Studies on the Heterocyclisation Reactions of Isocyanides and Isocyanide Dihalides

by

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Thesis Presented for the Degree of Doctor of Philosophy
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Experimental

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

This 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 1990 and September 1993.
I am deeply indebted to my supervisor, Dr. G. Tennant, for his constant guidance and encouragement throughout this project.

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The following courses were attended between October 1990 and July 1993.

1. Royal Society of Chemistry - Perkin Division
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This thesis is concerned with the synthesis of five-, six-, seven-, and eight-membered heterocycles by the cyclisation reactions of isocyanides and isocyanide dihalides, and the chemical manipulation of the products so obtained.

The Lewis acid promoted cyclisation reactions of 2-phenoxyphenyl and 2-phenylthiophenyl isocyanide derivatives gave the corresponding C-11 unsubstituted dibenz[b,f][1,4]oxazepine and dibenzo[b,f][1,4]thiazepine derivatives. Further investigations of this reaction demonstrated that the nature of the Lewis acid and the presence and nature of substituents in the isocyanide substrate were critical factors in determining the success of the reaction. In contrast the Lewis acid promoted cyclisation reactions of isocyanides with carbon-carbon double bonds, in the case of cis- and trans-2-(2-phenylethenyl)phenyl isocyanides and 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide were found to be unsuccessful.

The ability of isocyanide dihalides to undergo intramolecular Lewis acid promoted heterocyclisation reactions was also investigated. Such reactions of 2-phenoxy-, 2-phenylthio-, 2-phenylamino-, and 2-benzylphenyl isocyanide derivatives, and of 2-phenoxy- and 2-phenylthiopyridinyl isocyanide dihalides were found to provide an extremely useful and high yielding synthetic route to the corresponding halogenated tricyclic heteroamines. The nucleophilic displacement reactions of these halogenated products were also briefly investigated.

It was also shown that six-membered heterocycles could be prepared
by the Lewis acid promoted cyclisation of 1,1'-biphenyl-2-isocyanides and 1,1'-biphenyl-2-isocyanide dihalides, to give a variety of phenanthridine derivatives. The formation of six-membered rings by the Lewis acid promoted cyclisation of heteroaromatic isocyanide dihalides was also investigated.

In addition, it was shown that dibenz[b,f]azocine derivatives could be obtained by the Lewis acid promoted cyclisation reactions of cis-2-(2-phenylethenyl)phenyl isocyanide dichloride and 2-(2-phenylethyl)phenyl isocyanide dihalides.

The Lewis acid promoted reactions of some alkyl isocyanides and isocyanide dihalides in the case of 3-methoxybenzyl isocyanide and 2-phenylethyl isocyanide were examined and were found to be largely unsuccessful.
Although isocyanides and isocyanide dihalides have been known for over a century, it was not until the 1960's that general methods for their synthesis became available. With the greater accessibility of isocyanides and isocyanide dihalides from the 1960's onwards, these compounds became the focus of numerous investigations during the next 30 years. However, despite the increasing interest in isocyanides and isocyanide dihalides, a great deal about their chemistry remains to be uncovered. Therefore, it was of interest to investigate the chemical reactivity of such compounds, with particular emphasis on their cyclisation reactions.

The following thesis is concerned with the development of new synthetic routes to functionalised heterocycles by the heterocyclisation reactions of isocyanides and isocyanide dihalides. By way of an introduction, Chapter 1 provides a survey of the existing methods for the preparation of isocyanides and isocyanide dihalides and a review of their known reactivity. This is followed in Chapters 2 to 4 by an account of the results obtained in the present studies.
CHAPTER 1

A SURVEY OF THE SYNTHESIS AND REACTIVITY
OF ISOCYANIDES AND ISOCYANIDE DIHALIDES
11.1 INTRODUCTION

In the following survey discussion is restricted to the synthesis and reactivity of $N$-aryl and $N$-alkyl isocyanides. The synthesis of isocyanides has been reviewed\(^1\) and only the most important methods are presented here. Under the heading of reactivity, no attempt has been made to discuss the much studied chemistry of isocyanide-transition metal complexes,\(^2,^3\) the three and four component condensations of isocyanides (the Passerini and Ugi reactions), or the oligomerisation and polymerisation\(^4\) of isocyanides. Likewise the chemistry of $\alpha$-metallated isocyanides, which has been thoroughly investigated and has been the subject of two comprehensive reviews,\(^5,^6\) is not discussed here.

The synthesis\(^7,^9\) and reactivity\(^8,^9\) of isocyanide dihalides have been reviewed elsewhere and the present survey makes no attempt to present an exhaustive account of the chemistry of these compounds. Only the major synthetic routes to $N$-aryl and $N$-alkyl isocyanide dihalides are presented, and the discussion as a whole is restricted to isocyanide dichlorides and dibromides.

1.2 THE SYNTHESIS AND REACTIVITY OF ISOCYANIDES

Throughout this thesis the isocyanide group will, for simplicity, be drawn as a nitrogen-carbon triple bond in which the charges will be omitted. The full structure is shown in Section 1.2.2, Scheme 7. For the same reason isocyanide systems will be drawn as non-linear.
1.2.1 The Synthesis of Isocyanides

The first isocyanide syntheses appeared in 1866-1869 when Gautier\(^1\) reported the preparation of methyl, ethyl, and isopropyl isocyanides by the reaction of silver cyanide with the appropriate alkyl iodides. This result was somewhat unexpected as the normal products from the reaction of free cyanide ion with alkyl halides are nitriles with isocyanides produced only in small amounts if at all. Complexation of cyanide ion with a metal such as silver(I) or copper(I) however leads to preferential alkylation on nitrogen rather than carbon. For example (Scheme 1) methyl isocyanide (3) results\(^1\) from the reaction of methyl iodide (1) with silver cyanide or cuprous cyanide, via the intermediate isocyanide-metal complex (2) which liberates the product (3) on decomposition with potassium cyanide. However, this type of process suffers from low yields which at best never exceed 55%, and the fact that product mixtures containing both the isocyanide and the corresponding nitrile are usually obtained. A more recent modification of this process, which considerably increases its synthetic potential, is the reaction of an onium dicyanoargentate with alkyl halides to give high yields of isocyanides with no contamination from the corresponding nitriles.\(^1\)\(^2\) Such isocyanating agents are readily prepared by the reaction of silver cyanide with tetramethylammonium chloride, and they have the advantage of giving

\[
\text{MeI} + \text{MCN} \rightarrow [\text{MeNC-MI}] \xrightarrow{(i) \text{KCN}} \text{MeN≡C} \]

\((M=\text{Ag,Cu})\)

Scheme 1
(i) CHCl₃, NaOH (:CCl₂), MeOH.

Scheme 3
homogeneous reaction mixtures in dipolar aprotic solvents. Thus (Scheme 2) benzhydryl isocyanide (5) has been prepared in 92% yield by reaction of benzhydryl bromide (4) with tetramethylammonium dicyanoargentate at room temperature.

Another classic method of isocyanide preparation, reported almost simultaneously with Gautier's first syntheses, is the Hofmann carbylamine reaction which involves reaction of primary amines with chloroform and strong bases such as solid sodium hydroxide or ethanolic potassium hydroxide. For instance (Scheme 3) 4-isocyanobenzoic acid (9) is formed in 51% yield by reaction of 4-aminobenzoic acid (6) with chloroform in the presence of powdered sodium hydroxide. The Hofmann synthesis is believed to proceed by reaction of dichlorocarbene (formed in situ from chloroform and the base) with the amine producing an intermediate such as (7). This in turn rearranges to a neutral species [e.g. (8)] which undergoes sequential β-elimination then α-elimination of two molecules of hydrogen chloride to furnish the final isocyanide product [e.g. (9)]. Although long believed to be the most useful isocyanide synthesis, the carbylamine reaction suffers from low yields, is often accompanied by tarry by-products, and lacks generality due to experimental difficulties. A significant improvement of this method,
reported by Weber and Gokel,\textsuperscript{15} entails the use of benzyltriethylammonium chloride, aqueous sodium hydroxide, and chloroform to generate dichlorocarbene under phase transfer conditions. Using this method the authors have prepared phenyl isocyanide from aniline in 57\% yield. The yields for this one-step amine to isocyanide transformation (41-60\%) compare favourably with the overall yields obtained using the two-step formylation-dehydration procedure (50-80\%), as discussed later, although it still suffers from the serious restriction in that it cannot be used if the starting material or product are sensitive to base.

The dehydration of \textit{N}-monosubstituted formamides as a method of isocyanide synthesis (Scheme 4) was discovered almost simultaneously by Hagedorn,\textsuperscript{16} Corey,\textsuperscript{17} and Ugi.\textsuperscript{18} Subsequent studies by Ugi\textsuperscript{11} showed (Scheme 4) phosgene in combination with triethylamine to be the best dehydrating system, but the extreme toxicity and handling difficulties of phosgene have curtailed the application of this procedure. Consequently a wide range of alternative dehydrating agents have been developed to

\[
\begin{align*}
\text{RN} & \quad \text{RN} = \text{C} \\
\text{RN} - \text{CHO} & \quad \text{(i)-(v)} \\
\end{align*}
\]

(i) COCl\textsubscript{2}, Et\textsubscript{3}N, solvent.
(ii) POCl\textsubscript{3}, i-Pr\textsubscript{2}NH, CH\textsubscript{2}Cl\textsubscript{2}, room temp.
(iii) (CF\textsubscript{3}SO\textsubscript{2})\textsubscript{2}O, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, -78\textdegree.
(iv) Ph\textsubscript{3}P, CCl\textsubscript{4}, Et\textsubscript{3}N, Cl(CH\textsubscript{2})\textsubscript{2}Cl, 60\textdegree.
(v) SOCl\textsubscript{2}, DMF, Na\textsubscript{2}CO\textsubscript{3}, -50\textdegree to room temp.

\textbf{Scheme 4}
Scheme 5

Scheme 6

(i) oxomethylenebis-(3H + -imidazolium)bis(methanesulphonate), tetramethylurea, MeCN, room temp.
(ii) HO₂C-CO₂H·2H₂O, MeOH, 35°.
overcome these problems, notably phosphoryl chloride in conjunction with diisopropylamine, trifluoromethanesulphonic anhydride in combination with N-ethyl-diisopropylamine, carbon tetrachloride, triphenylphosphine, and triethylamine, and chlorodimethylformimmonium chloride [prepared in situ from dimethylformamide (DMF) and thionyl chloride] in conjunction with sodium carbonate. The mechanism of the formamide to isocyanide dehydration is illustrated in Scheme 5 for the phosphoryl chloride-diisopropylamine promoted transformation. Initial phosphorylation on oxygen leads to the intermediate formimidate which undergoes a base-induced α-elimination to give the isocyanide product. Isocyanide formation using other dehydrating agents proceeds analogously. By such dehydration procedures, formamides, which themselves are readily available in high yields by formylation of the corresponding amines, can be converted into isocyanides in consistently high yields (70-90%). However, the aforementioned dehydration procedures cannot generally be applied to the synthesis of chiral isocyanides bearing an α-hydrogen atom due to the acidity of the latter and consequent racemisation under the basic reaction conditions. For example, reaction of chiral methyl N-formylvalinate with phosphoryl chloride in the presence of diisopropylamine gave completely racemic methyl 2-isocyanopropanoate. To overcome this problem a non-basic dehydrating system has been developed. Thus (Scheme 6) methyl L-2-isocyno-3-phenylpropanoate (13), whose α-hydrogen atom is particularly labile, was prepared in 80% yield by dehydration of methyl L-2-formylamino-3-phenylpropanoate (12) with oxomethylenebis-(3H⁺-imidazolium) bis-methanesulphonate. Hydration of the isocyanide (13) back to the formamide (12) with oxalic acid dihydrate and comparison of its optical rotation with that of an authentic sample indicated that the degree of racemisation was only 1%.
Isocyanides can also be obtained from isocyanates and isothiocyanates although the applicability of these methods is limited. Reaction of isocyanates with triethylphosphite at 150° affords a number of isocyanides in variable yields (20-57%), but the elevated temperature involved often leads to significant decomposition and thermal rearrangement of the product to the corresponding nitrile. Mukaiyama's reagent, 2-phenyl-3-methyl-1,3,2-oxazaphosphoridine, can be used at room temperature but is difficult to prepare and store. A recent development is the use of the trichlorosilane-triethylamine system which reduces isocyanates and isothiocyanates to isocyanides in moderate to good yields under mild conditions. The isocyanate/isothiocyanate route has not found widespread application as it is generally less direct and less economical than the formamide dehydration procedure described previously.

1.2.2 Reactivity of Isocyanides

The isocyano group is unique in that it is the only stable functional group to incorporate divalent carbon, with its electronic structure (Scheme 7)

\[
\begin{align*}
R^+ - N\equiv C & \leftrightarrow R \equiv N \equiv C & \leftrightarrow R=N^+ = C:
\end{align*}
\]

(14a) (14b) (14c)

Scheme 7

being a resonance hybrid of three possible canonical forms (14a-c). The dipolar form (14a) is predominant while the carbenic form (14b) makes a lesser contribution, and it appears there is little or no contribution from structure (14c; R = Aryl). Accordingly the reactivity of the isocyano group is governed by a desire to regain the stable tetravalent state at the terminal
\[ \text{(17)} \]
\[ \text{(16)} \]
\[ \text{(15)} \]
\[ \text{(18)} \]
\[ \text{(20)} \]

(i) \( H^+, H_2O \).
(ii) \( \text{HN}_3 \).
(iii) \( \text{HX} \).
(iv) \( X_2 \).

**Scheme 8**

\[ \text{(22)} \]
\[ \text{(23)} \]

(i) \( \text{PhNC, HCl, Et}_2\text{O} \).

**Scheme 9**
carbon, and hence isocyanides tend to undergo electrophilic rather than nucleophilic attack (i.e. react as nucleophiles rather than electrophiles) and insertion rather than addition. Isocyanides had until recently been a relatively little investigated class of compounds, mainly due to the absence of adequate synthetic methods for their preparation. The advent of the formamide dehydration procedure however has heralded a rapid growth in isocyanide chemistry in the last thirty years.

α-ADDITION REACTIONS

The reactivity of the isocyanide group is dominated by its tendency to undergo α-addition reactions,\(^3\) where the two groups of a reactant X-Y add to the divalent isocyano carbon. The first step in such reactions is the nucleophilic attack of the isocyano carbon on the electrophilic component of the reactant, and consequently α-additions to isocyanides are often acid catalysed with the proton acting as the electrophile. This type of reactivity is epitomised by the simple reactions shown in Scheme 8. The α-addition of water to an isocyanide [Scheme 8; (15)→(16)→(17)] is an acid catalysed process and results in hydrolysis to the corresponding formamide. The formation of formidoyl halide salts by the α-addition of anhydrous hydrogen halides to isocyanides [Scheme 8; (15)→(20), X = Cl, Br, I] is a well known\(^{27}\) reaction which likewise proceeds by initial protonation. This reaction is often violent but can be controlled at low temperature to give the formidoyl halide salts in good yields. Reaction of isocyanides with hydrazoic acid generates primary α-addition products (18) which are unstable and tautomerise to afford the corresponding tetrazoles (19). The simplicity and generality of this procedure makes it a valuable synthetic route to 1-substituted tetrazoles. Halogens react with isocyanides, often violently, to afford high yields of the
(i) piperidine, CuCl, 110-120°.
(ii) H$_2$C=CHCH$_2$OH, Cu, 120°.

Scheme 10

(i) CH$_2$=CH(CH$_2$)$_3$COCl, CH$_2$Cl$_2$, 25°.
(ii) CF$_3$SO$_3$Ag, CH$_2$Cl$_2$, 0°.

Scheme 11
corresponding isocyanide dihalides [Scheme 8; (15)→(21), X = Cl, Br, I]. This reaction is discussed further in Section 1.3.1.

Electron rich heterocycles may also act as the nucleophilic component in the acid catalysed α-addition reactions of isocyanides. This is demonstrated (Scheme 9) by the reaction of phenyl isocyanide with 1-methylpyrrole (22) in the presence of hydrochloric acid\textsuperscript{28} to give the Schiff base derivative (23) as its hydrochloride salt, which can then be hydrolysed to 1-methylpyrrole-2-carboxaldehyde. Given that isocyanides combine readily with hydrogen halides, this reaction may be viewed as an electrophilic attack of the C-protonated isocyanide on the pyrrole ring.

Isocyanides are reluctant to undergo α-addition reactions with heteroatom-hydrogen bonds such as O-H, N-H, P-H, or S-H except under drastic and synthetically useless conditions. Insertion into these bonds can be smoothly effected however by employing group IB and IIB metal catalysts, especially copper compounds. The development of these catalysts stemmed from the observation that both isocyanides and the aforementioned heteroatoms form coordination compounds with copper. Such reactions are exemplified by (Scheme 10) the reaction of cyclohexyl isocyanide (24) with piperidine in the presence of cuprous chloride to afford the formamidine (25) in almost quantitative (96%) yield.\textsuperscript{29} The reaction of alcohols with isocyanides is also effectively catalysed by group IB and IIB metal compounds, and these can be separated into two classes. The first class [metallic copper and oxides of copper (I) and (II), silver (I), and mercury (II)] catalyse the reaction of isocyanides with a wide range of alcohols, while the second class [chlorides of copper (I), silver (I), zinc (II), and cadmium (II)] only catalyse insertions of isocyanides into specific alcohols. This difference in catalytic activity can be attributed to the relative coordination tendencies of the isocyanides and alcohols by assuming that reaction takes place within the
(i) BuLi, -10°, tetrahydrofuran.
(ii) EtBr, tetrahydrofuran, -10°.
(iii) steam distillation.
(iv) propylene oxide, tetrahydrofuran, -10°.
(v) HCl, NH₄Cl, H₂O, tetrahydrofuran, reflux.

Scheme 12
sphere of a ternary complex comprising the metal catalyst, the isocyanide, and the alcohol. Indeed, these reactions have been shown to proceed via a detectable metal-carbene complex. In general, metallic copper and copper oxides are the best catalysts, as shown (Scheme 10) by the copper catalysed reaction of cyclohexyl isocyanide (24) with allyl alcohol to afford the formimidate (26) in 95% yield. Similar metal catalysed insertion reactions can be carried out with thiols, silanes, and phosphines to give the corresponding formimidic acid derivatives.

Although isocyanides are generally stable towards alkylating agents, they react readily via an α-addition mechanism with acid halides to afford α-ketoimidoyl halides. As might be predicted, acid bromides are more reactive than acid chlorides in this respect. The α-ketoimidoyl halide products are easily prepared and have considerable synthetic potential, as demonstrated (Scheme 11) by Livinghouse's expeditious synthesis of 1-acyl-3,4-dihydroisoquinolines. The intermediate α-ketoimidoyl chloride (27) is obtained in quantitative yield, and on treatment with silver ion this generates a nitrogen stabilised carbocation which cyclises to give the product (28) in 87% overall yield for the two steps.

A further manifestation of the α-addition chemistry of isocyanides is their reaction with organometallic compounds such as organolithium and Grignard reagents to give metalloaldimines. These synthetically versatile compounds are easily accessible and undergo a variety of useful transformations as acyl carbanion equivalents. For example (Scheme 12) 1,1,3,3-tetramethyl-butyl isocyanide (29) reacts with n-butyllithium to give the lithium aldimine (30) in quantitative yield. Subsequent reaction in situ with ethyl bromide followed by hydrolysis affords 3-heptanone (31) in 90% yield, and with propylene oxide followed by hydrolysis gives 2-hydroxy-4-octanone (32), also in 90% yield. Metalloaldimines can react with a multitude of
(i) BCl₃, Cl(CH₂)₂Cl, reflux.
(ii) PhCH₂NC, Et₃N, Cl(CH₂)₂Cl, reflux.
(iii) AcOH, HCl.

**Scheme 13**

(i) tBuN≡C + F₃C≡C≡CN → F₃C≡C≡CN

(ii) 0°.

(iii) tert-BuNC.
different organic reactants, and the organic component of the organometallic reagents may be varied to increase their potential application in synthesis.

An unusual application of the α-addition chemistry of isocyanides is found in a report by Sugasawa and co-workers who have developed a valuable route to ortho-formylated anilines, compounds which were previously accessible only by lengthy synthetic routes. This is illustrated in Scheme 13 by the preparation of N-methylaminobenzaldehyde (36) by reaction of benzyl isocyanide (41) with N-methylanilinodichloroborane (34). The reaction proceeds through a cyclic transition state to give the intermediate (35), which liberates the formylated product (36) in 65% yield after hydrolysis.

CYCLOADDITION REACTIONS

Cycloaddition reactions represent a major feature of isocyanide reactivity and have been extensively studied. Isocyanides react readily with most of the common multiple bonds allowing easy access to a variety of four-, five-, and six-membered heterocycles via formal (1:1), (2:1), or (1:2) substrate:isocyanide additions. Generally these reactions proceed through a dipolar intermediate which achieves ring closure by combination with another molecule of substrate or isocyanide.

Four-membered rings can be prepared by the reaction of isocyanides with electron deficient olefins, as demonstrated (Scheme 14) by the formation of the unstable bis-imino cyclobutane derivative from tert-butyl isocyanide (37) and 1,1-ditrifluoromethyl-2,2-dicyanoethylene (38). Nucleophilic attack by the isocyanide on the electrophilic double bond produces the dipolar intermediate (39) which is intercepted by another molecule of tert-butyl isocyanide to give the product (40), whose structure was formulated on the basis of its fluorine and proton n.m.r. spectra. Similar
(i) Ph$_2$C=C=O, -20°.
(ii) Ph$_2$C=C=O.

Scheme 15

(i) tert-butylcyanoketene, benzene, room temp.

Scheme 16
Cycloaddition reactions with aldehydes and ketones afford 2,3-bis-imino oxetanes by a (1:2) substrate:isocyanide Lewis acid catalysed process.

Ketenes participate in cycloadditions with isocyanides in a ratio of 2:1 to afford a number of functionalised five-membered rings. This is illustrated (Scheme 15) by the reaction of benzyl isocyanide (41) with diphenylketene to give the dipolar intermediate (42) by nucleophilic addition of the isocyanide to the alkene double bond of the ketene. The intermediate (42) then combines with a further equivalent of diphenylketene to afford the aminocyclopentanetrione derivative (43) in 76% yield. This process represents the normal mode of reaction of isocyanides with ketenes, however an anomalous reaction was reported by Moore and Yu (Scheme 16) whereby benzyl isocyanide (41) adds across the carbon-oxygen double bond of tert-butylcyanoketene leading to the zwitterionic intermediate (44). Unlike the conventional mechanism [Scheme 15; (42)→(43)] this intermediate reacts with a further molecule of ketene at oxygen rather than carbon, again adding across the carbon-oxygen double bond, to give the iminolactone (45) in 73% yield. The authors suggest that the lactone (45) represents the kinetic product of this reaction and that reaction of the intermediate (44) with the ketene at carbon is inhibited by the steric demands of the proximate tert-butyl group.

[1+4] Cycloaddition reactions of isocyanides are common and give rise to various five-membered heterocycles such as imino-oxazolones and imino-oxazolethiones by reaction with acyl and thioacyl isocyanates and isothiocyanates respectively.

The use of isocyanide cycloadditions as a route to six-membered rings has been less well investigated, one example however is the preparation of triazenes in high yield by reaction of isocyanides in a 1:2 ratio with hydrogen thiocyanate.
(i) Ph₅Sn₂, tBuNC, benzene, hv, 40°.
Scheme 16

(i) Me₆Sn₂, PhNC, tBuPh, hv, 150°.
RADICAL REACTIONS

The carbenic properties of isocyanides bestow upon the group an ability to participate in a variety of radical reactions, some of which involve $\alpha$-additions of radicals to the isocyanide. This aspect of isocyanide reactivity has been exploited using tert-butyl isocyanide (37) to effect intermolecular trapping of the transient radical (47) which arises from cyclisation of the open chain radical derived from the bromo-acetal (46). Trapping results in the formation of the transient imidoyl radical (48) which in turn achieves stability by extrusion of a tert-butyl radical to furnish the final cyano product (49). Imidoyl radicals such as (48) are the key intermediates in all radical reactions of isocyanides, and once formed they can undergo a variety of useful transformations. An elegant demonstration of this is found in the single-step synthesis of cyclopenta-fused quinolines from aromatic isocyanides and acyclic radical precursors. For example (Scheme 18) reaction of the iodopentyne (50) with hexamethylditin generates the corresponding radical and this initiates the reaction sequence by combining with phenyl isocyanide to generate the intermediate imidoyl radical (51). Successive ring closures onto the triple bond then the aromatic ring give 9-methyl-2,3-dihydro-1H-cyclopenta[b]quinoline (52) in high yield (70%). This reaction is the first example of a [4+1] radical annulation and is made possible by the unique carbene-like character of the isocyano group.

MISCELLANEOUS REACTIONS

Due to their primarily nucleophilic character isocyanides are reluctant to undergo nucleophilic attack, accounting for their relative stability towards alkaline hydrolysis, however the intramolecular addition of a carbanion to an isocyanide has been demonstrated in a synthesis of indoles, as shown in
(i) LiNPr$_2$, diglyme, -78° to room temp.
(ii) Lithium tetramethylpiperidide, diglyme, -78°.
(iii) RBr, diglyme, -78°.
(iv) Lithium tetramethylpiperidide, diglyme, -78°.

Scheme 12
Scheme 19. Lithiation at the methyl group of 2-isocyanotoluene (53), which is assisted by the activating effect of the isocyano group, can be achieved with a non-nucleophilic lithium amide base. The resulting ortho-metallated intermediate can be cyclised to give indole (54) in quantitative yield, or can be sequentially alkylated and remetallated allowing access to a range of 3-substituted indoles (55) in excellent yields (78-95%).

1.3 SYNTHESES AND REACTIVITY OF ISOCYANIDE DIHALIDES

1.3.1 The Synthesis of Isocyanide Dihalides

The most important synthetic route to isocyanide dihalides is the halogenation of isocyanides [Scheme 8; (15)→(21), facing page 7]. This process, which has been applied to many different isocyanide dichlorides and dibromides, is easy to carry out and generally gives the products in quantitative yields under mild conditions (room temperature or below). The reaction is conducted in an inert solvent using molecular chlorine or bromine, although it is generally more convenient to use sulphuryl chloride in place of chlorine gas to limit any unwanted chlorination reactions. The reaction mechanism involves an α-addition of the halogen to the isocyanide, and may be regarded as an oxidation of the latter (see Section 1.2.2). An interesting aspect of this type of reaction is its apparent involvement in the formation of two naturally occurring isocyanide dichlorides which have been isolated from the marine sponge *Pseudaxinyssa pitys*. This sponge is capable of chlorination reactions and the authors suggest that the dichlorides are biosynthesised by enzymatic chlorination of the corresponding isocyanides.

As a consequence of the lack of suitable synthetic methods for isocyanide preparation prior to 1960 the classical method for the preparation of isocyanide dichlorides was the chlorination of isothiocyanates. For example (Scheme 20) phenyl isocyanide dichloride (58) is formed in 85-
(56) \[ \text{(i) Cl}_2, \text{CCl}_4, 0^\circ \]  

Scheme 20

(i) \( \text{SOCl}_2, \text{SO}_2\text{Cl}_2, \text{room temp. then } 80^\circ \)

Scheme 21
90% yield by chlorination of phenyl isothiocyanate (56) in carbon tetrachloride. The use of carbon tetrachloride as the solvent is important as it minimises any competing ring chlorination which can occur in chloroform solution. Although this method is widely applicable to a variety of isothiocyanates, the possibility of side reactions and the need for purification of the product (usually by distillation) makes it less appealing in a practical sense than the straightforward halogenation of isocyanides. In addition, it is recommended that the reaction mixture be washed with aqueous sodium sulphite and sodium carbonate to remove impurities prior to distillation, and this can reduce yields to as low as 70%, presumably due to hydrolysis of the reactive dichlorides. The mechanism of the chlorination of isothiocyanates involves initial formation of a 1-(chlorothio)formidoyl chloride [e.g. (57)] which takes up a further equivalent of chlorine to give the product by extrusion of sulphur dichloride.

Isocyanide dichlorides may also be obtained by chlorination of imidoyl chlorides, which themselves are available from the corresponding N-monosubstituted formamides. Scheme 21 illustrates this process for the preparation of phenyl isocyanide dichloride (58). Treatment of formanilide (59) with thionyl chloride gives rise to the intermediate salt (60) which loses sulphur dioxide to afford the imidoyl chloride salt (61). Further chlorination with sulphuryl chloride then furnishes phenyl isocyanide dichloride (58) in 51% yield. The use of chlorine gas in place of sulphuryl chloride can give rise to nuclear chlorination products. Thus reaction of formanilide with excess chlorine gives significant amounts of 4-chlorophenyl isocyanide dichloride. A wide range of isocyanide dichlorides has been prepared by this method but its synthetic utility is curtailed by the variable yields (20-80%), the potential side reactions with thionyl chloride, and its inapplicability to the synthesis of isocyanide dibromides.
A number of other methods for the synthesis of aromatic and aliphatic isocyanide dichlorides and dibromides exist, such as the chlorination of isocyanates with phosphorous pentachloride and the high temperature halogenation of tertiary amines, but none have achieved synthetic prominence due to their lack of generality, complicating side reactions, and typically poor yields.

1.3.2 Reactivity of isocyanide Dihalides

The structural similarity of the isocyanide dihalides to phosgene implies that their chemical reactivity is related and this is indeed the case. Aryl isocyanide dihalides are generally more reactive than the alkyl series, although both are less reactive than acid chlorides. This is demonstrated (Scheme 22) by the reaction of para-chlorocarbonyl phenyl isocyanide dichloride (62) with aniline to give the amide (63), indicating that the acid chloride function is the preferred reaction site. In general isocyanide

(i) PhNH₂.
(i) Na$_2$S, acetone, H$_2$O.
(ii) RNHCONH$_2$.
(iii) NaN$_3$, 1,2-dimethoxyethane, room temp.
(iv) NaN$_3$, acetone, reflux.

Scheme 23
dihalides are more stable to heat and less stable to hydrolysis than isocyanides, and are free of the offensive odours which accompany the latter.

A survey of the chemical literature reveals that the chemistry of isocyanide dichlorides has been investigated to a far greater degree than that of the isocyanide dibromides, due mainly to the greater availability of synthetic methods for the preparation of the former.

**NUCLEOPHILIC DISPLACEMENT REACTIONS**

The principal reactions of isocyanide dihalides involve nucleophilic displacement of one or both halogen atoms. After substitution of one halogen atom the reactivity of the remaining one is reduced, and this allows successive displacement of both halogen atoms with different nucleophiles or the isolation and subsequent manipulation of the intermediate imidoyl halides after one displacement.

Open-chain substitution products are obtained by nucleophilic displacement of halide with simple monofunctional reagents. For example, reaction of phenyl isocyanide dichloride (58) with hydrogen sulphide has been reported to afford phenyl isothiocyanate (56) in quantitative yield, although the success of this procedure has been disputed. An alternative approach (Scheme 23) is to use sodium or ammonium sulphide in place of hydrogen sulphide and this gives good yields (up to 80%) of a number of aromatic and aliphatic isothiocyanates, although this method can be applied only to preparations where the starting isocyanide dichlorides and the product isothiocyanates are stable under the reaction conditions (aqueous acetone at 20-50°C).

Isocyanide dihalides have found widespread application in the synthesis of heterocyclic rings via an extensive range of ring closure reactions with bifunctional nucleophilic compounds. The exploitation of
isocyanide dihalides in this respect has been reviewed\textsuperscript{8,9} and only brief illustrative examples are given here. Due to their ease of formation and potential as biologically active agents, the preparation of five-membered rings has been the major focus of attention. An example of this (Scheme 23) is the synthesis\textsuperscript{45} of the 2,5-diamino-1,3,4-oxadiazole derivative (64), which exhibits H\textsubscript{2} antihistaminic activity, from phenyl isocyanide dichloride (58) and a semicarbazide derivative. A further illustration of the ability of isocyanide dihalides to act as the lynchpin in the synthesis of heterocyclic molecules is

\[ \text{Scheme 24} \]

found (Scheme 24) in the reaction of 2,6-dichlorophenyl isocyanide dichloride (68) with the diamine (69) to furnish the anilino-imidazoline derivative\textsuperscript{46} (70), which was prepared as an analogue of the antihypertensive drug clonidine. The preparation of four-, six-, and higher membered rings can be easily accomplished by variation of the length of the connecting chain between the two reactive centres of the bis-nucleophilic reactant.

One or both halogen atoms of an isocyanide dihalide can be displaced by azide ion to afford 5-halogeno or 5-azido tetrazoles respectively. For instance\textsuperscript{47} (Scheme 23) reaction of phenyl isocyanide dichloride (58) with one
(i) AlCl₃, PhOMe.
(ii) AlCl₃, PhCN.
(iii) PhHgCCl₂F, NaI, 1,2-dimethoxyethane, reflux.
(iv) HOSO₂F⁻.

Scheme 28
equivalent of sodium azide gives rise to the intermediate (65) which spontaneously ring closes to give 5-chloro-1-phenyltetrazole (66) in 92% yield. The remaining chlorine atom in the chlorotetrazole (66) is sufficiently reactive to allow nucleophilic displacement, as demonstrated by its reaction with a further equivalent of sodium azide to afford 5-azido-1-phenyltetrazole (67) in 77% yield. This method offers a general synthetic route to 1,5-disubstituted tetrazoles, and is closely related to and complements the preparation of 1-monosubstituted tetrazoles from isocyanides (see Section 1.2.2).

ELECTROPHILIC REACTIONS

Of the few known electrophilic reactions of isocyanide dihalides, Friedel-Crafts reactions have been the most investigated. The reaction of phenyl isocyanide dichloride (58) with benzene in the presence of aluminium trichloride was first reported in 1942, with benzanilide being isolated as the sole product (97%) after quenching of the reaction mixture with water. Further investigations by Kühle et al. (Scheme 25) have shown that the imidoyl chloride (71) can be obtained as the primary product from the aluminium trichloride promoted reaction of phenyl isocyanide dichloride (58) with anisole. The reaction generally stops at this stage and the second chlorine cannot normally be substituted even using an excess of Lewis acid. One exception to this is that pentachlorophenyl isocyanide dichloride gives N-(diphenylmethylene)pentachloroaniline (55%) when heated in benzene in the presence of aluminium trichloride. This type of reactivity has been utilised to prepare (Scheme 25) 2-chloro-4-phenylquinazoline (73) by an aluminium trichloride mediated reaction of phenyl isocyanide dichloride (58) with benzonitrile. The first step in this transformation is presumably the formation of the nitrilium salt (72) which cyclises spontaneously to afford the
(i) NaHCO₃, CH₂=CHCH₂NHBOc, EtOAc, room temp.
(ii) NaOH, Bu₄NHSO₃, tetrahydrofuran, H₂O, 60°.
(iii) HCl, EtOAc.

Scheme 26

(i) N-chlorosuccinimide, 1,2-dimethoxyethane, reflux.
(ii) KHCO₃, CH₂=CHCH₂OH, 1,2-dimethoxyethane, 25°.

Scheme 27
MISCELLANEOUS REACTIONS

Addition to the carbon-nitrogen double bond of isocyanide dihalides is rare, one example being the addition of azide ion to afford tetrazoles [see Scheme 23; (58)→(66), facing page17]. A further example of this unusual aspect of isocyanide dihalide reactivity (Scheme 25) is the addition of carbenes to afford highly substituted aziridines.\textsuperscript{50} Generation of chlorofluorocarbene [by the action of sodium iodide on phenyl(2-fluorodichloromethyl)mercury] in the presence of phenyl isocyanide dichloride (58) gave 1-phenyl-2,2,3-trichloro-3-fluoroaziridine (74) in 70% yield.

In recent years dichloro and dibromoformaldoximes have found increasing application as precursors to chloro- and bromonitrile oxides, useful intermediates which participate in a range of 1,3-dipolar cycloaddition reactions. The synthesis\textsuperscript{51} (Scheme 26) of racemic dihydromuscimol (79), which is a conformationally restricted GABA analogue with powerful antagonist activity, is illustrative. Reaction of dibromoformaldoxime (76) with sodium bicarbonate generates bromonitrile oxide (77) \textit{in situ}. Subsequent cycloaddition to the alkene bond of N-Boc protected allylamine gives the bromoisoxazoline (78) in 91% yield as the major regioisomer. Hydrolysis followed by amino deprotection then furnishes racemic dihydromuscimol (79) as its hydrochloride salt. Despite the synthetic potential of the dihaloformaldoximes their use has been limited due to their high toxicity and the inconvenient methods available for their synthesis.\textsuperscript{52} Accordingly, an alternative strategy has been devised\textsuperscript{53} whereby dihaloformaldoximes are
easily prepared in situ in quantitative yield by halogenation of glyoxylic acid aldoxime with N-bromosuccinimide or N-chlorosuccinimide, and this strategy has been applied in a one-pot synthesis (Scheme 27) of 3-chloroisoxazolines. Generation of dichloroformaldoxime (81) from glyoxylic acid aldoxime (80) followed by reaction with potassium bicarbonate and allyl alcohol gave 3-chloro-5-(hydroxymethyl)-2-isoxazoline (83) in the highly respectable overall yield of 78% for the three steps.

As weak bases isocyanide dichlorides can serve as precursors to a variety of phosgeneimminium salts by reaction with strong acids and alkylating agents, as illustrated in Scheme 25 by the reaction of phenyl isocyanide dichloride (58) with fluorosulphonic acid to give the salt (75) in 96% yield. These highly reactive salts are more prone to addition across the multiple bond than phosgene or the corresponding isocyanide dichlorides, and they also undergo synthetically useful displacements of one or both chlorine atoms with a wide variety of nucleophiles such as amines, stabilised carbanions, or Grignard reagents.
CHAPTER 2

INVESTIGATIONS OF NEW SYNTHETIC STRATEGIES FOR TRICYCLIC HETEROCYCLES BASED ON ISOCYANIDE AND ISOCYANIDE DIHALIDE HETEROCYCLISATION REACTIONS
(Ar = Aromatic or heteroaromatic nucleus)
(X = NH, CH$_2$, O, S)
INVESTIGATIONS OF NEW SYNTHETIC STRATEGIES FOR TRICYCLIC HETEROPINES BASED ON ISOCYANIDE AND ISOCYANIDE DIHALIDE HETEROCYCLISATION REACTIONS

2.1 INTRODUCTION

The potential of tricyclic heteropines [Scheme 28; (84) and (85)] as biologically active agents has been recognised for many years and has generated a large number of investigations on their preparation and biological and clinical evaluation. As a result of their interactions with a wide range of neuroreceptors, compounds of general structures (84) and (85) have potential application as chemotherapeutic agents for a variety of medical conditions as diverse as schizophrenia, Alzheimer's disease, anxiety, and depression. At present the most important of these is Alzheimer's disease which claims more lives per year in the western world than any other ailment with the exception of heart disease, cancer, and stroke, and is the only one of the aforementioned neurological disorders for which no treatment is currently available.

