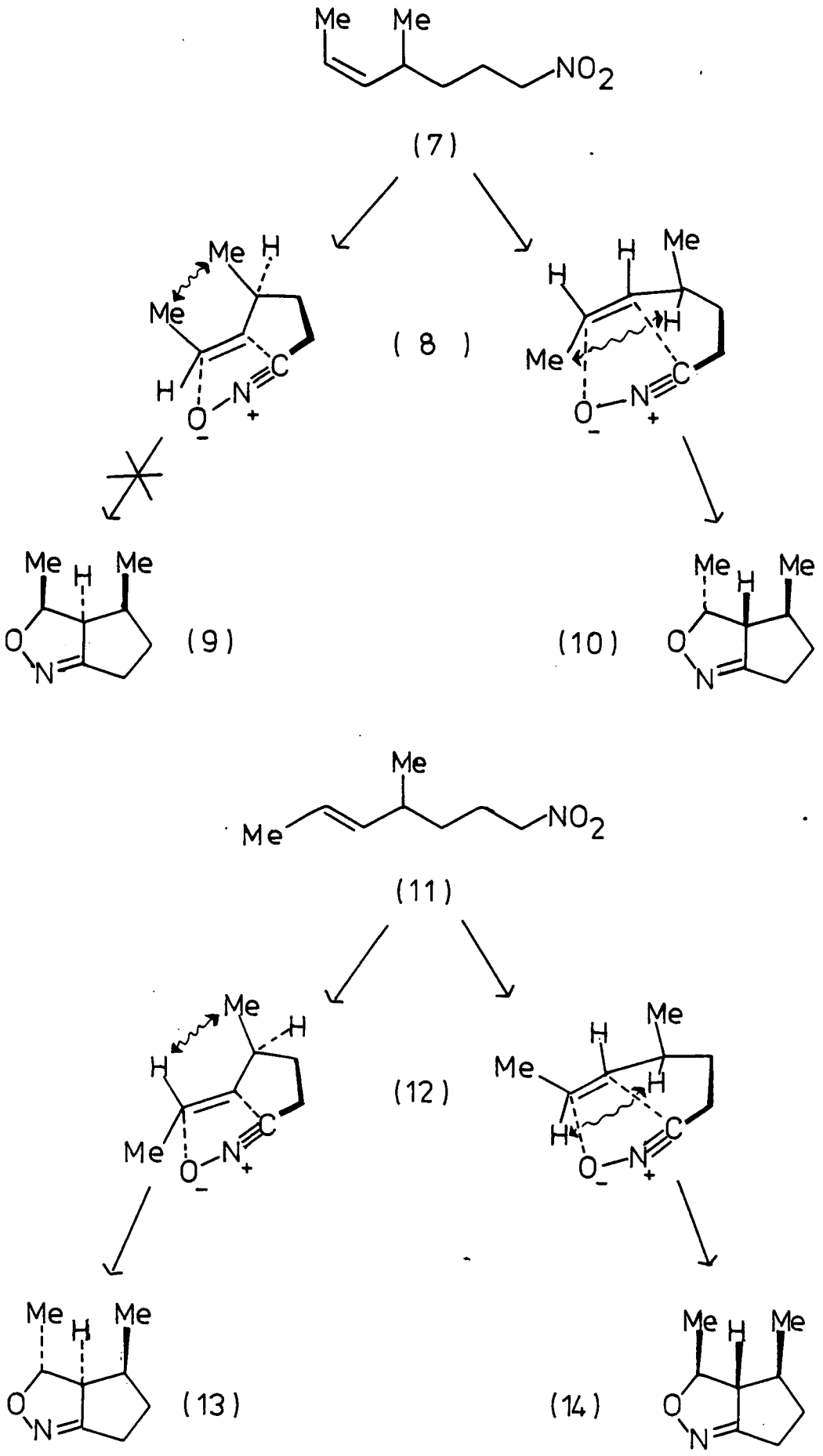
A second class of effects of the dipole-dipolarophile linkage is dealt with in the following section.

1.2.3 Alternative Modes of Reaction

Where 1,3-dipoles are geometrically constrained with respect to the dipolarophile so that they cannot attain the normal transition state for cycloaddition, or where a functional group is present in the dipole-dipolarophile linkage, alternative modes of reaction may be available.

In the case of a dipolarophile close to, and conjugated to the 1,3-dipole, electrocyclisation reactions may occur. An example is the formation of the oxadiazole (16) from the nitrile imine (15)[29] (Scheme 6).

Scheme 5


Me
Me
NO2
(7)
Me
H
Me
H
O
N
(8)
H
Me
H
Me
H
O
N
Me
H
Me
O
N
(9)
Me
H
Me
O
N
(10)
Me
Me
NO2
(11)
Me
H
H
Me
O
N
(12)
Me
H
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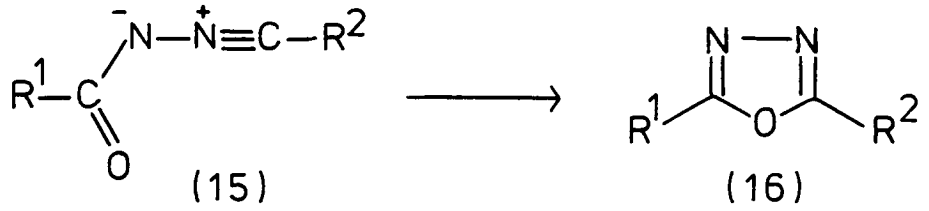
O
N
(13)
Me
H
Me
O
N
(14)

Scheme 6

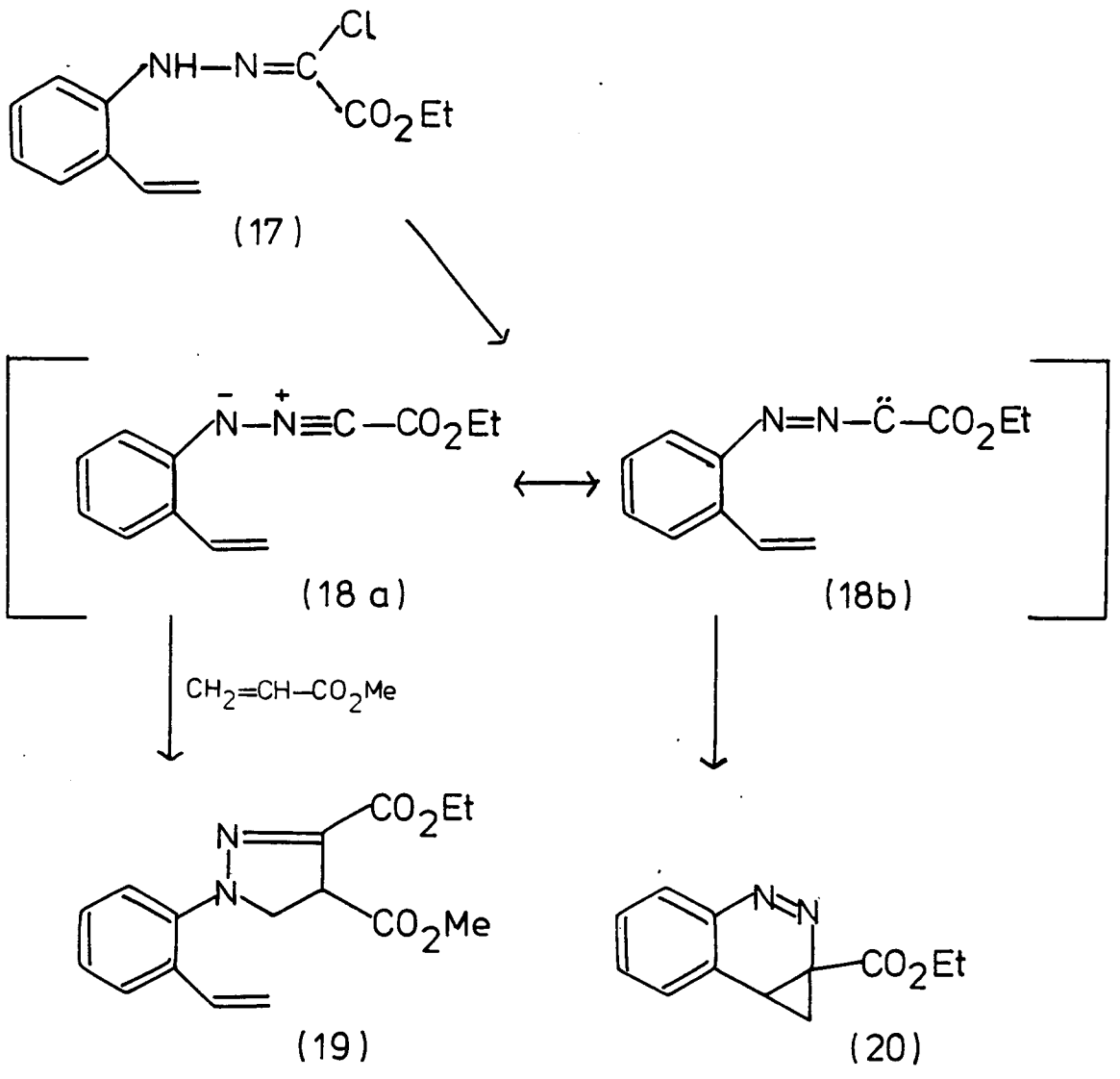


(15) (16)

Such cyclisations form the basis of an extensive area of synthetic chemistry which has been reviewed[29,30] and will not be further discussed here.

Nitrile ylides and nitrile imines can undergo 1,1-cycloaddition *via* their carbenic resonance forms (R-C̈-N=X; X=NR, CR_2). For instance, the nitrile imine (18a), has been trapped with methyl acrylate (Scheme 7); however, it cannot gain the transition state necessary for 1,3-dipolar cyclo-addition with the styrene double bond and, in the absence of other dipolarophiles, undergoes an intramolecular 1,1-cyclo-addition, *via* its carbene form (18b), giving the cyclo-propa[*a*]cinnoline (20).

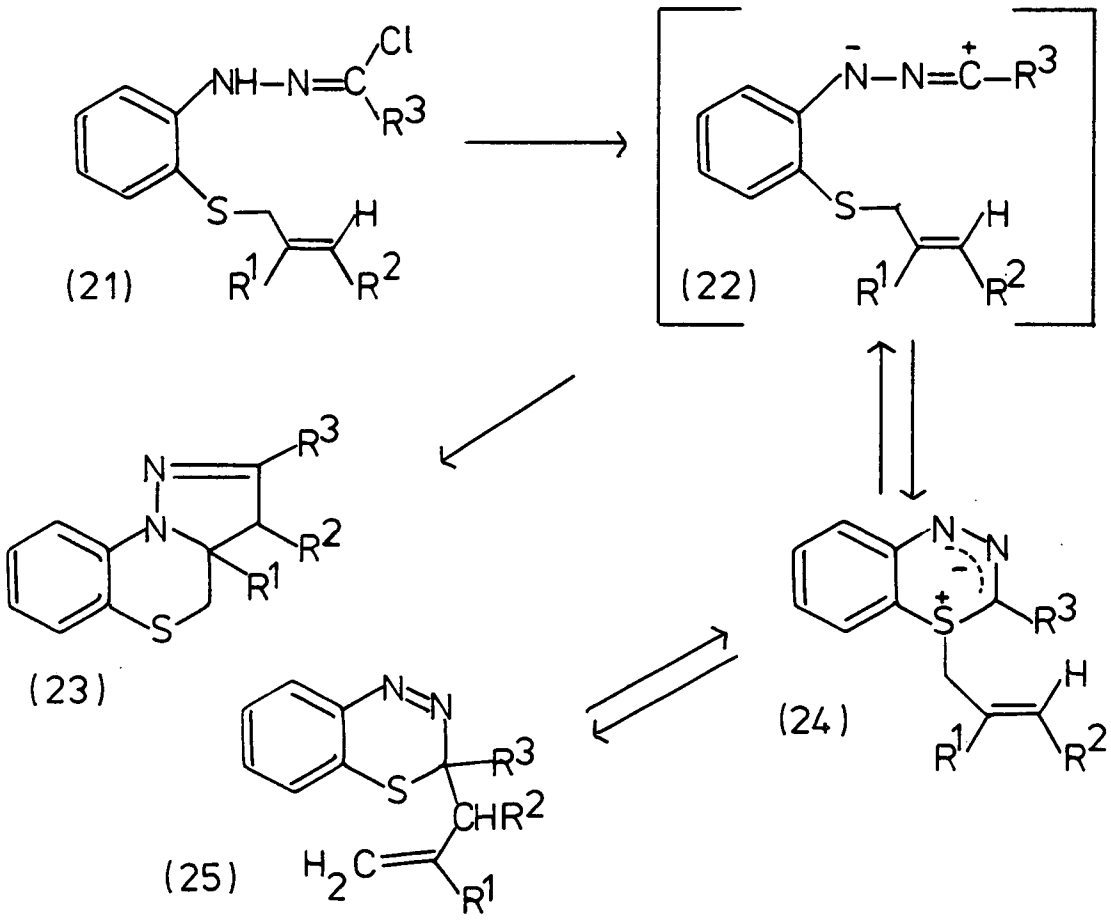
Scheme 7



The nitrile ylide (22) (Scheme 8) cycloadds to its alkene bond to give the expected product (23). However, the benzothiadiazine (25) is also formed as a result of an intramolecular capture of the nitrile imine by the sulphide function.[31] This product is isolable, but in certain cases thermally labile, regenerating the nitrile ylide (which could then be trapped with dimethyl acetylenedicarboxylate) on

heating and giving the tricyclic pyrazoline derivative (23) as the final thermodynamic product.

Scheme 8



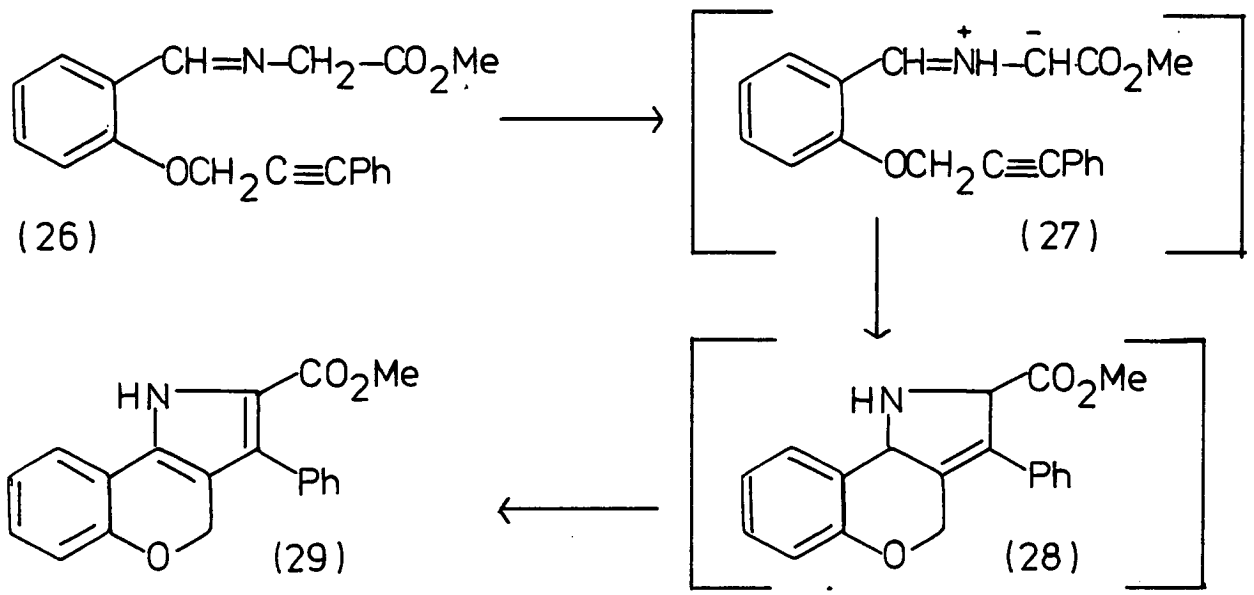
1.2.4 Spontaneous Product Modifications

On account of the often complex nature of the products formed by intramolecular 1,3-dipolar cycloadditions, the initial cycloadducts are frequently found to react further under the prevailing conditions.

For example the azomethine ylide tautomer (27) of the imine (26) undergoes intramolecular cycloaddition with the

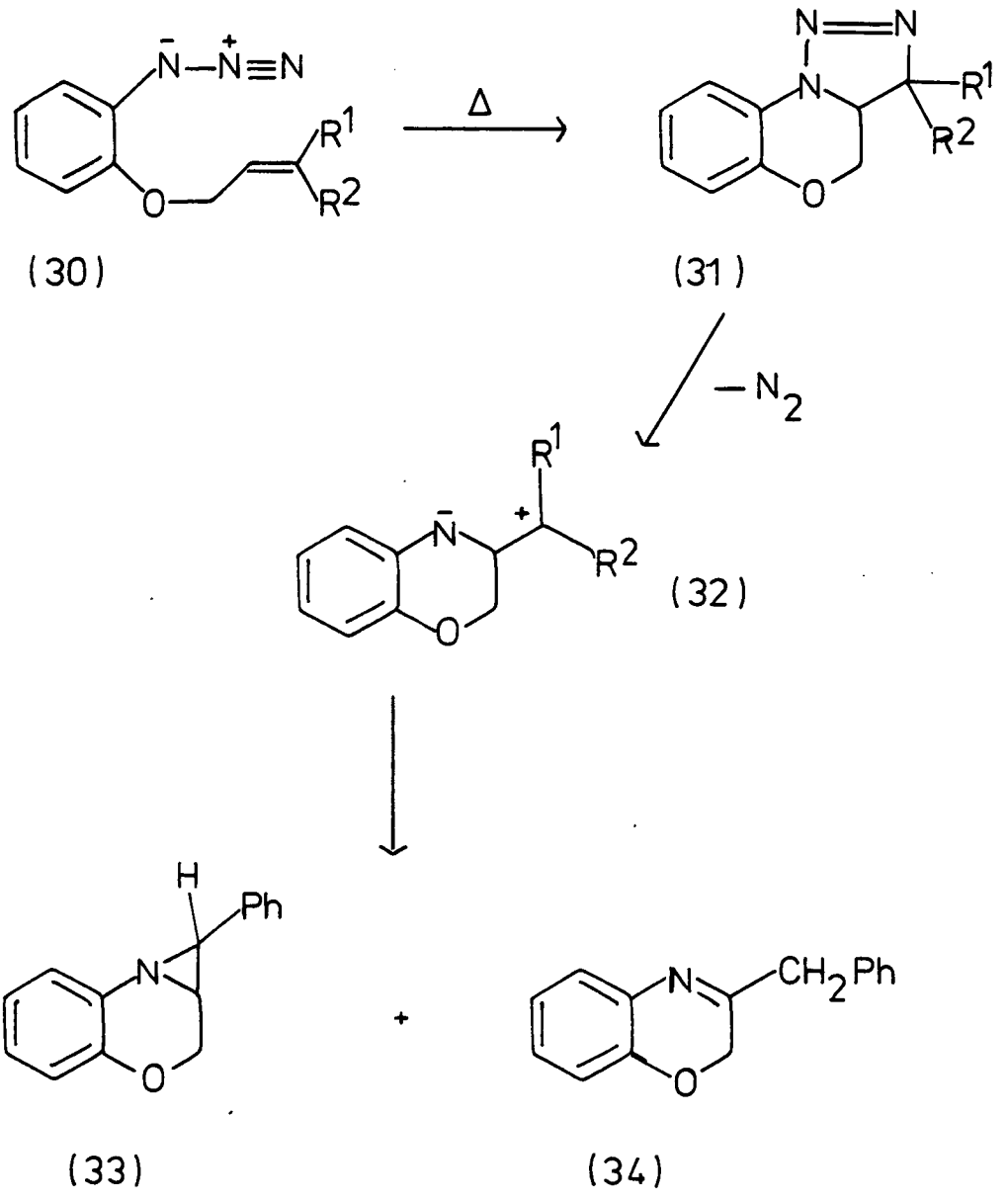
acetylene function giving the initial cycloadduct (28) (Scheme 9). Under the reaction conditions rapid oxidation takes place yielding the pyrrole system (29).

Scheme 9



In several cases the initial cycloadduct reacts further by extrusion of a small stable molecule. For instance, nitrogen is often eliminated from the initial cycloadducts of diazoalkanes or azides. An example is shown in Scheme 10.

Scheme 10



(30) (31) (32) (33) (34)

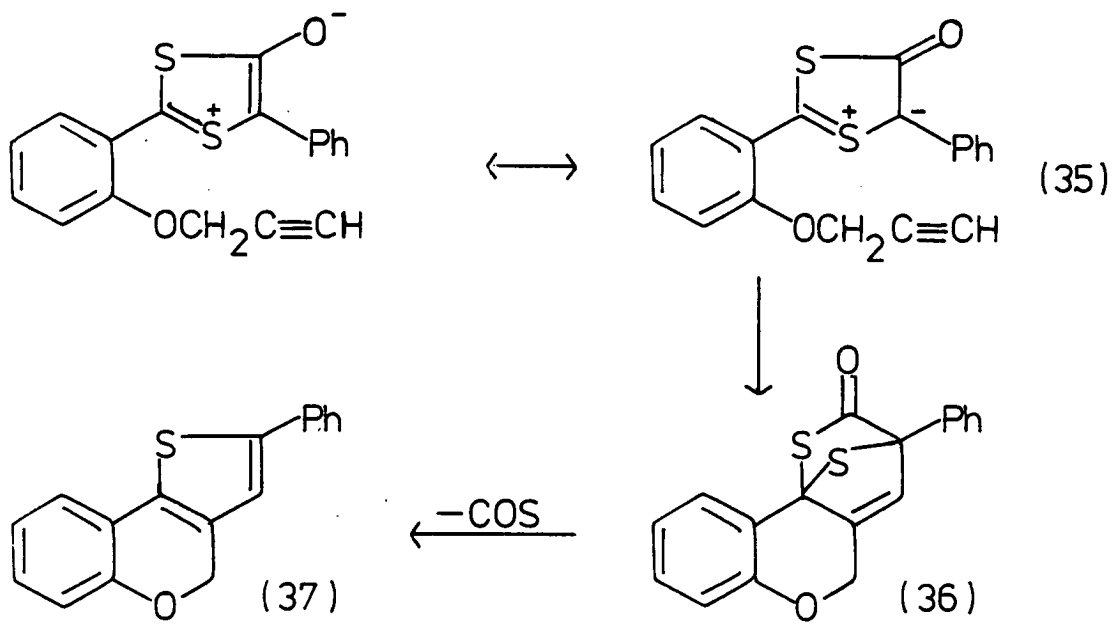
(30),(31),(32) a: R^1=H, R^2=Ph;

b: R^1=Ph, R^2=H.

Both azide isomers (30a) and (30b) gave the same ratio of products (33) and (34) suggesting a common intermediate (32). This is formed by loss of nitrogen from the initial cycloadduct (31) and may be a zwitterion or a diradical.

Such extrusions are not limited to nitrogen. The thiocarbonyl ylide (35) cycloadds to the adjacent acetylene group yielding an initial cycloadduct (36) (Scheme 11). Spontaneous loss of carbon oxysulphide from (36) leads to the thiophene derivative (37).

Scheme 11

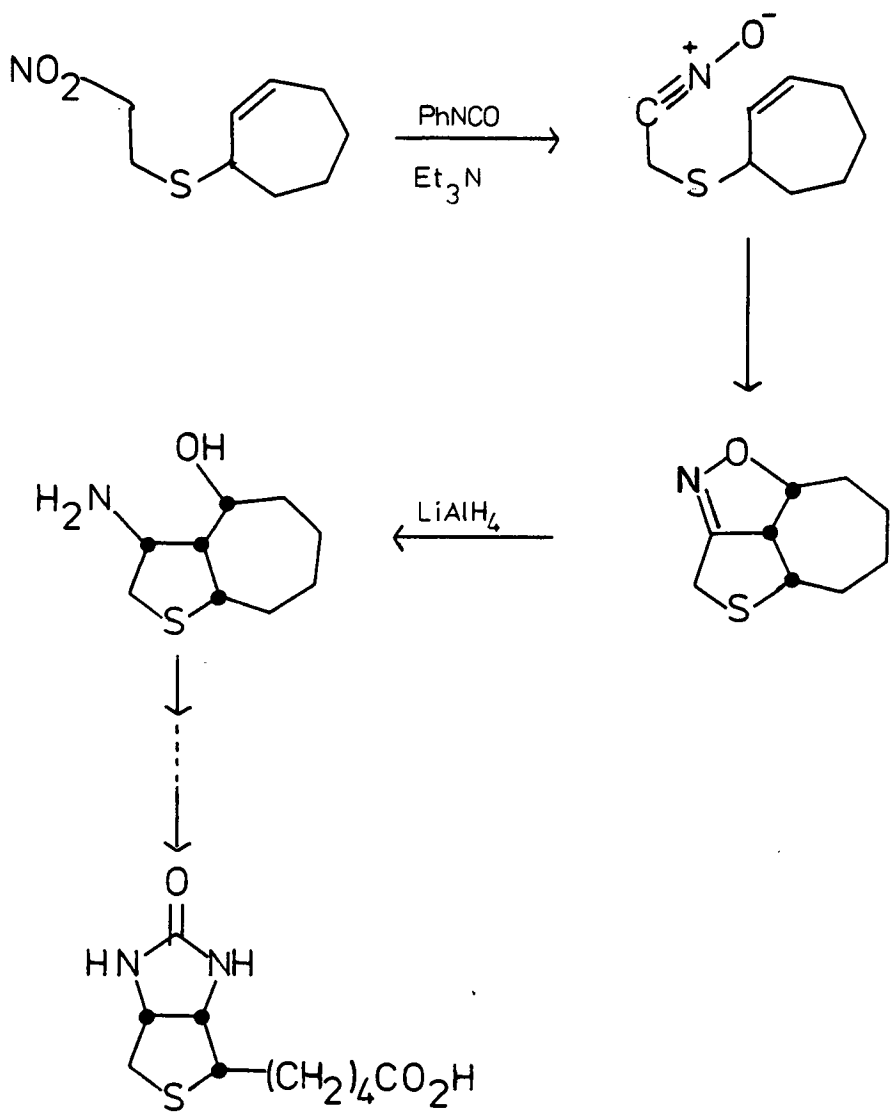


1.2.5 Conclusions

While the more unusual aspects of intramolecular 1,3-dipolar cycloadditions have been highlighted in the above sections, many such reactions do proceed in a perfectly predictable manner. The reaction has been extensively used

in natural product synthesis where the high stereo- and regio-selectivity of product formation can be a major advantage. For example, the stereospecificity of the cycloaddition has been exploited in the synthesis of (±)biotin shown in Scheme 12.

Scheme 12



Overall, the intramolecular 1,3-dipolar cycloaddition reaction has received less attention than its intermolecular counterpart. However, the scope for future development is

large and there is a considerable amount of activity in this area.

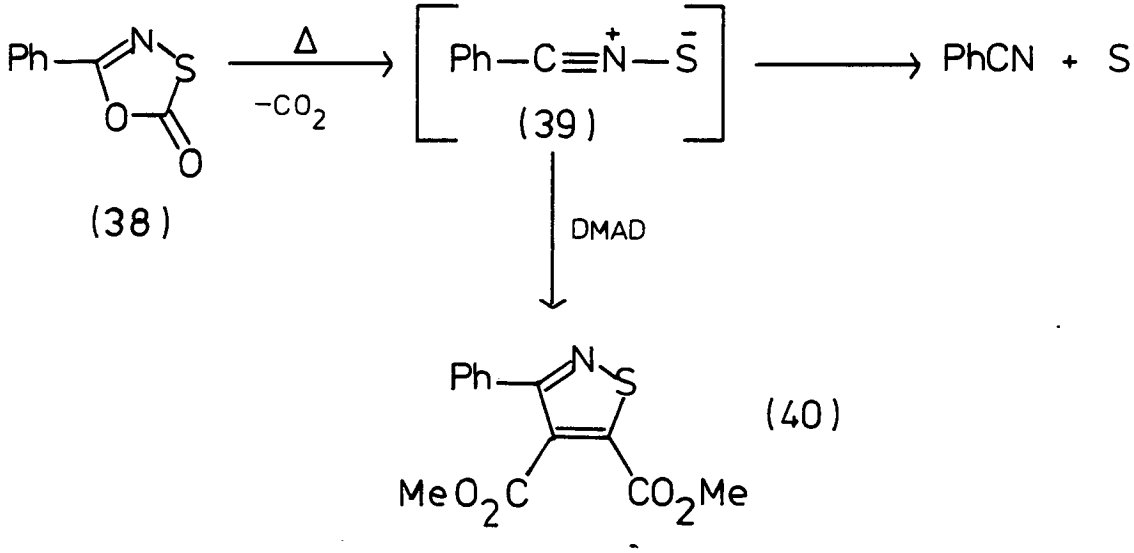
1.3 NITRILE SULPHIDES

1.3.1 Evidence for the Existence of Nitrile Sulphides

Evidence for the existence of nitrile sulphides was first obtained by Franz and Black in 1970.[19] Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one (38) gave benzonitrile and sulphur with the evolution of carbon dioxide (Scheme 13). When the reaction was performed in the presence of the electron deficient dipolarophile dimethyl acetylenedicarboxylate (DMAD) the isothiazole (40) was formed in 90% yield. This was taken as good evidence for the intermediacy of benzonitrile sulphide (39).

Since this first report, nitrile sulphides have been generated by a number of photochemical and thermal routes and have been trapped by a variety of multiple bonds.

Scheme 13

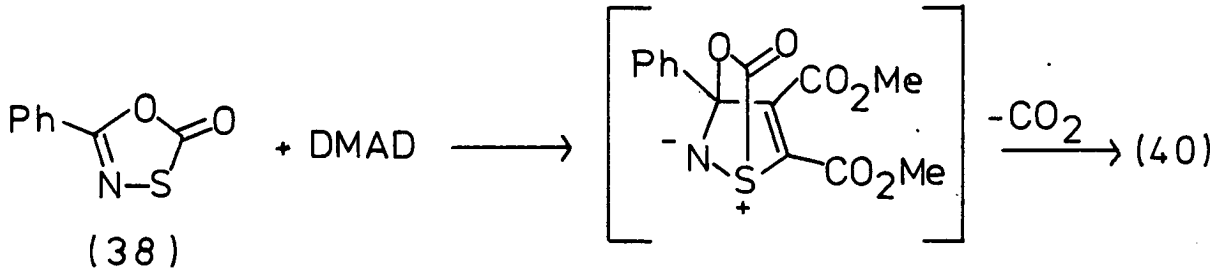


Direct evidence for the existence of nitrile sulphides is, however, limited. Photolytically generated nitrile sulphides have been trapped at low temperatures in glasses

or in films and studied spectroscopically. The u.v. and i.r. spectra of benzonitrile sulphide in a poly(vinyl chloride) film have been recorded. Over a temperature range 15-150K u.v. absorptions at 240 nm and 340 nm were observed[32] and at 85K an i.r. absorption at 2185 cm^{-1} is reported.[33]

Kinetic studies of the thermolysis of oxathiazolone (38) in the presence and absence of dipolarophiles (Scheme 13) have also been performed.[20,34] The rate of disappearance of oxathiazolone (38) and the rates of formation of isothiazole (40) and benzonitrile were all found to be equal, first order, and independent of the concentration of dipolarophile. These findings are consistent with the existence of benzonitrile sulphide as a discrete intermediate in the reaction pathway shown in Scheme 13. They preclude an associative mechanism for the formation of isothiazole (40), shown in Scheme 14, which was initially considered as an alternative.

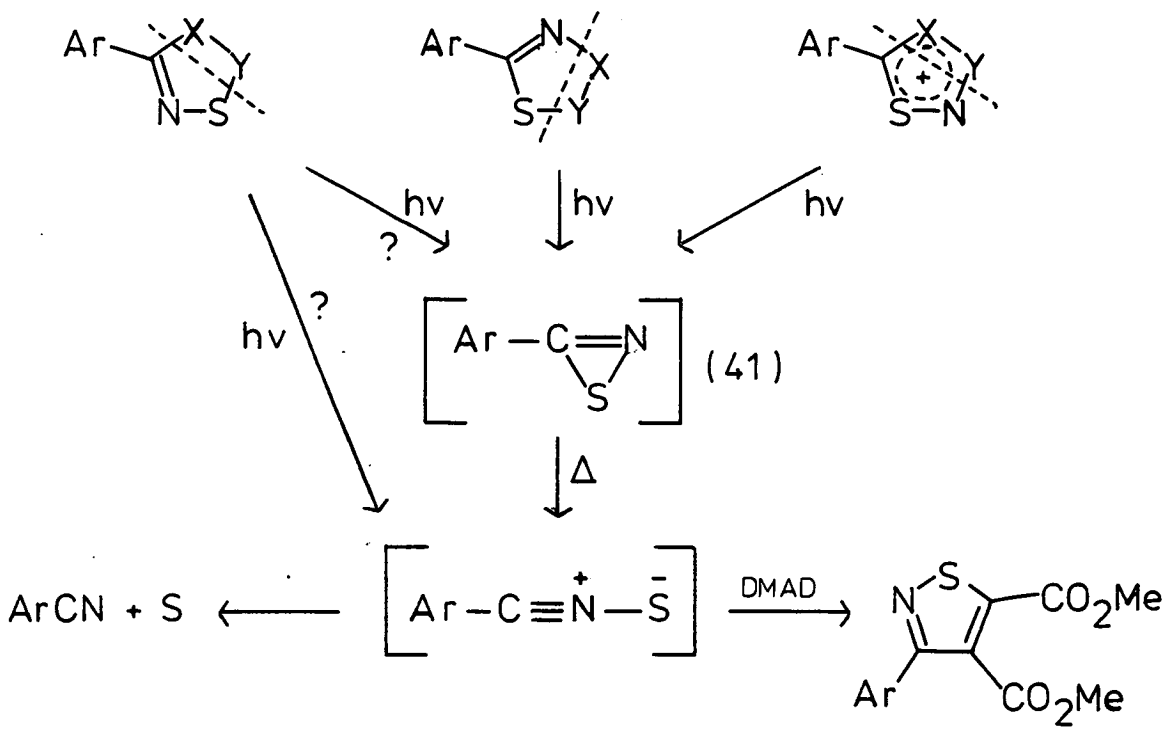
Scheme 14



1.3.2 Photolytic Generation of Nitrile Sulphides

Photolysis of sulphur-nitrogen heterocycles with the following general structures leads to the formation of nitrile sulphides which can be trapped with dipolarophiles such as DMAD (Scheme 15).

Scheme 15



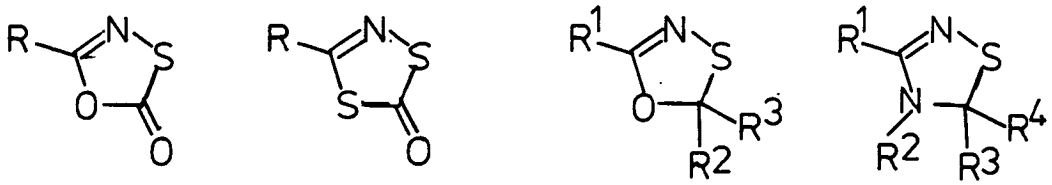
where X-Y=CO, CO_2, COS, CS_2, N_2 *etc.*

It has been suggested[32] that the initial intermediate formed in all these photolyses is the thiazirine (41) which thermally ring opens to give the nitrile sulphide. The yields of isothiazole cycloadducts derived from photochemically generated nitrile sulphides are generally low (5-21%)[35] when compared to those for thermal routes (*vide infra*). This has been attributed[35] to destruction of the nitrile sulphide by energy transfer from excited species or by direct photolysis.

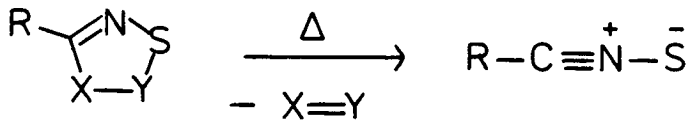
1.3.3 Generation of Nitrile Sulphides by Thermal Cycloreversion Reactions

The four heterocyclic systems shown below have been

found to give nitrile sulphide on thermolysis.



(i) (ii) (iii) (iv)



All four undergo cycloreversion on heating eliminating carbon dioxide, carbon oxysulphide, a carbonyl compound or an imine, respectively, and generating nitrile sulphide. However, the efficiency and hence the synthetic utility of these sources varies.

(i) and (ii) 1,3,4-Oxathiazol-2-ones and 1,3,4-Dithiazol-2-ones

Thermolysis of oxathiazolones was historically the first reported source of nitrile sulphides[19] and it remains the first choice in synthesis. Oxathiazolones are easily prepared (Section 1.5.1) and have a long shelf-life. They give nitrile sulphides efficiently on heating at a temperature above *ca.* 130°C. With a good dipolarophile the nitrile sulphide can be trapped almost quantitatively (Section 1.4).

The dithiazolones provide a similar source of nitrile sulphides. However, they are less easily prepared,[36] require

higher temperatures and longer reaction times and they give lower yields of cycloaddition products.[37]

(iii) and (iv) 1,3,4-Oxathiazoles and 1,2,4-Thiadiazolines

On heating above 160°C both these heterocycles cyclorevert to give a nitrile sulphide. The oxathiazoles are an efficient source of nitrile sulphides giving high yields of cycloadducts.[38] However, they are difficult to prepare, except by the forward cycloaddition of nitrile sulphides (generated from oxathiazolones) to electron deficient carbonyl compounds[39] (Section 1.4.5).

The thiadiazolines may decompose thermally by routes other than cycloreversion and are therefore not an efficient source; only low yields of cycloadducts have been obtained.[40]

1.3.4 Generation of Nitrile Sulphides by Thermal Elimination Reactions

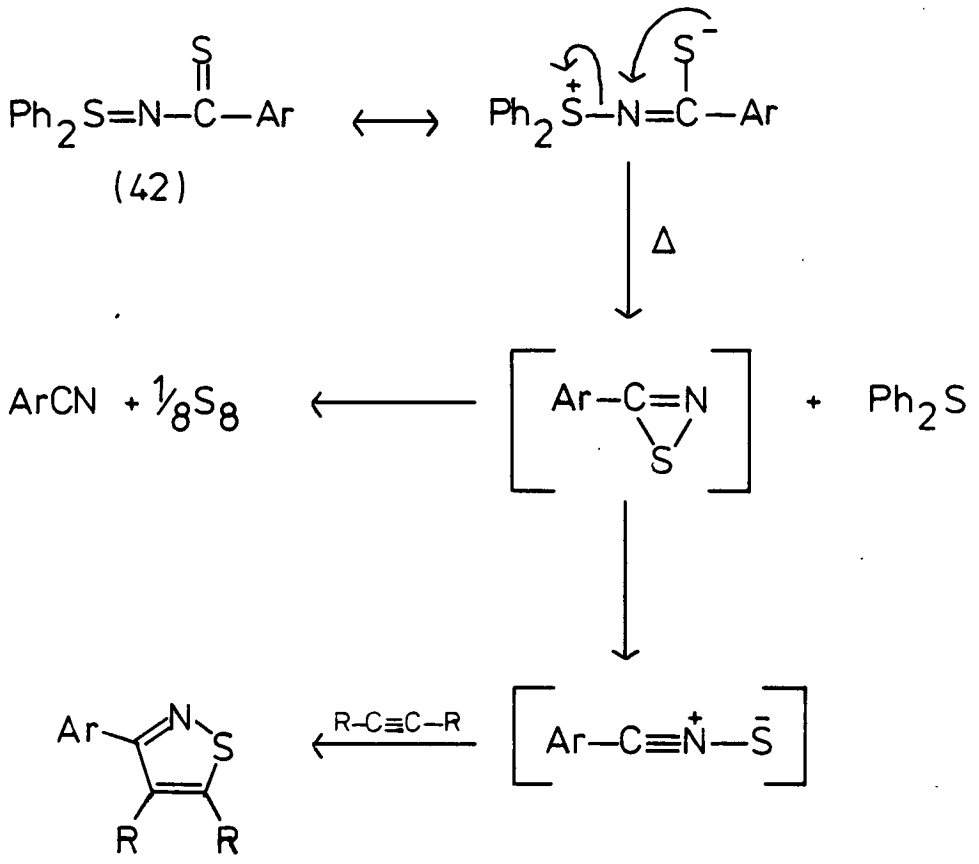
Two classes of acyclic compounds have been found to give nitrile sulphides by thermal elimination reactions.

(i) *N*-Thiocarbonyl Diphenylsulphimides

N-Thiocarbonyl diphenylsulphimides (42) decompose thermally at 70°C to diphenyl sulphide, nitrile and sulphur. In the presence of electron deficient acetylenes, however, isothiazoles are formed. The mechanism shown in Scheme 16 has been proposed on the basis of kinetic measurements.[41]

The yields of cycloadducts where the dipolarophile is DMAD are moderate (27-34%). The instability of the precursor at room temperature may limit the synthetic use of this route.

Scheme 16

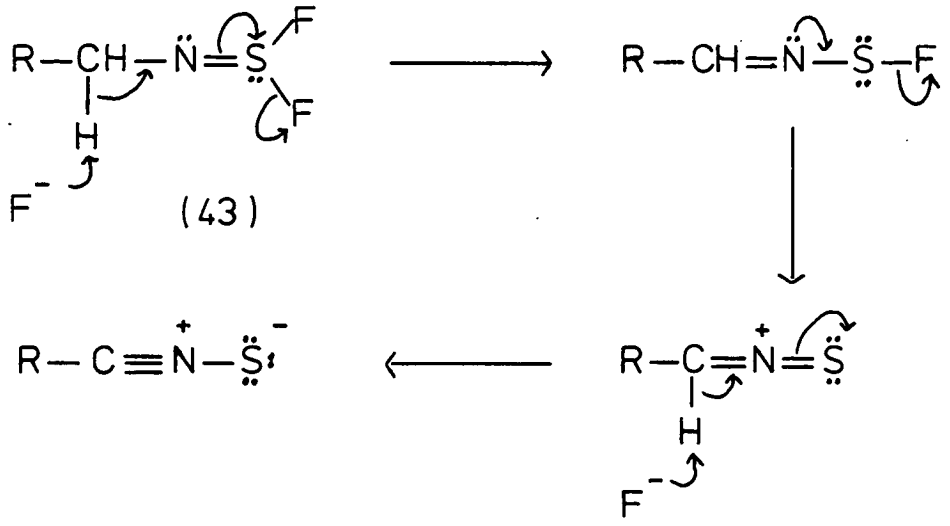


(ii) Iminosulphur Difluorides

Iminosulphur difluorides (43) undergo a rare 1,3-elimination on heating at 132°C, involving two moles of hydrogen fluoride and giving rise to nitrile sulphides by the mechanism shown in Scheme 17.[42] Yields of the cyclo-adduct with DMAD are reasonable (≲65%).

The regioselectivity of reactions using this source of nitrile sulphide may be affected by the action of hydrogen fluoride, produced in the reaction, on the dipolarophile. For example, in the reaction of benzonitrile sulphide with ethyl propiolate a ratio of isothiazole-4 to 5-carboxylate

Scheme 17



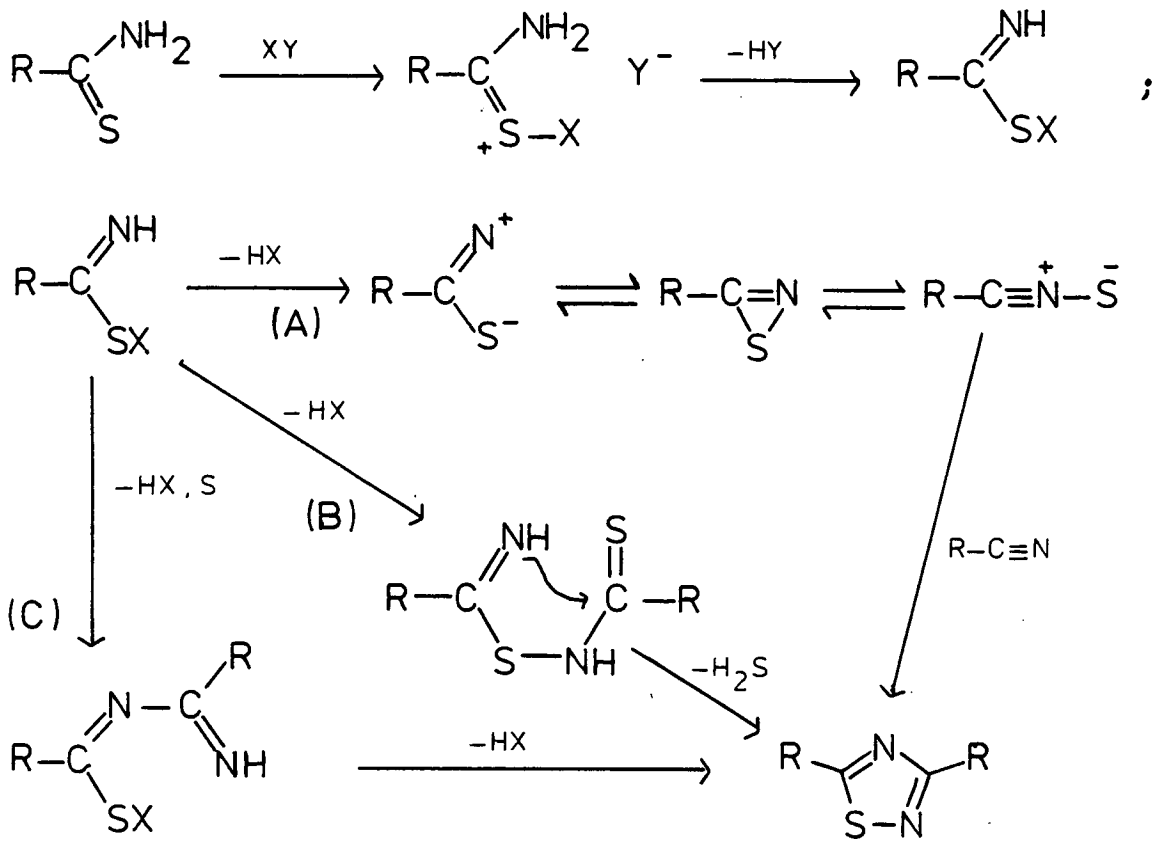
(43)

of 3:2 was found compared with 1:1 when the source of benzonitrile sulphide was oxathiazolone (see Section 1.1.3). This was considered to be due to protonation of the carbonyl of ethyl propiolate by hydrogen fluoride with a consequent change in orbital energies and coefficients.[13]

1.3.5 The Oxidative Dimerisation of Thioamides

A number of reports[43-46] have mentioned the possibility of nitrile sulphide intermediates being present in the oxidative dimerisation of thioamides to 1,2,4-thiadiazoles. However, alternative mechanisms are possible and the evidence is presently conflicting. The general mechanisms which have been proposed are outlined in Scheme 18.

Scheme 18



References: Pathway (A)[44], (B)[44], (C)[46].

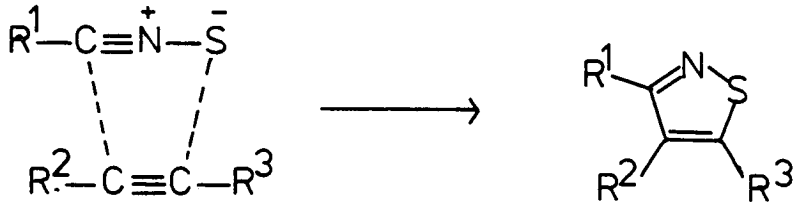
Several sets of conditions have been used for this reaction *viz:* H_2O_2/HCl,[43] *tert*-butyl hypochlorite,[44] aerobic photolysis,[45] pyridinium salts with dimethyl sulphoxide.[46] It is possible that different mechanisms are operating under the various conditions.

1.4 1,3-DIPOLAR CYCLOADDITIONS OF NITRILE SULPHIDES

The nitrile sulphide 1,3-dipole has been found to undergo 1,3-dipolar cycloaddition reactions with five classes of multiple bond: C≡C, C=C, C≡N, C=N, C=O. The reaction will be reviewed generally under corresponding headings. Unless otherwise stated the nitrile sulphides were generated by thermolysis of the corresponding oxathiazolones.

1.4.1 Acetylenes

Nitrile sulphides react with electron deficient acetylenes to give isothiazoles:

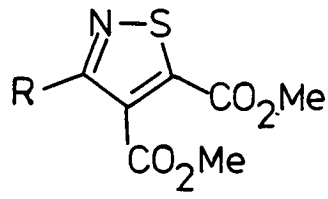


DMAD has been used to trap nitrile sulphides from all known sources. Table 2 shows the maximum yields of isothiazole adducts that have been reported from the various sources of nitrile sulphide described in Sections 1.3.2-1.3.4.

Ethyl and methyl propiolates react with nitrile sulphides yielding a mixture of isothiazole-4 and 5-carboxylates. Isomer ratios are generally *ca.* 1:1 and combined yields are good with nitrile sulphides derived from oxathiazolones (but see Sections 1.1.3 and 1.3.4).

Nitrile sulphides from *N*-thiocarbonyl diphenylsulphimides have been reacted with dibenzoylacetylene to give isothiazoles

Table 2 Yields of Dimethyl 3-R-isothiazole-4,5-dicarboxylate

Precursor ⟶ R-C≡N⁺-S⁻ —DMAD→ 

Source of Nitrile Sulphide	R	Yield, %
Photolytic[35] (1,2,3,4-thiatriazole 3-oxide)	Ph	21
Oxathiazolone[19]	Ph	>90
Dithiazolone[37]	Ph	52
	4-$MeOC_6H_4$	60
Oxathiazole[38]	Ph	88
	Me	92
Thiadiazoline[40]	4-$MeOC_6H_4$	12
N-Thiocarbonyl diphenylsulphimide[41]	3-$MeOC_6H_4$	34
Iminosulphur difluoride[42]	Ph	65

Footnote: Maximum reported yields are given.
In addition, yields with benzonitrile sulphide are quoted where these are available and different from the maximum.

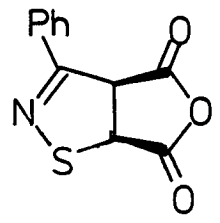
in moderate yield. However, using the same nitrile sulphides no cycloadduct with diphenylacetylene could be isolated.[41]

Recently it has been claimed that benzonitrile sulphide is formed during the photo-oxidation of thiobenzamide and can be trapped by phenylacetylene. A single product, 3,4-diphenylisothiazole (yield 22%), is reported.[45] Benzonitrile sulphide, generated from *N*-benzyliminosulphur difluoride, gave no cycloadduct with phenylacetylene.[47]

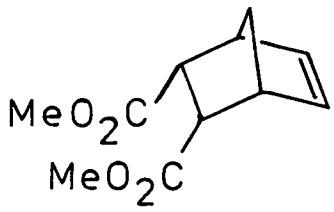
1.4.2 Olefins

The first reaction of this class was with maleic anhydride which was found to cycloadd to benzonitrile sulphide derived from *N*-benzyliminosulphur difluoride to give the *cis*-fused isothiazoline derivative (44) in 20% yield.[42] Since this finding several olefins have been added to nitrile sulphides derived from oxathiazolones. Further symmetrical olefins reported to give cycloadducts include dimethyl fumarate, the norbornene derivative (45), *N*-ethyl- and *N*-phenyl-maleimides,[17] diethyl fumarate and diethyl maleate.[48] All these except diethyl maleate retain the configuration of the double bond in the product. Diethyl maleate, however, gives the *trans* product (46) identical to that obtained from diethyl fumarate. It is thought that the initial cycloadduct is the *cis* isomer (47), but this rapidly isomerises to the more thermodynamically stable *trans* product (46).[48]

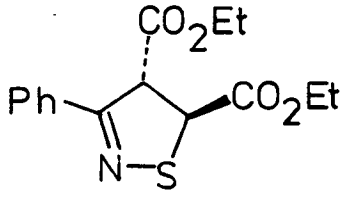
Naphtho- and benzo-quinones also cycloadd to nitrile sulphides. Naphthoquinones give an isothiazole product (48) which is thought to arise by oxidation of the first formed



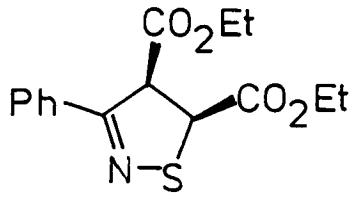
(44)



(45)

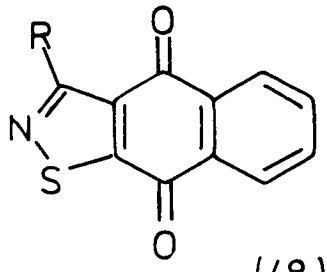


(46)

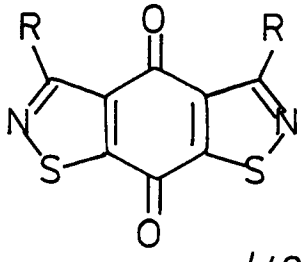


(47)

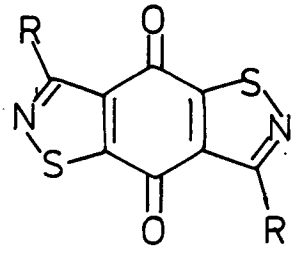
isothiazoline adduct by unreacted naphthoquinone.[49,50] Benzoquinones show a similar phenomenon but they react with two moles of nitrile sulphide to give the *bis*-isothiazole adducts (49) and (50).[49]



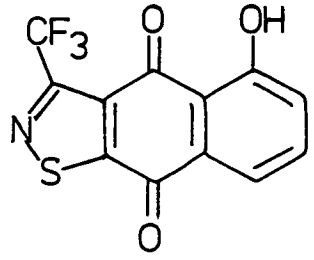
(48)



(49)



(50)



(51)

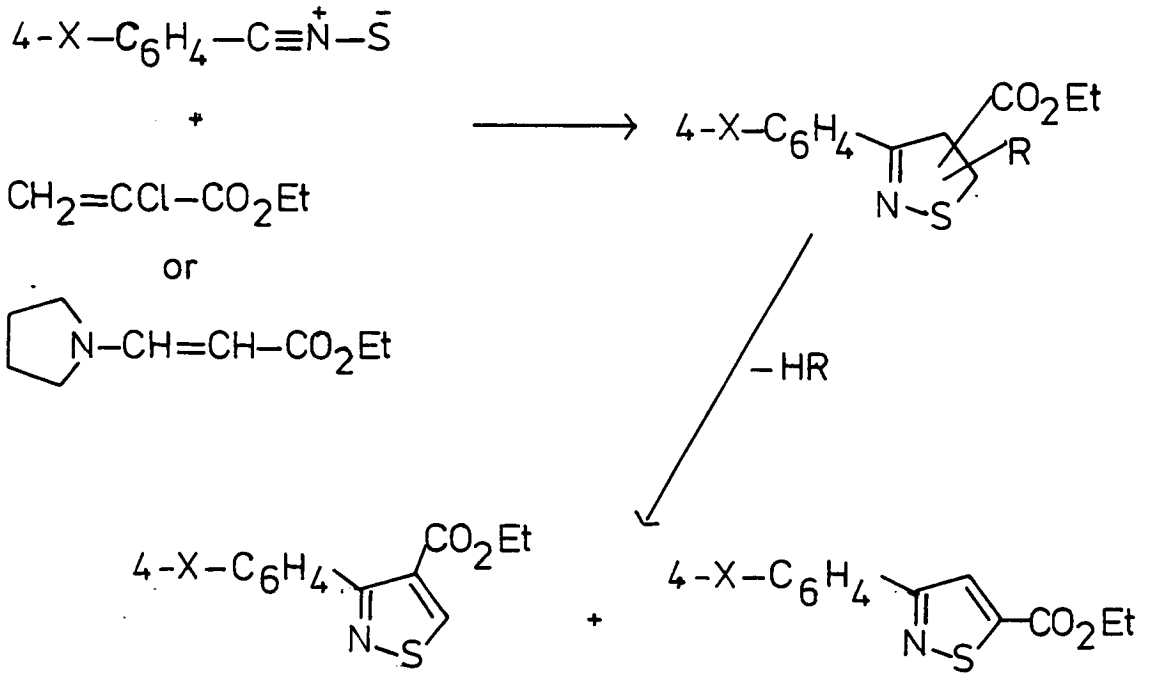
Cycloadditions to the unsymmetrical compounds 5-acetamido- and 5-hydroxy-naphthoquinone have also been studied. The former gave only trace quantities of isothiazole adducts[51] whereas the latter gave a 14% yield of a single isothiazole thought to have structure (51).[50] Trifluoroacetonitrile sulphide derived from an iminosulphur difluoride was used in this case.

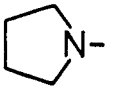
Acrylate esters and their derivatives undergo cycloaddition with nitrile sulphides. Phenyl[17] and isobutyl[18] acrylates each gave a mixture of isothiazoline-4 and 5-carboxylates in a combined yield of *ca.* 60 %. The regiochemistry of this process has already been discussed in Section 1.1.3.

Cycloaddition of nitrile sulphides to ethyl 2-chloroacrylate and ethyl β-pyrrolidinylacrylate gave a mixture of isothiazole-4 and 5-carboxylates presumably by loss of HCl and pyrrolidine respectively from initial isothiazoline adducts.[17] (Scheme 19).

Nitrile sulphides have been found <u>not</u> to react with carbon-carbon double bonds in β-nitrostyrene, 3-nitrostyrene, tetraethyl ethylenetetracarboxylate[17] or tetracyanoethylene.[52] It has been reported that benzonitrile sulphide produced during the photo-oxidation of thiobenzamide is trapped by the electron rich alkene 2,3-dimethylbut-2-ene.[45]

Scheme 19



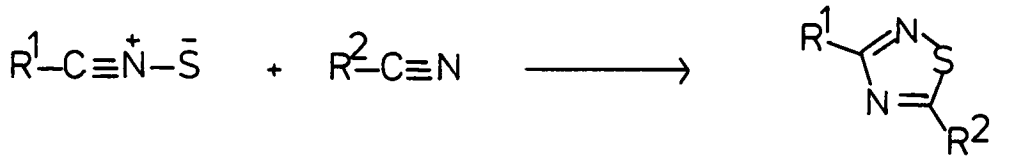
	4-	Yields, %	5-
X=Cl; R=Cl	28		49
X=H; R= 	8		2

1.4.3 Nitriles

Various nitriles cycloadd to nitrile sulphides giving 1,2,4-thiadiazoles. The scope of this reaction is illustrated in Scheme 20. Some of the interest in this reaction is due to the biological properties of certain thiadiazoles.

