Studies of Novel Heterocyclisation Reactions of

*ortho*-Substituted Nitrobenzene Derivatives

by

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Thesis presented for the degree of

Doctor of Philosophy

University of Edinburgh

1989
This thesis is dedicated to the memory of Mark McGuire
Acknowledgements

I would like to thank Dr. G. Tennant for his supervision and encouragement during the course of my research.

I would like to thank the University of Edinburgh for the provision of laboratory and library facilities.

I would also like to acknowledge the help and expertise of the technical staff of the Department of Chemistry, University of Edinburgh, notably Mr. L. Bell and Mr. J. Millar for the measurement of n.m.r. spectra, Mr. J. Grunbaum and Mrs. E. McDougall for the determination of microanalyses and Mr. A.T. Taylor and Mr. D. Thomas for the mass spectra recorded in this thesis.

Finally, I am grateful to Dr. A.J. Blake and Dr. R.O. Gould for the X-ray structure determinations.
Postgraduate Lecture Courses Attended
between October 1983 and September 1985

"Current Topics in Organic Chemistry"
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The subject matter of this thesis is concerned with investigations of novel heterocyclisation reactions of ortho-substituted nitrobenzene derivatives. The description of the results obtained in these studies is preceded in chapter 1 by a survey of known literature heterocyclisation reactions of such derivatives, mostly under base-catalysis.

Chapter 2 describes investigations into the synthesis of 2-nitrobenzyl heterocumulenes to provide suitable intermediates for reaction with active methylene compounds affording acetamidine, thioacetamide and amide derivatives, themselves capable of base-catalysed cyclisation. The cyclisation reactions, carried out under a variety of base-catalysis conditions, gave rise to quinoxaline derivatives often with unusual and otherwise difficult to obtain substitution patterns. Subsequent studies on the reactivity of the quinoxaline derivatives including their further heterocyclisation reactions affording e.g. imidazoquinoxalines are also reported in this chapter.

Chapter 3 describes the synthesis of 2-nitrobenzoylmethylene triphenylphosphorane derivatives and the investigations into their cyclisation reactions. 1-Bromo and 1-ester derivatives failed to cyclise but 1-arylazo derivatives underwent cyclisation under various reaction conditions. Depending on the cyclisation conditions, reaction yielded cinnolinyltriphosphorylphosphonium nitrites (shown to be reaction intermediates), 1-arylaminocinnolin-3-ones and 1-arylindole-2,4-diones in varying proportions. Investigations into the mechanisms of such reactions are also described.

In the final chapter studies on the synthesis and base catalysed reaction of N,N-disubstituted 2-nitrobenzylamine derivatives are described. Base treatment of the benzylamine derivatives produced substituted indazoles and/or 2-hydroxyaminobenzoylamines. The pathway of such reactions was probed and a mechanism to explain the formation of both types of product is proposed.
Ortho-substituted nitrobenzene derivatives are currently of interest because of their utility as intermediates in the synthesis of heteroaromatic compounds with potentially important chemical and biological properties - e.g. certain N-oxygenated heterocycles are known to exhibit radio sensitising activity, important in the treatment of certain cancer tumour cells.

Heterocyclisation reactions of ortho-substituted nitrobenzene derivatives can involve direct displacement of the nitro group by the ortho-side chain or reaction of an acidic centre within the ortho-side chain with the nitro-group nitrogen in aldol-like processes. Such heterocyclisation reactions, often achieved under base-catalysis may furnish a wide range of heteroaromatic products, frequently with unambiguous N-oxygenation and/or unusual substitution patterns.

These interesting and potentially important properties prompted investigations into novel synthetic routes to ortho-substituted nitrobenzene derivatives and their subsequent conversion into novel or otherwise difficult to obtain heterocycles.

The results of these investigations are reported in the following thesis and, by way of introduction, are preceded by a survey of known literature methods for the synthesis of ortho-nitrobenzene derivatives and their conversion into heteroaromatic ring systems.
CHAPTER ONE  INTRODUCTION: A Survey of Heterocyclisation Reactions Involving the Direct Nucleophilic Interaction of Aromatic Nitro Groups with Ortho Side-chains

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Chapter 1

A SURVEY OF HETEROCYCLISATION REACTIONS INVOLVING THE DIRECT NUCLEOPHILIC INTERACTION OF AROMATIC NITRO GROUPS WITH ORTHO SIDE-CHAINS.
A Survey of Heterocyclisation Reactions Involving
The Direct Nucleophilic Interaction of Aromatic Nitro
Groups with Ortho Side-Chains.

The objective of this introductory chapter is to provide a limited but relevant review of heterocyclisation reactions of ortho-substituted nitrobenzene derivatives involving the direct interaction of the nitro-group with a nucleophilic centre in the ortho-side-chain. Such heterocyclisations can be of two broad classes depending on whether interaction involves nucleophilic attack on the nitro group in an intramolecular aldol-type condensation or alternatively nucleophilic displacement of the nitro-group. The reactions discussed in this survey are therefore grouped according to which of these two types of nucleophilic interaction is involved, with further subdivision under each heading depending on whether C-C bond formation or C-heteroatom bond formation occurs.

Previous reviews\textsuperscript{1,2} of the literature concerning heterocyclisation reactions of ortho-substituted nitrobenzene derivatives involving nucleophilic ortho-side-chain nitro-group interaction are comprehensive and therefore this chapter will be selective in its coverage, drawing on examples, mainly of base-catalysed processes to illustrate the scope and synthetic utility of such reactions.

1.1 Heterocyclisations Involving Base-catalysed condensation of Aromatic Nitro-groups with ortho side-chains.

The detailed mechanisms by which heterocyclisations involving
Scheme 1

(1) \[ X - N O - O^- \] (2) \[ N^+ - O - O^- \] (3) \[ N^+ - O - O^- \] (4) \[ X - N - OH \] (5) \[ X - N - O^- \]

(\( X = CR \) or \( N \))

(a) \[ \text{Reactions} \]

(b) \[ \text{Mechanisms} \]
(6) 

(i) Na$_2$CO$_3$, EtOH, H$_2$O, reflux.

Scheme 2

(8) 

(i) NaOAc, EtOH, H$_2$O, reflux. 

(R = H or MeO) 

(Ar = Ph or 4-ClC$_6$H$_4$)

Scheme 3

(7) R 

a; CN 

b; CONH$_2$
base-catalysed nitro-group/side-chain condensation occurs have never been unambiguously determined. It is possible that such reactions may involve (Scheme 1) radical anion coupling processes [path (a): (1) → (2) → (3) → (4) → (5)] akin to those demonstrated by Kornblum\(^3\) in the case of intermolecular base-catalysed reactions of nitro-compounds with carbanions. However, the heterocyclisations discussed in the present survey are for convenience considered mechanistically as simple intramolecular aldol-type condensations [Scheme 1, path (b): (1) → (3) → (4) → (5)]. Such heterocyclisations are synthetically useful since they often afford \(N\)-oxygenated heterocycles of pre-determined orientation and from which the parent heterocycle can be obtained by subsequent reduction.

Depending on whether the nucleophilic centre in the ortho side-chain is a carbon-atom or a nitrogen atom, cyclisation will result in carbon-nitrogen or nitrogen-nitrogen bond formation. Heterocyclisations of the former type will be discussed first followed by those resulting in nitrogen-nitrogen bond formation.

1.1.1 Heterocyclisations Involving C-N Bond Formation

The base-catalysed cyclisations (Scheme 2) of 2-nitrobenzylmalonic ester derivatives (6) which contain a moderately acidic centre at the \(\alpha\)-position of the ortho side-chain affords 1-hydroxyindoles (7)\(^4\). The electron-withdrawing effect of e.g. ester or cyano groups at the \(\alpha\)-position of the ortho side-chain increases the acidity of the \(\alpha\)-methine substituent and generally increases the reactivity of the 2-nitrobenzyl derivatives (6) towards cyclisation. In a similar reaction (Scheme 3) the 2-nitrobenzoylacetaldehyde derivatives (8) require only heating with sodium acetate in aqueous ethanol.
Scheme 4

(i) DMF, C$_5$H$_{10}$N, reflux.
(17) R
   a; H
   b; Me-C-
   c; Ph-C-
   d; CO₂Et

(i) NaOMe, MeOH, reflux.

Scheme 5

(18)

(21) Me₃SO₃⁻
(22) Me₃SO₃⁻

(23) (29-38%)

(i) NaOMe, MeOH, reflux.

[τ = 4-MeC₆H₄]

Scheme 6

(24) (10-23%)
to give the 2-arylisatogens (9) in good yield.

Fused pyrrole ring-formation can also occur when the nitro-group is an ortho-substituent on a ring other than benzene as in the case (Scheme 4) of the 5-nitro-6-styryluracil derivative (10). Yoneda and his co-workers have shown that when heated with piperidine in N,N-dimethylformamide (DMF), the uracil derivative (10) cyclises to give 1,3-dimethyl-7-hydroxy-6-phenylpyrrolo[3,2-d]pyrimidine-2,4(1H,3H)-dione (16) in 42% yield. This transformation can be explained in terms of a mechanism (Scheme 4) involving redox interaction between the nitro-group and the ortho side-chain in an initially formed piperidine adduct [(10) → (11) → (12) → (13) → (14)] prior to heterocyclisation as opposed to direct cyclisation via the intact nitro-group. Subsequent cyclisation of the resulting nitroso intermediate (14) would afford the tautomeric N-hydroxypyrrolopyrimidine derivative (15) reduction of which in the alkaline medium then explains the formation of the parent pyrrolopyrimidine product (16).

There are numerous examples of heterocyclisation reactions involving nucleophilic nitro-group/ortho side-chain interaction leading to N-oxygenated benzimidazole derivatives. For example (Scheme 5) the treatment of 2-nitro-N-(4-nitrobenzyl) aniline (17a) and its N-acyl derivatives (17b-d) with boiling methanolic sodium methoxide results in the formation of 1-hydroxy-2-(2-nitrophenyl) benzimidazole (18). Cyclisation of the N-acyl compounds (17b-d) is presumed by the authors to involve preliminary hydrolysis to 2-nitro-N-(4-nitrobenzyl) aniline (17a) whose heterocyclisation in turn can be explained by base-catalysed aldol-type condensation between the nitro-group and the acidic benzyl group in the ortho side-chain. In the
(i) Na₂CO₃, MeOH, reflux.

Scheme 7

(i) KCN, MeOH, reflux.

Scheme 8

(R = 4-NO₂, 4-Me, 4-OMe, 4-Cl, 2-Cl or 2-OMe)
Scheme 9

(i) 2M NaOH, H₂O, room temp.
related cyclisation (Scheme 6) of N-4-nitrobenzyl-N-(toluene-4-sulphonyl)-2-nitroaniline (19) formation of the N-hydroxybenzimidazole (23) product (yield 29-38%) is accompanied by the N-methoxy derivative (24) (yield 10 - 23%).

The authors explain the formation of the latter product by reaction of the anion of the hydroxybenzimidazole (21) with methyl toluene-4-sulphonate (22) formed as a by-product in the reaction. In other studies it was shown that under slightly different conditions (Scheme 7) a similar N,N-disubstituted 2-nitroaniline (25) cyclised to give N-(toluene-4-sulphonyl benzimidazol-2-one) (26) in poor yield.

1-Hydroxy-2-arylbenzimidazoles (28) are also prepared (Scheme 8) in moderate to good yield by the treatment of benzylidene 2-nitroanilines (27) with potassium cyanide in anhydrous methanol. Brown and co-workers in an analogous reaction (Scheme 9) have cyclised the N-(5-nitropyrimidinyl) aminoacetaldehyde (29a) using cold dilute aqueous sodium hydroxide to give 9-methylguanine-7-oxide (32) in good yield. Formic acid has been detected as a by-product in this reaction and in the related cyclisation of the N-(5-nitropyrimidinyl) aminoacetophenone (29b), benzoic acid is also isolated. The acidic by-products of these reactions are consistent with the reaction mechanism shown in Scheme 9, which involves the initial formation of a carbanion intermediate (30) which can cyclise by interaction of the nucleophilic centre in the side-chain with the nitro-group. Aromatisation of the resulting cyclic intermediate (31) by deacylation and loss of hydroxide ion then accounts for the formation of the purine derivative (32). Such a straightforward mechanism however cannot easily explain why the reaction fails in the case of the ester (29c) and the nitrile (29; CN for RC=O).
Scheme 10

(i) Et₃N, EtOH, 10-20°.

Scheme 11

(i) CO₂Et·CH₂SH, Et₃N, EtOH, -5°.
Scheme 12

Scheme 13
Benzothiazole derivatives are the products of the base-catalysed cyclisation reactions of 2-nitrophenylthioalkyl derivatives capable of providing an appropriate nucleophilic centre in the ortho-side-chain. Thus Wagner and his co-workers have prepared (Scheme 10) 2-nitrophenylthioglycolic acid ethyl esters (34) and have shown that treatment of these with triethylamine in ethanol or methanol at 10-20° results in the formation of ethyl benzothiazole-2-carboxylate N-oxides (35) in good yield. In a completely analogous reaction (Scheme 11), Senga et al treated a mixture of the 4-chloro-5-nitouracil derivative (36) and methyl thioglycollate in ethanol with triethylamine and obtained 6-carbamethoxy-1,3-dimethylthiazolo[5,4-d] pyrimidine-2,4(1H,2H)-dione 5-N-oxide (37) as the product in 50% yield.

Substituent interaction in ortho substituted nitrobenzene derivatives can also lead to the formation of a variety of six-membered heterocycles. A simple example of the formation of quinolines is described by Zaky and Iskander (Scheme 12). The 2,4-dinitrophenyl derivatives of 4-phenyl acetoacetic acid (38a) and its ethyl ester (38b) are shown to cyclise on heating with ethanolic sodium ethoxide to give the quinoline N-oxide derivatives (39). Again these cyclisation reactions can be regarded as simple intramolecular aldol-type processes as discussed before.

Quinazoline derivatives can be synthesised by the base-catalysed cyclisation of N-substituted 2-nitrobenzamide derivatives. For example the cyclisation (Scheme 13) of N-substituted 2-nitrobenzoylaminoacetonitriles (40) to give 1-hydroxyquinazoline-2,4-diones (41) is achieved in high yield by heating in ethanolic sodium ethoxide.
(i) 4% NaOH(aq), reflux.
(ii) 20% KOH(aq), reflux.
(iii) NaOH(aq), EtOH, reflux.

Scheme 14
(i) CH₃OH, room temp.

Scheme 15
(i) DMF, reflux.

Scheme 16

(i) NaOEt, EtOH, room temp.  

Scheme 17
Quinoxalines and related heterocycles are also prepared by various routes which utilize the cyclisation under base-catalysis of 2-nitrobenzene derivatives. One general method (Scheme 14) for the synthesis\textsuperscript{16,17} of the otherwise inaccessible quinoxalin-2(1H)-one 3-N-oxides (43),(44) and (45) is the base-catalysed cyclisation of α-substituted 2-nitroacetanilides (42). These cyclisation reactions proceed in high yield under a variety of basic conditions. Strauss and his co-workers\textsuperscript{18} prepared (Scheme 15) the naphthylacetamidine derivative (47) by reacting 1-methoxy-2,4-dinitronaphthalene (45) with α-phenyl-N,N-dimethylacetamidine (46). On standing for 5 days in methanol the naphthylacetamidine derivative (47) cyclised to give the benzo[\textit{h}]quinoxaline (50) [Scheme 15: (47) $\rightarrow$ (48) $\rightarrow$ (49) $\rightarrow$ (50)] in 71% yield. In a mechanistically similar reaction (Scheme 16) the condensation\textsuperscript{19} of the aminouracil derivative (51) with the chloronitouracil (36) yielded the N-substituted aminouracil (52) which under the reaction conditions cyclised to give the pyrimidopteridine-10-oxide (54) in moderate yield. In a further example of the formation of fused pyrazine ring structures (Scheme 17), pyrimidoacetamidines (56) prepared by the condensation of chloronitropyrimidines (55) with α-phenyl-N,N-dimethylacetamidine (46), are shown to\textsuperscript{20} cyclise on treatment with ethanolic sodium ethoxide to give 4-substituted 7-(N,N-dimethylamino)-6-phenylpteridines (57).

1.1.2 Heterocyclisations Involving N-N Bond Formation

The base-catalysed cyclisation (Scheme 18) of 2-nitrophenyl hydrazine (58) to 1-hydroxybenzo-1,2,3-triazole (62) has been studied by Munson and Hodgkins\textsuperscript{21}. These workers postulate a mechanism for this reaction involving attack of the β-hydrazino nitrogen on the nitro-group
(i) NaOH(aq), room temp.

Scheme 18

(i) HCl, EtOH, reflux.

Scheme 19
(i) NaOH(aq), MeOH or NaOMe, MeOH, reflux.

Scheme 20
nitrogen with elimination of water [Scheme 18; (59) → (60) → (61) → (62)] as the mechanism which best fitted the observed experimental data. Azapurine derivatives can also be synthesised by the intramolecular condensation of a phenylhydrazine substituent with an ortho nitro-group but using acid as opposed to base-catalysis. Thus, treatment\textsuperscript{23} (Scheme 19) of 1-(4-chloro-5-nitropyrimido)-2-phenylhydrazine (63) with ethanolic hydrochloric acid results in an excellent yield of the 8-azapurine N-oxide (64).

The formation of various cinnoline N-oxide derivatives is often easily achieved by the base-catalysed cyclisation of an aromatic nitro-group with an ortho side-chain bearing a suitably positioned amino group. A simple example of this type of reaction is the conversion\textsuperscript{23} (Scheme 20) of various biphenyl derivatives (65) into benzo[c]cinnoline N-oxides (69) in excellent yield. Deprotonation of the amino-group is probably the first step in the reaction mechanism, followed by cyclisation [Scheme 20; (65) → (66) → (67)]. Rearrangement with subsequent loss of hydroxide ion then gives the fully aromatised heterocyclic N-oxide [Scheme 20; (67) → (68) → (69)].

Fused six-membered heterocycles containing three nitrogen atoms are also available via the base-catalysed cyclisation of ortho nitro-benzene derivatives. The treatment (Scheme 21) of 2-nitrophenylguanidine (67) with aqueous sodium hydroxide has been known since 1913\textsuperscript{24} to give high yields of 3-aminobenzo-1,2,4-triazine 1-N-oxide (68). Similarly, 2-nitrophenylurea (69a) and 2-nitrophenylthiourea (69b) cyclise under basic conditions to give the benzotriazinone N-oxide (70a) and benzotriazinethione N-oxide (70b) respectively\textsuperscript{24,25}. Another high yielding example of benzo-1,2,4-triazine formation has been described by Ahmad and Smith\textsuperscript{26}. These workers report
(67) $\xrightarrow{\text{(i)}}$ (68)

(i) 1M NaOH, reflux.

Scheme 21

(69) $\xrightarrow{\text{(i)}}$ (70)

$X$
a; O
b; S

(71) $\xrightarrow{\text{(i)}}$ (72)

(i) KOH(aq), reflux.

Scheme 22

(Ar = Ph, 4-ClC₆H₅, 4-MeC₆H₆)
(R = Me, CH_2Ph, Ph)

(i) NaOEt, EtOH, reflux.

Scheme 23
(Scheme 22) the isolation of 3-arylpiazolo[5,2-c]benzo-1,2,4-triazine 5-N-oxides (72) via the treatment of 5-amino-4-aryl-1-(2-nitrophenyl)pyrazoles (71) with 5% aqueous potassium hydroxide. These cyclisations can be explained in terms of a mechanism analogous to that proposed for the base-catalysed cyclisation of amino-nitробiphenyl derivatives (See Scheme 20).

1.2 Processes Involving the Nucleophilic Displacement of Nitro-groups.

Reactions involving direct displacement of a nitro-group by a nucleophilic centre in an ortho side-chain allow the synthesis of a wide range of heterocyclic molecules. Obviously, the type of bond formed during ring-closure will depend on the character of the nucleophilic centre in the side-chain (i.e. whether a carbon atom or a heteroatom is involved). Thus, examples of such cyclisation reactions involving C-C bond formation will first be discussed and those involving C-heteroatom bond formation will be dealt with subsequently.

1.2.1 Heterocyclisations Involving C-C Bond Formation

In a straightforward example of the base-catalysed displacement of an aromatic nitro-group by an ortho side-chain, Spence and Tennant demonstrated\(^\text{28}\) (Scheme 23) that the N-substituted 2-nitrobenzamides (75) cyclised in ethanolic sodium ethoxide via direct displacement of the aromatic nitro-group \([(75) \to (76) \to (77)]\) to give the 3-oxo-isoindoline-1-carbonitriles (78). Kröhnke and Reuschling have also reported cyclisation reactions involving the intramolecular displacement of aromatic nitro-groups by nucleophilic carbon centres. For example the treatment\(^\text{29}\) (Scheme 24) of N-picrylmethylpyridinium betaines (79) with piperidine in dimethylsulphoxide (DMSO) at room temperature affords benzo[a]indolizines (81) via the
Scheme 24

(i) piperidine, DMSO, room temp.
Scheme 25

(i) CHCl₃, heat.
(ii) MeOH or DMF, reflux.

(i) 10% NaOH, MeOH, heat.

Scheme 26
(R = Me, CF₃, NO₂, CN, F)

(i) DMSO or acetone, 25-100°C
mechanism shown in Scheme 24 [(79) → (80) → (81)]. In an analogous reaction (Scheme 24) under similar conditions the cyclisation of an N-substituted 2-(4-carbomethoxy-2,6-dinitrobenzylidene)quinoline (82) to afford a polycyclic isoquinoline derivative (84) has been achieved.

Pyrazolo[3,4-d]pyrimidines are made available (Scheme 25) via the thermal condensation reactions of 6-chloro-1,3-dimethyl-5-nitouracil (36) with hydrazones (85) in boiling chloroform. The isolable intermediates (86) in these reactions are converted in high yield into pyrazolopyrimidines (87) on warming in various polar solvents.

1.2.2 Heterocyclisations Involving C-Heteroatom Bond Formation.

Access to a number of heterocycles is provided by the intramolecular displacement of an aromatic nitro-group by a nucleophilic heteroatom in an ortho side-chain. For example (Scheme 26) 1-arylindazoles (90) are prepared in quantitative yield by heating dinitrobenzylidene arylhydrazones (88) in 10% methanolic sodium hydroxide.

Rasheed and Warkentin have studied (Scheme 27) the thermal cyclisation of a variety of substituted N,N-dimethyldinitrophenyl dithiocarbamates (91) which results in the formation of nitro-1,3-benzodithiol-2-ones (92) together with the disulphide products (93). The mechanism of such reactions is thought to involve nucleophilic attack by sulphur which displaces the nitro-group [(Scheme 27): (91) → (94)]. The nitrite ion so liberated can then attack the dithiole intermediate (94) and the resultant nitrite ester (95) can subsequently undergo thermal rearrangement to afford the benzodithiolones (92) via intermediates of the type (96).
 Scheme 28

Scheme 29
Scheme 30

(i) DMF.

(ii) PCl₃ - CHCl₃, reflux.

Scheme 31

(i) DMF, reflux.
Evidence for the involvement of the latter is provided by the co-formation in some cases of the disulphide products (93). These could arise from the intermediates (96) by the pathway outlined in Scheme 27 [(96) → (97) → (98) → (99) → (93)].

Martin and his co-workers have investigated the intramolecular displacement of aromatic nitro-groups by oxygen nucleophiles. Reaction (Scheme 28) of the disodium salt of 2-mercaptopyridin-3-ol (101) with 2-chloronitrobenzene derivatives (100) in N,N-dimethylformamide (DMF) followed by cyclisation of the intermediates (102) results in the formation of the corresponding 7-substituted 1-azaphenoxathiins (103). As only the 7-substituted derivatives (103) are isolated, the authors conclude that the Smiles rearrangement [Scheme 28; (102) → (104) → (105) → (106)] which would give the 8-substituted heterocycle (106) does not occur. The preparation (Scheme 29) of a 1-azaphenoxathiin (108) by a virtually identical route using 2,6-dichloronitrobenzene (107) was reported in a later paper by the same author. In a mechanistically similar synthesis Caldwell and Martin have reacted (Scheme 30) 3-chloro-4-nitropyridine N-oxide (109) with the disodium salt of 2-mercaptophenol (110) to afford 2-azaphenoxathiin 2-N-oxide (111), which can be deoxygenated to the parent heterocycle (112) on treatment with phosphorous trichloride. The same workers have also used (Scheme 31) the disodium salt of 2-mercaptopyridin-3-ol (101) and 2-chloro-3-nitropyridine (113) to synthesise 1,9-diazaphenoxathiin (114) in a directly comparable and high-yielding reaction.

The base-catalysed cyclisation of ortho-nitrobenzene derivatives can also be used to synthesise other types of six-membered rings containing two
Scheme 32

(i) NaOH, EtOH, reflux.

Scheme 33

(i) KOH, EtOH, heat.
heteroatoms. This type of reaction is exemplified by the work of Gupta, Ojha and Kumar\textsuperscript{38}. The condensation (Scheme 32) of 3-chloro or 3-methyl-2-aminobenzene thiols (116) with ortho-halonitrobenzenes (115) using ethanolic sodium hydroxide yields biphenyl sulphides (117). The sulphides (117) can then undergo a Smiles rearrangement to give biphenylamines [Scheme 32; (117) $\rightarrow$ (118)] which subsequently react with nucleophilic displacement of the nitro-group to afford substituted 1-nitrophenothiazines (119).

Finally, it is also known that six-membered rings containing three heteroatoms are accessible by the base-catalysed intramolecular displacement of an aromatic nitro-group by an oxygen nucleophile. Thus, treatment (Scheme 33) of the 2,4-dinitrophenylamidoxime (120) with ethanolic potassium hydroxide is reported\textsuperscript{39} to yield the benzoxadiazine (123). The mechanism of this cyclisation is not straightforward in that a spiro Mesienhelmer-type intermediate (121) is thought to be formed under the basic reaction conditions. This intermediate can rearrange to give the 2-nitrophenylamidoxime anion (122) which can then undergo cyclisation with displacement of the ortho-nitro group to give the 3-(4-methylphenyl)-7-nitrobenzoxadiazine (123).
Chapter 2

STUDIES OF BASE-CATALYSED HETEROCYCLISATION REACTIONS
OF N-(2-NITROPHENYL)ACETAMIDINE DERIVATIVES
AND RELATED COMPOUNDS
Scheme 34

(Y = an electron withdrawing group)

(i) base

Scheme 35
Studies of base-catalysed Heterocylisation Reactions

_N-(2-Nitrophenyl)acetamidine Derivatives and Related Compounds_

2.1 Introduction

The objectives of the studies discussed in this chapter were to devise a general strategy for the synthesis of N-oxygenated quinoxaline derivatives and to investigate the reactivity of such molecules. There is current interest in the biological properties of heterocyclic N-oxides and in particular in quinoxaline N-oxides, which are known to be potentially cytotoxic towards hypoxic tumour cells. Hypoxic tumour cells are a major cause of tumour recurrence due to their resistance to the killing effects of X-rays. Compounds (Scheme 34) such as quindoxin (124) are known to be radiation sensitive agents for selectively killing radiation resistant hypoxic tumour cells but are also known to be mutagenic. The quinoxaline N-oxide derivatives (125) and (126) do not, however exhibit mutagenic properties and retain the antimicrobial and potential hypoxic cell killing properties.

Although simple quinoxaline N-oxides may be prepared by peracid oxidation of quinoxalines this method is only applicable to compounds without oxidation sensitive functional groups. Simple oxidation reactions therefore are of no use in the preparation of the most biologically interesting quinoxaline N-oxides i.e. quinoxalinone N-oxides, quinoxalinethione N-oxides and aminoquinoxaline N-oxides. However, a valuable alternative method for a synthesis of quinoxaline N-oxides with oxidation sensitive functional groups which, unlike peracid oxidation, provides unambiguous orientation of the
Scheme 36

Scheme 37
Scheme 38

(i) NaOMe, MeOH, reflux.

Scheme 39

(i) 5-20% KOH(aq), 60-65°.

Scheme 40

(i) diketene, pyridine, 60°.
(ii) 5% NaOH(aq), room temp.
N-oxide group, is the base-catalysed cyclisation (scheme 35) of 2-nitro acetanilide derivatives (127a) to afford quinoxaline-2(1H)-one 4-N-oxides (128a) in high yield. Thus the treatment (scheme 36) of α-cyano-2-nitroacetanilide (129) with boiling ethanolic sodium ethoxide, as described by Tennant44 gives 3-cyanoquinoxalin-2(1H)-one 4-N-oxide (130) in 42-53% yield. Simultaneously with this work Fusco and his co-workers45 described the same cyclisation using aqueous barium hydroxide. Similarly, α-aryl-2-nitro-acetanilides have been cyclised to give quinoxalinones as demonstrated by Ahmad et al46. Thus treatment (scheme 37) with 20% aqueous potassium hydroxide at 100° converts α-phenyl-2-nitroacetanilides (131) into 3-arylquinoxalin-2(1H)-one 4-N-oxides (132) in good yield. Later workers have extended the scope of this type of heterocyclisation reaction. For example te Nijenhuis and his co-workers47 have shown (scheme 38) that when the α-methoxycarbonyl-2-nitroacetanilide (133) is heated under reflux in methanolic sodium methoxide, cyclisation takes place to give the 3-methoxycarbonylquinoxalin-2(1H)-one 4-N-oxide derivative (134). A further variation of this type of reaction (scheme 39) has also been used to prepare quinoxalin-2(1H)-one 4-N-oxides unsubstituted at the 3-position.

4-Substituted α-acyl-ortho-nitoracetanilides [e.g. (135)] undergo cyclisation48 on heating with 5-20% aqueous potassium hydroxide to give the corresponding quinoxalin-2(1H)-one N-oxides [e.g. (136)] in excellent yield. In a later paper44, this synthetic strategy was extended (Scheme 40) to give a tricyclic product (139). Derivatisation of 8-nitro-1,2,3,4-tetrahydroisoquinoline (137) by reaction with diketene gave the N-acetylaceto-derivative (138), cyclisation of which in aqueous sodium hydroxide yielded the pyridoquinoxalin-5(4H)-one 7-N-oxide (139).
(140) + H\text{CH}Na^+ \rightarrow (142)

$N=\overset{\text{X}}{C}=\overset{\text{Y}}{X}
\overset{\text{Z}}{Y}$

(Y, Z = electron-withdrawing groups).

(i) base.

Scheme 41

(145) \rightarrow (146)

(i) R-N=C=O

(ii) XCH$_2$Y, base (X, Y = electron-withdrawing groups).

(iii) base.

Scheme 42
The present studies describe the extension of the general type of cyclisation [Scheme 35, (127) \(\rightarrow\) (128)] to the synthesis of hitherto unknown aminoquinoxaline N-oxides (128b) and quinoxalinethione N-oxides (128c) only one example of which has been reported in the literature to date\(^{45}\). It was decided to obtain the key starting-materials for such cyclisations via the addition reactions of 2-nitrophenyl heterocumulenes (i.e. 2-nitrophenyl carbodiimides and 2-nitrophenyl isothiocyanates) with stabilised carbanions. Such addition reactions are well documented in the literature\(^{50-52}\). Thus the general strategy envisaged (Scheme 41) was firstly reaction of a 2-nitrophenyl heterocumulene (140) with the sodium salt of an active methylene compound (141) to give the corresponding acetamidine (142a), thioacetanilide(142b), or acetanilide (142c) derivatives. Base-catalysed cyclisation of these ortho-substituted nitrobenzene derivatives should then provide a flexible, general route to quinoxaline-2(1H)-imine 4-N-oxides (143a) tautomeric with 2-aminoquinoxaline 4-N-oxides (144), and also quinoxaline-2(1H)-thione 4-N-oxides (143b) and quinoxalin-2(1H)-one 4-N-oxides (143c). The rationale behind this strategy was based on the known propensity of carbodiimides\(^{50}\), isothiocyanates\(^{51}\), and isocyanates\(^{52}\), to undergo addition reactions with stabilised carbanions to afford adducts of the general type (142).

2.2 Novel Base-catalysed Cyclisation Reactions of \(\alpha,\alpha\)-Disubstituted \(N\)-(2-Nitrophenyl)acetamidine Derivatives to 2-Aminoquinoxaline N-oxides

The general strategy (Scheme 42) for the preparation of the \(\alpha,\alpha\)-disubstituted \(N\)-(2-nitrophenyl)acetamidines (147) required for subsequent cyclisation involved the initial synthesis of 2-nitrophenyl carbodiimide derivatives (146). The well known\(^{53}\) reaction of \(N\)-phenyl triphenylphosphinimine with phenyl isocyanate to give \(N,N\)-diphenyl
(149) \[ \text{NH}_2 \quad \text{NO}_2 \]

(i), (ii) \[ \rightarrow \quad \text{N}_3 \quad \text{NO}_2 \]

(150)

(iii) \[ \quad \rightarrow \quad \text{N} = \text{PPh}_3 \quad \text{NO}_2 \]

(152)

(iv) \[ -\text{N}_2 \]

(v) \[ \quad \rightarrow \quad \text{N} = \text{PPh}_3 \quad \text{NO}_2 \]

(vi) \[ \quad \rightarrow \quad \text{N} = \text{PPh}_3 \quad \text{NO}_2 \]

(154)

(151)

(153)

(vii) \[ \quad \rightarrow \quad \text{N} = \text{PPh}_3 \quad \text{NO}_2 \]

(155)

[ A]

(C)

(D)

(E)

(i) NaNO\(_2\), HCl, -10°.

(ii) Na\(_2\)N\(_3\), H\(_2\)O, room temp.

(iii) Ph\(_2\)P, ether, room temp.

(iv) CHCl\(_3\), reflux.

(v) PhN=\text{C}=O, DME, room temp.

(vi) chromatography over SiO\(_2\).

(viii) MeCCH\(_2\)CMe, NaH, DME, room temp.

Scheme 43
carbodiimide prompted the investigation of the analogous synthesis of the required 2-nitrophenyl carbodiimides (146) by reaction of N-2-nitrophenyl triphenylphosphinimines (145) with isocyanates. The synthesis (Scheme 43) of the parent 2-nitrophenyl triphenylphosphinimine (152) was readily accomplished by the literature method as outlined in Scheme 43. Diazotisation of 2-nitroaniline (149) followed by reaction with sodium azide gave 2-nitrophenyl azide (150) which condensed smoothly with triphenylphosphine to give phosphinimine (152). The previously unreported reaction of the phosphinimine (152) with phenyl isocyanate occurred smoothly to give the required 2-nitrophenyl carbodiimide (153). This compound showed the expected i.r. heterocumulene absorption at 2160 cm\(^{-1}\) but due to its ready solvolysis was not characterised directly. Instead chromatography of the crude carbodiimide (153) over silica converted it in high yield (75%) into the urea derivative (154) which analysed correctly and showed spectroscopic properties consistent with the assigned structure.

Initially the reaction (Scheme 43) of the carbodiimide (153) with sodium acetylacetonate was investigated and afforded a moderate yield (42%) of the expected acetamidine derivative (155). This product gave a correct combustion analysis and showed mass and i.r. spectra consistent with the assigned structure (155). However, its \(^1\)H n.m.r. spectrum lacked any obvious absorption due to a CH-substituent but contained signals assignable to an NH and an OH group or to two NH substituents. These features exclude (at least in solution) both of the two simple NH-tautomeric structures (155a) or (155b) in favour of the hydrogen-bond stabilised enol structures (155c) or (155d) or the ene-diamine structure (155e). A specific choice among these structures is not possible on the basis of the available
Scheme 44

(i) Et$_3$N, EtOH, room temp.
(ii) NaOEt, EtOH, reflux.
(iii) KOH or Na$_2$CO$_3$, EtOH, reflux.
(iv) piperidine, EtOH, reflux.
(v) PCl$_3$, CHCl$_3$, reflux.
(vi) P(2EtO)$_3$, reflux.
evidence and purely for convenience this molecule, and closely related
derivatives described later will be formulated as simple NH-tautomeric
structures [ie (155a)].

In further accord with its structure the acetamidine derivative (155)
underwent deacylation (Scheme 44) on treatment with triethylamine to afford
a yellow oil whose combustion analysis and mass spectrum were consistent
with the molecular formula $C_{16}H_{15}N_3O_3$ indicating the loss of one acetyl group
from the starting material (155). In accord with the structure (156), the
product of deacylation showed i.r. NH-absorption at $3320 \text{ cm}^{-1}$ and carbonyl
absorption at $1720 \text{ cm}^{-1}$ and its $^1\text{H n.m.r.}$ spectrum showed signals at $5.27$
and $2.08$ attributable to the protons of a methylene and a methyl group
respectively. The further characterisation of the oily acetamidine (156) by
conversion into an oxime derivative was unsuccessful, this reaction giving
only a series of intractable multicomponent gums. However the gross
structure of the oily acetamidine derivative (156) was verified by its
hydrolysis in ethanolic hydrochloric acid, though in low yield, to
2-nitroaniline.

With the firmly characterised acetamidine derivative (155) readily
available attention was next turned to the investigation of its base-catalysed
cyclisation (Scheme 44). It was anticipated, by analogy with processes
already described in detail in Chapter 1 (see Scheme 1), that this
transformation would lead to the phenylaminoquinazoline N-oxide (159) or
its product of deacetylation (161). In practice, heating the acetamidine
derivative (155) with ethanolic sodium ethoxide afforded a product in high
yield (75%) which analysed correctly and showed spectroscopic properties in
(161) → (164)

(i) $\text{PCl}_3, \text{CHCl}_3, \text{reflux.}$

Scheme 45
accord with its formulation as the previously unknown 3-phenylamino quinoxaline 1-N-oxide (161). Confirmation by its orthodox reduction\textsuperscript{55} to 2-phenylaminoquinoxaline (163) using sodium dithionite or hydrogen in the presence of palladium-on-charcoal, failed, giving either a high recovery of the unreacted starting-material (161) or complex mixtures. Heating with phosphorus trichloride in chloroform is a useful method for the deoxygenation of heterocyclic N-oxides to the parent heterocycles\textsuperscript{56}. However under these conditions the N-oxide (161) underwent both deoxygenation and chlorination at the 3-position giving the known\textsuperscript{57} 3-chloro-2-phenylamino quinoxaline (162) albeit only in low yield. This product had a melting point somewhat lower than that described in the literature\textsuperscript{57} but otherwise showed analytical and spectroscopic properties which fully confirmed its assigned structure. The formation of the chlorinated quinoxaline (162) from the quinoxaline N-oxide (161) can be readily explained by the course outlined in Scheme 45 involving nucleophilic attack by chloride ion at the 3-position of an initially formed phosphorus complex (164) followed by rearomatisation of the latter by expulsion of the nitrogen-bound phosphorus residue [(165) → (162)]. Triethyl phosphite\textsuperscript{58} is also a widely used reagent for the deoxygenation of the heterocyclic N-oxides and in the present studies was found to smoothly convert the quinoxaline N-oxide (161) in high yield (70%) into 2-phenylaminoquinoxaline (163). This is a known compound\textsuperscript{59,60} and although the literature melting point\textsuperscript{60} was somewhat higher than that found in the present work, the compound gave a combustion analysis and showed i.r. and \textsuperscript{1}H n.m.r. absorption fully consistent with its formulation as the phenylaminoquinoxaline (163). The formation of this compound by triethyl phosphite deoxygenation of the N-oxide (161) provides confirmatory proof for the structure of the latter.
The cyclisation of the acetamidine (155) to the quinoxaline \(N\)-oxide (161) was found to be accomplished in even higher yield (99%) using ethanolic potassium hydroxide as the basic catalyst. This reaction and that involving ethanolic sodium ethoxide as the basic catalyst can be explained by a course (Scheme 44) involving initial aldol-type condensation between the nitro-group and the carbanion centre in the ortho-amidine side-chain in (155) to afford after aromatisation by deacetylation of the resulting intermediate (158), 2-acetyl-3-phenylaminoquinoxaline \(1-N\)-oxide (159). This compound is presumably unstable under the reaction conditions and suffers further deacetylation to give the quinoxaline \(N\)-oxide end-product (161). It is also possible that deacetylation of the acetamidine derivative (155) occurs prior to cyclisation giving the compound (156) which can in turn undergo aldol-type cyclisation to (159) followed by deacetylation as before to give the \(N\)-oxide (161). It has already been shown (see before) that treatment with triethylamine effects the conversion of the diacetyl compound (155) into the monoacetyl derivative (156) and this compound was found to undergo sodium-ethoxide catalysed cyclisation to 3-phenylaminoquinoxaline \(1-N\)-oxide (161) in good yield (68%).

In the cyclisation reactions of the amidine derivatives (155) and (156) catalysed by ethanolic sodium ethoxide or potassium hydroxide there was no evidence for the formation of 2-acetyl-3-phenylaminoquinoxaline \(1-N\)-oxide (159) proposed as intermediate. On the assumption that this compound was not surviving the strongly basic conditions involved, the behaviour of the amidine derivative (155) toward milder basic catalysts was investigated in the hope of achieving its cyclisation to 2-acetyl-3-phenylaminoquinoxaline \(1-N\)-oxide (159) without further deacetylation.
Scheme 46

(i) RCCH₂CPh, NaH, DME, room temp.

(ii) RCCH₂CO₂Et, NaH, DME, room temp.

(iii) NaOEt or KOH, EtOH, reflux.
However heating the acetamidine derivative (155) with aqueous ethanolic sodium carbonate again afforded only the N-oxide (161) though in low yield (46%) together with a complex gum which yielded no identifiable material. In contrast warming the acetamidine derivative (155) with piperidine in ethanol gave a low yield (34%) of a product which analysed correctly and showed mass, i.r., and $^1$H n.m.r. spectra consistent with the quinoxaline structure (160). The isolation of this product can be explained (Scheme 44) in terms of the formation and in situ reduction of 2-acetyl-3-phenylamino quinoxaline 1-N-oxide (159) in the ethanolic alkaline medium. Such media are known to promote the reduction of heterocyclic N-oxides to the parent heterocycle but it is surprising that analogous reduction is not observed in the cyclisation reactions catalysed by ethanolic sodium ethoxide or potassium hydroxide.

Further attempts to achieve the cyclisation of the amidine derivative (155) to the acetylquinoxaline N-oxide (159) without further deacetylation to the N-oxide (161) were made by heating with the hindered bases 1,5-diazabicyclo(4,3,0)non-5-ene (DBN) and 1,8-diaza bicyclo(5,4,0)undec-7-ene (DBU) in ethanol. However, both of these reactions led to complex mixtures which yielded no identifiable material.