Consideration of the pathology of Alzheimer's disease\textsuperscript{55,56} reveals the potential opportunities for pharmacological intervention using a tricyclic heteropine derived agent. The disease involves a selective degeneration of cholinergic neurons in the brain, particularly in those areas associated with higher functions such as memory and cognition. It therefore comes as no surprise that efforts to enhance cholinergic function have formed the basis of most therapeutic strategies. The events at the cholinergic nerve terminal offer three distinct possibilities for the enhancement of acetylcholine function. Firstly, inhibition of acetylcholinesterase, which breaks down acetylcholine in the nerve synapse. Secondly, antagonism of presynaptic muscarinic m\textsubscript{2} receptors, which regulate acetylcholine release by a negative feedback
mechanism. Thirdly, agonism of the postsynaptic muscarinic m₁ receptors in order to mimic the action of acetylcholine. It is the latter possibility that represents the best opportunity for chemical intervention as the postsynaptic m₁ receptors are not depleted in Alzheimer's disease. However, the use of an agonist at these receptors raises the obvious question of selectivity of action. Not only must the agent target cholinergic receptors but it must be selective for the muscarinic type and further, it must discriminate between the different muscarinic subtypes. Already it is clear that to assume that this involves simply m₁/m₂ selectivity is to underestimate the problem as at least four distinct muscarinic receptor genes have been identified, and this number is likely to increase.

The tricyclic heteropines, exemplified (Scheme 29) by clozapine (86), pirenzepine (87), and nevirapine (88), are potentially useful probes for the further subclassification of receptors as the appropriate structural modifications around the tricyclic nucleus can dramatically alter the receptor selectivity. For example clozapine (86), which is in clinical use as an antischizophrenic agent, binds to dopaminergic receptors (which produces the antipsychotic effect), muscarinic receptors (which prevents the extrapyramidal side effects usually associated with antipsychotic agents), and has also been shown⁵⁸ to bind to a third class of receptors which are non-dopaminergic and non-muscarinic in nature. Replacement⁵⁹ of both diazepine nitrogen atoms in clozapine with carbon increases binding affinity at dopaminergic sites and reduces affinity at muscarinic sites. Conversely methylation of the bridge nitrogen atom reduces dopaminergic binding but does not affect muscarinic binding, and replacement of the bridge nitrogen atom with oxygen increases affinity at dopaminergic sites. Replacement of the nitrogen atom at the 4-position of the piperazine moiety with carbon has
(i) polyphosphoric acid, 150°C. 

\[ \text{(90)} \]

\[ (X = \text{NMe,CH}_2,\text{O,S}) \]

\[ (R = \text{H,Me}) \]

(i) K$_2$CO$_3$.

\[ \text{(93)} \]

(i) 200°C.

\[ \text{(95)} \]

\[ (R = \text{OMe}) \]

Scheme 30
little effect, while a similar replacement at the 1-position of piperazine drastically reduces binding at all three sites.

Pirenzepine\textsuperscript{60} (87), which still contains the basic heteropine nucleus, has a completely different mode of action from clozazine and is used clinically for the treatment of gastric and duodenal ulcers. Pirenzepine is a selective m\textsubscript{2} antagonist which blocks the receptors controlling gastric acid secretion and does not produce any central nervous system effects as its hydrophilicity results in poor penetration of the blood-brain barrier.

Nevirapine (88) was recently reported\textsuperscript{61} as a novel non-nucleoside inhibitor of HIV-1 reverse transcriptase which shows less side effects than nucleoside based agents (such as AZT) and is highly selective, inhibiting HIV-1 reverse transcriptase at low concentrations without affecting any mammalian polymerases. Subsequent studies\textsuperscript{62,63} showed that dibenz[b,f][1,4]oxazepinones and various pyridobenzoxazepinones were similarly active, and that substitution around the pyridine or benzene rings, or at the lactam nitrogen, had a dramatic effect on biological potency.

It is clear from the strikingly different biological actions of the compounds shown in Scheme 29, and the further modification of their individual activity profiles by more subtle structural variations, that it is desirable to have ready access to as wide a range of such structures as possible, and to be able to synthesise and modify them in a rational manner in order to provide the necessary candidates for biological evaluation.

Although the literature is replete with references to tricyclic heteropines, the available general strategies for their construction are relatively few, and the vast majority of syntheses rely on one of three major approaches. Firstly (Scheme 30), Bischler-Napieralski type ring close of appropriately substituted amides [e.g. (89) $\rightarrow$ (90)\textsuperscript{64}] has formed the basis of many synthetic routes to a variety of systems such as dibenzothiazepines\textsuperscript{65}
(i) \( \text{H}_{2}\text{Ar} \).
(ii) Lewis acid.
(iii) \( R^1\text{COCl} \).

\( \text{Ar} = \text{Aromatic or heterocaromatic nucleus} \)
\( X = \text{NR, CH}_2, \text{O, S} \)
\( \text{Hal} = \text{Cl, Br} \)

\text{Scheme 31}
and dibenzoxazepines. An alternative strategy (Scheme 30) involves initial construction of the amide, or imine, link by the condensation of an aromatic amine with an appropriate carbonyl compound [e.g. a carboxylic acid derivative or an aldehyde or ketone] [e.g. (91) + (92) → (93) → (94)].

Similar cyclocondensations with amines and amides have also been demonstrated. The third major strategy (Scheme 30) involves the initial formation of the heteroatom bridge between the two aromatic rings with ring closure then being effected by cyclocondensation of an amine with an aldehyde or ketone to form the imine, or with a carboxylic acid derivative to give the corresponding lactam [e.g. (95) → (96)]. In practice this approach often involves reductive cyclisation of the appropriate nitro compound and has been applied to the synthesis of many heteropine derivatives such as dibenzodiazepines and dibenzoxazepines. These routes, and many other less widely used methods which have not been discussed here, have been used to prepare a myriad of tricyclic heteropine derivatives, however they can all suffer from certain drawbacks. The most important of these are harsh reaction conditions, particularly in the ring closure steps, and the limited availability of the required starting materials which can limit their synthetic versatility and their utility for the synthesis of the required range of structures.

It was anticipated that a more versatile synthetic strategy for tricyclic heteropines could be developed by the exploitation of isocyanides and isocyanide dihalides as shown in Scheme 31. Thus direct Lewis acid promoted cyclisation of the isocyanides themselves [(97) → (100)] or of the derived α-ketoimidoyl chlorides [(97) → (101)] or isocyanide dihalides [(97) → (98) → (99)] would afford convenient routes to a variety of tricyclic heteropines which could serve as key intermediates for the preparation of a wide range of structural analogues. This chapter describes investigations which demonstrate the utility of this new strategy for the synthesis of a variety
Scheme 32
of tricyclic heteropines (Scheme 32), namely derivatives of the dibenz[b,f][1,4]oxazepine (102), dibenzo[b,f][1,4]thiazepine (103), dibenzo[b,e][1,4]diazepine (104), pyrido[2,3-b][1,4]benzoxazepine (105), pyrido[3,2-b][1,5]benzoxazepine (106), pyrido[3,4-b][1,5]benzoxazepine (107), pyrido[2,3-b][1,4]benzothiazepine (108), pyrido[2,3-b][1,4]benzodiazepine (109), and dibenz[b,e]azepine (110) ring systems.

2.2 SYNTHESIS OF DIBENZ[b,f][1,4]OXAZEPINE DERIVATIVES

Brief mention was made in Section 2.1 of the general strategies available for the preparation of tricyclic heteropines, and all of these apply to dibenz[b,f][1,4]oxazepines. This section describes work carried out to develop an alternative synthetic route to such compounds by exploitation of isocyanides and isocyanide dihalides as the key starting materials. At the outset of the present investigations there were only a limited number of literature reports (excluding the field of isocyanide polymerisation) concerning the interaction of Lewis acids with isocyanides, most of which were structural studies or were related to catalysis of the Passerini reaction. Such studies apart, little is known about the mode of interaction of isocyanides and isocyanide dihalides with Lewis acids, and the exploitation of such interactions in heterocyclisation reactions has not been reported hitherto. The aim of the present studies was therefore to investigate the potential of Lewis acid promoted cyclisation of isocyanides and isocyanide dihalides as a new procedure for the synthesis of dibenz[b,f][1,4]oxazepine derivatives, as outlined in Scheme 31 [(97) → (100) and (97) → (98) → (99); Ar = benzene, \( X = O \)]. Initially it was anticipated that coordination of a Lewis acid to the isocyano group would activate it towards nucleophilic attack by a proximate aromatic ring, the net result being cyclisation via insertion of the isocyanide into an aromatic C-H bond.
(i) NaH, DMF, 100°.
(ii) H₂, 10% Pd-C, EtOAc, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) SOCl₂, DMF, Na₂CO₃, -50° to room temp. (R=OMe).
(v) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(vi) (MeO)₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60° (R=OMe).

Scheme 33
In order to assess the feasibility of heterocyclisation of the type [(97 → (100); Ar = benzene, X = O] 2-(3-methoxyphenoxy)phenyl isocyanide (116a) was selected as a model substrate, because (Scheme 33) it has an appropriately positioned activating substituent (methoxy) to increase the likelihood of reaction and also because it was expected that it would be readily available through the synthetic route shown in Scheme 33. Thus the sodium hydride promoted reaction of 2-fluoronitrobenzene (111) with 3-methoxyphenol (112a) gave the known nitro compound (113a) in excellent yield (91%), and reduction of this compound to the known amine (114a) was readily effected in quantitative yield by catalytic hydrogenation. This amine was in turn readily converted into the formamide (115a) in high yield (93%) by heating under reflux in formic acid. The proton n.m.r. spectrum of this compound contains a one proton multiplet at δ8.49-8.37 which partially simplifies on shaking with deuterium oxide, and is assigned to the formyl proton. This complex multiplet, which is observed with almost all of the formamides described in this thesis, could not be resolved and its origin is not clear although the fact that the formamide group may exist partially in an enol form, which itself has two geometrical isomers, is a likely cause. Conversion of the formamide (115a) into the isocyanide (116a) was first attempted using thionyl chloride and dimethylformamide (DMF), a procedure previously described by Walborsky and Niznik,22 and this gave a crude product mixture whose t.l.c. and i.r. spectrum showed the formamide (115a) to be the major constituent. The low yield and inconvenience of this method in practice prompted its abandonment in favour of a more convenient procedure reported by Ziehn et al.21 This involved reaction of the formamide (115a) with a 20% excess of triphenylphosphine and equimolar amounts of carbon tetrachloride and triethylamine and afforded the oily isocyanide (116a), though only in moderate yield (60%). In keeping with the reaction mechanism, which
(i) MeCOCl, Et$_2$O, 0°C.
(ii) MeCOCl, 1,2-dimethoxyethane, reflux.
(iii) see Table 1.
(iv) TiCl$_4$, CH$_2$Cl$_2$, reflux.

Scheme 24
involves initial formation of an adduct between triphenylphosphine and carbon tetrachloride, the use of an excess of carbon tetrachloride, along with an excess of triethylamine to maximise the efficiency of the final $\alpha$-elimination, gave the isocyanide (116a) in a considerably improved yield (87%). This yield has since proved to be consistently reproducible. One drawback to this method is the formation of triphenylphosphine oxide as a by-product, the removal of which requires chromatography and can be problematic, particularly on a large scale. In an attempt to overcome this difficulty trimethylphosphite was used in place of triphenylphosphine in the anticipation that the by-product, trimethylphosphate, being water soluble should be easily removable. Unfortunately, however, application of these conditions resulted only in a high recovery (88%) of the uncharged starting material (115a). The identity of the previously unknown isocyanide (116a) was established by its combustion analysis and spectroscopic properties and was further confirmed by its acidic hydrolysis to afford the amine (114a) in quantitative yield. Like many liquid isocyanides, (116a) was found to be prone to decomposition upon prolonged storage (several weeks) even at -20°C, and was also unstable to distillation.

Having obtained the isocyanide (116a) its reactions with acid chlorides were first investigated (Scheme 34). The insertion of isocyanides into the C-Cl bond of acid chlorides is well known and it was anticipated that the resulting $\alpha$-ketoimidoyl chloride (117) could be cyclised with the aid of a Lewis acid. The cyclisation of $\alpha$-ketoimidoyl chlorides derived from alkyl isocyanides using stannic chloride as the Lewis acid had been previously reported by Livinghouse et al. In the present studies however, reaction of the isocyanide (116a) with acetyl chloride at 0°C gave only a quantitative recovery of the starting material while heating the same mixture under reflux in 1,2-dimethoxyethane (DME) gave a complex mixture from which no
<table>
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a, polymer only obtained; b, 56% starting material obtained; c, t.l.c indicated mixture of starting material (116a) and formamide (115a); d, yields determined by ¹H n.m.r of the crude reaction mixture.
identifiable material was obtained. This lack of reactivity is at variance with literature reports\textsuperscript{3,33} which indicate that alkyl isocyanides insert readily into the C-Cl bond. It would appear however that there is an appreciable difference in reactivity between alkyl and aryl isocyanides, presumably due to the extra canonical form [see Chapter 1, Scheme 7; (14c)] available only to aryl isocyanides in which the negative charge is delocalised into the aromatic ring.

It was next decided to investigate the direct cyclisation of the isocyanide (116a) using different Lewis acids (Scheme 34) and the results of this study are summarised in Table 1. Cyclisation was first attempted (Table 1, entry 1) by heating the isocyanide (116a) under reflux in methylene chloride with an excess of aluminium trichloride. Disappointingly however, the only product isolated under these conditions was a high melting amorphous solid which could not be resolved by t.l.c. or purified by crystallisation, and whose i.r. spectrum contained no intelligible absorption. Likewise (Table 1, entry 2) reaction of the isocyanide (116a) with an excess of stannic chloride in refluxing 1,2-dichloroethane gave a similar high melting unidentifiable solid product whose i.r. and proton n.m.r. spectra contained no assignable absorptions and whose E.I. mass spectrum contained numerous high molecular weight ion peaks. It was suspected at this stage that these unidentified products might be isocyanide-metal complexes, as the formation of defined coordination compounds with a variety of metals is a well known property of isocyanides,\textsuperscript{3} but this possibility was excluded by the absence of any isocyano absorption in their i.r. spectra. Isocyanide-metal complexes retain the characteristic isocyano absorption in their i.r. spectra, although it is shifted to a higher or lower frequency depending on the nature of the isocyanide-metal bonding. In addition, isocyanides can generally be regenerated from their metal complexes and indeed metal complexation\textsuperscript{3} has been used to protect isocyano groups from potentially destructive
reaction conditions (e.g. acidic hydrolysis). However, the product obtained from the reaction of the isocyanide (116a) with stannic chloride was recovered unchanged in 78% yield after heating under reflux with 20% w/v aqueous potassium hydroxide solution in ethanol. It is therefore probable that the unidentified products obtained from these reactions are in fact isocyanide polymers. A number of Lewis acids, including aluminium trichloride and stannic chloride, are known to polymerise isocyanides and have been used synthetically for this purpose. These polymerisations are extremely fast intermolecular reactions which proceed readily even at low temperatures (0°C to -80°C), and in the case of the isocyanide (116a) polymer formation is evidently favoured over the intended intramolecular cyclisation. The formulation of these products as polymers is consistent with their observed properties, namely high melting point, low solubility, and the absence of any characteristic i.r. or proton n.m.r. absorption. Rigorous characterisation of such polymers would not be possible without recourse to specialised techniques such as thermogravimetric analysis, viscometry, and osmometry and therefore no attempt was made to conduct such analysis in the present studies. An attempt (Table 1, entry 3) to circumvent the problem of stannic chloride induced polymerisation by conducting the reaction at -10°C was unsuccessful. The use of a five fold excess of the Lewis acid was suspected as being a factor in producing the unwanted polymerisations, and it was therefore decided to investigate if this excess was necessary for cyclisation and if a reduction in the amount of Lewis acid would avoid polymerisation. Thus a solution of the isocyanide (116a) in methylene chloride was treated with one equivalent of stannic chloride at -10°C and the i.r. spectrum of the mixture was immediately recorded. The characteristically strong isocyano absorption, which appears at 2120 cm⁻¹ in the free isocyanide, had completely disappeared showing that complexation and subsequent reaction
occur almost instantaneously. Consequently a final attempt (Table 1, entry 4) to effect cyclisation using stannic chloride was made by lowering the reaction temperature further and using only one equivalent of Lewis acid. Once again, however, only an intractable polymeric product was obtained. A similar result (Table 1, entry 5) was obtained when boron trifluoride was employed as the Lewis acid, although this is unsurprising as boron trifluoride is also known to oligomerise and polymerise isocyanides. It is logical that cyclisation of the isocyanide (116a) occurs via initial coordination of the Lewis acid with the lone pair of the isocyano carbon atom. It has been suggested however that such a complex would be too stable to undergo rapid polymerisation, and that polymerisation proceeds through an energy rich complex in which the Lewis acid coordinates via the lone pair of the isocyano nitrogen atom. In the dipolar form of the isocyano group [see Chapter 1, Scheme 7; (14a)] carbon would obviously be preferred over nitrogen as the coordination site, and even in the carbenic form (14b) carbon should still be preferred as its lower electronegativity means that its lone pair is held more loosely, and would therefore be more available than that on nitrogen. The results obtained in the present studies using aluminium trichloride, stannic chloride, and boron trifluoride suggest that these strong Lewis acids do not discriminate between the two coordination sites and so polymer formation, being extremely rapid, is observed to the exclusion of cyclisation. It was therefore decided to attempt cyclisation using a weak Lewis acid in the hope that this would provide the selectivity of coordination necessary to achieve cyclisation without inducing polymerisation. In practice (Table 1, entry 6) heating the isocyanide (116a) under reflux in methylene chloride with a five fold excess of zinc chloride gave the desired 3-methoxydibenz[b,f][1,4]oxazepine (118) in moderate yield, accompanied by unchanged starting material (116a) (56%). The observed boiling point of the known dibenzoazepine (118) was in agreement with the
literature value, and its identity was further established by its combustion analysis and spectroscopic properties. In an effort to improve the efficiency of the cyclisation [(116a) → (118)] the reaction was run in refluxing acetonitrile, but these conditions (Table 1, entry 7) gave only a mixture of the unchanged starting material (116a) and the formamide (115a). Conversely, the use of the higher boiling solvent 1,2-dichloroethane (Table 1, entry 8) did afford the dibenzoazepine (118), though only in poor yield. Since the preceding results indicated that the strength of the Lewis acid was an important factor in determining the success of cyclisation, it was decided to investigate the applicability of a Lewis acid of intermediate strength, namely titanium tetrachloride. Thus (Table 1, entry 9) heating the isocyanide (116a) under reflux with a five fold excess of titanium tetrachloride in methylene chloride gave the cyclised product (118) in greatly improved yield. It was suspected however that the prolonged heating of the mixture was limiting the potential yield. This was confirmed by conducting the reaction at low temperature (-10°) (Table 1, entry 10), these conditions furnishing the dibenzoazepine (118) cleanly in quantitative yield.

The cyclisation of the isocyanide (116a) can potentially lead to two isomeric products, namely the 3-methoxydibenzoazepine (118) shown and its 1-methoxy isomer, however the product obtained was found to be exclusively the 3-methoxy product (118). This structural assignment was made on the basis of the compound's proton n.m.r. spectrum. This contained a one proton doublet (J = 8.5 Hz) centred at δ7.22, assignable to the proton at position 1, while a one proton double doublet (J = 8.5 and 2.5 Hz) centred at δ6.70 can be assigned to H-2, and the isolated proton at position 4 appears as a doublet (J = 2.5 Hz) centred at δ6.66. This splitting pattern in the substituted ring of the cyclised product is characteristic only of the 3-methoxy structure (118). This regioselectivity is proposed to arise from steric factors in
the coordinated intermediate as illustrated in Scheme 35. Although the exact nature of Lewis acid coordination to the isocyanato group is not known, it is assumed that the species which undergoes cyclisation must involve coordination of titanium at the isocyanato carbon atom and at both ether oxygen atoms. The steric demands of the extremely bulky titanium tetrachloride groups would dictate that structure (120) is the preferred conformation, leading to the 3-methoxydibenzoazepine (118). The conformation (121) which is required for cyclisation to the 1-methoxy isomer is subject to extreme steric congestion and so is highly disfavoured.

The initial use of five equivalents of Lewis acid was designed to allow for complexation at both ether oxygen atoms of (116a) as well as at the isocyanato group. To ascertain if this excess of Lewis acid was really necessary for cyclisation a series of reactions was undertaken (Table 1, entries 11-13) employing differing isocyanide:titanium tetrachloride ratios. The use of a four fold (Table 1, entry 11) or three fold (Table 1, entry 12) excess of Lewis acid caused a significant drop in the yield of the cyclic product (118) compared to that obtained using a five fold excess under otherwise identical conditions, and paralleling this drop in yield was the formation of significant quantities of the formamide (115a). The relative yields of the dibenzoazepine (118) and the formamide (115a) in these reactions were determined by analysis of the proton n.m.r. spectrum of the crude reaction mixture. The methoxy group of the dibenzoazepine (118) resonates at a slightly higher frequency (δ3.82) than that of the formamide (115a) (δ3.76) and the composition of the product mixture was therefore readily established from the integrated ratio of these two peaks. Reaction (Table 1, entry 13) of the isocyanide (116a) with one equivalent of titanium tetrachloride failed to produce the dibenzoazepine (118) and the only product was the formamide (115a), isolated in high yield. These results
clearly indicate that, at least at low temperature, a large excess of Lewis acid is required for efficient cyclisation. The possibility also exists however, that high yields of cyclic product could be obtained with a lesser excess of Lewis acid if higher temperatures were employed.

The mechanism of the cyclisation \([116a \rightarrow 118]\), as with many Lewis acid mediated processes, is not obvious and would be extremely difficult to elucidate without further extensive investigations which were outwith the scope of the present studies. Nevertheless, it is clear from the limited evidence obtained so far that the first step must involve coordination between the isocyanide and the Lewis acid, although the precise nature of this interaction is not known. This suggestion is supported by the formation of the formamide (115a) as a by-product. The stability of isocyanides towards alkaline hydrolysis \(^4\) indicated that the formamide (115a) cannot simply arise from hydrolysis of the free isocyanide in the course of the basic work-up. This was confirmed by the stability of the isocyanide (116a) when it was subjected to hydrolytic conditions identical to those which prevail in the work-up (i.e. treatment with saturated aqueous sodium hydrogen carbonate solution at room temperature). The stability of the isocyanide (116a) to mild acidic hydrolysis was also demonstrated by its treatment with hydrochloric acid prior to its exposure to the alkali, as these conditions also returned (116a) unchanged in quantitative yield. These observations suggest that the formation of the formamide (115a) as a by-product is not the result of simple hydrolysis of the isocyanide (116a) but rather stems from hydrolytic decomposition of an initially formed isocyanide-Lewis acid complex. Indeed, metal complex formation is known\(^79\) to promote the hydrolysis of isocyanides. Further evidence for complex formation between the isocyanide (116a) and the Lewis acid was provided by an i.r. study of the reaction. When a solution of the isocyanide (116a) in methylene chloride was treated with one
equivalent of titanium tetrachloride at 0°, the i.r. spectrum of the mixture showed that the characteristic triple bond absorption, which appears at 2120 cm⁻¹ in the free isocyanide, had shifted to higher frequency giving two new bands at 2200 and 2160 cm⁻¹. The direction and magnitude of this shift in triple bond absorption is consistent with the formation (Scheme 35) of an isocyanide-metal complex (122) in which the isocyanide group forms a σ-bond to titanium via the carbon atom lone pair of electrons. A number of isocyanide-titanium complexes of this type have been prepared and characterised, supporting the mode of coordination shown in structure (122) rather than insertion of the isocyanide into the Ti-Cl bond to give an imino chloride structure, as was originally proposed. If (122) is the intermediate which undergoes hydrolysis to the formamide (115a) it should also be capable of spontaneous cyclisation to give the dibenzoxazepine (118), but this does not happen. The reason for this is unknown and the resolution of this problem would require the elucidation of the precise nature of the isocyanide-titanium tetrachloride interaction. It is possible that coordination of the first equivalent of titanium tetrachloride may involve (116a) acting as a bidentate donor to the metal through a combination of the isocyano group and either of the ether oxygen atoms. Such coordination (Scheme 35) could result in a structure such as (123) which is still activated towards alkaline hydrolysis but is held in the wrong conformation for cyclisation. Addition of further equivalents of the Lewis acid may disrupt this complex to give a structure such as (120), which maintains coordination at all donor sites of the substrate and is capable of cyclisation as well as hydrolysis. Indeed, the use (Table 1, entry 12) of three equivalents of titanium tetrachloride affords a moderate yield of the dibenzoxazepine. Unfortunately however, the absence of any detailed mechanistic investigations means that any attempts to
rationalise the mechanism of this cyclisation reaction must remain tentative at present.

Having demonstrated the successful cyclisation of the methoxy isocyanide (116a) it was next decided to investigate whether the methoxy group was necessary for cyclisation to occur. In order to address this question [(Scheme 33) facing page 27] the analogous 2-phenoxyphenyl isocyanide (116b) was chosen for investigation. This compound was prepared in high overall yield [67% from 2-fluoronitrobenzene (111) and phenol (112b)] by a synthetic route entirely analogous to that used for the methoxy isocyanide (116a), as outlined in Scheme 33. The known nitro compound81 (113b), amine76 (114b), and formamide82 (115b) all had melting points in good agreement with the literature values. As with all of the liquid isocyanides described in this thesis, the previously undescribed isocyanide (116b) was found to be unstable towards storage, darkening quickly at room temperature. Consequently it proved impossible to obtain a satisfactory combustion analysis and (116b) was characterised by high resolution mass spectrometry and its other spectroscopic data.

Application (Scheme 34) of the cyclisation conditions which succeeded with the methoxy derivative (116a) (i.e. heating under reflux with five equivalents of titanium tetrachloride in methylene chloride) to the parent isocyanide (116b) failed to give the anticipated dibenz[b,f][1,4]oxazepine (119) and yielded instead a mixture of the formamide (115b) (61%) and the amine (114b) (16%). This result demonstrates that coordination of the isocyanide (116b) with the Lewis acid does take place but the adjacent phenyl ring is insufficiently nucleophilic for cyclisation to occur. With cyclisation thus precluded, the complexed isocyanide undergoes simple hydrolytic conversion to the formamide (115b) and hence the amine (114b) is also observed as a product.
(i) NaH, DMF, 100°.
(ii) H₂, 10% Pd-C, EtOAc, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Bu₃N, Cl(CH₂)₂Cl, 60°.
(v) TiCl₄, CH₂Cl₂, -10°.
Having established that the success of cyclisation of the type [(116a) \( \rightarrow \) (118)] is dependent on the phenyl ring involved in ring closure being substantially nucleophilic, it was of interest to explore the effect on the course of cyclisation of substituents in the other phenyl ring. This was considered pertinent in view of the proposal\(^8\) that an isocyano group on a phenyl ring can interact strongly with a para electron-withdrawing or electron-donating group. On this basis it might be predicted that para electron-withdrawing groups in this ring would hinder cyclisation by reducing the electron density at the isocyano group and consequently suppressing coordination with the Lewis acid, and vice-versa for electron-donating groups. To evaluate the effect of a moderately electron-withdrawing substituent it was decided to investigate the Lewis acid promoted cyclisation (Scheme 36) of the 4-chlorophenyl isocyanide derivative (128). This substrate was readily synthesised in moderate overall yield [49% from 2,4-dichloronitrobenzene (124) and 3-methoxyphenol (112a)] in an entirely analogous fashion to the compounds (116a) and (116b), as outlined in Scheme 36. The isocyanide derivative (128) was found to be particularly unstable, visibly darkening within minutes of isolation, and so could not be purified beyond flash-chromatography. This observation is not surprising as Ugi and Meyr\(^6\) have also noted the relative instability of 2- and 4-chlorophenyl isocyanides. In addition, Hammick \textit{et al.}\(^7\) have reported the following order of instability of para substituted isocyanides towards spontaneous decomposition: (Cl > CH\(_3\) > OCH\(_3\)).

Cyclisation of the isocyanide (128) was attempted by its reaction with five equivalents of titanium tetrachloride in methylene chloride at low temperature, however the dibenzoxazepine (129) was not formed and the only product obtained was the formamide (127), in good yield (69%). This lack of reactivity is difficult to rationalise since once coordination occurs at the
(i) NaH, DMF, 100°.
(ii) 15% aq. TiCl₃, tetrahydrofuran, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(v) POCl₃, i-Pr₂NEt, CH₂Cl₂, room temp. (X=Br).

Scheme 37
isocyano group cyclisation should follow as the adjacent phenyl ring is known to be sufficiently nucleophilic [see Scheme 34; (116a) \(\rightarrow\) (118)]. The absence of any cyclised product therefore suggests that coordination has not occurred. On the other hand, this conclusion is inconsistent with the formation of the formamide (127) which, as already discussed, is derived from the coordinated isocyanide rather than the isocyanide itself. In the absence of further information the reasons underlying this observation are not clear and could only be elucidated by further mechanistic studies, which were outwith the scope of the present investigations.

As discussed previously (see Chapter 1, Section 1.2.2) the insertion of isocyanides into organometallic reagents to give synthetically useful metalloaldimines is well known, and it was envisaged that this aspect of reactivity could be exploited to develop a synthetic route to tricyclic heteropines. In order to investigate the potential of such reactivity in this respect (Scheme 37) the halogenated isocyanide derivatives (134a) and (134b), which were expected to serve as precursors to organometallic compounds suitable for intramolecular cyclisation onto the proximate isocyano group, were chosen for study. It was anticipated that metallation at the halogen atom would give rise to an organometallic species into which the isocyanide would insert to give a C-11 metallated dibenzoxazepine. The cyclised product would then be capable of further elaboration at the metallated position.

In practice (Scheme 37) the sodium hydride promoted reaction of 2-fluoronitrobenzene (111) with 2-bromophenol (130a) gave the required nitro compound (131a) in excellent yield (93%). Unfortunately however, the attempted catalytic hydrogenation of this compound to give the amine (132a) resulted in debromination as well as nitro group reduction, the sole product isolated being 2-phenoxyaniline hydrobromide (70%). In contrast, the use of
titanium trichloride in aqueous tetrahydrofuran (THF) as the reducing agent gave the required amine (132a), although in variable yield. It was found that a ten fold excess of titanium trichloride is required for the optimum yield of the amine (132a) (88%), although the reason for this is not clear. A long reaction time (65-70h) was also found to be necessary and reduction of this lowers the yield of amine (71%), particularly if the excess of titanium trichloride is simultaneously reduced (32%). The amine (132a) was then converted into the formamide (133a) (91%) and thence into the isocyanide (134a) (63%) by the previously described formylation and dehydration procedures. The isocyanide (134a) was later obtained in a substantially improved yield (86%) through a modification of the phosphoryl chloride-diisopropylamine procedure reported by Ugi et al., in which diisopropylamine was replaced with the more basic N-ethyldiisopropylamine. All of the previously undescribed compounds (131a) to (134a) exhibited analytical and spectroscopic properties fully in accord with their assigned structures.

\[(134) \xrightarrow{(i)-(v)} (139)\]

(i) n-butyllithium, tetrahydrofuran, -78° (X = Br).
(ii) Bu3SnH, azo-bis-isobutyronitrile, benzene, reflux (X = Br).
(iii) Mg, Et2O, reflux.
(iv) Mg, tetrahydrofuran, reflux (X = I).
(v) Mg, (n-Bu)2O, 80-85° (X = I).

Scheme 38
The initial efforts (Scheme 38) to cyclise the bromo isocyanide (134a) were aimed at the preparation of dibenz[b,f][1,4]oxazepine (119). Disappointingly however, attempted metal exchange with the bromine atom by reaction of the isocyanide (134a) with n-butyllithium in THF at -78° gave only an intractable mixture from which no identifiable material was obtained. The ability of isocyanides to participate in radical reactions is well documented, but an attempt to induce cyclisation of the isocyanide (134a) by reaction with tributyltin hydride in refluxing benzene afforded an 81% recovery of the unchanged starting material (134a) as the only identifiable product. The reasons for the failure of these reactions are not clear, but it is known that butyllithium can cause dimerisation of isocyanides and that tributyltin hydride can reduce isocyanides to the corresponding hydrocarbons, and these complicating side reactions may be contributory factors. In an effort to effect cyclisation via a Grignard reagent the isocyanide (134a) was heated under reflux with magnesium metal in ether, but this gave a product mixture containing only unchanged isocyanide and the formamide (133a), the latter being formed by hydrolysis of the isocyanide (134a) in the acidic work-up.

In view of the lack of reactivity observed with the bromo isocyanide (134a) it was next decided to investigate its iodo analogue (134b), which it was hoped would be more reactive towards Grignard formation. This compound was readily prepared in an entirely analogous manner to its bromo analogue (134a), as shown in Scheme 37. The sodium hydride promoted reaction of 2-fluoronitrobenzene (111) with 2-iodophenol (130b) gave the nitro compound (131b) (93%), which was recovered unchanged in good yield from attempted catalytic hydrogenation in ethyl acetate (78%) and in acetic acid (86%). The desired amine (132b) was eventually obtained in moderate yield (68%) by reduction of the nitro compound (131b) with ten equivalents of aqueous titanium trichloride solution, and this was converted into the
formamide (133b) (94%) and thence into the isocyanide (134b) (75%) by the standard procedures. Although the previously undescribed compounds (131b), (132b), and (134b) exhibited satisfactory analytical and spectroscopic properties, the formamide (133b) consistently failed to produce an acceptable combustion analysis and so was characterised by high resolution mass spectrometry along with the rest of its spectroscopic data.

The attempted reaction of the iodo isocyanide (134b) with magnesium in refluxing ether failed to give the desired dibenzoazepine (119), and only a product mixture containing unchanged isocyanide (134b) and the formamide (133b) was obtained. Attempts to encourage Grignard formation by conducting the reaction either in THF under reflux or in di-n-butyl ether at 80-85° were similarly unsuccessful, again giving only a mixture of the isocyanide (134b) and the formamide (133b). The recovery of the isocyanides (134a) and (134b) and the formamides (133a) and (133b) as the sole reaction products illustrates that the halogen atom is apparently unreactive towards Grignard formation. The reason for this is unknown at present, but may involve some inactivation of the magnesium by an interaction with the isocyano group.

The failure of the preceding organometallic reactions prompted a reinvestigation of the possibility of introducing functionality into the cyclised product by reaction of the isocyanide (116a) with an acid chloride, followed by ring closure. Although the attempted insertion of (116a) into the C-Cl bond of acid chlorides was previously shown to be unsuccessful (see Scheme 34), it was envisaged that complexation of acetyl chloride with a Lewis acid prior to reaction with the isocyanide would not only encourage insertion into the C-Cl bond, but the Lewis acid present would also promote cyclisation of the intermediate α-ketoimidoyl chloride.
(i) NaCN, AcOH, room temp.
(ii) KCN, AcOH, room temp.
(iii) NaCN, EtOH, room temp.
(iv) see Table 2.
(v) NaN₃, AcOH, room temp.

Scheme 40
Accordingly (Scheme 39) the isocyanide (116a) was heated under reflux in methylene chloride with a preformed aluminium trichloride-acetyl chloride mixture, but these conditions produced only an intractable polymeric solid. Heating (116a) under reflux in methylene chloride with a titanium tetrachloride-acetyl chloride mixture afforded the 11-unsubstituted dibenzoxazepine (118) (22%) as the only identifiable product, while running the same reaction at -10° gave only a complex mixture with no evidence for the formation of the desired 11-acetyldibenzoxazepine (135). It is therefore apparent that the reaction of isocyanides with Lewis acid-acid chloride complexes is not a viable route to structures such as (135) because the free Lewis acid, which is in equilibrium with the acid chloride complex, interacts with the isocyano group and results either in polymerisation or cyclisation of the isocyanide, depending on its nature.

As a result of the incompatibility of the Lewis acid promoted cyclisation of the isocyanide (116a) with the introduction of functionality into position 11 of the dibenzoxazepine (118), it was next decided to investigate the direct functionalisation of (118) by reaction at the C-N double bond. Although very
Table 2: Oxidation Reactions of 11-Cyano-3-methoxy-10,11-
dihydrobenz[b,f][1,4]oxazepine (138)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidising Agent</th>
<th>Solvent</th>
<th>Reaction Temp. (°C)</th>
<th>Time (h)</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(137)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(136)</td>
</tr>
<tr>
<td>1</td>
<td>MnO₂</td>
<td>DME</td>
<td>room temp.</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>MnO₂</td>
<td>CH₂Cl₂</td>
<td>room temp.</td>
<td>0.5</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>MnO₂</td>
<td>AcOH</td>
<td>room temp.</td>
<td>0.5</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>MnO₂</td>
<td>MeCN</td>
<td>room temp.</td>
<td>67.5</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>MnO₂</td>
<td>MeCN</td>
<td>room temp.</td>
<td>0.5</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>MnO₂</td>
<td>MeCN</td>
<td>room temp.</td>
<td>0.5</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>Pb(OAc)₄</td>
<td>MeCN</td>
<td>room temp.</td>
<td>0.5</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>NaOCl</td>
<td>dioxane/H₂O</td>
<td>room temp.</td>
<td>0.5</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>10% Pd-C</td>
<td>MeCN</td>
<td>room temp.</td>
<td>0.5</td>
<td>0</td>
</tr>
</tbody>
</table>

a, t.l.c. indicated that remaining material contained the product (137), starting material (136), and 3-methoxydibenzo[b,f][1,4]oxazepine (118); b, t.l.c. indicated that the remaining material contained the product (137) and starting material (136); c, t.l.c. indicated the remaining material to be a complex mixture; d, t.l.c. indicated that the remaining material contained the product (137) and 3-methoxydibenzo[b,f][1,4]oxazepine (118); e, t.l.c. indicated that the remaining material contained starting material (136) and 3-methoxydibenzo[b,f][1,4]oxazepine (118).
little chemistry of this type pertaining to dibenzoxazepines has been reported, the acid promoted addition of cyanide ion to imines in general is a well documented reaction and provided an attractive point of departure for this study. Thus (Scheme 40) reaction of the dibenzoxazepine (118) with four equivalents of sodium cyanide in acetic acid at room temperature gave the cyclic amino nitrile derivative (136) in high yield (83%). Conducting the reaction in a closed system in an attempt to prevent the escape of hydrogen cyanide surprisingly caused a drop in the yield (48%), but the cyano product was eventually obtained in near quantitative yield (95%) by using potassium cyanide in acetic acid. The requirement for the presence of acid was demonstrated by the absence of any cyanide addition product when the dibenzoxazepine (118) was treated with sodium cyanide in ethanol, with the starting material being recovered unchanged in high yield (91%). The amino nitrile (136) was found to be extremely prone to loss of hydrogen cyanide and consequent regeneration of the dibenzoxazepine (118), which was obtained in 86% yield upon attempted distillation of (136). Consequently a satisfactory combustion analysis could not be obtained and (136) was characterised by high resolution mass spectrometry and proton and carbon n.m.r. spectroscopy.

A number of attempts were made (Scheme 40) to oxidise the amino nitrile derivative (136) to the unsaturated 11-cyanodibenzoxazepine (137), and the results of these studies are shown in Table 2. Manganese dioxide was found to be the best oxidising agent (Table 2, entries 1-6), although yields were generally low and at best never exceeded 50%. The optimum oxidation conditions with manganese dioxide combined a long reaction time with ambient temperatures (Table 2, entry 4), and indeed heating of the reaction mixture was found to be detrimental (Table 2, entries 5 and 6) due to the competing thermal elimination of hydrogen cyanide from (136). Lead
(i) HCl, H₂O, EtOH, reflux.
(ii) HCl(g), EtOH, 0°.
(iii) HCl(g), Et₂O, 0°.
(iv) Ac₂O, 100° then room temp.
(v) MeCOCI, Et₂O, room temp. then 0°.

Scheme 41
tetraacetate (Table 2, entry 7) and aqueous sodium hypochlorite solution (Table 2, entry 8) were also found to effect oxidation of (136) under mild conditions, although yields of the cyanodibenzoxazepine (137) were extremely low. Attempted dehydrogenation (Table 2, entry 9) of the amino nitrile (136) using 10% palladium-on-charcoal failed to give any oxidised product, with the unchanged starting material being recovered in quantitative yield.

