STUDIES ON THE SYNTHESIS AND REACTIVITY

OF FIVE-MEMBERED HETEROCYCLIC DIAZONIUM CATIONS

by

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Thesis presented for the degree of Doctor of Philosophy

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1976 and September 1979.

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Summary

The diazotisation of a series of five-membered heterocyclic primary amines has been examined and after satisfactory conditions had been established the resulting "diazo intermediates" were subjected to dediazoniation reactions and coupling with active methylene compounds, in the latter case with the objective of the cyclisation of the hydrazone products to novel bicyclic systems.

5-Amino-3-phenylisoxazole was prepared and diazotised under several sets of conditions to give principally 3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime and 5-amino-3-phenyl-4-(3'-phenyl-isoxazol-5'-ylazo) hydrazone. An investigation was carried out into the chemistry of 3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime with particular regard to its reactions with nucleophiles.

The diazotisation of 2-aminothiazole and 2-aminobenzothiazole was achieved and in situ dediazoniation and coupling reactions with active methylene compounds met with limited success. 2-N-Hydroxy-azobenzothiazole and benzothiazole-2-diazonium fluoroborate were prepared and their reactions were examined, with particular reference to dediazoniation processes. Methyl 4-amino-2-methylmercapto-thiazole-5-carboxylate was prepared and under suitable conditions was diazotised and the diazonium salt subjected successfully to dediazoniation and coupling under controlled pH with active methylene compounds.

5-Amino-3-methylisothiazole-4-carbonitrile was prepared,

diazotised and coupled with acetylacetone to give the corresponding hydrazone in moderate yield. 5-Nitrosamino-3-methylisothiazole-4-carbonitrile was also prepared and was found to be a synthetically useful intermediate. The corresponding diazonium salt could not be isolated.

Two 5-amino-1,2,4-thiadiazoles were synthesised, their respective nitrosamines prepared, and 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate isolated from the corresponding nitrosamine. However only limited success was achieved in utilising these isolable intermediates as diazonium salt precursors. The diazotisation of 5-amino-1,2,4-thiadiazoles and subsequent <u>in situ</u> reactions of the resulting diazonium salts were not particularly fruitful. The synthesis and diazotisation of 3-amino-5-phenyl-1,2,4-thiadiazole was achieved but satisfactory transformations of derived diazonium salts were not successful. Neither 3-nitrosamino-5-phenyl-1,2,4-thiadiazole nor 5-phenyl-1,2,4-thiadiazole-3-diazonium fluoroborate could be isolated. 2-Amino-5-phenyl-1,3,4-thiadiazole was prepared and satisfactorily diazotised and coupled with acetylacetone. 2-Nitros-amino-5-phenyl-1,3,4-thiadiazole was also prepared and its synthetic usefulness demonstrated.

The discovery of a novel thermal and photochemical decomposi-tion of 5-azido-3-methylisothiazole-4-carbonitrile to afford 2-amino-1,1-dicyanoprop-1-ene inspired the synthesis of other 5-azidoiso-thiazole-4-carbonitriles (via dediazoniation reactions of the corrés-ponding diazonium salts) and the study of their similar thermal and

photochemical decomposition. A mechanism is proposed for such fragmentation reactions but attempts to prove it were unsuccessful. Azidodediazoniation reactions of most of the heterocyclic diazonium salts prepared before were carried out and the thermolysis and photolysis of the resulting azido compounds investigated. However no general decomposition pathway was observed.

CONTENTS

CHAPTER ONE

Introduction

INTRODUCTION

The following thesis is concerned with the general study of the diazotisation of heterocyclic amines having a five-membered ring containing an oxygen or sulphur atom and one or two nitrogen atoms, and with the synthetic utility of the resulting diazonium and nitrosamino products. By way of introduction the discussion of the results obtained is preceded by a review of the chemistry of arenediazonium salts in general and hetaryldiazonium salts in particular.

A Review of the Chemistry of Diazonium Salts

(a) Arenediazonium Salts

(i) Synthesis

The process of diazotisation can be defined as the transformation of a primary amine (1) into the corresponding diazonium salt (2) (Scheme 1). In the present section discussion will be confined to the

$$R-NH_2 \longrightarrow R-\overset{+}{N}{\equiv}N \ \ \overset{-}{X}$$

$$(1) \qquad\qquad\qquad (2)$$
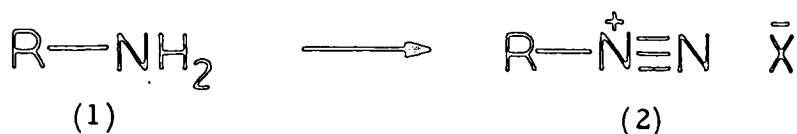
<u>Scheme 1</u>

diazotisation of primary arylamines and the chemistry of the resulting arenediazonium salts. The study of the diazotisation of aniline and similar compounds has a long history, stretching back to 1858 when Griess inadvertently produced the diazonium salt of picramic acid by passing

$$\underset{\text{(3)}}{\overset{\displaystyle \text{NH}_2}{\underset{\displaystyle \text{NH}_2}{\overset{\displaystyle |}{\underset{\displaystyle |}{\text{CO}}}}}} + 2HNO_2 \longrightarrow CO_2 + 2N_2 + 3H_2O$$

$$\underset{\text{(4)}}{\overset{\displaystyle \text{OH}}{\underset{\displaystyle \text{NH}_2}{\overset{\displaystyle |}{\underset{\displaystyle |}{\text{SO}_2}}}}} + HNO_2 \longrightarrow H_2SO_4 + N_2 + H_2O$$
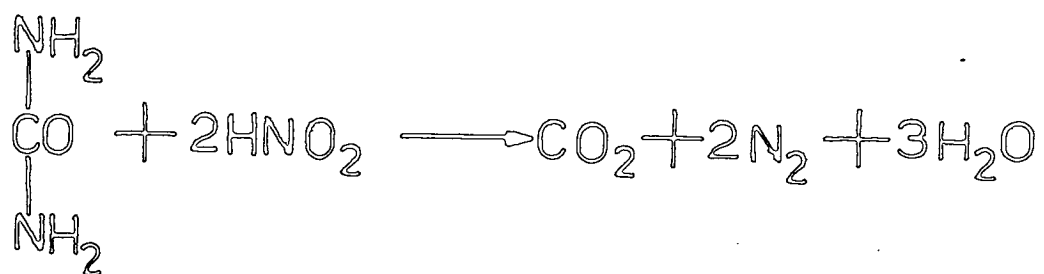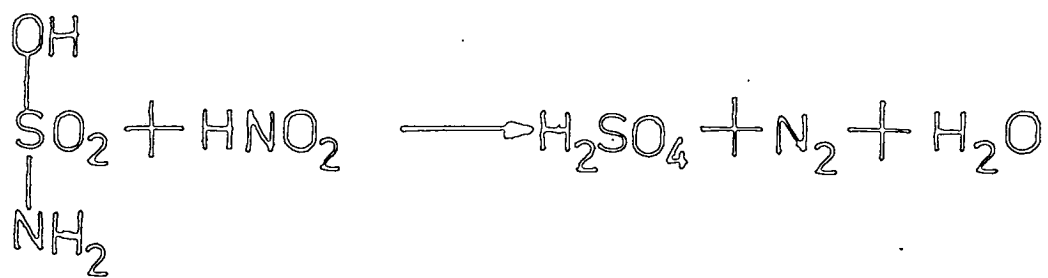
Scheme 3

nitrous gases through an alcoholic solution of the corresponding arylamine.[1] Knoevenagel[2] used esters of nitrous acid, such as ethyl nitrite and amyl nitrite, as nitrosating agents for the diazotisation of arylamines and succeeded in isolating the corresponding diazonium salts. However as arenediazonium salts are not very stable, they are normally reacted in situ and not isolated. Martius[3] discovered that the most convenient method for the preparation of arenediazonium salts was to treat a solution of the amine in a mineral acid with sodium nitrite (Scheme 2), and this is the usual method of choice. From Scheme 2

$$Ar{-}NH_2 + 2HX + NaNO_2 \longrightarrow Ar{-}\overset{+}{N}_2\ \bar{X} + NaX + 2H_2O$$
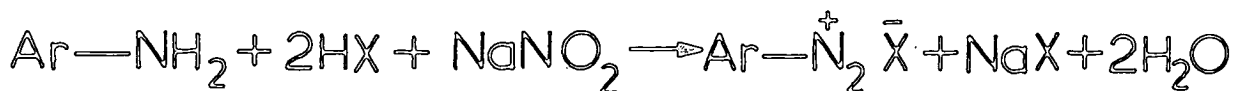
<u>Scheme 2</u>

it can be seen that to effect diazotisation two equivalents of acid are required and normally at least another half equivalent is used. However, only one equivalent of sodium nitrite is necessary and it is normally disadvantageous to have excess of nitrite in the reaction mixture. Gies and Pfeil[4] have shown that excess of nitrite can reduce the stability of diazonium solutions and can also result in unwanted nitrosation of the reactants. Excess of nitrite ion can be destroyed by adding urea (3) or sulphamic acid (4) to the reaction mixture (Scheme 3). Diazotisation is normally carried out at $0^{\circ}C$, achieved by external cooling or by adding ice to the reaction mixture, conditions which inevitably result in a lower rate of reaction and reduced solubility of the amine. However these undesirable features are outweighed by the necessity of maintaining a s

low a temperature as possible in order to minimise decomposition of the diazonium product and to maximise the solubility of the free nitrous acid in the acid medium. The pH at which diazotisation is carried out is also important and is normally lower than pH2 to ensure that the equilibrium between the free base (5) and the ammonium salt (6) (Scheme 4) lies towards the right thus ensuring a homogeneous solution, the free

$$Ar-NH_2 \rightleftharpoons Ar-\overset{+}{N}H_3$$
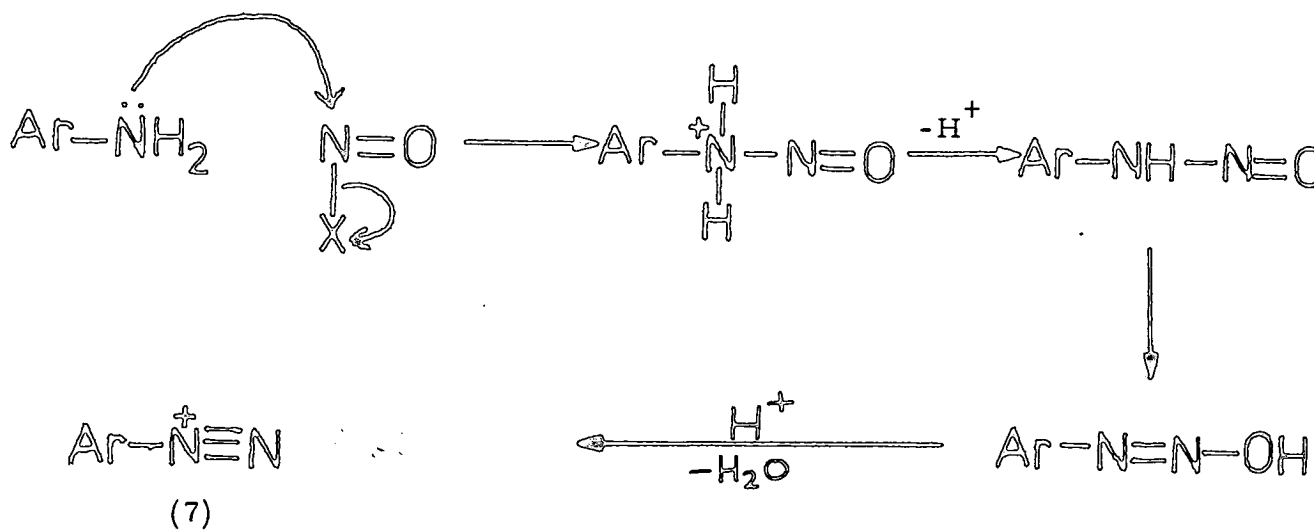
$$\quad (5) \qquad\qquad\qquad (6)$$

Scheme 4

arylamine (5) not usually being very water soluble. In addition the presence of the free base in any concentration may lead to the formation of a diazoamino product by coupling between the amine and the diazonium cation. In the case of weakly basic amines the equilibrium (Scheme 4) lies towards the left and consequently the solubility of these amines is reduced and the efficiency of their diazotisation reactions is impaired. The diazotisation of weakly basic amines therefore requires more con- centrated acid to ensure that sufficient amine molecules become proto- nated. The ideal situation is that the equilibrium concentration of base should correspond to that of its saturated solution. However there are complicating factors involving the use of more concentrated acid solutions. For example with hydrochloric acid greater than 25% in concentration, nitrous acid has an oxidising effect (Scheme 5). Also, when sodium nitrite solution is added to sulphuric acid or nitric acid solutions greater than 25% in concentration, nitrous gases are evolved at a greater rate

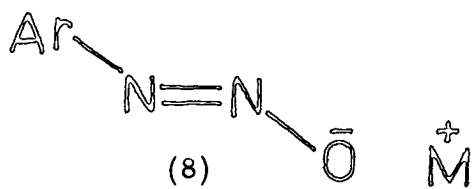$$2NO_2^- + 2Cl^- + 4H^+ \longrightarrow 2NO + Cl_2 + 2H_2O$$

Scheme 5

than that at which nitrosation takes place thus resulting in inefficient diazotisation. Fortunately solid sodium nitrite can be dissolved in 90-96% sulphuric acid at 0-10°C without evolution of gas to form nitrosylsulphuric acid. Diazotisation can then be achieved by adding the amine directly to the nitrosylsulphuric acid or by adding nitrosylsulphuric acid to a solution of the amine in concentrated sulphuric acid. Diazotisation with nitrosylsulphuric acid can be carried out at room temperature but is often a slow process[5] because the concentration of the free amine in the reaction mixture is so low. This problem can be overcome by diluting the nitrosylsulphuric acid with either phosphoric or acetic acid.[6,7] Alternatively naphthalenesulphonic acid in conjunction with concentrated sulphuric acid (20-60%) can be employed as the acid medium for diazotisation.[8] The addition of naphthalene-1-sulphonic acid to concentrated sulphuric acid reduces greatly the amount of nitrous fumes evolved on adding nitrite solutions compared with a solution of sulphuric acid of similar concentration. Diazotisation can also be carried out in organic solvents such as ethanol by passing in hydrogen chloride until the solution is saturated and then treating with amyl nitrite or ethyl nitrite. The solid diazonium salt can often be isolated under these conditions by diluting the reaction mixture with ether.

$$\text{Ar}-\ddot{\text{N}}\text{H}_2 \qquad \text{N}=\text{O} \longrightarrow \longrightarrow \text{Ar}-\overset{+}{\underset{|}{\text{N}}}-\text{N}=\text{O} \xrightarrow{-\text{H}^+} \text{Ar}-\text{NH}-\text{N}=\text{O}$$

$$\text{X}$$

$$\text{Ar}-\overset{+}{\text{N}}\equiv\text{N} \qquad\qquad \xleftarrow[-\text{H}_2\text{O}]{\text{H}^+} \qquad \text{Ar}-\text{N}=\text{N}-\text{OH}$$

(7)

Scheme 6

$$\underset{\text{Ar}}{\overset{\displaystyle}{\text{N}}}=\text{N} \qquad \overset{-}{\text{O}} \qquad \overset{+}{\text{M}}$$

(8)

The first step in the diazotisation of an amine is nitrosation by a species derived from nitrous acid, $\overset{+}{N}=O \; or$ X-N=O. Such species can be:
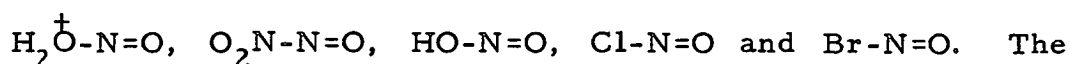
$H_2\overset{+}{O}-N=O$, $O_2N-N=O$, $HO-N=O$, $Cl-N=O$ and $Br-N=O$. The exact nature of the nitrosating species will depend on the pH and the type of acid employed and it is possible that more than one species will be involved under any particular reaction conditions. The general mechanism is shown in Scheme 6. For arenediazonium salts this rearrangement to the diazonium salt (7) occurs rapidly and the various intermediates are not usually isolated. However anti-diazotates (8) can be prepared by mixing diazonium and highly concentrated alkaline solutions.[9]

(ii) Reactions

As already mentioned, diazonium salts are not very stable and therefore are normally reacted in situ. Saunders[10] has classified the reactions of diazonium salts into five groups. Substitution or solvolysis at the aryl nucleus, which does not affect the diazonium group will be ignored. In this present review the remaining four classes of reaction of diazonium salts as defined by Saunders will be condensed into only two principal types of reaction. Firstly, the direct displacement of nitrogen to give a substitution product, a process which is known as a dediazoniation reaction. Secondly reaction of the diazonium group with another moiety with retention of nitrogen to give a coupled product. Dediazoniation reactions of arenediazonium salts will first be discussed. A large number of dediazoniation reactions are of the S_N1 type involving initial loss of nitrogen to give an aryl cation which then reacts with an

available nucleophile to give the product (Scheme 7).

$$Ar-\overset{+}{N}\equiv N \xrightarrow{\text{slow}} \overset{+}{Ar} + N_2$$

$$\overset{+}{Ar} + \bar{X} \xrightarrow{\text{fast}} Ar-X$$
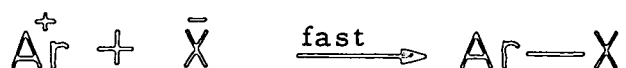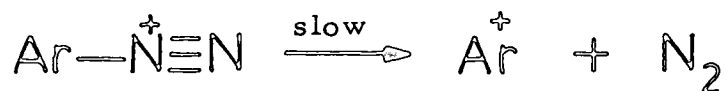
Scheme 7

The $S_N 1$ mechanism (Scheme 7) for dediazoniation reactions is supported

by the fact that the reaction rate for X=halogen is independent of the

concentration and type of the halide ion.[11-16] A synthetically useful

displacement reaction of this type is the formation of phenols when

strongly acidic solutions of diazonium salts are heated under reflux.

However the low pH and the elevated temperatures involved in such

displacements can sometimes cause unwanted side reactions particularly

if the diazonium cation contains other sensitive groups. Recent

studies[17] demonstrate that phenol formation from diazonium salts can

be effected at low temperature and neutral pH under catalysis by cupric

nitrate and cuprous oxide to give equivalent or better yields than in

the uncatalysed processes. Moreover, in certain cases the catalysed

transformation succeeds where the uncatalysed method fails. It has

also been found[17] that the presence of silver ion in the Cu(I)-Cu(II)

mixture results in enhanced yields of phenols. Another useful trans-

formation of arenediazonium salts is hydrogenodediazoniation, that

is the replacement of the diazonium group by hydrogen.   Griess[18]

first carried out this reaction by reducing the diazonium cation with

ethanol.   However the most widely used method is that of Mai[19] who

employed hypophosphorous acid (Scheme 8).   A radical mechanism

$$Ar—\overset{+}{N}_2 + H_3PO_2 \xrightarrow{H_2O} Ar—H + H_3PO_3 + N_2$$
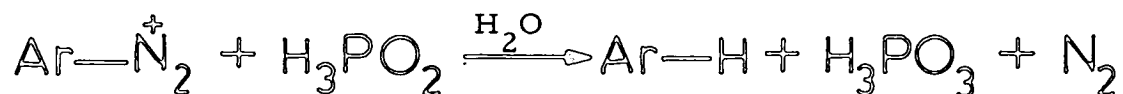
<p align="center">Scheme 8</p>

is proposed for the reaction.

Many dediazoniation reactions only occur when a catalyst is

present.   Pschorr[20] was among the first to demonstrate this type of

reaction, using copper powder to catalyse nitrogen loss (Scheme 9).
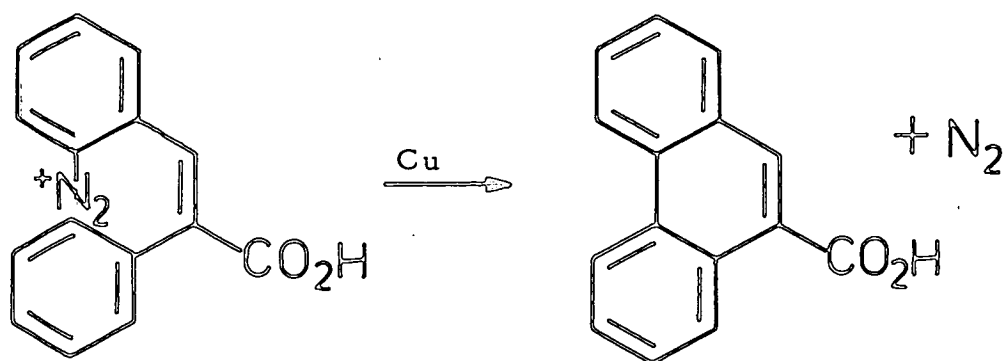
<p align="center">Scheme 9</p>

Such dediazoniations are believed to occur by a radical mechanism.

One of the best known of such catalysed dediazoniation reactions and

one of the most useful synthetically is the Sandmeyer reaction.   Such

displacement of the diazonium group by halogens was first discovered

by Griess[21] in 1866 but it was not of preparative use until the

discovery by Sandmeyer[22] in 1884 that the reaction could be catalysed

with cuprous salts.   The Sandmeyer method involves the addition of

the diazonium solution to the cuprous halide in the corresponding halogen

acid.   The Sandmeyer reaction can be extended to other nucleophilic

reagents such as cyanide ion,[23] nitrite ion[24] and thiocyanate ion[25]

although the reactions with nitrite ion are of limited applicability.
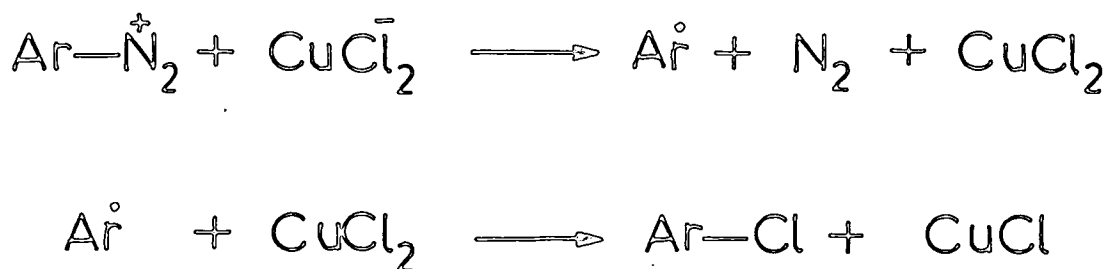
Another synthetically useful reaction of this type is the Beech reaction[26]

whereby the diazonium group is substituted by a formyl group.   The

Beech reaction is carried out by adding the diazonium solution to a

mixture of formaldoxime (9) and a copper catalyst (Scheme 10).   A

$$Ar-\overset{+}{N}_2 + CH_2\!=\!NOH \xrightarrow{\;Cu\;} Ar-CH\!=\!NOH \xrightarrow[H_2O]{H^+} Ar-CHO$$
$$(9)$$
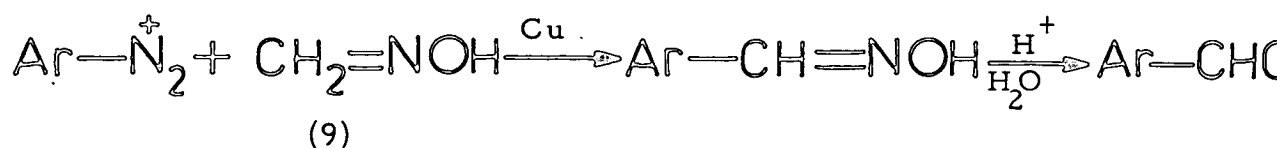
Scheme 10

radical mechanism has been proposed for the Sandmeyer reaction

(Scheme 11)[27] although a complex formed between the copper catalyst

and the diazonium group is also a possibility.[28]   Gattermann[29] found

$$Ar-\overset{+}{N}_2 + Cu\bar{C}l_2 \longrightarrow A\overset{\circ}{r} + N_2 + CuCl_2$$

$$A\overset{\circ}{r} + CuCl_2 \longrightarrow Ar-Cl + CuCl$$

Scheme 11

$$Ar\!-\!N_2^+ \;+\; N_3^- \;\longrightarrow\; Ar\!-\!N_3 \;+\; N_2$$

Scheme 12

$$Ar\!-\!\overset{+}{N}\!\equiv\!\overset{15}{N} \;+\; \overset{-}{N}\!=\!\overset{+}{N}\!=\!\overset{-}{N}$$

$$\downarrow$$

$$Ar\!-\!N\!=\!\overset{15}{N}\!-\!N\!=\!\overset{+}{N}\!=\!\overset{-}{N} \;\longrightarrow\; Ar\!-\!N\!=\!\overset{15}{N}\!\overset{+}{=}\!\overset{-}{N} \;+\; N\!\equiv\!N$$

$$(10)$$

$$\downarrow$$

(12)

$$Ar\!-\!N\!=\!\overset{+}{N}\!=\!\overset{-}{N} \;+\; \overset{15}{N}\!\equiv\!N$$

$$(11)$$
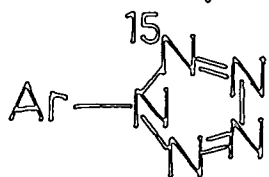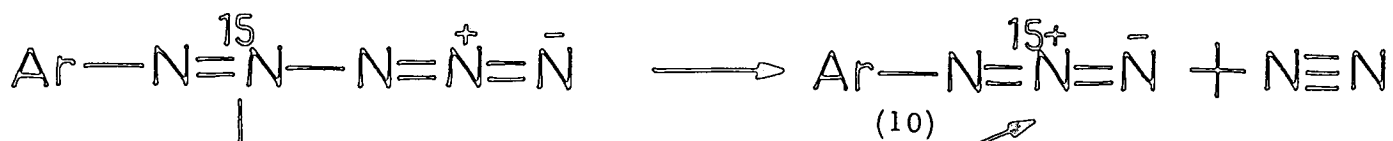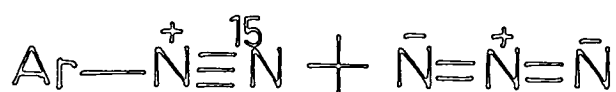
Scheme 13

that the Sandmeyer reaction gave equally good yields if finely powdered copper was used as catalyst instead of cuprous salts. The Sandmeyer reaction is unsuitable for preparing aryl fluorides as cuprous fluoride disproportionates to copper and cupric fluoride at room temperature.[30] Aryl fluorides can be prepared by the method of Schiemann[31] which involves heating the corresponding diazonium fluoroborates. Mechanistic[32] studies have shown that the nucleophile involved is the fluoroborate ion (BF_4^-) and that the reaction involves the rate determining formation of a singlet aryl cation.
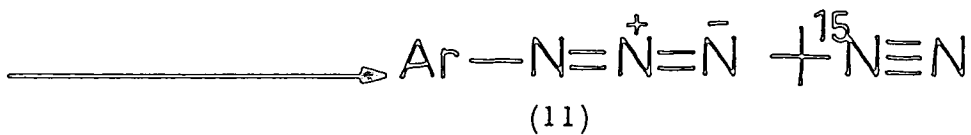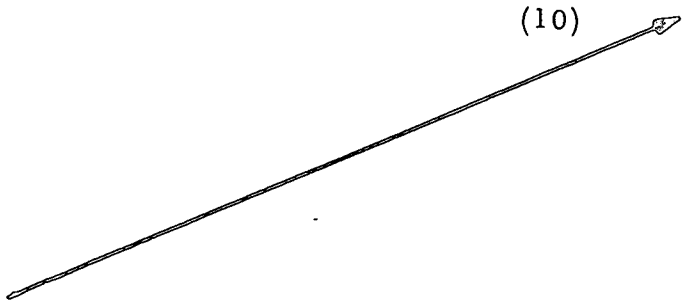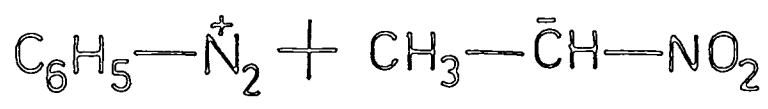
Recent work on the decomposition of diazonium cations has shown that there are at least two different mechanisms of dediazonation.[33] Bunnett[34-36] has demonstrated that numerous arenediazonium salts decompose in methanol in the absence of oxygen to give the corresponding arenes, whereas decomposition in the presence of oxygen gives the methoxy ethers. The former result is explained in terms of a radical mechanism and the latter result by an ionic process which competes as a result of oxidative inhibition of the radical process. These results demonstrate that there are at least two discrete mechanisms of dediazoniation excluding catalysed processes.

It is convenient to consider the reaction of diazonium salts with azide ion under the heading of nucleophilic displacement reactions although the mechanism has been shown to be more complicated than one would naively imagine from Scheme 12 and does not follow the classic S_N1 pathway. Clausius, Hürzeler and Vecchi[37,38] have shown using ^{15}N labelling that a mixture of two differently labelled aryl azide products (10) and (11) is obtained (Scheme 13). Formation of the two differently

$$C_6H_5-\overset{+}{N}_2 + CH_3-\overset{-}{C}H-NO_2$$

$$HSO_4^- \qquad\qquad \overset{+}{Na}$$

$$(13) \qquad\qquad\qquad (14)$$

$$C_6H_5-N=N-CH-NO_2$$
$$\underset{CH_3}{|}$$

$$(15)$$

Scheme 14

$$2(C_6H_5\overset{+}{N}_2\ \overset{-}{Cl}) + CH_3-CO-CH_3$$

$$C_6H_5-N=N-C=N-NH-C_6H_5$$
$$\underset{CO-CH_3}{|}$$
$$(16)$$
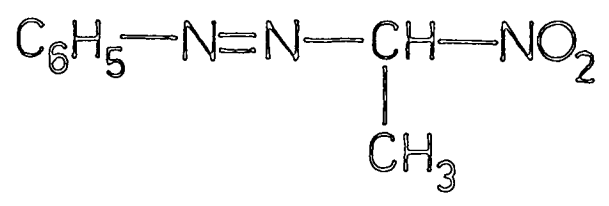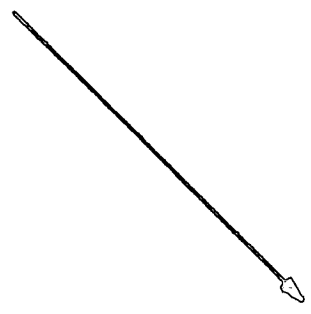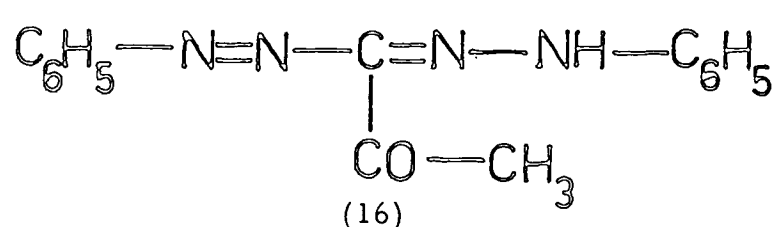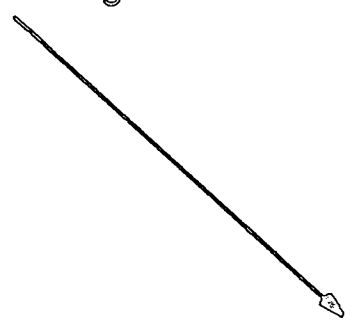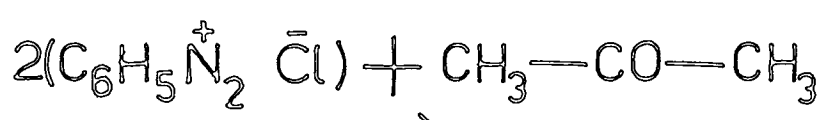
labelled aryl azides has been rationalised by Ugi and Huisgen[39-42] on the basis of preparative and kinetic experiments and the mechanism shown in Scheme 13 involving a pentazole intermediate (12) has been proposed. Ugi and Huisgen showed that not only does the reaction take place quantitatively, but nitrogen evolution is observed to occur in two steps. Moreover Ugi[42] subsequently succeeded in isolating a pentazole derivative akin to that (12) proposed as intermediate (Scheme 13). It can thus be seen that the reaction of azide ion with the diazonium cation is not a simple nucleophilic substitution but has more in common with the coupling reactions discussed later.

The other important type of reaction to which a diazonium salt can be subjected is coupling where, in contrast to dediazoniation, the diazonium group is retained in the product formed. Diazonium cations are relatively weakly electrophilic species and will attack the centre of highest electron density in the coupling component. Normally in diazonium chemistry this is a carbon atom but oxygen or amino nitrogen are also possible sites of attack. As the diazonium cation is a reagent of low reactivity and therefore high selectivity, the coupling component must have a structure with a high electron density at one or more carbon atoms. A diazonium cation can couple with either an aromatic or an aliphatic carbon atom provided that the atom in question is suitably activated. The first reported example of the coupling of an arenediazo-nium salt with an aliphatic compound was by Meyer[43] who found that benzenediazonium sulphate (13) reacted with the sodium salt of nitro-ethane (14) to give the coloured azo compound (15) (Scheme 14). Coupling of diazonium cations with ketones occurs under alkaline conditions but

$$Ar\overset{+}{-}\overset{..}{N}\equiv N + \cdot\overset{\overset{R^1}{|}}{\underset{\underset{R^2}{|}}{CH}} \longrightarrow Ar-N=N-\overset{\overset{R^1}{|}}{\underset{\underset{R^2}{|}}{CH}}$$

(17)　　　　(18)　　　　　　　(19)
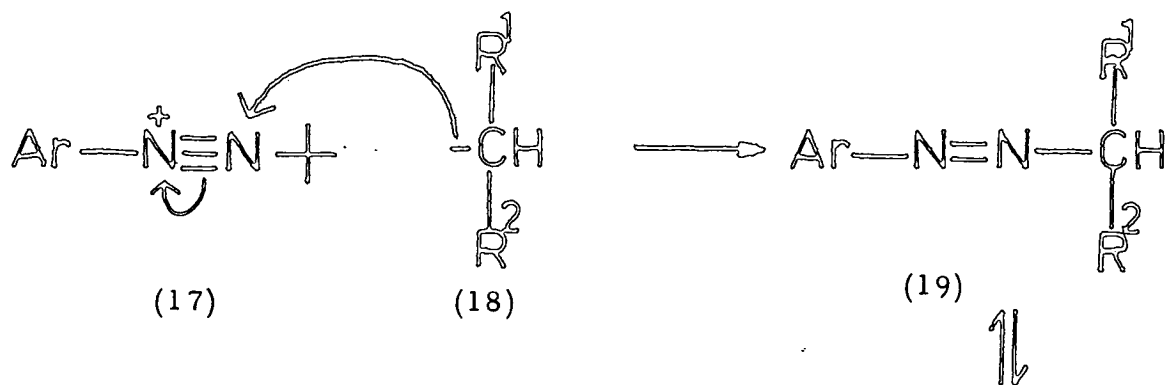
$$[R^1, R^2 = COCH_3, CO_2CH_3, CO_2Et, CN, NO_2, etc]$$

$$Ar-NH-N=\overset{\overset{R^1}{|}}{\underset{\underset{R^2}{|}}{C}}$$

(20)

Scheme 16

$$R-CH_2-\overset{\overset{O}{||}}{C}-R' \rightleftharpoons R-CH=\overset{\overset{OH}{|}}{C}-R'$$

(21)　　　　　　　　　　(22)

Scheme 17

$$Ar\overset{+}{N}_2 \ \overset{-}{Y} + CH_2(CO_2H)_2 \longrightarrow Ar-NH-N=CH-CO_2H$$

$$\downarrow ArN_2^+ \ Y^-$$

$$Ar-NH-N=C(N=N-Ar)_2 \xleftarrow{ArN_2^+ \ Y^-} Ar-NH-N=CH-N=N-Ar$$
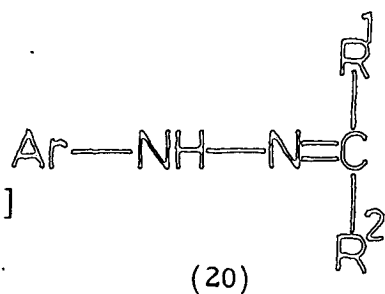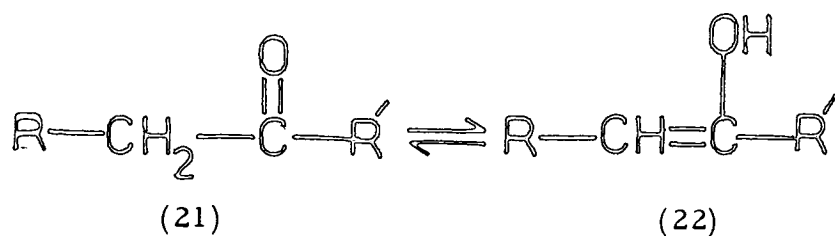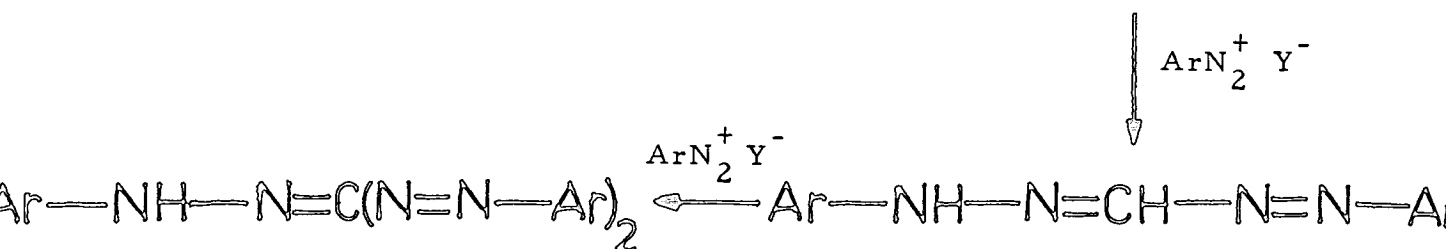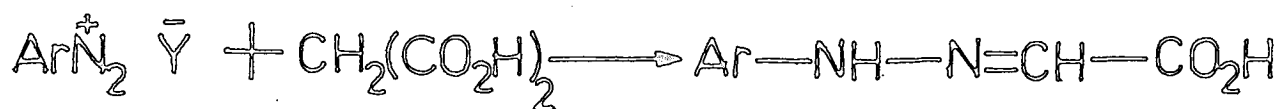
in these ketone reactions two moles of the diazonium salt are involved. For example the reaction of acetone[44] with benzenediazonium chloride under alkaline conditions gives the formazan (16) (Scheme 15). Common coupling components are active methylene compounds, in which the methylene centre is activated by two electron withdrawing groups. These methylene compounds are normally coupled with arenediazonium salts under neutral or basic conditions to yield hydrazones (20), rather than azo compounds (19), the hydrazone being the more stable tautomer (Scheme 16). Coupling reactions of this type have been reported[45] for a large number of arenediazonium salts (17) and methylene compounds (18) containing a wide variety of electron withdrawing substituents. The coupling reaction of an arenediazonium cation (17) with an active methylene compound at pH>7 can be explained (Scheme 16) in terms of nucleophilic attack by the methylene carbanion (18) at the diazonium group of the arenediazonium cation (17) to give an unstable azo intermediate (19) convertible by tautomerism into the hydrazone product (20). Though methylene compounds normally require neutral or basic conditions for satisfactory coupling, reaction can also occur under acidic conditions with the unionised methylene compound (21) in the enol tautomeric form (22) (Scheme 17). Where the diazonium salt is in excess the methylene component can undergo multiple coupling as exemplified by the reaction of malonic acid[46] with one, two or three moles of arenediazonium salt (Scheme 18). An arenediazonium salt will only couple with a saturated aliphatic compound if the latter is activated by two electron withdrawing groups. However nitroparaffins are exceptional and will couple with arenediazonium salts despite the fact that they contain only one activating group. A special case of the

$$C_6H_5\overset{+}{N}_2\ \overset{-}{C}l + CH_3-CO-CH-CO_2-C_2H_5$$

$$\underset{\displaystyle CH_3}{\big|}$$

(23)

$$\xrightarrow{\quad H_2O \quad}$$

$$CH_3-CO_2H + CH_3-\underset{\displaystyle \underset{CO_2-C_2H_5}{|}}{C}=N-NH-C_6H_5$$

Scheme 19

$$CH_3-CO-CH-\overset{-}{C}O_2\ \overset{+}{N}a + C_6H_5\overset{+}{N}_2$$

$$\underset{\displaystyle CH_3}{\big|}$$

(24)

$$\xrightarrow{\quad H_2O \quad}$$

$$HC\overset{-}{O_3} + CH_3-CO-\underset{\displaystyle \underset{CH_3}{|}}{C}=N-NH-C_6H_5$$

Scheme 20

$$\overset{\displaystyle H}{\underset{\displaystyle R}{\diagup}}C + Ar\overset{+}{N}_2 \longrightarrow \left[\overset{\displaystyle X}{\underset{\displaystyle Y}{\diagup}}C\overset{\displaystyle N=N-Ar}{\underset{\displaystyle R}{\diagdown}}\right] \xrightarrow{\ H_2O\ } X-\underset{\displaystyle \underset{R}{|}}{C}=N-NH-$$

(25)
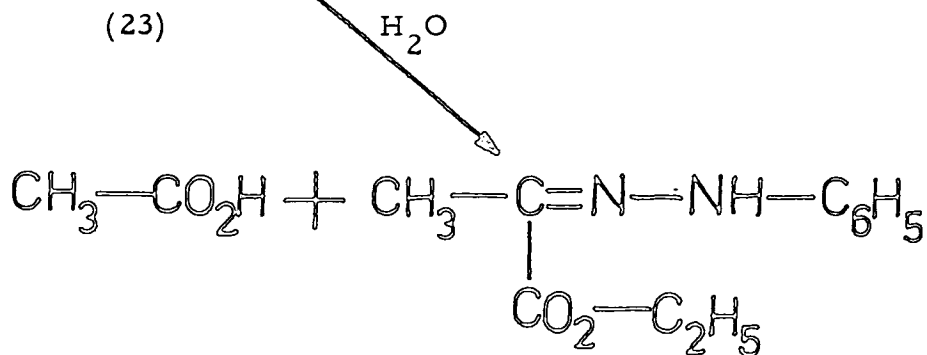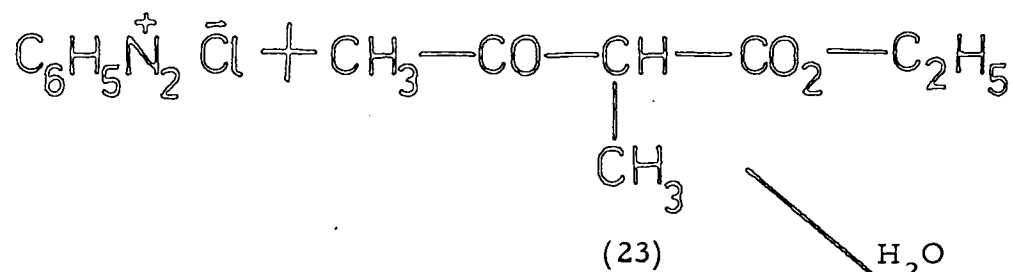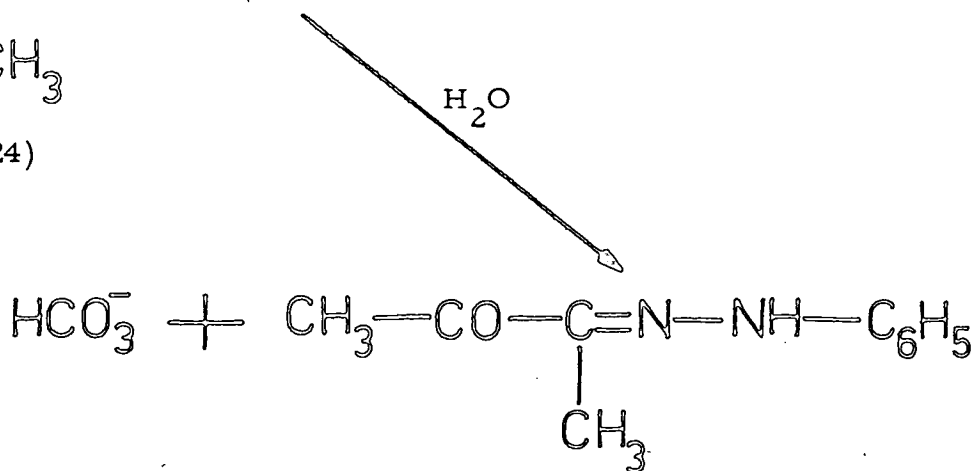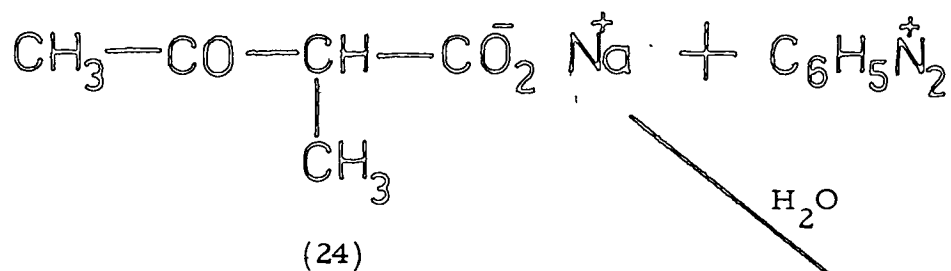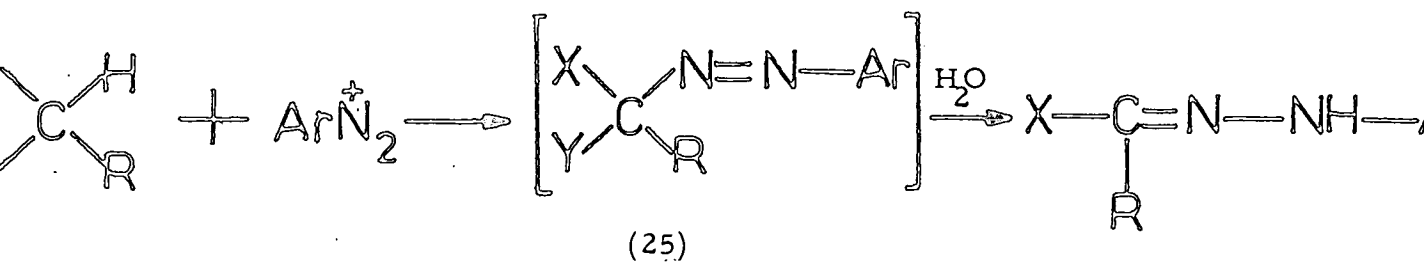
X, Y = electron withdrawing groups)

$$+YOH$$

Scheme 21

coupling of arenediazonium cations with active methylene compounds

is the Japp-Klingemann reaction, a process involving coupling

accompanied by deacylation discovered by Japp and Klingemann[47] when

they attempted to couple benzenediazonium chloride with ethyl 2-

methylacetoacetate (23) (Scheme 19). Subsequently Japp and Klingemann

discovered[48] that if the ester (23) was saponified and the reaction

carried out with the sodium salt (24), the carboxylate function rather

than the acetyl group was lost (Scheme 20). To succeed, the Japp-

Klingemann reaction normally requires two or three electron-withdrawing

groups attached to the methinyl group although the reaction can occur

with only one such group present. The Japp-Klingemann reaction affords

the possibility of preparing hydrazones otherwise inaccessible by

direct coupling with a methylene compound. The reaction can be

generalised as shown in Scheme 21. The intermediate (25) apparently

undergoes solvolysis almost as rapidly as it is formed.

Diazonium cations are known to couple with olefins,[49,50] although

even when the reactive diazonium salt (26) prepared from p-nitroaniline

is used the yields are low (Scheme 22). Intramolecular coupling reactions

with olefins are also known, a classic example being the Widman-Stoermer

synthesis of cinnolines[51-53] (Scheme 23) which allows access to a variety

of cinnoline derivatives (27).

Another type of reaction of arenediazonium cations which is

conveniently considered under the heading of coupling with aliphatic

molecules is the formation of diazoamino compounds. These are com-

pounds which are formed by the coupling of a diazonium cation with

ammonia or a primary or secondary amine to give a compound of the

Scheme 22

Scheme 23

Ar—N=N—NH—Ar $\xrightarrow{\text{H}^+}$ Ar—$\overset{+}{\text{N}}$≡N

(28)   (29)

R

$\cdots$NH

$\downarrow$ -H$^+$

R

Ar—N=N—◯—NH$_2$

(30)

Scheme 24

Ar—$\overset{+}{\text{N}}$≡N $\bar{\text{X}}$

(33)

◯—NH$_2$ ◯—OH

(32)   (34)

pH <7   pH >7

Ar—N=N—◯—NH$_2$ Ar—N=N—◯—OH

(31)   (35)
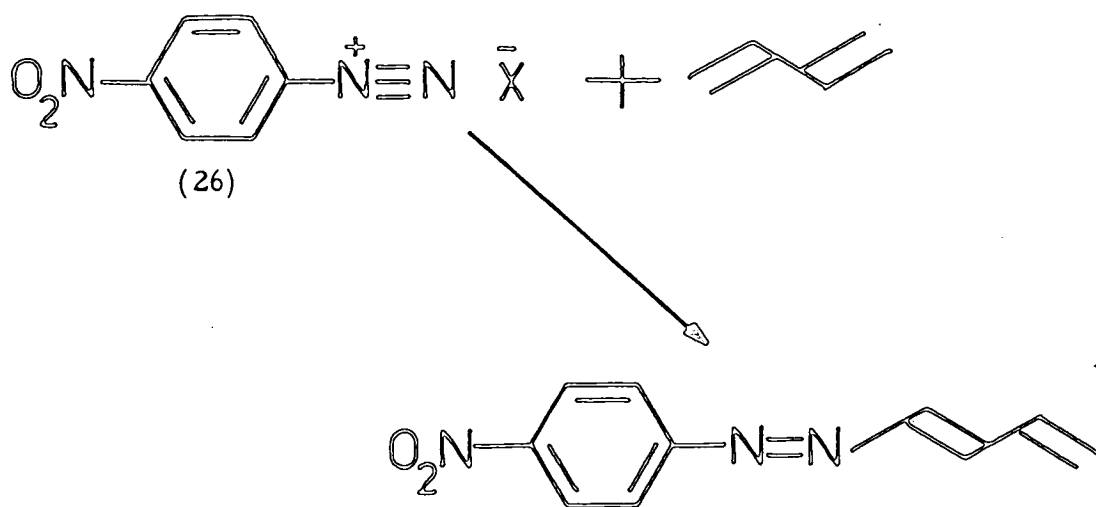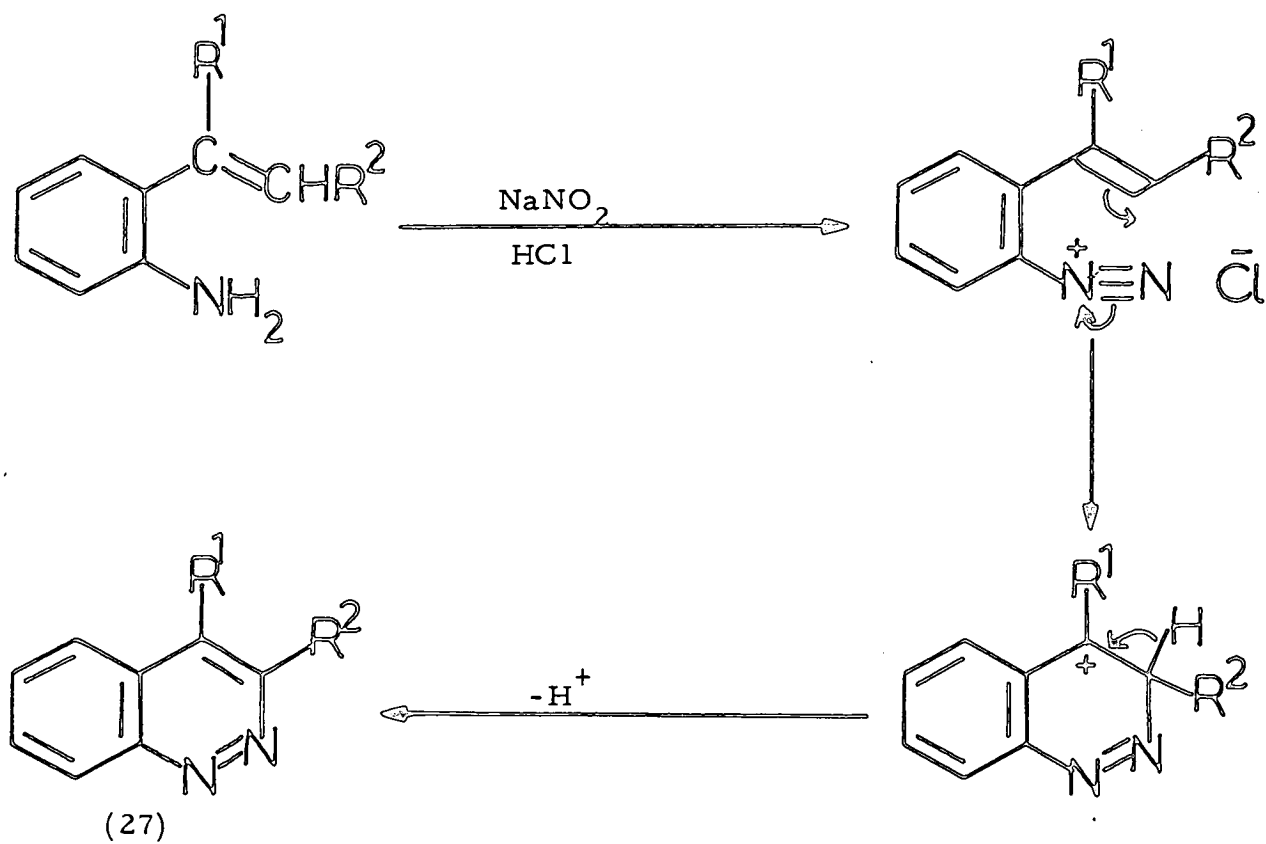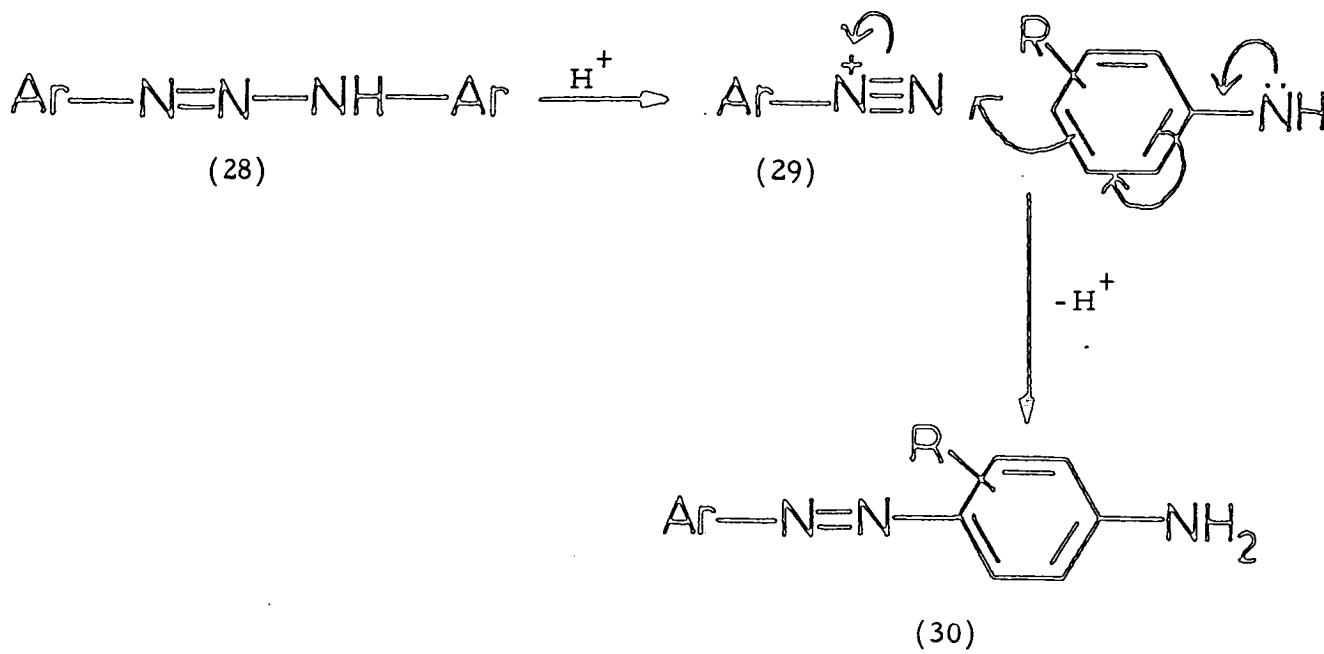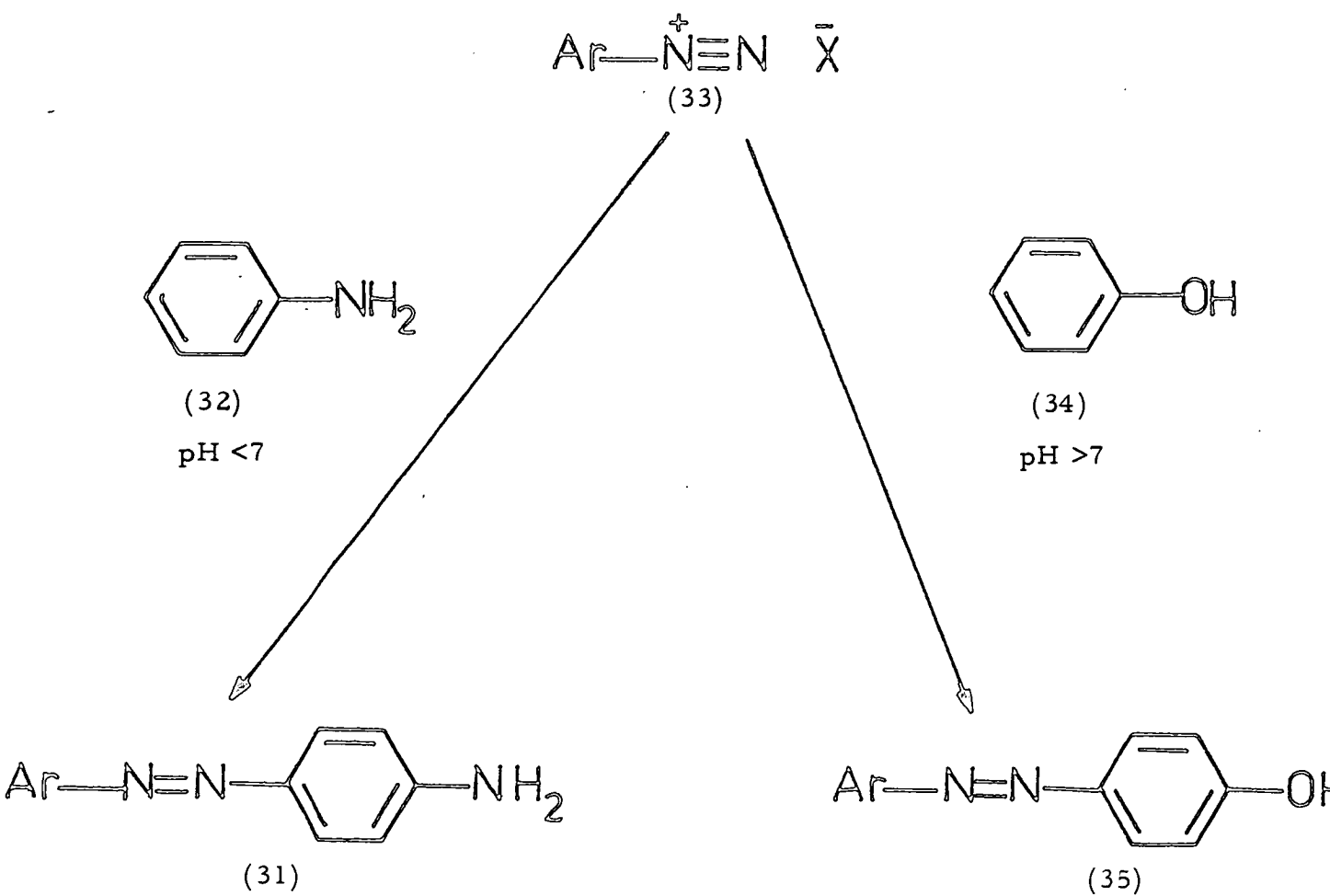
Scheme 25

general formula $ArN=N-NR_1(R_2)$, a derivative of the unknown parent compound triazene ($HN=N-NH_2$). Diazoamino compounds can be prepared from aniline or substituted anilines by diazotising with a deficiency of acid in the reaction mixture.[54] However the diazoamino compounds (28) are not stable under acidic conditions and can rearrange via the arenediazonium cations (29) to the isomeric aminoazo compounds[55] (30) (Scheme 24). Formation of diazoamino compounds from nitrosamines will be discussed later.

Diazonium cations will couple readily with aromatic molecules which are activated towards electrophilic substitution. It is therefore necessary for efficient coupling that the aromatic molecule has an electron releasing group attached to the ring. Both the hydroxyl and amino groups are electron releasing and will activate an aromatic nucleus in the ortho and para positions but coupling normally occurs preferentially at the para position. It is important to control the pH of the medium in which coupling takes place. Phenol (34) for example couples most efficiently (Scheme 25) with diazonium cations (33) under mildly alkaline conditions as the phenoxide ion is more strongly activated towards electrophilic substitution than phenol itself. In contrast aniline (32) couples most readily with diazonium cations (33) under mildly acidic conditions. More strongly acidic conditions would result in protonation of the aniline, and the resulting anilinium cation is not sufficiently activated towards electrophilic substitution for coupling to occur. Coupling of arenediazonium salts (33) with phenols and arylamines occurs readily giving azo products [e. g. (31) and (35)] many of which are valuable as dyestuffs.

(36)

−H$^+$

(37)

Scheme 26

(38)

+H$^+$

−H$^+$

(39)

(40)

(41)
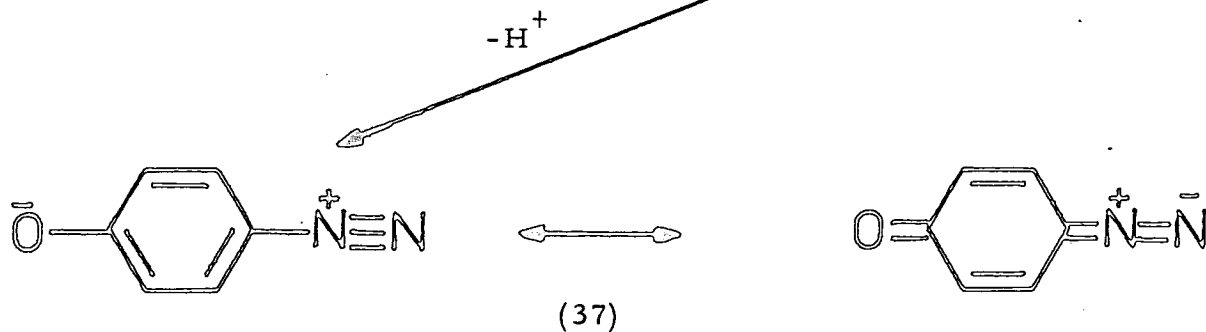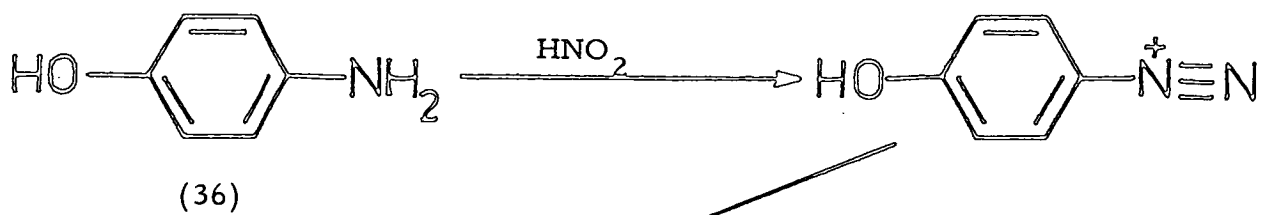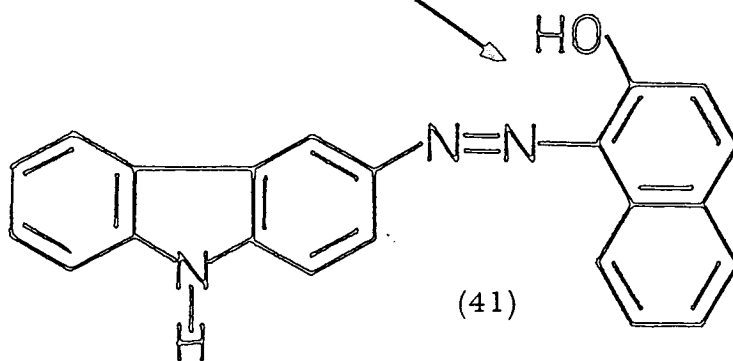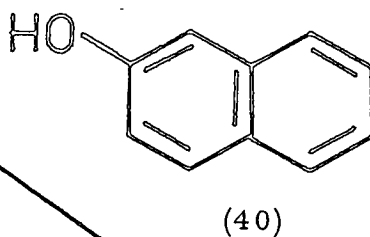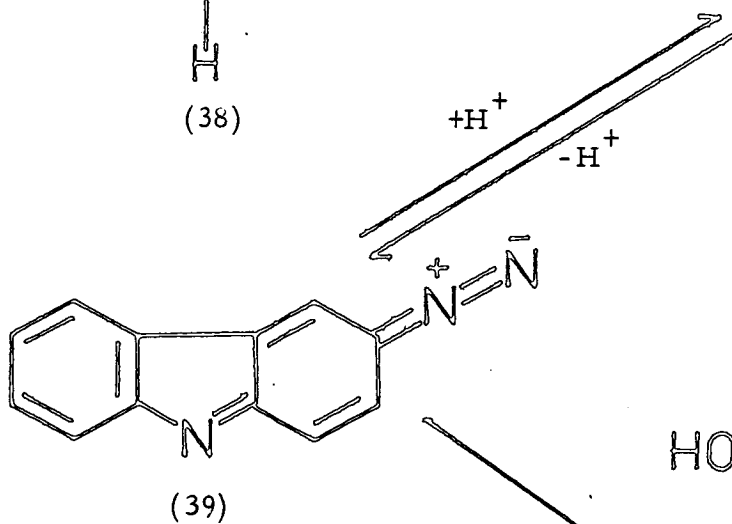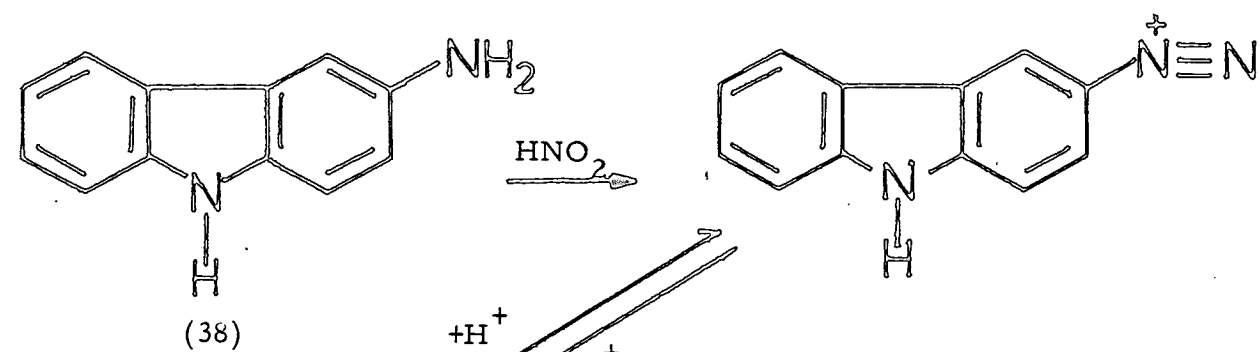
Scheme 27

The diazotisation of arylamines which contain an acidic proton affords the possibility of forming diazo compounds by deprotonation of the initially formed diazonium salt. For example the diazotisation (Scheme 26) of p-hydroxyaniline (36) under mildly acidic conditions[56] yields the diazo compound (37). The diazotisation of 3-aminocarbazole (38) and subsequent treatment of the diazonium solution with strong alkali gives the diazo compound (39) as an unstable red solid which couples instantly with β-naphthol (40) to give the azo compound (41) (Scheme 27).

(b)   Hetaryldiazonium Salts

Since the diazotisation of heterocyclic primary amines has not been studied to anything like the same extent as arylamines the literature on hetaryldiazonium salts is fairly limited. Many heterocyclic primary amines can be diazotised in the same manner as arylamines to give diazonium salts which display the familiar range of reactions. However many heterocyclic amines are less basic than arylamines and consequently are more difficult to diazotise. Additionally their diazonium salts do not exhibit the same sort of reactivity as arenediazonium salts. Although the diazotisation process for heterocyclic amines (Scheme 28) is the same as that for arylamines, it is occasionally possible to isolate certain of the intermediates such as the nitrosamine (42) and the N-hydroxy-azo compound (43).

The diazotisation of six-membered heterocyclic primary amines will be considered initially since the isolation of the intermediates in the diazotisation process has not been successful and the chemistry of six-

| (44) | (45) | (46) | (47) |

$$ArNH_2 \xrightarrow{\text{HONO}} Ar\overset{+}{N}H_2NO \overset{H^+}{\rightleftharpoons} ArNHNO$$

(42)

$$Ar\overset{+}{N_2} \ \overset{-}{X} \ \rightleftharpoons \ ArN=NOH$$

(43)
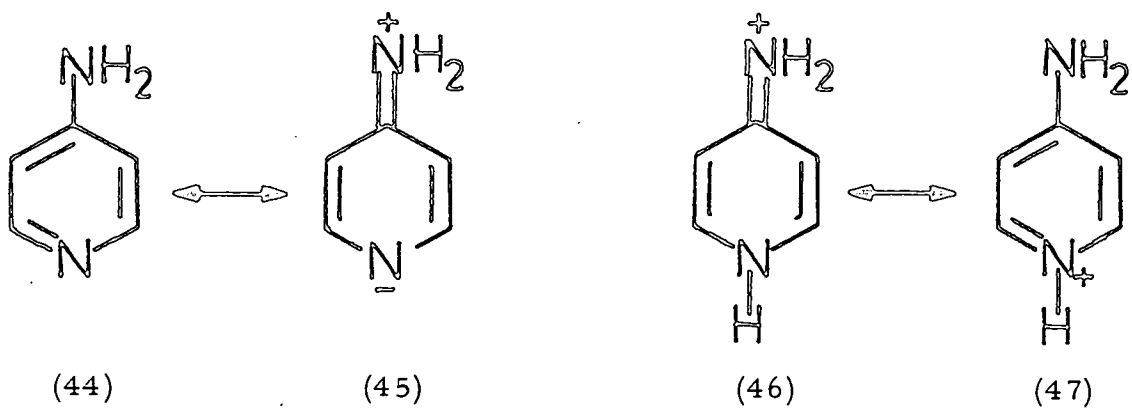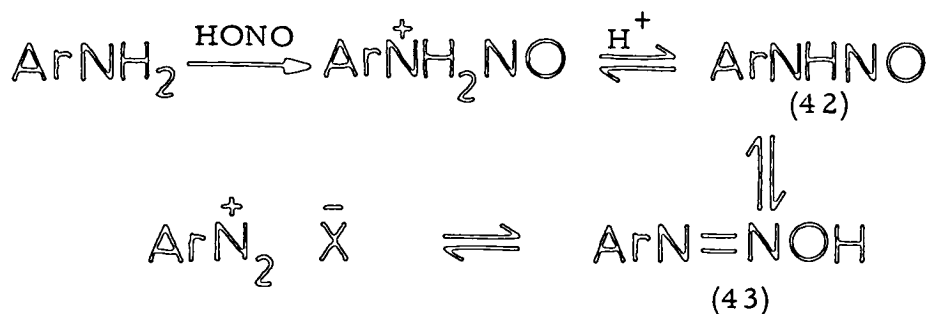
<u>Scheme 28</u>

membered hetaryldiazonium salts is broadly similar to that of

arenediazonium salts.

3-Aminopyridine is readily diazotised in dilute mineral acids

and behaves like a normal aromatic amine forming diazonium salts

which undergo orthodox coupling reactions.[57] The diazotisation of 2-

aminopyridine and 4-aminopyridine is more difficult to achieve and

normally requires the use of concentrated acidic media. It is possible

to diazotise these amines in dilute mineral acids but the resulting

diazonium salt solution must be quickly added to alkaline β-naphthol in

order to trap the diazonium cation as an azo dyestuff.[58] Diazonium

salts formed from 2- and 4-aminopyridines have a great tendency to

decompose giving the corresponding hydroxy compounds (or the halogeno

compounds where halogen acids are used).[59] The lower reactivity of

2-amino and 4-aminopyridines towards diazotisation can be explained

by the base weakening effect of the heterocyclic nitrogen atom. If

4-aminopyridine (44) is taken as an example (Scheme 29), the contribution

of the canonical form (45) which will not readily nitrosate at the amino

group will inhibit diazotisation. Additionally the possibility of protona-

tion of the ring nitrogen atom at the pH of the reaction, affording contri-

buting canonical forms (46) and (47), will also inhibit nitrosation of

the amino group and hence the diazonium process. Diazotisation of

(48)   (49)   (50)

(51)   (52)

Scheme 30

(53)

$$[X = O, S, NH, CH_2]$$

(54)

Scheme 31

(55) (R=H, Me)

(56)

(57)
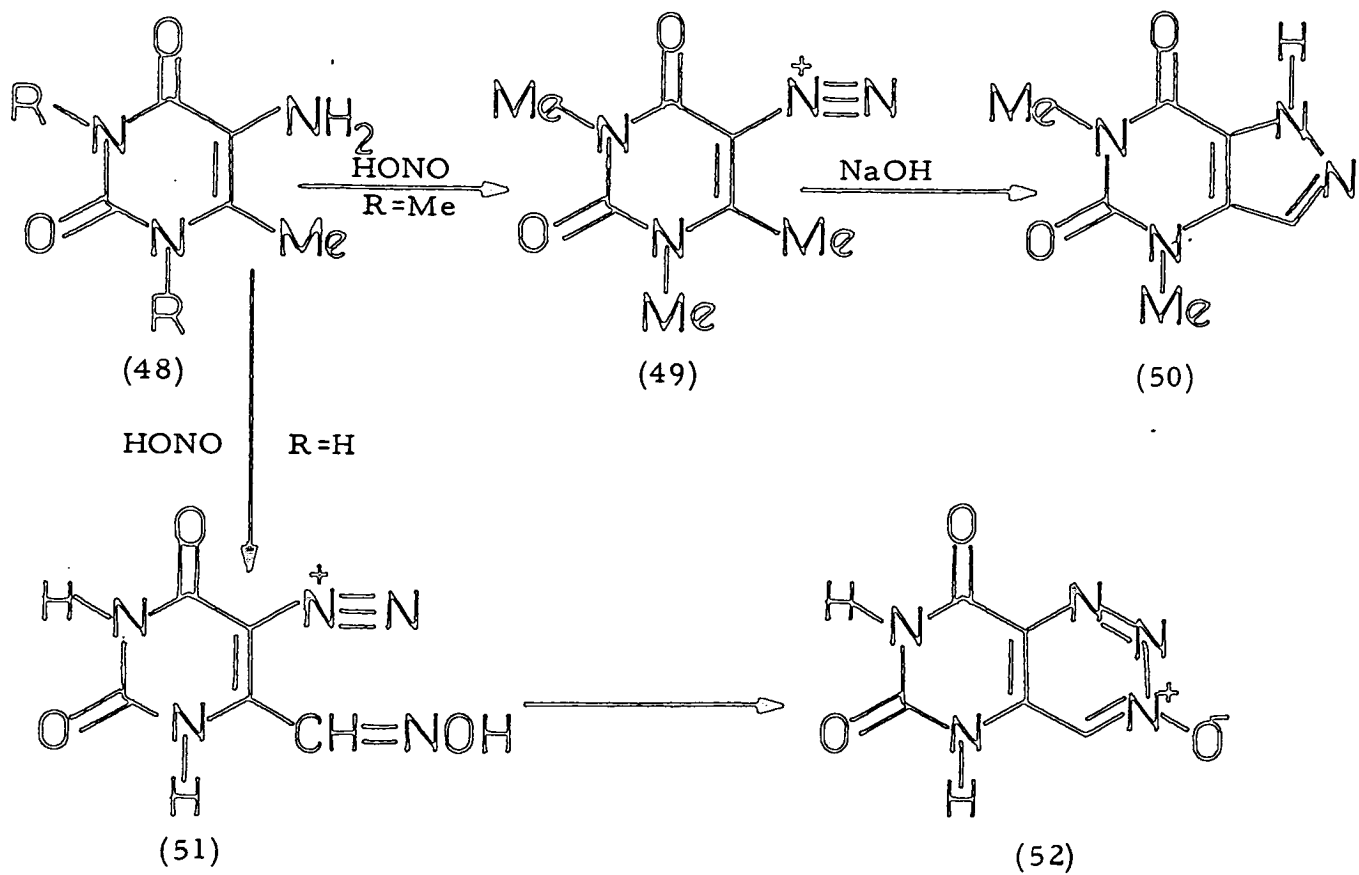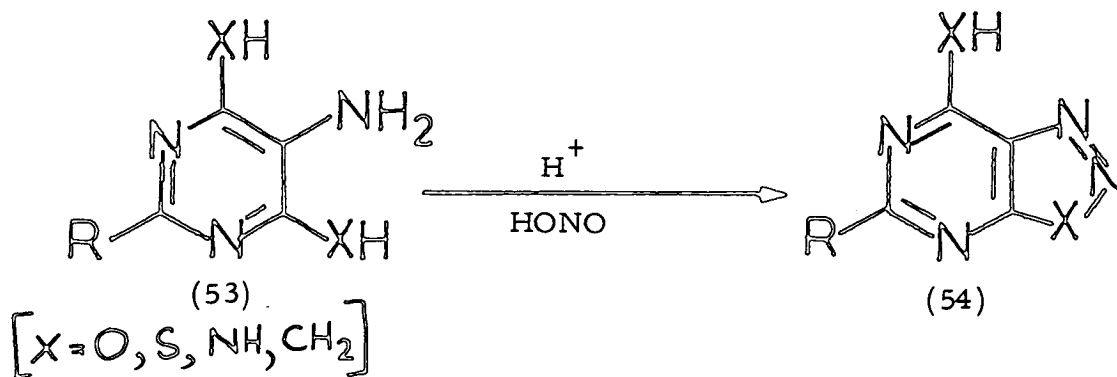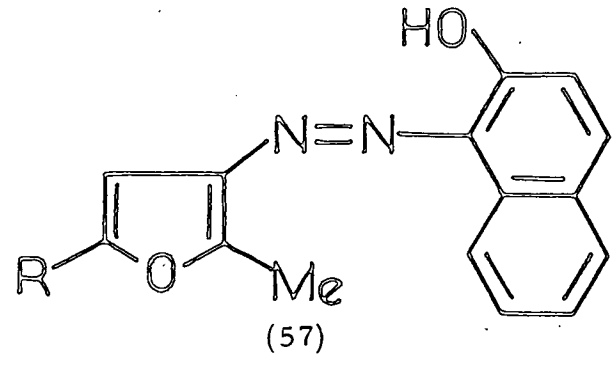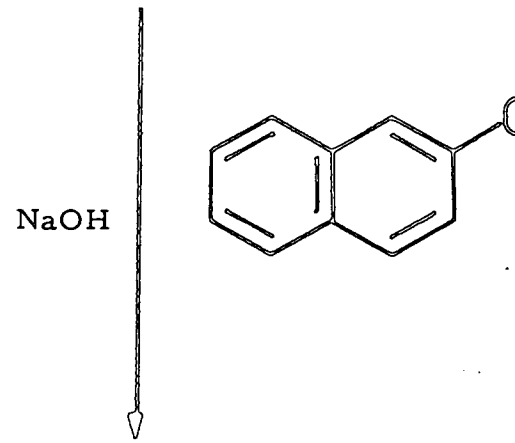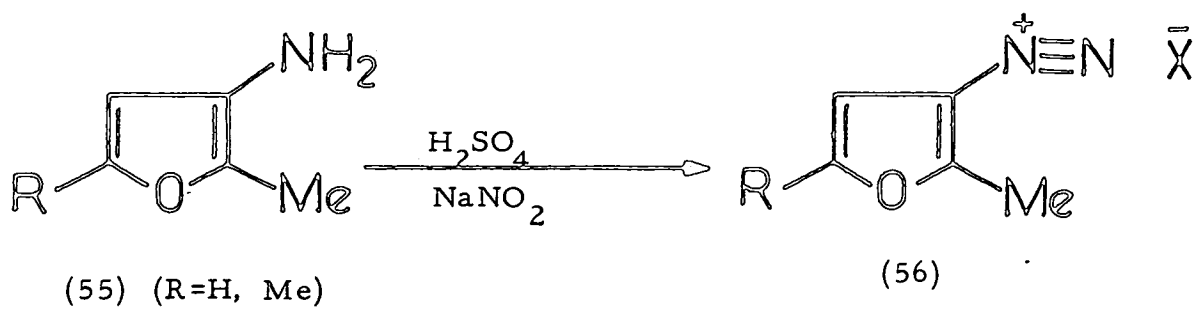
Scheme 32

many other substituted aminopyridines using either halogen acids or fluoroboric acid has been used to prepare many halogeno pyridines.[57] Some work recently carried out on aminopyrimidines gave similar results to those already discussed for aminopyridines. 4-Amino-pyrimidines, in which the amino group is both α and γ to an sp^2 nitrogen atom, cannot be diazotised;[60-62] instead they tend to undergo nitrosation at the most reactive C(5) position. 5-Aminopyrimidine has been reported[63] not to give a diazonium salt but certain substituted 5-aminopyrimidines are readily diazotised.[64] For example, diazotisation of 1,3,6-trimethyl-5-aminouracil (48; R=Me) gives the corresponding diazonium salt (49) which can be cyclised to the pyrazolopyrimidine (50) with strong base (Scheme 30).[65] In contrast, treatment of 5-amino-6-methyluracil (48; R=H) with excess of nitrous acid in acetic acid gives the pyrimidotriazine N-oxide (52) via a route which is believed to involve the diazonium cation (51). In general a range of fused pyrimidine derivatives (54) can be prepared from suitably substituted 5-amino-pyrimidines (53) (Scheme 31). By this method 1,2,3-oxadiazolo-, 1,2,3-thiadiazolo- and 1,2,3-triazolopyrimidines can be prepared. In the case where $X=CH_2$, alkaline conditions are required for successful cyclisation.[57]

Not a great deal of work has been carried out into the diazotisation of non-azole heterocyclic amines owing to the limited amount of stable examples available. Diazotisation of 3-aminofurans (55) is achieved[66] with sodium nitrite in dilute sulphuric acid and the diazonium salts (56) can be successfully coupled with β-naphthol to give the azo compounds (57) in high yields (Scheme 32). However coupling reactions
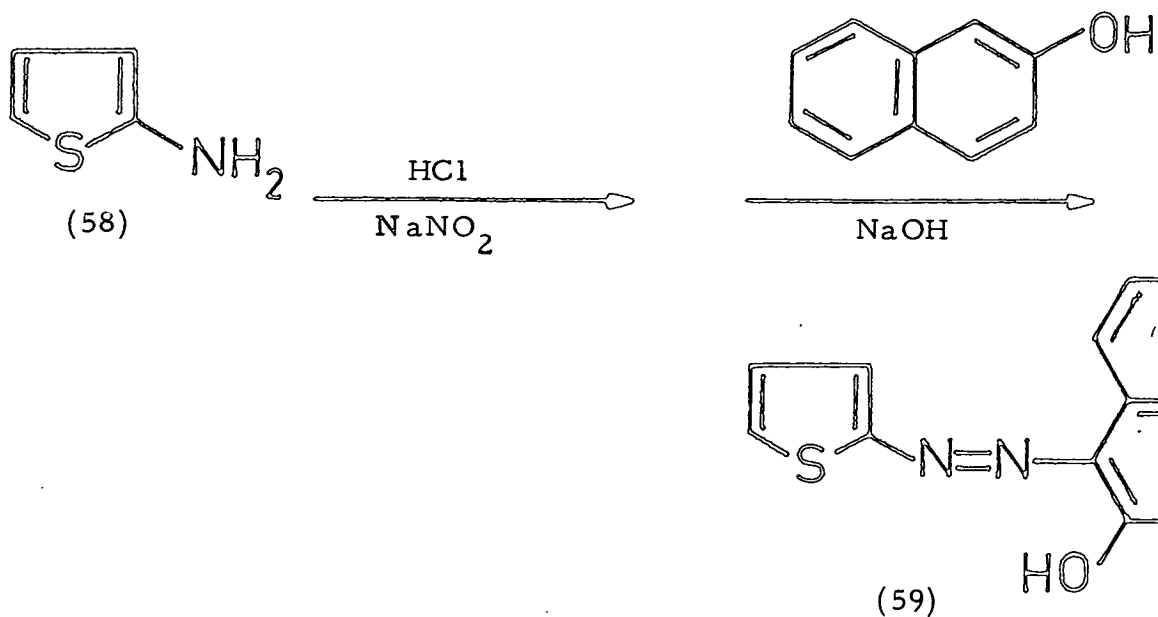
Scheme 33
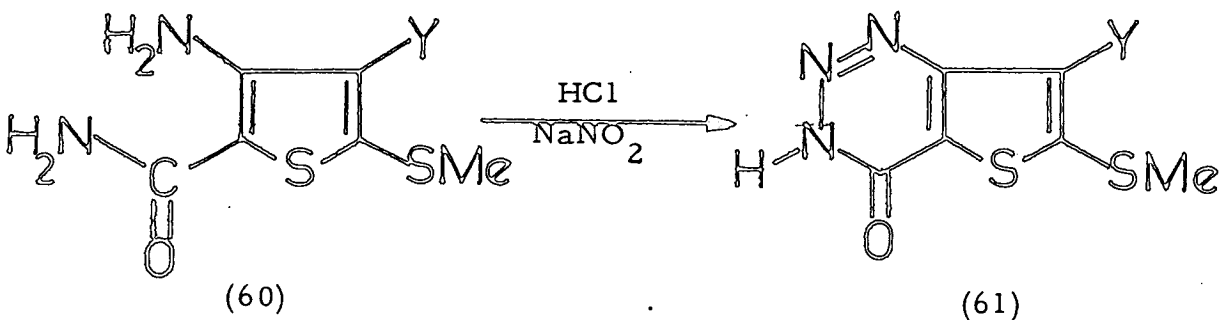
Scheme 34
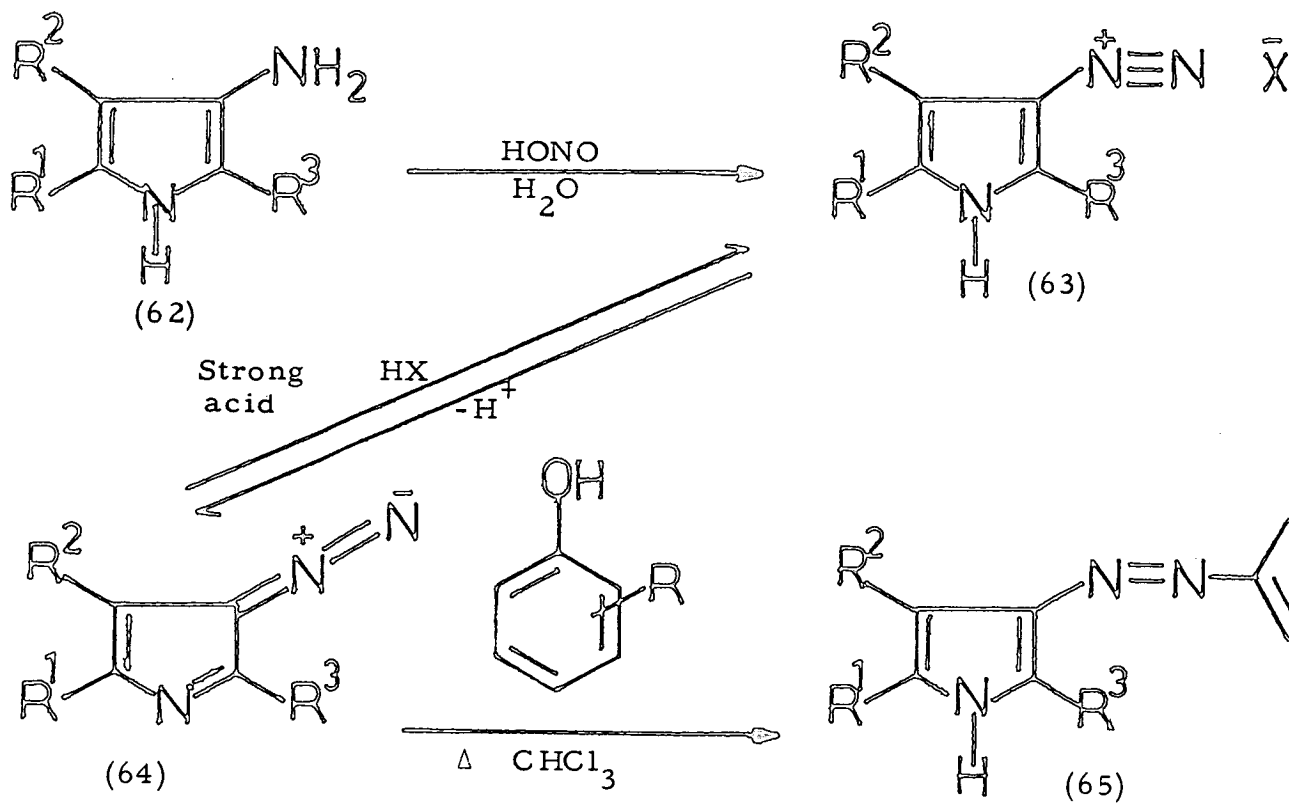
Scheme 35

of furan-3-diazonium salts with other activated arenes have not given azo compounds. Dediazoniation reactions of furan-3-diazonium salts have also failed.

2-Aminothiophene (58) can be successfully diazotised in 10% hydrochloric acid with sodium nitrite and coupled with a range of activated arenes to give the azo compounds,[67,68] useful as dyestuffs [e.g. (58) → (59)] (Scheme 33). Diazotisation of 3-aminothiophene-2-carboxamides (60) in concentrated hydrochloric acid is reported[69] to give the thieno-1,2,3-triazines (61), presumably by cyclisation of the diazonium cation (Scheme 34).

Diazotisation of 3-aminopyrroles (62), where the ring nitrogen atom carries a proton, in dilute acidic media gives the diazo compounds (64)[70] directly (Scheme 35). The mechanism involves deprotonation of the diazonium cation (63). 3-Diazopyrroles (64) are stable yellow solids provided that they are not exposed to heat or light. They are soluble in organic solvents and exhibit the characteristic diazo peak in the infra-red spectrum (2080-2180 cm^{-1}). 3-Diazopyrroles (64) will give the diazonium salts (63) on treatment with strong acids. 3-Diazopyrroles will not couple with phenols under normal conditions but if they are refluxed with phenols in a solvent such as chloroform, then azo compounds (65) can be prepared[70] (Scheme 35). The coupling reaction is presumably initiated by proton transfer from the phenol to the diazo compound. 2-Diazopyrroles also exist but are less stable than 3-diazopyrroles. Diazo-indoles are very similar in properties to diazopyrroles. The diazotisation of ring N- substituted amino-pyrroles can be effected in hydrochloric acid[57] and the diazonium salts
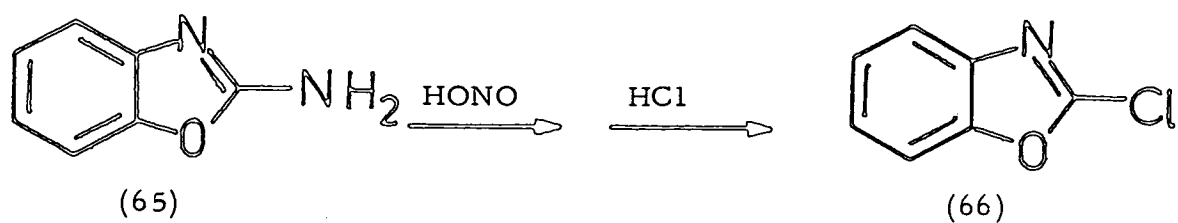
Scheme 36
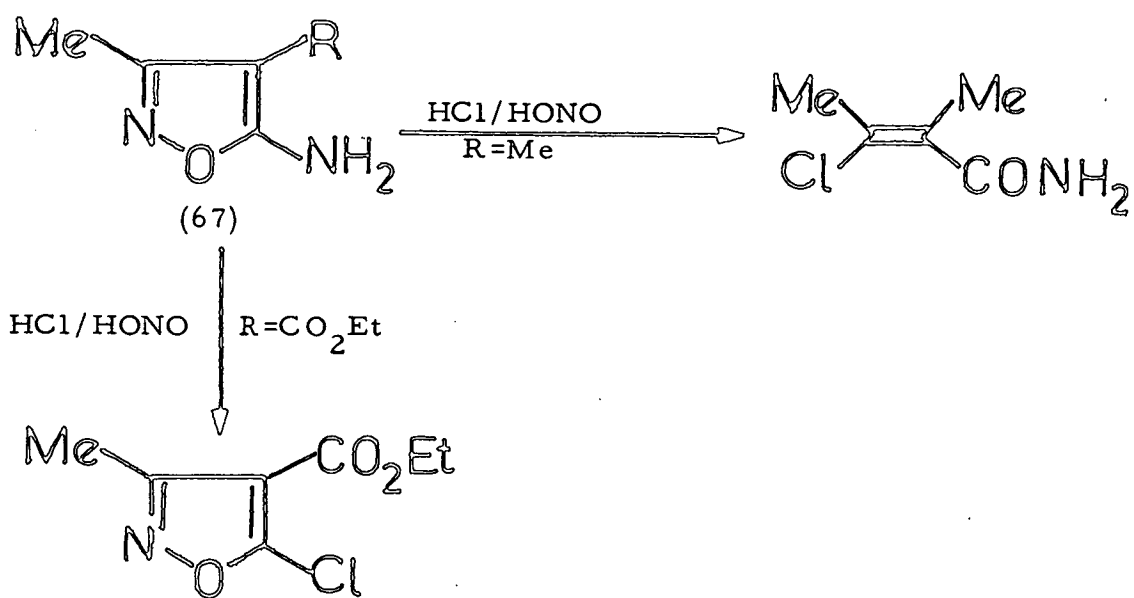
Scheme 37
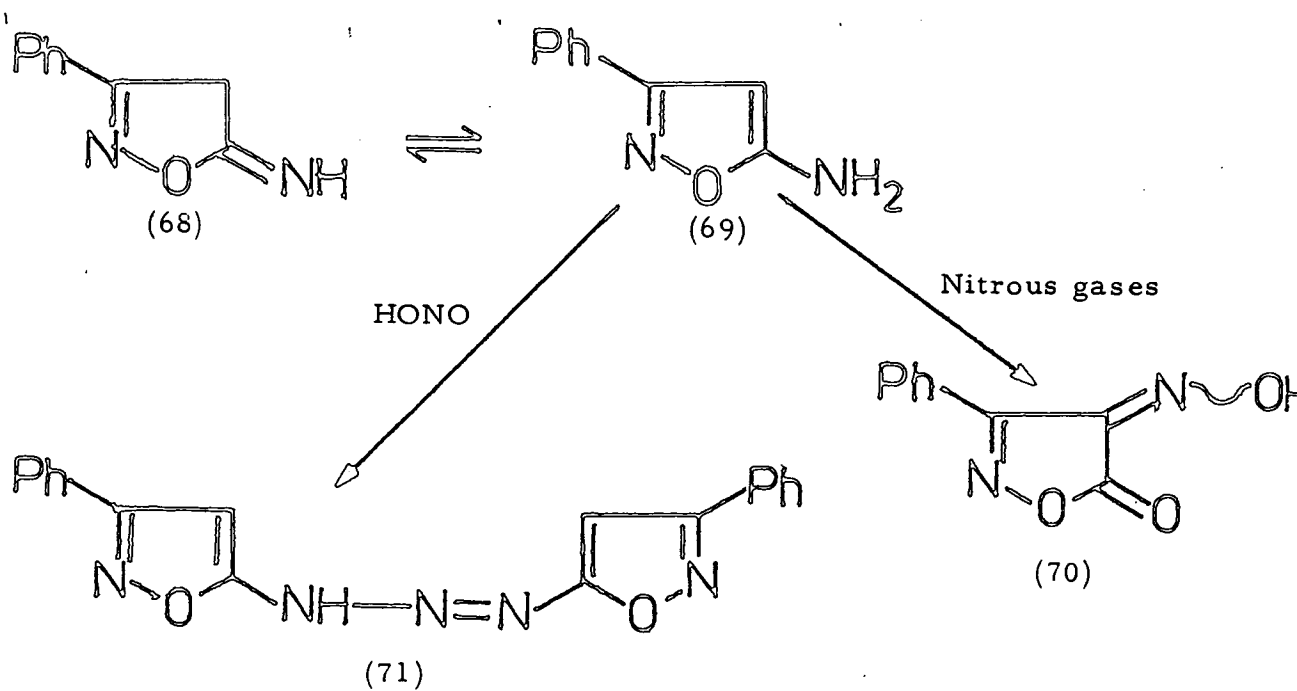
Scheme 38

formed in solution undergo nitrodediazoniation and hydrogenodediazo-niation. Some evidence of coupling in situ has also been obtained.[57]

The diazotisation of 2-aminobenzoxazole (65) gives products which cannot be isolated. However treatment of the diazonium solution with concentrated hydrochloric acid gives 2-chlorobenzoxazole (66)[71] (Scheme 36).

The results of diazotising 5-amino-3-methylisoxazoles (67) in a large excess of hydrochloric acid have been shown to depend on the nature of the substituent at the C(4) position[72] (Scheme 37). The reactions of 5-amino-3-phenylisoxazole with nitrosating agents have been studied by Musante[73] and Quilico.[74] Musante treated an alcoholic solution of 5-amino-3-phenylisoxazole (69) with nitrous gases to afford 3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (70) (Scheme 38). Quilico has reported (70) as the principal product obtained on treating the amine (69) with nitrous acid, together with the diazoamino compound (71). The reactions of 5-amino-3-phenylisoxazole (69) can be partly explained by the tautomerism of (69) to the imino form (68). Studies by Vernin and Metzger[75] on the aprotic diazotisation of 5-amino-3,4-dimethyl-isoxazole (72) in the presence of amyl nitrite show clearly that the 5-isoxazolyl radical (75) must be involved. It is believed that the radical (75) could arise from either the diazonium salt (73) or the N-hydroxy-azo compound (74) (Scheme 39). Decomposition of the diazonium salt (73) in arene or heterocylic solvents gives the product (76) in a pseudo-Gomberg type reaction. The 5-iodo compound (77) has been prepared from the diazonium salt (73) by reaction with molecular iodine. Hydrogenodediazoniation of the diazonium salt
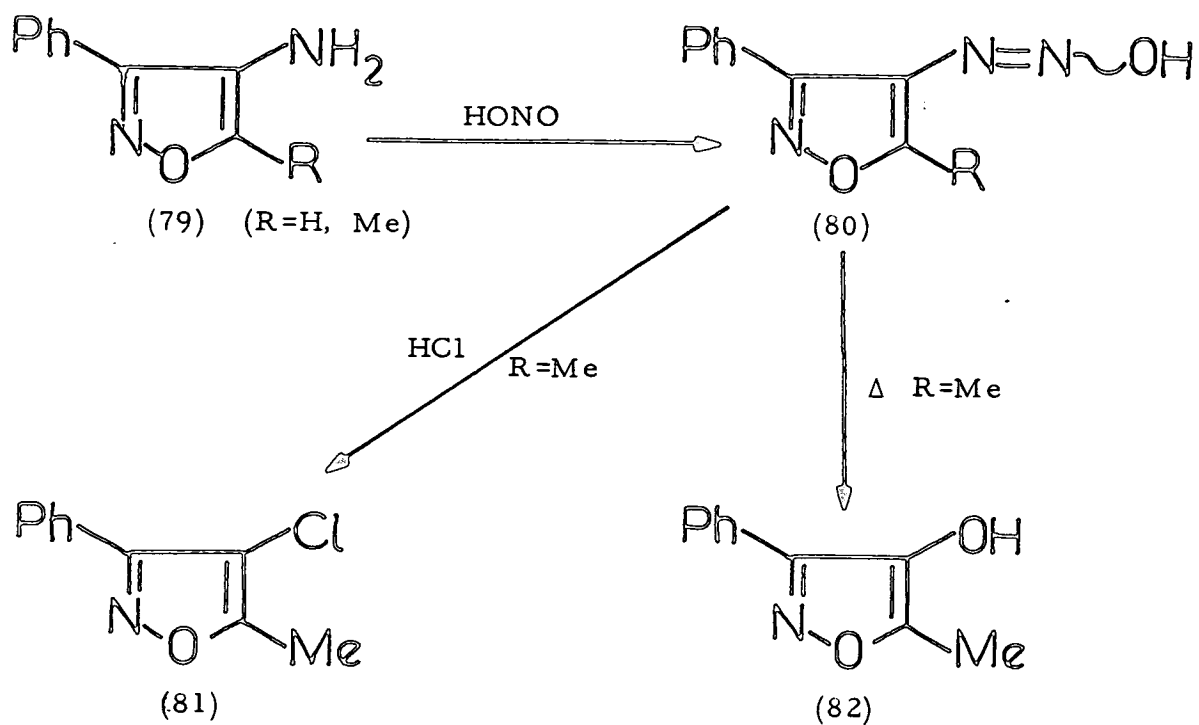
Scheme 40

(73) using copper and ethanol can also be accomplished to give 3,4-dimethylisoxazole (78). Diazotisation of 4-amino-3-phenylisoxazoles (79) has been reported[76,77] to give the unstable diazo compounds which are believed to have the N-hydroxy-azo structure (80) (Scheme 40). Treatment of this unstable species (80, R=Me) with concentrated hydrochloric acid gives the 4-chloro compound (81). Direct heating of (80, R=Me) gives the 4-hydroxy compound (82).

It is instructive to consider the isolation of primary nitros-amines (84) and N-hydroxy-azo compounds (86) on diazotisation of heterocyclic primary amines. Theoretically the products of diazotisation of the amine (83) could exist in any of the forms (84)-(88) (Scheme 41). Structure (85) can be ruled out by spectroscopic data.[57] The attempted isolation of primary nitrosamines on diazotisation of carbo-cyclic aromatic amines has not been successful.[57] There is evidence that some examples of this class of compound can be isolated by acidification of basic solutions of benzenediazotates containing an electron-withdrawing para group.[78] However the compounds formed were unstable, only available in an impure state and positive structure determination was impossible. Some primary nitrosamines[79] can be prepared from substituted anilines on treatment with nitrosyl chloride at -78°C in an anhydrous medium under nitrogen. It is therefore quite surprising that stable primary nitrosamines can be prepared from heterocyclic amines under normal diazotisation conditions and their isolation is good evidence for the participation of the nitrosamine as an intermediate in the diazotisation process. There are several factors which seem to influence the formation of nitrosamines and N-hydroxy-

Scheme 41

(89)
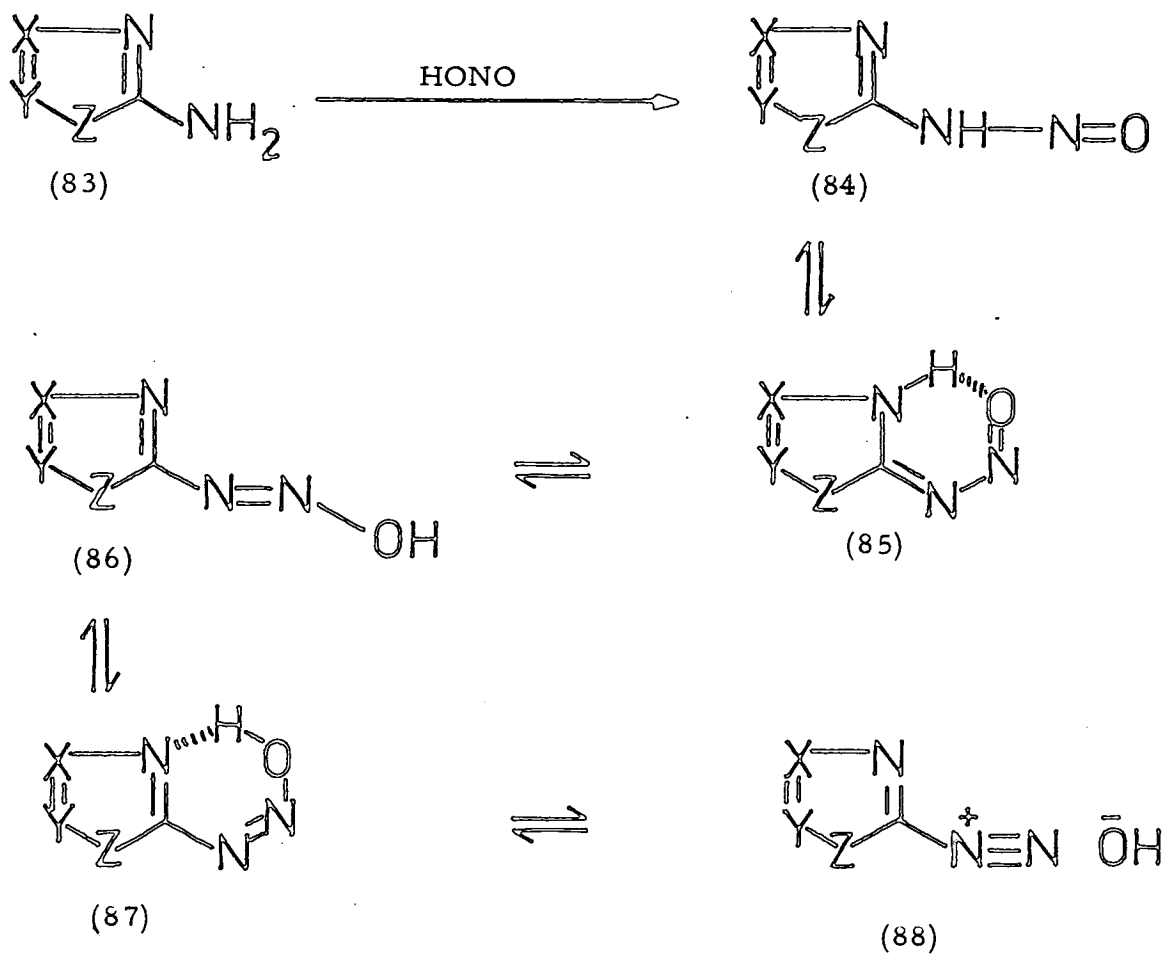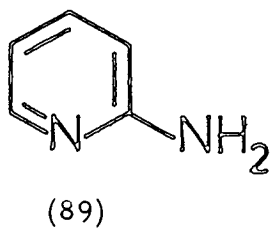
azo compounds. Firstly, dilute acidic diazotisation media favour

nitrosamine and N-hydroxy-azo formation, whereas concentrated

acidic conditions favour diazonium salt formation. Secondly, amines

containing electron-withdrawing groups and electron-withdrawing rings

favour nitrosamine and N-hydroxy-azo formation. This can probably

be explained by resonance stabilisation of the nitrosamines (see later)

and the destabilising effect electron-withdrawing groups and rings can

have on the diazonium cation (88). Thirdly, amines containing labile

ring protons favour diazonium salt formation. Fourthly, the presence

of an amino group adjacent to a ring nitrogen atom favours N-hydroxy-

azo formation because hydrogen bonding can stabilise the syn form

of the N-hydroxy-azo compound (87). The factors which favour nitrosamin

formation can be rationalised by considering that the diazotisation

process for heterocyclic amines will stop at structure (87) and con-

sequently an N-hydroxy-azo compound or nitrosamine will be isolated,

if satisfactory hydrogen bonding can stabilise (85) or (87). However

if the reaction medium is too acidic, protonation of the nitrosamino

group or heterocyclic ring will disrupt the hydrogen bonding. Similarly

the presence of a labile proton on the heterocyclic ring will disrupt

hydrogen bonding. This argument is fairly convincing, but it is worth

considering that many six-membered heterocyclic amines, such as

2-aminopyridine (89), satisfy the above criteria for nitrosamine formation.