This reaction has also been used to prepare the natural product dendrodoine (52) which contains a 1,2,4-thiadiazole

Scheme 20

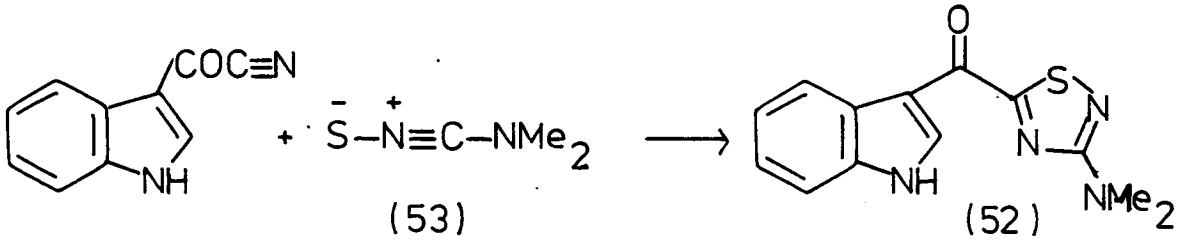


R^1=Alkyl, Aryl, $-CO_2Et$[53]

R^2=$-CH_2CO_2Et$[54], $-CO_2Et$[54], $-CCl_3$[55]; also X-C_6H_4- where X=H[54], 4-Me[54], 4-Cl[54], 4-CO_2Et[53], 2-CN[56], 2-CO_2Me[56], 3-CF_3[56].

(Scheme 21).[57] This example shows the potential versatility of the substituent on the nitrile sulphide itself. The dimethylaminonitrile sulphide (53) was generated from an oxathiazolone which could be prepared in good yield[57] in the normal way (*vide infra*, Section 1.5.1).

Scheme 21

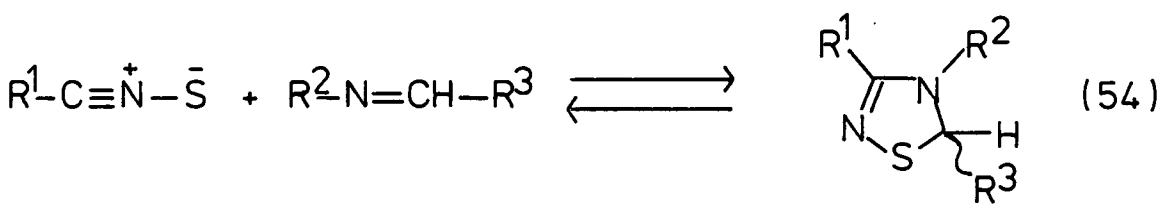


Nitrile sulphides also react periselectively with the nitrile groups of tetracyanoethylene giving *mono*- and *bis*-thiadiazole adducts.[52] Several isomers of the *bis*-adduct were formed.

1.4.4 Imines

Some Schiff's bases have been found to form cycloadducts with nitrile sulphides. The products, 1,2,4-thiadiazolines (54) (Scheme 22) are formed in low yields and are not very stable under the reaction conditions. They undergo a cyclo-reversion reaction re-producing nitrile sulphide but may also decompose by other routes.[58]

Scheme 22



(54)

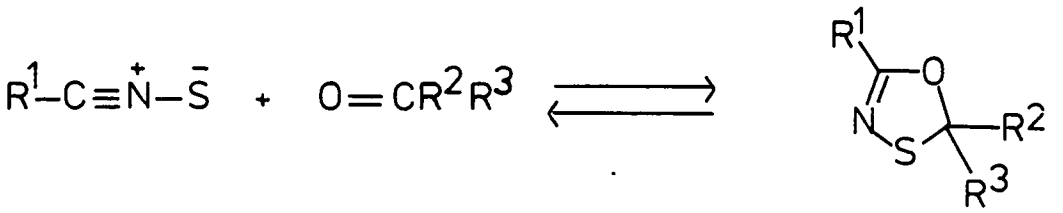
R^1 = 4-MeO-C_6H_4- ; R^2 = Ph.

R^3 :	Ph ;	4-Cl-C_6H_4- ;	4-NO_2-C_6H_4-.
Yields%:	2	7	13

1.4.5 Carbonyl Compounds

Nitrile sulphides have been found to react with the carbonyl group of chloral, hexachloroacetone and α,α,α-trifluoroacetophenone to give 1,3,4-oxathiazoles (55) (Scheme 23).[39,59] These oxathiazoles can thermally cyclorevert to the carbonyl compound and nitrile sulphide.[38]

Scheme 23



(55)

R^1= Alkyl, Aryl;

R^2= CCl_3, R^3=H ;

R^2= CF_3, R^3=Ph ;

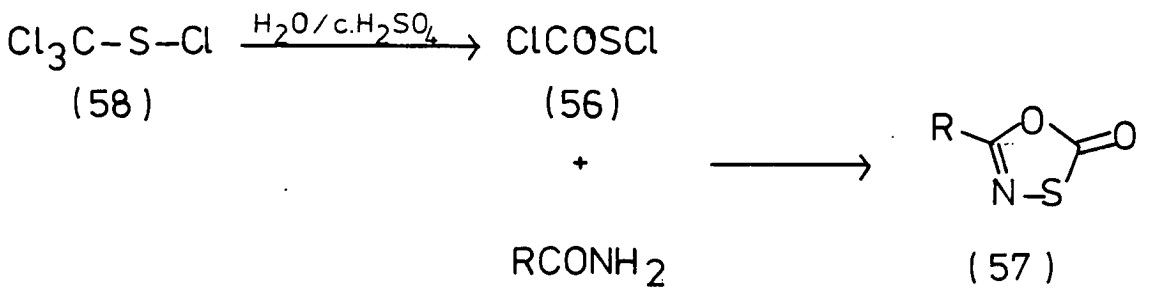
R^2=R^3= CCl_3.

1.5 1,3,4-OXATHIAZOL-2-ONES

1.5.1 Preparation

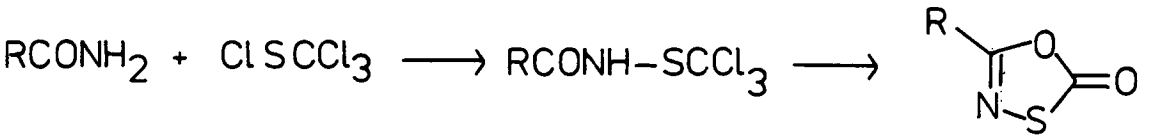
The preparation of 1,3,4-oxathiazol-2-ones was first reported in 1965. Mühlbauer and Weiss heated carboxylic acid amides together with chlorocarbonylsulphenyl chloride (56) and obtained oxathiazolones (57),[60] (Scheme 24). The reagent (56) is easily obtained by partial hydrolysis of perchloromethyl mercaptan (58) using concentrated sulphuric acid.[61,62]

Scheme 24



Independently, Senning used perchloromethyl mercaptan directly, forming the *N*-trichloromethylsulphenylamide derivative (59) which could then be cyclised to the oxathiazolone by the action of a second mole of amide.[63,67] (Scheme 25). Subsequently, other conditions for the second, cyclisation, step have been reported employing water,[64] acid or alkali,[65] or triethylamine.[66]

Scheme 25



(58) (59) (57)

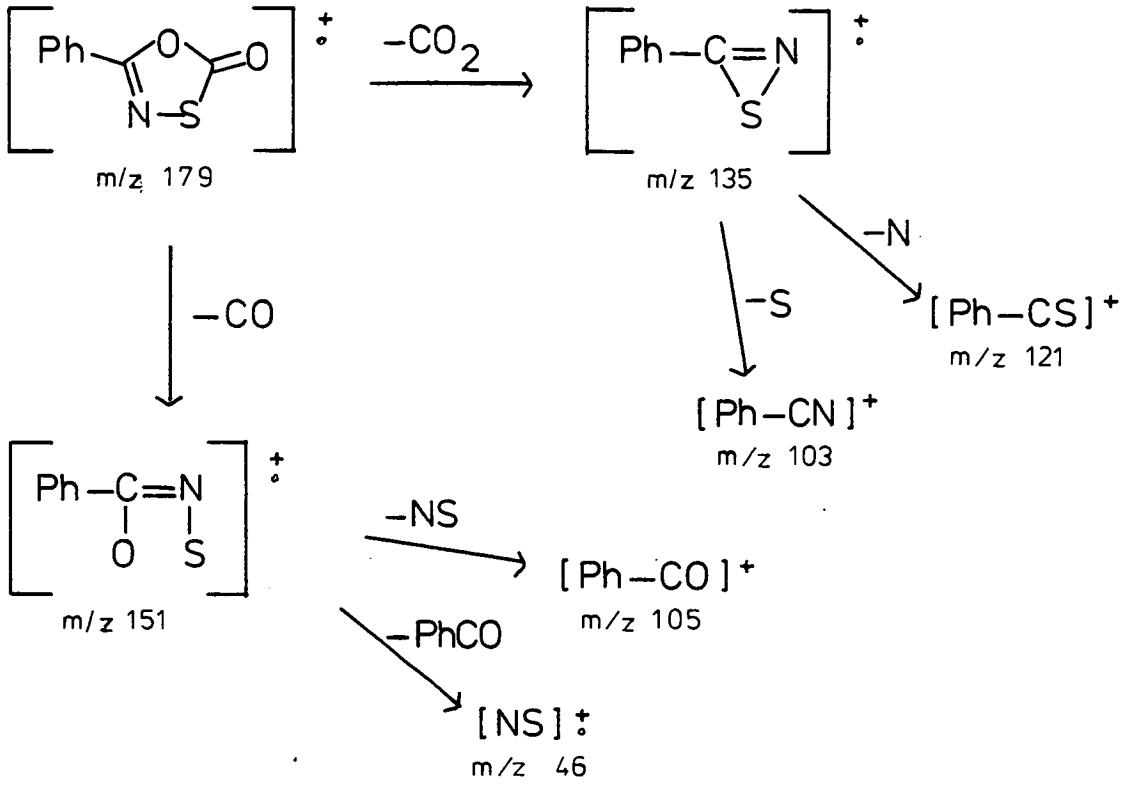
Both general methods of preparation can be performed in a variety of solvents and over a range of temperatures allowing the reactions to be tailored to suit particular substituents. Chlorocarbonylsulphenyl chloride has generally been the reagent chosen in recent synthetic work.

1.5.2 Properties

The molecular structure of the parent oxathiazolone (57; R=H) has been studied using microwave, infrared and Raman spectroscopy and by electron diffraction in the vapour phase. A coplanar structure was established.[68]

The mass spectrum of the 5-phenyl derivative (57; R=Ph) has two fragmentation pathways ascribable to the heterocycle,[63] these are shown in Scheme 26.

Scheme 26

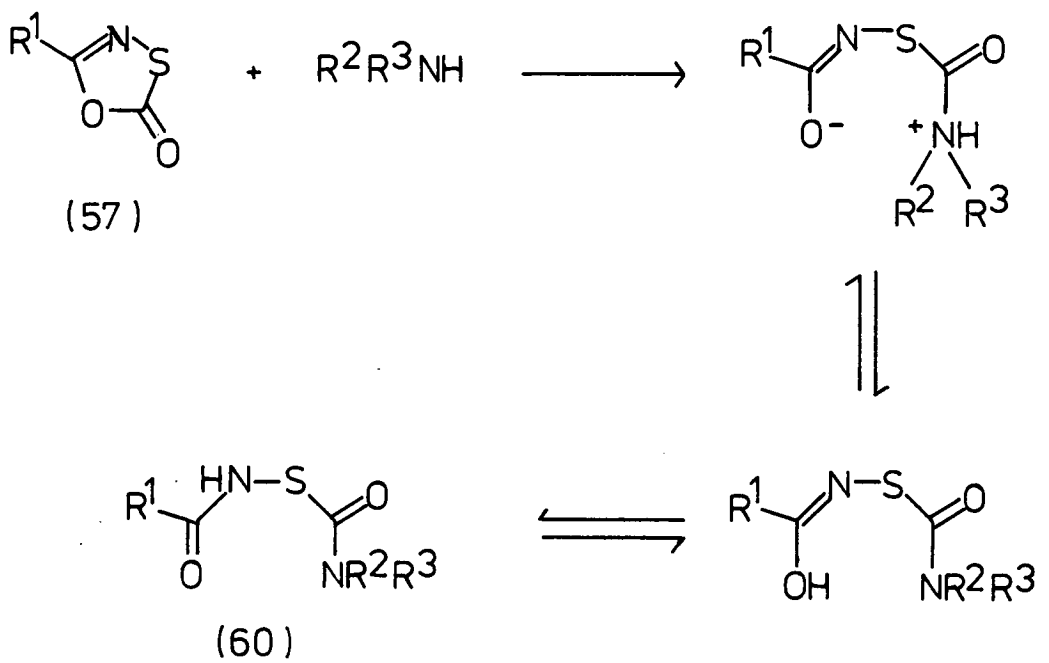


1.5.3 Reactions

Apart from the thermolytic[19] and photolytic[69] cyclo-reversions of oxathiazolones to give the nitrile sulphide 1,3-dipole, which are discussed in Sections 1.3.2 and 1.3.3, few reactions of oxathiazolones are known.

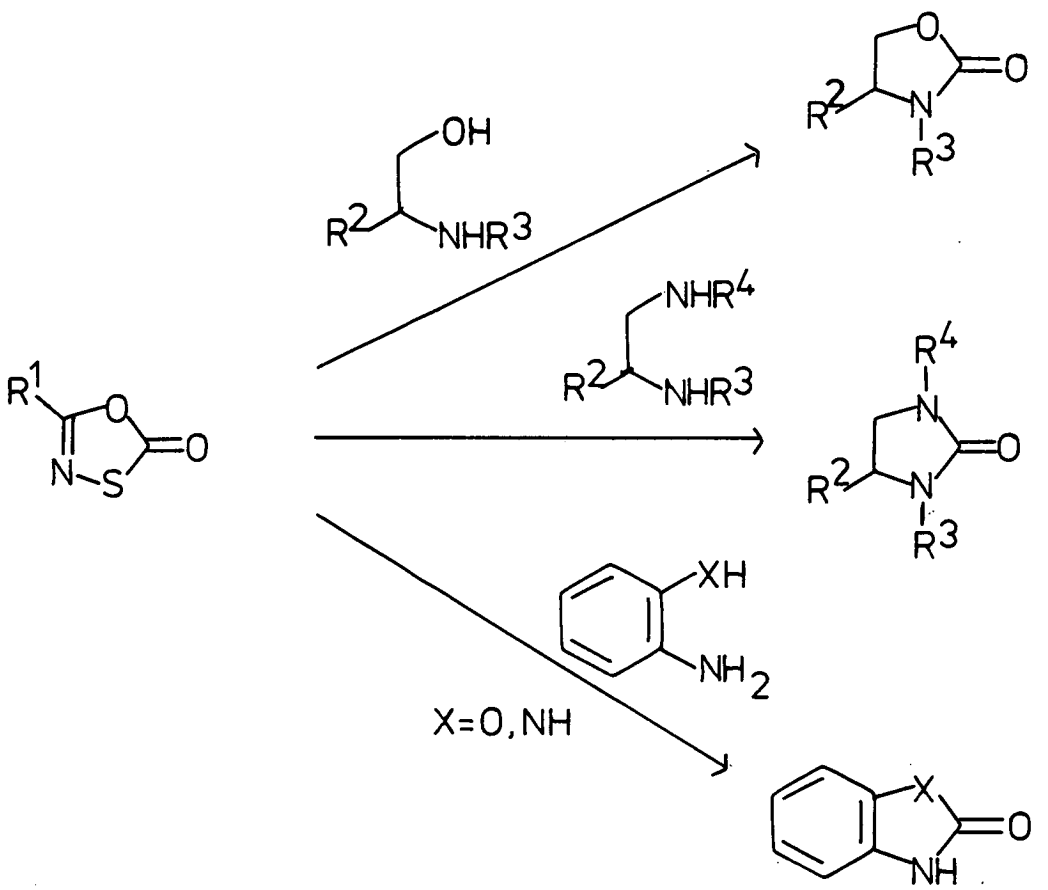
Amines are reported to attack oxathiazolones at the 2-position, with ring cleavage, leading to *N*-acyl-*S*-amino-carbonyl thiohydroxylamines (60),[70] (Scheme 27).

Scheme 27



This reaction has been extended in recent work where the oxathiazolone is used as a carbonylating reagent for the bifunctional compounds 2-aminoalcohols, 1,2-diamines and *o*-aminophenols; oxazoles and imidazoles are formed in good yield,[71] (Scheme 28).

Scheme 28

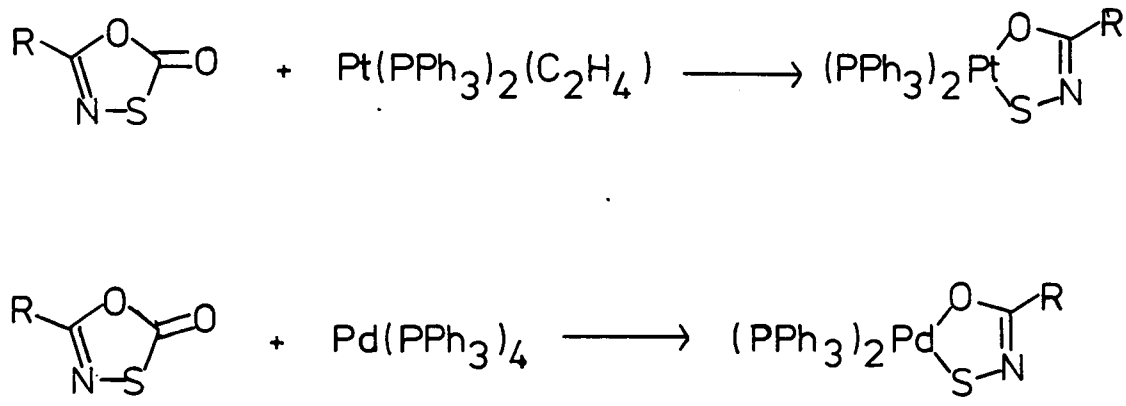


R^1=Ph; 2,4-$Cl_2C_6H_3$-.

Oxidative addition of oxathiazolones to platinum (Ø) and palladium (Ø) compounds has been reported to give complexes with the anion of *N*-thiohydroxamic acid and its derivatives as chelating ligands,[72] (Scheme 29).

When tetrakis(triphenylphosphine) palladium (Ø)is used, liberated triphenylphosphine reacts with the oxathiazolone to produce, nitrile, carbon dioxide and triphenylphosphine sulphide.[72] The reaction appears analogous to the removal of oxygen from nitrile oxides by triphenylphosphine.[73] However, triphenylphosphine is known to remove sulphur from heterocyclic compounds[74] and there is no evidence for nitrile

Scheme 29



R=H, alkyl, alkenyl, aryl.

sulphide itself being involved in the present case.

An extensive study has been made of the effect of the 1,3,4-oxathiazol-2-one-5-yl substituent on electrophilic substitution on an aromatic ring.[75,76] The substituent is found to be *ortho,para* directing and deactivating for the nitration of the aromatic ring.

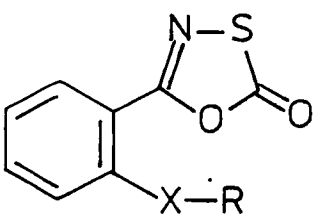
Oxathiazolones bearing alkenyl substituents have been used in polymer chemistry to provide cross-linked polymers by cycloaddition reactions of nitrile sulphides generated from polymer-bound oxathiazolones.[77]

Overall, although oxathiazolones have been used for fifteen years as a source of nitrile sulphides, little else is known about their chemistry.

1.6 OBJECTIVES OF RESEARCH

The original objectives of this project were to perform intramolecular 1,3-dipolar cycloadditions of nitrile sulphides, a type of reaction which had not been reported, and to investigate the chemistry of 1,3,4-oxathiazol-2-ones.

For the first objective compounds having the general structure (61) were chosen for study. These combine an oxathiazolone, as the source of the nitrile sulphide, with an activated dipolarophile. Neither these types of oxathiazolones nor the expected products of their intramolecular cycloadditions were known in the literature and it was hoped that the reaction would provide a useful synthetic route to some novel fused-ring heterocycles.



(61) X = O, NH; R = $COCR^1=CR^2R^3$, $COC\equiv CR^4$

(62) X = O; R = H

(63) X = O; R = $COCH_3$

(64) X = NH; R = $COCH_3$

A further objective, which was developed from the one outlined above, was the investigation of cycloaddition reactions of the *o*-hydroxyphenyloxathiazolone (62), its acetyl derivative (63), and the *o*-acetamidophenyloxathiazolone

(64). The oxathiazolone (62), a literature compound,[76] was involved as a key intermediate in one of the synthetic sequences devised for the *o*-acyloxyphenyloxathiazolones (61, X=O).

The second original objective, that of investigating the general chemistry of oxathiazolones, was not extensively pursued. However, the reactions of oxathiazolones with diazo compounds and with triphenylphosphine were studied and proved noteworthy.

2. DISCUSSION

2.1 SYNTHESIS OF *o*-ACYLOXYPHENYLOXATHIAZOLONES

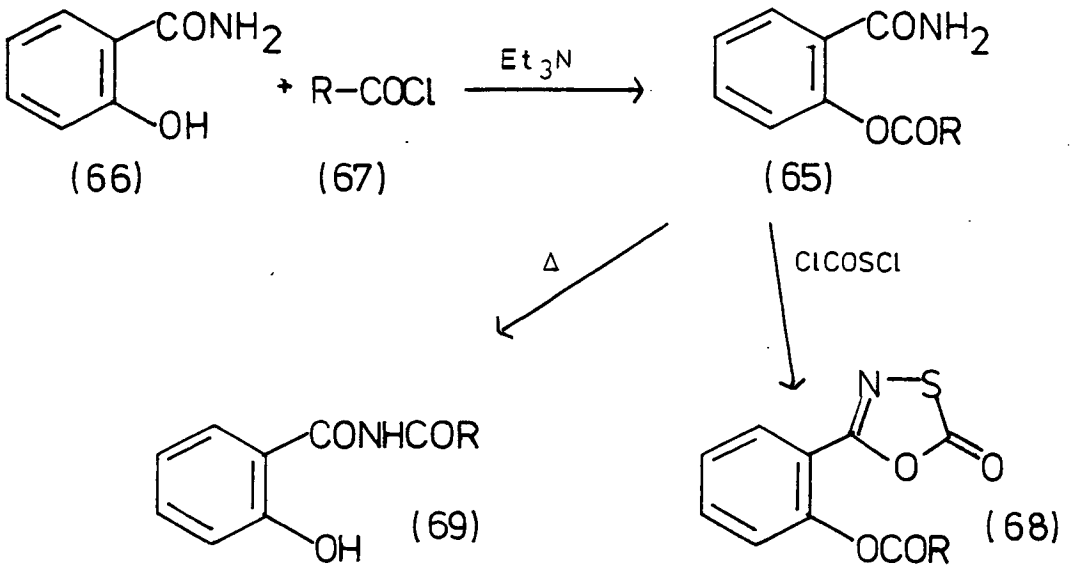
Prior to the present work no compounds of this type had been reported in the literature with the exception of *o*-acetoxyphenyloxathiazolone (63). This had been prepared by Senning and Rasmussen[76] using the method of Mühlbauer and Weiss,[60] that is, from *o*-acetoxybenzamide and chlorocarbonylsulphenyl chloride. This strategy, shown in Scheme 30, was initially employed to synthesise some of the more complex *o*-acyloxyphenyloxathiazolones required here: those bearing a dipolarophile.

o-Acyloxybenzamides (65) were prepared by acylation of salicylamide (66) using the appropriate acid chloride (67) in the presence of a base. *o*-Acyloxyphenyloxathiazolones (68) were obtained from these amides by their reaction with chlorocarbonylsulphenyl chloride.

With the exception of the acetoxy derivatives,[76,78] all the amides and oxathiazolones mentioned above are new compounds. They are generally colourless solids; a number of the oxathiazolones gave very fine, long fibres on recrystallisation.

Their spectroscopic properties are not exceptional and are recorded in the experimental section and the appendices (as are those of all new compounds produced in this work). In a typical pair of examples, the cinnamate esters (65, 68; R=CH=CHPh), the i.r. spectrum of the amide shows NH_2 ($\nu_{max.}$ 3400, 3150 cm^{-1}) and carbonyl [$\nu_{max.}$ 1710

Scheme 30



RCO_2-	Yields % (65)[b]	(68)[c]
acetate[a]	63	16
monoethyl fumarate	92	41
cinnamate[a]	70	60
p-chlorocinnamate	87	51
p-methoxycinnamate	90	37
p-methylcinnamate	95	70
3-(2-furyl)acrylate	93	61
2-furoate	34	62
3-furoate	51	55

Footnotes:

[a] Pyridine used in place of Et_3N. [b] Crude yields.

[c] Recrystallised yields.

(ester), 1680 cm^{-1} (amide)] absorbancies; the carbonyl frequencies of the oxathiazolone are 1759 cm^{-1} (ring) and 1725 cm^{-1} (ester).

In the ^{1}H n.m.r. spectra both groups of compounds show a characteristic aromatic doublet of doublets at *ca.*8 δ p.p.m. which is assigned to the proton *ortho* to the amide or oxathiazolonyl substituent. The ^{13}C n.m.r. signals of the oxathiazolone ring occur at typical[39] values: C-2, *ca.*172 δp.p.m. and C-5, *ca.* 154 δ p.p.m.

The above strategy for the preparation of *o*-acyloxyphenyloxathiazolones has, however, a major drawback. The required *o*-acyloxybenzamide intermediates (65) undergo facile thermal isomerisation in solution to give *N*-acylsalicylamides (69). This phenomenon has been known in the case of the acetyl derivative for many years[78] but is now found to occur for all the compounds of this type examined here, to varying degrees. The isomerisation affects the efficiency of each stage of this synthesis.

In the first stage, the production of the *o*-acyloxybenzamide (65), the problem can be largely overcome. A reaction temperature of below -15°C ensures the sole formation of the desired kinetic product (65). However, it is necessary for the reaction to be very clean as it is difficult to purify the compound without causing its isomerisation to the unwanted thermodynamic product (69). It was found that pyridine, the base used in early literature work, was unsuitable in this respect as it gave rise to by-products; in contrast triethylamine gave excellent results.

The second step of the synthesis requires the

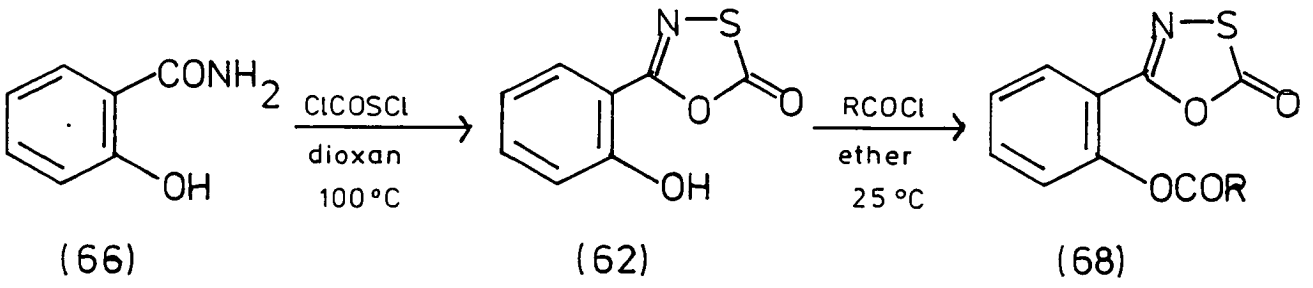
o-acyloxybenzamide to be held in solution either for a lengthy reaction time or at an elevated temperature. In either case the material was found to partially isomerise reducing the yields of the desired oxathiazolone (68).

An alternative and more convenient synthetic route was developed, relying on *o*-hydroxyphenyl-1,3,4-oxathiazol-2-one (62) as a key intermediate. This compound had previously been prepared from salicylamide in 51% yield by Senning and Rasmussen[76] using the method of Mühlbauer and Weiss[60] at a moderate temperature (40-45°C) over 144 hours. Acylation of (62) using the appropriate acid chloride at room temperature in ether was found here to give the required *o*-acyloxyphenyloxathiazolones (68) often in excellent yield (Scheme 31).

The efficiency and convenience of the first step was improved by modifying the conditions. Heating salicylamide with chlorocarbonylsulphenyl chloride under reflux in dioxan (*ca*,100°C) gave a good yield of *o*-hydroxyphenyloxathiazolone (62), 78% recrystallised material, in only 1.5 hours.

In three examples a direct comparison was made between the two routes described. *o*-Acetoxy- and *o*-cinnamoyloxyphenyloxathiazolone, (63) and (70), were produced in 9% and 42% yields respectively by the first described route but in 72% and 66% yields respectively by the second method; these yields are with respect to salicylamide. *o*-Acryloyloxyphenyloxathiazolone (71) could not be made at all by the first route, but was obtainable in 55% yield overall from salicylamide by the second.

Scheme 31



(66) (62) (68)

RCO_2^-	Yield %[a] (68)
acetate	86
acrylate	70
cinnamate	85
2,6-dichlorocinnamate	59
2,4,6-trimethylcinnamate	68
α-methylcinnamate	71
β-methylcinnamate	32
3-phenylpropiolate[b]	40
3-(*p*-chlorophenyl)propiolate	46

Footnotes:

[a] Recrystallised yields from (62). [b] Prepared by Alan Sutherland as part of a B.Sc. Honours project.

The key compound, *o*-hydroxyphenyloxathiazolone (62), is an easily purified, highly crystalline solid with a good shelf life which can be prepared in large batches. Its i.r. spectrum shows hydroxyl ($\nu_{max.}$ 3200 cm^{-1}) and carbonyl ($\nu_{max.}$ 1759 cm^{-1}) resonances. As for the esters derived from it, in the ^1H n.m.r. spectrum there is a characteristic aromatic signal for H-6', in this case a doublet of doublets of doublets (J=8,2,1Hz), at 7.66 δ p.p.m. The hydroxyl proton appears as a sharp peak at 9.70 δ p.p.m.

Apart from this compound's use in the above syntheses the cycloaddition reactions of *o*-hydroxybenzonitrile sulphide, generated by thermolysis of (62), were investigated and are described in Section 2.4.

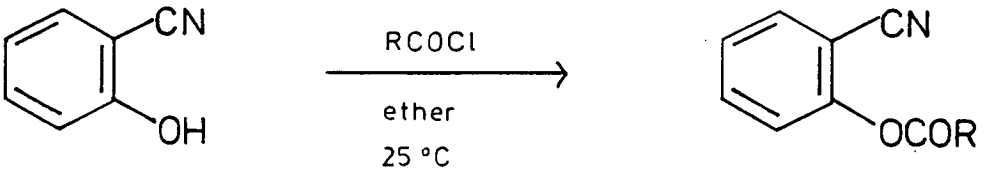
In several instances hereonward *o*-acyloxyphenyloxathiazolones are referred to simply in terms of their carboxylate ester portion and it should be understood that this implies such an ester of *o*-hydroxyphenyloxathiazolone unless otherwise stated.

Corresponding esters (72) of *o*-cyanophenol (73) were prepared by room temperature acylation of (73) using the relevant acid chloride (Scheme 32). With one exception these compounds were unknown in the literature. However, they were only employed here as authentics for the nitriles formed as by-products during thermolysis of the oxathiazolones described above; their chemical properties were not otherwise investigated.

Spectroscopically they are similar to the related amides and oxathiazolones, excepting the nitrile group (i.r.: $\nu_{max.}$ 2238-2225 cm^{-1}) and, more notably, the proton *ortho* to it

which, in their ^{1}H n.m.r. spectra, is not significantly deshielded relative to the other aromatic protons.

Scheme 32



(73) (72)

RCO_2	Yield %[a]
acetate[79]	56[b]
acrylate	100[c]
monoethyl fumarate	89[b]
cinnamate	66
p-chlorocinnamate	29
p-methoxycinnamate	52
p-methylcinnamate	71
2,6-dichlorocinnamate	79
2,4,6-trimethylcinnamate	77
α-methylcinnamate	39[d]
β-methylcinnamate	36
3-(2-furyl)acrylate	68
3- phenylpropiolate	71[e]
3-(*p*-chlorophenyl)propiolate	47
2-furoate	59

Footnotes:

[a] Recrystallised yields except where stated. [b] Distilled. [c] Crude. [d] Prepared by Alan Cunningham. [e] Prepared by Alan Sutherland

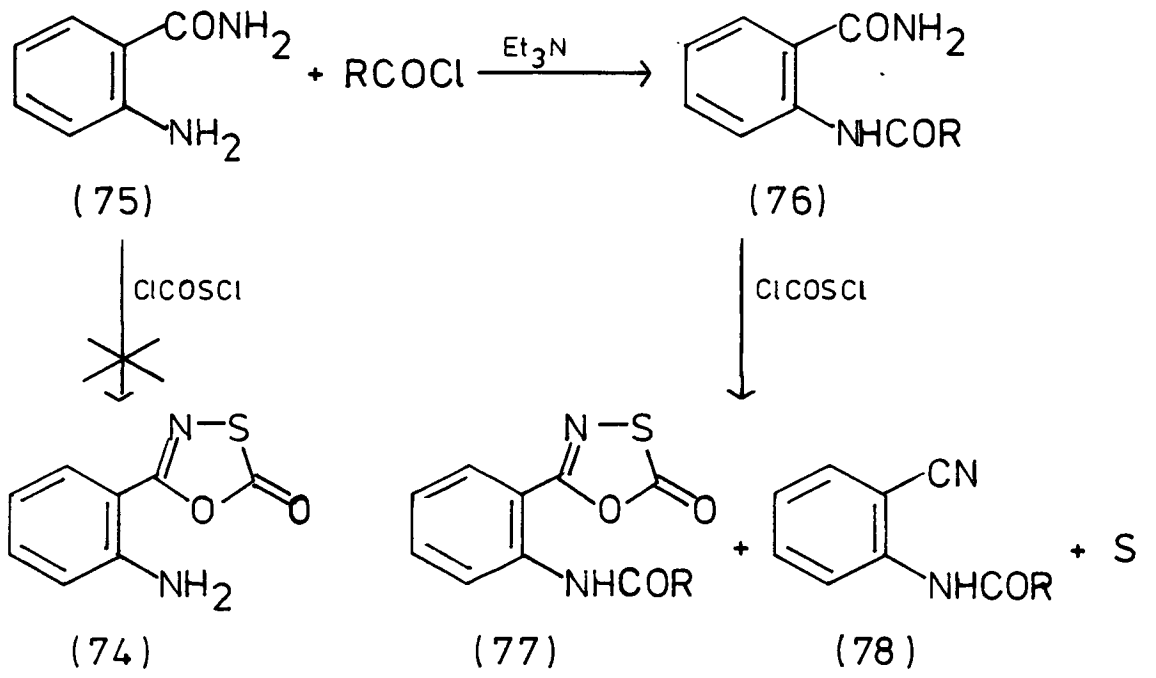
2.2 SYNTHESIS OF *o*-ACYLAMIDOPHENYLOXATHIAZOLONES

No compounds of this type had been reported prior to the present work. It was, therefore, again necessary to develop a suitable synthesis. Two routes were investigated, analogous to those discussed in the previous section for *o*-acyloxyphenyloxathiazolones.

In view of the successful use of *o*-hydroxyphenyloxathiazolone (62) described above, an attempt was made to produce the *o*-aminophenyloxathiazolone (74) by treatment of anthranilamide (75) with chlorocarbonylsulphenyl chloride. However, this reaction yielded a different product and is discussed later in this section.

The alternative strategy *via* *o*-acylamidobenzamides (76) proved successful and is outlined in Scheme 33.

Scheme 33



RCONH	Yield %[a]	
	(77)	(78)
acetamido	17	19
3-phenylpropiolamido	36	b

Footnotes:

[a] From flash chromatography. [b] Not quantified.

Treatment of a solution of anthranilamide (75) and triethylamine in dioxan with the relevant acid chloride at room temperature afforded the required *o*-acylamidobenzamides (76) in reasonable yield without the problems of isomerisation encountered with the *o*-acyloxy analogues.

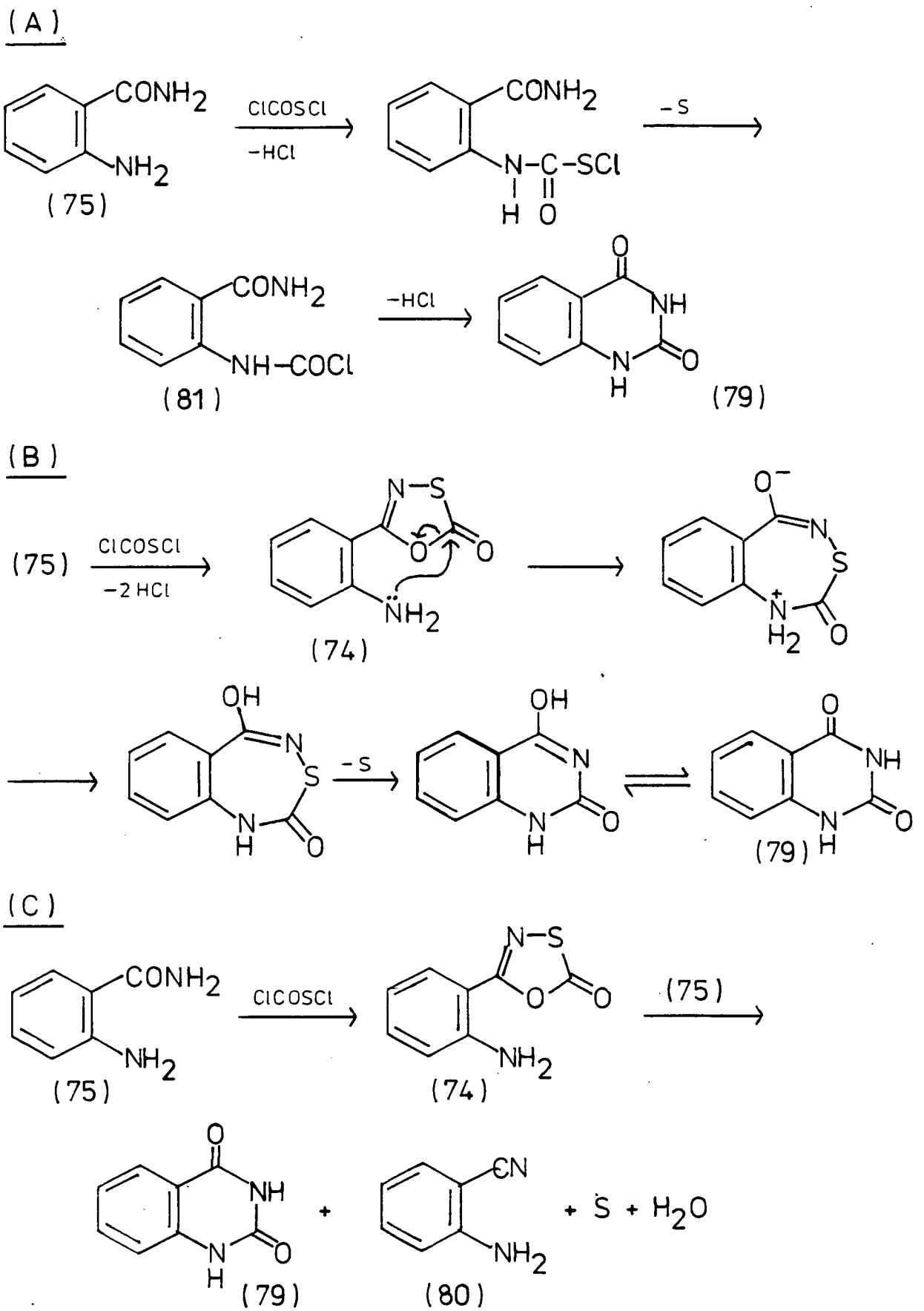
However, the second step of the synthesis was less easily accomplished. The best conditions which could be discovered for production of the *o*-acylamidophenyloxathiazolones (77) involved stirring a mixture of the amide (76) and chlorocarbonylsulphenyl chloride, dissolved in dioxan, at room temperature for *ca.* 48 hours. Under such conditions the reaction did not go to completion but a low to moderate yield of the desired oxathiazolone (77) was obtained.

The reaction was not particularly clean but the product could be separated from impurities by chromatography. By-products included the corresponding *o*-acylamidobenzonitrile (78) and sulphur. However, it is unlikely that these arise *via* thermal decomposition of the oxathiazolone (77) in view of the mild conditions employed. It must be supposed, therefore, that these by-products occur through the involvement of the neighbouring amide group. Authentic *o*-acetamidobenzonitrile[80] was prepared by acetylation of anthranilonitrile.

This nitrile and the above *o*-acylamidophenyloxathiazolones (77) were generally less soluble and higher melting than their oxygen analogues previously discussed; spectroscopically they differed significantly only as a result of the amide linkage.

Returning to the reaction of chlorocarbonylsulphenyl chloride with anthranilamide, the main product obtained was 2,4-quinazolinedione (79). The formation of this compound may be explained in a number of ways by analogy with known reactions of chlorocarbonylsulphenyl chloride and oxathiazolones. Three such reaction pathways are shown in Scheme 34.

Scheme 34

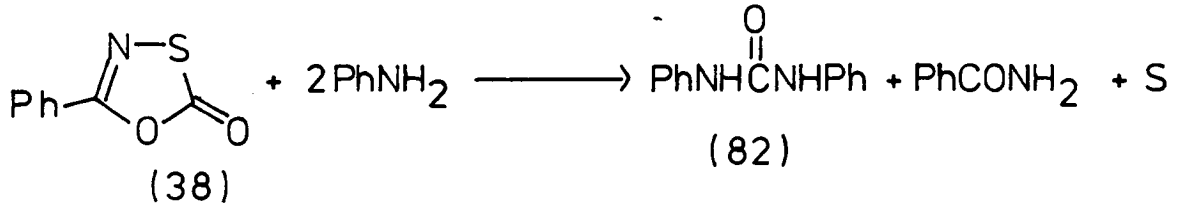

(A)
CONH2
NH2
(75)
ClCOSCl
-HCl
CONH2
N-C-SCl
H O
-S
CONH2
NH-COCl
(81)
-HCl
O
NH
N
H
O
(79)
(B)
(75)
ClCOSCl
-2 HCl
N-S
O
O
NH2
(74)
O⁻
N
S
N
H2
O
OH
N
S
N
H
O
-S
OH
N
N
H
O
NH
N
H
O
(79)
(C)
CONH2
NH2
(75)
ClCOSCl
N-S
O
O
NH2
(74)
(75)
O
NH
N
H
O
(79)
+
CN
NH2
(80)
+ S + H2O

Of these possibilities pathway (A) would seem most probable. Pathways (B) and (C), which depend on the reported reactions of oxathiazolones with amines[70] and difunctional compounds[71] respectively, assume the initial formation of the desired product *o*-aminophenyloxathiazolone (74). However, no trace of this compound was detected at any stage of the reaction. Also, the rate of the reaction was observed to be greater than that expected for the formation of an oxathiazolone. In addition, pathway (C) would also produce anthranilonitrile (80) which was not detected.

In contrast, pathway (A) relies on a known[62] reaction of chlorocarbonylsulphenyl chloride with amines to give a carbamoyl chloride (81) followed by a ring closure, with loss of HCl, to give the observed product.

In the same vein, the stability of phenyloxathiazolone (38) in the presence of aniline was investigated. The compounds were stirred together at room temperature in xylene for ten days. Under such conditions the phenyloxathiazolone was found to be essentially stable although a minor product, diphenylurea (82), was detected (Scheme 35). Its formation is analogous to the reported[71] reaction of diamines with oxathiazolones where a carbonyl group is inserted between two amine functions.

Scheme 35



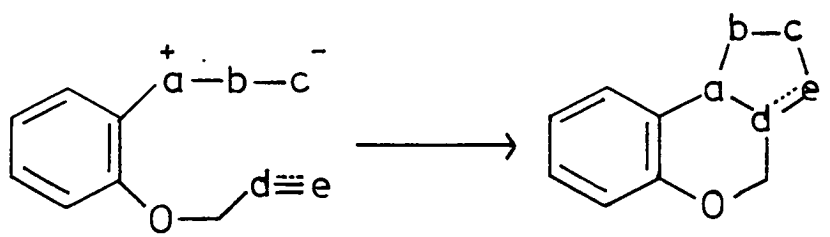
(38) (82)

2.3 INTRAMOLECULAR CYCLOADDITION REACTIONS OF NITRILE SULPHIDES

2.3.1 Introduction

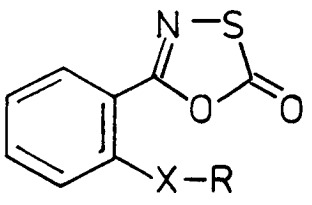
The number of examples of intramolecular 1,3-dipolar cycloadditions which have been reported in the literature steadily increases from year to year.[2,24,81] Most types of 1,3-dipole have been involved but, until the present work, there had been no report of an intramolecular cycloaddition involving a nitrile sulphide. Dipolarophile units have generally been alkenes or alkynes although nitriles and carbonyl compounds have also been employed. A number of such reactions have been discussed in Section 1.2.

In many examples the link between the dipole and the dipolarophile has been provided by an *ortho*-disubstituted benzene ring with other chain units being added to give the molecule a suitable geometry favouring cycloaddition. For instance, several of the compounds previously studied have had the general structure (83),[24,81] which on cycloaddition give the tricyclic structure (84).

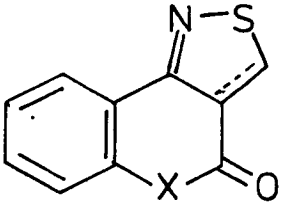


(83) (84)

For cycloaddition involving a nitrile sulphide an electron deficient dipolarophile is required. Molecules with the general structure (61) were chosen as satisfying the requirements of having an activated dipolarophile in a suitable relationship to the oxathiazolone ring which was to serve as a precursor to the nitrile sulphide dipole. Synthetic routes to these compounds have been discussed in the preceding sections.



(61)



(85)

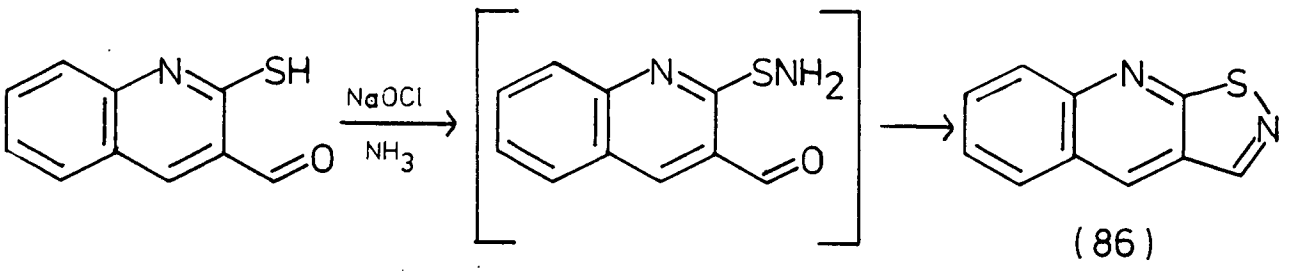
X=O, NH ;

R=$-COCR^1=CR^2R^3$;

$-COC\equiv CR^4$.

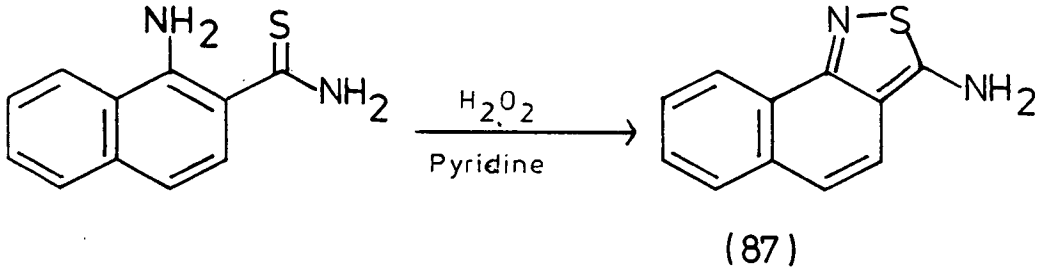
The anticipated products of such cycloadditions would contain the general part-structure (85) which has a novel mode of ring fusion whether X=O or X=NH. Examples of isothiazoles fused to other heterocycles are relatively limited. For instance, the recent reference work "Comprehensive Heterocyclic Chemistry"[82] cites only one tricyclic type, the isothiazolo[5,4-*b*]quinoline (86) (Scheme 36),[83] and its derivatives.[84]

Scheme 36



However, the naphtho[1,2-*c*]isothiazole (87) having the same general mode of fusion as (85) is also known (Scheme 37).[85]

Scheme 37

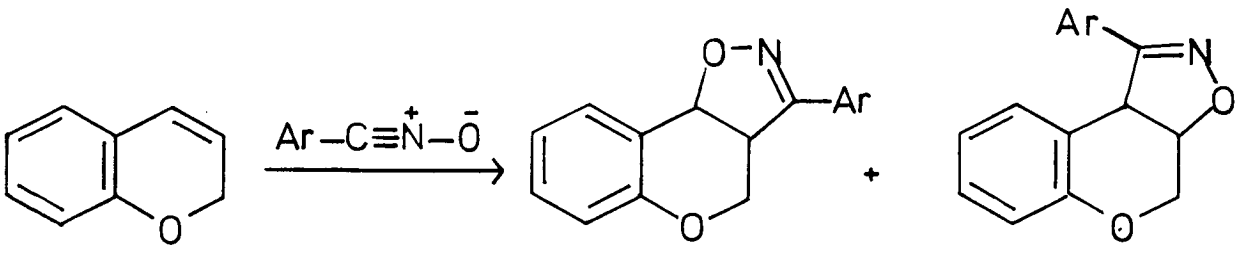


In addition a number of closely related isoxazole and isoxazoline analogues are known (Scheme 38) including some produced by intramolecular 1,3-dipolar cycloadditions: (88) and (89).

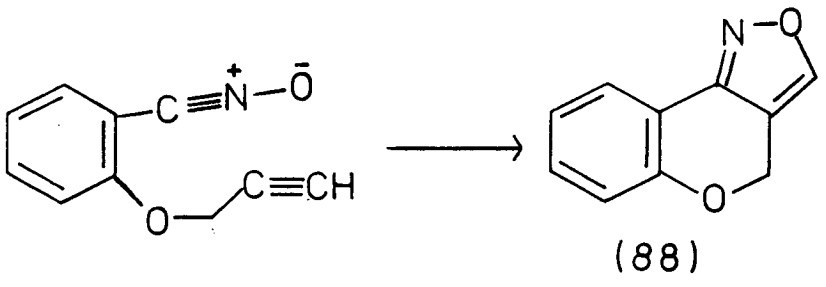
The reactions described below and in Section 2.4 demonstrate the utility of nitrile sulphides in the preparation of heterocycle-fused isothiazoles and point the way to further development in this area.

In consequence of the relative ease of synthesis of

Scheme 38

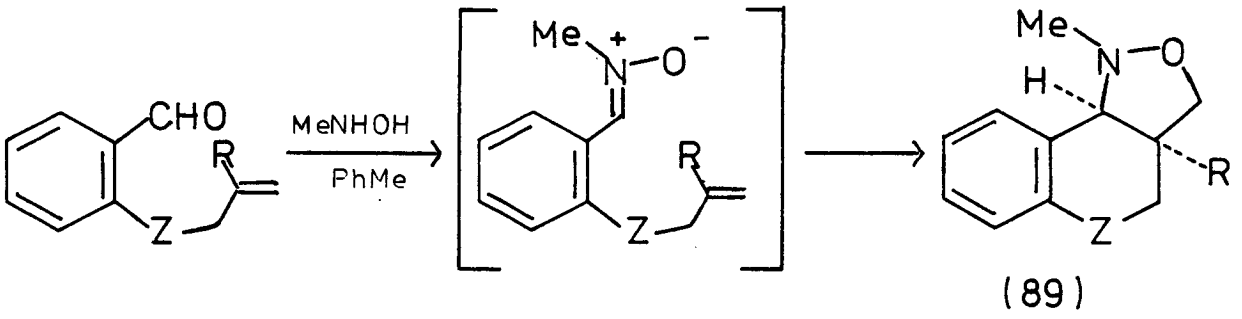


Ar = Mesityl; Reference 86a



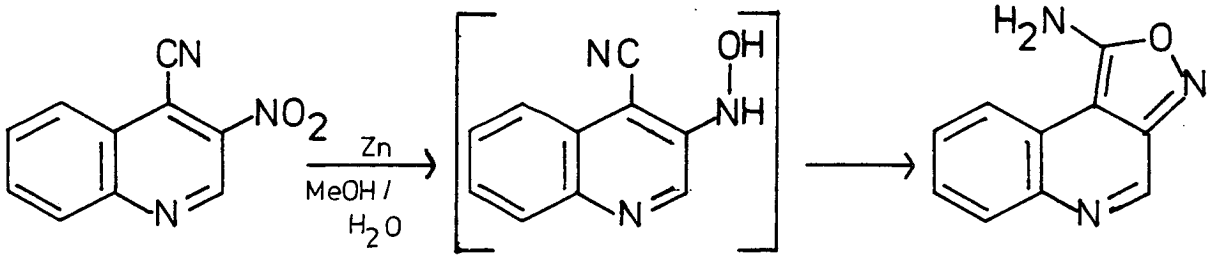
(88)

Reference 86b



(89)

Z = O, NHCO; Reference 86c



Reference 87

compounds (61, X=O) having the ester linkage the reactions of this group have been studied much more extensively than those with the amide linkage (61, X=NH).

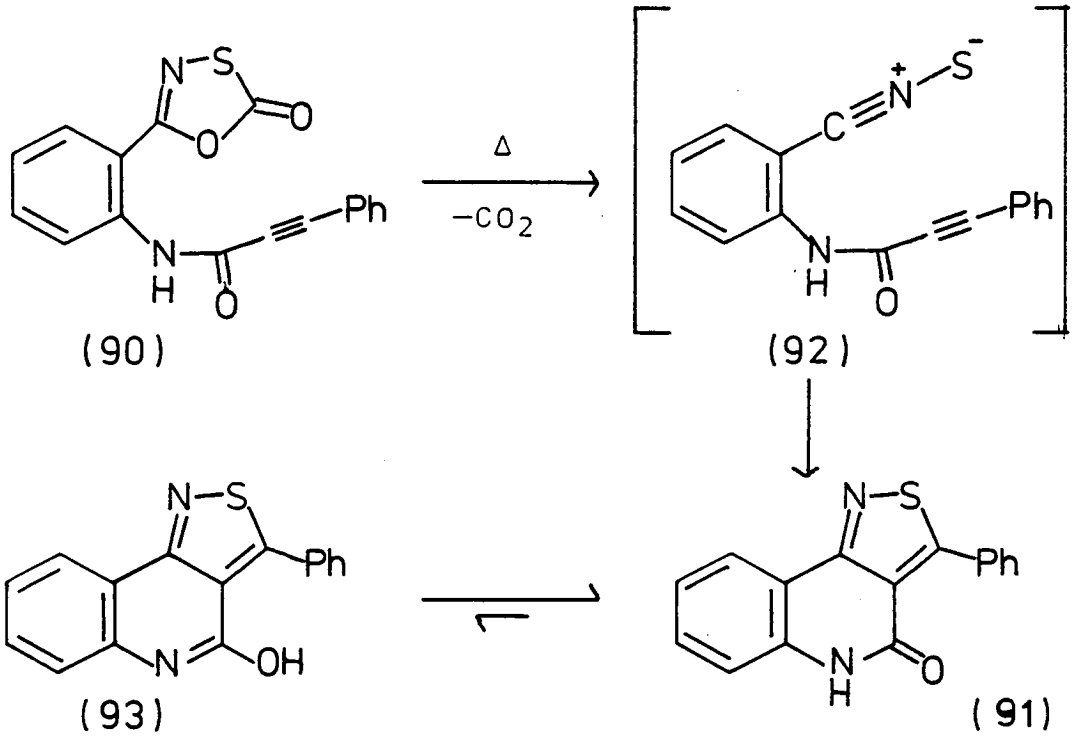
Thermolyses of the oxathiazolones (61) were carried out by heating the compound in sodium dried xylene under reflux at a temperature of *ca.* 138°C. Heating was continued until no starting material could be detected by h.p.l.c., which generally took from 14 to 16 hours. In many cases yields were determined by h.p.l.c. analysis after isolation of pure samples of the products.

2.3.2 Thermolysis of Oxathiazolones Bearing an Alkyne Substituent

2.3.2.1 3-Phenylpropiolamido Substituent

Thermolysis of 5-[*o*-(3-phenylpropiolamido)phenyl]-1,3,4-oxathiazol-2-one (90) under the conditions mentioned gave a single product, 3-phenylisothiazolo[4,3-*c*]quinolin-4(5*H*)-one (91), *via* intramolecular 1,3-dipolar cycloaddition of the nitrile sulphide to the adjacent acetylene in intermediate (92). The product (91) was obtained on cooling of the reaction mixture in 81% yield as a highly crystalline solid (Scheme 39).

Scheme 39

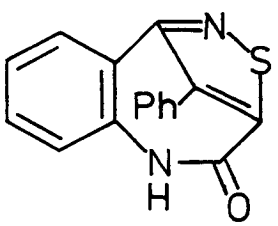


The compound is high melting (m.p. 303-304°C) and exceedingly insoluble in most common organic solvents.

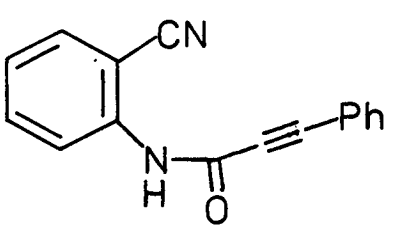
Its identity was confirmed by its mass spectrum [*m/z* 278 (M^+)], its i.r. spectrum [$\nu_{max.}$ 3130 (NH); 1675 cm^{-1} (CO)] and its n.m.r. spectra, particularly the ^{13}C n.m.r. spectrum which can be compared to related products obtained in other reactions (*vide infra*). Such a comparison is displayed in Table 3, page 72.

The product is thought to exist as the 5*H* tautomer [as opposed to the 2-hydroxyquinoline form (93)] partly on the basis of its i.r. spectrum, which shows typical amide signals, and also by analogy with 2-hydroxyquinoline itself which has been shown to exist predominantly as its 2-oxo form.[88]

In this reaction, and in the similar examples which follow, it is not unexpected that a single regioisomer is formed. The geometrical constraints of the dipole-dipolarophile linkage preclude the alternative bridged product (94).