In view of the successful preparation of the amino nitrile (136) it was decided to attempt (Scheme 40) to prepare the amino azide (138) by an analogous reaction of the dibenzoxazepine (118) with sodium azide in acetic acid but this was surprisingly unsuccessful, giving only a quantitative recovery of the unchanged starting material (118). The formation of the amino azide (138) at some stage in the reaction cannot be excluded however, as its expected instability towards loss of hydrogen azide could lead to regeneration of the dibenzoxazepine (118) during isolation. Similarly poor results were obtained from the attempted reactions of the dibenzoxazepine (118) with a number of other nucleophiles. Thus unreacted starting material was obtained in high yields (86-100%) from reaction of (118) with aqueous or ethanolic dimethylamine solution at room temperature, with sodium ethoxide in refluxing ethanol, and with the anion of diethyl malonate in DMeF at 100°. All of these reactions were conducted in basic media, however, and their failure may be ascribed to the absence of any acid catalysis to facilitate addition to the C-N double bond of the dibenzoxazepine (118).

The electrophilic reactions of imines with alkylating agents to afford imminium salts are also well known, and in view of the limited success of nucleophilic addition to the dibenzoxazepine (118) its reactions with electrophiles were considered worthy of investigation. Thus (Scheme 41) the dibenzoxazepine (118) was heated under reflux with aqueous hydrochloric
acid solution in ethanol, and these conditions gave a poor yield (38%) of 3-methoxydiben zb,f][1,4]oxazepine hydrochloride (139). Hydrogen chloride gas was found to be a more effective reagent, giving the hydrochloride salt (139) in excellent yield (90%) upon reaction with the dibenzoxazepine (118) in ethanol at 0°. Conducting the same reaction in ether caused a surprising reduction in the yield (62%) of the salt (139). This product was found to have a certain instability towards crystallisation and storage and so a satisfactory combustion analysis could not be obtained, although characterisation of the salt (139) was made through its other spectroscopic properties. The identity of (139) was further confirmed by its treatment with 10% w/v aqueous sodium hydrogen carbonate solution, which gave the dibenzoxazepine (118) in quantitative yield. In view of the ready formation of the hydrochloride salt (139) the addition of acetylacetone to the dibenzoxazepine (118) in the presence of hydrogen chloride gas was attempted, but gave only a quantitative recovery of the unchanged starting material. Similarly unsuccessful was the attempted alkylation on nitrogen by reaction of the dibenzoxazepine (118) with methyl iodide at room temperature which failed to give the anticipated quaternary imminium salt and afforded instead a quantitative recovery of the starting material (118).

The reaction of the dibenzoxazepine (118) with acylating agents were also investigated (Scheme 41) and were found to be more facile than the analogous alkylation reactions. While the reaction of the dibenzoxazepine (118) with acetic anhydride at 100° or with acetyl chloride at 0° failed to give the hoped for N-acetyl imminium salts (140a) and (140b), the disubstituted benzaldehyde derivative (141) was isolated in 46% and 53% yields respectively. The formation of this ring opened product confirms the formation at some stage of the imminium salts (140a) and (140b) which, as might be expected for such reactive compounds, suffer hydrolysis during
isolation to give the benzaldehyde derivative (141). This result therefore illustrates the possibility that functionalisation at C-11 of the dibenzoxazepine (118) could be effected by quaternisation of the imine nitrogen atom with an acylating agent followed by treatment with an appropriate nucleophile, by analogy with the well known\textsuperscript{88} formation of Reissert compounds from quinolines and isoquinolines.

A report by Brewster et al\textsuperscript{89} describes the oxidation of the dibenzoxazepine (118) with peracetic acid to give a mixture of rearranged products, the formation of which is ascribed to acid catalysed side reactions of the intermediate oxaziridine. In an attempt to circumvent these wasteful side reactions the oxidation of the dibenzoxazepine (118) in basic media was studied. The attempted reactions of (118) with alkaline hydrogen peroxide or with aqueous sodium hypochlorite solution at room temperature were unsuccessful however, giving only unchanged starting material in 67% and 100% yields respectively.

In view of the inability of the isocyanide (116a) to allow access to functionalised dibenzoxazepines and the difficulty encountered in attempting to directly functionalise the dibenzoxazepine (118), it was next decided to investigate the potential of the corresponding isocyanide dihalides as cyclisation substrates. As previously mentioned (Chapter 1, Section 1.3.2; Scheme 25) phenyl isocyanide dichloride had been reported\textsuperscript{8} to react with anisole in the presence of a Lewis acid to give the iminochloride (71), and it was anticipated that this type of reactivity could be manipulated in an intramolecular sense to afford C-11 halogenated dibenz[b,f][1,4]oxazepines, as outlined in Section 2.1 [Scheme 31; (97) $\rightarrow$ (98) $\rightarrow$ (99)]. It was also expected that the halogen atom in the cyclised products (99) would be available for further elaboration by nucleophilic displacement reactions, allowing access to a wide variety of C-11 substituted dibenzoxazepines.
(i) SO$_2$Cl$_2$, CH$_2$Cl$_2$, -10$^\circ$.  
(ii) Br$_2$, CH$_2$Cl$_2$, -10$^\circ$.  
(iii) AlCl$_3$, CH$_2$Cl$_2$, reflux.  
(iv) AlBr$_3$, CH$_2$Cl$_2$, -10$^\circ$.  

Scheme 42
In practice (Scheme 42) reaction of the isocyanide (116a) with an equimolar quantity of sulphuryl chloride or bromine in methylene chloride at -10° furnished the isocyanide dichloride (142a) and dibromide (142b) respectively, both in quantitative yield. As with all isocyanide dihalides described in this thesis, (142a) and (142b) were found to be extremely unstable, being readily hydrolysed by atmospheric moisture immediately upon isolation. As a result of this instability (142a) and (142b) were characterised only on the basis of their i.r. spectra, with the latter showing the characteristic C-N double bond absorption at 1650 cm\(^{-1}\) for the dichloride (142a) and at 1690 cm\(^{-1}\) for the dibromide (142b). All isocyanide dihalides described in this thesis have been prepared separately for characterisation purposes, but their cyclisation reactions were carried out in a one-pot procedure involving sequential treatment of the appropriate isocyanide with the halogenating agent followed by the Lewis acid.

Cyclisation of the isocyanide dichloride (142a) was first attempted by heating under reflux in methylene chloride with a two fold excess of aluminium trichloride but these conditions failed to produce the desired 11-chlorodibenzoxazepine (143a), giving instead a complex mixture which proved unresolvable by chromatography. Similarly, reaction of the isocyanide dibromide (142b) with a two fold excess of aluminium tribromide in methylene chloride at -10° gave only an intractable mixture from which no identifiable material was obtained. The failure of these reactions is somewhat surprising as the isocyanide dihalides (142a) and (142b) contain a highly activated aromatic ring which would be expected to react readily under Friedel-Crafts conditions. It has been demonstrated\(^9\) however that the use of an excess of Lewis acid with polyether aromatic systems can lead to a complete reversal of the electron donating ability of the ether oxygen atoms due to complexation with the Lewis acid, and consequent deactivation of the aromatic ring. In
Scheme 43

(i) Br₂, CH₂Cl₂, -10°.
(ii) AlBr₃, CH₂Cl₂, reflux (R = H).
(iii) AlBr₃, CH₂Cl₂, room temp. (R = Br).

(a; H) s; (b; Br)
such cases, ether cleavage by the excess of Lewis acid can also be a significant side reaction. In order to overcome this problem it was decided to investigate (Scheme 43) the Lewis acid promoted cyclisation of the unsubstituted isocyanide dibromide (144a), which should not be subject to the same complication. Thus (Scheme 43) reaction of 2-phenoxyphenyl isocyanide (116b) with bromine at -10° gave the isocyanide dibromide (144a) in quantitative yield which, on reaction with two equivalents of aluminium tribromide under reflux in methylene chloride, gave 11-bromodibenz[b,f][1,4]oxazepine (145a) in high yield (79%). This result confirms that only one ether oxygen atom is tolerated in the cyclisation substrate under these conditions. The bromodibenzoazepine (145a) exhibited considerable instability towards storage and partially decomposed to the corresponding lactam (146) during crystallisation from light petroleum, as indicated by t.l.c and the appearance of i.r. absorptions at 3180 cm⁻¹ and 1676 cm⁻¹ corresponding to the lactam N-H and C=O groups respectively. Further crystallisations from light petroleum-toluene and then from ethanol caused complete conversion of (145a) to the lactam (146). Consequently a pure sample of the bromodibenzoazepine (145a) could not be obtained for combustion analysis and this compound was characterised by high resolution mass spectrometry along with its other spectroscopic data.

The successful cyclisation of the isocyanide dibromide (144a) demonstrates that activation of the adjacent phenyl ring by an electron-donating group is not required for cyclisation, unlike the cyclisation of the corresponding isocyanide. In order to further assess the electronic factors governing the reactivity of this attacking ring, the cyclisation (Scheme 43) of the bromo isocyanide dibromide (144b), in which the bromine atom exerts a deactivating effect on the ring, was investigated. The required isocyanide dibromide (144b) was readily prepared in 100% yield by low temperature
(i) NaH, piperidine, DMF, 100° (R = H).
(ii) NaH, piperidine, DMF, room temp. (R = Br).
(iii) (Et$_3$N)$_\text{+}$ (CN)$_\text{−}$, MeCN, room temp.
(iv) NaN$_3$, DMF, 100° (R = H).

Scheme 44
bromination of the isocyanide (134a), and on reaction with two equivalents of aluminium tribromide in methylene chloride at room temperature this compound yielded the 4,11-dibromodibenzoxazepine derivative (145b) in excellent yield (80%). This result illustrates that even a moderately deactivated aromatic ring can participate in cyclisation with an isocyanide dibromide under mild conditions, greatly enhancing the scope of the reaction and demonstrating its superiority over the Lewis acid promoted cyclisation of isocyanides. In mechanistic terms the cyclisation of isocyanide dihalides can be viewed as being analogous to the Friedel-Crafts acylation of aromatic rings with acid chlorides, however a more detailed discussion of the mechanism will be deferred until Chapter 3, Section 3.2.

A key feature of the isocyanide dihalide cyclisation was the expected synthetic potential of the cyclised product via manipulation of the reactive halogen at the imine bridge. The instability of the bromodibenzoxazepines (145a) and (145b) towards moisture suggested that the bromine atom should be readily displaceable, and this was confirmed by their successful reactions with a number of nucleophiles (Scheme 44). In terms of biological activity the optimum substituent at the C-11 position of dibenzoxazepines is an alkylamino group. Accordingly, the sodium hydride promoted reaction of the bromodibenzoxazepine (145a) with piperidine in DMF at room temperature furnished the piperidinodibenzoxazepine derivative (147a) in moderate yield (64%). Similarly, reaction of (145a) with tetraethylammonium cyanide in acetonitrile and with sodium azide in DMF gave the 11-cyanodibenzoxazepine (148a) (100%) and the tetrazolodibenzoxazepine (149a) (94%) derivatives respectively. The dibromodibenzoxazepine (145b) reacted analogously with sodium piperidide to give the piperidinodibenzoxazepine derivative (147b) in good yield (76%), and also with tetraethylammonium cyanide to afford the cyano dibenzoxazepine...
(i) NaH, DMF, 100°.
(ii) 15% aq. TiCl₃, tetrahydrofuran, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(v) TiCl₄, CH₂Cl₂, reflux (R = OMe).

Scheme 45
derivative (148b) in quantitative yield. The piperidino derivative (147b) was accompanied by a small amount of the corresponding lactam (150), presumably formed by reaction of the bromodibenzoazepine (145b) with traces of water present in the piperidine. All of the previously undescribed compounds, (147) to (150), in this sequence were fully characterised by their analytical and spectroscopic properties.

The ease of introduction of various functionalities into the tricyclic nucleus by this method demonstrates the real synthetic potential of cyclic intermediates such as (145a) and (145b). Their scope is further extended by the fact that the functionality so introduced may be manipulated to allow access to an increasingly wide range of structures. For example the cyano group could lead to the carboxylic acid or the methyleneamine by hydrolysis or reduction respectively, and the tetrazole moiety could serve as a source of a primary amine via the phosphineimine.

2.3 SYNTHESIS OF DIBENZOB,F][1,4]THIAZEPINE DERIVATIVES

The dibenzo[b,f][1,4]thiazepines are of considerable chemical and biological interest due to their antihistaminic and antianaphylactic activity, and as previously mentioned (Section 2.1) a number of synthetic strategies have been used for their preparation. With the successful cyclisation of isocyanides and isocyanide dihalides to give dibenzoxazepines having been demonstrated however (Section 2.2), it was decided to investigate the applicability of this reaction to the synthesis of the corresponding dibenzo[b,f][1,4]thiazepines.

Due to its structural similarity (Scheme 45) to the methoxyphenoxy phenyl isocyanide (116a) described in Section 2.2, the methoxyphenylthio phenyl isocyanide (156a) was initially selected for study. Thus (Scheme 45) the methoxynitro thioether (153a) was prepared in near quantitative yield.
(98%) by the sodium hydride promoted reaction of 2-chloronitrobenzene (151) with 3-methoxythiophenol (152a), as previously described by Weddell.\textsuperscript{76} Reduction of this compound with aqueous titanium trichloride solution at room temperature then gave the amine (154a), although in poor yield (49%). This low yield may be attributed to the use of only seven equivalents of titanium trichloride, as it was later discovered that ten equivalents are needed to maximise the yield of titanium trichloride reductions in general. The amine (154a) was easily converted into the formamide (155a) (82%) and thence into the isocyanide (156a) (73%) by the standard formylation and dehydration protocols.

Application of the cyclisation conditions initially found to be successful in the preparation of the dibenzoazepine (118) (i.e. heating under reflux in methylene chloride with five equivalents of titanium tetrachloride) to the isocyanide (156a) afforded the desired 3-methoxydibenzo[b,f][1,4]thiazepine (157a) in moderate yield (62%) after distillation. The analytical and spectroscopic characteristics of the cyclic product (157a) were fully confirmative of its assigned structure, and examination of its proton n.m.r. spectrum indicated that the product obtained was exclusively the 3-methoxy isomer. This spectrum contained a one proton doublet ($J = 8.3$ Hz) centred at $\delta 7.29$ which corresponds to H-1, a second doublet ($J = 2.5$ Hz) centred at $\delta 6.95$ can be assigned to H-4, while the double doublet ($J = 8.3, 2.5$ Hz) centred at $\delta 6.84$ corresponds to the proton at position 2. This splitting pattern in the substituted ring of the cyclised product is consistent only with the 3-methoxy isomer (157a), and excludes the presence of the corresponding 1-methoxydibenzothiazepine. This regioselectivity of cyclisation is attributed to the same steric factors which were discussed in relation to the dibenzoazepine (118) in Section 2.2.
(i) Br₂, CH₂Cl₂, -10°C.
(ii) AlBr₃, CH₂Cl₂, reflux.
(iii) NaH, piperidine, DMF, 100°C.
(iv) (Et₄N)⁺(CN)⁻, MeCN, room temp.

Scheme 46
Although the yield of the dibenzothiazepine (157a) is somewhat lower than expected, this should be improvable by lowering the reaction temperature and avoiding distillation in favour of chromatography as the method of product isolation. Notwithstanding the low yield, this procedure appears to be considerably simpler than a recently patented route to 11-unsubstituted dibenzo[b,f][1,4]thiazepines which involves preparation of the corresponding lactams, chlorination of the latter with phosphorus pentachloride and phosphoryl chloride, and final reductive dechlorination to give the product.

Although the successful cyclisation of the isocyanide (156a) was pleasing, the absence of any functionality at position 11 of the product dibenzothiazepine (157a) was a drawback and this prompted an investigation of the isocyanide dibromide cyclisation as a source of more diverse structures. Since previous work (see Section 2.2) had demonstrated that activation of the phenyl ring involved in ring closure was not necessary for the successful cyclisation of isocyanide dibromides, the unsubstituted isocyanide [Scheme 45; (156b)] was selected as a suitable substrate. This compound was prepared by an analogous route to that used for its methoxy analogue, as outlined in Scheme 45.

Reaction of 2-fluoronitrobenzene (222) with the anion of thiophenol (152b) gave the known nitrodiphenylsulphide (153b) in excellent yield (94%), and this was subsequently converted into the known amine (154b) by reduction with ten equivalents of titanium trichloride at room temperature. Formylation of the amine (154b) gave the formamide (155b) (93%) which was then transformed into the desired isocyanide (156b) (85%) by the standard dehydration procedure.

Reaction (Scheme 46) of the isocyanide (156b) with one equivalent of bromine in methylene chloride at -10° then gave the isocyanide dibromide
(i) KF, 180°.
(ii) NaH, PhCH$_2$Br, DMF, room temp.
(iii) H$_2$, 10% Pd-C, EtOAc($R = OMe$) or DMF($R = H$), room temp.
(iv) 98-100% HCO$_2$H, reflux.
(v) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60°.

Scheme 47
(158) in quantitative yield. Reaction of this compound with two equivalents of aluminium tribromide under reflux in methylene chloride gave the desired 11-bromodibenzothiazepine (159) in good yield (78%) (56% overall yield from 2-fluoronitrobenzene and thiophenol). The bromodibenzothiazepine (159) proved to be rather unstable towards moisture and so a satisfactory combustion analysis proved unattainable, and characterisation of this compound was made by high resolution mass spectrometry along with its other spectroscopic data.

The synthetic utility of the bromodibenzothiazepine (159) was demonstrated by its reaction (Scheme 46) with sodium piperidide in DMF at 100° to afford the known94 11-piperidinodibenzothiazepine (160) in 73% yield, and with tetraethylammonium cyanide in acetonitrile at room temperature to give the previously undescribed 11-cyano derivative (161) in similarly high yield (79%). The use of 11-chlorodibenzothiazepines as intermediates for the preparation of functionalised tricyclic systems had been reported previously,95 but as is the case with the majority of tricyclic heteropines the 11-chloro intermediate is usually prepared by chlorination91 of the corresponding lactam. The Lewis acid promoted cyclisation of isocyanide dihalides not only eliminates the need for this frequently harsh step, but also allows the direct construction of the 11-bromodibenzothiazepines which, due to their greater reactivity, are more synthetically useful than the analogous 11-chloro compounds.

2.4 SYNTHESIS OF DIBENZO[b,e][1,4]DIAZEPINE DERIVATIVES

Of all the tricyclic heteropines, the dibenzodiazepines have generated the most interest as a result of their extremely wide ranging biological properties. Consequently a large number of compounds of this type have been prepared, and most preparations rely on one of the three major
(i) TiCl₄, CH₂Cl₂, reflux.
(ii) Br₂, CH₂Cl₂, -10°.
(iii) SO₂Cl₂, CH₂Cl₂, -10°.

Scheme 48
synthetic strategies outlined in Section 2.1. As previously mentioned however, these routes can often suffer from troublesome drawbacks and it was therefore considered of interest to explore the potential of the Lewis acid promoted cyclisations of isocyanides and isocyanide dihalides in the synthesis of these important compounds.

The successful cyclisations of the methoxy isocyanides (116a) (Section 2.2) and (156a) (Section 2.3) immediately suggested the analogous (Scheme 47) methoxyphenylaminophenyl isocyanide derivative (167a) as a substrate for initial study. The synthesis (Scheme 47) of this compound began with the known methoxynitrodiphenylamine (163a) which was prepared in excellent yield by the potassium fluoride promoted coupling of 2-fluoronitrobenzene (111) with 3-methoxyaniline (162a). This compound was subsequently converted into the N-benzylnitrodiphenylamine (164a) (82%) and thence into the corresponding amine (165a) (66%) by literature procedures. Heating the amine (165a) under reflux in formic acid gave the formamide (166a) in good yield (76%), which was then converted into the isocyanide (167a) (83%) by the standard dehydration protocol. The previously undescribed formamide (166a) and isocyanide (167a) both had analytical and spectroscopic properties which were fully in accord with their assigned structures.

Cyclisation of the isocyanide (167a) was then attempted (Scheme 48) by heating under reflux in methylene chloride with five equivalents of titanium tetrachloride, but these conditions failed to give the desired N-benzyldibenzodiazepine (168a) and only a complex mixture which proved inseparable by chromatography was obtained. The failure of this reaction is somewhat surprising in light of the successful preparations of the analogous dibenzoxazepine (Section 2.2) and dibenzothiazepine (Section 2.3), and the reasons for this are not known at present. Accordingly, further investigations into this reaction were terminated at this point and attention was turned to the
cyclisation of isocyanide dihalides as a potential synthetic route to dibenzodiazepines.

As electronic activation of the phenyl ring participating in the ring closure step had previously been shown to be unnecessary for the cyclisation of isocyanide dibromides (see Sections 2.2 and 2.3), the easily accessible unsubstituted phenylaminophenyl isocyanide derivative (167b) was first investigated. This compound was prepared in moderate overall yield [40% from 2-fluoronitrobenzene (111) and aniline (162b)] by a route entirely analogous to that employed for its methoxy analogue (167a), as outlined in Scheme 47. The known nitrodiphenylamine (163b) had a melting point consistent with the literature value and all other compounds, (164b) to (167b), in this sequence had analytical and spectroscopic characteristics fully in accord with their assigned structures.

Reaction (Scheme 48) of the isocyanide (167b) with one equivalent of bromine in methylene chloride at -10° unexpectedly failed to give the anticipated isocyanide dibromide (169c), and only a multicomponent oil which proved inseparable by chromatography was obtained. Similarly unsuccessful was the reaction of the isocyanide (167b) with sulphuryl chloride at -10°, which also gave a multicomponent product mixture from which no identifiable material was obtained. As no characterisable products were isolated from these reactions the fate of the isocyanide (167b) upon attempted halogenation is not known. It is reported however that the N-benzyl protecting group reacts with both chlorine and bromine without generation of the deprotected amine, and this is a probable competing reaction. In addition, the freely available lone pair of the tertiary nitrogen atom will provide considerable activation of the unsubstituted aromatic ring and may lead to competing ring halogenation. This latter possibility seems less likely, however, as the highly activated aromatic ring in the methoxy isocyanide
(i) see Table 3 (R = H).
(ii) NaH, TsCl, DMF, 100° (R = Cl).
(iii) 15% aq. TiCl₃, tetrahydrofuran, room temp. (R = H).
(iv) SnCl₂, HCl, H₂O, reflux (R = Cl).
(v) SnCl₂, HCl, H₂O, tetrahydrofuran, room temp. (R = Cl).
(vi) 98-100% HCO₂H, reflux.
(vii) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(viii) POCl₃, i-Pr₂NEt, CH₂Cl₂, room temp. (R = Cl).

(Ts = toluene-4-sulphonyl)
(116a) had previously been shown (Section 2.2; Scheme 42) to be stable under chlorination and bromination conditions.

In view of the complications associated with the N-benzyl protecting group, it was decided to investigate the toluene-4-sulphonyl (tosyl) group as an alternative method of amino protection. It was expected that the use of this protecting group would eliminate any problems associated with benzylic halogenation and, due to electron withdrawal by the sulphonyl group, was also expected to reduce the electronic activation of the unsubstituted aromatic ring. Protection (Scheme 49) of the nitrodiphenylamine (163b) by its sodium hydride promoted reaction with tosyl chloride proved to be more difficult than expected (see Table 3). In contrast to the high yielding benzylation of (163b) its reaction (Table 3, entry 1) with one equivalent of tosyl chloride under similar conditions gave only a poor yield of the desired N-tosyl nitrodiphenylamine (171a). Surprisingly, increasing the reaction temperature and the excess of tosyl chloride (Table 3, entries 2 and 3) caused a reduction in the yield of the protected product (171a). It was suspected that toluene-4-sulphonic acid, which can be a significant contaminant in tosyl chloride, was

<table>
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<th>Entry</th>
<th>(163b):TsCl Ratio</th>
<th>Solvent</th>
<th>Reaction Temp.(°C)</th>
<th>Time (h)</th>
<th>Products (%)</th>
</tr>
</thead>
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<td></td>
<td>(163b)</td>
<td>TsCl</td>
<td></td>
<td></td>
<td>(171a)</td>
</tr>
<tr>
<td>1</td>
<td>1:1</td>
<td>DMF</td>
<td>room temp.</td>
<td>24</td>
<td>41</td>
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<tr>
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<td>1:2</td>
<td>DMF</td>
<td>100</td>
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<tr>
<td>3</td>
<td>1:4</td>
<td>DMF</td>
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<td>1:1a</td>
<td>DMF</td>
<td>100</td>
<td>22</td>
<td>61</td>
</tr>
</tbody>
</table>

a; freshly crystallised tosyl chloride used.
(i) Br₂, CH₂Cl₂, -10°.
(ii) AlBr₃, CH₂Cl₂, reflux.
(iii) AlBr₃, CH₂Cl₂, room temp. (R = Cl).
(iv) NaH, N-methylpiperazine, DMF, 100°.
(v) NaH, N-methylpiperazine, 1,2-dimethoxyethane, reflux.
(vi) N-methylpiperazine, dioxane, reflux.

\[ R \]
\[ a; H \]
\[ b; Cl \]
suppressing the reaction by quenching the anion of the nitrodiphenylamine (163b). In accordance with this suggestion, the yield of the N-tosyl product (171a) was optimised (Table 3, entry 4) by the reaction of (163b) with one equivalent of freshly crystallised tosyl chloride in the presence of sodium hydride.

In light of the unsatisfactory yield of the N-tosyl derivative (171a) obtained by tosylation of the diphenylamine (163b), an alternative strategy for its preparation was sought. It was therefore decided to investigate the reaction of N-toluene-4-sulphonylaminobenzene, which was prepared in 92% yield by the reaction of aniline (162b) and tosyl chloride, with 2-fluoronitrobenzene (111) in the presence of sodium hydride. Unfortunately, however, heating this mixture at 100°C in DMF gave only a good recovery of both starting materials (93% and 63% respectively). Consequently the direct tosylation of the nitrodiphenylamine (163b) remained the favoured route to the N-tosyl derivative (171a). Reduction of (171a) with ten equivalents of titanium trichloride at room temperature gave the amine (172a) in good yield (78%), and this was then converted into the formamide (173a) (86%) and thence into the desired isocyanide (174a) (72%), by the standard formylation and dehydration procedures respectively. The previously undescribed diphenylamine derivatives (171a) to (174a) all exhibited analytical and spectroscopic properties fully in accord with their assigned structures.

It was pleasing to find that the reaction (Scheme 50) of the isocyanide (174a) with bromine at -10°C proceeded smoothly, giving the anticipated isocyanide dibromide (175a) in quantitative yield. This compound readily underwent cyclisation upon heating under reflux in methylene chloride with two equivalents of aluminium tribromide to give the 11-bromo-5-tosyl-dibenzodiazepine derivative (176a), also in quantitative yield. This compound exhibited the now familiar instability towards moisture, and so was
characterised by a combination of combustion analysis, high resolution mass spectrometry, and its i.r. and proton n.m.r. spectra.

A substituent which is commonly found at position 11 of biologically active dibenzodiazepines is the N-methylpiperazine moiety, and it was therefore decided to investigate the introduction of this group into the dibenzodiazepine (176a) by nucleophilic displacement of the bromine atom. Disappointingly however, reaction (Scheme 50) of the bromodibenzodiazepine (176a) with the anion of N-methylpiperazine in DMF at 100° gave only the dibenzodiazepin-11-one (179) (47%) rather than the desired 11-({4-methylpiperazin-1-yl} derivative (177), presumably by reaction of (176a) with traces of water present in the N-methylpiperazine which was not purified prior to use.

Having established the compatibility of the isocyanide dibromide cyclisation reaction with the preparation of the dibenzodiazepine ring system, it was next decided to apply this reaction to the preparation of clozapine (86), an antipsychotic agent currently in use for the treatment of schizophrenia. Clozapine and its analogues have been intensively studied over the last 20-25 years and numerous syntheses have been reported. Hunziker et al. 9 prepared clozapine by the displacement of a chlorine atom or methylthio group from the C-11 position of 8-chlorodibenzo[b,e][1,4]diazepine with N-methylpiperazine, with the reactive starting materials having been prepared from the corresponding lactam and thiolactam respectively. A similar chlorination-displacement procedure has been employed by other workers to prepare numerous clozapine analogues. 100 Wander has reported the preparation of clozapine by the cyclisation of an N-methylpiperazino urea derivative with phosphoryl chloride, 94 and also by the cyclocondensation of an amino amide derivative. 101 As previously mentioned however (Section 2.1), synthetic routes such as those outlined above can require forcing reaction
conditions and can be restricted by inconvenient preparation of the starting materials. It was therefore of interest to prepare clozapine by the cyclisation of an isocyanide dibromide as a comparison with the literature methods.

The required isocyanide (174b) was prepared as shown in Scheme 49. Firstly, displacement of the activated chlorine atom in 2,5-dichloronitrobenzene with aniline under the conditions described by Ullman gave the chlorodiphenylamine (170) in good yield (80%). Reaction of this compound with sodium hydride and two equivalents of fresh tosyl chloride in DMF at 100° gave the N-tosyl derivative (171b) in moderate yield (50%), along with a small amount of unchanged starting material (170) (23%). Reduction of (171b) to give the amine (172b) was accomplished in 74% yield by its reaction with an excess of stannous chloride in refluxing aqueous hydrochloric acid, however it was later discovered that a similar yield of amine (71%) could be obtained by running the reaction at room temperature with THF as co-solvent. The amine (172b) was easily converted into the formamide (173b) (93%) which was then dehydrated with triphenylphosphine, carbon tetrachloride, and triethylamine, or in an improved procedure with phosphoryl chloride and N-ethyl-diisopropylamine, to give the isocyanide (174b) in 52% and 86% yields respectively. All of the previously undescribed compounds (171b) to (174b) in this sequence were fully characterised by their analytical and spectroscopic properties.

Reaction (Scheme 50) of the isocyanide (174b) with one equivalent of bromine at -10° gave the anticipated isocyanide dibromide (175b) in quantitative yield as a moisture-sensitive oil. This was then heated under reflux in methylene chloride with two equivalents of aluminium tribromide to give the desired 11-bromo-8-chlorodibenzodiazepine derivative (176b) in high yield (79%). Conducting the same reaction at room temperature offered no improvement in the yield (67%). The bromodibenzodiazepine (176b) was
Figure 1
### Table 4: Bond Lengths (Angstroms) with Standard Deviations

<table>
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<tr>
<th>Bond</th>
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<th>Bond</th>
<th>Length (Å)</th>
<th>Bond</th>
<th>Length (Å)</th>
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<td>C(1)-C(11A)</td>
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<td>C(2)-C(3)</td>
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<td>C(3)-C(4)</td>
<td>1.364(12)</td>
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<tr>
<td>C(4)-C(4A)</td>
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<td>C(4A)-N(5)</td>
<td>1.434(10)</td>
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<td>C(4A)-C(11A)</td>
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### Table 5: Bond Angles (Degrees) with Standard Deviations

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<th>Angle (°)</th>
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<th>Angle (°)</th>
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<td>C(3)-C(4)-C(4A)</td>
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<tr>
<td>C(4)-C(4A)-N(5)</td>
<td>119.3(6)</td>
<td>C(4A)-N(5)-C(5A)</td>
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<td>N(5)-C(4A)-C(11A)</td>
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<td>C(4A)-N(5)-S</td>
<td>116.4(6)</td>
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<tr>
<td>C(4A)-N(5)-S</td>
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<td>C(5A)-N(5)-S</td>
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<td>N(5)-C(5A)-C(9A)</td>
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<td>C(6)-C(5A)-C(9A)</td>
<td>119.6(8)</td>
<td>C(5A)-C(6)-C(7)</td>
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<td></td>
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<tr>
<td>C(6)-C(7)-C(8)</td>
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<td>C(7)-C(8)-Cl</td>
<td>119.0(7)</td>
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<tr>
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<td>C(7)-C(8)-Cl</td>
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<td>C(8)-C(9)-C(9A)</td>
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<td>120.7(7)</td>
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<td>C(5A)-C(9A)-N(10)</td>
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<td>C(9A)-N(10)-C(11)</td>
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<tr>
<td>N(10)-C(11)-C(11A)</td>
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<td>113.8(6)</td>
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<tr>
<td>C(1)-C(11A)-C(4A)</td>
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<td>C(1)-C(11A)-C(11)</td>
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<tr>
<td>C(4A)-C(11A)-C(11)</td>
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</tr>
<tr>
<td>N(5)-S-O(2)</td>
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<td>C(22)-C(21)-C(26)</td>
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<td>C(22)-C(23)-C(24)</td>
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<tr>
<td>C(23)-C(24)-C(25)</td>
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<td>C(23)-C(24)-C(24m)</td>
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<td>C(25)-C(24)-C(24m)</td>
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<td>C(24)-C(25)-2(26)</td>
<td>122.2(8)</td>
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<td>C(21)-C(26)-C(25)</td>
<td>118.9(9)</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>
(i) Na, NH$_3$(l), -33°.
(ii) Na, n-BuOH, reflux.
(iii) 30% w/v HBr-AcOH, reflux.
(iv) 30% w/v HBr-AcOH, room temp.
(v) conc. H$_2$SO$_4$, AcOH, 100°.

Scheme 51
found to be typically unstable towards moisture and so was characterised by a combination of combustion analysis, high resolution mass spectrometry, and its other spectroscopic data. In addition (Figure 1 and Tables 4 and 5) an X-ray crystal structure of this compound was obtained. This clearly shows that the central seven membered ring is considerably non-planar, allowing the molecule to take on a puckered conformation. The aromatic ring of the tosyl group is positioned underneath the tricyclic nucleus, and there may be a π-stacking interaction between this ring and the chlorinated ring of the dibenzodiazepine.

The N-protected clozapine derivative (178) was prepared (Scheme 50) from the bromodibenzodiazepine (176b) by replacement of the bromine atom with N-methylpiperazine under various conditions. In all cases the N-methylpiperazine had been distilled from calcium hydride prior to use to prevent any competing lactam formation. Reaction of (176b) with the anion of N-methylpiperazine in DMF at 100° gave a lower than expected yield (54%) of the amino product (178), while conducting the reaction under reflux in DME offered no improvement (56%). The optimum yield of the clozapine derivative (178) (88%) was finally obtained by heating the bromodibenzodiazepine (176a) under reflux in dioxane with four equivalents of N-methylpiperazine.

The final step in the preparation of clozapine required (Scheme 51) the deprotection of the diazepine nitrogen atom in (178). This was first attempted by reaction of the N-tosyl clozapine derivative (178) with sodium in liquid ammonia at -33°, however this gave only a good recovery (79%) of the unchanged starting material. Similarly, reaction of (178) with sodium in refluxing n-butanol also failed to furnish clozapine (86), giving instead a poor recovery (38%) of unchanged starting material as the only identifiable product. A commonly used method for the removal of tosyl protecting groups from amines is the reaction with hydrogen bromide, generally under
reflux. Thus the diazepine (178) was heated under reflux with 30% hydrogen bromide in acetic acid for 8h, but this gave only a complex mixture from which no identifiable material was obtained. Conducting the same reaction under reflux for 1h also gave an intractable mixture, while stirring the mixture at room temperature for 1h gave a good recovery (77%) of the unchanged starting material (178), with no evidence for the formation of clozapine. A final attempt to effect deprotection was made by heating the N-tosyl derivative (178) at 100° with concentrated sulphuric acid, but these conditions resulted only in an intractable mixture which was not investigated further.

While the failure of the preceding deprotection reactions to furnish clozapine (86) was disappointing it was not entirely surprising given the fact that the tosyl group is one of the most stable nitrogen protective groups. This indeed is one of its main advantages but it can also be a problem when it comes to deprotection. The deprotection methods attempted in the present study represent those most commonly used for removal of the tosyl group, and although other methods are available, for example perchloric acid, electrolysis, or irradiation, they often involve specialised reaction conditions and are not generally applicable. It is evident therefore that further work is necessary to identify an alternative method of amino protection in the synthesis of dibenzodiazepines by the cyclisation of isocyanide dibromides.

2.5 SYNTHESIS OF PYRIDO[2,3-b][1,4]BENZOXAZEPINES, PYRIDO[3,2-b][1,5]BENZOXAZEPINES, AND PYRIDO [3,4-b][1,5]BENZOXAZEPINES

While the literature abounds with references to dibenzoxazepines and their derivatives, reports of the analogous pyridobenzoxazepine derivatives are much less common. Pyrido[2,3-b][1,4]benzoxazepine derivatives have been prepared either by reaction of a salicyclic acid or salicylaldehyde
(i) NaH, DMF, 100°.
(ii) H₂, 10% Pd-C, EtOAc, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Et₂N, Cl(CH₂)₂Cl, 60°.

Scheme 52
derivative with an appropriate amino-2-chloropyridine, followed by base induced ring closure,\textsuperscript{68,103,104} or with a 2-chloro-3-nitropyridine derivative followed by reductive cyclisation.\textsuperscript{68,104} Considering the scarcity of general methods for the construction of this ring system, it was considered worthwhile to investigate the applicability of the Lewis acid promoted cyclisation of isocyanides and isocyanide dihalides to its synthesis. The development of a flexible synthetic route to these compounds is given added significance by the recent discovery\textsuperscript{62} that several pyrido[2,3-b][1,4]- and pyrido[2,3][1,5]benzoxazepines are strong inhibitors of HIV-1 reverse transcriptase, and so may have potential as anti-AIDS agents.

The initial studies, which were directed at the preparation of C-6 unsubstituted pyrido[2,3-b][1,4]benzoxazepines, required the preparation (Scheme 52) of the methoxypyridinyl isocyanide (184a). This began with the previously described\textsuperscript{76} sodium hydride promoted reaction of 2-chloro-3-nitropyridine (180) and 3-methoxyphenol (112a) which gave the nitropyridylether (181a) in moderate yield (61%). Reduction of (181a) by catalytic hydrogenation gave the known\textsuperscript{76} amine (182a) (69%), and this was converted into the formamide (183a) (82%) and thence into the desired isocyanide (184a) in good yield (80%) by the established formylation and dehydration procedures. Both the previously undescribed formamide (183a) and isocyanide (184a) had analytical and spectroscopic properties which were fully in accord with their assigned structures.

Cyclisation of the isocyanide (184a) was first attempted (Scheme 53) using the conditions which were initially found to effect cyclisation of the analogous methoxyphenoxy isocyanide (116a) (see Section 2.2). Thus, the isocyanide (184a) was heated under reflux in methylene chloride with five equivalents of titanium tetrachloride, but these conditions failed to give the desired pyridobenzoxazepine (185a) and the only product isolated was the
(i) TiCl₄, CH₂Cl₂, reflux.
(ii) SnCl₄, Cl(CH₂)₂Cl, reflux.
(iii) Br₂, CH₂Cl₂, -10°.
(iv) AlBr₃, CH₂Cl₂, reflux.
(v) NaH, piperidine, DMF, room temp.
(vi) (Et₄N)⁺(CN)⁻, MeCN, room temp.

