STUDIES OF SUBSTITUENT INTERACTIONS IN
ORTHO-SUBSTITUTED NITROBENZENE DERIVATIVES

by

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Declaration

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

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant, between October 1979 and September 1982.
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Summary

The subject matter of this thesis concerns the study of substituent interactions in ortho-substituted nitrobenzene derivatives.

The preparation of a series of 2-diazo-1-[(2-nitrophenyl) -3-phenylpropane-1,3-diones and their subsequent thermally induced rearrangement to the corresponding 2-phenyl-3,1-benzoxazin-4-one are described. Also the mechanism of these rearrangements have been investigated.

The synthesis of 1-(2-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone and its fragmentation on heating to 1-phenyl-1H-indole-2,3-dione and triphenylphosphine oxide has been investigated. In addition, the preparation of a series of substituted arylazomethyleneophosphoranes and their thermally induced fragmentation to the corresponding α-N-phenyliminobenzeneacetonitrile and triphenylphosphine oxide are described.

The novel synthesis of a series of 3-acyl-1-hydroxy-1H-indazoles is described. The structures of such 1-hydroxy-1H-indazoles have been established by physical methods and chemical transformations.

The previously-known synthesis of 2-alkyl-2H-indazoles from the base-catalysed cyclisation of N,N-dialkyl-2-nitrobenzylamines has been extended to afford a route to the less accessible 2-aryl-2H-indazoles. Investigation of the mechanism involved in these cyclisations is also described.
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Chapter 1

A Survey of Heterocyclic Syntheses Involving Nitro-group Side-chain Interaction in Ortho-substituted Nitrobenzene Derivatives
A Survey of Heterocyclic Syntheses Involving Nitro-group Side-chain Interaction in Ortho-substituted Nitrobenzene Derivatives

The purpose of this introductory chapter is to provide a general review of reactions of 2-substituted nitroaromatic derivatives leading to heterocyclic products. Heterocyclisations of this type include both catalysed (acid- or base-promoted) processes and uncatalysed (thermally or photochemically induced) processes and hence are conveniently discussed under these headings.

There have been two earlier and more complete reviews of the literature\(^1,²\) concerning reactions of 2-substituted nitrobenzene derivatives. Consequently the present survey is not intended to be exhaustive but rather deals with selected examples which illustrate the scope of cyclisation reactions involving nitro-group ortho side-chain interaction and their value for the synthesis of various types of heterocyclic products.

1.1 Catalysed Processes

The nitro-group is unique among simple functional groups in combining dipolar character with \(\pi\)-unsaturation akin to the carbonyl group. This unique electronic structure confers bifunctional reactivity, the nitro-group being prone to nucleophilic attack at the nitrogen atom [Scheme 1; (1)\(\rightarrow\)(2)] and electrophilic attack at oxygen [Scheme 1; (1)\(\rightarrow\)(3)]. Reaction with carbon and nitrogen nucleophiles (Scheme 2) can yield N-oxide products [i.e. nitrones (4) or azoxy-
Scheme 1

Scheme 2
compounds (5)] in processes (Scheme 2) akin to the aldol reaction. However intermolecular examples of such nitro-group condensation reactions are rare. The base-catalysed condensation (Scheme 3) of 2-nitrobenzaldehyde (7) with indan-1-one (6) to give the N-oxide (9) is suggested to occur by initial condensation between the nitro-group and C-2 of the indan-1-one to give the nitrone intermediate (8) which can cyclise through the aldehyde group and C-3 of the indanone moiety to give the observed product (9). However, further evidence supporting the structure of the product as (9) rather than the alternative (11), formed by cyclisation of the more likely intermediate (10), is needed before the base-catalysed condensation of 2-nitrobenzaldehyde (7) with indan-1-one (6) can be definitely accepted as an example of a process initiated by intermolecular condensation of a carbanion species with a nitro-group [Scheme 3; (6)+(7)+(8)].

In contrast to the lack of intermolecular examples of the condensation of nitro-groups with nucleophiles, intramolecular processes of this type are well known and are discussed in detail later. The detailed mechanisms of such reactions have been little investigated and though it is convenient to formulate them as purely ionic aldol-type processes, there is indirect evidence in the literature that they may in fact involve radical anion intermediates (Scheme 4). Thus, Kornblüm and his co-workers observed (Scheme 5) that the base-catalysed condensation of 4-nitrobenzyl chloride (13) with 2-nitropropane (12) is inhibited by the presence of an electron-acceptor (e.g. 1,4-dinitrobenzene). The authors rationalise this observation by the radical-anion mechanism shown in Scheme 5.
Scheme 3
\[
\text{Me}_2\text{CHNO}_2 \quad \text{\textsuperscript{(i)}} \quad -\text{H}^+ \quad \Rightarrow \quad \text{Me}_2\text{C}--\text{NO}_2 \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- + \quad \text{O}_2\text{N}--\text{C}_2\text{Cl}\quad \text{(13)}
\]

\[
\text{Me}_2\text{C}--\text{NO}_2 \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- + \quad \text{O}_2\text{N}--\text{C}_2\text{Cl}\quad \text{(13)}
\]

\[
\text{Me}_2\text{C}--\text{NO}_2 \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- \quad \Leftrightarrow \quad \text{Me}_2\text{C}++\text{NO}_3^- + \quad \text{O}_2\text{N}--\text{C}_2\text{Cl}\quad \text{(13)}
\]

\[
\text{i} \quad \text{base}
\]

**Scheme 5**
Reaction of nitro-groups with carbon and nitrogen-centred electrophiles (Scheme 6) can result in simple neighbouring-group participation \([(14)+(15)+(16)+(17)+(18)]\) and \([(21)+(22)+(23)+(24)+(25)]\) or if the electrophilic centre bears a proton, to oxidation-reduction \([(14)+(15)+(16)+(19)+(20)]\) and \([(21)+(22)+(23)+(26)+(27)]\). As in the case of reaction with nucleophiles (see before), intermolecular examples of the processes outlined in Scheme 6 appear to be unknown. However a number of intramolecular examples of such transformations are described in the literature and will be discussed in detail later.

The scope and mechanism of reactions involving the interaction of aromatic nitro-groups with nucleophilic and electrophilic centres in ortho side-chains will now be discussed in detail.
Scheme 6
1.1.1 Reactions Involving the Interaction of Aromatic Nitro-groups with Nucleophilic Ortho Side-chains

As already mentioned, reactions involving intermolecular aldol-type condensations between aromatic nitro-groups and nucleophiles are rare. This is probably because of the suppressed electrophilic reactivity of the nitro-group due to resonance. In contrast, reactions initiated by intramolecular nucleophilic attack on a nitro-group are well known and indeed often provide valuable synthetic routes to otherwise inaccessible heterocyclic compounds. The success of such intramolecular aldol-type condensations is presumably due to the more favourable steric situation compared with the corresponding intermolecular processes. 2-Nitrophenacyl derivatives in which the acidity of the methylene group is increased by electron-withdrawing substituents would be expected to undergo base-catalysed cyclisation involving nucleophilic attack by the ortho side-chain on the nitro-group. An example (Scheme 7) of ortho nitro-group interaction with a phenacyl side-chain is the conversion of the 2-nitrophenylketones (28), in good

\[
\begin{align*}
\text{(28)} & \quad \xrightarrow{\text{(i) NaOAc}} \quad \text{(29)} \\
\text{[(R}^1 \text{=} \text{H, Cl or Me; R}^2 \text{=} \text{H or Cl)]}
\end{align*}
\]

Scheme 7
yield, into the corresponding 2-phenylisatogens (29) on
treatment with sodium acetate. 5 A further example of such
base-catalysed cyclisations of 2-nitrophenacyl derivatives to
give isatogens was reported by Wibberley and his co-workers
in 1961 (Scheme 8). Methyl 2-nitrobenzoylacetic (30) is
converted into the 2-substituted isatogen (33) on treatment
with sodium hydrogen carbonate. Formation of the isatogen (33)
is rationalised (Scheme 8) by an initial self-condensation of
the keto-ester (30) to form the intermediate (31) which frag-
ments to (32). Cyclisation of the intermediate (32) by the
same process as in Scheme 7 then gives the isatogen (33).

In contrast (Scheme 9) to the foregoing base-catalysed
cyclisation reactions undergone by 2-nitrophenacyl derivatives,
2-nitro-isobutyrophenone (34) is converted by treatment with
sodamide in liquid ammonia into the acyclic azoxy products
(38) and (39). 7 In the case of 2-nitro-isobutyrophenone
(34), direct base-catalysed conversion into an isatogen
derivative is blocked, and the reaction course (Scheme 9) can
be explained by ring-opening of the initial cyclic inter-
mediate (35) to give the nitrone (36) followed by hydrolysis
to 2-hydroxyaminobenzamide (37), self-condensation of which,
would account for the observed products (38) and (39), the
latter compound being derived by hydrolysis of the former.

The isatogen products formed by base-catalysed ortho
nitro-group interaction with phenacyl side-chains containing
a halogen or similar functional group alpha to the keto-group
are prone to hydrolysis and further rearrangement. Thus
(Scheme 10), heating 2-nitrophenacyl chloride (40) with aqueous
ethanolic potassium hydroxide yields anthranil-3-carboxylic
acid (43). 8 The formation of this product can be explained
\[ \text{(i) NaHCO}_3, \text{ H}_2\text{O} \]

Scheme 8
Scheme 9
by initial cyclisation to the chloro-isatogen (41) followed by hydrolysis to 1-hydroxyisatin (42) which is known to undergo base-catalysed isomerisation to anthranil-3-carboxylic acid (43).

(i) KOH, EtOH, H₂O

Scheme 10

Treatment of cyanomethyl-2-nitrobenzamides [Scheme 11; (44)] with ethanolic sodium ethoxide results in their cyclisation, in good yield (70-90%), to the corresponding N-
(i) NaOEt, EtOH

Scheme 11
hydroxyquinazolinediones (46). The authors\textsuperscript{10} propose a mechanism (Scheme 11) for these reactions which is initiated by base-promoted aldol-type cyclisation of the cyanomethyl-2-nitrobenzamides (44) to the N-oxide intermediates (45). Hydrolysis and subsequent loss of hydrogen cyanide then leads to the observed products (46). Treatment\textsuperscript{11} (Scheme 12) of the N-cyanobenzyl-2-nitrobenzamides (47) with ethanolic sodium ethoxide gives a mixture of the cyanophthalimidine (50) and the hydrolytically derived amide (51) as well as the parent phthalimidine (52). Formation of the cyanophthalimidine (50) can be rationalised (Scheme 12) by initial formation of the carbanion (48) followed by intramolecular nucleophilic addition to give the intermediate (49), loss of nitrite ion from which would give the observed product (50). Hydrolysis of the latter would then afford the amide (51), further hydrolysis of which and decarboxylation would account for the formation of the parent phthalimidine (52).

Ortho-nitrobenzyl compounds containing an active methylene-group are also suitable substrates for base-catalysed aldol-type cyclisation. Thus, (Scheme 13), addition of hydrogen cyanide to the ortho-nitrobenzylidene derivative (53) affords the adduct (54) which, when treated with base, yields the 1-hydroxyindole (55).\textsuperscript{12} Alternatively, the 1-hydroxyindole (55) is obtained directly by treatment of the ortho-nitrobenzylidene derivative (53) with ethanolic potassium cyanide (Scheme 13).\textsuperscript{12} Cyclisation of the adduct (54) to the 1-hydroxyindole (55) can be explained in terms of the aldol-type process shown in Scheme 13. Treatment of 2'-hydroxy-5'-methyl-2-nitrochalcone (56) with sodium hydroxide
Scheme 12

(i) NaOEt, EtOH

(R=Me, CH$_2$Ph, Ph)
(53) \[ \text{KCN, EtOH} \]

(ii) \[ \text{Na}_2\text{CO}_3, \text{H}_2\text{O} \]

Scheme 13
gives 10-hydroxy-2-methyl-11H-benzo[b]pyrano[3,2-b]indole-11-one (58) in moderate yield (Scheme 14). This cyclisation can be explained (Scheme 14) by base-promoted Michael addition of the hydroxyl group to the double bond with concomitant nucleophilic attack on the nitro-group followed by dehydration and proton transfer to give the observed product (58).

Aldol-type cyclisations of the type being discussed involving aromatic nitro-groups and ortho side-chains are not limited to the formation of heterocycles containing only one hetero-atom. 2-Aryl-1-hydroxyimidazoles (60) are isolated in moderate yield when N-substituted N-aryl-2-nitroanilines (59) are treated with methanolic sodium methoxide (Scheme 15). As shown in Scheme 15, two possible mechanisms can be postulated to account for the formation of the heterocyclic products (60). However, kinetic studies have shown that route B is the major pathway, i.e. aldol-type condensation occurs as the initial step in these transformations. An analogous cyclisation (Scheme 16) has been reported by Preston and Sood who showed that treatment of the thiophene derivative (61a) with methanolic sodium hydroxide results in aldol-type cyclisation to the N-oxide (62a) in 53% yield. In contrast, similar treatment of the N-methyl compound (61b) affords, not the expected N-oxide (62b) but rather 3-hydroxy-2-nitrobenzo[b]thiophene (63). The failure of the N-methyl compound (61b) to undergo aldol-type cyclisation indicates a special need for a free N-H group in the side-chain in this type of cyclisation.

As discussed earlier (Scheme 13), the action of potassium
Scheme 14

(i) NaOH, H₂O
Scheme 15

R

(i) NaOMe, MeOH

Scheme 16

(i) NaOH, MeOH

R

a; H
b; Me
cyanide on 2-nitrobenzylidene derivatives can yield heterocycles via aldol-type cyclisation of intermediate hydrogen cyanide adducts. In a related process (Scheme 17), the Schiff base, N-benzylidene-2-nitroaniline (64) reacts with potassium cyanide in methanol to give the tautomeric 1-hydroxy-2-phenylbenzimidazole (66) in good yield (79%). This transformation can be explained by a course (Scheme 17) involving initial formation of the hydrogen cyanide adduct (65) followed by aldol-type cyclisation with accompanying hydrolytic loss of the cyano-substituent to give the benzimidazole derivative (66).

Treatment (Scheme 18) of the 5-nitropyrimidinylaminoacetaldehyde (67) with cold base converts it quantitatively into 9-methylguanine-7-oxide (69). This transformation presumably proceeds via base-catalysed aldol-type interaction between the electron-rich methylene group in the side-chain and the electron-deficient nitrogen centre of the aromatic nitro-group followed by deformylation of the initial product (68) (Scheme 18).

Sulphur-containing heterocycles can also be formed by aldol-type cyclisations involving aromatic nitro-groups and ortho side-chains. Thus, triethylamine catalyses the reaction (Scheme 19) of 2-chloronitrobenzene (70) with ethyl 2-mercaptoacetate (71) to give ethyl benzothiazole-2-carboxylate N-oxide (73). This transformation presumably involves the intermediate formation and base-catalysed cyclisation of ethyl 2-nitrophenylthioacetate (72) (Scheme 19).
Scheme 17

(i) KCN, MeOH

Scheme 18

(i) NaOH, H₂O
(ii) H₂O
Six-membered heterocycles containing two hetero-atoms are also accessible by base-catalysed interaction of aromatic nitro-groups with suitable ortho side-chains. Thus (Scheme 20), the dinitronaphthalene (74) undergoes base-catalysed condensation with N,N-dimethylphenylacetamidine (75) to give the benzoquinoxaline N-oxide (77) as the final product. This reaction can be rationalised in terms of the intermediate formation and base-catalysed cyclisation of the amnide intermediate (76). Tetrahydrophenazine derivatives (81) are the end-products of the treatment of 3-(2-nitroanilino)cyclohex-2-enones (78) with sodium t-butoxide in t-butanol (Scheme 21). These cyclisations can be explained by a course
(74) + PhCH₂C=NMe₂ → (76)

(77)

(i) MeOH

Scheme 20
BuO

H

Y

Cl

H

+"C O

2

(i)

HOJ

14

O

o

(R=H or Me; X=H, Me or OMe)

Me

ZIIIcI)1I7

0

(81)

(82)

(i) KOBu\textsuperscript{+}, Bu\textsuperscript{+}OH

Scheme 21
(Scheme 21) involving aldol-type cyclisation to the N-oxides (80) which then suffer reduction to the tetrahydrophenazine products (81) in the alkaline medium. In support of the intermediacy of the N-oxides (80), treatment of the nitroanilinocyclohexenones (78) with sodium hydroxide in t-butanol affords\textsuperscript{20} the quinoxaline N-oxides (82) whose isolation is consistent with the intermediate formation and hydrolytic scission of the N-oxides (80). The benzyl substituent in the 5-nitropyrimidyl-substituted acetamidines [Scheme 22; (83)] is also sufficiently acidic to allow the base-catalysed cyclisation\textsuperscript{21} of these compounds to the corresponding pteridine N-oxides (84), which are of interest because of their potential biological activity.

In all of the examples of base-catalysed aldol-type cyclisation of nitrobenzene derivatives so far discussed, the nucleophilic centre in the ortho side-chain has been sited on carbon. This, of course, need not be the case and there are many examples described in the literature of intramolecular nucleophilic attack by a nitrogen substituent in an ortho side-chain on an aromatic nitro-group which result in heterocyclisation (see Scheme 2). For example (Scheme 23), reaction of 2-nitrobenzylidene aniline (85) with aqueous potassium cyanide followed by acetic acid gives 3-cyano-2-phenylindazole 1-N-oxide (87) in unspecified yield.\textsuperscript{22} This reaction probably involves the intermediate formation and base-catalysed cyclisation of the corresponding hydrogen cyanide adduct (86) as evidenced by the conversion of this compound in warm aqueous sodium hydroxide or sodium carbonate into the indazole
Scheme 22

(i) NaOEt

Scheme 23

(i) KCN
(ii) AcOH
1-N-oxide (87). In a closely related reaction (Scheme 24), heating 2-bromomethyl-3-nitropyridine (88) with a two-fold excess of a primary arylamine in ethanol gives the corresponding 2-aryl-3-arylamino-2H-pyrazolo[4,3-b]pyridine (92). This process most likely involves the formation of the arylaminomethylpyridine derivative (89) and its cyclisation to the N-oxide (90). Nucleophilic addition of a second molecule of arylamine at the 3-position of the N-oxide (90) followed by dehydration of the intermediate adduct (91) then explains the formation of the observed product (92). The intermediacy of the initial substitution products (89) is supported by their isolation when 2-bromomethyl-3-nitropyridine (88) is treated with an arylamine in ethanol at room temperature. Indazole derivatives are also the products of cyclisations involving the intramolecular nucleophilic displacement of aromatic nitro-groups by ortho side-chains containing a hydrazone substituent. This type of indazole synthesis is illustrated (Scheme 25) by the potassium hydroxide-catalysed cyclisation of the hydrazone (93) with accompanying hydrolysis of the ester group to give the 1-N-phenylindazole-3-carboxylic acid (94).
Scheme 24

(i) $\text{ArNH}_2$

(88) $\rightarrow$ (89)

(90) $\rightarrow$ (91)

(92)

Scheme 24
Nietzki and Braunschweig\textsuperscript{25} isolated the sodium salt of 1-hydroxybenzotriazole [Scheme 26; (97)] after treating 2-nitrophenylhydrazine (95) with warm aqueous sodium hydroxide. Cyclisation of the hydrazine (95) to the benzotriazole (97) can be explained (Scheme 26) by an aldol-type condensation between the nitro-group and the terminal nitrogen centre in the ortho-hydrazine side-chain giving the N-oxide (96) which then tautomerises to the more stable N-hydroxy form (97).

\textit{N,N'}-Disubstituted 2-nitrophenylhydrazine derivatives [Scheme 27; (98)] undergo cyclisation on treatment with hot hydrochloric acid giving moderate yields of the corresponding benzotriazole 1-N-oxides (100) together with the parent benzotriazoles (101).\textsuperscript{26} Although this transformation occurs in an acidic medium rather than a basic medium, the mechanistic
Scheme 26
Scheme 27
rational again involves nucleophilic attack by the electron-rich tertiary nitrogen centre in the side-chain on the nitro-group to give, after dehydration, the cationic intermediates (99). Dealkylation of the latter would then account for the benzotriazole N-oxide products (100) which would be prone to undergo reduction in the reaction medium thus explaining the co-formation of the parent benzotriazoles (101) (Scheme 27). This mechanism is supported by the isolation of by-products derived from the benzotriazolium cations (99).

1.1.2 Reactions Involving the Interaction of Aromatic Nitro-groups with Electrophilic Ortho Side-chains

As already discussed, intermolecular reaction of aromatic nitro-groups with electrophiles appear to be unknown. However, as with nucleophilic attack at an ortho nitro-group (see Section 1.1.1), reactions initiated by intramolecular electrophilic attack on an aromatic nitro-group are well known and indeed often provide valuable synthetic routes to otherwise inaccessible heterocyclic products.

Anthranil derivatives, or compounds derived from them are often the products of acid-catalysed cyclisation reactions involving electrophilic attack by an ortho side-chain at the nitro-group in nitrobenzene derivatives. Thus (Scheme 28), 2-nitrobenzhydryl bromide (102) cyclises to 5-bromo-3-phenylanthranil (106) in good yield when treated with hydrogen bromide in acetic acid.27 The initial step in this transformation is presumably intramolecular nucleophilic displacement of the bromo-substituent by the ortho nitro-group
Scheme 28

(i) HBr
Subsequent proton loss and ring-opening with net oxygen transfer would then give the nitroso-intermediate (104) in a process corresponding to an internal redox reaction, the nitro-group being effectively reduced to nitroso at the same time as the side-chain is oxidised to a keto-group. Subsequent reaction of the nitroso-ketone (104) with hydrogen bromide could next result in reduction with accompanying introduction of a bromo-group giving the hydroxyamino-ketone (105), cycloaddition of which would yield the observed anthranil product (106). In a closely related transformation (Scheme 29), treatment of an ethereal solution of 2-nitrobenzaldehyde (7) and phenol with hydrogen chloride affords the 3-(3′-hydroxyphenyl)anthranil (108) in moderate yield. It has been postulated that this reaction proceeds via initial condensation of 2-nitrobenzaldehyde (7) with phenol to give the 2-nitrobenzhydrol intermediate (107) whose conversion into the final anthranil product (108) can be explained by a mechanism (Scheme 29) akin to that already outlined (Scheme 28) for the transformation of the 2-nitrobenzhydryl bromide (102) into the anthranil derivative (106). A further example (Scheme 30) of the acid-catalysed conversion of a 2-nitrobenzene derivative into an anthranil derivative has been described by Bakke, who isolated the anthranil derivative (113) from the reaction of 1-(2-nitrophenyl)-2-phenylethanol (109) with toluene-p-sulphonic acid. Again this transformation can be explained (Scheme 30) in terms of initial nucleophilic displacement of the hydroxyl substituent followed by proton loss and ring opening to give the nitroso-intermediate (110).
Scheme 29

(i) HCl (g)

(7) + (107)

(108)
which exists in equilibrium with the enol (111). Cyclisation of (111) gives the anthranil (112) which is then oxidised to afford the observed anthranil product (113). Anthranil syntheses of this type are not restricted to the formation of 3-aryl- or 3-alkyl derivatives. Thus, Van Allan and Reynolds\(^{31}\) have shown (Scheme 31) that the pyran derivative (114) is converted into the pyrilium salt (116) on treatment with perchloric acid. A plausible mechanism (Scheme 31) accounting

\[ \text{(i) } H^+ \]

\[ \text{(ii) } H_2O \]
(114) $\xrightarrow{(i)}$ (115)

$\xrightarrow{\text{[H]}^-}$

$\xrightarrow{-\text{CN}^-}$

$\xrightarrow{-\text{H}_2\text{O}}$ (116)

(i) $\text{HClO}_4$
for this transformation is akin to that already postulated to explain the acid-catalysed formation of anthranils from other 2-nitrobenzene derivatives (see Schemes 28-30). As shown in Scheme 31, possible initial steps in the reaction sequence are protonation followed by intramolecular nucleophilic displacement of the cyano-group then oxygen transfer to give the nitroso-intermediate \((115)\). As before, reduction of \((115)\) and subsequent cyclisation yields the product \((116)\) (Scheme 31). Heating under reflux in a four-fold excess of thionyl chloride converts \(^{32}\) (Scheme 32) methyl 2-nitromandelate \((117)\) into methyl 5-chloroanthranil-3-carboxylate \((118)\) in 86% yield. \(^{32}\) In contrast, identical treatment of methyl 5-chloro-2-nitromandelate \((119)\) failed to effect anthranil formation but conversion of the mandelic ester \((119)\) into methyl 5,7-dichloranthranil-3-carboxylate \((120)\) is achieved, however, by heating under reflux in a seventy-fold excess of thionyl chloride. The difference in reactivity between the mandelate \((117)\) and its 5-chloro derivative \((119)\) may be due to the increased steric hindrance to introduction of chloride ion in the formation of the corresponding hydroxyamino intermediate prior to cyclisation. \(^{32}\)

Although anthranils are the most common products of acid-catalysed reactions involving interaction between aromatic nitro-groups and electron-deficient ortho side-chains, competing reactions leading to other types of heterocyclic product are also observed. Thus, treatment \(^{33}\) (Scheme 33) of a mixture of 2-nitrobenzaldehyde \((7)\) and naphthalene with polyphosphoric acid yields benzo[c]acridone \((124)\) together with 3-(naph-2-yl)
(117)  

(i) $\text{SOCl}_2$  

(ii) $\text{HCl}$  

Scheme 32
Scheme 33

(7)  

\[
\begin{align*}
\text{HCHO} \quad \text{and} \quad \text{2-naphthalene} \\
\xrightarrow{(i)} \quad \text{Product}
\end{align*}
\]

(i) \( \text{P}_2\text{O}_5, \text{H}_3\text{PO}_3 \)

\[
\begin{align*}
\text{(121)} \\
\rightarrow \\
\text{(122)} \\
\rightarrow \\
\text{(124)}
\end{align*}
\]

\[
\begin{align*}
\text{(123)} \\
\rightarrow \\
\text{(125)}
\end{align*}
\]
anthranil (125). Formation of these products can be explained as shown in Scheme 33 with the nitroso-ketone (121) being the common intermediate. Direct cyclisation of the nitroso-ketone (121) to the N-hydroxyacridone (122) followed by reduction would account for the acridone product (124). Correspondingly, initial reduction of the nitroso-compound (121) to the hydroxyamino-compound (123) followed by cyclisation accounts for the formation of the anthranil derivative (125). The course shown (Scheme 33) for acridone formation is supported by the isolation of 1-hydroxyacridones from such transformations by altering the acidic medium used in the reaction. It has also been observed that condensation of 2-nitrobenzaldehyde (7) with more reactive aromatic substrates gives anthranils as the sole heterocyclic products. For example (Scheme 34) 2-nitrobenzaldehyde (7) reacts with aniline in the presence of zinc chloride to afford the anthranil derivative

\[
\begin{align*}
\text{(7)} & \quad \text{(i)} \quad \text{PhNH}_2, \text{ZnCl}_2 \\
\text{(126)} & + \\
\text{(127)}
\end{align*}
\]

Scheme 34
Anthranils are also products of the acid-catalysed rearrangement of 2-nitrophenylethylene oxides. Thus (Scheme 35), when 2-nitrophenylglycidic acid (128) is steam-distilled or heated in glacial acetic acid, it is converted into a mixture of anthranil (129) and its aldehyde (130). Scheme 35

\[
\begin{align*}
\text{(128)} & \xrightarrow{(i) \ H^+} \text{(129)} + \text{(130)} \\
(i) & \text{H}^+
\end{align*}
\]

formations of this type can also yield heterocyclic products other than anthranils. For example (Scheme 36), trans 1-acyl-2-nitrophenylethylene oxides (131a and c) are converted by treatment with hydrogen chloride into the chlorinated 1-hydroxyquinolones (132b and d). Treatment with hydrogen chloride in the presence of hydroquinone or use of hydrogen bromide as the catalyst gives halogen-free products (132a and c). The diacyl epoxides (131d and e) as well as the cis epoxide (131b) likewise afford enhanced yields of the chloro-1-hydroxyquinolones (132b and d). The increased efficiency of
\[ \text{(131)} \quad \xrightarrow{(i)} \quad \text{(132)} \]

\[
\begin{array}{ccc}
R^1 & R^2 \\
a; & COPh & H \\
b; & H & COPh \\
c; & COMe & H \\
d; & COMe & COMe \\
e; & COPh & COPh \\
\end{array}
\]

(i) $\text{HCl}_\text{(g)}$ or $\text{HBr}_\text{(g)}$

\text{Scheme 36}

\[
\begin{array}{ccc}
\text{(133)} & \xrightarrow{(i)} & \text{(134)} \\
\end{array}
\]

(i) $\text{HCO}_2\text{H}$

\text{Scheme 37}

\[
\begin{array}{ccc}
\text{(135)} & \xrightarrow{(i)} & \text{(136)} \\
\end{array}
\]

(i) conc. $\text{H}_2\text{SO}_4$, $-20^\circ$

\text{Scheme 38}
the latter reactions compared with those of the trans epoxides (131a and c) is attributed\textsuperscript{36,37} to the steric effect of the cis-acyl group in the compounds (131b, d and e). The acid-catalysed behaviour (Scheme 37) of the parent epoxide, 2-nitrophenylethylene oxide (133) has also been studied.\textsuperscript{38} Treatment of the epoxide (133) with formic acid yields 2-nitrosobenzoylmethanol (134). Further reduction of this compound does not occur under these reaction conditions thus inhibiting subsequent anthranil formation. The acid-catalysed rearrangement (Scheme 38) of 2-nitrophenylcyclopropane (135) is also reported to afford the nitroso-ketone (136).\textsuperscript{39}

Treatment (Scheme 39) of 2-nitrobenzylidene derivatives (137) with hydrogen chloride affords the corresponding chlorinated 1-hydroxyquinolones (140) while reaction with hydrogen bromide yields the halogen-free products (140; H for Cl).\textsuperscript{40} These transformations can be explained (Scheme 39) in terms of the formation of nitroso-ketone intermediates (138) which can either suffer indirect reduction by reaction with hydrogen chloride to give chlorinated phenylhydroxylamines (139) or direct reduction with hydrogen bromide to give unhalogenated phenylhydroxylamines (139; H for Cl). Subsequent cyclisation in either case affords the observed N-hydroxyquinolone products (140) or (140; H for Cl).

2-Nitrophenylacetylene derivatives are converted under acidic conditions into 2-substituted isatogens. Baeyer,\textsuperscript{41} in 1881, showed (Scheme 40) that treatment of ethyl 2-nitrophenylpropiolate (141) with concentrated sulphuric acid gives the corresponding isatogen (142) in unspecified yield. A more recently observed example of such a transformation
(137) \( R = \text{COMe, CO}_2\text{Et} \)

\[ R \quad H \quad \text{NH} \quad \text{OH} \quad (139) \]

(i) \( \text{HCl(g)} \) or \( \text{HBr(g)} \)

Scheme 39

(141) \( R = \text{COMe, CO}_2\text{Et} \)

(i) conc. \( \text{H}_2\text{SO}_4 \), room temp.

Scheme 40
(Scheme 41) is the acid-catalysed conversion of 2-nitrotolan (143) into 2-phenylisatogen (145) together with 3-benzoyl-anthranil (113). A plausible mechanism (Scheme 41) which explains the formation of both of these heterocyclic products involves initial protonation of the acetylenic side-chain followed by electrophilic interaction with the ortho nitro-group to yield the nitroso-ketone intermediate (144), different reaction modes of which account for the observed products (145) and (113).
Scheme 41

(i) $\text{H}^+$

(ii) $\text{H}_2\text{O}$
1.2 Uncatalysed Processes

As was mentioned earlier in this chapter, interaction between an aromatic nitro-group and an ortho side-chain can either be catalysed (acid- or base-promoted) or uncatalysed (thermally or photochemically induced). A brief survey and discussion of catalysed processes (acid- and base-promoted) was given in Section 1.1 and uncatalysed processes (thermally or photochemically induced) will now be briefly reviewed and discussed in the following sections.

1.2.1 Reactions Involving Thermally Induced Interaction of Aromatic Nitro-groups with Ortho Side-chains

Certain 2-nitrobenzene derivatives are known to be heat sensitive and this reactivity, in many cases, is not observed in the un-nitrated parent compound. Such thermally initiated reactivity can often be attributed, therefore, to interaction of the aromatic nitro-group with the ortho side-chain. Mechanisms which explain transformations involving thermally induced interaction between an aromatic nitro-group and an ortho side-chain are of two types. The first type to be discussed involves cycloaddition of an aromatic nitro-group to a 1,3-dipolar ortho side-chain.

Because of its dipolar character, the nitro-group is potentially capable of functioning as a 1,3-dipole in 1,3-dipolar cycloaddition with other 1,3-dipolar species (Scheme 42). 1,3-Dipolar cycloaddition of this type has been proposed as the initial step (Scheme 43) in a possible mechanism (route A) for the thermal conversion of 2-nitro-
\[ \text{Route A} \quad \text{Route B} \]

(i) PhCOCl, heat

Scheme 42

Scheme 43

Scheme 44
phenyl azide (147) into benzofuroxan (150). An alternative mechanism (route B) for this transformation involves initial cyclisation to give the five-membered intermediate (149), subsequent loss of nitrogen from which, accounts for the observed product (150). A third possible mechanism involving initial azide decomposition to give a nitrene intermediate followed by insertion into the nitro-group appears to be unlikely as the temperature required to achieve the conversion [(147)→(150)] lies considerably below the minimum decomposition temperature of the parent compound, phenyl azide. In a variant of the 2-nitrophenyl azide thermal cyclisation, Smalley and his co-workers have shown (Scheme 44) that heating 2-nitrophenyl azide (147) in the presence of benzoyl chloride (Scheme 44) results in its reductive cyclisation to benzofurazan (151).

Thermally initiated rearrangement (Scheme 45) of the diaziridines (152) gives the corresponding 2-substituted-6-nitrobenzotriazole N-oxides (157) in good yield. A plausible initial step in these deep-seated transformations involves ring-opening of the diaziridine ring in (152) to form the dipolar intermediates (153). Two subsequent routes can then be postulated to account for the formation of the heterocyclic products (157) from the dipolar intermediates (153). Route A (Scheme 45) involves 1,3-dipolar cycloaddition to the nitro-group leading to the intermediates (154) which can ring-open with loss of cyclohexanone to give the nitroso-derivatives (156), spontaneous cyclisation of which, would yield the benzo-1,2,3-triazole N-oxide product (157).
[R=H, Me, CH(Me)₂, Ph]

route A

route B

(i) heat

Scheme 45
Cyclisation to the intermediate (155) followed by extrusion of cyclohexanone would be a plausible alternative pathway (Scheme 45; route B) from the dipolar intermediate (153) to the nitroso-compound (156). Williard and his co-workers\textsuperscript{45} favour route B, though evidence excluding the alternative route A is lacking.

The formation (Scheme 46) of benzofurazan (15.1) by thermally induced rearrangement of the iminophosphonium ylide (158) can be explained\textsuperscript{46} by mechanisms akin to those already discussed for the conversion of 2-nitrophenyldiaziridines into benzo-1,2,3-triazole N-oxides (Scheme 45), namely via initial 1,3-dipolar cycloaddition (Scheme 46; route A) or via initial electrophilic attack by the side-chain on the nitro-group (Scheme 46; route B). A third pathway (Scheme 47) which could account for the transformation [(158)+(151)] involves initial decomposition of (158) to benzofuroxan N-oxide (150) and the phosphole (161) followed by the known\textsuperscript{47} deoxygenation of the former by the latter. However, kinetic studies\textsuperscript{46} have shown that this mechanism (Scheme 47) does not operate. The authors\textsuperscript{46} favour the mechanism involving initial electrophilic attack on the nitro-group by the side-chain (Scheme 46; route B) rather than initial 1,3-dipolar cycloaddition (Scheme 46; route A) though no evidence against the latter pathway is cited.\textsuperscript{46}

Thermal decomposition (Scheme 48) of alkyl 2-nitrophenylcarbamates (162) gives moderate yields of benzofurazan (151), the highest yield of the latter product being obtained from the methyl ester (162; R=Me).\textsuperscript{48} The lower yields with other 2-nitrophenylcarbamates (162; R=Et, Pr\textsuperscript{1}, Ph) may be due to
Scheme 46
Scheme 47
Scheme 48
side-reactions resulting from the thermolysis of the more complex ester substituents. These thermally induced nitro-group ortho side-chain interactions can be explained (Scheme 48) by initial thermolysis of the carbamates (162) to 2-nitrophenyl isocyanate (163), the thermolytic conversion of carbamates to isocyanates being a well known process.\textsuperscript{49} The conversion of 2-nitrophenylisocyanate into benzofurazan (151) could then follow two possible pathways (Scheme 48). In one possibility (Scheme 48; route A), initial intramolecular 1,3-dipolar cycloaddition of the nitro-group to the ortho-isocyanate substituent would afford a cycloadduct (165), thermal extrusion of carbon dioxide from which would yield the observed product (151). Alternatively (Scheme 48; route B), nucleophilic attack by the nitro-group on the ortho-isocyanate substituent followed by ring-opening of the resulting intermediate (164) would lead to the nitroso-nitrene (166), a plausible precursor of the final benzofurazan product (151). The experimental evidence,\textsuperscript{48} however, suggests that neither of the routes A or B (Scheme 48) is the major reaction pathway involved in the thermal conversion of the carbamates (162) into benzofurazan (Scheme 48). Thus, pyrolysis of 2-nitrophenylisocyanate (163) results in the formation of benzofurazan (151) in greatly reduced yield compared to that of the urethane transformations [(162)→(151)]. Since 2-nitrophenylisocyanate (163) would appear not to be an intermediate in such transformations, it is possible that these follow a pathway (Scheme 48; route C) in which initial nucleophilic attack by the nitro-group on the side-chain ester substituent is followed by deprotonation by the liberated alkoxide ion and then
decarboxylation to give the nitroso-nitrene (166) which further reacts to give benzofurazan (151).

Thermolysis (Scheme 49) of any of the heterocyclic precursors (168)-(170) is believed to generate 2-nitrophenyl-carbodiimide (171) which is rapidly transformed, via interaction of the aromatic nitro-group with the ortho-carbodiimide side-chain, in high yield into 2-phenylbenzotriazole (172) and carbon dioxide. In a more recent communication, the thermally initiated transformations (Scheme 50) of nitrobiphenylcarbodiimide (173) and nitronaphthylcarbodiimide (178) into benzimidazo[1,2-f]phenanthridine (177) and benz[c,d]indazole N-oxide (179) respectively, were described. The transformation [(173)→(177)] can be rationalised by a mechanism (Scheme 50) involving initial interaction between the aromatic nitro-group and the ortho-carbodiimide side-chain of (173), giving the eight-membered ring intermediate (174). This is postulated to undergo ring-contraction to the six-membered intermediate (175) which then affords the radical intermediate (176) by expulsion of the nitro-substituent. Cyclisation of the radical intermediate (176) then accounts for the formation of the benzimidazophenanthridine product (177).

The second general class of thermally initiated transformations of ortho-substituted nitrobenzene derivatives include reactions which can be rationalised by mechanisms involving nitrene-insertion processes. When heated in sand at 220°, N-cyclohexyl-2-nitroaniline [Scheme 51; (180)] is converted into hexahydroazepino-(1',2-1',2)-benzimidazole (186) in 15% yield. Abramovitch and Davies, by analogy with the
Scheme 49

(i) heat
Scheme 50

(i) heat
Scheme 51
pyrolysis of aryl azides, postulated route A (Scheme 51) involving formation of the nitrene intermediate (181) as the initial step to account for this transformation. Formation of the nitrene (181) is followed by insertion into the ortho-amino-substituent to give the dihydrospirobenzimidazole (183). Dehydrogenation of (183) followed by rearrangement of the resulting spirobenzimidazole (185) then accounts for the observed product (186). However, a second mechanism (Scheme 51, route B) has been suggested to account for the formation of the fused benzimidazole (186). This involves initial formation of the aci-nitro tautomer (182) of the nitroaniline (180), cyclodehydration of which is postulated to give the N-oxide (184). Deoxygenation of the latter under the reaction conditions then gives the same penultimate reaction intermediate (185) proposed in route A. Although there is no evidence in support of either of these mechanisms, it appears to be accepted in the literature that route B (Scheme 51) is followed in the transformation [(180)→(186)]. Similar mechanisms can be proposed to account for the thermally induced transformation (Scheme 52) of 2-nitrobiphenylamine (187) into phenazine (188) and of N-benzyl-2-nitroaniline (189) into 2-phenylbenzimidazole (190).
1.2.2 Reactions Involving Photochemically Induced Interaction of Aromatic Nitro-groups with Ortho Side-chains

Heterocyclisation reactions of ortho-substituted aromatic and heteroaromatic nitro-compounds can also be photochemically induced. Such heterocyclisations are often (though not always) initiated by a light-induced redox process involving the intramolecular transfer of an oxygen atom from the nitro-group to an ortho side-chain with initial formation of an ortho-nitroso intermediate which can then suffer further photo-conversion into a heterocyclic product. The required ortho relationship between the nitro-group and the side-chain necessary for oxygen-transfer was recognized as early as 1904 when Sachs and Hilpert\textsuperscript{55} proposed that, "all aromatics which
have a hydrogen ortho to a nitro-group will be light sensitive. The earliest illustration of this light sensitivity was the conversion (Scheme 53) of 2-nitrobenzaldehyde (7) into 2-nitrosobenzoic acid (193) in strong sunlight as observed by Ciamician and Silber in 1901. This transformation occurs both in solution and in the solid state, and therefore is probably intramolecular in character. Two plausible mechanisms (Scheme 53) have been suggested for the photo-conversion of 2-nitrobenzaldehyde (7) into 2-nitrosobenzoic acid (193). Horspool suggests that oxygen-transfer occurs by initial dipolar cycloaddition of the nitro-group across the carbonyl double bond to give the intermediate (192) whose conversion into 2-nitrosobenzoic acid (193) requires bond reorganisation accompanied by hydrogen shift (Scheme 53). This mechanism is supported by the observation that photo-excited aromatic nitro-groups undergo intermolecular cycloaddition to alkenes (Scheme 54) giving 1,3,2-dioxazolidines.
CHO

NO

2

H

ud

V1-

CO H

a,

NO

(i) hv

Scheme 53
Such processes are believed to involve the nitro-group reacting in an n→π* triplet excited state in a two-step electrophilic process. Though unlikely, it is also possible that such nitro-group-alkene cycloadditions involve the formation and ring-expansion of a four-membered cyclic intermediate of the type. In contrast, De Mayo and Reid propose a mechanism (Scheme 53) in which the initial step is abstraction of the benzylic hydrogen atom by the photoactivated nitro-group to give a diradical species. Electron redistribution in the latter then leads to the aci-nitroketene, further reorganisation of which, affords 2-nitrosobenzoic acid. Joshua and Ramadas propose the hydrogen abstraction mechanism to account for the photochemical transformation (Scheme 55) of 2,2'-dinitrodiphenylmethane derivatives into a mixture of the corresponding acridones and the corresponding dibenzodiazepine 5-oxides in moderate yields. These photochemical heterocyclisations are considered to occur (Scheme 55) by initial hydrogen abstraction followed by oxygen transfer to give nitrosobenzhydrol intermediates. Further oxygen-transfer (with net dehydration) in the latter leads to dinitrosobenzophenone intermediates, cyclisation of which, accounts for the observed products and (203). The photolytic rearrangement (Scheme 56) of 2-(2'-nitro-2-biphenyl) N-phenylglycinonitrile to 6-cyanophenantridine has been suggested to occur by hydrogen abstraction by the photoactivated nitro-group to give an intermediate convertible by dehydration into the nitroso-imine, which then
(X=H, Cl, Br)
\[(\text{204}) \xrightarrow{(i) \ hv} (\text{207}) \xrightarrow{(i) \ hv} (\text{206}) \xrightarrow{(i) \ hv} (\text{208})\]

Scheme 56
rearranges via a 4-membered ring species (207) to give the final product (208).

Barclay and McMaster have described the photolytic conversion (Scheme 57) of 2,4,6-tri-\(\text{t}\)-butylnitrobenzene (209) into 5,7-di-\(\text{t}\)-butyl-3,3-dimethyloxindole (212). The proposed initial step in this transformation is of interest as it involves photolytic hydrogen abstraction by an activated aromatic nitro-group from an apparently unreactive side-chain, namely a tertiary butyl substituent, to give the intermediate (210) which cyclises and dehydrates to give the \(\text{N}\)-oxide (211). Further rearrangement of the \(\text{N}\)-oxide (211) then affords the heterocyclic product (212).

As already discussed (see earlier), photo-excited aromatic nitro-groups are capable of undergoing intermolecular cycloaddition to alkenes. Such photocycloadditions can also occur intramolecularly to give heterocyclic products. Perhaps the simplest examples of such photo-heterocyclisations are the light-induced conversions (Scheme 58) of 2-nitrostilbenes (213; \(n=1\)) into the isatogens (214; \(n=0\)) in moderate yield. U.v. spectroscopy allowed the detection of intermediates in these reactions formulated as the \(\text{N}\)-oxides (215; \(n=0\)) which give isatogens (214; \(n=0\)) by subsequent dark reactions involving net oxidation. Leznoff and Hayward extended photo-cyclisations of this type (Scheme 58) to include 1-nitrophenyl-4-phenyl-1,3-butadiene (213; \(n=2, R=R'=\text{H}\)) and the hexatriene (213; \(n=3, R=R'=\text{H}\)) which, when irradiated with ultraviolet light, give the corresponding 2-substituted isatogens (214; \(n=1\) or \(2, R=\text{H}, \text{Ar} = \text{phenyl}\)) though only in low yield. Closely related to these photo-heterocyclisations is the photolytic
Scheme 57

1. $hv$

2. $Me - H_2O$
(R=H or NO2)

(R1=H, OH, OMe, Cl, NO2, NMe2)

Scheme 58
conversion (Scheme 59) of the 2-nitrobenzylideneepyrany
(216) into the spiro-compound (218).\textsuperscript{65} This photochemical
transformation proceeds in excellent yield and is suggested
to involve a 1,3,2-dioxazolidine intermediate (217) of the
type isolated by de Mayo\textsuperscript{58} in his work on intermolecular
cycloadditions of nitro-groups to alkenes (see before).

2-Nitrophenylacetylene derivatives are also susceptible
to intramolecular cyclisations to the corresponding isatogens
via photoactivated nitro-group interaction with the unsaturated
side-chain. These transformations proceed, as with stilbenes,
by direct oxygen transfer without initial hydrogen abstraction.
Thus Ambramovitch and Cue\textsuperscript{66} have shown (Scheme 60) that
irradiation of 2-nitrophenylpropionitrile (219) affords
2-cyanoisatogen (222) in 48% yield. The authors do not
speculate on a possible mechanism for this transformation which
is unlikely to involve initial cycloaddition of the photo-
activated nitro-group to the acetylenic triple bond (Scheme
60) because of the highly strained nature of the adduct (220)
formed. An alternative possibility (Scheme 60) is that
interaction between the photo-activated nitro-group and the
acetylenic side-chain leads to a nitroso-carbene intermediate
(221) which could cyclise, as shown, to the observed isatogen
product (222). In a related transformation\textsuperscript{64} (Scheme 60),
the nitronaphthylacetylene (223) undergoes photocyclisation
to 3-oxo-2-phenylbenzo[d,e]quinoline N-oxide (224), though in
poor yield (18%). This reaction demonstrates that formation
of a six-membered as opposed to a five-membered heterocyclic
ring is also feasible in such photoheterocyclisations.
Scheme 59

(i) hv
Scheme 60
2-Nitrophenylacetylene derivatives are also convertible into isatogens (Scheme 61) via initial photochemical addition of pyridine to form styrylpyridinium betaines (226) followed by photocyclisation. For example, prolonged irradiation of 2-nitrotolane (225) in pyridine gives 2-phenylisatogen (145) in 75% yield. Loudon and Tennant rationalise this type of photocyclisation by postulating the nitroso-compound (227) as a possible intermediate (Scheme 61). However, formation of the pyridinium betaine (226) is probably the only reaction step which is photo-initiated. The remaining reaction steps are probably thermally induced rather than photochemically promoted.

Photochemically initiated intramolecular cycloaddition involving nitro-groups need not only involve carbon-carbon multiple bonds. Thus, Maki and his co-workers have shown (Scheme 62) that N-2-nitrophenylhydrazones of types (229) and (233) readily undergo photocyclisation to give the corresponding 1,2,3-triazole N-oxides (232) and (234) though in low yield (10-35%). These photoheterocyclisations can be envisaged as occurring (Scheme 62) by intramolecular cycloaddition of the photo-excited nitro-group across the imine double bond to give an intermediate (230) which can undergo fragmentation to benzaldehyde and a nitroso-nitrene (231), cyclisation of which, explains the observed triazole N-oxide product (232).

A photoactivated nitro-group also has the capability of initiating heterocyclisations by radical attack at the electron deficient centre of a carbonyl group. Photolysis (Scheme 63) of a variety of N-acetyl-2-nitrodiphenylamines (235)
Scheme 61

(i) pyridine, hv
Scheme 62
(R=H, Me, OMe, CO₂Me)

(i) hv

Scheme 63
gives, in moderate to poor yield, the corresponding 1-substituted phenazine N-oxides (238). These reactions can be considered to occur (Scheme 63) by radical attack by the photoactivated nitro-group on the N-acetyl carbonyl group of the diphenylamines (235) followed by loss of an acetoxy radical (MeCO₂⁻) from the intermediate (237) produced and subsequent ring closure via the generated nitroso-species (236).
Chapter 2

Studies of the Thermal Rearrangement of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones and Related Compounds
Studies of the Thermal Rearrangement of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones and Related Compounds

2.1 Introduction

As already discussed (see Chapter 1, Section 2.1) certain 2-nitrobenzene derivatives undergo thermal rearrangement with involvement of the ortho nitro-group. For example (Scheme 1) the 2-nitrophenyltetrazole (1) is transformed thermally via a presumed carbodiimide intermediate (2) into 2-phenylbenzotriazole (7). These thermal transformations can be explained in terms of interaction between the nitro-group and the ortho-carbodiimide side-chain of (2) giving the six-membered ring intermediate (3). This is postulated to rearrange to a second six-membered ring species (4) which exists in equilibrium with the isocyanate (5). Subsequent recyclisation to (6) followed by extrusion of carbon dioxide affords the benzotriazole (7). Closely related thermal transformations (Scheme 2) are possible for the 2-diazo-1-(2-nitrophenyl)ethanones (8) which can rearrange thermally or photochemically to heterocumulenes (ketenes) (9) which are ideally set up for interaction between the nitro-group and the ortho-ketene side-chain.