(94)



(95)

It is more surprising that in this reaction no trace of *o*-(3-phenylpropiolamido)benzonitrile (95) or products derived from it could be detected. This by-product would be expected to arise together with sulphur by fragmentation of the nitrile sulphide (92), a process which competes with cycloaddition in most reactions of this dipole.[54]

Some light is thrown on this by observations made of

the melting-point behaviour of the starting oxathiazolone (90). On initial melting at 163-165°C bubbles of a gas were seen to form in the melt. After cooling and resolidification the same sample was reheated and found to melt at 297-300°C; the product (91) described above had a melting point of 303-304°C. The parity between these two values suggests that this intramolecular cycloaddition is almost quantitative, even in the concentrated conditions of a melt. Such conditions would be expected to maximise fragmentation of the nitrile sulphide as this process is considered to be bimolecular.[56]

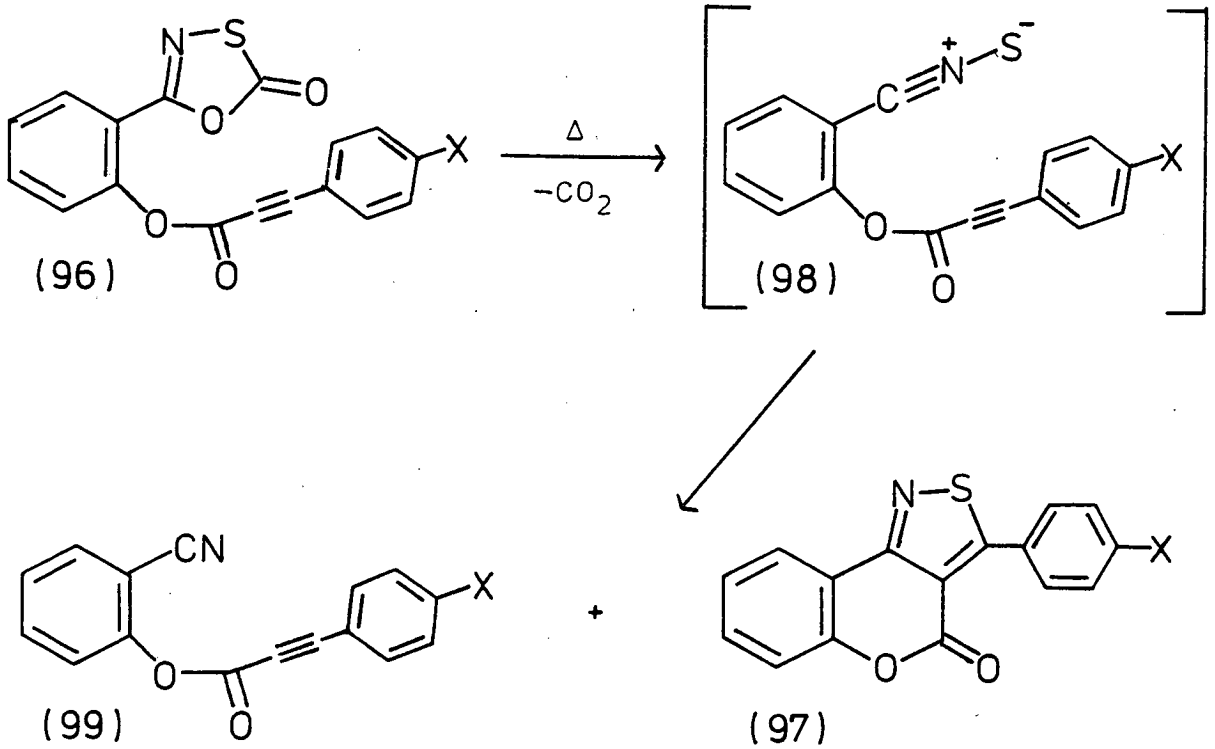
2.3.2.2 3-Phenyl- and 3-(*p*-Chlorophenyl)-propiolate Ester Substituents

Thermolysis of the 3-phenylpropiolate esters of *o*-hydroxyphenyloxathiazolone (96a and b) gave similar results to that described above (Scheme 40).

5-[*o*-(3-Phenylpropioloyloxy)phenyl]-1,3,4-oxathiazol-2-one (96a) was prepared, and its reactions studied by Alan Sutherland as part of his B.Sc. Honours project.

Thermolysis of (96a) gave as the major product 4-oxo-3-phenyl-4*H*-chromeno[4,3-*c*]isothiazole (97a) *via* an intramolecular cycloaddition reaction of the nitrile sulphide (98a). Only a trace of *o*-cyanophenyl 3-phenylpropiolate (99a) could be detected in the reaction mixture; however, it was established that this nitrile was essentially stable under the conditions of the thermolysis.

Scheme 40



	Yields %[a]	
	(99)	(97)
a; X=H	<1%	69%
b; X=Cl	74%	19%

Footnote:

[a] Determined by h.p.l.c.

In contrast, under similar conditions, thermolysis of (96b) gave only a 19% yield of the cycloaddition product, 3-(*p*-chlorophenyl)-4-oxo-4*H*-chromeno[4,3-*c*]isothiazole (97b), but a 74% yield of *o*-cyanophenyl 3-(*p*-chlorophenyl)propiolate (99b). It is difficult to explain either the large difference in reactivity between the two oxathiazolones (96a) and (96b) or the virtual absence of the nitrile (99a) on thermolysis of (96a).

The structures of the chromenoisothiazole products were confirmed by their spectroscopic properties. Mass spectra showed the expected parent ion peaks for compounds (97a and b): *m/z* 279 (M^+) and *m/z* 315/313 (M^+) respectively; i.r. spectra displayed carbonyl stretching frequencies fairly typical for δ-lactones [(97a): $\nu_{max.}$ 1730 cm^{-1}; (97b): $\nu_{max.}$ 1750 cm^{-1}].

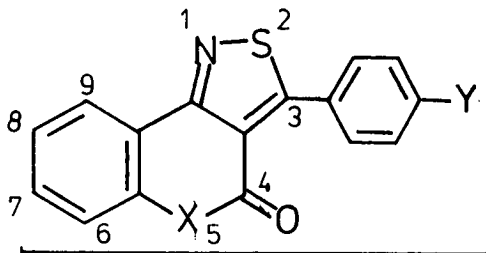
^1H N.m.r. spectra were not useful diagnostically but a characteristic aromatic doublet of doublets was again present [(97a): 8.27 δ p.p.m., J=8, 1.3Hz; (97b): 8.30 δ p.p.m., J=8, 2Hz]. This is assigned to H-9 in the chromenoisothiazole ring system.

^{13}C N.m.r. spectroscopy has been a particularly useful tool in the determination of the structures of these compounds and of most of the other products obtained in this work. Fully proton coupled ^{13}C n.m.r. spectra have been employed in a number of cases.

For the chromenoisothiazoles the ^{13}C n.m.r. spectra are consistent with the proposed structure. Correlation with the spectra of all the related compounds prepared here (*vide infra*) has allowed assignment of most of the important resonances, despite a slightly ambiguous fully coupled spectrum for compound (97a). The ^{13}C n.m.r. spectra of compounds (97a,b) and (91) are displayed in Table 3.

In a more extensive comparison of the ^{13}C n.m.r. spectra of ten related chromenoisothiazoles (Appendix 4.3.2) it is found that much of the framework is unaffected by variations in the substitution at C-3. The resonances for C-5a (152.2-152.8 δ p.p.m.), C-9a (116.1-117.3 δ p.p.m.),

Table 3. ^{13}C N.m.r. Spectra of Chromenoisothiazoles (97a,97b) and Isothiazoloquinoline (91)



(91): X=NH, Y=H. (97a): X=O, Y=H. (97b): X=O, Y=Cl.

Compound	C-3	C-9b	C-4	C-5a	ArCH	C-4'	2ArCH	C-1'	2ArCH	ArCH	ArCH	C-3a	C-9a	ArCH
	δ_C p.p.m.													
(91)[a,c,e]	173.42	162.95	157.58	137.91	130.78	129.74	129.25	128.76	127.98	123.51	122.07	121.57	116.18	115.62
(97a)[b,d,f]	177,91	162.43	156.24	152.32	131.78	130.84	129.22	128.05	128.60	124.58	124.04	117.13	116.73	116.88
(97b)[a,d,g]	176.59	162.81	156.37	152.62	132.04	137.44	130.64	126.69	129.07	124.81	124.30	117.33	117.24	117.10

Footnotes:

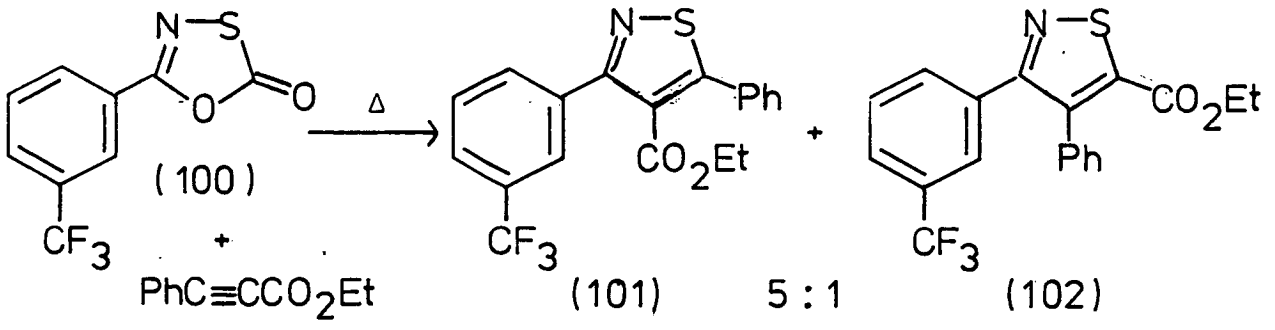
[a] 50 MHz. [b] 20 MHz. [c] Solvent and standard $(CD_3)_2SO$. [d] Solvent and standard $CDCl_3$.

[e] 357K. [f] 298K. [g] 303K.

C-9b (161.2-162.8 δ p.p.m.) and the other fused benzo carbons occur within tight ranges. The signals for carbons C-3, C-3a and to a lesser extent the carbonyl C-4 are, however, shifted by changes in the C-3 substituent. These observations have been useful in recognising part-structures of other compounds described in later sections whose constitutions were less easily determined.

An intermolecular analogue of the present reaction has been reported by Howe *et al.*[20] who thermolysed oxathiazolone (100) (Scheme 41) in the presence of a ten-fold excess of ethyl 3-phenylpropiolate. A mixture of the isothiazole carboxylates (101) and (102) was formed; the yields were 47% and 9.5% respectively (determined by g.c.).

Scheme 41



It is interesting to note that the regioselectivity of this reaction strongly favours the isothiazole-4-carboxylate (101),[20] whereas for ethyl propiolate itself, with the same oxathiazolone, there is little preference between the isothiazole-4 and 5-carboxylates.[20] In the intramolecular reactions discussed here the isothiazole-5-carboxylate is precluded by steric factors.

In summary, nitrile sulphides produced by the thermolysis

of oxathiazolones undergo intramolecular 1,3-dipolar cycloaddition to activated acetylene substituents giving novel polycyclic [*c*]-fused isothiazole derivatives.

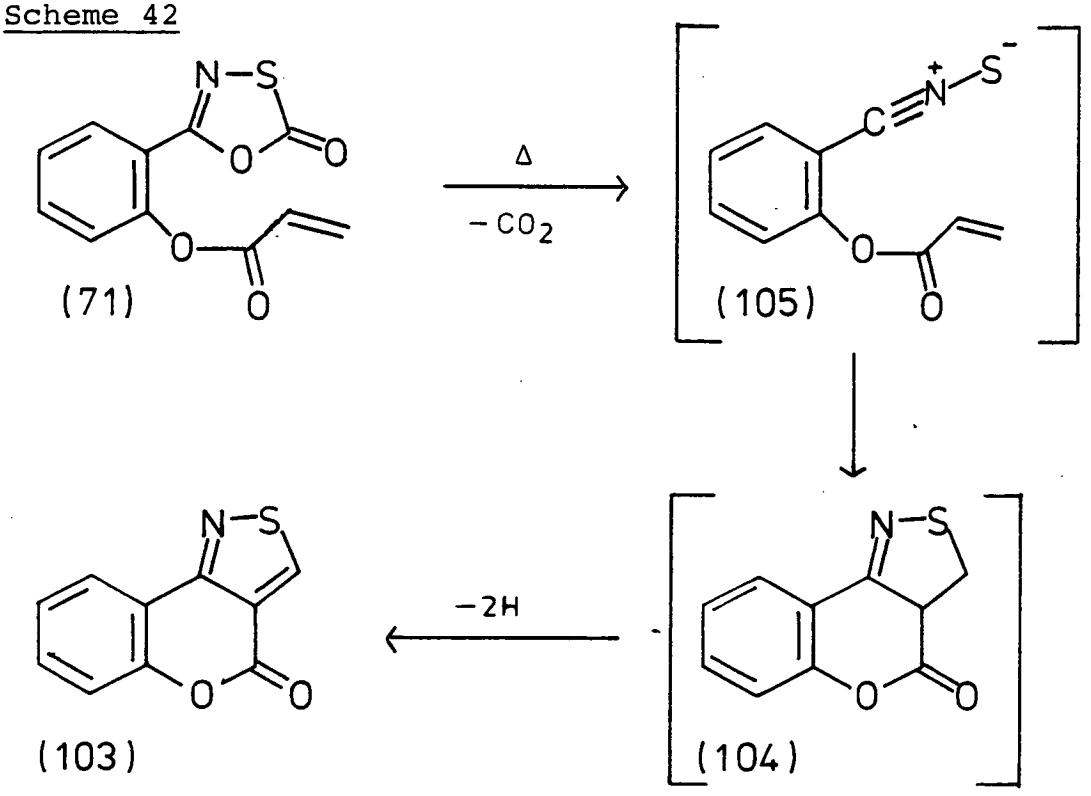
2.3.3 Thermolysis of Oxathiazolones Bearing an Alkene Substituent

A series of oxathiazolones formally derived from acrylate esters of *o*-hydroxyphenyloxathiazolone, and so bearing alkene substituents, has been synthesised and the thermolysis of each has been studied.

2.3.3.1 The Acrylate Ester

The parent member of this series, oxathiazolone (71), was thermolysed under the standard conditions mentioned above; from the reaction mixture 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole (103) was isolated in 24% yield. It was presumed that this was formed by a rapid dehydrogenation of the isothiazoline derivative (104) which would result from intramolecular cycloaddition of nitrile sulphide (105) as shown in Scheme 42.

Scheme 42



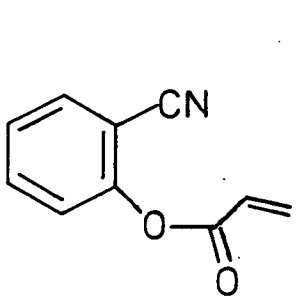
The product was clearly the chromenoisothiazole (103) as opposed to the chromenoisothiazoline (104) as evidenced by its n.m.r. spectra. No saturated C-H resonances were observed, but a sharp 1-H singlet at 9.72 δ p.p.m. in the ^{1}H n.m.r. spectrum is assigned to H-3. This corresponds to a strong signal at 156.77 δ p.p.m. in the ^{13}C n.m.r. spectrum which otherwise resembles a typical chromenoisothiazole as discussed in Section 2.3.2.2.

The oxidation of (104) to (103) was not entirely unexpected as it is known that Δ^2-isothiazolines undergo easy dehydrogenation to give isothiazoles. In the presence of good oxidising agents such as naphtho- or benzo-quinones,[17,49] or hypochlorite with a phase transfer catalyst,[89] Δ^2-isothiazolines are oxidised rapidly. They are also known to oxidise more slowly on heating in the presence of sulphur and air,[89] or simply on standing in solution in acetone for several days.[17]

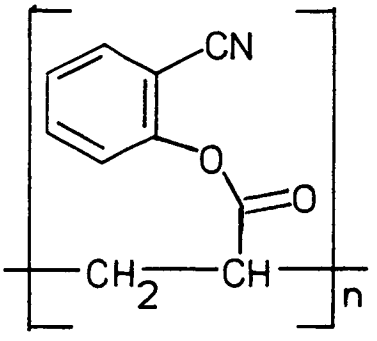
In the present case fragmentation of the nitrile sulphide is likely to result in reactive sulphur species[56] which may take part in this oxidation. At no stage of the reaction could any intermediates be detected by h.p.l.c. suggesting that the rate of oxidation is fast. This may imply a strong driving force for the formation of the chromenoisothiazole ring system.

The expected nitrile by-product (106) could not be detected in the reaction mixture at any stage. However, an authentic sample prepared by acylation of *o*-cyanophenol was found to polymerise rather easily even at moderate

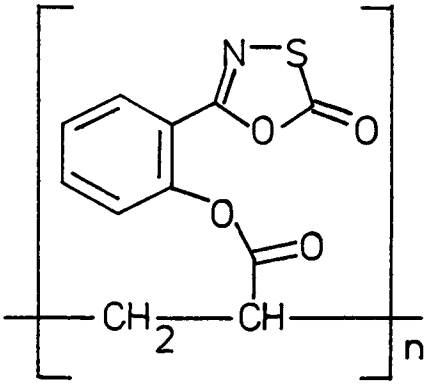
temperatures. It is, therefore, likely that under the reaction conditions this by-product has polymerised. It was found that washings from the chromatography column used to work up the reaction showed a nitrile absorbance ($\nu_{max.}$ 2230 cm^{-1}) in their i.r. spectrum. This may be due to the polymerised nitrile by-product (107).



(106)



(107)



(108)

Polymer (107) might also arise *via* thermolysis of an initial product (108) formed by polymerisation of the starting material (71). Similar polymeric oxathiazolones have been prepared[77,90] and their reactions and properties studied.

At this point it might be noted that cross reaction products, formed by cycloaddition of one nitrile sulphide intermediate to the dipolarophile portion of a second molecule, were not observed in any of the reactions described here. A dilute solution (0.04M) of oxathiazolone was generally used in thermolyses while in the above example a further dilution to 0.01M oxathiazolone was used in an attempt to reduce polymerisation. A parallel experiment in which

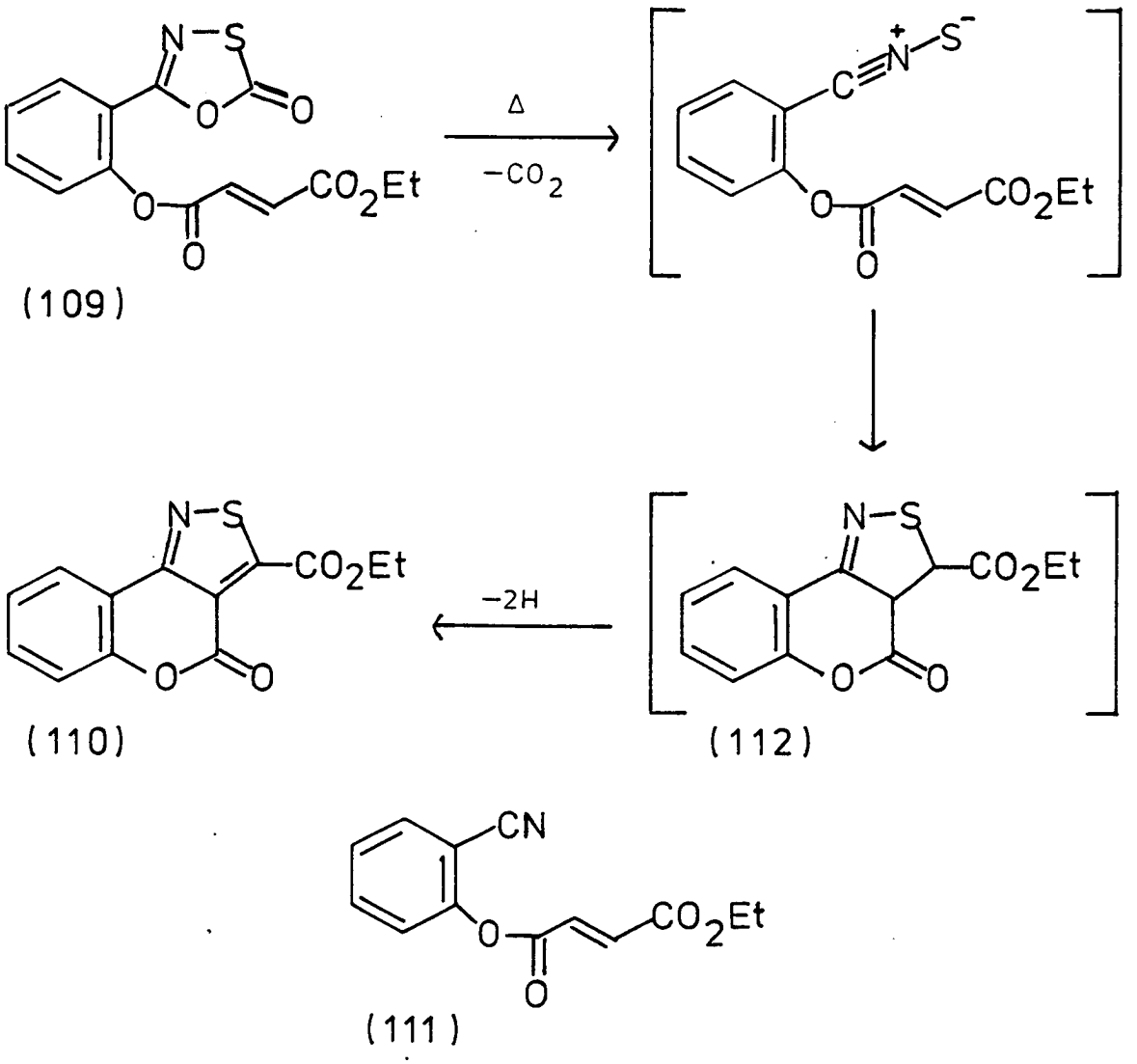
the reaction solution contained the inhibitor hydroquinone monomethyl ether and had been flushed with nitrogen gave an identical yield of chromenoisothiazole (103) as judged by h.p.l.c.

2.3.3.2 The Mono Ethyl Fumarate Ester

Thermolysis of oxathiazolone (109) gave results similar to those described above for the acrylate ester. A single major product, ethyl 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylate (110) (Scheme 43), was isolated in 28% yield; a number of unidentified coloured by-products were also present in the reaction mixture. o-Cyanophenyl ethyl fumarate (111), could not be detected at any stage of the reaction.

As in the previous example it is assumed that the chromenoisothiazole (110) is produced by rapid oxidation of the initial intramolecular cycloadduct, the chromenoisothiazoline (112), under the reaction conditions.

Scheme 43



(109) (110) (111) (112)

The product shows typical spectroscopic properties for its class with the exception of the C-4 signal in its ^{13}C n.m.r. spectrum. This is shifted upfield to 153.80 δ p.p.m. compared to a range of 156.2-156.8 δ p.p.m. for a compound with an aromatic C-3 substituent; the C-3 and C-3a signals are also shifted but these vary fairly widely over the whole class. The homologous methyl ester described in Section 2.4.2 shows a similar effect.

2.3.3.3 The Cinnamate Esters

The thermolysis of cinnamate esters of *o*-hydroxyphenyloxathiazolone has been studied in more detail than the examples discussed above as a rather interesting mixture of products was generally obtained. An attempt has also been made to explain the mechanism of their formation.

The *para*-substituted cinnamate esters of *o*-hydroxyphenyloxathiazolone (113b,c,d) each gave four products, in addition to sulphur, on thermolysis. These were identified by their spectroscopic properties (*vide infra*) and are shown in Scheme 44 with their yields in Table 4.

Scheme 44

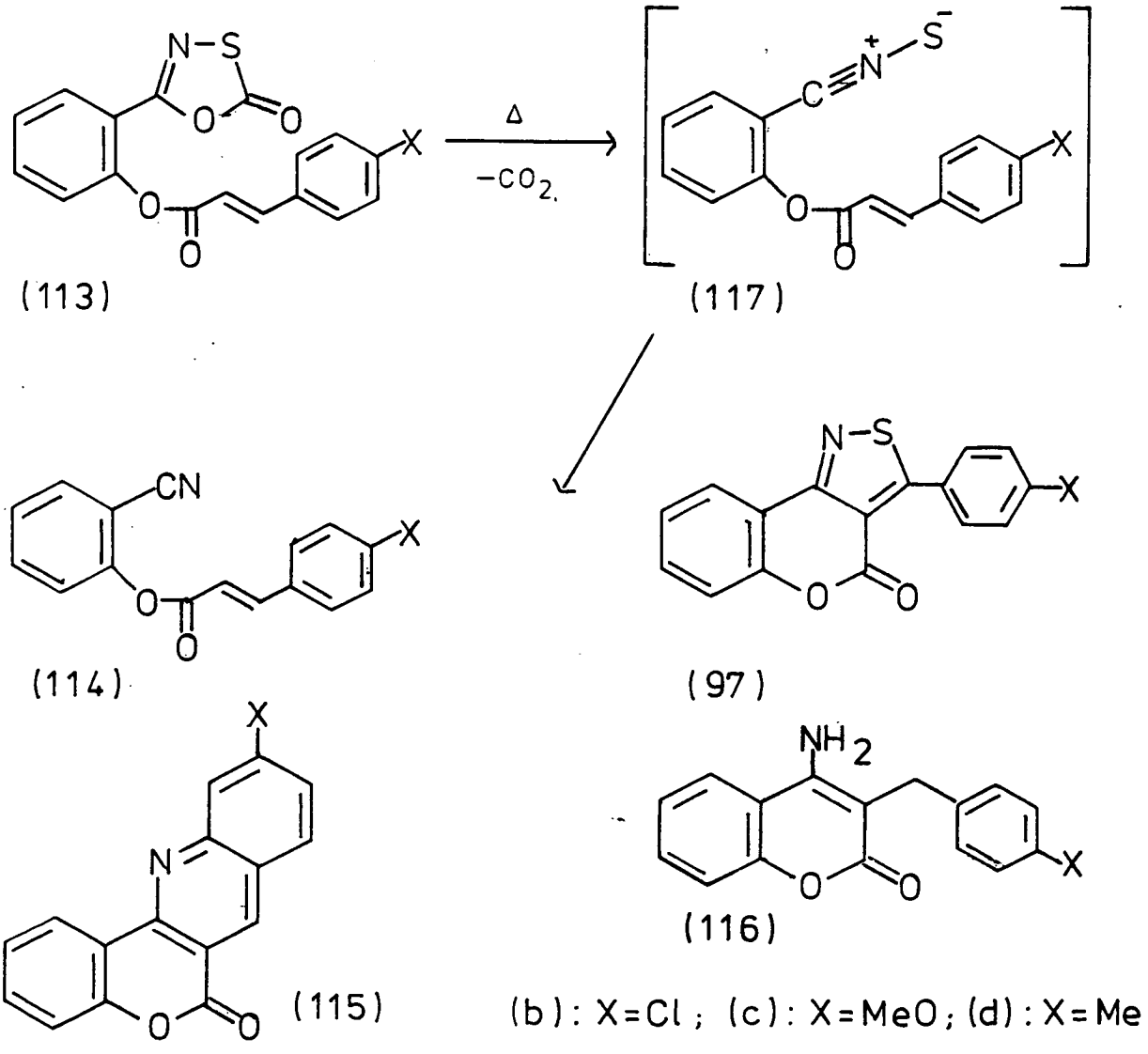


Table 4

Thermolysis of Cinnamate Esters: Product Yields

Oxathiazolone (113)	X=	Yields % (114)[a]	(97)[a]	(115)[a]	(116)
(a)	H	27	14	13	b
(b)	Cl	33	21	8	28[c]
(c)	MeO	35	14	14	12[d]
(d)	Me	34	30	3	25[d]

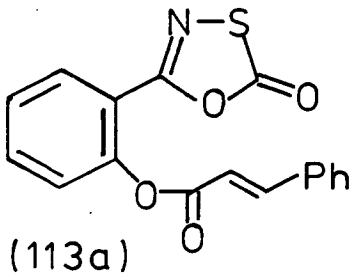
Footnotes:

[a] Determined by h.p.l.c. [b] Not isolated.

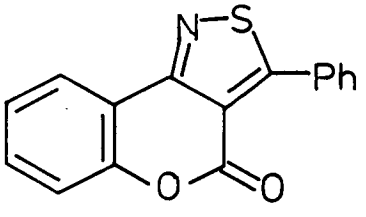
[c] From column chromatography. [d] Isolated as precipitates.

For example, thermolysis of 5-[*o*-(*p*-methoxycinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113c) yielded *o*-cyanophenyl *p*-methoxycinnamate (114c), 3-(*p*-methoxyphenyl)-4-oxo-4*H*-chromeno[4,3-*c*]isothiazole (97c), 10-methoxy-6-oxo-6*H*-chromeno[4,3-*b*]quinoline (115c) and 4-amino-3-(*p*-methoxybenzyl)-2-oxo-2*H*-chromene (116c).

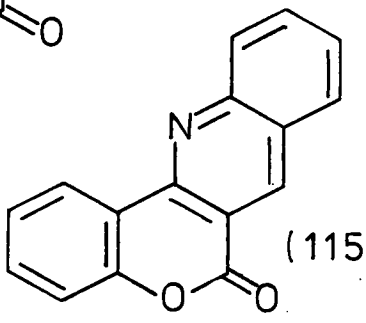
Thermolysis of the unsubstituted cinnamate ester (113a, X=H) which, chronologically, was the first case to be studied, gave a slight variation on these results. The nitrile (114a), chromenoisothiazole (97a) and chromenoquinoline (115a) products were all isolated (yields in Table 4), but the aminochromene (116a) was not detected. However, a fourth product was formed as a precipitate from the refluxing reaction mixture. The identity of this product has not been confirmed but, as it is of some interest, its properties are discussed in detail in Section 2.3.3.4.



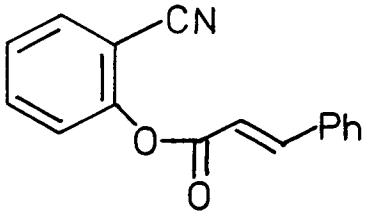
(113a)



(97a)



(115a)



(114a)

The aminochromenes (116) proved easy to separate from the product mixture: (116b) by chromatography, being considerably more polar than the other products, and (116c and d) by their insolubility; they precipitated from the reaction

mixture on cooling. These compounds were too polar to run on normal phase h.p.l.c. and their isolated yields are therefore quoted.

The aminochromenes, (116b,c,d) and those mentioned in the following section, are all new compounds. Of a fairly large number of 4-amino-3-substituted-2-oxochromenes mentioned in the literature none have a benzyl derived 3-substituent although 3-alkyl and the 3-phenyl derivatives are known.[91]

The compounds obtained here are all colourless, crystalline solids; their structures were inferred from their spectroscopic properties. The parent ion peaks of the mass spectra implied molecular weights which are 2 and 4 units greater than the corresponding nitriles (114) and chromenoquinolines (115) respectively. Infra red spectroscopy showed that two hydrogens are present in an NH_2 group [(116c); $\nu_{max.}$ 3470, 3340, 3230 cm^{-1}]; an amide-like carbonyl is also present [(116c): $\nu_{max.}$ 1640 cm^{-1}].

^1H N.m.r. spectra show the amino substituent [(116c): 7.02 δ p.p.m., broad, 2H] and a further 2H signal corresponding to an aliphatic CH_2 [(116c): 3.76 δ p.p.m., s, 2H]. In addition aromatic resonances similar to those observed for the chromene portion of the chromenoisothiazoles (97) are present, in particular the downfield doublet of doublets [(116c): 8.06 δ p.p.m., d of d, J=10, 2Hz, 1H]. Finally the pendant phenyl is preserved [(116c): 7.22, 6.79 δ p.p.m., each a 2H doublet, J=9Hz].

Further confirmation of the aminochromene structure was obtained from ^{13}C n.m.r. spectra, especially a fully proton coupled spectrum of compound (116c) which shows long range

couplings consistent with the proposed structure. This is summarised in Table 5.

After removal of the aminochromenes the remaining product mixtures proved very difficult to separate. However, the use of h.p.l.c. analysis eased the situation allowing total yields to be determined providing a small, pure sample of each product could be obtained. In the more awkward mixtures repetitive chromatography was necessary and the isolated yields were sometimes of the order of one percent.

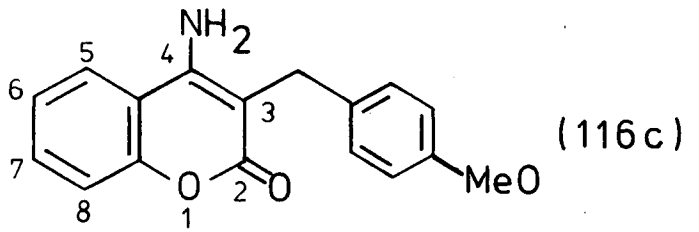
The problem of separation was further reduced by the preparation of authentic samples of the nitriles (114) (Section 2.1). This obviated the necessity of isolating the nitriles pure as the authentics could be used as standards in the h.p.l.c. analysis. Nitriles (114a and b) were, however, isolated and found to be identical to the compounds prepared by acylation of *o*-cyanophenol.

Nevertheless, the remaining task of separating and purifying the chromenoisothiazoles (97) and chromeno-quinolines (115) was in no way trivial due to their similar polarities and solubilities.

Chromenoisothiazoles (97a and b) produced by these reactions are identical to those prepared from the phenyl-propiolate esters (96a and b) already discussed in Section 2.3.2.2. Compounds (97c and d) provide an extension to the range of this class but do not differ significantly in properties from the members described earlier.

The unsubstituted chromenoquinoline (115a) is a literature compound. It has been prepared previously by two routes[92,93] each starting from 4-hydroxycoumarin (118) as

Table 5. ^{13}C N.m.r. Spectrum of Aminochromene (116c)



(116c)

	C-2	C-4'	C-4	C-8a	C-1'	ArCH	2ArCH	ArCH	ArCH	ArCH	C-4a	2ArCH	C-3	OCH_3	CH_2
δ_C ppm[a]	161.16	157.49	152.22	150.51	132.03	131.18	128.96	123.16	122.95	116.39	114.84	113.54	95.88	54.96	28.58
Multi-plicity	s,t	s,m	s,t(b)	s,t	s,t	d	d	d	d	d	x	d	s,t	q	t

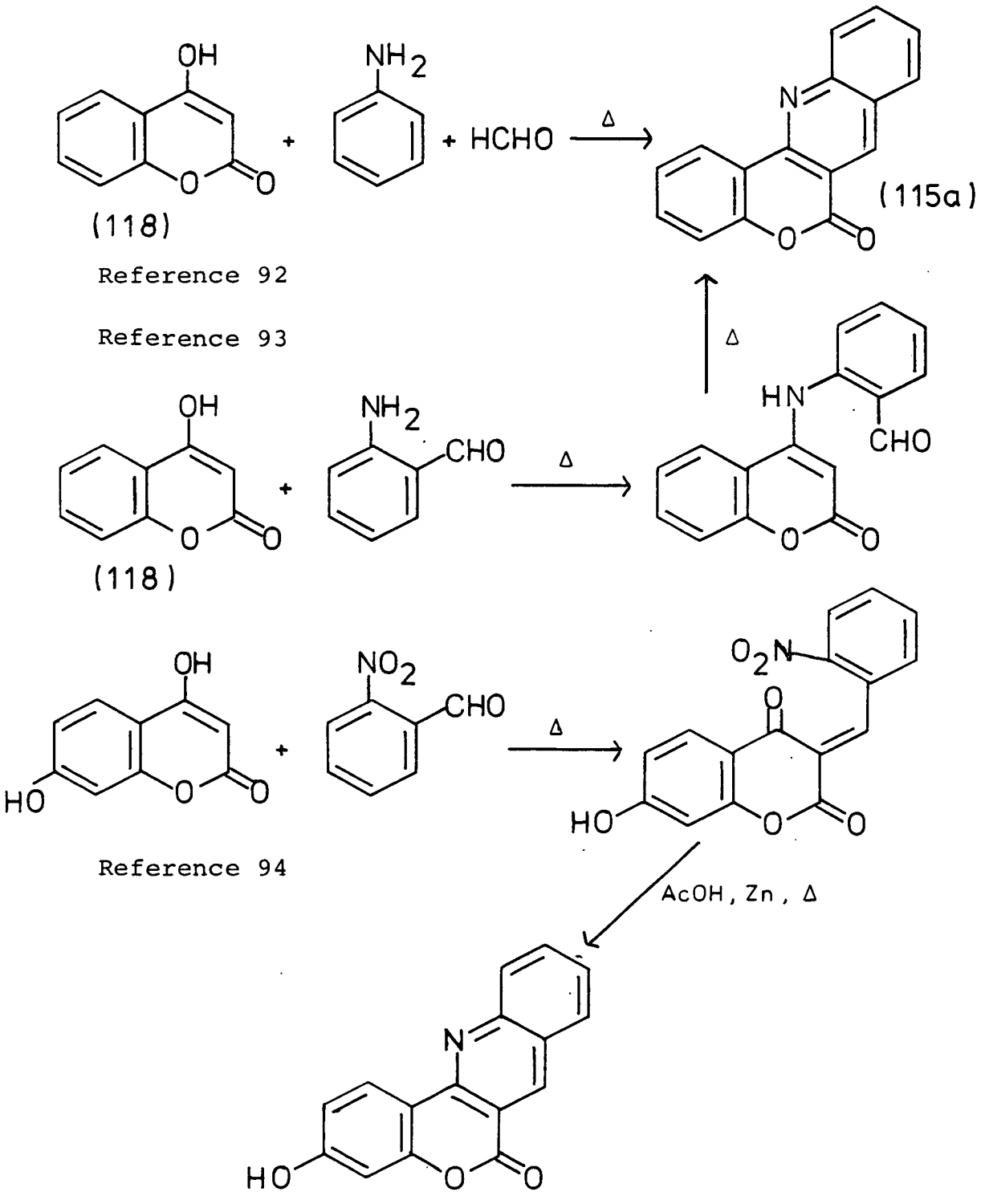
Footnotes:

[a] 50MHz, solvent and standard $(CD_3)_2SO$, 303K.

x: Not distinguishable.

shown in Scheme 45. A third method[94] is also shown which has been used to obtain substituted derivatives and ones with further rings fused to the benzene ring of the coumarin. These compounds have been studied on account of their relationship with the known carcinogen benz[*a*]acridine[92] and have also been tested for their antispasmodic properties.[94]

Scheme 45



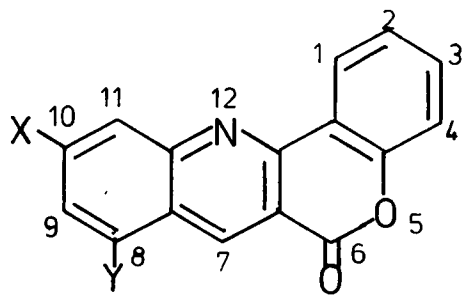
An authentic sample of chromenoquinoline (115a) was prepared by Buu Hoi's method[92] using a high temperature, three part condensation between 4-hydroxycoumarin, aniline and paraformaldehyde. A large number of by-products are formed in this reaction but prior experience of the desired product allowed it to be separated with relative ease. The compound (115a) produced by thermolysis of oxathiazolone (113a) was found to be identical to this authentic in all respects.

Spectroscopic comparisons of (115a) with the further chromenoquinolines (115b,c,d), which were all colourless, crystalline solids, implied their structural similarity. Mass spectra show clear parent ion peaks with initial fragmentation by loss of CO [(115a): *m/z* 247 (M^+), 219 (M^+-CO); *cf.* literature[92]]. The δ-lactone carbonyl signals in the i.r. spectra are in the range $\nu_{max.}$ 1740-1730 cm^{-1}.

A partial assignment of the ^1H n.m.r. spectra has been possible due to the wide range of chemical shifts observed for the aromatic protons (typically 9.2-7.3 δ p.p.m.); this is displayed in Table 6. The ^{13}C n.m.r. spectra bear some similarity to those of the chromenoisothiazoles in their signals for the chromene system and are shown in Table 7.

The unexpected products which were found to arise on thermolysis of the cinnamate esters (113) prompted an investigation of the mechanisms responsible for their formation. This is described in the following Section.

Table 6. ^{1}H N.m.r. Spectra of Chromenoquinolines (115a,b,c,d) and (149)



(115)	X	Y
a	H	H
b	Cl	H
c	MeO	H
d	Me	H
(149)	H	Cl

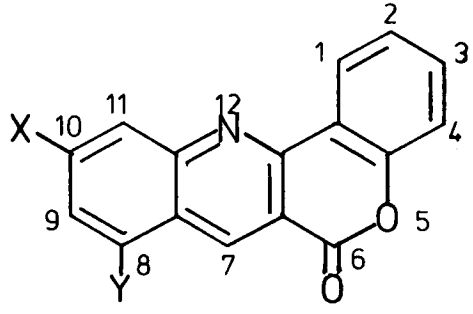
Compound	H-7	H-1	H-11	H-9	H-2/3	H-8/4	H-2/3	H-8/4	Others
	δ_H p.p.m.[a]								
(115b)[b]	9.18d	8.73d,d[e]	8.22d[e]	7.95d	7.60t,d	7.58d,d	7.43t,d	7.38d,d	
J/Hz[d]	1,	8,2	2	9	9,2	7,2	7,1	8,2	
(115a)[c]	9.21d	8.78d,d[e]	8.24d,d,d	8.07-7.30 multiplet 6H (including H-10)					
(115c)[c]	9.05d	8.70d,d[e]		7.85d	7.60-7.16 multiplet 5H (including H-11)				4.03s; OCH_3
(115d)[b]	9.12s	8.74d,d	7.99s	7.88d	7.57t,d	7.47-7.35 multiplet 3H			2.62s; CH_3
(149)[c]	9.58d	8.74d,m	8.14d,d,d	7.90-7.22 multiplet 8H					

Footnotes;

[a] Solvent $CDCl_3$, standard $CHCl_3$; 303K. [b] 200MHz. [c] 80MHz. [d] To nearest integer.

[e] Further small couplings apparent.

Table 7. ^{13}C N.m.r. Spectra of Chromenoquinolines (115a,b,c,d) and (149)



(115)	X	Y
a	H	H
b	Cl	H
c	MeO	H
d	Me	H
(149)	H	Cl

Compound	C-4a, 6, 11a, 12a				C-7	C-10	b	C-8	C-9, 11		C-7a	b	b	C-12b	b	C-6a	CH_3
	δ_C p.p.m.[a]																
(115a)	161.13	152.53	151.08	149.59	140.88	133.15	132.22	129.56	129.27	127.26[c]	127.26[c]	125.23	124.81	119.65	117.28	115.80	-
(115b)	d	152.88	151.32	150.63	140.74	139.68	132.67	130.39	128.55[c]	128.55[c]	125.63	125.35	124.96	119.35	117.37	115.95	-
(115c)	161.40	153.33	152.78	150.06	140.02	163.94	132.07	130.40	121.32	106.91	122.88	125.02	124.65	119.67	117.27	113.66	55.74
(115d)	161.33	152.70	151.31	149.64	140.41	144.40	132.05	129.74	128.88	128.42	125.47	125.13	124.73	119.77	117.25	115.04	22.18
(149)	160.68	152.90	151.61	150.25	138.20	132.71[c]	132.71[c]	133.08	128.64	127.14	125.74	125.39	124.94	119.13	117.36	116.40	-

Footnotes:

[a] 50MHz, solvent and standard $CDCl_3$, 303K. [b] C-1,2,3,4. [c] Signals superimposed. [d] Signal not distinguished.

2.3.3.4 Mechanistic Considerations

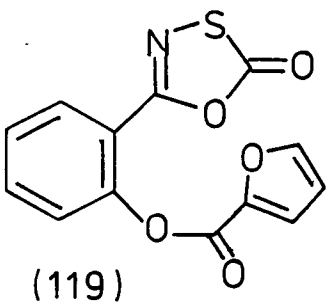
Of the four products generally observed on thermolysis of simple cinnamate esters of *o*-hydroxyphenyloxathiazolone it is easy to explain the formation of two. The *o*-cyanophenyl cinnamate ester (114) is the expected nitrile by-product arising from fragmentation of the nitrile sulphide intermediate (117). Nitriles are formed on thermolysis of all the cinnamate esters of *o*-hydroxyphenyloxathiazolone which have been investigated.

The chromenoisothiazole product (97) is probably the result of intramolecular 1,3-dipolar cycloaddition of nitrile sulphide (117) to the adjacent alkene followed by dehydrogenation of the initial chromenoisothiazoline cycloadduct as discussed in Section 2.3.3.1.

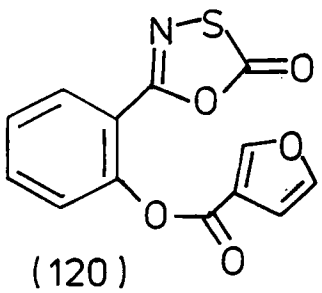
The formation of the chromenoquinoline (115) and aminochromene (116) products is, however, more difficult to rationalise. It was noticed that the chromenoquinoline is formally a dehydrogenated [4+2] intramolecular Diels-Alder product of the *o*-cyanophenyl ester (114), the components being the nitrile group and the diene consisting of the exocyclic and one endocyclic double bond of the styryl moiety. However, on heating *o*-cyanophenyl cinnamate (114a) under reflux in xylene for up to six weeks no chromenoquinoline could be detected.

The possibility that a [4+2] cycloaddition occurred involving the nitrile sulphide intermediate itself, before loss of sulphur, was then examined by the following experiments. The 2- and 3-furoate esters of *o*-hydroxyphenyloxathiazolone, (119) and (120), were synthesised and

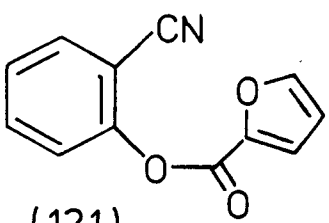
thermolysed. It was thought that one of these might be able to attain the transition state necessary for [4+2] cycloaddition between the furyl diene and the C-N bonds of the nitrile sulphide; structural models suggested that the 3-furoate ester (120) was most likely to do so. In the event, however, no products other than the corresponding *o*-cyanophenyl 2- and 3-furoates (121) and (122) were detected on thermolysis of oxathiazolones (119) and (120) respectively.



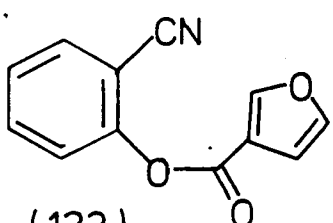
(119)



(120)



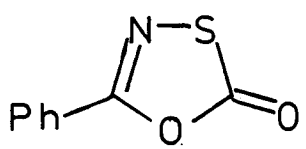
(121)



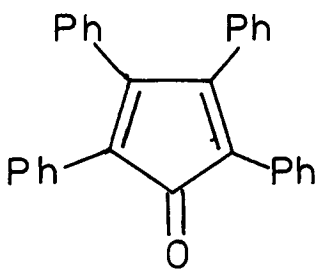
(122)

An intermolecular equivalent of this reaction was also investigated. Phenyloxathiazolone (38) was heated under reflux in xylene in the presence of a twofold excess of tetraphenylcyclopentadienone (123) until there was no oxathiazolone remaining. To all intents and purposes there was no reaction other than the decomposition of phenyloxathiazolone to benzonitrile and sulphur. However, two minor

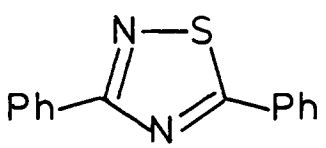
products (yields ≤0.1%) were tentatively identified by their mass spectra. These were 3,5-diphenyl-1,2,4-thiadiazole (124), presumably formed by the [3+2] cycloaddition of benzonitrile sulphide to the benzonitrile produced by its decomposition, and pentaphenylpyridine (125). The latter is the expected [4+2] cycloaddition product after loss of carbon monoxide; however, it is known that benzonitrile and tetraphenylcyclopentadienone react to give pentaphenylpyridine in moderate yields at *ca.* 300°C.[95] The minute yield of pentaphenylpyridine formed in the present reaction, carried out at 138°C, suggests that benzonitrile sulphide is not activated towards [4+2] cycloaddition with dienes as compared with benzonitrile.



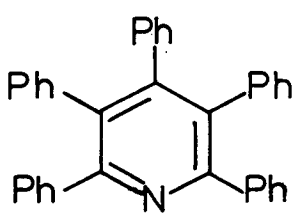
(38)



(123)



(124)

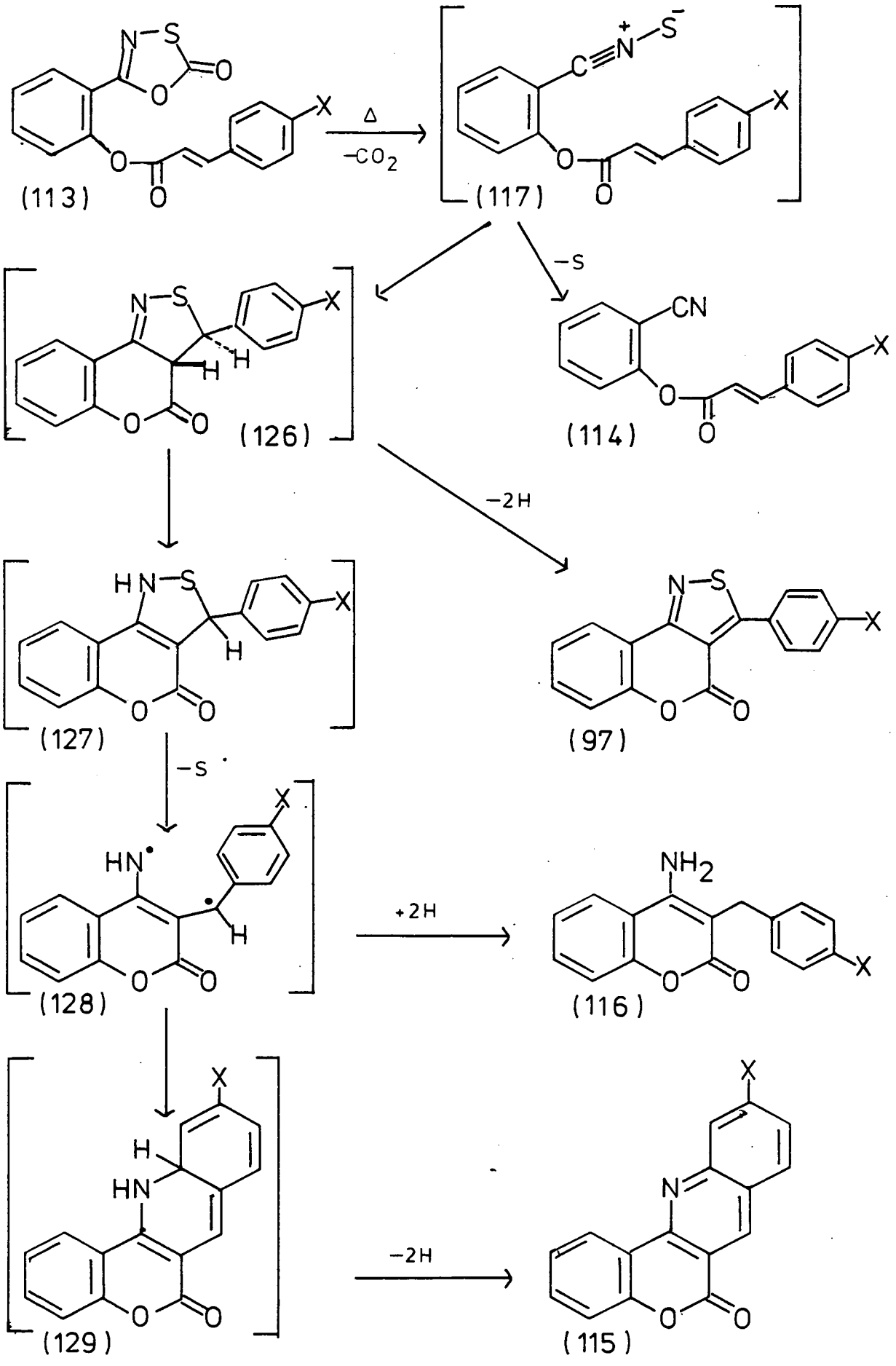


(125)

In summary, the four experiments described above are thought to preclude the formation of chromenoquinoline (115) by an intramolecular [4+2] cycloaddition.

A more satisfactory mechanism explaining the formation of all four products generally observed on thermolysis of cinnamate esters of *o*-hydroxyphenyloxathiazolone can be proposed on the basis of further experiments. It is set out in Scheme 46.

Scheme 46



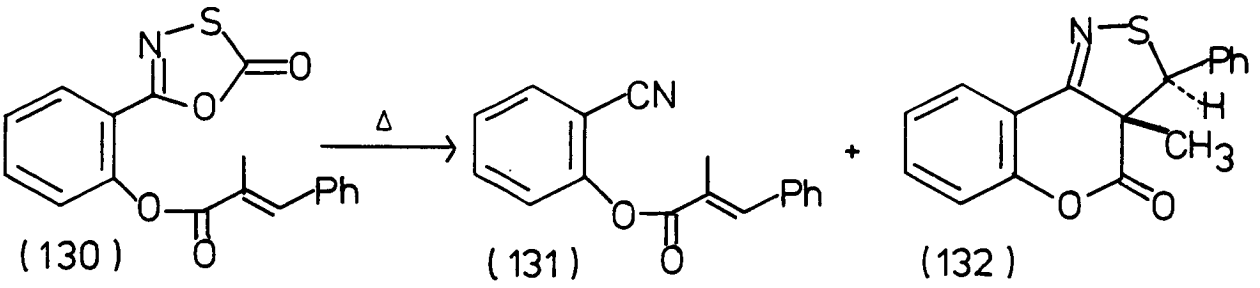
It is suggested that initially competition between fragmentation and cycloaddition of nitrile sulphide (117) gives nitrile (114) and a chromenoisothiazoline (126); the latter may dehydrogenate leading to the chromenoisothiazole (97) as discussed earlier.

Alternatively isothiazoline (126) may tautomerise resulting in the chromene fused Δ^3-isothiazoline (127). Extrusion of sulphur from this, by an unknown mechanism, leads to the intermediate (128) which may be a diradical, as shown, a dipolar species, or may contain the 1-azabutadiene unit derived from either of these. Whatever the nature of intermediate (128) it may gain hydrogen to give the observed aminochromene (116) or may cyclise onto the *ortho* position of the phenyl ring giving the dihydroquinoline derivative (129). Finally, dehydrogenation would yield the chromenoquinoline (115).

Evidence for the formation of an isothiazoline as the initial cycloadduct was provided by the thermolysis of the α-methylcinnamate ester (130). This yielded two products only, *o*-cyanophenyl α-methylcinnamate (131) (81%) and the methylisothiazoline derivative (132) (5%) as shown in Scheme 47.

The nature of compound (132) is clearly demonstrated by the high field signals of its n.m.r. spectra (^{1}H n.m.r.: 5.93 δ p.p.m., s, 1H, H-3; 1.15 δ p.p.m., s, 3H, CH_3; ^{13}C n.m.r.: 61.07 δ p.p.m., C-3a; 59.66 δ p.p.m., C-3; 17.61 δ p.p.m., CH_3). No other products were detected showing that a free hydrogen at the 4-position of the isothiazoline is essential to further reaction.

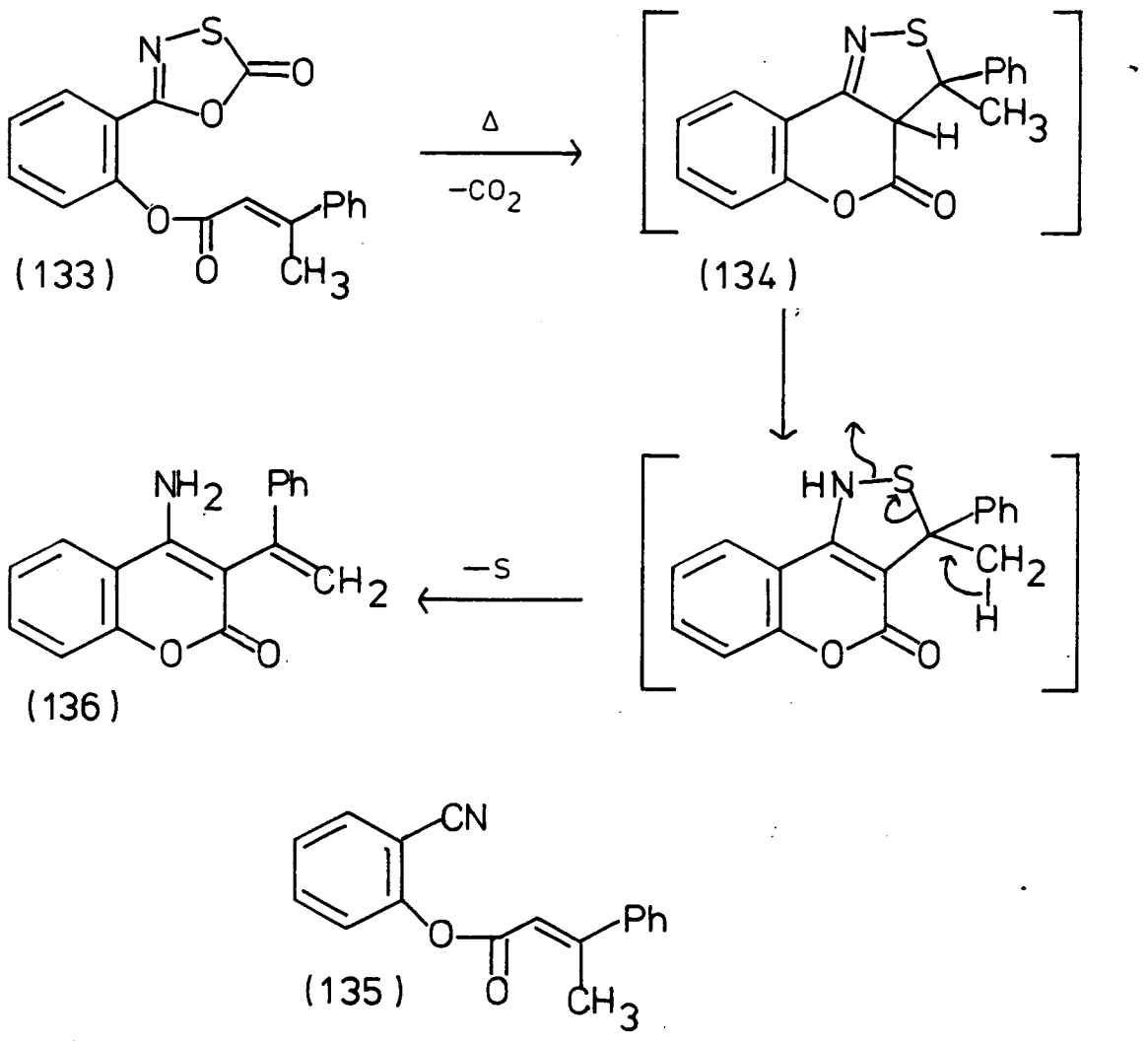
Scheme 47



(130) (131) (132)

Support for this was found in the reaction of the related β-methylcinnamate ester (133) shown in Scheme 48. In this case the essential free hydrogen is present in the initial isothiazoline cycloadduct (134) but dehydrogenation to an isothiazole is again blocked. The products of this thermolysis were *o*-cyanophenyl β-methylcinnamate (135) (85%) and 4-amino-2-oxo-3-(α-styryl)-2*H*-chromene (136) (15%).