However, neither nitrosamines nor N-hydroxy-azo compounds can be

isolated on diazotising six-membered heterocyclic amines and if they

are formed they must be very unstable. Perhaps six-membered hetero-

cyclic amines do not form nitrosamines or N-hydroxy-azo compounds

on diazotisation simply because they are more basic than five membered

heterocyclic amines and that even in weakly acidic media the hetero-

cyclic nuclei are still protonated, making stabilisation of the syn-N-

hydroxy-azo tautomers by hydrogen bonding impossible.

The diazotisation of 2-aminothiazole in dilute acid[80,81] gives

an unstable compound believed to be the N-hydroxy-azo derivative,

which on treatment with concentrated hydrochloric acid affords 2-

chlorothiazole. The diazotisation of 2-aminothiazole and 2-amino-

benzothiazole in concentrated hydrochloric acid gives the 2-chloro

compounds directly.[80,82] 2-Aminothiazoles and 2-aminobenzothiazoles

can be diazotised in strong acids such as nitric, sulphuric or

phosphoric[80,83] giving diazonium salts which can be coupled with

activated arenes[83] and acetylacetone to give azo compounds and

hydrazones respectively (Scheme 42). Treatment of the thiazole-2-

diazonium cation (90) with copper powder results in dediazoniation to

give thiazole (91)[84] (Scheme 42). However a wide range of dediazo-

niation reactions of 3,4-disubstituted thiazole-2-diazonium fluoroborates

(92) has been achieved[85-90] (Scheme 43). Copper catalysis is

required for chlorodediazoniation. The azide group has also been

introduced into the C(2) position, of the thiazole ring but the product

isolated is the thiazolotetrazole (93).[85,86] Recently[91] diazotates

and nitrosamines have been obtained as solvolysis products of benzo-

thiazole-2-diazonium fluoroborates. Treatment of the diazonium

salts with dilute hydroxide gives the diazotates in 5-18% yields, which

on subsequent acidification with 50% acetic acid afford the nitrosamines

quantitatively. The diazotisation of 2-aminothiazoles (94) under

Scheme 42

(92) (R^1, R^2=alkyl, aryl)   (X=F, Cl, Br, I, SCN, NO$_2$)

(93)

Scheme 43

i AmONO

(94)

(95)

(96)

Scheme 44

BF$_4^-$

(98)

OH

HO

N=N

(97)

HCl, Cu$_2$Cl$_2$

Cl

(99)

Scheme 45

(100) (R=CO₂Et, CN)

(101)

(102)

(103)

(104)

Scheme 46

(105) (R=H, Me)

(106)

(107)

(108)

(109)
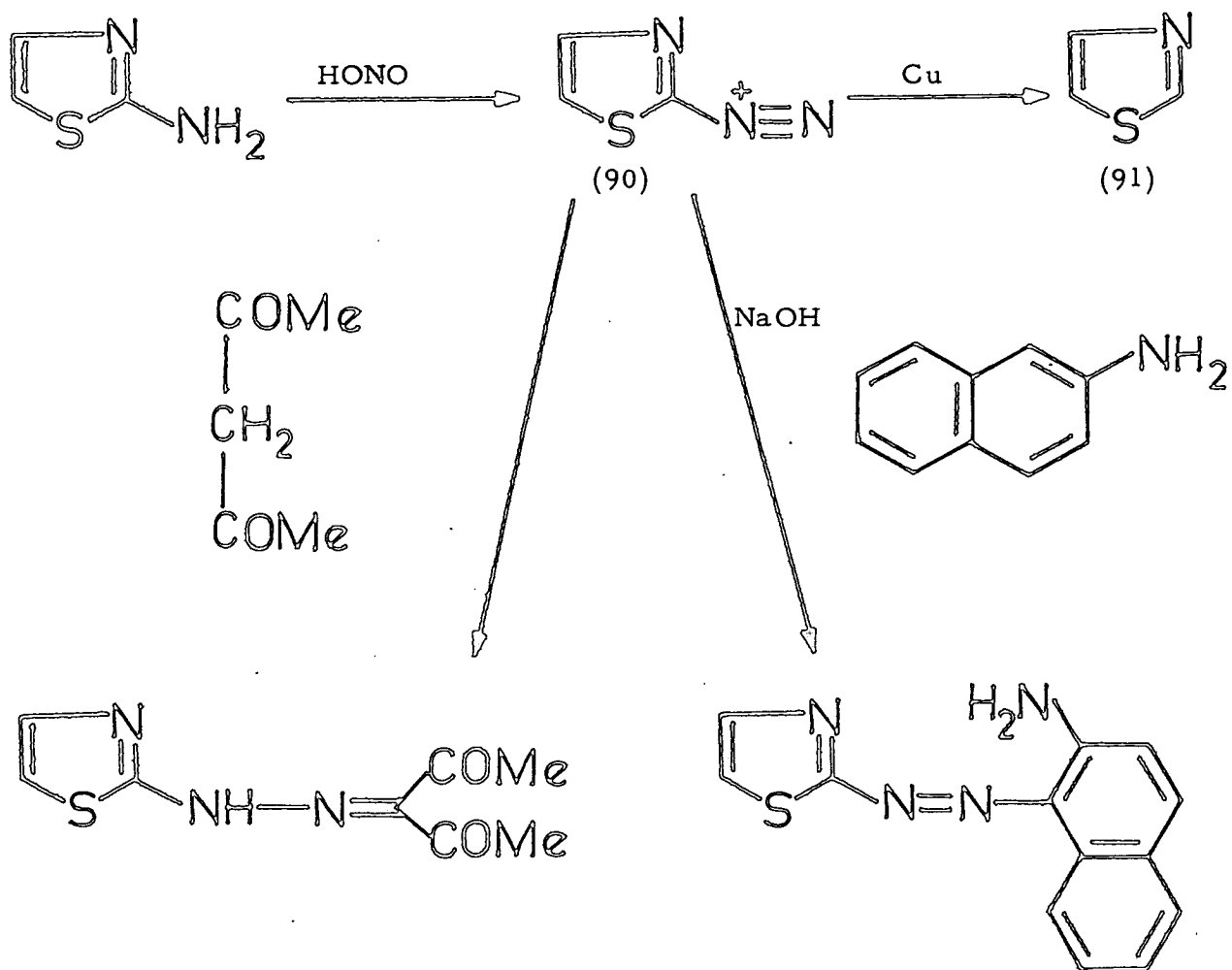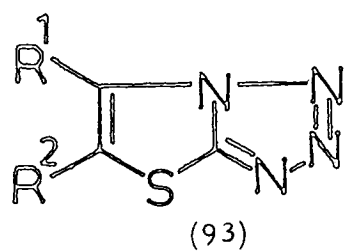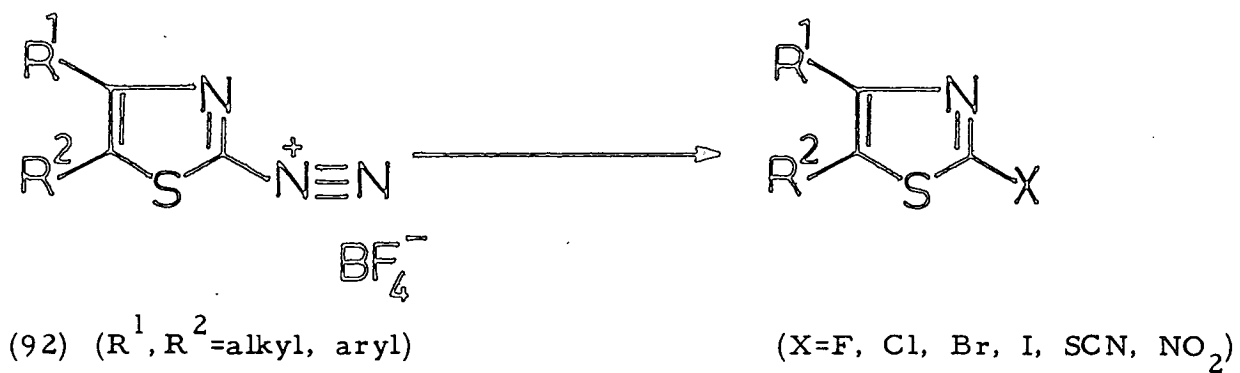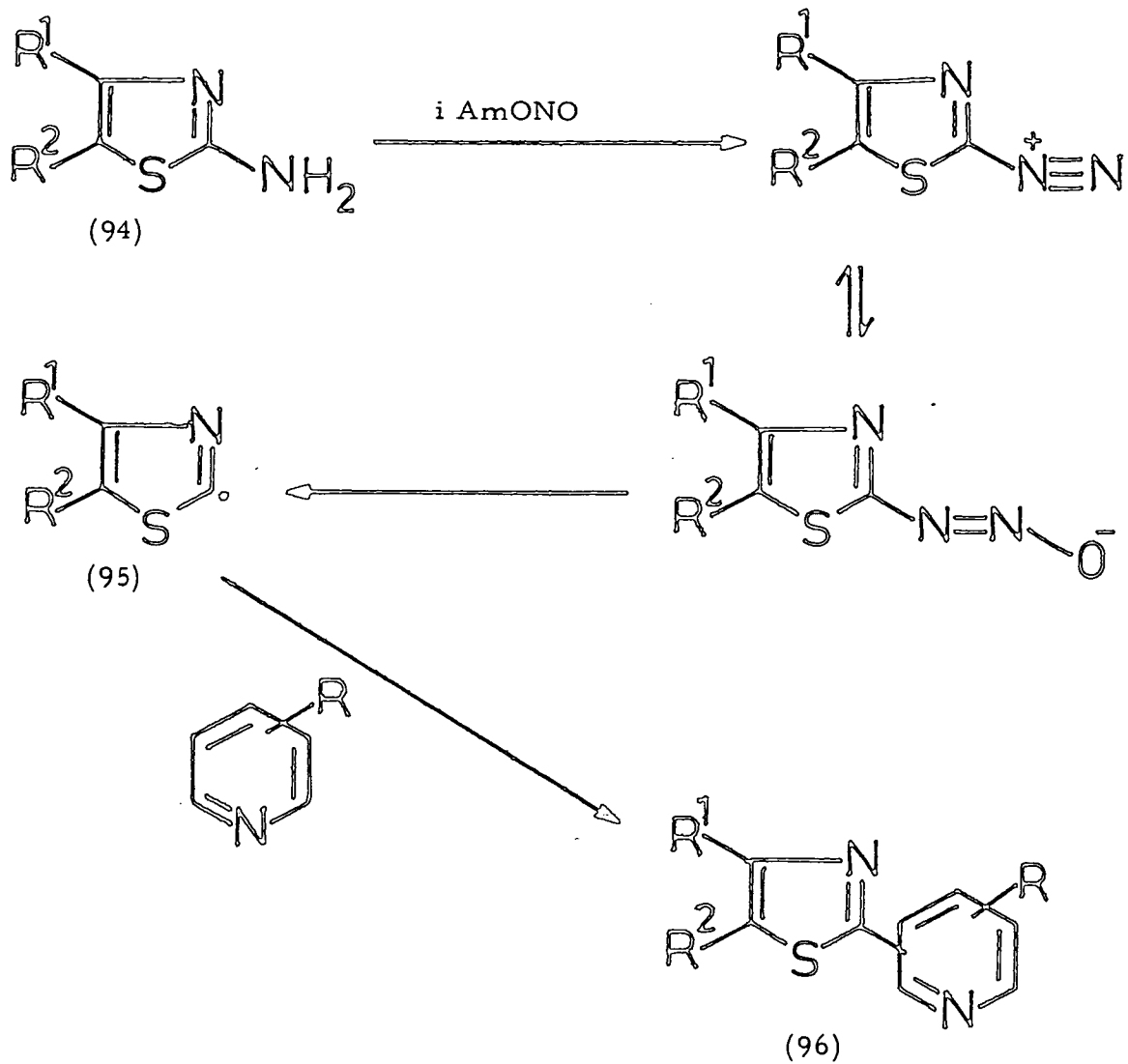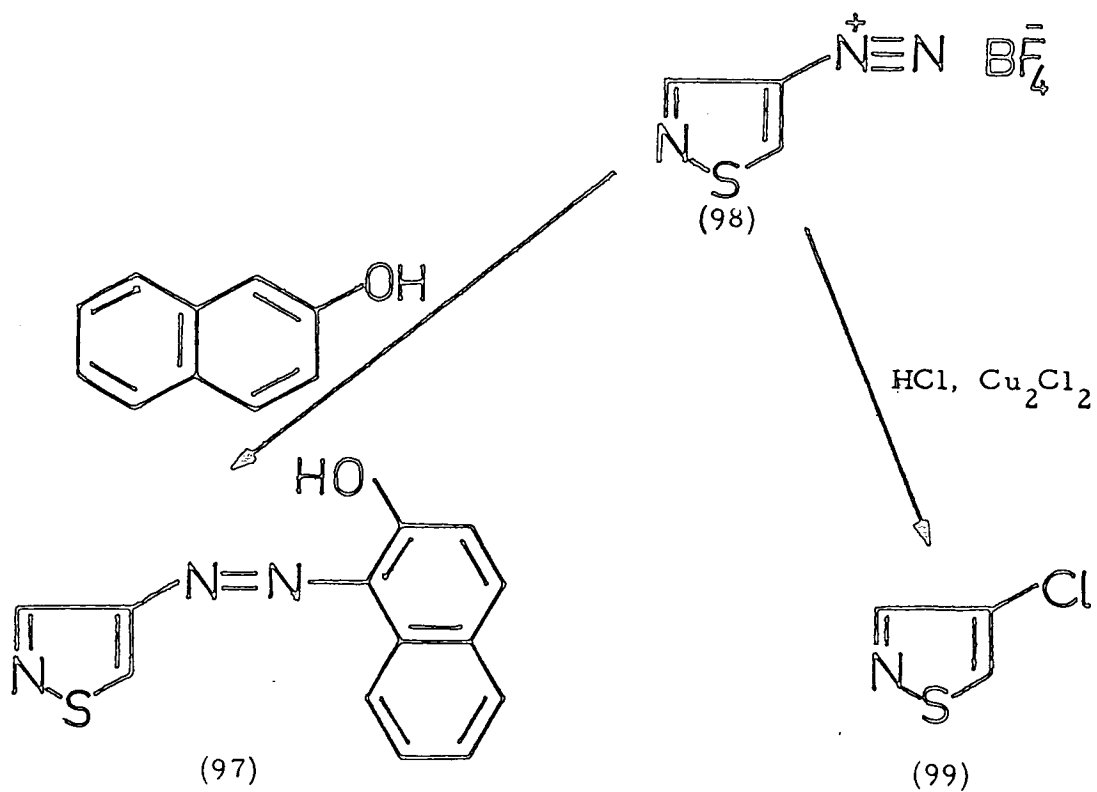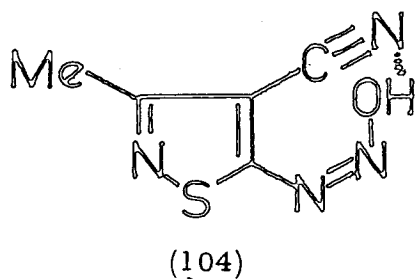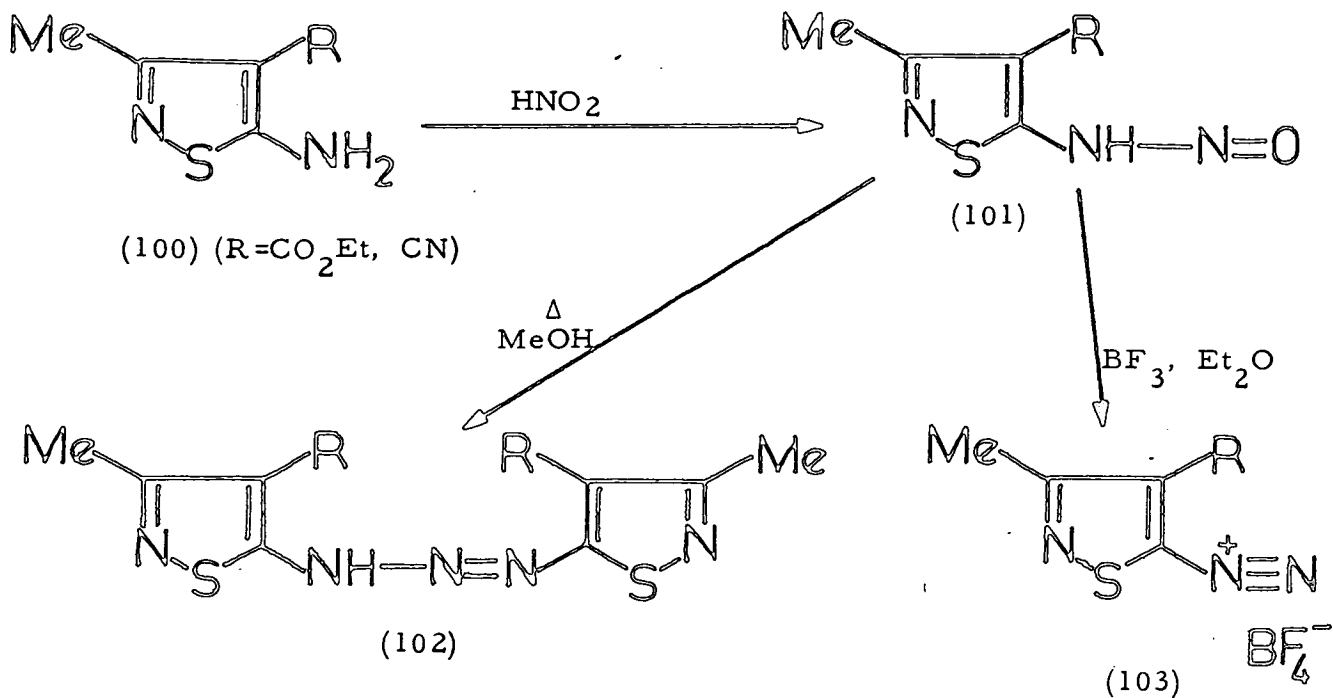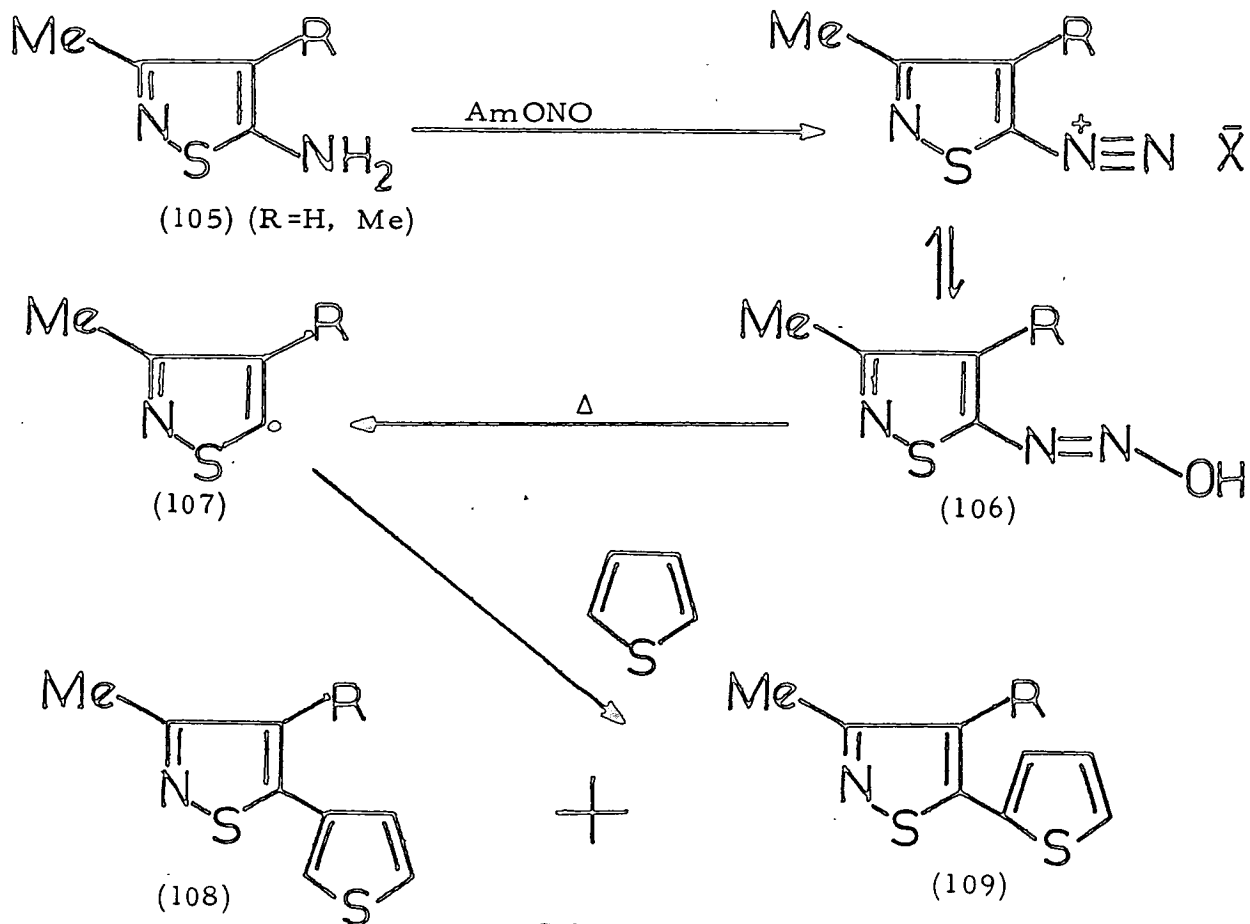
Scheme 47

aprotic conditions[92] gives thiazol-2-yl radicals (95) via the thermolysis of diazotates. The radicals (95) can subsequently couple with aromatic molecules such as pyridine to give bihetaryl products (96) (Scheme 44).

The diazotisation of 3-, 4-, and 5-aminoisothiazoles with nitrosyl tetrafluoroborate in a 1:1 mixture of acetic and propionic acids can be used to isolate the respective diazonium fluoroborates.[93] These diazonium salts [e. g. (98)] can be coupled with activated arenes to give azo compounds [e. g. (97)] and undergo dediazoniation to give halogeno-isothiazoles [e. g. (99)] (Scheme 45).[93,94] Certain 5-amino-isothiazoles (100) can be treated with sodium nitrite in dilute sulphuric acid, 80% phosphoric acid or formic acid to give stable nitrosamines (101) which on heating in methanol afford diazoamino compounds (102) (Scheme 46).[93] The diazonium fluoroborates (103) can be prepared by treating the corresponding nitrosamines (101) with boron trifluoride in ether. The nitrosamines (101) are not of the type in which the N-hydroxy-azo tautomer can be stabilised by hydrogen bonding between a ring nitrogen atom and an α-nitrosamino group (see before). The existence of the nitrosamines (101) as stable compounds can be explained in terms of stabilisation of their N-hydroxy-azo tautomers by hydrogen-bonding with adjacent polar substituents (R) [cf. (104)]. The diazotisation of 5-aminoisothiazoles (105) with amyl nitrite in aprotic media gives 5-isothiazolyl radicals (107) via thermal decomposition of N-hydroxy-azo intermediates (106) (Scheme 47). The 5-isothiazolyl radicals (107) can couple with heterocyclic molecules such as thiophene to give bihetaryl products (108) and (109) in yields of 20-40%.[95]

(110) + (111) → (112)

$(R^1 = COMe)$

$(R^2 = CO_2H, CO_2R)$

(114)

(113)

Scheme 48

(115) $\xrightarrow{\text{NaOH}}$ (116)
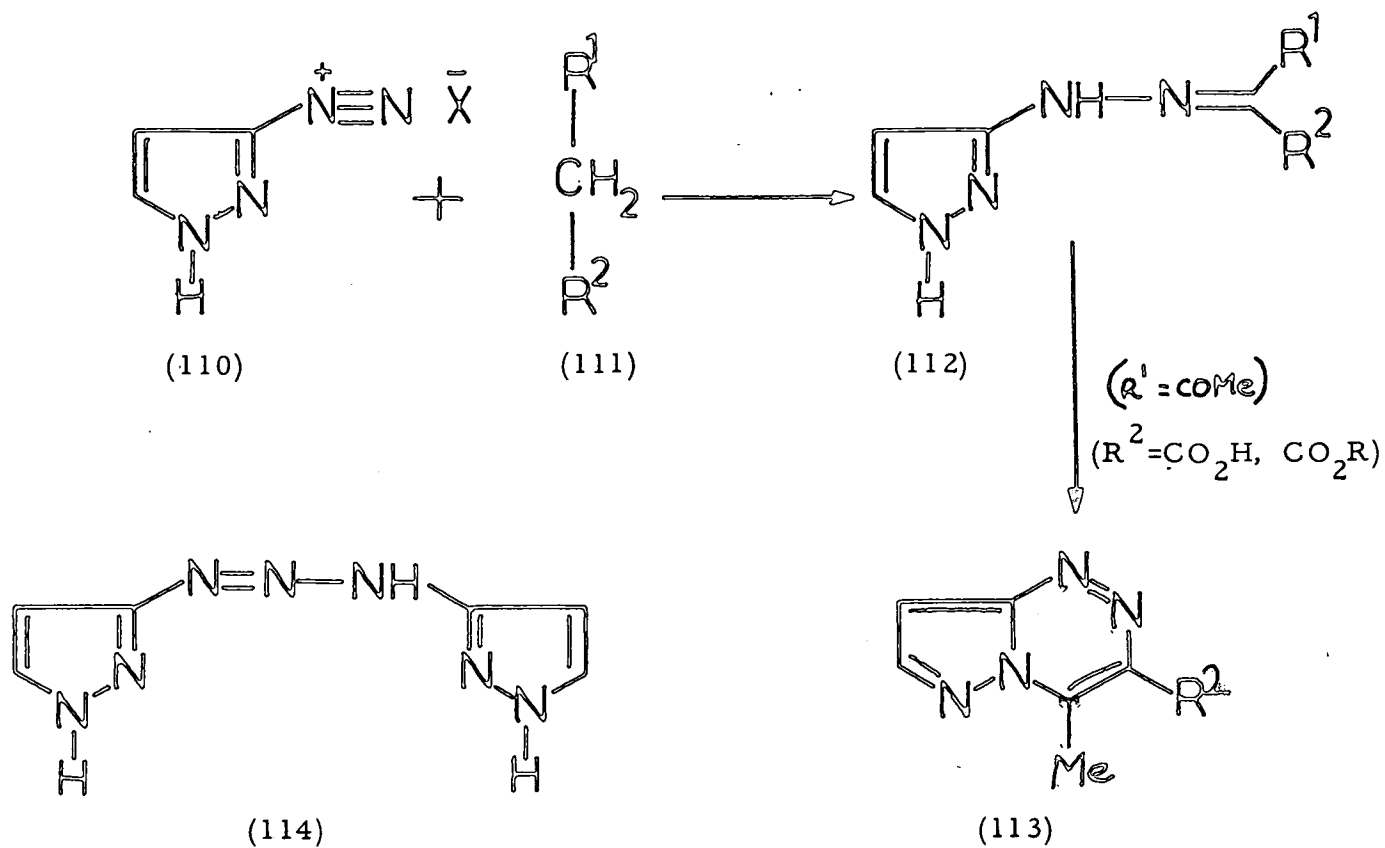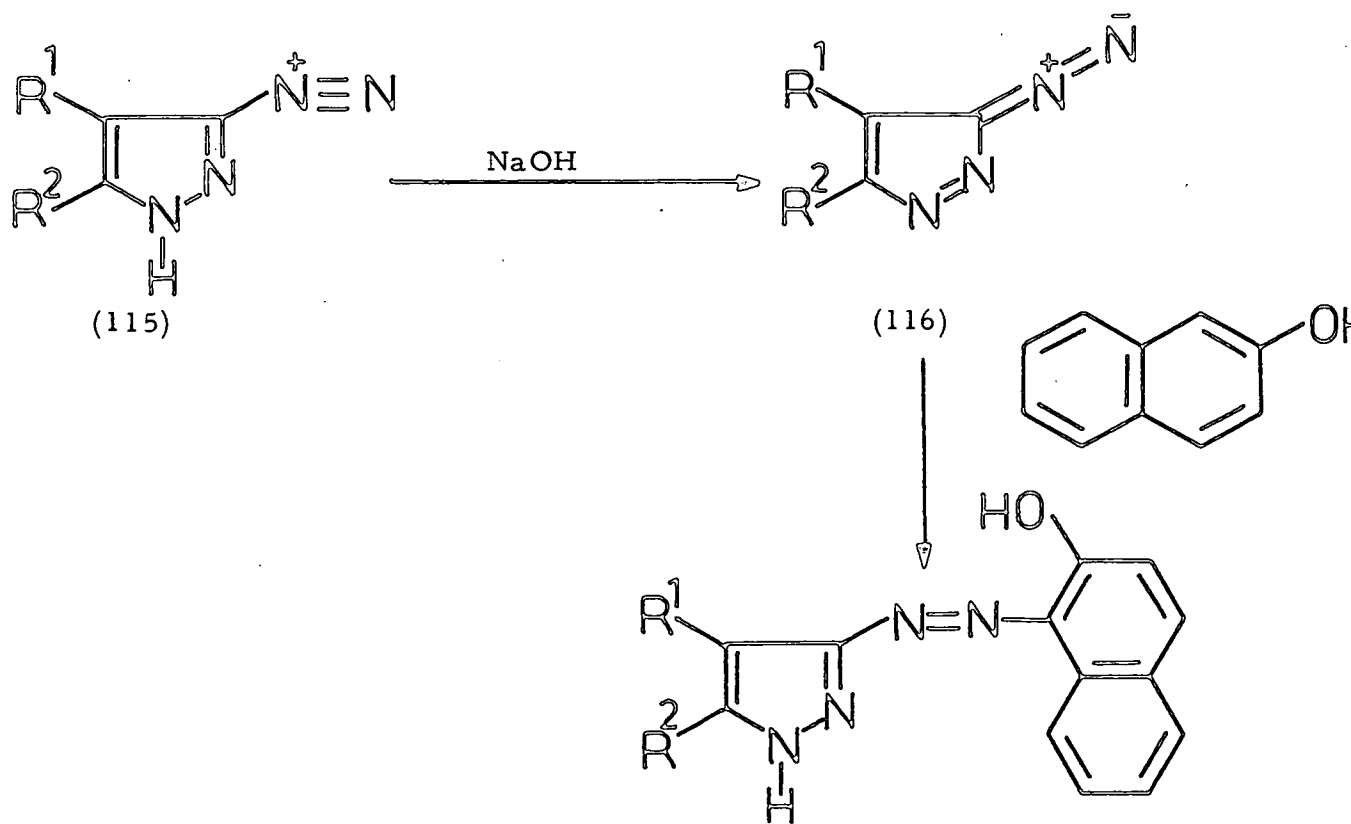
Scheme 49

Diazotisation of 3-aminopyrazoles in concentrated phosphoric

or hydrochloric acid yields pyrazole-3-diazonium salts which can be

isolated and undergo normal dediazoniation and coupling reactions.[57]

Pyrazole-3-diazonium salts (110) can be coupled with active methylene

compounds (e. g. 111) to give hydrazones (e. g. 112). If the methylene

coupling component is a β-keto acid or ester then the hydrazone is

not isolated but cyclises spontaneously to the pyrazolotriazine (e. g.

113) (Scheme 48).[96] Indazole-3-diazonium fluoroborates are also

readily prepared[97] and couple with active methylene compounds to

yield hydrazones.[97,98] Heating of suitable hydrazones of this type

yields indazolotriazines of the same general structure as (113).

Diazotisation of 3-aminopyrazole in acetic acid gives the diazoamino

compound (114).[99] 4-Aminopyrazoles can also be diazotised under

strongly acidic conditions and the resulting diazonium salts can be

isolated and coupled with β-naphthol and active methylene compounds.[97,100]

[101] Treatment of pyrazole-3-diazonium salts (115) or pyrazole-4-

diazonium salts with base, results in deprotonation to 3-diazopyrazoles

(116) and 4-diazopyrazoles respectively.[70] Diazopyrazoles are not

very stable compounds and will readily couple with β-naphthol to give

azo compounds (Scheme 49).[70] Diazoindazole, discovered by Bamberger

in 1899,[102] was the first diazo compound to be isolated and is prepared

in the same way as diazopyrazoles and reacts in the same manner as

the latter.

2-Aminoimidazoles can be diazotised and the resulting diazonium

salts coupled _in situ_ with activated aromatic molecules[57] to give azo
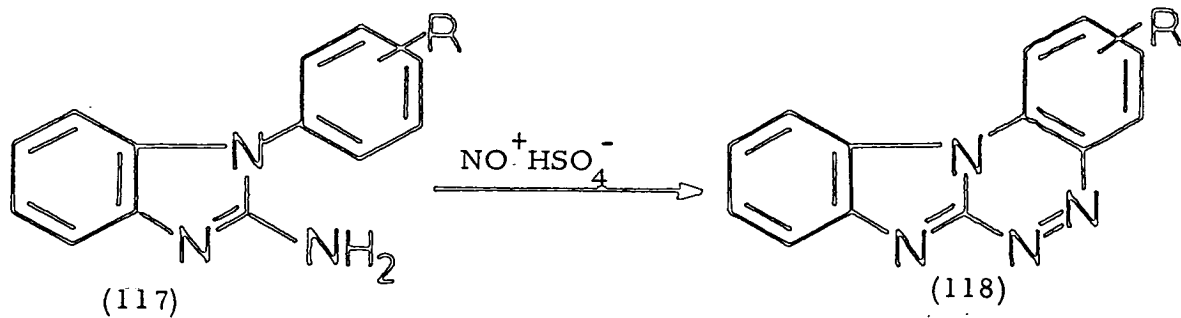
Scheme 50
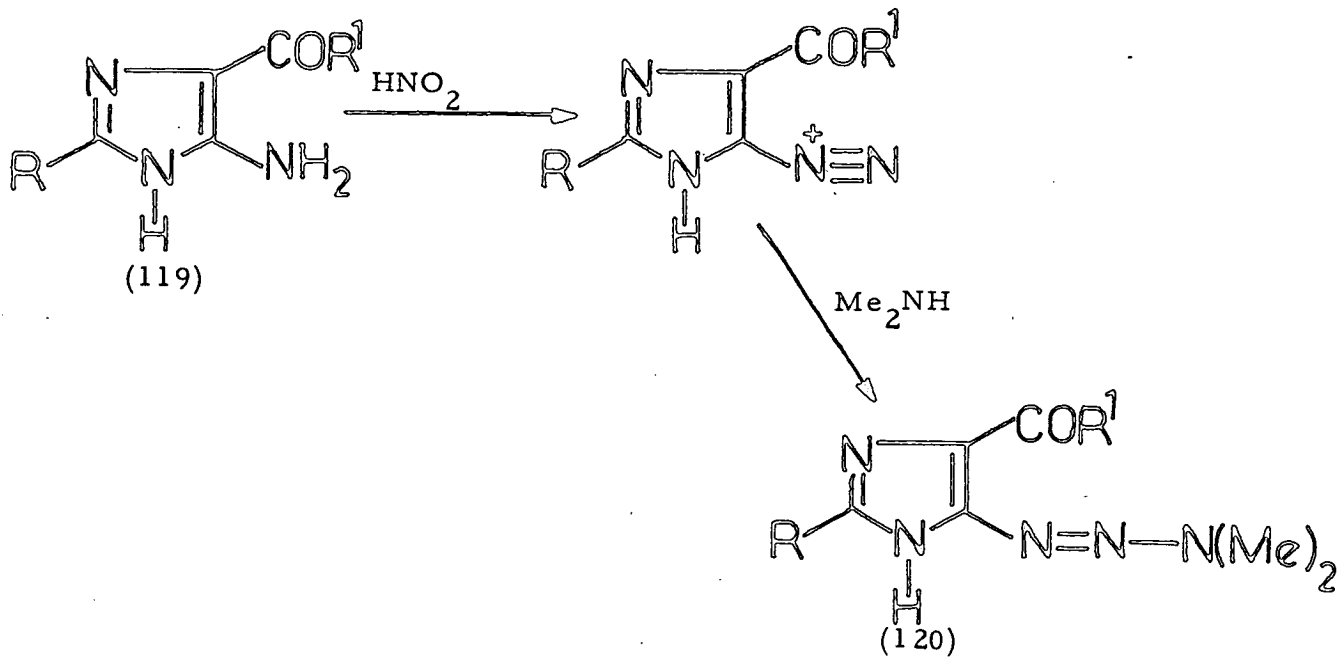
Scheme 51
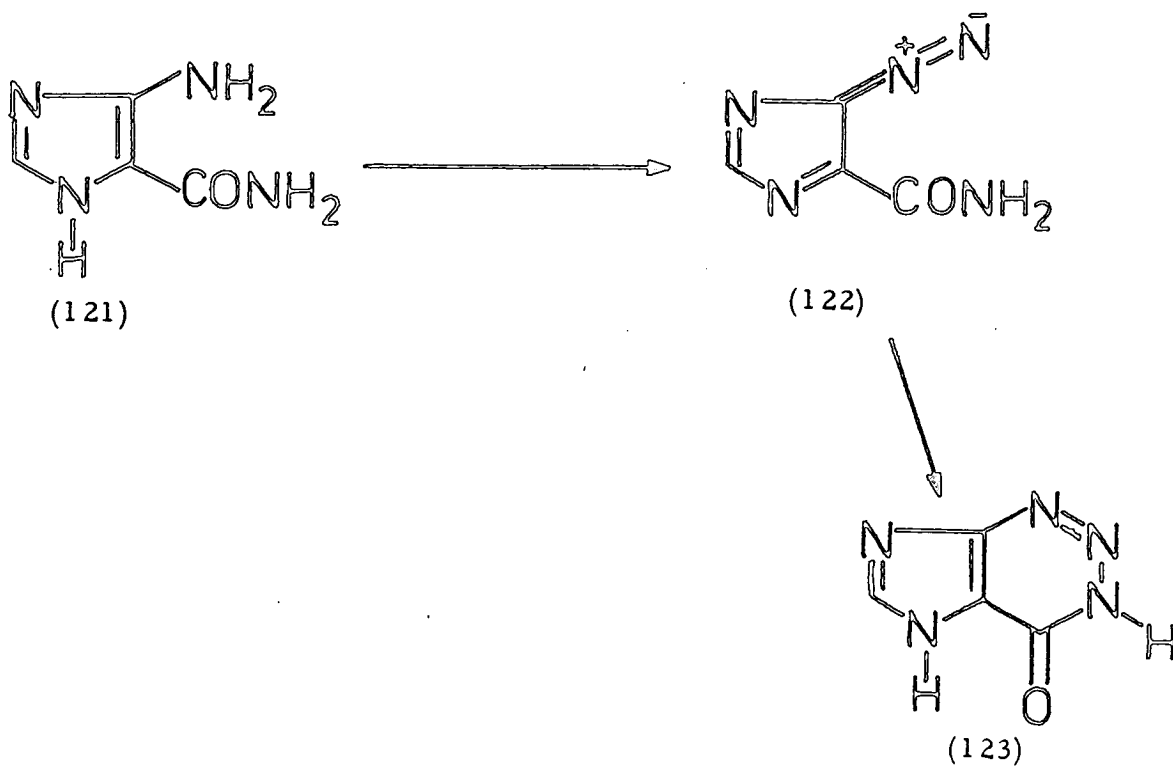
Scheme 52
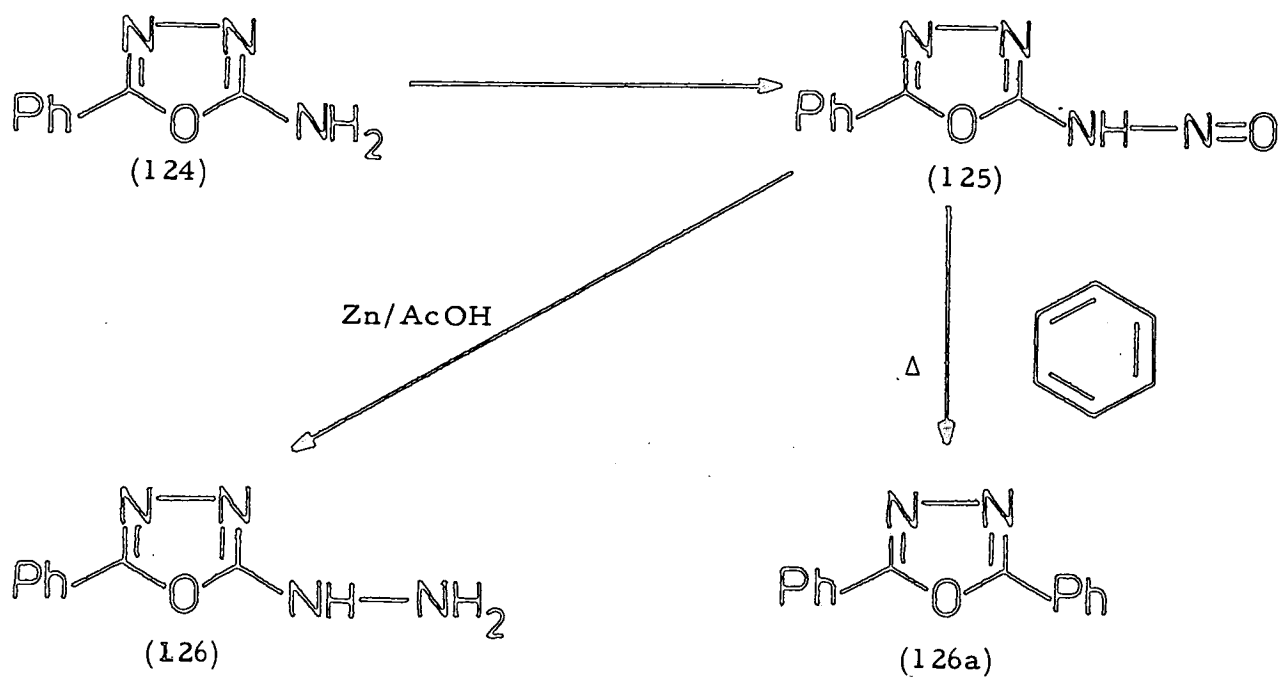
Scheme 53

compounds and subjected to dediazoniation reactions such as the nitro-Sandmeyer reaction.[103]   Diazotisation of 2-amino-1-$\underline{N}$-phenyl-imidazoles (e. g. 117) with nitrosylsulphuric acid gives imidazotriazines (e. g. 118) [105] by an intramolecular coupling reaction (Scheme 50). Recently nitrosamines[106] have been prepared from 2-aminobenzimidazoles by diazotisation under basic conditions, followed by acidification.   4-Aminoimidazoles (119) can be diazotised and coupled _in situ_ with dimethylamine to give the diazoamino compounds (120) (Scheme 51). 2-Fluoro- and 4-fluoroimidazoles can be prepared from the respective aminoimidazoles by diazotisation in fluoroboric acid followed by _in situ_ irradiation of the resulting diazonium fluoroborates.   Diazotisation of aminoimidazoles containing electron-withdrawing groups yields diazo-imidazoles directly.[57,107]   For example diazotisation of 5-amino-imidazole-4-carboxamide (121) with sodium nitrite in dilute hydrochloric acid gives the 5-diazoimidazole compound (122) directly (Scheme 52) which cyclises to the 2-azahypoxanthine (123) on storage in solution.

The diazotisation of 2-amino-5-phenyloxadiazole (124) with sodium nitrite in hydrochloric acid gives the stable primary nitros-amine (125)[108] which can be reduced with zinc and acetic acid to the hydrazine (126) (Scheme 53).   Gomberg-Bachman arylation of the nitrosamine (125) can be accomplished by heating in benzene to give (126a).

The diazotisation of 5-amino-1,2,4-thiadiazoles (127) with sodium nitrite in dilute sulphuric acid gives stable products[109] whose infrared and ultraviolet spectra are consistent with nitrosamine

Scheme 54

R⟨thiadiazole⟩C–NH₂

(127)
(R=H, Me)

NO⁺ BF₄⁻ in HOAc

R⟨thiadiazole⟩C–NH–N=O

(128)

(R=Me, Et, OMe, CH₂Ph, Ph, SCH₃, SPh)

HX in HOAc or / BF₃ in Et₂O →

R⟨thiadiazole⟩C–N⁺≡N

(130)

X⁻

BF₃ in Et₂O

R⟨thiadiazole⟩C–N=N–OR¹

(133)

(R=Ph) [R¹=Me, Et, C(CH₃)₃]
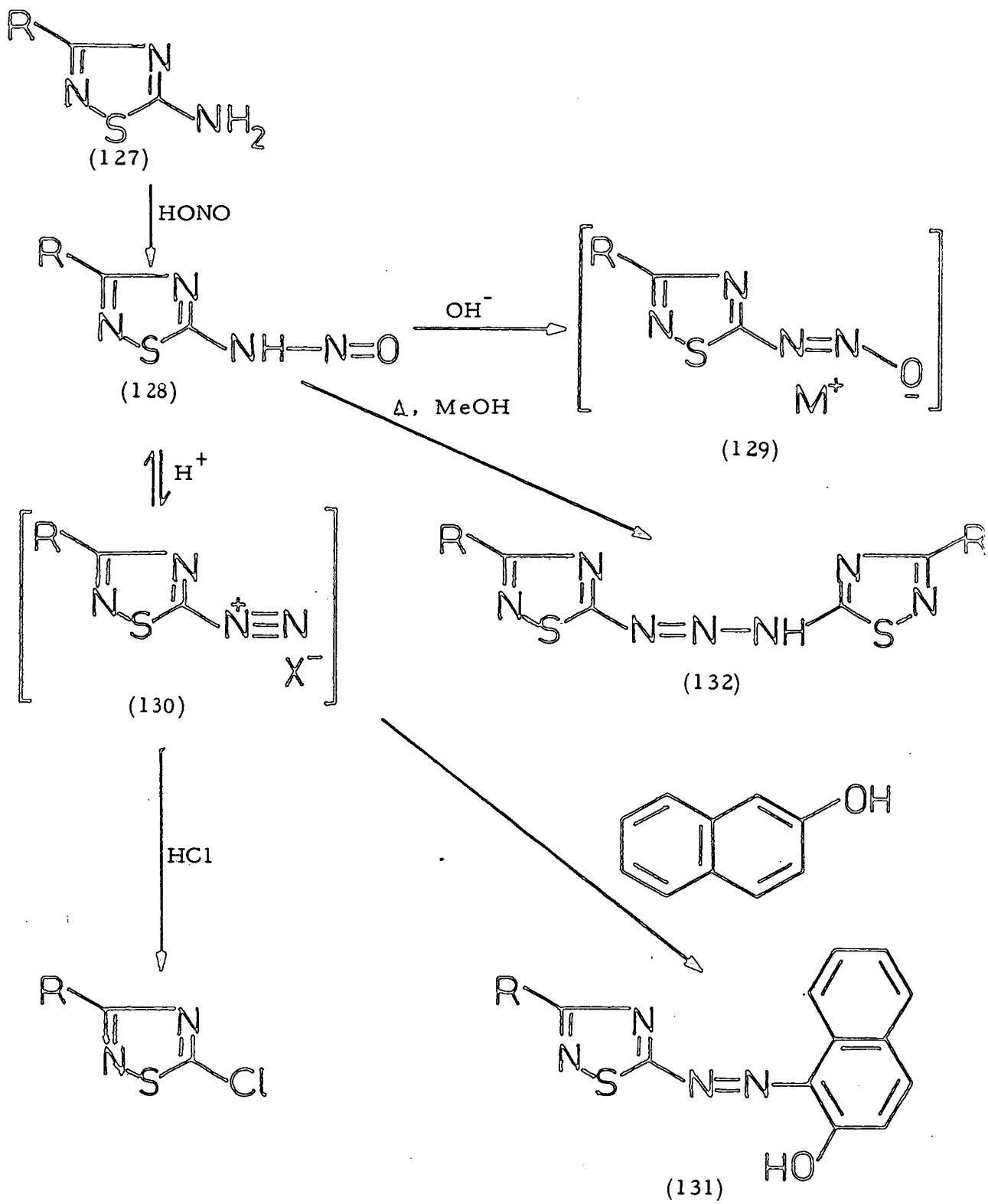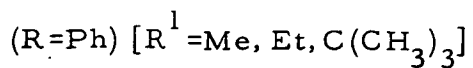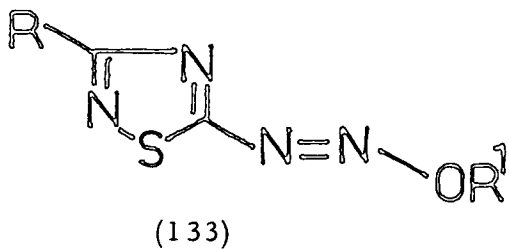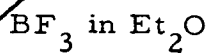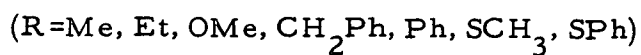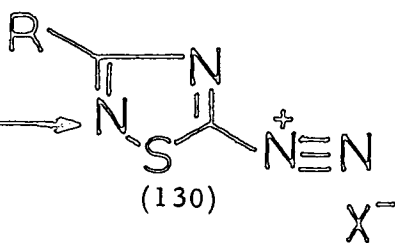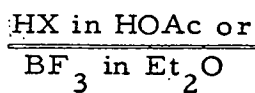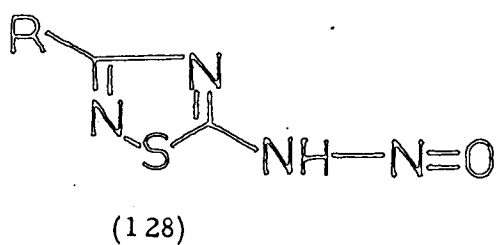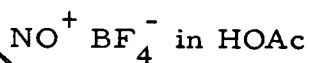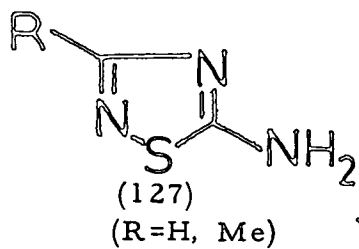
Scheme 55

structures (128) (Scheme 54). The yields of nitrosamines (128) are found to vary inversely with the acidity of the diazotisation medium and electron-withdrawing substituents are found to favour nitrosamine formation. Alkaline solutions of these nitrosamines (128) show properties consistent with the presence of anti-diazotates (129). It is believed that in acidic media the nitrosamines (128) are in equilibrium with the diazonium cations (130) and successful coupling with β-naphthol to give azo compounds (131)[109-111] under acidic conditions is evidence for this. Hydroxy- and chlorodediazoniation reactions of 1,2,4-thiadiazole-5-diazonium salts are also possible under acidic conditions[109] (Scheme 54). Heating of the nitrosamines (128) in methanol gives the triazenes (132).[112] Diazotisation of 5-amino-1,2,4-thiadiazoles using the normal conditions leads to nitrosamines (see before). In order to isolate the 1,2,4-thiadiazole-5-diazonium salts (130) special conditions must be employed[110] (Scheme 55). For example diazotisation of 5-amino-1,2,4-thiadiazoles (127; R=H or Me) with nitrosyl tetra-fluoroborate in acetic acid yields the diazonium fluoroborates (130; X=BF$_4$). Diazonium fluoroborates or perchlorates (130; X=BF$_4$ or ClO$_4$) can also be prepared from the nitrosamines (128) by treatment with fluoroboric acid, perchloric acid, or boron trifluoride in ether. Similarly 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborates can likewise be prepared by treating the compounds (133) with boron tri-fluoride in ether.

The conversion of 3-amino-1,2,4-thiadiazoles into nitrosamino derivatives has so far proved unsuccessful. The diazotisation of 3-amino-1,2,4-thiadiazoles gives unstable diazonium salts[113] which
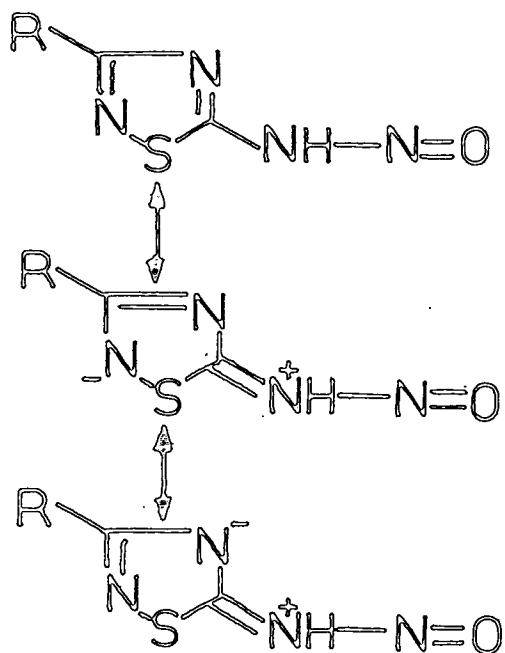
Scheme 56

Scheme 57

Scheme 58

(140)

H_2SO_4
$NaNO_2$

(141)

(144)

(142)

(143)
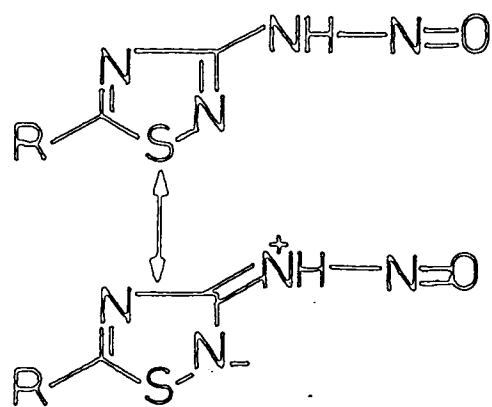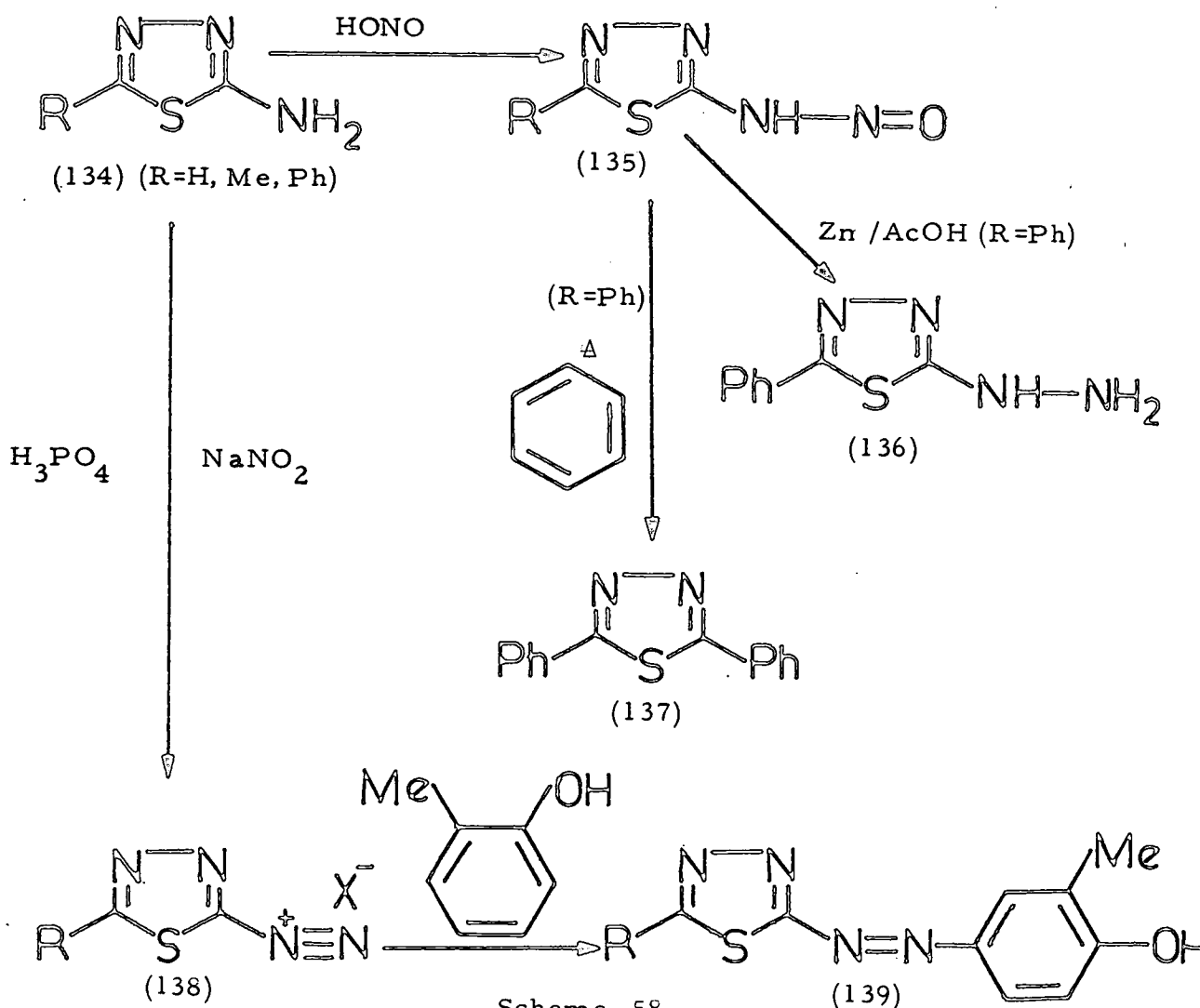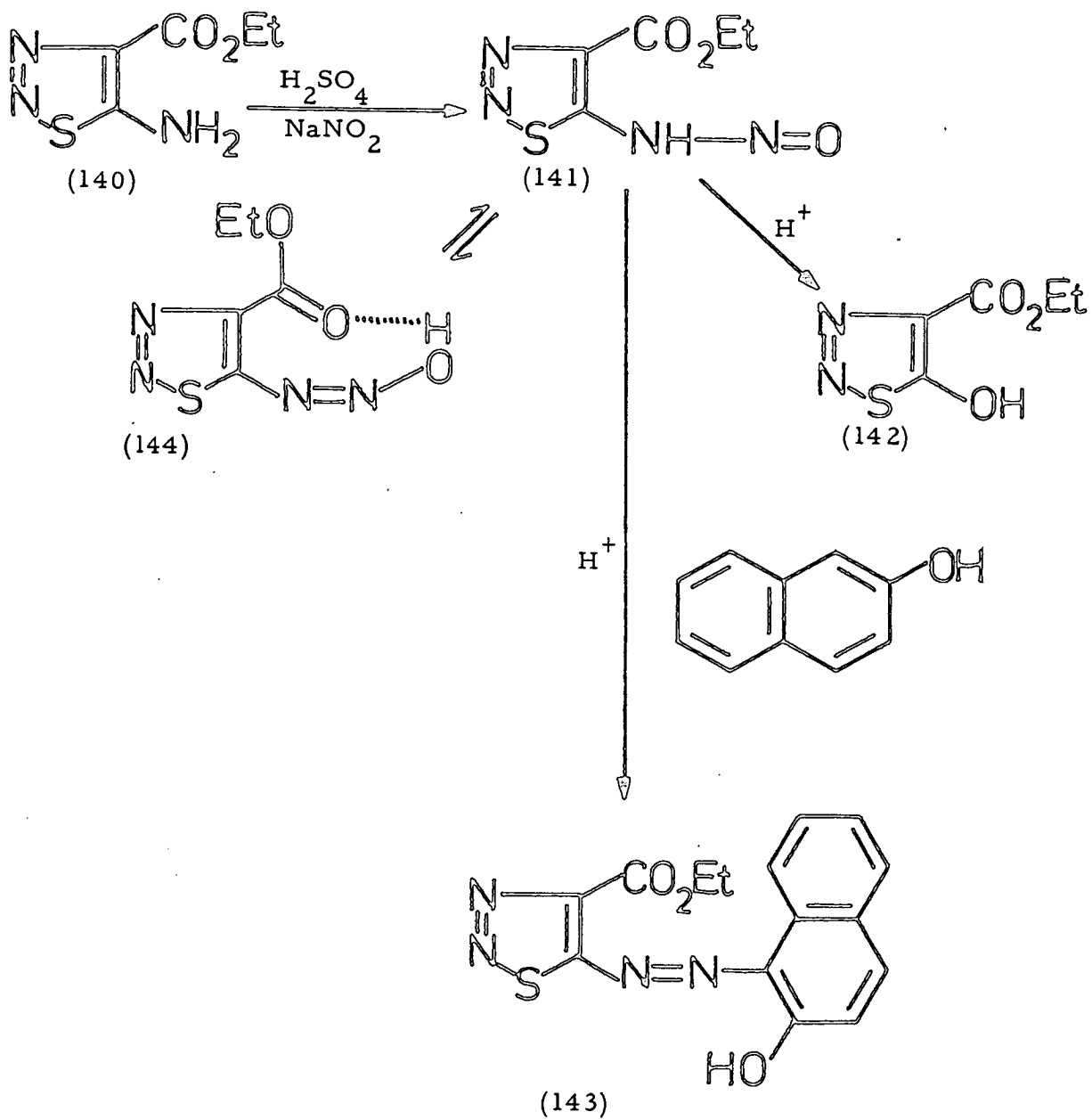
Scheme 59

readily undergo halogenodediazoniation giving 3-halogeno-1,2,4-thiadiazoles.[110,114] Goerdeler[109] has rationalised the contrasting stability of 5-nitrosamino-1,2,4-thiadiazoles with the apparent instability of 3-nitrosamino-1,2,4-thiadiazoles by the lack of one contributing canonical form in the latter (Schemes 56 and 57).

By analogy with 5-amino-1,2,4-thiadiazoles and in contrast to 3-amino-1,2,4-thiadiazoles, the diazotisation of 2-amino-1,3,4-thiadiazoles (134) with sodium nitrite in dilute hydrochloric acid gives stable nitrosamines (135)[108,115] which can be reduced with zinc and acetic acid to hydrazines (136), and undergo homolytic reactions [(135) -> (137)][108] on heating in benzene (Scheme 58). Diazotisation of 2-amino-1,3,4-thiadiazoles (134) with sodium nitrite in phosphoric acid affords diazonium salts (138) which couple readily in situ with arenes[111] to give azo compounds (e. g. 139) (Scheme 58).

Diazotisation of ethyl 5-amino-1,2,3-thiadiazole-4-carboxylate (140) with sodium nitrite in dilute sulphuric acid gives a stable nitrosamine (141)[116] (Scheme 59). This nitrosamine (141) undergoes normal dediazoniation reactions in acidic media without catalysis to afford the corresponding halogenothiadiazoles and ethyl 5-hydroxy-1,2,3-thiadiazole-4-carboxylate (142).[116] The intermediacy of the corresponding diazonium salt in these reactions is supported by the successful coupling of (141) in acidic media with β-naphthol to give the azo compound (143). The nitrosamine (141) is another example of this class of compound which does not have the nitrosamino group adjacent to a ring nitrogen atom. The stability of (141) can be explained by the hydrogen bonding possible between the hydroxy-azo group and the ortho

(145)   NaNO$_2$/HCl (18%)   (146)   Zn / AcOH   (149)

EtOH/H$^+$

NaNO$_2$/HCl (20%)

NaNO$_2$/HCl (5-10%)

(150)

(147)
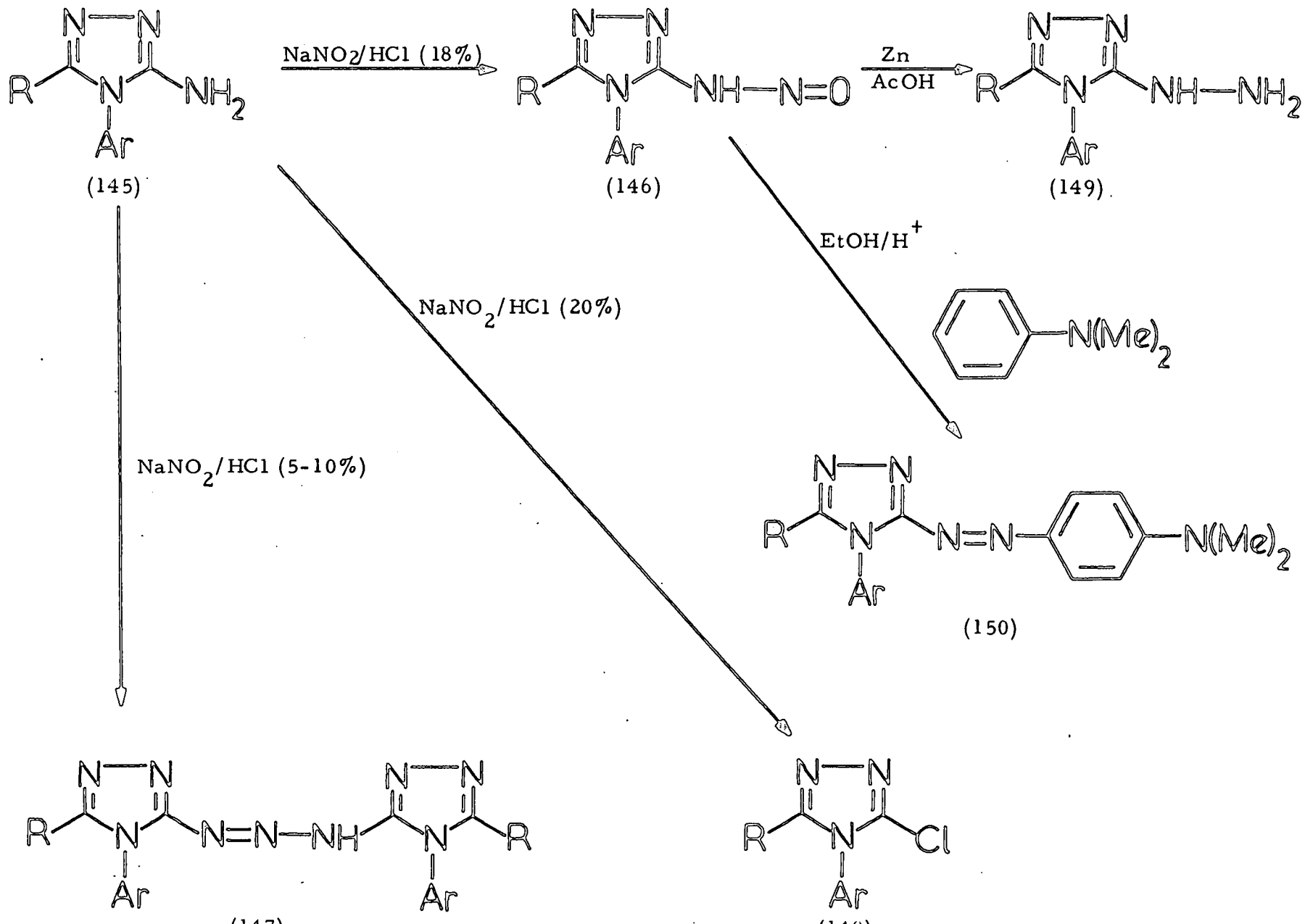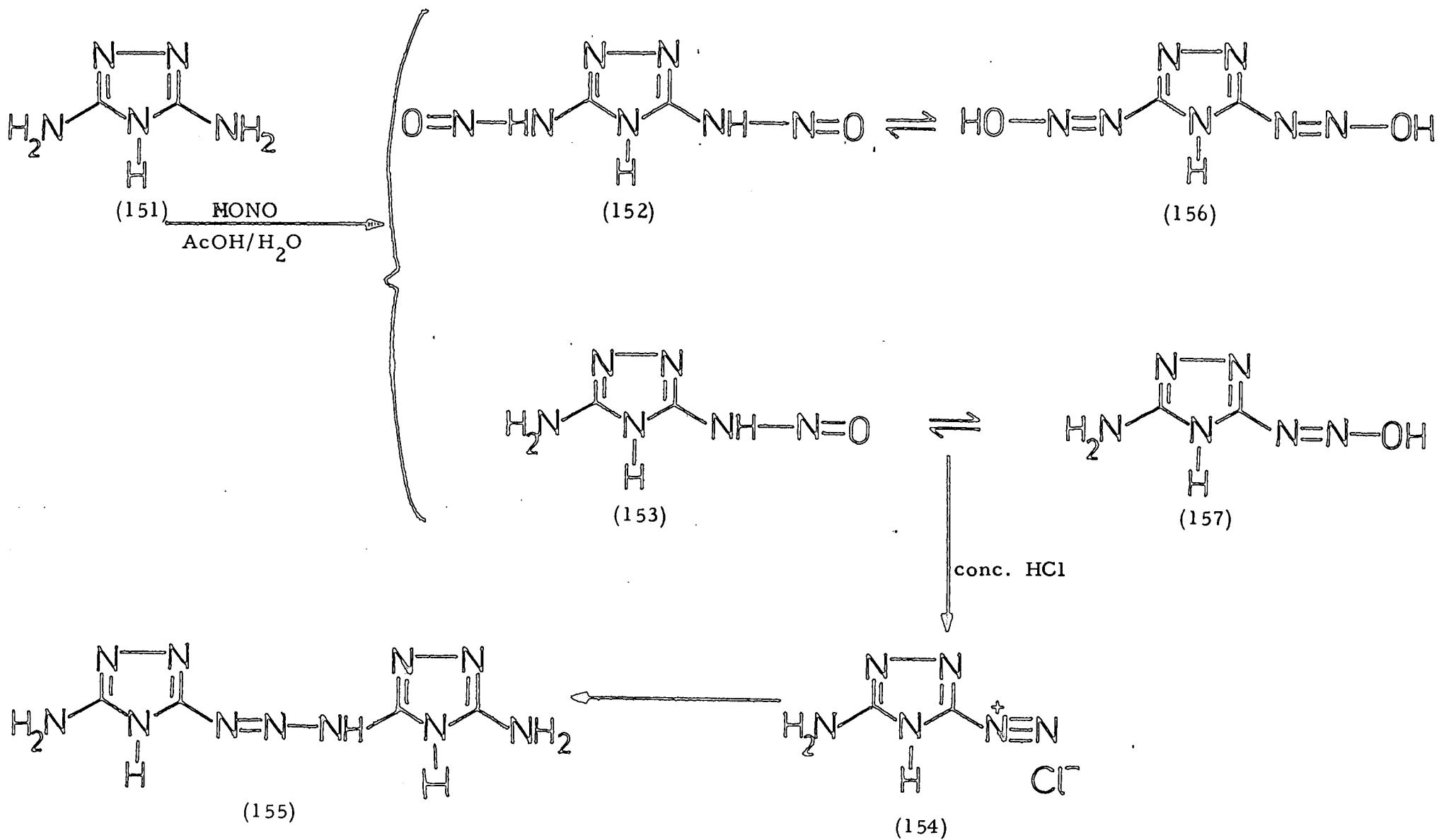
Scheme 61

ester group in the N-hydroxy-azo tautomer (144).

Many 1,2,4-triazole-5-diazonium salts can be isolated and subsequent azido-, hydroxy- and nitrodediazoniation reactions can be carried out.[57] Coupling reactions of 1,2,4-triazole-5-diazonium salts with nitroalkanes under alkaline conditions to give hydrazones and with activated aromatic molecules to give azo compounds are also successful.[57,117] Diazotisation of 4-N-substituted-5-amino-1,2,4-triazoles (145) with sodium nitrite in hydrochloric acid gives stable primary nitrosamines (146) (Scheme 60).[118] This reaction is very sensitive to the concentration of acid used. It was found that 18% hydrochloric acid was the optimum concentration for preparing the nitrosamine (146). Lower acid concentrations yield the triazenes (147), while higher acid concentrations afford the chloro compounds (148). The nitrosamines (146) can be reduced under mild conditions with zinc dust and acetic acid to yield the hydrazines (149).[108] The nitrosamines (146) can be coupled in acidic alcoholic solution with activated aromatic compounds such as N,N-dimethylaniline to give the azo-compounds (150).[118] The diazotisation of 3,5-diamino-1,2,4-triazole (151) with sodium nitrite in dilute acetic acid gives a mixture of the nitrosamines (152) and (153) (Scheme 61)[119,120] which are the only known examples of nitrosamines derived from N-unsubstituted azoles. Treatment of the nitrosamine (153) with concentrated hydrochloric acid gives the diazonium salt (154), which can be coupled with the parent amine to afford the diazoamino compound (155).[121] It should be emphasised that convincing proof of the structures of (152) and (153) has not been provided and these molecules may in fact have the N-
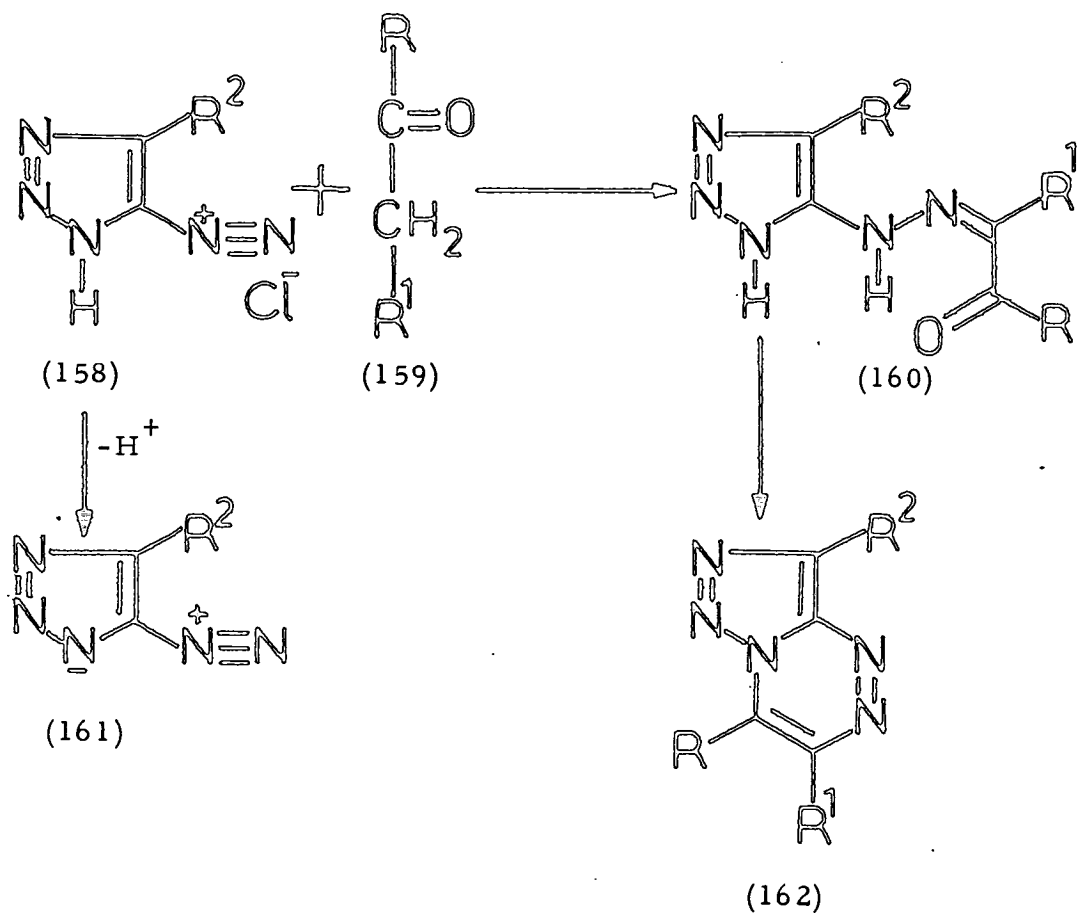
Scheme 62
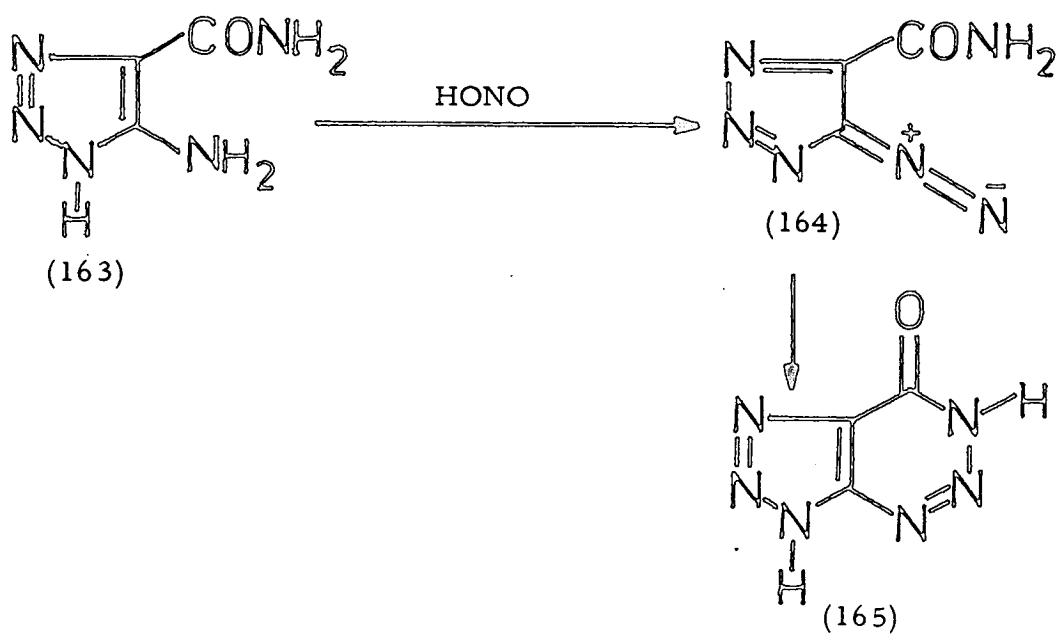
Scheme 63

hydroxy-azo structures (156) and (157).

5-Amino-1,2,3-triazoles[122] can be diazotised with amyl nitrite in methanolic hydrogen chloride to give isolable diazonium chlorides. These 1,2,3-triazole-5-diazonium chlorides (158) can be coupled under buffered conditions with active methylene compounds (159) to give the hydrazones (160) which in some cases cyclise spontaneously to yield the triazolotriazines (162) (Scheme 62). Since these coupling reactions occur under neutral conditions it is possible that they involve the corresponding diazo compound (161). There is one reported example[107] of an isolable diazo-1,2,3-triazole. Diazotisation of 5-aminotriazole-4-carboxamide (163) with amyl nitrite in acetic acid gives the diazo compound (164) directly (Scheme 63). Treating a solution of the diazo compound (164) with base results in cyclisation to 2,8-diazahypoxanthine (165).

The attempted diazotisation of 5-amino-1,2,3,4-thiatriazole results in decomposition.[57]

Diazotisation of 5-aminotetrazole with sodium nitrite in hydrochloric acid yields the explosive tetrazole-5-diazonium salt which can be isolated[123-125] and undergoes hydrogenodediazoniation on treatment with hypophosphorus acid to give tetrazole thus providing a convenient synthesis of the latter. The diazotisation of aminotetrazoles in which the labile ring hydrogen atom is replaced by an alkyl or aryl group, gives stable nitrosamines.[108,127,128] These nitrosamines (166) can be readily reduced using zinc and aqueous acetic acid giving the hydrazines (168) (Scheme 64). Heating the nitrosamines (166) in aromatic hydrocarbons gives aryltetrazoles (169).[108] This reaction
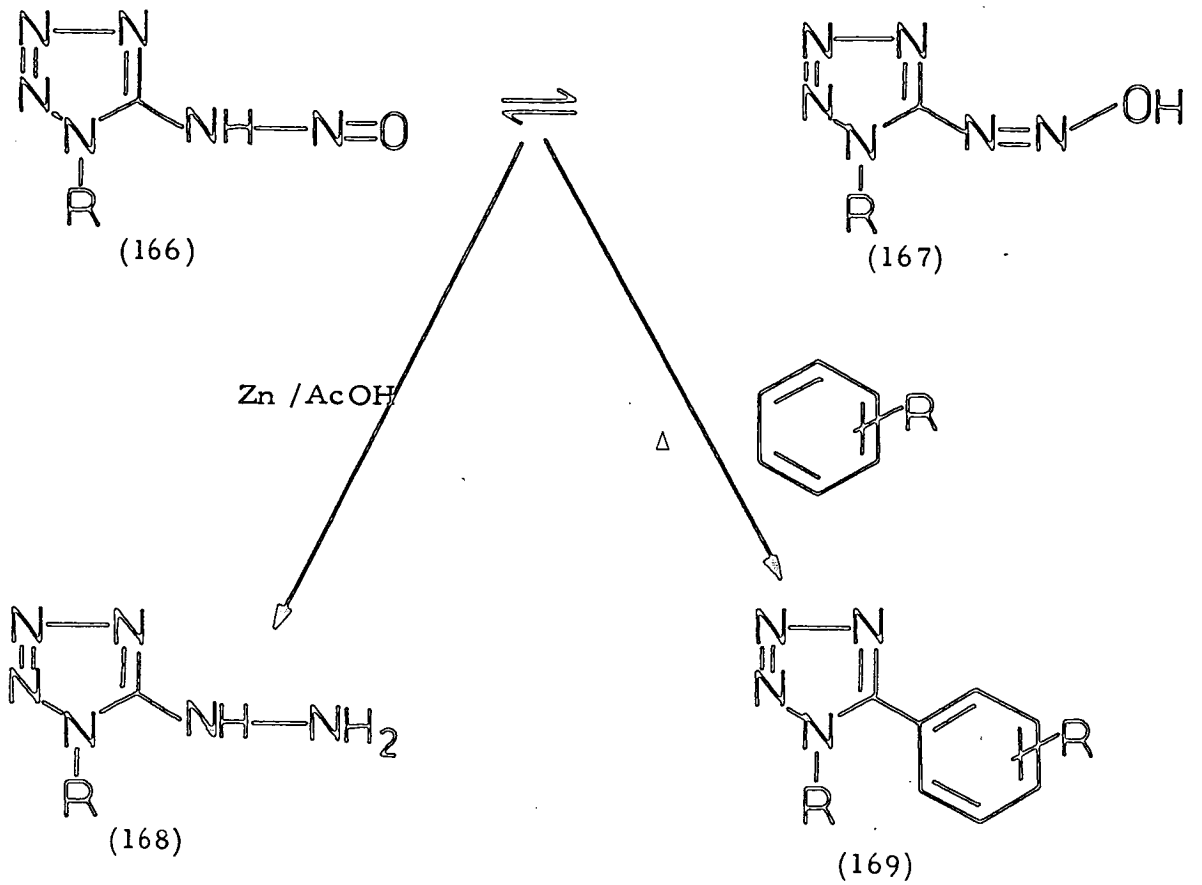
Scheme 64

is believed to be of the Gomberg-Bachman type proceeding via initial homolysis of the $\underline{N}$-hydroxy-azo compound (167). Spectra of 5-nitros-aminotetrazoles suggest that both tautomeric forms (166) and (167) are present. Recently the diazotisation of 5-aminotetrazole followed by $\underline{in}$ $\underline{situ}$ reduction with stannous chloride ($SnCl_2$) and coupling with phenol to give the azo compound has been reported.[117]

CHAPTER TWO

Studies of the Products derived by Nitrosation of

5-Amino-3-phenylisoxazole

Studies of the Products derived by Nitrosation of 5-Amino-

3-phenylisoxazole

Investigations into the diazotisation of aminoisoxazoles were carried out for two reasons: firstly, to establish satisfactory conditions for the diazotisation of these amines, and secondly, to use the diazonium salts thus prepared as synthetic intermediates. It was anticipated that two types of synthetically useful reaction could be performed on isoxazolediazonium salts: firstly, displacement of the diazonium moiety by nucleophilic reagents as a means for the introduction of new substituents into the isoxazole ring, and secondly, coupling reactions with active methylene compounds to afford hydrazones useful as intermediates for the synthesis of novel heterocyclic ring systems.

3-, 4- and 5-amino-isoxazoles are known and a limited number of attempts to diazotise them have been recorded in the literature.[129] 4-Aminoisoxazoles are aromatic in character and their nitrosation is reported to yield stable diazonium salts only if the isoxazole ring is substituted at the 3- and 5-positions.[129] Nitrosation of 3-methyl- and 5-methyl-4-aminoisoxazoles in the presence of mineral acids yields unstable diazo compounds which decompose even at low temperature with loss of nitrogen.[129] However despite this instability coupling reactions of isoxazole-4-diazonium salts with aromatic amines and phenols have been recorded.[129] Isoxazole-3-amines are represented by 3-aminoisoxazole which is aromatic in character and shows a strong tendency to form a diazoamino compound on nitrosation.[129] Strong hydrochloric acid is necessary for the satisfactory

$$PhCOCH_2CN \xrightarrow{NH_2OH} \left[\begin{array}{c} Ph-C-CH_2C{\equiv}N \\ \| \\ N \\ \diagdown OH \end{array} \right]$$

(170)

Ph—⟨isoxazole ring⟩—NH₂

(171)
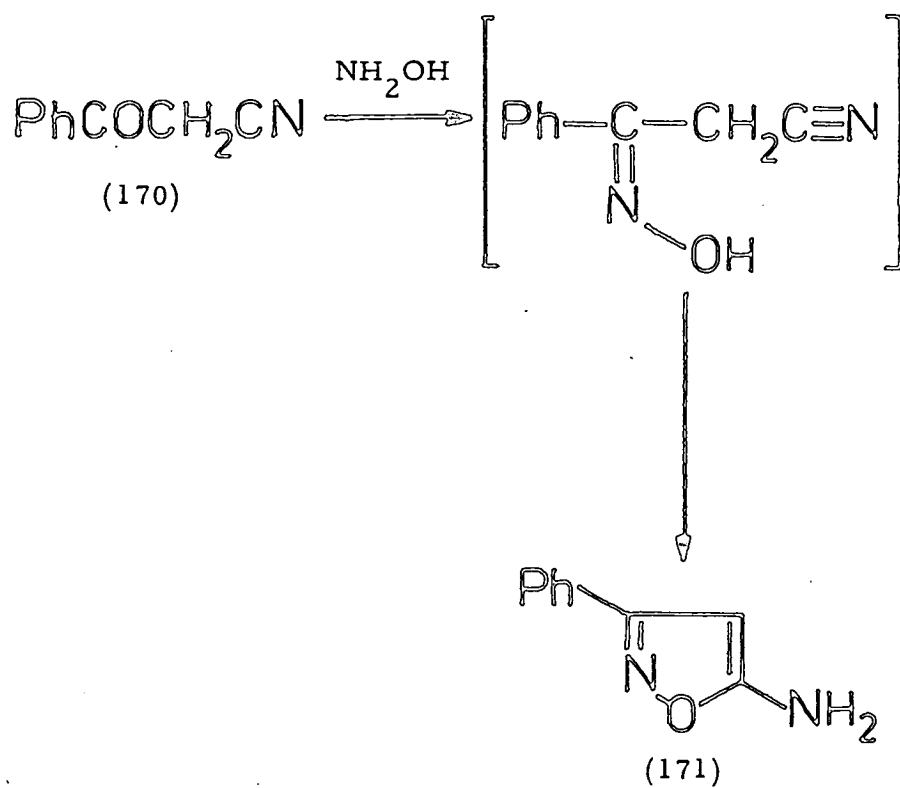
Scheme 65

diazotisation of 3-aminoisoxazole and the resulting diazonium salt couples with activated aromatic molecules under these conditions.[129] 5-Aminoisoxazoles are believed to exist in tautomeric equilibrium with 5-iminoisoxazolines and the chemical behaviour of these compounds is consistent with the participation of both tautomers.[129] The imino tautomer is involved in the hydrolytic cleavage of 5-aminoisoxazoles by acids to yield the corresponding isoxazolin-5-ones.[129] The amino form is responsible for the typical amine reactions of 5-aminoisoxazoles such as acetylation, benzoylation and condensation with aromatic aldehydes to form Schiff bases.[129]

5-Amino-3-phenylisoxazole[130] (171) (Scheme 65) was chosen for investigation in the present studies because it is readily synthesised and because the hydrophobic phenyl group should facilitate the recovery of products from aqueous media. The nitrosation of this compound has been investigated by Quilico[74] and Musante[73] but these studies were limited and a more detailed investigation was regarded as desirable. 5-Amino-3-phenylisoxazole (171) was readily prepared in good yield by the method of Obregia[130] involving the cyclisative condensation of the readily accessible benzoylacetonitrile (170) with hydroxylamine hydrochloride (Scheme 65).

Initially attempts were made to diazotise 5-amino-3-phenylisox-azole (171) in dilute mineral acid using sodium nitrite and to intercept the resulting diazonium cation by coupling with the active methylene compound, acetylacetone. This reaction was carried out in both sulphuric acid and nitric acid and in each case a product subsequently identified as 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole
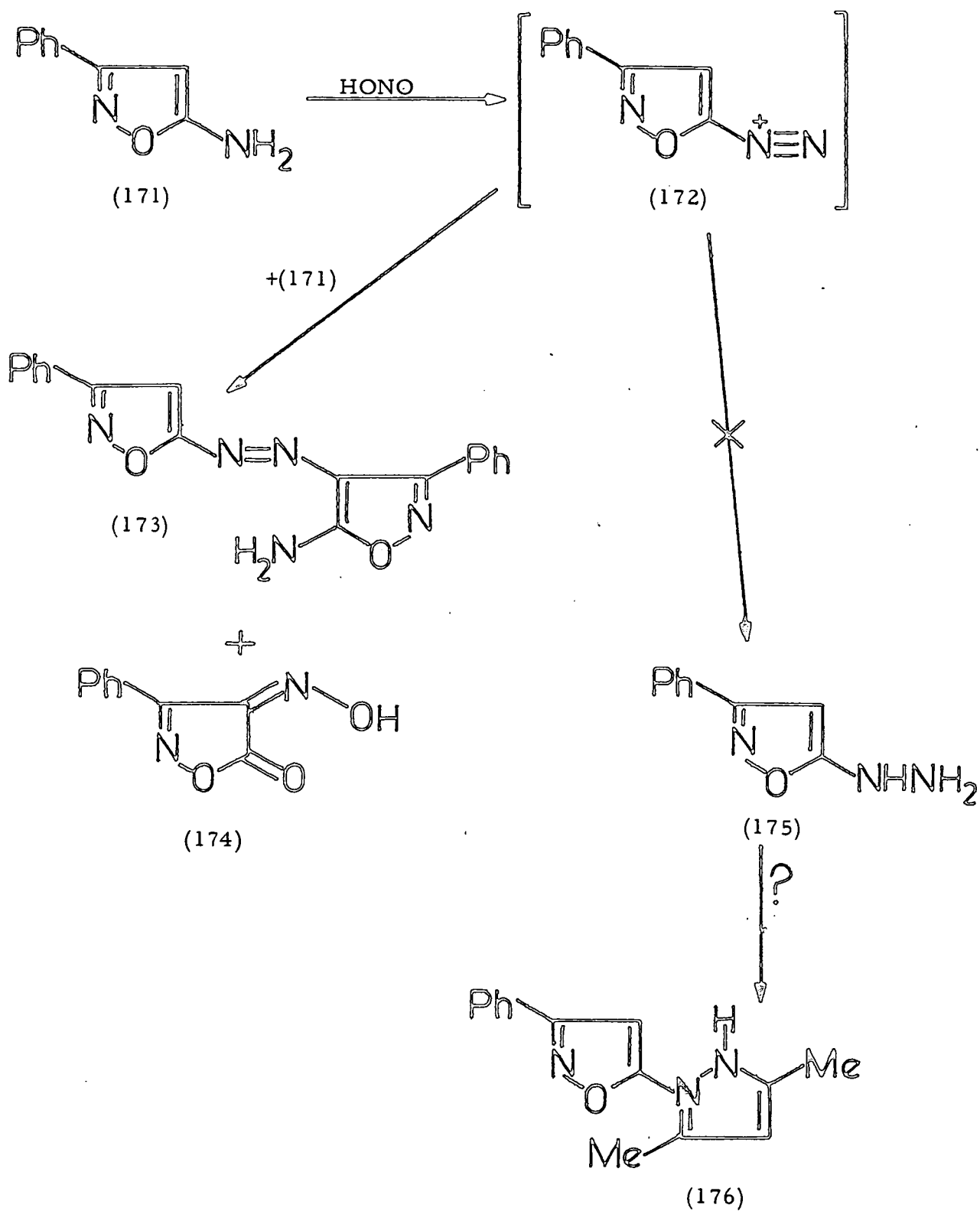
Scheme 66

(173) was isolated in 33% and 21% yields respectively. Acidification of the buffered aqueous mother liquor from the diazotisation in sulphuric acid also afforded a second product in moderate yield whose properties are consistent with it being syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174). Further work up of the reaction mixture from the diazotisation in nitric acid also gave after crystallisation syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174) (Scheme 66). Since the products isolated from the attempted diazotisation of 5-amino-3-phenyl-isoxazole (171) in sulphuric acid and nitric acid are clearly derived solely from the amine, its diazotisation in the absence of a coupling component was next investigated. The attempted diazotisation of 5-amino-3-phenylisoxazole using sodium nitrite in a mixture of sulphuric acid and acetic acid gave 5-amino-4-(3'-phenylisoxazole-5'-ylazo)-3-phenylisoxazole (173) in 42% yield and syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174) in 34% yield. The attempted diazotisation of the amine (171) using sodium nitrite in phosphoric acid also gave a mixture of the azo compound (173) and the syn-oxime (174) together with a third unidentified compound.

Though attempts to trap the diazonium cation (172) from 5-amino-3-phenylisoxazole with acetylacetone were unsuccessful, the in situ formation and subsequent transformation of this cation would account for the isolation of the azo product (173) (see later). In a further attempt to demonstrate the transient formation of the 3-phenylisoxazole-5-diazonium cation (172), the diazonium solution from the amine (171) and sodium nitrite in sulphuric acid was treated with sulphur dioxide in the hope of reducing the cation (172) to the hydrazine (175) convertible by reaction with acetylacetone into the pyrazole derivative (176)

(173)

(177)

H^+/H_2O

(178)

NH_2NH_2

(179)
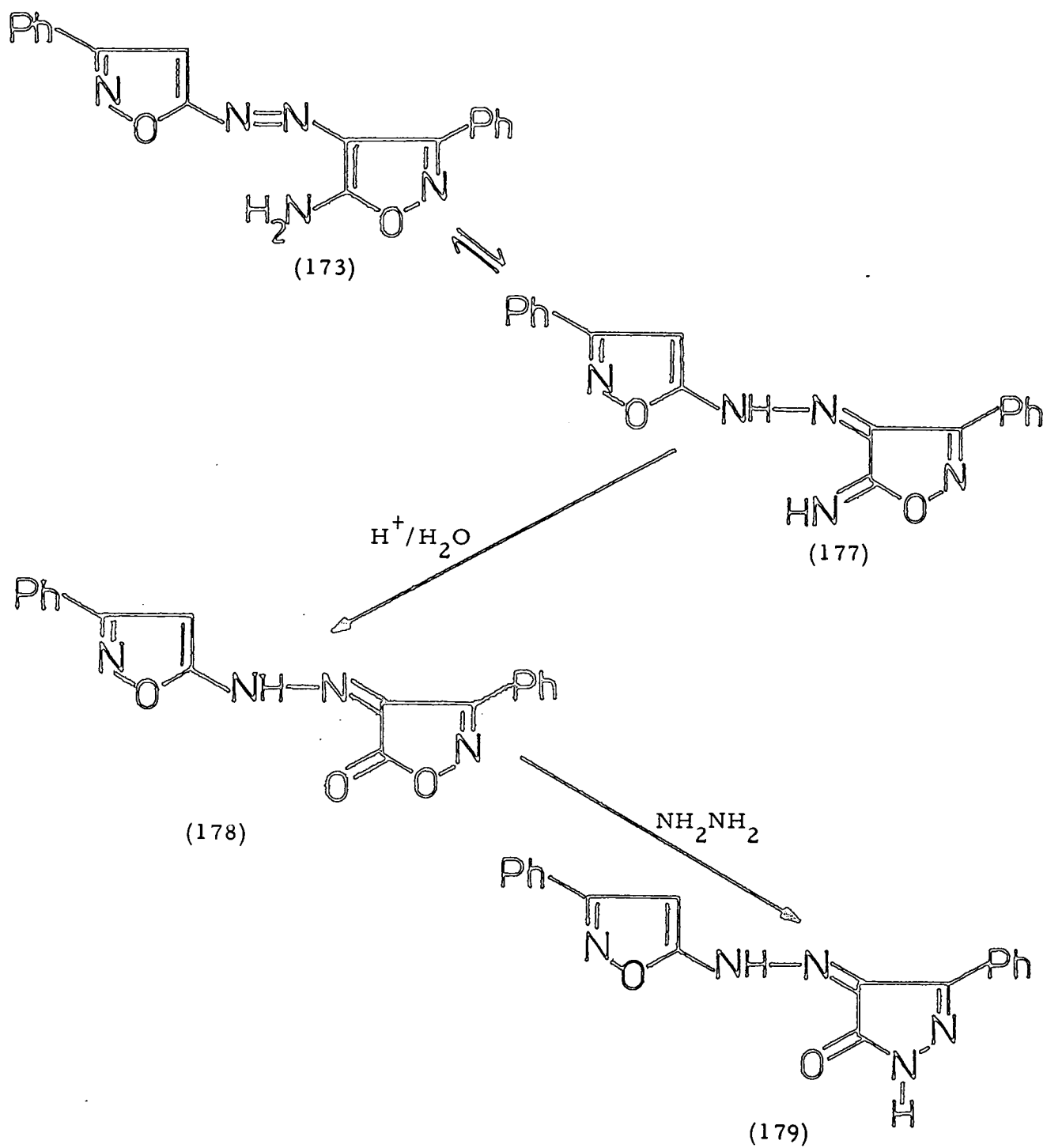
Scheme 67

(Scheme 66). In practice only the syn-oxime (174) and the azo compound (173) were isolated under these conditions.

5-Amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) gave analytical data consistent with the assigned structure. A compound having the same molecular formula was obtained by Quilico[74] by treating 5-amino-3-phenylisoxazole (171) with nitrous gases and assigned the triazene structure (190) (Scheme 71). However this structure is inconsistent with the spectroscopic properties of the product obtained in the present studies. The amino-azo structure (173) is assigned to the product since its i. r. spectrum contains bands more typical of a primary amino group than an NH group. In addition its ^{1}H n. m. r. spectrum contains a one proton singlet at $\delta 7.03$ attributable to the single isoxazole proton at C(4) in the structure (173). This feature is inconsistent with the triazene structure (190) which contains two isoxazole protons. The deep yellow-orange colour of the compound is also consistent with the azo structure (173).

Despite the apparent presence of a primary amino group the amino-azo compound (173) failed to acetylate under mild conditions. However this lack of reactivity is readily explained in terms of the existence of the azo compound (173) predominately in the imino tautomeric form (177) (Scheme 67) (c.f. 5-amino-3-phenylisoxazole[129]) which would be less prone to acetylation. On the other hand the azo-compound (173) was smoothly hydrolysed by aqueous hydrochloric acid to afford a product which gave analytical and spectroscopic data consistent with the hydrazone structure (178) (Scheme 67). In particular a carbonyl band at 1730 cm^{-1} in its i. r. spectrum is consistent with the presence of the isoxazolin-5-one nucleus while a signal at $\delta 6.71$ in its ^{1}H n. m. r.

(173)

(177)

-NH₃

(180)

Ac₂O
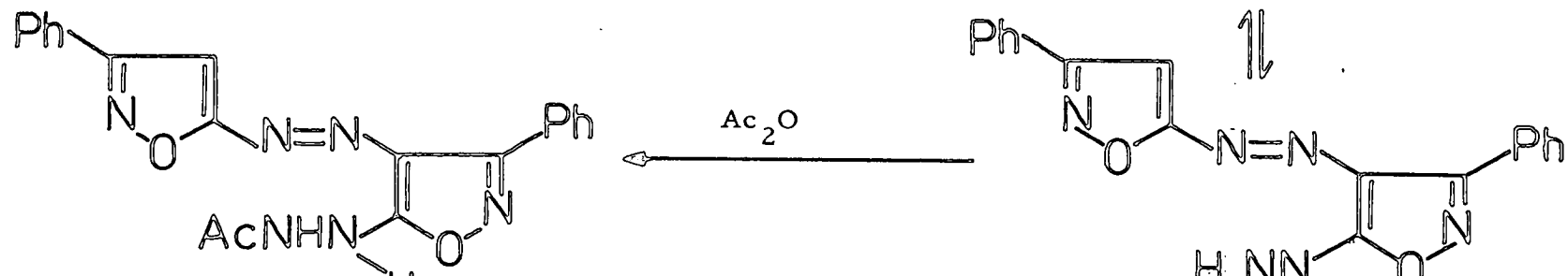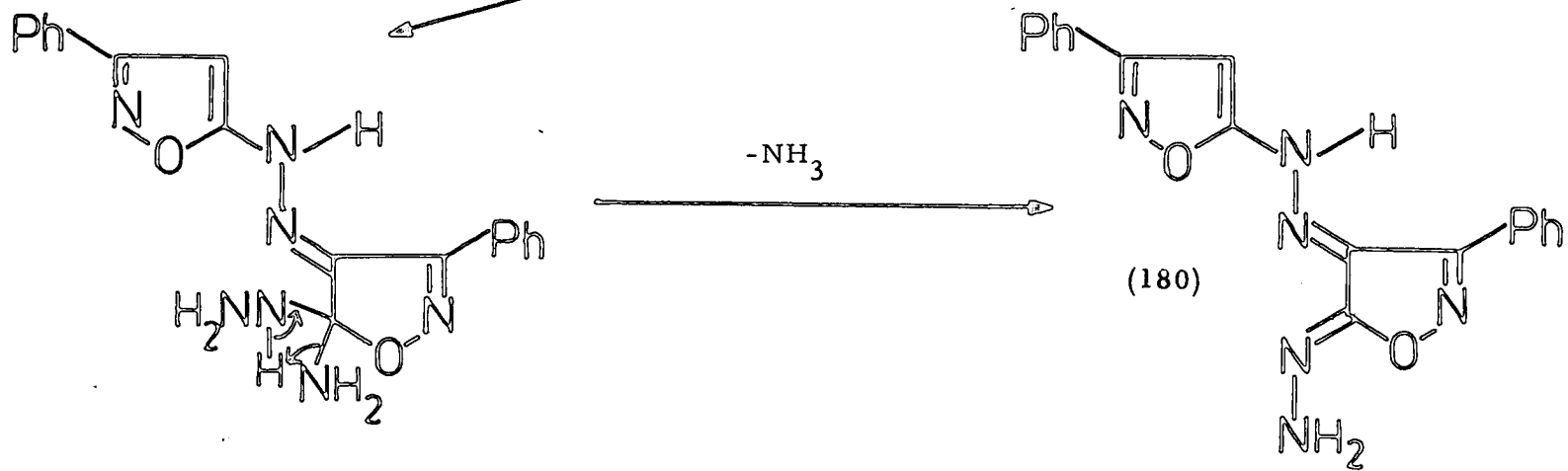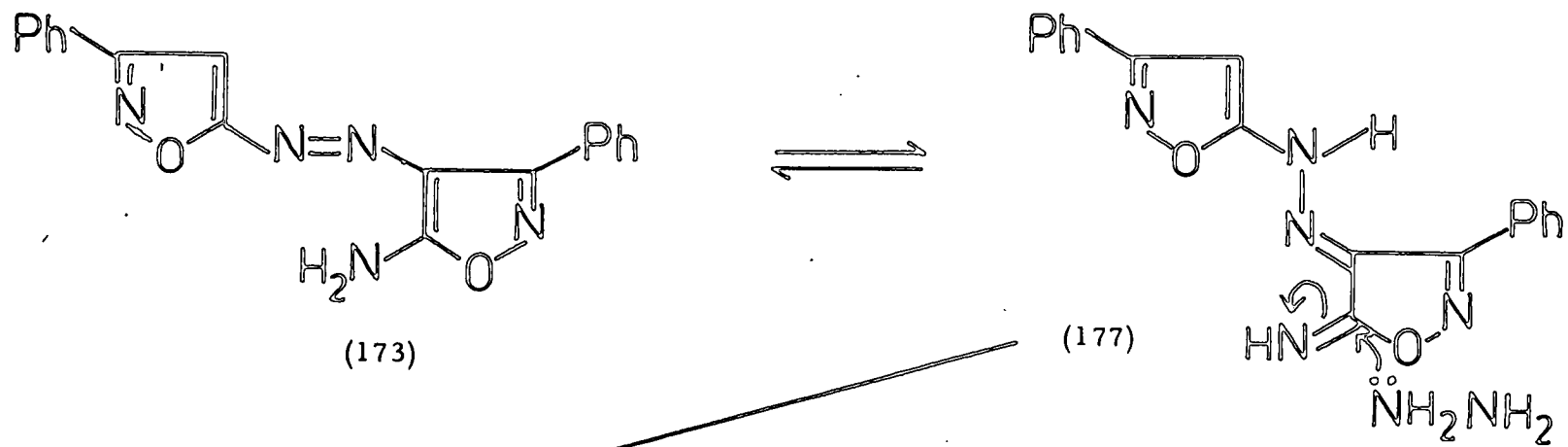
spectrum can be assigned to the proton at the 4-position in an
isoxazole ring. The isoxazolin-5-one structure (178) for the
hydrolysis product of the azo-compound (173) was further substantiated
by its reaction with hydrazine to give the pyrazole derivative (179)
(Scheme 67). The reaction of isoxazolin-5-one derivatives with
hydrazines will be fully discussed later in this chapter. An attempt
to acetylate the hydrazone (179) with acetic anhydride gave only
unreacted starting material. 5-Amino-4-(3'-phenylisoxazol-5'-
ylazo)-3-phenylisoxazole (173) also reacted with hydrazine to give
a product in good yield which analysed correctly for $C_{18}H_{14}N_6O_2$
and is tentatively assigned the tautomeric bis-hydrazone structure
[(180)$\rightleftharpoons$(181)] (Scheme 68). This structure is substantiated by amino
absorption in the range 3600-3150 cm^{-1} in its i.r. spectrum and the
presence of a signal at $\delta 6.53$ in its ^{1}H n.m.r. spectrum due to an
isoxazole C(4) proton. The bis-hydrazone [(180)$\rightleftharpoons$(181)] also formed
a monoacetyl derivative (182) (Scheme 68) whose structure is consistent
with spectroscopic evidence. Its i.r. spectrum contains NH absorption
and bands at 1700 and 1680 cm^{-1} assignable to carbonyl and C=N groups.
Its ^{1}H n.m.r. spectrum showed signals at $\delta 2.06$ and 6.72 attributable
to a single methyl group and a solitary C(4) isoxazole proton. Forma-
tion of the bis-hydrazone (181) can be rationalised (Scheme 68) by
hydrazinolysis of the imino tautomer (177) of the azo compound (173).