The acid-catalysed cyclisation (Scheme 3) of 2-nitrobenzoyldiazomethane (10) to 1-hydroxy-1H-indole-2,3-dione, (1-hydroxyisatin) (12) can also be considered to proceed via interaction of an aromatic nitro-group and an ortho-ketene side-chain. Initial extrusion of gaseous nitrogen from the diazomethane (10) (Scheme 3; route A) followed by a Wolff rearrangement would give the ketene intermediate (11) which can further rearrange to the observed product (12) as shown.
(1) Ph

C=NPh

NO₂

\[ \text{(1)} \] \[ \xrightarrow{(i) \text{ heat}} \] \[ \text{N} = C = N\text{Ph} \]

(2)

(3)

N=N

N

Ph

N

Ph

(3)

\[ \text{(3)} \] \[ \text{N} = C = N\text{Ph} \]

(4)

(5)

N=N

N

Ph

N

Ph

(5)

\[ \text{(5)} \] \[ \text{N} = C = O \]

(6)

(7)

N-N

Ph

(7)

\[ \text{(7)} \]

\text{Scheme 1}
Scheme 2

(8) \[ \text{NO}_2 \quad C \quad - \quad N_2 \quad \rightarrow \quad \text{NO}_2 \quad C \quad - \quad R \]

(9) \[ R \quad C \quad = \quad C \quad = \quad C \quad = \quad \rightarrow \quad \text{PRODUCTS} \]
Scheme 3
However, carbon labelling studies\textsuperscript{72} have shown that this transformation (Scheme 3) does not proceed via a Wolff re-
arrangement as outlined in route A. Instead the formation of 1-hydroxyisatin (12) most probably occurs\textsuperscript{73} by an alternative pathway (Scheme 4; route B) which involves initial protonation of the ortho side-chain to give the diazonium cation inter-
mediate (13). Subsequent nucleophilic attack by the oxygen atom of the nitro-group on the ortho side-chain would then give a six-membered intermediate (14) which can ring-open to give 2-nitrosophenylglyoxal (15). Ring-closure of the latter compound would then afford the observed product, 1-hydroxyis-
atin (12). However evidence in support of this latter mechanism (Scheme 4; route B) has yet to be described in the literature.

In view of the lack of information concerning the mechanism of the acid-catalysed rearrangement (Schemes 3 and 4) of 2-nitrobenzoyldiazomethane (10) to 1-hydroxyisadin (12) and the apparent absence of any study of the thermal and photochemical behaviour of 2-diazo-1-(2-nitrophenyl) ethanones in general, it was of interest to prepare compounds of this general type and study their behaviour when subjected to heating.

2.2 The Synthesis and Thermal Rearrangement of 2-Diazo-1-
(2-nitrophenyl)-3-phenylpropane-1,3-diones (21a-d)

2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) is readily prepared (Scheme 5) by the triethylamine catalysed diazo-transfer reaction of 1-(2-nitrophenyl)-3-phenylpropane-
1,3-dione (20a) with toluene-\textsubscript{p}-sulphonyl (tosyl) azide.
Scheme 4

(i) AcOH
Scheme 5

(i) $\text{SOCl}_2$

(ii) Mg, EtOH or NaOEt, EtOH, $\Phi_3\text{COCH}_2\text{CO}_2\text{Et}$

(iii) $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$, EtOH

(iv) $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$

(v) $\text{TSO}_2\text{N}_3$, Et$_3\text{N}$ ($\text{T}=\text{4-MeC}_6\text{H}_4$)

(vi) heat

(vii) NaOH, $\text{H}_2\text{O}$
1-(2-Nitrophenyl)-3-phenylpropane-1,3-dione (20a) was prepared by hydrolysis and subsequent decarboxylation of ethyl 2-benzoyl-3-(2-nitrophenyl)-3-oxopropanoate (18a). The preparation of the diketo-ester (18a) was achieved by base-catalysed condensation of 2-nitrobenzoyl chloride (17a) (prepared by the reaction of 2-nitrobenzoic acid with thionyl chloride) with ethyl benzoylacetate. The conditions of this condensation had to be substantially altered from those described in the literature which employed sodium ethoxide as the condensation catalyst. In the present studies, this method led to only low yields of the diketo-ester (18a). A greatly increased yield (81%) of the latter compound resulted when 2-nitrobenzoyl chloride (17a) was condensed with the magnesium enolate of ethyl benzoylacetate. The diketo-ester (18a) produced by the latter method was found to be identical (m.p. and i.r. spectrum) to material obtained by the condensation using sodium ethoxide as the catalyst.

The diketo-esters (18b-d) (Scheme 5) were similarly obtained by condensation of the appropriate 2-nitrobenzoyl chlorides (17b-d) with the magnesium enolate of ethyl benzoylacetate. Condensation of 5-methyl-2-nitrobenzoyl chloride (17b), prepared as described in the literature, with the magnesium enolate of ethyl benzoyl acetate afforded ethyl 2-(5-methyl-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18b) as an unpurified brown oil. The i.r. spectrum of this compound showed an absorption band at 1710 cm⁻¹, characteristic of an ester carbonyl stretching vibration together with absorption bands at 1520 and 1345 cm⁻¹ typical of the symmetric and anti-symmetric stretching vibrations of a nitro-group. The ¹H n.m.r. spectrum of the diketo-ester (18b) showed signals
due to the protons of two methyl substituents and two ethoxy-carbonyl groups. These unexpected features of the $^1$H n.m.r. spectrum of the diketo-ester (18b) may be attributed to the presence in solution of both keto and enol forms of the compound. Nitration of 3-chlorobenzoic acid gave 5-chloro-2-nitrobenzoic acid (16c) (yield 80%) which was identified by comparison of its melting-point with that of the literature value. Treatment of the carboxylic acid (16c) with thionyl chloride afforded the acid chloride (17c) which also condensed with the magnesium enolate of ethyl benzoylacetate to give the diketo-ester (18c). Condensation of the isomeric acid chloride (17d) with the magnesium enolate of ethyl benzoylacetate likewise gave the diketo-ester (18d) as a brown oil (yield 100%) whose structure was assigned on the basis of i.r. and $^1$H n.m.r. evidence. Because of lack of conclusive structural proof for the crude oils (18b-d), it was considered desirable to attempt to prepare solid derivatives of the diketo-esters (18b-d) which would allow their positive characterisation. Thus (Scheme 5) ethanolic solutions of the crude oils (18c and d) were treated with hydrazine hydrate in the hope of obtaining the solid pyrazole derivatives (19c and d). However in both cases reaction of the oily diketo-esters (18c and d) with hydrazine hydrate gave only multicomponent mixtures from which none of the required pyrazole derivatives (19c and d) could be isolated.

Treatment of the diketo-ester (18a) with 13M aqueous sulphuric acid resulted in hydrolysis to the diketone [Scheme 5; (20a)] in high yield (87%). The diketone (20a) was identified by its melting-point which was identical to the literature value. The i.r. spectrum of the diketone (20a) showed broad, low-frequency carbonyl absorption at 1640-1600
cm⁻¹ demonstrating its existence in the solid state largely in the enol form. Similar treatment of the diketo-esters (18b-d) yielded the diketones (20b-d) in moderate yield (39-71%) which were identified by their analytical and spectroscopic properties. The i.r. spectra of the diketones (18b-d) again showed broad, low-frequency carbonyl absorption between 1640 and 1600 cm⁻¹ due to the enol tautomeric forms as already discussed.

Treatment of an ethanolic solution of the diketone (20a) with tosyl azide in the presence of triethylamine as described by Regitz, afforded 2-diazo-1-(2-nitrophenyl)-3-phenyl-propane-1,3-dione (21a) in excellent yield (85%). The diazo-diketone (21a) was identified by its melting-point which was identical to that reported by Regitz. Similar treatment of the diketone (20b) with tosyl azide in the presence of triethylamine gave, in good yield (81%), the corresponding diazo-diketone (21b) whose structure was assigned on the basis of the following evidence. The compound gave analytical data consistent with the molecular formula C₁₆H₁₁N₃O₄ and its i.r. spectrum showed the expected diazo-absorption at 2120 cm⁻¹. The mass spectrum of the compound showed a parent ion at M⁺, 281 corresponding to the ready loss of nitrogen from the parent ion (M⁺, 309). Treatment of the diketone (20c) with tosyl azide in the presence of triethylamine gave the expected diazo-diketone (21c) in high yield. The compound (21c) gave analytical data and showed an i.r. spectrum in full agreement with the assigned structure. However the mass spectrum of the diazo-diketone (21c) showed a parent ion at M⁺, 285/283 as opposed to a molecular ion at m/e 331/329 expected on the
basis of the molecular formula \( \text{C}_{15}\text{H}_8\text{ClN}_3\text{O}_4 \), and indicating the loss of the nitro-group from the molecular ion. A similar fragmentation involving loss of the nitro-group is observed in the mass spectrum of the diketone (20c). Mass spectral fragmentation involving the loss of an aromatic nitro-group para to an electron withdrawing group appears contrary to literature expectations\(^8\) and there is no obvious explanation for the mass-spectral fragmentation of the compounds (20c) and (21c) observed in the present studies.

Normal workup, involving an aqueous alkali wash, of the reaction mixture obtained by treating the diketone (20d) with tosyl azide in the presence of triethylamine gave (Scheme 6) in good yield (73%) a compound identified as 4-chloro-2-nitrobenzoyldiazomethane (24) on the basis of the following evidence. The compound gave an elemental analysis consistent with the molecular formula \( \text{C}_8\text{H}_4\text{ClN}_3\text{O}_3 \) and its i.r. spectrum showed diazo-absorption at 2170 and 2130 \( \text{cm}^{-1} \), carbonyl-absorption at 1610 \( \text{cm}^{-1} \), and nitro-absorption at 1535 and 1375 \( \text{cm}^{-1} \). The \(^1\text{H}\) n.m.r. spectrum of the compound in deuteriodimethylsulphoxide showed a one proton singlet at 66.72 attributable to the hydrogen atom of the diazo-group in 4-chloro-2-nitrobenzoyldiazomethane (24). The mass spectrum of the compound showed a parent ion at \( M^+ \), 186/184 as opposed to a molecular ion at \( m/e \) 227/225 expected on the basis of the molecular formula \( \text{C}_8\text{H}_4\text{ClN}_3\text{O}_3 \). The parent ion at \( M^+ \) 186/184 is readily explained by mass spectral fragmentation of the diazo-ketone (24) with loss of the diazomethyl moiety (CHN\(_2\)).

As already mentioned in this chapter, 2-nitrobenzoyldiazomethane [Scheme 3; (10)] rearranges to 1-hydroxyisatin (12) on treatment with acid.\(^9,\)\(^7\) It seemed likely therefore
(i) $\text{TSO}_2\text{N}_3, \text{Et}_3\text{N} (T=4-\text{MeC}_6\text{H}_4)$
(ii) $\text{NaOH, H}_2\text{O}$
(iii) $\text{HCO}_2\text{H, AcOH}$

Scheme 6
(Scheme 6) that 4-chloro-2-nitrobenzoyldiazomethane (24) encountered in the present studies would undergo similar acid-catalysed rearrangement to the corresponding 1-hydroxyisatin derivative (25) thus providing further evidence for the structure of the diazoketone (24). However, treatment of the diazo compound (24) with mixed formic and acetic acids gave only the unreacted starting-material (24). Unfortunately, due to lack of time, further studies of the acid-catalysed transformation of the diazo-ketone (24) into the 1-hydroxyisatin (25) could not be attempted.

It is probable that the isolation of 4-chloro-2-nitrobenzoyldiazomethane (24) from the reaction of the diketone (20d) with tosyl azide in the presence of triethylamine is the result of base-promoted cleavage of the initially formed diazo-diketone (21d) which occurs during workup. Indeed it was found that treatment of the diketone (20d) with tosyl azide in the presence of triethylamine with omission of the aqueous alkali wash in the workup resulted in a good yield (71%) of a compound identified as (4-chloro-2-nitrophenyl)-2-diazo-3-phenylpropane-1,3-dione (21d) on the basis of its elemental analysis and its i.r. and $^1H$ n.m.r. spectra. The mass spectrum of the diazo-diketone (21d), however, showed a parent ion at $M^+$, 259/257 rather than at m/e 331/329 expected on the basis of the molecular formula, $C_{15}H_{8}ClN_{3}O_{4}$. The ion at m/e 259/257 can be attributed to electron impact-induced fragmentation of the diazo-diketone (21d) with loss of nitrogen and carbon dioxide (see later).

By way of confirming that 4-chloro-2-nitrobenzoyldiazomethane (24) can be produced by the action of aqueous alkali
on the diazo-diketone (21d), a 1,2-dimethoxyethane solution of the latter was treated with aqueous 2M sodium hydroxide. However workup of the resulting mixture gave only a multicomponent oil together with a good yield (74%) of benzoic acid. Formation of the latter product is evidence for the expected base-catalysed cleavage of the diazo-diketone (21d), the diazo-ketone (24) cleavage product presumably being destroyed under the reaction conditions.

As indicated in Section 2.1, it was of interest to study the thermal behaviour of 2-diazo-1-(2-nitrophenyl)ethanones. Initially the behaviour of 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) on heating in a suitable solvent was investigated. Heating the diazo-diketone (21a) in anhydrous toluene resulted in vigorous gas evolution. Workup of the resulting solution gave a product mixture which was chromatographed over silica (as opposed to alumina - see later) to afford as the main component (yield 58%) a compound identified as 2-phenyl-3,1-benzoxazin-4-one (22a) on the basis of the following evidence. The product gave analytical and mass spectral data consistent with the molecular formula C₁₄H₉NO₂ and its i.r. spectrum showed carbonyl absorption at 1770 cm⁻¹ characteristic of a 6-lactone grouping. Confirmation of the benzoxazinone structure (22a) was provided by the identity of the melting-points of the product and that of benzoxazin-4-one (22a) described in the literature. The product of the thermal rearrangement of the diazo-diketone (21a) was further characterised as 2-phenyl-3,1-benzoxazin-4-one (22a) by its base-catalysed hydrolysis (Scheme 5) to afford N-benzoylanthranilic acid (23a) identified by comparison with
Chromatography of the mixture obtained from the thermolysis of the diazo-diketone (21a) over alumina (rather than silica - see before) did not yield any of the benzoxazin-4-one (22a) but afforded instead, as the only characterised material, a small quantity of 3-benzoyl-2,1-benzisoxazole [Scheme 7; (26)] which was identified by comparison with an authentic sample prepared by an alternative synthetic route (see later).

It seems probable that both the benzoxazin-4-one (22a) and the benzisoxazole (26) are products of the thermal rearrangement of the diazo-diketone (21a) but that chromatography of the crude reaction mixture over alumina results in hydrolysis of the benzoxazin-4-one (22a) to N-benzoylanthranilic acid (23a), which, because of its acidity, would be expected to resist elution from the basic stationary phase of the chromatography column thus accounting for the non-isolation of the benzoxazin-4-one (22a). Conversely, chromatography of the crude reaction product over silica must result in the small amount of benzisoxazole (26) present forming part of the unresolved fraction isolated thus accounting for the apparent non-isolation of the compound (26) under these separation conditions.
Heating the diazo-diketone (21b) in toluene gave a product mixture which on chromatography over silica afforded 6-methyl-2-phenyl-3,1-benzoxazin-4-one (22b) in moderate yield (42%). The benzoxazin-4-one (22b) was identified on the basis of the following evidence. The compound gave analytical and mass spectral data consistent with the molecular formula of \( \text{C}_{15}\text{H}_{11}\text{NO}_2 \) and its i.r. spectrum showed carbonyl absorption at 1760 cm\(^{-1}\) consistent with its oxazinone structure (22b) (see before). Similar heating of a toluene solution of the diazo-diketone (21d) gave a product mixture chromatography of which gave, as the only identified material, the benzoxazin-4-one (22d) whose analytical and spectroscopic properties were fully in accord with its assigned structure. Heating the diazo-diketone (21c) in toluene afforded a product mixture which on workup gave 6-chloro-2-phenyl-3,1-benzoxazin-4-one (22c) in low yield (32%). The analytical and spectroscopic properties of this compound were again fully in accord with the assigned structure (22c).

Despite significant differences in the site and electronic character of the substituents in the benzoyl nucleus of the diazo-diketones (21) these compounds show a marked uniformity in their thermal rearrangement to the corresponding benzoxazinones (22). These reactions are remarkable for the deep-seated nature of the skeletal rearrangement involved resulting as it does in the apparent detachment of the phenyl-substituent and its attached carbon atom from the side-chain and its re-attachment at the nitrogen atom of the nitro-group. It was of interest therefore to seek evidence for the mechanism of these novel rearrangements.
2.3 Investigations of the Mechanism of the Thermal Rearrangement of 2-Diazo-1-(2-nitrophenyl)-3-phenyl-propane-1,3-diones (21a-d) to 2-Phenyl-3,1-benzoxazin-4-ones (22a-d)

The thermal transformation of the diazo-diketone (21a) into the benzoazin-4-one (22a) requires a deep-seated rearrangement the course of which is not obvious even after the limited mechanistic probing described in the present section. It is possible to speculate on two main pathways (A and B – see Schemes 8 and 9) both of which originate in the nitroso-carbene intermediate (30). Formation of the latter can be readily explained by loss of nitrogen from the diazo-diketone (21a) and Wolff rearrangement of the resulting diketocarbene (27) to the ketene (28) followed by nitro-group side-chain interaction and loss of CO₂ to give the nitroso-carbene (30).

Pathway A (Scheme 9) involves cyclisation of the nitroso-carbene (30) to 3-benzoyl-2,1-benzisoxazole (26) and ring-opening of the latter to give the nitrene-intermediate (32). Cyclisation of the latter, via an insertion process, would give the oxirane derivative (34), which is also common to pathway B (Scheme 9), but in the latter case arises by initial rearrangement of the nitroso-carbene (30) to the nitroso-oxirene (31) followed by electrocyclisation to the intermediate (33) and further electron reorganisation to give the oxirane intermediate (34). Two plausible routes can be proposed to explain the conversion of the oxirane (34) into the benzoazin-4-one (22a). One possibility involves ring-opening of the oxirane (34) to the ketene (35) and subsequent recyclication to the benzoazin-4-one (22a). Alternatively the oxirane (34)
(21a) 

\[
\begin{align*}
\text{(28)} & \quad \rightarrow \quad \text{(29)} \\
\text{(30)} & \quad \rightarrow \quad \text{(27)} \\
\text{(i) heat} & 
\end{align*}
\]

Scheme 8
Scheme 9
could undergo a [1,3]-shift to give the zwitterionic intermediate (36) ring-opening of the oxirane moiety in which would lead as shown (Scheme 9) to the benzoxazinone (22a).

The reported rearrangement of 3-benzoyl-2,1-benzisoxazole (26) to the benzoxazin-4-one (22a) on heating at 158-161° by Pinkus and his co-workers\(^8\) suggested that the route followed in the thermal rearrangement of the diazo-diketone (21a) to the benzoxazinone (22a) involved pathway A rather than pathway B (Scheme 9). It was therefore decided to synthesise the benzisoxazole derivative (26) and investigate its behaviour towards heating under the conditions of the diazo-diketone to benzoxazin-4-one rearrangement.

3-Benzoyl-2,1-benzisoxazole (26) can be prepared (Scheme 10) by a method described in the literature\(^8\) which involves the treatment of a benzene solution of 2,1-benzisoxazole-3-carbonyl chloride (39) with diphenylcadmium. 2,1-Benzisoxazole-3-carbonyl chloride (39) is available by the reaction of 2,1-benzisoxazole-3-carboxylic acid (38a) with thionyl chloride, the carboxylic acid (38a), in turn being obtained by the acid-catalysed cyclisation\(^8\) of ethyl 2-nitrophenylacetate (37). The formation of 2,1-benzisoxazole-3-carboxylic acid (38a) from ethyl 2-nitrophenylacetate (37) can be rationalised by the initial cyclisation of the latter to the ethyl ester (38b) followed by hydrolysis to the carboxylic acid (38a). By analogy (Scheme 11), the similar acid-catalysed cyclisation of 2-(2-nitrophenyl)-1-phenylethanone (41) should yield the required 3-benzoyl-2,1-benzisoxazole (26) directly thus providing a simpler route to the latter compound. The 2-(2-nitrophenyl)-1-phenylethanone (41) required for direct cyclisation to the
Scheme 10

(i) conc. $\text{H}_2\text{SO}_4$
(ii) $\text{SOCl}_2$
(iii) CdPh$_2$, benzene
(40) \[ \text{PhH, AlCl}_3 \]
(ii) conc. \( \text{H}_2\text{SO}_4 \)
(iii) hydrolysis

\[ \text{Scheme 11} \]
2,1-benzisoxazole derivative (26) was readily prepared in high yield (74%) by the Friedel-Crafts reaction of benzene with 2-nitrophenylacetyl chloride (40) as described in the literature, and had a melting-point in agreement with the literature value. The attempted cyclisation (Scheme 11) of 2-(2-nitrophenyl)-1-phenylethanone (41) by heating with concentrated sulphuric acid at 110° gave none of the required benzisoxazole derivative (26) but afforded benzoic acid and a low yield (22%) of an oil identified as 2,1-benzisoxazole (42) on the basis of its mass spectrum which showed a parent ion at m/e 119 (2,1-benzisoxazole requires M, 119) and by comparison of its ¹H n.m.r. spectrum with that of an authentic sample. The formation of 2,1-benzisoxazole (42) and benzoic acid from the reaction of 2-(2-nitrophenyl)-1-phenylethanone (41) with concentrated sulphuric acid at 110° can be rationalised by initial formation of 3-benzoyl-2,1-benzisoxazole (26) which then suffers solvolytic cleavage to 2,1-benzisoxazole (26) and benzoic acid in the reaction mixture. In an effort to prevent this solvolytic cleavage and hence allow the isolation of the required 3-benzoyl-2,1-benzisoxazole (26), the acid-catalysed cyclisation of 2-(2-nitrophenyl)-1-phenylethanone (41) was attempted under milder conditions. However the ketone (41) was recovered unchanged in good yield after treatment with concentrated sulphuric acid at 50° and at room temperature. The attempted cyclisation of the ketone (41) to the 2,1-benzisoxazole derivative (26) was no more successful using polyphosphoric as the acid catalyst, workup of the mixture giving a good recovery of the starting-material (41).

As already discussed in Chapter 1, it has been shown (Scheme 12) that heating 2-nitrobenz-
Scheme 12

(i) HBr, AcOH, heat
hydryl bromide (43) with hydrogen bromide in glacial acetic acid results in cyclisation to 5-bromo-3-phenyl-2,1-benzisoxazole (46). The initial step in this transformation most likely involves neighbouring-group interaction of the nitro-group with the ortho side-chain with expulsion of the bromine substituent and net oxygen-transfer to afford 2-nitrosobenzophenone (44). Subsequent reduction of the latter by hydrogen bromide with concomitant introduction of bromine into the benzene nucleus would then afford the hydroxyamino-ketone (45) spontaneous cyclisation of which then accounts for the formation of the 2,1-benzisoxazole product (46). By analogy with the acid-catalysed transformation of 2-nitrobenzhydryl bromide (43) into the 2,1-benzisoxazole derivative (46) it was anticipated (Scheme 13) that the analogous acid-catalysed cyclisation of 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (47) would provide a convenient method for the synthesis of the required 3-benzoyl-2,1-benzisoxazole (26).

2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (47) was readily obtained by the bromination of 2-(2-nitrophenyl)-1-phenylethanone (41) in glacial acetic acid as described in the literature. Heating the bromo-ketone (47) in glacial acetic acid afforded not the expected 2,1-benzisoxazole (26) but rather a crimson product, in moderate yield, (58%), whose properties are entirely in accord with its formulation as 5-bromo-2-phenylindol-1-en-3-one N-oxide (5-bromo-2-phenylisatogen) (51). Thus it gave analytical and mass spectral data consistent with the molecular formula C_{14}H_{8}BrNO_{2}. Moreover its mass spectrum in addition to the parent ion peaks at m/e 303/301 showed fragment ion peaks at m/e 286/284 consistent with proton transfer
Scheme 13

(i) $\text{Br}_2$, AcOH
(ii) AcOH, heat
(iii) HBr
followed by the loss of OH, a characteristic fragment of other heterocyclic N-oxides. The crimson product also showed high frequency carbonyl absorption at 1725 cm\(^{-1}\) anticipated for the indolenone N-oxide structure (51).

Though unexpected, the formation of the isatogen (51) is readily explained (Scheme 13) on the basis of the expected initial formation of 2-nitrosobenzil (48) which then suffers reduction with introduction of bromine to give the brominated phenylhydroxylamine (49) rather than the hoped-for unbrominated hydroxyamino-diketone precursor (50) of the 2,1-benzisoxazole derivative (26). Spontaneous dehydrative cyclisation of the bromophenylhydroxylamine derivative (49) then accounts for the formation of the isatogen derivative (51).

With the intention of obtaining evidence in support of the mechanism shown in Scheme 13 for the acid-catalysed conversion of the bromo-ketone (47) into the isatogen (51), the former compound was treated with silver nitrate in acetonitrile which should still promote the initial conversion into 2-nitrosobenzil (48) but by scavenging the bromide ion produced should terminate the process at this stage thus permitting the isolation of the nitroso-compound (48) hence substantiating the proposed mechanism (Scheme 13). In practice heating the bromoketone (47) with silver nitrate in acetonitrile gave only a multi-component gum plus a low recovery (30%) of the starting-material (47). In contrast, heating the bromo-ketone (47) with sodium acetate in glacial acetic acid afforded a low yield (21%) of a colourless product which analysed correctly for C\(_{14}H_9NO_3\). This product is formulated as 1-benzoyl-2,1-benzisoxazol-3-one (52) on the basis of its melting-point which is identical to that of an authentic sample.\(^{91}\) The structure (52) for the
product is also substantiated by the presence of lactonic and amidic carbonyl bands at 1790 and 1680 cm$^{-1}$ respectively and by its mass-spectral fragmentation pattern which shows the loss of CO$_2$ from the parent ion as well as cleavage to a benzoyl moiety. The mode of formation of the 2,1-benzisoxazole(52) from the bromoketone (47) is not clear and requires further investigation.

Due to the lack of success in finding a simpler alternative route to 3-benzoyl-2,1-benzisoxazole (26), it was decided to prepare this compound via the route (see Scheme 10) described in the literature.$^8$ Again however, it was decided to seek an alternative method to that based on the relatively difficultly accessible ethyl 2-nitrophenylacetate (37) for the synthesis of 2,1-benzisoxazole-3-carboxylic acid (38a) required as starting-material. It has been reported$^8$ (Scheme 14), that 2-chloro-1-(2-nitrophenyl)ethanone (54a), readily available by the chlorination of 2-nitroacetophenone (53), is converted by treatment with aqueous sodium hydroxide in good yield into 2,1-benzisoxazole-3-carboxylic acid (38a). This unusual transformation is suggested$^8$ to occur by initial cyclisation to 2-chloroisatogen (55a) followed by hydrolysis to 1-hydroxyisatin [(55a)$\rightarrow$(57)$\rightarrow$(12)] which is known$^8$ to undergo base-catalysed rearrangement to 2,1-benzisoxazole-3-carboxylic acid (38a). In the present studies 2-chloro-1-(2-nitrophenyl)-ethanone (54a) was readily prepared in good yield (53%) by the chlorination of commercially available 2-nitroacetophenone (53) using sulphuryl chloride. However, heating the chloroketone (54a) with aqueous sodium hydroxide gave the starting-material (54a) in moderate yield together with an uncharacterised
(i) $\text{SO}_2\text{Cl}_2, \text{AcOH}$

(ii) $\text{Br}_2, \text{AcOH}$

(iii) $\text{NaOH, H}_2\text{O}$

(iv) $\text{PhSO}_2\text{Na}^+$

Scheme 14
gum. Repetition of this reaction using ethanol as co-solvent gave the 2,1-benzisoxazole carboxylic acid (38a) but in insufficient yield (4%) to make this transformation useful for the synthesis of the carboxylic acid (38a).

The failure to obtain a reasonable yield of 2,1-benzisoxazole-3-carboxylic acid (38a) by the base-promoted cyclisation of the chloro-ketone (54a) prompted the investigation (Scheme 14) of the analogous sodium hydroxide-catalysed cyclisation of 2-bromo-1-(2-nitrophenyl)ethanone (54b) which it was hoped might be a more efficient precursor of the carboxylic acid (38a). The bromo-ketone (54b) was readily prepared by the bromination of 2-nitroacetophenone (53) as described in the literature. Unfortunately, heating the bromo-ketone (54b) with aqueous sodium hydroxide again gave the required carboxylic acid (38a) in only low yield (4%) together with unreacted starting-material (54b) (yield 32%).

In a further attempt to synthesise 2,1-benzisoxazole-3-carboxylic acid (38a) by the strategy outlined in Scheme 14, it was decided to investigate the possible base-catalysed cyclisation of 2-benzenesulphonyl-1-(2-nitrophenyl)ethanone (56) whose close structural relationship to the halogeno-ketones (54a and b) suggested its suitability as a precursor of the carboxylic acid (38a). The benzenesulphonyl derivative (56) was readily prepared in good yield (78%) by the reaction of the bromo-ketone (54) with sodium benzenesulphinate as described by other workers. Disappointingly, heating the benzenesulphonyl derivative (56) with aqueous alkali failed to afford the carboxylic acid (38a), the starting-material (56) being recovered unchanged in high yield (80%).
Having failed to obtain reasonable yields of 2,1-benzisoxazole-3-carboxylic acid (38a) by the sodium hydroxide-catalysed cyclisation of the ethanone derivatives (54a and b) and (56) it was decided to revert to the literature procedure for the preparation of 2,1-benzisoxazole-3-carboxylic acid (38a) involving the acid-catalysed cyclisation (Scheme 10) of ethyl 2-nitrophenylacetate (37), readily prepared in turn from commercially available 2-nitrophenylacetic acid via the reaction of 2-nitrophenylacetetyl chloride (40) with ethanol. The acid-catalysed cyclisation of ethyl 2-nitrophenylacetate (37) occurred smoothly in concentrated sulphuric acid giving 2,1-benzisoxazole-3-carboxylic acid (38a) in moderate yield (57%). Treatment of 2,1-benzisoxazole-3-carboxylic acid (38a) with thionyl chloride gave a moderate yield (50%) of the corresponding acid chloride (39) which showed i.r. absorption at 1750 cm$^{-1}$ attributable to the chlorocarbonyl substituent. Finally, the reaction of the acid chloride (39) with diphenylcadmium in benzene gave 3-benzoyl-2,1-benzisoxazole (26), albeit in low yield (22%), whose melting-point corresponded to that reported in the literature.

As discussed before (see Scheme 9) 3-benzoyl-2,1-benzisoxazole (26) is a possible intermediate in the thermally-initiated rearrangement of the diazo-diketone (21a) to the benzoxazin-4-one (22a). If this hypothesis is correct the 2,1-benzisoxazole derivative (26) should be converted into the benzoxazin-4-one (22a) on heating in toluene. However heating 3-benzoyl-2,1-benzisoxazole (26) under reflux in toluene for 1h was without effect, the 2,1-benzisoxazole derivative (26) being recovered unchanged in quantitative yield. This result would
appear to exclude 3-benzoyl-2,1-benzisoxazole (26) as an intermediate on the pathway from the diazo-diketone (21a) to the benzoazinone (22a) (see Schemes 8 and 9).

By way of further probing the mechanism of the thermal diazo-diketone to benzoazinone rearrangement, attempts (Scheme 15) were made to trap the ketene derivative (28) postulated as an early intermediate on the reaction pathway. It is known that ketenes readily add nucleophilic reagents across the carbon-carbon double bond and hence if the ketene (28) is involved as a discrete intermediate it might be trappable by carrying out the thermal rearrangement of the diazo-diketone (21a) in the presence of nucleophiles such as ethanol, piperidine, and hydrazine. In practice, heating the diazo-diketone (21a) in toluene in the presence of ethanol gave no material identifiable as the β-keto ester (59) derived by trapping of the ketene intermediate (28) with ethanol. Instead this reaction gave only a multicomponent gum from which no identifiable material could be isolated. Heating the diazo-diketone (21a) in toluene in the presence of piperidine likewise afforded none of the hoped-for ketene adduct (60) but only a series of multicomponent oils. Trapping of the ketene intermediate (28) in the form of the pyrazolone derivative (61) was equally unsuccessful, heating the diazo-diketone (21a) in toluene containing hydrazine hydrate affording only a moderate yield (45%) of the benzoazinone derivative (22a), together with a multicomponent gum. It appears from these results that either the ketene derivative (28) is not involved as a discrete intermediate or its trapping by nucleophilic addition across the carbon-carbon double bond is too inefficient to give recognisable products in isolable
Scheme 15
quantities. However, the failure of these trapping experiments could also be due to the rapidity with which intramolecular nitro-group side-chain interaction (see Scheme 8) occurs in the ketene intermediate (28).

In a further attempt to demonstrate the involvement of ketene intermediates in the thermal rearrangement of the diazo-diketones (21) to the benzoxazinones (22) it was decided to investigate the thermolysis (Scheme 16) of the para-nitro-diazo-diketone (65). This compound still retains an activating nitro-group and has all of the other structural features necessary for the preliminary rearrangement to the presumed ketene intermediate (66). However its nitro-substituent, being para cannot become involved in neighbouring-group interaction with the ketene side-chain hence allowing greater opportunity for the trapping of the para-nitro derivative (66) as compared with its ortho-nitro analogue (28) (see before). Regitz reported the preparation of the required para-nitro-diazo-diketone (65) by the diazo-transfer reaction of the diketone (64) with tosyl azide in the presence of triethylamine. The diketone (64) was synthesised in good yield by the reaction of 4-nitrobenzoyl chloride (62) with the magnesium enolate of ethyl benzoylacetaote followed by acid-catalysed hydrolysis of the resulting β-keto-ester (63), whose melting-point corresponded to that reported in the literature. The melting-point of the crude diketone (64) differed from that recorded in the literature, but its structure was fully substantiated by its i.r. spectrum which lacked carbonyl absorption due to an ester group but showed the broad absorption around 1630 cm\(^{-1}\) attributable to the enolic β-diketone structure (64). Contrary to
(i) Mg, EtOH, PhCOCH$_2$CO$_2$Et  
(ii) $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$  
(iii) TSO$_2$N$_3$, Et$_3$N ($T=4$-MeC$_6$H$_4$)  
(iv) heat  

Scheme 16
the results obtained by Regitz,\textsuperscript{80} treatment of the β-diketone (64) with tosyl azide in the presence of triethylamine gave none of the expected diazo-diketone (65) but instead a dark red multicomponent oil which yielded no identifiable product. Toluene-p-sulphonamide, identified by comparison with an authentic sample was also isolated in good yield (95\%) from this reaction. Lack of time prevented further attempts to synthesise the required para-nitro-diazo-diketone (65). The thermal behaviour of this compound therefore awaits further study.

2.4 Further Investigations of the Scope of the Thermal Rearrangement of 2-Diazo-1-(2-nitrophenyl)ethanones

In view of the unique nature of the thermal rearrangement of 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones (21) to 3,1-benzoxazin-4-ones (22), it was of interest to investigate the scope of such reactions in terms of 2-diazo-1-(2-nitrophenyl)ethanone derivatives in general and in particular those derived by replacing the non-nitrated benzoyl nucleus in 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones (21) by other electron-withdrawing substituents (Schemes 17 and 18). The compounds chosen for study were the diazo-diketone (69a), the diazo-keto-ester (69b), and the diazo-keto-sulphone (70).

Regitz\textsuperscript{80} has reported the preparation of 2-diazo-1-(2-nitrophenyl)butane-1,3-dione (69a) by the piperidine-catalysed diazo-transfer reaction of the diketone (68a) with tosyl azide. The diketone (68a) was readily synthesised (Scheme 17) by the sodium ethoxide-catalysed condensation of 2-nitrobenzoyl...
(17a) 

(i) NaOEt, EtOH

(ii) H₂SO₄, H₂O or NH₃, H₂O

(iii) TSO₂N₃, piperidine (T=4-MeC₆H₄)

R

a; Me

b; OEt

Scheme 17
Scheme 18

(i) $\text{TSO}_2\text{N}_3$, $\text{Et}_3\text{N}$ (T=4-$\text{MeC}_6\text{H}_4$)

(ii) toluene, heat

(iii) EtOH
chloride (17a) with ethyl acetoacetate followed by hydrolysis of the resulting diketo-ester (67) sodium salt and was readily identified on the basis of its melting-point which corresponded to that of the literature value. Contrary to the result reported by Regitz the attempted reaction of the diketone (68a) with tosyl azide in the presence of piperidine afforded none of the expected diazo-diketone (69a) but rather a multicomponent brown oil chromatography of which yielded no identifiable material. The attempted diazo-transfer reaction of the diketone (68a) to give the diazo-diketone (69a) using tosyl azide in the presence of triethylamine was no more successful, giving largely a multicomponent oil from which no identifiable material could be obtained. Lack of time prevented further attempts to obtain the diazo-diketone (69a) the investigation of whose chemical behaviour will provide the basis of future studies.

Having failed to readily obtain the diazo-diketone (69a), attention was next directed to the synthesis and study of the thermal behaviour of the diazo-keto-ester (69b). It was intended to synthesise the latter compound by the diazo-transfer reaction of ethyl 3-(2-nitrophenyl)-3-oxopropanoate (68b). This β-keto-ester was readily prepared, though only in low yield (22%) by treatment of the sodium salt of the β-keto-ester (67) with aqueous ammoniacal ammonium chloride as described in the literature. Unfortunately, however, the attempted conversion of the β-keto-ester (68b) into the diazo-keto-ester (69b) by treatment with tosyl azide in the presence of triethylamine gave in addition to toluene-2-sulphonamide only complex mixtures which failed to yield any characterisable product.

Despite the failure of the attempted syntheses of the diazo-diketone (69a) and the diazo-keto-ester (69b), it was
decided to attempt the synthesis (Scheme 18) of the diazo-keto-sulphone (70), with the intention of studying its thermal behaviour. It was anticipated that this compound would be accessible by the diazo-transfer reaction of the keto-sulphone (56) whose preparation has been described earlier in this chapter (see Section 2.3). In practice the keto-sulphone (56) reacted smoothly with tosyl azide in the presence of triethylamine to give a product in high yield (93%) whose properties are in accord with its formulation as the diazo-keto-sulphone (70). Thus it gave analytical and mass spectral data consistent with the molecular formula $C_{14}H_9N_3O_5S$ and its i.r. spectrum showed a strong absorption band at 2130 cm$^{-1}$ which is characteristic of a diazo-group.

Heating the diazo-keto-sulphone (70) under reflux in toluene for 3h resulted in its conversion into a product mixture chromatography of which yielded two main components. The minor product (yield 20%) showed i.r. absorption at 2140, 1755, 1535, and 1340 cm$^{-1}$ attributable to the heterocumulene and carbonyl components and the nitro-substituent of the ketene derivative (71). Though this structure assignment for the minor product is tentative, it is supported by the conversion of the product on crystallisation from ethanol into a new compound whose analytical and spectroscopic properties are consistent with its formulation as the ester derivative (73). The formation of the presumed ketene derivative (71) lends support to the proposal (see before) that the thermal rearrangement of the diazo-diketones (21) to the benzoazinones (22) involves the formation of ketene intermediates [e.g. (28)] derived by Wolff rearrangement in initially formed keto-carbene species [e.g. (27)] (see Scheme 8). However, more rigorous structure
proof for the ketene (71) and the derived ester (73) will be required before the initial stages of the proposed thermal rearrangement mechanism (Scheme 8) can be definitely stated to be correct. The major product (41%) was a bright yellow solid formulated as the heterocyclic product (72) on the basis of its high resolution mass spectrum which was consistent with a molecular formula of $C_{14}H_{9}NO_{5}S$ and an i.r. spectrum which showed carbonyl absorption at 1750 and 1630 cm$^{-1}$.

Because of the unexpected formation of the 1H-indole-2,3-dione (isatin) derivative (72) it was of interest to obtain chemical evidence for its constitution (Scheme 19). A possible N-oxide structure for this product was readily excluded by its recovery unchanged after attempted hydrogenation over palladium-on-charcoal, conditions known$^{101}$ to readily reduce heterocyclic N-oxides to the parent heterocycle.

The presence of the benzenesulphonyloxy-substituent and the isatin nucleus was readily established by mild hydrolysis with aqueous alkali to afford a quantitative yield of a deep red compound whose 7-hydroxyisatin structure (75) is based on the following evidence. The compound gave analytical and mass spectral data consistent with the molecular formula $C_8H_5NO_3$. In addition its mass spectrum showed intense peaks at m/e 135 and 107 accurate mass measurement on which gave molecular ion formulae of $C_7H_5NO_2$ and $C_6H_5NO$ corresponding to fragmentation by sequential loss of two CO fragments. The i.r. spectrum of the compound showed absorption at 3360, 1740, and 1720 cm$^{-1}$ attributable to the NH group and the two carbonyl substituents of an isatin nucleus. In addition to the presence of two one-proton signals assignable to the protons of the NH and OH substituents in the structure (75), the $^1$H n.m.r. spectrum of the compound also showed a splitting pattern for the benzenoid
(i) ortho-phenylenediamine

(ii) NaOH, H₂O

(iii) Me₂SO₄, NaOH, H₂O

Scheme 19
protons in accord with the presence of a 1,2,3-trisubstituted benzene nucleus,\textsuperscript{102} thus pinpointing the C-7 position for the hydroxyl substituent in the isatin derivative (75) and hence for the benzenesulphonyloxy-substituent in the original compound (72). The structure of the hydroxyisatin derivative (75) was further verified by its reaction, in expected fashion, with ortho-phenylenediamine in glacial acetic acid to afford a virtually quantitative yield of a product which analysed correctly for C\textsubscript{14}H\textsubscript{9}N\textsubscript{3}O, and lacked i.r. carbonyl absorption but showed i.r. OH and NH absorption in accord with its formulation as 4-hydroxy-5H-indolo[2,3-b]quinoxaline (77).

The structure of the original benzenesulphonyloxyisatin derivative (72) was further verified by its reaction with aqueous alkali in the presence of dimethyl sulphate to give a high yield of a product which analysed correctly for a mono-methyl derivative of the hydroxyisatin (75) and whose spectroscopic properties are fully consistent with its formulation as 7-methoxyisatin (76). The formation of this compound from the benzenesulphonyloxyisatin (72) presumably involves initial hydrolysis to the hydroxyisatin (75) followed by methylation.

The benzenesulphonyloxyisatin (72) contrasted with the parent 7-hydroxyisatin (75) in its reaction with ortho-phenylenediamine. Thus, heating the 7-benzenesulphonyloxyisatin (72) with ortho-phenylenediamine in ethanol gave a high yield (95%) of a product (Scheme 19) which is assigned the imine structure (74) on the basis of the following evidence. It gave analytical and mass spectral data consistent with the molecular formula C\textsubscript{20}H\textsubscript{15}N\textsubscript{3}O\textsubscript{4}S while its i.r. spectrum showed absorption at 3460 and 3320 cm\textsuperscript{-1} due to a primary amino-group and carbonyl absorption at 1660 cm\textsuperscript{-1} consistent with the presence of a
cyclic amide group. The partial condensation of the benzenesulphonyloxyisatin (72) with ortho-phenylenediamine to give the imine (74) rather than the corresponding quinoxaline derivative is surprising in view of the reaction of the isatin derivative (75) with ortho-phenylenediamine to give the indoloquinoxaline (77) (see before). No attempt was made to cyclise the imine (74) to the corresponding quinoxaline derivative.

The thermal transformation of the benzenesulphonyldiazoketone (70) into the benzenesulphonyloxyisatin derivative (72) requires a deep-seated rearrangement (Scheme 20) which can be explained by a mechanism involving initial loss of nitrogen to give a carbene intermediate (78), Wolff rearrangement of which accounts for the concomitant formation of the ketene derivative (71) (see before). Interaction of the nitro-group with the carbene centre in the intermediate (78) would then afford a nitroso-intermediate (80) convertible as shown (Scheme 20) into a benzenesulphonyloxyisatogen derivative (82). Thermally-promoted migration of the phenylsulphonyl-group in the latter to give the N-benzenesulphonyloxyisatin derivative (83) followed by a [3,3]-sigmatropic rearrangement of this compound then accounts for the formation of 7-benzenesulphonyloxyisatin (72). Of course this mechanistic explanation (Scheme 20) is purely speculative and further studies will have to be carried out to obtain firm evidence for the reaction course suggested.
Scheme 20
2.5 Experimental

General experimental details are described in the Appendix.

5-Chloro-2-nitrobenzoic Acid (16c)

5-Chloro-2-nitrobenzoic acid (16c) was prepared by the nitration of 3-chlorobenzoic acid as described in the literature,\textsuperscript{103} yield 80\%, m.p. 128-130° (lit.,\textsuperscript{103} 139°), and was used without further purification.

Preparation of 2-Nitrobenzoyl Chloride Derivatives (17a-d)

(a) 2-Nitrobenzoyl Chloride (17a)

2-Nitrobenzoyl chloride (17a) was prepared by the reaction of 2-nitrobenzoic acid with thionyl chloride as described in the literature,\textsuperscript{104} yield 90\%, b.p. 106°/0.6mmHg (lit.,\textsuperscript{104} 152°/18mmHg), and was used without further purification.

(b) 4-Chloro-2-nitrobenzoyl Chloride (17d)

4-Chloro-2-nitrobenzoyl chloride (17d) was prepared by the reaction of 4-chloro-2-nitrobenzoic acid with thionyl chloride as described in the literature,\textsuperscript{105} yield 100\%, m.p. 28-30° (lit.,\textsuperscript{105} 34-36°), and was used without further purification.

(c) 5-Chloro-2-nitrobenzoyl Chloride (17c)

5-Chloro-2-nitrobenzoyl chloride (17c) was prepared by the reaction of 5-chloro-2-nitrobenzoic acid (16c) with thionyl chloride as described in the literature,\textsuperscript{106} yield 74\%, b.p. 150°/1.5mmHg (lit.,\textsuperscript{106} 167°/17mmHg), and was used without further
(d) 5-Methyl-2-nitrobenzoyl Chloride (17b)

5-Methyl-2-nitrobenzoyl chloride (17b) was prepared by the reaction of 5-methyl-2-nitrobenzoic acid with thionyl chloride as described in the literature,\textsuperscript{107} yield 95\%, m.p. 35-36\(^\circ\) (lit.,\textsuperscript{107} 46\(^\circ\)), and was used without further purification.

4-Nitrobenzoyl Chloride (62)

4-Nitrobenzoyl chloride (62) was prepared by the reaction of 4-nitrobenzoic acid with thionyl chloride as described in the literature,\textsuperscript{108} yield 92\%, m.p. 70-73\(^\circ\) (lit.,\textsuperscript{108} 75\(^\circ\)), and was used without further purification.

Preparation of Ethyl 2-Benzoyl-3-(2- and 4-nitrophenyl)-3-
oxopropanoates (18a-d and 63)

(a) Magnesium turnings (1.0 g, 0.04 mol) (previously well washed in anhydrous diethyl ether), absolute ethanol (1.0 ml) and carbon tetrachloride (0.2 ml) were stirred together for 5 min. The mixture was diluted with anhydrous diethyl ether (30.0 ml) and the resulting suspension was treated dropwise with stirring and gentle heating with a solution of ethyl benzoylacacetate (7.9 g, 0.04 mol) in absolute ethanol (4.1 ml) and anhydrous diethyl ether (5.2 ml). The mixture was heated under reflux for 5 h and the resulting solution of the magnesium enolate was then treated dropwise with stirring and gentle heating with a solution of the corresponding nitrobenzoyl
chloride (0.04 mol) in anhydrous diethyl ether (20.0 ml). Stirring and heating were continued for 30 min.

The mixture was cooled to room temperature, treated with stirring with aqueous 2M sulphuric acid (50.0 ml) and stirred at room temperature for 30 min then worked up as described for the individual reactions below.

(i) The mixture from 2-nitrobenzoyl chloride (17a) was filtered and the solid combined with a second crop obtained by extracting the aqueous mother liquor with diethyl ether and triturating the orange oil obtained with light petroleum, to give ethyl 2-benzoyl-3-(2-nitrophenyl)-3-oxopropanoate (18a) (total 11.3 g; 81%) which formed cream coloured prisms, m.p. 79-83°C, $\nu_{\text{max}}$ 1710 and 1670 (CO) and 1530 and 1350 (NO$_2$) cm$^{-1}$, identical (m.p. and i.r. spectrum) to a sample prepared as described in (b) below.

(ii) The mixture from 5-methyl-2-nitrobenzoyl chloride (17b) was separated, the aqueous layer was extracted with diethyl ether and the combined organic extracts were evaporated to give ethyl 2-(5-methyl-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18b) as a brown oil (14.3 g; 98%), $\nu_{\text{max}}$ 1710 and 1670 (CO) and 1520 and 1345 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 8.08-7.20 (10H, m, CH and ArH), 4.18 (2H, q, J6Hz, CH$_2$), 3.70 (2H, q, J6Hz, CH$_2$), 2.44 (3H, s, CH$_3$), 2.33 (3H, s, CH$_3$), 1.04 (3H, t, J6Hz, CH$_3$), and 0.67 (3H, t, J6Hz, CH$_3$) which was used without further purification.

(iii) The mixture from 5-chloro-2-nitrobenzoyl chloride (17c) was separated, the aqueous layer was extracted with diethyl ether and the combined organic extracts were evaporated to give ethyl 2-(5-chloro-2-nitrobenzoyl)-3-phenyl-3-oxo-
propanoate (18c) as a brown oil (14.8 g; 99%), \( \nu_{\text{max}} \) 1720 and 1670 (CO) and 1530 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta (\text{CDCl}_3) \) 8.15-7.25 (10H, m, CH and ArH), 4.50-3.60 (4H, m, CH\(_2\)), 1.09 (3H, t, J7Hz, CH\(_3\)), and 0.69 (3H, t, J7Hz, CH\(_3\)) which was used without further purification.

(iv) The mixture from 4-chloro-2-nitrobenzoyl chloride (17d) was separated, the aqueous layer was extracted with diethyl ether and the combined organic extracts were evaporated to give ethyl 2-(4-chloro-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18d) as an orange oil (15.4 g; 100%), \( \nu_{\text{max}} \) 1710 and 1670 (CO) and 1540 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta (\text{CDCl}_3) \) 8.15-7.25 (10H, m, CH and ArH), 4.17 (2H, q, J7Hz, CH\(_2\)), 3.73 (2H, q, J7Hz, CH\(_2\)), 1.12 (3H, t, J7Hz, CH\(_3\)), and 0.69 (3H, t, J7Hz, CH\(_3\)) which was used without further purification.

