

STUDIES ON THE NUCLEOPHILIC SUBSTITUTION  
REACTIONS OF N-OXYGENATED QUINOXALINONES

by

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Thesis presented for the degree of Doctor of Philosophy

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1978



To Helen and Stephen

and my parents



## 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 1974 and September 1977.

## ACKNOWLEDGEMENTS

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## SUMMARY

The conversion of 4-acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate into the ring-contracted product 1-benzoyl-6-chlorobenzimidazol-2-one and 6,8-dichloro-7-hydroxyquinoxalin-2(1H)-one, by treatment with water, is described and mechanisms accounting for these rearrangements are discussed. The attempted base-catalysed ring contraction of 4-acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorate using triethylamine and hydroxide ion as catalysts proved unsuccessful.

The reactions of a series of 4-acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium perchlorates with morpholine have been investigated. Mechanisms accounting for the formation of the products of morpholine-substitution and/or ring contraction are discussed.

The scope of the nucleophilic substitution reactions of 4-N-acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one has been investigated. Reaction to afford 7-substituted quinoxalin-2(1H)-ones has been demonstrated with chloride, bromide, azide, cyanate, thiocyanate and hydride ions. Reaction with benzenesulphinate and cyanide ion gave unresolved mixtures of 5- and 7-substituted quinoxalin-2(1H)-ones. Reaction with iodide and fluoride ions and with hydrobromic acid gave 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one. Mechanisms accounting for the formation of these products are discussed. Attempted reaction with phenoxide and acetylacetonate ions, diethylamine and ethyl magnesium bromide proved unsuccessful.

Treatment of 4-N-acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one with boron trifluoride-etherate in dioxan gave di(6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl) ether. A mechanism to account for this rearrangement is proposed.

A series of 3-cyanoquinoxalin-2(1H)-one 4-oxides has been prepared by the base-catalysed cyclisation of the appropriate 2-nitro- $\alpha$ -cyanoacetanilides. The reactions of these compounds and those of 3-cyano-1-methylquinoxalin-2(1H)-one 4-oxide, 3-benzoylquinoxalin-2(1H)-one

4-oxide and 3-aminoquinoxalin-2(1H)-one 4-oxide with acetyl chloride in acetic acid have been investigated. Mechanisms accounting for the formation of the products of these reactions are proposed and discussed. The reactions of selected 3-cyanoquinoxalin-2(1H)-ones with acetic anhydride have also been investigated and mechanisms are proposed to account for the mode of reaction observed.

A series of 1-hydroxyquinoxaline-2,3(1H,4H)-diones has been prepared by base-catalysed conversion of the appropriate 2-nitro- $\alpha$ -cyanoacetanilides. The attempted base-catalysed syntheses of 1-hydroxy-6-methylquinoxaline-2,3(1H,4H)-dione and 6,7-dimethyl-1-hydroxyquinoxaline-2,3(1H,4H)-dione from both the corresponding 2-nitro- $\alpha$ -cyanoacetanilides and 3-cyanoquinoxalin-2(1H)-one 4-oxides proved unsuccessful. The reactions of the 1-hydroxyquinoxaline-2,3(1H,4H)-diones and a series of 4-alkyl-1-hydroxyquinoxaline-2,3(1H,4H)-diones with acetyl chloride in acetic acid and with acetic anhydride have been investigated and mechanisms are discussed to account for the formation of the products of substitution and ring-contraction obtained.

A series of 3-cyano-1-hydroxyquinoxaline-2(1H)-one 4-oxides has been prepared by the base-catalysed reaction of ethyl cyanoacetate with the appropriate benzofuroxan. The base-catalysed conversion of the 3-cyano-1-hydroxyquinoxaline-2(1H)-one 4-oxides into 1,4-di-N-hydroxyquinoxaline-2,3(1H,4H)-diones is described and mechanisms accounting for the formation of these products are discussed.

The reactions of 1,4-di-N-hydroxyquinoxaline-2,3(1H,4H)-diones with acetyl chloride and acetyl bromide in acetic acid have been investigated. Mechanisms are proposed for the formation of the products of substitution and ring-contraction obtained. The attempted reaction of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione with acetic anhydride and with sodium acetate in acetic anhydride proved unsuccessful as did attempts to demonstrate nucleophilic substitution of the quinoxalinedione nucleus by toluene-*p*-sulphonyl chloride in the presence of dimethylformamide, aqueous sodium hydroxide, and triethylamine. Evidence for the formation of chloroquinoxalinediones was obtained in the reaction of 1,4-dihydroxyquinoxaline-

2,3(1H,4H)-dione with tosyl chloride in dimethylformamide in the presence of triethylamine.

The thermal rearrangement of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione to the 7-acetoxy isomer and the thermally induced ring-contraction of 1-acetoxyquinoxaline-2,3(1H,4H)-diones to benzimidazolone derivatives has been demonstrated and mechanisms accounting for these transformations are discussed. The attempted thermal rearrangement of 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione proved unsuccessful. The thermolytic deoxygenation of 1-hydroxyquinoxaline-2,3(1H,4H)-diones to the parent heterocycle in high boiling solvents has been demonstrated. The attempted thermolytic deoxygenation of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione proved unsuccessful as did the attempted photolytic deoxygenation of 1-hydroxyquinoxaline-2,3(1H,4H)-dione.



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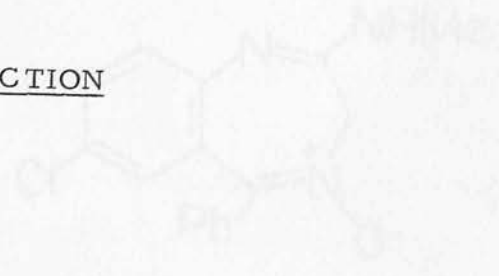
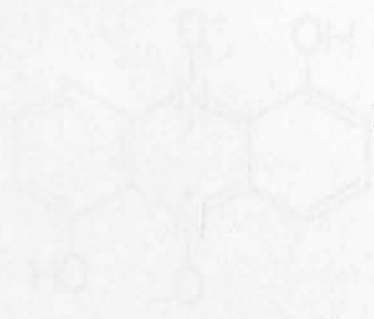
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CHAPTER ONE

INTRODUCTION

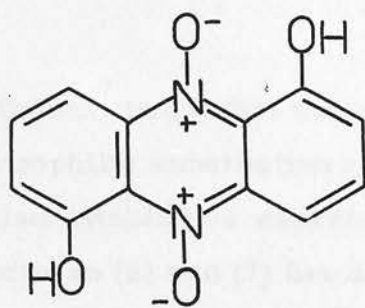


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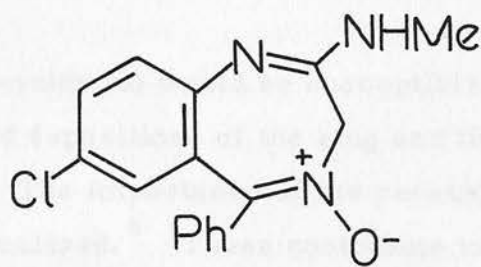
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## 1.1 Introduction

N-Oxygenated heterocycles are of particular interest due to their enhanced reactivity in comparison with the parent heterocycle. The manifold reactions of N-oxides have found extensive application in synthetic work and are also of mechanistic interest.<sup>1, 2</sup> N-Oxides occur in limited numbers in nature. The first naturally occurring heterocyclic N-oxide, to be reported was geneserine, the N-oxide of the alkaloid eserine, isolated by Polonovski from Calabar beans.<sup>3</sup> The discovery that certain biologically active natural products contain the N-oxide functional group has stimulated considerable interest in the study of the general chemistry of N-oxides. Typical of the biologically active heterocyclic N-oxides is the potent



(1)

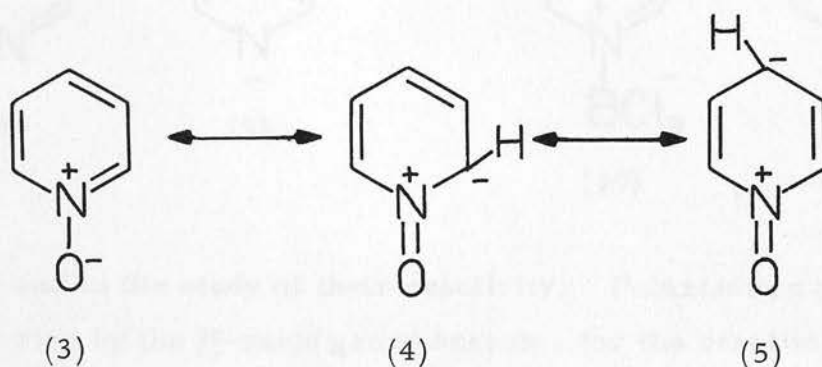


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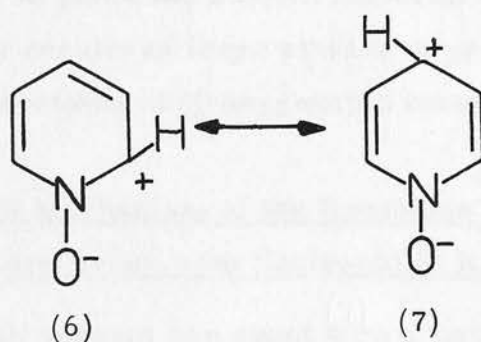
antibiotic iodinin (1,6 dihydroxyphenazine-5,10-dioxide) (1). The antibiotic aspergillilic acid, which has been shown to possess an antibacterial range greater than that of penicillin is known to be a hydroxypyrazine N-oxide.<sup>4</sup> The synthetic benzodiazepine, chlordiazepoxide (2), is the active ingredient of the presently marketed psychosedative and tranquilising agent 'Librium.'

An early development of significance in the chemistry of the heterocyclic N-oxides was the preparation of pyridine 1-oxide (3) by Meisenheimer,<sup>5</sup> by perbenzoic acid oxidation of pyridine. It was, however, the observation by Linton,<sup>6</sup> that the dipole moment of pyridine 1-oxide (3) is significantly lower than the predicted value, which must be considered to be the first major advance in the field. Linton reasoned that the reduction in the dipole moment of pyridine 1-oxide (3) indicated a considerable back polarisation of electrons into the pyridine ring from the N-oxide group due to conjugation of the negatively charged oxygen atom with the  $\pi$ -electrons of the aromatic ring (3). The dipole moment of the N-oxide group is

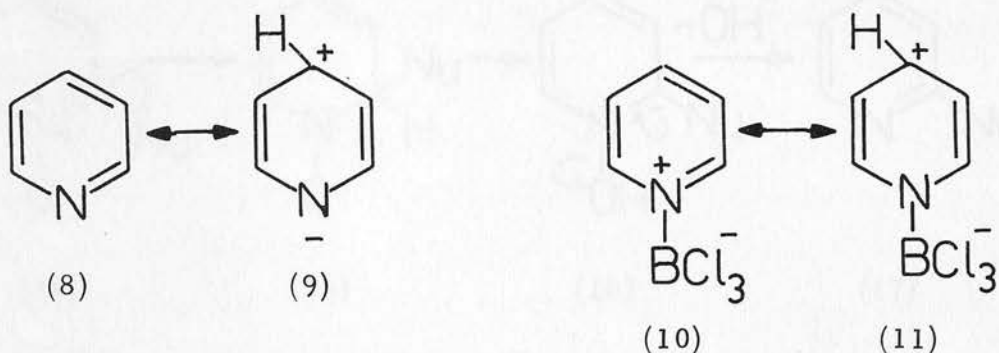
partially cancelled by the shift of electrons from the oxygen atom to the aromatic ring. This indicated that the canonical forms (4) and (5) must make a significant contribution to the resonance hybrid. These results



led Ochiai<sup>7</sup> to predict that pyridine 1-oxide (3) would be susceptible to electrophilic substitution at the 2- and 4-positions of the ring and this he also established experimentally. The importance of the resonance structures (6) and (7) has also been realised.<sup>8</sup> These contribute to the resonance hybrid due to polarisation in the opposite direction and account for the reactivity of pyridine 1-oxide (3) towards nucleophilic substitution at the  $\alpha$ - and  $\delta$ -positions. The situation in pyridine 1-oxide (3) is in



fundamental contrast to that appertaining to pyridine (8) and to coordination complexes such as the pyridine-boron trichloride complex (10) where significant resonance is limited to canonical forms of the type [(8)  $\longleftrightarrow$  (9)] and [(10)  $\longleftrightarrow$  (11)] respectively. It is the remarkable ability of the N-oxide group to polarise a heteroaromatic ring in both possible electronic senses which has promoted the widespread interest in the synthesis of

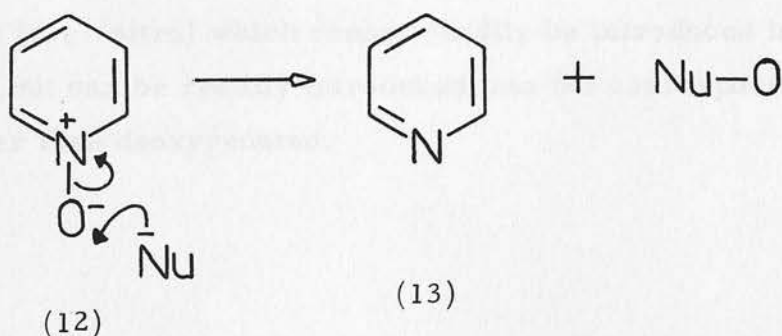


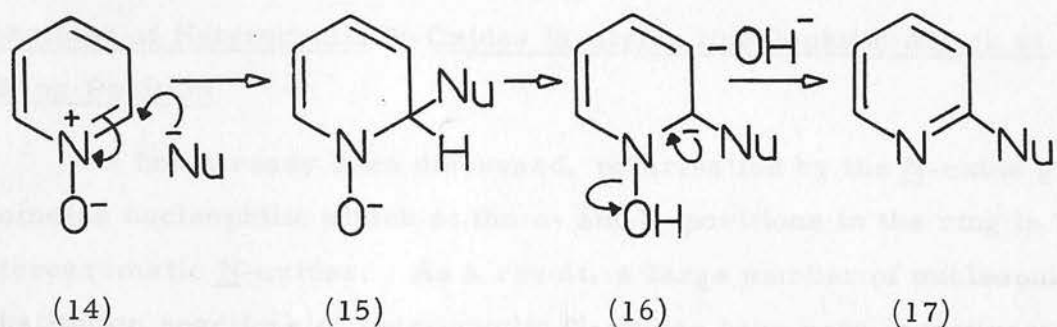
N-oxides and in the study of their reactivity. Polarisation of the hetero-aromatic ring by the N-oxide group accounts for the reactivity of heterocyclic N-oxides towards both electrophiles and nucleophiles.

The reactivity of N-oxides can be broadly classified under five headings, namely (i) reaction at the oxygen atom of the N-oxide group with electrophiles, (ii) electrophilic substitution in the ring, (iii) reaction at the oxygen atom of the N-oxide group with nucleophiles, (iv) nucleophilic substitution in the ring (often involving initial electrophilic attack at the oxygen atom of the N-oxide group), and (v) activation of exocyclic substituents by the N-oxide group. The present thesis is concerned with studies of the reactivity of certain N-oxygenated heterocycles towards nucleophilic reagents. In order to place the subject material of the work in context, the discussion of the results of these studies is preceded by a short up to date review of the reactions of N-oxygenated heterocycles with nucleophiles.

## 1.2 The Scope and Mechanism of the Reactions of N-Oxygenated Heterocycles with Nucleophilic Reagents

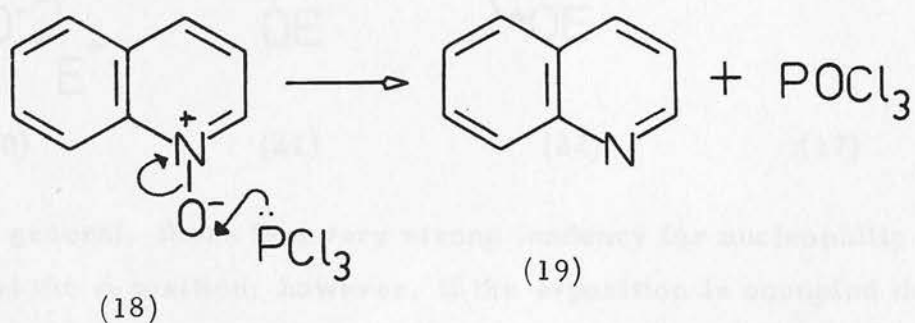
A nucleophilic reagent can react with a heterocyclic N-oxide either at the N-oxide oxygen atom [cf (12)  $\rightarrow$  (13)] or at a ring position  $\alpha$ - or  $\gamma$ - to the N-oxide group [e.g. (14)  $\rightarrow$  (15)  $\rightarrow$  (16)  $\rightarrow$  (17)].





### Reactions of Heterocyclic N-Oxides Involving Nucleophilic Attack at the N-Oxide Group

The simplest type of reaction between a heterocyclic N-oxide and a nucleophile is deoxygenation of the heterocyclic N-oxide to the parent heterocycle [cf (12)  $\rightarrow$  (13)]. Many reactions lead to loss of the N-oxide oxygen atom in this way, but those in which the nucleophile is a trivalent phosphorus reagent are perhaps the best known. Thus, quinoline 1-oxide (18) is deoxygenated to quinoline (19) by phosphorus trichloride.<sup>9</sup> Phosphorus trihalides in general and trialkyl and triarylphosphite esters can

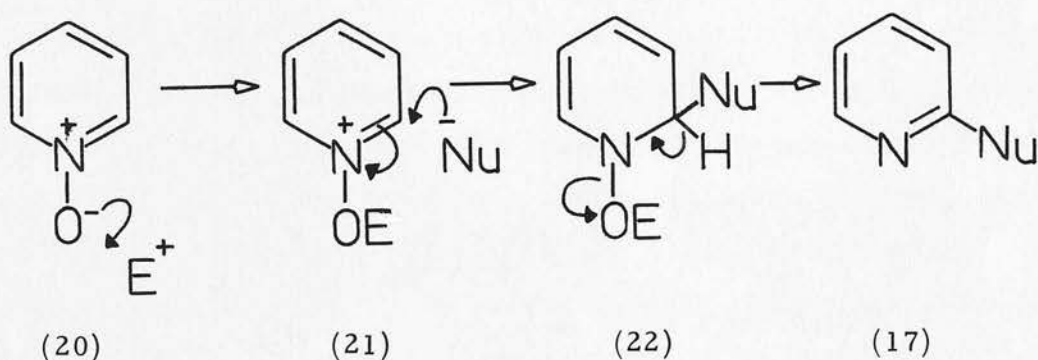


all be used as reagents in reactions of this type. This reaction is important for the indirect synthesis of pyridine derivatives containing substituents (e. g. nitro) which cannot readily be introduced into the parent heterocycle but can be readily introduced into the corresponding N-oxide, and the latter then deoxygenated.



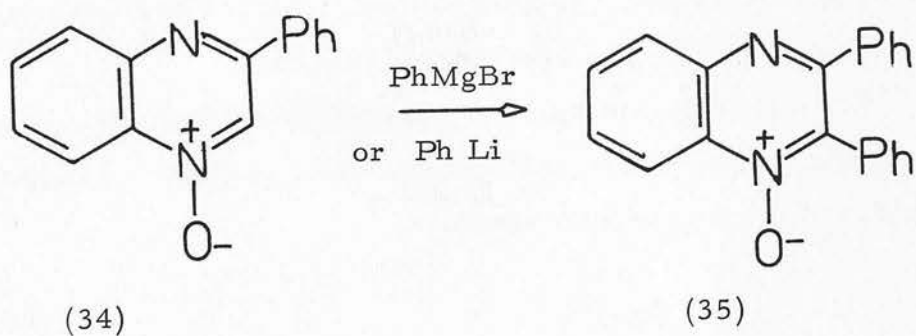
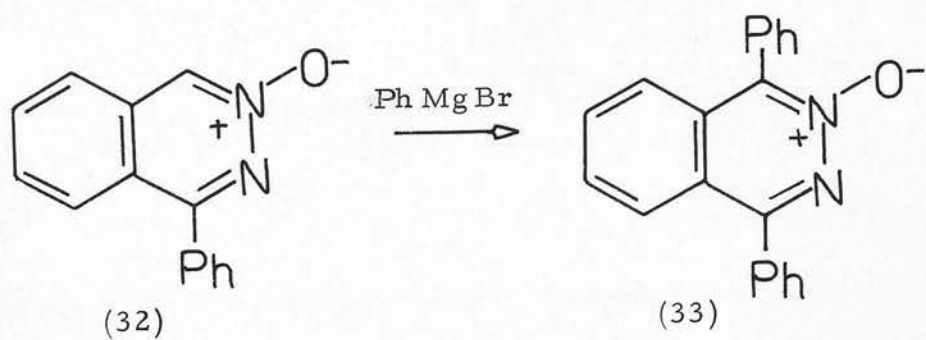
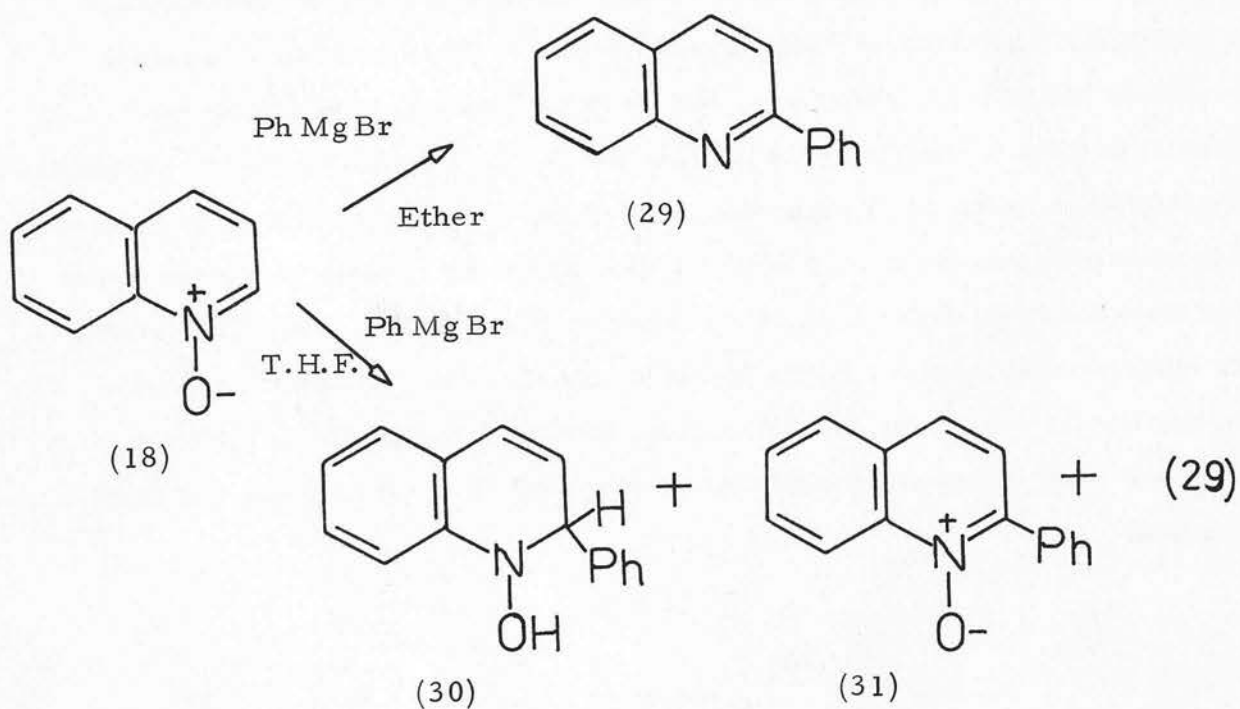
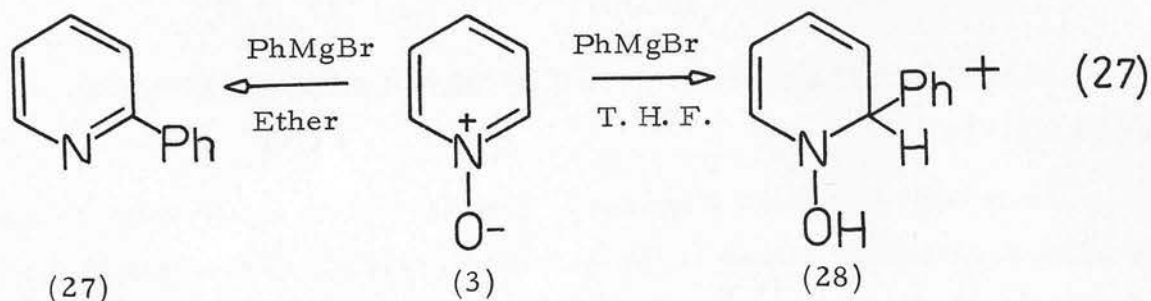
## Reactions of Heterocyclic N-Oxides Involving Nucleophilic Attack at a Ring Position

As has already been discussed, polarisation by the N-oxide group promotes nucleophilic attack at the  $\alpha$ - and  $\gamma$ -positions in the ring in the heteroaromatic N-oxides. As a result, a large number of nucleophilic substitution reactions of heterocyclic N-oxides have been investigated. In nearly all of these reactions, the N-oxide group is lost giving the substituted deoxy-heterocycle [cf (14)  $\rightarrow$  (17)]. Usually only the strongest nucleophiles, such as the carbanions derived from organometallic reagents, can attack an uncoordinated heterocyclic N-oxide. Many more examples are known of nucleophilic attack where the N-oxide has previously added an electrophilic species at the N-oxide oxygen atom [(20)  $\rightarrow$  (21)], thus enhancing its reactivity to nucleophilic attack. Nucleophilic addition [(21)  $\rightarrow$  (22)] followed by elimination [(22)  $\rightarrow$  (17)] then gives the final product.



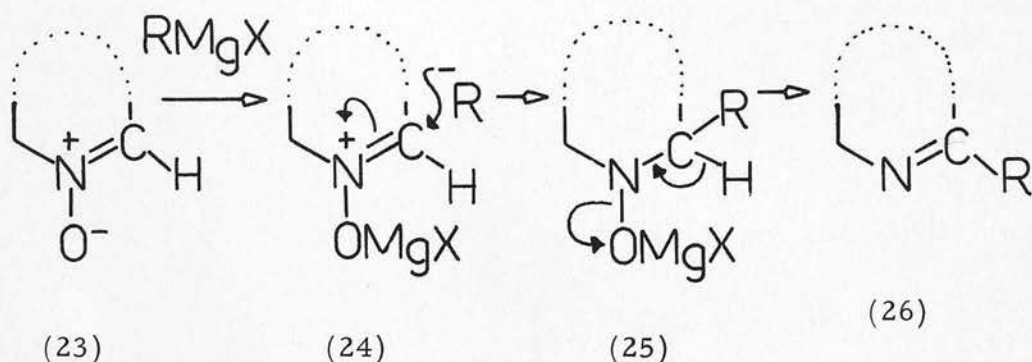
In general, there is a very strong tendency for nucleophilic attack to occur at the  $\alpha$ -position, however, if the  $\alpha$ -position is occupied then nucleophilic attack occurs at the  $\gamma$ -position. If both the  $\alpha$ - and  $\gamma$ -positions on the heterocyclic ring are substituted, reaction can occur at a more remote site, for example a fused benzene ring.

The following examples of nucleophilic substitution reactions of heterocyclic N-oxides demonstrate the wide variety of nucleophilic reagents with which these compounds react.



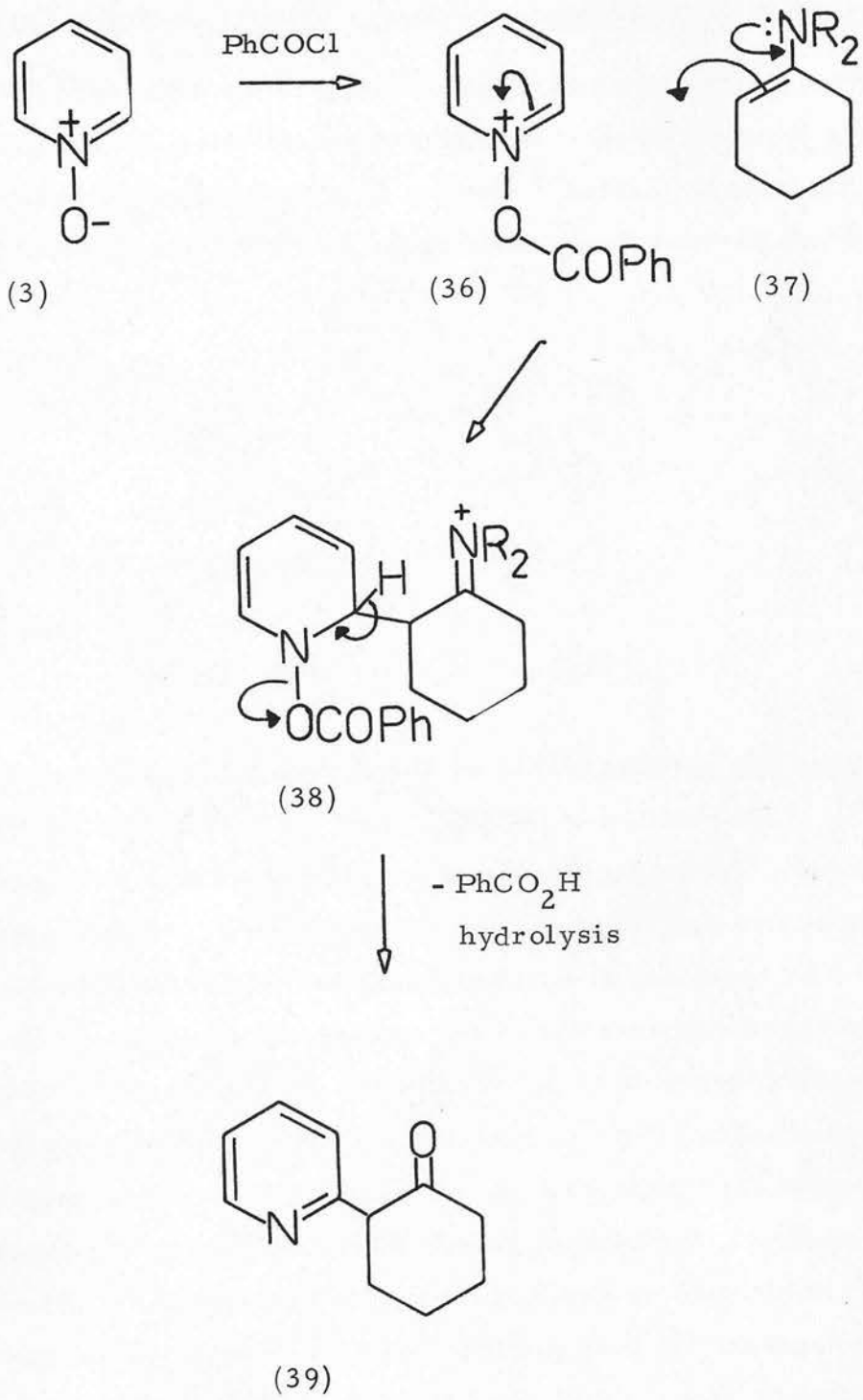
a) Reactions of Heterocyclic N-Oxides with Carbanionic Reagents

Grignard reagents and organolithium compounds react with heterocyclic N-oxides to give  $\alpha$ -alkyl and  $\alpha$ -aryl heterocycles [(23)  $\rightarrow$  (26)]. It has been suggested<sup>10</sup> that the Grignard reagent coordinates with the oxygen atom of the N-oxide group to give a complex (24) which

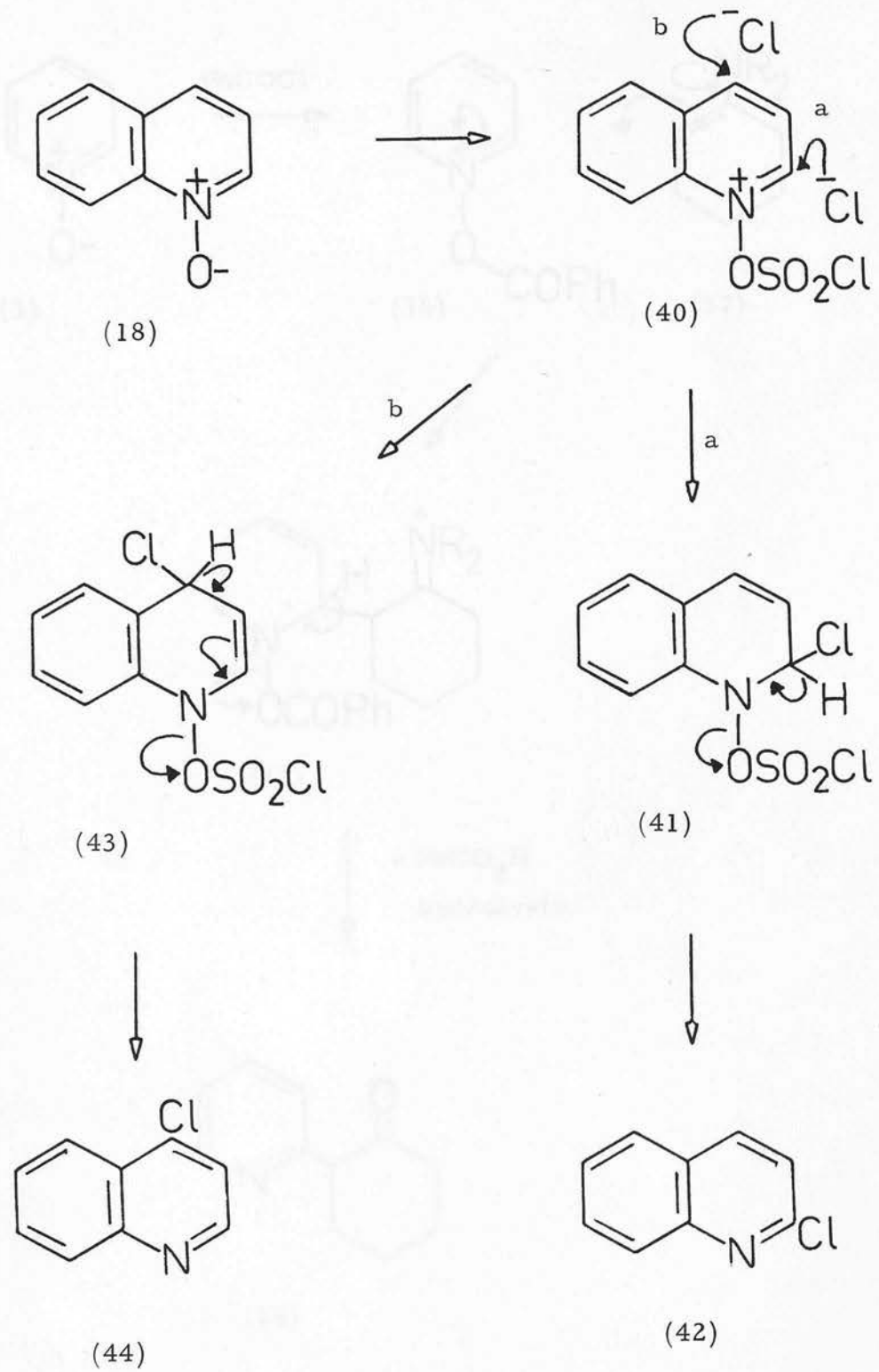


then undergoes nucleophilic attack by the carbanion to yield the intermediate (25). Elimination of ( $HOMgX$ ) from the intermediate (25) gives the product (26). Heterocyclic N-oxides also react with Grignard reagents as oxidising agents and deoxygenated heterocycles are often formed as by-products. The reactions of pyridine 1-oxide (3) and quinoline 1-oxide (18) with Grignard reagents have been extensively studied. With ethereal phenylmagnesium bromide, the products are 2-phenylpyridine (27)<sup>11, 12</sup> and 2-phenylquinoline (29).<sup>11</sup> However, in tetrahydrofuran as solvent, pyridine 1-oxide (3) reacts with phenyl magnesium bromide to give 1-hydroxy-2-phenyl-1, 2-dihydropyridine (28) in addition to the expected product (27) which may be obtained from (28) by heating.<sup>13</sup> The reaction of quinoline 1-oxide (18) with phenylmagnesium bromide in the presence of tetrahydrofuran is similar and gives the adduct (30), 2-phenylquinoline (29) and also 2-phenylquinoline 1-oxide (31).<sup>13</sup> 2-Phenylquinoline 1-oxide (31) is considered to be derived from the adduct (30) by oxidation since (30) is converted into (31) in the presence of air.<sup>13</sup> Retention of the N-oxide group is not uncommon in reactions of heteroaromatic N-oxides with organometallic reagents. Thus, 1-phenylphthalazine 3-oxide (32) reacts with phenylmagnesium bromide to give 1,4-diphenylphthalazine





Scheme 1



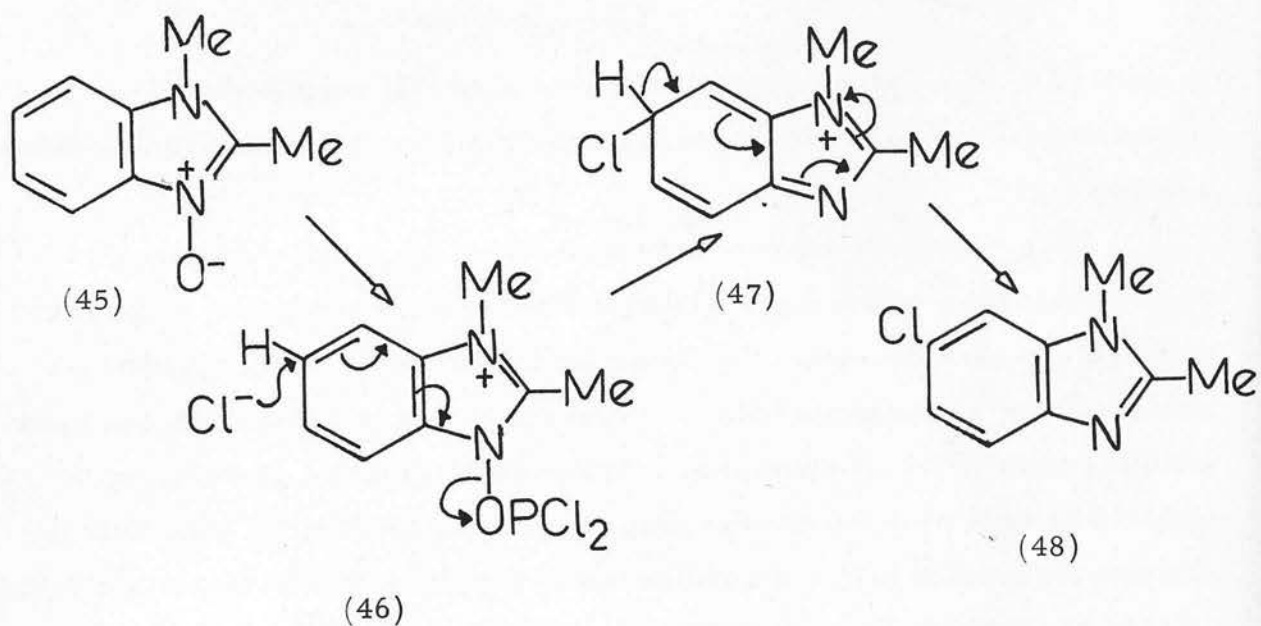
Scheme 2

2-oxide (33)<sup>14</sup> and 3-phenylquinoxaline 1-oxide (34) reacts with both phenylmagnesium bromide and phenyllithium to give 2, 3-diphenylquinoxaline 1-oxide<sup>15</sup> (35).

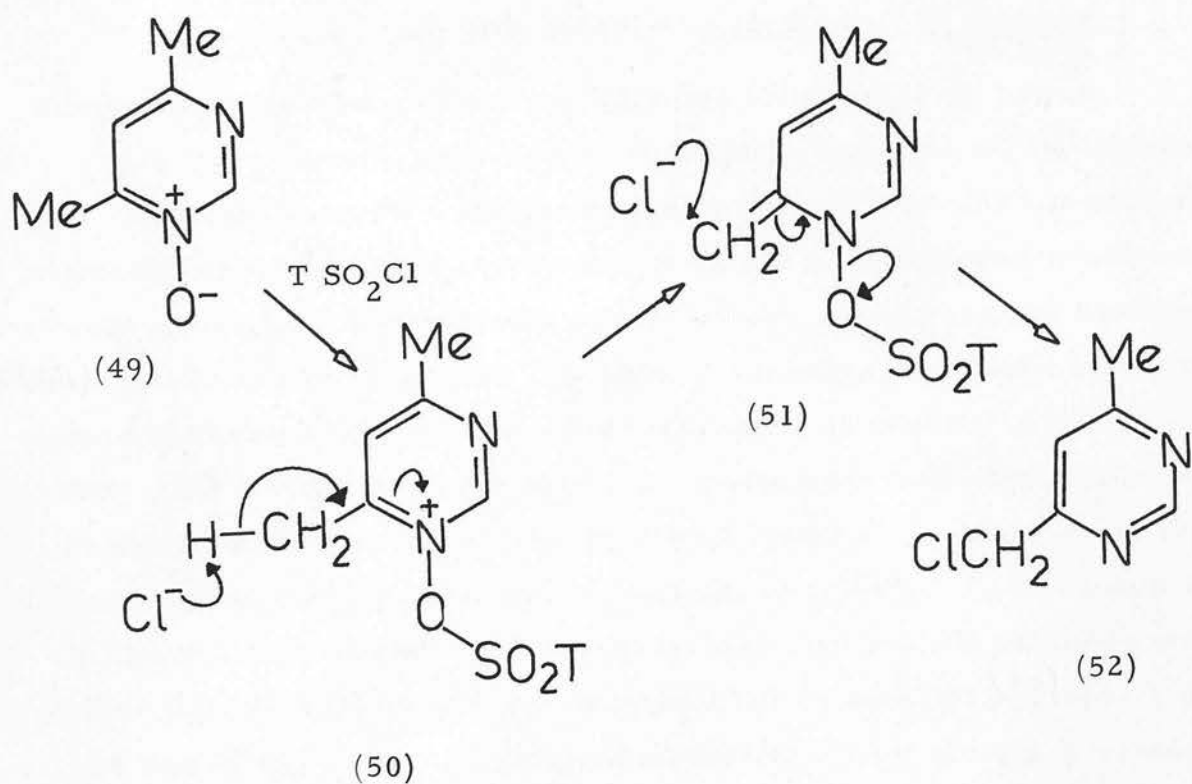
Heterocyclic N-oxides react with enamines in the presence of benzoyl chloride, toluene p-sulphonyl chloride (tosyl chloride) or acetic anhydride to give ketones. Nucleophilic attack by the carbanion occurs preferentially at the  $\alpha$ -position. However, if this position is blocked the enamine attacks the  $\gamma$ -position. The general reaction mechanism is outlined in scheme 1 for the reaction of pyridine 1-oxide (3) with dialkylaminocyclohexenes (37). Coordination of the N-oxide with benzoyl chloride affords the intermediate (36) which then undergoes nucleophilic attack by the enamine (37) at the  $\alpha$ -position of the hetero ring to yield the adduct (38). Loss of benzoic acid from the latter followed by hydrolysis furnishes the ketonic product (39).

#### b) Reaction of Heterocyclic N-Oxides with Acid Halides

$\alpha$ - and  $\gamma$ -chlorinated heterocycles are formed from heterocyclic N-oxides by the action of phosphorus oxychloride, phosphorus pentachloride and sulphuryl and sulphonyl chlorides. Of these reagents, phosphorus oxychloride is the most frequently used. These halogenation reactions are assumed to proceed by the mechanism illustrated in scheme 2 for the conversion of quinoline 1-oxide (18) into the 2- and 4-chloroquinolines<sup>16</sup> (42) and (44). It is considered that the N-oxide group of quinoline 1-oxide (18) coordinates with the sulphuryl chloride to give the cation (40), which undergoes nucleophilic attack by chloride ion at the  $\alpha$ -position to afford the adduct (41). Subsequent expulsion of the leaving group on the nitrogen atom gives the 2-chlorinated heterocycle (42). Alternatively, attack at the  $\gamma$ -position followed by the analogous mechanism [(40)  $\rightarrow$  (43)  $\rightarrow$  (44)] (scheme 2) affords the 4-chlorinated heterocycle (44). The 2- and 4-chloroquinolines are produced in comparable amounts. The ratio of the  $\alpha$ - to  $\gamma$ -derivatives obtained has been found to be affected by the nature of the substituents on the fused benzenoid nucleus, but not by the reaction conditions. If the  $\alpha$ - and  $\gamma$ -positions of the hetero ring are occupied, then nucleophilic substitution by chloride ion may also occur in a fused

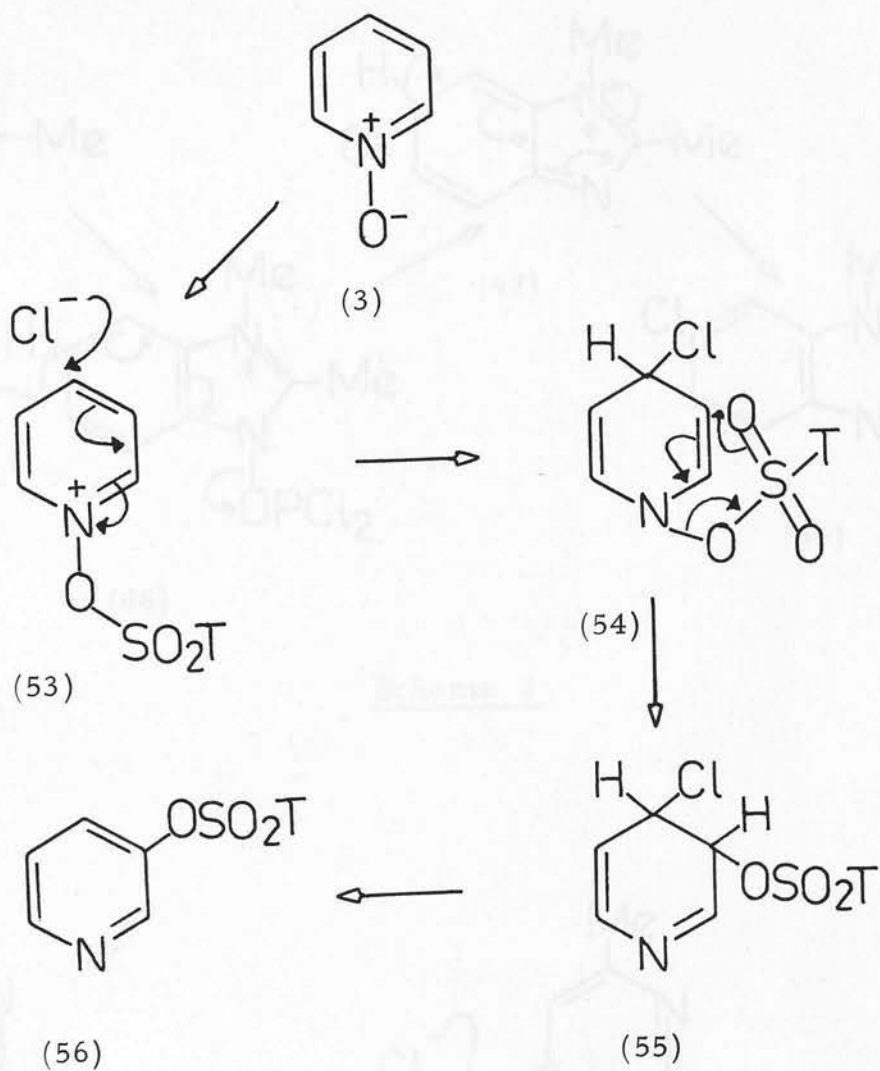


Scheme 3



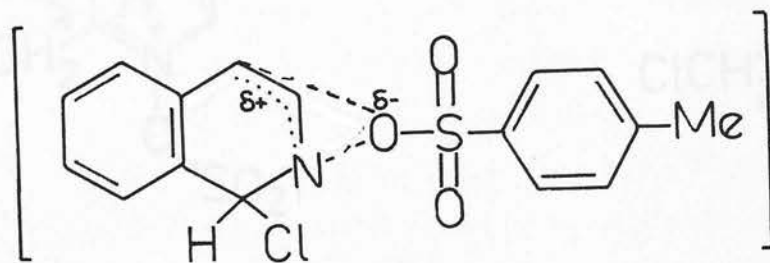
[T = para-tolyl]

Scheme 4



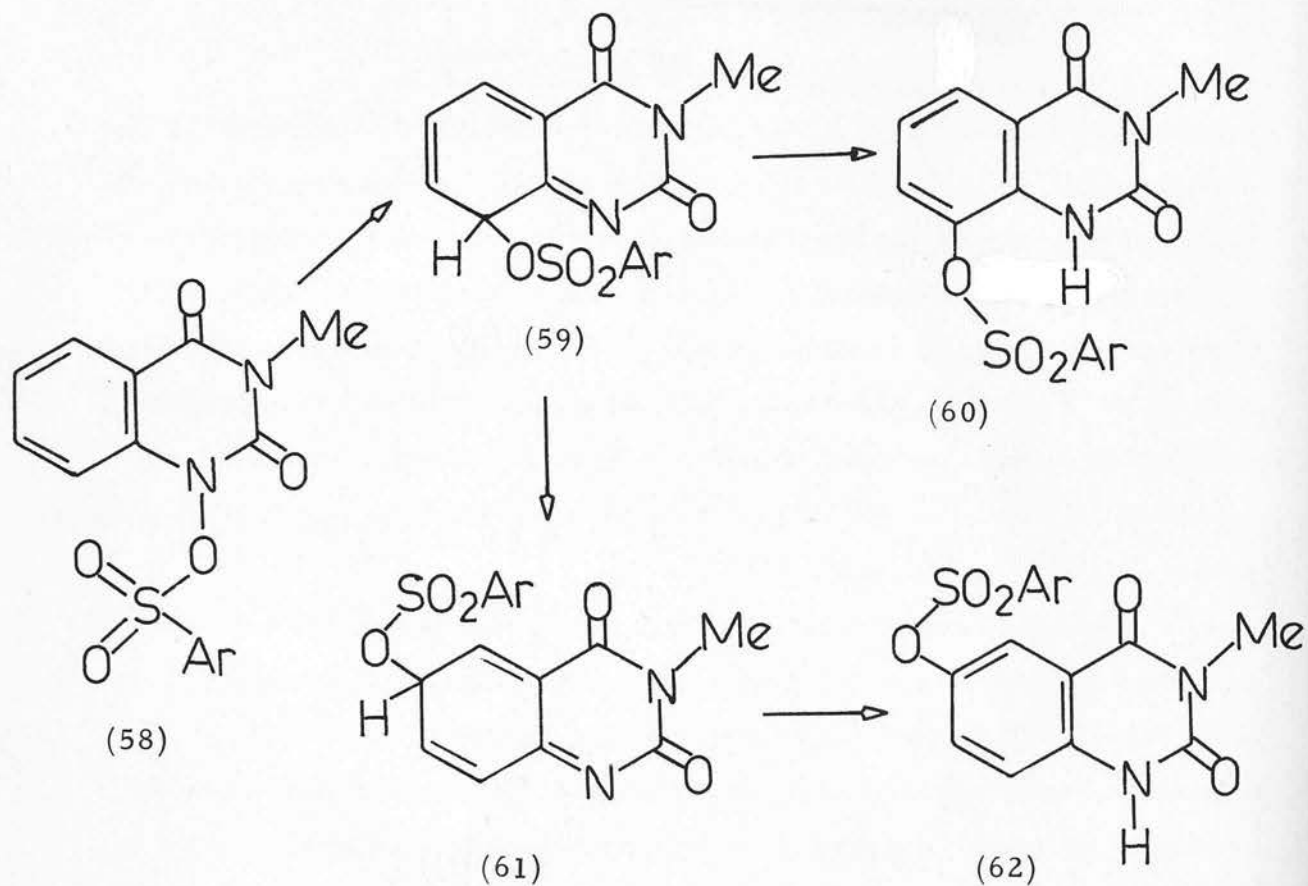
[T = para-tolyl]

Scheme 5

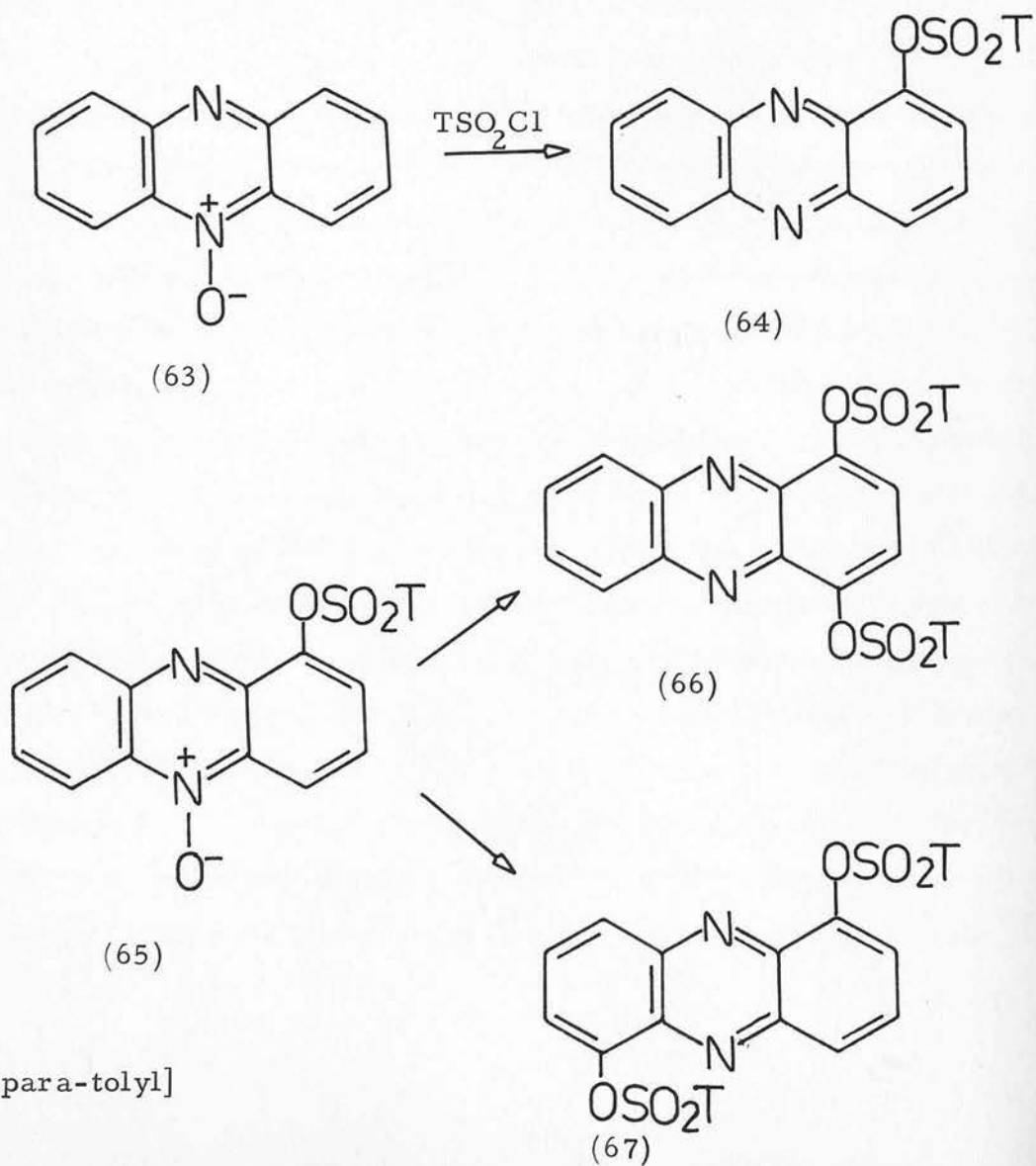


benzene nucleus. Thus, 1,2-dimethylbenzimidazole 3-oxide (45) reacts with phosphoryl chloride to afford 6-chloro-1,2-dimethylbenzimidazole<sup>17</sup> (48), presumably by the mechanism shown in scheme 3. Direct chlorination of the ring is less commonly observed with arenesulphonyl chlorides. However, reaction of arenesulphonyl chlorides or phosphorus oxychloride with  $\alpha$ - or  $\gamma$ -methyl substituted heterocyclic N-oxides can introduce a chlorine atom into the methyl group. 4,6-Dimethylpyrimidine 1-oxide (49) reacts in this manner with tosyl chloride to give 4-chloromethyl-6-methyl pyrimidine (52)<sup>18</sup> [cf. scheme 4].

Whereas heterocyclic N-oxides react with sulphonyl halides in the presence of base to give predominantly  $\alpha$ -substituted products [cf (18)  $\rightarrow$  (42) scheme 2], in the absence of base the reaction takes a different course and sulphonyloxylation may occur. When pyridine 1-oxide (3) is heated with tosyl chloride 3-tosyloxy pyridine (56) is formed<sup>19</sup> by the reaction sequence outlined in scheme 5. The reaction is interesting in that the position  $\beta$ - to the N-oxide function is attacked. In this reaction the N-oxide group is considered to coordinate with the arenesulphonyl halide to give the cation (53) which then undergoes nucleophilic attack by chloride ion at the  $\gamma$ -position to afford the adduct (54). An intramolecular rearrangement of the type [(54)  $\rightarrow$  (55)] followed by expulsion of the elements of hydrochloric acid from the resulting intermediate (55) then yields the  $\beta$ -substituted product (56). The labelling pattern of the  $\beta$ -sulphonyloxy product formed in the reaction of isoquinoline N-oxide with tosyl chloride uniformly labelled with <sup>18</sup>O, indicates that the migration of the toluene-sulphonate group proceeds mainly via an oxygen bridged ion pair intermediate of the type (57).<sup>20, 21</sup> It seems probable that a similar intermediate is involved in the corresponding reaction of pyridine 1-oxide (3) [cf. scheme 5]. It has been demonstrated that N-sulphonyloxyquinazolones (58), in which the  $\beta$ -position in the hetero ring is substituted, undergo thermal rearrangements of the type illustrated in scheme 6, wherein formal  $\beta$ -substitution occurs in the fused benzene ring.<sup>22</sup> These reactions are readily explained by a formal shift of the sulphonyloxy group from N-1 to C-8 to afford the non-aromatic intermediate (59) which yields the 8-sulphonyloxyquinazolone (60) directly by rapid rearomatisation. The intermediate (59) may

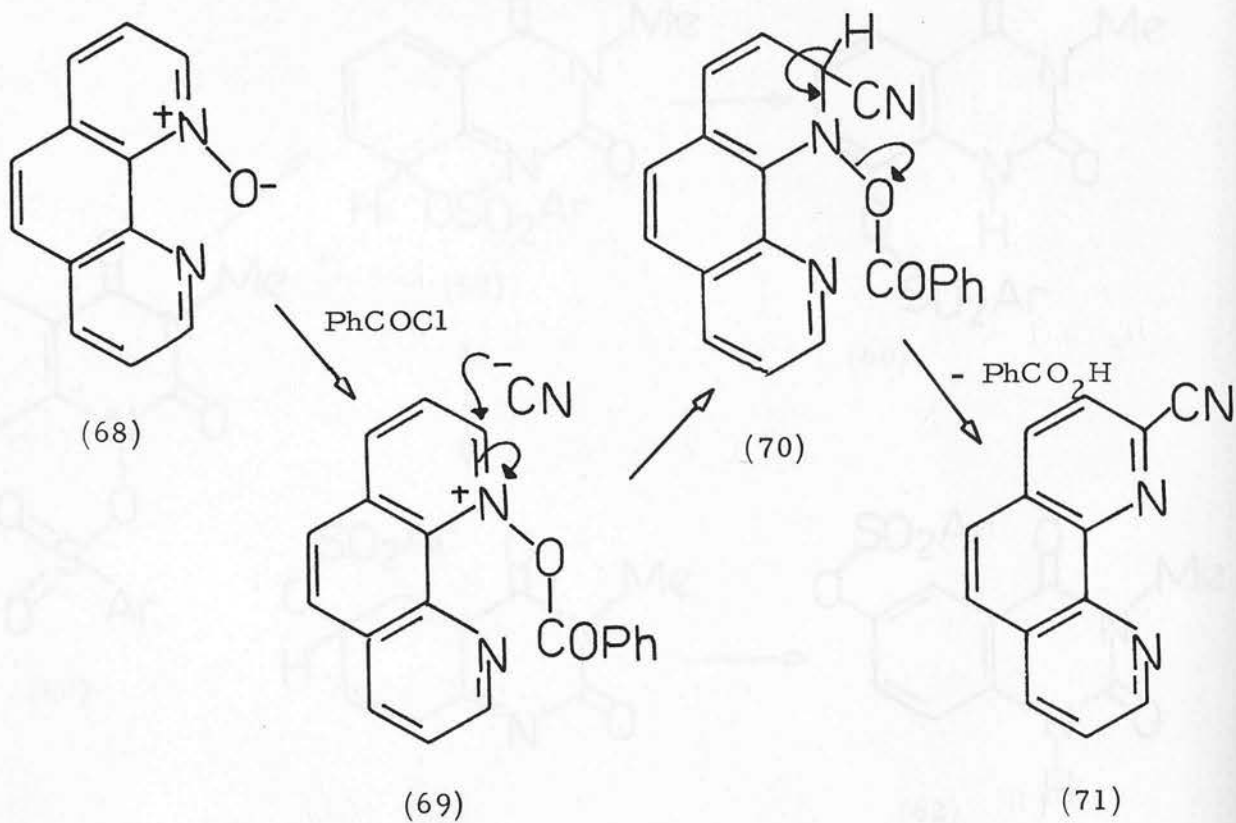


Scheme 6

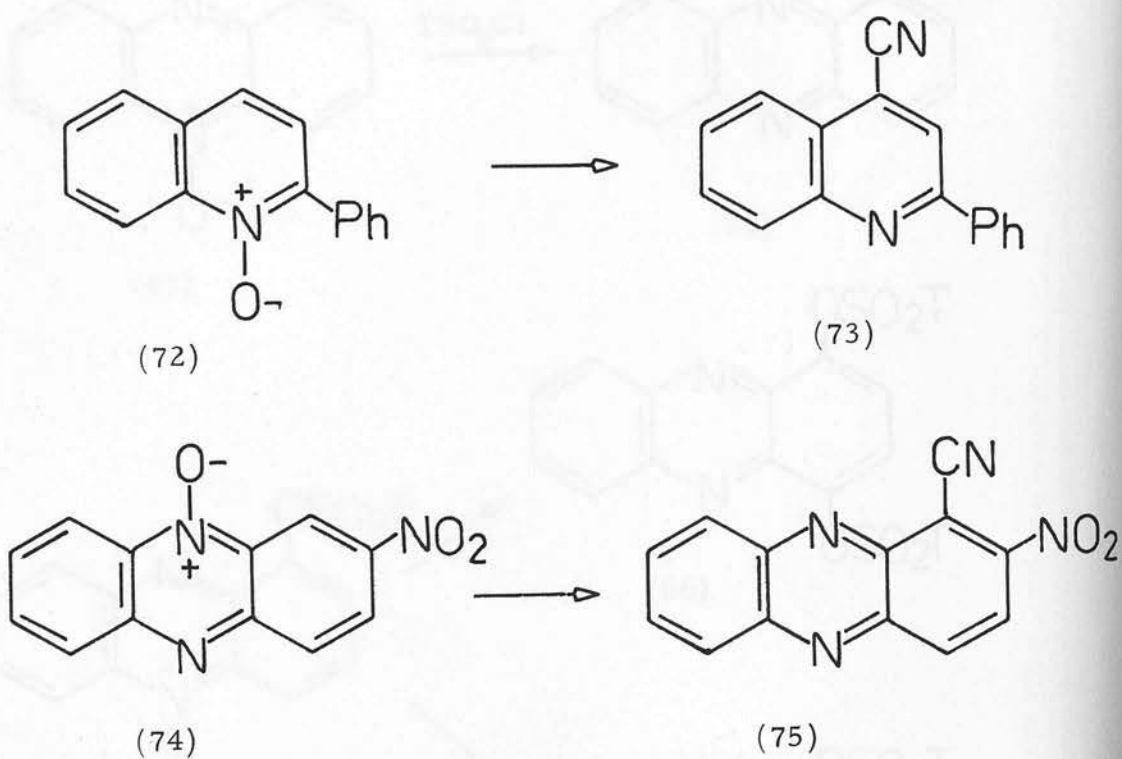


[T = para-tolyl]





Scheme 7

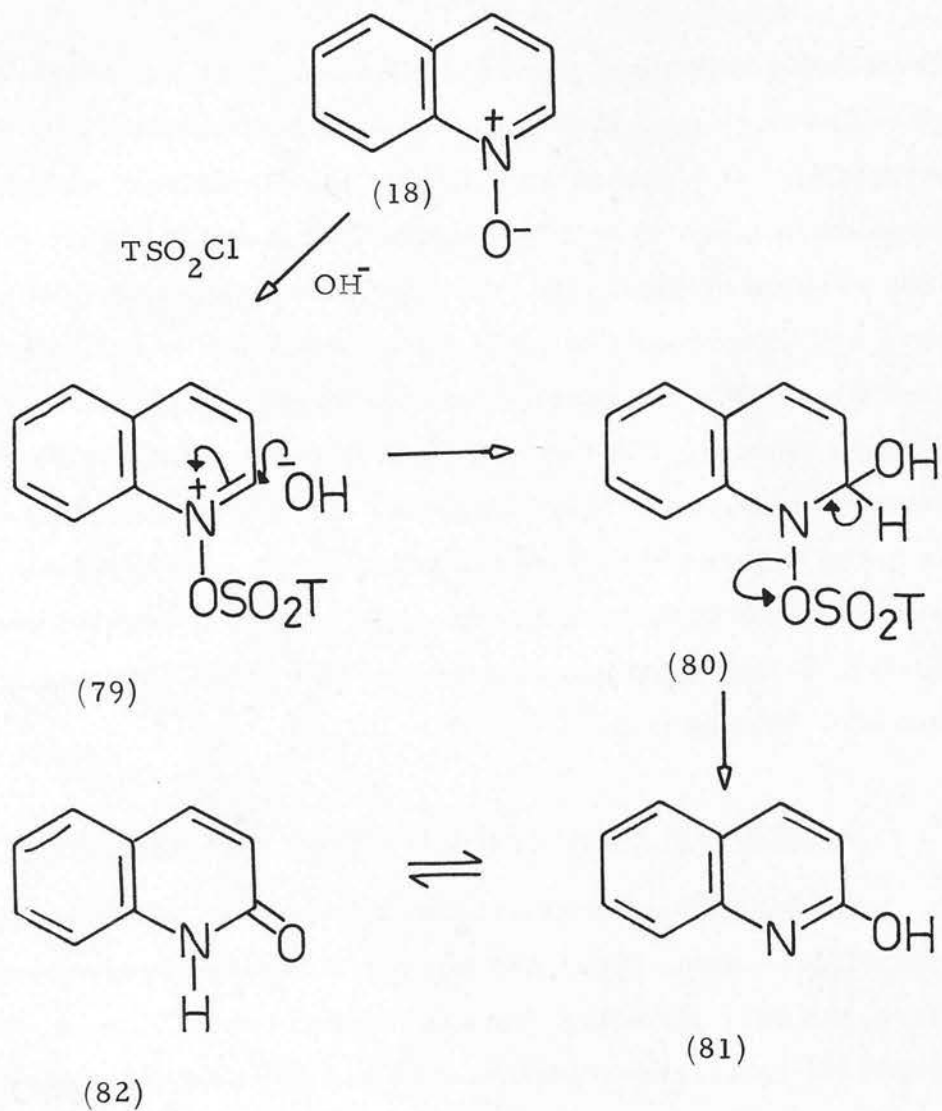




alternatively undergo a second [1, 3]-shift of the sulphonyloxy group from C-8 to C-6 giving a second non aromatic intermediate (61) which may rearomatise via a proton shift to give the 6-sulphonyloxyquinazolone (62). The position taken up by the sulphonyloxy group in (62) is essentially  $\beta$ - to the position originally occupied by the sulphonyloxy group in (58). These rearrangements provide evidence for the intermediacy of adducts of the type (54) in the reaction of heterocyclic N-oxides with arene-sulphonyl halides. The synthesis of 1-tosyloxyphenazine (64) from phenazine 5-oxide and tosyl chloride<sup>23</sup> further exemplifies substitution in a fused benzene ring when the positions  $\beta$ - to the N-oxide group in the hetero ring are blocked to attack. On further treatment with tosyl chloride, 1-tosyloxyphenazine 5-oxide (65) gives 1,4- and 1,6-ditosyloxyphenazine (66) and (67).<sup>23</sup>

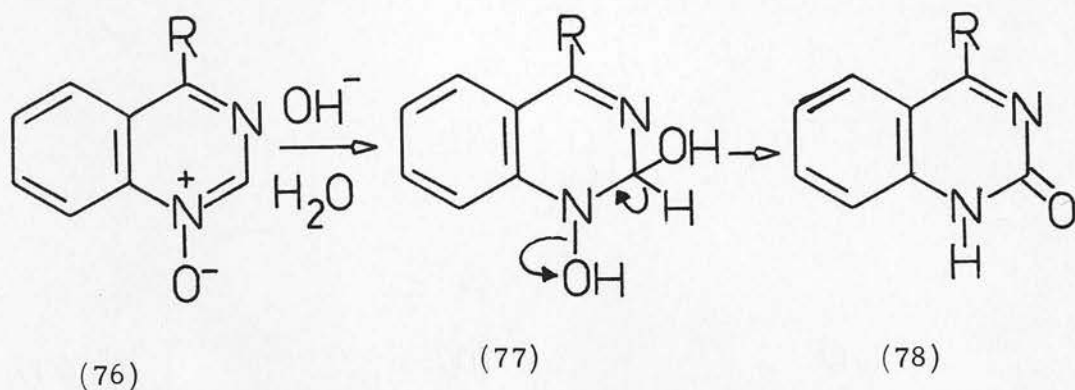
#### c) Reactions of Heterocyclic N-Oxides with Anionic Reagents

A wide variety of heterocyclic N-oxides, with the notable exception of pyridine 1-oxide, react with cyanide ion in the presence of acid halides to form the corresponding  $\alpha$ -cyano derivatives. Thus, 1,10-phenanthroline 1-oxide (68) undergoes reaction with benzoyl chloride and potassium cyanide at room temperature<sup>29</sup> to afford the  $\alpha$ -cyano derivative (71) [cf. scheme 7]. It is suggested that in reactions of this type, the N-oxide (68) initially coordinates with the benzoyl chloride, thus enhancing its reactivity towards nucleophilic attack in the position  $\alpha$ - to the N-oxide group. The resulting adduct (69) then undergoes nucleophilic attack in the  $\alpha$ -position by cyanide ion to give the intermediate (70). Elimination of the elements of benzoic acid from the latter subsequently affords the 2-cyanophenanthroline (71). This reaction, which constitutes a general synthetic route to cyanoheterocycles, is analogous to the Reissert reaction. When the  $\alpha$ -position is occupied, attack by cyanide ion may occur in the  $\gamma$ -position, as is exemplified by the reaction of 2-phenylquinoline 1-oxide (72) with benzoyl chloride and cyanide ion to afford 4-cyano-2-phenylquinoline (73).<sup>25</sup> When both the  $\alpha$ - and  $\gamma$ -positions are blocked, nucleophilic substitution may again occur in a fused benzene ring. Thus, 2-nitrophenazine 10-oxide (74) gives 1-cyano-2-nitrophenazine (75).<sup>26</sup>

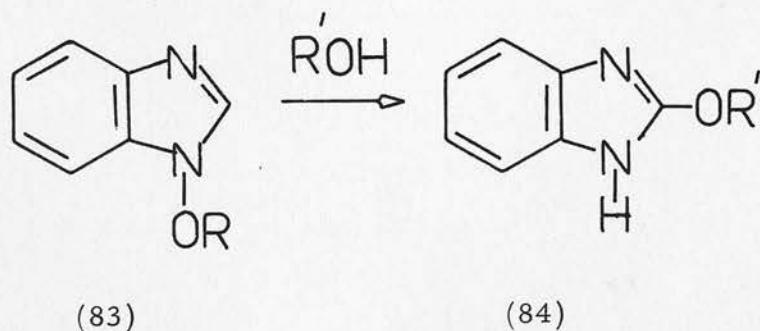


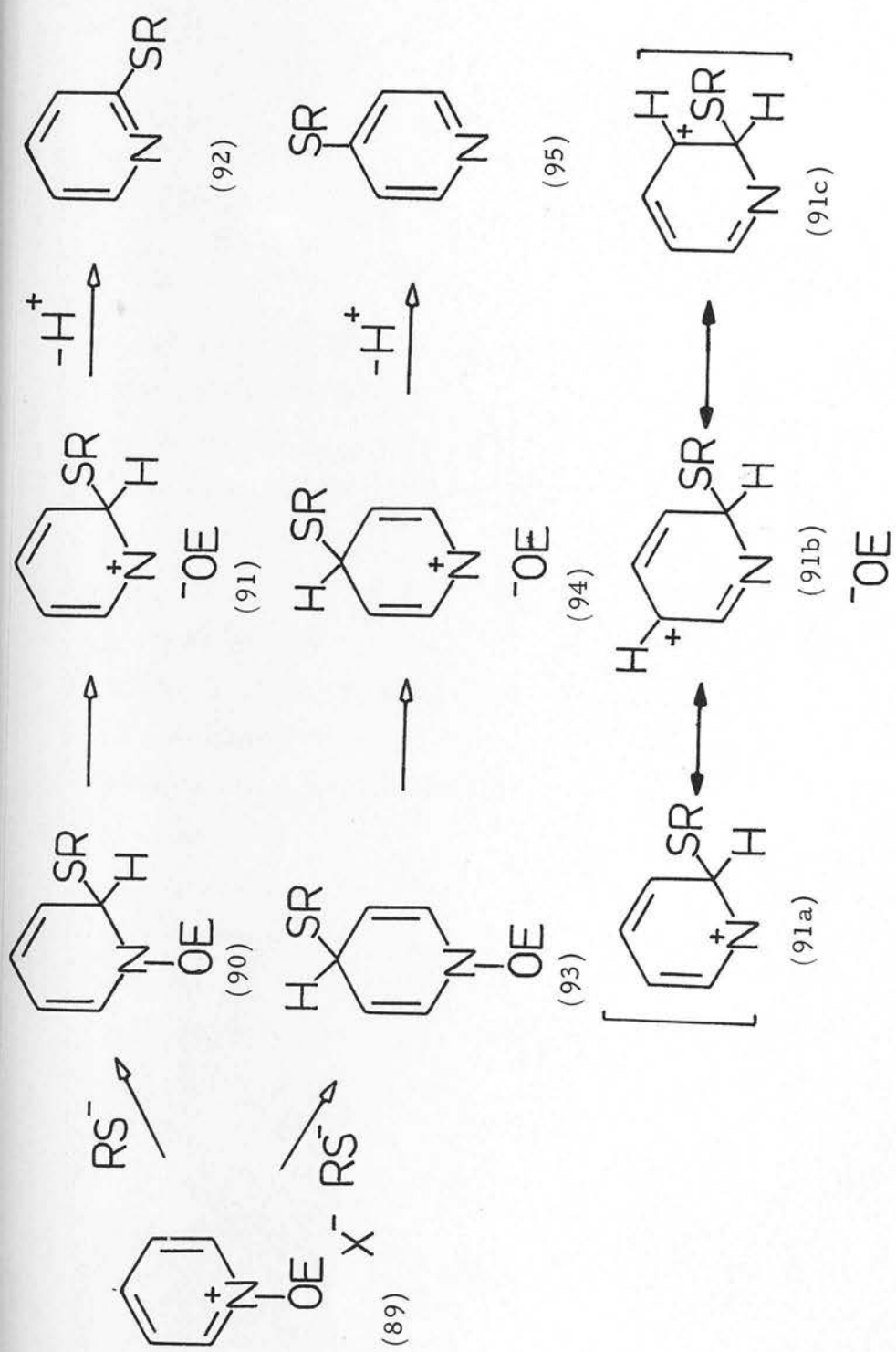
Scheme 8

Heteroaromatic N-oxides in which the ring contains two or more hetero atoms are often susceptible to nucleophilic attack by hydroxide or alkoxide ions under basic conditions, or by water or alcohols under essentially neutral conditions. In aqueous alkali, quinazoline 1-oxides (76) are converted into 2-quinazolones (78).<sup>27</sup> These reactions probably

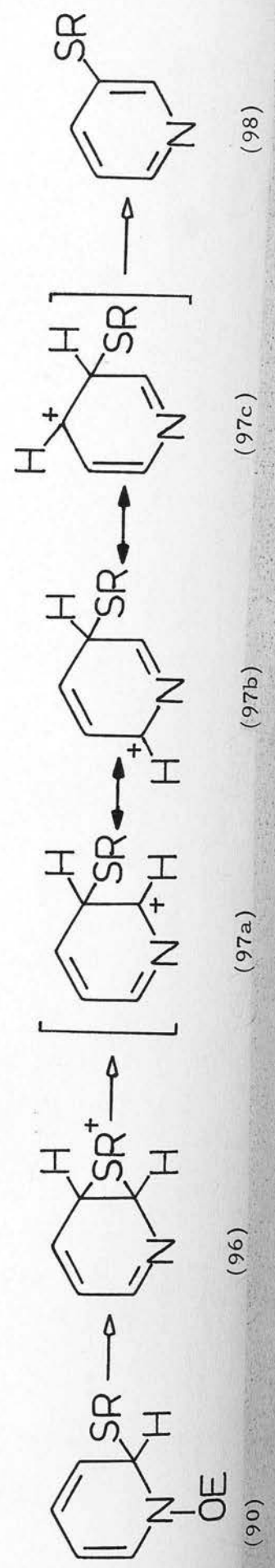


occur via covalently hydrated intermediates of the type (77).<sup>28</sup> However, hydroxide ions attack heterocyclic N-oxides more readily in the presence of acid chlorides. As already discussed, coordination of the N-oxide oxygen atom with the acid chloride enhances the reactivity of the  $\alpha$ -position towards nucleophilic attack. Thus quinoline 1-oxide (18) is readily converted into 2-hydroxyquinoline (81) in an aqueous alkaline medium in the presence of tosyl chloride.<sup>29</sup> The N-oxide oxygen of the quinoline 1-oxide (18) coordinates with the tosyl chloride to give the intermediate (79). Nucleophilic attack by hydroxide ion at the 2-position in the intermediate (79) would give the adduct (80) which by elimination of the tosyloxy group would then afford 2-hydroxyquinoline (81) tautomeric with quinolin-2-one (82). Nucleophilic attack by alkoxide ion on an N-oxygenated heterocycle is exemplified by the formation of 2-alkoxybenzimidazoles (84) when 1-alkoxybenzimidazoles (83) are boiled in alcohols.<sup>30</sup>

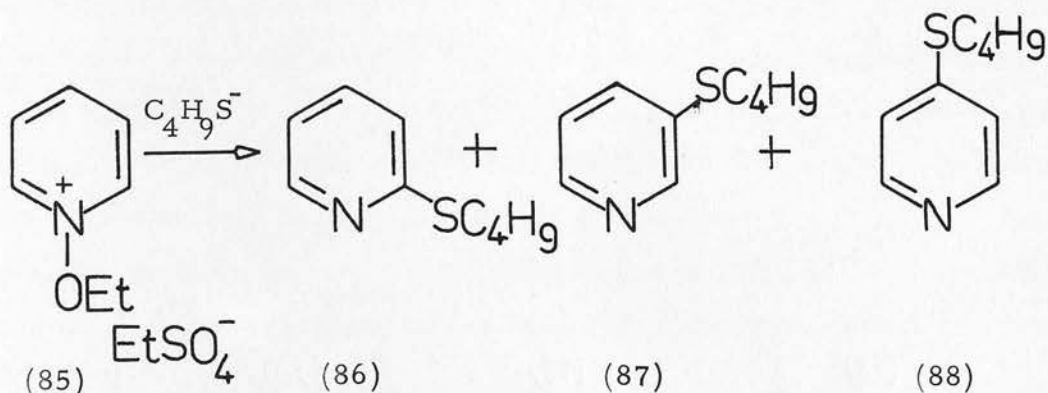




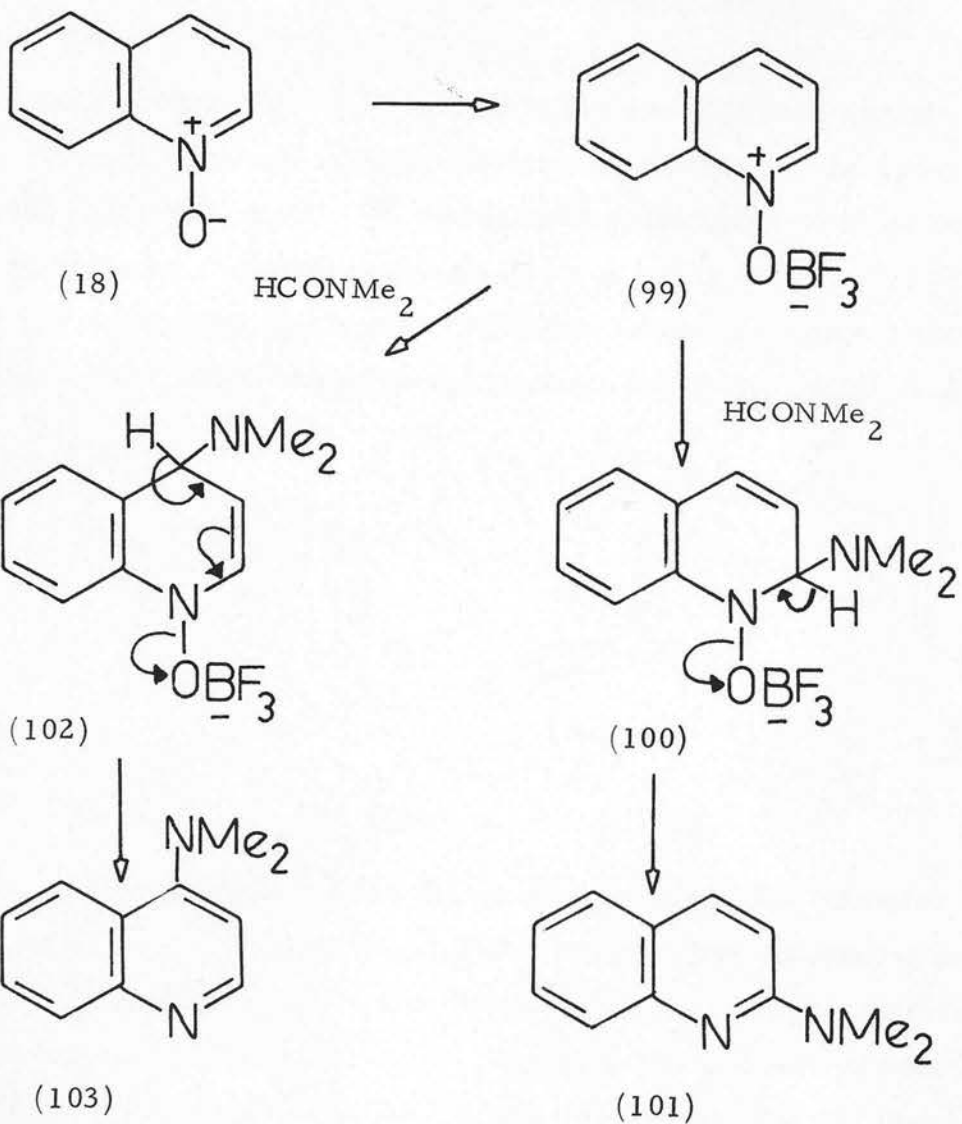
Scheme 9



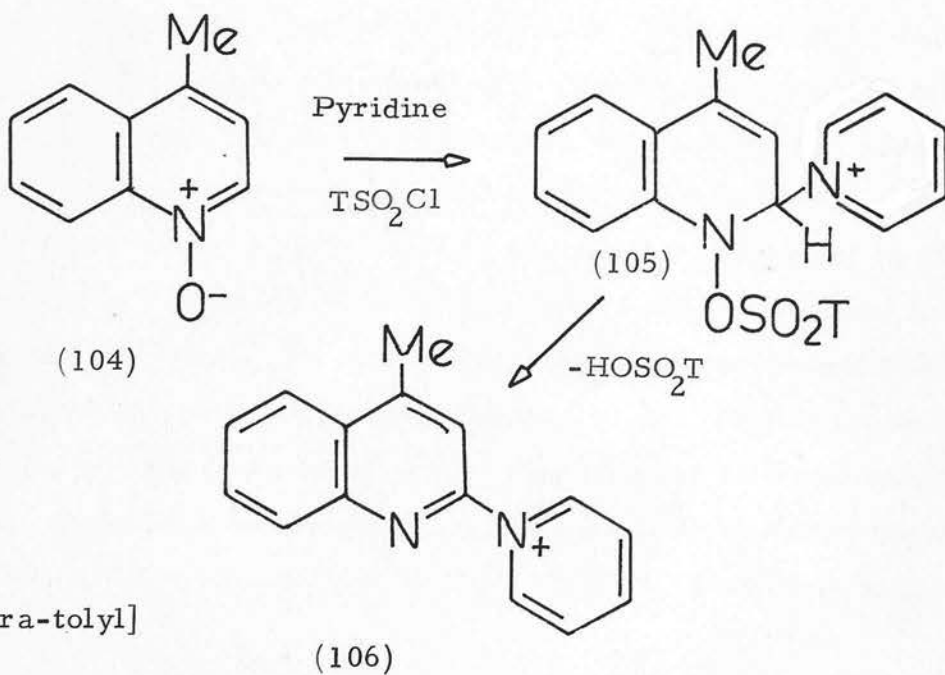
It has been demonstrated that on treatment with butane-1-thiol in the presence of sodium n-butylmercaptide, pyridine 1-oxide (3) fails to form sulphur substituted derivatives.<sup>31</sup> When, however, pyridine 1-oxide (3) is in the form of an *N*-alkoxy pyridinium salt, reaction is undergone with mercaptide and with thiophenoxide ions to yield a mixture of pyridine and 2-, 3- and 4-alkyl mercaptopyridines. Thus, 1-ethoxy pyridinium



ethyl sulphate (85) yields 2-, 3- and 4-mercaptopyridine (86), (87) and (88) on treatment with sodium n-butylmercaptide.<sup>32</sup> A variety of quaternising agents, including acetic anhydride and benzoyl chloride, have been used in reactions of this type.<sup>31, 33</sup> The general mechanism favoured to account for such reactions is that outlined in schemes 9 and 10. The first step (which generally occurs *in situ*) is the quaternisation of pyridine 1-oxide (3) to furnish the pyridinium salt (89). Attack by thiolate anion at the electrophilically enhanced  $\alpha$ - and  $\gamma$ -positions in (89) yields the intermediates (90) and (93). It is considered that the intermediate (90) affords the 2-substituted product (92) via the resonance stabilised [cf. (91a) ↔ (91b) ↔ (91c)] ion pair intermediate (91) within the confines of a solvent cage. The ion pair (91) then loses the proton at the C-2 position to give the product (92). The route to the 4-substituted product (95) is considered analogous to that leading to the 2-substituted product (92) and proceeds via the resonance stabilised ion pair (94) [cf. (91)] and deprotonation at C-4 to give (95). It is postulated that formation of the episulphonium ion (96) competes with deprotonation at the 2- and 4-positions and that the 3-substituted pyridine (98) is formed from the episulphonium ion (96) via the resonance stabilised [(97a) ↔ (97b) ↔ (97c)] intermediate (97) (Scheme 10).



Scheme 11



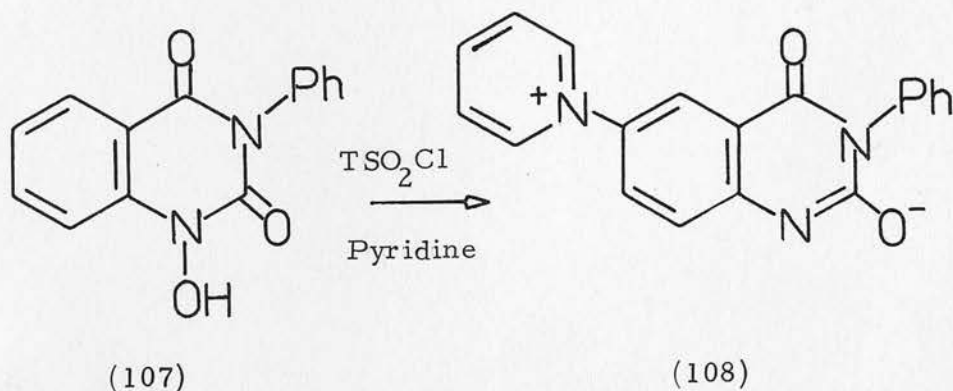
(106)

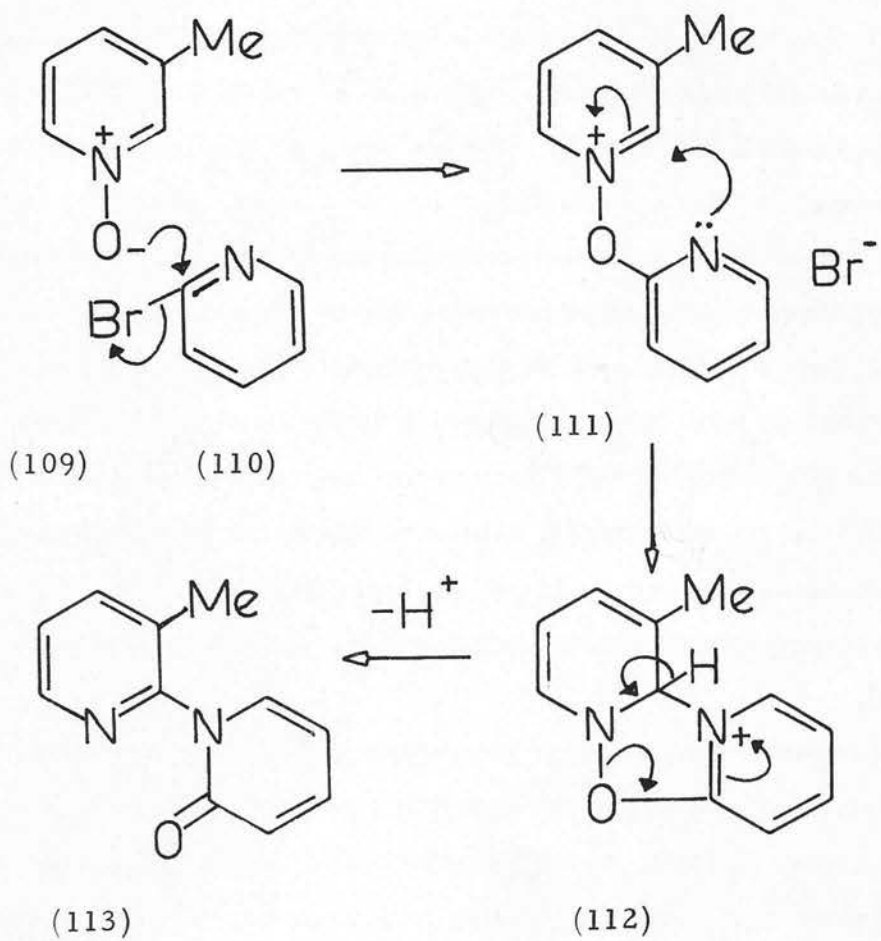


d) Reactions of Heterocyclic N-Oxides with Amines

Heterocyclic N-oxides undergo nucleophilic substitution reactions with amines subsequent to the formation of quaternary cations or Lewis acid intermediates [cf (99)]. Substitution by the amine occurs in the  $\alpha$ - or  $\gamma$ -position of the hetero ring. By and large, amines are not sufficiently nucleophilic to react with non-coordinated N-oxides. Nucleophilic reactions of this type are exemplified (scheme 11) by the conversion of quinoline 1-oxide (18) into a mixture of 2- and 4-dimethylaminoquinolines (101) and (103) on heating with boron trifluoride in dimethylformamide.<sup>34</sup> Coordination of the N-oxide (18) with boron trifluoride to form the Lewis acid adduct (99), followed by nucleophilic attack in the  $\alpha$ - or  $\gamma$ -position of the hetero ring by dimethylamine (produced by decomposition of the dimethylformamide) and subsequent aromatisation accounts for the formation of the products (101) and (103).