The base-catalysed cyclisation reactions (Scheme 44) of the acetamidine derivatives (155) and (156) represent viable methods for the synthesis of the aminoquinoxaline N-oxide (161). It was therefore decided to attempt to extend the strategy represented in Schemes 43 and 44 to the synthesis of otherwise inaccessible 3-aminoquinoxaline 1-N-oxide derivatives in general. To this end (Scheme 46) the addition reactions of the
carbodiimide (153) with the carbanions derived from benzoylacetonate and
dibenzoylmethane were investigated in the expectation of obtaining the
acetamidine derivatives (166a and b) which it was hoped would undergo
base-catalysed cyclisation with retention of the relatively inert benzoyl
substituent thus providing two alternative routes to the usefully
functionalised 2-benzoyl-3-phenylaminoquinoxaline 1-N-oxide (168). In
practice reaction of the carbodiimide (153) with sodium benzoylacetonate
afforded a low yield (33%) of a product which analysed correctly and showed
mass and i.r. spectra consistent with the expected acetamidine structure
(166a). However, as in the case of the diacetyl compound (155), the 1H
n.m.r. spectrum of the acetamidine derived from benzoylacetonate showed no
absorption due to a CH-proton but contained two exchangeable signals
assignable to an OH and an NH or two NH groups. These features are
consistent with the existence of the molecule, at least in solution, as an enol
or ene-diamine structure akin to (155c,d, or e) (see Scheme 43) rather than
the simple amidine structure (166a). In contrast to the successful reaction
of sodium benzoylacetonate with the carbodiimide (153) the attempted
reaction of the latter with the sodium salt of dibenzoylmethane gave only a
complex mixture with no evidence for the formation of the expected
acetamidine derivative (166b). As in the case of the diacetyl derivative (155),
heating the acetamidine (166a) with potassium hydroxide in ethanol resulted
in its smooth cyclisation to 3-phenylaminoquinoxaline 1-N-oxide (161) in
high yield (96%). There was no evidence for the formation of 2-benzoyl-3-
phenylaminoquinoxaline 1-N-oxide (168) in this reaction though this
compound is a plausible intermediate.

The carbodiimide (153) also reacted readily (Scheme 46) with the
sodium salts of ethyl acetoacetate, ethyl benzoylacetate, or diethyl malonate
giving good yields (59-67%) of the expected acetamidine derivatives (167 a-c).
All of these compounds analysed correctly and showed mass and i.r. spectra
consistent with their assigned structures. However, though they are
formulated for convenience as simple acetamidine derivatives (162a-c), their
'H n.m.r. absorption is, as in the case of the diacetyl derivative (155) (see
Scheme 43 before), more in accord with enol or ene-diamine structures (see
155c, d or e).

Heating with sodium ethoxide or potassium hydroxide in ethanol
promoted the smooth cyclisation of the acetamidine esters (167 a-c) to the
quinoxaline carboxylic acid N-oxide (169) in moderate to good yield (58-70%),
together with its product of decarboxylation, 3-phenylaminoquinoxaline 1-N-oxide (161). Though relatively unstable to crystallisation due to its ready
decarboxylation, the previously unknown carboxylic acid (169) was readily
purified by flash-chromatography and gave analytical and mass spectra data,
as well as i.r. and 'H n.m.r. spectra in support of its assigned structure.
Formation of the carboxylic acid (169) from the acetamidine derivatives
(167a-c) can be explained by base-catalysed, aldol-type, cyclisation processes
akin to that already discussed in the case of the diacetyl derivative (155)
(see Scheme 44). The initial product in all three cases is presumably the
quinoxaline ester N-oxide (169; CO₂Et for CO₂H) which then undergoes in
situ hydrolysis under the alkaline reaction conditions to afford the observed
carboxylic acid product (169).

With a view to further extending the novel base-catalysed
cyclisation reactions of N-(2-nitrophenyl)acetamidine derivatives to otherwise
(153) \[ \text{N} = \text{C} = \text{NPh} \]

(170) \[ \text{O} \quad \text{CN} \quad \text{CH}_2 \]

(171) \[ \text{N} = \text{C} = \text{NPh} \]

(i) \[ \text{NaH, DME, room temp.} \]

(ii), (iii) or (iv) \[ (\text{ii}), (\text{iii}) \text{ or (iv) } \]

(172) \[ \text{H} \quad \text{N} < \text{NPh} \quad \text{CN} \quad \text{C} = \text{C} = \text{N} \quad \text{R} \]

(173) \[ \text{H} \quad \text{N} = \text{C} = \text{NPh} \quad \text{CN} \quad \text{C} = \text{C} = \text{N} \quad \text{R} \]

R

a; \text{Ph}
b; \text{OEt}

(174)

(175)

(iii) \[ \text{NaOEt, EtOH, reflux.} \]

(iv) \[ \text{Na}_2 \text{CO}_3, \text{reflux.} \]

Scheme 47
inaccessible 3-aminoquinoxaline 1-N-oxide derivatives attention was next turned to the study (Scheme 47) of the base-catalysed cyclisation of substrates containing cyano-substituents. The cyanoacetamidine derivatives (171 a and b) were readily synthesised in yields of 33% and 75% respectively by reaction of the carbodilimide (153) with the sodium salts of benzoylacetonitrile (170a) and ethyl cyanoacetate (170b). The analytical and spectroscopic properties of the cyanoacetamidine derivatives (171a and b) were fully in accord with their assigned structures.

It was anticipated (Scheme 47) that the base-catalysed cyclisation of the cyanoacetamidines (171a and b) would lead by preferential loss of the benzoyl and ethoxycarbonyl substituents respectively, to the same product, namely 2-cyano-3-phenylaminoquinoxaline 1-N-oxide (174). This compound has not been described in the literature to date and by analogy with structurally related 3-cyanoquinoxalin-2(1H)-one 4-N-oxides it was possible that under the basic conditions of cyclisation it might react further with loss of cyano-group giving the novel cyclic hydroxamic acid (176) as the end-product. In practice, the cyano-benzoyl derivative (171a) was recovered unchanged in high yield (80%) after heating under reflux with potassium hydroxide in ethanol for 6h. The cyano-ester (171b) showed a similar inertness to attempted base-catalysed cyclisation. Thus heating with ethanolic potassium hydroxide afforded a gum whose t.l.c. showed only the presence of the unreacted starting-material (171b) together with some 2-nitroaniline presumably formed by hydrolysis of the amidine side-chain in (171b). Heating the cyano-ester (171b) under reflux with sodium ethoxide in ethanol was no more successful, the starting-material (171b) being recovered unchanged in essentially quantitative yield. The attempted base-catalysed
(i) NaH, DME, room temp.
(ii) KOH, EtOH, reflux.
(iii) MeCCl, Et3N, DMF, room temp.
(iv) Na2S2O4, DMF, H2O, reflux

Scheme 48
(i) NaOH, MeOH, heat.

Scheme 49
cyclisation of the cyano-ester (171b) by heating under reflux with sodium carbonate in aqueous ethanol likewise gave only a high recovery (77%) of the unreacted starting-material (171b). The reluctance of the cyanoacetamidine derivatives (171a and b) to undergo base-catalysed cyclisation to the cyanoquinoxaline N-oxide (174) contrasts markedly with the case of corresponding base-catalysed cyclisation reactions of the acetamidines (155), (166a), and (167a-c). The inertness of the cyanoacetamidines (171a and b) to base-catalysed cyclisation is particularly surprising in view of the ready base-catalysed cyclisation of structurally related nitro-cyanoacetanilide derivatives to cyanoquinoxalinone N-oxides (see Scheme 36). Enhanced stability of the derived carbanion intermediates due to resonance of the type [Scheme 47: (172) \leftrightarrow (173)] provides a possible, though not particularly convincing, explanation for the reluctance of the cyanoacetamidine derivatives (171a and b) to undergo base-catalysed cyclisation.

In a further effort to extend the scope of the conversion of appropriate N-(2-nitrophenyl) acetamidine derivatives into aminoquinoxaline N-oxides it was next decided to investigate (Scheme 48) the possible base-catalysed cyclisation of the N-(2-nitrophenyl)acetamidine derivative (178) containing a benzenesulphonyl moiety. This compound was chosen in the expectation that its base-catalysed cyclisation would lead to the usefully functionalised benzenesulphonylquinoxaline N-oxide (179) or to the cyclic hydroxamic acid (176) derived by \textit{in situ} nucleophilic displacement of the benzenesulphonyl substituent in (179) by hydroxide ion [(179) \rightarrow (175) \rightarrow (176)]. Analogous nucleophilic displacement of a benzenesulphonyl substituent occurs in the course (Scheme 49) of the sodium hydroxide catalysed conversion of 2-(benzenesulphonylmethyl)-2'-nitrobiphenyl (182) in
methanol into the $N$-hydroxyphenanthridinone (187) described by Muth and his co-workers.$^{62}$

The benzenesulphonylacetamidine (178) was readily synthesised in good yield (66%) by reaction of the carbodiimide (153) with the sodium salt of benzensulphonylacetone (177) under standard conditions and showed analytical and spectroscopic properties which fully support its assigned structure. Heating the benzenesulphonylacetamidine derivative (178) under reflux with potassium hydroxide in ethanol converted it in good yield (75%) into product which gave a combustion analysis and showed a parent ion in its mass spectrum corresponding to the molecular formula $C_{14}H_{11}N_3O_2$. The formulation of this product as the expected cyclic hydroxamic acid (176) follows from its i.r. and $^1$H n.m.r. absorption and its chemical transformations (Scheme 48). In particular the product's i.r. spectrum showed absorption at 3200-2500 and 1640 cm$^{-1}$ assignable to the hydroxyl and carbonyl substitutents of the potentially tautomeric hydroxamic acid structure [(175)-(176)]. In addition its $^1$H n.m.r. spectrum showed two exchangeable one-proton singlets attributable to the NH and OH protons of the structure (176). This structure was conclusively established by the conversion of the compound into a monoacetyl derivative (180) which exhibited i.r. carbonyl absorption at 1800 cm$^{-1}$ characteristic of a cyclic $N$-acetoxy substituent. Further support for the structures of the cyclic hydroxamic acid (176) and its $N$-acetoxy derivative (180) was provided by the reduction of the latter to the known$^{63}$ quinoxalinone derivative (181). The $N$-acetoxyquinoxalinone (180) was unexpectedly stable to hydrogenolysis over palladium-on-charcoal, but was readily reduced by heating with sodium dithionite in aqueous DMF to give 3-phenylaminoquinoxalin-2(1H)-one (181)
(i) NaH, DME, room temp.

Scheme 50
identical in all respects with an authentic sample.

The efficient transformation of the benzenesulphonylacetamidine (178) into the N-hydroquinoxalinone derivative (176) represents an interesting and useful variant of what, from the present studies, appears to be a general tendency for nitrobenzene derivatives with ortho-acetamidine side-chains containing a potential carbanion centre, to undergo base-catalysed cyclisation to otherwise difficultly accessible aminoquinoxaline N-oxide derivatives. In order to get some idea of the level of carbanion stability necessary for successful cyclisation it was decided to investigate the synthesis (Scheme 50) and base-catalysed cyclisation of the phenyl-substituted acetamidine derivative (189) in which stabilisation of the derived side-chain carbanion should be substantially diminished compared with for example the diacetyl compound (155) (see Scheme 43 before). Unexpectedly however the reaction of the carbodiimide (153) with the sodium salt of benzyl methyl ketone (188) under standard conditions yielded none of the expected acetamidine derivative (189) but instead gave a product in low yield (30%) whose analytical and spectroscopic properties show it to be the aminoquinoxaline N-oxide derivative (190). Formation of this product is presumably the result of the spontaneous cyclisation of the initially produced acetamidine derivative (189) under the conditions of its formation from the carbodiimide (153) and the sodium salt of benzyl methyl ketone. At no time was spontaneous cyclisation of the acetamidines (155), (166a), (167a-c), or (178) observed under the conditions of their preparation. The spontaneous nature of the cyclisation [(189) → (190)] irrespective of its relative inefficiency appears to indicate the facilitating effect of a phenyl substituent on the base-catalysed cyclisation of N-(2-nitrophenyl)acetamidine
(i) Ph-CN=NC=O, DME, room temp.
(ii) Me₃SiN=NC=O, DME reflux.
(iii) CH₃CCH₂CCH₃, NaH, DME room temp.
(iv) base.

Scheme 51
derivatives to the corresponding aminoquinoloxaline N-oxides. However, further studies will be needed to establish the generality of this observation.

Since up to this point the study of the base-catalysed cyclisation of N-(2-nitrophenyl)acetamidine derivatives to aminoquinoloxaline N-oxides had for convenience been confined to substrates derived from the readily available 1-(2-nitrophenyl)-3-phenylcarbodiimide (153), it was next decided to expand these investigations to include 2-nitrophenylacetamidines other than N-phenyl derivatives. Of particular Interest (Scheme 51) were N-(2-nitrophenyl)acetamidine derivatives such as (192) containing a readily removable substituent. Successful base-catalysed cyclisation of such molecules would provide a viable route to quinoloxaline N-oxides containing primary amino substituents [e.g. (192) → (194) → (196)]. Unfortunately this strategy was thwarted either by the difficulty of obtaining the required carbodiimide intermediates [e.g. (191a)] or by the instability of the N-substituted acetamidine under the conditions of its formation [e.g. (192)]. Thus, the attempted reaction of N-(2-nitrophenyl) triphenylphosphinimine (152) with trimethylsilyl isocyanate in DME under prolonged reflux afforded only a high recovery (81%) of the unreacted phosphinimine (152). On the other hand reaction of the phosphinimine (152) with benzoyl isocyanate at room temperature in DME followed by immediate treatment with a DME solution of sodium acetylacetonate afforded after workup a low yield (32%) of a product which analysed correctly and showed spectroscopic properties consistent with its formulation as the acetanilide derivative (195). The structure of this compound also follows from its formation by the reaction of 2-nitrophenylisocyanate with sodium acetylacetonate as discussed later. The formation of the acetanilide derivative (195) in the reaction of the
Scheme 52

(i) Ac$_2$O, heat.
(i) Ph-N=C=O, solvent, heat.

Scheme 53
phosphinimine (152) with benzoyl isocyanate followed by sodium acetylacetone is most probably due to subsequent hydrolysis of the initially formed acetamidine derivative (192) reacting in its alternative imine tautomeric form (193).

2.3 Studies of the Reactivity of 3-Phenylaminoquinoxaline 1-N oxide (161) towards Acylating Agents.

Heterocyclic N-oxides lacking substituents α to the N-oxide group are well known to undergo novel rearrangements on reaction with a wide variety of acylating agents. A classic example (Scheme 52) of such a process is the rearrangement of pyridine N-oxide (196) on heating with acetic anhydride to afford, after hydrolytic workup, pyridin-2(1H)-one (201). This interesting transformation is believed to occur by the course shown in Scheme 52. Since the previously unreported 3-phenylaminoquinoxaline 1-N-oxide (161) had become readily available in the course of the present studies it was considered of interest to investigate the behaviour of this α-unsubstituted N-oxide towards acylating agents.

In practice heating the aminoquinoxaline N-oxide (161) with acetic anhydride or acetyl chloride in acetic acid gave only complex mixtures from which no identifiable material could be obtained. However more success was achieved using phenyl isocyanate as the acylating agent. The behaviour of the N-oxide (161) towards this reagent was of particular interest since two distinct modes of reaction were possible (Schemes 53 and 54). Analogy with quinoxalin-2-(1H)-one 4-N-oxide (202), which reacts with phenyl isocyanate by cycloaddition followed by retro-cycloaddition giving 3-phenylaminoquinoxalin-2(1H)-one (181) as the end-product, would predict the
(i) R\textsubscript{NCO}, DMF, reflux.

(ii) H\textsubscript{2}N\textsubscript{C}NH\textsubscript{2}, DMF, reflux.

Scheme 54
course [Scheme 53; (161) → (204) → (205) → (207)]. On the other hand, studies by Iijima would indicate alternative reaction (Scheme 54) by simple addition of phenyl isocyanate at the phenylamino-group giving an adduct of the type (208a). The latter might then undergo cyclisation by intramolecular nucleophilic attack by the terminal amino-substituent of the urea side-chain, α to the N-oxide group giving the imidazoquinazoline (211) as the ultimate product. In practice the latter course was followed. Thus heating the aminoquinazoline N-oxide (161) with phenyl isocyanate in dimethylformamide gave in addition to unreacted starting-material (42%), a low yield (6%) of a product which analysed for C₂₁H₁₄N₄O and showed a parent ion at m/z 338 consistent with its formulation as the known imidazoquinazoline derivative (211a). In further support of this structure the product showed i.r. carbonyl absorption at 1740 cm⁻¹ attributable to the presence of a fused N,N-disubstituted imidazolone nucleus. However the melting point (181-182°) of the compound (211a) obtained in the present studies differed markedly from that (275-276°) reported by Iijima for the same compound obtained by another route. Since the evidence in support of the imidazoquinazoline structure (211a) for the product of the reaction of the aminoquinazoline N-oxide (161) with phenyl isocyanate is unambiguous, the melting point discrepancy appears to cast doubt on the structure of the product reported by Iijima.

The aminoquinazoline N-oxide (161) also reacted with methyl isocyanate in DMF under reflux giving a low yield (33%) of a product formulated on the basis of its analytical and spectroscopic properties as the previously unknown imidazoquinazoline derivative (211b). Formation of this product can be explained by a process (Scheme 54) akin to that proposed
(i) RNCS, DMF, reflux.
(ii) $\text{H}_2\text{NCONH}_2$, DMF, reflux.

Scheme 55
for the di-N-phenyl derivative (211a) [ie (161) \(\rightarrow\) (208b) \(\rightarrow\) (209b) \(\rightarrow\) (210b) \(\rightarrow\) (211b)]. This course for formation of the imidazoquinoxalinone derivatives (211a and b) is supported by the isolation of the parent imidazoquinoxalinone derivative (211c) in moderate yield (55%) when the aminoquinoxaline N-oxide (161) was heated with urea in DMF. This transformation is best rationalised in terms of the intermediate formation and subsequent cyclisation of the urea derivative (208c).

The cyclisation of urea derivatives (208 a-c) by intramolecular nucleophilic attack by the urea side-chain \(\alpha\) to the N-oxide group proposed as a key step in the formation of the imidazoquinoxalinone derivatives (211a-c) from the aminoquinoxaline N-oxide (161) implies that the latter might be susceptible to nucleophilic attack by amines at the 2-position. However the attempted reaction of the N-oxide (161) with aniline by heating under reflux in DMF gave only a multicomponent gum which yielded no identifiable material. This result suggests that nucleophilic attack \(\alpha\) to the N-oxide substituent in the quinoxaline derivative (161) occurs best when intramolecular.

The reactions of the aminoquinoxaline N-oxide (161) with phenyl isothiocyanate, methyl isothiocyanate, and thiourea were also investigated in the expectation that a similar course to the reactions with phenyl isocyanate, methyl isocyanate, and urea would be followed giving the corresponding imidazoquinoxalinethiones (211a-c; S for O) as end-products. However this was not the case (Scheme 55). In complete contrast to the reactions with phenyl isocyanate, methyl isocyanate, and urea, there was no evidence for imidazoquinoxalinethione formation when the aminoquinoxaline
N-oxide (161) was heated with phenyl isothiocyanate, methyl isothiocyanate, or thiourea in DMF. Instead, all three reactions afforded a mixture of the same two products one of which (yield 6-35%) contained sulphur and the other (yield 10-29%) was sulphur-free. The sulphur-containing compound gave a combustion analysis and showed a parent ion in its mass spectrum at m/z 253 consistent with the molecular formula C_{14}H_{11}N_{3}S. This evidence in conjunction with its i.r. and ^1H n.m.r. absorption allow the formulation of the sulphur-containing compound as the previously unknown quinoxaline derivative 3-phenylaminoquinoxaline-2(1H)-thione (219). The sulphur-free product was found to be identical in all respects to an authentic sample of 2-phenylaminoquinoxaline (163) already encountered as a reduction product of the aminoquinoxaline N-oxide (161) (see Scheme 44).

The reaction of the 3-phenylaminoquinoxaline 1-N-oxide with the reagents phenyl isothiocyanate, methyl isothiocyanate, and thiourea to give in each case the quinoxalinethione (219) can be rationalised by the course outlined in Scheme 55. Initial formation of the thiourea derivatives (212) is followed by cyclisation, but involving nucleophilic attack by sulphur rather than nitrogen \( \alpha \) to the N-oxide substituent, giving after dehydration the fused imino-thiazoles (215). Subsequent hydrolytic ring-opening of the latter and further hydrolysis by the water produced in the step \([214] \rightarrow [215]\) then accounts for the isolation of the tautomeric quinoxalinethione \([218] \rightarrow [219]\). The formation of 2-phenylaminoquinoxaline (163) in the reactions of phenyl isothiocyanate, methyl isothiocyanate, or thiourea with the aminoquinoxaline N-oxide (161) is most probably the result of the simple reduction of the latter by any one of the various sulphur species [e.g. \(218 \rightarrow 219\)] present in the reaction mixtures.
(i) NH$_2$CN, DMF, reflux.

Scheme 56
In view of the susceptibility of the aminoquinoxaline N-oxide (161) to react with urea and thiourea via presumed adducts of the types (208c) and (212c) it was of interest to know if a related process (Scheme 56) would take place with cyanamide and lead ultimately to the formation of the aminoimidazoquinoxaline derivative (224). In practice, heating the aminoquinoxaline N-oxide (161) with cyanamide in DMF afforded only a good recovery (68%) of the unreacted starting-material, together with intractable gums, with no evidence for the formation of the imidazoquinoxaline derivative (224).

### 2.1 Novel Base-catalysed Cyclisation Reactions of α,α-Disubstituted 2-Nitrophenylthioacetanilide Derivatives to N-oxygenated Quinoxaline-2(1H)-thiones

As already described in Section 2.2 N-(2-nitrophenyl)acetamidine derivatives containing an active methine centre in the ortho-acetamidine side-chain are readily accessible by conjugate addition of stabilised carbanions to 1-(2-nitrophenyl)-3-phenylcarbodiimide, and undergo base-catalysed cyclisation to provide a moderately general route to otherwise inaccessible 3-aminoquinoxaline N-oxide derivatives. In view of these results it was of interest to investigate the analogous conjugate addition reactions (Scheme 57) of 2-nitrophenyl isothiocyanate (225) and the behaviour of the resulting α,α-disubstituted 2-nitrophenylacetanilide derivatives [e.g. (226)] towards base-catalysed cyclisation. Processes of these types have not previously been described in the literature and would provide a useful route to otherwise inaccessible N-oxygenated quinoxaline-2(1H)-thione derivatives [e.g. (231)], only one example of which has been reported\(^{45}\) to date.
(i) CS₂, toluene, 80.
(ii) Cl₂C=S, CHCl₃, reflux.
(iii) RCCH₂CR, NaH, DME, room temp.
(iv) KOH, EtOH, reflux.

Scheme 57
2-Nitrophenyl isothiocyanate (225) is readily accessible\(^6\) by reaction (Scheme 57) of 2-nitroaniline (149) with thiophosgene. However in the present studies it was initially decided to evaluate an alternative route (Scheme 57) to 2-nitrophenyl isothiocyanate (225) avoiding the use of the noxious thiophosgene. This was based on the known\(^6\) reaction of N-phenyl triphenylphosphinimine with carbon disulphide to give phenyl isothiocyanate. Unfortunately the analogous reaction of the N-(2-nitrophenyl)triphenyl phosphinimine (152) with carbon disulphide in toluene at 80\(^\circ\) was unsuccessful, the starting-material (152) being recovered in high yield (100\%) with no evidence for the formation of the required isothiocyanate (225). However, the reaction of 2-nitroaniline (149) with thiophosgene in chloroform under reflux essentially as described by Ulrich et al\(^6\) gave the required 2-nitrophenyl isothiocyanate (225) in substantially greater yield (82\%) than that (21\%) reported in the literature\(^6\).

2-Nitrophenyl isothiocyanate (225) reacted as expected with sodium acetylacetonate in DME at room temperature (Scheme 57) to give an excellent yield (92\%) of a product which analysed correctly and gave mass and i.r. spectra in accord with the thioacetanilide structure (226a). However, its 1H n.m.r. spectrum in deuteriochloroform lacked any obvious signal due to a methine (CH) proton but contained two broad, exchangeable, one-proton singlets attributable to the protons of NH, OH, or SH substituents. It is therefore probable that in solution at least, the molecule exists as a thioenol tautomer (227a) (or an alternative enol structure). However, for simplicity the product of the reaction of 2-nitrophenyl isothiocyanate (225) and sodium acetylacetonate and related compounds discussed later will be referred to as N-(2-nitrophenyl)-thioacetamide.
(i) Na$_2$S$_2$O$_4$, EtOH(aq) or DMF(aq) or AcOH, reflux.
(ii) MeI, NaH, DMF, room temp.

Scheme 58
derivatives (226).

In an analogous fashion to the \(\alpha,\alpha\)-disubstituted 2-(2-nitrophenyl)acetamidine (155) (see Scheme 44), and also structurally related 2-nitrophenylacetanilide derivatives\(^{16}\), heating the thioacetanilide derivative (226a) with potassium hydroxide in ethanol resulted in its conversion in high yield (89\%) into a product whose melting-point agreed closely with that reported\(^{45}\) for quinoxaline-2(1H)-thione 4-N-oxide (231). This structure for the product of the base-catalysed cyclisation of the 2-nitrothioacetanilide derivative (226a) was firmly established by its analytical and mass, i.r., and \(^1\)H n.m.r. spectral properties, and its simple chemical transformations (Scheme 58). Thus it was readily reduced, though in low yield, by heating with sodium dithionite in glacial acetic acid or in aqueous DMF to give the known\(^{25,70}\) compound quinoxaline-2(1H)-thione (232). The melting-point of this compound obtained in the present studies closely agreed with the literature value\(^{25}\) and its structure was verified by its combustion analysis and mass, i.r. and \(^1\)H n.m.r. spectra. The sodium hydride catalysed reaction of the quinoxaline-thione N-oxide (231) with methyl iodide in DMF afforded a good yield (64\%) of a monomethyl derivative whose analytical and spectroscopic properties were consistent with its identity as 3-methyl thioquinoxaline 1-N-oxide (233). This formulation rather than the alternative N-methyl structure (231; Me for H) was firmly established by the dithionite reduction of the compound in moderate yield (43\%) to the known\(^{71}\) 2-methyl thioquinoxaline (235). The product derived by reduction of the N-oxide (233) gave a combustion analysis and showed mass, i.r., and \(^1\)H n.m.r. spectra consistent with the structure (235). Moreover its melting-point (41-42\°) agreed closely with that (46\°) reported\(^{71}\) for 2-methylthioquinoxaline (235) but
differed markedly from that (123-125°) recorded\textsuperscript{71} for 1-methylquinoxaline-2(1H)-thione (234).

The formation of the quinoxalinethione N-oxide (231) from the 2-nitrothioacetanilide derivative (226a) can be explained by a course [Scheme 57; (226a) → (228a) → (229a) → (230a) → (231)] analogous to that proposed for the formation of the aminoquinoxaline N-oxide (161) from the N-(2-nitrophenyl)acetamidine derivative (155) (see Scheme 44). This course infers the intermediate formation and \textit{in situ} deacetylation of 3-acetyl quinoxaline-2(1H)-thione 4-N-oxide (230a) none of which could be detected in the reaction mixture from the base-catalysed cyclisation of the 2-nitrothioacetanilide derivative (226a). With the intention of obtaining evidence for the intermediacy of 2-acylquinoxaline-2(1H)-thione 4-N-oxide derivatives in this type of cyclisation it was decided to synthesise the dibenzoyl 2-nitrothioacetanilide and investigate its base-catalysed cyclisation. It was reasoned in this case that the benzoyl substituent being less prone to solvolytic removal than an acetyl group would allow the isolation of 2-benzoyl quinoxaline-2(1H)-thione 4-N-oxide (230b) as the end-product of cyclisation.

2-Nitrophenyl isothiocyanate (225) reacted with the sodium salt of dibenzoylmethane in DME at room temperature to give, in addition to unreacted 2-nitrophenyl isothiocyanate (225) (35%), a low yield (41%) of a product which analysed correctly and gave mass and i.r. spectra consistent with the expected 2-nitrophenylthioacetanilide structure (226b). As in the case of the diacetyl compound (226a), the dibenzoyl derivative (226b) showed \textsuperscript{1}H n.m.r. absorption in deuteriochloroform more in accord with a thioenol structure (227b) (or a tautomerically related enol structure) than the
(i) RCH₂CO₂Et, NaH, DME, room temp.
(ii) KOH, EtOH, reflux.

Scheme 59
thioacetanilide structure (226b). However, on heating with potassium hydroxide in ethanol, the compound was converted in essentially quantitative yield into quinoxaline-2(1H)-thione 4-N-oxide (231) identical in all respects to the sample obtained from the 2-nitrothioacetanilide derivative (226a) as described before. There was no evidence for the formation of the initially expected 3-benzoylquinoxaline-2(1H)-thione 4-N-oxide (230b) in this reaction, demonstrating the ready debenzoylation of this compound under the reaction conditions. In support of the intermediate formation and in situ debenzoylation of the benzoylquinoxalinethione N-oxide (230b), benzoic acid was isolated in quantitative yield as a by-product of the reaction.

Because of the failure of the diacyl 2-nitrothioacetanilide derivatives (226a and b) to undergo base-catalysed cyclisation to isolable 3-acyl quinoxalinethione 4-N-oxides (230a and b), it was of interest to investigate the related cyclisation reactions (Scheme 59) of the ester derivatives (236a and b). By analogy with the structurally related acetamidine derivatives (167a and c) (see Scheme 46) it was anticipated that base-catalysed cyclisation of the esters (236a and b) would afford the relatively stable N-oxygenated quinoxalinethione ester or carboxylic acid derivatives (237a or b). In practice (Scheme 59), 2-nitrophenyl isothiocyanate (225) reacted smoothly with the sodium salts of ethyl acetoacetate and diethyl malonate in DME to afford high yields (93% and 71% respectively) of the expected 2-nitrothioacetanilide derivatives (236a) and (236b), the former as a colourless crystalline solid and the latter as a yellow oil. Both 2-nitrothioacetanilide derivatives (236a and b) gave analytical and mass spectral data and i.r. absorption consistent with their assigned structures. As in the cases of the diacyl compounds (226a and b) (see Scheme 57), the $^1$H n.m.r. spectra
of the esters (236a and b) in deuteriochloroform suggested their existence in thioenol (or enol) tautomeric forms akin to (227a and b).

Disappointingly the attempted cyclisation of the keto-ester (236a) by heating with potassium hydroxide in ethanol afforded only low yields of an orange solid which decomposed on attempted purification, and a red gum which yielded no identifiable material. In contrast, the analogous base-catalysed cyclisation of the diester (236b) resulted in the unexpected formation in good yield (59%) of the N-hydroxyquinoxalinethione derivative (240) which was identical in all respects to a sample prepared by an alternative route as discussed later. The mode of formation of the cyclic hydroxamic acid derivative (240) by base-catalysed transformation of the 2-nitrothioacetanilide derivative (236b) is not clear but may involve initial cyclisation (Scheme 59) to give the N-oxygenated quinoxalinethione ester (237a) and then by hydrolysis the acid (237b). Nucleophilic attack by hydroxide ion at the highly electrophilic 2-position in the acid (237b) followed by decarboxylation of the resulting adduct (238) and final in situ oxidation of the decarboxylated intermediate (239) would then account for the formation of the observed product (239). A similar oxidative step has been proposed to account for the conversion of the quinoxalinone N-oxide (231; O for S, Me for H) in warm aqueous ethanolic potassium hydroxide into the N-hydroxyquinoxalinedione (240; O for S, Me for H). An alternative course for the transformation [(236b) → (240)] would involve the formation and decarboxylation of the acid (237b) to give quinoxaline-2(1H)-thione 4-N-oxide (231) followed by reaction of the latter at the 2-position with hydroxide ion to give the adduct (239) then in situ oxidation of the latter as before. However this course for the formation of the cyclic hydroxamic acid (240)
(i) NaH, DME, room temp.
(ii) KOH, EtOH, reflux.

Scheme 60
from the 2-nitrothioacetanilide derivative (236b) is excluded by the inertness of quinoxaline-2(1H)-thione 4-N-oxide (231) to alkaline conditions as discussed later.

In a further attempt to achieve the base-catalysed conversion of an \( \alpha,\alpha \)-disubstituted 2-nitrothioacetanilide derivative into a 3-substituted quinoxaline-2(1H)-thione 4-N-oxide attention was next turned to the investigation of the synthesis and base-catalysed reaction (Scheme 60) of the cyano-amide (242). It was hoped that the base-catalysed cyclisation of the latter would proceed with loss of the cyano substituent \(^4\) to afford 3-carbamoylquinoxaline-2(1H)-thione 4-N-oxide (245) which might be stable to further hydrolysis under the reaction conditions. The reaction of 2-nitrophenyl isothiocyanate (225) with the sodium salt of cyanoacetamide (241) in DME at room temperature proceeded as expected to afford the required 2-nitrothioacetanilide derivative (242) in good yield (60%). The analytical and spectroscopic properties of the 2-nitrothioacetanilide derivative (242) were fully in accord with its assigned structure. However the compound was surprisingly inert to base-catalysed cyclisation, being recovered unchanged in high yield (91%) after heating under reflux with potassium hydroxide in ethanol. The reluctance of the cyano-amide (242) to undergo base-catalysed cyclisation resembles that of the cyano-substituted \( N \)-(2-nitrophenyl)acetamidine derivatives (173a and b) (see Scheme 47) and may be due to enhanced resonance stabilisation of the presumed carbanion intermediate \([242] \rightarrow [244]\) as argued for the compounds (173a and b) before (see Scheme 47).

As already discussed in section 2.2 (see Scheme
(225) + (177) \rightarrow (246)

(i) NaH, DME, room temp.
(ii) KOH, EtOH, reflux.
(iii) MeCCl, Et₃N, DMF, room temp.

(iv) PhNCO, DMF, room temp.
(v) Na₂S₂O₄, DMF(aq), reflux.

Scheme 61
the base-catalysed cyclisation of the acetyl-benzenesulphonyl-substituted $N$-(2-nitrophenyl)acetamidine derivative (178) occurs with ultimate nucleophilic displacement of the benzenesulphonyl substituent thus providing a useful route to 1-hydroxy-3-phenylamino-quinoxalin-2(1$H$)-one (176). It was therefore of interest to know (Scheme 61) if the corresponding acetyl-benzenesulphonyl functionalised 2-nitrothioacetanilide derivative (246) would undergo analogous base-catalysed cyclisation with loss of benzenesulphonyl moiety to afford the previously undescribed $N$-hydroxy quinoxalinone-thione (240). The required acetyl-benzenesulphonyl 2-nitrophenylthioacetanilide derivative (246) was readily prepared in high yield (81%) by the conjugate addition of the sodium salt of benzenesulphonylacetone (177) to 2-nitrophenyl isothiocyanate (225). The 2-nitrophenylthioacetanilide derivative (246) analysed correctly and gave mass and i.r. spectra consistent with its assigned structure. However its $^1$H n.m.r. spectrum in deuteriochloroform unlike those of the structurally related 2-nitrophenylthioacetanilide derivatives (226a and b) contained only one broad signal due to the proton of an NH or SH group and a one proton singlet at $\delta_1$ 5.94 attributable to a CH group, suggesting that the molecule exists in the thione form (246) (or possibly the related thiol structure).

Heating with potassium hydroxide in ethanol converted the 2-nitrophenylthioacetanilide derivative (246) in moderate yield (55%) into a product which analysed correctly and showed mass, i.r. and $^1$H n.m.r. spectra in accord with its formulation as the $N$-hydroxyquinoxalinone-thione structure (240). However attempts to firmly establish this structure by chemical transformation were unsuccessful (Scheme 61). Thus, unlike the amino-$N$-hydroxyquinoxalinone derivative (176) (see Scheme 48), reaction with acetyl chloride in the presence of triethylamine afforded only an intractable brown
Scheme 62

(i) Ac₂O, reflux.
gum with no evidence for the formation of the expected N-acetoxy derivative (249a). The attempted acylation of the N-hydroxyquinoxaline-thione (240) with phenyl isocyanate in DMF at room temperature to afford the urethane derivative (249b) was also unsuccessful giving only the starting-material (240) and diphenylurea. The attempted reduction of the N-hydroxy compound (240) to the quinoxaline-thione (250) by heating with sodium dithionite in aqueous DMF also failed, only a small amount of an intractable gum being obtained.

2.5 Studies of the Chemical Reactivity of Quinoxaline-2(1H)-thione 4-N-oxide (231) and 3-Methylthioquinoxaline 1-N-oxide (233).

Quinoxaline-2(1H)-thione 4-N-oxide (231) and 3-methylthioquinoxaline 1-N-oxide (233) are examples of heterocyclic N-oxides lacking a substituent α to the N-oxide function and by analogy with the structurally related compound quinoxalin-2(1H)-one 4-N-oxide (202) should exhibit enhanced reactivity at the 3-position towards both acylating agents and nucleophilic reagents. Since the N-oxides (231) and (233) had been made readily available by the syntheses developed in the present studies it was decided for comparison with the quinoxaline N-oxide (202) to investigate their previously undescribed behaviour towards acylation and nucleophilic substitution.

By analogy with pyridine N-oxide (196) (see Scheme 52) reaction of quinoxaline-2(1H)-thione 4-N-oxide (231) was initially expected to afford (Scheme 62) the quinoxaline-thione (250). In practice, heating the N-oxide (231) under reflux with acetic anhydride afforded a single product in high yield (72%) which analysed correctly for C_{16}H_{16}N_{4}S_{2} and showed a parent ion
Figure 1
Table 1. Bond Lengths (Å) with Standard Deviations

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<th>Bond</th>
<th>Length (Å)</th>
<th>Standard Deviation</th>
</tr>
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<tbody>
<tr>
<td>S(13) - C(13a)</td>
<td>1.732(11)</td>
<td>0.011</td>
</tr>
<tr>
<td>S(13) - C(5a')</td>
<td>1.769(11)</td>
<td>0.011</td>
</tr>
<tr>
<td>N(14) - C(4a)</td>
<td>1.362(11)</td>
<td>0.011</td>
</tr>
<tr>
<td>N(5) - C(5a)</td>
<td>1.270(14)</td>
<td>0.014</td>
</tr>
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Table 2. Angles (degrees) and Torsion Angles with Standard Deviations

<table>
<thead>
<tr>
<th>Angle</th>
<th>Value</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(13a)-S(13)-C(5a')</td>
<td>108.4(5)</td>
<td>0.05</td>
</tr>
<tr>
<td>C(4a)-N(5)-C(5a)</td>
<td>118.2(9)</td>
<td>0.09</td>
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<tr>
<td>C(13a)-N(14)-C(14a)</td>
<td>119.9(8)</td>
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</tr>
<tr>
<td>S(13)-C(13a)-N(14)</td>
<td>114.3(8)</td>
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</tr>
<tr>
<td>S(13)-C(13a)-C(5a')</td>
<td>127.7(8)</td>
<td>0.08</td>
</tr>
<tr>
<td>N(14)-C(13a)-C(5a)</td>
<td>117.9(9)</td>
<td>0.09</td>
</tr>
<tr>
<td>N(5)-C(4a)-C(4)</td>
<td>119.0(7)</td>
<td>0.07</td>
</tr>
<tr>
<td>C(5a')-S(13)-C(13a)-N(14)</td>
<td>-178.8(8)</td>
<td>0.08</td>
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<tr>
<td>C(5a')-S(13)-C(13a)-C(5a)</td>
<td>-1.4(11)</td>
<td>0.05</td>
</tr>
<tr>
<td>C(13a)-S(13)-C(13a)-N(14)</td>
<td>178.9(8)</td>
<td>0.08</td>
</tr>
<tr>
<td>C(5a)-N(5)-C(4a)-C(4a)</td>
<td>1.4(10)</td>
<td>0.06</td>
</tr>
<tr>
<td>C(5a)-N(5)-C(5a)-C(13a)</td>
<td>-0.6(12)</td>
<td>0.06</td>
</tr>
<tr>
<td>C(4a)-N(5)-C(5a)-C(13a)</td>
<td>0.6(15)</td>
<td>0.06</td>
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<tr>
<td>C(4a)-N(5)-C(5a)-S(13')</td>
<td>-179.9(7)</td>
<td>0.08</td>
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<tr>
<td>C(14a)-N(14)-C(13a)-S(13)</td>
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<td>C(14a)-N(14)-C(13a)-C(5a)</td>
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<td>0.06</td>
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<tr>
<td>C(11a)-S(13')-C(5a)-C(13a)</td>
<td>-1.4(10)</td>
<td>0.06</td>
</tr>
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</table>

Primed atoms are related to their unprimed equivalents by inversion through (0,0,1/2).
at m/z 320 in its mass spectrum consistent with this molecular formula. The i.r. spectrum of the compound lacked any significant absorption $> 1500 \text{ cm}^{-1}$ and its $1\text{H}$ n.m.r. spectrum showed absorption due only to aromatic protons. These features together with the product's high melting-point ($>358^\circ$) indicated it to have a highly condensed structure. The formulation of the product of the reaction of the N-oxide (231) with acetic anhydride as the known $^{79}$ dithilno-diquinoxaline (253) is consistent with the high melting-point ($>360^\circ$) reported $^{79}$ for this compound and was firmly established by X-ray analysis (see Figure 1). The formation of the pentacyclic product (252) from the N-oxide (231) in hot acetic anhydride can be explained (Scheme 62) by initial activation of (231) by conversion into an N-acetoxyquinoxalinium salt (251). Self-condensation of two molecules of the latter by mutual nucleophilic attack by sulphur at the 3-position followed by expulsion of two molecules of acetic acid then accounts for the observed product [Scheme 62; (251) + (251) → (252) → (253)]. In contrast to the N-oxide (231) (Scheme 62), 3-methylthioquinoxaline 1-N-oxide (233) reacted in orthodox fashion $^{66}$ on heating with acetic anhydride giving a low yield (37%) of a product whose analytical and spectroscopic properties are consistent with those expected for the previously undescribed compound 3-methylthioquinoxalin-2(1H)-one (254).

As already discussed (see Scheme 53), quinoxalin-2(1H)-one 4-N-oxide (202) reacts with phenyl isocyanate by initial formation of a cycloadduct (203) which undergoes spontaneous decarboxylative fragmentation affording 3-phenylaminoquinoxalin-2(1H)-one (181) as the end-product. $^{66}$ It was therefore of interest to know if quinoxaline-2(1H)-thione 4-N-oxide (231) would react analogously with phenyl isocyanate (Scheme 63).
Scheme 63

(i) Ph-N=C=O, DMF, reflux.
(ii) Ph-N=C=O, toluene, reflux.
giving 3-phenylaminoquinoxalin-2(1H)-thione (219). In fact heating quinoxaline-2(1H)-thione 4-N-oxide (231) with phenyl isocyanate in DMF gave a readily separated mixture of two products in very low yield which were identified by comparison with authentic samples as the dithiino-
diquinoxaline (253) and the aminoquinoxalinethione (219). The latter compound had already been encountered (see Scheme 55) as a product of the reaction of 3-phenylaminoquinoxaline 1-N-oxide (161) with phenyl isothiocyanate, methyl isothiocyanate, or thiourea and its formation in the reaction of quinoxaline-2(1H)-thione 4-N-oxide (231) with phenyl isocyanate can be rationalised by the course outlined in Scheme 63. The formation of the dithiino-diquinoxaline (253) in the reaction of the N-oxide (231) with phenyl isocyanate is also readily explained by a process similar to that outlined in Scheme 62 for the formation of the dithiino-diquinoxaline (253) when the N-oxide (231) reacts with acetic anhydride.