(v) The mixture from 4-nitrobenzoyl chloride (62) was separated, the aqueous layer was extracted with diethyl ether and the combined organic extracts were evaporated to give ethyl 2-benzoyl-3-(4-nitrophenyl)-3-oxopropanoate (63) (13.7 g; 98%), m.p. 74-75\(^\circ\) (lit., 86-87\(^\circ\)), \( \nu_{\text{max}} \) 1680 and 1650 (CO) and 1520 and 1350 (NO\(_2\)) cm\(^{-1}\) which was used without further purification.

(b) Ethyl 2-benzoyl-3-(2-nitrophenyl)-3-oxopropanoate (18a) was prepared by the reaction of 2-nitrobenzoyl chloride (17a) with the sodium salt of ethyl benzoylacette as described in the literature,\(^7\) yield 44%, m.p. 66-69\(^\circ\) (lit., 87-88\(^\circ\)), and was used without further purification.
Ethyl 2-Acetyl-3-(2-nitrophenyl)-3-oxopropanoate (67) Sodium Salt

Ethyl 2-acetyl-3-(2-nitrophenyl)-3-oxopropanoate (67) sodium salt was prepared by the reaction of ethyl acetoacetate with 2-nitrobenzoyl chloride (17a) as described in the literature,¹⁰⁹ yield 80%, and was used without further purification.

The Attempted Reaction of Ethyl 2-Benzoyl-3-(2-nitrophenyl)-3-oxopropanoates (18c and d) with Hydrazine Hydrate

A solution of the diketo-esters (18c and d) (1.5 g, 0.004 mol) in ethanol (10.0 ml) was treated with 100% hydrazine monohydrate (0.22 g, 0.0044 mol) and the mixture was heated under reflux for 1 h, then worked up as described for the individual reactions below.

(a) The mixture from ethyl 2-(4-chloro-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18d) was evaporated to give a red oil (1.6 g) which was shown by t.l.c. in diethyl ether-toluene (50:50) over silica to be an unresolvable multicomponent mixture which was not further investigated.

(b) The mixture from ethyl 2-(5-chloro-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18c) was evaporated to give a red oil (1.6 g) which was shown by t.l.c. in diethyl ether-toluene (50:50) over silica to be an unresolvable multicomponent mixture and was not further investigated.

The Preparation of 1-(2-Nitrophenyl)-3-phenylpropane-1,3-diones (20a-d)

The corresponding ethyl 2-benzoyl-3-(2-nitrophenyl)-3-
oxopropanoate (18a-d) (0.03 mol) was treated with aqueous 2.5M sulphuric acid (19.0 ml) and the mixture was heated under reflux for 4 h. The mixture was cooled to room temperature then worked up as described for the individual reactions below.

(a) The mixture from ethyl 2-benzoyl-3-(2-nitrophenyl)-3-oxopropanoate (18a) was treated with diethyl ether to precipitate a solid which was combined with a second crop obtained by extracting the aqueous mother liquor with diethyl ether and triturating the resulting brown oil with diethyl ether to give 1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (20a) (total 7.0 g; 87%) which formed light brown plates, m.p. 105-107° (lit., 74° 116°), \( \nu_{\text{max}} \) 1640-1600 br (CO) and 1530 and 1350 (NO\(_2\)) cm\(^{-1}\), which was used without further purification.

(b) The mixture from ethyl 2-(5-methyl-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18b) was treated with diethyl ether to precipitate a solid which was collected, washed with saturated aqueous sodium hydrogen carbonate solution, and combined with a second crop obtained by triturating the brown oil, recovered from the organic layer with diethyl ether, to give 1-(5-methyl-2-nitrophenyl)-3-phenylpropane-1,3-dione (20b) (total 6.6 g; 66%) as pale yellow needles, m.p. 110-111° (from toluene-light petroleum), \( \nu_{\text{max}} \) 1650-1600 br (CO) and 1520 and 1360 (NO\(_2\)) cm\(^{-1}\), \( \delta \) [(CD\(_3\))\(_2\)SO] 8.14-7.44 (8H, m, ArH), 7.01 (2H, s, CH\(_2\)), and 2.46 (3H, s, CH\(_3\)).

Found: C, 67.5; H, 4.5; N, 4.7%; M*, 283.
\( \text{C}_{16}\text{H}_{13}\text{NO}_{4} \) requires: C, 67.8; H, 4.6; N, 5.0%; M, 283.

Evaporation of the diethyl ether mother liquor yielded a
brown oil (1.4 g) from which no further identifiable material could be obtained.

Acidification of the sodium hydrogen carbonate washings with aqueous 2M hydrochloric acid followed by extraction with methylene chloride afforded a gum (0.7 g) which was shown by t.l.c. in diethyl ether over silica to be a five-component mixture. The gum was not further investigated.

(c) The mixture from ethyl 2-(5-chloro-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18c) was extracted with diethyl ether. The organic extract was washed with saturated aqueous sodium hydrogen carbonate and evaporated to give the crude product (6.5 g) which was crystallised to afford 1-(5-chloro-2-nitrophenyl)-3-phenylpropane-1,3-dione (20c) (3.5 g; 39%) which formed light brown needles, m.p. 123-124\(^\circ\) (from toluene-light petroleum), \(\nu_{\text{max}}\) 1640-1600 br (CO) and 1525 and 1360 (NO\(_2\)) cm\(^{-1}\), \(\delta (\text{CDCl}_3)\) 7.92-7.40 (8H, m, ArH) and 6.38 (2H, s, CH\(_2\)).

\[
\begin{align*}
\text{Found:} & \quad \text{C, 58.8; H, 3.4; N, 4.4%; M}^+ & \quad 303.02986. \\
\text{C}_{15}\text{H}_{10}\text{ClNO}_4 \text{requires:} & \quad \text{C, 59.3; H, 3.3; N, 4.6%; M, 303.02983.}
\end{align*}
\]

Evaporation of the toluene-light petroleum mother liquor gave an oil (3.0 g) which was shown by t.l.c. in methylene chloride over silica to be a four-component mixture and was not further investigated.

Acidification of the aqueous sodium hydrogen carbonate washings with aqueous 2M hydrochloric acid and extraction with methylene chloride yielded a brown gum (0.3 g) which was shown by t.l.c. in diethyl ether over silica to be a three-component mixture. The gum was not further investigated.
(d) The mixture from ethyl 2-(4-chloro-2-nitrobenzoyl)-3-phenyl-3-oxopropanoate (18d) was treated with diethyl ether to precipitate a solid which was collected, washed with saturated aqueous sodium hydrogen carbonate solution and combined with a second crop obtained by trituration the brown oil recovered from the organic layer with diethyl ether to give 1-(4-chloro-2-nitrophenyl)-3-phenylpropane-1,3-dione (20d) (total 6.5 g; 71%) which formed yellow plates, m.p. 123-124° (from toluene-light petroleum), ν_max 1640-1600 br (CO) and 1530 and 1350 (NO_2) cm^{-1}, δ(CDC1_3) 7.93-7.25 (8H, m, ArH) and 6.43 (2H, s, CH_2).

Found: C, 59.4; H, 3.4; N, 4.6%; m/e 305/303.

C_{15}H_{8}ClN_{3}O_{4} requires: C, 59.3; H, 3.3; N, 4.6%; M, 320/334.

Evaporation of the diethyl ether mother liquor gave a brown oil (1.7 g) which was shown by t.l.c. in toluene over alumina to be an unresolvable multicomponent mixture. The oil was not further investigated.

Acidification of the aqueous sodium hydrogen carbonate washings with aqueous 2M hydrochloric acid followed by extraction with methylene chloride gave a brown oil (0.5 g) which was shown by t.l.c. in toluene over silica to be an unresolvable four-component mixture. The mixture was not further investigated.

1-(4-Nitrophenyl)-3-phenylpropane-1,3-dione (64)

1-(4-Nitrophenyl)-3-phenylpropane-1,3-dione (64) was prepared from ethyl 2-benzoyl-3-(4-nitrophenyl)-3-oxopropanoate (63) as described in the literature, yield 59%, m.p. 149-150°
1-(2-Nitrophenyl)butane-1,3-dione (68a)

1-(2-Nitrophenyl)butane-1,3-dione (68a) was prepared from ethyl 2-acetyl-3-(2-nitrophenyl)-3-oxopropanoate (67) sodium salt as described in the literature,\textsuperscript{98} yield 48\%, m.p. 49-50\° (lit.,\textsuperscript{98} 53-58\°), and was used without further purification.

Ethyl 3-(2-Nitrophenyl)-3-oxopropanoate (68b)

Ethyl 3-(2-nitrophenyl)-3-oxopropanoate (68b) was prepared from ethyl 2-acetyl-3-(2-nitrophenyl)-3-oxopropanoate (67) sodium salt as described in the literature,\textsuperscript{110} yield 22\%, m.p. 23-25\° (lit.,\textsuperscript{110} 25-26\°), and was used without further purification.

1-(2-Nitrophenyl)ethanone (53)

1-(2-Nitrophenyl)ethanone (53) was prepared by the condensation of 2-nitrobenzoyl chloride (17a) with diethyl malonate followed by hydrolysis and decarboxylation of the resulting condensate as described in the literature,\textsuperscript{98} yield 64\%, b.p. 156-159\°/13\,mmHg (lit.,\textsuperscript{98} 158-159\°/13\,mmHg), and was used without further purification.

2-Bromo-1-(2-nitrophenyl)ethanone (54b)

2-Bromo-1-(2-nitrophenyl)ethanone (54b) was prepared by the bromination of 1-(2-nitrophenyl)ethanone (53) as described in the literature,\textsuperscript{92} yield 78\%, m.p. 46-48\° (lit.,\textsuperscript{92} 54-55\°), and was used without further purification.
2-Benzanesulphonyl-1-(2-nitrophenyl)ethanone (56)

2-Benzanesulphonyl-1-(2-nitrophenyl)ethanone (56) was prepared from 2-bromo-1-(2-nitrophenyl)ethanone (54b) as described in the literature,\textsuperscript{93} yield 74%, m.p. 81-83\textdegree (lit.\textsuperscript{93} 84-86\textdegree), and was used without further purification.

Preparation of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones (21a-d)

A suspension of the corresponding finely powdered 1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (20a-d) (0.01 mol) in absolute ethanol (20.0 ml) was stirred and treated in one portion with triethylamine (1.1 g, 0.011 mol) then dropwise with tosyl azide (2.3 g, 0.11 mol). The mixture was stirred at room temperature for 15 min then at -78\textdegree (acetone-solid CO\textsubscript{2} bath) for 1 h, and worked up as described for the individual reactions below.

(a) The mixture from 1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (20a) was allowed to come to room temperature then concentrated to half volume to give a solid which was combined with a second crop obtained by evaporating the ethanolic filtrate, redissolving the oily residue in methylene chloride, washing the extract with aqueous 2M sodium hydroxide and trituration of the oil obtained on evaporation with light petroleum-diethyl ether, to give the diazodiketone (21a) (2.5 g; 85%), m.p. 63-68\textdegree (lit.\textsuperscript{80} 61-62\textdegree), $\nu_{\text{max}}$ 2140 and 2120 (N=\textequiv N), 1640 (CO), and 1530 and 1355 (NO\textsubscript{2}) cm\textsuperscript{-1}. The diazodiketone (21a) was used without further purification.

Acidification of the aqueous alkaline washings with
aqueous 2M hydrochloric acid followed by extraction with ethyl acetate gave toluene-\(p\)-sulphonamide (1.3 g; 75\%), m.p. 124-125° (lit.,\textsuperscript{111} 138-139°), identical (i.r. spectrum) to an authentic sample.

(b) The mixture from 1-(5-methyl-2-nitrophenyl)-3-phenylpropane-1,3-dione (20b) was allowed to come to room temperature and the precipitated solid was collected and combined with a second crop obtained by evaporating the filtrate, redissolving the oily residue in methylene chloride, washing with aqueous 2M sodium hydroxide and triturating the oil obtained from the methylene chloride phase with diethyl ether to give 2-diazo-1-(5-methyl-2-nitrophenyl)-3-phenylpropane-1,3-dione (21b) (total 2.5 g; 81\%) which formed pale yellow plates, m.p. 119-120° (from ethanol-dimethylformamide), \(\nu_{\text{max}}\) 2120 (\(\mathsf{\overset{\neq}{N}}\)), 1650 and 1630 (CO), and 1500 and 1340 (NO\(_2\)) cm\(^{-1}\), \(\delta[(\text{CD}_3)_2\text{SO}]\) 8.09 (1H, d, J8Hz, H-3), 7.88-7.36 (7H, m, ArH), and 2.41 (3H, s, CH\(_3\)).

\textbf{Found:} C, 62.4; H, 3.6; N, 13.4\%; (M\(^+\)-N\(_2\)), 281. 
\textit{C}_{16}\text{H}_{11}\text{N}_3\text{O}_4 \text{requires:} \ C, 62.1; \ H, 3.6; \ N, 13.6\%; \ M, 309.

Evaporation of the diethyl ether mother liquor gave a brown oil (0.7 g) from which no further identifiable material could be obtained.

Acidification of the aqueous sodium hydroxide washings with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate gave toluene-\(p\)-sulphonamide (1.0 g; 58\%), m.p. 125-127° (lit.,\textsuperscript{111} 138-139°), identical (i.r. spectrum) to an authentic sample.
(c) The mixture from 1-(5-chloro-2-nitrophenyl)-3-phenyl-propane-1,3-dione (20c) was allowed to come to room temperature then concentrated to half volume and the precipitated solid was collected and combined with a second crop obtained by evaporating the filtrate, redissolving the oily residue in methylene chloride, washing with aqueous 2M sodium hydroxide, and re-evaporation, to give 1-(5-chloro-2-nitrophenyl)-2-diazo-3-phenylpropane-1,3-dione (21c) (total 2.6 g; 79%) which formed light brown needles, m.p. 124-125° (from ethanol-glacial acetic acid), v_{max} 2180 and 2120 (N≡N), 1650 and 1620 (CO), and 1510 and 1340 (NO2) cm⁻¹, δ[(CD₃)₂SO] 8.23 (1H, d, J8Hz, H-3) and 7.87-7.37 (7H, m, ArH).

**Found:**  C, 54.6; H, 2.4; N, 12.7%; (M⁻-NO₂) 285/283.

**C₁₅H₈ClN₃O₄ requires:**  C, 54.6; H, 2.3; N, 12.6%; M, 329/331.

Acidification of the aqueous sodium hydroxide washings with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate gave toluene-ž-sulphonamide (1.0 g; 58%), m.p. 113-115° (lit.,¹¹¹ 138-139°), identical (i.r. spectrum) to an authentic sample.

(d) The mixture from 1-(4-chloro-2-nitrophenyl)-3-phenyl-propane-1,3-dione (20d) was allowed to come to room temperature.

(i) In one run evaporation of the mixture gave a red oil (5.6 g) which was treated with diethyl ether-toluene to afford toluene-ž-sulphonamide (0.85 g; 50%), m.p. 124-125° (lit.,¹¹¹ 138-139°), identical (i.r. spectrum) to an authentic sample.

Evaporation of the diethyl ether-toluene mother liquor yielded a red oil (4.4 g) which was triturated with diethyl ether to afford 1-(4-chloro-2-nitrophenyl)-2-diazo-3-phenyl-
propane-1,3-dione (21d) (2.3 g; 71%) as yellow plates, m.p. 92-93° (from ethanol), \( \nu_{\text{max}} \) 2150 and 2120 (\( \tilde{N}=\tilde{N} \)), 1640 (CO), and 1525 and 1355 (NO\(_2\)) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.27 (1H, d, J2Hz, H-3), 7.95 (1H, dd, J\(_{\text{ortho}}\) 8Hz, J\(_{\text{meta}}\) 2Hz, H-5), and 7.84-7.36 (6H, m, ArH).

**Found:** C, 54.7; H, 2.5; N, 12.4%; (M\(^+\)-N\(_2\)/-CO\(_2\)), 259/257.

**C\(_{15}\)H\(_8\)ClN\(_3\)O\(_4\):** C, 54.6; H, 2.4; N, 12.7%; M, 329 requires: C, 54.6; H, 2.4; N, 12.7%; M, 329.

Evaporation of the diethyl ether mother liquor gave a brown oil (0.3 g) which was shown by t.l.c. in diethyl ether over silica to be a two component mixture. The oil was not further investigated.

(ii) In another run evaporation of the mixture yielded a red oil (6.3 g) which was redissolved in methylene chloride and the solution washed with aqueous 2M sodium hydroxide. Evaporation of the organic phase afforded a gum which was treated with diethyl ether-light petroleum to give a solid. This was combined with a second crop, obtained by chromatography in toluene over alumina of the red gum obtained by evaporating the diethyl ether-light petroleum mother liquor to give 2-diazo-1-(4-chloro-2-nitrophenyl)ethanone (24) (total 1.7 g; 73%) which formed pale brown needles, m.p. 118-119° (from ethanol), \( \nu_{\text{max}} \) 2170 and 2130 (\( \tilde{N}=\tilde{N} \)), 1610 (CO), and 1535 and 1375 (NO\(_2\)) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.30-7.36 (3H, m, ArH) and 6.72 (1H, s, CH).

**Found:** C, 43.0; H, 1.8; N, 18.3%; (M\(^+\)-CHN\(_2\)), 186/184.

**C\(_8\)H\(_4\)ClN\(_3\)O\(_3\):** requires: C, 42.7; H, 1.8; N, 18.6%; M, 225/227.

Acidification of the aqueous sodium hydroxide washings
with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded toluene-\(p\)-sulphonamide (1.7 g; 99%), m.p. 112-113° (lit., \(111\) 138-139°), identical (i.r. spectrum) to an authentic sample.

The Attempted Preparation of 2-Diazo-1-(4-nitrophenyl)-3-phenylpropane-1,3-dione (65)

A suspension of finely powdered 1-(4-nitrophenyl)-3-phenylpropane-1,3-dione (64) (4.0 g, 0.015 mol) in absolute ethanol (30.0 ml) was stirred and treated in one portion at room temperature with triethylamine (1.7 g, 0.017 mol) then dropwise with tosyl azide (3.3 g, 0.017 mol). The mixture was stirred at room temperature for 22 h then evaporated to afford a dark red oil (8.3 g) which was redissolved in methylene chloride and the solution washed with aqueous 2M sodium hydroxide. Evaporation of the organic phase yielded a dark orange oil (4.5 g) which was shown by t.l.c. in methylene chloride over alumina to be an unresolvable multicomponent mixture and was not further investigated.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded toluene-\(p\)-sulphonamide (2.6 g; 95%), m.p. 114-116° (lit., \(111\) 138-139°), identical (i.r. spectrum) to an authentic sample.

The Attempted Preparation of 2-Diazo-1-(2-nitrophenyl)butane-1,3-dione (69a)

(a) A solution of 1-(2-nitrophenyl)butane-1,3-dione (68a)
(4.1 g, 0.02 mol) in anhydrous methylene chloride (50.0 ml) was treated with piperidine (1.7 g, 0.02 mol), cooled to 0-3° (ice-salt bath) and treated dropwise with stirring, with tosyl azide (4.4 g, 0.022 mol) over 1-2 min. The mixture was stirred at 0-3° for 0.5 h then allowed to come to room temperature. The mixture was washed with aqueous 0.2M potassium hydroxide, and the organic phase was evaporated to give a brown oil (5.3 g) which was chromatographed in toluene over alumina to yield a solid (1.5 g), m.p. 62-65°, \( \nu_{\text{max}} \) 2100 (N=\( \equiv \)N), 1610 (CO), and 1530 and 1350 (NO\(_2\)) \( \text{cm}^{-1} \), which was shown by t.l.c. in diethyl ether over alumina to be an unresolvable multicomponent mixture and was not further investigated.

Further elution with toluene afforded an unidentified brown oil (3.3 g).

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid yielded toluene-p-sulphonamide (1.8 g; 53%), m.p. 92-93° (lit., 111 138-139°), identical (i.r. spectrum) to an authentic sample.

Extraction of the aqueous acidic mother liquor with ethyl acetate gave an oil (1.5 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture. This was not further investigated.

(b) A suspension of finely powdered 1-(2-nitrophenyl)butane-1,3-dione (68a) (2.1 g, 0.01 mol) in absolute ethanol (20.0 ml) was stirred and treated in one portion with triethylamine (1.1 g, 0.011 mol) then dropwise with tosyl azide (2.3 g, 0.011 mol) and the mixture was stirred at room temperature for 15 min then at -78° (acetone-solid CO\(_2\) bath) for 1 h. The mixture
was allowed to come to room temperature and evaporated to give a red oil (4.9 g) which was redissolved in methylene chloride and the solution washed with aqueous 2M sodium hydroxide. Evaporation of the organic phase gave an orange oil (3.1 g) which was chromatographed over silica. Elution with methylene chloride-light petroleum/b.p. 40-60° (50:50) afforded tosyl azide as an oil (0.8 g) which was identical (i.r. spectrum) to an authentic sample.

Elution with methylene chloride-diethyl ether (40:60) yielded an orange oil (2.2 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable three-component mixture and was not further investigated.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded toluene-p-sulphonamide (0.7 g; 41%), m.p. 121-122° (lit., 111 138-139°), identical (i.r. spectrum) to an authentic sample.

The Attempted Preparation of Ethyl 2-Diazo-3-(2-nitrophenyl)-3-oxopropanoate (69b)

A suspension of finely powdered ethyl 3-(2-nitrophenyl)-3-oxopropanoate (68b) (2.4 g, 0.01 mol) in absolute ethanol (20.0 ml) was stirred and treated in one portion with triethylamine (1.1 g, 0.011 mol) then dropwise with tosyl azide (2.3 g, 0.011 mol). The mixture was stirred at room temperature for 15 min then at -78° (acetone-solid CO₂ bath) for 1 h. The mixture was allowed to come to room temperature and evaporated to yield a brown gum (5.2 g) which was redissolved in methylene chloride and the solution washed with aqueous 2M sodium
hydroxide. Evaporation of the organic phase afforded an oil (3.9 g) which was treated with diethyl ether to give a solid (1.3 g). This was shown by t.l.c. in toluene over silica to be a multicomponent mixture and was not further investigated.

Evaporation of the ethereal mother liquor gave a brown oil (1.3 g) which was shown by t.l.c. in toluene over silica to be a multicomponent mixture and was not further investigated.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded toluene-$p$-sulphonamide (1.4 g; 82%), m.p. 125-126$^\circ$ (lit.,$^{111}$ 138-139$^\circ$), identical (i.r. spectrum) to an authentic sample.

2-Benzenesulphonyl-2-diazo-1-(2-nitrophenyl)ethanone (70)

A suspension of finely powdered 2-benzenesulphonyl-1-(2-nitrophenyl)ethanone (56) (12.2 g, 0.04 mol) in absolute ethanol (80.0 ml) was stirred and treated in one portion with stirring with triethylamine (4.5 g, 0.044 mol) then dropwise with tosyl azide (9.0 g, 0.044 mol). The mixture was stirred at room temperature for 15 min then at -78$^\circ$ (acetone-solid CO$_2$ bath) for 1 h. The mixture was allowed to come to room temperature and the precipitated solid was collected to give 2-benzenesulphonyl-2-diazo-1-(2-nitrophenyl)ethanone (70) (12.3 g; 93%) which formed orange plates (from ethanol-dimethylformamide), m.p. 121-122$^\circ$, $\nu_{\text{max}}$ 2130 (N≡N), 1650 (CO), and 1530 and 1350 (NO$_2$) cm$^{-1}$, $\delta$(CD$_3$)$_2$SO 8.25-7.47 (m, ArH).

Found: C, 50.4; H, 2.7; N, 12.5%; M, 331.
C$_{14}$H$_9$N$_3$O$_5$S requires: C, 50.8; H, 2.7; N, 12.7%; M, 331.
The ethanolic filtrate was evaporated and the oily residue was redissolved in methylene chloride and the solution washed with aqueous 2M sodium hydroxide, and evaporated to give a red oil (3.9 g) which was shown by t.l.c. in diethyl ether over silica to be a multicomponent mixture. The oil was not further investigated.

Acidification of the sodium hydroxide washings with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded toluene-\(\text{P}\)-sulphonamide (6.0 g; 88%), m.p. 124-125° (lit., 111 138-139°), identical (i.r. spectrum) to an authentic sample.

The Thermolysis of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-diones (21a-d) in Toluene

A solution of the corresponding 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a-d) (0.004 mol) in anhydrous toluene (40.0 ml) was heated under reflux for 1 h, and the individual reactions were then worked up as described for the individual reactions below.

(a) The mixture from 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) was evaporated to give a yellow gum (1.0 g) of which (0.48 g) was chromatographed over silica.

Elution with toluene afforded 2-phenyl-3,1-benzoaxin-4-one (22a) (0.25 g; 56%) which formed colourless needles, m.p. 119-120° (from light petroleum/b.p. 80-100°) (lit., 82 122-123°), \(v_{\text{max}}\) 1770 (\(\text{C}=\text{O}\)) cm\(^{-1}\).

\[\text{Found: } \text{C}, 75.1; \text{H}, 3.9; \text{N}, 6.2%; \text{M}^+, 223.\]

\[\text{Calc.: for } \text{C}_{14}\text{H}_9\text{NO}_2: \text{C}, 75.3; \text{H}, 4.1; \text{N}, 6.3%; \text{M}, 223.\]
Subsequent elution with toluene-diethyl ether (90:10) followed by ethyl acetate gave gums (total 0.23 g) from which no identifiable material could be obtained.

The remainder of the original yellow gum (0.52 g) was chromatographed over alumina and elution with toluene afforded 3-benzoyl-2,1-benzisoxazole (26) (0.06 g; 13%), m.p. 95-96°, identical (m.p. and i.r. spectrum) to a sample prepared later.

Subsequent elution with toluene-diethyl ether (50:50) followed by ethyl acetate gave gums (total 0.15 g) from which no identifiable material could be obtained.

(b) The mixture from 2-diazo-1-(5-methyl-2-nitrophenyl)-3-phenylpropane-1,3-dione (21b) was evaporated to afford an orange oil (1.2 g) which was chromatographed over silica.

Elution with toluene yielded 6-methyl-2-phenyl-3,1-benzoazain-4-one (22b) (0.4 g; 42%) which formed light orange needles, m.p. 97-98° (from toluene-light petroleum), νmax 1760 (CO) cm⁻¹, δ(CDCl₃) 8.38-7.04 (8H, m, ArH) and 2.03 (3H, s, CH₃).

Found: C, 75.4; H, 4.6; N, 5.8%; M⁺, 237.
C₁₅H₁₁NO₂ requires: C, 75.9; H, 4.7; N, 5.9%; M, 237.

Subsequent elution with toluene-methylene chloride followed by methylene chloride-diethyl ether, then diethyl ether gave only gums (total 0.5 g) which were shown by t.l.c. to be unresolvable multicomponent mixtures and were not further investigated.

(c) The mixture from 1-(5-chloro-2-nitrophenyl)-2-diazo-3-phenylpropane-1,3-dione (21c) was evaporated to yield a brown gum (1.1 g). This was treated with diethyl ether-light
petroleum to give 6-chloro-2-phenyl-3,1-benzoxazin-4-one (22c) (0.33 g; 32%) which formed pale yellow needles, m.p. 195-196 ° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 1760 (CO) cm$^{-1}$, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.28-7.50 (m, ArH).

Found: C, 64.7; H, 3.0; N, 5.4%; M$^+$, 259.0212 and 257.0243.

C$_{14}$H$_8$ClNO$_2$ requires: C, 65.2; H, 3.1; N, 5.4%; M, 259.0214 and 257.0243.

Evaporation of the diethyl ether-light petroleum mother liquor afforded a brown oil (0.75 g) from which no identifiable material could be obtained by preparative t.l.c. over silica in toluene.

(d) The mixture from 1-(4-chloro-7-nitrophenyl)-2-diazo-3-phenylpropane-1,3-dione (21d) was evaporated to give an orange oil (1.1 g) which was chromatographed over silica.

Elution with methylene chloride afforded 7-chloro-2-phenyl-3,1-benzoxazin-4-one (22d) (0.5 g; 49%) which formed colourless plates, m.p. 197-198 ° (from toluene-light petroleum/ b.p. 80-100 °), $\nu_{\text{max}}$ 1765 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 8.30-7.18, (m, ArH).

Found: C, 65.0; H, 3.1; N, 5.4%; M$^+$, 259/257.

C$_{14}$H$_8$ClNO$_2$ requires: C, 65.2; H, 3.1; N, 5.4%; M, 257.0259.

Further elution with methylene chloride followed by methylene chloride-diethyl ether, then diethyl ether, and finally methanol gave only a series of gums and oils (total 0.7 g) which were shown by t.l.c. to be unresolvable multi-component mixtures and were not further investigated.
N-Benzoylanthranilic Acid (23a)

A solution of 2-phenyl-3,1-benzoxazin-4-one (22a) (0.22 g, 0.001 mol) in ethanol (10.0 ml) was treated with aqueous 2M sodium hydroxide (2.5 ml) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and acidified with aqueous 2M hydrochloric acid. Extraction with ethyl acetate yielded N-benzoylanthranilic acid (23a) (0.16 g; 66%), m.p. 171-172°C (from toluene) (lit., 112 177°C).

Found: M+ 241.
Calc. for C14H11NO3: M, 241.

2-Nitrophenylacetyl Chloride (40)

A slurry of 2-nitrophenylacetic acid (19.8 g, 0.12 mol) and thionyl chloride (freshly distilled from quinoline) (17.2 g, 0.15 mol) was stirred and heated at 50°C for 1 h by which time all of the suspended solid had dissolved. Evaporation of the mixture gave 2-nitrophenylacetyl chloride (40) (24.0 g; 100%) as a brown oil, νmax 1730 (CO) and 1520 and 1340 (NO2) cm⁻¹, which was used without further purification.

2-(2-Nitrophenyl)-1-phenylethanone (41)

2-(2-Nitrophenyl)-1-phenylethanone (41) was prepared by the aluminium trichloride catalysed reaction of 2-nitrophenylacetyl chloride (40) with benzene as described in the literature, 86 yield 74%, m.p. 68-70°C (lit., 86 79-81°C), and was used without further purification.

The Attempted Preparation of 3-Benzoyl-2,1-benzisoxazole (26) from 2-(2-Nitrophenyl)-1-phenylethanone (41)

(a) Finely powdered 2-(2-nitrophenyl)-1-phenylethanone (41)
(1.2 g, 0.005 mol) was added with stirring and ice-cooling to concentrated sulphuric acid (5.0 ml) and the mixture was stirred and heated at 110° (oil bath) for 1 h. The mixture was then treated with ice and methylene chloride and filtered to give a solid which was treated with saturated aqueous sodium hydrogen carbonate solution to give unreacted 2-(2-nitrophenyl)-1-phenylethanone (41) (0.08 g; 7%), m.p. 75-80°, identical (m.p. and i.r. spectrum) to an authentic sample.

The methylene chloride layer was separated, washed with saturated aqueous sodium chloride and evaporated to give 2,1-benzisoxazole (42) as an oil (0.13 g; 22%), δ(CDCls) 9.07 (1H, s, H-3) and 7.72-6.84 (4H, m, ArH).

Found: M⁺, 119.
Calc. for C₇H₅NO: M, 119.
which was identical (¹H n.m.r. spectrum) to an authentic sample.¹¹³

Acidification of the aqueous sodium hydrogen carbonate washings with aqueous 2M hydrochloric acid followed by extraction with methylene chloride gave benzoic acid (0.1 g; 16%), m.p. 115-117° (lit.¹¹⁴ 122°), which was identical (m.p. and i.r. spectrum) to an authentic sample.

Neutralisation of the original aqueous sulphuric acid mother liquor with solid sodium hydrogen carbonate followed by solid sodium acetate and extraction with methylene chloride yielded only a negligible amount of gum.

(b) Finely powdered 2-(2-nitrophenyl)-1-phenylethanone (41) (1.2 g, 0.005 mol) was added with stirring and ice-cooling to concentrated sulphuric acid (5.0 ml). The mixture was stirred
at room temperature for 1 h, then treated with ice and extracted with methylene chloride to give a brown solid (0.87 g) which was washed with saturated aqueous sodium hydrogen carbonate to yield unreacted 2-(2-nitrophenyl)-1-phenylethanone (41) (0.8 g; 68%), m.p. 65-67°, which was identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

(c) Finely powdered 2-(2-nitrophenyl)-1-phenylethanone (41) (1.2 g, 0.005 mol) was added with stirring and ice-cooling to concentrated sulphuric acid (5.0 ml) and the mixture was stirred and heated at 50° (water bath) for 1 h. The mixture was treated with ice and extracted with methylene chloride to give a brown solid (1.3 g) which was washed with saturated aqueous sodium hydrogen carbonate to yield unreacted 2-(2-nitrophenyl)-1-phenylethanone (41) (0.76 g; 63%), m.p. 72-75°, which was identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

(d) Finely powdered 2-(2-nitrophenyl)-1-phenylethanone (41) (1.2 g, 0.005 mol) was added with stirring and ice-cooling to polyphosphoric acid (5.0 ml) and the mixture was then stirred and heated at 80° (oil bath) for 1 h. The mixture was diluted with water to yield a brown solid (1.5 g) which was washed with saturated aqueous sodium hydrogen carbonate to yield unreacted 2-(2-nitrophenyl)-1-phenylethanone (41) (1.0 g; 85%), m.p. 75-80°, which was identical (m.p. and i.r. spectrum) to an authentic sample prepared before.
2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (47)

2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (47) was prepared by the bromination of 2-(2-nitrophenyl)-1-phenylethanone (41) as described in the literature,\(^8\) yield 85\%, m.p. 106-108\(^\circ\) (lit.,\(^9\) 115-116\(^\circ\)), and was used without further purification.

The Attempted Preparation of 3-Benzoyl-2,1-benzisoxazole (26) from 2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (47)

(a) A solution of 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (47) (0.64 g, 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 6 h. Evaporation of the mixture gave a brown gum which was treated with diethyl ether to yield 5-bromo-2-phenylindolinone 1-N-oxide (51) (0.35 g; 58\%) which formed orange plates, m.p. 190-191\(^\circ\) (from toluene), \(\nu_{\text{max}}\) 1725 (CO) cm\(^{-1}\), \(\delta(\text{CDCl}_3)\), 8.70-8.50 (2H, m, ArH), 7.86-7.22 (6H, m, ArH).

Found: C, 55.6; H, 2.6; N, 4.8\%; M\(^+\), 303/301 and 286/284.

\(\text{C}_{14}\text{H}_8\text{BrNO}_2\) requires: C, 55.6; H, 2.7; N, 4.6\%; M\(^+\), 303/301 and 286/284.

Evaporation of the diethyl ether mother liquor afforded a red gum (0.3 g) which was shown by t.l.c. in toluene over silica to be a multicomponent mixture and was not further investigated.

(b) Solutions of 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (47) (0.64 g, 0.002 mol) in dry acetonitrile (10.0 ml) and silver nitrate (0.37 g, 0.0022 mol) in dry acetonitrile (10.0 ml) were mixed and the mixture was heated under reflux for
0.5 h. The mixture was cooled, filtered to remove the inorganic residue, and the filtrate evaporated to yield a brown oil (0.49 g) which was treated with diethyl ether-light petroleum/b.p. 40-60° to give unreacted 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (47) (0.19 g; 30%), m.p. 98-101° (lit., 115-116°), which was identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the diethyl ether-light petroleum mother liquor gave a brown gum (0.3 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture. The gum was not further investigated.

(c) A solution of 2-bromo-2-(2-nitrophenyl)-1-phenylethanone (47) (0.64 g, 0.002 mol) and fused sodium acetate (0.18 g, 0.0022 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1 h. Evaporation of the mixture yielded a brown gum which was treated with water (5.0 ml) and extracted with methylene chloride. Evaporation of the organic extract yielded a dark brown gum (0.44 g) which was treated with diethyl ether to afford 1-benzoyl-2,1-benzisoxazol-3-one (52) (0.1 g; 21%) which formed cream-coloured needles, m.p. 153-154° (from ethanol-dimethylformamide) (lit., 153-154°), $\nu_{\text{max}}$ 1790 and 1680 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.14-7.44 (,m, ArH).

Found: C, 70.0; H, 3.9; N, 5.6%; m/e 239 (M$^+$), 223 (M$^+$-16), 195 (M$^+$-CO$_2$), and 105 (M$^+$-C$_7$H$_4$NO$_2$).

Calc. for C$_{14}$H$_9$NO$_3$: C, 70.3; H, 3.8; N, 5.9%; M, 239.

Evaporation of the diethyl ether mother liquor gave a brown gum (0.32 g) which was shown by t.l.c. in toluene over silica to be an unresolvable multicomponent mixture and was not further investigated.
The Attempted Preparation of 2,1-Benzisoxazole-3-carboxylic Acid (38a) from 2-Benzenesulphonyl-1-(2-nitrophenyl)ethanone (56)

2-Benzanesulphonyl-1-(2-nitrophenyl)ethanone (56) (0.61 g, 0.002 mol) was heated under reflux with aqueous 1M sodium hydroxide (2.0 ml) for 4 h. Extraction with methylene chloride gave a solid which was combined with a second crop obtained by acidification of the aqueous phase with aqueous 2M hydrochloric acid and extraction with methylene chloride, to give unreacted 2-benzenesulphonyl-1-(2-nitrophenyl)ethanone (56) (total 0.49 g; 80%), m.p. 73-74°, identical (m.p. and i.r. spectrum) to an authentic sample.

2-Chloro-1-(2-nitrophenyl)ethanone (54a)

A solution of 1-(2-nitrophenyl)ethanone (53) (1.7 g, 0.01 mol) in glacial acetic acid (10.0 ml) was treated with sulphuryl chloride (1.4 g, 0.01 mol) and the mixture was heated under reflux for 2 h. A second portion of sulphuryl chloride (1.4 g, 0.01 mol) in glacial acetic acid (2.0 ml) was added and heating under reflux was continued for a further 2 h. Evaporation of the mixture yielded a brown oil (2.8 g) which was dissolved in methylene chloride and the solution washed with saturated aqueous sodium hydrogen carbonate solution. Evaporation of the organic phase gave an orange oil (1.3 g) which when treated with diethyl ether yielded 2-chloro-1-(2-nitrophenyl)-ethanone (54a) (1.1 g; 53%), m.p. 39-40° (lit., 9 66-67°), which was used without further purification.

Evaporation of the diethyl ether mother liquor gave a negligible amount of gum.
**Ethyl 2-Nitrophenylacetate (37)**

2-Nitrophenylacetyl chloride (40) was dissolved in absolute ethanol (150 ml) and the solution was left at room temperature for 2 h. Evaporation of the solution yielded a brown gum which was dissolved in methylene chloride and the solution washed with saturated aqueous sodium hydrogen carbonate solution. Evaporation of the organic phase afforded ethyl 2-nitrophenylacetate (37) (22.7 g; 91%), m.p. 62-63° (lit., 115-69°), ν_{max} 1740 (CO), and 1540 and 1350 (NO₂) cm⁻¹, which was used without further purification.

**2,1-Benzisoxazole-3-carboxylic Acid (38a)**

(a) A suspension of 2-chloro-1-(2-nitrophenyl)ethanone (54a) (0.8 g, 0.004 mol) in aqueous 1M sodium hydroxide (4.0 ml) was heated under reflux for 4.5 h by which time solution was complete. The hot solution was clarified with charcoal and the cooled filtrate was extracted with methylene chloride to give the unreacted starting-material (54a) (0.4 g; 50%), m.p. 41-45°, which was identical (m.p. and i.r. spectrum) to an authentic sample.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with methylene chloride gave an intractable brown oil (0.1 g) which was not further investigated.

(b) A solution of 2-chloro-1-(2-nitrophenyl)ethanone (54a) (0.6 g, 0.003 mol) in ethanol (5.0 ml) was treated with aqueous 1M sodium hydroxide (2.0 ml) and the mixture was heated under reflux for 6 h. Evaporation of the mixture, treatment
with water (5.0 ml) and extraction with ethyl acetate afforded a brown oil (0.36 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

Acidification of the aqueous alkaline phase with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate yielded 2,1-benzisoxazole-3-carboxylic acid (38a) (0.02 g; 4%), m.p. 170-173°, identical (m.p. and i.r. spectrum) to a sample prepared in (d) later.

(c) 2-Bromo-1-(2-nitrophenyl)ethanone (54b) (0.48 g, 0.002 mol) was heated under reflux with aqueous 1M sodium hydroxide (4.0 ml) for 5 h. Extraction of the mixture with methylene chloride gave unreacted 2-bromo-1-(2-nitrophenyl)ethanone (54b) as an oil (0.16 g; 32%) which was identical (i.r. spectrum) to an authentic sample.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with ethyl acetate afforded a gum which was treated with ethanol to yield 2,1-benzisoxazole-3-carboxylic acid (38a) (0.02 g; 4%), m.p. 146-150°, identical (m.p. and i.r. spectrum) to a sample prepared in (d) later.

Evaporation of the ethanol mother liquor yielded an uncharacterised brown gum (0.07 g).

(d) 2,1-Benzisoxazole-3-carboxylic acid (38a) was prepared by the cyclisation of ethyl 2-nitrophenylacetate (37) in concentrated sulphuric acid as described in the literature, \(^\text{85}\) yield 57%, m.p. 190-192° (lit.\(^{85}\) 198°), and was used without further purification.
2,1-Benzisoxazole-3-carbonyl Chloride (39)

2,1-Benzisoxazole-3-carbonyl chloride (39) was prepared by the reaction of 2,1-benzisoxazole-3-carboxylic acid (38a) with thionyl chloride as described in the literature,116 yield 50%, ν max 1750 cm⁻¹, and was used without further purification.

3-Benzoyl-2,1-benzisoxazole (26)

3-Benzoyl-2,1-benzisoxazole (26) was prepared by the reaction of 2,1-benzisoxazole-3-carbonyl chloride (39) with diphenylcadmium as described in the literature,84 yield 22%, m.p. 88-89° (lit.,84 95-96°), and was used without further purification.

The Attempted Thermolysis of 3-Benzoyl-2,1-benzisoxazole (26) in Toluene

A solution of 3-benzoyl-2,1-benzisoxazole (26) (0.45 g, 0.002 mol) in anhydrous toluene (20.0 ml) was heated under reflux for 1 h. Evaporation afforded unreacted 3-benzoyl-2,1-benzisoxazole (26) (0.45 g; 100%), m.p. 80-82°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Thermolysis of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) in the Presence of Ethanol

A solution of 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) (0.58 g, 0.006 mol), in anhydrous toluene (10.0 ml) containing absolute ethanol (2.0 ml) was heated under reflux for 4.5 h. The mixture was evaporated to yield an orange oil (0.58 g) which was shown by t.l.c. in diethyl ether-
light petroleum (50:50) over silica to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Thermolysis of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) in the Presence of Piperidine

A solution of 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) (1.2 g, 0.004 mol) in anhydrous toluene (40.0 ml) was treated with piperidine (0.51 g, 0.006 mol) and the mixture was heated under reflux for 1 h. Evaporation of the mixture afforded a dark brown oil (1.6 g), chromatography of which in toluene over silica, gave only a series of intractable oils which were not investigated further.

The Attempted Reaction of 2-Diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) with Hydrazine Hydrate

A solution of 2-diazo-1-(2-nitrophenyl)-3-phenylpropane-1,3-dione (21a) (0.35 g, 0.0012 mol) in anhydrous toluene (20.0 ml) was treated with 100% hydrazine monohydrate (0.066 g, 0.0013 mol) and the mixture was heated under reflux for 1 h. Evaporation of the mixture gave an orange gum (0.32 g) which was treated with hot light petroleum to give 2-phenyl-3,1-benzoazin-4-one (22a) (0.12 g; 45%), m.p. 97-99°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the light petroleum mother liquor gave a gum (0.2 g) which was shown by t.l.c. in toluene over silica to be an unresolvable multicomponent mixture, and was not further investigated.
Reaction of 1-(4-Chloro-2-nitrophenyl)-2-diazo-ethanone (24) with Acetic Acid-Formic Acid

A slurry of 1-(4-chloro-2-nitrophenyl)-2-diazo-ethanone (24) (0.34 g, 0.0015 mol) in glacial acetic acid (2.0 ml) was treated with 98-100% formic acid (1.0 ml) and the mixture was stirred at room temperature for 1 h. Evaporation of the mixture gave an orange gum (0.34 g) which was redissolved in methylene chloride and the solution washed with aqueous 2M sodium hydroxide and evaporated to yield 1-(4-chloro-2-nitrophenyl)-2-diazo-ethanone (24) (0.25 g; 74%), m.p. 108-110°, which was identical (m.p. and i.r. spectrum) to a sample obtained before.

Acidification of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid followed by extraction with methylene chloride afforded only a negligible amount of gum.

The Reaction of 1-(4-Chloro-2-nitrophenyl)-2-diazo-3-phenyl-propane-1,3-dione (21d) with Aqueous Sodium Hydroxide

A solution of the diazo-diketone (21d) (0.66 g, 0.002 mol) in 1,2-dimethoxyethane (20.0 ml) was treated with aqueous 2M sodium hydroxide (5.0 ml) and the mixture was stirred at room temperature for 0.5 h. The mixture was evaporated, the residue was treated with water (5.0 ml) and the solution was extracted with chloroform to give an uncharacterised oil (0.12 g), $\nu_{\text{max}}$ 2100 (N=) and 1525 and 1340 (NO$_2$) cm$^{-1}$, which was shown by t.l.c. in diethyl ether over silica to be a close-running four-component mixture and was not further investigated.

Acidification of the aqueous mother liquor with aqueous 2M hydrochloric acid followed by extraction with chloroform yielded benzoic acid (0.18 g; 74%), m.p. 114-116°, identical (m.p. and i.r. spectrum) to an authentic sample.
Neutralisation of the aqueous acidic mother liquor with solid sodium acetate and extraction with ethyl acetate yielded only a negligible amount of oil.

The Thermolysis of 2-Benzenesulphonyl-2-diazo-1-(2-nitrophenyl)ethanone (70) in Toluene

A solution of 2-benzenesulphonyl-2-diazo-1-(2-nitrophenyl)ethanone (70) (5.2 g, 0.016 mol) in anhydrous toluene (160 ml) was heated under reflux for 3 h. Evaporation of the mixture gave a brown gum (5.1 g) which was chromatographed over silica.

Elution with toluene-methylene chloride afforded an unidentified yellow oil (0.18 g).

Elution with methylene chloride gave a brown oil (1.93 g) which was treated with diethyl ether to afford 3-benzene-sulphonyl-3-(2-nitrophenyl)ketene (71) (1.1 g; 20%), \( \nu_{\text{max}} \) 2140 (C=O) and 1535 and 1340 (NO\(_2\)) cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 8.18-7.24 (m, ArH) which was converted by crystallisation from ethanol into ethyl 2-benzenesulphonyl-2-(2-nitrophenyl)ethanoate (73) which formed cream plates, m.p. 95-96\(^\circ\), \( \nu_{\text{max}} \) 1755 (CO) and 1535 and 1340 (NO\(_2\)) cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 8.20-7.23 (9H, m, ArH), 6.35 (1H, s, CH), 4.20 (2H, q, J7Hz, CH\(_2\)), and 1.18 (3H, t, J7Hz, CH\(_3\)).

\text{Found: M}^+, 349.06176
\text{C}_{16}H_{15}NO_{6}S \text{ requires: M, 349.06200}

Elution with methylene chloride-diethyl ether yielded 7-benzenesulphonyloxy-1H-indole-2,3-dione (72) (2.0 g; 41\%) which formed yellow needles, m.p. 211-212\(^\circ\) (from ethanol-dimethylformamide), \( \nu_{\text{max}} \) 1750 and 1630 (CO) cm\(^{-1}\), \( \delta \) [(CD\(_3\))\(_2\)SO] 7.98-6.92 (m, ArH).

\text{Found: M}^+, 303.01914
\text{C}_{14}H_{9}NO_{5}S \text{ requires: M, 303.02014}
Further elution with methylene chloride-diethyl ether then diethyl ether-ethyl acetate yielded gums (total 0.4 g) whose t.l.c. showed them to be multicomponent mixtures which were not further investigated.

The Reaction of 7-Benzensulphonyloxy-1H-indole-2,3-dione (72) with ortho-Phenylenediamine

A solution of 7-benzenesulphonyloxy-1H-indole-2,3-dione (72) (0.06 g, 0.0002 mol) and ortho-phenylenediamine (0.022 g, 0.0002 mol) in ethanol (10.0 ml) was heated under reflux for 1 h. Evaporation afforded a dark red oil (0.08 g) which solidified in contact with diethyl ether-light petroleum to yield 7-benzenesulphonyloxy-3-N-(2-aminophenyl)imino-1H-indole-2-one (74) (0.075 g; 95%) which formed yellow needles, m.p. 227-228° (from ethanol-dimethylformamide), ν_{max} 3460 and 3320 (NH) and 1660 (CO) cm^{-1}, δ[(CD₃)₂SO] 8.02-7.28 (11H, m, ArH and NH), 6.99-6.95 (1H, m, ArH), 6.60-6.52 (1H, m, ArH), and 6.07 (2H, s, NH).

Found: M^+, 393.07869
C_{20}H_{15}N_{3}O_{4}S requires: M, 393.07832

The Attempted Catalytic Hydrogenolysis of 7-Benzensulphonyloxy-1H-indole-2,3-dione (72)

7-Benzensulphonyloxy-1H-indole-2,3-dione (72) (0.3 g, 0.001 mol) was hydrogenated in absolute ethanol (200 ml) over 10% palladium-on-charcoal (0.03 g). The mixture was filtered through celite and the filtrate was evaporated to yield unchanged 7-benzenesulphonyloxy-1H-indole-2,3-dione (72) (0.24 g;
80%), m.p. 201-203°, identical (m.p. and i.r. spectrum) to an authentic sample.

7-Hydroxy-1H-indole-2,3-dione (75)

A suspension of 7-benzenesulphonyloxy-1H-indole-2,3-dione (72) (0.5 g, 0.0016 mol) in 10% w/v aqueous sodium hydroxide (10.0 ml) was shaken at room temperature for 1 h during which time the suspended solid dissolved. The solution was cooled in ice, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate to yield 7-hydroxy-1H-indole-2,3-dione (75) (0.26 g; 100%) which formed deep red plates, m.p. 276-277° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 3360 (NH) and 1740 and 1720 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 10.90 (1H, s, OH or NH), 10.11 (1H, s, NH or OH), 7.09 (1H, d, $J_{\text{ortho}}$ 8Hz, $J_{\text{meta}}$ 2Hz, ArH), 7.00 (1H, d, $J_{\text{8Hz}}$, ArH), and 6.92 (1H, t. $J_{\text{8Hz}}$, ArH).