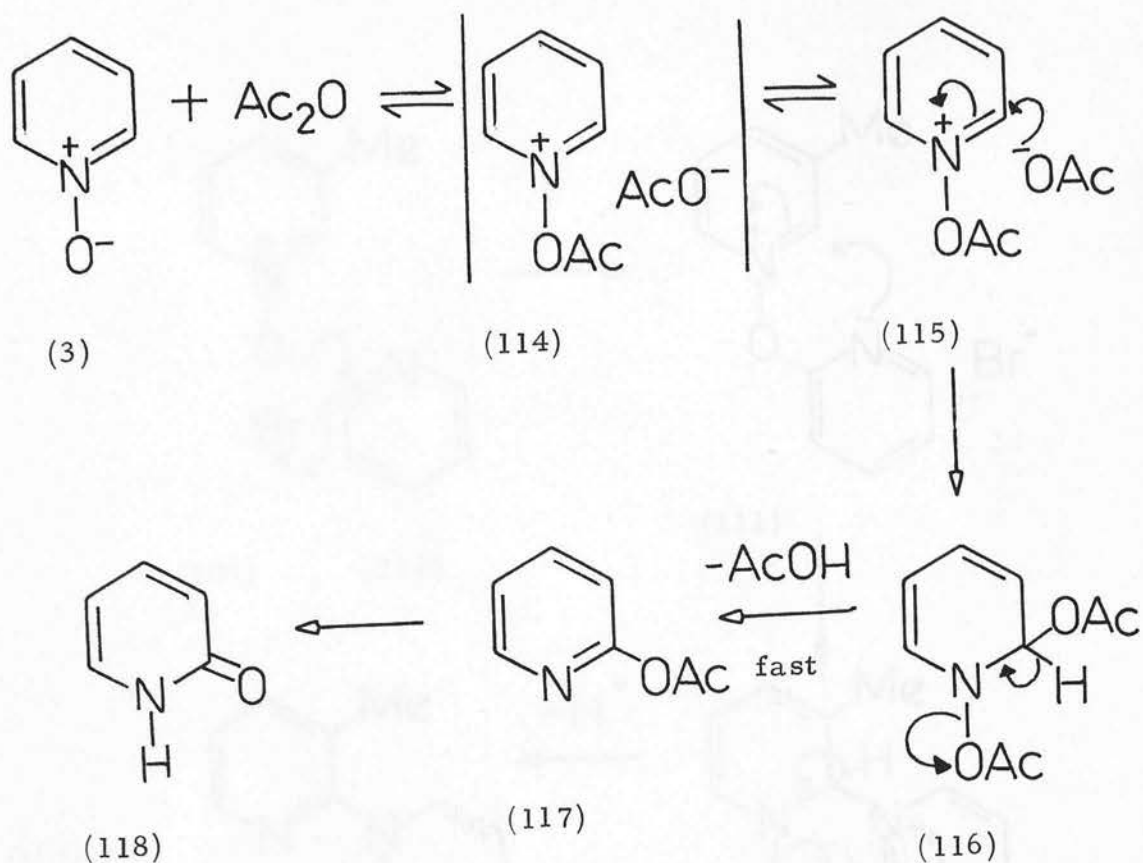
Aromatic amines also react with quaternary derivatives of heterocyclic N-oxides and again substitution occurs in positions  $\alpha$ - and  $\gamma$ - to the N-oxide group. Thus, 4-methylquinoline 1-oxide (104) reacts with pyridine in the presence of tosyl chloride to yield the 2-pyridinio-substituted quinoline (106) via the intermediate adduct (105).<sup>35</sup> In 2-methylquinoline 1-oxide, where the  $\alpha$ -position is occupied, the 4-pyridinio-substituted quinoline is isolated.<sup>35</sup> Substitution of a pyridine moiety in a fused benzene ring has also been observed in reactions of this type. The isolation of the betaine (108) has been reported<sup>22</sup> on reaction of 1-hydroxy-3-phenylquinazolinone (107) with pyridine in the presence of tosyl chloride.



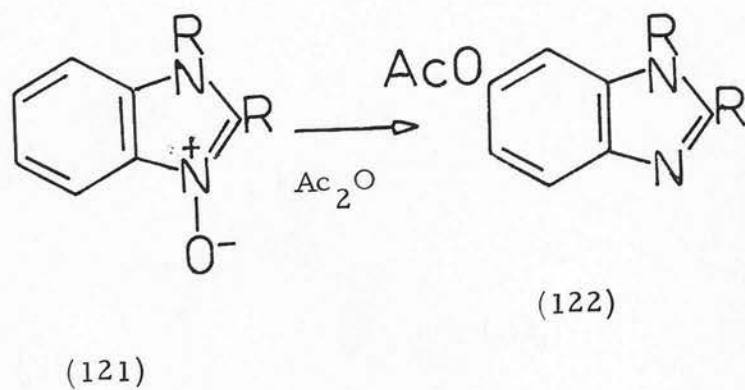
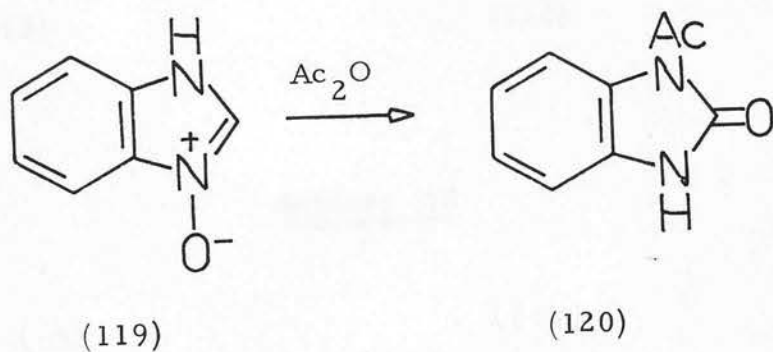


Scheme 12





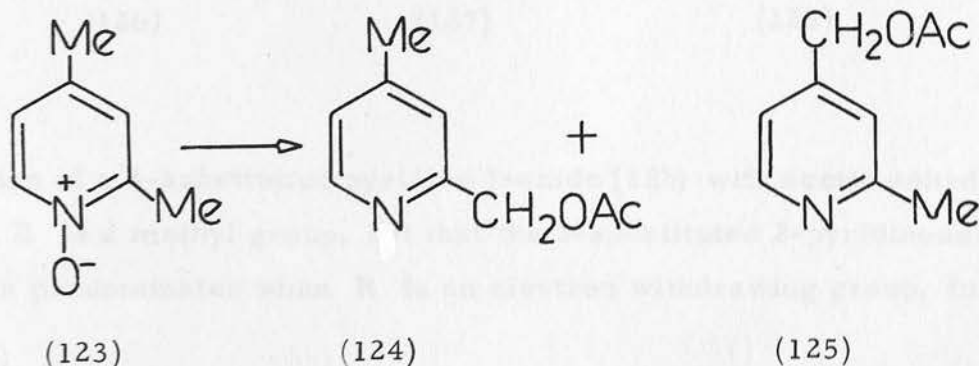
Scheme 13



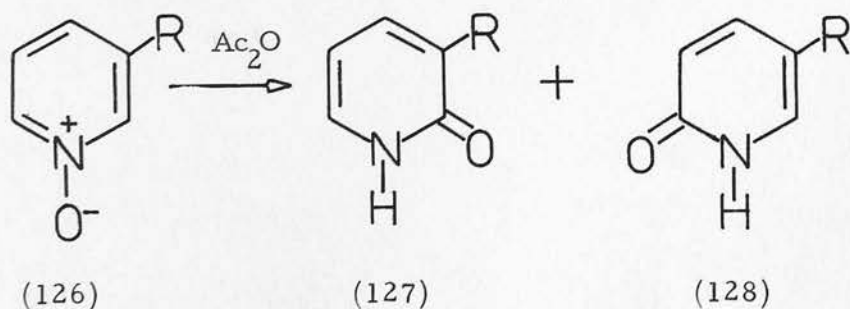
Heterocyclic N-oxides may also undergo reaction with 2-halogenopyridines. Reactions of this type are interesting in that the 2-halogenopyridine acts both as the coordinating species and as the nucleophile. Thus 3-picoline 1-oxide (109) reacts with  $\alpha$ -bromopyridine (110)<sup>36</sup> according to the mechanism shown in scheme 12.

e) Reactions of Heterocyclic N-Oxides with Acid Anhydrides

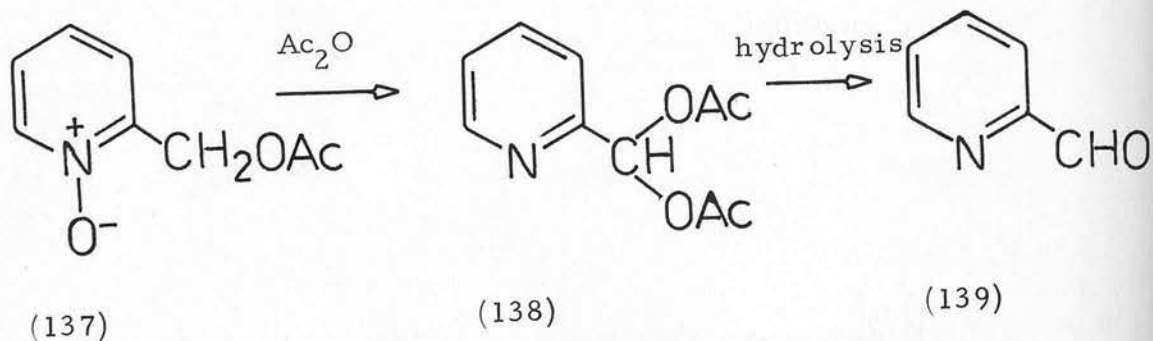
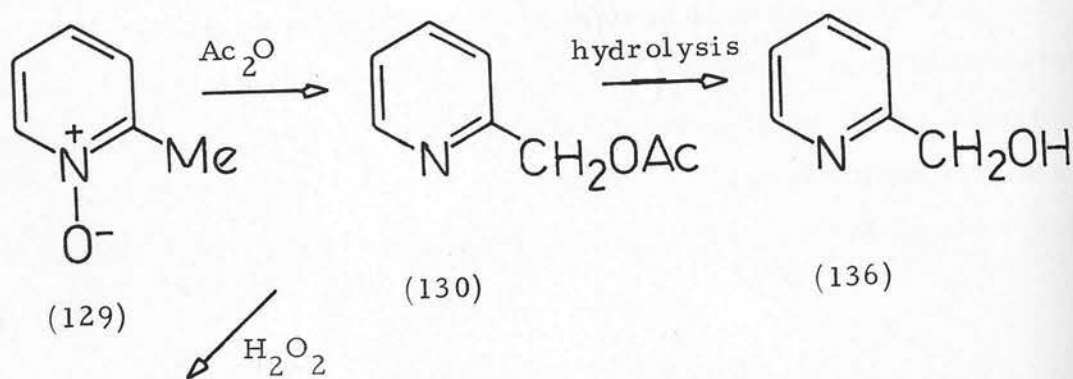
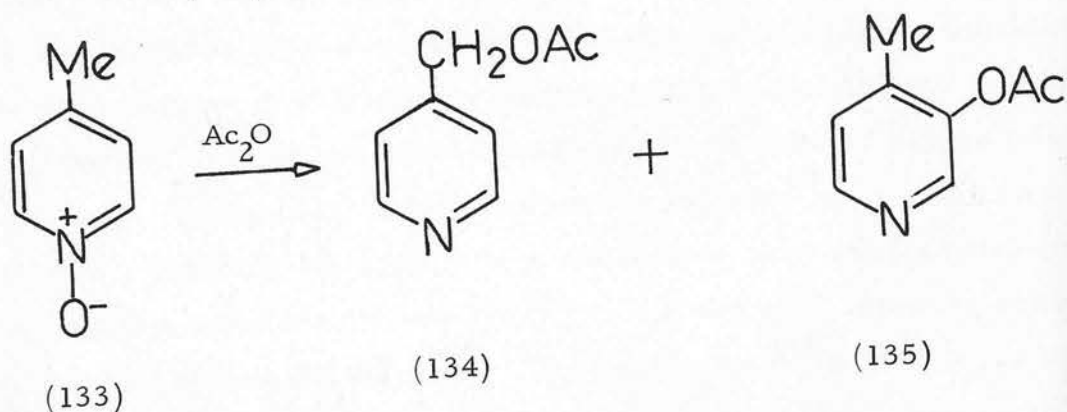
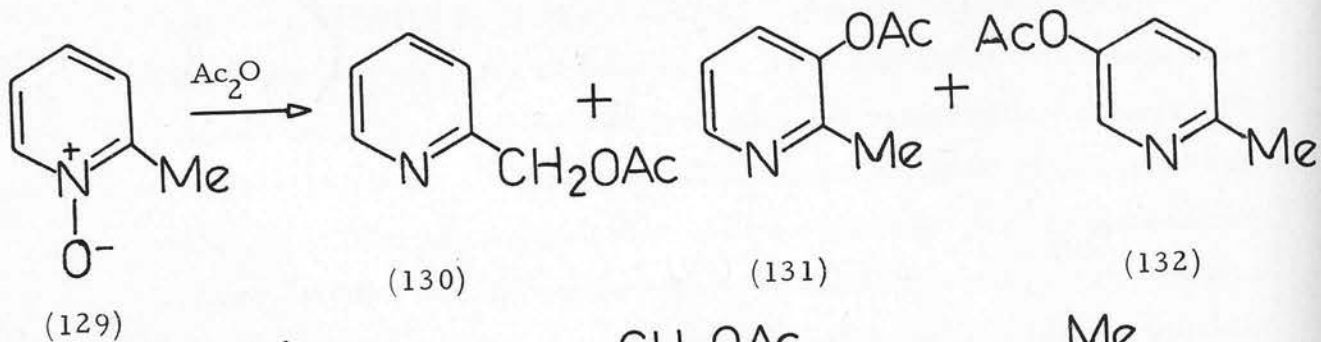
Since Katada<sup>37</sup> first discovered the rearrangement of pyridine 1-oxide (3) to pyridin-2-one (118) by reaction with acetic anhydride, much attention has been focussed on this classic heterocyclic N-oxide reaction both for mechanistic reasons and because of its synthetic value. Katada found that pyridine 1-oxide (3) rearranged on heating under reflux with acetic anhydride to 2-acetoxypyridine (117) which was hydrolysed in the course of the work up to give pyridin-2-one (118) (cf scheme 13). This reaction has since been considerably developed and has been found to be general for most ring systems. Typically, nucleophilic substitution by acetic anhydride occurs predominantly in the  $\alpha$ -position but when this position is blocked substitution can take place at the  $\delta$ -position. If all the available  $\alpha$ - and  $\delta$ -positions on the hetero ring are substituted, reaction may also occur in a fused benzene nucleus. Thus, benzimidazole 1-oxide (119) reacts with acetic anhydride at room temperature to give 3-acetylbenzimidazolin-2-one (120),<sup>38</sup> whereas 2,3-disubstituted benzimidazole 1-oxides (121) react with acetic anhydride to give 5-acetoxybenzimidazoles (122).<sup>39</sup> Rearrangements of this type involving methyl substituents in the  $\alpha$ - and  $\delta$ -positions of pyridine N-oxides have also been widely observed. For example, the reaction of 2,4-lutidine 1-oxide (123) with acetic anhydride gives the  $\alpha$ -acetoxymethyl derivative (124) and the  $\delta$ -acetoxymethyl derivative (125).<sup>40</sup>



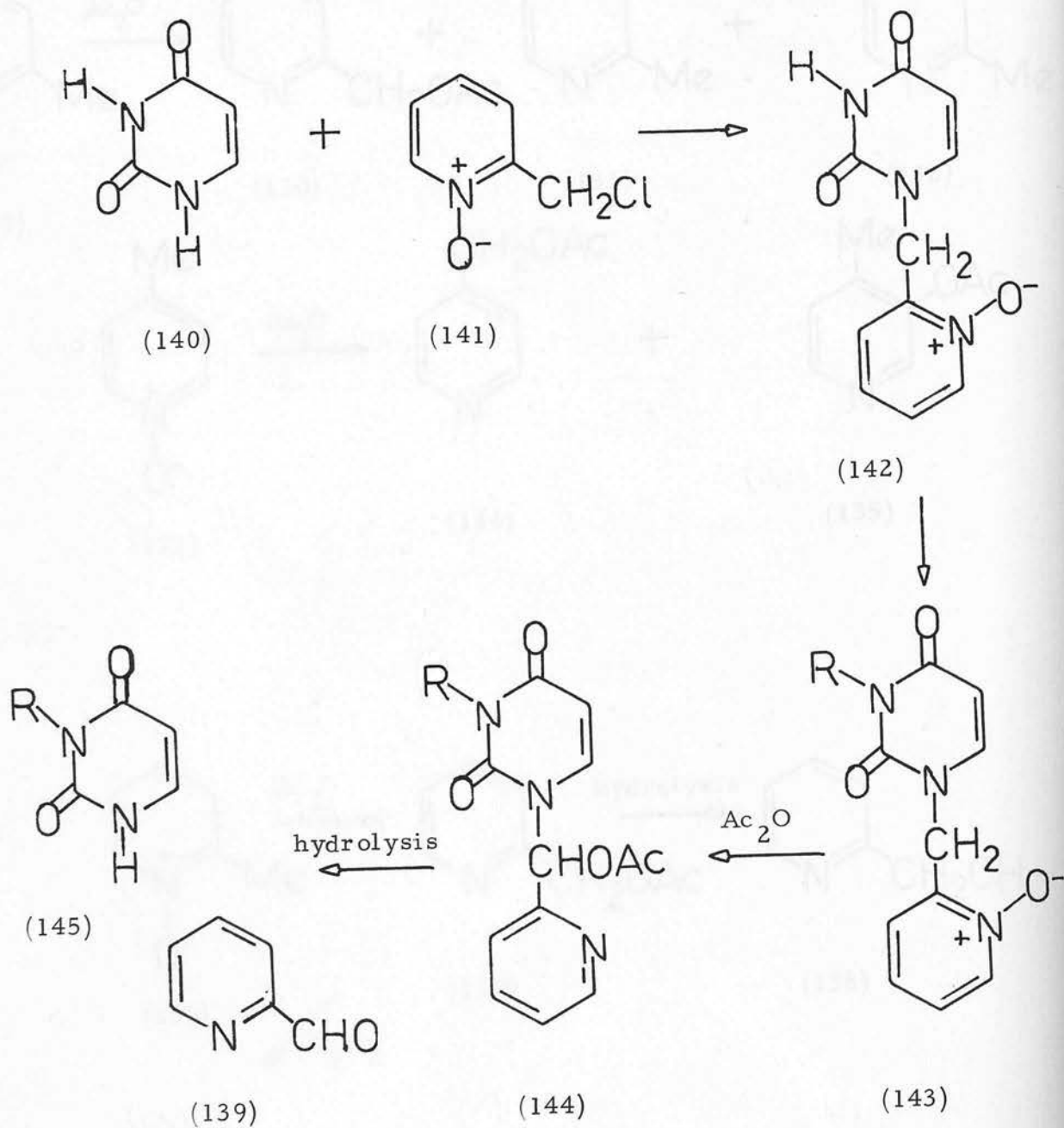
The detailed mechanism of the reaction of pyridine 1-oxide (3) with acetic anhydride has been the subject of considerable controversy. The reaction of pyridine 1-oxide (3) with an excess of acetic anhydride has been shown to exhibit first order kinetics.<sup>41</sup> It has also been demonstrated that the reaction rate decreases when sodium acetate is added to the system and that no gaseous by-products such as carbon dioxide or methane are liberated making a radical process unlikely.<sup>41</sup> These results indicate that an ionic mechanism is operative but fail to distinguish between an intermolecular pathway and one involving an intimate ion pair. Oae<sup>42</sup> and his co-workers have used isotopic labelling to exclude an intimate ion pair process and to eliminate the possibility of a radical cage process. On the basis of these results the ionic mechanism depicted in scheme 13 has been proposed.<sup>43</sup> The initial step in the reaction is electrophilic attack by the acetic anhydride at the N-oxide oxygen atom to produce the 1-acetoxypyridinium acetate (114) which is in equilibrium with the N-oxide (3). The 1-acetoxypyridinium cation (114) then undergoes nucleophilic attack by acetate ion to give the adduct (116) which loses the elements of acetic acid to afford the  $\alpha$ -substituted product (117). Kinetic isotope studies<sup>43</sup> indicate that nucleophilic attack by acetate ion at the  $\alpha$ -position of the hetero ring [(115)  $\rightarrow$  (116)] is the rate determining step and this supports earlier kinetic evidence.<sup>41</sup> The observation<sup>44</sup> that equal amounts of the isomeric pyridinones (127) and (128) are obtained in the



reaction of a 3-substituted pyridine 1-oxide (126) with acetic anhydride when R is a methyl group, but that the 3-substituted 2-pyridinone (127) always predominates when R is an electron withdrawing group, further



Scheme 14



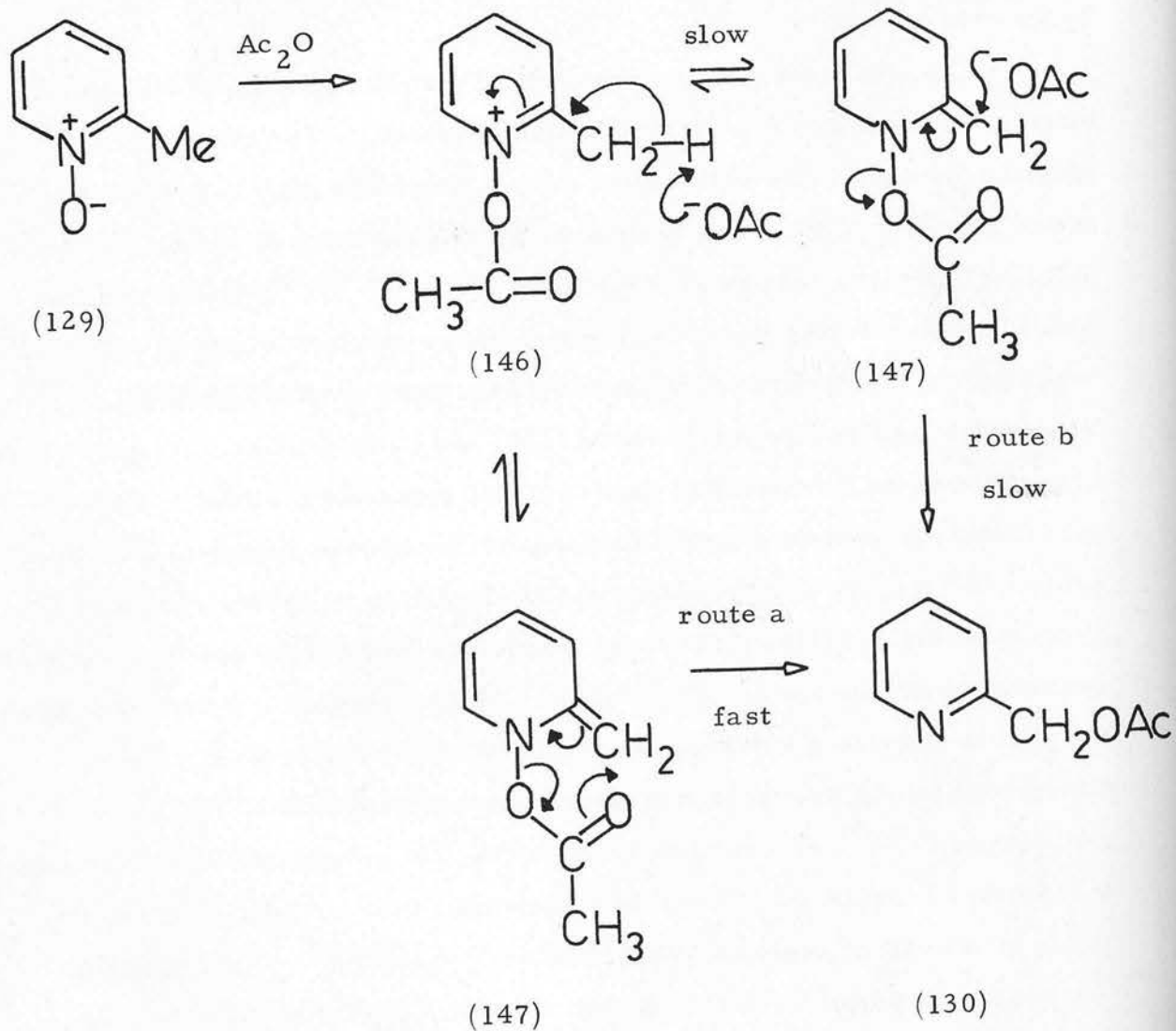
Scheme 15

supports the idea that the reaction proceeds via nucleophilic attack by acetate ion.

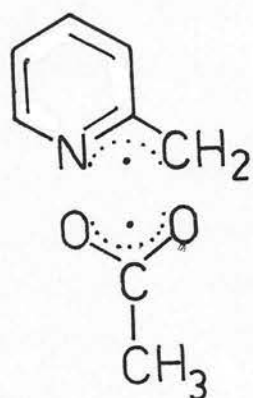
The mechanism of the reaction of picoline N-oxides with acetic anhydride has also been thoroughly investigated. The reaction of 2-picoline N-oxide (129) with acetic anhydride yields mainly 2-acetoxymethylpyridine (130) together with smaller quantities of 3-acetoxy-2-picoline (131) and 5-acetoxy-2-picoline (132).<sup>45,46,47</sup> Under similar conditions 4-picoline N-oxide yields a binary mixture which is richer in 4-acetoxymethylpyridine (134) than in 3-acetoxy-4-picoline (135).<sup>48,49</sup> The reaction of 2-picoline N-oxide (129) has been extended to many other ring systems and constitutes an important synthetic method. Thus it provides a convenient general method for the hydroxylation of  $\alpha$ -methyl groups in heterocyclic N-oxides [as exemplified by the synthesis of 2-hydroxymethylpyridine (136) from 2-picoline N-oxide by conversion into 2-acetoxymethylpyridine (130) followed by hydrolysis]. It has also been adapted to provide a valuable synthesis of heterocyclic aldehydes as illustrated by the conversion of 2-acetoxymethylpyridine (130) into pyridine 2-aldehyde (139)<sup>45</sup> as shown in scheme 14. In an adaptation of this process a 2-picoly 1-oxide substituent has been used as a protecting group for imino functions in purine and pyrimidine synthesis.<sup>50</sup> This elegant method is exemplified by the transformations shown in scheme 15.

Bullitt and Maynard<sup>45</sup> originally suggested that the reaction of 2-picoline 1-oxide (129) with acetic anhydride proceeds via rearrangement of an anhydro base intermediate (147) analogous to that proposed by Pachter<sup>51</sup> to account for the reaction of quinaldine N-oxide with benzoyl chloride to afford 2-benzoylmethylquinaldine. Their mechanism (cf. scheme 16), which has been generally accepted for this and related reactions, requires nucleophilic attack by the N-oxide (129) oxygen atom on acetic anhydride with the generation of the 1-acetoxy-2-alkylpyridinium ion (146) and acetate ion. The anhydro base (147) results from the abstraction of an acidic proton from the 2-methyl group in (146) by acetate ion. It was considered<sup>45</sup> that the anhydro base (147) was converted into 2-acetoxymethylpyridine (130) either by an intramolecular cyclic rearrangement [cf route a, (scheme 16)] or by an intermolecular route involving

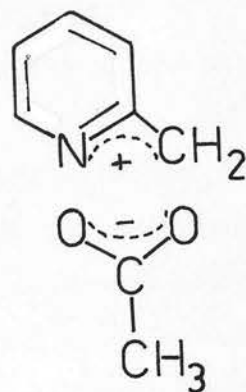




Scheme 16

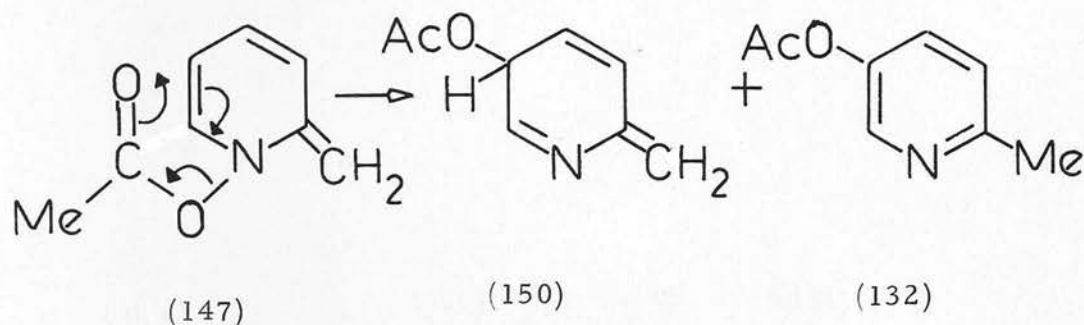


(148)



(149)

nucleophilic attack by acetate anion on the methylene carbon atom of (147) with elimination of acetate ion [cf route b, (scheme 16)]. Not only does rearrangement of the anhydro base (147) account for the production

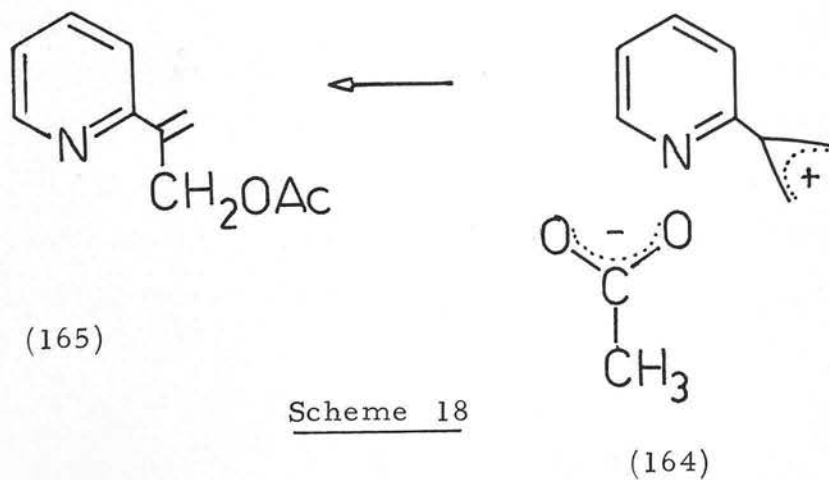
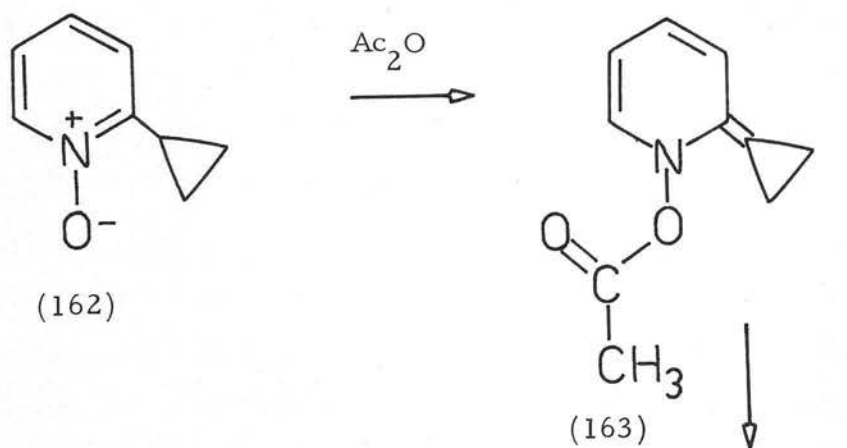
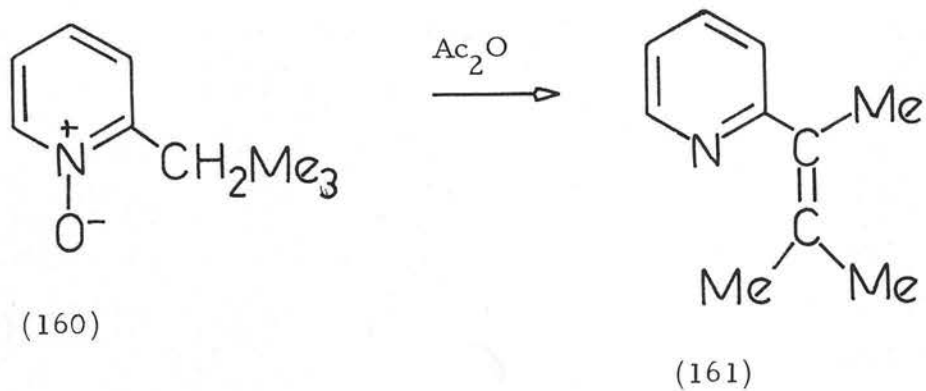
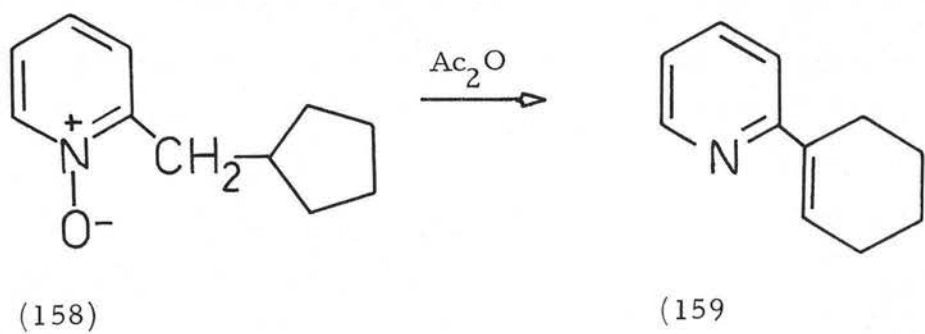


of the major  $\alpha$ -acetoxymethyl product (130), but it can also account for the  $\beta$ -acetoxymethyl by-products also isolated. Thus the latter may be derived by subsequent rearrangement of (147) to the isomer (150), aromatisation of which would yield the  $\beta$ -acetoxymethyl product (132). The isolation of the cation (146) has subsequently been accomplished as the picrate salt which has been converted in turn into the acetoxymethyl derivative (130) by treatment with triethylamine.<sup>52</sup> These observations support the proton abstraction stage [(146)  $\rightarrow$  (147)] in the mechanism (cf. scheme 16). An alternative suggestion<sup>53</sup> that the 1-acetoxy-2-alkylpyridinium ion (146) is converted into 2-acetoxymethylpyridine (130) by a radical chain mechanism subsequent to homolytic cleavage of the N-O bond in (146) was later discounted by Traynelis and Martello.<sup>54</sup> These workers demonstrated that the yield of 2-acetoxymethylpyridine (130) was not appreciably affected by the presence of the free radical inhibitors *p*-benzoquinone and *m*-dinitrobenzene in the reaction medium. They also demonstrated that 2-picoline 1-oxide (129) underwent reaction with butyric anhydride in the presence of sodium acetate to give 2-butyrylmethylpyridine, only. The lack of formation of 2-acetoxymethylpyridine (130) in this reaction indicates that the step [(147)  $\rightarrow$  (130)] is intramolecular, and it was noted that this step might proceed either by homolytic cleavage of the N-O bond in the anhydro base (147) to give a radical pair (148), or by heterolytic cleavage to give an ion pair (149), followed in both cases by recombination to afford the



ester (130). Alternatively, the formation of (130) could be rationalised by the concerted rearrangement [(147)  $\rightarrow$  (130)] [cf. route a, (scheme 16)]. Traynelis and Pacini<sup>55</sup> have demonstrated spectroscopically that the anhydro base (147) does not accumulate in the course of the reaction. They also showed by labelling studies that the conversion of the alkylpyridinium ion (146) into the anhydro base (147) is the, essentially irreversible, rate determining step, whereas conversion of the anhydro base (147) into the ester product (130) is fast.

The precise mechanism of the final rearrangement of the anhydro base (147) to product (130) has been the subject of considerable controversy. Oae<sup>56, 57</sup> and his coworkers have studied the rearrangement of 2-picoline 1-oxide (129) in a tracer experiment using acetic anhydride in which all three oxygen atoms were equally enriched with <sup>18</sup>O. The results obtained demonstrate that both oxygen atoms of the acetoxy group become equivalent in the course of the reaction and hence favour a mechanism in which fission of the N-O bond occurs to give either a radical pair [cf. (148)] or an ion pair [cf. (149)] intermediate rather than an intramolecular cyclic rearrangement [(147)  $\rightarrow$  (130)] [cf. route a, (scheme 16)]. Oae has interpreted these results in terms of a radical pair mechanism. Homolytic cleavage of the N-O bond in the anhydro base (147) gives a radical pair (148) which thus results in rapid equivalence of the two oxygen atoms of the acetoxy group. It is suggested that homolytic scission is followed by rapid recombination of the acetoxy and 2-picolyl radicals, within the confines of a solvent cage, wherein the reaction is not affected by such changes as the amount or type of solvent or the addition of radical scavengers. The small amounts of carbon dioxide and methane formed during the course of the reaction are considered to arise from the decomposition of acetoxy radicals which escape from the solvent cage. However, it has been shown<sup>58</sup> that 2-picoline 1-oxide (129) undergoes reaction with phenylacetic anhydride (151) presumably via the anhydro base intermediate (152) to give a good yield of the rearranged ester (153). If a radical pair (154) mechanism was operative in this reaction, the exceedingly unstable phenylacetoxy radical would be involved as an intermediate. The phenylacetoxy radical is deemed so unstable<sup>59</sup> that it is extremely unlikely that it is capable of



Scheme 18

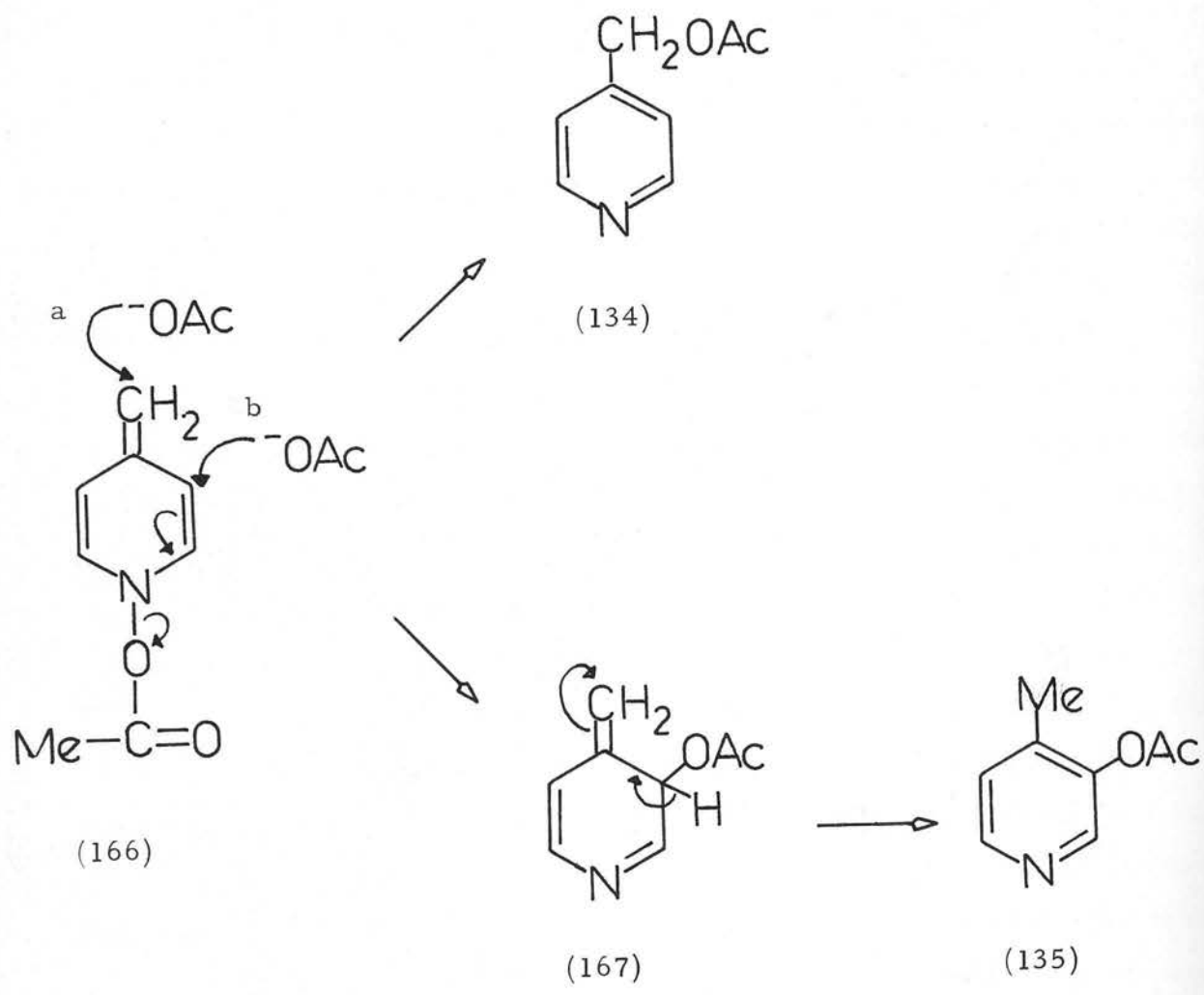
existence and consequently no ester product (153) would be expected via this route. However, the isolation of a small percentage of radical coupling product (157) indicates a degree of competition from a radical mechanism and this is supported by kinetic evidence.<sup>60</sup> The absence of C. I. D. N. P. emission in the  $^1\text{H}$  n. m. r. of the reaction mixture of 2-picoline 1-oxide and acetic anhydride further substantiates a non-radical pair pathway.<sup>61</sup>

Katritzky<sup>62</sup> has demonstrated that 2-cyclopentylcarbonylpyridine 1-oxide (158) and 2-neopentylpyridine 1-oxide (160) on treatment with acetic anhydride undergo rearrangements of the alkyl group which are typical of carbonium ion processes. The isolation of products (159) and (161) indicates the involvement of carbonium ion intermediates, probably in the form of ion pairs [cf. (149)]. Carbonium ion rearrangements of the type [(158)  $\rightarrow$  (159)] and [(160)  $\rightarrow$  (161)] are commonplace whereas analogous fast rearrangements of radicals would be unexpected. In further support of an ion pair process, it has been demonstrated that when the 2-cyclopropylpyridine 1-oxide (162) is heated with acetic anhydride the major product obtained is 2-(2-pyridyl)-2-propenyl acetate (165).<sup>63</sup> The intramolecular ionic pathway outlined in scheme 18 has been proposed to account for this rearrangement.

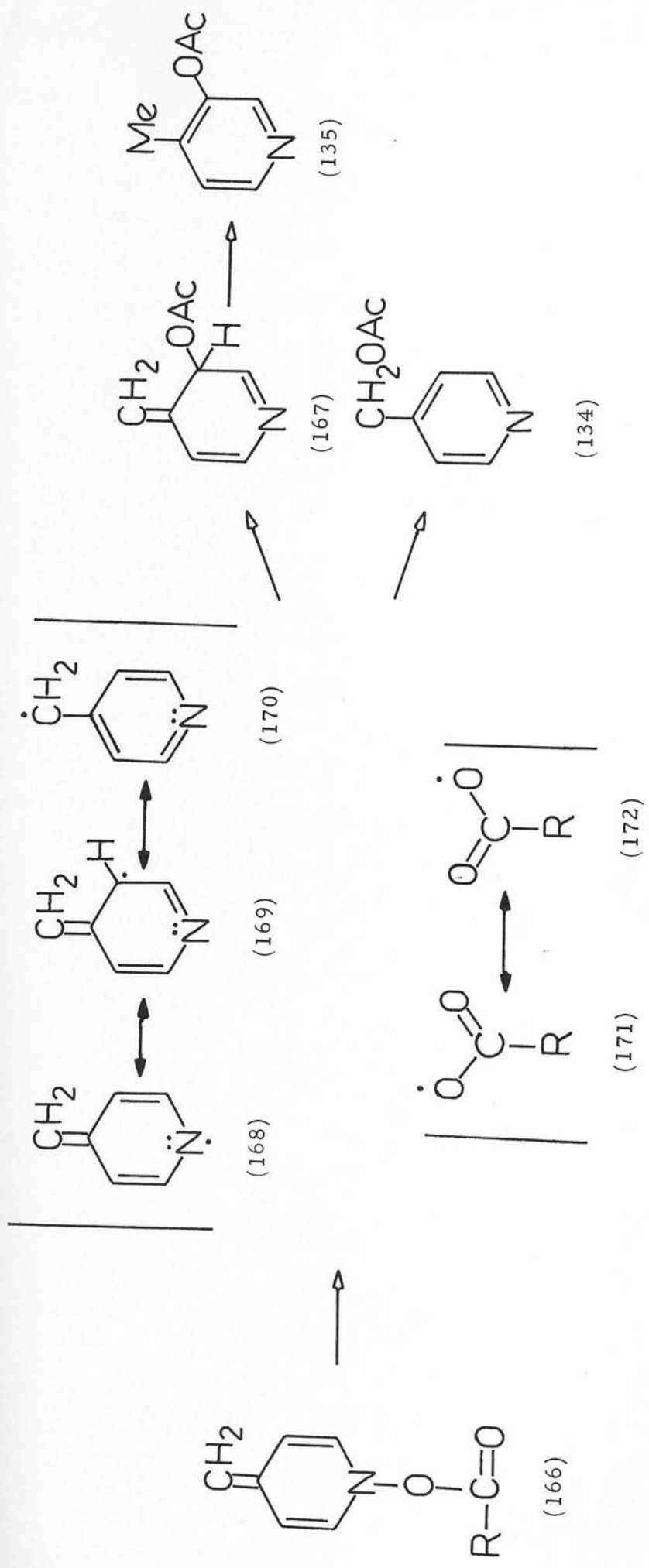
Taking the evidence as a whole, it seems probable that the mechanism of the reaction of 2-picoline 1-oxide (129) with acetic anhydride proceeds via heterolytic cleavage of the N-O linkage in an anhydro base intermediate to give an ion pair intermediate of the type (149) within the confines of a solvent cage. Collapse of the ion pair within the solvent cage then gives the product. This mechanism is also consistent with the finding that reaction is facilitated by the presence of electron donor substituents in the ring.<sup>64</sup> The ion pair mechanism explains the results of Oae's labelling experiments, although it does not account for the formation of methane, carbon dioxide and 2-picoline as by-products. These contradictory observations are reconciled by the proposition that a major part of the reaction proceeds by heterolytic cleavage of the N-O bond of the anhydro base, while the remaining portion of the reaction proceeds via a homolytic cleavage of the N-O bond.<sup>65</sup>

The earlier experimentation and mechanistic proposals for the





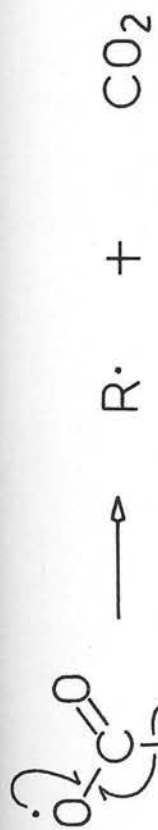
Scheme 19



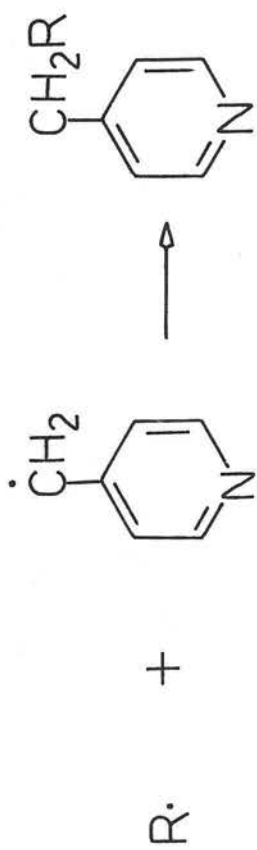
Scheme 20

- R = CH<sub>3</sub>
- = CH(CH<sub>3</sub>)<sub>2</sub>
- = C(CH<sub>3</sub>)<sub>3</sub>

reaction of 4-picoline 1-oxide (133) with acetic anhydride closely parallel those for 2-picoline 1-oxide,<sup>48,49</sup> and this reaction is considered to proceed via an anhydro base intermediate (166) analogous to that generated in the 2-picoline 1-oxide reaction. It has been demonstrated that in the reaction of 4-picoline 1-oxide (133) with n-butyric anhydride containing sodium acetate, no acetylated ester (134) is formed, demonstrating the intramolecular character of the reaction, and a radical mechanism was proposed.<sup>49</sup> In marked contrast early labelling studies appeared to exclude an intramolecular rearrangement and favoured intermolecular nucleophilic attack by acetate ion<sup>66</sup> [cf. scheme 19]. The anhydro base (166), generated in a fashion analogous to the generation of (147) in the 2-picoline 1-oxide reaction [cf. scheme 16], is subject to nucleophilic attack a) at the methylene group and b) at the C-3 position of the anhydro base (166) to yield the observed products (134) and (135), after rearrangement of the intermediate (167) by an allylic shift of the C-3 hydrogen atom. Later labelling studies<sup>67</sup> demonstrated the solvent dependent nature of the mechanism. The reaction was found to proceed via an intramolecular radical cage process in xylene, whereas in n-butyric acid or in the absence of solvent an intermolecular process, involving both heterolytic and homolytic cleavage of the N-O bond, followed by a radical transfer became the main route. Qualitative evidence in support of a radical explanation for the origin of the esters (134) and (135) is reported<sup>68</sup> in the study of the reaction of 4-picoline 1-oxide (133) with various acid anhydrides wherein a variety of acyloxy radical intermediates of differing stabilities are postulated to account for the results obtained. The radical mechanism proposed is outlined in scheme 20. Homolytic cleavage of the N-O bond in the anhydro base (166) would give the picolyl radical [(168)  $\leftrightarrow$  (169)]  $\leftrightarrow$  [(170)] and the acyloxy radical [(171)  $\leftrightarrow$  (172)]. Recombination of these radicals would produce the ester (134) and the intermediate (167). In view of the very short lifetime of the acyloxy radicals, such a radical pair combination would be required to occur within a solvent cage. It was observed that as the ease of decomposition of the acyloxy radical [(171)  $\leftrightarrow$  (172)] increased, so the yields of the ester products (134) and (135) decreased. Further as the stability of the acyloxy radical [(171)  $\leftrightarrow$  (172)] decreased,

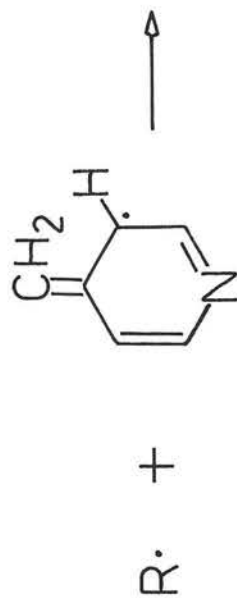


(171)

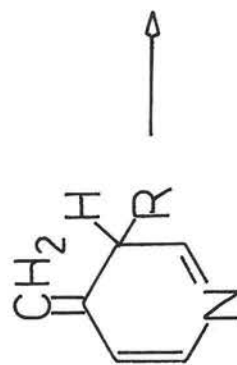


(170)

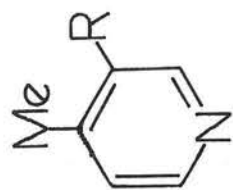
(173)



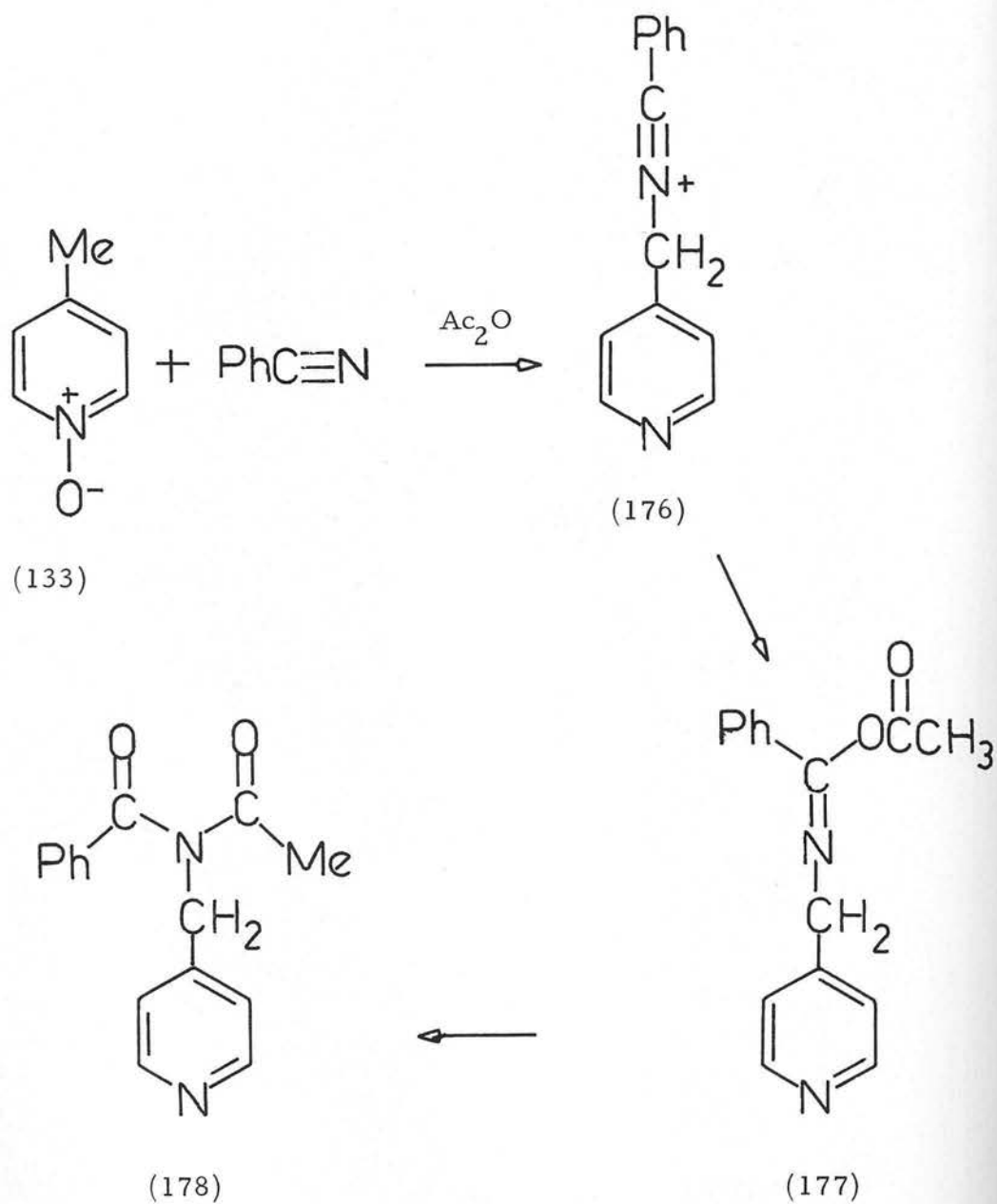
(169)



(174)



(175)



Scheme 22

the yields of  $\text{CO}_2$  and the alkylpyridine by-products (173) and (175) (derived by radical coupling) increased [cf scheme 21]. Recent C. I. D. N. P. studies<sup>69</sup> also suggest the possible involvement of radical intermediates in the reactions of 4-picoline 1-oxide (133) with acid anhydrides. However, Cohen and Deets<sup>70</sup> have demonstrated that if the reaction of 4-picoline 1-oxide with acetic anhydride is carried out in the presence of anisole, o- and p-picolylanisoles are formed. The isomer ratio in this reaction was considered to be consistent with a cationic process, but not with a radical process. In benzonitrile, the picolyl group was found to attack the nitrogen atom of the cyano group almost exclusively to yield the imide (178). This is indicative of a cationic reaction, proceeding via the intermediates (176) and (177) rather than a radical reaction in which radical attack on the phenyl ring of benzonitrile rather than at the cyano group, would be expected.

Thus the mechanism involved in the reaction of 4-picoline 1-oxide (133) with acid anhydrides is not completely resolved.

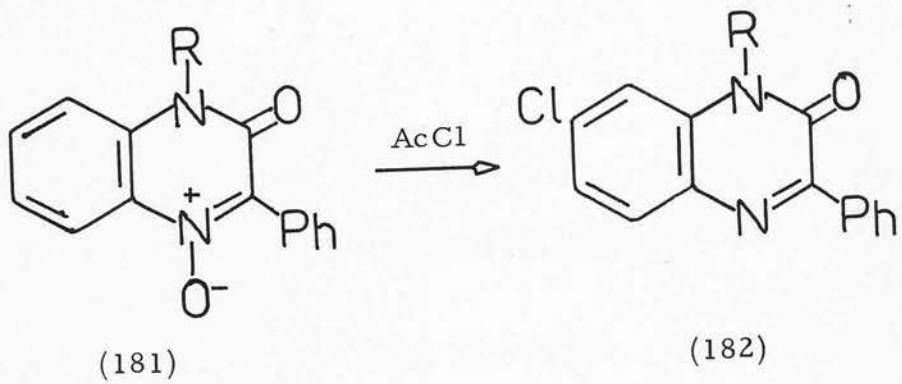


CHAPTER TWO

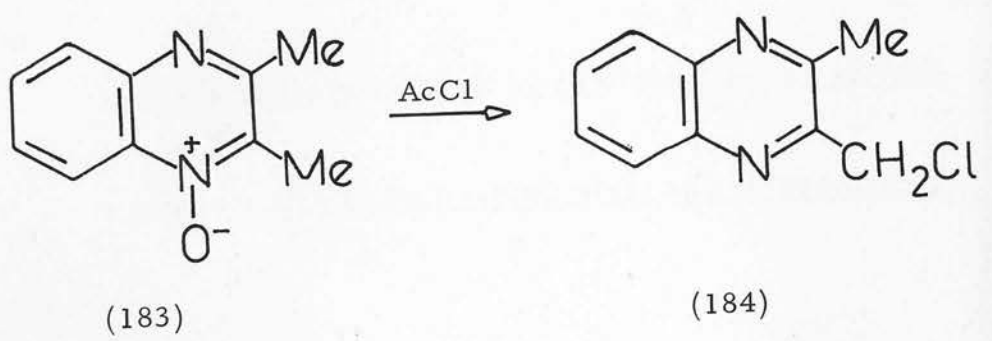
DISCUSSION

Studies on the Reactivity of N-Acetoxyquinoxalinium

Perchlorates and their Derived Morpholine Adducts



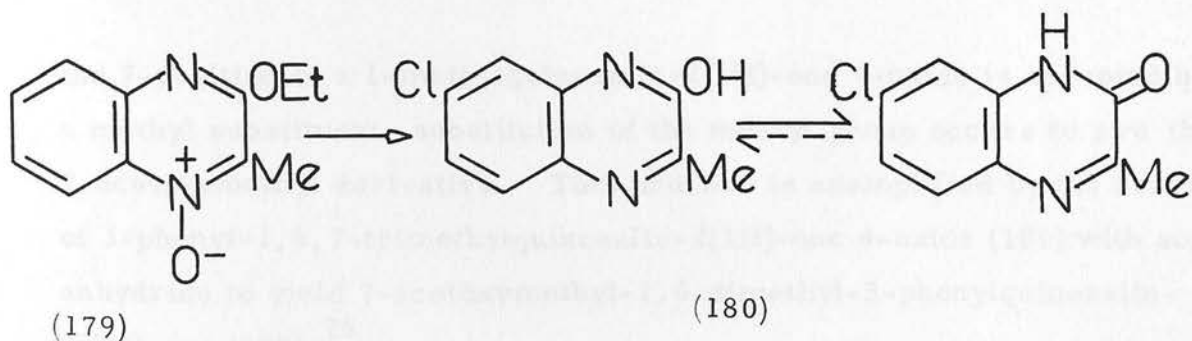
R  
 a ; H  
 b ; Me



Studies on the Reactivity of N-Acetoxyquinoxalinium  
Perchlorates and their Derived Morpholine Adducts

### 2.1 Introduction

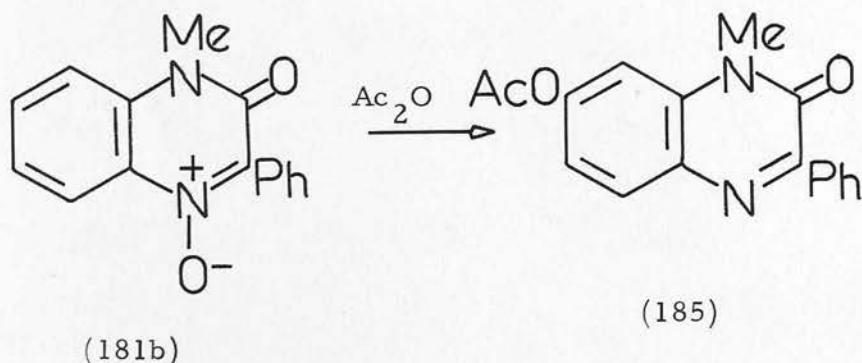
As was discussed in chapter 1, heterocyclic N-oxides are susceptible to nucleophilic substitution in positions α- and δ- to the N-oxide functional group. When the α- and δ-positions of the hetero ring are occupied, nucleophilic substitution may occur in a fused benzenoid nucleus. Quinoxaline N-oxides in which the α- and δ-positions are blocked to attack by nucleophiles are known to undergo nucleophilic substitution in the fused benzene ring. One of the earliest examples of such a reaction is the generation of 7-chloro-3-methylquinoxalin-2(1H)-one (180) from 3-ethoxy-2-methylquinoxaline 1-oxide (179) on treatment with boiling ethanolic hydrogen chloride.<sup>71</sup> Similarly, it has been



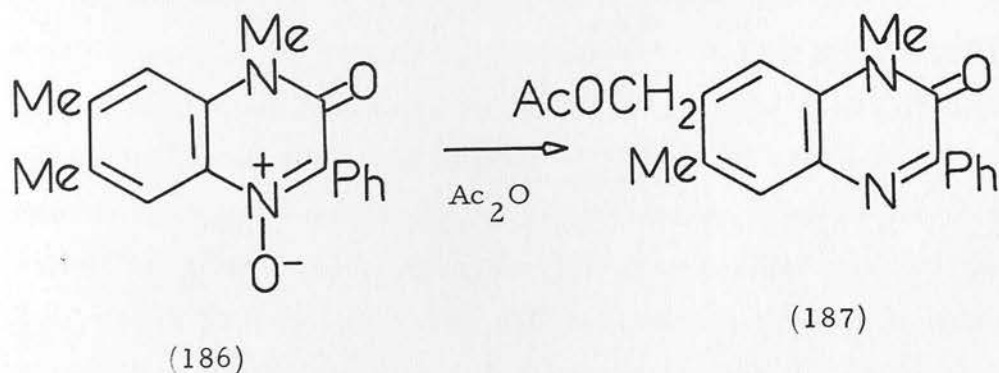
demonstrated that on reaction with acetyl chloride at elevated temperature the quinoxaline N-oxides (181a) and (181b) afford the 7-chloroquinoxalinones (182a) and (182b).<sup>72, 73</sup> It appears that reactions of this type, wherein nucleophilic substitution occurs in the benzene nucleus of a quinoxaline derivative are considerably facilitated by the presence of an oxygen function at C-3 in the hetero ring. It has been shown that 2-phenyl and 2,3-diphenylquinoxaline 1-oxide fail to undergo analogous nucleophilic substitution and that 2,3-dimethylquinoxaline 1-oxide (183) affords 2-chloromethyl-3-methylquinoxaline (184) on reaction with acetyl chloride,<sup>74</sup> although the N-oxide (183) differs from (179) only in the nature of the

substituent at C-3. Likewise, the presence of a strongly electronegative chloro group at the C-3 position in the hetero ring also fails to promote nucleophilic attack in the fused benzene nucleus. Thus, 3-chloro-2-phenylquinoxaline 1-oxide does not undergo nucleophilic substitution on treatment with acetyl chloride.<sup>74</sup>

In a reaction closely related to the chlorination of the N-oxide (181b) to furnish the derivative (182b), the N-oxide (181b) reacts with hot acetic anhydride to afford 7-acetoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (185) in high yield.<sup>75</sup> Further, it has been shown that when

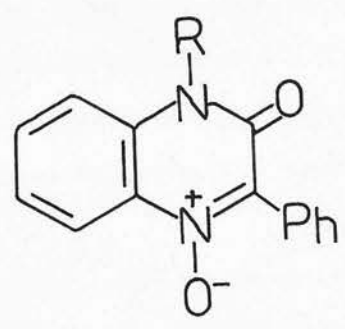


the 7-position of a 1-methylquinoxalin-2(1H)-one 4-oxide is occupied by a methyl substituent, substitution of the methyl group occurs to give the 7-acetoxymethyl derivative. This process is exemplified by the reaction of 3-phenyl-1,6,7-trimethylquinoxalin-2(1H)-one 4-oxide (186) with acetic anhydride to yield 7-acetoxymethyl-1,6-dimethyl-3-phenylquinoxalin-2(1H)-one (187).<sup>76</sup>

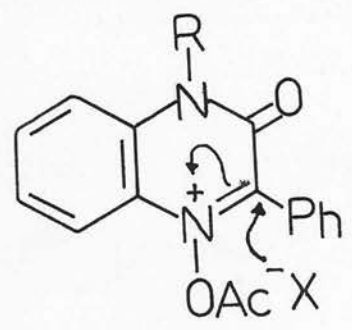
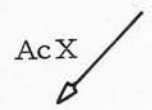


In marked contrast to the N-methyl N-oxide (181b), however, reaction of 3-phenylquinoxalin-2(1H)-one 4-oxide (181a) with hot acetic

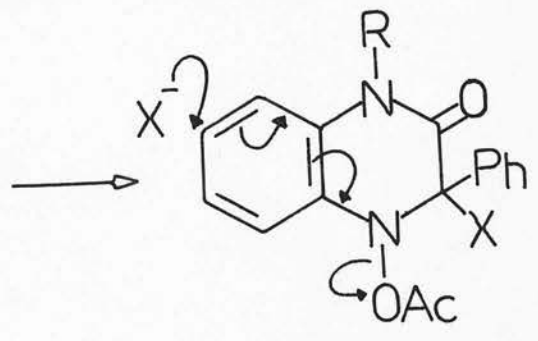
$\underline{R}$   
 a ; H  
 b ; Me



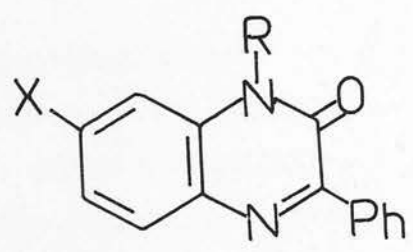
(181)



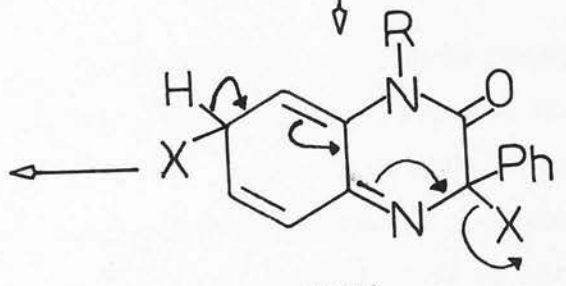
(190)



(191)



(193)

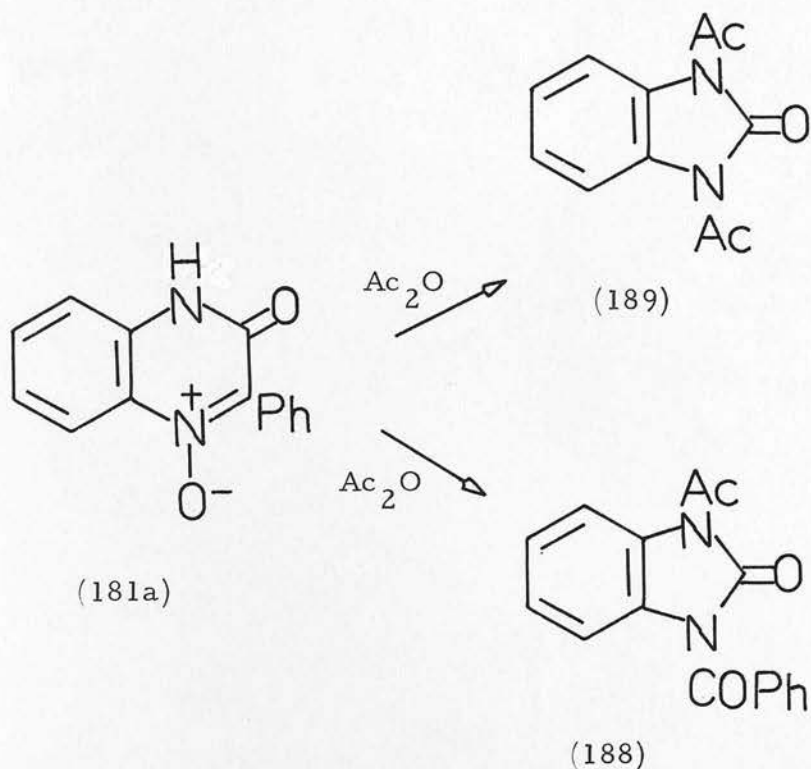


(192)

R=H ; X=Cl  
 R=Me ; X=Cl, OAc

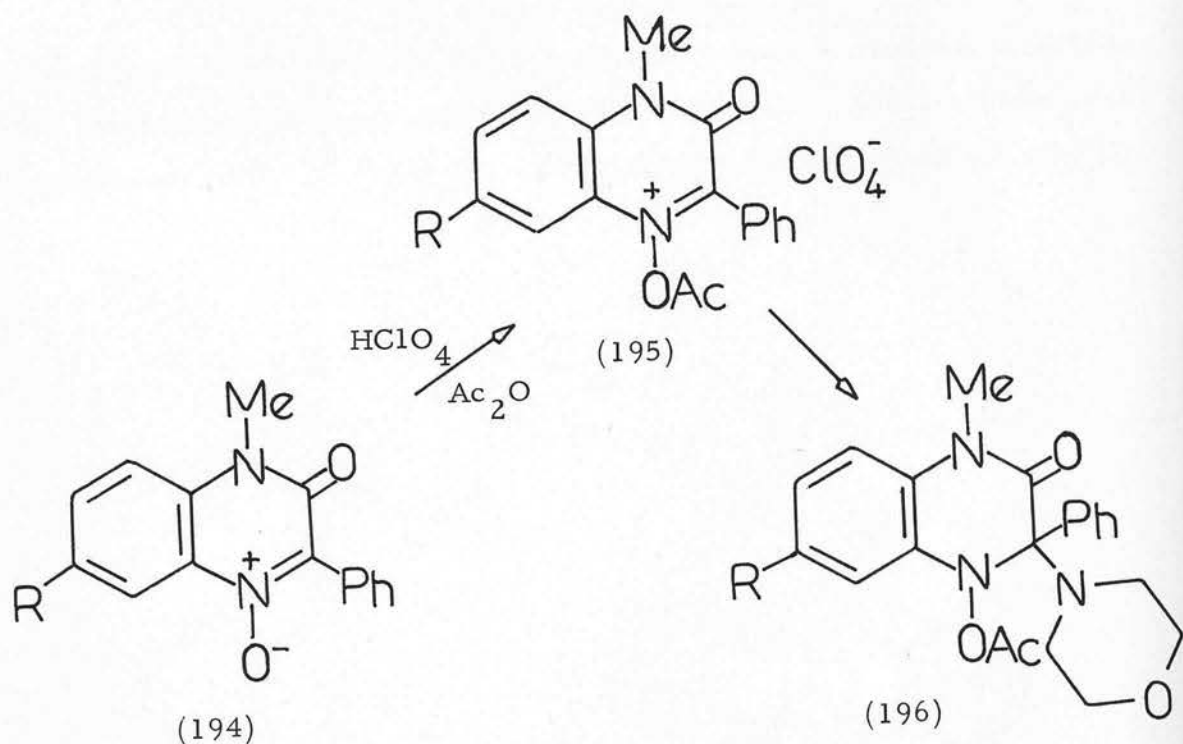
Scheme 23

anhydride results in ring contraction to the N-acetyl N-benzoylbenzimidazol-2-one (188).<sup>75</sup> Under extended reflux in acetic anhydride, (181a) affords the di-N-acetylbenzimidazol-2-one (189).<sup>75</sup> The formation of the

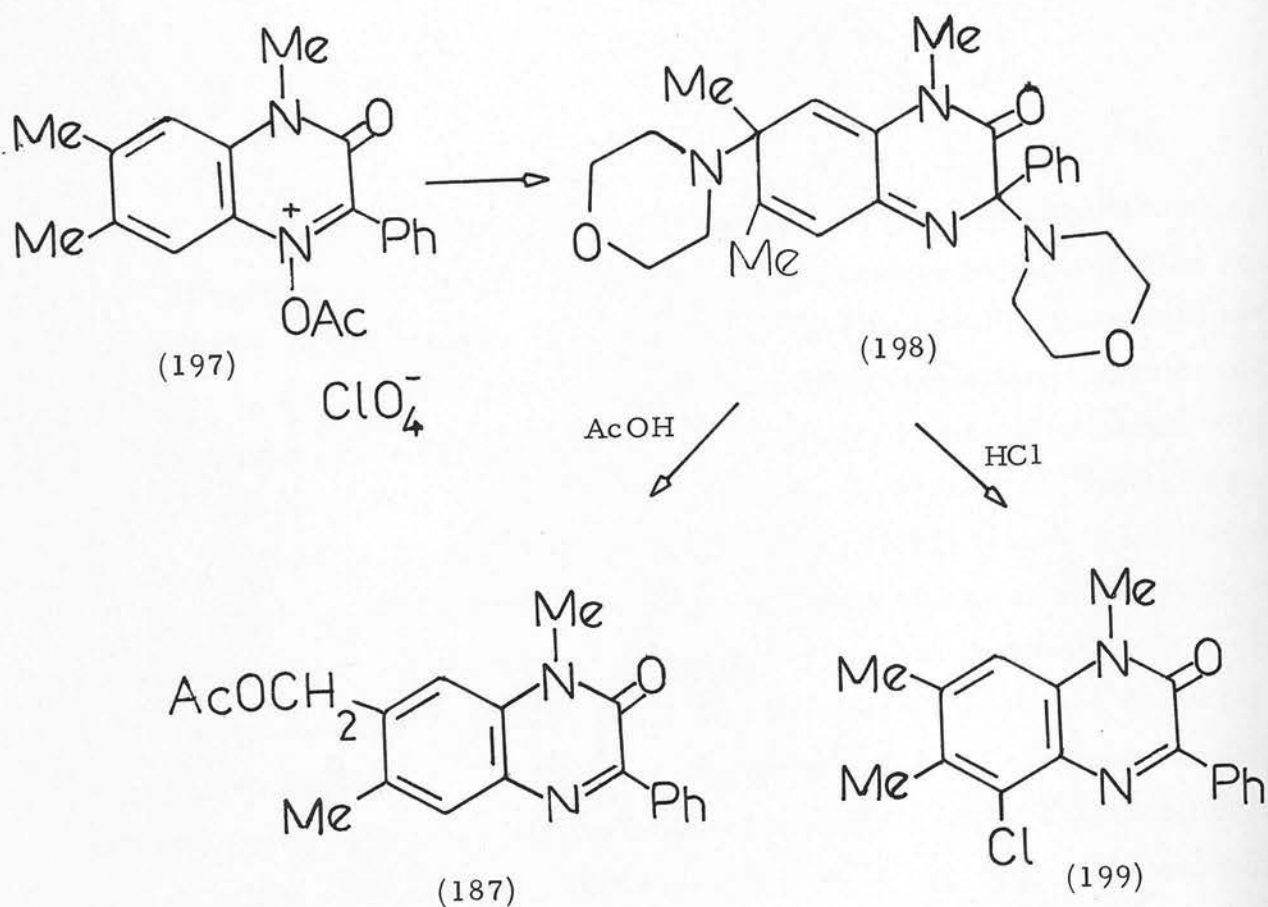


7-chloroquinoxalinones (182a and b) and the 7-acetoxyquinoxalinone (185) may be rationalised by the general mechanism outlined in scheme 23. This involves preliminary acetylation of the N-oxides (181) to afford the N-acetoxyquinoxalinium cation intermediates (190) which undergo nucleophilic attack by acetate or chloride ion at the C-3 position of the hetero ring to afford the N-acetoxy adducts (191). The generation of the 7-substituted products (193) is then explicable by a course involving synchronous nucleophilic attack by acetate or chloride ion on (191) and loss of the N-acetoxy leaving group to give the para-quinonoid intermediates (192) which subsequently lose HX on rearomatisation to furnish the observed products (193). The reactivity of cations of the type (190) is fully in accord with the proposal that they are intermediates in substitution reactions of the type [(181) → (190) → (193); scheme 23]. Thus N-

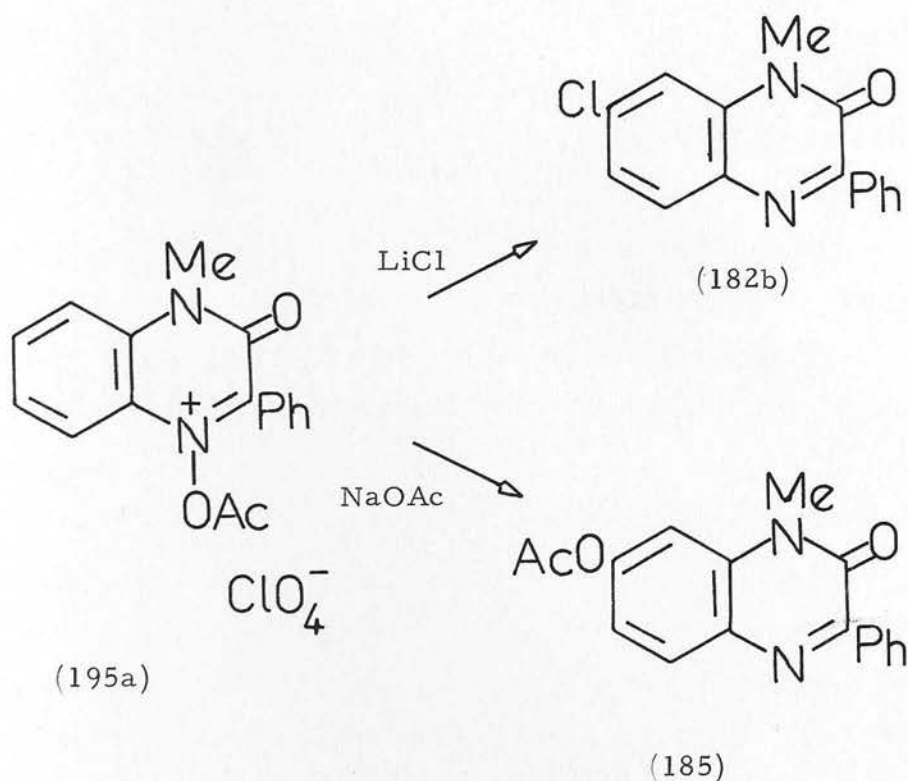




$\underline{R}$   
 a ; H  
 b ; Cl

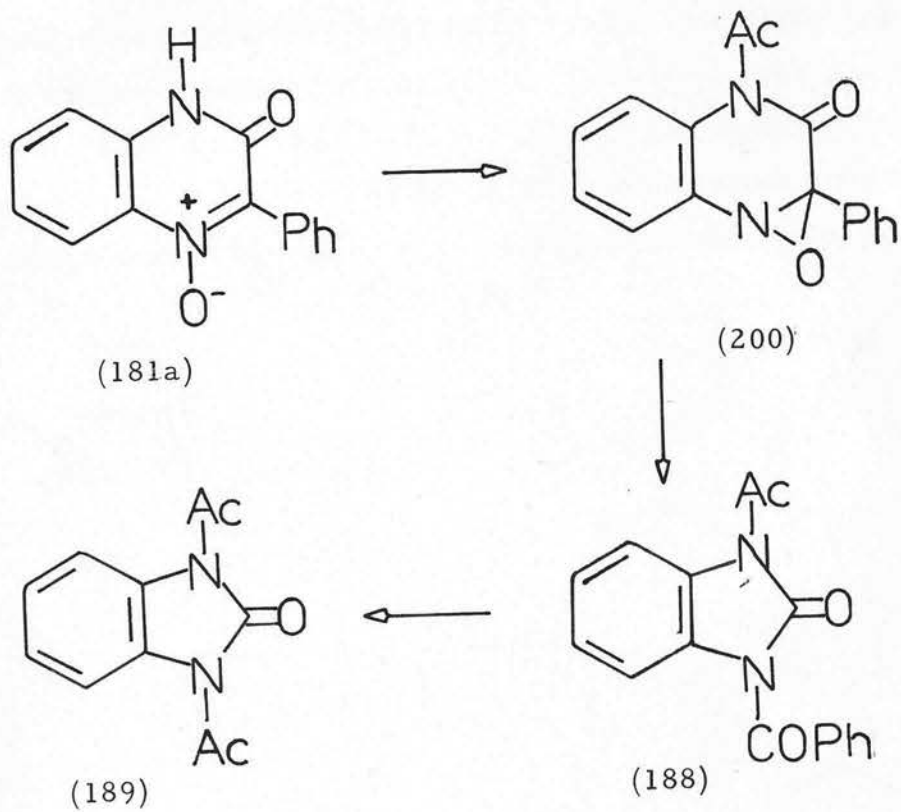


acetoxyquinoxalinium cations of the type (190) are readily prepared as perchlorate salts by reaction of the corresponding N-oxides (181) with acetic anhydride in the presence of perchloric acid and their ready reaction with nucleophilic reagents demonstrated.<sup>77</sup> In particular, the N-acetoxyquinoxalinium perchlorate (195a) reacts readily with lithium

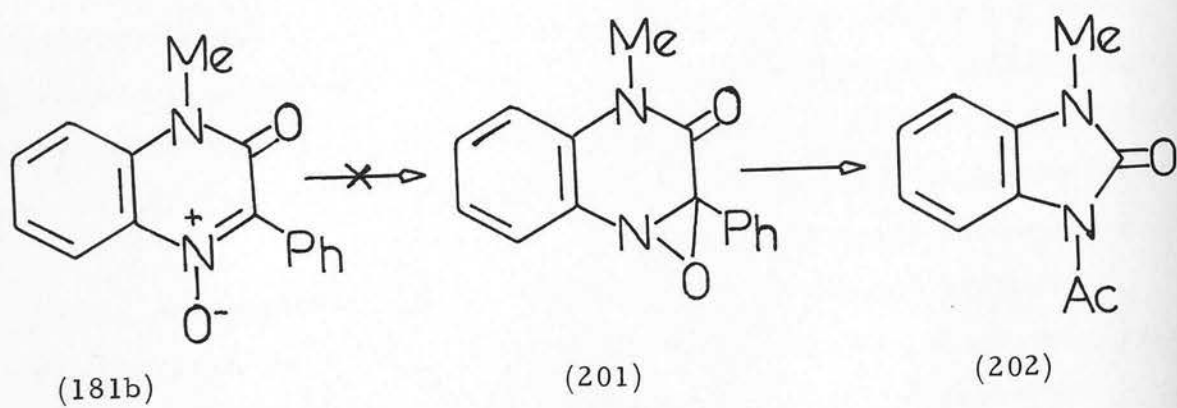


chloride and sodium acetate to afford the 7-chloro- and 7-acetoxyquinoxalinones (182b) and (185) respectively.<sup>77</sup> These reactions demonstrate that the cation (190b) is a possible intermediate in the reaction of the N-oxide (181b) with acetyl chloride and acetic anhydride to give the 7-chloro- and 7-acetoxy-derivatives (182b) and (185).

Further support for the mechanism shown in scheme 23, and in particular the key intermediates (191) and (192) has been obtained from a study of N-acetoxyquinoxalinium perchlorate salts with amines.<sup>77</sup> In particular, the salts (195a and b) prepared from the N-oxides (194), react with morpholine in ether to give compounds characterised as the adducts (196a and b).<sup>77</sup> It has also been found<sup>77</sup> that reaction of the salt (197)



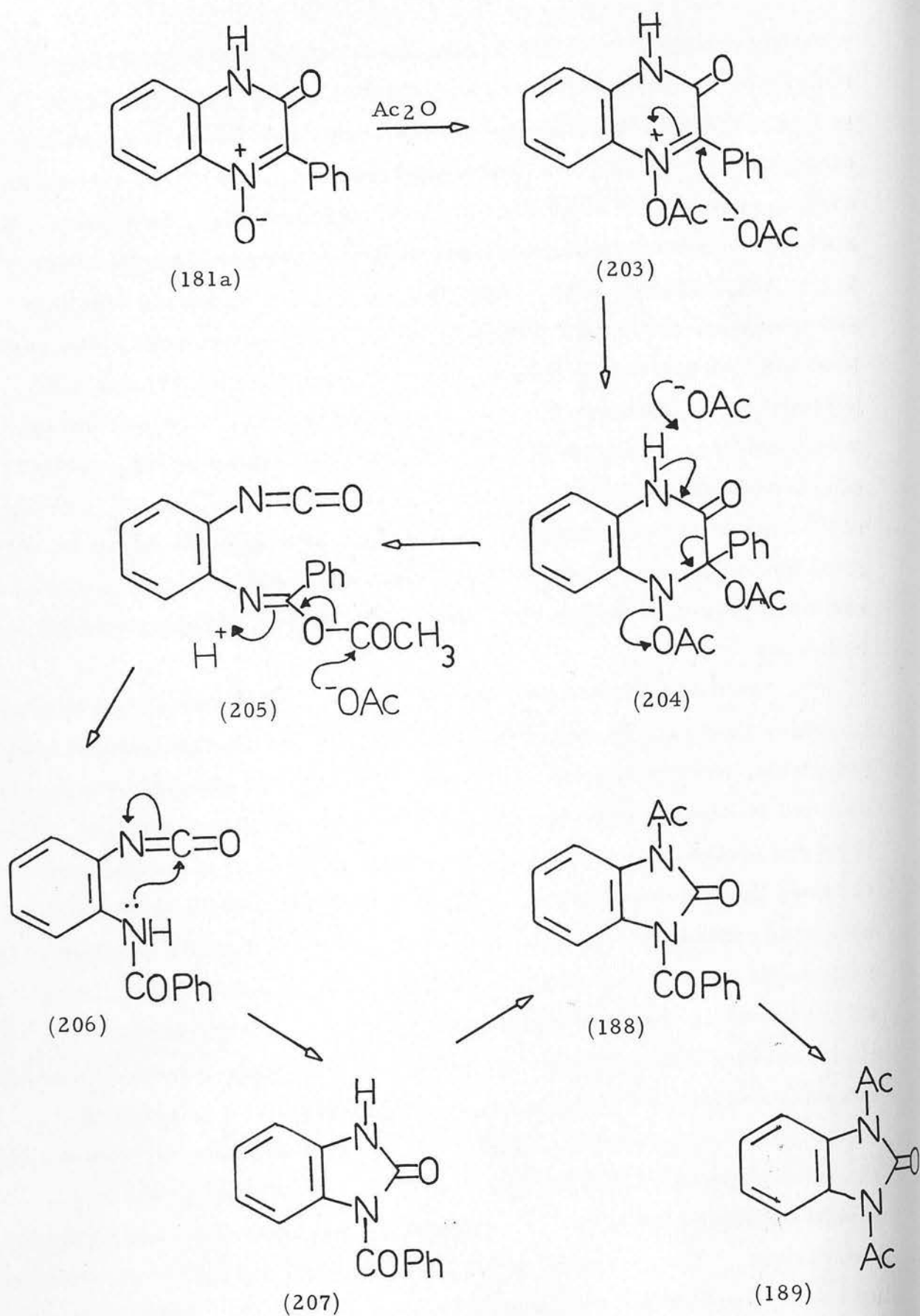
Scheme 25



Scheme 26

with morpholine gives a bis-adduct whose properties are fully consistent with its being the bis-morpholine derivative (198). The successful isolation of this para-quinonoid intermediate is presumably due to the presence of the methyl groups which make rearomatisation less easy. The formation of the bis-adduct (198) lends support to the intermediacy [cf. scheme 23] of such intermediates in the reactions of N-methylquinoxaline N-oxides with acetic anhydride and acetyl chloride. Moreover, in accord with this intermediacy, the adduct (198) was shown<sup>77</sup> to react smoothly with acetic acid and hydrochloric acid to afford the very products (187) and (199) obtained by the reaction of the N-oxide (186) with acetic anhydride and acetyl chloride, respectively.<sup>73</sup> The mode of formation and reactivity of quinoxalinium salts of the type (195) and the derived adducts (196) and (198) support the involvement of such intermediates in the reactions of N-methylquinoxalinone N-oxides with acetic anhydride and acetyl chloride and hence substantiate the mechanism [cf. scheme 23] proposed for such reactions.