The very low yield (3%) of the aminoquinoxalinethione (219) formed in the reaction of the N-oxide (231) with phenyl isocyanate contrasts with the excellent yield (99%) of 3-phenylaminoquinoxalin-2(1H)-one (181) obtained in the corresponding reaction of the quinoxalinone N-oxide (202) (see Scheme 53 before). The contrasting efficiencies of the N-oxides (202) and (231) towards reaction with phenyl isocyanate indicates the much greater electrophilic reactivity of the 2-position in the former compared with the latter. The reaction (Scheme 63) of 3-methylthioquinoxaline 1-N-oxide (233) with phenyl isocyanate in DMF under reflux afforded only intractable gums with no evidence for the formation of 2-methylthio-3-
phenylaminoquinoxaline (256) expected by analogy with the reaction of the quinoxalinethione N-oxide (231) with phenyl isocyanate to give the
(i) KCN, H₂O, 100.
(ii) MeI, NaH, DMF, room temp.

Scheme 64
aminoquinoxalinethione (219). This result is not surprisingly in view of the expected lower electrophilic reactivity of the 2-position in the methylthio compound (233) compared with that in the thione (231).

Quinoxalin-2(1H)-one 4-N-oxide (202) exhibits enhanced reactivity towards substitution at the electron-deficient 2-position by nucleophilic reagents such as cyanide ion and stabilised carbanions.\textsuperscript{72} It was therefore of interest to know if the structurally related quinoxaline-2(1H)-thione 4-N-oxide (231) as well as the methylthioquinoxaline N-oxide (233) would show a similar tendency to undergo nucleophilic attack at the 2-position. In practice (Scheme 64), the quinoxalinethione N-oxide (231) reacted readily on warming with aqueous potassium cyanide to afford a high yield (81%) of a product which analysed correctly and showed i.r. cyano absorption at 2240 cm\textsuperscript{-1} thus allowing its formulation as the cyanoquinoxalinethione (258). This structure was further confirmed by the conversion of the compound in high yield (87%) into the S-methyl derivative (259). The assignment of the latter structure rather than the alternative N-methyl structure (260) to this product is based on the analogous S-methylation of the quinoxalinethione N-oxide (231) to the methylthioquinoxaline N-oxide (233) (see before) and on the close similarity in chemical shift of the \textsuperscript{1}H n.m.r. signals of the methyl protons in both compounds (259) and (233). The formation of the cyanoquinoxalinethione (258) from the quinoxalinethione N-oxide (231) can be explained by a course (Scheme 64) analogous to that proposed\textsuperscript{72} for the similar transformation of quinoxalin-2(1H)-one 4-N-oxide (202) into 3-cyanoquinoxalin-2(1H)-one (258; O for S).

In accord with its anticipated lower reactivity towards nucleophilic
(i) KCN, H₂O, 100°.
(ii) KCN, EtOH, H₂O, reflux.

Scheme 65
attack at the 2-position, the methylthioquinoxaline N-oxide (233) reacted much less readily than the quinoxalinethione N-oxide (231) with cyanide ion (Scheme 65). The methylthioquinoxaline N-oxide (233) was largely recovered unchanged (yield 92%) after heating at 100° with aqueous potassium cyanide. Also isolated in low yield from this reaction was a product identical in all respects to an authentic sample of 3-methylthioquinoxaline-2(1H)-one (254) obtained previously (see Scheme 62).

The isolation of this product is most readily explained (Scheme 65) in terms of the initial formation of the expected nitrile (259) and its subsequent further reaction by nucleophilic displacements as observed in the case of 3-cyanoquinoxalin-2(1H)-one derivatives. Formation of the methylthioquinoxaline derivative (254) by direct nucleophilic attack at the 2-position in the N-oxide (233) by hydroxide ion is unlikely and is excluded by the lack of formation of (254) when the N-oxide (233) is heated under reflux with aqueous ethanolic potassium hydroxide. Quinoxaline-2(1H)-thione 4-N-oxide (231) shows a similar lack of reactivity towards nucleophilic attack at the 2-position by both hydroxide ion and ethoxide ion, being recovered unchanged in high yield (90%) after heating under reflux with either aqueous ethanolic sodium hydroxide or ethanolic sodium ethoxide. However, heating the methylthioquinoxaline N-oxide (233) under reflux with aqueous ethanolic potassium cyanide converted it in high yield (84%) into the amide (262). The analytical and spectroscopic properties of this compound were fully in accord with its assigned structure. The isolation of the amide (262) in the reaction of the N-oxide (233) with cyanide ion provides strong evidence for the intermediacy of 2-cyano-3-methylthioquinoxaline (259) in this transformation. The reason for the differing modes of reaction of 3-methylthioquinoxaline 1-N-oxide (233) with cyanide ion under purely
Scheme 66

(i) CO₂, toluene, heat
(ii) NaN₃, acetone, H₂O, 0, then heat.
(iii) RCH₂CMe, NaH, DME, room temp.
(iv) KOH, EtOH, reflux.
aqueous as opposed to aqueous ethanolic conditions, is not clear.

Unlike its ready reaction with cyanide ion, the quinoxalinethione N-oxide (231) was inert to nucleophilic attack by primary amines. Thus it was recovered unchanged in quantitative yield after heating under reflux with benzylamine in ethanol. In addition the reactivity of the N-oxide (231) towards nucleophilic attack by stabilised carbanions did not parallel that observed with quinoxalin-2(1H)-one 4-N-oxide (202). Thus, heating the N-oxide (231) with acetylacetone in ethanol in the presence of piperidine gave only an intractable gum together with a low recovery (28%) of unreacted starting material (231). The attempted reaction of the N-oxide (231) with sodium acetylacetonate in DMF under reflux was no more successful these conditions leading only to a low yield of an intractable gum. The application of the latter conditions to the methylthioquinoxaline N-oxide (233) produced the same result.

2.6 Studies of the Synthesis and Base-catalysed Cyclisation Reactions of \(\alpha,\alpha\)-Disubstituted 2-Nitroacetanilide Derivatives

Studies under this heading were prompted by the successful syntheses and base-catalysed cyclisation reactions of \(\alpha,\alpha\)-disubstituted \(N\)-(2-nitrophenyl) acetamidines and \(\alpha,\alpha\)-disubstituted 2-nitrophenyl thioacetanilide derivatives already discussed in sections 2.2 and 2.4. The formation of \(N\)-oxygenated quinoxalinones by the base-catalysed cyclisation of \(\alpha\)-substituted 2-nitrophenylacetanilides is already well documented in the literature (see Section 2.1). However it was decided in the course of the present studies to evaluate the base-catalysed cyclisation reactions of \(\alpha,\alpha\)-disubstituted 2-nitroacetanilides, potentially generally accessible (Scheme 66).
by the conjugate addition of stabilised carbanions to 2-nitrophenyl isocyanate (264), as alternative flexible methods for the synthesis of N-oxygenated quinoxalinone derivatives.

The most convenient literature method\textsuperscript{74} for the preparation of 2-nitrophenyl isocyanate (264) involves the reaction of 2-nitrobenzoyl chloride (263) with sodium azide in aqueous acetone, followed by the thermal Curtius rearrangement of the resulting 2-nitrobenzoyl azide (263; N\textsubscript{3} for Cl). Because of the potentially hazardous nature of the stage of this procedure it was decide to evaluate a safer route (Scheme 66) involving the carboxylation of the readily available N-(2-nitrophenyl) triphenylphosphinimine (152) (see before). The reaction of N-phenyl triphenylphosphinimine with carbon dioxide to give phenyl isocyanate has been reported in the literature.\textsuperscript{69} However in the present studies it was found that N-(2-nitrophenyl) triphenylphosphinimine (152) failed to react with carbon dioxide in refluxing toluene being recovered unchanged in essentially quantitative yield. This result and the related lack of reactivity of N-(2-nitrophenyl) triphenylphosphinimine (152) towards carbon disulphide (see Scheme 57) contrast with the ready reaction with carbon dioxide and carbon disulphide reported\textsuperscript{69} for the parent compound N-phenyl triphenylphosphinimine. The lack of reactivity of N-(2-nitrophenyl) triphenylphosphinimine (152) towards carbon dioxide and carbon disulphide can therefore be attributed to a reduction in the nucleophilic character of the imine nitrogen atom due to electron-withdrawal by the ortho nitro-group. The development of a safer route having been unsuccessful, 2-nitrophenyl isocyanate (264) was prepared in high yield (84\%) from 2-nitrobenzoyl chloride (263) and sodium azide as described in the literature.\textsuperscript{74}
2-Nitrophenyl isocyanate (264) reacted smoothly with sodium acetonylacetonate in DME at room temperature to afford a high yield (84%) of a product identical in all respects to a sample of the diacetyl 2-nitroacetanilide derivative (265a) obtained from the 2-nitrophenyl carbodiimide (153) as described before (see Scheme 51). Disappointingly, the attempted base-catalysed cyclisation of the diacetyl 2-nitroacetanilide derivative (265a) by heating with potassium hydroxide in ethanol, gave none of the 2-acetyquinoxalinone N-oxide (266) expected as product, but instead a moderate yield (50%) of the known\textsuperscript{16} quinoxalinone N-oxide (202). This product was identified by comparison with an authentic sample\textsuperscript{16} and presumably results from the 2-nitroacetanilide derivative (265a) by initial base-catalysed cyclisation to the 2-acetyquinoxalinone N-oxide (266) and spontaneous deacetylation of the latter under the reaction conditions.

Having demonstrated the base-catalysed cyclisation of the diacetyl 2-nitroacetanilide (265a) to the quinoxalinone N-oxide (202) but having failed to isolate the primary acetyquinoxalinone N-oxide cyclisation product (266) attention was next turned to the synthesis (Scheme 66) of the ester derivative (265b). It was hoped that base-catalysed cyclisation of this substrate would yield the quinoxalinone ester N-oxide (268) or the corresponding acid. The required 2-nitrophenylacetanilide derivative (265b) was readily obtained in good yield (60%) by conjugate addition of the sodium salt of ethyl acetoacetate to 2-nitrophenyl isocyanate (264) under standard conditions. The compound (265b) gave a combustion analysis and mass, i.r. and \textsuperscript{1}H n.m.r. spectra entirely consistent with the assigned structure. However its attempted cyclisation by heating with potassium hydroxide in ethanol under reflux resulted in hydrolytic cleavage to 2-nitroaniline in low
yield (34%) with no evidence for the formation of the quinoxalinone N-oxide (268) or the derived acid.

In a final attempt to achieve the efficient base-catalysed transformation of an α,α-disubstituted 2-nitroacetanilide derivative into an N-oxygenated quinoxalinone the α-acetyl α-benzenesulphonyl 2-nitroacetanilide (265c) was synthesised (Scheme 66) and its behaviour towards base-catalysed cyclisation studied. By analogy with the structurally related acetamidine derivative (178) (see Scheme 48), cyclisation of the benzenesulphonyl 2-nitroacetanilide (265c) was expected to lead (Scheme 66) through the intermediacy of the 2-benzenesulphonylquinoxalinone N-oxide (267) to the known 16 N-hydroxyquinoxalinedione (269). The acetyl benzenesulphonyl 2-nitroacetanilide (265c) was obtained in excellent yield (98%) by the reaction of the sodium salt of benzenesulphonylacetone with 2-nitrophenyl isocyanate (264) in DME at room temperature and showed analytical and spectroscopic properties in accord with its structure. Again however the attempted cyclisation of the 2-nitroacetanilide derivative (265c) by heating with ethanolic potassium hydroxide gave only a complex mixture containing 2-nitroaniline with no evidence for the formation of the expected N-hydroxyquinoxalinedione derivative (269). The investigation of the synthesis and base-catalysed cyclisation of α,α-disubstituted 2-nitroacetanilide derivatives was terminated at this point.
2.7 Experimental

General Experimental Details

Infrared spectra were recorded for Nujol suspensions or thin films using a Perkin-Elmer 781 spectrophotometer. I.r. bands were strong and sharp unless specified as w (weak), br (broad) or vs (very strong).

1H and 13C N.m.r. spectra were measured in the stated solvent at 80 MHz or 200 MHz using Bruker WP-80SY and WP-200SY spectrometers. Signals were sharp singlets unless specified as br (broad); d = doublet; dd = double doublet; t = triplet; q = quartet; m = multiplet.

Mass spectral and accurate mass data were obtained using A.E.I. MS-902 and Kratos MS-50TC instruments. Fast atom bombardment (FAB) mass spectra were measured for matrices in glycerol.

Microanalyses were determined on a Carlo-Erba Strumentazione Elemental Analyser MOD 1106. Melting points (m.p.) of all analytical samples were determined on a Kofler hot-stage and are uncorrected.

All organic extracts were dried over anhydrous magnesium sulphate prior to evaporation under reduced pressure. Solvents were of technical grade unless otherwise specified and unless otherwise indicated light petroleum had b.p. 60 - 80°
Wet column flash-chromotography was carried out over silica (Merck grade 60, type 9385) and dry-column flash-chromotography was carried out over t.l.c. grade silica. (Merck grade 60, type 7736). T.l.c. was carried out using Polygram SIL G/UV_254 precoated plastic sheets.

For X-ray analyses compounds were crystallised from DMF-toluene or light petroleum-toluene to give diffraction quality crystals. X-ray diffraction data were collected on a Stoe Stadi-4 four circle diffractometer.

N-(2-Nitrophenyl) Triphenylphosphinimine (152)

N-(2-Nitrophenyl) triphenylphosphinimine (152) was prepared by the reaction of 2-nitrophenyl azide (150) with triphenylphosphine as described by Cadogan and his co-workers^54 yield 78%, m.p. 144 - 146° (lit.,54 141-142°) and was used without further purification.

1-(2-Nitrophenyl)-3-phenylurea (154)

Solutions of the phosphinimine (152) (1.5g, 0.004 mol) in anhydrous toluene (40.0 ml) and phenyl isocyanate (0.48g, 0.004 mol) in anhydrous toluene (5.0 ml) were mixed and the mixture was stirred at room temperature for 4h. The mixture was evaporated to give an orange semi-solid (2.0 g) which was triturated with ether to afford triphenylphosphine oxide, (0.70g; 63%), m.p. 156-158° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethereal mother liquor gave an orange oil (1.0 g) whose i.r. spectrum showed it to be largely 1-(2-nitrophenyl)-3-phenyl carbodiimide (153). ð_max 2160 vs (N=C=N) cm^-1.
Flash chromatography of the oil over silica eluting with methylene chloride-ethyl acetate (10:1) gave \(1\text{-}(2\text{-nitrophenyl})\text{-3-phenylurea} (154)\), (0.77g; 75%) which formed light yellow needles, m.p. 167 - 168° (from light petroleum - toluene) (lit., \(75\) 174-175°), \(\delta_{\text{max}}\) 3320 and 3280 (NH), 1650 (CO), and 1540 and 1340 (NO\(_2\)) cm\(^{-1}\).

**Found:** C, 60.5; H, 4.2; N, 16.1%; M, 257.

**Calc. for C\(_{15}\)H\(_{11}\)N\(_2\)O:** C, 60.7; H, 4.3; N, 16.3% M, 257.

**Benzoylacetonitrile (170a)**

Benzoylacetonitrile (170a) was prepared by the reaction of 2-bromoacetophenone with potassium cyanide as described by Obriega\(^76\), yield 83%, and had m.p. 75-78° (lit., \(76\) 80-81°).

**Benzenesulphonylacetonitrile (177)**

Benzenesulphonylacetonitrile (177) was prepared by the reaction of chloroacetone with sodium benzenesulphinate as described by Troger and Hille\(^77\), yield 86%, and had m.p. 55-58° (lit., \(77\) 55-58°).

**Reactions of 1-(2-Nitrophenyl)-3-phenylcarbodiimide (153) with Active Methylene compounds**

**(a) 1-(2-Nitrophenyl)-3-phenylcarbodiimide (153)**

Solutions of the phosphinimine (152), (4.0 g, 0.01 mol) in anhydrous 1,2-dimethoxyethane (DME) (10.0 ml) and phenyl isocyanate (1.2 g, 0.01 mol) in anhydrous DME (5.0 ml) were mixed and the mixture was stirred at room temperature for 4h. The mixture was evaporated to give an orange semi-solid (5.9 g) which on trituration with anhydrous ether gave triphenylphosphine oxide (2.2 g; 79%), m.p. 151-155°, identified by
comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethereal mother liquor gave crude 1-(2-nitrophenyl)-3-phenylcarbodiimide (153) as an orange oil (3.2 g), $\delta_{\text{max}}$ 2160 (vs, N=C=N) cm$^{-1}$, containing a small amount of triphenylphosphine oxide (i.r. evidence). The crude product (153) was dissolved in anhydrous DME (20.0 ml) and the solution was reacted with active methylene compounds as described in (b) below.

(b) Reactions of 1-(2-nitrophenyl)-3-phenylcarbodiimide (153) with active methylene compounds.

A solution of the active methylene compound (0.011 mol) in anhydrous DME (100 ml) was mixed with a stirred suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous DME (10.0 ml) and after hydrogen evolution had ceased (5-10 min) the mixture was treated with stirring at room temperature with the solution of crude 1-(2-nitrophenyl)-3-phenyl carbodiimide (153) (3.2 g) in anhydrous DME (20.0 ml) prepared as described in (a) before. The mixture was stirred for 2-4 h at room temperature then worked up as described for the individual reactions below.

(i) The reaction mixture from acteylacetonone was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown oil. Trituration of the brown oil with ether afforded 3-[1-(2-nitrophenyl)-3-phenylformamidinyl]pentane-2,4-dione (155) (42%) as a yellow solid m.p. 119-120° (from light petroleum-toluene), $\delta_{\text{max}}$ 3200-2500 br (OH, NH), 1600 br (CO), and 1530 and 1340 (NO$_2$) cm$^{-1}$, $\delta_H$ 13.07 (1H, s, OH or NH) (exch.).
7.80 (1 H, dd, J0.7Hz and 1.5 Hz, H-3), 7.25-6.71 (9H, m, ArH and NH) and 2.49 (6H, s, CH₃).

Found: C, 63.8; H, 5.1; N, 12.3%; M⁺, 339.

C₁₈H₁₄N₂ requires: C, 63.7; H, 5.0; N, 12.4%; M, 339.

Evaporation of the ethereal mother liquor gave a brown oil whose t.l.c. in methylene chloride over silica showed it to contain at least five components. The oil was flash-chromatographed over silica.

Elution with methylene chloride-n-hexane (3:1) gave a multicomponent red oil (t.l.c in methylene chloride over silica) which was not further investigated.

Further elution with methylene chloride gave an oil which was triturated with ether to afford a second crop of 3-[1-(2-nitrophenyl)]-3-phenylformamidinylpentane-2,4-dione (155), (7%), m.p. 119-120° identified by comparison (m.p. and i.r. spectrum) with the sample obtained before.

Final elution with ethyl acetate through to ethanol gave only intractable gums which were not further investigated.

(ii) The reaction mixture from benzoylacetone was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown oil which was triturated with light petroleum-ether to afford 2-[1-(2-nitrophenyl)]-3-phenylformamidinyl-1-phenylbutane-1,3-dione (166a), (33%) as a yellow solid m.p. 154-156° (from toluene-light petroleum), θ_max 3200 -
2500 br (OH, NH), 1600 br (CO), and 1520 and 1345 (NO₂) cm⁻¹, δH (CDCl₃) 12.78 (1H, bs, NH or OH) (exch.), 12.52 (1H, bs, NH or OH) (exch.), 7.85-7.68 (3H, m, ArH), 7.54 - 7.33 (3H, m, ArH), 7.24 - 6.79 (8H, m, ArH) and 1.88 (3H, s, CH₃).

**Found:**

C₇nH₈N₂O₄ requires:

C, 68.8; H, 4.7; N, 10.5%; M⁺, 401.

The light petroleum-ether mother liquor was evaporated to give an orange oil which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to ethanol gave only a series of gums whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

(iii) The reaction mixture from dibenzoylmethane was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown gum which was flash chromatographed over silica.

Elution with methylene chloride gave as the first fraction an orange gum whose i.r. spectrum and t.l.c. in methylene chloride over silica showed it to be a mixture consisting mainly of dibenzoylmethane. The gum was not further investigated.

Further elution with methylene chloride followed by methylene chloride-ethyl acetate (1:1) gave a series of multicomponent oils which
yielded no identifiable material apart from triphenylphosphine oxide which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(iv) The reaction mixture from ethyl acetoacetate was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give an orange gum. Trituration of the gum with ether afforded ethyl 2-[1-(2-nitrophenyl)-3-phenylformamidinyl]-3-oxobutanoate (167a) as a yellow solid (64%) m.p. 156-158° (from light petroleum -toluene), \( \delta_{\text{max}} 3110 \) (w, \( \text{NH} \)), 1650 (CO) and 1520 and 1340 (NO\(_2\)) cm\(^{-1}\). \( \delta_{\text{H}}(\text{CDCl}_3) 14.0 - 12.0 \) (2H, bs, NH, OH), 7.77 (1H, d, J10Hz, H-3), 7.14 - 6.76 (8H, m, ArH), 4.32 (2H, q, J7Hz, CH\(_2\)), 2.50 (3H, s, CH\(_3\)) and (3H, t, J7Hz, CH\(_3\)).

Found: C, 62.1; H, 5.3; N, 11.3%; M, 369.  
C\(_{16}\)H\(_{16}\)N\(_2\)O\(_5\) requires: C, 61.8; H, 5.2; N, 11.4%; M, 369

Evaporation of the ethereal mother liquor gave a red oil flash-chromatography of which over silica eluting with methylene chloride through ethyl acetate to ethanol gave only a series of intractable oils.

(v) The reaction mixture from ethyl benzoylacetate was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a yellow semi-solid. This was triturated with ether to afford ethyl 2-[1-(2-nitrophenyl)-3-phenylformamidinyl]-3-phenyl-3-oxopropanoate (167b) (67%) as a yellow solid, m.p. 184-186° (from light petroleum-toluene), \( \delta_{\text{max}} 3200 \) (NH), 1670 and 1630 (CO), and 1520 and 1310 (NO\(_2\)) cm\(^{-1}\).
δ<sub>H</sub>(CDCl<sub>3</sub>) 12.64 (1H, bs, NH or OH) (exch.), 11.68 (1H, bs, NH or OH) (exch.), 7.89 - 6.79 (14H, m, ArH), 3.86 (2H, q, J7Hz, CH<sub>2</sub>) and 0.68 (3H, t, J7Hz, CH<sub>3</sub>).

Found: C, 67.2; H, 5.0; N, 9.5%; M*, 431.

C<sub>9</sub>H<sub>11</sub>N,O<sub>2</sub>, requires: C, 66.8; H, 4.9; N, 9.7%; M, 431.

The ethereal mother liquor was evaporated to give a red oil whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(vi) The reaction mixture from diethyl malonate was evaporated and the residue was treated with water (40.0 ml), and the solution acidified with glacial acetic acid and extracted with methylene chloride to give an orange semi-solid. This was triturated with ether to afford diethyl 2-[1-[2-nitrophenyl]-3-phenylformimidinyl]-1,3-propanedioate (167c) (59%) which formed yellow needles, m.p. 122 -123° (from light petroleum-toluene). δ<sub>max</sub> 3190 (NH), 1660-1610 br (CO) and 1530 and 1340 (NO<sub>2</sub>) cm<sup>-1</sup>, δ<sub>H</sub>(CDCl<sub>3</sub>) 11.57 (1H, s, NH or OH) (exch.), 7.86(1H, d, J9Hz, H-3), 7.20 - 6.74 (8H, m, ArH), 4.26 (4H, q, J7Hz, CH<sub>2</sub>) and 1.33 (6H, t, J7Hz, CH<sub>3</sub>).

Found: C, 59.9; H, 5.2; N, 10.5%; M*, 399

C<sub>16</sub>H<sub>14</sub>N,O<sub>2</sub>, requires: C, 60.2; H, 5.3; N, 10.5%; M, 399.

Evaporation of the ethereal mother liquor gave a brown oil which was flash chromatographed over silica.

Elution with methylene chloride gave an orange solid which was washed with ether to afford a second crop of the product (167c) (5%), m.p.
122-124°, identified by comparison (m.p. and i.r. spectrum) with a sample obtained before.

Further elution with methylene chloride through ethyl acetate to ethanol gave only intractable multicomponent gums which were not further investigated.

(vii) The reaction mixture from benzoylacetonitrile was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a red-brown gum which was flash-chromotographed over silica.

Elution with methylene chloride gave an orange oil whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Further elution with methylene chloride gave a yellow oil which was triturated with ether to afford 2-[1-(2-nitrophenyl)-3-phenylformamidinyl]-3-phenyl-3-oxopropanenitrile (171a) (33%) as a yellow solid, m.p. 159-160° (from light petroleum-toluene), \( \delta_{\text{max}} \) 3310 (NH), 2180 (CN), 1620 br (CO), and 1530 and 1335 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{H}(\text{CDCl}_3)} \) 10.17 (1H, bs, NH or OH), 7.08 (1H, bs, NH or OH), 6.25 - 6.08 (3H, m, ArH) and 5.96 - 5.45 (11H, m, ArH).

**Found:** C, 68.9; H, 4.2; N, 14.4%, M\(^+\), 384.

**C\(_2\text{H}_{16}\text{N}_2\text{O}_4\) requires:** C, 68.8; H, 4.2; N, 14.4%; M, 384.

Further elution with ethyl acetate and finally methanol gave only intractable brown gums from which no further identifiable material could be
obtained.

The reaction mixture from ethyl cyanoacetate was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown oil. Trituration of the brown oil with ether afforded ethyl 2-cyano-2-1-[2-nitrophenyl]-3-phenylformamidinyl] ethanoate (171b) (64%) as a yellow solid, m.p. 139-140° (from light petroleum-toluene), δmax 3200 (NH), 2205 (CN), 1665 (CO) and 1520 and 1350 (NO2) cm⁻¹, δH(CDCl₃) 10.98 (1H, s, NH or OH) (exch.), 8.95 (1H, s, NH or OH) (exch.), 7.98 (1H, dd, J1.3 and J8.2Hz, H-3), 7.38 - 6.89 (8H, m, ArH), 4.29 (2H, q, J7Hz, CH₂).

Found : C, 61.5; H, 4.6; N, 15.8%; M⁺, 352.

C₁₇H₁₃N₂O₄ requires: C, 61.4; H, 4.5; N, 15.9%; M, 352.

Evaporation of the ethereal mother liquor gave a brown oil whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture. Flash-chromatography of the oil over silica eluting with methylene chloride gave a second crop of the product (171b) (11%), m.p. 125-132° identified by comparison (m.p. and i.r. spectrum) with a sample obtained before.

Further elution with methylene chloride through ethyl acetate to ethanol gave only intractable gums which were not further investigated.

(ix) The reaction mixture from benzenesulphonylacetone was evaporated and the residue was treated with water (40.0 ml), and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown oil. The brown oil was triturated with ether-light
petroleum (b.p. 40-60°)- n-hexane to afford 1-benzencesulphonyl-1-[1-(2-nitrophenyl)-3-phenylformamidinyl]propanone (178) (66%) as a yellow solid m.p. 124 - 126° (from light petroleum-toluene), \( \delta_{\text{max}} \) 3300 (NH), 1610 br (CO), 1530 and 1340 (NO\(_2\)), and 1280 and 1140 (SO\(_2\)) cm\(^{-1}\). \( \delta_{\text{H}}(\text{CDCl}_3) \) 10.42 (1H, bs, NH or OH) (exch.), 9.65 (1H, bs NH or OH) (exch.), 7.91 - 7.68 (3H, m, ArH), 7.45 - 6.72 (11H, m, ArH) and 2.57 (3H, s, CH\(_3\)).

\[
\text{Found:} \quad \text{C, 60.6; H, 4.3; N, 9.7%; M, 437.}
\]

\[
\text{C}_{16}\text{H}_{10}\text{N}_2\text{O}_5\text{S requires:} \quad \text{C, 60.4; H, 4.4; N, 9.6%; M, 437.}
\]

Evaporation of the trituration mother liquor gave a yellow oil whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

(x) The reaction mixture from benzyl methyl ketone was evaporated and the residue was treated with water (40.0 ml) and the solution acidified with glacial acetic acid and extracted with methylene chloride to give a brown oil which was flash-chromotographed over silica.

Elution with methylene chloride gave a series of orange gums whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

Further elution with methylene chloride gave a yellow gum which was triturated with ether to afford 2-phenyl-3-phenylaminoquinoxaline 1-N-oxide (190) (30%) which formed yellow needles, m.p. 170-172° (from toluene-light petroleum). \( \delta_{\text{max}} \) 3260 (NH), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.46 (1H, d, J8Hz, H-3), 7.92 - 7.06 (13H, m, ArH) and 6.47 (1H, s, NH).
Further elution with methylene chloride-ethyl acetate (10:1) through ethyl acetate to ethanol gave only a series of intractable multicomponent gums whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

1-{[1-(2-Nitrophenyl)-3-phenylformamidinyl]propan-2-one (156)

A hot solution of the acetamidine derivative (155) (0.69 g, 0.002 mol) in ethanol (10.0 ml) was treated with triethylamine (0.81 g, 0.008 mol) and the mixture was heated under reflux for 1.5 h. The mixture was evaporated to give a red oil (0.73 g) which was flash chromatographed over silica.

Elution with methylene chloride gave the acetamidine derivative (156) (0.60 g; quant.) as a yellow oil, b.p. 120°/0.5mm Hg, \( \delta_{\text{rmax}} \) 3320 (NH), 1720 (CO), and 1510 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{r}}(\text{CDCl}_3) \) 8.78 (1H, s, NH) (exch.) 8.14 - 6.98 (9H, m, ArH), 5.27 (2H, s, CH\(_2\)), and 2.08 (3H, s, CH\(_3\)).

Further elution with ethyl acetate through to ethanol gave only a brown gum (0.05 g) which was not further investigated.
The Attempted Reaction of the Acetamidine Derivative (156) with Hydroxylamine

Solutions of the acetamidine (156) (0.30 g, 0.001 mol) in ethanol (5.0 ml) and hydroxyammonium hydrochloride (0.56 g, 0.008 mol) in water (1.0 ml) were mixed and the mixture was treated with a solution of sodium acetate (0.66 g, 0.008 mol) in water (1.5 ml) and then heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) to give a gummy suspension. This was extracted with methylene chloride to give an orange gum (0.17 g), whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

The Reaction of the Acetamidine Derivative (156) with Aqueous Hydrochloric Acid

A solution of the amidine (156), (0.59 g, 0.002 mol) in ethanol (10.0 ml) was treated with 2M aqueous hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was concentrated under reduced pressure to remove the ethanol and extracted with methylene chloride to give an orange gum (0.36 g) which was flash chromatographed over silica.

Elution with methylene chloride gave 2-nitroaniline (0.16 g; 58%) m.p. 70 - 72°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-ethyl acetate (5:1) gave an orange gum (0.11 g) which was triturated with ether to afford an
unidentified orange solid (0.04 g). Evaporation of the ethereal mother liquor gave an intractable brown gum (0.05 g) which was not further investigated.

Further elution with methylene chloride-ethyl acetate (1:1) and finally ethanol gave only intractable brown gums (total 0.10 g).

The aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and was extracted with methylene chloride to give an orange oil (0.05 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

2-Acetyl-3-phenylaminoquinoxaline (160)

A solution of the acetamidine derivative (155) (0.69 g, 0.002 mol) in refluxing ethanol (10.0 ml) was treated with piperidine (0.69 g, 0.008 mol) and the mixture was heated under reflux for 24h. The mixture was evaporated to give a brown gum (0.85 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave the quinoxaline derivative (160), (0.18 g; 34%) which formed orange needles, m.p. 132 - 134% (from light petroleum -toluene), $\delta_{\text{max}}$ 3260 (NH) and 1665 (CO) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 10.69 (1H, s, NH), 7.98 - 7.09 (9H, m, ArH) and 2.92 (3H, s, CH$_3$).

Found: C, 72.8; H, 4.9; N, 15.9%; M$^+$, 263.

C$_{16}$H$_{13}$N$_2$O requires: C,73.0; H, 4.9; N, 16.0%; M, 263.

Further elution with methylene chloride-ethyl acetate (10:1)
through to ethyl acetate and finally ethanol gave only unresolvable multicomponent gums (total 0.71 g).

3-Phenylaminoquinoxaline 1-N-oxide (161)

(ii) A solution of the acetamidine derivative (155), (1.1 g, 0.0033 mol) in warm anhydrous ethanol (5.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g atom.) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and the insoluble solid collected to afford the quinoxaline derivative (161), (0.69 g; 75%) which formed green needles m.p. 214 - 216° (from ethanol). \( \delta_{\text{max}} \) 3300 (NH) and 1625 (NH def.) cm\(^{-1}\), \( \delta_{\text{H}} \) (CDCl\(_3\)) 9.73 (1H, s, NH) (exch.), 8.40-8.20 (2H, m, ArH), 7.95 - 7.70 (4H, m, ArH), 7.60 - 7.35 (3H, m, ArH) and 7.10 - 7.00 (1H, m, ArH).

Found: C, 70.2; H, 4.7; N, 17.5%; M\(^+\), 237.0904.

C\(_{14}\)H\(_{11}\)N\(_3\)O requires: C, 70.9; H, 4.6; N, 17.6%; M, 237.0902

Acidification of the aqueous mother liquor with 10M aqueous hydrochloric acid and extraction with methylene chloride gave a dark brown oil (0.38 g) whose t.l.c. in methylene chloride - ethyl acetate (10:1) showed it to be an unresolvable multicomponent mixture.

(ii) A solution of the mono-acetyl acetamidine derivative (156), (0.59 g, 0.002 mol) in anhydrous ethanol (25.0 ml) was treated with a solution of sodium (0.18 g, 0.0008 g atom) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and the insoluble solid collected to afford the quinoxaline derivative (161), (0.32 g;
68%) m.p. 190 - 195°C, identified by comparison (i.r. spectrum) with the sample previously prepared as described in (i).

Acidification of the aqueous mother liquor with 10M aqueous hydrochloric acid followed by extraction with methylene chloride yielded only a small amount of brown gum (0.04 g) which was not further investigated.

(iii) A solution of the acetamidine derivative (155) (10.2 g, 0.03 mol) in ethanol (120 ml) was treated with a warm solution of potassium hydroxide (8.4 g, 0.15 mol) in ethanol (160 ml) and the mixture was heated under reflux for 1.25h. The mixture was evaporated and the residue was treated with water (80.0 ml) and filtered to afford the quinoxaline derivative (161), (7.0 g; 99%), m.p. 199-205°C, identified by comparison (m.p. and i.r. spectrum) with the sample obtained previously in (i).

(iv) A solution of the acetamidine derivative (155) (0.68 g, 0.002 mol) in ethanol (10.0 ml) was treated with 1M aqueous sodium carbonate (5.0 ml) and the mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a three-phase system which was filtered to afford the quinoxaline derivative (161), (0.22 g; 46%), m.p. 203-213°C, identified by comparison (m.p. and i.r. spectrum) with the sample previously obtained in (i).

The methylene chloride phase was evaporated to yield a red gum (0.18 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.
The Attempted Reduction of 3-Phenylaminoquinoxaline 1-N-oxide (161)

(a) A solution of the quinoxaline N-oxide derivative (161) (0.20 g, 0.0084 mol) in 70% v/v aqueous ethanol (10.0 ml) was treated with sodium dithionite (0.21 g) and the mixture was heated under reflux for 1 h after which time a second portion of sodium dithionite (0.20 g) was added and heating continued for a further 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a brown gum (0.10 g) whose t.l.c. in methylene chloride over silica showed it to be a complex multicomponent mixture which was not further investigated.

Work-up of the aqueous mother liquor gave no further material.

(b) A solution of the quinoxaline N-oxide derivative (161) (0.24 g, 0.001 mol) in ethanol (50.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.024 g) at room temperature and atmospheric pressure for 2.5 h. The mixture was filtered through celite and the filtrate was evaporated to give impure starting-material (0.20 g; 83%), m.p. 161-169°, identified by comparison (i.r. spectrum) with an authentic sample.

(c) Repetition of the reaction described in (b) in the presence of acetic anhydride (0.10 g, 0.001 mol) for 4.5 h gave, after filtration and evaporation, a green semi-solid (0.26 g) which was triturated with ether to afford unchanged starting material (161), (0.07 g; 29%), m.p. 195 - 205°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethereal mother liquor gave a green gum (0.17
g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

2-Chloro-3-phenylaminoquinoxaline (162)

A solution of the quinoxaline N-oxide derivative (161) (0.48 g 0.002 mol) in chloroform (25.0 ml) was treated with phosphorous trichloride (0.3 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml), basified with 2M aqueous methylene chloride to give a brown gum (0.45 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 2-chloro-3-phenylaminoquinoxaline (162) (0.12 g; 23%) which formed orange needles m.p. 86-87° (from light petroleum). (lit., 57 73-76°, δmax 3410 (NH) cm⁻¹, δH(CDCl₃) 7.91-7.13 (m, ArH and NH).

Found: C, 65.7; H, 3.9; N, 16.2% M⁺, 257, 255.
Calc for C₁₄H₁₀ClN₂: C, 65.8; H, 3.9; N, 16.4%; M, 255.5

Further elution with methylene chloride gave an orange gum (0.01 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.

Further elution with methylene chloride- ethyl acetate (5:1) through to ethyl acetate and finally ethanol gave only a series of intractable gums (total 0.25 g) whose t.l.c. in methylene choride over silica showed them to be complex mixtures which were not further investigated.
2-Phenylaminoquinoxaline (163)

The quinoxaline N-oxide derivative (161) (0.47 g, 0.002 mol) was treated with freshly distilled triethyl phosphite (4.9 g, 5.0 ml, 0.03 mol) and the mixture was heated under reflux for 6 h. The mixture was evaporated and the residue was dissolved in ether (20.0 ml) and washed with water (2 x 10.0 ml). Evaporation of the ethereal extract gave an orange semi-solid (0.44 g) which was dry-column flash-chromatographed over silica.

Elution with methylene chloride gave a red gum (0.03 g) which was not further investigated.

Further elution with methylene chloride-ethyl acetate (5:1) gave the known \(^{50,60}\) 2-phenylaminoquinoxaline (163), (0.31 g ; 70%), which was purified by dry column flash-chromatography in methylene chloride-ethyl acetate (5:1) over silica, m.p. 127-129° (lit.\(^{60}\) 135-137°), \(\delta_{\text{max}}\) 3300 (NH) and 1620 (NH def.) cm\(^{-1}\), \(\delta_{\text{p}}\) (CDCl\(_3\)) 8.44 (1H, s, NH) (exch.) and 7.99-7.02 (1OH, m, ArH).

**Found:** C, 76.1; H, 5.0; N, 18.7%; M\(^{+}\), 221.

**Calc. for C\(_{14}\)H\(_{11}\)N\(_{2}\):** C, 76.0; H, 5.0; N, 19.0 %; M, 221.

Further elution with methylene chloride-ethyl acetate (2:1) through ethyl acetate to methanol gave only small amounts of gums (total 0.06 g) which were not further investigated.

The Attempted Cyclisation of the Acetamidine Derivative (155) using 1,5 Diazabicyclo[4.3.0]non-5-ene (DBN)

A solution of the acetamidine derivative (155) (0.69 g, 0.002 mol)
in anhydrous ethanol (20.0 ml) was treated with 1,5-diazabicyclo[4.3.0]non-5-ene (0.27 g, 0.0022 mol) and the mixture was stirred at room temperature for 24h. The mixture was evaporated and the residue was treated with 2M aqueous hydrochloric acid (5.0 ml) and extracted with methylene chloride to give a red gum (0.55 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture.

Flash-chromotography of the gum over silica eluting with methylene chloride through ethyl acetate to ethanol gave only a series of intractable gums (total 0.44 g) which yielded no identifiable material.

**The Attempted Cyclisation of the Acetamidine Derivative (155) using 1,8-Diazabicyclo[5.4.0]undec-5-ene (DBU)**

A solution of the acetamidine derivative (155) (0.68 g, 0.002 mol) in anhydrous DME (10.0 ml) was treated with DBU (0.91 g, 0.006 mol) and the mixture was heated at 60° for 1 h. The mixture was then filtered to afford the DBU salt of the starting acetamidine derivative (155) (0.91 g, 93%), which formed yellow prisms, m.p. 151-152° (from toluene-acetonitrile).

**Found:** C, 66.2; H, 6.8; N, 14.2%

**C_{17}H_{21}N_{2}O_{2} requires :** C, 66.0; H, 6.7; N, 14.3%.

The filtrate was evaporated to give an intractable brown oil (0.61 g) which yielded no identifiable material.

**The Cyclisation of 2-[1-(Nitrophenyl)-3-phenylformamidinyl]-1-phenylbutane 1,3-dione (166a) using Ethanolic Potassium Hydroxide**

A solution of the acetamidine derivative (166a), (0.80 g, 0.002 mol)
in ethanol (25.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated, the residue was treated with water (10.0 ml) and the insoluble solid was collected to afford the quinoxaline N-oxide derivative (161) (0.45 g; 96%), m.p. 195 - 204°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

The Attempted Acetylation of 3-Phenylaminoquinoxaline \(1\)-N-oxide (161)

(a) A solution of the phenylaminoquinoxaline \(N\)-oxide derivative (161) (0.24 g, 0.001 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated under high vacuum (oil pump) to give a green-brown gum (0.29 g) whose t.l.c. in methylene chloride-ethyl acetate (10:1) showed it to be a multicomponent mixture. The gum was flash-chromotographed over silica.

Elution with methylene chloride through ethyl acetate to ethanol gave only a series of intractable gums (total 0.19 g) which yielded no identifiable material.

(b) The phenylaminoquinoxaline \(N\)-oxide derivative (161) (0.47 g, 0.002 mol) was treated with glacial acetic acid (2.5 ml) and acetyl chloride (7.5 ml) and the mixture was heated under reflux for 3 h. The mixture was evaporated to give an intractable brown semi-solid (0.62 g) from which no identifiable material could be obtained.
The Reaction of 3-Phenylaminoquinoxaline 1-N-oxide (161) with Phenyl Isocyanate

A solution of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in anhydrous DMF (5.0 ml) was treated with phenyl isocyanate (0.26 g, 0.0022 mol) and the mixture was heated under reflux for 4 h. The mixture was cooled, treated with water (10.0 ml) and filtered to afford a green-brown solid (0.35 g) which was triturated with methylene chloride to give unchanged starting material (161), (0.20 g; 42%), m.p. 204 - 208°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The methylene chloride mother liquor was evaporated to give a brown solid (0.09 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 1,3-diphenyl-1 h-imidazo[4,5-b]quinoxalin-2(3H)-one (211a), (0.04 g; 6%) which formed pale yellow needles, m.p. 181-182° (from toluene-light petroleum) (lit. 275-276°), $\delta_{\text{max}}$ 1740 (CO) cm$^{-1}$.

**Found:** C, 74.6; H, 4.0; N, 16.5%; M+, 338.
**Calc. for C$_2$H$_{14}$N$_2$O:** C, 74.6; H, 4.1; N, 16.6%; M, 338

Further elution with methylene chloride-ethyl acetate gave only an intractable brown gum (0.04 g) which was not further investigated.