Found: C, 58.5; H, 3.1; N, 8.5%; m/e 163 (M$^+$), 135 and 107.

C$_7$H$_5$NO$_3$ requires: C, 58.8; H, 3.1; N, 8.6%; M, 163.

Found: M$^+$, 135.03207.

C$_7$H$_5$NO$_2$ requires: M, 135.03203.

Found: M$^+$, 107.03760.

C$_6$H$_5$NO requires: M, 107.03711.

7-Methoxy-1H-indole-2,3-dione (76)

A suspension of 7-benzenesulphonyloxy-1H-indole-2,3-dione (72) (0.3 g, 0.001 mol) in 10% w/v aqueous sodium hydroxide (5.0 ml) was treated with dimethyl sulphate (1.0 ml) and the mixture was shaken at room temperature for 1 h. The mixture
was cooled in ice, acidified with concentrated hydrochloric acid, and extracted with ethyl acetate to give 1-methoxy-1H-indole-2,3-dione (76) (0.16 g; 90%) which formed deep red needles, m.p. 229-230° (from ethanol), $\nu_{\text{max}}$ 1745 and 1720 (CO) cm$^{-1}$, $\delta[(\text{CD}_3)_2\text{SO}]$ 11.10 (1H, s, NH), 7.35-7.03 (3H, m, ArH), and 3.86 (3H, s, CH$_3$).

Found: M$^+$, 177.04266.
C$_9$H$_7$NO$_3$ requires: M, 177.04259.

4-Hydroxy-5H-indolo[2,3-b]quinoxaline (77)

A solution of 7-hydroxy-1H-indole-2,3-dione (75) (0.05 g, 0.0003 mol) and ortho-phenylenediamine (0.032 g, 0.0003 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 3 h. Evaporation of the mixture yielded 4-hydroxy-5H-indolo[2,3-b]-quinoxaline (77) (0.07 g; 99%) which formed yellow plates of the monohydrate, m.p. 310-311° (from ethanol-dimethylformamide-water), $\nu_{\text{max}}$ 3500 br (OH) and 3000 br (NH) cm$^{-1}$, $\delta[(\text{CD}_3)_2\text{SO}]$ 8.23 (1H, dd, $J_{\text{ortho}}$ 8Hz, $J_{\text{meta}}$ 2Hz, ArH), 8.05 (1H, dd, $J_{\text{ortho}}$ 8Hz, $J_{\text{meta}}$ 2Hz, ArH), and 7.90-7.10 (5H, m, ArH).

Found: C, 66.7; H, 4.2; N, 16.5%; M$^+$, 235.
C$_{14}$H$_9$N$_3$O.H$_2$O requires: C, 66.4; H, 4.3; N, 16.6%; (M-H$_2$O), 235.
Chapter 3

Thermal Rearrangements of Some 1-Aryl-2-arylaizo-2-

triphenylphosphoranylidene-ethanones
Thermal Rearrangements of Some 1-Aryl-2-arylazo-2-triphenylphosphoranylidene-ethanones

3.1 Introduction

Indolinone N-oxides (isatogens) are of interest (Scheme 1) because of their unique aza-enone N-oxide structures (1).

However relatively few synthetic routes to isatogens are available and most involve direct nitro-group side-chain interaction in ortho-substituted nitrobenzene derivatives. The general scope of such isatogen syntheses are restricted largely to the preparation of 2-aryl- and 2-ethoxycarbonyl derivatives, typical examples of which have already been discussed in Chapter 1. A particularly interesting isatogen synthesis of this type, described by Abramovitch and Cue is outlined in Scheme (2) and involves the thermal conversion of the phosphorane (2) into the cyano-alkyne (3), photo-cyclisation of which yielded the isatogen derivative (4). This work prompted the idea (Scheme 3) that 1-(2-nitrophenyl)-2-triphenylphosphoranylidene-ethanones of the general type (7) might be useful synthetic intermediates for the general synthesis of isatogens (Scheme 3). Thus 1-(2-nitrophenyl)-2-triphenylphosphoranylidene-ethanones (7), potentially

![Scheme 1](image-url)
(i) heat
(ii) hv

Scheme 2
(i) $\text{Ph}_3\text{P}$
(ii) base
(iii) heat

Scheme 3
available by the reaction of γ-halo-ketones (5) with triphenylphosphine followed by treatment of the resulting phosphonium salts (6) with base, could afford isatogen derivatives (10) in two ways. Firstly, thermal elimination of triphenylphosphine oxide could provide general access to 2-nitrophenylalkynes (8) suitable for conversion into isatogens as already outlined in Chapter 1. Alternatively, it is possible that nitro-group side-chain interaction in the phosphorane (7) could lead via a Wittig-type process involving direct expulsion of triphenylphosphine oxide, to the isatogen (Scheme 3; (7)→(9)→(11)→(10)).

With the exception of the aforementioned studies by Abramovitch and Cue, 1-(2-nitrophenyl)-2-triphenylphosphoranylidene-ethanones (7) have not previously been investigated as general precursors of isatogens. The study of the synthesis and reactivity of phosphoranes of the type (7) was therefore undertaken in the present work in the hope of developing new general routes to novel isatogen derivatives. Initially it was decided to investigate (Scheme 4) the synthesis and thermolysis of 1-(2-nitroaryl)-2-arylazo-2-triphenylphosphoranylidene-ethanones (14) in the expectation that such compounds might undergo cyclisation to 2-arylazo-isatogens (15) examples of hitherto unknown 2-aminated isatogens. It was anticipated that the required phosphoranes (14) would be readily prepared by coupling the corresponding 2-nitrobenzoylmethyl(triphenylphosphonium salts (12), through the intermediacy of the phosphoranes (13) with aryldiazonium salts. Märkl has described the preparation of the parent 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (14; R=H, Ar=Ph,
Scheme 4

(i) base

(ii) ArN₂⁺
H for NO₂) by coupling benzoylemethylenetriphenylphosphonium bromide (12; R=H, X=Br, H for NO₂) with benzenediazonium chloride in the presence of base.

3.2 The Synthesis and Thermal Rearrangement of 1-(2-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19)

The previously unknown 1-(2-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19) was readily synthesised as outlined in Scheme (5). 2-Bromo-1-(2-nitrophenyl)ethanone (16) (prepared as described in Chapter 2) reacted readily on heating with triphenylphosphine in toluene to afford the expected phosphonium salt (17) in high yield (93%). The compound (17) gave analytical and mass spectral data fully consistent with the assigned structure which was further confirmed by its i.r. spectrum which showed carbonyl absorption at 1680 cm⁻¹ and nitro absorption at 1530 and 1350 cm⁻¹. The ¹H n.m.r. spectrum of the salt (17) contains a two proton doublet with a coupling constant of 12Hz characteristic of ³¹P-¹H coupling, thus allowing the assignment of the doublet to the methylene protons of the salt (17).

The phosphonium salt (17) coupled readily with benzenediazonium chloride in the presence of sodium acetate to give a high yield (89%) of a solid whose properties are fully in accord with the arylazomethylene phosphorane structure (19). Thus, it analysed correctly for C₃₂H₂₄N₃O₃P though it failed to exhibit the expected parent ion at m/e 528 in its mass spectrum, the ion of highest mass appearing at m/e 458. This unintelligible mass spectral behaviour is presumably due to
Scheme 5

(i) \( \text{Ph}_3\text{P} \)

(ii) \( \text{NaOAc} \)

(iii) \( \text{PhN}_2^+\text{Cl}^- \)
thermal decomposition of the highly involatile arylazo-
methyleneephosphorane (19) in the mass spectrometer probe.
The arylazomethyleneephosphorane (19) showed no carbonyl
absorption in its i.r. spectrum indicating that it exists
predominantly in the phospho-betaine form [Scheme 5; (19b)].
Acyilmethylenephosphoranes in general have been shown\textsuperscript{120} to
exist predominantly in the phospho-betaine forms.

The attempted thermolysis of the arylazomethylenephos-
phorane (19) by heating at 180° under reduced pressure in a
Kugelrohr apparatus in the hope of obtaining the azo-isatogen
(20), gave instead a good yield (60%) of triphenylphosphine
oxide which was identified by comparison with an authentic
sample and intractable gums which failed to yield any identifi-
able material. In contrast (Scheme 6), heating the arylazo-
methyleneephosphorane (19) in dimethylformamide gave an orange
product (m.p. 141°) in lowish yield (36%) together with
triphenylphosphine oxide (yield 40%) and unidentified gums.
The orange product gave analytical and mass spectral data in
accord with the molecular formula C\textsubscript{14}H\textsubscript{9}NO\textsubscript{2} and its i.r.
spectrum showed carbonyl absorption at 1750 and 1620 cm\textsuperscript{-1}.
These properties are consistent with the formulation of the
orange product as the known heterocyclic compound 1-phenyl-
1H-indole-2,3-dione (1-phenylisatin) (21) (m.p. 139°)\textsuperscript{121} rather
than the alternative isomeric structures (23)-(25). The
isatin structure (21) for the orange solid was verified by
the high resolution mass spectrum of the compound which showed
the successive loss of two CO fragments identified by accurate
mass measurement. In further support of its isatin structure
(21), the orange product reacted smoothly on heating with
Scheme 6

(i) heat

(ii) ortho-phenylenediamine
ortho-phenylenediamine to give the indolo[2,3-b]quinoxaline derivative (22) in quantitative yield. The structure of the compound (22) follows from its mode of formation, its combustion analysis and mass spectrum, and the lack of carbonyl absorption in its i.r. spectrum.

It is not at all clear how the thermolysis of the phenylazomethylene phosphorane (19) leads to the isatin derivative (21). One possibility (Scheme 7) is that the isatin derivative (21) is a further thermal rearrangement product of the hoped-for 2-phenylazoisatogen (20) derived by a Wittig-type cyclisation of the azophosphorane (19) (Scheme 7). Thus thermal rearrangement of the isatogen could give an oxazirane intermediate (28) convertible by further rearrangement with loss of nitrogen as shown into 1-phenylisatin (21). The thermal rearrangement of an isatogen to an oxazirane intermediate has been proposed as the initial step in other isatogen thermal rearrangements.\textsuperscript{117} The prior thermal formation of 2-phenylazoisatogen (20) from the arylazomethylene phosphorane (19) is unlikely to involve (Scheme 8) initial extrusion of triphenylphosphine oxide to give the 2-nitrophenylalkyne (31) since it is known\textsuperscript{122} that such processes require a substantially greater temperature than that required for the thermal conversion of the arylazomethylene phosphorane (19) into the isatin derivative (21).

Trippet and Walker\textsuperscript{122} showed (Scheme 9) that 1,2-diphenyl-2-phosphoranylidenemethanone (34) thermally extrudes triphenylphosphine oxide when heated at 300° to give 1,2-diphenylethyne (35). It was therefore of interest to study the behaviour of the phosphorane (34) when heated under similar
Scheme 7

(i) heat
Scheme 8

(i) heat
\[
\begin{align*}
\text{(32)} & \quad \overset{(i)}{\rightarrow} \quad \text{(33)} \\
\text{(34)} & \quad \overset{(i)}{\rightarrow} \quad \text{Ph—C} & \quad \overset{(ii)}{\rightarrow} \quad \text{(35)} \\
\text{(i)} & \quad \text{PPh}_3 \\
\text{(ii)} & \quad \text{Na}_2\text{CO}_3, \text{H}_2\text{O} \\
\text{(iii)} & \quad \text{heat}
\end{align*}
\]

Scheme 9
conditions to those which resulted in the thermal transformation [(19)→(21)] (Scheme 7). As outlined in Scheme 9, the phosphorane (34) can be readily obtained by treating the phosphonium salt (33) with base, the salt (33) itself being available by the reaction of the bromo-ethanone (32) with triphenylphosphine. 2-Bromo-1,2-diphenylethanone (32) was readily synthesised by the bromination of commercially available 1,2-diphenylethanone in good yield (67%) as described in the literature.\textsuperscript{123} The bromo-ethanone (32) reacted readily with triphenylphosphine to afford the phosphonium salt (33) whose analytical and spectroscopic properties were fully in accord with the assigned structure. The phosphonium salt (33) was converted into the phosphorane (34) in good yield (60%) by treatment with aqueous sodium carbonate. However, heating a dimethylformamide solution of the phosphorane (34) under conditions which successfully achieved the transformation [(19)→(21)], in the case of the phosphorane (34) gave only unreacted starting-material.

From this result, it seems likely that the rearrangement [Scheme 7; (19)→(21)] does not proceed via the azo-alkyne (31) but instead involves initial Wittig-type condensation between the nitro-group and the phosphorus substituent in the ortho side-chain of the arylazomethylenephosphorane (19) to form the heterocyclic intermediate (27) which then extrudes triphenylphosphine oxide to give the proposed isatogen intermediate (20).
3.3 The Synthesis and Thermal Rearrangement of 1-Phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38)

As already discussed, the stability of 1,2-diphenyl-2-phosphoranylidene-ethanone (34) to heating under reflux in dimethylformamide could be taken as evidence that arylazo-isatogen formation from the arylazomethylenephosphorane (19) is not preceded by extrusion of triphenylphosphine oxide to give the alkyne (31) followed by cyclisation. However it could be argued that the arylazo-substituent in the arylazo-phosphorane (19) might exert a conjugative stabilising influence on alkyne formation thus promoting extrusion of triphenyl-phosphine oxide at a lower temperature than in the case of 1,2-diphenyl-2-phosphoranylidene-ethanone (34). Consequently it was considered more appropriate to compare the thermal behaviour of the nitrated arylazomethylenephosphorane (19) with that (Scheme 10) of the parent 1-phenyl-2-phenylazo-2-phosphoranylidene-ethanone (38).

The parent arylazomethylene phosphorane (38), a known compound previously prepared by Märkl,118 was readily synthesised as outlined in Scheme 10. Commercially available 2-bromo-1-phenylethanone (36) reacted readily with triphenyl-phosphine by the method described in the literature124 to give the phosphonium salt (37) which coupled readily with benzene-diazonium chloride in the presence of sodium acetate to give a high yield (95%) of a bright yellow solid whose properties are fully in accord with the arylazomethylene phosphorane structure (38). Thus, it gave elemental analysis and mass spectral data fully consistent with the molecular formula C$_{32}$H$_{25}$N$_2$OP and its melting-point corresponded closely to the
(i) $\text{Ph}_3\text{P}$
(ii) $\text{PhN}_2^+\text{Cl}^-, \text{NaOAc}$
(iii) heat
(iv) $\text{H}_2\text{SO}_4, \text{H}_2\text{O}$
(v) KOH
(vi) MnO$_2$

Scheme 10
literature value cited\textsuperscript{118} for the aryloxymethyleneephosphorane (38).

The thermolysis of the aryloxymethyleneephosphorane (38) by heating under reduced pressure at 210°C/0.2mmHg in a Kugelrohr apparatus gave a yellow distillate which solidified on cooling, and an involatile residue which gave a good yield (99%) of triphenylphosphine oxide on trituration with ethyl acetate. The yellow product gave an elemental analysis and showed a parent ion in its mass spectrum consistent with the molecular formula $C_{14}H_{10}N_2$. The i.r. spectrum of the yellow compound contained a band at 2220 cm\textsuperscript{-1} characteristic\textsuperscript{125} of an acetylenic or cyano substituent. These properties are in accord with the azo-alkyne structure (39) for the yellow product. Moreover this compound was already described in the literature having been prepared (Scheme 11) by Huang and his co-workers\textsuperscript{126} by the reaction of silver phenylacetylide (43) with benzenediazonium chloride, and had a melting-point (64-66°C) close to that (70-71°C) of the yellow product from the thermolysis of the aryloxymethyleneephosphorane.

In order to positively establish the identity of the yellow product as the azo-alkyne (39) it was decided to seek chemical evidence for its structure. However treatment of the yellow product with aqueous sulphuric acid instead of

\[
\text{PhC≡C}^+ \text{Ag}^+ \xrightarrow{(i)} \text{PhC≡C}^- \text{N=NPh}^- \\
\text{(43)} \rightarrow \text{(39)} \\
(i) \text{PhN}_2^+\text{Cl}^- \\
\text{Scheme 11a}
\]


leading to hydration of the triple bond in the azo-alkyne (39) resulted in hydrolytic degradation to benzoic acid in good yield (66%). Since this hydrolytic behaviour was not entirely consistent with the azo-alkyne structure (39), the alkaline hydrolysis of the yellow product was also investigated. However, heating the yellow product with 20% w/v aqueous potassium hydroxide afforded a product, identified by comparison, with an authentic sample, as benzanilide (41) (Scheme 10). This result is inconsistent with the formulation of the yellow product as the azo-alkyne (39) but is readily explained if the yellow compound is in fact α-N-phenylimino-benzeneacetonitrile (40) (Scheme 10) which could afford benzanilide (41) on alkaline hydrolysis. In accord with the cyano-imine structure (40) for the yellow product it was shown to be identical to an authentic sample of α-N-phenylimino-benzeneacetonitrile (40) prepared by the oxidation of the known compound α-N-phenylaminobenzeneacetonitrile (42) using activated manganese dioxide.

The thermal transformation (Scheme 10) of 1-phenyl-2-phenylazo-2-triphenylphosphoranylidenemethanone (38) into α-N-phenyliminobenzeneacetonitrile (40) in the absence of solvent required a temperature of 210° whereas the thermal conversion (Scheme 6) of 1-(2-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidenemethanone (19) into 1-phenylisatin (21) occurred at 153° in refluxing dimethylformamide. It was therefore of interest to investigate the behaviour of the arylazophosphorane (38) when heated in solution. In practice heating the arylazophosphorane (38), in dimethylformamide resulted in the formation of a red oil which was separated by chromatography.
into the imino-nitrile (40) (55%) and triphenylphosphine oxide together with some benzanilide (41) (8%). The isolation of the latter product can be explained by some hydrolysis of the imino-nitrile (40) in the course of chromatographic separation of the crude reaction product. While the thermally initiated rearrangement of the arylazomethylenephosphorane (38) to the imino-nitrile (40) and triphenylphosphine oxide does occur in solution at a lower temperature than that required to effect the same rearrangement of (38) in the absence of solvent the yields of the products obtained are greatly reduced.

The mode of formation of the imino-nitrile (40) and triphenylphosphine oxide in the thermally-initiated rearrangement of the arylazomethylenephosphorane (38) can be rationalised by the series of transformations outlined in Scheme 11. Initial fragmentation of the arylazomethylenephosphorane reacting in the resonance form (38a), through the four-membered intermediate (44) would afford benzoyl cyanide (46) and N-phenyltriphenylphosphineimine (47). Recombination of these molecules could then afford by a Wittig-type condensation involving the four-membered intermediate (45), the cyano-imine (40) and triphenylphosphine oxide observed as products. The mechanism outlined in Scheme 11, if correct, implies that thermolysis of the arylazomethylenephosphorane (38) is initiated by extrusion of N-phenyltriphenylphosphineimine (47) in preference to triphenylphosphine oxide. This type of competitive thermal fragmentation has not been reported in the literature to date. A further implication of the mechanism shown in Scheme 11 is that benzoyl cyanide (46) should react
Scheme 11
with \( \text{N-phenyltriphenylphosphineimine} \) (47) to give the cyano-imine (40) and triphenylphosphine oxide. Since this type of Wittig condensation was of interest it was decided to investigate the thermal reaction of benzoyl cyanide (46) with \( \text{N-phenyltriphenylphosphineimine} \) (47).

Benzoyl cyanide (46) was readily prepared by the reaction of benzoyl chloride with copper (I) cyanide as described in the literature. \(^{129}\) \( \text{N-Phenyltriphenylphosphineimine} \) (47) was also readily prepared by the reaction of phenyl azide with triphenylphosphine as described by Staudinger and Meyer. \(^{130}\)

In accord with the suggested mechanism (Scheme 11) for the thermolysis of the arylazomethylenephosphorane (38) to \( \alpha-\text{N-phenyliminobenzeneacetonitrile} \) (40) and triphenylphosphine oxide, the latter two compounds were formed in excellent yield (>90%) by heating benzoyl cyanide (46) with \( \text{N-phenyltriphenylphosphineimine} \) (47) in toluene or in the absence of a solvent in a Kugelrohr apparatus. The demonstration of the ready thermal reaction of benzoyl cyanide (46) with \( \text{N-phenyltriphenylphosphineimine} \) (47) to give the cyano-imine (40) and triphenylphosphine oxide in high yield provides concrete support for the mechanism shown in Scheme 11.

3.4 The Synthesis and Thermal Rearrangement of 1-Aryl-2-arylazo-2-triphenylphosphoranylidene-ethanones (54a-c and 60a-c)

The results described in section 3.3 before indicate that the thermolysis of 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38) follows the course outlined in Scheme 11. A consequence of this mechanism is that thermal extrusion of \( \text{N-phenyltriphenylphosphineimine} \) (47) in the azo-phosphorane
(38) occurs in preference to thermal elimination of triphenylphosphine oxide. It follows that 1-aryl-2-aryl-azo-2-triphenylphosphoranylidene-ethanones in general should be useful molecules for the study of thermal elimination involving competitive P=O and P=N formation. Thus (Scheme 12) the phospho-nitrogen betaine resonance form (49) of the arylazomethylenephosphorane (48) should be stabilised by electron-withdrawing substituents (R²) in the arylazo-nucleus thus promoting thermolysis to the aroyl cyanide (51) and the N-aryltriphenylphosphineimine (52). Conversely electron-donating substituents (R²) in the arylazo-nucleus by destabilising the resonance form (49) should inhibit cleavage to the aroyl cyanide (51) and the N-aryltriphenylphosphineimine (52) thus allowing the alternative thermal cleavage to the azo-alkyne (53) and triphenylphosphine oxide, to operate. The role of the substituent (R¹) in the aroyl-nucleus is not so clear. However, broadly, electron-withdrawing substituents (R¹) should destabilise the phospho-oxygen betaine resonance form (50) thus suppressing thermolysis to the azo-alkyne (53) and triphenylphosphine oxide. As a consequence, arylazomethylenephosphoranes (48) in which R¹ = an electron-withdrawing group should thermolyse preferentially to aroyl cyanides (51) and triphenylphosphineimines (52) and thence (see Scheme 10) by recombination of these two species, the corresponding N-aryliminobenzeneacetonitriles and triphenylphosphine oxide. Conversely, electron-donating substituents (R¹) in the aroyl-nucleus should favour the phospho-oxygen betaine resonance form (50), thus promoting thermolysis to the azo-alkyne (53) and triphenylphosphine oxide rather than to aroyl cyanides (51) and
Scheme 12
triphenylphosphineimines (52).

Because of the possible electronic effects of substituents on the mode of thermolysis of arylazomethylenephosphoranes it was of interest to investigate the synthesis and course of the thermolysis of a series of 1-aryl-2-arylazo-2-triphenylphosphoranylidenethanones having electron-donating and electron-withdrawing substituents in the aroyl- and arylazo-nuclei. Initially it was decided to study (Scheme 13) the synthesis and thermolysis of 1-phenyl-2-arylazo-2-triphenylphosphoranylidenethanones (54) substituted in the arylazo-nucleus and unsubstituted in the aroyl-nucleus. The azomethylenephosphoranes (54) required for study were readily prepared as in the case of the parent compound [Scheme 10; (38)] by the coupling reaction (Scheme 13) of benzoylmethyltriphenylphosphonium bromide (37) with the appropriate aryldiazonium salt in the presence of sodium acetate. Coupling of the salt (37) under these conditions with an aqueous solution of 4-nitrobenzenediazonium chloride afforded 2-(4-nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidenethanone (54a) as an orange solid in essentially quantitative yield. The compound (54a) analysed correctly for the assigned structure but its mass spectrum lacked a parent ion peak at m/e 529, the ion of highest mass number appearing at m/e 398. This mass spectral behaviour can be attributed to thermally initiated loss of benzooyl cyanide in the mass spectrometer probe prior to ionisation. The azomethylenephosphorane (54a) showed the expected nitro-absorption at 1510 and 1350 cm\(^{-1}\) in its i.r. spectrum but lacked carbonyl absorption in accord with its existence predominantly in the resonance form (55a).
Scheme 13

(i) ArN₂⁺Cl⁻, NaOAc  
(ii) heat
The phosphonium salt (37) also coupled smoothly with an aqueous ethanolic solution of 2-nitrobenzenediazonium chloride buffered with sodium acetate to afford the expected azo-phosphorane (54b) in high yield (99%). This product showed analytical and spectral properties fully in accord with its assigned structure. Reaction of the phosphonium salt (37) with 4-methoxybenzenediazonium chloride in aqueous ethanol gave a high yield (96%) of a yellow solid which analysed correctly for the azo-phosphorane structure (54c). As with other azomethylenephosphoranes encountered in the present studies, the compound (54c) did not show the expected parent ion peak at m/e 514 in its mass spectrum, the peak at highest mass number appearing at m/e 504. Again this mass spectral behaviour can be attributed to prior thermal decomposition in the mass spectrometer probe. The i.r. spectrum of the azomethylenephosphorane (54c) lacked carbonyl absorption consistent with the predominance of the resonance form (55c).

As already discussed, the presence of an electron-withdrawing substituent ($R^2$) in the arylazo-moiety of the azomethylenephosphorane (54) might be expected to promote thermolysis to benzoyl cyanide and the corresponding $N$-aryl-triphenylphosphineimine and thence by further recombination-refragmentation the $N$-aryliminobenzeneacetonitrile (56). In practice, heating the nitrophenylazomethylenephosphorane (54a) at 175°/0.2mmHg in a Kugelrohr apparatus gave a several component gum which was separated by chromatography into a high yield (90%) of triphenylphosphine oxide and a low yield (25%) of a product which analysed correctly for $C_{13}H_{10}N_2O_3$ and gave an i.r. spectrum which showed NH absorption at 3350 cm$^{-1}$, carbonyl absorption at 1665 cm$^{-1}$, and nitro absorption
at 1510 and 1350 cm\(^{-1}\). These properties are consistent with the formulation of the product as 4'-nitrobenzanilide (57a) and this structure assignment was confirmed by the product's melting-point which was identical to that of an authentic sample of 4'-nitrobenzanilide (57a). This compound is presumably formed from the azomethylenephosphorane (54a) by the expected rearrangement to the cyano-imine (56a) which then suffers hydrolysis to 4'-nitrobenzanilide (57a) on workup of the reaction mixture. The low yield of the rearrangement product (57a) from the nitrophenylazomethylenephosphorane (54a) does not support the hypothesis (see before) that para-electron-withdrawing substituents (ie. nitro) in the arylazo-nucleus of 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanones [ie. (54a)] promote the thermolysis of the latter to cyano-imines [ie. (56a)].

The thermolysis of the 2-nitrophenylazomethylenephosphorane (54b) by heating in a Kugelrohr apparatus at 180°/0.2mmHg also gave only low yields of rearrangement products. Chromatography of the crude reaction mixture gave, together with a high yield (94%) of triphenylphosphine oxide, low yields (11 and 4%) of two products whose analytical and spectroscopic properties are entirely in accord with their formulation as N-(2-nitrophenyl)-iminobenzeneacetonitrile (56b) and 2'-nitrobenzanilide (57b) respectively. The inefficiency of the thermal rearrangement of the 2-nitrophenylazomethylenephosphorane (54b) reinforces the results obtained in the thermolysis of the 4-nitrophenylazomethylenephosphorane (54a) (see before) and indicates that electron-withdrawing substituents in the arylazo-nucleus of azomethylenephosphoranes (54) have an inhibiting rather than
the predicted promoting effect on thermolysis. It was therefore of interest to see how the electron-donating 4-methoxy-substituent in the arylazomethylenephosphorane (54c) would affect the course of its thermolysis.

In practice heating the 4-methoxyphenylazomethylenephosphorane (54c) at 190°/0.2mmHg in a Kugelrohr apparatus gave a product mixture which was separated by chromatography into triphenylphosphine (38%), triphenylphosphine oxide (56%) and a yellow solid (44%). The latter product gave analytical and mass spectral data consistent with the molecular formula $C_{15}H_{12}N_2O$ and showed i.r. and $^1H$ n.m.r. absorption entirely consistent with its formulation as $N$-(4-methoxyphenyl)iminobenzeneacetonitrile (56c). The efficiency of the thermal rearrangement of the 4-methoxyphenylazomethylenephosphorane (54c) was not improved by heating in solution. Thus, heating the azomethylenephosphorane (54c) in dimethylformamide gave a product mixture separated by chromatography into triphenylphosphine (31%), triphenylphosphine oxide (38%), and the imine (56c) (21%).

The low recoveries of the rearrangement products (56b and c) and (57a and b) in the thermolyses of the arylazomethylenephosphoranes (54a-c) make it difficult to draw any firm conclusions regarding the electronic effect of substituents in the arylazo-nucleus on the course of thermal rearrangement. Moreover, the formation of triphenylphosphine in the thermolysis of the arylazomethylenephosphorane (54c) is puzzling and tends to suggest the operation of an alternative reaction pathway the nature of which is not clear. Further experimentation will be necessary to clarify the mode of formation
of the triphenylphosphine in the thermolysis of the arylazomethylene phosphorane (54c).

Having investigated possible electronic effects of substituents in the arylazo-nucleus on the course of the thermolysis of arylazomethylene phosphoranes (54) it was of interest to study analogous effects of substituents in the aroyl-nucleus (Scheme 14). It was therefore decided to investigate the synthesis and thermolysis of the 4-nitro- and 4-methoxyphenyl-phenylazotriphenylphosphoranylidene-ethanones (60a and b). Both of these compounds were synthesised (Scheme 14) as for the parent 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38) [see Scheme 10]. Thus, 2-bromo-1-(4-nitrophenyl)ethanone (58a) was prepared in good yield (75%) by the bromination of the commercially available 1-(4-nitrophenyl)ethanone as described in the literature. Stirring a benzene solution of the bromo-ketone (58a) with triphenylphosphine at room temperature afforded a good yield (86%) of a solid whose melting-point (213-214°) was considerably higher than the value (150°) quoted for the phosphonium salt (59a) prepared by other workers. However the analytical and spectroscopic properties of the product obtained in the present studies were fully in accord with its formulation as the phosphonium bromide (59a) and it can only be presumed that the literature melting-point cited for this compound is in error. Stirring an aqueous ethanolic solution of the phosphonium salt (59a) containing sodium acetate, with a freshly prepared aqueous solution of benzenediazonium chloride resulted in the precipitation in high yield (92%) of a bright yellow solid, identified as the arylazomethylene-
(58) $R^1$
  a; NO$_2$
  b; MeO

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

(ii) $\text{ArN}_2^+\text{Cl}^-, \text{NaOAc}$

(iii) heat

(59) $R^1$
  a; NO$_2$
  b; MeO

(60) $\leftrightarrow$ (61)

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

(63) $R^1$  $R^2$
  a; NO$_2$  H
  b; MeO  H
  c; MeO  MeO

Scheme 14
phosphorane (60a) on the basis of the following evidence. The compound gave analytical and mass spectral data consistent with the molecular formula $\text{C}_{32}\text{H}_{24}\text{N}_{3}\text{O}_{3}\text{P}$. Its i.r. spectrum showed nitro absorption at 1525 and 1365 cm$^{-1}$ but lacked carbonyl absorption in accord with its existence predominantly in the resonance form (61a). The $^1\text{H}$ n.m.r. spectrum of the arylazomethylenephosphorane (60a) was also fully consistent with the assigned structure.

4-Methoxybenzoylmethyltriphenylphosphonium bromide (59b) was also prepared in good yield (91%) by the reaction of the commercially available bromo-ketone (58b) with triphenylphosphine as described in the literature. The phosphonium bromide (59b) coupled smoothly with benzenediazonium chloride in aqueous ethanolic solution buffered with sodium acetate to afford a high yield (99%) of the bright yellow arylazomethylenephosphorane (60b). This product analysed correctly for the expected molecular formula, $\text{C}_{33}\text{H}_{27}\text{N}_{2}\text{O}_{2}\text{P}$, but it failed to show the expected parent ion peak at m/e 514 in its mass spectrum, the ion of highest mass number appearing at m/e 504. This unintelligible mass spectral behaviour can again be attributed to premature thermal decomposition of the arylazomethylenephosphorane (60b) in the mass spectrometer probe. The $^1\text{H}$ n.m.r. spectrum of the phosphorane (60b) was also in accord with the assigned structure but as with analogous compounds described before, its i.r. spectrum lacked carbonyl absorption, demonstrating the existence of the compound predominantly in the resonance form (61b).

Heating the nitro-substituted arylazomethylenephosphorane (60a) at 190°/0.1mmHg in a Kugelrohr apparatus gave a crude
product mixture which was separated by chromatography into a high yield (99%) of triphenylphosphine oxide and two yellow products in yields of 63% and 9%. The more abundant compound gave an elemental analysis and a mass spectrum consistent with the molecular formula, \( \text{C}_{14}\text{H}_{9}\text{N}_{3}\text{O}_{2} \). This evidence together with the presence of nitrile absorption at 2200 cm\(^{-1}\) and nitro absorption at 1515 and 1345 cm\(^{-1}\) allows the formulation of this product as the imino-nitrile (62a). The yellow product formed in low yield was identified as 4-nitrobenzanilide (63a) by comparison with an authentic sample. The significantly greater efficiency of the thermal rearrangement of the 4-nitrophenyl-phenylazomethylene phosphorane (60a) contrasts with that of the phenyl-nitrophenylazomethylenephosphoranes (54a and b) (see Scheme 13 before) and supports the proposal (see before) that electron-withdrawing substituents (ie. nitro) in the \textit{para}-position of the aroyl nucleus by disfavouring competing thermolysis to an azo-alkyne derivative should promote thermolysis to an aroyl cyanide and an N-arylphosphineimine and thence by recombination to an imino-nitrile [ie. (62a)] as found.

In view of the apparent promoting effect of an electron-withdrawing \textit{para}-substituent (ie. nitro) in the aroyl-nucleus of the 1-methoxyphenyl-2-phenylazo2-triphenylphosphoranylidene-ethanone (60b) whose methoxy-substituent should favour thermolysis to the corresponding azo-alkyne and triphenylphosphine oxide rather than to the
corresponding aroyl cyanide and \(N\)-aryltriphenylphosphineimine (see Scheme 12 before). In practice, heating the phenylazo-methylenephosphorane (60b) at 170°/0.1mmHg in a Kugelrohr apparatus, followed by chromatography of the crude reaction product gave good yields (>60%) of triphenylphosphine oxide and a product identified on the basis of its analytical and spectroscopic properties as the imino-nitrile (62b). The broadly equivalent yields of similar rearrangement products from the thermolyses of both the nitro-compound (60a) and the methoxy-derivative (60b) indicate that the electronic character of the para-substituent in the aroyl-nucleus has little or no effect on the mode of thermolysis of 1-aryl-2-phenylazo-2-triphenylphosphoranylidene-ethanones (60).

The foregoing results indicate that the thermal rearrangement of the arylazomethylenephosphoranes (60a and b) to imino-nitriles [e.g. (62a and b)] and derived products occurs more readily than the analogous thermal rearrangement of the arylazomethylenephosphoranes (54a-c) (see before). The reason for the differing reactivity is not apparent at the present time. However, it was further of interest to discover the outcome of the thermolysis (Scheme 14) of 1-(4-methoxyphenyl)-2-(4-methoxyphenylazo)-2-triphenylphosphoranylidene-ethanone (60c). Having an electron-donating substituent in both the aroyl- and the arylazo-nuclei, this compound would be predicted to be the most likely to undergo thermolysis to the corresponding azo-alkyne and triphenylphosphine oxide as opposed to the latter and the corresponding imino-nitrile (see before).

\[
1-(4\text{-}\text{methoxyphenyl})-2-(4\text{-}\text{methoxyphenylazo})-2\text{-}\text{triphenyl-}
\]
phosphoranylidene-ethanone (60c) was readily synthesised in high yield (97%) by the reaction of the already described phosphonium salt (59b) with 4-methoxybenzenediazonium chloride in aqueous ethanol in the presence of sodium acetate. The compound (60c) gave a combustion analysis and showed a $^1$H n.m.r. spectrum fully in accord with the assigned structure. However its mass spectrum lacked the expected parent ion peak at m/e 544 and showed instead a major ion peak at m/e 383 which can be explained by the thermally-initiated loss of 4-methoxybenzoyl cyanide in the mass spectrometer probe. As with the other arylazomethylenephosphoranes already studied, the i.r. spectrum of the compound (60c) lacked carbonyl absorption indicating that it exists predominantly in the resonance form (61c).

The thermolysis of the arylazomethylenephosphorane (60c) was carried out at 190°/0.2mmHg in a Kugelrohr apparatus and gave a product mixture which was readily separated by chromatography into triphenylphosphine (52%), triphenylphosphine oxide (32%), and a yellow product (yield 49%) whose properties are in agreement with the imino-nitrile structure (62c). Even in the case of the dimethoxy-derivative (60c) therefore, thermolysis avoids the formation of the corresponding azoalkyne and leads as for the other arylazomethylenephosphoranes studied, to the corresponding imino-nitrile (62c). The formation of triphenylphosphine in the thermolysis of the compound (60c) was unexpected but was also observed in the case of the arylazomethylenephosphorane (54c) (see before). The isolation of triphenylphosphine in the thermolyses of the phosphoranes (54c) and (60c) appears to be associated with the presence of
the 4-methoxyphenylazo-substituent in these compounds and suggests the operation of an alternative thermolysis process the elucidation of which will require further study.

3.5 The Synthesis and Attempted Thermal Rearrangement of 1-Phenylazo-1-triphenylphosphoranylideneopropan-2-one (67a) and Ethyl 2-Phenylazo-2-triphenylphosphoranylidene-ethanoate (67b)

As already described (see sections 3.3 and 3.4) 1-aryl-2-arylazo-2-triphenylphosphoranylidene-ethanones in general undergo thermolysis predominantly to N-arylimino-arylacetanitriles and triphenylphosphine oxide. These reactions can be explained by a mechanism (Scheme 11) involving initial fragmentation to an aroyl cyanide and an N-aryltriphenylphosphineimine followed by a Wittig-type recombination of the former with the latter to give the N-arylimino-arylacetanitriles and triphenylphosphine oxide observed as products. As logical extensions of such reactions, the thermolyses (Scheme 15) of 1-phenylazo-1-triphenylphosphoranylideneopropan-2-one (67a) and ethyl 2-phenylazo-2-triphenylphosphoranylidene-ethanoate (67b) were also investigated. If the thermal behaviour of these compounds is similar to that of the 1-aryl-2-arylazo-2-triphenylphosphoranylidene-ethanones already described (see sections 3.3 and 3.4) they should undergo initial thermolysis to the corresponding acyl cyanides (69a and b) and N-phenyltriphenylphosphineimine (47). Subsequent recombination of acetyl cyanide (69a) with the latter would then afford the imino-nitrile (70a) and triphenylphosphine
Scheme 15

(i) Ph₃P
(ii) PhN₂⁺Cl⁻, NaOAc
(iii) Na₂CO₃
(iv) heat

(64) \( R \ X \)

a; Me Cl
b; EtO Br

(65) \( R \ X \)

a; Me Cl
b; EtO Br

(66)

(67)

(68)

(69)

(47)

(70)
oxide. In the case of ethoxycarbonyl cyanide (69b) the sluggish reactivity of the ester-carbonyl group might prevent further reaction with the iminophosphorane (47) thus allowing the isolation of the acyl cyanide (69b) and so providing evidence for the mode of thermolysis of arylazomethylene-phosphoranes of the type (67).

1-Phenylazo-1-triphenylphosphoranylidene propan-2-one (67a) was readily prepared in good yield (80%) by the reaction of 1-chloropropan-2-one (chloroacetone) (64a) with triphenylphosphine to give the known $^{133}$ phosphonium salt (65a) followed by coupling of the latter with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate. However, the melting-point (175-176 °) of the resulting bright yellow product obtained in the present studies was significantly higher than the literature value (167°) reported $^{134}$ for the known arylazomethylene-phosphorane (67a). On the other hand the analytical and spectroscopic properties of the product obtained in the present studies are fully consistent with the resonance-stabilised phosphorane structure [(67a)↔(68a)] and it must be assumed therefore that the melting-point quoted $^{134}$ in the literature for this compound is incorrect.

Heating the phosphorane (67a) at 200 °/0.2mmHg in a Kugelrohr apparatus gave a crude product mixture which was separated by chromatography into triphenylphosphine (72%) and triphenylphosphine oxide (13%) as the only characterisable products. The high yield of triphenylphosphine and the low yield of triphenylphosphine oxide produced under these conditions suggest the operation of a different thermolysis pathway to that followed by 1-aryl-2-arylazo-2-triphenylphosphor-
anylidene-ethanones (see sections 3.3 and 3.4). On the assumption that other products of the thermal decomposition of the phosphorane (67a) were being lost due to their volatility, the thermolysis of the phosphorane (67a) was also studied in solution. However heating the phosphorane (67a) in dimethylformamide again gave triphenylphosphine (53%) and triphenylphosphine oxide (40%) as the only identified products. Lack of time prevented the further elucidation of the mode of thermolysis of 1-phenylazo-1-triphenylphosphoranylidene-propan-2-one (67a).

Ethyl 2-phenylazo-2-triphenylphosphoranylidene-ethanoate (67b) was readily prepared (Scheme 15) in good yield (71%) by the reaction of ethyl bromoacetate (64b) with triphenylphosphine to give the known \( ^{135} \) phosphonium salt (65b) followed by coupling of the latter with benzenediazonium chloride under the usual conditions, and treatment of the intermediate phosphonium salt (66) obtained, with sodium carbonate. The melting-point of the arylazomethylene phosphorane (67b) prepared in the present work was in full agreement with that quoted \( ^{134} \) for this known compound in the literature. The combustion analysis and spectroscopic properties of the phosphorane (67b) were also fully in accord with the assigned structure.

Heating ethyl 2-phenylazo-2-triphenylphosphoranylidene-ethanoate (67b) at 165°/0.2mmHg in a Kugelrohr apparatus gave a product mixture which was readily separated by chromatography into triphenylphosphine (43%), triphenylphosphine oxide (12%), and a moderate yield (37%) of a third product identified by comparison with an authentic sample as N-phenyltriphenyl-phosphineimine (47). The isolation of the latter compound
suggests that thermolysis of the phosphorane (67b) does occur as anticipated to give the iminophosphorane (47) and ethoxycarbonyl cyanide (69b) though none of the latter product was isolated, possibly due to its volatility or instability under the thermolysis conditions used. Moreover the formation of triphenylphosphine in significant yield again suggests the simultaneous operation of an alternative thermolysis pathway for the phosphorane (67b). However, lack of time prevented further experiments being conducted to elucidate the nature of the thermolysis of the phosphorane (67b) in more detail.
3.6 Experimental

General experimental details are described in the Appendix.

2-Bromo-1-(2-nitrophenyl)ethanone (16)

2-Bromo-1-(2-nitrophenyl)ethanone (16) was prepared as described in Chapter 2, Section 5.

2-Nitrobenzoylmethyltriphenylphosphonium Bromide (17)

A solution of triphenylphosphine (6.3 g, 0.024 mol) in anhydrous toluene (30.0 ml) was added, dropwise with stirring at room temperature to a solution of 2-bromo-1-(2-nitrophenyl)ethanone (16) (3.9 g, 0.016 mol) in anhydrous toluene (10.0 ml) and the mixture was heated under reflux for 20 h. The cooled mixture deposited 2-nitrobenzoylmethyltriphenylphosphonium bromide (17) (7.5 g; 93%) which formed colourless plates, m.p. 215-216° (from ethanol), \( \nu_{\text{max}} \) 1680 (CO) and 1530 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta \) [(CD\(_3\))\(_2\)SO] 8.35-7.66 (19H, m, ArH) and (2H, d, J12Hz, CH\(_2\)).

Found: C, 62.0; H, 4.1; N, 2.7%; (M\(^+\)-Br), 426. \( \text{C}_{26}\text{H}_{21}\text{BrNO}_{3}\text{P} \) requires: C, 61.7; H, 4.2; N, 2.8%; M, 506.

Evaporation of the toluene mother liquor yielded a brown gum (2.8 g) which was shown by t.l.c. in toluene over silica to be a mixture consisting largely of unreacted triphenylphosphine.
1-(2-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19)

A solution of redistilled aniline (0.72 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated, dropwise at 0-5° (ice-salt bath), with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting benzenediazonium chloride solution was stirred for a further 5 min then added dropwise with stirring at 0-5°, to a solution of 2-nitrobenzoylmethyltriphenylphosphonium bromide (17) (3.8 g, 0.0075 mol) and anhydrous sodium acetate (1.6 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml). The mixture was stirred in the melting ice bath for 1 h, then filtered to afford 1-(2-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19) (3.3 g; 89%) which formed bright yellow plates, m.p. 136-137° (from ethanol-dimethylformamide), $\nu_{\text{max}}$ 1530 and 1345 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 8.02-6.58 (m, ArH).

Found: C, 72.7; H, 4.6; N, 8.0%; m/e 458.

C$_{32}$H$_{24}$N$_3$O$_3$P requires: C, 72.6; H, 4.6; N, 7.9%; M, 529.

Evaporation of the aqueous ethanol mother liquor gave a gum which was treated with water (5.0 ml) and extracted with methylene chloride to yield a red gum (0.8 g) which was shown by t.l.c. in toluene over alumina to be an unresolvable three-component mixture which was not further investigated.

The Thermolysis of 1-(2-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19)

(a) A solution of 1-(2-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19) (1.3 g, 0.0025 mol) in
dimethylformamide (25.0 ml) was heated under reflux for 10 min. Evaporation afforded a dark red gum (1.3 g) which was chromatographed over silica.

Elution with toluene gave an uncharacterised brown oil (0.05 g).

Elution with toluene-methylene chloride (80:20) yielded 1-phenyl-1H-indole-2,3-dione (21) (0.2 g; 36%) which formed orange needles, m.p. 140-141° (from toluene-light petroleum/ b.p. 80-100°) (lit., 121 138°), $\nu_{\text{max}}$ 1750 and 1620 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 7.70-6.82 (m, ArH).

**Found:** C, 75.0; H, 4.1; N, 6.0%; M, 223.

**Calc.** for C$_{14}$H$_9$N: C, 75.3; H, 4.1; N, 6.3%; M, 223.

Elution with methylene chloride followed by diethyl ether gave only uncharacterisable gums (total 0.47 g).

Elution with ethyl acetate afforded triphenylphosphine oxide (0.28 g; 40%), m.p. 153-154° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methanol gave an uncharacterised gum (0.4 g).

(b) 1-(2-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (19) (1.6 g, 0.003 mol) was heated under reduced pressure in a Kugelrohr apparatus at 180°/0.2mmHg for 1 h. No material distilled and the residual brown gum (1.6 g) was chromatographed over alumina.

Elution with toluene-methylene chloride (50:50) gave an
uncharacterised brown gum (0.21 g).

Elution with diethyl ether yielded triphenylphosphine oxide (0.5 g; 60%), m.p. 153-154° (lit., 157-158°), which was identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate followed by methanol gave only intractable brown gums (total 0.31 g).

6-Phenylindolo[2,3-b]quinoxaline (22)

A solution of 1-phenyl-1H-indole-2,3-dione (21) (0.025 g, 0.0001 mol) and ortho-phenylenediamine (0.01 g, 0.0001 mol) in glacial acetic acid (1.0 ml) was heated under reflux for 3 h. Evaporation afforded 6-phenylindolo[2,3-b]quinoxaline (22) (0.03 g; 100%) which formed bright yellow needles, m.p. 237-238° (from ethanol-dimethylformamide), $\nu_{\text{max}}$ 1640 (C=N) cm$^{-1}$.

Found: C, 81.0; H, 4.3; N, 14.0%; M$^+$, 295.

C$_{20}$H$_{13}$N$_3$ requires: C, 81.4; H, 4.4; N, 14.2%; M, 295.

Benzoylmethyltriphenylphosphonium Bromide (37)

Benzoylmethyltriphenylphosphonium bromide (37) was prepared (yield 98%) by the reaction of 2-bromo-1-phenyl-ethanone (36) with triphenylphosphine as described in the literature, m.p. 269-271° (lit., 273-274°), and was used without further purification.

1-Phenyl-2-phenylazo-2-triphenylphosphoranylidenemethanone (38)

A solution of redistilled aniline (0.72 g, 0.0078 mol)
in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise, with stirring at 0-5° (ice-salt bath), with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting benzenediazonium chloride solution was stirred for a further 5 min then added dropwise, with stirring at 0-5°, to a solution of benzoylmethyltriphenylphosphonium bromide (37) (3.5 g, 0.0075 mol) and anhydrous sodium acetate (1.6 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration yielded a solid which was combined with a second crop obtained by evaporating the filtrate, treating the residue with water (5.0 ml), extraction with methylene chloride, and treatment of the gum with diethyl ether to give 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38) (3.2 g; 95%) which formed bright yellow plates, m.p. 163-164° (lit., 118 160-162°) (from ethanol-dimethylformamide), δ(CDCl₃) 8.04-6.88 (m, ArH).

**Found:** C, 79.3; H, 5.3; N, 5.8%; M⁺, 484.
**Calc. for C₃₂H₂₅N₂OP:** C, 79.4; H, 5.2; N, 5.8%; M, 484.

Evaporation of the ethereal mother liquor afforded a negligible amount of a brown gum.

**The Thermolysis of 1-Phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38)**

(a) A solution of 1-phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38) (12.1 g, 0.025 mol) in dimethylformamide (250 ml) was heated under reflux for 0.5 h. Evaporation afforded a dark red oil (12.0 g) which was chromatographed over silica.
Elution with toluene-light petroleum/b.p. 40-60° (40:60) yielded α-N-phenyliminobenzeneacetonitrile (40) (2.8 g; 55%) which formed bright yellow plates (from light petroleum), m.p. 70-71° (lit., 72°), $\nu_{\text{max}}$ 2220 (C=N) and 1580 (C=N) cm$^{-1}$.

Found: C, 81.7; H, 5.1; N, 13.5%; M$^+$, 206.
Calc. for C$_{14}$H$_{10}$N$_2$: C, 81.6; H, 4.9; N, 13.6%; M, 206.

Elution with toluene-methylene chloride (50:50) gave a brown oil (0.42 g) which was treated with diethyl ether-light petroleum to yield benzanilide (41) (0.39 g; 8%), m.p. 156-158° (lit., 165°), identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the diethyl ether-light petroleum mother liquor gave a negligible amount of gum.

Elution with methylene chloride-diethyl ether (80:20) afforded an uncharacterised dark red oil (3.6 g) which was shown by t.l.c. in methylene chloride to be a three-component mixture which was not further investigated.

Elution with diethyl ether-ethyl acetate (50:50) gave triphenylphosphine oxide (2.9 g; 42%), m.p. 158-159° (lit., 157-158°), which was identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethanol afforded an uncharacterised brown oil (1.6 g).