The mode of formation of benzimidazolone products from quinoxaline N-oxides bearing a proton at the N-1 position, on reaction with hot acetic anhydride, has not been ascertained. Ahmad<sup>75</sup> has proposed the mechanism outlined in scheme 25 to account for this ring contraction process. This involves preliminary acetylation of the N-oxide (181a) at the N-1 position followed by rearrangement to an oxaziridine intermediate (200) which in turn ring contracts to the benzimidazolone (188). Further reaction of (188) with acetic anhydride then affords the diacetyl derivative (189). However, this mechanism does not explain why 1-methyl-3-phenylquinoxalin-2-(1H)-one 4-oxide (181b) undergoes substitution to 7-acetoxy-1-methyl-3-phenylquinoxalin-2(1H)-one (185) rather than ring contraction to 1-acetyl-3-methylbenzimidazolin-2-one (202) in hot acetic anhydride [cf. scheme 26]. It seems improbable that the presence of the N-1 methyl group would inhibit the formation of the corresponding oxaziridine (201) and hence ring contraction. The formation of the products (188) and (189) may alternatively be rationalised by the mechanism shown in scheme 27. This mechanism involves initial coordination of the oxygen atom of the N-oxide (181a) with

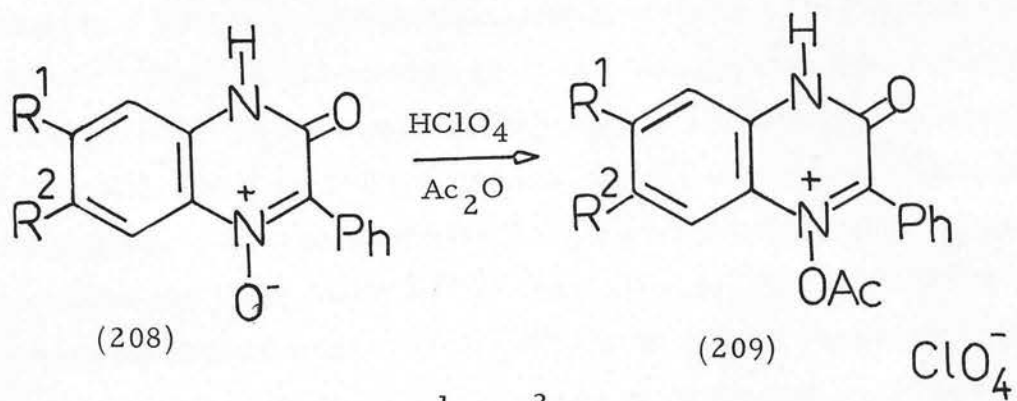


Scheme 27

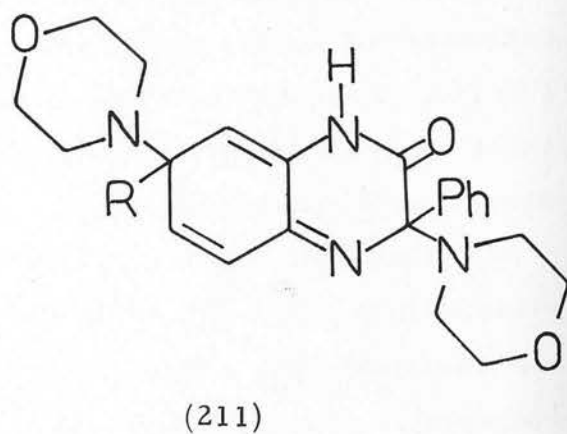
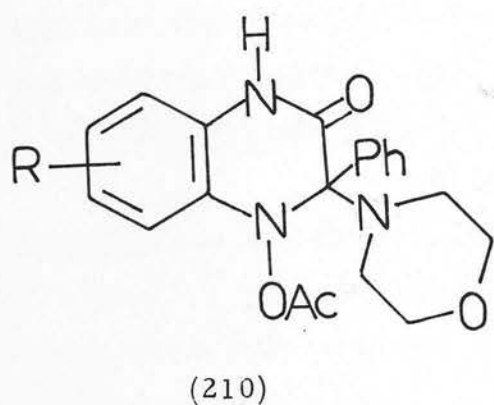
acetic anhydride to give the N-acetoxyquinoxalinium salt (203) which in turn undergoes nucleophilic attack by acetate ion at the C-3 position of the hetero ring to afford the N-acetoxy adduct (204). Proton abstraction by acetate ion from the N-1 position of the adduct (204), followed by ring opening, would give the isocyanate intermediate (205), subsequent cyclisation of which [(205)  $\rightarrow$  (206)  $\rightarrow$  (207)] would yield the benzimidazolone (207). Further reaction of the latter with acetic anhydride then gives the observed ring contraction products (188) and (189). The key intermediates in this mechanistic scheme, namely the N-acetoxyquinoxalinium cation (203) and the N-acetoxy adduct (204) are analogous to the intermediates (190) and (191) in the mechanism proposed for the formation of the 7-substituted derivatives (193) [cf scheme 23]. The mechanism outlined in scheme 27 accounts for the exclusive substitution observed in the reactions of the N-methylquinoxalinone (181b) with acetic anhydride and acetyl chloride since, lacking an N-H group, (181b) cannot undergo ring opening to an isocyanate intermediate of the type (205) requisite for benzimidazolone formation. Conversely, the inability of the much less basic chloride ion (compared with acetate ion) to effect proton removal and hence ring opening to an isocyanate intermediate, explains the lack of ring contraction and consequently exclusive substitution observed in the reaction of the quinoxaline N-oxide (181a) with acetyl chloride.

In the light of the above, it was considered of interest to prepare a series of N-H quinoxalinium perchlorate salts of the type (209) and to study their reactivity with a view to demonstrating the intermediacy of N-acetoxyquinoxalinium cation intermediates of the type (203) in the ring contraction undergone by quinoxaline N-oxides bearing a proton at the N-1 position on reaction with acetic anhydride [cf. scheme 27]. In particular, if the ring contraction mechanism does proceed via the route outlined in scheme 27, then the perchlorate salts (209) should undergo ring contraction to benzimidazolones under basic conditions by a route analogous to that outlined in scheme 27 [cf. (203)  $\rightarrow$  (207)]. Consequently, it was considered that treatment of these quinoxalinium perchlorate salts (209) with basic reagents might prove an enlightening area of study. Further, the



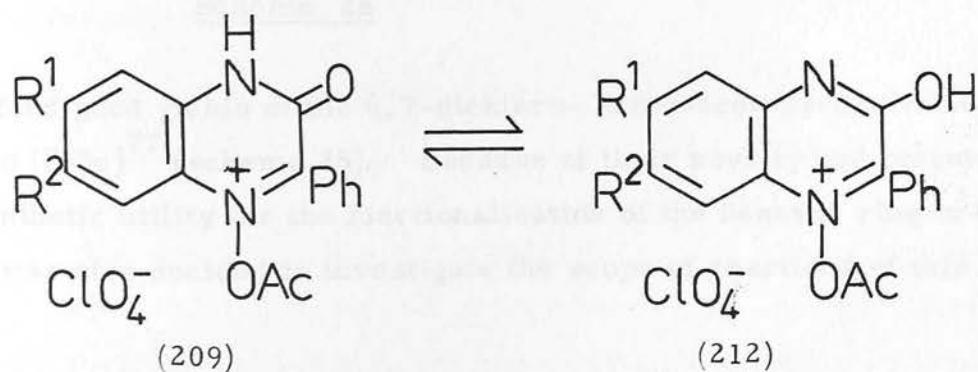


	$\underline{\text{R}^1}$	$\underline{\text{R}^2}$
a ;	H	H
b ;	H	Cl
c ;	H	Me
d ;	Me	Me



reaction of the N-methylquinoxalinium perchlorate salts (195) and (197) with morpholine furnished the mono-morpholino- and bis-morpholino-adducts (196) and (198) respectively, thus, as previously described, providing evidence in support of the substitution mechanism outlined in scheme 23. In view of this fact, it was considered that a comparable study of the reactions of quinoxalinium perchlorate salts of the type (209) should be undertaken with a view to preparing analogous morpholino adducts [cf. (210) and (211)] and studying in turn their reactivity. Again, if the ring contraction mechanism outlined in scheme 27 is operative, such adducts should be susceptible to deprotonation by bases with the formation of isocyanate intermediates analogous to (205) and thence products of ring contraction.

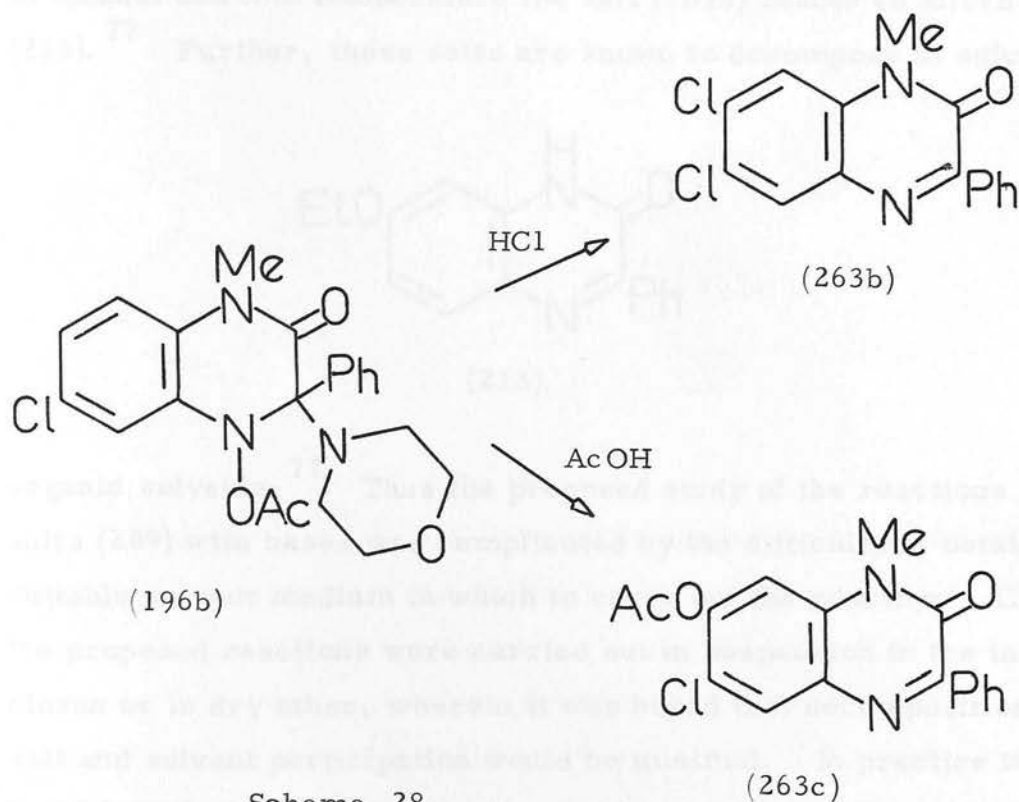
The quinoxalinium perchlorate salts [209 (a-d)] were readily prepared by reaction of the corresponding N-oxides (208) with acetic anhydride in the presence of perchloric acid.<sup>77</sup> It has been observed<sup>77</sup> that perchlorate salts bearing a substituent at the N-1 position are considerably less stable than those bearing a proton at the N-1 position, possibly because of the tautomerism which the latter can exhibit [cf. (209)  $\rightleftharpoons$  (212)]. Previous attempts<sup>77</sup> to demonstrate the intermediacy of



NH-quinoxalinium salts of the type (209) in the ring contraction of NH-quinoxalinone N-oxides to benzimidazolone derivatives [cf (203)  $\rightarrow$  (207); scheme 27] were largely unsuccessful and no benzimidazolones were obtained. In order to gain further insight into the mechanism involved in the acetic anhydride induced ring contraction of quinoxaline N-oxides to benzimidazolones, it was decided to investigate further the reactions

of perchlorate salts of the type (209) with bases.

It has also been observed that when the adduct (196b) is treated with aqueous hydrochloric acid and glacial acetic acid respectively, at room temperature, it is susceptible to facile nucleophilic substitution to

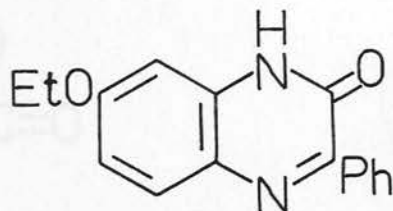


Scheme 28

afford good yields of the 6,7-dichloro- and 7-acetoxy-derivatives (263b) and (263c)<sup>77</sup> (scheme 28). Because of their novelty and potential synthetic utility for the functionalisation of the benzene ring in quinoxalines, it was also decided to investigate the scope of reactions of this type.

## 2.2 Studies on the Reactions of 4-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorates with Bases

Quinoxalinium perchlorate salts of the type (209) show a strong tendency to undergo reaction with hydroxylic solvents. Thus, on stirring in ethanol at room temperature the salt (209a) reacts to afford the ether (213).<sup>77</sup> Further, these salts are known to decompose in solution in



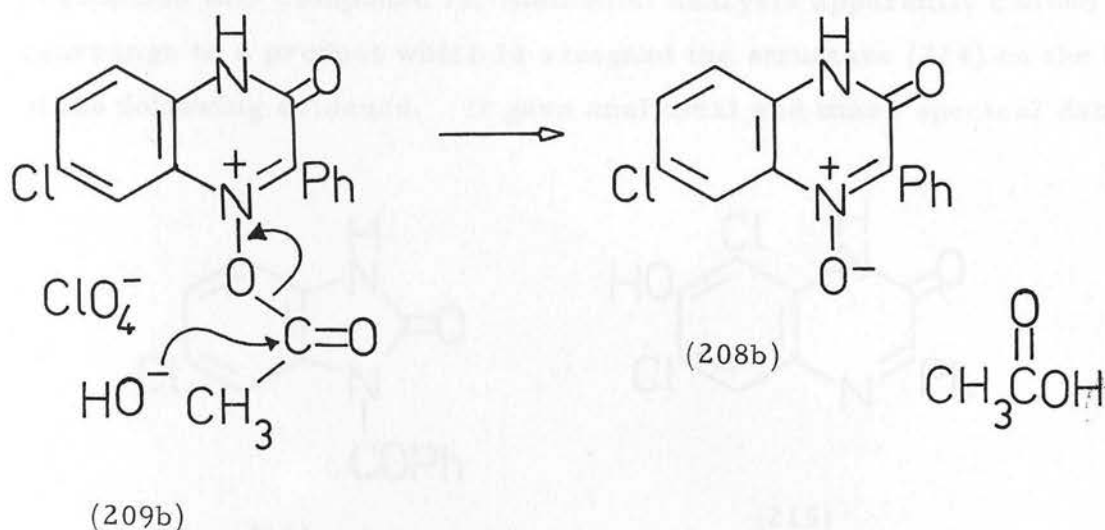
(213)

organic solvents.<sup>77</sup> Thus the proposed study of the reactions of the salts (209) with bases was complicated by the difficulty of obtaining a suitable solvent medium in which to carry out the reaction. Consequently, the proposed reactions were carried out in suspension in the inert solvent dioxan or in dry ether, wherein it was hoped that decomposition of the salt and solvent participation would be minimal. In practice this was found largely to be the case.

### a) The Reaction of 4-Acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b) with Water, Hydroxide Ion and Triethylamine.

The substrate chosen for study with these basic reagents was the perchlorate salt (209b) since this was found to be a relatively stable species, possibly because of the electron withdrawing substituent on the benzene nucleus. In an attempt to demonstrate the ring contraction and hence the intermediacy of salts of the type (203) [cf scheme 27] in the quinoxalinone to benzimidazolone transformations, the reaction of the perchlorate salt (209b) with hydroxide ion was studied. It was hoped that in this reaction deprotonation would occur, followed by ring opening to an isocyanate and then recyclisation to give a benzimidazolone, in accord with the mechanism

shown in scheme 27. In fact the salt (209b) reacted with hydroxide ion to afford the parent N-oxide (208b) in high yield. Simple solvolysis of the N-acetoxy group [(209b)  $\rightarrow$  (208b); scheme 29] is thus observed.



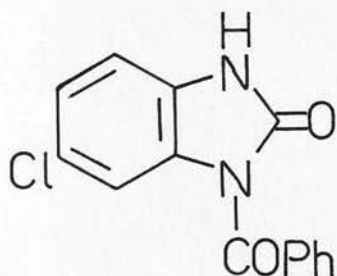
Scheme 29

Triethylamine was also investigated as the catalyst but this reagent again converted the salt principally into the N-oxide (208b) together with a viscous dark gum, whose t.l. c. showed it to be a mixture of several components, and a small quantity of a solid which crystallised as cream coloured needles. The mass spectrum of this compound contained parent ion peaks at 314 and 316 mass units with an isotopic pattern characteristic of a molecule containing one chlorine atom. The i. r. spectrum contained absorption bands at 1770, 1740 and 1700  $\text{cm}^{-1}$ , which are higher than would be expected for the carbonyl absorption of a quinoxalinone nucleus. The aromatic region of the  $^1\text{H}$  n. m. r. spectrum contained an exceedingly complex multiplet, while the non-aromatic region contained two signals at  $\delta$ 2.68 and  $\delta$ 2.60. The overall ratio of aromatic to non-aromatic protons was 5:4. No sensible molecular formula could be assigned to the analytical data obtained. Unfortunately, lack of material prevented attempts to characterise this compound by chemical methods and it therefore remains uncharacterised pending further investigation.

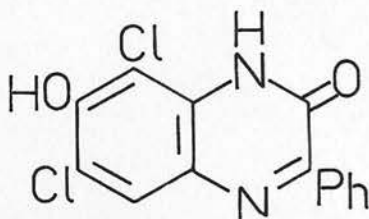
As a last resort, the reaction of the salt (209b) with water was investigated in the hope that ring contraction might be induced under these



mild conditions. Reaction of the salt (209b) with water at room temperature gave a moderate yield of a yellow solid whose i.r. spectrum contained absorption bands at 1755 and 1650  $\text{cm}^{-1}$ . An attempt to crystallise this compound for elemental analysis apparently caused it to rearrange to a product which is assigned the structure (214) on the basis of the following evidence. It gave analytical and mass spectral data fully



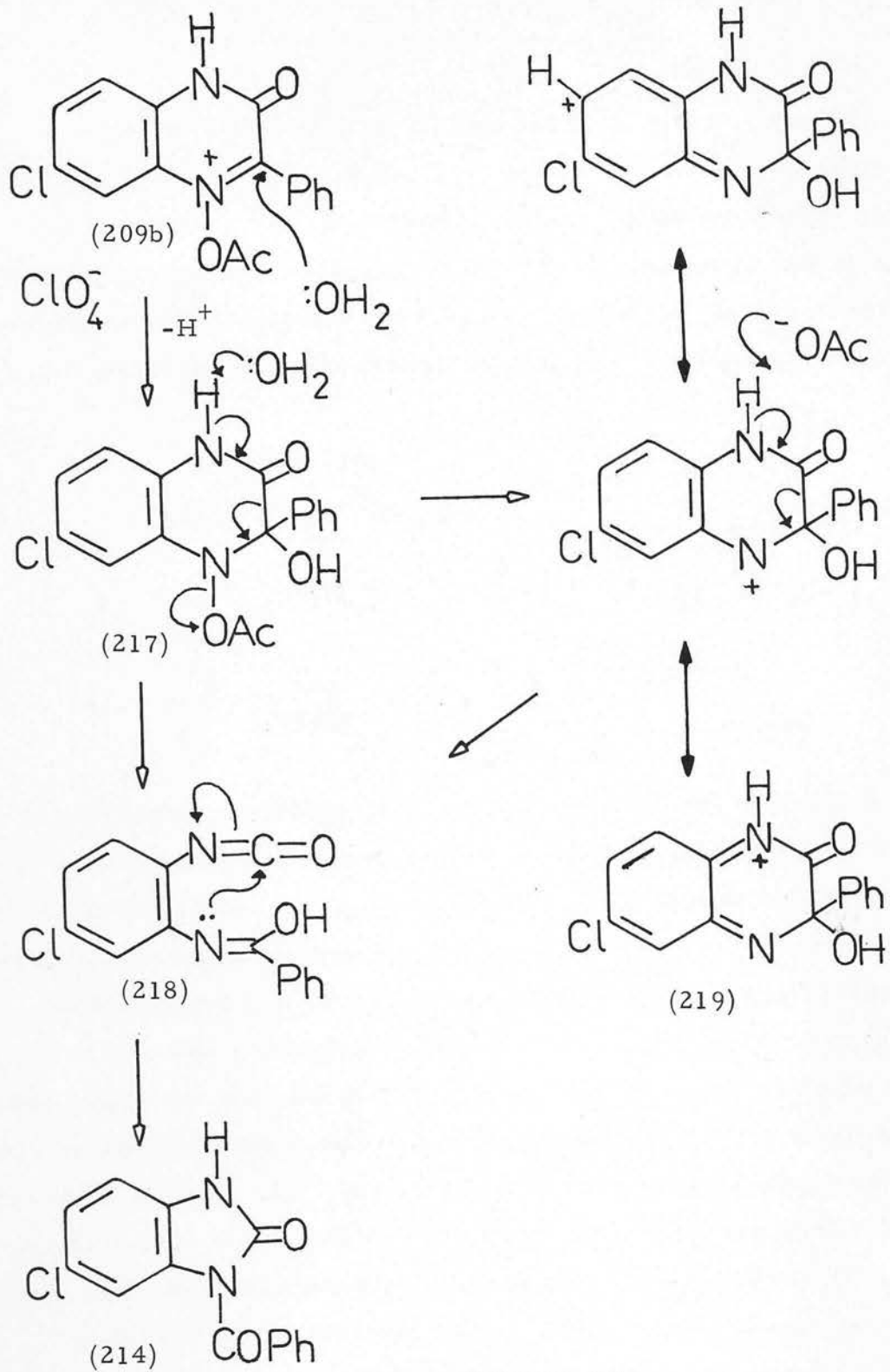
(214)



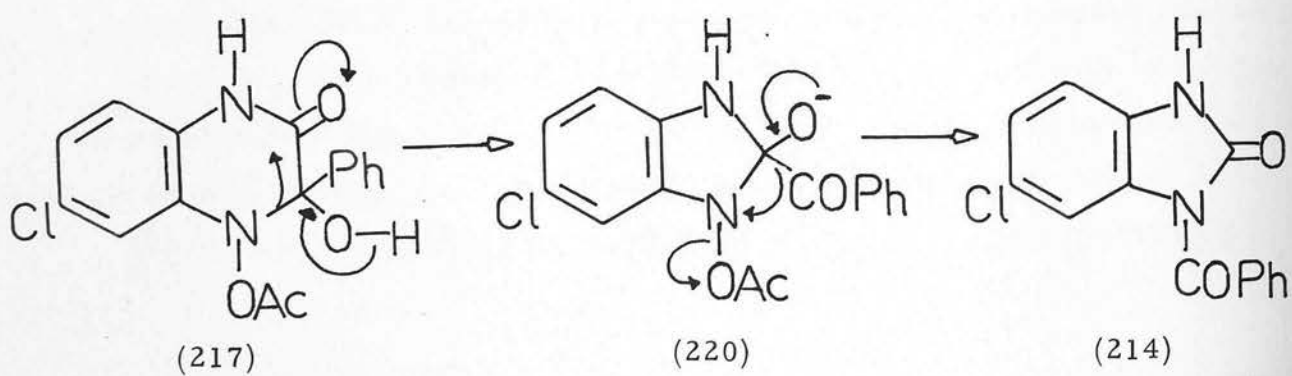
(215)

in accord with this structure. Also, its i.r. spectrum lacked an i. r. carbonyl absorption at ca 1670  $\text{cm}^{-1}$  due to a quinoxalinone nucleus but showed NH absorption at 3200  $\text{cm}^{-1}$  and a broad carbonyl band at 1730  $\text{cm}^{-1}$  indicative of a benzimidazolone ring. Presumably the absorption bands of the benzoyl group and the benzimidazolone ring are superimposed. The  $^1\text{H}$  n. m. r. spectrum of the product (214) showed a one proton resonance at  $\delta$ 7.08 which is assigned to the proton at C-4, because the signal showed up as a doublet with a coupling constant of 8.0Hz, characteristic of coupling between aromatic protons ortho to one another. The signal farther downfield at  $\delta$ 7.25 is assigned to the proton at C-5 because it appears as a double doublet with coupling constants corresponding to ortho and meta coupling between aromatic protons. Assignment of the  $^1\text{H}$  n. m. r. absorption corresponding to the proton at C-7 was not possible due to overlap with the absorption of the phenyl protons of the benzoyl group. A second product obtained from the reaction of the salt (209b) with water is assigned the structure (215) for reasons which will be discussed later. The other product of this reaction was a viscous gum which was shown by t.l.c. to be an unresolvable multicomponent mixture. This reaction proved highly irreproducible and subsequent attempts to obtain the N-benzoyl-



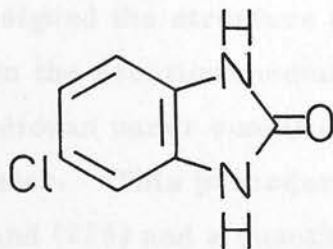


Scheme 30



Scheme 31

benzimidazolone (214) in order that it might be hydrolysed to the parent benzimidazolone (216), a known compound, and hence prove its structure were unsuccessful giving only moderate yields of the dichlorophenol (215) and viscous black gums from which no identifiable material could be obtained.

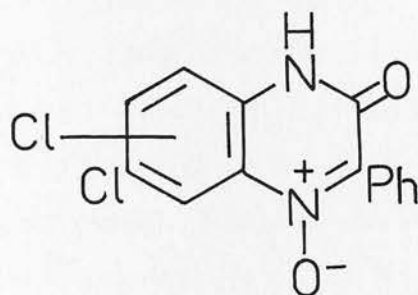


(216)

The formation of the product (214) under such mild conditions is not easy to explain. One possible mechanism for its formation is that outlined in scheme 30 [(209b)  $\rightarrow$  (217)  $\rightarrow$  (218)  $\rightarrow$  (214)], which is analogous to the general mechanism for ring contraction outlined in scheme 27. Nucleophilic attack by water at the C-3 position of the salt (209b) with subsequent loss of a proton would afford the adduct (217). Proton abstraction by a water molecule [cf (217)  $\rightarrow$  (218)] from the N-1 position in the adduct (217) would give the isocyanate intermediate (218), ring closure of which would then furnish the observed product (214). It is unlikely, however, that the proton at the N-1 position would be sufficiently acidic to be removed by the very weakly basic water molecule. An alternative route to the isocyanate intermediate (218) and consequently the benzimidazolone (214) involves initial departure of acetate ion from the adduct (217) with the generation of the resonance stabilised nitrenium ion intermediate (219). The isocyanate (218) would then be formed by proton abstraction by the basic acetate ion [cf (219)  $\rightarrow$  (218)] from this intermediate. The involvement of nitrenium ions in related rearrangements will be discussed later in this chapter. It is possible, however, that under these mild conditions deprotonation of the N-1 position in the adduct (217) is not a prerequisite for the formation of the observed benzimidazolone (214). Thus, the formation of (214) is also explicable by the rearrangement of the adduct (217) outlined in scheme 31. Removal of the acidic proton of the hydroxyl function at C-3 with a concordant bond

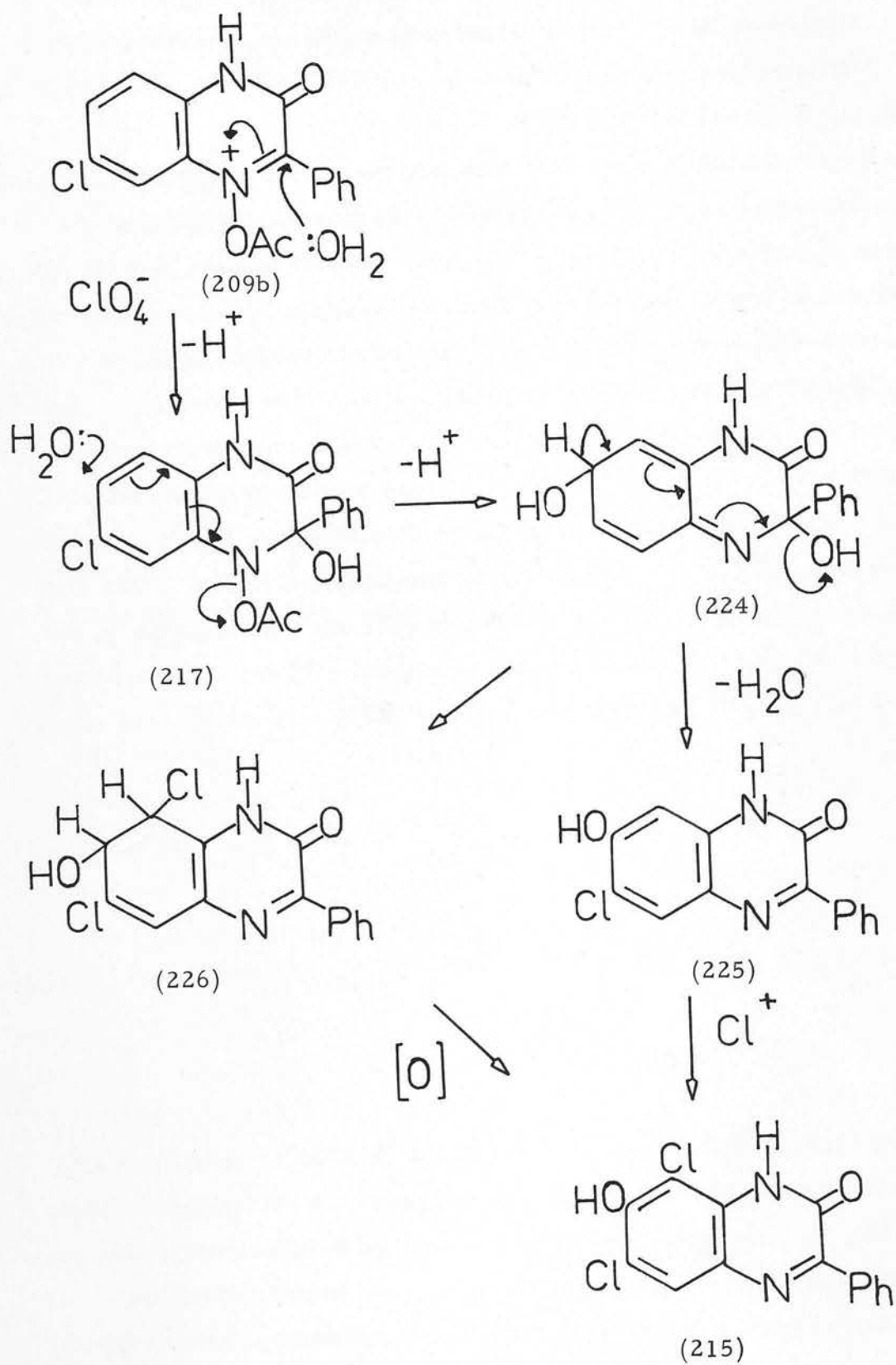
shift as shown [(217)  $\rightarrow$  (220)] would give the anionic intermediate (220). Departure of the acetoxy leaving group and a concerted [1, 2] acyl shift of the benzoyl group from C-2 to N-1 [(220)  $\rightarrow$  (214)] would furnish the observed product (214).

In an attempt to determine whether the rather surprising formation of the compound assigned the structure (215) was dependent upon the presence of water in the reaction medium, the perchlorate salt (209b) was stirred in dry dioxan under conditions identical to those employed in its reaction with water. This procedure led to the formation of a low yield of the compound (215) and a quantity of an intractable gum. Satisfactory elemental analytical data was obtained for (215) corresponding to the molecular formula  $C_{14}H_8N_2O_2Cl_2$  and the mass spectrum contained parent ion peaks at 306, 308 and 310 mass units displaying an isotopic pattern characteristic of a molecule containing two chlorine atoms. The i. r. spectrum contained an absorption band at  $1635\text{ cm}^{-1}$  assignable to the carbonyl absorption of a quinoxalinone nucleus. These analytical and spectral data also fit the isomeric N-oxide (221). However, the phenolic



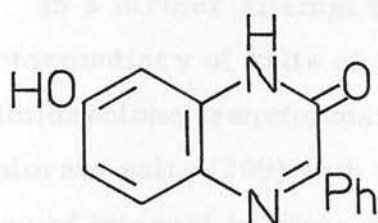
(221)

structure (215) is preferred on the basis of its  $^1\text{H}$  n. m. r. spectrum and the results obtained on treatment of the compound with ferric chloride in ethanol. The aromatic region of the  $^1\text{H}$  n. m. r. spectrum contained an unsplit signal which integrated for one proton together with two multiplets, which integrated for two and three protons respectively and which are attributable to the phenyl group at C-3. This indicates that only one position on the fused benzene ring remains unsubstituted, at variance with the situation in the N-oxide (221). Treatment of an ethanolic solution of the compound with ferric chloride gave a red-brown coloration.

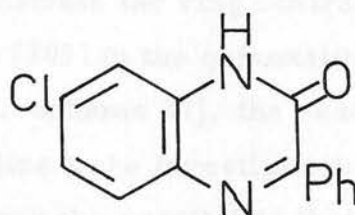


Scheme 32

Treatment of the phenol (222) with ferric chloride gave a similar coloration



(222)



(223)

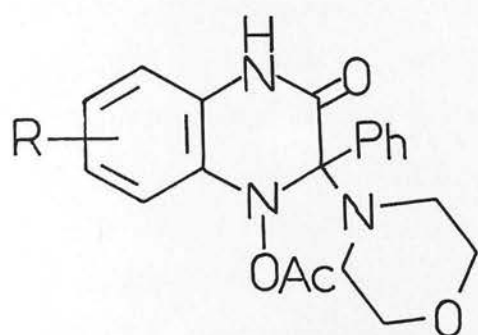
whereas treatment of the quinoxalinone (223) did not. These observations further substantiate the assigned phenolic structure (215).

The formation of the dichloro-compound (215) under the conditions described is difficult to rationalise. One possible explanation for the generation of this compound on reaction of the salt (209b) in dioxan with water requires the initial formation of the phenol (225) as outlined in scheme 32. Thus the N-acetoxy intermediate (217) could undergo nucleophilic substitution at the C-7 position of the fused benzene nucleus with expulsion of the acetoxy leaving group to furnish the para-quinonoid intermediate (224) which upon rearomatisation [(224)  $\rightarrow$  (225)] furnishes the phenol (225). Electrophilic substitution by  $\text{Cl}^+$  at the C-8 position, ortho to the hydroxyl group, would then afford the compound (215). However, the presence of  $\text{Cl}^+$  in the reaction mixture is somewhat unlikely as the perchlorate would not be degraded to this species. An alternative course involves nucleophilic attack by chloride ion at the C-8 position of the para-quinonoid intermediate (224) with expulsion of hydroxide ion to give the dihydro intermediate (226). Oxidation of (226) by the oxidative<sup>78</sup> perchlorate ion would give the phenol (215). Neither of these mechanisms satisfactorily explain the formation of (215) in the absence of water. Since the reaction was conducted in an unstoppered flask, it is conceivable that atmospheric moisture was sufficient to catalyse the reaction. Time did not permit the further study of this system under completely anhydrous conditions.



b) The Reaction of 4-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorates (209) with Morpholine.

In a further attempt to demonstrate the ring contraction and hence the intermediacy of salts of the type (203) in the quinoxalinone to benzimidazolone transformation [cf. scheme 27], the reactions of the perchlorate salts (209) with morpholine were investigated. A further feature of interest in these studies was the possibility that quinoxalinone adducts of the type (210) and (211), analogous to the morpholino adducts (196) and (198) obtained by treatment of the N-methylquinoxalinium



(210)

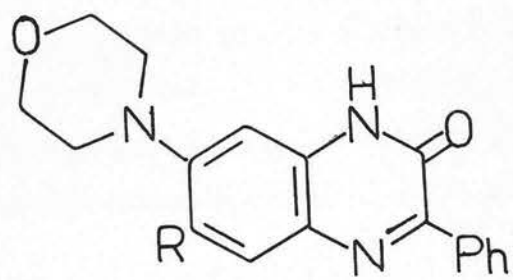


(211)

perchlorate salts (195) and (197) respectively, with morpholine, might be generated. Since the compounds (210) are direct analogues of the intermediate (204) [scheme 27], demonstration of their base catalysed ring contraction would endorse the intermediacy of (204) in the quinoxalinone to benzimidazolone rearrangement. As was the case in the study of the NH-quinoxalinium perchlorate salts (209) with hydroxide ion, triethylamine and water, the proposed study of the salts (209) with morpholine was complicated by the difficulty of obtaining a suitable solvent medium in which to carry out the reactions. In these studies the reactions of the salts (209) with morpholine were carried out in suspension in ether.

The perchlorate salt (209a) reacted with morpholine at room temperature to give a moderate yield of a product which analysed correctly and exhibited a mass spectrum consistent with the 7-morpholinoquinoxalinone





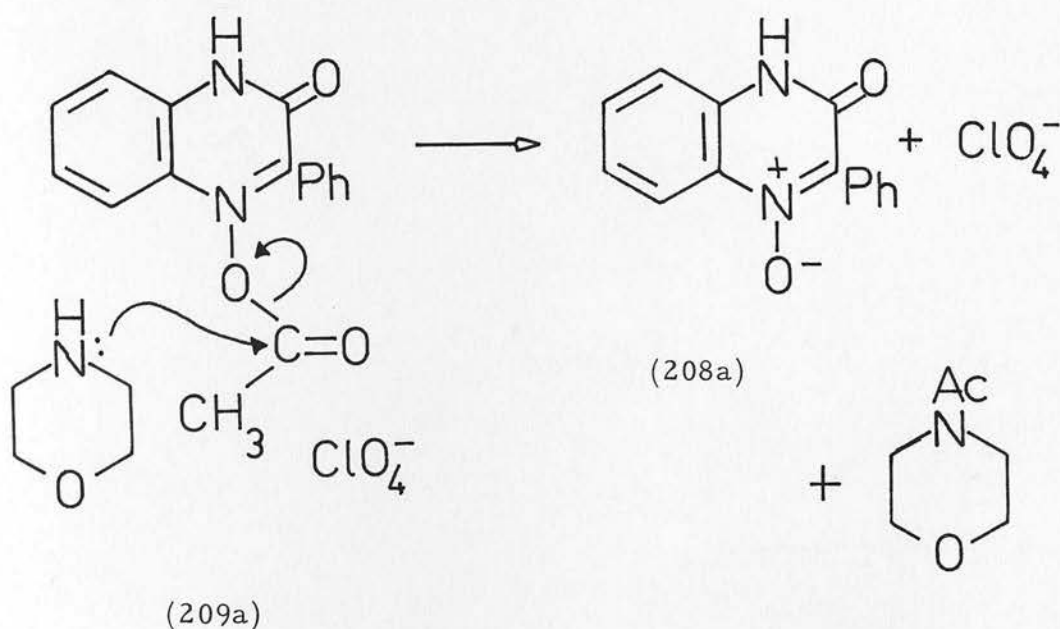
(227)

R

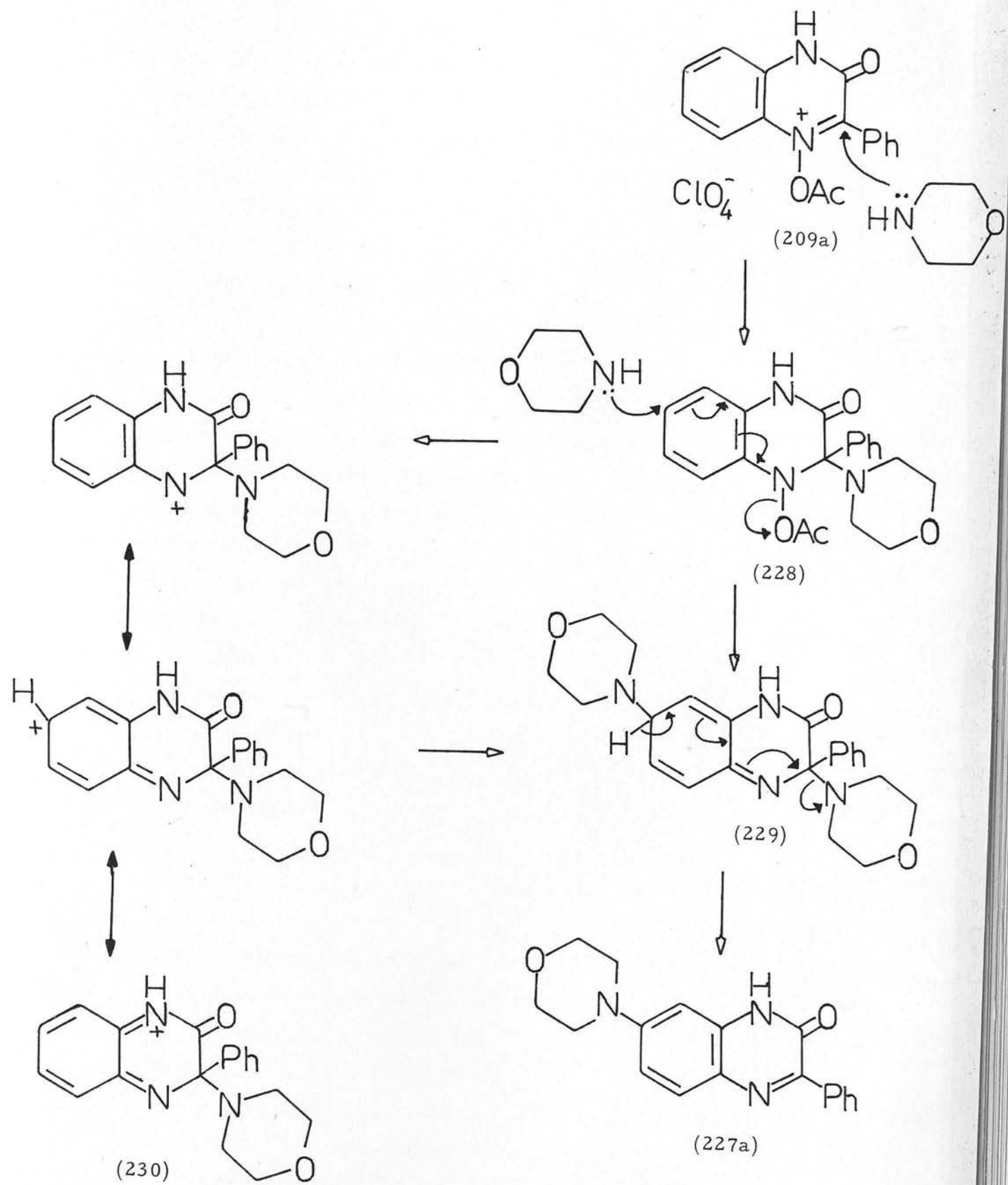
a ; H

b ; Cl

structure (227a). That the morpholine residue had entered the C-7 position of the benzene nucleus was indicated by the  $^1\text{H}$  n. m. r. spectrum of the product which, in addition to proton absorptions due to a single morpholine group, showed an aromatic absorption pattern characteristic of a 1, 2, 4-trisubstituted benzene derivative. The one proton absorption at  $\delta 7.62$  is assigned to H-5 because this signal showed up as a doublet with a coupling constant of 8Hz which is characteristic of the coupling constant between aromatic protons ortho to one another. The one proton signal farther upfield at  $\delta 6.95$  is assigned to H-6 because it appears as a doublet with coupling constants corresponding to ortho and meta coupling between aromatic protons. In further accord with the assigned structure (227a), the  $^1\text{H}$  n. m. r. spectrum contained a doublet at  $\delta 6.66$  with a coupling constant characteristic of meta coupling and assignable to H-8. The parent N-oxide (208a), which was characterised by comparison with an authentic sample, was also obtained from the reaction mixture. The N-oxide could be formed by solvolysis of unreacted perchlorate salt (209a) on work up, or by nucleophilic attack by morpholine at the N-acetoxy group [cf. scheme 33]. The N-acetylmorpholine was not detected in the reaction mixture. Nucleophilic attack at the carbonyl group of an N-acetoxy



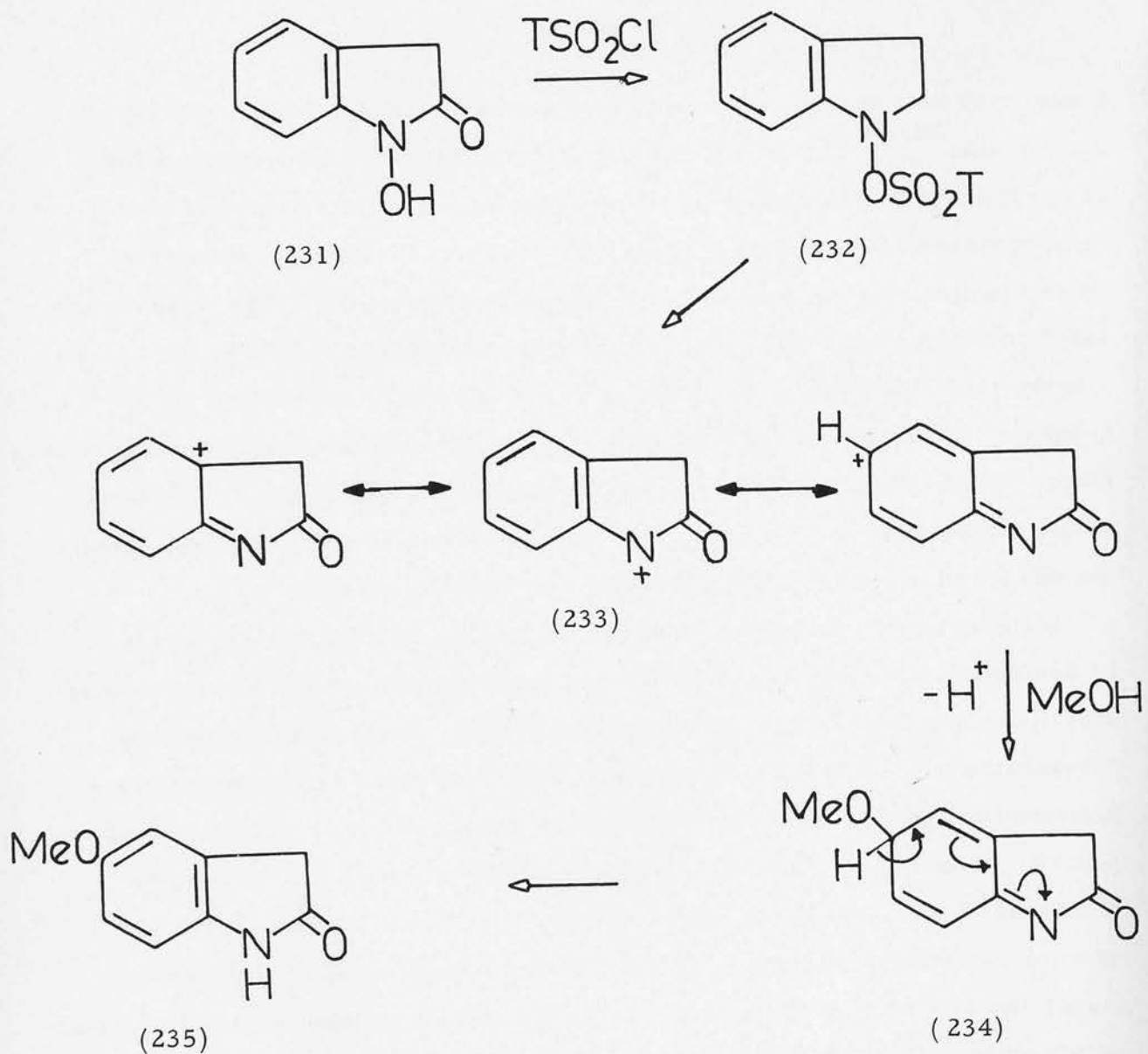
Scheme 33



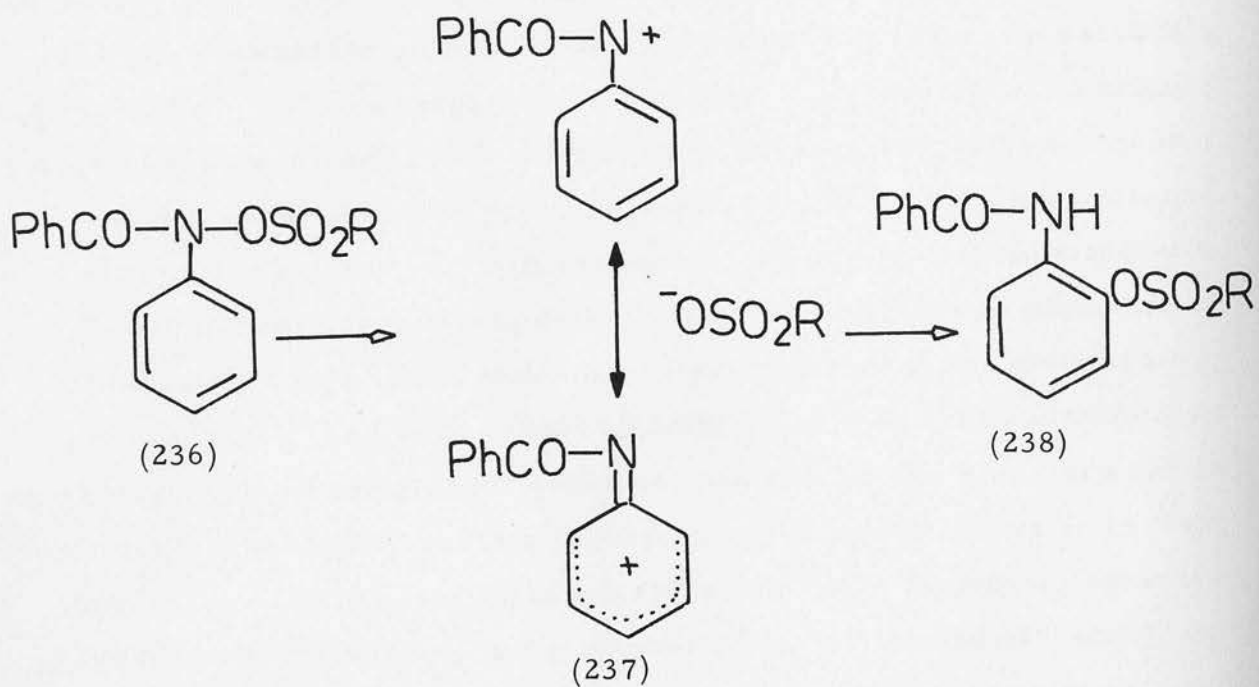
Scheme 34

quaternary salt has been reported as a characteristic reaction of such compounds.<sup>55, 79</sup> No product of ring contraction, nor morpholino adduct of the type (210) was obtained from this reaction. The formation of the 7-morpholinoquinoxalinone (227a) from the perchlorate salt (209a) may be rationalised by the mechanism outlined in scheme 34. The perchlorate salt undergoes nucleophilic substitution by morpholine at C-3 in the hetero ring to give the adduct (228) which then affords the 7-substituted para-quinonoid intermediate (229) by a course involving synchronous nucleophilic attack by morpholine and loss of the N-acetoxy leaving group. Elimination of the elements of morpholine from (229) upon rearomatisation then gives the observed product (227a) [cf (228)  $\rightarrow$  (229)  $\rightarrow$  (227a)].

Alternatively, nucleophilic attack by morpholine might be preceded by ionisation with loss of the N-acetoxy leaving group to give the resonance stabilised nitrenium cation intermediate (230). Nucleophilic attack by morpholine at C-7 in the intermediate (230) then gives the para-quinonoid intermediate (229) which rearomatises to the observed product as described before [scheme 34; (228)  $\rightarrow$  (230)  $\rightarrow$  (229)  $\rightarrow$  (227a)]. The crucial mechanistic question is therefore whether loss of the acetoxy leaving group and nucleophilic attack by morpholine is concerted or stepwise. Reactions of this type therefore have added interest because of the possible involvement of nitrenium ion intermediates [cf (230)], transient species whose existence has been the subject of some controversy.<sup>80, 81</sup> Resonance stabilised nitrenium ions have been invoked as intermediates in the conversion of 1-hydroxyindole (231) into 5-methoxyindole (235)<sup>82</sup> on treatment with methanol in the presence of tosyl chloride. The two step mechanism proposed requires heterolytic cleavage of the N-O bond in the indole sulphonate (232) to afford the resonance stabilised nitrenium ion (233). Nucleophilic attack by methanol at the C-5 position, followed by loss of a proton, gives the para-quinonoid intermediate (234), which upon rearomatisation affords 5-methoxyindole (235). Further, it is considered on the basis of evidence obtained from labelling studies that the rearrangement of *o*-(arenesulphonyl)-phenylhydroxylamines (236) to *o*-arenesulphonyl-*o*-benzamidophenols (238)<sup>83</sup> (in which the ortho position is preferentially substituted) is best explained by assuming that heterolysis of the N-O bond takes place to give an intimate ion pair [cf (237)] consisting of a resonance stabilised aryl nitrenium ion and tosylate ion, recombination of



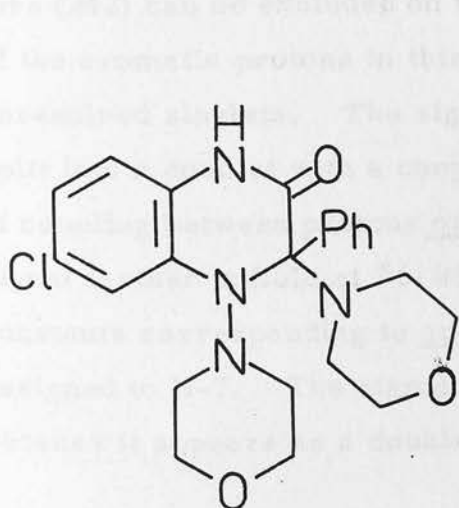
Scheme 35



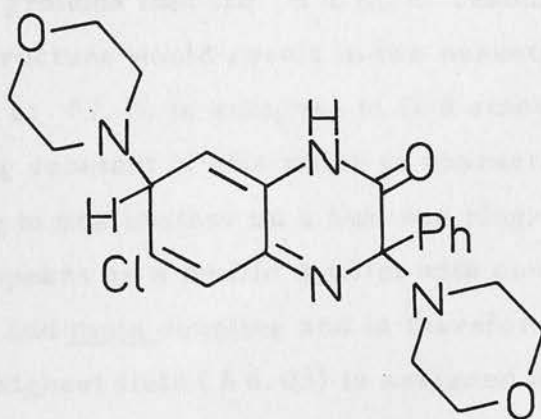
Scheme 36

which, within the confines of a solvent cage furnishes the observed products [scheme 36; (236)  $\rightarrow$  (237)  $\rightarrow$  (238)].

In a further attempt to demonstrate ring contraction, the quinoxalinium perchlorate salt (209b) was treated with morpholine. It was considered that the chloro substituent on the fused benzene ring should increase the acidity of the proton at N-1 by inductive electron withdrawal, thus increasing the likelihood of its abstraction by morpholine. It was, however, realised that the C-7 position would simultaneously be activated towards nucleophilic attack by the presence of the chloro substituent at the neighbouring carbon atom. Three different products were obtained from the reaction of the salt (209b) with morpholine. The first, which was isolated in good yield is assigned the structure (227b) on the basis of analytical and mass spectral evidence and its  $^1\text{H}$  n.m.r. absorption. This showed the presence of one morpholino group and the fact that this was in the 7-position was established by the appearance of the aromatic protons of the fused benzene ring as two discrete signals. The absence of any splitting in the aromatic proton resonances uniquely defines the position of substitution in the molecule as C-7 since substitution at any other site would lead to observable splitting in the signals due to the aromatic protons. The second product was isolated from the reaction mixture in good yield in the form of yellow needles which analysed correctly and gave mass spectral data consistent with a dimorpholino-product having one or other of the structures [(239)  $\rightarrow$  (242)]. In particular, its mass

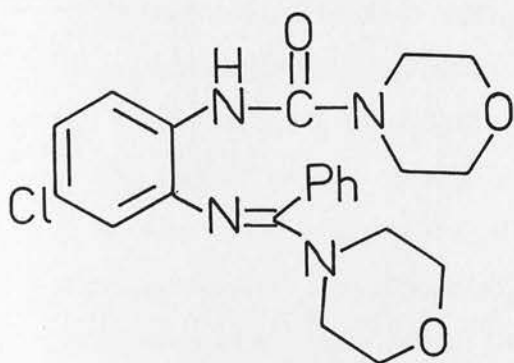


(239)

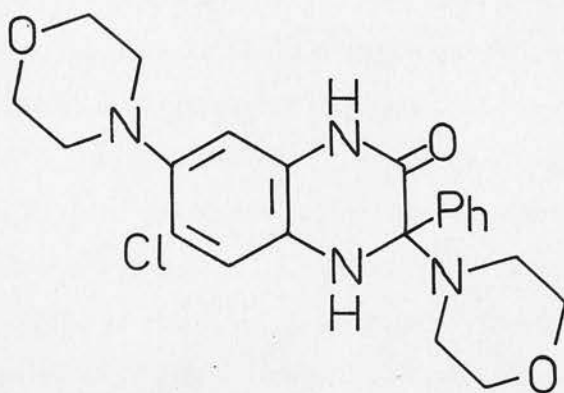


(240)



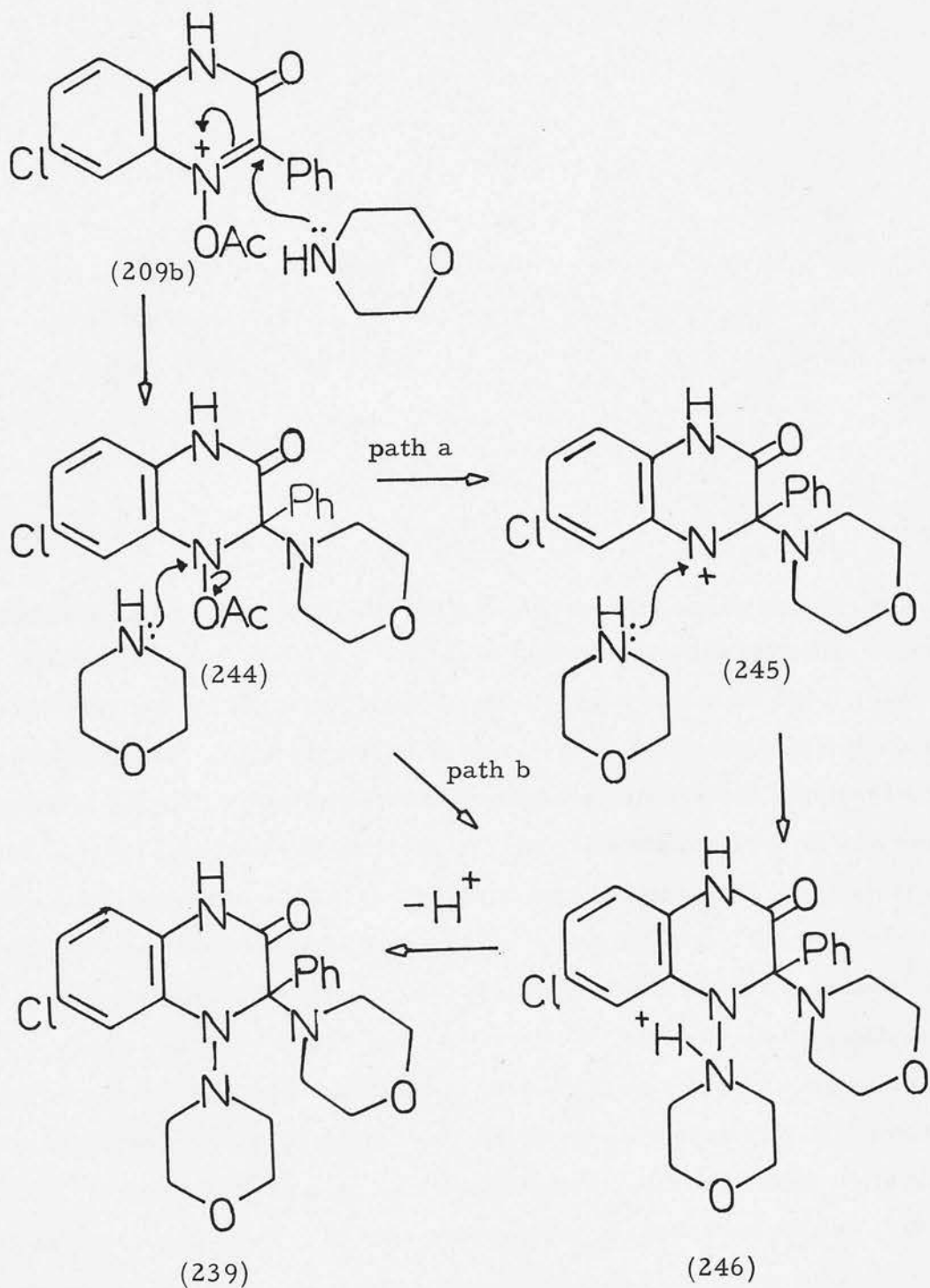


(241)

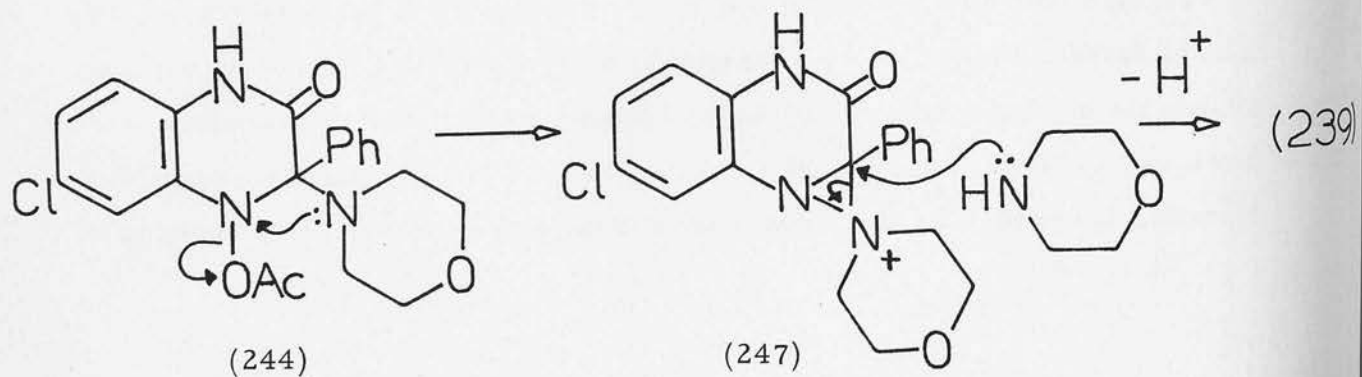


(242)

spectrum showed parent ion peaks at 428 and 430 mass numbers corresponding to the presence of a single chlorine atom and two morpholino residues. The  $^1\text{H}$  n. m. r. spectrum of the compound further showed the presence of two morpholine residues in the molecule and also contained signals in the aromatic region characteristic of a 1, 2, 4-trisubstituted benzene and is thus consistent with the structures (239) and (241). It is improbable that the isomeric structure (240), although analogous to the adduct (198), would give rise to a splitting pattern in the aromatic region of the  $^1\text{H}$  n. m. r. spectrum characteristic of a trisubstituted benzene. The vinylic protons H-5 and H-8 and the proton at C-7 would all be expected to occur at higher field than the signals observed in the actual spectrum. In any case it is probable that the structure (240) would not be stable but would readily rearomatise with loss of morpholine. Structure (242) can be excluded on the grounds that the  $^1\text{H}$  n. m. r. resonance of the aromatic protons in this structure would result in two essentially unresolved singlets. The signal at  $\delta 7.76$  is assigned to H-8 since it is split into a doublet with a coupling constant of 8Hz which is characteristic of coupling between protons ortho to one another on a benzene ring. The signal farther upfield at  $\delta 6.69$  appears as a double doublet with coupling constants corresponding to ortho and meta coupling and is therefore assigned to H-7. The signal at highest field ( $\delta 6.05$ ) is assigned to H-5 because it appears as a doublet with a coupling constant characteristic of

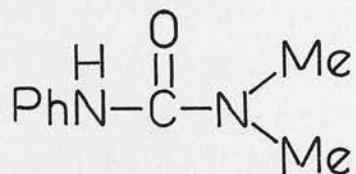


Scheme 37



Scheme 38

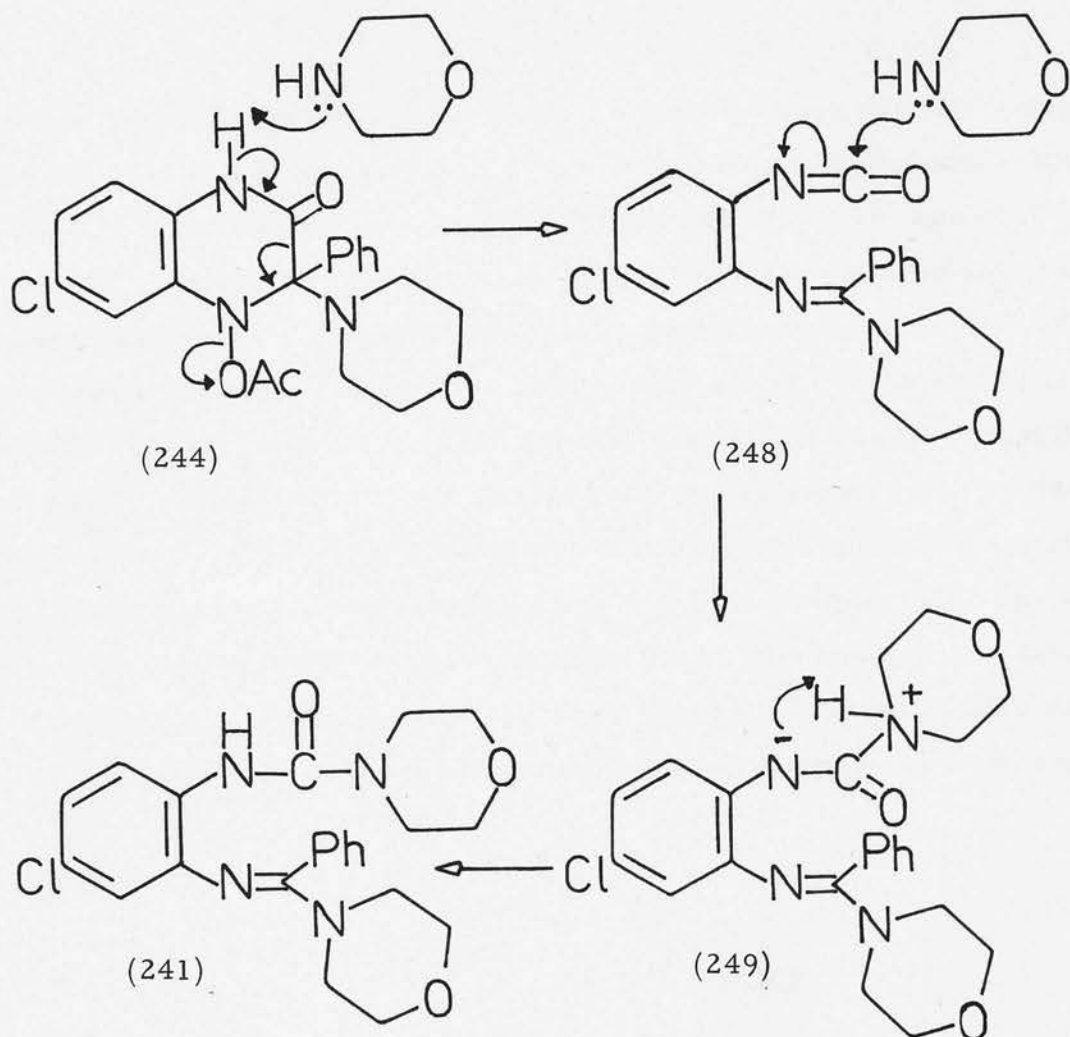
coupling between meta protons. These assignments were fully established by spin-decoupling experiments. Irradiation at  $\delta$  6.69 caused the signals at  $\delta$  7.76 and  $\delta$  6.05 to collapse to singlets and irradiation at  $\delta$  6.05 caused the double doublet at  $\delta$  6.69 to collapse to a doublet. The signal at  $\delta$  7.75, which moved downfield on irradiation at  $\delta$  6.69, is assigned to the proton at N-1 in the hetero ring. It follows that only structures (239) and (241) are consistent with the  $^1\text{H}$  n.m.r. absorption. Neither structure can be excluded on the basis of the i. r. evidence. The i. r. spectrum showed a sharp NH absorption band at  $3340\text{ cm}^{-1}$  and a strong carbonyl absorption at  $1650\text{ cm}^{-1}$ , assignable to both the quinoxalinone nucleus and the carbonyl functional group in the open chain structure (241). It has been observed<sup>83</sup> that the carbonyl absorption band in the i. r. spectrum of 1,1-dimethyl-3-phenylurea (243) appears at  $1660\text{ cm}^{-1}$ .



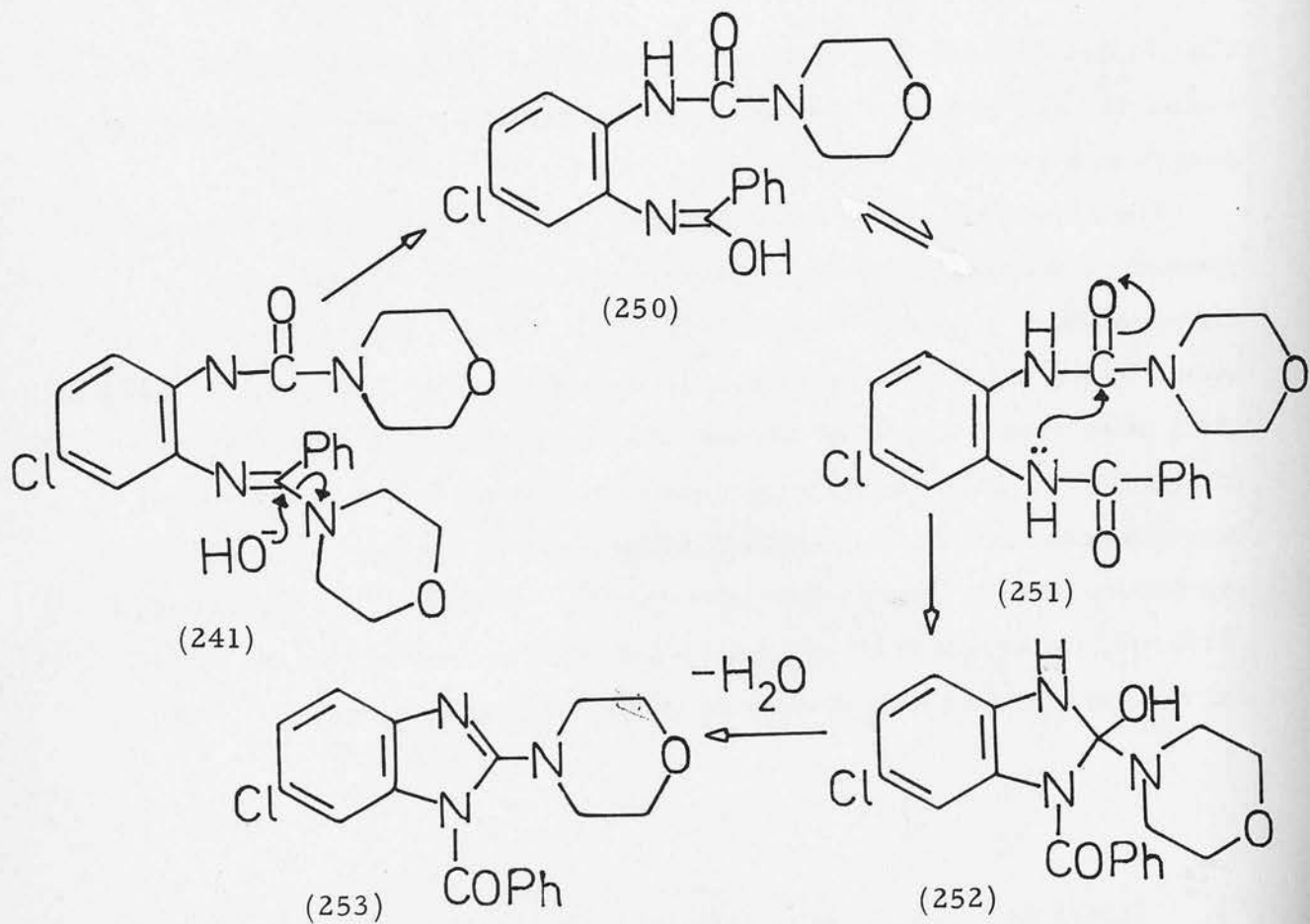
(243)

This molecule embodies structural features of marked similarity to the molecule (241) and the carbonyl group in the latter would be expected to absorb at a similar i. r. frequency.

The conversion of the salt (209b) by reaction with morpholine into a product of the type (239) would require nucleophilic substitution at a nitrogen atom, a rarely observed process. This would occur (scheme 37) either by an  $\text{SN}_1$  type substitution in the presumed N-acetoxy intermediate (244) after departure of the acetoxy leaving group and formation of a nitrenium ion (245) [scheme 37; path a] or by an  $\text{SN}_2$  type of process involving concerted nucleophilic displacement of the N-acetoxy group in the adduct (244) by morpholine [scheme 37; path b]. The formation of (239) might also occur by the mechanism outlined in scheme 38. An intramolecular  $\text{SN}_2$  type displacement of the N-acetoxy group by the



Scheme 39



Scheme 40

morpholine residue at C-3 would give the intermediate (247). Nucleophilic attack by morpholine at C-3 would then furnish the bis-morpholino compound (239). A tentative mechanistic rationalisation for the mode of formation of the alternative open chain structure (241) is outlined in scheme 39. Deprotonation of the N-acetoxy intermediate (244) would give the isocyanate intermediate (248), which upon nucleophilic attack at the carbonyl functional group by morpholine, would give the intermediate (249) and thence the adduct (241). On the basis of the structural evidence so far obtained it is not possible to come down in favour of either of the two proposed structures, namely (239) and (241), and further investigation of this area of work is required.

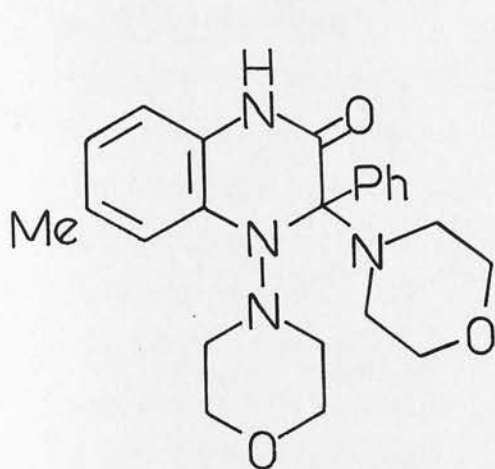
The third product isolated from the reaction of the salt (209b) with morpholine was obtained in low yield from the reaction mixture in the form of pale yellow needles which analysed correctly and gave mass spectral data consistent with a mono-morpholino-derivative, isomeric with the compound (227b). In particular, its mass spectrum showed parent ion peaks at 341 and 343 mass numbers corresponding to the presence of a single chlorine atom and a single morpholine residue. The i. r. spectrum contained absorption bands at 1750 and 1700  $\text{cm}^{-1}$  which are rather higher than would be expected for a quinoxalinium nucleus, this suggesting that the quinoxalinone had undergone rearrangement. The  $^1\text{H}$  n. m. r. spectrum was very poorly resolved and of little help in assigning structure. The aromatic region contained an exceedingly complex multiplet which was not suited to decoupling experiments. The morpholine residue showed up as two poorly resolved clusters at  $\delta 3.49$ - $\delta 3.31$  and  $\delta 3.19$ - $\delta 3.01$ . The evidence available at this stage of the experimentation barely warrants the assignation of a structure. It is speculatively proposed, however, that the unidentified third compound from this reaction may be the N-benzoylbenzimidazole (253) and a possible course for its formation is tentatively described in scheme 40. Hydrolysis of the open chain adduct (241) in the aqueous work up would afford the intermediate (250), tautomeric with the intermediate (251). Ring closure in the manner shown  $[(251) \rightarrow (252)]$  and a proton shift would



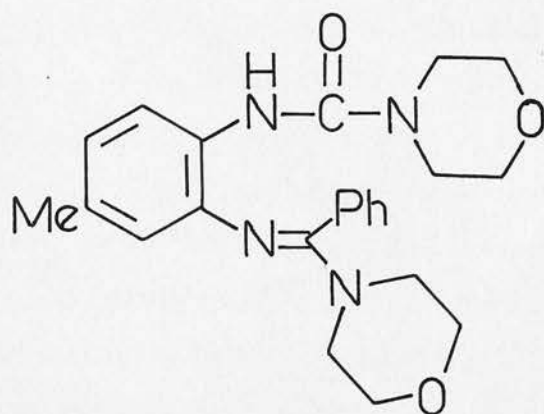
afford the benzimidazole (252) which on loss of the elements of water would furnish the benzimidazole (253). The speculative nature of this mechanism and structure assignment is stressed however.

In contrast to the corresponding reaction of the parent salt (209a), none of the parent N-oxide (208b) was formed in the reaction of the chloroquinoxalinium salt (209b) with morpholine. The greater efficiency of the latter reaction demonstrates the activating effect towards nucleophilic substitution in the C-7 position by the electron withdrawing chlorine substituent at C-6. The apparent lack of products of ring contraction in the reactions of the salts [209 (a and b)] with morpholine may be taken to indicate that deprotonation at N-1 followed by ring opening to an isocyanate [cf scheme 27] does not compete with nucleophilic substitution in these reactions. In an attempt to tip the balance in favour of ring opening and hence ring contraction, the reaction of the methyl-substituted salt (209c) with morpholine was next investigated. It was hoped that the electron donating 6-methyl substituent in the salt (209c), by hindering nucleophilic attack at C-7, would favour ring-contraction over substitution. In practice, the major product of the reaction of the salt (209c) with morpholine was the parent N-oxide (208c) which was identified by comparison with an authentic sample. The N-oxide (208c) is presumably generated, as previously described, by the route outlined in scheme 33. The reaction also gave a second product, isolated from the reaction mixture in low yield as a yellow solid which analysed correctly and gave mass spectral data consistent with a dimorpholino-product. In particular its mass spectrum showed a parent ion peak at 408 mass numbers, corresponding to the presence of two morpholine residues. The i. r. spectrum contained a strong carbonyl absorption band at  $1645\text{ cm}^{-1}$ . Unfortunately, since the solid was isolated in such low yield, insufficient material was available for a conclusive  $^1\text{H}$  n. m. r. spectrum to be obtained. It is probable, however, that this product is analogous to the bis-morpholino compound obtained from the reaction of the salt (209b) with morpholine, and consequently, for the reasons already mentioned, it is considered to have either structure (254) or (255). From the predominant formation of





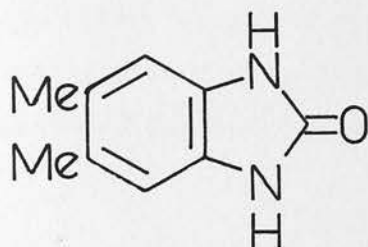
(254)



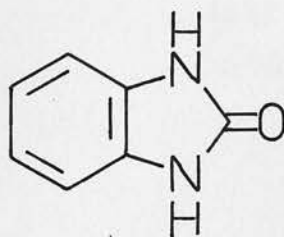
(255)

the N-oxide (208c) in the reaction of the salt (209c) with morpholine it would appear that in default of nucleophilic substitution in the benzene ring, nucleophilic attack on the N-acetoxy group rather than ring contraction, prefers to occur.

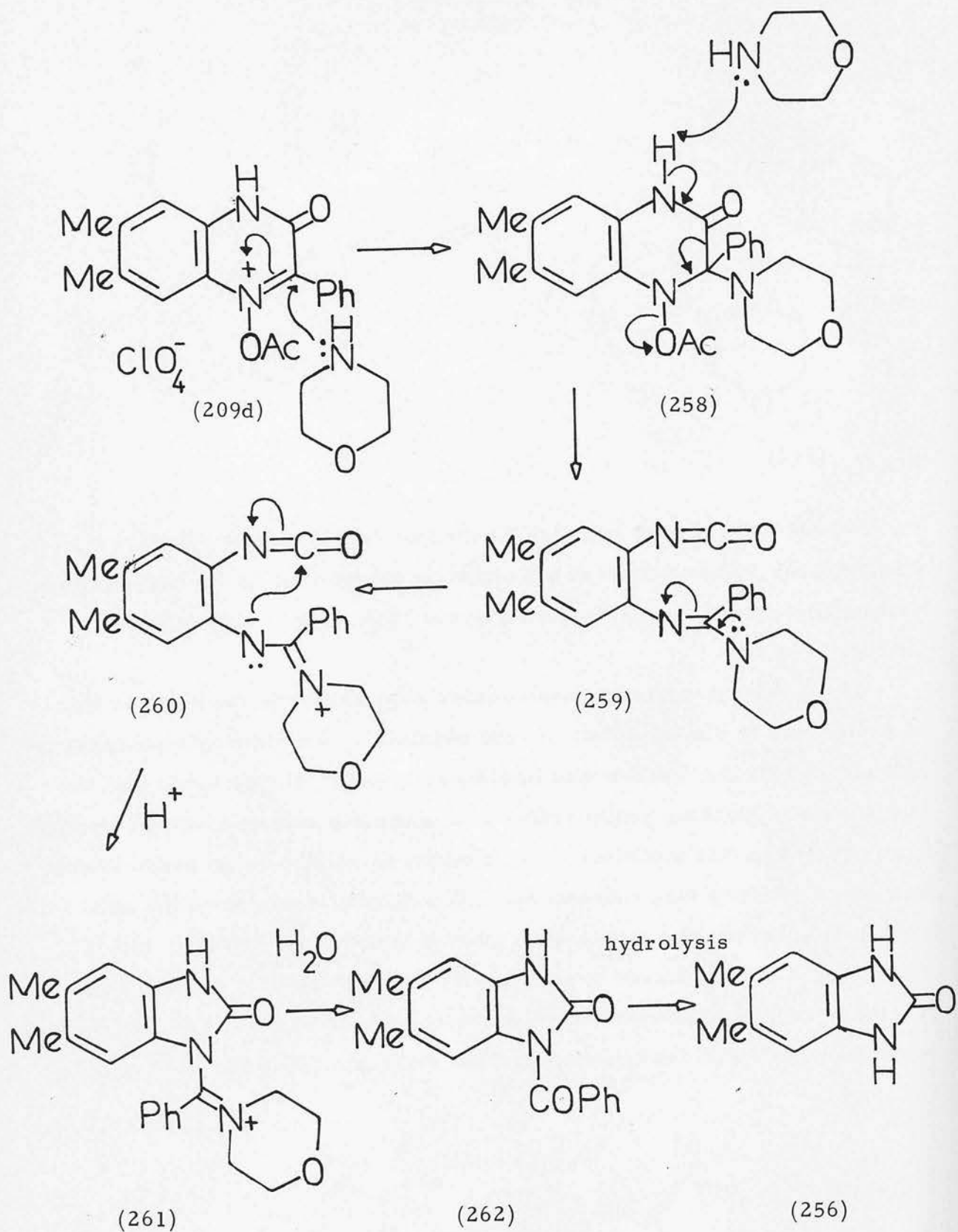
With a view to excluding nucleophilic substitution in the benzene ring in preference to ring contraction, the reaction of the dimethylquinoxalinium salt (209d) with morpholine was next investigated. It was hoped that the presence of a blocking group at C-7 in conjunction with an electron donating group at C-6 in this molecule would completely inhibit nucleophilic attack and hence promote ring contraction. In practice, reaction of the salt (209d) with morpholine gave a good yield of the N-oxide (208d). Again therefore, reaction occurs preferentially at the N-acetoxy group. However, a minor product, which analysed correctly and whose mass spectral features were in accord with the benzimidazolone structure (256) was also obtained.



(256)



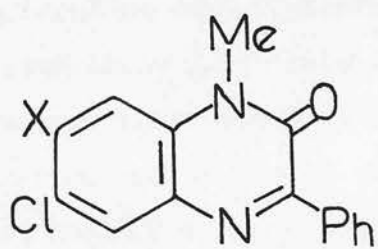
(257)



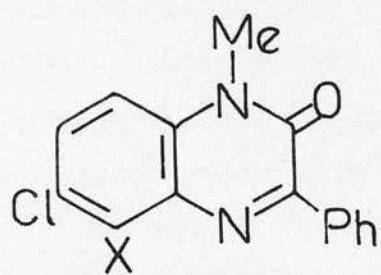
Scheme 41

The i. r. spectrum of this compound contained a broad carbonyl absorption band at  $1660-1690\text{ cm}^{-1}$ , which is slightly lower than would have been expected for the carbonyl absorption of a benzimidazolone nucleus. [e. g. The carbonyl absorption band in a synthetic sample of the benzimidazolone (257) appears at  $1710\text{ cm}^{-1}$ ]. The  $^1\text{H}$  n. m. r. spectrum of the product was consistent with the structure (256), however. Because of the symmetrical nature of the molecule, the aromatic protons showed up as a singlet at  $\delta 6.74$  while the NH protons and methyl substituents gave rise to two singlets at  $\delta 9.94$  and  $\delta 2.12$  respectively. The formation of the benzimidazole (256) is explicable by the mechanism outlined in scheme 41. Thus, proton abstraction from N-1 of the morpholino-adduct (258) gives the isocyanate intermediate (259), ring closure of which [(259)  $\rightarrow$  (260)  $\rightarrow$  (261)] affords the benzimidazolone (261). Hydrolysis of (261) yields the N-benzoylbenzimidazolone (262) which undergoes further hydrolysis to furnish the observed product (256).

In a further attempt to demonstrate ring contraction of perchlorate salts of the type (209), the reaction of the salts [209 (a and b)] with morpholine at  $0^\circ$  was investigated. It was hoped that deprotonation, and hence ring contraction, might compete favourably with substitution at low temperature. This was found partly to be the case. Thus, whereas the reaction of the salt (209a) with morpholine at  $0^\circ$  was akin to the room temperature reaction in giving the 7-morpholinoquinoxalinone (227a) together with the N-oxide (208a), reaction of the chloro-compound (209b) with morpholine at  $0^\circ$  took a course different to that of the room temperature reaction. In this case the products were the 7-morpholinoquinoxalinone (227b) and a new product whose properties were consistent with its being the N-benzoylbenzimidazolone (214). This product was identified by comparison with a sample prepared before. The formation of the benzimidazolone (214) in this reaction may be rationalised by a mechanism analogous to that described before for the formation of the benzimidazolone (256) [cf scheme 41].



(263)



(274)

a ; H  
 b ; Cl  
 c ; AcO  
 d ; EtO  
 e ; OH  
 f ; Br  
 g ; F  
 h ; I  
 i ; N<sub>3</sub>  
 j ; CN  
 k ; PhSO<sub>2</sub>  
 l ; CNO  
 m ; N≡C-S  
 n ; S=C=N  
 o ; Et<sub>2</sub>N

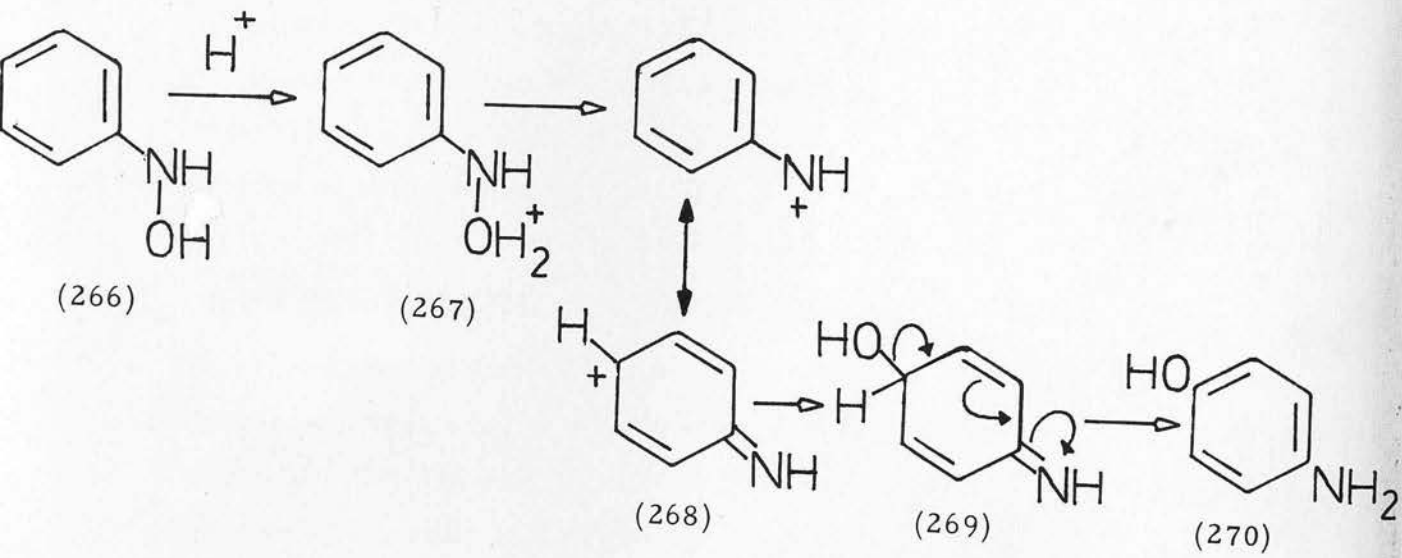
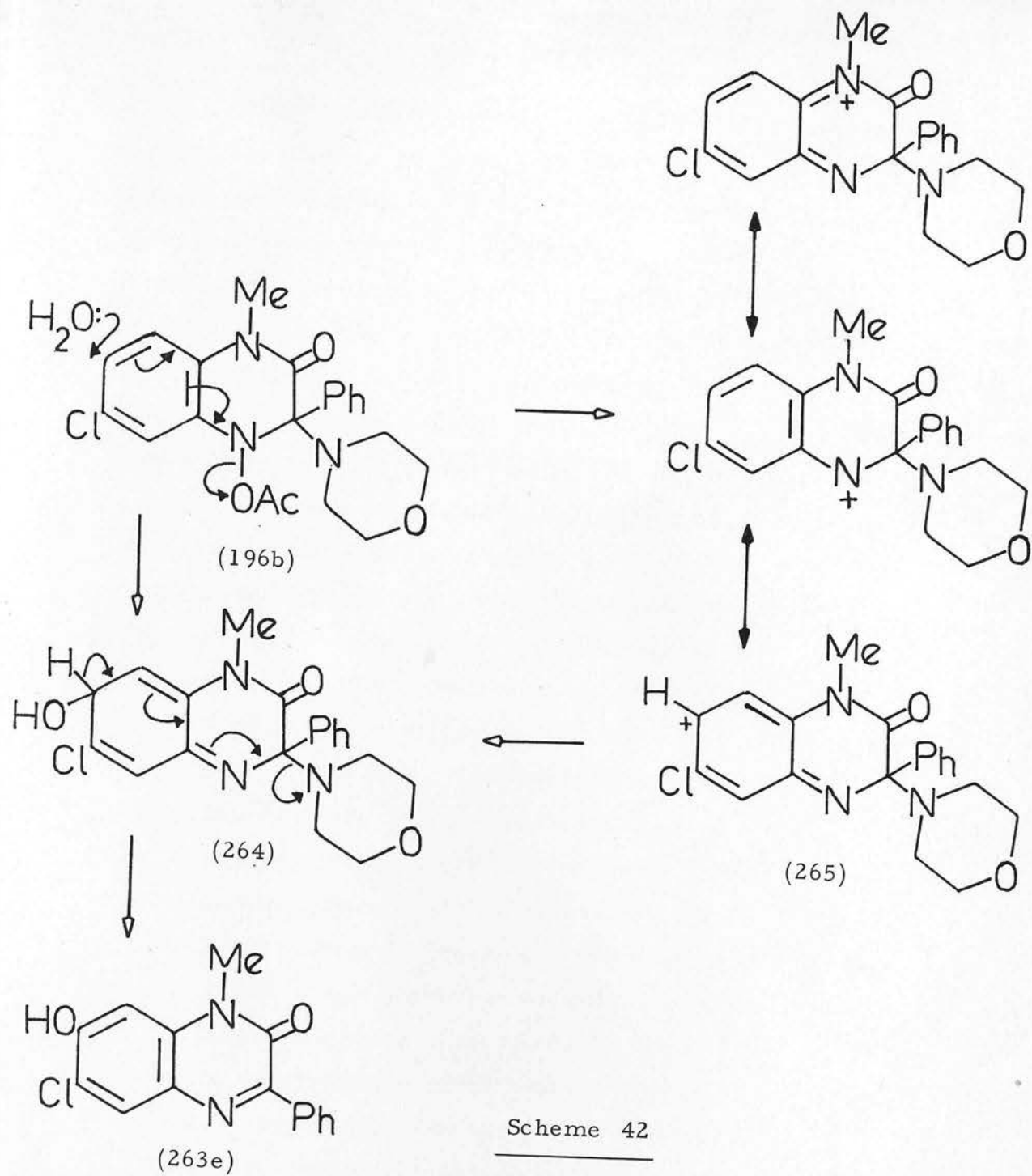
a ; CN  
 b ; PhSO<sub>2</sub>

2.3 The Scope of the Nucleophilic Substitution Reactions of  
4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3phenyl-  
quinoxalin-2(1H)-one (196b)

As previously described, the morpholino-adduct (196b) affords the 6,7-dichloro- and 7-acetoxyquinoxalinones (263b) and (263c) on treatment with aqueous hydrochloric acid and glacial acetic acid at room temperature.<sup>77</sup> The ready nucleophilic substitution in the benzene ring undergone by the adduct (196b) is remarkable in view of the poorly nucleophilic character of the reagents (acetic acid and chloride ion) involved. These reactions appear to be unprecedented. Because of their novelty and potential synthetic utility, it was decided to investigate the scope of reactions of this type.