The Reaction of 3-Phenylaminoquinoxaline 1-N-oxide (161) with Methyl Isocyanate

A solution of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in DMF (5.0 ml) was treated with methyl isocyanate (0.13 g, 0.0022 mol) and
the mixture was heated under reflux for 1 h, after which time a further portion of methyl isocyanate (0.13 g, 0.0022 mol) was added and heating under reflux continued for a further 1.5 h. The mixture was cooled and treated with another portion of methyl isocyanate (0.13 g, 0.0022 mol) and the mixture was heated under reflux for 1.5 h. The mixture was cooled, treated with water (10.0 ml) and filtered to afford a brown solid (0.34 g) which was dry-column flash-chromatographed over silica.

Elution with methylene chloride gave 1-methyl-3-phenyl-1H-imidazo[4,5-b]quinoxalin-2(3H)-one (211b) (0.18 g; 33%) which formed buff-coloured needles, m.p. 224-225° (from light petroleum-toluene), $\delta_{\text{max}}$ 1740 (CO) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.05-7.41 (9H, m, ArH) and 3.64 (3H, s, CH$_3$).

Found: C, 69.6; H, 4.3; N, 20.1%; M+. 276.
$C_{16}H_{12}N,O$ requires: C, 69.6; H, 4.4; N, 20.3%; M, 276.

Further elution with ethyl acetate then ethanol gave only small amounts of gums (total 0.03 g) which were not further investigated.

Extraction of the aqueous mother liquor with methylene chloride yielded a yellow gum (0.08 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was therefore not further investigated.

The Reaction of 3-Phenylaminogulnoxaline 1-N-oxide (161) with Urea

Solutions of the quinoxaline N-oxide (161), (0.47 g, 0.002 mol) in anhydrous DMF (5.0 ml) and urea (0.13 g, 0.0022 mol) in anhydrous DMF (5.0 ml) were mixed and the mixture was heated under reflux for 24 h. The
mixture was evaporated and the residue was treated with water (10.0 ml) followed by methylene chloride and the resulting three-phase mixture was filtered to afford 1-phenyl-1H-imidazo[4,5-b]quinoxalin-2(3H)-one (211c) (0.29 g; 55%) which formed brown microcrystals m.p. >350° (from glacial acetic acid - dimethyformamide), δmax 3200-2500 br (NH,OH) and 1750 (CO)cm⁻¹, δh(CDCl₃) 13.0-11.4 (1H, bs, NH) (exch.) and 7.95-7.45 (9H, m, ArH).

Found: C, 68.8; H, 3.8; N, 21.1%; M⁺, 262.

C₁₄H₁₂N₂O requires: C, 68.7; H, 3.8; N, 21.4%; M, 262.

The methylene chloride extract was evaporated to give a brown oil (0.20 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

The Attempted Reaction of 3-Phenylaminoquinazoline 1-N-oxide (161) with Aniline

A solution of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in anhydrous DMF (5.0 ml) was treated with aniline (0.20 g, 0.0022 mol) and the mixture was heated under reflux for 5.5 h.

The mixture was diluted with water (10.0 ml) and extracted with ethyl acetate to give a red gum (0.41 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.
The Reaction of 3-Phenylaminoquinoxaline 1-N-oxide (161) with Phenyl Isothiocyanate

A solution of the quinoxaline N-oxide (161) (0.47 g; 0.002 mol) in anhydrous DMF (5.0 ml) was treated with phenyl isothiocyanate and the mixture was heated under reflux for 4 h.

The mixture was diluted with water (10.0 ml) and extracted with methylene chloride to give a brown oil (0.66 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded 3-phenylaminoquinoxaline-2(1H)-thione (219) (0.05 g; 10%) which formed yellow needles, m.p. 234-236° (from toluene-light petroleum), \( \delta_{\max} \) 3300 (NH) and 3200-2500 br (NH, SH) cm\(^{-1}\), \( \delta_{\nu}[(CD_3)_2SO] \) 14.61 (1H, bs, NH or SH) (exch.), 9.49 (1H, s, NH) (exch.) and 8.08 - 6.99 (9H, m, ArH).

Found: C, 66.6; H, 4.3; N, 16.4%; M, 253.

C\(_{14}\)H\(_{11}\)N\(_2\)S requires: C, 66.4; H, 4.3; N, 16.4%; M, 253

Elution with methylene chloride-ethyl acetate (5:1) afforded diphenylurea (0.08 g; 19%), which formed cream needles, m.p. 242 - 243° (from toluene - ethanol) and was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Final elution with methylene chloride-ethyl acetate (2:1) afforded 2-phenylaminoquinoxaline (163) (0.04 g; 10%), m.p. 127 - 129°, identical (m.p.
and i.r. spectrum) with a sample prepared before.

The Reaction of 3-Phenylaminoquinoxaline 1-N-oxide (161) with Methyl Isothiocyanate

A solution of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in anhydrous DMF (5.0 ml) was treated with methyl isothiocyanate (0.16 g, 0.0022 mol) and the mixture was heated under reflux for 20 h.

The mixture was diluted with water (10.0 ml) and extracted with methylene chloride to give a brown oil (0.50 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded 3-phenylaminoquinoxaline-2(1H)-thione (219), (0.18 g; 35%), m.p. 229 - 231° which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Elution with methylene chloride-ethyl acetate (10:1) afforded impure 2-phenylaminoquinoxaline (163) (0.13 g; 29%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with methylene chloride-ethyl acetate (5:1), through ethyl acetate to ethanol afforded only a series of brown intractable gums (total 0.09 g) which were not further investigated.

The Reaction of 3-Phenylaminoquinoxaline 1-N-oxide (161) with Thiourea

A solution of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in
anhydrous DMF (5.0 ml) was mixed with a solution of thiourea (0.17 g, 0.0022 mol) in anhydrous DMF (2.5 ml) and the mixture was heated under reflux for 44 h.

The mixture was evaporated and the red gum obtained was flash-chromatographed over silica.

Elution with methylene chloride afforded 3-phenylaminoquinoxaline-2-(1H)-thione (219) (0.03 g; 6%), m.p. 206-210°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Elution with methylene chloride-ethyl acetate (5:1) afforded 2-phenylaminoquinoxaline (163) (0.11 g; 25%), m.p. 127-129°, identical (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Reaction of 3-Pheny laminoquinoxaline 1-N-oxide (161) with Cyanamide

Solutions of the quinoxaline N-oxide (161) (0.47 g, 0.002 mol) in anhydrous DMF (5.0 ml) and cyanamide (0.09 g, 0.002 mol) in anhydrous DMF (5.0 ml) were mixed and the mixture was heated under reflux for 48 h. The mixture was evaporated to give a brown oil (0.72 g) which was triturated with methylene chloride to give unchanged starting material (161) (0.32 g; 68%), m.p. 197-204°, identified by comparison (m.p and i.r. spectrum) with an authentic sample.

The methylene chloride mother liquor was evaporated to give a brown oil (0.43 g) which was dry column flash-chromatographed over silica.
Elution with methylene chloride through ethyl acetate to methanol gave only intractable gums (0.21 g) which yielded no identifiable material.

Base-catalysed Cyclisation Reactions of Ethyl 2-[1-(2-nitrophenyl)-3-phenylformamidinyl]-3-oxobutanoate (167a)

(a) A solution of the acetamidine derivative (167a) (0.74 g, 0.002 mol) in ethanol (30.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 1 h. The mixture was filtered to afford the sodium salt of 3-phenylaminoquinoxaline-3-carboxylic acid 1-N-oxide (0.53 g; 57%), m.p. 220 - 225°. This was slurried with 2M aqueous hydrochloric acid (5.0 ml) to afford 3-phenylaminoquinoxaline-3-carboxylic acid 1-N-oxide (169) (0.33 g; 59%) which formed red needles, m.p. 214-216° (decomp.) (after purification by flash-chromatography in methylene chloride over silica), \( \delta_{\text{max}} \) 3200-2500 br (NH, OH) and 1685 (CO) cm\(^{-1} \), \( \delta_{(\text{CDCl}_3)} \) 11.19 (1H, s, OH), 8.44 - 8.32 (1H, m, ArH), and 7.89 - 7.05 (10H, m, ArH + NH).

Found: C, 63.5; H, 4.0; N 14.6%; M\(^+\), 281; [M.H]\(^+\), 282.0879
C\(_{10}\)H\(_{11}\)N\(_2\)O\(_3\) requires: C, 64.1; H, 3.9; N, 14.9%; M, 281; [M.H], 282.0879.

The original aqueous ethanolic filtrate was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give an orange solid (0.09 g), m.p. 270-300° (decomp.), whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.

(b) A solution of the acetamidine derivative (167a) (0.74 g, 0.002
mol) in anhydrous ethanol (25.0 ml) was treated with a solution of sodium (0.18 g, 0.0008 g atom) in anydrous ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was filtered to obtain the sodium salt of the product (0.51 g) which was slurried with 2M aqueous hydrochloric acid to afford the quinoxaline-3-carboxylic acid N-oxide (169) (0.38 g; 67%), m.p. 210-220° (decomp.), identified by comparison (m.p. and i.r. spectrum) with the sample prepared in (a) before.

The ethanolic filtrate was evaporated and the residue was treated with water (5.0 ml) and filtered to give only a small amount of a green solid (0.04 g) which was not further investigated.

The Cyclisation of Ethyl 2-[1-{2-nitrophenyl}-3-phenylformamidinyl]-3-phenyl-3-oxopropanoate (167b) using Ethanolic Potassium Hydroxide

A solution of the acetamidine derivative (167b), (0.86 g, 0.002 mol) in ethanol (10.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 40 min. The insoluble sodium salt (0.56 g) was collected from the cooled reaction mixture and was slurried with 2M aqueous hydrochloric acid to afford the quinoxaline carboxylic acid N-oxide (169) (0.09 g; 19%), m.p. 208 - 212° (decomp.) identified by comparison (m.p. and i.r. spectrum) with an authentic sample obtained before.

The Cyclisation of Diethyl 2-[1-{2-nitrophenyl}-3-phenylformamidinyl]-1,3-propanedioate (167c) using Ethanolic Potassium Hydroxide

A solution of the acetamidine derivative (167c) (0.80 g, 0.002 mol) in ethanol (25.0 ml) was treated with a solution of potassium hydroxide
(0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 45 min. The mixture was cooled and the insoluble sodium salt (0.78 g) was collected and slurried with 2M aqueous hydrochloric acid to afford the quinoxaline carboxylic acid N-oxide derivative (169) (0.39 g; 70%), m.p. 204-210° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The ethanolic mother liquor was evaporated and the residue was treated with water (5.0 ml) and the solid collected to give 3-phenylaminoquinoxaline 1-N-oxide (161) (0.065 g; 14%), m.p. 210-216°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The Attempted Cyclisation of 2-[1-(2-nitrophenyl)-3-phenylformamidinyl]-3-phenyl-3-oxopropanenitrile (171a) using Ethanolic Potassium Hydroxide

A solution of the acetamidine derivative (171a) (0.77 g, 0.002 mol) in ethanol (30.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 6 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a yellow gum (0.93 g) which was triturated with ether to give unchanged starting material (171a) (0.61 g; 80%), m.p. 157-160°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the ethereal mother liquor yielded an intractable brown gum (0.07 g) which was not further investigated.
Attempted Base-catalysed Cyclisation Reactions of Ethyl 2-Cyano-2-[1-(2-nitrophenyl)-3-phenylformamidinyl]ethanoate (171b)

(a) A solution of the acetamidine derivative (171b) (0.70 g, 0.002 mol) in ethanol (10.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a yellow-brown gum (0.52 g) whose t.l.c. in methylene chloride over silica showed it to be largely two components, corresponding to 2-nitroaniline and the unreacted acetamidine derivative (171b). The gum was not further investigated.

(b) A solution of the acetamidine derivative (171b) (0.70 g, 0.002 mol) in anhydrous ethanol (20.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g atom) in anhydrous ethanol and the mixture was heated under reflux for 2.5 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give unchanged starting material (171b) (0.70 g; quant.), m.p. 132-138°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(c) A solution of the amidine (171b) (0.70 g, 0.002 mol) in ethanol (20.0 ml) was treated with 1M aqueous sodium carbonate (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was filtered to remove inorganic material and the filtrate was evaporated and the residue treated with water (5.0 ml). Filtration afforded unchanged starting-material (171b) which was combined with a second crop obtained by extracting the aqueous mother liquor with methylene chloride (total 0.54 g; 77%), m.p.
138-139°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

1-Hydroxy-3-phenylaminoquinoxalin-2(1H)-one (176)

A solution of the acetamidine derivative (178) (1.8 g, 0.004 mol) in ethanol (30.0 ml) was treated with a solution of potassium hydroxide (1.1 g, 0.02 mol) in ethanol (20.0 ml) and the mixture was heated under reflux for 2.5 h. The mixture was evaporated and the residue was treated with water (20.0 ml) and extracted with methylene chloride to give a brown oil (0.28 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture.

The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid and filtered to give the N-hydroxyquinoxalinone derivative (176) (0.75 g; 75%) which formed light brown needles, m.p. 239-241° (from glacial acetic acid), $\lambda_{\text{max}}$ 3345 (NH), 3200-2500 br (NH,OH), and 1640 (CO) cm$^{-1}$, $\delta_{\text{DMSO}}$ 13.75-13.50 br (NH, OH) (exch.), 11.20 (1H, s, NH) (exch.), 8.25 - 8.00 (2H, m, ArH) and 7.70 - 6.95 (7H, m, ArH).

Found: C, 66.4; H, 4.4; N, 16.2%; M$^+$, 253.

C$_{14}$H$_{11}$N$_3$O$_r$ requires: C, 66.4; H, 4.4; N, 16.4%; M, 253.

1-Acetoxy-3-phenylaminoquinoxalin-2(1H)-one (180)

A solution of the N-hydroxyquinoxalinone derivative (176) (0.37 g, 0.0015 mol) in anhydrous dimethylformamide (DMF) (10.0 ml) was treated with triethylamine (0.17 g; 0.0017 mol) and the mixture was stirred at room temperature for 5 min. The mixture was then treated with acetyl chloride (0.12 g, 0.0015 mol) and was stirred at room temperature for 0.5 h. The
mixture was evaporated and the residue was treated with water and filtered to afford the acetoxyquinoxalinone derivative (180). (0.37 g; 84%) which formed off-white needles, m.p. 176 - 178\(^\circ\) (from ethanol-glacial acetic acid), \(\delta_{\text{max}}\) 3290 (NH), and 1800 and 1720 (CO) cm\(^{-1}\); \(\delta_{\text{H}}(\text{CDCl}_3)\) 8.26 (1H, s, NH) (exch.), 7.99 -7.10 (9H, m, ArH) and 2.51 (3H, s, CH\(_3\)).

Found: C, 65.1; H, 4.4; N, 14.3%; M \(^*\), 295.

C\(_{11}\)H\(_{13}\)N\(_2\)O\(_3\) requires: C, 65.1; H, 4.4; N, 14.2%; M, 295

The Attempted Hydrogenolysis of 1-Acetoxy-3-phenylaminoquinoxalin-2(1H)-one (180)

A solution of the N-acetoxyquinoxalinone (180) (0.22 g, 0.00075 mol) in glacial acetic acid (40.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.022 g) at room temperature and atmospheric pressure for 2.5 h. The mixture was filtered through celite and the filtrate was evaporated to give unchanged starting material (180) (0.21 g; 95%), m.p. 176 - 178\(^\circ\), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

3-Phenylaminoquinoxalin-2(1H)-one (181)

A solution of the N-acetoxyquinoxalinone (180) (0.15 g, 0.0005 mol) in 70% v/v aqueous dimethylformamide (10.0 ml) was treated with sodium dithionite (0.15 g) and the mixture was heated under reflux for 1 h after which time a further portion of sodium dithionite (0.15 g) was added and heating under reflux continued for a further 1 h. The mixture was then, evaporated and the residue was treated with water (50.0 ml) and filtered to afford the quinoxalinone derivative (181) (0.11 g; 92%), m.p. 246 - 252\(^\circ\) (lit., 251 - 252\(^\circ\)), identified by comparison (m.p. and i.r. spectrum) with an authentic sample\(^{63}\).
The Attempted Reaction of N-(2-Nitrophenyl)Triphenylphosphinimine (152) with Trimethylsilyl Isocyanate

A solution of the phosphinimine (152) (2.0 g, 0.005 mol) in anhydrous DME (10.0 ml) was treated under nitrogen with 85% trimethylsilyl isocyanate (0.68 g, 0.005 mol) and the mixture was stirred at room temperature for 2 h. The mixture was then heated under reflux for 20 min. after which time an i.r. spectrum of a sample of the mixture showed that no reaction had taken place. A further portion of 85% trimethylsilyl isocyanate (0.68 g, 0.005 mol) was added and the mixture was heated under reflux for 1.5 h. I.r. evidence again showed that no reaction had taken place and the mixture was cooled, treated with 85% trimethylsilyl isocyanate (1.0 g, 0.0075 mol) and was stirred at room temperature for 48 h. The mixture was evaporated to give a yellow semi-solid (2.1 g) which was triturated with ether to afford the unchanged phosphinimine (152) (1.6 g; 81%), m.p. 135-140°, identified by comparison (m.p. and i.r. spectrum with an authentic sample).

The ethereal mother liquor was evaporated to give a yellow gum (0.32 g) whose t.l.c. in methylene chloride-n-hexane (5:1) over alumina showed it to be largely the unreacted phosphinimine (152). The oil was not further investigated.

Benzoyl Isocyanate

Benzoyl isocyanate was prepared by the reaction of benzamide with oxalyl chloride in carbon tetrachloride as described by Speciale and Smith78 yield 57%, and had b.p. 104°/35 mm Hg (lit., 97 - 98°/23mm Hg).
The Attempted Reaction of N-(2-Nitrophenyl) triphenylphosphinimine (152) with Benzoyl Isocyanate

(a) Solutions of the phosphinimine derivative (152) (4.0 g, 0.01 mol) and benzoyl isocyanate (1.5 g, 0.01 mol) in anhydrous DME (10.0 ml) were mixed and the mixture was stirred at room temperature for 1.5 h. The filtered solution was then used immediately as described in (b) below.

(b) A stirred suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous DME (10.0 ml) was treated with a solution of pentane-2,4-dione in anhydrous DME (10.0 ml) and the mixture was stirred at room temperature for 5 min. by which time gas evolution had ceased. The solution prepared in (a) before was then added and the mixture stirred at room temperature for 1 h.

The mixture was filtered and the insoluble salt was dissolved in water (15.0 ml) and acidified with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford 3-[N-(2-nitrophenyl)carbamoyl] pentane-2,4-dione (195) (1.2 g; 32%), which formed yellow crystals, m.p. 130 - 132° (from toluene-light petroleum), \( \delta_{\text{max}} \) 2500 br (NH, OH), 1630 br (CO), and 1510 and 1350 (NO₂) cm⁻¹, \( \delta_{\text{H}}(CDCl₃) \) 10.39 (1H, bs, NH or OH), 8.90 - 7.13 (5H, m, CH and ARH), 2.49 (3H, s, CH₃), and 2.27 (3H, s, CH₃).

**Found:** C, 54.3; H, 4.5; N, 10.5%; M⁺, 264.

**C₁₁₂H₁₄N₂O₆ requires:** C, 54.5; H, 4.5; N, 10.6%; M, 264

The DME mother liquor was treated with water (40.0 ml), acidified with glacial acetic acid and extracted with methylene chloride to give a brown gum (2.2 g) which was flash-chromatographed over silica. Elution
with methylene chloride-hexane (2:1), through methylene chloride and ethyl acetate to ethanol gave only a series of complex gums which yielded no identifiable material.

The Attempted Reaction of $N$-[2-Nitrophenyl]triphenylphosphinimine (152) with Carbon Disulphide

Solutions of the phosphinimine (152) (1.6 g, 0.004 mol) in anhydrous toluene (20.0 ml) and carbon disulphide (0.30 g, 0.004 mol) in anhydrous toluene (5.0 ml) were mixed and the mixture was stirred and heated at 80° (oil bath) for 2.5 h. The mixture was evaporated to give the starting material (152) (1.6 g; quant.), m.p. 133-134°, identified in comparison (i.r. spectrum) with an authentic sample.

2-Nitrophenyl Isothiocyanate (225)

A solution of thiophosgene (17.2 g; 0.15 mol) in chloroform (50.0 ml) was heated under reflux and treated dropwise with a solution of 2-nitroaniline (13.8 g, 0.1 mol) in chloroform (80.0 ml) over a period of 2 h and the mixture then heated under reflux for a further 3 h. The mixture was cooled, filtered to remove some 2-nitroaniline hydrochloride (1.0 g) and evaporated to give a yellow solid (19.8 g) which was dry column flash-chromatographed over silica. Elution with methylene chloride-n-hexane (1:1) gave 2-nitrophenyl isothiocyanate (225), (14.8 g; 82%) as a pale yellow solid m.p. 71 - 74° (lit. 68. 73 - 74°, $\nu_{\text{max}}$ 21.05 (N=C=S) and 1530 and 1340 (NO$_2$) cm$^{-1}$).
Reactions of 2-Nitrophenyl Isothiocyanate (225) with Active Methylene Compounds.

A solution of the corresponding active methylene compound (0.0055 mol) in anhydrous DME (5.0 ml) was mixed with a stirred suspension of sodium hydride (0.12 g, 0.005 mol) in anhydrous DME (10.0 ml) and after hydrogen evolution had ceased the mixture was treated with stirring with a solution of 2-nitrophenyl isocyanate (225) (0.9 g, 0.005 mol) in anhydrous DME (5.0 ml). The mixture was stirred at room temperature for the stated time then worked up as described for the individual reactions below.

(i) The reaction mixture from acetylacetone was stirred at room temperature for 1 h and was then evaporated. The residue was treated with water (20.0 ml) and the solution acidified with glacial acetic acid and filtered to afford 3-[N-(2-nitrophenyl)thiocarbamyl]pentane-2,4-dione (226a) (92%), which formed pale yellow plates m.p. 147 - 151° (from light petroleum toluene) \( \delta_{\text{max}} \) 3280 (NH), 2500 br (SH), and 1520 and 1340 (NO\(_2\)) cm\(^{-1}\).

\[ \delta_{\text{H}}(\text{CDCl}_3) 11.02 \text{ (1H, bs, NH, SH, or OH)}, \quad 0.11 \text{ (1H, bs, NH, SH or OH)}, \quad 8.25 \text{ (1H, d, J9Hz, ArH)}, \quad 7.75 \text{ (1H, t, J8Hz, ArH)}, \quad 7.50 - 7.32 \text{ (2H, m, ArH)}, \quad \text{and} \quad 2.24 \text{ (6H, s, CH}_3\text{}). \]

Found: \[ C, 51.6; H, 4.3; N, 9.8%; \quad M^+, 280. \]

C\(_{11}H_{12}N\text{O}_2S\) requires: \[ C, 51.4; H, 4.3; N, 10.0%, M, 280 \]

The aqueous mother liquor was extracted with methylene chloride to give only a small amount of an intractable brown gum.

(ii) The reaction mixture from dibenzoylmethane was stirred at
room temperature for 2 h and was then evaporated. The residue was

treated with water (20.0 ml) and the solution acidified with 10 M aqueous

carbonate acid and extracted with methylene chloride to give an orange oil

which was dry-column flash-chromatographed over silica.

Elution with methylene chloride gave unreacted 2-nitrophenyl

isothiocyanate (225) (35%), m.p. 70 - 72°, identified by comparison (m.p. and

i.r. spectrum) with an authentic sample prepared before.

Further elution with methylene chloride gave a yellow gum which

was triturated with ether to afford 1,3 -diphenyl-2-[N-(2-

nitrophenyl)]thiocarbamoyl]ethane-1,3-dione (226b) (41%), which formed yellow

prisms, m.p. 107-111° (from light petroleum-toluene). \( \delta_{\max} \) 3250 (NH), 2500

br (SH), 1620 (CO), and 1500 and 1335 (NO\(_2\)) cm\(^{-1}\), \( \delta_{n}(CDCl_3) \) 12.18 (1H, bs,

NH, SH or OH), and 8.83 - 7.05 (14 H, m, ArH).

Found: C, 64.70; H, 3.9; N, 6.9%; M, 404.
C\(_{21}\)H\(_{16}\)N\(_2\)O\(_2\)S requires: C, 65.3; H, 4.0; N, 6.9%; M, 404.

(iii) The mixture from ethyl acetoacetate was stirred at room

temperature for 1 h and was then evaporated, the residue treated with water

(40.0 ml), and the solution acidified with glacial acetic acid and extracted

with methylene chloride to give ethyl 2-[N-(2-nitrophenyl)]thiocarbamoyl]-3-

oxobutanoate (236a) (93%) which formed off-white microcrystals, m.p. 75 -

76° (from light petroleum-toluene). \( \delta_{\max} \) 3200 (NH), 2500 br (SH), 1680 (CO),

and 1500 and 1345 (NO\(_2\)) cm\(^{-1}\), \( \delta_{n}(CDCl_3) \) 16.10 (1H, bs. NH, SH, or OH),

14.25 (1H, bs. NH, SH, or OH), 8.70 - 6.80 (4H, m, ArH), 4.30 (2H, q, J7Hz,CH\(_2\))

250(3H\(_3\),CH\(_3\)) and 1.40 (3H, t, J7Hz, CH\(_3\)).
(iv) The mixture from diethyl malonate was stirred at room temperature for 1 h then evaporated. The residue was dissolved in water (20.0 ml) and the solution acidified with 10M aqueous hydrochloric acid and extracted with methylene chloride to give an orange oil (1.8 g) which was purified by flash-chromatography in methylene chloride over silica, followed by Kugelrohr distillation to afford diethyl 2-[N-(2-nitrophenyl)thiocarbamoyl]propanedioate (236b) (71%), as a yellow oil, b.p. 120 - 140°/0.3 mm Hg, δ<sub>max</sub> 3300 br (NH), 1740 br (CO), and 1520 and 1370 (NO<sub>2</sub>) cm<sup>-1</sup>, δ<sub>δ</sub>(CDCl<sub>3</sub>) 11.90 (1H, bs, NH, SH, or OH), 8.70 (1H, d, J8Hz, ArH), 8.14 (1H, d, J8Hz, ArH), 7.92 - 7.25 (ZH, m, ArH), 5.13 (1H, s, CH), 4.30 (4H, q, J7Hz, 2 x CH<sub>2</sub>), and 1.31 (6H, t, J7Hz, 2 x CH<sub>3</sub>).

Found:  (M·H), 341.0807.

C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>O<sub>5</sub>S requires:  (M·H), 341.0807.

(v) The mixture from cyanoacetamide was stirred at room temperature for 3.5 h. The insoluble salt was collected, dissolved in water (10.0 ml) and acidified with 2M aqueous hydrochloric acid to afford 2-cyano-2-[N-(2-nitrophenyl)thiocarbamoyl]ethanamide (242) (60%), which formed yellow needles, m.p. 170 -172° (sealed tube), δ<sub>max</sub> 3420, 3340, and 3240 (NH), 2500 br (SH), 2200 (CH), 1665 (CO), and 1500 and 1350 (NO<sub>2</sub>) cm<sup>-1</sup>.

Found:  C, 45.3; H, 2.9; N, 21.1%; (M'·NO<sub>2</sub>) 218.

C<sub>13</sub>H<sub>16</sub>N<sub>3</sub>O<sub>5</sub>S requires:  C, 45.5; H, 3.0; N, 21.2%; M, 264.

Workup of the DME mother liquor gave no further identifiable
The reaction mixture from benzenesulphonylacetone was stirred at room temperature for 2 h and was then evaporated. The residue was treated with water (10.0 ml), and the mixture acidified with glacial acetic acid and treated with methylene chloride. The resulting three-phase mixture was filtered and the solid washed with ether to afford 1-benzenesulphonyl-1-[N-(2-nitrophenyl)thiocarbamoyl]propanone (246) which was combined with a second crop obtained by evaporating the methylene chloride layer and triturating the brown semisolid obtained with ether (total 81%), which formed yellow plates, m.p. 171-173° (from toluene), $\delta_{\text{max}}$ 3270 (NH), 1725 (CO), and 1520 and 1330 (NO$_2$) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 11.71 (1H, bs, NH or SH), 8.45 - 7.24 (9H, m, ArH), 5.94 (1H, s,CH), and 2.57 (3H, s, CH$_3$).

Found: C, 50.6; H, 3.6; N, 7.5%; (M.H)$^+$, 379.
C$_{11}$H$_8$N$_2$O$_2$S$_2$ requires: C, 50.8; H, 3.7; N, 7.4%; M, 378.

Quinoxaline-2(1H)-thione 4-N-oxide(231)

Solutions of the thioacetanilide derivative (226a) (22.4, 0.08 mol) in ethanol (600 ml) and potassium hydroxide (22.4 g, 0.4 mol) in ethanol (400 ml) were mixed and the mixture was heated under reflux for 1 h. The mixture was treated with water, (100 ml), and the solution acidified with 10M hydrochloric acid and filtered to afford the quinoxalinethione N-oxide (231) (12.7 g; 89%), (lit. 15 183°), $\delta_{\text{max}}$ 3200-2500 br (NH, SH), $\delta_{\text{H}}$(CD$_3$)$_2$SO] 13.98 (1H, bs, NH or SH), 8.29 (1H, s, CH), 8.15 (1H, d, J8Hz, ArH), and 7.88 - 7.36 (4H, m, ArH).

Found: C, 53.8; H, 3.4; N, 15.6%; M$^+$, 178.
(ii) Solutions of the thioacetanilide derivative (226b) (0.72 g; 0.0018 mol) in ethanol (25.0 ml) and potassium hydroxide (0.42 g, 0.0075 mol) in ethanol (10.0 ml) were mixed and the mixture was heated under reflux for 1.5 h. The mixture was evaporated and the residue was treated with water (10.0 ml), the resulting solution acidified with 10M aqueous hydrochloric acid and filtered to afford the quinoxalinethione N-oxide (231) (0.33 g; quant.), m.p. 176 - 180°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared in (i) before.

Quinoxaline-2(1H)-thione (232)

(i) A solution of the quinoxalinethione-N-oxide (231) (0.72 g, 0.004 mol) in glacial acetic acid (25.0 ml) was treated with sodium dithionite (0.72 g) and the mixture was heated under reflux for 1 h after which time a second portion of sodium dithionite (0.72 g) was added and heating under reflux continued for a further 1 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and filtered to afford a brown solid (0.61 g) which was triturated with methylene chloride to yield unchanged starting-material (231) (0.24 g; 30%), m.p. 176 - 182°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the methylene chloride mother liquor gave a brown solid (0.24 g) which was dry column flash-chromatographed over silica.

Elution with methylene chloride gave sulphur (0.06 g).
Further elution with methylene chloride - ethyl acetate gave quinoxaline-2-(1H)-thione (232), (0.10 g; 15%) which formed yellow needles, m.p. 202 - 204° (from toluene) (lit.,[25,70] 204 - 205°), $\delta_{\text{max}}$ 3200 - 2500 br (NH, SH), $\delta_{\text{NH}}$(CDCl$_3$) 14.4 (1H, s, NH) (exch.), 8.54 (1H, s, H-2) and 7.92 - 7.34 (4H, m, ArH).

**Found:**

C, 59.8; H, 3.8; N, 17.3%; M$^+$, 162.

**Calc. for C$_7$H$_5$N$_2$:**

C, 59.3; H, 3.7; N, 17.3%; M, 162.

(ii) A solution of the quinoxaline-thione N-oxide (231) (0.72 g, 0.004 mol) in 70% v/v aqueous DMF (25.0 ml) was treated with sodium dithionite (0.72 g) and the mixture was heated under reflux for 1 h. after which time a second portion of sodium dithionite (0.72 g) was added and heating under reflux continued for a further 1 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a brown semi-solid (0.53 g). The semi-solid was dry column flash-chromatographed over silica.

Elution with methylene chloride gave some brown solid (0.04 g) which was not further investigated.

Further elution with methylene chloride-ethyl acetate (10:1) gave quinoxaline-2(1H)-thione (232) (0.20 g; 31%), m.p. 200 - 204°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared in (i) before.

Further elution with methylene chloride-ethyl acetate (5:1) through
ethyl acetate to methanol gave only a series of intractable gums (total 0.18 g)

3-Methylthioquinoxaline 1-N-oxide (233)

A stirred suspension of sodium hydride (0.058 g, 0.0024 mol) in anhydrous DMF (2.5 ml) was treated with a solution of the quinoxaline N-oxide (231) (0.36 g, 0.002 mol) in anhydrous DMF (5.0 ml) and the mixture was stirred at room temperature for 15 min. after which time the mixture was treated with methyl iodide (0.57 g, 0.004 mol) and stirred at room temperature for 24 h. The mixture was treated with water (15.0 ml) and extracted with methylene chloride to give a brown semi-solid which was flash-chromatographed over silica.

Elution with methylene chloride gave the methylthioquinoxaline N-oxide (233) (0.24 g; 64%) which formed buff coloured needles, m.p. 94-95° (from light petroleum-toluene). δ_H(DCl3) 8.52 - 8.40 (1H, m, ArH), 8.22 (1H, s, H-3), 8.01 - 7.45 (3H, m, ArH), and 2.68 (3H, s, CH3).

Found: C, 56.4; H, 4.1; N, 14.7%; M*, 192.

C9H6N2S requires: C, 56.2; H 4.2; N, 14.6%; M, 192.

Further elution with ethyl acetate then methanol yielded only a brown gum (0.02 g) which was not further investigated.

3-Methylthioquinoxaline (235)

A solution of the methylthioquinoxaline N-oxide (233) (0.28 g, 0.002 mol) in 70% v/v aqueous ethanol (10.0 ml) was treated with sodium dithionite (0.38 g) and the mixture was heated under reflux for 1 h after
which time a further portion of sodium dithionite (0.38 g) was added and heating under reflux was continued for a further 1 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a gum (0.23 g) which was flash-chromatographed in methylene chloride over silica to give 3-methylthioquinoxaline (235) (0.15 g; 43%), which formed yellow microcrystals, m.p. 41- 42° (from light petroleum) (lit., 71 46°), δ H(CDC13) 8.60 (1H, s, H-3), 8.02 - 7.56 (4H, m, ArH) and 2.70 (3H, s, CH3).

Found: C, 61.5; H, 4.5; N, 15.8%; M⁺, 176.
Calc. for C11H9N5S: C, 61.4; H, 4.5; N, 15.9%; M, 176.

Further elution with methylene chloride through ethyl acetate to methanol gave only intractable gums (total 0.06 g) which were not further investigated.

The Attempted Cyclisation of Ethyl 2-[N-(2-nitrophenyl)thiocarbamoyl]-3-oxobutanoate (236a) Using Ethanolic Potassium Hydroxide.

A solution of the thioacetanilide derivative (236a) (0.62 g, 0.002 mol) in ethanol (10.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 1 h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and the resulting solution acidified with 2M aqueous hydrochloric acid to afford an orange solid (0.20 g) which decomposed on attempted crystallisation and therefore could not be characterised.
Elution of the aqueous acidic mother liquor with methylene chloride gave only a red gum (0.14 g) which yielded no identifiable material.

The Cyclisation of Diethyl 2-[N-(2-nitrophenyl)thiocarbamoyl]propanedioate (236b) using Ethanoic Potassium Hydroxide

A solution of the thioacetanilide derivative (236b) (0.68 g, 0.002 mol) in ethanol (30.0 ml) was treated with solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 3 h.

The mixture (containing a solid) was evaporated and the red gummy residue was treated with water (10.0 ml) and acidified with 10M aqueous chloride to give a three-phase mixture which filtered to afford 1-N-hydroxyquinolin-2(1H)-one-3(4H)-thione (240) (0.23 g; 59%), which formed yellow brown crystals, m.p. 216 - 218° (from toluene-DMF), and was identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared later.

The Attempted Cyclisation of 2-Cyano-2-[N-(2-nitrophenyl)thiocarbamoyl]acetamide (242) using Ethanoic Potassium Hydroxide

A solution of the thioacetanilide derivative (242) (0.53 g; 0.002 mol) in ethanol (10.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was cooled and filtered to afford an insoluble solid (0.61 g) which was dissolved in water (10.0 ml) and the solution acidified with 2M aqueous hydrochloric acid to precipitate a solid which was
combined with a second crop obtained by extracting the aqueous acidic mother liquor with methylene chloride to afford unchanged starting material (0.48; 91%), m.p. 166 - 170°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The original ethanolic filtrate was evaporated and the residue was treated with water (10.0 ml), acidified with 10M aqueous hydrochloric acid and extracted with methylene chloride to give only a small amount of yellow gum (0.05 g) which was not further investigated.

1-N-Hydroxyquinoxalin-2(1H)-one-3(4H)-thione (240)

A solution of the thioacetanilide derivative (246) (3.8 g, 0.01 mol) in ethanol (450 ml), was treated with a solution of potassium hydroxide (2.8 g, 0.05 mol) in ethanol (50.0 ml) and the mixture was heated under reflux for 2 h. The mixture was then evaporated and the residue was treated with water (50.0 ml) and the solution acidified with 2M aqueous hydrochloric acid to afford 1-N-hydroxyquinoxalin-2(1H)-one-3(4H)-thione (240) (1.1 g; 55%) which formed brown crystals, m.p. 218 - 219° (from glacial acetic acid - DMF), $\delta_{\text{max}}$ 3170 and 3110 (NH and OH) and 1630 (CO) cm$^{-1}$. $\delta_{\text{H}}$(CD$_3$)$_2$SO 7.54 - 7.21 (m, ArH, NH and OH) (exch.)

Found: C, 49.3; H, 3.1; N, 14.2%; M’, 194

C$_9$H$_7$N$_2$O$_2$S requires: C, 49.5; H, 3.1; N, 14.4%; M, 194.

The aqueous acidic mother liquor was extracted with methylene chloride to yield a brown oil (1.7 g) flash-chromatography of which in methylene chloride through ethyl acetate to methanol over silica gave only a series of intractable gums which yielded no identifiable material.
The Attempted Acetylation of 1-N-Hydroxyquinoxaline-2(1H)-one-3(4H)-thione (240)

A solution of the N-hydroxyquinoxaline derivative (240) (0.39 g; 0.002 mol) in anhydrous DMF (10.0 ml) was treated with triethylamine (0.22, 0.0022 mol) and the mixture was stirred at room temperature for 5 min. The mixture was then treated with acetyl chloride (0.16 g; 0.002 mol) and was stirred at room temperature for 0.5 h. The mixture was filtered to remove triethylamine hydrochloride (0.14 g) and the filtrate was evaporated to yield a brown gum (0.56 g) which yielded no identifiable material.

The Attempted Reaction of 1-N-Hydroxyquinoxaline-2(1H)-one-3(4H)-thione (240) with Phenyl Isocyanate

A solution of the N-hydroxyquinoxaline derivative (240) (0.39 g, 0.002 mol) in anhydrous DMF (5.0 ml) was stirred and treated with phenyl isocyanate (0.24 g, 0.002 mol) and the mixture was stirred at room temperature for 35 h. The mixture was evaporated under high vacuum (oil pump) to give a green semisolid (0.54 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable mixture of the starting material (240) and diphenylurea.

The Attempted Reduction of 1-N-Hydroxyquinoxaline-2(1H)-one-3(4H)-thione (240) with Sodium Dithionite in Aqueous Dimethylformamide

A solution of the N-hydroxyquinoxaline derivative (240) (0.14 g, 0.0007 mol) in 70% v/v aqueous DMF (10.0 ml) was treated with sodium dithionite (0.14 g) and the mixture was heated at 100° for 1 h. The mixture was then treated with a second portion of sodium dithionite (0.14 g) and
heating at 100° was continued for a further 1 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with water and extracted with methylene chloride to afford only a small amount (0.02 g) of an intractable gum.

[1,4]Dithiino[2,3-b:5,6-b']diquinoxaline (253)

A solution of quinoxalin-2(1H)-thione 4-N-oxide (231) (0.36 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was cooled and filtered to afford the dithiino-diquinoxaline (253) (0.23 g; 72%) which formed brown crystals, m.p. > 358° (lit., 73 > 360°), δ$_{1}$([CD$_{3}$]$_{2}$SO] 8.01 - 7.96 (4H, m, ArH) and 7.84 - 7.79 (4H, m, ArH).

Found: C, 60.0; H, 2.4; N, 17.4%; M', 320.
Calc. for C$_{16}$H$_{9}$N$_{5}$S$_{2}$: C, 60.00; H, 2.5; N, 17.5%; M, 320.

The acetic anhydride mother liquor was evaporated to afford a brown oil (0.14 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

3-Methylthioquinoxalin-2(1H)-one (254)

A solution of 3-methylthioquinoxaline 1-N-oxide (233) (0.38 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated, and the resulting oil was triturated with ether to afford 3-methylthioquinoxalin-2(1H)-one (254) (0.14 g; 37%) which formed grey crystals, m.p. 248 - 251° (from toluene), δ$_{max}$ 3200 - 2500 (NH, OH) (exch.), 7.77 (1H, d J8HZ, ArH), 7.42 - 7.25 (3H, m, ArH) and 2.60 (1H, s, CH$_{3}$).
Found: C. 56.2; H. 4.2; N, 14.6%; M. 192.

C₉H₈N₄O₅S requires: C. 56.3; H. 4.0; N, 14.8%; M. 192

The ethanol mother liquor was evaporated to give a brown gum (0.25 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Reaction of Quinoxaline-2(1H)-thione 4-N-oxide (231) with Phenyl Isocyanate

A solution of the quinoxalinethione N-oxide (231) (0.89 g, 0.005 mol) in anhydrous DMF (10.0 ml) was treated with phenyl isocyanate (0.65 g, 0.005 mol) and the mixture was heated under reflux for 3 h. The mixture was then cooled, treated with water (20.0 ml) and extracted with methylene chloride. The resulting three-phase mixture was filtered to afford [1,4]dithiino[2,3-b:5,6-b']diquinoxaline (253) (0.055 g; 8%), m.p. > 358°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

The methylene chloride extract was evaporated to give a brown oil (1.2 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 3-phenylaminoquinoxaline-2(1H)-thione (219) (0.04 g; 3%) which formed yellow needles, m.p. 234-236° (from light petroleum -toluene), identical (m.p. and i.r. spectrum) with a sample prepared before.

Further elution with methylene chloride-ethyl acetate (2:1) gave a
brown semi-solid (0.26 g) which was triturated with ether to afford
diphenylurea (0.08 g; 4%) m.p. 238 - 240°, identified by comparison (m.p.
and i.r. spectrum) with an authentic sample.

The Attempted Reaction of 3-Methylthioquinoxaline 1-N-oxide (233) with
Phenyl Isocyanate.

A solution of the methylthioquinoxaline 1-N-oxide (233) (0.38 g,
0.002 mol) in anhydrous toluene (10.0 ml) was treated with phenyl
isocyanate (0.26 g, 0.0022 mol) and the mixture was heated under reflux for
96 h. The mixture was evaporated to give a brown gum (0.62 g) which was
dry column flash chromatographed over silica.

Elution with methylene chloride through ethyl acetate to ethanol
gave only a series of intractable multicomponent mixtures (total 0.48 g)
which were not further investigated.

3-Cyanoquinoxaline-2(1H)-thione (258)

A suspension of the quinoxalinethione N-oxide (231) (0.36, 0.002
mol) in water (5.0 ml) was treated with solid potassium cyanide (0.14 g,
0.0022 mol) and the mixture was heated at 100° (water bath) for 15 min.
The mixture was cooled and washed with methylene chloride to remove a
small amount of a brown gum (0.05 g).