With a view to firmly establishing the structure of the amino-
azo compound (173) an attempt was made to synthesise unambiguously
the derived hydrazone (178) by condensing the amine (171) with the
available oxime (174) (Scheme 69). In practice these two compounds
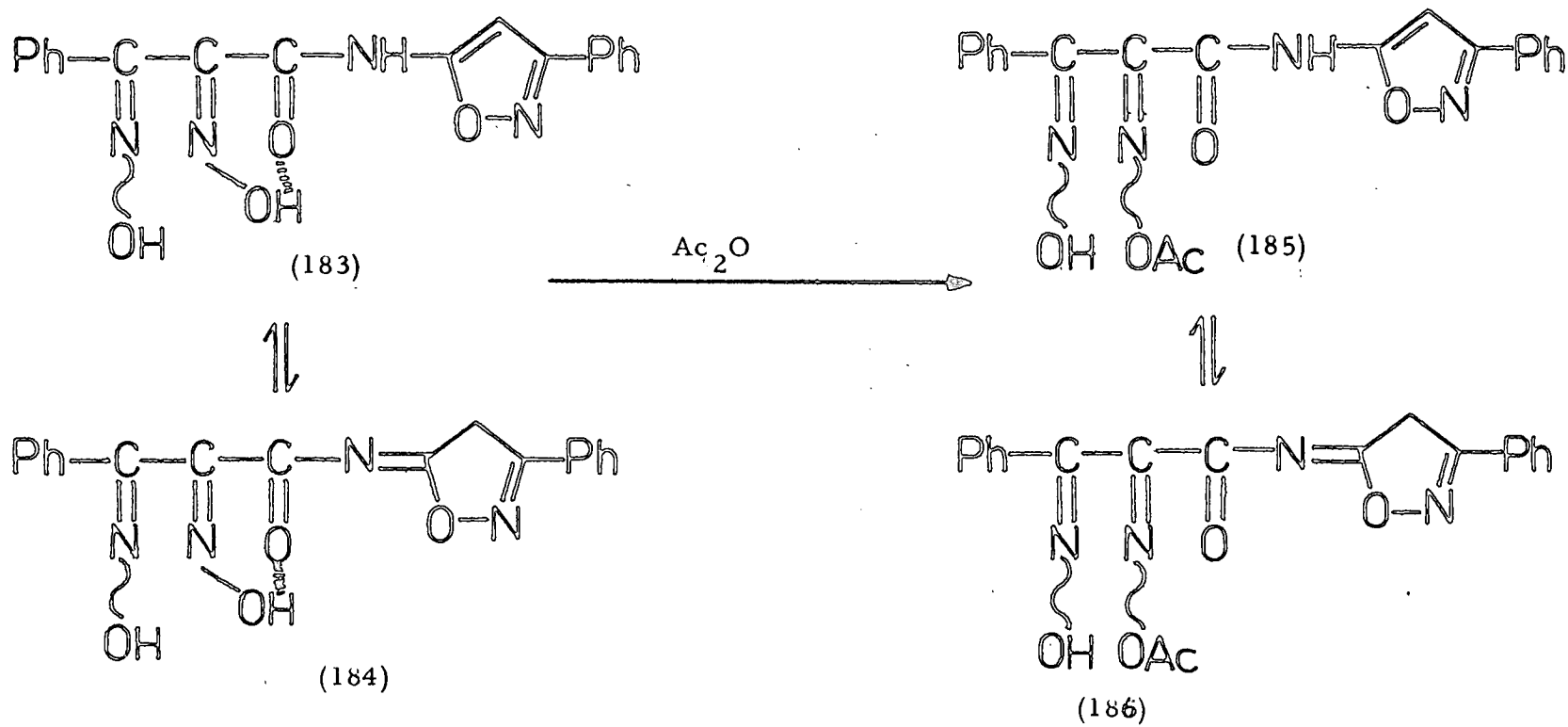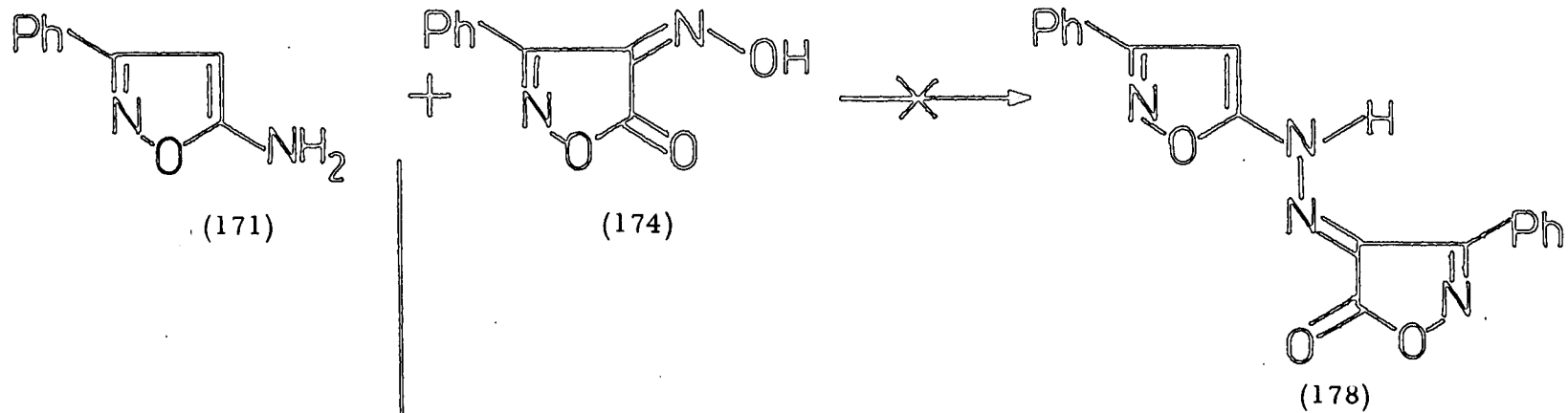
Scheme 69

condensed together in acetic acid to give a product which despite

its anomalous mass spectrum (M^+251) analysed correctly for a

simple adduct of the two starting materials. Its i.r. spectrum

contains several bands (3580-3140 cm^{-1}) characteristic of hydroxyl

and NH absorption and a high frequency carbonyl band at 1775 cm^{-1}.

Its ^{1}H n.m.r. spectrum contains a signal at δ5.43 due to a single

isoxazole C(4) proton. Closely related reactions of the syn-oxime

(174) with other aromatic amines will be discussed later. The

adduct (183) underwent acetylation to give a monoacetyl derivative

which showed high frequency i.r. carbonyl absorption at 1815 cm^{-1}

consistent[131] with the presence of an N-acetoxy group. Its mass

spectrum showed a parent ion peak at m/e 203. Though not entirely

consistent with certain of its spectroscopic properties the adduct is

tentatively formulated as the tautomeric system [(183)⇌(184)] and its

acetyl derivative correspondingly as [(185)⇌(186)]. The tentative

structure [(183)⇌(184)] is supported by hydrolysis of the adduct in

dilute sulphuric acid to give a product whose i.r. spectrum indicated

that it was a mixture of the anti-3-phenyl-Δ^2-isoxazolin-4,5-dione 4-

oxime (188), (see later) and 3-phenyl-Δ^2-isoxazolin-5-one (189) (Scheme

70). Crystallisation of the mixture failed to afford the isoxazolone (189)

but resulted in the isolation of the pure syn-oxime (174) derived by

(184)

(187)

(171)

(174)

(188)

(189)

Scheme 70

(171)

HONO

(172)

+(171)

(173)

+(171)
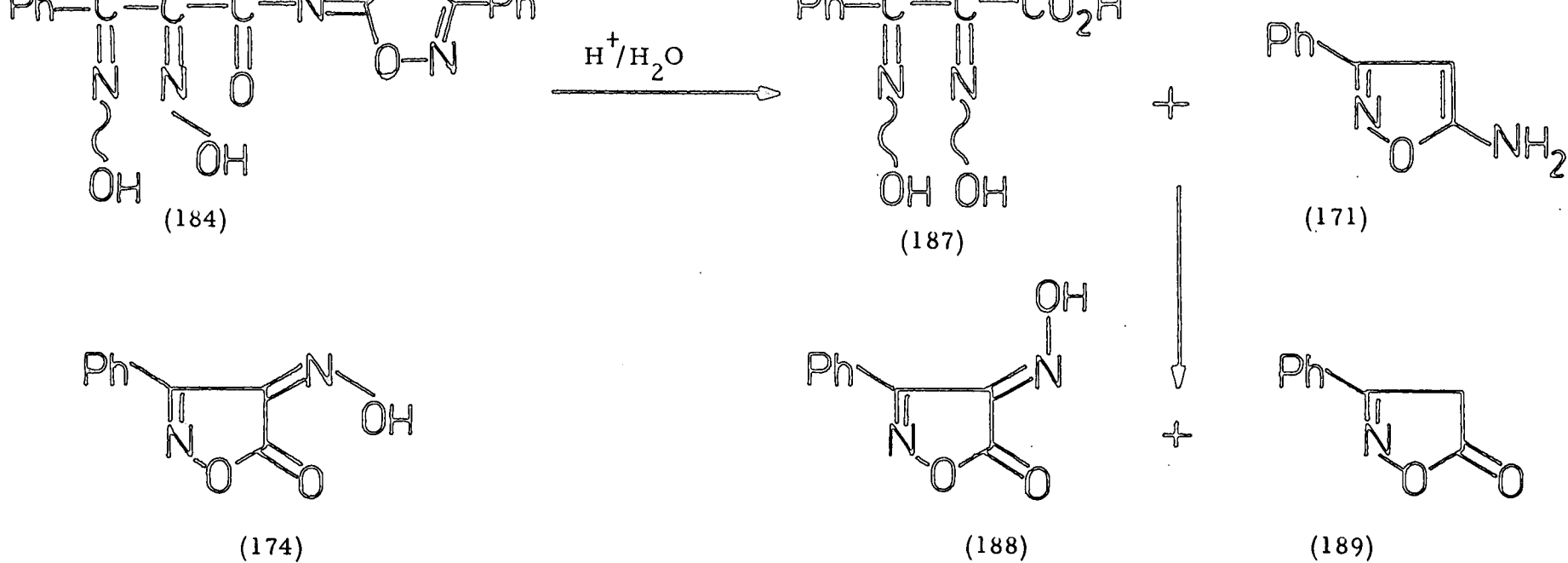
(190)
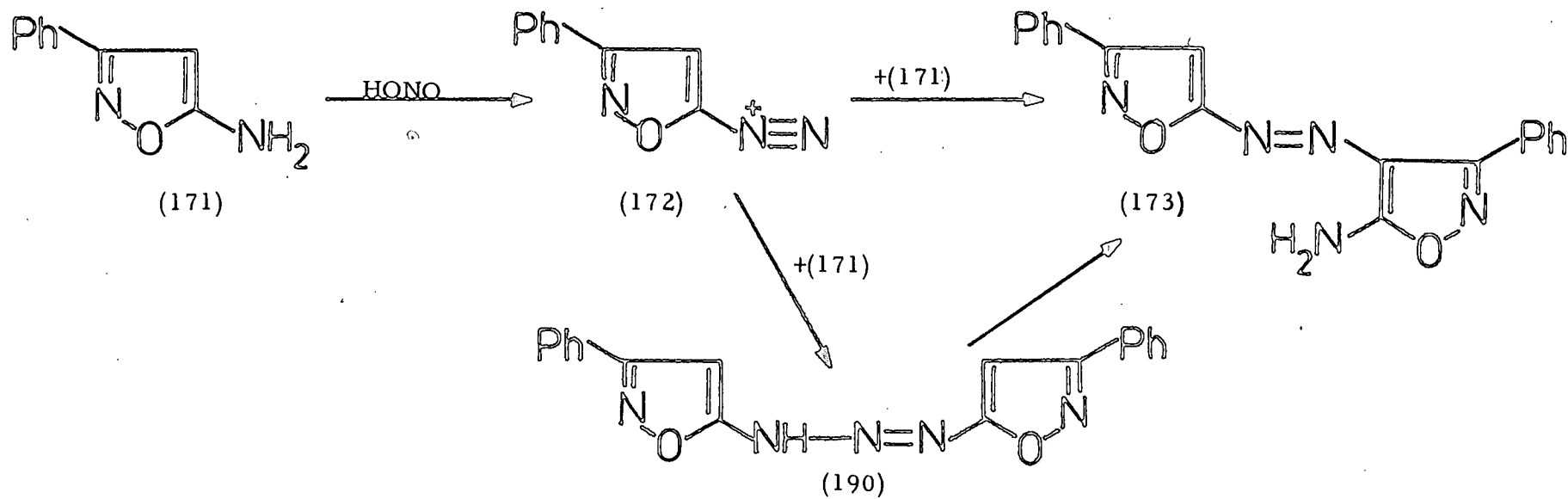
isomerisation of the anti-isomer (188). The formation of the anti-
oxime (188) and the isoxazolin-5-one (189) can be explained by
hydrolysis of the adduct (184) to yield the amine (171) and the dioximino-
carboxylic acid (187). Hydrolysis of the amino group in the former
would then account for the formation of the isoxazoline (189) while
cyclisation of the dioximino acid (187) would afford the anti-oxime
(188) (Scheme 70).

5-Amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173)
can be formed either by direct coupling of the diazonium cation (172)
with the C(4) position in unreacted 5-amino-3-phenylisoxazole (171)
or by initial formation of the triazene (190) (Scheme 71). Triazenes
are a class of compounds known[57] to rearrange under acidic conditions
to afford, via the regenerated diazonium cation [e.g. (172)], amino-azo
compounds [e.g. (173)] (Scheme 71). The nitration reactions of 5-
amino-3-phenylisoxazole (171) described before were carried out by
treating an acidic solution of the amine (171) with a nitrosating agent
and yielded two identifiable products, one derived exclusively from the
amine [the syn-oxime (174)] and the other [the amino-azo compound
(173)] derived presumably by coupling of the diazonium cation (172)
with unreacted amine (171). If this reasoning is correct reversing
the addition process by adding the acidic solution of the amine to an
aqueous solution of sodium nitrite should greatly reduce the opportunity
for reaction between the diazonium cation (172) and unreacted amine
(171) and hence the syn-oxime (174) should be the exclusive product.
In practice the product mixture obtained contained a significant
amount of the azo compound (173). One must deduce from this result

(174)

Ac$_2$O

(191)

(193)

Me—⬡—SO$_2$Cl

(192)
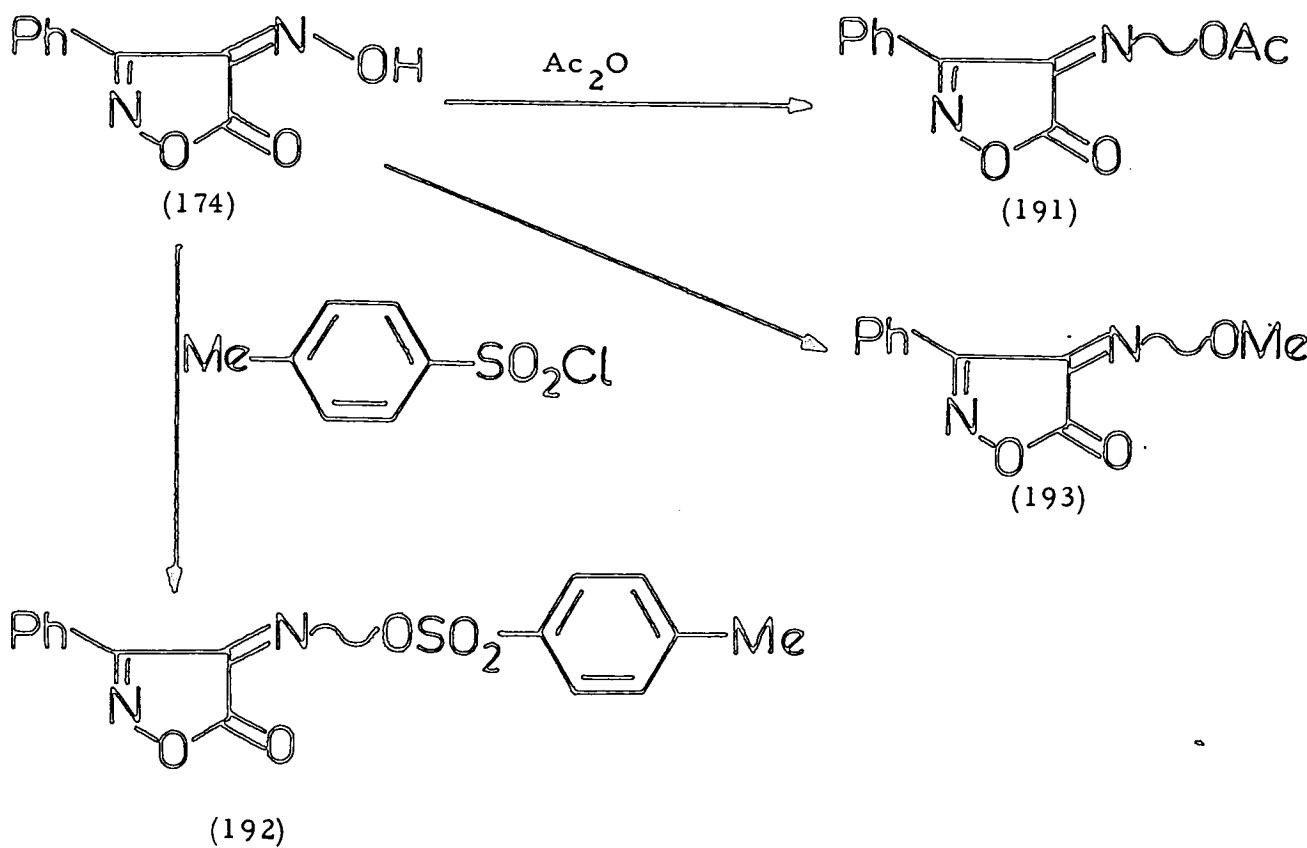
Scheme 72

that the formation of the oxime (174) is a relatively slow process compared with the coupling of the diazonium cation (172) with un-reacted amine (171).

The diazotisation of 5-amino-3-phenylisoxazole (171) has been shown to afford two products namely, 5-amino-4-(3'-phenylisoxazole-5'-ylazo)-3-phenylisoxazole (173) as discussed before and a second compound whose properties are consistent with it being _syn_-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174). A compound formulated as 3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (196) (Scheme 75) was claimed as the product of the reaction of 5-amino-3-phenylisoxazole (171) with nitrosating agents by Quilico[74] and Musante.[73] Furthermore the melting point reported by Musante[73] (157°) is in close agreement with that ($155-156^{\circ}$) obtained for the _syn_-oxime in the present study. The _syn_-oxime structure (174) was established spectroscopically and by chemical transformations, and was confirmed by synthesis. Its i.r. spectrum contained hydroxyl absorption at 3230 cm^{-1} attributable to an N-hydroxyl substituent and a high frequency carbonyl band at 1760 cm^{-1} consistent with the presence of an isoxazolin-5-one nucleus. Its ^{1}H n.m.r. spectrum showed only signals due to aromatic protons. The presence of the oximino substituent in (174) was further indicated by its conversion into a monoacetyl derivative whose i.r. spectrum contained a carbonyl band at 1815 cm^{-1} confirming[131] the N-acetoxy structure (191) (Scheme 72). The compound (174) also formed a monotosylate formulated by analogy as (192) (Scheme 72). The configuration of neither of the esters (191) or (192) could be established unequivocally. The product (174) also reacted readily with diazomethane
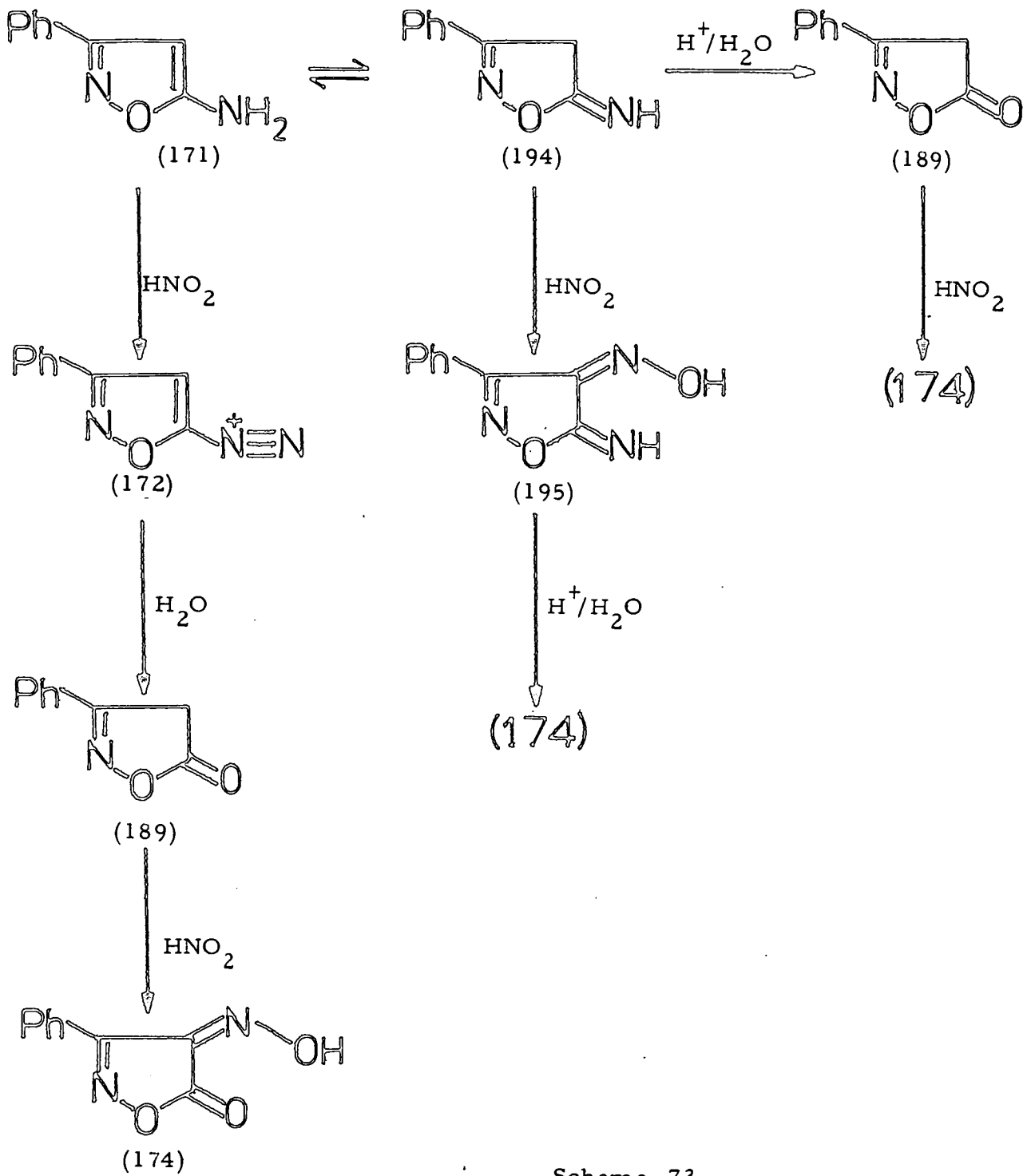
Scheme 73

to afford a single monomethyl derivative whose properties are
consistent with the N-methoxy structure (193) (Scheme 72) but do not
allow the assignment of its configuration.   Reduction of the syn-oxime
(174) was attempted using both sodium dithionite and catalytic hydro-
genation but neither method yielded any identifiable material.   The
attempted catalytic reduction of the oxime acetate (191) gave a gum
which was shown by t.l.c. to contain mainly starting material.   The
structure of the oxime (174) was firmly established by comparison with
a sample prepared by nitrosation of the isoxazolone (189).   Evidence
for the syn configuration of (174) will be discussed later.

There are several possible mechanisms which can account for
the formation of the syn-oxime (174) from the amine (171) (Scheme 73).
The most straightforward pathway involves diazotisation of the amine
(171) to afford the diazonium cation (172) which subsequently
hydrolyses to yield the isoxazolinone (189) nitrosation of which in the
C(4)-position would give the oxime (174).   The last step of this
mechanism is supported by the demonstration that nitrosation of 3-
phenyl-Δ^2-isoxazolin-5-one (189) with sodium nitrite in sulphuric
acid gives the syn-oxime (174) in high yield.   The other conceivable
mechanisms for the formation of the syn-oxime on nitrosation of 5-
amino-3-phenylisoxazole (171) under acidic conditions involve the
participation of the tautomeric 5-imino-3-phenyl-Δ^2-isoxazoline (194)
which is known[129] to cleave hydrolytically in the presence of acids to
afford 3-phenyl-Δ^2-isoxazolin-5-one (189).   The syn-oxime (174) can
then either be derived by nitrosation of the isoxazolinone (189) or by
nitrosation of the imino tautomer (194) followed by hydrolysis of the

imino group. The involvement of the diazonium cation (172) tends to be supported by the co-formation of the diazoamino compound (173) (Scheme 71). However the involvement of the other pathways to (174) cannot be excluded.

It was discovered that if syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174) was chromatographed on a silica column a different compound was obtained. The product eluted in very high yield from the column had a carbonyl band at 1790 cm^{-1} in its i.r. spectrum, whereas the syn-oxime (174) had a band at 1760 cm^{-1}. Crystallisation of this compound from toluene, or treatment with sodium hydrogen carbonate followed by acidification of the resulting solution, reformed the syn-oxime (174). Carbonyl absorption at 1790 cm^{-1}, indicating the presence of a third product was noted in the i.r. spectra of some of the mixtures formed on nitrosation of 5-amino-3-phenylisoxazole (171). As these mixtures were subsequently worked up using sodium hydrogen carbonate solution and the syn-oxime (174) isolated by acidification, it is possible that the product absorbing at 1790 cm^{-1} was the original product of nitrosation. As the i.r. spectra of this compound and that of the syn-oxime (174) were identical in solution, the compound with i.r. carbonyl absorption at 1790 cm^{-1} is formulated as anti-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (188) (Scheme 70). The discrete existence of syn and anti isomers of oximes is well known as demonstrated by Goldschmidt and Beckmann[132] and the interconversion of the geometrical isomers photochemically, thermally and by acid and base catalysis has been achieved.[133, 134] Palm and Werbin[135] have shown for a series of oximes that the solid state infrared

spectra differ between geometrical isomers but that in solution both isomers give identical spectra. The configurations of the syn- and anti-oximes (174) and (188) were assigned on the basis of their respective i. r. carbonyl stretching frequencies. Thus, the configuration assigned to the syn-oxime (174) is based on the ability of its oxime hydroxyl group to hydrogen bond intramolecularly with the carbonyl group (Scheme 74) thus resulting in a lowering of its i. r. stretching frequency (1760 cm^{-1}) compared with that (1790 cm^{-1}) of the anti-oxime (188) which cannot, for steric reasons, exhibit intramolecular hydrogen bonding (Scheme 74). The reliability of the variation in the isoxazolin-5-one carbonyl stretching frequency as a means of assigning the oxime configuration is vindicated by the high frequency (1790 cm^{-1}) of the C(5) carbonyl group in the oxime acetate (191) (Scheme 72) in which hydrogen bonding is no longer possible.

Several chemical transformations were carried out on the anti-oxime (188) to confirm its structure and compare its behaviour with the syn-isomer (174). Reaction with diazomethane under very mild conditions gave a monomethyl ether identical to that of unknown configuration [Scheme 72; (193)] formed by the syn-oxime (174). The formation of an identical methyl ether under very mild conditions is very convincing evidence that both of the compounds in question are geometrically isomeric oximes. Acetylation of the anti-oxime (188) likewise yielded the same oxime acetate [Scheme 72; (191)] as prepared from the syn-oxime (174). The attempted catalytic reduction of the anti-oxime (188) gave an intractable red solid which was shown by t. l. c. to be a multicomponent mixture.

(188)

(174)

Scheme 74

(196)

[(187)]

(197)

Scheme 75

(198)

H^+

OH^-

(199)
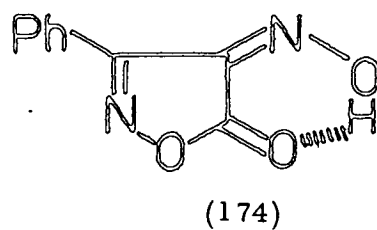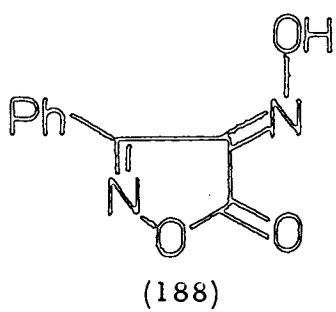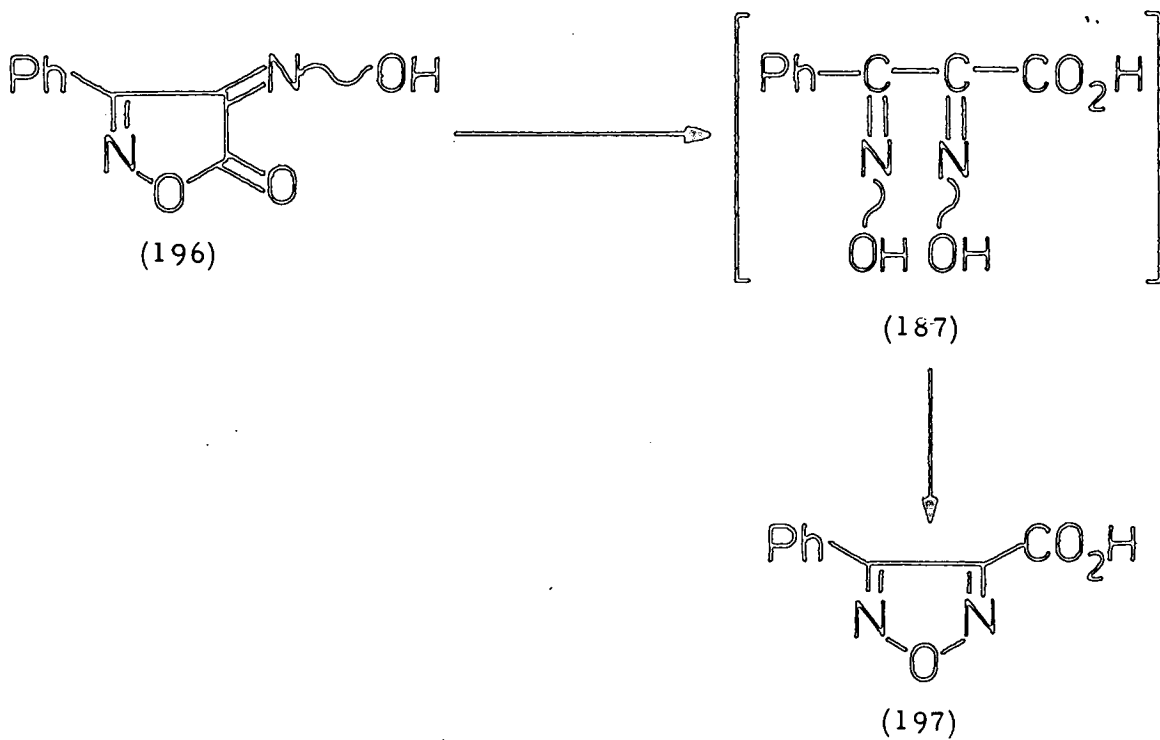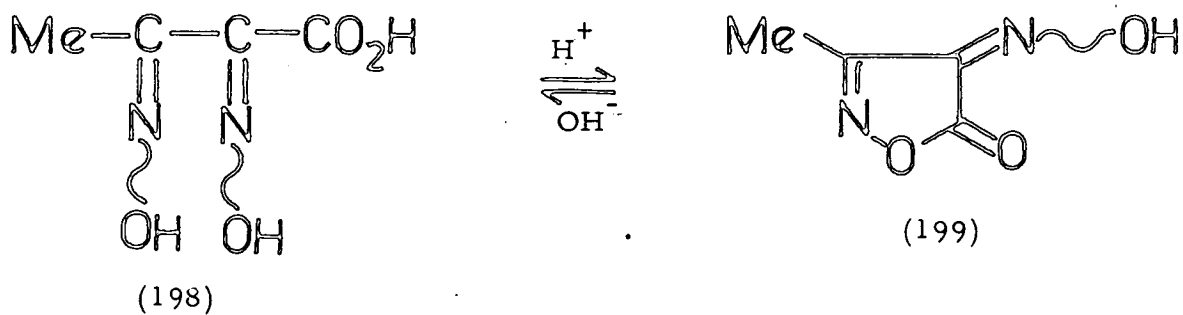
Scheme 76

Reports in the literature by Musante[73] and Nussberger[136]

indicate that treatment of 3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime

(196) with hot saturated aqueous sodium carbonate solution followed by

acidification with sulphuric acid affords 3-phenyl-1, 2, 5-oxadiazole-4-

carboxylic acid (197) via the postulated dioximino carboxylic acid

intermediate (187) (Scheme 75). Furthermore it is known[129, 136] that

2, 3-dioximinobutyric acid (198) exists in equilibrium in aqueous solution

with 3-methyl- Δ^2-isoxazoline-4, 5-dione 4-oxime (199) (Scheme 76).

The cyclic compound (199) is reformed on acidification or by evaporating

an ethereal solution of the acid (198). The equilibrium can be dis-

placed towards the dioxime (198) in strong alkali or hot carbonate

solutions (Scheme 76). In order to see if the syn-oxime (174) would

behave similarly it was treated with aqueous sodium carbonate and

the resulting solution was acidified with dilute sulphuric acid to give

a compound whose i.r. spectrum differed from the syn-oxime (174)

in containing a broad absorption at 2650 cm^{-1} and a carbonyl band at

1765 cm^{-1} indicating (despite the somewhat high frequency of the

latter) that it might be the carboxylic acid (187) (Scheme 75). However,

though the nature of this substance has not been definitely established

it is in all probability simply a monohydrate of the syn-oxime (174).

This contention is supported by the formation of the compound when

a solution of the syn-oxime (174) in aqueous sodium hydroxide is

acidified with sulphuric acid. Moreover the compound and the syn-

oxime (174) show identical i.r. spectra in solution and the former

may be converted into the latter simply on crystallisation from toluene.

Also methylation of the presumed hydrate with diazomethane under
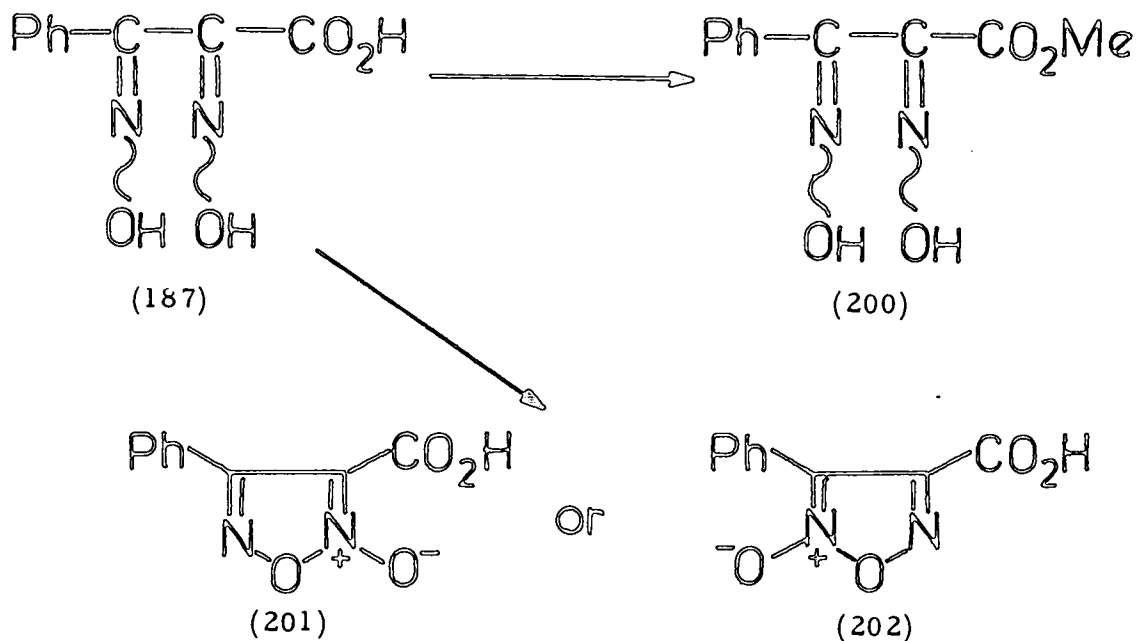
Scheme 77
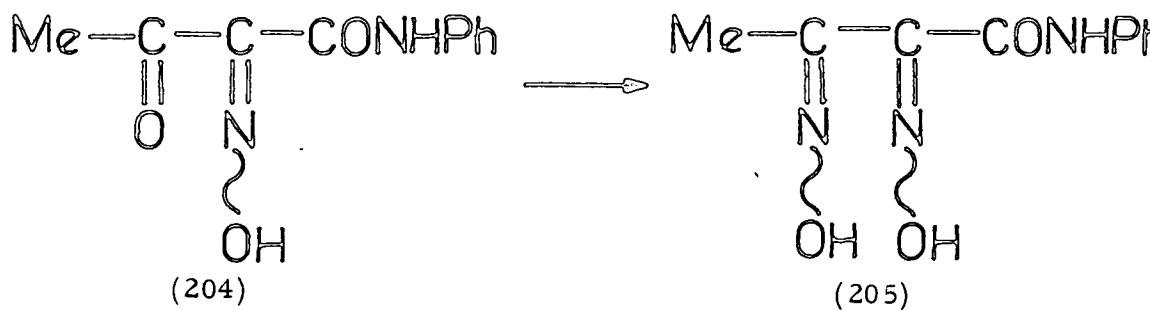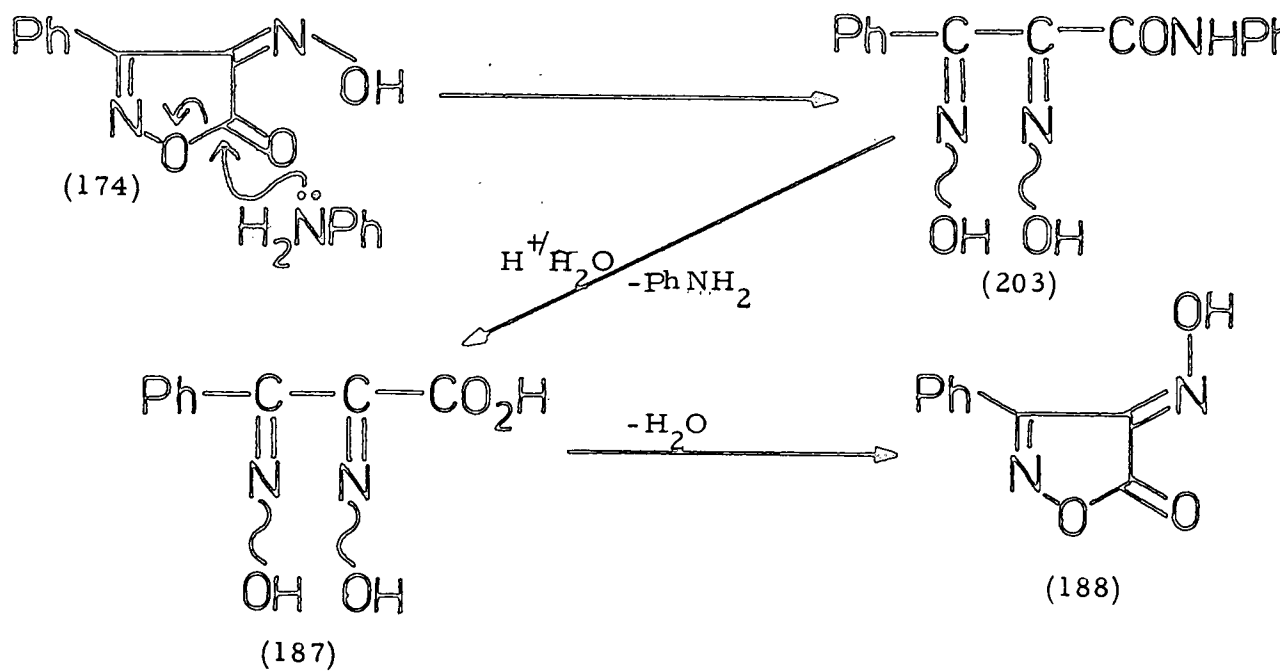
Scheme 78

mild conditions gave the methyl ether (193) (Scheme 72) prepared previously from the syn-oxime (174), and not the methyl ester (200) (Scheme 77) anticipated had the carboxylic acid structure (187) been correct. In addition, the compound failed to undergo manganese dioxide oxidation to either of the furoxans (201) or (202) also expected on the basis of the carboxylic acid structure (187).

As already discussed the reaction of syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174) with 5-amino-3-phenylisoxazole (171) gave the adduct (183) (Scheme 69). In view of this result it was considered of interest to investigate the generality of the reactions of the oxime (174) with other amines. The syn-oxime (174) was therefore reacted with the simplest aromatic amine, aniline, by stirring a solution of the reactants in acetic acid at room temperature for 47 h to afford a quantitative yield of a product which analysed for $C_{15}H_{13}N_3O_3$ and is formulated as the dioximinoanilide (203) (Scheme 78) on the basis of the following evidence. Its i. r. spectrum contained a single carbonyl band at 1660 cm^{-1} indicative of the presence of an amide group and demonstrating the absence of an isoxazolin-5-one nucleus. This absence can be explained if ring-opening has occurred to give a dioximino grouping, the presence of which in the product (203) is substantiated by hydroxyl absorption at 3450-3050 cm^{-1} in its i. r. spectrum. Formation of the dioximino compound (203) is readily explained (Scheme 78) by attack of the amino group of aniline at the C(5) carbonyl group of the syn-oxime (174), followed by opening of the isoxazolinone ring and proton transfer. The methyl analogue (205) of the dioximino compound (203) has been

Ph—C—C—CONHPh   [O]   Ph——CONHPh

‖ ‖

N N

OH OH

(203)

O⁻—N⁺—O—N

(206)

Scheme 79

Ph—C—C—CONHPh

‖ ‖

N N

HO HO

(207)

Ph—C—C—CONHPh

‖ ‖

N N

HO OH

(208)

Ph—C—C—CONHPh

‖ ‖

N N

HO OH

(209)

Ph—C—C—CONHPh

‖ ‖

N N

OH OH

(210)
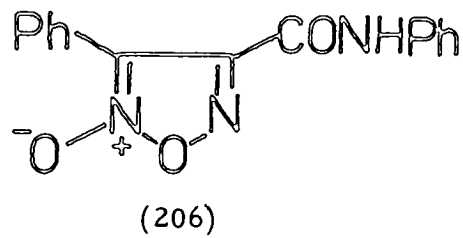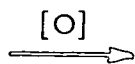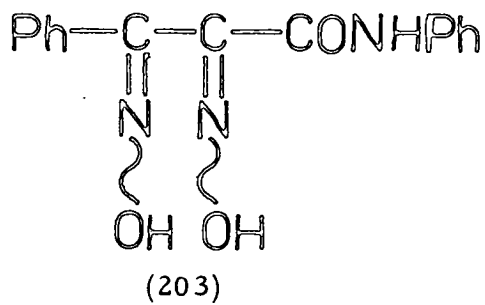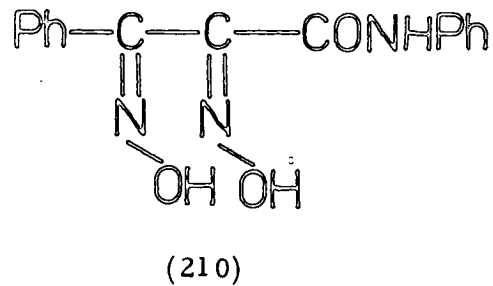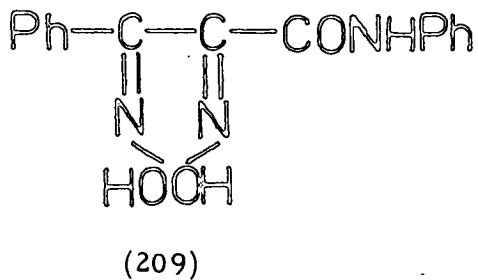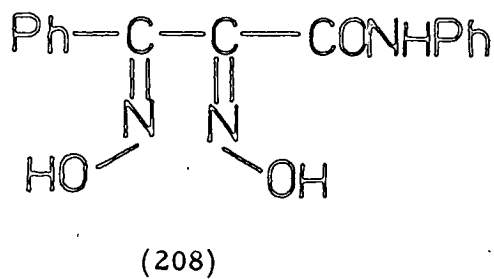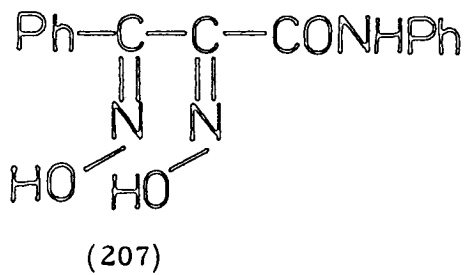
Scheme 80

prepared[137] by reacting the oxime (204) with hydroxylamine hydrochloride (Scheme 78). The attempted acetylation of the dioximino-anilide (203) under both mild and forcing conditions gave only intractable gums rather than the sought for diacetyl derivative. However, in accord with the assigned structure, acidic hydrolysis of the dioxime (203) gave aniline and the anti-oxime (188) whose formation is readily explained (Scheme 78) by ring-closure of the dioximino carboxylic acid (187) formed by initial hydrolysis.

In further support of the assigned structure the oxidation of the dioxime (203) with manganese dioxide in refluxing dioxan afforded a small amount of a solid, m. p. 139°, whose i. r. and mass spectra are consistent with the furoxan structure (206) (Scheme 79). However insufficient material was obtained for elemental analysis or further characterisation. In an attempt to obtain the presumed furoxan (206) in larger quantity the manganese dioxide oxidation of the dioxime (203) was carried out under milder conditions at room temperature. However these conditions gave a beige solid which changed on crystallisation from ethyl acetate to give a colourless solid with vastly different melting point and i. r. spectrum. The colourless solid was shown by elemental analysis to be isomeric with the dioxime (203) and both compounds had identical mass spectroscopic fragmentation patterns. The similarity of the i. r. spectra of the two isomeric solids and the unstable beige solid is consistent with their being configurationally isomeric dioximes (207)-(210) (Scheme 80) or mixtures thereof.

An attempt was also made to firmly establish the structure of the dioxime (203) by independent synthesis. This was based on the

PhNH$_2$ + PhCOCH$_2$CO$_2$Et $\longrightarrow$ PhCOCH$_2$CONHPh

(211)

$\downarrow$ NH$_2$OH

HNO$_2$

PhCO—C—CONHPh
$\parallel$
N
$\sim$
OH

(212)

$\left[\text{Ph—C—CH}_2\text{CONHPh} \right]$
$\parallel$
N
$\sim$
OH

(213)

Ph—C—C—CONHPh
$\parallel$ $\parallel$
N N
$\sim$ $\sim$
OH OH

(203)

(189)

Scheme 81

(174)
Ph—C ... N—OH
$\parallel$
N—O ... O

$\xrightarrow{\text{PhCH}_2\text{NH}_2}$

Ph—C—C—CONHCH$_2$Ph
$\parallel$ $\parallel$
N N
$\sim$ $\sim$
OH OH

(214)
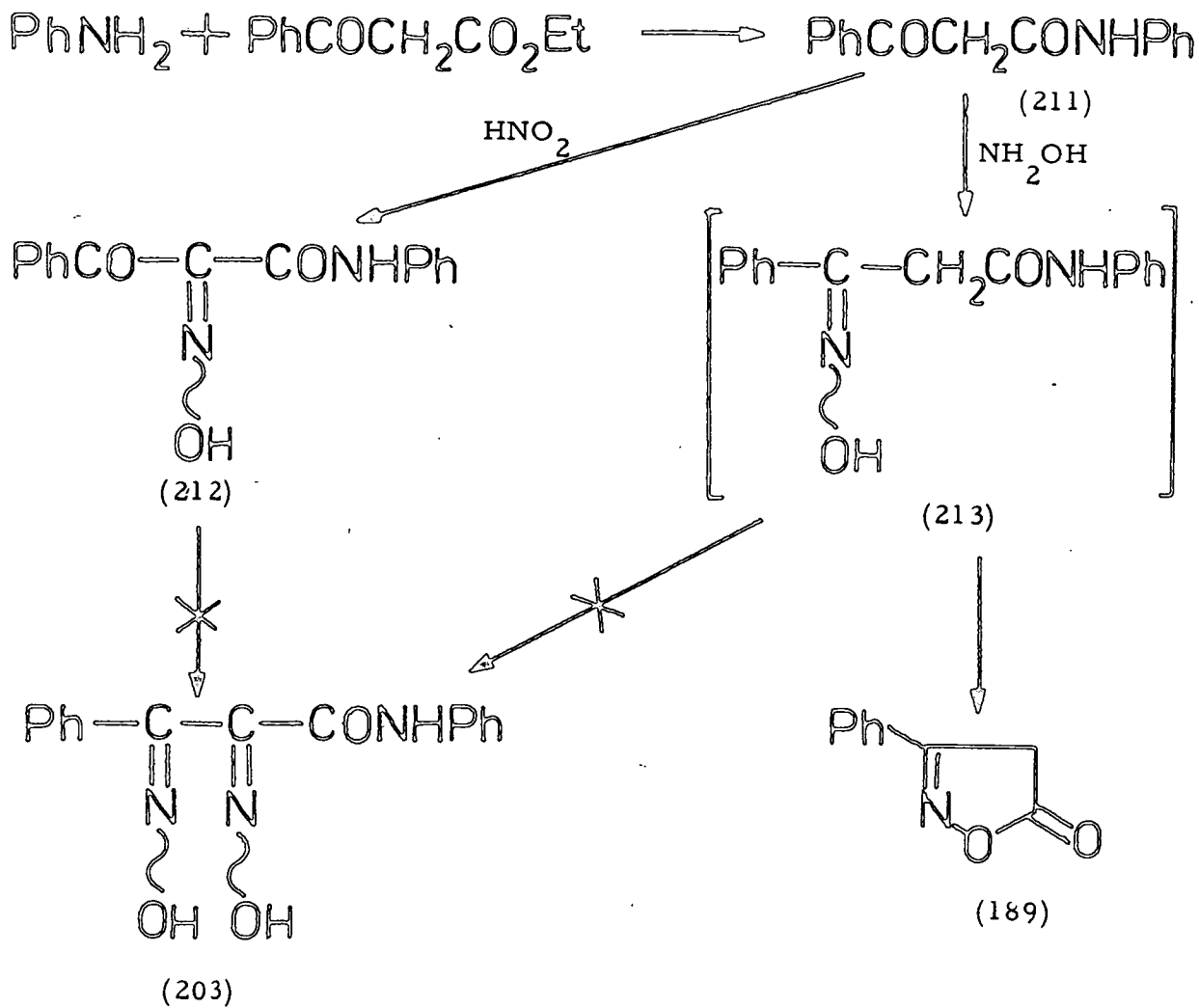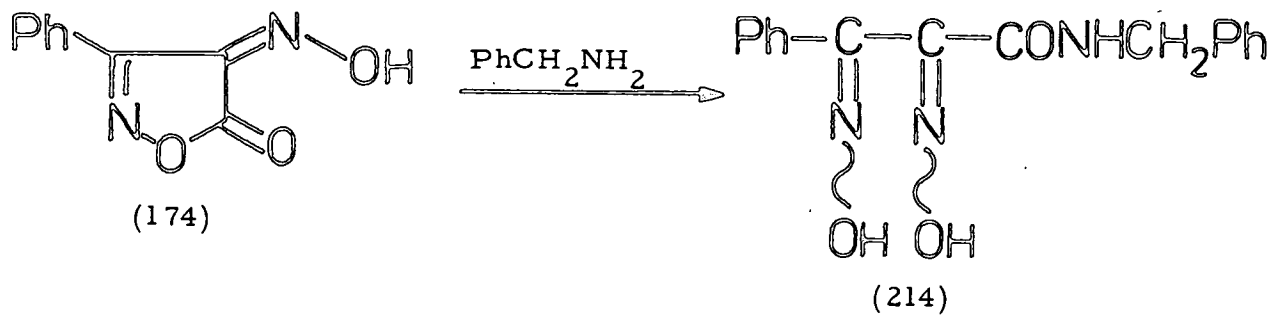
Scheme 82

stepwise oximation of benzoylacetanilide (211) readily available by

the reaction[138] of ethyl benzoylacetate with aniline (Scheme 81).

The nitrosation of the anilide (211) occurred smoothly using sodium

nitrite in a mixture of acetic acid and phosphoric acid to afford $\underline{N}$,

3-diphenyl-2, 3-dioxopropionamide 2-oxime (212) in high yield.

However attempts to convert the monoxime (212) into the dioxime

(203) by reaction with hydroxylamine were unsuccessful, only starting

material being recovered. The alternative approach to (203) of

reacting benzoylacetanilide (211) initially with hydroxylamine to give

the isomeric monoxime (213) followed by nitrosation was thwarted by

the spontaneous cyclisation of the oxime (213) to 3-phenyl-Δ^2-isoxazolin-

5-one (189) (Scheme 81).

The $\underline{syn}$-oxime (174) also reacted readily with the aliphatic

primary amine, benzylamine, to afford a product which gave analytical

data and showed spectroscopic properties consistent with the dioxime

structure (214) (Scheme 82) analogous to the products obtained by

reacting the $\underline{syn}$-oxime (174) with aniline and 5-amino-3-phenylisox-

azole (171). The i.r. spectrum of (214) contained hydroxyl and NH

absorption at 3410-3180 cm^{-1} and also a carbonyl band at 1640 cm^{-1}

typical of an amide. The ^{1}H n.m.r. spectrum clearly showed the

incorporation of the benzyl residue into the product. The $\underline{syn}$-oxime

(174) also reacted with ammonia in ethanol to afford an orange-pink

solid which was separated by heating with toluene into a soluble

component identical with the starting oxime (174) and an insoluble

pink solid. The latter could not be crystallised and on treatment

with dilute hydrochloric acid afforded the hydrate of the oxime (174)

described previously.   This behaviour together with the mass spectrum of the pink solid which showed a parent ion at m/e 190 indicate it to be the ammonium salt of the oxime (174).   This assignment is supported by the i.r. spectrum which contains NH absorption at 3150 and 3050 cm^{-1}.   The syn-oxime (174) also reacted readily with N-methylaniline to afford an orange-pink solid, m.p. 80-83°, which when crystallised from benzene–light petroleum gave the anti-oxime (188).   It is tentatively suggested that this orange-pink solid is an unstable N-methylanilinium salt of the oxime (174).   In contrast, reaction of the syn-oxime (174) with piperidine gave a stable piperidinium salt which could be crystallised unchanged and gave analytical and spectroscopic data and showed chemical properties consistent with the structure (215) (Scheme 83).   Thus its i.r. spectrum contained several NH bands between 3070 and 2420 cm^{-1} and its ^{1}H n.m.r. spectrum contained signals due to both a phenyl group and a piperidine group.   However its mass spectrum showed a parent ion at m/e 190, consistent more with a molecular complex than an ionic structure (215).   On the other hand the piperidinium salt structure (215) is in accord with the conversion of the compound in dilute hydrochloric acid in quantitative yield into the hydrate of the oxime (174).

In view of the readiness with which the oxime (174) reacts with amines it was of interest to study the extension of such reactions to hydrazines.   The reaction of the syn-oxime (174) with two equivalents of hydrazine hydrate at room temperature afforded a product in moderate yield whose elemental analysis and spectroscopic properties

suggested that it might be a hydrazine salt of the pyrazolinone (216)

(Scheme 84). Thus its mass spectrum showed a parent ion at m/e

189 and its i. r. spectrum contained several bands in the OH/NH

stretching region together with a carbonyl band at 1700 cm^{-1}. In

an attempt to obtain the known[139] free pyrazolinone (216), the reaction

of the syn-oxime (174) with one equivalent of hydrazine in acetic acid

was attempted. However the unidentified product of this reaction

analysed for $C_{12}H_{14}N_4O_3$ and was shown by its i. r. and ^1H n. m. r.

spectra to contain two acetyl groups. The syn-oxime (174) also

reacted with phenylhydrazine in acetic acid to afford a product in

moderate yield whose properties are consistent with it being syn-

1, 3-diphenyl- Δ^2-pyrazoline-4, 5-dione 4-oxime (218) (Scheme 84).

Its i. r. spectrum contained a hydroxyl band at 3130 cm^{-1} and a

carbonyl band at 1685 cm^{-1} indicating clearly that the isoxazolinone

ring was no longer present. The structure of this product was

verified by its independent synthesis by nitrosation of 1, 3-diphenyl-

Δ^2-pyrazolin-5-one (217) as described by Knorr and Klotz.[140] The

anti-oxime (188) also gave the same product (218) in similar yield

on reaction with phenylhydrazine. Reduction of syn-1, 3-diphenyl-

Δ^2-pyrazoline-4, 5-dione 4-oxime (218) with sodium dithionite afforded

a good yield of a brick red solid which analysed for $C_{30}H_{21}N_5O_2$ and

gave mass spectroscopic data consistent with the structure (219).

However the i. r. spectrum of the product was ill-defined and the

assignment of structure (219) remains tentative for the present.

Syn-1, 3-diphenyl- Δ^2-pyrazoline-4, 5-dione 4-oxime (218) reacted

under mild conditions with acetic anhydride to afford the acetyl
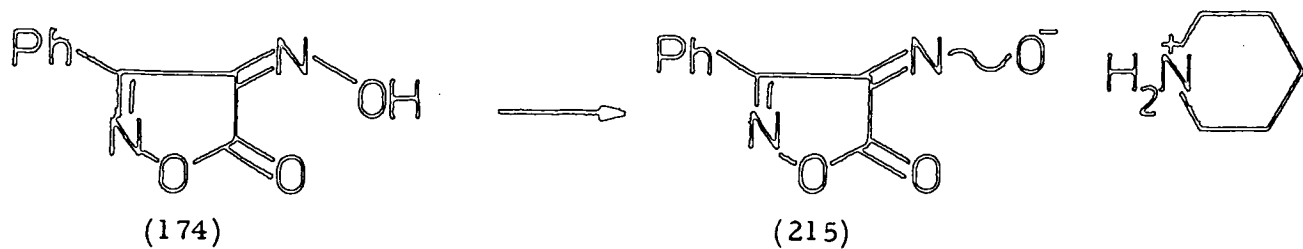
Scheme 83
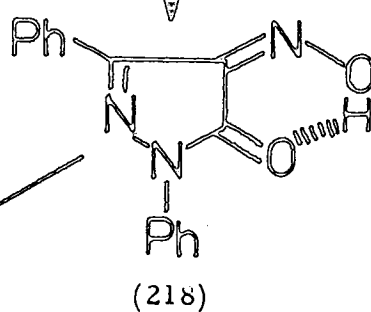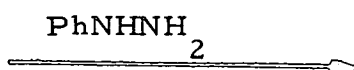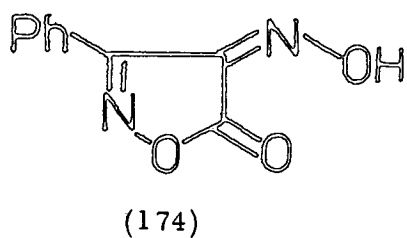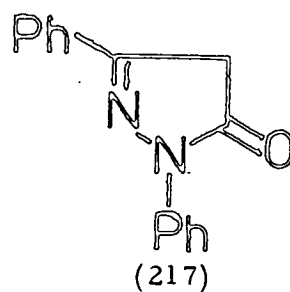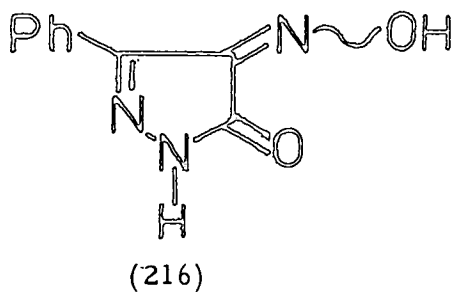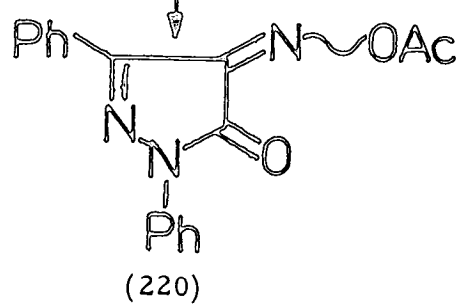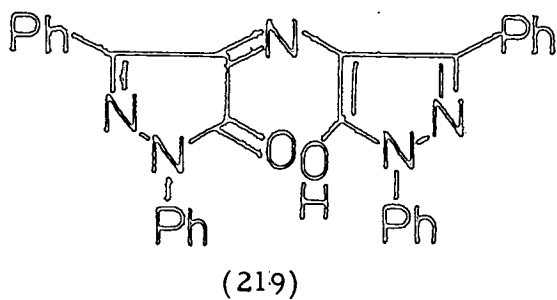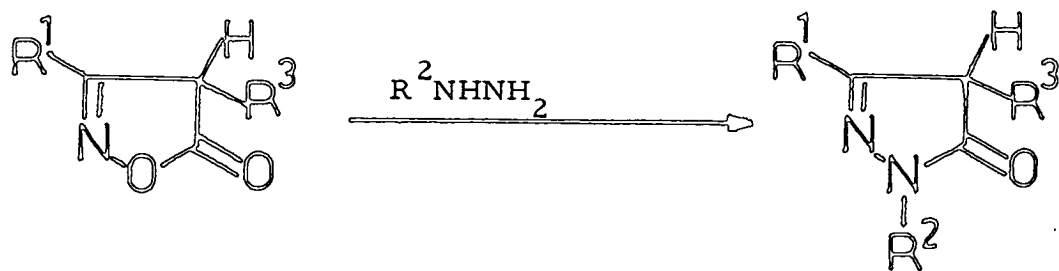
Scheme 84

(R'=Me, Ph),   (R^2=H, Ph),   (R^3=H, -N=N-Ar)

Scheme 85

(221)

PhNHNH$_2$
EtOH/ Δ

(222)

AcOH/ Δ

(223)
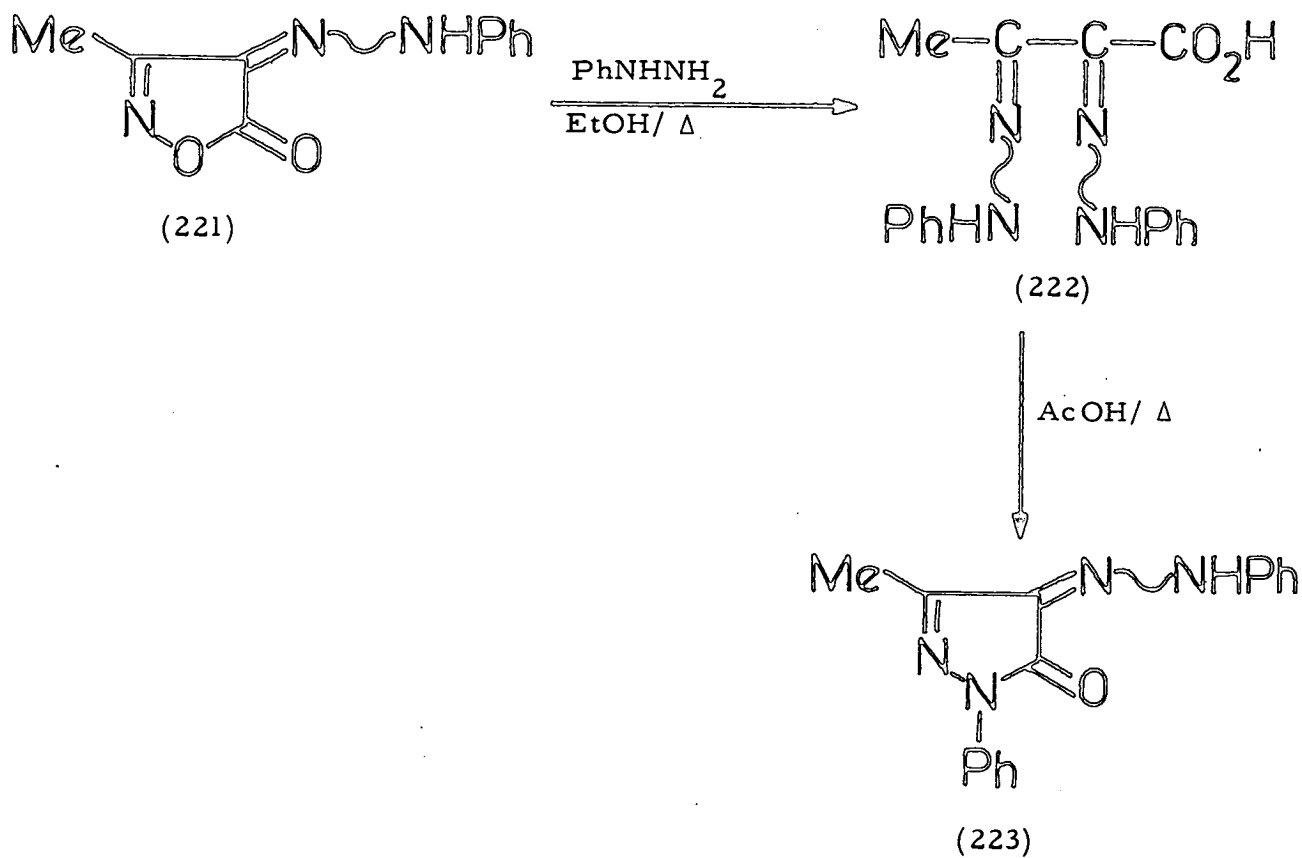
Scheme 86

derivative (220) (Scheme 84) in good yield. It was possible to assign the syn configuration to the oxime (218) on account of the increased i.r. frequency of the pyrazolinone carbonyl group from 1685 cm^{-1} to 1725 cm^{-1} on acetylation. This large change in i.r. carbonyl frequency can be attributed to the disruption of intramolecular hydrogen bonding in the oxime (218) and hence the syn configuration of the oximino group. The acetyl derivative (220) was subsequently reduced catalytically to give a low yield of a red solid whose properties are consistent with it being the product (219) prepared previously by reducing the oxime (218). The attempted reaction of the syn-oxime (174) with hydroxylamine in aqueous solution resulted in the isolation of the hydrate of the oxime (174) obtained before.

Several different reactions have been carried out between the syn-oxime (174) and nitrogen nucleophiles including some primary and secondary amines. In addition a few reactions have been performed between hydrazine hydrate and azo dimers containing isoxazole or isoxazoline nuclei. It is clear that no one general reaction occurs with nitrogen nucleophiles, and indeed no general pattern can be discerned in the reactions with amines. From the results obtained several trends can be identified. The syn-oxime (174) yields salts on treatment with secondary amines and ammonia. It is possible that steric crowding around the nitrogen atom of secondary amines reduces the nucleophilicity of these amines. Salts are therefore formed if the amines are sufficiently basic. Primary amines attack the isoxazolin-5-one ring at the C(5) position with subsequent ring-opening and proton transfer to afford dioximino amides (see Schemes 69, 78
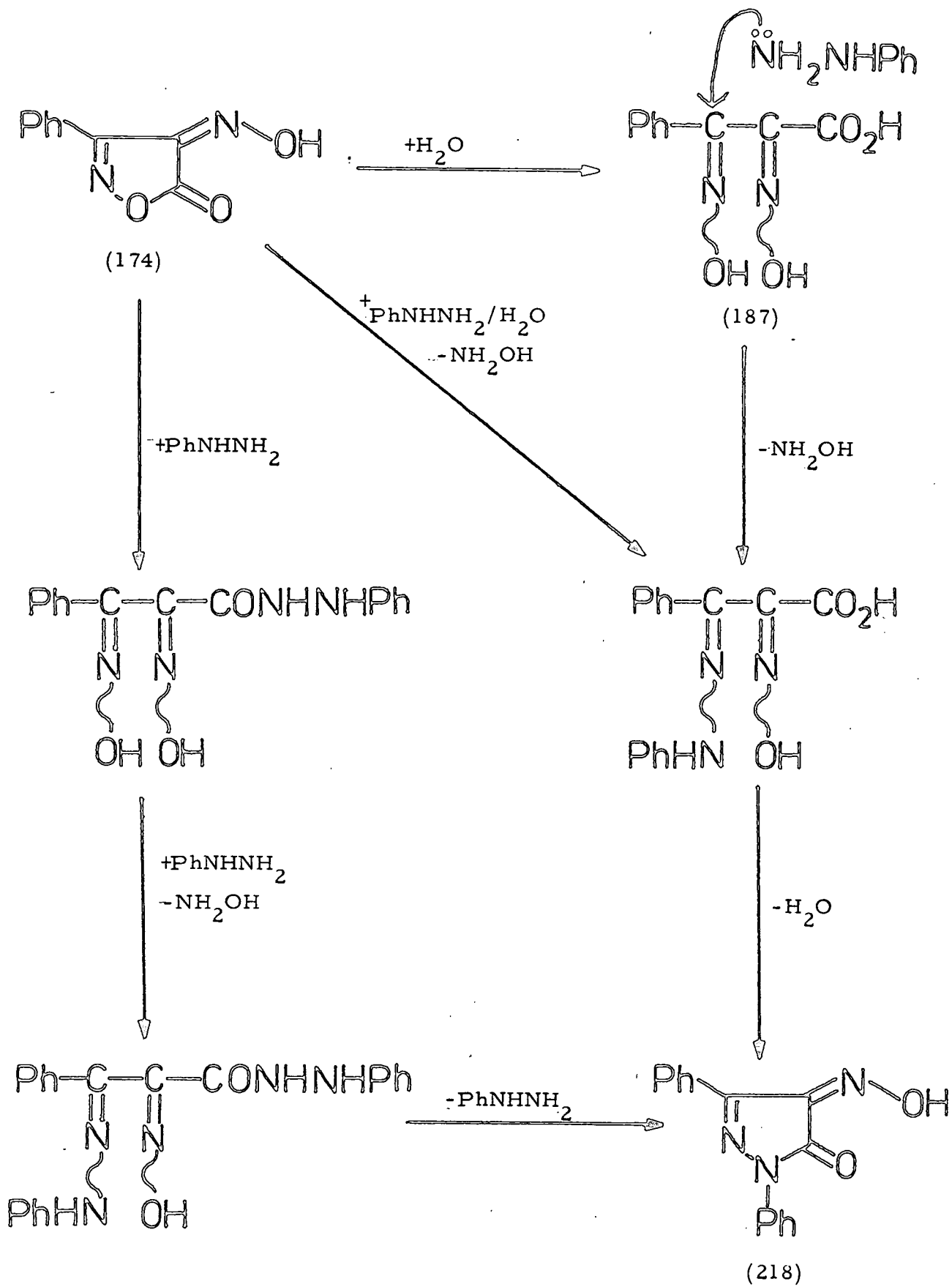
Scheme 87

and 82). The literature[129] contains several examples of the reactions
of hydrazines with isoxazoles and isoxazolines to afford pyrazoles
and pyrazolines (Scheme 85). The <u>syn</u>-oxime (174) was successfully
reacted with phenyl hydrazine to afford <u>syn</u>-1, 3-diphenyl-Δ^2-pyrazoline-
4, 5-dione 4-oxime (218). Attempts to prepare the analogous compound
(216) with hydrazine were not successful as discussed previously.
A similar type of reaction was observed in the reaction of 3-phenyl-
Δ^2-isoxazoline-4, 5-dione-4-(3'-phenylisoxazol-5'-yl) hydrazone (178)
with hydrazine to afford the pyrazoline hydrazone (179) (Scheme 67).
Evidence for the mechanism of the reactions of isoxazoline ring
systems with hydrazines has been provided by Bulow, Posner and
Knorr[137, 141, 142] who showed (Scheme 86) that phenylhydrazine
reacts with 3-methyl-Δ^2-isoxazoline-4, 5-dione 4-phenylhydrazone
(221) on heating in ethanol to give 2, 3-dioxobutyric acid <u>bis</u>-phenyl-
hydrazone (222) which cyclised on heating in acetic acid to afford the
pyrazoline derivative (223) (Scheme 86). Several mechanisms can
be written for the reaction between the <u>syn</u>-oxime (174) and phenyl-
hydrazine (Scheme 87). The initial attack can be considered to
occur either at the C(3) or C(5) position. However only attack at
the C(3) position would afford the type of intermediate (222) isolated
by Knorr[137] and in the absence of other evidence this must be the
favoured mechanism.

Experimental

5-Amino-3-phenylisoxazole (171)

(a) Benzoylacetonitrile (170) was prepared by the reaction of phenacyl bromide with potassium cyanide as described by Obregia[130] (97%), m.p. 74-78° (lit.,[130] m.p. 80-81°).

(b) 5-Amino-3-phenylisoxazole (171) was prepared by the reaction of benzoylacetonitrile (170) with hydroxylamine hydrochloride as described by Obregia[130] (73%), m.p. 107-109° (lit.,[130] m.p. 110-112°).

The Attempted Diazotisation of 5-Amino-3-phenylisoxazole (171) and Coupling with Acetylacetone.

(a) A solution of 5-amino-3-phenylisoxazole (171) (1.12 g; 0.007 mol) in glacial acetic acid (5.0 ml) was mixed with a solution of concentrated sulphuric acid (0.6 ml) in water (6.6 ml) and the mixture was treated dropwise with stirring at 0-5° with a 1M solution of sodium nitrite (7.0 ml). The suspension which formed was stirred for a few minutes and then a solution of acetylacetone (0.61 g; 0.006 mol) and anhydrous sodium acetate (9.47 g) in ethanol (50.0 ml) and water (30.0 ml) was added dropwise at 0-5°. The yellow suspension was stirred at 0-5° for 2 hours and then left at room temperature overnight. Filtration gave a yellow solid which was recrystallised from ethanol to afford 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) (0.38 g; 33%) as yellow needles, m.p. 167-167.5°, ν_{max} 3350w and 3150w (NH$_2$) and 1640 (NH def.) cm^{-1}, δ [(CD$_3$)$_2$SO]

9.60-9.20 (2H, brs, NH_2), 8.12-8.00 (2H, m, ArH), 8.00-7.88 (2H, m, ArH), 7.62-7.48 (6H, m, ArH) and 7.03 (1H, s, isoxazole CH).

Found: C, 65.5; H, 4.0; N, 21.3%; M^+331.

$C_{18}H_{13}N_5O_2$ requires: C, 65.3; H, 3.9; N, 21.2%; M 331.

The aqueous mother liquor was acidified with aqueous dilute hydrochloric acid to give a cloudy suspension which was extracted with methylene chloride to afford a yellow solid. This was crystallised from toluene to give syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (0.31 g; 23%) as cuboid crystals, m.p. 155-156°, ν_{max} 3230 br (OH) and 1760 (CO) cm^{-1}, ν_{max} (CHCl$_3$) 1785 cm^{-1}

Found: C, 57.0; H, 3.3; N, 14.5%; M^+190.

Calc. for $C_9H_6N_2O_3$: C. 56.9; H, 3.2; N, 14.7%; M 190.

(b) 5-Amino-3-phenylisoxazole (171) (1.21 g; 0.0076 mol) in glacial acetic acid (5.0 ml) was mixed with a solution of concentrated nitric acid (1.0 ml) in water (2.5 ml) and the mixture was treated dropwise with stirring at 0° with a solution of sodium nitrite (0.53 g; 0.0077 mol) in water (2.0 ml). The light brown suspension was stirred for 10 min and then a solution of acetylacetone (0.99 g; 0.01 mol) and anhydrous sodium acetate (8.93 g) in ethanol (50.0 ml) and water (30.0 ml) was added dropwise at 0-6°. The suspension was stirred for 2 h then left at room temperature overnight. Filtration gave 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) (0.26 g; 21%), m.p. 166-169°, identical (m.p. and i.r. spectrum) to a sample prepared before. The filtrate was concentrated to remove the ethanol, diluted with an equal volume of water and extracted with

chloroform (2x30 ml). The chloroform extract was washed with a saturated solution of sodium hydrogen carbonate (3x5 ml). Acidification of the sodium hydrogen carbonate washings with aqueous dilute hydrochloric acid and extraction with chloroform (2x20 ml) afforded an orange solid (0.10 g; 7%), m.p. 140.5-142°, ν_{max} 3150 br (OH) and 1790 and 1760 w (CO) cm^{-1}, which on crystallisation from toluene gave syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174), identical (m.p. and i.r. spectrum) to a sample prepared before.

The original aqueous mother liquor was acidified with aqueous dilute hydrochloric acid and extracted with chloroform (2x20 ml) to give a yellow solid (0.07 g; 5%), m.p. 145-148°, identical (i.r. spectrum) to a sample of syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) prepared before.

The Attempted Reductive Condensation of 3-Phenylisoxazole 5-diazonium Cation (172) with Acetylacetone.

A solution of 5-amino-3-phenylisoxazole (171) (1.13 g; 0.007 mol) in glacial acetic acid (10.0 ml) was mixed with a solution of concentrated sulphuric acid (0.6 ml) in water (6.6 ml) and the mixture was treated dropwise with stirring at 0-5° with a 1M solution of sodium nitrite (7.0 ml). The yellow suspension which formed was stirred for 10 min and then treated with an 80% v/v aqueous ethanol solution (70.0 ml) which had been previously saturated with sulphur dioxide. A brown solution formed and this was resaturated with sulphur dioxide and stirred at room temperature for 16 h. The resulting suspension was treated with acetylacetone (0.70 g; 0.007 mol)

and the mixture was heated under reflux for 2 h. The solution obtained was evaporated, treated with water and filtered to yield an orange solid (1.13 g), m.p. 138-148°, whose t.l.c. in ethyl acetate over silica and i.r. spectrum indicated it to be a mixture of <u>syn</u>-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) and 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173).

The Attempted Diazotisation of 5-Amino-3-phenylisoxazole (171).

(a) <u>Using sodium nitrite-sulphuric acid</u>

A solution of the amine (171) (20.0 g; 0.125 mol) in glacial acetic acid (100 ml) was mixed with a solution of concentrated sulphuric acid (10.6 ml) in water (120 ml) and the mixture was treated dropwise with stirring at 0-5° with a 1M solution of sodium nitrite (128 ml). A yellow suspension containing some brown gum formed and was stirred for 5 min, then treated with water (26 ml). Stirring was continued for 30 min at 0° and the mixture was then extracted with portions of methylene chloride (total 600 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate solution (4x250 ml) then water (100 ml), and evaporated to give 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) (8.59 g; 42%), m.p. 151-154°, identical (i.r. spectrum) to a sample prepared previously.

The combined aqueous sodium hydrogen carbonate washings were acidified with aqueous dilute hydrochloric acid and extracted with methylene chloride (4x250 ml) to give <u>syn</u>-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (8.14 g; 34%), m.p. 137-139°, identical

(i. r. spectrum) to a sample prepared before.

(b) Using sodium nitrite-sulphuric acid.

A solution of 5-amino-3-phenylisoxazole (171) (1. 12 g; 0. 007 mol) in glacial acetic acid (5. 0 ml) was mixed with a solution of concentrated sulphuric acid (0. 6 ml) and water (6. 0 ml) and added dropwise at 0-5° to a solution of sodium nitrite (0. 48 g; 0. 007 mol) in water (7. 0 ml). The reaction mixture was stirred for 23 h to give a yellow solid (0. 92 g), m. p. 64-67° whose t. l. c. in ethyl acetate over silica showed four close-running components one of which was 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) as indicated by the i. r. spectrum of the solid, ν_{max} 3560, 3460w, 3370w, 3140 br and 2760 br (OH, NH) and 1640 (NH def.) cm^{-1}.

(c) Using sodium nitrite-phosphoric acid.

5-Amino-3-phenylisoxazole (171) (2. 24 g; 0. 014 mol) was dissolved with gentle warming in 88% phosphoric acid (15. 0 ml) and the solution was cooled to 0° and treated with solid sodium nitrite (0. 97 g; 0. 014 mol) to give a thick yellow suspension which was stirred for 10 min at 0°. Sulphamic acid (1. 36 g; 0. 014 mol) was added and the suspension was stirred at 0° for a further 30 min. The reaction mixture was then poured onto ice (100 g) to precipitate a gummy yellow solid (2. 03 g) m. p. 75-79° whose i. r. spectrum, ν_{max} 3450-3100 (NH, OH), 1800 and 1770 (CO) and 1640 (NH_2 def.) cm^{-1} showed it to be a mixture of 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) and the syn (174) and anti (188) isomers of 3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime. The filtrate was extracted with methylene chloride (2x30 ml) to give an unidentified red oil (0. 14 g).

The Attempted Reaction of 5-Amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) with Acetic Anhydride.

The amino-azo compound (173) (0.32 g; 0.001 mol) was dissolved in warm acetic anhydride (2.25 ml) and heated on a boiling water bath for 20 min. On cooling crystallisation occurred and the mixture was treated with ether and the solid was collected and combined with a second crop obtained by treating the evaporated filtrate with water to give unreacted starting material (0.27 g; 84%) identical (m.p. and i.r. spectrum) with an authentic sample.

3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-(3'-phenylisoxazol-5'-yl)-hydrazone (178).

5-Amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (173) (1.34 g; 0.004 mol) was treated with aqueous 2M hydrochloric acid (5.0 ml) in acetic acid (100 ml) at 100° for 2 h. The light red solution was allowed to stand at room temperature overnight and the yellow solid which separated was collected and crystallised from acetic acid-dimethyl formamide to give orange crystals of the hydrazone (178) (0.45 g; 34%), m.p. 209-213°, ν_{max} 3160 w (NH), 1730 (CO) and 1630 (C=N) cm^{-1}, δ [(CD$_3$)$_2$SO] 8.08-7.97 (2H, m, ArH), 7.89-7.80 (2H, m, ArH), 7.63-7.46 (6H, m, ArH) and 6.71 (1H, s, isoxazole CH).

Found: C, 64.7; H, 3.6; N, 16.7% M$^+$ 332.
C$_{18}$H$_{12}$N$_4$O$_3$ requires: C, 65.1; H, 3.6; N, 16.9% M 332.

Evaporation of the acetic acid filtrate gave unreacted starting material (173) (0.99 g), m.p. 143-148°, identical (i.r. spectrum) with an authentic sample.

3-Phenyl-Δ^2-pyrazoline-4,5-dione 4-(3'-phenylisoxazol-5'-yl) hydrazone (179)

A solution of 3-phenyl-Δ^2-isoxazoline-4,5-dione-4-(3'-phenyl-isoxazol-5'-yl) hydrazone (178) (0.40 g; 0.0012 mol) in methanol (100 ml) and acetic acid (55.0 ml) was heated under reflux with 85% aqueous hydrazine hydrate (0.33 ml) for 3 h. The reaction mixture was then concentrated to give 3-phenyl-Δ^2-pyrazoline-4,5-dione 4-(3'-phenyl-isoxazol-5'-yl) hydrazone (179) as an orange solid which was combined with a second crop obtained by evaporating the filtrate, and crystallised from acetic acid to give orange-red needles (0.37 g; 93%), m.p. 222-227°, ν_{max} 3200 br and 3130 w (NH), 1665 (CO), and 1620 (C=N) cm^{-1}, $\delta[(CD_3)_2SO]$ 8.13-8.00 (2H, m, ArH), 7.93-7.81 (2H, m, ArH), 7.57-7.44 (6H, m, ArH) and 6.78 (1H, s, isoxazole CH).

Found: C, 65.3; H, 4.0; N, 21.4%; M$^+$ 331.

$C_{18}H_{13}N_5O_2$ requires: C, 65.3; H, 4.0; N, 21.1%; M 331.

The Attempted Reaction of 3-Phenyl-Δ^2-pyrazoline-4,5-dione 4-(3'-phenylisoxazol-5'-yl) hydrazone (179) with Acetic Anhydride.

The hydrazone (179) (0.10 g; 0.0003 mol) was heated with acetic anhydride (1.35 ml) at 100° (steam bath) for 5 min. The suspension was cooled and diluted with ether to give unreacted starting material (0.08 g; 80%), m.p. 193-195°, identical (i.r. spectrum) with an authentic sample.

The Attempted Condensation of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) with 5-Amino-3-phenylisoxazole (171).

The oxime (174) (0.32 g; 0.0017 mol) and the amine (171)

(0.27 g; 0.0017 mol) were dissolved in acetic acid (8.0 ml) and the solution was stirred at room temperature for 48 h. Evaporation of the mixture gave a yellow solid which was crystallised from toluene to afford the adduct (183) (0.49 g; quant.) as orange cubes, m.p. 130-134°, ν_{max} 3580 w, 3450, 3370 and 3140 w (NH, OH), 1775 (CO), and 1635 (C=N), δ (CDCl$_3$) 8.00-7.88 (2H, m, ArH), 7.73-7.61 (2H, m, ArH), 7.46-7.32 (6H, m, ArH) and 5.43 (1H, s, isoxazole CH).

Found: C, 61.2; H, 4.1; N, 15.7%; M^{+}251. C$_{18}$H$_{14}$N$_4$O$_4$ requires: C, 61.7; H, 4.0; N, 16.0%; M 350.

Acetylation of the Adduct (183)

The adduct (183) (0.35 g; 0.01 mol) was dissolved with heating in acetic anhydride (1.35 ml) and the solution was heated at 100° (steam bath) for 20 min. On cooling a yellow solid crystallised. The mixture was diluted with ether and the solid was collected and recrystallised from toluene-light petroleum to give the monoacetyl derivative (185) as pale yellow crystals (0.23 g; 59%), m.p. 110-116°, ν_{max} 3530 w, 3370 w and 3180 w (NH, OH), and 1815, 1790 and 1690 (CO) cm^{-1}; δ (CDCl$_3$) 8.84-8.75 (2H, m, ArH), 7.82-7.70 (2H, m, ArH), 7.52-7.36 (6H, m, ArH), 6.71 (1H, s, isoxazole CH), and 2.24 (3H, s, Me).

Found: C, 61.1; H, 4.0; N, 14.2%; M^{+}203. C$_{20}$H$_{16}$N$_4$O$_5$ requires: C, 61.2; H, 4.1; N, 14.3%; M 392.

Hydrolysis of the Adduct (183)

A solution of the adduct (183) (0.35 g; 0.001 mol) in ethanol

(5. 0 ml) was mixed with aqueous 20% sulphuric acid (2. 5 ml) and the mixture was heated under reflux for 30 min. Concentration followed by filtration gave a gummy solid (0. 34 g), m. p. 108-112°, which contained a mixture of 3-phenyl-Δ^2-isoxazolin-5-one (189) and anti-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (188) (i. r. spectrum). Crystallisation of the solid from toluene-light petroleum gave syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (174), m. p. 142-145°, identical (i. r. spectrum and mass spectrum) with an authentic sample.

3-Phenyl-Δ^2-isoxazolin-5-one (189)

A solution of 5-amino-3-phenylisoxazole (171) (0. 16 g; 0. 001 mol) in ethanol (5. 0 ml) was mixed with aqueous 20% sulphuric acid (2. 5 ml) and the mixture was heated under reflux for 30 min. Dilution with water, followed by concentration gave 3-phenyl-Δ^2-isoxazolin-5-one (189) as a colourless solid (0. 13 g; 81%), m. p. 151-153° (lit.,[143] m. p. 152°), ν_{max} 1810 (CO) cm^{-1}.

The Reaction of 5-Amino-4-(3'-phenylisoxazole-5'-ylazo)-3-phenyl-isoxazole (173) with Hydrazine Hydrate.

The amino-azo compound (173) (0. 65 g; 0. 002 mol) was dissolved in methanol (60. 0 ml) and heated under reflux with 85% aqueous hydrazine hydrate (0. 5 ml) for 40 min. Filtration gave an orange solid which was crystallised from acetic acid to afford the dihydrazone (180) as orange-red needles (0. 48 g; 70%), m. p. 218-220°, ν_{max} 3580 w, 3350 w, and 3180 w (NH) cm^{-1}, δ [(CD$_3$)$_2$SO] 8. 17-8. 04 (2H, m, ArH), 7. 92-7. 80 (2H, m, ArH), 7. 61-7. 44 (6H, m, ArH), and

6.53 (1H, s, isoxazole CH).

<div align="center">

Found: C, 63.0; H, 4.2; N, 23.8%; M^+346.

</div>

$C_{18}H_{14}N_6O_2$ requires: C, 62.4; H, 4.1; N, 24.3%; M 346.

Acetylation of the Dihydrazone (180)

A suspension of the dihydrazone (180) (0.14 g; 0.0004 mol) in acetic anhydride (1.35 ml) was warmed until the suspended solid dissolved. The mixture solidified on cooling and was treated with ether to give the monoacetyl derivative (182) as a yellow solid which crystallised from acetic acid as yellow crystals (0.14 g; 89%), m.p. 207-208°, ν_{max} 3150 w, 3100 w and 3050 (NH), 1700 (CO) and 1680 (C=N) cm^{-1}, δ [(CD$_3$)$_2$SO] 8.13-8.00 (2H, m, ArH), 7.93-7.80 (2H, m, ArH), 7.63-7.42 (6H, m, ArH), 6.72 (1H, s, isoxazole CH) and 2.06 (3H, s, Me).

<div align="center">

Found: C, 62.0; H, 4.1; N, 21.6%; M^+388.

</div>

$C_{20}H_{16}N_6O_3$ requires: C, 61.9; H, 4.1; N, 21.6%; M388.

Methylation of syn-3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime (174)

A solution of the oxime (174) (0.95 g; 0.005 mol) in anhydrous dioxan (10.0 ml) was mixed with a solution of diazomethane[144] (0.032-0.035 mol) in ether (125 ml). The mixture was left at room temperature for 5 min during which time gas evolution occurred. Evaporation of the ethereal mixture gave a gum which was triturated with light petroleum to afford the methyl derivative (193) as a yellow solid (0.87 g; 85%), m.p. 98-99° [from petroleum ether (b.p. 80-100°)], ν_{max} 1780 (CO) cm^{-1}, δ(CDCl$_3$) 8.00-7.88 (2H, m, ArH), 7.53-7.41 (3H,

m, ArH), and 4.43 (3H, s, Me).

Found: C, 58.8; H, 3.9; N, 14.0%; M^+204.

$C_{10}H_8N_2O_3$ requires: C, 58.8; H, 3.9; N, 13.7%; M 204.

3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime Acetate (191)

Syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (0.94 g; 0.005 mol) was dissolved with heating in acetic anhydride (4.5 ml). The mixture was cooled and diluted with ether and the yellow solid was collected and crystallised from ethanol to give the monoacetate (191) as yellow needles (0.96 g; 83%), m.p. 154-156°, ν_{max} 1815 and 1790 (CO) cm^{-1}, δ (CDCl$_3$) 8.15-8.03 (2H, m, ArH), 7.60-7.46 (3H, m, ArH) and 2.41 (3H, s, Me).

Found: C, 57.1; H, 3.6; N, 11.9%; M^+232.

$C_{11}H_8N_2O_4$ requires: C, 56.9; H, 3.5; N, 12.1%; M 232.

3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime Toluene-p-sulphonate (192).

A solution of syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (0.38 g; 0.002 mol) in anhydrous dioxan (5.0 ml) was treated with triethylamine (0.35 ml; 0.0025 mol) followed by a solution of toluene-p-sulphonyl chloride (0.42 g; 0.0022 mol) in anhydrous dioxan (1.0 ml) and the suspension was stirred at room temperature for 15 min. Triethylamine hydrochloride was removed by filtration and the filtrate was evaporated at room temperature to give a yellow gummy solid (1.31 g). This was triturated with ethyl acetate-light petroleum to afford the toluene-p-sulphonate (192) which crystallised from

toluene-light petroleum (b. p. 100-120°) as yellow needles (0. 59 g; 86%), m. p. 163-165°, ν_{max} 1805 (CO) cm^{-1}, δ (CDCl$_3$) 8.00-7.81 (4H, m, ArH), 7.60-7.31 (5H, m, ArH), and 2.47 (3H, s, Me).

<div align="center">Found: C, 55.7; H, 3.7; N, 7.8%; M$^+$344.</div>

C$_{16}$H$_{12}$N$_2$O$_5$S requires: C, 55.8; H, 3.5; N, 8.1%; M 344.

The Attempted Reduction of syn-3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime (174)

(a) A solution of the oxime (174) (0. 19 g; 0. 001 mol) in 70% aqueous ethanol was heated under reflux with sodium dithionite (0. 19 g) for 30 min and then for a further 30 min with a second portion of dithionite (0. 19 g). After hot filtration to remove inorganic material, the filtrate was evaporated, treated with water and then extracted with chloroform (2x10 ml). Evaporation of the chloroform extract gave an intractable red-orange gum.

(b) A solution of the oxime (174) (0. 19 g; 0. 001 mol) in ethanol (50. 0 ml) was hydrogenated at room temperature and at atmospheric pressure over palladium-on-charcoal (0. 02 g) for 3. 25 h. The mixture was filtered through Kieselguhr and evaporated to give a gummy red solid (0. 16 g), m. p. 45-47°, whose t. l. c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

The Attempted Catalytic Hydrogenation of 3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime Acetate (191)

A solution of the monoacetate (191) (0. 46 g; 0. 002 mol) in

ethanol (55.0 ml) was hydrogenated over palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 4 h. No hydrogen was absorbed and the reaction mixture was filtered through kieselguhr and evaporated to give a red gum whose t.l.c. in acetone over silica showed a single spot corresponding to the starting material.

syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174).

A solution of 3-phenyl-Δ^2-isoxazolin-5-one (189) (0.40 g; 0.0025 mol) in aqueous 2M sodium hydroxide (2.0 ml) was mixed with a solution of sodium nitrite (0.35 g; 0.005 mol) in water (2.0 ml) and the mixture was treated dropwise with stirring at 0-5° with 2M aqueous sulphuric acid (4.0 ml). Initially an orange suspension formed, but on stirring for 15 min the colour changed to yellow and filtration yielded syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (0.44 g; 94%), m.p. 160-161°, identical (i.r. spectrum) with a sample prepared previously.

anti-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (188).

syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (2.0 g; 0.011 mol) was chromatographed in ethyl acetate:methylene chloride (1:9) over silica to give the anti isomer (188) (1.82 g; 91%), m.p. 147-148°, ν_{max} 3230 br and 3120 br (OH) and 1790 (CO) cm^{-1}, ν_{max} (CHCl$_3$) 1785 (CO)cm^{-1}. Crystallisation of the anti isomer from toluene gave the syn isomer (174), m.p. 142-143°, identical (i.r. spectrum) with an authentic sample.

Methylation of anti-3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime (188).

A solution of the oxime (188) (0.95 g; 0.005 mol) in anhydrous dioxan (10.0 ml) was mixed with a solution of diazomethane[144] (0.032-0.035 mol) in ether (125 ml) and the mixture was left at room temperature for 5 min during which time gas evolution occurred. Evaporation of the mixture at room temperature gave a yellow gum which was triturated with light petroleum to afford the methyl derivative (193) as a yellow solid (0.70 g; 69%), m.p. 87-88°, δ (CDCl$_3$) 8.00-7.89 (2H, m, ArH), 7.54-7.42 (3H, m, ArH) and 4.43 (3H, s, Me), identical (i.r. spectrum) with a sample prepared previously.

Acetylation of anti-3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime (188).

A solution of anti-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (188) (0.19 g; 0.001 mol) in acetic anhydride (1.8 ml) was heated at 100° for 5 min. On cooling the acetate (191) crystallised (0.18 g; 78%), m.p. 157-158°, identical (i.r. spectrum and m.p.) with a sample prepared previously.

The Attempted Catalytic Hydrogenation of anti-3-Phenyl-Δ^2-isoxazoline -4, 5-dione 4-Oxime (188).

A solution of the oxime (188) (0.19 g; 0.001 mol) in ethanol (50.0 ml) was hydrogenated over palladium-on-charcoal (0.02 g) at room temperature and atmospheric pressure for 2 h. Hydrogen was absorbed and the reaction mixture was filtered through kieselguhr and evaporated to give an intractable red solid (0.18 g), m.p. 65-70°, whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture.

The Behaviour of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) in Alkaline Solutions.

(a) The oxime (174) (0.19 g; 0.001 mol) was treated with 20% aqueous sodium carbonate (10.0 ml) and the solution obtained immediately acidified with dilute sulphuric acid to give the hydrate of the oxime (174) as a yellow solid (0.18 g; 95%), m.p. 146-147°, ν_{max} 3560, 3470, 3150w and 2650 br (OH, NH) and 1765 (CO) cm^{-1}, ν_{max} (CHCl$_3$) 1785 (CO) cm^{-1}, which on crystallisation from toluene gave syn-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) identical (m.p. and i.r. spectrum) with an authentic sample.

(b) The oxime (174) (0.19 g; 0.001 mol) was treated with 2M aqueous sodium hydroxide (5.0 ml) and the solution obtained was immediately acidified with dilute sulphuric acid to give the hydrate of the oxime (174) as a yellow solid (0.16 g; 84%), m.p. 148-150°, identical (m.p. and i.r. spectrum) with a sample prepared before.

Methylation of the Hydrate of the Oxime (174).

A solution of the hydrate of the oxime (174) (0.39 g; 0.002 mol) in anhydrous dioxan (10.0 ml) was mixed with a solution of diazomethane[144] (0.032-0.035 mol) in ether (125 ml), and the mixture was left at room temperature for 15 min, during which time gas evolution occurred. Evaporation of the mixture at room temperature gave a gummy yellow solid which was triturated with light petroleum to afford the methyl derivative (193) as an orange-yellow solid (0.42 g; quantitative), m.p. 69-73°, identical (i.r. spectrum) with a sample prepared previously.

The Attempted Oxidation of the Hydrate of the Oxime (174).

A solution of the hydrate of the oxime (174) (0.38 g; 0.002 mol) in anhydrous dioxan (10.0 ml) was heated under reflux with manganese dioxide (1.39 g; 0.016 mol) for 45 min. Filtration of the reaction mixture, followed by evaporation of the filtrate gave an intractable red gum (0.32 g) from which no identifiable material could be obtained.

The Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) with Aniline.

A solution of the oxime (174) (1.90 g; 0.01 mol) and redistilled aniline (0.93 g; 0.01 mol) in acetic acid (25.0 ml) was stirred at room temperature for 47 h. Evaporation of the reaction mixture gave the dioxime (203) which crystallised from ethanol-water as colourless crystals, m.p. 164-166°, ν_{max} 3440, 3290, 3170 br, and 3050 br (NH, OH), and 1660 (CO) cm^{-1}.

Found: C, 63.6; H, 4.7; N, 15.1%; M^{+}283.

$C_{15}H_{13}N_3O_3$ requires: C, 63.6; H, 4.6; N, 14.8%; M 283.

The Attempted Acetylation of the Dioxime (203).

(a) A solution of the dioxime (203) (0.16 g; 0.0006 mol) in acetic anhydride (0.9 ml) was heated at 100° (steam bath) for 5 min. The reaction mixture was evaporated, treated with water and extracted with methylene chloride to yield a yellow gum (0.20 g) which proved to be intractable and from which no identifiable material could be obtained.

(b) A solution of the dioxime (203) (0.28 g; 0.001 mol) in acetic anhydride (1.8 ml) was heated under reflux for 3 h. Evaporation

of the reaction mixture gave an intractable gum from which no identifiable material could be obtained.

Hydrolysis of the Dioxime (203)

The dioxime (203) (0.28 g; 0.001 mol) in ethanol (5.0 ml) was heated under reflux with aqueous 20% sulphuric acid (2.5 ml) for 1.5 h. Concentration of the reaction mixture followed by filtration gave anti-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (188) as a yellow solid (0.12 g; 63%), m.p. 156-158.5°, M^+ 190, identical (i.r. spectrum) to a sample prepared previously.

The filtrate was neutralised with aqueous dilute sodium hydroxide and extracted with methylene chloride (2x25 ml) to give aniline as a yellow oil (0.04 g; 44%) identical (i.r. spectrum) with an authentic sample.

The Attempted Oxidation of the Dioxime (203)

(a) A solution of the dioxime (203) (0.56 g; 0.002 mol) in anhydrous dioxan (13.0 ml) was heated under reflux with manganese dioxide (1.39 g; 0.016 mol) for 1.5 h. The reaction mixture was hot filtered to remove inorganic material and the filtrate was evaporated to give a dark gum (0.42 g) which was extracted with hot light petroleum to afford a pale yellow solid (0.005 g; 1%), m.p. 133-139°, ν_{max} 3320 (NH) and 1680 (CO) cm^{-1}, M^+, 281, M^+-16, 265 (M=281, C$_{15}$H$_{11}$N$_3$C

(b) A solution of the dioxime (203) (0.56 g; 0.002 mol) in anhydrous dioxan (13.0 ml) was stirred at room temperature for 24 h with manganese dioxide (1.39 g; 0.016 mol). The reaction mixture was filtered to remove inorganic material and the filtrate was

evaporated to give a beige solid (0.64 g), m.p. 106-110°, ν_{max} 3250 br and 3170 br (OH, NH) and 1660 (CO) cm^{-1}, which was crystallised from ethyl acetate to afford an unidentified, colourless solid, m.p. 170-171°, ν_{max} 3290 br and 3200 br (OH, NH) and 1705 and 1665 (CO) cm^{-1}.

Found: C, 63.1; H, 4.6; N, 14.7%; M^{+}283.

$C_{15}H_{13}N_3O_3$ requires: C, 63.6; H, 4.6; N, 14.8%; M283.

Identical (mass spectrum) with the dioxime starting material (203).

The Attempted Synthesis of the Dioxime (203).

(a) Benzoylacetanilide (211)

Benzoylacetanilide was prepared in 50% yield by the reaction of ethyl benzoylacetate with aniline using the method of Kibler and Weissberger,[138] m.p. 103-104° (from benzene-light petroleum)(lit[138], m.p. 106-106.5°).

(b) The Nitrosation of Benzoylacetanilide (211)

A solution of benzoylacetanilide (211) (2.39 g; 0.01 mol) in acetic acid (25.0 ml) was mixed with 88% phosphoric acid (0.5 ml) and the mixture was treated dropwise with stirring at 25° with a solution of sodium nitrite (0.70 g; 0.01 mol) in water (5.0 ml). The temperature rose to 33° and the resulting suspension was stirred for 18 h. Dilution with water (25.0 ml) gave a pale yellow solid which was crystallised from ethanol-water to yield N, 3-diphenyl-2, 3-dioxopropionamide 2-oxime (212) as pale yellow needles (2.37 g; 88%), m.p. 173-174.5°, ν_{max} 3320 and 3200 (OH), 3050 (NH) and 1680 and 1660 (CO) cm^{-1}.

Found: C, 67.0; H, 4.6; N, 10.3%; M$^+$268.

C$_{15}$H$_{12}$N$_2$O$_3$ requires: C, 67.2; H, 4.5; N, 10.4%; M 268.

(c) The Attempted Reaction of N, 3-Diphenyl-2, 3-dioxopropion-amide 2-Oxime (212) with Hydroxylamine Hydrochloride.

A solution of the oxime (212) (0.54 g; 0.002 mol) in ethanol (10.0 ml) was mixed with a solution of hydroxylamine hydrochloride (0.5 g; 0.007 mol) in water (2.0 ml) which had been neutralised with sodium acetate, and the mixture was heated at 100° (steam bath) for 2 h. The mixture was evaporated and treated with water (5.0 ml) and then extracted with methylene chloride (3x20 ml). Evaporation of the methylene chloride extract gave an orange gum (0.49 g) which was triturated with benzene to give unreacted starting-material (0.24 g; 40%), m.p. 133-135°, identical (i.r. spectrum) with an authentic sample.

(d) The Reaction of Benzoylacetanilide (211) with Hydroxyl-amine Hydrochloride.

A solution of benzoylacetanilide (211) (0.48 g; 0.002 mol) in ethanol (10.0 ml) was mixed with a solution of hydroxylamine hydro-chloride (0.5 g; 0.007 mol) in water (2.0 ml) which had been neutralised with sodium acetate and the mixture was heated under reflux for 2 h. Concentration of the reaction mixture followed by treatment with water gave 3-phenyl-Δ^{2}isoxazolin-5-one (189) as a yellow solid (0.29 g; 91%), m.p. 136-139°, identical (i.r. spectrum) with a sample prepared previously.

The Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) with Benzylamine.

A solution of the oxime (174) (0.38 g; 0.002 mol) in acetic acid (5.0 ml) was stirred with benzylamine (0.22 g; 0.002 mol) at room temperature for 27 h. Evaporation of the reaction mixture gave a red gum (0.87 g). This was triturated with ethyl acetate-light petroleum to give the dioxime (214) which crystallised from ethanol-water as colourless cuboids (0.29 g; 48%), m.p. 163-164°, ν_{max} 3410, 3310, and 3180 br (NH, OH) and 1640 (CO) cm^{-1}, δ [(CD$_3$)$_2$SO] 8.65 (1H, t, J 7Hz, CH$_2$-$\underline{NH}$), 7.35 (5H, s, ArH), 7.25 (5H, s, ArH) and 4.35 (2H, d, J 7Hz, NH-$\underline{CH}_2$).

Found: C, 64.8; H, 5.2; N, 14.1%; M$^+$297.
C$_{16}$H$_{15}$N$_3$O$_3$ requires: C, 64.7; H, 5.1; N, 14.1%; M297.

The Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) with Ammonia.

A solution of the oxime (174) (0.38 g; 0.002 mol) in absolute ethanol (30.0 ml) was mixed with a solution of absolute ethanol (100 ml) which had been saturated with ammonia and the mixture was left stoppered overnight at room temperature. Evaporation of the reaction mixture gave an orange-red gummy solid (0.38 g) which was triturated with ethyl acetate-light petroleum to afford an orange-pink solid (0.27 g), m.p. 100-103°. The orange-pink solid (0.27 g) was heated in boiling toluene to afford an insoluble, pink-purple solid (0.17 g), m.p. 99-100°, ν_{max} 3150 and 3050 (NH) and 1710, 1695 and 1670 (CO) cm^{-1}, M$^+$190, which resisted crystallisation but when slurried (0.05 g) with dilute aqueous hydrochloric acid yielded the hydrate of the oxime (174)

as an orange solid (0.04 g), m.p. 110-114°, identical (i.r. spectrum) with a sample prepared before.

The toluene mother liquor was evaporated to give a yellow gum which was triturated with toluene-light petroleum to afford a yellow solid (0.02 g; 5%), m.p. 108-110°, whose i.r. spectrum showed it to contain the syn (174) and anti (188) isomers of 3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime.

The Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime with N-methylaniline.

A solution of the oxime (174) (0.38 g; 0.002 mol) in acetic acid (5.0 ml) was stirred with N-methylaniline (0.22 g; 0.002 mol) at room temperature for 27 h. Evaporation of the reaction mixture gave an orange-pink solid (0.50 g), m.p. 80-83°, ν_{max} 1710 cm^{-1}, which on crystallisation from benzene-light petroleum gave anti-3-phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (188), m.p. 147-148°, identical (i.r. spectrum) with a sample prepared previously.

The Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-Oxime (174) with Piperidine.

A solution of the oxime (174) (0.38 g; 0.002 mol) in acetic acid (5.0 ml) was stirred with piperidine (0.17 g; 0.002 mol) at room temperature for 27 h. Evaporation of the reaction mixture gave a red oil (0.74 g) which crystallised overnight to give the piperidinium salt (215) as red needles (0.42 g; 76%), m.p. 126-127° (from ethanol), ν_{max} 3070, 2720, 2640, 2590, 2520 and 2420 (NH) and 1725 (CO)cm^{-1}, δ [(CD$_3$)$_2$SO] 8.16-8.05 (2H, m, ArH), 7.50-7.44 (3H, m, ArH), 3.13-2.99 (4H, m, CH$_2$) and 1.75-1.58 (6H, m, CH$_2$).

Found: C, 61.0; H, 6.3; N, 15.1%; M^+190.

$\underline{C_{14}H_{17}N_3O_3}$ requires: C, 61.1; H, 6.2; N, 15.3%; M275.

Hydrolysis of the Piperidinium Salt (215).

The piperidinium salt (215) (0.55 g; 0.002 mol) was mixed with aqueous 2M hydrochloric acid (5.0 ml) at 0° and the suspension was stirred for 10 min to give the hydrate of the oxime (174) as a yellow solid (0.40 g; quantitative), m.p. 144-145°, identical (i.r. spectrum) with a sample prepared previously.

The Reaction of $\underline{syn}$-3-Phenyl-Δ^2-isoxazoline-4, 5-dione 4-Oxime (174) with Hydrazine Hydrate.

(a) A solution of the oxime (174) (0.38 g; 0.002 mol) in acetic acid (5.0 ml) was stirred with 100% hydrazine monohydrate (0.20 g; 0.004 mol) at room temperature for 24 h. Evaporation of the mixture gave an orange gum (0.88 g) which was triturated with ethyl acetate-ethanol and crystallised from ethanol-light petroleum, to afford the hydrazine salt of the pyrazolone (216) as orange needles (0.12 g; 27%), m.p. 138-141°, ν_{max} 3340 br and 3100 br (OH, NH) and 1700 (CO) cm^{-1}.

Found: C, 47.1; H, 5.0; N, 29.3%; M^+189.

$\underline{C_9H_{11}N_5O_2}$ requires: C, 48.9; H, 5.0; N, 31.7%; M221.

(b) A solution of the oxime (174) (0.38 g; 0.002 mol) in acetic acid (5.0 ml) was stirred with 100% hydrazine monohydrate (0.10 g; 0.002 mol) at room temperature for 24 h. Evaporation of the reaction mixture gave an orange-red gum (0.85 g) which was triturated with

ethanol and crystallised to give a diacetyl product as colourless crystals (0.23 g: 44%), m.p. 178.5-179°, ν_{max} 3250 br (OH, NH) and 1680, 1665 and 1640 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 10.06 (1H, s, OH/NH), 7.40 (5H, s, ArH), 1.99 (3H, s, Me) and 1.92 (3H, s, Me).

Found: C, 55.3; H, 5.4; N, 21.5%; M$^+$262.

$\underline{C_{12}H_{14}N_4O_3}$ requires: C, 55.0; H, 5.3; N, 21.4%; M 262.

syn-1,3-Diphenyl-$\underline{\Delta^2}$-pyrazoline-4,5-dione 4-Oxime (218).

(a) syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (174) (1.90 g; 0.01 mol) in glacial acetic acid (25.0 ml) was stirred with redistilled phenylhydrazine (1.08 g; 0.01 mol) at room temperature for 24 h. Filtration gave syn-1,3-diphenyl-Δ^2-pyrazoline-4,5-dione 4-oxime (218) as an orange-red solid which was combined with a second crop obtained from the filtrate on standing and crystallised from ethanol to give red-orange needles (0.79 g; 30%), m.p. 194-196° (lit.,[140] m.p. 197-200°), ν_{max} 3130 w (OH) and 1685 (CO) cm^{-1}.

Found: C, 68.1; H, 4.1; N, 15.9%; M$^+$265.

Calc. for $\underline{C_{15}H_{11}N_3O_2}$: C, 67.9; H, 4.1; N, 15.9%; M 265.

Work up of the filtrate gave no further material.