(b) 1-Phenyl-2-phenylazo-2-triphenylphosphoranylidene-ethanone (38) (1.9 g, 0.004 mol) was gradually heated under reduced pressure to 210°/0.2mmHg over 40 min in a Kugelrohr apparatus. The distillate obtained was shown to be α-N-phenyliminobenzeneacetonitrile (40) (0.71 g; 86%), m.p. 66-68° (lit., 72°), identical (m.p. and i.r. spectrum) to an authentic sample.
The involatile gum (1.2 g) was triturated with ethyl acetate to yield triphenylphosphine oxide (1.1 g; 99%), m.p. 152-155° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

The Hydrolysis of α-N-Phenyliminobenzeneacetonitrile (40)

(a) α-N-Phenyliminobenzeneacetonitrile (40) (0.2 g, 0.001 mol) was stirred in concentrated sulphuric acid (5.0 ml) at room temperature for 1 h. The solution was treated with ice (50.0 g) and the mixture was extracted with methylene chloride to give an orange oil (0.12 g) which was treated with light petroleum to afford benzoic acid (0.08 g; 66%), m.p. 121-122° (lit., 113-122°), identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the light petroleum mother liquor yielded a brown gum (0.04 g) which was not further investigated.

(b) A solution of α-N-phenyliminobenzeneacetonitrile (40) (0.2 g, 0.001 mol) in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide (2.5 ml) and the mixture was heated under reflux for 1 h. Evaporation and treatment with water (2.0 ml) precipitated benzanilide (41) (0.1 g; 51%), m.p. 165-166° (lit., 137 163°), identical (m.p. and i.r. spectrum) to an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride yielded a negligible amount of gum.

Acidification of the aqueous layer with concentrated hydrochloric acid and extraction with methylene chloride also afforded a negligible amount of gum.
Benzoyl Cyanide (46)

Benzoyl cyanide (46) was prepared (yield 14%) by the reaction of benzoyl chloride with copper cyanide as described in the literature, 129 m.p. 31-33° (lit., 129 32-33°), and was used without further purification.

N-Phenyltriphenylphosphineimine (47)

N-Phenyltriphenylphosphineimine (47) was prepared (yield 85%) by the reaction of phenyl azide with triphenylphosphine as described by Staudinger and Meyer, 130 m.p. 123-124° (lit., 130 130-131°), and was used without further purification.

α-N-Phenylaminobenzeneacetonitrile (42)

α-N-Phenylaminobenzeneacetonitrile (42) was prepared (yield 70%) by the reaction of benzaldehyde with aniline and potassium cyanide as described in the literature, 128 m.p. 75-77° (lit., 128 84-85°), and was used without further purification.

α-N-Phenyliminobenzeneacetonitrile (40)

(a) A solution of N-phenyltriphenylphosphineimine (47) (0.71 g, 0.002 mol) and benzoyl cyanide (46) (0.26 g, 0.002 mol) in anhydrous toluene (30.0 ml) was heated under reflux for 4 h. Evaporation gave a yellow solid (0.96 g) which was extracted with boiling light petroleum leaving insoluble triphenylphosphine oxide (0.5 g; 90%), m.p. 154-155° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.
Evaporation of the light petroleum mother liquor afforded α-N-phenylinminobenzeneacetonitrile (40) (0.4 g; 97%), m.p. 65-67° (lit., 127 72°), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (c) later.

(b) An intimate mixture of benzoyle cyanide (46) (0.52 g, 0.004 mol) and N-phenyltriphenylphosphineimine (47) (1.4 g, 0.004 mol) was gradually heated under reduced pressure in a Kugelrohr apparatus. The distillate at 170°/0.1 mmHg was collected to give α-N-phenylinminobenzeneacetonitrile (40) (0.8 g; 97%), m.p. 65-67° (lit., 127 72°), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (c) later.

The involatile residue was triphenylphosphine oxide (1.1 g; 99%), m.p. 151-153° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

(c) α-N-Phenylinminobenzeneacetonitrile (40) was prepared (yield 66%) by the oxidation of α-N-phenylaminobenzeneacetonitrile (42) and manganese dioxide as described by Aurich, m.p. 69-70° (lit., 127 72°).

2-Bromo-1,2-diphenylethanone (32)

2-Bromo-1,2-diphenylethanone (32) was prepared (yield 67%) by the bromination of 1,2-diphenylethanone as described in the literature, m.p. 46-49° (lit., 54-55°), and was used without further purification.

α-Benzoylbenzyltriphenylphosphonium Bromide (33)

A solution of 2-bromo-1,2-diphenylethanone (32) and
triphenyolphosphine (6.6 g, 0.025 mol) in anhydrous benzene (150 ml) was heated under reflux for 17 h. Filtration of the cooled mixture gave a solid which was combined with a second crop obtained by evaporating the filtrate and triturating the residue with diethyl ether to give α-benzoylbenzyl-triphenyolphosphonium bromide (33) (5.2 g; 77%) which formed colourless microcrystals, m.p. 153-154° (from ethyl acetate-ethanol), $\nu_{\text{max}}$ 1665 (CO) cm$^{-1}$, δ[(CD$_3$)$_2$SO] 8.38 (1H, d, J12Hz, CH) and 8.19-6.99 (25H, m, ArH).

Found: M+, 457.17204.

C$_{32}$H$_{26}$OP requires: M, 457.17212.

Evaporation of the diethyl ether mother liquor gave a brown oil (4.0 g) which was shown by t.l.c. in toluene over silica to be a mixture of triphenyolphosphine and α-benzoylbenzyltriphenyolphosphonium bromide (33). No attempt was made to resolve the mixture.

1,2-Diphenyl-2-triphenyolphosphoranylidene-ethanone (34)

A suspension of α-benzoylbenzyltriphenyolphosphonium bromide (33) (5.7 g, 0.01 mol) in 10% w/v aqueous sodium carbonate (50.0 ml) was stirred at room temperature for 17 h. Filtration gave 1,2-diphenyl-2-triphenyolphosphoranylidene-ethanone (34) (4.6 g; 100%), m.p. 190-192° (lit., 122 191-192°), $\nu_{\text{max}}$ 1665 (CO) cm$^{-1}$, and was used without further purification.

The Attempted Thermolysis of 1,2-Diphenyl-2-triphenyolphosphoranylidene-ethanone (34)

A solution of 1,2-diphenyl-2-triphenyolphosphoranylidene-
ethanone (34) (1.8 g, 0.004 mol) in dimethylformamide (60.0 ml) was heated under reflux for 6.5 h. Evaporation gave the unreacted phosphorane (34) (1.8 g; 100%), m.p. 184-186°, identical (m.p. and i.r. spectrum) to an authentic sample.

2-Bromo-1-(4-nitroph enyl)ethanone (58a)

2-Bromo-1-(4-nitroph enyl)ethanone (58a) was prepared (yield 75%) by the bromination of 1-(4-nitroph enyl)ethanone as described in the literature, \(^{131}\) m.p. 92-94° (lit., \(^{131}\) 98°), and was used without further purification.

4-Nitrobenzoylmethyltriphenylphosphonium Bromide (59a)

A solution of 2-bromo-1-(4-nitroph enyl)ethanone (58a) (12.2 g, 0.05 mol) in anhydrous benzene (60.0 ml) was added, with swirling, to a solution of triphenylphosphine (12.6 g, 0.048 mol) in anhydrous benzene (50.0 ml) and the mixture was left stoppered at room temperature for 17 h by which time a precipitate had formed. Filtration gave 4-nitrobenzoylmethyltriphenylphosphonium bromide (59a) (20.9 g; 86%) which formed yellow microcrystals, m.p. 213-214° (from ethyl acetate-ethanol) (lit., \(^{132}\) 150°), \(v_{\text{max}}\) 1690 (CO) and 1525 and 1345 (NO\(_2\)) cm\(^{-1}\), \(\delta\) [(CD\(_3\))\(_2\)SO] 8.42-7.70 (m, ArH).

\[\text{Found: } M^+ , 426.12581.\]

Calc. for C\(_{26}\)H\(_{21}\)BrNO\(_3\)P: M, 426.12590.

Evaporation of the benzene filtrate afforded an unidentified brown oil (3.0 g).
1-(4-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60a)

A solution of redistilled aniline (0.72 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise at 0-5° (ice-salt bath), with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting benzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of 4-nitrobenzoylmethyltriphenylphosphonium bromide (59a) (3.8 g, 0.0075 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml). The mixture was stirred in the melting ice bath for 1 h, then filtered to yield 1-(4-nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60a) (3.4 g; 92%) which formed yellow microcrystals, m.p. 139-140° (from ethanol-dimethylformamide), \( \nu_{\text{max}} \) 1525 and 1365 (NO\(_2\)) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.22 (2H, d, J9Hz, ArH), 8.05 (2H, d, J9Hz, ArH), and 7.80-6.79 (20H, m, ArH).

Found: M\(^{+}\), 529.15521.
C\(_{32}\)H\(_{24}\)N\(_3\)O\(_3\)P requires: M, 529.15552.

Evaporation of the aqueous ethanolic filtrate gave a gum which was treated with water (5.0 ml) and extracted with methylene chloride to yield a dark red oil (0.45 g) which was shown by t.l.c. in toluene over alumina to be an unresolvable three-component mixture which was not further investigated.

The Thermolysis of 1-(4-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60a)

1-(4-Nitrophenyl)-2-phenylazo-2-triphenylphosphoranylidene-
ethanone (60a) (2.1 g, 0.004 mol) was gradually heated to 190°/0.1 mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (2.1 g) which was chromatographed over alumina.

Elution with toluene-light petroleum/b.p. 40-60° (75:25) afforded α-N-phenylimino-4-nitrobenzeneacetonitrile (62a) (0.63 g; 63%) which formed yellow microcrystals, m.p. 127-128° (from light petroleum/b.p. 80-100°), ν max 2200 (C≡N) and 1515 and 1345 (NO₂) cm⁻¹, δ[(CD₃)₂SO] 8.40-7.11 (m, ArH).

Found: C, 66.9; H, 3.6; N, 16.4%; M⁺, 251.
C₁₄H₉N₃O₂ requires: C, 66.9; H, 3.6; N, 16.7%; M, 251.

Elution with toluene afforded a negligible amount of brown gum.

Elution with methylene chloride gave 4-nitrobenzanilide (63a) (0.09 g; 9%) which formed yellow microcrystals, m.p. 210-211° (from ethanol-glacial acetic acid) (lit., 137 216°), ν max 3330 (NH), 1650 (CO), and 1520 and 1350 (NO₂) cm⁻¹, δ[(CD₃)₂SO] 10.57 (1H, s, NH), 8.38 (2H, d, J2Hz, ArH), 8.35 (2H, d, J2Hz, ArH), and 7.80-7.14 (5H, m, ArH).

Found: M⁺, 242.06762.

Elution with diethyl ether yielded triphenylphosphine oxide (1.1 g; 99%), m.p. 155-156° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

4-Methoxybenzoylmethyltriphenylphosphonium Bromide (59b)

4-Methoxybenzoylmethyltriphenylphosphonium bromide (59b) was prepared (yield 91%) by the reaction of 2-bromo-1-(4-methoxyphenyl)ethanone (58b) with triphenylphosphine as
described in the literature, \( m.p. \ 220-221^\circ \) (lit., 222°), and was used without further purification.

**1-(4-Methoxyphenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60b)**

A solution of redistilled aniline (0.72 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise at 0-5°C (ice-salt bath) with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting benzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°C, to a solution of 4-methoxybenzoylmethyltriphenylphosphonium bromide (59b) (3.7 g, 0.0075 mol) and anhydrous sodium acetate (1.6 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml), and the mixture was stirred in the melting ice bath for 1 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to give an orange oil (4.0 g) which solidified in contact with diethyl ether to yield 1-(4-methoxyphenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60b) (3.8 g; 99%) which formed bright yellow needles of the ethanol solvate, m.p. 94-95°C (from ethanol-glacial acetic acid), \( \delta(CDCI_3) \ 8.08-6.84 \) (24H, m, ArH) and 3.80 (3H, s, CH\(_3\)).

*Found: C, 75.2; H, 5.9; N, 4.9%; m/e 504.*

\( C_{33}H_{27}N_2O_2P\cdot EtOH \) requires: C, 75.0; H, 5.8; N, 5.0%; M, 514.

Evaporation of the ethereal mother liquor afforded only a negligible amount of gum.
The Thermolysis of 1-(4-Methoxyphenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60b)

1-(4-Methoxyphenyl)-2-phenylazo-2-triphenylphosphoranylidene-ethanone (60b) (2.1 g, 0.004 mol) was gradually heated to 170°/0.1mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (2.1 g) which was chromatographed over silica.

Elution with toluene-light petroleum/b.p.40-60° (75:25) yielded α-N-phenylimino-4-methoxybenzeneacetonitrile (62b) (0.65 g; 69%) which formed bright yellow plates, m.p. 118-119° (from light petroleum/b.p.80-100°), v_max 2220 (C≡N) and 1610 (C=N) cm⁻¹, δ(CDCl₃) 8.07 (2H, d, J10Hz, ArH), 7.50-6.95 (7H, m, ArH), and 3.87 (3H, s, CH₃).

Found: C, 76.4; H, 5.2; N, 11.4%; M⁺, 236. C₁₅H₁₂N₂O requires: C, 76.3; H, 5.1; N, 11.9%; M⁺, 236.

Elution with toluene and methylene chloride gave uncharacterised oils (total 0.25 g).

Elution with diethyl ether yielded triphenylphosphine oxide (0.72 g; 65%), m.p. 149-151° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethanol gave an uncharacterised gum (0.31 g).

2-(4-Methoxyphenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54c)

A solution of 4-methoxyaniline hydrochloride (1.3 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The
resulting 4-methoxybenzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of benzoylmethyltriphenylphosphonium bromide (37) (3.5 g, 0.0075 mol) and anhydrous sodium acetate (2.3 g, 0.028 mol) in water (4.0 ml) and ethanol (30.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration afforded 2-(4-methoxyphenylazo)-1-phenylphosphoranylidene-ethanone (54c) (3.7 g; 96%) which formed bright yellow needles, m.p. 178-179° (from ethanol-dimethylformamide), δ(CDCl₃) 8.08-7.20 (20H, m, ArH), 6.89 (2H, d, J10Hz, ArH), 6.63 (2H, d, J10Hz, ArH), and 3.66 (3H, s, CH₃).

Found: C, 77.0; H, 5.4; N, 5.5%; m/e 504.

C₃₃H₂₇N₂O₂P requires: C, 77.0; H, 5.3; N, 5.4%; M, 514.

Evaporation of the ethanolic filtrate gave a gum which was treated with water (5.0 ml) and extracted with methylene chloride to give only a negligible quantity of red oil.

The Thermolysis of 2-(4-Methoxyphenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54c)

(a) A solution of 2-(4-methoxyphenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54c) (2.6 g, 0.005 mol) in dimethylformamide (120 ml) was heated under reflux for 20 min. Evaporation gave a dark red oil (2.5 g) which was chromatographed over silica.

Elution with toluene-light petroleum/b.p. 40-60° (40:60) yielded triphenylphosphine (0.41 g; 31%), m.p. 72-74° (lit., 136 80°), identical (m.p. and i.r. spectrum) to an authentic sample.
Elution with toluene afforded α-N-(4-methoxyphenyl)iminobenzeneacetonitrile (56c) (0.25 g; 21%) which formed bright yellow needles, m.p. 78° (from light petroleum), ν\textsubscript{max} 2210 (C≡N) cm\textsuperscript{-1}, δ(CDC\textsubscript{3}) 8.16-7.42 (5H, m, ArH), 7.28 (2H, d, J8Hz, ArH), 6.94 (2H, d, J8Hz, ArH), and 3.79 (3H, s, CH\textsubscript{3}).

Found: C, 76.6; H, 5.1; N, 11.9%; M\textsuperscript{+}, 236.

C\textsubscript{15}H\textsubscript{12}N\textsubscript{2}O requires: C, 76.3; H, 5.1; N, 11.9%; M, 236.

Elution with toluene-methylene chloride (60:40), methylene chloride-diethyl ether (60:40), and diethyl ether gave unidentified oils (total 1.5 g).

Elution with ethyl acetate yielded triphenylphosphine oxide (0.53 g; 38%), m.p. 151-152° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethanol gave an uncharacterised brown oil (0.25 g).

(b) 2-(4-Methoxyphenylazo)-1-phenyl-2-triphenylphosphoranylideneyethanone (54c) (1.0 g, 0.002 mol) was gradually heated to 190°/0.2mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (1.0 g) which was chromatographed over silica.

Elution with light petroleum/b.p. 40-60° yielded triphenylphosphine (0.2 g; 38%), m.p. 68-70° (lit., 136 80°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with toluene-light petroleum/b.p. 40-60° (25:75) afforded α-N-(4-methoxyphenyl)iminobenzeneacetonitrile (56c) (0.21 g; 44%), m.p. 67-68°, identical (m.p. and i.r. spectrum) to a sample obtained in (a) before.

Elution with toluene gave an uncharacterised dark brown gum (0.22 g).
Elution with diethyl ether gave triphenylphosphine oxide (0.32 g; 56%), m.p. 153-154° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

1-(4-Methoxyphenyl)-2-(4-methoxyphenylazo)-2-triphenylphosphoranylidene-ethanone (60c)

A solution of 4-methoxyaniline hydrochloride (2.5 g, 0.016 mol) in 5M aqueous hydrochloric acid (7.8 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (1.1 g, 0.016 mol) in water (4.0 ml). The resulting 4-methoxybenzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of 4-methoxybenzoylmethyltriphenylphosphonium bromide (59b) (7.4 g, 0.015 mol) and anhydrous sodium acetate (4.6 g, 0.056 mol) in water (8.0 ml) and ethanol (60.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration gave 1-(4-methoxyphenyl)-2-(4-methoxyphenylazo)-2-triphenylphosphoranylidene-ethanone (60c) (7.9 g; 97%) which formed yellow plates, m.p. 179-180° (from ethanol-dimethylformamide), δ(CDCl₃) 8.10-6.59 (23H, m, ArH), 3.84 (3H, s, CH₃), and 3.68 (3H, s, CH₃).

Found: C, 74.8; H, 5.2; N, 5.0%; (M⁺-4-MeOC₆H₄COCN), 383.

C₃₄H₂₃N₂O₃P requires: C, 75.0; H, 5.3; N, 5.2%; M, 544.

Evaporation of the ethanolic filtrate gave a gum which was treated with water (10.0 ml) and extracted with methylene chloride to yield a brown oil (0.35 g) which was shown by t.l.c. in methylene chloride over alumina to be a multicomponent
mixture which was not further investigated.

The Thermolysis of 1-(4-Methoxyphenyl)-2-(4-methoxyphenylazo)-2-triphenylphosphoranylidene-ethanone (60c)

1-(4-Methoxyphenyl)-2-(4-methoxyphenylazo)-2-triphenylphosphoranylidene-ethanone (60c) (1.6 g, 0.003 mol) was gradually heated to 190°/0.2mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (1.6 g) which was chromatographed over alumina.

Elution with toluene-light petroleum/b.p. 40-60° (50:50) gave triphenylphosphine (0.41 g; 52%), m.p. 76-77° (lit., 136 80°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with toluene afforded α-N-(4-methoxyphenyl)imino-4-methoxybenzeneacetonitrile (62c) (0.39 g; 49%) which formed bright yellow plates, m.p. 95-96° (from light petroleum/b.p. 80-100°), $\nu_{\text{max}}$ 2220 (C≡N) and 1610 (C=N) cm$^{-1}$, δ(CDC$_3$) 8.05 (2H, d, J8Hz, ArH), 7.30-6.90 (6H, m, ArH), 3.88 (3H, s, OCH$_3$), and 3.82 (3H, s, OCH$_3$).

Found: C, 72.5; H, 5.4; N, 10.8%; M$^+$, 266.

C$_{16}$H$_{14}$N$_2$O$_2$ requires: C, 72.2; H, 5.3; N, 10.5%; M, 266.

Further elution with toluene and methylene chloride gave uncharacterised brown gums (total 0.5 g).

Elution with diethyl ether afforded triphenylphosphine oxide (0.27 g; 32%), m.p. 148-150° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.
2-(4-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54a)

A solution of 4-nitroaniline hydrochloride (1.4 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting 4-nitrobenzenediazofluoride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of benzoylmethyltriphenylphosphonium bromide (37) (3.5 g, 0.0075 mol) and anhydrous sodium acetate (2.3 g, 0.028 mol) in water (4.0 ml) and ethanol (30.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration afforded 2-(4-nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54a) (3.9 g; 99%) which formed orange microcrystals, m.p. 182-183° (from ethanol-dimethylformamide), \[ \nu_{\text{max}} \] 1510 and 1350 (NO₂) cm⁻¹, δ(CDCł) 8.06-6.85 (m, ArH). Found: C, 72.6; H, 4.2; N, 7.5%; (M⁺,-PhCOCN), 398. C₃₂H₂₄N₃O₃P requires: C, 72.6; H, 4.5; N, 7.9%; M, 529.

Evaporation of the filtrate gave a gum which was treated with water (5.0 ml) and extracted with methylene chloride to give only a negligible amount of dark red gum.

The Thermolysis of 2-(4-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54a)

2-(4-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54a) (1.6 g, 0.003 mol) was gradually heated to 175°/0.2mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (1.6 g) which was chromatographed over alumina.
Elution with toluene-light petroleum/b.p. 40-60° and toluene afforded small amounts of uncharacterised brown gums (total 0.08 g).

Elution with toluene-methylene chloride (50:50) yielded 4'-nitrobenzanilide (57a) (0.18 g; 25%) which formed colourless needles, m.p. 201-202° (from toluene-ethyl acetate) (lit., 138 199°), $v_{\text{max}}$ 3350 (NH), 1665 (CO), and 1510 and 1350 (NO$_2$) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.32-7.53 (m, ArH).

Found: C, 72.8; H, 4.8; N, 7.9%; M$^+$, 242.
Calc. for C$_{13}$H$_{10}$N$_2$O$_3$: C, 72.6; H, 4.5; N, 7.9%; M, 242.

Elution with toluene-methylene chloride (25:75) gave an uncharacterised red gum (0.4 g).

Elution with ethyl acetate afforded triphenylphosphine oxide (0.75 g; 90%), m.p. 151-152° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

2-(2-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethanone (54b)

A solution of 2-nitroaniline (1.1 g, 0.0078 mol) in 5M aqueous hydrochloric acid (3.9 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting 2-nitrobenzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of benzoylmethyltriphenylphosphonium bromide (37) (3.5 g, 0.0075 mol) and anhydrous sodium acetate (1.6 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration afforded a solid which was combined with a second crop obtained
by evaporating the filtrate, treatment of the residue with water (5.0 ml), extraction of the resulting solution with methylene chloride, and treatment of the gum obtained with diethyl ether to give 2-(2-nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethane (54b) (3.9 g; 99%) which formed orange microcrystals, m.p. 172-173° (from ethanol-dimethylformamide), νmax 1515 and 1340 (NO2) cm⁻¹, δ(CDC13) 8.03-6.78 (m, ArH).

Found: C, 72.8; H, 4.8; N, 7.9%; M⁺, 529.

C32H24N3O3P requires: C, 72.6; H, 4.5; N, 7.9%; M, 529.

Evaporation of the ethereal mother liquor gave a negligible amount of gum.

The Thermolysis of 2-(2-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethane (54b)

2-(2-Nitrophenylazo)-1-phenyl-2-triphenylphosphoranylidene-ethane (54b) (1.6 g, 0.003 mol) was gradually heated to 180°/0.2 mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (1.6 g) which was chromatographed over alumina.

Elution with toluene-light petroleum/b.p. 40-60° (25:75) yielded α-N-(2-nitrophenyl)iminobenzeneacetonitrile (56b) (0.08 g; 11%) which formed yellow needles, m.p. 107-108° (from light petroleum/b.p. 80-100°), νmax 2200 (C≡N), 1610 (C=N), and 1520 and 1340 (NO2) cm⁻¹, δ(CDC13) 8.34-7.22 (m, ArH).

Found: M⁺, 251.06941.

C14H9N3O2 requires: M, 251.06947.

followed by 2'-nitrobenzanilide (57b) (0.03 g; 4%) which formed yellow needles, m.p. 92° (from light petroleum/b.p.
40-60° (lit., 139 92°), νmax 3460 (NH), and 1500 and 1340 (NO₂) cm⁻¹.

Found: M⁺, 242.06808.  

Further elution with toluene-light petroleum/b.p. 40-60° gave only uncharacterised gums (total 0.38 g).

Elution with diethyl ether yielded triphenylphosphine oxide (0.78 g; 94%), m.p. 148-150° (lit., 136 157-158°), identical (m.p. and i.r. spectrum) to an authentic sample.

**Acetylmethyltriphenylphosphonium Chloride (65a)**

Acetylmethyltriphenylphosphonium chloride (65a) was prepared (yield 56%) by the reaction of 1-chloropropan-2-one (64a) and triphenylphosphine as described in the literature, m.p. 233-236° (lit., 133 237°), and was used without further purification.

**1-Phenylazo-1-triphenylphosphoranylidenepropan-2-one (67a)**

A solution of redistilled aniline (1.0 g, 0.011 mol) in 5M aqueous hydrochloric acid (5.2 ml) was stirred and treated dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.79 g, 0.012 mol) in water (3.0 ml). The resulting benzenediazonium chloride solution was stirred for 5 min then added dropwise, with stirring at 0-5°, to a solution of acetylmethyltriphenylphosphonium chloride (65a) (3.6 g, 0.01 mol) and anhydrous sodium acetate (2.1 g, 0.025 mol) in water (5.0 ml) and ethanol (60.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Filtration afforded
1-phenylazo-1-triphenylphosphoranylidenepropan-2-one (67a) (3.4 g; 80%) which formed bright yellow needles, m.p. 175-176° (from ethanol) (lit., 134 167°), δ(CDCl₃) 7.70-6.94 (20H, m, ArH) and 2.62 (3H, s, CH₃).

Found: C, 76.5; H, 5.5; N, 6.7%; M⁺, 422.
Calc. for C₂₇H₂₃N₂OP: C, 76.8; H, 5.5; N, 6.6%; M, 422.

Evaporation of the ethanolic filtrate gave a gum which was treated with water (10.0 ml) and extracted with methylene chloride to give a red oil (1.3 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multi-component mixture and was not further investigated.

The Attempted Thermolysis of 1-Phenylazo-1-triphenylphosphoranylidenepropan-2-one (67a)

(a) A solution of 1-phenylazo-1-triphenylphosphoranylidenepropan-2-one (67a) (1.1 g, 0.0025 mol) in dimethylformamide (25.0 ml) was heated under reflux for 1.5 h. Evaporation afforded a brown oil (1.1 g) which was chromatographed over silica.

Elution with methylene chloride-light petroleum/b.p.40-60° (60:40) gave triphenylphosphine (0.35 g; 53%), m.p. 78-80° (lit., 136 80°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride-diethyl ether (60:40) gave an intractable oil (0.21 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable four-component mixture which was not further investigated.

Elution with ethyl acetate yielded triphenylphosphine
oxide (0.28 g; 40%), m.p. 147-148° (lit.,
identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethanol afforded an intractable brown gum
(0.2 g) from which no identifiable material could be obtained.

(b) 1-Phenylazo-1-triphenylphosphoranylidene propan-2-one
(67a) (1.7 g, 0.004 mol) was gradually heated to 200°/0.2 mmHg
over 40 min in a Kugelrohr apparatus to give a brown gum (1.7
g) which was chromatographed over alumina.

Elution with toluene-light petroleum/b.p. 40-60° (30:70)
gave triphenylphosphine (0.75 g; 72%), m.p. 69-71° (lit.,
80°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with toluene, followed by methylene chloride,
then diethyl ether afforded only small amounts of intractable
gums (total 0.24 g).

Elution with ethanol yielded triphenylphosphine oxide
(0.14 g; 13%), m.p. 153-154° (lit.,
identical (m.p. and i.r. spectrum) to an authentic sample.

Ethoxycarbonylmethyltriphenylphosphonium Bromine (65b)

Ethoxycarbonylmethyltriphenylphosphonium bromide (65b)
was prepared (yield 100%) by the reaction of ethyl bromo-
acetate (64b) with triphenylphosphine as described in the
literature, m.p. 154-155° (lit.,
and was used
without further purification.

α-Phenylazo-ethoxycarbonylmethyltriphenylphosphonium Bromide
(66)

A solution of redistilled aniline (0.72 g, 0.0078 mol) in
5M aqueous hydrochloric acid (3.9 ml) was stirred and treated
dropwise at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.55 g, 0.008 mol) in water (2.0 ml). The resulting benzenediazonium chloride solution was then added dropwise with stirring at 0-5°, to a solution of ethoxycarbonylmethyltriphosphonium bromide (65b) (3.2 g, 0.0075 mol) and anhydrous sodium acetate (1.6 g, 0.02 mol) in water (4.0 ml) and ethanol (30.0 ml) and the mixture was stirred in the melting ice bath for 1 h. Evaporation, treatment of the residue with water (5.0 ml) and extraction of the solution with methylene chloride gave an orange oil (4.4 g) which when treated with diethyl ether-methylene chloride yielded α-phenylazo-ethoxycarbonylmethyltriphenylphosphonium bromide (66) (2.9 g; 71%) which formed bright yellow plates, m.p. 146-147° (from ethyl acetate-ethanol), \( \nu_{\text{max}} \) 1710 (CO) cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 8.00-6.96 (20H, m, ArH), 4.24 (2H, q, J8Hz, CH\(_2\)) and 0.82 (3H, t, J8Hz, CH\(_3\)).

**Found:** C, 63.2; H, 4.8; N, 5.2%; (M\(^+\),-Br), 453.

C\(_{28}\)H\(_{26}\)BrN\(_2\)O\(_2\)P requires: C, 63.0; H, 4.9; N, 5.3%; M, 533.

Evaporation of the diethyl ether-methylene chloride mother liquor afforded an orange oil (1.4 g) which resisted further trituration and was shown by t.l.c. in diethyl ether over silica to be a two component mixture which was not further investigated.

**Ethyl 2-Phenylazo-2-triphenyolphosphoranylidene-ethanoate (67b)**

A suspension of α-phenylazo-ethoxycarbonylmethyltriphenylphosphonium bromide (66) (1.6 g, 0.003 mol) in 10% w/v aqueous sodium carbonate (15.0 ml) was stirred at room temperature for 17 h. Filtration gave ethyl 2-phenylazo-2-triphenylphos-
phoranylidene-ethanoate (67b) (1.4 g; 100%) which formed orange plates, m.p. 178-179° (from ethanol) (lit., 134 172°), \(v_{\text{max}}\) 1660 (CO) cm\(^{-1}\), \(\delta\) (CDCl\(_3\)) 7.74-6.94 (20H, m, ArH), 4.10 (2H, q, J7Hz, CH\(_2\)), and 1.05 (3H, t, J7Hz, CH\(_3\)).

Found: C, 74.1; H, 5.6; N, 6.1%; M\(^+\), 452.
Calc. for C\(_{28}\)H\(_{25}\)N\(_2\)O\(_2\)P: C, 74.3; H, 5.5; N, 6.2%; M, 452.

The Attempted Thermolysis of Ethyl 2-Phenylazo-2-triphenylphosphoranylidene-ethanoate (67b)

Ethyl 2-phenylazo-2-triphenylphosphoranylidene-ethanoate (67b) (1.4 g, 0.003 mol) was gradually heated to 165°/0.2mmHg over 40 min in a Kugelrohr apparatus to give a brown gum (1.4 g) which was chromatographed over alumina.

Elution with light petroleum/b.p. 40-60° gave triphenylphosphine (0.34 g; 43%), m.p. 69-71° (lit., 136 80°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with toluene followed by methylene chloride afforded only intractable gums (total 0.29 g).

Elution with diethyl ether yielded triphenylphosphine oxide (0.1 g; 12%), m.p. 151-153° (lit., 136 157-158°), identical to an authentic sample.

Elution with ethanol gave N-phenyltriphenylphosphineimine (47) (0.39 g; 37%) which formed light brown plates, m.p. 116-117° (from ethanol-water), \(v_{\text{max}}\) no significant absorption >1500 cm\(^{-1}\), \(\delta\) [(CD\(_3\))\(_2\)SO] 8.03-6.88 (m, ArH).

Found: M\(^+\), 353.
Calc. for C\(_{24}\)H\(_{20}\)NP: M, 353.

which was identical (m.p. and i.r. spectrum) to an authentic sample prepared before.
Chapter 4

Base-catalysed Cyclisation Réactions of 2-(2-Nitrophenyl)ethanone Oxime Tosylates – Novel Syntheses of 3-Acyl-1-hydroxy-1H-indazoles
4.1 Introduction

The base-catalysed rearrangement (Scheme 1) of α-methylene ketoxime tosylates to α-amino-ketones was first reported by Neber\textsuperscript{140} in 1926 and is now well known as the Neber rearrangement. A typical example is the sodium ethoxide catalysed rearrangement of 1-phenylpropanone oxime tosylate (1) to 1-amino-1-phenylpropanone (5) which tends to dimerise to give the 2,5-dihydropyrazine (6) which spontaneously oxidises in air to give the pyrazine derivative (7). The Neber rearrangement is now accepted to occur via the intermediate formation and ring-opening of azirine intermediates (3) as depicted [(2)→(3)→(4)→(5)] in Scheme 1. Indeed, while attempting to elucidate the course of the rearrangement, Neber\textsuperscript{141,142} showed (Scheme 2) that treatment of the oxime tosylates of 1-(2,4-dinitrophenyl)propanone (8a) and 2-(2,4-dinitrophenyl)-1-phenylethanone (8b) with ethanolic ammonia gave unstable intermediates which he formulated on the basis of their chemical transformations as the azirine derivatives (9a and b). Woodward\textsuperscript{143} proposed that these compounds were in fact 1-hydroxyindazole derivatives (11a and b) but the azirine formulations (9a and b) of Neber were subsequently fully vindicated by Cram and Hatch.\textsuperscript{144} However, in view of the known tendency\textsuperscript{1,2} of aromatic nitro-groups to undergo aldol-type condensation with amino-substituents in ortho side-chains to give heterocyclic products, it is possible that 2-amino-
Scheme 1

(i) NaOEt, EtOH

(ii) $\text{H}_2\text{O}$

(iii) $[\text{O}]$ (air)

(T = 4-MeC$_6$H$_4$)
Scheme 2

(8) \( \rightarrow \) (9)

(i) \( \text{NH}_3, \text{EtOH} \)

(8) \( (T=4-\text{MeC}_6\text{H}_4) \)

(10) \( \rightarrow \) (11)

(11)

R

a; Me

b; Ph
2-nitrophenylethanones (10) of the type derived by the Neber rearrangement might undergo base-catalysed cyclisation to hitherto unknown 3-acyl-1-hydroxyindazole derivatives (11). Indeed, in the course of his studies on the Neber rearrangement, Neber reported the isolation (Scheme 3) of a product from the base-catalysed rearrangement of 1-(2-nitrophenyl)-propanone oxime tosylate (12) which analysed correctly for the molecular formula C_{18}H_{16}N_{4}O_{4} and was therefore formulated as the dihydropyrazine derivative (16). However the stability of the compound is inconsistent with this formulation which would be expected to undergo spontaneous oxidation in air to give the corresponding pyrazine derivative. Also inconsistent with its formulation as the dihydropyrazine structure (16) was the reported acidity of the compound as shown by its formation of an insoluble potassium salt. On the other hand, acidic character would be consistent with the 1-hydroxyindazole structure (15) which having the molecular formula C_{9}H_{8}N_{2}O_{2} would give the combustion analysis data reported by Neber. In view of the possible incorrect formulation by Neber of the product of the base-catalysed reaction of the oxime tosylate (12), it was decided to reinvestigate this transformation.

4.2 The Synthesis of 1-(2-Nitrophenyl)propanone Oxime Tosylate (12) and its Base-catalysed Cyclisation to 3-Acetyl-1-hydroxy-1H-indazole (15)

As already discussed (Scheme 3), treatment of 1-(2-nitrophenyl)propanone oxime tosylate (12) with ethanolic sodium ethoxide or ammonia affords a product whose reported properties are not consistent with the assigned dihydropyrazine
Scheme 3

(i) NaOEt, EtOH

(ii) NH₃, EtOH
structure (16) but rather with the 3-acetyl-1-hydroxy-1H-
indazole structure (15) a hitherto unreported type of indazole
derivative. Formation of such an indazole derivative can
be readily rationalised (Scheme 4) by initial Neber rearrange-
ment of the oxime tosylate (12) to the amino ketone (14)
followed by base-catalysed aldol-type interaction (see Chapter
1) between the amino-substituent and the \textit{ortho} nitro-group to
give the observed product (15).

Base-catalysed condensation of amino-substituents and
\textit{ortho} nitro-groups are well known.\textsuperscript{1,2} For example (Scheme 5),
Ahmad and Smith\textsuperscript{145} cited such a process to explain the pyridine-
catalysed conversion of the 5-amino-1-(2-nitrophenyl)pyrazole
derivatives (20) into the corresponding triazines (21). A
further example (Scheme 5) of such an aldol-type condensation
is the base-catalysed cyclisation of N-2-nitrobenzylidene-
aniline (22) to the cinnoline N-oxide (24) which is thought\textsuperscript{146}
to involve the initial formation of the amino-intermediate (23)
prior to condensation of the \textit{ortho} nitro-group with the amino-
substraituent.

The oxime tosylate (12) was readily available\textsuperscript{140} (Scheme
6) from the oxime (28) by its base-catalysed reaction with
toluene-\textit{p}-sulphonyl (tosyl) chloride. The oxime (28) was
available in turn by the oximation of 1-(2-nitrophenyl)propan-
2-one (27), the latter being accessible from 2-nitrophenyl-
acetyl chloride (25) via initial base-catalysed condensation
of the latter with diethyl malonate to afford the keto-diester
(26) followed by hydrolysis and subsequent decarboxylation.
2-Nitrophenylacetyl chloride (25) was obtained by heating
commercially available 2-nitrophenylacetic acid at 50° with
Scheme 4

(i) NaOEt, EtOH

(ii) NH₃, EtOH
(i) pyridine

(ii) KCN, MeOH

Scheme 5
(25) $\text{NO}_2$Cl + $\text{CO}_2\text{Et}$ + $\text{CH}_2$ + $\text{CO}_2\text{Et}$ → (i) $\text{NO}_2$ $\text{CO}_2\text{Et}$

(ii) $\text{NO}_2$

(iii) $\text{NO}_2$Me

(iv) $\text{NO}_2$Me

(12) $\text{TSO}_2\text{Cl}$, pyridine

(i) Mg, EtOH

(ii) $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$

(iii) $\text{NH}_2\text{OH}$, NaOAc

(iv) $\text{TSO}_2\text{Cl}$, pyridine

Scheme 6
thionyl chloride as an impure brown oil whose i.r. spectrum showed absorption at 1790 cm\(^{-1}\) characteristic of an acid chloride carbonyl stretching vibration as well as nitro absorption at 1520 and 1330 cm\(^{-1}\). This brown oil was condensed with the magnesium enolate of diethyl malonate to give an oil, presumed to be the keto-diester (26), which was hydrolysed and decarboxylated by heating with a mixture of aqueous acetic acid and sulphuric acid to afford an oil identified as 1-(2-nitrophenyl)propan-2-one (27) on the basis of its i.r. spectrum which showed carbonyl absorption at 1730 cm\(^{-1}\) and nitro absorption at 1530 and 1350 cm\(^{-1}\). Treating an aqueous ethanolic solution of the ketone (27) with hydroxylamine hydrochloride and sodium acetate gave an almost quantitative yield (98%) of a cream coloured solid whose properties were consistent with those expected for the oxime (28). The solid gave elemental analysis and mass spectral data fully in accord with the molecular formula C\(_9\)H\(_{10}\)N\(_2\)O\(_3\) and gave an i.r. spectrum which showed absorption at 3200 cm\(^{-1}\) characteristic of an N-OH stretching vibration, and nitro absorption at 1530 and 1350 cm\(^{-1}\). In addition the melting-point of the oxime (28) corresponded well with that reported in the literature for this known compound which is formed as a syn/anti geometrical isomer mixture.

Stirring a pyridine solution of the oxime (28) with tosyl chloride gave a good yield (76%) of a colourless solid which was identified as the desired oxime tosylate (12) on the basis of its elemental analysis and mass and i.r. spectra. In addition the melting-point of the tosylate (12) obtained in the present studies corresponded well with the literature value
reported\textsuperscript{140} for this known compound. The tosyrate (12) as prepared is probably a single geometrical isomer\textsuperscript{140} but no attempt was made to investigate the configuration in the present studies.

Treatment of the oxime tosylate (12) with ethanolic ammonia as described by Neber\textsuperscript{140} gave a colourless solid in high yield (96%), whose m.p. and elemental analysis agree with those of the product described by Neber\textsuperscript{140} and formulated by him as 3,6-dihydro-2,5-dimethyl-3,6-di-(2-nitrophenyl)-pyrazine [Scheme 3; (16)]. However the compound gave a mass spectrum which showed a parent ion at m/e 176 which is not consistent with Neber's dihydropyrazine structure (16) but is in accord with 3-acetyl-1-hydroxy-1H-indazole [Scheme 7; (15)]. The i.r. spectrum of the compound showed broad absorption at 2660 cm\textsuperscript{-1} attributable to an N-hydroxy-substituent together with a carbonyl band at 1630 cm\textsuperscript{-1} whose relatively low frequency can be attributed to resonance interaction with the N-hydroxy substituent [Scheme 7; (15)\rightleftharpoons (29)]. The \textsuperscript{1}H n.m.r. spectrum of the compound showed only signals due to the protons of a phenyl group and a methyl group respectively and contained no absorption attributable to the CH protons expected on the basis of the dihydropyrazine structure [Scheme 3; (16)]. The spectroscopic properties of the product are therefore totally inconsistent with the dihydropyrazine structure [Scheme 3; (16)] proposed by Neber\textsuperscript{140} but are fully consistent with the 1-hydroxyindazole structure (15) which having the molecular formula C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}O\textsubscript{2} would give the same analytical data as the dihydropyrazine (16) (molecular formula C\textsubscript{18}H\textsubscript{16}N\textsubscript{4}O\textsubscript{4}). The identity of the product as 3-acetyl-1-hydroxy-1H-indazole
Scheme 7

(12) \[ \text{(T=4-MeC}_6\text{H}_4) \]

(i) \[ \text{NH}_3, \text{EtOH} \]

(ii) \[ \text{RNH}_2 \]

(iii) \[ \text{Na}_2\text{S}_2\text{O}_4, \text{EtOH, heat} \]

(iv) \[ \text{Ac}_2\text{O, heat} \]

(v) \[ \text{H}_2, \text{Pd-C} \]

(vi) \[ \text{MeMgBr, H}_2\text{O} \]
was firmly established by its chemical transformations discussed below.

The solid formulated as the 1-hydroxyindazole (15) was conclusively shown to contain a ketonic carbonyl group by the formation of typical carbonyl derivatives with hydroxylamine and hydrazines. Thus, heating an aqueous ethanolic solution of the 1-hydroxyindazole (15) with hydroxylamine hydrochloride and sodium acetate gave an excellent yield (95%) of a colourless solid whose properties were in full accord with the oxime structure (30a). Thus, the solid gave elemental and mass spectral data consistent with the molecular formula $C_9H_9N_3O_2$ and gave an i.r. spectrum which lacked carbonyl absorption but showed absorption at 3220 cm$^{-1}$ due to an N-OH group. A dark red solid identified as the hydrazone (30b) was isolated in good yield (93%) from the reaction of the 1-hydroxyindazole (15) with 2,4-dinitrophenylhydrazine. The dark red hydrazone (30b) gave elemental and spectroscopic data fully consistent with the assigned structure. The 1-hydroxyindazole (15) also reacted readily with tosylhydrazine to give the corresponding tosylhydrazone (30c) whose analytical and spectroscopic properties completely verified its structure.

If the compound obtained by treating the oxime tosylate (12) with ethanolic ammonia is indeed 3-acetyl-1-hydroxy-1H-indazole (15) then due to the presence of the N-OH group it would be expected to form an N-acetoxy derivative under mild acetylation conditions. Indeed, briefly heating a suspension of the compound (15) in acetic anhydride afforded an excellent yield (90%) of a pale yellow solid whose properties are consistent with the N-acetoxy structure (31). Thus, the
yellow solid gave an elemental analysis and a mass spectrum in accord with the molecular formula $\text{C}_{11}\text{H}_{10}\text{N}_{2}\text{O}_{3}$ and also showed i.r. absorption at $1820 \text{ cm}^{-1}$ which is characteristic of the carbonyl stretching vibration of an N-acetoxy group.

It would be expected that reduction of the compound believed to be the 1-hydroxyindazole (15) would afford the known 3-acetyl-$1^\text{H}$-indazole (33). This indazole derivative (33) was previously prepared in 1926 by Meisenheimer and Diedrich via initial reaction of 3-cyano-indazole (32) with methylmagnesium iodide and subsequent acid hydrolysis. It was therefore of interest to attempt to reduce the 1-hydroxyindazole (15) and thus provide further evidence that the latter did indeed have an N-OH type structure. In practice, heating the product believed to be the 1-hydroxyindazole (15) with the reducing agent, sodium dithionite in aqueous ethanol gave a colourless product in moderate yield (56%) whose properties were fully in accord with its formulation as the indazole (33). Thus, it gave elemental and mass spectral data consistent with the molecular formula $\text{C}_{9}\text{H}_{8}\text{N}_{2}\text{O}_{2}$ and had a melting-point (188-190$^\circ$) in reasonable agreement with the corresponding value (182$^\circ$) cited by Meisenheimer and Diedrich$^{150}$ for 3-acetyl-$1^\text{H}$-indazole (33). The compound also gave i.r. and $^1\text{H}$ n.m.r. spectra which were fully in accord with the structural assignment (33). The successful reduction of the compound believed to be the 1-hydroxyindazole (15) to the known 1-acetyl-$1^\text{H}$-indazole (33) is clear evidence that the structural assignment (15) of the former compound derived by ammonia-catalysed rearrangement of the oxime tosylate (12) is correct. This structure assignment was further substantiated by the
catalytic hydrogenolysis of the N-acetoxy-derivative (31) of the 1-hydroxyindazole (15) to 3-acetyl-1H-indazole (33) identical to a sample prepared by direct reduction of the 1-hydroxyindazole (15) as described before. In contrast to its N-acetoxy-derivative (31) the 1-hydroxyindazole (15) was recovered unchanged after attempted reduction with hydrogen over palladium-on-charcoal at atmospheric temperature and pressure.

Neber reported that the product now firmly identified as 3-acetyl-1-hydroxy-1H-indazole (15) was also formed when the oxime tosylate (12) was treated with ethanolic potassium ethoxide. However in the present studies, heating the oxime tosylate (12) under reflux with ethanolic sodium ethoxide gave intractable gums which yielded no identifiable material. Treatment of the oxime tosylate (12) with triethylamine in ethanol at room temperature also gave only uncharacterisable gums. These results indicate that the choice of basic catalyst is crucial for the successful rearrangement of the oxime tosylate (12) to 3-acetyl-1-hydroxy-1H-indazole (15). A possible explanation of this influence of the basic catalyst on the success or otherwise of the rearrangement [(12)→(15)] is that this transformation presumably involves (Scheme 3) the azirine (13) and the α-amino-ketone (14) as intermediates both of which might well be sensitive to the particular basic conditions employed.

4.3 Investigations of the Chemical Reactivity of 3-Acetyl-1-hydroxy-1H-indazole (15)

The successful synthesis of 3-acetyl-1-hydroxy-1H-indazole
prompted investigations into the reactivity of this new type of indazole derivative. Initially it was considered of interest to study the possible reduction (Scheme 8) of the ketonic function of the indazole (15) to form the corresponding secondary alcohol derivative (34). However, stirring an ethanolic solution of the 1-hydroxyindazole (15) with a large excess of sodium borohydride, gave, after workup, only a multicomponent brown gum from which no identifiable material could be obtained. The complexity of this reaction is surprising and suggests over reduction is taking place. Regrettably lack of time prevented an in depth study of the behaviour of the 1-hydroxyindazole (15) to other selective reducing agents.

The behaviour of the 1-hydroxyindazole (15) towards oxidation was also investigated (Scheme 8). It seemed likely that treatment of the 1-hydroxyindazole (15) with strong oxidising agents could result in oxidative loss of the acetyl side-chain with possible formation of the indazolone derivative (36). Alternatively, oxidation of the acetyl group could lead to the carboxylic acid (37). In practice, heating the 1-hydroxyindazole (15) with chromium trioxide in aqueous acetic acid gave neither of the possible products (36) or (37) but surprisingly afforded instead a lowish yield (38%) of a product identical in every respect to 3-acetyl-1H-indazole (33) prepared before. The mechanism of the oxidative deoxygenation implied by the chromium trioxide promoted conversion of the 1-hydroxyindazole (15) into the parent indazole derivative (33) is not clear at the present time and will require further experimentation for its elucidation.
(i) NaBH₄, EtOH
(ii) CrO₃, AcOH, H₂O
(iii) NaOCl, dioxane
(iv) Ac₂O, heat

Scheme 8
It is well known\cite{151} that the hypochlorite oxidation of ketones results in the formation of carboxylic acids. This haloform reaction involves the treatment of the ketone with aqueous sodium hypochlorite solution and in many cases\cite{151} affords high yields of the corresponding carboxylic acid. Thus, it was of interest in the course of the present studies to attempt (Scheme 8) to generate the carboxylic acid (37) via such a hypochlorite oxidation of the 1-hydroxyindazole (15). However, when a dioxane solution of the latter was heated at 70° with aqueous sodium hypochlorite solution workup gave only an orange multicomponent oil from which no identifiable material could be isolated. Again, treatment of the 1-hydroxyindazole (15) with aqueous sodium hypochlorite under these conditions appears to involve over-reaction but lack of time prevented the investigation of conditions suitable for single product formation.