Scheme 53
formamide (183a) in high yield (86%). It was suspected at this stage that electron withdrawal by the pyridine ring may be suppressing the reaction by reducing the electron availability at the isocyano group and so inhibiting coordination with titanium. Consequently it was decided to attempt cyclisation using a stronger Lewis acid. Unfortunately however, the reaction of the isocyanide (184a) with an excess of stannic chloride in refluxing 1,2-dichloroethane gave only a polymeric material, similar to that obtained from previous reactions with this Lewis acid (Section 2.2). The reaction of the isocyanide (184a) with titanium tetrachloride provides a contradictory result in that the formation of the formamide (183a) suggests that coordination has taken place, while the absence of any cyclised product suggests that it has not. Although the reasons for the lack of any cyclisation are not clear, it is possible that the electron-donating effect of the pyridylphenylether oxygen atom is being completely drawn into the pyridine ring by a combination of the electronegative isocyano group and the increased electron deficiency of the pyridine ring due to complexation with titanium at the ring nitrogen atom and at the isocyano group. This would leave the adjacent phenyl ring effectively activated by only one ether group, and it has previously been shown (see Section 2.2) that this is insufficient to induce cyclisation. Consequently the coordinated intermediate suffers hydrolytic degradation to give the formamide (183a).

In view of the disappointing results obtained from the attempted cyclisation of the isocyanide (184a), attention was next turned to the preparation (Scheme 52) of the unsubstituted pyridinyl isocyanide (184) with a view to the cyclisation of the corresponding isocyanide dibromide. Thus 3-nitro-2-phenoxyypyridine (181b) and 3-amino-2-phenoxyppyridine (182b) were prepared by literature procedures in 87% and 98% yields respectively, and the amine (182b) was then converted into the formamide (183b) in excellent
yield (96%) by the standard formylation conditions (i.e. heating under reflux in 98-100% formic acid). The desired isocyanide (184b) was then obtained in good yield (67%) by dehydration of the formamide (183b) under standard conditions, along with a small amount (20%) of unchanged starting material. The previously unknown formamide (183b) and isocyanide (184b) were fully characterised by their analytical and spectroscopic properties.

Reaction (Scheme 53) of the isocyanide (184b) with bromine at -10° gave the isocyanide dibromide (186b) in quantitative yield. This compound was isolated as an unusually stable solid which could be crystallised and for which a satisfactory combustion analysis was obtained. Heating this compound under reflux in methylene chloride with two equivalents of aluminium tribromide then afforded 6-bromopyrido[2,3-b][1,4]benzoxazepine (187b) in excellent yield (90%), without the need for chromatography. Unfortunately, this product did not show the same level of stability as its isocyanide dibromide precursor (186b), and so a satisfactory combustion analysis could not be obtained. It was observed during handling of the bromopyridobenzoxazepine (187b) that it had a strong irritant effect on the skin, similar to that which had previously been reported for the 3-methoxydibenzoazepine (118) and its derivatives.

As had been hoped, the bromine atom in the cyclised product (187b) was found to be typically reactive, being readily displaced (Scheme 53) with the anion of piperidine in DMF at room temperature to afford the 11-piperidinopyridobenzoxazepine (188b) in high yield (79%). An initial attempt to prepare the corresponding 11-cyano derivative by heating the bromopyridobenzoxazepine (187b) under reflux in acetonitrile with a two fold excess of tetraethylammonium cyanide gave only an intractable black gum, but the desired product (189b) was obtained in excellent yield (95%) by conducting the same reaction at room temperature. The spectroscopic
(111) + (112) → (113)

(i) NaH, DMF, 100°.
(ii) H₂, 10% Pd-C, EtOAc, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(v) Br₂, CH₂Cl₂, -10°.
(vi) AlBr₃, CH₂Cl₂, reflux.
(vii) AlBr₃, Cl(CH₂)₂Cl, reflux.

Scheme 54
properties of this compound fully supported its assigned structure, but due to the limited availability of material a combustion analysis was not obtained and further structural confirmation was obtained by high resolution mass spectrometry.

Having clearly demonstrated the compatibility of the isocyanide dibromide cyclisation with a pyridine ring bearing the isocyano group, it was next decided to investigate the ability of pyridine to act as the nucleophilic ring in the ring closure step. In order to address this question, the readily available pyridyloxyphenyl isocyanide derivative (194) was chosen for study. The synthesis (Scheme 54) of this compound began with the sodium hydride promoted reaction of 2-fluoronitrobenzene (111) and 3-hydroxypyridine (190), which gave the nitrophenoxypyridine (191) in 79% yield. The high yield of this procedure and its simplicity in practice make it more attractive than the somewhat more arduous preparation of (191) reported by Abramovitch et al.105 This compound was then converted into the corresponding amine\textsuperscript{105} (192) in quantitative yield by catalytic hydrogenation. Reaction of the amine (192) with refluxing formic acid gave the formamide (193) in near quantitative yield (96%) and this was subsequently converted into the isocyanide (194), although in unusually low yield (38%), by the established dehydration procedure. The previously undescribed formamide (193) and isocyanide (194) both exhibited analytical and spectroscopic properties fully in accord with their assigned structures.

The isocyanide dibromide (195), which was prepared in quantitative yield by the reaction of the isocyanide (194) with bromine in methylene chloride at -10°, was found to be an unusually high melting and insoluble solid which decomposed on attempted crystallisation. Consequently this compound was characterised by high resolution mass spectrometry rather than combustion analysis. The initial attempt at cyclisation of the isocyanide
(i) NaH, DMF, 100°.
(ii) 15% aq. TiCl₃, tetrahydrofuran, room temp.
(iii) 98-100% HCO₂H, reflux.
(iv) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.

Scheme 55
dibromide (195) involved heating under reflux in methylene chloride with two equivalents of aluminium tribromide, but these conditions gave only a good recovery (77%) of the isocyanide dibromide (195), with no evidence for either of the two possible isomeric pyridobenzoxazepines (196) or (197). Elevation of the reaction temperature by using refluxing 1,2-dichloroethane as the solvent was similarly unsuccessful, giving only a complex mixture from which no identifiable material was obtained.

Although the failure of this cyclisation reaction was a disappointment it was not entirely unexpected as formation of the pyridobenzoxazepines (196) or (197) would require cyclisation onto positions 2 or 4 of the pyridine ring respectively. These are the positions which carry the least $\pi$-electron density and so are the most reluctant to undergo electrophilic substitution, and this situation will be exacerbated by coordination of the pyridine nitrogen atom with the Lewis acid. It is clear that the activation provided by the single ether oxygen atom in the isocyanide dibromide (195) is insufficient, but it may be possible to effect cyclisation with a more highly activated pyridine ring. Also, the lack of cyclisation onto the 2 and 4 positions of the pyridine ring does not exclude the possibility of cyclisation onto the 3 or 5 positions which are more susceptible to electrophilic attack. Unfortunately however, time restrictions dictated that investigation of the above possibilities was not possible in the present study.

2.6 SYNTHESIS OF PYRIDO[2,3-b][1,4]BENZOTHIAZEPINE DERIVATIVES

The pyridobenzothiazepines in general have not been as widely investigated as the corresponding pyridobenzoxazepines, but the limited reports available suggest that some of these compounds may have potential as biologically active agents. For example, there are a few reports
(i) Br₂, CH₂Cl₂, -10°.
(ii) AlBr₃, CH₂Cl₂, room temp.
(iii) NaH, piperidine, DMF, room temp.
(iv) (Et₄N)⁺(CN)⁻, MeCN, room temp.

Scheme 56
concerning the preparation of pyrido[2,3-b][1,5]benzothiazepine derivatives and their biological evaluation as antiallergic\textsuperscript{106} and anti-H\textsuperscript{107}V agents. The pyrido[2,3-b][1,4]benzothiazepine ring system was unknown in the literature until a recent report\textsuperscript{108} described the low yielding photochemical preparation of pyrido[2,3-b][1,4]benzothiazepin-6-one. Considering the rarity of literature reports of this ring system, it was decided to investigate the application of the Lewis acid promoted isocyanide dibromide cyclisation to its synthesis.

The synthesis (Scheme 55) of the required substrate isocyanide (201) began with the preparation of the known\textsuperscript{109} nitropyridylthioether (198), which was accomplished in 78\% yield by the sodium hydride promoted reaction of 2-chloro-3-nitropyridine (180) with thiophenol (152b). The nitro compound (198) was then converted into the known\textsuperscript{109} amine (199) in good yield (79\%) by reduction with ten equivalents of titanium trichloride in aqueous THF at room temperature. Formylation of the amine (199) was easily accomplished with formic acid to afford the formamide (200) (90\%), which in turn furnished the desired isocyanide (201) in moderate yield (59\%) on reaction with carbon tetrachloride, triphenylphosphine, and triethylamine in 1,2-dichloroethane at 60\°.

Reaction (Scheme 56) of the isocyanide (201) with one equivalent of bromine at -10\° gave the isocyanide dibromide (202) in quantitative yield, and this readily underwent cyclisation on reaction with two equivalents of aluminium tribromide in methylene chloride at room temperature to give 6-bromopyrido[2,3-b][1,4]benzothiazepine (203) in excellent yield (90\%). The analytical and spectroscopic properties of this previously unknown compound were fully in accord with its assigned structure.

Despite the somewhat atypical stability of the pyridobenzothiazepine (203) towards moisture in comparison to the other bromo-heteropines prepared in Sections 2.2 to 2.5, the bromine atom proved to be easily
displaceable under mild conditions. Thus (Scheme 56), reaction of (203) with
the anion of piperidine in DMF at room temperature gave the 6-
piperidinopyridobenzothiazepine derivative (204) in high yield (88%). The
corresponding 6-cyano derivative (205) was also obtained in good yield (82%)
by the reaction of the bromo compound (203) with tetraethylammonium
cyanide in acetonitrile at room temperature. Both of the previously
undescribed pyridobenzothiazepine derivatives (204) and (205) exhibited
analytical and spectroscopic properties which were fully confirmative of their
assigned structures.

The successful preparation of the two novel pyrido[2,3-b][1,4]benzothiazepine
derivatives (204) and (205) in high yields [26% and
24% respectively from 2-chloro-3-nitropyridine (180) and thiophenol (152b)]
and under mild conditions throughout is a prime example of the synthetic
potential of the Lewis acid promoted cyclisation of isocyanide dibromides in
the construction of tricyclic molecules of this type.

2.7 SYNTHESIS OF PYRIDO[2,3-b][1,4]BENZODIAZEPINE
DERIVATIVES

Pyrido[2,3-b][1,4]benzodiazepines are an important class of tricyclic
heteropines as a result of their wide ranging biological properties, and it was
therefore decided to investigate the applicability of the cyclisation of
isocyanide dibromides to this ring system. Accordingly, the anti-ulcer drug
pirenzepine (87) immediately suggested itself as a synthetic target for this
purpose. Pirenzepine and its structural analogues have been the subject of
much chemical and biological investigation over the past few years, but the
majority of reported syntheses make use of one of the three main strategies
(Section 2.1) for the construction of tricyclic heteropines. For example,
pirenzepine has been prepared\textsuperscript{110} by the condensation of 2-nitrobenzoyl
(i) di-$n$-butylether, reflux.
(ii) NaH, TsCl, DMF, 100$^\circ$.
(iii) SnCl$_2$, HCl, H$_2$O, reflux.
(iv) 98-100% HCO$_2$H, reflux.
(v) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60$^\circ$.
(vi) POCl$_3$, i-Pr$_2$NEt, CH$_2$Cl$_2$, room temp.

(Ts = toluene-4-sulphonyl)
chloride and 3-amino-2-chloropyridine followed by reductive cyclisation to give pyrido[2,3-b][1,4]benzodiazepin-6-one, which was converted into pirenzepine in 32% overall yield by sequential reaction with chloroacetyl chloride then N-methylpiperazine. It has also been shown that 6-phenylpyrido[2,3-b][1,4]benzodiazepine derivatives exhibit promising antidepressant activity,\textsuperscript{111} and such compounds have been prepared\textsuperscript{112} by the rather austere reaction of 2-aminobenzophenone derivatives with 3-amino-2-chloropyridines at 190°.

The present synthesis of pirenzepine (Scheme 57) required the preparation of the isocyanide (210). This began with the reaction of 2-chloro-3-nitropyridine (180) with aniline (162b), as described by Bacon and Hamilton,\textsuperscript{113} which gave the nitropyridylarylamine (206) in excellent yield (94%). This compound was protected at the amino nitrogen atom by its reaction with one equivalent of fresh tosyl chloride in the presence of sodium hydride in DMF at 100°, giving the N-tosyl derivative (207) in poor yield (34%) along with a good recovery (47%) of the unchanged starting material (206). The yield of the protected amine (207) was marginally increased (to 45%) by the use of two equivalents of tosyl chloride under otherwise identical conditions. Reduction of the nitro compound (207) was readily effected with stannous chloride in refluxing hydrochloric acid to give the amine (208) in near quantitative yield (95%), and this was heated under reflux in formic acid to afford the formamide (209) in equally good yield (95%). The required isocyanide (209) was then obtained in moderate yield (60%) by dehydration of the formamide (208) with carbon tetrachloride, triphenylphosphine, and triethylamine, but was later procured in significantly improved yield (86%) by the use of the phosphoryl chloride-N-ethyldiisopropylamine dehydrating system. All of the previously undescribed compounds, (207) to (210), in this synthetic sequence had analytical and spectroscopic characteristics fully in accord with their assigned structures.
(i) Br₂, CH₂Cl₂, -10°.
(ii) AlBr₃ (2 equivalents), CH₂Cl₂, reflux.
(iii) AlBr₃ (3 equivalents), CH₂Cl₂, reflux.
(iv) AlBr₃ (5 equivalents), Cl(CH₂)₂Cl, reflux.
(v) hydrolysis.
(vi) deprotection.
(vii) ClCH₂COCl.
(viii) N-methylpiperazine.

Scheme 55
The isocyanide (210) reacted readily (Scheme 58) with one equivalent of bromine in methylene chloride at -10° to give a quantitative yield of the isocyanide dibromide (211). This compound was isolated as a moisture-sensitive solid for which a satisfactory combustion analysis could not be obtained, but which was sufficiently stable to allow characterisation by high resolution mass spectrometry and proton and carbon n.m.r. spectroscopy. In addition, an X-ray crystal structure of (211) was obtained (see Figure 2) (over page), although the instability of the compound limited the resolution of the X-ray analysis and hence no bond length or bond angle data could be obtained. The structure of the isocyanide dibromide (211) was further confirmed by its hydrolysis to the amine (208) in 84% yield with benzyltrimethylammonium hydroxide in dioxane at room temperature.

The initial attempt to cyclise the isocyanide dibromide (211) involved its reaction with two equivalents of aluminium tribromide under reflux in methylene chloride, but these conditions surprisingly gave the unchanged isocyanide dibromide (211) in high yield (98%), with no evidence for the formation of the desired pyridobenzodiazepine (212). It was believed at this stage that the pyridine nitrogen atom and the nitrogen and oxygen atoms of the N-tosyl group were inhibiting cyclisation by coordinating with the Lewis acid thereby removing it from the reaction. Consequently, an attempt was made to overcome this problem by using a three fold excess of aluminium tribromide under otherwise identical conditions, but this also gave the isocyanide dibromide (211) in good yield (69%) as the only identifiable product. In a final effort to prepare the bromopyridobenzodiazepine (212) the isocyanide dibromide was subjected to more forcing conditions by heating it under reflux in 1,2-dichloroethane with five equivalents of aluminium tribromide, but these conditions gave only a complex mixture which was not investigated further.
Figure 2
At present it is unclear why the attempted cyclisation of the isocyanide dibromide (211) was unsuccessful, and it is also surprising since pyridin-3-yl isocyanide dibromide derivatives had previously been successfully cyclised with aluminium tribromide to give the corresponding pyridobenzoxazepines (Section 2.5) and pyridobenzothiazepines (Section 2.6). In addition, the N-tosyl bridge had previously been shown (Section 2.4) to be compatible with the cyclisation of phenylaminophenyl isocyanide dibromide derivatives to give N-tosyl dibenzodiazepines. Evidently, cyclisation is only inhibited when the substrate contains a pyridine ring bearing the isocyano group in combination with an N-tosyl bridge, and this suggests that there may be some kind of chelate formation between the aluminium tribromide, the pyridine nitrogen atom, and the oxygen atoms of the sulphonyl group. Although such coordination might not deactivate the system to the extent where no reaction occurs, it may be holding the molecule in a conformation where the isocyanide dibromide group is too remote from the adjacent phenyl ring to permit cyclisation. It therefore remains possible that cyclisation of isocyanide dibromide derivatives such as (211) could be achieved if a different method of amino protection was used, although the choice of an appropriate protecting group is not easy. Not only must it be compatible with halogenation and strong Lewis acids it also cannot contain a coordinating centre which would be placed close to the pyridine nitrogen atom in the cyclisation substrate. These restrictions rule out all of the commonly used amino protecting groups such as amide, carbamate, and benzyl groups, and clearly further work is necessary to resolve this problem.

As insufficient time was available in the present study to investigate an alternative method of amino group protection, it was not possible to carry out the remainder of the synthetic sequence (Scheme 58) leading to pirenzepine. It was envisaged that this would involve hydrolysis of the
(i) 98-100% HCO$_2$H, reflux.
(ii) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60°.
(iii) Br$_2$, CH$_2$Cl$_2$, -10°.
(iv) AlBr$_3$, CH$_2$Cl$_2$, reflux.

Scheme 92
bromopyridobenzodiazepine (212) to the corresponding lactam (213), followed by deprotection of the amino nitrogen atom to give the pyridobenzodiazepin-6-one (214). As this compound has previously\textsuperscript{110} been converted into pirenzepine by reaction with chloroacetyl chloride then $N$-methylpiperazine, its preparation would constitute a formal synthesis of pirenzepine (87).

2.8 SYNTHESIS OF 11H-DIBENZ[b,e]AZEPINE AND 11-OXODIBENZ[b,e]AZEPINE DERIVATIVES

There is a great deal of biological interest in the dibenz\[b,e\]azepines due to their activity as anticonvulsant, antihypoglycaemic, antidepressant, and anti-Parkinson's agents to name but a few, and consequently a huge number of derivatives of this ring system have been prepared. A number of these syntheses\textsuperscript{114-116} have exploited the displacement of a chlorine atom from the C-5 position of the dibenzazepine nucleus with various nucleophiles, with the 5-chloro starting material having been prepared by chlorination of the appropriate lactam. In view of the biological significance of the dibenz\[b,e\]azepine derivatives it was considered worthwhile to increase the accessibility of these compounds by application of the isocyanide dibromide cyclisation to their synthesis.

This objective initially required the preparation (Scheme 59) of the benzylphenyl isocyanide (217), and this began with commercially available 2-benzylaniline (215) which was easily formylated by heating under reflux in formic acid to give the formamide (216) in near quantitative yield (97%). This was then converted into the previously undescribed isocyanide (217) in good yield (78%), along with a small amount of unchanged starting material (216) (16%), by the standard dehydration protocol.
(i) piperidine, MeCN, reflux.
(ii) (Et$_4$N)$^+$ (CN)$^-$, MeCN, room temp. then reflux.
(iii) NaN$_3$, DMF, 100°C.
(iv) NaOEt, EtOH, reflux.
(v) NaOH, H$_2$O, dioxane, reflux.

Scheme 60
Reaction (Scheme 59) of the isocyanide (217) with one equivalent of bromine at -10° gave the isocyanide dibromide (218) (100%) which, like the isocyanide (217), was isolated as an unstable oil and was therefore characterised by high resolution mass spectrometry. On reaction with two equivalents of aluminium tribromide in refluxing methylene chloride, the isocyanide dibromide (218) was smoothly converted into the desired 5-bromodibenz[b,e]azepine (219) in high yield (88%). This compound was isolated as an oil which was prone to hydrolysis by atmospheric moisture, and so was unsuitable for combustion analysis. Consequently (219) was characterised by high resolution mass spectrometry along with the rest of its spectroscopic data.

The reaction sequence shown in Scheme 59 not only provides a short (three practical operations) and high yielding [67% overall yield from 2-benzylaniline (215)] route to the synthetically useful 5-bromodibenzazepine (219), but it also demonstrates that the Lewis acid promoted cyclisation of isocyanide dibromides can take place easily with only the minimum of activation of the attacking phenyl ring.

Considering the literature reports\textsuperscript{114-116} which describe the facile displacement of a chlorine atom from the C-5 position of dibenz[b,e]azepines, the bromine atom in the dibenzazepine (219) was expected to be at least as reactive. This was confirmed by its reactions with a variety of nucleophiles, as shown in Scheme 60. Unfortunately, reaction of (219) with two equivalents of piperidine in refluxing acetonitrile gave a solid product mixture from which no identifiable material could be obtained. The anomalous failure of this reaction is believed to be a freak result which would be rectified by using different reaction conditions (e.g. the anion of piperidine in DMF), however time was not available to re-investigate this reaction. More successful were the reactions of the bromodibenzazepine (219) with tetraethylammonium
(i) 98-100% HCO₂H, reflux.
(ii) Pb₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(iii) Br₂, CH₂Cl₂, -10°.
(iv) AlBr₃, CH₂Cl₂, reflux.

Scheme 61
cyanide in refluxing acetonitrile to give 5-cyanodibenz[b,e]azepine (221) in high yield (87%), and with sodium azide in DMF at 100° to give the tetrazolodibenzazepine derivative (222) in equally good yield (85%). It is of interest to note that a range of dibenz[b,e]azepine derivatives incorporating 5,6-fused heterocycles have been prepared\textsuperscript{117} and have shown promising activity as sedatives and antidepressants.\textsuperscript{118} The bromine atom in (219) was also easily displaced with sodium ethoxide in refluxing ethanol to give the 5-ethoxy derivative (223) (84%) and with aqueous sodium hydroxide in refluxing dioxane to give the known\textsuperscript{131} lactam (224) in near quantitative yield (96%). Dibenz[b,e]azepin-5-ones such as (224) have been used\textsuperscript{119} to prepare functionalised derivatives by metallation at C-11 with butyllithium\textsuperscript{20} followed by reaction with various electrophiles. All of the new compounds, (221) to (223), shown in Scheme 60 had analytical and spectroscopic properties which were fully confirmative of their assigned structures.

The 11-oxodibenz[b,e]azepines and their derivatives also exhibit a wide spectrum of biological activity and in particular C-11 acetonitrile derivatives, prepared\textsuperscript{121} by a Wittig reaction of 11-oxodibenz[b,e]azepines with a suitable phosphonate, are powerful neuroleptic agents which possess several times the biological potency of clozapine.\textsuperscript{122} Several 5-chloro-11-oxodibenz[b,e]azepines have been prepared\textsuperscript{121} by chlorination of the corresponding lactams, and the chlorine atom has been shown\textsuperscript{123} to be readily displaceable. It was therefore decided to investigate the preparation (Scheme 61) of 5-bromo-11-oxodibenz[b,e]azepine (229) by the Lewis acid promoted cyclisation of the corresponding isocyanide dibromide (228).

Preparation (Scheme 61) of the substrate isocyanide (227) began with the reaction of commercially available 2-aminobenzophenone (225) with refluxing formic acid, which gave the known\textsuperscript{124} formamide (226) in quantitative yield. This was subsequently converted into the isocyanide (227) in good
yield (73%) by the established dehydration protocol. The previously unknown isocyanide (227) was fully characterised through its analytical and spectroscopic properties.

The isocyanide dibromide (228) was then obtained in quantitative yield by the low temperature reaction of the isocyanide (227) with one equivalent of bromine in methylene chloride. This compound was found to be extremely unstable, fuming immediately on exposure to the air and whose i.r. spectrum showed an intense absorption at 2296 cm⁻¹, indicating rapid hydrolysis to the corresponding isocyanate. As a result of this instability, no molecular ion corresponding to (228) could be detected under electron impact or fast atom bombardment mass spectrometry conditions. Cyclisation of the isocyanide dibromide (228) was attempted by its reaction with two equivalents of aluminium tribromide under reflux in methylene chloride, but these conditions failed to yield the desired bromodibenzazepinone (229), and gave only a complex mixture which could not be separated by chromatography.

The failure of this cyclisation reaction may be ascribed to the deactivation of the attacking phenyl ring due to the electron-withdrawing effect of the carbonyl group in the isocyanide dibromide (228), an effect which will be considerably increased by complexation of the Lewis acid with the carbonyl oxygen atom. In addition, Lewis acid catalysed rearrangement reactions of (228) may be a complicating factor. This result, although negative, is still useful in the sense that it provides a measure of deactivation of the attacking aromatic ring which is tolerated in the Lewis acid promoted cyclisation of isocyanide dibromides. It is clear that an electron poor ring such as pyridine (Section 2.5), or a strongly deactivated benzene ring [e.g. (228)], cannot participate in ring closure reactions with isocyanide dibromides, at least with aluminium tribromide as the Lewis acid. On the other hand, the
successful cyclisation of 2-benzylphenyl isocyanide dibromide (218) to give the bromodibenzazepine (219) (see Scheme 59) demonstrates that activation of the attacking phenyl ring is not a requirement for cyclisation to occur.

2.9 EXPERIMENTAL

General Experimental Details

Infrared spectra were recorded using a Perkin-Elmer 298 spectrophotometer or a Bio-Rad FTS-7 Fourier-Transform spectrophotometer, and bands were strong and sharp unless specified as w (weak) or br (broad). Solids were measured as suspensions (mulls) in Nujol and liquids as thin films.

$^1$H n.m.r. spectra were measured in the stated solvent at 80 MHz using a Bruker WP-80SY instrument, at 200 MHz using a Bruker WP-200SY instrument, or at 360 MHz using a Bruker WH-360 instrument. Signals were sharp unless specified as bs (broad singlet); s = singlet, d = doublet, dd = double doublet, ddd = double double doublet, dt = double triplet, t = triplet, td = triple doublet, q = quartet, and m = multiplet. $^{13}$C n.m.r. spectra were recorded at 50 MHz using a Bruker WP-200SY instrument and were fully decoupled. Signals were sharp andquat = quaternary carbon atom. Quaternary carbon atoms and methylene groups were identified by 3$n$/4 DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence spectra.

Electron impact (El) mass spectra were recorded at 70 eV on A.E.I. MS-902 and Kratos-MS-50TC instruments. Fast Atom Bombardment (FAB) mass spectra were measured on a Kratos-MS-50TC instrument for matrices in thioglycerol.
X-ray diffraction data were collected using a Stoe-Stadi four circle diffractometer on single crystals grown from the stated crystallisation solvent.

Microanalyses were determined using Carlo-Erba Strumentazione 1106 or Perkin-Elmer 2400 elemental analysers. Routine melting points (m.p.) were carried out using a Gallenkamp apparatus and are uncorrected. Melting points of analytical samples were determined using a Kofler hot-stage apparatus and are uncorrected.

All reagents were laboratory grade unless specified. Sodium hydride was an 80% or 60% dispersion in mineral oil and was washed with anhydrous ether before use. Solvents were of technical grade unless otherwise stated. Organic extracts were dried over anhydrous magnesium sulphate prior to filtration and rotary evaporation under reduced pressure.

Wet column chromatography was carried out over silica (Fluka Kieselgel 60, 220-440 mesh) or over alumina (Merck Aluminium oxide 90,70-230 mesh). Thin layer chromatography (t.l.c.) was carried out using Polygram SIL G/UV$_{254}$ or Polygram ALOXN/UV$_{254}$ precoated plastic sheets. Preparative t.l.c. and dry column chromatography were carried out over silica (Fluka Kieselgel GF$_{254}$).

**Anhydrous Solvents**

Solvents were dried as described below.

1. Acetonitrile, dimethylformamide, di-$n$-butylether, methylene chloride, and 1,1,2,2-tetrachloroethane were distilled and stored over 5A molecular sieves.
2. 1,2-Dichloroethane, dioxane, and 1,2-dimethoxyethane were distilled from calcium hydride and stored over 5A molecular sieves.
3. Benzene and ether were dried with sodium wire.
4. Ethanol was distilled from magnesium and iodine and stored over 5A molecular sieves.

5. Tetrahydrofuran was distilled under nitrogen from sodium benzophenone ketyl and stored over 5A molecular sieves.

**ANALYTICAL AND MASS SPECTROSCOPIC DATA**

For analytical and mass spectroscopic data, see Table 6, page 199.

2-Aryloxy-2-nitrobenzenes (113a and b), (125) and (131a and b)

A suspension of sodium hydride (2.6 g; 0.11 mol) in anhydrous dimethylformamide (40.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of the corresponding phenol (0.1 mol) in anhydrous dimethylformamide (20.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-fluoronitrobenzene (111) (14.1 g; 0.1 mol) or 2,4-dichloronitrobenzene (124) (14.1 g; 0.1 mol) in anhydrous dimethylformamide (30.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1 h then worked up as described for the individual reactions below.

(i) **2-Phenoxy-2-nitrobenzene (113b)**

The cooled mixture from phenol (112b) and 2-fluoronitrobenzene (111) was treated with water (25.0 ml), stirred at room temperature for 10 min, and rotary evaporated to give an oil. This was treated with water (200.0 ml) and extracted with methylene chloride to give an orange oil (25.2 g) which was distilled to give 2-phenoxy-2-nitrobenzene (113b) as an orange oil (18.7 g; 87%), b.p. 115-119°/0.1-0.2 mmHg (lit., 152°/1.9 mmHg), m/z (ElMS) 215 (M+).
(ii) 2-(3-Methoxyphenoxy)nitrobenzene (113a)

The cooled mixture from 3-methoxyphenol (112a) and 2-fluoronitrobenzene (111) was treated with water (25.0 ml), stirred at room temperature for 10 min, and rotary evaporated to give an oil which solidified on cooling to afford 2-(3-methoxyphenoxy)nitrobenzene (113a) as a yellow solid (22.3 g; 91%), m.p. 47-51° (lit., 76° 54-57°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(iii) 2-(2-Bromophenoxy)nitrobenzene (131a)

The cooled mixture from 2-bromophenol (130a) and 2-fluoronitrobenzene (111) was treated with water (25.0 ml), stirred at room temperature for 10 min, and rotary evaporated to give an oil. This was treated with water (200.0 ml) and extracted with methylene chloride to give an oil which solidified on cooling to afford 2-(2-bromophenoxy)nitrobenzene (131a) (93%) which formed colourless crystals, m.p. 45-46° (from hexane), $v_{\text{max}}$ 1525 and 1350 (NO$_2$) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.03-6.77(8H, m, ArH).

(iv) 2-(2-Iodophenoxy)nitrobenzene (131b)

The cooled mixture from 2-iodophenol (130b) and 2-fluoronitrobenzene (111) was treated with water (25.0 ml), stirred at room temperature for 10 min, and rotary evaporated to give an oil. This was treated with water (200.0 ml) and extracted with methylene chloride to give an oil which solidified on cooling to afford 2-(2-iodophenoxy)nitrobenzene (131b) (93%) which formed colourless crystals, m.p. 65-66° [from hexane-ethyl acetate (10:1)], $v_{\text{max}}$ 1530 and 1365 (NO$_2$) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.92(2H, td, J 8, 8, and 2 Hz, ArH) and 7.57-6.78(6H, m, ArH).

(v) 4-Chloro-2-(3-methoxyphenoxy)nitrobenzene (125)

The cooled mixture from 3-methoxyphenol (112a) and 2,4-dichloronitrobenzene (124) was treated with water (25.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was
treated with water (200.0 ml) and extracted with methylene chloride to give a brown oil (29.0 g) which was distilled to give an orange oil (1.0 g), b.p. 81-85°/0.05-0.10 mmHg, whose t.l.c. in methylene chloride over silica showed it to be a mixture of 2,4-dichloronitrobenzene (124) and the desired product (125), followed by 4-chloro-2-(3-methoxyphenoxy)nitrobenzene (125) as an orange oil (20.3 g; 77%), b.p. 155-159°/0.05-0.10 mmHg, \( \nu_{\text{max}} \) 1525 and 1340 (NO\(_2\)) cm\(^{-1}\), \( \delta_H(\text{CDCl}_3) \) 7.90(1H, d, J 9 Hz, ArH), 7.39-6.55(6H, m, ArH), and 3.79(3H, s, OCH\(_3\)).

2-Phenoxyaniline (114b)

2-Phenoxyaniline (114b) was prepared by the catalytic hydrogenation of 2-phenoxy nitrobenzene (113b) as described by Weddel\(^76\) as a colourless solid (yield 97%), and had m.p. 41-43° (lit.,\(^{125} 44-45°\)).

2-(3-Methoxyphenoxy)aniline (114a)

2-(3-Methoxyphenoxy)aniline (114a) was prepared by the catalytic hydrogenation of 2-(3-methoxyphenoxy)nitrobenzene (113a) as described by Weddel\(^76\) as a brown oil (yield 99%), identical (i.r. spectrum) to an authentic sample.

The Attempted Catalytic Reduction of 2-(2-Bromophenoxy)nitrobenzene (131a)

A solution of 2-(2-bromophenoxy)nitrobenzene (131a) (5.9 g; 0.02 mol) in ethyl acetate (30.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.59 g) at room temperature and atmospheric pressure for 8.5h, during which time hydrogen (1792 ml; 0.08 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give a waxy solid which was washed with ethyl acetate to
afford a pale brown solid. This was combined with further material obtained by rotary evaporation of the ethyl acetate filtrate and trituration of the resulting residue with ethyl acetate to give 2-phenoxyaniline hydrobromide as a light brown solid (3.7 g; 70%), m.p. 180-184°. Treatment of this solid with 10% w/v aqueous sodium hydrogen carbonate solution (20.0 ml) and extraction with methylene chloride gave 2-phenoxyaniline (114b) as a light brown solid (2.3 g; 62%), m.p. 44-45° (lit.,125 44-45°).

Rotary evaporation of the ethyl acetate mother liquor gave an oil (1.2 g), flash chromatography of which over silica gave no characterisable material.

The Attempted Catalytic Reduction of 2-(2-iodophenoxy)nitrobenzene (131b)

(a) In ethyl acetate

A solution of 2-(2-iodophenoxy)nitrobenzene (131b) (6.8 g; 0.02 mol) in ethyl acetate (30.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.68 g) at room temperature and atmospheric pressure for 3h, during which time hydrogen (37 ml; 0.002 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give an oil which was triturated with hexane-ethyl acetate to give a yellow solid. This was combined with further material obtained by rotary evaporation of the organic mother liquor and trituration of the residue with ethanol to afford unchanged 2-(2-iodophenoxy)nitrobenzene (131b) as a yellow solid (5.3 g; 78%), m.p. 68-71°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethanolic mother liquor gave an intractable waxy solid (0.45 g) which was not further investigated.
(b) In glacial acetic acid

Repetition of the reaction described in (a) above using glacial acetic acid as the solvent gave unchanged 2-(2-iodophenoxy)nitrobenzene (131b) as a yellow solid (86%), m.p. 61-67°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

2-Aryloxyaniline Derivatives (132a) and (132b)

A solution of the aryloxy nitrobenzene derivative (131a) or (131b) (0.02 mol) in tetrahydrofuran (200.0 ml) was stirred under nitrogen and treated portionwise with 15% w/v aqueous titanium trichloride solution (230.0 ml; 0.2 mol). The mixture was stirred at room temperature, under nitrogen, for 48-70h then worked up as described for the individual reactions below.

(i) 2-(2-Bromophenoxy)aniline (132a)

(a) After 70h the mixture from 2-(2-bromophenoxy)nitrobenzene (131a) was rotary evaporated to give an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (20.0 ml), and extracted with methylene chloride to give a solid. This was combined with further material obtained by stirring the aqueous mother liquor at room temperature overnight, filtration to remove titanium residues, and extraction with methylene chloride, to give 2-(2-bromophenoxy)aniline (132a) (4.7 g; 88%) which formed colourless crystals, m.p. 55-56° (from hexane), $\nu_{max}$ 3460 and 3380 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.60(1H, dd, 8 and 2 Hz, ArH), 7.31-6.57(7H, m, ArH), and 3.82(2H, bs, NH$_2$) (exch).

(b) After 48h the mixture from 2-(2-bromophenoxy)nitrobenzene (131a) gave an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (20.0 ml) and extracted with methylene chloride to give 2-(2-bromophenoxy)aniline (132a) as a brown oil (71%), identical [i.r.
spectrum and t.l.c. in hexane-methylene chloride (1:3) over silica] to a sample prepared in (a) before.

The aqueous mother liquor was stirred at room temperature overnight, filtered to remove titanium residues, and extracted with methylene chloride to give no material.

(c) Repetition of the reaction described in (a) before using six equivalents of 15% w/v aqueous titanium trichloride solution for 65h gave an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (40.0 ml), and extracted with methylene chloride to give an oil. This was triturated with hexane to afford a brown solid, which was combined with further material obtained by rotary evaporation of the hexane mother liquor and trituration of the residue with hexane, to give 2-(2-bromophenoxy)aniline (132a) as a brown solid (58%), m.p. 50-53°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Rotary evaporation of the hexane mother liquor gave a brown oil whose t.l.c. in hexane-methylene chloride (1:3) over silica showed it to be a mixture of unchanged starting material (131a) and the desired product (132a) which was not further investigated.

The aqueous mother liquor was stirred at room temperature overnight, filtered to remove titanium residues, and extracted with methylene chloride to give no material.

(d) Repetition of the reaction described in (a) before using seven equivalents of 15% w/v aqueous titanium trichloride solution for 64h gave an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (40.0 ml), and extracted with methylene chloride to give an oil. This was triturated with hexane to give a solid, which was combined with further material obtained by rotary evaporation of the hexane mother liquor and trituration of the residue with hexane, to afford 2-(2-
bromophenoxy)aniline (132a) as a pale brown solid (55%), m.p. 47-50°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Rotary evaporation of the hexane mother liquor gave an oil whose t.l.c. in hexane-methylene chloride (1:3) over silica showed it to be a complex mixture containing more of the desired product (132a), which was not further investigated.

The aqueous mother liquor was stirred at room temperature overnight, filtered to remove titanium residues, and extracted with methylene chloride to give no material.

(ii) 2-(2-Iodophenoxy)aniline (132b)

After 66h the mixture from 2-(2-iodophenoxy)nitrobenzene (131b) was rotary evaporated to give an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (20.0 ml), and extracted with methylene chloride to give a solid. This was combined with further material obtained by stirring the aqueous mother liquor at room temperature overnight, filtration to remove titanium residues, and extraction with methylene chloride to afford 2-(2-iodophenoxy)aniline (132b) (4.3 g; 68%) which formed colourless crystals, m.p. 84° [from hexane-ethyl acetate (9:1)], ν_{max} 3460 and 3380 (NH) cm^{-1}, δ_{H}(CDCl_{3}) 7.82(1H, dd, J 8 and 2 Hz, ArH), 7.33-6.67(7H, m, ArH), and 3.82-3.78(2H, bs, NH2) (exch).

2-(2-Bromophenoxy)aniline (132a)

A solution of 2-(2-bromophenoxy)nitrobenzene (131a) (5.9 g; 0.02 mol) in tetrahydrofuran (100.0 ml) was stirred under nitrogen and treated portionwise with 15% w/v aqueous titanium trichloride solution (46.0 ml; 0.04 mol), then the mixture was stirred at room temperature, under nitrogen, for 2.5h. Successive further portions of 15% w/v aqueous titanium chloride
solution (23.0 ml; 0.02 mol) were added at time intervals of 3h, 15.5h, 8h, and finally the mixture was stirred at room temperature, under nitrogen, for a further 19h.

Rotary evaporation of the mixture gave an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (20.0 ml), and extracted with methylene chloride to give an oil which was triturated with hexane-ether to afford 2-(2-bromophenoxo)aniline (132a) as a pale brown solid (1.7 g; 32%), m.p. 54-59°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the hexane-ether mother liquor gave an oil (1.3 g) whose t.l.c. in hexane-methylene chloride (1:3) over silica showed it to be a mixture of unchanged starting material (131a) and the desired product (132a), which was not further investigated.

The aqueous mother liquor was stirred at room temperature overnight, filtered to remove titanium residues, and extracted with methylene chloride to give no material.