Scheme 48

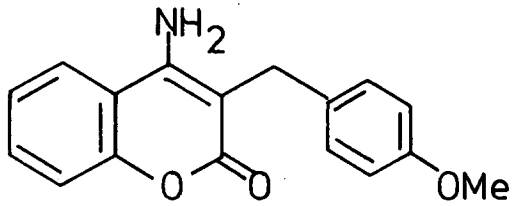


In contrast with aminochromenes (116b,c,d) compound (136) could not be crystallised and existed as a clear glass at room temperature, it was also much more soluble. However, spectroscopic data suggested that they were related. The i.r. spectrum [$\nu_{max.}$ 3430, 3340, 3210 (NH_2), 1665 cm^{-1} (C=O)] and the ^{13}C n.m.r. spectrum (Table 8) clearly demonstrated that compound (136) contained a free phenyl and a 4-amino-2-oxo-chromene system. Signals for the remaining two carbons (139.99, 118.24 δ p.p.m.) taken together with information from the ^{1}H n.m.r. spectrum and consideration of the starting

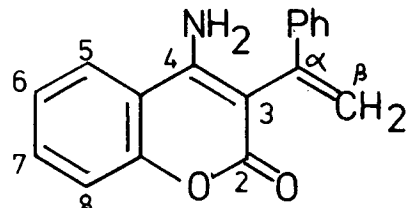
material suggested the 1,1-ethylene link between the two above units. A 360MHz ^{1}H n.m.r. spectrum allowed an almost complete assignment of the signals (Table 9). The methylene protons (6.00, 5.39 δ p.p.m.) show a small coupling to each other appearing as fine doublets (J=1.16Hz).

Further support for the structure of compound (136) was provided by a N.O.E. experiment. Selective irradiations of the relevant protons demonstrated the spatial proximity of the methylene protons to each other, of the pendant phenyl *ortho*-protons to one methylene proton, and of the amino protons to the adjacent H-5 proton (thereby confirming the assignment of the characteristic doublet of doublets to this proton). The results of this experiment are displayed in Figure 4.

Table 8. ^{13}C N.m.r. Spectra of Aminochromenes (116c) and (136)



(116c)



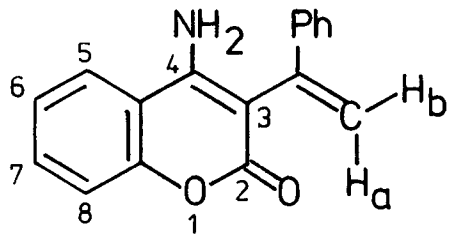
(136)

Compound	C-2	C-4'	C-4	C-8a	C-1'	ArCH	2ArCH	ArCH	ArCH	ArCH	C-4a	2ArCH	C-3	Others
	δ_C p.p.m.													
(116c)[a]	162.16	157.49	152.22	150.51	132.03	131.18	128.96	123.16	122.95	116.39	114.84	113.54	95.88	54.96 (OMe); 28.58 (CH_2)
(136)[b]	161.19	127.53	152.43	150.65	137.63	131.17	127.84	123.03	121.88	116.52	113.47	125.15	98.82	139.99 (C-α); 118.24 (C-β)

Footnotes:

[a] 50MHz, solvent and standard $(CD_3)_2SO$, 303K. [b] 50MHz, solvent and standard $CDCl_3$, 303K.

Table 9. ^{1}H N.m.r. Spectrum of 4-Amino-2-oxo-3(α-styryl)-2*H*-chromene (136)



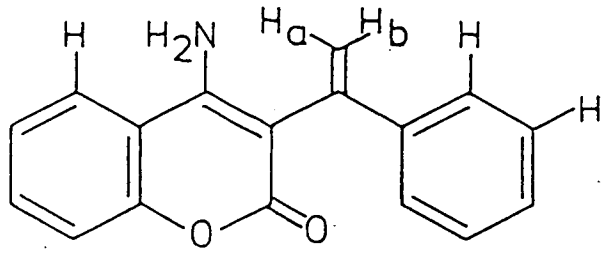
(136)

	H-5[c]	H-6 or 7	H-2',6'	H-8[c]	H-3',4',5' and H-6 or 7	H-b[c]	NH_2	H-a[c]
δ_Hp.p.m.[a]	7.66	7.50	7.39-7.37	7.27	7.23-7.17	6.00	5.51	5.39
Integral	1	1	2	1	4	1	2	1
Multiplicity	d,d	t,d	m	d,d	m	d	b	d
J/Hz	8,1	8,1		8,1		1.16		1.16

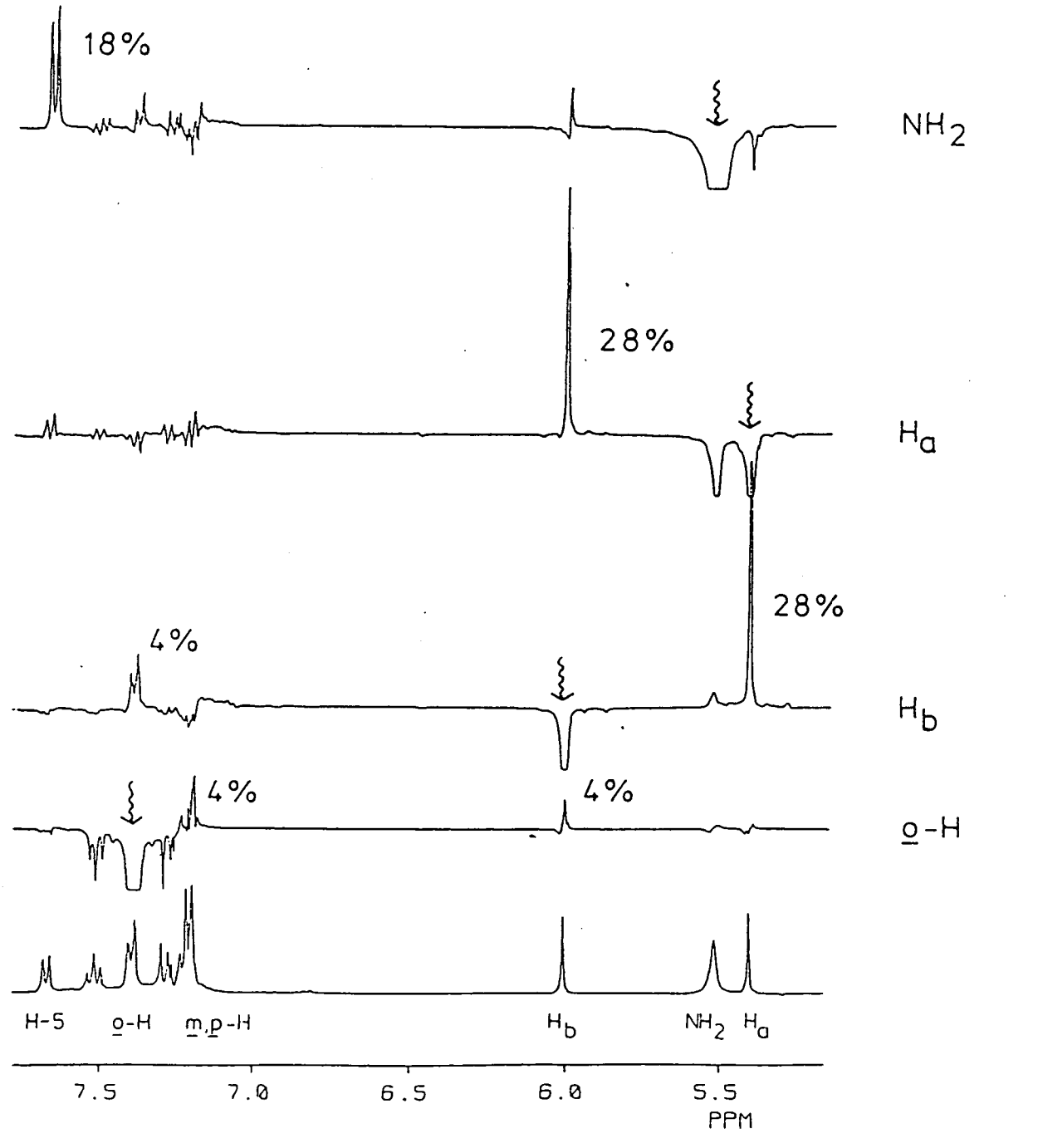
Footnotes:

[a] 360MHz, solvent $CDCl_3$, standard $CHCl_3$, 298K. [b] Broad. [c] Distinguished by the N.O.E. experiment summarised in Figure 4.

Figure 4: N.O.E. Difference Spectra of Aminochromene (136)



(136)

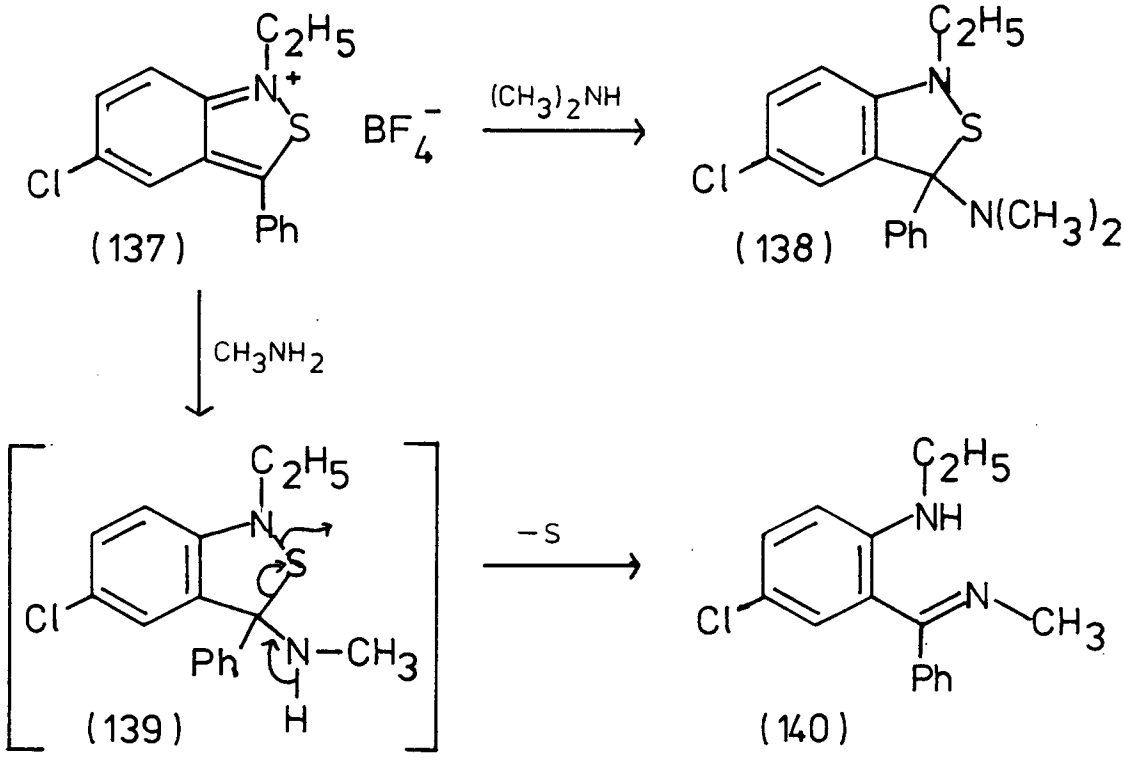


Interestingly neither the methylene protons nor the phenyl *ortho*-protons showed an interaction with the amino group suggesting the styryl unit is twisted away from the plane of the chromene system.

The (α-styryl) chromene (136) is thought to be formed in the manner shown in Scheme 48 which is related to a mechanism proposed in the literature and involving a similar intermediate.

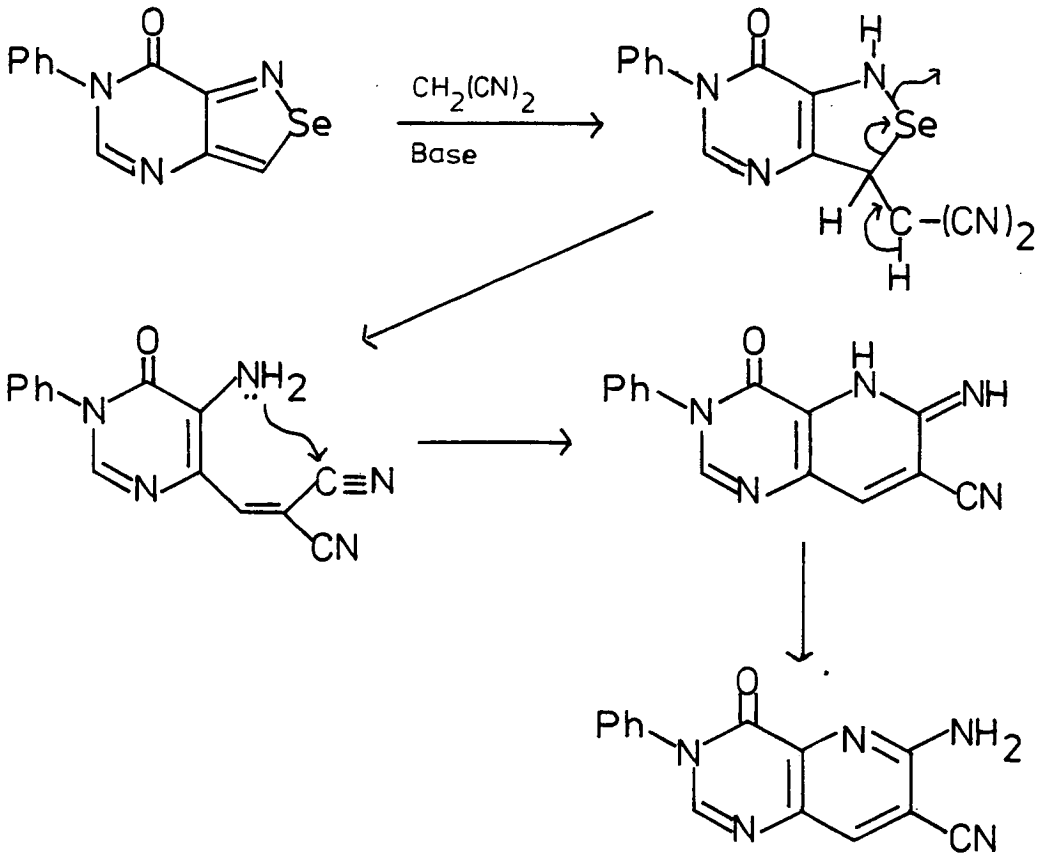
The reactions shown in Scheme 49 are the work of Aki *et al.*[96] Treatment of 1-alkyl-3-arylbenz[*c*]isothiazolium tetrafluoroborates (137) with a secondary amine yielded the isolable Δ^3-isothiazoline (138). However, when a primary amine was used the Δ^3-isothiazoline intermediate (139) extruded sulphur as shown giving the azomethine structure (140).

Scheme 49



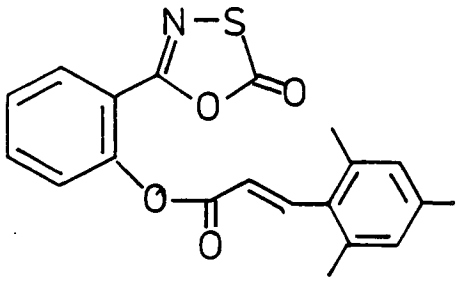
A very similar mechanism has also been proposed for the reaction of isoselenazoles with carbanions;[97] this is shown in Scheme 50.

Scheme 50

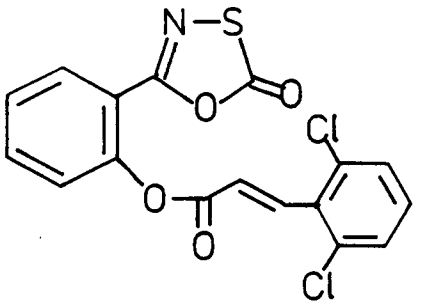


The fact that no chromenoquinoline product is observed in the present reaction of the β-methylcinnamate ester (133) suggests that the above mechanism for the extrusion of sulphur, if operative, is more favourable than that leading to the diradical type intermediate proposed earlier. It is only when a hydrogen-bearing substituent is present at the 5-position of the Δ^3-isothiazoline that this latter, more facile, extrusion of sulphur is possible.

Returning to the main reaction mechanism under consideration, further confirmation can be obtained by the use of blocking groups affecting the later stages of the pathway shown in Scheme 46. To this end the *ortho*-disubstituted cinnamates (141) and (142) were synthesised and their reactions studied.



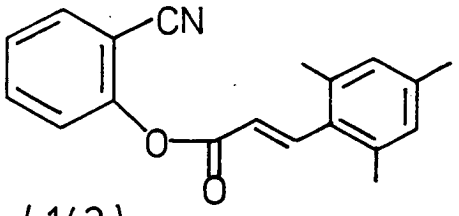
(141)



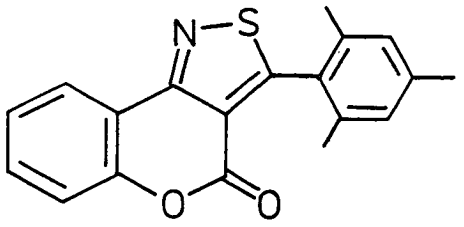
(142)

Thermolysis of the 2,4,6-trimethylcinnamate ester (141) yielded the expected nitrile (143) (34%), the chromenoisothiazole (144) (33%), and the aminochromene (145) (24%) only. This shows that the diradical type intermediate proposed cannot cyclise onto the *ortho*-position of the pendant phenyl when that position is blocked by a methyl substituent. No products derived from the dihydroquinoline (146) were detected in the reaction.

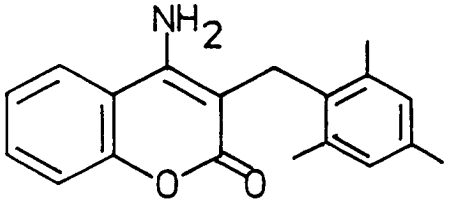
In contrast, thermolysis of the 2,6-dichlorocinnamate ester (142) yielded the nitrile (147) (7%), the chromenoisothiazole (148) (31%) and 8-chloro-6-oxo-6*H*-chromeno[4,3-*b*]-quinoline (149) (29%) [*m/z* 283/281 (M^+)].



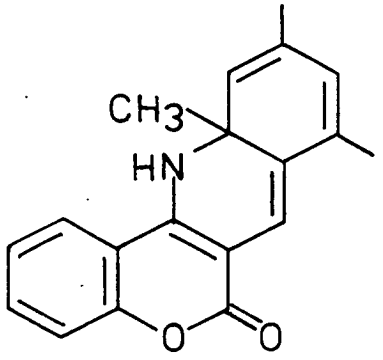
(143)



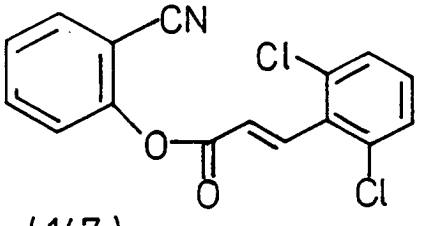
(144)



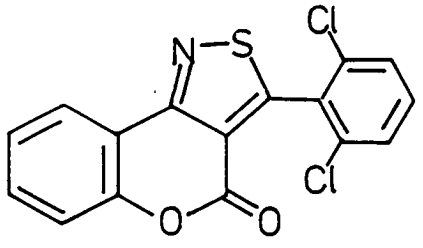
(145)



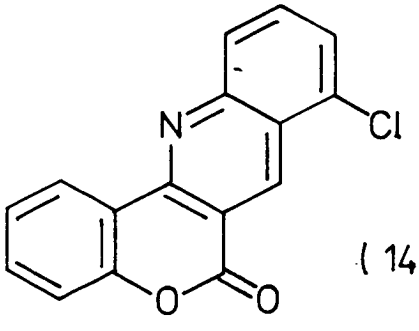
(146)



(147)



(148)



(149)

No aminochromene product could be found in this reaction mixture, although other unidentified by-products were present. The relatively high yield of chromenoquinoline may explain the absence of any aminochromene. This yield (29%) is the highest obtained for a chromenoquinoline in this work and suggests that ring closure is favoured in this case, loss of HCl then giving the observed mono-chloro product.

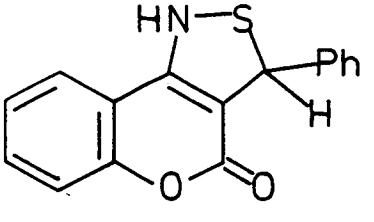
It was mentioned earlier that on thermolysis of the unsubstituted cinnamate ester of *o*-hydroxyphenyloxathiazolone (113a) the aminochromene product was not detected. A fourth product was, however, isolated. This was highly insoluble in most common solvents, only DMF and DMSO giving solutions of sufficient strength for n.m.r. spectra to be recorded at room temperature.

In an attempted recrystallisation from benzonitrile, heating at *ca.* 150°C, it was found that the product was unstable at such temperatures when in solution; as an impure solid it had a sharp melting point at 228-230°C. Heating the compound for 1h under reflux in benzonitrile (*ca.* 188°C) resulted in its complete disappearance as judged by t.l.c. Investigation of the reaction mixture by h.p.l.c. showed that both chromenoisothiazole (97a) and chromenoquinoline (115a) were present indicating that the unknown material may be an intermediate in the reaction pathway to these compounds.

Characterisation of this unknown material has been particularly troublesome due mainly to its insolubility. It exists as a white powder which it has been impossible to recrystallise. Its sharp melting point (228-230°C) and

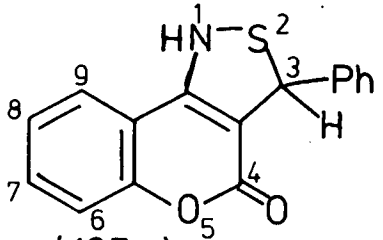
fairly clean n.m.r. spectra confirm it is predominantly a single compound, however, micro-analytical results are not consistent with the molecular formula ($C_{16}H_{11}NO_2S$) inferred from spectroscopic data. Mass spectra of the compound do not show a parent ion peak corresponding to this molecular formula (*m/z* 281) but a strong peak at *m/z* 279 suggests that decomposition to the chromenoisothiazole (97a) occurs in the spectrometer analogously to the observed lability in solution.

The i.r. spectrum shows a relationship between this compound and the aminochromene series with NH peaks ($\nu_{max.}$ 3430, 3360, 3250 cm^{-1}) and an amide-like carbonyl ($\nu_{max.}$ 1630 cm^{-1}). This relationship is given further strong support by the ^{13}C n.m.r. spectrum which displays signals entirely compatible with a 2-oxo-chromene unit (see Table 10). However, it is clear from chemical and spectroscopic observations that the compound contains sulphur and considering all the available information it would appear that the most likely structure for this product is the chromene fused Δ^3-isothiazoline (127a).

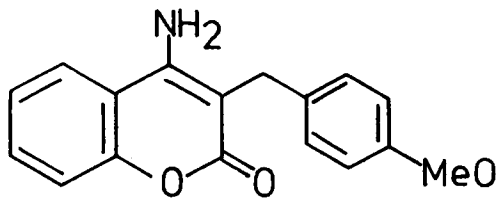


(127a)

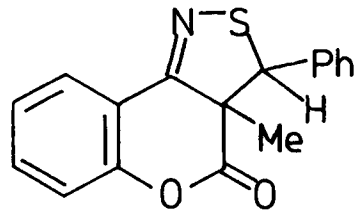
Table 10. Comparison of ^{13}C N.m.r. Spectra of Compounds (127a), (116c), (132) and (97a)



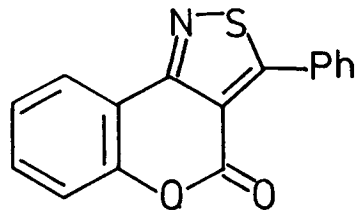
(127a)



(116c)



(132)



(97a)

Compound	C-4	C-9b	C-5a	C-1'	ArCH	2ArCH	2ArCH	C-4'	ArCH	ArCH	ArCH	C-9a	C-3a	C-3
	δ_C p.p.m.													
(127a)[a]	161.00	152.29	151.06	138.91	131.82	128.06	127.85	126.92	123.37	123.26	116.47	114.56	95.12	53.25
Multiplicity	s,d	s,t	s,t	s,m	d	d	d	d	d	d	d	s,m	s,d	d,t
(116c)[a,c,d]	161.16	152.22	150.51		131.18				123.16	122.95	116.39	114.84	95.88	28.58
(132)[a,c]	168.35	161.25	151.85		132.26				125.46	125.06	116.87	117.25	61.07	59.66
(97a)[b,c]	156.24	162.43	152.32		131.78				124.58	124.04	116.88	116.73	117.13	177.91

Footnotes:

[a] 50MHz, 303K, solvent and standard $(CD_3)_2SO$.

[b] 20MHz, 298K, solvent and standard $CDCl_3$.

[c] Pendant phenyl group (and methoxy) omitted.

[d] Numbering as for the equivalent carbons of (127a).

Further evidence in support of this claim is given by the n.m.r. signals assigned to the ring methyne (C-3: 53.25 δ p.p.m.; H-3: 5.89 δ p.p.m., s, 1H) which are comparable to the corresponding data for the methylisothiazoline derivative (132) (C-3: 59.66 δ p.p.m.; H-3: 5.93 δ p.p.m.). A ^{13}C n.m.r. spectrum run using the DEPT pulse sequence had demonstrated that this signal was in fact due to a methyne carbon.

Other information from ^{1}H n.m.r. spectra was limited by excessive line broadening even at 360MHz. The NH proton signal could not be recognised although integrations implied it was present masked by the closely-ranged aromatic peaks. A characteristic doublet of doublets (8.07 δ p.p.m., d of d, J=9,2Hz) was again present which was assigned to H-9.

Finally a fully proton coupled ^{13}C n.m.r. spectrum shows long range couplings consistent with the proposed structure (127a) for this problematic compound.

It is difficult, however, to explain the isolation of this material in the unsubstituted case only. Its insolubility and yet proven instability in solution may provide an explanation but leave the question of why the compound is particularly insoluble unanswered.

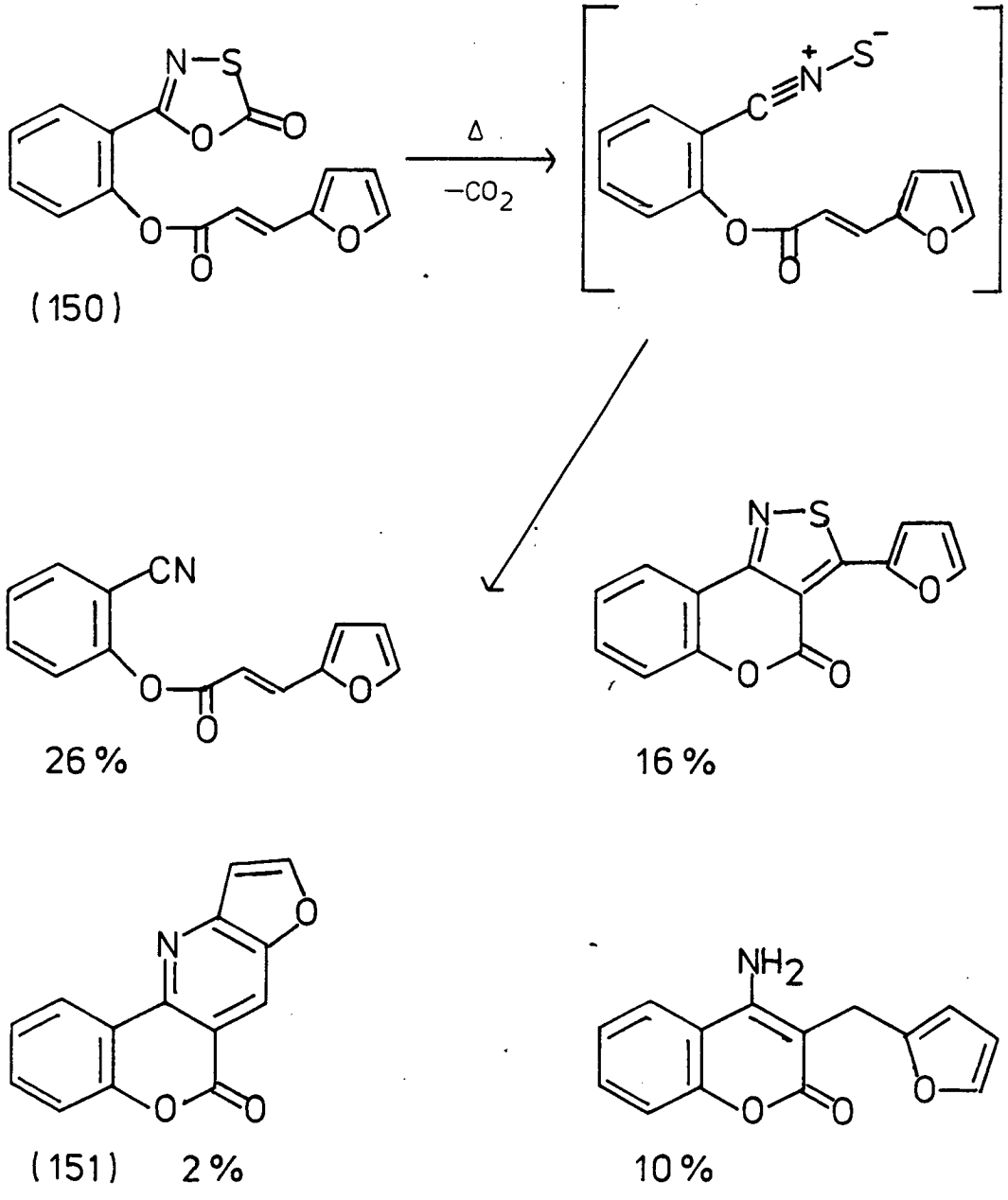
2.3.3.5 Conclusions

The intramolecular cycloaddition of nitrile sulphides bearing alkenyl substituents has proved to be an interesting reaction from the mechanistic, rather than synthetic, point of view. Even in examples where a chromenoisothiazole is obtained alone, better methods have been developed to such

products (*vide infra*, Section 2.4.3). The reactions of the cinnamate esters provide a mechanistic problem for which an explanation has been suggested.

It should be noted that this reaction is not limited to cinnamate esters. Thermolysis of the 3-(2-furyl)acrylate ester (150) gives a similar array of products, the chromeno-quinoline being replaced by 6-oxo-6*H*-chromeno[4,3-*b*]furo-[2,3-*e*]pyridine (151) as shown in Scheme 51. The mechanism is presumably the same.

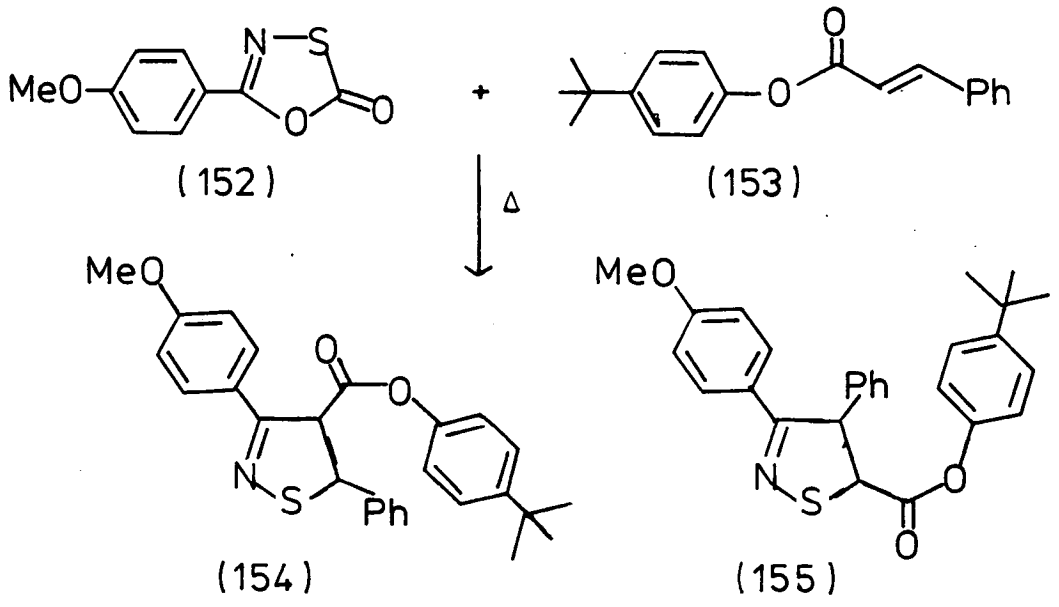
Scheme 51



The corresponding intermolecular cycloaddition of nitrile sulphides and cinnamate esters has not been reported in the literature. The reaction of 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-one (152) and *p*-*tert*-butylphenyl cinnamate (153) was therefore examined and found to occur but in rather low yield (Scheme 52).

The oxathiazolone (152) was added in small portions over five hours to a five-fold excess of the cinnamate (153) heated under reflux in xylene. After a further five hours heating no oxathiazolone could be detected by h.p.l.c.

Scheme 52



A mixture of the two regioisomeric isothiazoline cycloadducts (154) and (155) was isolated. The isomers could not be separated by h.p.l.c. but a combined yield of *ca*.7% was estimated. The ^{1}H n.m.r. spectrum of the mixture showed the two doublets characteristic of unfused isothiazolines (5.48 δ p.p.m., d, J=3Hz, H-5; 4.48 δ p.p.m., d,

J=3Hz, H-4) although the signals for the different isomers were not resolved. The peaks corresponding to the methoxy groups were, however, sufficiently separated (3.86, 3.75 δ p.p.m.) for the isomer ratio to be estimated as *ca.* 1:1.

The major product of the reaction was *p*-methoxybenzonitrile produced by decomposition of the nitrile sulphide; no further products were noted.

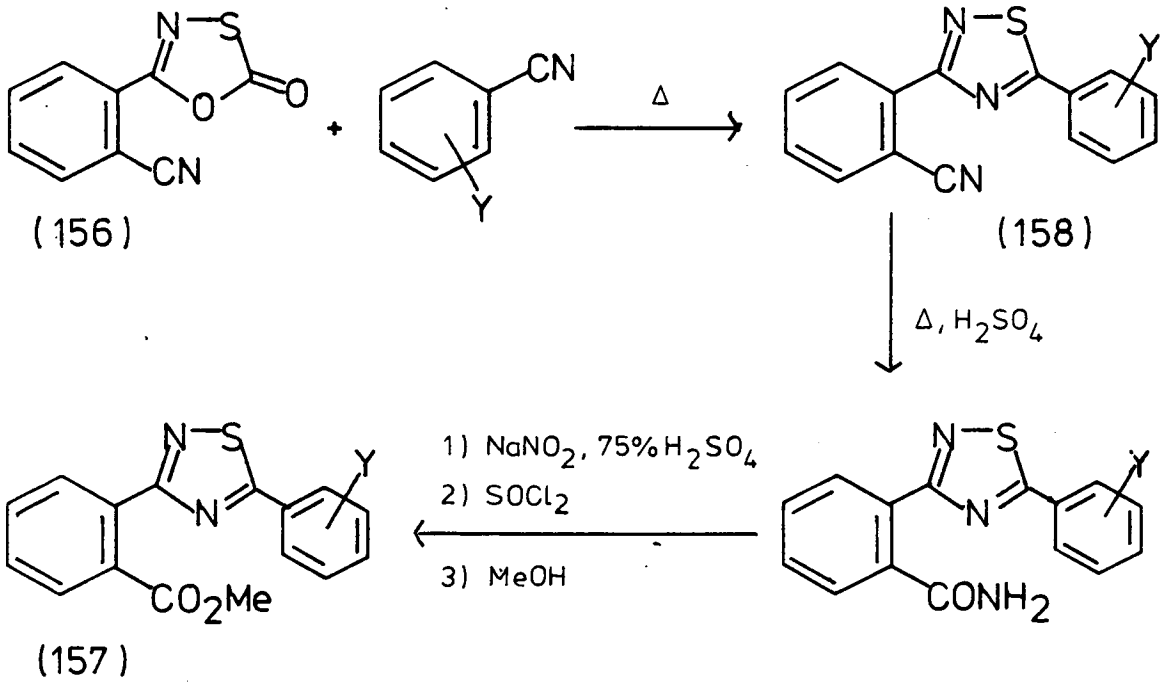
2.4 INTERMOLECULAR CYCLOADDITION REACTIONS OF SOME *ortho*-SUBSTITUTED BENZONITRILE SULPHIDES

2.4.1 Introduction

Although several *ortho*-substituted phenyloxathiazolones have been synthesised, particularly by Senning and Rassmussen,[76] there is only one report in the literature of such a compound undergoing cycloaddition reactions *via* the *ortho*-substituted benzonitrile sulphide derived therefrom.

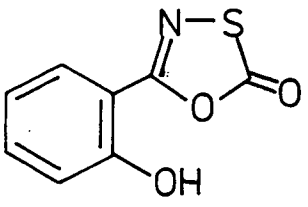
Howe and Shelton[56] utilised the reaction of *o*-cyano-phenyloxathiazolone (156) with substituted benzonitriles in the preparation of 2-(5-aryl-1,2,4-thiadiazol-3-yl)benzoates (157) as shown in Scheme 53. These compounds were found to have herbicidal and plant growth regulator properties, but their activities were lower than the 1,2,4-oxadiazole analogues.[56]

Scheme 53

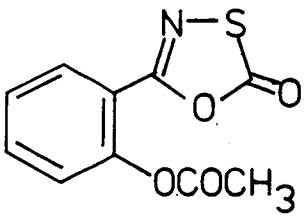


Yields of (158): Y=3-CF_3, 41%; Y=4-Cl, 21%.

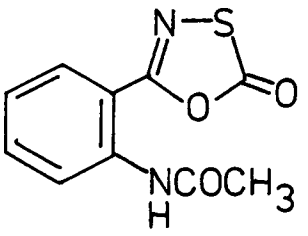
In the present work reactions of *o*-hydroxy-, *o*-acetoxy-, and *o*-acetamido-phenyloxathiazolone, (62), (63) and (64) respectively, with some common activated dipolarophiles have been studied.



(62)



(63)



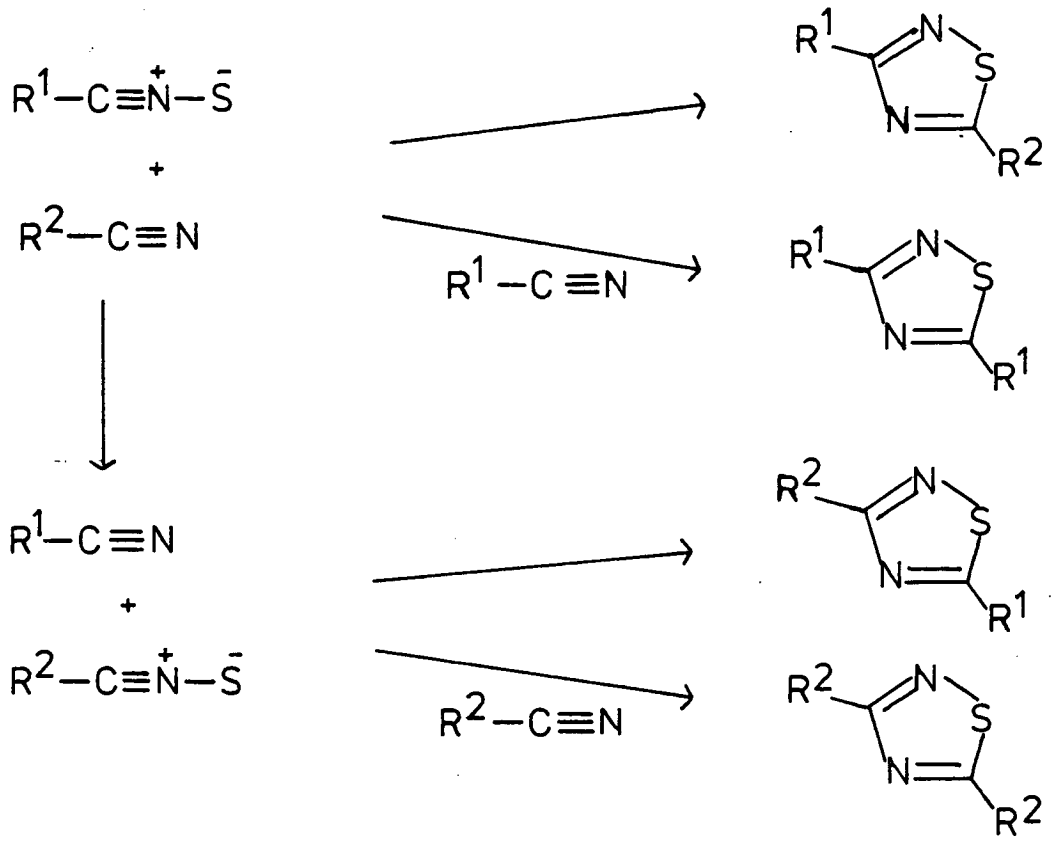
(64)

In several of the examples discussed the initial product of the cycloaddition can undergo a further reaction, either spontaneously or as a separate second step, which depends on the presence of the *ortho*-substituent.

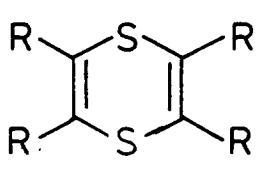
In reactions of nitrile sulphides with certain dipolarophiles by-products resulting from mechanisms other than direct cycloaddition sometimes occur.

Aromatic nitriles, when used as dipolarophiles, may undergo sulphide transfer from one nitrile sulphide, generating a second species of the dipole and giving rise to by-products.[54] Cycloaddition of a nitrile sulphide to the nitrile formed by its decomposition might also occur and thus, potentially, four different 1,2,4-thiadiazoles are possible as shown in Scheme 54.

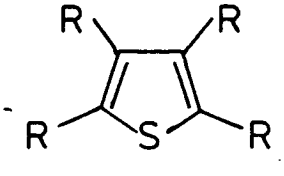
Scheme 54



Acetylenic dipolarophiles such as dimethyl acetylene-dicarboxylate (DMAD) are sometimes found to give rise to small quantities of thiophene and dithiin by-products,[20] for example (159) and (160), in reactions with nitrile sulphides. These are presumed to result from combination of the acetylene with reactive sulphur species formed by the decomposition of the dipole.



(159) R = CO_2Me



(160)

Olefinic dipolarophiles, particularly acrylate esters, may polymerise under the conditions of a reaction with a nitrile sulphide. It may also be possible for such dipolarophiles to combine with sulphur in a similar fashion to the acetylenes.

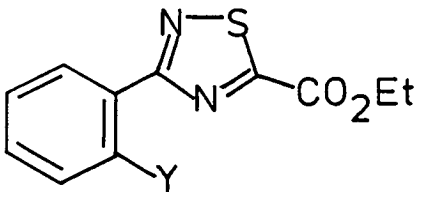
2.4.2 Reactions with Ethyl Cyanoformate

Ethyl cyanoformate (ECF) is a particularly reactive dipolarophile which has been used to trap nitrile sulphides in almost quantitative yield. In some ways it is a better choice of reagent, when trapping of a nitrile sulphide is the only requirement, than DMAD which has been more generally used. ECF gives a very clean reaction with no by-products resulting from sulphide transfer as observed[54] with less active nitrile dipolarophiles; and it is very easy to remove from a reaction mixture (b.p. 115-116°C[98]).

A two-fold, or larger, excess of ECF was therefore used to trap nitrile sulphides generated from the *ortho*-substituted phenyloxathiazolones (62), (63) and (64) giving 1,2,4-thiadiazoles (161), (162) and (163) respectively, in high yields as shown in Table 11.

The products were all pale yellow crystalline solids. ^{13}C N.m.r. chemical shifts of the heterocyclic ring carbons are similar to those of the simple phenyl derivative (C-3: 174.2 δ p.p.m.; C-5 178.6 δ p.p.m.[99]) and are also displayed in Table 11.

Table 11



	Y	Yield %[a]	^{13}C n.m.r. Chemical Shifts[b] δ p.p.m. C-3	C-5
(161)	-OH	85	173.70	177.83
(162)	$-OCOCH_3$	73	171.21	178.25
(163)	$-NHCOCH_3$	98	173.09	177.70

Footnotes:

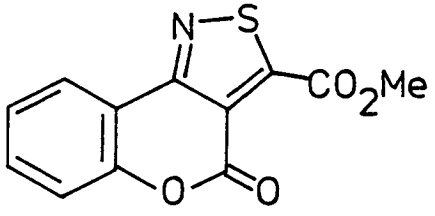
[a] Recrystallised, crude yields were each 100%.

[b] Recorded in $CDCl_3$.

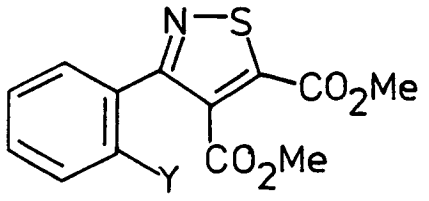
2.4.3 Reactions with Dimethyl Acetylenedicarboxylate

Cycloaddition of the nitrile sulphides generated from *o*-hydroxy-, *o*-acetoxy-, and *o*-acetamido-phenyloxathiazolones, (62), (63) and (64), with a two-fold excess of DMAD yielded compounds (164), (165) and (166) respectively. Nitrile by-products (167a,b,c), formed by fragmentation of the nitrile sulphides, were also observed. Yields are shown in Table 12.

Table 12

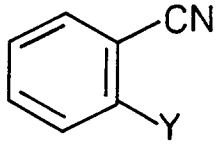


(164)



(165) Y = $OCOCH_3$

(166) Y = $NHCOCH_3$



Y = OH (167a)

(167b)

(167c)

	Yield %	(Recrystallised %)		Yield %
(164)	91[a]	(75)	(167a)	8[a]
(165)	90[a]	(76)	(167b)	10[a]
(166)	67[b]	(18)	(167c)	33[b]

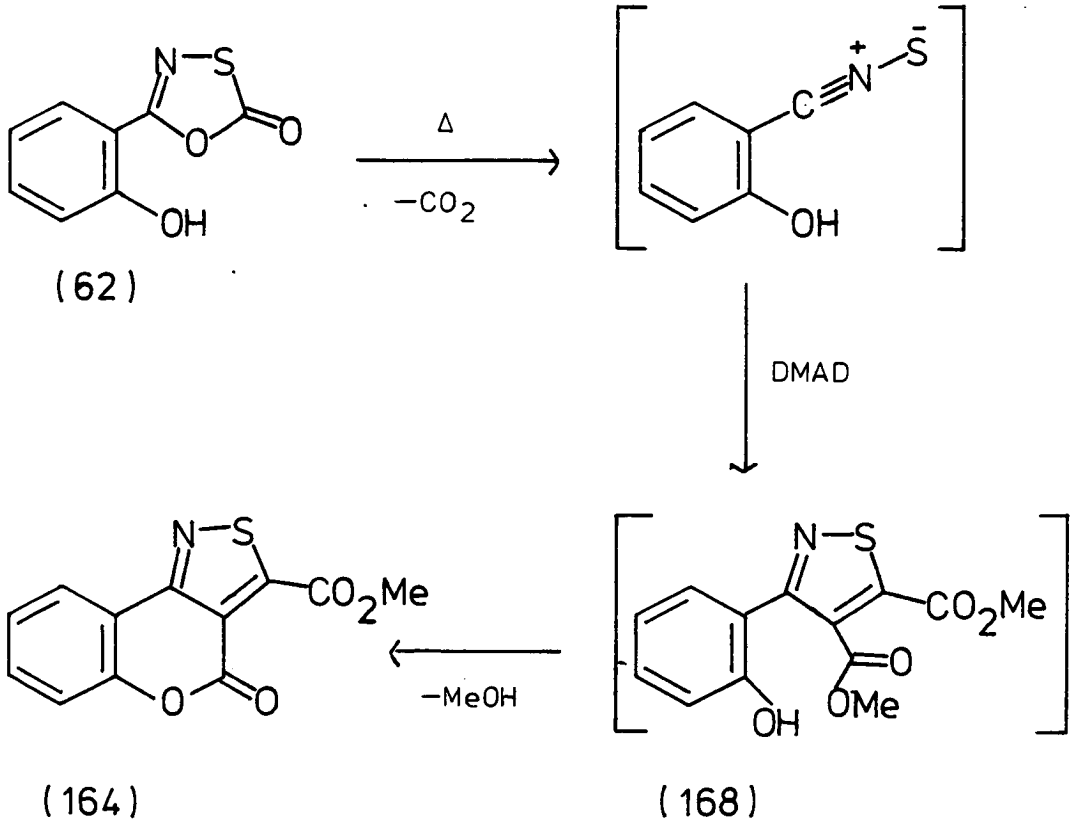
Footnotes:

[a] From flash chromatography. [b] H.p.l.c. estimate.

Treatment of *o*-hydroxyphenyloxathiazolone (62) with DMAD gave methyl 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylate (164), presumably by intramolecular elimination of methanol between the hydroxy function and the methyl ester at the 4-position of the initial isothiazole adduct (168) as shown in Scheme 55. Such an elimination is a known way of producing fused δ-lactone systems (*e.g.* Reference 100).

The chromenoisothiazole ring system so formed is the same as that obtained in some of the intramolecular cyclo-additions described earlier. Its ^{13}C n.m.r. spectrum differs from that of the ethyl oxochromenoisothiazol-3-carboxylate (110) by no more than 0.3 δ p.p.m. for any of the ring carbons.

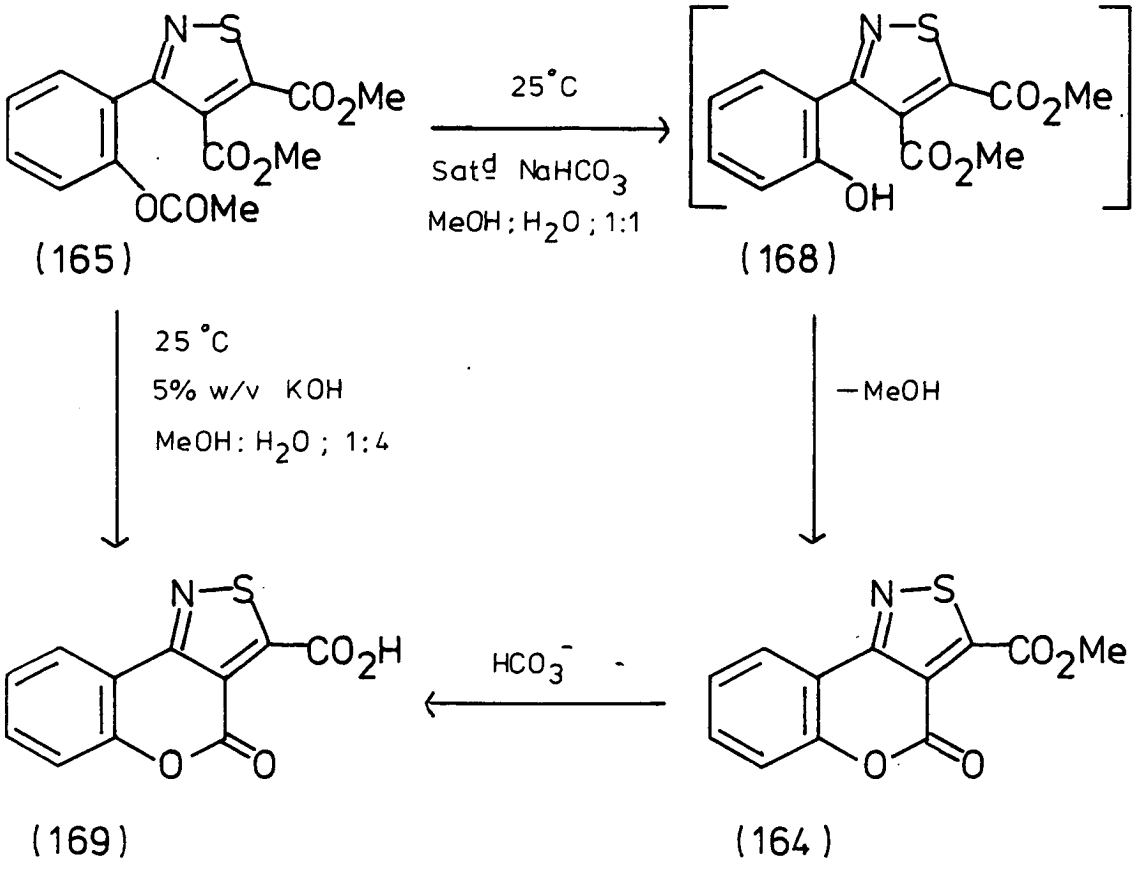
Scheme 55



(62) (164) (168)

It was not certain whether the facility of this elimination of methanol was due solely to the high temperature used in these thermolyses (*ca.* 138°C) or if the isothiazole intermediate (168) would also be unstable at room temperature. To investigate this the *o*-acetoxyphenylisothiazole derivative (165) was subjected to a mild hydrolysis using sodium bicarbonate in an attempt to selectively hydrolyse the acetoxy group, hopefully releasing a free hydroxyl but leaving the methyl esters intact. However, on work-up of the hydrolysate a mixture of the starting material (165), the chromenoisothiazolecarboxylate (164) and the acid (169) was obtained as shown in Scheme 56. The compound (168) with the free phenolic hydroxyl could not be detected.

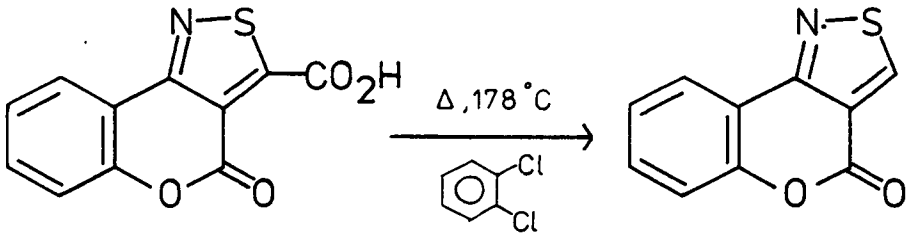
Scheme 56



4-Oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylic acid (169) was also prepared in good yield (87%) by complete hydrolysis of isothiazole (165) using potassium hydroxide, followed by ring closure. The acid was found to decarboxylate under certain conditions: in the mass spectrometer [*m/z* 247 (M^+), 203 (M^+-CO_2)], slowly on standing in solution (making n.m.r. data difficult to obtain) and more rapidly on heating.

The acid was preparatively decarboxylated by heating under reflux in *o*-dichlorobenzene (*ca.*178°C) for one hour. This gave the parent 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole (103), identical to that formed by intramolecular cycloaddition of the acrylate ester described in Section 2.3.3.1, but obtainable by the present method in much higher yield (Scheme 57).

Scheme 57



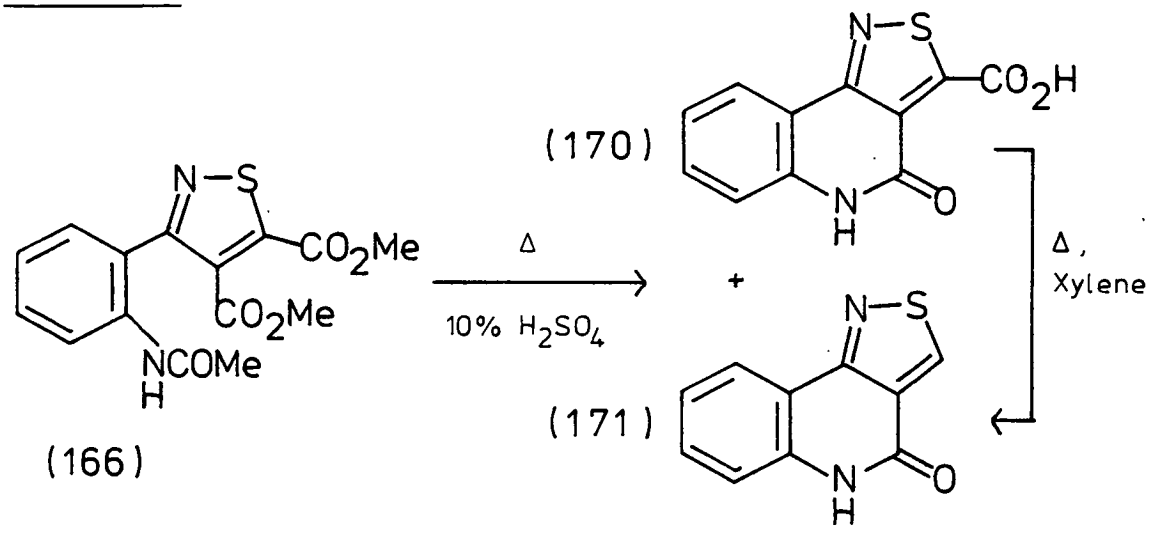
(169) (103)

The overall yield of chromenoisothiazole (103) prepared from *o*-hydroxyphenyloxathiazolone (62) *via* the acetoxy derivative in four steps, as described above was 55%. This might be improved to a two-step sequence by direct reaction of (62) with DMAD, giving chromenoisothiazole (164), followed by a vigorous hydrolysis and decarboxylation step; the potential yield of this route is estimated as >64%. This

compares with a 17% yield from oxathiazolone (62) *via* the acrylate ester (71).

Dimethyl 3-(*o*-acetamidophenyl)isothiazole-4,5-dicarboxylate (166) was also hydrolysed giving a similar reaction (Scheme 58). In this case the conditions used were more vigorous (the compound was heated under reflux in 10% v/v sulphuric acid for 1.5h) and partial decarboxylation of the acid (170) occured. Complete decarboxylation was effected by heating the mixture under reflux in xylene for 20h to give the parent isothiazolo[4,5-*c*]quinolin-4(5*H*)-one (171) in *ca.* 75% yield overall from isothiazole (166).

Scheme 58

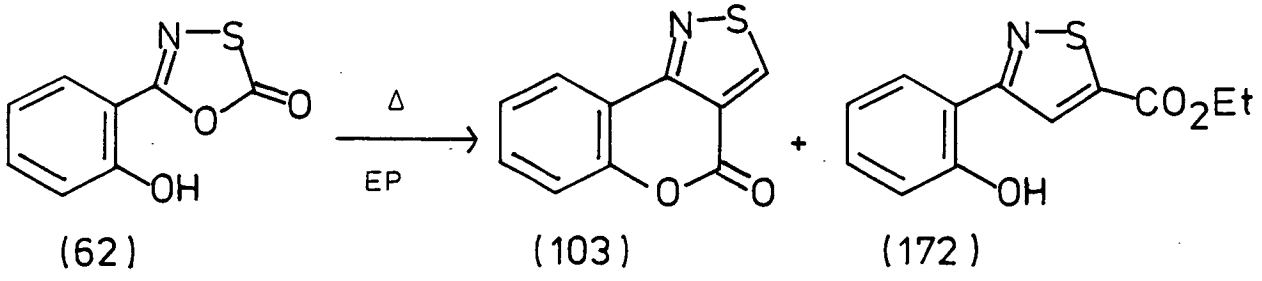


The final product (171) has a similar ^{13}C n.m.r. spectrum to the 3-phenyl derivative (91) already discussed (Section 2.3.2.1) with the exception of the C-3 and C-3a signals (155.22, 127.93 δ p.p.m. respectively). Its ^{1}H n.m.r. spectrum has a sharp singlet for H-3 (9.99 δ p.p.m.) and a very broad peak for the NH (*ca.* 11.4 δ p.p.m.).