The behaviour of the 1-hydroxyindazole towards Baeyer-Villiger oxidation was also investigated. Baeyer-Villiger oxidation involves the treatment of ketones with peracetic acid which is normally formed \textit{in situ} from 30% aqueous hydrogen peroxide and glacial acetic acid and would be expected (Scheme 9) to convert the 1-hydroxyindazole (15) into either the methyl ester (40) or the indazolone (36) depending on whether the methyl group or the indazole nucleus undergoes 1,2 C=O bond shift in the oxonium intermediate (39). In practice heating the 1-hydroxyindazole (15) with 30% hydrogen peroxide in glacial acetic acid at 50° gave a good yield of a product whose m.p. and i.r. spectrum were identical to those of an authentic sample of benzoic acid. The formation of benzoic
(i) \( \text{H}_2\text{O}_2, \text{AcOH, H}_2\text{O} \)

Scheme 9
acid by peracetic acid oxidation of 3-acetyl-1-hydroxy-1H-indazole (15) requires a deep-seated transformation of the latter the nature of which is not obvious. However a possible course of this transformation (Scheme 9) might involve the initial formation of the expected N-hydroxyindazolone (36) which then suffers hydrolytic ring-opening to the azimine (42) loss of nitrogen from which would account for the formation of benzoic acid.

Because of its N-hydroxy structure it was also of interest (Scheme 8) to investigate the acetylative rearrangement\textsuperscript{152} of the 1-hydroxyindazole (15). Thus it was hoped that prolonged heating of the 1-hydroxyindazole (15) with acetic anhydride might yield via the intermediacy of the previously characterised N-acetoxy-derivative (31), the rearranged, ring-substituted acetoxy-derivative (35). However, it was found that heating the 1-hydroxyindazole (15) with acetic anhydride for 3 h and 72 h gave only moderate yields (37-55\%) of 1-acetoxy-3-acetyl-1H-indazole (31) which was identified by comparison (m.p. and i.r. spectrum) to a sample prepared before.

In addition to the foregoing studies of the chemical behaviour of the 1-hydroxyindazole (15) it was considered of interest to study transformations of the derived oxime (30a). For example, it is known\textsuperscript{153} that oximes or the corresponding oxime tosylates can form substituted amides via a Beckmann rearrangement. Thus, the oxime (30a) should also undergo a Beckmann rearrangement to give (Scheme 10) one of two possible amide derivatives. Beckmann rearrangement of the oxime (30a) via path (a) would involve methyl group migration with loss of the N-hydroxyl group to give the carbocation (44) which can then react with water to give the amide (46). Alternatively,
(30a) \[ \text{(Me)} \quad (a) \quad (b) \quad \text{(N)} \quad \text{(OH)} \]

path (a) (ii) \[ \text{path (a) (ii)} \]

\[ \begin{array}{c}
\text{(44)} \\
\text{H}_2\text{O} \\
\text{(46)} \\
\end{array} \]

path (b) \[ \text{path (b)} \]

\[ \begin{array}{c}
\text{(45)} \\
\text{H}_2\text{O} \\
\text{(47)} \\
\end{array} \]

(i) TSO_2Cl, pyridine

(ii) H^+

Scheme 10
rearrangement of the oxime (30a) via path (b) would involve migration of the heterocyclic moiety to afford the carbocation (45) and subsequently the amide (47). In practice the attempted promotion of the Beckmann rearrangement of the oxime (30a) using hot polyphosphoric acid as catalyst gave only a multicomponent mixture which could not be separated to give any identifiable product. In view of this failure to achieve the clean Beckmann rearrangement of the oxime (30a) attention was turned to the derived tosylate (43) which should rearrange even more readily than the parent oxime (30a) by paths (a) and (b) to give the amides (46) and (47) respectively. Unfortunately the attempted preparation of the oxime tosylate (43) by reaction of the oxime (30a) with tosyl chloride in the presence of pyridine gave only a multicomponent mixture which failed to yield any identifiable material. Lack of time prevented further attempts to prepare the tosylate (43), or to investigate other conditions for the Beckmann rearrangement of the oxime (30a).

4.4 Investigations of the Synthetic Scope of Base-catalysed Cyclisation Reactions of 2-(2-Nitrophenyl)ethanone Oxime Tosylates to 3-Acyl-1-hydroxy-1H-indazoles

As already described (see Section 4.2) treatment (Scheme 3) of 1-(2-nitrophenyl)propan-2-one oxime tosylate (12) with ethanolic ammonia affords not the dihydropyrazine (16) as reported by Neber, but rather 3-acetyl-1-hydroxy-1H-indazole (15) an example of a hitherto unknown class of indazole derivative. In view of this it was of interest to study the extension of this novel cyclisative-rearrangement reaction to
the general synthesis of 3-acyl-1-hydroxy-1H-indazoles as well as the relatively inaccessible 3-acyl-1H-indazoles derived by reduction.

Initially it was decided to investigate (Scheme 11) simple extensions of the base-catalysed cyclisation of 1-(2-nitrophenyl)propan-2-one oxime tosylate (12) to 3-acetyl-1-hydroxy-1H-indazole (15) already described in Section 4.2. The benz-substituted 1-(2-nitrophenyl)propan-2-one oxime tosylates (52a-c) and (8a) chosen for study were synthesised from the corresponding benz-substituted 1-(2-nitrophenyl)propan-2-one oximes (51a-d) which were available in turn from the respective ketones (50a-d). With the exception of the dimethoxy-compound (50c) the latter were prepared from the corresponding 2-nitrophenylacetic acids (48a,b and d) through the reaction (Scheme 11) of their acid chlorides (49a,b and d) with the magnesium enolate of diethyl malonate as already described for 2-nitrophenylacetyl chloride (see before). 2,4-Dinitrophenylacetic acid (48d) was commercially available while the methyl- and methoxy-substituted 2-nitrophenylacetic acids (48a) and (48b) were prepared, albeit in low yield (22 and 36%) from the corresponding 2-nitrotoluene derivatives as described in the literature. 2,4-Dinitrophenylacetic acid (48d) was commercially available while the methyl- and methoxy-substituted 2-nitrophenylacetic acids (48a) and (48b) were prepared, albeit in low yield (22 and 36%) from the corresponding 2-nitrotoluene derivatives as described in the literature. 4,5-Dimethoxy-2-nitrophenylacetic acid (48c), on the other hand was prepared in quantitative yield by the nitration of commercially available 3,4-dimethoxyphenylacetic acid as described in the literature. The carboxylic acids (48a,b and d) reacted as expected on heating with thionyl chloride to give the oily acid chlorides (49a,b and d) in essentially quantitative yields. No attempt was made to purify the heat and moisture sensitive acid chlorides (49a,b and d) which were characterised by their i.r. spectra
(i) $\text{SOCl}_2$

(ii) $\text{CH}_2(\text{CO}_2\text{Et})_2$, Mg, EtOH

(iii) $\text{H}_2\text{SO}_4$, $\text{H}_2\text{O}$, heat

(iv) $\text{NH}_2\text{OH}$

(v) $\text{TSO}_2\text{Cl}$, pyridine

(vi) $\text{NH}_3$, EtOH

(vii) $\text{Ac}_2\text{O}$

(viii) $\text{H}_2$, Pd-C

Scheme 11
which lacked absorption due to a carboxylic acid group but contained high frequency carbonyl absorption at ca 1800 cm$^{-1}$ characteristic of the chlorocarbonyl substituent. In contrast, the dimethoxyphenylacetic acid (48c), due to its insolubility required the use of dimethylformamide as co-solvent in its attempted reaction with thionyl chloride. However, even heating with thionyl chloride in dimethylformamide failed to convert the dimethoxyphenylacetic acid (48c) into the acid chloride (49c) thus precluding the use of the latter for the synthesis of the ketone (50c) which had to be prepared by a different route (see later).

The crude methyl- and methoxy-substituted 2-nitrophenylacetyl chlorides (49a and b) condensed readily with the magnesium enolate of diethyl malonate to afford after hydrolysis and decarboxylation, high yields (82 and 91%) of the expected ketones (50a and b) whose analytical and spectroscopic properties were fully in accord with the assigned structures. In contrast the analogous reaction of 2,4-dinitrophenylacetyl chloride (49d) with the magnesium enolate of diethyl malonate followed by hydrolysis and decarboxylation gave a low yield (23%) of an oil which could not be purified by bulb-to-bulb distillation and is assigned the ketone structure (50d) on the basis of its i.r. spectrum which showed carbonyl absorption at 1730 cm$^{-1}$ as well as nitro absorption at 1540 and 1350 cm$^{-1}$, and its $^1$H n.m.r. spectrum which contained a two-proton singlet at $\delta$4.15 due to a methylene group and a three-proton singlet at $\delta$2.35 due to a methyl group.

As a result of the failure to obtain 4,5-dimethoxy-2-nitrophenylacetyl chloride (49c) by the reaction of thionyl chloride with the carboxylic acid (48c) as discussed earlier in this
section, it was necessary to prepare 1-(4,5-dimethoxy-2-nitrophenyl)propan-2-one (50c) via an alternative synthetic route to that outlined in Scheme 11. Thus (Scheme 12), it appeared likely that nitration of the commercially available 1-(3,4-dimethoxyphenyl)propan-2-one (57) offered a possible method for the preparation of the ketone (50c). In practice it was found that treatment of the ketone (57) with concentrated nitric acid resulted in nitration to give a good yield (71%) of a mono-nitro product whose properties are consistent with the required 1-(4,5-dimethoxy-2-nitrophenyl)propan-2-one (50c). Thus the product gave an elemental analysis and a mass spectrum in accord with the molecular formula C_{11}H_{13}NO_5. Also its i.r. spectrum showed carbonyl absorption at 1715 cm\(^{-1}\) and nitro absorption at 1530 and 1355 cm\(^{-1}\), and its \(^1\)H n.m.r. spectrum contained two one-proton singlets at 6.71 and 6.63 attributable to H-3 and H-6 in the structure (50c) hence verifying the 1,2,4,5-tetrasubstituted pattern of the benzene nucleus in the nitration product and further demonstrating the position of the nitro-substituent in the latter.

The ketones (50a-c) reacted with hydroxylamine hydrochloride in the presence of sodium acetate under standard conditions to afford the expected oximes (51a-c) in essentially quantitative yields. The analytical and spectroscopic properties of the oximes (51a-c) were fully in accord with their assigned structures. Moreover, the presence in their \(^1\)H n.m.r. spectra of signals due only to a single methylene group and a single side-chain methyl substituent indicates the predominance of a single geometrical isomer, though no attempt was made to establish the configurations of the oximes (51a-c)
Scheme 12

(i) HNO₃
in the present studies. The impure 1-(2,4-dinitrophenyl)propan-2-one (50d) also reacted with hydroxylamine hydrochloride in the presence of sodium acetate to afford a low yield (20%) of a solid product whose melting-point agreed reasonably well with that reported\textsuperscript{148} for the known oxime (51d).

The oximes (51a-c) reacted readily with tosyl chloride in pyridine solution to give high yields (77-86%) of products whose analytical and spectroscopic properties, mass spectra excluded are entirely consistent with their formulation as the desired oxime tosylates (52a-c). Like the parent oximes (51a-c), the derived tosylates (52a-c) showed \textsuperscript{1}H n.m.r. absorption consistent with the presence of only a single methylene group and a single side-chain methyl substituent thus demonstrating that they exist predominantly in only one of the two possible geometrically isomeric forms. Again, no attempt was made to establish the precise configuration of the oxime tosylates (52a-c). None of the latter compounds showed parent ion peaks in their mass spectra presumably due to their initial thermal decomposition in the mass spectrometer probe.

The conversion of 1-(2,4-dinitrophenyl)propan-2-one oxime (51d) into its tosylate (8a). was found to be most conveniently achieved by reaction with tosyl chloride in 1,2-dimethoxyethane in the presence of triethylamine. Under these conditions, the oxime (51d) gave a moderate yield (51%) of a pale yellow product whose melting-point agreed well with the value reported in the literature\textsuperscript{144} for the known tosylate (8a). This constitution for the compound was further verified by its combustion analysis and its i.r. and \textsuperscript{1}H n.m.r. spectra. Like
the structurally similar tosylates (52a-c), 1-(2,4-dinitrophenyl)propan-2-one oxime tosylate (8a) failed to exhibit a peak due to the parent ion in its mass spectrum and again this mass spectral behaviour can be attributed to premature thermal decomposition of the tosylate (8a) in the mass spectrometer probe.

In reactions analogous to that of 1-(2-nitrophenyl)propan-2-one oxime tosylate (12) (see Section 4.2 before), the oxime tosylates (52a-c) were smoothly converted by treatment with ethanolic ammonia in good yield (65-68%) into acidic products which analysed correctly for the respective 1-hydroxyindazole structures (53a-c). These structures were further substantiated by the acidic products' mass and $^1$H n.m.r. spectra, and in particular by their i.r. spectra which lacked absorption due to a nitro-group, but contained broad absorption around 2660 cm$^{-1}$ characteristic of a hydrogen bonded N-hydroxyl substituent. As a final confirmation of their structures, the N-hydroxyindazoles (53a-c) were reacted with acetic anhydride to give high yields (89-92%) of monoacetyl derivatives whose N-acetoxy-structures (54a-c) were firmly established by their analytical and spectroscopic properties. In particular, their i.r. spectra showed high frequency carbonyl absorption at ca 1800 cm$^{-1}$ diagnostic of an N-acetoxy substituent, and therefore also of the presence of an N-hydroxyl substituent in the parent indazoles (53a-c).

As discussed before (see Section 4.1 and Scheme 2), Neber$^{140,141}$ treated the oxime tosylate (8a) with ethanolic ammonia to obtain an unstable product which he formulated as the azirine derivative (9a). Although Woodward$^{143}$ speculated
that this unstable product might have the 1-hydroxyindazole structure (11a) Neber's original structure assignment was later vindicated by Cram and Hatch.\textsuperscript{144} Since the azirine derivative (9a) is a potential intermediate en route from the tosylate (8a) to the N-hydroxyindazole (11a), it was of interest to obtain the azirine derivate (9a) as described by Neber\textsuperscript{141} and demonstrate its conversion into the hitherto unreported 1-hydroxyindazole (11a). In the present studies, treatment of the oxime tosylate (8a) with ethanolic ammonia as described by Neber,\textsuperscript{141} gave a complex mixture which failed to yield any characterisable product. Lack of time prevented a more detailed investigation of the base-catalysed transformation of the oxime tosylate (8a).

The foregoing studies conclusively demonstrate that the base-catalysed cyclisation of easily accessible 1-(2-nitrophenyl)propan-2-one oxime tosylates (52) provides an efficient method for the general synthesis of 1-hydroxy-1H-indazoles (53), a previously unknown type of indazole derivative. In view of the virtual lack of methods for the synthesis of 3-acyl-1H-indazoles\textsuperscript{156} it was also of interest to demonstrate the value of the 1-hydroxyindazoles (53) as precursors of the parent 3-acetyl-1H-indazoles (55). Rather than directly reduce the 1-hydroxyindazoles (53) to the 3-acetylindazoles (55) using sodium dithionite (see before) it was found more expedient to reduce the derived N-acetoxy derivatives (54). Thus it was found that the latter compounds (54a-c) underwent smooth hydrogenolysis over 10% palladium-on-charcoal to afford high yields (68-100%) of products whose analytical and spectroscopic properties are entirely in accord with their formulation.
as the 3-acetyl-1H-indazoles (55a-c). A particular feature of the i.r. spectra of these compounds is the presence of NH-absorption at ca 3250 cm⁻¹ and a band at 1660 cm⁻¹ attributable to the carbonyl moiety of the 3-acetyl substituent.

The exceptionally low frequency of this i.r. carbonyl absorption is a measure of the resonance interaction between the ring-NH and the 3-acetyl group [(55)+→(56)]. The resulting suppression of the carbonyl character of the 3-acetyl substituent also accounts for its stability to reduction under the conditions of the catalytic hydrogenolysis of the N-acetoxyindazoles (54a-c) to the indazole-ketones (55a-c).

In view of the demonstration that the base-catalysed cyclisation of 1-(2-nitrophenyl)propan-2-one oxime tosylates (52) provides a general synthetic route to 3-acetyl-1-hydroxy-1H-indazoles (53) it was of further interest to attempt the extension of such cyclisations to other 1-(2-nitrophenyl)-ethanone oxime tosylates. Of particular interest in this context (Scheme 13) were the oxime tosylates (62) and (8b) of 1-phenyl-2-(2-nitrophenyl)ethanones (60). By analogy with the successful cyclisations [Scheme 11; (52)+(53)] it was anticipated that the base-catalysed cyclisation of the tosylates (62) and (8b) should provide a general synthetic route to 3-benzoyl-1-hydroxy-1H-indazoles (65) and (11b). As discussed before (see Section 4.1 and Scheme 2) Neber¹⁴² had previously studied the reaction of the oxime tosylate (8b) with ethanolic ammonia and had reported the isolation of a product to which he ascribed the azirine structure (9b). This structure was later confirmed by the studies of Cram and Hatch.¹⁴⁴ Since the azirine (9b) is a potential precursor, via rearrangement
Scheme 13
to the amino-ketone (10b), of the 1-hydroxyindazole (11b)

it was of interest in the present studies to reinvestigate

the behaviour of the oxime tosylate (8b) toward prolonged
treatment with ethanolic ammonia in the expectation that the
1-hydroxyindazole (11b) might be formed by subsequent reaction
of the azirine derivative (9b) isolated by Neber. In
parallel with the study of the dinitro-compound (8b), it was
also decided to investigate the mono-nitro oxime tosylate (62).

It was proposed to synthesise the oxime tosylate (62)
and the known dinitro-analogue (8b) by tosylation of the
known oximes (61a and b), the latter being readily
accessible by oximation of the corresponding ketones (60a and
b). The preparation of the ketone (60a) has already been
discussed in chapter 2 (page 41) and involves the Friedel-
Crafts reaction of 2-nitrophenylacetyl chloride (25) with
benzene. The other ketone (60b), however, is reported to be readily prepared by the reaction of 1-chloro-2,4-dinitro-
benzene (58) with the sodium salt of 1-phenylbutane-1,3-
dione (59). However in the present work the attempted
reaction of 1-chloro-2,4-dinitrobenzene (58) with the sodium
salt of 1-phenylbutane-1,3-dione (59) as described in the
literature gave only a multicomponent mixture from which
none of the desired ketone (60b) could be isolated. However
the ketone (60b) was readily prepared, though in low yield
(36%) by the Friedel-Crafts reaction of benzene with 2,4-
dinitrophenylacetyl chloride (49d). The ketone (60b) so
prepared was identified by its i.r. spectrum and melting-point
the latter agreeing well with the literature value.
The ketones (60a and b) reacted smoothly with hydroxylamidine hydrochloride in the presence of sodium acetate to afford good yields (67% and 95% respectively) of the corresponding known oximes (61a and b) which had melting-points in agreement with the literature values. Surprisingly the attempted conversion of the oxime (61a) into the tosylate (62) by treatment with tosyl chloride in pyridine solution gave only a multicomponent brown gum from which no identifiable material could be obtained. The attempted tosylation of the oxime (61b) using tosyl chloride and pyridine was equally unsuccessful, the product being a multicomponent orange gum from which no characterisable material could be separated. An alternative attempt to tosylation the oxime (61b) using tosyl chloride in the presence of triethylamine also failed, the oxime (61b) being recovered unchanged in high yield.

The failure to convert the oximes (61a and b) into simple tosyl derivatives (62) and (8b) is surprising and may be due to the enhanced reactivity of the latter as indicated by the formation of complex mixtures under the reaction conditions used. In view of the non-availability of the tosylates (62) and (8b) it was not possible to study their cyclisation to the 1-hydroxyindazoles (65) and (11b). Consequently it was decided to evaluate an alternative synthetic route to the latter via the independent synthesis and cyclisation of the amino-ketones (64) and (10b) presumed as intermediates in the Neber rearrangement route [(8b) → (11b)] or [(62) → (65)]. Thus (Scheme 14) it was hoped that the amino-ketone (64) could be prepared by reaction of the bromo-ketone (66) prepared earlier (see Chapter 2) with ethanolic ammonia, and would cyclise in situ to the 1-hydroxyindazole
Scheme 14

(i) $\text{NH}_3$, EtOH
In practice treatment of the bromo-ketone (66) with ethanolic ammonia led to the formation of a multicomponent mixture from which no characterisable material could be obtained. Due to lack of time studies in this area were terminated at this point.

4.5 Experimental

General experimental details are described in the Appendix.

2-Nitrophenylacetic Acids (48a-c)

(a) 5-Methyl-2-nitrophenylacetic Acid (48a)

5-Methyl-2-nitrophenylacetic acid (48a) was prepared (yield 22%) by the base-catalysed reaction of 1,5-dimethyl-2-nitrobenzene with diethyl oxalate followed by treatment with hydrogen peroxide as described in the literature, \[154\] m.p. 141-142° (lit., \[154\] 149°), and was used without further purification.

(b) 5-Methoxy-2-nitrophenylacetic Acid (48b)

5-Methoxy-2-nitrophenylacetic acid (48b) was prepared (yield 36%) by the base-catalysed reaction of 5-methoxy-2-nitrotoluene with diethyl oxalate followed by treatment with hydrogen peroxide as described in the literature, \[154\] m.p.174-175° (lit., \[154\] 175°), and was used without further purification.
(c) 4,5-Dimethoxy-2-nitrophenylacetic Acid (48c)

4,5-Dimethoxy-2-nitrophenylacetic acid (48c) was prepared (yield 100%) by the nitration of commercially available 3,4-dimethoxyphenylacetic acid as described in the literature,155 m.p. 207-208° (lit.,155 206-208°), and was used without further purification.

Substituted 2-Nitrophenylacetyl Chlorides (25) and (49a and b)

A slurry of the respective 2-nitrophenylacetic acids (0.05 mol) and thionyl chloride (7.0 g, 4.3 ml, 0.058 mol) was stirred and heated at 50° (water bath) for 1 h. The excess of thionyl chloride was distilled off under reduced pressure (water pump) to yield the respective 2-nitrophenylacetyl chlorides.

(a) 2-Nitrophenylacetyl chloride (25) was obtained as a brown oil (100%), $\nu_{\text{max}}$ 1790 (CO) and 1520 and 1330 (NO$_2$) cm$^{-1}$, which was used without further purification.

(b) 5-Methyl-2-nitrophenylacetyl chloride (49a) was obtained as a brown oil (100%), $\nu_{\text{max}}$ 1800 (CO) and 1520 and 1330 (NO$_2$) cm$^{-1}$, which was used without further purification.

(c) 5-Methoxy-2-nitrophenylacetyl chloride (49b) was obtained as a brown oil (100%), $\nu_{\text{max}}$ 1810 (CO) and 1500 and 1340 (NO$_2$) cm$^{-1}$, which was used without further purification.

The Attempted Preparation of 4,5-Dimethoxy-2-nitrophenylacetyl Chloride (49c)

A solution of 4,5-dimethoxy-2-nitrophenylacetic acid (48c) (4.2 g, 0.02 mol) in chloroform (15.0 ml) and anhydrous
dimethylformamide (15.0 ml) was treated with thionyl chloride (2.6 g, 1.6 ml, 0.022 mol) and the mixture was stirred at 50° (water bath) for 0.5 h.

Evaporation of the mixture yielded a brown gum (4.9 g) which was triturated with toluene to give unreacted 4,5-dimethoxy-2-nitrophenylacetic acid (48c) (4.0 g; 97%), m.p. 187-189° (lit., 155 206-208°), identical (i.r. spectrum) to an authentic sample.

Evaporation of the toluene mother liquor afforded an intractable gum (0.8 g) which was not further investigated.

1-(2-Nitrophenyl)propan-2-ones (27) and (50a-c)

A mixture of magnesium turnings (2.0 g, 0.082 mol) (previously well washed with anhydrous diethyl ether), absolute ethanol (2.0 ml) and carbon tetrachloride (0.4 ml) was stirred at room temperature for 5 min then diluted with anhydrous diethyl ether (60.0 ml). The resulting suspension was treated dropwise, with stirring and gentle heating, with a solution of diethyl malonate (13.2 g, 0.08 mol) in anhydrous diethyl ether (10.4 ml) and absolute ethanol (8.2 ml). The mixture was then heated under reflux for 4.5 h by which time no magnesium turnings remained in suspension. The resulting magnesium enolate solution was treated dropwise with stirring and gentle heating with a solution of the respective 2-nitrophenylacetyl chlorides (25) or (49a and b) (0.0082 mol) in anhydrous diethyl ether (40.0 ml) and stirring and heating were continued for 0.5 h. The mixture was then cooled to room temperature and treated dropwise with stirring over 0.5 h with 2M aqueous sulphuric acid (100 ml). The ethereal layer
was separated and the aqueous layer was washed with diethyl ether (100 ml). Evaporation of the combined diethyl ether extracts gave an oil which was treated with glacial acetic acid (24.0 ml), water (16.0 ml), and concentrated sulphuric acid (3.8 ml) and the mixture heated under reflux for 2.5-4 h. The mixture was cooled, basified with 20% w/v aqueous potassium hydroxide solution, and extracted with methylene chloride to give the corresponding 1-(2-nitrophenyl)propan-2-ones.

(a) 1-(2-Nitrophenyl)propan-2-one (27) was obtained as a brown oil (14.4 g; 98%), ν\text{max} 1730 (CO) and 1530 and 1350 (NO₂) cm\textsuperscript{-1}.

(b) 1-(5-Methyl-2-nitrophenyl)propan-2-one (50a) formed light brown plates (13.0 g; 82%), m.p. 60-61 ° (from ethanol-light petroleum/b.p. 80-100 °), ν\text{max} 1720 (CO) and 1510 and 1345 (NO₂) cm\textsuperscript{-1}, δ(CDC\textsubscript{3}) 8.04 (1H, d, J\textsubscript{ortho} 8Hz, H-3) 7.23-7.04 (2H, m, ArH), 4.05 (2H, s, CH\textsubscript{2}), 2.41 (3H, s, CH\textsubscript{3}), and 2.30 (3H, s, CH\textsubscript{3}).

Found: C, 62.2; H, 5.8; N, 7.2%; M⁺, 193.
C\textsubscript{10}H\textsubscript{11}NO\textsubscript{3} requires: C, 62.2; H, 5.7; N, 6.9%; M, 193.

(c) 1-(5-Methoxy-2-nitrophenyl)propan-2-one (50b) formed cream coloured needles (15.6 g; 91%), m.p. 52-53 ° (from toluene-light petroleum), ν\text{max} 1715 (CO) and 1510 and 1350 (NO₂) cm\textsuperscript{-1}, δ(CDC\textsubscript{3}) 8.14 (1H, d, J\textsubscript{ortho} 8Hz, H-3), 6.86 (1H, dd, J\textsubscript{ortho} 8Hz, J\textsubscript{meta} 2Hz, H-4), 6.69 (1H, d, J\textsubscript{meta} 2Hz, H-6), 4.08 (2H, s, CH\textsubscript{2}), 3.84 (3H, s, CH\textsubscript{3}), and 2.30 (3H, s, CH\textsubscript{3}).

Found: C, 56.9; H, 5.2; N, 6.6%; M⁺, 209.
C\textsubscript{10}H\textsubscript{11}NO\textsubscript{4} requires: C, 57.4; H, 5.3; N, 6.7%; M, 209.
**1-(4,5-Dimethoxy-2-nitrophenyl)propan-2-one (50c)**

A solution of 1-(3,4-dimethoxyphenyl)propan-2-one (57) (3.9 g, 0.02 mol) in glacial acetic acid (10.0 ml) was cooled to 0–10°C (ice bath) and treated dropwise, with stirring with concentrated nitric acid (S.G.1.42) (6.0 ml) at such a rate that the temperature of the mixture did not rise above 65°C. The solution was stirred for a further 0.5 h after addition was complete then filtered to afford 1-(4,5-dimethoxy-2-nitrophenyl)propan-2-one (50c) (3.7 g; 77%) which formed colourless needles, m.p. 127–128°C (from toluene), ν\text{max} 1715 (CO) and 1530 and 1355 (NO\textsubscript{2}) cm\textsuperscript{-1}, δ(CDCl\textsubscript{3}) 7.71 (1H, s, H-3), 6.63 (1H, s, H-6), 4.06 (2H, s, CH\textsubscript{2}), 3.95 (6H, s, 2 x overlapping CH\textsubscript{3}), and 2.31 (3H, s, CH\textsubscript{3}).

**Found:** C, 55.0; H, 5.6; N, 5.7%; M\textsuperscript{+}, 239.

C\textsubscript{11}H\textsubscript{13}NO\textsubscript{5} requires: C, 55.2; H, 5.5; N, 5.9%; M, 239.

Extraction of the aqueous acidic mother liquor gave only an intractable oil (0.1 g).

**1-(2-Nitrophenyl)propan-2-one Oximes (28) and (51a-c)**

A solution of the respective 1-(2-nitrophenyl)propan-2-ones (27) or (50a-c) (0.02 mol) in ethanol (25.0 ml) was treated at room temperature with a solution of hydroxylamine hydrochloride (1.5 g, 0.022 mol) in water (1.0 ml) followed by a solution of anhydrous sodium acetate (2.0 g, 0.02 mol) in water (2.0 ml). The mixture was cooled in a refrigerator for 1 h then filtered to give the respective 1-(2-nitrophenyl)-propan-2-one oximes.

(a) 1-(2-Nitrophenyl)propan-2-one oxime (28) was obtained
as a syn/anti isomer mixture (3.8 g; 98%) which formed cream plates, m.p. 131-132° (from methanol) (lit., 148 133°), $\nu_{\text{max}}$ 3200 (N-OH) and 1530 and 1350 (NO$_2$) cm$^{-1}$.

Found: C, 55.4; H, 5.2; N, 14.2%; M$,^+$ 194.  
Calc. for C$_9$H$_{10}$N$_2$O$_3$: C, 55.6; H, 5.2; N, 14.4%; M, 194.

Evaporation of the aqueous ethanolic mother liquor, treatment of the resulting residue with water (10.0 ml), and extraction of the solution with methylene chloride gave only a negligible amount of gum.

(b) 1-(5-Methyl-2-nitrophenyl)propan-2-one oxime (51a) 
was obtained as a colourless solid (4.2 g; 100%) which formed cream needles, m.p. 144-145° (from ethanol-water), $\nu_{\text{max}}$ 3200 (N-OH) and 1510 and 1340 (NO$_2$) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 10.47 (1H, s, N-OH), 7.85 (1H, d, $J_{\text{ortho}}$8 Hz, H-3), 7.30-7.22 (2H, m, ArH), 3.78 (2H, s, CH$_2$), 2.36 (3H, s, CH$_3$), and 1.76 (3H, s, CH$_3$).

Found: C, 57.5; H, 5.9; N, 13.0%; M$,^+$, 208.  
C$_{10}$H$_{12}$N$_2$O$_3$ requires: C, 57.7; H, 5.8; N, 13.5%; M, 208.

Extraction of the aqueous mother liquor with methylene chloride afforded only a negligible amount of gum.

(c) 1-(5-Methoxy-2-nitrophenyl)propan-2-one oxime (51b) 
was obtained as a colourless solid (4.5 g; 100%) which formed colourless needles, m.p. 154-155° (from ethanol-water), $\nu_{\text{max}}$ 3250br (N-OH) and 1510 and 1340 (NO$_2$) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 10.45 (1H, s, N-OH), 8.04 (1H, d, $J_{\text{ortho}}$8 Hz, H-3), 7.06-6.90 (2H, m, ArH), 3.85 (2H, s, CH$_2$), 3.84 (3H, s, CH$_3$), and 1.78 (3H, s, CH$_3$).

Found: C, 53.7; H, 5.3; N, 12.2%; M$,^+$, 224.  
C$_{10}$H$_{12}$N$_2$O$_4$ requires: C, 53.6; H, 5.4; N, 12.5%; M, 224.
Extraction of the aqueous mother liquor with methylene chloride gave only a negligible amount of brown gum.

(d) 1-(4,5-Dimethoxy-2-nitrophenyl)propan-2-one oxime (51c) was obtained as a colourless solid (4.8 g; 89%) which formed colourless plates, m.p. 170-171° (from ethanol-glacial acetic acid), $\nu_{\text{max}}$ 3200 br (N-OH) and 1525 and 1330 cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 10.44 (1H, s, N-OH), 7.57 (1H, s, H-3), 6.99 (1H, s, H-6), 3.78 (2H, s, CH$_2$), 3.83 (3H, s, CH$_3$), 3.80 (3H, s, CH$_3$), and 1.78 (3H, s, CH$_3$).

Found: C, 51.7; H, 5.5; N, 10.7%; M, 254.

C$_{14}$H$_{14}$N$_2$O$_5$ requires: C, 52.0; H, 5.6; N, 11.0%; M, 254.

Extraction of the ethanolic filtrate with methylene chloride gave only a negligible amount of gum.

1-(2-Nitrophenyl)propan-2-one Oxime Tosylates (12) and (52a-c)

A solution of the respective 1-(2-nitrophenyl)propan-2-one oximes (28) or (51a-c) (0.05 mol) in Analar pyridine (47.5 ml) was cooled (ice-water bath) and treated in portions with stirring with finely powdered tosyl chloride (10.0 g, 0.05 mol). The mixture was stirred at room temperature for 4 h then poured with stirring and cooling (ice bath) into 20% w/v aqueous sulphuric acid solution (230 ml). Filtration afforded the respective 1-(2-nitrophenyl)propan-2-one oxime tosylates.

(a) 1-(2-Nitrophenyl)propan-2-one oxime tosylate (12) was obtained as a colourless solid (13.3 g; 76%) which formed colourless plates, m.p. 105-107° (from methanol) (lit., 140 109°), $\nu_{\text{max}}$ 1530 and 1350 (NO$_2$) cm$^{-1}$.
Found: C, 55.4; H, 4.7; N, 8.2%; M⁺, 348.
Calc. for C₁₆H₁₆N₂O₅S: C, 55.2; H, 4.6; N, 8.0%; M, 348.

Extraction of the aqueous acidic mother liquor with methylene chloride gave only a negligible amount of gum.

(b) 1-(5-Methyl-2-nitrophenyl)propan-2-one oxime tosylate (52a) was obtained as a light brown solid (15.7 g; 86%) which formed light brown plates, m.p. 140-142°C (from dimethylformamide-water), νmax 1515 and 1350 (NO₂) cm⁻¹, δ[(CD₃)₂SO] 7.97 (1H, d, Jortho 8Hz, H-3, ArH), 7.28-7.12 (6H, m, ArH), 3.92 (2H, s, CH₂), 2.38 (3H, s, CH₃), 2.34 (3H, s, CH₃), and 1.96 (3H, s, CH₃).

Found: C, 56.2; H, 5.1; N, 7.5%; m/e 352.
C₁₇H₁₈N₂O₅S requires: C, 56.3; H, 5.0; N, 7.7%; M, 362.

Extraction of the aqueous acidic filtrate with methylene chloride gave only a negligible amount of gum.

(c) 1-(5-Methoxy-2-nitrophenyl)propan-2-one oxime tosylate (52b) was obtained as a cream solid (14.5 g; 77%) which formed cream plates, m.p. 129-130°C (from dimethylformamide-water), νmax 1510 and 1340 (NO₂) cm⁻¹, δ[(CD₃)₂SO] 8.14 (1H, d, Jortho 8Hz, H-3), 7.41 (2H, d, Jortho 7Hz, ArH), 7.34 (2H, d, Jortho 7Hz, Ar-H), 7.11 (1H, dd, Jortho 8Hz, Jmeta 2Hz, H-4), 6.87 (1H, d, Jmeta 2Hz, H-6), 3.97 (2H, s, CH₂), 3.86 (3H, s, CH₃), 2.39 (3H, s, CH₃), and 1.99 (3H, s, CH₃).

Found: C, 54.2; H, 4.7; N, 7.3%; m/e 262.
C₁₇H₁₈N₂O₆S requires: C, 54.0; H, 4.8; N, 7.4%; M, 378.

Extraction of the aqueous acidic filtrate with methylene chloride yielded only a negligible amount of brown gum.
(d) 1-(4,5-Dimethoxy-2-nitrophenyl)propan-2-one oxime tosylate (52c) was obtained as a colourless solid (16.1 g; 78%) which formed colourless plates, m.p. 119-120° (from ethanol-dimethylformamide), $\nu_{\text{max}}$ 1500 and 1320 (NO$_2$) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 7.66 (1H, s, H-3), 7.47 (2H, d, J7Hz, ArH), 7.27 (2H, d, J7Hz, ArH), 6.93 (1H, s, H-6), 3.94 (2H, s, CH$_2$), 3.90 (3H, s, CH$_3$), 3.79 (3H, s, CH$_3$), 2.40 (3H, s, CH$_3$), and 2.00 (3H, s, CH$_3$).

Found: C, 52.6; H, 5.0; N, 6.7%; m/e 367.

C$_{18}$H$_{20}$N$_2$O$_7$S requires: C, 52.9; H, 4.9; N, 6.9%; M, 408.

Extraction of the aqueous acidic filtrate with methylene chloride yielded only a negligible amount of gum.

3-Acetyl-1-hydroxy-1H-indazoles (15) and (53a-c)

The respective 1-(2-nitrophenyl)propan-2-one oxime tosylates (12) or (52a-c) (0.024 mol) were added to a saturated solution of ammonia in ethanol (300 ml) and the mixture was shaken at room temperature for 2 h then left stoppered at room temperature for 24 h.

The mixture was diluted with water (120 ml), concentrated to one third of the original volume, treated with animal charcoal, filtered through celite, and the filtrate acidified with 2M aqueous hydrochloric acid to yield the respective 3-acetyl-1-hydroxy-1H-indazoles.

(a) 3-Acetyl-1-hydroxy-1H-indazole (15) was obtained as colourless needles (4.1 g; 96%), m.p. 193-195° (from ethanol-water) (lit., 140 186°), $\nu_{\text{max}}$ 2660 br (N-OH) and 1630 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.24-8.12 (1H, m, ArH), 7.70-7.26 (3H, m, ArH),
and 2.57 (3H, s, CH$_3$).

Found: C, 61.1; H, 4.5; N, 15.8%; M$^+$, 176.

Calc. for C$_9$H$_8$N$_2$O$_2$: C, 61.3; H, 4.6; N, 15.9%; M, 176.

Extraction of the aqueous filtrate with methylene chloride gave a brown gum (0.28 g), which was shown by t.l.c. in methylene chloride over silica to be a multicomponent mixture and was not further investigated.

(b) 3-Acetyl-1-hydroxy-5-methyl-1H-indazole (53a) was obtained as a colourless solid (3.0 g; 65%) which formed colourless needles, m.p. 170-171$^\circ$ (from ethanol-water), $\nu_{\text{max}}$ 2660 br (N-OH) and 1670 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 7.95 (1H, d, J$_{\text{meta}}$ 2Hz, H-4), 7.53 (1H, d, J$_{\text{ortho}}$ 8Hz, H-7), 7.29 (1H, dd, J$_{\text{ortho}}$ 8Hz, J$_{\text{meta}}$ 2Hz, H-6), 2.52 (3H, s, CH$_3$), and 2.43 (3H, s, CH$_3$).

Found: M$^+$, 190.07405.

C$_{10}$H$_{10}$N$_2$O$_2$ requires: M, 190.07422.

Extraction of the aqueous filtrate with methylene chloride gave only an intractable brown gum (0.1 g).

(c) 3-Acetyl-1-hydroxy-5-methoxy-1H-indazole (53b) was obtained as a light brown solid (3.4 g; 68%) which formed light brown needles, m.p. 194-196$^\circ$ (from ethanol-water), $\nu_{\text{max}}$ 2660 br (N-OH) and 1650 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 7.58-7.53 (2H, m, ArH), 7.14 (1H, dd, J$_{\text{ortho}}$ 4Hz, J$_{\text{meta}}$ 1Hz, H-6), and 3.83 (3H, s, CH$_3$).

Found: M$^+$, 206.06919.

C$_{10}$H$_{10}$N$_2$O$_3$ requires: M, 206.06914.

Extraction of the aqueous filtrate with methylene chloride gave only a negligible amount of brown gum.
(d) 3-Acetyl-5,6-dimethoxy-1-hydroxy-1H-indazole (53c) was obtained as a cream solid (3.8 g; 67%) which formed cream needles, m.p. 221-222° (from ethanol-water), $\nu_{\text{max}}$ 3520 (N-OH) and 1665 (CO) cm$^{-1}$, $\delta$(CD$_3$)$_2$SO 7.46 (1H, s, H-4), 7.02 (1H, s, H-7), 3.87 (3H, s, CH$_3$), 3.77 (3H, s, CH$_3$), and 2.52 (3H, s, CH$_3$).

Found: C, 55.8; H, 5.0; N, 11.8%; M$^+$, 236.

C$_{11}$H$_{12}$N$_2$O$_4$ requires: C, 55.9; H, 5.1; N, 11.9%; M, 236.

Extraction of the combined aqueous mother liquors with methylene chloride gave only a small amount of brown gum.

The Attempted Triethylamine-catalysed Cyclisation of 1-(2-Nitrophenyl)propan-2-one Oxime Tosylate (12)

A solution of 1-(2-nitrophenyl)propan-2-one oxime tosylate (12) (1.3 g, 0.004 mol) in ethanol (10.0 ml) was treated with triethylamine (1.6 g, 0.016 mol) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to yield an orange oil (0.19 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give a dark brown gum (0.85 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.
The Attempted Sodium Ethoxide-catalysed Cyclisation of 1-(2-Nitrophenyl)propan-2-one Oxime Tosylate (12)

1-(2-Nitrophenyl)propan-2-one oxime tosylate (12) (1.3 g, 0.004 mol) was treated with a solution of sodium (0.37 g, 0.016 g atm.) in absolute ethanol (25.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to afford a brown gum (0.13 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid to yield a dark brown gum (0.37 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

1-Acetoxy-3-acetyl-1H-indazoles (31) and (54a-c)

(a) The respective 3-acetyl-1-hydroxy-1H-indazoles (15) or (53a-c) (0.0025 mol) were treated with acetic anhydride (0.22 mol) and the suspension was heated at 100° (steam bath) for 10 min then left at room temperature for 20 min. The solution obtained was diluted with water (10.0 ml) to precipitate respective 1-acetoxy-3-acetyl-1H-indazoles which were purified as described for the individual reactions below.

(i) 1-Acetoxy-3-acetyl-1H-indazole (31) was obtained as a pale yellow solid (0.49 g; 90%) which formed pale yellow microcrystals, m.p. 84-85° (from ethanol), \( \nu_{\text{max}} \) 1820 and 1695 (CO) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.28-7.80 (4H, m, ArH), 2.58 (3H, s,
CH₃), and 2.54 (3H, s, CH₃).

Found: C, 60.6; H, 4.7; N, 12.9%; M⁺, 218.

C₁₁H₁₀N₂O₃ requires: C, 60.5; H, 4.6; N, 12.8%; M, 218.

(ii) 1-Acetoxy-3-acetyl-5-methyl-1H-indazole (54a) was obtained as a colourless solid (0.52 g; 89%) which formed colourless plates, m.p. 144-145° (from ethanol-water), v_max 1810 and 1680 (CO) cm⁻¹, δ[(CD₃)₂SO] 8.05 (1H, d, Jmeta 2Hz, H-4), 7.67 (1H, d, Jortho 8Hz, H-7), 7.44 (1H, dd, Jortho 8Hz, Jmeta 2Hz, H-6), 2.57 (3H, s, CH₃), 2.52 (3H, s, CH₃), and 2.48 (3H, s, CH₃).

Found: C, 62.4; H, 5.1; N, 12.1%; M⁺, 232.

C₁₂H₁₂N₂O₃ requires: C, 62.0; H, 5.2; N, 12.1%; M, 232.

(iii) 1-Acetoxy-3-acetyl-5-methoxy-1H-indazole (54b) was obtained as a cream solid (0.55 g; 89%) which formed cream plates, m.p. 115-117° (from ethanol-water), v_max 1820 and 1685 (CO) cm⁻¹, δ[(CD₃)₂SO] 7.70 (1H, d, Jortho 8Hz, H-7), 7.58 (1H, d, Jmeta 2Hz, H-4), 7.20 (1H, dd, Jortho 8Hz, Jmeta 2Hz, H-6), 3.71 (3H, s, CH₃), 2.51 (3H, s, CH₃), and 2.50 (3H, s, CH₃).

Found: M⁺, 248.08014.

C₁₂H₁₂N₂O₄ requires: M, 248.07970.

(iv) 1-Acetoxy-3-acetyl-5,6-dimethoxy-1H-indazole (54c) was obtained as a colourless solid (0.6 g; 92%) which formed colourless plates, m.p. 157-159° (from ethanol-water), v_max 1800 and 1680 (CO) cm⁻¹, δ[(CD₃)₂SO] 7.46 (1H, s, H-4), 7.20 (1H, s, H-7), 3.82 (3H, s, CH₃), 3.79 (3H, s, CH₃), 2.50 (3H, s, CH₃), and 2.48 (3H, s, CH₃).
Found: C, 55.9; H, 5.1; N, 10.1%; M+, 278.
\( \text{C}_{13}\text{H}_{14}\text{N}_{2}\text{O}_{5} \) requires: C, 56.1; H, 5.1; N, 10.1%; M, 278.

(b) 3-Acetyl-1-hydroxy-1H-indazole (15) (0.18 g; 0.001 mol) was heated under reflux with acetic anhydride (5.0 ml) for 3 h and 72 h. The mixtures were diluted with water (5.0 ml) and the solids were collected to give 1-acetoxycarbonyl-3-acetyl-1H-indazole (31) (37-55%), m.p. 79-81°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

3-Acetyl-1H-indazoles (33) and (55a-c)

(a) The respective 1-acetoxycarbonyl-3-acetyl-1H-indazoles (31) or (54a-c) (0.002 mol) in absolute ethanol (35.0 ml) were hydrogenated over 10% palladium-on-charcoal (0.08 g) at room temperature and atmospheric pressure for 2.5 h by which time 48.0 ml of hydrogen had been absorbed. The mixture was filtered through celite and the filtrate was evaporated to yield the respective 3-acetyl-1H-indazoles.

(i) 3-Acetyl-1H-indazole (33) was obtained as a colourless solid (0.26 g; 81%), m.p. 178-182°, identical (m.p. and i.r. spectrum) to a sample prepared in (b) later.

(ii) 3-Acetyl-5-methyl-1H-indazole (55a) was obtained as a light brown solid (0.35 g; 100%) which formed light brown plates, m.p. 170-171° (from ethanol-water), \( \nu_{\text{max}} \) 3250 br (NH) and 1660 (CO) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 7.95 (1H, d, J_{\text{meta}} 2Hz, H-4), 7.58 (1H, d, J_{\text{ortho}} 8Hz, H-7), 7.25 (1H, dd, J_{\text{ortho}} 8Hz, J_{\text{meta}} 2Hz, H-6), 2.60 (3H, s, \text{CH}_3), and 2.42 (3H, s, \text{CH}_3).
Found: C, 69.3; H, 5.7; N, 16.1%; M⁺, 174.

C₁₀H₁₀N₂O requires: C, 68.9; H, 5.8; N, 16.1%; M, 174.

(iii) 3-Acetyl-5-methoxy-1H-indazole (55b) was obtained as a colourless solid (0.36 g; 95%) which formed colourless needles, m.p. 208-209° (from ethanol-water), ν max 3200 br (NH) and 1660 (CO) cm⁻¹, δ[(CD₃)₂SO] 7.60 (1H, d, Jortho 8Hz, H-7), 7.53 (1H, d, Jmeta 2Hz, H-4), 7.08 (1H, dd, Jortho 8Hz, Jmeta 2Hz, H-6), 3.82 (3H, s, CH₃), and 2.61 (3H, s, CH₃).

Found: M⁺, 190.07445.

C₁₀H₁₀N₂O₂ requires: M, 190.07422.

(iv) 3-Acetyl-5,6-dimethoxy-1H-indazole (55c) was obtained as a colourless solid (0.28 g; 68%) which formed colourless plates, m.p. 197-198° (from ethanol-water), ν max 3250 br (NH) and 1660 (CO) cm⁻¹, δ[(CD₃)₂SO] 7.47 (1H, s, H-4), 7.03 (1H, s, H-7), 3.82 (3H, s, CH₃), 3.78 (3H, s, CH₃), and 2.56 (3H, s, CH₃).

Found: M⁺, 220.08388.

C₁₁H₁₂N₂O₃ requires: M, 220.08344.

(b) 3-Acetyl-1-hydroxy-1H-indazole (15) (0.18 g; 0.001 mol) was heated under reflux with sodium dithionite (0.18 g) in 70% v/v aqueous ethanol (5.0 ml) for 0.5 h. A second portion (0.18 g) of sodium dithionite was added and heating under reflux was continued for a further 0.5 h. The mixture was evaporated, the residue was treated with water, and the solid was collected and crystallised to afford 3-acetyl-1H-indazole (33) (0.09 g; 56%) which formed colourless plates, m.p. 188-190° (from ethanol-water) (lit., 150 182°), ν max 3200 br (NH) and 1660 cm⁻¹, δ[(CD₃)₂SO] 8.30-7.24 (4H, m, ArH) and
2.68 (3H, s, CH₃).

Found: C, 67.6; H, 5.2; N, 17.6%; M⁺, 160.
Calc. for C₉H₈N₂O: C, 67.5; H, 5.0; N, 17.5%; M, 160.

The aqueous mother liquor was evaporated and the residue was extracted with boiling ethyl acetate to give unreacted 3-acetyl-1-hydroxy-1H-indazole (15) (0.085 g; 43%), m.p. 172-173°C, identical (m.p. and i.r. spectrum) to a sample prepared before.

3-Acetyl-1-hydroxy-1H-indazole Oxime (30a)

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.88 g, 0.005 mol) in ethanol (25.0 ml) was treated with a solution of hydroxylamine hydrochloride (0.69 g, 0.01 mol) followed by a solution of anhydrous sodium acetate (1.23 g, 0.015 mol) in water (2.0 ml) and the mixture was heated under reflux for 2 h. The cooled mixture was diluted with water (60.0 ml) and the precipitated solid was collected and combined with a second crop obtained by evaporating the aqueous ethanolic mother liquor, and treatment of the residue with water (30.0 ml) to yield 3-acetyl-1-hydroxy-1H-indazole oxime (30a) (total 0.9 g; 95%) which formed colourless needles, m.p. 184-185°C (from ethanol-water), νmax 3220 (N-OH) cm⁻¹, δ[(CD₃)₂SO] 11.21 (1H, s, N-OH), 8.13-7.08 (4H, m, ArH), and 2.24 (3H, s, CH₃).

Found: C, 56.7; H, 4.7; N, 22.1%; M⁺, 191.
Calc. for C₉H₈N₃O₂ requires: C, 56.5; H, 4.8; N, 22.0%; M, 191.

3-Acetyl-1-hydroxy-1H-indazole 2,4-Dinitrophenylhydrazone (30b)

A suspension of 2,4-dinitrophenylhydrazine (0.4 g, 0.002
mol) in methanol (5.0 ml) containing concentrated hydrochloric acid (0.8 ml) was heated under reflux for 10 min until all of the suspended solid had dissolved. The resulting solution was mixed with a solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.18 g, 0.001 mol) in methanol (3.0 ml) and the mixture was heated under reflux for 3 min, cooled and filtered to afford 3-acetyl-1-hydroxy-1H-indazole 2,4-dinitrophenylhydrazone (30b) (0.33 g; 93%) which formed dark red plates, m.p. 268-269 ° (from glacial acetic acid), \( \nu_{\text{max}} \) 3220 (NH) and 1520, 1505, 1360, and 1315 (NO\(_2\)) cm\(^{-1}\).