4-Chloro-2-(3-methoxyphenoxy)aniline (126)

A solution of 4-chloro-2-(3-methoxyphenoxy)nitrobenzene (125) (5.6 g; 0.02 mol) was hydrogenated over 10% palladium-on-charcoal (0.56 g) at room temperature and atmospheric pressure for 8h, during which time hydrogen (1850 ml; 0.08 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give 4-chloro-2-(3-methoxyphenoxy)aniline (126) as a colourless oil (5.1 g; 100%), b.p. 128-132°/0.05-0.10 mmHg, νmax 3480 and 3360 (NH) cm⁻¹, δH(CDCl₃) 7.32-6.46(7H, m, ArH), 4.00-3.50(2H, bs, NH₂) (exch).
M-(2-Aryloxy)phenylformamides (115a and b), (127), and (133a and b)

A mixture of the appropriate 2-aryloxyaniline derivative (0.03 mol) and 98-100% formic acid (80.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1-3h then worked up as described for the individual reactions below.

(i) **N-(2-Phenoxy)phenylformamide (115b)**

After 2h at reflux the cooled mixture from 2-phenoxyaniline (114b) was rotary evaporated to afford N-(2-phenoxy)phenylformamide (115b) as a colourless solid (97%), m.p. 89-91° (lit., 82-92.5°).

(ii) **N-[2-(3-Methoxyphenoxy)phenyl]formamide (115a)**

After 3h at reflux the cooled mixture from 2-(3-methoxyphenoxy)aniline (114a) was rotary evaporated to give an oil which was dissolved in methylene chloride and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml) then rotary evaporated to give an oil. On cooling, this solidified to afford N-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (93%) which formed colourless plates, m.p. 77-78° [from hexane-toluene (5:1)], b.p. 171-174°/1.0 mmHg, \( \nu_{\text{max}} \) 3140 (NH) and 1690 (C=O) cm\(^{-1}\), \( \delta_{\text{H(CDCI}_3)} \) 8.49-8.37(1H, m, CHO), 7.70(1H, bs, NH) (exch), 7.33-6.49(8H, m, ArH), and 3.76(3H, s, OCH\(_3\)).

(iii) **N-[2-(2-Bromophenoxy)phenyl]formamide (133a)**

After 1h at reflux the cooled mixture from 2-(2-bromophenoxy)aniline (132a) was rotary evaporated to give an oil. This solidified on cooling to afford N-[2-(2-bromophenoxy)phenyl]formamide (133a) (91%) which formed colourless crystals, m.p. 107-108° [from hexane-ethyl acetate (4:1)], \( \nu_{\text{max}} \) 3360-3220 (NH) and 1665 (C=O) cm\(^{-1}\), \( \delta_{\text{H(CDCI}_3)} \) 8.50-8.38(1H, m, CHO), 8.00-7.75(1H, bs, NH), and 7.70-6.65(8H, m, ArH).
(iv) \(N\)-[2-(2-iodophenoxy)phenyl]formamide (133b)

After 1h at reflux the cooled mixture from 2-(2-iodophenoxy)aniline (132b) was rotary evaporated to give an oil which was triturated with hexane-ethyl acetate to afford \(N\)-[2-(2-iodophenoxy)phenyl]formamide (133b) (9.6 g; 94%) which formed colourless plates, m.p. 75-76° [from hexane-ethyl acetate (4:1)], \(v_{\text{max}}\) 3240-3160 (NH) and 1690 (C=O) cm\(^{-1}\), \(\delta_H (\text{CDCl}_3) 8.48-8.47(1\text{H, s, CHO}), 7.87(1\text{H, dd, J 5 and 2 Hz, ArH}), 7.90-7.84(1\text{H, bs, NH}), 7.36-7.24(2\text{H, m, ArH}), 7.18-6.87(4\text{H, m, ArH}), \) and \(6.78-6.71(1\text{H, m, ArH})\).

(v) \(N\)-[4-Chloro-2-(3-methoxyphenoxy)phenyl]formamide (127)

After 2h at reflux the cooled mixture from 4-chloro-2-(3-methoxyphenoxy) aniline (126) was rotary evaporated to give an oil which was dissolved in methylene chloride and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml). Rotary evaporation of the combined methylene chloride extracts gave \(N\)-[4-chloro-2-(3-methoxyphenoxy)phenyl]formamide (127) (77%) which formed colourless plates, m.p. 85-86° [from hexane-toluene (5:1)], \(v_{\text{max}}\) 3260 (NH) and 1690 (C=O) cm\(^{-1}\), \(\delta_H (\text{CDCl}_3) 8.43(1\text{H, d, J 2 Hz, CHO}), 7.70(1\text{H, bs, NH})\) (exch), 7.38-6.54(7\text{H, m, ArH}), and 3.78(3\text{H, s, OCH}_3).

2-Aryloxyphenyl leucyanides (116a and b), (128), and (134a and b)

(a) A solution of the corresponding \(N\)-(2-aryloxy)phenylformamide derivative (0.02 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was stirred and treated with carbon tetrachloride (3.7 g; 0.024 mol) then triphenylphosphine (6.3 g; 0.024 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (4.0 g; 0.04 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric
moisture, for 2.5h then worked up as described for the individual reactions below.

(i) 2-Phenoxyphenyl Isocyanide (116b)

The cooled mixture from N-(2-phenoxy)phenylformamide (115b) was rotary evaporated to give a semi-solid which was treated with water (25.0 ml) and extracted with methylene chloride to give an oil (13.3 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 2-phenoxyphenyl isocyanide (116b) as an unstable orange-yellow oil (3.2 g; 82%), \( \nu_{\text{max}} 2120 \text{ cm}^{-1} \), \( \delta(\text{CDCl}_3) 7.45-6.70(9\text{H, m, ArH}) \).

Elution with hexane-ethyl acetate (6:4) gave unchanged N-(2-phenoxy)phenylformamide (115b) as an orange oil (0.85 g; 20%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

Final elution with methanol gave an oil which was triturated with ethyl acetate to afford triphenylphosphine oxide as a cream solid (5.2 g), m.p. 150-156° (lit., \( 126 \) 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

(ii) 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a)

The cooled mixture from N-[2-(3-methoxyphenoxy)phenyl]formamide (115a) was rotary evaporated to give a semi-solid which was treated with water (20.0 ml) and extracted with methylene chloride to give an oil which was triturated with ether to afford triphenylphosphine oxide as a cream solid (4.0 g), m.p. 147-152° (lit., \( 126 \) 152-153°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil (9.0 g) which was flash-chromatographed over silica.
Elution with hexane-ethyl acetate (9:1) gave 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as an unstable orange-yellow oil (3.9 g; 87%) which decomposed on attempted distillation, $\nu_{\text{max}} 2120$ (NC) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.48-6.53(8H, m, ArH) and 3.78(3H, s, OCH$_3$).

Elution with methanol gave a viscous brown oil (3.9 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of unreacted starting material (115a) and triphenylphosphine oxide which was therefore not further investigated.

(b) 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a)

A solution of $N$-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (4.8 g; 0.02 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (3.1 g; 0.02 mol), followed by triphenylphosphine (6.4 g; 0.024 mol) then triethylamine (2.0 g; 0.02 mol) and the mixture was stirred and heated at 60$^\circ$ (oil bath), with exclusion of atmospheric moisture, for 2.5h.

Rotary evaporation of the cooled mixture gave a semi-solid which was treated with water (20.0 ml) and extracted with methylene chloride to give a solid (11.7 g) which was flash-chromatographed over silica.

Elution with hexane ethyl acetate (8:2) gave 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as a yellow-orange oil (3.0 g; 67%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (7:3) gave unreacted $N$-[2-(3-methoxyphenoxy)phenyl]formamide (115a) as a viscous orange oil (0.40 g; 8%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (3:7) through to ethyl acetate gave triphenylphosphine oxide as a colourless solid (4.8 g), m.p. 155-157$^\circ$ (lit.,$^{126}$ 152-153$^\circ$), identical (m.p. and i.r. spectrum) to an authentic sample.
Final elution with methanol gave a semi-solid (1.2 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to contain mainly triphenylphosphine oxide.

(c) A solution of the corresponding N-(2-aryloxy)phenylformamide derivative (0.015 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was stirred and treated with carbon tetrachloride (2.3 g; 0.015 mol), followed by triphenylphosphine (4.7 g; 0.018 mol), then triethylamine (3.0 g; 0.03 mol) and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h then worked up as described for the individual reactions below.

(i) 2-(2-Bromophenoxy)phenyl Isocyanide (134a)

The cooled mixture from N-[2-(2-bromophenoxy)phenyl]formamide (133a) was rotary evaporated to give a semi-solid which was treated with water (25.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 2-(2-bromophenoxy)phenyl isocyanide (134a) (63%) which formed pale yellow crystals, m.p. 57-58° (from hexane), ν\textsubscript{max} 2120 (NC) cm\textsuperscript{-1}, δ\textsubscript{H}(CDCl\textsubscript{3}) 7.66(1H, dd, J 6 and 2 Hz, ArH), 7.45(1H, dd, J 6 and 2 Hz, ArH), 7.38-7.25(2H, m, ArH), 7.15-7.01(3H, m, ArH), and 6.74(1H, dd, J 8 and 1 Hz, ArH).

Elution with hexane-ethyl acetate (7:3) gave unreacted N-[2-(2-bromophenoxy)phenyl]formamide (133a) as a yellow solid (20%), m.p. 95-99°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (2:8) through to ethyl acetate gave triphenylphosphine oxide as a colourless solid (1.6 g), m.p. 150-154° (lit.,\textsuperscript{126} 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.
Final elution with methanol gave a semi-solid whose t.l.c. in hexane-
ethyl acetate (1:1) over silica showed it to contain mainly triphenylphosphine
oxide.

(ii) 2-(2-Iodophenoxy)phenyl Isocyanide (134b)

The cooled mixture from N-[2-(2-iodophenoxy)phenyl]formamide
(133b) was rotary evaporated to give a semi-solid which was treated with
water (25.0 ml) and extracted with methylene chloride to give a brown oil
which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 2-(2-iodophenoxy)phenyl
isocyanide (134b) (75%) which formed pale yellow crystals, m.p. 72-73°C
[from hexane-ethyl acetate (20:1)], \( \nu_{\text{max}} \) 2120 (NC) cm\(^{-1}\), \( \delta_{\text{H(CDCI3)}} \) 7.94-7.82(1H, m, ArH) and 7.50-6.67(7H, m, ArH).

Further elution with methanol gave a semi-solid whose t.l.c. in hexane-
ethyl acetate (1:1) over silica showed it to be a mixture of unchanged starting
material (133b) and triphenylphosphine oxide which was not further
investigated.

(iii) 4-Chloro-2-(3-methoxyphenoxy)phenyl Isocyanide (128)

The cooled mixture from N-[4-chloro-2-(3-methoxyphenoxy)phenyl]
formamide (127) was rotary evaporated to give a semi-solid which was
treated with water (25.0 ml) and extracted with methylene chloride to give an
oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 4-chloro-2-(3-
methoxyphenoxy)phenyl isocyanide (128) as an unstable orange-brown oil
(3.2 g; 82%), \( \nu_{\text{max}} \) 2120 (NC) cm\(^{-1}\), \( \delta_{\text{H(CDCI3)}} \) 7.40-6.54(7H, m, ArH) and
3.80(3H, s, OCH\(_3\)).

Elution with hexane-ethyl acetate (7:3) gave a brown oil (0.90 g) whose
t.l.c. in hexane-ethyl acetate showed it to be a mixture of the unreacted
starting material (127) and the desired product (128) which was not further investigated.

Elution with methanol gave a semi-solid (4.2 g) which was triturated with ethyl acetate to afford triphenylphosphine oxide as a pale brown solid (3.9 g), m.p. 144-147° (lit., 126 152-153°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

2-(2-Bromophenoxy)phenyl isocyanide (134a)

A solution of $N$-[2-(2-bromophenoxy)phenyl]formamide (133a) (5.8 g; 0.02 mol) in anhydrous methylene chloride (50.0 ml) was stirred and treated with $N$-ethyldiisopropylamine (7.2 g; 0.056 mol) then dropwise at 0° (ice bath) with phosphoryl chloride (3.4 g; 0.022 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h.

The mixture was treated portionwise with 2 M aqueous sodium carbonate solution (22.0 ml), stirred at room temperature for 1h, then treated with water (20.0 ml) and extracted with methylene chloride. The combined extracts were washed twice with water (2 x 10.0 ml) and rotary evaporated to give an oil (7.1 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 2-(2-bromophenoxy)phenyl isocyanide (134a) (4.7 g; 86%) as a pale green solid, m.p. 56-58°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with methanol gave a viscous intractable brown oil (1.5 g) which was not further investigated.

The Attempted Reaction of $N$-[2-3-Methoxyphenoxy)phenyl]formamide (115a) with Thionyl Chloride in Dimethylformamide

A solution of $N$-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (1.2 g; 0.005 mol) in anhydrous dimethylformamide (10.0 ml) was stirred under
nitrogen and treated dropwise at -50° (liquid nitrogen-chloroform slush bath) with a solution of thionyl chloride (0.62 g; 0.0052 mol) in anhydrous dimethylformamide (1.5 ml) and the mixture was momentarily allowed to warm to -45° then recooled to -50°, treated in one portion with sodium carbonate (1.1 g; 0.01 mol), and stirred at room temperature, under nitrogen, for 18h.

The mixture was treated with ice-cold water (20.0 ml) and extracted with ether to give a yellow-brown oil (1.2 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture containing mainly unchanged starting material (115a), which therefore was not further investigated.

The Attempted Preparation of 2-(3-Methoxyphenoxo)phenyl isocyanide (116a) using Trimethylphosphite

A solution of N-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (2.4 g; 0.01 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was treated with carbon tetrachloride (1.5 g; 0.01 mol), followed by trimethylphosphite (1.5 g; 0.012 mol), then triethylamine (1.0 g; 0.01 mol) and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

Rotary evaporation of the cooled mixture gave an oil which was treated with water (20.0 ml) and extracted with methylene chloride to give unchanged N-[2-(3-methoxyphenoxy)phenyl]formamide (115a) as a colourless solid (2.1 g; 88%); m.p. 80-82°, identical (m.p. and i.r. spectrum) to a sample prepared previously.
**The Hydrolysis of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Ethanoic Hydrochloric Acid**

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in ethanol (10.0 ml) was treated with 2 M aqueous hydrochloric acid solution (2.5 ml) and the mixture was stirred and heated under reflux for 1 h.

Rotary evaporation of the cooled mixture gave an oil which was treated with water (5.0 ml) and extracted with methylene chloride to give 2-(3-methoxyphenoxy)aniline (114a) as a brown oil (0.40 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

**The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Acetyl Chloride**

(a) **In diethyl ether**

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous ether (5.0 ml) was stirred and treated dropwise at -10 ° (ice-salt bath) with a solution of acetyl chloride (0.16 g; 0.002 mol) in anhydrous ether (5.0 ml) and the mixture was stirred at -10°, with exclusion of atmospheric moisture, for 2 h.

The mixture was rotary evaporated to give unchanged 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as a brown oil (0.46 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(b) **In 1,2-dimethoxyethane**

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was treated with a solution of acetyl chloride (0.16 g; 0.002 mol) in anhydrous 1,2-
dimethoxyethane (5.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 26h.

The cooled mixture was rotary evaporated to give an oil (0.47 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) to hexane-ethyl acetate (3:7) gave only a series of intractable oils and gums (0.40 g) from which no identifiable material could be obtained.

Final elution with methanol gave a brown semi-solid (0.07 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which was not further investigated.

**The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Aluminium Trichloride in Methylene Chloride**

A suspension of anhydrous aluminium trichloride (2.4 g; 0.018 mol) in anhydrous methylene chloride (10.0 ml) was stirred, treated dropwise at room temperature with a solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 2h.

The mixture was cooled (ice bath) and treated dropwise with a solution of concentrated hydrochloric acid (1.0 ml) in water (5.0 ml), then diluted with water (10.0 ml) and filtered to remove aluminium residues. Separation of the filtrate and extraction of the aqueous layer with methylene chloride gave a brown gum (0.60 g) which was triturated with ether to afford a dark brown polymeric solid (0.30 g), m.p. 265-270\(^\circ\), whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.
Rotary evaporation of the ethereal mother liquor gave a brown gum (0.15 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture which yielded no identifiable material.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Stannic Chloride

(a) In 1,2-dichloroethane under reflux

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred under nitrogen, treated dropwise at room temperature with a solution of stannic chloride (6.5 g; 0.025 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture was stirred and heated under reflux, under nitrogen, for 15h.

The mixture was cooled (ice bath) and treated dropwise with 60% w/v aqueous sodium hydroxide solution (17.0 ml; 0.25 mol) then stirred in the ice-bath for 15 min, diluted with water (50.0 ml), and extracted with methylene chloride to give a brown froth (1.1 g). This was washed with ether to give a brown solid (0.87 g), m.p. 308-315°, m/z (El/MS) >400, which could not be crystallised or resolved by t.l.c. in ethyl acetate, or in hexane-ethyl acetate (1:1), over silica and therefore was not further investigated.

Rotary evaporation of the ethereal mother liquor gave a red gum (0.22 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which was not further investigated.

(b) In methylene chloride at -10°

Repetition of the reaction described in (a) above for 2h at -10° (ice-salt bath) using methylene chloride as the solvent gave a dark brown polymeric solid (1.0 g), m.p. 295-325°, which could not be crystallised or resolved by t.l.c. in hexane-ethyl acetate (1:1) over silica.
(c) **In methylene chloride at -78°**

A solution of stannic chloride (0.52 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen and treated dropwise at -78° (solid CO₂-acetone bath) with a solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) and the mixture was stirred at -78°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 10 min, and filtered to remove tin residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a dark brown polymeric solid (0.50 g), m.p. 55-65°, which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) through to methanol gave only a series of intractable oils (0.20 g) which were not further investigated.

**The Attempted Reaction of the Polymer Obtained from the Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Stannic Chloride, with Ethanolic Potassium Hydroxide**

A solution of the product [obtained from the reaction of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) with stannic chloride in refluxing 1,2-dichloroethane (0.45 g)] in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide solution (2.5 ml) and the mixture was stirred and heated under reflux for 2h.

The cooled mixture was filtered to give unchanged starting material (0.35 g; 78%), m.p. 300-310°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
Rotary evaporation of the aqueous ethanolic mother liquor gave a gum which was treated with water (5.0 ml) and extracted with methylene chloride to give a brown gum (0.08 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl isocyanide (116a) with Stannic Chloride in Methylene Chloride Monitored by Infrared Spectroscopy

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen and treated dropwise at -10° (ice-salt bath) with a solution of stannic chloride in anhydrous methylene chloride (2.0 ml of a 1.0 M solution; 0.002 mol) and the mixture was shaken, a portion removed and its i.r. spectrum recorded. This showed the complete absence of any isocyano absorption, therefore the mixture was not further investigated.

3-Methoxydibenzo[b,f][1,4]oxazepine (118)

(a) A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (2.3 g; 0.01 mol) in anhydrous methylene chloride or anhydrous 1,2-dichloroethane (40.0 ml) was stirred and treated portionwise at 0° (ice bath) with a suspension of powdered zinc chloride (6.8 g; 0.05 mol) in anhydrous methylene chloride (25.0 ml) or anhydrous 1,2-dichloroethane (75.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 24h, then worked up as described for the individual reactions below.

(i) Using methylene chloride as the solvent

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the ice bath
for 15 min, then diluted with water (40.0 ml) and filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (2.3 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unchanged 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as a yellow oil (1.3 g; 56%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

Elution with hexane-ethyl acetate (8:2) gave 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (1.1 g; 47%), b.p. 160-170°/3.5-4.0 mmHg (lit., 69 152-154°/0.1 mmHg), $\nu_{\text{max}}$ 1610 (Ar) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.37(1 H, s, N=CH), 7.33-7.06(5H, m, ArH), 6.78-6.48(2H, m, ArH), and 3.82(3H, s, OCH$_3$), $\delta_{\text{c}}$(CDCl$_3$) 163.9(quat), 161.6(quat), 160.0(N=CH), 152.1(quat), 140.4(quat), 131.3(CH), 129.0(CH), 128.3(CH), 125.5(CH), 121.1(CH), 120.1(quat), 110.8(CH), 105.2(CH), and 55.4(OCH$_3$).

Further elution with hexane-ethyl acetate (7:3) through to methanol gave no material.

(ii) Using 1,2-dichloroethane as the solvent

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.05 mol), stirred in the ice bath for 10 min, then diluted with water (60.0 ml) and filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a red oil which was purified by distillation to afford 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow oil (33%), b.p. 160-170°/0.5-1.0 mmHg (lit., 69 152-154°/0.1 mmHg), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.
Distillation left a black residue (0.50 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which was not further investigated.

(b) A solution of 2-(3-methoxyphenoxo)phenyl isocyanide (116a) (2.3 g; 0.01 mol) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (9.5 g; 5.5 ml; 0.05 mol) in anhydrous methylene chloride (25.0 ml), and the mixture stirred and heated under reflux, under nitrogen, for 24h.

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (33 ml; 0.5 mol), stirred in the ice bath for 15 min, then diluted with water (40.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (2.0 g; 89%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(c) The reaction mixture from repetition of the reaction described in (b) above at -10° for 2h was treated dropwise at -10° (ice-salt bath) with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the cooling bath for 0.5h, then diluted with water (30.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (100%), δH(CDCl3) 8.38(1H, s, N=CH), 7.35-7.32(1H, m, ArH), 7.22(1H, d, J 9 Hz, ArH), 7.19-7.07(3H, m, ArH), 6.70(1H, dd, J 9 and 3 Hz, ArH), 6.66(1H, d, J 3 Hz, ArH), and 3.82(3H, s, OCH3).

(d) The reaction mixture from repetition of the reaction described in (c) above using four equivalents of titanium tetrachloride (7.6 g; 4.4 ml; 0.04 mol)
was poured into 10% w/v aqueous sodium hydrogen carbonate solution (308 ml; 0.4 mol), stirred at room temperature for 10 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a yellow oil whose t.l.c. in hexane-ethyl acetate (1:1) over silica and proton n.m.r. spectrum showed it to be a mixture of \( N\)-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (58%) and 3-methoxydibenzo[b,f][1,4]oxazepine (118) (42%).

(e) The reaction mixture from repetition of the reaction described in (c) before using three equivalents of titanium tetrachloride (5.5 g; 3.5 ml; 0.03 mol) was poured into 10% w/v aqueous sodium hydrogen carbonate solution (231 ml; 0.3 mol), stirred at room temperature for 10 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an orange oil whose t.l.c. in ether over silica and proton n.m.r. spectrum showed it to be a mixture of \( N\)-[2-(3-methoxyphenoxy)phenyl]formamide (115a) (56%) and 3-methoxydibenzo[b,f][1,4]oxazepine (118) (44%).

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Zinc Chloride in Acetonitrile

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol) in anhydrous acetonitrile (25.0 ml) was stirred and treated portionwise at 0° (ice bath) with a suspension of powdered zinc chloride (3.4 g; 0.025 mol) in anhydrous acetonitrile (40.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 24h.

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (17.0 ml; 0.25 mol), stirred in the ice bath
for 20 min, then diluted with water (25.0 ml) and filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a red-brown oil (1.0 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of unreacted starting material (116a) and N-[2-(3-methoxyphenoxy)phenyl]formamide (115a), which was not further investigated.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl isocyanide (116a) with One Equivalent of Titanium Tetrachloride in Methylene Chloride

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen and treated dropwise at -10 °C (ice-salt bath) with a solution of titanium tetrachloride (0.38 g; 0.22 ml; 0.002 mol) in anhydrous methylene chloride (5.0 ml) and the mixture was stirred at -10 °C, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 15 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.48 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave N-[2-(3-methoxyphenoxy)phenyl]formamide (115a) as a viscous yellow oil (0.41 g; 90%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

Final elution with methanol gave no material.
The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Aqueous Sodium Hydrogen Carbonate

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.23 g; 0.001 mol) in anhydrous methylene chloride (10.0 ml) was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol) and the mixture was stirred at room temperature for 10 min.

The mixture was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were rotary evaporated to give unchanged 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as a yellow oil (0.22 g; 97%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Aqueous Hydrochloric Acid then Aqueous Sodium Hydrogen Carbonate

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.23 g; 0.001 mol) in anhydrous methylene chloride (10.0 ml) was stirred and treated in one portion with 2 M aqueous hydrochloric acid solution (2.0 ml; 0.004 mol) and the mixture was stirred at room temperature for 5 min. 10% w/v aqueous sodium hydrogen carbonate solution (8.0 ml; 0.01 mol) was added in one portion and the mixture was stirred at room temperature for 10 min.

The mixture was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were rotary evaporated to give unchanged 2-(3-methoxyphenoxy)phenyl isocyanide (116a) as a yellow oil (0.24 g; 100%), identical (i.r. spectrum and t.l.c. in ether over silica) to a sample prepared previously.
The Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Titanium Tetrachloride in Methylene Chloride Monitored by Infrared Spectroscopy

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen and treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride in anhydrous methylene chloride (2.0 ml of a 1.0 M solution; 0.002 mol) and the mixture was shaken, a portion withdrawn, and its i.r. spectrum recorded. Further portions of the 1.0 M titanium tetrachloride solution (2.0 ml; 0.002 mol) were added at 15 min intervals until a total of 10.0 ml had been added. Immediately after each addition a portion of the mixture was withdrawn and its i.r. spectrum was recorded.

The mixture was stirred at -10° for a further 1 h then treated dropwise with 60% w/v aqueous sodium hydroxide solution (7.0 ml; 0.1 mol), stirred at room temperature for 17 h, then treated with water (10.0 ml) and filtered to remove titanium residues. The filtrate was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were rotary evaporated to give 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange-yellow oil (0.20 g; 44%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide (116a) with Boron Trifluoride Etherate in Methylene Chloride

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred, treated dropwise at 0° (ice bath) with a solution of boron trifluoride etherate (1.4 g; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was
stirred and heated under reflux, with exclusion of atmospheric moisture, for 24h.

The mixture was cooled (ice bath) and treated with ice (10.0 g), stirred in the cooling bath for 1h, then extracted with methylene chloride to give a dark brown polymeric solid (0.52 g), m.p. 285-290°, which could not be purified by crystallisation or resolved by t.l.c. in hexane-ethyl acetate (1:1) over silica, and therefore was not further investigated.

The Attempted Reaction of 2-Phenoxyphenyl Isocyanide (116b) with Titanium Tetrachloride in Methylene Chloride

A solution of 2-phenoxyphenyl isocyanide (116b) (2.0 g; 0.01 mol) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (9.5 g; 5.5 ml; 0.05 mol) in anhydrous methylene chloride (25.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 24h.

The mixture was cooled (ice bath), treated dropwise with 60% w/w aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the ice bath for 20 min, then diluted with water (40.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (2.0 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a red oil (0.30 g). This was distilled to give a colourless oil, b.p. 115-125°/0.05-1.0 mmHg, which solidified to afford 2-phenoxyaniline (114b) as a cream solid (0.10 g; 6%), m.p. 39-42° (lit.,125 44-45°).

Elution with hexane-ethyl acetate (8:2) gave N-(2-phenoxy)phenylformamide (115b) as a red oil (1.3 g; 61%), identified by
comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (2:1) over silica] to a sample prepared previously.

Final elution with methanol gave an intractable brown semi-solid (0.50 g) which was not investigated further.

**The Attempted Reaction of 4-Chloro-2-(3-methoxyphenoxy)phenyl Isocyanide (128) with Titanium Tetrachloride in Methylene Chloride**

A solution of 4-chloro-2-(3-methoxyphenoxy)phenyl isocyanide (128) (2.6 g; 0.01 mol) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (9.5 g; 5.5 ml; 0.05 mol) in anhydrous methylene chloride (25.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was treated dropwise at -10° (ice-salt bath) with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the cooling bath for 15 min, then treated with water (40.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined extracts gave crude \(N\)-[4-chloro-2-(3-methoxyphenoxy)phenyl]formamide (127) as a red oil (1.9 g; 69%) which was distilled to afford pure \(N\)-[4-chloro-2-(3-methoxyphenoxy)phenyl] formamide (127) as a yellow oil (1.1 g; 40%), b.p. 160-170°/0.05-0.10 mmHg, identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

Distillation left an intractable black residue (0.50 g) which was not further investigated.
The Attempted Reaction of 2-(2-Bromophenoxy)phenyl Isocyanide (134a) with n-Butyllithium in Tetrahydrofuran

A solution of 2-(2-bromophenoxy)phenyl isocyanide (134a) (1.1 g; 0.004 mol) in anhydrous tetrahydrofuran (20.0 ml) was stirred under nitrogen and treated dropwise at -78° (solid CO₂-acetone bath) with n-butyllithium (2.8 ml; 0.004 mol) and the mixture was stirred at room temperature, under nitrogen, for 17h.

The mixture was treated with saturated aqueous ammonium chloride solution (25.0 ml), stirred at room temperature for 10 min, and extracted with methylene chloride to give a solid (0.90 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) through to methanol gave a series of complex oils and solids (0.88 g) from which no identifiable material was obtained and which were therefore not investigated further.

The Attempted Reaction of 2-(2-Bromophenoxy)phenyl Isocyanide (134a) with Tributyltin Hydride in Benzene

A solution of azo-bis-isobutyronitrile (0.015 g) in anhydrous benzene (20.0 ml) was stirred under nitrogen and treated in one portion with a solution of 2-(2-bromophenoxy)phenyl isocyanide (134a) (1.1 g; 0.004 mol) in anhydrous benzene (10.0 ml) then dropwise with a solution of tributyltin hydride (1.5 g; 0.005 mol) in anhydrous benzene (10.0 ml) and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was rotary evaporated to give an oil (3.0 g) which was washed with hexane to leave unchanged 2-(2-bromophenoxy)phenyl isocyanide (134a) as an orange-yellow solid (0.54 g; 49%), m.p. 54-58°, identical (m.p. and i.r. spectrum) to a sample prepared previously.
Rotary evaporation of the hexane mother liquor gave an orange oil (1.9 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave an orange oil (0.97 g) which was triturated with hexane to afford 2-(2-bromophenoxy)phenyl isocyanide (134a) as a yellow solid (0.35 g; 32%), m.p. 58-60°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ethyl acetate (7:3) through to methanol gave no further identifiable material.

The Attempted Reaction of 2-(2-Bromophenoxy)phenyl Isocyanide (134a) with Magnesium in Ether

A solution of 2-(2-bromophenoxy)phenyl isocyanide (134a) (0.55 g; 0.002 mol) in anhydrous ether (20.0 ml) was stirred and treated with Grignard grade magnesium turnings (0.048 g; 0.002 mol) followed by a crystal of iodine then stirred and heated under reflux, with exclusion of atmospheric moisture, for 2h. Since there was no apparent reaction two drops of 1,2-dibromoethane were added, and stirring and heating under reflux with exclusion of atmospheric moisture was continued for a further 14h.

The cooled mixture was treated with 2 M aqueous hydrochloric acid solution (5.0 ml), stirred at room temperature for 1h, and extracted with methylene chloride to give a brown oil (0.69 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the unreacted starting material (134a) and N-[2-(2-bromophenoxy)phenyl]formamide (133a) which therefore was not further investigated.
The Attempted Reaction of 2-(2-Iodophenoxy)phenyl Isocyanide (134b) with Magnesium

(a) In diethyl ether

A solution of 2-(2-iodophenoxy)phenyl isocyanide (134b) (0.64 g; 0.002 mol) in anhydrous ether (20.0 ml) was stirred and treated at room temperature with Grignard grade magnesium turnings (0.048 g; 0.002 mol) followed by a crystal of iodine then stirred and heated under reflux, with exclusion of atmospheric moisture, for 4 h. Since there was no apparent reaction another crystal of iodine was added and stirring and heating under reflux with exclusion of atmospheric moisture continued for a further 2 h. As there still appeared to be no reaction occurring two drops of 1,2-dibromoethane were added and stirring and heating under reflux with exclusion of atmospheric moisture continued for a further 1.5 h.

The cooled mixture was treated with 2 M aqueous hydrochloric acid solution (5.0 ml), stirred at room temperature for 0.5 h, and extracted with methylene chloride to give a brown oil (0.70 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the unreacted starting material (134b) and N-[2-(2-iodophenoxy)phenyl]formamide (133b) which was therefore not further investigated.

(b) In tetrahydrofuran

A suspension of Grignard magnesium turnings (0.048 g; 0.002 mol) in anhydrous tetrahydrofuran (20.0 ml) was stirred, treated with one drop of methyl iodide and the mixture was warmed gently then treated dropwise with a solution of 2-(2-iodophenoxy)phenyl isocyanide (134b) (0.64 g; 0.002 mol) in anhydrous tetrahydrofuran (5.0 ml). The mixture was stirred at room temperature for 0.5 h then stirred and heated under reflux, with exclusion of atmospheric moisture, for 3 h. Since there was no apparent reaction a crystal
of iodine was added and stirring and heating under reflux with exclusion of atmospheric moisture continued for a further 3h.

The cooled mixture was treated with 2 M aqueous hydrochloric acid solution (5.0 ml), stirred at room temperature for 1h, and extracted with methylene chloride to give a brown oil (0.58 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the unchanged starting material (134b) and \(N\)-(2-(2-iodophenoxy)phenyl)formamide (133b) which was therefore not further investigated.

(c) In di-n-butyl ether

A suspension of Grignard grade magnesium turnings (0.048 g; 0.002 mol) in anhydrous di-n-butyl ether (20.0 ml) was stirred and treated with a crystal of iodine, then warmed to 50-90° (oil bath) and treated dropwise with stirring with a solution of 2-(2-iodophenoxy)phenyl isocyanide (134b) (0.64 g; 0.002 mol) in anhydrous di-n-butyl ether (5.0 ml). The mixture was then stirred and heated at 80-85° (oil bath), with exclusion of atmospheric moisture, for 2h.

The cooled mixture was treated with 2 M aqueous hydrochloric acid solution (5.0 ml), stirred at room temperature for 1h, then filtered to remove an unidentified brown solid (0.08 g), m.p. >330°. The filtrate was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were rotary evaporated to give an oil (0.61 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a multicomponent oil (0.16 g) which could not be resolved by preparative t.l.c. in hexane-ethyl acetate (9:1) over silica.

Further elution with hexane-ethyl acetate (9:1) gave a brown oil (0.24 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the unreacted starting material (134b) and \(N\)-(2-(2-
iodophenoxy)phenyl[formamide (133b) which could not be separated by preparative t.l.c. in hexane-ethyl acetate (1:1) over silica.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl isocyanide (116a) with Acetyl Chloride in the Presence of Aluminium Trichloride

A suspension of anhydrous aluminium trichloride (0.67 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was stirred, treated dropwise at -10° (ice-salt bath) with a solution of acetyl chloride (0.40 g; 0.005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 10 min. A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was added in one portion and the mixture was stirred at room temperature for 0.5h then stirred and heated under reflux, with exclusion of atmospheric moisture for 2h.

The cooled mixture was treated with a solution of concentrated hydrochloric acid (1.0 ml) in water (5.0 ml), stirred at room temperature for 15h, then treated with water (10.0 ml) and extracted with methylene chloride to give a dark red-brown polymeric solid (1.4 g), m.p. >350°, m/z (FABMS) > 400, which could not be crystallised or resolved by t.l.c. in hexane-ethyl acetate (1:1) over silica and was therefore not further investigated.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl isocyanide (116a) with Acetyl Chloride in the Presence of Titanium Tetrachloride

(a) Under reflux

A solution of titanium tetrachloride (0.95 g; 0.55 ml; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of acetyl chloride (0.40 g; 0.005 mol) in anhydrous methylene chloride (5.0 ml) and the mixture was
stirred at room temperature for 10 min then treated in one portion with a
solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol)
in anhydrous methylene chloride (10.0 ml). The mixture was then stirred at
room temperature for 0.5 h then stirred and heated under reflux, under
nitrogen, for 24 h.

The mixture was cooled (ice bath), treated dropwise with stirring with
60% w/v aqueous sodium hydroxide solution (4.0 ml; 0.05 mol), stirred in the
ice bath for 15 min, then diluted with water (20.0 ml) and filtered to remove
titanium residues. Separation of the filtrate, extraction of the aqueous layer
with methylene chloride, and rotary evaporation of the combined organic
extracts gave a gum (1.0 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave an oil (0.30 g) which was
distilled to afford 3-methoxydibenzo[b,f][1,4]oxazepine (118) as a yellow oil
(0.24 g; 22%), b.p. 168-175°/0.30-0.50 mmHg (lit., 152-154°/0.1 mmHg),
identical (i.r. and proton n.m.r. spectra, and t.l.c. in methylene chloride over
silica) to a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) through to hexane-ethyl acetate
(2:8) gave only a series of intractable red oils (0.51 g) from which no
identifiable material was obtained.

Final elution with methanol gave a brown semi-solid (0.08 g) whose
t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex
mixture, which was not investigated further.

(b) At -10°

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (1.1 g; 0.005 mol) in anhydrous methylene chloride (20.0 ml) was stirred under
nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium
tetrachloride (4.8 g; 2.8 ml; 0.025 mol) in anhydrous methylene chloride (20.0
ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. The mixture
was then treated in one portion with a solution of acetyl chloride (2.0 g; 0.025 mol) in anhydrous methylene chloride (5.0 ml) and stirring was continued at -10°, under nitrogen, for a further 1 h.

The mixture was treated dropwise with stirring at -10° with 60% w/v aqueous sodium hydroxide solution (17.0 ml; 0.25 mol), stirred at -10° for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an orange oil (1.3 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) through ethyl acetate to methanol gave only a series of multicomponent oils (1.1 g) which could not be separated by further flash chromatography over silica.

11-Cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136)

(a) A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.90 g; 0.004 mol) in glacial acetic acid (10.0 ml) was treated with sodium cyanide (0.80 g; 0.016 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 18 h.

The mixture was treated with water (10.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a semi-solid which was treated with water (15.0 ml) and extracted with methylene chloride. The organic extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 5.0 ml) then rotary evaporated to give an oil (0.90 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 11-cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136) as a yellow oil (0.83 g; 83%), νmax 3460 (NH) and 2240 (wk) (CN) cm⁻¹, δm(CDCl₃) 7.24-6.59 (7H, m, ArH), 5.27 (1H, s, CH), 4.33 (1H, s, NH) (exch), and 3.79 (3H, s, OCH₃), δc(CDCl₃)
161.5(quat), 157.9(quat), 144.7(quat), 134.9(quat), 128.6(CH), 124.9(CH),
121.9(CH), 121.4(CH), 119.5(CH), 118.2(CN), 116.4(quat), 110.4(CH),
106.8(CH), 55.4(OCH₃), and 48.2(CH).

\[
\begin{align*}
\text{Distillation of 11-cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136) (0.40 g) gave 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow oil (0.30 g; 84%), b.p. 125-135°/0.05 \text{mmHg (lit.,69 152-154°/0.1 mmHg), identical (i.r., proton n.m.r., and E.I. mass spectra) to a sample prepared previously.} \\
\text{(b) A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (2.3 g; 0.01 mol) in glacial acetic acid (10.0 ml) was treated with sodium cyanide (2.9 g; 0.06 mol) and the mixture was stoppered and stirred at room temperature for 22h.} \\
\text{Rotary evaporation of the mixture gave a semi-solid which was treated with water (25.0 ml) and extracted with methylene chloride. The organic extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml) then rotary evaporated to give an oil (2.4 g) which was flash-chromatographed over silica.} \\
\text{Elution with hexane-methylene chloride (3:7) gave 11-cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136) as a yellow oil (1.2 g; 48%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.} \\
\text{Further elution with methanol gave unreacted 3-methoxydibenz[b,f][1,4]oxazepine (118) as a brown-orange oil (1.2 g; 52%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.} \\
\text{(c) A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (2.3 g; 0.01 mol) in glacial acetic acid (15.0 ml) was treated with potassium cyanide (2.6 g;}
\end{align*}
\]
0.04 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 2h.