(b) anti-3-Phenyl-Δ^2-isoxazoline-4,5-dione 4-oxime (188) (0.38 g; 0.002 mol) in glacial acetic acid (5.0 ml) was stirred with redistilled phenylhydrazine (0.22 g; 0.002 mol) at room temperature for 43 h. Filtration gave syn-1,3-diphenyl-Δ^2-pyrazoline-4,5-dione 4-oxime (218) as an orange solid which was combined with a second crop obtained from the filtrate on standing (total 0.15 g; 28%), m.p. 193-195° (lit.,[140] m.p. 197-200°), identical (i.r. spectrum) with a sample prepared previously.

1, 3-Diphenyl-Δ^2-pyrazoline-4, 5-dione 4-Oxime Acetate (220).

The oxime (218) (0.43 g; 0.0016 mol) was dissolved with warming in acetic anhydride (2.7 ml) and the solution was heated at 100° (steam bath) for 5 min. The mixture was diluted with ether and the dark red solid was recrystallised from ethanol to give the oxime acetate (220) as dark orange-red needles (0.34 g; 68%), m.p. 162-164°, ν_{max} 1805 and 1725 (CO) cm^{-1} $\delta[(CD_3)_2SO]$ 8.10-7.80 (4H, m, ArH), 7.76-7.30 (6H, m, ArH) and 1.88 (3H, s, Me).

Found: C, 66.1; H, 4.3; N, 13.6%; M$^+$307.

$C_{17}H_{13}N_3O_3$ requires: C, 66.5; H, 4.2; N, 13.7%; M307.

The Attempted Reduction of syn-1, 3-Diphenyl-Δ^2-pyrazoline-4, 5-dione 4-Oxime (218).

A solution of the oxime (218) (0.26 g; 0.001 mol) in 70% aqueous ethanol (25.0 ml) was heated under reflux with sodium dithionite (0.26 g) for 30 min and then with a second portion of dithionite (0.26 g) for a further 30 min. The reaction mixture was hot filtered to remove inorganic material, evaporated, and treated with water to give the compound (219) which crystallised from toluene-light petroleum as brick red needles (0.17 g; 71%), m.p. 256-258°.

Found: C, 74.7; H, 4.5; N, 14.1%; M$^+$483.

$C_{30}H_{21}N_5O_2$ requires: C, 74.5; H, 4.4; N, 14.5%; M483.

The Attempted Reduction of 1, 3-Diphenyl-Δ^2-pyrazoline-4, 5-dione 4-Oxime Acetate (220).

A solution of the oxime acetate (220) (0.31 g; 0.001 mol) in ethanol (125 ml) was hydrogenated over palladium-on-charcoal (0.03 g)

at room temperature and atmospheric pressure for 1 h.   Hydrogen

was absorbed and the mixture was filtered through kieselguhr and

evaporated to give a red gum (0.28 g) which was triturated with ethyl

acetate and crystallised from acetic acid to give the compound

(219)   (0.03 g; 12%), m.p. 234-236°, M^{+}483).

syn-1,3-Diphenyl-Δ^2-pyrazoline-4,5-dione 4-Oxime (218).

   (a) 1,3-Diphenyl-Δ^2-pyrazolin-5-one (217) was prepared in 82%

yield by the reaction of ethyl benzoylacetate with phenylhydrazine

according to the method of Knorr and Klotz,[140] and had m.p. 127-129°

(from ethanol) (lit.,[140] m.p. 137°), ν_{max} 3430 br (OH) cm^{-1}.

   (b) syn-1,3-Diphenyl-Δ^2-pyrazoline-4,5-dione 4-oxime (218)

was prepared in 91% yield by treating 1,3-diphenyl-Δ^2-pyrazolin-5-

one (217) with nitrous acid according to the method of Knorr and

Klotz,[140] m.p. 201-203° (lit.,[140] m.p. 197-200°), identical (i.r.

spectrum) to a sample prepared previously.

The Attempted Reaction of syn-3-Phenyl-Δ^2-isoxazoline-4,5-dione

4-Oxime with Hydroxylamine Hydrochloride.

   A solution of the oxime (174) (0.38 g; 0.002 mol) in methanol

(10.0 ml) was mixed with a solution of hydroxylamine hydrochloride

(0.50 g; 0.007 mol) in water (2.0 ml) which had been neutralised with

sodium acetate.   The mixture was stirred at room temperature for

24 h and then evaporated at room temperature and treated with water

to give the hydrate of the oxime (174) which was combined with a second

crop obtained from the filtrate on standing overnight (total 0.30 g; 79%),

m.p. 149-151°, identical (i.r. spectrum) with a sample prepared

previously.

CHAPTER THREE

Investigations on the Preparation and Dediazoniation and Coupling Reactions of Thiazolediazonium Salts

(224)

(225)

(226)

HNO$_2$

NaNO$_2$/HCl

NaNO$_2$/H(

(227)

(228)

(229)

Scheme 88

(230)

HNO$_2$

(231)

(232)

$+$ CH$_2$ CO$_2$E / COR^2

(233)

(234)

-EtOH

(235)
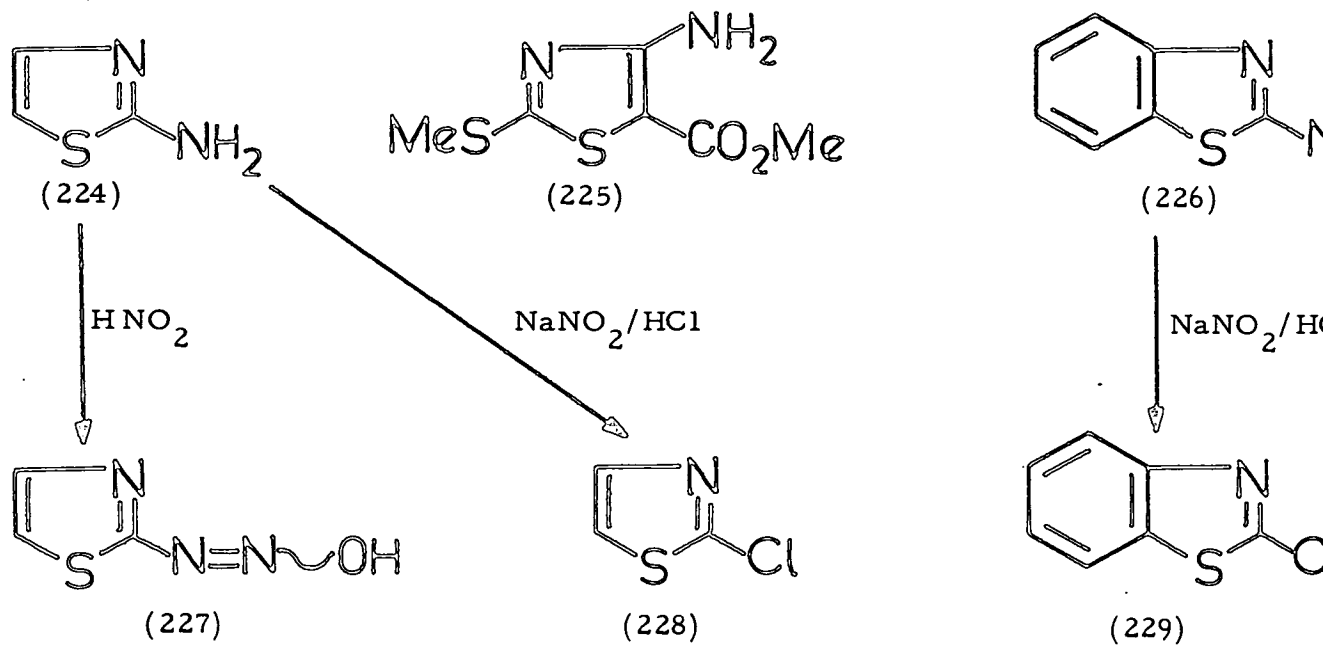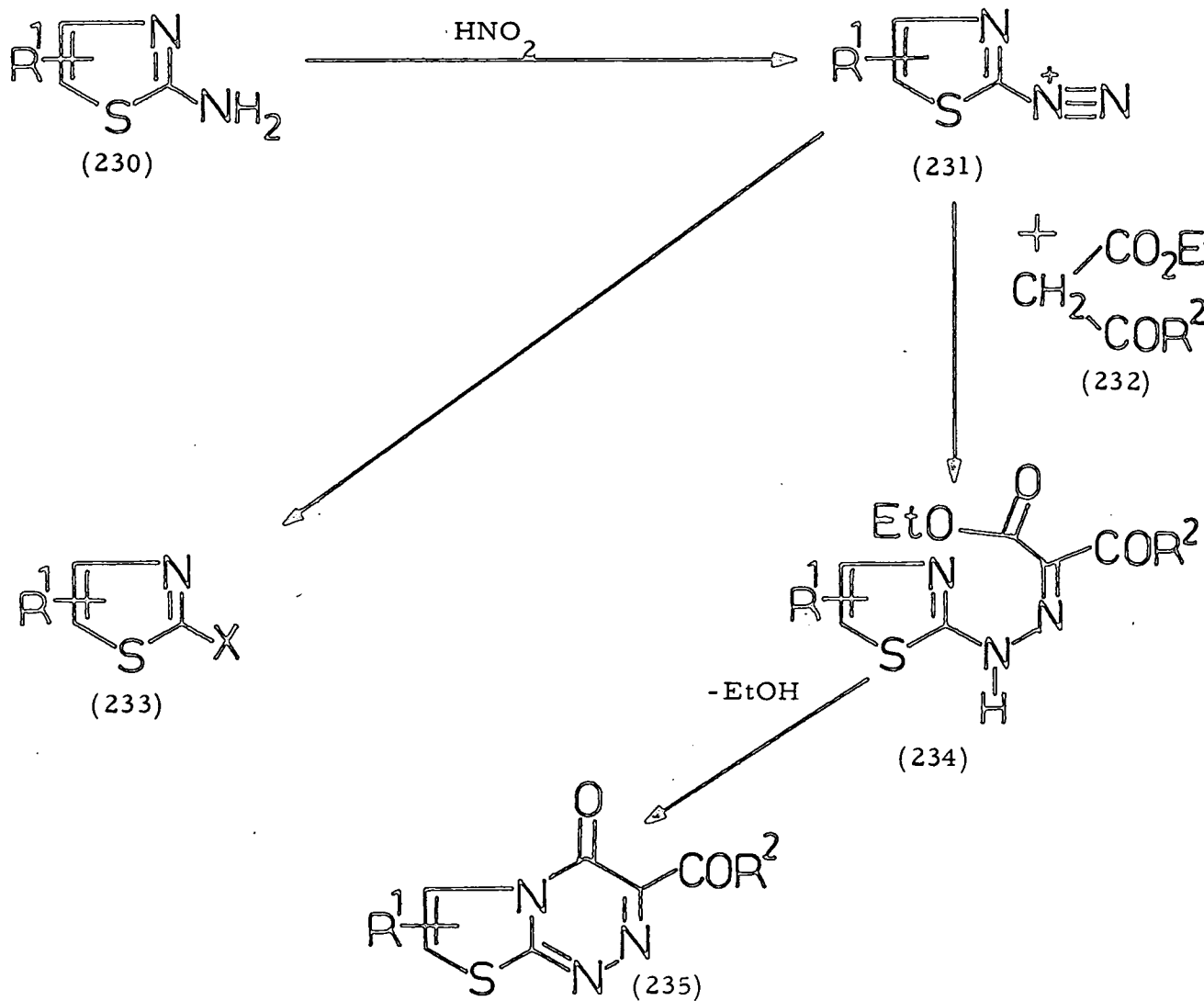
Scheme 89

Investigations on the Preparation and Dediazoniation and Coupling
Reactions of Thiazolediazonium Salts.

The studies described in this chapter are concerned with the
diazotisation of 2-aminothiazole, [Scheme 88; (224)], methyl 4-amino-
2-methylmercaptothiazole-5-carboxylate (225) and 2-aminobenzothiazole
(226) and subsequent reactions of the species produced. A number of
investigations of the diazotisation of 2-aminothiazoles and 2-amino-
benzothiazoles have been reported in the literature but little is known
regarding the diazotisation of 4-amino- and 5-aminothiazole derivatives.
The diazotisation of 2-aminothiazole (224) in dilute acids has been
reported to afford the N-hydroxy azo derivative (227)[80,81] (Scheme
88). On the other hand the diazotisation of 2-aminothiazole (224) and
2-aminobenzothiazole (226) in concentrated hydrochloric acid is
reported to yield the 2-chloro compounds (228) and (229).[80,82] However
diazotisation of 2-aminothiazole (224) and 2-aminobenzothiazole (226)
in other strong acids yields diazonium salts which undergo coupling
reactions with activated arenes and active methylene compounds[80,83]
and a wide variety of dediazoniation reactions have been carried out
on substituted thiazole-2-diazonium salts.[84-90]

The present investigation of the diazotisation of 2-aminothiazoles
(230) had several objectives (Scheme 89). Firstly, it was hoped to
establish satisfactory conditions for the smooth diazotisation of the
aminothiazoles under consideration and to react the resulting diazo-
nium cations (231) with nucleophiles to afford nuclear substituted thia-
zoles (233) (Scheme 89). It was also hoped to couple the diazonium
cations (231) with active methylene compounds (232) to afford
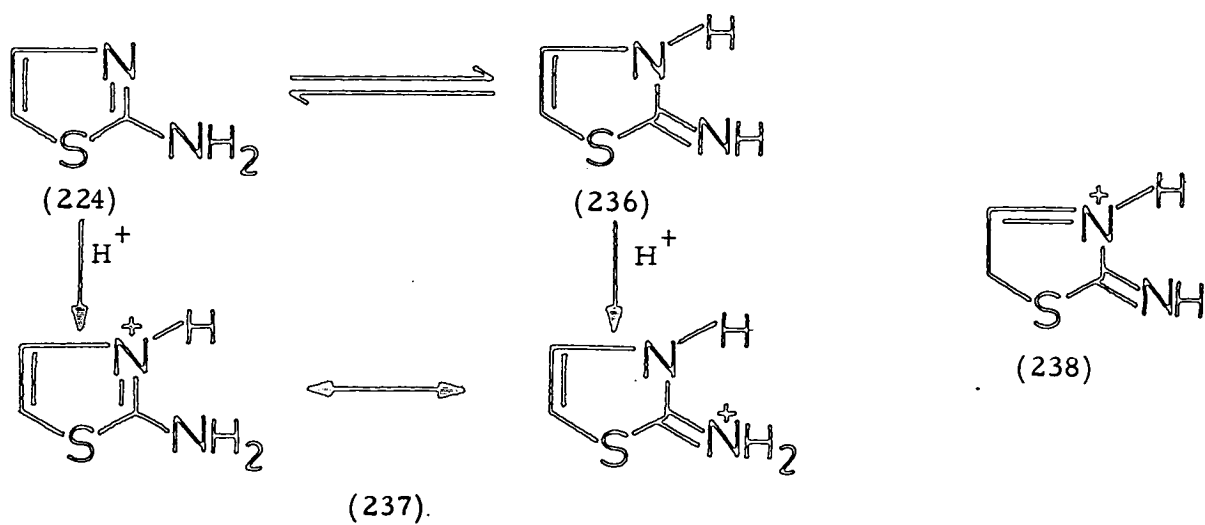
Scheme 90
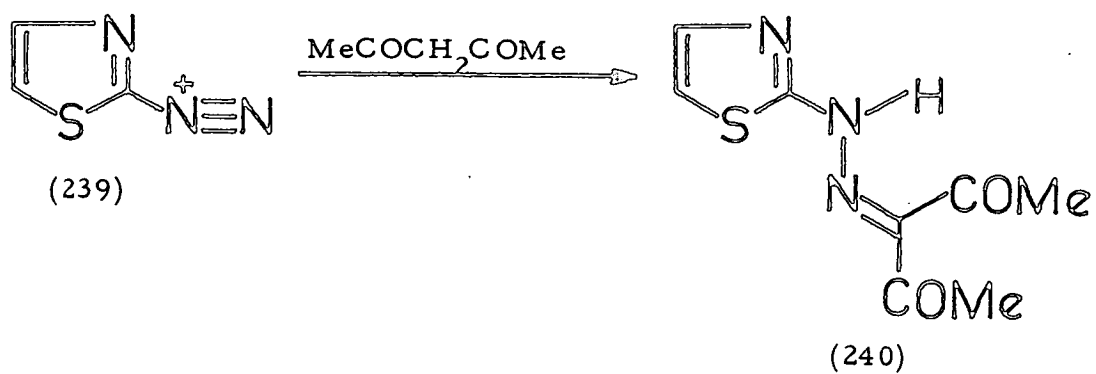
Scheme 91

hydrazones (234) which it was anticipated might cyclise, possibly

spontaneously, to yield bicyclic systems (235) (Scheme 89) as

demonstrated for 5-amino-1, 2, 3-triazoles.[122]

The diazotisation of the readily available 2-aminothiazole (224)

was initially investigated. Two protonated forms (Scheme 90) are

possible for 2-aminothiazole (224) in acidic media, namely the

mesomeric cation (237) derived by protonation of the amino tautomer

(224) on the ring nitrogen or by protonation of the imine tautomer (236)

at the imino group and the cationic species (238).[145] No evidence

for the latter has been described so far. Protonated forms akin to

(237) are present in acidic solutions of 4- and 5-aminothiazoles.[145]

It was found in the present studies that diazotisation of 2-aminothiazole

using sodium nitrite in dilute sulphuric acid generates the thiazole-2-

diazonium cation (239) as demonstrated by its coupling under neutral

conditions with acetylacetone to afford a moderate yield (26%) of a

compound having the same melting point as the hydrazone (240)

(Scheme 91) reported by Morgan and Morrow[80] as the product of the

diazotisation of the amine (224) in nitric acid with sodium nitrite and

subsequent coupling with acetylacetone under neutral conditions.

Morgan and Morrow[80] did not prove the structure of the hydrazone

(240) which was established in the present studies by the presence of

carbonyl and NH absorption in its i.r. spectrum and the presence in

its ^{1}H n.m.r. spectrum of signals attributable to two thiazole protons

and the two methyl groups of the hydrazone side-chain. 2-Amino-

thiazole was also found to be diazotisable using one equivalent of

sodium nitrite in concentrated phosphoric acid though subsequent

coupling with acetylacetone gave the hydrazone (240) only in poor

yield (19%). However sodium nitrite is believed to decompose in

concentrated acids and when two equivalents of sodium nitrite were

used, conditions frequently employed for the diazotisation of heterocyclic

amines by Goerdeler,[83, 109, 110] a 58% yield of the hydrazone (240)

was obtained on coupling with acetylacetone. Attempts to couple the

diazonium cation (239) with other active methylene compounds were

unsuccessful. Thus the attempted coupling of ethyl acetoacetate or

diethyl malonate with the diazonium solution from 2-aminothiazole

(224) and sodium nitrite in dilute sulphuric acid gave only unreacted

methylene compound, while ethyl cyanoacetate gave a multicomponent

mixture from which no identifiable material could be obtained. The

attempted coupling of ethyl acetoacetate or diethyl malonate with the

diazonium solution from 2-aminothiazole (224) and sodium nitrite in

concentrated phosphoric acid likewise gave no identifiable products.

Despite the apparent conversion of 2-aminothiazole (224) in solution

into a diazonium cation (239) capable of being trapped as the hydrazone

(240), the attempted formation and isolation of thiazole-2-diazonium

chloride was unsuccessful. Thus the reaction of 2-aminothiazole (224)

hydrochloride with amyl nitrite under conditions[146] suitable for the

conversion of 5-amino-1H-1, 2, 3-triazoles into isolable diazonium

chlorides, gave no identifiable material.

The relative instability of the thiazole-2-diazonium cation (239)

indicated by the foregoing studies prompted the investigation of the

diazotisation of the structurally closely related 2-aminobenzothiazole

(226). Literature reports[83] suggested that 2-aminobenzothiazole (226)

(226)

HONO

(241)

Cl⁻

CH₂=NOH/H⁺

(229)

HBr

⁻SCN

⁻CN

(247)

(242)

(245)

(243)

(244)

(246)
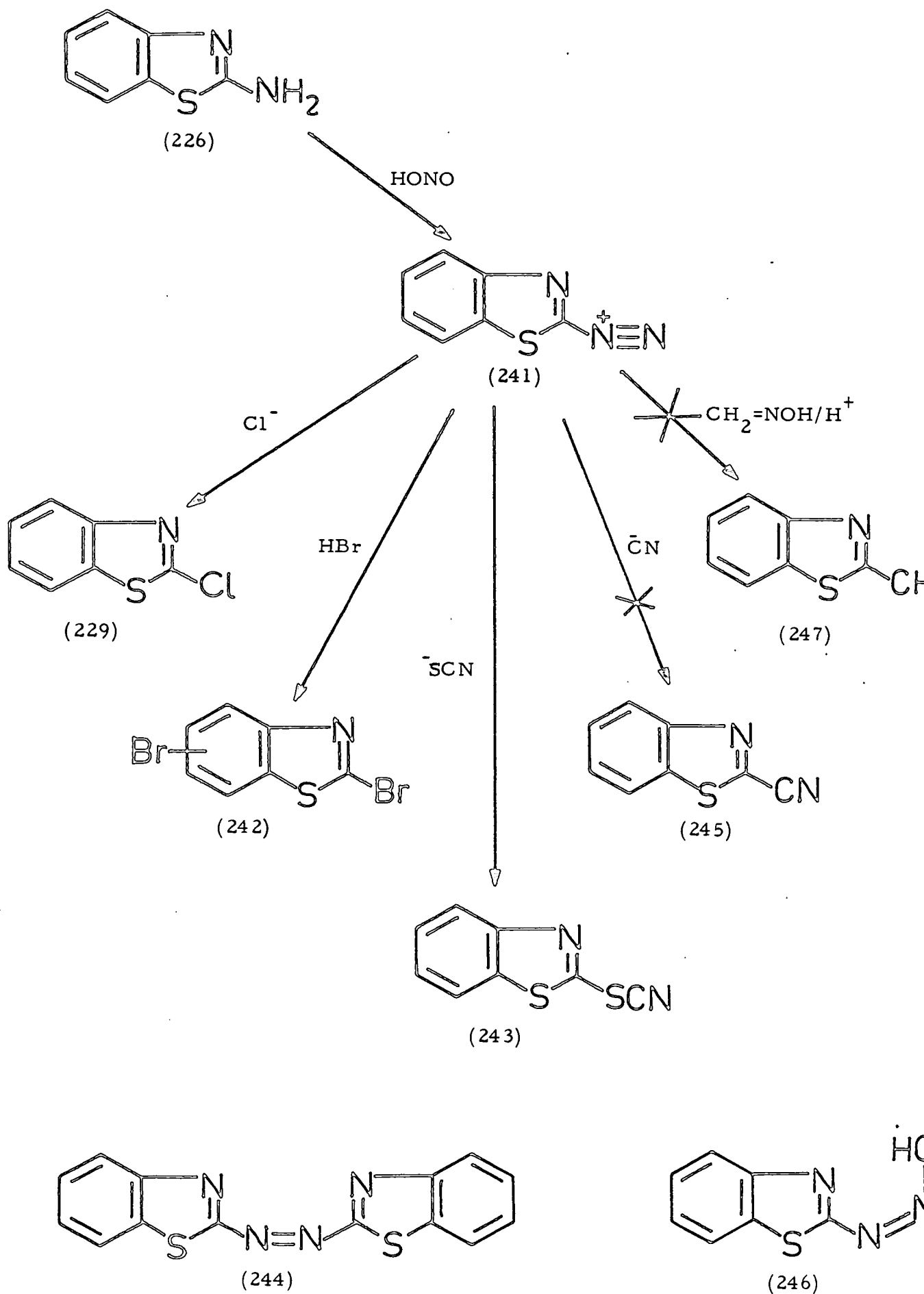
Scheme 92

could be diazotised with sodium nitrite in concentrated strong acids

and the diazonium cation (241) successfully coupled with activated

aromatic molecules. It was hoped that the benz-fused structure of

this molecule would confer enhanced stability on the derived benzo-

thiazole-2-diazonium cation (241) thus facilitating the study of its

reactivity and its isolation in the form of suitable diazonium salts.

However, in confirmation of literature reports[80, 81] the diazotisation

of 2-aminobenzothiazole using sodium nitrite in concentrated hydro-

chloric acid resulted in the direct formation of 2-chlorobenzothiazole

(229) (Scheme 92) albeit in low yield (25%). The reaction of 2-amino-

benzothiazole (226) with sodium nitrite in hydrobromic acid likewise

gave a dibromobenzothiazole (242) in low yield together with an un-

identified red solid. The assignment of a 2-bromobenzothiazole

structure (242) to the dibromobenzothiazole product is supported by the

absence of a thiazole proton in its ^{1}H n. m. r. spectrum. The position

of the second bromine atom could not be determined owing to the

complicated nature of the aromatic multiplet in the compound's ^{1}H

n. m. r. spectrum. Formation of the 2-halogenobenzothiazoles (229)

and (242) can be rationalised by the conversion of 2-aminobenzothiazole

into the corresponding diazonium halides followed by spontaneous

nucleophilic displacement of nitrogen in the latter by the halide counter-

ion. It was found that this spontaneous decomposition of the benzo-

thiazole-2-diazonium cation (241) can be circumvented by diazotising

2-aminobenzothiazole (226) with sodium nitrite in phosphoric acid.

Treatment of such a diazonium solution with potassium thiocyanate

gave a low yield of 2-thiocyanatobenzothiazole (243) demonstrating the

inability of the poorly nucleophilic phosphate anion to compete for the benzothiazole-2-diazonium cation. Although the elemental analysis of the thiocyanato compound (243) was not perfect, the structure of the product was confirmed by its mass spectrum and the presence of a thiocyanato band in its i.r. spectrum at 2160 cm^{-1}.

In an attempt to improve the low yield of 2-thiocyanatobenzothiazole (243) obtained, the thiocyanatodediazoniation of 2-aminobenzothiazole was repeated with the modifications that the diazonium solution was treated with sulphamic acid prior to addition of the potassium thiocyanate, to scavenge excess of nitrite ion, and the thiocyanate addition was carried out at strictly neutral pH. However under these conditions no 2-thiocyanatobenzothiazole was isolated, the product instead being an orange-brown solid (A), m.p. 215° which analysed for $C_{14}H_8N_4S_2$, but had an anomalous mass spectrum. The azo-structure (244) which was considered as a possibility for this solid, has been claimed by two groups of workers as the product formed by oxidising 2-aminobenzothiazole (226) with sodium hypochlorite. According to Bhargava and Baliga[147] this reaction gave a purple solid, m.p. 159°C, which crystallised from chloroform whereas Kirk[148] reported the formation of a dark red solid, m.p. 295° (decomp.). In the light of the confusing literature evidence and the lack of further information on this orange-brown solid, its structure remains indefinite at present. On the other hand the diazonium solution from 2-aminobenzothiazole in phosphoric acid underwent copper catalysed reaction[149] with thiocyanate ion to give a much improved yield (34%) of 2-thiocyanato-benzothiazole (243). Unexpectedly the diazotisation of 2-aminobenzo-
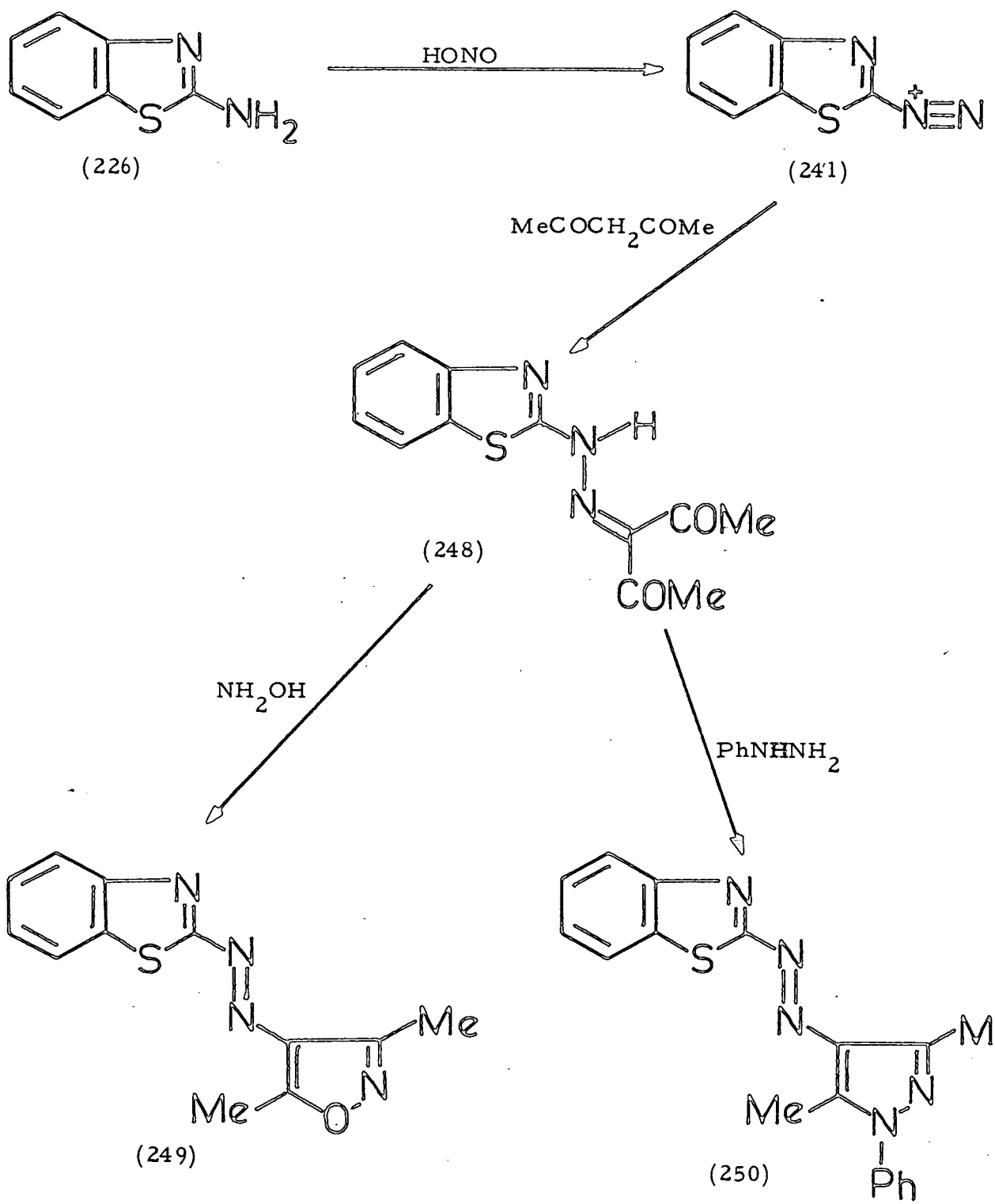
Scheme 93

thiazole (226) in phosphoric acid followed by reaction with sodium

cyanide gave not the expected 2-cyanobenzothiazole (245) (Scheme 92)

but instead a high yield of an explosive orange solid whose properties

are consistent with it being 2-hydroxyazobenzothiazole (246) as

discussed in detail later. An attempt was made to react the diazonium

suspension, prepared by treating the amine (226) in phosphoric acid

with sodium nitrite, with formaldoxime to afford the synthetically

useful aldehyde (247) (Scheme 92). However this reaction (the Beech

reaction[26]; see Chapter 1, page 8), was unsuccessful, only a salt of

2-aminobenzothiazole (226) being isolated.

Diazonium solutions derived from 2-aminobenzothiazole (226)

could also be successfully coupled with active methylene compounds.

However such reactions of the benzothiazole-2-diazonium cation (241)

were only successful under strongly acidic conditions. Thus, diazoti-

sation of the amine (226) using sodium nitrite in dilute sulphuric acid

and reaction of the resulting diazonium solution with acetylacetone

under neutral conditions gave only an intractable gum. When the

amine (226) was diazotised in a mixture of dimethylformamide and

phosphoric acid with sodium nitrite and the diazonium mixture was

reacted with acetylacetone under neutral conditions, only the starting

amine (226) was recovered. On the other hand the diazonium solution

obtained by treating 2-aminobenzothiazole (226) with sodium nitrite

in phosphoric acid reacted directly with acetylacetone to give the

hydrazone (248) (Scheme 93) in high yield. The structure of the

hydrazone (248) was proved by its elemental analysis, the presence

of NH and carbonyl absorption in its i.r. spectrum and the presence
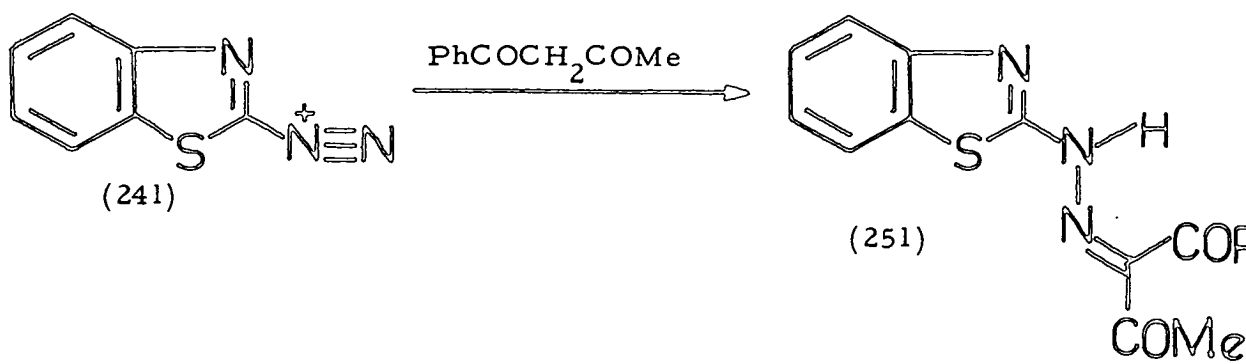
Scheme 94
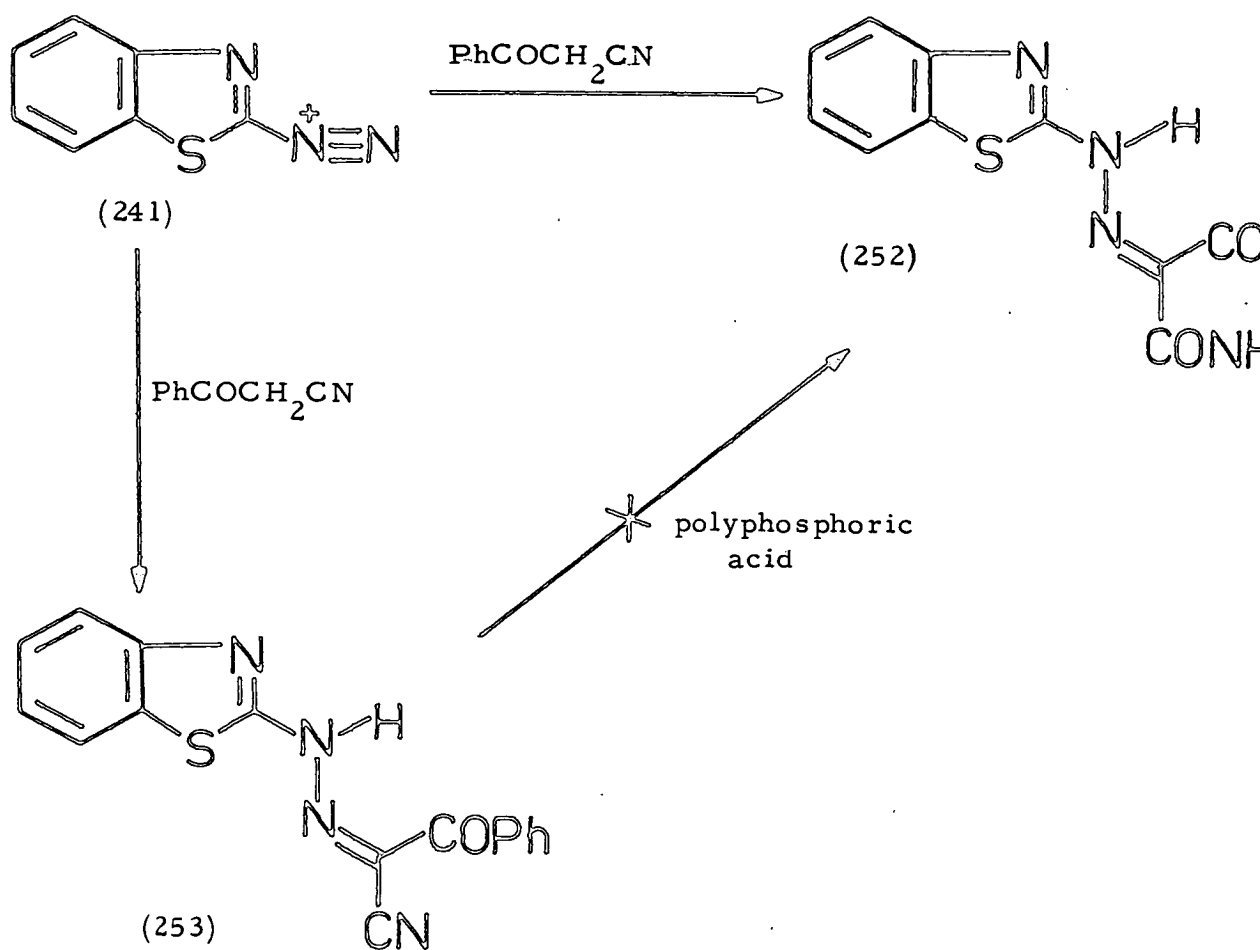
Scheme 95

of two methyl signals in its [1]H n. m. r. spectrum. Furthermore the

hydrazone (248) reacted with hydroxylamine to give the isoxazole (249)

in high yield and with phenylhydrazine to afford the pyrazole (250) also

in high yield. The benzothiazole-2-diazonium cation (241) also

coupled with benzoylacetone in phosphoric acid to afford the correspond-

ing hydrazone (251) (Scheme 94) in low yield (21%). The yield of the

product (251) was found to be substantially increased (to 70%) by

carrying out the coupling reaction in the presence of sulphamic acid

to scavenge the excess of nitrite ion. The enhanced yield of the hydrazone

(251) under these conditions can be attributed to inhibition of nitrosation

of the active methylene compound which would otherwise reduce the

amount of the latter available for coupling. The attempted reaction

of benzothiazole-2-diazonium cation (241) with ethyl acetoacetate or

ethyl benzoylacetate under a variety of conditions gave intractable

gums together with unreacted methylene compound and in some instances

rather surprisingly, unreacted 2-aminobenzothiazole (226). Attempts

to couple the benzothiazole-2-diazonium cation (241) with diethyl

malonate or ethyl cyanoacetate were equally unsuccessful, the products

of these reactions being intractable brown solids which could not be

characterised. Likewise, only unreacted amine was isolated when

2-aminobenzothiazole (226) was diazotised in phosphoric acid and the

resulting diazonium solution was reacted with cyanoacetamide. In

contrast, benzoylacetonitrile coupled with benzothiazole-2-diazonium

cation (241) in phosphoric acid to give in low yield, a product which

is assigned the hydrazone structure (252) (Scheme 95) on the basis of

its combustion analysis and spectroscopic properties. The amide
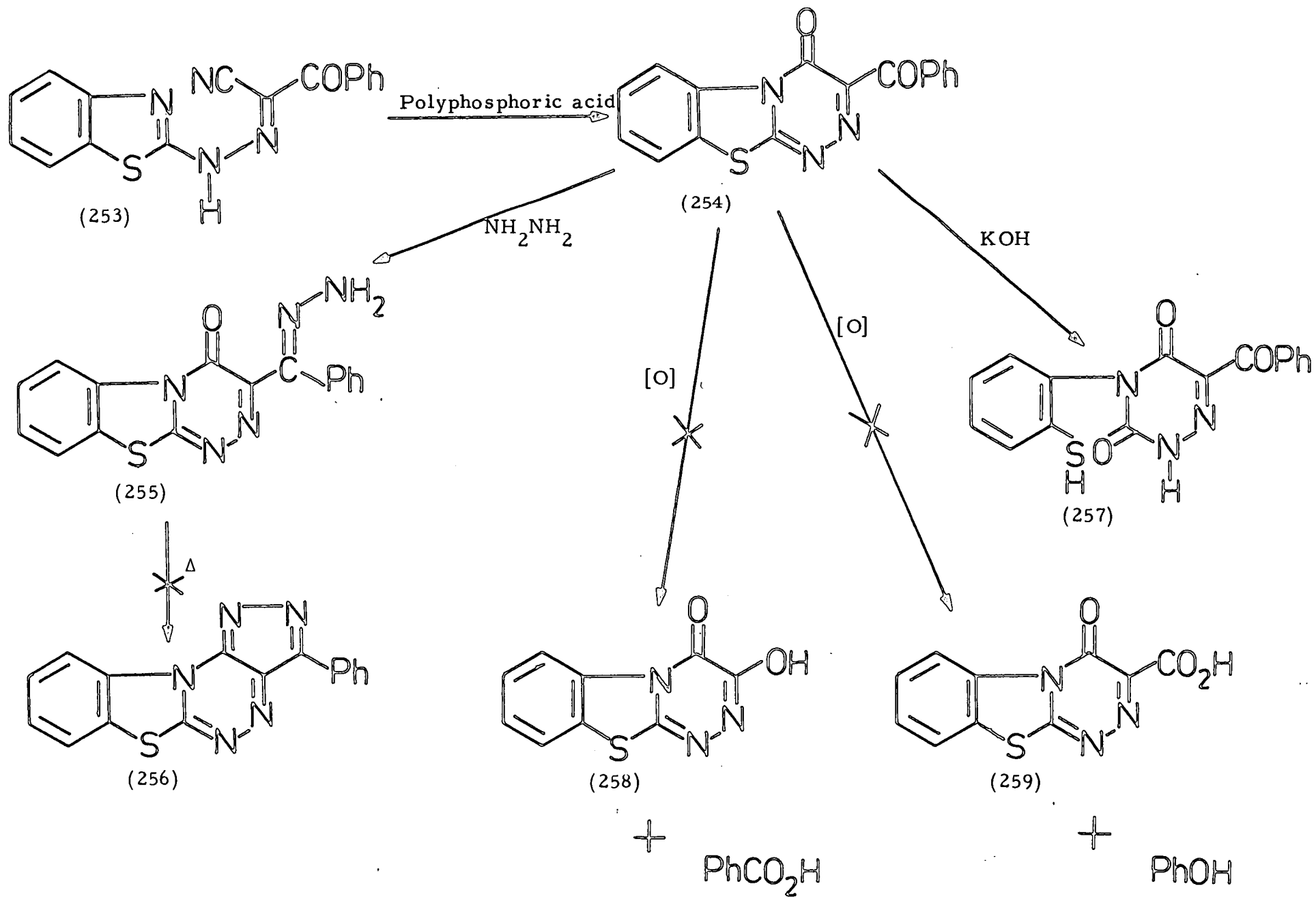
Scheme 96

structure (252) was established by the presence of two carbonyl bands in the product's i. r. spectrum and the corresponding absence of a nitrile band. However the product showed an unusual mass spectroscopic fragmentation, M^+174, 150 (M324), corresponding to N-N bond cleavage. Formation of the amide (252) can be explained in terms of orthodox coupling between benzothiazole-2-diazonium cation (241) and benzoylacetonitrile to give the nitrile (253) followed by hydrolysis. In support of this course, treatment of the diazonium solution from 2-aminobenzothiazole (226) in phosphoric acid with sulphamic acid prior to coupling with benzoylacetonitrile gave the nitrile (253) (Scheme 95) in excellent yield (92%). The attempted interrelation of the nitrile (253) and the amide (252) by hydrolysis of the former to the latter in polyphosphoric acid was thwarted by the alternative formation in high yield of the 1, 2, 4-triazinobenzothiazolone (254) (Scheme 96). The compound (254) exhibited spectroscopic properties and chemical transformations consistent with the assigned structure. The i. r. spectrum contained carbonyl absorption but lacked NH or nitrile absorption. Furthermore the mass spectrum and elemental analysis agreed with the proposed formula. In further accord with the assigned structure the 1, 2, 4-triazinobenzothiazolone (254) reacted with hydrazine to give the hydrazone (255) (Scheme 96). On the other hand the attempted cyclisation of the hydrazone (255) to the fused pyrazole (256) (Scheme 96) by heating it in acetic acid gave only an intractable red solid which could not be characterised. The structure of the 1, 2, 4-triazinobenzothiazolone (254) is also substantiated by its hydrolysis to the acidic 1, 2, 4-triazinedione derivative (257) (Scheme 96).

(260)

(261)

MeCOCH₂COMe

(248)
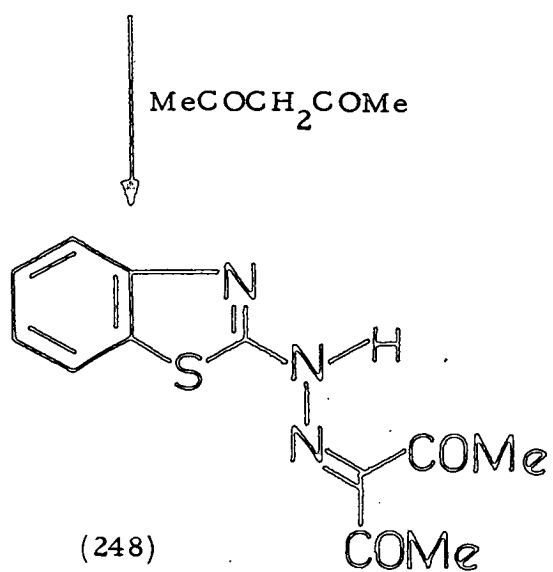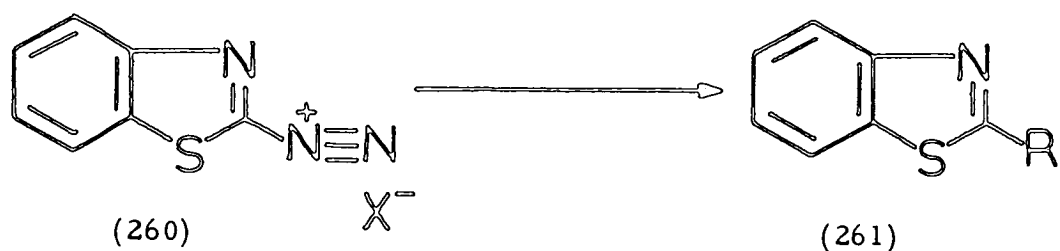
	R
a;	Cl
b;	Br
c;	I
d;	F
e;	NO₂
f;	SO₂Ph
g;	OMe
h;	CN
i;	SCN

Scheme 97

The 1,2,4-triazinedione derivative (257) was identified by its elemental analysis, mass spectrum, and the presence of a carbonyl band in its i.r. spectrum. The attempted Baeyer-Villiger oxidation of the 1,2,4-triazinobenzothiazolone (254) with hydrogen peroxide gave neither of the expected products (258) or (259) (Scheme 96) but merely a low yield of a gum which was shown to contain starting material.

In order to be able to exercise greater control over reactions undergone by the benzothiazole-2-diazonium cation (241) it was next decided to attempt the synthesis and isolation of suitable benzothiazole-2-diazonium salts for reactivity studies. However the attempted preparation of benzothiazole-2-diazonium chloride (260; X=Cl) (Scheme 97) by reacting 2-aminobenzothiazole (226) hydrochloride with amyl nitrite in various solvents under conditions successful[146] for the conversion of 5-amino-1$\underline{H}$-1,2,3-triazoles into 1$\underline{H}$-1,2,3-triazole-5-diazonium chlorides, was unsuccessful. On the other hand benzo-thiazole-2-diazonium fluoroborate (260; X=BF$_4^-$) (Scheme 97) was successfully prepared and isolated in good yield by diazotising a solution of the amine (226) in aqueous 40% w/v hydrofluoroboric acid with sodium nitrite. The diazonium salt (260; X=BF$_4$) was moderately stable in the solid state but its decomposition with gas evolution on attempted crystallisation precluded attempts to purify it and hence to obtain accurate analytical data. The identity of the compound was confirmed by the presence of a diazonium (N$\overset{+}{\equiv}$N) band at 2270 cm^{-1} in its i.r. spectrum, and its purity was indicated by its conversion into 2-azidobenzothiazole in high yield (see Chapter 6). The ready

(226)

HONO
$\longrightarrow$
H_2O
$\longleftarrow$
(-HONO)

(262)

(260)

$H_2O(-H^+)$
$\longrightarrow$
$\longleftarrow$

(246)
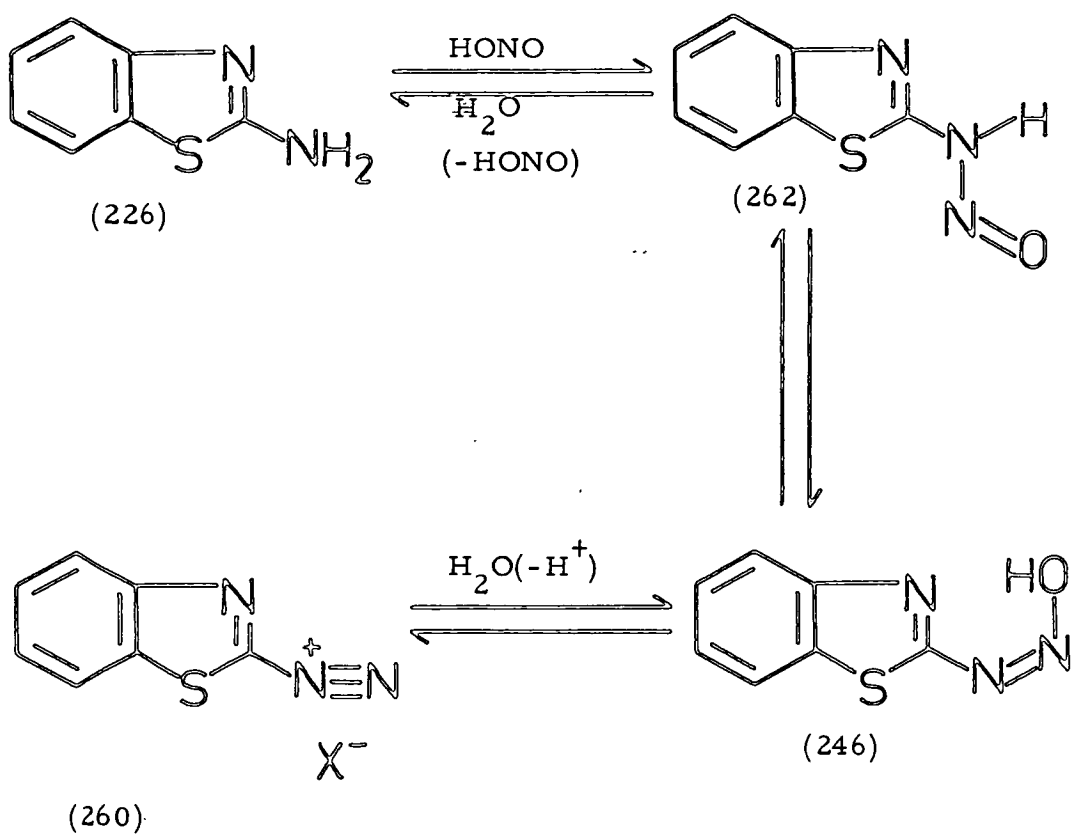
Scheme 98

availability of the solid diazonium salt (260; $X=BF_4$) permitted the

study of its dediazoniation under a variety of conditions. Initially

attempts were made to effect the halogeno-dediazoniation of the salt

(260; $X=BF_4^-$) by reacting it with the different halogen acids. This

type of reaction has been demonstrated for 1, 2, 4-thiadiazole-3-

diazonium salts[110, 114] and for thiazole-2-diazonium salts.[80, 82] In

contrast, reaction of the salt (260; $X=BF_4$) with concentrated aqueous

hydrochloric acid gave not 2-chlorobenzothiazole (261a) (Scheme 97)

but rather unexpectedly the amine (226) together with a multicomponent

gum. The salt (260; $X=BF_4$) also reacted with aqueous hydrobromic

acid to give the amine (226) rather than 2-bromobenzothiazole (261b)

plus a red solid which decomposed on attempted purification. Reaction

of the salt (260; $X=BF_4$) with aqueous hydroiodic acid, in contrast gave

only an intractable tar and not the iodo compound (261c). The forma-

tion of 2-aminobenzothiazole (226) from benzothiazole-2-diazonium

fluoroborate (260; $X=BF_4$) must involve a reversal of the diazotisation

process (Scheme 98), presumably involving the nitrosamine (262) and

the N-hydroxyazo compound (246) as intermediates. The attempted

pyrolytic conversion of the diazonium salt (260; $X=BF_4$) into 2-

fluorobenzothiazole (261d) (the Schiemann Reaction) gave an intractable

brown solid.

Benzothiazole-2-diazonium fluoroborate (260; $X=BF_4$) reacted

with aqueous sodium nitrite to give the unidentified compound (A)

obtained before, together with a product whose properties are con-

sistent with it being the known[148] 2-nitrobenzothiazole (261e) (Scheme

97) which has been prepared[148] by diazotisation of 2-aminobenzothiazole

(226) in hydrofluoroboric acid with sodium nitrite followed by treatment

with further sodium nitrite, copper and the application of heat. The

product was identified by the similarity of its melting point to the literature value,[148] its mass spectrum M^+180 (M180) and i. r. spectrum. In an attempt to improve the yield of the nitro compound (261e) the copper catalysed[150] reaction of the salt (260; $X=BF_4$) with sodium nitrite was investigated. However these reaction conditions gave only an intractable gum. The attempted conversion of the salt (260; $X=BF_4$) by reaction with sodium benzenesulphinate or sodium methoxide into the substitution products (261f and g) (Scheme 97) gave only the unidentified compound (A) obtained before. An attempt to prepare 2-cyanobenzothiazole (261h) (Scheme 97) by treating an aqueous suspension of the fluoroborate (260; $X=BF_4$) with sodium cyanide gave a good yield of the unidentified compound (A) obtained before. This reaction was repeated using a copper cyanide catalyst[151] but these conditions gave only an intractable gum. Treatment of the diazonium fluoroborate (260; $X=BF_4$) with thiocyanate ion in an attempt to obtain 2-thiocyanatobenzothiazole (261i) (Scheme 97) gave an unidentified solid. Treatment of the diazonium salt (260; $X=BF_4$) with a copper thiocyanate catalyst[149] was no more successful and gave only intractable gums. The only replacement reaction of the diazonium fluoroborate (260; $X=BF_4$) which was really successful was the preparation of 2-azidobenzothiazole, discussed in Chapter 6.

The investigation of the reactions of benzothiazole-2-diazonium fluoroborate (260; $X=BF_4$) was extended to coupling with the active methylene centre in acetylacetone. The latter reacted with the diazonium fluoroborate (260; $X=BF_4$) in ethanol solution at room
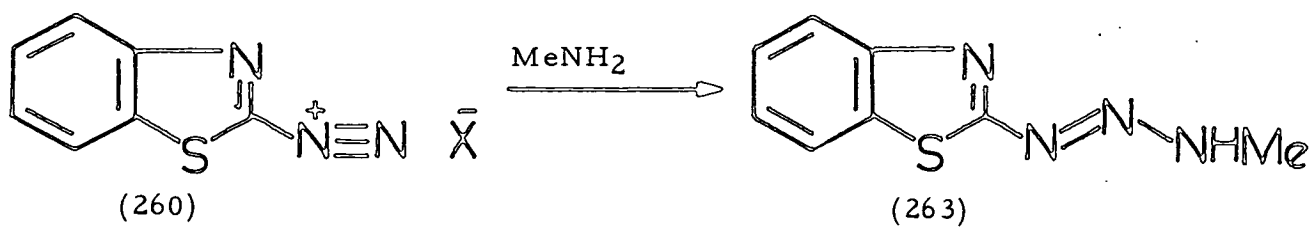
Scheme 99
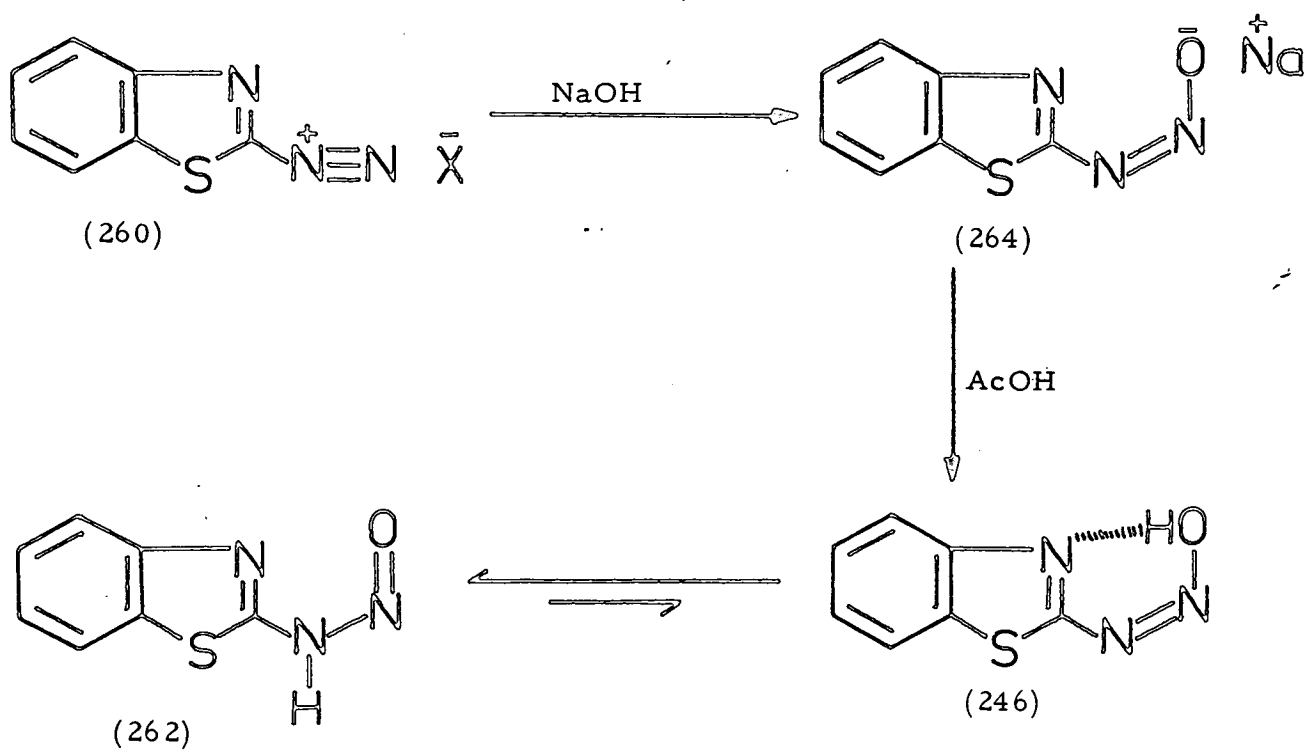
Scheme 100

temperature to give a low yield of the hydrazone (248) prepared

previously (Scheme 97). In an attempt to improve the yield of this

coupling reaction, the sodium salt of acetylacetone rather than

acetylacetone itself was used. However this reaction gave only the

unidentified compound (A) prepared previously.

The diazonium fluoroborate (260; X=BF_4) was treated with an

aqueous solution of methylamine in an attempt to prepare the triazene

(263) (Scheme 99). Work up however only afforded an intractable

black solid together with a small amount of the unidentified compound

(A) obtained before.

As discussed briefly before, the diazotisation of 2-aminobenzo-

thiazole in phosphoric acid and the subsequent reaction of the diazonium

solution with sodium cyanide gave a highly reactive product which

decomposed on melting or on attempted crystallisation and burned in

a flame with an energetic flash. The same product was obtained in

moderate yield by diazotising 2-aminobenzothiazole in concentrated

phosphoric acid with sodium nitrite. Although attempts to purify this

product were precluded by its thermal instability, a diazonium salt

structure is excluded by the lack of diazo absorption in its i. r. spectrum.

This reactive solid is tentatively assigned the N-hydroxyazo structure

(246) (Scheme 100) on the basis of its mass spectrum, the presence

of a broad band at 3000 cm^{-1} in its i. r. spectrum and on the basis of

chemical transformations to be described later. Recently[91] Russian

workers have claimed the isolation of the tautomeric 2-nitrosamino-

benzothiazole (262) (Scheme 100). Treatment[91] of benzothiazole-2-

diazonium fluoroborate (260; X=BF_4) with dilute sodium hydroxide

(246)   (265)

[H]

(267)   (266)

Scheme 101

(246)   (262)

-H⁺

-HNO₂
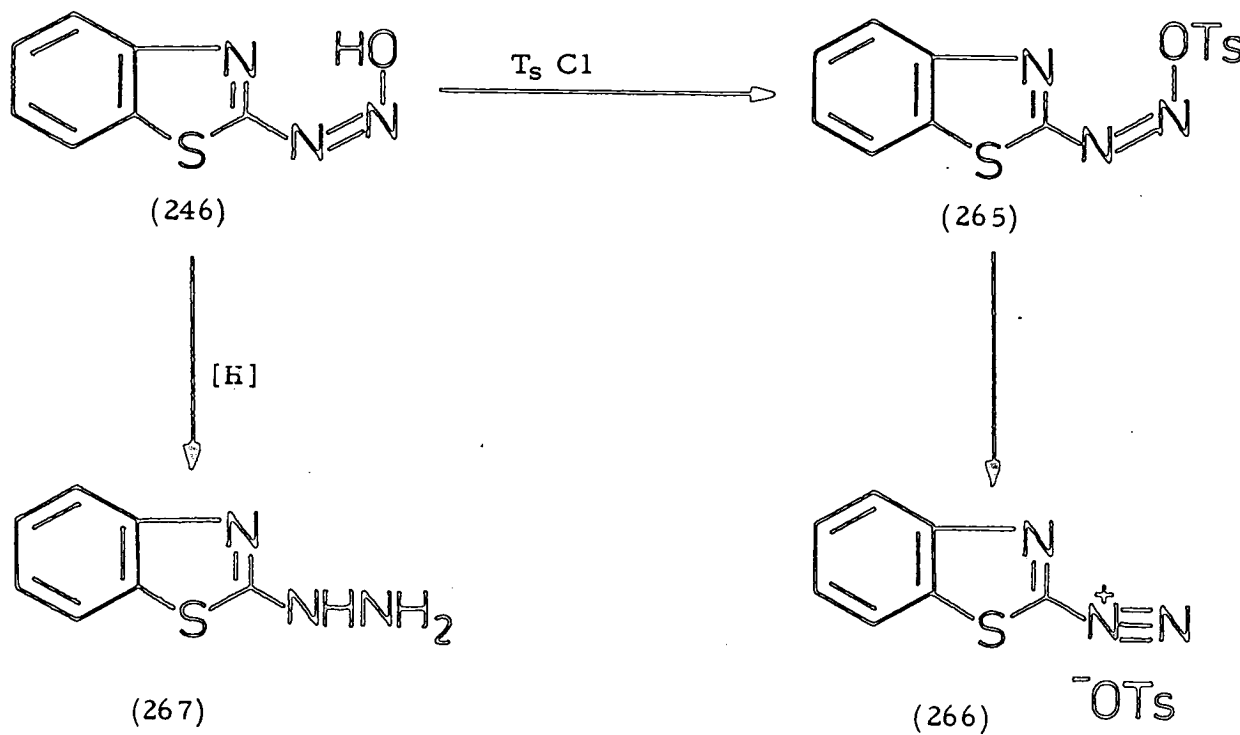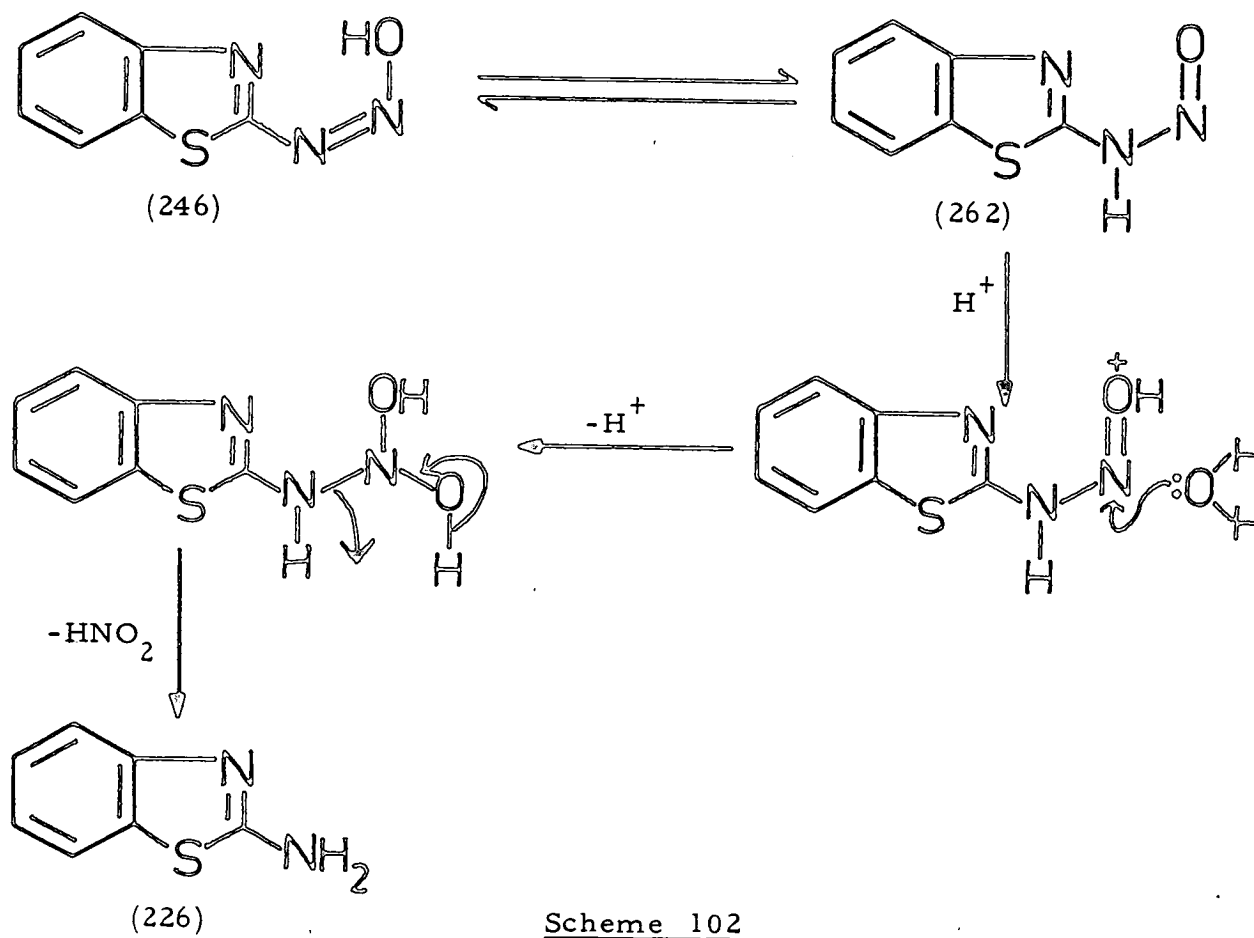
(226)   Scheme 102

is reported to yield the diazotate (264) which is quantitatively

converted into the nitrosamine (262) on acidification with 50% aqueous

acetic acid (Scheme 100). The isolation of a "diazo intermediate" on

treatment of 2-aminobenzothiazole (226) under standard diazotisation

conditions is consistent with the rules proposed by Butler.[108] This

is because the N-hydroxyazo tautomer (246) can be stabilised by

intramolecular hydrogen bonding between the hydroxyl group and the

adjacent ring nitrogen atom (Scheme 100).

The chemical reactivity of the presumed N-hydroxyazo compound

(246) was investigated in an effort to substantiate its structure. In

particular, an attempt was made to convert it into a characterisable

N- or O-methyl derivative by reaction with dimethyl sulphate in the

presence of alkali.[152] However this reaction gave only a small

amount of an unidentified solid. An attempt to acetylate the com-

pound (246) by treating it with acetyl chloride under basic conditions

was also unsuccessful and yielded only an intractable red gum. The

reaction of the N-hydroxyazo compound (246) with toluene-p-sulphonyl

chloride under basic conditions was also investigated (Scheme 101).

It was anticipated that initial tosylation to afford the tosylate (265)

might be followed by spontaneous elimination to afford the diazonium

tosylate (266) (Scheme 101). In practice however the only product

isolated in this reaction was the unidentified compound (A) encountered

previously. This same unidentified compound (A) was also the

exclusive product of the attempted reduction of the N-hydroxyazo-

benzothiazole (246) to the hydrazine (267) using sulphur dioxide (Scheme

101).
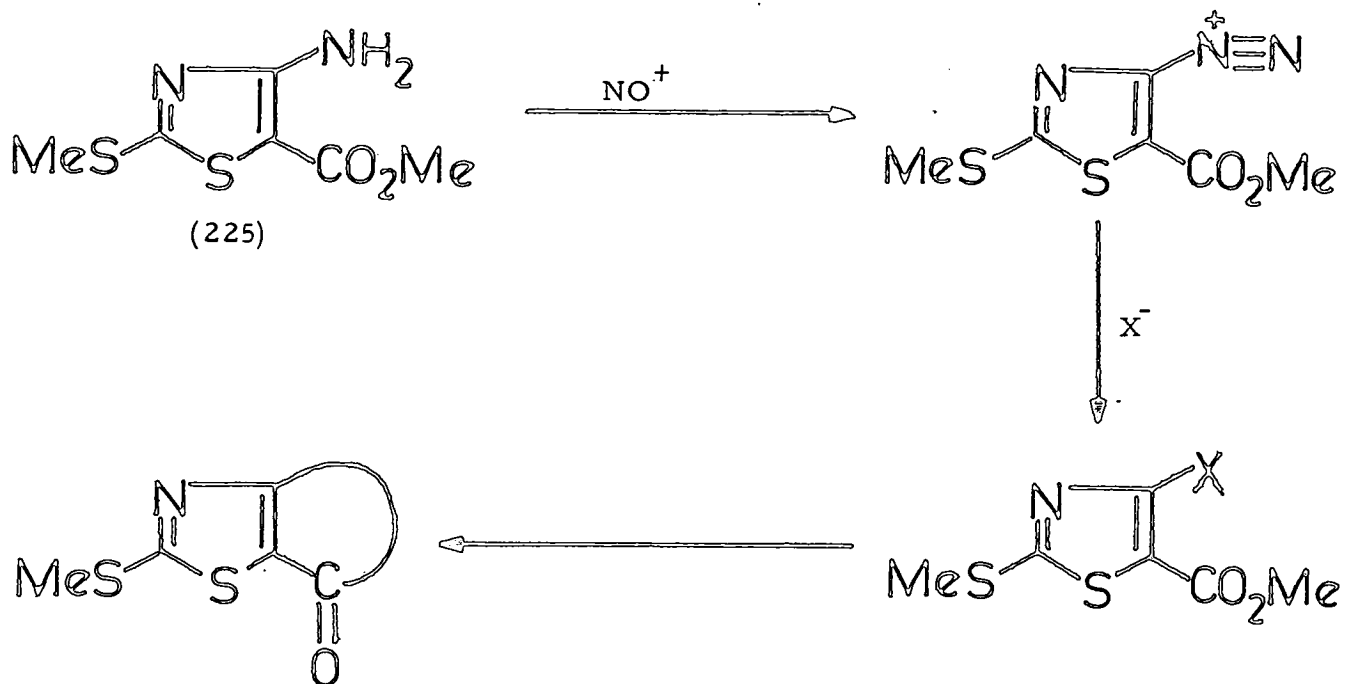
Scheme 103
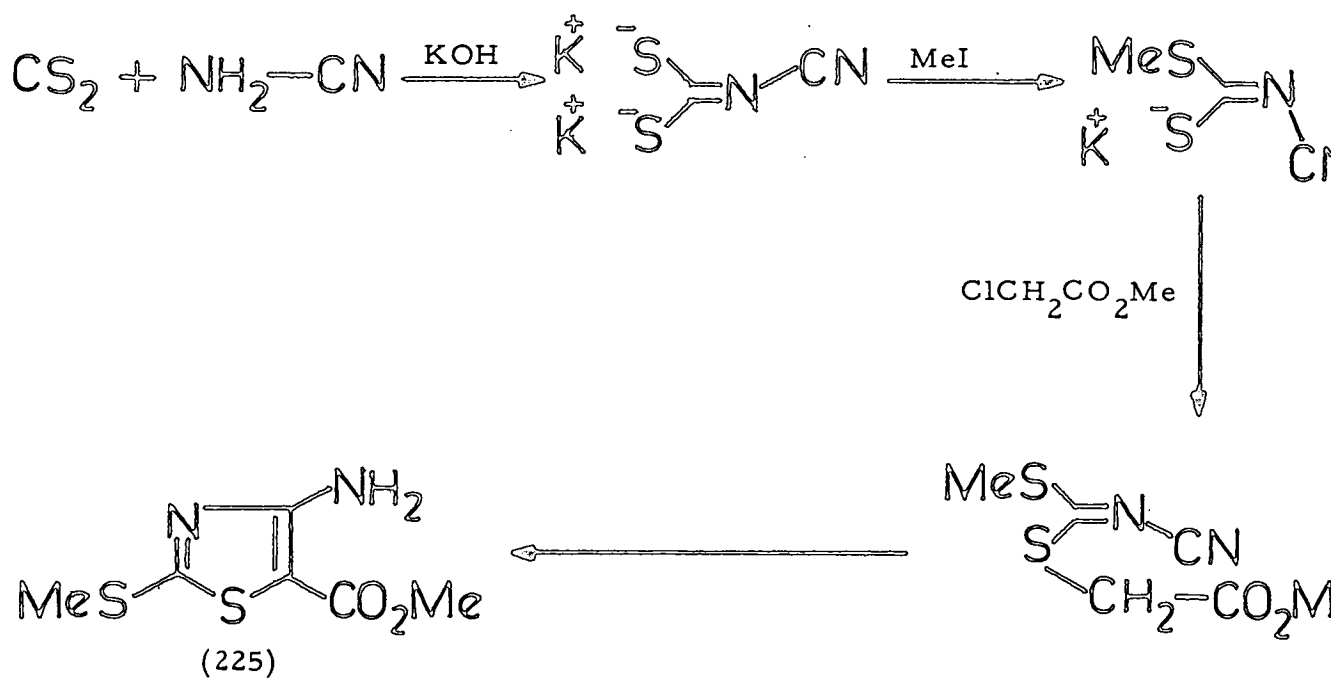
Scheme 104

The utility of the $\underline{N}$-hydroxyazobenzothiazole (246) as a precursor of stable salts of the benzothiazole-2-diazonium cation (241) was also investigated. In practice treatment of the compound (246) with concentrated hydrochloric acid gave not the expected benzothiazole-2-diazonium chloride (260; X=Cl) but unexpectedly 2-aminobenzothiazole (226) (Scheme 102). This result is explicable (Scheme 102) in terms of 'dehydronitrosation' and supports the contention that for heterocyclic primary amines the first step in the diazotisation process (Scheme 98) is in fact reversible. In contrast to the result observed in hydrochloric acid, treatment of the $\underline{N}$-hydroxyazo compound (246) in acetic acid with aqueous 40% w/v hydrofluoroboric acid afforded benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) identified by comparison with a sample prepared by diazotisation of the amine (226) in hydrofluoroboric acid (see before). This transformation and the conversion of the $\underline{N}$-hydroxyazo compound (246), by reaction with sodium azide, into 2-azidobenzothiazole (discussed in Chapter 6) provide strong evidence for the structure (246).

Attention was next directed to the investigation of the diazotisation of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225). This substrate was chosen for study for several reasons. Firstly, the literature contains few reports on the diazotisation of 4-aminothiazoles. Secondly the amine (225) is readily synthesised. Thirdly the presence of a reactive functional group ortho to the amino group in the molecule (225) affords the possibility subsequent to diazotisation and dediazoniation, of preparing 4,5-bifunctional

MeS—⟨thiazole⟩—NH₂ (with CO₂Me) → (NO⁺) → MeS—⟨thiazole⟩—N⁺≡N (with CO₂Me)

(225) → (268)

(268) → (SCN⁻) → (269)

(269): MeS—⟨thiazole⟩ bearing SCN and CO₂Me

(270): MeS—⟨thiazole⟩ bearing SCN and CO₂H

(272): MeS—⟨thiazole⟩ bearing SCN and CONH₂

(271): bis-thiazole disulfide with CO₂Me groups
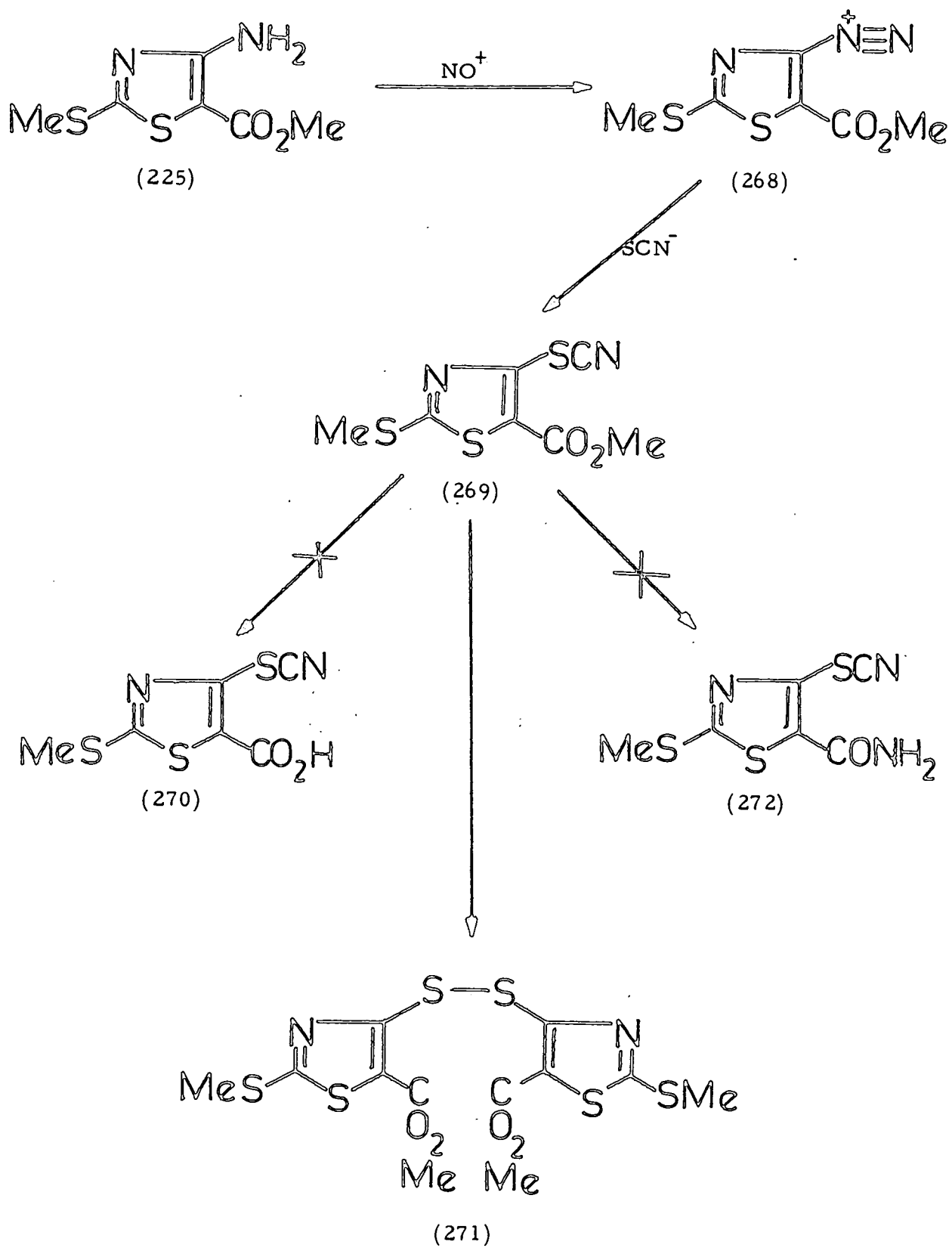
Scheme 105

thiazoles of potential value as intermediates for the synthesis of fused thiazoles (Scheme 103).

Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) was readily prepared in good yield as described in the literature, [153-155] by the reaction of potassium methyl cyanodithioiminocarbonate with methyl chloroacetate (Scheme 104).

The foregoing studies had shown that 2-aminothiazoles are diazotised most satisfactorily using sodium nitrite in phosphoric acid. These reagents were also found to be successful for the diazotisation of the amine (225) as demonstrated by the reaction of the derived diazonium suspension with copper thiocyanate catalyst[149] at pH 5-7 to afford methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate (269) (Scheme 105) albeit in low yield (17%). Unreacted amine (225) was detected in the mother liquor from this reaction. The thiocyanato compound (269) was identified by its elemental analysis and the presence of a band at 2170 cm^{-1} in its i.r. spectrum. In an attempt to hydrolyse the thiocyanato compound (269) to give the acid (270) (Scheme 105) it was mixed with concentrated sulphuric acid to afford a moderate yield of di-(5-carbomethoxy-2-methylmercaptothiazol-4-yl) disulphide (271). The structure of the disulphide dimer (271) was established by its elemental analysis, mass spectrum, the presence of two signals in its ^{1}H n.m.r. spectrum indicating only two distinct methyl groups and by the absence of a thiocyanato band in its i.r. spectrum. A good yield of the disulphide (271) was also obtained when the thiocyanato compound (269) was treated with ammonia in an attempt to prepare the amide (272) (Scheme 105).

(225)   (268)

(273)   (274)
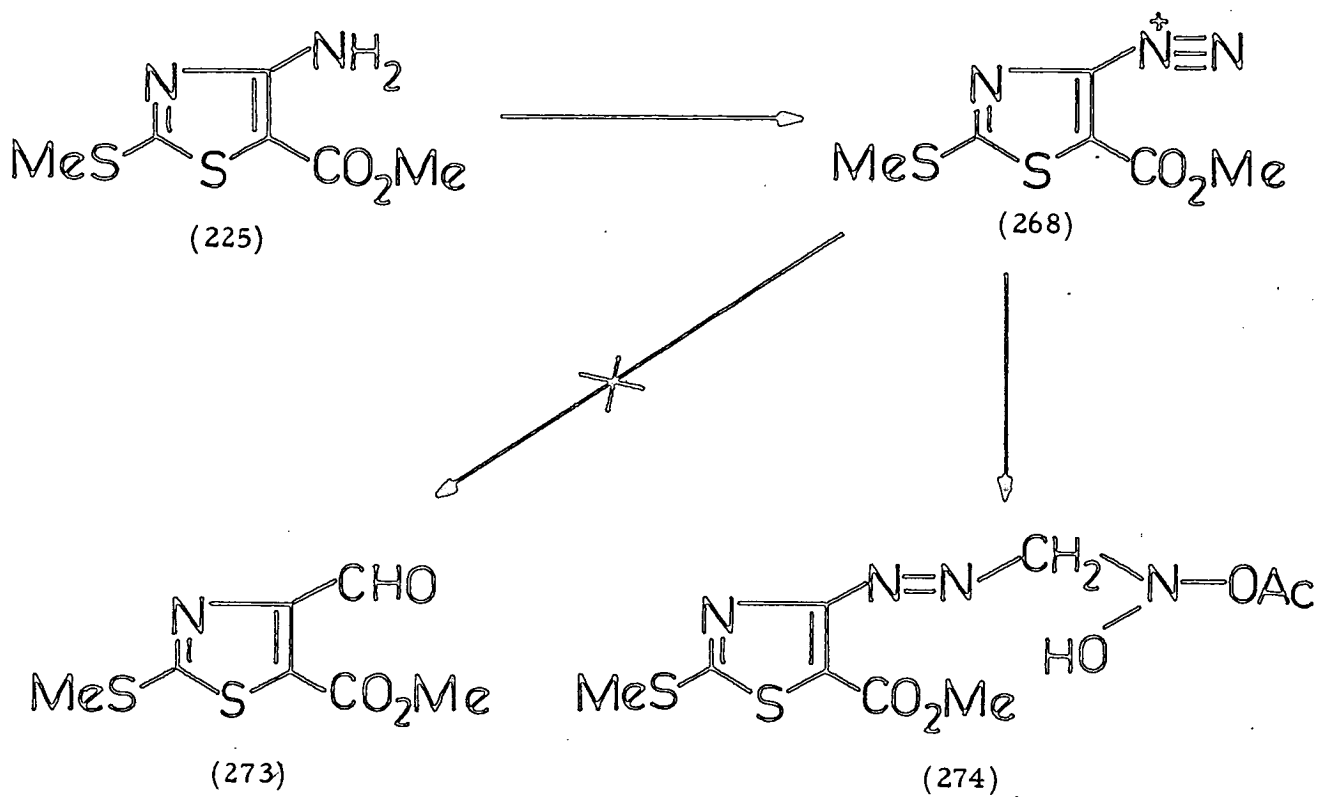
, <u>Scheme 106</u>

The formation of a disulphide from a thiocyanato compound is a known reaction.[156] With a view to improving the efficiency of the formation of the diazonium cation (268) and its subsequent dediazoniation, the amine (225) was diazotised using the more powerful nitrosating agent nitrosylsulphuric acid and the resulting diazonium suspension was reacted with copper thiocyanate catalyst.[149] Under these conditions the yield of the thiocyanatothiazole (269) was raised to 48%, and there was no evidence of unreacted amine (225). The yield enhancement observed under these conditions can be attributed to the strongly acidic conditions apparently necessary for the successful diazotisation of the amine (225). However the important role also played by copper catalysis is indicated by the low yield (17%) of the thiocyanato product (269) isolated when the amine (225) is treated with nitrosylsulphuric acid followed by potassium thiocyanate.

The successful thiocyanatodediazoniation of the diazonium cation (268) derived from the amine (225) prompted attempts to extend such dediazoniations using other nucleophilic reagents. However the attempted reaction of the diazonium mixture, obtained by treating the amine (225) with nitrosylsulphuric acid, with copper cyanide[151] or copper nitrite catalyst[150] afforded only multicomponent gums from which no identifiable material could be isolated. The attempted conversion of the amine (225) into the aldehyde (273) (Scheme 106) by treatment with nitrosylsulphuric acid followed by formaldoxime (the Beech Reaction[26] - see Chapter 1, page 8) gave a low yield of a product which analysed as $C_9H_{12}N_4O_5S_2$ and is tentatively assigned the azo structure (274) (Scheme 106). This assignment is based on

Scheme 107

	R[1]	R[2]
a;	COMe	Me
b;	COMe	Ph
c;	CO$_2$Et	Me
d;	CO$_2$Et	Ph
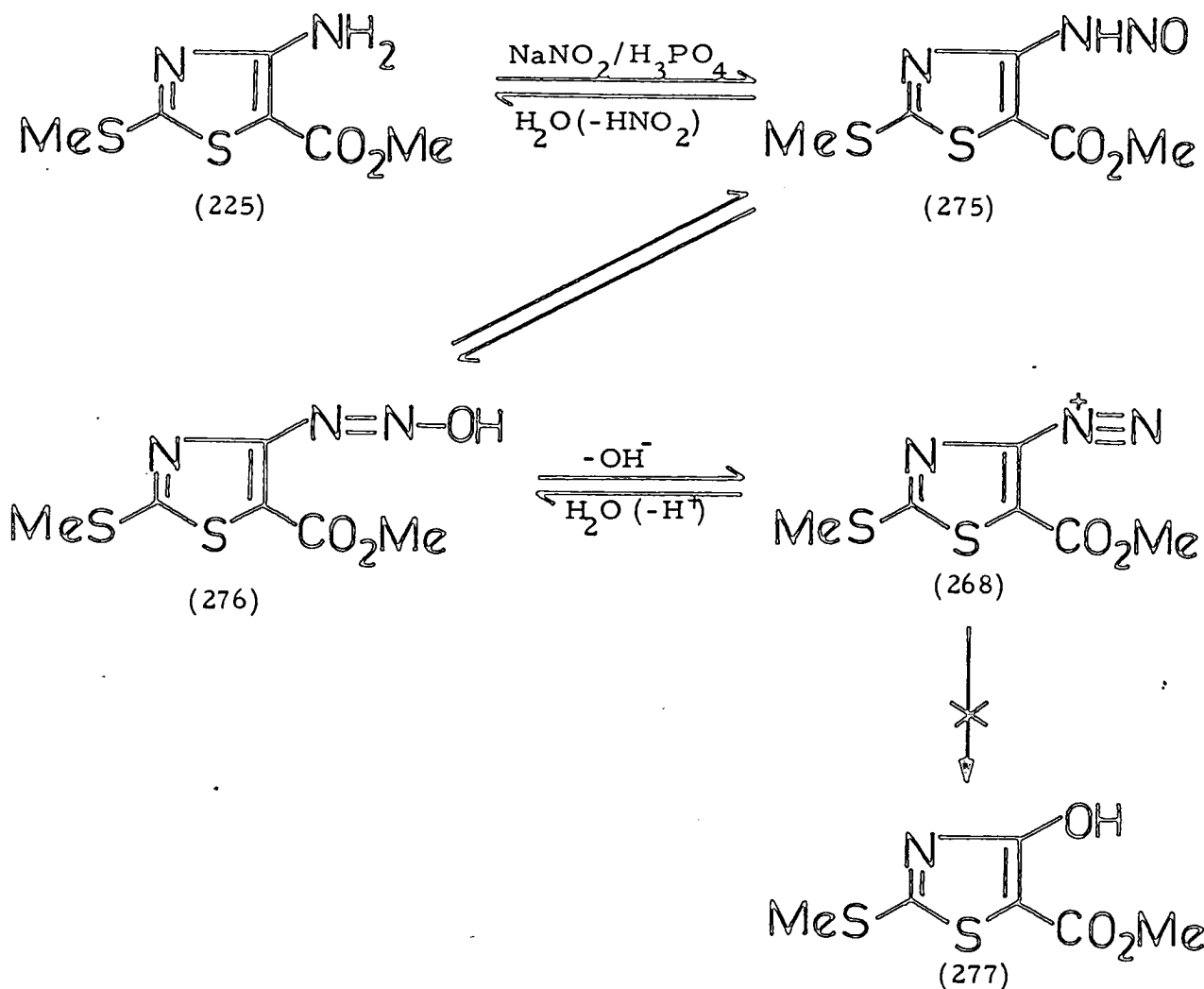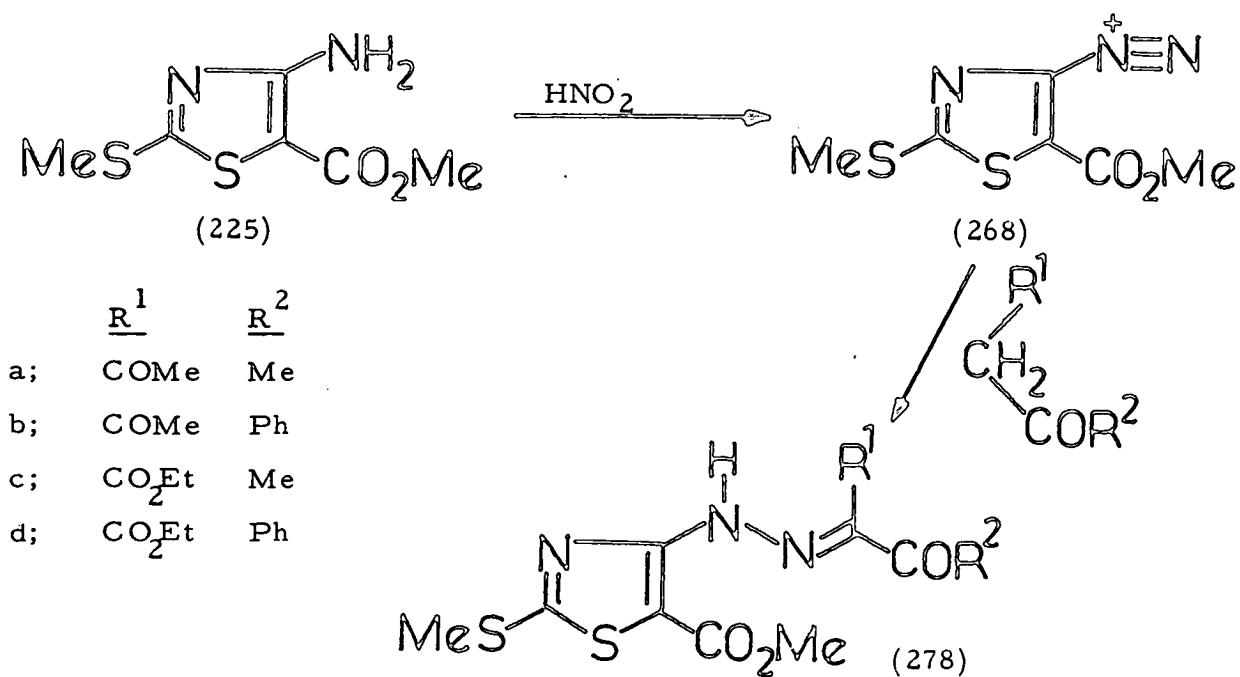
Scheme 108

the ^{1}H n.m.r. spectrum which shows the presence of three different methyl groups and one methylene group and the i.r. spectrum which shows two carbonyl groups including a high frequency resonance at 1770 cm^{-1} characteristic[131] of an N-acetoxy group, and a hydroxyl band at 3200 cm^{-1}. In an attempt to confirm the azo structure (274), the compound was heated under reflux with aqueous ethanol, aqueous acetic acid and aqueous sodium carbonate. However none of these reactions yielded any identifiable hydrolysis product. Quenching the diazonium solution obtained from the amine (225) and sodium nitrite in phosphoric acid with ice gave not the expected hydroxythiazole (277) (Scheme 107) but rather unreacted amine (225). Since sodium nitrite-phosphoric acid has already been shown to convert the amine (225) into a species which behaves as the diazonium cation (268) [or the N-hydroxyazo species (276)], reformation of the amine (225) by hydrolytic quenching of the diazonium cation [or the N-hydroxyazo intermediate (276)] provides evidence for the total reversibility of the diazotisation process [i.e. Scheme 107; (225)⇌(275)⇌(276)⇌(268)].

Satisfactory conditions having been devised for the diazotisation of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) and certain of the dediazoniation reactions of the derived diazonium cation, attention was turned to the study of coupling reactions of the latter. Thus, diazotisation of the amine (225) using sodium nitrite in phosphoric acid followed by reaction with acetylacetone gave the expected hydrazone (278a) (Scheme 108) in good yield. This assignment is consistent with the elemental analysis and mass spectrum of the product and the presence of four methyl signals in its ^{1}H n.m.r.

(225)

(268)

(279)

(280)
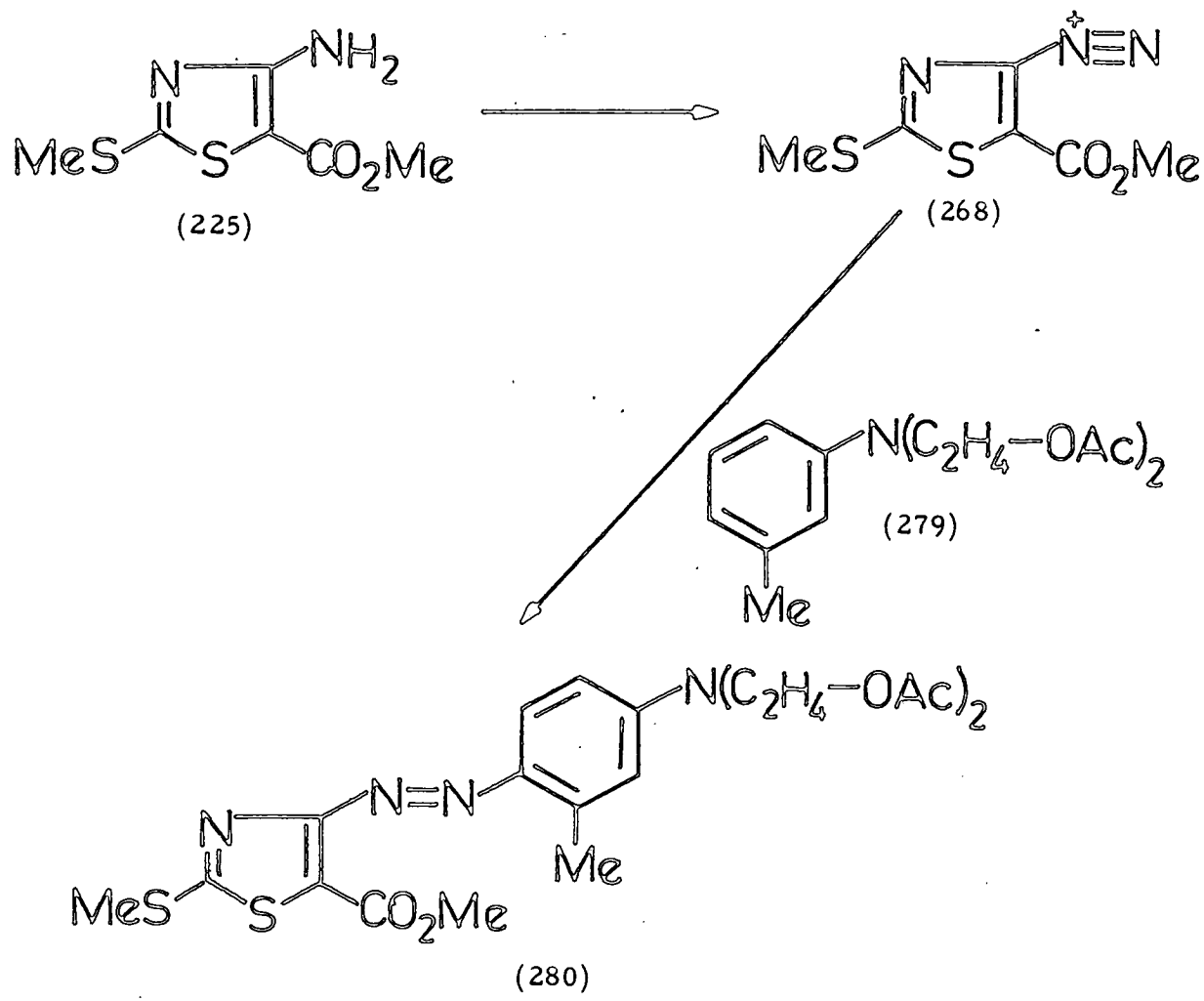
Scheme 109

spectrum as well as three distinct carbonyl bands in its i.r. spectrum. The diazonium mixture obtained by treating the amine (225) with nitrosylsulphuric acid in acetic acid also reacted readily at pH 6-9 with active methylene compounds. Under these conditions benzoylacetone and ethyl acetoacetate coupled to afford the expected hydrazones (278b) and (278c) (Scheme 108) in quantitative yield. The structures of the products were confirmed by elemental analysis and their mass and [1]H n.m.r. spectra. In contrast, ethyl benzoylacetate coupled to afford only a low yield (33%) of the anticipated hydrazone (278d) (Scheme 108). The structure of this product was confirmed by its elemental analysis, mass spectrum and the presence of signals due to two methyl groups and one ethyl group in its [1]H n.m.r. spectrum. Diethyl malonate and ethyl cyanoacetate coupled to give intractable purple materials from which no identifiable material could be obtained.

Acid solutions of the diazonium cation (268) also coupled in orthodox fashion with electron-rich arenes. Thus the diazonium solution obtained by treating the amine (225) with sodium nitrite in phosphoric acid, coupled with an acidic solution of <u>N</u>, <u>N</u>-<u>bis</u>-(β-acetoxyethyl)-meta-toluidine (279) (Scheme 109) to give a red solid which was shown by t.l.c. to be a mixture of two red components. As it was thought that one of these products was simply a de-acetylated version of the other, the solid mixture was heated with acetic anhydride to give a moderate yield of a red solid which was shown by t.l.c. to be a single compound. The azo structure (280) (Scheme 109) for this product was confirmed by its elemental analysis and its i.r. and [1]H n.m.r. spectra. The i.r. spectrum contains several carbonyl bands
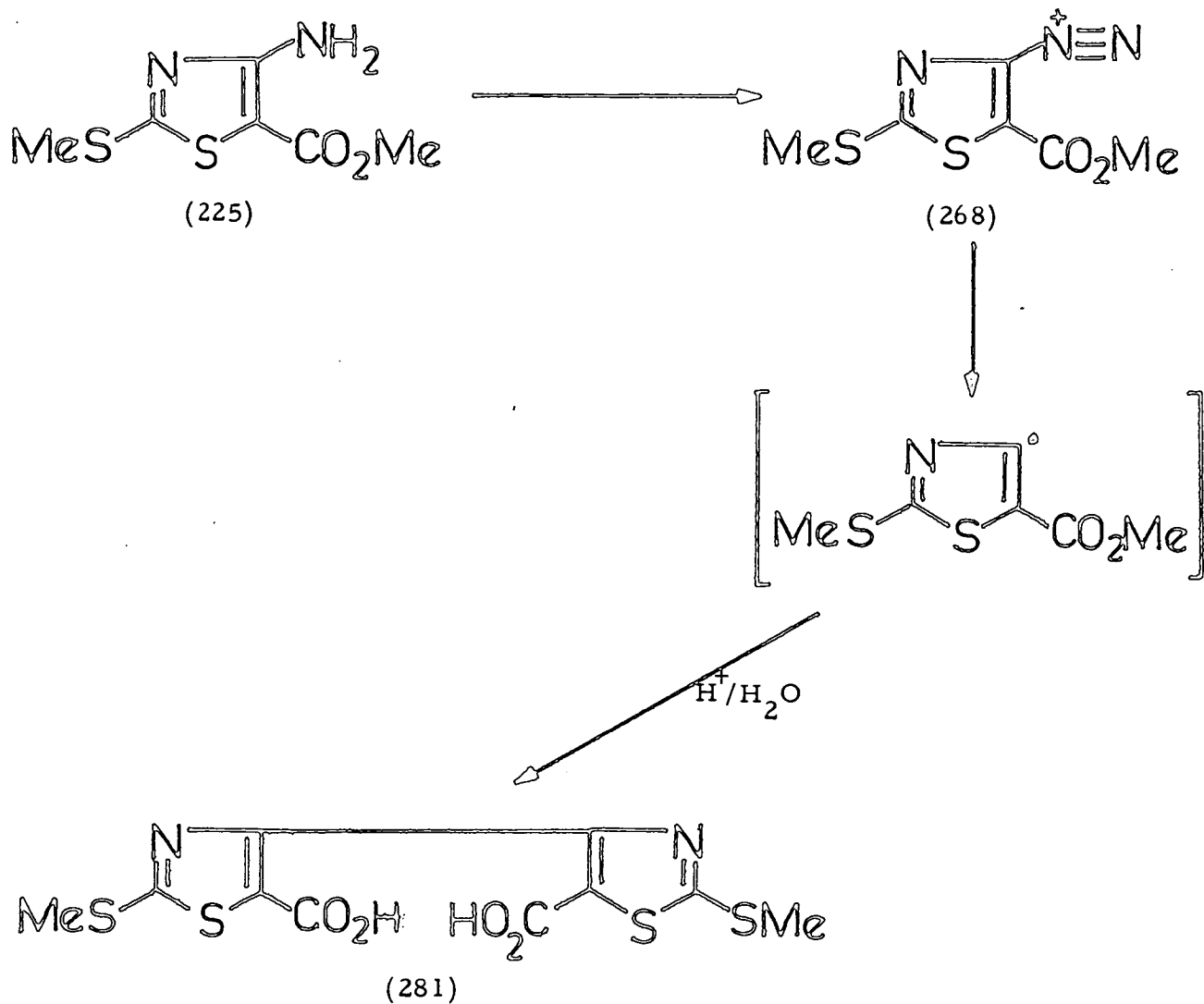
Scheme 110
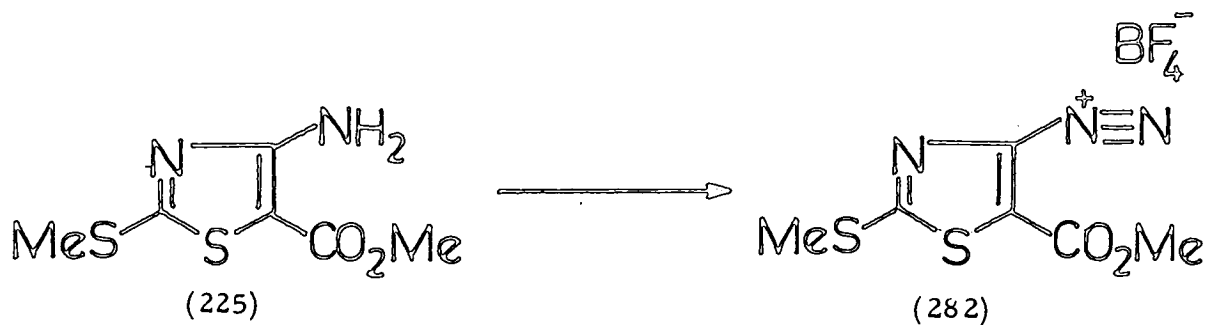
Scheme 111

whereas its [1]H n. m. r. spectrum shows three aromatic protons, two of which are ortho coupled, two identical -CH$_2$-CH$_2$- groups, three different methyl signals and two identical methyl groups.

Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) is an amine which according to Butler[108] ought to form a stable nitrosamine (275) or N-hydroxyazo compound (276) (Scheme 107). This is because it is a five-membered heterocyclic amine with its amino group adjacent to a ring nitrogen atom. Attempts were therefore made to convert the amine (225) into the corresponding nitrosamine (275) or tautomeric N-hydroxyazo derivative (276) using established methods.[108,10] However treatment of the amine (225) with sodium nitrite in aqueous sulphuric acid under conditions[109] successful for the conversion of 5-amino-1, 2, 4-thiadiazoles into 5-nitrosamino-1, 2, 4-thiadiazoles (see Chapter 5) gave a good yield of a yellow solid which analysed for C$_{10}$H$_8$N$_2$O$_4$S$_4$ although its mass spectrum was anomalous. This solid is tentatively assigned the dimeric structure (281) (Scheme 110) and its formation would presumably involve the self-coupling of the 5-carbomethoxy-2-methylmercaptothiazol-4-yl radical. Correspondingly the reaction of the amine (225) with sodium nitrite in aqueous hydrochloric acid under conditions[108] suitable for the conversion of 2-amino-5-phenyl-1, 3, 4-thiadiazole into 2-nitrosamino-5-phenyl-1, 3, 4-thiadiazole gave only unreacted amine (225) plus an intractable gum. The use[109] of sodium nitrite in aqueous formic acid was no more successful and also gave only intractable gums.

Attempts were also made to convert the amine (225) into the diazonium fluoroborate (282) (Scheme 111) which it was presumed would

be isolable as a relatively stable solid suitable for reactivity studies under a variety of conditions. In practice diazotisation of the amine (225) with sodium nitrite in hydrofluoroboric acid afforded a low yield of a yellow solid which gave a positive test with 1-acetamido-8-hydroxy-3,6-naphthalenedisulphonic acid (acetyl $\underline{H}$ acid), indicative of a diazonium salt. The presumed diazonium salt (282) decomposed on attempted crystallisation but its diazonium structure is supported by the presence of diazo absorption in its i.r. spectrum. The reaction of the amine (225) with sodium nitrite in hydrofluoroboric acid also afforded a second yellow solid which gave an elemental analysis similar to the solid obtained on attempted nitrosation of the amine (225) in sulphuric acid and tentatively assigned the dimeric structure (281). In a further attempt to prepare the diazonium fluoroborate (282) in improved yield the amine (225) was diazotised in concentrated phosphoric acid with sodium nitrite and the resulting diazonium suspension was treated with hydrofluoroboric acid. However the solid product obtained lacked diazo absorption in its i.r. spectrum, failed to give a positive test with acetyl $\underline{H}$ acid, and decomposed on attempted purification, thus precluding its characterisation.

Experimental

Pentane-2,3,4-trione 3-(thiazol-2'-yl)hydrazone (240).

(a) A solution of 2-aminothiazole (224) (1.45 g; 0.0145 mol) in concentrated sulphuric acid (2.4 ml) was diluted with water (13.2 ml) and treated dropwise with stirring at 0-5° with 1M aqueous sodium nitrite solution (14.0 ml). The mixture was stirred at 0-5° for a few minutes and then treated dropwise with stirring at 0-5° with a solution of acetylacetone (1.20 g; 0.012 mol) and anhydrous sodium acetate (2.70 g) in water (8.0 ml) and ethanol (20.0 ml). The mixture was stirred in the melting ice bath for 2 h and then neutralised with sodium carbonate and extracted with chloroform to give a black solid (1.15 g). This was extracted with light petroleum in a soxhlet apparatus to give the hydrazone (240) as a yellow solid (0.67 g; 26%), m.p. 120-122° (from toluene) (lit.,[80] m.p. 120°), ν_{max} 3060 br (NH) and 1660 and 1630 (CO) cm^{-1}, δ (CDCl$_3$) 7.45 (1H, d, J_{ortho} 4Hz, thiazole CH), 6.96 (1H, d, J_{ortho} 4Hz, thiazole CH), 2.60 (3H, s, Me), and 2.46 (3H, s, Me).