The adduct (196b) was prepared by treatment of a vigorously stirred suspension of the perchlorate salt (195b) in ether with an ethereal solution of morpholine.<sup>77</sup> As previously mentioned, perchlorate salts of the type (195) have a tendency to decompose in organic solvents and for this reason and because of the inherent instability<sup>77</sup> of the adduct (196b) itself, it proved difficult to consistently prepare (196b) in high yield and yields varied from ca 40%-80%. The compound, which was identified by comparison with an authentic sample,<sup>77</sup> showed a strong absorption band at  $1790\text{ cm}^{-1}$  in its i. r. spectrum, which is characteristic<sup>84</sup> of a cyclic N-acetoxy group. The <sup>1</sup>H n. m. r. spectrum was consistent with the structure (196b).<sup>77</sup> The mass spectrum of (196b), however, did not contain a peak corresponding to the parent ion. The highest peak in the mass spectrum occurred at M-60 which corresponds to loss of the elements of acetic acid from the adduct (196b).<sup>77</sup> Analytical data for the compound (196b) could not be obtained because it was unstable and could not be crystallised. Because of the tendency for the N-acetoxy compound (196b) to undergo nucleophilic substitution by hydroxylic solvents such as ethanol or acetic acid, affording the 7-acetoxy- and 7-ethoxyquinoxalinones (263c) and (263d),<sup>77</sup> reactions with nucleophilic reagents were carried out at room temperature in aqueous dioxan. However, there was always a degree of competition between the nucleophile under consideration and the water present for the adduct (196b) as was demonstrated by a preliminary study of the effect of this solvent system on the adduct (196b) in the absence of another nucleophilic reagent. Thus, the N-acetoxyquinoxalinone (196b) was found to







react with water in aqueous dioxan to give a high yield of the phenol (263e). The phenolic product (263e) was characterised by comparison with an authentic sample. This reaction is remarkable in that it represents the nucleophilic substitution of a benzene nucleus by water (a relatively poor nucleophile) under unusually mild conditions. The formation of the phenol (263e) can be explained by a course (scheme 42) involving synchronous nucleophilic attack at the C-7 position by water and loss of the N-acetoxy leaving group, giving the para-quinonoid intermediate (264). Elimination of morpholine from this intermediate then furnishes the observed product (263e) [cf (196b)  $\rightarrow$  (264)  $\rightarrow$  (263e)]. Alternatively, nucleophilic attack by water might be preceded by ionisation to the resonance stabilised nitrenium ion (265) by elimination of the N-acetoxy group. Nucleophilic attack by water at the 7-position of the intermediate (265) then gives the intermediate (264) which affords the phenol (263e) as described before [cf (196b)  $\rightarrow$  (265)  $\rightarrow$  (264)  $\rightarrow$  (263e); scheme 42]. A resonance stabilised nitrenium ion has been invoked as a possible intermediate<sup>85</sup> in the similar formation of p-aminophenol (270) from phenylhydroxylamine (266) on treatment with dilute sulphuric acid<sup>86</sup> [cf scheme 43], although it is noted that this reaction may also proceed in a concerted manner. Despite the reactivity of the adduct (196b) with water in dioxan it was decided to use this solvent system as the medium for the study of the scope of its reactivity towards nucleophiles in the expectation that the nucleophilic reagent would react faster than water with the adduct. In practice this was found to be the case and in general the reactions of the adduct (196b) with nucleophiles gave the 7-substituted quinoxalinone. The formation of the 7-substituted quinoxalinones (263) in general may be rationalised by the mechanism outlined in scheme 42 to account for the formation of the phenol (263e) and may proceed in either a concerted or stepwise fashion.

#### a) The Attempted Reaction with Sodium Phenoxide

As already mentioned, previous work had shown that the N-acetoxy-quinoxalinone (196b) reacts readily with ethanol to afford the corresponding ether (263d). Consequently it was of interest to see if this reaction could be extended to the synthesis of the corresponding aryl ethers. It was

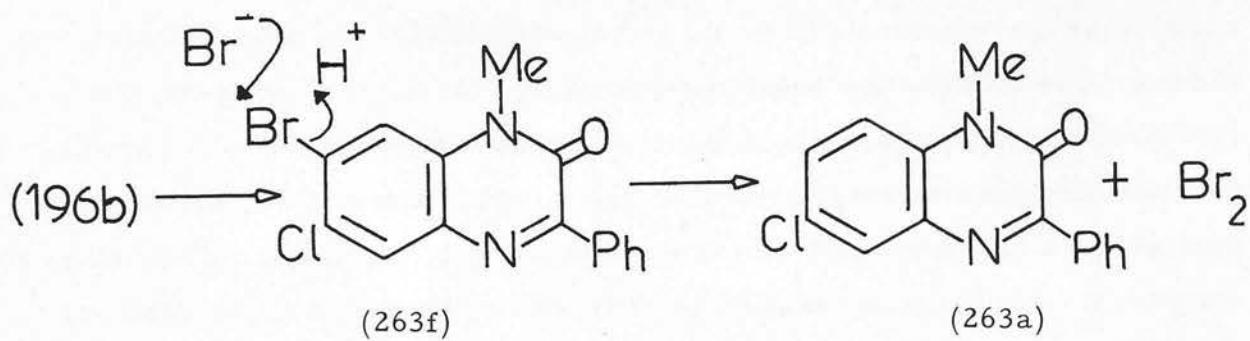
anticipated that phenol itself would not be nucleophilic enough to effect the requisite substitution and consequently the reaction of the N-acetate (196b) with sodium phenoxide in aqueous dioxan was studied. In practice this reaction gave a low yield of the phenol (263e) plus a dark, intractable gum whose t. l. c. showed it to contain numerous components. Formation of the phenol (263e) in this reaction is presumably the result of the reaction of the N-acetate (196b) with the aqueous medium.

#### b) Reaction with Halide Ions

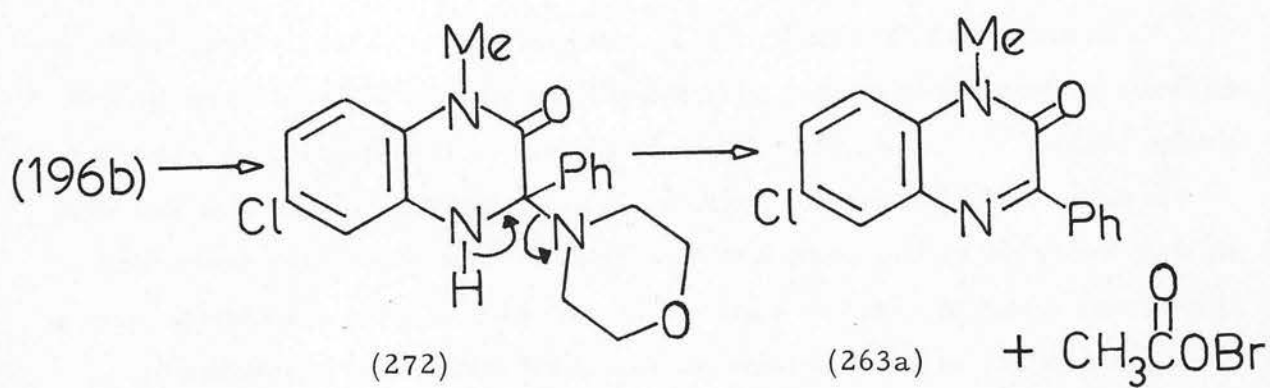
As mentioned previously, the N-acetoxy adduct (196b) reacts with aqueous hydrochloric acid to give a high yield of the 6, 7-dichloroquinoxalinone (263b).<sup>77</sup> It was therefore of interest to investigate the reactivity of the adduct (196b) towards nucleophilic substitution by chloride ion with lithium chloride as the source of the latter. The N-acetoxy compound (196b) was found to react in aqueous dioxan with lithium chloride to give a good yield of the dichloroquinoxalinone (263b) which was identified by comparison with an authentic sample.<sup>73</sup> The parent N-oxide (194b) has been shown to undergo reaction on heating with acetyl chloride to afford the 6, 7-dichloro-compound (263b).<sup>72</sup> Thus the demonstration that the N-acetoxy compound (196b) reacts with chloride ion to give a product (263b) identical to that from the acetyl chloride reaction supports the intermediacy of the non-isolable intermediate (271) in the reaction of the N-oxide (194b) with acetyl chloride [cf scheme 23].



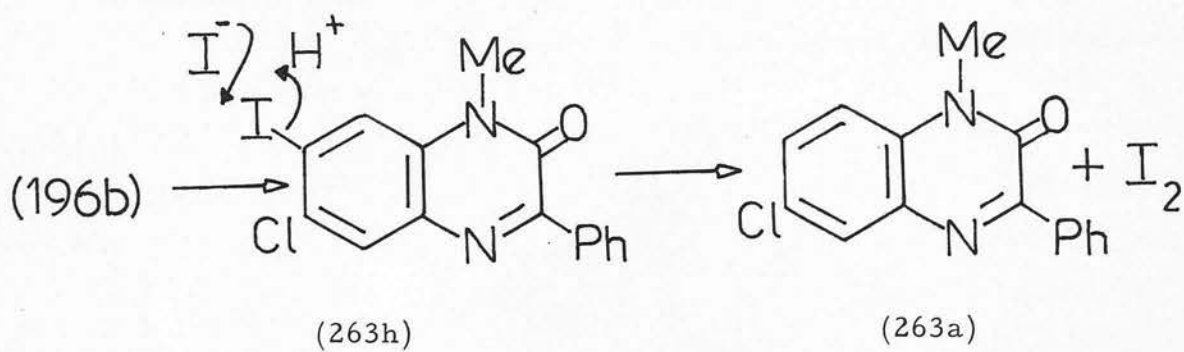
(271)



Scheme 44



Scheme 45



Scheme 46

As a direct extension of these studies, the reactivity of the N-acetate (196b) towards aqueous hydrobromic acid was investigated. The N-acetate (196b) reacted with aqueous 5M hydrobromic acid to give the deoxygenated quinoxalinone (263a). This product was characterised by comparison with an authentic sample.<sup>73</sup> The formation of the quinoxalinone (263a) may be rationalised by formation of the expected bromo-compound (263f), followed by reductive debromination [cf scheme 44]. Alternatively, the reducing action of the hydrogen bromide may be enlisted to promote direct hydrogenolysis followed by elimination of morpholine as shown in scheme 45.

In a further attempt to demonstrate the synthesis of 7-bromoquinoxalinone (263f) and also to gain further insight into the mode of formation of the quinoxalinone (263a) on reaction of the N-acetate (196b) with hydrobromic acid, the reaction of (196b) with lithium bromide was investigated. The N-acetoxy compound (196b) reacted with lithium bromide in aqueous dioxan to afford the bromo-chloroquinoxalinone (263f). The mass spectrum of (263f) showed parent ion peaks at 348, 350 and 352 mass numbers, displaying an isotopic pattern in accord with a molecule containing one chlorine and one bromine atom. The i. r. spectrum contained a strong carbonyl absorption band at  $1670\text{ cm}^{-1}$ , assignable to a quinoxalinone nucleus. Unfortunately, insufficient material was obtained for analytical and  $^1\text{H}$  n. m. r. characterisation of (263f). The fact that lithium bromide reacts with the N-acetate (196b) to give the product (263f) indicates that it is exceedingly unlikely that the quinoxalinone (263a) is formed from the bromo-compound (263f) by debromination by bromide ion [cf scheme 44], since similar debromination would have been expected in the reaction with lithium bromide.

Reaction of the N-acetoxy compound (196b) in aqueous dioxan with lithium fluoride failed to give the corresponding fluorino-derivative (263g). Instead, the product isolated in good yield was the phenol (263e). This result demonstrates that fluoride ion is not a sufficiently good nucleophile<sup>87</sup> to compete favourably with the water present in the reaction mixture in the nucleophilic substitution of the N-acetoxyquinoxalinium salt (196b).

Treatment of the N-acetoxy compound (196b) in aqueous dioxan with

sodium iodide was found to give the compound (263a) in good yield together with a low yield of the phenol (263e). The identity of the quinoxalinone (263a) was established by comparison with an authentic sample.<sup>73</sup> The conversion of the N-acetoxy compound (196b) into the quinoxalinone (263a) was unexpected. However, it is possible that the expected iodo-substitution product (263h) is formed but undergoes subsequent deiodination to the reduced compound (263a) [cf scheme 46].

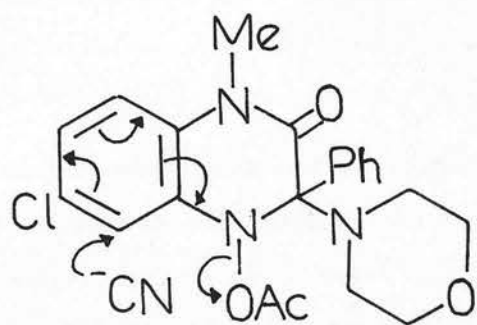
#### c) Reaction with Azide Ion

In accord with its potency as a nucleophile, azide ion (in the form of sodium azide) reacted with the quinoxaline derivative (196b) in aqueous dioxan to give a high yield of 7-azido-1-methyl-3-phenylquinoxalin-2(1H)-one (263i). The phenol (263e) was also isolated as a minor by-product. The azide (263i) was initially isolated as light yellow needles which darkened on standing. It gave analytical and mass spectral data fully consistent with its assigned structure which was further supported by bands at  $2100\text{ cm}^{-1}$  and  $1670\text{ cm}^{-1}$  in its i. r. spectrum attributable to an azido group and a quinoxalinone carbonyl group, respectively. The C-7 position for the azido group was established unambiguously by its  $^1\text{H n.m.r.}$  spectrum. This contained two one proton signals in the aromatic region assignable to the protons at C-5 and C-8. The absence of any splitting in these singlets uniquely defines the orientation of the azidoquinoxalinone as (263i). Any other orientation for the product would result in ortho and meta coupling of the two aromatic hydrogens and hence a more complex splitting pattern.

#### d) Reaction with Cyanide Ion

As might be expected the N-acetoxy compound (196b) reacted with sodium cyanide in aqueous dioxan to yield a minor amount of the phenol (263e) plus a good yield of a product which gave correct analytical and mass spectral data for a mono-cyano derivative. This constitution was also supported by the presence in the i. r. spectrum of the product of cyano absorption at  $2230\text{ cm}^{-1}$ . However, its  $^1\text{H n.m.r.}$  spectrum contained



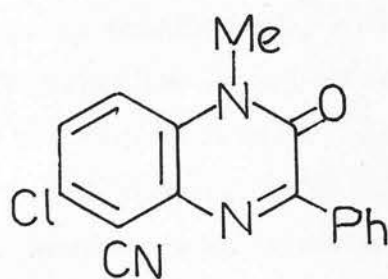


(196b)

stepwise  
or  
concerted



(273)



(274a)

Scheme 47



two three proton singlets at  $\delta$ 4.42 and  $\delta$ 4.02 demonstrating the presence of two isomeric cyanoquinoxalinones. Unfortunately, the aromatic region of the  $^1\text{H}$  n. m. r. spectrum was not sufficiently well resolved to permit the assignment of structures to the components of the isomer mixture, though it is probable that they are the 5- and 7-cyanoquinoxalinones (274a) and (263j), respectively. No attempt was made to resolve the mixture by column chromatography since t. l. c. studies over both silica and alumina in a wide variety of solvents failed to separate the mixture into its two components, presumably because of their chemical similarity. An attempted separation by High Pressure Liquid Chromatography will be undertaken in the near future. The formation of this mixture in high yield from the N-acetoxyquinoxalinone (196b) is in marked contrast to the behaviour of the N-acetoxyquinoxalinium salt (195b) on attempted substitution with sodiumcyanide.<sup>77</sup> This reaction afforded the phenol (263e) as the exclusive product. The formation of the 5-substituted quinoxalinone (274a) is explicable by a course involving nucleophilic attack by cyanide ion at the C-5 position of the adduct (196b) to give the intermediate (273) and thence the product (274a) by loss of the elements of morpholine [cf scheme 47].

#### e) Reaction with Benzenesulphinate Ion

A solution of the N-acetoxy compound (196b) in aqueous dioxan reacted with sodium benzene sulphinate to give a yellow solid in high yield accompanied as usual by the phenol (263e). The yellow product gave analytical and mass spectral data consistent with the benzenesulphinate structure (263k) which was further indicated by the presence of S=O absorption at  $1140\text{ cm}^{-1}$  in its i. r. spectrum. However, as in the case of the product of the reaction of the N-acetate (196b) with cyanide ion, the benzenesulphinate product showed  $^1\text{H}$  n. m. r. absorption at  $\delta$ 4.75 and  $\delta$ 4.62 attributable to two discrete N-methyl groups. It follows that the product must therefore be an isomer mixture, presumably of the 5- and 7-benzenesulphanylquinoxalinones (274b) and (263k). Unfortunately, the aromatic region of the  $^1\text{H}$  n. m. r. spectrum of the product was complex, thus preventing the unambiguous assignment of structures to the



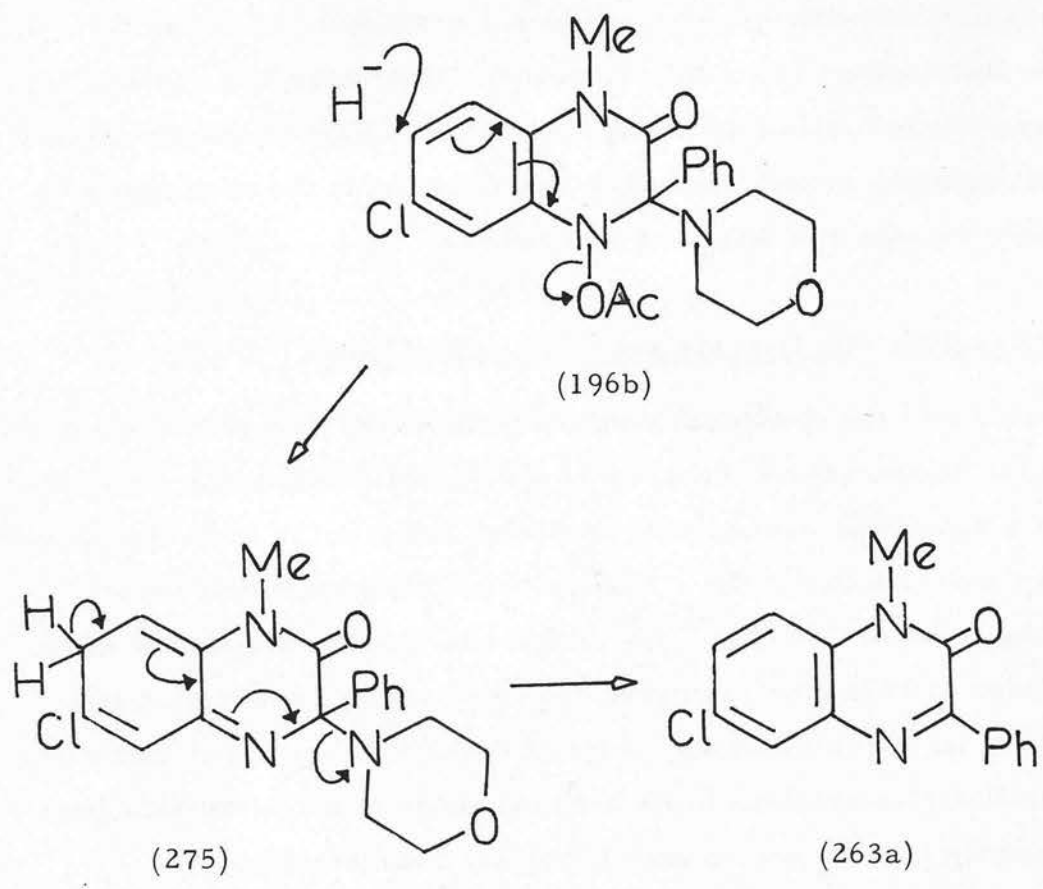
benzenesulphinat isomers present in the mixture. The mixture failed to be resolved in t.l.c. experiments in a variety of organic solvents over both silica and alumina. Again, High Pressure Liquid Chromatography experiments will be conducted in the near future in an attempt to separate this isomer mixture.

f) The Reaction with Cyanate and Thiocyanate Ions

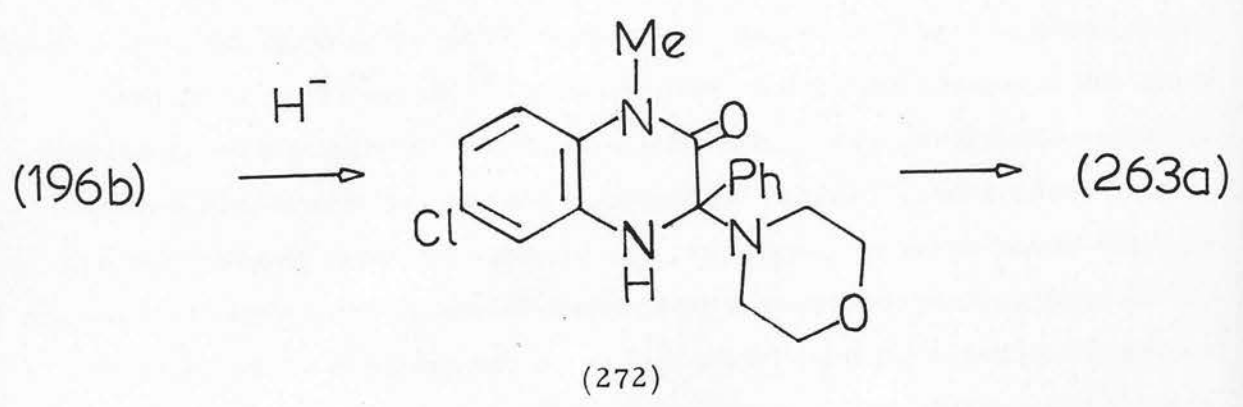
Reaction of the N-acetoxyquinoxalinone (196b) with potassium cyanate in aqueous dioxan gave a low yield of the phenol (263e) and a moderate yield of a compound whose mass spectrum indicated it to be the expected cyanatoquinoxalinone (263l). The i. r. spectrum contained a weak absorption band at  $2250\text{ cm}^{-1}$  attributable to cyanate absorption and a strong band at  $1670\text{ cm}^{-1}$  assignable to the carbonyl absorption in a quinoxalinone. Unfortunately, the attempted purification of this compound by crystallisation resulted in its decomposition to an intractable gum. Consequently it could not be unambiguously characterised.

The N-acetoxy compound (196b) also reacted with the "pseudo-halide" sodium thiocyanate in aqueous dioxan to give a product whose properties were consistent with it being the thiocyanate derivative (263m). Thus it gave an exact mass measurement accurate to within five parts per million of that required for the structure (263m) and its spectrum showed, as well as carbonyl absorption, a band at  $2190\text{ cm}^{-1}$  which can be assigned to the thiocyanate group. However, the product differed in m. p. and i. r. spectrum from the isomeric compound (263n) obtained<sup>77</sup> in the reaction of the corresponding N-acetoxyquinoxalinium salt (195b) with sodium thiocyanate in anhydrous ether. Since it is unlikely that an isothiocyanate would survive under aqueous conditions, the product from the N-acetoxyquinoxalinone (196b) with sodium thiocyanate in aqueous dioxan is tentatively formulated as the thiocyanate (263m), while that from the reaction of the salt with sodium thiocyanate under anhydrous conditions is formulated as the isothiocyanate (263n).

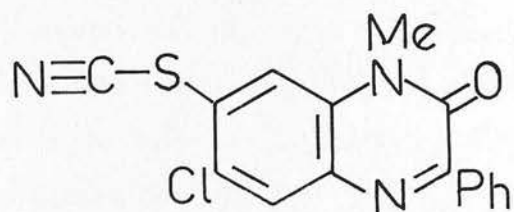




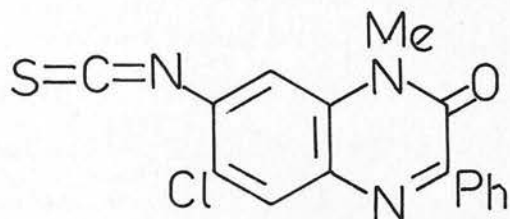
Scheme 48



Scheme 49



(263m)



(263n)

### g) Reaction with Hydride Ion

The N-acetoxy compound (196b) also reacted readily with hydride ion. Thus, reaction at room temperature with sodium borohydride afforded the quinoxalinone derivative (263a) in good yield and again the phenol (263e) was isolated as a minor product. The formation of (263a) from the N-acetate (196b) may be explained in terms of nucleophilic substitution in the fused benzene ring by hydride ion [(196b)  $\rightarrow$  (275)  $\rightarrow$  (263a); scheme 48] or by hydrogenolysis of (196b) to the intermediate (272) and then by elimination of morpholine to (263a) [cf scheme 49].

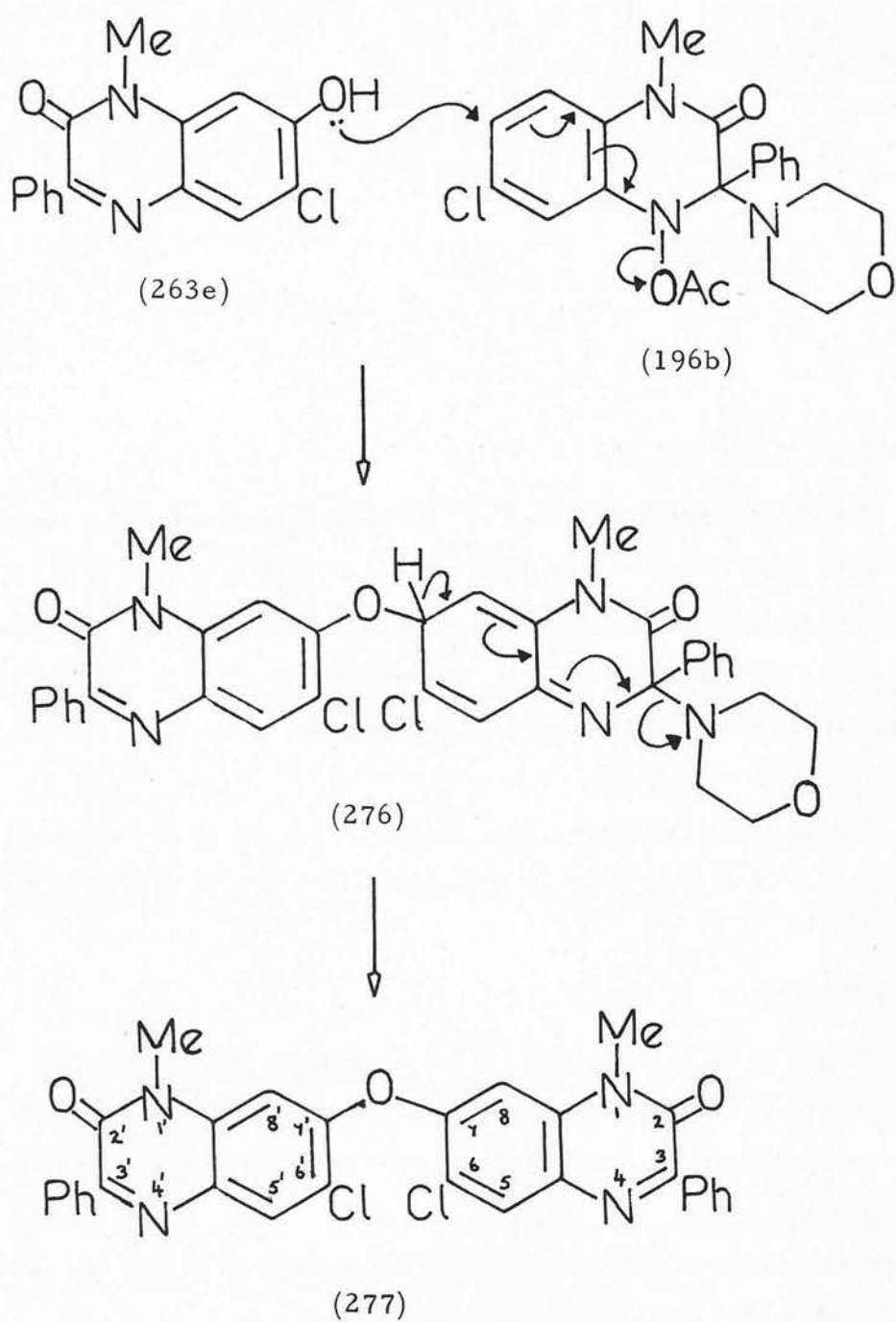
### h) Reaction with Carbanions

Having demonstrated that the N-acetate (196b) reacted readily with a wide variety of nucleophilic reagents it remained to investigate its possible reactivity with carbanionic reagents such as Grignard reagents and metal enolates.

In practice, treatment of the N-acetate (196b) with ethyl magnesium bromide in dry dioxan or with sodium acetylacetonate in aqueous dioxan in both cases gave multicomponent mixtures from which no identifiable material could be isolated.

### i) The Attempted Reaction with Acetate Ion

Whereas the N-acetoxyquinoxalinium perchlorate salt (195b)



Scheme 50



reacted with sodium acetate in anhydrous ether to give a good yield of the 7-acetoxyquinoxalinone (263c),<sup>77</sup> reaction of the N-acetate (196b) in aqueous dioxan took a different course and failed to furnish the expected 7-acetoxy derivative (263c). The product which was isolated from the reaction mixture in lowish yield, together with the phenol (263e), is assigned the structure (277) for reasons which will be discussed at a later stage. The surprising formation of the ether (277) in this reaction is explicable by the mechanistic route outlined in scheme 50, involving nucleophilic attack by the phenol (263e) on the N-acetoxy compound (196b). Thus, nucleophilic attack by the phenol (263e), presumably formed by initial reaction of the N-acetoxy compound (196b) with the aqueous medium, at the C-7 position of (196b) affords, with loss of a proton, the para-quinonoid intermediate (276). Loss of the elements of morpholine from the intermediate (276) then furnishes the observed ether (277). Thus acetate ion apparently fails to compete favourably with water present in the reaction medium for substitution of the N-acetate (196b). It is conceivable that nucleophilic attack by acetate ion does occur to give the 7-acetoxy derivative (263c) which is then further hydrolysed in the course of the reaction to the phenol (263e), however, no evidence that this was the case was obtained.

#### j) The Attempted Reaction with Diethylamine

It has been shown<sup>77</sup> that the N-acetoxyquinoxalinium salt (195b) reacts with diethylamine to give a low yield of the 7-diethylaminoquinoxalinone (263o). In view of the enhanced efficiency of the N-acetate (196b) towards nucleophilic substitution, it was anticipated that it might undergo reaction with amines to afford high yields of the corresponding 7-aminated quinoxalinones. In practice, the N-acetoxyquinoxalinone (196b) reacted with diethylamine in aqueous dioxan to give a low yield of a yellow solid and a dark gum, both of which were intractable, multicomponent mixtures. The nature of these products awaits further experimentation.

k) The Attempted Rearrangement of the N-Acetate (196b) with Boron Trifluoride-etherate.

Having investigated the reactions of the N-acetate (196b) with the wide variety of nucleophilic reagents described above, it was of interest to attempt to induce rearrangement of the quinoxalinone (196b) by removal of the acetoxy group in the absence of a nucleophilic reagent. Towards this end, the N-acetate (196b) was treated in anhydrous dioxan with boron trifluoride-etherate in the hope that this reagent would complex with the acetoxy group resulting in its removal. In practice, the products isolated from this reaction were the ether (277), which was obtained in lowish yield and the phenol (263e). The ether was isolated as light yellow prisms. It gave analytical and mass spectral data fully consistent with its assigned structure which was further supported by bands at  $1660\text{ cm}^{-1}$  and  $1260\text{ cm}^{-1}$  in its i.r. spectrum attributable to quinoxalinone carbonyl absorption and the C-O absorption of a diaryl ether, respectively. The C-7 position for nucleophilic attack was established unambiguously by its  $^1\text{H}$  n. m. r. spectrum. This contained two two proton singlets in the aromatic region assignable, because of the symmetrical nature of the molecule, to protons at C-5 and C-5' and at C-8 and C-8'. The absence of any splitting in these singlets uniquely defines the orientation of the ether as (277) since any other orientation for the product would have reduced the symmetry of the molecule and would have resulted in ortho and meta coupling of the aromatic hydrogens and hence a more complex splitting pattern. In further support of the symmetrical structure (277), the methyl groups at N-1 and N-1' gave rise to a singlet at  $\delta 3.53$ .

The formation of the phenol (263e) and consequently the ether (277) in the presence of boron trifluoride-etherate in anhydrous dioxan is difficult to rationalise. It is possible that the phenol (263e) was formed by reaction of the adduct (196b) with atmospheric moisture absorbed into the reaction mixture during the course of the reaction and the ether (277) then formed by its reaction with the N-acetate (196b). Alternatively, the phenol (263e) and the ether (277) may have been produced during the aqueous work-up. The investigation of the reaction of the adduct (196b)

with boron trifluoride-etherate under more strictly anhydrous conditions awaits further experimentation.

The Rearrangement of 4-N-Acetoxy-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196a) in Sunlight.

The N-acetoxy compound (196a) was prepared by treatment of the salt (195a) with morpholine in dry ether,<sup>77</sup> in the manner previously described for the preparation of the N-acetate (196b). When the compound (196a) was allowed to stand in bright sunlight it was observed to decompose.

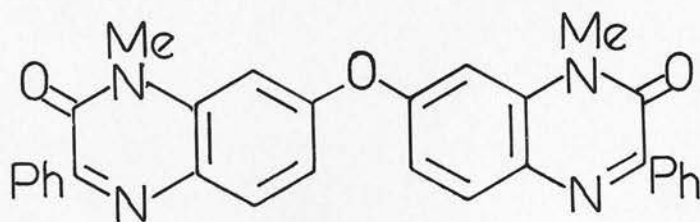


(196a)



(278)

An examination of the product of decomposition showed it to be a mixture of the phenol (278), which was characterised by comparison with an authentic sample<sup>73</sup> and a compound whose properties are consistent with its assigned structure (279). The i. r. spectrum of (279) contained a



(279)

strong absorption band at  $1660\text{ cm}^{-1}$  attributable to carbonyl absorption within a quinoxalinone nucleus. Unfortunately insufficient material was

obtained for a  $^1\text{H}$  n. m. r. spectrum and hence the structure of (279) was not unequivocally determined. Again the formation of the phenol (278) and the ether (279) under these conditions is difficult to rationalise. It is possible that the efficiency of reaction of (196a) with nucleophilic reagents allows the formation of the phenol (278) by reaction of (196a) with atmospheric moisture, the reaction being photolytically catalysed. The formation of the ether (279) is then explicable by a course analogous to that outlined in scheme 50.

## CHAPTER 50

### EXPERIMENTAL SECTION





A. The Synthesis of N-Acetoxyquinoxalinium Perchlorates

General Method<sup>77</sup>

Acetic anhydride (20 ml) was cooled in an ice bath and treated dropwise with stirring with 60% w/v aqueous perchloric acid (0.6 ml) at such a rate that the temperature did not exceed 20°C.

The perchloric acid-acetic anhydride solution was then added dropwise with stirring to an ice cooled suspension of the quinoxaline N-oxide (194) or (208) in glacial acetic acid (3.0 ml) and acetic anhydride (6.0 ml). The resulting red solution was stirred in the ice bath for 1 h and the N-acetoxyquinoxalinium perchlorate (195) or (209) which crystallised from the reaction mixture was collected by filtration, washed thoroughly with dry ether and sucked dry,  $\nu_{\max}$  1845-1830 (cyclic  $\ddot{N}$ . OAc).

The N-acetoxyquinoxalinium perchlorates (195) and (209) were relatively stable in the absence of air and light, but under normal conditions they tended to decompose to intractable brown gums. Consequently, the quinoxalinium perchlorates were used directly in subsequent reactions without purification.

B. Studies on the Reactions of 4-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorates (209) with Bases.

1) The Reaction of 4-Acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b) with Hydroxide Ion.

A vigorously stirred suspension of the perchlorate salt (209b)<sup>77</sup> [freshly prepared from the N-oxide (208b)<sup>88</sup> (2.18 g; 0.008 mol) in dry dioxan (20.0 ml), was treated with a mixture of dry dioxan (5.0 ml) and aqueous 2M sodium hydroxide (5.0 ml). The mixture was stirred at room temperature for 0.5 h and then evaporated. The residue was treated with water to yield the N-oxide (208b) more of which was obtained by acidifying the aqueous mother liquor with aqueous 2M hydrochloric acid (total 0.83 g; 76%), m. p. 297-9° (lit<sup>88</sup> 312-13°) identical (i. r. spectrum) with an authentic sample.<sup>73</sup> Extraction of the acidic aqueous mother liquor



with chloroform yielded a dark gum (0.20 g) which was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture.

2) The Reaction of 4-Acetoxy-6-chloro-1, 2-dihydro-2-oxo-3-phenyl-quinoxalinium Perchlorate (209b) with Triethylamine

A vigorously stirred suspension of the perchlorate salt (209b)<sup>77</sup> [freshly prepared from the N-oxide (208b)<sup>88</sup> (2.18 g, 0.008 mol)] in dry ether (40.0 ml) was treated dropwise with a solution of the triethylamine (2.02 g) in dry ether (10.0 ml). The mixture was stirred at room temperature for 0.5 h, then filtered and the residue was washed with water to give the N-oxide (208b) (0.93 g; 43%), m. p. 305-7° (lit<sup>88</sup> 312-13°), identical (i. r. spectrum) with an authentic sample.<sup>73</sup> The ether filtrate was evaporated and the residue was treated with water (4.0 ml) and extracted into chloroform. Evaporation of the chloroform extract and trituration of the residue with ether gave a second crop of N-oxide (208b) (0.30 g; 14%), identical (m. p. and i. r. spectrum) with an authentic sample.<sup>73</sup> Evaporation of the ether mother liquor and further trituration of the residue with ether gave a yellow solid (0.15 g) which crystallised as pale yellow needles, m. p. 135-7° (from light petroleum-ethanol),  $\nu_{\max}$  1770, 1740 and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.16-7.20 (m, ArH), 2.68 (s) and 2.60 (s).

Found: C, 58.4; H, 3.6; N, 9.9%; M<sup>+</sup> 314, 316.

Evaporation of the ether mother liquor gave a brown gum (0.29 g) which was shown by t. l. c. in ethyl acetate over silica to be an unresolvable multicomponent mixture.

3) The Reaction of 4-Acetoxy-6-chloro-1, 2-dihydro-2-oxo-3-phenyl-quinoxalinium Perchlorate (209b) with Water.

A vigorously stirred suspension of the perchlorate salt (209b)<sup>77</sup> [freshly prepared from the N-oxide (208b)<sup>88</sup> (1.09 g; 0.004 mol)] in dry dioxan (20.0 ml) was treated dropwise with a mixture of water (5.0 ml) and dioxan (5.0 ml). The mixture was stirred at room temperature for 0.5 h, then evaporated and the residual gum was treated with methanol to

give a yellow solid, m. p.  $215-18^{\circ}$ ,  $\nu_{\max}$  1755 and 1650 (CO)  $\text{cm}^{-1}$ . An attempt to crystallise this solid for elemental analysis gave 1-benzoyl-6-chlorobenzimidazol-2-one (214) (0.42 g; 36%), m. p.  $210-11^{\circ}$  (from ethanol),  $\nu_{\max}$  3200 w (NH) and 1730 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [ $(\text{CD}_3)_2\text{SO}$ ] 7.85-7.45 (6H, m, ArH), 7.25 (1H, dd,  $J_{\text{ortho}}$  8Hz,  $J_{\text{meta}}$  2Hz, H-5) and 7.08 (1H, d,  $J_{\text{ortho}}$  8Hz, H-4).

Found: C, 61.8; H, 3.3; N, 10.2%;  $M^+$  272, 274.

$\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}_2$  requires: C, 61.7; H, 3.3; N, 10.3%;  $M$  272.5

Evaporation of the methanolic mother liquor and trituration of the residue with ethyl acetate gave 6,8-dichloro-7-hydroxyquinoxalin-2(1H)-one (215) (0.15 g; 10%), m. p.  $260-3^{\circ}$ , identical (i. r. spectrum) with a sample prepared later. The ethyl acetate mother liquor was evaporated to give a dark gum (0.24 g) which was shown by t. l. c. in ether over alumina to be an unresolvable multicomponent mixture.

### 3a) The Attempted Repetition of the Reaction of 4-Acetoxy-6-chloro-1, 2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b) with Water.

A vigorously stirred suspension of the perchlorate salt (209b)<sup>77</sup> [freshly prepared from the N-oxide (208b)<sup>88</sup> (1.09 g; 0.004 mol)] in dry dioxan (20.0 ml) was treated dropwise with a mixture of water (5.0 ml) and dioxan (5.0 ml). The mixture was stirred at room temperature for 0.5 h, then evaporated and the residual gum treated with methanol to give 6,8-dichloro-7-hydroxyquinoxalin-2(1H)-one (215) (0.22 g; 14%), m. p.  $261-3^{\circ}$ , identical (i. r. spectrum) with an authentic sample. Evaporation of the methanolic mother liquor gave an intractable black gum which was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture.

### 4) The Reactions of 4-Acetoxy-1, 2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorates (209) with Morpholine at Room Temperature.

#### General Method

A vigorously stirred suspension of the quinoxalinium perchlorate (209)

[freshly prepared from 0.008 mol of the corresponding N-oxide (208)] in dry ether (40.0 ml) was treated dropwise with a solution of morpholine (1.6 ml) in dry ether (10.0 ml). The mixture was stirred at room temperature for 0.5 h, then filtered to remove insoluble solid and further worked up as described for the individual reactions.

a) The insoluble solid from 4-Acetoxy-1, 2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209a) was washed with water and extracted with boiling ethanol. Crystallisation of the insoluble material gave 7-morpholino-3-phenylquinoxalin-2(1H)-one (227a) (1.04 g; 42%) as yellow plates, m. p. 339-40<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3150 w (NH) and 1645 (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.38-8.22 (2H, m, ArH), 7.62 (1H, d, J<sub>ortho</sub> 8Hz, H-5), 7.47-7.35 (3H, m, ArH), 6.95 (1H, dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-6), 6.66 (1H, d, J<sub>meta</sub> 2Hz, H-8), 3.82-3.67 (4H, m, CH<sub>2</sub>) and 3.32-3.19 (4H, m, CH<sub>2</sub>).

Found: C, 70.0; H, 5.5; N, 13.8%; M<sup>+</sup> 307.

C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 70.3; H, 5.6; N, 13.7%; M 307.

Evaporation of the ethanol mother liquor and trituration of the residue with ethyl acetate gave the N-oxide (209a) (0.35 g; 18%), m. p. 279-80<sup>o</sup> (lit<sup>89</sup> 285<sup>o</sup>), identical (i. r. spectrum) with an authentic sample.<sup>89</sup>

Evaporation of the ethylacetate mother liquor gave a gum (0.21 g) whose t. l. c. in chloroform over alumina showed it to be an unresolvable multi-component mixture.

b) The insoluble solid from 4-Acetoxy-6-chloro-1, 2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b)<sup>77</sup> was washed with water to give 6-chloro-7-morpholino-3-phenylquinoxalin-2(1H)-one (227b) (1.29 g; 67%) which formed yellow prisms, m. p. 319-20<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3150 w (NH) and 1645 (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.38-8.21 (2H, m, ArH), 7.79 (1H, s, H-5), 7.54-7.39 (3H, m, ArH), 7.95 (1H, s, H-8), 3.85-3.72 (4H, m, CH<sub>2</sub>) and 3.19-3.00 (4H, m, CH<sub>2</sub>).

Found: C, 62.8; H, 4.7; N, 12.0%; M<sup>+</sup> 341, 343.

C<sub>18</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub> requires: C, 63.2; H, 4.7; N, 12.3%; M 341.5.

The ethereal mother liquor was evaporated and treated with ether and

water leaving an insoluble solid which was crystallised to afford the bis-morpholino compound (239)/(241) as yellow needles (0.51 g; 14%), m.p. 167-8° (from ethanol),  $\nu_{\max}$  3340 (NH) and 1650 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.76 (1H, d, J<sub>ortho</sub> 8Hz, H-8), 7.75 (1H, s, NH), 7.41-7.13 (5H, m, ArH), 6.69 (1H, dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-7), 6.05 (1H, d, J<sub>meta</sub> 2Hz, H-5), 3.74-3.60 (8H, m, CH<sub>2</sub>) and 3.56-3.38 (8H, m, CH<sub>2</sub>). Irradiation of the double doublet at  $\delta$  6.69 caused the doublets at  $\delta$  7.76 and  $\delta$  6.05 to collapse to singlets and the signal at  $\delta$  7.75 moved downfield to  $\delta$  7.90 on irradiation at  $\delta$  6.69. Irradiation of the doublet at  $\delta$  6.05 caused the double doublet at  $\delta$  6.69 to collapse to a doublet.

Found: C, 61.7; H, 5.8; N, 12.9%; M<sup>+</sup> 428, 30.

C<sub>22</sub>H<sub>25</sub>ClN<sub>4</sub>O<sub>3</sub> requires: C, 61.6; H, 5.9; N, 13.1%; M 428.5.

Evaporation of the ethereal extract and trituration of the residue with light petroleum-ethyl acetate gave 1-benzoyl-6-chloro-2-morpholinobenzimidazole (253) (0.32 g; 17%) which crystallised as pale yellow needles, m.p. 188-9° (from ethanol),  $\nu_{\max}$  1750 and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CO<sub>3</sub>)<sub>2</sub>SO] 7.89-7.41 (3H, m, ArH), 3.49-3.31 (4H, m, CH<sub>2</sub>) and 3.19-3.01 (4H, m, CH<sub>2</sub>).

Found: C, 62.9; H, 4.7; N, 12.1%; M<sup>+</sup> 341, 3.

C<sub>18</sub>H<sub>16</sub>ClN<sub>3</sub>O<sub>2</sub> requires: C, 63.2; H, 4.7; N, 12.3%; M 341.5.

c) The insoluble solid from 4-Acetoxy-6-methyl-1, 2-dihydro-2-oxo-3-phenyl-quinoxalinium Perchlorate (209c) was washed with water to give the N-oxide (208c) (1.88 g; 94%), m.p. 292-4°, (lit<sup>73</sup> 296°), identical (i. r. spectrum) with an authentic sample.<sup>73</sup> The ethereal filtrate was evaporated and the residual gum was treated with water and ether leaving the bis-morpholine compound (254)/(255) as a yellow, amorphous solid (0.25 g; 6%), m.p. 154-5° (from light petroleum-toluene),  $\nu_{\max}$  3100 w (NH) and 1640 (CO)  $\text{cm}^{-1}$ .

Found: C, 67.9; H, 6.9; N, 13.4%; M<sup>+</sup> 408.

C<sub>23</sub>H<sub>28</sub>N<sub>4</sub>O<sub>3</sub> requires: C, 67.6; H, 6.9; N, 13.7%; M 408.

Evaporation of the ether extract gave a negligible quantity of gum.



d) The insoluble solid from 4-Acetoxy-6,7-dimethyl-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209d)<sup>77</sup> was washed with water to afford the N-oxide (208d) (1.65 g; 76%), m. p. 278-81° (lit.<sup>73</sup> 286°), identical (i. r. spectrum) with an authentic sample.<sup>73</sup> Evaporation of the ethereal filtrate and trituration of the residue with ether gave 5,6-dimethyl-benzimidazol-2-one (256) (0.12 g; 9%), which crystallised as yellow prisms, m. p. 320-2° (from glacial acetic acid),  $\nu_{\max}$  3160 br (NH) and 1660-90 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 9.94 br (2H, s, NH), 6.74 (2H, s, ArH) and 2.12 (6H, s, ArMe).

Found: C, 66.5; H, 6.2; N, 17.0%;  $M^+$  162.

C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O requires: C, 66.7; H, 6.2; N, 17.3%; M 162.

Evaporation of the ether mother liquor gave a negligible quantity of gum.

#### 5. The Reaction of the 4-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorates (209a and b) with Morpholine at 0°.

##### General Method

A vigorously stirred suspension of the quinoxalinium perchlorates (209a or b)<sup>77</sup> [freshly prepared from 0.004 mol of the corresponding N-oxides (208a or b)] in dry ether (20.0 ml) at 0° was treated dropwise with a solution of morpholine (0.8 ml) in dry ether (5.0 ml). The mixture was stirred at 0° for 10 min, then filtered to remove insoluble solid and further worked up as described for the individual reactions.

a) The insoluble solid from 4-Acetoxy-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209a)<sup>77</sup> (1.80 g) was crystallised from glacial acetic acid to afford 7-morpholino-8-phenylquinoxalin-2(1H)-one (227a) which was combined with an identical crop obtained by evaporation of the ethereal mother liquor (total 0.80 g; 33%), m. p. 333-4°, identical (i. r. spectrum) with an authentic sample. Evaporation of the acetic acid mother liquor and trituration of the residue with ether gave the N-oxide (208a) (0.65 g; 34%), m. p. 284-5° (lit.<sup>89</sup> 285°), identical (i. r. spectrum) with an authentic sample. The ether mother liquor was evaporated to give a

dark gum (0.37 g) which was shown by t.l.c. in ether over silica to be an unresolvable multicomponent mixture.

b) The insoluble solid from 4-Acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b)<sup>77</sup> was washed with water and extracted with boiling ethanol to give 6-chloro-7-morpholino-3-phenylquinoxalin-2(1H)-one (227b) (0.64 g; 47%), m.p. 317-18<sup>o</sup>, identical (i.r. spectrum) with an authentic sample.

Evaporation of the ethanol extract and trituration of the residue with toluene gave 1-benzoyl-6-chlorobenzimidazol-2-one (214) (0.19 g; 17%), identical (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the toluene mother liquor gave a negligible quantity of gum.

#### 6. The Rearrangement of 4-Acetoxy-6-chloro-1,2-dihydro-2-oxo-3-phenylquinoxalinium Perchlorate (209b) in Dioxan.

A suspension of the perchlorate salt (209b)<sup>77</sup> [freshly prepared from the N-oxide (208b)<sup>88</sup> (1.09 g; 0.004 mol)] was stirred at room temperature in dry dioxan (20.0 ml) for 0.5 h. The mixture was evaporated under reduced pressure and the residual black gum was triturated with ether-ethyl acetate to yield 6,8-dichloro-7-hydroxyquinoxalin-2(1H)-one (215) (0.23 g; 18%), which crystallised as golden prisms, m.p. 263-4<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3060 w (NH) and 1635 (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.28-8.17 (2H, m, ArH), 7.76 (1H, s, C-5) and 7.49-7.36 (3H, m, ArH).

Found: C, 54.2; H, 2.6; N, 8.9%; M<sup>+</sup> 306, 308, 310.

C<sub>14</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub> requires; C, 54.7; H, 2.6; N, 9.1%; M 307.

Evaporation of the ether-ethyl acetate mother liquor gave an intractable black gum which was shown by t.l.c. in ether over silica to be an unresolvable multicomponent mixture.



C. The Synthesis of the 4-N-Acetoxy-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-ones (196a and b)

General Method

A stirred suspension of the perchlorate salts (195a or b) [freshly prepared from 0.008 mol of the corresponding N-oxides (194a or b)] in dry ether (40.0 ml), was treated in a dropwise manner, at room temperature, with a solution of morpholine (1.6 ml; 0.018 mol) in dry ether (10.0 ml). The suspension was stirred at room temperature for 0.5 h and the solid was collected and washed with water (5.0 ml) to give the corresponding morpholine-adduct (196a or b). The ether mother liquor was evaporated at room temperature and the residue was further worked up as described for the individual reactions.

- 1) 4-Acetoxy-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (195a)<sup>77</sup> reacted with morpholine to give 4-N-acetoxy-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196a) (1.24 g; 46%), m. p. 83-5° (lit<sup>77</sup> 86°), identical (i. r. spectrum) with an authentic sample.<sup>77</sup> The residue from the ether mother liquor was treated with water (5.0 ml) and extracted with chloroform to give a dark gum (0.43 g) which was shown by t. l. c. in chloroform over alumina to be an unresolvable multicomponent mixture. This was not further investigated.
- 2) 4-Acetoxy-6-chloro-1-methyl-2-oxo-3-phenylquinoxalinium Perchlorate (195b)<sup>77</sup> reacted with morpholine to give 4-N-acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) which was combined with a second crop obtained by trituration of the residue from the ethereal mother liquor with ethyl acetate (total 2.45 g; 74%), m. p. 97-9° (lit<sup>77</sup> 108°), identical (i. r. spectrum) with an authentic sample. Evaporation of the ethyl acetate mother liquor gave a dark gum (0.05 g) which was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture. Extraction of the aqueous washings with chloroform gave 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (263e) (0.20 g; 9%), m. p. 255-8° (lit<sup>77</sup> 261°), identical (i. r. spectrum) with an authentic sample.<sup>77</sup>

D. Nucleophilic Substitution Reactions of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b)

1) The reaction of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) with Water.

A solution of the N-acetoxy compound (196b) (0.10 g; 0.0003 mol) in redistilled dioxan (5.0 ml) and water (1.7 ml) was stirred at room temperature for 3 h. Evaporation of the mixture and trituration of the residue with ether gave 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (263e) (0.05 g; 83%), m. p. 260-1° (lit<sup>77</sup> 261°), identical (i. r. spectrum) with an authentic sample.<sup>77</sup> Evaporation of the ether mother liquor gave a negligible quantity of a gum.

2) The Reaction of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) with Nucleophilic Reagents.

General Method

A stirred solution of the N-acetoxy compound (196b) (0.42 g; 0.001 mol) in redistilled dioxan (20.0 ml) and water (7.5 ml) was treated dropwise with a saturated aqueous solution of the nucleophilic reagent (0.004 mol). The mixture was stirred at room temperature for 3 h, then evaporated and the residue (A) was washed with water (5.0 ml) and aqueous 2M sodium hydroxide (4.0 ml), unless otherwise specified. The alkaline washings were acidified with aqueous 2M hydrochloric acid to give 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (263e) (7-71%), m. p. 255-60° (lit<sup>77</sup> 261°), identical (i. r. spectrum) with an authentic sample.<sup>77</sup> The residue (A) was further worked up as described for the individual reactions below.

a) Reaction with Phenoxide Ion

The N-acetoxy compound (196b) reacted with sodium phenoxide to give a residue (A) which was washed with water only and extracted into chloroform to give a dark gum (0.29 g). This was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture.

b) Reaction with Chloride Ion

The N-acetoxy compound (196b) reacted with lithium chloride to give (A) 6,7-dichloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263b) (81%) as an amorphous, yellow solid, m. p. 168-70° (lit<sup>73</sup> 171°), identical (i. r. spectrum) with an authentic sample.<sup>73</sup>

c) Reaction with Bromide Ion

The N-acetoxy compound (196b) reacted with lithium bromide to give (A) 7-bromo-6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263f) (77%) as an amorphous, yellow solid, m. p. 265-70° (from dimethylformamide-water),  $\nu_{\max}$  3100 w (NH) and 1670 (CO)  $\text{cm}^{-1}$ .

M<sup>+</sup> found: 348, 350, 352

C<sub>15</sub>H<sub>10</sub>BrClN<sub>2</sub>O requires: 349.5.

Insufficient material was obtained for elemental analysis and <sup>1</sup>H n. m. r. spectrum.

d) Reaction with Iodide Ion

The N-acetoxy compound (196b) reacted with sodium iodide to give (A) 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263a) (0.19 g; 70%), m. p. 159-60° (lit<sup>73</sup> 162°), identical (i. r. spectrum) with an authentic sample.

e) Reaction with Fluoride Ion

The N-acetoxy compound (196b) reacted with lithium fluoride to give only inorganic material (A) and a high yield of 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (263e) identical (m. p. and i. r. spectrum) with an authentic sample.

f) Reaction with Azide Ion

The N-acetoxy compound (196b) reacted with sodium azide to give 7-azido-6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263i) (0.23 g; 71%). This formed yellow needles which darkened on standing, m. p. 177-80° (from glacial acetic acid),  $\nu_{\max}$  2100 (N≡N) and 1670 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.34-8.19 (2H, m, ArH), 7.96 (1H, s, H-5), 7.58-7.50 (3H, m, ArH), 7.48 (1H, s, H-8) and 3.7 (3H, s, NMe).

Found: C, 58.0; H, 3.2; N, 22.3%;  $M^+$  311, 313.

$C_{15}H_{10}ClN_5O$  requires: C, 57.8; H, 3.6; N, 22.5%;  $M^+$  311.5.

g) Reaction with Cyanide Ion

The N-acetoxy compound (196b) reacted with sodium cyanide to give an unresolved mixture (A) of 6-chloro-5-cyano-1-methyl-3-phenylquinoxalin-2(1H)-one (274a) and 6-chloro-7-cyano-1-methyl-3-phenylquinoxalin-2(1H)-one (263j) (0.24 g; 82%), m. p. 188-90° (from glacial acetic acid),  $\nu_{\max}$  2230 w (CN) and 1660 (CO)  $cm^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.67-8.47 (8H, m, ArH), 7.95-7.80 (6H, m, ArH), 4.42 (3H, s, NMe) and 4.02 (3H, s, NMe).

Found: C, 64.7; H, 3.4; N, 14.1%;  $M^+$  295, 297.

$C_{16}H_{10}ClN_3O$  requires: C, 65.0; H, 3.4; N, 14.2%;  $M^+$  295.5.

Attempts to separate the isomer mixture (A) by t.l.c. in a variety of organic solvents over silica and alumina proved unsuccessful.

h) Reaction with Benzenesulphinate Ion

The N-acetoxy compound (196b) reacted with sodium benzenesulphinate to give an unresolved mixture (A) of 6-chloro-5-benzenesulphinyl-1-methyl-3-phenylquinoxalin-2(1H)-one (274b) and 6-chloro-7-benzenesulphinyl-1-methyl-3-phenylquinoxalin-2(1H)-one (263k) (0.35 g; 85%), which crystallised as pale yellow needles, m. p. 208-11° (from glacial acetic acid),  $\nu_{\max}$  1650(CO) and 1140 (S=O)  $cm^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.30-7.32 (24H, m, ArH), 4.75 (3H, s, Me) and 4.62 (3H, s, NMe).

Found: C, 61.1; H, 3.7; N, 7.0%;  $M^+$  410, 412.

$C_{21}H_{15}ClN_2O_3S$  requires: C, 61.4; H, 3.7; N, 6.8%;  $M^+$  410.5.

i) Reaction with Cyanate Ion

The N-acetoxy compound (196b) reacted with potassium cyanate to give 6-chloro-7-cyanato-1-methyl-3-phenylquinoxalin-2(1H)-one (263l) (0.10 g; 37%), m. p. 198-200°,  $\nu_{\max}$  2250 (C=N=O) and 1670 (CO)  $cm^{-1}$ .

$M^+$  found: 311, 313.

$C_{16}H_{10}ClN_3O_2$  requires: 311.5.



Attempted crystallisation of the cyanate (2631) resulted in its conversion into an intractable gum.

j) Reaction with Thiocyanate Ion

The N-acetoxy compound (196b) reacted with sodium thiocyanate to give 6-chloro-1-methyl-3-phenyl-7-thiocyanatoquinoxalin-2(1H)-one (83%) as an amorphous, yellow solid, m. p. 143-5<sup>o</sup> (from glacial acetic acid-water),  $\nu_{\max}$  2190 (CN) and 1660 (CO) cm<sup>-1</sup>. Insufficient material was obtained for a <sup>1</sup>H n. m. r. spectrum.

Found: C, 58.5; H, 3.4; N, 11.6%; M<sup>+</sup> 327, 329.

C<sub>16</sub>H<sub>10</sub>ClN<sub>3</sub>OS requires: C, 58.6; H, 3.1; N, 12.8%; M 327.5.

Exact Mass Measurement

Found: 327.022081.

Found: 329.018705.

C<sub>16</sub>H<sub>10</sub>Cl<sup>35</sup>N<sub>3</sub>OS requires: 327.023308. C<sub>16</sub>H<sub>10</sub>Cl<sup>37</sup>N<sub>3</sub>OS requires: 329.020358.

error < 4 p. p. m.

error < 5 p. p. m.

k) Reaction with Acetylacetonate Ion

The N-acetoxy compound (196b) reacted with sodium acetylacetonate to give a yellow solid (0.27 g), m. p. 110-15<sup>o</sup> (decomp), whose t. l. c. in ether showed it to be a multicomponent mixture.

l) Reaction with Hydride Ion

The N-acetoxy compound (196b) reacted with sodium borohydride to give 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263a) (0.22 g; 84%), m. p. 161-2<sup>o</sup> (lit<sup>73</sup> 162<sup>o</sup>), identical (i. r. spectrum), with an authentic sample.

m) Reaction with Acetate Ion

The N-acetoxy compound (196b) reacted with sodium acetate to give di-(6-chloro-1,2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl) ether (277) (0.10 g; 18%), m. p. 280-2<sup>o</sup>, identical (i. r. spectrum) with an authentic sample.

n) Reaction with Diethylamine

The N-acetoxy compound (196b) reacted with diethylamine to give a residue (A) which was triturated with chloroform to yield a yellow solid (0.14 g). This melted over a wide range (190-260<sup>o</sup>) and its t.l.c. in ether over silica showed it to be a multicomponent mixture. Evaporation of the chloroform mother liquor gave an intractable gum (0.26 g) which was also shown by t.l.c. in toluene over silica to be a multicomponent mixture.

3) The Reaction of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) with Hydrobromic Acid.

A suspension of the N-acetoxy compound (196b) (0.21 g; 0.0005 mol) in aqueous 5M hydrobromic acid (2.5 ml) was stirred at room temperature for 15 min. The mixture was filtered and the residue was washed with aqueous sodium hydrogen carbonate to give 6-chloro-1-methyl-3-phenylquinoxalin-2(1H)-one (263a) (0.11 g; 84%), m.p. 159-60<sup>o</sup> (lit<sup>73</sup> 162<sup>o</sup>), identical (i. r. spectrum) with an authentic sample. The filtrate was acidified with aqueous 2M hydrochloric acid and extracted with chloroform to give a negligible quantity of gum.

4) The Reaction of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) with Ethyl Magnesium Bromide.

A stirred solution of the N-acetoxy compound (196b) (0.42 g; 0.001 mol) in redistilled dioxan (20.0 ml) was treated under nitrogen with ethyl magnesium bromide (0.53 g; 0.004 mol) [prepared from the reaction of ethyl bromide with magnesium in dry ether under nitrogen<sup>90</sup>]. The mixture was stirred at room temperature under nitrogen for 3 h and then diluted with water (20.0 ml). An exothermic reaction occurred and the yellow mixture turned deep red. Stirring was continued at room temperature for 15 min and the mixture was then extracted into chloroform to give a gum (0.07 g) which was shown by t.l.c. in chloroform over alumina to be an unresolvable multicomponent mixture



E. The Attempted Rearrangement of 4-N-Acetoxy-6-chloro-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196b) using Boron Trifluoride-etherate

A stirred solution of the N-acetoxy compound (196b) (0.42 g; 0.001 mol) in redistilled dioxan (20.0 ml) was treated dropwise with boron-trifluoride-etherate (3.0 ml). The mixture was stirred at room temperature for 1 h, then evaporated and the residual gum was washed with water (5.0 ml) and 2M aqueous sodium hydroxide (4.0 ml) to give di-(6-chloro-1, 2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl) ether (277) (0.14 g; 26%), which crystallised as yellow prisms, m. p. 285-7° (from dimethylformamide),  $\nu_{\max}$  1660 (CO) and 1260 (C-O)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.40-8.15 (4H, m, ArH), 8.06 (2H, s, ArH), 7.51-7.37 (6H, m, ArH), 7.18 (2H, s, ArH) and 3.53 (6H, s, NMe).

Found: C, 65.1; H, 3.6; N, 10.1%; M<sup>+</sup> 554, 556 and 558.

C<sub>30</sub>H<sub>20</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub> requires: C, 65.0; H, 3.7; N, 10.6%; M 555.

Acidification of the alkaline washings with aqueous 2M hydrochloric acid gave 6-chloro-7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (263e) (0.11 g; 39%), m. p. 256-8° (lit<sup>77</sup> 261°), identical (i. r. spectrum) with an authentic sample. Extraction of the acidic mother liquor with chloroform gave a quantity of gum (0.16 g) which was shown by t. l. c. in ether over silica to be a mixture of several components.

F. The Rearrangement of 4-N-Acetoxy-1-methyl-3-morpholino-3-phenylquinoxalin-2(1H)-one (196a) at Room Temperature in Sunlight

The N-acetoxy compound (196a) (0.76 g; 0.002 mol) was allowed to stand in bright sunlight for ca 4 h, during which time it decomposed to a gummy solid. This was extracted with aqueous 2M sodium hydroxide (5.0 ml) to leave di-(1, 2-dihydro-1-methyl-2-oxo-3-phenylquinoxalin-7-yl) ether (279) (0.20 g; 15%), m. p. 283-5° (from glacial acetic acid-water),

$\nu_{\text{max}}$  1660 (CO) and 1240 (C-O)  $\text{cm}^{-1}$ .

Found: C, 74.9; H, 4.8; N, 10.8%;  $M^+$  486.

$\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_3$  requires: C, 74.1; H, 4.5; N, 11.5%;  $M$  486.

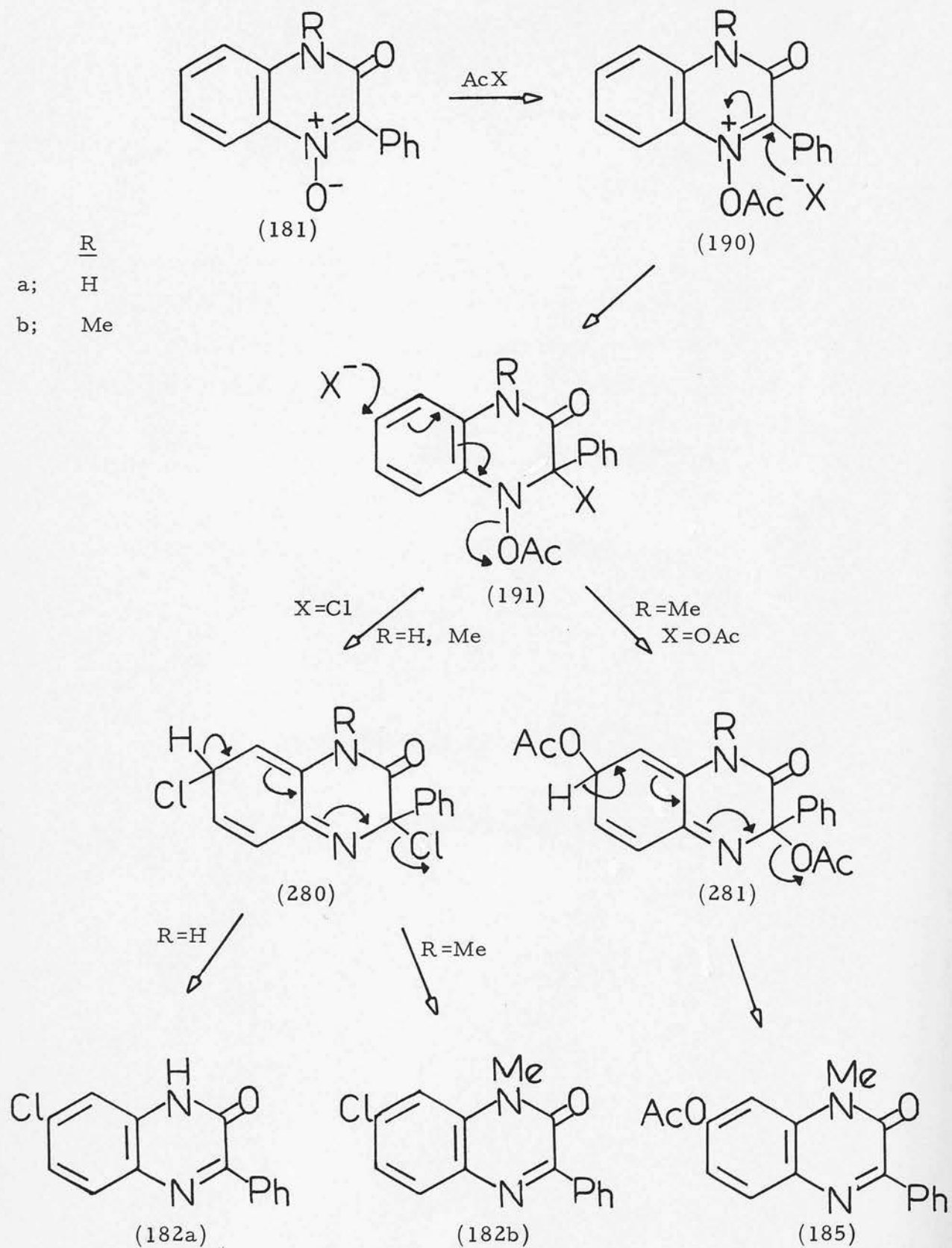
Due to lack of material, better analytical data could not be obtained for this product. Acidification of the alkaline extract with aqueous 2M hydrochloric acid gave 7-hydroxy-1-methyl-3-phenylquinoxalin-2(1H)-one (278) (0.39 g; 78%), m. p.  $297-9^{\circ}$  (lit<sup>73</sup>  $300^{\circ}$ ), identical (i. r. spectrum) with an authentic sample.<sup>73</sup>

CHAPTER THREE

DISCUSSION

Studies on the Reactions of Quinoxalinone

N-Oxides with Acylating Agents



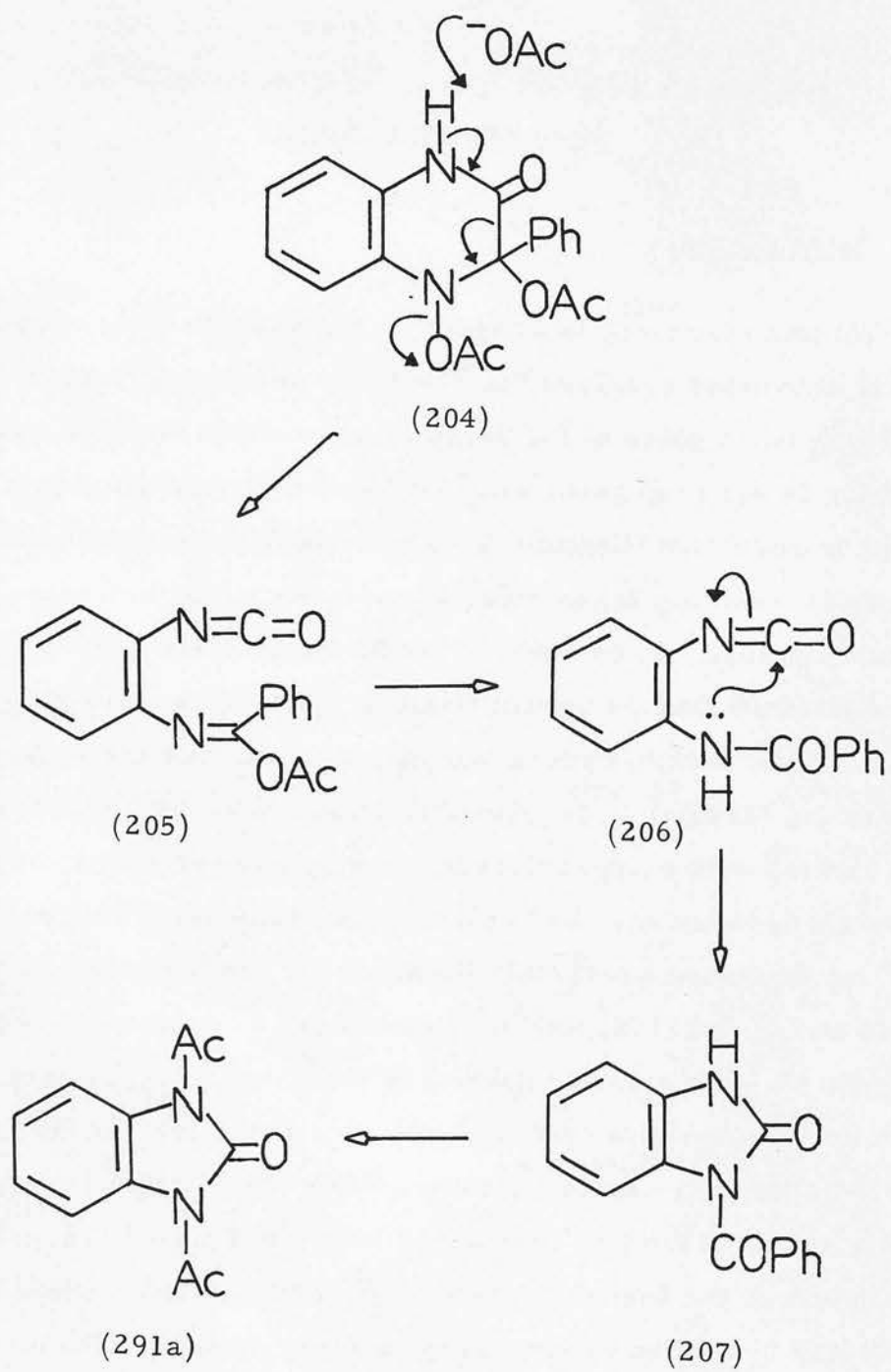
Scheme 51

Studies on the Reactions of Quinoxalinone N-Oxides  
with Acylating Agents

### 3.1 Introduction

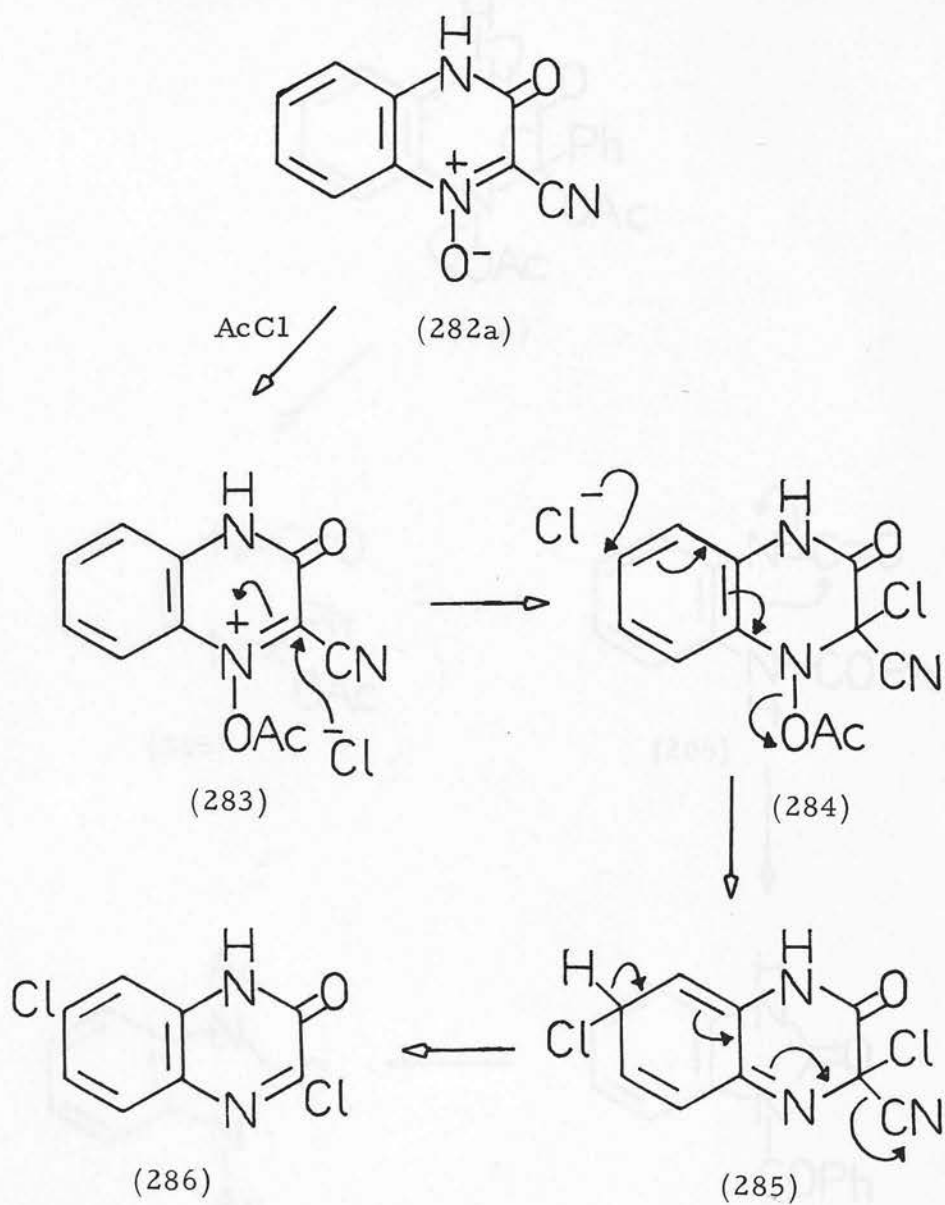
As was discussed in Chapter 2, the N-oxide (181b) reacts with hot acetic anhydride to afford the 7-acetoxy derivative (185).<sup>75</sup> Substitution in (181b) takes place at the 7-position, which is unusual since this position is not conjugated with the N-oxide functional group. As mentioned in the introduction (Chapter 1), nucleophilic substitution in heterocyclic N-oxides normally takes place at positions which are conjugated with the N-oxide group. In contrast to the N-methyl derivative (181b) it has been demonstrated that the parent N-oxide (181a) undergoes ring contraction on treatment with hot acetic anhydride to produce the benzimidazolone derivative (291a).<sup>75</sup> On the other hand, when the N-oxides (181a) and (181b) are treated with acetyl chloride, no ring contraction is observed and the products isolated are the 7-chloroquinoxalinones (182a) and (182b).<sup>72, 73</sup>

As discussed previously (Chapter 2), the formation of the products (182a and b) and (185) may be rationalised as outlined in the general scheme 51. Initial coordination of the N-oxide oxygen atom in (181) with acetic anhydride or acetyl chloride would lead to the formation of the N-acetoxyquinoxalinium cation (190) which would be subject to nucleophilic attack at the C-3 position to afford adducts of the type (191). The formation of the 7-acetoxy derivative (185) and the 7-chloro compounds (182a and b) is then explicable by courses (Scheme 51) involving nucleophilic attack by acetate or chloride ion on the adducts (191) either with synchronous expulsion of the N-acetoxy leaving group or subsequent to departure of the leaving group with formation of a nitrenium ion [cf (191)  $\rightarrow$  (280) — (281)]. Rearomatisation of the resulting paraquinonoid intermediates (280) and (281) with loss of the elements of acetic or hydrochloric acid furnishes the observed products (182a and b) and (185). Conversely, formation of the benzimidazolone (291a) is readily explained by ring opening of the adduct (204) to an isocyanate (205), ring closure of which [(205)  $\rightleftharpoons$  (206)  $\rightarrow$  (207)] would yield the N-



Scheme 52





Scheme 53

benzoylbenzimidazolone (207). Subsequent reaction of the latter with acetic anhydride would then yield the observed product (291a) [cf. scheme 52]. These mechanistic schemes account for the exclusive substitution observed in the reaction of the N-methyl compound (181b) with acetic anhydride and acetylchloride since, lacking an N-H group, (181b) cannot undergo ring opening to the isocyanate intermediate (205) requisite for benzimidazolone formation. Conversely, the inability of the much less basic chloride ion (compared with acetate ion) to effect proton removal and hence ring opening to the isocyanate (205), explains the lack of ring contraction and consequently exclusive substitution observed in the reaction of the quinoxaline N-oxide (181a) with acetyl chloride.

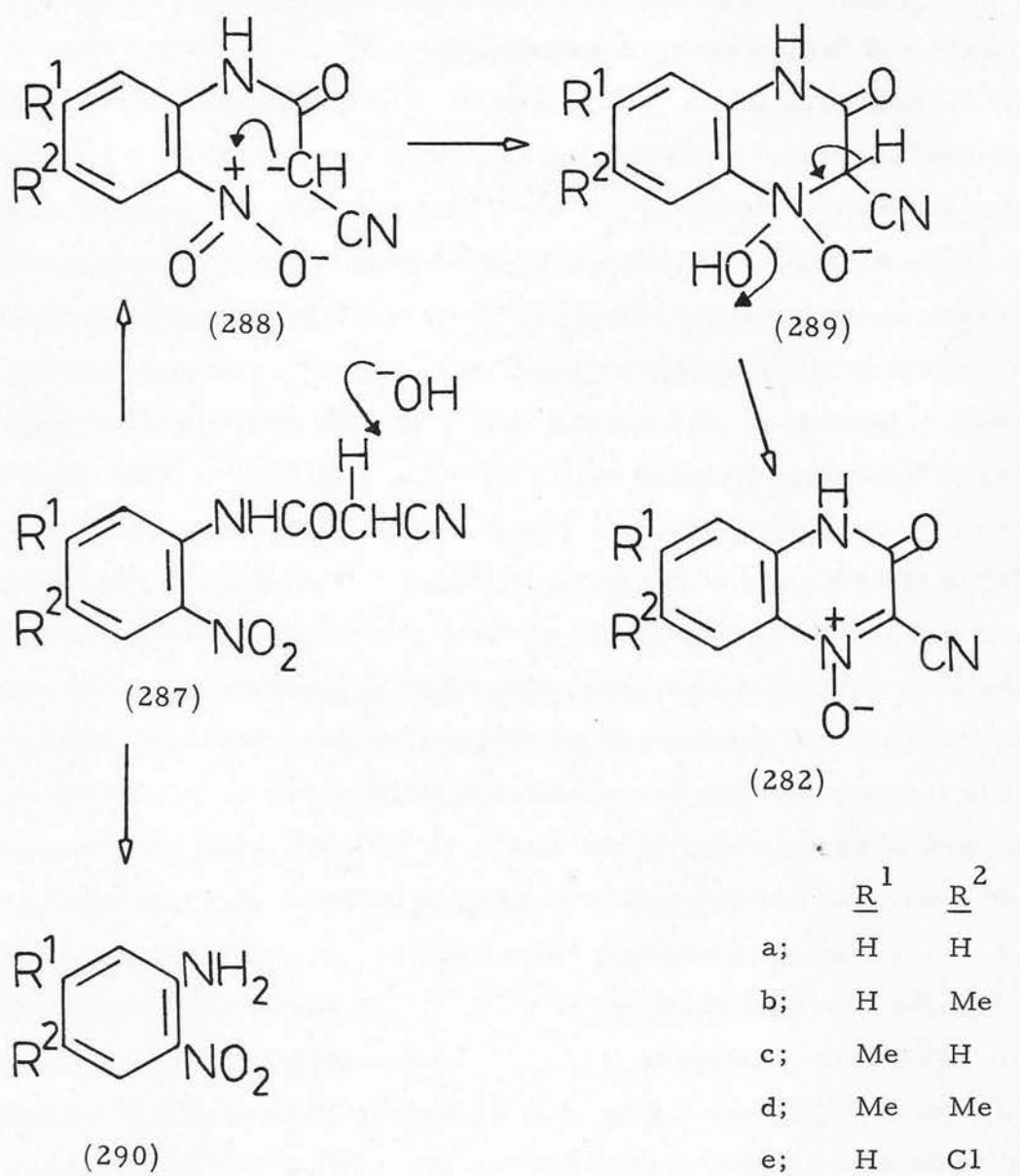
Evidence for the intermediacy of salts of the type (190) and the derived adducts (191) in the mechanistic scheme 51 was presented in Chapter 2. However, because of their controlling influence on the course of the reactions of quinoxalinone N-oxides with acylating agents, it was of interest to seek further evidence for the intermediacy of the adducts (191). Since these are produced by nucleophilic addition at the C-3 position in the salts (190), their ease of formation and hence the overall course of reaction, should be sensitive to the electronic effect of the C-3 substituent. Consequently, it was decided to investigate the reactions with acylating agents of quinoxalinone N-oxides bearing both electron-donating and electron-withdrawing substituents at C-3.

### 3.2 The Reactions of 3-Cyanoquinoxalinone N-Oxides with Acetyl Chloride in Acetic Acid.

The initial substrate chosen for study was 3-cyanoquinoxalin-2(1H)-one (282a). This molecule was of particular interest since the electron withdrawing cyano group should enhance the electrophilic character of the C-3 position and hence should promote formation of the intermediate adduct (284). Moreover, the fact that the cyano is a good leaving group allows the possibility of an alternative pathway involving loss of the cyano group [cf (285)  $\rightarrow$  (286); scheme 53] thereby providing indirect evidence for the initial formation of the adduct (284).

The N-oxide (282a) was readily available by the base catalysed cyclisation of 2-nitro- $\alpha$ -cyanoacetanilide (287a)<sup>89</sup> the mechanism of which is discussed later. A brief study<sup>75</sup> had previously shown that the N-oxide (282a) underwent ring contraction in hot acetic anhydride to give the benzimidazolone (291a). This result is not unexpected in view of the analogous reaction undergone by the 3-phenyl compound (181a). However, in the present studies the N-oxide (282a) was found to react on heating with acetyl chloride in acetic acid to afford a moderate yield of a product identical in all respects with a sample of the benzimidazolone (291a). Unreacted N-oxide (282a) was also isolated from the reaction mixture in moderate yield. Formation of the ring contracted product (291a) in the reaction of the N-oxide (282a) with acetyl chloride in acetic acid is surprising and contrasts with the exclusive substitution undergone by the 3-phenyl compound (181a) under analogous conditions (see before). Thus the course of reaction is markedly altered by the introduction of the cyano group into the C-3 position in place of the phenyl group. Since a mixture of acetyl chloride and acetic acid is essentially a mixture of acetic anhydride and hydrochloric acid, it contains both the weakly basic chloride ion and more strongly basic acetate ion. Consequently, it is possible that the benzimidazolone (291a) is formed from the cyano N-oxide (282a) in an analogous fashion to its formation from the N-oxide (181a), namely (scheme 52) by base catalysed ring opening to an isocyanate intermediate and subsequent recyclisation. However, this course is also open to the 3-phenyl analogue (181a) which prefers to undergo substitution rather than ring contraction.

Because of the unexpected ring contraction undergone by the cyano N-oxide (282a) in hot acetyl chloride/acetic acid, it was of interest to investigate the scope of reactions of this type for a series of cyano N-oxides (282) containing substituents in the C-6 and C-7 positions. The compounds [282 (b-f)] investigated were chosen because of their structural features (see later) and because of their ready availability by base catalysed cyclisation of the corresponding cyanoacetanilides (287). The N-oxides [282 (b-d)] were obtained in moderate yield by treatment of the corresponding cyanoacetanilides [287 (b-d)] with aqueous sodium hydroxide in pyridine.<sup>89</sup>



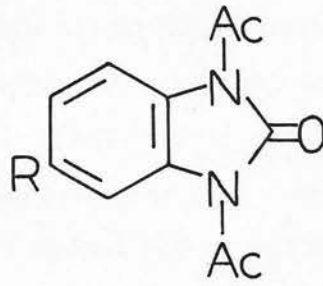
Scheme 54

The N-oxides [282 (e-f)] were obtained in high yield by treatment of the corresponding cyanoacetanilides [287 (e-f)] with aqueous 20% potassium hydroxide.<sup>22</sup> Formation of the N-oxides [282 (b-d)] was accompanied by the formation of the parent amines [290 (b-d)] in good yield. Thus because of the inefficiency of the cyclisation reaction in these cases, cleavage of the cyanoacetanilide to the amine becomes competitive. The i. r. spectra of the N-oxides (282) contained absorption bands at ca. 3100  $\text{cm}^{-1}$  and 2200  $\text{cm}^{-1}$ , attributable to NH and  $\text{C}\equiv\text{N}$  absorptions respectively, and quinoxalinone carbonyl absorptions at ca. 1660  $\text{cm}^{-1}$ .

Formation of the N-oxides (282) is readily explained by the mechanism outlined in scheme 54. Proton abstraction by hydroxide ion from the acidic methylene carbon atom of the acetanilides (287) affords the carbanionic intermediates (288) which ring-close by intramolecular nucleophilic attack on the nitro group [cf (288)  $\rightarrow$  (289)] to give the cyclic -intermediate (289). Loss of the elements of water from (289) then furnishes the N-oxides (282).

In view of the ring contraction undergone by the parent N-oxide (282a) on treatment with acetyl chloride in acetic acid at elevated temperature it was of interest to investigate the analogous reaction of the N-oxide (282e). The electron withdrawing chloro-substituent in this compound would be expected to enhance the electrophilic character of the neighbouring C-7 position thus promoting nucleophilic attack and possibly directing the course of the reaction from ring contraction to substitution in the fused benzene nucleus. In practice, the N-oxide (282e) reacted with hot acetyl chloride/acetic acid to give an increased yield of the ring-contracted product 1, 3-diacetylbenzimidazolone (291b) which was obtained in high yield and characterised by comparison with an authentic sample.<sup>75</sup> No product of ring substitution was obtained from this reaction.