Rotary evaporation of the mixture gave a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride. The organic extracts were washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 5.0 ml) then rotary evaporated to give 11-cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136) as a brown oil (2.4 g; 95%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Sodium Cyanide in Aqueous Ethanol

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.23 g; 0.001 mol) in ethanol (5.0 ml) was treated in one portion with a solution of sodium cyanide (0.20 g; 0.004 mol) in water (0.4 ml) and the mixture was stirred at room temperature for 22h.

Rotary evaporation of the mixture gave a semi-solid which was treated with water (5.0 ml) and extracted with methylene chloride to give unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (0.21 g; 91%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

11-Cyano-3-methoxydibenz[b,f][1,4]oxazepine (137)

(a) A solution of 11-cyano-3-methoxy-10,11-dihydrodibenz[b,f][1,4]oxazepine (136) (0.50 g; 0.002 mol) in the appropriate solvent (10.0 or 20.0 ml) was treated with activated manganese dioxide (Aldrich 21,764-6) (1.0 g) and the mixture was stirred at room temperature,
with exclusion of atmospheric moisture, for 0.5-67.5h then worked up as described for the individual reactions below.

(i) After 20h the mixture from anhydrous 1,2-dimethoxyethane (20.0 ml) was filtered through celite and the filtrate was rotary evaporated to give a waxy solid which was washed with ether to afford 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) (0.10 g; 20%) which formed yellow needles, m.p. 173-175° (from ethanol), ν\text{max} 1610 (Ar) cm\(^{-1}\), δ\text{H}(CDCl\(_3\)) 7.61(1H, d, J 9 Hz, ArH), 7.37(1H, dt, J 8, 8, and 2 Hz, ArH), 7.30-7.19(2H, m, ArH), 7.12(1H, dd, J 8 and 2 Hz, ArH), 6.80(1H, dd, J 8 and 2 Hz, ArH), 6.69(1H, d, J 3 Hz, ArH), and 3.86(3H, s, OCH\(_3\)).

Rotary evaporation of the ethereal mother liquor gave an oil (0.40 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the desired product (137), the unchanged starting material (136), and 3-methoxydibenz[b,f][1,4]oxazepine (118), which was not further investigated.

(ii) After 0.5h the mixture from anhydrous methylene chloride (10.0 ml) was filtered through celite and the filtrate was rotary evaporated to give a waxy solid which was washed with ether to afford 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as a yellow solid (12%), m.p. 159-163°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Rotary evaporation of the ethereal filtrate gave a gum whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to contain unreacted starting material (136) and a small amount of the cyano product (137), and was not further investigated.

(iii) After 0.5h the mixture from glacial acetic acid (10.0 ml) was filtered through celite and the filtrate was rotary evaporated to give a semi-solid which was dissolved in methylene chloride, the solution washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml), and the
combined organic extracts rotary evaporated to give a semi-solid which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (4:6) gave 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as an orange solid (36%), m.p. 168-171°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with methanol gave a brown gum whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture, which therefore was not further investigated.

(iv) After 67.5h the mixture from anhydrous acetonitrile (20.0 ml) was filtered through celite and the filtrate was rotary evaporated to give a semi-solid which was washed with ether to afford 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as a yellow solid (0.25 g; 50%), m.p. 163-168°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethereal mother liquor gave a semi-solid (0.13 g) from which no identifiable material was obtained.

(b) A solution of 11-cyano-3-methoxy-10,11-dihyrodibenz[b,f][1,4]oxazepine (136) (0.50 g; 0.002 mol) in anhydrous acetonitrile (20.0 ml) was treated with activated manganese dioxide (Aldrich 21,764-6) (1.0 g) and the mixture was stirred and heated at 50° (oil bath) or under reflux, with exclusion of atmospheric moisture, for 0.5h.

(i) At 50°

The cooled mixture was filtered through celite and the filtrate was rotary evaporated to give a waxy solid which was washed with ether to afford 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as a yellow solid (0.20 g; 40%), m.p. 158-162°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
Rotary evaporation of the ethereal mother liquor gave a yellow oil (0.21 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the unreacted starting material (136), the desired product (137), and 3-methoxydibenz[b,f][1,4]oxazepine (118), which was not further investigated.

(ii) **Under reflux**

The cooled mixture was filtered through celite and the filtrate was rotary evaporated to give a waxy solid which was washed with ether to afford 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as a yellow solid (0.17 g; 34%), m.p. 154-158°C, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(c) A solution of 11-cyano-3-methoxy-10,11-dihydroidibenz[b,f][1,4]oxazepine (136) (0.25 g; 0.001 mol) in anhydrous acetonitrile (5.0 ml) was treated with dry lead tetraacetate (0.44 g; 0.001 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 0.5h.

The mixture was treated with water (5.0 ml), stirred at room temperature for 0.5h, then treated with methylene chloride (20.0 ml) and filtered through celite. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.35 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (4:6) gave 11-cyano-3-methoxydibenz[b,f][1,4]oxazepine (137) as a yellow solid (0.04 g; 18%), m.p. 161-166°C, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a brown gum (0.20 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.
(d) A solution of 11-cyano-3-methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine (136) (0.50 g; 0.002 mol) in dioxane (10.0 ml) was stirred and treated dropwise with 10-14% w/v aqueous sodium hypochlorite solution (6.0 ml) and the mixture was stirred at room temperature for 0.5h.

Rotary evaporation of the mixture gave a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride to give a semi-solid which was washed with ether to afford 11-cyano-3-methoxydibenzo[b,f][1,4]oxazepine (137) as a yellow solid (0.10 g; 20%), m.p. 151-157°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Rotary evaporation of the ethereal mother liquor gave a brown gum (0.25 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of unreacted starting material (136) and 3-methoxydibenzo[b,f][1,4]oxazepine (118), which was not investigated further.

Acidification of the aqueous mother liquor with 2 M aqueous hydrochloric acid solution and extraction with methylene chloride gave no material.

The Attempted Reaction of 11-Cyano-3-methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine (136) with Palladium-on-Charcoal in Acetonitrile

A solution of 11-cyano-3-methoxy-10,11-dihydrodibenzo[b,f][1,4]oxazepine (136) (0.25 g; 0.001 mol) in anhydrous acetonitrile (10.0 ml) was treated with 10% palladium-on-charcoal (0.03 g) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 0.5h.
The mixture was filtered through celite and the filtrate was rotary evaporated to give unchanged 11-cyano-3-methoxy-10,11-dihydridibenz[b,f][1,4]oxazepine (136) as a yellow oil (0.27 g; 100%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Sodium Azide in Acetic Acid

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in glacial acetic acid (10.0 ml) was treated with sodium azide (0.52 g; 0.008 mol) and the mixture was stirred at room temperature for 18h.

Rotary evaporation of the mixture gave a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride. The organic extracts were washed five times with 10% w/v aqueous sodium hydrogen carbonate solution (5 x 5.0 ml) then rotary evaporated to give unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange-brown oil (0.45 g; 100%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Dimethylamine

(a) Using 25% aqueous dimethylamine

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in ethanol (10.0 ml) was stirred and treated dropwise with 25% w/v aqueous dimethylamine solution (5.0 ml) and the mixture was stirred at room temperature for 19h.

Rotary evaporation of the mixture gave an oil which was treated with water (5.0 ml) and extracted with methylene chloride to give unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow oil (0.43 g; 96%),
identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

(b) Using 33% ethanolic dimethylamine

Repetition of the reaction described in (a) before using 33% w/v ethanolic dimethylamine solution (5.0 ml) gave unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow-brown oil (0.42 g; 93%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Ethanolic Sodium Ethoxide

A solution of sodium (0.18 g; 0.008 mol) in anhydrous ethanol (5.0 ml) was stirred and treated dropwise at room temperature with a solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in anhydrous ethanol (10.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 2h.

The cooled mixture was treated with water (5.0 ml) and rotary evaporated to give an oil which treated with water (10.0 ml), acidified with 2 M aqueous hydrochloric acid solution, and extracted with methylene chloride to give unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (0.40 g; 89%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with the Anion of Diethyl Malonate

A suspension of sodium hydride (0.053 g; 0.0022 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated dropwise at -10° (ice-salt bath) with a solution of diethyl malonate (0.32 g; 0.002 mol) in anhydrous
dimethylformamide (2.5 ml) and the mixture was stirred at room temperature for 15 min. A solution of 3-methoxydibenzo[bf][1,4]oxazepine (118) (0.45 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1 h.

The cooled mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was treated with water (20.0 ml) and extracted with methylene chloride to give an oil (0.80 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unreacted diethyl malonate as a pale yellow oil (0.24 g; 75%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

Elution with hexane-ethyl acetate (8:2) gave unchanged 3-methoxydibenzo[bf][1,4]oxazepine (118) as a yellow oil (0.45 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

3-Methoxydibenzo[bf][1,4]oxazepine Hydrochloride (139)
(a) A solution of 3-methoxydibenzo[bf][1,4]oxazepine (118) (0.45 g; 0.002 mol) in ethanol (15.0 ml) was treated with 2 M aqueous hydrochloric acid solution (2.5 ml) and the mixture was stirred and heated under reflux for 1 h.

The cooled mixture was rotary evaporated to give an oil which was treated with water (10.0 ml) and extracted with methylene chloride to give a semi-solid. This was washed with ether to afford 3-methoxydibenzo[bf][1,4]oxazepine hydrochloride (139) (0.20 g; 38%) which formed yellow plates, m.p. 159-163° (from acetonitrile), \( \nu_{\text{max}} \) 2300, 2080, and
1940 (H̃N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$), 8.71(1H, s, N=CH), 8.00-7.46(3H, m, ArH), 7.37(1H, t, J 2 Hz, ArH), 7.27-6.73(3H, m, ArH), and 3.95(3H, s, OCH$_3$).

Rotary evaporation of the ethereal mother liquor gave unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as an orange oil (0.20 g; 44%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

A solution of 3-methoxydibenz[b,f][1,4]oxazepine hydrochloride (139) (0.10 g) in methylene chloride was washed with 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml) and the organic extracts were rotary evaporated to give 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow-brown oil (0.10 g; 100%); identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

(b) A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in the appropriate solvent (10.0 or 20.0 ml) was saturated at 0°C (ice bath) with hydrogen chloride for 2h, and the mixture was stoppered and stored in a refrigerator for 17 or 216 h, then worked up as described for the individual reactions below.

(i) After 17h the mixture from anhydrous ethanol (10.0 ml) was rotary evaporated to give a waxy solid (0.60 g) which was washed with ether-ethanol to afford 3-methoxydibenz[b,f][1,4]oxazepine hydrochloride (139) as a yellow solid (0.47 g; 90%), m.p. 165-175°C, identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the organic mother liquor gave an orange gum (0.09 g) whose t.l.c. in hexane-ethyl acetate (2:1) over alumina showed it to be a mixture containing more of the desired product (139), which was not further investigated.

(ii) After 216h the mixture from anhydrous ether (20.0 ml) was filtered to give 3-methoxydibenz[b,f][1,4]oxazepine hydrochloride (139) as a yellow solid
(0.32 g; 62%), m.p. 171-176°, identified by comparison (m.p. and i.r. and proton n.m.r. spectra) with a sample prepared previously.

Rotary evaporation of the ethereal mother liquor gave an oil (0.20 g) whose t.l.c. in methylene chloride over silica showed it to be a mixture containing more of the desired product (139) which was not further investigated.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Acetylacetone in the Presence of Hydrogen Chloride

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in glacial acetic acid (10.0 ml) was treated in one portion with acetylacetone (0.20 g; 0.002 mol) then the mixture was cooled to -10° (ice-salt bath) and saturated with hydrogen chloride for 1h. The mixture was then stoppered and stored in a refrigerator overnight.

Rotary evaporation of the mixture gave an oil (0.80 g) which was dissolved in methylene chloride and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 2.5 ml). Rotary evaporation of the combined organic extracts gave unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as a red oil (0.48 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Methyl Iodide in Ether

A solution of 3-methoxydibenz[b,f][1,4] oxazepine (118) (0.45 g; 0.002 mol) in anhydrous ether (10.0 ml) was stirred and treated in one portion with a solution of methyl iodide (0.26 g; 0.002 mol) in anhydrous ether (5.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric
moisture, for 4h. The mixture was then stoppered and stored in a refrigerator overnight.

Rotary evaporation of the mixture gave unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow-brown oil (0.48 g; 100%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

**The Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Acetic Anhydride**

A mixture of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.045 g; 0.002 mol) and acetic anhydride (0.5 ml) was heated at 100° (water bath), with exclusion of atmospheric moisture, for 10 min then left at room temperature, with exclusion of atmospheric moisture, for 20 min.

Rotary evaporation of the mixture gave an orange oil which was dissolved in methylene chloride, treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0 ml), and the mixture was stirred at room temperature for 10 min. Separation of the mixture, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an orange oil (0.49 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave unchanged 3-methoxydibenz[b,f][1,4]oxazepine (118) as a yellow oil (0.22 g; 49%), identical (i.r. spectrum and t.l.c. in ether over silica) to a sample prepared previously.

Elution with hexane-ethyl acetate (6:4) gave 2-(2-acetamidophenoxy)-4-methoxybenzaldehyde (141) as a viscous yellow oil (0.26 g; 46%), b.p. 200-210°/0.005-0.10 mmHg, $\nu_{\text{max}}$ 3320 (NH) and 1700-1670 (br) (C=O) cm$^{-1}$, $\delta_H$(CDCl$_3$) 10.24(1H, s, CHO), 8.36(1H, dd, J 7 and 2 Hz, ArH), 8.03(1H, bs,
NH), 7.37-6.54(5H, m, ArH), 6.35(1H, d, J 2 Hz, ArH), 3.74(3H, s, OCH₃), and 2.13(3H, s, CH₃).

The Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Acetyl Chloride in Ether

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in anhydrous ether (10.0 ml) was stirred and treated in one portion with a solution of acetyl chloride (0.16 g; 0.002 mol) in anhydrous ether (5.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h. The mixture was then stoppered and stored in a refrigerator overnight.

The mixture was filtered to give 3-methoxydibenz[b,f][1,4]oxazepine hydrochloride (139) as a yellow solid (0.09 g; 17%), m.p. 163-170°, identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethereal mother liquor gave an oil which was distilled to afford 2-(2-acetamidophenoxy)-4-methoxybenzaldehyde (141) as a yellow oil (0.30 g; 53%), b.p. 200-210°,0.05-0.10 mmHg, identical (i.r. spectrum and t.l.c. in ether over silica) to a sample prepared previously.

The Attempted Reaction of 3-Methoxydibenz[b,f][1,4]oxazepine (118) with Alkaline Hydrogen Peroxide

A solution of 3-methoxydibenz[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in ethanol (20.0 ml) was treated in one portion, with stirring, with 2 M aqueous sodium hydroxide solution (5.0 ml) followed by 30% w/v aqueous hydrogen peroxide solution (1.0 ml) and the mixture was stirred at room temperature for 17h.

Rotary evaporation of the mixture gave an oil which was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which
was combined with further material, obtained by neutralisation of the aqueous mother liquor with 2 M aqueous hydrochloric acid solution and sodium acetate and extraction with methylene chloride, to give unchanged 3-methoxydibenzo[b,f][1,4]oxazepine (118) as a brown oil (0.30 g; 67%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

Rotary evaporation of the neutral aqueous mother liquor and extraction of the resulting residue with boiling ethyl acetate gave no material.

The Attempted Reaction of 3-Methoxydibenzo[b,f][1,4]oxazepine (118) with Aqueous Sodium Hypochlorite Solution

(a) For 10 min

A solution of 3-methoxydibenzo[b,f][1,4]oxazepine (118) (0.45 g; 0.002 mol) in dioxane (10.0 ml) was stirred and treated dropwise with 10-14% w/v aqueous sodium hypochlorite solution (6.0 ml) and the mixture was stirred at room temperature for 10 min.

Rotary evaporation of the mixture gave a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride to give unchanged 3-methoxydibenzo[b,f][1,4]oxazepine (118) as an orange-brown oil (0.50 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(b) For 18h

Repetition of the reaction described in (a) before for 18h gave unchanged 3-methoxydibenzo[b,f][1,4]oxazepine (118) as a red oil (0.50 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.
2-(3-Methoxyphenoxy)phenyl isocyanide Dichloride (142a) and (142b)

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride or bromine (0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) 2-(3-Methoxyphenoxy)phenyl isocyanide Dichloride (142a)

The mixture from reaction with sulphuryl chloride was rotary evaporated to give 2-(3-methoxyphenoxy)phenyl isocyanide dichloride (142a) as an unstable pale brown oil (100%), $\nu_{\text{max}}$ 1660 (N=C) cm$^{-1}$.

(ii) 2-(3-Methoxyphenoxy)phenyl Isocyanide Dibromide (142b)

The mixture from reaction with bromine was rotary evaporated to give 2-(3-methoxyphenoxy)phenyl isocyanide dibromide (142b) as an unstable brown oil (0.83 g; 100%), $\nu_{\text{max}}$ 1690 (N=C) cm$^{-1}$, which decomposed on attempted purification by distillation.

The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide Dichloride (142a) with Aluminium Trichloride in Methylene Chloride

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.53 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.
The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.46 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (6:4) through methylene chloride to methanol gave only a series of multicomponent mixtures (0.25 g) which were not investigated further.

**The Attempted Reaction of 2-(3-Methoxyphenoxy)phenyl Isocyanide Dibromide (142a) with Aluminium Tribromide in Methylene Chloride**

A solution of 2-(3-methoxyphenoxy)phenyl isocyanide (116a) (0.45 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.69 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) through ether to methanol gave only a series of complex mixtures (0.31 g) which were not investigated further.
2-Phenoxyphenyl Isocyanide Dibromide (144a)

A solution of 2-phenoxyphenyl isocyanide (116b) (0.098 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.08 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h.

 Rotary evaporation of the mixture gave 2-phenoxyphenyl isocyanide dibromide (144a) as a brown oil (0.18 g; 100%), \( \nu_{\text{max}} \) 1692 (N=C) cm\(^{-1}\).

11-Bromodibenz[b,f][1,4]oxazepine (145a)

A solution of 2-phenoxyphenyl isocyanide (116b) (0.59 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (1.6 g; 0.006 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.81 g) which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave 11-bromodibenz[b,f][1,4]oxazepine (145a) (0.65 g; 79%) as an unstable yellow solid, m.p. 54-57°, \( \nu_{\text{max}} \) 1621 (N=C) cm\(^{-1}\), \( \delta_H \)(CDCl\(_3\)) 7.80-7.07(8H, m, ArH).

Crystallisation of 11-bromodibenz[b,f][1,4]oxazepine (145a) from light petroleum (b.p. 40-60°), then light petroleum (b.p. 40-60°)-toluene (1:2), and
finally from ethanol gave dibenz[b,f][1,4]oxazepin-11(10H)-one (146) as
colourless needles, m.p. 212-213°, \( \nu_{\text{max}} \) 3181 (NH) and 1677 (C=O) cm\(^{-1}\),
\( \delta_H[(CD_3)SO] \) 10.49 (1H, bs, NH) (exch) and 7.83-7.10 (8H, m, ArH).

Final elution with methanol gave brown gum (0.02 g) whose t.l.c. in
hexane-ether (2:1) over silica showed it to be a complex mixture.

2-(2-Bromophenoxy)phenyl isocyanide Dibromide (144b)

A solution of 2-(2-bromophenoxy)phenyl isocyanide (134a) (0.27 g;
0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under
nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of
bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and
the mixture was stirred at -10°, under nitrogen for 1h.

Rotary evaporation of the mixture gave 2-(2-bromophenoxy)phenyl
isocyanide dibromide (144b) as a brown oil (0.43 g; 100%), \( \nu_{\text{max}} \) 1690 (N=C)
\( \text{cm}^{-1} \).

4,11-Dibromodiben[b,f][1,4]oxazepine (145b)

A solution of 2-(2-bromophenoxy)phenyl isocyanide (134a) (3.3 g;
0.012 mol) in anhydrous methylene chloride (20.0 ml) was stirred under
nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of
bromine (1.9 g; 0.012 mol) in anhydrous methylene chloride (20.0 ml), and
the mixture was stirred at -10°, under nitrogen, for 1h. A solution of
aluminium tribromide (6.4 g; 0.024 mol) in anhydrous methylene chloride
(40.0 ml) was added portionwise and the mixture was stirred at room
temperature, under nitrogen, for 20h.

The mixture was poured into 10% w/v aqueous sodium hydrogen
carbonate solution (185 ml; 0.24 mol), stirred at room temperature for 5 min,
then filtered to remove aluminium residues. Separation of the filtrate,
extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 4,11-dibromidibenz[b,f][1,4]oxazepine (145b) (3.4 g; 80%) which formed irregular cream plates, m.p. 105-107° (from cyclohexane), $\nu_{\text{max}}$ 1624 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.86(1H, dd, J 8 and 2 Hz, ArH), 7.77(1H, dd, J 8 and 2 Hz, ArH), 7.57-7.49(1H, m, ArH), and 7.39-7.02(4H, m, ArH).

11-Piperidinodibenz[b,f][1,4]oxazepine (147a)

A suspension of sodium hydride (0.053 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of piperidine (0.17 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 11-bromodibenz[b,f][1,4]oxazepine (145a) (0.55 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 2h.

The cooled mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.78 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave a viscous oil. This slowly solidified to afford 11-piperidinodibenz[b,f][1,4]oxazepine (147a) (0.34 g; 64%) which formed colourless plates, m.p. 98-99° (from ethanol), $\nu_{\text{max}}$ 1592 (N=C) cm$^{-1}$, $\delta$(CDCl$_3$) 7.45-6.89(8H, m, ArH), 3.47(4H, bs, 2xCH$_2$), and 1.68(6H, bs, 3xCH$_2$).
11-Cyanodibenz[b,f][1,4]oxazepine Derivatives (148a) and (148b)

A solution of the corresponding 11-bromodibenz[b,f][1,4]oxazepine (145a) or (145b) (0.002 mol) in anhydrous acetonitrile (10.0 ml) was treated portionwise with a solution of tetraethylammonium cyanide (0.62 g; 0.004 mol) in anhydrous acetonitrile (5.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 2-24h then worked up as described for the individual reactions below.

(i) 11-Cyanodibenz[b,f][1,4]oxazepine (148a)

After 24h the mixture from 11-bromodibenz[b,f][1,4]oxazepine (145a) was rotary evaporated to give a solid which was treated with 2 M aqueous hydrochloric acid solution (5.0 ml) and extracted with methylene chloride to give 11-cyanodibenz[b,f][1,4]oxazepine (148a) (0.45 g; 100%) which formed yellow needles, m.p. 118-119° (from ethanol), $\nu_{\text{max}}$ 2221 (w) (CN) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.77-7.07 (8H, m, ArH).

(ii) 4-Bromo-11-cyanodibenz[b,f][1,4]oxazepine (148b)

After 2h the mixture from 4,11-dibromodibenz[b,f][1,4]oxazepine (145b) was rotary evaporated to give a semi-solid which was treated with 2 M aqueous hydrochloric acid solution (15.0 ml) and extracted with methylene chloride to give 4-bromo-11-cyanodibenz[b,f][1,4]oxazepine (148b) (100%), which formed yellow needles, m.p. 162-163° (from glacial acetic acid), $\nu_{\text{max}}$ 2226 (w) (CN) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.80(1H, dd, J 8 and 2 Hz, ArH), and 7.71-7.06(6H, m, ArH).

Tetrazolo[1,5-m]dibenz[b,f][1,4]oxazepine (148a)

A solution of 11-bromodibenz[b,f][1,4]oxazepine (145a) (0.55 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was treated with sodium azide (0.13 g; 0.002 mol) and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.
The cooled mixture was rotary evaporated to give a solid which was treated with water (5.0 ml) and extracted with methylene chloride to give tetrazolo[1,5-m]dibenz[b,f][1,4]oxazepine (149a) (0.44 g; 94%) which formed colourless needles, m.p. 208-209° (from glacial acetic acid), νₘₐₓ 1612 (Ar) cm⁻¹, δₜ[(CD₃)₂SO] 8.02(1H, m, ArH), 7.95(1H, m, ArH), and 7.76-7.51(6H, m, ArH).

4-Bromo-11-piperidinodibenz[b,f][1,4]oxazepine (147b)

A suspension of sodium hydride (0.079 g; 0.0033 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of piperidine (0.26 g; 0.003 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 4,11-dibromodibenz[b,f][1,4]oxazepine (145b) (1.1 g; 0.003 mol) in anhydrous dimethylformamide (10.0 ml) was added in one portion and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 6h.

The mixture was treated with water (2.5 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (10.0 ml) and extracted with methylene chloride to give a pale brown solid (0.91 g), m.p. 163-165°, most of which was crystallised from toluene to give 4-bromodibenz[b,f][1,4]oxazepin-11(10H)-one (150) as colourless needles, m.p. 265-267°, νₘₐₓ 3173 (NH) and 1668 (C=O) cm⁻¹. The remainder of the initial pale brown solid (0.09 g) was flash-chromatographed over silica. Elution with hexane-ether (9:1) gave 4-bromo-11-piperidinodibenz[b,f][1,4]oxazepine (147b) (0.08 g) which formed colourless plates, m.p. 167-168° (from toluene), νₘₐₓ 1582 (N=C) cm⁻¹, δₜ(CDCl₃) 7.64(1H, dd, J 8 and 2 Hz,
ArH), 7.46-6.90(6H, m, ArH), 3.51-3.42(4H, m, 2xCH$_2$), and 1.66-1.27(6H, m, 3xCH$_2$).

2-Phenyldithionitrobenzene (153b)

A suspension of sodium hydride (2.6 g; 0.11 mol) in anhydrous dimethylformamide (40.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of thiophenol (11.0 g; 0.1 mol) in anhydrous dimethylformamide (30.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-fluoronitrobenzene (111) (14.1 g; 0.1 mol) in anhydrous dimethylformamide (30.0 ml) was added portionwise and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was treated with water (25.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was treated with water (100.0 ml) and extracted with methylene chloride to give a waxy solid which was washed with hexane-ether to give a yellow solid. This was combined with further material, obtained by rotary evaporation of the organic mother liquor and flash-chromatography of the residue in hexane-ethyl acetate (95:5) over silica, to give 2-phenyldithionitrobenzene (153b) as a yellow solid (21.8 g; 94%), m.p. 75-77° (lit., 92° 77°).

2-(3-Methoxyphenylthio)nitrobenzene (153a)

2-(3-Methoxyphenylthio)nitrobenzene (153a) was prepared by the reaction of the sodium salt of 3-methoxythiophenol (152a) and 2-chloronitrobenzene (151), as described by Weddell, as a yellow-brown solid (98% yield) and had m.p. 118-121° (lit., 76° 118-121°).
2-Phenylthioaniline (154b)

A solution of 2-phenylthionitrobenzene (153b) (20.8 g; 0.09 mol) in tetrahydrofuran (400.0 ml) was stirred under nitrogen and treated portionwise with 15% w/v aqueous titanium trichloride solution (789 ml; 0.9 mol) and the mixture was stirred at room temperature, under nitrogen, for 70h.

Rotary evaporation of the mixture gave an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (200.0 ml), and extracted with methylene chloride to give a cream solid. This was combined with further material, obtained by stirring the aqueous mother liquor at room temperature overnight, filtration to remove titanium residues, and extraction with methylene chloride to afford 2-phenylthioaniline (154b) as a cream solid (17.5 g; 97%), m.p. 33-35° (lit.,31 31-32°), m/z (EI-MS) 201 (M+).

2-(3-Methoxyphenylthio)aniline (154a)

A solution of 2-(3-methoxyphenylthio)nitrobenzene (153a) (11.8 g; 0.045 mol) in tetrahydrofuran (200.0 ml) was stirred under nitrogen, treated dropwise with 15% w/v aqueous titanium trichloride solution (362 ml; 0.32 mol), and the mixture was stirred at room temperature, under nitrogen, for 62h.

The mixture was rotary evaporated to give an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (30.0 ml), and extracted with methylene chloride. This was combined with further material, obtained by stirring the aqueous mother liquor at room temperature overnight, filtration to remove titanium residues, and extraction with methylene chloride, to give an oil which was distilled to afford 2-(3-methoxyphenylthio)aniline (154a) as a yellow oil (5.1 g; 49%), b.p. 180-195°/0.40-0.30 mmHg, νmax 3460 and 3360 (NH) cm⁻¹, identical (i.r. spectrum) to an authentic sample.
\(N\)-(2-Arylthio)phenylformamides (155a) and (155b)

A mixture of the corresponding 2-arylthioaniline derivative (154a) or (154b) (0.02 mol) and 98-100% formic acid (50.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1-3h then worked up as described for the individual reactions below.

(i) \(N\)-(2-Phenylthio)phenylformamide (155b)

After 3h at reflux the cooled mixture from 2-phenylthioaniline (154b) was rotary evaporated to give an oil which solidified rapidly to afford \(N\)-(2-phenylthio)phenylformamide (155b) (93%) which formed colourless plates, m.p. 88-89° (lit. 128 89°) (from cyclohexane), \(\nu_{\text{max}}\) 3237 (NH) and 1666 (C=O) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3)\) 8.56-8.35(1H, m, CHO), 8.80-7.80(1H, bs, NH) (exch), and 7.64-6.96(9H, m, ArH).

(ii) \(N\)-(2-(3-Methoxyphenylthio)phenyl)formamide (155a)

After 1h at reflux the cooled mixture from 2-(3-methoxyphenylthio)aniline (154a) was rotary evaporated to give a yellow solid which was crystallised from hexane-toluene (4:1) to afford \(N\)-(2-(3-methoxyphenylthio)phenyl)formamide (155a) (4.2 g; 82%) which formed colourless plates, m.p. 108-109° [from hexane-toluene (4:1)], \(\nu_{\text{max}}\) 3250 (NH) and 1670 (C=O) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3)\) 8.55-8.35(1H, m, CHO), 8.20(1H, bs, NH), 7.64-7.03(5H, m, ArH), 6.75-6.55(3H, m, ArH), and 3.70(3H, s, OCH\(_3\)).

2-Phenylthiophenyl iso cyanide (156b)

A solution of \(N\)-(2-phenylthio)phenylformamide (155b) (4.6 g; 0.02 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was treated with carbon tetrachloride (3.7 g; 0.024 mol) followed by triphenylphosphine (6.3 g; 0.024 mol) and the mixture was stirred at room temperature for 15 min.
Triethylamine (4.0 g; 0.04 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (20.0 ml) and extracted with methylene chloride to give a viscous oil which was triturated with ether to afford triphenylphosphine oxide as a light brown solid (5.2 g), m.p. 148-151° (lit.126 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil (8.3 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave 2-phenylthiophenyl isocyanide (156b) as an orange oil (3.6 g; 85%), ν\text{max} 2117 (NC) cm\textsuperscript{-1}.

Elution with hexane-ether (6:4) gave unchanged N-(2-phenylthiophenyl)formamide (155b) as a cream solid (0.59 g; 13%), m.p. 84-86°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a dark brown oil (2.8 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to contain mainly triphenylphosphine oxide.

**2-(3-Methoxyphenylthio)phenyl isocyanide (156a)**

A solution of N-[2-(3-methoxyphenylthio)phenyl]formamide (155a) (2.1 g; 0.008 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (1.2 g; 0.008 mol), followed by triphenylphosphine (2.5 g; 0.0096 mol), then triethylamine (1.6 g; 0.016 mol) and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (15.0 ml) and extracted with methylene chloride to give an oil (4.8 g) which was flash-chromatographed over silica.
Elution with hexane-ethyl acetate (9:1) gave 2-(3-methoxyphenylthio)phenyl isocyanide (156a) (1.4 g; 73%) which formed colourless plates, m.p. 69-70° (from hexane), $\nu_{\text{max}}$ 2120 (NC) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.33-6.85(8H, m, ArH) and 3.77(3H, s, OCH$_3$).

Elution with hexane-ethyl acetate (8:2) gave unchanged N-[2-(3-methoxyphenylthio)phenyl]formamide (155a) as a yellow solid (0.50 g; 24%), m.p. 96-102°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave triphenylphosphine oxide as a pale brown solid (1.9 g), m.p. 142-149° (lit.,$^{126}$ 152-153°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

3-Methoxydibenzo[b,f][1,4]thiazepine (157a)

A solution of 2-(3-methoxyphenylthio)phenyl isocyanide (156a) (1.2 g; 0.005 mol) in anhydrous methylene chloride (25.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (4.8 g; 2.8 ml; 0.025 mol) in anhydrous methylene chloride (20.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 24h.

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (17.0 ml; 0.25 mol), stirred at room temperature for 15 min, then diluted with water (30.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which was distilled to give a yellow oil (0.80 g), b.p. 210-220°/0.80-1.0 mmHg, which solidified on cooling to afford 3-methoxydibenzo[b,f][1,4]thiazepine (157a) (0.74 g; 62%) as a yellow solid, m.p. 89-91°, $\nu_{\text{max}}$ 1590 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.77(1H, s, N=CH), 7.40-
7.31(1H, m, ArH), 7.30(1H, d, J 8 Hz, ArH), 7.29-6.98(3H, m, ArH), 6.95(1H, d, J 3Hz, ArH), 6.84(1H, dd, J 8 and 3 Hz, ArH), and 3.80(3H, s, OCH₃).

δ(CDCls) 161.7(N=CH), 160.1(quat), 148.6(quat), 140.6(quat), 132.6(CH), 131.0(CH), 130.0(quat), 129.2(CH), 128.3(quat), 126.9(CH), 126.9(CH), 116.1(CH), 114.1(CH), and 55.4(OCH₃).

2-Phenylthiophenyl Isocyanide Dibromide (158)

A solution of 2-phenylthiophenyl isocyanide (156b) (0.21 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

The mixture was rotary evaporated to give 2-phenylthiophenyl isocyanide dibromide (158) as a dark brown oil (0.36 g; 97%), νmax 1686 (N=C) cm⁻¹.

11-Bromodibenz[bf][1,4]thiazepine (152)

A solution of 2-phenylthiophenyl isocyanide (156b) (0.84 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (2.1 g; 0.008 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the
filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a brown oil (1.2 g) which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave 11-bromodibenzo[b,f][1,4]thiazepine (159) (0.90 g; 78%) which formed colourless plates, m.p. 107-108° (from cyclohexane), $\nu_{\text{max}}$ 1636 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.84-7.03(8H, m, ArH).

Elution with hexane-ether (95:5) through ether to methanol failed to give any further identifiable material.

11-Piperidinodibenzo[b,f][1,4]thiazepine (160)

A suspension of sodium hydride (0.053 g; 0.0022 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of piperidine (0.17 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 11-bromodibenzo[b,f][1,4]thiazepine (159) (0.58 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was added portionwise and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 2h.

The cooled mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (1.0 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave 11-piperidinodibenzo[b,f][1,4] thiazepine (160) (0.43 g; 73%) which formed yellow hexagons, m.p. 128-129° (from ethanol), (lit., 94 133-134°). $\nu_{\text{max}}$ 1589 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 9.01-8.27(8H, m, ArH), 4.92(4H, m, 2xCH$_2$), and 3.11(6H, m, 3xCH$_2$).
Elution with methanol gave an intractable gum (0.05g) which was not further investigated.

11-Cyanodibenzo[b,f][1,4]thiazepine (161)

A solution of 11-bromodibenzo[b,f][1,4]thiazepine (159) (0.58 g; 0.002 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated portionwise with a solution of tetraethylammonium cyanide (0.62 g; 0.004 mol) in anhydrous acetonitrile (10.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 80h.

Rotary evaporation of the mixture gave a semi-solid which was treated with 2 M aqueous hydrochloric acid solution (10.0 ml) and extracted with methylene chloride to give an oil (0.72 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 11-cyanodibenzo[b,f][1,4]thiazepine (161) (0.37 g; 79%) which formed yellow plates, m.p. 107-108° (from ethanol), $\nu_{\text{max}}$ 2223 (w) (CN), $\delta_H$(CDCl$_3$) 7.61(1H, dt, J 7, 1, and 1 Hz, ArH) and 7.70-7.25(7H, m, ArH).

Elution with methanol gave a brown gum (0.03 g) whose t.l.c. in hexane-ether (2:1) over silica showed it to be a complex mixture which was not further investigated.

2-(Al-Aryl)aminonitrobenzene Derivatives (163 a and b) and (170)

(a) 2-Phenylaminonitrobenzene (163b)

A mixture of 2-fluoronitrobenzene (111) (28.2 g; 0.02 mol), freshly distilled aniline (162b) (37.2 g; 0.04 mol), and anhydrous potassium fluoride (11.6 g; 0.2 mol) was stirred and heated at 180° (oil bath), with exclusion of atmospheric moisture, for 48h.
The cooled mixture was treated with water (500.0 ml) and extracted with methylene chloride. The organic extracts were washed twice with 2 M aqueous hydrochloric acid solution (2 x 400.0 ml) and twice with water (2 x 400.0 ml) then rotary evaporated to afford 2-phenylaminonitrobenzene (163b) as a red solid (42.7 g; 100%), m.p. 70-72° (lit.,96 75°).

(b) 2-[N-(3-Methoxyphenyl)]aminonitrobenzene (163a)

2-[N-(3-Methoxyphenyl)]aminonitrobenzene (163a) was prepared by the potassium fluoride promoted reaction of 2-fluoronitrobenzene (111) with 3-methoxyaniline (162a) as described by Weddell,76 as a red solid (yield 95%), and had m.p. 53-56° (lit.,76 57-58°).

5-Chloro-2-phenylaminonitrobenzene (170)

5-Chloro-2-phenylaminonitrobenzene (170) was prepared by the reaction of aniline (162b) with 2,5-dichloronitrobenzene in the presence of sodium acetate as described by Ullmann,102 as a red solid (yield 80%), and had m.p. 57-59° (lit.,102 61°).

N-Protected 2-(N-Aryl)aminonitrobenzene Derivatives (164 a and b) and (171 a and b)

(a) 2-(N-Benzyl-N-phenyl)aminonitrobenzene (164b)

A suspension of sodium hydride (4.0 g; 0.165 mol) in anhydrous dimethylformamide (75.0 ml) was stirred and treated portionwise at 0° (ice bath) with a solution of 2-phenylaminonitrobenzene (163b) (32.1 g; 0.015 mol) in anhydrous dimethylformamide (100.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of benzyl bromide (25.7 g; 0.15 mol) in anhydrous dimethylformamide (100.0 ml) was then added portionwise and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 20h.
The mixture was treated with water (50.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give a semi-solid. This was treated with water (300.0 ml) and extracted with methylene chloride to give an orange solid which was collected with the aid of a little ether-methanol. This was combined with further material, obtained by rotary evaporation of the organic mother liquor and flash-chromatography of the resulting residue in hexane-ether (8:2) over silica, to afford 2-(N-benzyl-N-phenyl)aminonitrobenzene (164b) (41.5 g; 91%) which formed orange needles, m.p. 110-111° (from ethanol), \( \nu \text{max} \) 1524 and 1339 (NO\(_2\)) cm\(^{-1}\), \( \delta \text{H} \text{(CDCl}_3) \) 8.90-6.70(14H, m, ArH) and 4.97(2H, s, CH\(_2\)).