The aqueous mother liquor was acidified with glacial acetic acid to
afford 3-cyanoquinoxaline-2(1H)-thione (258) (0.30 g; 81%) which formed red
crystals, m.p. 242 -244° (from glacial acetic acid), δ_{max} 3200 - 2500 br (NH,
SH) and 2240 w (CN) cm⁻¹, δ_{1H}(CDCl₃)₂SO] 8.42 - 7.99 (m, ArH and NH).
2- Cyano-3-methylthioquinoxaline (259)

A stirred suspension of sodium hydride (0.20 g, 0.0084 mol) in anhydrous DMF (10.0 ml) was treated with a solution of the 3-cyanoquinoxaline-2-thione (258) (1.3 g, 0.007 mol) in anhydrous DMF and the mixture was stirred at room temperature for 15 min. The mixture was treated with methyl iodide (2.0 g, 0.014 mol) and stirring was continued at room temperature for 24 h.

The mixture was treated with water (50.0 ml) and filtered to afford the cyanomethylthioquinoxaline derivative (259) (1.2 g; 87%), which formed green-brown needles, m.p. 148 - 149° (from light petroleum-toluene), $\delta_{\text{max}} 2220 \text{ w (CN)} \text{ cm}^{-1}$, $\delta_{\text{1}}(\text{CDCl}_3) 8.03 (1H, d, J 8\text{Hz, ArH}), 7.70 (1H, t J 8\text{Hz ArH}),$ and 2.74 (3H, s, CH$_3$).

Extraction of the aqueous mother liquor with methylene chloride gave an intractable brown gum (0.14 g) which was not further investigated.

Reactions of 3-Methylthioquinoxaline 1-N-oxide (233) with Potassium Cyanide

(l) A suspension of the methylthioquinoxaline N-oxide (233) (0.38 g, 0.002 mol) in water (5.0 ml) was treated with potassium cyanide (0.14 g, 0.0022 mol) and the mixture was heated at 100° (water bath) for 15 min. The mixture was extracted with methylene chloride to give impure
starting-material (233) (0.35 g; 92%), m.p. 75 - 80°, identified by comparison (i.r. spectrum) with an authentic sample.

The aqueous mother liquor was acidified with glacial acetic acid and extracted with methylene chloride to give 3-methylthioquinoxalin-2(1H)-one (254) (0.02 g; 6%), m.p. 240 -245°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

(ii) Solutions of the methylthioquinoxaline N-oxide (233) (0.38 g, 0.002 mol) in ethanol (10.0 ml) and potassium cyanide (0.39 g, 0.006 mol) in water (2.0 ml) were mixed and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give 3-methylthioquinoxaline-2-carboxamide (262) (0.37 g, 84%), which formed yellow needles, m.p. 200 - 201° (from toluene), δ max 3250, 3260, and 3180 (NHa) and 1700 (CO) cm⁻¹. δH(CDCl3) 8.05 - 7.60 (4H, m, ArH) and 2.62 (3H, s, CH₃).

Found: C, 54.8; H, 4.1; N, 19.2; % M, 219.

C₁₀H₈N₂O requires: C, 54.8; H, 4.1; N, 19.2; % M, 219.

The aqueous alkaline mother liquor was acidified with 2M aqueous hydrochloric acid (gas evolution) and extracted with methylene chloride to give the methylthioquinoxalinone (254) (0.05 g; 13%), m.p. 240 - 250°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.
The Attempted Reaction of Quinoxaline-2(1H)-thione 4-N-oxide (231) with Ethanolic Sodium Ethoxide

A suspension of the quinoxalinethione N-oxide (231) (0.38 g, 0.002 mol) in anhydrous ethanol (15.0 ml) was treated with a solution of sodium (0.18 g, 0.008 g atom) in anhydrous ethanol (10.0 ml) and the resulting solution was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml), acidified with 10M aqueous hydrochloric acid and filtered to afford unchanged starting material (231) (0.35 g; 90%), m.p. 178 - 180°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of Quinoxaline 2(H)-thione 4-N-oxide (231) with 2M Aqueous Sodium Hydroxide

A solution of the quinoxalinethione N-oxide (231) (0.39 g, 0.002 mol) in 2M aqueous sodium hydroxide (5.0 ml) was heated under reflux for 5 h. The mixture was cooled, acidified with 2M aqueous hydrochloric acid, and filtered to give unchanged starting-material (231) (0.35 g; 90%), m.p. 180 - 182°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of 3-Methylthioquinoxaline 1-N-oxide (233) with Aqueous Ethanolic Sodium Hydroxide

A solution of the methylthioquinoxaline N-oxide derivative (233) (0.19 g, 0.001 mol) in ethanol (10.0 ml) was treated with 2 M aqueous sodium hydroxide (2.5 ml) and the mixture was heated under reflux for 2 h. The mixture was concentrated under vacuum to remove the ethanol and then extracted with methylene chloride to give only a negligible amount of
an orange solid.

Acidification of the aqueous alkaline mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride afforded only a small amount of a pink solid (0.07 g) whose t.l.c. in methylene chloride over silica showed it to be a several component mixture which was therefore not further investigated.

The Attempted Reaction of Quinoxaline-2(H)-thione 4-N-oxide (231) with Benzylamine in Ethanol

A suspension of the quinoxalinethione N-oxide (231) (0.36 g, 0.002 mol) in anhydrous ethanol (15.0 ml) was treated with benzylamine (0.43 g, 0.004 mol) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the brown oil obtained was triturated with methylene chloride to afford crude starting-material (0.36 g: quant.), m.p. 149 - 151°, identified by comparison (i.r. spectrum) with an authentic sample.

Attempted Reactions of Quinoxaline-2(1H)-thione 4-N-oxide (231) with Acetylacetone

(i) A suspension of the quinoxalinethione N-oxide derivative (231) (0.36 g, 0.002 mol) in ethanol (15.0 ml) was treated with acetylacetone (0.2 g, 0.002 mol) followed by piperidine (0.3 ml, 0.003 mol) and the mixture was heated under reflux for 0.5 h. The mixture was cooled and evaporated to give a brown gum which was treated with 2M aqueous hydrochloric acid (2.0 ml) and extracted with methylene chloride to give a dark brown gum (0.30 g). The gum was dry column flash-chromatographed over silica.
Elution with methylene chloride-ethyl acetate (5:1) gave a small amount of a brown gum (0.04 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

Further elution with methylene chloride-ethyl acetate (3:1) gave impure unreacted starting-material (231) (0.10 g; 28%), m.p. 167 - 169°, identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-ethyl acetate (2:1) through ethyl acetate to ethanol gave only a series of intractable gums (total 0.04 g) which were not further investigated.

(ii) A stirred suspension of sodium hydride (0.05 g, 0.002 mol) in anhydrous DMF (5.0 ml) was treated with acetylacetone (0.22 g, 0.0022 mol) and the mixture was stirred at room temperature for 0.5 h. The mixture was then treated with a solution of the quinoxalinethione N-oxide derivative (231) (0.36 g, 0.002 mol) in anhydrous DMF and the mixture was stirred at room temperature for 4 h. after which time a t.l.c. of the mixture in methylene chloride over silica showed no sign of reaction. The mixture was heated under reflux for 40 min. then evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give an intractable brown gum (0.13 g) which was not further investigated.

The aqueous mother liquor was acidified with 10 M aqueous hydrochloric acid and extracted with methylene chloride to give a brown gum whose t.l.c. in methylene chloride over silica showed it to be a
multicomponent mixture which was not further investigated.

The Attempted Reaction of 3-Methylthioquinoxaline 1-N-oxide (233) with Acetylacetone

A stirred suspension of sodium hydride (0.05 g, 0.002 mol) in anhydrous DMF (5.0 ml) was stirred and treated at room temperature with acetylacetone (0.22 g, 0.0033 mol) and the mixture was stirred at room temperature for 5 min. The resulting solution of the sodium salt of acetylacetone was treated with a solution of the methylthioquinoxaline N-oxide (233) (0.38 g, 0.002 mol) in anhydrous DMF (5.0 ml) and the mixture was stirred at room temperature for 4 h after which time t.l.c. of the mixture in methylene chloride over silica showed no sign of reaction. The mixture was therefore heated under reflux for 0.5 h then evaporated under high vacuum (oil pump) and the residue treated with water (5.0 ml) and extracted with methylene chloride to give a small amount of brown gum whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The aqueous alkaline mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give only a small amount of a brown gum (0.03 g) which was not further investigated.

The Attempted Reaction of N-2-Nitrophenyl Triphenyphosphinimine (152) with Carbon Dioxide

A solution of the phosphinimine (152) (1.6 g, 0.004 mol) in anhydrous toluene (40.0 ml) was heated at 80° (oil bath) while a stream of carbon dioxide was bubbled through the mixture for 2 h. The mixture was
evaporated to give unchanged starting-material (152) (1.6 g; quant.), m.p.
137 -148°, identified by comparison (m.p. and i.r. spectrum) with an
authentic sample.

2-Nitrophenyl Isocyanate (264)

A solution of 2-nitrobenzoyl chloride (263) (1.8 g 0.01 mol) in
Analar acetone (25.0 ml) was treated dropwise with stirring at 0° (ice-salt
bath) with a solution of sodium azide (0.68 g, 0.01 mol) in water (5.0 ml)
and the mixture was stirred at 0° for 0.5 h. The mixture was diluted with
water (50.0 ml) and extracted with ether to give a yellow semi-solid mixture
of 2-nitrobenzoyl azide (263; N₃ for Cl) and 2-nitrophenyl isocyanate (264)
(1.6 g), δₘₐₓ 2260 (NCO), 2115 (N₃), and 1700 (CO) cm⁻¹.

A solution of the semi-solid (1.5 g) in anhydrous benzene (20.0 ml)
was heated under reflux for 1 h. after which time the mixture was
evaporated to give 2-nitrophenyl isocyanate (264) as a yellow solid (1.4 g;
84%), m.p. 34 - 38° (lit., 74° 40°) which was used without further purification.

3-[N-(2-nitrophenyl)carbamoyl]pentane-2,4-dione (265a)

A suspension of sodium hydride (0.24 g, 0.01 mol) in anhydrous
DME (20.0 ml) was stirred and treated at room temperature with
acetylacetone (1.1 g, 0.011 mol). The suspension was stirred at room
temperature for 5 min. then treated with a solution of 2-nitrophenyl
isocyanate (264) (1.6 g, 0.01 mol) in anhydrous DME (10.0 ml) and stirring
continued at room temperature for 1 h. The insoluble salt was collected,
dissolved in water (15.0 ml) and acidified with 10M aqueous hydrochloric
acid to afford 3-[N-(2-nitrophenyl)carbamoyl]pentane-2,4-dione (265a) (2.2 g:
84%), which formed yellow crystals, m.p. 130 - 132° (from toluene-light petroleum), $\delta_{\text{max}}$ 3100 - 2500 br (NH, OH), and 1600 br (CO) cm$^{-1}$, $\delta_{\text{H}}$ (CDCl$_3$) 10.39 (1H, bs, NH), 8.84 (1H, dd, $J_{\text{ortho}}$ 9Hz $J_{\text{meta}}$ 1Hz ArH), 8.16 (1H, qd, $J_{\text{ortho}}$ 9Hz $J_{n}$ 1Hz ArH), 7.65 (1H, qd, $J_{\text{ortho}}$ 9Hz $J_{\text{meta}}$ 1Hz ArH) 7.32 - 7.13 (1H, m, ArH) and 2.27 (6H, s, 2 x CH$_3$), and was identified by comparison (m.p. and i.r. and 1 h n.m.r. spectra) with a sample prepared before.

The DME mother liquor was evaporated to give an orange gum (0.19 g) from which no other identifiable material could be obtained.

Quinoxalin-2(1H)-one 4-N-oxide (202)

A solution of the acetanilide derivative (265a) (0.53 g, 0.002 mol) in ethanol (15.0 ml) was treated with a solution of potassium hydroxide (0.56g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under reflux for 1 h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and the resulting solution acidified with 10 M aqueous hydrochloric acid and filtered to afford quinoxalin-2(1H)-one 4-N-oxide (202) (0.16 g; 50%), m.p. 265 -270° (lit.$^{16}$ 276°) identified by comparison (m.p. and i.r. spectrum) with an authentic sample$^{16}$.

Extraction of the aqueous acidic mother liquor with methylene chloride gave only a small amount of yellow oil (0.03 g) which was not further investigated.
Ethyl 2-[N-(2-Nitrophenyl)carbamoyl]-3-oxobutanoate (265b)

A stirred suspension of sodium hydride (0.20 g, 0.008 mol) in anhydrous DME (10.0 ml) was treated with ethyl acetoacetate (1.2 g, 0.009 mol) and the mixture was stirred at room temperature for 10 min. The resulting solution was then treated with a solution of 2-nitrophenyl isocyanate (264) (1.4 g, 0.008 mol) in anhydrous DME (10.0 ml) and the mixture was stirred at room temperature for 0.5 h. The insoluble salt was collected, treated with 2M aqueous hydrochloric acid (10.0 ml) and the mixture extracted with methylene chloride to give ethyl 2-[N-nitrophenyl]carbamoyl]3-oxobutanoate (265b) (1.8 g; 60%), which formed pale yellow crystals, m.p. 79 - 80° (from light petroleum-toluene), \( \delta_{max} \) 3150 (NH), 1675 (C=O), and 1500 and 1375 (NO₂) cm⁻¹. \( \delta_{\text{H}}(\text{CDCl}_3) \) 14.41 (1H, s, OH), 12.38 (1H, s, NH), 8.34 (1H, dd \( J_{\text{ortho}} 8 \text{ Hz} \ J_{\text{meta}} 2 \text{ Hz} \text{ ArH} \)), 8.11 (1H, dd \( J_{\text{ortho}} 8 \text{ Hz} \ J_{\text{meta}} 2 \text{ Hz} \text{ ArH} \)), 7.60 (1H, td \( J_{\text{ortho}} 8 \text{ Hz} \ J_{\text{meta}} 2 \text{ Hz} \text{ ArH} \)), 7.32 - 7.11 (1H, m, ArH), 4.36 (2H, q \( J 7 \text{ Hz} \text{ CH}_2 \)), 2.48 (3H, s, CH₃).

Found: C, 52.6; H, 4.7; N, 9.5%; M⁺, 294.

C₁₄H₁₄N₂O₆ requires: C, 53.1; H, 4.8; N, 9.5%; M, 294.

Evaporation of the DME mother liquor gave an intractable orange gum (0.39 g) which was not further investigated.

The Attempted Cyclisation of Ethyl 2-[N-(2-nitrophenyl)carbamoyl]-3-oxobutanoate (265b) using Ethanolic Potassium Hydroxide

A solution of the acetanilide derivative (265b) (0.59 g, 0.002 mol) in ethanol (10.0 ml) was treated with a solution of potassium hydroxide (0.56 g, 0.01 mol) in ethanol (10.0 ml) and the mixture was heated under
reflux for 1 h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and filtered to afford 2-nitroaniline (0.095 g; 34%), m.p. 72 - 74°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride gave only a small amount of an orange oil which was not further investigated.

1-Benzencesulphonyl-1-[N-(2-nitrophenyl)carbamoyl]propanone (265c)

A stirred suspension of sodium hydride (0.38 g, 0.016 mol) in anhydrous DME (30.0 ml) was treated with benzenesulphonylacetonite (3.5 g, 0.018 mol) and the mixture was stirred at room temperature for 10 min. The mixture was then treated with a solution of 2-nitrophenyl isocyanate (264) (2.6 g, 0.016 mol) in anhydrous DME (20.0 ml) and the mixture was stirred at room temperature for 0.5 h. The mixture was evaporated and the residue was treated with water (50.0 ml), acidified with 10M aqueous hydrochloric acid and extracted with methylene chloride to give 1-benzenesulphonyl-1-[N-(2-nitrophenyl)carbamoyl]propanone (265c) (5.7 g; 98%), which formed yellow needles, m.p. 168 - 170° (from toluene), $\delta_{\text{max}}$ 3260 (NH), 1720 and 1685 (CO), and 1505 and 1375 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 17.19 (1H, s, OH), 11.73 (1H, bs NH), 8.52 - 7.14 (4H, m, ArH), and 2.42 (3H, s, CH$_3$)

Found: C, 53.2; H,3.9; N, 7.7%; M, 362.

C$_{14}$H$_{14}$N,O,S requires: C, 53.2; H,3.8; N,7.9%; M, 362.
The Attempted Cyclisation of 1-Benzensulphonyl 1-[N-(2-nitrophenyl)carbamoyl]propanone (265c) using Ethanolic Potassium Hydroxide

A solution of the acetanilide derivative (265c) (1.8 g, 0.005 mol) in ethanol (30.0 ml) was treated with a solution of potassium hydroxide (1.4 g, 0.025 mol) in ethanol (25.0 ml) and the mixture was heated under reflux for 3 h. The mixture was evaporated and the residue was treated with water (15.0 ml), acidified with 2M aqueous hydrochloric acid, and extracted with methylene chloride to give an intractable brown oil (1.5 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture containing 2-nitroaniline. The oil was not further investigated.
Chapter 3

INVESTIGATIONS OF HETEROCYCLISATION REACTIONS OF
2-NITROBENZOYL METHYLENETRIPHENYLPHOSPHORANE
DERIVATIVES AND RELATED COMPOUNDS
(i) NaOEt, EtOH, reflux.

Scheme 67
3.1. Introduction

As already discussed in detail in Chapter 1, a variety of nitrobenzene derivatives capable of furnishing a stabilised carbanion centre in an ortho side-chain undergo base-catalysed aldol-type cyclisation reactions which provide practical methods for the synthesis of otherwise inaccessible types of N-oxygenated heterocyclic products. Compelling evidence that these novel types of heterocyclisation reactions can occur by direct nucleophilic attack by the carbanion centre in the ortho side-chain on the intact nitro-group is provided by the behaviour of certain 2-nitrobenzoyl derivatives. For example (Scheme 67) N-cyanomethyl 2-nitrobenzamide derivatives (270) on heating with ethanolic sodium ethoxide are smoothly converted in high yield into N-hydroxyquinazolinedione derivatives (275). These transformations can be rationalised by a course (scheme 67) initiated by direct nucleophilic attack by the cyanomethyl carbanion centre in the ortho side-chain on the nitro-group and leading to the intermediate formation of the corresponding 2-cyanoquinazolinone N-oxides [(270) \(\rightarrow\) (271) \(\rightarrow\) (272) \(\rightarrow\) (273)]. Hydrolytic decyanation of the latter under the reaction conditions then accounts for the observed N-hydroxyquinazolinedione products [(273) \(\rightarrow\) (274) \(\rightarrow\) (275)].

The efficiency of the useful heterocyclisation reactions [Scheme 67; (270) \(\rightarrow\) (275)] can be attributed, at least in part, to the increased electrophilicity of the nitro-group imparted by the carbonyl substituent in the ortho acyl side-chain. This supposition, if correct, implies that nitrobenzene
(i) Br₂, AcOH, heat.
(ii) Ph₃P, toluene, room temp.
(iii) NaOH or Na₂CO₃, H₂O, room temp.
(iv) toluene, xylene, diglyme or HCO₂H-AcOH, heat or h¹/toluene.
(v) Br₂, NaOH, AcOH, 10-15°.
(vi) xylene, heat.

Scheme 68
derivatives with appropriately structured ortho acylcarbanion side-chains should show an enhanced tendency to undergo aldol-type heterocyclisation. Of particular interest in this context (Scheme 68) are readily accessible 2-nitrobenzoylmethylenetriphenylphosphorane derivatives such as the parent compound (280). This molecule, reacting in its betaine resonance form (279), has the potential to undergo novel, uncatalysed, thermal cyclisation to afford 1H-indol-3-one 1-N-oxide (isatogen) (283), the elusive parent of a rare class of heterocyclic compounds.\(^79\) This transformation would involve the condensation of a phosphorus-stabilised carbanion with a nitro-group in a hitherto unknown variant [(279) \(\rightarrow\) (281) \(\rightarrow\) (283)] of the well known Wittig reaction.\(^80\) In view of this and the potential of processes of the type [(279) \(\rightarrow\) (283)] for the convenient synthesis of otherwise unknown or difficultly accessible isatogen derivatives,\(^79\) it was decided in the present studies to carry out a general investigation of the synthesis and uncatalysed thermal cyclisation reactions of 2-nitrobenzoylmethylene triphenylphosphorane derivatives.

3.2 Investigations of the Synthesis and Uncatalysed Thermal Cyclisation Reactions of 2-Nitrobenzoylmethylenetriphenylphosphorane Derivatives

It was recognised at the outset of these studies that a process (Scheme 69) which might compete with the hoped-for Wittig-like cyclisation [(280) \(\rightarrow\) (283)] was thermal elimination involving expulsion of triphenylphosphine oxide via the betaine resonance form (285) to give an alkyne (286). However, even if this was the pathway followed it would still be of interest as a valuable route to otherwise difficult to obtain 2-nitrophenylalkynes [e.g. (286)] useful as intermediates in isatogen synthesis.\(^79\)
(280) $\stackrel{(i)}{\longrightarrow} (285)$

(i) $\text{Ph}_3\text{P}=\text{O}$

(286) \[ \xrightarrow{h\nu} \]

(283)

(287) $\stackrel{(i)}{\longrightarrow} (288)$

(i) $\text{Ph}_3\text{P}=\text{O}$

(289) \[ \xrightarrow{h\nu} \]

(290)

(i) heat.
(ii) $h\nu$, benzene.

Scheme 69
Indeed Abramovitch and Cue have shown (Scheme 69) that thermolysis of the cyano-substituted 2-nitrobenzoylmethylenetriphenylphosphorane (287) affords the cyano-alkyne (289) which in turn undergoes photocyclisation to yield 2-cyanoisatogen (290).

The initial compound chosen for study in the present investigations was the parent 2-nitrobenzoylmethylenetriphenylphosphorane (280). This molecule had been synthesised in the course of other studies at Edinburgh and was readily prepared by the standard procedure outlined in Scheme 68. This involved the bromination of the readily accessible 2-nitroacetophenone (276) followed by reaction of the resulting, known bromo-ketone (277) with triphenylphosphine and treatment of the phosphonium salt (278) obtained with aqueous sodium carbonate or sodium hydroxide. An initial attempt to achieve the thermal cyclisation [(280) \(\rightarrow\) (283)] by heating under reflux in toluene gave only a high recovery of the unreacted starting-material (280). Prolonged heating of the phosphorane (280) in the higher boiling solvent xylene also afforded unreacted starting-material (280) though in much lower yield (56%). Also isolated under these conditions was triphenylphosphine oxide indicating that some form of reaction had occurred though no other co-product could be identified. Heating the phosphorane (280) under reflux in the higher boiling solvent diglyme gave only a complex gum which yielded no identifiable material. An attempt to catalyse the thermolysis of the phosphorane (280) by heating under reflux with formic acid in acetic acid was also unsuccessful, the starting-material (280) being recovered unchanged in high yield (88%). The phosphorane (280) was also found to be stable to photolysis, prolonged irradiation at 254 nm in toluene giving only a good recovery (82%) of unreacted starting-material (280).
The thermal and photochemical stability of the phosphorane (280) was disappointing and in the light of the successful thermolysis of the cyano-substituted phosphorane (287) reported by Abramovitch and Cue\textsuperscript{81} (See Scheme 69 before) it was next decided to investigate the thermal behaviour of 2-nitrobenzoylmethylenetriphenylphosphoranes bearing an electron-withdrawing group at the methylene centre. Despite the extrusion reaction [(287) $\rightarrow$ (289)] reported by Abramovitch and Cue\textsuperscript{81} it was reasoned that the effect of an electron-withdrawing group at the methylene centre of the phosphorane (280) would be to suppress betaine-character of the type (288) and hence enhance the opportunity for nucleophilic cyclisation of the Wittig-type [Scheme 68; (279) $\rightarrow$ (281) $\rightarrow$ (283)]. The initial 2-nitrobenzoyl methylenetriphenylphosphorane chosen for study in this context (Scheme 68) was the bromo-compound (282). The bromination of arylmethylenetriphenyl phosphoranes at the methylene centre is a well known\textsuperscript{85} process and the analogous bromination of the already available 2-nitrobenzoylmethylene triphenylphosphorane (280) afforded the previously unreported bromo-derivative (282) in quantitative yield. Though the bromophosphorane (282) failed to show a peak due to the parent ion in its mass spectrum its analytical and spectroscopic properties were otherwise in accord with its assigned structure.

Disappointingly, heating the bromophosphorane (282) under reflux in xylene in an attempt to achieve cyclisation to the unknown bromoisatogen (284) gave instead only a complex mixture which contained no identifiable material apart from triphenylphosphine oxide.

Despite the lack of success in the attempted thermal cyclisation of
(i) toluene, room temp.
(ii) toluene, xylene or diglyme, reflux or kugelrohr distillation.

Scheme 70
the bromo-phosphorane (282), attention was next turned to the investigation of the synthesis and thermolysis (Scheme 70) of a second type of 2-nitrobenzoylmethylenetriphenylphosphorane bearing an electron-withdrawing group at the methylene centre, namely the ester derivative (293). It was hoped that this compound would undergo thermal cyclisation to the isatogenic ester (294) which, being a known compound would be more readily identifiable in any product mixture. Acylation of the readily available ethoxycarbonylmethylenetriphenylphosphorane (292) by acid chlorides is known to occur at the methylene centre giving corresponding acyl-ethoxycarbonylmethylenetriphenylphosphoranes. In the present studies it was found that ethoxycarbonylmethylenetriphenylphosphorane (292) reacted smoothly with 2-nitrobenzoyl chloride (291) in toluene at room temperature to give a high yield (85%) of the required ethoxycarbonyl-2-nitrobenzoylmethylenetriphenylphosphorane (293). This previously undescribed compound analysed correctly and showed mass, i.r. and $^1$H n.m.r. spectra consistent with its structure. Unfortunately various attempts to achieve the thermal cyclisation of the phosphorane (293) to the isatogenic ester (294) proved unsuccessful. Thus heating under reflux in toluene or xylene was without effect, the starting-material (293) being recovered unchanged in essentially quantitative yield. In contrast heating under reflux in diglyme afforded a multicomponent mixture from which no identifiable material could be obtained. Thermolysis of the neat phosphorane (293) by Kugelrohr distillation was no more successful, these conditions giving only complex gums and oils together with a low recovery (38%) of the starting material (293).

The lack of success in the investigation of the thermolysis
(i) DMF, reflux.

Scheme 71
(i) PhN₂Cl, NaOAc, EtOH, H₂O, 0-20°.
(ii) toluene, reflux.
(iii) NaOH(aq), EtOH, reflux.
(iv) HCl(aq), heat.
(v) diglyme, reflux.

Scheme 72
reactions of the structurally simple 2-nitrobenzoylmethylene triphenylphosphorane derivatives (280), (282), and (293) prompted the similar, but more successful studies with arylazo 2-nitrobenzoylmethylene phosphoranes discussed in the following section.

3.3 Investigations of the Synthesis and Uncatalysed Reactions of Arylazo 2-Nitrobenzoylmethylene triphenylphosphorane Derivatives.

In the course of other investigations at Edinburgh, Steel found (Scheme 71) that heating 1-phenylazo-1-(2-nitrobenzoyl)methylene triphenylphosphorane (295) under reflux in DMF resulted in its conversion into the known 1-phenyl-1H-indol-2,3-dione (1-phenylisatin) (301) in moderate yield (36%) together with triphenylphosphine oxide (40%). This novel transformation can be explained by a course (Scheme 71) involving Wittig-like condensation between the nitro-group and the ortho phosphorane side-chain in (295) to give the phenylazo-isatogen derivative (298). Rearrangement of the latter by a process well documented for other isatogen derivatives would then afford an intermediate [(299 → (300)] set up for fragmentation and phenyl migration as shown (Scheme 71) to give 1-phenylisatin (301) observed as the product. However, no evidence in support of this pathway for the transformation [(295) → (301)] was provided by the previous studies. In view of this and the possible involvement of the Wittig-like condensation [(295) → (296) → (297) → (298)] as a key step in the transformation [(295) → (301)] it was decided as part of the present studies to investigate the general scope and if possible the mechanism of such transformations.

Initial studies (Scheme 72) centred on the parent phenylazo-
### Table 3. Bond Lengths (Å) with Standard Deviations

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Standard Deviation (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1) - C(2)</td>
<td>1.368(3)</td>
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</tr>
<tr>
<td>N(1) - C(7A)</td>
<td>1.428(3)</td>
<td></td>
</tr>
<tr>
<td>N(1) - N(11)</td>
<td>1.430(3)</td>
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</tr>
<tr>
<td>C(2) - O(2)</td>
<td>1.214(3)</td>
<td></td>
</tr>
<tr>
<td>C(2) - C(3)</td>
<td>1.538(3)</td>
<td></td>
</tr>
<tr>
<td>C(3) - O(3)</td>
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<td></td>
</tr>
<tr>
<td>C(3A) - C(4)</td>
<td>1.388(3)</td>
<td></td>
</tr>
<tr>
<td>C(3A) - C(7A)</td>
<td>1.287(3)</td>
<td></td>
</tr>
<tr>
<td>C(4) - C(5)</td>
<td>1.380(3)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Angles (degrees) and Torsion Angles with Standard Deviations

<table>
<thead>
<tr>
<th>Angle Combination</th>
<th>Angle (degrees)</th>
<th>Standard Deviation (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2) - N(1) - C(7A)</td>
<td>110.13(16)</td>
<td></td>
</tr>
<tr>
<td>C(2) - N(1) - C(11)</td>
<td>124.63(17)</td>
<td></td>
</tr>
<tr>
<td>C(7A) - N(1) - C(11)</td>
<td>125.23(17)</td>
<td></td>
</tr>
<tr>
<td>N(1) - C(2) - O(2)</td>
<td>27.17(19)</td>
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<tr>
<td>N(1) - C(2) - C(3)</td>
<td>106.41(17)</td>
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<tr>
<td>O(2) - C(2) - C(3)</td>
<td>126.41(19)</td>
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<td></td>
</tr>
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<td>C(2) - C(3) - C(3A)</td>
<td>105.31(17)</td>
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<tr>
<td>O(3') - C(3) - C(3A)</td>
<td>130.73(17)</td>
<td></td>
</tr>
<tr>
<td>C(3) - C(3A) - C(4)</td>
<td>131.17(19)</td>
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<tr>
<td>C(5) - C(3A) - C(7A)</td>
<td>107.73(17)</td>
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</tr>
<tr>
<td>C(4) - C(3A) - C(7A)</td>
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<td>C(3A) - C(4) - C(5)</td>
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<td></td>
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</tr>
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</tr>
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<td>C(3A) - C(4) - C(5) - C(6)</td>
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<td></td>
</tr>
<tr>
<td>C(3A) - C(4) - C(5) - C(6)</td>
<td>177.42(21)</td>
<td></td>
</tr>
<tr>
<td>C(3A) - C(4) - C(5) - C(6)</td>
<td>0.74(22)</td>
<td></td>
</tr>
<tr>
<td>C(3A) - C(4) - C(5) - C(6)</td>
<td>-1.9(4)</td>
<td></td>
</tr>
<tr>
<td>C(3A) - C(4) - C(5) - C(6)</td>
<td>-178.63(22)</td>
<td></td>
</tr>
</tbody>
</table>


phosphorane (295). This compound was readily prepared in high yield (88%) by coupling the phosphonium salt (278) (see before) with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate as described by Steel. The phenylazo-phosphorane (295) and structurally analogous derivatives described later, lack any significant carbonyl absorption in their i.r. spectra, indicating their existence largely in the betaine resonance form [e.g. (302)]. However, throughout the following discussion such arylazo-phosphorane derivatives are formulated for convenience as acylimethylenephosphorane structures [i.e. (295)].

The yield of 1-phenylisatin (301) produced by heating the phenylazo-phosphorane (295) in DMF was only 38% and it was initially of interest to discover if the use of other appropriate solvents would lead to a more efficient process. In fact heating the phenylazo-phosphorane (295) in diglyme resulted in a decreased yield (14%) of the isatin derivative (301) together with triphenylphosphine oxide and complex gums. The only literature method for the synthesis of 1-phenylisatin (301) is complicated and hence Steel had been unable to firmly verify the structure of this product by comparison with an authentic sample. However, the structure of the isatin derivative (301) has been firmly established in the present studies by x-ray diffraction (see Figure 2 and Tables 3 and 4).

Because of the poor yields of 1-phenylisatin (301) produced by heating the phenylazo-phosphorane (295) in the high-boiling solvents DMF and diglyme it was next decided to investigate the use of the lower-boiling toluene as the solvent for the transformation. In practice, heating the phenylazo-phosphorane (295) under reflux in toluene gave, in addition to an
Figure 3
### Table 5. Bond Lengths (Å) with Standard Deviations

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length (Å)</th>
<th>Standard Deviation (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1) - N(2)</td>
<td>1.346(4)</td>
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<tr>
<td>N(1) - C(8a)</td>
<td>1.389(4)</td>
<td></td>
</tr>
<tr>
<td>N(1) - C(11)</td>
<td>1.444(5)</td>
<td></td>
</tr>
<tr>
<td>N(2) - C(3)</td>
<td>1.301(5)</td>
<td></td>
</tr>
<tr>
<td>C(3) - C(4)</td>
<td>1.440(6)</td>
<td></td>
</tr>
<tr>
<td>C(4) - O(4)</td>
<td>1.246(5)</td>
<td></td>
</tr>
<tr>
<td>C(4) - C(4a)</td>
<td>1.444(5)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a)</td>
<td>1.402(5)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(5)</td>
<td>1.401(5)</td>
<td></td>
</tr>
<tr>
<td>C(8a) - C(8)</td>
<td>1.406(5)</td>
<td></td>
</tr>
<tr>
<td>C(5) - C(6)</td>
<td>1.362(5)</td>
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<tr>
<td>C(6) - C(7)</td>
<td>1.397(5)</td>
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<tr>
<td>C(7) - C(8)</td>
<td>1.368(5)</td>
<td></td>
</tr>
<tr>
<td>C(11) - C(12)</td>
<td>1.376(5)</td>
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</tr>
<tr>
<td>C(11) - C(16)</td>
<td>1.380(5)</td>
<td></td>
</tr>
<tr>
<td>C(12) - C(13)</td>
<td>1.387(6)</td>
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<tr>
<td>C(13) - C(14)</td>
<td>1.379(7)</td>
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</tr>
<tr>
<td>C(14) - C(15)</td>
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<tr>
<td>C(15) - C(16)</td>
<td>1.385(6)</td>
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### Table 6. Angles (degrees) and Torsion Angles with Standard Deviations

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<tr>
<th>Bond</th>
<th>Angle (degree)</th>
<th>Standard Deviation (degree)</th>
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<td>N(2) - N(1) - C(8a)</td>
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</tr>
<tr>
<td>N(2) - N(1) - C(11)</td>
<td>114.0(3)</td>
<td></td>
</tr>
<tr>
<td>C(8a) - C(11) - C(3)</td>
<td>118.4(3)</td>
<td></td>
</tr>
<tr>
<td>N(1) - N(2) - C(3)</td>
<td>125.9(4)</td>
<td></td>
</tr>
<tr>
<td>C(3) - C(4) - O(4)</td>
<td>122.0(4)</td>
<td></td>
</tr>
<tr>
<td>C(3) - C(4) - C(4a)</td>
<td>114.1(4)</td>
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</tr>
<tr>
<td>C(4) - C(4a) - C(8a)</td>
<td>123.9(4)</td>
<td></td>
</tr>
<tr>
<td>C(4) - C(4a) - C(5)</td>
<td>121.5(3)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(3)</td>
<td>119.8(3)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(11)</td>
<td>119.2(3)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(1)</td>
<td>121.1(3)</td>
<td></td>
</tr>
<tr>
<td>C(8a) - C(4a) - C(3)</td>
<td>119.0(3)</td>
<td></td>
</tr>
<tr>
<td>N(1) - C(8a) - C(4a)</td>
<td>118.9(3)</td>
<td></td>
</tr>
<tr>
<td>N(1) - C(8a) - C(8)</td>
<td>121.1(3)</td>
<td></td>
</tr>
<tr>
<td>C(8a) - N(2) - C(3)</td>
<td>2.5(5)</td>
<td></td>
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<tr>
<td>C(11) - N(1) - C(8a)</td>
<td>177.4(3)</td>
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</tr>
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<td>N(2) - N(1) - C(8a) - C(8)</td>
<td>175.5(3)</td>
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</tr>
<tr>
<td>C(11) - N(1) - C(8a) - C(4a)</td>
<td>-177.8(3)</td>
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<tr>
<td>N(2) - N(1) - C(11) - C(12)</td>
<td>-61.3(4)</td>
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<td>N(2) - N(1) - C(11) - C(16)</td>
<td>118.9(4)</td>
<td></td>
</tr>
<tr>
<td>C(8a) - N(1) - C(8a) - C(4a)</td>
<td>-177.0(4)</td>
<td></td>
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<td>C(4a) - C(8a) - C(3)</td>
<td>117.8(3)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(11)</td>
<td>1.1(5)</td>
<td></td>
</tr>
<tr>
<td>N(1) - C(8a) - C(8)</td>
<td>-0.4(6)</td>
<td></td>
</tr>
<tr>
<td>C(11) - N(1) - C(8a) - C(4a)</td>
<td>-0.4(6)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(3)</td>
<td>-0.4(6)</td>
<td></td>
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<tr>
<td>C(4a) - C(8a) - C(8)</td>
<td>-177.8(3)</td>
<td></td>
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<tr>
<td>C(4a) - C(8a) - C(11)</td>
<td>-0.7(5)</td>
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<td>0.2(6)</td>
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<tr>
<td>C(3) - C(4) - O(4)</td>
<td>-0.2(6)</td>
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<tr>
<td>N(1) - C(11) - C(12)</td>
<td>113.7(4)</td>
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</tr>
<tr>
<td>C(8a) - N(1) - C(11) - C(16)</td>
<td>-66.2(5)</td>
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<tr>
<td>N(1) - N(2) - C(3)</td>
<td>117.8(4)</td>
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<td>C(3) - C(4) - O(4)</td>
<td>179.8(4)</td>
<td></td>
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<td>N(1) - C(11) - C(12)</td>
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<td>C(4a) - C(8a) - C(5)</td>
<td>-177.2(4)</td>
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<td>C(4a) - C(8a) - C(11)</td>
<td>-178.9(4)</td>
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<td>C(4a) - C(8a) - C(8a)</td>
<td>0.2(5)</td>
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</tr>
<tr>
<td>C(4a) - C(8a) - C(11)</td>
<td>1.0(6)</td>
<td></td>
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<tr>
<td>C(4a) - C(8a) - C(8a)</td>
<td>178.6(4)</td>
<td></td>
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<tr>
<td>C(4a) - C(8a) - C(5)</td>
<td>1.3(6)</td>
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<tr>
<td>C(4a) - C(8a) - C(4a)</td>
<td>178.3(4)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(11)</td>
<td>1.3(6)</td>
<td></td>
</tr>
<tr>
<td>O(4) - C(4a) - C(8a)</td>
<td>178.3(4)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - C(5)</td>
<td>2.0(7)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - N(1)</td>
<td>0.9(5)</td>
<td></td>
</tr>
<tr>
<td>C(4a) - C(8a) - N(1)</td>
<td>0.9(5)</td>
<td></td>
</tr>
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</table>
improved yield (42%) of the isatin derivative (301) and the triphenylphosphine oxide (61%), a good yield 57% of a new product whose properties and transformations are consistent with its formulation as the novel cinnolinyltriphenylphosphonium nitrite salt (303). Thus, though its combustion analysis was outwith the required limits of accuracy it gave a correct accurate mass analysis and reacted positively in the starch iodide test\textsuperscript{88} for nitrite ion. The compound was stable to heating with water and attempted hydrolysis by heating with aqueous hydrochloric acid resulted in the formation of a material which analysed correctly as the chloride hydrochloride dihydrate structure (305). In contrast, heating the phosphonium salt (303) with aqueous ethanolic sodium hydroxide resulted in its smooth hydrolysis to triphenylphosphine oxide (yield 92%) and a compound (yield 56%) which gave a combustion analysis and mass spectrum and showed i.r. and n.m.r. absorption in full accord with the 1-phenyl aminocinnolinone structure (304). This product was also formed in moderate yield (45%), together with triphenylphosphine oxide (84%), when the phenylazo-phosphorane (295) was heated under reflux with aqueous ethanolic sodium hydroxide, presumably via the intermediate formation and subsequent hydrolysis of the cinnolinyltriphenylphosphonium nitrite (303). The Alkaline hydrolysis of cinnolinylphosphonium salts structurally related to (303), to the corresponding cinnolinones was reported in the literature\textsuperscript{89} after the completion of the present studies. The structure of the cinnolinone (304) was firmly established by X-ray diffraction (see Figure 3 and Table 5\textsuperscript{58}) its formation by alkaline hydrolysis of the salt (303) provides verification of the structure of the latter.

Significantly it was found that heating the cinnolinyltriphenyl
Scheme 73

(i) Me₂S₂N₂, toluene, 50°.
(ii) PhN₂Cl⁺, NaOAc, EtOH, H₂O, 0-20°.
(iii) NaOAc, EtOH, H₂O, reflux.
phosphonium nitrite salt (303) in diglyme gave 1-phenylisatin (301) in a yield (40%) comparable to that observed in the direct thermolysis reactions of the phenylazo-phosphorane (295). Triphenylphosphine oxide was also formed in essentially quantitative yield in this reaction. These observations strongly imply the intermediacy of the cinnolinyltriphenylphosphonium salt (303) in the thermal transformations of the phenylazo-phosphorane (295) into 1-phenylisatin (301) and, as discussed in detail later, exclude the pathway (Scheme 71) previously proposed for this transformation.

Because of the unprecedented nature of the transformation [(295)\(\rightarrow\)(303)] it was thought advisable to fully verify the structure of the cinnolinyltriphenylphosphonium nitrite (303) by alternative synthesis (Scheme 73). (It was anticipated by analogy with closely related cyclisations of 2-nitrobenzoylalkylidene hydrazones to cinnolinones that base-catalysed cyclisation of the bromo derivative (307) under mild conditions would afford the bromocinnolinone (308). It was then hoped to convert the latter by reaction with triphenylphosphine into the cinnolinyltriphenylphosphonium salt (303) or a simple derivative thereof. However the attempted coupling of the available bromo-ketone (277) with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate afforded none of the expected hydrazone (307). The only product isolated under these conditions, in addition to complex oils and gums was 2-nitrobenzoic acid (yield 48%). The origin of this product is not clear. However the required bromo-hydrazone (307) was readily prepared by an alternative route (Scheme 73) based on the known tendency of acyimethylenesulphonium bromide salts to couple with arenediazonium cations with subsequent rearrangement to afford the corresponding acylbromomethylene hydrazones. Thus the known
Scheme 74
(314)

(315)

(i) Na$_2$CO$_3$, p-benzoquinone, EtOH, H$_2$O, reflux.