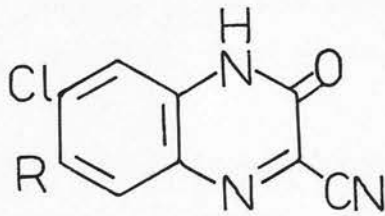
Since the presence of an electron withdrawing substituent in the C-6 position appeared to facilitate the ring contraction process it was of interest to examine in turn the effect of an electron releasing substituent at this position. When the N-oxide (282b), bearing a methyl substituent in the C-6 position, was heated with acetyl chloride/acetic acid both ring contraction of the quinoxalinone (282b) to a benzimidazolone and substitution



(291)

R

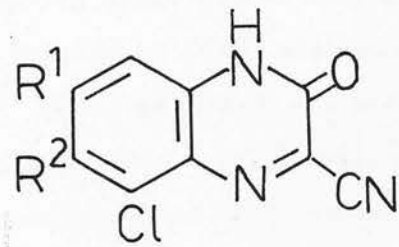
- a; H
- b; Cl
- c; Me
- d; MeO



(292)

R

- a; Me
- b; MeO

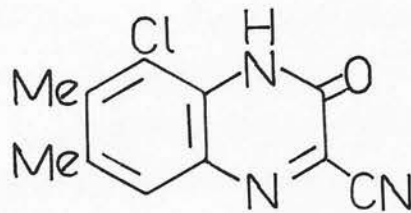


(293)

R<sup>1</sup>

R<sup>2</sup>

- a; Me      H
- b; Me      Me



(294)



at the C-7 position occurred. The products, isolated in the ratio of 3:1, were the 7-chloroquinoxalinone (292a) and the 1,3-diacetylbenzimidazolone (291c). The 7-chloroquinoxalinone (292a) gave analytical and mass spectral data fully consistent with its assigned structure which was further supported by absorption bands at 3150, 2200 and 1660  $\text{cm}^{-1}$  attributable to the presence of quinoxalinone NH, cyano and carbonyl groups, respectively. The C-7 position for the chloro-substituent was determined unambiguously by the  $^1\text{H}$  n.m.r. spectrum of the compound. This contained two one proton singlets in the aromatic region assignable to the protons at C-5 and C-8. The absence of any splitting in these singlets uniquely defines the orientation of the chloroquinoxalinone as (292a). Any other orientation of the product would result in ortho and meta coupling of the two aromatic hydrogens and hence a more complex splitting pattern. Satisfactory analytical and mass spectral evidence were also obtained for the benzimidazolone (291c). Its i.r. spectrum contained bands at 1750  $\text{cm}^{-1}$  and 1705  $\text{cm}^{-1}$  assignable to ring N-acetyl and benzimidazolone carbonyl groups, respectively. The assigned structure was further supported by the  $^1\text{H}$  n.m.r. spectrum which showed a splitting pattern in the aromatic region consistent with a 1,2,4-trisubstituted benzene ring and contained a singlet at  $\delta$  2.65 integrating for six protons and attributable to the two acetyl groups in the molecule. In view of the exclusive ring contraction observed in the reactions of the cyano N-oxides [282 (a and e)] with hot acetyl chloride it is rather surprising that the N-oxide (282b) is subject to substitution at the C-7 position under the same conditions. It would have been expected that the electron releasing effect of the methyl substituent at the C-6 position would have reduced the susceptibility of the neighbouring C-7 position to nucleophilic substitution thus favouring ring contraction. A possible explanation of this result is that electron donation by the C-6 methyl group inhibits proton loss at N-1 and hence ring contraction.

The effect of a more strongly electron releasing substituent at the C-6 position was investigated by heating the 6-methoxyquinoxalinone N-oxide (282f) with acetyl chloride in glacial acetic acid. This reaction furnished a solid whose spectral properties indicated that it was a 3:2

mixture of the 7-chloro-6-methoxyquinoxalinone (292b) and the 5-methoxybenzimidazolone (291d). In particular, the mass spectrum contained parent ion peaks at 235 and 237 mass units displaying an isotopic pattern characteristic of a molecule containing one chlorine atom and corresponding to the quinoxalinone (292b), and a further peak at 248 mass units attributable to the benzimidazolone (291d). The i. r. spectrum contained absorption bands at  $3100\text{ cm}^{-1}$ ,  $2200\text{ cm}^{-1}$  and  $1660\text{ cm}^{-1}$ , attributable to the NH, cyano and carbonyl group absorptions in the quinoxalinone (292b) and also, absorption bands at  $1750\text{ cm}^{-1}$  and  $1700\text{ cm}^{-1}$  assignable to the ring N-acetyl group and benzimidazolone carbonyl absorption in the compound (291d). The aromatic region of the  $^1\text{H}$  n. m. r. of the product was more complex than would have been expected for either of the individual constituents (291d) or (292b). The signals at  $\delta 7.92$ , which showed up as a doublet with a coupling constant of 8Hz, characteristic of ortho coupling, at  $\delta 7.65$ , which appeared as a doublet with a coupling constant of 2Hz, characteristic of meta coupling and at  $\delta 6.80$  (which was split into a double doublet with coupling constants of 2Hz and 8Hz) are assigned to the H-7, H-4 and H-6 protons of the benzimidazolone (291d), respectively, since the splitting pattern of these signals is characteristic of a 1, 2, 4-trisubstituted benzene derivative. The unsplit singlets at  $\delta 7.46$  and  $\delta 7.40$  are assigned to the H-5 and H-8 protons of the quinoxalinone (292b). The absence of any splitting in these singlets uniquely defines the position of substitution in the quinoxalinone (292b) as C-7. The N-acetyl protons of the benzimidazolone (291d) gave rise to a singlet at  $\delta 2.62$  while the signals at  $\delta 4.91$  and  $\delta 3.75$  are attributed to the methoxyl protons of (291d) and (292b), respectively. The ratio of the aromatic signals of the benzimidazolone (291d) to the aromatic signals of the quinoxalinone (292b) was one to one, thus indicating that the ratio of quinoxalinone (292b) to benzimidazolone (291d) in the mixture was three parts to two. Attempts to separate the mixture by crystallisation proved unsuccessful and unfortunately, insufficient material was available for separation by chromatographic means. Consequently, the benzimidazolone (291d) and the quinoxalinone (292b) were not unambiguously characterised.

The proportion of ring contracted product (291d) (compared with substitution product) obtained from the reaction of the 6-methoxyquinoxalinone (282f) with acetyl chloride/acetic acid was greater than the proportion of ring contraction observed in the analogous reaction of the 6-methylquinoxalinone (282b). This observation suggests that, as would be expected, substitution is retarded by greater electron donation from the C-6 position.

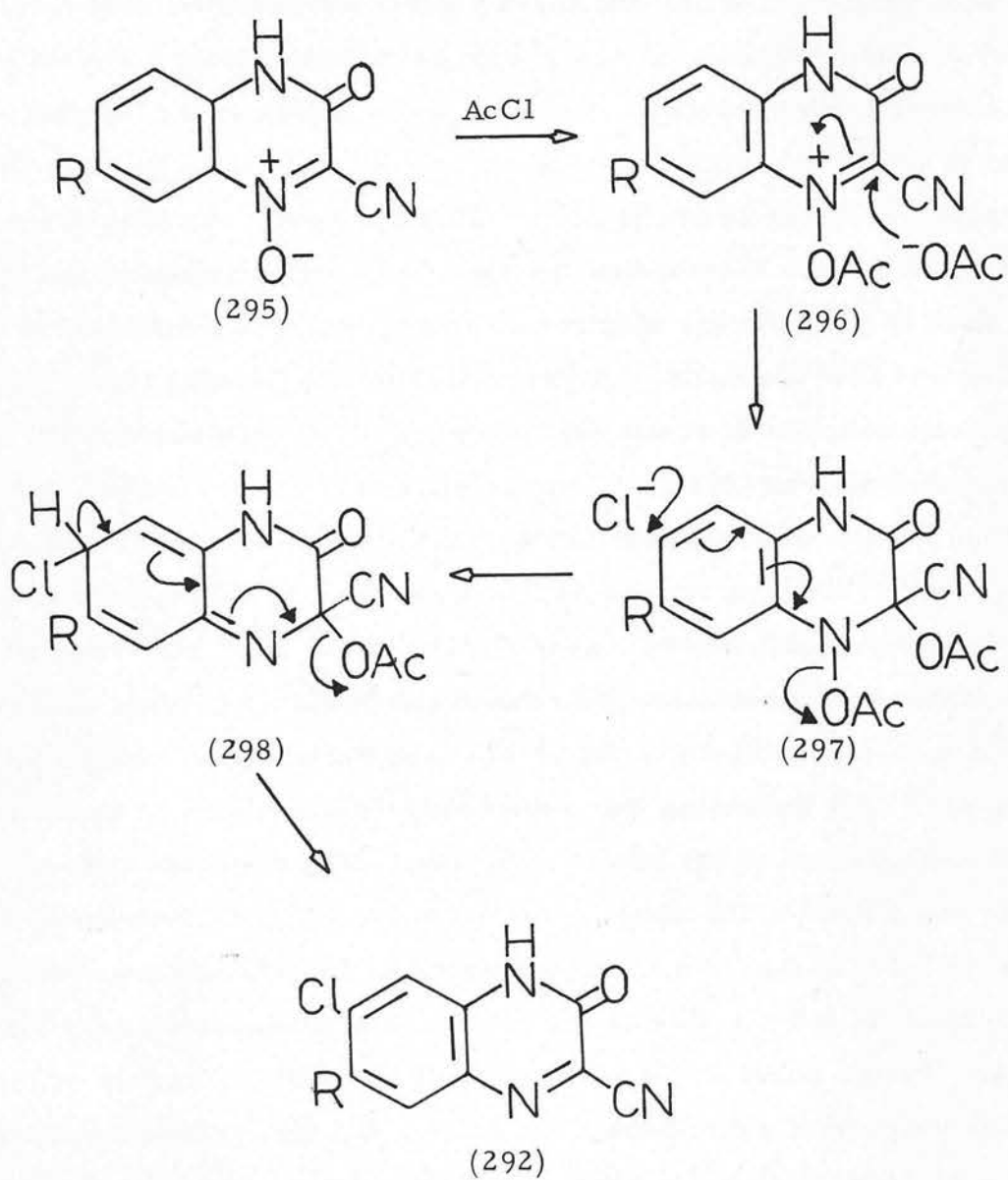
As a direct extension of these studies, the reaction of the 7-methylquinoxalinone N-oxide (282c) with hot acetyl chloride/acetic acid was investigated. The N-oxide (282c) was of interest since the methyl substituent at C-7, as well as effectively blocking nucleophilic attack at C-7, should also retard nucleophilic substitution on the ring in general. Thus, the possibility that substitution may be completely inhibited by the presence of the C-7 methyl substituent (thus facilitating ring contraction) or alternatively, that substitution might occur either at the substituent or at an alternative site in the molecule, is introduced. In practice, the N-oxide (282c) reacted with hot acetyl chloride to furnish exclusively the 5-chloroquinoxalinone derivative (293a) in high yield. The analytical and mass spectral evidence obtained for the quinoxalinone (293a) were fully in accord with the assigned structure which was further supported by absorption bands in the i. r. spectrum at  $3100\text{ cm}^{-1}$ ,  $2200\text{ cm}^{-1}$  and  $1670\text{ cm}^{-1}$  attributable to quinoxalinone NH, cyano and carbonyl absorptions, respectively. The position of substitution was unambiguously determined as C-5 by the compound's  $^1\text{H}$  n. m. r. spectrum. This contained two one-proton signals in the aromatic region which showed up as doublets with a coupling constant of 2Hz, characteristic of the coupling constant of protons situated meta to each other on a benzene nucleus. The orientation of the product is uniquely defined by such  $^1\text{H}$  n. m. r. absorption since substitution at any other site would not give rise to meta coupling. The formation of ring contracted product is inhibited by the presence of the electron releasing methyl substituent at the C-7 position since no benzimidazolone could be isolated from this reaction.

In the light of the observations that the presence of a methyl substituent at the C-6 position in the N-oxide (282b) apparently permits

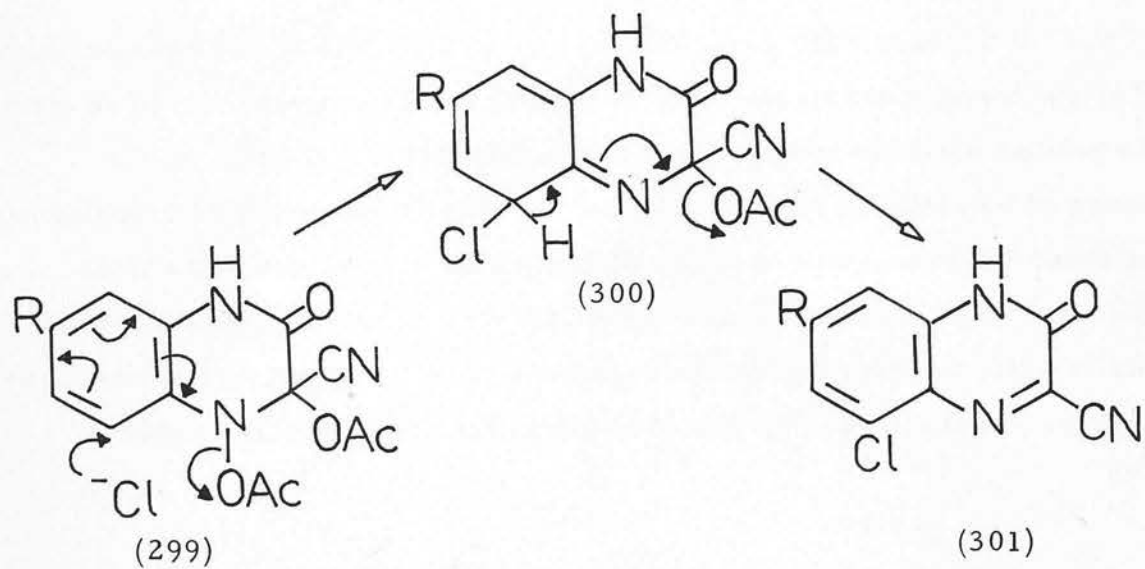
ring contraction of the quinoxalinone nucleus to the benzimidazolone (291c) whereas ring contraction is apparently completely inhibited by the presence of a methyl substituent at the C-7 position in the N-oxide (282c), it was of interest to study the reaction of the quinoxaline N-oxide (282d) with acetyl chloride in acetic acid. This compound was chosen for investigation since it embodies the twin structural features of the N-oxides (282 band c) in that it has electron releasing methyl substituents at both the C-6 and C-7 positions. It was found that the N-oxide (282d) reacted with acetyl chloride in acetic acid under reflux to give exclusively the 5-chloroquinoxalinone (293b). The analytical and mass spectral data obtained for the quinoxalinone (293b) were fully in accord with the assigned structure. This structure assignment was further substantiated by its i. r. spectrum which showed bands at  $3100\text{ cm}^{-1}$ ,  $2200\text{ cm}^{-1}$  and  $1670\text{ cm}^{-1}$  attributable to quinoxalinone NH, cyano and carbonyl groups, respectively. The  $^1\text{H}$  n. m. r. spectrum of the product showed an unsplit single proton signal at  $\delta 7.65$  indicating that substitution had occurred in either the C-5 or the C-8 position of the benzene nucleus. The chemical shift of this signal was closer to the shift of the H-5 signal ( $\delta 7.79$ ) than the H-8 signal ( $\delta 7.39$ ) in the  $^1\text{H}$  n. m. r. spectrum of the quinoxalinone (292a). However, it is not possible on the basis of this evidence alone to differentiate between the two possible structures (293b) and (294). In view of the fact that the position of substitution in the corresponding quinoxalinone (293a) was determined as C-5, by analogy, substitution at C-5 is considered a more favourable process than substitution at C-8 and thus the structure (293b) is favoured over (294).

Thus, it appears that the observed ring contraction of the quinoxalinones (282) to the benzimidazolones (291) on reaction with acetyl chloride in glacial acetic acid at elevated temperature is considerably facilitated by the presence of an electron withdrawing chloro substituent at the C-6 position of the fused benzene nucleus. In marked contrast, the presence of an electron releasing methyl substituent at the C-7 position apparently completely inhibits the ring contraction process and the course of the reaction is diverted to substitution by chloride ion in the fused benzene nucleus.

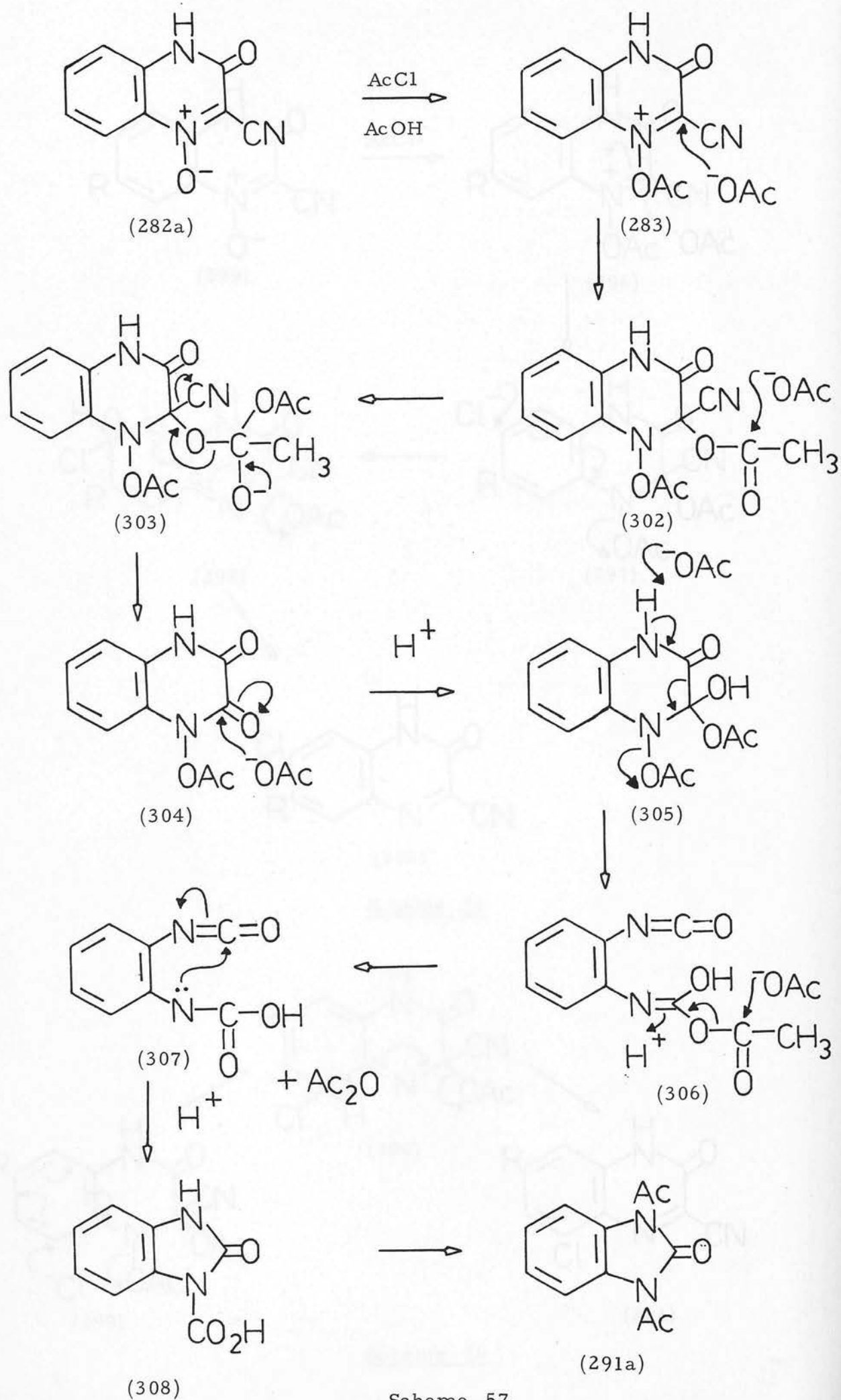




Scheme 55



Scheme 56



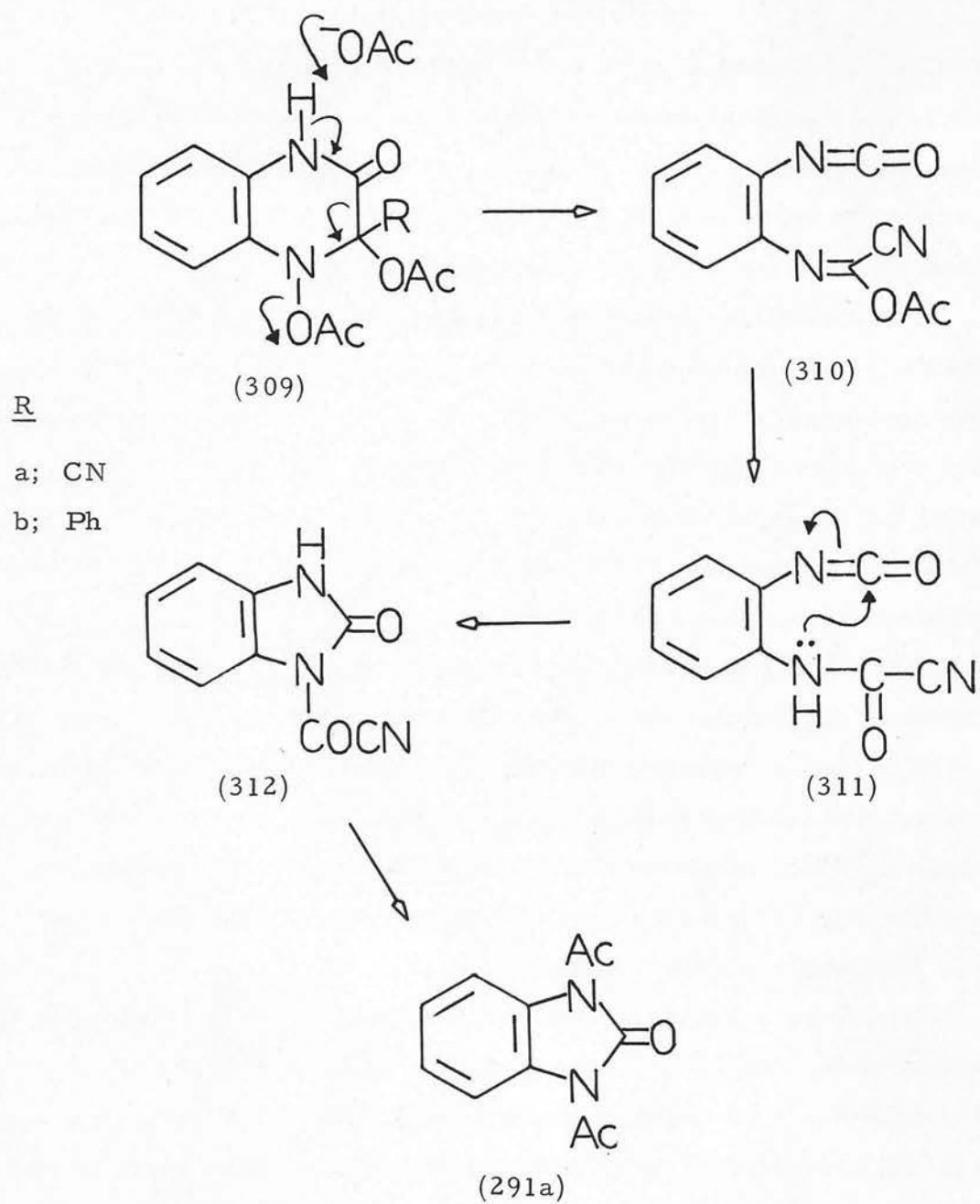
Scheme 57



Substitution by chloride ion at the C-7 position is promoted, at the expense of the ring contraction process, by the presence of an electron releasing substituent at C-6. However, the more strongly electron releasing is the substituent at C-6, the more favourable becomes the ring contraction process and the less efficient is substitution at C-7.

The formation of the 7-chloroquinoxalinones (292a and b) may be rationalised by the mechanistic route outlined in scheme 55. This course, which is analogous to that proposed for the reaction of the corresponding 3-phenyl N-oxides (181) with acetyl chloride (cf. scheme 51), requires the initial formation of the adducts (297) [cf. (191); scheme 51]. The formation of the products (292) is then explicable by a course involving synchronous nucleophilic attack at the C-7 position of the adducts (297) with expulsion of the N-acetoxy leaving group to afford the para-quinonoid intermediates (298) which upon rearomatisation give the observed products (292). With the C-7 position occupied by a methyl substituent, nucleophilic attack occurs at the C-5 position of the adduct (299) to afford the intermediate (300) which furnishes the product (301) upon rearomatisation [cf. scheme 56]. The formation of the 5-chloroquinoxalinones (293a and b) is explicable by this mechanistic route.

In view of the fact that the 3-cyano N-oxide (282a) undergoes ring contraction to the benzimidazolone (291a) on treatment with hot acetyl chloride whereas the 3-phenyl N-oxide (181a) affords the 7-chloroquinoxalinone (182a) exclusively, under identical conditions, it is possible that the ring contraction of the 3-cyano N-oxide (282a) follows a different mechanism to that proposed in scheme 52 for the ring contraction of the 3-phenyl N-oxide (181a) in acetic anhydride. One such alternative mechanistic route is that outlined in scheme 57 wherein ring contraction is dependent upon the initial formation of the N-acetoxyquinoxalinedione intermediate (304) from the N-oxide (282a) by displacement of the cyano group from the C-3 position (cf. scheme 57). Nucleophilic attack at the C-3 position of the dione (304) in turn, with addition of a proton, would give the adduct (305). The formation of the benzimidazolone (291a) is then explicable by a course (scheme 57) involving base catalysed deprotonation of the adduct (305) to afford the isocyanate intermediate (306), ring closure of which [(306)→(307)→(308)] would give the benzimidazolone (308). Subsequent



Scheme 58

reaction of the latter with acetic anhydride would furnish the diacetylbenzimidazolone (291a). Since the phenyl group at the C-3 position in the N-oxide (181a) cannot function as a leaving group, the formation of the N-acetoxyquinoxalinedione (304), and hence the adduct (305), would be inhibited, thus preventing ring contraction. Although this mechanism would account for the different modes of reaction of the N-oxides (181a and 282a) with acetyl chloride/acetic acid, subsequent studies (see Chapter 4) have demonstrated that it is exceedingly unlikely that the ring contraction occurs by this route.

The formation of the benzimidazolone (291a) from the cyano N-oxide (282a) on treatment with hot acetyl chloride in acetic acid is also explicable by the route outlined in scheme 58. Namely by base catalysed deprotonation of the N-1 position in the adduct (309a) and ring opening to the isocyanate intermediate (310) with subsequent cyclisation [(310)  $\rightarrow$  (311)  $\rightarrow$  (312)] to the benzimidazolone intermediate (312). Reaction of (312) with acetic anhydride would then provide the observed product (291a). To satisfactorily account for, on one hand, the exclusive formation of the 7-chloroquinoxalinone (182a) from the N-oxide (181a) on treatment with hot acetyl chloride/acetic acid and on the other hand the exclusive ring contraction by the N-oxide (282a) under analogous conditions, it is necessary to assume that a fine balance is established between deprotonation at N-1 by acetate ion and nucleophilic substitution by chloride ion in the fused benzene ring. The presence of the cyano group at the C-3 position in the N-oxide (282a) would favour the ring contraction process on two counts. Firstly, the electron withdrawing effect of this substituent would weaken the C-C bond in the hetero ring in the adduct (309a) thus aiding its fission and consequently facilitating the formation of the isocyanate intermediate (310). Secondly, it would be expected that the presence of the electron withdrawing cyano group at the C-3 position in the adduct (309a) would increase in turn the electron withdrawing effect of the carbonyl group at C-2, thus making the proton at N-1 in the adduct (309a) more acidic and consequently more susceptible to removal by a basic reagent. It is reasonable to assume that for these reasons, substitution by chloride

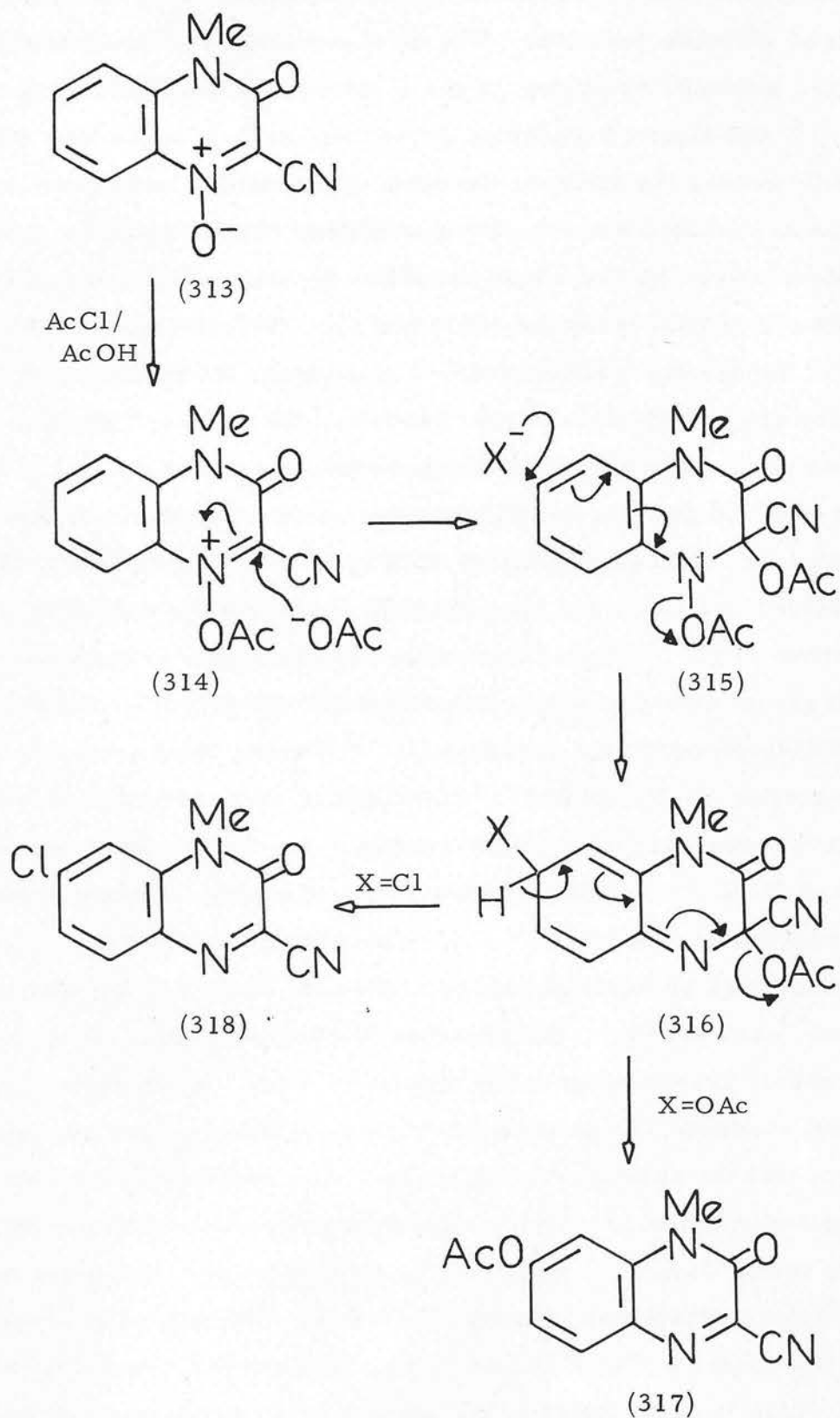
ion in the benzene nucleus fails to compete with the ring contraction process and consequently only the benzimidazolone (291a) is obtained from the reaction of the N-oxide (282a) with acetyl chloride in acetic acid. In direct contrast, the electron withdrawing effect of the phenyl substituent at the C-3 position in the adduct (309b) (cf. 191; scheme 51) is markedly reduced in comparison to that of the cyano group. Thus the C-C bond in the hetero nucleus of (309b) would not be similarly weakened by electron withdrawal and the acidity of the proton at N-1 would be reduced. These assumptions are in accord with the observed exclusive formation of the 7-chloro derivative (182a) from the 3-phenyl N-oxide (181a) on reaction with hot acetyl chloride. In this reaction, substitution at the C-7 position of the fused benzene nucleus by chloride ion is a more facile process than deprotonation at N-1 by acetate ion. Thus, substitution occurs to the exclusion of ring contraction.

The effect of the electron withdrawing chloro substituent at the C-6 position of the N-oxide (282e) would be to increase the acidity of the proton at N-1 by conjugative electron withdrawal, thus facilitating its removal and making the base-catalysed ring contraction process [cf scheme 58] even more favourable than in the unsubstituted N-oxide (282a). This assumption is in accord with the increased yield of the benzimidazolone (291b) obtained in the reaction of the N-oxide (282e) with hot acetyl chloride. On the other hand, the effect of an electron releasing substituent at the C-6 position would be to reduce the relative acidity of the proton at N-1, thus making the base-catalysed ring contraction process (scheme 58) less favourable and allowing nucleophilic substitution at the C-7 position to compete. Thus, the reaction of the 6-methylquinoxaline N-oxide (282b) affords a mixture of both the 7-substituted quinoxalinone (292a) and the benzimidazolone (291c). However, a further effect of an electron releasing substituent at C-6 would be to reduce the electrophilic character of the C-7 position, making it less susceptible to nucleophilic attack by chloride ion. This would tend to act in favour of the occurrence of the ring contraction process and explains the increased formation of ring contracted benzimidazolone from the 6-methoxyquinoxaline N-oxide (282f)



relative to that obtained from the 6-methylquinoxaline N-oxide (282b) in the acetyl chloride reaction. The most significant substituent effect, however, would be reduction of the electrophilic character of the C-3 position by an electron releasing substituent at C-7, since this would markedly reduce the effect of the cyano group at C-3 and favour substitution at the expense of the base-catalysed ring contraction process. For this reason, the 7-methylquinoxaline N-oxides (282 c and d) furnish only the chloroquinoxalinones (293a and b). With the electron withdrawing effect of the cyano substituent at C-3 countered, the reactions of these N-oxides are closely akin to the reaction of the 3-phenyl N-oxide (181a) with acetyl chloride and no ring contraction is observed.

In order to gain further information on the mechanism of the reactions of 3-cyanoquinoxalinone N-oxides with acetyl chloride in acetic acid, it was decided to investigate the behaviour of the readily available N-methyl derivative (313).<sup>89</sup> If ring contraction is controlled by proton loss from the NH group, this compound, in contrast to the parent N-oxide (282a), should undergo exclusive substitution. This was found to be the case. Thus, heating the N-oxide (313) under reflux with acetyl chloride in acetic acid gave moderate yields of the 7-acetoxy and 7-chloroquinoxalinones (317) and (318). The analytical and mass spectral evidence obtained for the 7-acetoxy derivative (317) were fully in accord with the assigned structure which is further supported by bands in its i. r. spectrum at  $1670\text{ cm}^{-1}$  and  $2250\text{ cm}^{-1}$  attributable to quinoxalinone carbonyl and cyano group absorptions, respectively, and at  $1770\text{ cm}^{-1}$  assignable to the carbonyl absorption of an acetoxy group attached to a benzene nucleus. The fact that the acetoxy substituent had entered the 7-position in the quinoxalinone nucleus is demonstrated unambiguously by the splitting pattern in the  $^1\text{H}$  n. m. r. spectrum of the compound. This was typical of a 1, 2, 4-trisubstituted benzene derivative. The signal at lowest field, due to the proton at C-5, showed up as a doublet with a coupling constant of 9Hz which is characteristic for protons ortho to one another on a benzene ring. The proton at C-8 appeared farther upfield as a doublet with a coupling constant of 2.5Hz, characteristic of a meta split proton. The signal farthest upfield was assigned to H-6 since this appeared as a



Scheme 59

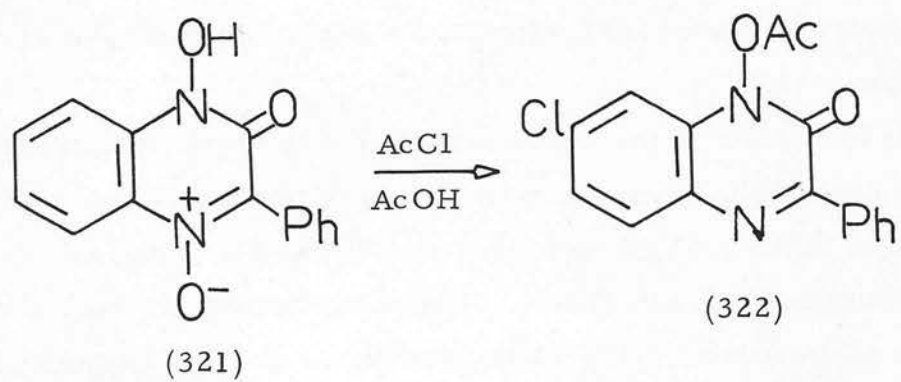
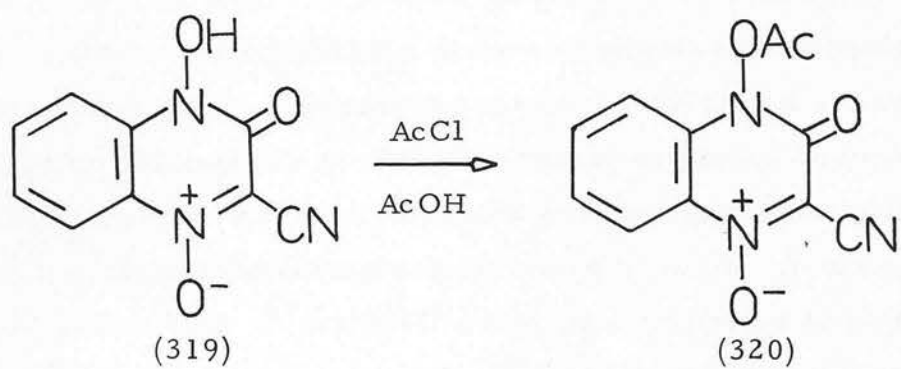


double doublet with coupling constants characteristic of ortho and meta coupling. The second product obtained from this reaction is tentatively assigned the structure (318) on the basis of mass and i. r. spectral evidence. Because of its highly insoluble nature, attempts to unambiguously characterise this compound by obtaining analytical and  $^1\text{H}$  n. m. r. evidence for its structure proved unsuccessful. The mass spectrum of the compound contained parent ion peaks at 219 and 221 mass numbers displaying an isotopic pattern characteristic of a molecule containing one chlorine atom. Its i. r. spectrum contained bands at  $2200\text{ cm}^{-1}$ , assignable to a cyano group, and at  $1660\text{ cm}^{-1}$ , attributable to a quinoxalinone carbonyl absorption. The proposed site of substitution by chloride ion is C-7 since it has been demonstrated that in an analogous reaction, the 3-phenyl N-oxide (181b) affords the 7-chloroquinoxalinone (182b)<sup>72, 73</sup> (cf. scheme 51).

The formation of the 7-acetoxy and 7-chloroquinoxalinones (317) and (318) is explicable by mechanistic routes directly analogous to these outlined in scheme 51 for the formation of the 7-acetoxy and 7-chloroquinoxalinones (185) and (182b). Thus, nucleophilic attack at the C-7 position of the adduct (315) would give the para-quinonoid intermediate (316) which on rearomatisation, with expulsion of the elements of acetic acid, would give the observed products (317) [cf (315)→(316)→(317); scheme 59] and (318) [cf. (315)→(316)→(318); scheme 59].

As a further extension of these studies the reaction of the cyano N-oxide (319) with hot acetyl chloride was investigated. This substrate was of particular interest in the context of the process of substitution since, bearing both N-hydroxy and N-oxide functional groups it might be susceptible to bis-substitution in the fused benzene ring. On the other hand, ring contraction of the quinoxalinone hetero-ring might afford an N-hydroxybenzimidazolinone, a compound of a type not readily accessible by more orthodox synthesis.

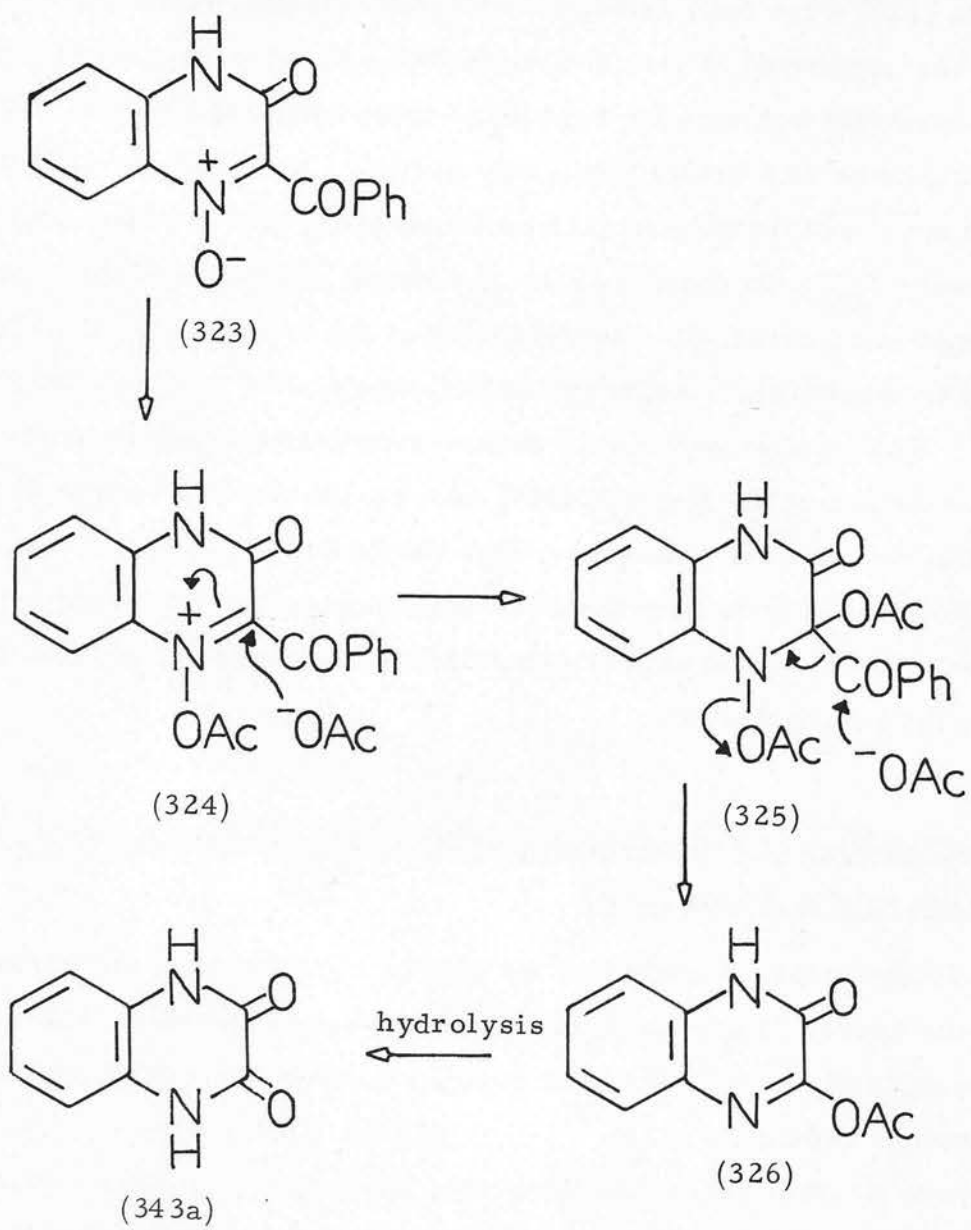
In practice, the N-oxide (319) reacted with acetyl chloride in glacial acetic acid to furnish an excellent yield of 1-acetoxy-3-cyanoquinoxalin-2(1H)-one 4-oxide (320), and no products of substitution or ring contraction were produced. The analytical and mass spectral data obtained for the



N-acetate (320) were fully in accord with the assigned structure which was further supported by its  $^1\text{H}$  n. m. r. and i. r. spectra. In particular, its i. r. spectrum contained a strong absorption band at  $1820\text{ cm}^{-1}$  which is characteristic of a cyclic N-acetoxy group,<sup>84</sup> and bands at  $2250\text{ cm}^{-1}$  and  $1695\text{ cm}^{-1}$  attributable to quinoxalinone cyano and carbonyl absorptions, respectively. The formation of the N-acetoxy derivative (320) is surprising and is to be contrasted with the reactivity of the 3-phenyl N-oxide (321) which in hot acetyl chloride/acetic acid furnishes the 7-chloro derivative (322).<sup>73</sup> The non-formation of a chloro-substituted analogue of the type (322) on reaction of the N-oxide (319) with acetyl chloride/acetic acid is difficult to rationalise. However, this result does substantiate the proposition that ring contraction of 3-cyanoquinoxalinone N-oxides with acetyl chloride in acetic acid is controlled by deprotonation of the NH group in the hetero nucleus.

### 3.3 The Reaction of 3-Benzoylquinoxalin-2(1H)-one 4-Oxide (323) with Acetyl Chloride in Acetic Acid.

To study further the effect of an electron withdrawing substituent at C-3 on the course of the reactions of quinoxalinone N-oxides with acetyl chloride in acetic acid it was next decided to investigate the behaviour of the 3-benzoyl compound (323).<sup>91</sup> The results obtained from the study of the 3-cyano N-oxide (282a) indicated that the benzoyl compound (323) might likewise undergo ring contraction to the benzimidazolone (291a). In practice, heating the N-oxide (323) with acetyl chloride in glacial acetic acid gave a good yield of a single product, identical in all respects to an authentic sample (see later) of quinoxaline-2, 3(1H, 4H)-dione (343a). Products derived by ring contraction or substitution were not detected in the reaction mixture. The formation of the quinoxalinedione (343a) may be rationalised by the mechanism outlined in scheme 60. Initial electrophilic attack at the oxygen atom of the N-oxide group in (323) would give the cationic intermediate (324) which would then undergo nucleophilic attack by acetate ion [cf (324)  $\rightarrow$  (325)] at the electrophilically enhanced C-3 position of the hetero ring giving the adduct (325). Further nucleophilic

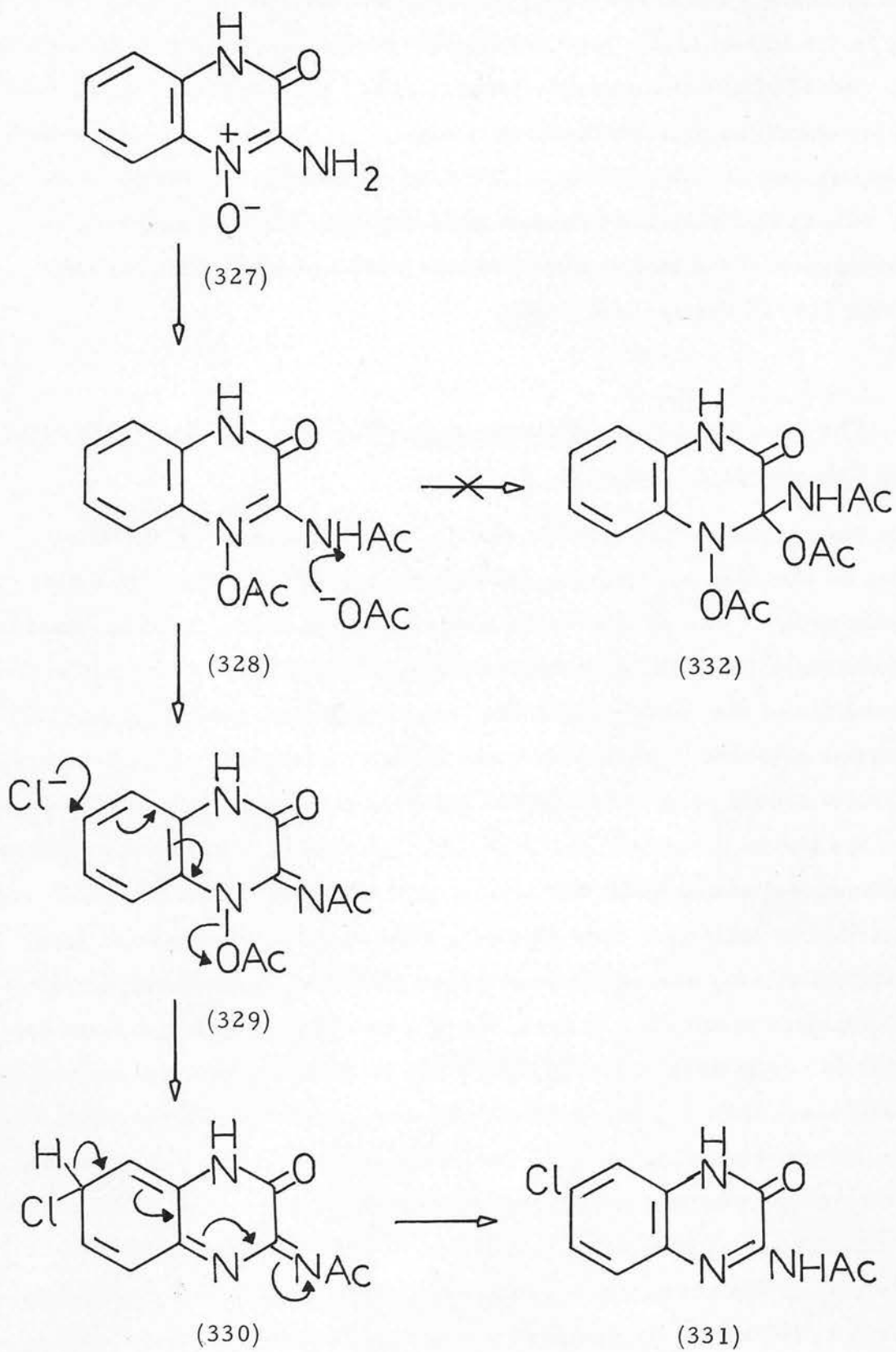


Scheme 60

attack by acetate ion at the highly electrophilic carbon atom of the benzoyl group in the adduct (325), with subsequent expulsion of the acetoxy leaving group, would afford the unstable product (326), hydrolysis of which would yield the observed quinoxalinedione (343a). The lack of formation of ring contracted or substitution products in the reaction of the N-oxide (323) with acetyl chloride in acetic acid may therefore be attributed to decomposition of the intermediate adduct (325) by an alternative mode involving loss of the benzoyl group.

#### 3.4 The Reaction of 3-Aminoquinoxalin-2(1H)-one 4-Oxide (327) with Acetyl Chloride in Acetic Acid.

In view of the outcome of the reactions of quinoxalinone N-oxides bearing an electron withdrawing substituent at C-3 with acetyl chloride in acetic acid, it was of interest to investigate the corresponding reaction of a quinoxalinone N-oxide having an electron releasing substituent at C-3. The reaction of the readily available 3-aminoquinoxalinone 4-oxide (327)<sup>91</sup> with acetyl chloride in acetic acid was therefore studied. The 3-amino substituent should not prevent initial salt formation after possible acetylation at the amino group [cf. (327)  $\rightarrow$  (328); scheme 61] but it was anticipated that subsequent nucleophilic addition to give the expected adduct (332) would be retarded or inhibited, thus diverting the course of the reaction from substitution or ring contraction and hence providing further insight into the mechanism involved. In fact, the N-oxide (327) reacted with acetyl chloride in acetic acid to give a good yield of the chlorinated acetylaminoquinoxalinone (331). The analytical and mass spectral evidence obtained for the chloroquinoxalinone (331) were fully in accord with the assigned structure which was further supported by its i. r. spectrum. This contained absorption bands at  $3380\text{ cm}^{-1}$  and  $3150\text{ cm}^{-1}$  attributable to the NH absorptions of the acetylamino group and the quinoxalinone respectively. The band at  $1680\text{ cm}^{-1}$  is assigned to the acetylamino carbonyl function, while that at  $1660\text{ cm}^{-1}$  is attributed to quinoxalinone carbonyl absorption. The splitting pattern in the aromatic region of the <sup>1</sup>H n. m. r. spectrum of the compound was characteristic of a 1, 2, 4-trisubstituted benzene derivative.



Scheme 61



The proton at C-5, which would be deshielded to the greatest extent by the unsubstituted N-4 hetero atom, showed up at lowest field as a doublet with a coupling constant of 8Hz, characteristic of ortho coupled protons. These  $^1\text{H}$  n. m. r. features uniquely define the position of substitution as C-7, since substitution at the only alternative position, i. e. C-6, would have caused the H-5 proton to show up as a doublet with a coupling constant of ca 2Hz, characteristic of meta coupled protons.

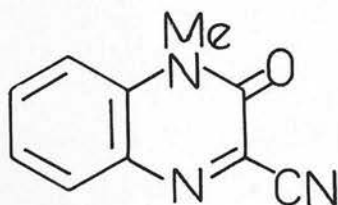
Formation of (331) is readily rationalised as shown in scheme 61, wherein adduct formation [(328)  $\rightarrow$  (332)] is by-passed in favour of deprotonation of the initial salt (328) to give the iminoacetyl compound (329). This could then undergo nucleophilic substitution by chloride ion as shown (scheme 61) to give the observed product (331). In the absence of the adduct (332), base catalysed deprotonation of the N-1 position with the formation of an isocyanate intermediate and subsequent ring closure to afford a benzimidazolone product is no longer possible and consequently no products of ring contraction are obtained.

### 3.5 The Reaction of 3-Cyanoquinoxalinone 4-Oxides with Acetic Anhydride.

The nature of the products and the effect of substituents on the course of the reactions of quinoxalinone N-oxides bearing electron withdrawing and electron donating substituents at C-3 with acetyl chloride in acetic acid are broadly in accord with the general substitution mechanism outlined in scheme 51 and the base catalysed ring contraction mechanism detailed in scheme 52. It was of interest therefore to study some of the corresponding reactions of such N-oxides with acetic anhydride to see how far they would duplicate the acetyl chloride/acetic acid transformation.

Ahmad and his coworkers<sup>75</sup> reported that the cyanoquinoxalinone N-oxide (282a) was converted in hot acetic anhydride in low yield into the di-N-acetylbenzimidazolone (291a). This result has been confirmed in the present studies, prolonged heating of the N-oxide (282a) in acetic anhydride giving the benzimidazolone (291a) as the exclusive product together with unreacted N-oxide. In marked contrast, when the N-oxide (313)

was heated under reflux with acetic anhydride the product obtained in low yield was the deoxy-compound (333), identical in every respect with



(333)

an authentic sample.<sup>89</sup> No products of ring contraction or acetoxy substitution could be detected in the reaction of the N-oxide (313) with acetic anhydride. This reaction differs markedly therefore from that undergone by (313) in acetyl chloride/acetic acid. The simple deoxygenation of (313) observed in hot acetic anhydride is without precedent for similar quinoxalinone N-oxides under similar reaction conditions. As described in the experimental section, the crude product was purified by Kugelrohr distillation. This purification was accompanied by considerable decomposition and it is possible that the deoxygenation observed was effected by the tarry by-products and was not the direct result of heating the N-oxide (313) in acetic anhydride. Many N-oxides are converted into the parent bases if they are heated strongly, either alone or in the presence of various solid catalysts. For example, simply heating pyridine N-oxide (3) at 220<sup>o</sup> gives some pyridine and this deoxygenation is catalysed by copper or zinc powder.<sup>1b</sup> Formation of the deoxygenated heterocycle (333) from the N-oxide (313) by means other than a thermal process would be difficult to rationalise, though the apparent ability of acetic anhydride to effect the deoxygenation of certain N-oxides has been observed.<sup>1b</sup>

The outcome of the reaction of the cyano N-oxide (319) with hot acetic anhydride was similar to its reaction under reflux with acetyl chloride in glacial acetic acid and the product obtained in high yield was the N-acetoxy compound (320) which was characterised by comparison with an authentic sample. No products of ring contraction nor ring substitution were isolated from the reaction of the N-oxide (319).

General Method

Cyanoacetic acid (5.0 g, 0.105 mol) in anhydrous ether (100 ml) was treated in one portion at room temperature with phosphorus pentachloride (2.5 g, 0.01 mol) and the mixture was stirred at room temperature for 10 minutes. Removal of the ether and phosphorus oxychloride by rotary evaporation gave cyanacetyl chloride as a pale yellow oil, which was dried in anhydrous ether (100 ml) and removed at 100° for 1.5 h. The 2-nitroacetyl chloride (10.0 g, 0.05 mol) was added to the mixture. The residue [287] was collected from the cooled mixture and combined with further material recovered from the mixture after 10 h by concentration.

CHAPTER THREE

EXPERIMENTAL SECTION

a) 2-Nitro-2-(4-oxocyclohexylidene)propane (287) (10.0 g, 0.05 mol) was obtained as pale yellow needles, m.p. 130-3° (lit. 134°),  $\nu_{max}$  1700 (C=O), 1695 (C=O), 1500 (C=C), 1330 (C-O), 1100 (C-O), 740 (C=C), 690 (C=C), 530 (C-O), 480 (C=C), 330 (C-H), 310 (C-H), 290 (C-H), 270 (C-H), 250 (C-H), 230 (C-H), 210 (C-H), 190 (C-H), 170 (C-H), 150 (C-H), 130 (C-H), 110 (C-H), 90 (C-H), 70 (C-H), 50 (C-H) cm<sup>-1</sup> (KBr);  $\lambda_{max}$  210 (E), 230 (E), 250 (E), 270 (E), 290 (E), 310 (E), 330 (E), 350 (E), 370 (E), 390 (E), 410 (E), 430 (E), 450 (E), 470 (E), 490 (E), 510 (E), 530 (E), 550 (E), 570 (E), 590 (E), 610 (E), 630 (E), 650 (E), 670 (E), 690 (E), 710 (E), 730 (E), 750 (E), 770 (E), 790 (E), 810 (E), 830 (E), 850 (E), 870 (E), 890 (E), 910 (E), 930 (E), 950 (E), 970 (E), 990 (E), 1010 (E), 1030 (E), 1050 (E), 1070 (E), 1090 (E), 1110 (E), 1130 (E), 1150 (E), 1170 (E), 1190 (E), 1210 (E), 1230 (E), 1250 (E), 1270 (E), 1290 (E), 1310 (E), 1330 (E), 1350 (E), 1370 (E), 1390 (E), 1410 (E), 1430 (E), 1450 (E), 1470 (E), 1490 (E), 1510 (E), 1530 (E), 1550 (E), 1570 (E), 1590 (E), 1610 (E), 1630 (E), 1650 (E), 1670 (E), 1690 (E), 1710 (E), 1730 (E), 1750 (E), 1770 (E), 1790 (E), 1810 (E), 1830 (E), 1850 (E), 1870 (E), 1890 (E), 1910 (E), 1930 (E), 1950 (E), 1970 (E), 1990 (E), 2010 (E), 2030 (E), 2050 (E), 2070 (E), 2090 (E), 2110 (E), 2130 (E), 2150 (E), 2170 (E), 2190 (E), 2210 (E), 2230 (E), 2250 (E), 2270 (E), 2290 (E), 2310 (E), 2330 (E), 2350 (E), 2370 (E), 2390 (E), 2410 (E), 2430 (E), 2450 (E), 2470 (E), 2490 (E), 2510 (E), 2530 (E), 2550 (E), 2570 (E), 2590 (E), 2610 (E), 2630 (E), 2650 (E), 2670 (E), 2690 (E), 2710 (E), 2730 (E), 2750 (E), 2770 (E), 2790 (E), 2810 (E), 2830 (E), 2850 (E), 2870 (E), 2890 (E), 2910 (E), 2930 (E), 2950 (E), 2970 (E), 2990 (E), 3010 (E), 3030 (E), 3050 (E), 3070 (E), 3090 (E), 3110 (E), 3130 (E), 3150 (E), 3170 (E), 3190 (E), 3210 (E), 3230 (E), 3250 (E), 3270 (E), 3290 (E), 3310 (E), 3330 (E), 3350 (E), 3370 (E), 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A. The Synthesis of 2-Nitro- $\alpha$ -cyanoacetanilides (287)General Method<sup>89</sup>

Cyanoacetic acid (9.0 g; 0.105 mol) in anhydrous ether (80.0 ml) was treated in one portion at room temperature with phosphorus pentachloride (24 g; 0.11 mol) and the mixture was stirred at room temperature for 30 minutes. Removal of the ether and phosphorus oxychloride in vacuo gave cyanoacetyl chloride as a pale yellow oil, which was dissolved in anhydrous benzene (20.0 ml) and warmed at 100° for 2.0 h. with the 2-nitroaniline derivative (290) (0.1 mol) in anhydrous benzene (80.0 ml). The anilide (287) was collected from the cooled mixture and combined with further material recovered from the benzene mother liquor by concentration.

a) 2-Nitro- $\alpha$ -cyanoacetanilide (287a) (20.4 g; 95%) was obtained as pale yellow needles, m. p. 150-2° (lit<sup>89</sup> 154°), identical (i. r. spectrum) with an authentic sample.<sup>89</sup>

b) 4-Methyl-2-nitro- $\alpha$ -cyanoacetanilide (287b) (20.6 g; 94%) was obtained as bright yellow needles, m. p. 150-1° (from toluene),  $\nu_{\max}$  3290 br (NH), 2240 (CN), 1695 (CO), and 1500 and 1330 (NO<sub>2</sub>) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.80 br (1H, s, ArH), 7.53 br (2H, s, ArH), 3.98 (2H, s, CH<sub>2</sub>), and 2.37 (3H, s, ArMe).

Found: C, 54.6; H, 4.1; N, 19.3%; M<sup>+</sup> 219.

C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 54.8; H, 4.1; N, 19.2%; M 219.

c) 5-Methyl-2-nitro- $\alpha$ -cyanoacetanilide (287c) (98%) obtained by the above general method had m. p. 155-7° (from light petroleum-ethanol),  $\nu_{\max}$  3300 (NH), 2220 (CN), 1670 (CO), and 1540 and 1340 (NO<sub>2</sub>) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.84 (1H, d, J<sub>ortho</sub> 8Hz, H-3), 7.48 (1H, d, J<sub>meta</sub> 2Hz, H-6), 7.16 (1H, dd, J<sub>ortho</sub> 8Hz and J<sub>meta</sub> 2Hz, H-4), 3.93 (2H, s, CH<sub>2</sub>) and 2.33 (3H, s, ArMe).

Found: C, 54.8; H, 4.2; N, 19.6%; M<sup>+</sup> 219.

C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 54.8; H, 4.1; N, 19.2%; M 219.

d) 4,5-Dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) (20.4 g; 88%) was obtained as lemon yellow needles, m. p. 188-9° (from toluene),  $\nu_{\max}$  3250 (NH), 2240 (CN), 1650 (CO), and 1500 and 1330 (NO<sub>2</sub>) cm<sup>-1</sup>,

δ [(CD<sub>3</sub>)<sub>2</sub>SO] 7.80 (1H, s, H-3), 7.46 (1H, s, H-6), 3.96 (2H, s, CH<sub>2</sub>), and 2.30 (6H, s, ArMe).

Found: C, 56.5; H, 4.7; N, 18.0%; M<sup>+</sup> 233.

C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 56.6; H, 4.7; N, 18.0%; M 233

e) 4-Chloro-2-nitro-*α*-cyanoacetanilide (287e) (23.1 g; 96%) was obtained as pale yellow needles, m. p. 185-8° (lit<sup>92</sup> 191-2°).

f) 4-Methoxy-2-nitro-*α*-cyanoacetanilide (287f) (89%) was obtained as lemon yellow needles, m. p. 129-31° (lit<sup>92</sup> 132-4°).

B. The Base Catalysed Cyclisation of 2-Nitro-*α*-cyanoacetanilides (287) to 3-Cyanoquinoxalin-2(1H)-one 4-N-Oxides (282).

General Method (A)<sup>89</sup>

A solution of the 2-nitro-*α*-cyanoacetanilide (287) (0.02 mol) in pyridine (40.0 ml) was treated with aqueous 1M sodium hydroxide (20.0 ml) and stirred at room temperature for 16 h. The mixture was diluted with water (45.0 ml) and then further worked up as described for the individual reactions below.

a) The mixture from 2-nitro-*α*-cyanoacetanilide (287a) was filtered to give 2-nitroaniline (290a) (2%), m. p. 68-70° (lit 71°) identical (i. r. spectrum) with an authentic sample, and extracted with chloroform to give a viscous gum (1.6 g) which was shown by t.l.c. in ether over silica to be an unresolvable multicomponent mixture. Acidification of the aqueous mother liquor gave 3-cyanoquinoxalin-2(1H)-one 4-oxide (282a) (46%), m. p. 275-7° (lit<sup>92</sup> 278°), identical (i. r. spectrum) with an authentic sample.<sup>22</sup> Extraction of the acidic mother liquor with chloroform gave a negligible quantity of gum.

b) The mixture from 4-methyl-2-nitro-*α*-cyanoacetanilide (287b) was extracted with chloroform to give 4-methyl-2-nitroaniline (290b) (1.38 g; 46%), m. p. 112-114° (lit 117°), identical (i. r. spectrum) with an authentic sample. The aqueous mother liquor was acidified with aqueous 2M



hydrochloric acid to give 3-cyano-6-methylquinoxalin-2(1H)-one 4-oxide (282b) (1.90 g; 47%), m. p. 280-2°, identical (i. r. spectrum) with an authentic sample (see later). Extraction of the acidic mother liquor gave a negligible quantity of gum.

c) The mixture from 5-methyl-2-nitro- $\alpha$ -cyanoacetanilide (287c) was extracted with chloroform to give 5-methyl-2-nitroaniline (290c) (1.2 g; 41%), m. p. 100-3° (lit 110°), identical (i. r. spectrum) with an authentic sample. The aqueous mother liquor was acidified with aqueous 2M hydrochloric acid to give 3-cyano-7-methylquinoxalin-2(1H)-one 4-oxide (282c) (2.02 g; 46%) which crystallised as yellow needles, m. p. 298-9° (from glacial acetic acid),  $\nu_{\max}$  3100 (NH), 2200 (CN), and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 12.81 br (1H, s, NH), 7.95 (1H, d, J<sub>ortho</sub> 8Hz, H-5), 7.23 (1H, d, J<sub>meta</sub> 2Hz, H-8), 7.20 (1H, dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-6), and 2.42 (3H, s, ArMe).

Found: C, 59.2; H, 3.5; N, 20.6%; M<sup>+</sup> 201.

C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> requires: C, 59.6; H, 3.5; N, 20.9%; M 201.

Extraction of the acidic mother liquor with chloroform gave a negligible quantity of gum.

d) The mixture from 4,5-dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) was filtered to give unreacted 4,5-dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) (0.20 g; 43%), m. p. 188-90°, identical (i. r. spectrum) with an authentic sample. Extraction of the mixture with chloroform gave 4,5-dimethyl-2-nitroaniline (290d) (0.08 g; 24%), m. p. 134-7° (lit. 139-40°), identical (i. r. spectrum) with an authentic sample. The aqueous mother liquor was acidified with aqueous 2M hydrochloric acid to yield 3-cyano-6,7-dimethylquinoxalin-2(1H)-one 4-oxide (282d) (0.12 g; 28%) which crystallised as pale yellow needles, m. p. 300-2° (from ethanol),  $\nu_{\max}$  3100 (NH), 2200 (CN) and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.81 (1H, s, H-5), 7.12 (1H, s, H-8), 2.35 (3H, s, ArMe), and 2.32 (3H, s, ArMe).

Found: C, 61.1; H, 4.2; N, 18.8%; M<sup>+</sup> 215.

C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub> requires: C, 61.4; H, 4.2; N, 19.3%; M 215



General Method (B)<sup>22</sup>

A solution of the 2-nitro- $\alpha$ -cyanoacetanilide (287) (0.01 mol) in aqueous 20% w/v potassium hydroxide (20.0 ml) was stirred at room temperature for 0.5 h. during which time an orange solid was precipitated. The mixture was filtered and the residue was treated with aqueous 2M hydrochloric acid (10.0 ml) to give the N-oxide (282). The aqueous filtrate was acidified with aqueous 2M hydrochloric acid and any further product was collected.

a) The cyclisation of 4-chloro-2-nitro- $\alpha$ -cyanoacetanilide (287e) gave 6-chloro-3-cyanoquinoxalin-2(1H)-one 4-oxide (282e) (0.95 g; 43%), m. p. 284-6° (lit<sup>92</sup> 285°), identical (i. r. spectrum) with an authentic sample.<sup>22</sup> Acidification of the aqueous filtrate gave 7-chloro-1-hydroxyquinoxaline-2,3 (1H, 4H)-dione (343b) (1.00 g; 56%), decomp. 340° (lit<sup>22</sup> >340°), identical (i. r. spectrum) with an authentic sample (see later).

b) The cyclisation of 4-methoxy-2-nitro- $\alpha$ -cyanoacetanilide (287f) gave 3-cyano-6-methoxyquinoxalin-2(1H)-one 4-oxide (282f) (2.16 g; 100%) m. p. 260-4° (lit<sup>92</sup> 267°), identical (i. r. spectrum) with an authentic sample.<sup>22</sup> Acidification of the aqueous filtrate gave no further material. 3-Benzoylquinoxalin-2(1H)-one 4-Oxide (323) was prepared by the method of Tennant.<sup>91</sup>

3-Aminoquinoxalin-2(1H)-one 4-Oxide (327) was prepared by the method of Tennant.<sup>91</sup>

3-Cyano-1-hydroxyquinoxalin-2(1H)-one 4-Oxide (319) was prepared by the method of Seng and Ley.<sup>93</sup>

3-Cyano-1-methylquinoxalin-2(1H)-one 4-Oxide (313) was prepared by the method of Tennant.<sup>89</sup>

C. The Reaction of the 3-Cyanoquinoxalin-2(1H)-one 4-Oxides (282), (313) and (319) with Acetyl Chloride in Acetic Acid.

General Method

The corresponding N-oxide (0.002 mol) was heated under reflux with a

mixture of acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. Unless otherwise mentioned, the mixture was cooled to give solid material (A) and then worked up as described for the individual reactions below.

a) Evaporation of the mixture from 3-cyanoquinoxalin-2(1H)-one 4-oxide (282a) and trituration of the residue with ether-ethyl acetate gave a yellow solid which was extracted with hot ethanol to leave unreacted N-oxide (282a) (0.20 g; 52%), m. p. 277-8° (lit<sup>92</sup> 278°), identical (i. r. spectrum), with an authentic sample. 1,3-Diacetylbenzimidazol-2-one (291a) (0.18 g; 40%), m. p. 143-4° crystallised from the ethanolic extract and was identified by comparison (m. p. and i. r. spectrum) with an authentic sample. Evaporation of the ethanol mother liquor gave a brown gum (0.02 g) from which no further identifiable material could be obtained.

b) Evaporation of the mixture from 6-chloro-3-cyanoquinoxalin-2(1H)-one 4-oxide (282e) and trituration of the resulting gum with toluene gave 5-chloro-1,3-diacetylbenzimidazol-2-one (291b) (0.43 g; 77%), which crystallised as yellow needles, m. p. 169-70° (lit<sup>75</sup> 172-3°), identical (i. r. spectrum) with a synthetic sample.<sup>75</sup>

c) Evaporation of the mixture from 3-cyano-6-methylquinoxalin-2(1H)-one 4-oxide (282b) and trituration of the residue with ether-ethyl acetate gave a yellow solid which was crystallised from ethanol to afford 1,3-diacetyl-5-methylbenzimidazol-2-one (291c) (24%) as yellow needles, m. p. 174-5°,  $\nu_{\max}$  1750 and 1705 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.92 (1H, d, J<sub>ortho</sub> 8Hz, H-7), 7.91 (1H, d, J<sub>meta</sub> 2Hz, H-4), 7.06 (1H, dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-6), 2.65 (6H, s, Me) and 2.35 (3H, s, ArMe).

Found: C, 62.1; H, 5.1; N, 12.2%; M<sup>+</sup> 232.

C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub> requires: C, 62.1; H, 5.1; N, 12.1%; M 232.

Evaporation of the crystallisation mother liquor gave 7-chloro-3-cyano-6-methylquinoxalin-2(1H)-one (292a) (60%), as orange rhomboids, m. p. 288-9° (from glacial acetic acid),  $\nu_{\max}$  3150 w (NH), 2200 w (CN), and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.79 (1H, s, H-5), 7.39 (1H, s, H-8), and 2.41 (3H, s, ArMe).

Found: C, 54.9; H, 2.9; N, 19.2%;  $M^+$  219, 221.

$C_{10}H_5ClN_3O$  requires: C, 54.8; H, 2.7; N, 19.2%; M 219.5.

d) Evaporation of the mixture from 3-cyano-6-methoxyquinoxalin-2(1H)-one 4-oxide (282f) and trituration of the resulting gum with ether-ethyl acetate gave a brown solid (0.40 g) which was crystallised from ethanol to give a 3:2 mixture of 1,3-diacetyl-5-methoxybenzimidazol-2-one (291d) and 7-chloro-3-cyano-6-methoxyquinoxalin-2(1H)-one (292b), m. p. 159-60<sup>o</sup>,  $\nu_{\max}$  3100 w (NH), 2200 (CN), and 1750, 1700 and 1660 (CO)  $cm^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] (291d) 7.92 (d,  $J_{ortho}$  8Hz, H-7), 7.65 (d,  $J_{meta}$  2Hz, H-4), 6.80 (dd,  $J_{ortho}$  8Hz,  $J_{meta}$  2Hz, H-6), 4.91 (s, MeO) and 2.62 (s, Me), and  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] (292b) 7.46 (s, H-5), 7.40 (s, H-8) and 3.75 (s, MeO).

$M^+$  found: 235, 237 and 248

$C_{12}H_{12}N_2O_4$  (291d) requires: 248.

$C_{10}H_6ClN_3O_2$  (292b) requires: 235.5

Evaporation of the ether-ethyl acetate mother liquor gave a negligible quantity of gum.

e) The mixture from 3-cyano-7-methylquinoxalin-2(1H)-one 4-oxide (282c) was cooled to give (A) 5-chloro-3-cyano-7-methylquinoxalin-2(1H)-one (293a) which was combined with a second crop obtained by evaporation of the filtrate and trituration of the residue with ethyl acetate (99%), and crystallised to give yellow needles, m. p. 238-40<sup>o</sup> (from dimethylformamide-water),  $\nu_{\max}$  3100 (NH), 2200 (CN) and 1670 (CO)  $cm^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.72 (1H, d,  $J_{meta}$  2.0Hz, H-8), 7.36 (1H, d,  $J_{meta}$  2.0 Hz, H-6), and 2.75 (3H, s, ArMe).

Found: C, 54.5; H, 2.8; N, 18.7%;  $M^+$  219, 221.

$C_{10}H_6ClN_3O$  requires: C, 54.8; H, 2.7; N, 19.2%; M 219.5.

f) The mixture from 3-cyano-6,7-dimethylquinoxalin-2(1H)-one 4-oxide (282d) was cooled to give (A) 5-chloro-3-cyano-6,7-dimethylquinoxalin-2(1H)-one (293b) which was combined with a second crop obtained by evaporation of the filtrate and trituration of the residue with light petroleum-

ethyl acetate (0.37 g; 81%), and crystallised to give yellow needles, m. p. 301-2<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3100 w (NH), 2200 (CN) and 1670 (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.65 (1H, s, H-8), 2.44 (3H, s, ArMe) and 2.39 (3H, s, ArMe).

Found: C, 56.6; H, 3.4; N, 11.1%; M<sup>+</sup> 233, 235.

C<sub>11</sub>H<sub>8</sub>ClN<sub>3</sub>O requires: C, 56.5; H, 3.4; N, 10.9%; M 233.5.

Evaporation of the light petroleum-ethyl acetate mother liquor gave a brown gum (0.04 g) from which no further identifiable material could be obtained.

g) The mixture from 3-cyano-1-methylquinoxalin-2(1H)-one 4-oxide (313) was cooled to give (A) 7-chloro-3-cyano-1-methylquinoxalin-2(1H)-one (318) (0.11 g; 26%), m. p. 303-5<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  2200 w (CN) and 1660 (CO) cm<sup>-1</sup>.

M<sup>+</sup> found: 219, 221.

C<sub>10</sub>H<sub>6</sub>ClN<sub>3</sub>O requires: 219.5

Because of the highly insoluble nature of the solid (318) attempts to purify it for elemental and <sup>1</sup>H n.m.r. analysis proved unsuccessful.

Evaporation of the acetyl chloride/acetic acid mother liquor and trituration of the residue with ether-ethyl acetate gave 7-acetoxy-3-cyano-1-methylquinoxalin-2(1H)-one (317) (0.18 g; 38%), which crystallised as yellow needles, m. p. 189-90<sup>o</sup> (from ethanol),  $\nu_{\max}$  2250 (CN), 1770 and 1670 (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.98 (1H, d, J<sub>ortho</sub> 9Hz, H-5), 7.52 (1H, d, J<sub>meta</sub> 2.5Hz, H-8), 7.34 (1H, dd, J<sub>ortho</sub> 9Hz, J<sub>meta</sub> 2.5Hz, H-6), 3.59 (3H, s, NMe) and 2.35 (3H, s, Me).

Found: C, 58.5; H, 3.6; N, 17.3%; M<sup>+</sup> 243.

C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 59.2; H, 3.7; N, 17.3%; M 243.

Evaporation of the ether-ethyl acetate mother liquor gave a negligible quantity of gum.

h) Evaporation of the mixture from 3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (319) and trituration of the residual gum with methanol gave 1-acetoxy-3-cyanoquinoxalin-2(1H)-one 4-oxide (320) (0.31 g; 75%), which crystallised as bright yellow needles, m. p. 185-7<sup>o</sup> (from ethanol-glacial



acetic acid),  $\nu_{\max}$  2250 (CN), 1820 and 1695 (CO)  $\text{cm}^{-1}$ ,  $\delta [(\text{CD}_3)_2\text{SO}]$  8.32-7.4 (4H, m, ArH) and 2.59 (3H, s, Me).

Found: C, 53.6; H, 2.9; N, 17.0%;  $M^+$  245.

$\text{C}_{11}\text{H}_7\text{N}_3\text{O}_4$  requires: C, 53.9; H, 2.9; N, 17.1%; M 245

Evaporation of the methanol mother liquor gave a dark intractable gum (0.06 g).

D. The Reaction of 3-Benzoylquinoxalin-2(1H)-one 4-Oxide (323) with Acetyl Chloride in Acetic Acid.

3-Benzoylquinoxalin-2(1H)-one 4-oxide (323) (0.53 g; 0.002 mol) was heated under reflux with acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. Evaporation of the mixture and trituration of the residue with light petroleum-ethyl acetate gave quinoxaline-2,3(1H,4H)-dione (343a) (0.46 g; 67%) which crystallised as pink needles, m. p.  $>350^\circ$  (from glacial acetic acid) identical (i. r. spectrum) with an authentic sample (see later). Evaporation of the light petroleum-ethyl acetate mother liquor gave a dark, viscous gum (0.05 g) which was shown by t. l. c. in toluene over alumina to be an unresolvable multicomponent mixture.

E. The Reaction of 3-Aminoquinoxalin-2(1H)-one 4-Oxide (327) with Acetyl Chloride in Acetic Acid.

3-Aminoquinoxalin-2(1H)-one 4-oxide (327) (0.36 g; 0.002 mol) was heated under reflux with acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. The mixture was hot-filtered to give 3-acetyl-amino-7-chloroquinoxalin-2(1H)-one (331) which was combined with a second crop obtained by cooling the filtrate (0.33 g; 85%), and crystallised to give fawn rhomboids, m. p.  $325-7^\circ$  (from dimethylformamide),  $\nu_{\max}$  3380 and 3150 (NH), 1680 and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta [(\text{CD}_3)_2\text{SO}]$  7.54 (1H, d,  $J_{\text{ortho}}$  8Hz, H-5), 7.24 (1H, d,  $J_{\text{meta}}$  2Hz, H-8), 7.20 (1H, dd,  $J_{\text{ortho}}$  8Hz,  $J_{\text{meta}}$  2Hz, H-6) and 2.37 (3H, s,  $\text{CH}_3$ ).



Found: C, 50.5; H, 3.6; N, 17.7%;  $M^+$  237, 239

$C_{10}H_8ClN_3O_2$  requires: C, 50.6; H, 3.4; N, 18.0%;  $M$  237.5.

Evaporation of the mother liquors gave a quantity of dark gum (0.04 g) from which no identifiable material could be obtained.

F. The Reactions of 3-Cyanoquinoxalin-2(1H)-ones with Acetic Anhydride

General Method

The N-oxide (0.004 mol) was heated under reflux with acetic anhydride (20.0 ml) for 48 h. The mixture was cooled and then worked up as described for the individual experiments.

a) The mixture from 3-cyanoquinoxalin-2(1H)-one 4-oxide (282a) was filtered to give unreacted N-oxide (282a) (0.28 g; 37%), m. p.  $273-5^\circ$  (lit.<sup>92</sup>  $278^\circ$ ), identical (i. r. spectrum), with an authentic sample. Evaporation of the filtrate and trituration of the residue with toluene gave 1,3-diacetylbenzimidazol-2-one (291a) (0.40 g; 43%), which crystallised as yellow needles, m. p.  $153-4^\circ$  (from ethanol) (lit.<sup>75</sup>  $153-4^\circ$ ),  $\nu_{\max}$  1760 and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 8.10 (2H, q,  $J_{\text{ortho}}$  6Hz,  $J_{\text{meta}}$  2Hz, H-4, 7), 7.25 (2H, q,  $J_{\text{ortho}}$  6Hz,  $J_{\text{meta}}$  2Hz, H-5, 6) and 2.62 (6H, s, Me).

Found: C, 60.3; H, 4.6; N, 12.9%;  $M^+$  218.

Calc. for  $C_{11}H_{10}N_2O_3$ : C, 60.5; H, 4.6; N, 12.9%;  $M$  218.

Evaporation of the toluene mother liquor gave a negligible quantity of gum.

b) The mixture from 3-cyano-1-methylquinoxalin-2(1H)-one 4-oxide (313) was filtered to give an intractable black solid (0.14 g), m. p.  $>300^\circ$ , from which no identifiable material could be obtained. Evaporation of the filtrate gave a dark gum which was trituated with water, followed by toluene to give a black solid (0.56 g), -m. p.  $120-40^\circ$ . Kugelrohr distillation of this solid under reduced pressure gave 3-cyano-1-methylquinoxalin-2(1H)-one (333) (0.28 g; 30%), m. p.  $200-2^\circ$ , (lit.<sup>89</sup>  $211^\circ$ ),  $\nu_{\max}$  2200 (CN) and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.99-7.39 (4H, m. ArH) and 3.65 (3H, s, NMe).

Found: C, 64.9; H, 3.9; N, 22.9%;  $M^+$  185.

Calc. for  $C_{10}H_7N_3O$ : C, 64.9; H, 3.9; N, 22.7%  $M$  185.

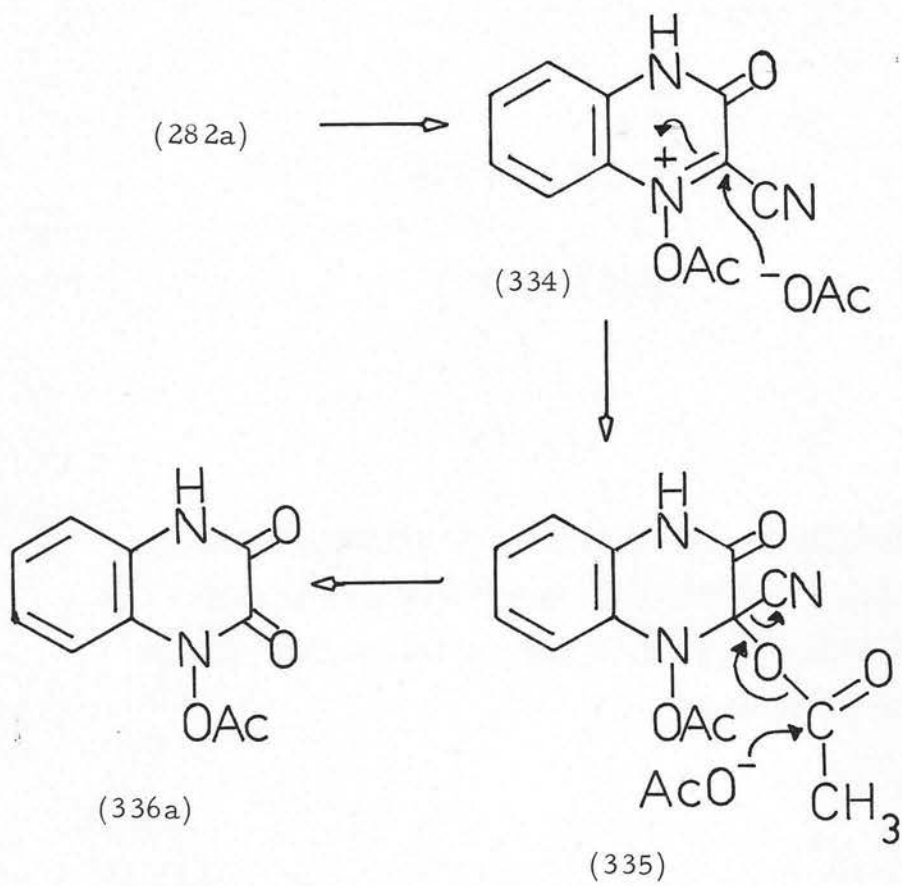
No further identifiable material could be obtained from the residual char (0.23 g).

c) Evaporation of the mixture from 3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (319) and trituration of the residue with toluene gave a solid which was combined with a second crop obtained by evaporating the toluene mother liquor and treatment with ether to give 1-acetoxy-3-cyano-quinoxalin-2(1H)-one 4-oxide (320) (0.78 g; 79%), m. p.  $185-7^{\circ}$ , identical (i. r. spectrum) with a sample obtained previously. Evaporation of the ether mother liquor gave a dark intractable gum (0.12 g), which was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture.

## CHAPTER FOUR

### DISCUSSION

Studies on the Reactions of N-Hydroxyquinoxaline-  
2, 3(1H, 4H)-diones with Acetyl Chloride in Acetic  
Acid and with Acetic Anhydride and on their Ther- -  
molytic Reactions.

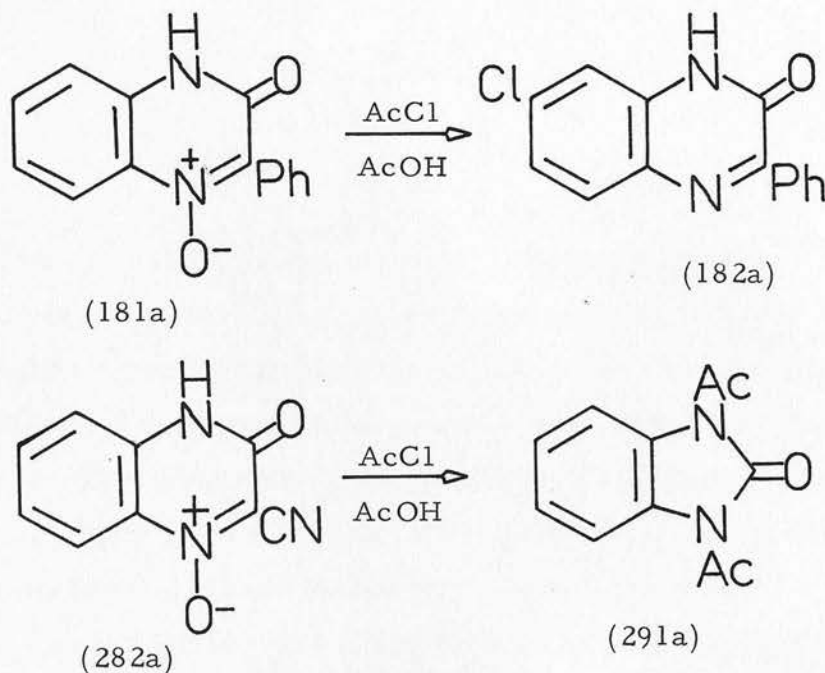


Scheme 62

4. 1 Reactions of 1-Hydroxyquinoxaline-2,3(1H,4H)-diones  
with Acetyl Chloride in Acetic Acid and with Acetic  
Anhydride

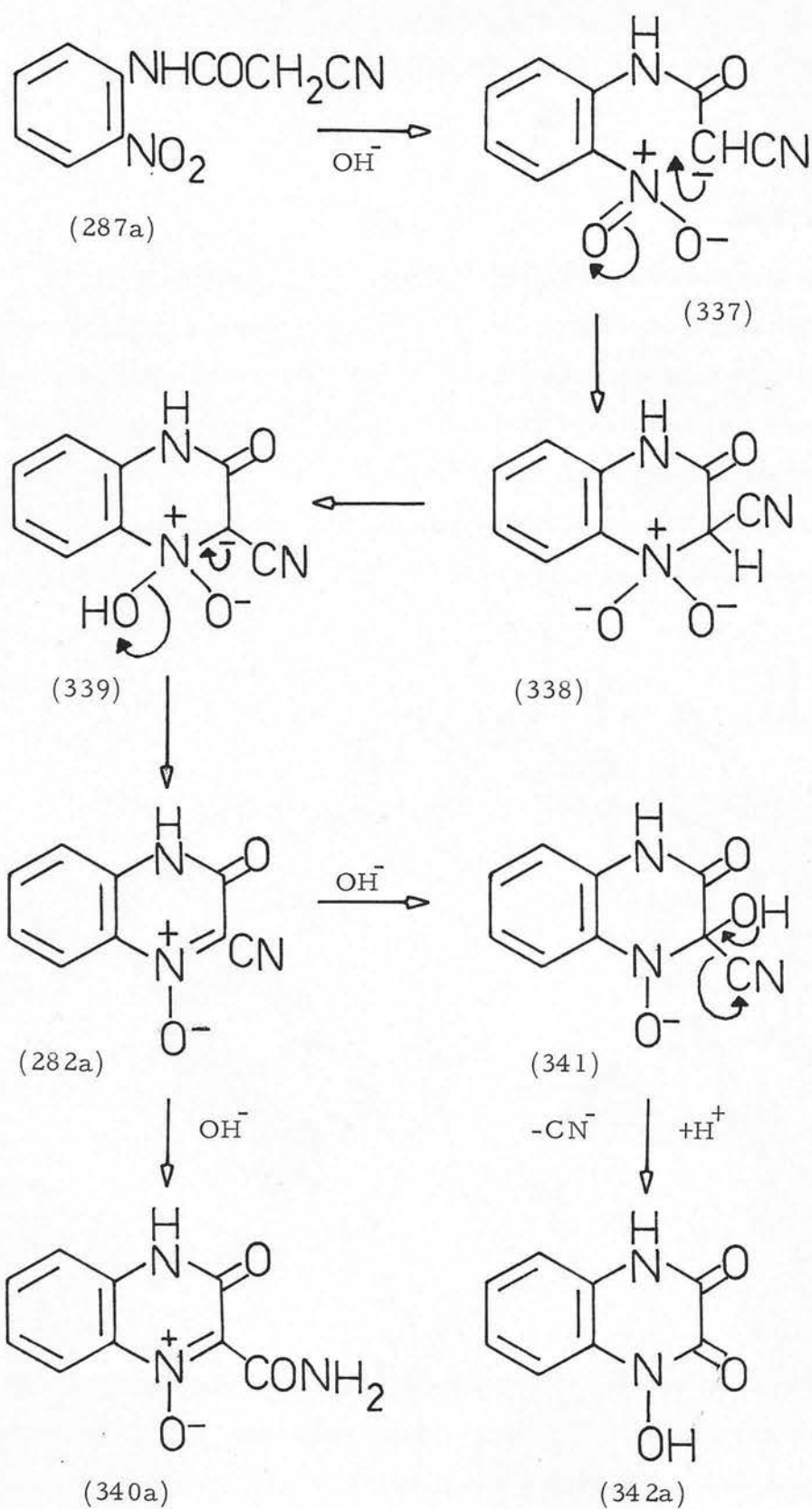
a) Introduction

As was discussed in Chapter 3, when the N-oxide (181a) is heated with acetyl chloride, the product isolated is the 7-chloro derivative (182a). In marked contrast, when the N-oxide (282a), in which the substituent at the C-3 position of the hetero ring is a cyano group, is similarly treated with acetyl chloride, no chloro-substituted derivative is produced. Instead, the compound isolated is the benzimidazolone (291a). As already mentioned (Chapter 3), it is conceivable that prior



to reaction with the nucleophilic reagent, the cyano group in the N-oxide (282a) is displaced from the C-3 position furnishing the quinoxalinedione (336a) [cf. scheme 62]. Hence the ring contraction [(282a)  $\rightarrow$  (291a)] (as opposed to substitution) observed in the reaction of the cyano N-oxide (282a) with acetyl chloride might be a transformation of the N-acetoxyquinoxalinedione (336a) and not the N-oxide (282a) itself. Consequently



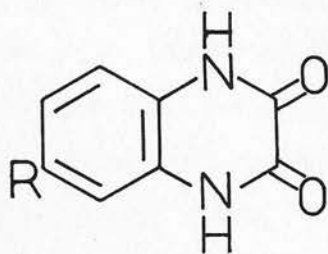


Scheme 63

it was considered of interest to synthesise the N-hydroxyquinoxalinedione (342a) and to study its reactivity with acetyl chloride in an attempt to observe ring contraction to the benzimidazolone (291a).

b) Reactions of N-Hydroxyquinoxalinediones (342) with Acetyl Chloride in Acetic Acid.