(b) 2-[N-Benzyl-N-(3-methoxyphenyl)]aminonitrobenzene (164a)

2-[N-Benzyl-N-(3-methoxyphenyl)]aminonitrobenzene (164a) was prepared by the reaction of 2-[N-(3-methoxyphenyl)]aminonitrobenzene (163a) with benzyl bromide in the presence of sodium hydride as described by Weddell\(^\text{,}^76\) as an orange solid (yield 82%), and had m.p. 82-85° (lit.,\(^\text{,}^76\) 84-85°).

(c) 2-(N-PhenykN-tolulene-4-sulphOflyl)aminonitrobenzene (171a)

A suspension of sodium hydride (0.053 g; 0.0022 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of 2-phenylaminonitrobenzene (163b) (0.43 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of toluene-4-sulphonyl chloride (0.002-0.008 mol) in anhydrous dimethylformamide (5.0 ml) was added in one portion and the mixture was stirred at room temperature or at 100° (oil bath), with exclusion of atmospheric moisture, for 24h then worked up as described for the individual reactions below.

(i) The mixture from one equivalent (0.002 mol) of toluene-4-sulphonyl chloride at room temperature was treated with water (5.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a semi-solid. This was
treated with water (10.0 ml) and extracted with methylene chloride to give an oil (1.3 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave unchanged 2-phenylaminonitrobenzene (163b) as a red solid (0.24 g; 56%), m.p. 71-73°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ether (4:6) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171a) (0.30 g; 41%) which formed cream plates, m.p. 128-129° (from ethanol), $\nu_{\text{max}}$ 1528 and 1353 (NO$_2$) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.85(1H, dd, J 8 and 2 Hz, ArH), 7.60-7.20(12H, m, ArH), and 2.41(3H, s, CH$_3$).

Elution with methanol gave a brown gum (0.03 g) from which no identifiable material was obtained.

(ii) The cooled mixture from two equivalents (0.004 mol) of toluene-4-sulphonyl chloride at 100° was treated with water (5.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give a semi-solid. This was treated with water (10.0 ml), the mixture was made basic with 2 M aqueous sodium hydroxide solution, then extracted with methylene chloride to give an oil (1.0 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave unchanged 2-phenylaminonitrobenzene (163b) as an orange solid (0.27 g; 63%), m.p. 72-74°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ether (1:1) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171a) as a brown solid (0.25 g; 34%), m.p. 119-122°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (i) before.

Elution with methanol gave an intractable brown gum (0.03 g) which was not further investigated.
The cooled mixture from four equivalents (0.008 mol) of toluene-4-sulphonyl chloride at 100° was treated with water (5.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was treated with water (10.0 ml), the mixture was made basic with 2 M aqueous sodium hydroxide solution, then extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave unchanged 2-phenylaminonitrobenzene (163b) as an orange-red solid (57%), m.p. 72-74°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ether (1:1) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171a) as a brown solid (33%), m.p. 124-126°, identical (m.p. and i.r. spectrum) to a sample prepared in (i) before.

Elution with methanol gave an intractable brown gum which was not investigated further.

The cooled mixture from one equivalent (0.002 mol) of freshly crystallised toluene-4-sulphonyl chloride at 100° was treated with water (5.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a gum. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave unchanged 2-phenylaminonitrobenzene (163b) as a red solid (30%), m.p. 70-72°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ether (1:1) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171a) as a light brown solid (61%), m.p. 123-125°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave an intractable brown gum which was not further investigated.
A suspension of sodium hydride (4.0 g; 0.165 mol) in anhydrous dimethylformamide (75.0 ml) was stirred and treated dropwise at 0°C (ice bath) with a solution of 5-chloro-2-phenylanilino nitrobenzene (170) (37.3 g; 0.15 mol) in anhydrous dimethylformamide (75.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of fresh toluene-4-sulphonyl chloride (57.2 g; 0.3 mol) in anhydrous dimethylformamide (150.0 ml) was added in one portion and the mixture was stirred and heated at 100°C (oil bath), with exclusion of atmospheric moisture, for 24 h.

The cooled mixture was treated with water (25.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (150.0 ml), the mixture was made basic with 2 M aqueous sodium hydroxide solution, and extracted with methylene chloride to give an oil (65.1 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 5-chloro-2-phenylanilino nitrobenzene (170) as a waxy red solid (8.7 g; 23%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] with a sample prepared previously.

Elution with hexane-ether (1:1) gave 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171b) (30.4 g; 50%) which formed yellow plates, m.p. 158-159°C (from glacial acetic acid), νmax 1536 and 1354 (NO2) cm⁻¹, δH(CDCl₃) 7.84(1H, d, J 3 Hz, ArH), 7.57-7.24(11H, m, ArH), and 2.42(3H, s, CH₃).

A solution of freshly distilled aniline (162b) (9.3 g; 0.1 mol) and freshly crystallised toluene-4-sulphonyl chloride (19.1 g; 0.1 mol) in anhydrous
ethanol (500.0 ml) was treated with anhydrous sodium acetate (9.0 g; 0.11 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1 h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (100.0 ml) and extracted with ether. The ethereal extracts were washed twice with 2 M aqueous hydrochloric acid solution (2 x 50.0 ml) then twice with water (2 x 50.0 ml) then rotary evaporated to give a white solid which was dissolved in 2 M aqueous sodium hydroxide solution (60.0 ml) and the mixture was washed twice with methylene chloride (2 x 50.0 ml). The aqueous layer was acidified with 2 M aqueous hydrochloric acid solution and extracted with methylene chloride to give N-toluene-4-sulphonylaminobenzene as a colourless solid (22.6 g; 92%), m.p. 99-101° (lit., 98-103°).

**The Attempted Reaction of 2-Fluoronitrobenzene (111) with N-Toluene-4-sulphonylaminobenzene in the Presence of Sodium Hydride**

A suspension of sodium hydride (0.11 g; 0.0044 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of N-toluene-4-sulphonylaminobenzene (0.99 g; 0.004 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-fluoronitrobenzene (111) (0.56 g; 0.004 mol) in anhydrous dimethylformamide (10.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1 h.

The cooled mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil. This was combined with further material, obtained by acidification of the
aqueous mother liquor with 2 M aqueous hydrochloric acid solution and
extraction with methylene chloride, to give an oil (1.3 g) which was flash-
chromatographed over silica.

Elution with hexane-ether (95:5) gave unreacted 2-fluoronitrobenzene
(111) as an orange oil (0.35 g; 63%), identical [i.r. spectrum and t.l.c. in
hexane-ether (1:1) over silica] to an authentic sample.

Elution with hexane-ether (8:2) gave unchanged N-toluene-4-
sulphonylaminobenzene as a yellow solid (0.92 g; 93%), m.p. 99-101°,
identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with methanol gave an intractable brown gum (0.04 g) which
was not further investigated.

2-(N-Aryl-N-benzyl)aminoaniline Derivatives (165a) and (165b)

(a) 2-(N-Benzyl-N-phenyl)aminoaniline (165b)

A solution of 2-(N-benzyl-N-phenyl)aminonitrobenzene (164b) (39.5 g;
0.13 mol) in dimethylformamide (450.0 ml) was hydrogenated over 10%
palladium-on-charcoal (4.0 g) at room temperature and atmospheric pressure
for 2h, during which time hydrogen (10120 ml; 0.45 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary
evaporated to give an oil which was triturated with ether to afford a cream
solid. This was combined with further material, obtained by rotary
evaporation of the ethereal mother liquor and flash-chromatography of the
resulting residue in hexane-ether (95:5) over silica to afford 2-(N-benzyl-N-
phenyl)aminoaniline (165b) (28.3 g; 80%) which formed colourless plates,
m.p. 118-119° (from ethanol), v_max 3461 and 3368 (NH) cm^{-1}, δ_H(CDCl_3) 7.42-
6.61(14H, m, ArH), 4.87(2H, s, CH_2), and 3.55(2H, s, NH_2) (exch).

Also eluted with hexane-ether (95:5) was 2-phenylaminoaniline (0.60
g; 3%) which formed light brown plates, m.p. 78-79° (lit.,^{127} 79-80°) (from
cyclohexane), $\nu_{\text{max}}$ 3464, 3414, and 3368 (NH), $\delta_H(\text{CDCl}_3)$ 7.32-6.63 (9H, m, ArH) and 4.50-3.50 (3H, bs, NH and NH$_2$) (exch).

(b)  2-[N-Benzyl-N-(3-methoxyphenyl)]aminoaniline (165a)

2-[N-Benzyl-N-(3-methoxyphenyl)]aminoaniline (165a) was prepared by the catalytic hydrogenation of 2-[N-benzyl-N-(3-methoxyphenyl)]aminonitrobenzene (164a) as described by Weddell, as a yellow solid (yield 66%), and had m.p. 72-74° (lit., 75-77°).

2-(N-Phenyl-N-toluene-4-sulphonylaminoaniline Derivatives (172a) and (172b)

(a)  2-(N-Phenyl-N-toluene-4-sulphonylaminoaniline (172a)

A solution of 2-(N-phenyl-N-toluene-4-sulphonylaminoaniline (171a) (4.1 g; 0.011 mol) in tetrahydrofuran (200.0 ml) was stirred and treated dropwise with 15% w/v aqueous titanium trichloride solution (97.0 ml; 0.11 mol) and the mixture was stirred at room temperature, under nitrogen, for 70h.

The mixture was rotary evaporated to give an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (100.0 ml), and extracted with methylene chloride to give a waxy solid (5.3 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave 2-(N-phenyl-N-toluene-4-sulphonylaminoaniline (172a) (2.9 g; 78%) which formed cream plates, m.p. 137-138° (from ethanol), $\nu_{\text{max}}$ 3057, 3476, 3418, and 3386 (NH) cm$^{-1}$, $\delta_H(\text{CDCl}_3)$ 7.65-7.62 (2H, m, ArH), 7.40-7.20 (8H, m, ArH), 7.15-7.12 (1H, m, ArH), 6.85-6.77 (2H, m, ArH), 6.65-6.61 (1H, m, ArH), 4.23 (2H, s, NH$_2$) (exch), and 2.46 (3H, s, CH$_3$).

Final elution with methanol gave a dark brown gum (0.10 g) from which no identifiable material was obtained.
(b) 5-Chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminoaniline (172b)

(i) A mixture of 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171b) (1.6 g; 0.004 mol) and 2 M aqueous hydrochloric acid solution (40.0 ml) was treated with stannous chloride (4.0 g) and the mixture was stirred and heated under reflux for 2h.

The cooled mixture was made basic with 30% w/v aqueous sodium hydroxide solution, stirred at room temperature for 15 min, and extracted with methylene chloride to give an oil (1.7 g) which was flash-chromatographed over silica.

Elution with hexane-ether (1:1) gave 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminoaniline (172b) (1.1 g; 74%) which formed pale yellow plates, m.p. 142-143° (from glacial acetic acid), $v_{\text{max}}$ 3468 and 3379 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.60(2H, d, J 8 Hz, ArH), 7.33-7.22(7H, m, ArH), 6.75(1H, d, J 2 Hz, ArH), and 6.72(1H, d, J 8 Hz, ArH) (NH 2 not observed).

Elution with hexane-ether (3:7) through ether to methanol gave only multicomponent oils and gums (0.16 g) which were not further investigated.

(ii) A solution of 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminonitrobenzene (171b) (8.1 g; 0.02 mol) in tetrahydrofuran (200.0 ml) was stirred and treated in one portion with a solution of stannous chloride (20.0 g) in 2 M aqueous hydrochloric acid (200.0 ml), and the mixture was stirred at room temperature for 18h.

Rotary evaporation of the mixture gave an oil (8.2 g). This was made basic with 30% w/v aqueous sodium hydroxide solution and extracted with methylene chloride to give an oil which was triturated with ether to afford 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminoaniline (172b) as an off-white solid (5.3 g; 71%), m.p. 135-137°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
 Rotary evaporation of the ethereal mother liquor gave a brown oil (1.6 g) whose t.l.c. in hexane-ether (1:1) over alumina showed it to be a complex mixture, which was not further investigated.

### N-[2-(N-Aryl-N-benzyl)amino]phenylformamides (166a) and (166b)

A mixture of the corresponding 2-(N-aryl-N-benzyl)aminoaniline (165a) or (165b) (0.04 mol) and 98-100% formic acid (100.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1-3h then worked up as described for the individual reactions below.

(a) **N-[2-(N-Benzyl-N-phenyl)amino]phenylformamide (166b)**

After 3h at reflux the cooled mixture from 2-(N-benzyl-N-phenyl)aminoaniline (165b) was rotary evaporated to give a brown oil which was dissolved in methylene chloride and the solution was washed five times with 10% w/v aqueous sodium hydrogen carbonate solution (5 x 10.0 ml). Rotary evaporation of the methylene chloride layer gave a cream solid which was collected with the aid of a little ether. This was combined with further material, obtained by rotary evaporation of the ethereal mother liquor and flash-chromatography over silica of the resulting residue [elution with hexane-ether (8:2)], to afford \( N-[2-(N\text{-benzyl-N-phenyl})\text{amino}]\text{phenylformamide} \) (166b) (79%) which formed colourless plates, m.p. 85-86° (from ethanol), \( \nu_{\text{max}} \) 3339 (NH) and 1674 (C=O) cm\(^{-1} \), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.45-8.13(2H, m, CHO and NH), 7.62-6.61(14H, m, AM), and 4.80(2H, s, CH\(_2\)).

(b) **N-[2-(N-Benzyl-N-(3-methoxyphenyl)amino]phenylformamide (166a)**

After 1h at reflux the cooled mixture from 2-[N-benzyl-N-(3-methoxyphenyl)]aminoaniline (165a) was rotary evaporated to give an oil which was dissolved in methylene chloride and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0 ml). Rotary evaporation of the organic layer gave an orange oil which was
distilled to give \( N\{-2-[N\text{-benzyl}-N\text{-}(3\text{-methoxyphenyl})]amino\}\text{phenylformamide} \) (166a) as an orange solid (10.1 g; 76%) which formed colourless crystals, m.p. 102-103° [from hexane-toluene (5:1)], \( \nu_{\text{max}} \) 3460 (NH) and 1670 (N=C) \( \text{cm}^{-1} \), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.44-8.12(1H, m, CHO), 7.59-7.51(1H, bs, NH), 7.39-6.97(10H, m, ArH), 6.44-6.21(3H, m, ArH), 4.79(2H, s, CH\(_2\)), and 3.67(3H, s, OCH\(_3\)).

\( N\{-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]amino\}\text{arylformamides (173a) and (173b)} \)

A mixture of the corresponding \( N\{-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]aminoaniline \) derivative (172a) or (172b) (0.008 mol) and 98-100% formic acid (40.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h then worked up as described for the individual reactions below.

(a) \( N\{-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]amino\}\text{phenylformamide (173a)} \)

The cooled mixture from \( 2\{(N\text{-phenyl}-N\text{-toluene-4-sulphonyl})\text{aminoanil)}} \) (172a) was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml) then rotary evaporated to give \( N\{-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]amino\}\text{phenylformamide (173a)) \) (2.5 g; 86%) which formed colourless plates, m.p. 169-170° (from ethanol), \( \nu_{\text{max}} \) 3292 (NH) and 1690 (C=O) \( \text{cm}^{-1} \), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.57-8.31(2H, m, CHO and NH), 7.56(2H, d, J 8 Hz, ArH), 7.36-6.85(11H, m, ArH), and 2.45(3H, s, CH\(_3\)).

(b) \( N\{-5\text{-Chloro}-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]amino\}\text{phenylformamide (173b)} \)

The cooled mixture from \( 5\text{-chloro-2-[N\text{-phenyl}-N\text{-toluene-4-sulphonyl}]aminoaniline (172b) \) was rotary evaporated to give an oil which was dissolved
in methylene chloride, and the solution was washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 2.5 ml) then rotary evaporated to afford \(N\)-[5-chloro-2-(\(N\)-phenyl-\(N\)-toluene-4-sulphonyl)amino]phenylformamide (173b) (93%) which formed cream needles, m.p. 146-147\(^\circ\) (from ethanol), \(\nu_{\max}\) 3364 (NH) and 1690 (C=O) cm\(^{-1}\), \(\delta_{H}(CDCl_3)\) 8.48-8.44(1H, m, CHO), 8.42(1H, d, J 1 Hz, NH), 7.54(2H, d, J 8 Hz, ArH), 7.37-7.21(8H, m, ArH), 6.98(1H, dd, J 8 and 2 Hz, ArH), 6.77(1H, d, J 8 Hz, ArH), and 2.46(3H, s, CH\(_3\)).

2-(\(N\)-Aryl-\(N\)-benzyl)aminophenyl isocyanides (167a) and (167b)

(a) 2-(\(N\)-Benzyl-\(N\)-phenyl)aminophenyl isocyanide (167b)

A solution of \(N\)-[2-(\(N\)-benzyl-\(N\)-phenyl)amino]phenylformamide (166b) (3.0 g; 0.01 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was treated with carbon tetrachloride (1.9 g; 0.012 mol) then triphenylphosphine (3.1 g; 0.012 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (2.0 g; 0.02 mol) was added and the mixture was stirred and heated at 60\(^\circ\) (oil bath), with exclusion of atmospheric moisture, for 2.5h.

Rotary evaporation of the cooled mixture gave a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (8.6 g) which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 2-(\(N\)-benzyl-\(N\)-phenyl)aminophenyl isocyanide (167b) (2.0 g; 70%) which formed pale brown plates, m.p. 87-88\(^\circ\) (from cyclohexane), \(\nu_{\max}\) 2126 (NC), \(\delta_{H}(CDCl_3)\) 7.44-7.12(11H, m, ArH), 6.91-6.72(4H, m, ArH), and 5.02(2H, s, CH\(_2\)).

Elution with hexane-ether (1:1) gave unchanged \(N\)-[2-(\(N\)-benzyl-\(N\)-phenyl)amino]phenylformamide (166b) as a cream solid (0.70 g; 23%), m.p. 80-82\(^\circ\), identical (m.p. and i.r. spectrum) to a sample prepared previously.
Final elution with methanol gave an intractable brown oil (4.3 g) which was not further investigated.

(b) 2-[N-Benzyl-N-(3-methoxyphenyl)]aminophenyl isocyanide (167a)

A solution of \(N\)-[2-[N-benzyl-N-(3-methoxyphenyl)]amino]phenylformamide (166a) (0.50 g; 0.015 mol) in anhydrous 1,2-dichloroethane (60.0 ml) was treated with carbon tetrachloride (2.3 g; 0.015 mol), followed by triphenylphosphine (4.7 g; 0.018 mol), then triethylamine (3.0 g; 0.03 mol), and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5 h.

Rotary evaporation of the cooled mixture gave a semi-solid which was treated with water (25.0 ml) and extracted with methylene chloride to give an oil (12.7 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 2-[N-benzyl-N-(3-methoxyphenyl)]aminophenyl isocyanide (167a) (3.9 g; 83%) which formed colourless plates, m.p. 91-92° [from hexane-toluene (20:1)], \(\nu_{\text{max}}\) 2115 (N\&C) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3)\) 7.41-6.97 (10H, m, ArH), 6.49-6.25 (3H, m, ArH), 4.96 (2H, s, CH\(_2\)), and 3.67 (3H, s, OCH\(_3\)).

Elution with hexane-ethyl acetate (7:3) through ethyl acetate to methanol gave only a series of oily multicomponent mixtures (8.5 g) which were not further investigated.

2-([N-Phenyl-N-toluene-4-sulphonyl]aminoaryl isocyanides (174a) and (174b)

(a) 2-([N-Phenyl-N-toluene-4-sulphonyl]aminophenyl isocyanide (174a)

A solution of \(N\)-[2-([N-phenyl-N-toluene-4-sulphonyl]amino]phenylformamide (173a) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (1.1 g; 0.0072 mol) followed by triphenylphosphine (1.9 g; 0.0072 mol) and the mixture was stirred at room
temperature for 15 min. Triethylamine (1.2 g; 0.0012 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (6.0 g) which was flash-chromatographed over silica.

Elution with hexane-ether (6:4) gave 2-((N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174a) (1.5 g; 72%) which formed colourless plates, m.p. 126-127° (from ethanol), $\nu_{\text{max}}$ 2125 (NC) cm$^{-1}$, \(\delta_{\text{H}}(\text{CDCl}_3)\) 7.66-7.63(2H, m, ArH), 7.57-7.23(11H, m, ArH), and 2.43(3H, s, CH$_3$).

Elution with hexane-ether (3:7) gave unchanged N-[2-((N-phenyl-N-toluen4-sulphonyl)amino)phenyl]formamide (173a) as a light brown solid (0.24 g; 11%), m.p. 160-162°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a complex brown gum (3.3 g) which was not investigated further.

(b) 5-Chloro-2-((N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174b)

(i) The cooled mixture from repetition of the reaction described in (a) before using N-[5-chloro-2-((N-phenyl-N-toluene-4-sulphonyl)amino)phenyl]formamide (173b) was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 5-chloro-2-((N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174b) (52%) which formed colourless
plates, m.p. 159-161° (from ethanol), $v_{\text{max}}$ 2129 (NC) cm$^{-1}$, $\delta_{H}(\text{CDCl}_3)$ 7.67-7.22(12H, m, ArH), and 2.44(3H, s, CH$_3$).

Elution with hexane-ether (7:3) gave unchanged $N$-[5-chloro-2-($N$-phenyl-4-sulphonylaminophenyl)formamide (173b) as a pale brown solid (17%), m.p. 137-139°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a brown oil whose t.l.c. in hexane-ether (1:1) over alumina showed it to be a complex mixture which was not further investigated.

(ii) A solution of $N$-[5-chloro-2-($N$-phenyl-4-sulphonyl)aminophenyl]formamide (173b) (0.80 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred and treated at 0° (ice bath) with $N$-ethyldiisopropylamine (0.72 g; 0.0056 mol) then dropwise with phosphoryl chloride (0.34 g; 0.0022 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h.

The mixture was treated with 2 M aqueous sodium carbonate solution (2.2 ml), stirred at room temperature for 1h, then treated with water (10.0 ml) and extracted with methylene chloride. The organic extracts were washed twice with water (2 x 5.0 ml) then rotary evaporated to give a waxy solid which was crystallised from ethanol to afford 5-chloro-2-($N$-phenyl-4-sulphonyl)aminophenyl isocyanide (174b) as a cream solid (0.66 g; 86%), m.p. 158-160°, identical (m.p. and i.r. spectrum) to a sample prepared in (i) before.
The Attempted Reaction of 2-[N-Benzyl-N-(3-methoxyphenyl)]aminophenyl isocyanide (167a) with Titanium Tetrachloride in Methylene Chloride

A solution of 2-[N-benzyl-N-(3-methoxyphenyl)]aminophenyl isocyanide (167a) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (9.5 g; 5.5 ml; 0.05 mol) in anhydrous methylene chloride (25.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 24 h.

The mixture was cooled (ice bath) and treated dropwise with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the ice bath for 15 min, then diluted with water (30.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a dark red oil (3.4 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture. Attempted distillation of this oil gave no identifiable material.

The Attempted Reaction of 2-[N-Benzyl-N-phenyl]aminophenyl isocyanide (167b) with Halogenating Agents

A solution of 2-(N-benzyl-N-phenyl)aminophenyl isocyanide (167b) (0.57 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine or sulphuryl chloride (0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h then worked up as described for the individual reactions below.

(i) Reaction with bromine

Rotary evaporation of the mixture gave a brown oil which was flash-chromatographed over silica.
Elution with hexane-ether (98:2) through ether to methanol gave only a series of multicomponent oils and gums which were not further investigated.

(ii) **Reaction with sulphuryl chloride**

Rotary evaporation of the mixture gave a green-brown oil (0.76 g), whose t.l.c. in hexane-ether (2:1) over silica showed it to be a multicomponent mixture which was not further investigated.

2-(N-Phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide Dibromide (175a) and (175b)

A solution of the corresponding 2-(N-phenyl-N-toluene-4-sulphonyl) aminophenyl isocyanide (174a) or (174b) (0.0005 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.08 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) **2-(N-Phenyl-N-toluene-4-sulphonyl)aminophenyl Isocyanide Dibromide (175a)**

The mixture from 2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174a) was rotary evaporated to give 2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide dibromide (175a) as a yellow oil (100%), \( \nu_{max} \ 1695 \ \text{(N=C)} \ \text{cm}^{-1} \).

(ii) **5-Chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl Isocyanide Dibromide (175b)**

The mixture from 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl) aminophenyl isocyanide (174b) was rotary evaporated to give 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide dibromide (175b) as a viscous orange oil (100%), \( \nu_{max} \ 1694 \ \text{(N=C)} \ \text{cm}^{-1} \).
11-Bromo-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176a)

A solution of 2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174a) (0.80 g; 0.0023 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.37 g; 0.0023 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (1.2 g; 0.0046 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2 h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (35.0 ml; 0.046 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 11-bromo-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176a) (0.98 g; 100%) which formed colourless plates, m.p. 197-200° (from acetonitrile), \( \nu_{\text{max}} 1627 \text{ (N=C)} \text{ cm}^{-1}, \delta_{\text{H}}(\text{CDCl}_3) 7.73-7.20(12\text{H, m, ArH}) \) and 2.40(3H, s, CH₃).

The Attempted Reaction of 11-Bromo-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176a) with Sodium N-Methylpiperazine in Dimethylformamide

A suspension of sodium hydride (0.066 g; 0.0028 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of \( N \)-methylpiperazine (0.25 g; 0.0025 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 11-bromo-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4] diazepine (176a) (1.1 g; 0.0025 mol) in anhydrous dimethylformamide
(10.0 ml) was added in one portion and the mixture was stirred, with exclusion of atmospheric moisture, at room temperature for 3 h then at 100° (oil bath) for 3 h.

The cooled mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give a waxy solid. This was washed with ethyl acetate to afford 5-(toluene-4-sulphonyl) dibenzo[b,e][1,4]diazepine-11(10H)-one (179) (0.43 g; 47%) which formed pale yellow plates, m.p. 295-297° (from aqueous acetic acid), νₘₐₓ 3180 (w) (NH) and 1660 (C=O) cm⁻¹, δ(H)[(CD₃)₂SO] 10.15 (1H, s, NH) (exch), 7.73-7.65 (2H, m, ArH), 7.53-7.49 (3H, m, ArH), 7.36-7.27 (5H, m, ArH), 7.19 (1H, dt, J 8, 8, and 2 Hz, ArH), 7.07 (1H, dd, J 8 and 2 Hz, ArH), and 2.50 (3H, s, CH₃).

Rotary evaporation of the organic mother liquor gave an oil (0.54 g) which was flash-chromatographed over silica.

Elution with hexane-ether (7:3) gave unchanged 11-bromo-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176a) as a yellow solid (0.19 g; 18%), m.p. 188-190°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.09 g) which was not investigated further.

**11-Bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b)**

A solution of 5-chloro-2-(N-phenyl-N-toluene-4-sulphonyl)aminophenyl isocyanide (174b) (0.77 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene-
chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred at room temperature or under reflux, under nitrogen, for 2 or 3 h then worked up as described for the individual reactions below.

(i) **Under reflux**

After 2 h the cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol) stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (1.2 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 11-bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b) (0.73 g; 79%) which formed colourless plates, m.p. 195-196° (from ethyl acetate), $\nu_{\text{max}}$ 1632 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.74-7.20(11 H, m, ArH) and 2.42(3H, s, CH$_3$).

Elution with methanol gave an intractable brown gum (0.10 g) which was not further investigated.

(ii) **At room temperature**

After 3 h the mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 11-bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b) as a pale brown solid (67%),
m.p. 192-194°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with methanol gave a brown gum (0.10 g) from which no identifiable material was obtained.

8-Chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176)

(a) A suspension of sodium hydride (0.053 g; 0.0022 mol) in the appropriate anhydrous solvent (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of anhydrous N-methylpiperazine (0.20 g; 0.002 mol) in the appropriate anhydrous solvent (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 11-bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b) (0.92 g; 0.002 mol) in the appropriate anhydrous solvent (10.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath) or under reflux, with exclusion of atmospheric moisture, for 2-7h.

(i) In dimethylformamide at 100°

After 2h the cooled mixture was treated with water (2.5 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.88 g) which was flash-chromatographed over alumina.

Elution with hexane-ethyl acetate (8:2) gave 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) (0.52 g; 54%) which formed cream plates, m.p. 197-198° (from acetonitrile), \( \nu_{\text{max}} \) 1596 (N=C) cm\(^{-1} \), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.54-6.94 (11H, m, ArH), 3.10-3.00 (3H, bs, CH\(_3\)), 2.39 (7H, s, 2xCH\(_2\) and CH\(_3\)), and 2.31 (4H, s, 2xCH\(_2\)).

Elution with methanol gave an intractable brown gum (0.07 g) which was not further investigated.
(ii) In 1,2-dimethoxyethane under reflux

After 7h the cooled mixture was treated with water (2.5 ml), stirred at room temperature for 15 min, and rotary evaporated to give a gum. This was treated with water (10.0 ml) and extracted with methylene chloride to give a gum which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unchanged 11-bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b) as a brown solid (11%), m.p. 190-192°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ethyl acetate (8:2) gave 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) as a cream solid (56%), m.p. 193-195°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

(b) A solution of 11-bromo-8-chloro-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (176b) (3.7 g; 0.008 mol) in anhydrous dioxane (50.0 ml) was treated in one portion with anhydrous N-methylpiperazine (3.2 g; 0.032 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 6h.

The cooled mixture was rotary evaporated to give a solid. This was treated with water (25.0 ml) and extracted with methylene chloride to give a solid which was washed with hexane to afford 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) as a light brown solid (3.4 g; 88%), m.p. 192-194°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the hexane mother liquor gave an intractable orange gum (0.32 g) which was not investigated further.
The Attempted Reaction of 8-Chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) with Sodium in Liquid Ammonia

A suspension of 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) (0.48 g; 0.001 mol) in liquid ammonia (20.0 ml) was treated portionwise at -33°C (solid CO₂-acetone bath) with sodium (0.072 g; 0.003 mol). The mixture was stirred at -33°C for 0.5h, then treated with enough ammonium chloride to discharge the blue colour and allowed to evaporate overnight.

The solid residue was treated with water (10.0 ml) and filtered to give unchanged 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) as a brown solid (0.38 g; 79%), m.p. 190-192°C, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Neutralisation of the aqueous mother liquor with 2 M aqueous hydrochloric acid solution and extraction with methylene chloride gave no material.

The Attempted Reaction of 8-Chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) with Sodium in n-Butanol

A solution of 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl) dibenzo[b,e][1,4]diazepine (178) (0.48 g; 0.001 mol) in n-butanol (20.0 ml) was stirred and heated under reflux and treated portionwise with sodium (0.3 g) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 0.5h. Further sodium (0.3 g) was added portionwise and stirring and heating under reflux, with exclusion of
atmospheric moisture, was continued for a further 0.5h by which time all of
the sodium had dissolved.

The cooled mixture was rotary evaporated to give a solid which was
treated with water (10.0 ml) and extracted with methylene chloride. The
organic extracts were washed twice with water (2 x 2.5 ml) and rotary
evaporated to give a gum (0.31 g). This was triturated with ether to give
unchanged 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-
sulphonyl)dibenzo[b,e][1,4]diazepine (178) as a cream solid (0.18 g; 38%),
m.p. 193-195°, identical (m.p. and i.r. spectrum) to a sample prepared
previously.

Rotary evaporation of the ethereal mother liquor gave an intractable
brown gum (0.10 g) which was not further investigated.

The Attempted Reaction of 8-Chloro-11-(4-methylpiperazin-1-yl)-5-
(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) with 30%
Hydrogen Bromide in Acetic Acid

A mixture of 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-
sulphonyl)dibenzo[b,e][1,4]diazepine (178) (0.48 g; 0.001 mol) and 30% w/v
hydrogen bromide in acetic acid solution (5.0 ml) was stirred at room
temperature or under reflux for 1-8h, then worked up as described for the
individual reactions below.

(i) **Under reflux for 8h**

The cooled mixture was rotary evaporated to give a gum which was
treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0 ml)
and extracted with methylene chloride to give a dark brown oil (0.30 g) whose
t.i.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex
mixture from which no identifiable material was obtained.
At room temperature for 1h

The mixture was rotary evaporated to give a foam which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0 ml) and extracted with methylene chloride to give a brown gum (0.38 g). This was tritutrated with ether to afford unchanged 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) as a light brown solid (0.37 g; 77%), m.p. 192-194°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Rotary evaporation of the ethereal mother liquor gave negligible material.

Under reflux for 1h

The cooled mixture was rotary evaporated to give a gum which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0 ml) and extracted with methylene chloride to give an intractable brown gum (0.30 g) from which no identifiable material was obtained.

The Attempted Reaction of 8-Chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) with Concentrated Sulphuric Acid

A suspension of 8-chloro-11-(4-methylpiperazin-1-yl)-5-(toluene-4-sulphonyl)dibenzo[b,e][1,4]diazepine (178) (0.48 g; 0.001 mol) in glacial acetic acid (1.0 ml) was stirred and treated slowly at 0° (ice bath) with concentrated sulphuric acid (1.0 ml) and the mixture was stirred and heated at 100° (oil bath) for 1h.

The mixture was cooled (ice bath), treated with ice (2.0 g), then made basic with 30% w/v aqueous sodium hydroxide solution and extracted with methylene chloride to give a viscous brown oil (0.41 g) whose t.l.c. in hexane-
ethyl acetate (1:1) over alumina showed it to be a complex mixture which was not further investigated.

2-Aryloxy-3-nitropyridine Derivatives (181a) and (181b)
(a) 3-Nitro-2-phenoxy pyridine (181b)

3-Nitro-2-phenoxy pyridine (181b) was prepared by the reaction of 2-chloro-3-nitropyridine (180) with the sodium salt of phenol (112b) as described by Weddell, as an orange-brown solid (yield 87%), and had m.p. 89-91° (lit., 94°).

(b) 2-(3-Methoxyphenoxy)-3-nitropyridine (181a)

2-(3-Methoxyphenoxy)-3-nitropyridine (181a) was prepared by the reaction of 2-chloro-3-nitropyridine (180) with the sodium salt of 3-methoxyphenol (112a) as described by Weddell, as a brown solid (yield 61%), and had m.p. 80-83° (lit., 81-85°).

3-Amino-2-aryloxy pyridine Derivatives (182a) and (182b)
(a) 3-Amino-2-phenoxy pyridine (182b)

3-Amino-2-phenoxy pyridine (182b) was prepared by the catalytic hydrogenation of 3-nitro-2-phenoxy pyridine (181b) as described by Weddell, as a yellow-brown solid (yield 98%), and had m.p. 95-97° (lit., 100-102°).

(b) 3-Amino-2-(3-methoxyphenoxy)pyridine (182a)

3-Amino-2-(3-methoxyphenoxy)pyridine (182a) was prepared by the catalytic hydrogenation of 2-(3-methoxyphenoxy)-3-nitropyridine (181a) as described by Weddell, as a pale yellow solid (yield 69%), and had m.p. 72-76° (lit., 73-75°).
N-(2-Aryloxypyridin-3-yl)formamides (183a) and (183b)

A mixture of the corresponding 3-amino-2-aryloxypyridine (182a) or (182b) (0.035 mol) and 98-100% formic acid (70.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1-3 h then worked up as described for the individual reactions below.

(i) \(N-(2\text{-Phenoxy}pyridin-3\text{-yl})\text{formamide (183b)}\)

After 3 h the cooled mixture from 3-amino-2-phenoxy pyridine (182b) was rotary evaporated to give an oil which was triturated with ether to give a pale brown solid. This was combined with further material obtained by rotary evaporation of the ethereal mother liquor and flash-chromatography of the resulting residue in hexane-ethyl acetate (7:3) over silica to give \(N-(2\text{-phenoxy}pyridin-3\text{-yl})\text{formamide (183b)}\) (96%) which formed pale brown plates, m.p. 97-98° (from toluene), \(\nu_{\text{max}}\) 3175 (\(\text{NH}\)) and 1689 (C=O) cm\(^{-1}\), \(\delta_{\text{h}}(\text{CDCl}_3)\) 8.71(1H, dd, J 8 and 2 Hz, ArH), 8.51(1H, d, J 1 Hz, CHO), 8.11-7.78(1H, bs, \(\text{NH}\)) (exch), 7.84(1H, dd, J 5 and 2 Hz, ArH), and 7.54-6.91(6H, m, ArH).

(ii) \(N-(2\text{-[3-Methoxyphenoxy]}pyridin-3\text{-yl})\text{formamide (183a)}\)

After 1 h the cooled mixture from 3-amino-2-(3-methoxyphenoxy)pyridine (182a) was rotary evaporated to give a viscous oil which slowly solidified to afford \(N-[2\text{-[3-methoxyphenoxy]}pyridin-3\text{-yl}]\text{formamide (183a)}\) (82%) which formed colourless crystals, m.p. 69-70° [from hexane-toluene (3:1)], \(\nu_{\text{max}}\) 3300 (\(\text{NH}\)) and 1680 (C=O) cm\(^{-1}\), \(\delta_{\text{h}}(\text{CDCl}_3)\) 8.71(1H, dd, J 8 and 2 Hz, ArH), 8.50(1H, d, J 1 Hz, CHO), 7.95(1H, bs, \(\text{NH}\)) (exch), 7.86(1H, dd, J 5 and 2 Hz, ArH), 7.40-7.19(1H, m, ArH), 7.00(1H, dd, J 8 and 5 Hz, ArH), 6.84-6.62(3H, m, ArH), and 3.78(3H, s, OCH\(_3\)).
2-Aryloxypyridin-3-yl Isocyanides (184a) and (184b)

(a) 2-Phenoxypyridin-3-yl Isocyanide (184b)

A solution of N-(2-phenoxypyridine-3-yl)formamide (183b) (3.1 g; 0.015 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (2.8 g; 0.018 mol) followed by triphenylphosphine (4.7 g; 0.018 mol), and the mixture was stirred at room temperature for 15 min. Triethylamine (3.0 g; 0.03 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (20.0 ml) and extracted with methylene chloride to give an oil (10.3 g) which was flash-chromatographed over silica.

Elution with hexane-ether (7:3) gave 2-phenoxypyridin-3-yl isocyanide (184b) (1.9 g; 67%) which formed pale brown plates, m.p. 93-94° (from cyclohexane), ν_max 2125 (N=C) cm⁻¹, δ_H (CDCl_3) 8.12 (1H, dd, J 5 and 2 Hz, ArH), 7.74 (1H, dd, J 8 and 2 Hz, ArH), and 7.56-6.93 (6H, m, ArH).

Elution with hexane-ether (4:6) gave unchanged N-(2-phenoxypyridin-3-yl)formamide (183b) as a pale yellow solid (0.63 g; 20%), m.p. 80-83°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable oil (5.7 g) which was not investigated further.

(b) 2-(3-Methoxyphenoxy)pyridin-3-yl Isocyanide (184a)

A solution of N-[2-(3-methoxyphenoxy)pyridin-3-yl]formamide (183a) (2.4 g; 0.01 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was treated with carbon tetrachloride (1.5 g; 0.01 mol), followed by triphenylphosphine (3.1 g; 0.012 mol), then triethylamine (2.0 g; 0.02 mol) and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.
The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (15.0 ml) and extracted with methylene chloride to give an oil (6.3 g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 2-(3-methoxyphenoxy)pyridin-3-yl isocyanide (184a) (1.8 g; 80%) which formed colourless needles, m.p. 65-66° (from hexane), $\nu_{\text{max}}$ 2120 (NC) cm$^{-1}$, $\delta_H(\text{CDCl}_3)$ 7.90 (1 H, dd, J 5 and 2 Hz, ArH), 7.74 (1 H, dd, J 8 and 2 Hz, ArH), 7.44-7.20 (1 H, m, ArH), 7.02 (1 H, dd, J 8 and 5 Hz, ArH), 6.88-6.69 (3 H, m, ArH), and 3.81 (3 H, s, OCH$_3$).