Scheme 75
S,S-dimethyl 2-nitrobenzoylmethylene sulphonium bromide (306) coupled readily with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate to afford the expected bromo-hydrazone (307) in good yield (61%). The previously unreported bromo-hydrazone (307) analysed correctly and showed mass i.r., and ¹H n.m.r. absorption in accord with its assigned structure. Unfortunately the bromo-hydrazone (307) was stable to attempted cyclisation to the cinnolinone (308) under mild basic conditions known to effect this type of process. Since the use of more strongly basic conditions to achieve the cyclisation [(307) → (308)] was considered impractical, attempts to achieve the unambiguous synthesis of the salt (303) were halted at this point.

The thermal conversion of the phenylazo-phosphorane (295) into cinnolinyltriphenylphosphonium nitrite (303) can be simply explained (Scheme 74) by nucleophilic displacement of the nitro-group by the arylazo side-chain in the betaine resonance form (309). Closely related cyclisations involving the base-catalysed nucleophilic displacement of aromatic nitro-groups by diacylmethylidene hydrazone side-chains [(311) → (312)] have been reported in the literature. Closely related processes (Scheme 75) are known in which cyclisation occurs by the formal displacement of hydride ion ortho or para to an aromatic nitro-group by a carbanion centre contained in an amidic side-chain [e.g. (313) → (314) + (315)]. In the context of such cyclisations and the thermal transformation [(295) → (303)] uncovered in the present studies it was of interest to determine (Scheme 76) if 1-(3-nitrobenzoyl)-1-phenylazomethylene triphenylphosphorane (318) would undergo thermal cyclisation by analogous formal hydride ion displacement giving one or other or a mixture of the two nitrocinnolinyltriphenyl
(i) Ph₃P, toluene, reflux.
(ii) PhN₂Cl⁺, NaOAC, EtOH, H₂O, 0-20°.
(ii) toluene, reflux.

Scheme 76
phosphonium nitrites (319) and/or (322).

In practice the nitrobenzoyl-phenylazo-phosphorane (318) required for study was readily synthesised (Scheme 76) in good overall yield by conversion of the readily available bromo-ketone (316) into the phosphonium salt (317) followed by coupling of the latter with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate. The phenylazo-phosphorane (318) analysed correctly and gave mass, i.r. and 'H n.m.r. fully consistent with its structure. Prolonged heating of the phenylazo-phosphorane in toluene failed to give either of the two anticipated nitrocinnolinyltriphenylphosphonium nitrites (319) or (322). Instead the product, obtained in moderate yield (52%) together with triphenylphosphine oxide (yield 79%), was identified on the basis of its combustion analysis and mass, i.r., and 'H n.m.r. spectra as the imino-nitrile (323). Formation of this product can be explained (Scheme 76) by pyrolytic fragmentation of the phenylazo-phosphorane (318) to 3-nitrobenzoyl cyanide (320) and N-phenyl triphenylphosphinimine (321) followed by recombination of these two species by an aza-Wittig type process. Analogous fragmentation-recombination reactions have been demonstrated for other aroyl-arylamethylenetriphenylphosphoranes.

Though the thermal conversion of the nitrobenzoyl-phenylazo-methylenetriphenylphosphorane (295) into the cinnolinyltriphenyl phosphonium nitrite (303) is readily explained as already discussed, that of the further thermal rearrangement of the phosphonium salt (303) to 1-phenylisation (301) is not. In order to probe the pathway involved in this remarkable deep-seated rearrangement it was decided to synthesise and
(i) ArN₂Cl⁻, NaOAc, EtOH, H₂O, 0-20°.
(ii) toluene or diglyme, heat.
(iii) 2M HCl(aq), EtOH, reflux.

Scheme 77
investigate the thermal rearrangement (Scheme 77) of 2-nitrobenzoyl-arylazomethylenetriphenylphosphoranes (324) bearing electron-withdrawing or electron-donating substituents at para-position of the azo-aryl moiety. It was hoped that the electronic effect of these substituents would influence the outcome of thermal rearrangement and hence provide information on its course.

All of the 2-nitrobenzoyl-arylazomethylenetriphenylphosphoranes (324) investigated were readily synthesised in high yield (78 -100%) by coupling 2-nitrobenzoylmethylenetriphenylphosphonium bromide (278) with the corresponding arenediazonium salts in aqueous ethanol in the presence of sodium acetate. As in the case of the parent 2-nitrobenzoyl-phenylazomethylenetriphenylphosphorane (295) (see before), none of the arylazomethylene phosphoranes (324) showed a parent ion in their mass spectra, but all analysed correctly and showed i.r. and $^1$H n.m.r. absorption in accord with their structures.

Thermolysis of the arylazomethylene phosphoranes (324) was largely carried out by heating in anhydrous toluene. In all cases brown fumes were evolved indicating the production of free dinitrogen tetroxide ($N_2O_4$) in the course of thermolysis. The thermolyses of the methyl and chloro-derivatives (324c) and (324d) were carried out for 21 - 22 h. and gave mixtures consisting of the same two types of product identified on the basis of their analytical and spectroscopic properties as the expected cinnolinyltriphenylphosphonium nitrites (325a) and (325c) and the 1-arylisatins (327a) and (327c) respectively. In both cases the phosphonium salts (325a) and (325c) and 1-arylisatins (327a) and 327c) were isolated in
essentially similar yields (78 - 80% and 12 - 20% respectively) indicating little or no effect on the course of thermolysis of replacing an electron-donating methyl group by an electron-withdrawing chloro substituent.

More dramatic effects were noted in the corresponding thermolyses of the nitro-compound (324b) and the methoxy-derivative (324d) in keeping with the greater extremes of substituent electronic character involved. In both cases relatively brief heating in toluene was sufficient to cause thermolysis to mixtures of the expected cinnolinyltriphenylphosphonium nitrites (325b) and (326) and arylisatins (327b) and (329) all of whose structures were fully confirmed by combustion and spectroscopic analysis. Moreover, the respective proportions of the two types of product formed in the two cases were markedly different. In the case of the nitro-compound (324b), thermolysis resulted in a preponderance (yield 51%) of the isatin derivative (327b) the phosphonium nitrite (325b) being isolated in substantially lesser amount (28%). In the case of the methoxy-derivative (324d) on the other hand, thermolysis afforded the phosphonium salt (326) as the major product (yield 78%), the corresponding isatin derivative (327) being formed in only minor amount (5%). A third product isolated in low yield (9%) from the thermolysis of the methoxyphenylazo-phosphorane (324d) gave a combustion analysis and showed a parent ion at m/z 252 in its mass spectrum consistent with the molecular formula C_{19}H_{12}N_{2}O_{2}. This formula together with the presence at absorption of 3320 cm\(^{-1}\) due to an NH-group as well as carbonyl absorption at 1725 cm\(^{-1}\) in the i.r. spectrum of the product allow its formulation as the imino-indolone derivative (328). This structure was firmly established by hydrolysis of the compound in aqueous hydrochloric acid to give the isatin derivative (329) in essentially
(i) NaOAc, EtOH, H₂O, room temp.

Scheme 78
quantitative yield. As discussed later, the formation of the imino-indoline
(328) in the thermolysis of the methoxyphenylazo-phosphorane (324d) has an
important bearing on a possible mechanism for thermal rearrangements of
the type \( [(303) \rightarrow (301)] \), \( [(325\ a-c) \rightarrow (327\ a-c)] \), and \( [(326) \rightarrow (329)] \). The
observation that, under essentially similar conditions, thermolysis of the
methoxy-derivative (324d) in toluene affords largely the cinnolinyltriphenyl
phosphonium nitrite salt (326) whereas the nitro-derivative (324b) gives
mainly the 1-arylisatin (327b) implies that thermal arrangements of the type
\( [(325) \rightarrow (327)] \) are assisted by an electron-withdrawing group at the para
position of the azo-aryl nucleus. Heating the methoxyphenylazo-
phosphorane (324d) in the higher boiling solvent diglyme in an attempt to
force the exclusive formation of the isatin derivative (329) succeeded in so
far as none of the corresponding cinnolinyltriphenylphosphonium nitrite salt
(326) was formed though triphenylphosphine oxide was isolated in high yield
(90%). However the isatin derivative (329) itself was isolated only in low
yield (25%) under these conditions. In contrast to the result observed in
toluene (see before), heating the nitrophenylazo-phosphorane (324b) in
diglyme gave only a complex mixture containing triphenylphosphine oxide.

In a further attempt to probe the mechanism of thermal
rearrangements of the type \( [(303) \rightarrow (301)] \) it was decided to investigate the
synthesis and thermal behaviour (Scheme 78) of the mesitylazo-phosphorane
(331). It was hoped that, because of the steric bulk of its arylazo - moiety,
thermal rearrangement of this molecule might follow a different pathway
compared with the simple case \( [(303) \rightarrow (301)] \) and thus provide some insight
into the course of the latter. In practice however the attempted synthesis of
the mesitylazo-phosphorane (331) by coupling 2-nitrobenzoylmethylene
phosphonium bromide (278) with the diazonium salt (330) in aqueous ethanol in the presence of sodium acetate gave a totally unexpected result. This reaction gave, instead of the expected arylazo-phosphorane (331), two isomeric products in low yield (13 - 14%) together with triphenylphosphine oxide (yield 48%). Both products had similar melting points and both analysed for C_{17}H_{16}N_2O and in accord with this molecular formula showed parent ion peaks at m/z 264 in their mass spectra. The two isomeric products are assigned the structures (332) and (333) on the basis of their i.r. and ¹H n.m.r. absorption which closely resembles that of the cinnolinone (304) and iminoindolone (328) of unambiguous structure.

The isolation of the products (332) and (333) in the coupling reaction of the phosphonium bromide (278) with the diazonium salt (330) is most readily explained by the intermediate formation and spontaneous cyclisation of the mesitylazo-phosphorane (331). The formation of the cinnolinone (332) from the latter presumably involves base-catalysis under the weakly basic conditions of coupling and thus resembles the sodium hydroxide catalysed cyclisation of the phenylazo-phosphorane (295) to the cinnolinone (304) described before (see Scheme 72). The formation of the imino-indolone (333) from the arylazo-phosporane (331) is likewise analogous to the thermal cyclisation of the methoxyphenylazo-phosphorane (324d) to the methoxy-imino-indolone (328) described before (see Scheme 77). However the mild conditions (0 - 20°) under which the transformation [(331) → (333)] occurs is surprising given the apparent need for heat in the related process [(324d) → (328)].

The foregoing results do not shed a great deal of light on the
Scheme 79
pathway followed in the deep-seated thermal rearrangements of cinnolinylphosphonium nitrites such as \([303] \rightarrow [301]\) and further extensive studies will be necessary before this is elucidated. However a possible working hypothesis for the mechanism of such thermal rearrangements is outlined in Scheme 79. This proposes as the first step the thermal fragmentation of the phosphonium salt (334) to the nitrite ester (335) and triphenylphosphine. Analogous fragmentation reactions of phosphonium salts are well known in the literature. Subsequent rearrangement of the nitrite ester (335) by \(N \rightarrow O\) migration of the nitroso-group would then afford an \(N\)-nitroso intermediate (336). Deoxygenation of the latter by triphenylphosphine generated in the first step would next give an \(N\)-nitrene intermediate (337) thermal extrusion of nitrogen from which accounts for the observed isatin product (338). This mechanism accounts for the concomitant formation of triphenylphosphine oxide in such reactions but does not explain the coformation of imino-indolones [eg. (328)] occasionally observed. An explanation for the formation of these by-products awaits the outcome of further detailed studies.


In the light of the foregoing studies and those already described in Chapter 2, it was considered of interest to investigate the synthesis and thermal behaviour (Schemes 80 and 81) of N-(2-nitrophenyl)carbamoylmethylene methylenetriphenylphosphorane derivatives such as (341) and (343). In the former case it was anticipated that thermolysis might occur by extrusion of triphenylphosphine oxide and formation of the known quinoxalinone \(N\)-oxide
(i) Ph₃P, CH₂Cl₂, CHCl₃, room temp. or toluene, reflux.
(ii) Na₂CO₃, H₂O, room temp.
(iii) xylene, reflux.

Scheme 80
In the case of the phenylazo-phosphorane (343) analogous thermolysis with elimination of triphenylphosphine oxide would lead to the phenylazoquinoxalinone N-oxide. If successful, such thermal cyclisation reactions of \(N\)-(2-nitrophenyl)carbamoylmethylenetriphenylphosphorane derivatives would provide a useful alternative method for the synthesis of \(N\)-oxygenated quinoxalines (see Chapter 2).

The simple \(N\)-(2-nitrophenyl)carbamoylmethylenetriphenylphosphorane (341) was synthesised in two steps\(^2\) (Scheme 80) in good overall yield via the phosphonium chloride (340). Neither of the phosphorus derivatives (340) or (341) had been reported in the literature previously but both compounds showed analytical and spectroscopic properties consistent with their assigned structures. Disappointingly the attempted thermolysis of the phosphorane (341) in toluene gave only a high recovery (96%) of the unreacted starting material. In contrast thermolysis of the phosphorane (341) in refluxing anhydrous xylene resulted in fragmentation to 2-nitroaniline (149) (50%), and triphenylphosphine oxide (68%) with no evidence for the formation of the quinoxaline N-oxide (202). Since the xylene used was anhydrous the origin of the products (342) and (149) of apparent hydrolysis is not immediately obvious.

The phenylazo-phosphorane (343) was readily synthesised (Scheme 81) in excellent yield (43%) by coupling the phosphonium salt (340) with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate. The previously unknown phenylazo-phosphorane (343) analysed correctly and gave mass, i.r., and \(^1\)H n.m.r. spectra fully consistent with its structure. As in the case of the simple phosphorane (341), thermolysis of
Scheme 81

(i) PhN₂Cl⁻, NaOAc, EtOH, H₂O, 0-20°
(ii) diglyme, reflux.
the phenylazo-phosphorane (343) in refluxing diglyme afforded none of the hoped-for phenylazoquinoxaline N-oxide (344) but instead only a moderate yield (52%) of 2-nitroaniline (149) together with triphenylphosphine oxide.
3.5 Experimental

General Experimental Details

For details of general experimental procedures see Chapter 2, section 2.7, page 50.

1-(2-Nitrophenyl)ethanone (276)

1-(2-Nitrophenyl) ethanone (276) was prepared by the condensation of 2-nitrobenzoyl chloride with diethyl malonate, followed by hydrolysis and decarboxylation of the resulting condensate as described by Kermack and Smith\(^9\) yield 64%, b.p. 158 - 159° 13 mm Hg (lit.,\(^9\) 158-159°/13 mm Hg), and was used without further purification.

2-Bromo-1-(2-nitrophenyl)ethanone (277)

2-Bromo-1-(2-nitrophenyl)ethanone (277) was prepared by the bromination of 1-(2-nitrophenyl)ethanone (276) as described by Gevekoht,\(^84\) yield 72%, m.p. 50 - 54° (lit.,\(^84\) 55 - 56°), and was used without further purification.

2-Nitrobenzoyltriphenylphosphonium Bromide (278)

A solution of 2-bromo-1-(2-nitrophenyl) ethanone (277) (24.4 g, 0.1 mol) in anhydrous toluene (70.0 ml) was treated dropwise with stirring with a solution of triphenylphosphine (39.3 g, 0.15 mol) in anhydrous toluene (250 ml) and the mixture was stirred at room temperature for 17 h. The mixture was filtered to afford 2-nitrobenzoyltriphenylphosphonium bromide (278) (45.1 g; 89%), m.p. 211-216°. (lit.,\(^82\) m.p 215 - 216°), \(\delta_{\text{max}}\)}
1675 (CO) and 1520 and 1345 (NO₂) cm⁻¹, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.⁵²

2-Nitrobenzoylmethylene-triphenylphosphorane (280)

(a) A solution of 2-nitrobenzoylmethyltriphenylphosphonium bromide (278) (35.4 g, 0.07 mol) in hot water (800 ml) was treated with 2M aqueous sodium hydroxide (35.0 ml). The mixture was cooled and filtered to afford 2-nitrobenzoylmethylene-triphenylphosphorane (280) (26.9 g, 90%), m.p. 160 - 165° (lit.,³² 174 - 175°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.⁵²

(b) A suspension of the phosphonium salt (278) (2.5 g, 0.005 mol) in 10% w/v aqueous sodium carbonate (25.0 ml) was stirred at room temperature for 17 h. The mixture was filtered and the yellow solid was recrystallised from aqueous ethanol to give 2-nitrobenzoylmethylene-triphenylphosphorane (280) (2.1 g, quant.), m.p. 165 - 173°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Thermolysis of 2-Nitrobenzoylmethylene-triphenylphosphorane (280)

(a) A solution of the phosphorane (280) (1.7 g, 0.004 mol) in anhydrous toluene (60.0 ml) was heated under reflux for 4 h. The solution was evaporated to give unchanged starting material (280) (1.7 g, quant.), m.p. 165 - 170° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(b) The phosphorane (280) (1.7 g, 0.004 mol) in anhydrous
xylene (60.0 ml) was heated under reflux for 27 h. The mixture was evaporated to give a brown solid (1.8 g) which was flash-chromatographed over silica.

Elution with methylene chloride followed by methylene chloride-ethyl acetate (5:1) gave only unidentified oils and gums (total 0.2 g).

Further elution with methylene chloride-ethyl acetate (3:1) gave a brown gum (1.3 g) which was triturated with toluene-methanol to afford the unreacted phosphorane (280). (0.95 g; 56%), m.p. 164 - 167°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Final elution with ethanol gave a brown oil (0.21 g) whose t.l.c. in methylene chloride over silica showed it to be a mixture of unreacted starting-material (280) and triphenylphosphine oxide.

(c) A solution of the phosphorane (280) (1.7 g, 0.004 mol) in anhydrous diglyme (50.0 ml) was heated under reflux and monitored by t.l.c. for consumption of the starting material (280). After 16 h the mixture was evaporated under high vacuum (oil-pump) to give a brown oil (1.8 g) which was flash-chromatographed over silica.

Elution with cyclohexane through methylene chloride to ethyl acetate gave only a series of intractable oils (total 0.39 g) from which no identifiable material could be obtained.
Final elution with ethanol gave an intractable brown gum (1.4 g) whose t.l.c. in ethyl acetate-ethanol (5:1) and i.r. spectrum showed it to be largely triphenylphosphine oxide. The gum was not further investigated.

(d) A solution of the phosphorane (280) (1.7 g, 0.004 mol) in glacial acetic acid (2.5 ml) was treated with formic acid (0.5 ml) and the mixture was stirred at room temperature for 0.5 h. The mixture was evaporated under high vacuum (oil-pump) to give a yellow semi-solid (1.6 g) which was triturated with toluene to afford impure starting-material (280) (1.5 g; 88%) m.p. 138 - 143°, identified by comparison (i.r. spectrum) with an authentic sample.

Evaporation of the toluene mother liquor gave only a small amount of a yellow gum (0.01 g) which was not further investigated.

The Attempted Photolysis of 2-Nitrobenzoylmethylenetriphenylphosphorane (280)

A solution of the phosphorane (280) (0.85 g, 0.002 mol) in anhydrous toluene (150 ml) was irradiated under nitrogen in a Hanovia medium pressure photochemical reactor for 26 h. The mixture was then evaporated to give a brown semi-solid (1.0 g) which was triturated with ether to afford impure starting-material (280) (0.70 g, 82%), m.p. 149 - 153°, which was identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Evaporation of the ethereal mother liquor gave a brown gum (0.16 g) whose t.l.c. in methylene chloride-ethyl acetate (2:1) over silica
showed it to be a multicomponent mixture containing mostly unreacted starting-material (280), which was not further investigated.

1-Bromo-1-(2-nitrobenzoyl)methylenetriphenylphosphorane (282)

A solution of 2-nitrobenzoylmethylenetriphenylphosphorane (280) (1.7 g, 0.004 mol) and anhydrous sodium acetate (0.40 g, 0.005 mol) in glacial acetic acid (10.0 ml) was treated dropwise with stirring with a solution of bromine (0.64 g, 0.004 mol) in glacial acetic acid (2.0 ml) and the mixture was stirred at 10 - 15° (ice bath) for 20 min. The mixture was treated with 10M aqueous hydrochloric acid (2.0 ml) and evaporated under high vacuum (oil-pump). The residue was treated with water (10.0 ml) and the resulting solution was basified with 2M aqueous sodium hydroxide and extracted with methylene chloride to give 1-bromo-1-(2-nitrobenzoyl)methylenetriphenylphosphorane (282) (2.0 g; quant.) which formed orange crystals, m.p. 201 - 203° (from toluene), δmax 1700 (CO) and 1520 and 1345 (NO₂) cm⁻¹, δH (CDCl₃) 7.92 - 7.41 (m, ArH).

Found: C, 62.2; H, 3.9; N, 2.6%

C₉H₁₉NBrO₅P: C, 61.9; H, 3.8; N, 2.9%

The Attempted Thermolysis of 1-Bromo-(2-nitrobenzoyl)methylenetriphenylphosphorane (282)

A solution of the phosphorane (282) (1.1 g, 0.002 mol) in anhydrous xylene (25.0 ml) was heated under reflux for 48 h. The mixture was evaporated to give a brown oil (1.2 g) which was flash-chromatographed over silica.

Elution with methylene chloride-n-hexane (1:1) through to
methylene chloride-ethyl acetate (1:1) gave a series of oils (total 0.57 g) whose t.l.c. in methylene chloride over silica showed them to be unresolvable multicomponent mixtures.

Further elution with ethyl acetate gave a yellow gum (0.34 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) over silica showed it to contain starting-material (282), triphenylphosphine oxide and other components. The gum was not further investigated.

Final elution with ethanol gave a brown gum (0.32 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a mixture of starting-material (282) and triphenylphosphine oxide. The gum was not further investigated.

**Ethoxycarbonylmethylenetriphenylphosphorane (292)**

Ethoxycarbonylmethylenetriphenylphosphorane (292) was prepared by the reaction of ethyl bromoacetate with triphenylphosphine then reaction of the resulting phosphonium salt with base as described by O. Isler et al., yield 81%, and had m.p. 110 - 114° (lit., 116 - 117°).

**1-Ethoxycarbonyl-1-(2-nitrobenzoyl)methylenetriphenylphosphorane (293)**

A solution of ethoxycarbonylmethylenetriphenylphosphorane (292) (13.9 g, 0.04 mol) in anhydrous toluene (100 ml) was treated dropwise with stirring at room temperature with a solution of 2-nitrobenzoyl chloride (291) (3.7 g, 0.02 mol) in anhydrous toluene (30.0 ml) and the mixture was stirred at room temperature for 3 h. The mixture was then filtered to afford a yellow solid (15.0 g) which was heated under reflux with ethyl acetate and
filtered hot to give ethoxycarbonylmethylenetriphenylphosphonium chloride (7.7 g; quant.), m.p. 87 - 98°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.99

The ethyl acetate mother liquor was evaporated to give a yellow solid (6.5 g) which was flash chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) followed by methylene chloride gave intractable gums (total 0.22 g) which were not further investigated.

Further elution with methylene chloride-ethyl acetate (3:1) gave 1-ethoxycarbonyl-1-(2-nitrobenzoyl)methylenetriphenylphosphorane (293) (8.6 g; 86%) which formed pale yellow crystals, m.p. 140 - 142° (from light petroleum-toluene), δmax 1665 (CO) and 1515 and 1335 (NO2) cm⁻¹, δ(CDCl₃) 8.13 - 7.11 (19 H, m, ArH), 3.56 (2 H, q, J7Hz, CH₂) and 0.49 (3H, t, J7Hz, CH₃).

[Chemical data]

Final elution with ethanol gave an intractable yellow gum (2.2 g) from which no identifiable material could be obtained.

The Attempted Thermolysis of 1-Ethoxycarbonyl-1-(2-nitrobenzoyl)
methylenetriphenylphosphorane (293)

(a) A solution of the phosphorane (293) (0.99 g, 0.002 mol) in anhydrous toluene (25.0 ml) was heated under reflux for 6 h. The mixture
was evaporated to give unreacted starting material (293) (1.0 g; quant.) m.p. 125 - 135°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a) but heating under reflux in anhydrous xylene gave unreacted starting-material (293) (0.98 g; 99%), m.p. 153 - 158°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

(c) A solution of the phosphorane (293) (0.99, 0.002 mol) in anhydrous diglyme (25.0 ml) was heated under reflux and monitored by t.l.c. Heating was continued for 33 h after which time the mixture was evaporated under high vacuum (oil pump) to give a red oil (1.1 g) whose t.l.c. in methylene chloride-ethyl acetate (10:1) showed it to be an unresolvable multicomponent mixture which was not further investigated.

(d) The phosphorane (292) (0.99 g, 0.002 mol) was heated in a Kuglerohr distillation apparatus under high vacuum (oil pump). A yellow oil distilled at 250°/0.4 mm Hg leaving a brown residue.

The yellow oil (0.21 g) was flash-chromatographed over silica but elution with n-hexane-methylene chloride through methylene chloride to ethyl acetate and finally ethanol gave only a series of complex oils and semi-solids (total 0.21 g) which yielded no identifiable material.

The brown residue (0.72 g) was flash-chromatographed over silica.
Elution with methylene chloride-ethyl acetate (5:1) gave unchanged starting material (293) (0.38 g; 38%), m.p. 146 - 149°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate followed by ethanol gave gums (total 0.33 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not further investigated.

1-Arylazo-1-(2-nitrobenzoyl)methylenetriphenylphosphoranes (295) and (324)

(a) A solution of the corresponding aniline derivative (0.021 mol) in 5M aqueous hydrochloric acid (10.4 ml) was treated dropwise with stirring at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (1.5 g, 0.022 mol) in water (5.3 ml) and the mixture was stirred at 0 - 5° for 10 min. The diazonium solution was then filtered through glass wool and added dropwise with stirring at 0 - 5° (ice-salt bath) to a solution of 2-nitrobenzoyl methyltriphenylphosphonium bromide (278) (10.1 g, 0.02 mol) and anhydrous sodium acetate (4.4 g, 0.053 mol) in water (10.7 ml) and ethanol (80.0 ml). The mixture was stirred in the melting ice-salt bath for 2 h then filtered and the solid arylazomethylenetriphenylphosphoranes purified as described for the individual reactions below.

(l) Aniline gave 1-(2-nitrobenzoyl)-1-phenylazomethylenetriphenyl phosphorane (295) (88%) m.p. 135 - 145°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.82

The aqueous mother liquor was extracted with methylene chloride to give an intractable brown gum (1.4 g) which was not further investigated.
(ii) The crude solid product from 4-methylaniline was purified by flash-chromatography over silica eluting with methylene chloride-ethyl acetate (20:1) to give 1-(4-methylphenylazo)-1-(2-nitrobenzoyl)methylene triphenylphosphorane (324c) as a yellow solid (88%), m.p. 138 - 139°, $\delta_{\text{max}}$ 1520 and 1350 (NO$_2$) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.03 (1H, d, J8Hz, ArH), 7.83 - 7.39 (18H, m, ArH), 6.88 (2 H, d, J8Hz, ArH), 6.66 (2 H, d, J8Hz, ArH), and 2.20 (3H, s, CH$_3$).

Found: C, 72.7; H, 4.8; N, 7.6%
C$_{36}$H$_{33}$N$_3$O$_6$P requires: C, 72.9; H, 4.8; N, 7.7%

The aqueous filtrate was extracted with methylene chloride to give a brown oil whose t.l.c. in methylene chloride ethyl acetate (20:1) over silica showed it to be a complex mixture which was not further investigated.

(iii) The crude solid product from 4-nitroaniline was purified by flash-chromatography over silica eluting with toluene-ethyl acetate (3:1) to give 1-(2-nitrobenzoyl)-1-(4-nitrophenylazo)methylene triphenylphosphorane (324b) as a red solid, (quant.), m.p. 162 - 164°, $\delta_{\text{max}}$ 1500 and 1310 (NO$_2$) cm$^{-1}$, $\delta_{\text{H}}$ (CDCl$_3$), 7.89 (2 H, d, J9Hz, ArH), 7.80 - 7.20 (19H, m, ArH), and 6.67 (2 H, d, J9Hz, ArH).

Found: C, 66.6; H, 4.1; N, 9.7%
C$_{36}$H$_{33}$N$_3$O$_6$P requires: C, 66.9; H, 4.0; N, 9.8%

(iv) The crude solid product from 4-chloroaniline was flash-chromatographed over silica eluting with methylene chloride-ethyl acetate (20:1) to give 1-(4-chlorophenylazo)-1-(2-nitrobenzoyl)methylene triphenylphosphorane (324a) as an orange solid (82%), m.p. 146 - 151°, $\delta_{\text{max}}$
1530 and 1340 (NO₂) cm⁻¹, δₜ (CDCl₃) 8.00 (1H, d, J8Hz, ArH), 7.80 - 7.39 
(18H, m, ArH), 7.0 (2 h, d, J8Hz, ArH) and 6.64 (2 h, d, J8Hz, ArH).

**Found:**
C₆H₅ClN₂O₃P requires: C, 68.1; H, 4.1; N, 7.4%

(v) The crude solid product from 4-methoxyaniline was flash-chromatographed over silica eluting with toluene-ethyl acetate (3:1) to give 1-(4-methoxyphenylazo)-(2-nitrobenzoyl)methylene triphenylphosphorane (323d) (62%) as a brown solid, m.p. 153 - 157°, δ max 1510 and 1340 (NO₂) cm⁻¹, δₜ (CDCl₃) 8.01 - 6.81 (23H, m, ArH) and 3.77 (3H, s, CH₃).

**Found:**
C₆H₅N₂O₃P requires: C, 70.5; H, 4.7; N, 7.3%

Further elution with ethyl acetate gave unreacted starting material (278) (20%), m.p. 147 - 155°, identified by comparison (i.r. spectrum) with an authentic sample.

**Thermolysis Reactions of 1-(2-Nitrobenzoyl)-1-phenylazomethylene triphenylphosphorane (295)**

(a) A solution of the phosphorane (295) (2.1 g, 0.004 mol) in anhydrous (2-methoxyethyl) ether (diglyme) (25.0 ml) was heated under reflux for 15 min. and was then evaporated under high vacuum (oil-pump) to give a brown oil (2.4 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (10:1) gave an orange semi-solid (0.29 g) which was triturated with cyclohexane-toluene to afford
1-phenyl-1 H-indole-2,3-dione (301) (0.13 g; 14%) as orange-red needles, m.p. 138 - 139° (from toluene-light petroleum) (lit. 138°) \( \delta_{\text{max}} \) 1735 and 1690 (CO) cm\(^{-1}\), \( \delta_{\text{H}} \) (CDCl\(_3\)) 7.74 - 7.14 (8H, m, ArH) and 6.88 (1H, d, J8Hz, ArH).

**Found:**
- C, 75.4; H, 4.0; N, 6.3%; M, 223

**Calc. for C\(_{21}\)H\(_{12}\)NO\(_2\):**
- C, 75.3; H, 4.0; N, 6.3%; M, 223.

Further elution with methylene chloride-ethyl acetate gave only a series of multicomponent gums (total 0.21 g) which were not further investigated.

Final elution with ethanol gave a brown semi-solid (1.5 g) whose i.r. spectrum and t.l.c. in ethyl acetate over silica showed it to be largely triphenylphosphine oxide. The semi-solid was not further investigated.

(b) A solution of the phosphorane (295) (4.2 g, 0.008 mol) in anhydrous toluene (125 ml) was heated under reflux for 1 h during which time some brown gas was evolved and a solid precipitated out of solution. The mixture was filtered to afford [1-phenylcinnolin-4(1H)-on-3-yll(phenylphosphonium nitrite (303) (2.4 g; 57%), which formed yellow-brown crystals, m.p. 165 - 173° (decomp.), \( \delta_{\text{max}} \) 1620 (CO) cm\(^{-1}\), \( \delta_{\text{H}} \)(CDCl\(_3\)) 8.34 - 7.17 (24 H, m, ArH).

**Found:**
- M, 483.1626

**Calc. for C\(_{21}\)H\(_{12}\)N\(_2\)OP requires:**
- M, 483.1626.

and gave a positive test for nitrite ion with starch iodide reagent\(^{89}\)

The toluene filtrate was evaporated to give a red solid (2.4 g) which was flash-chromatographed over silica.
Elution with methylene chloride-n-hexane (1:1) gave as the first fraction a yellow oil (0.10 g) which yielded no identifiable material.

Further elution with methylene chloride followed by methylene chloride-ethyl acetate (10:1) gave 1-phenyl-1H-indole-2,3-dione (301) (0.75 g; 42%), m.p. 138° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Final elution with ethanol gave triphenylphosphine oxide (1.4 g; 61%) m.p. 148 - 149°, identified by comparison (m.p. and i.r. spectrum), with an authentic sample.

The Attempted Aqueous Hydrolysis of [1-N-Phenylcinnolin-4(1H)-on-3-yl]triphenylphosphonium Nitrite (303)

The phosphonium nitrite (303) (0.26 g, 0.005 mol) was warmed with water (5.0 ml) until the suspended solid dissolved. The solution was cooled and extracted with methylene chloride to give the unreacted starting material (303) (0.26 g; 100%), identified by comparison (i.r. spectrum and t.l.c. in ethanol over silica) with an authentic sample prepared before.

[1-N-Phenylcinnolin-4(1H)-on-3-yl]triphenylphosphonium Chloride Hydrochloride Dihydrate (305).

The phosphonium nitrite (303) (0.26 g, 0.0005 mol) was treated with 2M aqueous hydrochloric acid (10.0 ml) and the mixture was heated at 100° for 1 h. The mixture was then evaporated under high vacuum (oil-pump) to afford the phosphonium chloride hydrochloride dihydrate (305)
(0.24 g; 81%), which formed pale yellow crystals, m.p. 168 - 170° (from 2M aqueous hydrochloric acid). $\delta_{\text{max}}$ 1620 (CO) cm$^{-1}$. $\delta_{\text{H}}$ (CDCl$_3$) 8.27 (1H, d, J7Hz, ArH), 7.97 - 7.39 (23H, m, ArH), and 2.01 (s, H$_2$O).

Found: C, 65.0; H, 4.8; N, 4.8%

C$_{14}$H$_{12}$ClN$_2$O$_3$P requires: C, 64.9; H, 4.9; N, 4.7%

1-N-Phenylcinnolin-4(1H)-one (304)

(a) A suspension of the phosphonium nitrite (303) (1.1 g, 0.002 mol) in ethanol (20.0 ml) was treated with 2M aqueous sodium hydroxide (5.0 ml) and the mixture was heated under reflux for 6 h.

The mixture was concentrated to remove the ethanol, diluted with water (5.0 ml) and extracted with methylene chloride to give a yellow solid (0.72 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave as the first fraction 1-N-phenylcinnolin-4(1H)-one (304) (0.25 g; 56%) which formed colourless plates, m.p. 135 - 135° (from light petroleum-toluene). $\delta_{\text{max}}$ 1630 (CO) cm$^{-1}$.

$\delta_{\text{H}}$(CDCl$_3$) 8.35 (1H, dd, J8 and 2 Hz, ArH), 7.94 (1H, s, ArH) and 7.70 - 7.13 (8H, m, ArH).

Found: C, 75.6; H, 4.5; N, 12.6%; M$, 222.

C$_{14}$H$_{10}$N$_2$O requires: C, 75.7; H, 4.5; N, 12.6%; M, 222

Further elution with ethyl acetate then ethanol gave triphenylphosphine oxide (0.48 g; 92%) m.p. 145 - 150°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Work-up of the aqueous mother liquor gave only a small amount
of an orange gum which was not further investigated.

(b) A suspension of the phenylazophosphorane derivative (295) (1.1 g, 0.002 mol) in ethanol (20.0 ml) was treated with 2M aqueous sodium hydroxide (5.0 ml) and the mixture was heated under reflux for 6 h. The mixture was concentrated to remove the ethanol and the residue was diluted with water (10.0 ml) and extracted with methylene chloride to give a yellow solid (0.69 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (10:1) gave as the first fraction 1-N-phenylcinnolin-4(1H)-one (304) (0.20 g; 45%) m.p. 135 - 136°, identified by comparison (m.p. and i.r. spectrum) with the sample prepared in (a) before.

Further elution with ethyl acetate followed by ethanol gave triphenylphosphine oxide (0.47 g; 84%), m.p. (154 - 156°), identified by comparison [m.p., i.r. spectrum, and t.l.c. in methylene chloride-ethyl acetate (5:1) over silica] with an authentic sample.

The original aqueous mother liquor was acidified with 10M aqueous hydrochloric acid and extracted with methylene chloride to give an orange gum (0.20 g) whose t.l.c. in methylene chloride-ethyl acetate (10:1) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.
The Thermolysis of [1-N-Phenylcinnolin-4(1H)-on-3-yl]triphenylphosphonium Nitrite (303) in Diglyme.

A solution of the phosphonium nitrite (303) (1.6 g, 0.003 mol) in anhydrous diglyme (35.0 ml) was heated under reflux for 30 min. and was then evaporated under high vacuum (oil pump) to give a brown oil (1.5 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 1-phenyl-1H-indole-2,3-dione (301) (0.26 g; 37%), m.p. 132 - 136°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with methylene chloride-ethyl acetate (10:1) to methylene chloride-ethyl acetate (3:1) gave only a series of intractable gums and oils (total 0.30 g) which were not further investigated.

Further elution with methylene chloride-ethyl acetate (1:1) through to ethyl acetate gave triphenylphosphine oxide (0.79 g; 100%), m.p. 146 - 150°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Final elution with ethanol gave an intractable brown gum (0.13 g) which was not further investigated.

The Attempted Reaction of 2-Bromo-1-(2-nitrophenyl)ethanone (277) with Benzenediazonium Chloride

(a) A solution of aniline (0.48 g; 0.0052 mol) in 5M aqueous hydrochloric acid (2.6 ml) was treated dropwise with stirring at 0° (ice-salt
bath) with a solution of sodium nitrite (0.37 g; 0.0053 mol) in water (1.3 ml) and the mixture was stirred at 0 - 5° for 10 min. The resulting diazonium solution was then used as described in (b) below.

(b) A mixture of 2-bromo-1-(2-nitrophenyl)ethanone (277) (1.2 g, 0.005 mol) and anhydrous sodium acetate (2.2 g, 0.04 mol) in water (4.0 ml) and ethanol (30.0 ml) was treated dropwise with stirring at 0 - 5° (ice-salt bath) with the diazonium solution prepared in (a) before. The mixture was stirred in the melting ice-bath for 2 h and was then concentrated to remove the ethanol and extracted with methylene chloride to give a red oil (1.7 g). The oil smelled of acetic acid and was therefore redissolved in methylene chloride and the solution washed twice with saturated aqueous sodium hydrogen carbonate (2 x 15.0 ml) then evaporated to give a red oil (1.0 g) which was flash-chromatographed over silica.

Elution with n-hexane-methylene chloride (2:1) gave as the first fraction 2-nitrobenzoic acid (0.4 g; 48%), identified by comparison (i.r. and t.l.c. in hexane methylene chloride over silica) with an authentic sample.

Further elution with n-hexane -methylene chloride through to methylene chloride, ethyl acetate and finally ethanol gave only a series of intractable oils and gums (total 0.56 g) which were not further investigated.

S,S-Dimethyl 2-Nitrobenzoylmethylenesulphonium Bromide (306)

A solution of 2-bromo-1-(2-nitrophenyl)ethanone (277) (2.4 g, 0.01 mol) in anhydrous toluene (15.0 ml) was stirred and treated under an atmosphere of nitrogen with dimethyl sulphide (0.93 g, 0.015 mol) and the
mixture was stirred and heated with a further portion of dimethyl sulphide (0.93 g; 0.015 mol) and stirring and heating at 50° continued for 2 h after which time a further portion of dimethyl sulphide (0.93 g; 0.015 mol) was added, and stirring and heating at 50° continued for a final 2 h. The mixture was then filtered to afford S,S-dimethyl 2-nitrobenzoylmethylene sulphonium bromide (306) (0.70 g; 23%) which formed colourless needles, m.p. 139 - 142° (from ethanol - DMF), $\delta_{\text{max}}$ 1700 (CO) and 1520 and 1350 (NO$_2$) cm$^{-1}$, $\delta_H$ [($\text{CD}_3$)$_2$SO] 8.23 (1H, d, J7Hz, ArH), 8.00 - 7.90 (3H, m, ArH), 5.45 (2H, s, CH$_2$) and 3.03 (6H, s, CH$_3$).

Found: C, 38.9; H, 3.7; N, 4.7%.

C$_{10}$H$_2$BrNO$_2$S requires: C, 39.2; H, 3.9; N, 4.6%

The toluene filtrate was evaporated to give a yellow oil (1.9 g) which was shown by t.l.c. in methylene chloride over silica to be largely starting material (277) and was not therefore further investigated.

1-Bromo-2-(2-nitrophenyl)ethane-1,2-dione 1-Phenylhydrazone (307).

A solution of redistilled aniline (0.28 g, 0.0031 mol) in 5M aqueous hydrochloric acid (1.6 ml) was treated dropwise with stirring at 0 - 5° (ice salt bath) with a solution of sodium nitrite (0.22 g, 0.0032 mol) in water (0.8 ml) and the mixture was stirred at 0 - 5° for 10 min. The resulting benzenediazonium solution was then added dropwise with stirring at 0 - 5° (ice-salt bath) to a mixture of the sulphonium salt (306), (0.92 g, 0.003 mol) and anhydrous sodium acetate (1.3 g, 0.024 mol) in water (24.0 ml) and ethanol (18.0 ml) and the mixture was stirred in the melting ice-bath for 2 h. The mixture was then concentrated to remove the ethanol and extracted with methylene chloride to give a red oil (1.2 g) with was dry-column flash-
chromatographed over silica.

Elution with methylene chloride-\textit{n}-hexane (2:1) gave as the first fraction 1-bromo-2-(2-nitrophenyl)ethane-1,2-dione 1-phenylhydrazone (307) (0.64 g; 61%), which formed yellow crystals, m.p. 123 - 124° (from toluene-light petroleum), \(\delta_{\text{max}}\) 3270 (NH), 1670 (CO), and 1540 and 1350 (NO\(_2\)) cm\(^{-1}\), \(\delta_{\text{H}}(\text{CDCl}_3)\) 8.53 (1H, bs, NH) (exch.), 8.25 - 8.13 (1H, m, ArH), 7.79 - 7.30 (3H, m, ArH) and 7.21 - 6.75 (5H, m, ArH).

Found: C, 48.9; H, 2.9; N, 12.2%; M*, 349, 347.

C\(_{14}\)H\(_{10}\)BrN\(_2\)O\(_2\) requires: C, 48.3; H, 2.87; N, 12.1%; M, 348.

Further elution with methylene chloride through to ethyl acetate and finally ethanol gave only a series of gums (total 0.20 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not therefore further investigated.

The Attempted Base-catalysed Cyclisation of 1-Bromo-2-(2-nitrophenyl)ethane-1,2-dione 1-Phenylhydrazone (307).

A solution of the hydrazone derivative (307) (0.35 g, 0.001 mol) in ethanol (10.0 ml) was treated with 1M aqueous sodium acetate (2.5 ml) and the mixture was heated under reflux for 2 h. The mixture was concentrated to remove the ethanol and the aqueous residue extracted with methylene chloride to give an intractable brown oil (0.32 g) whose t.l.c. in methylene chloride-ethyl acetate (3:1) over silica showed it to be an unresolvable multicomponent mixture which yielded no identifiable material.
The Thermolysis of 1-(4-Methylphenylazo)-1-(2-nitrobenzoyl)methylene triphenylphosphorane (324c) in Toluene.