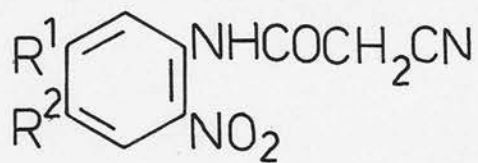
The N-hydroxyquinoxalinedione (342a) is readily synthesised on a relatively small scale by cyclisation of the cyanoacetanilide (287a) in hot aqueous 20% potassium hydroxide.<sup>89</sup> However on a larger scale this method is complicated by co-formation of the reduced quinoxalinedione (343a),<sup>22</sup> presumably as a result of reduction of the N-hydroxyquinoxaline-



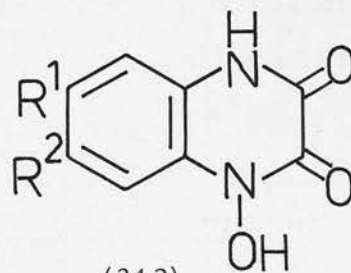
(343)

R  
a; H  
b; Cl

dione (342a) in the alkaline medium. However, in the present studies, the N-hydroxyquinoxalinedione (342a) was found to be readily formed in high yield by simply stirring the anilide (287a) in cold aqueous 20% potassium hydroxide. The known amide (340a)<sup>94</sup> was also formed as a minor by-product. The structure of the N-hydroxyquinoxalinedione (342a) was confirmed by mild acetylation to the N-acetoxy derivative (336a) whose i. r. spectrum showed a band at  $1800\text{ cm}^{-1}$  characteristic<sup>84</sup> of a cyclic N-acetoxy group. Unexpectedly this acetylation also afforded as a by-product the N,N-diacetylbenzimidazolone (291a) which was identified by comparison with an authentic sample. The mode of formation of the product (291a) will be discussed later. The base-catalysed cyclisation of the cyanoacetanilide (287a) to the N-hydroxyquinoxalinedione (342a) can be rationalised by the mechanism outlined in scheme 63. Proton abstraction from the active methylene group in (287a) is followed by nucleophilic attack on the nitro group by the resulting carbanion (337) to give the cyclic adduct (338). Loss of the elements of water from the latter yields the cyanoquinoxalinone N-oxide (282a) which then undergoes nucleophilic substitution by hydroxide

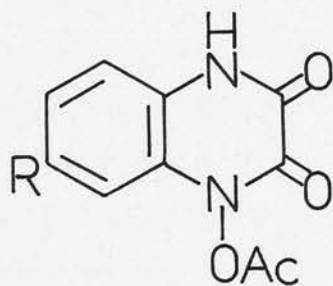


(287)



(342)

	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>
a;	H	H
b;	H	Me
c;	Me	H
d;	Me	Me
e;	H	Cl
f;	H	MeO



(336)

	<u>R</u>
a;	H
b;	Cl

ion at C-3, with displacement of the cyano group, to give the N-hydroxyquinoxalinedione (342a).

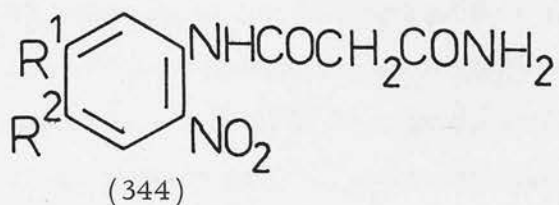
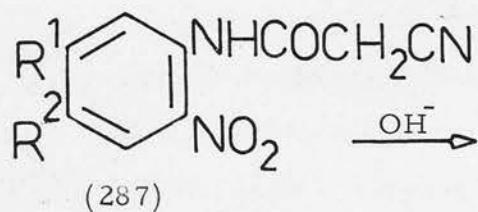
The N-hydroxy compound (342a) reacted with acetyl chloride in glacial acetic acid to give a moderate yield of the 7-chloro derivative (343b). This compound was characterised by comparison with an authentic sample (see later). The predominant chloro-substitution and lack of ring contraction observed in the reaction of the N-hydroxy compound (342a) with acetyl chloride in acetic acid is in marked contrast to the predominant ring contraction which occurs in the analogous reaction of the N-oxide (282a). Hence the N-acetoxy compound (336a) cannot (as postulated previously) be an intermediate in the latter reaction. However, as noted in chapter 3, the mode of reaction of 3-cyanoquinoxalinone N-oxides with acetyl chloride in acetic acid is markedly influenced by the nature of substituents in the benzene ring, some substituted quinoxalinones undergoing chloro-substitution as opposed to the ring-contraction observed with the parent N-oxide (282a). It was therefore considered of interest to study in turn the reactions of N-hydroxyquinoxalinediones, substituted in the benzene ring, with acetyl chloride in acetic acid in the hope that the behaviour of such substituted compounds might shed further light on the mechanisms involved in chloro-substitution and ring-contraction. Towards this end, attention was directed to the synthesis of a series of substituted N-hydroxyquinoxalinediones (342b-f).

The N-hydroxy compounds (342b) and (as described in chapter 3) (342e) were formed in moderate yield, as for the parent compound (342a), by cyclising the corresponding cyanoacetanilides (287b and e) in aqueous 20% w/v potassium hydroxide at room temperature. In contrast to the reaction leading to the parent compound (342a) however, cyclisation of the anilides (287b and e) also resulted in formation of the N-oxides (282b and e). The attempted cyclisation of the cyanoacetanilide (287d) in cold aqueous potassium hydroxide produced the N-oxide (282d) in low yield, the major proportion of the cyanoacetanilide (287d) being recovered unchanged. The isolation of the intermediate N-oxides (282b, d and e) in these reactions indicated that the reaction conditions were too mild to fully convert the cyanoacetanilides (287b, d and e) into the corresponding

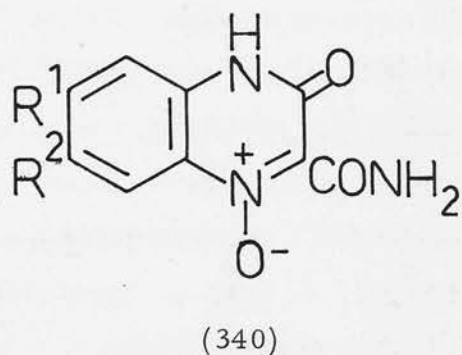
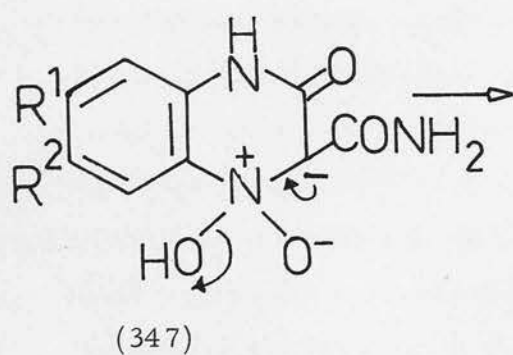
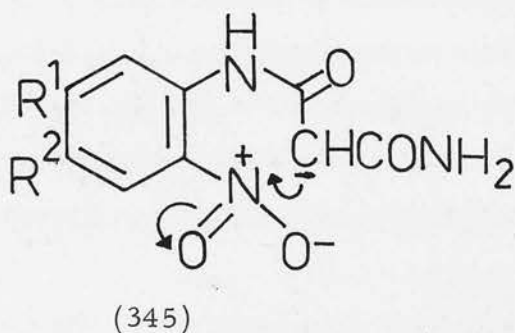
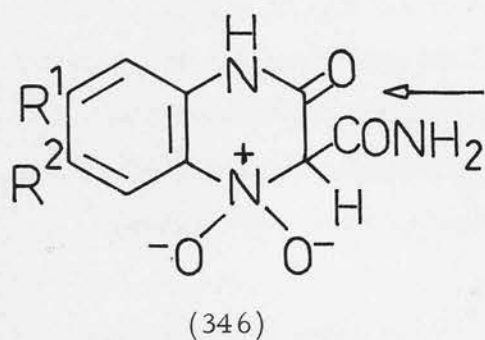
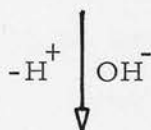
N-hydroxy compounds (342). When the cyclisation of the anilides (287b and e) was carried out in aqueous 20% potassium hydroxide at 50°C, the N-hydroxy compounds (342b and e) were produced in high yield. The compound (342e) was characterised by comparison with an authentic sample.<sup>22</sup> The methyl derivative (342b) had not been prepared previously. However, satisfactory spectral evidence was obtained for the assigned structure. Its i. r. spectrum contained broad bands at 3450 and 1690 cm<sup>-1</sup> characteristic of an N-hydroxyquinoxalinedione derivative while its <sup>1</sup>H n. m. r. spectrum contained a broad unsplit signal assigned to the proton at N-4 and a three proton singlet at δ2.69 attributable to an aromatic C-methyl group. The aromatic region of the <sup>1</sup>H n. m. r. spectrum contained a poorly resolved multiplet which could not be unequivocally assigned to a 1,2,4-trisubstituted benzene derivative. The structure assigned to the N-hydroxy compound (342e) was further established by mild acetylation to the N-acetoxy compound (336b) which showed spectroscopic properties consistent with its cyclic N-acetoxy structure.

The N-hydroxy compound (342f) was synthesised in moderate yield by cyclisation of the cyanoacetanilide (287f) in aqueous potassium hydroxide at 50°C. However, the N-oxide (282f) was also produced in good yield in this reaction. Both of the compounds (282f) and (342f) were characterised by comparison with authentic samples.<sup>22</sup> Base catalysed cyclisation of the cyanoacetanilide (287c), bearing a methyl substituent at a position para to the nitro group, at 50°C gave only a low yield of the N-hydroxy compound (342c) which gave analytical and mass spectral data and showed spectroscopic properties consistent with the assigned structure. In particular, it showed i. r. absorption consistent with a cyclic hydroxamic acid structure and its <sup>1</sup>H n. m. r. spectrum exhibited a splitting pattern in the aromatic region characteristic of a 1,2,4-trisubstituted benzene derivative. The base-catalysed cyclisation of the anilide (287c) also gave a by-product whose analytical and spectral properties were consistent with its being the amide (340c). The attempted synthesis of the N-hydroxy compound (342d) from the dimethylanilide (287d) in aqueous 20% potassium hydroxide at 50°C proved unsuccessful, the product being a mixture of the





- |    |                          |                          |
|----|--------------------------|--------------------------|
|    | $\underline{\text{R}}^1$ | $\underline{\text{R}}^2$ |
| a; | H                        | H                        |
| c; | Me                       | H                        |
| d; | Me                       | Me                       |

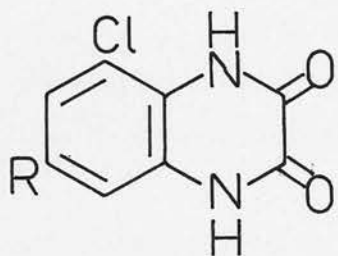


Scheme 64

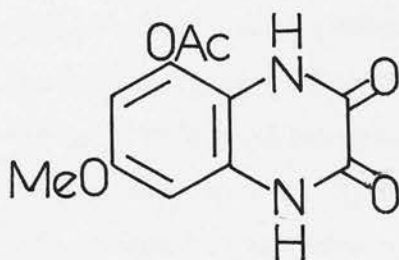
parent amine (290d) and the quinoxalinecarboxamide (340d) both of which were characterised by comparison with authentic samples. The base-catalysed formation of the amides (340a, c and d) from the anilides (287a, c and d) is explicable either by initial hydrolysis of the cyano group in the corresponding cyanoacetanilides (287) to give the amides (344) followed by base-catalysed cyclisation (scheme 64) or by the intermediate formation and subsequent hydrolysis of the cyanoquinoxalinone N-oxides [cf (282a)  $\rightarrow$  (340a); scheme 63].

In an attempt to improve the yield of the N-hydroxy compound (342c), the cyano N-oxide (282c) was treated with aqueous 1M sodium hydroxide under reflux. However, the only product obtained under these conditions was the amide (340c) which was identified by comparison with a sample obtained before. Similarly, an attempt to synthesise the N-hydroxy compound (342d) by treatment of the cyano N-oxide (282d) with aqueous 20% w/v potassium hydroxide gave a low yield of the amide (340d) together with a high yield of unreacted N-oxide (282d). The amide (340d) showed spectral properties consistent with the assigned structure but analysed as a dimethylformamide solvate.

It might reasonably be expected that the introduction of an electron donating methyl substituent into the C-7 position of the N-hydroxy compound (342a) would reduce the electrophilic character of the neighbouring C-6 position thus making the methyl derivative (342b) less susceptible to nucleophilic attack at C-6 than the parent N-hydroxy compound (342a). Correspondingly, if the processes of substitution and ring contraction occur competitively, the presence of a C-7 methyl group might promote ring contraction at the expense of substitution. The formation of a product of ring contraction would provide indirect evidence for the intermediacy of an N-acetoxyquinoxalinedione of the type (336a) in the reactions of the cyano N-oxides (282) with acetyl chloride in acetic acid. However, when the N-hydroxy compound (342b) was heated under reflux with acetyl chloride in acetic acid, the sole product isolated was the chloro-derivative (348a). No product of ring contraction could be detected in the reaction mixture. Satisfactory mass and i. r. spectral evidence was obtained for the assigned structure (348a). The  $^1\text{H}$  n. m. r.



(348)



(349)

R

a; Me

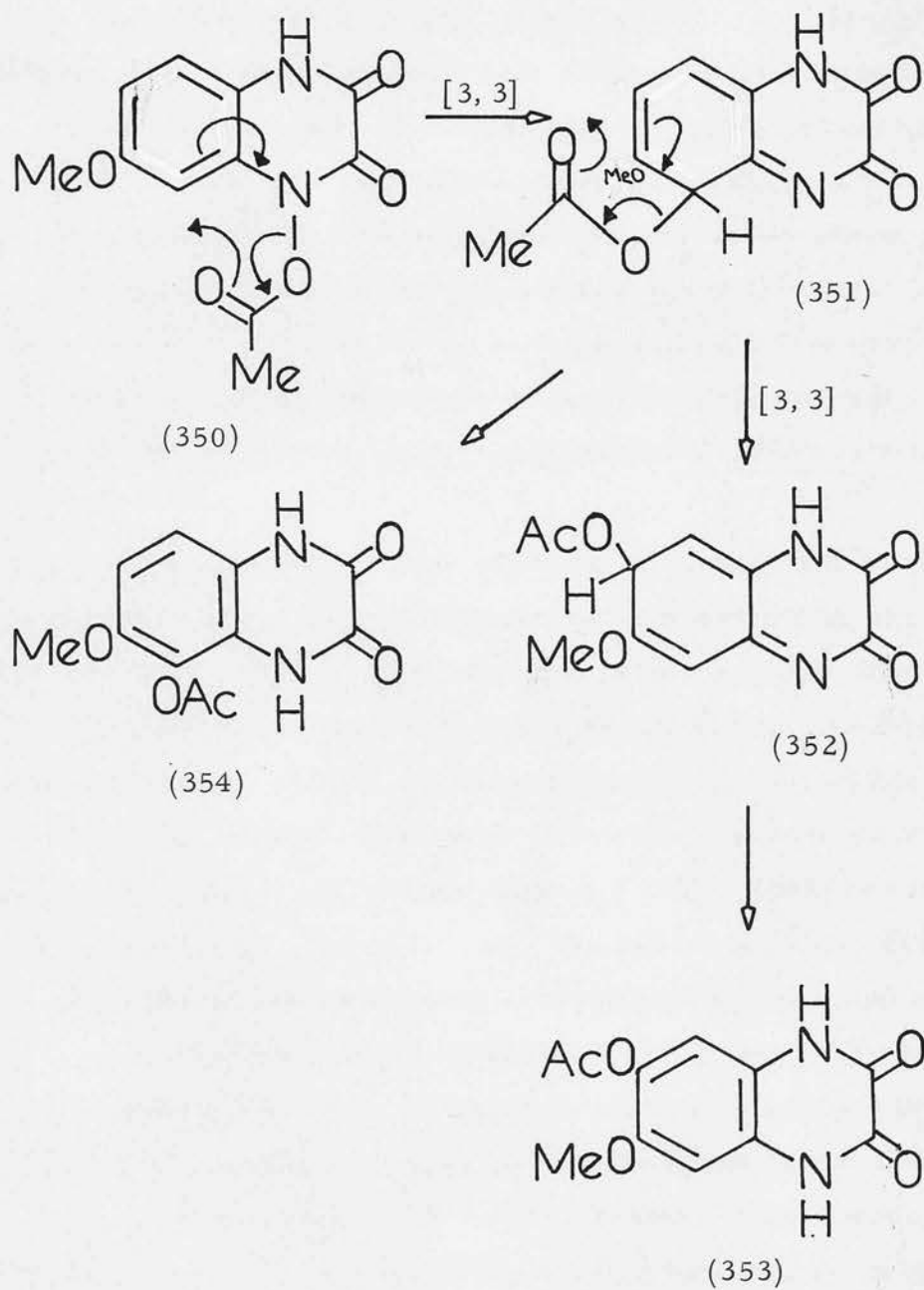
b; MeO

c; Cl

spectrum contained a three proton singlet at  $\delta 2.25$  which is assigned to the methyl group at C-6. The aromatic region of the spectrum contained two one proton signals which showed up as doublets with coupling constants of 2Hz, characteristic of meta coupling, thus unambiguously defining the orientation of the chloroquinoxalinedione as (348a). No other orientation would result in meta coupling of the two aromatic hydrogens. The failure of the N-hydroxyquinoxalinediones (342a and b) to undergo ring contraction on heating with acetyl chloride in acetic acid makes it unlikely that the ring contraction observed with the 3-cyanoquinoxalinone N-oxides (282) involves N-hydroxyquinoxalinedione intermediates.

The effect of the even more strongly electron releasing methoxyl group on the course of the reaction was studied by reacting the N-hydroxy compound (342f) with acetyl chloride in acetic acid. This reaction gave a readily separated mixture of the 5-chloro- and 5-acetoxy-derivatives (348b) and (349) the former predominating. The elemental analyses and mass spectra of both products were fully consistent with the assigned structures (348b) and (349). The i. r. spectrum of the product (349) contained bands at  $3350\text{ cm}^{-1}$  and  $1690\text{ cm}^{-1}$  and  $1760\text{ cm}^{-1}$  consistent with the presence of a quinoxalinedione nucleus and a C-acetoxy group, respectively. The i. r. spectrum of the chloro compound (348b) was likewise typical of a quinoxalinedione derivative. The C-5 position for the entering chloro- or acetoxy-substituent in the compounds (348b) and (349) is unambiguously demonstrated by their  $^1\text{H}$  n. m. r. spectra which show aromatic splitting patterns characteristic of 1,2,3,5-tetrasubstituted benzene derivatives.

The outcome of the reaction of the methoxy compound (342f) with acetyl chloride in acetic acid is surprising for two reasons. Firstly, because of the predominant formation of the acetoxy derivative (349) rather than the 5-chloro derivative (348b). This contrasts with all of the other reactions involving acetyl chloride where the chloro-substituted product is exclusively formed. Secondly, because the position substituted (i.e. C-5) is atypical of reactions of this type wherein nucleophilic attack would have been expected to be directed to the C-6 (or C-8) positions



Scheme 65



by loss of the N-hydroxy group. Moreover, the formation of the acetoxy-derivative (349) cannot be rationalised by stepwise [3,3] sigmatropic shifts of the type shown in scheme 65, since these processes would again lead to placement of the acetoxy group in the C-6 or C-8 positions. Possible mechanisms for the formation of the products (348b) and (349) will be discussed later.

On the initial assumption that ring contraction of the N-hydroxy-quinoxalinediones might involve deprotonation at N-4 with ring opening to an isocyanate intermediate (see chapter 2 and later), it was anticipated that an electron withdrawing chloro substituent at C-7 in an N-hydroxy-quinoxalinedione (342) might promote ring contraction to a benzimidazolone derivative. Thus, electron withdrawal by the C-7 chloro group should enhance the acidity of the proton at N-4 making proton withdrawal and hence ring-opening and subsequent ring contraction (see chapter 2, scheme 27) occur more readily. In practice, however, though heating the chloro-compound (342e) with acetyl chloride in acetic acid did give the ring contracted compound 5-chloro-1,3-diacetylbenzimidazol-2-one (291b), the major product was the 5,7-dichloroquinoxalinedione (348c). The products (348c) and (291b) were isolated in the ratio of 4:1. The melting point of the ring contracted product from the 1-hydroxyquinoxalinedione (342e) was identical to that of the benzimidazolone (291b) described by Ahmad et al.<sup>75</sup> and its analytical and spectral properties further confirmed the identity of this compound. The product (348c) analysed correctly for the assigned structure and its mass spectrum contained peaks at 230, 232, and 234 mass units with the isotopic pattern characteristic of a molecule containing two chlorine atoms. Likewise its ir. spectrum showed bands attributable to a quinoxalinedione structure and its <sup>1</sup>H n. m. r. spectrum contained two one proton doublets at  $\delta$ 7.25 and  $\delta$ 7.08, each with a coupling constant of 2Hz, characteristic of benzenoid protons situated meta to each other and assigned to the C-8 and C-6 protons, respectively. The lower field position for the proton at C-8 is in accord with its close proximity to N-1.

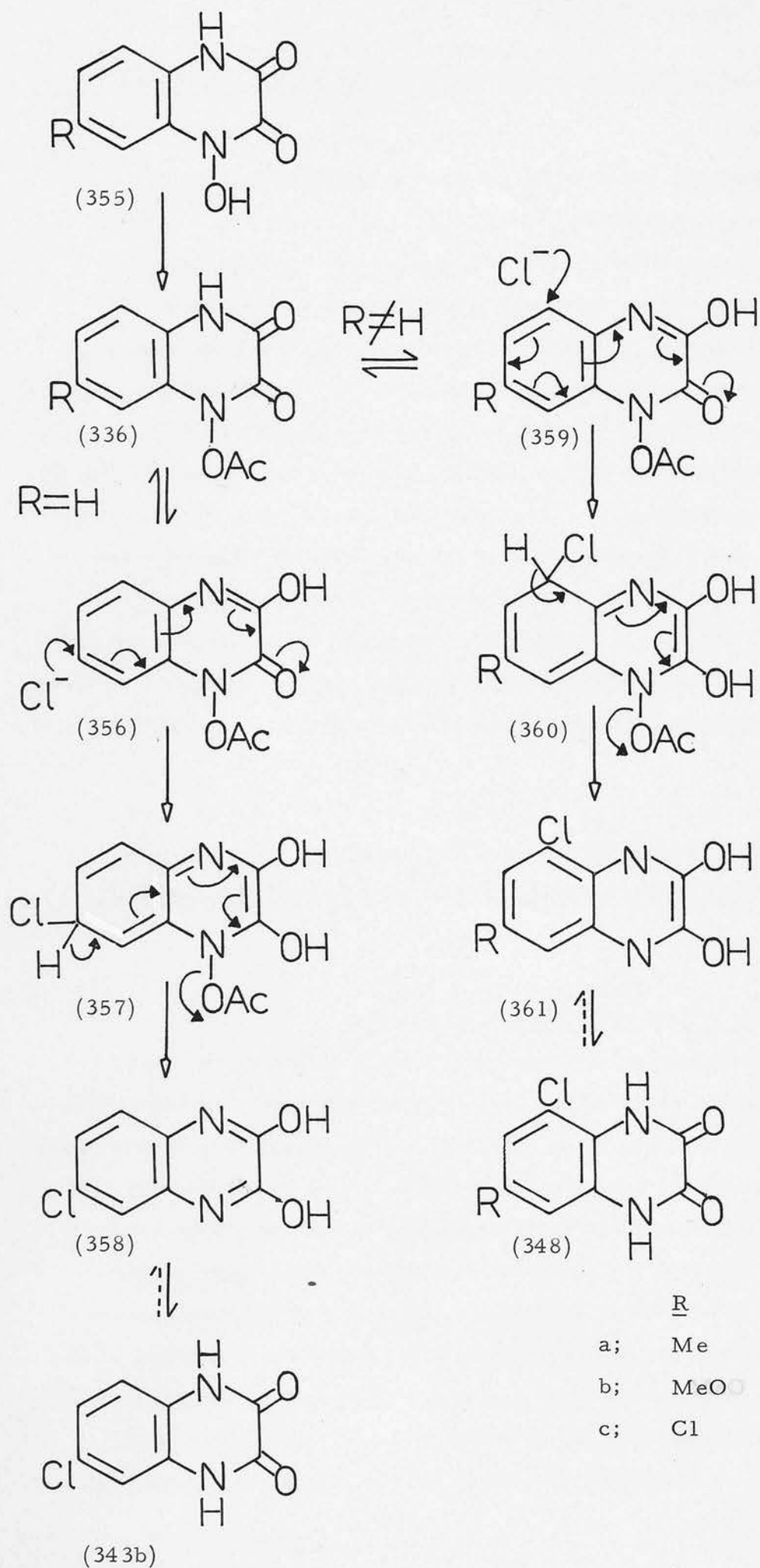
c) Reactions of the N-Hydroxyquinoxalinediones (342a and e) with Acetic Anhydride.

The predominant substitution as opposed to ring contraction observed in the reactions of the N-hydroxyquinoxalinediones (342) with acetyl chloride in acetic acid prompted a study of the corresponding reactions with acetic anhydride to see if substitution was again the preferred course followed. However, heating the N-hydroxy compound (342a) under reflux in acetic anhydride gave the di-N-acetylbenzimidazolone (291a) in quantitative yield. The similar reaction of the chloro-derivative (342e) likewise resulted entirely in ring contraction to the benzimidazolone (291b) rather than substitution. Also isolated in this latter reaction was a product subsequently identified as the chloroquinoxalinedione (343b). The mode of formation of this product is not clear but must involve reduction at some stage. It is possible that the deoxygenation of (342e) to (343b) in hot acetic anhydride is a thermal process. Studies concerning the thermal deoxygenation of N-oxygenated quinoxalinediones are described later.

d) Discussion of the Mechanisms of the Reactions of 1-Hydroxy-quinoxaline-2,3(1H,4H)-diones with Acetyl Chloride in Acetic Acid and Acetic Anhydride.

(i) Substitution by Chloride Ion and Acetate Ion

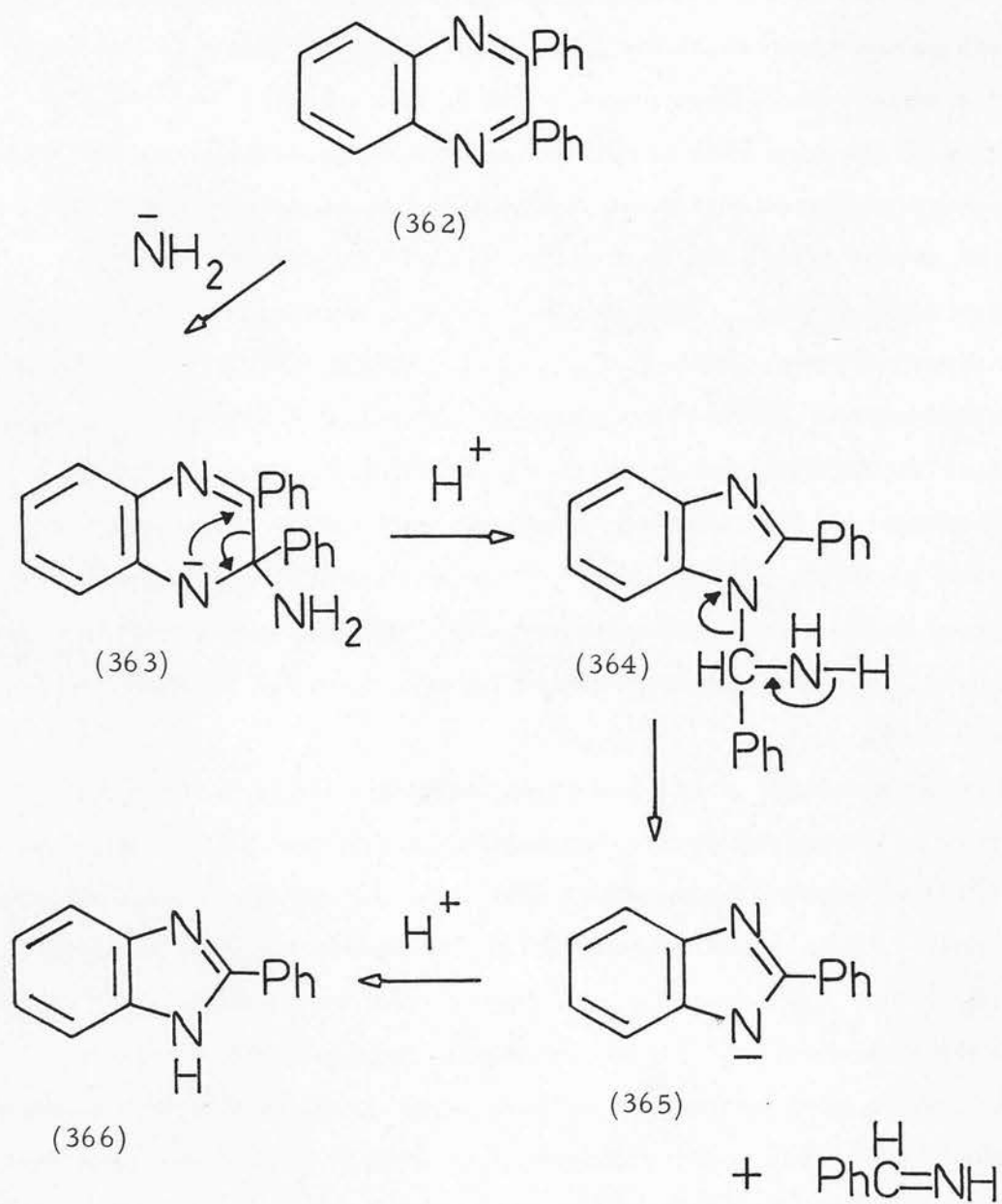
As mentioned previously, had nucleophilic attack on the fused benzene nucleus in the reactions of the N-hydroxyquinoxalinediones (342) with acetyl chloride in acetic acid been directed by loss of the 1-hydroxy group, substitution would have been expected to occur at the C-6 (or C-8) position. Since substitution in these reactions was observed to occur at the C-5 or C-7 positions, the substitution reactions undergone by the quinoxalinediones (342) cannot be rationalised by a mechanistic scheme analogous to that proposed in chapter 3 to account for the formation of the chloro-substituted products on reaction of the 3-cyano N-oxides (282) with acetyl chloride in acetic acid [cf. scheme 53]. The formation of the 7-chloroquinoxalinedione (343b) and the 5-chloroquinoxalinediones (348)



Scheme 66

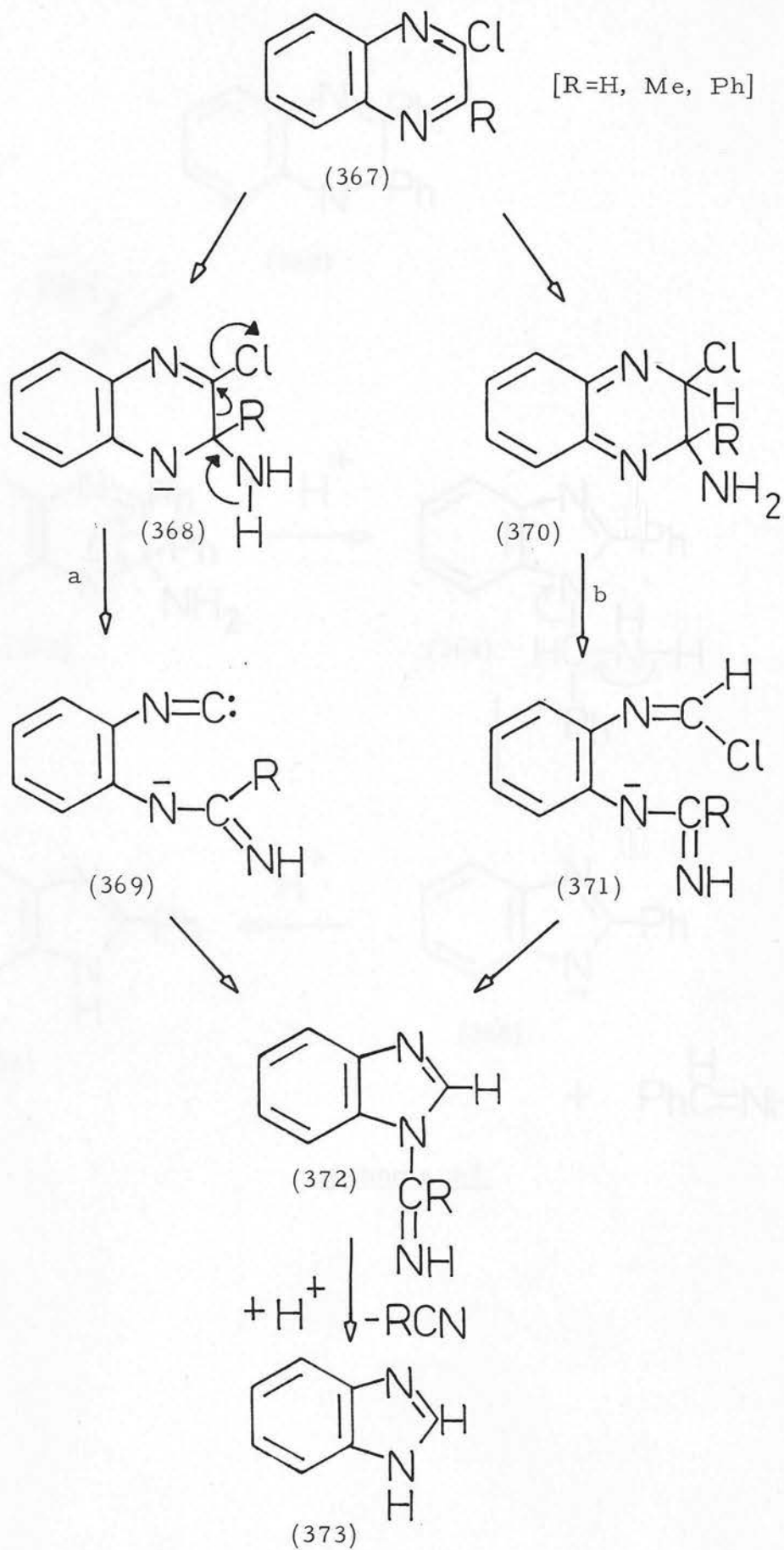
is explicable by the courses outlined in scheme 66. The key step in this mechanism involves reaction of the presumed N-acetoxy intermediate (336) in the enolic form as shown, thus accounting for the C-5 and C-7 substitution observed. Thus nucleophilic attack by chloride ion at the C-7 position of the enol (356) would afford the paraquinonoid intermediate (357) which upon rearomatisation, with expulsion of the elements of acetic acid, would afford the enol (358) which is tautomeric with the observed product (343b). With the C-7 position blocked, nucleophilic attack is directed towards the C-5 position. Thus, the formation of the 5-chloro derivatives (348a-c) may be rationalised analogously. Nucleophilic attack by chloride ion at the C-5 position of the enol (359) would afford the adduct (360), convertible into the enol (361), tautomeric with the observed products (348), by loss of the elements of acetic acid. Formation of the 5-acetoxyquinoxalinedione (349) can be rationalised by a course analogous to that proposed for formation of the 5-chloro derivatives (348).

The involvement of an N-acetoxy intermediate in these substitution mechanisms is supported by the demonstration that the N-hydroxy compound (342e) is recovered unchanged after heating with hydrochloric acid in acetic acid. This result shows that the N-hydroxy group, even when protonated, is not a sufficiently good leaving group to promote nucleophilic attack on the benzene ring. In an attempt to demonstrate the intermolecular nature of the substitution reactions, the N-acetoxyquinoxalinedione (336a) was heated under reflux with propionic acid in the hope that propionate ion would substitute the fused benzene nucleus where its presence would be readily detected by spectroscopic means. In practice, however, the N-acetoxyquinoxalinedione (336a) gave a good yield of the quinoxalinedione (343a) when heated with propionic acid and no product of propionate substitution could be detected. The formation of the quinoxalinedione (343a) from the N-acetoxy compound (336a) in hot propionic acid is difficult to rationalise although it must involve reduction at some stage. It is possible that the deoxygenation process is thermal. Studies concerning the thermal deoxygenation of N-oxygenated quinoxalinediones are described later.

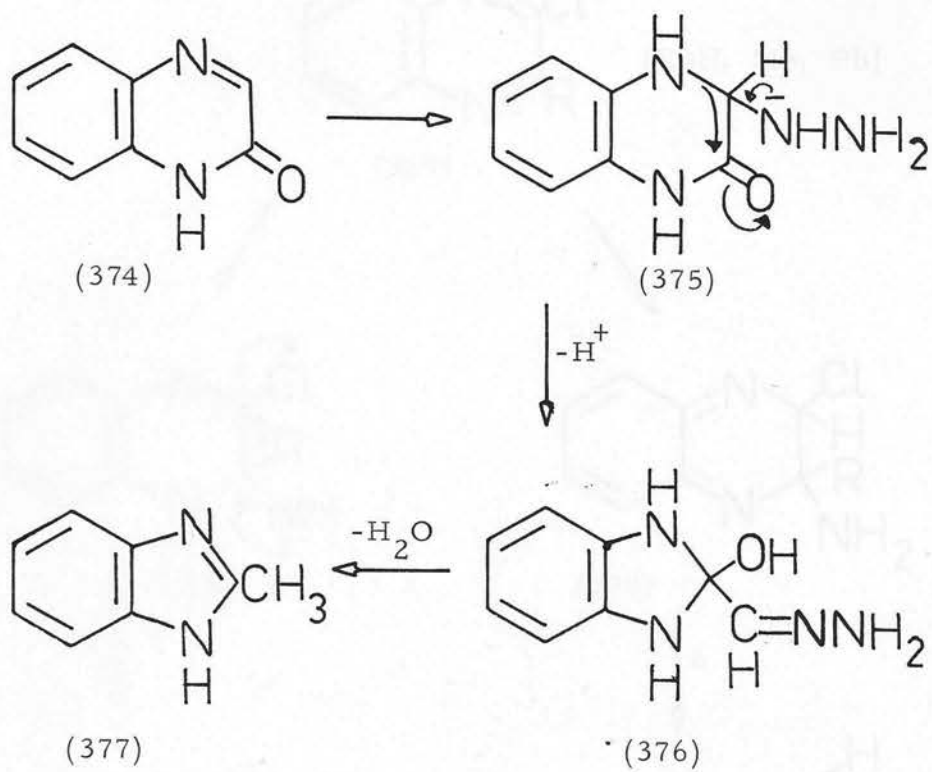


Scheme 67





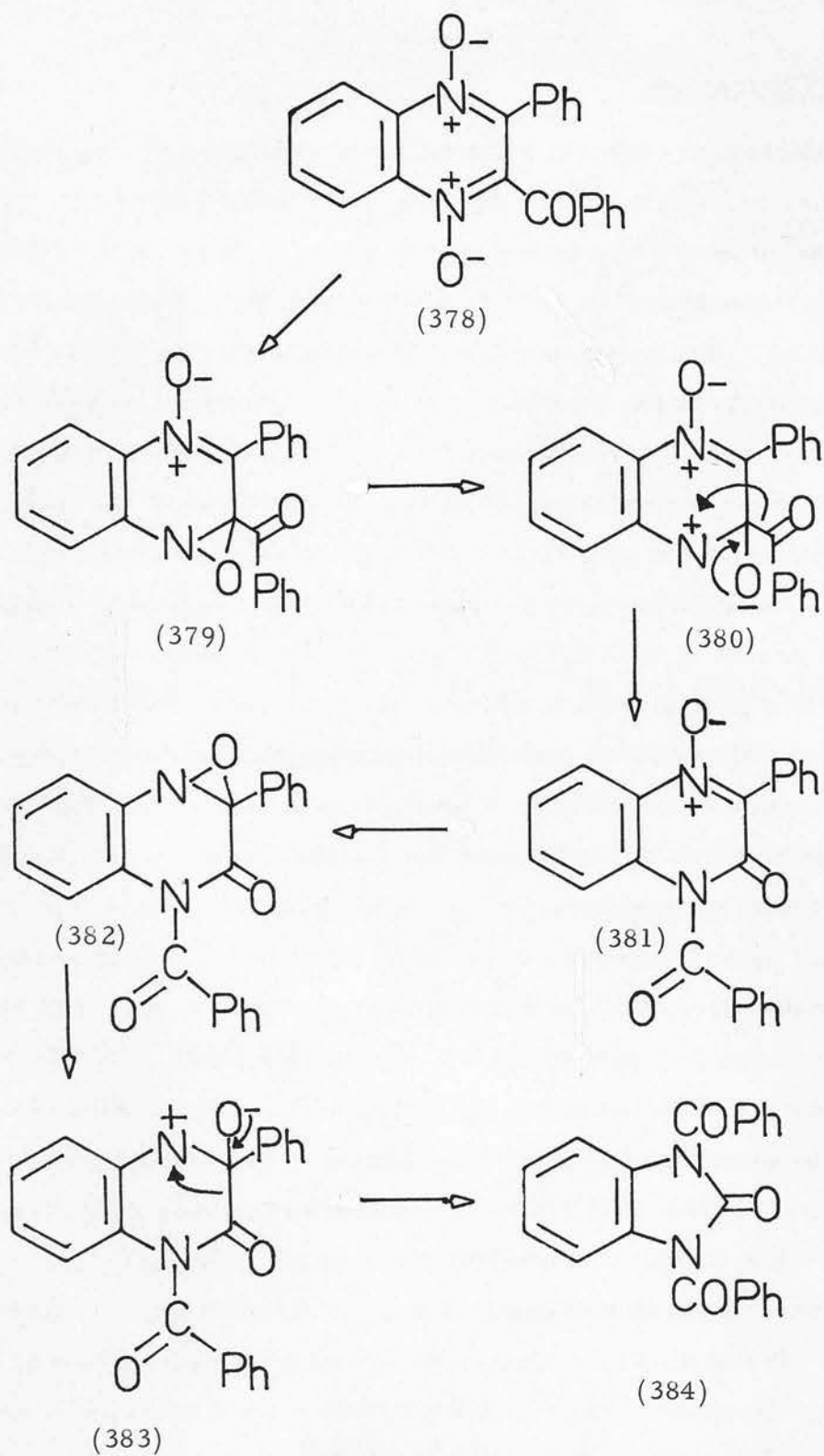
Scheme 68



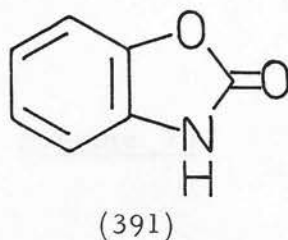
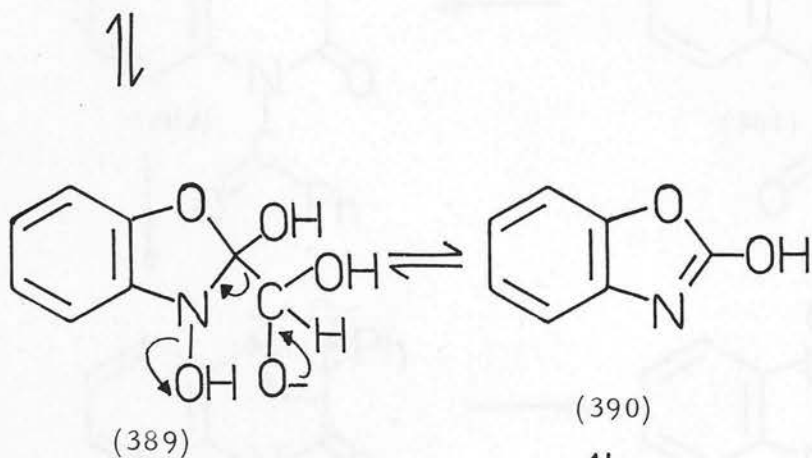
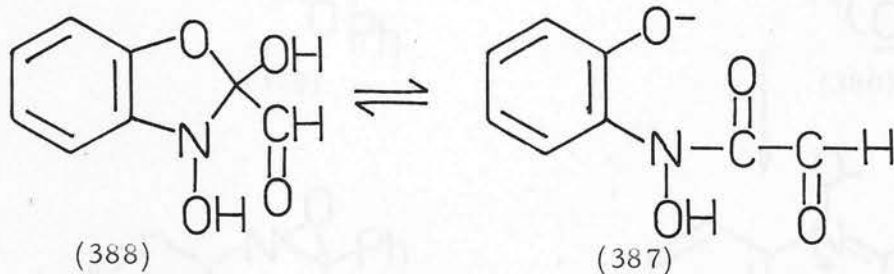
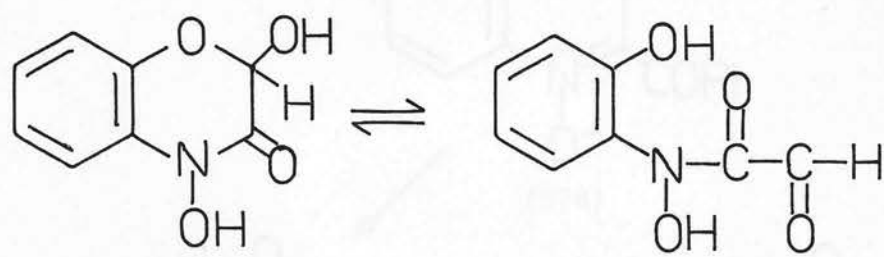
Scheme 69

(ii) Ring Contraction

The literature contains relatively few examples of ring contraction of quinoxalines to benzimidazole derivatives. Ring contraction to afford benzimidazole products has been found to occur on treatment of quinoxalines bearing substituents on the heteroring with potassium amide in liquid ammonia. Thus, heating 2,3-diphenylquinoxaline (362) with potassium amide in liquid ammonia gives the 2-phenylbenzimidazole (366).<sup>95</sup> It is considered that this reaction occurs by the mechanism outlined in scheme 67, namely by nucleophilic attack by amide ion at the C-2 position of the hetero ring in the quinoxaline (362) to afford the anionic intermediate (363) which then undergoes an intramolecular rearrangement with the addition of a proton to give the benzimidazole intermediate (364). Abstraction of a proton from the amino-group in (364) and subsequent expulsion of the elements of phenylmethyylimine yields the intermediate (365) which furnishes the observed product on protonation. Almost identical results were obtained when the 2-chloroquinoxalinones (367) were treated with potassium amide in liquid ammonia at low temperature<sup>96</sup> (scheme 68). It is tentatively suggested<sup>96</sup> that this ring contraction occurs according to the mechanism outlined in scheme 68, via an initial attack of amide ion at the C-3 position in the quinoxaline (367). Whether in this reaction course an isonitrile (369) [route a] or iminochloride (371) [route b] is involved has not been determined. The formation of a nitrile fragment [cf (372)  $\rightarrow$  (373)] in this reaction is however confirmed by the fact that when R=Ph, benzamidine is isolated. Benzamidine is probably formed by the addition of potassium amide to benzonitrile, formed as a by-product. It has also been demonstrated that hydrazinolysis of 2-oxo-1,2-dihydroquinoxaline (374) in boiling 50% aqueous hydrazine leads to the formation of 2-methylbenzimidazole (377) (cf scheme 69).<sup>97</sup> This transformation is thought to occur by initial addition of hydrazine at the C-3 position of the quinoxalinone (374). Ring contraction [(375)  $\rightarrow$  (376)] followed by reductive conversion of the  $-\text{HC}=\text{N}-\text{NH}_2$  group into a methyl group by a Wolff-Kishner type process, together with dehydration then accounts for the observed product (377). This reaction is of interest in the present context as it involves initial nucleophilic attack at an electro-



Scheme 70

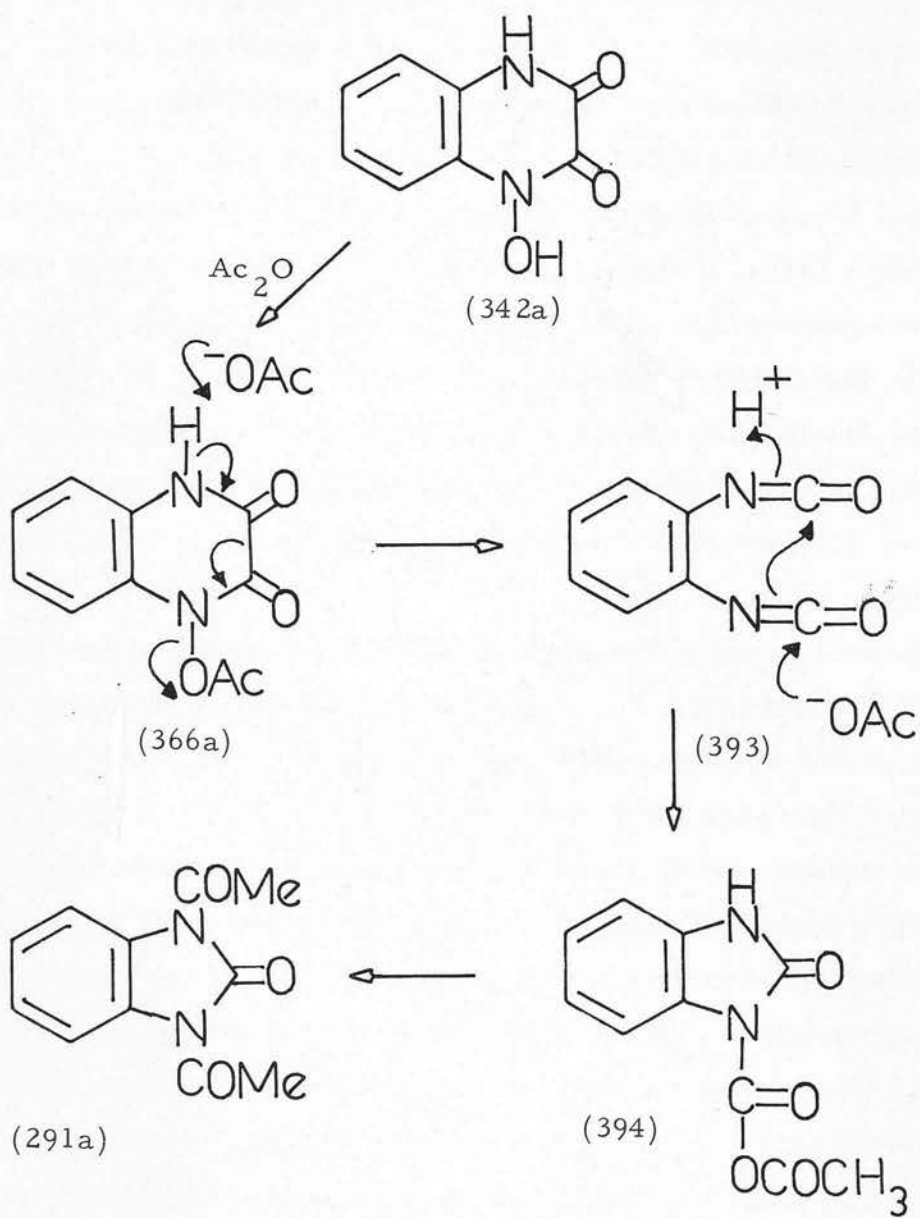


Scheme 71

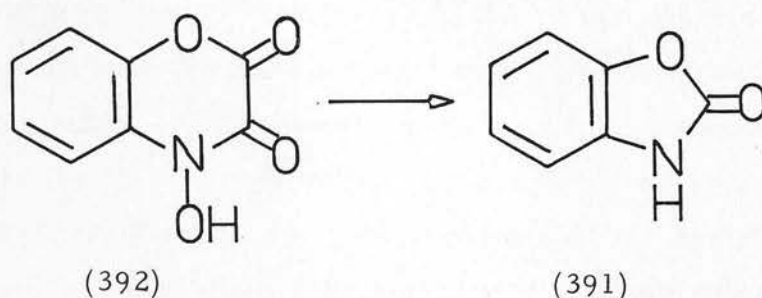


philic centre adjacent to a carbonyl group in a quinoxaline ring. The photochemical ring contraction of 2-benzoyl-3-phenylquinoxaline-di-N-oxide (378) to 1,3-dibenzoylbenzimidazolone (384) has been reported.<sup>98</sup> The mechanism proposed for this transformation is that outlined in scheme 70. Irradiation of the di-N-oxide (378) induces formation of the oxaziridine (379), thermal heterolytic N-O bond fission in which affords the intermediate (380). This then undergoes a [1,2]-benzoyl migration to the electron deficient nitrogen giving the N-benzoyl derivative (381). The driving force for this shift is presumably supplied by the negative charge on the oxygen atom. Repetition of these processes [Scheme 70; (381)  $\rightarrow$  (382)  $\rightarrow$  (383)  $\rightarrow$  (384)] furnishes the observed product (384).

Apparently more directly related to the present studies are the ring contraction reactions undergone by various benzoxazinones, as recently reported by Smissmann and coworkers.<sup>99</sup> These workers have demonstrated that when the 2,4-dihydroxy-1,4-benzoxazin-3-one (385) is heated in aqueous or alcoholic solution, the corresponding benzoxazol-2-one (391) is rapidly formed with the liberation of formic acid, which has been established to arise from the C-2 position of the hetero ring. The mechanism postulated for this transformation is that outlined in scheme 71. In this mechanism, the intermediate (388) is in equilibrium with the parent benzoxazine system through the open forms (386) and (387). The attack of hydroxide ion or water on the carbonyl compound (388) followed by the loss of an acid anion with concomitant displacement of OH from the nitrogen in (389) would afford (390) a tautomer of (391). Such a mechanism is analogous to eliminative decarboxylation. It has also been reported<sup>99</sup> that the oxidised analogue of (385) i. e. 4-hydroxy-1,4-benzoxazine-2,3-dione (392) is also rearranged to the benzoxazolone (391) under similar conditions. The compound (392) is extremely similar to the N-hydroxyquinoxalinediones (342) in that it contains carbonyl groups in positions  $\alpha$  and  $\beta$  to the N-hydroxy function in the hetero ring. However, the reaction conditions under which ring-contraction of 1-hydroxyquinoxalinediones occurs are significantly different making it unlikely that a similar mechanism is operative in the N-hydroxyquinoxaline-



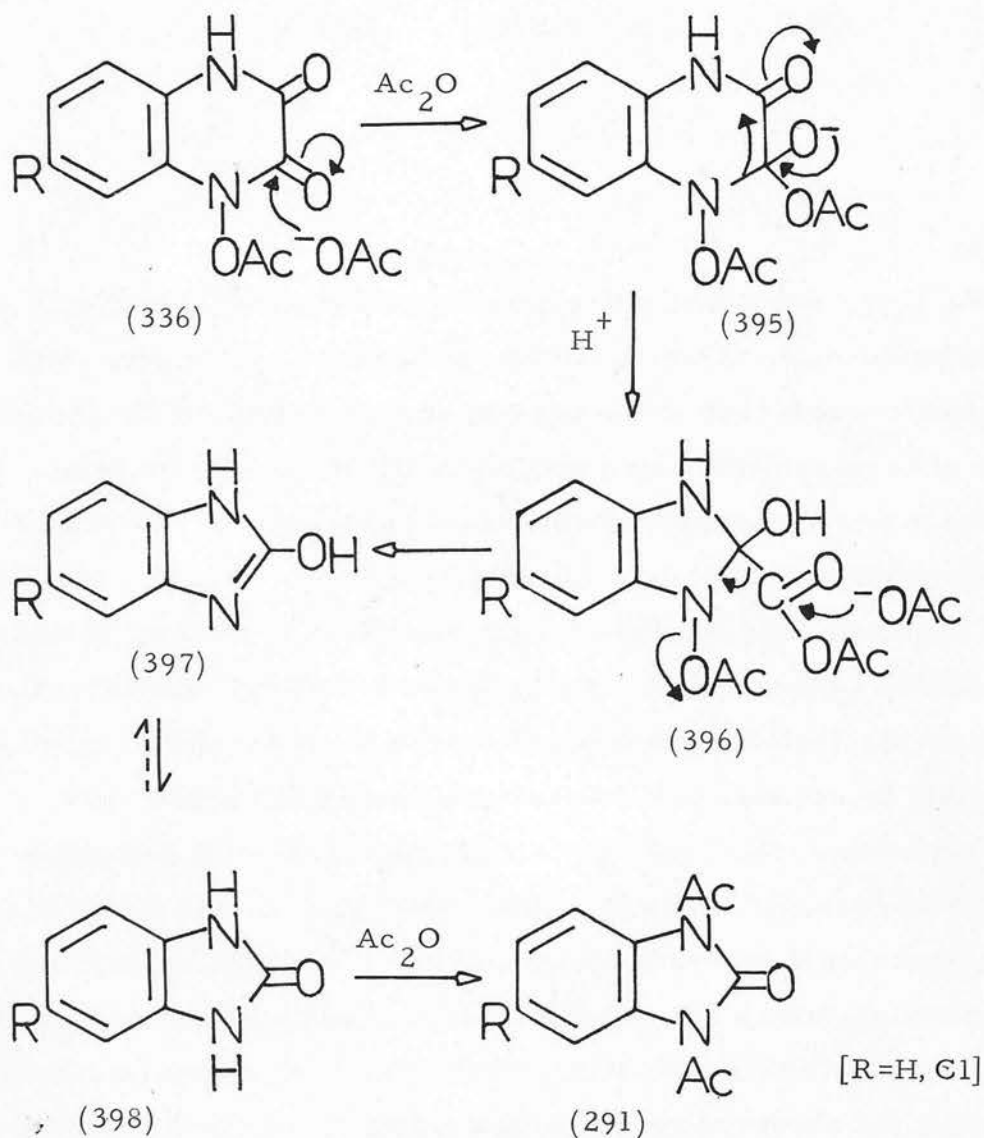
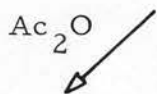
Scheme 72



dione case.

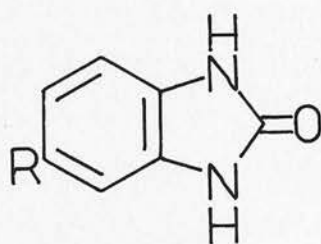
The ring contraction of the quinoxalinedione (342a) to the di-N-acetylbenzimidazolone (291a) on heating at elevated temperature with acetic anhydride observed in the present studies is explicable (scheme 72) in terms of base-catalysed ring opening of the N-acetoxy derivative (336a) to give the bis-isocyanate (393) which then recycles as shown (scheme 72) to give the benzimidazolone intermediate (394). Further acetylation and acyl exchange then accounts for the formation of the diacetylbenzimidazolone (291a). The similar formation of the diacetylbenzimidazolone (291b) from the 7-chloroquinoxalinedione (342e) in hot acetic anhydride is explicable by an analogous mechanistic route. However, this mechanism is dependent upon base-catalysed deprotonation of the N-4 position of the quinoxalinedione. Subsequent studies (see later) have demonstrated that N-hydroxyquinoxalinediones bearing a substituent at the N-4 position, which are not amenable to deprotonation, undergo ring-contraction under reflux with acetic anhydride. It is therefore exceedingly unlikely that the observed ring contractions of the quinoxalinediones (342a and e) in hot acetic anhydride proceed via base catalysed deprotonation to afford an isocyanate intermediate of the type (393) as outlined in scheme 72. The consideration of an alternative mechanistic pathway is therefore necessary. The formation of the 1,3-diacetylbenzimidazolones (291a and b) may alternatively be rationalised by the mechanism outlined in scheme 73. This mechanism embodies features of several of the aforementioned transformations. Thus, nucleophilic attack by acetate ion at the C-3

(342a or e)



Scheme 73

position of the hetero ring in the presumed N-acetoxy intermediate (336) would give the adduct (395) which could then ring contract as shown [(395)  $\rightarrow$  (396)] with the addition of a proton to afford the benzimidazole intermediate (396). Further nucleophilic attack by acetate ion and departure of the N-acetoxy leaving group in (396) would give the enol (397), tautomeric with the benzimidazolone (398). Acetylation of the benzimidazolone (398) on further reaction with acetic anhydride would then account for the observed products (291). In an attempt to substantiate that, as indicated in scheme 73, ring-contraction is induced by nucleophilic attack by acetate ion on an N-acetoxy intermediate of the type (336), the N-acetoxy compound (336a) was heated under reflux with sodium acetate in dimethylformamide. The benzimidazolone (399a) was isolated in low yield from this reaction lending some support to the mechanism shown in scheme 73. The benzimidazolone product (399a) in this reaction was accompanied by the reduced compound (343a). As will be described later the formation of (343a) in this reaction is possibly thermally induced. The generation of 1,3-diacetyl-5-chlorobenzimidazolone (291b) on reaction of the 7-chloroquinoxalinedione (342e) with acetyl chloride in acetic acid at elevated temperature is explicable by a course directly analogous to that outlined in scheme 73.



(399)

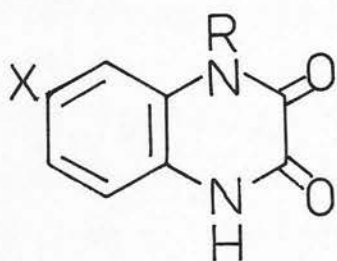
	<u>R</u>
a;	H
b;	Cl





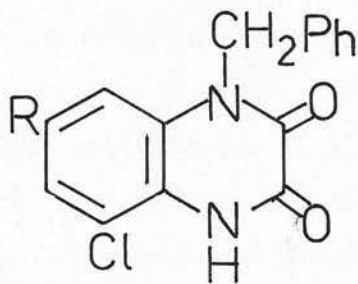
(400)

	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>
a;	Me	H
b;	PhCH <sub>2</sub>	H
c;	PhCH <sub>2</sub>	Cl
d;	PhCH <sub>2</sub>	Me



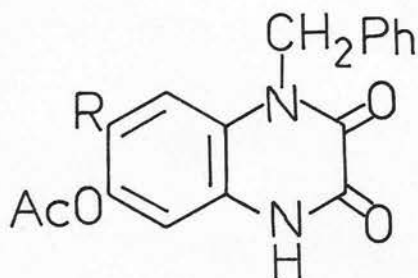
(401)

	<u>R</u>	<u>X</u>
a;	Me	Cl
b;	Me	AcO
c;	PhCH <sub>2</sub>	Cl
d;	PhCH <sub>2</sub>	AcO
e;	Me	Pr <sup>n</sup> CO <sub>2</sub>



(402)

	<u>R</u>
a;	Cl
b;	Me



(404)

	<u>R</u>
a;	Cl
b;	Me

4.2 Reactions of N-Substituted-N-Hydroxyquinoxalinediones with Acetyl Chloride in Acetic Acid and with Acetic anhydride.

a) Reactions of N-Substituted-N-Hydroxyquinoxalinediones (400) with Acetyl Chloride in Acetic Acid.

In terms of the mechanism shown in scheme 66, a prerequisite of the observed substitution by chloride and acetate ion undergone by the N-hydroxyquinoxalinediones (342) is the existence of these compounds in their enol form. It was therefore considered of interest to investigate the corresponding reaction of the readily available <sup>91</sup> N-methyl-N-hydroxyquinoxalinedione (400a) with acetyl chloride in acetic acid since, bearing a substituent at the N-4 position, this compound is not amenable to enolisation. Consequently, the quinoxalinedione (400a) would not be expected to undergo substitution in a fashion analogous to that observed for the N-hydroxyquinoxalinediones (342) on reaction with hot acetyl chloride. This was found to be the case. Thus, heating the N-hydroxy compound (400a) under reflux with acetyl chloride in glacial acetic acid gave a high yield of the 7-chloroquinoxalinedione (401a). Satisfactory analytical, mass and i. r. spectral evidence was obtained for the assigned structure (401a). However, the aromatic region of the <sup>1</sup>H n. m. r. spectrum of this compound contained a complex splitting pattern not readily reconciled with a trisubstituted benzene derivative and for this reason the C-7 position for substitution was not unequivocally determined. The 7-chloro structure (401a) is assigned on the basis of analogy with similar products (see later). As an extension of these studies the reaction of the readily available <sup>22</sup> N-benzylquinoxalinedione (400b) with acetyl chloride was investigated. The N-benzyl compound (400b) also underwent ready chlorination when it was heated with acetyl chloride in glacial acetic acid. The product, isolated in high yield, showed properties fully in accord with the chloroquinoxalinedione structure (401c). However the C-7 position for the chlorine substituent could not be demonstrated unambiguously by the <sup>1</sup>H n. m. r. spectrum due to overlap of the signals

due to the aromatic protons of the fused benzene ring and those of the benzyl group thus precluding the observation of the expected splitting pattern characteristic of a 1,2,4-trisubstituted benzene derivative and again the 7-chloro structure (401c) is assigned on the basis of analogy with similar products (see later).

With a view to gaining further insight into the mechanism of the substitution reactions undergone by the N-methyl and N-benzylquinoxalinediones (400a and b) the reaction of 1-benzyl-7-chloroquinoxalinedione (400c) with acetyl chloride was next studied. This compound was of particular interest since with the apparently preferred position of nucleophilic attack, namely C-7, blocked by a chloro substituent, nucleophilic attack might either be inhibited or induced to occur at some other site. In practice, the N-hydroxyquinoxalinedione (400c) reacted readily with hot acetyl chloride in acetic acid to give a high yield of the chloro-compound (402a). This structure for the product is based on elemental and mass spectral analysis and the presence in its i. r. spectrum of bands at  $3100-2700\text{ cm}^{-1}$  and  $1680\text{ cm}^{-1}$  typical of the  $\text{NH(OH)}$  and carbonyl absorption of an N-hydroxyquinoxalinedione nucleus. The C-5 position for the entering chlorine atom is established by the  $^1\text{H}$  n. m. r. spectrum of the product which showed an aromatic splitting pattern typical for two protons situated meta to each other. It was next decided to investigate the reaction of the 7-methyl-N-hydroxyquinoxalinedione (400d) with acetyl chloride in acetic acid. In addition to the possible inhibition of nucleophilic attack or alternative substitution at C-5 in this compound, it was also anticipated that substitution might involve the methyl group. Substitution of aromatic methyl groups under conditions of acetylation have been discussed before (see chapter 1). In practice, heating the methyl derivative (400d) with acetyl chloride in acetic acid gave a good yield of a product which gave analytical and mass spectral data consistent with the structure (402b). The i. r. spectrum of the product confirmed the presence of a quinoxalinedione nucleus and its  $^1\text{H}$  n. m. r. spectrum lacked signals due to the protons of a methylene group showing that substitution had not occurred at the methyl group. Unfortunately, however, the aromatic region of the  $^1\text{H}$  n. m. r. spectrum, run both in  $(\text{CD}_3)_2\text{SO}$  and in trifluoroacetic acid was

complicated by overlap in the signals due to the aromatic protons of the fused benzene ring and the benzyl group so that unambiguous assignment of the position of the entering chlorine atom was not possible. The C-5 position for the chlorine substituent in (402b) is therefore based on analogy with the dichloro-compound (402a).

No products of ring-contraction were detected in the reactions of the N-substituted quinoxalinediones (400) with acetyl chloride in glacial acetic acid at elevated temperature.

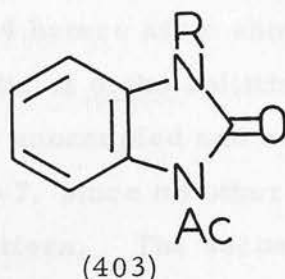
b) Reactions of N-Substituted N-Hydroxyquinoxalinediones (400) with Acetic Anhydride.

In view of the contrasting behaviour of the parent N-hydroxyquinoxalinediones (342) in undergoing substitution on treatment with hot acetyl chloride-acetic acid but ring contraction on reaction with hot acetic anhydride, it was of interest to see if the N-substituted-N-hydroxyquinoxalinediones (400) exhibited the same contrasting behaviour. As has been previously mentioned, if ring contraction of these compounds does occur via proton abstraction from the N-4 position of the hetero-ring with ring opening to an isocyanate intermediate and subsequent ring closure to furnish benzimidazolone products (cf. scheme 72), then no product of ring contraction would be expected to result from the reaction of the N-hydroxy-N-methylquinoxalinedione (400a) with acetic anhydride. In practice, the reaction of the N-hydroxy-N-methylquinoxalinedione (400a) with hot acetic anhydride was found to give two products. The major product gave analytical and spectroscopic data consistent with its being the product of acetoxy substitution (401b). In particular, its i. r. spectrum showed bands at 1740 and  $1690\text{ cm}^{-1}$  attributable to the carbonyl absorption of an acetoxy group and a quinoxalinedione nucleus respectively. The position of the acetoxy group was unambiguously defined as C-7 by the splitting pattern in the aromatic region of the  $^1\text{H}$  n. m. r. spectrum of the compound. The doublet at  $\delta 7.19$  shows a coupling constant of 8.5 Hz characteristic of ortho splitting and is assigned to H-5 on the basis of its low field position which results from deshielding by the adjacent N-4 hetero atom. It follows that the C-6



position must be unoccupied. The signal further upfield at  $\delta 7.14$  is assigned to H-8 and in accord with this assignment it appears as a doublet with a coupling constant of 2.5 Hz characteristic of coupling between meta protons. The signal furthest upfield at  $\delta 6.92$  is assigned to H-6 since this position should be least deshielded and in accord with this assignment, the signal appears as a double doublet with coupling constants corresponding to ortho and meta splitting.

The product formed in lower yield in the reaction of the N-hydroxy-N-methylquinoxalinedione (400a) with acetic anhydride gave combustion and mass spectral analysis consistent with the molecular formula  $C_{10}H_{10}N_2O_2$  and showed a melting point ( $121-2^\circ C$ ) identical to that reported<sup>100</sup> for 1-acetyl-3-methylbenzimidazol-2-one (403a). In accord



	<u>R</u>
a;	Me
b;	PhCH <sub>2</sub>

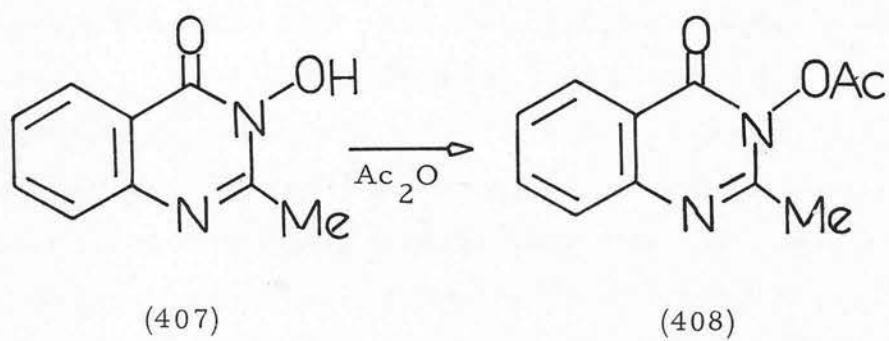
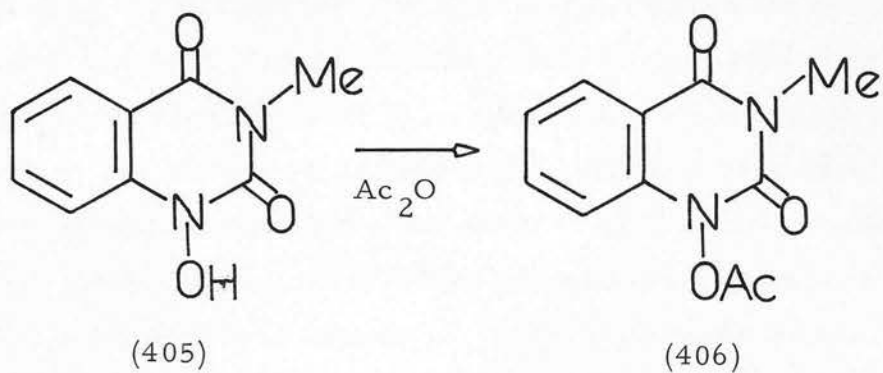
with this structure the i. r. spectrum of the product showed a broad carbonyl band at  $1700\text{ cm}^{-1}$  attributable to the overlapping absorption of the N-acetyl and benzimidazolone carbonyl groups. The substitution as well as ring-contraction observed in the reaction of the N-methyl-N-hydroxyquinoxalinedione (400a) with acetic anhydride stands in contrast to the apparently exclusive ring contraction undergone by the parent N-hydroxyquinoxalinedione (342a) on reaction with acetic anhydride. The formation of the benzimidazolone (403a) in the reaction of the quinoxalinedione (400a) with acetic anhydride is directly contrary to the proposition that the ring-contraction of N-hydroxyquinoxalinediones occurs via a base-catalysed deprotonation with ring-opening to afford an isocyanate intermediate and subsequent ring closure to afford benzimidazolone products (cf. scheme 72).



In an attempt to further observe ring-contraction of an N-substituted-N-hydroxyquinoxalinedione, the reaction of the N-benzyl-N-hydroxy compound (400b) with acetic anhydride was investigated. Heating the N-hydroxy compound (400b) with acetic anhydride gave rise to two different products. The major product gave analytical and mass spectral data consistent with the structure (401d). Its i. r. spectrum confirmed the presence of a quinoxalinedione nucleus and also contained an absorption band at  $1740\text{ cm}^{-1}$  attributable to the carbonyl absorption of a C-acetoxy group. The position of the acetoxy group was again unambiguously determined as C-7 by the splitting pattern observed in the aromatic region of the  $^1\text{H}$  n. m. r. spectrum of the product which was characteristic of a 1,2,4-trisubstituted benzene derivative. The signal at lowest field, assigned to H-5 because of its close proximity to the deshielding N-4 hetero atom showed up as a doublet with a coupling constant characteristic of ortho splitting. It follows, therefore, that the C-6 position must be unoccupied and consequently that the acetoxy substituent is sited at C-7, since no other orientation would give rise to the observed splitting pattern. The secondary product formed in the reaction of the N-hydroxyquinoxalinedione (400b) with acetic anhydride gave analytical and mass spectral analyses fully in accord with the assigned benzimidazolone structure (403b) and this assignment is supported by the i. r. spectrum of the product which shows bands at  $1730$  and  $1690\text{ cm}^{-1}$ , attributable to the carbonyl absorption of an N-acetyl group and a benzimidazolone nucleus, respectively. The  $^1\text{H}$  n. m. r. spectrum of the product contained a complex multiplet in the aromatic region which integrated for four protons indicating that no substitution had occurred in the fused benzene ring. It also contained signals at  $\delta 5.41$  and  $\delta 3.00$ , which can be attributed to the methylene protons of the benzyl group and the methyl protons of the acetyl group, respectively, in the benzimidazolone (403b). The formation of the benzimidazolone (403b) in the reaction of the N-hydroxy compound (400b) with acetic anhydride is further evidence that the ring contractions undergone by N-hydroxyquinoxalinediones do not proceed via a base-catalysed deprotonation mechanism of the type outlined in scheme 72.

In view of the results obtained in the reactions of the N-hydroxyquinoxalinediones (400a and b) with acetic anhydride, it was of interest to investigate the corresponding reaction of the 7-chloro compound (400c) (in which the preferred position of substitution by acetate ion is blocked by the chloro-substituent at C-7) in the hope that substitution might either be inhibited, possibly increasing the extent of ring contraction, or directed towards an alternative site. In practice, treating the 7-chloro-N-hydroxy compound (400c) with hot acetic anhydride gave a good yield of a product which is assigned the 6-acetoxyquinoxalinedione structure (404a). Satisfactory accurate mass spectral evidence was obtained for the assigned structure (404a) which was further substantiated by the i. r. spectrum of the product. This confirmed the presence of a quinoxalinedione nucleus and showed a band at  $1760\text{ cm}^{-1}$  attributable to the carbonyl absorption of a C-acetoxy group. The only other product obtained from the reaction of the N-hydroxy compound (400c) with acetic anhydride was a viscous dark gum from which no further identifiable material could be obtained. No product derived by ring-contraction could be identified in this reaction.

The reaction of 6-methylquinoxalinedione (400d) with hot acetic anhydride was next examined in the hope that substitution might involve the methyl group at the C-6 position. In practice, this reaction afforded a high yield of a compound which gave analytical and mass spectral data fully consistent with the assigned structure (404b). The i. r. spectrum of this product contained absorption bands attributable to a quinoxalinedione nucleus and to a C-acetoxy group. The C-6 position for the acetoxy group was established unambiguously by its  $^1\text{H}$  n. m. r. spectrum. This contained two one proton singlets in the aromatic region assignable to the protons at C-5 and C-8. The absence of any splitting in these signals uniquely defines the orientation of the acetoxyquinoxalinedione as (404b). Any other orientation for the product would result in ortho and meta coupling of the two aromatic protons and hence a more complex splitting pattern. Thus, with the C-6 position of the fused benzene ring occupied by a methyl substituent, the next most reactive centre in the N-hydroxy compound (400d) is apparently C-7. No benzimidazolone product was



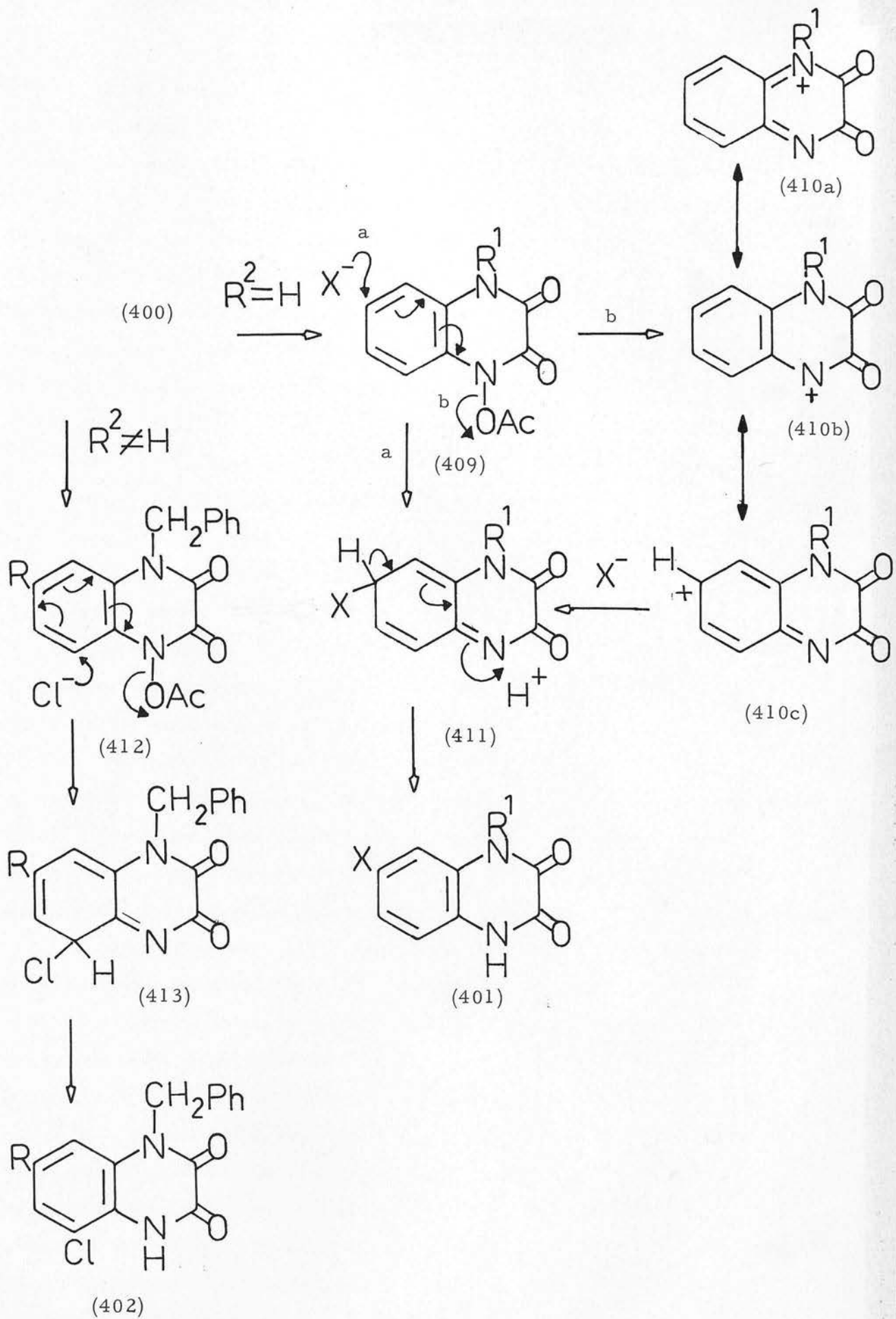
detected in the reaction of the N-benzyl compound (400d) with hot acetic anhydride.

In an attempt to investigate the effect of a change in the nature of the hetero ring on the course of the reaction of cyclic hydroxamic acids with acetic anhydride, the reaction of the readily available N-hydroxyquinazolinedione (405)<sup>101</sup> with hot acetic anhydride was next investigated under identical conditions to the N-hydroxyquinoxalinedione reactions. Whereas in the quinoxalinedione ring system the carbonyl groups are adjacent to one another, in the quinazolinedione ring system they are separated by a nitrogen atom. However, the quinazolinedione (405) still retains a carbonyl group in the position  $\alpha$ - to the N-hydroxy group. Heating the N-hydroxyquinazolinedione (405) under reflux with acetic anhydride gave an excellent yield of the N-acetoxy compound (406) which was identical in every respect with an authentic sample.<sup>101</sup> No product of substitution in the fused benzene nucleus nor of ring-contraction was detected in the reaction of the N-hydroxy compound (405) with acetic anhydride. The stability of the quinazolinedione (405) compared to the corresponding quinoxalinedione (400a) towards substitution or ring-contraction on reaction with acetic anhydride is difficult to rationalise. However, this result is in accord with the observation<sup>102</sup> that the N-hydroxyquinazolinedione (407) undergoes simple acetylation [(407)  $\rightarrow$  (408)] when similarly treated with acetic anhydride.

c) Discussion of the Mechanisms of the Reactions of N-Substituted-N-Hydroxyquinoxaline-2, 3(1H, 4H)-diones (400) with Acetyl Chloride in Acetic Acid and with Acetic Anhydride.

(i) Substitution by Chloride Ion and Acetate Ion

The formation of the 7-acetoxyquinoxalinediones (401b and d) and the 7-chloroquinoxalinediones (401a and c) is explicable by the mechanistic route outlined in scheme 74. Thus nucleophilic attack by  $X^-$  (acetate or chloride ion) at the C-7 position of the presumed N-acetoxy intermediates (409) (route a; scheme 74) with synchronous expulsion of the N-acetoxy



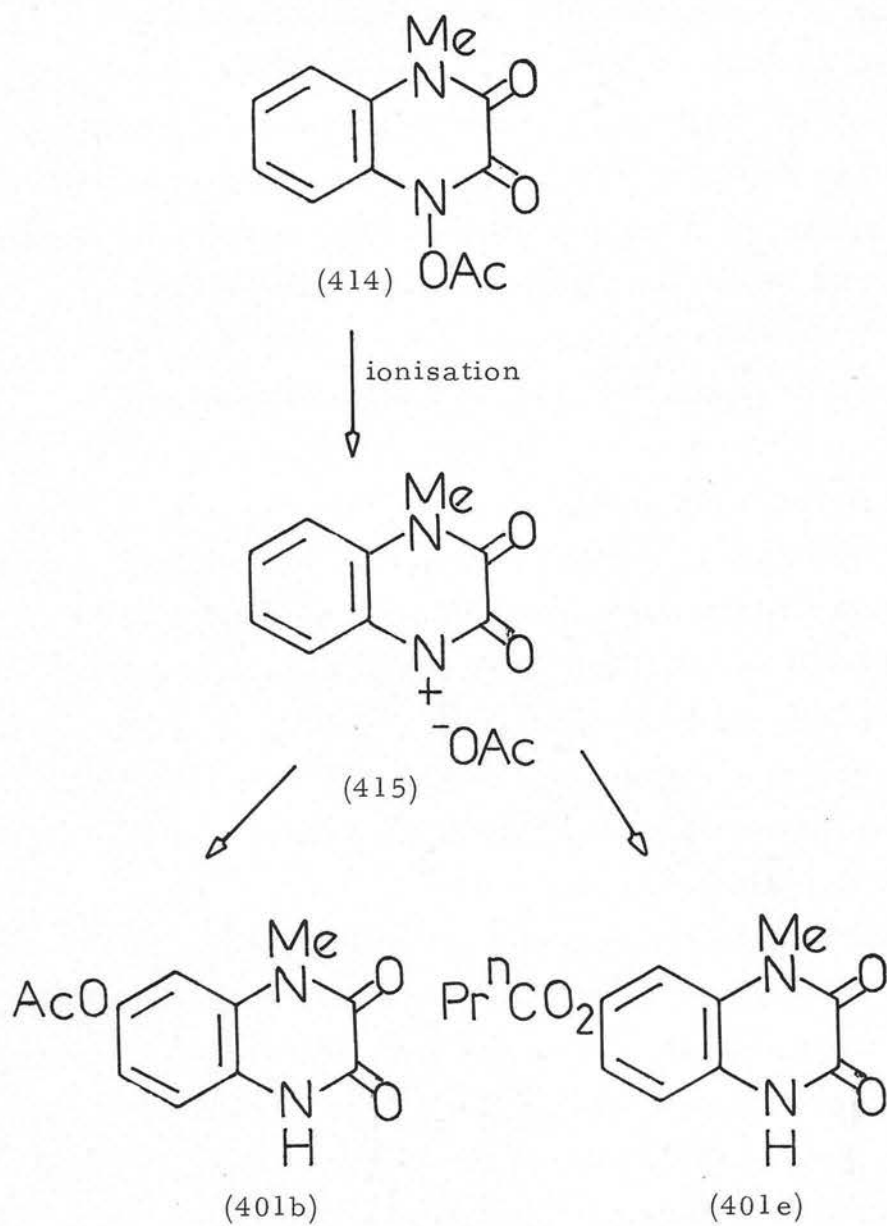
Scheme 74



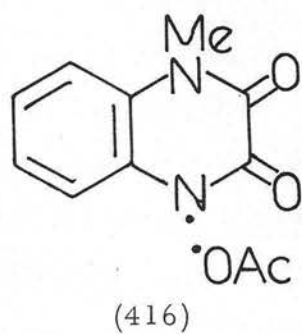
leaving group could afford the para-quinonoid intermediates (411). Rearomatisation of the intermediates (411) would then furnish the observed products (401) [(400)  $\rightarrow$  (409)  $\rightarrow$  (411)  $\rightarrow$  (401)]. Alternatively, the N-acetoxy intermediates (409) could eliminate the N-acetoxy leaving group to form the resonance stabilised nitrenium intermediates (410). Nucleophilic attack by  $X^-$  (acetate or chloride ion) at the 7-position of the intermediates (410) would give the observed products (401) as described above [(409)  $\rightarrow$  (410)  $\rightarrow$  (411)  $\rightarrow$  (401)]. The intermediate (410) should show enhanced stability due to resonance stabilisation as shown in scheme 74.

With the preferred C-7 position of substitution occupied by a substituent, nucleophilic attack is directed towards the C-5 position. The formation of the 5-chloroquinoxalinediones (402a and b) is explicable by the course [(400)  $\rightarrow$  (412)  $\rightarrow$  (413)  $\rightarrow$  (402)] outlined in scheme 74. Thus, nucleophilic attack by chloride ion at the C-5 position of the N-acetoxy intermediate (412) with synchronous or stepwise departure of the N-acetoxy leaving group affords the intermediate (413) which furnishes the observed products on rearomatisation.