<u>Found:</u>   C, 45.4; H, 4.2; N, 19.8%; M$^+$211.

Calc. for C$_8$H$_9$N$_3$O$_2$S: C, 45.5; H, 4.3; N, 19.9%; M 211.

The insoluble residue from the soxhlet extraction was an intractable black solid.

(b) 2-Aminothiazole (224) (1.02 g; 0.01 mol) was dissolved in 88% orthophosphoric acid (30.0 ml) with gentle warming and the solution was treated in portions with stirring at 0-5° with solid sodium nitrite (0.70 g; 0.01 mol). The thick yellow suspension which formed was stirred for 5 min and then acetylacetone (0.90 g; 0.009 mol) was

added dropwise at 0-5°. A clear brown solution formed and was stirred for 2 h in the melting ice-bath before being poured onto ice (∿100 g). Extraction with chloroform gave a brown oil which was dissolved in water, neutralised with aqueous 2M sodium hydroxide and extracted with chloroform (2x30 ml) to give a dark solid. Crystallisation of the latter from light petroleum gave the yellow hydrazone (240) (0.37 g; 19%), m.p. 121-124°, identical (m.p. and i.r. spectrum) with a sample prepared before.

(c) 2-Aminothiazole (224) (0.52 g; 0.005 mol) was dissolved in 88% orthophosphoric acid (30.0 ml) with gentle warming, and the solution was cooled to 0-5° and treated with solid sodium nitrite (0.71 g; 0.01 mol). The resulting suspension was stirred for 10 min at 0-7° and formed a clear solution. A solution of acetylacetone (0.50 g; 0.005 mol) in methanol (5.0 ml) was added dropwise with stirring at 5-10° and the reaction mixture was stirred at 5-10° for 30 min and then poured onto ice (∿100 g). Extraction with chloroform (2x40 ml) gave only a small amount (0.03 g) of a brown intractable solid. The aqueous mother liquor was cooled, neutralised with dilute sodium hydroxide and filtered to give the hydrazone (240) more of which was obtained by extracting the aqueous filtrate with chloroform (2x50 ml). The hydrazone (240) formed yellow needles (0.61 g; 58%), m.p. 122-125°, identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Coupling of the Thiazole-2-diazonium Cation (239) with Ethyl Acetoacetate.

(a) A solution of 2-aminothiazole (224) (0.69 g; 0.007 mol) in

concentrated sulphuric acid (1.2 ml) was diluted with water (6.6 ml)
and treated dropwise with stirring at 0° with aqueous 1M sodium nitrite
solution (7.0 ml). The mixture was stirred for a few min and then
treated dropwise with stirring at $0-5^o$ with a solution of ethyl aceto-
acetate (0.79 g; 0.006 mol) and anhydrous sodium acetate (5.22 g)
in ethanol (40.0 ml) and water (16.0 ml). The resulting solution was
stirred in the melting ice-bath for 2 h and then extracted with chloro-
form. Evaporation of the extract gave a red liquid smelling strongly
of ethyl acetoacetate. Neutralisation of the aqueous mother liquor and
extraction with chloroform gave no material.

(b) A solution of 2-aminothiazole (224) (0.69 g; 0.007 mol) in
concentrated sulphuric acid (1.2 ml) was diluted with water (6.6 ml)
and treated dropwise with stirring at 0° with aqueous 1M sodium
nitrite solution (7.0 ml). The mixture was stirred for several min
at 0° and then treated dropwise with stirring at $0-5^o$ with a solution
of ethyl acetoacetate (0.80 g; 0.006 mol) in aqueous 2M sodium
hydroxide (15.0 ml). Stirring was continued at $0-10^o$ for 2 h and the
mixture was then extracted with chloroform (2x30 ml) giving a dark red
oil smelling strongly of ethyl acetoacetate. The aqueous layer was
filtered to remove some insoluble material, neutralised with dilute
sodium hydroxide and extracted with chloroform (2x30 ml). Evapora-
tion of the chloroform extract gave an intractable red-black gum.

(c) 2-Aminothiazole (224) (0.50 g; 0.005 mol) was dissolved
in 88% phosphoric acid (30.0 ml) with gentle warming and then treated
dropwise with stirring at 0° with solid sodium nitrite (0.68 g; 0.01 mol).
The reaction mixture was stirred at 0° for 10 min and then treated

dropwise with stirring at 0° with a solution of ethyl acetoacetate (0.67 g; 0.005mol) in methanol (5.0 ml). The mixture was stirred for 30 min at 0-5° and then poured onto ice giving a dark solution which was neutralised with aqueous dilute sodium hydroxide solution to afford an intractable black solid (0.20 g), m.p. >300°. Extraction of the filtrate with chloroform gave an intractable black gum.

The Attempted Coupling of the Thiazole-2-diazonium Cation (239) with Diethyl Malonate.

(a) A solution of 2-aminothiazole (224) (0.70 g; 0.007 mol) in concentrated sulphuric acid (1.2 ml) was diluted with water (6.6 ml) and treated dropwise with stirring at 0° with aqueous 1M sodium nitrite (7.0 ml). The mixture was stirred for 5 min and then treated dropwise with stirring at 0° with a solution of diethyl malonate (1.00 g; 0.006 mol) and anhydrous sodium acetate (1.37 g) in water (4.0 ml) and ethanol (10.0 ml). After stirring for 2 h in the melting ice-bath the reaction mixture was extracted with chloroform (3x30 ml) to give a liquid which was largely unreacted diethyl malonate. Neutralisation of the aqueous mother liquor and extraction with chloroform gave no identifiable material.

(b) 2-Aminothiazole (224) (0.50 g; 0.005 mol) was dissolved in 88% phosphoric acid (30.0 ml) with gentle warming, and the solution was treated with stirring at 0-5° with solid sodium nitrite (0.69 g; 0.01 mol). The yellow suspension which formed was stirred for 10 min at 0-5° and was then treated dropwise with stirring at 0-5° with a solution of diethyl malonate (0.81 g; 0.005 mol) in methanol (5.0 ml).

The mixture was stirred at 5-10° for 30 min and poured onto ice (∿100 g). The resulting black solution was neutralised with solid potassium hydroxide and some water was added to dissolve inorganic material. Extraction of the resulting solution gave no identifiable material.

The Attempted Coupling of the Thiazole-2-diazonium Cation (239) with Ethyl Cyanoacetate.

A solution of 2-aminothiazole (224) (0.71 g; 0.007 mol) in concentrated sulphuric acid (1.2 ml) was diluted with water (6.6 ml) and the solution was treated dropwise at 0° with stirring with aqueous 1M sodium nitrite solution (7.0 ml). The solution was stirred for a few min and then treated dropwise at 0-5° with stirring with a solution of ethyl cyanoacetate (0.69 g; 0.006 mol) and anhydrous sodium acetate (1.34 g) in water (4.0 ml) and ethanol (10.0 ml). The reaction mixture was stirred for 2 h in the melting ice-bath and then extracted with chloroform (2x30 ml). Evaporation of the organic extract gave a dark brown liquid whose t.l.c. in chloroform over silica showed it to be an unresolvable multicomponent mixture.

The Attempted Preparation of Thiazole-2-diazonium Chloride

A solution of 2-aminothiazole (224) (1.71 g; 0.017 mol) in methanol (50.0 ml) was saturated at 0° with hydrogen chloride, then treated dropwise with stirring at 0° with amyl nitrite (2.29 g; 0.19 mol). Work up of the reaction mixture gave no identifiable material.

2-Chlorobenzothiazole (229)

A suspension of 2-aminobenzothiazole (226) (0.68 g; 0.0045 mol) in concentrated hydrochloric acid (30.0 ml) was treated dropwise at 0° with stirring with a solution of sodium nitrite (1.50 g; 0.022 mol) in water (30.0 ml). The resulting orange solution was stirred for 10 min at 0° and then for 15 min at room temperature before being extracted with methylene chloride (2x20 ml) to give a red oil which was distilled using a Kugelrohr apparatus to afford 2-chlorobenzothiazole (229) as a yellow solid (0.19 g; 25%) which melted at room temperature (lit.,[157] m.p. 24°), M^{+} 171, 169; C_7H_4NSCl requires 171, 169.

Dibromobenzothiazole (242)

A suspension of 2-aminobenzothiazole (226) (1.37 g; 0.0091 mol) in 49% w/v hydrobromic acid (60.0 ml) was treated dropwise at 0° with stirring with a solution of sodium nitrite (2.99 g; 0.0433 mol) in water (60.0 ml) to give a yellow-brown suspension. This was stirred for 15 min and the resulting red solid (2.30 g), m.p. $95-105^{\circ}$, was collected and heated under reflux with toluene to leave an un-identified red solid (0.19 g), m.p. $262-264^{\circ}$, which could not be purified. The brown solid which crystallised from the toluene filtrate was recrystallised from light petroleum to afford the dibromobenzo-thiazole (242) as colourless cuboid crystals (0.21 g; 8%), m.p. $116-118^{\circ}$, δ (CDCl$_3$) 7.92-7.59 (3H, m, ArH).

Found: C, 28.8; H, 1.1; N, 4.8%; M^{+}293.
C_7H_3NBrS requires: C, 28.7; H, 1.0; N, 4.8%; M 295, 293, 291.

The Attempted Conversion of 2-Aminobenzothiazole (226) into

2-Cyanobenzothiazole (245).

2-Aminobenzothiazole (226) (0.74 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was treated at 0° with stirring with solid sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension. This was stirred for 10 min and then treated dropwise at 0-10° with stirring with a solution of sodium cyanide (0.24 g; 0.005 mol) in water (5.0 ml). The resulting brown suspension was stirred for 40 min at 0° and then poured onto ice (50 g) to give an orange solid (0.80 g; 91%), m.p. 83-86° (violent decomposition), identical (i.r. spectrum) with an authentic sample of 2-N-hydroxyazobenzothiazole (246) prepared later.

The Attempted Conversion of 2-Aminobenzothiazole (226) into

2-Thiocyanatobenzothiazole (243).

(a) 2-Aminobenzothiazole (226) (0.74 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.68 g; 0.01 mol) to afford a yellow suspension which was stirred at 0° for 10 min and then treated dropwise at 0-10° with stirring with a solution of potassium thiocyanate (0.49 g; 0.005 mol) in water (5.0 ml). The resulting oily brown suspension was stirred for 30 min at 0° then poured onto ice and extracted with methylene chloride (4x20 ml). A brown solid (0.68 g) was soluble in neither phase and when slurried in dilute hydrochloric acid and neutralised with concentrated ammonia solution yielded unreacted 2-aminobenzothiazole (0.40 g; 54%), m.p.

114-120°, identical (i. r. spectrum) to an authentic sample.

Evaporation of the methylene chloride extract gave an orange gum which on trituration with ether afforded 2-thiocyanatobenzothiazole (243) as an orange solid (0.04 g; 4%), m.p. 74-77°, identical (i. r. spectrum and mass spectrum) to a sample prepared in (c) below.

(b) 2-Aminobenzothiazole (226) (1.50 g; 0.01 mol) was dissolved with gentle warming in 88% phosphoric acid (20.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (1.38 g; 0.02 mol) to give a yellow suspension which was stirred at 0° for 10 min, treated with sulphamic acid (1.94 g; 0.02 mol) and stirred for a further few min. The diazonium suspension was then added in portions, together with aqueous 10M sodium hydroxide (55.0 ml), at pH 6 - pH 8 and at room temperature to a stirred solution of potassium thiocyanate (1.06 g; 0.011 mol) in water (50.0 ml). The resulting brown suspension was stirred at room temperature for 1 h to give an orange solid which contained inorganic material. This orange solid was extracted with ethyl acetate (400 ml) to give a brown gum (1.02 g) which was triturated with ethyl acetate-ether-light petroleum to yield an unidentified orange-brown solid (A) (0.38 g), m.p. 211-215° (from dimethylformamide-water).

Found: C, 56.1; H, 2.8; N, 19.1%; M$^+$ 416
$C_{14}H_8N_4S_2$ requires: C, 56.8; H, 2.7; N, 18.9%; M 296.

T.l.c. of the trituration mother liquor in ethyl acetate over silica showed it to contain an unresolvable multicomponent mixture.

(c) 2-Aminobenzothiazole (226) (1.50 g; 0.01 mol) was dissolved with gentle heating in 88% phosphoric acid (20.0 ml) and the solution

was treated with sodium nitrite (1.40 g; 0.02 mol) at 0-5° to yield

a yellow suspension which was stirred for 10 min at 0°, treated with

sulphamic acid (1.94 g; 0.02 mol) and then stirred for a further few

minutes. The diazonium suspension was then added in portions,

together with aqueous 10M sodium hydroxide, at pH 6-7 and 15-40°

to a suspension of copper thiocyanate catalyst (1.22 g) [prepared by

mixing solutions of copper sulphate pentahydrate (4.8 g) and hydrated

ferrous sulphate (9.2 g) in water (30.0 ml) and potassium thiocyanate

(2.0 g) in water (5.0 ml) and collecting the grey solid formed] in a

solution of potassium thiocyanate (6.0 g; 0.062 mol) in water (50.0

ml). The resulting brown suspension was stirred mechanically at

room temperature for 1 h then extracted with ethyl acetate (300 ml)

to give a red oil (0.89 g) which was triturated with light petroleum-

ethyl acetate to afford 2-thiocyanatobenzothiazole (243) as colourless

needles (0.65 g; 34%), m.p. 74-77° (from light petroleum-benzene),

ν_{max} 2160 cm^{-1} (SCN).

Found: C, 52.3; H, 2.2; N, 14.1%; M$^+$192.

$C_8H_4N_2S_2$ requires: C, 50.0; H, 2.1; N, 14.6%; M 192.

The Attempted Reaction of the Benzothiazole-2-diazonium Cation

(241) with Formaldoxime.

A solution of 2-aminobenzothiazole (226) (3.75 g; 0.025 mol)

in dimethylformamide (15.0 ml) was mixed with 88% phosphoric acid

(5.0 ml) and water (15.0 ml) and the resulting colourless suspension

was treated at 0° with stirring with sodium nitrite (1.78 g; 0.026 mol)

to give a yellow suspension which was stirred for 10 min and then

neutralised with sodium acetate. The neutral diazonium mixture was then treated at 5-10° with a formaldoxime suspension [prepared by neutralising a solution of paraformaldehyde (1.19 g; 0.039 mol) and hydroxylamine hydrochloride (2.59 g; 0.037 mol) in water (17.0 ml) with sodium acetate, refluxing for 15 min, cooling the solution and adding copper sulphate (0.65 g) and sodium sulphite (0.11 g)]. The reaction mixture was stirred for 1 h at 5-10° and the solid was collected and treated with aqueous sodium hydrogen carbonate to give unreacted 2-aminobenzothiazole (226) identical (m.p. and i.r. spectrum) with an authentic sample.

Pentane-2, 3, 4-trione 3-(benzothiazol-2'-yl)hydrazone (248).

(a) A solution of 2-aminobenzothiazole (226) (1.05 g; 0.007 mol) in a mixture of concentrated sulphuric acid (0.6 ml) and water (6.6 ml) was treated dropwise at 0-5° with stirring with an aqueous 1M solution of sodium nitrite (7.0 ml). The yellow diazonium suspension was stirred for a few min and then treated dropwise at 5-10° with a solution of acetylacetone (0.61 g; 0.006 mol) and sodium acetate (2.49 g) in water (8.0 ml) and ethanol (20.0 ml). The reaction mixture was stirred in the melting ice bath for 2 h then filtered to remove inorganic material. Extraction of the filtrate with chloroform (2x30 ml) gave an intractable, viscous, brown oil whose t.l.c. in ethyl acetate over alumina showed it to be an unresolvable multi-component mixture.

(b) 2-Aminobenzothiazole (226) (2.52 g; 0.015 mol) was suspended in a mixture of dimethylformamide (10.0 ml), water (10.0 ml) and 88% phosphoric acid (0.72 ml) and treated at 0° with stirring

with solid sodium nitrite (1.05 g; 0.015 mol) to give a pale yellow suspension which was stirred for 15 min at 0°. The diazonium suspension was then treated dropwise at 0° with stirring with a solution of acetylacetone (1.51 g; 0.015 mol) and sodium acetate (1.62 g) in water (4.0 ml) and ethanol (10.0 ml). The resulting yellow suspension was stirred for 2 h at 0-10°, then diluted with water and the solid was collected and treated with aqueous sodium carbonate to give unreacted 2-aminobenzothiazole (226) identical (m.p. and i.r. spectrum) with an authentic sample.

(c) 2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0-5° with stirring with sodium nitrite (0.70 g; 0.01 mol) to afford a yellow suspension which was stirred at 5° for 10 min. The diazonium suspension was then treated at 5-10° with stirring with acetylacetone (0.51 g; 0.005 mol), stirred for 30 min at 5-10° and poured onto ice (100 g) to give a yellow solid which was crystallised from ethanol-acetic acid to yield pentane-2,3,4-trione 3-(benzothiazol-2'-yl)hydrazone (248) as yellow needles (1.26 g; 97%), m.p. 194-197° ν_{max} 3080 br (NH) and 1685 and 1640 (CO) cm^{-1}, δ [(CD$_3$)$_2$SO] 7.80-7.10 (4H, m, ArH), 2.40 (3H, s, Me), and 2.30 (3H, s, Me).

Found: C, 55.0; H, 4.3; N, 15.7%; M$^+$261.

C$_{12}$H$_{11}$N$_3$O$_2$S requires: C, 55.2; H, 4.2; N, 16.1%; M 261.

1-Phenylbutane-1,2,3-trione 2-(benzothiazol-2'-yl)hydrazone (251)

(a) 2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution

was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min at 0°. The diazonium suspension was then treated dropwise at 0-5° with stirring with a solution of benzoylacetone (0.82 g; 0.005 mol) in methanol (5:0 ml), stirred for 30 min and then poured onto ice (100 g). The resulting yellow solid (1.61 g), which became brown and gummy on warming to room temperature, was triturated with methanol and crystallised from ethanol to afford <u>1-phenylbutane-1,2,3-trione 2-(benzothiazol-2'-yl)hydrazone</u> (251) as a dark green solid (0.34 g; 21%), m.p. 198-201°, ν_{max} 3140 br (NH) and 1680 and 1640 (CO) cm^{-1}, δ [(CD$_3$)$_2$SO] 7.80-7.06 (9H, m, ArH) and 2.52 (3H, s, Me).

<u>Found</u>: C, 62.8; H, 4.2; N, 12.6%; M$^+$323.

<u>C$_{17}$H$_{13}$N$_3$O$_2$S</u> requires: C, 63.2; H, 4.0; N, 13.0%; M 323.

(b) 2-Aminobenzothiazole (226) (0.76 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 20 min and treated with sulphamic acid (0.99 g; 0.01 mol). The diazonium suspension was then treated dropwise at 0-5° with stirring with a solution of benzoylacetone (0.82 g; 0.005 mol) in methanol (5.0 ml). The mixture became green in colour on stirring for 30 min and was poured onto ice (100 g) to give a brown solid (1.14 g; 70%), m.p. 150-160°, identical (i.r. spectrum) with a sample of 1-phenylbutane-1,2,3-trione 2-(benzothiazol-2'-yl)hydrazone (251) prepared in (a) above.

The Attempted Coupling of the Benzothiazole-2-diazonium Cation (241) with Ethyl Acetoacetate.

(a) 2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0-5° with stirring with sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension. This was stirred for 10 min and then treated dropwise at 5-10° with a solution of ethyl acetoacetate (0.65 g; 0.005 mol) in methanol (5.0 ml). The reaction mixture was stirred for 30 min at 5-10° then poured onto ice (100 g) to yield a purple solid (1.05 g), m.p. 64-66°, which decomposed on standing or attempted purification.

(b) 2-Aminobenzothiazole (226) (1.50 g; 0.01 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (1.38 g; 0.02 mol). The resulting yellow suspension was stirred at 0° for 10 min, treated with sulphamic acid (1.94 g; 0.02 mol) and stirred for a further few min. The diazonium mixture was then added in portions together with aqueous 10M sodium hydroxide (87.0 ml) at pH 7 - pH 8 and 30-35° to a solution of ethyl acetoacetate (1.44 g; 0.011 mol) in water (50.0 ml). The reaction mixture was stirred for 1 h at room temperature to give a purple solid (containing inorganic material) which was extracted with methylene chloride to afford an intractable purple gum (1.77 g).

The aqueous mother liquor was extracted with chloroform (2x30 ml) to give a yellow oil (0.30 g; 21%) identical (i.r. spectrum) with an authentic sample of ethyl acetoacetate.

The Attempted Coupling of the Benzothiazole 2-diazonium Cation (241) with Ethyl Benzoylacetate.

2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min at 0° and treated with sulphamic acid (0.97 g; 0.01 mol). A solution of ethyl benzoylacetate (0.98 g; 0.005 mol) in methanol (5.0 ml) was added dropwise at 0° with stirring to the diazonium suspension and the mixture was stirred for 30 min at 0° then poured onto ice (100 g). Extraction of the mixture with methylene chloride (2x30 ml) gave a dark intractable gum (0.89 g) whose t.l.c. in ethyl acetate over alumina showed it to be an unresolvable multicomponent mixture.

Neutralisation of the aqueous mother liquor gave a pale green solid which was combined with a second crop obtained by extracting the filtrate with methylene chloride to give unreacted 2-aminobenzothiazole (0.44 g; 11%), m.p. 129-132°, identical (i.r. spectrum) to an authentic sample.

The Coupling of the Benzothiazole-2-diazonium Cation (241) with Benzoylacetonitrile.

(a) 2-Aminobenzothiazole (226) (0.76 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol). The resulting yellow suspension was stirred for 10 min at 0° and then treated dropwise at $0-5^{\circ}$ with a solution of

benzoylacetonitrile (0.72 g; 0.005 mol) in methanol (5.0 ml). The mixture was stirred for 30 min then poured onto ice (100 g) to precipitate a yellow solid which on collection decomposed to a dark tar.

The aqueous mother liquor was neutralised with aqueous sodium hydroxide and extracted with chloroform (2x50 ml) to afford a red oil which was triturated with toluene to give 2,3-dioxo-3-phenylpropion-amide 2-(benzothiazol-2'-yl)hydrazone (252) as a yellow solid (0.14 g; 9%), m.p. 117-118° (from toluene-light petroleum), ν_{max} 3400, 3300, 3180 m and 3050 w (NH_2/NH) and 1665 and 1630 (CO) cm^{-1}.

Found: C, 59.9; H, 4.0; N, 16.9%; M^+174, 150. $C_{16}H_{12}N_4O_2S$ requires: C, 59.3; H, 3.7; N, 17.3%; M 324.

(b) 2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 15 min and then treated with sulphamic acid (0.97 g; 0.01 mol). A solution of benzoylacetonitrile (0.72 g; 0.005 mol) in methanol (5.0 ml) and then added dropwise at 0° with stirring to the diazonium mixture and the brown suspension was stirred for 30 min at 0° and poured onto ice (100 g) to yield a brown solid which was crystallised from toluene to give 2,3-dioxo-3-phenylpropionitrile 2-(benzothiazol-2'-yl)hydrazone (253) as yellow cubes (1.41 g; 92%), m.p. 230-233°, ν_{max} 3050 br (NH), 2210 w (CN) and 1630 (CO) cm^{-1}.

Found: C, 62.6; H, 3.4; N, 17.7%; M^+306. $C_{16}H_{10}N_4OS$ requires: C, 62.7; H, 3.3; N, 18.3%; M 306.

The Attempted Coupling of the Benzothiazole-2-diazonium Cation (241) with Diethyl Malonate.

2-Aminobenzothiazole (226) (0.76 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0-5° with stirring with sodium nitrite (0.71 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min and then ι treated dropwise at 0-5° with a solution of diethyl malonate (0.79 g; 0.005 mol) in methanol (5.0 ml). The mixture was stirred for 30 min at 0-5° then poured on to ice (100 g). The resulting gummy solid (0.52 g) was triturated with ethanol to afford a brown solid (0.30 g), m.p. 155-157°, ν_{max} 1675 cm^{-1}, M^{+} 417, 284 which could not be purified.

The aqueous mother liquor was neutralised with aqueous sodium hydroxide and extracted with chloroform to give an intractable black oil.

The Attempted Coupling of the Benzothiazole-2-diazonium Cation (241) with Ethyl Cyanoacetate.

(a) 2-Aminobenzothiazole (226) (0.76 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (30.0 ml) and the solution was treated at 0-5° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min and treated dropwise at 5-7° with a solution of ethyl cyanoacetate (0.58 g; 0.005 mol) in methanol (5.0 ml). The reaction mixture was stirred for 40 min at 5-10° then poured on to ice (100 g) to give a gummy brown solid (0.56 g) which was triturated with ethanol to

afford a brown solid (0.26 g), m.p. 148-156°. All attempts to purify this product resulted in its decomposition to tars.

Neutralisation of the aqueous mother liquor with sodium hydroxide and extraction with chloroform gave an intractable black gum.

(b) 2-Aminobenzothiazole (226) (0.76 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min, treated firstly with sulphamic acid (0.97 g; 0.01 mol) and then dropwise at 0-5° with a solution of ethyl cyanoacetate (0.64 g; 0.006 mol) in methanol (5.0 ml). The mixture was stirred for 30 min and then poured on to ice (100 g) to give a yellow solid (0.80 g), m.p. 245-248°, which was shown to be a salt of 2-aminobenzothiazole by dissolving it in aqueous dilute hydrochloric acid and making the solution basic with concentrated aqueous ammonia to afford 2-amino-benzothiazole, m.p. 132-134°, identical (i.r. spectrum) with an authentic sample.

Neutralisation of the aqueous mother liquor with concentrated aqueous ammonia and extraction with methylene chloride (2x30 ml) gave a colourless solid (0.07 g; 9%), m.p. 131-133°, identical (i.r. spectrum) with authentic 2-aminobenzothiazole.

The Attempted Coupling of the Benzothiazole-2-diazonium Cation (241) with Cyanoacetamide.

2-Aminobenzothiazole (226) (0.75 g; 0.005 mol) was dissolved

with gentle warming in 88% phosphoric acid (10.0 ml) and the solution

was treated at 0° with stirring with sodium nitrite (0.69 g; 0.01 mol)

to give a yellow suspension which was stirred for 10 min, treated

firstly with sulphamic acid (0.97 g; 0.01 mol) and then dropwise at

0° with a solution of cyanoacetamide (0.42 g; 0.005 mol) in methanol

(10.0 ml).   The reaction mixture was stirred for 30 min at 0°, poured

on to ice (100 g), neutralised with concentrated aqueous ammonia and

extracted with methylene chloride (2x40 ml) to afford a light brown

solid (0.34 g; 45%), m.p. 129-131°, identical (i.r. spectrum) with

an authentic sample of 2-aminobenzothiazole.

Cyclisation Reactions of Pentane-2,3,4-trione 3-(benzothiazol-2'-yl)-hydrazone (248).

(a) A solution of the hydrazone (248) (0.52 g; 0.002 mol) in

methanol (40.0 ml) and acetic acid (70.0 ml) was treated with a solution

of hydroxylamine [prepared by dissolving hydroxylamine hydrochloride

(0.13 g; 0.002 mol) in water (5.0 ml) and neutralising the solution

with sodium acetate] and the mixture was heated under reflux for

1.5 h.   The mixture was evaporated to give a brown solid which was

treated with a little water and filtered to afford the isoxazole (249)

as orange needles (0.38 g; 75%), m.p. 159-161° (from ethanol-water),

δ [$(CD_3)_2SC$] 8.20-7.50 (4H, m, ArH), 2.79 (3H, s, Me), and 2.48

(3H, s, Me).

Found: C, 55.8; H, 4.0; N, 21.7%; M^+ 258

$C_{12}H_{10}N_4OS$ requires: C, 55.8; H, 3.9; N, 21.7%; M 258.

(b) The hydrazone (248) (0.52 g; 0.002 mol) was heated under reflux in glacial acetic acid (50.0 ml) with redistilled phenylhydrazine (0.23 g; 0.002 mol) for 3 h. The mixture was evaporated to give the pyrazole (250) as a yellow solid (0.57 g; 86%), m.p. 160-162° (from ethanol-water), $\delta[(CD_3)_2SO]$ 8.10-7.44 (9H, m, ArH), 2.66 (3H, s, Me), and 2.50 (3H, s, Me).

Found: C, 64.6; H, 4.7; N, 20.7%; M^+333.
$C_{18}H_{15}N_5S$ requires: C, 64.9; H, 4.5; N, 21.0%; M 333.

2-Benzoyl-1,2,4-triazino[3,4-b]benzothiazol-1-one (254).

The hydrazone (253) (1.00 g; 0.0033 mol) was heated in polyphosphoric acid (7.5 ml) at 80° for 3 h. The mixture was treated with ice-water (70 ml) to give the triazine (254) as yellow crystals (1.09 g; quantitative), m.p. 184-187° (from ethanol-acetic acid-water), ν_{max} 1715, 1690, and 1655 (CO) cm^{-1}.

Found: C, 62.3; H, 2.9; N, 13.5%; M^+307
$C_{16}H_9N_3O_2S$ requires: C, 62.5; H, 2.9; N, 13.7%; M 307.

2-Benzoyl-1,2,4-triazino[3,4-b]benzothiazol-1-one Hydrazone (255)

The triazinobenzothiazole (254) (0.31 g; 0.001 mol) was heated under reflux with 100% hydrazine hydrate (0.1 g; 0.002 mol) in ethanol (120 ml) for 1 h. A second portion of hydrazine hydrate (1.0 g; 0.02 mol) dissolved in ethanol (5.0 ml) was added and refluxing was continued for 1.5 h. Further hydrazine hydrate (1.0 g; 0.02 mol) dissolved in ethanol (5.0 ml) was added and refluxing was continued for a further 2 h. The mixture was left at room temperature overnight and the orange solid was collected and crystallised from acetic acid to give the hydrazone (255) as orange-red crystals (0.14 g;

44%), m. p. 272-274°, ν_{max} 3320 br and 3110 br (NH$_2$), 1660 (CO), and 1630 (NH def.) cm^{-1}.

Found: C, 59.4; H, 3.5; N, 21.6%; M$^+$321.

C$_{16}$H$_{11}$N$_5$OS requires: C, 59.8; H, 3.4; N, 21.8%; M 321.

Evaporation of the ethanol filtrate gave an intractable orange gum.

6-Benzoyl-4-(2'-mercaptophenyl)-1,2,4-triazine-3,5(2H,4H)-dione (257)

The triazinobenzothiazole (254) (0.31 g; 0.001 mol) suspended in ethanol (5.0 ml) was heated under reflux with 20% w/v aqueous potassium hydroxide (5.0 ml) for 45 min. The resulting solution was concentrated, treated with water (2.0 ml) and filtered to give a brown solid (0.22 g), m. p. >300°. This was slurried with aqueous dilute hydrochloric acid, collected and combined with a second crop obtained by acidifying the alkaline filtrate to give the triazinedione (257) which formed yellow crystals (0.22 g; 69%), m. p. 160-164° (from ethanol-water), ν_{max} 1660 (CO) cm^{-1}.

Found: C, 58.8; H, 3.3; N, 13.7%; M$^+$325.

C$_{16}$H$_{11}$N$_3$O$_3$S requires: C, 59.1; H, 3.4; N, 12.9%; M 325.

m/e : 325.052146

C$_{16}$H$_{11}$N$_3$O$_3$S requires: 325.052108.

The Attempted Oxidation of the Triazinobenzothiazole (254).

The triazinobenzothiazole (254) (0.30 g; 0.001 mol) was heated with aqueous 30% hydrogen peroxide (2.5 ml) in glacial acetic acid

(15. 0 ml) at 50° for 22 h, diluted with water (30 ml) and extracted with methylene chloride (2x30 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate (6x5 ml) and evaporated to give an orange gum (0. 03 g) which was shown by t. l. c. in ether over silica to contain starting material.

Work up of the aqueous sodium hydrogen carbonate washings gave no further material.

The Attempted Cyclisation of the Hydrazone (255).

The hydrazone (255) (0. 09 g; 0. 0003 mol) was heated under reflux in acetic acid (5. 0 ml) for 30 min and the solution was evaporated to give an intractable, red solid (0. 1 g), m. p. 111-115°, ν_{max} 3340 br and 3180 br (NH) and 1700 and 1650 (CO) cm^{-1}.

The Attempted Preparation and Isolation of Benzothiazole-2-diazonium Chloride (260; X=Cl)

(a) 2-Aminobenzothiazole (226) (2. 55 g; 0. 017 mol) was dissolved in methanol (10. 0 ml) and the solution was cooled to 0° and saturated with hydrogen chloride then treated dropwise with stirring with amyl nitrite (2. 27 g; 0. 019 mol). The mixture was stirred for 1. 5 h in the melting ice-bath. Filtration gave colourless needles which were combined with further crops obtained by concentrating the filtrate, to give 2-aminobenzothiazole hydrochloride (total 3. 0 g), m. p. 237-241°, which was slurried with aqueous sodium hydrogen carbonate to give the unreacted amine, identical (i. r. spectrum) with an authentic sample.

(b) A solution of 2-aminobenzothiazole hydrochloride (2. 56 g;

0.0137 mol) in methanol (20.0 ml) and acetic acid (25.0 ml), was cooled to 0° and treated dropwise with stirring with amyl nitrite (2.52 g; 0.0215 mol). The mixture was stirred in the melting ice-bath for 1.5 h and then filtered to give a colourless solid which was combined with further material obtained by concentrating the filtrate to give unreacted 2-aminobenzothiazole hydrochloride (2.25 g), m.p. 237-241°, identical (i.r. spectrum) with an authentic sample.

Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$)

A suspension of 2-aminobenzothiazole (226) (0.75 g; 0.005 mol) in 40% w/v aqueous hydrofluoroboric acid (15.0 ml) was treated at 0° with a solution of sodium nitrite (2.5 g; 0.036 mol) in water (15.0 ml). The resulting yellow suspension was stirred at 0° for 10 min then at room temperature for 10 min to give benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) as an orange solid (0.88 g; 71%), m.p. 89-90° (violent decomposition), ν_{max} 2270 cm^{-1} (N$\overset{+}{\equiv}$N).

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Hydrochloric Acid.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.13 g; 0.0045 mol) was added in portions at 0° with stirring to aqueous concentrated hydrochloric acid (5.0 ml) and the resulting suspension was stirred for 3 h at 0-10°. The mixture was then treated with water (10.0 ml) and extracted with methylene chloride (2x25 ml) to give a black gum whose t.l.c. in ethyl acetate over alumina showed it to be an unresolvable multicomponent mixture.

The aqueous mother liquor was neutralised with aqueous dilute sodium hydroxide and extracted with methylene chloride (2x25 ml) to afford 2-aminobenzothiazole (226) as a brown solid (0.01 g; 1%), m.p. 112-113°, identical (i.r. spectrum) with an authentic sample.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Hydrobromic Acid.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.12 g; 0.0045 mol) was added in portions at room temperature with stirring to 49% (constant boiling) hydrobromic acid (5.0 ml) and the mixture was stirred for 3 h. A suspension formed, a gas was evolved and the mixture was treated with water (10.0 ml) to give a dark red solid (0.71 g), m.p. 111-115°, which decomposed on attempted purification.

The aqueous mother liquor was neutralised with aqueous dilute sodium hydroxide and extracted with methylene chloride (2x10 ml) to give 2-aminobenzothiazole (226) (0.05 g; 7%), m.p. 103-105°, identical (i.r. spectrum) with an authentic sample.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Hydroiodic Acid.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g; 0.005 mol) was added in portions at room temperature with stirring to 55% hydroiodic acid (5.0 ml) and the resulting brown suspension was stirred for 3 h. The mixture, containing a gum, was extracted with methylene chloride (2x50 ml) to afford an intractable black gum (0.53 g) whose t.l.c. in ethylacetate over alumina showed it to be an unresolvable multicomponent mixture.

The Attempted Preparation of 2-Fluorobenzothiazole (261d).

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g; 0.005 mol) was suspended in tetrahydronaphthalene (15.0 ml) and heated in an oil bath. As the temperature rose towards the boiling point of tetra-hydronaphthalene, gas evolved and a solution formed. Cooling the reaction mixture gave an intractable brown solid (0.90 g), m.p. >300°. Evaporation of the mother liquor gave an intractable brown gum (0.21 g).

2-Nitrobenzothiazole (261e).

A suspension of benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.21 g; 0.005 mol) in water (20.0 ml) was treated dropwise at 0° with stirring with a solution of sodium nitrite (0.34 g; 0.005 mol) in water (5.0 ml) and the resulting suspension was stirred for 30 min at 0° to give a brown solid (1.01 g), m.p. 139-144°. This solid (0.43 g) which contained inorganic material, was taken and heated under reflux with ethanol to leave a brown residue (0.20 g). The mother liquor, on cooling, afforded yellow crystals (0.07 g), m.p. 233-234°, of (A), identical (i.r. spectrum) with a sample prepared previously. On standing the mother liquor deposited brown crystals of 2-nitro-benzothiazole (261e) (0.04 g; 10%), m.p. 160-165° (lit.,[148] 158°), ν_{max} 1540 and 1375 (NO$_2$) cm^{-1}, M$^+$ 180 (C$_7$H$_4$N$_2$O$_2$S requires M 180).

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Nitrite Ion using Copper Catalysis.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g;

0.005 mol) was added in portions to a suspension of copper catalyst

(0.8 g) [prepared by adding copper sulphate pentahydrate (1.5 g) to a

solution of anhydrous sodium sulphite (1.5 g) in water (5.0 ml),

warming the mixture and collecting the catalyst as a brown solid]

in a solution of sodium nitrite (3.1 g; 0.045 mol) in water (12.5 ml).

The mixture was stirred for 3.5 h to give a brown solid (1.50 g) which

was heated under reflux with ethyl acetate to leave an insoluble

inorganic residue.   Evaporation of the ethyl acetate extract gave a

brown gum (0.26 g) from which no identifiable material could be

obtained.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate

(260; X=BF$_4$) with Sodium Cyanide.

A suspension of benzothiazole-2-diazonium fluoroborate (260 ;

X=BF$_4$) (1.24 g; 0.005 mol) in water (30.0 ml) was treated dropwise

at 0-5° with stirring with a solution of sodium cyanide (0.25 g;

0.005 mol) in water (5.0 ml) and the resulting brown suspension was

stirred at 0° for 30 min.   Crystallisation of the resulting brown solid

from acetic acid-water gave (A) (1.07 g), m.p. 194-202°, identical

(i.r. spectrum and mass spectrum) to a sample of (A) prepared

previously.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate

(260; X=BF$_4$), with Copper Cyanide.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g;

0.005 mol) was added over 20 min in portions at 50° with stirring to a

solution of copper cyanide catalyst [prepared by mixing solutions of copper sulphate pentahydrate (1.5 g) in water (5.0 ml) and ice (2.5 g) and potassium cyanide (1.6 g; 0.024 mol) in water (5.0 ml) and adding sodium hydrogen carbonate (3.4 g) and benzene (5.0 ml)]. The mixture was stirred vigorously for 30 min and then extracted with benzene (50 ml) to give a negligible amount of material.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Potassium Thiocyanate.

A suspension of benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g; 0.005 mol) in water (20.0 ml) was treated dropwise at 0-5° with stirring with a solution of potassium thiocyanate (0.48 g; 0.005 mol) in water (5.0 ml) and the suspension was stirred for 30 min at 0° to afford an orange solid. This solid was crystallised from dimethylformamide-water to give an unidentified brown solid (1.12 g), m.p. 154-160°.

Found: C, 52.9; H, 2.7; N, 16.8%; M$^+$ no ion pressure obtained.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Thiocyanate Ion using Copper Catalysis.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (2.48 g; 0.01 mol) was added with stirring in portions at 60-65° to a suspension of copper thiocyanate catalyst (1.23 g) [prepared by mixing solutions of copper sulphate pentahydrate (4.8 g) and hydrated ferrous sulphate (9.2 g) in water (20.0 ml) and potassium thiocyanate (2.0 g) in water

(5.0 ml) and collecting the grey solid] in a solution of potassium thiocyanate (6.0 g; 0.06 mol) in water (10.0 ml). The mixture was stirred for 1 h at 60-65°, and cooled to give a brown solid (3.28 g) which was extracted with ethyl acetate to leave an insoluble inorganic residue. Evaporation of the ethyl acetate mother liquor gave a brown gum (0.56 g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture, and from which no identifiable material could be obtained.

The aqueous mother liquor was extracted with ethyl acetate (2x30 ml) to afford a purple gum (0.36 g) which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Sodium Benzenesulphinate.

A suspension of benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g; 0.005 mol) in water (20.0 ml) was treated dropwise at 0° with stirring with a solution of sodium benzenesulphinate di-hydrate (1.00 g; 0.005 mol) in water (5.0 ml) to give a suspension which was stirred for 30 min at 0° to afford a brown solid (1.55 g), m.p. 135-140°. This solid was crystallised from ethanol to give the unknown product (A) as a brown solid, m.p. 222-225°, identical (i.r. spectrum) with a sample of (A) prepared previously.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Sodium Methoxide.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.24 g;

0.005 mol) was added to a freshly prepared solution of sodium (0.13 -g; 0.0056 g atom) in methanol (20.0 ml) and the resulting green suspension was stirred at room temperature for 4 h to give a brown inorganic solid (0.51 g). The mother liquor was evaporated and treated with water (20.0 ml) to give further in organic solid (0.21 g). On standing the mother liquor deposited a brown solid (0.16 g), m.p. 199-203°, which was recrystallised from acetic acid to give (A), identical (i.r. spectrum and mass spectrum) to a sample prepared previously.

The Attempted Reaction of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Methylamine.

Benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (1.12 g; 0.0045 mol) was added in portions to a 25-30% w/v aqueous solution of methylamine (2.5 ml) and the resulting brown suspension was stirred at room temperature for 3 h. The gummy mixture was extracted with methylene chloride (2x20 ml) to give a black, intractable solid (0.11 g), m.p. 57-60°.

The aqueous phase was filtered to give a brown inorganic solid (0.54 g) and the mother liquor was neutralised with aqueous dilute hydrochloric acid and extracted with methylene chloride to afford a gummy orange solid (0.07 g), m.p. 188-193°, identical (i.r. spectrum and mass spectrum) to a sample of (A) prepared previously.

The Attempted Coupling of Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$) with Acetylacetone.

(a) A mixture of benzothiazole-2-diazonium fluoroborate (260;

X=BF$_4$) (1.24 g; 0.005 mol) and acetylacetone (0.50 g; 0.005 mol) in 99.5% ethanol (20.0 ml) was stirred at room temperature for 30 min to give an unidentified brown solid (0.78 g), m.p. >300°, M$^+$417.

The mother liquor was evaporated, treated with water (2.0 ml) and extracted with methylene chloride (2x15 ml) to give a dark gum (0.33 g) which was triturated with ethyl acetate to give pentane-2,3,4-trione 3-(benzothiazol-2'-yl)hydrazone (248) as a red-brown solid (0.09 g; 7%), m.p. 185-188°, identical (i.r. spectrum) with a sample prepared previously. The ethyl acetate mother liquor was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture.

(b) A solution of acetylacetone (0.35 g; 0.0035 mol) and anhydrous sodium acetate in ethanol (3.5 ml) an d water (1.5 ml) was treated dropwise at 0-5° with stirring with a suspension of benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) (0.86 g; 0.0035 mol) in water (10.0 ml) and ethanol (15.0 ml). The resulting suspension was stirred for 2 h at 0° to give a brown solid (0.26 g), m.p. 234-237°, identical (i.r. spectrum and mass spectrum) to a sample of (A) prepared previously. Concentration of the mother liquor and extraction with methylene chloride (2x20 ml) afforded an intractable gum.

2-N̰-Hydroxyazobenzothiazole (246).

2-Aminobenzothiazole (226) (1.50 g; 0.01 mol) was dissolved with gentle warming in 88% phosphoric acid (20.0 ml) and the solution was treated at 0° with stirring with portions of sodium nitrite (1.38 g; 0.02 mol) to give a yellow suspension which was stirred for 10 min

then treated with sulphamic acid (1.94 g; 0.02 mol) and stirred for 1.5 h at 0°. The mixture was poured onto ice (200 g) to give 2-N̲-hydroxyazobenzothiazole (246) as a yellow-brown solid (1.11 g; 62%), m.p. 65° (violent decomposition), $(M^{+}+1)$, 180 $C_7H_5N_3OS$ requires M, 179. The compound (246) burned in a flame with an energetic flash.

The Attempted Reaction of 2-N̰-Hydroxyazobenzothiazole (246) with Methyl Sulphate.

2-N̲-Hydroxyazobenzothiazole (246) (0.18 g; 0.001 mol) was suspended in 10% aqueous sodium hydroxide (4.0 ml) and treated with methyl sulphate (0.7 ml). The mixture was shaken at room temperature for 0.5 h, then extracted with methylene chloride (2x5 ml) to give a dark gum (0.10 g) which was triturated with ethyl acetate to afford an unidentified brown solid (0.02 g), m.p. $103-105^{\circ}$, $M^{+}444$.

The Attempted Reaction of 2-N̰-Hydroxyazobenzothiazole (246) with Acetyl Chloride.

A solution of 2-N̲-hydroxyazobenzothiazole (246) (0.36 g; 0.002 mol) in dry dioxan (50.0 ml) was treated with stirring at room temperature with triethylamine (0.35 g; 0.0025 mol) followed by a solution of acetyl chloride (0.18 g; 0.0022 mol) in dry dioxan (1.0 ml). The mixture was stirred for 20 min at room temperature, filtered to remove triethylamine hydrochloride and evaporated to give an intractable red gum from which no identifiable material could be obtained.

The Attempted Reaction of 2-N-Hydroxyazobenzothiazole (246) with Toluene-p-sulphonyl Chloride.

A suspension of 2-N-hydroxyazobenzothiazole (246) (0. 26 g; 0.0015 mol) in dry dioxan (5. 0 ml) was treated with stirring at room temperature with triethylamine (0. 28 ml) followed by a solution of toluene-p-sulphonyl chloride (0. 31 g; 0. 0016 mol) in dry dioxan (1. 0 ml). The mixture was stirred at room temperature for 30 min. Gas was evolved and the mixture was filtered to remove triethylamine hydrochloride and evaporated to afford a red gum (0. 59 g) which was triturated with ethyl acetate-light petroleum-ethanol to give a dark red solid (0. 17 g), m. p. 97-105°, whose t. l. c. in methylene chloride over silica showed it to contain three components. The red solid was purified by crystallisation from acetic acid-water to yield a brown solid, m. p. 196-200°, M$^+$416, identical (mass spectrum) to (A) prepared before. The ethyl acetate-light petroleum mother liquor was shown by t. l. c. in methylene chloride over silica to be an unresolvable multicomponent mixture.

The Attempted Reaction of 2-N-Hydroxyazobenzothiazole (246) with Hydrochloric Acid.

A suspension of 2-N-hydroxyazobenzothiazole (246) (0. 18 g; 0. 001 mol) in concentrated hydrochloric acid (5. 0 ml) was stirred for 1. 5 h at room temperature then poured onto ice (20 g) to precipitate an intractable brown solid (0. 03 g), m. p. 155-158°, M$^+$416.

The aqueous mother liquor was neutralised with sodium acetate and extracted with methylene chloride (2x15 ml) to give a gummy

yellow solid (0.12 g) which was crystallised from benzene-light petroleum (b.p. 80-100°) to afford colourless crystals (0.02 g; 13%), m.p. 111-112°, of 2-aminobenzothiazole (226), identical (m.p. and i.r. spectrum) with an authentic sample.

The Conversion of 2-N̲-Hydroxyazobenzothiazole (246) into Benzothiazole-2-diazonium Fluoroborate (260; X=BF$_4$).

A suspension of 2-N̲-hydroxyazobenzothiazole (246) (0.45 g; 0.0025 mol) in acetic acid-propionic acid (5:1) (10.0 ml) was treated at 0° with aqueous 40% hydrofluoroboric acid (1.29 g) and the mixture was stirred for 5.25 h at 0-5°. The mixture was cooled to 0° for 1 h to afford benzothiazole-2-diazonium fluoroborate (260; X=BF$_4$) as a red-brown solid (0.20 g; 32%), m.p. 64-66°, identical (i.r. spectrum) with a sample prepared previously.

The Attempted Reduction of 2-N̲-Hydroxyazobenzothiazole (246).

A solution of 2-N̲-hydroxyazobenzothiazole (246) (0.36 g; 0.002 mol) in aqueous 70% dioxan (50.0 ml) was saturated with sulphur dioxide at 0° and the solution was left securely stoppered at room temperature for 24 h. Filtration of the reaction mixture gave a brown solid (0.03 g), m.p. 220-225°, M$^+$416, identical (mass spectrum) to a sample of (A) prepared previously. The mother liquor was evaporated to afford an intractable gummy solid which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture.

Methyl 4-Amino-2-methylmercaptothiazole-5-carboxylate (225).

(a) Dipotassium N̲-cyanodithiocarbamate, m.p. 225-230°, was

prepared in 84% yield from cyanamide, carbon disulphide and

potassium hydroxide as described by Hantzsch and Wolvekamp.[153]

(b) Potassium methyl cyanodithioimidocarbonate, m.p. 204-

206° (lit.,[154] 214-216°), was prepared in 69% yield by treating

dipotassium N-cyanodithiocarbamate with methyl iodide as described

by Timmons and Wittenbrook.[154]

(c) Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate

(225), m.p. 103-104° (lit.,[155] 104-105°), was prepared in 60% yield

by the reaction of potassium methyl cyanodithioimidocarbonate with

methyl chloroacetate using the method of Walek, Pallas and Augustin.[155]

Methyl 2-Methylmercapto-4-thiocyanatothiazole-5-carboxylate (269).

(a) Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate

(225) (1.02 g; 0.005 mol) was dissolved with gentle warming in 88%

phosphoric acid (5.0 ml) and the solution was treated in portions at

0° with solid sodium nitrite (0.70 g; 0.01 mol) to give a thick yellow

suspension which was stirred at 0° for 10 min and then treated with

sulphamic acid (0.97 g; 0.01 mol). The diazonium suspension was

then stirred for a further few minutes and then added in portions with

aqueous 2M sodium hydroxide (90 ml), at pH 5 - pH 7, at 0-30° to a

thiocyanate
stirred suspension of copper/catalyst (0.61 g) [prepared by treating a

solution of copper sulphate pentahydrate (1.2 g) and ferrous sulphate

(2.3 g) in water (10.0 ml) with a solution of potassium thiocyanate

(0.5 g) in water (3.0 ml)] in a solution of potassium thiocyanate (3.0 g;

0.03 mol) in water (50.0 ml). The mixture was then stirred for 1 h

to give a gummy yellow solid which was extracted with hot ethyl acetate

to afford a brown gum (0.73 g). This was triturated with ethyl acetate to yield methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate(269) as pale yellow needles (0.21 g; 17%), m.p. 138-139° (from light petroleum-toluene), ν_{max} 2170 w (SCN) and 1695 (CO) cm^{-1}, δ(CDCl$_3$) 3.89 (3H, s, Me) and 2.78 (3H, s, Me).

Found: C, 34.6; H, 2.5; N, 11.3%; M$^+$246

C$_7$H$_6$N$_2$O$_2$S$_3$ requires: C, 34.1; H, 2.4; N, 11.4%; M 246.

The ethyl acetate mother liquor was shown by t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica to contain a close-running mixture of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) and methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate (269).

(b) A solution of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (2.04 g; 0.01 mol) in acetic acid (20.0 ml) was treated dropwise at 10-15° with nitrosylsulphuric acid (2.0 ml) [prepared by mixing sodium nitrite (40.0 g) and concentrated sulphuric acid (100 ml)] and the resulting suspension was stirred for 15 min to afford a yellow solution. The diazonium solution was then added dropwise together with aqueous 10M sodium hydroxide (35.0 ml) at pH 6 - pH 8, and at 20-38°, to a stirred suspension of copper thiocyanate catalyst (1.22 g) [obtained as a grey solid by mixing solutions of copper sulphate pentahydride (4.8 g) and ferrous sulphate (9.2 g) in water (30.0 ml) and potassium thiocyanate (2.0 g) in water (5.0 ml)] in a solution of potassium thiocyanate (6.0 g; 0.06 mol) in water (50.0 ml). The reaction mixture was then stirred for 2.25 h and the brown

solid (2.58 g) was collected and extracted with hot ethyl acetate to yield a brown gummy solid (1.90 g) which was triturated with ethyl acetate to afford methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate (269) as a beige solid (1.17 g; 48%), m.p. 124-125°, identical (i.r. spectrum) to a sample prepared in (a) above.

(c) A solution of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (2.04 g; 0.01 mol) in acetic acid (10.0 ml) was stirred mechanically and treated in portions at 15° with a suspension of nitrosylsulphuric acid (2.8 g; 0.022 mol) in acetic acid (10.0 ml). The yellow diazonium solution was stirred for 15 min and then added dropwise together with aqueous 10M sodium hydroxide (31.0 ml) at pH 6 - pH 8 and 16-40°, to a stirred solution of potassium thiocyanate (6.0 g; 0.06 mol) in water (50.0 ml). The reaction mixture was stirred mechanically for 1 h and then extracted with methylene chloride (2x100 ml) to give a dark red gum (1.48 g) which was triturated with ethyl acetate to yield a beige solid (0.42 g; 17%), m.p. 115-117°, identical (i.r. spectrum) with a sample of methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate (269) prepared in (a) above.

Di-(5-Carbomethoxy-2-methylmercaptothiazol-4-yl)disulphide (271).

(a) Methyl 2-methylmercapto-4-thiocyanatothiazole-5-carboxylate (269) (0.49 g; 0.002 mol) was mixed with concentrated sulphuric acid (2.0 ml) and the mixture was stirred at room temperature for 1 h, cooled in ice and then treated with ice (10 g) to precipitate a gummy yellow solid which was extracted with methylene chloride (2x30 ml).

Evaporation of the extract gave an orange gum (0.38 g) which was

triturated with ether to yield di-(5-carbomethoxy-2-methylmercapto-

thiazol-4-yl)disulphide (271) as pale yellow crystals (0.19 g; 43%),

m.p. 135-137° (from toluene-light petroleum), ν_{max} 1710 and 1695

(CO) cm^{-1}, δ(CDCl$_3$) 3.84 (6H, s, 2Me) and 2.50 (6H, s, 2Me).

Found: C, 33.3; H, 2.7; N, 6.3%; M$^+$440.

C$_{12}$H$_{12}$N$_2$O$_4$S$_6$ requires: C, 32.7; H, 2.7; N, 6.4%; M 440.

(b) A solution of methyl 2-methylmercapto-4-thiocyanato-

thiazole-5-carboxylate (269) (0.49 g; 0.002 mol) in methanol (150 ml)

was mixed with a saturated solution of ammonia in methanol (10.0 ml)

and the mixture was left tightly stoppered at room temperature for

18 h. Evaporation of the mixture gave a yellow semi-solid which

was triturated with ethanol to afford di-(5-carbomethoxy-2-methyl-

mercaptothiazol-4-yl)disulphide (271) (0.30 g; 68%), m.p. 129-132°

(from toluene-light petroleum), identical (i.r. spectrum and mass

spectrum) to a sample prepared in (a) above.

The Attempted Reaction of the 5-Carbomethoxy-2-methylmercapto-

thiazole-4-diazonium Cation (268) with Cyanide Ion.

A solution of methyl 4-amino-2-methylmercaptothiazole-5-

carboxylate (225) (1.02 g; 0.005 mol) in glacial acetic acid (10.0 ml)

was added dropwise with stirring at 10-15° to 40% w/v nitrosylsulphuric

acid (1.0 ml). The diazonium solution was stirred for 30 min and

then added dropwise with aqueous 2M sodium hydroxide (95.0 ml) at

pH 6-7 and 45-55°, to a stirred solution of copper cyanide catalyst

[prepared by mixing a solution of copper sulphate pentahydrate (1.5 g)

in water (10. 0 ml) with a solution of potassium cyanide (1. 6 g;

0. 025 mol) in water (5. 0 ml) at 0-20° and making the mixture up to

50.0 ml with water]. The reaction mixture was stirred for a further

1 h and the brown solid (0. 85 g) was collected and extracted with hot

ethyl acetate to afford a brown gum (0. 62 g), whose t. l. c. in toluene-

acetone-acetic acid (90:10:0. 5) over silica showed it to be an un-

resolvable multicomponent mixture.

The Attempted Reaction of the 5-Carbomethoxy-2-methylmercapto-

thiazole-4-diazonium Cation (268) with Nitrite Ion.

A solution of methyl 4-amino-2-methylmercaptothiazole-5-

carboxylate (225) (1. 02 g; 0. 005 mol) in glacial acetic acid (10. 0 ml)

was added dropwise with stirring at 15-17° to 40% w/v nitrosylsulphuric

acid (1. 0 ml). The diazonium solution was stirred for 30 min and

then added dropwise with aqueous 2M sodium hydroxide (80. 0 ml) at

pH 6-8, and 25-32°, to a stirred suspension of copper catalyst

(0. 8 g) [prepared as a red solid by heating copper sulphate pentahydrate

(4. 0 g) and sodium sulphite hydrate (4. 0 g) in water (10. 0 ml)] in a

solution of sodium nitrite (2. 0 g; 0. 029 mol) in water (50. 0 ml).

The resulting green suspension was stirred mechanically for 30 min

and then extracted with ethyl acetate to give an intractable brown gum

(0. 73 g) from which no identifiable material could be obtained.

The Reaction of the 5-Carbomethoxy-2-methylmercaptothiazole-4-

diazonium Cation (268) with Formaldoxime.

A solution of methyl 4-amino-2-methylmercaptothiazole-5-

carboxylate (225) (1. 02 g; 0. 005 mol) in acetic acid (10. 0 ml) was

added dropwise at 15° to 40% w/w nitrosylsulphuric acid (1.0 ml) and the resulting yellow solution was stirred for 30 min. The diazonium solution was then added dropwise together with aqueous 2M sodium hydroxide (91.0 ml) at pH 6 - pH 8 and 10-15°, to a stirred solution containing formaldoxime and copper catalyst [prepared by dissolving paraformaldehyde (0.23 g; 0.0075 mol) and hydroxylamine hydrochloride (0.53 g; 0.0075 mol) in water (3.4 ml) with heating, neutralising the solution with sodium acetate, heating under reflux for 15 min and finally cooling and treating with a solution of copper sulphate penta-hydrate (0.13 g), hydrated sodium sulphite (0.04 g) and hydrated sodium acetate (5.47 g) in water (3.6 ml)]. The reaction mixture was then stirred mechanically for 30 min, acidified with concentrated hydrochloric acid and extracted with ethyl acetate (2x100 ml). Evaporation of the extract gave a brown gum (1.42 g) which was chromatographed over silica. Elution with toluene-chloroform gave a yellow gum (0.13 g) which was triturated with light petroleum to afford an unidentified pale yellow solid (0.04 g), m.p. 64-66°. Elution with chloroform-ethyl acetate gave an orange gum (0.60 g) which was triturated with toluene-light petroleum to yield yellow crystals of the azo compound (274) (0.29 g; 23%), m.p. 127-129° (from toluene-light petroleum), ν_{max} 3200 w (OH) and 1770 and 1685 (CO) cm^{-1}, δ(CDCl$_3$) 5.90 (2H, s, CH$_2$), 3.80 (3H, s, Me), 2.68 (3H, s, Me), and 2.19 (3H, s, Me).

Found: C, 34.0; H, 3.6; N, 17.2%; M$^+$320.

C$_9$H$_{12}$N$_4$O$_5$S$_2$ requires: C, 33.8; H, 3.7; N, 17.5%; M 320.

The Attempted Hydrolysis of the Azo Compound (274).

(a) A solution of the azo compound (274) (0.16 g; 0.0005 mol) in 70% v/v aqueous ethanol (5.0 ml) was heated under reflux for 1 h and then evaporated to give a brown gum which was triturated with benzene to afford a yellow solid (0.03 g; 19%), m.p. 114-116°, identical (i.r. spectrum) with an authentic sample of the starting material. T.l.c. of the benzene mother liquor in ethyl acetate over silica showed the presence of four close-running components, one of which was the starting material (274).

(b) A solution of the azo compound (274) (0.16 g; 0.0005 mol) in 70% v/v aqueous acetic acid (5.0 ml) was heated under reflux for 1 h and then evaporated to give a yellow gum which was treated with water and extracted with methylene chloride to afford a yellow gum (0.11 g). Trituration of the gum with ether-ethyl acetate gave unreacted starting material (0.01 g; 6%), m.p. 111-113°, identical (i.r. spectrum) with an authentic sample. T.l.c. of the ethyl acetate mother liquor in ethyl acetate over silica showed the presence of three close-running components, one of which was the starting material (274).

(c) A solution of the azo compound (274) (0.16 g; 0.0005 mol) in ethanol (5.0 ml) was mixed with aqueous 1M sodium carbonate (1.0 ml) and the mixture was heated under reflux for 1 h. Work up of the mixture gave no identifiable material.

The Attempted Hydrolysis of the 5-Carbomethoxy-2-methylmercapto-thiazole-4-diazonium Cation (268).

Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (1.02 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was treated in portions at 0° with stirring with sodium nitrite (0.70 g; 0.01 mol). The resulting yellow suspension was stirred for 10 min and then treated with sulphamic acid (0.97 g; 0.01 mol). After stirring for a further five min the reaction mixture was poured on to ice to give a yellow solid which was combined with a second crop obtained from the filtrate on standing to give unreacted starting material (total 0.83 g; 81%), m.p. 92-95°, identical (i.r. spectrum) to an authentic sample.

Pentane-2,3,4-trione 3-(5'-carbomethoxy-2'-methylmercaptothiazole-4'-yl) hydrazone (278a).

Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (1.02 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was treated with stirring at 0° with sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension. This was stirred for 10 min at 0° and then treated with sulphamic acid (0.97 g; 0.01 mol). After stirring for a further five min, the diazonium suspension was treated dropwise at 0-5° with a solution of acetylacetone (0.50 g; 0.005 mol) in methanol (5.0 ml). The mixture was stirred for 3.5 h and then poured on to ice (25 g) to give a bright yellow solid which was crystallised from light petroleum-toluene to afford pentane-2,3,4-trione 3-(5'-carbomethoxy-2'-methylmercapto-

thiazol-4'-yl)hydrazone (278a) (1.17 g; 74%), m.p. 150-151°,

ν_{max} 1695, 1680, and 1645 (CO) cm^{-1}, δ (CDCl$_3$) 3.90 (3H, s, Me),

2.72 (3H, s, Me), 2.58 (3H, s, Me), and 2.49 (3H, s, Me).

<u>Found:</u>   C, 42.1;   H, 4.1;   N, 13.0%;   M$^+$315.

<u>C$_{11}$H$_{13}$N$_3$O$_4$S$_2$</u> requires: C, 41.9;   H, 4.1;   N, 13.3%;   M 315.

Extraction of the mother liquor with ethyl acetate gave a dark intractable gum (0.33 g) whose t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica showed four close-running spots one of which corresponded to methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225).

<u>Coupling Reactions of the 5-Carbomethoxy-2-methylmercaptothiazole-4-diazonium Cation (268) with Active Methylene Compounds.</u>

A solution of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (2.04 g; 0.01 mol) in glacial acetic acid (10.0 ml) was treated at 10-15° with stirring with a suspension of nitrosyl-sulphuric acid (2.8 g; 0.022 mol) in glacial acetic acid (10.0 ml) and the mixture was stirred for 20-30 min.   The diazonium solution was then added dropwise together with aqueous 10M sodium hydroxide (34 ml) at pH 6 - pH 9 and 15-25°, to a stirred solution of the active methylene compound (0.011 mol) in water (50-100 ml).   The reaction mixture was stirred mechanically for 30-60 min and then worked up as described for the individual reactions below.

(a) The reaction mixture from benzoylacetone gave an orange solid which was crystallised from toluene-light petroleum to afford 1-phenylbutane-1,2,3-trione 2-(5'-carbomethoxy-2'-methylmercapto-

thiazol-4'-yl)hydrazone (278b) as bright yellow crystals (3.78 g;

quantitative), m.p. 152-153°, ν_{max} 3150 w (NH) and 1685 and 1670

(CO) cm^{-1}, δ(CDCl$_3$) 8.11-8.00 (2H, m, ArH), 7.56-7.28 (3H, m,

ArH), 3.91 (3H, s, Me), and 2.58 (6H, s, 2Me).

Found: C, 51.0; H, 3.9; N, 11.0%; M$^+$377.

$\underline{C_{16}H_{15}N_3O_4S_2}$ requires: C, 50.9; H, 4.0; N, 11.1%; M 377.

(b) The reaction mixture from ethyl acetoacetate gave a brown

solid which was crystallised from toluene-light petroleum to afford

ethyl 2,3-dioxobutanoate 2-(5'-carbomethoxy-2'-methylmercapto-

thiazol-4'-yl)hydrazone (278c) as an orange-brown solid (3.53 g;

quantitative), m.p. 132-133°, ν_{max} 3150 w (NH) and 1690 (CO) cm^{-1},

δ(CDCl$_3$) 4.42 (2H, q, J 7Hz, $\underline{CH_2}$-CH$_3$), 3.87 (3H, s, Me), 2.72

(3H, s, Me), 2.50 (3H, s, Me), and 1.74 (3H, t, J 7Hz, CH$_2$-$\underline{CH_3}$).

Found: C, 41.9; H, 4.5; N, 12.0%; M$^+$345.

$\underline{C_{12}H_{15}N_3O_5S_2}$ requires: C, 41.7; H, 4.4; N, 12.2%; M 345.

(c) The reaction mixture from ethyl benzoylacetate was extracted

with ethyl acetate (300 ml) to give a brown gummy solid (3.12 g) which

was triturated with ethyl acetate to afford ethyl 2,3-dioxo-3-phenyl-

propanoate 2-(5'-carbomethoxy-2'-methylmercaptothiazol-4'-yl)-

hydrazone (278d) as yellow crystals (1.33 g; 33%), m.p. 142-143°

(from toluene-light petroleum). ν_{max} 3140 (NH) and 1750, 1690, and

1675 (CO) cm^{-1}, δ (CDCl$_3$) 8.08-7.96 (2H, m, ArH), 7.52-7.37 (3H,

m, ArH), 4.37 (2H, q, J 8Hz, $\underline{CH_2}$-CH$_3$), 3.87 (3H, s, Me), 2.60

(3H, s, Me), and 1.28 (3H, t, J 8Hz, CH$_2$-$\underline{CH_3}$).

Found: C, 50.3; H, 4.1; N, 10.0%; M^+407.

$C_{17}H_{17}N_3O_5S_2$ requires: C, 50.1; H, 4.2; N, 10.3%; M 407.

T.l.c. of the ethyl acetate mother liquor in methylene chloride over silica showed four close-running spots, one of which corresponded to the hydrazone (278d).

(d) The reaction mixture from diethyl malonate gave a grey solid (2.55 g) which was extracted with hot ethanol to leave an inorganic residue. Evaporation of the ethanol extract gave a purple gum (1.43 g) from which no identifiable material . could be obtained.

(e) The reaction mixture from ethyl cyanoacetate gave a dark red solid which was crystallised from toluene to afford dark purple crystals of an unidentified compound (3.34 g), m.p. 222-226°, ν_{max} 1690 and 1680 cm^{-1}.

Found: C, 36.7; H, 2.8; N, 19.7%; M^+471.

The Coupling of the 5-Carbomethoxy-2-methylmercaptothiazole-4-diazonium Cation (268) with N, N-Bis-(β-acetoxyethyl)-meta-toluidine (279).

Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (1.02 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was treated at 0° with stirring with solid sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min and then treated with sulphamic acid (0.97 g; 0.01 mol). After stirring for a further few min, the diazonium suspension was added in portions at 0° with

stirring to aqueous 2M hydrochloric acid (20. 0 ml) and water (180 ml)

containing 2. 28 g (0.005 mol) of a 61. 3% solution of $\underline{N}$, $\underline{N}$-$\underline{bis}$-(β-

acetoxyethyl)-meta-toluidine (279) in glacial acetic acid.   The mixture

was stirred for 30 min to give a red solid whose t. l. c. in toluene-

acetone-acetic acid (90:10:0. 5) over silica showed two spots, one of

which disappeared on heating the solid with acetic anhydride.

Subsequent crystallisation of the red solid from toluene light petroleum

gave the azo compound (280) as red crystals (1. 57 g; 53%), m. p.

132-132. 5°, ν_{max} 1750, 1730, and 1685 (CO) cm^{-1}, δ [$(CD_3)_2SO$]

7. 63 (1H, d, J_{ortho} 10Hz, ArH), 6. 80 (1H, s, ArH), 6. 84 (1H, d,

J_{ortho} 10Hz, ArH), 4. 26 (4H, t, J 6Hz, 2 $\underline{CH_2}$-CH_2), 3. 84 (3H, s, Me),

3. 78 (4H, t, J 6Hz, 2 CH_2-$\underline{CH_2}$), 2. 80 (3H, s, Me), 2. 61 (3H, s, Me)

and 2. 06 (6H, s, 2Me).

<u>Found:</u> C, 50. 8; H, 5. 6; N, 11. 1%; M$^+$494.

$\underline{C_{21}H_{26}N_4O_6S_2}$ requires: C, 51. 1; H, 5. 3; N, 11. 3%; M 494.

The aqueous filtrate was extracted with ethyl acetate (2x150 ml)

to give a red gum (0. 69 g) whose t. l. c. in toluene-acetone-acetic acid

(90:10:0. 5) over silica showed seven close-running components.

Neutralisation of the residual aqueous fraction with concentrated

aqueous ammonia and extraction with ethyl acetate (2x100 ml) gave

a brown gum (0. 22 g) whose t. l. c. in toluene-acetone-acetic acid

(90:10:0. 5) over silica showed five close-running components.

<u>The Attempted Preparation of Methyl 2-Methylmercapto-4-nitros-</u>

<u>aminothiazole-5-carboxylate</u> (275).

(a) A suspension of methyl 4-amino-2-methylmercaptothiazole-

5-carboxylate (225) (0.51 g; 0.0025 mol) in aqueous 2M sulphuric acid (5.0 ml) was treated at 0° with stirring with a solution of sodium nitrite (0.20 g; 0.0029 mol) in water (1.0 ml). The mixture was stirred for 15 min at 0-5° to give a yellow solid which was combined with a second crop obtained from from the filtrate on standing and crystallised from dimethylformamide-water to give the product (281) as a yellow-brown solid (0.44 g; quant.) m.p. 134-136°.

Found: C, 35.1; H, 2.2; N, 8.0%; M$^+$581, 440.

$\underline{C_{10}H_8N_2O_4S_4}$ requires: C, 34.5; H, 2.3; N, 8.0%; M 348.

(b) A suspension of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (0.80 g; 0.004 mol) in a solution of sodium nitrite (1.05 g; 0.015 mol) in water (10.0 ml) was treated dropwise at 0° with stirring with aqueous 10% v/v hydrochloric acid (10.0 ml). The mixture was stirred for 3 h at 0-5° to give a yellow solid which was washed with aqueous 2M sodium carbonate (10.0 ml) to afford a brown solid (0.14 g; 18%), m.p. 85-87°, identical (i.r. spectrum) with an authentic sample of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate. No material was obtained on acidification of the sodium carbonate washings.

Extraction of the original mother liquor with ethyl acetate (2x30 ml) gave an orange gum (0.37 g) from which no identifiable material could be obtained.

(c) A suspension of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (1.02 g; 0.005 mol) in 90% v/v aqueous formic acid (10.0 ml) was treated dropwise at 0-5° with stirring with a solution of sodium nitrite (0.40 g; 0.0058 mol) in water (2.5 ml).

The mixture was stirred for 30 min at 0-5°, poured on to ice (25 g) and extracted with ethyl acetate (2x50 ml) to give an intractable red gum (0.70 g) whose t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica showed it to be an unresolvable multicomponent mixture.

Neutralisation of the aqueous mother liquor with concentrated aqueous ammonia and extraction with ethyl acetate (2x30 ml) gave an intractable red gum (0.10 g) which was not further investigated.

The Attempted Preparation of 5-Carbomethoxy-2-methylmercapto-thiazole-4-diazonium Fluoroborate (282).

(a) A suspension of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate (225) (1.02 g; 0.005 mol) in 40% w/v aqueous hydro-fluoroboric acid (10.0 ml) was treated at 0-5° with stirring with a solution of sodium nitrite (2.5 g; 0.036 mol) in water (15.0 ml). The mixture was stirred for 10 min at 0° and then for 10 min at room temperature to give a gummy orange solid (0.36 g), which gave a positive test with acetyl-H-acid and $\underline{N}$, $\underline{N}$-$\underline{bis}$-(β-acetoxyethyl)-meta-toluidine, and was triturated with ethyl acetate to yield a bright yellow solid (0.18 g), m.p. 106-108°, ν_{max} 2280 (N≡N) and 1740 (CO) cm^{-1}, which decomposed on attempted crystallisation.

The aqueous mother liquor, on standing at room temperature overnight, gave an orange solid, which gave a negative test with acetyl-H-acid, and crystallised from acetic acid-water to afford

possibly (281)

a yellow solid (0.47 g; 54%), m.p. 101-102°.

Found: C, 34.4; H, 2.3; N, 8.0%; M^{+}440.

$C_{10}H_8N_2O_4S_4$ requires: C, 34.5; H, 2.3; N, 8.0%; M 348.

(b) Methyl 4-amino-2-methymercaptothiazole-5-carboxylate (225) (0.51 g; 0.0025 mol) was dissolved with gentle warming in 88% phosphoric acid (2.5 ml) and the solution was treated in portions at 0° with stirring with solid sodium nitrite (0.35 g; 0.005 mol). The resulting yellow suspension was stirred for 10 min at $0-5^{\circ}$, treated with sulphamic acid (0.49 g; 0.005 mol) and then stirred for a further 10 min before being treated with 40% w/v aqueous fluoroboric acid (1.0 ml; 1.3 g). The reaction mixture was stirred for 15 min at $0-5^{\circ}$, treated with ice (15 g) and left for 2.25 h to give a solid (0.45 g), m.p. $100-105^{\circ}$, which gave a negative test with acetyl-H-acid, and decomposed on attempted crystallisation.

Extraction of the mother liquor with ethyl acetate (2x25 ml) gave an oily brown gum (0.19 g) from which no identifiable material could be obtained.

CHAPTER FOUR

Studies of the Synthesis and Reactivity of 4-Cyano-
3-methylisothiazole-5-diazonium Salts
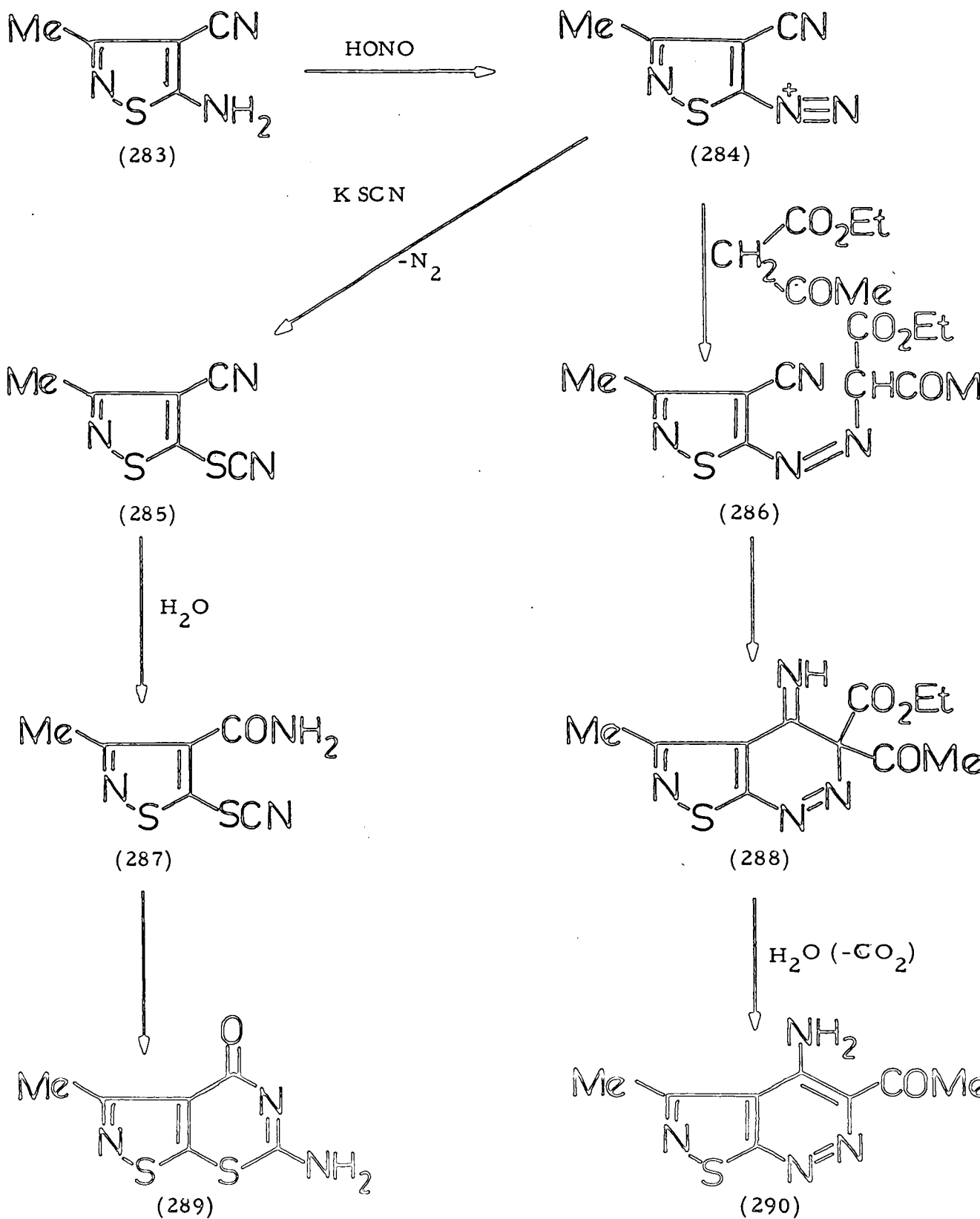
Scheme 112

Studies of the Synthesis and Reactivity of 4-Cyano-3-methyliso-thiazole-5-diazonium Salts.

The investigation of the diazotisation of the readily accessible 5-amino-3-methylisothiazole-4-carbonitrile (283) (Scheme 112) was initiated with a view to exploiting dediazoniation and/or coupling reactions of the diazonium cation (284) for the synthesis of substrates suitable for the preparation of novel fused isothiazoles. The reactions outlined in Scheme 112 illustrate the basic synthetic strategy involved. Furthermore it was considered interesting to compare the diazotisation behaviour of aminoisothiazoles with that of aminothiazoles and aminoisoxazoles discussed in Chapters 2 and 3. The diazotisation of aminoisothiazoles has been studied only to a limited extent. Diazonium fluoroborates[93] can be isolated from 3-amino-, 4-amino- and 5-aminoisothiazoles by treating the respective amines with nitrosyl tetrafluoroborate in organic acids. These diazonium fluoroborates although rather unstable, undergo halogenodediazonia-tion reactions and can be coupled with activated arenes to form azo compounds.[93, 94] 5-Aminoisothiazoles behave as weakly basic amines but they form acetyl derivatives and can be diazotised.[158] The initial objectives of the present studies were to determine the most suitable conditions for the diazotisation of the amine (283) and to establish the most convenient form in which to handle the resulting "diazo intermediate" produced. 5-Amino-3-methylisothiazole-4-carbonitrile (283) was chosen for study because of its synthetic accessibility. Thus it is readily prepared by the four step sequence

CH$_2$(CN)$_2$ + H$_3$CC(OEt)$_3$ ⟶ (291) $\xrightarrow{\text{H}_2\text{S}}$ (292)

(291): H$_3$C, CN, EtO, CN

(292): H$_3$C, CN, EtO, CSNH$_2$

(292) $\xrightarrow{\text{NH}_3}$ (293)

(293): H$_3$C, CN, H$_2$N, CSNH$_2$

(293) $\xrightarrow{\text{H}_2\text{O}_2}$ (283)

(283): Me, CN, N, S, NH$_2$ (isothiazole ring)

Scheme 113

(283) ⟶ (294)

(294): Me, CN, N, S, N$\equiv$N$^+$ X$^-$

(283) ⟶ (295)

(295): Me, CN, N, S, N–N=O, H

(295) ⇌ (296)

(296): Me, C$\equiv$N, N–H, O, N=N, N, S
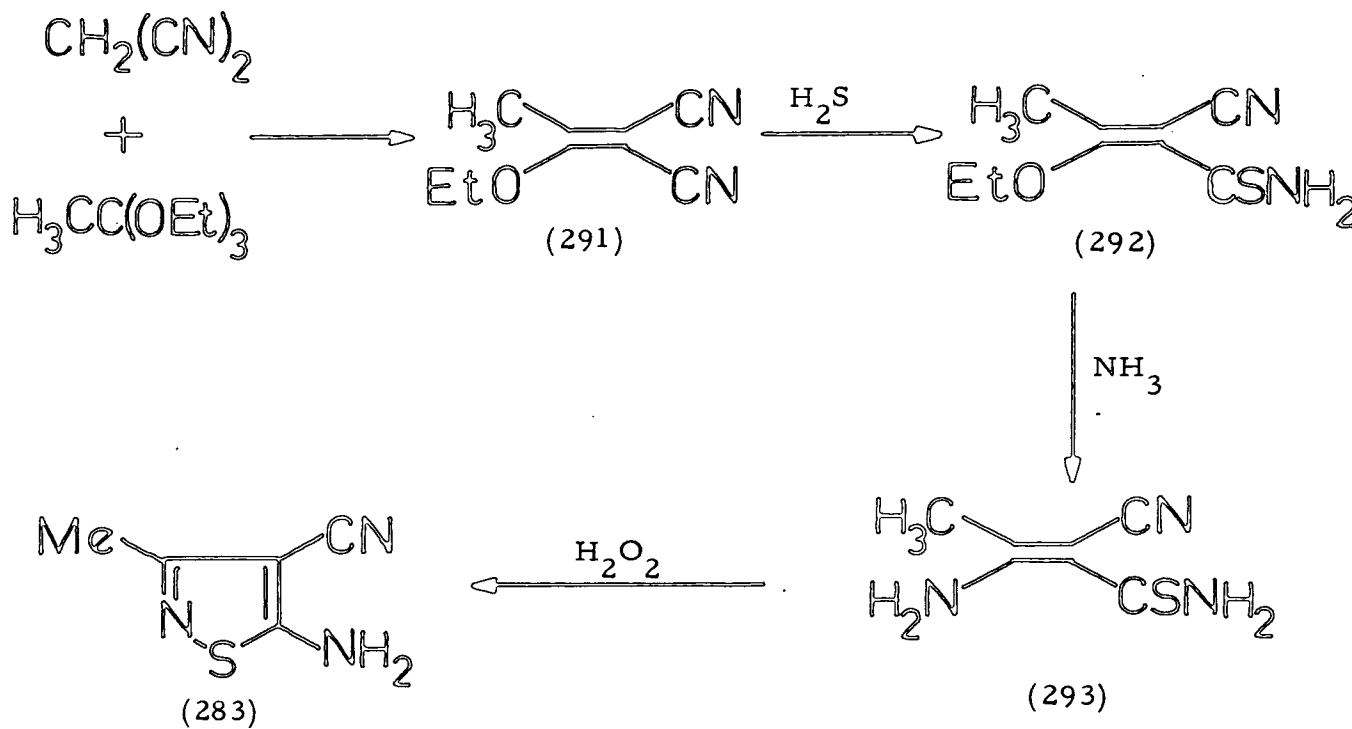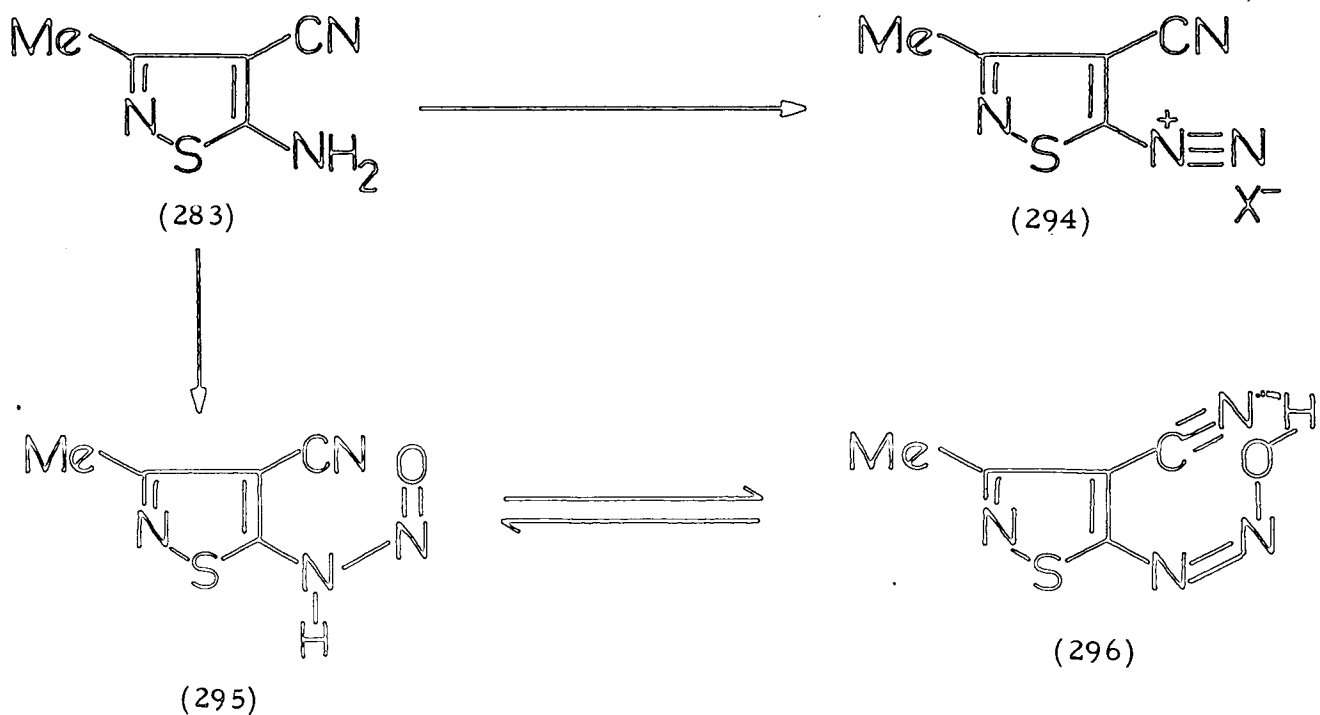
Scheme 114

outlined in Scheme 113. Firstly malononitrile was condensed with triethyl orthoformate to give 1,1-dicyano-2-ethoxyprop-1-ene (291) in essentially quantitative yield as described by McCall[159] but with the modification that the product was isolated by diluting the reaction mixture with light petroleum rather than by distillation. McCall's conditions[159] were next employed for the conversion in high yield of the enol ether (291) by reaction with hydrogen sulphide into 2-cyano-3-ethoxythiocrotonamide (292). 3-Amino-2-cyanothiocrotonamide (293) was in turn prepared[159] in quantitative yield by treating an ethanolic solution of the enol ether (292) with ammonia. Finally 5-amino-3-methylisothiazole-4-carbonitrile (283) was prepared in high yield by the oxidative cyclisation of (293) using hydrogen peroxide, as described by Anderson and Hsiao.[160]

Since 5-aminoisothiazoles are reported in the literature[93] to form well-defined diazonium fluoroborates, an attempt was initially made to convert 5-amino-3-methylisothiazole-4-carbonitrile (283) into the corresponding diazonium fluoroborate (294; $X=BF_4$) (Scheme 114) by diazotisation with sodium nitrite in aqueous 40% hydro-fluoroboric acid. However these conditions converted the amine (283) in good yield into 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) which was also the product of the attempted diazotisation of the amine (283) using sodium nitrite in phosphoric acid followed by treatment with aqueous hydrofluoroboric acid. The nitrosamine (295) could also be prepared in high yield (85-96%) by nitrosating the amine (283) either in aqueous sulphuric acid or in aqueous hydrochloric acid. The nitrosamine (295) has been described

previously by Goerdeler[93] who recorded a melting point of 115-120°.
In the present studies attempts to purify the nitrosamine (295) by
crystallisation were unsuccessful due to its instability and the crude
compound exhibited violent decomposition over the temperature range
73-94°. The i.r spectrum of the compound lacked a band due to a
diazo group but contained broad absorption at 3100-2600 cm^{-1}
attributable to a hydrogen-bonded hydroxyl group. These features
exclude a diazonium structure for the compound but suggest that it
exists, at least in part, as the N-hydroxyazo tautomer (296) (Scheme
114) thus accounting for its instability and its ready conversion, by
reaction with sodium azide into 5-azido-4-cyano-3-methylisothiazole
as discussed in Chapter 6. The efficiency of the latter reaction
serves to confirm the constitution and homogeneity of the tautomeric
nitrosaminoisothiazole [(295)⇌(296)]. However it is interesting to
note that the existence of the nitrosamine (295) as a relatively stable
entity conflicts with the set of rules propounded by Butler[108] which
predict stability for such nitrosamines only when the nitrosamino
group is adjacent to a ring nitrogen atom. It has been suggested[158]
that the unanticipated stability of the nitrosamine (295) is due to the
presence of the electron-withdrawing 4-cyano group. However
Butler[108] accounts for the anomalous stability of (295) in terms of
intramolecular hydrogen-bonding between the hydroxyazo group and
the ortho-cyano group [cf. (296)].

Since attempts to convert the amine (283) into the isolable
diazonium fluoroborate (294; X=BF$_4$) had proved unsuccessful it was
decided to attempt to generate and study the reactivity of the
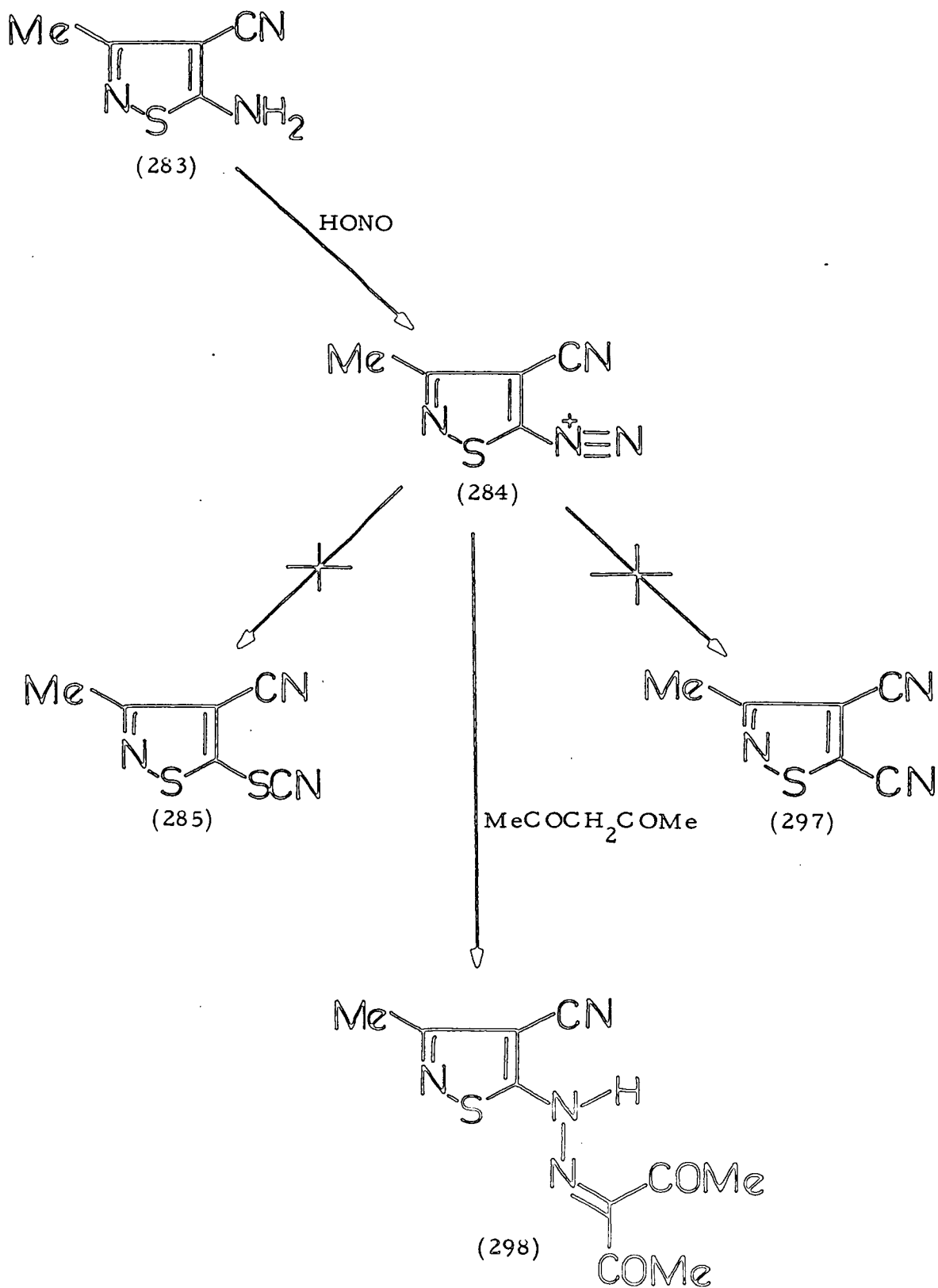
Scheme 115

diazonium cation (284) (Scheme 115) _in situ_. However the attempted

diazotisation of the amine (283) using sodium nitrite in phosphoric

acid or nitrosylsulphuric acid in acetic acid followed by reaction with

copper thiocyanate catalyst[149] at controlled pH gave no identifiable

material. This result contrasts with the successful thiocyanode-

diazoniation reactions of 2-amino and 4-aminothiazoles discussed in

Chapter 3. Likewise the attempted reaction of the diazonium mixture

obtained from the amine (283) and sodium nitrite in phosphoric acid,

with copper cyanide catalyst[151] at controlled pH gave not the hoped

for dicyanoisothiazole (297) but only small amounts of intractable

gums. Since _in situ_ dediazoniation reactions of the diazonium cation

(284) (Scheme 115) had been unsuccessful attention was directed to

its _in situ_ coupling in particular with acetylacetone. Thus, diazotisa-

tion of the amine (283) with sodium nitrite in phosphoric acid followed

by reaction of the diazonium mixture with acetylacetone gave the

expected hydrazone (298) (Scheme 115) in moderate yield together

with unreacted amine (283). The hydrazone (298) gave analytical and

mass spectroscopic data consistent with the assigned structure which

is also supported by the presence of NH, cyano and carbonyl

absorption in its i.r. spectrum. In addition its ^{1}H n.m.r. spectrum

showed signals due to three distinct methyl groups.

Attempts to prepare the diazonium fluoroborate (294; X=BF$_4$)

directly from the amine (283) having been unsuccessful and _in situ_

reactions of the diazonium cation (284) being only of limited success,

attention was turned to the nitrosamine (295) as a possible synthetic

precursor of the diazonium cation (284) either _in situ_ or as the
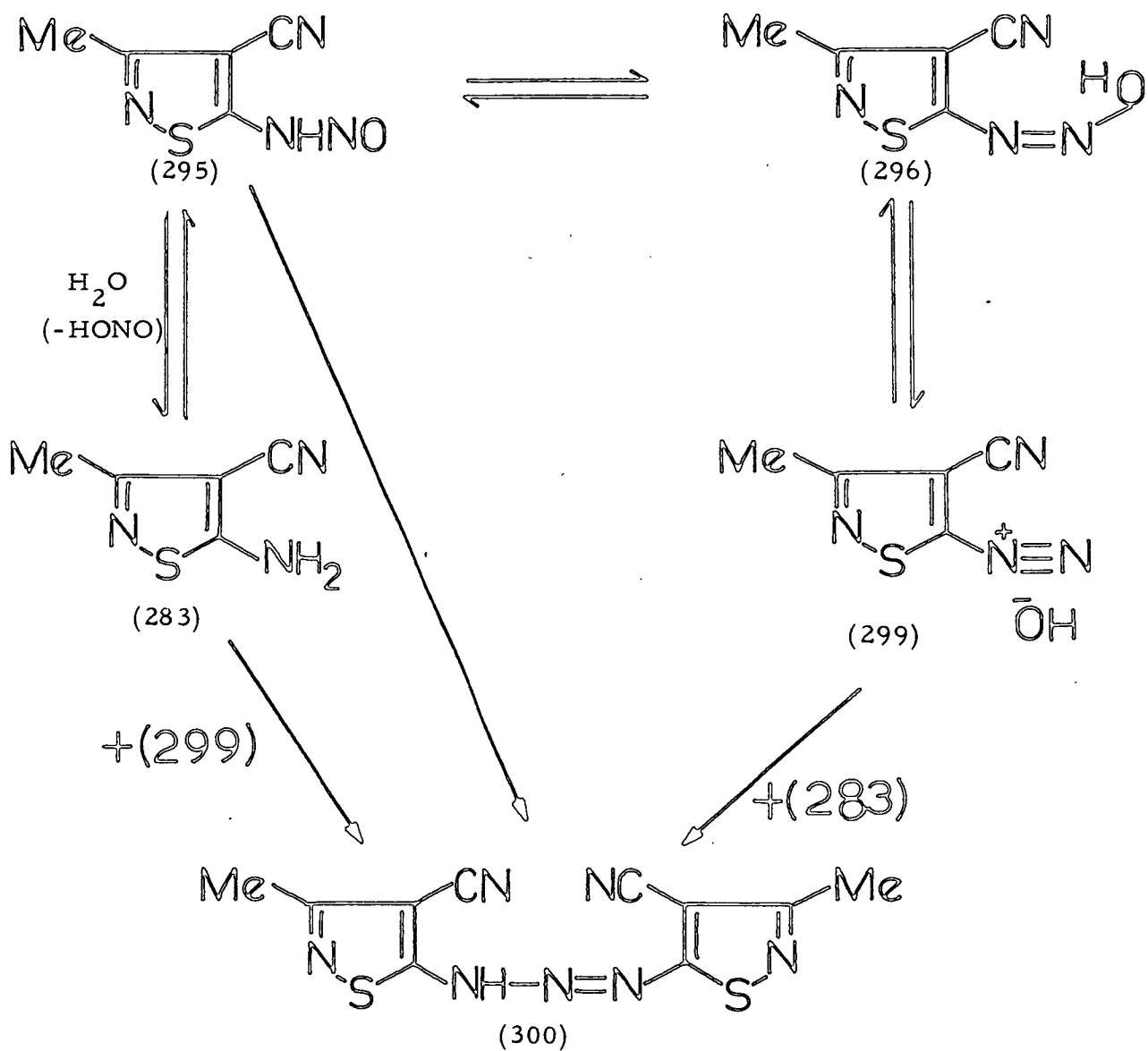
Scheme 116

potentially isolable fluoroborate (294; X=BF$_4$). However treatment

of a suspension of the nitrosamine (295) in a mixture of acetic acid

and propionic acid with hydrofluoroboric acid gave a moderate yield

of the triazene (300) (Scheme 116), m.p. 200-202°. A compound

formulated as the triazene (300) but having a melting-point of 250°

(with decomposition) was reported by Goerdeler[93] as the product

obtained when the nitrosamine (295) is heated in methanol. In the

present studies the triazene structure (300) is assigned on the basis

of the compound's elemental analysis, mass spectrum, the presence

of NH and nitrile absorption in its i.r. spectrum, and signals due to

two similar but non-equivalent methyl groups and an NH group, in

its ^{1}H n.m.r. The conversion of the nitrosamine (295) into the

triazene (300) could occur by two possible pathways (Scheme 116).

Thus, prior equilibration of the nitrosamine (295) with the amine (283)

on the one hand and the diazonium hydroxide (299) on the other

would permit coupling of the latter with the former to give the

observed product. Alternatively, as suggested by Goerdeler,[112]

triazene (300) formation could be the result of direct condensation

between two molecules of nitrosamine (295). Goerdeler[112] does

not propose a mechanism for this mode of formation, but claims that

the reaction is acid catalysed and demonstrates the participation of

two molecules of nitrosamine from the fact that the majority of the

triazene product obtained by reacting an amine with a nitrosamine

is in fact derived exclusively from two molecules of the nitrosamine.

Goerdeler[93] has reported that the nitrosamine (295) is converted

into the diazonium fluoroborate (294; X=BF$_4$) by treatment with boron
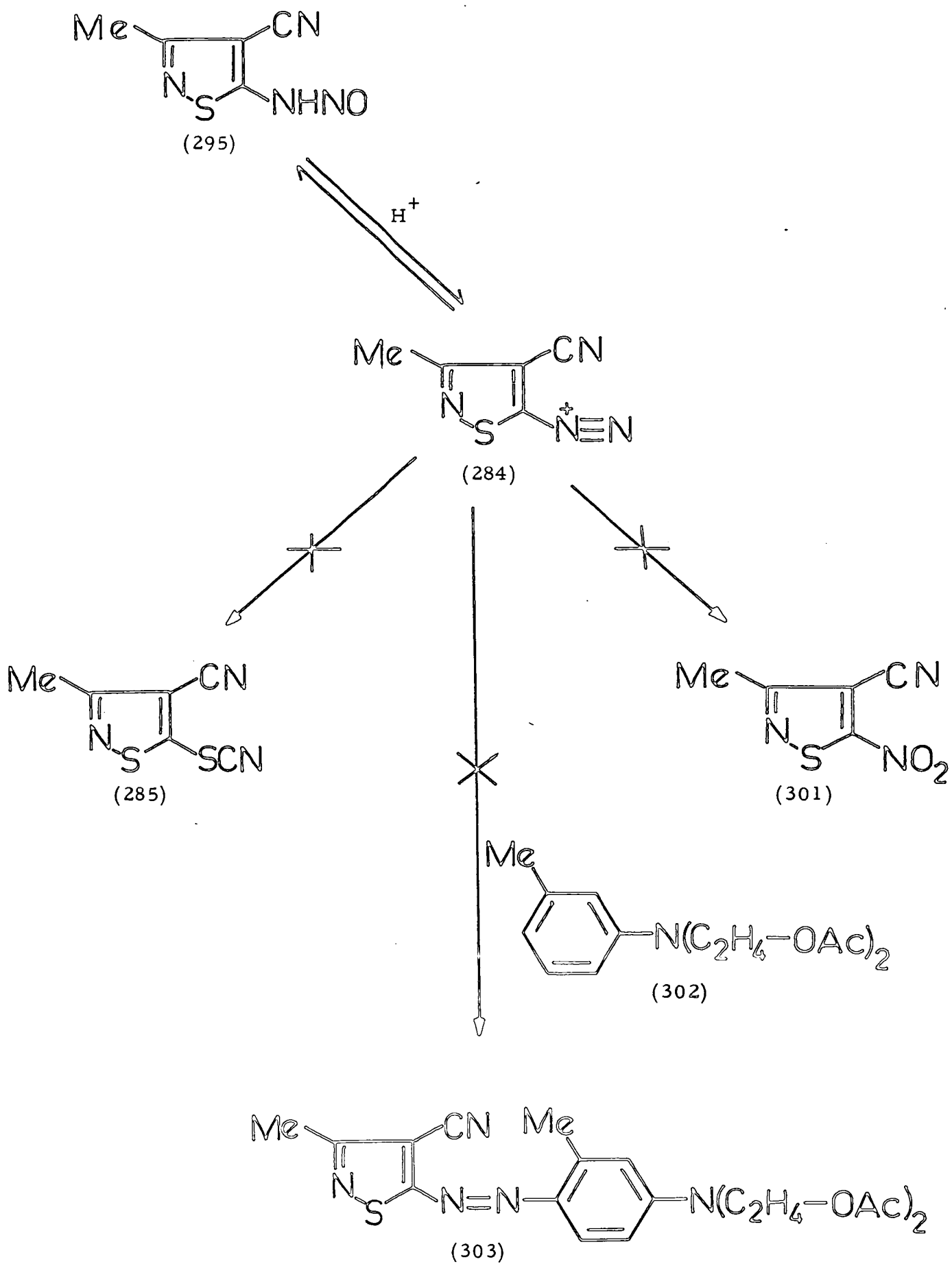
Scheme 117

trifluoride-etherate. However, in the present studies, this reaction gave a pink product which, though giving a positive coupling test with N,N-bis-(β-acetoxyethyl)-m-toluidine indicative of the presence of a diazonium group, on crystallisation merely yielded the triazene (300) obtained before. It is likely, therefore, that the pink product is simply a mixture of the triazene (300) and unreacted nitrosamine (295). A final attempt to obtain the diazonium acetate (294; X=OAc) by reaction of the nitrosamine (295) with acetic anhydride gave only a low yield of the triazene (300).

Since attempts to convert the nitrosamine (295) into an isolable isothiazole-5-diazonium salt had been unsuccessful, the utility of the nitrosamine (295) as an in situ diazonium precursor was next investigated. It is believed[57,109] that nitrosamines in aqueous solutions exist in equilibrium with the corresponding diazonium cation and that this equilibrium lies further towards the latter, the lower the pH. The nitrosamine (295) was therefore added to an acidic solution of N,N-bis-(β-acetoxyethyl)-m-toluidine (302) in an attempt to effect coupling to give the azo compound (303) (Scheme 117). However this reaction afforded only a low yield of an intractable purple solid which could not be characterised, together with an intractable gum. Dediazoniation reactions of the nitrosamine (295) were also investigated. However, though the nitrosamine (295) reacted smoothly with sodium azide under acidic conditions to afford 5-azido-3-methylisothiazole-4-carbonitrile in high yield (see Chapter 6) attempts to react the nitrosamine (295) with other nucleophiles were unsuccessful. For example the attempted reaction of the nitrosamine (295) under acidic

conditions with copper thiocyanate catalyst[149] gave not the hoped

for 2-thiocyanatoisothiazole (285) but a yellow gum from which no

identifiable material could be obtained.   This reaction was carried

out under strongly acidic conditions in order to ensure that a high

concentration of the diazonium cation (284) was present in the mixture.

However at low pH, the concentration of free thiocyanate ion in the

mixture would be relatively low thus possibly accounting for the lack

of thiocyanodediazoniation under acidic conditions.   That the pH of

the mixture is not the only controlling factor is demonstrated by the

observation that the nitrosamine (295) in phosphoric acid reacts with

copper thiocyanate under neutral conditions to afford 5-amino-3-

methylisothiazole-4-carbonitrile (283) as the only isolable product.

This result once again demonstrates the reversible nature of the

diazotisation process (Chapter 1, Scheme 41).   The attempted

reaction of a solution of the nitrosamine (295) in phosphoric acid

with copper nitrite catalyst[150] at pH 3.5-4.0 gave not 3-methyl-5-

nitroisothiazole-4-carbonitrile (301) but rather unreacted starting

material together with a low yield of an intractable brown gum.

The foregoing studies clearly demonstrate the contrasting

reactivity towards diazotisation of the 5-aminoisothiazole (283)

compared with aminothiazoles such as 2-aminothiazole (see Chapter

3).   They also highlight the difference in reactivity of the respective

diazonium cations and nitrosamines particularly towards dediazo-

niation.

Experimental

5-Amino-3-methylisothiazole-4-carbonitrile (283).

(a) 1,1-Dicyano-2-ethoxyprop-1-ene (291) was prepared by the method of McCall[159] by reacting triethyl orthoacetate with malononitrile.   The product was isolated in 98% yield, by diluting the cooled reaction mixture with light petroleum, and had m.p. 86-89° (lit.,[159] 93-94°).

(b) 2-Cyano-3-ethoxythiocrotonamide (292) was prepared by the method of McCall[159] by passing hydrogen sulphide through a solution of 1,1-dicyano-2-ethoxyprop-1-ene (291) in toluene, yield 80%, m.p. 157-158° (lit.,[159] 173-174°).

(c) 3-Amino-2-cyanothiocrotonamide (293) was prepared in quantitative yield by passing ammonia through an alcoholic solution of 2-cyano-3-ethoxythiocrotonamide (292) as described by McCall,[159] and had m.p. 147-150° (lit.,[159] 179-180°).

(d) 5-Amino-3-methylisothiazole-4-carbonitrile (283) was prepared from 3-amino-2-cyanothiocrotonamide (293) by the method of Anderson and Hsiao[160] in 82% yield and had m.p. 206-207° (lit.,[160] 202-204°).