A solution of the phosphorane derivative (324c) (2.7 g, 0.005 mol) in anhydrous toluene (100 ml) was stirred and heated under reflux. Brown fumes were evolved and a solid separated from the hot solution. The suspension was stirred and heated under reflux for a total of 22 h then hot filtered to afford [1-N-(4-methylphenylcinnolin-4(1H)-on-3-yl)triphenylphosphonium nitrite (325c) (1.9 g; 70%), m.p. 185 - 190°, $\delta_{\text{max}}$ 1630 (CO) cm$^{-1}$, which decomposed on attempted purification by crystallisation.

The toluene filtrate was evaporated to give a red semi-solid (0.64 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 1-(4-methylphenyl)-1H-indole-2,3-dione (327c) (0.14 g; 12%) which formed orange needles, m.p. 144 - 145° (from toluene -light petroleum). $\delta_{\text{max}}$ 1735 (CO) cm$^{-1}$. $\delta_{H}$ (CDCl$_3$) 7.67 (1H, dd, J8 and 1.6Hz, ArH), 7.30 - 7.04 (5H, m, ArH) and 6.84 (1H, dd, J8 and J1.6Hz, ArH).

Found: C, 75.8; H, 4.6; N, 5.9%; M*, 237.
C$_{11}$H$_{14}$NO requires: C, 76.0; H, 4.6; N, 5.9%; M, 237.

Further elution with methylene chloride-ethyl acetate (10:1) gave a small amount of a brown oil (0.09 g) which was not further investigated.

Final elution with ethanol gave impure triphenylphosphine oxide (0.32 g; 24%) m.p. 134 - 145°, identified by comparison (i.r. spectrum) with
Thermolysis Reactions of 1-(2-Nitrobenzoyl)-1-(4-nitrophenylazo)methylene triphenylphosphorane (324b)

(a) In anhydrous toluene

A solution of the phosphorane (324b) (2.3 g, 0.004 mol) in anhydrous toluene (50.0 ml) was heated under reflux for 2 h. The mixture was then filtered to afford [1-N-(4-nitrophenyl)cinnolin-4(1H)-on-3-yl]triphenylphosphonium nitrite (325b) (0.63 g; 28%) which formed colourless crystals m.p. 269 - 272° (from toluene-ethanol), $\delta_\text{max}$ 1630 (CO) and 1520 and 1350 (NO$_2$) cm$^{-1}$, $\delta_\text{h}(\text{CDCl}_3)$ 8.39 - 7.17 (m, ArH).

$\text{Found: }$ C, 66.2; H, 4.1; N, 9.5%; (M-NO$_2$), 528.

$\text{C}_{32}\text{H}_{23}\text{N}_7\text{O}_5\text{P}$ requires: C, 66.9; H, 4.0; N, 9.8%; M, 574.

$\text{Found: }$ (M.H)$^+$, 528.1477

$\text{C}_{32}\text{H}_{23}\text{N}_7\text{O}_5\text{P}$ requires: (M.H), 528.1477.

The toluene filtrate was evaporated to give an orange solid (1.3 g) which was flash-chromatographed over silica.

Elution with methylene chloride through to methylene chloride-ethyl acetate (2:1) gave 1-(4-nitrophenyl)-1H-indole-2,3-dione (327b) (0.55 g; 51%) which formed orange needles, m.p. 244 - 245° (from glacial acetic acid - DMF). $\delta_\text{max}$ 1740 (CO) cm$^{-1}$. $\delta_\text{h}([\text{CD}_2]_2\text{SO})$ 8.50 - 8.35 (2 H, m, ArH), 7.88 - 7.56 (4H, m, ArH) and 7.34 - 6.99 (2 H, m, ArH).

$\text{Found: }$ C, 62.9; H, 3.0; N, 10.6%; M$^+$, 268.

$\text{C}_{18}\text{H}_{13}\text{N}_3\text{O}_3$ requires: C, 62.7; H, 3.0; N, 10.4%; M, 268.
Further elution with ethyl acetate and finally ethanol gave a semi-solid (0.66 g) whose i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (1:1) over silica showed it to be largely triphenylphosphine oxide. The semi-solid was not therefore further investigated.

(b) In anhydrous diglyme

A solution of the phosphorane derivative (324b) (2.3 g, 0.004 mol) in anhydrous diglyme (20.0 ml) was heated under reflux for 2.5 h. The mixture was evaporated under high vacuum to give a brown oil (2.7 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) and methylene chloride through to ethyl acetate gave only a series of gums and semi-solids (total 1.3 g) whose t.l.c. in methylene chloride over silica showed them to be unresolvable mixtures which were not further investigated.

Final elution with ethanol gave a brown semi-solid (1.3 g) whose i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be largely triphenylphosphine oxide. The semisolid was not therefore further investigated.

The Thermolysis of 1-(4-Chlorophenylazo)-1-(2-nitrobenzoyl)methylenetriphenyl phosphorane (324a) in Toluene.

A solution of the phosphorane derivative (324a) (2.8 g, 0.005 mol) in anhydrous toluene (100 ml) was stirred and heated under reflux. Brown fumes were evolved and a solid separated from the hot solution. The resulting suspension was stirred and heated under reflux for a total of 21 h
and was then hot filtered to afford [1-N-(4-chlorophenyl)cinnolin-4(1H)-on-3-yl]triphenylphosphonium nitrite (325a) (2.3 g; 80%), which formed yellow crystals, m.p. 145 - 149° (from toluene-ethanol), \( \delta_{\text{max}} \) 1620 (CO) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.35 - 7.00 (m, ArH).

Found: C, 68.8; H, 4.4; N, 6.2%

\( \text{C}_{22} \text{H}_{15} \text{ClN}_2 \text{OP} \) requires: C, 68.1; H, 4.1; N, 7.5%

Found: M*, 517.1237

\( \text{C}_{22} \text{H}_{15} \text{ClN}_2 \text{OP} \) requires: M, 517.1236.

Evaporation of the toluene filtrate gave a red solid (0.69 g) which was flash-chromatographed over silica.

Elution with methylene chloride followed by methylene chloride-ethyl acetate (10:1) gave 1-(4-chlorophenyl-1H-indole-2,3-dione (327a) (0.26 g; 20%), which formed orange needles, m.p. 200 - 201° (from toluene-light petroleum), \( \delta_{\text{max}} \) 1735 (CO) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.74 - 6.92 (7H, m, ArH) and 6.87 (1H, d J8Hz, ArH).

Found: C, 65.6; H, 3.1; N, 5.4%; M*, 259, 257.

\( \text{C}_{14} \text{H}_{8} \text{ClNO} \) requires: C, 65.5; H, 3.1; N, 5.4%; M, 257.5.

Final elution with ethanol gave a pale yellow semi-solid (0.30 g) whose i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (2:1) over silica showed it to be largely triphenylphosphine oxide and was not therefore further investigated.
Thermolysis Reactions of 1-(4-Methoxyphenylazo)-1-(2-nitrobenzoyl) methylenetriphenylphosphorane (324d)

(a) In anhydrous toluene

A solution of the phosphorane derivative (324d) (4.5 g, 0.08 mol) in anhydrous toluene (200 ml) was heated under reflux for 0.5 h. The mixture was then hot filtered to afford [1-N-(4-methoxyphenyl)cinnolin-4-on-3-yl]triphenylphosphonium nitrite (326) (3.5 g; 78%) which formed yellow microcrystals, m.p. 224 - 231° (decomp.) (from toluene - ethanol) δ (CDCl3) 8.35 - 8.23 (1H, m, ArH), 7.93 - 7.38 (20H, m, ArH) 7.11 - 7.00 (2 h, m, ArH) and 3.87 (3H, s, CH3).

Found: C, 68.3; H, 4.5; N, 7.3%; M*, 462.
C26H26N2O.P requires: C, 70.8; H, 4.6; N, 7.5; M, 559

The filtrate was evaporated to give a red solid (0.72 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (20:1) gave 1-(4-methoxyphenyl)-1 H-indole-2,3-dione (329) (0.11 g; 5%) which formed orange needles m.p. 169 - 170° (from toluene - light petroleum), δ max 1740 (CO) cm⁻¹, δ (CDCl3) 7.67 (1H, d, J=8Hz, ArH) and 3.85 (3H, s, CH3).

Found: C, 71.4; H, 4.4; N, 5.5% M*, 253
C15H11NO2 requires: C, 71.1; H, 4.4; N, 5.5%; M, 253

Further elution with methylene chloride-ethyl acetate (10:1) through to (5:1) afforded 1-(4-methoxyphenyl)-1 H-indol-3-one-2-imine (328) (0.19 g; 9%) which formed orange needles m.p. 169 - 171° (from toluene-light petroleum), δ max 3320 (NH) and 1725 (CO) cm⁻¹, δ (CDCl3) 8.55 (1H, s,
NH) (exch.), 7.76 - 6.77 (8H, m, ArH) and 3.86 (3H, s, CH₃).

**Found:**
C. 71.6; H. 4.6; N. 10.8%; M⁺. 252.

**C₃₀H₂₂N₉O₉ requires:**
C. 71.4; H. 4.8; N. 11.1%; M. 252.

Final elution with ethanol gave triphenylphosphine oxide (0.34; 15%), m.p. 140 - 148°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(b) **In anhydrous diglyme**

A solution of the phosphorane derivative (324d) (2.2 g, 0.004 mol) in anhydrous diglyme (20.0 ml) was heated under reflux for 40 min. The mixture was evaporated to give a brown oil (2.4 g) which was flash-chromatographed over silica.

Elution with toluene through to toluene-methylene chloride (1:1) gave only a series of oils (total 0.52 g) whose t.l.c. in toluene over silica showed them to be complex mixtures which therefore were not further investigated.

Further elution with methylene chloride gave 1-(4-methoxyphenyl)-1H-indole-2,3-dione (329) (0.22 g; 25%), m.p. 169 - 170°, identified by comparison (m.p. and i.r. spectrum) with the sample prepared in (a) before.

Further elution with methylene chloride-ethyl acetate (10:1) through to (1:1) gave only a series of intractable gums (total 0.38 g) which were not further investigated.
Final elution with ethyl acetate followed by ethanol gave triphenylphosphine oxide (1.0 g; 90%), m.p. 140 - 148°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Hydrolysis of 1-(4-Methoxyphenyl)-1H-indol-3-one-2-imine (328) with Aqueous Hydrochloric Acid.

A solution of the imine (328) (0.05 g, 0.0002 mol) in ethanol (5.0 ml) was treated with 2M aqueous hydrochloric acid (0.5 ml) and the mixture was heated under reflux for 15 min. The mixture was evaporated to give 1-(4-methoxyphenyl)-1H-indole-2,3-dione (329) (0.05 g; 98%), m.p. 161 - 164°, identified by comparison (m.p. and i.r. spectrum) with a sample obtained before.

The Base-catalysed Reaction of 2-Nitrobenzoylmethytriphenylphosphonium Bromide (278) with 2,4,6-Trimethylbenzenediazonium Chloride (330)

A solution of 2,4,6-trimethylaniline (mesitidine) in 5M aqueous hydrochloric acid (3.1 ml) was treated dropwise with stirring at < 5° (ice-salt bath) with a solution of sodium nitrite (0.44 g, 0.0064 mol) in water (1.6 ml) and the mixture was stirred at 0 - 5° for 10 min. The diazonium solution was then added dropwise with stirring at 0° (ice salt bath) to a mixture of the phosphonium salt (278) (3.0 g, 0.006 mol) and anhydrous sodium acetate (2.5 g, 0.03 mol) in water (4.8 ml) and ethanol (35.0 ml) and the mixture was stirred at room temperature for 2 h. The mixture was concentrated to remove the ethanol and extracted with methylene chloride to give a yellow oil (3.8 g). The oil was triturated with ether-methylene chloride to afford a solid (0.73 g) which quickly became an intractable brown gum on standing in air and was not further investigated.
The ether-methylene chloride mother liquor was evaporated to give an orange oil (2.6 g) which was dry-column flash-chromatographed over silica.

Elution with methylene chloride gave 1-(2,4,6-trimethylphenyl)-1-\(\text{H}\)-indol-3-one-2-imine (333) (0.23 g; 14%) which formed orange prisms, m.p. 149 - 151\(^\circ\) (from toluene-light petroleum), \(\varepsilon_{\text{max}}\) 3300 (NH) and 1685 (CO) cm\(^{-1}\), \(\delta_{\text{H}}(\text{CDCl}_3)\) 9.60 (1H, s, NH) (exch.), 8.00 (1H, d, J8Hz, ArH), 7.35 (1H, t, J8Hz, ArH), 6.98 (2 H, s, ArH), 6.75 (1H, t, J8Hz, ArH), 6.30 (1H, d, J8Hz), 2.33 (3H, s, CH\(_3\)) and 2.12 (6H, s, CH\(_2\)).

Found: \(\text{C, 77.3; H, 6.1; N, 10.5%; M\textsuperscript{+}, 264.}\)
\(\text{C}_{17}\text{H}_{16}\text{N}_{9}\text{O}\) requires: \(\text{C, 77.3; H, 6.1; N, 10.6%; M, 264.}\)

Further elution with methylene chloride through to methylene chloride-ethyl acetate (5:1) gave only a series of oils (total 0.33 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were therefore not further investigated.

Further elution with methylene chloride-ethyl acetate (2:1) gave 1-N-(2,4,6-trimethylphenyl)cinnolin-4(1H)-one (332) (0.20 g; 13%) which formed colourless microcrystals, m.p. 147 - 150\(^\circ\) (from toluene-light petroleum), \(\varepsilon_{\text{max}}\) 1630 (CO) cm\(^{-1}\), \(\delta_{\text{H}}(\text{CDCl}_3)\) 8.40 (1H, d, J8Hz, ArH), 8.02 (1H, s, ArH), 6.90 (1H, t, J7Hz, ArH), 2.39 (3H, s, CH\(_3\)) and 1.93 (6H, s, CH\(_3\))

Found: \(\text{C, 77.4; H, 6.2; N, 10.0%; M\textsuperscript{+}, 264.1264}\)
\(\text{C}_{17}\text{H}_{16}\text{N}_{9}\text{O}\) requires: \(\text{C, 77.3; H, 6.1; N, 10.6%; M, 264.1263}\).

Further elution with ethyl acetate gave triphenylphosphine oxide.
(0.75g: 48%) identified by comparison (i.r. spectrum) with an authentic sample.

Final elution with ethanol gave a brown semi-solid (0.30 g) whose i.r. spectrum and t.l.c. in methylene chloride-ethyl acetate (1:1) over silica showed it to be impure triphenylphosphine oxide. The semi-solid was not therefore further investigated.

2-Bromo-1-(3-nitrophenyl)ethanone (316)

A solution of 3-nitroacetophenone (24.8 g, 0.15 mol) in glacial acetic acid (75.0 ml) was treated with bromine (24.0 g; 0.15 mol) and the mixture was heated at 100° then poured into water (350 ml) and the precipitated solid was collected and recrystallised from toluene-light petroleum to yield 2-bromo-1-(3-nitrophenyl)ethanone (316) (25.5 g; 69%) as an off-white solid, m.p. 93 - 96° (lit., 96°), \( \delta_{\text{max}} \) 1700 (CO) and 1525 and 1350 (NO₂) cm⁻¹.

Evaporation of the crystallisation mother liquor gave a brown oil (8.2 g) which was not further investigated.

3-Nitrobenzoylmethylenetriphenylphosphonium Bromide (317)

A solution of 2-bromo-1-(3-nitrophenyl)ethanone (316) (12.2 g, 0.05 mol) in anhydrous toluene (100 ml) was stirred at room temperature and treated dropwise with a solution of triphenylphosphine (19.6 g, 0.075 mol) in anhydrous toluene (125 ml) over a period of 0.5 h. The mixture was then heated under reflux for 10 min, stirred for a further 1 h at room temperature, then filtered and the solid combined with a second crop
obtained by trituration of the glassy filter residue with ethanol-ethyl acetate to afford 3-nitrobenzoylmethylenetriphenylphosphonium bromide (317) (20.9 g; 83%), which formed colourless microcrystals, m.p. 203 - 205° (from ethanol - ethyl acetate), $\tilde{\nu}_{\text{max}}$ 1665 (CO) and 1520 and 1310 (NO$_2$) cm$^{-1}$.

δ$_{t}$ (CDCl$_3$) (9.30 (1H, d, J7.6Hz, ArH), 8.74 (1H, t, J1.8Hz, ArH), 8.36 (1H, dd, J7.7 and 1.6Hz, ArH), 8.08 - 7.48 (16H, m, ArH), and 6.62 (1H, s, CH), and 6.47 (1H, s, CH).

**Found:**  C. 61.7; H, 4.1; N, 2.7%

C$_{31}$H$_{26}$BrNO$_2$P requires:  C. 61.7; H, 4.2; N, 2.8%

The ethanol-ethyl acetate mother liquor was evaporated to give a yellow gum (2.0 g) which was not further investigated.

Evaporation of the original toluene filtrate gave an off-white semi-solid (6.9 g) whose t.l.c. in toluene over silica showed it to be mainly triphenylphosphine. The semi-solid was not further investigated.

1-(3-Nitrobenzoyl)-1-phenylazomethylenetriphenylphosphorane (318)

A solution of aniline (0.97 g, 0.01 mol) in 5M aqueous hydrochloric acid (5.2 ml) was treated dropwise with stirring at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (0.74 g, 0.01 mol) in water (2.6 ml) and the mixture was stirred at 0 - 5° for 10 min. The diazonium solution was then added dropwise at 0 - 5° (ice-salt bath) to a mixture of 3-nitrobenzoylmethyl triphenylphosphonium bromide (317) (5.1 g, 0.01 mol) and anhydrous sodium acetate (4.4 g, 0.08 mol) in ethanol (60.0 ml) and water (8.0 ml). The mixture was stirred at room temperature for 2 h and then filtered to afford 1-(3-nitrobenzoyl)-1-phenylazomethylenetriphenylphosphorane (318) (4.9 g;
93%) which formed orange crystals, m.p. 195 - 197° (from toluene). \( \delta_{\text{max}} \) 1520 and 1345 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{r}}(\text{CDCl}_3) 8.98 \) (1H, t, J1.8Hz, ArH), 8.36 - 8.19 (2 h, m, ArH) and 7.85 - 6.86 (2OH, m, ArH).

**Found:**
C, 71.3; H, 4.6; N, 7.5%; M* 529.

**C\(_{14}\)H\(_{20}\)N\(_2\)O\(_5\)P requires:**
C, 72.6; H, 4.5; N, 7.9%; M, 529.

The aqueous ethanolic filtrate was extracted with methylene chloride to give a red-brown oil (0.06 g) which was not further investigated.

**The Thermolysis of 1-(3-Nitrobenzoyl)-1-phenylazomethylenetriphenylphosphorane (318) in Anhydrous Toluene**

A solution of the phosphorane derivative (318) (2.6 g, 0.005 mol) in anhydrous toluene (100 ml) was heated under reflux for 50 h. The mixture was evaporated to give a brown oil (2.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride-n-hexane (3:2) gave as the first fraction triphenylphosphine (0.08 g; 6%), m.p. 69 - 73°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-n-hexane (5:1) afforded \( \alpha \)-N-phenylimino-3-nitrobenzeneacetonitrile (323) (0.65 g; 52%) which formed yellow needles, m.p. 101 - 102° (from toluene-light petroleum), \( \delta_{\text{max}} \) 1520 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{r}}(\text{CDCl}_3) 9.02 - 8.97 \) (1H, m, ArH), 8.52 - 8.36 (2 H, m, ArH) and 7.84 - 7.20 (6H, m, ArH).

**Found:**
C, 67.1; H, 3.5; N, 16.7%; M* 251.

**C\(_{14}\)H\(_{10}\)N\(_2\)O\(_3\) requires:**
C, 66.9; H, 3.6; N, 16.7%; M, 251.
Further elution with methylene chloride through to ethyl acetate gave only a series of gums (total 0.70 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not further investigated.

Final elution with ethanol gave triphenylphosphine oxide (1.1 g; 79%), m.p. 147 - 151° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

\[ \alpha \text{-Chloro-2-nitroacetanilide (339)} \]

\[ \alpha \text{-Chloro-2-nitroacetanilide (339) was prepared by the reaction of 2-nitroaniline (149) with chloracetyl chloride as described in the literature}^{16} \text{ yield 98%, and had m.p. 88 - 90° (lit.}^{16}, 90°). \]

\[ \text{N-(2-Nitrophenyl)carbamoylmethylenetriphenyolphosphonium Chloride (340)} \]

(a) Solutions of \( \alpha \text{-chboro-2-nitroacetanilide (339)} \) (2.1 g, 0.01 mol) in chloroform (5.0 ml) were mixed and the mixture was left stoppered at room temperature for 17 h.

The mixture was diluted with ether (40.0 ml) and the precipitated solid was collected and combined with further material obtained by evaporating the filtrate, dissolving the residue in chloroform (10.0 ml) and diluting the solution with ether to afford \( \text{N-(2-nitrophenyl)carbamoylmethylenetriphenyolphosphonium chloride (340)} \) (0.33 g; 7%) which formed pale yellow prisms, m.p. 183 - 185° (from methanol). \( \tilde{\nu}_{\text{max}} 3100 - 2500 \text{ br (NH), 1680 (CO), and 1520 and 1330 (NO}_2\text{) cm}^{-1}, \delta_{\text{H}} [\text{CD}_3]_2\text{SO} 7.99 - 7.31 \text{ (19H, m, ArH), 5.48 (1H, s, CH), and 5.30 (1H, s, CH).} \]
The ethereal mother liquor was evaporated to give a yellow solid (4.1 g) whose t.l.c. in toluene over silica showed it to be a mixture of the two starting materials which was not therefore further investigated.

(b) Solutions of α-chloro-2-nitroacetanilide (339) (8.6 g, 0.04 mol) in anhydrous toluene (50.0 ml) and triphenylphosphine (10.4 g, 0.04 mol) in anhydrous toluene (50.0 ml) were mixed and the mixture was heated under reflux for 16 h. The cooled mixture was then filtered to afford N-(2-nitrophenyl)carbamoylmethylenetriphenylphosphonium chloride (340) (12.4 g; 65%), m.p. 183 - 185°, identified by comparison (m.p. and i.r. spectrum) with the sample prepared in (b) before.

The toluene filtrate was evaporated to give a brown oil (8.3 g) whose t.l.c. in toluene over silica showed it to be a mixture of the two starting materials, which was not further investigated.

N-(2-Nitrophenyl)carbamoylmethylenetriphenylphosphorane (341)

A suspension of the phosphonium chloride (340) (4.8 g, 0.01 mol) in 10% w/v aqueous sodium carbonate solution (125 ml) was stirred at room temperature for 4 h. The mixture was filtered to afford N-(2-nitrophenyl)carbamoylmethylenetriphenylphosphorane (341) (4.3 g; 98%) which formed red needles, m.p. 198 - 200° (from toluene - DMF) \( \nu_{max} \) 3360 (NH) and 1560 and 1330 (NO2) cm\(^{-1}\), \( \delta_{n}(CDCl_3) \) 10.09 (1H, bs, NH), 8.89 - 8.70 (1H, m, ArH) 8.17 - 8.05 (1H, m, ArH), 7.84 - 7.16 (17H, m, ArH and...
CH), and 6.90 - 6.69. (1H, m, ArH).

Found: C, 71.2; H, 4.7; N, 6.1%; M*, 440.

C_{36}H_{37}N_3O_3P requires: C, 70.9; H, 4.8; N, 6.4%; M, 440.

The filtrate was extracted with methylene chloride to give a brown gum (0.07 g) which was not further investigated.

The Thermolysis Reactions of \(N\)-(2-Nitrophenyl)carbamoylmethylene triphenylphosphorane (341)

(a) In anhydrous toluene

A solution of the phosphorane (341) (0.88 g, 0.002 mol) in anhydrous toluene was heated under reflux for 5 h after which time the solution was evaporated to afford unreacted starting material (341) (0.85 g; 96%), m.p. 174 - 180°, identified by comparison (i.r. spectrum) with an authentic sample.

(b) In anhydrous xylene

A solution of the phosphorane (341) (0.88 g, 0.002 mol) in anhydrous xylene (50.0 ml) was heated under reflux for 28 h.

The mixture was evaporated and the residual brown oil (0.85 g) was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (1:1) gave impure 2-nitroaniline (149) (0.28 g; 50%) identified by comparison (i.r. spectrum) with an authentic sample.
Elution with methylene chloride-ethyl acetate (1:2) afforded 2-nitroacetanilide (342) (0.12 g; 33%), which formed orange needles, m.p. 90 - 91° (from toluene-light petroleum) (lit., 93°), \( \delta_{\max} \) 3360 (NH), 1695 (CO), and 1510 and 1340 (NO_2) cm\(^{-1}\).

Found: C, 53.7; H, 4.5; N, 15.4%
Calc. for \( \text{C}_9\text{H}_9\text{N}_2\text{O}_2 \): C, 53.3; H, 4.4; N, 15.6%.
identified by comparison (m.p. and i.r. spectrum) with an authentic sample.\(^{100}\)

Further elution with ethyl acetate then ethanol afforded triphenylphosphine oxide (0.38 g; 68%), m.p. 150 - 154°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

1-[\( \text{N-(2-Nitrophenyl)carbamoyl} \)]-1-phenylazomethylenetriphenylphosphorane (343)

A solution of aniline (0.96 g, 0.01 mol) in 5M aqueous hydrochloric acid (5.23 ml) was treated dropwise with stirring at 0 - 5° (ice-salt bath) with a solution of sodium nitrite (0.74 g, 0.011 mol) in water (2.6 ml) and the mixture was stirred at 0 - 5° for 10 min. The resulting diazonium solution was then added dropwise with stirring at 0 - 5° (ice-salt bath) to a mixture of the phosphonium chloride (340) (4.8 g, 0.01 mol) and anhydrous sodium acetate (4.4 g, 0.01 mol) in ethanol (60.0 ml) and water (8.0 ml). The mixture was stirred at room temperature for 2 h and then filtered to afford 1-[\( \text{N-(2-nitrophenyl)carbamoyl} \)]-1-phenylazomethylenetriphenylphosphorane (343) (5.1 g; 93%) which formed orange needles, m.p. 228 - 230° (from toluene - DMF), \( \delta_{\max} \) 1530 and 1320 (NO_2) cm\(^{-1}\), \( \delta_{\text{H}} \) (CDCl\(_3\)) 14.04 (1H, bs, NH) (exch.), 8.60 (1H, d, J9Hz, ArH), 8.08 (1H, d, J9Hz, ArH) and
7.88 - 7.02 (22 h, m, ArH).

**Found:**

\[C_8H_{14}N_2O_P\] requires:

\[C, 70.6; H, 4.5; N, 10.2\%; M^+, 544.\]

The aqueous ethanolic filtrate was extracted with methylene chloride to give a red gum (0.39 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

**The Thermolysis of 1-[N-(2-Nitrophenyl)carbomoyl]-1-phenylazomethylene triphenylphosphorane (343) in Dilyme**

A solution of the phosphorane derivative (343) (2.2 g, 0.004 mol) in anhydrous diglyme (40.0 ml) was heated under reflux for 23 h. The mixture was then evaporated to give a brown oil (2.1 g) which was flash-chromatographed over silica.

Elution with methylene chloride-\(n\)-hexane (5:1) through to methylene chloride gave as the first fraction 2-nitroaniline (149) (0.29 g; 52%), m.p. 69 - 71\(^\circ\), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-ethyl acetate (5:1) through to ethyl acetate gave only a series of gums (total 0.78 g) whose t.l.c. in methylene chloride over silica showed them to be unresolvable multicomponent mixtures.

Final elution with ethanol gave a brown semi-solid (0.99 g) whose
i.r. spectrum and t.l.c. in methylene chloride -ethyl acetate (1:1) over silica showed it to be largely triphenylphosphine oxide. The semi-solid was not further investigated.
Chapter 4

STUDIES OF NOVEL BASE - CATALYSED HETEROCYCLISATION REACTIONS OF N,N-DISUBSTITUED 2-NITROBENZYLAMINE DERIVATIVES.
(i) HNO₃, H₂SO₄.
(ii) Me₂NH, ether, 0°.

Scheme 82
(i) RCH$_2$NHCH$_2$R, DMF, room temp. or heat.
(ii) KOH, EtOH, room temp. or heat.

Scheme 83
4.1. Introduction

In 1970, Patey and Waldron reported (Scheme 82) that attempted nitration of \( N,N \)-dimethyl-4-nitrobenzylamine (345) or reaction of 2,4-dinitrobenzyl chloride (346) with dimethylamine lead in both cases to the formation of 2-methyl-6-nitro-2H-indazole (348). These authors made no detailed comment on the pathway or pathways involved in these remarkable indazole syntheses, though they speculated upon, but did not demonstrate, the probable common intermediacy of \( N,N \)-dimethyl-2,4-dinitrobenzylamine (347) in both processes. Subsequent investigations at Edinburgh on the scope and mechanism of these novel indazole syntheses (Scheme 83) demonstrated that treatment of performed \( N,N \)-dimethyl-2,4-dinitrobenzylamine (350a) with ethanolic potassium hydroxide did indeed lead to base-catalysed cyclisation to 2-methyl-6-nitro-2H-indazole (351a) in good yield (76%). Moreover the analogous cyclisation of the \( N,N \)-dibenzyl derivative (350b) was shown to give an even better yield of the corresponding \( N \)-benzylindazole (351b). Base-catalysed indazole formation (Scheme 83) was also found to occur smoothly and in high yield (90-100%) with a variety of simple \( N,N \)-dialkyl-2-nitrobenzylamines \([(353a-c) \rightarrow (354a-c)]\) and in all cases the alkyl group lost in the course of cyclisation was shown to be converted into the corresponding aldehyde (352a and b) and (355a-c). In contrast (Scheme 84) base-catalysed transformation of \( N,N \)-disubstituted-2-nitrobenzylamines bearing sterically demanding alkyl or
(i) KOH, EtOH, room temp.

Scheme 84
Scheme 85
cycoalkyl groups (356) and (358) gave not the corresponding indazoles but followed a different course to give high yields (70 - 100%) of N,N-
disubstituted-2-hydroxyaminobenzamides (357) and (359). Aldersley and Tennant\textsuperscript{100} rationalised indazole formation on the one hand and 2-
hydroxyaminobenzamide formation on the other by two discreet pathways (Schemes 85 - 86) originating in a common aci-nitro tautomeric intermediate (360). Transformation of the latter into the observed indazole and aldehyde products (354) and (355) was postulated to occur (Scheme 85) by rearrangement via the resonance form (361) with loss of hydroxide ion to give a bipolar intermediate (362) followed by cyclisation of the latter and fragmentation of the resulting benzoxadiazine intermediate (363). 2-
Hydroxyaminobenzamide formation on the other hand was considered\textsuperscript{100} to involve (Scheme 86) addition of hydroxide ion to the aci-nitro intermediate [(360) \rightarrow (364)], followed by elimination of hydroxide ion to afford a nitroso species [(365) \rightarrow (367)]. Internal oxidation-reduction in the latter by stepwise prototropic shifts then explains the formation of the observed 2-
hydroxyaminobenzamide product [(365) \rightarrow (366) \rightarrow (367)]. Related base-
catalysed redox processes of \textit{ortho}-substituted nitrobenzene derivatives are well known in the literature\textsuperscript{1}. The objectives of the present studies were to further investigate the scope of the base-catalysed transformations of N,N-
disubstituted 2-nitrobenzylamines and to obtain further evidence for the mechanism of such processes, particularly those leading to indazole formation (see Scheme 85).

4.2 **Investigations of the Scope and Mechanism of Novel Base-catalysed Transformations of N,N-Disubstituted 2-Nitrobenzylamine Derivatives.**

With the intention of demonstrating the value of base-catalysed
Scheme 86
Scheme 87

(i) PhCH₂NH₂, DMF, room temp.
(ii) PhNHMe, DMF, heat.
(iii) KOH, EtOH, reflux.
cyclisation of 2-nitrobenzylamine derivatives for the synthesis of N-unsubstituted indazoles, it was decided to investigate the synthesis and base-catalysed cyclisation (Scheme 87) of the known\textsuperscript{101} compound N-benzyl-2-nitrobenzylamine (369). It was hoped that this 2-nitrobenzylamine derivative might undergo base-catalysed cyclisation by a process akin to that outlined in Scheme 85 to afford 2H-indazole (371) tautomeric with 1H-indazole, (373) and benzaldehyde. N-Benzyl-2-nitrobenzylamine (369) was readily prepared in good yield (79%) by the reaction of 2-nitrobenzyl bromide (368) with benzylamine in DMF. However its attempted cyclisation under standard conditions by heating with potassium hydroxide in ethanol afforded only a complex mixture which yielded no identifiable material.

Only very limited success was achieved in the attempted application of base-catalysed \( N,N \)-disubstituted 2-nitrobenzylamine cyclisation to the synthesis of a 2-arylindazole (Scheme 87). Thus, heating the readily accessible \textsuperscript{82,102} N-methyl-N-phenyl-2-nitrobenzylamine (370) with potassium hydroxide in ethanol gave a complex mixture chromatography of which allowed the isolation of a very low yield (3%) of 2-phenyl-2H-indazole (372). Though the melting-point of this known indazole derivative was somewhat lower than that reported\textsuperscript{103} in the literature, it gave an accurate mass consistent with the assigned structure.

Attention was next turned to the investigation of the synthesis and base-catalysed transformations (Scheme 88) of \( N \)-2-nitrobenzyl derivatives (375a - c) of the cyclic secondary amines, piperidine, morpholine, and pyrrolidine. It was hoped that the behaviour of the 2-nitrobenzylamine derivatives (375a - c) towards base-catalysed cyclisation might provide
\[
\text{(368) + (374) \rightarrow (375) \rightarrow (376) \rightarrow (377) \rightarrow (378)}
\]

(i) DMF, room temp.
(ii) KOH, EtOH, reflux.

Scheme 88
support for the reaction pathway outlined in Scheme 85 by affording benzoxadiazepine intermediates (376a - c) sufficiently stable for isolation. Alternatively these might also undergo spontaneous fragmentation to afford indazole derivatives (378a - c) retaining the aldehyde moiety again providing further evidence for the proposed course (Scheme 85) for indazole formation.

The known compounds N-(2-nitrobenzyl)piperidine (375a)\textsuperscript{104} and N-(2-nitrobenzyl)pyrrolidine (375c)\textsuperscript{105}, and the previously undescribed compound N-(2-nitrobenzyl)morpholine (375b) were readily prepared in excellent yield (99 - 100%) by the reaction of 2-nitrobenzyl bromide (368) with piperidine, pyrrolidine or morpholine in DMF at room temperature. All three compounds (375a), (375b), and (375c) were oils which gave the correct combustion analysis or accurate mass and showed i.r. and \textsuperscript{1}H n.m.r. absorption consistent with the assigned structures. Contrary to expectations but in accordance with the behaviour of N,N-disubstituted 2-nitrobenzylamine derivatives containing bulky alkyl groups (see before), heating the piperidine and morpholine derivatives (375a and b) with potassium hydroxide in ethanol afforded low yields (18 - 25%) of the corresponding 2-hydroxyaminobenzamide derivatives (377a and b) with no evidence for the formation of either the benzoxadiazepine derivatives (376a and b) or the indazole derivatives (378a and b). The 2-hydroxyamino benzamide derivatives (377a and b) analysed correctly and also showed i.r. and \textsuperscript{1}H n.m.r. absorption which fully supported their assigned structures. In contrast to the behaviour of the piperidine and morpholine derivatives (375a and b), heating N-(2-nitrobenzyl)pyrrolidine with potassium hydroxide in ethanol yielded a complex mixture from which no identifiable material could be obtained.
(i) DMF, room temp.
(ii) KOH, EtOH, heat.

Scheme 89
In a further attempt to probe the mechanism of indazole formation and accumulate evidence consistent with the pathway outlined in Scheme 85 it was next decided to investigate the behaviour towards base-catalysed cyclisation (Scheme 89) of the N-(2-nitrobenzyl) tetrahydroisoquinoline derivative (380). On the basis of the proposed course for indazole formation (Scheme 85) this molecule might react under basic conditions to afford an aci-nitro intermediate (381) capable of reacting in the resonance form (382) by elimination-fragmentation and simultaneous expulsion of hydroxide ion to give the nitroso-compound (383). The latter might be isolable or by analogy with the known cyclisation of 2-nitroso-azobenzenes to benzo-1,2,3-triazole N-oxides might cyclise to the indazole N-oxide (384). In either case, the outcome would support the initial stage of the proposed mechanism for indazole formation (Scheme 85).

The known\textsuperscript{104} N-(2-nitrobenzyl)tetrahydroisoquinoline derivative (380) was readily prepared in high yield (85%), by the reaction of 2-nitrobenzyl bromide with 1,2,3,4-tetrahydroisoquinoline (379) in DMF at room temperature. The isoquinoline derivative (380) so obtained showed a substantially lower melting-point (82 - 84\degree) than that (111\degree) reported in the literature,\textsuperscript{104} but otherwise analysed correctly and gave mass, i.r., and \textsuperscript{1}H n.m.r. spectra consistent with the assigned structure. Disappointingly, heating the isoquinoline derivative (380) with potassium hydroxide in ethanol gave only a complex mixture from which no identifiable material could be obtained, with no evidence for the presence of either of the two expected products (383) or (384).

A consequence of the proposed course (Scheme 85) for the base-
(i) PhCH₂NHMe, DMF, room temp.
(ii) KOH, EtOH, reflux.

Scheme 90
catalysed conversion of \( \text{N,N-disubstituted 2-nitrobenzylamine derivatives} \) into indazoles is the more acidic of two different \( N \)-alkyl groups should be preferentially lost in the course of indazole formation \( \text{[ie. for} (353) \rightarrow \rightarrow (354), \text{R}_1 \text{less acidic than CH}_2\text{R}_j]. \) It was therefore of considerable interest to investigate the outcome of the base-catalysed transformations of \( \text{N,N-dialkyl-2-nitrobenzylamine derivatives} \) containing two alkyl groups of significantly different acidity. In this context the behaviour \( \text{(Scheme 90)} \) of \( \text{N-benzyl-N-methyl-2-nitrobenzylamine} \) \( (385) \) towards treatment with ethanolic potassium hydroxide was of interest. In-so-far as the protons of a benzyl substituent are more acidic than those of a methyl group\(^{106} \) and benzyl carbanions are correspondingly more stable than methyl carbanions\(^{107} \) base-catalysed cyclisation of the \( \text{2-nitrobenzylamine derivative} \) \( (385) \) should lead to the predominant formation of \( \text{2-methyl-2H-indazole} \) \( (386; \text{Me for CH}_2\text{Ph}) \) rather than \( \text{2-benzyl-2H-indazole} \) \( (386). \) In practice, heating the known\(^{82} \) \( \text{N-benzyl-N-methyl-2-nitrobenzylamine} \) \( (385) \) with potassium hydroxide in ethanol afforded a readily separated mixture of two compounds one of which was neutral and the other acidic. The neutral compound predominated in the mixture \( \text{(yield 41%)} \) and was identical in all respects to an authentic sample of \( \text{2-benzyl-2H-indazole} \) \( (386). \)\(^{82} \) The acidic product on the other hand was formed in only low yield \( \text{(6%)} \) and is assigned the \( \text{2-hydroxyaminobenzamide structure} \) \( (389) \) on the basis of its analytical and spectroscopic properties.

The apparently exclusive formation of \( \text{2-benzyl-2H-indazole} \) \( (386) \) rather than \( \text{2-methyl-2H-indazole} \) \( (386; \text{Me for CH}_2\text{Ph}) \) in the base catalysed cyclisation of the \( \text{2-nitrobenzylamine derivative} \) \( (385) \) casts doubt on the mechanism proposed in Scheme 85 for indazole formation. However this result is made less meaningful by the low mass yield \( \text{(47%)} \) of identified material recovered from the reaction mixture and the possibility therefore that \( \text{2-methyl-2H-} \)
(368) + (388) 

(i) 

(389) 

(ii) 

(386) + (390) 

and/or

(391) + (392) 

R

a; NO₂

b; MeO

(i) DMF, room temp.

(ii) KOH, EtOH, reflux.

Scheme 91
indazole (386; Me for CH₂Ph) was also formed but despite strenuous efforts could not be isolated from the complex mixture of by-products also produced.

In a further effort to clarify the question of which of a pair of N-alkyl substituents differing in acidity would be lost in the course of indazole formation, attention was turned (Scheme 91) to N,N-dibenzyl-2-nitrobenzylamine derivatives (389) in which one of the benzyl substituents contained an electron-withdrawing group (NO₂) or an electron-donating group (MeO) in the para-position. In terms of the mechanism for indazole formation already outlined in Scheme 85, base-catalysed cyclisation of the para-nitro derivative (389a) should lead to preferential loss of the more acidic para-nitrobenzyl substituent and hence predominant formation of 2-benzyl-2H-indazole (386) and para-nitrobenzaldehyde. Conversely, base-catalysed cyclisation of the para-methoxy compound (389b) should result in the formation of 2-(4-methoxybenzyl)-2H-indazole (391 b) and benzaldehyde derived by retention of the less acidic para-methoxybenzyl group.

The N,N-dibenzyl-2-nitrobenzylamine derivatives (389a and b) required for study were obtained in high yield (70 - 84%) by the condensation fo 2-nitrobenzyl bromide (368) with the previously undescribed N-(4-nitrobenzyl)benzylamine (388a) and the known¹⁰⁸ N-(4-methoxybenzyl)benzylamine (388b) respectively in DMF at room temperature. Both compounds (389a and b) showed analytical and/or spectroscopic properties in accord with their assigned structures. Unfortunately however, the results of the base-catalysed cyclisation reactions of the N,N-dibenzyl-2-nitrobenzylamine derivatives (389a and b) were unmeaningful in relation to the
Scheme 92

(i) NaOEt, EtOH, room temp.
(ii) NaBH₄, KOH, EtOH, reflux.
(ii) 5M HCl(aq), room temp.

(386) + PhCH=O

(392)
question of the preferential loss of one benzyl substituent versus the other. In the case of the para-nitrobenzyl derivative (389a) heating with potassium hydroxide in ethanol gave only an intractable mixture which yielded no identifiable material. On the other hand, similar treatment of the para-methoxybenzyl compound (389b) afforded a separable mixture of roughly equal amounts (28% and 36% respectively) of 2-benzyl-2H-indazole (386) and 2-(4-methoxybenzyl)-2H-indazole (391b) as well as benzaldehyde (392) (20%) and 4-methoxybenzaldehyde (390b) (17%). The previously unknown compound, 2-(4-methoxybenzyl)-2H-indazole (391b) was identified on the basis of its combustion analysis and its mass, i.r. and 'H n.m.r. spectra.

The formation of approximately equal amounts of both possible indazole products (386 and 391b) in the base-catalysed cyclisation of the para-methoxybenzyl-2-nitrobenzylamine derivative (389b) indicates that difference in acidity is not a particularly important factor in the determination of which two benzyl substituents is lost in the course of indazole formation. This result is again difficult to reconcile with the key step [(361) → (362)] in the proposed pathway for indazole formation outlined in Scheme 85. However, alternative support for the latter was provided by a study of the cyclisation (Scheme 92) of N,N-dibenzyl-2-nitrobenzylamine (393) using different basic catalysts.