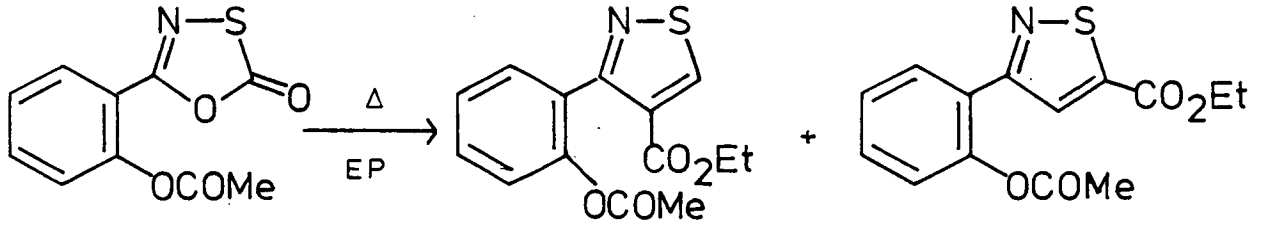
2.4.4 Reactions with Ethyl Propiolate

Cycloaddition of the unsymmetrical alkyne ethyl propiolate (EP) to the nitrile sulphides generated from oxathiazolones (62) and (63) gave a mixture of compounds as shown in Scheme 59. A four-fold excess of EP was used.

Scheme 59



(62) (103) (172)



(63) (173) (174)

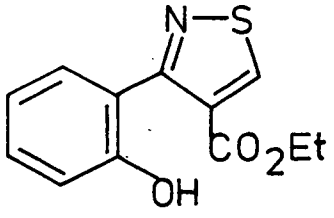
	Yield %	(Recrystallised %)
(103)	20[a]	(10)
(172)	20[b]	(8)
(173)	47[c]	
(174)	46[c]	

Footnotes:

[a] Determined by h.p.l.c. [b] Determined by n.m.r.

[c] Isolated by flash chromatography.

In the reaction with *o*-hydroxyphenyloxathiazolone one product is the parent chromenoisothiazole (103) which, by analogy with the DMAD case, is presumed to arise by elimination of ethanol from the initial cycloadduct (175). The reaction provides a third, but lower yielding route to the parent compound.



(175)

On attempting to purify isothiazoles (173) and (174) it was found that they underwent facile de-acetylation to give products identical to compounds (103) and (172).

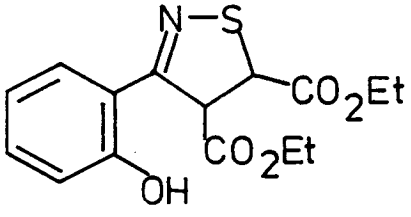
The products (172, 173, 174) show typical properties of disubstituted isothiazoles. ^{1}H N.m.r. spectra show sharp singlets for the heterocyclic ring hydrogen [H-4: 8.11 (172), 8.02 (174) δ p.p.m.; H-5: 9.30 (173) δ p.p.m.].

Both cycloadditions shown in Scheme 59 give a 1:1 ratio of (initial) isothiazole isomers, similar to the ratio reported for phenyloxathiazolone.[20] It can therefore be concluded that small *ortho*-substituents such as those involved here have no effect on the regioselectivity of cycloaddition (*cf.* Section 1.1.3).

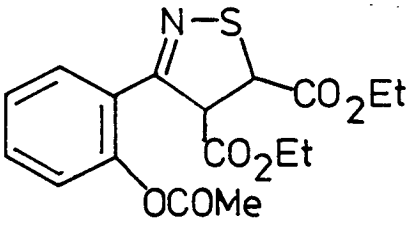
2.4.5 Reactions with Diethyl Fumarate

Cycloadditions of nitrile sulphides derived from oxathiazolones (62) and (63) with diethyl fumarate (DEF) were found not to be such clean reactions as those described for ECF, DMAD and EP. Large amounts of, presumably, oligomeric materials having only ethyl hydrogens, as shown by ^{1}H n.m.r., were often found to contaminate the reaction mixtures making isolation of the desired products difficult.

However, both reactions gave the expected isothiazolines, (176) and (177), as initial adducts in *ca.*26% and *ca.*56% yields respectively. These were found to be rather unstable and were not purified; in their impure states each was a yellow oil.



(176)



(177)

They were recognised by their ^{1}H n.m.r. spectra which each showed the characteristic pair of doublets of the isothiazoline 4- and 5-protons [(176): 5.20 δ p.p.m., d, J=2.7Hz, H-5; 4.65 δ p.p.m., d, J=2.7Hz, H-4. (177): 5.32 δ p.p.m., d, J=4.5Hz, H-5; 4.88 δ p.p.m., d, J=4.5Hz, H-4]. The spectrum of compound (176) also displayed a sharp singlet (11.15 δ p.p.m.) corresponding to the hydroxyl proton.

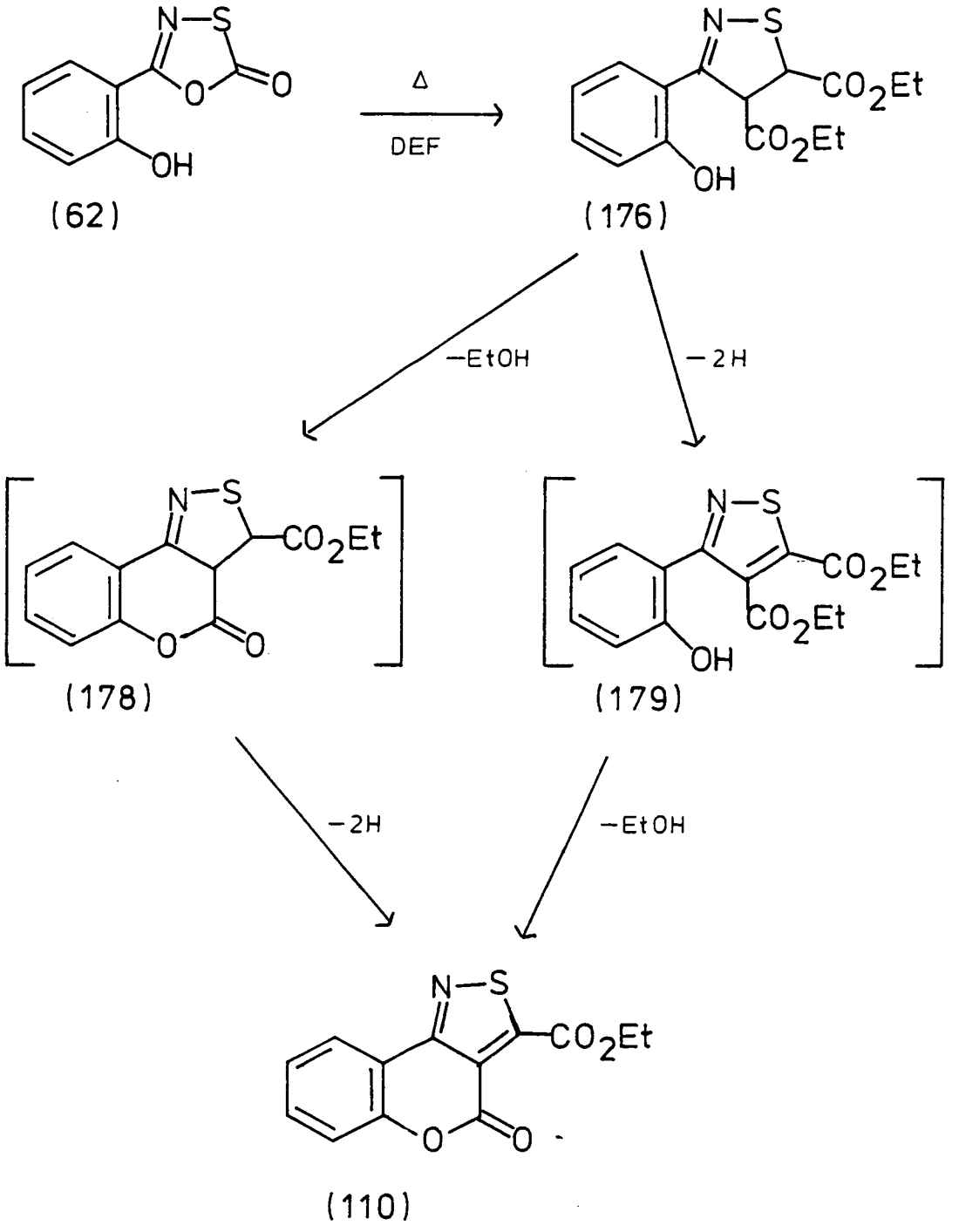
The relative stability of the *o*-hydroxyphenylisothiazoline (176), compared with the similar isothiazole (168) prepared from DMAD, is presumably due to the steric arrangement of the molecule. In addition to the impure isothiazoline (176) a quantity of the ring-closed chromenoisothiazole (110) was isolated from this reaction (15% yield) and found to be identical to the major product of the intramolecular cycloaddition of the monoethyl fumarate ester (109) described in Section 2.3.3.2.

On repeating the cycloaddition of *o*-hydroxyphenyloxathiazolone (62) with DEF the reaction was first stopped after 18h when ^{1}H n.m.r. confirmed the presence of the initial isothiazoline adduct (176) in a sample of the whole reaction mixture (two doublets: 5.19, 4.65 δ p.p.m.). The yield of chromenoisothiazole (110) at that time was determined as 18% by h.p.l.c., which also confirmed that no starting oxathiazolone remained. The whole reaction mixture was then heated under reflux in xylene for a further 40h. At the end of this time ^{1}H n.m.r. showed that none of the isothiazoline (176) remained while the yield of chromenoisothiazole (110) had increased to 26% as determined by h.p.l.c.

The formation of the final product may be explained by one of the alternative mechanistic pathways shown in Scheme 60. Both intermediates proposed, (178) and (179), would be expected, by analogy with experiments already described, to rapidly convert to the chromenoisothiazole (110). However, with the information available it is impossible to

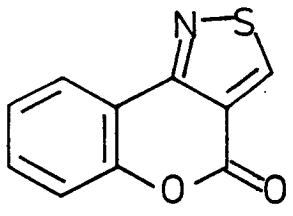
say definitely whether the rate determining factor is governed by dehydrogenation of the unfused isothiazoline or by the steric barrier to formation of the pyran ring.

Scheme 60

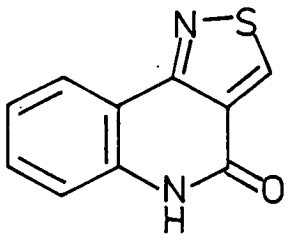


2.4.6 Conclusions

The experiments which have been described above demonstrate that functionalised oxathiazolones can undergo reactions with a typical range of dipolarophiles, *via* cycloadditions of the derived nitrile sulphide dipoles. Those initial products which contain a reactive group may undergo further *in situ* reactions. This process has provided an effective route to the previously unreported fused heterocyclic systems such as the parent members (103) and (171).



(103)



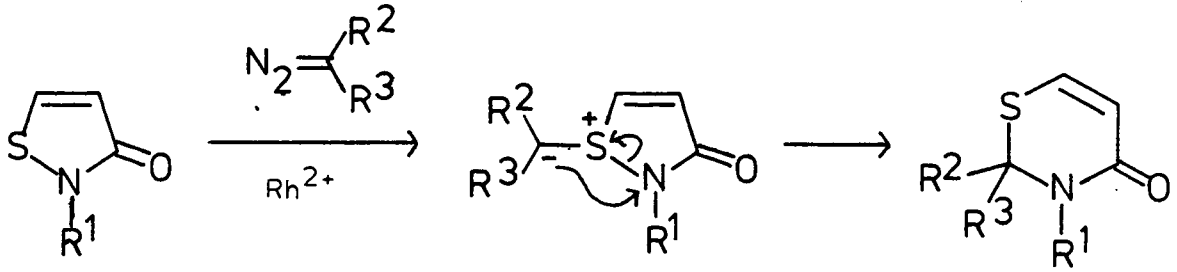
(171)

These methods widen the range, and indicate the potential of this relatively neglected area of heterocyclic synthesis.

2.5 REACTIONS OF DIAZO COMPOUNDS WITH A 1,3,4-OXATHIAZOL-2-ONE

Recently the rhodium(II) catalysed reactions of a number of diazo compounds with isothiazol-3(2*H*)-ones have been reported.[101] The products, 3,4-dihydro-1,3-thiazin-4(2*H*)-ones (180), were thought to arise *via* trapping of a carbene or carbenoid species to form an intermediate sulphonium ylide (181) followed by ring expansion by a 1,2-shift as shown in Scheme 61. This reaction sequence constituted a novel type of S-N bond cleavage of the isothiazole ring system.[101].

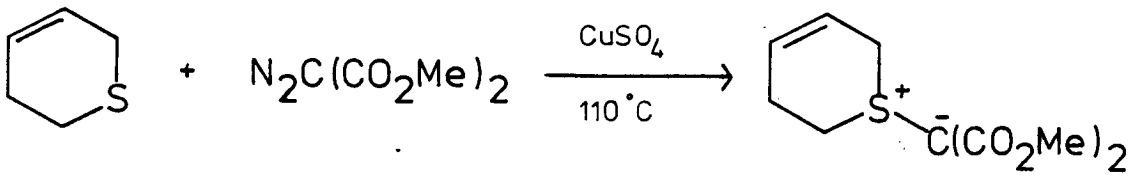
Scheme 61



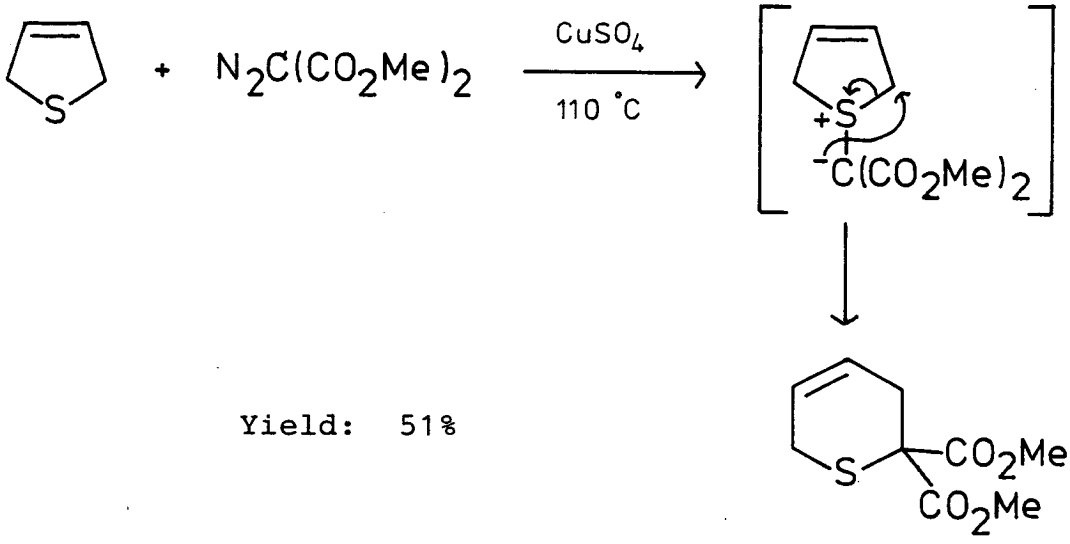
The chemistry of sulphur ylides has been well documented;[102] catalysed reactions of diazo compounds with sulphides, *via* a carbene or carbenoid species, provide one of the major routes to such ylides. Formerly copper(II) compounds were the usual catalysts but more recently rhodium(II) complexes have been found to give higher yields of products.[103,104]

Many examples of stable sulphur ylides are known,[102] but there are also a large number where rearrangements or eliminations occur;[102,105] two examples are shown in Scheme 62.[105,106]

Scheme 62



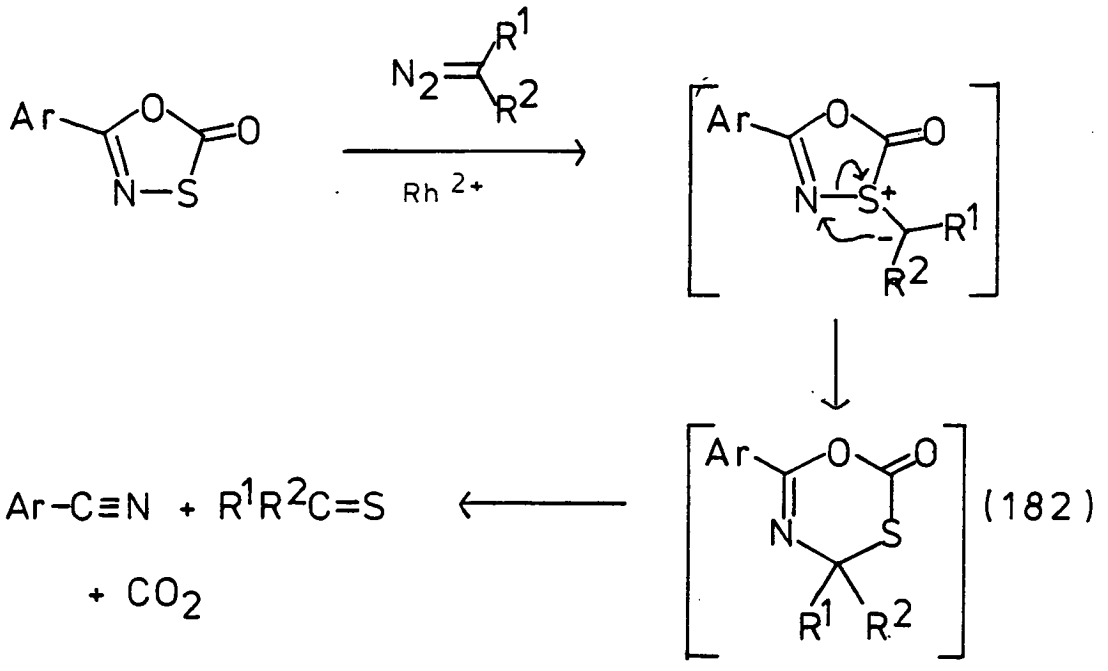
Yield: 66%; m.p.: 103-104°C.



Yield: 51%

It was thought that 1,3,4-oxathiazol-2-ones should be susceptible to a reaction similar to that of isothiazol-3(2*H*)-ones described above. However, the analogous ring expansion product, in this case a 1,3,5-oxathiazin-2(4*H*)-one (182), might be expected to fragment to carbon dioxide, a nitrile and a thiocarbonyl compound as shown in Scheme 63. It was thus with the intention of developing a novel synthesis of thiocarbonyl compounds that the reaction was attempted with a 1,3,4-oxathiazol-2-one.

Scheme 63

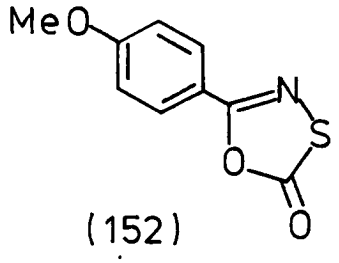


The conditions employed for the reaction were similar to the optimum conditions described by Gillespie and Porter[104] for the reaction of butyl diazoacetoacetate with thiophene. The oxathiazolone and a catalytic amount of rhodium(II) acetate[107] were dissolved in dry benzene then heated to, and held at 75°C using a water bath. The diazo compound[108] was added dropwise, as a solution in dry benzene, over 15 min. The mixture was heated for a further 10 min after which time evolution of nitrogen had become negligible.

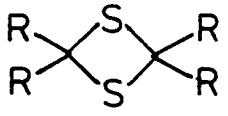
Using a 1.1 molar excess of diazo compound resulted in incomplete consumption of the oxathiazolone; however, this was preferable to the formation of carbene decomposition products which occured when larger excesses were used.

Under these conditions the reactions of dimethyl and diethyl diazomalonates with 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-one (152) gave high yields of the expected

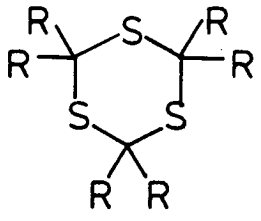
anisonitrile and thiocarbonyl-derived compounds, presumably by the mechanism outlined in Scheme 63. The thiones were not isolated as monomers but as oligomers believed to be the dimeric 1,3-dithietanes (183) or possibly the trimeric 1,3,5-trithianes (184).



(152)



(183 a,b)



(184 a,b)

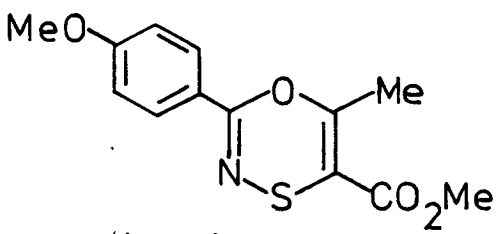
a: R = CO_2Me ; b: R = CO_2Et

There is some doubt as to the nature of these thiocarbonyl oligomers. The 1,3-dithietane (183b) has been reported in the literature on two occasions as a crystalline solid with melting point 51-55°C[109] or 59.5-60°C.[110] The compound isolated in the present case gave good, colourless plates from cold pentane, but these melted below room temperature even after repeated recrystallisations. Its mass spectrum, however, apparently showed a clear parent ion peak for the dimer [*m/z* 380 (M^+)]. ^{13}C N.m.r. signals for the ring carbons appeared as a single peak at 51.54 δ p.p.m. making contamination by a higher oligomer unlikely. The corresponding data for the literature compound is unavailable.

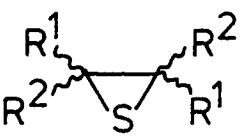
These oligomers were rather unstable. Attempted

recrystallisation of the methyl ester (183a or 184a) resulted in its decomposition to sulphur and tetramethyl ethylenetetracarboxylate. Such alkenes are known to be thermal derivatives of thiocarbonyl compounds.[111,112]

The reaction of methyl diazoacetoacetate with *p*-methoxyphenyloxathiazolone (152) gave additional products. Anisonitrile and thiocarbonyl-derived compounds were again formed but a small yield of methyl 2-(*p*-methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate (185) was also obtained (8% yield on 78% conversion of oxathiazolone).



(185)



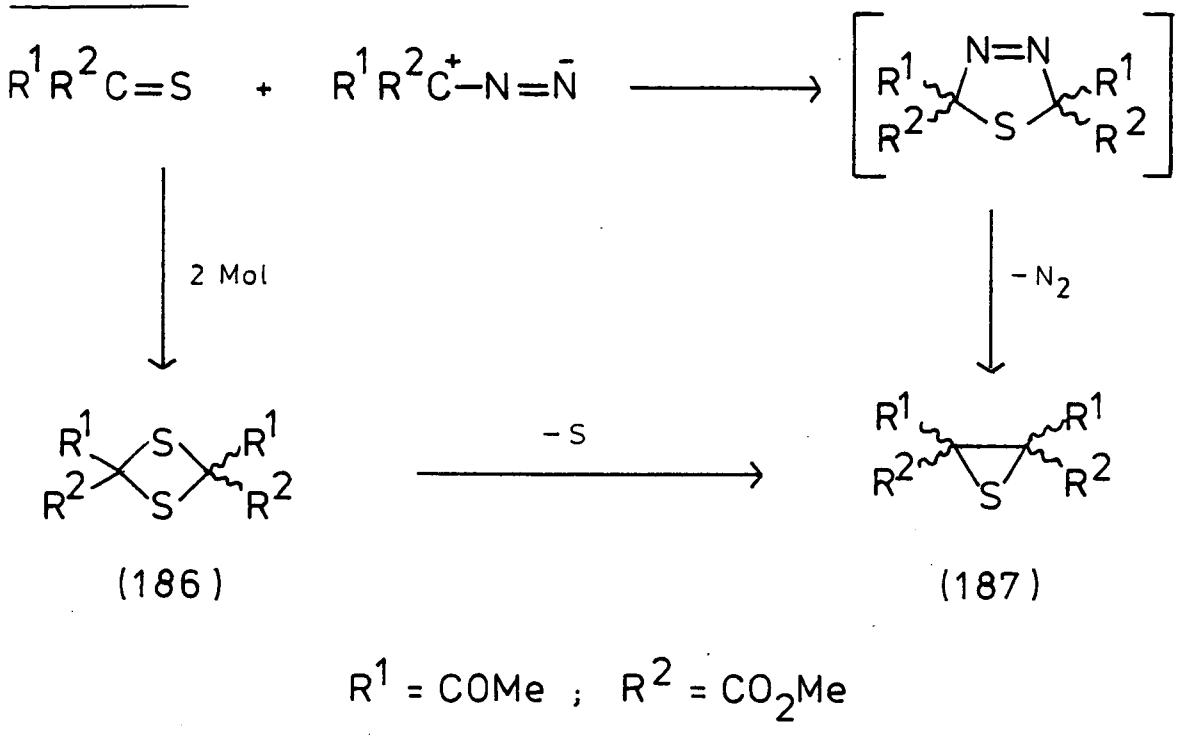
(187)

R^1=COMe ; R^2=CO_2Me

Three thiocarbonyl-derived products were isolated. One is believed to be the 1,3-dithietane (186), a pair of geometric isomers [*m/z* 292 (M^+); ^{13}C n.m.r.: all ring carbons coincident at 29.34 δ p.p.m.]; its identity is by implication subject to the same doubts as expressed for the previous examples. The second was the thiirane (187), a mixture of geometric and optical isomers [*m/z* 260 (M^+); ^{13}C n.m.r.: all ring carbons coincident at 29.41 δ p.p.m.]. This may be derived from the diazo compound and the thiocarbonyl monomer by initial 1,3-dipolar cycloaddition followed by loss of nitrogen and ring contraction.[113,114] Alternatively it might arise *via* extrusion of sulphur from the

dithietane (186). These possibilities are shown in Scheme 64. The third thiocarbonyl-derived product, which was not well characterised, was possibly a higher oligomer or polymer of the thione.

Scheme 64

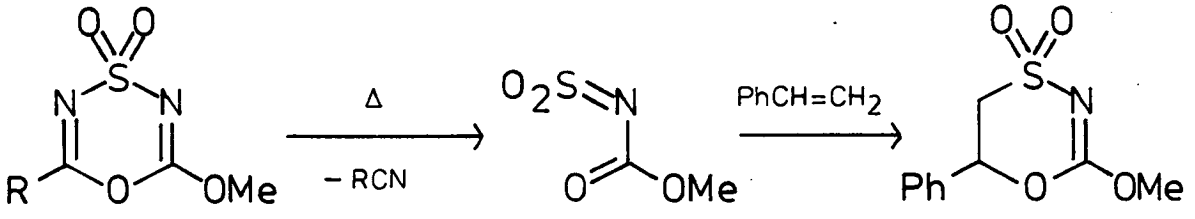


$R^1 = COMe$; $R^2 = CO_2Me$

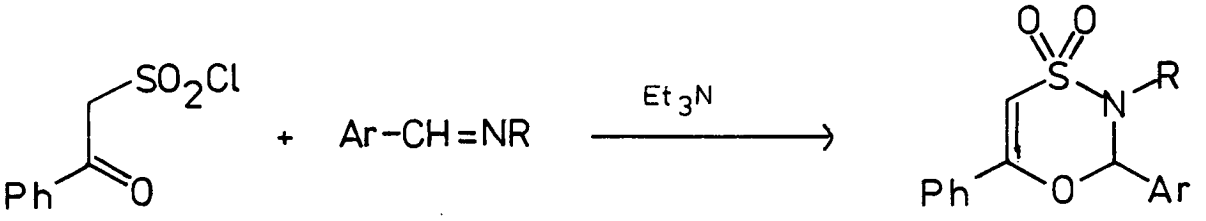
As mentioned above an additional product in this particular reaction was the oxathiazine (185). 1,4,3-Oxathiazines form a fairly small class of heterocycles.[82] Most members have a partially or fully saturated ring and an oxidised sulphur atom; typical examples and their sources are shown in Scheme 65.

Scheme 65

Reference 115



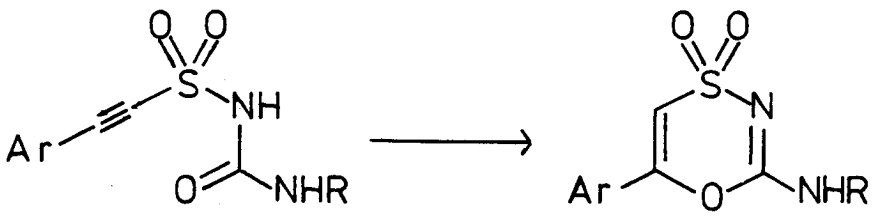
Reference 116



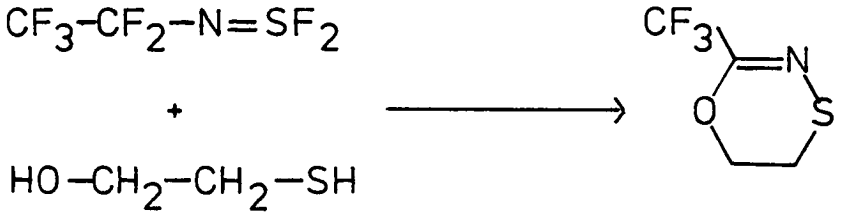
In few cases is the 1,4,3-oxathiazine ring system fully unsaturated, similarly few contain a sulphide bridge; two examples are shown in Scheme 66. It appears that the oxathiazine isolated in the reaction described here is unique in combining full unsaturation with a sulphide bridge.

Scheme 66

Reference 117

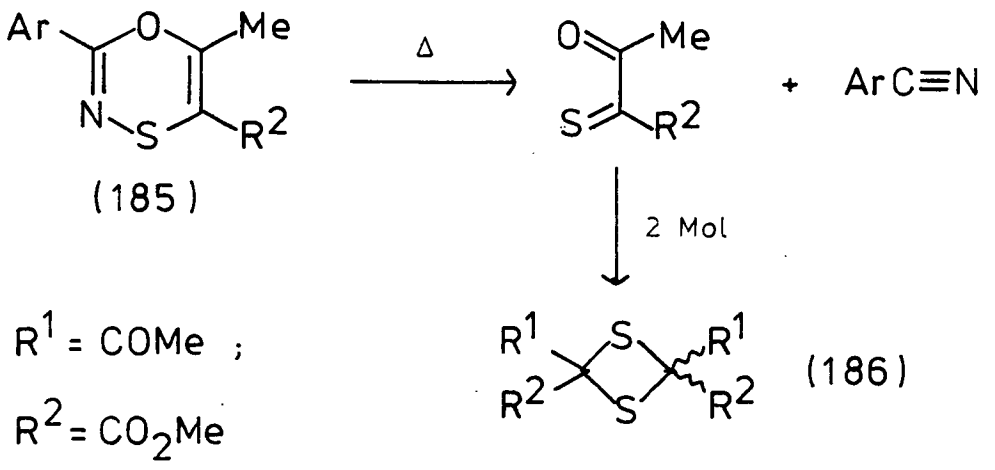


Reference 118



The present oxathiazine (185) was isolated from the reaction mixture by repetitive flash chromatography, being difficult to separate from anisonitrile. It was obtained as a bright yellow, crystalline solid, stable at room temperature but decomposing on melting (m.p. 104-105°C) or on heating in solution. After 20h under reflux in dry benzene none of the compound remained. The decomposition products were identified as anisonitrile and the material thought to be the thiocarbonyl dimer (186), both of which may result by a Diels-Alder retro-cycloaddition as shown in Scheme 67.

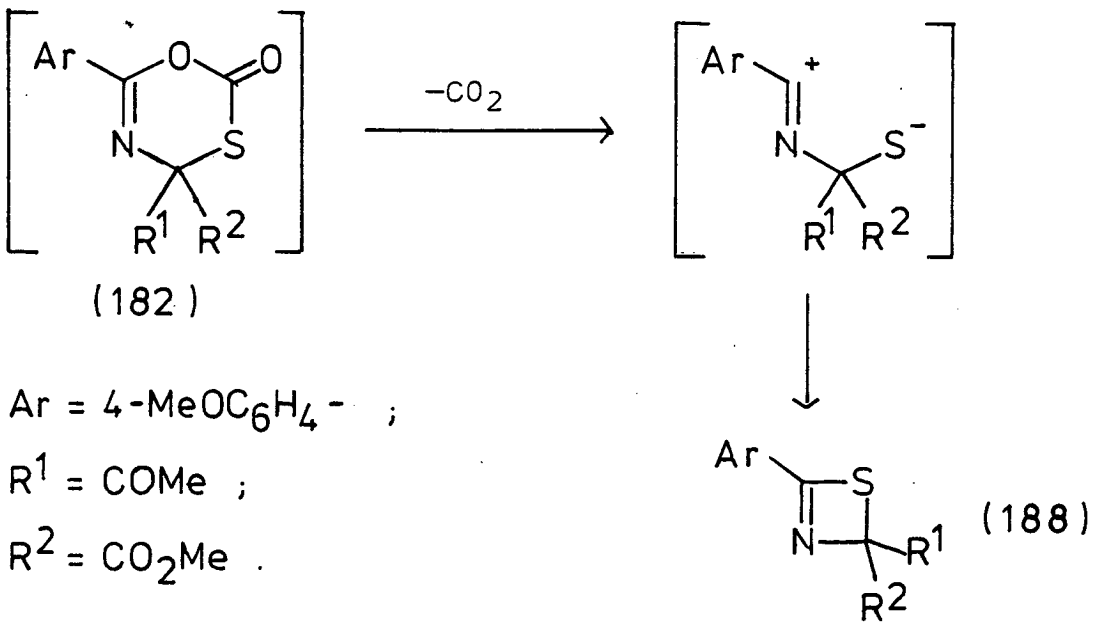
Scheme 67



The yellow colour of the oxathiazine corresponds to an absorbance at $\lambda_{max.}$ (CH_2Cl_2) 372nm (ε 1136 $dm^3mol^{-1}cm^{-1}$) in the visible spectrum; a stronger u.v. absorbance is also present [$\lambda_{max.}$ (CH_2Cl_2) 273nm (ε22719 $dm^3mol^{-1}cm^{-1}$)]. In the $^{1,3}C$ n.m.r. spectrum signals for the oxathiazine ring carbons appear at 156.25 δ p.p.m., C-6; 153.07 δ p.p.m., C-2; and 105.74 δ p.p.m., C-5.

However, the structure of the compound could not be absolutely assigned on the basis of spectroscopic evidence alone; an alternative isomeric structure, the 1,3-thiazete derivative (188), had also to be considered. This has analogues in the literature[119] and a plausible mode of formation in the present reaction from the 1,3,5-oxathiazine intermediate (182) (Scheme 63) proposed as the precursor of the nitrile and thione products. This hypothetical sequence is shown in Scheme 68.

Scheme 68



(182)

Ar = 4-$MeOC_6H_4$- ;

R^1 = COMe ;

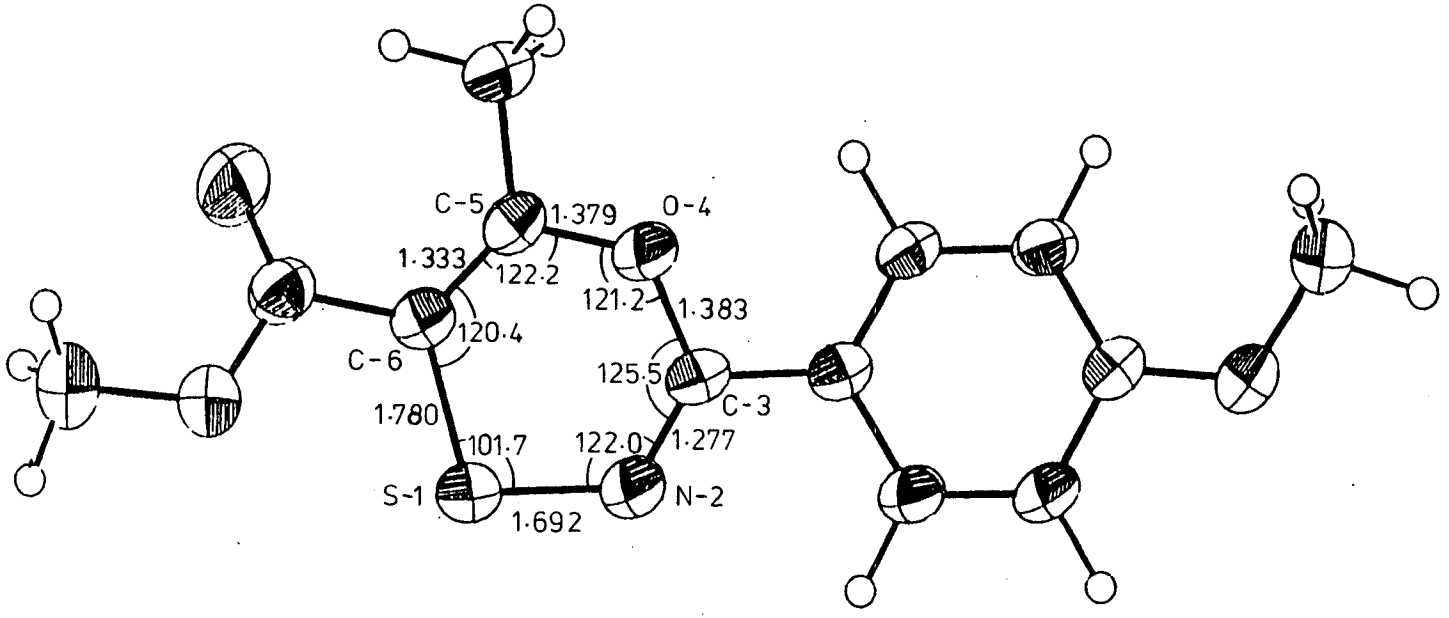
R^2 = CO_2Me .

(188)

In view of this uncertainty a single crystal X-ray diffraction study of the product was undertaken. This confirmed the identity of the material as the 1,4,3-oxathiazine (185). The crystal structure is shown in Figure 5 together with selected bond lengths and angles.

The bond lengths are not unusual for a heterocycle containing nitrogen, oxygen and sulphur. The S-N-C-O portion has bond lengths very similar to those of the 1,3,4-oxathiazole ring as found in 5-(*p*-methoxyphenyl)-2-phenyl-2-trifluoromethyl-1,3,4-oxathiazole (189).[120] The C=C (1.33Å) and C=N (1.28Å) bond lengths are consistent with localised double bonds. The oxathiazine ring is not planar, being folded along the S-O axis to an angle of *ca.* 20°. Also the benzene ring is raised from the S-N-C-O plane by *ca.* 6° and twisted with respect to it by *ca.* 6°. Figure 6 shows the stereochemical arrangement in an exaggerated form.

Figure 5: Crystal Structure of Methyl 2-(*p*-Methoxyphenyl)-6-Methyl-1,4,3-oxathiazin-5-carboxylate[a] with Selected Bond Lengths[b] and Bond Angles[c]

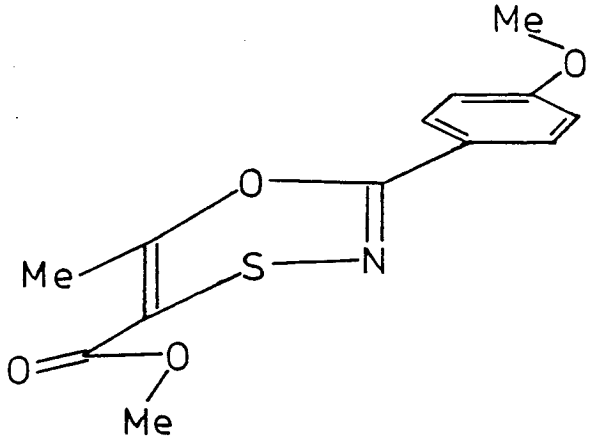


Footnotes:

[a] The atom numbering given is that used in the full tables of crystallographic data presented in Appendix 4.6; this does not correspond to the usual nomenclature having sulphur as position one instead of oxygen.

[b] In Angstroms. [c] In degrees.

Figure 6: Stereochemistry of Methyl 2-(*p*-Methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate with Selected Torsion Angles

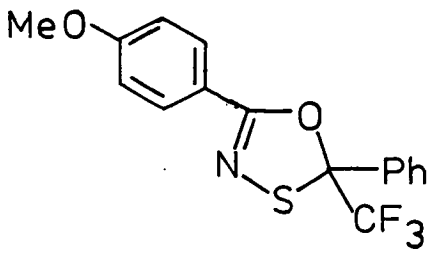


Torsion Angles[a] (Degrees)

C(6)-S(1)-N(2)-C(3)	20.0
N(2)-S(1)-C(6)-C(5)	-17.5
C(6)-C(5)-O(4)-C(3)	23.7
N(2)-C(3)-O(4)-C(5)	-21.8
O(4)-C(3)-N(2)-S(1)	-3.4
O(4)-C(5)-C(6)-S(1)	-1.7
C(31)-C(3)-N(2)-S(1)	173.71
N(2)-C(3)-C(31)-C(32)	-6.7
C(51)-C(5)-C(6)-S(1)	179.8
O(4)-C(5)-C(6)-C(61)	177.3
C(51)-C(5)-C(6)-C(61)	-1.1

Footnote:

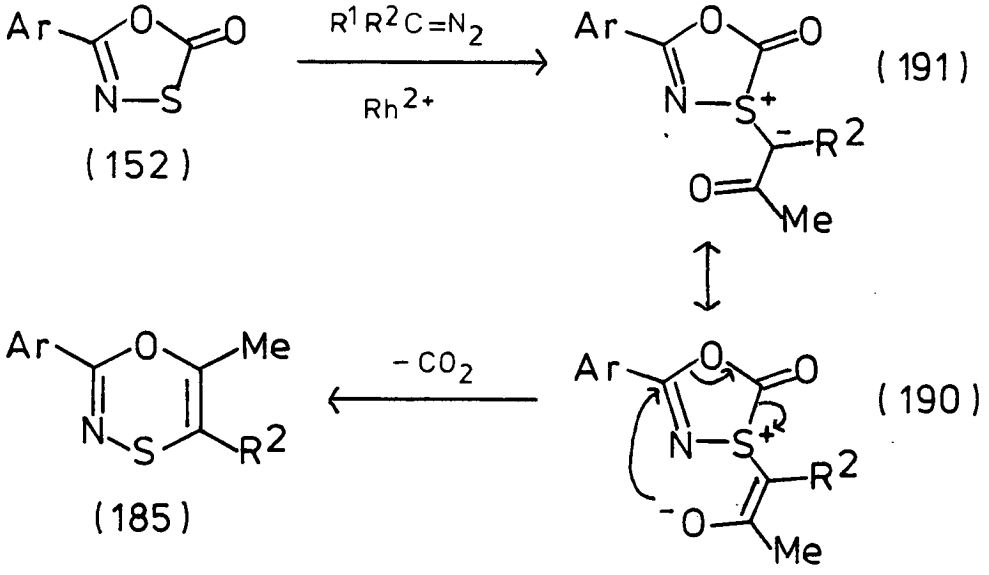
[a] Atom numbering as in Figure 5.



(189)

The most likely mechanism for the formation of the oxathiazine is thought to be the intramolecular displacement of carbon dioxide in the enolate anion canonical form (190) of the initial sulphur ylide (191), as shown in Scheme 69.

Scheme 69



Ar = 4-$MeOC_6H_4$; R^1 = COMe ; R^2 = CO_2Me .

The isolation of the oxathiazine in one example of this reaction, that using methyl diazoacetoacetate, casts some doubt on the reaction mechanism invoked for the earlier examples using dimethyl and diethyl diazomalonates. The

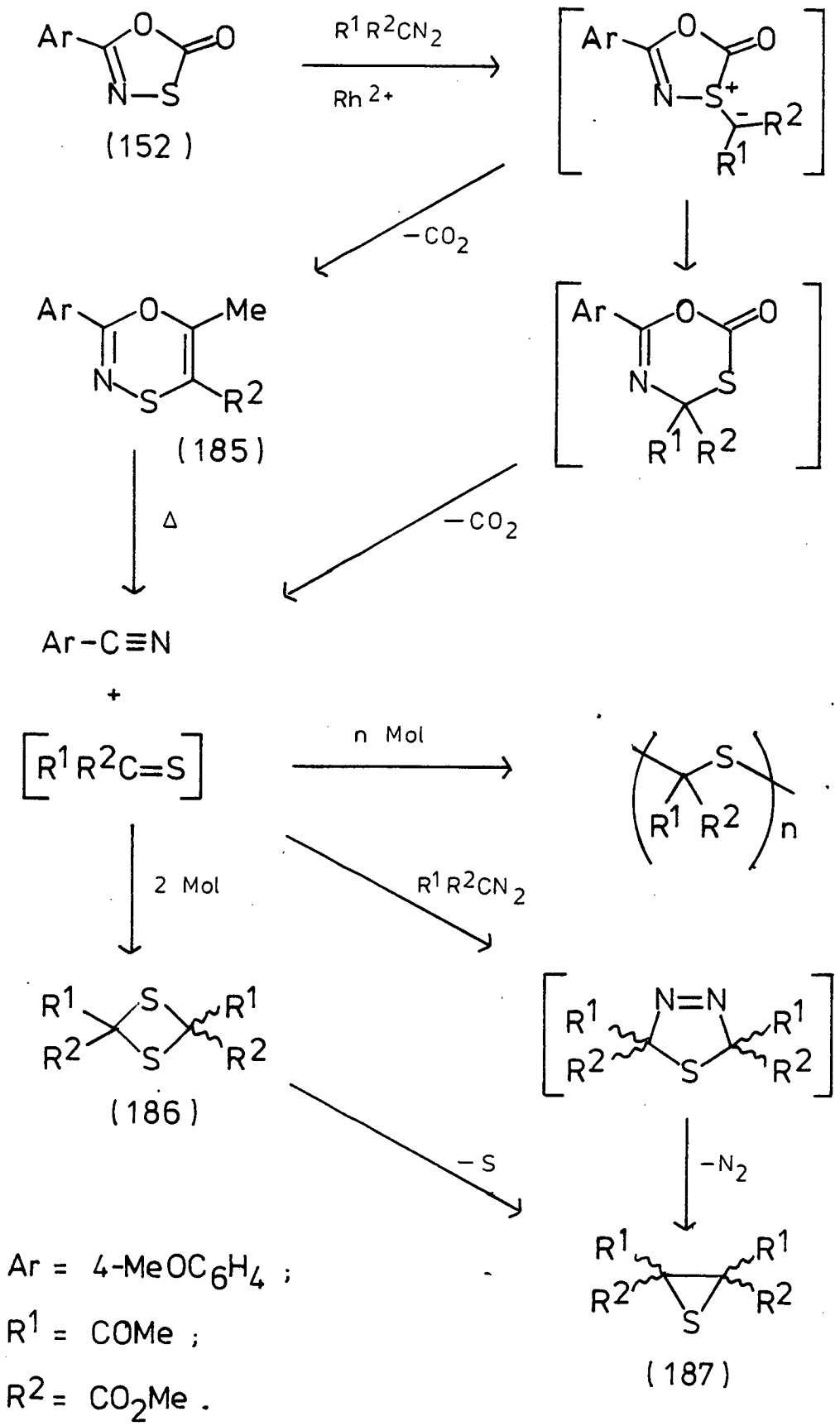
final products of the reaction pathway, anisonitrile and thiocarbonyl oligomers, could arise *via* retro-cyclo-addition of a 1,4,3-oxathiazine as has been shown to occur for the isolable example, rather than by fragmentation of the proposed 1,3,5-oxathiazin-2-one intermediate (182).

There is, however, no evidence to support the intermediacy of a 1,4,3-oxathiazine; its bright yellow colour was not observed during reactions with the diazomalonates but it was very obvious in the reaction of methyl diazoacetoacetate. Also the relative stability of the isolated 1,4,3-oxathiazine contrasts with the observed rapid rate of the initial reactions.

It seems likely, therefore, that two competitive mechanisms are open to an initial sulphur ylide of the type (191). The proposed ring expansion, ring fragmentation sequence shown in Scheme 63 leading directly to the thione and anisonitrile with loss of carbon dioxide may occur whatever the carbene component. The alternative formation of the 1,4,3-oxathiazine ring (Scheme 69) appears to be available only when the carbene component bears a ketone substituent. The various possible pathways of this reaction are drawn together and summarised in Scheme 70.

It should also be noted that there is no direct evidence for the 1,3,5-oxathiazin-2-one (182) intermediate proposed for these reactions; its existence is merely assumed by analogy with the stable products derived from related ylides.[101] It is conceivable that other mechanisms exist for the breakdown of the initial sulphur ylide.

Scheme 70



Ar = 4-$MeOC_6H_4$;

R^1 = COMe ;

R^2 = CO_2Me .

Summary

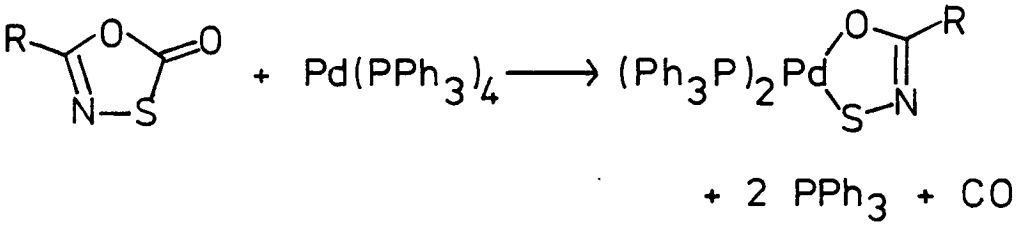
The reaction of 1,3,4-oxathiazol-2-ones with diazo compounds under rhodium(II) catalysis has been shown to provide a novel route to thiocarbonyl compounds. Additionally, in one case, a further material of interest was isolated. This has been shown, by X-ray analysis, to be methyl 2-(*p*-methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate, a new and unusual member of a rare class of heterocycles. It is thought that a competing mechanism is responsible for this compound the availability of which depends on the nature of the diazo component in the reaction.

Potential extensions to this work include the following. The use of a diazo component that would lead to a stable thiocarbonyl compound would be desirable. Also the identification of any other diazo compounds yielding a 1,4,3-oxathiazine would provide further evidence concerning the mechanism proposed above.

2.6 THE REACTION OF TRIPHENYLPHOSPHINE WITH A 1,3,4-OXATHIAZOL-2-ONE

In the introduction (Section 1.5.3, page 45), the reaction[72] of an oxathiazolone with tetrakis(triphenylphosphine)palladium (Ø) was discussed. The main product is a palladium complex of the anion of a *N*-thiohydroxamic acid derivative and is shown again in Scheme 71.

Scheme 71



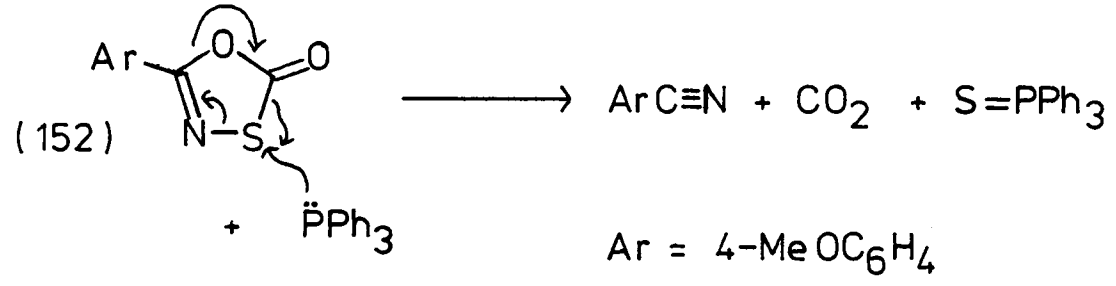
In this process nitrile, triphenylphosphine sulphide and carbon dioxide were also observed as by-products. It was assumed that these arose by removal of sulphur from the oxathiazolone by liberated triphenylphosphine. However, the suggestion that a free nitrile sulphide might be involved was implied by a mention[72] of the analogous removal of oxygen from nitrile oxides by triphenylphosphine.[73] Also there was no report of the sulphur extraction occuring in a mixture free from any metal complex.

This ambiguity is clarified by the present work where the room temperature reaction of triphenylphosphine with 5-(*p*-methoxyphenyl)-1,3,4-oxathiazol-2-one (152) has been studied. An equimolar mixture of these reactants in

methylene chloride gave an immediate effervescence. This subsided after several minutes when t.l.c. showed little oxathiazolone remaining. Flash chromatography of the reaction mixture yielded some unreacted oxathiazolone, anisonitrile, and triphenylphosphine sulphide. The separation of these compounds was poor but small pure samples were obtained which were identified by ^1H n.m.r. and by mixed melting point comparisons with authentic materials.

The demonstration that triphenylphosphine will readily remove sulphur from 1,3,4-oxathiazol-2-ones using conditions under which the heterocycle alone shows no tendency to fragment, makes it unlikely that either a free nitrile sulphide, or any metallated species is involved in the reactions[72] discussed above leading to a nitrile and triphenylphosphine sulphide. The mechanism is instead likely to proceed *via* attack at sulphur by the phosphine, resulting in ring fragmentation as shown in Scheme 72. The reaction thus provides a complementary process to that concerning diazo compounds described in Section 2.5.

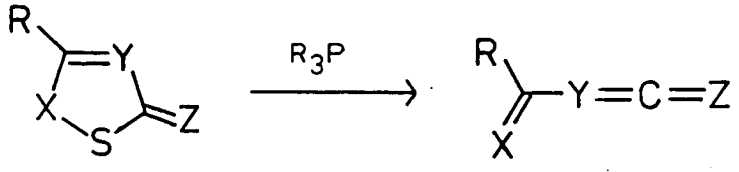
Scheme 72



The present observation can be compared to the work of Goedler[74] who has shown that, in general, tertiary phosphines aid the extrusion of sulphur from five membered

heterocycles of the type (192). This reaction has been used in the preparation of a number of conjugated and/or cumulated hetero-polyene systems as shown in Scheme 73.

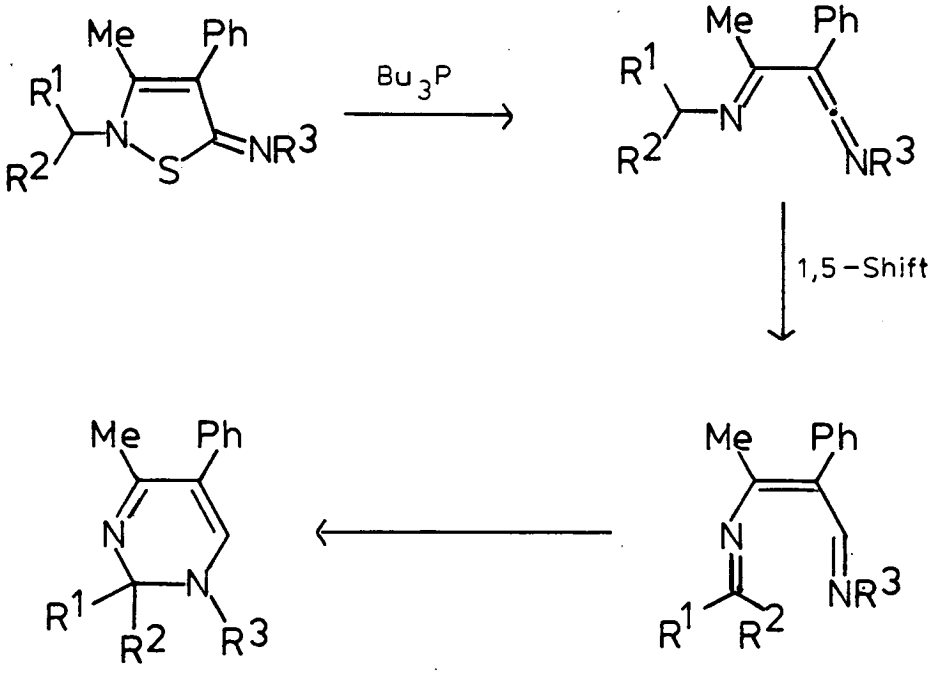
Scheme 73



(192)

X,Z = NR,S ; Y=CR,N

Example:[74]



3. EXPERIMENTAL

3.1 GENERAL

3.1.1 Glossary of Terms, Symbols and Abbreviations

AO	atomic orbital
b.p.	boiling point
br	broad
CNDO	complete neglect of d-orbitals
δ	chemical shift
Δ	thermal energy
d	doublet
decomp.	decomposition
DEF	diethyl fumarate
DEPT	distorsionless enhancement by polarisation transfer
dioxan	1,4-dioxan
DMAD	dimethyl acetylenedicarboxylate
DMF	dimethylformamide
DMSO	dimethylsulphoxide
ε	extinction coefficient
ECF	ethyl cyanoformate
EP	ethyl propiolate
ether	diethyl ether
eV	electron volt
FMO	frontier molecular orbital
g.c.	gas chromatography
h	hour
$h\nu$	photolytic energy

HOMO	highest occupied molecular orbital
h.p.l.c.	high performance liquid chromatography
i.r.	infra red
J	coupling constant
λmax.	wavelength of absorbance maximum (U.V.)
LUMO	lowest unoccupied molecular orbital
m	multiplet
M	molar
M^+	mass of molecular ion
min	minute
mmol	millimole
MO	molecular orbital
mol	mole
m.p.	melting point
m.s.	mass spectroscopy
m/z	mass to charge ratio
νmax.	wavenumber of absorbance maximum (i.r.)
NOE	nuclear Overhauser enhancement
n.m.r.	nuclear magnetic resonance
p.p.m.	parts per million
q	quartet
R.T.	room temperature (25°C)
s	singlet
t	triplet
t.l.c.	thin layer chromatography
u.v.	ultra violet
xylene	mixed *o*,*m*,*p*-xylenes

3.1.2 Instrumentation

(i) Elemental Analysis

Elemental analyses were performed by Mr. J. Grunbaum using a Perkin-Elmer 204 apparatus or by Mrs. E. McDougal using a Carlo Erba Elemental Analyser Model 1106.

(ii) Infra Red Spectroscopy

I.r. spectra were recorded as Nujol mulls or as liquid films on a Perkin-Elmer 781 spectrophotometer.

(iii) Mass Spectroscopy

Mass spectra and exact mass measurements were obtained on an A.E.I. MS902 or a Kratos MS 50TC instrument by Mr. D. Thomas, Mr. A. Thomson and Miss E. Stevenson.

(iv) Melting Points

Melting points were measured in open capillary tubes using an Electrothermal 1A6304 or a Gallenkamp MFB595 apparatus.

(v) Nuclear Magnetic Resonance Spectroscopy

^{1}H n.m.r. spectra were recorded on three Brucker instruments: WP80, WP200 and WH360; by Mr. L.H. Bell, Mr. J.R.A. Millar and Dr. D. Reed respectively.

^{13}C n.m.r. spectra were recorded by Mr. J.R.A. Millar on a Varian CFT20 or a Brucker WP200 spectrometer.

Chemical shifts (δ) in all n.m.r. spectra are measured in parts per million downfield from tetramethylsilane ($\delta=0.0$).

(vi) Ultra Violet Spectroscopy

U.v. spectra were recorded using a Pye Unicam SP8-400 spectrophotometer.

(vii) X-Ray Diffraction Analysis

The X-ray diffraction analysis of compound (185) was performed by Dr. A. Blake using a STADI-2 diffractometer.

3.1.3 Chromatography

(i) High Performance Liquid Chromatography

H.p.l.c. analyses were performed using a 15 x 0.5 cm column packed with Spherisorb 5 μm silica gel (50% water deactivated). Peak detection employed a Cecil CE 212 u.v. monitor set at 254 nm linked to a chart recorder and a Venture Mark II digital integrator.

Elution was with isocratic mixtures of ether or dioxan in hexane (50% water saturated; Rathburn, h.p.l.c. grade).