The Attempted Preparation of 4-Cyano-3-methylisothiazole-5-diazonium Fluoroborate (294: X=BF$_4$).

(a) A suspension of 5-amino-3-methylisothiazole-4-carbonitrile (283) (2.80 g; 0.02 mol) in 40% aqueous hydrofluoroboric acid (40.0 ml) was stirred and treated at 0° with a solution of sodium nitrite (10.0 g; 0.14 mol) in water (50.0 ml) to give a yellow suspension

which was stirred for 15 min at 0° and then for 15 min at room temperature. Filtration of the reaction mixture gave a brown solid (2.89 g; 85%), m.p. 73-74°, identical (i.r. spectrum) with a sample of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) prepared later.

(b) A solution of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.35 g; 0.0025 mol) in 88% phosphoric acid (2.5 ml) was stirred and treated with solid sodium nitrite (0.35 g; 0.005 mol) at 0° and the resulting suspension was stirred at 0-5° for 15 min, treated with sulphamic acid (0.49 g; 0.005 mol) and stirred for a further 5 min. 40% Aqueous hydrofluoroboric acid (1.0 ml) was then added dropwise at 0-5° to afford a suspension which was stirred for 15 min at 0-5° and poured into ice-water (30 ml) to yield a brown solid (0.33 g; 79%), m.p. 85-89°, identical (i.r. spectrum) with a sample of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) prepared later.

The Attempted Preparation of 3-Methyl-5-thiocyanatoisothiazole-4-carbonitrite (285) from 5-Amino-3-methylisothiazole-4-carbonitrile (283).

(a) A solution of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.70 g; 0.005 mol) in 88% phosphoric acid (5.0 ml) was treated in portions at 0° with stirring with sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension which was stirred at 0-5° for 15 min, treated with sulphamic acid (0.97 g; 0.01 mol) and stirred

for a further 5 min. The diazonium suspension was then added dropwise together with aqueous 2M sodium hydroxide (62.0 ml) at pH 6-8 and 55-60° to a suspension of copper thiocyanate catalyst (0.61 g) [prepared by mixing solutions of copper sulphate pentahydrate (2.4 g) and hydrated ferrous sulphate (4.6 g) in water (10.0 ml) and potassium thiocyanate (1.0 g) in water (5.0 ml) and collecting the grey solid formed] in a solution of potassium thiocyanate (3.0 g; 0.03 mol) in water (50.0 ml). The reaction mixture was stirred mechanically at 55-60° for 1 h and the green solid (0.51 g) was collected and extracted with hot ethyl acetate to afford a brown gum (0.05 g), whose t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica showed four components, one of which corresponded to 5-amino-3-methylisothiazole-4-carbonitrile (283).

The aqueous mother liquor was extracted with ethylacetate (2x50 ml) to give an intractable red-brown gum (0.17 g) from which no identifiable material could be obtained.

(b) A solution of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.70 g; 0.005 mol) in a mixture of acetic acid and propionic acid (6:1) (14.0 ml) was added dropwise with stirring to 40% w/w nitrosylsulphuric acid (1.0 ml) at 0-5°. The yellow suspension was stirred for 15 min at 0-5° and then added dropwise together with aqueous 2M sodium hydroxide (122 ml) at pH 6-8 and 50-60° to a stirred suspension of copper thiocyanate catalyst (0.61 g) [prepared by mixing solutions of copper sulphate pentahydrate (2.4 g) and hydrated ferrous sulphate (4.6 g) in water (10.0 ml) and potassium thiocyanate (1.0 g) in water (5.0 ml) and collecting the grey solid

formed] in a solution of potassium thiocyanate (3.0 g; 0.03 mol) in water (50.0 ml). The reaction mixture was then stirred at 50-60° for 1 h. Work up gave no identifiable material.

The Attempted Preparation of 4,5-Dicyano-3-methylisothiazole (297) from 5-Amino-3-methylisothiazole-4-carbonitrile (283).

A solution of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.70 g; 0.005 mol) in 88% phosphoric acid (5.0 ml) was stirred and treated in portions at 0° with sodium nitrite (0.70 g; 0.005 mol) to give a yellow suspension which was stirred at 0-5° for 15 min, treated with sulphamic acid (0.97 g; 0.01 mol), and stirred for a further 5 min. The diazonium suspension was then added in portions together with 2M sodium hydroxide at pH 6-8 and 48-60° to a stirred suspension of copper cyanide catalyst [prepared by mixing aqueous solutions of copper sulphate pentahydrate (1.5 g) and potassium cyanide (1.6 g; 0.025 mol) at less than 20° and making the mixture up to 50 ml]. The reaction mixture was stirred mechanically at 48-60° for 1 h. Work up gave only small quantities of unidentified gums.

Pentane-2,3,4-trione 3-(4'-cyano-3'-methylisothiazol-5'-yl)hydrazone (298).

A solution of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.70 g; 0.005 mol) in 88% phosphoric acid (5.0 ml) was stirred and treated in portions at 0° with sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min at 0°, treated with sulphamic acid (0.97 g; 0.01 mol) and stirred for a further 5 min. A solution of acetylacetone (0.50 g; 0.005 mol) in methanol (5.0 ml) was then added dropwise with stirring at 0-5° to give a red solution

which was stirred for 45 min at 0°. The reaction mixture was poured on to ice (25 g) to give a brown solid which was crystallised from light petroleum-toluene to afford <u>pentane-2, 3, 4-trione 3-(4'-cyano-3'-methylisothiazol-5'-yl)hydrazone</u> (298) as orange crystals (0.61 g; 49%), m.p. 132-132.5°, ν_{max} 3120 w (NH), 2220 (CN), and 1680 and 1650 (CO) cm^{-1}, δ (CDCl$_3$) 2.65 (3H, s, Me), 2.55 (3H, s, Me), and 2.47 (3H, s, Me).

<u>Found:</u> C, 48.0; H, 4.0; N, 22.3%; M$^+$250.

$\underline{C_{10}H_{10}N_4O_2S}$ requires: C, 48.0; H, 4.0; N, 22.4%; M 250.

The aqueous mother liquor was extracted with ethyl acetate (2x40 ml) to give a purple gummy solid (0.52 g) which on trituration with toluene-ether gave 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.17 g; 24%), m.p. 161-163°, identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to an authentic sample.

<u>3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile</u> (295).

(a) 5-Amino-3-methylisothiazole-4-carbonitrile (283) (0.56 g; 0.004 mol) was suspended in a solution of sodium nitrite (1.05 g; 0.015 mol) in water (10.0 ml) and treated at 0-5° with stirring with 10% aqueous hydrochloric acid (10.0 ml) to give a yellow suspension which was stirred at 0-5° for 3 h. The yellow solid was collected to give 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.65 g; 96%), m.p. 94° (violent decomposition) (lit.,[93] 115-120°), ν_{max} 3090 m, 2740 br, and 2630 br (OH/NH), and 2250 (C≡N) cm^{-1}.

(b) A suspension of 5-amino-3-methylisothiazole-4-carbonitrile (283) (0.70 g; 0.005 mol) in aqueous 2M sulphuric acid (9.0 ml) was

treated at 0° with stirring with a solution of sodium nitrite (0.40 g; 0.0058 mol) in water (2.0 ml). The resulting thick yellow suspension was stirred for 10 min at 0-5° to give 3-methyl-5-nitrosaminoiso-thiazole-4-carbonitrile (295) as a yellow solid (0.72 g; 85%), m.p. 77° (violent decomposition), identical (i.r. spectrum and t.l.c. in ethyl acetate over silica) with a sample prepared previously.

The Attempted Preparation of 4-Cyano-3-methylisothiazole-5-diazonium Fluoroborate (294; X=BF$_4$) from 3-Methyl-5-nitrosamino-isothiazole-4-carbonitrile (295).

(a) A suspension of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.84 g; 0.005 mol) in a mixture of acetic acid (6.7 ml) and propionic acid (3.3 ml) was stirred and treated in portions at 0-5° with 40% aqueous fluoroboric acid (2.58 g). The reaction mixture was stirred for 3 h at 0-10° to give a yellow solid, m.p. 208-209°, which was crystallised from acetic acid-water to give the triazene (300) as dark red crystals (0.29 g; 40%), m.p. 200-202° [lit.[93] 250° (decomp.)], ν_{max} 3200 and 3100 m (NH) and 2250 and 2235 (CN) cm^{-1} δ [(CD$_3$)$_2$CO] 7.96 (1H, s, NH), 2.60 (3H, s, Me), and 2.58 (3H, s, Me).

Found: C, 41.5; H, 2.5; N, 32.8%; M$^+$289.

Calc. for C$_{10}$H$_7$N$_7$S$_2$:   C, 41.5; H, 2.4; N, 33.9%; M 289.

Exact Mass Found: M$^+$, 289.019211.

C$_{10}$H$_7$N$_7$S$_2$ requires: M, 289.020434.

(b) A suspension of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.84 g; 0.005 mol) in   sodium dried ether (15.0 ml)

was stirred and treated with a 48% solution of boron trifluoride in ether (1.43 g; 0.01 mol) at room temperature. The reaction mixture was stirred for 30 min to give an unidentified pink solid (1.12 g), m.p. 157-159°, which gave a positive test with $\underline{N}$,$\underline{N}$-$\underline{bis}$-(β-acetoxyethyl)-$\underline{m}$-toluidine and on attempted crystallisation from aqueous ethanol afforded the triazene (300), m.p. 205-207°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Preparation of 4-Cyano-3-methylisothiazole-5-diazonium Acetate (294; X=OAc).

3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.34 g; 0.002 mol) was mixed with acetic anhydride (2.25 ml). Heat was liberated and the dark suspension was treated with ether to give an orange solid (0.06 g; 21%), m.p. 197-198°, identical (i.r. spectrum) to a sample of the triazene (300) prepared previously.

T.l.c. of the ethereal mother liquor over silica using a variety of solvents showed four close-running components which were not further investigated.

The Attempted Reaction of $\underline{N}$, $\underline{N}$-Bis-(β-acetoxyethyl)-$\underline{m}$-toluidine with 3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (295).

3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.20 g; 0.0012 mol) was added in portions at 0° to a stirred mixture containing a 61.3% w/w solution of $\underline{N}$,$\underline{N}$-$\underline{bis}$-(β-acetoxyethyl)-$\underline{m}$-toluidine in acetic acid (0.41 g; 0.0009 mol), 2M sulphuric acid (5.0 ml), and water (45.0 ml). The mixture was stirred for 30 min at 0° to give

a purple solid (0. 17 g), m. p. 88-89°, which could not be purified by crystallisation and whose t. l. c. in toluene-acetone-acetic acid (90:10:0. 5) over silica showed it to be an unresolvable three component mixture.

Extraction of the aqueous filtrate with ethyl acetate (2x30 ml) gave a purple gum (0. 29 g) whose t. l. c. in toluene-acetone-acetic acid (90:10:0. 5) over silica showed it to be an unresolvable multi-component mixture.

The Attempted Preparation of 3-Methyl-5-thiocyanato isothiazole-4-carbonitrile (285) from 3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (295).

(a) A solution of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0. 84 g; 0. 005 mol) in 88% phosphoric acid (15. 0 ml) was added dropwise with stirring at 60-70° to a suspension of copper thiocyanate catalyst (0. 61 g) [prepared by mixing solutions of copper sulphate pentahydrate (2. 4 g) and hydrated ferrous sulphate (4. 6 g) in water (10. 0 ml) and potassium thiocyanate (1. 0 g) in water (5. 0 ml) and collecting the grey solid formed] in a solution of potassium thiocyanate (3. 0 g; 0. 03 mol) in water (5. 0 ml). The reaction mixture was stirred mechanically at 60-70° for 1 h and allowed to reach room temperature, then quenched with ice (25 g) to precipitate a brown solid (2. 11 g). This was extracted with hot ethyl acetate to afford a yellow gum (0. 69 g) which was triturated with ethylacetate to yield an uncrystallisable and unidentified yellow solid (0. 23 g), m. p. 172-174°. T. l. c. of the ethyl acetate mother liquor in toluene-acetone-acetic acid (90:10:0. 5) over silica showed the presence of four close-

running components.

The aqueous filtrate was extracted with ethyl acetate (2x40 ml) to afford an intractable yellow gum (0.26 g) whose t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica showed the presence of five close-running components.

(b) A solution of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.84 g; 0.005 mol) in 88% phosphoric acid (15.0 ml) was added dropwise together with aqueous 2M sodium hydroxide (150 ml) at pH 6-8 and 60-80° to a stirred suspension of copper thiocyanate catalyst (0.61 g) [prepared by mixing solutions of copper sulphate pentahydrate (2.4 g) and hydrated ferrous sulphate (4.6 g) in water (10.0 ml) and potassium thiocyanate (1.0 g) in water (5.0 ml) and collecting the grey solid] in a solution of potassium thiocyanate (3.0 g; 0.03 mol) in water (50.0 ml).   The mixture was stirred mechanically at 60-80° for 1.25 h to give a brown solid (0.60 g) which was extracted with hot ethyl acetate to afford a brown gum (0.08 g) whose t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over silica showed it to contain two unresolvable components.

The aqueous filtrate was extracted with ethyl acetate (2x70 ml) to give a brown gum (0.16 g) which was triturated with ether-ethyl acetate to yield a yellow-brown solid (0.02 g; 3%), m.p. 207-210°, identical (i.r. and mass spectra) with an authentic sample of 5-amino-3-methylisothiazole-4-carbonitrile (283).

T.l.c. of the ethyl acetate mother liquor in toluene-acetone-acetic acid (90:10:0.5) over silica showed the presence of three unresolvable components.

The Attempted Preparation of 3-Methyl-5-nitroisothiazole-4-carbonitrile (301) from 3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (295).

A solution of 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (295) (0.84 g; 0.005 mol) in 88% phosphoric acid (15.0 ml) was added dropwise together with aqueous 2M sodium hydroxide (100 ml) at 0-20° and pH 3.5-4.0 to a stirred suspension of copper catalyst (0.8 g) [prepared by heating a solution of copper sulphate pentahydrate (4.0 g) and hydrated sodium sulphate (4.0 g) in water (10.0 ml) until a brown suspension formed then collecting the solid] in a solution of sodium nitrite (3.1 g; 0.045 mol) in water (50.0 ml). The mixture was stirred mechanically at 0-20° for 2.5 h, then the pH was lowered to 3.0 by the addition of concentrated sulphuric acid and gave a positive test with $\underline{N}, \underline{N}$-$\underline{bis}$-(β-acetoxyethyl)-$\underline{m}$-toluidine. The reaction mixture was therefore stirred overnight at room temperature and the green solid obtained was extracted with hot ethyl acetate to afford 3-methyl-5-nitrosaminoisothiazole-4-carbonitrile (0.34 g; 41%), m.p. 55° (violent decomposition), identical (i.r. spectrum) with an authentic sample.

The aqueous filtrate was extracted with ethyl acetate (2x50 ml) to yield an intractable brown gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed the presence of four unresolvable components.

CHAPTER FIVE

Studies of the Synthesis and Reactivity of 1, 2, 4-
and 1, 3, 4-Thiadiazolediazonium Salts

Studies of the Synthesis and Reactivity of 1, 2, 4- and 1, 3, 4- Thia-
diazolediazonium Salts.

Five-membered cyclic structures containing one sulphur and
two nitrogen atoms are represented by the 1, 2, 3- (304), 1, 2, 4- (305),
1, 3, 4- (306) and 1, 2, 5- (307) thiadiazole ring systems (Scheme 118).
The studies described in the present Chapter are concerned with the
investigation of the diazotisation of primary amines of two of these
ring systems namely 1, 2, 4-thiadiazoleamines and 1, 3, 4-thiadiazole-
amines.

The diazotisation of 2-amino-1, 3, 4-thiadiazoles in dilute acid
is reported[108] to yield relatively stable nitrosamines. On the other
hand when the diazotisation of 2-amino-1, 3, 4-thiadiazoles is conducted
in concentrated acid the products are reported[83, 161-163] to be
diazonium salts which undergo dediazoniation reactions of the
Sandmeyer type and can be coupled with activated arenes. Both
3-amino- and 5-amino-1, 2, 4-thiadiazoles are known and the diazotisa-
tion of the latter has been studied in some depth by Goerdeler[109, 110, 111]
who has shown that diazotisation in dilute acid media affords the
corresponding nitrosamines which in strongly acidic media are
converted in turn into the respective diazonium salts. In practice
special conditions have to be employed[110] to isolate the 1, 2, 4-
thiadiazole-5-diazonium salts from the 5-amino- or 5-nitrosamino-
1, 2, 4-thiadiazoles. The diazotisation of 3-amino-1, 2, 4-thiadiazoles
has only been studied to a limited extent and such amines are in
general less reactive towards diazotisation than their 5-amino counter-
parts. However 1, 2, 4-thiadiazole-3-diazonium salts undergo

R

a; Me
b; Ph   (308)

⇌

(309)

Scheme 119

(310)   —KSCN→   (308)

(311)

R

a;   Me

b;   Ph

(312)

(313)
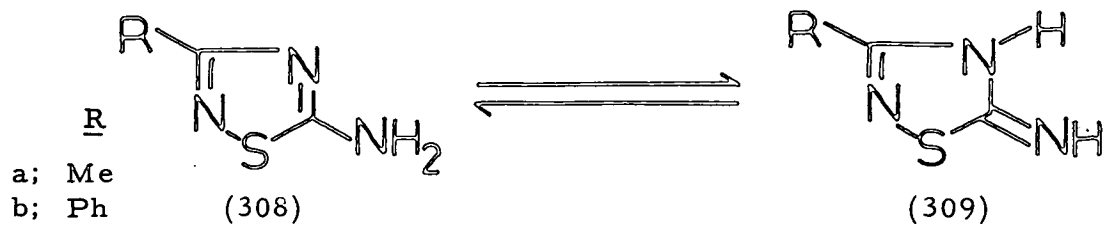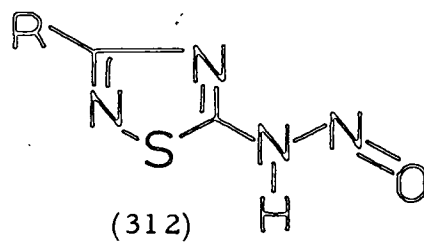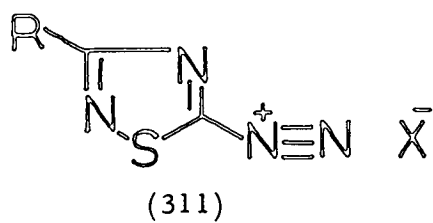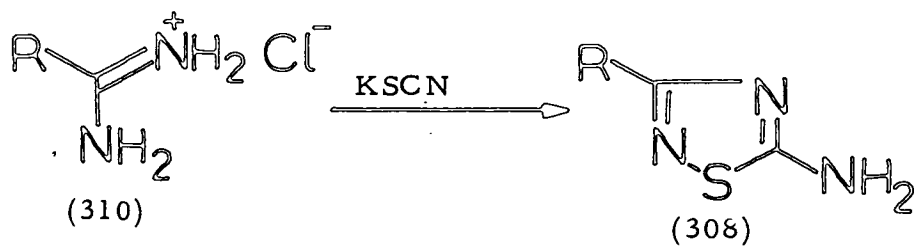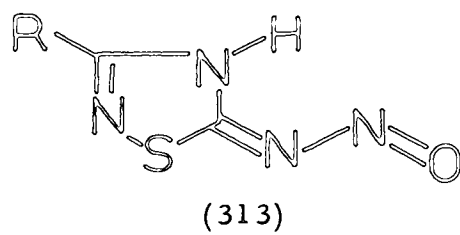
Scheme 120

orthodox dediazoniation reactions and couple as expected with

activated arenes.[110, 113, 114] 3-Nitrosamino-1, 2, 4-thiadiazoles

do not appear to have been reported in the literature to date. The

objectives of the present studies were to establish convenient methods

for the diazotisation/nitrosation of 3-amino- and 5-amino-1, 2, 4-

thiadiazoles and 2-amino-1, 3, 4-thiadiazoles and to investigate the

scope of the dediazoniation and coupling reactions of the resulting

diazonium or nitrosamino species produced. Coupling reactions

with active methylene compounds were of particular interest because

of the potential use of the hydrazone products for the synthesis of

fused heterocyclic systems.

(A)   Amino-1, 2, 4-thiadiazoles

5-Amino-1, 2, 4-thiadiazoles

5-Amino-1, 2, 4-thiadiazoles (308) are generally stable, colourless,

odourless compounds which are weak bases although they can undergo

typical amine reactions such as acetylation.[164] Of the two possible

tautomeric forms of 5-amino-1, 2, 4-thiadiazoles (Scheme 119) the

enamine tautomer (308) is apparently more stable than the ketimine

tautomer (309).[164] The behaviour towards diazotisation of two

5-amino-1, 2, 4-thiadiazoles, namely the 3-methyl and 3-phenyl

derivatives (308a and b), (Scheme 120) was investigated. Both amines

(308a and b) were synthesised in moderate yield by the method of

Goerdeler[165] involving the cyclisative condensation of acetamidine

or benzamidine hydrochloride (310) with potassium thiocyanate.

However the synthesis of the methyl compound (308a) was found not

to be reproduc̥ble thus curtailing the study of its diazotisation

reactions.

Initially, attempts were made to convert 5-amino-3-methyl-

1, 2, 4-thiadiazole (308a) into isolable diazonium salts. However the

reaction of the hydrochloride of the amine (308a) with amyl nitrite

under conditions[146] successful for the synthesis of 1$\underline{H}$-1, 2, 3-triazole-

5-diazonium salts, gave only unreacted amine (308a). An attempt was

also made to convert the amine (308a) by reaction with sodium nitrite

in hydrofluoroboric acid into 3-methyl-1, 2, 4-thiadiazole-5-diazonium

fluoroborate [Scheme 120; (311a; X=BF$_4$)]. However this reaction

gave only 3-methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a) together

with an unidentified orange solid which could not be purified. The

nitrosamine (312a) was identified by its violent behaviour on melting

and the absence of diazo absorption in its i.r. spectrum. The identity

of the nitrosamine (312a) was confirmed when an identical product

was prepared using Goerdeler's[109] method for the preparation of 3-

methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a). The melting point

found for the nitrosamine in the present work was somewhat below

that reported by Goerdeler[109], but no attempt was made to purify the

compound on account of its reactive nature. An attempt was also

made to prepare and isolate 3-phenyl-1, 2, 4-thiadiazole-5-diazonium

fluoroborate (311b, X=BF$_4$) directly from the corresponding amine

(308b). However diazotisation of the amine (308b) in hydrofluoroboric

acid with sodium nitrite gave a quantitative yield of the corresponding

nitrosamine (312b) which decomposed violently at 120° and was

identical with an authentic sample, m.p. 126-128°, prepared as

described by Goerdeler[109] who reported a melting point of $180°$.

The identity of the solid as the nitrosamine (312b) was further

substantiated by its mass spectrum. The formation of the nitros-

amines (312a and b) rather than the diazonium salts (311a and b;

X=BF$_4$) when the amines (308a and b) are diazotised under aqueous

acidic conditions is consistent with the findings of other workers.[164]

5-Nitrosamino-1, 2, 4-thiadiazoles (312) are a fairly well defined group

of compounds, nitrosation of 5-amino-1, 2, 4-thiadiazoles (308) having

been shown[164] to occur at the side-chain and not at the nucleus.

Moreover the nitrosamino structure (312) as opposed to the alternative

nitrosimino formulation (313) (Scheme 120) has been fully confirmed[164]

for these compounds.

The ready availability of the nitrosamines (312a and b) prompted

their evaluation as precursors of 1, 2, 4-thiadiazole-5-diazonium salts

(311). Thus, in an attempt to prepare the diazonium salt (311a;

X=Cl), the nitrosamine (312a) was treated with methanolic hydrogen

chloride. The product of this reaction was a yellow solid (B) which

gave analytical and mass spectroscopic data consistent with the

formula $C_3H_5N_3S$. The i. r. spectrum contained NH absorption at

3280-3140 cm^{-1} and several bands attributable to NH deformation

between 1695 and 1645 cm^{-1}. However signals at δ 2. 32 and 2. 40 in

its ^{1}H n. m. r. spectrum attributable to two methyl groups clearly

indicated the yellow solid (B) to be a mixture. On one occasion

repetition of the reaction of the nitrosamine (312a) with methanolic

hydrogen chloride gave a different yellow solid (C) which gave analytical

and mass spectroscopic data in accord with the formula $C_3H_4N_2OS$.

This product exhibited a ^{1}H n.m.r. spectrum identical to that of the product (B) but had a different melting-point and showed a different i.r. spectrum. The i.r. spectrum of (C) contained NH absorption at 3420 cm^{-1} and a solitary band at 1670 cm^{-1} assignable to a carbonyl group. In an attempt to clarify the nature of (B) and (C) their chemical behaviour was investigated. It was conceivable that products (B) and (C) were both derived from the amine (308a) (by reversal of the nitrosation process). However treatment of the amine (308a) with methanolic hydrogen chloride only afforded un-reacted starting material showing that both (B) and (C) were formed directly from the nitrosamine (312a). As the i.r. spectrum of (B) suggested the presence of an amino group, an attempt was made to acetylate it with acetic anhydride. This reaction gave a moderately good yield of a product (D) which analysed correctly for a mono-acetyl derivative but showed ^{1}H n.m.r. absorption at δ 2.34, 2.37 and 2.56 attributable to the presence of three methyl groups. Further-more the i.r. spectrum of the product (D) showed the presence of two carbonyl groups indicating clearly that it was a mixture of two acetyl derivatives of formula $C_5H_7N_3OS$. Comparison with an authentic sample of 5-acetamido-3-methyl-1,2,4-thiadiazole (314) [obtained by treating 5-amino-3-methyl-1,2,4-thiadiazole (308a) with acetic anhydride] demonstrated that the acetamido compound (314) (Scheme 121) was a component of the mixture (D) and hence that 5-amino-3-methyl-1,2,4-thiadiazole (308a) was present in the mixture (B). Since (B) analysed correctly for $C_3H_5N_3S$ it is clear that it is a mixture of the amine (308a) plus an isomer, possibly the

(314)

(315)   (316)

(317)
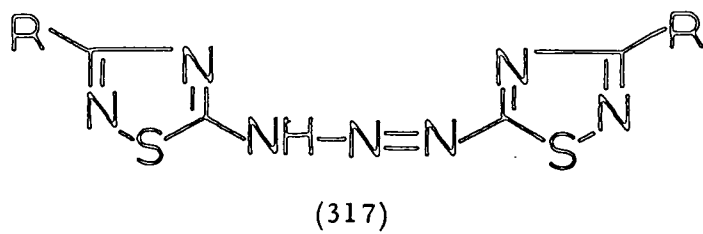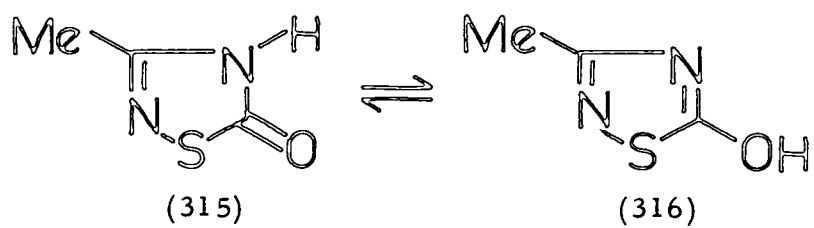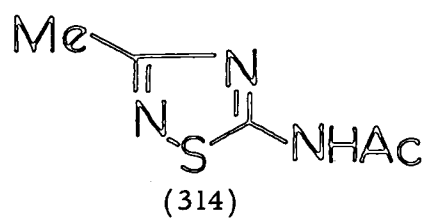
	R
a;	Me
b;	Ph

Scheme 121

tautomeric imine (309a) (Scheme 119). The mixture (B) was heated with dilute hydrochloric acid in the anticipation of hydrolysing any imine (309a) present to the thiadiazolin-5-one (315) (Scheme 121). However work up afforded only a low yield of the amine (308a) together with a very small amount of an unidentified solid. In a further attempt to investigate the nature of (B), it was treated with sodium nitrite in dilute sulphuric acid. This reaction gave a low yield of the nitrosamine (312a), confirming the presence in (B) of the amine (308a), together with a yellow solid which is assigned the thiadiazolin-5-one structure (315) (see later). Goerdeler[109] has reported the tautomeric 5-hydroxy-3-methyl-1, 2, 4-thiadiazole (316), without commenting on its properties, as being the product of treating the nitrosamine (312a) with 50% sulphuric acid at 60° (Scheme 121). Owing to the small quantities of (C) available the investigation of the nature of this product was limited. However, one can say that the major component present in (C) is 3-methyl-Δ^2-1, 2, 4-thiadiazolin-5-one (315) on the basis of analytical and mass spectroscopic data and the presence of carbonyl absorption in its i. r. spectrum.

An attempt was also made to prepare the diazonium salt (311a; $X=BF_4$), using the method of Goerdeler,[110] by treating the nitrosamine (312a) with boron trifluoride-etherate complex. This reaction gave a gummy deliquescent solid (E) whose nature could not be established owing to its unstable nature, but which was used unsuccessfully in an attempted coupling reaction with acetylacetone (see later). On standing the mother liquor from the reaction of the

nitrosamine (312a) with boron trifluoride-etherate deposited a

yellow solid, whose i. r. spectrum contained a weak band at 2260 cm^{-1}

suggesting that it contained some of the desired diazonium salt.

However crystallisation of this solid resulted in its conversion into a

second yellow solid whose combustion analysis did not allow the

assignment of a sensible molecular formula. However the latter

yellow solid had m.p. 224-226° and showed a parent ion peak in its

mass spectrum at m/e 241 suggesting that it might be a mixture con-

taining the triazene (317a) (Scheme 121). The triazene (317a)

prepared by Goerdeler[112] by treating the nitrosamine (312a) with

methanol is reported to have m.p. 224°.

Attention was next turned to the investigation of 5-nitrosamino-

3-phenyl-1, 2, 4-thiadiazole (312b) as a diazonium salt precursor.

However, treatment of the nitrosamine (312b) with hydrogen chloride

in methanolic acetic acid merely afforded 5-amino-3-phenyl-1, 2, 4-

thiadiazole (308b) in high yield again demonstrating the reversibility

of the diazotisation process. On the other hand when the nitrosamine

(312b) was treated with hydrofluoroboric acid as described by

Goerdeler[110] a solid was obtained whose i. r. spectrum contained a

strong band at 2300 cm^{-1} attributable to a diazonium group. . This

solid decomposed at 116° compared with 212°, the melting point

reported[110] for the diazonium fluoroborate (311b; X=BF$_4$). In view

of its anticipated instability no attempt was made to purify this solid

but the presence of weak NH absorption at 3140 cm^{-1} in its i. r.

spectrum indicated that some of the nitrosamine (312b) might still

be present, thus explaining the low decomposition point.

Goerdeler[83,110] has prepared a series of 3-substituted-1,2,4-thiadiazole-5-diazonium salts and has shown them to be very reactive species, which couple readily with aromatic molecules including even some relatively non-nucleophilic substrates. Indeed Goerdeler[83] has shown that 1,2,4-thiadiazole-5-diazonium salts are the most reactive of their kind with a greater capacity to participate in coupling than many other heterocyclic diazonium salts being more reactive even than 2,4-dinitrobenzenediazonium chloride. The 3-phenyl-1,2,4-thiadiazole-5-diazonium cation for example will displace a weaker coupling reagent from an azo compound.[166] Moreover the reactive nature of 1,2,4-thiadiazole-5-diazonium salts is not confined to coupling reactions but also extends to dediazoniation reactions which occur readily with potassium halides in the absence of catalysts giving 5-halogeno-1,2,4-thiadiazoles. The enhanced reactivity of 1,2,4-thiadiazole-5-diazonium salts can be attributed to the marked electron-deficiency of the diazonium substituent as a result of electron-withdrawal by the 1,2,4-thiadiazole nucleus.

Having achieved the synthesis of the 1,2,4-thiadiazole-5-diazonium fluoroborates [Scheme 122; (311a and b; $X=BF_4$)] from the corresponding 5-nitrosamino-1,2,4-thiadiazoles (312a and b) it was of interest to investigate their chemical reactivity. Thus, the reaction of the gummy deliquescent solid (E), obtained by treating the nitrosamine (312a) with boron trifluoride and formulated by Goerdeler[110] as the diazonium salt (311a), with acetylacetone was studied in an effort to obtain the hydrazone (318a) (Scheme 122). However this reaction gave no identifiable material, a result which

(312)   (311)

MeCOCH$_2$COMe

(318)

$\underline{R}$

a;   Me

b;   Ph

Scheme 122

PhCOCH$_2$COMe

(311b)   X$^-$ (319)
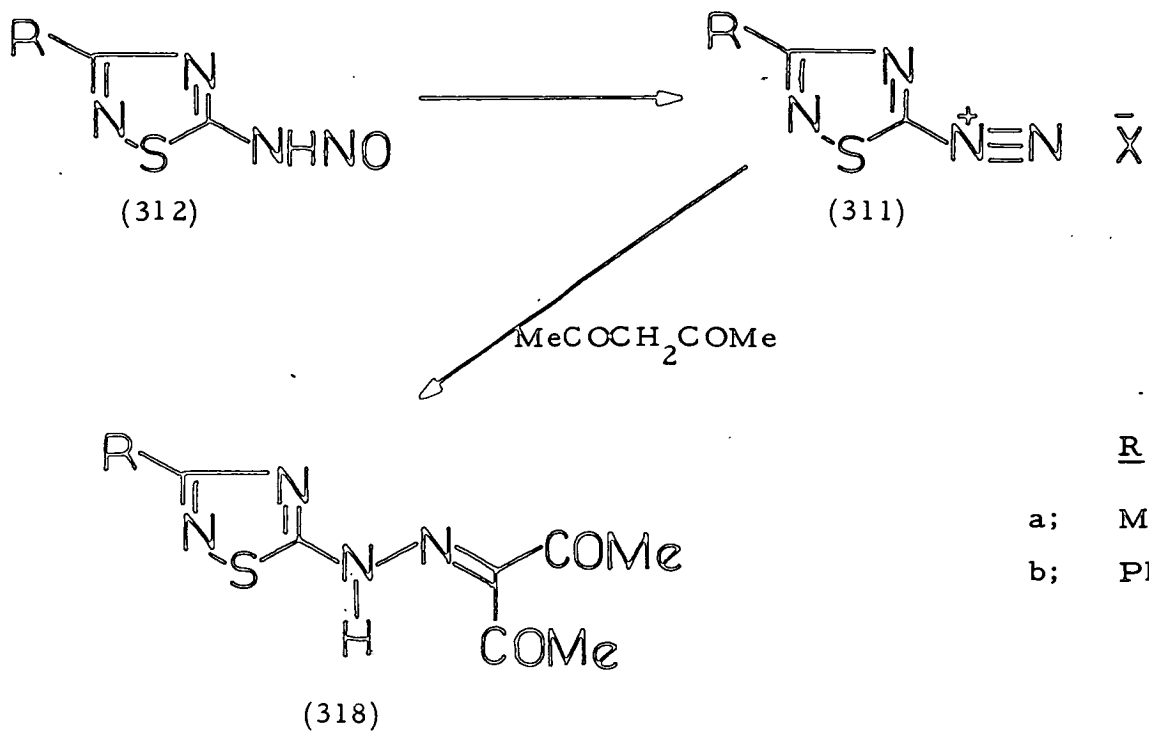
(321)   (320b)   (322)
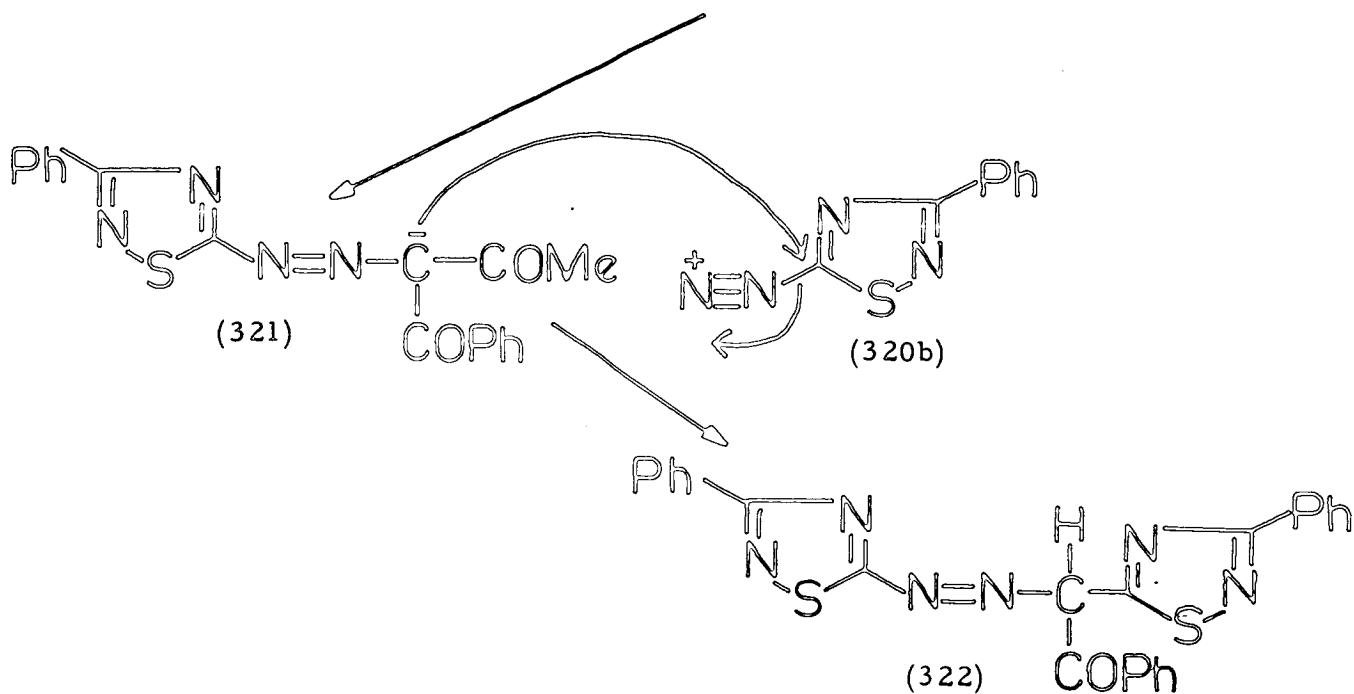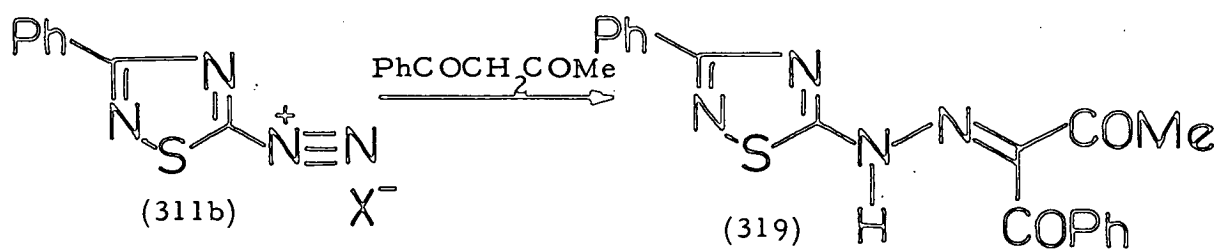
Scheme 123

casts some doubt on the formulation of Goerdeler's deliquescent solid as the diazonium salt (311a). In contrast 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; $X=BF_4$) was found to be a fairly stable compound and consequently its reactivity could be examined in some detail. It was considered of particular interest to investigate the coupling reactions of the salt (311b) with active methylene compounds. Thus the diazonium salt (311b) reacted readily with acetylacetone in acetone solution to give the hydrazone (318b) (Scheme 122) whose analytical and spectroscopic properties were consistent with the assigned structure. In particular its i.r. spectrum contained NH absorption at 3160 cm^{-1} and carbonyl bands at 1690 and 1660 cm^{-1}. Goerdeler[83] also obtained the hydrazone (318b) by diazotisation of the amine in phosphoric acid with sodium nitrite followed by addition of acetylacetone. Reaction of the diazonium salt (311b) with acetylacetone in the presence of triethyl-amine gave a similar yield of the hydrazone (318b). The triethyl-amine-catalysed condensation of the diazonium salt (311b; $X=BF_4$) with benzoylacetone gave three products the major one analysing correctly for $C_{18}H_{14}N_4O_2S$ and showing i.r. and ^1H n.m.r. consistent with it being the expected hydrazone (319). The other two products were an unidentified red solid and a yellow azo compound (322) (Scheme 123). The assignment of the azo structure (322) is tentative and is based on analytical data, the presence of a carbonyl band in the product's i.r. spectrum and on the absence of any other significant i.r. absorption. The mechanism proposed for the formation of the azo compound (322) is shown in Scheme 123 and
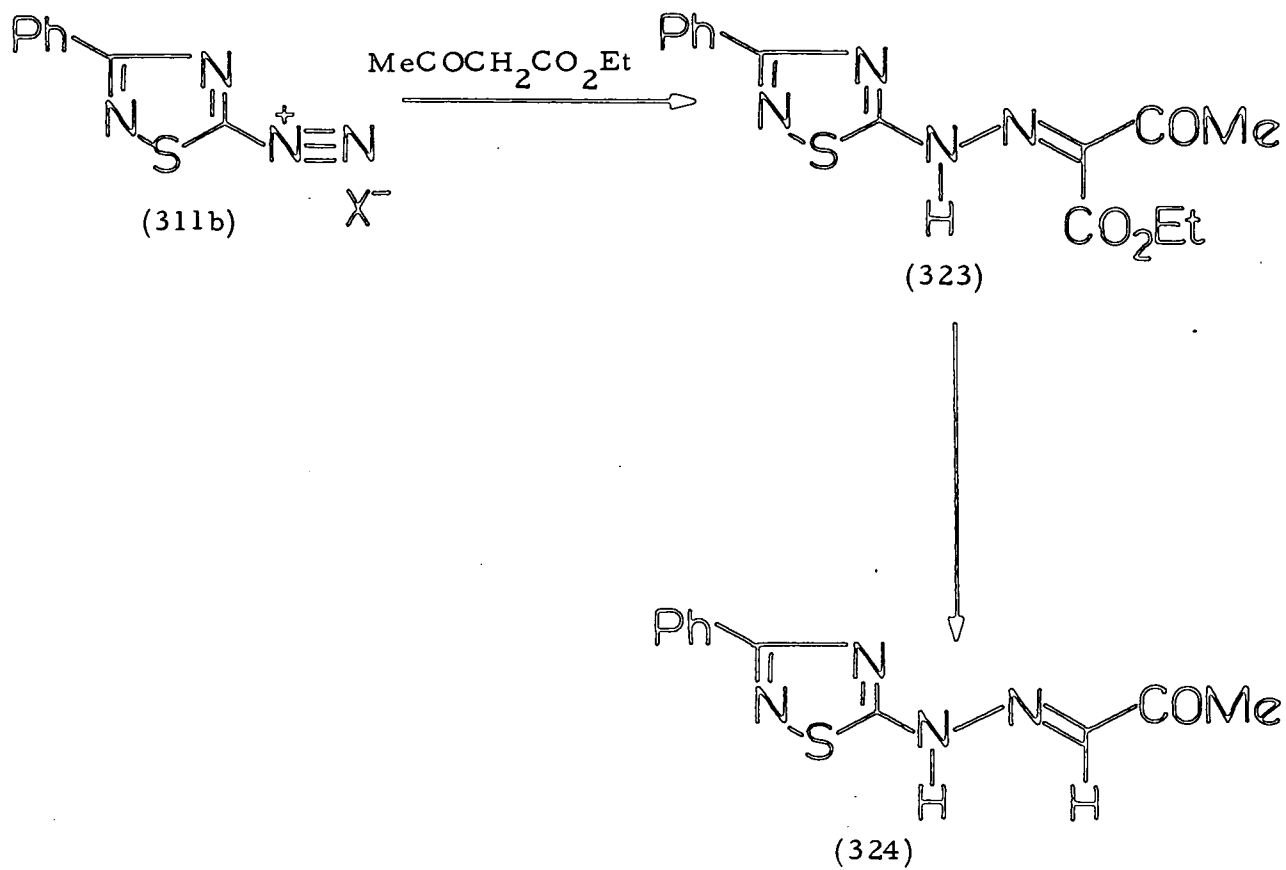
Scheme 124
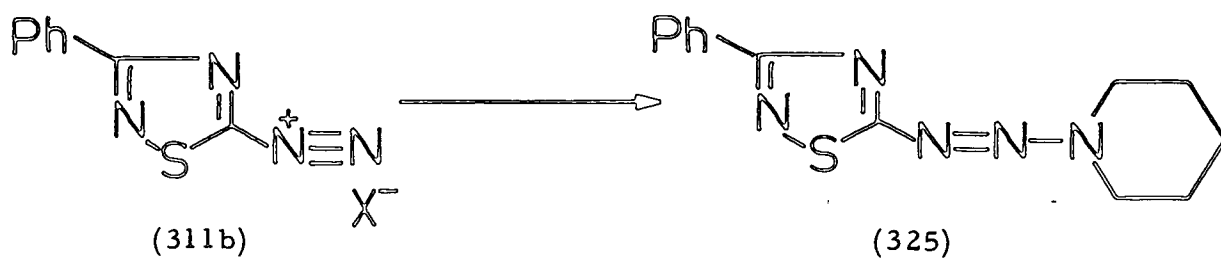
Scheme 125

involves the initial formation of the hydrazone (319) followed by reaction of the derived anion (321) with unreacted diazonium cation (320b) and subsequent deacetylation. The 1,2,4-thiadiazole-5-diazonium fluoroborate (311b; $X=BF_4$) also condensed with ethyl acetoacetate in the presence of triethylamine to afford not the expected hydrazone [Scheme 124; (323)] but rather a product which analysed correctly and showed spectroscopic properties consistent with the decarbethoxylated compound (324). This structure is assigned on the basis of the presence of a single carbonyl band in the product's i.r. spectrum and the absence of ethyl absorption in its ^{1}H n.m.r. spectrum. The isolation of (324) is readily explained in terms of the intermediate formation and decarbethoxylation of the hydrazone (323) in a process similar to the Japp-Klingmann Reaction.[47,48] In an attempt to improve the efficiency of the coupling reaction between the diazonium salt (311b; $X=BF_4$) and ethyl acetoacetate, the sodium salt of the latter was used as reagent. However, under these conditions the only product identified was the nitrosamine (312b).

Treatment of a solution of the diazonium salt (311b; $X=BF_4$) in acetone with piperidine in an attempt to prepare the corresponding triazene (325) (Scheme 125) merely gave a good yield of the triazene (317b) which is more fully discussed later.

A series of dediazoniation reactions of the diazonium salt (311b; $X=BF_4$) were also investigated. However reaction of the diazonium salt (311b; $X=BF_4$) in acetone with an aqueous solution of potassium cyanide afforded a high yield of a product which gave analytical and mass spectral data and had a melting point consistent
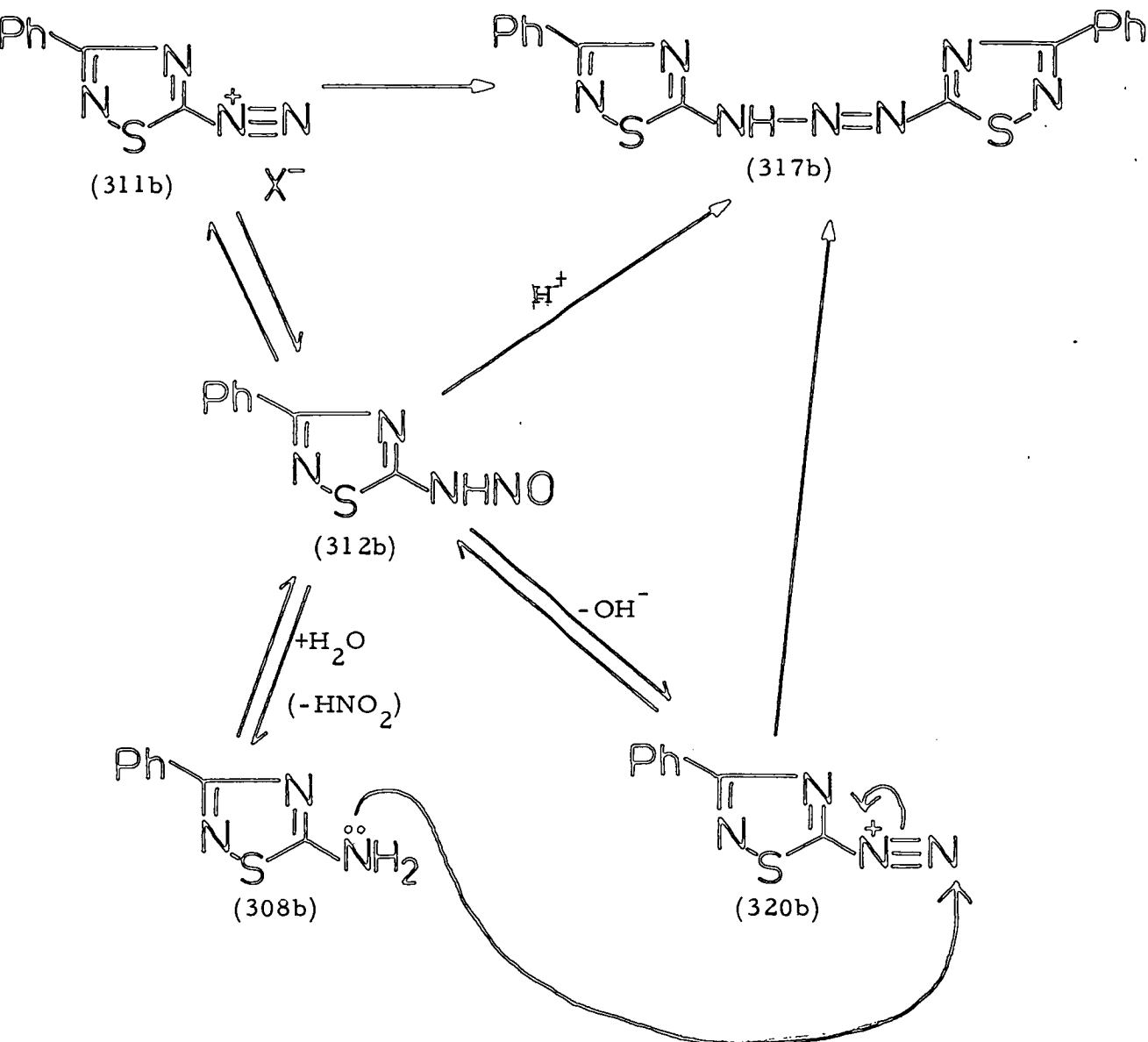
Scheme 126
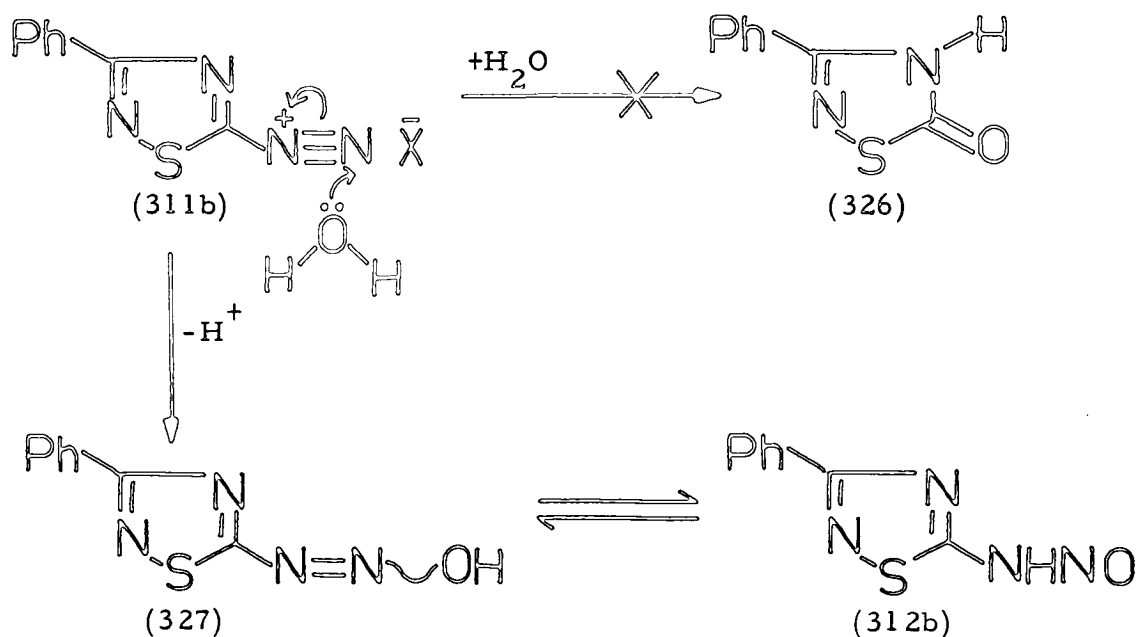
Scheme 127

with it being the known[112] triazene derivative (317b) (Scheme 126).

Furthermore its i.r. spectrum contained only one significant band,

namely an NH absorption at 3150 cm^{-1}. Goerdeler[112] obtained the

latter compound by treating a methanolic solution of the nitrosamine

(312b) with a few drops of concentrated sulphuric acid. The triazene

(317b) was also formed in good to moderate yield when a solution of

the diazonium salt (311b) in acetone was treated with potassium

thiocyanate or sodium iodide. The formation of triazenes from

nitrosamines is a known process and it is believed that the reaction

is catalysed by H$^+$ ions.[112, 164] There are several possible

mechanisms to explain this type of transformation. The most

straightforward mechanism involves equilibration of the nitrosamine

(312b) on the one hand with the amine (308b) and on the other with the

diazonium cation (320b) followed by coupling of these species to

afford the triazene (317b) (Scheme 126). However Goerdeler[112] has

cast doubt on this mechanism as the principal pathway for triazene

formation by examining the reactions of 3-substituted-1, 2, 4-thia-

diazole nitrosamines with the corresponding amines. These studies

indicate that the triazene product obtained is derived from two

molecules of nitrosamine thereby suggesting that the participation

of an amine species is less important. The exact mechanism for

the self condensation of nitrosamines to give the corresponding

triazene is not clear but the reaction must involve liberation of

nitrous acid. Stirring the diazonium salt (311b; X =BF$_4$) in water

for a short time at room temperature gave not the hoped for 1, 2, 4-

thiadiazolone (326) (Scheme 127) but a high yield of the nitrosamine

(312b). Formation of the latter compound is explicable in terms of hydration of the diazonium substituent in the salt (311b) [Scheme 127; (311b) -> (327)⇌(312b)].

Having explored the reactions of the 1,2,4-thiadiazole-5-diazonium salts (311a and b; X=BF$_4$) and found them not to be synthetically very useful, attention was turned to the nitrosamines (312a and b) as potential 5-diazo-1,2,4-thiadiazole precursors. The nitrosamines (312a and b) were readily available in moderate yield by nitrosation of the 5-amino-1,2,4-thiadiazoles (308a and b) using literature methods.[109] Attempts were made to couple 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) with acetylacetone under a variety of conditions. No reaction was observed under neutral conditions, the nitrosamine (312a) being recovered unchanged. Conversely heating the nitrosamine (312a) under reflux with acetylacetone in glacial acetic acid gave a low yield of a product which analysed for C$_9$H$_{10}$N$_4$OS. However the spectroscopic properties of this compound were not helpful in determining its structure and there was insufficient material for its further investigation. The attempted reaction of the nitrosamine (312a) with acetylacetone in the presence of hydrogen chloride was no more successful, the only product identified being 5-amino-3-methyl-1,2,4-thiadiazole (308a). Formation of this product demonstrates the reversibility of nitrosamine formation in the 5-amino-1,2,4-thiadiazole series. In contrast, phosphoric acid in acetic acid catalysed the condensation of the nitrosamine (312a) with acetylacetone giving the hydrazone (318a), albeit in low yield. The successful coupling of the nitrosamine (312a) with acetylacetone under strongly acidic conditions is consistent with the similar coupling

(312)　　　　　　　H⁺ →　　　　　　(320)

$$\underset{\text{Me}}{\overset{}{C}}\text{—OH}$$

(328)

(318)

R

a; Me

b; Ph
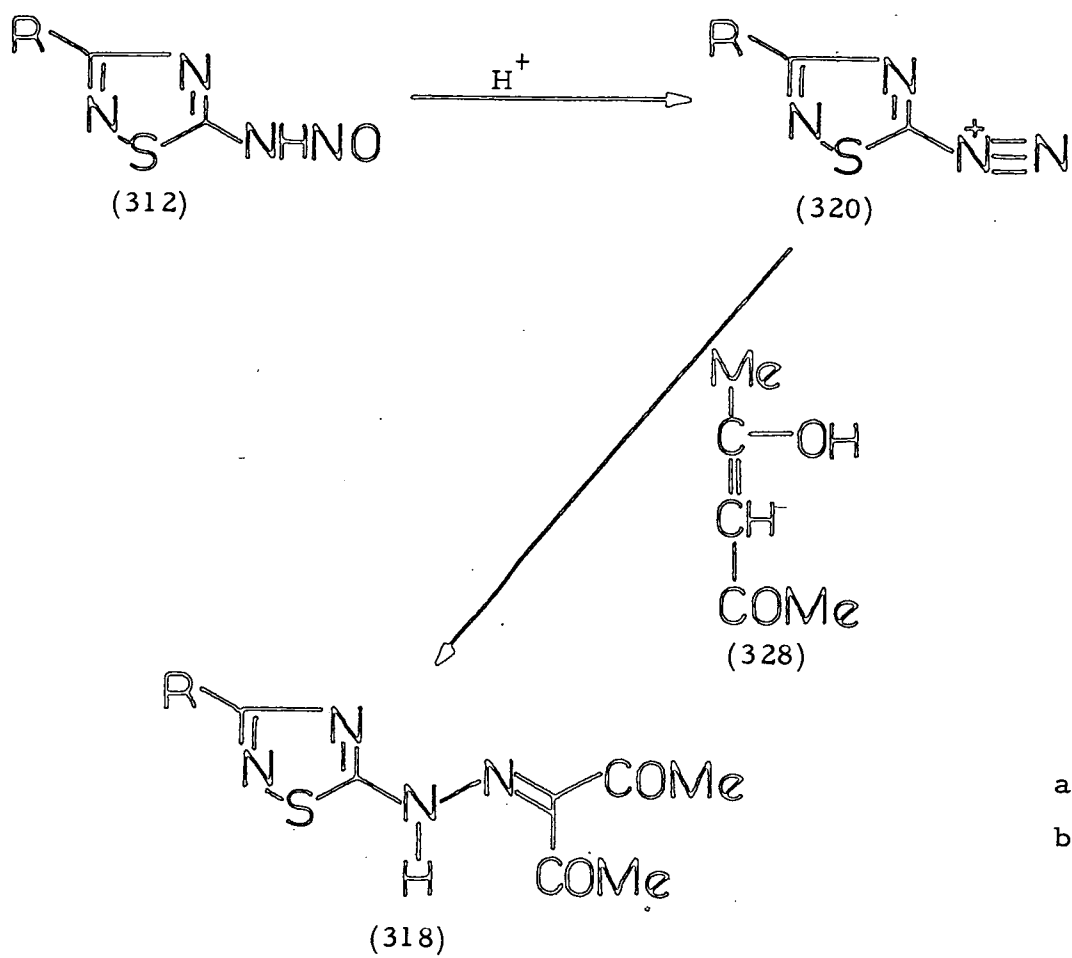
Scheme 128

reactions of 5-nitrosamino-1,2,4-thiadiazoles with phenols to give azo dyes as described by Goerdeler.[109, 167] Because of the low yield of the hydrazone (318a) obtained in the reaction of the nitrosamine (312a) with acetylacetone, similar condensations with other less active methylene compounds were not investigated. The formation of the hydrazone (318a) from the nitrosamine (312a) under acidic conditions is explicable (Scheme 128) in terms of the initial formation and subsequent coupling of 3-methyl-1,2,4-thiadiazole-5-diazonium cation (320a) with acetylacetone, the latter presumably reacting in the enol form (328). 5-Nitrosamino-3-phenyl-1,2,4-thiadiazole (312b) also reacted readily with acetylacetone in the presence of phosphoric acid giving the hydrazone (318b) (Scheme 128) in moderate yield (43%). The nitrosamine (312b) also condensed with benzoylacetone under similar conditions giving the corresponding hydrazone (319) in good yield.

Having demonstrated that 1,2,4-thiadiazole-5-diazonium salts and 5-nitrosamino-1,2,4-thiadiazoles can be successfully coupled with methylene compounds to give the expected hydrazones though only in low yield, it was decided to explore the possibility of effecting coupling reactions of this type directly from 5-amino-1,2,4-thiadiazoles. In practice the diazonium mixture from 5-amino-3-methyl-1,2,4-thiadiazole (308a) and sodium nitrite in aqueous sulphuric acid reacted readily with acetylacetone to give the hydrazone (318a), though only in low yield. Repetition of this coupling reaction using phosphoric acid as the medium gave only a marginally improved yield of the hydrazone (318a). In contrast an
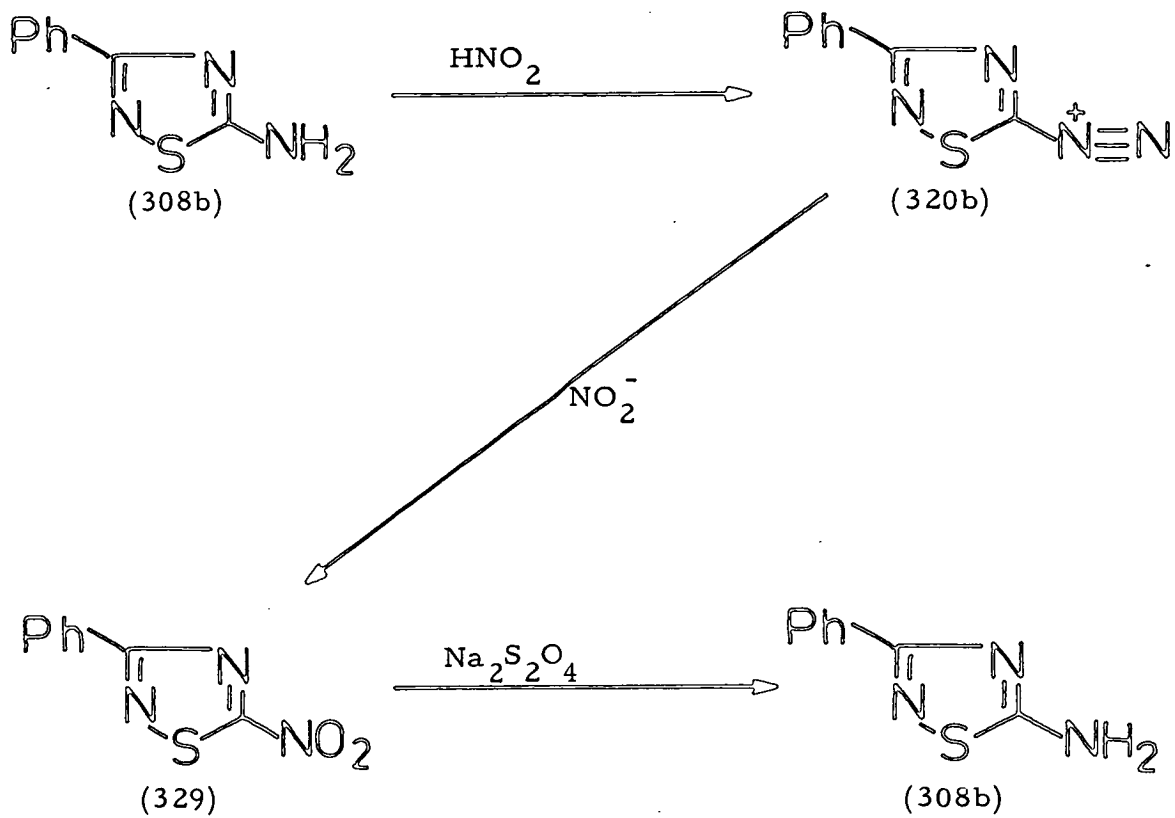
Scheme 129

attempt to repeat Goerdeler's[83] reaction by treating 5-amino-3-phenyl-1,2,4-thiadiazole (308b) with sodium nitrite in concentrated phosphoric acid followed by addition of acetylacetone did not yield the expected hydrazone (318b) but rather gave a high yield of a colourless solid which was formed in the absence of acetylacetone and gave analytical data consistent with the molecular formula $C_8H_7N_3O_3S$. This product is formulated as the hydrate of the hitherto unknown 5-nitro-3-phenyl-1,2,4-thiadiazole (329). Rather surprisingly the nitro compound (329) was stable to hydrogenation over palladium-on-charcoal but in support of the assigned structure, dithionite reduction (Scheme 129) gave 5-amino-3-phenyl-1,2,4-thiadiazole (308b) in moderate yield. Formation of the nitro compound (329) by treatment of the amine (308b) with sodium nitrite in phosphoric acid may be viewed (Scheme 129) as a nitrodediazoniation reaction of the 3-phenyl-1,2,4-thiadiazole-5-diazonium cation (320b) resulting from the excess of nitrite ion present and despite the subsequent addition of sulphamic acid to scavenge it. It is interesting that Goerdeler[83] despite using very similar conditions for diazotisation did not report this product.

3-Amino-1,2,4-thiadiazoles

3-Amino-1,2,4-thiadiazoles have been much less studied than 5-amino-1,2,4-thiadiazoles. 3-Amino-1,2,4-thiadiazoles are much weaker bases than the 5-amino isomers, although they still exhibit typical amine reactions such as acetylation.[164] 3-Amino-1,2,4-thiadiazoles have been successfully diazotised in concentrated

Scheme 130

($\underline{X}$=halogen, CN, SCN, NO$_2$)

Scheme 131
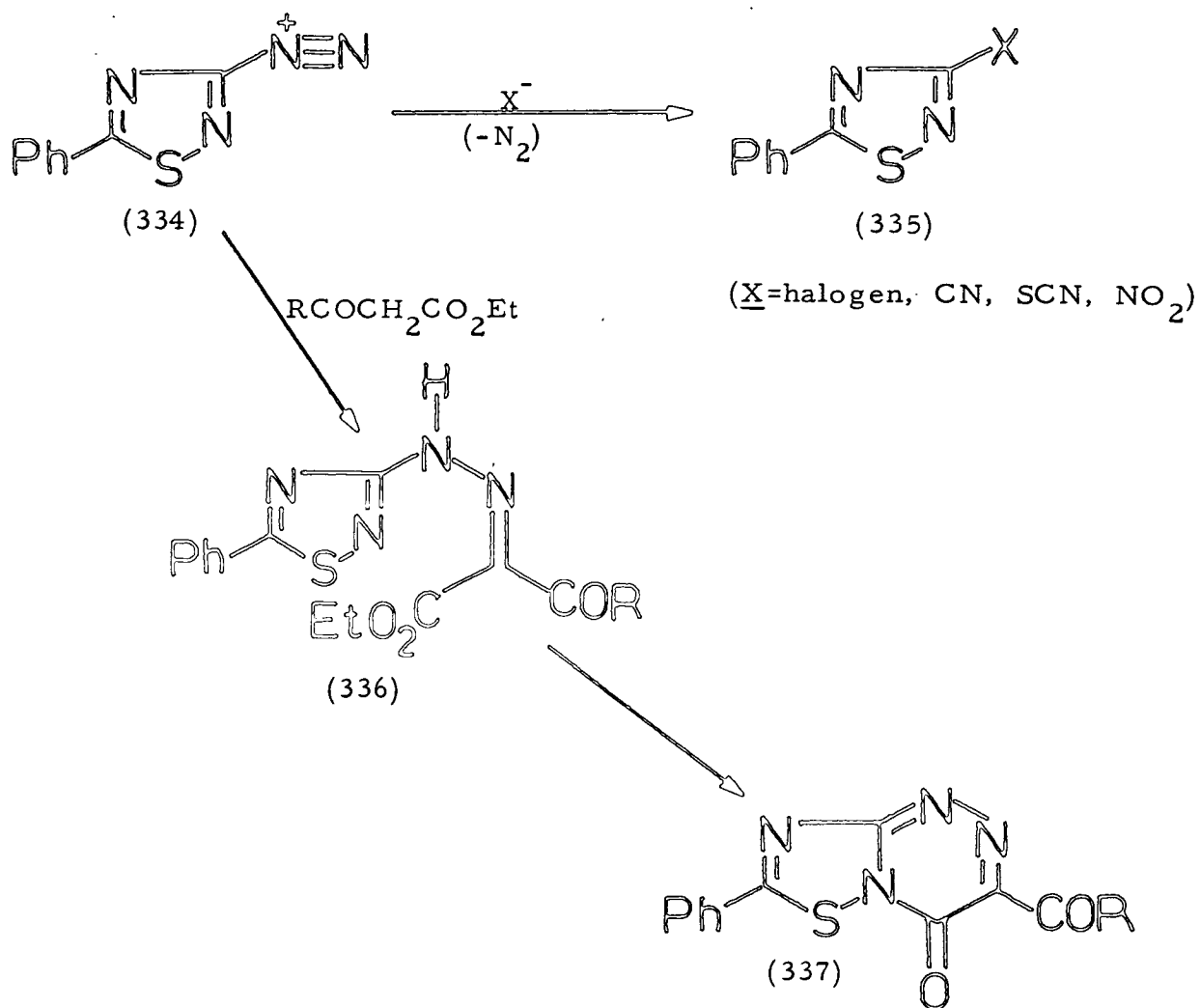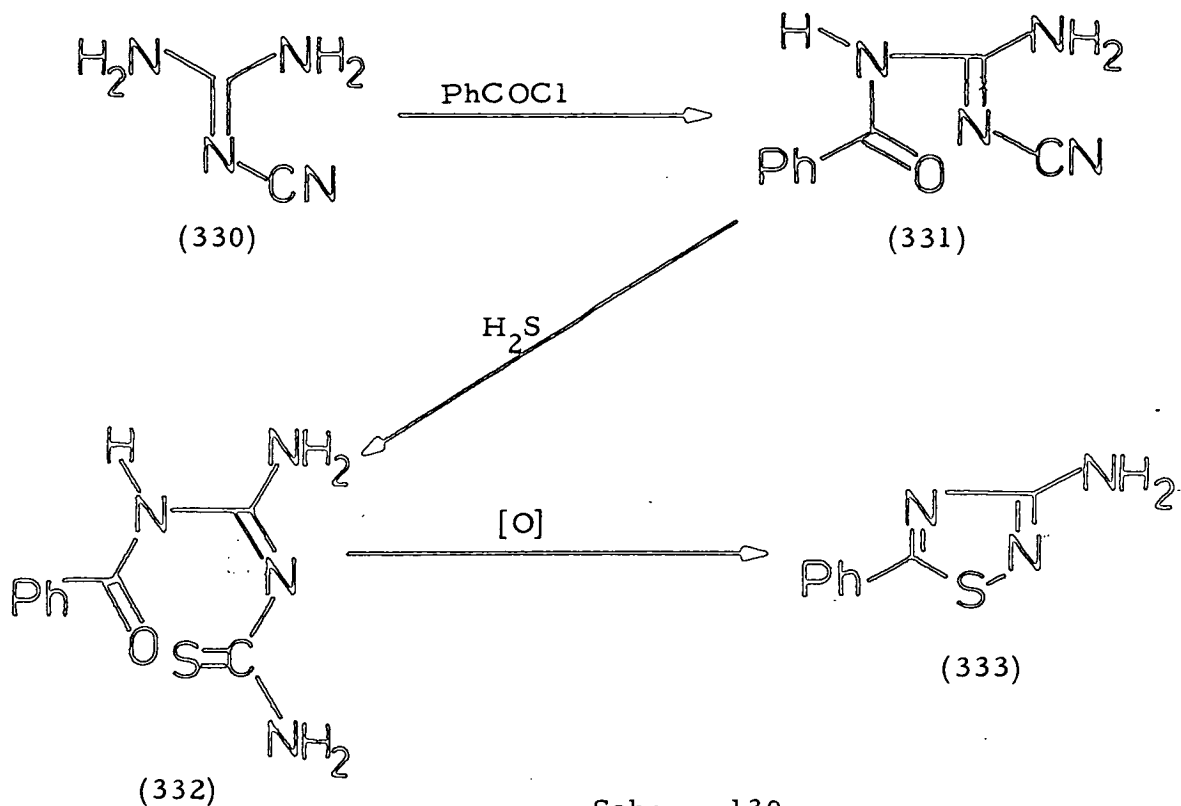
phosphoric acid using sodium nitrite, and the diazonium mixtures coupled with activated aromatic molecules.[167] Successful halogeno-dediazoniation reactions of 1, 2, 4-thiadiazole-3-diazonium salts have also been described by Goerdeler.[110] However stable 1, 2, 4-thiadiazole-3-diazonium salts and 3-nitrosamino-1, 2, 4-thiadiazoles do not appear to have been described in the literature.

3-Amino-1, 2, 4-thiadiazoles were studied in order to compare the reactivity of their diazonium salts with those derived from 5-amino-1, 2, 4-thiadiazoles. 3-Amino-5-phenyl-1, 2, 4-thiadiazole (333) (Scheme 130) was chosen for study because it was readily synthesised and because it was anticipated that the presence of the hydrophobic phenyl group would aid the recovery of products from aqueous media. It was proposed to investigate the dediazoniation reactions of the 5-phenyl-1, 2, 4-thiadiazole-3-diazonium cation [Scheme 131; (334) -> (335)] and also its coupling reactions with active methylene compounds to afford hydrazones potentially capable of cyclisation to novel fused heterocycles [Scheme 131; (334) -> (336) -> (337)]. 3-Amino-5-phenyl-1, 2, 4-thiadiazole (333) was readily synthesised in three steps (Scheme 130), involving benzoylation[168] of dicyandiamide (330) to give the product (331), followed by conversion with hydrogen sulphide into benzoylguanyl-thiourea (332),[168] and subsequent oxidative cyclisation of the latter to the amine (333).[169] The melting-point of the benzoyl derivative (331) was found to be substantially higher than that reported in the literature[168] but this may be accounted for by the presence of contaminating potassium chloride which was difficult to remove from

(338)

(339)

(340)

(341)
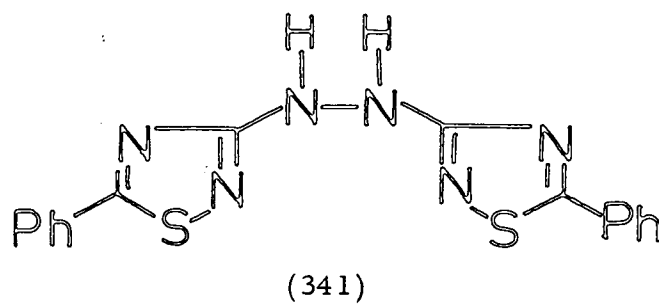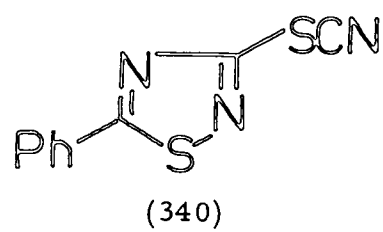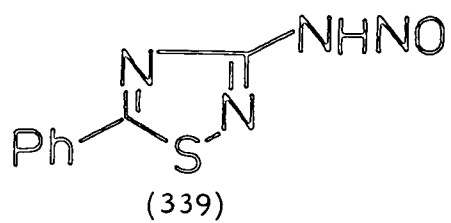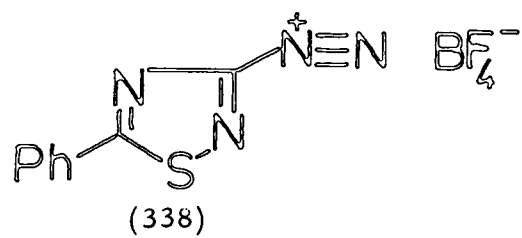
Scheme 132

the product (331) but which did not affect its subsequent conversion into (332).

Initially an attempt was made to prepare and isolate 5-phenyl-1,2,4-thiadiazole-3-diazonium fluoroborate (338) (Scheme 132). Thus, a solution of the amine (333) in aqueous hydrofluoroboric acid was treated with sodium nitrite. However this reaction gave no identifiable material. Attempts to synthesise 3-nitrosamino-5-phenyl-1,2,4-thiadiazole (339) (Scheme 132) as a potential "diazonium precursor" were equally unsuccessful. For example, treatment of a suspension of the amine (333) in aqueous hydrochloric acid or sulphuric acid with sodium nitrite under conditions suitable for the preparation of other heterocyclic nitrosamines[108,109] gave only unreacted amine (333). Conversely the attempted nitrosation of the amine (333) using sodium nitrite in formic acid[109] gave only an intractable gum from which no identifiable material could be isolated. Goerdeler[109] has rationalised the instability of 3-nitrosamino-1,2,4-thiadiazoles compared with the 5-nitrosamino analogues as being due to fewer contributing canonical forms (see Introduction, Chapter 1, page 26).

Attempts to synthesise the diazonium fluoroborate (338) and the nitrosamine (339) having failed, attention was turned to the study of in situ reactions of the 5-phenyl-1,2,4-thiadiazole-3-diazonium cation (334). However treatment of the diazonium mixture[167] from the amine and sodium nitrite in phosphoric acid with potassium thio-cyanate gave not the thiocyanato-1,2,4-thiadiazole (340) (Scheme 132) but rather a product which analysed for $C_{16}H_{12}N_6S_2$ and showed an i.r. spectrum consistent with the hydrazine structure (341) (Scheme
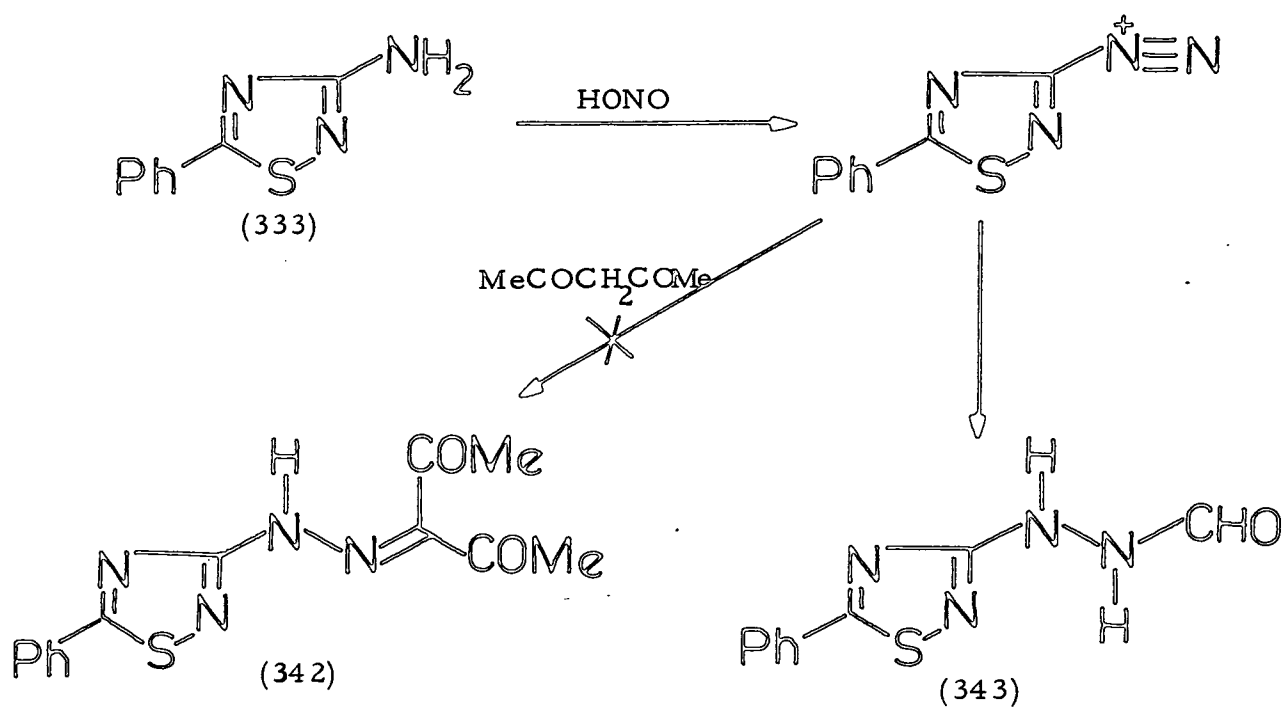
Scheme 133

132). In the absence of any firm evidence this structure must remain tentative, and a mechanism for its formation under non-reducing conditions is difficult to envisage. On the other hand, as discussed in Chapter 6, the diazonium mixture from the amine (333) and sodium nitrite in phosphoric acid, behaves orthodoxly in reacting with sodium azide to give 3-azido-5-phenyl-1, 2, 4-thia-diazole. The attempted coupling of the diazonium mixture from the amine (333) and sodium nitrite in phosphoric acid, with acetylacetone gave not the anticipated hydrazone (342) (Scheme 133) but rather a low yield of a colourless product which analysed correctly for $C_9H_8N_4OS$. The i.r. spectrum of this product contained NH absorption at 3380 cm^{-1} and carbonyl absorption at 1680 cm^{-1} attributable to an aldehyde group the presence of which was further substantiated by a one proton singlet at $\delta 10.3$ in its ^1H n.m.r. spectrum. These spectroscopic features together with the analytical data permit the tentative assignment of the formyl-hydrazine structure (343) to the product. However, the mode of formation of such a product under the reaction conditions used is not clear and further work will be needed to substantiate the structure (343).

(B) Amino-1, 3, 4-thiadiazoles

1, 3, 4-Thiadiazoles are the best known class of thiadiazoles and the reactions of amino-1, 3, 4-thiadiazoles including diazotisation have been particularly well studied. The amino-1, 3, 4-thiadiazoles are weak bases but are sufficiently nucleophilic to be readily
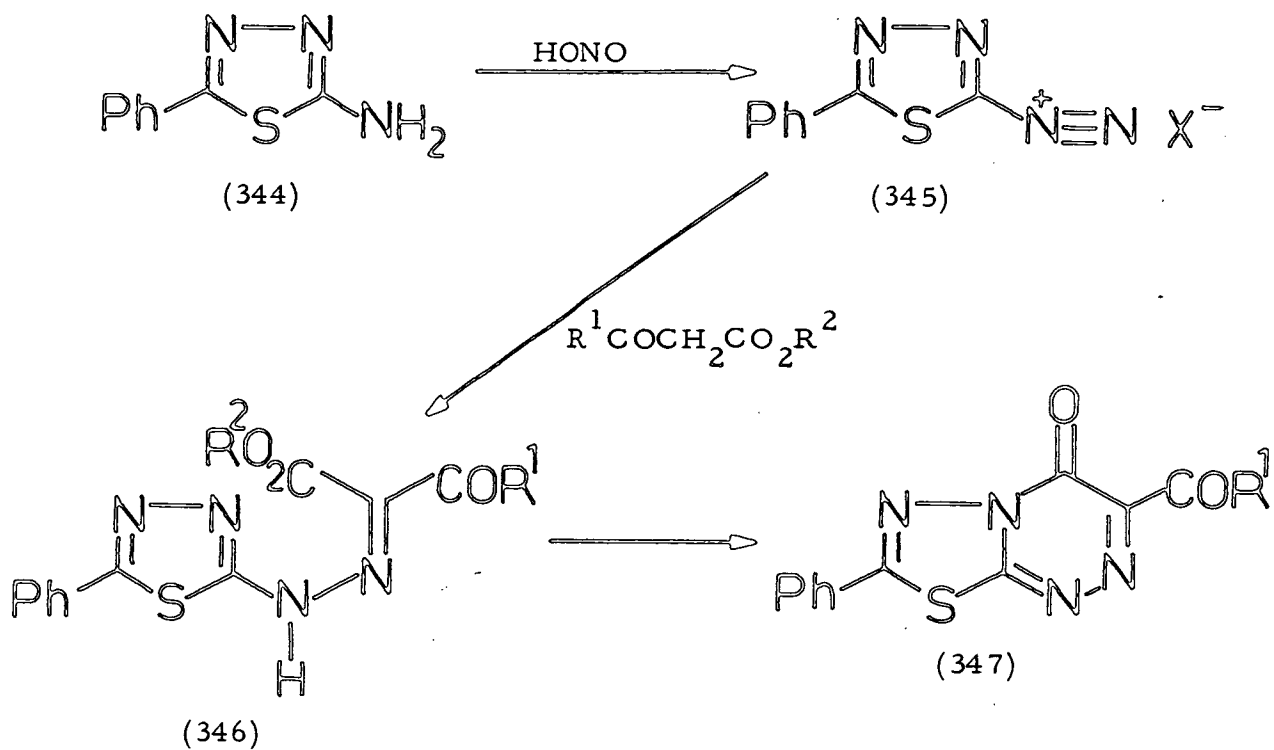
Scheme 134
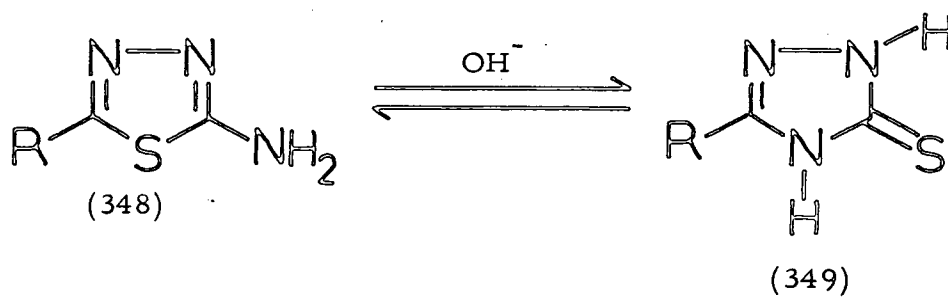
Scheme 135

acylated by acid chlorides and to react with aromatic aldehydes to form Schiff Bases.[170] Amino-1,3,4-thiadiazoles are readily diazotised in sufficiently acidic solutions to afford reactive diazonium salts[161] which have been shown[161] to couple readily _in situ_, even with weakly nucleophilic hydrocarbons such as m-xylene and mesitylene giving the corresponding azo-compounds in high yield.[83] Goerdeler and Kanaoka[162,163] have also succeeded in performing halogenodediazoniation reactions with 1,3,4-thiadiazolediazonium salts.   The nitrosation of amino-1,3,4-thiadiazoles in dilute (as opposed to concentrated) acidic solution results in the formation of stable nitrosamines whose chemistry has been the subject of studies by Butler.[108]

The diazotisation of amino-1,3,4-thiadiazoles was of interest in the present studies for several reasons: firstly, by way of comparison with the behaviour towards diazotisation of 5-amino and 3-amino-1,2,4-thiadiazoles discussed previously; secondly, in connection with the preparation of isolable 1,3,4-thiadiazole-diazonium salts (345) (Scheme 134) whose chemical reactivity could then be investigated under controlled conditions; and thirdly, with a view to the development of coupling reactions with active methylene compounds leading to hydrazones (346) (Scheme 134) suitable for cyclisation to novel fused 1,3,4-thiadiazoles (347).   2-Amino-5-phenyl-1,3,4-thiadiazole (344) was chosen for study for two reasons. Firstly it could be readily synthesised and secondly although amino-1,3,4-thiadiazoles (348) (Scheme 135) are known to rearrange to 1,2,4-triazole-3-thiones (349) (Scheme 135) under basic conditions,

PhCOCl

$+$

$H_2N-NH-\underset{\underset{S}{\|}}{C}-NH_2$

$\longrightarrow$

$\underset{O}{Ph-\underset{\|}{C}}-\underset{\underset{H}{|}}{N}-\underset{\underset{H}{|}}{N}-\underset{\underset{S}{\|}}{C}-NH_2$

(350)

H_3PO_4

Ph$-\underset{S}{\underset{N-N}{\overset{\diagup\diagdown}{}}}-NH_2$

(344)

Scheme 136

Me

$-N(C_2H_4-OAc)_2$

(351)

Ph$-\underset{S}{\underset{N-N}{\overset{\diagup\diagdown}{}}}-NHNO$

(352)

$\xrightarrow{\quad\times\quad}$

Ph$-\underset{S}{\underset{N-N}{\overset{\diagup\diagdown}{}}}-\overset{+}{N}\equiv N \ \bar{X}$

(345)
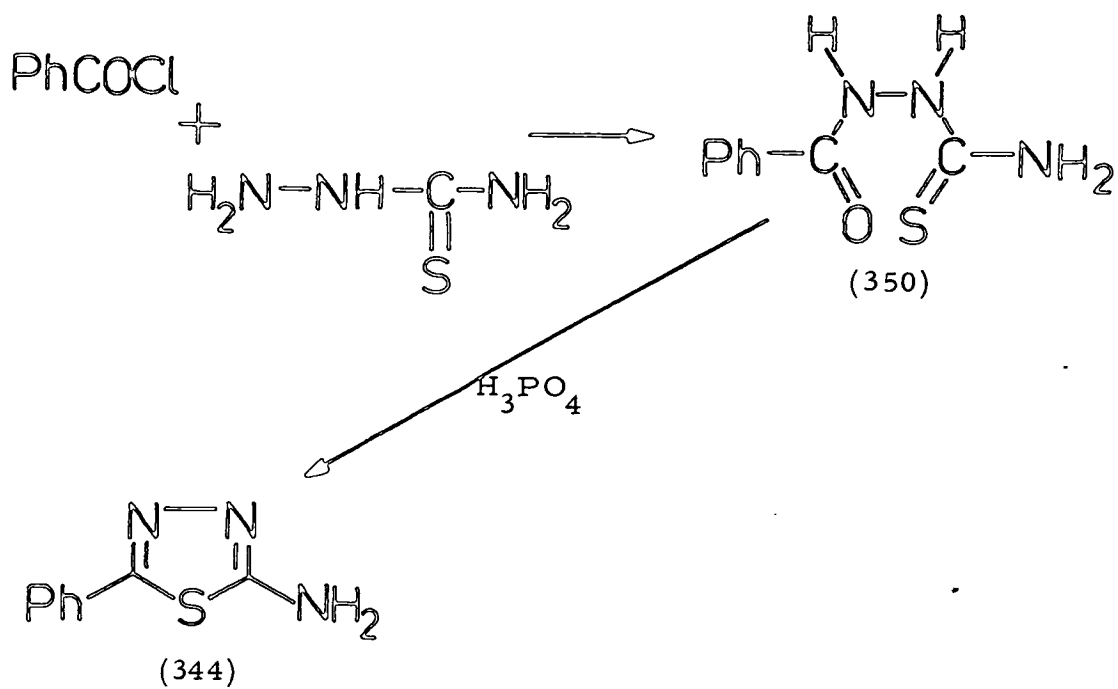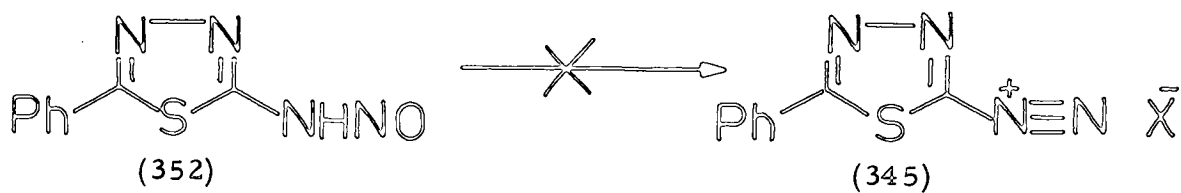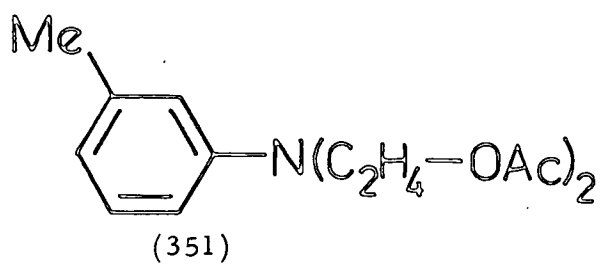
Scheme 137

the 5-phenyl analogue is stable to rearrangement of this type.[170]

2-Amino-5-phenyl-1,3,4-thiadiazole (344) was synthesised in two steps by the method of Hoggarth (Scheme 136)[171] involving benzoylation of thiosemicarbazide followed by phosphoric acid catalysed cyclisation of the benzoylthiosemicarbazide (350) produced.

Two established methods were employed in an attempt to prepare and isolate the diazonium fluoroborate (345; $X=BF_4$). Diazotisation of the amine (344) in aqueous hydrofluoroboric acid with sodium nitrite gave an intractable brown product with a melting point greater than 300°. Since this solid gave a negative test with N, N-bis-(β-acetoxyethyl)-m-toluidine (351) (Scheme 137) it can be safely assumed that it contained neither the sought for diazonium salt (345) nor the related nitrosamine (352). Diazotisation of the amine (344) in concentrated phosphoric acid using sodium nitrite, followed by treatment of the diazonium mixture with hydrofluoroboric acid gave a moderate yield of an orange solid which melted at $62-63^o$ with violent decomposition. This melting-point behaviour is similar to that of the nitrosamine (352) (Scheme 137) (see later). However, though the orange solid showed similar i.r. absorption to the nitrosamine (352) it differed from the latter in failing to couple with N, N-bis-(β-acetoxyethyl)-m-toluidine to give an azo dyestuff. Unfortunately attempts to purify the orange product resulted in its decomposition to an intractable high molecular weight solid, thus preventing its further characterisation.

Since attempts to prepare the diazonium fluoroborate (345; $X=BF_4$) directly were unsuccessful, it was decided to investigate
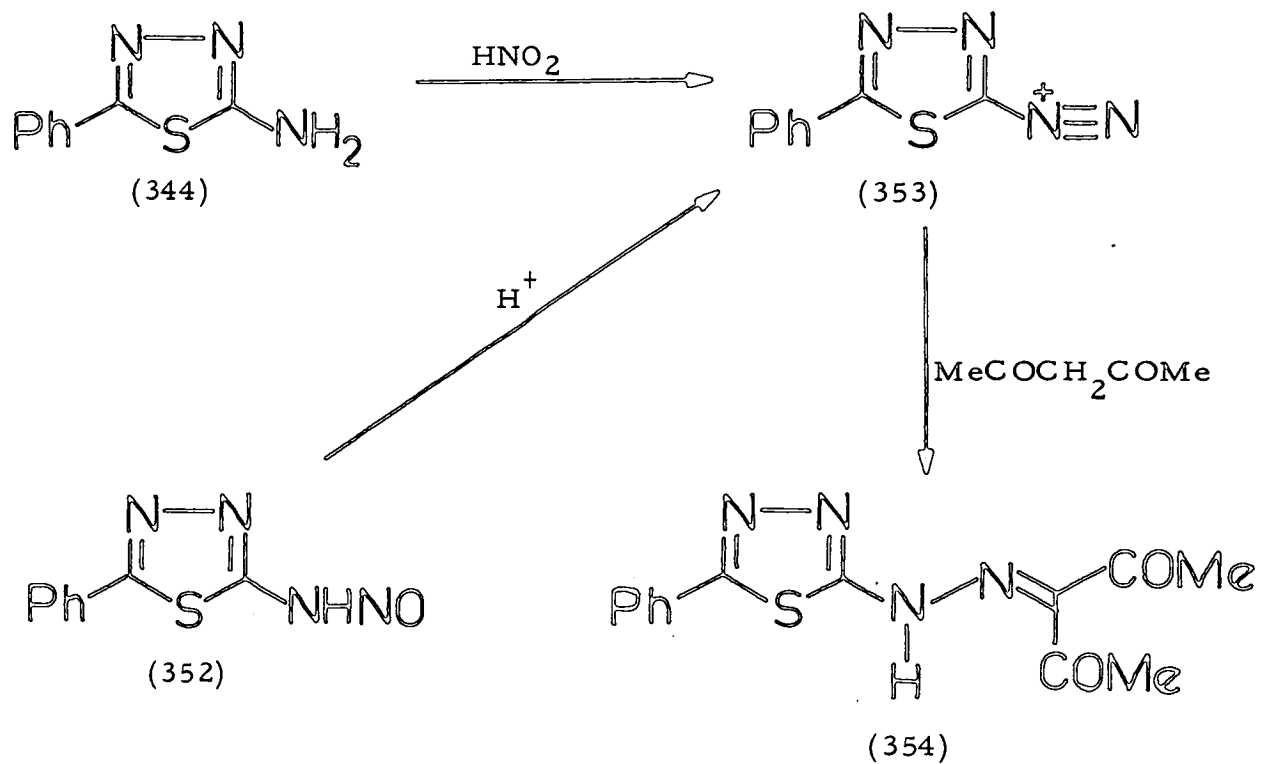
Scheme 138

the known[108] nitrosamine (352) (Scheme 137) as a possible precursor

of diazonium salts of the type (345).   2-Nitrosamino-5-phenyl-1,3,4-

thiadiazole (352) was prepared in high yield by the method of Butler.[108]

The melting point of the product (352) obtained in the present studies

was 91-93° as opposed to 104° as recorded by Butler.[108]   However

the enhanced thermal instability of the nitrosamine (352) precluded

any attempt to purify it.   The attempted conversion of the nitrosamine

(352), using hydrogen chloride in acetic acid and methanol, into the

diazonium chloride (345; X=Cl) led to an unidentified yellow solid

(F) which gave elemental analysis consistent with the formula

$C_{14}H_{12}N_6O_3S_2$.   However the spectroscopic properties of the

yellow solid were unhelpful in assigning its structure.   The reaction

of the nitrosamine (352) with boron trifluoride-etherate complex in

an attempt to prepare the diazonium fluoroborate (345; X=BF$_4$) gave

only a good recovery of the nitrosamine (352).

Since isolable salts of the 5-phenyl-1,3,4-thiadiazole-2-

diazonium cation (353) could not be obtained from the amine (344) or

the nitrosamine (352) attention was turned to the generation and

study of the diazonium cation (353) (Scheme 138) in situ.   As discovered

for other five-membered heterocyclic amines (see before), 2-amino-

5-phenyl-1,3,4-thiadiazole was found to be readily diazotised using

two equivalents of sodium nitrite in concentrated phosphoric acid.

The presence of the 5-phenyl-1,3,4-thiadiazole-2-diazonium cation

(353) in the resulting mixture was readily demonstrated by its

reaction with sodium azide to give 2-azido-5-phenyl-1,3,4-thia-

diazole (see Chapter 6).   The diazonium mixture from the amine

(344) also coupled readily with acetylacetone giving the expected hydrazone (354) (Scheme 138) in moderate yield. The identity of the hydrazone (354) was established by the presence of NH and carbonyl absorption in its i.r. spectrum and by the presence of signals due to two methyl groups in its ^{1}H n.m.r. spectrum. Surprisingly, the attempted extension of such coupling reactions to other active methylene compounds (benzoylacetone, ethyl benzoylacetate) gave gums, further work up of which afforded no identifiable material.

Since the diazotisation of 2-amino-5-phenyl-1,3,4-thiadiazole (344) and the subsequent in situ coupling of the 5-phenyl-1,3,4-thiadiazole-2-diazonium cation (353) with active methylene compounds (acetylacetone apart) had been unsuccessful attention was next directed to the nitrosamine (352) as a possible coupling partner for active methylene compounds. However the attempted condensation of the nitrosamine (352) with acetylacetone under essentially neutral conditions gave not the hydrazone (354) but rather the unidentified solid (F) obtained before. In contrast to its behaviour under neutral conditions, the nitrosamine (352) condensed with acetylacetone in phosphoric acid giving the hydrazone (354) albeit in only 28% yield. The successful coupling under acidic conditions can be attributed to preliminary equilibration of the nitrosamine (352) with the diazonium cation (353) followed by coupling with the enol form of acetylacetone (Scheme 138). Because of the low yield of the hydrazone (354) obtained from the nitrosamine (352) and acetylacetone under acidic conditions, the extension of such condensation reactions to other active methylene compounds was not investigated.

Experimental

A.   1, 2, 4 - Thiadiazoles

Synthesis of 5-Amino-1, 2, 4-thiadiazoles (308).

(a) 5-Amino-3-methyl-1, 2, 4-thiadiazole (308a) was prepared by the method of Goerdeler[165] from acetamidine hydrochloride and potassium thiocyanate in 36% yield, m. p. 193-194° (lit.,[165] 198-200°).

(b) 5-Amino-3-phenyl-1, 2, 4-thiadiazole (308b) was prepared by the method of Goerdeler[165] from benzamidine hydrochloride and potassium thiocyanate in 49% yield, m. p. 149-152° (lit.,[165] 155°).

The Attempted Conversion of 5-Amino-3-methyl-1, 2, 4-thiadiazole (308a) into 3-Methyl-1, 2, 4-thiadiazole-5-diazonium chloride (311a; X=Cl).

A solution of 5-amino-3-methyl-1, 2, 4-thiadiazole (308a) (1. 15 g; 0. 01 mol) in Analar methanol (30. 0 ml) was saturated at 0° with hydrogen chloride, treated dropwise with stirring with amyl nitrite (1. 12 g; 0. 011 mol) at 0° and stirred for 1. 5 h at 0°. The mixture was evaporated to give the unreacted amine (308a) as the hydrochloride which was dissolved in water, neutralised with sodium acetate and extracted with methylene chloride to give the starting amine (308a) as a colourless solid, m. p. 185-187°, identical (i. r. spectrum) with an authentic sample.

The Attempted Conversion of 5-Amino-3-methyl-1, 2, 4-thiadiazole (308a) into 3-Methyl-1, 2, 4-thiadiazole-5-diazonium Fluoroborate (311a; X=BF$_4$)

A solution of 5-amino-3-methyl-1, 2, 4-thiadiazole (308a) (1. 15 g; 0. 01 mol) in 40% aqueous hydrofluoroboric acid (10. 0 ml) was stirred and treated dropwise at 0° with a solution of sodium nitrite (4. 98 g; 0. 072 mol) in water (30. 0 ml). The resulting suspension was stirred for 10 min at 0° and then for 10 min at room temperature to afford a pink solid (0. 95 g; 66%), m. p. 72° (violent decomposition), identical (i. r. spectrum) with a sample of 3-methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a) prepared later.

The aqueous mother liquor on standing precipitated an unidentified orange solid (0. 33 g) m. p. 185-190°, which decomposed on attempted crystallisation.

3-Methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a).

3-Methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a) was prepared (yield 65%) by nitrosating 5-amino-3-methyl-1, 2, 4-thiadiazole (308a) according to the method of Goerdeler[109] and had m. p. 80° (violent decomposition) (lit.,[109] 114-120°).

The Attempted Conversion of 5-Amino-3-phenyl-1, 2, 4-thiadiazole (308b) into 3-Phenyl-1, 2, 4-thiadiazole-5-diazonium Fluoroborate (311b; $X=BF_4$)

A suspension of 5-amino-3-phenyl-1, 2, 4-thiadiazole (308b) (0. 35 g; 0. 002 mol) in aqueous 40% hydrofluoroboric acid (5. 0 ml) was stirred and treated dropwise at 0° with a solution of sodium nitrite (1. 0 g; 0. 014 mol) in water (6. 0 ml). The resulting frothy yellow suspension was stirred for 15 min at 0° then 30 min at room temperature. Filtration of the mixture gave a yellow solid (0. 64 g),

mp. 95° (violent decomposition), which was washed with water to afford 5-nitrosamino-3-phenyl-1, 2, 4-thiadiazole (312b) (quantitative), m.p. 120° (violent decomposition), identical (i. r. spectrum) with a sample prepared later.

5-Nitrosamino-3-phenyl-1, 2, 4-thiadiazole (312b).

The nitrosamine (312b) was prepared (yield quantitative) by nitrosating 5-amino-3-phenyl-1, 2, 4-thiadiazole (308b) according to the method of Goerdeler,[109] m.p. 126-128° (lit.,[109] 180°), M$^+$206, $C_8H_6N_4OS$ requires M, 206.

The Reaction of 3-Methyl-5-nitrosamino-1, 2, 4-thiadiazole (312a) with Hydrogen Chloride.

(a) A solution of the nitrosamine (312a) (0. 29 g; 0. 002 mol) in Analar methanol (10. 0 ml) was saturated at 0° with hydrogen chloride. The flask was sealed, the contents were allowed to reach room temperature, filtered to remove some insoluble material and evaporated to give a pale yellow gum. The gum was treated with water, neutralised with solid sodium acetate and extracted with methylene chloride (3x10 ml) to yield a pale yellow solid, which was crystallised from toluene to give an unidentified compound (B) as yellow needles (0. 10 g; 36%), m.p. 155-158°, ν_{max} 3280 and 3140 (NH), 1695, 1670, and 1645 (NH def.) cm^{-1}, $\delta(CDCl_3)$ 2. 40 (s, Me) and 2. 32 (s, Me).

Found: C, 31.1; H, 4.0; N, 35.5%; M$^+$115.

$C_3H_5N_3S$ requires: C, 31.3; H, 4.3; N, 36.5%; M, 115.

(b) A solution of the nitrosamine (312a) (1.16 g; 0.008 mol) in Analar methanol (40.0 ml) was saturated with hydrogen chloride at 0°. The flask was sealed, the contents were allowed to reach room temperature, then evaporated and treated with water (3.0 ml). The mixture was filtered to remove some insoluble material, neutralised with sodium acetate and extracted with methylene chloride (2x15 ml) to give a yellow solid which was crystallised from toluene-light petroleum to afford an unidentified compound (C) as pale yellow crystals (0.52 g; 56%), m.p. 87-89°, ν_{max} 3420 m (NH) and 1670 (CO) cm^{-1}, δ(CDCl$_3$) 2.40 (s, Me) and 2.32 (s, Me).

Found: C, 30.9; H, 3.5; N, 25.7%; M$^+$ 116.

C$_3$H$_4$N$_2$OS requires: C, 31.0; H, 3.5; N, 24.1%; M, 116.

The Attempted Reaction of 5-Amino-3-methyl-1,2,4-thiadiazole (308a) with Hydrogen Chloride.

A solution of the amine (308a) (0.24 g; 0.002 mol) in Analar methanol (10.0 ml) was saturated with hydrogen chloride at 0°. The reaction mixture was allowed to reach room temperature, treated with water (3.0 ml), concentrated, neutralised with sodium acetate and extracted with methylene chloride (2x15 ml) to afford the starting amine (308a) as a colourless solid (0.09 g; 38%), m.p. 192-194°, identical (m.p. and i.r. spectrum) with an authentic sample.

The Acetylation of Compound (B)

The compound (B) (0.40 g; 0.0035 mol) was dissolved with warming in acetic anhydride (0.9 ml) and the solution was heated on a boiling water-bath for 20 min. The mixture was treated with water

and extracted with methylene chloride (2x10 ml) to give a pink solid

which was crystallised from toluene to yield the acetyl derivative (D)

as colourless crystals (0. 33 g; 60%), m. p. 113-116°, ν_{max} 3150 m

(NH) and 1700 and 1665 (CO) cm^{-1}, δ (CDCl$_3$) 2. 56 (s, Me), 2. 37 (s,

Me), and 2. 34 (s, Me).

Found: C, 37.4; H, 4. 2; N, 25. 9%; M$^+$ 157

C$_5$H$_7$N$_3$OS requires: C, 38. 2; H, 4. 5; N, 26. 7%; M, 157.

Mixed   m. p. with authentic 5-acetamido-3-methyl-1, 2, 4-thiadiazole

(314) 115-125°.

5-Acetamido-3-methyl-1, 2, 4-thiadiazole (314).

5-Amino-3-methyl-1, 2, 4-thiadiazole (308a) (0 35 g; 0. 003 mol)

was dissolved with warming in acetic anhydride (1. 8 ml) and the

solution was heated on a boiling water bath for 20 min.   The mixture

was treated with water (2. 0 ml) and extracted with methylene chloride

(2x20 ml) to afford a pale yellow solid which was crystallised from

toluene-light petroleum to give 5-acetamido-3-methyl-1, 2, 4-thia-

diazole (314) as a colourless solid (0. 38 g; 80%), m. p. 156-157°,

ν_{max} 3150 m (NH) and 1655 (CO) cm^{-1}, δ (CDCl$_3$) 2. 56 (3H, s, Me)

and 2. 35 (3H, s, Me).

Found: C, 38. 0; H, 4. 4; H, 26. 3%; M$^+$, 157.

C$_5$H$_7$N$_3$OS requires: C, 38. 2; H, 4. 5; N, 26. 7%; M, 157.

Mixed m. p. with acetyl derivative (D) 115-125°.

The Reaction of Compound (B) with Hydrochloric Acid.

A solution of the compound (B) (0. 23 g; 0. 002 mol) in aqueous

2M hydrochloric acid (2. 5 ml) was heated on a steam bath for 30 min

then extracted with methylene chloride to give an unidentified yellow

solid (0.02 g), m.p. 114-117°, ν_{max} 3050 br and 2720 br (OH/NH)

and 1715 and 1670 (CO) cm^{-1}, M^{+} 256.