N,N-dibenzyl-2-nitrobenzylamine (393) had been prepared before as a yellow oil, by the reaction of 2-nitrobenzyl bromide (368) with dibenzylamine in DMF at room temperature. In the present studies the 2-nitrobenzylamine derivative (393) prepared similarly was isolated in high yield (92%) as a low-melting yellow solid which analysed correctly and
showed mass, i.r., and $^1$H n.m.r. spectra consistent with its structure. $N,N$-
Dibenzyl-2-nitrobenzylamine (393) had previously been shown$^{100}$ to undergo
smooth cyclisation in high yield (97%) to 2-benzyl-$2H$-indazole (386) by
heating with potassium hydroxide in ethanol (see Scheme 83 before). The
exclusively base-catalysed as opposed to acid-catalysed nature of this type of
process was indicated in the present studies by the demonstration that the
2-nitrobenzylamine derivative (393) is recovered unchanged in high yield
(92%) after heating with concentrated hydrochloric acid. On the other hand,
the recovery of $N,N$-dibenzyl-2-nitrobenzylamine (393) in good yield (77%)
after heating under reflux with piperidine in ethanol also shows that a
sufficiently potent basic catalyst is needed to achieve successful cyclisation.
In relation to the course (Scheme 92) proposed$^{100}$ for the base-catalysed
formation of 2-benzyl-$2H$-indazole (386) from $N,N$-dibenzyl-2-nitrobenzylamine
(393) (see also Scheme 85 before), this result indicates that piperidine is
insufficiently basic to catalyse the aci-nitro tautomerism involved in the first
step [(393) $\rightarrow$ (394)] or the elimination involved in the second [(395) $\rightarrow$ (396)].
In contrast the much stronger basic catalyst sodium hydride was found in
the present studies to achieve the cyclisation of the 2-nitrobenzylamine
derivative (393) to 2-benzyl-$2H$-indazole (386) in moderate yield (53%) in
DMF at room temperature. However the most important finding from the
point-of-view of the proposed course for 2-benzyl-$2H$-indazole (386) formation
(Scheme 92) was provided by the use of sodium ethoxide as the basic
catalyst.

Heating $N,N$-dibenzyl-2-nitrobenzylamine (393) under reflux with
sodium ethoxide in ethanol gave, in addition to a moderate yield (58%) of
the expected 2-benzyl-$2H$-indazole (386), a low yield (12%) of a second
compound which gave a combustion analysis in accord with the molecular
formula C_{21}H_{20}N_{2}O. This molecular formula was also consistent with the
presence of a parent ion at m/z 316 in the mass spectrum of the
compound. The assignment of the novel tetrahydrobenzoxadiazepine
structure (398) to the minor product of the sodium ethoxide-catalysed
reaction of N,N-dibenzyl 2-nitrobenzylamine (393) is based on its i.r. and \(^1\)H
and \(^{13}\)C n.m.r. absorption and its chemical properties. The compound
showed i.r. absorption at 3340 cm\(^{-1}\) due to an NH-group and its \(^1\)H n.m.r.
spectrum, in addition to absorption due to the protons of three benzene
nuclei, contained signals attributable to the protons of an NH and a CH
substituent as well as two CH\(_2\) groups. The compound's broad-band
decoupled \(^{13}\)C n.m.r. spectrum in conjunction with its \(\delta^\text{H}_C/\delta^\text{H}_C\)
dept. variant as well as confirming the presence of an aliphatic CH substituent and two CH\(_2\)
groups also demonstrated the presence of four quaternary carbon centres as
required by the structure (398). The compound was surprisingly stable to
attempted catalytic reduction, being recovered unchanged in high yield (82 -
84\%) after attempted hydrogenolysis over 10\% palladium-on-charcoal in both
the absence and the presence of glacial acetic acid. However, in accord with
its cyclic aminal structure (398) the compound was extremely labile under
acidic conditions. Thus, brief treatment with aqueous hydrochloric acid
converted it into a readily separated mixture of benzaldehyde (392) (100\%)
and a low-melting product (yield 57\%) whose analytical and spectroscopic
properties allow its formulation as the previously unreported \(N-(2-
hydroxyaminobenzyl)benzylamine (399). This compound gave a combustion
analysis and showed a parent ion at m/z 228 in its mass spectrum
consistent with the required molecular formula, C_{14}H_{16}N_{2}O. In addition its
\(^1\)H and \(^{13}\)C n.m.r. spectra contained, as well as the expected aromatic proton
and carbon CH-resonances, signals due to two CH$_2$ substituents and three quaternary carbon centres.

Regrettably various attempts to firmly establish the structure of the hydroxyamino benzylamine (399) by chemical methods, were unsuccessful. The compound (399) was recovered unchanged (yield 86%) after attempted hydrogenolysis in ethanol over 10% palladium-on-charcoal, while attempted selective oxidation using activated manganese dioxide in benzene at room temperature afforded only a low yield of a complex gum. Attempted dehydrative cyclisation of the 2-hydroxyamino benzylamine derivative (399) by heating with toluene-4-sulphonic acid (ptsa) in benzene under reflux, conditions closely similar to those applied successfully $^{62}$ in the cyclisation of 2-hydroxyamino benzamide derivatives to indazoles, also gave a mixture consisting largely of the unreacted starting-material (399).

The formation of the tetrahydrobenzoxadiazepine derivative (398) in the sodium ethoxide catalysed transformation of N,N-dibenzyl-2-nitrobenzylamine (393) is most readily explained (Scheme 92) in terms of the intermediate formation and reduction $^6$ in the alkaline medium of the dihydrobenzoxadiazepine derivative (397). In support of this contention, heating N,N-dibenzyl-2-nitrobenzylamine (393) with potassium hydroxide in ethanol in the presence of sodium borohydride afforded the tetrahydrobenzoxadiazepine (398) as the only identifiable product, albeit in only low yield (28%). Formation of the tetrahydrobenzoxadiazine (398) under these conditions by some form of direct reduction of N,N-dibenzyl-2-nitrobenzylamine (393) is excluded by the recovery of the latter unchanged in quantitative yield after heating under reflux with sodium borohydride in
ethanol alone.

The formation and isolation of the tetrahydrobenzoxadiazepine derivative (398) provides the strongest evidence to date for the course for base-catalysed indazole formation from N,N-dialkyl-2-nitrobenzylamine derivatives outlined in Schemes 85 and 92. After the present studies were completed Boyer and his coworkers\textsuperscript{109} in a short paper relating to the original work of Patey and Waldron\textsuperscript{60}, proposed an alternative radical pathway to account for the base-catalysed conversion (Scheme 82) of N,N-dimethyl-2,4-dinitrobenzylamine (347) into 2-methyl-6-nitro-2H-indazole (348) but without any conclusive evidence in support of their proposals. However it is obvious that further detailed investigations will be needed to firmly establish the precise course of such interesting transformations of N,N-disubstituted-2-nitrobenzylamine derivatives.
4.3. Experimental

General Experimental Details

For details of general experimental procedures see Chapter 2, Section 2.7.

N-Benzyl-2-nitrobenzylamine (369)

A solution of 2-nitrobenzyl bromide (368) (2.2 g, 0.01 mol) in anhydrous DMF (10.0 ml) was treated with benzylamine (2.1 g, 0.02 mol) and the mixture was stoppered and left at room temperature overnight.

The mixture was evaporated and the residual semi-solid was treated with 2M aqueous sodium hydroxide (15.0 ml) and extracted with methylene chloride to afford a brown oil (2.8 g) which was purified by flash-chromatography in toluene-ethyl acetate (3:1) over silica to give the known\textsuperscript{101} N-benzyl-2-nitrobenzylamine (369) as a yellow oil (1.9 g; 79%), $\nu_{\text{max}}$ 3320 (NH) and 1525 and 1350 (NO$_2$) cm$^{-1}$.

**Found:**

M', 242.

**Calc. for C$_{11}$H$_7$N$_2$O$_2$:**

M, 242.

which due to its instability was used without further purification.

The Attempted Reaction of N-Benzyl-2-Nitrobenzylamine (369) with Ethanolic Potassium Hydroxide

A solution of the amine (369) (1.2 g, 0.005 mol) was treated with finely powdered potassium hydroxide (1.4 g, 0.025 mol) and the mixture was heated under reflux for 4 h. The mixture was concentrated, treated with water (5.0 ml) and extracted with methylene chloride to give a red oil (0.98 g) whose t.l.c. in toluene over silica showed it to be a complex multicomponent mixture. Repeated attempts to separate the oil into its components failed, giving only a high recovery of oils whose t.l.c. in toluene-ethyl acetate eluants showed them to be inseparable.
multicomponent mixtures.

The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid, neutralised with solid sodium acetate and extracted with methylene chloride to give a brown gum (0.13 g) whose t.l.c. in toluene over silica showed it to be a complex mixture which was not further investigated.

N-Methyl-N-phenyl-2-nitrobenzylamine (370)

N-Methyl-N-phenyl-2-nitrobenzylamine (370) was prepared by the reaction of 2-nitrobenzyl bromide (368) with N-methylaniline in DMF as described by Steel,82 yield 76%, m.p. 64 - 66° (lit.,102 72°), and was used without further purification.

The Reaction of N-Methyl-N-phenyl-2-nitrobenzylamine (370) with Ethanolic Potassium Hydroxide

A solution of the amine (370) (2.4 g, 0.01 mol) in ethanol (50.0 ml) was treated with finely powdered potassium hydroxide (2.8 g, 0.05 mol) and the mixture was heated under reflux for 4 h. The mixture was then concentrated, treated with water (10.0 ml) and extracted with methylene chloride to give a brown oil (2.4 g) which was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (10:1) gave as the first fraction a yellow oil (0.12 g) whose t.l.c. in cyclohexane-ethyl acetate (10:1) showed it to be a complex mixture which was not further investigated.

Further elution with cyclohexane-ethyl acetate (5:1) afforded 2-N-phenyl-2H-indazole (372) (0.05 g; 3%), which formed pale yellow plates m.p. 71 - 72° (from
Further elution with cyclohexane-ethyl acetate (10:1) through to ethyl acetate and finally ethanol gave only a series of intractable gums (total 2.1 g) whose t.l.c. in cyclohexane-ethyl acetate (5:1) or (1:1) over silica showed them to be complex mixtures which were not further investigated.

**N-(2-Nitrobenzyl)piperidine (375a)**

A solution of 2-nitrobenzyl bromide (368) (8.6 g, 0.04 mol) in anhydrous DMF (25.0 ml) was treated with piperidine (374a) (6.8 g, 0.08 mol) and the mixture was stoppered and left at room temperature for 15 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (50.0 ml) and extracted with methylene chloride to give a brown oil (9.8 g) which was flash-chromatographed over silica.

Elution with toluene-ethyl acetate (5:1) gave the known\textsuperscript{104} \(N\)-(2-nitrobenzyl)piperidine (375a) (8.7 g; 99%), as a yellow oil, b.p. 136°/0.5 mmHg, \(\delta_{\text{max}}\) 1525 and 1355 (NO\textsubscript{2}) cm\textsuperscript{-1}, \(\delta_{\text{H}}(\text{CDCl}_3)\) 7.83 - 7.18 (4H, m, ArH), 3.70 (2H, s, CH\textsubscript{2}), 2.34 - 2.28 (4H, m, CH\textsubscript{2}) and 1.69 - 1.44 (6H, m, CH\textsubscript{2}).

**Found:** \(M^+\), 220.1209

**Calc. for C\textsubscript{13}H\textsubscript{15}N\textsubscript{2}O\textsubscript{2}:** \(M\), 220.1212

Further elution with methanol gave a brown gum (0.3 g) which was not further investigated.
The Reaction of \( N-(2\text{-Nitrobenzyl})piperidine \) (375a) with Ethanolic Potassium Hydroxide

A solution of the amine (375a) (2.2 g, 0.01 mol) in ethanol (50.0 ml) was treated with finely powdered potassium hydroxide (2.8 g, 0.05 mol) and the mixture was heated under reflux for 4 h. The mixture was then concentrated to remove most of the ethanol and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a brown foam (1.5 g) which was flash-chromatographed over silica.

Elution with toluene-ethyl acetate (5:1) through to (3:1) gave as the first fraction, \( N-(2\text{-hydroxyaminobenzoyl})piperidine \) (377a) (0.54 g; 25%), which formed colourless crystals, m.p. 127 - 130° (from light petroleum) \( \delta_{\text{max}} \) 3300 (NH), 3100 - 2500 br (OH), and 1660 (CO) cm\(^{-1}\). \( \delta_{1}(\text{CDCl}_3) \) 8.10 - 7.17 (5H, m, ArH, NH and OH), 6.74 - 6.53 (1H, m, ArH), 2.74 - 2.58 (4H, m, CH\(_2\)), and 1.84 - 1.25 (6H, m, CH\(_2\)).

\[
\text{Found:} \quad \begin{align*}
C & \quad 65.5; \\
H & \quad 7.1; \\
N & \quad 12.9%; \\
M & \quad 220
\end{align*}
\]

\[
\text{C}_{12}\text{H}_{18}\text{N}_{2}\text{O}_{2} \text{ requires:} \quad \begin{align*}
C & \quad 65.4; \\
H & \quad 7.3; \\
N & \quad 12.7%; \\
M & \quad 220
\end{align*}
\]

Further elution with toluene-ethyl acetate (1:1) through to methanol gave only a series of intractable oils (total 0.69 g) which were not further investigated.

\( N-(2\text{-Nitrobenzyl})\text{morpholine} \) (375b)

A solution of 2-nitrobenzyl bromide (368) (4.3 g, 0.002 mol) in anhydrous DMF (40.0 ml) was treated with morpholine (374b) (3.5 g, 0.04 mol) and the mixture was stoppered and left at room temperature for 40 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to afford \( N-(2-\)
nitrobenzyl)morpholine (375b) (4.4 g; quant.) as a brown oil, b.p. 162°/0.4 mm Hg, δ\text{max} 1525 and 1355 (NO$_2$) cm$^{-1}$, δ$_{\text{H}}$(CDCl$_3$) 7.85 - 7.25 (4H, m, ArH), 3.77 (2H, s, CH$_2$), 3.69 - 3.58 (4H, m, CH$_2$), and 2.47 - 2.35 (4H, m, CH$_2$).

Found: M*, 222.0999
C$_{11}$H$_{14}$N$_2$O$_2$ requires: M, 222.1004

The Reaction of N-(2-Nitrobenzyl)morpholine (375b) with Ethanoic Potassium Hydroxide

A solution of the amine (375b) (2.2 g, 0.01 mol) in ethanol (50.0 ml) was treated with finely powdered potassium hydroxide (2.8 g, 0.05 mol) and the mixture was heated under reflux for 4 h. The mixture was concentrated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a brown semi-solid (1.1 g) which was flash-chromatographed over silica.

Elution with toluene-ethyl acetate through ethyl acetate to methanol gave only complex oils and gums which yielded no identifiable material.

The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid, neutralised with solid sodium acetate and extracted with methylene chloride to afford a brown solid (0.39 g) which was flash-chromatographed over silica.

Elution with ethyl acetate-toluene (5:1) gave N-(2-hydroxyaminobenzoyl)morpholine (377b) (0.26 g; 18%), which formed colourless crystals, m.p. 158 - 161° (from light petroleum-toluene), δ$_{\text{max}}$ 3300 (NH), 3100 - 2500 br (OH), and 1660 (CO) cm$^{-1}$, δ$_{\text{H}}$(CDCl$_3$) 8.18 - 7.54 (1H, bs, OH), 7.95 (1H, d, J8Hz ArH), 7.54 - 7.20 (3H, m, ArH and NH), 6.78 - 6.58 (1H, m, ArH), 3.84 (4H, t, J4.6Hz, CH$_2$), and 2.82 (4H, t, J4.6Hz, CH$_2$).
Further elution with ethyl acetate and finally ethanol gave only an intractable brown semi-solid (0.15 g) which was not further investigated.

*N-(2-Nitrobenzyl)pyrrolidine (375c)*

A solution of 2-nitrobenzyl bromide (368) (4.3 g, 0.02 mol) in anhydrous DMF (20.0 ml) was treated with pyrrolidine (2.8 g, 0.004 mol) and the mixture was left at room temperature for 19 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to afford the known* N-(2-nitrobenzyl)pyrrolidine (375c) as a brown oil (4.1 g; 100%) \( \delta_{\text{max}} \) 1525 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{H}} \) 7.89 - 7.32 (4H, m, ArH), 3.92 (2H, s, CH\(_2\)), 2.60 - 2.39 (4H, m, CH\(_2\)) and 1.89 - 1.67 (4H, m, CH\(_3\)) which due to its instability was used without further purification.

The Reaction of *N-(2-Nitrobenzyl)pyrrolidine (375c)* with Ethanolic Potassium Hydroxide

A solution of the amine (375c) (2.1 g, 0.01 mol) in anhydrous ethanol (50.0 ml) was treated with finely powdered potassium hydroxide (2.8 g, 0.05 mol) and the mixture was heated under reflux for 4 h. The mixture was then concentrated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown foam (1.7 g) which was flash-chromatographed over silica.

Elution with toluene-ethyl acetate (1:1) through to ethyl acetate gave only
a series of oils (total 0.35 g) whose t.l.c. in toluene-ethyl acetate (1:1) showed them to be complex mixtures which were not further investigated.

Final elution with methanol gave a brown foam (1.2 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

N-2-Nitrobenzyl-1,2,3,4-tetrahydroisoquinoline (380)

A solution of 2-nitrobenzyl bromide (368) (4.3 g, 0.02 mol) in anhydrous DMF (20.0 ml) was treated with 1,2,3,4-tetrahydroisoquinoline (379) (5.3 g, 0.04 mol) and the mixture was stoppered and left at room temperature for 17 h.

The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to give a brown semi-solid (7.5 g) which was flash-chromatographed over silica. Elution with toluene then toluene-ethyl acetate (5:1) gave the known\textsuperscript{104} N-2-nitrobenzyl-1,2,3,4-tetrahydroisoquinoline (380) (4.2 g; 85%), which formed off-white needles, m.p. 82 - 84° (from light petroleum) (lit.,\textsuperscript{104} 111°), $\delta_{\text{max}}$ 1530 and 1340 (NO$_2$) cm$^{-1}$, $\delta$ (CDCl$_3$) 7.92 - 6.97 (8H, m, ArH), 3.98 (2H, s, CH$_2$), 3.66 (2H, s, CH$_2$) and 2.94 - 2.67 (4H, m, CH$_2$).

**Found:**

- C, 71.7; H, 6.1; N, 10.4%; M$^+$, 268.

**Calc. for C$_{16}$H$_{16}$N$_2$O$_2$:**

- C, 71.6; H, 6.0; N, 10.4%; M, 268

Final elution with ethanol gave only a small amount of an intractable brown gum which was not further investigated.
The Attempted Reaction of N-2-Nitrobenzyl-1,2,3,4-tetrahydrolsoquinoline (380) with Ethanolic Potassium Hydroxide.

A solution of the amine (380) (1.3 g, 0.005 mol) in anhydrous ethanol (50.0 ml) was treated with finely powdered potassium hydroxide (1.4 g, 0.025 mol) and the mixture was heated under reflux for 4 h.

The mixture was then concentrated, treated with water (10.0 ml) and extracted with methylene chloride to yield a brown gum (1.1 g) whose t.l.c. in toluene-ethyl acetate (5:1) over silica showed it to be a complex mixture.

Flash-chromotography of the gum over silica eluting with toluene-ethyl acetate (5:1) through to ethyl acetate and finally ethanol gave only a series of unidentifiable gums (total 1.1 g).

The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid, neutralised with solid sodium acetate and extracted with methylene chloride to give a brown oil (0.07 g).

Attempted preparative t.l.c. of the oil over silica eluting with methylene chloride-ethyl acetate (5:1) gave no identifiable material.

N-Benzyl-N-Methyl-2-nitrobenzylamine (385)

A solution of 2-nitrobenzyl bromide (368) (8.6 g, 0.04 mol) in anhydrous DMF (40.0 ml) was treated with N-benzylmethylamine (9.7 g, 0.08 mol) and the mixture was left at room temperature for 17 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to give a yellow oil (14.8
g) which was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (5:1) gave N-benzyl-N-methyl-2-nitrobenzylamine (385) (8.3 g; 81%), m.p. 42 - 45° (lit., 45 - 46°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with cyclohexane-ethyl acetate (5:1) through to ethyl acetate and finally methanol gave only a series of oils (total 3.3 g) whose t.l.c. in cyclohexane-ethyl acetate (3:1) showed them to be complex mixtures which were not further investigated.

The Reaction of N-Benzyl-N-methyl-2-nitrobenzylamine (385) with Ethanolic Potassium Hydroxide

(a) A solution of the amine (385) (5.1 g, 0.02 mol) in anhydrous ethanol (100 ml) was treated with finely powdered potassium hydroxide (5.6 g, 0.1 mol) and the mixture was heated under reflux for 4 h. The mixture was then concentrated, treated with water (20.0 ml) and extracted with methylene chloride to give a brown oil (5.8 g) which was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (5:1) gave 2-N-benzyl-2H-indazole (386) (1.7 g, 41%), which formed colourless needles, m.p. 66 - 67° (from light petroleum) (lit., 68 - 69°), δ(1)(CDCl3) 7.87 - 6.95 (10, m, ArH and CH) and 5.59 (2H, s, CH2).

Found: C, 80.6; H, 5.8; N, 13.5%; M+, 208
Calc. for C14H12N2: C, 80.7; H, 5.8; N, 13.5; M, 208.

Further elution with cyclohexane-ethyl acetate (3:1) through to (2:1) gave
a brown oil (1.0 g) which was further manipulated as described in (b) below.

Final elution with ethanol gave an intractable brown gum (0.64 g) which was not further investigated.

(b) The oil from (a) was re-flash-chromatographed over silica eluting with cyclohexane-ethyl acetate (1:1) to give N-([2-hydroxyaminobenzoyl]-N-methylbenzylamine (387) (0.33 g; 6%) which formed colourless crystals, m.p. 135 - 137° (from toluene), δmax 3290 (NH), 3100 - 2500 br (OH), and 1670 (CO) cm⁻¹.

**Found:**

C, 69.8; H, 6.5; N, 11.2%; M⁺, 256.1210.

C₁₅H₁₅N₂O₂ requires:

C, 70.3; H, 6.3; N, 10.9%; M⁺, 256.1212

Further elution with cyclohexane-ethyl acetate (1:1) through to ethyl acetate gave only a series of complex gums and oils (total 0.86 g) which were not further investigated.

**N-(4-Nitrobenzyl)benzylamine (388a)**

A solution of 4-nitrobenzyl bromide (4.3 g, 0.02 mol) in anhydrous DMF (400 ml) was treated with benzylamine (4.3 g, 0.04 mol) and the mixture was left at room temperature for 17 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to give a brown oil (6.3 g) which was flash-chromatographed over silica.

Elution with toluene gave an unidentified solid (0.25), m.p. 130 - 135° which was not further investigated.
Further elution with toluene-ethyl acetate (10:1) gave a red oil (0.38 g) whose t.l.c. in toluene over silica showed it to be a complex mixture which was not further investigated.

Further elution with toluene-ethyl acetate (5:1) afforded \(N\)-(4-nitrobenzyl)benzylamine (388a) (3.7 g; 76%) which formed colourless needles, m.p. 40 - 43° (from light petroleum), \(\delta_{\text{max}}\) 3310 (NH) and 1510 and 1345 (NO\(_2\)) cm\(^{-1}\), \(\delta_{\text{H}}\) (CDCl\(_3\)) 8.18 (2H, d, J7Hz, ArH), 7.52 (2H, d, J7Hz, ArH), 3.91 (2H, s, CH\(_2\)) and 3.81 (2H, s, CH\(_2\)).

**Found:**
C, 69.6; H, 5.9; N, 12.2%; M\(^+\), 242.1056

C\(_{14}\)H\(_{17}\)N\(_2\)O\(_2\) requires:
C, 69.4; H, 5.8; N, 11.6%; M, 242.1055

Further elution with toluene-ethyl acetate (2:1) through to ethyl acetate and finally methanol gave only a series of intractable brown gums (total 1.6 g) which were not further investigated.

\(N\)-(Nitrobenzyl)-\(N\)-(4-nitrobenzyl)benzylamine (389a)

A solution of 2-nitrobenzyl bromide (368) (1.6 g, 0.0075 mol) in anhydrous DMF (20.0 ml) was treated with \(N\)-(4-nitrobenzyl)benzylamine (388a) (3.6 g, 0.015 mol) and the mixture was stirred at room temperature overnight. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (10.0 ml) and extracted with methylene chloride to give a brown oil (3.8 g) which was flash - chromatographed over silica.

Elution with toluene gave \(N\)-(2-nitrobenzyl)-\(N\)-(4-nitrobenzyl)benzylamine (389a) as a yellow oil (2.4 g; 84%), \(\delta_{\text{max}}\) 1530 and 1350 (NO\(_2\)) cm\(^{-1}\).

**Found:**
M\(^+\), 377.
Further elution with toluene-ethyl acetate (5:1) gave a red oil (0.6 g) whose t.l.c. in toluene over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of N-(2-Nitrobenzyl)-N-(4-nitrobenzyl)benzylamine (389a) with Ethanoic Potassium Hydroxide

A solution of the amine (389a) (2.3 g, 0.006 mol) in ethanol (25.0 ml) was treated with finely powdered potassium hydroxide (1.7 g, 0.03 mol) and the mixture was heated under reflux for 4 h.

The mixture was then concentrated and the residue was treated with water (5.0 ml) to give a red oil (0.65 g) which was flash-chromatographed over silica.

Elution with toluene-ethyl acetate (3:1) through to ethyl acetate and finally methanol gave only a series of oils (total 0.62 g) whose t.l.c. in toluene-ethyl acetate (3:1) over silica showed them to be complex mixtures which were not further investigated.

The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid, neutralised with solid sodium acetate and filtered to afford a brown solid (0.99 g). The brown solid was washed with hot ethanol to leave an unidentified brown solid (0.44 g).
The ethanolic washings were evaporated to afford an intractable red gum (0.23 g) which was not further investigated.

The aqueous filtrate was extracted with methylene chloride to give a red oil (0.34 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

*N-(4-Methoxybenzyl)benzylamine (388b)*

A solution of benzylamine (6.8 g, 0.04 mol) in anhydrous DMF (40.0 ml) was treated with 4-methoxybenzylamine (11.0 g, 0.08 mol) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (50.0 ml) and extracted with methylene chloride to give an orange oil (15.0 g) which was flash-chromatographed over silica.

Elution with toluene through to toluene-ethyl acetate (5:1) gave as the first fractions only a series of intractable oils and semi-solids (total 3.4 g) which were not further investigated.

Further elution with ethyl acetate afforded the known \(^ {108} \) *N-(4-methoxybenzyl)benzylamine (388b)* as an oil (8.9 g; 98%) (lit. \(^ {108} \) oil b.p. 170 - 172°/3 mm Hg), 3290 (NH) which was used without further purification

*N-(4-Methoxybenzyl)-N-(2-nitrobenzyl)benzylamine (389b)*

A solution of 2-nitrobenzyl bromide (2.2 g, 0.01 mol) in anhydrous DMF (40.0 ml) was treated with *N-(4-methoxybenzyl)benzylamine (388b)* (4.5 g, 0.02 mol) and the mixture was left at room temperature for 17 h. The mixture was
evaporated under high vacuum (oil pump) and the residue was treated with 2M aqueous sodium hydroxide (25.0 ml) and extracted with methylene chloride to afford a brown oil (5.7 g) which was flash-chromatographed over silica.

Elution with toluene gave as the first fraction unreacted 2-nitrobenzyl bromide (368) (0.24 g; 11%), m.p. 40 - 44°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with toluene afforded N-(4-methoxybenzyl)-N-(2-nitrobenzyl)benzylamine (389b) (2.5 g; 70%) as a yellow oil, b.p. 220°/0.5 mmHg, \( \delta_{\text{max}} \) 1525 and 1345 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{n}(\text{CDCl}_3) \text{ s(5)} } \) 7.86 - 7.19 (11H, m, ArH), 6.85 (2H, d, J9Hz, ArH), 3.86 (2H, s, CH\(_2\)), 3.78 (3H, s, CH\(_3\)), 3.54 (2H, s, CH\(_3\)) and 3.49 (2H, s, CH\(_2\)).

**Found:** C, 72.0; H, 6.1; N, 7.5%; M, 362.1635

**C\(_{27}\)H\(_{27}\)N\(_2\)O, requires:** C, 72.9; H, 6.1; N, 7.7%; M, 362.1630.

Further elution with toluene-ethyl acetate (5:1) through to (1:1) gave a series of gums (total 0.42 g) whose t.l.c. in toluene-ethyl acetate (5:1) over silica showed them to be complex mixtures which were not further investigated.

**The Reaction of N-(4-Methoxybenzyl)-N-(2-nitrobenzylamine) (389b) with Ethanolic Potassium Hydroxide**

(a) A solution of the amine (389b) (2.2 g, 0.006 mol) in ethanol (30.0 ml) was treated with finely powdered potassium hydroxide (1.7 g, 0.03 mol) and the mixture was heated under reflux for 4 h. The mixture was concentrated and residue was treated with water (5.0 ml) and extracted with methylene chloride to afford a red oil (1.7 g) which was flash-chromatographed over silica.
Elution with cyclohexane-ethyl acetate (5:1) gave benzaldehyde as an oil (0.13 g; 20%), identified by comparison (i.r. and t.l.c. in toluene over silica) with an authentic sample.

Further elution with cyclohexane-ethyl acetate gave 4-methoxybenzaldehyde (390b) (0.14 g; 17%) as a red oil, $\delta_{\text{max}}$ 1680 (CO) cm$^{-1}$; identified by the preparation of its 2,4-dinitrophenylhydrazone derivative, m.p. 240 - 245° (from glacial acetic acid), (lit.,$^{10}$ m.p. 254°).

Further elution with cyclohexane-ethyl acetate (5:1) through to (1:1) gave two oils (total 0.82 g) whose t.l.c. in methylene chloride over silica showed them to be mixtures with common components. The oils were recombined and re-flash-chromatographed over silica.

Elution with methylene chloride gave impure 2-N-benzyl-2H-indazole (386) (0.36 g; 28%), m.p. 35 - 45° (lit.,$^{8}$ m.p. 63°), identified by comparison (i.r. spectrum and t.l.c. in methylene chloride over silica) with an authentic sample.

Further elution with methylene chloride-ethyl acetate (10:1) gave 2-N-(4-methoxybenzyl)-2H-indazole (391b) (0.5 g; 36%), which formed buff crystals, m.p 108 - 110° [from light petroleum (b.p. 80 - 100°)], $\delta_{\text{H}}$ (CDCl$_3$) 7.83 - 7.56 (3H, m, ArH), 7.37 - 7.02 (4H, m, ArH), 7.87 (2H, d, J9Hz, ArH), 5.52 (2H, s, CH$_2$), and 3.79 (3H, s, OCH$_3$).

**Found:**
- C, 75.4; H, 5.8; N, 11.7%; M*, 238.
**C$_{18}$H$_{14}$N$_2$O requires:**
- C, 75.6; H, 5.9; N, 11.8%; M, 238.
N,N-Dibenzyl-2-nitrobenzylamine (393)

A solution of 2-nitrobenzyl bromide (8.6 g, 0.04 mol) in anhydrous DMF (50.0 ml) was treated with dibenzylamine (15.8 g, 0.08 mol) and the mixture was left at room temperature for 17 h. The mixture was then filtered to remove dibenzylamine hydrobromide (7.1 g; 64%), m.p. 268 - 270° (lit., 111 266°).

The DMF filtrate was evaporated under high vacuum (oil pump) to give a yellow semi-solid (18.6 g) which was treated with 2M aqueous sodium hydroxide (50.0 ml) and extracted with methylene chloride to give a yellow oil (15.8 g) which was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (10:1) gave as the first fraction N,N-dibenzyl-2-nitrobenzylamine (393) as a yellow solid (12.2 g; 92%), m.p. 40 - 45°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.100

Further elution with cyclohexane-ethyl acetate (10:1) through to ethyl acetate gave only a series of oils (total 2.4 g) whose t.l.c. in cyclohexane-ethyl acetate (5:1) over silica showed them to be complex mixtures which were not further investigated.

Final elution with methanol gave an intractable brown gum (0.50 g) which was not further investigated.

Base-catalysed Cyclisation Reactions of N,N-Dibenzyl-2-nitrobenzylamine (393)

(a) Using ethanolic sodium ethoxide

Solutions of the amine (393) (1.3 g, 0.004 mol) in anhydrous ethanol (20.0
ml) and sodium (0.37 g, 0.016 g, atom) in anhydrous ethanol (10.0 ml) were mixed and the mixture was stirred at room temperature for 3 h. The mixture was evaporated and the residue was treated with water (20.0 ml) and extracted with methylene chloride to give a red oil (1.1 g) which was flash-chromatographed over silica.

Elution with methylene chloride-toluene (1:1) gave 8-benzyl-7-phenyl-2,7,8,9-tetrahydrobenz[c]-1,2,6-oxadiazepine (398) (0.15 g; 12%), which formed colourless needles, m.p. 126 - 128° (from toluene-light petroleum), $\delta_{max}$ 3340 (NH) cm$^{-1}$, $\delta_t$ (CDCl$_3$), 7.85 - 7.12 (14H, m, ArH), 6.44 - 6.35 (1H, m, ArH), 6.04 (1H, s, CH), 5.76 (1H, bs, NH), 5.09 (2H, s, CH$_2$), 3.65 (1H, s, CH), and 3.61 (1H, s, CH), $\delta$ (CDCl$_3$) 146.6 (quat.), 139.5 (quat.), 137.6 (quat.), 131.7 (quat.) 128.8 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 122.6 (CH), 120.1 (CH), 98.3 (CH), 74.0 (CH$_2$), and 49.0 (CH$_3$).

Found: C, 79.7; H, 6.0; N, 9.3% M, 316.
C$_{21}$H$_{20}$N$_2$O requires: C, 79.7; H, 6.3; N, 8.9; M, 316.

Further elution with methylene chloride-toluene (1:1) through to methylene chloride gave only a series of intractable gums (total 0.17 g) which were not further investigated.

Further elution with methylene chloride-ethyl acetate (5:1) afforded (2-N-benzyl-2H-indazole (386) (0.4 g; 58%), m.p. 59 - 62°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.$^{52}$

Further elution with ethyl acetate and finally ethanol yielded only intractable gums (total 1.23 g) which were not further investigated.
The aqueous mother liquor was acidified with 10M aqueous hydrochloric acid, neutralised with solid sodium acetate and extracted with methylene chloride to give a small amount of brown oil (0.06 g) which was not further investigated.

(b) Using sodium hydroxide

A solution of the amine (393) (1.3 g, 0.004 mol) in anhydrous DMF (10.0 ml) was treated with sodium hydride (0.38 g, 0.016 mol) and the mixture was stirred at room temperature for 3 h. The mixture was then treated with ethanol (10.0 ml) and water (20.0 ml) and was then extracted with methylene chloride to give a red gum (1.1 g) which was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (10:1) through to (3:1) gave only a series of oils (total 0.29 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not further investigated.

Further elution with cyclohexane-ethyl acetate (2:1) gave 2-N-benzyl-2H-indazole (386) (0.44 g; 53%), m.p. 55 - 61°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with cyclohexane-ethyl acetate through to ethyl acetate and finally ethanol gave only a series of complex mixtures (total 0.56 g) which were not further investigated.

(c) Using piperidine

A solution of the amine (393) (1.3 g, 0.004 mol) in anhydrous ethanol (25.0 ml) was treated with piperidine (1.4 g, 0.016 mol) and the mixture was stirred at room temperature for 3 h. after which time the mixture was heated under reflux
The mixture was then evaporated to give a semi-solid (1.6 g) which was recrystallised from ethanol to afford unreacted starting material (393) (1.0 g; 77%), m.p. 40 - 45°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the ethanol mother liquor gave a yellow oil (0.53 g) whose t.l.c. in toluene over silica showed it to consist largely of unreacted starting material (393) which was not therefore further investigated.

The Reaction of N-2-Nitrobenzyldibenzylamine (393) with Ethanol
icPotassium Hydroxide in the Presence of Sodium Borohydride

A solution of the amine (393) (9.9 g, 0.03 mol) in anhydrous ethanol (150 ml) was treated with finely powdered potassium hydroxide (8.4 g, 0.15 mol) and sodium borohydride (5.7 g, 0.05 mol) and the mixture was heated under reflux for 3 h. The mixture was hot filtered to remove inorganic material (6.0 g) and the filtrate was left to stand at 0° for 17 h. The filtrate was then filtered and the solid collected was washed well with methylene chloride and ether, leaving further inorganic material (0.48 g).

The combined filtrate and washings were evaporated to give a brown oil (7.9 g) which was triturated with ether to afford 8-benzyl-9-phenyl-2,7,8,9-tetrahydrobenz[c]-1,2,6-oxadiazepine (398) (2.7 g; 28%), m.p. 126 - 128° (from light petroleum),

**Found:**

\[
\begin{array}{ccc}
\text{C}, 79.1; \text{H}, 6.3; \text{N}, 8.7%; \text{M}, 316.1585 \\
\text{C}_{21}\text{H}_{20}\text{N}_2\text{O} \text{ requires:} \quad \text{C}, 79.7; \text{H}, 6.4; \text{N}, 8.9%; \text{M}, 316.1576
\end{array}
\]

identical (m.p., i.r. and ^1H and ^13C n.m.r. spectra) with a sample prepared before.
The ethereal mother liquor was evaporated to give an intractable brown oil (4.6 g) which yielded no further identifiable material.

The Attempted Catalytic Hydrogenation of the Benzoxadiazepine Derivative (398)

(a) A solution of the benzoxadiazepine derivative (398) (0.60 g, 0.0019 mol) in ethanol (150 ml) was hydrogenated over 10% palladium-on-charcoal (0.06 g) at room temperature and atmospheric pressure for 3 h. The reaction mixture was then filtered through celite and the filtrate was evaporated to afford unchanged starting material (398) (0.49 g; 82%), m.p. 120 - 123°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(b) Repetition of the reaction in the presence of glacial acetic acid (0.1 ml) for 5 h also gave only unreacted starting material (398) (84%).

The Reaction of the Benzoxadiazepine Derivative (398) with Aqueous Hydrochloric Acid

The benzoxadiazepine derivative (398) (0.63 g, 0.002 mol) was treated with 5M aqueous hydrochloric acid (5.0 ml) and the mixture was shaken at room temperature for 15 min. then extracted with ether to afford benzaldehyde as a clear oil (0.21 g; quant.), $\delta_{\text{max}}$ 1700 (CO) cm$^{-1}$, identified by comparison (i.r. spectrum) with an authentic sample and by the preparation of its 2,4-dinitrophenylhydrazone derivative, m.p. 236 - 237° (from ethanol-glacial acetic acid) (lit.,$^{112}$ 237°).

The aqueous mother liquor was basified with 2M aqueous sodium hydroxide and extracted with methylene chloride to give a light yellow oil (0.36 g) which was dry column flash-chromatographed over silica.

Elution with methylene chloride gave as the first fraction a yellow oil (0.07 g) whose t.l.c. in methylene chloride over silica showed it to be a complex
Further elution with methylene chloride afforded *N*-hydroxymethylbenzylamine (399) (0.26 g; 57%), m.p. 67 - 72° which was too unstable for further purification, *δ*<sub>max</sub> 3280 and 3180 (NH), and 3200 - 2700 br (OH) cm<sup>-1</sup>, δ<sub>H</sub> (CDCl<sub>3</sub>) 8.75, (1H, bs, OH or NH), 7.78 - 6.80 (9H, m, ArH), 5.25 (2H, s, CH<sub>2</sub>), 4.85 (1H, s, CH), and 4.71 (1H, s, CH), δ<sub>C</sub>(CDCl<sub>3</sub>) 147.3 (quat.) 137.4 (quat.), 129.2 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.0 (quat.), 119.1 (CH), 113.8 (CH), 63.5 (CH<sub>2</sub>) and 55.1 (CH<sub>2</sub>).

Found: C, 74.0; H, 6.4; N, 11.9%; M+, 228.

C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O requires: C, 73.7; H, 7.0; N, 12.3%; M, 228.

The Attempted Catalytic Hydrogenation of *N*-2-Hydroxyaminobenzylbenzylamine (399)

A solution of the benzylamine derivative (399) (0.21 g, 0.001 mol) in anhydrous ethanol (15.0 ml) was hydrogenated over 10% palladium-on-charcoal at room temperature and atmospheric pressure for 2 h. The mixture was then filtered through celite and the filtrate was evaporated to afford the unreacted amine (399) (0.18 g, 86%) identified by comparison (i.r. spectrum and t.l.c. in methylene chloride over silica) with an authentic sample.

The Attempted Oxidation of *N*-2-Hydroxyaminobenzylbenzylamine (399) with Activated Managanese Dioxide

A solution of the benzylamine derivative (399) (0.21 g, 0.001 mol) in anhydrous benzene (10.0 ml) was treated with activated manganese dioxide (2.0 g) and the mixture was stirred at room temperature for 22 h. The mixture was filtered through celite to remove the manganese dioxide and the filtrate was evaporated to
yield a red gum (0.08 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

The Attempted Dehydrative Cyclisation of N-(2-Hydroxyaminobenzyl)benzylamine (399) Using Toluene-4-sulphonic Acid

A solution of the benzylamine derivative (399) (0.18 g, 0.0008 mol) in anhydrous benzene (15.0 ml) was treated with toluene-4-sulphonic acid (0.01 g) and the mixture was heated under reflux for 84 h. The mixture was evaporated to give a green-brown gum (0.20 g) whose t.l.c. in methylene chloride over silica showed it to be a three-component mixture consisting largely of the unreacted starting material (399). The gum was not further investigated.

The Attempted Reaction of N,N-Dibenzyl-2-nitrobenzylamine (393) with Sodium Borohydride

A solution of the amine (393) (1.6 g, 0.005 mol) in ethanol (25.0 ml) was treated with sodium borohydride (0.95 g, 0.025 mol) and the mixture was heated under reflux for 4 h. The mixture was evaporated and the residue was treated with water (25.0 ml) and extracted with methylene chloride to afford the unreacted starting material (393) as an oil (1.6 g; quant.), identical (i.r. and t.l.c. in ethyl acetate over silica) with an authentic sample.

The Attempted Reaction of N,N-Dibenzyl-2-nitrobenzylamine (393) with Aqueous Hydrochloric Acid

A solution of the amine (393) (1.7 g, 0.0005 mol) in 10M aqueous hydrochloric acid (10.0 ml) was heated under reflux for 1 h. The mixture was then concentrated to ca 2 ml, diluted with water (2.5 ml), neutralised with solid sodium bicarbonate, and extracted with methylene chloride to afford unreacted starting
material (393) (1.5 g; 92%), m.p. 48 - 53°, identified by comparison (m.p. and i.r spectrum) with an authentic sample.
Bibliography


55. Ref. 43, chap. 3, pages 166-231.

56. Ref. 43, chap. 3, page 197.


64. Ref 43, chap. 3, pages 281-288.
100. M.F. Aldersley and G. Tennant, unpublished work.