Quantitative analyses were made by the internal standard method, with calibration standards in triplicate, leading to an estimated maximum absolute error of half a yield percentage point. On two occasions, noted below, this proved impossible and a simple peak area matching (external standard) technique was used giving a relative error estimated at 0.05.

(ii) Thin Layer Chromatography

T.l.c. was carried out using glass plates coated with silica gel containing a green fluorescent indicator (Merck, Silica gel G, type 60).

(iii) Flash Chromatography

Flash chromatography was performed on 15 x 2,4 or 6 cm silica gel columns (Merck, type 60, 230-400 mesh) under an applied nitrogen pressure of 0.5-1.0 atmospheres. The silica was regenerated by heating for 12h at 600°C and reused.

(iv) Gravity Column Chromatography

Gravity column chromatography was carried out on silica gel (Fis ons, 60-120 mesh, 5% water deactivated).

3.1.4 Solvents and Reagents

All solvents and reagents used were standard commercial grade with the exceptions noted below.

Anthranilamide (Lancaster Synthesis) was recrystalised from ethanol after hot, charcoal filtration.

Xylene was distilled from phosphorus pentoxide and stored over sodium wire.

Where dry ether or dry benzene is mentioned in the text, this had been dried over sodium wire.

Where dry chloroform is mentioned this had been distilled from and stored over anhydrous calcium chloride.

3.2 PREPARATION OF CARBOXYLIC ACIDS, CARBOXYLIC ACID CHLORIDES, ESTERS, AND SECONDARY AMIDES

3.2.1 Carboxylic Acids

(i) 3-(*p*-Chlorophenyl)propiolic Acid

This compound was prepared in four steps from *p*-chlorocinnamic acid, in almost quantitative yield, by common synthetic procedures. An outline is given below.

p-Chlorocinnamoyl chloride was prepared by heating *p*-chlorocinnamic acid in thionyl chloride (*cf.*Section 3.2.2). Ethyl *p*-chlorocinnamate was prepared by the reaction of *p*-chlorocinnamoyl chloride with ethanol in the presence of triethylamine (*cf.*Section 3.2.3). Ethyl *p*-chlorocinnamate was dibrominated using one equivalent of bromine. The resulting ethyl 2,3-dibromo-3-(*p*-chlorophenyl)propanoate was doubly dehydrobrominated and hydrolysed to give the desired product in a single step by heating under reflux with three equivalents of potassium hydroxide in ethanol.

The crude product was obtained as a beige powder in almost quantitative yield. It was recrystallised from a cyclohexane-chloroform mixture giving fine colourless needles, yield 72%, m.p. 200-202°C, (lit.,[121] 192-193°C).

(ii) β-Methylcinnamic Acid

This acid was prepared by the method of Lipkin and Stewart[122] from acetophenone and ethyl bromoacetate *via* the ethyl ester. The crude product was obtained in 59% yield as a yellow solid which was used directly in further synthesis without purification. In the present preparation

only the *E*-isomer was isolated, as demonstrated by n.m.r. spectra of its derivatives (*vide infra*). This contrasts with the literature report[122] where, by the same procedure, both *E*- and *Z*-isomers were obtained.

(iii) 2,4,6-Trimethylcinnamic Acid and (iv) 2,6-Dichlorocinnamic Acid

These *ortho*-disubstituted cinnamic acids were prepared *via* their ethyl esters by the method of Böck, Lock and Schmidt,[123] from appropriately substituted benzaldehydes and ethyl acetate, using sodium metal.

2,4,6-Trimethylcinnamic acid was obtained in 84% yield from mesitaldehyde and ethyl acetate, m.p. 172-175°C (lit.,[124] 176°C). 2,6-Dichlorocinnamic acid was prepared in 76% yield from 2,6-dichlorobenzaldehyde and ethyl acetate, m.p. 180-185°C (lit.,[125] 184°C).

3.2.2 Carboxylic Acid Chlorides

Where acid chlorides were not commercially available they were prepared by the following general procedure.

The carboxylic acid (0.1 mol) was mixed with thionyl chloride (25-50 ml, 0.35-0.7 mol) and heated under reflux until the production of sulphur dioxide and hydrogen chloride ceased (1-2h). Excess thionyl chloride was mostly evaporated under vacuum. If the product could be crystallised from the resulting oil it was washed with cold hexane to remove final traces of thionyl chloride. In other cases the product was distilled, recrystallised or used directly.

The acid chlorides prepared by this method are listed in Table 13.

Table 13: Acid Chlorides

Acid Chloride	Yield, %
monoethyl fumaroyl chloride	82[a]
p-chlorocinnamoyl chloride	54[b]
p-methoxycinnamoyl chloride	89[c]
p-methylcinnamoyl chloride	86[c]
α-methylcinnamoyl chloride	53[c]
β-methylcinnamoyl chloride	100[d]
2,6-dichlorocinnamoyl chloride	83[c]
2,4,6-trimethylcinnamoyl chloride	83[c]
3-(2-furyl)acryloyl chloride	73[c]
2-furoyl chloride	76[a]
3-furoyl chloride	40[c]
3-(*p*-chlorophenyl)propiolyl chloride	100[d]

Footnotes:

[a] Distilled

[b] Recrystallised

[c] Washed with hexane

[d] Unpurified

3.2.3 Preparation of Carboxylate Esters

A number of carboxylate esters were prepared from various acid chlorides with three main phenolic compounds: salicylamide (66), 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (62) and *o*-cyanophenol (73), as well as some miscellaneous compounds. They were all prepared by the same general procedure which is described below. The reactions were performed at room temperature except for those involving salicylamide. Esters of salicylamide were prepared at -15 to -30°C in order to maximise the desired product and reduce *O* to *N* isomerisation as discussed in Section 2.1.

General Procedure

The phenol or alcohol (0.05 mol) and the acid chloride (0.05 mol) were dissolved together in dry ether (250 ml) with mechanical stirring. Triethylamine (0.055 mol) was added dropwise over 5-10 min and stirring was continued for 30 min. A white precipitate of triethylamine hydrochloride formed. The work up depended on the solubility of the product in ether. For a soluble product the mixture was filtered and the precipitate washed with ether. The liquors were then washed with 2M aqueous hydrochloric acid (3x200 ml) and with water (200 ml). The ether phase was dried on anhydrous magnesium sulphate and evaporated under vacuum to give the crude product. For an insoluble product the mixture was filtered, the precipitate washed with 2M aqueous hydrochloric acid (3x200 ml) and water (200 ml), and the

remaining solid was dried to give the crude product.

3.2.3.1 Esters of Salicylamide

In the following preparations, performed at -15 to -30°C, the crude product was invariably a white powder, insoluble in ether, which was not usually purified.

For ^{1}H n.m.r. and ^{13}C n.m.r. spectra of these products see Appendix 4.1.1.

(i) *o*-Acetoxybenzamide (193)

The product was prepared from salicylamide and acetyl chloride by the above procedure using pyridine as base in place of triethylamine. This product was recrystallised from chloroform giving colourless lozenges (yield 63%) m.p. 124-128°C (lit.,[78] 138°C); νmax. (Nujol) 3400, 3170, 3075 (NH_2), 1760, 1670 (C=O) cm^{-1}. ^{1}H n.m.r. showed that the product contained *ca.*2% of the isomeric *N*-acetylsalicylamide.

(ii) *o-Carboxamidophenyl Ethyl Fumarate (194)*

The product was prepared from salicylamide and ethyl fumaroyl chloride by the above procedure. The product was a fine white powder (yield 92%), m.p. 126-129°C (Found: C, 59.3; H, 5.0; N, 5.4%. $C_{13}H_{13}NO_5$ requires: C, 59.3; H, 4.9; N, 5.3%); ν max. (Nujol) 3380, 3190, 3090 (NH_2), 1742, 1717, 1650 (C=O) cm^{-1}; *m/z* 263, 137, 127, 121, 120, 99, 92, 29.

(iii) *o-Cinnamoyloxybenzamide (195)*

The product was prepared from salicylamide and cinnamoyl chloride by the above procedure using pyridine as a base in place of triethylamine. The product was a fine white powder (yield 70%), m.p. 146-150°C (Found: C, 71.7; H, 4.7; N, 5.4%. $C_{16}H_{13}NO_3$ requires: C, 71.9; H, 4.9; N, 5.2%). νmax. (Nujol) 3400, 3150 (NH_2), 1710, 1680 (C=O) cm^{-1}; *m/z* 267, 249, 178, 137, 132, 131, 120, 103, 91, 77.

(iv) *o-(p-Chlorocinnamoyloxy)benzamide (196)*

The product was prepared from salicylamide and *p*-chlorocinnamoyl chloride by the above procedure. The product was a fine white powder (yield 87%), m.p. 156-158°C (Found: C, 63.7; H, 4.0; N, 4.6%. $C_{16}H_{12}ClNO_3$ requires: C, 63.5; H, 4.1; N, 4.6%); νmax. (Nujol) 3400, 3200 (NH_2), 1730, 1640 (C=O) cm^{-1}; *m/z* 303, 301, 183, 185, 167, 165, 139, 137, 121, 120, 102, 101.

(v) *o-(p-Methoxycinnamoyloxy)benzamide (197)*

The product was prepared from salicylamide and *p*-methoxycinnamoyl chloride by the above procedure. The product was a fine white powder (yield 90%), m.p. 141-144°C (Found: C, 68.7; H, 5.2; N, 4.8%. $C_{17}H_{15}NO_4$ requires: C, 68.7; H, 5.1; N, 4.7%); νmax. (Nujol) 3400, 3190 (NH_2), 1724, 1660 (C=O) cm^{-1}; *m/z* 297, 162, 161, 137, 133, 120, 92.

(vi) *o-(p-Methylcinnamoyloxy)benzamide (198)*

The product was prepared from salicylamide and *p*-methylcinnamoyl chloride by the above procedure. The product

was a white powder (yield 95%), m.p. 140-145°C (Found: C, 72.8; H, 5.5; N, 5.1%. $C_{17}H_{15}NO_3$ requires: C, 72.6; H, 5.3; N, 5.0%); νmax.(Nujol) 3470, 3290, 3180 (NH_2), 1722, 1660 (C=O) cm^{-1}; *m/z* 281, 145, 117, 115, 91.

(vii) *o-(2-Furoyloxy)benzamide (199)*

The product was prepared from salicylamide and 2-furoyl chloride by the above procedure. The product was a white powder (yield 34%), m.p. 107-109°C (Found: C, 62.2; H, 4.1; N, 6.1%. $C_{12}H_9NO_4$ requires: C, 62.3; H, 3.9; N, 6.1%); νmax.(Nujol) 3390, 3190 (NH_2), 1740, 1640 (C=O) cm^{-1}; *m/z* 231, 120, 95, 39.

(viii) *o-(3-Furoyloxy)benzamide (200)*

The product was prepared from salicylamide and 3-furoyl chloride by the above procedure. The product was an off white powder (yield 51%), m.p. 135-137°C (Found: C, 62.6; H, 4.2; N, 6.3%. $C_{12}H_9NO_4$ requires: C, 62.3; H, 3.9; N, 6.1%); νmax.(Nujol) 3390, 3185 (NH_2), 1745, 1650 (C=O) cm^{-1}; *m/z* 231, 120, 95, 39.

(ix) *o-[3-(2-Furyl)acryloyloxy]benzamide (201)*

The product was prepared from salicylamide and 3-(2-furyl)acryloyl chloride by the above procedure. The product was a coffee coloured powder (yield 93%), m.p. 144-146°C (Found: C, 65.2; H, 4.5; N, 5.5%. $C_{14}H_{11}NO_4$ requires: C, 65.4; H, 4.3; N, 5.5%); νmax.(Nujol) 3495, 3190 (NH_2), 1727, 1635 (C=O) cm^{-1}; *m/z* 257, 121, 65, 39.

3.2.3.2 Esters of 5-(*o*-Hydroxyphenyl)-1,3,4-oxathiazol-2-one

For the preparation of *o*-hydroxyphenyloxathiazolone (62) see Section 3.3.1. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra of the following products see Appendix 4.1.2.

(i) 5-(*o*-Acetoxyphenyl)-1,3,4-oxathiazol-2-one (63)

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and acetyl chloride by the above procedure. The product, soluble in ether, was obtained as a white solid. Recrystallisation from hexane gave white needles (yield 86%), m.p. 71-73°C, (lit.,[76] 70-71°C); νmax.(Nujol) 1767, 1754 (C=O) cm^{-1}; *m/z* 237, 195, 121, 43.

(ii) *5-{o-[3-(p-Chlorophenyl)propioloyloxy]phenyl}-1,3,4-oxathiazol-2-one (96b)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and 3-(*p*-chlorophenyl)propioloyl chloride by the above procedure. The product, insoluble in ether, was obtained as a white powder. Recrystallisation from an ethanol-chloroform mixture gave fine, colourless fibres (yield 46%), m.p. 133-135°C (Found: C, 56.8; H, 1.95; N, 3.8. $C_{17}H_8ClNO_4S$ requires: C, 57.1; H, 2.2; N, 3.9%); νmax. (Nujol) 1780, 1730 (C=O) cm^{-1}; *m/z* 359, 357, 312, 245, 243, 138, 136, 101.

(iii) *5-(o-Acryloyloxyphenyl)-1,3,4-oxathiazol-2-one (71)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and acryloyl chloride by the above procedure.

The product, soluble in ether, was obtained as a pale yellow solid. Recrystallisation from a hexane-ethyl acetate mixture in the freezer gave off white needles (yield 70%), m.p. 74-76°C (Found: C, 53.2; H, 2.8; N, 5.6%. $C_{11}H_7NO_4S$ requires: C, 53.0; H, 2.8; N, 5.6%); νmax. (Nujol) 1745 br (C=O) cm^{-1}; *m/z* 249, 203, 121, 87, 55.

(iv) *5-(o-Cinnamoyloxyphenyl)-1,3,4-oxathiazol-2-one (70)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and cinnamoyl chloride by the above procedure. The product, soluble in ether, was obtained as a white solid. Recrystallisation from ethanol gave colourless needles (yield 85%), m.p. 129-131°C (Found: C, 62.6; H, 3.3; N, 4.2%. $C_{17}H_{11}NO_4S$ requires: C, 62.8; H, 3.4; N, 4.3%); νmax. (Nujol) 1759, 1725 (C=O) cm^{-1}; *m/z* 325, 131, 103, 77.

(v) *5-[o-(α-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (130)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and α-methylcinnamoyl chloride by the above procedure. The product, soluble in ether, was obtained as a yellow solid. Recrystallisation from a hexane-ethyl acetate mixture gave colourless needles (yield 71%), m.p. 99-101°C (Found: C, 63.5; H, 3.8; N, 4.0%. $C_{18}H_{13}NO_4S$ requires: C, 63.7; H, 3.8; N, 4.1%); νmax. (Nujol) 1758, 1711 (C=O) cm^{-1}; *m/z* 339, 338, 262, 194, 145, 144, 116, 114, 90.

(vi) *5-[o-(β-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (133)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and β-methylcinnamoyl chloride by the above procedure. The product, soluble in ether, was obtained as a pink solid. Flash chromatography on silica eluting with ethyl acetate-hexane (15:85) yielded the product which was recrystallised from a hexane-ethyl acetate mixture giving off-white needles (yield 32%), m.p. 100.5-101.5°C (Found: C, 63.6; H, 3.8; N, 4.3%. $C_{18}H_{13}NO_4S$ requires: C, 63.7; H, 3.85; N, 4.15%); νmax. (Nujol) 1760, 1723 (C=O) cm^{-1}; *m/z* 339, 199, 195, 184, 145, 117, 115, 85, 83.

(vii) *5-[o-(2,4,6-Trimethylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (141)*

The product was prepared from *o*-hydroxyphenyloxathiazolone (62) and 2,4,6-trimethylcinnamoyl chloride by the above procedure. The product, insoluble in ether, was obtained as a white solid. Recrystallisation from an ethanol-chloroform mixture gave colourless needles (yield 68%), m.p. 142-144°C (Found: C, 65.6; H, 4.65; N, 3.95%. $C_{20}H_{17}NO_4S$ requires: C, 65.4; H, 4.65; N, 3.8%); νmax. (Nujol) 1758, 1742 (C=O) cm^{-1}; *m/z* 367, 291, 174, 145, 130, 129, 115.

(viii) *5-[o-(2,6-Dichlorocinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (142)*

The product was prepared from *o*-hydroxyphenyloxa-

thiazolone (62) and 2,6-dichlorocinnamoyl chloride by the above procedure. The product, insoluble in ether, was obtained as an off white powder. Recrystallisation from an ethanol-chloroform mixture gave long, off white needles (yield 59%), m.p. 159-161°C (Found: C, 51.6; H, 2.2; N, 3.3%. $C_{17}H_9Cl_2NO_4S$ requires: C, 51.8; H, 2.3; N, 3.6%); νmax. (Nujol) 1745 (C=O) cm^{-1}; *m/z* 394, 392, 313, 311, 201, 199, 173, 171, 136, 135, 99.

3.2.3.3 Esters of *o*-Cyanophenyl

For ^1H and ^{13}C n.m.r. spectra of these products see Appendix 4.1.3.

(i) *o*-Acetoxybenzonitrile (167b)

The product was prepared from *o*-cyanophenol and acetyl chloride by the above procedure. The crude product, soluble in ether, was obtained as an oil. Kugelrohr distillation (*ca.*120° at 0.05 mmHg) gave a colourless oil, (yield 56%), (b.p. lit.,[26] 252-254°C); νmax. (film) 2237, (C≡N), 1755 (C=O) cm^{-1}.

(ii) *o-Cyanophenyl 3-(p-Chlorophenyl)propiolate (99b)*

The product was prepared from *o*-cyanophenyl and 3-(*p*-chlorophenyl)propioloyl chloride. The product, insoluble in ether, was obtained as a white powder. Recrystallisation from ethanol gave white fibres (yield 47%), m.p. 131.5-133°C (Found: C, 68.05; H, 2.7; N, 5.1. $C_{16}H_8ClNO_2$ requires: C, 68.2; H, 2.8; N, 5.0%); νmax. (Nujol) 2230 (C≡N), 1740 (C=O) cm^{-1}; *m/z* 283, 281, 247, 245, 243, 217,

215, 148, 146, 101, 90.

(iii) *o-Cyanophenyl Acrylate (106)*

The product was prepared from *o*-cyanophenol and acryloyl chloride by the above procedure. The crude product, soluble in ether, was obtained as a colourless oil (yield 100%). This was not purified on account of its tendency to polymerise. (Found: M^+, 173.04773. $C_{10}H_7NO_2$ requires *M*, 173.04765); νmax.(film) 2237 (C≡N), 1750 (C=O) cm^{-1}; *m/z* 173, 119, 91, 55.

(iv) *o-Cyanophenyl Ethyl Fumarate (111)*

The product was prepared from monoethyl fumaroyl chloride and *o*-cyanophenol by the above procedure. The product, soluble in ether, was obtained as a white solid. Kugelrohr distillation (150°C at 0.05 mmHg) gave a white solid (yield 89%), m.p. 52-54°C (Found: C, 63.4; H, 4.5; N, 5.8%. $C_{13}H_{11}NO_4$ requires: C, 63.7; H, 4.5; N, 5.7%); νmax. (Nujol) 2235 (C≡N), 1781, 1723 (C=O) cm^{-1}; *m/z* 245, 200, 172, 127, 119, 99, 91.

(v) *o-Cyanophenyl Cinnamate (114a)*

The product was prepared from *o*-cyanophenol and cinnamoyl chloride by the above procedure. The product, soluble in ether, was obtained as a white solid. Recrystallisation from a hexane-toluene mixture gave fine white needles (yield 66%), m.p. 102.5-103.5°C (Found: C, 76.9; H, 4.3; N, 5.8%. $C_{16}H_{11}NO_2$ requires: C, 77.1; H, 4.4; N, 5.6%); νmax. (Nujol) 2233 (C≡N), 1732 (C=O) cm^{-1}; *m/z* 249, 131, 119, 103, 91, 77.

(vi) *o-Cyanophenyl p-Chlorocinnamate (114b)*

The product was prepared from *o*-cyanophenol and *p*-chlorocinnamoyl chloride by the above procedure. The crude product, soluble in ether, was obtained as a brown solid. Chromatography on silica eluting with ethyl acetate-light petroleum (b.p. 40-60°C) (15:85) followed by recrystallisation from cyclohexane gave branching colourless needles (yield 29%), m.p. 138-141°C (Found: C, 67.7; H, 3.45; N, 5.15%. $C_{16}H_{10}ClNO_2$ requires: C, 67.7; H, 3.55; N, 4.95%); νmax. (Nujol) 2230 (C≡N), 1735 (C=O) cm^{-1}; *m/z* 285, 283, 167, 165, 139, 137, 102, 101, 91, 77.

(vii) *o-Cyanophenyl p-Methoxycinnamate (114c)*

The product was prepared from *o*-cyanophenol and *p*-methoxycinnamoyl chloride by the above procedure. The product, only slightly soluble in ether, was obtained as a fine white powder. Recrystallisation from a cyclohexane-ethanol mixture gave small, colourless plates (yield 52%), m.p. 106-109°C (Found: C, 72.9; H, 4.8; N, 5.2%. $C_{17}H_{13}NO_3$ requires: C, 73.1; H, 4.7; N, 5.0%); νmax. (Nujol) 2238 (C≡N), 1720 (C=O) cm^{-1}; *m/z* 279, 162, 161, 133, 118, 90.

(viii) *o-Cyanophenyl p-Methylcinnamate (114d)*

The product was prepared from *o*-cyanophenol and *p*-methylcinnamoyl chloride by the above procedure. The product, insoluble in ether, was obtained as a white powder. Recrystallisation from a cyclohexane-ethyl acetate mixture

gave colourless needles (yield 71%), m.p. 122-124°C (Found: C, 77.8; H, 5.2; N, 5.5%. $C_{17}H_{13}NO_2$ requires: C, 77.6; H, 4.9; N, 5.3%); νmax. (Nujol) 2232 (C≡N), 1739 (C=O) cm^{-1}; *m/z* 263, 145, 117, 115, 91.

(ix) *o-Cyanophenyl 2-Furoate (121)*

The product was prepared from *o*-cyanophenol and 2-furoyl chloride by the above procedure. The product, insoluble in ether, was obtained as a white powder. Recrystallisation from a cyclohexane-ethyl acetate mixture gave very fine colourless needles (yield 59%), m.p. 118-120°C (Found: C, 67.6; H, 3.4; N, 6.6%. $C_{12}H_7NO_3$ requires: C, 67.6; H, 3.3; N, 6.6%); νmax. (Nujol) 2233 (C≡N), 1733 (C=O) cm^{-1}; *m/z* 213, 95, 39.

(x) *o-Cyanophenyl α-Methylcinnamate (131)*

The product was kindly prepared by Alan Cunningham from *o*-cyanophenol and α-methylcinnamoyl chloride by the above procedure. The product was crystallised from ether in the freezer giving white needles (yield 39%), m.p. 42-44°C (Found: C, 77.7; H, 4.95; N, 5.3%. $C_{17}H_{13}NO_2$ requires: C, 77.55; H, 4.95; N, 5.3%); νmax. (Nujol) 2230 (C≡N), 1730 (C=O) cm^{-1}; *m/z* 263, 145, 117, 115.

(xi) *o-Cyanophenyl β-Methylcinnamate (135)*

The product was prepared from *o*-cyanophenol and β-methylcinnamoyl chloride by the above procedure. The crude product, soluble in ether, was purified by flash chromatography on silica. Elution with ethyl acetate-hexane (20:80) yielded a pale yellow solid. Recrystallisation

from ether in the freezer gave beige needles (yield 36%), m.p. 80-81°C (Found: C, 77.85; H, 5.0; N, 5.45%. $C_{17}H_{13}NO_2$ requires: C, 77.55; H, 4.95; N, 5.3%); νmax. (Nujol) 2225 (C≡N), 1733 (C=O) cm^{-1}; *m/z* 263, 181, 179, 145, 117, 115, 102, 91.

(xii) *o-Cyanophenyl 2,4,6-Trimethylcinnamate (143)*

The product was prepared from *o*-cyanophenol and 2,4,6-trimethylcinnamoyl chloride by the above procedure. The crude product, soluble in ether, was obtained as a brown solid. Recrystallisation from a cyclohexane-chloroform mixture gave beige plates (yield 77%), m.p. 104-107°C (Found: C, 78.2; H, 5.7; N, 4.7%. $C_{19}H_{17}NO_2$ requires: C, 78.4; H, 5.8; N, 4.8%); νmax. (Nujol) 2227 (C≡N), 1742 (C=O) cm^{-1}; *m/z* 291, 173, 145, 130, 129, 128, 115.

(xiii) *o-Cyanophenyl 2,6-Dichlorocinnamate (147)*

The product was prepared from *o*-cyanophenol and 2,6-dichlorocinnamoyl chloride by the above procedure. The product, soluble in ether, was obtained as a brown solid. Recrystallisation from cyclohexane gave clusters of small, off white needles (yield 79%), m.p. 102-104°C (Found: C, 60.7; H, 3.0; N, 4.7%. $C_{16}H_9Cl_2NO_2$ requires: C, 60.4: H, 2.8: N, 4.4%); νmax. (Nujol) 2230 (C≡N), 1740 (C=O) cm^{-1}; *m/z* 318, 316, 279, 225, 223, 201, 119, 173, 171, 149.

(xiv) *o-Cyanophenyl 3-(2-Furyl)acrylate (202)*

The product was prepared from *o*-cyanophenol and

3-(2-furyl)acryloyl chloride by the above procedure. The crude product, insoluble in ether, was obtained as a coffee coloured powder. Hot filtration and recrystallisation from a cyclohexane-ethyl acetate mixture gave small, coffee coloured needles (yield 68%), m.p. 140-141.5°C (Found: C, 70.3; H, 4.0; N, 5.9%. $C_{14}H_9NO_3$ requires: C, 70.3; H, 3.8; N, 5.9%); νmax.(Nujol) 2225 (C≡N), 1740 (C=O) cm^{-1}; *m/z* 239, 121, 65, 39.

3.2.4 Preparation of Secondary Amides

The secondary amides *o-(3-phenylpropiolamido)benzamide* (203) *o*-acetamidobenzamide (204) and *o*-acetamidobenzonitrile were each produced from the appropriate aromatic amine and acid chloride by a similar general procedure described below. For ^1H n.m.r. and ^{13}C n.m.r. spectra of these products see Appendix 4.2.1.

General Procedure

The aromatic amine (0.05 mol) and triethylamine (0.055 mol) were dissolved together in the solvent (ether or dioxan, 100 ml) with mechanical stirring at room temperature. The acyl chloride (0.0525 mol) was added dropwise as a solution in the solvent (50 ml) over *ca.* 10 min. The mixture was stirred for a further 20 min, a precipitate formed. The mixture was filtered and the solid washed thoroughly with the solvent (3x50 ml). The combined liquors were evaporated under vacuum to give the crude product.

(i) *o*-(3-Phenylpropiolamido)benzamide (203)

The product was prepared from anthranilamide and 3-phenylpropioloyl chloride by the above procedure using dioxan as solvent. The crude product was a red glass. Crystallisation and recrystallisation from ethanol gave pale yellow needles (yield 24%), m.p. 179-181°C (Found: C, 72.6; H, 4.65; N, 10.7%. $C_{16}H_{12}N_2O_2$ requires: C, 72.75; H, 4.55; N, 10.6%); νmax.(Nujol) 3385, 3210 (NH), 2220 (C≡C), 1645 br (C=O) cm^{-1}; *m/z* 264, 246, 221, 193, 165, 124, 118, 102, 101.

(ii) *o*-Acetamidobenzamide (204)

The product was prepared from anthranilamide and acetyl chloride by the above procedure using dioxan as solvent. The crude product was an off-white solid. Recrystallisation from ethanol gave off-white needles (yield 90%), m.p. 176-180°C (lit., 170-171°C[80] or 177°C[126]); νmax.(Nujol) 3370, 3155 (NH), 1670, 1625 (C=O) cm^{-1}.

(iii) *o*-Acetamidobenzonitrile (167c)

The product was prepared from anthranilonitrile and acetyl chloride by the above procedure using ether as the solvent. The crude product was a yellow oil. Flash chromatography on silica eluting with ethyl acetate-hexane (30:70) yielded a white solid. Recrystallisation from a hexane-ethyl acetate mixture gave colourless needles (yield 19%), m.p. 129-130.5°C (lit.,[80] 132.5-133°C); νmax.(Nujol) 3320 (NH), 2230 (C≡N), 1705 (C=O) cm^{-1}.

3.3 PREPARATION OF 1,3,4-OXATHIAZOL-2-ONES

1,3,4-Oxathiazol-2-ones were prepared from carboxamides and chlorocarbonylsulphenyl chloride (ClCOSCl) by the method of Mühlbauer and Weiss.[60] The preparation of the latter reagent is described first followed by the general procedure for the preparation of oxathiazolones. The actual conditions used varied with the compound and are mentioned under individual sections.

Chlorocarbonylsulphenyl Chloride (56)

Chlorocarbonylsulphenyl chloride was prepared by the method of Weiss.[61]

Concentrated sulphuric acid (100 ml) was carefully added to water (8.6 g, 0.48 mol) with stirring and cooling using an ice bath. Perchloromethyl mercaptan (88.6 g, 0.48 mol) was added; the mixture was warmed to 45°C and held at that temperature, with vigorous mechanical stirring, for *ca.* 2h when the evolution of hydrogen chloride had almost ceased. On standing two layers formed. The upper, organic phase was separated giving the crude product as a pale yellow oil. This was conveniently distilled using a Buchi 'Rotavapour' fitted with a liquid nitrogen trap and heating gently with a hot air blower at a pressure of *ca.* 10mmHg. The product was a pale yellow oil (yield 42.1 g, 67%), b.p. 98°C (lit.,[62] 98°C) which was stored over molecular sieves.

νmax. (film) 1785 (C=O) cm^{-1}.

General Procedure for the Preparation of 1,3,4-Oxathiazol-2-ones

The amide (0.05 mol) was dissolved in the solvent (dry chloroform, dioxan or a mixture) with stirring and chlorocarbonylsulphenyl chloride (0.065-0.075 mol) was added (dropwise if the scale was larger). The mixture was heated under reflux until the evolution of hydrogen chloride had become negligible. Evaporation of the solvent under vacuum and trituration of the residue with ethanol generally gave a solid which could be recrystallised to give the pure product. In other cases chromatography was necessary.

3.3.1 Miscellaneous Oxathiazolones

(i) 5-Phenyl-1,3,4-oxathiazol-2-one (38)

The product was prepared from benzamide and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 14h. The crude product was obtained as a yellow oil. Crystallisation and recrystallisation from ethanol gave colourless needles (yield 59%), m.p. 68-69°C (lit.,[67] 68.5-70°C).

(ii) 5-(*p*-Methoxyphenyl)-1,3,4-oxathiazol-2-one (152)

The product was prepared from *p*-methoxybenzamide and ClCOSCl by the above procedure. The solvent was a mixture of dry chloroform and dioxan (3:1, b.p. 76°C), the reaction time was 5h. The crude product was obtained as a pale yellow solid. Recrystallisation from an ethanol-chloroform mixture gave off-white plates (yield 67%), m.p. 121-123°C,

(lit., 99-101°C[76] and 119-121°C[127]).

(iii) 5-(*o*-Hydroxyphenyl)-1,3,4-oxathiazol-2-one (62)

The product was prepared from salicylamide and ClCOSCl by the above procedure. The solvent was dioxan, the reaction time was 1.5h. The crude product was obtained as a yellow solid. Flash chromatography on silica eluting with ether-hexane (15:85) and recrystallisation from methanol gave colourless needles (yield 78%), m.p. 83-85°C (lit.,[76] 80-81°C) (Found: C, 49.5; H, 2.5; N, 7.2%. Calc. for $C_8H_5NO_3S$: C, 49.2; H, 2.6; N, 7.2%); νmax.(Nujol) 3200 (OH), 1759 (C=O) cm^{-1}; *m/z* 195, 167, 151, 121, 91. For ^1H n.m.r. and ^{13}C n.m.r. see Appendix 4.1.2.1.

(iv) Attempted Preparation of 5-(*o*-Aminophenyl)-1,3,4-oxathiazol-2-one: Reaction of Anthranilamide with Chlorocarbonylsulphenyl Chloride

Anthranilamide (1.36 g, 0.01 mol) was dissolved in dioxan (40 ml) and chlorocarbonylsulphenyl chloride (1.97 g, 0.015 mol) was added. The mixture was heated under reflux for 30 min. On cooling a precipitate formed. This was filtered out to give yellow needles of 2,4-quinazolinedione (yield 0.85 g, 52%) m.p. >350°C (lit.,[128] >350°C). The compound was identified by comparison of its ^1H n.m.r. spectrum (60MHz) with an authentic spectrum in the literature[129] and by its mass spectrum: *m/z* 162 (M^+).

3.3.2 Oxathiazolones from *o*-Acyloxybenzamides

For ^{1}H n.m.r. and ^{13}C n.m.r. spectra of these products see Appendix 4.1.2.

(i) *Ethyl o-(1,3,4-Oxathiazol-2-one-5-yl)phenyl Fumarate (109)*

The product was prepared from *o*-carboxamidophenyl ethyl fumarate [Section 3.2.3.1(ii)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 7h. The crude product was obtained as a yellow oil. Crystallisation and recrystallisation from ethanol gave colourless needles (yield 41%), m.p. 78-80°C (Found: C, 52.2; H, 3.4; N, 4.5%. $C_{14}H_{11}NO_6S$ requires; C, 52.3; H, 3.4; N, 4.4%); νmax.(Nujol) 1795, 1750, 1715 (C=O) cm^{-1}; *m/z* 321, 276, 127, 121, 99, 29.

(ii) *5-[o-(p-Chlorocinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113b)*

The product was prepared from *o*-(*p*-chlorocinnamoyloxy)-benzamide [Section 3.2.3.1(iv)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was obtained as a white solid. Recrystallisation from ethanol gave colourless fibres (yield 51%), m.p. 139-140°C (Found: C, 56.7; H, 2.7; N, 3.9%. $C_{17}H_{10}ClNO_4S$ requires: C, 56.8; H, 2.8; N, 3.9%); νmax.(Nujol) 1781, 1723 (C=O) cm^{-1}; *m/z* 361, 359, 167, 165, 139, 137, 102, 101.

(iii) *5-[o-(p-Methoxycinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113c)*

The product was prepared from *o*-(*p*-methoxycinnamoyloxy)benzamide [Section 3.2.3.1(v)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was a pale yellow solid. Recrystallisation from an ethanol-chloroform mixture gave colourless needles (yield 37%), m.p. 143-145°C (Found: C, 60.6; H, 3.8; N, 3.9%. $C_{18}H_{13}NO_5S$ requires: C, 60.9; H, 3.7; N, 3.9%); νmax. (Nujol) 1786, 1760, 1713 (C=O) cm^{-1}; *m/z* 355, 309, 279, 162, 161, 133.

(iv) *5-[o-(p-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113d)*

The product was prepared from *o*-(*p*-methylcinnamoyloxy)-benzamide [Section 3.2.3.1(vi)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was a yellow oil. Crystallisation and recrystallisation from ethanol gave colourless needles (yield 70%), m.p. 125-127°C (Found: C, 63.9; H, 4.1; N, 4.2%. $C_{18}H_{13}NO_4S$ requires: C, 63.7; H, 3.8; N, 4.1%); νmax. 1755, 1740 (C=O) cm^{-1}; *m/z* 339, 293, 163, 145, 117, 115, 91.

(v) *5-[o-(2-Furoyloxy)phenyl]-1,3,4-oxathiazol-2-one (119)*

The product was prepared from *o*-(2-furoyloxy)-benzamide [Section 3.2.3.1(vii)] and ClCOSCl by the above

procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was a white solid. Recrystallisation from ethanol gave colourless needles (yield 62%), m.p. 108-110°C (Found: C, 53.7; H, 2.6; N, 4.8%. $C_{13}H_7NO_5S$ requires: C, 54.0; H, 2.4; N, 4.8%); νmax. (Nujol) 1765, 1745, 1736 (C=O) cm^{-1}; *m/z* 289, 215, 120, 95, 39.

(vi) *5-[o-(3-Furoyloxy)phenyl]-1,3,4-oxathiazol-2-one (120)*

The product was prepared from *o*-(3-furoyloxy)benzamide [Section 3.2.3.1(viii)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was a white solid. Recrystallisation from ethanol gave colourless needles (yield 55%), m.p. 104-106°C (Found: C, 54.2; H, 2.6; N, 4.9%. $C_{13}H_7NO_5S$ requires: C, 54.0; H, 2.4; N, 4.8%); νmax. (Nujol) 1750 br (C=O) cm^{-1}; *m/z* 289, 215, 120, 95, 39.

(vii) *5-{o-[3-(2-Furyl)acryloyloxy]phenyl}-1,3,4-oxathiazol-2-one (150)*

The product was prepared from *o*-[3-(2-furyl)-acryloyloxy]benzamide [Section 3.2.3.1(ix)] and ClCOSCl by the above procedure. The solvent was dry chloroform, the reaction time was 16h. The crude product was obtained as a coffee coloured solid. Recrystallisation from ethanol gave very fine, coffee coloured needles (yield

61%), m.p. 143.5-145°C (Found: C, 57.0; H, 3.0; N, 4.5%; $C_{15}H_9NO_5S$ requires: C, 57.1; H, 2.9; N, 4.4%); νmax. (Nujol) 1757, 1722 (C=O) cm^{-1}; *m/z* 315, 121, 65, 39.

(viii) 5-(*o*-Acetoxyphenyl)- and 5-(*o*-Cinnamoyloxyphenyl)-1,3,4-oxathiazol-2-ones

These two products were initially prepared from *o*-acetoxy- and *o*-cinnamoyloxybenzamides [Sections 3.2.3.1(i) and (iii)] and ClCOSCl by the above procedure in 16% and 60% yields respectively. However, they were later more conveniently prepared from *o*-hydroxyphenyloxathiazolone and the relevant acid chloride, as has been described in Section 3.2.3.2(i) and (iv), in higher yields.

3.3.3 Oxathiazolones from *o*-Amidobenzamides

For ^{1}H n.m.r. and ^{13}C n.m.r. spectra of these products see Appendix 4.2.2.

N.B. The following reactions were carried out at room temperature.

(i) *5-(o-Acetamidophenyl)-1,3,4-oxathiazol-2-one (64)*

The product was prepared from *o*-acetamidobenzamide [Section 3.2.4(ii)] and ClCOSCl by the above procedure at room temperature. The solvent was dioxan, the reaction time was 96h. After a solid impurity had been filtered from the reaction mixture, the crude product was obtained as a yellow semi-solid. Flash chromatography on silica, eluting with ethyl acetate-hexane (40:60) yielded the desired product (17%), unreacted *o*-acetamidobenzamide (44%) and *o*-acetamidobenzonitrile (19%). The desired product was recrystallised from a cyclohexane-ethyl acetate mixture giving off-white needles (yield 10% or 18% on 56% conversion), m.p. 131-133°C (Found: C, 50.6; H, 3.2; N, 11.6%. $C_{10}H_8N_2O_3S$ requires: C, 50.9; H, 3.4; N, 11.9%); νmax. (Nujol) 3320 (NH), 1750, 1670 (C=O) cm^{-1}; *m/z* 236, 194, 192, 162, 150, 120, 118, 92.

(ii) *5-[o-(3-Phenylpropiolamido)phenyl]-1,3,4-oxathiazol-2-one (90)*

The product was prepared from *o*-(3-phenylpropiolamido)-benzamide [Section 3.2.4(i)] and ClCOSCl by the above procedure. The solvent was dioxan, the reaction time was 115h. A brown oil was obtained. Flash chromatography on

3.4 THERMOLYSIS OF 1,3,4-OXATHIAZOL-2-ONES BEARING DIPOLAROPHILE SUBSTITUENTS AND RELATED REACTIONS

1,3,4-Oxathiazol-2-ones bearing dipolarophile substituents were thermolysed under standard conditions described in the general procedure below. Isolation of the products involved a variety of techniques which are summarised for individual examples. Sections 3.4.1 and 3.4.2 refer to oxathiazolones bearing alkyne and alkene dipolarophiles respectively; Section 3.4.3 describes some related reactions.

General Procedure

The oxathiazolone (0.01 mol) was dissolved in dry xylene (250 ml) and heated under reflux (*ca.* 138°C) until h.p.l.c. analysis of the reaction mixture showed that no starting material remained. After cooling, the total volume of the reaction mixture was measured; a small sample was taken and stored in the freezer for eventual quantitative h.p.l.c. analysis if necessary. Any precipitate present in the reaction mixture was filtered out. The solvent was evaporated from the liquors under vacuum giving, generally a yellow solid residue. The residue was subjected to various separational procedures which are described for individual examples.

3.4.1 Thermolysis of Oxathiazolones Bearing an Alkyne Substituent

(i) Thermolysis of 5-[*o*-(3-Phenylpropiolamido-phenyl]-1,3,4-oxathiazol-2-one (90)

The oxathiazolone (0.334 g, 1.04 mmol) was dissolved in dry xylene (26 ml) and heated under reflux for 23h after which time no oxathiazolone could be detected by h.p.l.c. On cooling *3-phenylisothiazolo[4,3-c]quinolin-4(5H)-one* (91) crystallised from the reaction mixture and was filtered out giving colourless needles (yield 0.235 g, 81%), m.p. 303-304°C (Found: C, 68.8; H, 3.5; N, 9.9%. $C_{16}H_{10}N_2OS$ requires: C, 69.1; H, 3.6; N, 10.1%); νmax.(Nujol) 3130 (NH), 1675 (C=O) cm^{-1}; *m/z* 278, 277, 261, 248, 217, 139, 129, 121. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.1.

(ii) 5-{*o*-[3-(*p*-Chlorophenyl)propioloyloxy]phenyl}-1,3,4-oxathiazol-2-one (96b)

The oxathiazolone (3.58 g, 0.01 mol) was heated in dry xylene (250 ml) for 18h as described above. The residue obtained was subjected to flash chromatography on silica eluting with ethyl acetate-hexane (10:90). This yielded *3-(p-chlorophenyl)-4-oxo-4H-chromeno[4,3-c]isothiazole* (97b) (0.477 g, 15%) which was recrystallised from an ethanol-chloroform mixture giving colourless needles (yield 0.113 g, 4%), m.p. 216.5-217.5°C (Found: C, 61.15; H, 2.55; N, 4.55%. $C_{16}H_8ClNO_2S$ requires: C, 61.25; H, 2.55; N, 4.45%); νmax.(Nujol) 1750 (C=O) cm^{-1};

m/z 315, 313, 163, 139. For ^{1}H n.m.r. and ^{13}C n.m.r. of this product see Appendix 4.3.2.

o-Cyanophenyl 3-(*p*-chlorophenyl)propiolate (99b) was not isolated pure but its presence in the reaction mixture was demonstrated by t.l.c. and h.p.l.c. comparison with the authentic material described in Section 3.2.3.3(ii).

The total yields of the chromenoisothiazole (97b) (19%) and the *o*-cyanophenyl ester (99b) (74%) were determined by h.p.l.c. analysis of the reaction mixture sample.

3.4.2 Thermolysis of Oxathiazolones Bearing an Alkene Substituent

(i) 5-(*o*-Acryloyloxyphenyl)-1,3,4-oxathiazol-2-one (71)

The oxathiazolone (1.25 g, 0.005 mol) was heated in dry xylene (500 ml) for 10h as described above. The residue was subjected to flash chromatography eluting with ethyl acetate-hexane (20:80). This allowed the separation of *4-oxo-4H-chromeno[4,3-c]isothiazole* (103) which was recrystallised from ethanol giving colourless needles (0.154 g, 15%), m.p. 168-169°C. (Found: C, 59.0; H, 2.5; H, 6.85%. $C_{10}H_5NO_2S$ requires: C, 59.1; H, 2.45; N, 6.9%); νmax. (Nujol) 1740 (C=O) cm^{-1}; *m/z* 203, 175, 146, 120, 103. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.3.2.

H.p.l.c. analysis of the reaction mixture allowed the total yield of the product to be determined as 0.239 g, 24%.

The expected by-product, *o*-cyanophenyl acrylate (106), could not be detected by h.p.l.c. However, the washings from the chromatography column (a brown oil) showed a nitrile resonance in their i.r. spectrum (νmax. 2230 cm^{-1}). This may account for the nitrile by-product as an authentic sample [Section 3.2.3.3(iii)] was found to polymerise readily.

The experiment was repeated under nitrogen and in the presence of hydroquinone monomethyl ether (5 mg) as an inhibitor to polymerisation. These conditions had no effect on the yields or products observed.

(ii) Ethyl *o*-(1,3,4-Oxathiazol-2-one-5-yl)phenyl Fumarate (109)

The oxathiazolone (3.88 g, 0.012 mol) was heated in dry xylene (300 ml) for 14h as described above. The residue obtained was subjected to chromatography on silica eluting with ethyl acetate-petroleum ether (25:75). This yielded *ethyl 4-oxo-4H-chromeno[4,3-c]isothiazole-3-carboxylate* (110) as an off-white solid. Recrystallisation from cyclohexane gave colourless plates (yield 0.912 g, 28%), m.p. 118-120°C (Found: C, 56.5; H, 3.3; N, 5.0%. $C_{13}H_9NO_4S$ requires: C, 56.7; H, 3.3; N, 5.1%); νmax. (Nujol) 1730 (C=O) cm^{-1}; *m/z* 275, 230, 203, 159, 119, 90, 84, 29. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.3.2.

o-Cyanophenyl ethyl fumarate (111) could not be detected in the reaction mixture by t.l.c. or h.p.l.c. There were, however, several brightly coloured by-products

formed which were not identified.

The total yield of the chromenoisothiazole (110) (35%) was determined by h.p.l.c. analysis of the reaction mixture sample.

(iii) 5-(*o*-Cinnamoyloxyphenyl)-1,3,4-oxathiazol-2-one (113a)

The oxathiazolone (6.50 g, 0.02 mol) was heated in dry xylene (500 ml) for 8h as described above. A precipitate of uncertain identity was filtered from the reaction mixture giving a white powder. This was thought possibly to be *1,3-dihydro-4-oxo-3-phenyl-4H-chromeno[4,3-c]isothiazole* (127a) for reasons discussed in Section 2.3.3.4; (yield 1.287 g, 23%), m.p. 228-130°C; νmax.(Nujol) 3430, 3360, 3250 (NH), 1630 (C=O) cm^{-1}; *m/z* 279 (M^+-2H), 251, 250, 190, 146, 129, 121, 91, 77. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.5.

The residue obtained was subjected to extensive chromatography on silica leading to the isolation of the following three products.

4-Oxo-3-phenyl-4H-chromeno[4,3-c]isothiazole (97a) was recrystallised from cyclohexane giving colourless needles (yield 0.084 g, 1.5%), m.p. 166.5-168.5°C (Found: C, 68.75; H, 3.15; N, 4.9%. $C_{16}H_9NO_2S$ requires: C, 68.8; H, 3.25; N, 5.0%); νmax.(Nujol) 1730 (C=O) cm^{-1}; *m/z* 279, 129, 121, 89, 77. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.2.

6-Oxo-6*H*-chromeno[4,3-*b*]quinoline (115a) was recrystallised from ethyl acetate giving colourless,

branching needles (yield 0.192 g, 4%), m.p. 224-225°C (lit.,[92] 224°C); mixed m.p. 228-231°C, authentic compound m.p. 227-229°C [Section 3.4.3(iv)]. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Tables 6 and 7, Section 2.3.3.3.

o-Cyanophenyl cinnamate (114a) was recrystallised from cyclohexane giving colourless needles (yield 0.183 g, 4%), m.p. 102-103°C, authentic compound m.p. 102.5-103.5°C [Section 3.2.3.3(v)].

The total yields of the chromenoisothiazole (97a) (14%), the chromenoquinoline (115a) (13%) and the nitrile (114a) (27%) were determined by h.p.l.c. analysis of the reaction mixture sample.

(iv) 5-[*o*-(*p*-Chlorocinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113b)

The oxathiazolone (3.60 g, 0.01 mol) was heated in dry xylene (250 ml) for 22h as described above. The residue obtained was subjected to extensive chromatography on silica and alumina leading to the isolation of the following four compounds.

3-(*p*-Chlorophenyl)-4-oxo-4*H*-chromeno[4,3-*c*]isothiazole (97b) was recrystallised from ethyl acetate giving colourless needles (yield 0.046 g, 1.5%), m.p. 216-217°C, mixed m.p. with the same compound produced from the *p*-chlorophenyl-propiolate ester (96b): 216-217°C, see Section 3.4.1(ii) for further data.

10-Chloro-6-oxo-6H-chromeno[4,3-b]quinoline (115b) was obtained as a white solid (0.128 g, 5%) a portion of which was recrystallised from an ethyl acetate-cyclohexane

mixture; m.p. 231-234°C; νmax. (Nujol) 1737 (C=O) cm^{-1}; *m/z* 283, 281, 255, 253, 190. For ^{1}H n.m.r. and ^{13}C n.m.r. see Tables 6 and 7, Section 2.3.3.3.

4-Amino-3-(p-chlorobenzyl)-2-oxo-2H- chromene (116b) was obtained as a brown solid (yield 0.825 g, 28%) which was not purified; νmax. (Nujol) 3475, 3350, 3240 (NH_2) 1645 (C=O) cm^{-1}; *m/z* 287, 285, 256, 250, 146. For ^{1}H n.m.r. and ^{13}C n.m.r. specta see Appendix 4.3.4.

o-Cyanophenyl *p*-chlorocinnamate (114b) was recrystallised from cyclohexane giving colourless plates (yield 0.329 g, 12%), m.p. 139-143°C, authentic compound m.p. 138-141°C [Section 3.2.3.3(vi)].

The total yields of chromenoisothiazole (97b) (21%), chromenoquinoline (115b) (9%) and the nitrile (114b) (33%) were determined by h.p.l.c. analysis of the reaction mixture sample.

(v) 5-[*o*-(*p*-Methoxycinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113c)

The oxathiazolone (3.55 g, 0.01 mol) was heated in dry xylene (250 ml) for 20h as described above. A precipitate, *4-amino-3-(p-methoxybenzyl)-2-oxo-2H-chromene* (116c) (yield 0.336 g, 12%), was filtered out and recrystallised from acetic acid giving small, colourless needles (0.192 g, 7%), m.p. 240-243°C (Found: C, 72.75; H, 5.4; N, 4.9%. $C_{17}H_{15}NO_3$ requires: C, 72.6; H, 5.35; N, 5.0%); νmax. (Nujol) 3470, 3340, 3230 (NH_2), 1640 (C=O) cm^{-1}; *m/z* 281, 266, 252, 146, 121, 77. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.4.

The residue obtained was subjected to chromatography on silica eluting with methylene chloride-light petroleum (b.p. 40-60°C) (50:50). This yielded sulphur (0.210 g, 66%) and the following two compounds.

3-(p-Methoxyphenyl)-4-oxo-4H-chromeno[4,3-c]isothiazole (97c) was recrystallised from a hexane-ethyl acetate mixture giving colourless fibres (yield 0.234 g, 8%), m.p. (decomp.) 175-180°C (Found: C, 65.8; H, 3.8; N, 4.6%). $C_{17}H_{11}NO_3S$ requires: C, 66.0; H, 3.6; N, 4.5%); νmax. (Nujol) 1750 (C=O) cm^{-1}; *m/z* 309, 294, 279, 266, 161, 133, 118, 90, 77. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.2.

10-Methoxy-6-oxo-6H-chromeno[4,3-b]quinoline (115c) was recrystallised from ethyl acetate giving pale yellow fibres (yield 0.314 g, 11%), m.p. 236-238°C (Found: C, 73.5; H, 3.9; N, 5.0%. $C_{17}H_{11}NO_3$ requires: C, 73.7; H, 4.0; N, 5.1%); νmax. (Nujol) 1737 (C=O) cm^{-1}; *m/z* 277, 234, 206. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Tables 6 and 7, Section 2.3.3.3.

o-Cyanophenyl *p*-methoxycinnamate (114c) was not isolated pure but its presence in the reaction mixture was demonstrated by t.l.c. and h.p.l.c. comparisons with the authentic material described in Section 3.2.3.3(vii).

The total yields of the chromenoisothiazole (97c) (14%), the chromenoquinoline (115c) (14%) and the *o*-cyanophenyl ester (114c) (35%) were determined by h.p.l.c. analysis of the reaction mixture sample.

(vi) 5-[*o*-(*p*-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (113d)

The oxathiazolone (3.39 g, 0.01 mol) was heated in dry xylene (250 ml) for 24h as described above. A precipitate, *4-amino-3-(p-methylbenzyl)-2-oxo-2H-chromene* (116d) (yield 0.356 g, 13%) was filtered out and recrystallised from ethanol giving small, colourless needles (0.101 g, 4%), m.p. 203-206°C (Found: C, 76.8; H, 5.8; N, 5.2%. $C_{17}H_{15}NO_2$ requires: C, 77.0; H, 5.7; N, 5.3%); νmax.(Nujol) 3475, 3350, 3240 (NH_2), 1640 (C=O) cm^{-1}; *m/z* 265, 250, 236, 174, 146. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.4.

The residue obtained was dissolved in ether; a similar volume of methylene chloride was added to the solution which resulted in the precipitation of *3-(p-methylphenyl)-4-oxo-4H-chromemo[4,3-c]isothiazole* (97d). This was filtered out giving a white powder (yield 0.70 g, 24%) which was recrystallised from ethyl acetate giving colourless needles (0.409 g, 14%), m.p. 195-197°C (Found: C, 69.4; H, 3.9; N, 4.8%. $C_{17}H_{11}NO_2S$ requires: C, 69.6; H, 3.8; N, 4.8%); νmax.(Nujol) 1751 (C=O) cm^{-1}; *m/z* 293, 143. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.2.

The liquors were evaporated under vacuum and subjected to chromatography on silica eluting with methylene chloride-light petroleum (b.p. 40-60°C) (70:30) yielding *10-methyl-6-oxo-6H-chromeno[4,3-b]quinoline* (115d) which was recrystallised from ethyl acetate giving colourless needles (yield 0.037 g, 1%), m.p. 205-207°C (Found: C, 78.0; H, 4.3; N, 5.3%. $C_{17}H_{11}NO_2$ requires: C, 78.2; H, 4.2;

N, 5.4%); νmax.(Nujol) 1730 (C=O) cm^{-1} *m/z* 261, 232. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Tables 6 and 7, Section 2.3.3.3.

o-Cyanophenyl *p*-methylcinnamate (114d) was not isolated pure but its presence in the reaction mixture was demonstrated by t.l.c. and h.p.l.c. comparisons with the authentic material described in Section 3.2.3.3(viii).

The total yields of chromenoisothiazole (97d) (30%), chromenoquinoline (115d) (3%) and the *o*-cyanophenyl ester (114d) (46%) were determined by h.p.l.c. analysis of the reaction mixture sample.

(vii) 5-[*o*-(α-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (130)

The oxathiazolone (3.39 g, 0.01 mol) was heated in dry xylene (250 ml) for 19h as described above. The residue obtained was subjected to flash chromatography on silica eluting with ether-hexane (10:90) which yielded sulphur (0.279 g, 87%) and the following two products.

3,3a-Dihydro-3a-methyl-4-oxo-3-phenyl-4H-chromeno-[4,3-c]isothiazole (132) was obtained as a white solid (yield 0.151 g, 5%) which was recrystallised from cyclohexane giving colourless needles (0.071 g, 2%), m.p. 149-151°C (Found: C, 69.0; H, 4.2; N, 4.7%. $C_{17}H_{13}NO_2S$ requires: C, 69.2; H, 4.4; N, 4.8%); νmax.(Nujol) 1781 (C=O) cm^{-1}; *m/z* 295, 280, 266, 115. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.5.

o-Cyanophenyl α-methylcinnamate (131) was obtained as a white solid (yield 2.13 g, 81%) which had an identical

i.r. spectrum to that of the authentic described in Section 3.2.3.3(x).

(viii) 5-[*o*-(β-Methylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (133)

The oxathiazolone (5.09 g, 0.015 mol) was heated in dry xylene (375 ml) for 8h as described above. The residue obtained was subjected to flash chromatography on silica eluting first with ethyl acetate-hexane (20:80) then with methanol-chloroform (4:96). This yielded sulphur (0.435 g, 90%), *o*-cyanophenyl β-methylcinnamate (135) (3.35 g, 85%) and *4-amino-2-oxo-3-(α-styryl)-2H-chromene* (136) (0.61 g, 15%).

o-Cyanophenyl β-methylcinnamate (135) was recrystallised from ether in the freezer giving off-white needles (yield 2.36 g, 60%) m.p. 81-81.5°C, authentic described in Section 3.2.3.3(xi), m.p. 80-81°C; mixed m.p. 79.5-81°C.

4-Amino-2-oxo-3-(α-styryl)-2*H*-chromene (136) was rechromatographed, eluting with chloroform, giving a clear, pale yellow glass which could not be crystallised (yield 0.42 g, 11%), m.p. 175-178°C (Found: M^+ 263.0946. $C_{17}H_{13}NO_2$ requires: *M* 263.094622); νmax.(Nujol) 3430, 3340, 3210 (NH_2), 1665 (C=O) cm^{-1}; *m/z* 263, 262, 248, 234, 119, 91. For ^1H n.m.r., ^{13}C n.m.r. spectra see Appendix 4.3.4.

(ix) 5-[*o*-(2,4,6-Trimethylcinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (141)

The oxathiazolone (3.67 g, 0.01 mol) was heated in dry

xylene (250 ml) for 18h as described above. The residue obtained was subjected to flash chromatography on silica eluting with ether-hexane (15:85) which yielded sulphur (0.165 g, 52%) and the following three compounds.

4-Oxo-3-(2,4,6-trimethylphenyl)-4H-chromeno[4,3-c]-isothiazole (144) was recrystallised from a hexane-cyclohexane mixture giving colourless plates (yield 0.736 g, 23%), m.p. 159-160°C (Found: C, 71.35; H, 4.7; N, 4.6. $C_{19}H_{15}NO_2S$ requires: C, 71.05; H, 4.65; N, 4.35%); νmax. (Nujol) 1750 (C=O) cm^{-1}; *m/z* 321, 306, 304, 292, 289, 278, 260, 115, 91. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.2.

4-Amino-2-oxo-3-(2,4,6-trimethylphenyl)-2H-chromene (145) was recrystallised from ethyl acetate giving colourless needles (yield 0.436 g, 15%), m.p. 209-211°C (Found: C, 77.8; H, 6.55; N, 4.95%. $C_{19}H_{19}NO_2$ requires: C, 77.8; H, 6.5; N, 4.8%); νmax.(Nujol) 3480, 3340, 3200 (NH_2), 1665 (C=O) cm^{-1}; *m/z* 293, 288, 286, 248, 174, 132. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.4.

o-Cyanophenyl 2,4,6-trimethylcinnamate (143) was recrystallised from a cyclohexane-chloroform mixture giving large, colourless plates (yield 0.979 g, 34%), m.p. 106-108°C; authentic compound [Section 3.2.3.3(xii)], m.p. 104-107°C; mixed m.p. 104-108°C.

The total, crude, yields after chromatography were chromenoisothiazole (144) 33%, aminochromene (145) 24%, nitrile (143) 34%.