The aqueous layer was neutralised with sodium acetate and

extracted with methylene chloride (2x10 ml) to give 5-amino-3-methyl-

1,2,4-thiadiazole (308a) as a colourless solid (0.05 g; 22%), m.p.

165-168°, identical (i..r. spectrum) with an authentic sample.

Nitrosation of Compound (B)

A solution of the compound (B) (0.23 g; 0.002 mol) in aqueous

2M sulphuric acid (1.0 ml) was stirred and treated at 0° with a solution

of sodium nitrite (0.16 g; 0.0023 mol) in water (1.0 ml).   The

resulting yellow suspension was stirred at 0° for 20 min and the

solid was collected to afford 3-methyl-5-nitrosamino-1,2,4-thia-

diazole (312a) as a pale yellow solid (0.03 g; 10%), m.p. 55° (violent

decomposition), identical (i.r. spectrum) with a sample prepared

previously.

The aqueous mother liquor was extracted with methylene chloride

(2x10 ml) to give an unidentified yellow solid which was combined with

a second crop obtained by neutralising the aqueous layer with sodium

acetate and extracting with methylene chloride total (0.12 g), m.p.

95-97°, ν_{max} 3060 br and 2740 br (NH, OH) and 1690 (CO) cm^{-1}.

<u>Found:</u> M^{+}, 116.

C$_{3}$H$_{4}$N$_{4}$OS requires: M, 116.

The Attempted Preparation of 3-Methyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311a; X=BF$_4$) from 3-Methyl-5-nitrosamino-1,2,4-thiadiazole (312a).

A suspension of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) (1.44 g; 0.01 mol) in dry ether (10.0 ml) was treated at 0° with boron trifluoride-etherate complex (2.88 g; 0.02 mol) and the solution was stirred for 20 min, treated with dry ether (140 ml) and stirred for 2 h at 0°. The mixture was filtered to give an unidentified gummy deliquescent solid (E) and a mother liquor which was concentrated to give a brown oil. The oil gradually crystallised to give an unidentified yellow solid (0.37 g), m.p. 154-156° (gas evolution), ν_{max} 2260 w (N≡N) cm^{-1}, which was recrystallised from toluene-ethyl acetate to give an unidentified yellow solid, m.p. 224-226°, ν_{max} 3200 br cm^{-1}.

Found:　　C, 27.9; H, 3.2; N, 36.0%; M$^+$241.

$C_9H_{13}N_{10}O_2S_3$ requires: C, 27.8; H, 3.3; N, 36.0%; M, 389.

$C_6H_7N_7S_2$ requires:　　C, 29.9; H, 2.9; N, 40.7%; M, 241.

The Reaction of 5-Nitrosamino-3-phenyl-1,2,4-thiadiazole (312b) with Hydrogen Chloride.

A suspension of the nitrosamine (312b) (1.65 g; 0.008 mol) in a mixture of methanol (50.0 ml) and acetic acid (20.0 ml) was saturated at 0° with hydrogen chloride. The resulting solution was allowed to return to room temperature, treated with water (3.0 ml) and concentrated to give a yellow solid (1.18 g; 83%), m.p. 133-136° (from benzene=ethanol), identical (i.r. spectrum) with an authentic

sample of 5-amino-3-phenyl-1,2,4-thiadiazole (308b).

The Preparation of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) from 5-Nitrosamino-3-phenyl-1,2,4-Thiadiazole (312b).

The diazonium salt (311b; X=BF$_4$) was prepared (yield 64%) by the method of Goerdeler[110] from 5-nitrosamino-3-phenyl-1,2,4-thiadiazole (312b), m.p. 116° (decomp.) (lit.,[110] 212°), ν_{max} 3140 w (NH) and 2300 m (N≡N) cm^{-1}.

The Attempted Reaction of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) with Cyanide Ion.

A solution of the diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetone (30.0 ml) was stirred and treated at room temperature with a solution of potassium cyanide (0.13 g; 0.002 mol) in water (5.0 ml) and the mixture was stirred for 45 min. The green solid which separated was crystallised from ethanol-water to afford the triazene (317b) (0.36 g; 78%), m.p. 224-229° [lit.,[112] 225° (decomp.)], ν_{max} 3150 w (NH) cm^{-1}.

Found: C, 52.3; H, 3.1; N, 24.7%; M,$^+$ 365.
Calc. for C$_{16}$H$_{11}$N$_7$S$_2$: C, 52.6; H, 3.0; N, 26.8%; M, 365.

The Attempted Reaction of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) with Thiocyanate Ion.

A solution of the diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetone (30.0 ml) was stirred and treated with potassium thiocyanate (0.19 g; 0.002 mol). The resulting solution was stirred for 30 min at room temperature, evaporated, and

treated with water to give the triazene (317b) (0.22 g; 60%), m.p. 200-220° (decomp.) (from dimethyl formamide-water), identical (i.r. and mass spectra) with a sample prepared above.

The Attempted Reaction of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) with Iodide Ion.

A solution of the diazonium salt (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetone (30.0 ml) was stirred and treated with sodium iodide (0.30 g; 0.002 mol) to give a dark solution which was stirred for 30 min at room temperature to yield an unidentified yellow solid (0.02 g), m.p. >300°. The mother liquor was evaporated to give a brown semi-solid (0.84 g) which was triturated with ether to afford the triazene (317b) (0.18 g; 49%), m.p. 228-230° (from acetic acid), identical (m.p. and i.r. and mass spectra) with a sample prepared before.

The Reaction of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) with Water.

A suspension of the diazonium salt (311b; X=BF$_4$) (0.28 g; 0.001 mol) in water (5.0 ml) was stirred at 0° for 10 min and then at room temperature for 30 min to give 5-nitrosamino-3-phenyl-1,2,4-thiadiazole (312b) as a pink solid (0.19 g; 92%), m.p. 125-127°, identical (i.r. spectrum) with a sample prepared previously.

The Attempted Reaction of 3-Phenyl-1,2,4-thiadiazole-5-diazonium Fluoroborate (311b; X=BF$_4$) with Piperidine.

A solution of piperidine (0.20 g; 0.0024 mol) in acetone (30.0 ml)

was stirred and treated with the diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) and the resulting solution was stirred at room temperature for 30 min. Evaporation gave a dark gum which was triturated with ethanol to afford a beige solid (0.25 g; 68%), m.p. 225-227° (from ethanol-water), identical (m.p. and i.r. and mass spectra) with the triazine (317b) prepared previously.

Pentane-2,3,4-trione 3-(3'-methyl-1,2,4-thiadiazol-5'-yl)hydrazone (318a).

(a) 5-Amino-3-methyl-1,2,4-thiadiazole (308a) (0.81 g; 0.007 mol) was dissolved in a mixture of concentrated sulphuric acid (0.6 ml) and water (6.6 ml) and the solution was stirred and treated dropwise at 0-5° with aqueous 1M sodium nitrite (7.0 ml). The resulting yellow suspension was stirred for 10 min at 0° then treated dropwise at 0-5° with a solution of acetylacetone (0.70 g; 0.007 mol) in methanol (5.0 ml). The mixture was stirred for 2 h to give a pink solid (0.22 g; 22%), m.p. 73-74° (violent decomposition) identical (i.r. spectrum) with a sample of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) prepared previously.

The mother liquor, on standing overnight, precipitated an orange solid (0.13 g; 8%), m.p. 138-141°, identical (i.r. spectrum) with a sample of the hydrazone (318a) prepared in (b) below. The filtrate was extracted with methylene chloride (2x20 ml) to give a red oil (0.41 g; 59%), identical (i.r. spectrum) with an authentic sample of acetylacetone. The aqueous layer was neutralised with concentrated aqueous ammonia and extracted with methylene chloride (2x20 ml)

to give a yellow gum which was triturated with ether to afford a

yellow solid (0.03 g; 4%), m.p. 188-190°, identical (i.r. spectrum)

with an authentic sample of 5-amino-3-methyl-1,2,4-thiadiazole (308a).

(b) 5-Amino-3-methyl-1,2,4-thiadiazole (308a) (1.15 g; 0.01

mol) was dissolved with gentle warming in 88% phosphoric acid (10.0

ml) and the solution was stirred and treated at 0° with sodium nitrite

(1.38 g; 0.02 mol). The resulting yellow suspension was stirred

for 10 min at 0°, treated with sulphamic acid (1.94 g; 0.02 mol),

stirred for a further few min then treated dropwise at 0-10° with a

solution of acetylacetone (1.00 g; 0.01 mol) in methanol (5.0 ml).

The mixture was stirred for 30 min at 0° and poured on to ice (100 g)

to give a pink solid which was crystallised from toluene-light

petroleum to yield pentane-2,3,4-trione 3-(3'-methyl-1,2,4-thia-

diazol-5'-yl)hydrazone (318a) as pale green cuboids (0.42 g; 19%),

m.p. 157-161°, ν_{max} 3130 m (NH) and 1690 and 1655 (CO) cm^{-1},

$\delta(CDCl_3)$ 2.60 (3H, s, Me), 2.54 (3H, s, Me), and 2.45 (3H, s, Me).

Found: C, 42.4; H, 4.3; N, 24.6%; M$^+$, 226.

$C_8H_{10}N_4O_2S$ requires: C, 42.5; H, 4.4; N, 24.8%; M, 226.

The aqueous mother liquor was extracted with methylene chloride

(2x50 ml) to give a brown oil (0.33 g; 33%) identical (i.r. spectrum)

with an authentic sample of acetylacetone. The aqueous layer was

neutralised with concentrated aqueous ammonia and extracted with

methylene chloride (2x50 ml) to give a gummy yellow solid (0.13 g)

which was triturated with ether to afford 5-amino-3-methyl-1,2,4-

thiadiazole (308a) as a cream solid (0.07 g; 6%), m.p. 165-168°,

identical (i.r. spectrum) with an authentic sample.

The Attempted Reaction of the Product (E) with Acetylacetone.

A solution of the solid (E) (total amount) prepared previously in ethanol (5.0 ml) and water (5.0 ml) was added dropwise at 0° to a stirred solution of acetylacetone (1.01 g; 0.01 mol) and anhydrous sodium acetate (1.13 g) in ethanol (10.0 ml) and water (5.0 ml). The mixture was stirred at room temperature for 1 h, concentrated, and treated with water (3.0 ml) to give a negligible amount of solid. The aqueous mother liquor was extracted with methylene chloride to give an intractable yellow gum (0.02 g). Acidification of the aqueous layer with dilute aqueous hydrochloric acid and extraction with methylene chloride (2x15 ml) gave an intractable red gum (0.07 g).

Reactions of 3-Methyl-5-nitrosamino-1,2,4-thiadiazole (312a) with Acetylacetone.

(a) A solution of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) (0.58 g; 0.004 mol) in water (2.0 ml) and ethanol (10.0 ml) was stirred and added dropwise at 0° to a solution of acetylacetone (0.40 g; 0.004 mol) and sodium acetate (0.45 g) in water (2.0 ml) and ethanol (4.0 ml). The mixture was stirred for 1 h at 0°, concentrated, and acidified with dilute aqueous hydrochloric acid to give a colourless solid (0.58 g; quantitative), m.p. 80° (violent decomposition) identical (m.p. and i.r. spectrum) with an authentic sample of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a).

(b) A solution of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) (0.56 g; 0.004 mol) in acetic acid (3.0 ml) was mixed with acetylacetone (0.40 g; 0.004 mol) and the solution was heated under

reflux for 25 min, during which time gas evolution occurred. The mixture was treated with water (20.0 ml), filtered to remove a negligible amount of tar and extracted with methylene chloride (2x15 ml) to give a brown semi-solid which was triturated with ether to afford an unidentified yellow solid (0.09 g; 10%), m.p. 230-234° (from toluene-light petroleum), $\delta(CDCl_3)$ 2.57 (s, Me), 2.63 (s, Me) and 2.64 (s, Me).

Found: C, 46.0; H, 4.7; N, 25.2%; M^+, 222. $\underline{C_9H_{10}N_4OS}$ requires: C, 48.6; H, 4.5; N, 25.2%; M, 222.

(c) A solution of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) (0.58 g; 0.004 mol) in Analar methanol (20.0 ml) was treated with acetylacetone (0.40 g; 0.004 mol) and the mixture was saturated with hydrogen chloride at 0° then allowed to reach room temperature. The mixture was filtered to remove a negligible quantity of solid and the filtrate was treated with water (3.0 ml), concentrated, and extracted with methylene chloride (2x10 ml) to afford an intractable brown semi-solid (0.15 g) which was shown by t.l.c. in methylene chloride over alumina to contain three unresolvable components.

The aqueous layer was neutralised with sodium acetate and extracted with methylene chloride to give a gummy brown solid (0.08 g) which was triturated with ether-ethyl acetate to give 5-amino-3-methyl-1,2,4-thiadiazole (308a) as a brown solid (0.01 g; 2%), m.p. 174-175°, identical (i.r. spectrum) with an authentic sample.

(d) A solution of 3-methyl-5-nitrosamino-1,2,4-thiadiazole (312a) (1.36 g; 0.0094 mol) in acetic acid (8.0 ml) and 88% phosphoric

acid (16.0 ml) was stirred and treated dropwise with acetylacetone (1.01 g; 0.01 mol) at room temperature. The mixture was stirred for 1 h then poured on to ice (50 g) to give the hydrazone (318a) as a yellow solid (0.50 g; 24%), m.p. 147-149°, identical (i.r. spectrum) with a sample prepared previously.

Work up of the aqueous mother liquor gave no further material.

Pentane-2,3,4-trione 3-(3'-phenyl-1,2,4-thiadiazol-5'-yl)hydrazone (318b).

(a) A solution of 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) (0.56 g; 0.002 mol) in acetone (30.0 ml) was stirred and treated with acetylacetone (0.21 g; 0.002 mol). The mixture was stirred for 1 h at room temperature then evaporated to give a brown gum which was triturated with ether to yield an unidentified yellow solid (0.08 g), m.p. 227-230°, mass spectrum inconclusive.

The ethereal mother liquor was evaporated and the residue was triturated with ethanol-water to afford the hydrazone (318b) as a yellow-green solid (0.22 g; 37%), m.p. 172-175° (lit.[83] 169-170°), ν_{max} 3160 w (NH) and 1690 and 1660 (CO) cm^{-1}, M$^+$, 288; C$_{13}$H$_{12}$N$_4$O$_2$S requires M, 288.

(b) A solution of 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetone (30.0 ml) was mixed with a solution of acetylacetone (0.20 g; 0.002 mol) in acetone (2.0 ml) and the mixture was stirred and treated dropwise with triethylamine (0.22 g; 0.0022 mol). The solution changed

colour from yellow to dark red and was stirred for 30 min at room temperature then evaporated to give a dark gum which was triturated with ethanol-water to afford the hydrazone (318b) as a green solid (0.29 g; 41%), m.p. 155-158°, identical (i.r. spectrum) with a sample prepared in (a) before.

The aqueous-ethanol mother liquor was concentrated and extracted with methylene chloride to give a yellow gum (0.14 g) which was shown by t.l.c. in ethyl acetate over silica to contain five close-running components, one of which corresponded to the hydrazone (318b).

(c) A suspension of 5-nitrosamino-3-phenyl-1,2,4-thiadiazole (312b) (1.03 g; 0.005 mol) in 88% phosphoric acid (30.0 ml) was mixed with acetylacetone (0.51 g; 0.005 mol) and the mixture was stirred at room temperature for 1 h then poured on to ice (100 g). The resulting gummy beige solid (2.89 g) was triturated with ethanol-water to give the hydrazone (318b) as a brown solid (0.60 g; 43%), m.p. 160-164°, identical (i.r. spectrum) to a sample prepared in (a) before.

1-Phenylbutane-1,2,3-trione 2-(3'-phenyl-1,2,4-thiadiazol-5'-yl)-hydrazone (319).

(a) A solution of 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetone (30.0 ml) was mixed with a solution of benzoylacetone (0.32 g; 0.002 mol) in acetone (2.0 ml) and the mixture was stirred and treated dropwise with triethylamine (0.22 g; 0.0022 mol). The solution became darker in colour and was stirred at room temperature for 30 min,

evaporated, and the residue extracted with methylene chloride

(2x20 ml) to give a gum (0.58 g) which was chromatographed over

alumina.   Elution with toluene gave the azo compound (322) as

yellow needles (0.04 g; 8%), m.p. 210-211° (from acetic acid),

ν_{max} 1640 (CO) cm^{-1}.

Found: C, 61.6; H, 3.4; N, 17.8%; M^{+}, 468.

$C_{24}H_{16}N_{6}OS_{2}$ requires: C, 61.5; H, 3.4; N, 17.9%; M, 468.

Further elution with toluene gave a yellow crystalline solid (0.10 g;

17%), m.p. 126-130° (from benzene-light petroleum), identical (i.r.

spectrum) with the hydrazone (319) prepared in (b) below, followed

by an unidentified red solid (0.07 g), m.p. 55-60°, and finally an

intractable yellow gum (0.12 g).

(b) A suspension of 5-nitrosamino-3-phenyl-1,2,4-thiadiazole

(312b) (1.03 g; 0.005 mol) in 88% phosphoric acid (30.0 ml) was

mixed with a solution of benzoylacetone (0.81 g; 0.005 mol) in

methanol (3.0 ml) and the mixture was stirred at room temperature

for 1 h then poured on to ice (100 g).   The mixture was extracted with

methylene chloride (300 ml) to give a dark red gum (1.39 g) which

was triturated with ether to afford the hydrazone (319) as a yellow

solid (0.69 g; 40%), m.p. 139-140° (from ethanol-water), ν_{max}

3140 w (NH) and 1660 and 1655 (CO) cm^{-1}, δ (CDCl$_{3}$) 8.12-7.44

(10H, m, ArH) and 2.52 (3H, s, Me).

Found: C, 61.9; H, 3.9; N, 16.0%; M^{+}, 350.

$C_{18}H_{14}N_{4}O_{2}S$ requires: C, 61.7; H, 4.0; N, 16.0%; M, 350.

The aqueous phase was neutralised with concentrated aqueous

ammonia and extracted with methylene chloride (2x40 ml) to give a

yellow solid (0.02 g; 2%), m.p. 143-147°, identical (i.r. spectrum) with 5-amino-3-phenyl-1,2,4-thiadiazole (308b).

The Attempted Coupling of 3-Phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) with Ethyl Acetoacetate.

(a) A solution of 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) (0.56 g; 0.002 mol) in acetone (30.0 ml) was mixed with ethyl acetoacetate (0.28 g; 0.002 mol) and the mixture was stirred and treated dropwise at 0° with triethylamine (0.22 g; 0.0022 mol) to give a dark solution which was stirred at room temperature for 30 min. Evaporation of the reaction mixture gave a dark gum (1.06 g) which was chromatographed over alumina. Elution with methylene chloride-ethyl acetate gave colourless crystals of propane-1,2-dione 1-(3'-phenyl-1,2,4-thiadiazol-5'-yl)-hydrazone (324) (0.07 g; 14%), m.p. 204-207° (from toluene-light petroleum), ν_{max} 3130 w (NH) and 1660 (CO) cm^{-1}, δ(CDCl$_3$) 8.15-8.04 (3H, m, ArH), 7.44-7.03 (3H, m, ArH and =CH) and 2.40 (3H, s, Me).

Found: C, 54.1; H, 4.1; N, 22.1%; M$^+$, 246.

C$_{11}$H$_{10}$N$_4$OS requires: C, 53.7; H, 4.1; N, 22.8%; M, 246.

m/e: 246.055781.

C$_{11}$H$_{10}$N$_4$OS requires: 246.057528.

Further elution with ethanol-methanol gave an intractable brown gum (0.24 g).

(b) A suspension of 3-phenyl-1,2,4-thiadiazole-5-diazonium fluoroborate (311b; X=BF$_4$) (0.55 g; 0.002 mol) in acetonitrile

(30. 0 ml) was treated with the sodium salt of ethyl acetoacetate (0. 30 g; 0. 002 mol) [prepared by mixing solutions of ethyl aceto-acetate (1. 70 g; 0. 013 mol) in absolute ethanol (3. 0 ml) and sodium (0. 27 g; 0. 012 g atom) in absolute ethanol (50. 0 ml), stirring the mixture for 30 min followed by evaporation] and the mixture was stirred at room temperature for 30 min to give a yellow solid (0. 09 g; 22%), m. p. 130°, identical (i. r. spectrum) with 5-nitrosamino-3-phenyl-1, 2, 4-thiadiazole (312b).

Evaporation of the acetonitrile filtrate gave a brown gum (0. 63 g) which was chromatographed over alumina to give a yellow-brown gum (0. 25 g) which was triturated with ether-ethanol to afford a yellow solid (0. 05 g), m. p. 270-274°, M^{+}, 423 which decomposed on attempted crystallisation.

The Attempted Coupling of the 3-Phenyl-1, 2, 4-thiadiazole-5-diazonium Cation (320b) with Acetylacetone.

5-Amino-3-phenyl-1, 2, 4-thiadiazole (308b) (1. 77 g; 0. 01 mol) was dissolved with gentle warming in 88% phosphoric acid (10. 0 ml) and the solution was stirred and treated at 0° with solid sodium nitrite (1. 38 g; 0. 02 mol). The resulting thick yellow suspension was stirred for 10 min at 0°, treated with sulphamic acid (1. 94 g; 0. 02 mol), stirred for several more minutes then treated dropwise at 0-5° with a solution of acetylacetone (1. 00 g; 0. 01 mol) in methanol (5. 0 ml). The mixture was stirred for 30 min at 0° then poured on to ice-water (100 ml) to give the hydrate of 5-nitro-3-phenyl-1, 2, 4-thiadiazole (329) as a yellow solid (2. 2 g; quantitative),

m. p. 236-237° (from acetic acid), $_{max}$ 1645 w cm^{-1}.

Found: C, 42.7; H, 3.6; N, 18.4%; (M^{+}-30), 177.

C$_8$H$_5$N$_3$O$_2$S.H$_2$O requires: C, 42.7; H, 3.1; N, 18.7%; M, 207.

5-Nitro-3-phenyl-1,2,4-thiadiazole (329)

5-Amino-3-phenyl-1,2,4-thiadiazole (308b) (1.77 g; 0.01 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (1.38 g; 0.02 mol). The resulting yellow suspension was stirred at 0° for 10 min, treated with sulphamic acid (1.94 g; 0.02 mol), stirred for a further 30 min and poured into ice-water (100 ml) to afford the hydrate of the nitrothiadiazole (329) (2.2 g; quantitative), identical (m.p., and i.r. and mass spectra) with a sample prepared before.

The Attempted Reduction of 5-Nitro-3-phenyl-1,2,4-thiadiazole (329).

(a) The hydrate of the nitrothiadiazole (329) (0.22 g; 0.001 mol) was hydrogenated in methanol (120 ml) over 10% palladium-on-charcoal (0.02 g) at room temperature and atmospheric pressure. No uptake of hydrogen was observed. The mixture was filtered through a Kieselguhr pad and evaporated to give the starting material (329) (0.22 g; quantitative), m. p. 176-180°, identical (i.r. spectrum) with a sample prepared above.

(b) The hydrate of the nitrothiadiazole (329) (0.22 g; 0.001 mol) in 70% v/v aqueous ethanol (50.0 ml) was heated under reflux with sodium dithionite (0.22 g) for 30 min, treated with further

sodium dithionite (0. 22 g) and heated under reflux for a further 30 min. The mixture was hot filtered to remove inorganic material and the filtrate was concentrated and extracted with methylene chloride (2x15 ml) to give a yellow solid (0. 05 g; 28%), identical (m. p. and i. r. spectrum) with an authentic sample of 5-amino-3-phenyl-1, 2, 4-thiadiazole (308b).

Synthesis of 3-Amino-5-phenyl-1, 2, 4-thiadiazole (333).

(a) Benzoyldicyandiamide (331) was prepared (yield 23%) by the reaction of benzoyl chloride with dicyandiamide according to the method of Adams, [168] and had m. p. 287-294° (lit., [168] 205°).

(b) Benzoylguanylthiourea (332) was prepared (yield 86%) by the reaction of hydrogen sulphide with benzoyldicyandiamide as described by Adams [168] and had m. p. 162-165° (lit., [168] 174-176°).

(c) 3-Amino-5-phenyl-1, 2, 4-thiadiazole (333) was prepared (yield 60%) by the oxidation of benzoylguanylthiourea (332) with hydrogen peroxide as described by Kurzer [169] and had m. p. 123-125° (lit., [169] 132-134°).

The Attempted Preparation of 5-Phenyl-1, 2, 4-thiadiazole-3-diazonium Fluoroborate (338)

A solution of 3-amino-5-phenyl-1, 2, 4-thiadiazole (333) (0. 35 g; 0. 002 mol) in 40% aqueous hydrofluoroboric acid (10. 0 ml) was stirred and treated dropwise at 0-5° with a solution of sodium nitrite (1. 00 g; 0. 014 mol) in water (6. 0 ml). The resulting yellow

suspension was stirred for 10 min at 0° and 15 min at room temperature then extracted with methylene chloride (2x10 ml) to give an orange gum (0.24 g) which was triturated with ethyl acetate to yield an unidentified yellow solid (0.03 g), m.p. 164-171°. The ethyl acetate mother liquor was shown by t.l.c. in ethyl acetate over silica to be an unresolvable multicomponent. mixture.

The Attempted Nitrosation of 3-Amino-5-phenyl-1,2,4-thiadiazole (333).

(a) A suspension of the amine (333) (0.72 g; 0.004 mol) in a solution of sodium nitrite (1.05 g; 0.015 mol) in water (10.0 ml) was stirred and treated dropwise at 0° with 10% aqueous hydrochloric acid (10.0 ml) to give a yellow suspension which was stirred for 3.25 h at 0-5°. The resulting pale yellow solid was slurried with 20% aqueous sodium carbonate (10.0 ml) to yield a beige solid (0.54 g; 75%), identical (m.p. and i.r. spectrum) with an authentic sample of the starting amine (333).

Acidification of the sodium carbonate filtrate gave no further material.

(b) A suspension of the amine (333) (0.72 g; 0.004 mol) in aqueous 2M sulphuric acid (5.0 ml) was stirred and treated at 0° with sodium nitrite (0.34 g; 0.005 mol) and the mixture was stirred at 0-5° for 10 min to give a yellow solid (0.66 g; 92%), identical (m.p. and i.r. spectrum) with the starting amine (333).

(c) A suspension of the amine (333) (0.89 g; 0.005 mol) in 90% aqueous formic acid (10.0 ml) was stirred and treated dropwise at 0-5° with a solution of sodium nitrite (0.40 g; 0.0058 mol) in water (2.5 ml) and the mixture was stirred for 30 min at 0-5° then

diluted with water (10.0 ml). Extraction with methylene chloride (2x10 ml) gave an intractable brown gum (0.82 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable three component mixture.

The Attempted Reaction of the 5-Phenyl-1,2,4-thiadiazole-3-diazonium Cation (334) with Thiocyanate Ion.

3-Amino-5-phenyl-1,2,4-thiadiazole (333) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (1.38 g; 0.02 mol). The resulting yellow suspension was stirred for 10 min at 0°, treated with sulphamic acid (1.94 g; 0.02 mol), stirred for a few more min and treated dropwise at 0-10° with a solution of potassium thiocyanate (0.97 g; 0.01 mol) in water (5.0 ml). The mixture was stirred for 30 min, poured in to ice-water (100 ml) and extracted with ethyl acetate (2x100 ml) to give an orange gum (1.83 g) which was triturated with acetone to afford the hydrazine (341) as yellow crystals (0.30 g; 17%), m.p. 241-244° (from dimethyl-formamide-water), ν_{max} 3350 w and 3170 w (NH) cm^{-1}.

Found: C, 52.8; H, 3.4; N, 23.1%; M^{+}, 352.
$C_{16}H_{12}N_6S_2$ requires : C, 54.5; H, 3.4; N, 23.9%; M, 352.
Found: M^{+} 352.056 852
$C_{16}H_{12}N_6S_2$ requires : M 352.056 489.

The acetone mother liquor on concentration yielded a yellow solid (0.10 g; 6%), identical (m.p. and i.r. spectrum) with 3-amino-5-phenyl-1,2,4-thiadiazole (333).

The aqueous layer was neutralised with concentrated aqueous ammonia and extracted with methylene chloride (2x50 ml) to give

yellow gum (0.11 g) whose t.l.c. in ethyl acetate over silica showed it to contain two unresolvable components.

The Attempted Coupling of the 5-Phenyl-1,2,4-thiadiazole-3-diazonium Cation (334) with Acetylacetone.

3-Amino-5-phenyl-1,2,4-thiadiazole (333) (1.77 g; 0.01 mol) was dissolved with gentle warming in 88% phosphoric acid (10.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (1.38 g; 0.02 mol). The yellow suspension was stirred at 0° for 10 min, treated with sulphamic acid (1.94 g; 0.02 mol), stirred for a few more min and then treated dropwise at 0-5° with a solution of acetylacetone (1.01 g; 0.01 mol) in methanol (5.0 ml). The mixture was stirred at 0° for 30 min and poured on to ice (100 g) to give a gummy red solid which was triturated with methylene chloride-light petroleum to give the formylhydrazine (343) as a colourless solid (0.26 g; 12%), m.p. 189-191° (from acetic acid-water), $_{max}$ 3380 m (NH) and 1685 (CO) cm^{-1}, [$(CD_3)_2SO$] 10.30 (1H, s br, CHO), 8.00-7.50 (5H, m, ArH), and 7.30 (2H, s br, NH).

Found: C, 49.2; H, 3.6; N, 25.3%; M$^+$, 220.

$C_9H_8N_4OS$ requires: C, 49.1; H, 3.6; N, 25.5%; M, 220.

Extraction of the aqueous layer with methylene chloride (3x40 ml) afforded an orange gum which was triturated with ether to give a beige solid (0.05 g; 2%), m.p. 192-195°, identical (i.r. spectrum) with the compound (343) prepared before.

The aqueous layer was neutralised with concentrated aqueous ammonia and extracted with methylene chloride (2x40 ml) to give a

dark oil (1. 24 g) which was chromatographed over alumina. The only product recovered from the column was 3-amino-5-phenyl-1, 2, 4-thiadiazole (333) (24%), identical (i..r. spectrum) with an authentic sample.

B.   1, 3, 4-Thiadiazoles

2-Amino-5-phenyl-1, 3, 4-thiadiazole (344).

(a) 1-Benzoylthiosemicarbazide (350) was prepared (62%) from thiosemicarbazide and benzoyl chloride by the method of Hoggarth[171] as a colourless solid, m.p. 191-195° (lit.,[171] 196-198°).

(b) 2-Amino-5-phenyl-1, 3, 4-thiadiazole (344) was prepared from 1-benzoylthiosemicarbazide (350) by the method of Hoggarth[171] as a colourless solid (69%), m.p. 227-229° (lit.,[171] 224°).

The Attempted Conversion of 2-Amino-5-phenyl-1, 3, 4-thiadiazole (344) into 5-Phenyl-1, 3, 4-thiadiazole-2-diazonium Fluoroborate (345; X=BF$_4$).

(a) A suspension of 2-amino-5-phenyl-1, 3, 4-thiadiazole (344) (0. 35 g; 0. 002 mol) in 40% aqueous hydrofluoroboric acid (10. 0 ml) was stirred and treated dropwise at 0° with a solution of sodium nitrite (1. 00 g; 0. 014 mol) in water (6. 0 ml) to give a yellow suspension which was stirred for 10 min at 0° and for 10 min at room temperature.   The resulting yellow solid (0. 90 g), m. p. 85-100°,

when slurried with water (6.0 ml) afforded an unidentified brown solid (0.60 g), m.p. >300°, M^+ 545, which gave a negative test with $\underline{N}$, $\underline{N}$-bis-(β-acetoxyethyl)-$\underline{m}$-toluidine.

(b) 2-Amino-5-phenyl-1,3,4-thiadiazole (344) (0.88 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was stirred and treated at 0-5° with sodium nitrite (0.70 g; 0.01 mol) to give a yellow suspension which was stirred for 10 min, treated with sulphamic acid (0.97 g; 0.01 mol), stirred for 5 min and finally treated with 40% aqueous hydrofluoroboric acid (2.0 ml). The mixture was then stirred for 15 min and quenched with ice (25 g) to give an unidentified orange solid (0.60 g), m.p. 62-63° (violent decomposition), M^+ 497. This solid gave a negative test with $\underline{N}$, $\underline{N}$-bis-(β-acetoxyethyl)-$\underline{m}$-toluidine and on attempted crystallisation gave an unidentified intractable solid, m.p. >300°, M^+ 583.

2-Nitrosamino-5-phenyl-1,3,4-thiadiazole (352).

The nitrosamine (352) was prepared (82%), m.p. 91-93° (lit.,[108] 104°), from 2-amino-5-phenyl-1,3,4-thiadiazole (344) by the method of Butler.[108]

The Attempted Conversion of 2-Nitrosamino-5-phenyl-1,3,4-thiadiazole (352) into 5-Phenyl-1,3,4-thiadiazole-2-diazonium Chloride (345; X=Cl).

A solution of the nitrosamine (352) (0.39 g; 0.0019 mol) in a mixture of Analar methanol (20.0 ml) and acetic acid (10.0 ml) was

saturated with hydrogen chloride at 0°. The solution was allowed
to reach room temperature, concentrated, and treated with water
(2.0 ml) to afford an unidentified yellow solid (F) (0.35 g), m.p. 311-
312 (from ethanol),

Found: C, 44.5; H, 3.1; N, 21.8%; M^+ no ion pressure
identical (i.r. spectrum) with a sample of (F) prepared later.

The Attempted Conversion of 2-Nitrosamino-5-phenyl-1,3,4-
thiadiazole (352) into 5-Phenyl-1,3,4-thiadiazole-2-diazonium
Fluoroborate (345; X=BF$_4$).

A suspension of 2-nitrosamino-5-phenyl-1,3,4-thiadiazole
(352) (0.41 g; 0.002 mol) in sodium dried ether (4.0 ml) was stirred
and treated with boron trifluoride-etherate complex (0.59 g; 0.004
mol) at 0° and the mixture was stirred at 0° for 20 min, treated with
sodium dried ether (30.0 ml) and stirred at 0° for 2 h to give an
orange solid (0.30 g; 73%), m.p. 71° (violent decomposition),
identical (i.r. spectrum) with an authentic sample of the starting
material (352).

Pentane-2,3,4-trione 3-(5'-phenyl-1,3,4-thiadiazol-2'-yl)hydrazone
(354).

2-Amino-5-phenyl-1,3,4-thiadiazole (344) (1.77 g; 0.01 mol)
was dissolved with gentle warming in 88% phosphoric acid (10.0 ml)
and the solution was stirred and treated at 0° with sodium nitrite
(1.38 g; 0.02 mol) to give a yellow suspension. This was stirred
for 10 min at 0°, treated with sulphamic acid (1.95 g; 0.02 mol),

stirred for several more min, then treated dropwise with a solution

of acetylacetone (0.99 g; 0.01 mol) in methanol (5.0 ml). The

mixture was stirred for 30 min at 0° then poured on to ice (100 g)

to give a yellow solid which was crystallised from toluene-light

petroleum to afford the hydrazone (354) as pale yellow needles (1.67

g; 58%), m.p. 164-167°, ν_{max} 3470 br (NH) and 1690 (CO) cm^{-1},

$\delta[(CD_3)_2SO]$ 7.90-7.50 (5H, m$_o$ ArH), 2.40 (3H, s, Me) and 2.31

(3H, s, Me).

Found: C, 54.3; H, 4.2; N, 19.0%; M$^+$, 288.

$C_{13}H_{12}N_4O_2S$ requires: C, 54.2; H, 4.2; N, 19.4%; M, 288.

The aqueous mother liquor was extracted with methylene

chloride (2x30 ml) to give a dark intractable oil (0.13 g). The

aqueous layer was neutralised with concentrated aqueous ammonia

to afford a beige solid (0.25 g; 14%), m.p. 225-227°, identical (m.p.

and i.r. spectrum) with authentic 2-amino-5-phenyl-1,3,4-thia-

diazole (344).

The Attempted Coupling of the 5-Phenyl-1,3,4-thiadiazole-2-

diazonium Cation (353) with Benzoylacetone.

2-Amino-5-phenyl-1,3,4-thiadiazole (344) (0.89 g; 0.005 mol)

was dissolved with gentle warming in 88% phosphoric acid (5.0 ml)

and the solution was stirred and treated at 0° with sodium nitrite

(0.69 g; 0.01 mol) to give a yellow suspension. This was stirred

at 0° for 10 min, treated with sulphamic acid (0.97 g; 0.01 mol) and

then dropwise at 0-10° with a solution of benzoylacetone (0.81 g;

0.005 mol) in methanol (5.0 ml). The mixture was stirred for 30

min at 0°, poured on to ice (50 g) and extracted with methylene chloride (2x50 ml) to give a purple gum (1.34 g) which was chromatographed over alumina. Elution with ethyl acetate-methanol afforded a dark orange gum (0.86 g) which was triturated with ethyl acetate to yield orange crystals (0.46 g; 22%) of an unidentified product m.p. 148-152° (from light petroleum-toluene-ethanol), ν_{max} 3420 br and 3170 br cm^{-1}, $\delta[(CD_3)_2SO]$ 7.88-7.65 (4H, m, ArH), 7.56-7.38 (6H, m, ArH), 2.37 (3H, s, Me), and 1.66 (3H, s, Me).

Found: C, 52.4; H, 3.8; N, 13.3%; M$^+$, 374, 167. $\underline{C_{18}H_{16}N_4O_6S}$ requires: C, 51.9; H, 3.8; N, 13.5%; M, 416.

The aqueous mother liquor was neutralised with concentrated aqueous ammonia to give a beige solid (0.15 g; 17%), m.p. 229-232°, identical (m.p. and i.r. spectrum) with an authentic sample of 2-amino-5-phenyl-1,3,4-thiadiazole (344).

The Attempted Coupling of the 5-Phenyl-1,3,4-thiadiazole-2-diazonium Cation (353) with Ethyl Benzoylacetate.

2-Amino-5-phenyl-1,3,4-thiadiazole (344) (0.90 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension. This was stirred for 10 min at 0°, treated with sulphamic acid (0.97 g; 0.01 mol) stirred for several more min and then treated dropwise at 0-5° with a solution of ethyl benzoylacetate (0.96 g; 0.005 mol) in methanol (5.0 ml). The mixture was stirred for 30 min at 0°, poured on to

ice (50 g) and extracted with methylene chloride (2x40 ml) to give a purple gum (1.21 g) which was chromatographed over alumina. Elution with toluene gave a pale yellow oil (36%) identical (i.r. spectrum) with an authentic sample of ethyl benzoylacetate.

The aqueous mother liquor was neutralised with concentrated aqueous ammonia to give a pale green solid (0.24 g; 27%), m.p. 228-231^0, identical (m.p. and i.r. spectrum) with an authentic sample of 2-amino-5-phenyl-1,3,4-thiadiazole (344).

The Attempted Reaction of 2-Nitrosamino-5-phenyl-1,3,4-thia-diazole (352) with Acetylacetone.

(a) A solution of the nitrosamine (352) (0.50 g; 0.0025 mol) in ethanol (25.0 ml) and water (5.0 ml) was added dropwise with stirring at 0-5° to a solution of acetylacetone (0.25 g; 0.0025 mol) and anhydrous sodium acetate (0.30 g) in ethanol (2.0 ml) and water (1.0 ml). The mixture was stirred for 1 h at 0-5° and concentrated to afford an unidentified orange solid (F) (0.25 g; 27%), m.p. 338-340° (from toluene-ethanol).

Found: C, 44.2; H, 3.2; N, 22.1%; M$^+$, 278.

$C_{14}H_{12}N_6O_3S_2$ requires: C, 44.7; H, 3.2; N, 22.3%; M, 376.

Extraction of the aqueous mother liquor with methylene chloride (2x10 ml) gave an intractable brown gum (0.10 g). Acidification of the aqueous layer with aqueous dilute hydrochloric acid gave a yellow solid (0.10 g; 20%), m.p. 103° (violent decomposition), identical (i.r. spectrum) with an authentic sample of 2-nitrosamino-5-phenyl-1,3,4-thiadiazole (352).

(b) A solution of the nitrosamine (352) (0.51g; 0.0025 mol) in 88% phosphoric acid (15.0 ml) was stirred and treated dropwise with acetylacetone (0.25 g; 0.0025 mol) and the mixture was stirred for 2 h at room temperature then poured on to ice (50 g) to give an intractable tar.

The aqueous mother liquor was extracted with methylene chloride (2x20 ml) to give an orange solid (0.20 g; 28%), m.p. 148-150°, identical (i.r. spectrum) with pentane-2,3,4-trione 3-(5'-phenyl-1,3,4-thiadiazole-2'-yl)hydrazone (354) prepared previously.

CHAPTER SIX

Studies of the Synthesis and Fragmentation Reactions
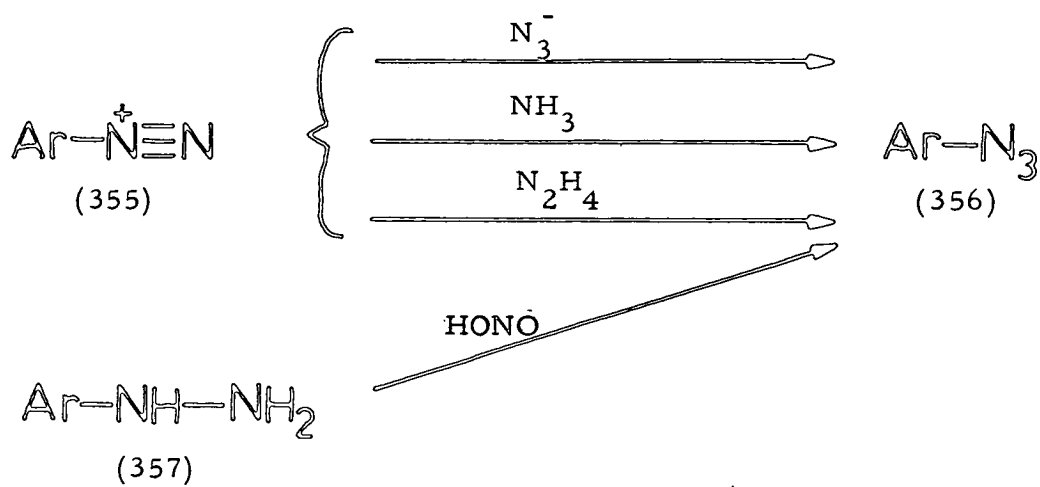
of Azidoazoles

Scheme 139

Scheme 140

Studies of the Synthesis and Fragmentation Reactions of Azidoazoles

One of the most common transformations of ar_{ene} diazonium salts
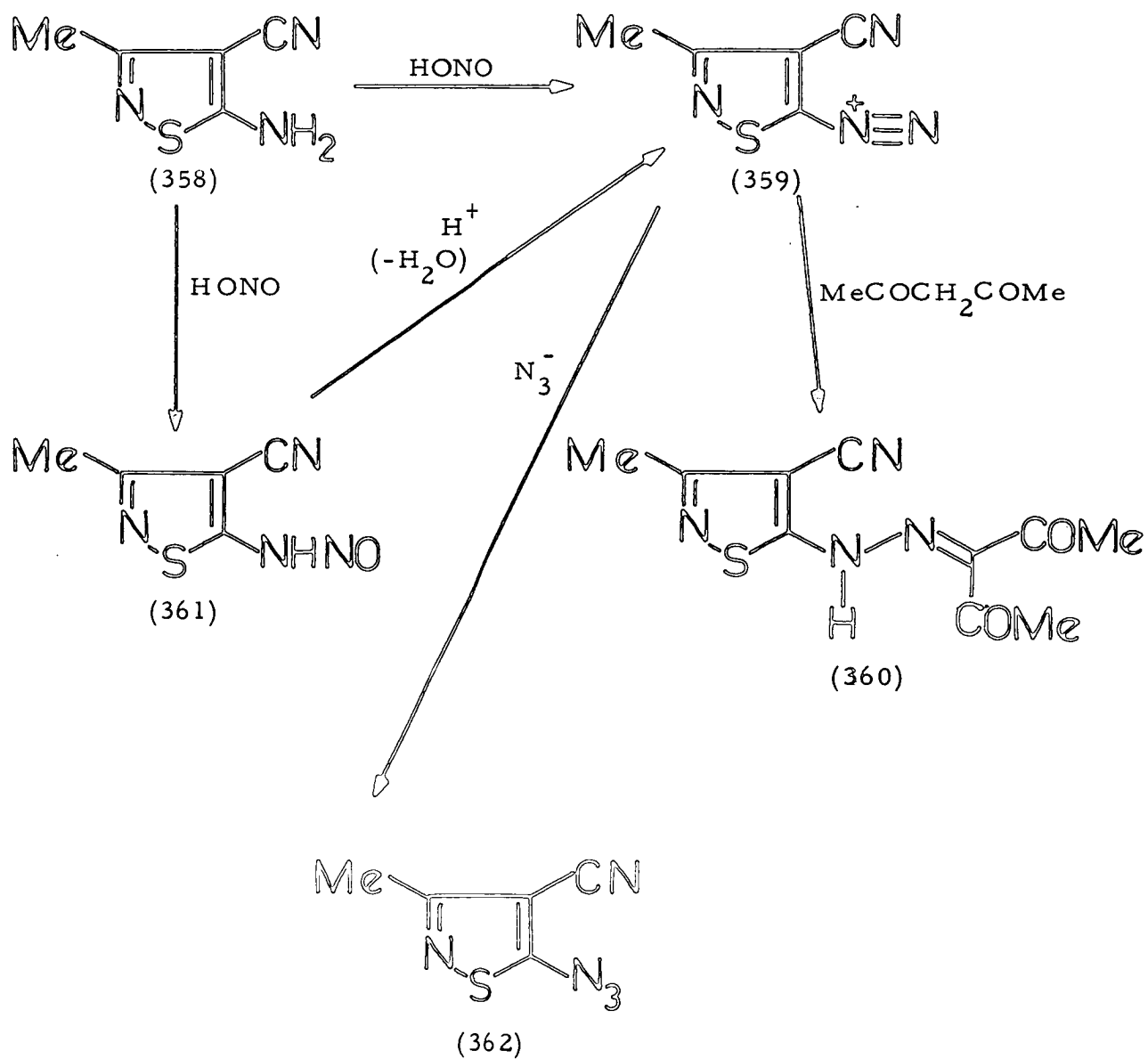(355) is their reaction with azide ion to afford aryl azides (356)
(Scheme 139).[172] Aryl azides can also be prepared by reacting
ar_{ene} diazonium salts (355) with ammonia or hydrazine or by diazotising
the corresponding arylhydrazine (357) (Scheme 139).[172] The
investigation of the reactions with azide ion of the azolediazonium
salts being studied in the present work was of interest for two
reasons: firstly, because the efficiency of the reactions of diazonium
mixtures from amino- or nitrosaminoazoles with azide ion to give
the respective azidoazoles provides a measure of the efficiency of
the original diazotisation process and of the in situ stability of the
corresponding azolediazonium cations; and secondly, in relation to the
investigation of the scope and mechanism of a novel fragmentation
reaction discovered in the present work while studying the reactivity
of an azidoisothiazole. The efficiency of the reaction of azide ion
with aryldiazonium cations is a consequence of the mechanism
involved. Unlike more orthodox dediazoniation reactions azido-
dediazoniation actually occurs by coupling between the diazonium
substituent and azide ion followed by loss of nitrogen (see Chapter 1,
page 9).

The attempted diazotisation of 5-amino-3-methylisothiazole-4-
carbonitrile (358)[160] was described in Chapter 4. The attempted
preparation of salts of the corresponding diazonium cation (359)
and their subsequent in situ reactions were unsuccessful, except
for coupling with acetylacetone to give the anticipated hydrazone (360)

(Scheme 140). Attempts to use the nitrosamine (361) as a precursor of the diazonium cation (359) were equally unsuccessful (see Chapter 4). In contrast, the diazonium mixture from the amine (358) and sodium nitrite in phosphoric acid reacted readily with sodium azide to afford 5-azido-3-methylisothiazole-4-carbonitrile (362) in 72% yield (Scheme 140). The azide structure (362) for this product is based on analytical data, the presence of nitrile and azide absorption in its i. r. spectrum and a solitary signal in its [1]H n. m. r. spectrum attributable to a methyl group. The azide (362) was also formed, though in lower yield (42%), by diazotising the amine (358) in a mixture of acetic acid and propionic acid with nitrosylsulphuric acid. However, the best overall yield (85%) of the azide (362) was obtained when a solution of the nitrosamine (361) in concentrated phosphoric acid was treated with sodium azide. Formation of the azide (362) under these conditions presumably involves the initial conversion of the nitrosamine (361) into the diazonium cation (359) (Scheme 140). Goerdeler[109, 167] has demonstrated that 5-nitrosamino-1, 2, 4-thia-diazoles, which can be prepared by nitrosation of 5-amino-1, 2, 4-thiadiazoles in dilute acid media, are converted in strongly acidic media into diazonium cations which can be coupled with activated aromatic molecules and undergo dediazoniation reactions.

5-Azido-3-methylisothiazole-4-carbonitrile (362) was found to be a potent nose and throat irritant but more interestingly it was observed to be photosensitive, taking on a blue colour on exposure to light. This observation prompted the investigation of its photo-chemical and thermal decomposition. Thus, irradiation of a
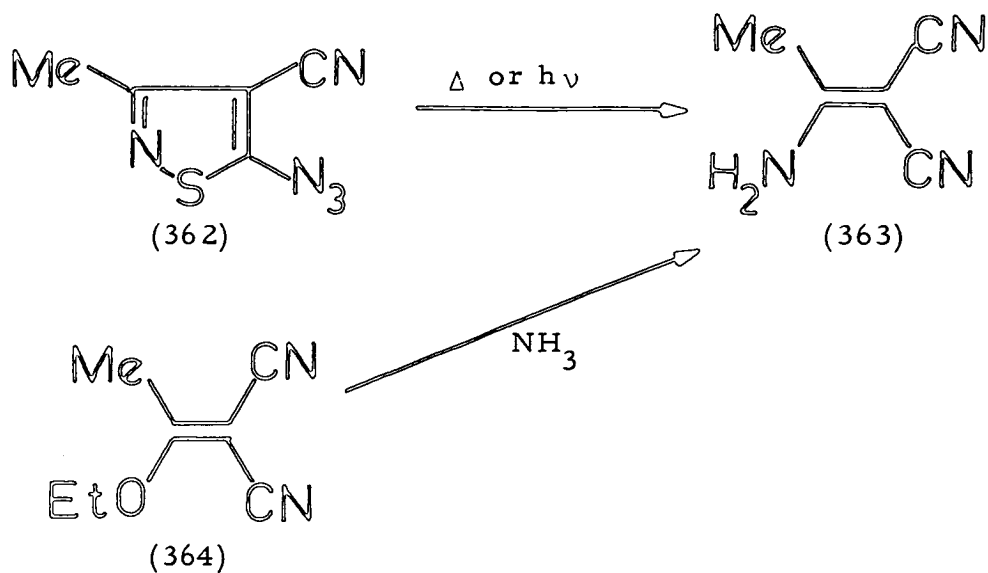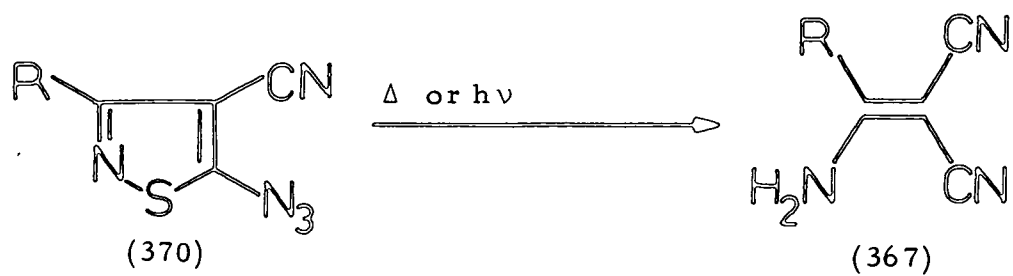
Scheme 141
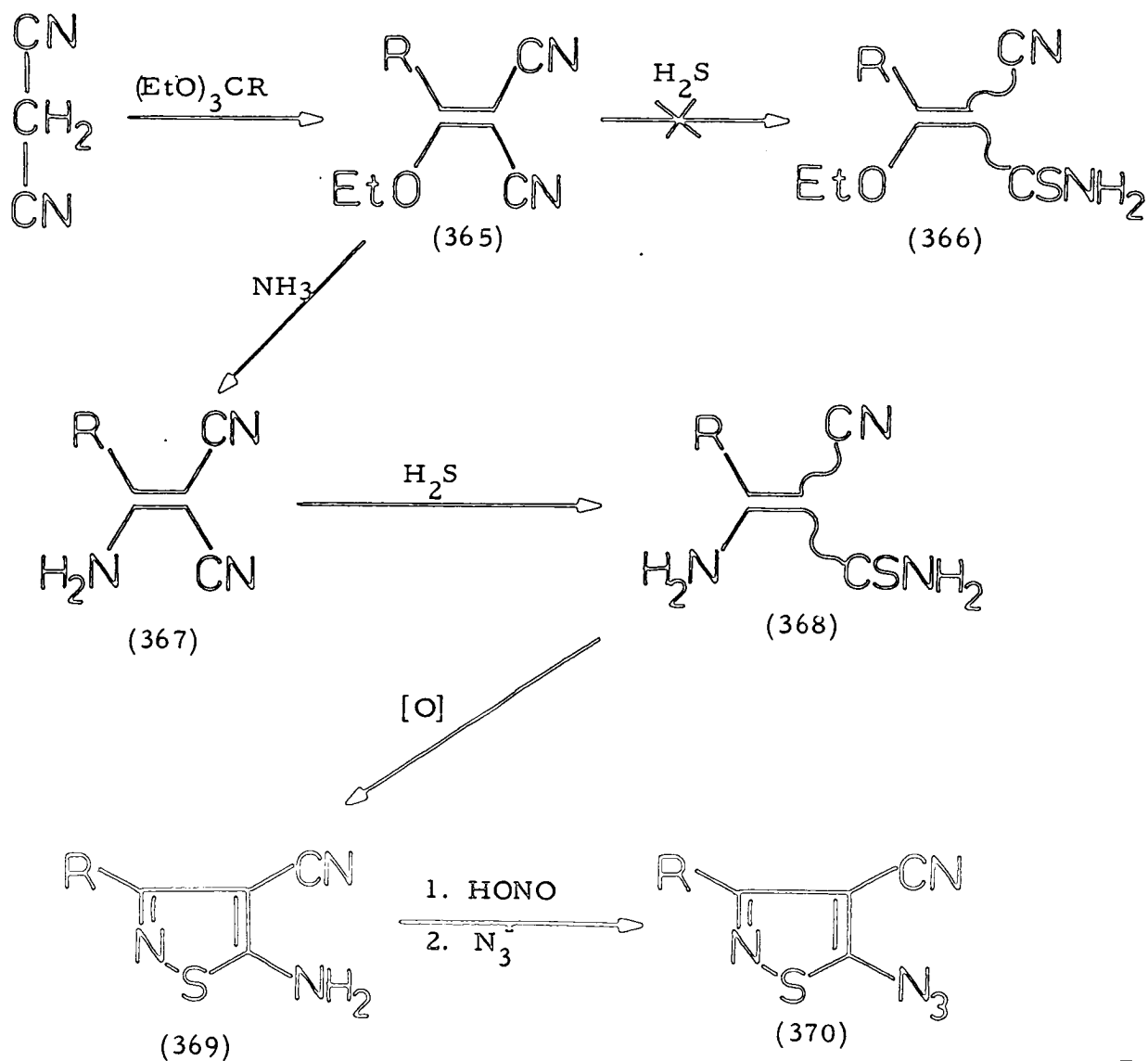
Scheme 142

solution of the azide (362) in dry benzene at 254 nm afforded a moderate yield (40%) of a product which gave analytical and spectroscopic data consistent with it being the known[173] 2-amino-1,1-dicyanoprop-1-ene (363) (Scheme 141). The identity of this product was fully substantiated by its unambiguous synthesis by reaction of 1,1-dicyano-2-ethoxyprop-1-ene[159] (364) with ammonia (Scheme 141). The alkene (363) was also formed in moderate yield (40%) by photolysis of the azide (362) in Analar acetone. A pronounced smell of hydrogen sulphide was noticed during the photolysis of the azide (362). Interestingly, the yield of the alkene (363) was raised to 77% when the azide (362) was photolysed at 254 nm in glacial acetic acid. The enhanced yield in this photolysis indicates acid catalysis of the photolytic process. A purely dark reaction in acetic acid at room temperature is excluded since the azide (362) is recovered in quantitative yield when it is left under these conditions. However heating the azide (362) under reflux in glacial acetic acid resulted in its quantitative conversion into the alkene (363). Quantitative conversion into the alkene (363) also results from the thermolysis of the azide (362) in toluene, thus demonstrating the purely thermal nature of alkene formation under these conditions.

Having discovered the interesting photochemical and thermal degradation of 5-azido-3-methylisothiazole-4-carbonitrile (362) to the dicyanoenamine (363) it was of interest to investigate the scope of this novel fragmentation reaction. Consequently attention was directed to the synthesis and thermal and photochemical decomposition of other 5-azidoisothiazoles (370a and b) (Scheme 142). As in the

case of 5-azido-3-methylisothiazole-4-carbonitrile (362) (Scheme

140) it was proposed to synthesise the azidoisothiazoles (370a and b)

(Scheme 142) by diazotisation of the corresponding amines (369a

and b) followed by azidodediazoniation. Unfortunately however, the

synthesis of the required amines (369a and b) as for 5-amino-3-

methylisothiazole-4-carbonitrile (see Chapter 4) was thwarted by

the failure of the readily available ethoxymethylenemalononitrile

derivatives (365) (Scheme 142) to react with hydrogen sulphide to

give the thioamides (366) required as starting-materials. However

5-aminoisothiazole-4-carbonitrile (369a) was readily prepared using

the alternative approach of Sayer and Campbell.[174] This involved

the ammonolysis of the ethoxymethylenemalononitrile (365a) to give

the enamine (367a). Reaction of the latter with hydrogen sulphide

readily afforded the thioamide (368a), the hydrogen peroxide catalysed

cyclisation of which yielded 5-aminoisothiazole-4-carbonitrile (369a)

in moderate yield. An analogous synthetic sequence (Scheme 142)

afforded 5-amino-3-ethylisothiazole-4-carbonitrile (369b) in good

yield. The analytical and spectroscopic properties of the amines

(369a and b) were fully in accord with the assigned structures.

The amines (369a and b) underwent smooth diazotisation on

treatment with sodium nitrite in phosphoric acid to give diazonium

mixtures which reacted readily with sodium azide to afford the 5-

azidoisothiazole-4-carbonitriles (370a and b) (Scheme 142) in

quantitative yield. Like the methyl compound (362) (see before)

the azides (370a and b) are potent nose and throat irritants and

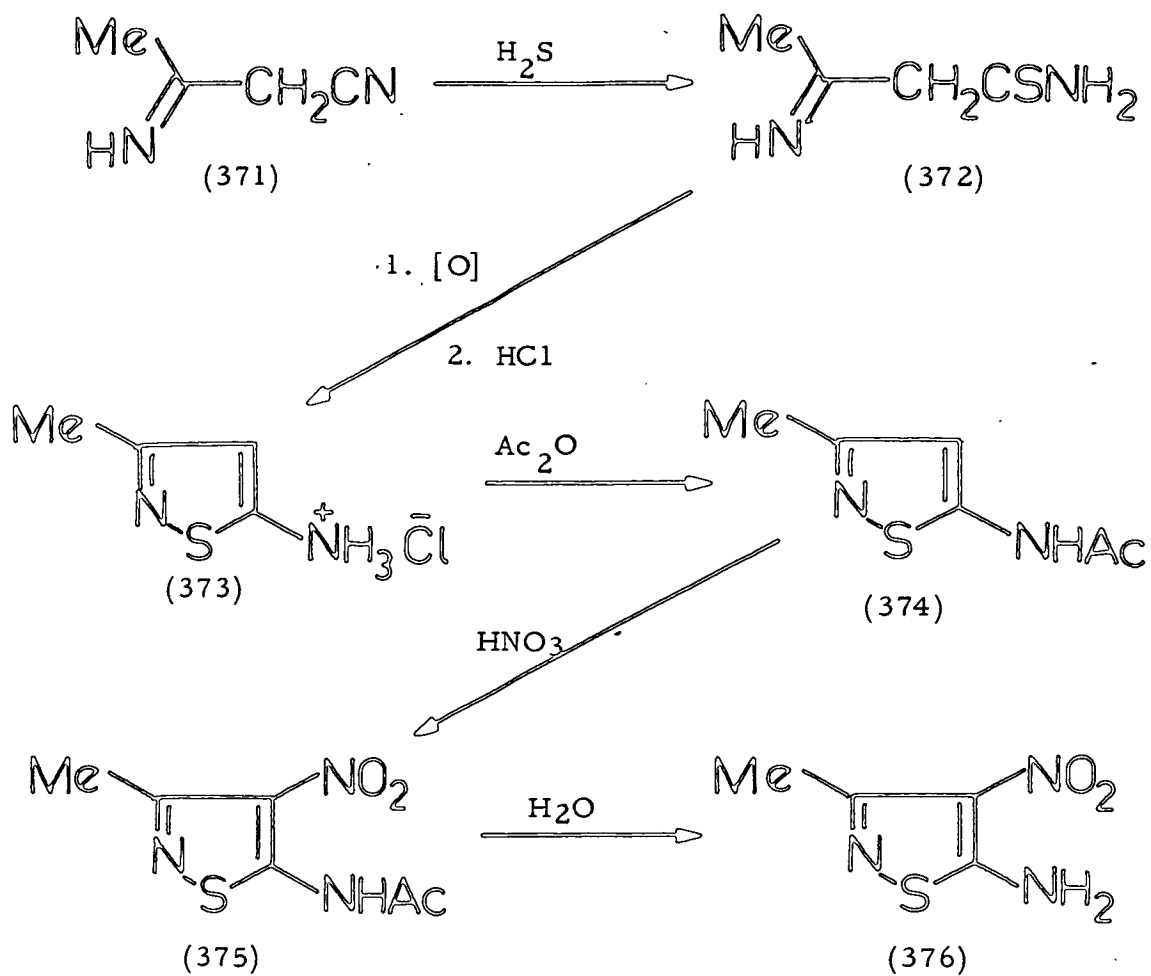change colour (from colourless to red) when exposed to light for

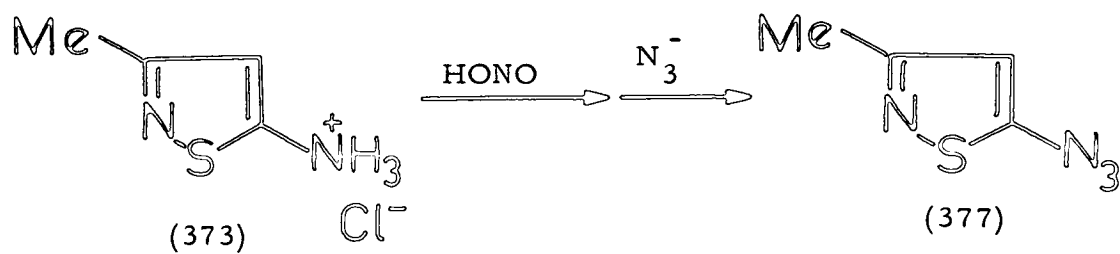|	R
a;	H
b;	Et

Scheme 143

any length of time.   In addition both azides (370a and b), like the

methyl analogue (362) were found to be thermolabile, decomposing

in refluxing glacial acetic acid to afford moderate to good yields of

products identical in every respect with the enamines (367) (Scheme

143) prepared previously.   Both azides (370a and b) also underwent

photodecomposition.   Thus, irradiation of the azide (370a) in dry

benzene gave the enamine (367a) (Scheme 143) in low yield (26%).

The low yield of the enamine (367a) formed under these conditions

can be attributed to the aprotic reaction medium employed and hence

the lack of a suitable source of hydrogen for abstraction by a possible

nitrene intermediate (see discussion of mechanism later).   In

support of this postulate, photolysis of the azide (370a) in undried

benzene resulted in a significant increase in the yield of the enamine

(367a).   5-Azido-3-ethylisothiazole-4-carbonitrile (370b) also

underwent photodecomposition in dry benzene, affording a low yield

of the anticipated 2-amino-1,1-dicyanobut-1-ene (367b) (Scheme 143)

together with a small amount of an unidentified solid (m/e 183) which

showed bands attributable to two distinct cyano groups as well as NH

absorption in its i.r. spectrum.

Having found that 5-azidoisothiazole-4-carbonitriles (370)

undergo general thermal and photochemical decomposition to afford

the corresponding 2-aminoalkylidenemalononitriles (367) (Scheme 143),

it was of interest to investigate the thermal and photochemical

behaviour of 5-azidoisothiazoles lacking a cyano group or containing

other substituents at the 4-position.   It was hoped that the behaviour

of such molecules might throw further light on the nature of the azide

Me—C(=NH)—CH₂CN → (via H₂S) ...

$$
\underset{\substack{\| \\ HN}}{Me-C}-CH_2CN \xrightarrow{\;H_2S\;} \underset{\substack{\| \\ HN}}{Me-C}-CH_2CSNH_2
$$

(371)   (372)

1. [O]
2. HCl

Me—[isothiazole]—$\overset{+}{N}H_3\ \bar{C}l$ $\xrightarrow{\;Ac_2O\;}$ Me—[isothiazole]—NHAc

(373)   (374)

HNO₃

Me—[isothiazole, NO₂]—NHAc $\xrightarrow{\;H_2O\;}$ Me—[isothiazole, NO₂]—NH₂

(375)   (376)

Scheme 144

Me—[isothiazole]—$\overset{+}{N}H_3$ Cl⁻ $\xrightarrow{\;HONO\;}$ $\xrightarrow{\;N_3^-\;}$ Me—[isothiazole]—N₃

(373)   (377)
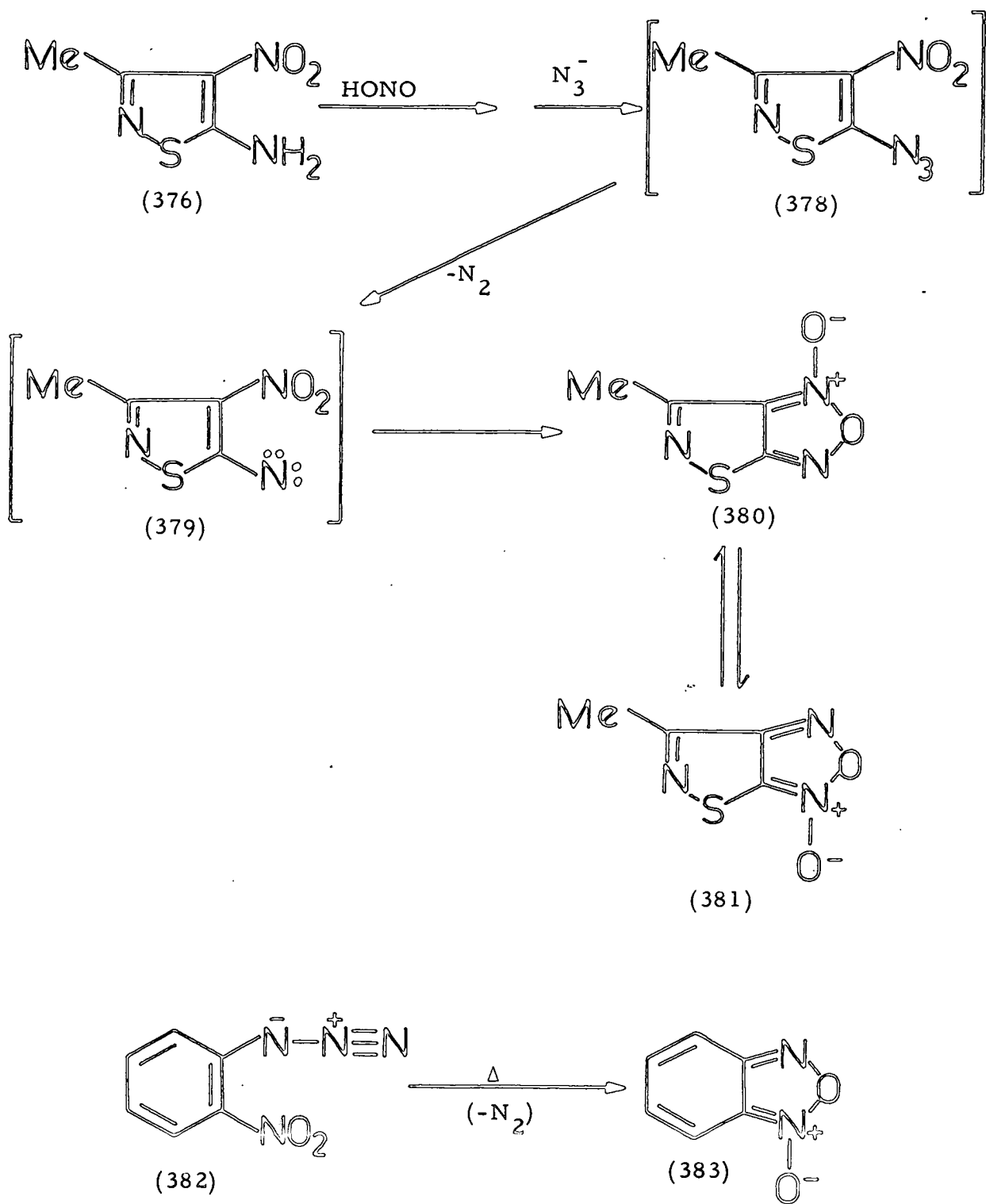
Scheme 145

fragmentation reactions. To this end 5-amino-3-methylisothiazole was prepared as the hydrochloride (373) (Scheme 144) by the conversion of 3-aminocrotononitrile (371) into β-iminothiobutyramide (372) using the method of Adams and Slack[175] followed by oxidative cyclisation of (372) using the method of Goerdeler and Pohland[176] as opposed to that of Adams and Slack[175] which could not be repeated. The amine hydrochloride (373) showed spectroscopic properties consistent with its structure but decomposed at 170° as opposed to 240° and 145° reported in the literature.[175,176] 5-Amino-3-methyl-4-nitroisothiazole (376) in turn was readily prepared in good yield from the isothiazoleamine hydrochloride (373) (Scheme 144) as described by Adams and Slack.[175]

5-Azido-3-methylisothiazole (377) was prepared in quantitative yield by diazotising the amine hydrochloride (373) in aqueous phosphoric acid with one equivalent of sodium nitrite and treating the resulting diazonium suspension with sodium azide (Scheme 145). The liquid product (377) was shown to be pure by combustion analysis and t.l.c. and it showed i.r. and [1]H n.m.r. absorption consistent with the assigned structure. However its mass spectrum showed an anomalous parent ion at m/e 138 instead of 140 expected on the basis of the structure (377). It is interesting to contrast the behaviour on diazotisation of 5-amino-3-methylisothiazole with the analogous 5-amino-3-phenylisoxazole discussed in Chapter 2. The attempted preparation of 5-azido-3-methyl-4-nitroisothiazole (378) was unsuccessful. Thus diazotisation of 5-amino-3-methyl-4-nitrosisothiazole (376) in concentrated phosphoric acid with sodium

Scheme 146

nitrite followed by reaction with sodium azide gave a quantitative

yield of a product whose analytical and spectroscopic properties are

consistent with either of the furoxan structures (380) or (381) (Scheme

146). In particular its i.r. spectrum lacked azide absorption while

its mass spectrum contained a fragment ion at $(M^{+}-16)$ typical of

the furoxan ring.[177] Formation of the furoxan (380) or (381) is

readily explained (Scheme 146) in terms of the formation and thermal

cyclisation of the azide (378) via the nitrene (379). The transforma-

tion [(378) -> (379) -> (380) or (381)] finds analogy in the well known[172]

transformation (Scheme 146) of 2-nitrophenyl azide (382) into benzo-

furoxan (383). In a further attempt to prepare the azide (378), 5-

amino-3-methyl-4-nitro isothiazole (376) was diazotised using

nitrosylsulphuric acid in acetic acid and the resulting diazonium

mixture treated with sodium azide. However, surprisingly, under

these conditions the amine (376) was recovered unchanged.

Having achieved the synthesis of 5-azido-3-methylisothiazole

(377) attention was directed to the study of its thermal and photo-

chemical decomposition. Thus, thermolysis of the azide (377) in

glacial acetic acid gave two products. The minor product contained

a parent ion at m/e 177 in its mass spectrum and showed i.r.

absorption indicative of the presence of, amino and cyano substituents.

Unfortunately there was insufficient of this material to allow its

characterisation. The major product of the thermolysis of the azide

(377) in glacial acetic acid was a yellow crystalline solid which gave

analytical data consistent with the molecular formula $C_8H_{10}N_4S_2$.

This product is tentatively assigned the symmetrical disulphide

Scheme 147

Scheme 148

(388) (389) (390) (391) (392) (393) (394) (395) (396) (397) (398)

Δ or hν
(-N₂)

A

B

R=H

R=CN

-S
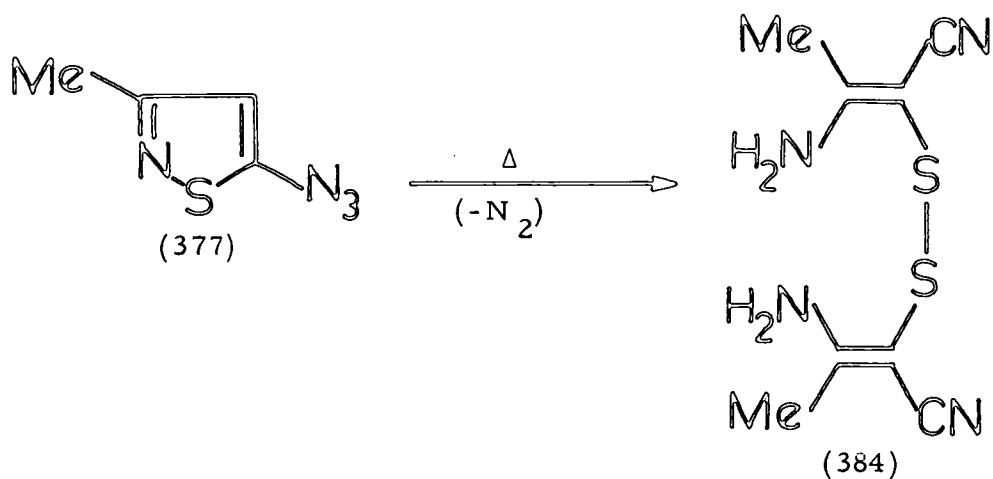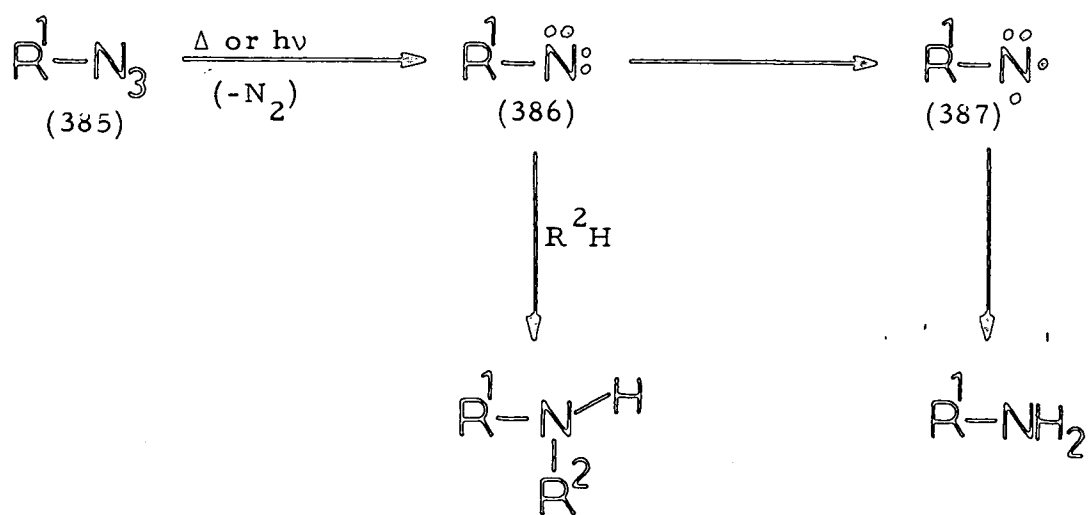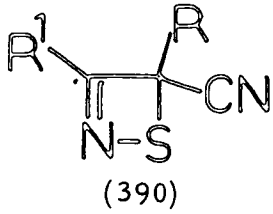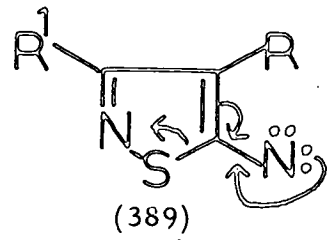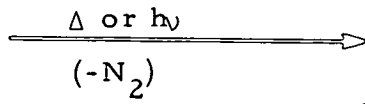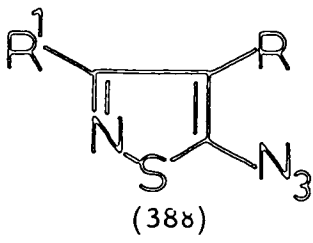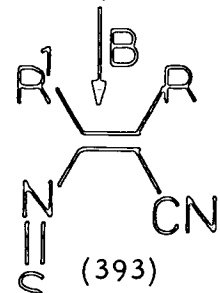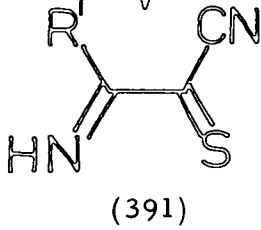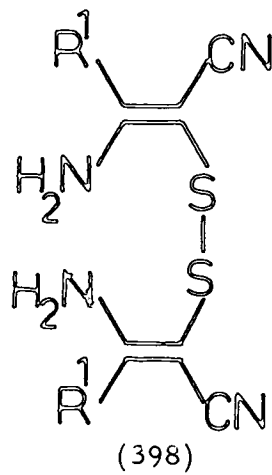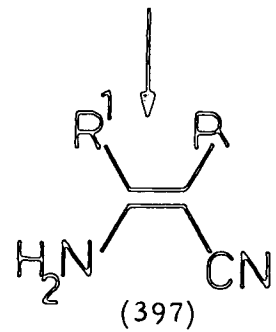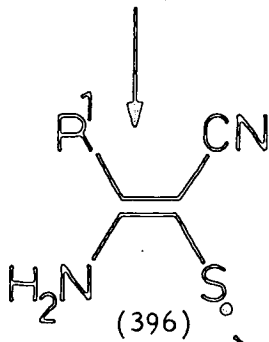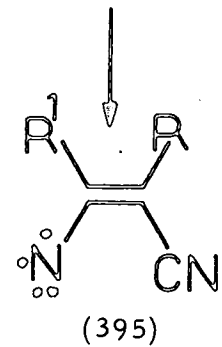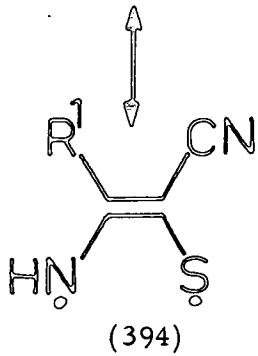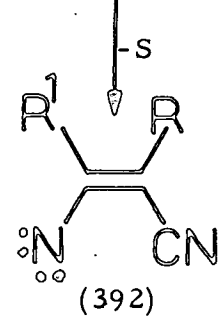
structure (384) (Scheme 147) on the basis of its spectroscopic properties. Thus its i. r. spectrum contained bands due to amino and cyano substituents and its ^{1}H n. m. r. spectrum showed a six proton singlet at δ 2.10 attributable to two equivalent methyl groups. The latter spectroscopic feature is consistent with the symmetrical character of the disulphide structure (384). 5-Azido-3-methyliso-thiazole (377) also underwent photolysis in benzene to give a product whose i. r. spectrum showed the presence of amino and cyano groups. However the decomposition of this product on attempted purification, precluded its identification.

Azides (385) are known^{172} to decompose under the influence of heat or high energy radiation (Scheme 148) to give nitrenes (386) and (387). The thermal and photochemical decomposition of azides (385) leads initially to the singlet nitrene (386) which typically will insert in a C-H bond (Scheme 148) or undergo intramolecular rearrangement to afford an electronically stable species. The singlet nitrene (386) can also revert to the ground state triplet nitrene (387) whose favoured mode of reaction is to abstract hydrogen from the solvent or other proton source to afford an amino species (Scheme 148). Two possible mechanisms (A) and (B) (Scheme 149) can be proposed to explain the fragmentation of 5-azidoisothiazoles (388) to yield the observed alkene products (397). Both mechanisms assume the initial generation of a singlet nitrene (389) which will tend to achieve stabilisation by electron migration to the deficient nitrogen atom. Such electronic reorganisation can lead to the formation of either a strained four-membered intermediate (390) or of an unstable
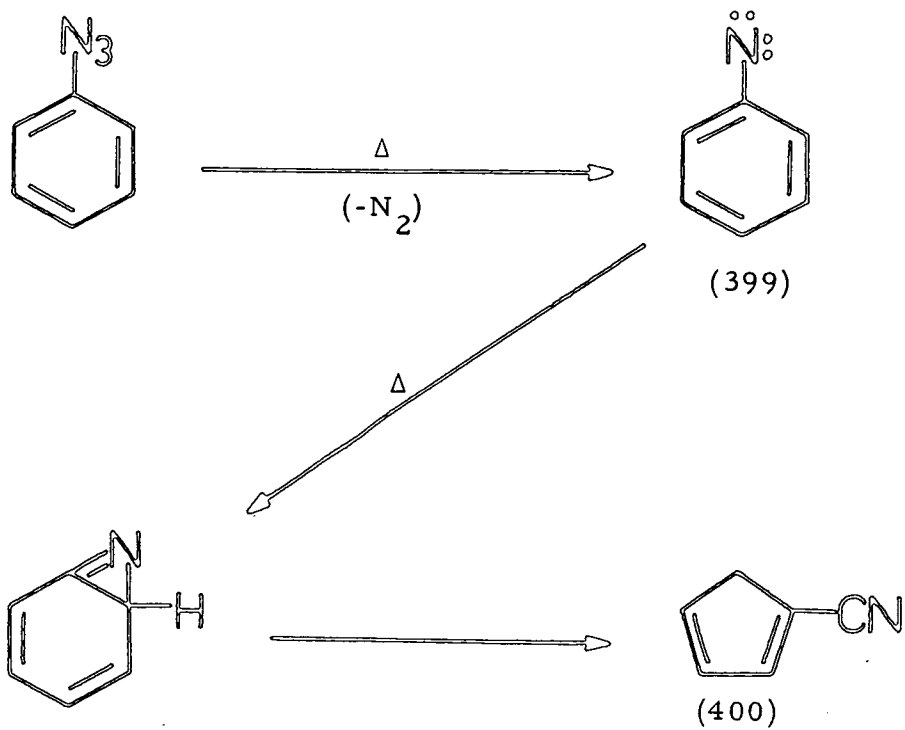
Scheme 150

thionitroso compound (393). The transformation (Scheme 150) of phenyl azide into 1-cyanocyclopentadiene (400) has been shown[172] to involve the intermediate formation and ring-contraction of phenyl-nitrene (399). Where (R=CN) both mechanisms (A) and (B) satisfactorily explain the formation of the alkene products (397) (Scheme 149). Thus the strained four-membered intermediate (390) and the thionitroso compound (393) can both extrude sulphur to afford the same singlet nitrene (392) which can revert to the triplet ground state (395) and thence by hydrogen abstraction afford the alkene product (397). The final stage of this mechanism, namely hydrogen abstraction, is supported by an examination of the yields achieved during the decomposition of 5-azidoisothiazoles in aprotic and protic media. Decomposition of these azides in protic media, such as acetic acid, normally leads to high yields of alkene (397), whereas decomposition in aprotic solvents such as benzene leads to yields of (397) less than 50%. In particular photolysis of 5-azidoisothiazole -4-carbonitrile in undried benzene gave a higher yield of 2-amino-1, 1-dicyanoethylene (367a) than the same reaction carried out in dry benzene. However mechanism (B) fails to explain the formation of a disulphide product (398) (Scheme 149) in the case of isothiazole azides (388; R=H) lacking a C(4) substituent. However the formation of a disulphide product (398) can be explained by opening of the strained four membered intermediate (390), with retention of sulphur, followed by proton transfer to afford the imine structure (391). This step is not possible in the case of 4-cyanoisothiazole azides (388; R=CN) and explains why a disulphide product was not obtained on decomposition

(401)

Δ PhCH₃
(−N₂)

(402)

39%
(403)

20%
(404)

Scheme 151

(362; R¹=Me, R=CN)

Δ (−N₂)

(393)

CO₂Me
C
‖‖
C
CO₂Me

(405)

PhN=C=O

(406)

or

(407)

Scheme 152

(377)

$\times$ Δ (-N$_2$)

(408)

Δ $MeO_2CC{\equiv}CCO_2Me$

CO_2Me
C
$\parallel\parallel\parallel$
C
CO_2Me

$\times$

(409)

(410)
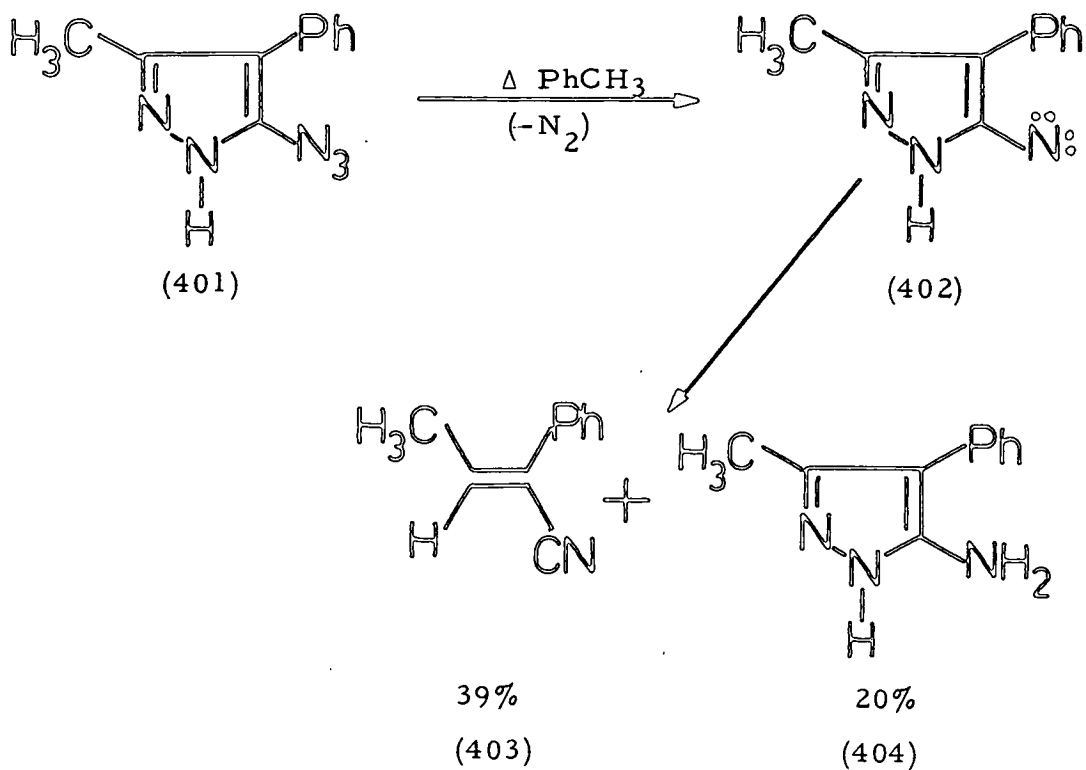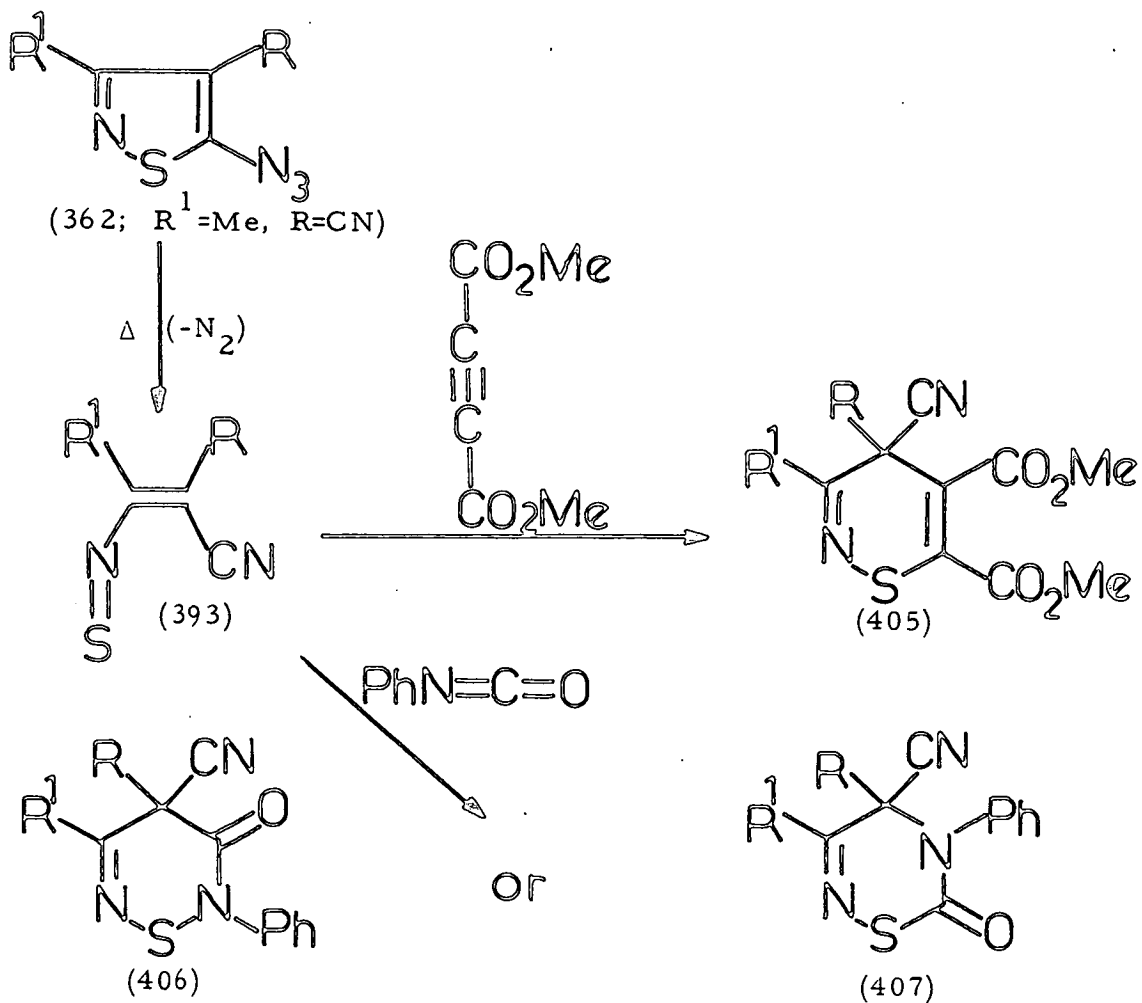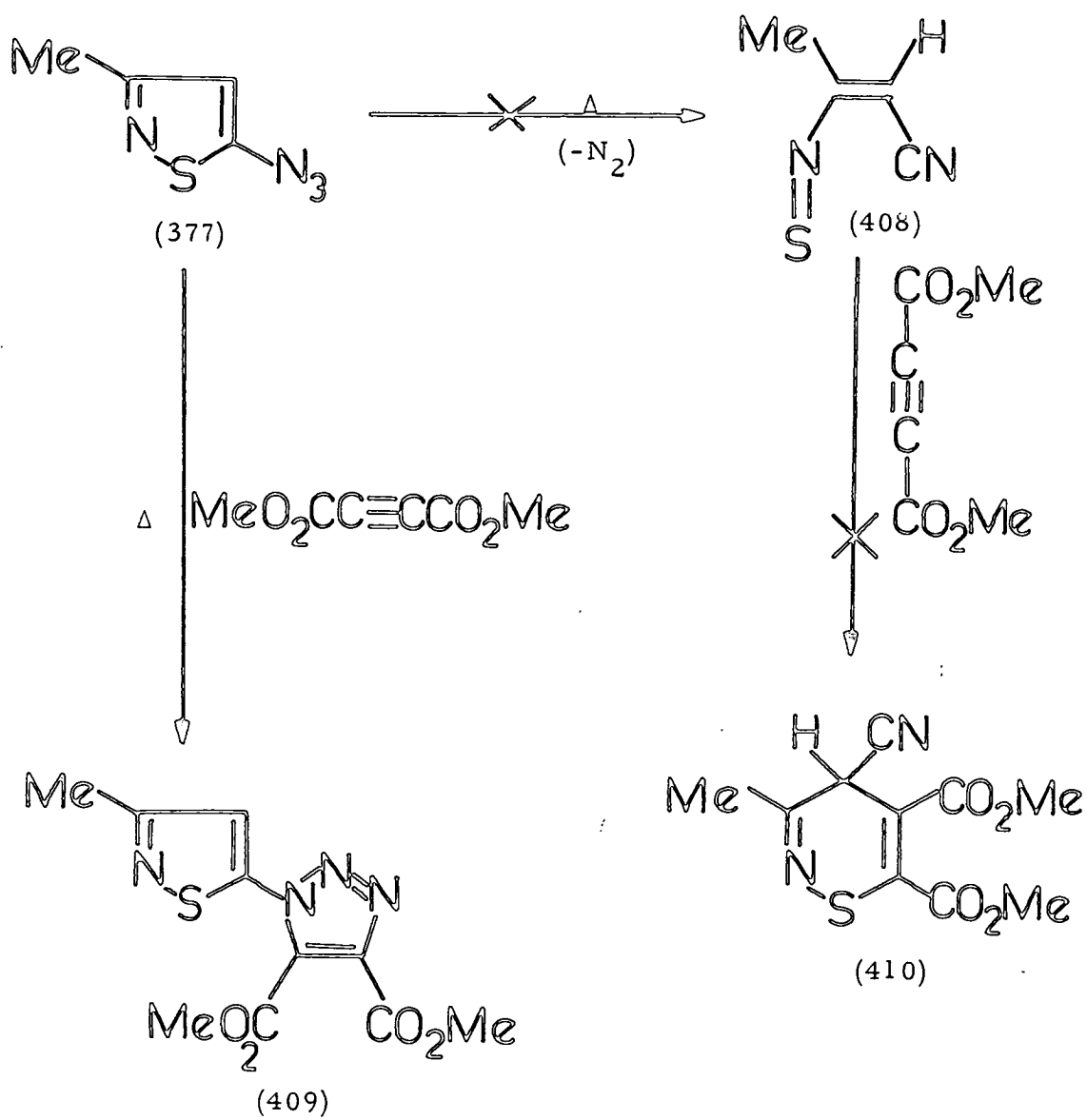
Scheme 153

of azidoisothiazole-4-carbonitriles. Hydrogen abstraction by the imine (391) possibly reacting as a diradical species (394) would afford the enamine radical species (396) dimerisation of which would give the disulphide species (398) isolated (Scheme 149). It follows that mechanism (A) (Scheme 149) is to be preferred on the basis of the available evidence since it satisfactorily explains the products formed on decomposition of the azidoisothiazoles.

One of the few literature[178] examples of the decomposition of heterocyclic azides involves fragmentation of the azidopyrazole (401) on thermolysis in toluene to afford the amine (404), together with the ethylene product (403) (Scheme 151). This reaction shows some similarities to the decomposition of azidoisothiazoles (Scheme 149) and work by Smith[178] clearly demonstrates that the first step in the decomposition of azidopyrazoles is generation of a nitrene (402).

In an effort to obtain further evidence in support of either of the proposed pathways (Scheme 149) leading to the alkene (397) attempts were made to trap the postulated thionitroso intermediate (393) using a suitable dienophile. To this end 5-azido-3-methyliso-thiazole-4-carbonitrile (362) was refluxed in toluene with dimethyl acetylenedicarboxylate and also with phenylisocyanate in an attempt to trap (393) as the Diels-Alder adducts (405) and (406) or (407) respectively (Scheme 152). However the only product isolated in either experiment was 2-amino-1,1-dicyanoprop-1-ene (363). In a further attempt to trap an intermediate such as (408) (Scheme 153), 5-azido-3-methylisothiazole (377) was heated under reflux with dimethyl acetylenedicarboxylate in the hope of obtaining the adduct (410). Work up of this reaction gave a low yield of dimethyl

Scheme 154

Scheme 155

1-N-(3'-methylisothiazol -5'-yl)-1, 2, 3-triazole-4, 5-dicarboxylate

(409) (Scheme 153) whose structure follows from its analytical and

spectroscopic properties. The triazole (409) is presumably simply

formed by cycloaddition of the azide (377) to the triple bond in the

acetylenic ester. The cycloaddition of azides to acetylenic triple

bonds is a well known[172] method for the synthesis of 1, 2; 3-triazoles.

In an effort to establish that generation of a nitrene (389) is

the first step in the decomposition process of azidoisothiazoles (388)

(Scheme 149), an attempt was made to trap the nitrene (411) (Scheme

154) with dimethylsulphoxide as the sulphoximide[187] (412). However

thermolysis of the azide (362) in dimethylsulphoxide merely afforded

2-amino-1, 1-dicyanoprop-1-ene (363). As it was not possible to

trap the nitrene intermediate (411) generated from the azide (362)

an attempt was made to prepare this species by an independent

route. To this end an attempt was made to oxidise 5-amino-3-

methylisothiazole-4-carbonitrile (358) to the nitrene (411) using

manganese dioxide (Scheme 155). However this reaction merely

gave a high recovery of unreacted starting material. On the other

hand, oxidation of the amine (358) with sodium hypochlorite,[178, 179]

while giving some unreacted starting material, also afforded a low

yield of the azo dimer (415) (Scheme 155) which was identified on

the basis of analytical data, the presence of a cyano band in its i. r.

spectrum and a solitary signal in its [1]H n. m. r. spectrum of $\delta 2.74$

attributable to two equivalent methyl groups. This result is in

broad agreement with the findings of Smith,[178] who obtained

fragmentation products on thermolysis of 5-azido-1,4-diphenyltriazole

(416)

$-N_2$

(417)

A

B

(418)

Y—Z   C≡N
X—S

PRODUCTS

(419)

$-N_2$

(420)

(421) + (422)
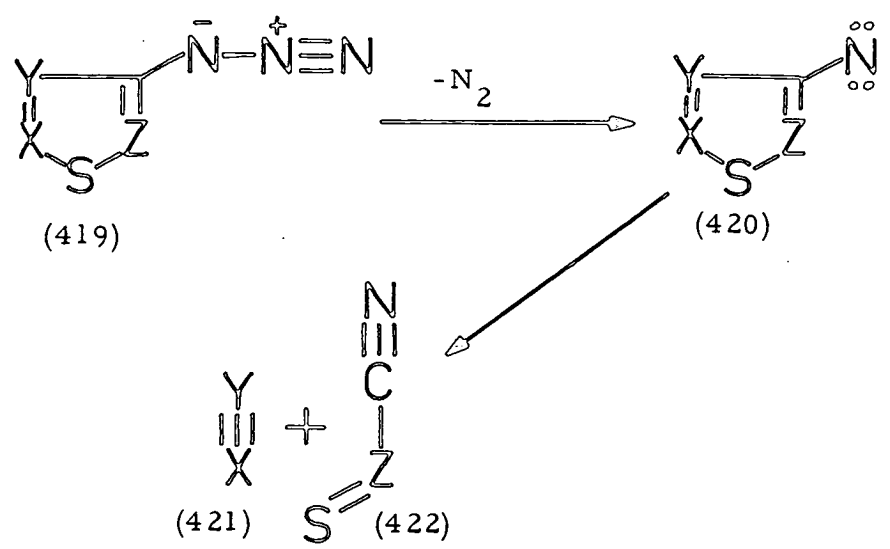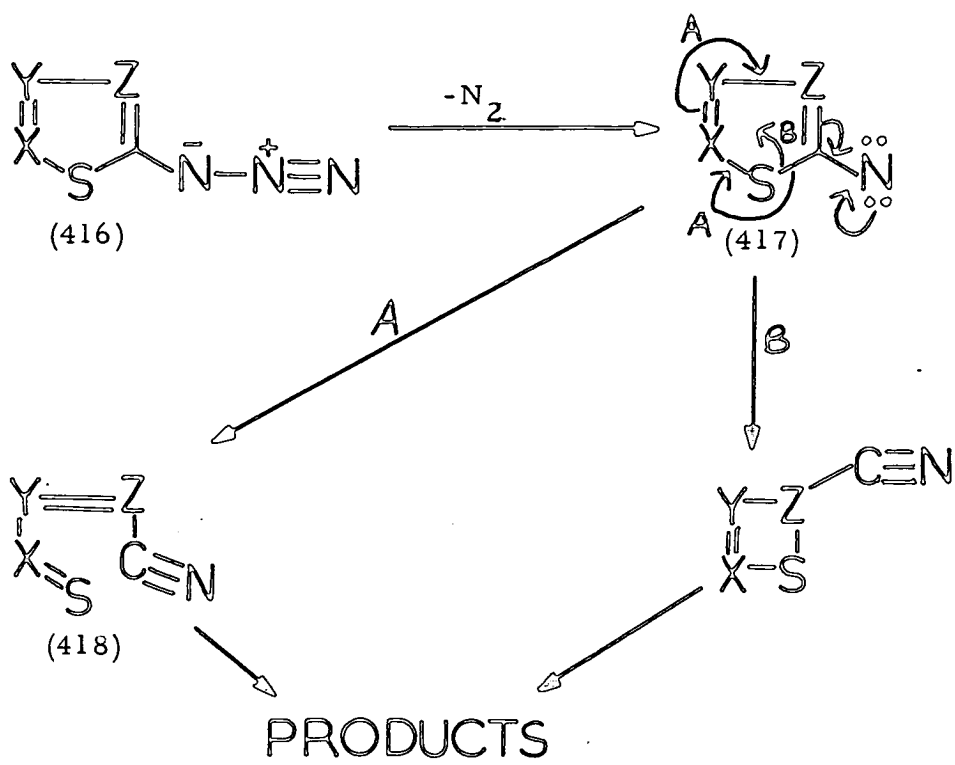
Scheme 156

but isolated the dimeric azotriazole as well as fragmentation

products on oxidation of 5-amino-1,4-diphenyltriazole. Smith[178]

postulates that formation of the azo product (e.g. 415) does not

involve the nitrene (411) but rather involves the dimerisation of an

intermediate amino radical (413), followed by oxidation of the hydrazine

(414) produced (Scheme 155). However, as azo compounds have been

demonstrated as the products of both pyrolysis and photolysis of

aryl azides,[172,180] it would seem that they can also be derived by

dimerisation of the corresponding nitrene. Further studies aimed

at firmly establishing the mechanisms and intermediates involved

in the oxidation of amines, and thermolysis and photolysis of azides

to afford decomposition products and dimeric azo compounds would

therefore be desirable.

·Having demonstrated the general character of the interesting

thermal and photochemical fragmentation of 5-azidoisothiazoles it

was of interest to seek similar fragmentation processes in azides

derived from structurally analogous five-membered heterocycles

containing nitrogen and sulphur. It was anticipated that two types

of fragmentation process might be observed depending on whether

the azide function is $\underline{\alpha}$ or $\underline{\beta}$ to the sulphur atom (Scheme 156). Thus,

$\underline{\alpha}$-azidothioheterocycles, by analogy with 5-azidoisothiazoles (see

before) might follow the fragmentation pathway [Scheme 156; (416) ->

(417) -> (418) -> etc] whereas $\underline{\beta}$-azidothioheterocycles could fragment

by the mode [Scheme 156; (419) -> (420) -> (421) + (422)]. With a

view to investigating the scope of the former type of fragmentation

it was decided to study the thermal and photochemical decomposition

(423)

(424)

1. HONO
2. N_3^-

H^+

(425)

N_3^-

(426) BF_4^-

N_3^-

(427)

(428)
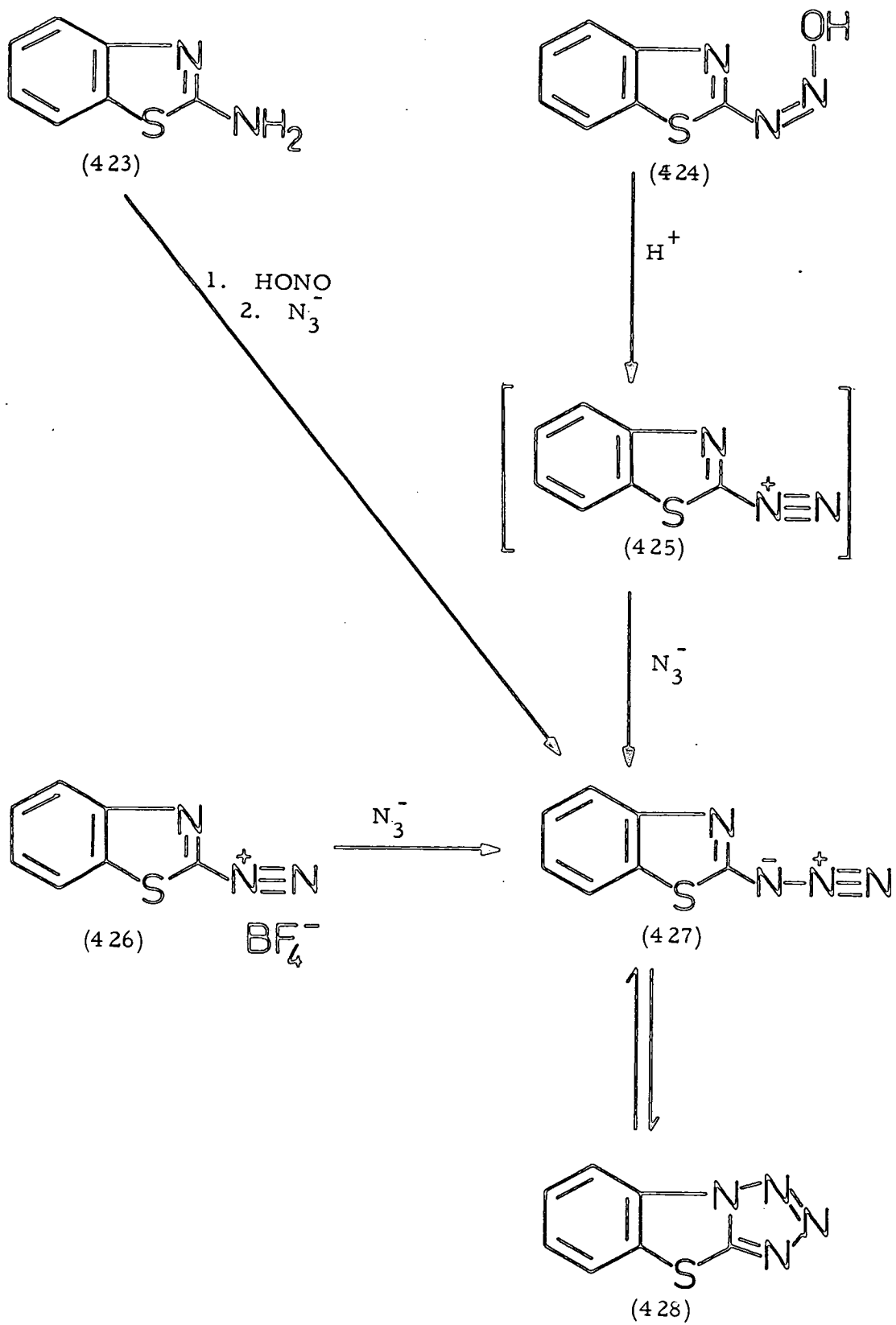
Scheme 157

of 2-azidobenzothiazole (427) (Scheme 157). The azide (427) was readily synthesised by azidodediazoniation of the benzothiazole-2-diazonium cation. In practice diazotisation of 2-aminobenzothiazole (423) using one equivalent of sodium nitrite in phosphoric acid followed by treatment with sodium azide gave only a low yield (26%) of the azide (427) whereas the use of two equivalents of sodium nitrite raised the yield of (427) to 92%. The use of excess of sodium nitrite offsets the decomposition of nitrous acid which occurs in phosphoric acid hence improving the efficiency of diazotisation and consequently of azidodediazoniation. The azide (427) was also formed (Scheme 157) in good to excellent yield by treating an aqueous suspension of benzothiazole-2-diazonium fluoroborate (426) with sodium azide or by reacting 2-N-hydroxyazobenzothiazole (424) (see Chapter 3) in phosphoric acid with sodium azide. The amine (423) was a by-product of the latter transformation which presumably involves the intermediate formation of the benzothiazole-2-diazonium cation (425) (Scheme 157). The high yields of the azide (427) formed from benzothiazole-2-diazonium cation (425) are in marked contrast to the inefficiency of other dediazoniation reactions of this cation (425) (see Chapter 3). 2-Azidobenzothiazole (427) is reported in the literature to exist in the tetrazole tautomeric form.[181,182] However the presence of strong azide absorption in the i.r. spectrum of the azide (427) obtained in the present work clearly indicates its predominant existence in the azide (427) as opposed to the tetrazole form (428) (Scheme 157). The thermolysis of 2-azidobenzothiazole (427) in glacial acetic acid gave a low yield of an unidentified solid which
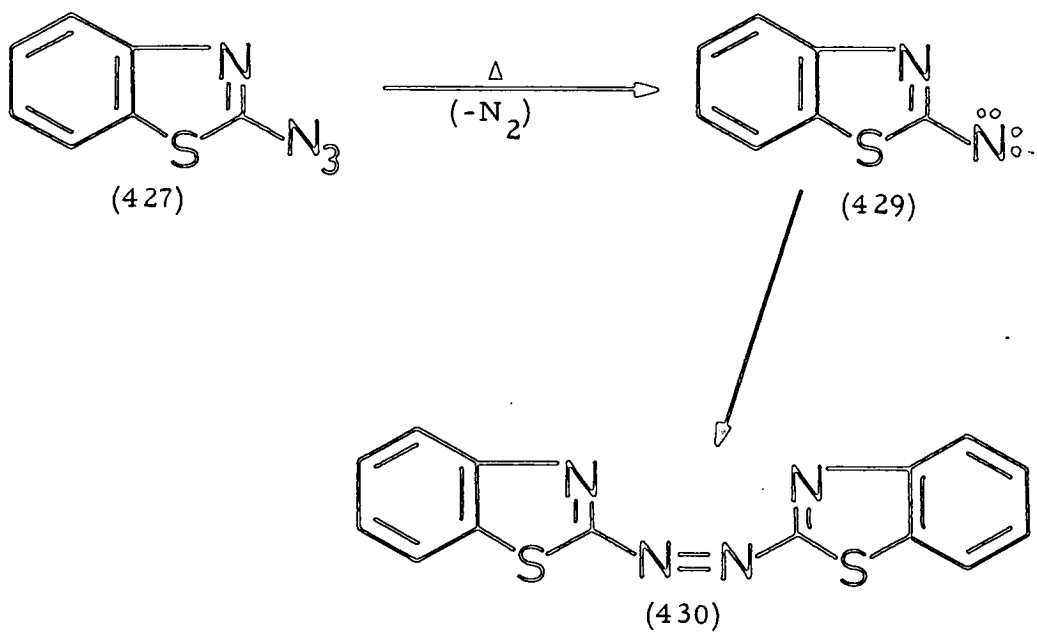
Scheme 158
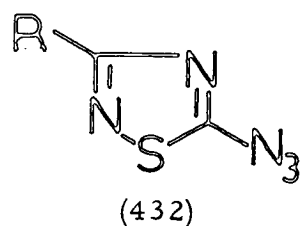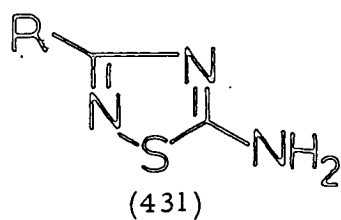
	R
a;	Me
b;	Ph
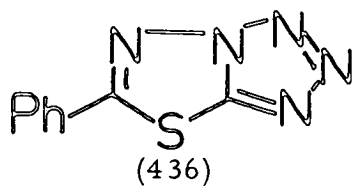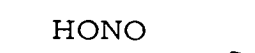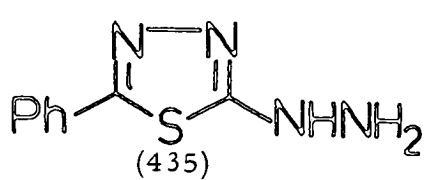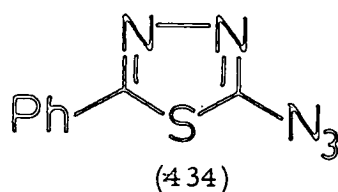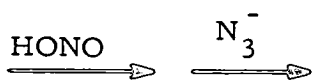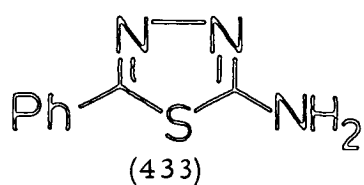
Scheme 159

analysed as a hydrate of the azo compound (430) (Scheme 158).
This product (430) could be derived by dimerisation of the nitrene
(429) formed on thermolysis. The photolysis of the azide (427) was
not attempted because of the low yield of material recovered from
the thermolysis reaction.