Found: M\(^+\), 356.08677.  
C\(_{15}\)H\(_{12}\)N\(_6\)O\(_5\) requires: M, 356.08691.

3-Acetyl-1-hydroxy-1H-indazole Tosylhydrazone (30c)

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.18 g, 0.001 mol) and toluene-4-sulphonylhydrazine (0.19 g, 0.001 mol) in absolute ethanol (5.0 ml) was heated under reflux for 0.5 h. The mixture was evaporated to give 3-acetyl-1-hydroxy-1H-indazole tosylhydrazone (30c) (0.34 g; 100%) which formed colourless needles, m.p. 199-200 ° (from dimethylformamide-water), \( \nu_{\text{max}} \) 3230 (NH) and 2660 br (N-OH) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.00-7.84 (3H, m, ArH), 7.48-7.10 (3H, m, ArH), 2.36 (3H, s, CH\(_3\)), and 2.29 (3H, s, CH\(_3\)).

Found: C, 55.5; H, 4.6; N, 16.2%; M\(^+\), 344.  
C\(_{16}\)H\(_{16}\)N\(_4\)O\(_3\)S requires: C, 55.8; H, 4.7; N, 16.3%; M, 344.

The Attempted Catalytic Reduction of 3-Acetyl-1-hydroxy-1H-indazole (15)

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.18 g,
0.001 mol) in absolute ethanol (20.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.02 g) at room temperature and atmospheric pressure for 4 h by which time no hydrogen had been absorbed. The mixture was filtered through celite and the filtrate was evaporated to yield unreacted 3-acetyl-1-hydroxy-1H-indazole (15) (0.14 g; 78%), m.p. 172-173°C, identical (m.p. and i.r. spectrum) to a sample obtained before.

**The Attempted Reduction of 3-Acetyl-1-hydroxy-1H-indazole (15) with Sodium Borohydride**

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.36 g, 0.002 mol) in absolute ethanol (10.0 ml) was treated with sodium borohydride (0.3 g, 0.008 mol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with water (5.0 ml), neutralised with 2M aqueous hydrochloric acid and glacial acetic acid and extracted with methylene chloride to yield a brown gum (0.14 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

**The Reaction of 3-Acetyl-1-hydroxy-1H-indazole (15) with Chromium Trioxide in Aqueous Acetic Acid**

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.18 g, 0.001 mol) in 70% v/v aqueous acetic acid (5.0 ml) was treated, in portions at 100°C (steam bath) with chromium trioxide (0.36 g) and the mixture was heated at 100°C for 1 h. The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give 3-acetyl-1H-indazole (33) (0.06 g; 38%), m.p. 184-186°C (lit., 150...
identical (m.p. and i.r. spectrum) to a sample obtained before.

The Reaction of 3-Acetyl-1-hydroxy-1H-indazole (15) with Hydrogen Peroxide and Glacial Acetic Acid

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.36 g, 0.002 mol) in glacial acetic acid (10.0 ml) was treated with 30% (100 vol.) aqueous hydrogen peroxide (5.0 ml) and the mixture was stirred and heated at 50°C (oil bath) for 16 h. The mixture was cooled, diluted with water (20.0 ml), neutralized with solid sodium acetate, and extracted with methylene chloride to yield benzoic acid (0.15 g; 61%), m.p. 113-114°C (lit., 114°C 122°C), identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 3-Acetyl-1-hydroxy-1H-indazole (15) with Sodium Hypochlorite

A solution of 3-acetyl-1-hydroxy-1H-indazole (15) (0.18 g, 0.001 mol) in redistilled dioxane (5.0 ml) was treated with 14% aqueous sodium hypochlorite solution (1.6 ml) and the mixture was heated at 70°C (water bath) for 1.5 h. The mixture was diluted with water (10.0 ml), and treated with solid sodium bisulphite until the mixture gave a negative starch iodide test with aqueous acidic potassium iodide solution. The mixture was then extracted with methylene
chloride to give an orange oil (0.17 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous mother liquor was made alkaline with 2M aqueous sodium hydroxide and extracted with methylene chloride to afford only a negligible quantity of gum.

The Attempted Reaction of 3-Acetyl-1-hydroxy-1H-indazole Oxime (30a) with Tosyl Chloride

A solution of 3-acetyl-1-hydroxy-1H-indazole oxime (30a) (0.38 g, 0.002 mol) in Analar pyridine (1.9 ml) was cooled (ice-water bath) and treated in portions, with stirring, with finely powdered tosyl chloride (0.8 g, 0.0042 mol). The mixture was stirred at room temperature for 4 h then poured with stirring and cooling (ice bath) into 20% w/v aqueous sulphuric acid solution. The mixture was extracted with methylene chloride to give an orange gum (0.24 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and anhydrous sodium acetate and extracted with methylene chloride to afford a brown gum (0.1 g) which was shown by t.l.c. in diethyl ether over silica to be an unresolvable multicomponent mixture, and was not further investigated.

The Attempted Reaction of 3-Acetyl-1-hydroxy-1H-indazole Oxime (30a) with Polyphosphoric Acid

3-Acetyl-1-hydroxy-1H-indazole oxime (30a) was added to
polyphosphoric acid (ca 12 g) and the mixture was stirred and heated at 120° (oil bath) for 10 min. The mixture was diluted with water (20.0 ml) and extracted with methylene chloride to give a brown oil (0.07 g) which was shown by t.l.c. in diethyl ether over silica to be a multicomponent mixture and was not further investigated.

The aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide and glacial acetic acid and extracted with methylene chloride to afford a brown gum (0.13 g) which was shown by t.l.c. in diethyl ether over silica to be an un-resolvable multicomponent mixture, and was not further investigated.

2,4-Dinitrophenylacetyl Chloride (49d)

A slurry of 2,4-dinitrophenylacetic acid (48d) (22.6 g, 0.1 mol) and thionyl chloride (89.5 g, 55.0 ml, 0.75 mol) was stirred and heated at 50° (water bath) for 7 h. The excess of thionyl chloride was distilled off under reduced pressure (water pump) to yield 2,4-dinitrophenylacetyl chloride (49d) as a brown gum (24.5 g; 100%), \( \nu_{\text{max}} \) 1790 (CO) and 1530 and 1350 (NO\(_2\)) cm\(^{-1}\), which was used without further purification.

1-(2,4-Dinitrophenyl)propan-2-one (50d)

A mixture of magnesium turnings (2.0 g, 0.082 mol) (previously well washed with anhydrous diethyl ether), absolute ethanol (2.0 ml), and carbon tetrachloride (0.4 ml) was stirred at room temperature for 5 min then diluted with anhydrous diethyl ether (60.0 ml). The resulting suspension was stirred
and treated dropwise with gentle heating (water bath) with a solution of diethyl malonate (13.2 g, 0.08 mol) in anhydrous diethyl ether (10.4 ml) and absolute ethanol (8.2 ml). The mixture was then heated under reflux for 4.5 h by which time no magnesium turnings remained in suspension. The resulting magnesium enolate solution was treated dropwise with stirring and gentle heating with a solution of 2,4-dinitrophenylacetyle chloride (49d) (20.1 g, 0.082 mol) in anhydrous diethyl ether (40.0 ml) and stirring and heating were continued for 0.5 h. The mixture was then cooled to room temperature and treated, dropwise with stirring over 0.5 h with 2M aqueous sulphuric acid (100 ml). The ether layer was separated and the aqueous layer was washed with further diethyl ether. Evaporation of the combined ether extracts gave an oil (26.5 g) which was treated with glacial acetic acid (24.0 ml), water (16.0 ml), and concentrated sulphuric acid (3.8 ml) and the mixture heated under reflux for 4 h. The mixture was cooled, basified with 20% w/v aqueous potassium hydroxide and extracted with methylene chloride to yield 1-(2,4-dinitrophenyl)propan-2-one (50d) as an oil (4.3 g; 23%), $\nu_{\text{max}}$ 1730 (CO) and 1540 and 1350 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$), 8.92 (1H, d, $J_{\text{meta}}$ 2Hz, H-3), 8.44 (1H, dd, $J_{\text{ortho}}$ 9Hz, $J_{\text{meta}}$ 2Hz, H-5), 7.48 (1H, d, $J_{\text{ortho}}$ 9Hz, H-6), 4.15 (2H, s, CH$_2$), and 2.35 (3H, s, CH$_3$), which could not be purified by bulb-to-bulb distillation and was used without further purification.

Neutralisation of the aqueous mother liquor with concentrated hydrochloric acid and anhydrous sodium acetate followed by extraction with methylene chloride afforded only a small amount (0.2 g) of an intractable brown gum.
1-(2,4-Dinitrophenyl)propan-2-one Oxime (51d)

A solution of 1-(2,4-dinitrophenyl)propan-2-one (50d) (2.3 g, 0.01 mol) in ethanol (100 ml) was treated with a solution of hydroxylamine hydrochloride (5.6 g, 0.08 mol) in water (10.0 ml) followed by a solution of anhydrous sodium acetate (6.6 g, 0.08 mol) in water (10.0 ml) and the mixture was then heated under reflux for 2 h. The mixture was evaporated and the residue was treated with water (25.0 ml) and extracted with methylene chloride to give a brown oil (1.8 g) which was triturated with diethyl ether-light petroleum to afford 1-(2,4-dinitrophenyl)propan-2-one oxime (51d) (0.48 g; 20%), m.p. 129-131° (lit., 148 140°), which was used without further purification.

Evaporation of the diethyl ether-light petroleum mother liquor gave a brown oil (1.3 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multi-component mixture.

1-(2,4-Dinitrophenyl)propan-2-one Oxime Tosylate (8a)

A solution of 1-(2,4-dinitrophenyl)propan-2-one oxime (51d) (0.48 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred and treated, in one portion, at room temperature with triethylamine (0.25 g, 0.0025 mol) followed dropwise by a solution of tosyl chloride (0.42 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove triethylamine hydrochloride (0.05 g; 18%), m.p. 252-254° (lit., 159 255°), identical (m.p. and i.r. spectrum)
to an authentic sample. Evaporation of the filtrate, treatment of the residue with water, and extraction with methylene chloride gave a brown oil (0.8 g) which was treated with diethyl ether to afford 1-(2,4-dinitrophenyl)propan-2-one oxime tosylate (8a) (0.4 g; 51%) which formed pale yellow plates, m.p. 128-129° (from dimethylformamide-methanol) (lit., 144 129-130°), $\nu_{\text{max}}$ 1610 (C=N) and 1540 and 1340 (NO$_2$) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.68 (1H,d, $J_{\text{meta}}$ 2Hz, H-3), 8.48 (1H, dd, $J_{\text{ortho}}$ 8Hz, H-5), 7.66 (1H, d, $J_{\text{ortho}}$ 8Hz, H-6), 7.38 (2H, d, $J$ 8Hz, ArH), 7.20 (2H, d, J8Hz, ArH), 4.10 (2H, s, CH$_2$), 2.38 (3H, s; CH$_3$), and 2.02 (3H, s, CH$_3$).

**Found:** C, 48.9; H, 3.6; N, 11.0%; m, 363.

Calc. for C$_{16}$H$_{15}$N$_3$O$_7$S: C, 48.8; H, 3.8; N, 10.7%; m, 393.

Evaporation of the diethyl ether mother liquor gave an orange oil (0.35 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture.

The Attempted Reaction of 1-(2,4-Dinitrophenyl)propan-2-one Oxime Tosylate (8a) with Ethanolic Ammonia

1-(2,4-Dinitrophenyl)propan-2-one oxime tosylate (8a) (1.6 g, 0.004 mol) was treated with a saturated solution of ammonia in ethanol (50.0 ml) and the mixture was shaken at room temperature for 2 h then left stoppered at room temperature for 24 h.

The mixture was diluted with water (20.0 ml) and concentrated to one third of the original volume. The solid precipitate was collected and combined with further material obtained by acidifying the aqueous mother liquor with 2M aqueous hydrochloric acid, to give an intractable red solid.
(total 0.57 g) whose t.l.c. in methylene chloride over alumina showed it to be an unresolvable multicomponent mixture and was not further investigated.

Extraction of the aqueous mother liquor with methylene chloride afforded only a small amount (0.06 g) of an uncharacterised gum.

2-(2-Nitrophenyl)-1-phenylethanone (60a)

2-(2-Nitrophenyl)-1-phenylethanone (60a) was prepared as described in chapter 2, page 80.

2-(2-Nitrophenyl)-1-phenylethanone Oxime (61a)

2-(2-Nitrophenyl)-1-phenylethanone oxime (61a) was prepared (yield 67%) by the reaction of 2-(2-nitrophenyl)-1-phenylethanone (60a) with hydroxylamine hydrochloride in the presence of sodium acetate as described in the literature,142 m.p. 115-116°C (lit.,142 118°C), and was used without further purification.

The Attempted Reaction of 2-(2-Nitrophenyl)-1-phenylethanone Oxime (61a) with Tosyl Chloride

A solution of 2-(2-nitrophenyl)-1-phenylethanone oxime (61a) (4.6 g, 0.018 mol) in Analar pyridine (17.1 ml) was cooled (ice-water bath) and treated in portions, with stirring, with finely powdered tosyl chloride (3.8 g, 0.02 mol). The mixture was stirred at room temperature for 4 h then poured with stirring and cooling (ice-bath) into 20% w/v aqueous sulphuric acid solution (110 ml). The mixture was extracted
with methylene chloride to afford a dark brown gum (5.2 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture. The gum was dissolved in methylene chloride and the solution was washed with 2M aqueous sodium hydroxide and evaporated to give a brown gum (4.4 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to yield a brown gum (0.09 g) which was not further investigated.

2-Bromo-2-(2-Nitrophenyl)-1-phenylethanone (66)

2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (66) was prepared as described in chapter 2, page 83.

The Attempted Reaction of 2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (66) with Ethanolic Ammonia

2-Bromo-2-(2-nitrophenyl)-1-phenylethanone (66) (1.3 g, 0.004 mol) was added to a saturated solution of ammonia in ethanol (50.0 ml) and the mixture was shaken at room temperature for 1 h then left stoppered at room temperature for 24 h.

The mixture was diluted with water (20.0 ml), concentrated to one third of the original volume and extracted with methylene chloride to give a dark brown oil (1.0 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.
Acidification of the aqueous mother liquor with 2M aqueous hydrochloride acid and extraction with methylene chloride afforded only a small amount (0.05 g) of a brown oil which was not further investigated.

2-(2,4-Dinitrophenyl)-1-phenylethanone (60b)

(a) The attempted preparation of 2-(2,4-dinitrophenyl)-1-phenylethanone (60b) by the reaction of 1-chloro-2,4-dinitrobenzene (58) with the sodium salt of 1-phenyl-1,3-butanedione (59) as described in the literature\textsuperscript{158} yielded an oil whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(b) A suspension of 2,4-dinitrophenylacetyl chloride (49d) (24.5 g, 0.1 mol) in anhydrous benzene (100 ml) was added dropwise over 45 min to a stirred suspension of aluminium trichloride (16.0 g) in anhydrous benzene (150 ml). The mixture was stirred and gradually heated to reflux over 2 h then heated under reflux for 1 h. The cooled mixture was poured into a slurry of 2M aqueous hydrochloric acid and ice (250 ml) and the benzene layer was separated and the aqueous layer was washed with further benzene (150 ml). Evaporation of the combined benzene extracts gave a brown gum (32.8 g) which was triturated with diethyl ether to afford 2-(2,4-dinitrophenyl)-1-phenylethanone (60b) (10.3 g; 36%), m.p. 128-130° (from ethanol) (lit.,\textsuperscript{158} 137°), \( v_{\text{max}} \) 1690 (CO) and 1530 and 1350 (NO\textsubscript{2}) cm\(^{-1}\), which was used without further purification.

The ethanol and diethyl ether mother liquors were combined
and evaporated to give a brown gum (21.5 g) which was shown by t.l.c. in toluene over alumina to be an unresolvable multi-component mixture and was not further investigated.

2-(2,4-Dinitrophenyl)-1-phenylethanone Oxime (61b)

A solution of 2-(2,4-dinitrophenyl)-1-phenylethanone (60b) (4.3 g, 0.015 mol) in ethanol (150 ml) was treated with a solution of hydroxylamine hydrochloride (8.3 g, 0.12 mol) and anhydrous sodium acetate (9.8 g, 0.12 mol) in water (15.0 ml) and the mixture was heated under reflux for 1 h. The mixture was cooled and the solid was collected and combined with a second crop obtained by evaporating the filtrate and treatment of the resulting residue with water (20.0 ml) to give 2-(2,4-dinitrophenyl)-1-phenylethanone oxime (61b) (total 4.3 g; 95%), m.p. 138-140° (lit., 157-142°), which was used without further purification.

Extraction of the aqueous mother liquor with methylene chloride gave only a small amount (0.15 g) of an intractable gum.

The Attempted Preparation of 2-(2,4-Dinitrophenyl)-1-phenylethanone Oxime Tosylate (8b)

(a) A solution of 2-(2,4-dinitrophenyl)-1-phenylethanone oxime (61b) (0.57 g, 0.002 mol) in Analar pyridine (1.9 ml) was cooled (ice-water bath) and treated in portions, with stirring, with finely powdered tosyl chloride (0.4 g, 0.0021 mol). The mixture was stirred at room temperature for 4 h then poured with stirring and cooling (ice bath) into 20% w/v
aqueous sulphuric acid solution (12.0 ml). The mixture was extracted with methylene chloride to afford an orange gum (0.63 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.

(b) A solution of 2-(2,4-dinitrophenyl)-1-phenylethanone oxime (61b) (0.57 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (15.0 ml) was stirred and treated in one portion at room temperature with triethylamine (0.25 g, 0.0025 mol) followed dropwise by a solution of tosyl chloride (0.42 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove triethylamine hydrochloride (0.05 g; 18%), m.p. 253-255° (lit., 159 255°), identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated and the residue was treated with water to yield unreacted 2-(2,4-dinitrophenyl)-1-phenylethanone oxime (61b) (0.57 g; 100%), m.p. 139-140° (lit., 157 142°), identical (m.p. and i.r. spectrum) to an authentic sample.

Extraction of the aqueous mother liquor with methylene chloride afforded only a negligible amount (0.045 g) of a yellow oil.
Chapter 5

Studies of Some Base-catalysed Transformations of $\text{N,N-Dialkyl-2-nitrobenzylamine Derivatives}$
Studies of Some Base-catalysed Transformations of N,N-Dialkyl-2-nitrobenzylamine Derivatives

5.1 Introduction

Patey and Waldron\textsuperscript{160} showed (Scheme 1) that either nitration of N,N-dimethyl-4-nitrobenzylamine (1) or reaction of 2,4-dinitrobenzyl bromide (2) with dimethylamine affords not the expected N,N-dimethyl-2,4-dinitrobenzylamine (3) but rather 2-methyl-6-nitro-2H-indazole (4), but made no attempt to rationalise these novel transformations. Subsequent studies at Edinburgh\textsuperscript{161} verified the earlier work by Patey and Waldron and demonstrated the likely intermediacy of N,N-dimethyl-2,4-dinitrobenzylamine (3) which was shown to undergo smooth cyclisation in high yield to 2-methyl-6-nitro-2H-indazole (4) on treatment with ethanolic potassium hydroxide. The Edinburgh studies\textsuperscript{161} also demonstrated (Scheme 2) that N,N-dialkyl-2-nitrobenzylamine derivatives (5) bearing simple N-alkyl substituents underwent smooth cyclisation in high yield on treatment with ethanolic potassium hydroxide providing a useful general route to 2-alkyl-2H-indazole derivatives (10). It was also shown that the alkyl substituent lost in these novel heterocyclisations is converted into an aldehyde by-product (11). On the basis of these observations the possible mechanism for indazole formation shown in Scheme 2 was suggested.\textsuperscript{16}

The Edinburgh studies\textsuperscript{161} also showed (Scheme 3) that when the alkyl substituents of the N,N-dialkyl-2-nitrobenzylamine derivative (12) are bulky, indazole formation is totally suppressed and the products obtained in high yield are the corresponding N,N-dialkyl-2-hydroxyaminobenzamides (18).
(1)  \[ \text{HNO}_3 \]

(ii)  \[ \text{Me}_2\text{NH} \]

(iii)  \[ \text{KOH, EtOH} \]

Scheme 1
(i) KOH, EtOH

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>a; H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>b; NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>c; H</td>
<td>Et</td>
<td>Me</td>
</tr>
<tr>
<td>d; NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Et</td>
<td>Me</td>
</tr>
<tr>
<td>e; H</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>Ph</td>
</tr>
<tr>
<td>f; NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Ph</td>
<td>Ph</td>
</tr>
</tbody>
</table>

Scheme 2
(i) KOH, EtOH

(ii) LiAlH₄

Scheme 3
The formation of these unexpected products can be explained (Scheme 3) in terms of the formation of nitroso-intermediates (15) which unlike those postulated as intermediates in indazole formation [Scheme 2; (8)] cannot, for steric and electronic reasons, undergo alkyl deprotonation and instead add hydroxide ion and undergo further transformations to afford the observed hydroxyaminobenzamide products (18). Because of the unusual nature of these products, attempts were made in the previous studies\textsuperscript{161} to establish their structures chemically. However, attempts to convert them into \textit{N}-acetoxy derivatives or to effect the oxidation of the hydroxyamino function were unsuccessful. On the other hand, reduction\textsuperscript{161} of the di-isopropyl compound (18a) with lithium aluminium hydride gave a product whose analytical and spectroscopic properties were consistent with the hydroxyaminobenzylamine structure (19). In view of the unexpected stability of the hydroxyamino-group in the compound (18a) to reduction and the failure of the hydroxyaminobenzamides (18a and b) to undergo typical hydroxyamine reactions, it was of further interest to seek definite chemical evidence for their structures. It was also of interest to further investigate the scope of the interesting base-catalysed transformations of \textit{N},\textit{N}-disubstituted 2-nitrobenzylamines outlined in Schemes 2 and 3.

5.2 Chemical Transformations of \textit{N},\textit{N}-Di-isopropyl- and \textit{N},\textit{N}-Dicyclohexyl-2-hydroxyaminobenzamides (18a and b)

Initially it was decided to verify the behaviour of \textit{N},\textit{N}-di-isopropyl-2-nitrobenzylamine (12a) towards heating with ethanolic potassium hydroxide as described in previous studies.
The amine (12a) was prepared (Scheme 4) by the reaction of 2-nitrobenzyl bromide (20) with di-isopropylamine (21a) as described in the previous work at Edinburgh but using an improved workup procedure. Heating an ethanolic solution of N,N-di-isopropyl-2-nitrobenzylamine (12a) with potassium hydroxide gave a product in good yield (65%) which analysed correctly and showed spectroscopic properties in agreement with those reported for N,N-di-isopropyl-2-hydroxyaminobenzamide (18a) in the previous studies at Edinburgh. In particular, the i.r. spectrum showed NH and OH absorption at 3320 and 3120 cm\(^{-1}\) and contained a band at 1660 cm\(^{-1}\) attributable to an amide carbonyl group.

In an attempt to verify the hydroxyamine structure (18a) for the product, its behaviour towards various oxidising agents was studied. Treatment of the compound with chromium trioxide in aqueous acetic acid at 100\(^{\circ}\) gave only small amounts of intractable gums. Attempted oxidation in toluene with manganese dioxide at room temperature was equally unsuccessful, the starting-material being recovered though only in low yield. In contrast, oxidation of the presumed hydroxyaminobenzamide (18a) with aqueous hydrogen peroxide in glacial acetic acid gave benzoic acid in moderate yield (45%). The conversion of the hydroxyaminobenzamide (18a) into benzoic acid on treatment with hydrogen peroxide in acetic acid can be explained by the mechanism shown in Scheme 4. Acylation of the hydroxyamino substituent to give the reactive ester (22) is followed by cyclisation and subsequent dealkylation to afford 2-(prop-2-yl)indazol-3(1H)-one (24). Further oxidative dealkylation of the latter would yield the N-hydroxyindazole. 

(20) CH$_2$BrNO$_2$ + (21) NH$_R$R $\rightarrow$ (12) RNO$_2$

(i) $R$  
   a: Pr$^i$  
   b: c-C$_6$H$_{11}$

(ii) (18)

(18a)

(18)

(22)

(18a)

(23)

(24)

(25)

(26)

(i) KOH, EtOH

(ii) H$_2$O$_2$, AcOH

(iii) H$_2$O

Scheme 4
(25), dehydration of which would afford the dehydroindazolone (26). The latter is known\textsuperscript{162} to be spontaneously unstable in aqueous media and to decompose with loss of nitrogen to afford benzoic acid.

Having been unsuccessful in obtaining evidence for the hydroxyaminobenzamide structure (18a) using oxidative methods, attention was next turned to the behaviour of the compound towards acylating agents. However, attempted reaction with phenyl isocyanate in 1,2-dimethoxyethane at room temperature gave only the unreacted starting-material (18a) in good yield (64%). Attempted acetylation of the hydroxyaminobenzamide (18a) by heating with acetic anhydride gave only intractable gums which also resulted on attempted reaction with benzoyl chloride or toluene-p-sulphonyl (tosyl) chloride in the presence of triethylamine. In contrast, the hydroxyaminobenzamide (18a) reacted smoothly with ethyl chloroformate in 1,2-dimethoxyethane in the presence of triethylamine (Scheme 5) to afford a product in moderate yield (51%) which analysed correctly for $C_{10}H_{12}N_2O$. The i.r. spectrum of the product contained bands at 2600 and 1620 cm\textsuperscript{-1} attributable to the NH and carbonyl absorption of a cyclic lactam structure. The $^1H$ n.m.r. spectrum of the product showed the presence of a single isopropyl group and a one proton singlet at $\delta$ 8.0 attributable to an NH-group. On the basis of these properties the product can be formulated as 2-(prop-2-yl)indazol-3(1H)-one (24). This structural assignment was fully confirmed by unambiguous synthesis (Scheme 6) involving the sodium hydroxide-catalysed cyclisation of $N$-(prop-2-yl)-2-nitroso-benzamide (32c) which was readily obtained by the photo-
(18a) → (27)

\(-\text{EtCO}_2^-\)

(i) \(\text{ClCO}_2\text{Et}, \text{Et}_3\text{N}\)

Scheme 5
(30) \[ \text{CH} = \text{O} \]

(i) \[ \rightarrow \]

(31) \[ \text{CH} = \text{NR} \]

(ii) \[ \rightarrow \]

(32) \[ \text{O} \quad \text{NHR} \]

(iii) \[ \rightarrow \]

(33) \[ \text{O} \quad \text{N} \quad \text{R} \]

(34) \[ \text{O} \quad \text{NHR} \]

(35) \[ \text{O} \quad \text{N} \quad \text{R} \]

(i) \(\text{RNH}_2\), diethyl ether
(ii) \(\text{hv}, \text{benzene}\)
(iii) \(\text{NaOH}, \text{EtOH}, \text{H}_2\text{O}, \text{heat}\)
    or \(\text{H}_2, 10\% \text{ Pd-C}\)
    or \(\text{NaBH}_4, \text{NaOH}, \text{H}_2\text{O}\)

\[ \text{R} \]

\(a; \text{Et}\)
\(b; \text{Pr}^n\)
\(c; \text{Pr}^i\)
\(d; \text{c}-\text{C}_6\text{H}_{11}\)
\(e; \text{CH}_2\text{Ph}\)
\(f; \text{CH(Me)}\text{Ph}\)
\(g; \text{CH(Ph)}_2\)

**Scheme 6**
rearrangement\textsuperscript{163} of \(N\)-(prop-2-yl)-2-nitrophenylmethanimine (31c) available as the unstable condensation product of 2-nitrobenzaldehyde (30) with 2-aminopropane. In the base-catalysed cyclisation of the nitrosobenzamide derivative (32c), the indazolone product (24) was formed in low yield and was accompanied by the corresponding azoxy-derivative (34c) whose analytical and spectroscopic properties were fully in accord with the assigned structure. The base-catalysed transformation of the nitrosobenzamide (32c) into the indazolone (24) involves reduction and is most readily explained in terms of the intermédiate formation and in situ reduction of the transient \(N\)-hydroxyindazolone (33c). However, attempts to halt the cyclisation at the \(N\)-hydroxyindazolone (33c) stage or to intercept this transient intermediate were unsuccessful. Thus, the attempted acid-catalysed cyclisation of the nitrosobenzamide (32c) to the \(N\)-hydroxyindazolone (33c) by heating with toluene-\(p\)-sulphonic acid in 1,2-dimethoxyethane gave only a quantitative recovery of the starting-material (32c). Alternatively, the attempted triethylamine-catalysed cyclisation of the nitrosobenzamide (32c) carried out in the presence of acetyl chloride in the hope of trapping the \(N\)-hydroxyindazolone (33c) as an \(N\)-acetoxy derivative, gave only triethylamine hydrochloride and an intractable gum. However, evidence for the intermediacy of the \(N\)-hydroxyindazolone (33c) was eventually obtained by heating the nitrosobenzamide (32c) with aqueous sodium carbonate. This reaction (Scheme 7) afforded a product in good yield (65\%) identical in every respect to the known\textsuperscript{164} propanone 2-carboxyphenylhydrazone (36). The formation of this product can be rationalised as
(i) Na$_2$CO$_3$, H$_2$O, heat

Scheme 7
shown in Scheme 7, thus supporting the intermediacy of the N-hydroxyindazolone (33c) in the base-catalysed conversion of the nitrosobenzamide (32c) into the indazolone derivative (24). Formation of the azoxy by-product (34c) in this reaction must also be the result of the ready reductive dimerisation of the nitrosobenzamide derivative (32c) in the ethanolic alkaline medium. Nitrosobenzene derivatives are well known to undergo reductive dimerisation to azoxybenzene products in alcoholic alkaline media. Such reactions (Scheme 8) involve partial reduction of the nitrosobenzene derivative (37) to the corresponding phenylhydroxylamine (38) followed by condensation of the latter with the former to afford the azoxybenzene product (40).

In accord with this supposition, treatment of the nitrosamide (32c) with sodium borohydride in aqueous sodium hydroxide
gave a good yield of the azoxybenzenedicarboxamide (34c) which was also formed in high yield when the nitroso-amide (32c) was hydrogenated over 10% palladium-on-charcoal.

It was found that N-alkyl-2-nitrophenylmethanimines (31) in general underwent photo-rearrangement (Scheme 6) in uniformly high yield (70-100%) to the corresponding N-alkyl-2-nitrosobenzamides (32), which in turn were in most cases converted by heating with ethanolic sodium hydroxide into readily separated mixtures of indazolones (35) and azoxybenzenedicarboxamides (34). The relative proportions (see Table 1) of these products was dependent on the bulk of the alkyl substituent, N-alkyl-2-nitrosobenzamides (32) with bulky alkyl substituents [e.g. (32g)] giving largely azoxybenzene

Table 1. The Conversion of N-Alkyl-2-nitrosobenzamides (32) by Ethanolic Sodium Hydroxide into Azoxybenzene-2,2'-dicarboxamides (34) and 2-Alkylindazol-3(1H)-ones (35)

<table>
<thead>
<tr>
<th>2-Nitrosobenzamide (32)</th>
<th>Azoxybenzenedicarboxamide (34); Yield (%)</th>
<th>Alkylindazolone (35); Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a; R=Et</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>b; R=Pr\textsuperscript{n}</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>c; R=Pr\textsuperscript{i}</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>d; R=\text{C}<em>6\text{H}</em>{11}</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>e; R=CH\textsubscript{2}Ph</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>f; R=CH(Me)Ph</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>g; R=CH(Ph)\textsubscript{2}</td>
<td>90</td>
<td>-</td>
</tr>
</tbody>
</table>
products [e.g. (34g)] with little or no indazolone formation, and the converse being true for N-alkyl-2-nitrosobenzamides with smaller alkyl groups [e.g. (32e)] which gave largely or exclusively the corresponding indazolone [e.g. (35e)].

Returning to the ethyl chloroformate-triethylamine catalysed cyclisation (Scheme 5) of the hydroxyaminobenzamide (18a) to the indazolone (24). This transformation involves the unusual monodealkylation of a tertiary amide and can be explained by the course shown in Scheme 5 whereby cyclisation promoted by the ethoxycarbonyloxy leaving group in the initially formed ethoxycarbonyloxyamino derivative (27) is followed by fragmentation of the resulting cyclic ammonium compound (28) to give the indazolone (24) and propene (29). In accord with this mechanism, it was found (Scheme 9) that N,N-dicyclohexyl-2-hydroxyaminobenzamide (18b), a compound obtained in the previous studies at Edinburgh161 by the ethanolic potassium hydroxide catalysed reaction (Scheme 4) of N,N-dicyclohexyl-2-nitrobenzylamine (12b), was converted by treatment with ethyl chloroformate in the presence of triethylamine in moderate yield to the N-ethoxycarbonyloxy-derivative (41). The analytical and spectroscopic properties of this compound were fully in accord with the assigned structure (41). In particular, its i.r. spectrum contained bands at 3320 and 1705 cm⁻¹ typical of an amide and, in addition, a carbonyl band at 1790 cm⁻¹ with the characteristically166 high frequency of a hydroxyamino ester substituent. The presence of the latter was also demonstrated by the product's ¹H n.m.r. spectrum which showed signals due to the protons of an ethyl group as well as signals attributable to
Scheme 9

(i) \( \text{ClCO}_2\text{Et, Et}_3\text{N} \)
(ii) DME, heat
the protons of two cyclohexyl substituents. Heating the hydroxyamino-ester (41) in 1,2-dimethoxyethane converted it in quantitative yield into 2-cyclohexyl-3(1H)-indazolone (35d) identical to an authentic sample prepared by the sodium hydroxide catalysed cyclisation (Scheme 6) of N-cyclohexyl-2-nitrosobenzamide (32d) (see before). Also formed was cyclohexene (43) whose presence in the reaction mixture was demonstrated by $^1$H n.m.r. spectroscopy.

In the previous studies at Edinburgh,\textsuperscript{161} it had been shown (Scheme 10) that lithium aluminium hydride reduction of N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) gave a product whose properties were consistent with its formulation as N,N-di-(prop-2-yl)-2-hydroxyaminobenzylamine (19). In view of the potential use of this compound in the ethyl chloroformate-triethylamine-type cyclisation already discussed and because of the unexpected stability of its hydroxyamino-substituent to reduction as revealed by the transformation [(18a)→(19)], an attempt was made to obtain more firm evidence for its structure (19). However the attempted alternative synthesis of this compound by lithium aluminium hydride reduction of the nitrobenzylamine derivative (12a) gave a new product whose analytical and spectroscopic properties are fully in accord with the hydrazine structure (45). Because of the close structural similarity of the hydroxyaminobenzylamine (19) to the hydroxyaminobenzamides (18a and b) an attempt was made to effect its ethyl chloroformate-triethylamine-promoted cyclisation to the indazoline derivative (46). However, in practice, reaction of the hydroxyaminobenzylamine (19) with ethyl chloroformate in the presence of triethylamine
(18a)

(i) \[ \text{LiAlH}_4 \]

(ii) \[ \text{ClCO}_2\text{Et}, \text{EtN}_3 \]

Scheme 10
gave triethylamine hydrochloride and an intractable multi-component oil from which no identifiable material could be obtained.

5.3 Investigations of the Scope and Mechanism of the Base-catalysed Transformations of N,N-Dialkyl-2-nitrobenzylamine Derivatives

As already briefly discussed (see page 199), the potassium hydroxide-catalysed conversion of N,N-dialkyl-2-nitrobenzylamines into 2-alkyl-2H-indazoles and/or N,N-dialkyl-2-hydroxyaminobenzamides can be explained in terms of the mechanism outlined in Schemes 2 and 3. In view of the very unusual nature of these reactions, it was of interest to seek evidence in support of the suggested mechanism (Schemes 2 and 3) and to further investigate the scope of such reactions.

Initially, it was decided to study the effect of changing the basic catalyst on the courses of the transformations of N,N-dialkyl-2-nitrobenzylamines into indazole derivatives on the one hand and N,N-dialkyl-2-hydroxyaminobenzamide products on the other. The compounds chosen for this study were the N,N-dibenzyl- and N,N-di-(prop-2-yl) derivatives [Scheme 2; (5e)] and [Scheme 3; (12a)] which had already been prepared during the course of the previous studies at Edinburgh. The particular amines (5e) and (12a) were chosen because the former is converted by treatment with ethanolic potassium hydroxide exclusively into 2-benzyl-2H-indazole [Scheme 2; (10e)] whereas the sole product of the reaction of the amine (12a) with ethanolic potassium hydroxide is the hydroxyaminobenzamide derivative [Scheme 3; (18a)].
It was hoped that treatment of the amines (5e) and (12a) with triethylamine in ethanol would divert the courses of the reactions to give products the nature of which would provide information on the reaction mechanism. In practice, the amines (5e) and (12a) were totally inert to heating with triethylamine in ethanol and were recovered unchanged in essentially quantitative yield.

It was next decided to investigate the sodium hydride-catalysed reactions of the amines (5e) and (12a). Here it was anticipated (Scheme 11) that sodium hydride as well as functioning as a basic catalyst for the earlier stages of reaction (see Schemes 2 and 3) might also trap the proposed nitroso-intermediates (8e) and (15a) as nitrosobenzylamine derivatives [i.e. (5e) or (12a) → (8e) or (15a) → (48a) or (48b)]. Treatment of the amine (5e) with sodium hydride in dimethylformamide at room temperature in fact gave 2-benzyl-2H-indazole (10e) in moderate yield, as the only isolated product. Similar treatment of N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) with sodium hydride in dimethylformamide gave largely starting-material (60%) together with the 2-hydroxyamino-benzamide (18a) (37%). An attempt was also made (Scheme 11) to trap the nitroso-intermediate (8e) with cyanide ion to give the nitrosobenzylamine product (49). However, heating the 2-nitrobenzylamine derivative (5e) with aqueous ethanolic potassium cyanide failed to achieve any reaction, the starting-material being recovered in high yield.

Since all of the heterocyclisations of N,N-dialkyl-2-nitrobenzylamines to the corresponding 2-alkyl-2H-indazole already discussed have involved symmetrically N,N-disubstituted
Scheme 11

(i) NaH, DMF
(ii) KCN, EtOH, H₂O, heat
substrates, it was thought that studying the ethanolic potassium hydroxide catalysed rearrangement of symmetrically substituted N,N-dialkyl-2-nitrobenzylamines might afford evidence that the mechanism outlined in Scheme 2 which rationalises this deep-seated transformation does indeed operate. Thus (Scheme 12) 2-nitrobenzyl bromide (20) was condensed with N-benzylmethylamine (51a) to give a light brown solid in moderate yield (60%) identified as the N,N-dialkyl-2-nitrobenzylamine (52a) on the basis of its analytical and spectroscopic properties. If the mechanism outlined in Scheme 2 does operate then it would be expected that the ethanolic potassium hydroxide catalysed transformation (Scheme 12) of the N,N-dialkyl-2-nitrobenzylamine (52a) would afford the indazole (10a) since formation of the nitroso-betaine (55a) should be favoured compared with formation of the corresponding nitroso-betaine (56a) because of the more acidic nature of the benzylic protons in the intermediate (53a) as opposed to the methyl protons of the intermediate (54a). However, treating N-benzyl-N-methyl-2-nitrobenzylamine (52a) with ethanolic potassium hydroxide did not afford any of the expected 2-methyl-2H-indazole (10a) but instead gave a high yield (95%) of a solid identical to a previously prepared sample of the alternative indazole product (10e). In view of this apparently contradictory result, it was decided to study the ethanolic potassium hydroxide-catalysed reaction (Scheme 12) of the nitrile-substituted N,N-dialkyl-2-nitrobenzylamine (52b) which was obtained in lowish yield (31%) by a method used in other studies at Edinburgh. As for the compound (52a) (see before) base-catalysed cyclisation
\[
\begin{align*}
\text{(20); Br} \\ 
\text{(50); Cl}
\end{align*}
\]
of the cyanomethyl derivative (52b) can be predicted on the basis of the mechanism outlined in Scheme 12 to afford 2-methyl-2H-indazole (10a) since the formation of the nitroso-betaine (55b) should be more favoured than that of the corresponding nitroso-betaine (56b) because of the greater acidity of the protons of the cyanomethyl group compared with those of the methyl group. In fact, the reaction of the N,N-dialkyl-2-nitrobenzylamine (52b) hydrochloride with ethanolic potassium hydroxide gave no characterisable material but only yielded multicomponent gums.

By analogy with the mechanism outlined in Scheme 2 which rationalises the ethanolic potassium hydroxide-catalysed transformation of the N,N-dialkyl-2-nitrobenzylamines (5) into the corresponding 2-alkyl-2H-indazoles (10), it might be expected (Scheme 13) that similar treatment of N,N-dimethyl-2-nitrobenzamide (59) would lead to the formation of the 1-hydroxyindazolone (65) via initial cyclisation to (60) followed by ring-opening and further rearrangement to give the nitroso-intermediate (64) then recyclisation. The 2-nitrobenzamide (59) was formed in moderate yield (58%) by the reaction of 2-nitrobenzoyl chloride (58) with dimethylamine. However, heating the 2-nitrobenzamide (59) with potassium hydroxide in ethanol gave a solid whose properties were consistent with the azobenzenedicarboxamide (63). Thus, the solid gave analytical data consistent with the molecular formula C_{18}H_{20}N_{4}O_{2} and showed an i.r. spectrum which contained amide carbonyl absorption at 1630 cm⁻¹. The room temperature ¹H n.m.r. spectrum of the product showed two non-equivalent methyl proton signals at 63.15 and 62.73 but these signals
(58)  \[ \text{Me}_2\text{NH} \]

(ii) KOH, EtOH

Scheme 13
were found to coalesce to a single peak at δ2.99 when heated to 90°. Formation of the azo-compound (63) can be rationalised by the intermediacy of the azoxy-dicarboxamide (61), the latter being formed by initial reduction of the 2-nitrobenzamide (59) to the corresponding 2-nitrosobenzamide and 2-hydroxyaminobenzamide followed by their self-condensation as discussed before. The failure to obtain any isolable amounts of the expected 1-hydroxyindazolone product (65) may in part be due to the relatively non-acidic character of the methyl protons of the cyclic intermediate (60) thus terminating any further reactions via this pathway.

As stated earlier in this section, it was of interest to further investigate the synthetic scope of the base-catalysed transformations of N,N-disubstituted-2-nitrobenzylamines into the corresponding 2-substituted-2H-indazoles. Since all of the N,N-dialkyl-2-nitrobenzylamine cyclisations studies during the present work and the previous studies had resulted in the formation of 2-alkyl-2H-indazoles it was of interest to see if such cyclisations could be extended to the synthesis of the less accessible 2-aryl-2H-indazoles. To this end (Scheme 14) it was decided to investigate the synthesis and base-catalysed cyclisation of N-methyl-N-phenyl-2-nitrobenzylamine (67) which by analogy with similar heterocyclisations described before should afford 2-phenyl-2H-indazole (68). N-Methyl-N-phenyl-2-nitrobenzylamine (67) was readily prepared in a straightforward manner in high yield (91%) by the reaction of 2-nitrobenzyl bromide (20) with N-methylaniline (66). Treatment of the 2-nitrobenzylamine derivative (67) gave a product mixture which was separated by preparative t.l.c. into
Scheme 14

(i) KOH, EtOH
a good yield (75%) of a colourless solid whose properties were entirely consistent with its identity as the known \textsuperscript{2} \text{2-phenyl-2H-indazole} (68). A second alkali-soluble product was also isolated from the base-catalysed cyclisation of the \textsuperscript{2} \text{2-nitrobenzylamine} derivative (67). This product was identified on the basis of its high resolution mass spectrum as the \textsuperscript{2} \text{2-hydroxyaminobenzamide} derivative (69). This structure was also supported by the compound's i.r. spectrum which showed NH and OH absorption at 3320 and 3120 cm\textsuperscript{-1}, as well as amide carbonyl absorption at 1670 cm\textsuperscript{-1}.

5.4 Experimental

General experimental details are described in the Appendix.

\textbf{N-Methyl-N-phenyl-2-nitrobenzylamine} (67)

A solution of 2-nitrobenzyl bromide (20) \textsuperscript{1} (1.1 g, 0.005 mol) in anhydrous dimethylformamide (10.0 ml) was treated with redistilled \textbf{N-methylaminating} (66) \textsuperscript{1} (1.1 g, 0.01 mol) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the residue was treated with 2M aqueous hydrochloric acid (17.5 ml) and extracted with methylene chloride to afford a brown solid (1.3 g) which was crystallised to yield \textbf{N-methyl-N-phenyl-2-nitrobenzylamine} (67) \textsuperscript{1} (1.1 g; 91\%), m.p. 62-64° (from toluene-light petroleum) \textsuperscript{1} (lit., \textsuperscript{1} \text{72°}), \nu_{\text{max}} 1505 and 1340 (NO\textsubscript{2}) cm\textsuperscript{-1}, \delta(CDCl\textsubscript{3}) 8.04 (1H, dd, J\textsubscript{ortho} 8Hz, \textsuperscript{1})
J_{meta}^{2\text{Hz}}, \text{ArH}), 7.52-6.58 (8\text{H}, \text{m, ArH}), 4.88 (2\text{H}, \text{s, CH}_2),
and 3.04 (3\text{H}, \text{s, CH}_3).

**Found:** \text{M}^+, 242.

**Calc. for C_{14}H_{14}N_2O_2:** \text{M}, 242.

The aqueous mother liquor was neutralised with solid sodium bicarbonate and extracted with methylene chloride to yield unreacted N-methylaniline (66) (0.33 g; 65%) identical (i.r. spectrum) to an authentic sample.

### The Reaction of N-Methyl-N-phenyl-2-nitrobenzylamine (67) with Ethanolic Potassium Hydroxide

A solution of N-methyl-N-phenyl-2-nitrobenzylamine (67) (0.48 g, 0.002 mol) in ethanol (10.0 ml) was treated with solid potassium hydroxide (0.5 g) and the mixture was heated under reflux for 5.5 h. The mixture was concentrated to half the original volume, diluted with water (10.0 ml), and extracted with methylene chloride to give a red oil (0.33 g) which was subjected to preparative t.l.c. in toluene-light petroleum/b.p. 40-60° (1:2) over alumina to give 2-phenyl-2H-indazole (68) (0.29 g; 75%) which formed colourless plates, m.p. 63-65° (from light petroleum/b.p. 80-100°) (lit., 168 83-84°), \(\nu_{\text{max}}\) 1610 (C=N) cm\(^{-1}\).

**Found:** \text{M}^+, 194.08567.

**Calc. for C_{13}H_{10}N_2:** \text{M}, 194 08439.

The aqueous mother liquor was neutralised with concentrated hydrochloric acid and solid sodium acetate and extracted with methylene chloride to yield N-methyl-N-phenyl-2-hydroxy-aminobenzamide (69) (0.08 g; 17%) which formed light brown
needles, m.p. 152-153° (from ethanol-water), \( \nu_{\text{max}} \) 3320 (NH), 3120 br (N-OH), and 1670 (CO) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 9.28 (1H, s, NH or OH), 7.90-6.65 (9H, m, ArH), and 3.15 (3H, s, CH\(_3\)).

**Found:** M\(^+\), 242.10365.

\[
\text{C}_{14}\text{H}_{14}\text{N}_{2}\text{O}_{2} \text{ requires: M, 242.10552.}
\]

**N-Benzyl-N-methyl-2-nitrobenzylamine (52a)**

A solution of 2-nitrobenzyl bromide (20) (4.4 g, 0.02 mol) in anhydrous dimethylformamide (20.0 ml) was treated with a solution of N-benzylmethylamine (51a) (4.8 g, 0.04 mol) in anhydrous dimethylformamide (20.0 ml) and the mixture was left stoppered at room temperature for 24 h. The mixture was evaporated and the residue was treated with 2M aqueous hydrochloric acid and extracted with methylene chloride to yield a brown froth (4.7 g) which was redissolved in methylene chloride and the solution was washed with 2M aqueous sodium hydroxide and evaporated to yield N-benzyl-N-methyl-2-nitrobenzylamine (52a) (3.1 g; 60%) which formed light brown plates, m.p. 45-46° (from toluene-light petroleum), \( \nu_{\text{max}} \) 1530 and 1360 (NO\(_2\)) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 7.82-7.22 (9H, m, ArH), 3.82 (2H, s, CH\(_2\)), 3.50 (2H, s, CH\(_2\)), and 2.08 (3H, s, CH\(_3\)).

**Found:** C, 70.3; H, 6.1; N, 10.8%; M\(^+\), 256.

\[
\text{C}_{15}\text{H}_{16}\text{N}_{2}\text{O}_{2} \text{ requires: C, 70.3; H, 6.3; N, 10.9%; M, 256.}
\]

Neutralisation of the aqueous mother liquor with solid sodium bicarbonate and extraction with methylene chloride afforded a brown oil (1.5 g) which was shown by t.l.c. in toluene over silica to be a multicomponent mixture and was not further investigated.
The Reaction of \textit{N}-Benzyl-\textit{N}-methyl-2-nitrobenzylamine (52a) with Ethano
cic Potassium Hydroxide

A solution of \textit{N}-benzyl-\textit{N}-methyl-2-nitrobenzylamine (52a) (1.0 g, 0.004 mol) in ethanol (20.0 ml) was treated with solid potassium hydroxide (1.0 g) and the mixture was heated under reflux for 3 h. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to yield a brown oil (0.9 g) which was purified by preparative t.l.c. in methylene chloride over silica to give 2-benzyl-2H-indazole (10e) (0.79 g; 95\%), m.p. 62-63°, identical (m.p. and i.r. spectrum) to a sample obtained later.

The aqueous mother liquor was cooled (ice-bath), acidified with concentrated hydrochloric acid, and extracted with methylene chloride to give a red oil (0.12 g) which was shown by t.l.c. in methylene chloride over silica to be a multicomponent mixture and was not further investigated.

\textbf{N-Methyl-\textit{N}- (2-nitrobenzyl)aminoacetonitrile (52b) Hydrochloride}

\textit{N}-Methyl-\textit{N}- (2-nitrobenzyl)aminoacetonitrile (52b) hydrochloride was prepared (yield 31\%) by the reaction of 2-nitrobenzyl chloride (50) with \textit{N}-methylaminoacetonitrile (51b) hydrochloride as described in the literature,\textsuperscript{167} m.p. 144-147° (lit.,\textsuperscript{167} 148°), and was used without further purification.