(x) 5-[*o*-(2,6-Dichlorocinnamoyloxy)phenyl]-1,3,4-oxathiazol-2-one (142)

The oxathiazolone (1.576 g, 0.004 mol) was heated in dry xylene (100 ml) for 18h as described above. The residue obtained was subjected to a series of chromatographic techniques leading to the isolation of the following two compounds.

3-(2,6-Dichlorophenyl)-4-oxo-4H-chromeno[4,3-c]-isothiazole (148) was recrystallised from ethyl acetate giving large, colourless lozenges (yield 0.173 g, 12%), m.p. 177.5-178°C (Found: C, 55.4; H, 1.95; N, 4.0%. $C_{16}H_7Cl_2NO_2S$ requires: C, 55.15; H, 2.0; N, 4.0%); νmax. (Nujol) 1737 (C=O) cm^{-1}; *m/z* 351, 349, 347, 314, 312, 156. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.2.

8-Chloro-6-oxo-6H-chromeno[4,3-b]quinoline (149) was recrystallised from ethyl acetate giving fine, colourless needles (yield 0.119 g, 11%), m.p. 235.5-237°C (Found: C, 67.9; H, 2.8; N, 5.1. $C_{16}H_8ClNO_2$ requires: C, 68.2; H, 2.85; N, 4.95%); νmax.(Nujol) 1728 (C=O) cm^{-1}; *m/z* 283, 281, 255, 253, 218, 191, 164, 163. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Tables 6 and 7, Section 2.3.3.3.

o-Cyanophenyl 2,6-dichlorocinnamate (147) was not isolated but its presence in the reaction mixture was demonstrated by t.l.c. and h.p.l.c. comparisons with the authentic material described in Section 3.2.3.3(xiii).

The total yields of chromenoisothiazole (148) (31%), chromenoquinoline (149) (28.5%), and the *o*-cyanophenyl ester (147) (7%) were determined by h.p.l.c. analysis of the reaction mixture sample.

(xi) 5-{*o*-[3-(2-Furyl)acryloyloxy]phenyl}-1,3,4-oxathiazol-2-one (150)

The oxathiazolone (3.15 g, 0.01 mol) was heated in dry xylene (250 ml) for 22h as described above. The residue obtained was subjected to a series of chromatographic techniques which led to the isolation of the following three products.

3-(2-Furyl)-4-oxo-4H-chromeno[4,3-c]isothiazole (205) was recrystallised from ethyl acetate giving colourless needles (yield 0.135 g, 5%), m.p. 251-254°C (Found: C, 62.2; H, 2.6; N, 5.1%. $C_{14}H_7NO_3S$ requires: C, 62.5; H, 2.6; N, 5.2%); νmax.(Nujol) 1760 (C=O) cm^{-1}; *m/z* 269, 240, 212. For ^1H n.m.r. and ^{13}C n.m.r. see Appendix 4.3.2.

6-Oxo-6H-chromeno[4,3-b]furo[2,3-c]pyridine (151) was recrystallised from methanol giving off-white needles (yield 0.014 g, 0.6%), m.p. 180-182°C (Found: M^+, 237.0418. $C_{14}H_7NO_3$ requires; *M*, 237.042573); νmax.(Nujol) 1725 (C=O) cm^{-1}; *m/z* 237, 209, 153, 127, 126. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.6.

4-Amino-3-furfuryl-2-oxo-2H-chromene (206) was recrystallised from ethyl acetate giving colourless needles (yield 0.067 g, 3%), m.p. 212-215°C (Found: C, 69.6; H, 4.4; N, 5.7%. $C_{14}H_{11}NO_3$ requires: C, 69.7; H, 4.6; N, 5.8%); νmax.(Nujol) 3410, 3250 (NH_2), 1630 (C=O) cm^{-1}; *m/z* 241, 212, 196, 184. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.4.

o-Cyanophenyl 3-(2-furyl)acrylate (202) was not isolated pure but its presence in the reaction mixture was demonstrated by t.l.c. and h.p.l.c. comparisons with the

authentic material described in Section 3.2.3.3(xiv).

The total yields of the above chromenoisothiazole (205) (16%), chromenofuropyridine (151) (2%) and *o*-cyanophenyl 3-(2-furyl)acrylate (202) (26%) were determined by h.p.l.c. analysis of the reaction mixture sample.

3.4.3 Related Reactions

(i) Thermolysis of 5[*o*-(2-Furoyloxy)phenyl]-1,3,4-oxathiazol-2-one (119)

The oxathiazolone (3.47 g, 0.012 mol) was heated in dry xylene (300 ml) for 8h as described in the general procedure above. The residue obtained was subjected to flash chromatography on silica eluting with ethyl acetate-hexane (20:80). This yielded one product only, *o*-cyanophenyl 2-furoate (121), which was recrystallised from a cyclohexane-ethyl acetate mixture giving colourless needles (yield 1.72 g, 58%), m.p. 117-120°C, authentic compound [Section 3.2.3.3(ix)] m.p. 118-120°C, mixed m.p. 118-119.5°C.

The total yield of *o*-cyanophenyl 2-furoate (121) (79%) was determined by h.p.l.c. analysis of the reaction mixture sample. No products other than this *o*-cyanophenyl ester were isolated or identified.

(ii) Thermolysis of 5-[*o*-(3-Furoyloxy)phenyl]-1,3,4-oxathiazol-2-one (120)

The oxathiazolone (1.01 g, 0.0035 mol) was heated in dry xylene (100 ml) for 24h as described in the general procedure above. The residue obtained, a yellow solid,

was recrystallised from cyclohexane with hot filtration to remove sulphur. This gave pale yellow needles of *o*-cyanophenyl 3-furoate (122) (yield 0.54 g, 73%), m.p. 118-121°C (Found: C, 67.7; H, 3.5; N, 6.5%. $C_{12}H_7NO_3$ requires: C, 67.6; H, 3.3; N, 6.6%); νmax.(Nujol) 2235 (C≡N), 1742 (C=O) cm^{-1}; *m/z* 213, 95, 39. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.1.3.2.

The total yield of *o*-cyanophenyl 3-furoate (122) (92%) was determined by h.p.l.c. analysis of the reaction mixture sample.

(iii) Thermolysis of *o*-Cyanophenyl Cinnamate (114a)

o-Cyanophenyl cinnamate (0.256 g, 1.03 mmol) was dissolved in dry xylene (25 ml) and heated under reflux. After 6 days h.p.l.c. analysis showed that no reaction had taken place. After 6 weeks, however, there had been some decomposition. The quantity of *o*-cyanophenyl cinnamate remaining (0.149 g, 58%) was determined by h.p.l.c. analysis. There were several minor, non-polar products shown by h.p.l.c., none were identified or isolated, but comparisons with an authentic sample of 6-oxo-6*H*-chromeno[4,3-*b*]quinoline (115a) demonstrated the total absence of this compound from the reaction mixture.

(iv) Preparation of 6-Oxo-6*H*-chromeno[4,3-*b*]quinoline (115a)

The authentic chromenoquinoline was prepared by the method of Buu Hoi *et al.*[92] 4-Hydroxycoumarin (118) (1.62 g, 0.01 mol) was mixed with aniline (0.93 g, 0.01 mol) and heated to reflux on an oil bath. Paraformaldehyde (0.45 g,

0.015 mol) was added in small portions down the condenser, heating was continued for a few minutes after the addition was complete. Kugelrohr distillation allowed the removal of unreacted aniline, however, the product could not be distilled cleanly. The residue was subjected to chromatography on silica eluting with ether-light petroleum (b.p. 40-60°C) (50:50). This yielded the desired product which was recrystallised from ethyl acetate giving pale yellow needles (yield 0.157 g, 6%), m.p. 227-229°C (lit.,[92] 224-225°C).

(v) Thermolysis of 5-Phenyl-1,3,4-oxathiazolone (38) in the Presence of Tetraphenylcyclopentadienone (123)

Phenyloxathiazolone (1.80 g, 0.01 mol) and tetraphenylcyclopentadienone (1.92 g, 0.05 mol) were dissolved in dry xylene (30 ml) and heated under reflux for 18h. After cooling the mixture was filtered giving black crystals of unreacted tetraphenylcyclopentadienone (0.75 g, 39%). The solvent and benzonitrile, produced by decomposition of phenyloxathiazolone, were evaporated from the liquors under vacuum. The residue was subjected to chromatography on silica eluting with ether-light petroleum (b.p. 40-60°C) (2.5:97.5). This yielded sulphur (0.32 g, 100%), the remaining unreacted tetraphenylcyclopentadienone (1.17 g, 61%) and two minor products. Both were contaminated but mass spectroscopy allowed the tentative identification of the major component of each. One was 3,5-diphenyl-1,2,4-thiadizole (124) (yield estimated to be $\leqslant$0.1%) *m/z* 238, 135, 103, 77. The other was pentaphenylpyridine (125)

(yield estimated to be ≤0.1%) *m/z* 459, 458, 356, 178, 77.

(vi) Reaction of 5-(*p*-Methoxyphenyl)-1,3,4-oxathiazol-2-one (152) with *p-tert*-Butylphenyl Cinnamate (153)

The oxathiazolone (1.175 g, 0.0056 mol) was added in small portions to a solution of *p-tert*-butylphenyl cinnamate (7.75 g, 0.028 mol) in dry xylene (50 ml) heated under reflux. The addition was made over 5h and the mixture heated for a further 5h. On cooling excess *p-tert*-butyl cinnamate crystallised and was filtered out giving colourless needles (4.63 g). The solvent was evaporated from the liquors under vacuum and the residue was subjected to a variety of chromatographic techniques. This eventually led to the isolation of anisonitrile (yield 0.65 g, 70%) which was identical to an authentic by i.r., and an inseparable mixture of two isothiazoline isomers. These isomers, *p-tert-butyl 3-(p-methoxyphenyl)-5-phenylisothiazoline-4-carboxylate* (154) and *p-tert-butyl 3-(p-methoxyphenyl)-4-phenylisothiazoline-5-carboxylate* (155), were obtained as a pinkish gum (yield 0.032 g, 1.3%), (Found: M^+, 445.1633. $C_{27}H_{27}NO_3S$ requires; *M*, 445.171153); νmax.(film) 1747 (C=O) cm^{-1} *m/z* 445, 294, 293, 280, 267, 165, 149, 135, 131, 121, 77. For the ^1H n.m.r. spectrum of this mixture see Appendix 4.4.3.

The two isomers were unresolved on h.p.l.c. Their combined yield was estimated as 7%±2% by h.p.l.c. analysis of a sample of the original reaction mixture using a peak area matching technique. ^1H n.m.r. showed the isomer ratio to be *ca.* 1:1.

3.5 INTERMOLECULAR CYCLOADDITIONS OF *O*-SUBSTITUTED BENZONITRILE SULPHIDES AND RELATED REACTIONS

Reactions of the *o*-substituted phenyloxathiazolones 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (62), 5-(*o*-acetoxyphenyl)-1,3,4-oxathiazol-2-one (63) and 5-(*o*-acetamidophenyl)-1,3,4-oxathiazol-2-one (64) with the dipolarophiles ethyl cyanoformate (ECF), dimethyl acetylenedicarboxylate (DMAD), ethyl propiolate (EP) and diethyl fumarate (DEF) are described in the following sections along with some related reactions.

3.5.1 Reactions with Ethyl Cyanoformate

(i) *Preparation of Ethyl 3-(o-Hydroxyphenyl)-1,2,4-thiadiazole-5-carboxylate* (161)

o-Hydroxyphenyloxathiazolone (62) (1.95 g, 0.01 mol) and ECF (1.98 g, 0.02 mol) were dissolved in dry xylene (25 ml) and heated under reflux for 18h. The solvent and excess ECF were evaporated under vacuum giving the crude product as a yellow solid; no *o*-cyanophenol could be detected by t.l.c. Recrystallisation from hexane gave pale yellow needles (yield 2.13 g, 85%), m.p. 93-95°C (Found: C, 52.7; H, 3.9; N, 11.2%. $C_{11}H_{10}N_2O_3S$ requires: C, 52.8; H, 4.0; N, 11.2%); νmax.(Nujol) 3170 (OH), 1745 (C=O) cm^{-1}; *m/z* 250, 222, 204, 151, 119, 91. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.4.1.

(ii) Preparation of *Ethyl 3-(o-Acetoxyphenyl)-1,2,4-thiadiazole-5-carboxylate* (162)

o-Acetoxyphenyloxathiazolone (63) (1.19 g, 0.005 mol) and ECF (1.0 g, 0.01 mol) were dissolved in dry xylene (20 ml) and heated under reflux for 18h. The solvent and excess ECF were evaporated under vacuum giving the crude product as a pale yellow solid (yield 1.47 g, 100%). No sulphur or *o*-acetoxybenzonitrile could be detected by t.l.c. Recrystallisation from a hexane-ethanol mixture gave pale yellow needles (yield 1.07 g, 73%), m.p. 86-87°C (Found: C, 53.3; H, 4.2; N, 9.4%. $C_{13}H_{12}N_2O_4S$ requires: C, 53.4; H, 4.1; N, 9.6%); νmax. (Nujol) 1750 (C=O) cm^{-1}; *m/z* 292, 250, 222, 203, 151, 122, 119. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.4.1.

(iii) Preparation of *Ethyl 3-(o-Acetamidophenyl)-1,2,4-thiadiazole-5-carboxylate* (163)

o-Acetamidophenyloxathiazolone (64) (0.47 g, 0.002 mol) and ECF (2.97 g, 0.03 mol) were dissolved in dry xylene (15 ml) and heated under reflux for 18h. The solvent and excess ECF were evaporated under vacuum giving a yellow crystalline solid, no *o*-acetamidobenzonitrile could be detected by t.l.c. Recrystallisation from cyclohexane gave pale yellow needles (yield 0.57 g, 98%), m.p. 114-116°C (Found: C, 53.7; H, 4.6; N, 14.2%. $C_{13}H_{13}N_3O_3S$ requires: C, 53.6; H, 4.5; N, 14.4%); νmax. (Nujol) 3190 (NH), 1745, 1693 (C=O) cm^{-1}; *m/z* 291, 249, 225, 221, 197, 160, 150, 118, 105, 91. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.4.1.

3.5.2 Reactions with Dimethyl Acetylenedicarboxylate

(i) Preparation of *Methyl 4-Oxo-4H-chromeno[4,3-c]-isothiazole-3-carboxylate* (164)

o-Hydroxyphenyloxathiazolone (62) (1.95 g, 0.01 mol) and DMAD (2.84 g, 0.02 mol) were dissolved in dry xylene (10 ml) and heated under reflux for 18h. On cooling a pale yellow solid crystallised, this was filtered out giving the crude product (yield 1.765 g, 68%). The solvent was evaporated from the remaining liquors under vacuum giving a yellow solid which was subjected to flash chromatography on silica eluting with ethyl acetate-hexane (20:80). This yielded *o*-cyanophenyl (0.01 g, 8%) and a further portion of crude product (0.61 g, 23%). The combined crude product (2.38 g, 91%) was recrystallised from ethanol giving pale yellow needles (yield 1.96 g, 75%), m.p. 158-160°C (Found: C, 55.0; H, 2.7; N, 5.3%. $C_{12}H_7NO_4S$ requires: C, 55.2; H, 2.7; N, 5.4%); νmax. (Nujol) 1755 (C=O) cm^{-1}; *m/z* 261, 230, 203, 159, 149, 119, 118. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.3.2.

(ii) Preparation of *Dimethyl 3-(o-Acetoxyphenyl)isothiazole-4,5-dicarboxylate* (165)

o-Acetoxyphenyloxathiazolone (63) (3.08 g, 0.013 mol) and DMAD (3.69 g, 0.026 mol) were dissolved in dry xylene (10 ml) and heated under reflux for 18h. The solvent was evaporated under vacuum and the resulting brown oil subjected to flash chromatography on silica, eluting with ether-hexane (20:80). This yielded excess DMAD which was

discarded, *o*-acetoxybenzonitrile (0.20 g, 10%) which was identified by t.l.c. and i.r. but not purified and the desired isothiazole as an off-white solid (3.93 g, 90%). Recrystallisation from a hexane-ethyl acetate mixture gave a white crystalline mass (yield 3.30 g, 76%), m.p. 88-90°C (Found: C, 53.5; H, 3.9; N, 4.1%. $C_{15}H_{13}NO_6S$ requires: C, 53.7; H, 3.9; N, 4.2%); νmax. (Nujol) 1730 br (C=O) cm^{-1}; *m/z* 335, 293, 261, 230, 203, 131. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.4.2.

(iii) Preparation of *Dimethyl 3-(o-Acetamidophenyl)-isothiazole-4,5-dicarboxylate* (166)

o-Acetamidophenyloxathiazolone (64) (0.95 g, 0.004 mol) and DMAD (4.26 g, 0.03 mol) were dissolved in dry xylene (10 ml) and heated under reflux for 18h. The solvent and some DMAD were evaporated under vacuum giving a brown oil which was subjected to flash chromatography on silica eluting with methanol-methylene chloride-hexane (4:46:50). This yielded the desired product as a brown gum, contaminated with a by-product derived from DMAD. Crystallisation and recrystallisation from ethanol gave off-white needles (yield 0.24 g, 18%), m.p. 144-146°C (Found: M^+, 334.0618. $C_{15}H_{14}N_2O_5S$ requires: *M*, 334.062335); νmax. (Nujol) 3360 (NH), 1730 (C=O) cm^{-1}; *m/z* 334, 302, 292, 261, 229, 202, 173, 91. For ^1H n.m.r. and ^{13}C n.m.r. of this product see Appendix 4.4.2.

H.p.l.c. analysis of a sample of the reaction mixture allowed the total yield of this product to be estimated

using a graphical, peak area matching technique. The estimated yield was 67%±3%.

(iv) Hydrolysis of 3-(*o*-Acetoxyphenyl)isothiazole-4,5-dicarboxylate (165); Attempted Preparation of Dimethyl 3-(*o*-Hydroxyphenyl)isothiazole-4,5-dicarboxylate (168)

Dimethyl 3-(*o*-acetoxyphenyl)isothiazole-4,5-dicarboxylate (165) (0.166 g, 0.5 mmol) was stirred in a saturated solution of sodium bicarbonate in aqueous methanol (50% v/v MeOH, 20 ml) at room temperature for 18h. The solution was acidified to pH 1 using concentrated hydrochloric acid; a white precipitate formed. This was filtered out, washed with water and dried to give a white powder (yield 0.030 g, 24%) which was shown by t.l.c. and ^{1}H n.m.r. to be the chromenoisothiazolecarboxylic acid (169) which is fully described in the following section [3.5.2(v)].

The acidic liquors were extracted with methylene chloride (4x20 ml). The combined extracts were dried over anhydrous magnesium sulphate and the solvent was evaporated under vacuum to give a colourless glass which partially crystallised (0.131 g). T.l.c. of this product showed it to be a mixture of the starting material and methyl 4-oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylate (164) the preparation of which is described above in Section 3.5.2(i).

There was no evidence to suggest that the desired product was present in the final reaction mixture.

(v) Preparation of *4-Oxo-4H-chromeno[4,3-c]isothiazole-3-carboxylic Acid* (169)

Dimethyl 3-(*o*-acetoxyphenyl)isothiazole-4,5-dicarboxylate (165) (1.00 g, 0.003 mol) was stirred in a solution of potassium hydroxide (5.0 g in 100 ml 20% v/v aqueous methanol) at room temperature for 18h. The solution was acidified to pH 1 using concentrated hydrochloric acid; a white precipitate slowly appeared. This was filtered out, washed with water and dried to give the chromenoisothiazolecarboxylic acid (169) as a white powder (yield 0.64 g, 87%), m.p. (decomp.) 171.5-172°C (Found: M^+, 246.9940. $C_{11}H_5NO_4S$ requires: *M*, 246.993926); νmax. (Nujol) 2720 (OH), 1770, 1750 (C=O) cm^{-1}; *m/z* 247, 230, 203, 175, 159, 146, 119.

(vi) Preparation of 4-Oxo-4*H*-chromeno[4,3-*c*]isothiazole (103) by Thermal Decarboxylation of 4-Oxo-4*H*-chromeno[4,3-*c*]isothiazole-3-carboxylic Acid (169)

The chromenoisothiazolecarboxylic acid (169) (0.144 g, 0.58 mmol) was dissolved in *o*-dichlorobenzene (50 ml) and heated under reflux (178°C) for 1h. The solvent was evaporated under vacuum giving the chromenoisothiazole (103) as an off-white solid (yield 0.089 g, 81%). The i.r. spectrum of the product was identical to that of the compound prepared by intramolecular cycloaddition of the *o*-acryloyloxyphenyloxathiazolone (71) described in Section 3.4.2(i).

It was found that the chromenoisothiazole carboxylic acid (169) also decarboxylated on standing in solution in

acetone for several days at room temperature.

(vii) Preparation of *Isothiazolo[4,3-c]quinolin-4(5H)-one* (171)

Dimethyl 3-(*o*-acetamidophenyl)isothiazole-4,5-dicarboxylate (166) (0.167 g, 0.5 mmol) was suspended in dilute sulphuric acid (20 ml, 10% v/v), with a few drops of methanol to allow wetting, and heated under reflux for 1.5h. A yellow precipitate slowly formed. The mixture was cooled and adjusted to pH 6 with sodium hydroxide solution; the precipitate was filtered off and dried giving a white powder (0.100 g). This was shown by ^{1}H n.m.r. and m.s. to be a mixture of isothiazolo[4,3-*c*]-quinolin-4(5*H*)-one (171) and *isothiazolo[4,3-c]quinolin-4(5H)-one-3-carboxylic acid* (170).

A portion of this mixture (0.060 g) was suspended in dry xylene (10 ml) and heated under reflux for 20h. After cooling the mixture was filtered to give a white powder (0.044 g) and the liquors were evaporated under vacuum giving a further quantity (0.012 g) of the same material. ^{1}H n.m.r. showed that this was a single compound isothiazolo[4,3-*c*]quinolin-4(5*H*)-one (171) (yield 0.056 g, 92%), m.p. (decomp) 232-233°C (Found: M^+, 202.0202. $C_{10}H_6N_2OS$ requires: *M*, 202.020082); νmax.(Nujol) 3115 (NH), 1665 (C=O) cm^{-1}; *m/z* 202, 145, 129, 118, 91. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.3.1.

3.5.3 Reactions with Ethyl Propiolate

(i) Preparation of *Ethyl 3-(o-Hydroxyphenyl)isothiazole-5-carboxylate* (172) and 4-Oxo-4*H*-chromeno[4,3-*c*]-isothiazole (103)

o-Hydroxyphenyloxathiazolone (62) (3.9 g, 0.02 mol) and EP (7.84 g, 0.08 mol) were dissolved in dry xylene (20 ml) and heated under reflux for 18h. The solvent and excess EP were evaporated under vacuum to give a brown oil which was subjected to flash chromatography eluting with ether-hexane (20:80). This yielded *o*-cyanophenol (1.08 g, 45%) which was identified by t.l.c. and i.r. but was not purified, and the following two products.

Ethyl 3-(*o*-hydroxyphenyl)isothiazole-5-carboxylate (172) was obtained as a yellow solid. Recrystallisation from cyclohexane gave small, off-white blocks (yield 0.41 g, 8%), m.p. 97-99°C (Found: C, 57.6; H, 4.3; N, 5.4%. $C_{12}H_{11}NO_3S$ requires: C, 57.8; H, 4.4; N, 5.6%); νmax. (Nujol) 3100 (OH), 1705 (C=O) cm^{-1}; *m/z* 249, 221, 204, 193, 175, 149, 146. For ^1H n.m.r. and ^{13}C n.m.r. spectra of this product see Appendix 4.4.2.

4-Oxo-4-*H*-chromeno[4,3-*c*]isothiazole (103) was also obtained as a yellow solid. Recrystallisation from ethanol gave pale yellow needles (yield 0.40 g, 10%). This product was identical to the compound prepared by thermolysis of 5-(*o*-acryloyloxyphenyl)-1,3,4-oxathiazol-2-one (71) described in Section 3.4.2(i); m.p. and mixed m.p. 168-169°C.

(ii) Preparation of *Ethyl 3-(o-Acetoxyphenyl)isothiazole-4- and 5-carboxylates* (173) and (174)

o-Acetoxyphenyloxathiazolone (63) (1.19 g, 0.005 mol) and EP (1.96 g, 0.02 mol) were dissolved in dry xylene (20 ml) and heated under reflux for 18h. The solvent and excess EP were evaporated under vacuum and the resulting brown oil subjected to flash chromatography on silica, eluting with ethyl acetate-hexane (20:80). This yielded *o*-acetoxybenzonitrile (0.04 g, 7%) which was identified by t.l.c. and i.r. but not purified, ethyl 3-(*o*-acetoxyphenyl)isothiazole-4-carboxylate (173) (0.68 g, 47%) as a yellow oil, and ethyl 3-(*o*-acetoxyphenyl)isothiazole-5-carboxylate (174) (0.67 g, 46%) also as a yellow oil. Attempted Kugelrohr distillation of each product resulted in its partial decomposition by deacetylation to give the same products as in the corresponding cycloaddition of EP to *o*-hydroxyphenyloxathiazolone (62), as described in the above Section [3.5.3(i)]. The decomposition products were identified by t.l.c. and ^{1}H n.m.r. comparisons with the authentics and in the case of the 4-oxo-4*H*-chromeno-[4,3-*c*]isothiazole (103), a portion of which was isolated, by mixed melting point (m.p. and mixed m.p. 168-169°C).

The experiment was repeated and spectroscopic data was collected on the crude products. Ethyl 3-(*o*-acetoxyphenyl)-isothiazole-4-carboxylate (173), b.p. (decomp.) 210°C at 1 mmHg (Found: M^+, 291.0568. $C_{14}H_{13}NO_4S$ requires: *M*, 291.056523); νmax. (film) 1770, 1725 (C=O) cm^{-1}; *m/z* 291, 249, 220, 203, 175, 146. For ^{1}H and ^{13}C n.m.r. spectra

of this and the following compound see Appendix 4.4.2. Ethyl 3-(*o*-acetoxyphenyl)isothiazole-5-carboxylate (174), b.p. (decomp.) 210°C at 1 mmHg (Found: M^+, 291.0569. $C_{14}H_{13}NO_4S$ requires: *M*, 291.056523); ν max. (film) 1770, 1725 (C=O) cm^{-1}; *m/z* 291, 249, 221, 161, 119, 91, 43.

3.5.4 Reactions with Diethyl Fumarate

(i) Formation and Decomposition of *Diethyl 3-(o-Hydroxyphenyl)isothiazoline-4,5-dicarboxylate* (176)

o-Hydroxyphenyloxathiazolone (62) (1.95 g, 0.01 mol) and DEF (6.88 g, 0.04 mol) were dissolved in dry xylene (30 ml), flushed with nitrogen, and heated under reflux for 18h under a nitrogen atmosphere. The solvent and some DEF were evaporated under vacuum giving a brown oil which was subjected to flash chromatography on silica eluting with ethyl acetate-hexane (15:85). This yielded *o*-cyanophenol, which was identified by t.l.c. and i.r. but was not purified or quantified, and the following compounds.

Ethyl 4-oxo-4-*H*-chromeno[4,3-*c*]isothiazole-3-carboxylate (110) was obtained as a white solid. Recrystallisation from cyclohexane gave colourless needles, (yield 0.41 g, 15%), m.p. 118-120°C; the material was identical to the compound prepared by intramolecular cycloaddition of the monoethyl fumarate ester (109) described in Section 3.4.2(ii), (m.p. 118-120°C, authentic 117-120°C).

The initial cycloadduct, diethyl 3-(*o*-hydroxyphenyl)-isothiazoline-4,5-dicarboxylate (176), was obtained as an impure, yellow oil but it could not be purified before it

decomposed (yield estimated as 26%), *m/z* (impure sample) 323, 275, 250, 218, 204, 203. For limited ^{1}H n.m.r. data see Appendix 4.4.3.

The experiment was repeated on half the above scale. After 18h heating the solvent was evaporated under vacuum and the presence of the initial isothiazoline adduct (176) demonstrated by ^{1}H n.m.r. A sample of the residue was analysed by h.p.l.c. and the yield of the chromenoisothiazole product (110) determined as 18%; no *o*-hydroxyphenyloxathiazolone remained. The residue was then redissolved in dry xylene and heated under reflux for a further 40h when ^{1}H n.m.r. showed that there was no isothiazoline remaining. H.p.l.c. analysis of the reaction mixture allowed determination of the final yield of chromenoisothiazole product (110) as 26%.

(ii) Preparation of *Diethyl 3-(o-Acetoxyphenyl)isothiazoline-4,5-dicarboxylate* (177)

o-Acetoxyphenyloxathiazolone (63) (1.19 g, 0.005 mol) and DEF (3.44 g, 0.02 mol) were dissolved in dry xylene (20 ml), flushed with nitrogen and heated under reflux for 18h under a nitrogen atmosphere. The solvent and some DEF were evaporated under vacuum and the resulting brown oil was subjected to flash chromatography on silica, eluting with ethyl acetate-hexane (30:70). Sulphur, excess DEF and *o*-acetoxybenzonitrile were isolated but not quantified. The desired product was obtained as a yellow oil (yield 1.03 g, 56%). Spectroscopic data was collected without further purification as the product was found to decompose

easily to a number of unidentified products, (Found: M^+, 365.0934. $C_{17}H_{19}NO_6S$ requires: M, 365.093298); νmax.(film) 1770, 1730 (C=O) cm^{-1}; m/z 365, 323, 292, 277, 275, 250, 224, 204. For ^1H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.4.3.

3.6 DIAZO COMPOUNDS AND THEIR REACTIONS WITH 5-(*p*-METHOXYPHENYL)-1,3,4-OXATHIAZOL-2-ONE

3.6.1(i) Preparation of Diazo Compounds

Dimethyl and diethyl diazomalonates and methyl diazoacetoacetate were prepared by the method of Regitz.[108] The results are summarised in Table 14.

Equimolar quantities of the active methylene compound and triethylamine were dissolved together in acetonitrile at room temperature. One equivalent of tosyl azide was added and the mixture was stirred until judged to be complete by t.l.c.

The literature work up procedure, evaporation followed by washing with potassium hydroxide solution, failed to remove the tosyl amide by-product in two cases. A chromatographic isolation proved possible as an alternative.

The products were obtained as yellow oils of sufficient purity for further reactions.

Table 14

$$R^1R^2CH_2 \longrightarrow R^1R^2CN_2$$

R^1	R^2	Reaction time /h	Isolation	Yield %
CO_2Me	COMe	1.5	a	88
CO_2Me	CO_2Me	8	b	17
CO_2Et	CO_2Et	3	c	58

Footnotes:

a Literature work up.[108]

b Flash chromatography eluting with ether.

c Flash chromatography eluting with ethyl acetate-hexane (15:85).

(ii) Preparation of Tosyl Azide

Tosyl azide was prepared, by the method of Curtius,[130] from sodium azide and tosyl chloride. It was obtained as a clear, colourless oil in 71% yield [νmax. (film) 2125 ($C=N_2$) cm^{-1}]; the product could be stored indefinitely in the freezer as a white solid.

(iii) Preparation of Rhodium(II) Acetate

Rhodium(II) acetate was prepared, by the method of Rempel *et al.*,[107] from rhodium trichloride and sodium

acetate. It was obtained in 53% yield as a bright-green, crystalline solid.

3.6.2 Reactions of Diazo Compounds with 5-(*p*-Methoxyphenyl)-1,3,4-oxathiazol-2-one

The reactions of dimethyl and diethyl diazomalonates and methyl diazoacetoacetate with *p*-methoxyphenyloxathiazolone (152) were performed by the following general procedure.

The oxathiazolone (2.09 g, 0.01 mol) and rhodium(II) acetate (0.015 g) were dissolved in dry benzene (30 ml). The solution was flushed with nitrogen and warmed to 75°C using a thermostatically controlled water bath. A solution of the diazo compound (0.011 mol) in dry benzene (20 ml), which had also been flushed with nitrogen, was added dropwise over 15 min with magnetic stirring and the mixture was heated for a further 5 to 10 min when effervescence had become negligible.

The mixture was cooled and the solvent evaporated using a cool water bath giving a brown, oily residue. Separation of the products was effected by flash chromatography on silica.

(i) Dimethyl Diazomalonate

Dimethyl diazomalonate (1.90 g, 0.012 mol) and *p*-methoxyphenyloxathiazolone (152) (2.09 g, 0.01 mol) were reacted together following the above procedure. The residue obtained was subjected to flash chromatography eluting with ether-hexane (10:90). This yielded unreacted oxathiazolone and anisonitrile (0.934 g, 70%) identified by t.l.c.

comparisons with authentics. Further elution with methylene chloride-hexane (50:50) gave a white, crystalline solid which was an oligomer of dimethyl 2-thiomalonate, possibly *tetramethyl 1,3-dithietane-2,2,4,4-tetracarboxylate* (183a) (yield 1.253 g, 77%), m.p. 80-82°C; νmax. (Nujol) 1723 (C=O) cm^{-1}; *m/z* 324, 292, 260, 230, 229, 198. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.5.1. Attempted recrystallisation of the material resulted in its decomposition to sulphur and tetramethyl ethylenetetracarboxylate which was isolated as colourless blocks, m.p. 120-122°C (lit.,[131] 121°C).

(ii) Diethyl Diazomalonate

Diethyl diazomalonate (2.05 g, 0.011 mol) and *p*-methoxyphenyloxathiazolone (152) (2.09 g, 0.01 mol) were reacted together following the above procedure. The residue obtained was subjected to flash chromatography eluting with ether-hexane (20:80); this yielded two major fractions. One was a mixture of unreacted oxathiazolone (1.126 g, 54%, estimated by ^{1}H n.m.r.) and anisonitrile (0.607 g, 46%, estimated by ^{1}H n.m.r.); obtained as a crystalline solid and identified by t.l.c. and ^{1}H n.m.r. comparisons with authentics. The other was a colourless oil which was purified by further flash chromatography (yield 1.119 g). This was thought to be tetraethyl 1,3-dithietane-2,2,4,4-tetracarboxylate (183b). It was recrystallised several times from cold pentane giving fine colourless needles, however, these consistently melted at less than room temperature in contrast with the

reported melting point, 51-55°C[109] or 59.5-60°C.[110] νmax. (film) 1750 (C=O) cm^{-1}; *m/z* 380, 348, 303, 271, 243, 226, 215, 197, 187, 169, 152, 125, 97, 53. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.5.1.

(iii) Methyl Diazoacetoacetate

Methyl diazoacetoacetate (1.56 g, 0.011 mol) and *p*-methoxyphenyloxathiazolone (152) (2.09 g, 0.01 mol) were reacted together following the above procedure. The residue obtained was subjedted to extensive flash chromatography leading to the isolation of the following six compounds.

Unreacted oxathiazolone (0.467 g, 22%) and anisonitrile (0.853 g, 64% or 82% on conversion of oxathiazolone) were each obtained as white crystalline solids, identified by t.l.c. comparisons with authentics.

Methyl 2-(p-methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate (185) was obtained as a bright yellow crystalline solid (yield 0.179 g, 6% or 8% on conversion). Recrystallisation from cold ether gave yellow, lozenge-shaped plates one of which was used in the X-ray diffraction analysis summarised in Appendix 4.6; m.p. 104-105°C; νmax. (Nujol) 1717, 1653 (C=O) cm^{-1}; λmax. (CH_2Cl_2) 273 (ε22719 $dm^3mol^{-1}cm^{-1}$) and 372nm (1136); *m/z* 279, 176, 134, 104, 90. For ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.5.3.

Three further products were each obtained as brown oils. These were not purified but were tentatively

identified by their mass spectra: *dimethyl 2,4-diacetyl-1,3-dithietane-2,4-carboxylate* (186) (yield 0.360 g, 25% or 32% on conversion), νmax. (film) 1715 (br) (C=O) cm^{-1}; *m/z* 292, 260, 250, 229, 228, 219, 217, 213, 181, 171, 159, 99, 59, 43, for ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.5.1; *dimethyl 2,3-diacetylthiirane-2,3-dicarboxylate* (187) (yield 0.133 g, 5%), νmax. (film) 1755, 1720, (C=O) cm^{-1}; *m/z* 260, 259, 228, 217, 216, 202, 200, 159, 99, 85, 71, 59, 43, for ^{1}H n.m.r. and ^{13}C n.m.r. spectra see Appendix 4.5.2; and an unknown oligomer of methyl 2-thioacetoacetate (yield 0.388 g, 27% as monomer), *m/z* 510, 480, 460, 326, 324, 294, 282, 250, 217, 191, 148, 116, 91, 59, 43.

3.7 REACTION OF TRIPHENYLPHOSPHINE WITH 5-(*p*-METHOXYPHENYL)-1,3,4-OXATHIAZOLE-2-ONE (152)

The oxathiazolone (0.418 g, 0.002 mol) and triphenylphosphine (0.524 g, 0.002 mol) were dissolved together in methylene chloride (50 ml) at room temperature with stirring. Rapid effervescence was observed, subsiding in a few minutes, after which no further reaction took place on prolonged stirring, as judged by t.l.c.

Flash chromatography on silica eluting with ethyl acetate-hexane (10:90-50:50) yielded unreacted oxathiazolone (0.030 g, 7%), anisonitrile [identified by its i.r. spectrum, νmax. (Nujol) 2220 (C≡N) cm^{-1}] as a mixture with triphenylphosphine sulphide (0.388 g) and pure triphenylphosphine sulphide (0.162 g, 28%). This was recrystallised from ethanol giving colourless needles (yield 0.125 g, 21%), m.p. 160-161°C (lit.,[132] 161°C); authentic sample m.p. 159.5-160.5°C; mixed m.p. 159.5-160°C.

4. APPENDICES

The following appendices, referred to in Section 3, contain n.m.r. data for most of the compounds prepared in this work (Appendices 4.1 to 4.5) and details of the X-ray crystal structure determination of methyl 2-(*p*-methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate (185) (Appendix 4.6).

Notes for Tables of N.m.r. Data

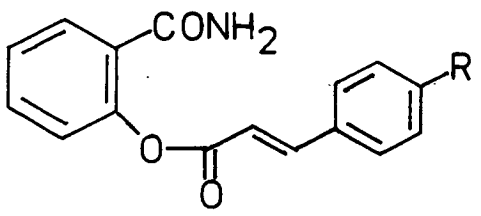
a	Solvent and standard	:	$CDCl_3$
b		:	$(CD_3)SO$
c		:	$(CD_3)CO$
d	Instrument frequency/MHz	:	20
e		:	50
f		:	80
g		:	200
h		:	360
i	Temperature : room temperature		
j	: 357K		
k	Selected data from a spectrum of the reaction mixture		

4.1 N.M.R. DATA OF ESTERS

4.1.1 Esters of Salicylamide

4.1.1.1 Cinnamate Esters of Salicylamide

^{1}H N.m.r. Spectra



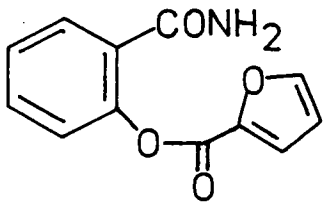
	R
(195)	H
(196)	Cl
(197)	MeO
(198)	Me

Compound Notes	δ_H p.p.m.			
	Aromatic	Olefinic	NH_2	Other
(195) a,g,i	7.90-7.15(9H)	7.89(1H,d,J16Hz) 6.64(1H,d,J16Hz)	6.43(1H,br) 6.25(1H,br)	
(196) a,g,i	7.89-7.15(8H)	7.84(1H,d,J16Hz) 6.61(1H,d,J16Hz)	6.33(1H,br) 5.99(1H,br)	
(197) a,g,i	7.88(1H,dd,J8,2Hz,6-H) 7.51(2H,d,J9Hz) 7.48(1H,td,J8,1Hz) 7.28(1H,td,J8,1Hz) 7.16(1H,dd,J8,1Hz,3-H) 6.90(2H,d,J9Hz)	7,83(1H,d,J16Hz) 6.49(1H,d,J16Hz)	6.50(2H,br)	3.83(3H,s,CH_3)
(198) a,f,i	7.88(1H,dd,J7,2Hz,6-H) 7.51-7.10(7H)	7.87(1H,d,J16Hz) 6.58(1H,d,J16Hz)	6.43(2H,br)	2.38(3H,s,CH_3)

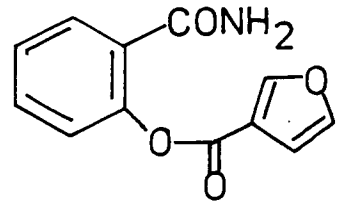
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.							
	$CONH_2$	CO_2	ArC	ArCH	2ArCH	C-β	C-α	Others
(196) b,d,i	167.08	164.58	148.04,135.50, 131,38,125.89	132.90,129.44, 129.28,123.33	130.32 129.13	144.96	118.21	
(198) a,e,i.	167.30	164.98	148.20,141.53, 131.05,127.42	132.05,130.33, 126.03,123.09	129.64 128.37	147.81	115.05	21.35 (CH_3)

4.1.1.2 Furoate Esters of Salicylamide



(199)



(200)

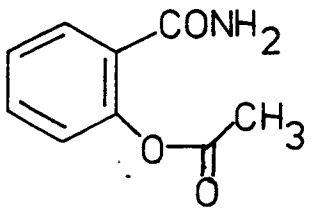
^{1}H N.m.r. Spectra

Compound Notes	δ_H p.p.m.	
	Aromatic and Furyl	NH_2
(199) a,f,i	7.85(1H,complex doublet,6-H),7.59(1H,dd,J2,1Hz,5'-H) 7.56-7.13(4H,m),6.51(1H,dd,J4,2Hz,4'-H)	6.67(2H,br)
(200) b,f,i	8.61-6.85(7H,m)	3.65(2H,br)

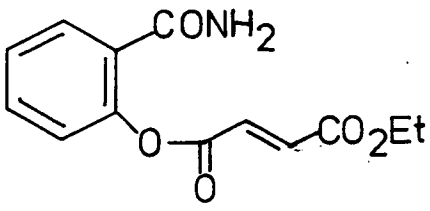
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.					
	$CONH_2$	CO_2	ArC	ArCH	Furyl-C	Furyl-CH
(199) a,e,i.	167.04	155.77	147.40 126.93	131.88,130.26, 126.04,122.72	143.13	147.30,120.07, 112.18
(200) b,e,i.	166.78	160.59	147.46 129.51	131.25,129.23, 125.94,123.28	118.25	149.62,145.00, 109.83

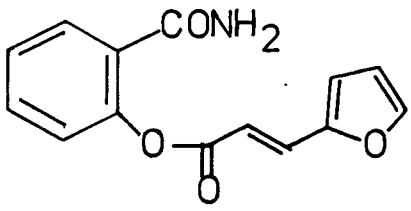
4.1.1.3 Miscellaneous Esters of Salicylamide



(193)



(194)



(201)

^{1}H N.m.r. Spectra

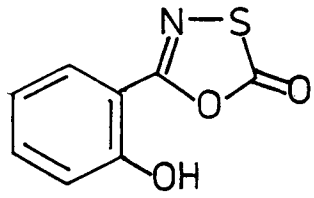
Compound Notes	δ_H p.p.m.			
	Aromatic & Furyl	Olefinic	NH_2	Other
(193) c,g,i.	7.78(1H,dd,J8,2Hz,6-H), 7.52(1H,td,J8,2Hz), 7.32(1H,td,J8,1Hz), 7.17(1H,dd,J8,1Hz,3-H)		2.88(2H,br)	2.28(3H,s,CH_3)
(194) a,g,i	7.83-7.13(4H, multiplicities as above)	7.05(2H,s)	6.10(2H,br)	4.28(2H,q,J7Hz,CH_2) 1.33(3H,t,J7Hz,CH_3)
(201) a,f,i	7.87(1H,dd,J7,2Hz,6-H) 7.59-7.08(4H,m) 6.69(1H,d,J3Hz,3'-H) 6.48(1H,dd,J3,2Hz,4'-H)	7.61(1H,d,J16Hz,β-H) 6.48(1H,d,J16Hz,α-H)	6.42(2H,br)	

^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.						
	$CONH_2$	CO_2	ArC	ArCH & C-β,C-α	Furyl-C	Furyl-CH	Other
(194) b,d,i	166.92	164.38, 163.00	147.73, 126.36	134.83,132.60,131.61, 129.43,128.92,123.17			61.39(CH_2), 14.03(CH_3)
(201) a,e,i	167.20	164.84	148.21, 127.26	133.61,132.08,130.40, 126.05,123.09,116.30	150.48	145.47,113.66, 112.51	

4.1.2 *o*-Hydroxyphenyloxathiazolone and its Esters

4.1.2.1 *o*-Hydroxyphenyloxathiazolone



(62)

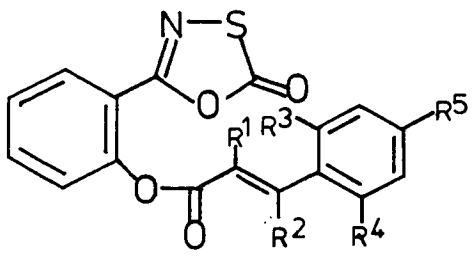
^{1}H N.m.r. Spectrum

Compound Notes	δ_H p.p.m.	
	OH	Aromatic
(62) a,f,i	9.70(1H,s)	7.66(1H,ddd,J8,2,1Hz,6-H) 7.55-6.83(3H,m)

^{13}C N.m.r. Spectrum

Compound Notes	δ_C p.p.m.			
	C-2	C-5 and C-2'	ArCH	C-1'
(62) a,e,i	170.82	159.10,158.52	134.68,128.11, 119.90,117.85	109.62

4.1.2.2 Cinnamate Esters of *o*-Hydroxyphenyloxathiazolone



(113a) R^{1-5}=H; (113b) R^{1-4}=H, R^5=Cl; (113c) R^{1-4}=H, R^5=MeO; (113d) R^{1-4}=H, R^5=Me; (130) R^1=Me, R^{2-5}=H; (133) $R^{1,3-5}$=H, R^2=Me; (141) $R^{1,2}$=H, R^{3-5}=Me; (142) $R^{1,2,5}$=H, $R^{3,4}$=Cl.

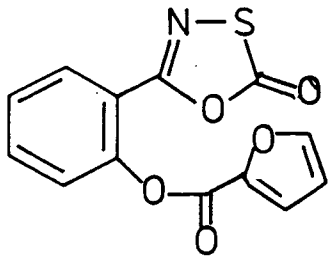
^{1}H N.m.r. Spectra

Compound Notes	δH p.p.m.		
	Aromatic	Olefinic	Others
(113a) a,f,i	7.88(1H,dd,*J*8,2Hz,6-H) 7.55-7.15(8H,m)	7.81(1H,d,*J*16Hz,β-H) 6.58(1H,d,*J*16Hz,α-H)	
(113b) a,g,i	7.98(1H,dd,*J*8,2Hz,6-H) 7.65-7.24(7H,m)	7.83(1H,d,*J*16Hz,β-H) 6.62(1H,d,*J*16Hz,α-H)	
(113c) a,f,i	7.96(1H,dd,*J*8,2Hz,6-H) 7.70-7.20(3H,m,ArCH) 7.55(2H,d,*J*9Hz,2xArCH) 6.92(2H,d,*J*9Hz,2xArCH)	7.85(1H,d,*J*16Hz,β-H) 6.51(1H,d,*J*16Hz,α-H)	3.84(3H,s,CH_3)
(113d) a,f,i	7.93(1H,dm,*J*8Hz,6-H) 7.59-7.24(7H,m)	7.89(1H,d,*J*16Hz,β-H) 6.63(1H,d,*J*16Hz,α-H)	2.37(3H,s,CH_3)
(130) a,g,i	7.49(1H,dm,*J*8Hz,6-H) 7.15-6.78(8H,m)	7.47(1H,d,β-H)	1.79(3H,s,CH_3)
(133) a,g,i	7.98(1H,dd,*J*8,1.5Hz,6-H) 7.64-7.24(8H,m)	6.44(1H,q,*J*1.3Hz,α-H)	2.63(3H,d, *J*1.3Hz, CH_3)
(141) a,f,i	8.06-7.25(4H,m,ArCH) 6.94(2H,s,br,H-3",5")	8.09(1H,d,*J*16Hz,β-H) 6.33(1H,d,*J*16Hz,α-H)	2.42(6H,s,2xCH_3) 2.33(3H,s,CH_3)
(142) b,g,i	7.98(1H,dd,*J*8,2Hz,6-H) 7.80-7.41(6H,m)	7.88(1H,d,*J*16Hz,β-H) 6.80(1H,d,*J*16Hz,α-H)	

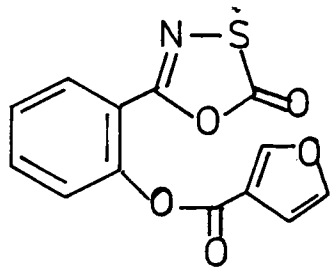
^{13}C N.m.r. Spectra

Compound Notes	δC p.p.m.						
	C-2 C-5	CO_2 C-2'	ArC	ArCH	2ArCH	C-β C-α	Others
(113a) a,d,i	172.77 154.54	164.88 149.04	133.88, 118.99	133.34,130.65, 129.98,126.21, 124.26	128.79, 128.23	147.16 116.49	
(113b) b,e,i	173.20 154.37	164.67 148.63	135.69,132.81, 119.09	134.04,130.17, 126.90,124.57	130.45, 129.17	145.60 117.63	
(113c) a,e,i	172.84 154.77	165.17 149.31	161.84,126.79, 119.20	133.30,130.02, 126.08,124.35	130.02, 114.38	146.92 113.97	55.24
(113d) a,e,i	172.57 154.50	164.82 149.04	141.01,131.12, 118.93	133.13,129.81, 125.94,124.17	129.40, 128.13	147.03 115.31	21.14
(130) a,e,i	172.73 154.68	166.84 149.51	135.39, 119.03	133.32,129.98, 128.58,126.09, 124.34	129.67, 128.28	141.31 127.15	13.99
(133) a,e,i	172.82 154.81	164.58 149.16	141.61, 119.27	133.33,129.99, 129.37,126.09, 124.44	128.48, 126.33	159.08 115.42	18.12
(141) a,e,i	172.62 154.67	164.89 149.19	138.66, 136.86(2xArC), 130.48,119.05	133.32,129.97, 126.17,124.34	129.13	145.85 121.55	20.87 (3xCH_3)
(142) b,e,i	172.35 153.89	163.42 148.15	133.77(2xArC), 130.83,118,54	133.53,131.01, 129.78,126.55, 124.09	128.83	139.56 124.09	

4.1.2.3 Furoate Esters of *o*-Hydroxyphenyloxathiazolone



(119)



(120)

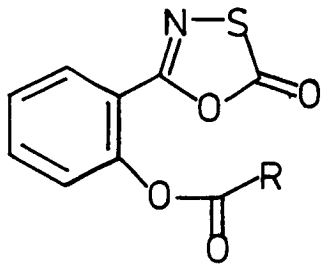
^{1}H N.m.r. Spectra

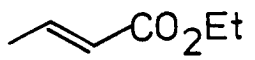
Compound Notes	δ_H p.p.m. Aromatic and Furyl
(119) a,f,i	7.96(1H,dm,*J*7Hz,6'-H), 7.70-7.26(4H,m), 7.66(1H,dd,*J*2,1Hz, 5"-H), 6.57(1H,dd,*J*4,2Hz,4"-H)
(120) a,f,i	8.20(1H,dd,*J*2,1Hz,2"-H), 7.95(1H,dm,*J*8Hz,6'-H), 7.68-7.21(3H,m), 7.32(1H,m,5"-H); 6.84(1H,dd,*J*2,1Hz, 4"-H)

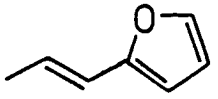
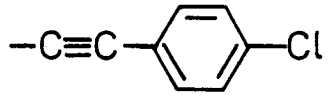
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m. C-2 C-5	CO_2 C-2'	ArC Furyl-C	ArCH	Furyl-CH
(119) a,e,i	172.59 154.46	156.25 148.39	119.14 143.61	133.38,130.08, 126.51,124.30	147.27,119.90, 112.08
(120) a,e,i	172.52 154.43	160.65 148.52	118.94 118.23	133.19,129.89, 126.18,124.21	148.83,143.85, 109.74

4.1.2.4 Miscellaneous Esters of *o*-Hydroxyphenyloxathiazolone



(63) R=CH_3; (71) R=$CH{=}CH_2$; (109) R= 

(150) R=  ; (96b) R= 

^{1}H N.m.r. Spectra

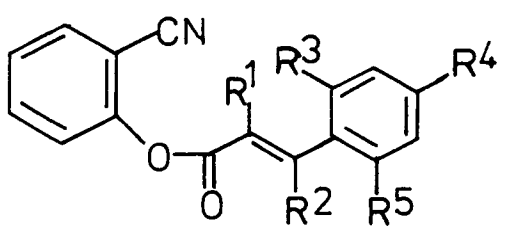
Compound Notes	δ_H p.p.m.		
	Aromatic and Furyl	Olefinic	Other
(63) a,g,i	7.98(1H,dd,J7,2Hz,6'-H) 7.70-7.11(3H,m)		2.34(3H,s,CH_3)
(71) a,f,i	7.95(1H,dd,J8,2Hz,6'-H) 7.69-7.14(3H,m)	6.77-5.95(3H,m)	
(109) a,f,i	7.94(1H,dd,J7,2Hz,6'-H) 7.67-7.11(3H,m)	7.05(2H,s)	4.28(2H,q,J7Hz,CH_2) 1.33(3H,t,J,7Hz,CH_3)
(150) a,f,i	7.97(1H,dd,J8,2Hz,6'-H) 7.71-7.19(3H,m) 7.53(1H,m,5"-H) 6.71(1H,d,J3.5Hz,3"-H) 6.50(1H,dd,J3.5,2Hz,4"-H)	7.63(1H,d,J16Hz,β-H) 6.52(1H,d,J16Hz,α-H)	
(96b) b,f,i	8.07-7.44(8H,m)		

^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.					
	C-2 C-5	CO_2	C-2', ArC and Furyl-C	ArCH	C-β C-α	Others
(63) a,d,i	172.60 154.43	169.13	148.87,118.74	133.39,129.91, 126.26,124.18		20.68(CH_3)
(71) a,e,i	172.65 154.44	164.03	148.79,118.90	133.38,129.94, 126.30,124.14	132.97 127.23	
(109) a,e,i	172.21 153.96	164.16, 162.93	148.19,118.45	133.34,129.91, 126.56,123.83	135.50 131.69	61.21(CH_2), 13.73(CH_3)
(150) a,d,i	172.94 154.63	165.06	150.57,149.16, 119.08	133.39,130.06, 126.26,124.35	133.16 115.95	145.26,114.04, 112.43(Furyl-CH)
(96b) b,e,i	172.85 153.86	161.15	148.44,135.40, 131.93,118.62	133.90,130.05, 127.14,124.35	141.79 111.74	131.93,128.68 (2xArCH)

4.1.3 Esters of *o*-Cyanophenol

4.1.3.1 Cinnamate Esters of *o*-Cyanophenol



(114a) R^{1-5}=H;
(114b) R^{1-4}=H, R^{5}=Cl;
(114c) R^{1-4}=H, R^{5}=MeO;
(114d) R^{1-4}=H, R^{5}=Me;
(131) R^{1}=Me, R^{2-5}=H;
(135) $R^{1,3-5}$=H, R^{2}=Me;
(143) $R^{1,2}$=H, R^{3-5}=Me; (147) $R^{1,2,5}$=H, $R^{3,4}$=Cl.