Support for the mechanistic pathways outlined in scheme 74 was obtained from an investigation of the reactions of the N-acetoxy compound (414)<sup>22</sup> [prepared by the mild acetylation of the N-hydroxyquinoxalinedione (400a)] with acetic acid and propionic acid at elevated temperatures. Thus, heating the N-acetoxy compound (414) with acetic acid gave a high yield of the 7-acetoxy compound (401b) which was identified by comparison with a previously obtained sample. The formation of the acetoxy derivative (401b) on reaction of the N-acetoxy compound (414) with acetic acid may occur either by intramolecular concerted rearrangement or by an intramolecular or intermolecular ion pair process. In an attempt to resolve which of these mechanistic processes is operative the N-acetoxy compound (414) was treated with hot propionic acid. This reaction afforded a mixture of the 7-acetoxy- and 7-propionyloxy-derivatives (401b and e), richer in the latter. The analytical and mass spectral evidence obtained for the propionyloxyquinoxalinedione (401e) was fully in accord with the assigned structure, which was further supported by its i. r. spectrum

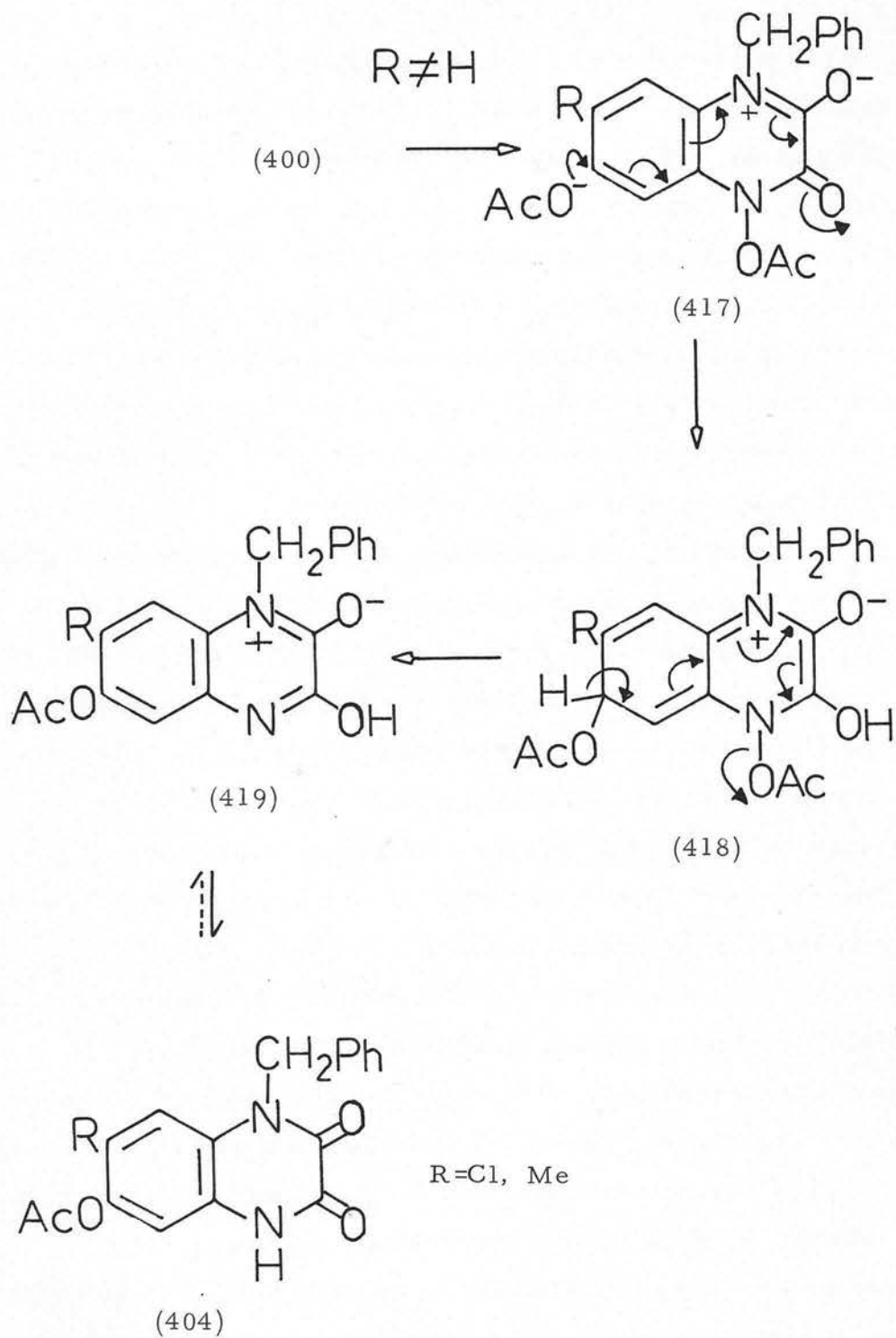


Scheme 75



This confirmed the presence of a quinoxalinedione nucleus and further, contained a band at  $1750\text{ cm}^{-1}$  attributable to the carbonyl absorption of a C-propionyloxy group. The presence of the latter was also clearly shown by  $^1\text{H}$  n. m. r. absorption at  $\delta 2.62$  (quartet) and  $\delta 1.15$  (triplet) and the position of substitution was unambiguously defined by the splitting pattern observed in the aromatic region of the  $^1\text{H}$  n. m. r. spectrum which was characteristic of a 1,2,4-trisubstituted benzene derivative. The signal at lowest field, assigned to H-5 because of its close proximity to the strongly deshielding N-4 hetero atom, showed up as a doublet with a coupling constant characteristic of ortho coupled protons. It therefore follows that the C-6 position is unsubstituted, thus defining the orientation of the propionyloxyquinoxalinedione as (401e). These results strongly suggest that the transformations of the N-acetate (414) in acetic acid and propionic acid occur according to the mechanism outlined in scheme 75. Ionisation of the N-acetoxy compound (414) gives the ion pair (415). If no other nucleophile is present, then the ion pair rearranges to the 7-acetoxy derivative (401b). This process could be intramolecular (tight ion pair) or intermolecular (loose ion pair). In the presence of propionic acid the ion pair (415) undergoes nucleophilic substitution at the C-7 position to give the 7-propionyloxy compound (401e). A radical-pair process [cf (416)] cannot be excluded for these transformations, but such a process is unlikely in view of the absence of coupling products resulting from radical decomposition. In a further attempt to demonstrate the ionic nature of the substitution process, the N-acetate (414) was heated under reflux with solid sodium acetate in ethanol. However, this procedure gave only the parent N-hydroxy compound (400a) in good yield and no product of acetate substitution could be detected in the reaction mixture. It is probable that (400a) is formed by nucleophilic attack of acetate ion at the N-acetoxy group.

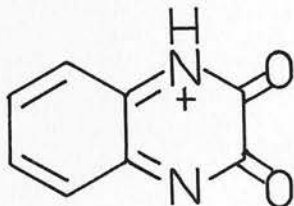
The formation of the 6-acetoxyquinoxalinediones (404a and b) on reaction of the N-hydroxy compounds (400c and d) with acetic anhydride at elevated temperature is difficult to rationalise. Clearly, the formation of these compounds is not explicable by the mechanism outlined in



Scheme 76

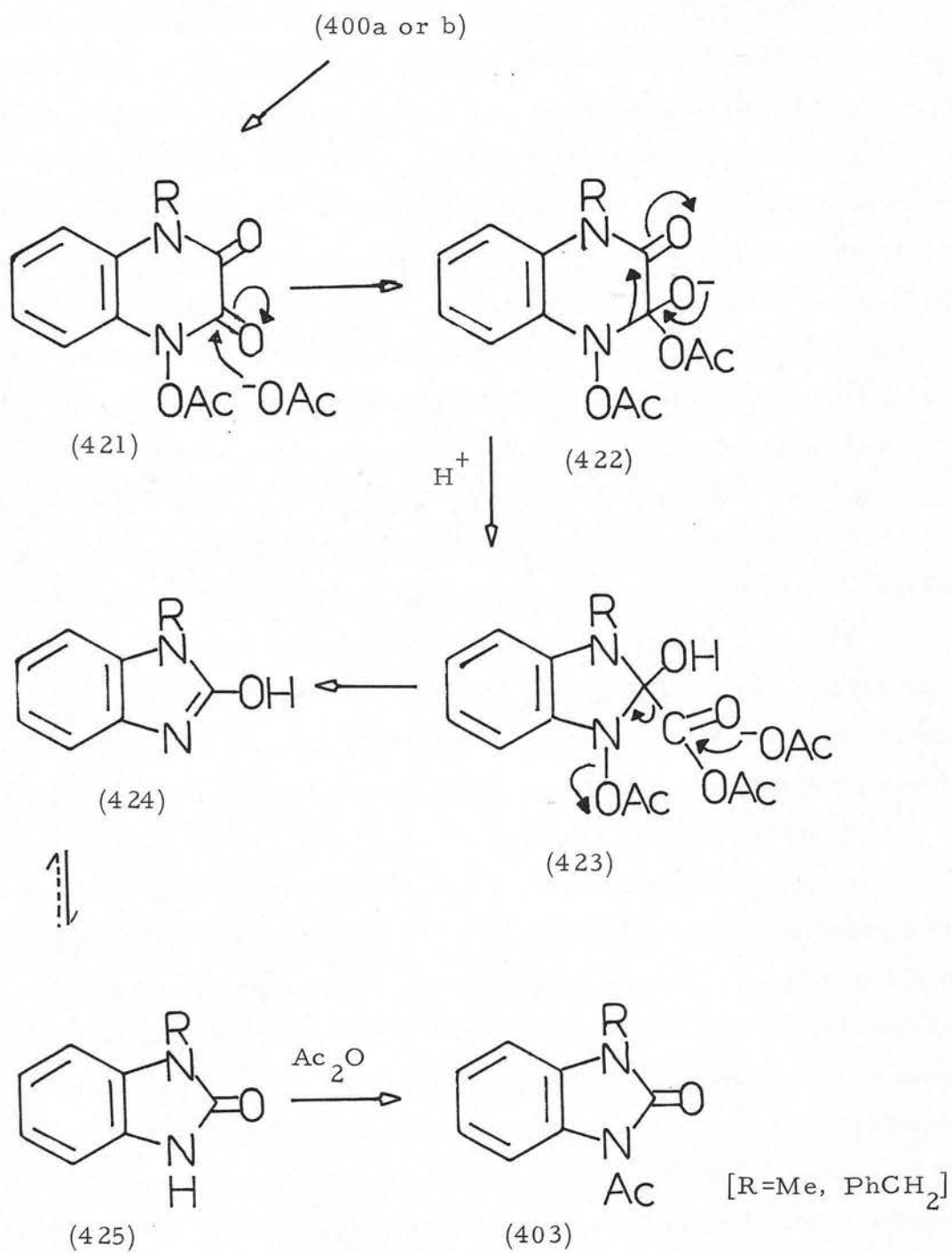
scheme 74 where substitution, dictated by the N-acetoxy function, is directed towards the C-5 and C-7 positions. It is therefore necessary to consider an alternative mode of substitution. It is tentatively suggested that the compounds (404a and b) may be generated via the mechanistic pathway outlined in scheme 76. The key step in this mechanism involves reaction of the presumed N-acetoxy intermediates (417) in their zwitterion form as shown, thus accounting for the C-6 substitution observed. Thus, nucleophilic attack by acetate ion at the C-6 position of the zwitterion (417) and addition of a proton would give the adduct (418). Elimination of the elements of acetic acid from the adduct (418) would furnish the enol (419), tautomeric with the observed product (404). Why the 7-substituted quinoxalinediones (400c and d) should undergo substitution by chloride ion at the C-5 position but at the C-6 position by acetate ion is not clear and it is evident that this area of study requires further investigation before the observed transformation can be fully understood.

The substitution by acetate ion undergone by the N-substituted-quinoxalinediones (400) on reaction with hot acetic anhydride occurs in marked contrast to the corresponding reactions of the N-H quinoxalinediones (342) wherein only ring-contraction to benzimidazolone product is observed under identical reaction conditions. The reason for these different modes of reaction is not clear. However, it is possible that the formation of the 7-acetoxyquinoxalinediones (401b and d) is facilitated by the increased stability of the nitrenium ion intermediates (410) [cf. scheme 74] brought about by reduction of the positive charge by electron donation by the electron releasing substituent at N-1 in the canonical form (410a). The corresponding nitrenium ion intermediate (420) would not be similarly stabilised by electron donation and it is conceivable that the reduced stability of this intermediate is sufficient to account for



(420)



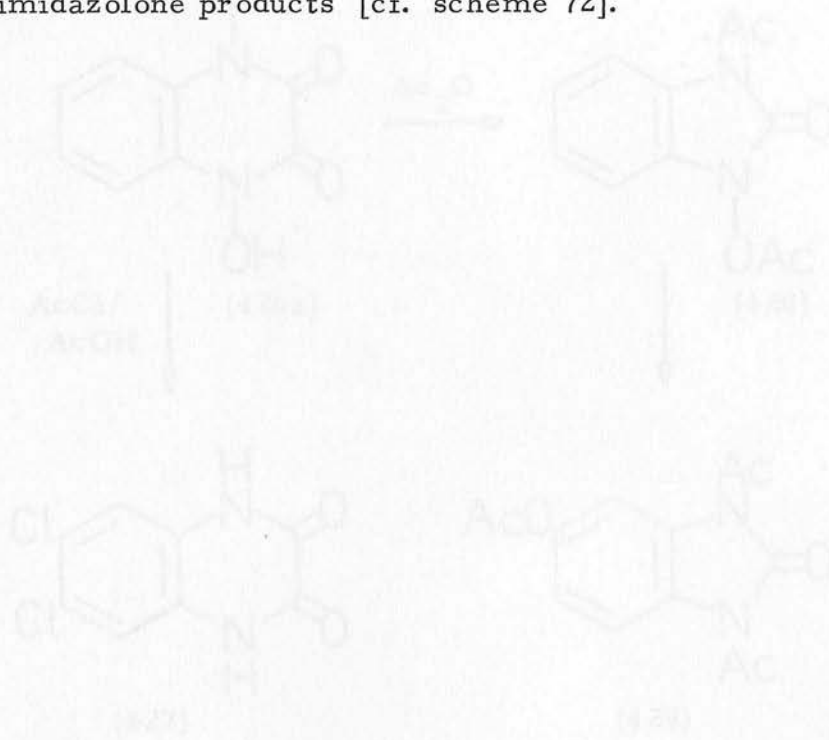


Scheme 77

the inhibition of substitution and the predominance of ring contraction in the reactions of the N-hydroxyquinoxalinediones (342) with acetic anhydride.

(ii) Ring Contraction

The generation of the benzimidazolones (403a and b) on reaction of the N-hydroxyquinoxalinediones (400a and b) with acetic anhydride at elevated temperature is explicable by a course (scheme 77) directly analogous to that described for the corresponding ring-contractions of the N-hydroxyquinoxalinediones (342a and e) [cf scheme 73]. As previously mentioned, the formation of products of ring contraction in the reactions of the N-substituted-quinoxalinediones (400) with acetic anhydride clearly excludes the possibility that these processes occur by base-catalysed deprotonation of the hetero ring with the formation of an isocyanate intermediate and subsequent ring-closure to form benzimidazolone products [cf. scheme 72].

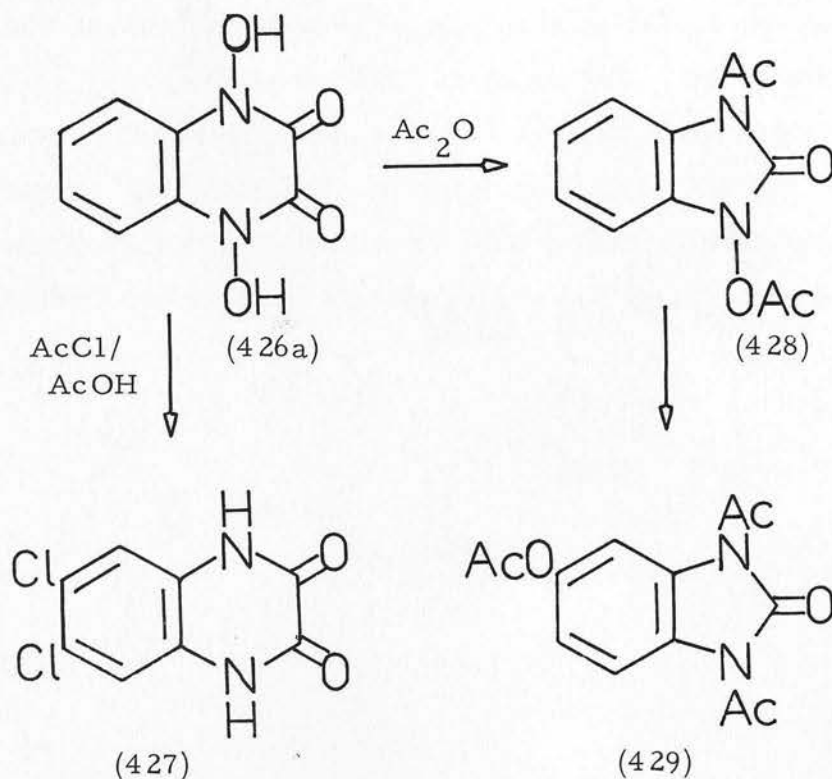


It has already been demonstrated that the effect of acetic anhydride on the reaction of 2,6-dichloro-

4.3 Studies on the Synthesis and Reactivity towards  
Acylating Agents of 1,4-Dihydroxyquinoxaline-2,3-  
(1H,4H)-diones (426)

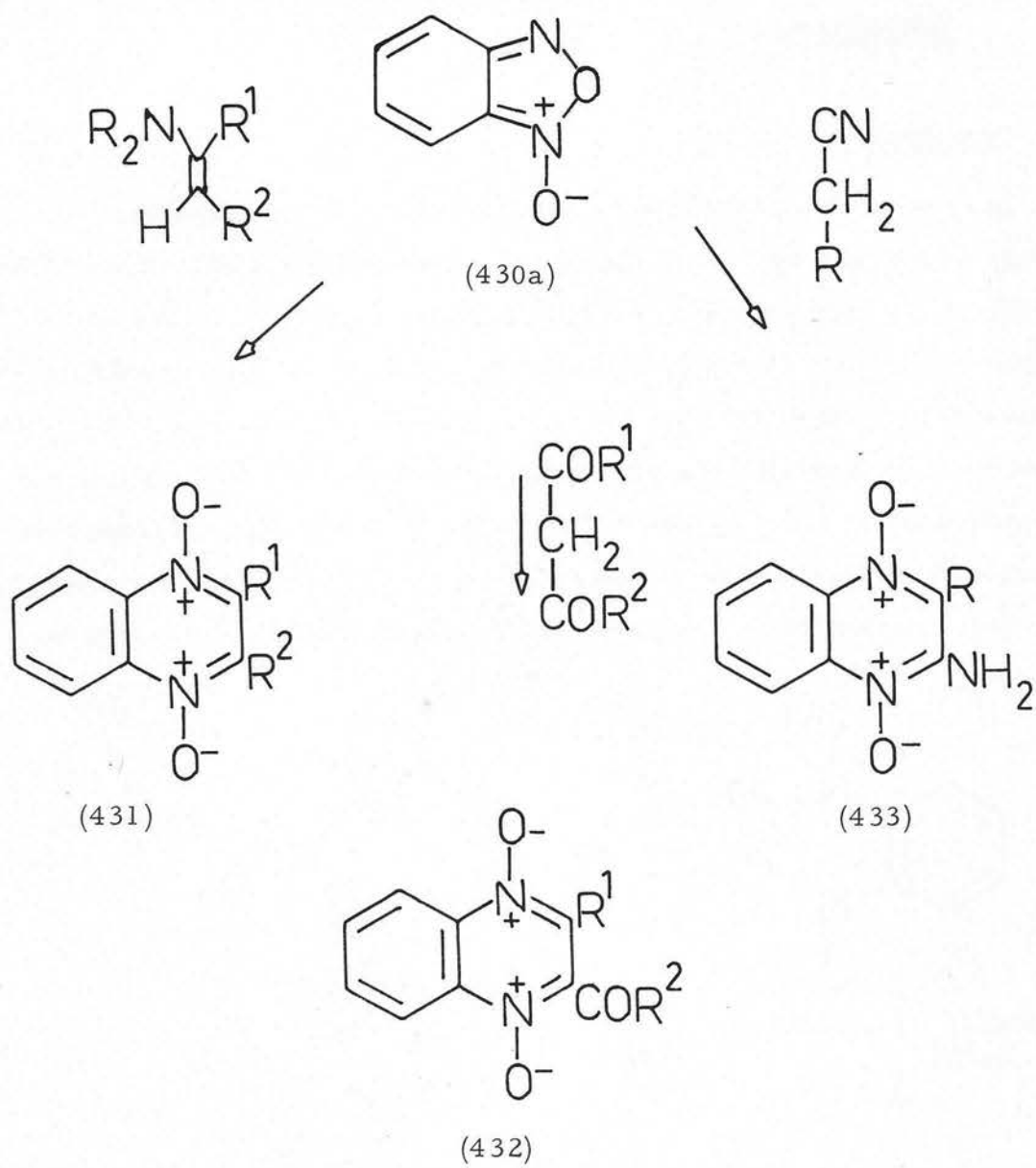
a) Introduction

In view of the interesting substitution and ring contraction reactions undergone by the 1-hydroxyquinoxaline-2,3(1H,4H)-diones (342) and (400) on reaction with both acetyl chloride in acetic acid and acetic anhydride it was considered that an investigation of the corresponding reactions of the 1,4-dihydroxyquinoxaline-2,3(1H,4H)-diones (426) under similar conditions might be a profitable area of study. Since such compounds contain two N-hydroxy functional groups it might reasonably be expected that they would be susceptible to bis-substitution by acylating agents [cf. scheme 78; (426a)  $\rightarrow$  (427)] under conditions which have



Scheme 78

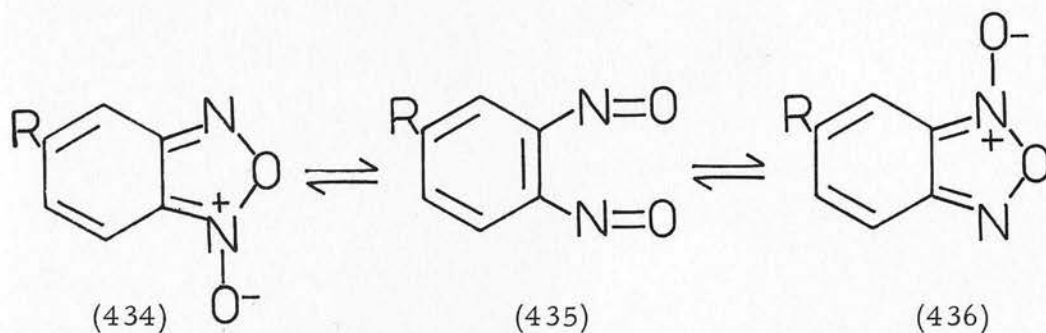
already been demonstrated to effect mono-substitution of mono-N-hydroxy-



Scheme 79

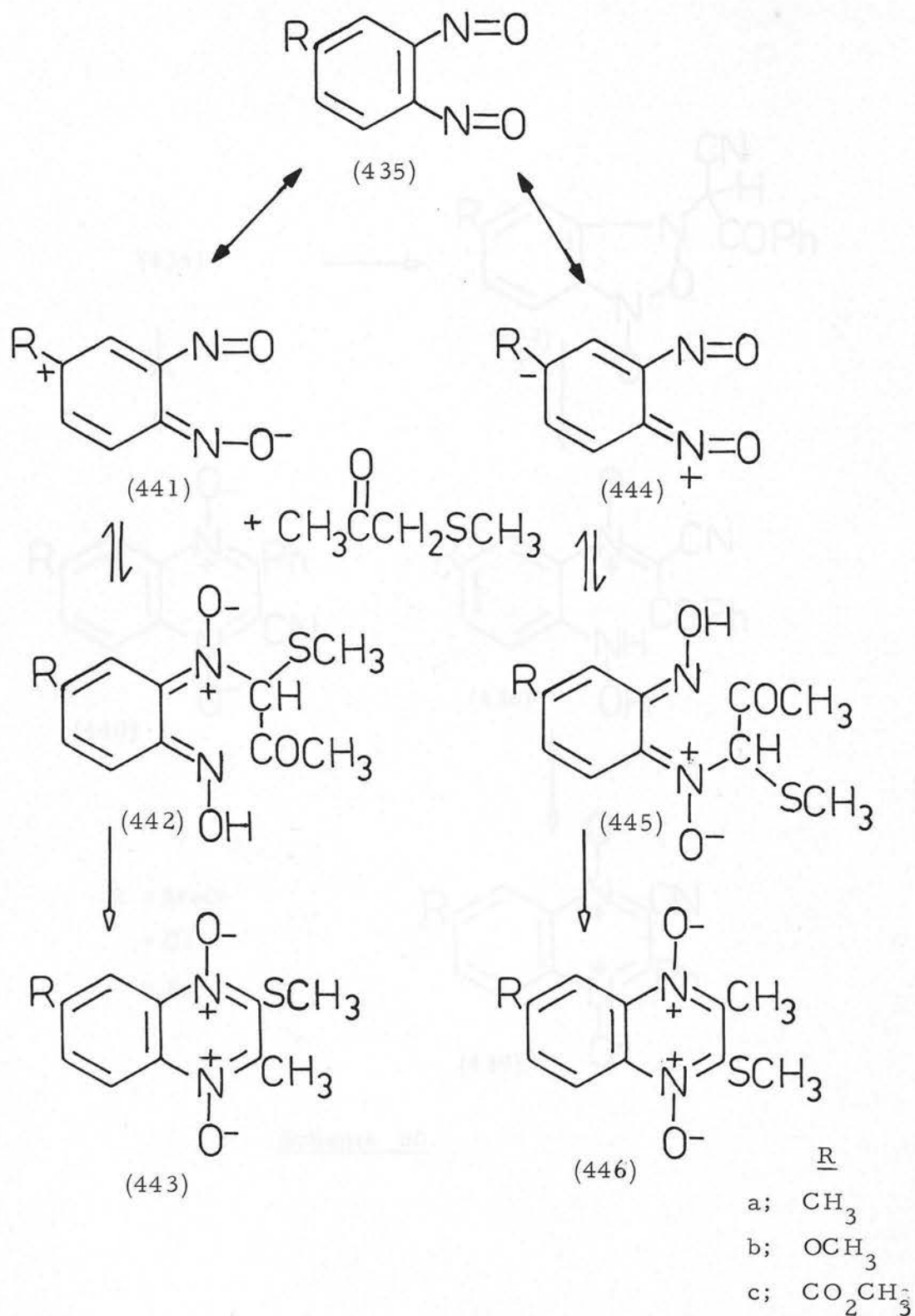
quinoxalinediones. Moreover, by analogy with mono-N-hydroxyquinoxalinediones, the di-N-hydroxy analogues (426) might undergo ring-contraction in hot acetic anhydride to afford otherwise inaccessible N-oxygenated heterocycles [cf scheme 78; (426a)  $\rightarrow$  (428)  $\rightarrow$  (429)]. Consequently it was decided to devise a suitable method for the synthesis of the hitherto unknown 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) and its derivatives.

Benzofuroxans (430) are versatile precursors for the synthesis of a variety of N-oxygenated heterocycles which are otherwise only accessible with difficulty. Thus, benzofuroxan (430a) reacts with enamines to afford a general route to the quinoxaline di-N-oxides (431)<sup>104</sup> [cf. (430a)  $\rightarrow$  (431); scheme 79]. Further, benzofuroxan (430a) undergoes facile base catalysed condensation reactions with active methylene compounds. Thus on base-catalysed reaction with  $\beta$ -diketones, benzofuroxan (430a) affords quinoxaline di-N-oxides of the type (432)<sup>105</sup> and a similar reaction with nitriles affords 2-aminoquinoxaline-di-N-oxides (433)<sup>106</sup> [cf. (430a)  $\rightarrow$  (433); scheme 79]. The mechanism of condensation reactions of this type has still not been established with any certainty. In particular, an unsymmetrically substituted benzofuroxan is potentially an equilibrium mixture of three tautomeric forms [cf. (434)  $\rightleftharpoons$  (435)  $\rightleftharpoons$  (436)] and it is not clear whether the species involved in condensation



is the dinitroso intermediate (435) or either of the benzofuroxan tautomers (434) or (436). Tennant and Mason<sup>76</sup> have reported that benzoylacetonitrile carbanion apparently reacts with 5(6)-substituted benzofuroxans in their more stable<sup>107</sup> tautomeric form to give the product (439) rather

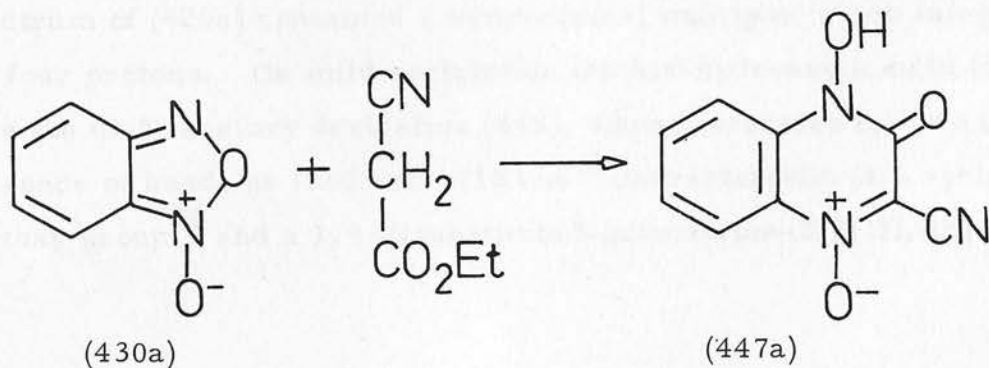




Scheme 81

than the other possible isomer (440). The authors account for the preferential formation of (439) by the mechanism outlined in scheme 80. Initial nucleophilic attack by benzoylacetonitrile carbanion on the benzofuroxan tautomer (434) gives the adduct (437), ring opening of which yields the hydroxyamino-nitrone intermediate (438). Cyclisation of the latter then affords the observed product (439). In contrast to the results obtained by Mason and Tennant, it has been found that 5(6)-substituted benzofuroxans (434) condense with acetyl methyl sulphide to produce a mixture of the 6- and 7-substituted quinoxaline di-N-oxides (443) and (446). The formation of both isomers has been rationalised<sup>108</sup> in terms of nucleophilic attack on the *o*-dinitrosobenzene derivative (435). The mechanism favoured for the formation of the isomers (443) and (446) is that outlined in scheme 81. An investigation of the effect of the nature of the substituent R on the course of the reaction supports this mechanism. An electron releasing substituent would stabilise the resonance form (441) over (444), while an electron accepting substituent would have the opposite effect. Accordingly, the *meta*-nitroso group would suffer initial nucleophilic attack in the former case while the *para*-nitroso group would be more reactive in the latter. Thus, 5(6)-methoxy and 5(6)-methylbenzofuroxan (434a and b) would be expected to furnish the 7-substituted compounds (443a and b) as the major isomers, while 5(6)-carbomethoxybenzofuroxan (434c) would be expected to furnish a greater proportion of the 6-isomer (446c). These mechanistically based predictions were fully substantiated by the experimental results.

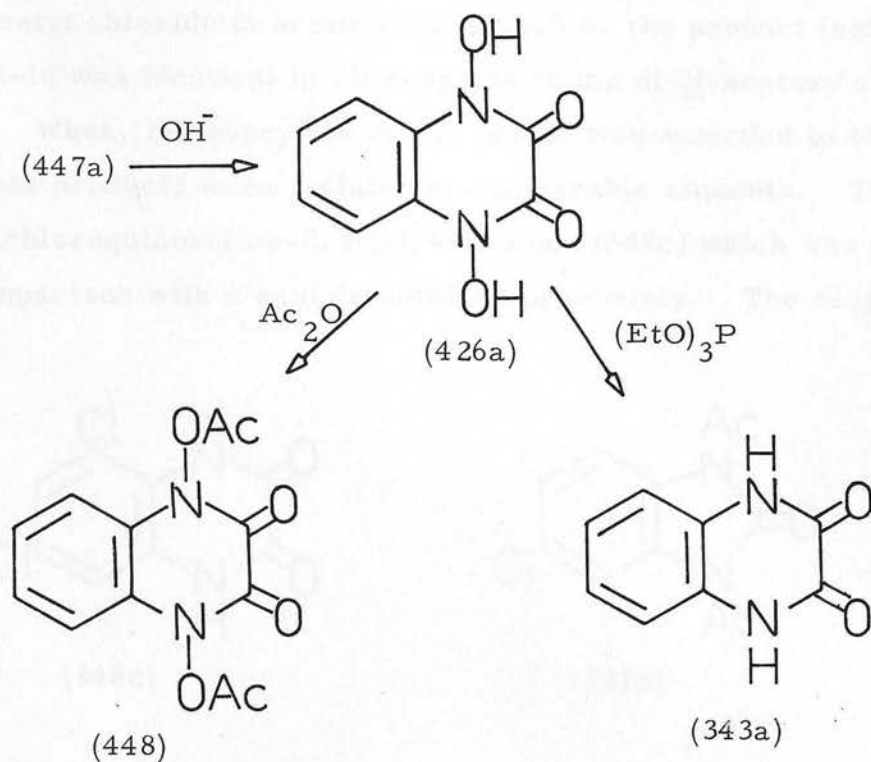
Of particular interest with respect to the present studies was the reported<sup>106</sup> condensation of benzofuroxan (430a) with ethyl cyanoacetate to afford the cyclic hydroxamic acid (447a) in good yield. This compound



already contains one hydroxamic acid function and molecules of this type are therefore attractive potential precursors for the synthesis of di-N-hydroxy compounds of the type (426). Thus by analogy with the conversion of 3-cyanoquinoxalin-2(1H)-one 4-oxides into 1-hydroxyquinoxaline-2,3(1H,4H)-diones discussed previously, nucleophilic displacement of the cyano group in the mono-hydroxamic acid (447a) by hydroxide ion should lead to the required bis-hydroxamic acid (426a). This was found to be the case and allowed the general synthesis of bis-hydroxamic acids of the type (426) from cyano-N-oxides of the type (447) which were readily available from benzofuroxans (430) using Ley's method.<sup>106</sup>

b) The Synthesis of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a).

The reaction of benzofuroxan (430a) with ethyl cyanoacetate in the presence of 1,5-diazabicyclo-[4.3.0]-non-5-ene (D.B.N.) proceeded as described in the literature<sup>106</sup> to give the cyanohydroxamic acid (447a). In accord with its constitution the i. r. spectrum of (447a) showed bands at 3300 and 1650  $\text{cm}^{-1}$  attributable to a cyclic hydroxamic acid structure and also a band at 2250  $\text{cm}^{-1}$  demonstrating the presence of a cyano group. In further support of the structure (447a) and in accord with expectations, refluxing the compound with aqueous ethanolic potassium hydroxide for 1 h gave a red salt, acidification of which afforded in high yield a new product whose properties and transformations were fully consistent with its being the required bis-cyclic hydroxamic acid (426a). It gave elemental and mass spectral data fully consistent with this structure which was further demonstrated by the presence of bands at 3400 and 1690  $\text{cm}^{-1}$  in its i. r. spectrum characteristic of a cyclic hydroxamic acid structure. In accord with the assigned structure, the aromatic region of the  $^1\text{H}$  n. m. r. spectrum of (426a) contained a symmetrical multiplet which integrated for four protons. On mild acetylation the bis-hydroxamic acid (426a) gave the di-N-acetoxy derivative (448), whose structure follows from the presence of bands at 1800 and 1710  $\text{cm}^{-1}$  characteristic of a cyclic N-acetoxy group<sup>84</sup> and a 1,4-disubstituted-quinoxaline-2,3[1H,4H]-dione



Scheme 82

nucleus,<sup>91</sup> respectively. Attempts to reduce the bis-cyclic hydroxamic acid (426a) to the known quinoxaline-2,3(1H,4H)-dione (343a) using either sodium dithionite or iron and acetic acid were unsuccessful as was attempted hydrogenolysis of the di-*N*-acetoxy compound<sup>84</sup> (448) over palladium charcoal. However, successful deoxygenation of the hydroxamic acid (426a) to the quinoxalinedione (343a) was readily achieved using triethyl phosphite. The reduction of the compound (426a) to the known quinoxalinedione (343a) provides rigorous evidence for the structure of the former compound. The conversion of the *N*-hydroxyquinoxalinone (447a) into the bis-hydroxamic acid (426a) is explicable as for the conversion of 3-cyanoquinoxalin-2(1H)-one 4-oxides into 1-hydroxyquinoxaline-2,3(1H,4H)-diones (see chapter 3, scheme 57).

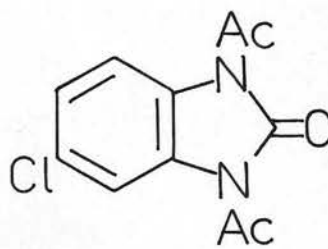
c) The Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetyl Chloride in Acetic Acid.

When the di-*N*-hydroxy compound (426a) was heated under reflux

with acetyl chloride in acetic acid for 1.5 h. the product isolated in high yield was identical in all respects to the di-N-acetoxy compound (448). When, however, the reflux period was extended to 48 h, two different products were isolated in comparable amounts. The first was 5,7-dichloroquinoxaline-2,3(1H,4H)-dione (348c) which was identified by comparison with a sample obtained previously. The second product



(348c)



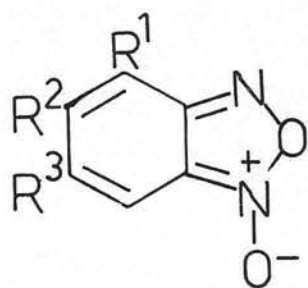
(291b)

was characterised as the benzimidazolone (291b) by comparison with an authentic sample. Formation of the compound (291b) is interesting in that it is the product of both substitution of the fused benzene ring in (426a) by chloride ion and also of ring-contraction of the hetero-ring in (426a).

d) The General Synthesis of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-diones (426) from 3-Cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxides (447).

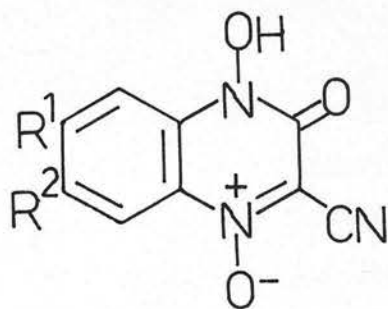
In view of the unexpected mode of substitution observed in the reaction of the di-N-hydroxy compound (426a) with acetyl chloride and the interesting substituent effects observed in the analogous chlorination reactions of substituted N-hydroxyquinoxalinediones (see 4.1 and 4.2) it was of interest to investigate the reactions of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-diones (426), bearing various substituents in the benzene ring, with acetyl chloride in acetic acid. The general formation of 1-hydroxy-3-cyanoquinoxalin-2(1H)-one 4-oxides (447) from substituted benzofuroxans (430) and ethyl cyanoacetate in the presence of DABCO according to the Ley procedure, and their general alkali-catalysed conversion into





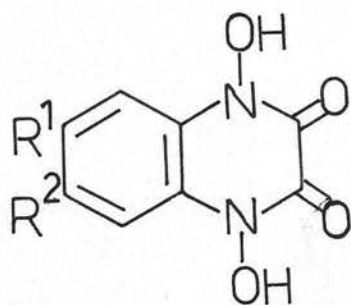
(430)

	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>	<u>R</u> <sup>3</sup>
a;	H	H	H
b;	H	Me	H
c;	H	Cl	H
d;	H	MeO	H
e;	H	Me	Me
f;	Cl	H	Cl



(447)

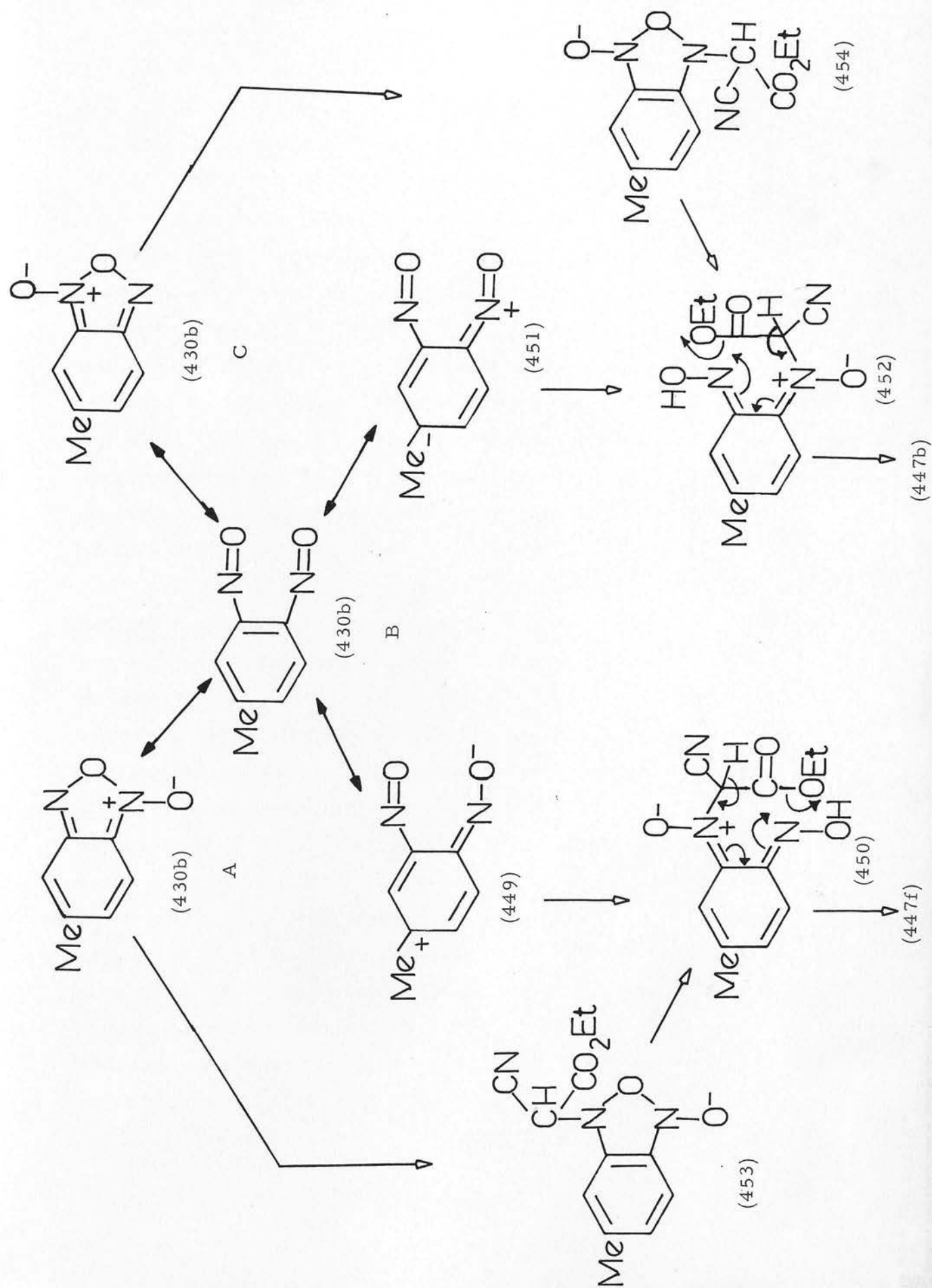
	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>
a;	H	H
b;	Me	H
c;	Cl	H
d;	MeO	H
e;	Me	Me
f;	H	Me
g;	H	Cl



(426)

	<u>R</u> <sup>1</sup>	<u>R</u> <sup>2</sup>
a;	H	H
b;	Cl	H
c;	Me	H
d;	Me	Me
e;	MeO	H

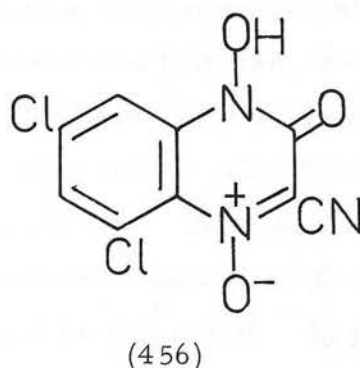
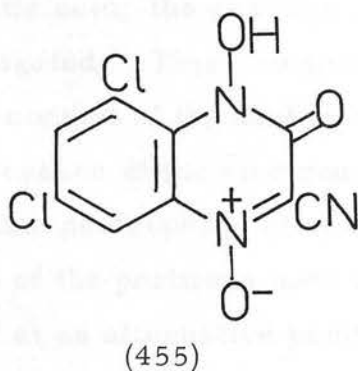
the corresponding 1,4-dihydroxyquinoxaline-2,3(1H,4H)-diones (426) was therefore investigated. Thus, 5-methylbenzofuroxan (430b) reacted with ethyl cyanoacetate in the presence of DABCO to give a moderate yield of a highly crystalline, light yellow solid which gave analytical and mass spectral data correct for a mono-methyl derivative of the N-hydroxy cyano N-oxide (447a). This formulation was also supported by its i. r. spectrum which contained bands at 3050 and 1630-1600  $\text{cm}^{-1}$  attributable to a cyclic hydroxamic acid grouping, and cyano absorption at 2200  $\text{cm}^{-1}$ . However, the splitting pattern in the aromatic region of its  $^1\text{H}$  n. m. r. spectrum was more in accord with the presence of both possible isomeric products (447b and f). In particular, the  $^1\text{H}$  n. m. r. spectrum contained a doublet at  $\delta 8.02$  with a coupling constant of 9Hz, characteristic of ortho-splitting, which is assigned to the proton at C-5 in the isomer (447b) on the basis of its low field position which results from deshielding by the adjacent N-4 hetero atom. The signal further upfield at  $\delta 7.8$  is assigned to the H-8 proton in the isomer (447b) since it appears as a doublet with a coupling constant of 2.5Hz, characteristic of coupling between meta protons. The signal furthest upfield at  $\delta 7.39$  is assigned to the proton at C-6 in the isomer (447b) since the signal appears as a double doublet with coupling constants corresponding to ortho and meta splitting. In accord with these proposals it was found in a decoupling experiment that irradiation of the doublet at  $\delta 8.02$  caused the double doublet at  $\delta 7.39$  to collapse to a singlet. The  $^1\text{H}$  n. m. r. spectrum was not suited to further decoupling experiments. In addition to these signals, the aromatic region contained a singlet at  $\delta 7.72$  which integrated for two protons and a doublet at  $\delta 7.61$ , corresponding to a single proton, with a coupling constant characteristic of meta splitting. These signals cannot be fully reconciled with the isomeric structure (447f) however, in view of the satisfactory combustion analysis data obtained, this is the most likely other component of what is indicated by  $^1\text{H}$  n. m. r. to be a mixture. Formation of both isomers (447b and f) can be rationalised either by reaction of the 5-methylbenzofuroxan (430b) in either the dinitroso tautomeric form B or the benzofuroxan tautomers A or C, as outlined in scheme 83. Thus nucleophilic attack by ethyl cyanoacetate anion on the



o-nitrosobenzene derivative (451) would afford the adduct (452) which would give the 7-methylquinoxalin-2(1H)-one (447b) on cyclisation with expulsion of the elements of ethanol [cf (451)  $\rightarrow$  (452)  $\rightarrow$  (447b); scheme 83]. Alternatively, the formation of the isomers (447b and f) is explicable by courses involving nucleophilic attack by ethyl cyanoacetate anion on the tautomers A and C with formation of the adducts (453) and (454). Ring opening of the latter would afford the intermediates (450) and (452) and thence the products (447f) and (447b) as described before.

Condensation of the 5-chlorobenzofuroxan (430c) with ethyl cyanoacetate in the presence of DABCO also gave a yellow solid in low yield whose elemental analysis and mass and i. r. spectral properties were fully consistent with the expected 6-chloro-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide structure (447c). Again, however, the aromatic splitting pattern in its  $^1\text{H}$  n. m. r. spectrum was not consistent with that of a simple 1,2,4-trisubstituted benzene derivative and though the signals were too complex to permit assignments to individual protons, the signals were approximately in accord with those expected for a mixture of both possible isomeric products (447c and g).

The base-catalysed reaction of 5,6-dimethylbenzofuroxan (430e) with ethyl cyanoacetate gave a high yield of a single product whose properties were fully consistent with the dimethyl-hydroxamic acid structure (447e). In particular, its  $^1\text{H}$  n. m. r. spectrum contained two one proton singlets assigned to the protons at C-5 and C-8. In this case the symmetrical nature of the benzofuroxan (430e) allows for the formation of only a single condensation product namely (447e). The attempted condensation of 5,7-dichlorobenzofuroxan (430f) with ethyl cyanoacetate in the presence of DABCO gave a very low yield of an orange product which gave an elemental analysis and showed spectral properties consistent with either of the N-oxide structures (455) or (456). In particular, its  $^1\text{H}$  n. m. r. spectrum contained two one proton signals which showed up as doublets with a coupling constant of 2Hz, characteristic of meta splitting. This indicates that only one of the two possible isomers (455) and (456) is obtained from this reaction, however, it is impossible to come down in



favour of either on the basis of the evidence available. The attempted reaction of 5-methoxybenzofuroxan (430d) with ethyl cyanoacetate in the presence of DABCO gave a dark, viscous gum from which no identifiable material could be obtained.

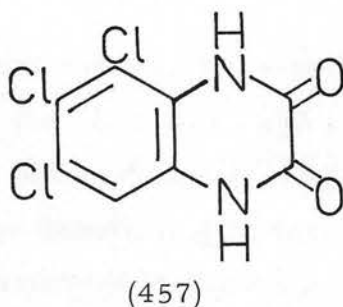
No attempt was made to separate the isomeric mixture of mono-chloro cyano N-oxides (447c and g) since both isomers should give the same mono-chloro di-N-hydroxyquinoxalinedione (426b). In accord with these expectations the isomer mixture was smoothly converted in aqueous ethanolic potassium hydroxide in high yield into a product whose properties were fully consistent with its being the required di-N-hydroxy compound (426b). The dimethyl N-oxide (447e) was likewise converted in high yield into the expected di-N-hydroxy compound (426d). In contrast, the attempted synthesis of the mono-methyl compound (426c) from the isomer mixture (447b)/(447f) in aqueous ethanolic potassium hydroxide gave only a low yield of the expected product (426c). The products (426b, c and d) gave elemental analyses and showed mass, i. r. and  $^1\text{H}$  n. m. r. spectral properties consistent with the assigned structure. The lack of the cyano N-oxide (447d) prevented the attempted synthesis of the 1,4-di-N-hydroxy compound (426e) using aqueous ethanolic potassium hydroxide.

e) The Reactions of the Di-N-hydroxyquinoxalinediones (426b and d) with Acetyl Chloride in Acetic Acid.

In the hope of obtaining further insight into the mode of reaction of 1,4-di-N-hydroxyquinoxaline-2,3(1H,4H)-diones with acetyl chloride



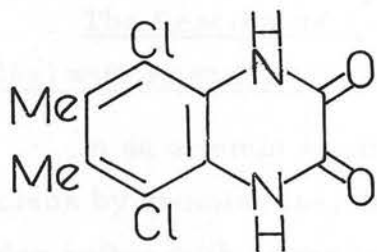
in acetic acid, the reaction of the chloro-derivative (426b) was investigated. This compound possesses two intrinsic features of interest in the context of the nucleophilic substitution by chloride ion. Firstly, the presence of the electron-withdrawing chloro substituent should facilitate nucleophilic attack by chloride ion. Secondly, since the site of one of the positions open to nucleophilic attack (i. e. C-6) is blocked, attack at an alternative position should be promoted. In practice, heating the chloro-compound (426b) with acetyl chloride in acetic acid gave a single product in high yield. This product is assigned the trichloroquinoxalinedione structure (457) on the basis of its mass spectral analysis which



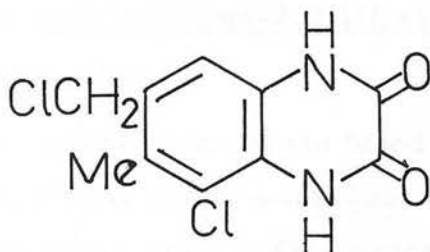
demonstrated conclusively the presence of three chlorine atoms. In further support of its structure the product (457) showed i. r. absorption typical of a quinoxaline-2,3-dione structure and its  $^1\text{H}$  n. m. r. spectrum contained a one proton singlet due to the single aromatic proton in the structure (457).

In contrast to the reaction of the parent di-N-hydroxyquinoxalinedione (426a) with acetyl chloride in acetic acid, the similar reaction of the chloro-compound (426b) gave no product of ring-contraction (i. e. benzimidazolone product). In view of this, the reaction of the dimethyl-di-N-hydroxyquinoxalinedione (426d) with acetyl chloride in acetic acid was of particular interest. Thus the presence of two electron releasing methyl substituents, as well as blocking two of the sites open to nucleophilic attack by chloride ion, might sufficiently deactivate the benzene nucleus to nucleophilic attack to permit ring contraction to compete. Reaction of the dimethyl compound (426d) with acetyl chloride in acetic

acid in fact gave two isomeric products whose elemental and mass spectral analyses and i. r. spectra were consistent with them being dichloroquinoxalinedione derivatives. The structures (458) and (459)

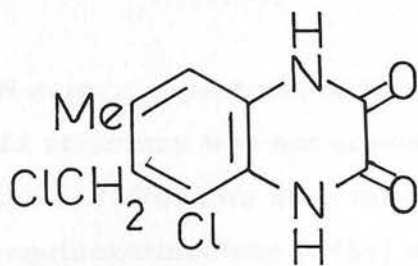


(458)



(459)

were assigned to these compounds on the basis of their  $^1\text{H}$  n. m. r. spectra. In the case of (458), the  $^1\text{H}$  n. m. r. spectrum lacked absorption in the aromatic region and showed a single sharp absorption due to the protons of both methyl groups demonstrating that both available sites in the benzene nucleus had been substituted by chloride ion giving the highly symmetrical structure (458) in which both methyl groups are equivalent. The  $^1\text{H}$  n. m. r. spectrum of the second product showed the presence of a single aromatic proton, a methylene group and a single methyl group. This absorption is consistent with either of the two possible structures (459) or (460). The lack of detectable splitting in the resonances due to the aromatic



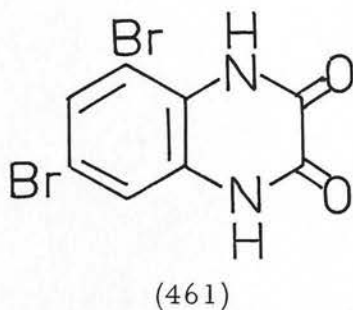
(460)

proton or the protons of the methyl group is tentatively considered as evidence in support of the former structure. Thus the structure (460) would be expected to exhibit coupling between the C-7 methyl group and the proton at C-8 resulting in splitting of the respective proton resonances

and this is not observed. The mono-methylated di-N-hydroxyquinoxalinedione (426c) was obtained in insufficient quantity to permit its reaction with acetyl chloride in acetic acid to be investigated.

f) The Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetyl Bromide in Acetic Acid.

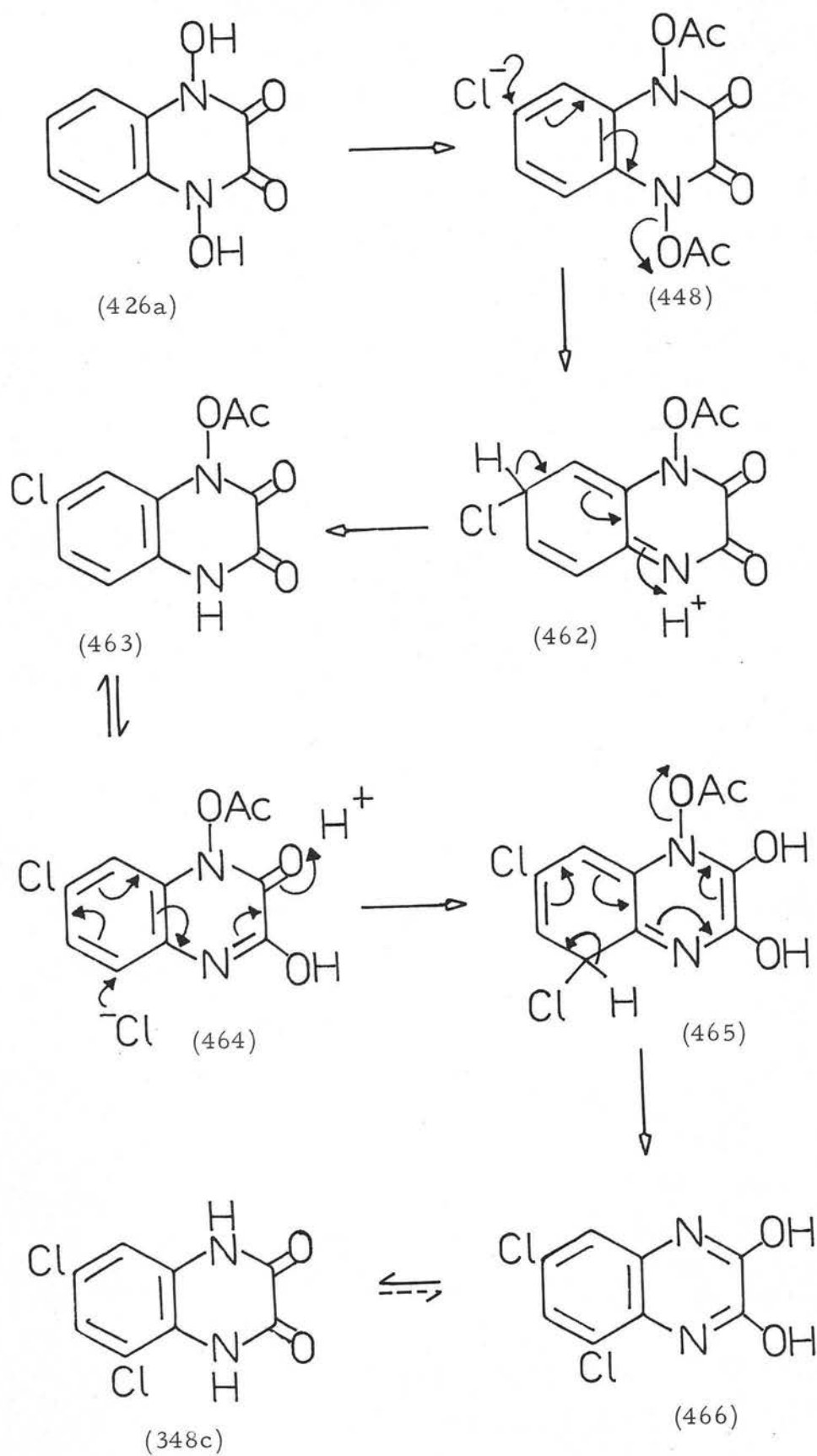
In an attempt to observe bis-substitution of the fused benzene nucleus by bromide ion, the di-N-hydroxy compound (426a) was heated under reflux with acetyl bromide in acetic acid. This procedure led, in the main, to the formation of the 1,4-di-N-acetoxyquinoxaline-2,3(1H,4H)-dione (448), identical in every respect with a sample obtained previously. However, the 5,7-dibromoquinoxalinedione (461) was also obtained in low yield from this reaction. The mass and i. r. spectral evidence obtained for the dibromoquinoxalinedione (461) were fully in accord with the assigned structure. Unfortunately, because of lack of



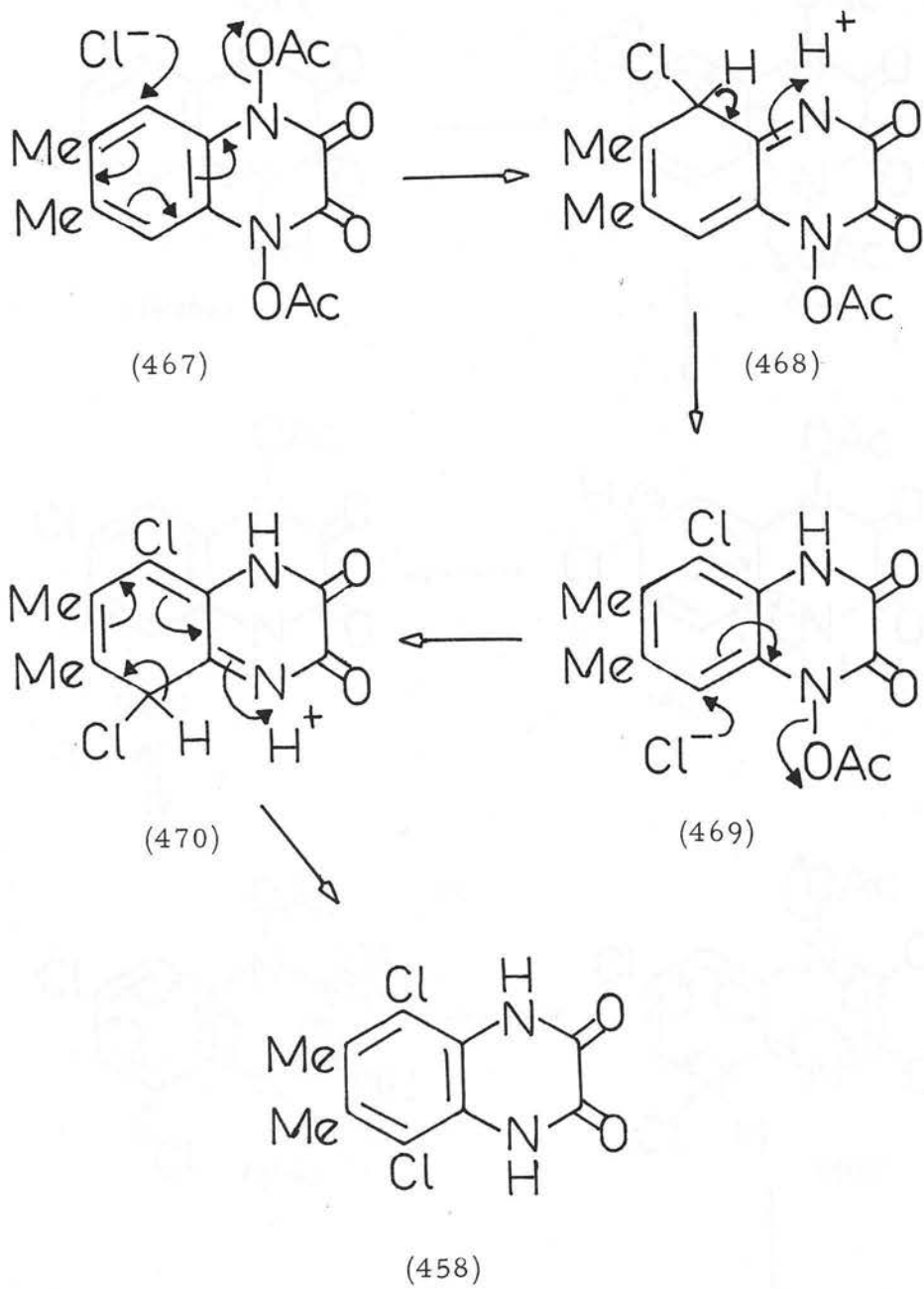
material, no  $^1\text{H}$  n. m. r. spectrum of this compound could be obtained and therefore its structure was not unambiguously determined. The assignment of the 5,7-dibromo structure (461) is based on analogy with the 5,7-dichloroquinoxalinedione (348c) obtained from the corresponding reaction of the di-N-hydroxyquinoxalinedione (426a) with acetyl chloride.

g) Discussion of the Mechanism of the Reactions of Di-N-Hydroxyquinoxaline-2,3(1H,4H)-diones (426) with Acetyl Chloride and Acetyl Bromide in Acetic Acid.

The formation of the 5,7-dichloro compound (348c) on reaction

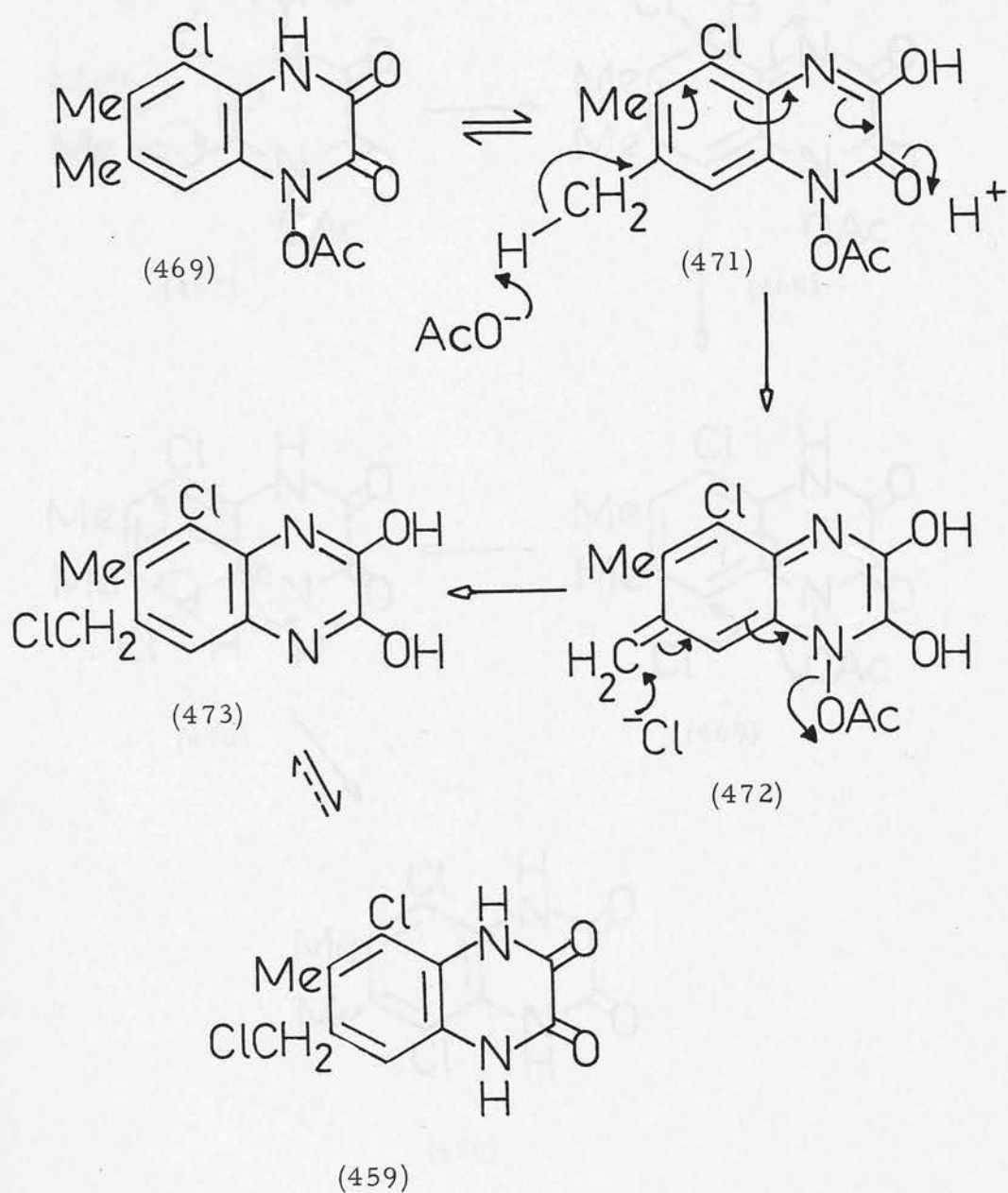


Scheme 84



Scheme 85

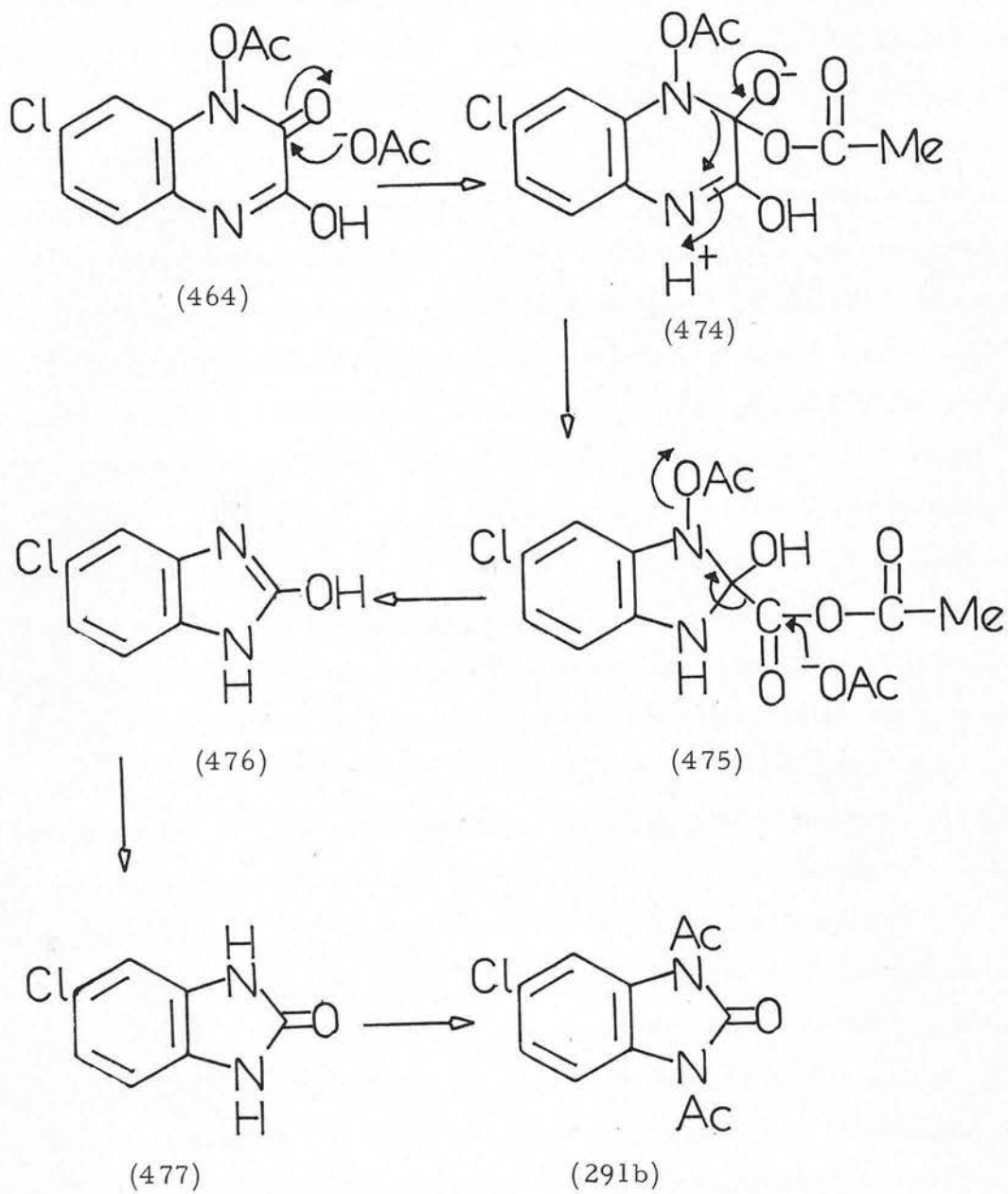




Scheme 86

of the di-N-hydroxyquinoxalinedione (426a) with acetyl chloride in acetic acid at elevated temperature is explicable by the mechanistic route outlined in scheme 84. Thus nucleophilic attack by chloride ion at the C-7 position of the presumed di-N-acetoxy intermediate (448) with concerted expulsion of the acetoxy group at N-4 would afford the para-quinonoid intermediate (462), which upon rearomatisation would give the N-acetoxy intermediate (463). The formation of the dichloro compound (348c) from the N-acetoxy intermediate (463) requires the reaction of this compound in its enol form (464). Thus nucleophilic attack by chloride ion at the C-5 position of the enol (464) and addition of a proton would give the adduct (465) which upon rearomatisation with expulsion of the elements of acetic acid would furnish the bis-enol (466), tautomeric with the observed product (348c). The formation of 5,6,7-trichloroquinoxalinedione (457) in the reaction of the bis-hydroxamic acid (426b) with acetyl chloride in acetic acid and the formation of 5,7-dibromoquinoxalinedione (461) on reaction of the bis-hydroxamic acid (426a) with acetyl bromide in acetic acid are explicable by courses directly analogous to that outlined in scheme 84, the formation of the dibromo compound (461) requiring nucleophilic attack by bromide ion.

As previously described, the reaction of the bis-hydroxamic acid (426d) with acetyl chloride in acetic acid at elevated temperature affords a mixture of the isomeric dichloro compounds (458) and (459). The formation of the 5,8-dichloroquinoxalinedione (458) may be rationalised by the mechanistic pathway outlined in scheme 85. Thus nucleophilic attack at the C-5 position of the di-N-acetoxy intermediate (467) with expulsion of the acetoxy group at N-4 affords the intermediate (468) which gives the N-acetoxy intermediate (469) upon rearomatisation. A repetition of this process [cf (469)  $\rightarrow$  (470)  $\rightarrow$  (458); scheme 85], then furnishes the observed dichloro-derivative (458). As outlined in scheme 86, the key step in the formation of the 7-chloromethyl-derivative (459) is deprotonation by acetate ion of the intermediate (469) in its enol form (471) to afford the para-quinonoid intermediate (472). Nucleophilic attack by chloride ion at the methylene centre in (472) then gives the bis-enol (473), tautomeric with the observed product (459).



Scheme 87

The ring-contraction undergone by the parent di-N-hydroxy compound (426a) on reaction with acetyl chloride is accountable by the course described in scheme 87. Nucleophilic attack by acetate ion at the C-2 position in the N-acetoxy intermediate (464) [cf. scheme 84] would afford the adduct (474) which would give the benzimidazole intermediate (475) on ring-contraction as shown [(474)  $\rightarrow$  (475); scheme 87]. Displacement of the acyloxycarbonyl side chain at C-2 and expulsion of the N-acetoxy leaving group from the intermediate (475) would afford the chlorobenzimidazolone (477). Further acetylation of (477) would then furnish the observed product (291b). The mechanistic course outlined for the ring-contraction of (426a) on reaction with acetyl chloride (scheme 87) is directly analogous to that outlined in scheme 73 for the corresponding ring-contraction undergone by the mono-N-hydroxy compound (342e) indicating the intermediacy of the latter in the reaction of the di-N-hydroxy compound (426a).

h) The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetic Anhydride.

As already demonstrated, the di-N-hydroxyquinoxalinedione (426a) reacts with acetyl chloride in acetic acid to afford products derived both by chlorination and ring-contraction. The formation of the same products from the mono-N-hydroxyquinoxalinedione (342e) under similar conditions indicates the intermediacy of (342e) in the corresponding reaction of the di-N-hydroxy compound (426a). It has also been shown that the reaction of the mono-N-hydroxyquinoxalinedione (342e) with hot acetic anhydride contrasts with that in hot acetyl chloride-acetic acid in resulting in ring-contraction rather than chlorination. In view of these results, it was of interest to investigate the prolonged reaction of the di-N-hydroxyquinoxalinedione (426a) with acetic anhydride, since a combination of acetoxy substitution/ring contraction or simple ring-contraction to a novel N-oxygenated benzimidazolone might result [cf scheme 78]. The sole product isolated from the prolonged heating of the di-N-hydroxy compound (426a) with acetic anhydride however, was a viscous black,

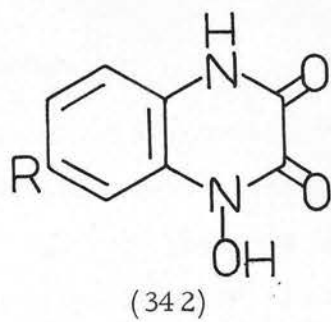
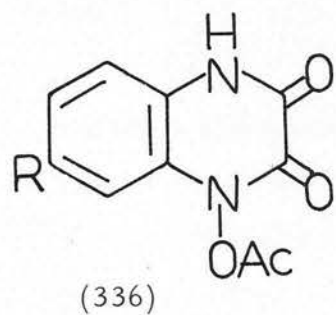
intractable gum which was shown by t.l.c. to be a multicomponent mixture and from which no identifiable material could be obtained by trituration. Separation of the gum by column chromatography was not attempted. The starting material (426a) is acidic and since it is probable that the products would also be acidic it was anticipated that efficient elution from a column would not be possible. In an attempt to simplify the course of the reaction of the di-N-hydroxy compound (426a) with acetic anhydride, the concentration of acetate ion in the mixture was increased by the addition of solid sodium acetate. However, heating the bis-hydroxamic acid (426a) with sodium acetate in acetic anhydride again gave a black viscous gum which was shown by t.l.c. to be a multicomponent mixture from which no identifiable material could be obtained.

i) The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Toluene-p-sulphonyl Chloride.

As was discussed in the introduction (chapter 1) of this thesis, N-oxygenated heterocycles can react with sulphonyl chlorides to afford  $\beta$ -sulphonyloxy derivatives and both  $\alpha$ - and  $\gamma$ -chlorinated heterocycles. In view of the reactivity of the di-N-hydroxy compound (426a) towards acetyl chloride, it was of interest to investigate the corresponding reactivity towards toluene-p-sulphonyl chloride (tosyl chloride). Because of the relative insolubility of the di-N-hydroxy compound (426a) its reaction with tosyl chloride was best investigated using dimethylformamide as co-solvent. In practice, however, reaction of the compound (426a) with tosyl chloride in dimethylformamide at room temperature gave, in addition to a good recovery of starting material, a low yield of a brown gum which yielded no identifiable material. In view of the failure to induce direct reaction between the di-N-hydroxy compound (426a) and tosyl chloride, attention was directed towards possible catalysis of this reaction by bases. However, attempted reaction of the compound (426a) with tosyl chloride in the presence of aqueous alkali, or triethylamine in dioxan, at room temperature gave largely unreacted starting material plus small amounts of intractable gums. On the other hand, reaction of

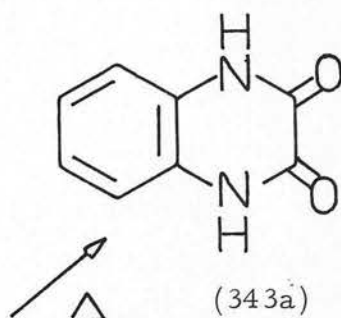
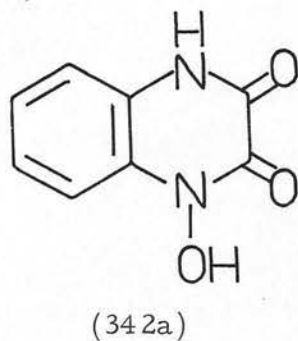
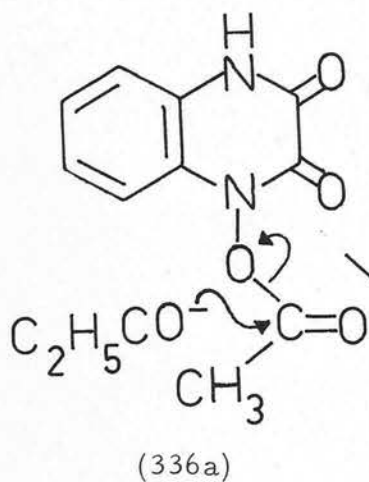
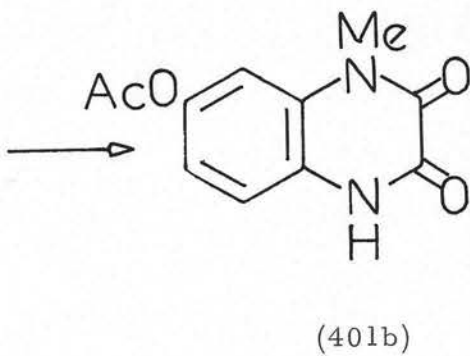
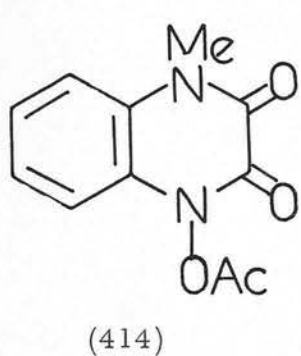
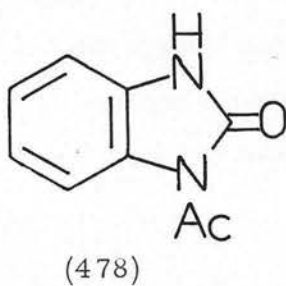
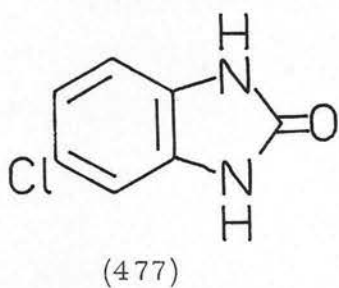


the di-N-hydroxy compound (426a) in dimethylformamide with tosyl chloride in the presence of triethylamine gave a low yield of a colourless product whose mass spectrum contained peaks at 196 and 198 and at 230, 232 and 234 mass units in accord with presence of mono- and dichloro-derivatives of the parent quinoxalinedione (343a). In support of the presence of a mixture of chloroquinoxalinediones, the i. r. spectrum of the product contained broad absorption bands at 3200 and 1690  $\text{cm}^{-1}$  attributable to a quinoxalinedione nucleus. However, attempts to obtain a pure sample of either a mono- or dichloroquinoxalinedione from the product of this reaction proved unsuccessful.



R  
a; H  
b; Cl

R  
a; H  
e; Cl



4. 4            Thermolytic Reactions of N-Oxygenated Quinoxaline-2, 3(1H, 4H)-diones

As discussed in previous sections, the reactions of N-hydroxyquinoxaline-2, 3(1H, 4H)-diones with acetic anhydride can, depending on the presence or absence of an alkyl group at N-4, result in three types of transformation, namely acetoxy-substitution in the benzene ring, ring-contraction, or reduction. The latter two processes are of particular interest since an acetoxy group is not incorporated in the product despite the fact that the corresponding N-acetoxyquinoxaline-2, 3(1H, 4H)-diones are probable intermediates in ring contraction and reduction. On the supposition that ring-contraction and reduction are purely thermal transformations of N-acetoxyquinoxalinediones, it was decided to investigate the thermolytic reactions of these derivatives.

Heating the N-acetoxyquinoxalinedione (336a) under reflux in diphenyl ether gave a good yield of a compound assigned the structure 1-acetylbenzimidazol-2-one (478) on the basis of its elemental and mass spectral analyses and the following spectral evidence. Its i. r. spectrum contained a strong carbonyl band at  $1725\text{ cm}^{-1}$ , attributable to a cyclic N-acetyl group and bands at  $3200\text{-}3100\text{ br}$  and  $1700\text{ cm}^{-1}$  which can be attributed to the NH(OH) and carbonyl absorption of a benzimidazolone nucleus. The presence of the N-acetyl group was further substantiated by a three proton singlet at  $\delta 2.59$  in the  $^1\text{H}$  n. m. r. spectrum of the product. Heating the chloro-substituted N-acetoxyquinoxalinedione (336b) in diphenyl ether also resulted in ring-contraction, the product, isolated in good yield being the benzimidazolone (477). The structure of the product is based on its spectral properties and its unambiguous synthesis by heating 4-chloro-1, 2-diaminobenzene with urea.

The thermal conversion of the N-acetoxyquinoxalinediones (336a and b) in diphenyl ether into the benzimidazolone derivatives (478) and (477) parallel to some extent the corresponding reactions of the N-hydroxyquinoxalinediones (342) with acetic anhydride (see chapter 4, part 1). However, since, in contrast to the reaction of the N-hydroxyquinoxalinedione (342e) with acetic anhydride, the thermal reaction of the chloro-

compound (336b) does not afford the quinoxalinedione (343b), a product of reduction, it is unlikely that N-acetoxyquinoxalinediones are intermediates in the reduction processes. Evidence that reduction is probably a thermal transformation of the free N-hydroxy compound will be discussed later. On the other hand, it would appear that the ring-contraction of N-hydroxyquinoxalinediones in hot acetic anhydride may be attributed to a purely thermal transformation of the corresponding N-acetoxy compounds. Since the N-alkyl-N-hydroxyquinoxaline-2,3(1H,4H)-diones (400) were found to undergo a combination of acetoxy substitution and ring-contraction in hot acetic anhydride, it was of interest to investigate the thermolysis of the N-methyl-N-acetoxyquinoxalinedione (414). Heating the acetoxy compound (414) in diphenyl ether gave a product in good yield, identical in all respects to the C-acetoxy isomer (401b) obtained previously. It follows that the thermal reaction of the N-acetoxy compound (414) in diphenyl ether parallels that of the corresponding N-hydroxy compound (400a) in hot acetic anhydride in resulting in acetoxy substitution but differs from the acetic anhydride promoted process in not giving rise to a product of ring-contraction. However, heating the N-acetoxy compound (414) in xylene, as well as giving the acetoxy compound (401b) also gave a product identical in all respects to an authentic sample of 1-acetyl-3-methylbenzimidazolone (403a). This reaction does therefore exactly parallel the transformation of the N-hydroxy compound (400a) in hot acetic anhydride indicating that acetoxy substitution and ring-contraction are both thermal transformations of an N-acetoxyquinoxalinedione intermediate. The requirement of an optimum temperature for the thermal acetoxy substitution and ring-contraction of the N-acetoxyquinoxalinedione (414) was demonstrated by the fact that it is stable to heating under reflux in ethanol.

As previously described (chapter 4, part 3) an attempt to observe acetoxy substitution or ring-contraction of the 1,4-di-N-hydroxyquinoxalinedione (426a) by examining its reaction with hot acetic anhydride proved unsuccessful. In the light of the thermal transformations undergone by the N-acetoxyquinoxalinedione (414), it was of interest to examine the corresponding reaction of the 1,4-diacetoxyquinoxalinedione (448) at elevated temperature in diphenyl ether in the hope that it would undergo

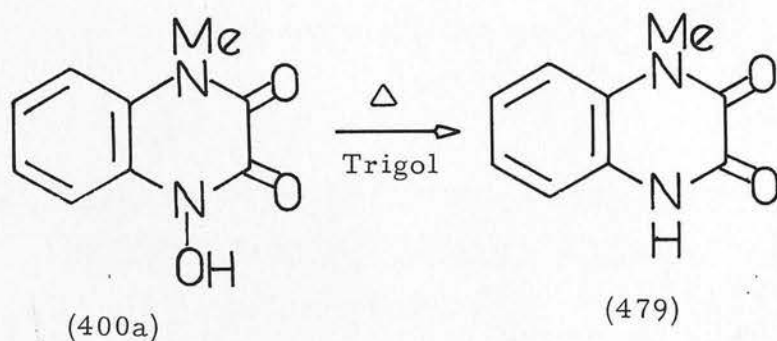
similar rearrangement. In practice, however, heating the diacetoxy compound (448) under reflux with diphenyl ether gave intractable products from which no identifiable material could be obtained.

As already mentioned, when the chloro N-hydroxyquinoxalinedione (342e) is heated under reflux in acetic anhydride the parent quinoxalinedione (343b) is produced in significant quantity. Since heating the N-acetoxyquinoxalinedione (336a) under reflux in diphenyl ether fails to afford the deoxygenated product (343a) it is exceedingly unlikely that the N-acetoxyquinoxalinedione (336b) is the species which is reduced in the reaction of (342e) with acetic anhydride. More probably it is the parent N-hydroxy compound (342e) itself which is subject to thermal deoxygenation at elevated temperature. The apparently contrasting formation of the quinoxalinedione (343a) in the reaction of the N-acetoxyquinoxalinedione (336a) with propionic acid would therefore be explicable by solvolysis of the N-acetate (336a) to furnish the N-hydroxy compound (342a) which would then afford the reduced product (343a) on thermal deoxygenation [Scheme 88]. Consequently it was of interest to study the thermal reactions of N-hydroxyquinoxalinedione derivatives. In practice, heating the N-hydroxyquinoxalinedione (342a) in cellosolve and the chloro-derivative (342e) in diphenyl ether resulted in the recovery of the unreacted starting materials. In contrast, thermolysis of the chloro-N-hydroxyquinoxalinedione (342e) in the higher boiling solvent trigol resulted in its smooth conversion in high yield into a product which gave analytical and spectral data fully in accord with the assigned structure (343b). However, it is probable that trigol, being alcoholic in character, is acting as a simple reducing medium in this reaction. In view of this, the thermolyses of the N-hydroxyquinoxalinediones (342a and e) were investigated in dibenzyl ether which has a boiling point analogous to that of trigol, but being non-alcoholic cannot function as a reducing agent. As hoped, heating the N-hydroxy compounds (342a and e) in dibenzyl ether resulted in their smooth conversion into the quinoxalinediones (343a and b). The mechanism of these interesting thermally induced reactions is not clear, but the process involved appears to be both acid and base catalysed. Thus, as discussed before, heating the N-acetoxyquinoxalinedione (336a) in propionic acid



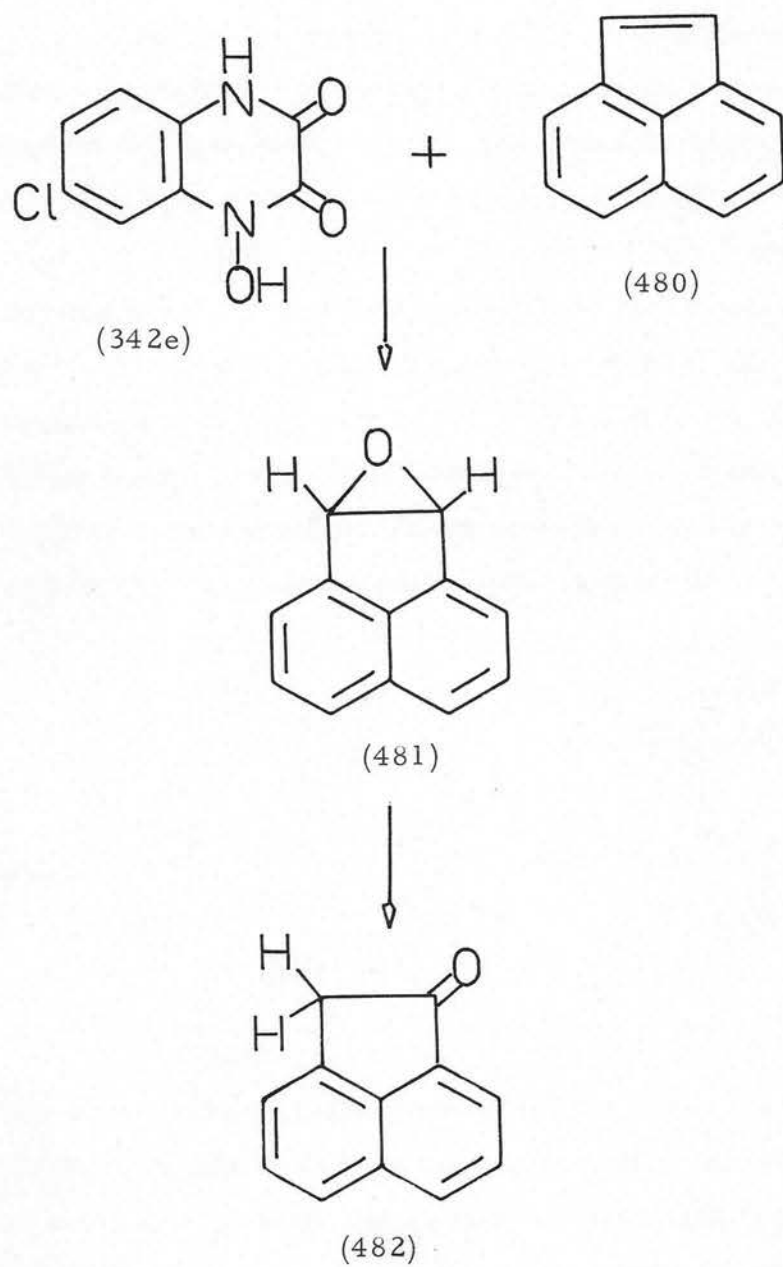
gives the quinoxalinedione (343a) in a reaction which has been demonstrated not to stem from the N-acetoxy compound (336a) itself and so must derive from the corresponding N-hydroxy compound (342a). Further, heating the chloro compound (342e) in N-methylaniline also results in the smooth formation of the quinoxalinedione (343b). Since propionic acid and N-methylaniline have lower boiling points than diphenyl ether which fails to effect thermal reduction (see before), it is deduced that the reduction observed in propionic acid and N-methylaniline must be acid and base-catalysed, respectively.

Thermal deoxygenations of N-oxygenated heterocycles are known processes<sup>1b</sup> but normally proceed in low yield and are accompanied by much decomposition of the substrate. The high yield thermal conversions of the N-hydroxyquinoxalinediones (342a and e) into the quinoxalinediones (343a and b) are therefore processes of considerable interest particularly since the N-hydroxy-N-methylquinoxalinedione (400a) is stable to thermolysis



in dibenzyl ether. The compound (400a) did undergo reduction to the reduced compound (479) in boiling trigol but in view of the stability of (400a) in dibenzyl ether, this reaction can be put down to reduction in the alcoholic medium. The product (479) showed a melting point (278-80°) which differed from that (257°) reported by Usherwood and Whiteley<sup>109</sup> for 1-methylquinoxaline-2,3(1H,4H)-dione, however, it was identical in all respects to an authentic sample prepared by dithionite reduction of the N-hydroxy compound (400a).