The Attempted Reaction of \textit{N}-Methyl-\textit{N}- (2-nitrobenzyl)amino
cetonitrile (52b) Hydrochloride with Ethano
cic Potassium Hydroxide.

A solution of \textit{N}-methyl-\textit{N}- (2-nitrobenzyl)aminoacetonitrile (52b) hydrochloride (0.48 g, 0.002 mol) in ethanol (20.0 ml)
was treated with solid potassium hydroxide (0.67 g, 0.012 mol) and the mixture was heated under reflux for 6 h. The mixture was then concentrated to one half of the original volume, diluted with water (20.0 ml) and extracted with methylene chloride to afford a brown gum (0.25 g) which was shown by t.l.c. in diethyl ether over silica to be a multi-component mixture and was not further investigated.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, and extracted with methylene chloride to yield a brown gum (0.07 g) which was shown by t.l.c. in diethyl ether over silica to be a multi-component mixture and was not further investigated.

N,N-Dibenzyl-2-nitrobenzylamine (5e)

A solution of 2-nitrobenzyl bromide (20) (11.0 g, 0.05 mol) in anhydrous dimethylformamide (50.0 ml) was treated with a solution of dibenzylamine (19.7 g, 0.1 mol) in anhydrous dimethylformamide (50.0 ml) and the mixture was left stoppered at room temperature for 17 h. The mixture was evaporated and the residue was treated with methylene chloride and the resulting suspension was filtered to give dibenzylamine hydrobromide (12.9 g; 98%), m.p. 264-265° (lit., 265°).

The methylene chloride filtrate was evaporated and the residue was treated with 2M aqueous hydrochloric acid and extracted with diethyl ether to remove a dark brown oil (3.3 g). The aqueous acidic mother liquor was made alkaline with 2M aqueous sodium hydroxide and extracted with methylene chloride to give the crude product as an orange oil (13.5 g). This was re-dissolved in anhydrous diethyl ether (100 ml) and
the solution treated with hydrogen chloride to give the hydrochloride which was collected and treated with 2M aqueous sodium hydroxide and the mixture extracted with methylene chloride to give \( \text{N,N-dibenzyl-2-nitrobenzylamine (5e)} \) as an oil (11.1 g; 67\%\), \( \nu_{\text{max}} \) 1530 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 8.34–7.34 (14H, m, ArH), 4.07 (2H, s, CH\(_2\)), and 3.33 (4H, s, CH\(_2\)), identical (i.r. and \(^1\text{H} \text{n.m.r. spectrum}) to an authentic sample. \(^{161}\)

The Attempted Reaction of \( \text{N,N-Dibenzyl-2-nitrobenzylamine (5e)} \) with Ethanollic Triethylamine

A solution of \( \text{N,N-dibenzyl-2-nitrobenzylamine (5e)} \) (1.7 g, 0.005 mol) in absolute ethanol (20.0 ml) was treated with triethylamine (2.0 g, 0.02 mol) and the mixture was heated under reflux for 6 h. The mixture was evaporated to yield unreacted \( \text{N,N-dibenzyl-2-nitrobenzylamine (5e)} \) as an orange oil (1.7 g; 100\%) which was identical (i.r. spectrum) to an authentic sample.

2-Benzyl-2H-indazole (10e)

A solution of \( \text{N,N-dibenzyl-2-nitrobenzylamine (5e)} \) (1.3 g, 0.004 mol) in anhydrous dimethylformamide (5.0 ml) was added dropwise over 20 min at room temperature under nitrogen, to a vigorously stirred suspension of sodium hydride (0.38 g, 0.016 mol) in anhydrous dimethylformamide (5.0 ml). Stirring was continued at room temperature for 1 h then the mixture was diluted with water, extracted with methylene chloride and the extract washed with saturated aqueous sodium hydrogen-sulphite solution and evaporated to afford a brown oil (0.93 g).
This was separated by preparative t.l.c. in methylene chloride over silica into an unidentified yellow gum (0.17 g) and 2-benzyl-2H-indazole (10e) (0.26 g; 31%) which formed colourless needles, m.p. 68-69° (from light petroleum/b.p. 80-100°), $\nu_{\text{max}}$ 1630 (C=N) cm$^{-1}$, $\delta$(CDCl$_3$) 7.83-6.97 (10H, m, ArH) and 5.56 (2H, s, CH$_2$).

**Found:** C, 81.1; H, 5.8; N, 13.3%; M$^+$, 208.
**Calc. for C$_{14}$H$_{12}$N$_2$:** C, 80.8; H, 5.8; N, 13.5%; M, 208.

Acidification of the saturated aqueous sodium hydrogen-sulphite washings with 2M aqueous sulphuric acid followed by extraction with methylene chloride afforded only a negligible amount of oil.

Acidification of the original aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride yielded benzoic acid (0.1 g; 20%), m.p. 113-114° (lit., 114 122°) identical (m.p. and i.r. spectrum) to an authentic sample.

**The Attempted Reaction of N,N-Dibenzyl-2-nitrobenzylamine (5e) with Ethanolic Potassium Cyanide**

A solution of N,N-dibenzyl-2-nitrobenzylamine (5e) (1.3 g, 0.004 mol) in ethanol (20.0 ml) was treated with solid potassium cyanide (1.3 g, 0.02 mol) and the mixture was heated under reflux for 4 h, by which time t.l.c. of the mixture in light petroleum-toluene (40:60) over silica showed that no reaction had taken place. One drop of water was then added and the mixture was heated under reflux for a further 20 h. The
mixture was concentrated to one half of the original volume, diluted with water (20.0 ml), and extracted with methylene chloride to afford unreacted N,N-dibenzyl-2-nitrobenzylamine (5e) (1.2 g; 88%) identical (i.r. spectrum) to an authentic sample.

Acidification of the aqueous mother liquor with 2M aqueous hydrochloric acid and extraction with methylene chloride gave only a negligible amount of brown gum.

N,N-Di-(prop-2-yl)-2-nitrobenzylamine (12a)

A solution of 2-nitrobenzyl bromide (20) (11.0 g, 0.05 mol) in anhydrous dimethylformamide (50.0 ml) was treated with di-(prop-2-yl)amine (21a) (10.1 g, 0.1 mol) and the mixture was left at room temperature for 24 h. The mixture was evaporated and the residue was treated with 2M aqueous hydrochloric acid (150 ml) and extracted with methylene chloride to give a brown oil (5.4 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multicomponent mixture and was not further investigated.

The aqueous phase was neutralised with solid sodium hydrogen carbonate and extracted with methylene chloride to afford a brown oil (7.0 g) which was purified by distillation to give N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) as an orange oil (5.4 g; 30%), b.p. 140°/2mmHg, \( \nu_{\text{max}} \) 1530 and 1350 (NO₂) cm⁻¹, identical (i.r. spectrum) to an authentic sample.

N,N-Di-(prop-2-yl)-2-hydroxyaminobenzamide (18a)

A solution of N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) (2.4 g, 0.01 mol) in ethanol (25.0 ml) was treated with solid
potassium hydroxide (2.5 g) and the mixture was heated under reflux for 6 h. The mixture was concentrated to half the original volume then diluted with water (50.0 ml) and extracted with methylene chloride to give unreacted \( \text{N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a)} \) as an orange oil (0.06 g; 12\%) identical (i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was neutralised with concentrated hydrochloric acid and anhydrous sodium acetate and extracted with methylene chloride to afford \( \text{N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a)} \) (1.6 g; 65\%) which formed colourless plates, m.p. 133-134° (from ethanol) (lit., \( 161, 136° \)), \( \nu_{\text{max}} \) 3320 (NH), 3120 br (N-OH), and 1660 (CO) \( \text{cm}^{-1} \), \( \delta[(\text{CD}_3)_2\text{SO}] \) 8.48 (1H, s, NH), 7.72 (1H, dd, \( J_{\text{ortho}} \) 8Hz, \( J_{\text{meta}} \) 2Hz, ArH), 7.40-7.18 (2H, m, ArH), 6.58-6.42 (1H, m, ArH), 3.16 (2H, m, 2xCH), 1.02 (3H, s, CH\(_3\)), 0.99 (3H, s, CH\(_3\)), 0.96 (3H, s, CH\(_3\)), and 0.93 (3H, s, CH\(_3\)).

Found: M\(^+\), 236.15253.
Calc. for C\(_{13}\)H\(_{20}\)N\(_2\)O\(_2\): M, 236.15247.

The Attempted Oxidation of \( \text{N,N-Di-(prop-2-yl)-2-hydroxyaminobenzamide (18a)} \) with Chromium Trioxide

A solution of \( \text{N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a)} \) (0.24 g, 0.001 mol) in 70\% v/v aqueous acetic acid (10.0 ml) was heated at 100° (steam-bath) and treated, in small portions, with chromium trioxide (0.5 g). Heating was continued for a further 0.5 h after addition was complete and the mixture was then treated with water (5.0 ml) and extracted with ethyl acetate to afford only a small amount (0.03 g) of a light green gum.
Evaporation of the aqueous mother liquor and hot-leaching of the residue with ethyl acetate gave only a small amount (0.03 g) of a brown gum.

The Attempted Oxidation of $N,N$-Di-$(\text{prop-2-yl})$-2-hydroxyaminobenzamide (18a) with Manganese Dioxide

A solution of $N,N$-di-$(\text{prop-2-yl})$-2-hydroxyaminobenzamide (18a) (0.24 g, 0.001 mol) in anhydrous toluene (20.0 ml) was treated with activated manganese dioxide (1.7 g) and the mixture was stirred at room temperature for 17 h. The mixture was filtered through celite and the filtrate was evaporated to give unreacted $N,N$-di-$(\text{prop-2-yl})$-2-hydroxyaminobenzamide (18a) (0.02 g; 8%), m.p. 125-127°, which was identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of $N,N$-Di-$(\text{prop-2-yl})$-2-hydroxyaminobenzamide (18a) with Aqueous Hydrogen Peroxide

A solution of $N,N$-di-$(\text{prop-2-yl})$-2-hydroxyaminobenzamide (18a) (0.48 g, 0.002 mol) in glacial acetic acid (10.0 ml) was treated with 30% w/v (100 volume) aqueous hydrogen peroxide (5.0 ml) and the mixture was stirred and heated at 50° (oil bath) for 24 h. The mixture was diluted with water (20.0 ml), neutralised with anhydrous sodium acetate, extracted with methylene chloride, and the extract washed with saturated aqueous sodium hydrogen carbonate and evaporated to afford only a small amount (0.04 g) of brown oil.

Acidification of the saturated aqueous sodium hydrogen carbonate washings with 2M aqueous hydrochloric acid and
extraction with methylene chloride yielded benzoic acid (0.11 g; 45%), m.p. 117-120° (lit., 114-122°), identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) with Phenyl Isocyanate

A solution of N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) (0.47 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was stirred at room temperature and treated with a solution of phenyl isocyanate (0.24 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). Stirring was continued at room temperature for 1 h, then the mixture was evaporated to afford a yellow gum (0.74 g) which, when treated with anhydrous diethyl ether, gave N,N'-diphenylurea (0.22 g; 52%), m.p. 235-238° (lit., 171-239-240°), identical (m.p. and i.r. spectrum) to an authentic sample.

The ethereal mother liquor was evaporated to yield a yellow gum (0.41 g) which was subjected to Kugelrohr distillation to give unreacted N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) (0.3 g; 64%), m.p. 125-128°, identical (m.p. and i.r. spectrum) to an authentic sample.

The distillation residue was a dark brown glass (0.11 g) from which no identifiable material could be obtained.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) with Acetic Anhydride

A suspension of N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) (0.24 g, 0.001 mol) in acetic anhydride (1.5 ml) was heated under reflux for 3 h, by which time the suspended
solid had dissolved.

The mixture was cooled, treated with water (10.0 ml) and extracted with methylene chloride to give a brown oil (0.23 g) which was shown by t.l.c. in methylene chloride-diethyl ether (50:50) over silica to be an unresolvable multi-component mixture and was not further investigated.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-hydroxyamino-benzamide (18a) with Benzoyl Chloride in the Presence of Triethylamine

A solution of N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) (0.48 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred at room temperature and treated in one portion with triethylamine (0.25 g, 0.0025 mol) followed drop-wise by a solution of benzoyl chloride (0.31 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 1 h, then filtered to yield triethylamine hydrochloride (0.24 g; 87%), m.p. 250-252° (lit., 253-254°), identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give a dark brown oil (0.77 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multi-component mixture and was not further investigated.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-hydroxyamino-benzamide (18a) with Tosyl Chloride in the Presence of
Triethylamine

A solution of \( N,N\text{-di-(prop-2-yl)}-2\text{-hydroxyaminobenzamide} \) (18a) (0.48 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred at room temperature and treated in one portion with triethylamine (0.51 g, 0.005 mol) followed by a solution of tosyl chloride (0.42 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). Stirring was continued at room temperature for 1 h, and the mixture was then filtered to remove triethylamine hydrochloride (0.06 g; 22%), m.p. 253-254° (lit., \(^{159}\) 253-254°), identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the filtrate, treatment of the residue with water (5.0 ml) and extraction with methylene chloride afforded a brown oil (0.93 g) which was shown by t.l.c. in ethyl acetate over alumina to be an unresolved mixture and was not further investigated.

2-(Prop-2-yl)indazol-3(1H)-one (24)

A solution of \( N,N\text{-di-(prop-2-yl)}-2\text{-hydroxyaminobenzamide} \) (18a) (0.48 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred at room temperature and treated in one portion with triethylamine (0.51 g, 0.005 mol) followed drop-wise with a solution of ethyl chloroformate (0.24 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 1 h, then filtered to remove triethylamine hydrochloride (0.27 g; 98%), m.p. 250-252° (lit., \(^{159}\) 253-254°), identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated and the residue was treated
with water (5.0 ml) and extracted with methylene chloride to give a brown oil (0.44 g) which was triturated with light petroleum to afford 2-(prop-2-yl)indazol-3(1H)-one (24) (0.18 g; 51%) which formed light brown plates, m.p. 149-150° (from toluene-light petroleum), $\nu_{\text{max}}$ 2600 br (NH) and 1620 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 8.00 (1H, s, NH), 7.80-7.04 (4H, m, ArH), 7.79 (1H, m, CH), 1.37 (3H, s, CH$_3$), and 1.30 (3H, s, CH$_3$).

Found: C, 68.5; H, 6.8; N, 16.2%; M$^+$, 176.

C$_{10}$H$_{12}$N$_2$O requires: C, 68.2; H, 6.9; N, 15.9%; M, 176.

Evaporation of the toluene-light petroleum mother liquor gave a brown oil (0.23 g) which was shown by t.l.c. in methylene chloride over silica to be a multicomponent mixture and was not further investigated.

N,N-Dicyclohexyl-2-nitrobenzylamine (12b)

A solution of 2-nitrobenzyl bromide (20) (4.4 g, 0.02 mol) in anhydrous dimethylformamide (20.0 ml) was treated with a solution of dicyclohexylamine (21b) (7.2 g, 0.04 mol) in anhydrous dimethylformamide (20.0 ml) and the mixture was left stoppered at room temperature for 24 h. The mixture was evaporated and the residue was treated with 2M aqueous hydrochloric acid (50.0 ml) followed by methylene chloride (50.0 ml) to give a three phase system which was filtered to afford N,N-dicyclohexylamine hydrochloride (5.5 g) identical (m.p. and i.r. spectrum) to a sample obtained later.

The filtrate was separated, the aqueous phase was further washed with methylene chloride, and the combined methylene chloride extracts were evaporated to yield a froth (7.3 g),
which was redissolved in methylene chloride (75.0 ml). The methylene chloride solution was washed with 2M aqueous sodium hydroxide (2x50 ml) and evaporated to afford N,N-dicyclohexyl-2-nitrobenzylamine (12b) (4.9 g; 78%), m.p. 74-76° (lit., 161 85°), ν\textsubscript{max} 1530 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}, identical (i.r. spectrum) to an authentic sample and was used without further purification.

Neutralisation of the aqueous hydrochloric acid mother liquor with solid sodium hydrogen carbonate and extraction with methylene chloride afforded only a negligible amount of brown gum.

N,N-Dicyclohexyl-2-hydroxyaminobenzamide (18b)

N,N-Dicyclohexyl-2-hydroxyaminobenzamide (18b) was prepared (yield 22%) by the reaction of N,N-dicyclohexyl-2-nitrobenzylamine (12b) with ethanolic potassium hydroxide as described by Aldersley and Tennant, 161 m.p. 205-206° (lit., 161 206-208°), and was used without further purification.

N,N-Dicyclohexyl-2-(ethoxycarbonyloxyamino)benzamide (41)

A solution of N,N-dicyclohexyl-2-hydroxyaminobenzamide (18b) (0.63 g, 0.002 mol) was stirred at room temperature and treated in one portion with triethylamine (0.51 g, 0.005 mol) followed dropwise with a solution of ethyl chloroformate (0.24 g, 0.0022 mol) in dry 1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 1 h, then filtered to remove N,N-dicyclohexylamine hydrochloride (0.25 g; 57%) which formed colourless needles, m.p. 322-324° (from dimethylformamide-water) (lit., 172 350°), ν\textsubscript{max} 2710, 2510, 2500, and
The filtrate was evaporated and the residue was treated with water (5.0 ml) and the solid was collected to afford N,N-dicyclohexyl-2-(ethoxycarbonyloxyamino)benzamide (41) (0.35 g; 45%) which formed pale yellow plates, m.p. 118-119° (from light petroleum), $v_{\text{max}}$ 3320 (NH), and 1790 and 1705 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 8.25 (1H, s, NH), 7.79-7.24 (3H, m, ArH), 6.60-6.42 (1H, m, ArH), 4.18 (2H, q, J7Hz, CH$_2$), 2.84 (2H, m, CH), 1.96-1.04 (20H, m, CH$_2$), and 1.40 (3H, t. J7Hz, CH$_3$).

Found: M$^+$, 388.23561.

C$_{22}$H$_{32}$N$_2$O$_4$ requires: M, 388.23619.

Extraction of the aqueous mother liquor with methylene chloride gave only a negligible amount of gum.

2-Cyclohexylindazol-3(1H)-one (35d)

A solution of N,N-dicyclohexyl-2-(ethoxycarbonyloxyamino)benzamide (41) (0.23 g, 0.0006 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was heated under reflux for 5.5 h. The solvent was distilled off under reduced pressure with collection of the distillate in a liquid nitrogen cooled trap, to leave 2-cyclohexylindazol-3(1H)-one (35d) (0.13 g; 100%) which formed colourless needles, m.p. 154-155° (from toluene), $v_{\text{max}}$ 2680 br (NH) and 1620 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 7.84-7.06 (4H, m, ArH), 4.36 (1H, m, CH), and 1.98-0.99 (10H, m, CH$_2$).

Found: M$^+$, 216.12618.

C$_{13}$H$_{16}$N$_2$O requires: M, 216.12626.
H N.m.r. analysis of the 1,2-dimethoxyethane distillate showed the presence of cyclohexene.

N-Alkyl-2-nitrophenylmethanimines (31a-g)

A solution of 2-nitrobenzaldehyde (30) (1.5 g, 0.01 mol) in anhydrous diethyl ether (10.0 ml) was mixed with a solution of the corresponding primary amine (0.01 mol) in anhydrous diethyl ether (5.0 ml) and the mixture was left stoppered at room temperature for 24 h. The mixture was then evaporated under reduced pressure at room temperature to give the respective N-alkyl-2-nitrophenylmethanimines which with the exception of the compound (31g) were heat and moisture sensitive oils and were used without further purification.

(i) Ethylamine afforded N-ethyl-2-nitrophenylmethanimine (31a) (98%), $\nu_{\text{max}}$ 1640 (C=N), and 1525 and 1345 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 8.66 (1H, s, CH), 8.08-7.41 (4H, m, ArH), 3.69 (2H, q, J8Hz, CH$_2$), and 1.30 (3H, t, J8Hz, CH$_3$).

(ii) 1-Aminopropane afforded N-(prop-1-yl)-2-nitrophenylmethanimine (31b) (100%), $\nu_{\text{max}}$ 1640 (C=N), and 1525 and 1350 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 8.67 (1H, s, CH), 8.10-7.22 (4H, m, ArH), 3.65 (2H, t, J6Hz, CH$_2$), 1.95-1.60 (2H, m, CH$_2$), and 0.98 (3H, t, J6Hz, CH$_3$).

(iii) 2-Aminopropane afforded N-(prop-2-yl)-2-nitrophenylmethanimine (31c) (86%), $\nu_{\text{max}}$ 1640 (C=N), and 1525 and 1345 (NO$_2$) cm$^{-1}$, $\delta$(CDCl$_3$) 8.68 (1H, s, CH), 8.06-7.42 (4H, m, ArH), 3.64 (1H, m, CH), and 1.26 (6H, d, J8Hz, 2xCH$_3$).

(iv) Cyclohexylamine afforded N-cyclohexyl-2-nitrophenylmethanimine (31d) (100%), $\nu_{\text{max}}$ 1640 (C=N), and 1530 and 1350
(NO₂) cm⁻¹, δ(CDCl₃) 8.68 (1H, s, CH), 8.08-7.40 (4H, m, ArH), 3.32 (1H, m, CH), and 2.06-1.19 (10H, m, CH₂).

(v) Benzylamine afforded N-benzyl-2-nitrophenylmethanimine (31e) (100%), νₘₐₓ 1640 (C=N), and 1520 and 1350 (NO₂) cm⁻¹, δ(CDCl₃) 8.76 (1H, s, CH), 8.10-7.19 (9H, m, ArH), and 4.82 (2H, s, CH₂).

(vi) 1-Phenylethylamine afforded N-(1-phenylethyl)-2-nitrophenylmethanimine (31f) (75%), νₘₐₓ 1640 (C=N), and 1525 and 1350 (NO₂) cm⁻¹, δ(CDCl₃) 8.78 (1H, s, CH), 8.14-7.22 (9H, m, ArH), 4.65 (1H, q, J₆Hz, CH), and 1.61 (3H, d, J₆Hz, CH₃).

(vii) Benzylhydrylamine afforded N-diphenylmethyl-2-nitrophenylmethanimine (31g) (100%) which formed colourless plates, m.p. 45-46° (from toluene), νₘₐₓ 1640 (C=N), and 1520 and 1350 (NO₂) cm⁻¹, δ(CDCl₃) 8.84 (1H, s, CH), 8.23-7.24 (14H, m, ArH), and 5.69 (1H, s, CH).

Found: C, 76.2; H, 5.0; N, 8.6%; M⁺, 316.

C₂₀H₁₆N₂O₂ requires: C, 75.9; H, 5.1; N, 8.9%; M, 316.

N-Alkyl-2-nitrosobenzamides (32a-g)

An oxygen free solution of the corresponding N-alkyl-2-nitrophenylmethanimines (31a-g) (0.01 mol) in anhydrous benzene (200 ml) was irradiated under nitrogen at 254 nm for 24 h using a Hanovia medium pressure photochemical reactor. The mixture was evaporated to give the corresponding crude N-alkyl-2-nitrosobenzamides which were purified as indicated for the individual compounds below.

(i) N-Ethyl-2-nitrophenylmethanimine (31a) gave a gum
which was triturated with diethyl ether-methanol to yield
N-ethyl-2-nitrosobenzamide (32a) (72%) which formed light
brown plates, m.p. 132-133° (from toluene), $\nu_{\text{max}}$ 3380 (NH)
and 1650 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.70 (1H, br, NH), 8.10-7.14
(3H, m, ArH), 6.62 (1H, d, $J_{\text{ortho}}$ 8Hz, ArH), 3.36 (2H, m, CH$_2$),
and (3H, t, J8Hz, CH$_3$).

Found: M$^+$, 178.07428.

C$_9$H$_{10}$N$_2$O$_2$ requires: M, 178.07425.

Evaporation of the diethyl ether-methanol mother liquor
afforded a brown gum (0.5 g) which was shown by t.l.c. in
methylene chloride over alumina to be a multicomponent mixture
and was not further investigated.

(ii) N-(Prop-1-yl)-2-nitrophenylmethanimine (31b) gave
N-(prop-1-yl)-2-nitrosobenzamide (32b) (72%) which formed
light brown plates, m.p. 135-136° (from toluene), $\nu_{\text{max}}$ 3260
(NH) and 1650 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 8.44 (1H, dd, $J_{\text{ortho}}$ 8Hz,
$J_{\text{meta}}$ 2H, ArH), 7.90-7.17 (2H, m, ArH), 6.10 (1H, dd, $J_{\text{ortho}}$ 8Hz,
$J_{\text{meta}}$ 2Hz, ArH), 3.58 (2H, m, CH$_2$), 1.66 (2H, m, CH$_2$), and
0.96 (3H, t, J6Hz, CH$_3$).

Found: M$^+$, 192.09023.

C$_{10}$H$_{12}$N$_2$O$_2$ requires: M, 192.08982.

Evaporation of the diethyl ether-methanol mother liquor
afforded a brown gum (0.5 g) which was shown by t.l.c. in
methylene chloride over alumina to be a multicomponent mixture
and was not further investigated.

(iii) N-(Prop-2-yl)-2-nitrophenylmethanimine (31c) gave
N-(prop-2-yl)-2-nitrosobenzamide (32c) (100%) which formed
light brown microcrystals, m.p. 135-137° (from toluene),
\( \nu_{\text{max}} \) 3230 (NH) and 1635 (CO) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 8.44 (1H, dd, J\text{ortho} 8Hz, J\text{meta} 2Hz, ArH), 7.90-7.19 (2H, m, ArH), 6.25 (1H, d, J8Hz, ArH), 4.48 (1H, m, CH), and 1.28 (6H, d, J6Hz, 2\times \text{CH}_3).

Found: M\(^+\), 192.08993.

C\(_{10}\)H\(_{12}\)N\(_2\)O\(_2\) requires: M, 192.08987.

(iv) N-Cyclohexyl-2-nitrophenylmethanimine (31d) gave N-cyclohexyl-2-nitrosobenzamide (32d) (100%) which formed light brown plates, m.p. 94-95 ° (from toluene), \( \nu_{\text{max}} \) 3240 (NH) and 1630 (CO) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 8.24 (1H, dd, J\text{ortho} 8Hz, J\text{meta} 2Hz, ArH), 8.10 (1H, m, NH), 7.90-7.18 (2H, m, ArH), 6.12 (1H, dd, J\text{ortho} 8Hz, J\text{meta} 2Hz, ArH), 4.18 (1H, m, CH), and 2.18-1.02 (10H, m, CH\(_2\)).

Found: C, 67.1; H, 6.6; N, 11.8%; M\(^+\), 232.

C\(_{13}\)H\(_{16}\)N\(_2\)O\(_2\) requires: C, 67.2; H, 6.9; N, 12.1%; M, 232.

(v) N-Benzyl-2-nitrophenylmethanimine (31e) gave a brown gum which was separated by preparative t.l.c. in methylene chloride over alumina to give unreacted N-benzyl-2-nitrophenylmethanimine (31e) (20%) which was identical (i.r. spectrum) to a sample obtained before, and N-benzyl-2-nitrosobenzamide (32e) (80%) which formed light brown plates, m.p. 130-131 ° (from ethyl acetate), \( \nu_{\text{max}} \) 3340 (NH) and 1650 (CO) cm\(^{-1}\), \( \delta[(\text{CD}_3)_2\text{SO}] \) 9.32 (1H, m, NH), 7.92-7.18 (8H, m, ArH), 6.31 (1H, d, J8Hz, ArH), and 4.62 (2H, d, J6Hz, CH\(_2\)).

Found: C, 70.2; H, 4.7; N, 11.6%; M\(^+\), 240.

C\(_{14}\)H\(_{12}\)N\(_2\)O\(_2\) requires: C, 70.0; H, 5.0; N, 11.7%; M, 240.
(vi) N-(1-Phenylethyl)-2-nitrophenylmethanimine (31f)
gave N-(1-phenylethyl)-2-nitrosobenzamide (32f) (100%) which
formed colourless plates, m.p. 170-171° (from ethanol-di-
methylformamide), \( \nu_{\text{max}} \) 3410 (NH) and 1660 (CO) cm\(^{-1}\),
\( \delta[(\text{CD}_3)_2\text{SO}] \) 9.25 (1H, d, \( J_{2\text{Hz}} \), NH), 7.94-7.19 (9H, m, ArH),
5.32 (1H, m, CH), and 1.45 (3H, d, \( J_{2\text{Hz}} \), CH\(_3\)).

Found: C, 70.6; H, 5.5; N, 10.8%; M\(^+\), 254.

\( C_{15}H_{14}N_2O_2 \) requires: C, 70.8; H, 5.6; N, 11.0%; M, 254.

(vii) N-(Diphenylmethyl)-2-nitrophenylmethanimine (31g)
gave N-diphenylmethyl-2-nitrosobenzamide (32g) (100%) which
formed olive green plates, m.p. 161-162° (from toluene),
\( \nu_{\text{max}} \) 3260 (NH) and 1640 (CO) cm\(^{-1}\), \( \delta(\text{CDCl}_3) \) 9.15 (1H, m, NH),
8.24 (1H, dd, \( J_{\text{ortho}8\text{Hz}}, J_{\text{meta}2\text{Hz}} \), ArH); 7.79-7.80 (1H, m,
ArH), 7.28-7.17 (11H, m, ArH), 6.34 (1H, d, \( J_{8\text{Hz}} \), CH), and
6.10 (1H, dd, \( J_{\text{ortho}8\text{Hz}}, J_{\text{meta}2\text{Hz}} \), ArH).

Found: C, 76.0; H, 5.1; N, 8.6%; M\(^+\), 316.

\( C_{20}H_{16}N_2O_2 \) requires: C, 75.9; H, 5.1; N, 8.9%; M, 316.

Reactions of N-Alkyl-2-nitrosobenzamides (32a-g) with
Ethanolic Sodium Hydroxide

A solution of the corresponding N-alkyl-2-nitrosobenz-
amide (0.006 mol) in ethanol (20.0 ml) was treated with a
solution of sodium hydroxide (1.2 g) in water (12.0 ml) and
the mixture was heated at 100° (steam bath) for 10 min, then
worked up as described for the individual reactions below.

(i) The mixture from N-ethyl-2-nitrosobenzamide (32a)
was evaporated and the residue was treated with water (20.0
ml) and extracted with methylene chloride to give a brown oil
whose t.l.c. in methylene chloride over alumina showed it to be an unresolvable multicomponent mixture which was not further investigated.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, extracted with methylene chloride and the extract washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield 2-ethylindazol-3(1H)-one (35a) (0.26 g; 27%) which formed light brown plates, m.p. 142-143° (from toluene), ν<sub>max</sub> 3100 br (NH) and 1630 (CO) cm<sup>-1</sup>, δ(CDCl<sub>3</sub>) 8.50 (1H, s, NH), 7.79-7.04 (4H, m, ArH), 3.92 (2H, q, J8Hz, CH<sub>2</sub>), and 1.28 (3H, t, J8Hz, CH<sub>3</sub>).

Found: C, 66.6; H, 5.9; N, 17.1%; M<sup>+</sup>, 162. C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O requires: C, 66.6; H, 6.2; N, 17.3%; M<sup>+</sup>, 162.

Acidification of the aqueous sodium hydrogen carbonate washings with 2M aqueous hydrochloric acid followed by extraction with methylene chloride yielded a brown gum (0.26 g) whose t.l.c. in diethyl ether over silica showed it to be a multicomponent mixture which was not further investigated.

(ii) The mixture from N-(prop-1-yl)-2-nitrosobenzamide (32b) was evaporated and the residue was treated with water (30.0 ml) and extracted with methylene chloride to give a dark red intractable oil whose t.l.c. in methylene chloride over alumina showed it to be a multicomponent mixture which was not further investigated.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, extracted with methylene chloride and the extract washed with saturated aqueous sodium
hydrogen carbonate then evaporated to yield an orange oil (0.51 g) whose t.l.c. in methylene chloride over silica showed it to be a multicomponent mixture which was not further investigated.

Acidification of the aqueous sodium hydrogen carbonate washings with 2M aqueous hydrochloric acid followed by extraction with methylene chloride yielded a brown gum (0.15 g) whose t.l.c. in diethyl ether showed it to be a multicomponent mixture which was not further investigated.

(iii) The mixture from N-(prop-2-yl)-2-nitrosobenzamide (32c) was concentrated to one third of the original volume and extracted with methylene chloride to yield a gum (0.46 g) which was triturated with diethyl ether to afford azoxybenzene-2,2'-di-N-(prop-2-yl)carboxamide (34c) (0.29 g; 26%) which formed pale yellow microcrystals, m.p. 210-212° (from ethanol-ethyl acetate), $\nu_{\text{max}}$ 3260 br (NH) and 1640 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) 7.96-7.26 (8H, m, ArH), 4.16 (2H, m, 2xCH), 1.13 (6H, d, J4Hz, 2xCH$_3$), and 1.06 (6H, d, J4Hz, 2xCH$_3$).

Found: M$^+$, 368.18441.

C$_{20}$H$_{24}$N$_4$O$_3$ requires: M, 368.18483.

Evaporation of the diethyl ether mother liquor gave a red gum (0.3 g) which was triturated with light petroleum to afford 2-(prop-2-yl)indazol-3(1H)-one (24) (0.27 g; 26%), m.p. 139-141°, which was identical (m.p. and i.r. spectrum) to a sample prepared before. Evaporation of the light petroleum mother liquor yielded a brown gum (0.2 g) from which no identifiable material could be obtained.

Acidification of the saturated aqueous sodium hydrogen
carbonate washings with 2M aqueous hydrochloric acid followed by extraction with methylene chloride yielded only an intracetable gum (0.1 g).

(iv) The mixture from N-cyclohexyl-2-nitrosobenzamide (32d) was evaporated and the residue was treated with water (5.0 ml) and the insoluble solid was collected to give azoxybenzene-2,2'-di-N-cyclohexylcarboxamide (34d) (0.84 g; 62%) which formed pale yellow needles, m.p. 230-231° (from ethanol-dimethylformamide), $v_{\text{max}}$ 3280 (NH) and 1630 (CO) cm$^{-1}$, $\delta$[(CD$_3$)$_2$SO] 8.12-7.60 (8H, m, ArH), 2.84 (2H, m, 2xCH), and 2.24-1.32 (20H, m, CH$_2$).

Found: M$^+$, 448.24658.

C$_{26}$H$_{32}$N$_4$O$_3$ requires: M, 448.24743.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, extracted with methylene chloride, and the extract washed with saturated aqueous sodium hydrogen carbonate, and evaporated to yield 2-cyclohexylindazol-3(1H)-one (35d) (0.21 g; 16%), m.p. 142-145°, which was identical (m.p. and i.r. spectrum) to a sample obtained before.

Acidification of the aqueous sodium hydrogen carbonate washings with 2M hydrochloric acid followed by extraction with methylene chloride gave only a small amount (0.12 g) of brown gum.

(v) The mixture from N-benzyl-2-nitrosobenzamide (32e) was evaporated and the residue was treated with water, and the solution was extracted with methylene chloride to give a brown gum (0.39 g) from which no identifiable material could be obtained.
The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, extracted with methylene chloride, and the extract washed with saturated aqueous sodium hydrogen carbonate and evaporated to yield 2-benzylindazol-3(1H)-one (35e) (0.75 g; 56%) which formed light brown plates, m.p. 160-161° (from toluene-ethyl acetate), $v_{\text{max}}$ 2680 br (NH) and 1630 (CO) cm\(^{-1}\), $\delta$(CDCl\(_3\)) 7.80 (1H, dd, J\(_{\text{ortho}}\) 8Hz, J\(_{\text{meta}}\) 2Hz, ArH), 7.56-7.06 (8H, m, ArH), and 4.99 (2H, s, CH\(_2\)).

Found: C, 74.8; H, 5.5; N, 12.2%; M\(^+\), 224.

C\(_{14}\)H\(_{12}\)N\(_2\)O requires: C, 75.0; H, 5.4; N, 12.5%; M, 224.

Acidification of the saturated aqueous sodium hydrogen carbonate washings with 2M aqueous hydrochloric acid followed by extraction with methylene chloride gave only a small amount (0.12 g) of brown gum.

(vi) The mixture from N-(1-phenylethyl)-2-nitrosobenzamide (32f) was evaporated and the residue was treated with water to afford a solid (1.1 g) which could not be purified and was shown by t.l.c. in methylene chloride over silica to be a multicomponent mixture which was not further investigated.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, extracted with methylene chloride, and the extract washed with saturated aqueous sodium hydrogen carbonate to yield 2-(1-phenylethyl)-indazol-3(1H)-one (35f) (0.24 g; 17%), which formed colourless plates, m.p. 182-184° (from toluene-ethanol), $v_{\text{max}}$ 3040 br (NH) and 1630 (CO) cm\(^{-1}\), $\delta$[CD\(_3\)]\(_2\)SO 10.02 (1H, s, NH), 7.66-5.63 (9H, m, ArH), 5.72 (1H, q, J2Hz, CH), and 1.72 (3H, d, J2Hz, CH\(_3\)).
Found: C, 75.9; H, 5.8; N, 11.5%; M⁺, 238.

\[
\text{C}_{15}\text{H}_{14}\text{N}_2\text{O} \text{ requires: C, } 75.6; \text{ H, } 5.9; \text{ N, } 11.8\%; \text{ M, 238.}
\]

Acidification of the aqueous sodium hydrogen carbonate washings with 2M aqueous hydrochloric acid followed by extraction with methylene chloride afforded only a small amount (0.06 g) of brown gum.

(vii) The mixture from N-diphenylmethyl-2-nitrosobenzamide (32g) was evaporated, the residue was treated with water, and the solid was collected to afford azoxybenzene-2,2'-di-N-diphenylmethylcarboxamide (34g) (1.7 g; 90%) which formed colourless needles, m.p. 250-251° (from ethanol-dimethylformamide), \( \nu_{\text{max}} \) 3280 (NH) and 1635 (CO) cm\(^{-1} \), \( \delta[(\text{CD}_3)_2\text{SO}] \) 9.60 (1H, d, J8Hz, NH), 9.23 (1H, d, J8Hz, NH), 7.60-7.12 (28H, m, ArH), and 6.31 (2H, d, J8Hz, 2×CH).

Found: M⁺, 616.24651.

\[
\text{C}_{40}\text{H}_{32}\text{N}_4\text{O}_3 \text{ requires: M, 616.24742.}
\]

Acidification of the aqueous mother liquor with concentrated hydrochloric acid and extraction with methylene chloride gave only a negligible quantity of gum.

The Hydrogenolysis of N-(prop-2-yl)-2-nitrosobenzamide (32c)

A solution of N-(prop-2-yl)-2-nitrosobenzamide (32c) (0.38 g, 0.002 mol) in absolute ethanol (30.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 3 h. Hydrogen (23.0 ml) was absorbed and the mixture was filtered through celite and evaporated to yield azoxybenzene-2,2'-di-N-(prop-2-yl)carboxamide (34c) (0.32 g; 87%), m.p. 205-206°, identical (m.p. and
i.r. spectrum) to a sample obtained previously.

The Reaction of \( N-(\text{prop-2-y1})-2\text{-nitrosobenzamide} \) (32c) with Sodium Borohydride

A solution of \( N-(\text{prop-2-y1})-2\text{-nitrosobenzamide} \) (32c) (0.38 g, 0.002 mol) in methanol (20.0 ml) was stirred and treated dropwise over 15 min at room temperature with a solution of sodium borohydride (0.33 g, 0.0088 mol) in 2M aqueous sodium hydroxide (5.0 ml). Stirring was continued at room temperature for 3 h and the mixture was then evaporated and the residue treated with water and filtered to give azoxybenzene-2,2'-di\( N\)-prop-2-y1)carboxamide (34c) (0.23 g; 62%), m.p. 204-208\(^\circ\), which was identical (m.p. and i.r. spectrum) to a sample obtained before.

Extraction of the aqueous filtrate with methylene chloride yielded only a small amount (0.02 g) of brown gum.

The Attempted Reaction of \( N-(\text{prop-2-y1})-2\text{-nitrosobenzamide} \) (32c) with Toluene-\( p\)-sulphonic Acid

A solution of \( N-(\text{prop-2-y1})-2\text{-nitrosobenzamide} \) (32c) (0.38 g, 0.002 mol) and toluene-\( p\)-sulphonic acid (0.01 g) in anhydrous 1,2-dimethoxyethane (10.0 ml) was heated under reflux for 4.5 h. The mixture was then evaporated, the residue was treated with water, and the insoluble solid was collected to give unreacted \( N-(\text{prop-2-y1})-2\text{-nitrosobenzamide} \) (32c) (0.38 g; 100%), m.p. 131-134\(^\circ\), identical (m.p. and i.r. spectrum) to an authentic sample.
The Attempted Reaction of N-(prop-2-yl)-2-nitrosobenzamide (32c) with Acetyl Chloride in the Presence of Triethylamine

A solution of N-(prop-2-yl)-2-nitrosobenzamide (32c) (0.38 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) was stirred at room temperature and treated in one portion with triethylamine (0.51 g, 0.005 mol) followed dropwise by a solution of acetyl chloride (0.17 g, 0.0022 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). Stirring was continued at room temperature for 1 h then the mixture was filtered to remove triethylamine hydrochloride (0.26 g; 95%), m.p. 249-251° (lit. 159 253-254°), identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated and the residue was treated with water and extracted with methylene chloride to afford a brown gum (0.51 g) which was shown by t.l.c. in diethyl ether over alumina to be an unresolvable multicomponent mixture and was not further investigated.

The Reaction of N-(prop-2-yl)-2-nitrosobenzamide (32c) with Aqueous Sodium Carbonate

A suspension of N-(prop-2-yl)-2-nitrosobenzamide (32c) (0.76 g, 0.004 mol) in 0.5M aqueous sodium carbonate (40.0 ml) was stirred at room temperature for 0.5 h. The mixture was filtered to yield azoxybenzene-2,2'-di-N-(prop-2-yl)carboxamide (34c) (0.07 g; 10%), m.p. 203-205°, identical (m.p. and i.r. spectrum) to a sample obtained before.

The aqueous filtrate was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to give
propanone (2-carboxyphenyl)hydrazone (36) (0.5 g; 65%) which formed brown plates, m.p. 174-176° (lit., 164-172°) (from toluene-light petroleum/b.p. 80-100°), v \text{max} 3430 (NH), 3140 br (OH), and 1660 (CO) cm^{-1}, \delta_H(CDCl_3) 10.45 (1H, s, NH or OH), 6.70 (4H, m, ArH), 2.09 (3H, s, CH_3), and 1.96 (3H, s, CH_3), \delta_C(CDCl_3) 173.47 (s, CO), 148.88 (s, ArC), 146.76 (s, ArC), 135.49 (d, ArCH), 131.65 (d, ArCH), 116.79 (s, C(CH_3)_2), 24.95 (q, CH_3), and 20.22 (q, CH_3).

Found: M⁺, 192.08832.
Calc. for C_{10}H_{12}N_2O_2: M⁺, 192.08987.

N,N-Di-(prop-2-yl)-2-hydroxyaminobenzylamine (19)

N,N-Di-(prop-2-yl)-2-hydroxyaminobenzylamine (19) was prepared (yield 50%) by the reaction of N,N-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) with lithium aluminium hydride as described by Aldersley and Tennant, m.p. 55-58° (lit., 61-63°), and was used without further purification.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-hydroxyaminobenzylamine (19) with Ethyl Chloroformate in the Presence of Triethylamine

A solution of N,N-di-(prop-2-yl)-2-hydroxyaminobenzylamine (19) (0.33 g, 0.0015 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred at room temperature and treated in one portion with triethylamine (0.35 g, 0.0035 mol) followed dropwise by a solution of ethyl chloroformate (0.18 g, 0.0017 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). Stirring was continued at room temperature for 1 h and the mixture was then
filtered to remove triethylamine hydrochloride (0.17 g; 82%), m.p. 254-255° (lit., 253-254°), identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated, the residue was treated with water, and the solution was extracted with methylene chloride to afford a green oil (0.34 g) which was shown by t.l.c. in methylene chloride over silica to be an unresolvable multi-component mixture and was not further investigated.

The Attempted Reaction of N,N-Di-(prop-2-yl)-2-nitrobenzylamine (12a) with Ethanolic Triethylamine

A solution of N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) (1.2 g, 0.005 mol) in absolute ethanol (20.0 ml) was treated with triethylamine (2.0 g, 0.02 mol) and the mixture was heated under reflux for 23 h. Evaporation of the mixture yielded unreacted N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) as a yellow oil (1.2 g; 100%) which was identical (i.r. spectrum) to an authentic sample.

The Reaction of N,N-Di-(prop-2-yl)-2-nitrobenzylamine (12a) with Sodium Hydride in Dimethylformamide

A solution of N,N-di-(prop-2-yl)-2-nitrobenzylamine (12a) (0.94 g, 0.004 mol) in anhydrous dimethylformamide (5.0 ml) was added dropwise at room temperature under nitrogen over 20 min to a vigorously stirred suspension of sodium hydride (0.38 g, 0.016 mol) in anhydrous dimethylformamide (5.0 ml). Stirring was continued at room temperature for 1 h then the mixture was treated with water (15.0 ml) and extracted with
methylene chloride to give unreacted $N,N$-di-(prop-2-yl)-2-nitrobenzylamine (12a) (0.56 g; 60%) identical (i.r. spectrum) to an authentic sample.

The aqueous mother liquor was cooled (ice bath) neutralised with concentrated hydrochloric acid and solid sodium acetate, and extracted with methylene chloride to yield $N,N$-di-(prop-2-yl)-2-hydroxyaminobenzamide (18a) (0.35 g; 37%), m.p. 123-126°, which was identical (m.p. and i.r. spectrum) to an authentic sample.

**Hydrazobenzene-2,2'-di-(N,N-di-prop-2-yl)carboxamide (45)**

A solution of $N,N$-di-(prop-2-yl)-2-nitrobenzylamine (12a) (0.94 g, 0.004 mol) in anhydrous tetrahydrofuran (10.0 ml) was added dropwise, under nitrogen at room temperature, to a stirred suspension of lithium aluminium hydride (2.0 g) in anhydrous tetrahydrofuran (35.0 ml). The mixture was then heated under reflux for 5 h, cooled and diluted with 50% v/v aqueous methanol (20.0 ml). The mixture was filtered to remove inorganic material, concentrated to one quarter of the original volume, and extracted with methylene chloride to afford an orange oil (0.9 g) which was triturated with light petroleum to yield hydrazobenzene-2,2'-di-(N,N-di-prop-2-yl)carboxamide (45) (0.23 g; 28%) which formed colourless plates, m.p. 168-169° (from light petroleum-toluene), $\nu_{\text{max}}$ 3210 (NH) cm$^{-1}$, $\delta$(CDCl$_3$) 8.08 (2H, br s, NH), 7.21-6.58 (8H, m, ArH), 3.77 (4H, s, 2xCH$_2$), 3.10 (2H, m, 2xCH), and 0.87 (12H, d, $J_{6Hz}$, 4xCH$_3$).

Found: C, 75.9; H, 10.4; N, 13.7%; M$^+$, 410.

$C_{26}H_{42}N_4$ requires: C, 76.0; H, 10.3; N, 13.6%; M$, 410.$
Evaporation of the light petroleum mother liquor afforded a red oil (0.65 g) which was shown by t.l.c. in methylene chloride over alumina to be an unresolvable multicomponent mixture and was not further investigated.

2-Nitrobenzoyl Chloride (58)

For the preparation of 2-nitrobenzoyl chloride (58), see Chapter 2, Section 5.

N,N-Dimethyl-2-nitrobenzamide (59)

N,N-Dimethyl-2-nitrobenzamide (59) was prepared (yield 58%) by the reaction of 2-nitrobenzoyl chloride (58) with dimethylamine as described in the literature,\textsuperscript{173} m.p. 77-78° (lit.,\textsuperscript{173} 78°), and was used without further purification.

The Reaction of N,N-Dimethyl-2-nitrobenzamide (59) with Ethanolic Potassium Hydroxide

A solution of N,N-dimethyl-2-nitrobenzamide (59) (0.78 g, 0.004 mol) in ethanol (20.0 ml) was treated with solid potassium hydroxide (1.1 g, 0.02 mol) and the mixture was heated under reflux for 1 h. The mixture was then concentrated to one half of the original volume, diluted with water (20.0 ml) and extracted with methylene chloride to afford azobenzene-2,2'-di-(N,N-dimethyl)carboxamide (63) (0.26 g; 40%) which formed light orange plates, m.p. 214-215° (from ethyl acetate), $\nu_{\max}$ 1630 (CO) cm$^{-1}$, $\delta$(CDCl$_3$) (at 30°) 7.75-7.25 (8H, m, ArH), 3.15 (6H, 2xCH$_3$), and 2.73 (6H, s, 2xCH$_3$), $\delta$(CDCl$_3$) (at 90°) 7.75-7.25 (8H, m, ArH) and 2.99 (12H, s, 4xCH$_3$).
Found:  C, 66.5; H, 6.3; N, 17.4%; [M⁺−N(CH₃)₂]⁺, 280.

C₁₈H₂₀N₄O₂ requires:  C, 66.6; H, 6.2; N, 17.3%;  M, 324.

The aqueous mother liquor was cooled (ice bath), acidified with concentrated hydrochloric acid, and extracted with methylene chloride to give a brown gum (0.22 g) which was shown by t.l.c. in ethyl acetate over silica to be a multicomponent mixture and was not further investigated.
Appendix
General Experimental Procedures

Crude solids obtained from reaction mixtures by filtration were dried in vacuo at room temperature unless otherwise stated.

Infra-red spectra were measured for nujol suspensions or thin films using a Perkin-Elmer 157G spectrophotometer. Bands were either strong or very strong, unless otherwise specified (w) weak or (br) broad.

Nuclear magnetic resonance (1H n.m.r.) spectra were measured at 100MHz using a Varian HA100 instrument. Signals are specified as: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (dd) double doublet.

Mass spectra were measured at 800KV on an A.E.I. MS902 instrument.

Microanalyses were carried out by Mr. J. Grunbaum, Department of Chemistry, Edinburgh University. Melting-point (m.p.) (uncorrected) of all analytical samples were determined on a Kofler block.

Thin layer chromatography (t.l.c.) was carried out in the specified solvent over silica, which was Kieselgel G.F. nach Stahl (Typ 60), or over alumina, which was Aluminium oxid G.F. 254 (Typ 60/E). Column chromatography was carried out over 5% deactivated alumina or Fisons Silica Gel (100-200 mesh).

Solvents were of technical grade, unless otherwise specified, and light petroleum had b.p. 60-80°.

Chloroform, methylene chloride, and ethyl acetate extracts were dried over anhydrous magnesium sulphate, and evaporated under reduced pressure.
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