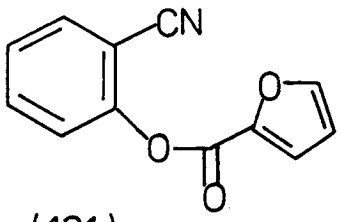
^{1}H N.m.r. Spectra

Compound Notes	δ_H p.p.m.		
	Aromatic	Olefinic	Other
(114a) a,g,i	7.71-7.29(9H,m)	7.95(1H,d,J16Hz,β-H) 6.66(1H,d,J16Hz,α-H)	
(114b) a,f,i	7.76-7.22(8H,m)	7.90(1H,d,J16Hz,β-H) 6.62(1H,d,J16Hz,α-H)	
(114c) a,f,i	7.72-7.18(4H,m) 7.53(2H,d,J9Hz) 6.91(2H,d,J9Hz)	7.89(1H,d,J16Hz,β-H) 6.49(1H,d,J16Hz,α-H)	3.82(3H,s,CH_3)
(114d) a,f,i	7.69-7.14(8H,m)	7.91(1H,d,J16Hz,β-H) 6.58(1H,d,J16Hz,α-H)	2.36(3H,s,CH_3)
(131) a,f,i	7.75-7.22(9H,m)	8.03(1H,d,J1.3Hz,β-H)	2.28(3H,d,J1.3Hz, CH_3)
(135) a,f,i	7.74-7.21(9H,m)	6.43(1H,d,J1.2Hz,α-H)	2.66(3H,d,J1.2Hz, CH_3)
(143) a,f,i	7.75-7.25(4H,m) 6.94(2H,sbr,3',5'-H)	8.19(1H,d,J16Hz,β-H) 6.33(1H,d,J16Hz,α-H)	2.42(6H,s,2xCH_3) 2.32(3H,s,CH_3)
(147) a,f,i	7.74-6.87(7H,m)	8.08(1H,d,J16Hz,β-H) 6.86(1H,d,J16Hz,α-H)	

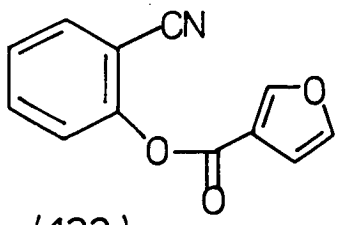
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.					
	CO_2 C≡N	ArC	ArCH	2xArCH	C-β C-α	Other
(114a) a,d,i	163.75 106.72	152.18,133.48, 114.98	133.73,132.95, 130.84,125.86, 122.96	128.74, 128.24	147.93 115.56	
(114b) a,d,i	163.61 106.78	152.18,136.45, 132.09,114.98	133.81,133.06, 125.98,122.98	129.47, 129.09	146.47 116.26	
(114c) a,d,i	164.12 106.78	161.86,152.39, 126.36,115.08	133.71,132.96, 125.73,123.04	130.09, 114.25	147.70 112.88	55.14 (CH_3)
(114d) a,e,i	163.79 106.71	152.26,141.33, 130.82,114.91	133.59,132.84, 125.68,122.91	129.41, 128.20	147.86 114.41	21.11 (CH_3)
(131) a,e,i	165.82 107.01	152.88,135.19, 115.07	133.77,133.08, 128.36,125.86, 123.17	129.79, 128.36	142.14 126.58	13.99 (CH_3)
(135) a,e,i	163.43 107.15	152.46,141.35, 115.14	133.69,133.06, 129.55,125.77, 123.24	128.48, 126.29	160.56 114.54	18.28 (CH_3)
(143) a,e,i	163.75 106.82	152.38,138.95, 137.07 (2xArCH), 129.93,114.90	133.64,132.95, 125.78,123.02	129.21	146.58 120.28	20.89 (2xCH_3), 20.80(CH_3)
(147) a,e,i	163.25 106.55	151.99, 135.03(2xArCH), 130.72,114.77	133.90,133.05, 130.33,126.12, 122.91	128.74	141.21 124.09	

4.1.3.2 Furoate Esters of *o*-Cyanophenol



(121)



(122)

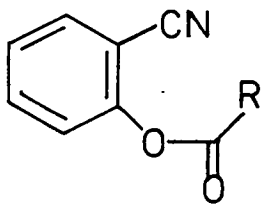
^{1}H N.m.r. Spectra

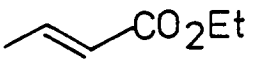
Compound Notes	δ_H p.p.m. Aromatic and Furyl
(121) a,f,i	7.76-7.23 (6H,m), 6.59 (1H,dd,J3.4, 1.7Hz, Furyl 4-H)
(122) a,f,i	7.72-7.20 (5H,m), 8.25 (1H,dd,J2,0.8Hz, Furyl 2-H) 6.86 (1H,dd,J2,0.8Hz, furyl 4-H)

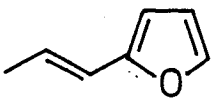
^{13}C N.m.r. Spectra

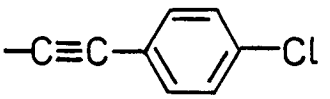
Compound Notes	δ_C p.p.m. CO_2	C≡N	ArC	ArCH	Furyl-C	Furyl-C-H
(121) a,d,i	155.14	106.71	151.50, 114.75	133.88,133.11, 126.22,122.91	142.52	147.84,120.69, 122.26
(122) a,e,i	159.67	106.79	151.89, 114.84	133.78,133.03, 126.02,122.98	117.61	149.23,144.18, 109.75

4.1.3.3 Miscellaneous Esters of *o*-Cyanophenol



(167b) R=CH_3; (106) R=CH=CH_2; (111) R= 

(202) R= 

(99b) R= 

^{1}H N.m.r. Spectra

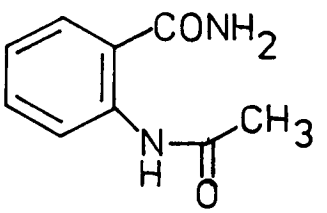
Compound Notes	δ_H p.p.m.		
	Aromatic and Furyl	Olefinic	Other
(167b) a,f,i	7.65-7.22(4H,m)		2.35(3H,s,CH_3)
(106) a,f,i	7.63-7.11(4H,m)	6.73-5.91(3H,m)	
(111) a,f,i	7.68-7.30(4H,m)	7.04(2H,s)	4.26(2H,q,J7Hz,CH_2) 1.30(3H,t,J7Hz,CH_3)
(202) a,f,i	7.74-7.20(4H,m) 6.73(1H,d,J3.5Hz,Furyl 3-H) 6.51(1H,dd,J3.5,2Hz, Furyl 4-H)	7.68(1H,d,J16Hz,β-H) 6.51(1H,d,J16Hz,α-H)	
(99b) b,f,i	8.12-7.44(8H,m)		

^{13}C N.m.r. Spectra

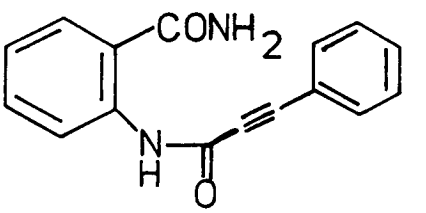
Compound Notes	δC p.p.m.					
	CO_2	CN	ArC and Furyl-C	ArCH	C-β C-α	Other
(167b) a,d,i	167.96	106.77	152.03,114.83	133.81,132.89, 126.03,122.94		20.41 (CH_3)
(106) a,d,i	162.97	106.71	151.93,114.81	133.85,133.04, 126.10,122.93	134.08 126.49	
(111) a,d,i	163.95 161.94	106.52	151.39,114.48	133.91,133.06, 126.43,122.64	136.35 130.93	61.39 (CH_2), 13.73 (CH_3)
(202) a,d,i	163.97	106.88	152.39,150.35, 115.05	133.79,133.09, 125.88,123.09	133.79 116.46	145.54,113.14, 112.50(Furyl-CH)
(99b) b,e,i	160.58	106.01	151.92,135.75, 131.75,114.84	135.09,133.59, 127.36,123.36	142.55 110.72	132.14,128.77 (2xArCH)

4.2 N.M.R. DATA OF SECONDARY AMIDES

4.2.1 *o*-Amidobenzamides



(204)



(203)

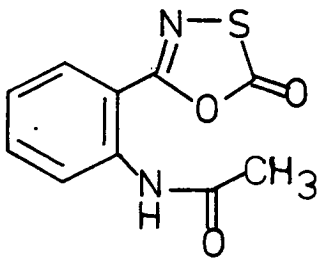
^{1}H N.m.r. Spectra

Compound / Notes	δ_H p.p.m.			
	Aromatic	NHCO	$CONH_2$	Other
(204) b,f,i	8.43(1H,dd) 7.77(1H,dd) 7.46(1H,td) 7.07(1H,td) All *J*8,1Hz	11.58(1H,b)	8.19(1H,b) 7.63(1H,b)	2.08(3H,s,CH_3)
(203) b,f,i	8.44(1H,d,*J*8Hz) 7.94-7.05 (4H,m, including one NH)	12.39(1H,b)	8.39(1H,b)	

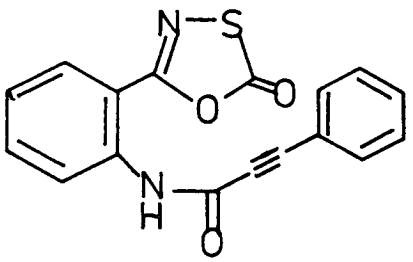
^{13}C N.m.r. Spectrum

Compound / Notes	δ_C p.p.m.				
	C=O	ArC	ArCH	2xArCH	C≡C
(203) b,e,i	170.58, 150.05	138.75,120.00, 119.21	132.32,130.62,128.69, 123.43,120.86	132.32, 128.95	84.56, 84.02

4.2.2 *o*-Amidophenyloxathiazolones



(64)



(90)

^{1}H N.m.r. Spectra

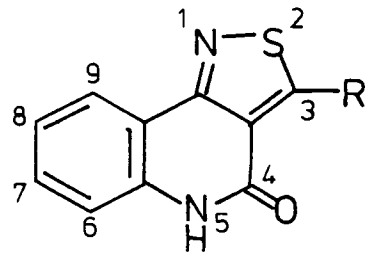
Compound	δ H p.p.m.		
Notes	NH	Aromatic	Other
(64) a,f,i	10.41(1H,b)	8.64(1H,dd,J8,1Hz) 7.77(1H,dd,J8,2Hz) 7.47(1H,td,J8,2Hz) 7.07(1H,td,J8,1Hz)	2.17(3H,s,CH_3)
(90) a,f,i	10.88(1H,b)	8.71(1H,dd,J8,1Hz) 7.89(1H,dd,J8,2Hz) 7.70-7.08(7H,m)	

^{13}C N.m.r. Spectra

Compound	δ C p.p.m.						
Notes	C-2 C-5	CONH	ArC	ArCH	2ArCH	C≡C	Other
(64) a,e,i	170.83 157.79	168.51	138.95, 111.25	133.68,129.11, 122.82,120.65			25.06 (CH_3)
(90) a,e,i	170.85 157.71	151.06	138.41, 119.84, 111.73	133.91,130.32, 129.39,123.74, 121.49	132.61, 128.48	86.23, 83.58	

4.3 N.M.R. DATA OF FUSED HETEROCYCLIC PRODUCTS

4.3.1 Isothiazolo[4,3-*c*]quinolines



(171) R=H

(91) R=Ph

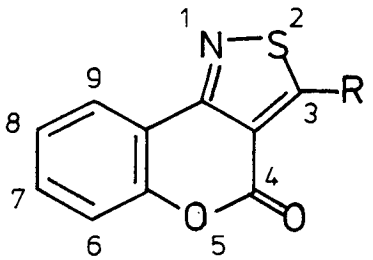
^{1}H N.m.r. Spectra

Compound Notes	δ_H p.p.m.		
	NH	Atomatic	Other
(171) b,f,i	11.47(1H,b)	8.23(1H,ddd,*J*8,1.6,0.6Hz,9-H) 7.66-7.14(3H,m)	9.98(1H,s,3-H)
(91) b,f,i	11.42(1H,b)	8.29(1H,dd,*J*7,1Hz,9-H) 7.89-7.25(8H,m)	

^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.					
	C(9b)=N C(4)=O	C-3 C-5a	C-3a C-9a	ArCH	2xArCH	C-1'
(171) b,e,i	161.55 157.69	155.22 138.14	127.93 116.13	131.05,123.77, 122.54,166.25		
(91) b,e,j	162.95 157.58	173.92 137.91	121.57 116.18	130.78,129.74, 123.51,122.07, 115.62	129.25, 127.98	128.76

4.3.2 Chromeno[4,3-*c*]isothiazoles



(103) R=H; (110) R=CO_2Et;
(164) R=CO_2Me;
(97a) R=Ph; (97b) R=4-ClC_6H_4;
(97c) R=4-$MeOC_6H_4$;
(97d) R=4-MeC_6H_4;
(144) R=mesityl;
(148) R=2,6-$Cl_2C_6H_3$; (205) R=2-furyl.

^{1}H N.m.r. Spectra

Compound Notes	δH p.p.m.	
	Aromatic	Other
(103) a,f,i	8.26(1H,dd,*J*8,2Hz,9-H) 7.65-7.23(3H,m)	9.72(1H,s,3-H)
(110) a,f,i	8.08(1H,dm,*J*8Hz,9-H) 7.56-7.11(3H,m)	4.47(2H,q,*J*7Hz,CH_2) 1.41(3H,t,*J*7Hz,CH_3)
(164) a,g,i	8.18(1H,dd,*J*8,2Hz,9-H) 7.52(1H,td,*J*8,2Hz) 7.34-7.26(2H,m)	4.04(3H,s,CH_3)
(97a) a,g,i	8.27(1H,dd,*J*8,2Hz,9-H) 7.78(2H,m),7.53(4H,m) 7.34(2H,m)	
(97b) a,f,i	8.30(1H,dd,*J*8,2Hz,9-H),7.82-7.27(3H,m) 7.74(2H,d,*J*9Hz),7.49(2H,d,*J*9Hz)	
(97c) a,f,i	8.25(1H,dd,*J*8,2Hz,9-H),7.46-7.25(3H,m) 7.78(2H,d,*J*9Hz),7.00(2H,d,*J*9Hz)	3.87(3H,s,CH_3)
(97d) a,f,i	8.25(1H,dd,*J*8,2Hz,9-H) 7.74-7.20(7H,m)	2.43(3H,s,CH_3)

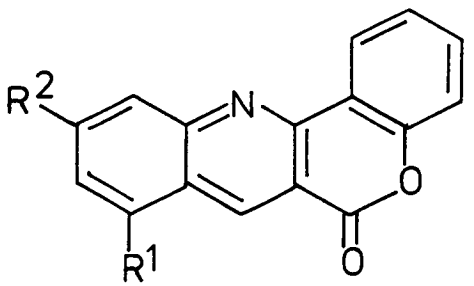
^{1}H N.m.r. Spectra (cont.)

Compound Notes	δ_H p.p.m.	
	Aromatic	Other
(144) a,f,i	8.33(1H,dd,J8,2Hz,9-H),7.58-7.28(3H,m) 7.03(2H,s)	2.38(3H,s,CH_3) 2.12(6H,s,2xCH_3)
(148) a,f,i	8.33(1H,dd,J8,2Hz,9-H) 7.66-7.25(6H,m)	
(205) a,g,i	8.26(1H,dm,J8Hz,9-H) 7.54(1H,td,J8,2Hz,8-H) 7.36(1H,dd,J8,1Hz,6-H) 7.34(1H,td,J8,1Hz,7-H)	8.16(1H,dd,J3.7,0.7Hz,5'-H) 7.62(1H,dd,J1.8,0.7Hz,3'-H) 6.68(1H,dd,J3.7,1.8Hz,4'-H)

^{13}C N.m.r. Spectra

Compound Notes	δC p.p.m.				
	C(9b)=N C(4)=O	C-3 C-5a	C-3a C-9a	ArCH	Substituent
(103) a,e,i	161.24 156.21	156.77 152.53	123.13 116.71	131.92,124.79, 124.17,117.21	
(110) a,d,i	161.87 153.80	164.28 152.17	120.46 116.10	132.13,124.64, 123.91,116.82	158.39(CO_2), 63.13(CH_2),13.72(CH_3)
(164) a,e,i	162.22 153.96	163.99 152.47	120.97 116.38	132.34,124.82, 124.18,117.06	159.01(CO_2),53.63(CH_3)
(97a) a,d,i	162.43 156.24	177.91 152.32	117.13 116.88	131.78,124.58, 124.04,116.88	129.22,128.60(2xArCH), 130.81(ArCH),128.05(ArC)
(97b) a,e,i	162.81 156.37	176.59 152.62	117.33 117.24	132.04,124.81, 124.30,117.10	130.64,129.07(2xArCH), 137.44,126.69(ArC)
(97c) a,e,i	162.62 156.57	178.10 152.51	117.43 116.13	131.71,124.55, 124.16,116.92	130.99,114.23(2xArCH), 161.98,120.66(ArC)
(97d) a,e,i	162.48 156.32	178.23 152.42	117.31 116.54	131.72,124.54, 124.10,116.90	129.36,129.17(2xArCH), 141.42,125.32(ArC)
(144) a,e,i	161.90 155.50	176.86 152.65	119.59 117.35	131.74,124.52, 123.94,117.03	128.43(2xArCH),139.45, 124.37(ArC),135.84(2xArC), 20.96(CH_3),20.18(2xCH_3)
(148) a,e,i	161.66 155.34	170.11 152.80	120.84 117.27	132.03,124.80, 124.13,117.27	128.17(2xArCH),131.55(ArCH), 134.63(2xArC),127.20(ArC)
(205) a,e,i	162.27 156.80	164.45 152.53	113.96 117.15	131.89,124.73, 124.34,117.59	145.56(C-5'),145.13(C-2'), 117.02(C-3'),113.51(C-4')

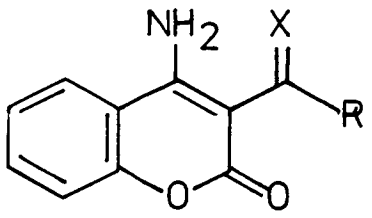
4.3.3 Chromeno[4,3-*b*]quinolines



(115a) $R^1=R^2=H$; (115b) $R^1=H$, $R^2=Cl$; (115c) $R^1=H$, $R^2=MeO$; (115d) $R^1=H$, $R^2=Me$; (149) $R^1=Cl$, $R^2=H$

^1H N.m.r. and ^{13}C n.m.r. spectra for this group of compounds are displayed in Tables 6 and 7 respectively, Section 2.3.3.3, pp.88,89.

4.3.4 Aminochromenes



(116b) X=2H, R=4-ClC_6H_4; (116c) X=2H, R=4-$MeOC_6H_4$;

(116d) X=2H, R=4-MeC_6H_4; (145) X=2H, R=mesityl;

(206) X=2H, R=2-furyl; (136) X=CH_2, R=Ph.

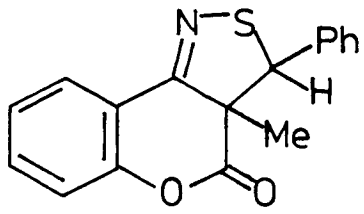
^{1}H N.m.r. Spectra

Compound Notes	δ_H p.p.m.			
	Aromatic	NH_2	Benzyl CH_2	Other
(116b) b,f,i	8.08(1H,dm,*J*8Hz,5-H) 7.59-7.20(7H,m)	7.12(2H,br)	3.81(2H,s)	
(116c) b,f,i	8.06(1H,dd,*J*10,2Hz,5-H) 7.57-7.13(3H,m) 7.22(2H,d,*J*9Hz) 6.79(2H,d,*J*9Hz)	7.02(2H,br)	3.76(2H,s)	3.68(3H,s,CH_3)
(116d) b,g,i	8.06(1H,dd,*J*8,2Hz,5-H) 7.55(1H,td,*J*8,2Hz) 7.34-7.26(2H,m) 7.18(2H,d,*J*8Hz) 7.03(2H,d,*J*8Hz)	7.05(2H,s)	3.78(2H,s)	2.22(3H,s,CH_3)
(145) a,f,i	7.46-7.18(4H,m) 6.86(2H,s)	4.70(2H,br)	4.03(2H,s)	2.31(6H,s,2xCH_3) 2.25(3H,s,CH_3)
(206) b,g,i	8.06(1H,dm,*J*8Hz,5-H) 7.61-7.27(3H,m)	7.15(2H,s)	3.83(2H,s)	7.48(1H,s,5'-H) 6.29(1H,m) 6.01(1H,m)
(136) a,h,i	7.67-7.17(9H) Details Table 9 Section 2.3.3.4	5.15(2H,br)		6.00(1H,d,*J*1.16Hz) 5.39(1H,d,*J*1.16Hz)

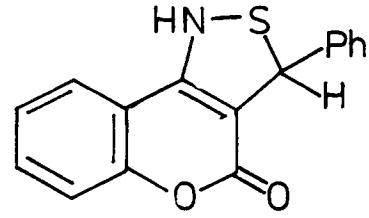
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.				
	C-2 C-4	C-8a C-4a	C-3 C(3)*C*XR	ArCH	Substituent
(116b) a,e,i	162.08 152.25	150.89 114.72	94.84 28.87	131.34,123.22, 123.03,116.44	139.21,130.24 (ArC), 129.82,127.87(2xArCH)
(116c) b,e,i	162.16 152.22	150.51 114.84	95.88 28.58	131.18,123.16, 122.95,116.39	152.22,132.03(ArC), 128.96,113.54(2xArCH), 54.96(CH_3)
(116d) b,e,i	162.17 152.30	150.68 114.85	95.59 29.08	131.26,123.22, 123.02,116.46	137.06,134.52(ArC), 128.58,127.95(2xArCH), 20.53(CH_3)
(145) a,e,i	163.01 152.46	149.46 114.79	97.18 26.62	130.93,123.29, 120.20,117.21	136.25,131.99(ArC), 137.11(2xArC),129.59(2xArCH), 20.63(CH_3),20.34(2xCH_3)
(206) b,e,i	161.72 152.27	151.12 114.76	92.10 23.22	131.43,123.23, 123.03,116.48	153.23(C-2'),141.04(C-5'), 110.22(C-3'),105.12(C-4')
(136) a,e,i	161.19 152.43	150.65 113.47	98.82 139.99	131.17,123.03, 121.88,116.52	118.24(X,CH_2), 137.63(ArC),127.53(ArCH), 127.84,125.15(2xArCH)

4.3.5 Chromeno[4,3-*c*]isothiazolines



(132)



(127a)

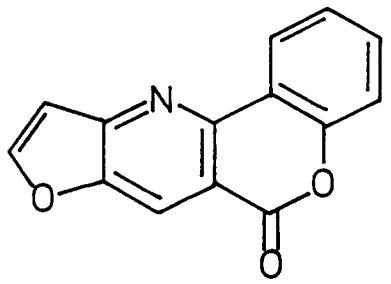
^{1}H N.m.r. Spectra

Compound Notes	δH p.p.m.		
	Aromatic	H-3	Other
(132) b,g,i	7.84(1H,dd,J8,2Hz, 9-H) 7.71-7.24(8H,m)	5.93(1H,s,H-3)	1.15(3H,s,CH_3)
(127a) b,f,i	8.07(1H,dm,J8Hz,9-H) 7.68-7.19(9H,m,ArH+NH)	5.89(1H,s,H-3)	

^{13}C N.m.r. Spectra

Compound Notes	δ C p.p.m.				
	C-4 C-9b	C-5a C-9a	C-3a C-3	ArCH	Substituents
(132) b,e,i	168.35 161.25	151.85 117.25	61.07 59.66	132.26,125.46, 125.06,116.87	132.98(ArC),128.46(ArCH), 130.40,128.27(2xArCH), 17.61(CH_3)
(127a) b,e,i	161.00 152.29	151.06 114.56	95.12 53.25	131.82,123.37, 123.26,116.47	138.91(ArC),126.92(ArCH), 128.06,127.85(2xArCH)

4.3.6 6-Oxo-6*H*-chromeno[4,3-*b*]furo[2,3-*e*]pyridine



(151)

^{1}H N.m.r. Spectrum

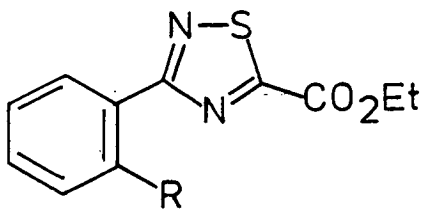
Compound	δ_H p.p.m.		
Notes	H-7	Benzo	Furo
(151) a,g,i	8.67(1H,d,*J*1Hz)	8.66(1H,dd,*J*8,2Hz,H-1) 7.60-7.35(3H,m,H-2,3,4)	8.14(1H,d,*J*2Hz,H-9) 7.15(1H,dd,*J*2,1Hz,H-10)

^{13}C N.m.r. Spectrum

Compound	δ_C p.p.m.					
Notes	C-4a C-6	C-10a C-11a	C-7a C-11b	C-1,2,3,4	C-9 C-10	C-7 C-6a
(151) a,e,i	161.56 153.46	151.77 148.66	147.03 119.55	131.40,124.62, 124.58,116.96	154.43 108.48	119.32 113.85

4.4 N.M.R. DATA OF MONOCYCLIC CYCLOADDUCTS

4.4.1 1,2,4-Thiadiazoles



(161) R=OH; (162) R=$OCOCH_3$; (163) R=$NHCOCH_3$

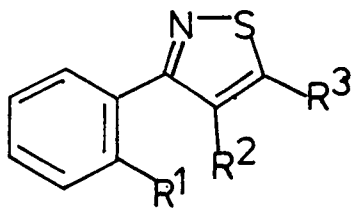
^{1}H N.m.r. Spectra

Compound Notes	δ H p.p.m.		
	Aromatic	Ethyl	R
(161) a,g,i	8.29(1H,dd,J8,2Hz) 7.36(1H,td,J8,2Hz) 7.05-6.90(2H,m)	4.51(2H,q,J7Hz) 1.45(3H,t,J7Hz)	10.54(1H,s,OH)
(162) a,f,i	8.39(1H,dd,J7,2Hz) 7.61-7.09(3H,m)	4.48(2H,q,J7Hz) 1.41(3H,t,J7Hz)	2.40(3H,s,$COCH_3$)
(163) a,f,i	8.53(1H,dd,J8,1Hz) 8.30(1H,dd,J8,2Hz) 7.33(1H,td,J8,2Hz) 7.00(1H,td,J8,1Hz)	4.43(2H,q,J7Hz) 1.38(3H,t,J7Hz)	11.18(1H,br,NH) 2.14(3H,s,$COCH_3$)

^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.					
	C-5 C-3	CO_2Et $COCH_3$	C-2' C-1'	ArCH	CH_2CH_3 CH_2CH_3	$COCH_3$
(161) a,e,i	177.83 173.70	157.73	157.55 115.84	132.94,129.60, 119.59,117.49	63.35 13.90	
(162) a,e,i	178.25 171.21	158.10 169.80	149.01 124.69	131.67,131.31, 126.08,123.83	62.91 13.83	20.92
(163) a,e,i	177.70 173.09	157.60 168.35	138.01 118.14	131.80,130.51, 122.80,120.54	63.16 13.78	24.96

4.4.2 Isothiazoles



(165) R^1=$OCOCH_3$, R^2=R^3=CO_2Me; (166) R^1=$NHCOCH_3$, R^2=R^3=CO_2Me;

(172) R^1=OH, R^2=H, R^3=CO_2Et; (173) R^1=$OCOCH_3$, R^2=CO_2Et, R^3=H;

(174) R^1=$OCOCH_3$, R^2=H, R^3=CO_2Et.

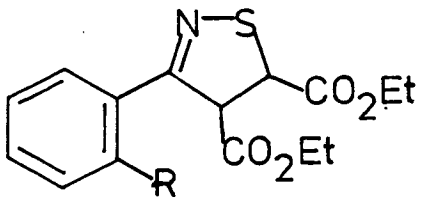
^{1}H N.m.r. Spectra

Compound Notes	δ H p.p.m.			
	Aromatic	R^1	R^2	R^3
(165) a,g,i	7.56(1H,dd,*J*8,2Hz) 7.45(1H,td,*J*8,2Hz) 7.29(1H,td,*J*8,1Hz) 7.17(1H,dd,*J*8,1Hz)	2.12(3H,s,$COCH_3$)	3.91,3.78 (each 3H,s, CO_2CH_3)	
(166) a,f,i	8.33(1H,dm,*J*8Hz) 7.49-7.00(3H,m)	9.52(1H,br,NH) 2.08(3H,s,$COCH_3$)	3.93,3.83 (each 3H,s, CO_2CH_3)	
(172) a,f,i	7.69-6.79(4H,m)	11.24(1H,s,OH)	8.11(1H,s,4-H)	4.41(2H,q,*J*7Hz,CH_2) 1.45(3H,t,*J*7Hz,CH_3)
(173) a,f,i	7.62-7.17(4H,m)	2.04(3H,s,$COCH_3$)	4.20(2H,q,*J*7Hz,CH_2) 1.14(3H,t,*J*7Hz,CH_3)	9.30(1H,s,5-H)
(174) a,f,i	7.92-7.19(4H,m)	2.27(3H,s,$COCH_3$)	8.02(1H,s,4-H)	4.40(2H,q,*J*7Hz,CH_2) 1.39(3H,t,*J*7Hz,CH_3)

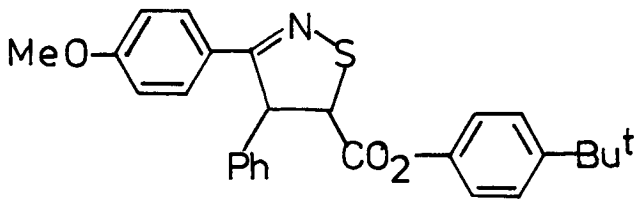
^{13}C N.m.r. Spectra

Compound Notes	δ_C p.p.m.						
	C-3 C-5	C-4	$COCH_3$ $COCH_3$	CO_2- Alkyl	C-2' C-1'	ArCH	Alkyl
(165)	163.06 156.11	132.85	168.14 20.21	162.82 158.84	147.71 126.72	130.27,130.19, 125.50,122.48	52.67, 52.32
(166)	164.69 155.87	134.33	168.18 24.56	163.95 158.89	136.41 136.41	130.64,128.51, 123.54,122.66	53.10 ($2xCH_3$)
(172) a,e,i	168.70 156.22	124.23		 159.67	157.61 117.46	131.51,127.52, 119.32,117.89	62.24, 13.00
(173) a,d,i	164.16 154.50	masked	168.26 20.48	161.80	148.04 128.34	130.47,129.93, 125.49,122.03	61.00, 13.62
(174) a,e,i	164.54 157.33	127.06	168.94 20.86	 159.78	147.90 127.19	130.35,130.04, 126.21,123.42	61.87, 13.98

4.4.3 Isothiazolines



(176) R=OH; (177) R=$OCOCH_3$



+ Regioisomer

(154/155) Mixture

^{1}H N.m.r. Spectra

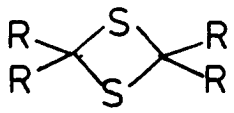
Compound / Notes	δ H p.p.m.			
	Aromatic	Isothiazoline	Alkyl	Other
(176) a,f,i,k		5.20(1H,d,J2.7Hz,5-H) 4.65(1H,d,J2.7Hz,4-H)		11.15(1H,s,OH)
(177) a,f,i	7.71-7.07(4H,m)	5.32(1H,d,J4.5Hz,5-H) 4.88(1H,d,J4.5Hz,4-H)	4.22(2H,q,J7Hz,CH_2) 4.02(2H,q,J7Hz,CH_2) 1.27(3H,t,J7Hz,CH_3) 0.95(3H,t,J7Hz,CH_3)	2.31(3H,s,$COCH_3$)
(154/155) a,f,i	7.82-6.70(26H,m)	5.48(2H,d,J3Hz,2x5-H) 4.47(2H,d,J3Hz,2x4-H)	1.31(6H,s,2xCH_3) 1.29(12H,s,4xCH_3)	3.86(3H,s,CH_3O) 3.75(3H,s,CH_3O)

^{13}C N.m.r. Spectrum

Compound / Notes	δ C p.p.m.							
	C-3	C-5 C-4	C=O	C-2' C-1'	ArCH	Ethyl CH_2	 CH_3	$COCH_3$
(177) a,d,i	159.02	60.91 52.37	170.11, 168.78, 167.55	148.13 126.43	130.42,130.25, 125.47,123.04	62.11, 61.81	13.79, 13.32	20.88

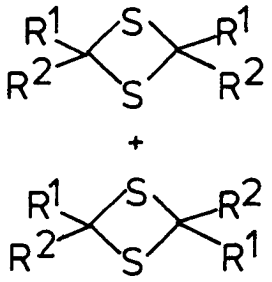
4.5 N.M.R. DATA OF DITHIETANES, THIIRANE AND OXATHIAZIN

4.5.1 Dithietanes



(183a) R=CO_2Me

(183b) R=CO_2Et



(186) R^1=COMe, R^2=CO_2Me

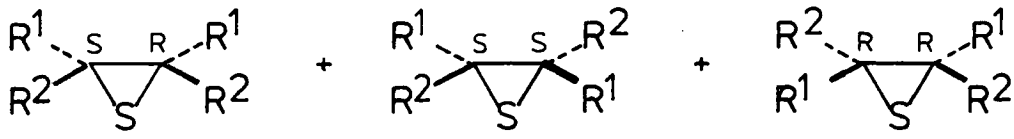
^{1}H N.m.r. Spectra

Compound	Notes	$^{\delta}$H p.p.m.	
		Alkoxy	Acetyl
(183a)	a,f,i	3.79(12H,s)	
(183b)	a,f,i	4.22(8H,q,*J*7Hz,4xCH_2) 1.24(12H,t,*J*7Hz,4xCH_3)	
(186)	a,f,i	3.81(6H,s) Isomer ratio 1:1 3.69(6H,s)	2.49(6H,s) 2.33(6H,s)

^{13}C N.m.r. Spectra

Compound	Notes	$^{\delta}$ H p.p.m.			
		C=O	C-2,4	Alkoxy	Acetyl
(183a)	a,e,i	164.56	51.12	53.90	
(183b)	a,e,i	163.99	51.54	62.91(CH_2), 13.47(CH_3)	
(186)	a,e,i	163.88, 163.77, 163.32	29.34	53.93, 51.88	23.56, 22.06

4.5.2 Dimethyl 2,3-Diacetylthiirane-2,3-dicarboxylate



(187) R^1=COMe , R^2=CO_2Me

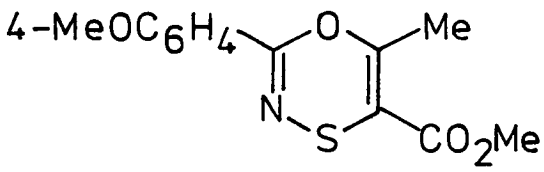
^{1}H N.m.r. Spectrum

Compound Notes	δH p.p.m.	
	CO_2Me	COMe
(187) a,f,i	3.81(6H,s) (Peak 3.69(6H,s) ratio 1:1)	2.33(6H,s) 2.29(6H,s)

^{13}C N.m.r. Spectrum

Compound Notes	δC p.p.m.			
	C=O	CH_3O	C-2,3	$COCH_3$
(187) a,e,i	166.23, 162.06, 159.07	53.60, 51.74	29.41	23.95, 14.04

4.5.3 Methyl 2-(*p*-Methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate



(185)

^{1}H N.m.r. Spectrum

Compound Notes	δ H p.p.m.		
	Aromatic	CH_3O	C(6)-Me
(185) a,g,i	7.79(2H,d,*J*9Hz) 6.87(2H,d,*J*9Hz)	3.83(3H,s) 3.75(3H,s)	2.38(3H,s)

^{13}C N.m.r. Spectrum

Compound Notes	δ C p.p.m.					
	CO_2 C-4'	C-6 C-2	C-1' C-5	2xArCH	CH_3O	$COCH_3$
(185) a,e,i	162.53 162.30	156.25 153.07	122.71 105.74	129.04, 113.67	55.27, 52.03	18.78

4.6 Crystallographic Data for Methyl 2-(*p*-Methoxyphenyl)-6-methyl-1,4,3-oxathiazin-5-carboxylate

The atom numbering employed in the crystallographic data is shown in Figure 7. This differs from that used in the normal nomenclature in having sulphur at position one rather than oxygen.

Tables 15 to 20 which follow display the full crystallographic data for this compound.

Figure 7. Atom Numbering for Compound (185) used in Tables of Crystallographic Data

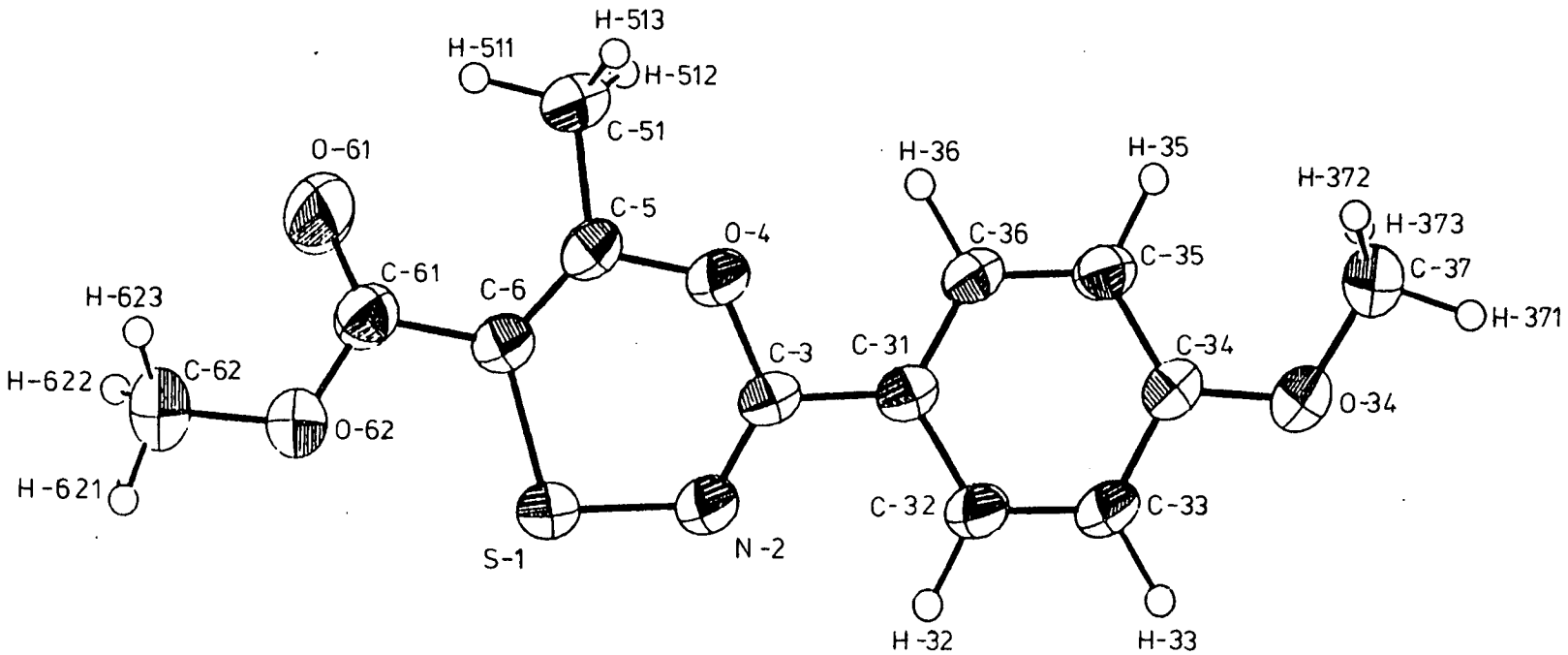


TABLE 15 FRACTIONAL COORDINATES OF ATOMS WITH STANDARD DEVIATIONS

	x	y	z	Ueq
S(1)	0.28182(6)	0.18904(9)	0.04771(8)	0.0529(6)
C(3)	0.40010(22)	0.3066(3)	-0.0662(3)	0.0394(16)
C(31)	0.49190(22)	0.3220(3)	-0.0993(3)	0.0386(16)
C(32)	0.57057(24)	0.2204(3)	-0.0489(3)	0.0497(19)
C(33)	0.65948(24)	0.2370(4)	-0.0743(3)	0.0516(19)
C(34)	0.67285(21)	0.3546(3)	-0.1516(3)	0.0419(17)
C(35)	0.59505(22)	0.4542(3)	-0.2040(3)	0.0444(17)
C(36)	0.50578(22)	0.4365(3)	-0.1768(3)	0.0438(17)
C(37)	0.7823(3)	0.4780(4)	-0.2469(3)	0.0584(22)
C(5)	0.23728(22)	0.4190(3)	-0.1206(3)	0.0434(17)
C(51)	0.1838(3)	0.5363(4)	-0.2114(3)	0.0591(21)
C(6)	0.20121(22)	0.3196(3)	-0.0560(3)	0.0434(17)
C(61)	0.09513(24)	0.3114(4)	-0.0636(3)	0.0526(20)
C(62)	-0.0183(3)	0.2127(5)	0.0364(4)	0.074(3)
N(2)	0.38359(20)	0.1958(3)	-0.0021(3)	0.0513(17)
O(34)	0.76501(15)	0.3638(3)	-0.16628(22)	0.0580(15)
O(4)	0.33732(15)	0.42846(22)	-0.10805(21)	0.0534(14)
O(61)	0.02742(20)	0.3756(5)	-0.1380(3)	0.0990(23)
O(62)	0.08249(17)	0.2232(3)	0.02819(23)	0.0620(16)

TABLE 16 FRACTIONAL COORDINATES OF HYDROGEN ATOMS

	x	y	z	Ueq
H(32)	0.5611	0.1285	0.0102	0.0500
H(33)	0.7195	0.1588	-0.0341	0.0500
H(35)	0.6037	0.5441	-0.2652	0.0500
H(36)	0.4456	0.5144	-0.2172	0.0500
H(371)	0.8597	0.4620	-0.2397	0.0500
H(372)	0.7710	0.5925	-0.2204	0.0500
H(373)	0.7370	0.4578	-0.3425	0.0500
H(511)	0.1065	0.5400	-0.2150	0.0500
H(512)	0.1892	0.5059	-0.3028	0.0500
H(513)	0.2171	0.6460	-0.1848	0.0500
H(621)	-0.0091	0.1544	0.1242	0.0500
H(622)	-0.0758	0.1579	-0.0375	0.0500
H(623)	-0.0389	0.3287	0.0450	0.0500

TABLE 17 ANISOTROPIC VIBRATION PARAMETERS WITH STANDARD DEVIATIONS

	U11	U22	U33	U23	U13	U12
S(1)	0.0492(5)	0.0447(5)	0.0608(6)	0.0143(4)	0.0210(4)	0.0090(3)
C(3)	0.0394(16)	0.0329(15)	0.0395(15)	-0.0005(12)	0.0048(13)	0.0051(11)
C(31)	0.0376(16)	0.0343(14)	0.0375(15)	-0.0030(12)	0.0037(12)	0.0012(12)
C(32)	0.0446(18)	0.0377(16)	0.0602(20)	0.0102(14)	0.0126(15)	0.0078(13)
C(33)	0.0442(18)	0.0401(16)	0.0649(20)	0.0096(15)	0.0166(15)	0.0149(14)
C(34)	0.0356(15)	0.0399(15)	0.0443(16)	-0.0039(13)	0.0068(13)	0.0047(12)
C(35)	0.0411(17)	0.0407(15)	0.0450(16)	0.0056(13)	0.0067(13)	0.0041(13)
C(36)	0.0367(16)	0.0414(15)	0.0464(17)	0.0033(13)	0.0049(13)	0.0076(12)
C(37)	0.0466(18)	0.0601(21)	0.0645(22)	0.0027(17)	0.0221(16)	0.0013(16)
C(5)	0.0396(16)	0.0413(16)	0.0447(16)	-0.0036(13)	0.0114(13)	0.0085(13)
C(51)	0.0524(20)	0.0581(20)	0.0606(21)	0.0186(17)	0.0158(16)	0.0175(16)
C(6)	0.0431(18)	0.0406(16)	0.0415(16)	-0.0007(13)	0.0108(14)	0.0050(13)
C(61)	0.0438(18)	0.0601(20)	0.0481(18)	0.0040(16)	0.0109(15)	0.0069(15)
C(62)	0.0511(22)	0.0820(27)	0.0869(28)	0.0047(22)	0.0319(21)	-0.0024(19)
N(2)	0.0441(16)	0.0411(14)	0.0634(17)	0.0084(12)	0.0166(13)	0.0075(11)
O(34)	0.0433(13)	0.0563(13)	0.0700(15)	0.0090(12)	0.0216(11)	0.0117(10)
O(4)	0.0448(13)	0.0388(11)	0.0709(15)	0.0121(10)	0.0184(11)	0.0099(9)
O(61)	0.0490(16)	0.1506(28)	0.0884(20)	0.0539(21)	0.0145(15)	0.0165(18)
O(62)	0.0463(14)	0.0665(15)	0.0685(15)	0.0136(12)	0.0212(12)	0.0020(11)

TABLE 18 BOND LENGTHS[A] WITH STANDARD DEVIATIONS

S(1) - C(6)	1.780(3)	C(34) -O(34)	1.362(4)
S(1) - N(2)	1.692(3)	C(35) -C(36)	1.393(4)
C(3) -C(31)	1.458(4)	C(37) -O(34)	1.423(4)
C(3) - N(2)	1.277(4)	C(5) -C(51)	1.486(5)
C(3) - O(4)	1.383(4)	C(5) - C(6)	1.333(4)
C(31) -C(32)	1.407(4)	C(5) - O(4)	1.379(4)
C(31) -C(36)	1.384(4)	C(6) -C(61)	1.476(5)
C(32) -C(33)	1.377(5)	C(61) -O(61)	1.201(5)
C(33) -C(34)	1.401(5)	C(61) -O(62)	1.342(4)
C(34) -C(35)	1.391(4)	C(62) -O(62)	1.456(5)

TABLE 19 ANGLES(DEGREES) WITH STANDARD DEVIATIONS

C(6) - S(1) - N(2)	101.66(14)		C(51) - C(5) - C(6)	129.2(3)	
C(31) - C(3) - N(2)	122.8(3)		C(51) - C(5) - O(4)	108.6(3)	
C(31) - C(3) - O(4)	111.68(24)		C(6) - C(5) - O(4)	122.2(3)	
N(2) - C(3) - O(4)	125.5(3)		S(1) - C(6) - C(5)	120.42(24)	
C(3) -C(31) -C(32)	119.6(3)		S(1) - C(6) -C(61)	116.22(22)	
C(3) -C(31) -C(36)	122.2(3)		C(5) - C(6) -C(61)	123.4(3)	
C(32) -C(31) -C(36)	118.2(3)		C(6) -C(61) -O(61)	126.6(3)	
C(31) -C(32) -C(33)	120.5(3)		C(6) -C(61) -O(62)	110.7(3)	
C(32) -C(33) -C(34)	120.6(3)		O(61) -C(61) -O(62)	122.7(3)	
C(33) -C(34) -C(35)	119.5(3)		S(1) - N(2) - C(3)	121.97(23)	
C(33) -C(34) -O(34)	115.5(3)		C(34) -O(34) -C(37)	118.2(3)	
C(35) -C(34) -O(34)	125.0(3)		C(3) - O(4) - C(5)	121.24(23)	
C(34) -C(35) -C(36)	119.3(3)		C(61) -O(62) -C(62)	116.4(3)	
C(31) -C(36) -C(35)	121.9(3)				

TABLE 20 TORSION ANGLES(DEGREES) WITH STANDARD DEVIATIONS

N(2) - S(1) - C(6) - C(5)	-17.5(3)		C(33) -C(34) -C(35) -C(36)	1.1(4)	
N(2) - S(1) - C(6) -C(61)	163.42(24)		O(34) -C(34) -C(35) -C(36)	-176.9(3)	
C(6) - S(1) - N(2) - C(3)	20.0(3)		C(33) -C(34) -O(34) -C(37)	178.1(3)	
N(2) - C(3) -C(31) -C(32)	-6.7(5)		C(35) -C(34) -O(34) -C(37)	-3.8(4)	
N(2) - C(3) -C(31) -C(36)	175.0(3)		C(34) -C(35) -C(36) -C(31)	-0.3(5)	
O(4) - C(3) -C(31) -C(32)	170.7(3)		C(51) - C(5) - C(6) - S(1)	179.8(3)	
O(4) - C(3) -C(31) -C(36)	-7.5(4)		C(51) - C(5) - C(6) -C(61)	-1.1(5)	
C(31) - C(3) - N(2) - S(1)	173.71(22)		O(4) - C(5) - C(6) - S(1)	-1.7(4)	
O(4) - C(3) - N(2) - S(1)	-3.4(4)		O(4) - C(5) - C(6) -C(61)	177.3(3)	
C(31) - C(3) - O(4) - C(5)	160.8(3)		C(51) - C(5) - O(4) - C(3)	-157.6(3)	
N(2) - C(3) - O(4) - C(5)	-21.8(4)		C(6) - C(5) - O(4) - C(3)	23.7(4)	
C(3) -C(31) -C(32) -C(33)	-177.0(3)		S(1) - C(6) -C(61) -O(61)	-170.3(3)	
C(36) -C(31) -C(32) -C(33)	1.3(5)		S(1) - C(6) -C(61) -O(62)	11.3(4)	
C(3) -C(31) -C(36) -C(35)	177.4(3)		C(5) - C(6) -C(61) -O(61)	10.6(6)	
C(32) -C(31) -C(36) -C(35)	-0.9(5)		C(5) - C(6) -C(61) -O(62)	-167.8(3)	
C(31) -C(32) -C(33) -C(34)	-0.6(5)		C(6) -C(61) -O(62) -C(62)	176.4(3)	
C(32) -C(33) -C(34) -C(35)	-0.6(5)		O(61) -C(61) -O(62) -C(62)	-2.0(5)	
C(32) -C(33) -C(34) -O(34)	177.5(3)				

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Tetrahedron Letters,Vol.26,No.31,pp 3727-3730,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

INTRAMOLECULAR CYCLOADDITION REACTIONS INVOLVING NITRILE SULPHIDES

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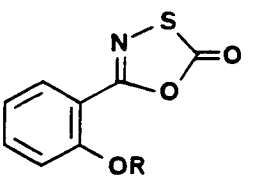
Summary: *ortho*-(Phenylpropioloxy)benzonitrile sulphide, generated *in situ* by thermal decarboxylation of the oxathiazolone (1), undergoes intramolecular 1,3-dipolar cycloaddition forming the chromenoisothiazole (4a); *ortho*-cinnamoylbenzonitrile sulphides also yield (4), together with nitrile, chromenoquinoline and aminochromene by-products.

The utility of 1,3-dipolar cycloaddition reactions for the preparation of 5-membered heterocycles has been appreciated[1] for more than 20 years. Recently the synthetic scope has been extended to include polycyclic systems formed *via* intramolecular cycloadditions.[2] Examples have been described for most 1,3-dipoles including the nitrilium betaines: nitrile ylides, nitrile imines, and nitrile oxides. We now report the first cases involving nitrile sulphides.

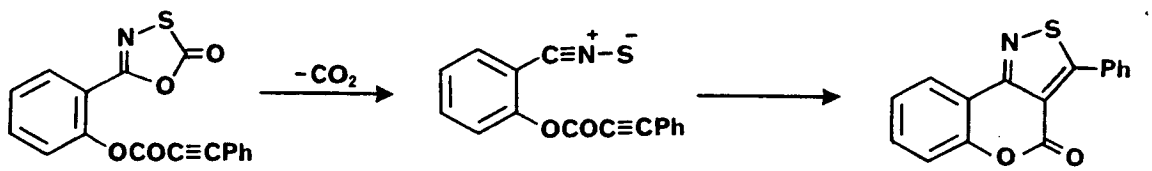
To establish the feasibility of such a process we examined the thermolysis of the *ortho*-(acyloxyphenyl)oxathiazolones, (1) and (2), which incorporate both an established source[3] of nitrile sulphides - the oxathiazolone - and an activated dipolarophile.



(1) R = COC≡CPh
(2) R = E-COCH=CHAr
(3) R = H

The acetylenic oxathiazolone (1) was prepared from salicylamide by treatment with chlorocarbonylsulphenyl chloride to give 5-(*o*-hydroxyphenyl)-1,3,4-oxathiazol-2-one (3), which was then acylated with phenylpropiolyl chloride. A solution of (1) in xylene was heated under reflux for 16 h. Removal of the solvent and chromatography of the residue (silica/hexane-diethyl ether) afforded 4-oxo-3-phenyl-4*H*-chromeno[4,3-*c*]isothiazole (4a)[4] (70%), consistent with initial decarboxylation of the oxathiazolone followed by intramolecular 1,3-dipolar cycloaddition of the resulting nitrile sulphide to the adjacent alkyne

(Scheme 1). The analogous intermolecular reaction between benzonitrile sulphide and ethyl phenylpropiolate is reported[3] to give a regio isomeric mixture of isothiazoles. In the intramolecular reaction steric constraints ensure that only one isomer is formed. Normally cycloadducts are accompanied by nitriles as by-products, often in substantial quantities, resulting from a competing fragmentation process.[5] In the present case, however, only a trace (<1%) of *o*-cyanophenyl phenylpropiolate could be detected by hplc.



(1) (4a)

Scheme 1

Having established that intramolecular cycloaddition could take place to an activated alkyne, the corresponding alkenes were studied. The olefinic oxathiazolones (**2**) were prepared, either from (**3**) and the appropriate cinnamoyl chloride, or by reaction of the 2-cinnamoyloxybenzamide with chlorocarbonylsulphenyl chloride. Thermolysis of (**2b**) in xylene (18 h) yielded a mixture of products: *o*-cyanophenyl *p*-methylcinnamate(**5b**) (35%), 4-oxo-3-(*p*-tolyl)-4*H*-chromeno[4,3-*c*]isothiazole (**4b**) (30%), 10-methyl-6-oxo-6*H*-chromeno-[4,3-*b*]quinoline (**6b**) (3%)[6], and 4-amino-3-(*p*-methylbenzyl)-2-oxochromene (**7b**) (15%)[7], which were separated by chromatography and crystallisation. The *para*-substituted cinnamate esters (**2a**), (**2c**) and (**2d**) each yielded a similar mixture of products (Table and Scheme 2).

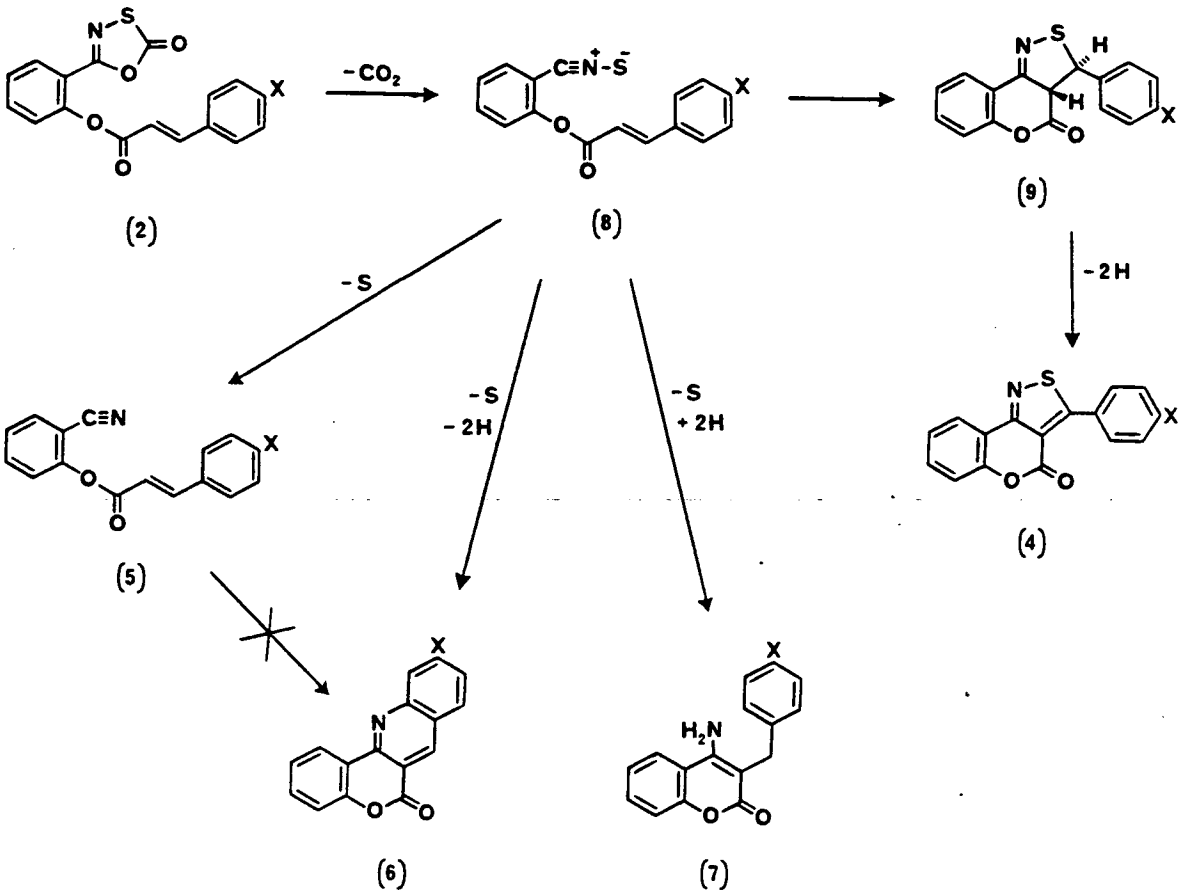
Table Products from the thermolysis of (2)

	Yields(%) of Products			
Reactant	(4)[a]	(5)[a]	(6)[a]	(7)[b]
(2a)	14	27	13	-[c]
(2b)	30	35	3	15
(2c)	21	33	8	28
(2d)	14	35	14	12

[a] Yields determined by hplc (silica/hexane-diethyl ether or dioxan)

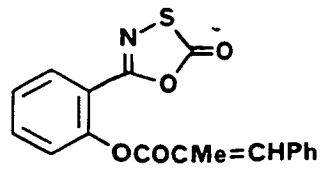
[b] Isolated yield

[c] Not determined

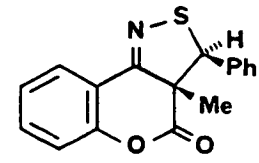


Scheme 2 (2),(4)-(9) a X=H; b, X=Me; c, X=Cl; d X=OMe

The formation of (5) and (4) can readily be explained in terms of competing fragmentation and cycloaddition of the intermediate nitrile sulphide (8), followed by rapid dehydrogenation of first-formed Δ^2-isothiazoline adduct (9). Isolation of (4) rather than (9) is not unexpected. Facile oxidation of Δ^2-isothiazolines has been observed previously.[8] To confirm that isothiazolines are the first-formed products the α-methylcinnamate derivative (10) was prepared and its thermolysis studied. In this case dehydrogenatioan is blocked and the isolated products are the methylisothiazoline (11) (5%)[9] and *o*-cyanophenyl α-methylcinnamate (81%). The modes of formation of the amino compound and the quinoline are not known. The latter is formally a 2 + 4-cycloadduct (with dehydrogenation) between the nitrile and the diene comprising the exocyclic and one of the endocyclic double bonds of the styrene group. However, failure to detect (6a) on heating a solution of *o*-cyanophenyl cinnamate (5a) in xylene for up to 6 weeks under reflux precludes its formation from this source. The mechanisms of these reactions are currently under investigation.



(10)



(11)

Acknowledgment We thank the SERC for the award of a studentship (to P.A.B.)

References and Footnotes

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2. A. Padwa, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 123.
3. R.K. Howe, T.A. Gruner, L.G. Carter, L.L. Black and J.E. Franz, *J. Org. Chem.*, 1978, **43**, 3736.
4. M.p. 166.5-168.5°C. Found: C, 68.8; H, 3.2; N, 4.9. $C_{16}H_9NO_2S$ requires C, 68.8; H, 3.2; N, 5.0%; ν_{max} 1730 cm $^{-1}$ (C=O); δ_C($CDCl_3$, 50 MHz) 177.9 (C-3), 162.4 (C-9b), 156.2 (C-4), 152.3 (C-5a), 131.8, 124.6, 124.0, 116.9 (CH-6,7,8,9), 130.8, 129.2, 128.6 (5 PhCH), 128.0 (PhC), 117.1 (C-3b), and 116.7 (C-9a); *m/z* 279 (M^+).
5. R.K. Howe and J.E. Franz, *J. Org. Chem.*, 1974, **39**, 962.
6. M.p. 205-207°C. Found: C, 78.0; H, 4.3; N, 5.3. $C_{17}H_{11}NO_2$ requires C, 78.2; H, 4.2; N, 5.4%; δ_C ($CDCl_3$, 50 MHz) 161.3, 152.7, 151.3, 149.6, 144.4, 125.5, 119.8, 115.0 (ArC), 140.4, 132.1, 129.7, 128.9, 128.4, 125.1, 124.7, 117.2 (ArCH), and 22.2 (CH_3); *m/z* 261 (M^+).
7. M.p. 203-206°C. Found: C, 76.8. H, 5.8; N, 5.2. $C_{17}H_{15}NO_2$ requires C, 77.0; H, 5.7; N, 5.3%; ν_{max} 3475, 3350, 3240 (NH_2), 1670, 1640 (C=O); δ_C (DMSO-d_6, 50 MHz) 162.2, 152.3, 150.7, 137.1, 134.5, 114.8, 95.6 (ArC) 131.2, 128.6, 127.9, 123.2, 123.0, 116.5 (ArCH), 29.1 (CH_2), and 20.5 (CH_3); *m/z* 265 (M^+).
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9. M.p. 149-151°C. Found: C, 69.0; H, 4.2; N, 4.7. $C_{17}H_{13}NO_2S$ requires C, 69.1; H, 4.4; N, 4.7%; δ_H (DMSO-d_6, 200 MHz) 7.2-7.9 (m, 9H, ArH), 5.93 (s, 1H, isothiazoline ring CH), and 1.15 (s, 3H, CH_3); δ_C (DMSO-d_6, 50 MHz) 168.3 (C-4), 161.2 (C-9b), 151.8 (C-5A), 133.0, 125.5, 125.1, 116.9 (CH-6,7,8,9), 132.2 (PhC), 130.4, 128.5, 128.3 (PhCH), 117.2 (C-9a), 61.1 (C-3a), 59.7 (CH-3), and 17.6 (CH_3); *m/z* 295 (M^+).

(Received in UK 10 June 1985)