5-Azido-1, 2, 4-thiadiazoles such as (432) (Scheme 159) have
structures which would be expected to undergo 'α-azidothio' type
thermal and photochemical fragmentation (see Scheme 156). Unfor-
tunately attempts to convert the readily available 5-amino-3-methyl-
and 5-amino-3-phenyl-1, 2, 4-thiadiazoles[165] (see Chapter 5) by
diazotisation and subsequent azidodediazoniation into the azides
(432a and b) (Scheme 159) were unsuccessful hence precluding the
study of their thermal and photochemical fragmentation. Thus the
attempted diazotisation of the methyl compound (431a) followed by
reaction with sodium azide gave only a low recovery of 5-amino-3-
methyl-1, 2, 4-thiadiazole. Correspondingly the attempted
diazotisation/azidodediazoniation of 5-amino-3-phenyl-1, 2, 4-thia-
diazole (431b) was thwarted by the formation of the hydrate of 5-
nitro-3-phenyl-1, 2, 4-thiadiazole (see Chapter 5). The attempted
reaction of 3-phenyl-1, 2, 4-thiadiazole-5-diazonium fluoroborate
(see Chapter 5) with sodium azide in aqueous solution gave a pink
solid whose i. r. spectrum showed azide absorption but on crystallisa-
tion merely afforded 5-N-hydroxyazo-3-phenyl-1, 2, 4-thiadiazole
(see Chapter 5). The attempted reaction of 3-phenyl-1, 2, 4-thia-
diazole-5-diazonium fluoroborate with sodium azide in aqueous
acetone gave only a low yield of an intractable solid.

$$\text{(434)} \xrightarrow[\;(-N_2)\;]{\Delta \quad \text{AcOH}} \text{[(437)]}$$
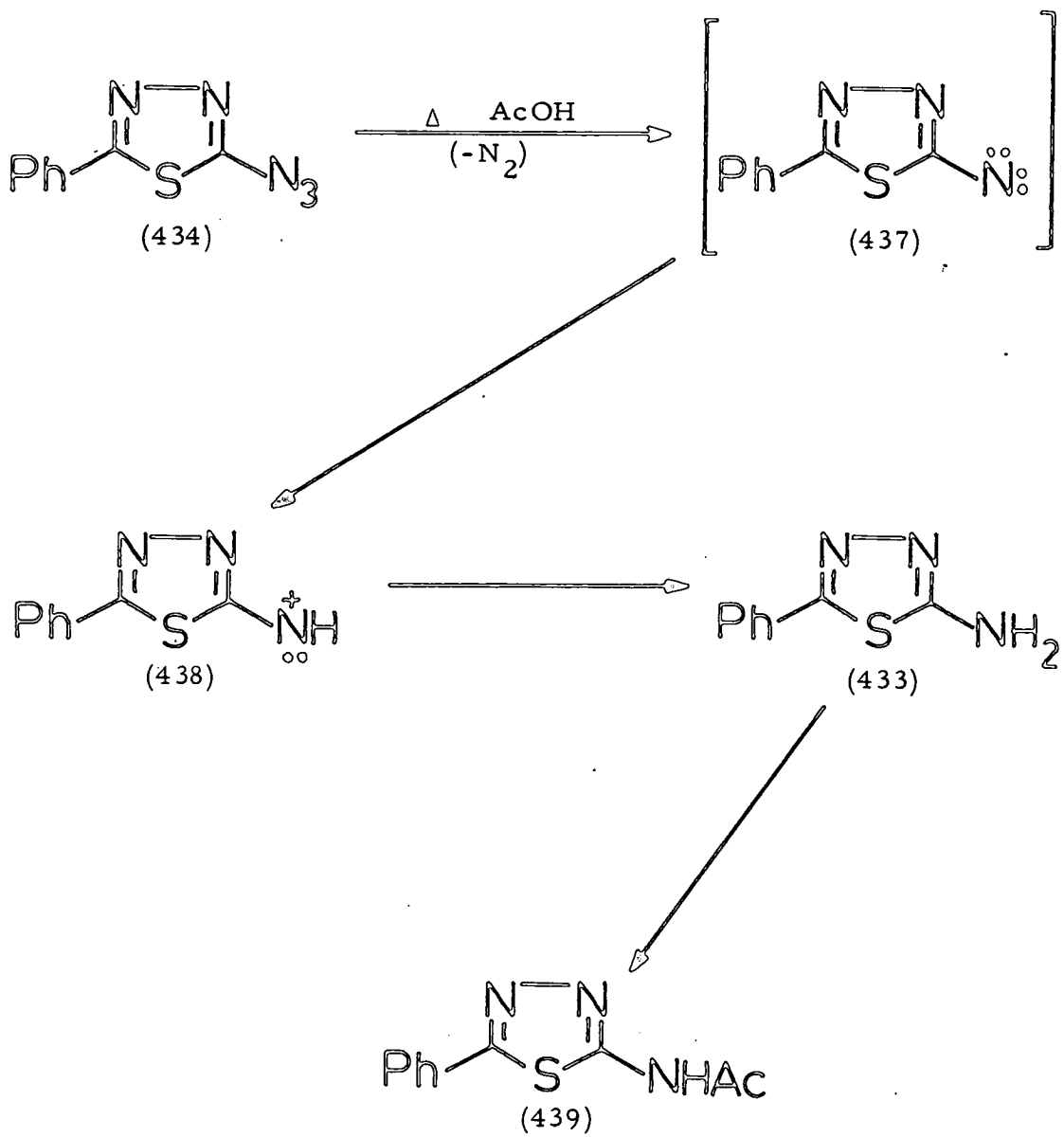
Scheme 160

In contrast to the lack of success in synthesising the azides (432a and b), 2-azido-5-phenyl-1,3,4-thiadiazole (434) (Scheme 159) was readily prepared in good yield by diazotising 2-amino-5-phenyl-1,3,4-thiadiazole[171] (see Chapter 5) with sodium nitrite in concentrated phosphoric acid and then treating the resulting diazonium suspension with aqueous sodium azide. Unreacted 2-amino-5-phenyl-1,3,4-thiadiazole was also recovered in this reaction. The product formed by treating 2-hydrazino-5-phenyl-1,3,4-thiadiazole (435) with nitrous acid was formulated by Kanaoka[183] as the tetrazole (436) rather than the azide (434) (Scheme 159). Conversely Sandstrom[170] has formulated the product as the azide (434) on the basis of the presence of azide absorption in its i.r. spectrum. The product obtained in the present studies by diazotisation/azidodediazoniation of the amine (433) had a melting point close to that reported by Kanaoka[183] but exhibited a band at 2130 cm^{-1} in its i.r. spectrum attributable to an azido group thus demonstrating its existence predominately in the azide tautomeric form (434). 2-Azido-5-phenyl-1,3,4-thiadiazole (434) underwent thermolysis on heating in glacial acetic acid to give a low yield of 2-acetamido-5-phenyl-1,3,4-thiadiazole (439) (Scheme 160). This product was identified by comparison with an authentic sample of the acetamidothiadiazole (439), prepared by acetylating the amine (433). Formation of the product (439) can be rationalised (Scheme 160) by decomposition of the azide to give the nitrene (437) protonation of which would give the nitrenium ion (438) convertible by sequential hydrogen abstraction and deprotonation into the amine (433) and thence by acetylation the
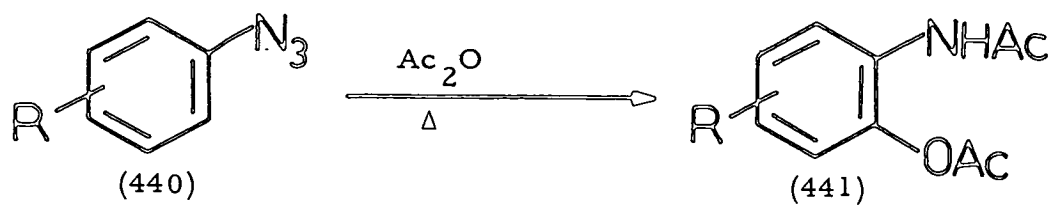
Scheme 161
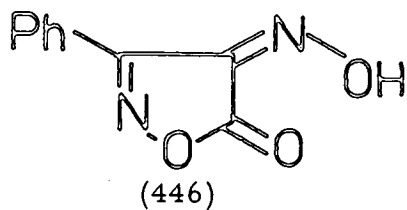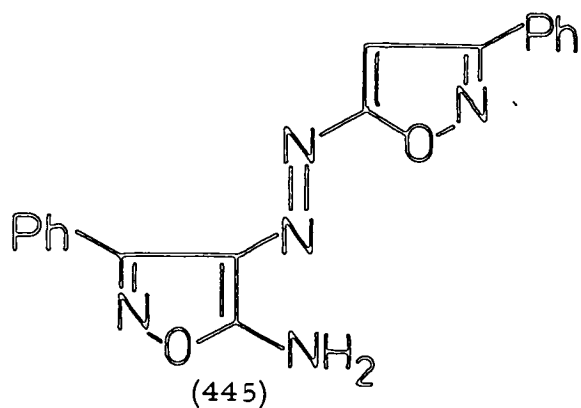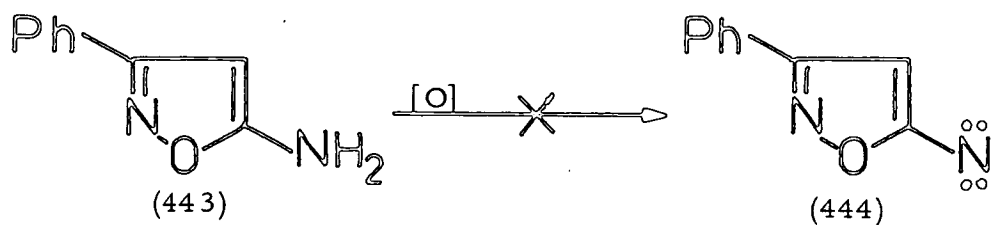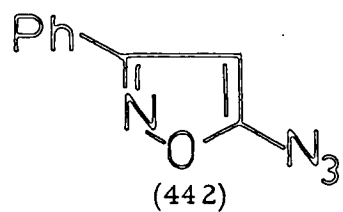
Scheme 162

product (439).   The transformation [Scheme 160; (434) -> (439)]

is akin to the conversion of aryl azides (440) in hot acetic anhydride

into acetanilide derivatives (441) (Scheme 161).[184] The stability of

the nitrene intermediate (437) to fragmentation is in contrast with

the behaviour of nitrenes derived from azidoisothiazoles (see before).

The photolysis of the azide (434) in glacial acetic acid also afforded

the acetamidothiadiazole (439) in low yield together with an

unidentified yellow solid which decomposed on attempted purification.

The preparation of 5-azido-3-phenylisoxazole (442) (Scheme

162) and the subsequent study of its thermolysis and photolysis

reactions would have been of particular interest since (442) is an

oxygen analogue of the 5-azidoisothiazoles (see before) and might

therefore have been expected to decompose in a similar manner.

Unfortunately, however the diazotisation/azidodediazoniation of

5-amino-3-phenylisoxazole (443)[130] (see Chapter 2) was thwarted

by the unorthodox behaviour of the amine (443) in the diazotisation

step.   Diazotisation of the amine (443) using nitrosylsulphuric acid

in glacial acetic acid followed by treatment with sodium azide afforded

a yellow solid whose i.r. spectrum indicated it to be a mixture of

5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (445)

and the hydrate of the syn-oxime (446), already encountered as

discussed in Chapter 2.   ·Diazotisation of the amine (443) with

sodium nitrite in concentrated phosphoric acid followed by treatment

with sodium azide gave a yellow solid whose t.l.c. and i.r. spectrum

indicated it to be a mixture of unreacted amine (443), 5-amino-4-

(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (445) and a third

component.   Examination of the i.r. spectrum of the mixture
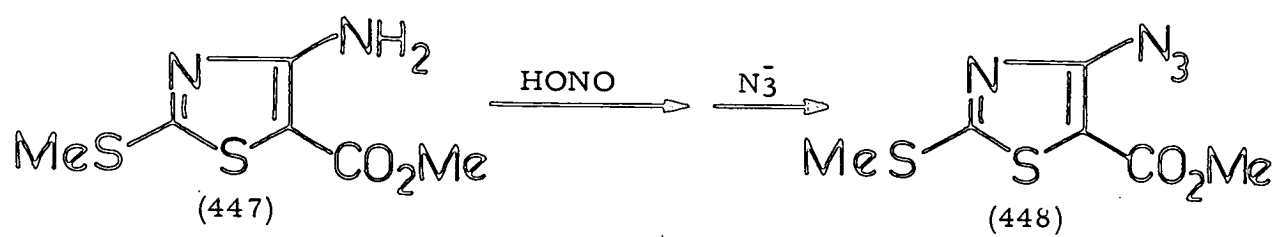
Scheme 163

revealed a band at 2130 cm^{-1} suggesting that the third component

of the mixture might have been the desired azide (442). Because of

its complexity no attempt was made to separate the mixture. The

foregoing attempts to synthesise the azide (442) demonstrate that

not even the rapid and efficient azidodediazoniation reaction is able

to intercept the unstable 3-phenylisoxazole-5-diazonium cation which

reacts as already discussed in Chapter 2. In an alternative approach

(Scheme 162) an attempt was made to generate the nitrene (444)

directly in the hope of observing its mode of fragmentation. To

this end the amine (443) was subjected to hypochlorite oxidation

under conditions believed[178,179] to effect the direct conversion of

amines into nitrenes. However work up of this reaction gave no

identifiable material.

Attention was next directed to the study of the synthesis and

reactivity of five-membered heterocyclic azides structurally suited

to undergo the 'β-azidothio' mode of fragmentation (Scheme 156).

To this end the readily accessible methyl 4-azido-2-methylmercapto-

thiazole-5-carboxylate (448) (Scheme 163) was synthesised in

quantitative yield by diazotising methyl 4-amino-2-methylmercapto-

thiazole-5-carboxylate (447)[155] with sodium nitrite in phosphoric

acid followed by treatment with sodium azide. A somewhat lower

yield of the azide (448) was obtained when the diazotisation step in

this transformation was carried out using nitrosylsulphuric acid in

glacial acetic acid. The overall efficiency of the diazotisation/

azidodediazoniation reactions of the amine (447) contrasts with the

low yields or total lack of reaction observed in other diazotisation/
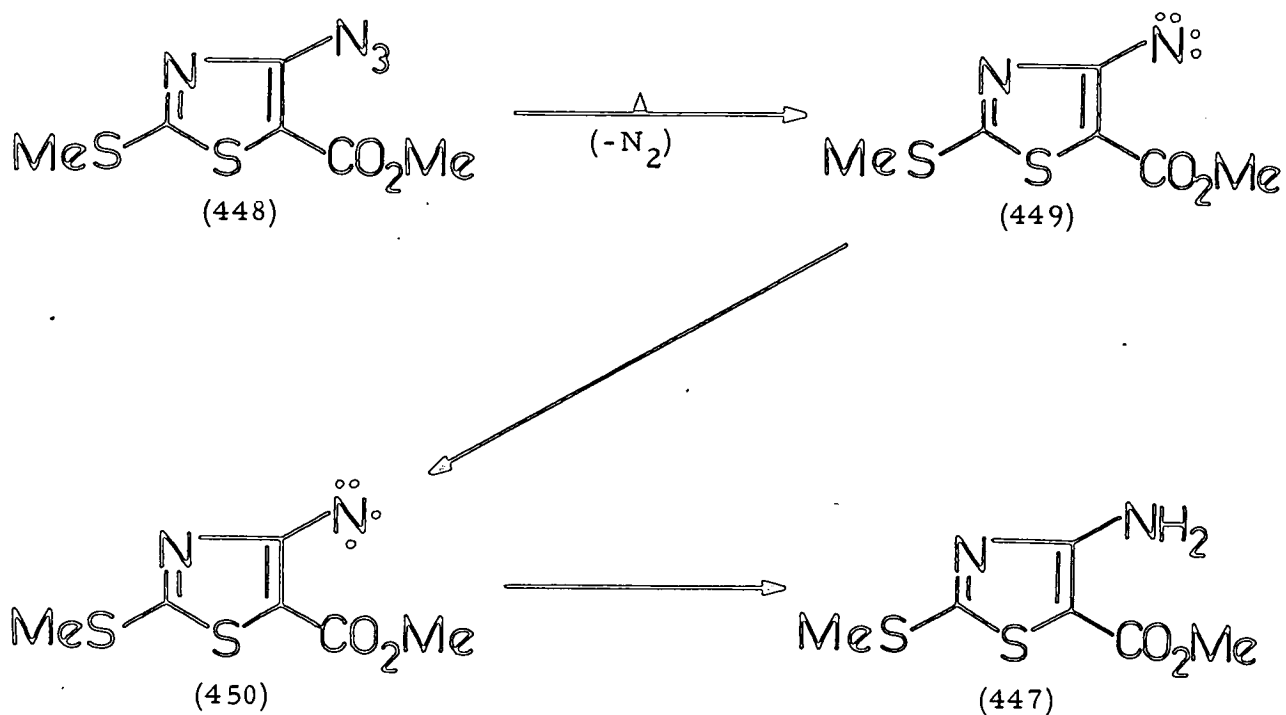
Scheme 164
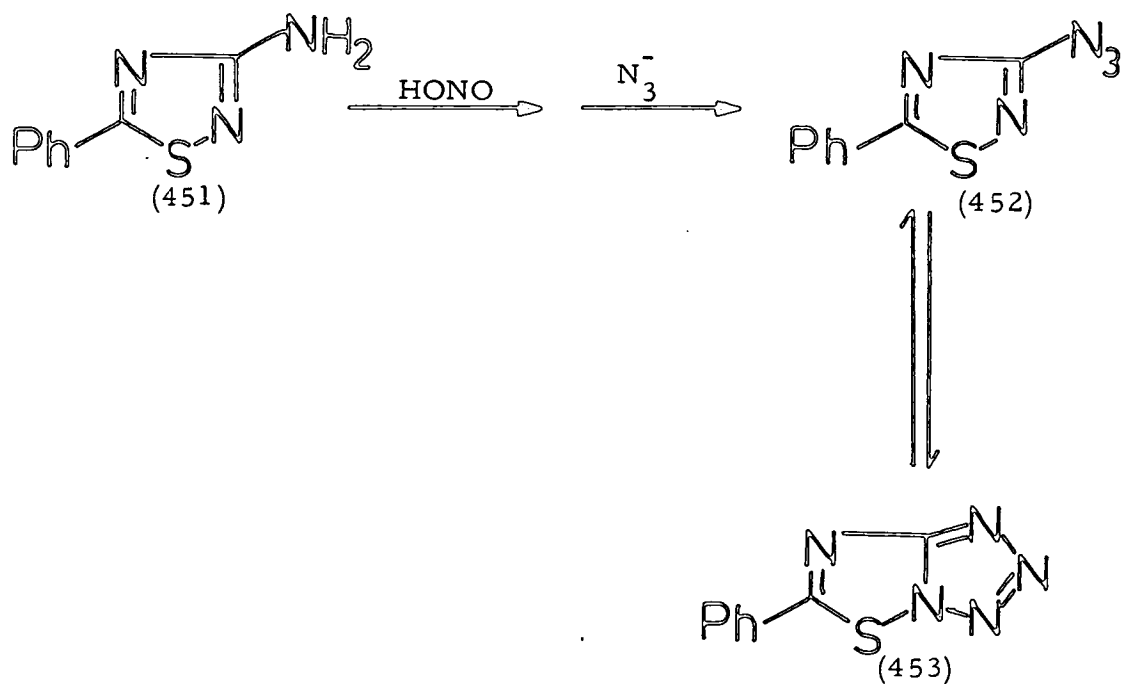
Scheme 165

dediazoniation reactions of this compound (see Chapter 3). The

formulation of the product of the diazotisation/azidodediazoniation

reactions of the amine (447) as the azide (448) is consistent with the

presence in its i.r. spectrum of azide absorption at <u>ca</u> 2000 cm^{-1}.

The azide (448) was found to be relatively stable to thermolysis

being recovered to a significant extent after being heated under reflux

in toluene. However thermolysis in refluxing xylene proceeded

more efficiently to give a moderate yield (39%) of 4-amino-2-methyl-

mercaptothiazole-5-carboxylate (447). The azide (448) must therefore

decompose initially to the singlet nitrene (449) and thence to the

triplet nitrene (450) which is capable of abstracting hydrogen from

the solvent to afford the amine (447) (Scheme 164). In contrast

with the nitrenes derived from the thermolysis and photolysis of

azidoisothiazoles (see before), it would appear that the nitrene (449)

formed by thermolysis of methyl 4-azido-2-methylmercaptothiazole-

5-carboxylate (448) is resistant to fragmentation. Photolysis of

the azide (448) did not yield any identifiable material. Irradiation

in benzene afforded a small amount of an unidentified solid whose

i.r. spectrum showed the presence of a hydroxyl group and two

carbonyl groups while irradiation in acetone merely gave an intractable

gum.

3-Azido-5-phenyl-1,2,4-thiadiazole (452) (Scheme 165) is

structurally suited to undergo fragmentation of the 'β-azidothio' type

(Scheme 156) and consequently it was of interest in the context of

the present studies to investigate its behaviour toward thermolysis

and photolysis. The azide (452) was readily prepared (Scheme 165)
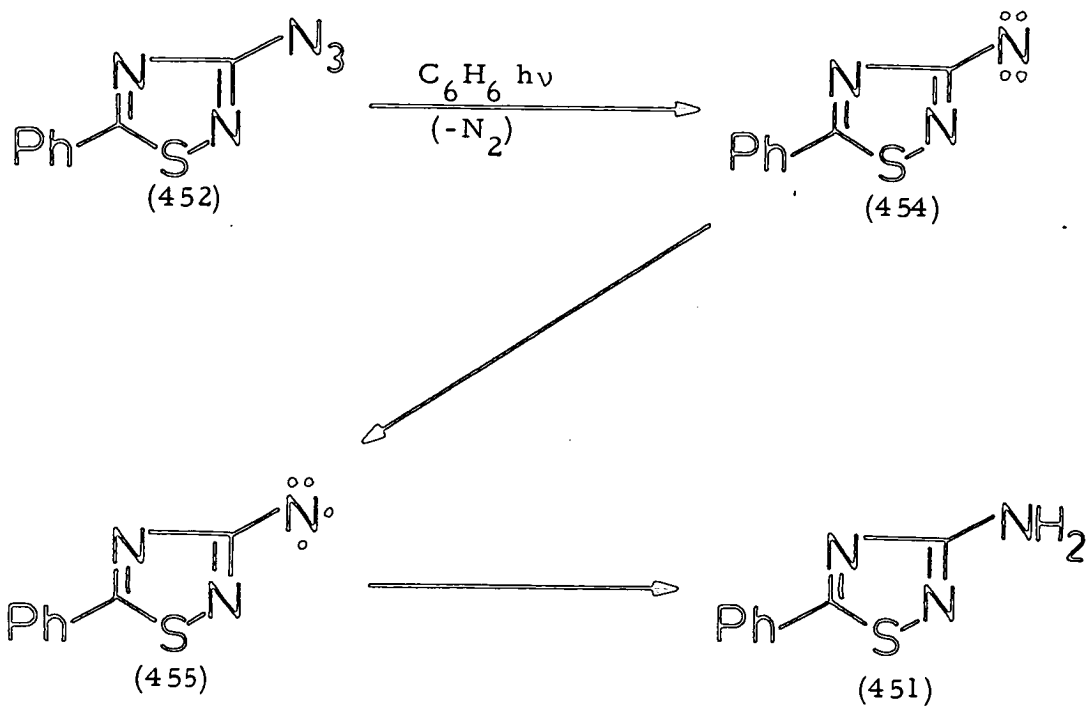
Scheme 166

in high yield by the diazotisation of 3-amino-5-phenyl-1, 2, 4-thia-
diazole (451)[169] using sodium nitrite in phosphoric acid, followed by
dediazoniation with sodium azide.   The formation of the product of
these transformations as the azide (452) and not the tetrazole tautomer
(453) follows from the presence in its i. r. spectrum of well-defined
azide absorption at $\underline{ca}$ 2000 cm^{-1}.   Surprisingly, the azide (452)
was largely stable to thermolysis, being recovered in quantitative
yield after heating in glacial acetic acid and being largely unaffected
when heated in xylene.   Photolysis of the azide (452) in dry benzene
also gave unreacted azide (452) together with a yellow solid identified,
by comparison with an authentic sample, as 3-amino-5-phenyl-1, 2, 4-
thiadiazole (451).   Formation of the latter can be explained by
decomposition of the azide (452) to the singlet nitrene (454) which
converts to the triplet nitrene (455) capable of abstracting hydrogen
from the solvent to give the amine (451) (Scheme 166).   Once again
it would appear that the nitrene (454) formed on decomposition of the
azide (452) does not fragment unlike nitrenes derived from azidoiso-
thiazoles (see before).

Experimental

5-Amino-3-methylisothiazole Hydrochloride (373)

(a) β-Iminothiobutyramide (372) was prepared (55%) by passing hydrogen sulphide through a solution of 3-aminocrotononitrile (371) in pyridine according to the method of Adams and Slack,[175] and had m.p. 128-132° (lit.,[175] 142°).

(b) 5-Amino-3-methylisothiazole hydrochloride (373) was prepared (70%) by oxidising β-iminothiobutyramide (372) with hydrogen peroxide according to the method of Goerdeler and Pohland[176] and had m.p. 170° (decomp.) [lit.,[176] 145° (decomp.); lit.,[175] 240° (decomp.)], ν_{max} 3210 br and 3060 br (NH$_2$) cm^{-1}.

Preparation of Ethoxymethylenemalononitrile Derivatives

(a) Ethoxymethylenemalononitrile (365a) was prepared according to Sayer and Campbell[174] by heating malononitrile (66.0 g; 1.0 mol) under reflux with triethyl orthoformate (152.0 g; 1.03 mol) in acetic anhydride (208 ml) for 25 h. The resulting red-brown solution was concentrated, cooled in ice, and treated with light petroleum to give the product (365a) as colourless crystals (70.9 g; 58%), m.p. 57-59° (from ethyl acetate-light petroleum) (lit.,[174] 67-68°).

(b) 1,1-Dicyano-2-ethoxybut-1-ene (365b)

A mixture of triethyl orthopropionate (42.2 g; 0.24 mol), malononitrile (13.2 g; 0.2 mol) and acetic acid (0.6 g) was stirred and heated at 120-130° (oil bath) with provision for the removal of

ethanol. After ethanol had ceased to distil over (ca 1 h) the mixture was allowed to cool and then distilled under reduced pressure to give 1,1-dicyano-2-ethoxybut-1-ene (365b) as a colourless liquid (25.8 g; 86%), b.p. 96°/0.5 mm Hg (lit.,[185] 150-153°/15 mm Hg), ν_{max} 2230 (CN) cm^{-1}.

Preparation of Aminomethylenemalononitrile Derivatives.

(a) 2-Amino-1,1-dicyanoethylene (367a) was prepared as described by Sayer and Campbell[174] by mixing a solution of ethoxy-methylenemalononitrile (365a) (54.9 g; 0.45 mol) in methanol (300 ml) with 25% aqueous ammonia (67.5 ml) and stirring the mixture for 3 h. The product (367a) was obtained by evaporating the mixture, as a colourless solid (yield quantitative), m.p. 140-143° (lit.,[174] 145°).

(b) 2-Amino-1,1-dicyanobut-1-ene (367b)

A solution of 1,1-dicyano-2-ethoxybut-1-ene (365b) (15.0 g; 0.1 mol) in methanol (100 ml) was treated with 25% aqueous ammonia (15.0 ml). Heat was liberated and the mixture was stirred for 2.25 h at room temperature then evaporated to give 2-amino-1,1-dicyanobut-1-ene (367b) as a colourless solid (11.9 g; quant.), m.p. 160-162° (lit.,[186] 164-165°), ν_{max} 3360 and 3220 (NH$_2$), 2220 and 2200 (CN), and 1680 (NH def) cm^{-1}.

Preparation of Aminomethylenethiocyanoacetamide Derivatives.

(a) 3-Amino-2-cyanothioacrylamide (368a) was prepared as described by Sayer and Campbell[174] by treating a solution of 2-amino-1,1-dicyanoethylene (367a) (27.9 g; 0.3 mol) in 99.5% ethanol

(450 ml) with triethylamine (0.45 ml) and then passing hydrogen sulphide through the solution at room temperature for 11.5 h, during which time more triethylamine (0.45 ml) was added. The mixture was cooled in ice and scratched to crystallise the product (368a) as a yellow solid which was combined with a second crop obtained by concentrating the mother liquor (total 16.5 g; 55%), m.p. 158-159° (lit.,[174] 155-159°).

(b) <u>3-Amino-2-cyanothiopent-2-enamide</u> (368b)

Hydrogen sulphide was bubbled through a solution of 2-amino-1,1-dicyanobut-1-ene (367b) (19.9 g; 0.098 mol) and triethylamine (0.67 ml) in absolute ethanol (250 ml) for 12 h until t.l.c. in methylene chloride and ethyl acetate over silica showed only a very faint trace of starting material. The mixture was concentrated to half volume and cooled in ice with scratching to give <u>3-amino-2-cyanothiopent-2-enamide</u> (368b) as colourless needles (17.7 g; 69%), m.p. 106-107° (from water), ν_{max} 3400, 3300, 3200 and 3130 m (NH), 2190 (CN), and 1635 and 1620 (NH def.) cm^{-1}, δ [(CD$_3$)$_2$SO] 8.92 (1H, br s, NH), 8.50 (1H, br s, NH), 7.70 (1H, br s, NH), 2.50 (2H, q, J 8Hz, <u>CH$_2$</u>-CH$_3$), and 1.18 (3H, t, J 8Hz, CH$_2$-<u>CH$_3$</u>).

<u>Found:</u> C, 46.6; H, 5.9; N, 27.4%; M$^+$, 155.

<u>C$_6$H$_9$N$_3$S</u> requires: C, 46.5; H, 5.8; N, 27.1%; M, 155.

<u>Preparation of 5-Aminoisothiazole-4-carbonitrile Derivatives</u>

(a) <u>5-Aminoisothiazole-4-carbonitrile</u> (369a) was prepared as described by Sayer and Campbell,[174] by treating a solution of 3-amino-2-cyanothioacrylamide (368a) (15.9 g; 0.125 mol) in

methanol (500 ml) dropwise with stirring with 30% aqueous

hydrogen peroxide (34.0 ml) followed by heating the mixture under

reflux with stirring for 1.75 h.   The mixture was concentrated until

crystallisation occurred and kept at 0° overnight to yield 5-aminoiso-

thiazole-4-carbonitrile (369a) as a pale yellow solid (14.2 g; 91%),

m.p. 191-192° (lit.,[174] 187-189°), identical (i.r. spectrum) with

a sample provided by Sayer and Campbell.

(b) <u>5-Amino-3-ethylisothiazole-4-carbonitrile</u> (369b)

A solution of 3-amino-2-cyanothiopent-2-enamide (368b) (12.4

g; 0.08 mol) in methanol (250 ml) was treated dropwise with stirring

with 30% aqueous hydrogen peroxide (22.0 ml) and the mixture was

heated under reflux with stirring for 3.5 h then carefully concentrated

until crystallisation occurred.   The mixture was cooled in ice and

scratched to afford <u>5-amino-3-ethylisothiazole-4-carbonitrile</u> (369b)

as colourless needles (11.3 g; 92%), m.p. 149-151° [from toluene-

light petroleum (b.p. 80-100°)], ν_{max} 3310 and 3110 (NH$_2$), 2220

(CN), and 1670 and 1645 (NH def.) .cm^{-1}, δ(CDCl$_3$) 5.43 (2H, br s,

NH$_2$), 2.75 (2H, q, J 8Hz, <u>CH</u>$_2$-CH$_3$) and 1.30 (3H, t, J 8Hz, CH$_2$-

<u>CH</u>$_3$)

Found: C, 47.1; H, 4.7; N, 27.3%; M$^+$, 153.

<u>C$_6$H$_7$N$_3$S</u> requires: C, 47.1; H, 4.6; N, 27.5%; M, 153.

<u>5-Amino-3-methyl-4-nitroisothiazole</u> (376).

(a) 5-Acetamido-3-methylisothiazole (374) was prepared (yield

quant.) according to the method of Adams and Slack[175] by acetylation

of 5-amino-3-methylisothiazole hydrochloride (373) and had m.p.

235-238° (lit.,[175] 180-181°).

(b) <u>5-Acetamido-3-methyl-4-nitro-isothiazole</u> (375)

was prepared (93%) according to the method of Adams and Slack[175]

by nitration of 5-acetamido-3-methylisothiazole (374) and had m.p.

176-177° (lit.,[175] 187°).

(c) <u>5-Amino-3-methyl-4-nitro-isothiazole</u> (376) was prepared

as described by Adams and Slack[175] by suspending 5-acetamido-3-

methyl-4-nitro-isothiazole (375) (5.50 g; 0.028 mol) in 4M aqueous

hydrochloric acid (75.0 ml) and heating the mixture under reflux for

4.25 h. The product (376) was obtained as colourless crystals (64%),

m.p. 180-183° (lit.,[175] 185-186°) by diluting the resulting solution

with hot water (75.0 ml) and cooling.

<u>5-Azido-3-methylisothiazole</u> (377)

5-Amino-3-methylisothiazole hydrochloride (373) (6.00 g;

0.04 mol) was dissolved with gentle warming in 88% phosphoric acid

(40.0 ml) and the solution was diluted with water (40.0 ml) and

treated dropwise with stirring at 0-5° with a solution of sodium

nitrite (2.80 g; 0.04 mol) in water (24.0 ml). The resulting yellow

suspension was stirred for 10 min then treated dropwise at 0-10°

with a solution of sodium azide (2.80 g; 0.043 mol) in water (20.0 ml).

The mixture was stirred for 30 min at 0° and extracted with ethyl

acetate (3x100 ml) to give <u>5-azido-3-methylisothiazole</u> (377) as a

brown liquid (5.78 g; quant.), ν_{max} 2000 (N_3) cm^{-1}, δ (CDCl$_3$)

6.57 (1H, s, CH) and 2.37 (3H, s, Me), which was shown to be pure

by t.l.c. in methylene chloride over silica. The product was purified by dissolving it in light petroleum (b.p. 40-60°), filtering the solution and evaporating the filtrate to give the azide (377) as a yellow oil.

Found: C, 34.0; H, 2.9; N, 39.9%; M^+, 138.

$C_4H_4N_4S$ requires: C, 34.5; H, 2.9; N, 40.3%; M, 140.

5-Azidoisothiazole-4-carbonitrile (370a).

5-Aminoisothiazole-4-carbonitrile (369a) (3.12 g; 0.025 mol) was dissolved with gentle warming in 88% phosphoric acid (25.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (3.45 g; 0.05 mol) to give a yellow suspension which was stirred for 10 min at 0°, treated with sulphamic acid (4.85 g; 0.05 mol), stirred for 5 min and then treated dropwise at 0-10° with a solution of sodium azide (1.75 g; 0.027 mol) in water (12.5 ml). The mixture was stirred for 30 min at 5-10° and poured on to ice (125 g) to give a buff coloured solid which was crystallised from light petroleum (80-100°) to afford 5-azidoisothiazole-4-carbonitrile (370a) as colourless needles (3.79 g; quant.), m.p. 86-89°, ν_{max} 2240 and 2200 m (CN) and 2130 (N_3) cm^{-1}, δ (CDCl$_3$) 8.36 (1H, s, CH).

Found: C, 32.1; H, 0.7; N, 45.8%; M^+, 151

$C_4H_1N_5S$ requires: C, 31.8; H, 0.7; N, 46.4%; M, 151.

5-Azidoisothiazole-4-carbonitrile (370a) became red on exposure to light and was found to be a nose and throat irritant.

5-Azido-3-methylisothiazole-4-carbonitrile (362)

(a) 5-Amino-3-methylisothiazole-4-carbonitrile[160] (358) (0.70 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.70 g; 0.01 mol). The resulting suspension was stirred for 15 min at 0°, treated with sulphamic acid (0.97 g; 0.01 mol), stirred for a further 5 min and then treated dropwise at $0-15^\circ$ with a solution of sodium azide (0.33 g; 0.005 mol) in water (2.5 ml). The mixture was stirred for 1.5 h and poured on to ice (25 g) to give 5-azido-3-methylisothiazole-4-carbonitrile (362) as a beige solid (0.61 g; 72%), m.p. 92°, identical (m.p. and i.r. spectrum) with a sample prepared in (b) later.

The aqueous mother liquor was extracted with ethyl acetate (2x30 ml) to afford a red-brown gum (0.19 g) which was triturated with ether-ethanol to give 5-amino-3-methylisothiazole-4-carbonitrile (358) as a beige solid (0.14 g; 20%), m.p. $174-179^\circ$, identical (i.r. spectrum) with an authentic sample.

(b) 5-Amino-3-methylisothiazole-4-carbonitrile[160] (358) (0.70 g; 0.005 mol) was dissolved with gentle warming in a mixture of acetic acid (11.0 ml) and propionic acid (2.0 ml) and the solution was added dropwise with stirring at $0-5^\circ$ to 40% w/w nitrosylsulphuric acid (1.0 ml). The thick yellow suspension was stirred for 30 min at $0-5^\circ$, until no amine could be detected by t.l.c. and then treated dropwise at $0-10^\circ$ with a solution of sodium azide (0.33 g; 0.005 mol) in water (2.5 ml). The resulting yellow solution was stirred for 30 min at $0-5^\circ$ and then poured on to ice (25 g) to precipitate a beige

solid which was crystallised from light petroleum to give <u>5-azido-</u>

<u>3-methylisothiazole-4-carbonitrile</u> (362) as colourless needles

(0.35 g; 42%), m.p. 93-93.5°, ν_{max} 2235 and 2210 w (CN) and

2130 (N$_3$) cm^{-1}, δ(CDCl$_3$) 2.52 (3H, s, Me).

<u>Found:</u>   C, 36.4; H, 1.6; N, 41.9%; M^{+}, 165.

<u>C$_5$H$_3$N$_5$S requires:</u>   C, 36.4; H, 1.8; N, 42.4%; M, 165.

5-Azido-3-methylisothiazole-4-carbonitrile became pale blue on

exposure to light and was found to be a nose and throat irritant.

The aqueous mother liquor was extracted with ethyl acetate

(2x40 ml) to give a brown solid (0.21 g), m.p. 92-98° whose i.r.

spectrum and t.l.c. in toluene-acetone-acetic acid (90:10:0.5) over

silica indicated it to be a mixture of 5-amino-3-methylisothiazole-

4-carbonitrile (358) and 5-azido-3-methylisothiazole-4-carbonitrile

(362). No attempt was made to resolve this mixture.

(c) 3-Methyl-5-nitrosaminoisothiazole-4-carbonitrile (prepared

as described in Chapter four) (361) (0.84 g; 0.005 mol) was dissolved

in 88% phosphoric acid (9.0 ml) and the solution was treated dropwise

with stirring at 0-10° with a solution of sodium azide (0.33 g; 0.005

mol) in water (5.0 ml) to give a colourless suspension which was

stirred at 0° for 1.25 h to afford 5-azido-3-methylisothiazole-4-

carbonitrile (362) as a pink solid (0.74 g; 89%), m.p. 79-79.5°,

identical (i.r. spectrum) with a sample prepared in (b) before.

<u>5-Azido-3-ethylisothiazole-4-carbonitrile</u> (370b)

5-Amino-3-ethylisothiazole-4-carbonitrile (369b) (0.75 g;

0.005 mol) was dissolved with gentle warming in 88% phosphoric

acid (5.0 ml) and the solution was treated at 0° with stirring with

sodium nitrite (0.69 g; 0.01 mol) to give a yellow suspension. This

was stirred for 10 min at 0°, treated with sulphamic acid (0.97 g;

0.01 mol), stirred for a further 5 min and then treated dropwise

at $0\text{-}10^\circ$ with a solution of sodium azide (0.35 g; 0.0055 mol) in

water (2.5 ml). The mixture was stirred for 30 min at 0° and

poured on to ice (25 g) to precipitate a colourless solid which was

crystallised from light petroleum (b.p.40-60°) to afford 5-azido-3-

ethylisothiazole-4-carbonitrile (370b) as colourless platelets (0.87

g; quant.), m.p. 49.5-50°, ν_{max} 2220 m (CN) and 2120 (N_3) cm^{-1};

δ(CDCl$_3$) 3.07 (2H, q, J 8Hz, $\underline{CH}_2$-CH$_3$) and 1.56 (3H, t, J 8Hz,

CH$_2$-$\underline{CH}_3$).

Found: C, 40.5; H, 2.9; N, 39.1%; M$^+$, 179.

$\underline{C_6H_5N_5S}$ requires: C, 40.2; H, 2.8; N, 39.1%; M, 179.

5-Azido-3-ethylisothiazole-4-carbonitrile became red on

exposure to light and was found to be a nose and throat irritant.

The Attempted Preparation of 5-Azido-3-methyl-4-nitroisothiazole

(378)

(a) 5-Amino-3-methyl-4-nitrosiothiazole (376) (3.20 g; 0.02

mol) was dissolved with gentle warming in 88% phosphoric acid

(25.0 ml) and the solution was treated at 0° with stirring with sodium

nitrite (2.80 g; 0.04 mol). The suspension obtained was stirred at

0° for 10 min, treated with sulphamic acid (3.88 g; 0.04 mol),

stirred for a further 5 min and then treated dropwise at $0\text{-}10^\circ$ with

a solution of sodium azide (1.52 g; 0.023 mol) in water (10.0 ml).

The mixture was stirred at 0-10° for 30 min and poured on to ice

(75 g) to precipitate a solid which was crystallised from light

petroleum (b. p. 100-120°) to give the furoxan (380) as orange

crystals (3.11 g; quant.), m.p. 100-108°, ν_{max} 1625 (C=N) cm^{-1},

δ (CDCl$_3$) 2.56 (3H, s, Me).

Found: C, 30.9; H, 2.1; N 26.3%; M$^+$, 157, 141 (M$^+$-16).

$\underline{C_4H_3N_3O_2S}$ requires: C, 30.6; H, 1.9; N, 26.7%; M, 157.

(b) A suspension of 5-amino-3-methyl-4-nitrosiothiazole (376)

(0.80 g; 0.005 mol) in acetic acid (10.0 ml) was treated at 10-15°

with stirring with a suspension of nitrosylsulphuric acid (1.4 g; 0.011

mol) in acetic acid (5.0 ml).   The resulting yellow suspension was

stirred for 20 min and then treated dropwise at 0-10° with a solution

of sodium azide (0.37 g; 0.0055 mol) in water (2.5 ml).   The

mixture was stirred for 40 min and poured on to ice (25 g) to

precipitate a yellow solid, m.p. 175-180°, identical (i.r. spectrum)

with 5-amino-3-methyl-4-nitroisothiazole (376), a second crop of

which was obtained by neutralising the aqueous mother liquor with

concentrated aqueous ammonia and extracting with ethyl acetate

(2x25 ml) (total 0.63 g; 79%).

The Thermolysis of 5-Azidoisothiazole Derivatives in Acetic Acid

(a) A solution of 5-azido-3-methylisothiazole (377) (1.68 g;

0.012 mol) in glacial acetic acid (30.0 ml) was heated under reflux

for 15 min.   Evaporation gave a dark gum (1.12 g) which was

chromatographed over alumina.

Elution with methylene chloride-ethyl acetate (70:30) afforded an unidentified yellow solid (0.04 g; 2%), m.p. 177-180°, ν_{max} 3290, 3210 and 3080 (NH_2), 2200 (CN) and 1645 and 1625 (NH def.) cm^{-1}, M^+177.

Elution with ethylacetate-ethanol (80:20) gave a brown solid which was crystallised from glacial acetic acid to yield S, S-di-(2-amino-1-cyanoprop-1-en-1-yl)disulphide (384) as pale yellow crystals (0.24 g; 18%), m.p. 212-214°, ν_{max} 3440, 3320, 3210, and 3180 (NH_2), 2170 (CN), and 1615 (NH def.) cm^{-1}, $\delta[(CD_3)_2SO]$ 8.02-7.90 (2H, br s, NH), 7.38-7.22 (2H, br s, NH) and 2.10 (6H, s, Me).

Found: C, 42.7; H, 4.5; N, 24.6%; M^+, 226.

$C_8H_{10}N_4S_2$ requires: C, 42.5; H, 4.4; N, 24.8%; M, 226.

(b) A solution of 5-azido-3-methylisothiazole (377) (0.42 g; 0.003 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 27 min. Evaporation gave a dark brown gum (0.50 g) which was triturated with ether-ethyl acetate to afford a brown solid (0.11 g; 32%), m.p. 192-193°, identical (i.r. spectrum) with the disulphide (384) prepared in (a) before.

The ether-ethyl acetate mother liquor was shown by t.l.c. in ethyl acetate over silica to contain an unresolvable four component mixture which was not further investigated.

(c) A solution of 5-azidoisothiazole-4-carbonitrile (370a) (0.90 g; 0.006 mol) in glacial acetic acid (30.0 ml) was heated under reflux for 45 min. Evaporation gave a brown gummy solid (0.71 g) which was chromatographed over alumina.

Elution with methylene chloride-ethylacetate (25:75) gave

a colourless solid which was combined with a second crop obtained

by eluting with ethyl acetate-ethanol (50:50) (total 0.27 g; 49%),

m.p. 144-145°, identical (m.p. and i.r. spectrum) with an authentic

sample of 2-amino-1,1-dicyanoethylene (367a).

(d) A solution of 5-azido-3-methylisothiazole-4-carbonitrile

(362) (2.47 g; 0.015 mol) in glacial acetic acid (70.0 ml) was heated

under reflux for 2 h.   Evaporation gave a brown solid (1.85 g;

quant.), which was crystallised from water to give colourless plates

of 2-amino-1,1-dicyanoprop-1-ene (363), m.p. 218-220°, identical

(i.r. spectrum) with an authentic sample.

(e) A solution of 5-azido-3-ethylisothiazole-4-carbonitrile

(370b) (1.08 g; 0.006 mol) in glacial acetic acid (30.0 ml) was

heated under reflux for 15 min.   Evaporation gave a brown gummy

solid (0.94 g) which was chromatographed in methylene chloride-

ethyl acetate (80:20) over alumina to afford a colourless solid (0.44

g; 61%), m.p. 160-161°, identical (m.p and i.r. spectrum) with

an authentic sample of 2-amino-1,1-dicyanobut-1-ene (367b).

The Thermolysis of 5-Azido-3-methylisothiazole-4-carbonitrile (362) in Toluene.

A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362)

(0.66 g; 0.004 mol) in anhydrous toluene (40.0 ml) was heated under

reflux for 15 min.   Evaporation gave a dark gummy solid (0.62 g)

which was triturated with ethyl acetate-ethanol to afford a brown

solid, m.p. 194-198°, identical (i.r. spectrum) with an authentic

sample of 2-amino-1,1-dicyanoprop-1-ene (363) more of which was

obtained from the ethyl acetate-ethanol mother liquor on standing

(total 0.42 g; 100%).

The Thermolysis of 5-Azido-3-methylisothiazole (377) in Dimethyl Acetylenedicarboxylate.

A solution of 5-azido-3-methylisothiazole (377) (0.42 g; 0.003

mol) in dimethyl acetylenedicarboxylate (10.0 ml) was heated at

60-70° for 1 h.   Evaporation of the solution gave a dark gum (3.55

g) which was chromatographed in toluene over alumina to afford a

colourless oil (0.37 g).   Trituration with ether yielded dimethyl

1-N-(3'-methylisothiazol-5'-yl)-1,2,3-triazole-4,5-dicarboxylate

(409) as colourless crystals (0.09 g; 11%), m.p. 72-73° [from

benzene-light petroleum (b.p. 40-60°)], ν_{max} 1735 (CO) cm^{-1},

δ(CDCl$_3$) 7.28 (1H, s, CH), 4.01 (3H, s, Me), 3.98 (3H, s, Me),

and 2.53 (3H, s, Me).

Found: C, 42.5; H, 3.5; N, 19.9%; M$^+$, 282.

C$_{10}$H$_{10}$N$_4$O$_4$S requires: C, 42.5; H, 3.5; N, 19.9%; M, 282.

Elution with toluene-methylene chloride (3:1) afforded an

intractable orange gum (0.28 g).

Elution with toluene-methylene chloride (1:1) yielded an

intractable brown gum (0.22 g).

The Attempted Reaction of 5-Azido-3-methylisothiazole-4-carbonitrile (362) with Dimethyl Acetylenedicarboxylate in Toluene

A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362) (0.66 g; 0.004 mol) and dimethyl acetylenedicarboxylate (0.62 g; 0.0044 mol) in anhydrous toluene (50.0 ml) was heated under reflux; for 15 min. The red solution was decanted from a small amount of tar and evaporated to give a dark red gum (0.87 g) which was triturated with ether-ethyl acetate to afford a brown solid (0.12 g; 28%), m.p. 195-197°, identical (i.r. spectrum) with an authentic sample of 2-amino-1,1-dicyanoprop-1-ene (363).

The ether-ethyl acetate mother liquor was shown by t.l.c. in ethyl acetate over silica to contain an unresolvable multicomponent mixture which was not further investigated.

The Attempted Reaction of 5-Azido-3-methylisothiazole-4-carbonitrile (362) with Phenylisocyanate in Toluene

A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362) (0.33 g; 0.002 mol) and phenylisocyanate (0.27 g; 0.0023 mol) in anhydrous toluene (30.0 ml) was heated under reflux for 15 min. The red solution was decanted from an intractable brown gum (0.09 g) and evaporated. Trituration of the residual red gum (0.20 g) with ether-ethyl acetate afforded a brown solid (0.04 g; 19%), m.p. 216-218°, identical (i.r. spectrum) with an authentic sample of 2-amino-1,1-dicyanoprop-1-ene (363).

The Thermolysis of 5-Azido-3-methylisothiazole-4-carbonitrile (362) in Dimethyl Sulphoxide.

A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362) (0.66 g; 0.004 mol) in dry dimethyl sulphoxide (15.0 ml) was stirred and heated at 120° for 15 min. The mixture was cooled and evaporated to give a brown gum (0.99 g) which was triturated with ethanol-ethyl acetate to yield an intractable brown solid (0.13 g), m.p. 158-160°.

Evaporation of the ethanol-ethyl acetate mother liquor and trituration of the residue with ethanol-light petroleum gave a brown solid (0.1 g; 23%), m.p. 193-197°, identical (i.r. spectrum) with an authentic sample of 2-amino-1,1-dicyanoprop-1-ene (363).

Photolysis of 5-Azidoisothiazole Derivatives in Benzene.

A solution of the 5-azidoisothiazole (0.004 mol) in sodium dried benzene (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm.

(a) Irradiation of 5-azido-3-methylisothiazole (377) for 48 h followed by filtration gave an unidentified colourless solid (0.19 g), m.p. 97-100°, ν_{max} 3420 w, 3310 w and 3160 br (NH_2), 2180 (CN) and 1625 (NH def.) cm^{-1}, which ran as a single spot on t.l.c. in methylene chloride over silica but decomposed on attempted crystallisation.

Evaporation of the benzene mother liquor gave a dark intractable gum (0.16 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture.

(b) Irradiation of 5-azidoisothiazole-4-carbonitrile (370a) for

90 h was followed by evaporation at room temperature to give a dark gum (0.37 g) which was chromatographed over alumina.

Elution with light petroleum-benzene (1:3) gave a colourless solid (0.03; 6%), m.p. 81-84°, identical (m.p. and i.r. spectrum) with an authentic sample of 5-azidoisothiazole-4-carbonitrile (370a).

Elution with methylene chloride-ethyl acetate gave a second colourless solid (0.08 g; 26%), m.p. 140-143°, identical (m.p. and i.r. spectrum) with an authentic sample of 2-amino-1,1-dicyano-ethylene (367a).

(c) Irradiation of 5-azidoisothiazole-4-carbonitrile (370a) in undried benzene for 45 h followed by evaporation gave a brown gummy solid (0.32 g). Trituration of this solid with ethyl acetate-light petroleum afforded a brown solid (0.14 g; 38%), m.p. 133-135°, identical (i.r. spectrum) with an authentic sample of 2-amino-1,1-dicyanoethylene (367a).

(d) Irradiation of 5-azido-3-methylisothiazole-4-carbonitrile (362) for 16 h was followed by evaporation to give a dark gummy solid (0.44 g) which was triturated with ethyl acetate and crystallised from water to yield 2-amino-1,1-dicyanoprop-1-ene (363) as colourless plates (0.17 g; 40%), m.p. 224-225°, identical (m.p. and i.r. spectrum) with an authentic sample.

(e) Irradiation of 5-azido-3-ethylisothiazole-4-carbonitrile (370b) for 49 h was followed by evaporation to give a brown gum (0.56 g). Trituration of this gum with ethyl acetate-light petroleum and crystallisation from ethyl acetate-light petroleum gave an unidentified colourless solid (0.01 g; 2%), m.p. 158-160°, ν_{max}

3170 (NH) and 2220 and 2210 m (CN) cm^{-1}, M$^+$183.

Evaporation of the ethyl acetate-light petroleum mother liquor afforded 2-amino-1,1-dicyanobut-1-ene (367b) as a brown solid (0.05 g; 14%), m.p. 158-160°, identical (m.p. and i.r. spectrum) with an authentic sample.

2-Amino-1,1-dicyanoprop-1-ene (363)

A solution of 1,1-dicyano-2-ethoxyprop-1-ene[159] (364) (1.36 g; 0.01 mol) in ethanol (50.0 ml) was stirred and treated with ammonia gas for 30 min. Heat was generated and the mixture was evaporated to give 2-amino-1,1-dicyanoprop-1-ene (363) as a beige solid (0.99 g; 92%), m.p. 220-225° (from water) (lit.,[173] m.p. 228°), ν_{max} 3350 and 3200 (NH$_2$), 2220 and 2200 (CN), and 1675 (NH def.) cm^{-1}, δ [(CD$_3$)$_2$SO] 8.64 (1H, br s, NH), 8.35 (1H, br s, NH), and 3.34 (3H, s, Me).

Found: C, 56.3; H, 4.6; N, 39.3%; M$^+$, 107.

Calc. for C$_5$H$_5$N$_3$: C, 56.1; H, 4.7; N, 39.3%; M, 107.

Photolysis of 5-Azido-3-methylisothiazole-4-carbonitrile (362) in Acetic Acid

(a) A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362) (0.66 g; 0.004 mol) in glacial acetic acid (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm for 5 h. The mixture was evaporated at room temperature to give a gummy brown solid (0.66 g) which was triturated with ether to afford a brown solid (0.33 g; 77%), m.p. 188-190°, identical (i.r. spectrum) with

an authentic sample of 2-amino-1,1-dicyanoprop-1-ene (363).

(b) A solution of 5-azido-3-methylisothiazole-4-carbonitrile

(362) (0.33 g; 0.002 mol) in glacial acetic acid (25.0 ml) was left

in the dark at room temperature for 62 h.   Evaporation of the solvent

gave the starting material (362) (quant.), m.p. 72-75°, identical

(i.r. spectrum) with an authentic sample.

Photolysis of 5-Azido-3-methylisothiazole-4-carbonitrile (362) in Acetone.

A solution of 5-azido-3-methylisothiazole-4-carbonitrile (362)

(0.66 g; 0.004 mol) in Analar acetone (200 ml) was irradiated in a

Hanovia medium pressure photochemical reactor at 254 nm for 16 h.

Evaporation of the mixture gave a red-brown gummy solid (0.70 g)

which was triturated with ether-methanol to afford 2-amino-1,1-

dicyanoprop-1-ene (363) as a brown solid (0.17 g; 40%), m.p. 208-

211°, identical (i.r. spectrum) with an authentic sample.

The Attempted Oxidation of 5-Amino-3-methylisothiazole-4-carbonitrile (358).

(a) A solution of 5-amino-3-methylisothiazole-4-carbonitrile

(358)[160] (0.56 g; 0.004 mol) in redistilled dioxan (10.0 ml) was mixed

with aqueous sodium hypochlorite (5-7% chlorine) (9.6 ml) and the

mixture was stirred for 5 min, diluted with water (20.0 ml) and

extracted with methylene chloride (2x50 ml) to give a beige solid

(0.06 g; 11%), m.p. 191-193°, identical (i.r. spectrum) with the

starting amine (358).

On standing overnight at room temperature, the aqueous mother liquor deposited a brown solid which was crystallised from ethanol to give 5, 5'-azobis-(4-cyano-3-methylisothiazole) (415) as rectangular orange crystals (0.13 g; 24%), m.p. 197-198°, ν_{max} 2220 (CN) cm^{-1}, δ (CDCl$_3$) 2.74 (6H, s, Me).

Found: C, 44.1; H, 2.2; N, 30.9%; M^{+}, 274.

C$_{10}$H$_6$N$_6$S$_2$ requires: C, 43.8; H, 2.2; N, 30.7%; M, 274.

Further extraction of the aqueous mother liquor with ethyl acetate yielded a second crop of the starting amine (0.04 g; 7%), m.p. 174-176°, identical (i.r. spectrum) with an authentic sample.

Acidification of the aqueous layer and extraction with ethyl acetate (2x25 ml) gave a brown solid (0.07 g), m.p. 155-160°, which was shown by t.l.c. in ethyl acetate over silica and i.r. spectrum to contain the starting amine (358) and a second unidentified compound.

(b) 5-Amino-3-methylisothiazole-4-carbonitrile[160] (358) (0.28 g; 0.002 mol) in anhydrous dioxan (10.0 ml) was heated under reflux with manganese dioxide (1.39 g; 0.016 mol) for 4.5 h. The mixture was filtered to remove the manganese dioxide and the filtrate was evaporated to afford the starting amine (358) as a colourless solid (0.23 g; 82%), m.p. 191-193°, identical (i.r. spectrum) with an authentic sample.

The Attempted Preparation of 5-Azido-3-phenylisoxazole (442).

(a) A solution of 5-amino-3-phenylisoxazole (443)[130] (0.80 g; 0.005 mol) in glacial acetic acid (5.0 ml) was added at 15-16° to a stirred suspension of nitrosylsulphuric acid (1.4 g; 0.011 mol) in

glacial acetic acid (5.0 ml). The resulting yellow suspension was stirred for 10 min at 15°, cooled and treated at $0-10^{\circ}$ with stirring with a solution of sodium azide (0.36 g; 0.0055 mol) in water (2.5 ml). The resulting orange solution was stirred at $0-10^{\circ}$ for 30 min and poured on to ice (25 g) to give an orange solid (0.62 g), m.p. $141-142^{\circ}$, whose i.r. spectrum, ν_{max} 3550 m, 3470 w, 3370 w, 3140 br and 2660 br (NH, OH), 1760 (CO), and 1640 (NH def.) cm^{-1}, showed it to be a mixture of 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (445) and the hydrate of the oxime (446) identical (i.r. spectrum) with a sample prepared in Chapter 2. The orange solid (0.60 g) was chromatographed over silica.

Elution with methylene chloride-ethyl acetate (9:1) gave an orange solid (0.54 g), m p. $125-126^{\circ}$, ν_{max} 3340 w and 3220 w (NH_2), 3140 br (OH), 1790 (CO), and 1640 (NH def.) cm^{-1}, which was shown by t.l.c. in ethyl acetate over silica to contain two components.

The solid (0.16 g) was dissolved in methylene chloride (50 ml) and washed with saturated aqueous sodium hydrogen carbonate (2x10 ml). Evaporation of the organic fraction gave an intractable red gum (0.04 g).

The sodium hydrogen carbonate washings were acidified with dilute aqueous hydrochloric acid and extracted with methylene chloride (2x30 ml) to afford a yellow solid (0.07 g), m.p. $149-150^{\circ}$, identical (m.p. and i.r. spectrum) with syn-3-phenyl-Δ^2-isoxazoline-4, 5-dione 4-oxime (446) prepared as described in Chapter 2.

The aqueous reaction mother liquor was extracted with

methylene chloride (2x40 ml) to give an intractable red gum (0.25 g).

(b) 5-Amino-3-phenylisoxazole (443)[130] (0.80 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was treated at 0° with stirring with sodium nitrite (0.70 g; 0.01 mol). The resulting yellow suspension was stirred for 10 min, treated with sulphamic acid (0.97 g; 0.01 mol), stirred for a further 5 min and then treated dropwise at $0\text{-}15^{o}$ with a solution of sodium azide (0.36 g; 0.0055 mol) in water (2.5 ml). The mixture was stirred for 30 min at 0° to give a yellow solid (0.76 g), m.p. $103\text{-}106^{o}$, ν_{max} 3460, 3370 m, 3280 br and 3120 (NH), 2130 (N$_3$), 1775 (CO), and 1640 (NH def.) cm^{-1}, which was shown by t.l.c. in ethyl acetate over silica and i.r. spectrum to contain 5-amino-3-phenylisoxazole (443) and 5-amino-4-(3'-phenylisoxazol-5'-ylazo)-3-phenylisoxazole (445) together with a small amount of a third unidentified compound.

The Attempted Oxidation of 5-Amino-3-phenylisoxazole (443).

A solution of 5-amino-3-phenylisoxazole (443)[130] (0.64 g; 0.004 mol) in redistilled dioxan (10.0 ml) was mixed with aqueous sodium hypochlorite (5-7% chlorine) (9.6 ml). Heat was evolved and the cloudy mixture was stirred for 5 min, diluted with water (20.0 ml) and extracted with methylene chloride (2x50 ml) to afford an intractable brown oil (0.54 g) which was shown by t.l.c. in ethyl acetate over silica to contain at least three close-running components one of which corresponded to 5-amino-3-phenylisoxazole (443).

Methyl 4-Azido-2-methylmercaptothiazole-5-carboxylate (448).

(a) Methyl 4-amino-2-methylmercaptothiazole-5-carboxylate[155] (447) (1.02 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (5.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (0.70 g; 0.01 mol). The resulting yellow suspension was stirred at 0-5° for 10 min, treated with sulphamic acid (0.97 g; 0.01 mol), stirred for a further 5 min and treated dropwise at 0-10° with a solution of sodium azide (0.33 g; 0.005 mol) in water (2.5 ml). The mixture was stirred for 30 min at 0° and poured on to ice (25 g) to give a pale yellow solid which was crystallised from ethanol-water to afford methyl 4-azido-2-methyl-mercaptothiazole-5-carboxylate (448) as yellow crystals (1.11 g; 97%), m.p. 72-73°, ν_{max} 2190 m, 2150 and 2050 (N_3) and 1725 (CO)cm^{-1}, δ(CDCl$_3$) 3.80 (3H, s, Me) and 2.68 (3H, s, Me).

Found: C, 31.4; H, 2.7; N, 23.9%; M$^+$, 230.

$C_6H_6N_4O_2S_2$ required: C, 31.3; H, 2.6; N, 24.3%; M, 230.

(b) A suspension of methyl 4-amino-2-methylmercaptothiazole-5-carboxylate[155] (447) (1.02 g; 0.005 mol) in glacial acetic acid (7.5 ml) was treated dropwise with stirring at 15-17° with nitro-sylsulphuric acid (1.0 ml) [prepared by mixing sodium nitrite (4.0 g) and concentrated sulphuric acid (10.0 ml)]. The mixture was stirred for 30 min at room temperature, cooled to 10°, and treated dropwise with a solution of sodium azide (0.36 g; 0.0055 mol) in water (2.5 ml). The resulting pale yellow suspension was stirred for 30 min and poured on to ice (25 g) to afford a pale yellow solid

(1.01 g; 88%), m.p. 64-66°, identical (i.r. spectrum) with a sample of methyl 4-azido-2-methylmercaptothiazole-5-carboxylate (448) prepared in (a) before.

Thermolysis of Methyl 4-Azido-2-methylmercaptothiazole-5-carboxylate (448).

(a) A solution of methyl 4-azido-2-methylmercaptothiazole-5-carboxylate (448) (0.46 g; 0.002 mol) in sodium dried toluene (20.0 ml) was heated under reflux for 2 h. Evaporation of the mixture gave a brown gum (0.51 g) which was triturated with toluene to give a yellow solid (0.11 g; 24%), m.p. 51-53°, identical (i.r. spectrum) with the starting azide (448).

The toluene mother liquor was shown by t.l.c. in toluene over silica to contain several close running components.

(b) A solution of methyl 4-azido-2-methylmercaptothiazole-5-carboxylate (448) (0.46 g; 0.002 mol) in sodium dried xylene (20.0 ml) was heated under reflux for 3 h. The mixture was evaporated to give a red gummy solid which was triturated with ether to afford a yellow solid (0.16 g; 39%), m.p. 94-95°, identical (i.r. spectrum and t.l.c.) with an authentic sample of methyl 4-amino-2-methyl-mercaptothiazole-5-carboxylate (447).

Evaporation of the ether mother liquor gave a gum (0.42 g) which was shown by t.l.c. in toluene over silica to be a close-running mixture of the amine (447), the azide (448) and two other unidentified components.

Photolysis of Methyl 4-Azido-2-methylmercaptothiazole-5-carboxylate (448).

(a) A solution of methyl 4-azido-2-methylmercaptothiazole-5-carboxylate (448) (0.92 g; 0.004 mol) in sodium dried benzene (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm for 40 h. Evaporation of the mixture gave a red-brown gum (0.89 g) which was triturated with ethyl acetate-methanol to give an unidentified beige solid (0.04 g), m.p. 123-130°, ν_{max} 3140 br (OH), 1730 and 1670 (CO) cm^{-1}.

The ethyl acetate-methanol mother liquor was shown by t.l.c. in methylene chloride over silica to contain an unresolvable three component mixture.

(b) A solution of methyl 4-azido-2-methylmercaptothiazole-5-carboxylate (448) (0.46 g; 0.002 mol) in Analar acetone (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm for 24 h. Evaporation of the mixture gave an intractable brown gum (0.49 g) whose t.l.c. in toluene over alumina showed it to be an unresolvable multicomponent mixture.

2-Azidobenzothiazole (427)

(a) 2-Aminobenzothiazole (423) (0.75 g; 0.005 mol) was dissolved with gentle warming in 88% phosphoric acid (12.0 ml) and the solution was stirred and treated at 0° with sodium nitrite (0.37 g; 0.0054 mol). The resulting yellow suspension was stirred for 10 min at 0° and then treated dropwise at 0-10° with a solution of sodium azide (0.33 g; 0.005 mol) in water (5.0 ml). The mixture

was stirred for 30 min at 0-5° and poured on to ice (50 g) to give a colourless solid (1.08 g) which contained inorganic impurities. The impure solid (1.02 g) was slurried with aqueous 2M hydrochloric acid to give 2-azidobenzothiazole (427) as a colourless solid (0.22 g; 26%), m.p. 104-105° (lit.,[181] 110-112°), ν_{max} 2210 w, 2160 m and 2120 (N$_3$) cm^{-1}.

The aqueous acidic mother liquor was neutralised with concentrated aqueous ammonia to afford a colourless solid which was combined with a second crop obtained on extraction with methylene chloride to give 2-aminobenzothiazole (423) (total 0.36 g; 51%), identical (i.r. spectrum) with an authentic sample.

(b) 2-Aminobenzothiazole (423) (6.00 g; 0.04 mol) was dissolved with gentle warming in 88% phosphoric acid (60.0 ml) and the solution was stirred and treated at 0-5° with sodium nitrite (5.60 g; 0.08 mol). The resulting yellow suspension was stirred at 0° for 10 min, treated with sulphamic acid (7.76 g; 0.08 mol), stirred for a further 5 min and finally treated dropwise at 0-10° with a solution of sodium azide (2.86 g; 0.044 mol) in water (20.0 ml). The mixture was stirred for 30 min at 0-10° and was poured on to ice (200 g) to afford 2-azido-benzothiazole (427) as a colourless solid (6.45 g; 92%), m.p. 100-101°, identical (i.r. spectrum) with a sample prepared in (a) before.

(c) A suspension of benzothiazole-2-diazonium fluoroborate (prepared as described in Chapter 3) (426) (1.24 g; 0.005 mol) in water (20.0 ml) was stirred and treated dropwise at 0-10° with a solution of sodium azide (0.33 g; 0.005 mol) in water (5.0 ml). The mixture was stirred for 30 min at 0°, during which time there was a

considerable amount of gas evolution.   Filtration gave 2-azido-

benzothiazole (427) as an orange solid (0.72 g; 82%), m.p. 101-106°,

identical (m.p. and i.r. spectrum) with a sample prepared in (a)

before.

(d) 2-N-Hydroxyazobenzothiazole (prepared as described in

Chapter 3) (424) (0.45 g; 0.0025 mol) was suspended in 88% phosphoric

acid (20.0 ml) and treated dropwise with stirring at 0° with a solution

of sodium azide (0.18 g; 0.0028 mol) in water (2.5 ml).   The mixture

was stirred at 0° for 30 min and poured on to ice (100 g) to give 2-

azidobenzothiazole (427) as a yellow solid (0.25 g; 57%), m.p.

89-94°, identical (i.r. spectrum) with a sample prepared in (a) before.

The aqueous mother liquor was neutralised with concentrated

aqueous ammonia and extracted with methylene chloride (2x30 ml)

to afford a colourless solid (0.18 g), m.p. 108-112°, whose i.r.

spectrum was identical to an authentic sample of 2-aminobenzothiazole

(423).

Thermolysis of 2-Azidobenzothiazole (427).

A solution of 2-azidobenzothiazole (427) (0.35 g; 0.002 mol)

in glacial acetic acid (20.0 ml) was heated under reflux for 3.5 h.

The mixture was evaporated to give a yellow gum (0.39 g) which was

triturated with ethyl acetate to afford colourless crystals of an

unidentified solid (0.08 g; 25%), m.p. 251-255° (from acetic acid-

water), ν_{max} 1655 cm^{-1}.

Found: C, 53.1; H, 3.3; N, 16.3%; M^{+}, 314, 298.

$C_{14}H_{10}N_4OS_2$ requires: C, 53.5; H, 3.2; N, 17.8%; M, 314.

The ethyl acetate mother liquor was shown by t. l. c. in methylene chloride over silica to contain several close-running components.

The Attempted Preparation of 5-Azido-3-methyl-1, 2, 4-thiadiazole (432a).

5-Amino-3-methyl-1, 2, 4-thiadiazole[165] (431a) (2. 31 g; 0. 02 mol) was dissolved with gentle warming in 88% phosphoric acid (20. 0 ml) and the solution was stirred and treated at 0° with sodium nitrite (2. 77 g; 0. 04 mol). The resulting yellow suspension was stirred for 10 min at 0°, treated with sulphamic acid (3. 87 g; 0. 04 mol) and then dropwise at $10\text{-}20^{\circ}$ with a solution of sodium azide (1. 30 g; 0. 02 mol) in water (10. 0 ml). The mixture was stirred for 30 min at $0\text{-}5^{\circ}$, poured on to ice (100 g) and extracted with methylene chloride (2x30 ml) to afford a yellow oil (0. 88 g) which was subjected to dry-column chromatography in ethyl acetate over silica. No material was recovered from the column.

The aqueous mother liquor was neutralised with concentrated aqueous ammonia and extracted with methylene chloride (2x30 ml) to give a colourless solid (0. 03 g; 1%), m. p. $184\text{-}188^{\circ}$, identical (i. r. spectrum) with an authentic sample of 5-amino-3-methyl-1, 2, 4-thiadiazole (431a).

The Attempted Preparation of 5-Azido-3-phenyl-1, 2, 4-thiadiazole (432b).

(a) 5-Amino-3-phenyl-1, 2, 4-thiadiazole (431b)[165] (1. 77 g; 0. 01 mol) was dissolved with gentle warming in 88% phosphoric acid

(10. 0 ml) and the solution was stirred and treated at 0° with sodium

nitrite (1. 38 g; 0. 02 mol). The resulting yellow suspension was

stirred for 10 min (during which time gas was evolved) treated with

sulphamic acid (1. 96 g; 0. 02 mol), stirred for a further 5 min and

then treated dropwise at 0-15° with a solution of sodium azide (0. 65 g;

0. 01 mol) in water (5. 0 ml). The mixture was stirred for 30 min

at 0° and poured on to ice-water (100 ml) to give a colourless solid

1. 63 g; 72%), m. p. 223-225° (from glacial acetic acid), identical

(i. r. spectrum and mass spectrum) with the hydrate of 5-nitro-3-

phenyl-1, 2, 4-thiadiazole (329) obtained as described in Chapter 5.

The aqueous mother liquor was extracted with methylene

chloride (2x40 ml) to give a colourless solid (0. 15 g; 8%), m. p.

138-139°, identical (i. r. spectrum) with an authentic sample of 5-

amino-3-phenyl-1, 2, 4-thiadiazole (431b).

(b) A suspension of 3-phenyl-1, 2, 4-thiadiazole-5-diazonium

fluoroborate (prepared as described in Chapter 5) (311b; X=BF$_4$)

(0. 83 g; 0. 003 mol) in water (10. 0 ml) was stirred and treated drop-

wise at 0° with a solution of sodium azide (0. 19 g; 0. 003 mol) in

water (5. 0 ml). The mixture was stirred for 40 min at 0-5° to give

a pink solid (0. 58 g), m. p. 123-126°, ν_{max} 3140 w (NH) and 2120 w

(N$_3$) cm^{-1}, M$^+$206. Crystallisation of the solid from ethanol-water

gave a yellow solid, m. p. 130-131°, M$^+$206, identical (i. r. spectrum)

with an authentic sample of 5-nitrosamino-3-phenyl-1, 2, 4-thiadiazole

(312b) (see Chapter 5).

(c) A solution of 3-phenyl-1, 2, 4-thiadiazole-5-diazonium

fluoroborate (prepared as described in Chapter 5) (311b; X=BF$_4$)

(0.55 g; 0.002 mol) in acetone (30.0 ml) was mixed with a solution

of sodium azide (0.13 g; 0.002 mol) in water (3.0 ml) to give a black

solution which was stirred at room temperature for 1 h. The

mixture was concentrated and extracted with methylene chloride to give

a brown gum (0.25 g) which was chromatographed over alumina to

yield an intractable yellow solid (0.06 g), m.p. 299-303°.

3-Azido-5-phenyl-1,2,4-thiadiazole (452)

3-Amino-5-phenyl-1,2,4-thiadiazole (451)[169] (1.76 g; 0.01 mol)

was dissolved with gentle warming in 88% phosphoric acid (10.0 ml)

and the solution was stirred and treated at 0° with sodium nitrite

(1.40 g; 0.02 mol). The resulting yellow suspension was stirred

at 0° for 10 min, treated with sulphamic acid (1.96 g; 0.02 mol),

stirred for a further 5 min and finally treated dropwise at 0-10° with

a solution of sodium azide (0.65 g; 0.01 mol) in water (5.0 ml).

The mixture was stirred for 30 min at 0-5° and poured on to ice

(50 g) to give a colourless solid which was crystallised from ethanol-

water to afford 3-azido-5-phenyl-1,2,4-thiadiazole (452) as colourless

needles (1.73 g; 85%), m.p. 96-98°, ν_{max} 2120 and 2140 (N$_3$) cm^{-1}.

Found: C, 47.3; H, 2.5; N, 34.3%; M$^+$, 203.

$C_8H_5N_5S$ requires: C, 47.3; H, 2.5; N, 34.5%; M, 203.

The aqueous mother liquor was extracted with methylene

chloride (2x40 ml) to yield a colourless solid (0.08 g; 5%), m.p.

120-122°, identical (i.r. spectrum) with an authentic sample of 3-

amino-5-phenyl-1,2,4-thiadiazole (451).

The Attempted Thermolysis of 3-Azido-5-phenyl-1,2,4-thiadiazole (452) in Acetic Acid.

A solution of 3-azido-5-phenyl-1,2,4-thiadiazole (452) (0.41 g; 0.002 mol) in glacial acetic acid (20.0 ml) was heated under reflux for 2.5 h. Evaporation of the mixture gave a yellow solid (0.41 g; quant.), m.p. 68-71°, identical (i.r. spectrum) with the unreacted azide (452).

Thermolysis of 3-Azido-5-phenyl-1,2,4-thiadiazole (452) in Xylene.

A solution of 3-azido-5-phenyl-1,2,4-thiadiazole (452) (0.41 g; 0.002 mol) in sodium dried xylene (125 ml) was heated under reflux for 3.5 h. The mixture was evaporated to give a yellow gummy solid (0.38 g) which was triturated with light petroleum-methylene chloride to afford a light coloured solid (0.12 g; 29%), m.p. 93-100°, identical (m.p., t.l.c., and i.r. spectrum) with the starting azide (452).

The light petroleum-methylene chloride mother liquor was shown by t.l.c. in ethyl acetate over silica to contain the azide (452) and several other close-running components.

Photolysis of 3-Azido-5-phenyl-1,2,4-thiadiazole (452) in Benzene

A solution of 3-azido-5-phenyl-1,2,4-thiadiazole (452) (0.47 g; 0.0023 mol) in sodium dried benzene (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm for 34 h. Evaporation of the mixture gave an orange gum (0.57 g) which was triturated with methylene chloride to afford a yellow solid (0.09 g),

m. p. 162-166° (from toluene), ν_{max} 3370 m and 3150 m (NH$_2$) and

1690 (NH def.) cm^{-1} identical (i. r. spectrum) with authentic 3-amino-

5-phenyl-1, 2, 4-thiadiazole (451).

The methylene chloride mother liquor was shown by t. l. c. in

ethyl acetate over silica to contain only unreacted azide (452).

2-Azido-5-phenyl-1, 3, 4-thiadiazole (434).

2-Amino-5-phenyl-1, 3, 4-thiadiazole[171] (433) (1. 77 g; 0. 01 mol)

was dissolved with gentle warming in 88% phosphoric acid (10. 0 ml)

and the solution was stirred and treated at 0° with sodium nitrite

(1. 38 g; 0. 02 mol).   The resulting yellow suspension was stirred

for 10 min at 0°, treated with sulphamic acid (1. 93 g; 0. 02 mol),

stirred for 5 min and finally treated dropwise at 0-10° with a solution

of sodium azide (0. 65 g; 0. 01 mol) in water (5. 0 ml).   The mixture

was stirred for 30 min at 0° and poured into ice-water (100 ml) to

give a yellow solid which was crystallised from ethanol-water to

afford 2-azido-5-phenyl-1, 3, 4-thiadiazole (434) as yellow crystals

(1. 11 g; 55%), m. p. 111. 5-112. 5° (lit.,[183] 103-104°), ν_{max} 2130

(N$_3$) cm^{-1}.

Found: C, 47.4; H, 2. 5; N, 33. 7%; M$^+$, 203.

Calc. for C$_8$H$_5$N$_5$S: C, 47. 3; H, 2. 5; N, 34. 5%; M, 203.

The aqueous mother liquor was neutralised with concentrated

aqueous ammonia to give a colourless solid (0. 18 g; 10%), m. p.

215-218°, identical (i. r. spectrum) with an authentic sample of 2-

amino-5-phenyl-1, 3, 4-thiadiazole (433).

Thermolysis of 2-Azido-5-phenyl-1,3,4-thiadiazole (434) in Acetic Acid.

A solution of 2-azido-5-phenyl-1,3,4-thiadiazole (434) (0.41 g; 0.002 mol) in glacial acetic acid (20.0 ml) was heated under reflux for 2.5 h. Evaporation of the mixture gave a yellow gum (0.46 g) which was triturated with ethyl acetate to afford 2-acetamido-5-phenyl-1,3,4-thiadiazole (439) as a yellow solid (0.12 g; 27%), m.p. 267-269° (from acetic acid-water) (lit.,[171] 281-282°), ν_{max} 3140 w (NH) and 1690 (CO) cm^{-1}.

Found: C, 54.9; H, 3.8; N, 18.3%; M$^+$, 219.

Calc. for $C_{10}H_9H_3OS$: C, 54.8; H, 4.1; N, 19.2%; M, 219.

The ethyl acetate mother liquor was shown by t.l.c. in ethyl acetate over alumina to be an unresolvable multicomponent mixture.

Photolysis of 2-Azido-5-phenyl-1,3,4-thiadiazole (434) in Acetic Acid.

A solution of 2-azido-5-phenyl-1,3,4-thiadiazole (434) (0.81 g; 0.004 mol) in glacial acetic acid (200 ml) was irradiated in a Hanovia medium pressure photochemical reactor at 254 nm for 5 h. Evaporation of the mixture gave an orange gum which was triturated with acetone to give a yellow solid (0.11 g), m.p. 153-156°, which decomposed on attempted crystallisation. Subsequent trituration of the residual gum from the acetone mother liquor with ethyl acetate-ethanol-acetone gave a second yellow solid (0.13 g; 15%), m.p. 221-225°, identical (i.r. spectrum) with 2-acetamido-5-phenyl-1,3,4-thiadiazole (439) prepared before.

The organic mother liquor was shown by t.l.c. in ethyl acetate

over silica to contain an unresolvable multicomponent mixture.

2-Acetamido-5-phenyl-1,3,4-thiadiazole (439)

A suspension of 2-amino-5-phenyl-1,3,4-thiadiazole (433) (0.35 g; 0.002 mol) in acetic anhydride (3.6 ml) was heated at 100° for 10 min. The mixture was cooled and triturated with ether to give the N-acetyl derivative (439) as a colourless solid (0.31 g; 70%), m.p. $277-279^{\circ}$ (lit.,[171] $281-282^{\circ}$), identical (i.r. spectrum) with a sample prepared before.

BIBLIOGRAPHY

Bibliography

1. P. Griess, *Annalen*, 1858, 106, 123.

2. E. Knoevenagel, *Chem. Ber.*, 1890, 23, 2994.

3. C. A. Martius, *J. prakt. Chem.*, 1866, 98, 94.

4. H. Gies and E. Pfeil, *Annalen*, 1952, 578, 11.

5. L. Blangey, *Helv. Chim. Acta*, 1925, 8, 780.

6. H. A. J. Schoutissen, *J. Amer. Chem. Soc.*, 1933, 55, 4531.

7. E. Misslin, *Helv. Chim. Acta*, 1920, 3, 626.

8. H. Zollinger, "Azo and Diazo Chemistry," Interscience,

   New York, 1961, p. 19.

9. ibid, p. 65.

10. K. H. Saunders, "The Aromatic Diazo Compounds,"

    Edward Arnold, London, 1949.

11. J. C. Cain, *Chem. Ber.*, 1905, 38, 2511.

12. A. Hantzsch and K. J. Thompson, *Chem. Ber.*, 1908, 41, 3519.

13. H. A. H. Pray, *J. Phys. Chem.*, 1926, 30, 1417.

14. H. A. H. Pray, *J. Phys. Chem.*, 1926, 30, 1477.

15. C. Schwalbe, *Chem. Ber.*, 1900, 33, 527.

16. C. Schwalbe, *Chem. Ber.*, 1905, 38, 3071.

17. T. Cohen, A. G. Dietz, and J. R. Miser, *J. Org. Chem.*, 1977,
    42, 2053.

18. J. P. Griess, *Phil. Trans.*, 1864, 164, 683.

19. J. Mai, *Chem. Ber.*, 1902, 35, 163.

20. R. Pschorr, *Chem. Ber.*, 1896, 29, 496.

21. P. Griess, *Annalen*, 1866, 137, 89.

22. T. Sandmeyer, <u>Chem. Ber.</u>, 1884, <u>17</u>, 1633.

23. T. Sandmeyer, <u>Chem. Ber.</u>, 1884, <u>17</u>, 2650.

24. K. J. P. Orton, <u>J. Chem. Soc.</u>, 1903, <u>83</u>, 806.

25. L. Gattermann and W. Haussknecht, <u>Chem. Ber.</u>, 1890, <u>23</u>, 738.

26. W. F. Beech, <u>J. Chem. Soc.</u>, 1954, 1297.

27. H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, 1961, p. 164.

28. W. A. Cowdrey and D. S. Davies, <u>Quart. Rev.</u>, 1952, <u>6</u>, 358.

29. L. Gattermann, <u>Chem. Ber.</u>, 1890, <u>23</u>, 1218.

30. A. F. Hegarty in "The Chemistry of Diazonium and Diazo Groups," Ed. S. Patai, Wiley, London, 1978, p. 525.

31. G. Balz and G. Schiemann, <u>Chem. Ber.</u>, 1927, <u>60</u>, 1186.

32. C. G. Swain and R. J. Rogers, <u>J. Amer. Chem. Soc.</u>, 1975, <u>97</u>, 799.

33. H. Zollinger, <u>Angew. Chem. Internat. Edn.</u>, 1978, <u>17</u>, 141.

34. T. J. Broxton, J. F. Bunnett, and C. H. Paik, <u>J. C. S. Chem. Comm.</u>, 1970, 1363.

35. J. F. Bunnett and C. Yijima, <u>J. Org. Chem.</u>, 1977, <u>42</u>, 639.

36. T. J. Broxton, J. F. Bunnett, and C. H. Paik, <u>J. Org. Chem.</u>, 1977, <u>42</u>, 643.

37. K. Clausius and H. Hürzeler, <u>Helv. Chim. Acta</u>, 1954, <u>37</u>, 798.

38. K. Clausius and M. Vecchi, <u>Helv. Chim. Acta</u>, 1956, <u>39</u>, 1469.

39. R. Huisgen and I. Ugi, <u>Chem. Ber.</u>, 1957, <u>90</u>, 2914.

40. I. Ugi, R. Huisgen, K. Clausius, and M. Vecchi, <u>Angew. Chem.</u>, 1956, <u>68</u>, 753.

41. I. Ugi and R. Huisgen, Chem. Ber., 1958, 91, 531.

42. I. Ugi, H. Perlinger, and L. Behringer, Chem. Ber., 1958, 91, 2324.

43. V. Meyer and G. Ambühl, Chem. Ber., 1875, 8, 751.

44. E. Bamberger and P. Wulz, Chem. Ber., 1891, 24, 2793.

45. S. M. Parmerter, Org. Reactions, 10, 1.

46. H. von Pechmann, Chem. Ber., 1892, 25, 3175.

47. F. R. Japp and F. Klingemann, Chem. Ber., 1887, 20, 2942.

48. F. R. Japp and F. Klingemann, Chem. Ber., 1888, 21, 549.

49. K. H. Meyer, Chem. Ber., 1919, 52, 1468.

50. A. P. Teren'ev and A. A. Demidova, J. Gen. Chem. U. S. S. R., 1937, 7, 2464; Chem. Abstr., 1938, 32, 2094.

51. O. Widman, Chem. Ber., 1884, 17, 722.

52. R. Stoermer and O. Gaus, Chem. Ber., 1912, 45, 3104.

53. R. Stoermer and H. Fincke, Chem. Ber., 1909, 42, 3115.

54. H. Zollinger, "Azo and Diazo Chemistry," Interscience, New. York, 1961, p. 177.

55. ibid, p. 182.

56. E. S. Lewis and M. D. Johnson, J. Amer. Chem. Soc., 1959, 81, 2070.

57. R. N. Butler, Chem. Rev., 1975, 75, 241.

58. E. Kalatzis, J. Chem. Soc. (B), 1967, 273.

59. E. Koenigs and H. Greiner, Chem. Ber., 1931, 64, 1049.

60. A. Albert, J. Chem. Soc. (B), 1966, 427.

61. Kyowa Fermentation Co. Ltd., French Patent 1415149; Chem. Abstr., 1966, 64, 5116b.

62. E. Carstens and H. G. Kazmirowski, East German Patent
    23,487; Chem. Abstr., 1963, 58, 9103h.

63. M. P. V. Boarland and J. F. W. McOmie, J. Chem. Soc.,
    1951, 1218.

64. A. Spiliadis, D. Bretcanu, C. Eftimescu, and R. T. Schip,
    Romanian Patent 50786; Chem. Abstr., 1969, 70, 4114h.

65. V. Papesch and R. M. Dobson, J. Org. Chem., 1965, 30, 199.

66. H. B. Stevenson and J. R. Johnson, J. Amer. Chem. Soc.,
    1937, 59, 2525.

67. N. I. Putokhin and V. I. Yakovlev, Sbornik Nauch. Trudov
    Kuibyshev. Ind. Inst., 1953, 4, 175; Chem. Abstr., 1956,
    50, 9741h.

68. N. I. Putokhin and V. I. Yakovlev, Doklady Akad. Nauk S. S. S. R.,
    1954, 98, 89; Chem. Abstr., 1955, 49, 12431c.

69. L. Henriksen and H. Autrup, Acta. Chem. Scand., 1972, 26,
    3342.

70. J. M. Tedder, Adv. Heterocyclic. Chem ., 1967, 8. 1.

71. R. D. Desai, R. F. Hunter, and A. R . K. Khalidi, J. Chem.
    Soc., 1934, 1186.

72. N. Saito, T. Kurihara, S. Yasuda, and M. Akagi, Yakugaku
    Zasshi, 1970, 90(1), 20 and 32; Chem. Abstr., 1970, 72,
    90352e, 90353f.

73. C. Musante, Gazzetta, 1943, 73, 366.

74. A. Quilico and V. Rosnati; un published results cited by
    A. Quilico, in "The Chemistry of Heterocyclic Compounds, "
    Ed. A. Weissberger and R. H. Wiley, 1962, 17, 136.

75 G. Vernin, C. Siv, S. Treppendahl, and J. Metzger, Helv. Chim. Acta, 1976, 59, 1705.

76. H. Wieland, Annalen, 1903, 328, 197.

77. A. Quilico, R. Fusco, and V. Rosnati, Gazzetta, 1946, 76, 87.

78. B.A. Porai-Koshits, V.I. Zaionts, and T.A. Eiges, Zhur. org.Khim., 1967, 3, 1262.

79. E. Muller and H. Haiss, Chem.Ber., 1963, 96, 570.

80. G.T. Morgan and G.V. Morrov, J.Chem.Soc., 1915, 1291.

81. A. Hantzsch, Annalen, 1888, 249, 1.

82. R.F. Hunter and J.W.T. Jones, J.Chem.Soc., 1930, 2190.

83. J. Goerdeler and H. Haubrich, Chem.Ber., 1960, 93, 397.

84. L.I. Denisova and K.E. Lotukova, Tr.Vses.Inst. Gel'mintol., 1969, 15, 97; Chem.Abstr., 1971, 75, 35866n.

85. C. Gruenert and K. Wiechert, Z.Chem., 1970, 10, 396; Chem. Abstr., 1971, 74, 13043u.

86. C. Gruenert, H. Schellong, and K. Wiechert, Z.Chem., 1970, 10, 116; Chem.Abstr., 1970, 72, 132594t.

87. A.D. Borthwick, M.W. Foxton, B.V. Gray, G.I. Gregory, P.W. Seale, and W.K. Warburton, J.C.S.Perkin I, 1973, 2769.

88. R.A. Parent, J.Org.Chem., 1962, 27, 2282.

89. B. Prijs, J.Ostertag, and E. Erlenmeyer, Helv.Chim.Acta, 1947, 30, 1200 and 2100.

90. G. Asato, G. Berkelhammer, and E.L.Moon, J. Medicin. Chem., 1969, 12, 374.

91. V. V. Shaburov, O. V. Vasil'eva, and A. V. El'tsov, Khim. geterotsikl Soedinenii, 1974, (3), 367; Chem. Abstr., 1974, 81, 25595h.

92. G. Vernin, M. A. Lebreton, H. J. M. Dou, and J. Metzger, Tetrahedron, 1974, 30, 4171.

93. J. Goerdeler and M. Roegler, Chem. Ber., 1970, 103, 112.

94. J. Goerdeler and U. Keuser, Chem. Ber., 1964, 97, 3106.

95. G. Vernin and J. Metzger, J. Org. Chem., 1975, 40, 3183.

96. M. V. Partridge and M. F. G. Stevens, J. Chem. Soc. (C), 1966, 1127.

97. R. Allmann, T. Debaerdemaeker, W. Grahn, and C. Reichardt, Chem. Ber., 1974, 107, 1555.

98. D. Fortuna, B. Stanovnik, and M. Tisler, J. Org. Chem., 1974, 39, 1833.

99. H. Reimlinger, A. van Overstraeten, and H. G. Viehe, Chem. Ber., 1961, 94, 1036.

100. G. T. Morgan and J. Reilly, J. Chem. Soc., 1913, 808.

101. G. T. Morgan and J. Reilly, J. Chem. Soc., 1914, 439.

102. E. Bamberger, Chem. Ber., 1899, 32, 1773.

103. G. C. Lancini and E. Lazzari, British Patent 1114154; Chem. Abstr., 1971, 75, 140848.

104. A. M. Simonov and Y. P. Andreichikov, Zhur. org. Khim., 1969, 5, 779.

105. S. N. Kolodyazhnaya, A. M. Simonov, N. N. Zheltikova, and A. F. Pozharskii, Khim. Geterotsikl. Soedin., 1973, (5), 714; Chem. Abstr., 1973, 79, 53266d.

106. A. M. Simonov, S. N. Kalodyazhnaya and L. N. Podladchikova, Khim. geterotsikl. Soedinenii, 1974, (5), 689; Chem. Abstr., 1974, 81, 77841e.

107. Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, J. Org. Chem., 1961, 26, 2396.

108. R. N. Butler, T. M. Lambe, J. C. Tobin, and F. L. Scott, J. C. S. Perkin I, 1973, 1357.

109. J. Goerdeler and K. Deselaers, Chem. Ber., 1958, 91, 1025.

110. A. Ginsberg and J. Goerdeler, Chem. Ber., 1961, 94, 2043.

111. J. Goerdeler and H. Haubrich, Chem. Ber., 1960, 93, 397.

112. J. Goerdeler, K. Deselaers, and A. Ginsberg, Chem. Ber., 1960, 93, 963.

113. J. Goerdeler and P. Mertens, Chem. Ber., 1970, 103, 1805.

114. F. Kurzer and S. A. Taylor, J. Chem. Soc., 1960, 3234.

115. M. Freund and C. Meinecke, Chem. Ber., 1896, 29, 2511.

116. J. Goerdeler and G. Gnad, Chem. Ber., 1966, 99, 1618.

117. I. L. Shegal. K. V. Stanovkina, N. G. Kovalenko and L. M. Shegal, Khim. geterotsikl. Soedinenii, 1974, (3), 422; Chem. Abstr., 1974, 81, 25609r.

118. H. Gehlen and J. Dost, Annalen, 1963, 665, 144.

119. R. Stolle and K. Krauch, J. prakt. Chem., 1913, 88, 311.

120. R. Stolle and W. Dietrich, J. prakt. Chem., 1934, 139, 193.

121. M. Hauser, J. Org. Chem., 1964, 29, 3449.

122. H. Mackie and G. Tennant, Tetrahedron Letters, 1972, 4719.

123. J. Thiele, Annalen, 1892, 270, 54.

124. P. B. Shevlin, _J. Amer. Chem. Soc._, 1972, 94, 1379.

125. S. Kammula and P. B. Shevlin, _J. Amer. Chem. Soc._, 1973, 95, 4441.

126. R. A. Henry and W. G. Finnegan, _J. Amer. Chem. Soc._, 1954, 76, 290.

127. J. C. Tobin, R. N. Butler, and F. L. Scott, _J. C. S. Chem. Comm._, 1970, 112.

128. R. Stolle, _J. prakt. Chem._, 1932, 134, 282.

129. A. Quilico, in "The Chemistry of Heterocyclic Compounds," Ed. A. Weissberger and R. H. Wiley, Interscience, New York, 1962, 17, p. 1-234.

130. A. Obregia, _Annalen_, 1891, 266, 324.

131. J. D. Loudon and I. Wellings, _J. Chem. Soc._, 1960, 3462.

132. G. Hallas, "Organic Stereochemistry," McGraw-Hill, London, 1965, p. 205.

133. C. G. McCarty, in "The Chemistry of the carbon nitrogen double bond," Ed. S. Patai, Wiley, London, 1969, pp. 363-464.

134. W. Z. Heldt and L. G. Donaruma, _Org. Reactions_, 1960, 11, 1.

135. A. Palm and H. Werbin, _Canad. J. Chem._, 1953, 31, 1004; _Chem. Abstr._, 1954, 48, 1810g.

136. G. Nussberger, _Chem. Ber._, 1892, 25, 2142.

137. L. Knorr and B. Reuter, _Chem. Ber._, 1894, 27, 1169.

138. C. J. Kibler and A. Weissberger, _Org. Synth._, 1945, 25, 7.

139. E. Muckermann, _Chem. Ber._, 1909, 42, 3456.

140. L. Knorr and C. Klotz, _Chem. Ber._, 1887, 20, 2547.

141. C. Bülow and A. Hecking, <u>Chem.Ber.</u>, 1911, <u>44</u>, 467.

142. T. Posner and G. Schreiber, <u>Chem.Ber.</u>, 1924, <u>57</u>, 1127.

143. T. Posner, <u>Chem.Ber.</u>, 1907, <u>40</u>, 226.

144. T.J. De Boer and H.J. Backer, <u>Org.Synth.</u>, 1956, <u>36</u>, 16.

145. R. Barone, M. Chanon, and R. Gallo, in "The Chemistry of
Heterocyclic Compounds," Ed. A. Weissberger, E.C. Taylor
and J.V. Metzger, Wiley, New York, 1979, Vol.34(2), p.31.

146. H. Mackie, Ph.D. Thesis, University of Edinburgh.

147. P.N. Bhargava and B.T. Baliga, <u>J. Indian Chem.Soc.</u>, 1958,
<u>35</u>, 807; <u>Chem.Abstr.</u>, 1959, <u>53</u>, 18941h.

148. W. Kirk, J.R. Johnson, and A.T. Blomquist, <u>J.Org.Chem.</u>,
1943, <u>8</u>, 557.

149. M. Bogemann, S. Peterson, O.E. Schultz, and H. Soll,
"Methoden der Organischen Chemie,"
<u>Houben Weyl,</u> 1955, <u>9</u>, 864.

150. W. Seidenfaden and D. Pawellek, <u>Houben Weyl,</u> "Methoden der Organischen Chemie," 1971, <u>10/1</u>,
836.

151. H. Koopman, <u>Rec.Trav.chim.</u>, 1961, <u>80</u>, 1075.

152. H. v. Pechmann and L. Frobenius, <u>Chem.Ber.</u>, 1894, <u>27</u>,
612; E. Bamberger, <u>ibid,</u> 1894, <u>27</u>, 917.

153. A. Hantzsch and M. Wolvekamp, <u>Annalen</u>, 1904, <u>331</u>, 282.

154. R.J. Timmons and L.S. Wittenbrook, <u>J.Org.Chem.</u>, 1967,
<u>32</u>, 1566.

155. W. Walek, M. Pallas, and M. Augustin, <u>Tetrahedron</u>, 1976,
<u>32</u>, 623.

156. R.G. Guy, in "The Chemistry of cyanates and their thio
derivatives," Ed. S. Patai, Wiley, Chichester, 1977, p.869.

157. A. W. Hofmann, Chem. Ber , 1880, 13, 9.

158. K. R. H. Wooldridge, Adv. Heterocyclic Chem., 1972, 14, 1.

159. M. A. McCall, J. Org. Chem., 1962, 27, 2433.

160. R. C. Anderson and Y. Y. Hsiao, J. Heterocyclic Chem.,
    1975, 12, 883.

161. R. Stolle and K. Fehrenbach, J. prakt. Chem., 1929, 122, 289.

162. M. Kanaoka, J. Pharm. Soc. Japan, 1955, 75, 1149; Chem.
    Abstr., 1956, 50, 5647.

163. J. Goerdeler, J. Ohm and O. Tegtmeyer, Chem. Ber.,
    1956, 89, 1534.

164. F. Kurzer, Adv. Heterocyclic Chem., 1965, 5, 119.

165. J. Goerdeler, K. Wember, and G. Worsch, Chem. Ber.,
    1954, 87, 57.

166. A. Treibs and R. Zimmer-Galler, Annalen, 1959, 627, 166.

167. J. Goerdeler and A. Fincke, Chem. Ber., 1956, 89, 1033.

168. P. Adams, D. W. Kaiser, D. E. Nagy, G. A. Peters,
    R. L. Sperry, and J. T. Thurston, J. Org. Chem., 1952, 17,
    1162.

169. F. Kurzer, J. Chem. Soc., 1956, 4524.

170. J. Sandström, Adv. Heterocyclic Chem., 1968, 9, 165.

171. E. Hoggarth, J. Chem. Soc., 1949, 1163.

172. R. A. Abramovitch and E. P. Kyba, in "The Chemistry of
    the azido group, " Ed. S. Patai, Wiley, 1971, p 221.

173. W. J. Middleton, J. Org. Chem., 1966, 31, 3731.

174. T. S. B. Sayer and J. S. Campbell, I. C. I. Organics Division,
    unpublished results.

175. A. Adams and R. Slack, J.Chem.Soc., 1959, 3061.

176. J. Goerdeler and H.W. Pohland, Chem.Ber., 1961, 94, 2950.

177. C. Yacomeni, Ph.D. Thesis, University of Edinburgh, 1975.

178. P.A.S. Smith, in "Nitrenes," ed. W. Lwowski, Interscience, New York, 1970, p.100.

179. T.L. Gilchrist and C.W. Rees, "Carbenes, Nitrenes and Arynes," Nelson, London, 1969, p.35.

180. G. Smolinsky, J.Org.Chem., 1961, 26, 4108.

181. V.Y. Pochinok, S.D. Zaitseva, and R.G. El'gort, Ukrain. khim. Zhur., 1951, 17, 509; Chem.Abstr., 1954, 48, 11392i.

182. M. Colonna, Pubbl.ist.Chim.univ.Bologna, 1943, 2, 3; Chem.Abstr., 1947, 41, 754i.

183. M. Kanaoka, Chem.Pharm.Bull.(Tokyo), 1958, 6, 382; Chem.Abstr., 1959, 53, 3200.

184. R.K. Smalley and H. Suschitzky, J.Chem.Soc., 1963, 5571.

185. H.D. Edwards, F.P. Doyle, and S.J. Palling, U.S. Patent 2721799; Chem.Abstr., 1956, 50, P1505e.

186. I.L. Knunyants, Otdel.Khim.Nauk., 1960, 221; Chem. Abstr., 1960, 54, 20870i.

187. A.W. Johnson, "Ylid Chemistry," Academic Press, New York, 1966, p.359.

APPENDIX

General Experimental Data

Unless otherwise stated, infrared spectra were measured for nujol suspensions using a Perkin Elmer 157G Spectrophotometer. Bands were strong and sharp, unless otherwise specified (w) as weak, (m) as medium or (br) as broad.

Nuclear magnetic resonance spectra were measured at 100 MHz using a Varian H.A.100 instrument or very occasionally at 360 MHz using a Brucker instrument by Mr. J. Millar, Department of Chemistry, University of Edinburgh. Signals were sharp unless otherwise specified (br) as broad; s = singlet; d = doublet; t = triplet; m = multiplet. Tetramethylsilane was used as internal standard.

Mass spectra and High Resolution Mass Spectral Analyses were measured at 70eV using an A.E.I. MS902 instrument by Mr. D. Thomas, Chemistry Department, University of Edinburgh.

Microanalyses were carried out by Mr. J. Grunbaum, Department of Chemistry, University of Edinburgh. Melting points of all analytical samples were determined using a Koffler hot-stage microscope and are uncorrected.

All azide decomposition experiments were followed by thin layer chromatography and the reaction stopped once the starting material had disappeared or a "steady-state" achieved. Photolytic decomposition reactions took place under a nitrogen atmosphere.

All organic extracts were dried over anhydrous magnesium sulphate, prior to evaporation under reduced pressure. Unless

otherwise specified, solvents were of technical grade and light petroleum had b. p. 60-80°. The concentrated orthophosphoric acid employed was 88% of density 1.75 g cm^{-3}.

Thin layer chromatography (t.l.c.) was carried out over silica [Merck Kieselgel G.F. 254 (Type 60)] or alumina [Merck G.F. 254 (Type E)], unless otherwise stated.

Dry column chromatography was carried over silica [Fison's (80-200 mesh), activity III] or alumina [Spence Type H, activity III].

Wet column chromatography was carried over silica [Fison's (80-200 mesh)] or alumina [Spence Type H].