In an attempt to determine the fate of the oxygen atom lost in the thermal conversion of (342a and e) into (343a and b), the N-hydroxy compound



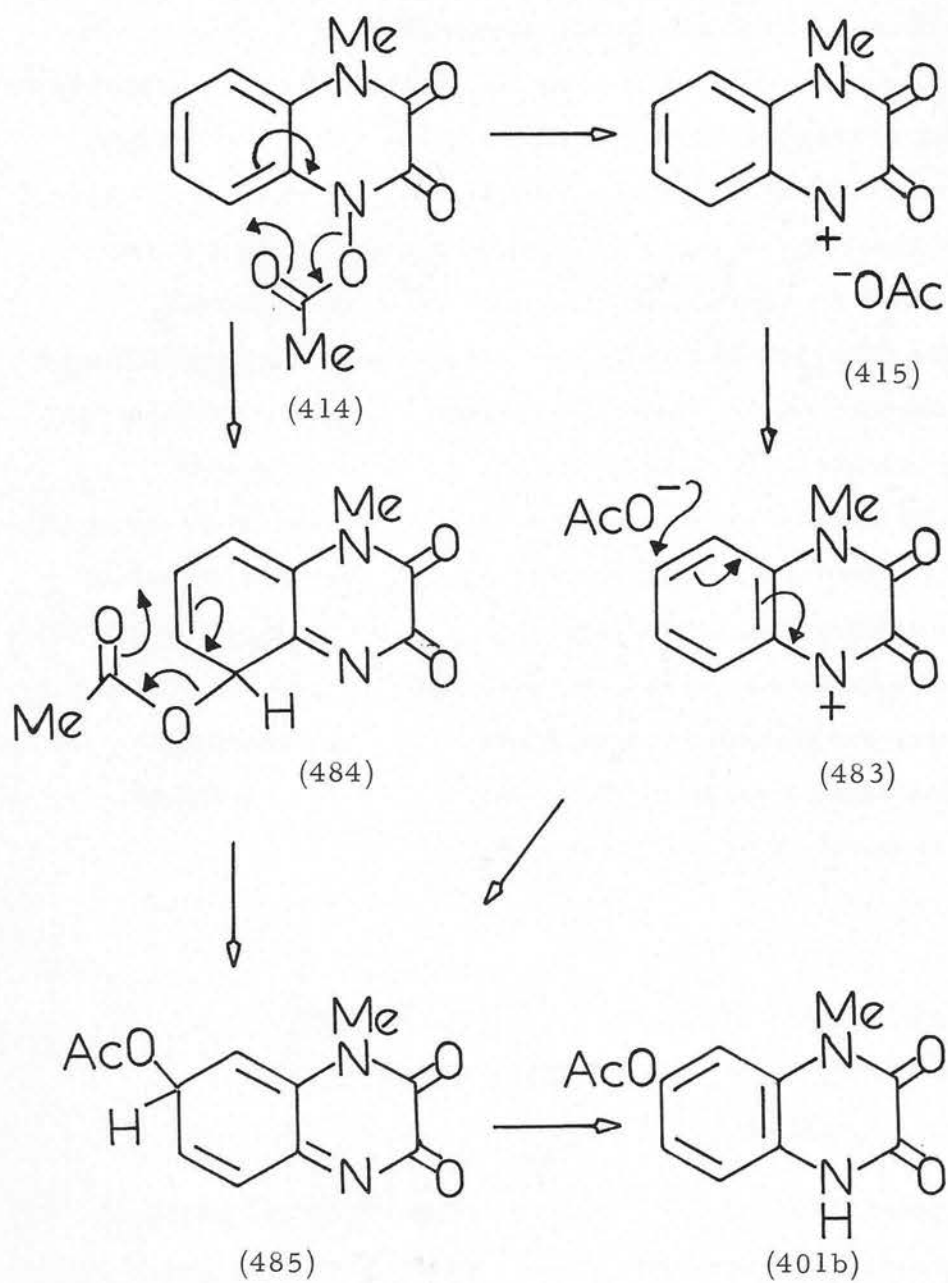
Scheme 89

(342e) was heated with acenaphthylene (480) in dibenzyl ether. It was hoped that this reaction might result in the oxygenation of the peri-double bond in the acenaphthylene (480) to give the epoxide (481) or acenaphthenone (482), derived by its rearrangement [cf. scheme 89]. In practice heating the N-hydroxy compound (342e) with acenaphthylene (480) in dibenzyl ether gave a high yield of the reduced compound (343b) together with a dark, viscous gum from which no identifiable material could be obtained.

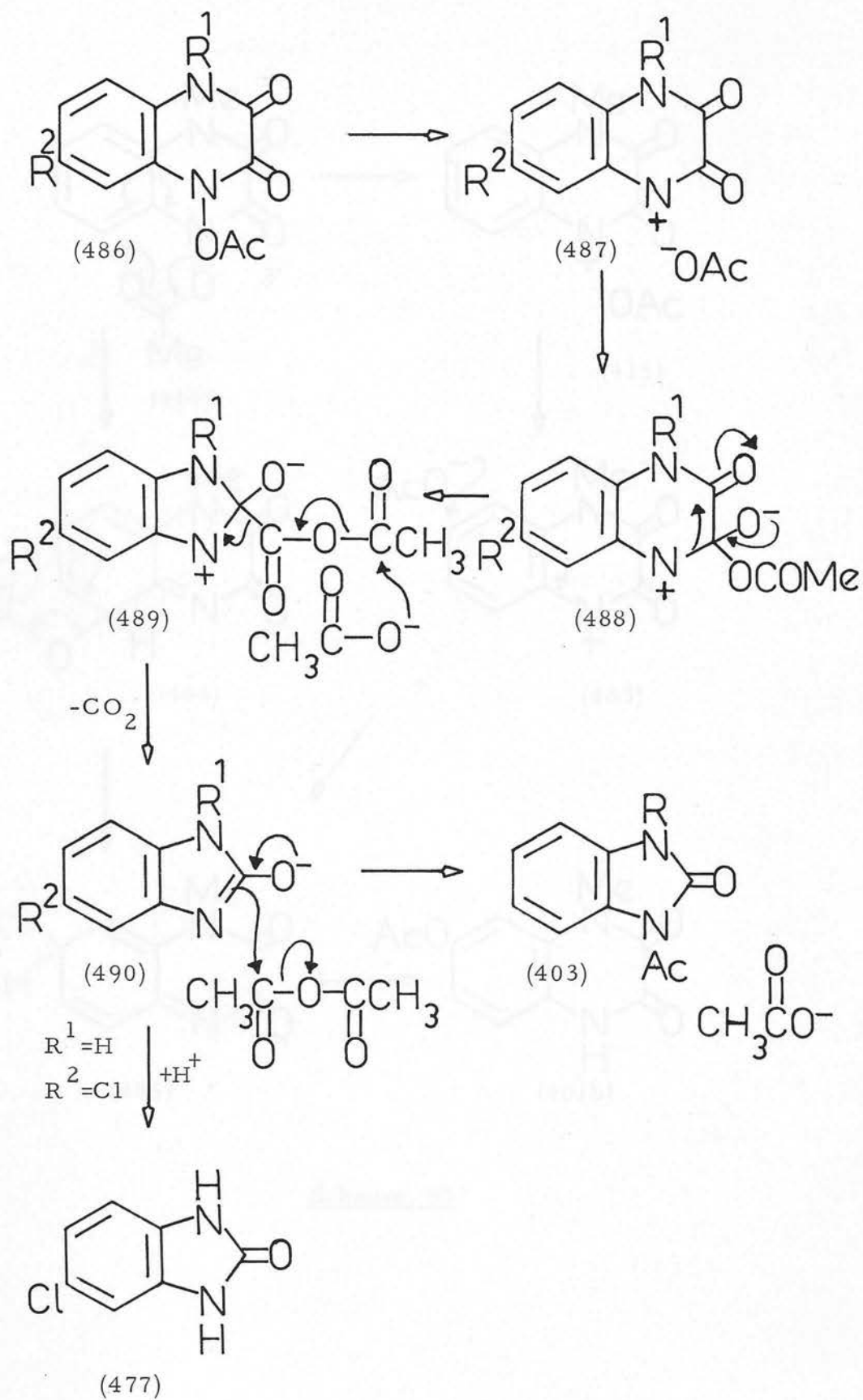
In view of the presence of two N-hydroxy groups, it was considered that the attempted thermolysis of the di-N-hydroxy compound (426a) might provide interesting results. However, heating the compound (426a) in dibenzyl ether resulted in the recovery of the starting material in moderate yield together with a small quantity of an unidentified, intractable solid. The possibility that deoxygenation of the N-hydroxyquinoxaline-2,3(1H,4H)-diones might be photochemically as well as thermally induced was also examined. However, the N-hydroxy compound (342a) was stable to prolonged irradiation using a medium pressure u. v. source, indicating that deoxygenation is purely thermally induced.

Discussion of the Mechanisms of the Thermal  
Transformations of N-Acetoxyquinoxaline-  
2,3(1H,4H)-diones

As already pointed out, the thermolysis of the N-H and N-alkyl-N-acetoxyquinoxaline-2,3(1H,4H)-diones (336a and b) and (414) give products of the same type as those encountered in the reaction of the corresponding N-hydroxyquinoxalinediones (342a and e) and (400a) with acetic anhydride. Possible mechanisms for these reactions have already been discussed (see 4.1, schemes 72 and 73 and 4.2, scheme 77) and involve substitution or semi-benzilic ring-contraction induced by acetate ion. However, the absence of an external source of acetate ion in the thermally promoted acetoxy-substitution and ring-contraction requires that the N-acetoxy compound itself provides the source of acetate ion. Thus the thermally catalysed rearrangement of 1-acetoxy-4-methyl-



Scheme 90

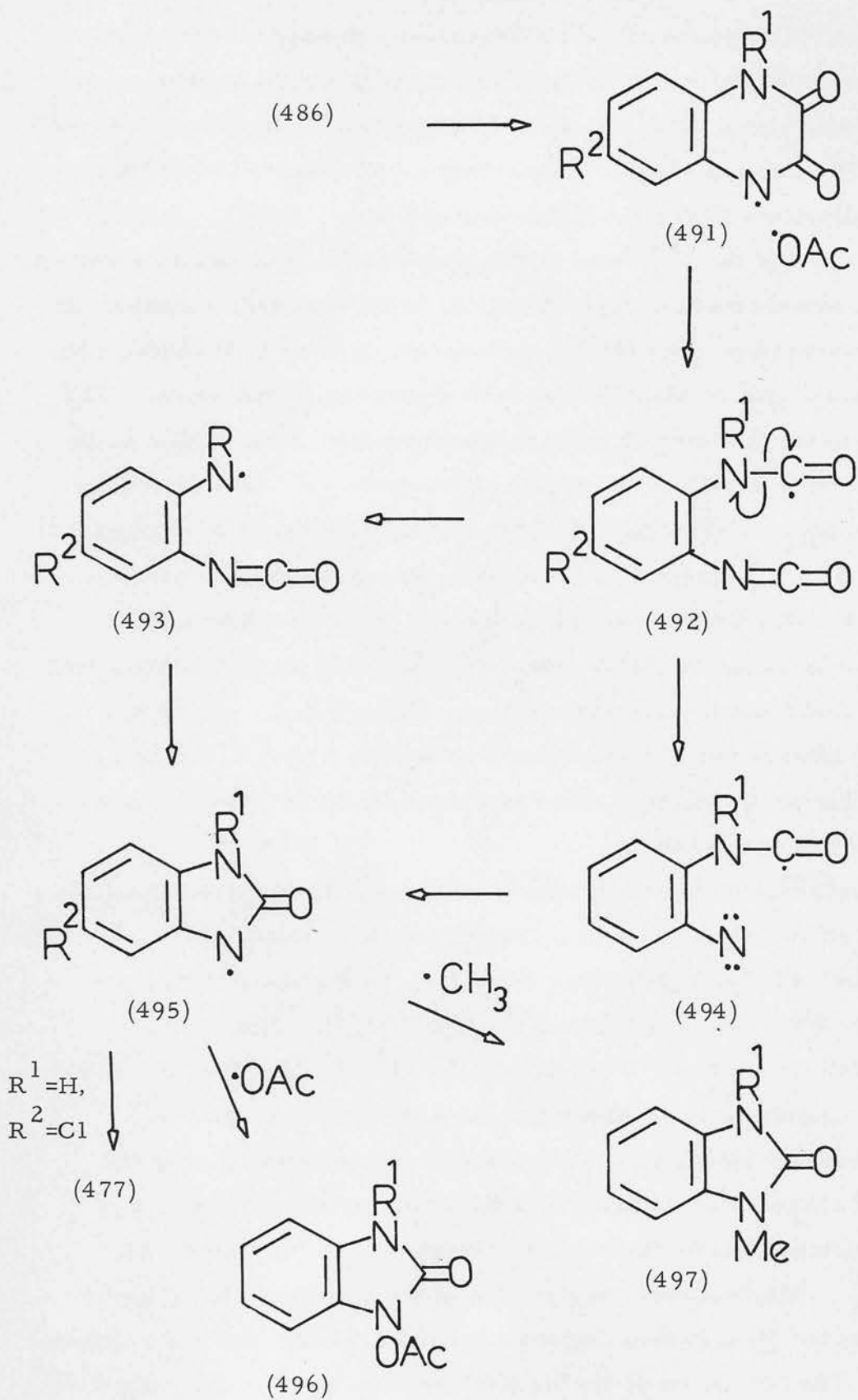


Scheme 91



quinoxalinedione (414) to the isomeric 7-acetoxy compound (401b) may be rationalised by initial ion pair (415) formation as shown in scheme 90. Nucleophilic attack by acetate ion at the C-7 position of the nitrenium ion intermediate (483) then gives the para-quinonoid intermediate (485) which upon rearomatisation affords the C-acetoxy derivative (401b). Initial homolytic scission of the N-O bond in the N-acetate (414) to afford a radical pair, with subsequent radical recombination, is an alternative mechanistic route to the observed product (401b). However, in view of the instability of acetoxy radicals, it is unlikely that such a process is operative. The absence of coupling products of radical decomposition (e. g. methylation products) is further evidence against a radical process. The formation of the 7-acetoxyquinoxalinedione (401b) from the N-acetoxy compound (414) is also explicable by sequential [3,3] sigmatropic shifts as outlined [(414)  $\rightarrow$  (484)  $\rightarrow$  (485)  $\rightarrow$  (401b)] in scheme 90. This mechanistic pathway cannot be excluded for the formation of (401b) on the basis of the evidence obtained from the thermal studies. However, in view of the fact that (414) affords the 7-propionyloxy derivative (401e) in a similar reaction with hot propionic acid, the ionic mechanism described above seems a more likely mechanism.

The mechanistic route outlined in scheme 91 is suggested to account for the ring-contraction undergone by the N-acetoxyquinoxalinediones (336a and b) and (414) in high boiling solvents. Thermal heterolysis of the N-acetoxy linkage in (486) gives the ion pair (487). Nucleophilic attack by acetate ion at the C-2 position of the hetero ring gives the adduct (488) which ring-contracts as shown to afford the intermediate (489). Further nucleophilic attack by acetate ion with the generation of acetic anhydride and carbon dioxide furnishes the intermediate (490) which on addition of a proton affords the benzimidazolone (477) [cf scheme 91;  $R^1 = H$ ,  $R^2 = Cl$ ]. Alternatively, acetylation of the intermediate (490), as shown, affords the N-acetylbenzimidazolone (403) [ $R = H$ , Me] and regenerates acetate ion. The formation of the benzimidazolone (477) is also explicable by a course involving the initial formation of a radical pair as outlined in scheme 92. Homolytic fission of the N-acetoxy bond in (486) would give the radical pair (491) which could ring open [(491)  $\rightarrow$  (492)] and extrude



Scheme 92

the elements of carbon monoxide to furnish either the radical intermediate (493) or the nitrene intermediate (494). Ring closure of these intermediates would give the benzimidazolone radical (495), which would give the benzimidazolone (477) on addition of a hydrogen atom. However, the formation of the N-acetylbenzimidazolones (403a) and (478) is not readily explained by such a radical process. There is no obvious source of acetyl [ $\text{CH}_3\text{CO}\cdot$ ] radical in the reaction medium. The expected products of a coupling reaction of the benzimidazolone radical (495) would be either the N-acetoxy derivative (496) [ $\text{R}^1 = \text{H}, \text{Me}$ ] or the N-methyl derivative (497), the latter formed by coupling of a methyl radical, formed by fragmentation of an acetoxy radical, with the radical (495). For this reason, the ionic mechanism outlined in scheme 91, involving initial formation of the ion pair (487), is favoured over a radical process [cf scheme 92] for the observed ring-contractions.

A. Base-Catalyzed Dehydration of Substituted 2-Nitro- $\alpha$ -hydroxyacetanilides (287) into 1-Hydroxy-2-nitrobenzimidazole-2,3-Diols (288)

General Method V

A solution of the 2-nitro- $\alpha$ -hydroxyacetanilide (287) (9.91 mmol) in aqueous 20% w/v potassium hydroxide (20.0 ml) was stirred at room temperature for 0.5 h. The mixture was then worked up as described for the individual reaction (see Table I).

CHAPTER FOUR

a) The mixture (A) from 2-nitro- $\alpha$ -hydroxyacetanilide (287) was acidified with aqueous 2M hydrochloric acid to yield 1-hydroxy-2-nitrobenzimidazole-2,3-diols (288).

EXPERIMENTAL SECTION

During the acidification, the solid material formed deposited quantitatively as 1-hydroxy-2-nitrobenzimidazole-2,3-diol (288) (10.11 g, 95%), as an amorphous yellow solid, m. p. 253-54°C (lit.<sup>10</sup> 256°C),  $\nu_{max}$  3320 (NH) and 1659 (CO)  $\text{cm}^{-1}$ .

Found: C, 53.6%; H, 3.4%; N, 29.6% M 205.  
Calc. for  $\text{C}_7\text{H}_5\text{N}_2\text{O}_3$ : C, 53.7%; H, 3.4%; N, 29.5% M 205.

Extraction of the filtrate with chloroform gave a negligible quantity of pure 5)

b) The mixture (A) from 2-methyl-2-nitro- $\alpha$ -hydroxyacetanilide (287b) was filtered to afford an orange acid which was treated with 2M hydrochloric acid (5.0 ml) to give 3-amino-6-methylbenzimidazole-2,3-diols (288b) (9.75 g, 38%), which crystallized as light yellow needles, m. p. 281-2°C (from glacial acetic acid),  $\nu_{max}$  3300 (NH), 1600 (CO) and 1640 (CO)  $\text{cm}^{-1}$ ,  $\lambda_{max}$  210 m $\mu$  (log  $\epsilon$  4.1),  $\epsilon$  11000 (log  $\epsilon$  4.04) (lit.<sup>10</sup> 281-2°C,  $\nu_{max}$  3300 (NH), 1600 (CO) and 1640 (CO)  $\text{cm}^{-1}$ ,  $\lambda_{max}$  210 m $\mu$  (log  $\epsilon$  4.1),  $\epsilon$  11000 (log  $\epsilon$  4.04).

Found: C, 59.3%; H, 5.1%; N, 20.6% M 201.  
Calc. for  $\text{C}_8\text{H}_9\text{N}_2\text{O}_3$ : C, 59.7%; H, 5.0%; N, 20.4% M 201.

Extraction of the filtrate gave 1-hydroxy-2-nitrobenzimidazole-2,3-diols (288) (11.16 g, 61%), m. p. 278-80°C, identical (lit. spectrum)

Part 1A. Base-Catalysed Conversions of Substituted 2-Nitro- $\alpha$ -cyanoacetanilides (287) into 1-Hydroxyquinoxaline-2,3(1H,4H)-diones (342)General Method I

A solution of the 2-nitro- $\alpha$ -cyanoacetanilide (287) (0.01 mol) in aqueous 20% w/v potassium hydroxide (20.0 ml) was stirred at room temperature for 0.5 h. The mixture (A) was then worked up as described for the individual reactions (a-c).

a) The mixture (A) from 2-nitro- $\alpha$ -cyanoacetanilide (287a) was acidified with aqueous 2M hydrochloric acid to yield 1-hydroxyquinoxaline-2,3(1H,4H)-dione (342a), (1.59 g; 90%), m. p. 288-9° (lit<sup>92</sup> 290°). On standing, the acidic mother liquor deposited quinoxalin-2(1H)-one-3-carboxamide 4-oxide (340a) (0.11 g, 5%), as an amorphous yellow solid, m. p. 255-6° (lit<sup>94</sup> 256°),  $\nu_{\max}$  3320 (NH) and 1650 (CO) cm<sup>-1</sup>

Found: C, 52.6; H, 3.4; N, 20.6%; M<sup>+</sup> 205.

Calc. for C<sub>9</sub>H<sub>7</sub>N<sub>2</sub>O<sub>3</sub>: C, 52.7; H, 3.4; N, 20.5%; M 205.

Extraction of the filtrate with chloroform gave a negligible quantity of gum.

b) The mixture (A) from 4-methyl-2-nitro- $\alpha$ -cyanoacetanilide (287b) was filtered to afford an orange solid which was treated with aqueous 2M hydrochloric acid (5.0 ml) to give 3-cyano-6-methylquinoxalin-2(1H)-one 4-oxide (282b) (0.75 g; 38%), which crystallised as bright yellow needles, m. p. 281-2° (from glacial acetic acid),  $\nu_{\max}$  3400 (NH), 2200 (CN), and 1640 (CO) cm<sup>-1</sup>,  $\delta$ [(CD<sub>3</sub>)<sub>2</sub>SO] 7.90 (1H, d, J<sub>meta</sub> 2Hz, H-5), 7.60 (1H, dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-7), 7.30 (1H, d, J<sub>ortho</sub> 8Hz, H-8) and 2.40 (3H, s, ArMe).

Found: C, 59.3; H, 3.5; N, 20.6%; M<sup>+</sup> 201.

C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub> requires: C, 59.7; H, 3.5; N, 20.9%; M 201.

Acidification of the filtrate gave 1-hydroxy-7-methylquinoxaline-2,3(1H,4H)-dione (342b) (1.16 g; 61%), m. p. 278-80°, identical (i. r. spectrum)



with an authentic sample (see later).

c) The mixture (A) from 4,5-dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) was filtered to afford a dark brown solid which was treated with aqueous 2M hydrochloric acid (10.0 ml) to give unreacted 4,5-dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) (2.11 g; 91%), m. p. 188-9<sup>o</sup>, identical (m. p. and i. r. spectrum) with an authentic sample. Acidification of the filtrate with aqueous 2M hydrochloric acid gave 6,7-dimethyl-3-cyanoquinoxalin-2(1H)-one 4-oxide (282d), m. p. 300-2<sup>o</sup>, identical (m. p. and i. r. spectrum) with an authentic sample.

### General Method II

A solution of the 2-nitro- $\alpha$ -cyanoacetanilide (287) (0.01 mol) in aqueous 20% w/v potassium hydroxide (20.0 ml) was stirred at 50<sup>o</sup> for 0.5 h. The mixture (B) was cooled and worked up as described for the individual reactions (d-h).

d) The mixture (B) from 4-methyl-2-nitro- $\alpha$ -cyanoacetanilide (287b) was acidified with aqueous 2M hydrochloric acid to give 1-hydroxy-7-methylquinoxaline-2,3(1H,4H)-dione (342b) (1.85 g; 96%), which crystallised as finely divided yellow needles, m. p. 278-80<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3450 (OH) and 1690 (CO) cm<sup>-1</sup>,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.30 (1H, s, NH), 7.70-7.23 (3H, m, ArH), and 2.69 (3H, s, ArMe).

<u>Found:</u>	$\text{M}^+$	192.053209
$\text{C}_9\text{H}_8\text{N}_2\text{O}_3$ requires:	M	192.053487
		error < 2 p. p. m.

The filtrate was extracted with chloroform to give a negligible quantity of gum.

e) The mixture (B) from 4-methoxy-2-nitro- $\alpha$ -cyanoacetanilide (287f) was filtered to afford a brown solid which was treated with aqueous 2M hydrochloric acid (5.0 ml) to give 3-cyano-6-methoxyquinoxalin-2(1H)-one 4-oxide (282e) (1.26 g; 46%), m. p. 260-4<sup>o</sup> (lit<sup>92</sup> 267<sup>o</sup>), identical (i. r. spectrum) with an authentic sample. Acidification of the filtrate with aqueous 2M hydrochloric acid gave 1-hydroxy-7-methoxyquinoxaline-

2,3(1H,4H)-dione (342f) (0.66 g; 31%), m. p.  $>350^{\circ}$  (lit<sup>92</sup>  $>350^{\circ}$ ), identical (i. r. spectrum) with an authentic sample.

f) The mixture (B) from 4-chloro-2-nitro- $\alpha$ -cyanoacetanilide (287e) was acidified with aqueous 2M hydrochloric acid to give 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (2.08 g; 97%), m. p.  $>350^{\circ}$ , (lit<sup>92</sup>  $>340^{\circ}$ ). On standing the filtrate deposited a small quantity of unidentified solid.

g) The mixture (B) from 5-methyl-2-nitro- $\alpha$ -cyanoacetanilide (287c) was acidified with aqueous 2M hydrochloric acid to give a yellow solid (1.94 g) which was extracted with hot dimethylformamide to leave 1-hydroxy-6-methylquinoxaline-2,3(1H,4H)-dione (342c) (0.64 g; 34%) which crystallised as colourless plates, m. p.  $278-9^{\circ}$  (from glacial acetic acid),  $\nu_{\max}$  2700-2400 br (NH) and 1690 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.35 (1H, d,  $J_{\text{ortho}}$  8Hz, H-8), 7.09-6.94 (2H, m. ArH), and 2.30 (3H, s, ArMe).

Found: C, 55.6; H, 4.3; N, 14.2%;  $M^+$  192  
 $\text{C}_9\text{H}_8\text{N}_2\text{O}_3$  requires: C, 56.3; H, 4.2; N, 14.6%;  $M$  192.

Partial evaporation of the dimethylformamide extract under reduced pressure gave 7-methylquinoxalin-2(1H)-one-3-carboxamide 4-oxide (340c) which was combined with a second crop obtained by complete evaporation of the mother liquor (total 0.97 g; 46%), and crystallised to give a yellow powder, m. p.  $274-5^{\circ}$  (from dimethylformamide-water),  $\nu_{\max}$  3460 and 3160 (NH), and 1650 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.10-7.80 (2H, m, ArH), 7.20 (1H, m. ArH) and 2.46 (3H, s, Me).

Found: C, 54.4; H, 4.2; N, 19.0%;  $M^+$  219  
 $\text{C}_{10}\text{H}_9\text{N}_3\text{O}_3$  requires: C, 54.8; H, 4.1; N, 19.2%;  $M$  219.

h) The mixture (B) from 4,5-dimethyl-2-nitro- $\alpha$ -cyanoacetanilide (287d) was filtered to give 4,5-dimethyl-2-nitroaniline (290d) (0.49 g; 36%), m. p.  $137-40^{\circ}$  (lit.  $139-40^{\circ}$ ), identical (i. r. spectrum) with an authentic sample. The filtrate was acidified with aqueous 2M hydrochloric acid to give 6,7-dimethylquinoxalin-2(1H)-one-3-carboxamide 4-oxide (340d) (1.43 g; 59%), identical (m. p. and i. r. spectrum) with a sample prepared previously.

B. The Attempted Base-catalysed Synthesis of 1-Hydroxy-6-methylquinoxaline-2,3(1H,4H)-dione (342c).

A solution of 3-cyano-7-methylquinoxalin-2(1H)-one 4-oxide (282c) (2.01 g; 0.01 mol) in aqueous 1M sodium hydroxide (25.0 ml) was heated under reflux for 0.5 h. The mixture was cooled and acidified with aqueous 2M hydrochloric acid to give 7-methylquinoxalin-2(1H)-one-3-carboxamide 4-oxide (340c) (1.90 g; 87%), m. p. 265-7°, identical (i.r. spectrum) with a sample prepared before. Extraction of the aqueous acidic mother liquor with chloroform gave a negligible quantity of a gum.

C. The Attempted Base-catalysed Synthesis of 6,7-Dimethyl-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342d).

A solution of 3-cyano-4,5-dimethylquinoxalin-2(1H)-one 4-oxide (282d) (0.43 g; 0.002 mol) in aqueous 20% potassium hydroxide (4.0 ml) was stirred at 50° for 1 h, during which time a brown precipitate formed. The mixture was filtered and the residue was treated with aqueous 2M hydrochloric acid (5.0 ml) to give unreacted 3-cyano-4,5-dimethylquinoxalin-2(1H)-one 4-oxide (282d) (0.33 g; 77%), m. p. 300-2°, identical (i. r. spectrum) with a sample prepared before. Acidification of the filtrate with aqueous 2M hydrochloric acid gave 6,7-dimethylquinoxalin-2(1H)-one-3-carboxamide 4-oxide (340d) (0.05 g; 10%), m. p. 279-80° (from dimethylformamide),  $\nu_{\max}$  3400 (NH) and 1685 (CO)  $\text{cm}^{-1}$ .

Found: C, 55.2; H, 6.0; N, 18.3%;  $M^+$  233.

$C_{11}H_{11}N_3O_3$  + 1 mol dimethylformamide requires: C, 54.9; H, 5.9; N, 18.3%

M 233.

D. Reactions of 1-Hydroxyquinoxaline-2,3(1H,4H)-diones (342) with Acetyl Chloride in Acetic Acid under Prolonged Reflux.

The 1-hydroxyquinoxalinedione (342) (0.002 mol) was heated under reflux with a mixture of acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h and the reaction mixture was worked up as described for the individual reactions (a-d).

a) The mixture from 1-hydroxyquinoxaline-2,3(1H,4H)-dione (342a) was cooled to give 6-chloroquinoxaline-2,3(1H,4H)-dione (343b) which was combined with a second crop obtained by evaporation of the mother liquor (total 0.30 g; 78%), identical (m. p. and i. r. spectrum) with an authentic sample (see later).

b) The mixture from 1-hydroxy-7-methylquinoxaline-2,3(1H,4H)-dione (342b) was cooled to give 5-chloro-7-methylquinoxaline-2,3(1H,4H)-dione (348a) which was combined with a second crop obtained by evaporation of the filtrate and trituration of the residue with toluene (total 0.36 g; 85%) and crystallised to give pale yellow needles, m. p.  $> 350^{\circ}$  (from glacial acetic acid),  $\nu_{\max} 3350$  w (NH) and  $1695$  (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}] 6.99$  (1H, d,  $J_{\text{meta}} 2\text{Hz}$ , H-8),  $6.80$  (1H, d,  $J_{\text{meta}} 2\text{Hz}$ , H-6) and  $2.25$  (3H, s, ArMe).

<u>Found:</u>	210.017697
<u><math>\text{C}_9\text{H}_7\text{Cl}^{35}\text{N}_2\text{O}_2</math> requires:</u>	210.019601
error < 10 p. p. m.	

<u>Found:</u>	212.014341
<u><math>\text{C}_9\text{H}_7\text{Cl}^{37}\text{N}_2\text{O}_2</math> requires:</u>	212.016651
error < 11 p. p. m.	

c) The mixture from 1-hydroxy-7-methoxyquinoxaline-2,3(1H,4H)-dione (342f) was hot-filtered to give 5-acetoxy-7-methoxyquinoxaline-2,3(1H,4H)-dione (349) (0.54 g; 55%) which crystallised as fine silver coloured needles, m. p.  $349-50^{\circ}$  (from dimethylsulphoxide-water),  $\nu_{\max} 3350$  (NH), and  $1690$  (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}] 6.64$  (1H, d,  $J_{\text{meta}} 2.5\text{Hz}$ , H-7),  $6.53$  (1H, d,  $J_{\text{meta}} 2.5\text{Hz}$ , H-5),  $3.74$  (3H, s, Me), and  $2.34$  (3H, s, Me).

<u>Found:</u>	C, 52.5; H, 4.1; N, 11.2%; $\text{M}^+$ 250.
<u><math>\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_5</math> requires:</u>	C, 52.8; H, 4.0; N, 11.2%; M 250.

Evaporation of the filtrate gave 5-chloro-7-methoxyquinoxaline-2,3(1H,4H)-dione (348a) (0.39 g; 43%), which crystallised as a colourless powder, m. p.  $328-9^{\circ}$  (from glacial acetic acid),  $\nu_{\max} 3300-3100$  br (NH) and



1690 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.14 (1H, d,  $J_{\text{meta}}$  2.5Hz, H-8), 6.96 (1H, d,  $J_{\text{meta}}$  2.5Hz, H-6) and 4.06 (3H, s, MeO).

Found: C, 47.9; H, 3.1; N, 12.3%;  $M^+$  226, 8.

$\text{C}_9\text{H}_7\text{ClN}_2\text{O}_7$  requires: C, 47.8; H, 3.1; N, 12.4%;  $M$  226.5

d) The mixture from 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) was cooled to yield 5,7-dichloroquinoxaline-2,3(1H,4H)-dione (348c) (0.35 g; 78%), which crystallised as pale yellow needles, m. p.  $>350^\circ$  (from ethanol-dimethylformamide),  $\nu_{\text{max}}$  3150 w (NH) and 1690 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.25 (1H, d,  $J_{\text{meta}}$  2Hz, H-8) and 7.08 (1H, d,  $J_{\text{meta}}$  2Hz, H-6).

Found: C, 41.8; H, 2.0; N, 11.9%;  $M^+$  230, 232, 234

$\text{C}_8\text{H}_4\text{Cl}_2\text{N}_2\text{O}_2$  requires: C, 41.6; H, 1.7; N, 12.1%;  $M$  231.

Evaporation of the filtrate and trituration of the residue with ether gave 5-chloro-1,3-diacetylbenzimidazol-2-one (291b) (0.09 g; 21%), m. p.  $171-3^\circ$  (lit<sup>75</sup>  $175-6^\circ$ ), identical (i. r. spectrum) with an authentic sample.

E. The Attempted Reaction of 7-Chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) with Concentrated Hydrochloric Acid in Glacial Acetic Acid.

A suspension of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.42 g; 0.002 mol) in glacial acetic acid (10.0 ml) was treated with concentrated hydrochloric acid (2.0 ml) and heated under reflux for 48 h. The mixture was cooled to give the unreacted starting material (342e) (0.38 g; 90%), identical (m. p. and i. r. spectrum) with an authentic sample.

F. Reactions of 1-Hydroxyquinoxaline-2,3(1H,4H)-diones (342) with Acetic Anhydride under Prolonged Reflux.

The quinoxalinedione (342) (0.002 mol) was heated under reflux with acetic anhydride (10.0 ml) for 24 h. The mixture was cooled and



filtered then further worked up as described below for the reactions (a-b).

a) 1-Hydroxyquinoxaline-2,3(1H,4H)-dione (342a) gave 1,3-diacetylbenzimidazol-2-one (291a) which was combined with a second crop obtained by evaporation of the filtrate (total 0.44 g; quantitative) and crystallised to give pale yellow needles, identical (m. p. and i. r. spectrum) with a sample obtained previously.

b) 7-Chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) gave 6-chloroquinoxalin-2,3(1H,4H)-dione (343b) (0.12 g; 31%), m. p.  $>350^{\circ}$ , identical (i. r. spectrum) with a sample obtained previously. Evaporation of the filtrate and trituration of the residue with ethyl acetate gave 5-chloro-1,3-diacetylbenzimidazol-2-one (291b) (0.21 g; 43%), m. p.  $165-7^{\circ}$ , identical (i. r. spectrum) with a sample prepared before. Evaporation of the ethyl acetate mother liquor gave a negligible quantity of gum.

G. The Reaction of 1-Acetoxyquinoxaline-2,3(1H,4H)-dione (336a) with Propionic Acid under Reflux.

A solution of 1-acetoxyquinoxaline-2,3(1H,4H)-dione (336a) (0.88 g; 0.004 mol) was heated under reflux in propionic acid (10.0 ml) for 3 h. The mixture was hot-filtered to afford quinoxaline-2,3(1H,4H)-dione (343a) which was combined with a second crop obtained by evaporation of the filtrate (0.66 g; 92%), m. p.  $>350^{\circ}$ , identical (i. r. spectrum) with a sample obtained previously.

H. The Reaction of 1-Acetoxyquinoxaline-2,3(1H,4H)-dione (336a) with Sodium Acetate in Dimethylformamide.

A solution of 1-acetoxyquinoxaline-2,3(1H,4H)-dione (336a) (0.44 g; 0.002 mol) in warm dimethylformamide (10.0 ml) was treated with fused sodium acetate (0.33 g; 0.004 mol) and the resulting suspension was heated under reflux for 48 h. The mixture was hot filtered and the residue was treated with water to leave a negligible quantity of solid. The filtrate was diluted with an equal volume of water and extracted with chloroform to give benzimidazol-2-one (399a) (0.04 g; 15%), m. p.  $305-7^{\circ}$  (lit  $307-8^{\circ}$ ),

identical (m. p. and i. r. spectrum) with a synthetic sample. The aqueous mother liquor was evaporated to dryness under reduced pressure and the residue was triturated with ether to give quinoxalin-2,3(1H,4H)-dione (343a) (0.17 g; 56%), m. p.  $>300^{\circ}$ , identical (i. r. spectrum) with a sample obtained before. Evaporation of the ethereal mother liquor gave a dark gum (0.06 g) from which no further identifiable material could be obtained.

I. The Formation of the 1-Acetoxyquinoxaline-2,3(1H,4H)-diones (336a and b) from the 1-Hydroxyquinoxaline-2,3(1H,4H)-diones (342a and e).

a) 1-Hydroxyquinoxaline-2,3(1H,4H)-dione (336a) (0.002 mol) was heated under reflux in acetic anhydride (8.0 ml) until all the solid dissolved. The mixture was cooled and allowed to stand at room temperature for 25 minutes then evaporated and the residue crystallised from glacial acetic acid to give 1-acetoxyquinoxaline-2,3(1H,4H)-dione (336a) (55%), m. p.  $198-201^{\circ}$  (lit<sup>91</sup>  $204^{\circ}$ ), identical (i. r. spectrum) with an authentic sample.<sup>22</sup> Evaporation of the light petroleum-ethyl acetate gave 1,3-diacetylbenzimidazol-2-one (291a) (25%), m. p.  $140-5^{\circ}$ , identical (i. r. spectrum) with a sample obtained before. Evaporation of the light petroleum-ethyl acetate mother liquor gave a negligible quantity of gum.

b) 7-Chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.001 mol) was heated under reflux in acetic anhydride (8.0 ml) for 10 minutes. The mixture was cooled and allowed to stand at room temperature for 20 minutes. The mixture was filtered to give 1-acetoxy-7-chloroquinoxaline-2,3(1H,4H)-dione (336b) (0.23 g; 92%), which crystallised as colourless needles, m. p.  $223-4^{\circ}$  (from glacial acetic acid),  $\nu_{\max}$  1780 and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.18-7.39 (3H, m, ArH), and 2.61 (3H, s, Me).

Found: C, 46.9; H, 2.8; N, 10.7%;  $M^+$  254, 256

$\text{C}_{10}\text{H}_7\text{ClN}_2\text{O}_4$  requires: C, 47.2; H, 2.8; N, 11.0%; M 254.5.

Evaporation of the filtrate gave a negligible quantity of solid.

Part II

A. 1-Hydroxy-4-methylquinoxaline-2, 3(1H, 4H)-dione (400a) was prepared by the method of Tennant.<sup>91</sup>

B. The 1-Benzyl-4-hydroxyquinoxaline-2, 3(1H, 4H)-diones (400b-d) were prepared by the method of Sandison and Tennant.<sup>22</sup>

C. Reactions of 4-Alkyl-1-hydroxyquinoxaline-2, 3(1H, 4H)-diones (400) with Acetyl Chloride in Acetic Acid under Prolonged Reflux.

General Method

The quinoxalinedione (400) (0.002 mol) was heated under reflux with a mixture of acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. The mixture was evaporated under reduced pressure and the residue was triturated with ethanol to afford the product. Evaporation of the ethanol mother liquor gave a negligible quantity of gum.

a) 1-Hydroxy-4-methylquinoxaline-2, 3(1H, 4H)-dione (400a) gave 7-chloro-1-methylquinoxaline-2, 3(1H, 4H)-dione (401a) (0.34 g; 81%) which crystallised as colourless needles, m. p. 325-7° (from glacial acetic acid),  $\nu_{\max}$  3110 w (NH) and 1690 (CO)  $\text{cm}^{-1}$ .  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.81-7.72 (1H, m, ArH), 7.57-7.49 (2H, m, ArH), and 3.84 (3H, s, NMe).

Found: C, 51.2; H, 3.4; N, 13.0% M<sup>+</sup> 210.212.

C<sub>9</sub>H<sub>7</sub>ClN<sub>2</sub>O<sub>2</sub> requires: C, 51.3; H, 3.4; N, 13.3%; M 210.5.

b) 1-Benzyl-4-hydroxyquinoxaline-2, 3(1H, 4H)-dione (400b) gave 1-benzyl-7-chloroquinoxaline-2, 3(1H, 4H)-dione (401c) (0.42 g; 74%) which crystallised as a colourless powder, m. p. 323-5° (from glacial acetic acid),  $\nu_{\max}$  1690 (CO)  $\text{cm}^{-1}$ ,  $\delta$  (CF<sub>3</sub>CO<sub>2</sub>H) 7.51-7.20 (8H, m, ArH) and 7.55 (2H, s, CH<sub>2</sub>).

Found: C, 62.7; H, 3.9; N, 9.8%; M<sup>+</sup> 286.288.

C<sub>15</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub> requires: C, 62.8; H, 3.9; N, 9.7%; M 286.5.

c) 1-Benzyl-7-chloro-4-hydroxyquinoxaline-2, 3(1H, 4H)-dione (400c) gave 1-benzyl-5, 7-dichloroquinoxaline-2, 3(1H, 4H)-dione (402a) (0.59 g; 94%) which crystallised as a colourless powder, m. p. 278-80° (from glacial acetic acid),  $\nu_{\max}$  3100-2700 (NH) and 1680 (CO)  $\text{cm}^{-1}$ .  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] 7.39 (1H, d, J<sub>meta</sub> 2Hz, H-8), 7.29 (5H, s, ArH), 7.14 (1H, J<sub>meta</sub> 2Hz, H-6) and 5.39 (2H, s, CH<sub>2</sub>).

Found: C, 55.6; H, 3.2; N, 8.7%;  $M^+$  320, 322, 324.  
 $C_{15}H_{10}ClN_2O_2$  requires: C, 56.1; H, 3.1; N, 8.7%;  $M$  321.

d) 1-Benzyl-4-hydroxy-7-methylquinoxaline-2,3(1H,4H)-dione (400d) gave 1-benzyl-5-chloro-7-methylquinoxaline-2,3(1H,4H)-dione (402b) (0.51 g; 82%) which crystallised as a colourless powder, m. p. 210-12° (from glacial acetic acid),  $\nu_{\max}$  3110 w (NH) and 1695 (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.35 (7H, m, ArH), 5.35 (2H, s,  $CH_2$ ) and 2.20 (3H, s, Me).

Found: C, 63.7; H, 4.5; N, 8.8%;  $M^+$  300, 302.  
 $C_{16}H_{13}ClN_2O_2$  requires: C, 63.9; H, 4.4; N, 9.3%;  $M$  300.5.

D. Reactions of 4-Alkyl-1-hydroxyquinoxaline-2,3(1H,4H)-diones (400) with Acetic Anhydride under Prolonged Reflux

#### General Method

The quinoxalinedione (400) (0.004 mol) was heated under reflux with acetic anhydride for 24 h. The mixture was evaporated under reduced pressure and the residue (A) was further worked up as described for the individual reactions (a-d).

a) The residue (A) from 1-hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) was triturated with ether-ethyl acetate to give 7-acetoxy-1-methylquinoxaline-2,3(1H,4H)-dione (401b) (63%), which crystallised as colourless prisms, m. p. 282-3° (from ethanol-glacial acetic acid),  $\nu_{\max}$  3100 w (NH), 1740 and 1690 (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.19 (1H, d,  $J_{ortho}$  8.5 Hz, H-5), 7.14 (1H, d,  $J_{meta}$  2.5 Hz, H-8), 6.92 (1H, dd,  $J_{ortho}$  8.5 Hz,  $J_{meta}$  2.5 Hz, H-6), 3.45 (3H, s, NMe), and 2.26 (3H, s, Me).

Found: C, 56.1; H, 4.4; N, 11.6%;  $M^+$  234.  
 $C_{11}H_{10}N_2O_4$  requires: C, 56.4; H, 4.3; N, 12.0%;  $M$  234.

Evaporation of the ether-ethyl acetate mother liquor and trituration of the residue with methanol gave 3-acetyl-1-methylbenzimidazol-2-one (403a) (13%) which crystallised as colourless needles, m. p. 121-2° (lit<sup>100</sup> 121-2°),  $\nu_{\max}$  1700 (CO)  $cm^{-1}$ .  $\delta[(CD_3)_2SO]$  7.99 (1H, m, ArH),



7.19 (3H, m, ArH), 3.29 (3H, s, Me), and 2.60 (3H, s, NMe).

Found: C, 62.8; H, 5.3; N, 14.9%;  $M^+$  190  
Calc. for  $C_{10}H_{10}N_2O_2$ : C, 63.1; H, 5.3; N, 14.7%; M 190.

b) Trituration of the residue (A) from 4-benzyl-1-hydroxyquinoxaline-2,3(1H,4H)-dione (400 b) with ether-ethyl acetate gave 7-acetoxy-1-benzylquinoxaline-2,3(1H,4H)-dione (401d) (0.56 g; 45%), which crystallised as colourless plates, m. p. 295-7° (from ethanol-glacial acetic acid),  $\nu_{\max}$  3120 w (NH), and 1740, 1700 and 1660 (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.62 (5H, s, ArH), 7.55 (1H, d,  $J_{ortho}$  8Hz, H-5), 7.33 (1H, d,  $J_{meta}$  2Hz, H-8), 7.27 (1H, dd,  $J_{ortho}$  8Hz,  $J_{meta}$  2Hz, H-6), 5.68 (2H, s,  $CH_2$ ), and 2.55 (3H, s, Me).

Found: C, 65.9; H, 4.5; N, 9.2%;  $M^+$  310  
 $C_{17}H_{14}N_2O_4$  requires: C, 65.8; H, 4.5; N, 9.0%; M 310.

Evaporation of the ether-ethyl acetate mother liquor gave 3-acetyl-1-benzylbenzimidazol-2-one (403b) (0.38 g; 36%) which crystallised as colourless needles, m. p. 115-16° (from light petroleum-ethanol),  $\nu_{\max}$  1730 and 1690 (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.75-7.43 (9H, m, ArH), 5.41 (2H, s,  $CH_2$ ) and 3.00 (3H, s, Me).

Found: C, 72.0; H, 5.2; N, 10.4%;  $M^+$  266  
 $C_{16}H_{14}N_2O_2$  requires: C, 72.1; H, 5.3; N, 10.5%; M 266.

c) Trituration of the residue (A) from 1-benzyl-7-chloro-4-hydroxyquinoxaline-2,3(1H,4H)-dione (400c) with toluene gave 6-acetoxy-1-benzyl-7-chloroquinoxaline-2,3(1H,4H)-dione (404a) which was combined with two further crops obtained by evaporation of the toluene mother liquor and trituration of the residue with ethyl acetate (total 0.97 g; 71%) and crystallised as a colourless powder, m. p. 250-3° (from glacial acetic acid),  $\nu_{\max}$  1760 and 1680 (CO)  $cm^{-1}$ . Because of difficulty encountered in crystallising (404a), no satisfactory  $^1H$  n. m. r. spectrum nor analytical data could be obtained.

Found: 344.053840



$C_{17}H_{13}Cl^{35}N_2O_4$  requires: 344.056378

error < 8 p. p. m.

Found: 346.051143

$C_{17}H_{13}Cl^{35}N_2O_4$  requires: 346.053428

error < 7 p. p. m.

d) Trituration of the residue (A) from 4-benzyl-6-methyl-1-hydroxy-quinoxaline-2,3(1H,4H)-dione (400d) with toluene gave 6-acetoxy-1-benzyl-7-methylquinoxaline-2,3(1H,4H)-dione (404b) which was combined with a second crop obtained by evaporation of the toluene mother liquor and treatment of the residue with water (total 1.06 g; 93%), and crystallised to give colourless needles, m. p. 248-50° (from ethanol-glacial acetic acid),  $\nu_{\max}$  1740 and 1700-1640 br (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.28 (5H, s, ArH), 7.10 (1H, s, H-5), 6.86 (1H, s, H-8), 5.31 (2H, s, CH<sub>2</sub>), 2.26 (3H, s, ArMe), and 2.01 (3H, s, Me).

Found: C, 66.6; H, 5.0; N, 8.6%; M<sup>+</sup> 324.

$C_{18}H_{16}N_2O_4$  requires: C, 66.7; H, 4.9; N, 8.6%; M 324.

Extraction of the aqueous mother liquor with chloroform gave a negligible quantity of a gum.

E. The Reaction of 1-Hydroxy-3-methylquinazoline-2,3(1H,4H)-dione (405) with Acetic Anhydride under Prolonged Reflux.

1-Hydroxy-3-methylquinazoline-2,3(1H,4H)-dione (405) (0.71 g; 0.004 mol) was heated under reflux with acetic anhydride (20.0 ml) for 48 h. Evaporation of the mixture and trituration of the residue with light petroleum-ethyl acetate gave 1-acetoxy-3-methylquinazoline-2,3(1H,4H)-dione (406) which was combined with a second crop obtained by evaporation of the light petroleum-ethyl acetate mother liquor (total 0.85 g; 96%), m. p. 125° (lit<sup>101</sup> 132°), identical (i. r. spectrum) with an authentic sample.<sup>101</sup>

F. The Formation of 1-Acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) from 1-Hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a).

1-Hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) (0.002 mol) was heated under reflux in acetic anhydride (8.0 ml) until all of the solid dissolved. The mixture was cooled and allowed to stand at room temperature for 25 minutes. The mixture was filtered to give 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) which was combined with a second crop obtained by evaporation of the filtrate and trituration of the residue with toluene (total 0.45 g; 98%), m. p. 175-7° (lit<sup>91</sup> 177°), identical (i. r. spectrum) with an authentic sample.<sup>22</sup> Evaporation of the toluene mother liquor gave a negligible quantity of gum.

G. The Rearrangement of 1-Acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) in Acetic Acid.

A solution of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) (0.47 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated and the residue was triturated with ethyl acetate to yield 7-acetoxy-1-methylquinoxaline-2,3(1H,4H)-dione (401b) (0.45 g; 96%), m. p. 280-2°, identical (i. r. spectrum) with a sample prepared before. Evaporation of the ethyl acetate mother liquor gave a negligible quantity of gum.

H. The Reaction of 1-Acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) with Propionic Acid.

A solution of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) (0.47 g; 0.002 mol) in propionic acid (5.0 ml) was heated under reflux for 3 h. The mixture was cooled to give 1-methyl-7-propionyloxyquinoxaline-2,3(1H,4H)-dione (401e) (0.24 g; 48%) which crystallised as colourless needles, m. p. 225-7° (from ethanol),  $\nu_{\max}$  3150 (NH), 1750 and 1690 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  12.0 (1H, s, NH), 7.19 (1H, d,  $J_{\text{ortho}}$  8Hz, H-5), 7.12 (1H, d,  $J_{\text{meta}}$  2Hz, H-8), 6.92 (1H, dd,  $J_{\text{ortho}}$  8Hz,  $J_{\text{meta}}$  2Hz, H-6), 3.45 (3H, s, NMe), 2.62 (2H, q,  $J$  8Hz,  $\text{CH}_2$ )

and 1.15 (3H, t, J. 8Hz, Me).

Found: C, 58.0; H, 4.8; N, 11.5%; M<sup>+</sup> 248.  
C<sub>10</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub> requires - C, 58.1; H, 4.8; N, 11.3%; M 248.

Evaporation of the filtrate and trituration of the residue with ethyl acetate gave a yellow solid (0.23 g), m.p. 190-4<sup>o</sup>, whose spectral properties showed it to be a 5:1 mixture of 1-methyl-7-propionyloxyquinoxaline-2, 3(1H, 4H)-dione (401e) and 7-acetoxy-1-methylquinoxaline-2, 3(1H, 4H)-dione (401b),  $\nu_{\max}$  3150 br (NH), 1750 and 1720-1660 br (CO) cm<sup>-1</sup>,  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] (401e) 7.19 (d, J<sub>ortho</sub> 8Hz, H-5), 7.12 (d, J<sub>meta</sub> 2Hz, H-8), 6.92 (dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-6), 3.45 (s, NMe), 2.62 (q, J 8Hz, CH<sub>2</sub>) and 1.15 (t, J 8Hz, Me),  $\delta$  [(CD<sub>3</sub>)<sub>2</sub>SO] (401b) 7.19 (d, J<sub>ortho</sub> 8Hz, H-5), 7.12 (d, J<sub>meta</sub> 2Hz, H-8), 6.92 (dd, J<sub>ortho</sub> 8Hz, J<sub>meta</sub> 2Hz, H-6), 3.45 (s, NMe) and 2.26 (s, Me).

I. The Attempted Reaction of 1-Acetoxy-4-methylquinoxaline-2, 3(1H, 4H)-dione (414) with Sodium Acetate in Ethanol.

A solution of 1-acetoxy-4-methylquinoxaline-2, 3(1H, 4H)-dione (414) (0.47 g; 0.002 mol) in ethanol (10.0 ml) was heated under reflux with anhydrous sodium acetate (0.33 g; 0.004 mol) for 48 h. The mixture was hot filtered to give a colourless solid which was dissolved in water (5.0 ml) and acidified with aqueous 2M hydrochloric acid to give 4-hydroxy-1-methylquinoxaline-2, 3(1H, 4H)-dione (400a) (0.38 g; 100%), m.p. 253-4<sup>o</sup> (lit<sup>22</sup> 254<sup>o</sup>), identical (i. r. spectrum) with an authentic sample. The acidic filtrate was extracted with chloroform to give a negligible quantity of gum.

Part IIIA. Synthesis of 3-Cyano-1-hydroxyquinoxaline-2(1H)-one 4-oxides  
(447)General Method

The syntheses of the 3-cyano-1-hydroxyquinoxaline-2(1H)-one 4-oxides (447) was carried out using the method of Seng and Ley.<sup>106</sup> A stirred solution of the benzofuroxan (430) (0.02 mol) and ethyl cyanoacetate (0.02 mol) in dimethylformamide (14.0 ml) was cooled to 10°C and treated dropwise with 1,5-diazabicyclo-[4.3.0]-non-5-ene (D.B.N.) (2.4 g). The internal temperature of the mixture increased to ca. 20-25°C. The mixture was stirred for 10 minutes in an ice bath during which time (unless otherwise described) a violet precipitate formed. The precipitated solid was dissolved in the minimum volume of water and acidified with aqueous 2M hydrochloric acid to furnish the 3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447).

a) Benzofuroxan<sup>110</sup> (430a) reacted with ethyl cyanoacetate, as described by Seng and Ley,<sup>106</sup> to afford 3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447a) (1.30 g; 62%), m. p. 238° (lit.<sup>106</sup> 242-5°),  $\nu_{\max}$  3300 (OH), 2250 (CN) and 1650 (CO) cm<sup>-1</sup>, which was sufficiently pure for further use.

b) 5(6)-Methylbenzofuroxan<sup>111</sup> (430b) reacted with ethyl cyanoacetate as described in the general method to give a mixture of 7-methyl-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447b) and 6-methyl-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447f) (1.87 g; 44%), which crystallised as yellow needles, m. p. 236-7°, (from light petroleum-ethanol),  $\nu_{\max}$  3050 (OH), 2220 (CN) and 1630-1600 br (CO) cm<sup>-1</sup>,  $\delta[(\text{CD}_3)_2\text{SO}]$  (447b) 8.02 (d,  $J_{\text{ortho}}$  9Hz, H-5), 7.80 (d,  $J_{\text{meta}}$  2.5 Hz, H-8), 7.39 (dd,  $J_{\text{ortho}}$  9Hz,  $J_{\text{meta}}$  2.5Hz, H-6), and 2.33 (s, ArMe);  $\delta[(\text{CD}_3)_2\text{SO}]$  (447f) 7.72 (s, ArH), 7.61 (d,  $J_{\text{meta}}$  2.5Hz, ArH), and 2.33 (s, ArMe).

Found: C, 55.3; H, 3.3; N, 19.3%;  $M^+$  217

$\text{C}_{10}\text{H}_7\text{N}_3\text{O}_3$  requires : C, 55.3; H, 3.2; N, 19.3%; M 217.



Extraction of the acidic filtrate with chloroform gave a negligible quantity of gum.

c) 5(6)-Chlorobenzofuroxan<sup>112</sup> (430c) reacted with ethyl cyanoacetate as described in the general method to give an unresolved mixture of 7-chloro-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447c) and 6-chloro-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447 g) (1.1 g; 23%), which crystallised as yellow prisms m. p. 245-7° (from light petroleum-ethanol),  $\nu_{\max}$  3150 (OH), 2200 (CN) and 1640 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.22-7.74 (complex multiplet).

Found: C, 45.2; H, 1.5; N, 17.4%;  $M^+$  237, 239.

$\text{C}_9\text{H}_4\text{ClN}_3\text{O}_3$  requires: C, 45.5; H, 1.7; N, 17.7%; M 237.5.

Extraction of the acidic mother liquor with chloroform gave a negligible quantity of gum.

d) 5(6)-Methoxybenzofuroxan<sup>111</sup> (430d) failed to yield a deep red precipitate on reaction with ethyl cyanoacetate under the conditions described in the general method. The mixture was diluted with an equal volume of water, acidified with aqueous 2M hydrochloric acid and extracted with chloroform to give a viscous, dark gum from which no identifiable material could be obtained.

e) 5,6-Dimethylbenzofuroxan<sup>113</sup> (430e) reacted with ethyl cyanoacetate as described in the general method to give 3-cyano-6,7-dimethyl-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447e) (2.05 g; 50%) as a light yellow powder, m. p. 244-5° (from light petroleum-ethanol)  $\nu_{\max}$  3480 (OH), 2220 (CN), and 1625 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.94 (1H, s, H-5), 7.61 (1H, s, H-8), 2.42 (3H, s, ArMe), and 2.35 (3H, s, ArMe).

Found: C, 57.1; H, 3.9; N, 18.4%;  $M^+$  231

$\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3$  requires: C, 57.1; H, 3.9; N, 18.2%; M 231.

Extraction of the acidic filtrate with chloroform gave a negligible quantity of gum.

f) 4,6-Dichlorobenzofuroxan<sup>114</sup> (430f) reacted with ethyl cyanoacetate as described in the general method to give the 3-cyano-dichloro-1-hydroxy-



quinoxalin-2(1H)-one 4-oxide (455)/(456) (0.41 g; 7%), which crystallised as orange plates, m. p. 239-40<sup>o</sup> (from light petroleum-ethanol),  $\nu_{\max}$  3100 w (OH), 2200 (CN) and 1665 (CO) cm<sup>-1</sup>,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.89 (1H, d,  $J_{\text{meta}}$  2Hz) and 7.79 (1H, d,  $J_{\text{meta}}$  2Hz).

Found: C, 40.0; H, 1.2; N, 15.5%;  $M^{+271, 273, 275}$

$\text{C}_9\text{H}_3\text{Cl}_2\text{N}_3\text{O}_3$  requires: C, 39.7; H, 1.1; N, 15.4%; M 273.

Extraction of the acidic mother liquor with chloroform gave a negligible quantity of gum. The dimethylformamide mother liquor was diluted with water, acidified with aqueous 2M hydrochloric acid and extracted with chloroform to give an intractable gum (3.42 g) which was shown by t. l. c. in ether over alumina to be an unresolvable multicomponent mixture.

#### B. Synthesis of 1,4-Di-N-Hydroxyquinoxaline-2,3(1H,4H)-diones (426)

##### General Method

A refluxing solution of the 3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447) (0.002 mol) in ethanol (15.0 ml) was treated dropwise with 20% w/v aqueous potassium hydroxide (2.5 ml) and heating under reflux was continued for 1 hour, during which time a red precipitate, which lightened in colour, formed. The mixture was cooled and filtered and the residual solid was dissolved in the minimum quantity of hot water. The aqueous solution was acidified with aqueous 2M hydrochloric acid to give the 1,4-di-N-hydroxyquinoxaline-2,3(1H,4H)-dione (426) and the ethanol mother liquor was further worked up as described for the individual reactions (a-d).

a) 3-Cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447a) gave 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.34 g; 87%) which crystallised as finely divided yellow needles, m. p. 278-80<sup>o</sup> (from water),  $\nu_{\max}$  3400 (OH) and 1690 (CO) cm<sup>-1</sup>,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.65-7.31 (4H, m, ArH).

Found: C, 49.4; H, 3.1; N, 14.2%;  $M^{+194}$ .

$\text{C}_8\text{H}_6\text{N}_2\text{O}_4$  requires: C, 49.5; H, 3.1; N, 14.4%; M 194.

The ethanol mother liquor was evaporated and the residue was treated with water and extracted with chloroform. Evaporation of the chloroform extract gave a negligible quantity of gum.

b) The isomer mixture of 7-chloro-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447c) and 6-chloro-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447g) gave 6-chloro-1,4-di-N-hydroxyquinoxaline-2,3(1H,4H)-dione (426b) (0.40 g; 87%) which crystallised as colourless needles, m. p. 249-51° (from water),  $\nu_{\max}$  3400 (OH) and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.55 (1H, d,  $J_{\text{ortho}}$  8Hz, H-8), 7.49 (1H, d,  $J_{\text{meta}}$  2Hz, H-5) and 7.35 (1H, dd,  $J_{\text{ortho}}$  8Hz,  $J_{\text{meta}}$  2Hz, H-7).

Found: C, 42.1; H, 2.4; N, 12.4%;  $M^+$  228, 230

$\text{C}_8\text{H}_5\text{ClN}_2\text{O}_4$  requires: C, 42.0; H, 2.2; N, 12.2%; M 228.5.

The ethanol filtrate was evaporated and the residue was dissolved in water, acidified with aqueous 2M hydrochloric acid and extracted with chloroform to give an unidentified gum (0.01 g).

c) The isomer mixture of 7-methyl-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447b) and 6-methyl-3-cyano-1-hydroxyquinoxalin-2(1H)-one 4-oxide (447f) gave 1,4-di-N-hydroxy-6-methylquinoxaline-2,3(1H,4H)-dione (426c) (0.10 g; 23%), which crystallised as colourless needles, m. p. 259-60° (from water),  $\nu_{\max}$  3400 (OH) and 1650 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.44 (1H, d,  $J_{\text{ortho}}$  8Hz, H-8), 7.49 (1H, d,  $J_{\text{meta}}$  2Hz, H-5), 7.10 (1H, dd,  $J_{\text{ortho}}$  8Hz,  $J_{\text{meta}}$  2Hz, H-7), and 2.39 (3H, s, ArMe).

Found: C, 47.8; H, 4.4; N, 12.4%;  $M^+$  208.

$\text{C}_9\text{H}_8\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$  requires: C, 47.8; H, 4.4; N, 12.6%; M 208.

d) 3-Cyano-6,7-dimethylquinoxalin-2(1H)-one 4-oxide (447e) gave 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426d), which was combined with a second crop obtained by evaporation of the ethanol mother liquor, dilution of the residue with minimum volume of hot water and acidification of the aqueous solution with aqueous 2M hydrochloric acid (total 0.38 g; 84%), m. p. 234-6° (from water),  $\nu_{\max}$  3300 (OH) and 1660 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.94 (1H, s, H-5), 7.59 (1H, s, H-8), and 2.39 (6H, s, ArMe).

Found:  $M^+$  222.064777

$C_{10}H_{10}N_2O_4$  requires :  $M$  222.064051

error < 4 p. p. m.

C. 1,4-Di-N-acetoxyquinoxaline-2,3(1H,4H)-dione (448)

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was stirred with acetic anhydride (1.0 ml) at room temperature for 18 h. Water was added to the mixture and stirring was continued for a further 1 h. Filtration of the residue gave 1,4-di-N-acetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.54 g; 95%) which crystallised as colourless plates, m. p.  $193-4^{\circ}$  (from glacial acetic acid),  $\nu_{\max}$  1800 and 1710 (CO)  $cm^{-1}$ ,  $\delta[(CD_3)_2SO]$  7.65-7.31 (4H, m, ArH) and 2.56 (6H, s, Me).

Found: C, 51.6; H, 3.5; N, 10.1%  $M^+$  278.

$C_{12}H_{10}N_2O_6$  requires : C, 51.8; H, 3.6; N, 10.1%;  $M$  278.

D. The Reduction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Triethyl Phosphite.

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was heated under reflux with triethyl phosphite (2 ml; 0.045 mol) for 2 h. The mixture was cooled to give quinoxaline-2,3(1H,4H)-dione (343a) (0.32 g; 97%), which crystallised as colourless needles, m. p.  $>350^{\circ}C$  (from dimethylformamide-water),  $\nu_{\max}$  3200 br (NH) and 1700 (CO)  $cm^{-1}$ .

Found: C, 59.1; H, 3.8; N, 17.4%;  $M^+$  162.

Calc. for  $C_8H_6N_2O_2$  : C, 59.3; H, 3.7; N, 17.3%;  $M$  162.

Evaporation of the filtrate gave a negligible quantity of gum.

E. The Attempted Reduction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) using Sodium Dithionite.

A solution of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in water (40.0 ml) was heated under reflux for 1 h

with sodium dithionite (0.8 g) (added in two equal portions, the second portion after 0.5 h). Hot-filtration gave a colourless solid (A) (0.38 g). Evaporation of the filtrate and treatment of the residue with water (5.0 ml) and aqueous 2M hydrochloric acid (4.0 ml) gave unreacted hydroxamic acid (426a) (0.07 g; 18%), m. p. 260-70° (decomp), identical (i. r. spectrum) with an authentic sample. Solid (A) (0.30 g) was stirred at room temperature with acetic anhydride (1.0 ml) for 18 h and the mixture was treated with water (1.0 ml) and stirred for a further 1 h. Filtration gave 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.33 g), m. p. 183-5°, identical (i. r. spectrum) with an authentic sample.

F. The Attempted Reduction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) using Iron Filings in Acetic Acid.

A solution of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in glacial acetic acid (15.0 ml) was heated under reflux with iron filings (1.95 g) for 1 hour. The mixture was filtered to remove inorganic material, evaporated and treated with water (5.0 ml) to give unreduced starting material (426a) (0.20 g; 51%), m. p. 268-70°, identical (i. r. spectrum) with an authentic sample. Extraction of the aqueous washings with chloroform gave a quantity of a dark gum (0.05 g), whose t. l. c. in ether over silica showed it to be a multicomponent mixture which was not further investigated.

G. The Attempted Hydrogenolysis of 1,4-Diacetoxyquinoxaline-2,3(1H,4H)-dione (448).

A solution of 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.39 g; 0.002 mol) in glacial acetic acid (100 ml) containing 10% palladium charcoal catalyst (0.03 g) was stirred under an atmosphere of hydrogen gas at room temperature and pressure for three hours, during which time 10.0 ml of hydrogen was absorbed. The mixture was filtered and evaporated to give unreacted 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.33 g; 85%), m. p. 190-2°, identical (i. r. spectrum) with an authentic sample.



H. The Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetyl Chloride in Acetic Acid to give 1,4-Diacetoxyquinoxaline-2,3(1H,4H)-dione (448).

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was heated under reflux with acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 1.5 h. Evaporation of the mixture and trituration of the residue with methanol gave 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.47 g; 85%), identical (m. p. and i. r. spectrum) with a sample prepared before. Evaporation of the methanol mother liquor gave a negligible quantity of gum.

I. Prolonged Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-diones (426) with Acetyl Chloride in Acetic Acid.

#### General Method

The 1,4-dihydroxyquinoxalinedione (426) (0.002 mol) was heated under reflux with a mixture of acetyl chloride (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. The mixture (A) was cooled and then further worked up as described for the individual reactions (a-c).

a) The mixture (A) from 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) was evaporated and the residue was treated with water to give a colourless solid, which crystallised from glacial acetic acid to give 5,7-dichloroquinoxaline-2,3(1H,4H)-dione (348c) as colourless needles, m. p.  $322-4^{\circ}$ , identical (i. r. spectrum) with a sample obtained previously. Evaporation of the acetic acid mother liquor gave 5-chloro-1,3-diacetylbenzimidazol-2-one (291b) (0.20 g; 40%), m. p.  $169-70^{\circ}$  (lit<sup>75</sup>  $175-6^{\circ}$ ),  $\nu_{\max}$  1770 and 1710 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.50-8.40 (2H, m, ArH), 7.72 (1H,  $J_{\text{ortho}}$  9Hz,  $J_{\text{meta}}$  2Hz, H-6), and 3.00 (6H, s, Me), identical (i. r. spectrum) with a synthetic sample.<sup>75</sup>

Found: C, 52.9; H, 3.7; N, 11.2%;  $M^+$  252, 254

Calc. for  $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}_2\text{O}_3$ : C, 52.4; H, 3.6; N, 11.1%; M 253.

b) The mixture (A) from 6-chloro-1,4-dihydroxyquinoxaline-2,3(1H,



4H)-dione (426b) was filtered to give 6,7,8-trichloroquinoxaline-2,3(1H,4H)-dione (457), which was combined with a second crop obtained by evaporation of the mother liquors and trituration of the residual gum with chloroform (98%) and which crystallised as pink prisms, m. p.  $>350^{\circ}$  (from glacial acetic acid),  $\nu_{\max}$  3100 w (NH), and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  7.29 (1H, s, H-5).

	<u>Found:</u>	$\text{M}^+$	263.928156
$\text{C}_8\text{H}_3\text{Cl}_3^{35}\text{N}_2\text{O}_2$	requires:	M	263.926009

error < 9 p. p. m.

	<u>Found:</u>	$\text{M}^+$	265.925215
$\text{C}_8\text{H}_3\text{Cl}^{37}\text{Cl}_2^{35}\text{N}_2\text{O}_2$	requires:	M	265.923060

error < 9 p. p. m.

	<u>Found:</u>	$\text{M}^+$	267.922788
$\text{C}_8\text{H}_3\text{Cl}_2^{37}\text{Cl}^{35}\text{N}_2\text{O}_2$	requires:	M	267.920110

error < 10 p. p. m.

c) The mixture (A) from 6,7-dimethylquinoxaline-2,3(1H,4H)-dione (426d) was filtered to give 5,8-dichloro-6,7-dimethylquinoxaline-2,3(1H,4H)-dione (458) (0.22 g; 43%), which crystallised as colourless plates, m. p.  $>350^{\circ}$  (from dimethylformamide),  $\nu_{\max}$  3120 w (NH) and 1725 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  2.36 (6H, s, ArMe).

	<u>Found:</u>	C, 46.8; H, 3.2; N, 10.9%;	$\text{M}^+$ 258,260
$\text{C}_{10}\text{H}_8\text{Cl}_2\text{N}_2\text{O}_2$	requires:	C, 46.4; H, 3.1; N, 10.8%;	M 259.

Evaporation of the filtrate and trituration of the residue with toluene gave 5-chloro-7-chloromethyl-6-methylquinoxaline-2,3(1H,4H)-dione (459) (0.22 g; 43%), which crystallised as pink prisms, m. p.  $>350^{\circ}\text{C}$  (from glacial acetic acid),  $\nu_{\max}$  3100 w (NH) and 1690 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  6.85 (1H, s, H-8), 2.29 (2H, s,  $\text{CH}_2$ ) and 2.20 (3H, s, ArMe).

Found:  $M^+$  257.997029

$C_{10}H_8Cl^{35}Cl^{35}N_2O_2$  requires: M 257.996279

error < 3 p. p. m.

Found:  $M^+$  259.995342

$C_{10}H_8Cl^{35}Cl^{37}N_2O_2$  requires: M 259.993329

error < 8 p. p. m.

Found:  $M^+$  261.992198

$C_{10}H_8Cl^{37}Cl^{37}N_2O_2$  requires: M 261.990380

error < 7 p. p. m.

Evaporation of the toluene mother liquor gave a negligible quantity of gum.

J. Prolonged Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetyl Bromide in Acetic Acid.

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was heated under reflux in a mixture of acetyl bromide (9.0 ml) and glacial acetic acid (9.0 ml) for 48 h. The mixture was evaporated and the resulting gum was triturated with ether-ethyl acetate to yield a colourless solid which was extracted with hot ethanol to leave 5,7-dibromoquinoxaline-2,3(1H,4H)-dione (461) (0.06 g; 10%), m. p. 332-4<sup>o</sup> (from glacial acetic acid),  $\nu_{\max}$  3100 w (NH) and 1705 (CO)  $cm^{-1}$ .

Found:  $M^+$  317.864427

$C_8H_4Br^{79}N_2O_2$  requires: M 317.864055

error < 2 p. p. m.

Found:  $M^+$  319.862935

$C_8H_4Br^{79}Br^{81}N_2O_4$  requires: M 319.862085

error < 3 p. p. m.

Found:  $M^+$  321.861128

$C_8H_4Br^{81}N_2O_4$  requires: M 321.860115

error < 4 p. p. m.

Evaporation of the ethanolic mother liquor gave 1,4-diacetoxyquinoxaline-

2,3(1H,4H)-dione (448) (0.41 g; 72%), identical (m. p. and i. r. spectrum) with an authentic sample.

K. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Acetic Anhydride.

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was heated under reflux with acetic anhydride (10.0 ml) for 24 h. The mixture was evaporated and the residue was treated with water and extracted with chloroform. Evaporation of the chloroform extract gave a dark gum which was treated with saturated aqueous sodium bicarbonate solution and re-extracted into chloroform. Evaporation of the chloroform extract gave an intractable gum (0.35 g) which was shown by t. l. c. in chloroform over alumina to be a multicomponent mixture. The aqueous sodium bicarbonate washings were acidified with aqueous 2M hydrochloric acid and extracted with chloroform. Evaporation of the chloroform gave a negligible quantity of a gum.

L. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Sodium Acetate in Acetic Anhydride.

1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) was heated under reflux with anhydrous sodium acetate (0.33 g; 0.004 mol) in acetic anhydride (10.0 ml) for 0.5 h. The mixture was evaporated, treated with water and extracted with chloroform. Evaporation of the chloroform extract gave an intractable gum (0.30 g) which was shown by t. l. c. in ethanol over alumina to be multi-component. Evaporation of the aqueous washings gave no further organic material.

M. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Toluene-p-Sulphonyl Chloride in Dimethylformamide.

A suspension of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in dimethylformamide (15.0 ml) was heated under reflux and treated in one portion with toluene-p-sulphonyl chloride.

Heating of the resulting black solution was continued for 0.5 h, during which time it lightened to a red colour before turning brown and depositing a brown solid (0.07 g). The solid was collected, triturated with hydrochloric acid and refiltered to give unreacted starting material (426a) (0.04 g; 10%), m. p. 263-5<sup>o</sup>, identical (i. r. spectrum) with an authentic sample. The filtrate was cooled, treated with water (10.0 ml) and extracted with chloroform. Evaporation of the chloroform extract and trituration of the residue with ether gave a further crop of unreacted starting material (426a) (0.25 g; 64%), m. p. 268-70<sup>o</sup>, identical (i. r. spectrum) with an authentic sample. Evaporation of the aqueous mother liquor gave a brown gum (0.08 g) which was shown by t. l. c. in a variety of eluents over silica and alumina to be a multicomponent mixture which was not further investigated.

N. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Toluene-p-sulphonyl Chloride in the presence of Aqueous Sodium Hydroxide.

A stirred solution of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in 10% aqueous sodium hydroxide (10.0 ml) was treated in portions with toluene-p-sulphonyl chloride (0.42 g; 0.002 mol). The mixture was stirred at room temperature for 1 h and filtered to give unreacted toluene-p-sulphonyl chloride (0.18 g), identical (i. r. spectrum) with an authentic sample. The filtrate was extracted with chloroform to give a negligible quantity of gum. 1. Acidification of the aqueous mother liquor with aqueous 2M hydrochloric acid gave unreacted hydroxamic acid (426a) (0.16 g; 46%), m. p. 270-2<sup>o</sup>, identical (i. r. spectrum) with an authentic sample. Extraction of the aqueous mother liquor with chloroform gave a brown gum (0.05 g) which was shown by t. l. c. in ether over silica to be an unresolvable multicomponent mixture.

O. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Toluene-p-sulphonyl Chloride and Triethylamine in Dioxan.

A stirred solution of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione



(426a) (0.39 g; 0.002 mol) in dry dioxan (15.0 ml) was treated dropwise with triethylamine (0.35 ml) and then with a solution of toluene-*p*-sulphonyl chloride (0.42 g; 0.002 mol) in dry dioxan (2.0 ml). The suspension was stirred at room temperature for 45 minutes and filtered to give unreacted starting material (426a) (0.29 g; 74%), m. p. 268-70°, identical (i. r. spectrum) with an authentic sample. Evaporation of the filtrate gave a dark gum (0.10 g) which was shown by t.l.c. in chloroform to be a multi-component mixture.

P. The Attempted Reaction of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) with Toluene-*p*-sulphonyl Chloride and Triethylamine in Dimethylformamide.

A stirred solution of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in dry dimethylformamide (24.0 ml) was treated dropwise with triethylamine (0.7 ml; 0.005 mol) then with a solution of toluene-*p*-sulphonyl chloride (1.0 g; 0.0054 mol) in dry dimethylformamide (2.0 ml). The mixture was stirred at room temperature for 0.5 h and then evaporated at low temperature to give a dark gum which was treated with water and chloroform. The two-phase mixture was filtered to remove some insoluble gummy brown solid (0.07 g) which was not identified. Evaporation of the chloroform layer gave a dark gum (0.3 g) which was shown by t.l.c. in a variety of solvents over silica and alumina to be a complex mixture. The gum was digested with aqueous 2M sodium hydroxide, charcoaled and acidified with aqueous 2M hydrochloric acid to give a solid which decomposed on attempted isolation. Extraction of the filtrate with chloroform gave a negligible quantity of gum. On standing, the aqueous fraction gave an amorphous white solid (0.13 g), m. p. >350°C [from glacial acetic acid),  $\nu_{\max}$  3200 br (NH) and 1690 br (CO) cm<sup>-1</sup>.

Found: C, 51.4; H, 4.0; N, 12.4%; M<sup>+</sup> 196, 198, 230, 232.

C<sub>8</sub>H<sub>4</sub>Cl<sub>1</sub>N<sub>2</sub>O<sub>2</sub> requires: M 231

C<sub>8</sub>H<sub>5</sub>Cl<sub>1</sub>N<sub>2</sub>O<sub>2</sub> requires: M 196.5



Part IVThermolytic Reactions of N-Oxygenated Quinoxaline-  
2,3(1H,4H)-dionesA. Thermal Rearrangements of 1-Acetoxyquinoxaline-2,3(1H,4H)-  
diones.a) The Thermal Rearrangement of 1-Acetoxyquinoxaline-2,3(1H,4H)-  
dione (336a) in Diphenyl Ether.

A suspension of 1-acetoxyquinoxaline-2,3(1H,4H)-dione (336a) (0.66g; 0.003M) in diphenyl ether (20.0 ml) was heated under reflux for 0.5 h. The mixture was hot-filtered to give 1-acetylbenzimidazolone (478) which was combined with a second crop obtained by dilution of the filtrate with light petroleum (total 0.50 g; 61%) and crystallised to give colourless needles, m. p. 209-10° (from ethanol),  $\nu_{\max}$  3200-3100 br (NH), and 1725 and 1700 (CO)  $\text{cm}^{-1}$ ,  $\delta[(\text{CD}_3)_2\text{SO}]$  8.04-7.89 (1H, m, ArH), 7.12-6.85 (3H, m, ArH), and 2.59 (3H, s, Me).

Found: C, 61.2; H, 4.7; N, 15.9%;  $M^+$  176.

$\text{C}_9\text{H}_8\text{N}_2\text{O}_2$  requires : C, 61.3; H, 4.5; N, 15.9%; M 176.

b) The Thermal Rearrangement of 7-Chloro-1-acetoxyquinoxaline-  
2,3(1H,4H)-dione (336b) in Diphenyl Ether.

A solution of 7-chloro-1-acetoxyquinoxaline-2,3(1H,4H)-dione (336b) (0.38 g; 0.0015 mol) in diphenyl ether (5.0 ml) was heated under reflux for 20 minutes. The mixture was cooled and diluted with light petroleum to give 5-chlorobenzimidazolone (477) which was combined with a second crop obtained by washing the ethereal mother liquor with sodium hydroxide (5.0 ml) and acidifying the alkaline washings with aqueous 2M hydrochloric acid (total 0.24 g; 88%), m. p. 298-301° (from water),  $\nu_{\max}$  3450-3300 br (NH) and 1740 (CO)  $\text{cm}^{-1}$ , identical (m. p. and i. r. spectrum) with a synthetic sample.

	<u>Found:</u> C, 50.0; H, 3.0; N, 16.7%; M <sup>+</sup> 168, 170.
<u>Calc. for C<sub>7</sub>H<sub>5</sub>ClN<sub>2</sub>O</u>	C, 50.0; H, 3.0; N, 16.7%; M 169.5

B. Thermal Rearrangements of 1-Acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414).

a) In Diphenyl Ether

A solution of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) (0.94 g; 0.004 mol) in diphenyl ether (10.0 ml) was heated under reflux for 20 minutes and cooled to give 7-acetoxy-1-methylquinoxaline-2,3(1H,4H)-dione (401b) which was combined with a second crop obtained by dilution of the ethereal mother liquor with light petroleum (total 0.51 g; 54%), m. p. 278-82<sup>o</sup>, identical (i. r. spectrum) with an authentic sample. Extraction of the filtrate with chloroform gave a negligible quantity of gum.

b) In Xylene

A solution of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) (0.47 g; 0.002 mol) in dry xylene (5.0 ml) was heated under reflux for 3 h. The mixture was cooled to give 7-acetoxy-1-methylquinoxaline-2,3(1H,4H)-dione (401b) (0.18 g; 38%), m. p. 279-82<sup>o</sup>, identical (i. r. spectrum) with a sample obtained before. Evaporation of the filtrate and trituration of the residue with ethanol gave 1-acetyl-3-methylbenzimidazol-2-one (403a) (0.18 g; 47%) which crystallised as colourless needles, m. p. 113-14<sup>o</sup>, identical (i. r. spectrum), with a sample obtained previously.

	<u>Found:</u> C, 62.9; H, 5.2; N, 14.5%; M <sup>+</sup> 190
<u>Calc. for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub></u>	C, 63.2; H, 5.3; N, 14.7%; M 190.

Evaporation of the ethanol trituration liquor gave a dark gum (0.02 g) which was not further investigated.

c) In Ethanol

A solution of 1-acetoxy-4-methylquinoxaline-2,3(1H,4H)-dione (414) (0.47 g; 0.002 mol) in ethanol (10.0 ml) was heated under reflux for 0.5 h. The mixture was cooled to give unreacted starting material

(414) which was combined with a second crop obtained by evaporating the ethanolic filtrate (total 0.46 g; 97%), m. p. 175-7<sup>o</sup>, identical (i. r. spectrum) with an authentic sample.

C. The Attempted Thermal Rearrangement of 1,4-Diacetoxyquinoxaline-2,3(1H,4H)-dione (448) in Diphenyl Ether.

A solution of 1,4-diacetoxyquinoxaline-2,3(1H,4H)-dione (448) (0.75 g; 0.003 mol) in diphenyl ether (10.0 ml) was heated under reflux for 0.5 h. The mixture was cooled to give a dark intractable solid (0.16 g) from which no identifiable material could be obtained. The filtrate was diluted with light petroleum to yield a gummy solid. This was extracted into ethanol, charcoaled and evaporated to yield a further gum (0.43 g) which was shown by t. l. c. in ethyl acetate over silica to be an unresolvable multicomponent mixture.

D. Thermolytic Reactions of 1-Hydroxyquinoxaline-2,3(1H,4H)-diones

a) In Dibenzyl Ether

A suspension of 1-hydroxyquinoxaline-2,3(1H,4H)-dione (342a) (0.71 g; 0.004 mol) in dibenzyl ether (10.0 ml) was heated under reflux for 15 minutes, during which time the bulk of the solid dissolved. The mixture was hot-filtered to give quinoxaline-2,3(1H,4H)-dione (343a) (0.30 g; 48%), m. p. >350<sup>o</sup>; identical (i. r. spectrum) with a sample obtained previously. The cooled mixture deposited unreacted hydroxamic acid (342a) (0.35 g; 50%), m. p. 268-70<sup>o</sup> (lit<sup>22</sup> 275-83<sup>o</sup>), identical (i. r. spectrum) with an authentic sample.

b) In Cellosolve (2-Ethoxy Ethanol)

A solution of 1-hydroxyquinoxaline-2,3(1H,4H)-dione (342a) (0.36 g; 0.002 mol) in cellosolve (50.0 ml) was heated under reflux for 1 h. Evaporation of the mixture gave unreacted hydroxamic acid (342a) (0.35 g; 97%), identical (m. p. and i. r. spectrum) with an authentic sample.

E. Thermolytic Reactions of 7-Chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e)

a) In Trigol

A suspension of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) in trigol (5.0 ml) was heated under reflux for 15 minutes. The mixture was cooled to give 6-chloroquinoxaline-2,3(1H,4H)-dione (343b) as a cream, amorphous solid, which was combined with a second crop obtained by diluting the mother liquor with water (total 0.26 g; 71%), m. p.  $>350^{\circ}$  (from dimethylformamide-water),  $\nu_{\max}$  3200 w (NH) and 1690 (CO)  $\text{cm}^{-1}$ .

Found: C, 49.0; H, 2.7; N, 14.4%;  $M^+$  196, 198.

$\text{C}_8\text{H}_5\text{ClN}_2\text{O}_2$  requires: C, 49.0; H, 2.6; N, 14.3%; M 196.5.

b) In Dibenzyl Ether

A suspension of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.21 g; 0.001 mol) in dibenzyl ether (10.0 ml) was heated under reflux for 15 minutes. The mixture was hot-filtered to give the 6-chloroquinoxaline-2,3(1H,4H)-dione (343b) (0.18 g, 95%), identical (m. p. and i. r. spectrum) with an authentic sample. Dilution of the filtrate with light petroleum gave a negligible quantity of gum.

c) In N-Methylaniline

A suspension of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.42 g; 0.002 mol) in N-methylaniline (15.0 ml) was heated under reflux for 2 hours. The mixture was hot-filtered and the residue was washed with ether (5.0 ml) to give 6-chloroquinoxaline-2,3(1H,4H)-dione (343b) (0.36 g; 95%), identical (m. p. and i. r. spectrum) with an authentic sample. The filtrate was acidified with aqueous 2M sulphuric acid and extracted with chloroform to give a negligible quantity of gum.

d) In Diphenyl Ether

A suspension of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.42 g; 0.002 mol) in diphenyl ether (5.0 ml) was heated under



reflux for 20 minutes and cooled to give unreacted starting material (0.39 g; 93%), identical (m. p. and i. r. spectrum) with an authentic sample.

F. The Attempted Reaction of 7-Chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) with Acenaphthylene in Diphenyl Ether

A solution of 7-chloro-1-hydroxyquinoxaline-2,3(1H,4H)-dione (342e) (0.30 g; 0.002 mol) and acenaphthylene (0.30 g; 0.002 mol) in diphenyl ether (5.0 ml) was heated under reflux for 15 minutes. The mixture was hot-filtered to give 6-chloroquinoxaline-2,3(1H,4H)-dione (343b) which was combined with a second crop obtained by dilution of the mother liquor with light petroleum (total 0.31 g; 82%), identical (m. p. and i. r. spectrum) with an authentic sample. The dibenzyl ether mother liquor was evaporated under reduced pressure to give a dark gum (0.39 g) which was shown by t. l. c. in ether over silica to be a multi-component mixture.

G. Thermolytic Reactions of 1-Hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a)

a) In Trigol

A solution of 1-hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) (0.39 g; 0.002 mol) in trigol (5.0 ml) was heated under reflux for 15 minutes. The mixture was cooled, diluted with an equal volume of water and extracted with chloroform. Evaporation of the chloroform extract and trituration of the residue with ether-ethyl acetate gave 1-methylquinoxaline-2,3(1H,4H)-dione (479) (0.28 g; 80%), m. p. 278-80° (lit<sup>109</sup> 257°), identical (i. r. spectrum) with a sample prepared as described later.

b) In Dibenzyl Ether

A solution of 1-hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) (0.39 g; 0.002 mol) in dibenzyl ether (5.0 ml) was heated under reflux for 15 minutes. The mixture was cooled to yield unreacted



hydroxamic acid (400a) which was combined with a second crop obtained by dilution of the mother liquor with light petroleum, (total 0.36 g; 92%), m. p. 250-3° (lit<sup>22</sup> 254°), identical (i. r. spectrum) with an authentic sample.

H. The Attempted Thermal Rearrangement of 1,4-Dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) in Dibenzyl Ether

A suspension of 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a) (0.39 g; 0.002 mol) in dibenzyl ether (10.0 ml) was heated under reflux for 15 minutes. The filtrate was hot-filtered and the residue was washed with light petroleum to give unreacted 1,4-dihydroxyquinoxaline-2,3(1H,4H)-dione (426a), which was combined with a second crop obtained by cooling the mother liquor (total 0.21 g; 54%), m. p. 275-8°, identical (i. r. spectrum) with an authentic sample. The mother liquor was diluted with light petroleum to give an off-white solid (0.03 g) which went gummy on standing. Attempts to crystallise this solid from a variety of solvents proved unsuccessful and it was not further investigated.

I. The Attempted Photolysis of 1-Hydroxyquinoxaline-2,3(1H,4H)-dione (342a)

A solution of 1-hydroxyquinoxaline-2,3(1H,4H)-dione (342a) (0.71 g; 0.004 mol) was irradiated under nitrogen, at room temperature, for 24 h in dioxan (200 ml), using a medium pressure Hanovia reactor. Evaporation of the mixture and trituration of the residue with chloroform gave the unreacted hydroxamic acid (342a) (0.69 g; 97%), m. p. 275-7° (lit<sup>22</sup> 275-83°), identical (i. r. spectrum) with an authentic sample.

J. The Reduction of 1-Hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) using Sodium Dithionite

A solution of 1-hydroxy-4-methylquinoxaline-2,3(1H,4H)-dione (400a) (0.77 g; 0.004 mol) in glacial acetic acid (40.0 ml) was heated under reflux for 1 h with sodium dithionite (1.54 g) [added in two portions, the second after 0.5 h]. The mixture was evaporated and the residue was

washed with water (5.0 ml) to give 1-methylquinoxaline-2,3(1H,4H)-dione (479), which was combined with a second crop obtained by extraction of the aqueous washings with chloroform (total 0.72 g; 92%), m. p. 280-3° (lit<sup>109</sup> 257°).

K. 5-Chlorobenzimidazol-2-one (477)

4-Chloro-o-phenylenediamine (2.84 g; 0.02 mol) was heated with urea (3.60 g; 0.06 mol) at 150° for 1 h. The mixture was cooled and the residue was triturated with ethyl acetate to afford a brown solid which was extracted with aqueous 2M sodium hydroxide (5.0 ml). The alkaline extract was treated with charcoal and acidified with aqueous 2M hydrochloric acid to give 5-chlorobenzimidazol-2-one (477) (3.10 g; 77%), m. p. 298-303° (lit<sup>115</sup> >270°),  $\nu_{\max}$  3450-3300 br (NH), and 1740 (CO)  $\text{cm}^{-1}$ .

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APPENDIX

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APPENDIX

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## General Experimental Data

Unless otherwise stated, infrared spectra were measured for nujol suspensions using a Pye-Unicam SP200 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. Signals were sharp unless otherwise specified (br) as broad; s = singlet; d = doublet; dd = double doublet; t = triplet; dt = double triplet; q = quartet; m = multiplet. In all cases tetramethylsilane was used as internal standard.

Mass spectra and high resolution mass spectral analyses were measured at 70eV using an A. E. I. MS 902 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 Kofler hot-stage microscope and are uncorrected.

All organic extracts were dried over anhydrous magnesium sulphate, prior to evaporation under reduced pressure. Unless otherwise specified, solvents were of technical grade. Benzene was sodium-dried and light petroleum had b. p. 60-80°.

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.

Preparative thin layer chromatography was carried out over silica [Merck Kieselgel G. F. 254 (Type 60), activity III].