Elution with hexane-ethyl acetate (7:3) through ethyl acetate to methanol gave a series of multicomponent mixtures (3.4 g) which were not further investigated.

**The Attempted Reaction of 2-(3-Methoxyphenoxy)pyridin-3-yl Isocyanide (184a) with Titanium Tetrachloride in Methylene Chloride**

A solution of 2-(3-methoxyphenoxy)pyridin-3-yl isocyanide (184a) (2.3 g; 0.01 mol) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (9.5 g; 5.5 ml; 0.05 mol) in anhydrous methylene chloride (25.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 24 h.

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (33.0 ml; 0.5 mol), stirred in the ice bath for 15 min, then diluted with water (40.0 ml) and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave N-[2-(3-methoxyphenoxy)pyridin-3-yl]formamide (183a) as a viscous
brown oil (2.1 g; 86%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

The Attempted Reaction of 2-(3-Methoxyphenoxy)pyridin-3-yl isocyanide (184a) with Stannic Chloride in 1,2-Dichloroethane

A solution of 2-(3-methoxyphenoxy)pyridin-3-yl isocyanide (184a) (0.68 g; 0.003 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred under nitrogen, treated dropwise at room temperature with a solution of stannic chloride (3.9 g; 1.7 ml; 0.015 mol) in anhydrous 1,2-dichloroethane (10.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 15h.

The mixture was cooled (ice bath), treated dropwise with 60% w/v aqueous sodium hydroxide solution (10.0 ml; 0.15 mol), stirred in the ice bath for 15 min, then diluted with water (40.0 ml) and extracted with methylene chloride to give a dark brown polymeric solid (0.66 g), m.p. 105-120°, which could not be resolved by t.l.c. in hexane-ethyl acetate (1:1) over silica and therefore was not investigated further.

2-Phenoxypyridin-3-yl isocyanide Dibromide (186b)

A solution of 2-phenoxy pyridin-3-yl isocyanide (184b) (0.19 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 2-phenoxy pyridin-3-yl isocyanide dibromide (186b) (0.35 g; 100%) which formed pale brown plates, m.p. 105-106° (from cyclohexane), \( \nu_{\text{max}} \) 1686 (N=C) cm\(^{-1}\), \( \delta_\text{H}(\text{CDCl}_3) \) 8.02(1H, dd, J 5 and 2 Hz, ArH) and 7.52-6.93(7H, m, ArH).
6-Bromopyrido[2,3-b][1,4]benzoxazepine (187b)

A solution of 2-phenoxy(pyridin-3-yl isocyanide (184b) (0.59 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (1.6 g; 0.006 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 6-bromopyrido[2,3-b][1,4]benzoxazepine (187b) (0.74 g; 90%) which formed pale brown needles, m.p. 153-154° (from cyclohexane), $\nu_{\text{max}}$ 1628 (N=C) cm$^{-1}$, $\delta$ (CDCl$_3$) 8.21 (1H, dd, J 5 and 2 Hz, ArH) and 8.13-7.15 (6H, m, ArH).

6-Piperidinopyrido[2,3-b][1,4]benzoxazepine (188b)

A suspension of sodium hydride (0.026 g; 0.0011 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of piperidine (0.09 g; 0.001 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 6-bromopyrido[2,3-b][1,4]benzoxazepine (187b) (0.28 g; 0.001 mol) in anhydrous dimethylformamide (5.0 ml) was added in one portion and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4 h.
The mixture was treated with water (5.0 ml), stirred at room temperature for 15 min, and rotary evaporated to give an oil. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.40 g) which was flash-chromatographed over silica.

Elution with hexane-ether (6:4) gave 6-piperidinopyrido[2,3-b][1,4]benzoaxazepine (188b) (0.22 g; 79%) which formed colourless plates, m.p. 160-161° (from ethanol), $\nu_{\text{max}}$ 1593 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.89(1H, dd, J 5 and 2 Hz, ArH), 7.58-7.02(6H, m, ArH), 3.54(4H, m, 2xCH$_2$), and 1.68(6H, m, 3xCH$_2$).

Final elution with methanol gave an intractable brown gum (0.02 g) which was not further investigated.

The Attempted Reaction of 6-Bromopyrido[2,3-b][1,4]benzoaxazepine (187b) with Tetraethylammonium Cyanide in Acetonitrile Under Reflux

A solution of 6-bromopyrido[2,3-b][1,4]benzoaxazepine (187b) (0.55 g; 0.002 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated portionwise with a solution of tetraethylammonium cyanide (0.62 g; 0.004 mol) in anhydrous acetonitrile (5.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1h.

The cooled mixture was rotary evaporated to give a solid which was treated with 2 M aqueous hydrochloric acid solution (5.0 ml) and water (10.0 ml) and extracted with methylene chloride to give a dark brown gum (0.58 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to be a complex mixture, which therefore was not investigated further.

6-Cyanopyrido[2,3-b][1,4]benzoaxazepine (189b)

A solution of 6-bromopyrido[2,3-b][1,4]benzoaxazepine (187b) (0.28 g; 0.001 mol) in anhydrous acetonitrile (5.0 ml) was treated portionwise with a
solution of tetraethylammonium cyanide (0.31 g; 0.002 mol) in anhydrous acetonitrile (5.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 2h.

Rotary evaporation of the mixture gave a semi-solid. This was treated with 2 M aqueous hydrochloric acid solution (5.0 ml) and extracted with methylene chloride to give 6-cyanopyrido[2,3-b][1,4]benzoxazepine (189b) (0.21 g; 95%) which formed brown plates, m.p. 186-188° (from acetonitrile), \( \nu_{\text{max}} \) 2226 (w) (CN), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.31 (1H, dd, J 5 and 2 Hz, ArH), 7.86 (1H, dd, J 8 and 2 Hz, ArH), 7.79-7.62 (2H, m, ArH), and 7.41-7.24 (4H, m, ArH).

3-(2-Nitrophenoxy)pyridine (191)

A suspension of sodium hydride (5.3 g; 0.22 mol) in anhydrous dimethylformamide (100.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of 3-hydroxypyridine (190) (19.0 g; 0.2 mol) in anhydrous dimethylformamide (50.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-fluoronitrobenzene (111) (28.2 g; 0.2 mol) in anhydrous dimethylformamide (50.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was treated with water (25.0 ml), allowed to stand overnight, and rotary evaporated to give an oil. This was treated with water (200.0 ml) and extracted with methylene chloride to give an oil (40.0 g) which was distilled to afford 3-(2-nitrophenoxy)pyridine (191) as an orange-brown oil (34.0 g; 79%), b.p. 121-124°/0.10 mmHg (lit.,\textsuperscript{105} 148-152°/0.42 mmHg), m/z (ElMS) 216 (M\textsuperscript{+}).
A solution of 3-(2-nitrophenoxy)pyridine (191) (21.6 g; 0.1 mol) in ethyl acetate (125.0 ml) was hydrogenated over 10% palladium-on-charcoal (2.2 g) at room temperature and atmospheric pressure for 7h, during which time hydrogen (7070 ml; 0.32 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give the known 105 3-(2-aminophenoxy)pyridine (192) as an orange oil (18.5 g; 100%), $\nu_{\text{max}}$ 3453, 3318, and 3194 (NH) cm$^{-1}$, m/z (ElMS) 186 (M$^+$.)

$N$-[2-(Pyridin-3-yloxy)phenyl]formamide (193)

A mixture of 3-(2-aminophenoxy)pyridine (192) (16.7 g; 0.09 mol) and 98-100% formic acid (90.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which solidified on cooling to afford $N$-[2-(pyridin-3-yloxy)phenyl]formamide (193) (18.5 g; 96%) which formed colourless needles, m.p. 103-104° (from toluene), $\nu_{\text{max}}$ 3179 (NH) and 1690 (C=O) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.77-8.28(4H, m, CHO and 3xArH), 7.41-7.33(2H, m, ArH), 7.25-7.08(2H, m, ArH), 6.96-6.91(1H, m, ArH), and 6.00(1H, bs, NH) (exch).

2-(Pyridin-3-yloxy)phenyl laucyanide (194)

A solution of $N$-[2-(pyridin-3-yloxy)phenyl]formamide (193) (8.6 g; 0.04 mol) in anhydrous 1,2-dichloroethane (80.0 ml) was treated with carbon tetrachloride (7.4 g; 0.048 mol) followed by triphenylphosphine (12.6 g; 0.048 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (8.1 g; 0.08 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.
The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (40.0 ml) and extracted with methylene chloride to give an oil (25.0 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:6) gave 2-(pyridin-3-yloxy)phenyl isocyanide (194) as a brown oil (3.0 g; 38%), $\nu_{\text{max}} 2125$ (NC) cm$^{-1}$.

Elution with hexane-ethyl acetate (1:1) through ethyl acetate to methanol gave only a series of intractable oils and gums (15.4 g) which were not investigated further.

2-(Pyridin-3-yloxy)phenyl Isocyanide Dibromide (195)

A solution of 2-(pyridin-3-yloxy)phenyl isocyanide (194) (0.20 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 2-(pyridin-3-yloxy)phenyl isocyanide dibromide (195) as an orange solid (0.35 g; 98%), m.p. 110-130° (decomp.), $\nu_{\text{max}} 1673$ (N=C) cm$^{-1}$.

The Attempted Reaction of 2-(Pyridin-3-yloxy)phenyl Isocyanide Dibromide (195) with Aluminium Tribromide

(a) In methylene chloride

A solution of 2-(pyridin-3-yloxy)phenyl isocyanide (194) (0.78 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (2.1 g; 0.008 mol) in anhydrous methylene chloride
(30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.8 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 2-(pyridin-3-yloxy)phenyl isocyanide dibromide (195) as a brown, glassy solid (1.1 g; 77%), m.p. 102-118°C (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(b) In 1,2-dichloroethane

Repetition of the reaction described in (a) above using anhydrous 1,2-dichloroethane as the solvent gave a viscous dark brown oil (0.89 g) whose t.l.c. in hexane-ethyl acetate (1:3) over silica showed it to be a complex mixture, and was therefore not further investigated.

3-Nitro-2-phenylthiopyridine (198)

A suspension of sodium hydride (2.6 g; 0.11 mol) in anhydrous dimethylformamide (30.0 ml) was stirred and treated dropwise at 0°C (ice bath) with a solution of thiophenol (152b) (11.0 g; 0.1 mol) in anhydrous dimethylformamide (30.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-chloro-3-nitropyridine (180) (15.9 g; 0.1 mol) in anhydrous dimethylformamide (60.0 ml) was added in one portion and the mixture was stirred and heated at 100°C (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was treated with water (20.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a solid. This was treated with water (100.0 ml) and extracted with methylene chloride to give a
semi-solid which was triturated with ethanol to give 3-nitro-2-phenylthiopyridine (198) as a light brown solid (18.1 g; 78%), m.p. 103-105° (lit., 108 103-104°).

Rotary evaporation of the ethanolic mother liquor gave a multicomponent brown oil (3.7 g) from which no identifiable material was obtained.

3-Amino-2-phenylthiopyridine (199)

A solution of 3-nitro-2-phenylthiopyridine (198) (15.1 g; 0.065 mol) in tetrahydrofuran (400.0 ml) was stirred under nitrogen, treated portionwise with 15% w/v aqueous titanium trichloride solution (572 ml; 0.65 mol), and the mixture was stirred at room temperature, under nitrogen, for 70 h.

The mixture was rotary evaporated to give an oil which was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (200.0 ml) and extracted with methylene chloride to afford 3-amino-2-phenylthiopyridine (199) as a light brown solid (10.4 g; 79%), m.p. 60-62° (lit., 108 66-68°).

N-(2-Phenylthiopyridin-3-yl)formamide (200)

A mixture of 3-amino-2-phenylthiopyridine (199) (10.1 g; 0.05 mol) and 98-100% formic acid (100.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3 h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed four times with 10% w/v aqueous sodium hydrogen carbonate solution (4 x 5.0 ml). Rotary evaporation of the organic layer gave N-(2-phenylthiopyridin-3-yl)formamide (200) (10.3 g; 90%) which formed colourless needles, m.p. 73-74° (from ethanol), ν_max 3231 (NH) and 1656 (C=O) cm^{-1}, δ_H (CDCl_3) 8.70(1H,
dd, J 8 and 2 Hz, ArH), 8.48(1H, d, J 2 Hz, CHO), 8.35(1H, dd, J 5 and 2 Hz, ArH), 8.10(1H, bs, NH) (exch.), and 7.43-7.26(6H, m, ArH).

2-Phenylthiopyridin-3-yl isocyanide (201)

A solution of N-(2-phenylthiopyridin-3-yl)formamide (200) (4.6 g; 0.02 mol) in anhydrous 1,2-dichloroethane (80.0 ml) was treated with carbon tetrachloride (3.7 g; 0.024 mol) followed by triphenylphosphine (6.3 g; 0.024 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (4.0 g; 0.04 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5 h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (25.0 ml) and extracted with methylene chloride to give an oil (14.2 g) which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 2-phenylthiopyridin-3-yl isocyanide (201) (2.5 g; 59%) which formed brown plates, m.p. 58-61° (from cyclohexane), ν\text{max} 2122 (NC) cm\(^{-1}\), δ\text{H}(CDCl\(_3\)) 8.32(1H, dd, J 5 and 2 Hz, ArH), 7.59-7.55(3H, m, ArH), 7.46-7.42(3H, m, ArH), and 7.05(1H, dd, J 8 and 5 Hz, ArH).

Elution with hexane-ether (1:1) through ether to methanol gave a series of multicomponent mixtures (9.4 g) which were not investigated further.

2-Phenylthiopyridin-3-yl isocyanide Dibromide (202)

A solution of 2-phenylthiopyridin-3-yl isocyanide (201) (0.21 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h.
Rotary evaporation of the mixture gave 2-phenylthiopyridin-3-yl isocyanide dibromide (202) as a dark brown oil (0.38 g; 100%), $\nu_{\text{max}}$ 1686 (N=C) cm$^{-1}$.

$\text{6-Bromopyrido}[2,3-b][1,4]\text{benzothiazepine (203)}$

A solution of 2-phenylthiopyridin-3-yl isocyanide (201) (1.1g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.80 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (2.7 g; 0.01 mol) in anhydrous methylene chloride (40.0 ml) was added portionwise and the mixture was stirred at room temperature, under nitrogen, for 20h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (77.0 ml; 0.01 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride and rotary evaporation of the combined organic extracts gave a waxy solid (1.4 g) which was flash-chromatographed over silica.

Elution with hexane-ether (7:3) gave 6-bromopyrido[2,3-b][1,4] benzothiazepine (203) (1.3 g; 90%) which formed yellow plates, m.p. 163-164° (from ethyl acetate), $\nu_{\text{max}}$ 1638 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.37(1H, dd, J 5 and 2 Hz, ArH), 7.77(1H, dd, J 8 and 2 Hz, ArH), 7.56(1H, dd, J 8 and 2 Hz, ArH), 7.51-7.36(4H, m, ArH), and 7.25(1H, dd, J 8 and 5 Hz, ArH).

Elution with methanol gave a brown gum (0.05 g) whose t.l.c. in hexane-ether (1:2) over silica showed it to be a complex mixture.
A suspension of sodium hydride (0.053 g; 0.0022 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of piperidine (0.17 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 6-bromopyrido[2,3-b][1,4]benzothiazepine (203) (0.58 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was added in one portion and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 3h.

The mixture was treated with water (2.5 ml), stirred at room temperature for 15 min, then rotary evaporated to give a solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give a semi-solid. This was washed with ether to afford 6-piperidinopyrido[2,3-b][1,4]benzothiazepine (204) (0.52 g; 88%) which formed colourless plates, m.p. 198-199° (from toluene), $\nu_{max}$ 1593 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.03(1H, dd, J 5 and 2 Hz, ArH), 7.62-7.25(5H, m, ArH), 7.07(1H, dd, J 8 and 5 Hz, ArH), 3.49-3.43(4H, m, 2xCH$_2$), and 1.68(6H, m, 3xCH$_2$).

A solution of 6-bromopyrido[2,3-b][1,4]benzothiazepine (204) (0.58 g; 0.002 mol) in anhydrous acetonitrile (25.0 ml) was stirred and treated portionwise with a solution of tetraethylammonium cyanide (0.62 g; 0.004 mol) in anhydrous acetonitrile (5.0 ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h.

Rotary evaporation of the mixture gave a waxy solid. This was treated with 2 M aqueous hydrochloric acid solution (10.0 ml) and extracted with
methylene chloride to give a waxy solid (0.48 g) which was flash-
chromatographed over silica.

Elution with hexane-ethyl acetate (6:4) gave 6-cyanopyrido[2,3-b][1,4]benzothiazepine (205) (0.39 g; 82%) which formed yellow needles, m.p. 181-182° (from ethanol), \( \nu_{\text{max}} \) 2227 (w) (CN) cm\(^{-1} \), \( \delta_\text{H}(\text{CDCl}_3) \) 8.46(1H, dd, J 5 and 2 Hz, ArH), 7.79(1H, dt, J 8, 1, and 1 Hz, ArH), 7.69(1H, dd, J 8 and 2 Hz, ArH), 7.60-7.58(2H, m, ArH), 7.51-7.46(1H, m, ArH), and 7.36(1H, dd, J 8 and 5 Hz, ArH).

Elution with methanol gave an intractable brown gum (0.05 g) which was not further investigated.

3-Nitro-2-phenylaminopyridine (206)

3-Nitro-2-phenylaminopyridine (206) was prepared by the reaction of 2-chloro-3-nitropyridine (180) with aniline (162b) in refluxing di-\( n \)-butyl ether as described by Bacon and Hamilton,\(^{113} \) as an orange-red solid (yield 94%), and had m.p. 69-71° (lit.,\(^{130} 75° \)).

3-Nitro-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (207)

(a) A suspension of sodium hydride (3.7 g; 0.15 mol) in anhydrous dimethylformamide (50.0 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of 3-nitro-2-phenylaminopyridine (206) (30.1 g; 0.14 mol) in anhydrous dimethylformamide (75.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of fresh toluene-4-sulphonyl chloride (26.7 g; 0.14 mol) in anhydrous dimethylformamide (75.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 24h.

The cooled mixture was treated with water (30.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give a semi-solid. This was
treated with water (150.0 ml) and extracted with methylene chloride to give an oil (43.0 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) gave unchanged 3-nitro-2-phenylaminopyridine (206) as an orange solid (14.2 g; 47%), m.p. 69-71° (lit., 130° 75°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ethyl acetate (4:6) gave 3-nitro-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (207) (17.7 g; 34%) which formed yellow plates, m.p. 162-163° (from glacial acetic acid), νmax 1531 and 1353 (NO2) cm⁻¹, δH(CDCl3) 8.63(1H, dd, J 5 and 2 Hz, ArH), 8.20(1H, dd, J 8 and 2 Hz, ArH), 7.52-7.42(5H, m, ArH), 7.31-7.20(5H, m, ArH), and 2.41(3H, s, CH3).

Elution with methanol gave a dark brown gum (5.9 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to be a complex mixture, which was therefore not further investigated.

(b) Repetition of the reaction described in (a) above using two equivalents (0.28 mol) of tosyl chloride followed by flash-chromatography of the product over silica gave unchanged 3-nitro-2-phenylaminopyridine (206) as a red solid (26%), m.p. 69-71° (lit., 130° 75°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Also obtained was 3-nitro-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (207) as a brown solid (45%), m.p. 161-162°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

3-Amino-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (208)

A mixture of 3-nitro-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (207) (18.5 g; 0.05 mol) and 2 M aqueous hydrochloric acid solution (500.0 ml) was treated with stannous chloride (50.0 g) and the mixture was stirred and heated under reflux for 2h.
The mixture was cooled (ice bath), made basic with 30% w/v aqueous sodium hydroxide solution, stirred at room temperature for 15 min, then extracted with methylene chloride to give 3-amino-2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridine (208) (16.1 g; 95%) which formed cream needles, m.p. 170-171° (from ethanol). $\nu_{\text{max}}$ 3480 and 3376 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.83(1H, dd, J 4 and 2 Hz, ArH), 7.67-7.63(2H, m, ArH), 7.46-7.42(2H, m, ArH), 7.28-7.19(5H, m, ArH), 7.08-7.03(2H, m, ArH), 4.50-4.00(2H, bs, NH$_2$) (exch), and 2.40(3H, s, CH$_3$).

N-[2-(N-Phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl]formamide (209)

A mixture of 3-amino-2-(N-phenyl-N-toluene-4-sulphonyl) aminopyridine (208) (13.6 g; 0.04 mol) and 98-100% formic acid (60.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml). Rotary evaporation of the organic layer gave N-[2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl]formamide (209) (13.0 g; 95%) which formed pale brown plates, m.p. 192-193° (from toluene), $\nu_{\text{max}}$ 3379 (NH) and 1701 (C=O) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.76(1H, dd, J 8 and 2 Hz, ArH), 8.51(1H, s, CHO), 8.50-8.30(1H, bs, NH) (exch), 8.16(1H, dd, J 5 and 2 Hz, ArH), 7.56-7.41(4H, m, ArH), 7.32-7.07(6H, m, ArH), and 2.42(3H, s, CH$_3$).

2-(N-Phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide (210)

(a) A solution of N-[2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl]formamide (209) (3.7 g; 0.01 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (1.8 g; 0.012 mol) followed by
triphenylphosphine (3.1 g; 0.012 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (2.0 g; 0.02 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (9.2 g) which was flash-chromatographed over silica.

Elution with hexane-ether (3:7) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide (210) (2.1 g; 60%) which formed colourless plates, m.p. 167-168° (decomp.) (from ethanol), $\nu_{\text{max}}$ 2122 (NC) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.49(1H, dd, J 5 and 2 Hz, ArH), 7.72(1H, dd, J 8 and 2 Hz, ArH), 7.66-7.65(2H, m, ArH), 7.41-7.21(8H, m, ArH), and 2.41(3H, s, CH$_3$).

Elution with methanol gave an intractable brown gum (5.3 g) which was not further investigated.

(b) A solution of $N$-[2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl]formamide (209) (3.7 g; 0.01 mol) in anhydrous methylene chloride (50.0 ml) was stirred and treated at 0° (ice bath) with $N$-ethyldiisopropylamine (3.5 g; 0.027 mol) then dropwise with phosphoryl chloride (1.7 g; 0.011 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h.

The mixture was treated dropwise with 2 M aqueous sodium carbonate solution (11.0 ml), stirred at room temperature for 1h, treated with water (30.0 ml), and extracted with methylene chloride. The combined organic extracts were washed twice with water (2 x 10.0 ml) then rotary evaporated to give an oil (5.1 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide (210) as a cream solid (3.0 g; 86%),
m.p. 160-162° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with methanol gave an intractable brown oil (0.73 g) which was not investigated further.

2-([N-Phenyl-N-toluene-4-Sulphonyl]amino)pyridin-3-yl isocyanide Dibromide (211)

A solution of 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide (210) (0.17 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.08 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide dibromide (211) (0.26 g; 100%) which formed pale brown plates, m.p. 129-130° (from acetonitrile), $\nu_{\text{max}}$ 1643 (N≡C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.34(1H, dd, J 5 and 2 Hz, ArH), 7.72(1H, dd, J 8 and 2 Hz, ArH), 7.30-7.20(12H, m, ArH), and 2.40(3H, s, CH$_3$), $\delta_{\text{C}}$(CDCl$_3$) 145.8(CH), 143.4(quat), 138.9(quat), 138.5(quat), 136.4(quat), 129.4-128.8(9xCH and 2xquat), 127.9(CH), 123.2(CH), and 21.5(CH$_3$).

The Hydrolysis of 2-(N-Phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide Dibromide (211)

A solution of 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide dibromide (211) (0.43 g; 0.008 mol) in dioxane (10.0 ml) was treated in one portion with 40% w/v aqueous benzyltrimethylammonium hydroxide solution (1.7 ml; 0.004 mol) and the mixture was stirred at room temperature for 6h.
Rotary evaporation of the mixture gave a semi-solid. This was treated with water (5.0 ml), and the mixture was acidified with 2 M aqueous hydrochloric acid solution and extracted with methylene chloride to give an oil (0.54 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave 3-amino-2-((N-phenyl-N-toluene-4-sulphonyl)aminopyridine (208) as a light brown solid (0.24 g; 84%), m.p. 162-164°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with methanol gave a brown gum (0.06 g) whose t.l.c in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture, which was not further investigated.

The Attempted Reaction of 2-(N-Phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide Dibromide (211) with Aluminium Tribromide

A solution of 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide (210) (1.4 g; 0.004 mol) in the appropriate anhydrous solvent (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.64 g; 0.004 mol) in the appropriate anhydrous solvent (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (0.008-0.02 mol) in the appropriate anhydrous solvent (30.0-80.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h then worked up as described for the individual reactions below.

(i) The cooled mixture from two equivalents (0.008 mol) of aluminium tribromide in anhydrous methylene chloride was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues.
Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide dibromide (211) as a brown oil (2.0 g; 98%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] with a sample prepared previously.

(ii) The cooled mixture from three equivalents (0.012 mol) of aluminium tribromide in anhydrous methylene chloride was poured into 10% w/v aqueous sodium hydrogen carbonate solution (92.0 ml; 0.12 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which was flash-chromatographed over silica.

Elution with hexane-ether (6:4) gave 2-(N-phenyl-N-toluene-4-sulphonyl)aminopyridin-3-yl isocyanide dibromide (211) as a brown solid (69%), m.p. 124-126°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with methanol gave an intractable brown gum which was not investigated further.

(iii) The cooled mixture from five equivalents (0.02 mol) of aluminium tribromide in anhydrous 1,2-dichloroethane was poured into 10% w/v aqueous sodium hydrogen carbonate solution (154 ml; 0.2 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Rotary evaporation of the filtrate gave a solid which was treated with water (100.0 ml) and extracted with methylene chloride to give a black gum whose t.l.c. in hexane-ether (1:1) over silica showed it to be a complex mixture, which was therefore not further investigated.
**N-(2-Benzyl)phenylformamide (216)**

A mixture of 2-benzylaniline (215) (7.3 g; 0.04 mol) and 98-100% formic acid (60.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give N-(2-benzyl)phenylformamide (216) (8.2 g; 97%) which formed colourless needles, m.p. 100-101° (from toluene), \( \nu_{\text{max}} \) 3248 (NH) and 1655 (C=O) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.49-7.88(2H, m, CHO and NH), 7.35-7.03(9H, m, ArH), and 3.98(2H, s, CH\(_2\)).

**2-Benzylphenyl isocyanide (217)**

A solution of N-(2-benzyl)phenylformamide (216) (4.2 g; 0.02 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was treated with carbon tetrachloride (3.7 g; 0.024 mol) followed by triphenylphosphine (6.3 g; 0.024 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (4.0 g; 0.04 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a waxy solid. This was treated with water (25.0 ml) and extracted with methylene chloride to give an oil (12.0 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 2-benzylphenyl isocyanide (217) as an orange-yellow oil (3.0 g; 78%), \( \nu_{\text{max}} \) 2119 (NC) cm\(^{-1}\).

Elution with hexane-ether (2:8) gave unchanged N-(2-benzyl)phenylformamide (216) as a colourless solid (0.79 g; 16%), m.p. 91-94°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave a viscous oil (6.9 g) which was triturated with ether to afford triphenylphosphine oxide as a cream solid.
(2.9 g), m.p. 149-152° (lit., 126 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the ethereal mother liquor gave a multicomponent oil (3.9 g) which was not further investigated.

2-Benzylphenyl isocyanide Dibromide (218)

A solution of 2-benzylphenyl isocyanide (217) (0.19 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 2-benzylphenyl isocyanide dibromide (218) as a yellow oil (0.36 g; 100%), \( \nu_{\text{max}} \) 1687 (\( \text{N=C} \)) cm\(^{-1}\).

6-Bromodibenzo[b,e]azepine (219)

A solution of 2-benzylphenyl isocyanide (217) (6.8 g; 0.035 mol) in anhydrous methylene chloride (30.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (5.6 g; 0.035 mol) in anhydrous methylene chloride (30.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (18.7 g; 0.07 mol) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (540 ml; 0.7 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (10.4 g) which was flash-chromatographed over silica.
Elution with hexane-ether (98:2) gave 5-bromodibenz[b,e]azepine (219) as an orange-yellow oil (8.4 g; 88%), b.p. 110-120°/0.40-0.10 mmHg, \( \nu_{\text{max}} \) 1620 (N=C) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.88-7.76 (1H, m, ArH), 7.54-7.18 (7H, m, ArH), and 3.71 (2H, s, CH\(_2\)).

Elution with methanol gave an intractable brown gum (0.74 g) which was not further investigated.

The Attempted Reaction of 5-Bromodibenz[b,e]azepine (219) with Piperidine

A solution of 5-bromodibenz[b,e]azepine (219) (0.54 g; 0.002 mol) in anhydrous acetonitrile (10.0 ml) was treated with piperidine (0.34 g; 0.004 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 23h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (5.0 ml) and extracted with methylene chloride to give a viscous oil which was dissolved in methylene chloride, and the solution was washed twice with 2 M hydrochloric acid solution (2 x 10.0 ml) and rotary evaporated to give a pale brown solid (0.51 g), m.p. 138-140°, flash-chromatography of which over silica gave no identifiable material.

5-Cyanodibenz[b,e]azepine (221)

A solution of 5-bromodibenz[b,e]azepine (219) (0.54 g; 0.002 mol) in anhydrous acetonitrile (5.0 ml) was stirred and treated portionwise with a solution of tetraethylammonium cyanide (0.31 g; 0.002 mol) in anhydrous acetonitrile (5.0 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 5h. A further portion of tetraethylammonium cyanide (0.31 g; 0.002 mol) was added and stirring and
heating under reflux, with exclusion of atmospheric moisture, was continued for a further 3h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with 2 M aqueous hydrochloric acid solution (5.0 ml) and extracted with methylene chloride to give an oil (0.58 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 5-cyanodibenz[b,e]azepine (221) (0.38 g; 87%) which formed yellow plates, m.p. 100-101° (from cyclohexane), \( \nu_{\text{max}} \) 2222 (w) (CN) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.91-7.24 (8H, m, ArH) and 3.68 (2H, s, CH\(_2\)).

Final elution with methanol gave a dark brown gum (0.05 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to be complex mixture.

**Tetrazolo[1,5-g]dibenz[b,e]azepine (222)**

A solution of 5-bromodibenz[b,e]azepine (219) (0.54 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was treated with sodium azide (0.13 g; 0.002 mol) and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was rotary evaporated to give a solid which was treated with water (5.0 ml) and extracted with methylene chloride to give a solid which was washed with hexane to afford tetrazolo[1,5-g]dibenz[b,e]azepine (222) (0.40 g; 85%) which formed colourless needles, m.p. 178-180° (from ethanol), \( \nu_{\text{max}} \) 1604 (Ar) cm\(^{-1}\), \( \delta_{\text{H}}[(\text{CD}_3)_2\text{SO}] \) 8.06-7.45 (8H, m, ArH) and 4.08 (2H, s, CH\(_2\)).

Rotary evaporation of the hexane mother liquor gave a yellow oil (0.19 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture of the starting material (219) and the desired product (222), which was not further investigated.
A solution of sodium (0.18 g; 0.008 mol) in anhydrous ethanol (7.5 ml) was treated portionwise with a solution of 5-bromodibenz[b,e]azepine (219) (0.54 g; 0.002 mol) in anhydrous ethanol (2.5 ml) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 1 h.

The cooled mixture was rotary evaporated to give a solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give 5-ethoxydibenz[b,e]azepine (223) (0.40 g; 84%) which formed cream plates, m.p. 101-102° (from ethanol), $v_{max}$ 1636 (Ar) cm$^{-1}$, $\delta$$_H$(CDCl$_3$) 7.73-7.04 (8H, m, ArH), 4.52 (2H, q, J 7 Hz, CH$_2$), 3.70 (2H, s, CH$_2$), and 1.48 (3H, t, J 7 Hz, CH$_3$).

A solution of 5-bromodibenz[b,e]azepine (219) (0.54 g; 0.002 mol) in dioxane (10.0 ml) was treated with 2 M aqueous sodium hydroxide solution (2.5 ml) and the mixture was stirred and heated under reflux for 99 h.

The cooled mixture was rotary evaporated to give a gum which was treated with water (5.0 ml), and the mixture was acidified with 2 M aqueous hydrochloric acid solution then extracted with methylene chloride to give an oil. This was triturated with ether to afford dibenz[b,e]azepin-5-(6H)-one (224) (0.40 g; 96%) which formed colourless plates, m.p. 200° [from glacial acetic acid-methanol (1:3)], (lit.,$^{131}$ 201-203°), $v_{max}$ 3162 ($\bar{N}$H) and 1643 (C=O) cm$^{-1}$, $\delta$$_H$[(CD$_3$)$_2$SO)] 10.44 (1H, s, $\bar{N}$H) (exch), 7.70 (1H, dd, J 8 and 1 Hz, ArH), 7.47 (1H, dt, J 8, 8, and 1 Hz, ArH), 7.38-7.29 (3H, m, ArH), 7.20-7.04 (3H, m, ArH), and 3.90 (2H, s, CH$_2$).

Rotary evaporation of the ethereal mother liquor gave a gum (0.03 g) which was not further investigated.
**N-(2-Benzoyl)phenylformamide (226)**

A mixture of 2-aminobenzophenone (225) (3.9 g; 0.02 mol) and 98-100% formic acid (30.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 10.0 ml). Rotary evaporation of the organic layer gave the known N-(2-benzoyl)phenylformamide (226) as a yellow-orange oil (4.5 g, 100%), $\nu_{\text{max}}$ 3316 (NH), 1698 (amide C=O), and 1636 (ketone C=O) cm$^{-1}$.

**2-Benzoylphenyl isocyanide (227)**

A solution of N-(2-benzoyl)phenylformamide (226) (4.1 g; 0.018 mol) in anhydrous 1,2-dichloroethane (30.0 ml) was treated with carbon tetrachloride (3.3 g; 0.022 mol) followed by triphenylphosphine (5.7 g; 0.022 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (3.6 g; 0.036 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (20.0 ml) and extracted with methylene chloride to give an oil (12.0 g) which was flash-chromatographed over alumina.

Elution with hexane-ether (6:4) gave 2-benzoylphenyl isocyanide (227) (2.7 g; 73%) which formed yellow needles, m.p. 87-88° (from cyclohexane), $\nu_{\text{max}}$ 2122 (NC) cm$^{-1}$ and 1659 (C=O) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.87-7.10(9H, m, ArH).

Elution with methanol gave a brown semi-solid (7.1 g) whose t.i.c. in hexane-ethyl acetate (1:1) over alumina showed it to be a multicomponent mixture which was not further investigated.
2-Benzoylphenyl Isocyanide Dibromide (228)

A solution of 2-benzoylphenyl isocyanide (227) (0.21 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 2-benzoylphenyl isocyanide dibromide (228) as an unstable brown oil (0.37 g; 100%), $\nu_{max}$ 1763 (N=O) and 1654 (C=O) cm$^{-1}$.

The Attempted Reaction of 2-Benzoylphenyl Isocyanide Dibromide (228) with Aluminium Tribromide in Methylene Chloride

A solution of 2-benzoylphenyl isocyanide (227) (0.41 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cold mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.59 g) which was flash-chromatographed over silica.
Elution with hexane-ethyl acetate (9:1) through ethyl acetate to methanol gave a series of multicomponent oils and gums (0.36 g) which were not investigated further.
Table 6: Analytical and Mass Spectroscopic Data

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*a,molecular ions detected by Electron Impact mass spectroscopy or, for values in parentheses, detected by Fast Atom Bombardment mass spectroscopy.*
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a, molecular ions detected by Electron Impact mass spectroscopy or, for values in parentheses, detected by Fast Atom Bombardment mass spectroscopy.
CHAPTER 3

INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF 1,1'-BIPHENYL-2-ISOCYANIDES AND 1,1'-BIPHENYL-2-ISOCYANIDE DIHALIDES AND RELATED COMPOUNDS
3.1 **INTRODUCTION**

The work described in Chapter 2 demonstrates the applicability of the Lewis acid promoted cyclisation reactions of isocyanides and isocyanide dihalides to the synthesis of a variety of tricyclic heteropine derivatives. This novel heterocyclisation reaction is of considerable synthetic interest as it provides a straightforward and efficient route to a range of functionalised heterocycles which may not be easily accessible by other means. It was therefore decided to examine more closely the scope and limitations of this reaction and its applicability to the preparation of other systems. The present chapter describes investigations carried out on the synthesis of six- and five-membered heterocycles by the Lewis acid promoted cyclisation of 1,1'-biphenyl-2-isocyanide and naphthalene-1-isocyanide, and their corresponding isocyanide dihalides, respectively. In addition the cyclisation reactions of heteroaromatic isocyanides and isocyanide dihalides were considered of interest. Although aromatic isocyanides have been widely reported, there has been little investigation of the chemistry of the heteroaromatic isocyanides. It was anticipated that the cyclisation reactions of these compounds would allow access to a range of unusual and synthetically useful heterocycles. Studies towards this objective are described in Sections 3.4 and 3.5.

Studies on the scope and limitations of the cyclisation of isocyanides and isocyanide dihalides are continued in Chapter 4, which describes investigations on the reaction of isocyanides and isocyanide dihalides with
carbon-carbon double bonds, and on the cyclisation of alkyl isocyanides and isocyanide dihalides.

3.2 LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF 1,1'-BIPHENYL-2-ISOCYANIDES AND 1,1'-BIPHENYL-2-ISOCYANIDE DIHALIDES

Despite the ready accessibility of 1,1'-biphenyl-2-isocyanide (232), the reactivity of this molecule has received scant attention. A survey of the chemical literature reveals that the only aspect of its reactivity to be studied to any extent is its photochemistry. Thus de Jong and Boyer have reported\textsuperscript{132-134} that irradiation of 1,1'-biphenyl-2-isocyanide with ultraviolet light gives a mixture of 1-azabenz[b]azulene and phenanthridine, the ratio of the two products depending on the particular reaction conditions. The authors also show that these transformations cannot be effected thermally and so conclude that irradiation increases the electrophilicity of the isocyano carbon atom, and this results in nucleophilic attack by the adjacent phenyl ring to give phenanthridine. Phenanthridine is also obtained\textsuperscript{135} as a minor product from the pyrolysis of \textit{N}-chloroacetyl-1,1'-biphenyl-2-amine at 850°C. The investigators propose that this process involves 1,1'-biphenyl-2-isocyanide as a transient intermediate which combines with liberated hydrochloric acid and undergoes cyclisation to phenanthridine, presumably via an \(\alpha\)-addition pathway. These results indicate that it is possible for 1,1'-biphenyl-2-isocyanide to undergo cyclisation to afford phenanthridine if its electrophilicity is enhanced, either by irradiation or with a protic acid. Therefore this compound suggested itself as a model substrate for investigations on the extension of the Lewis acid promoted cyclisation of isocyanides and their derivatives to give six membered heterocycles.
(i) 98-100% HCO₂H, reflux.

(ii) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.

(iii) MeCOCl, Et₂O, -10°.

(iv) MeCOCl, CH₂Cl₂, reflux.

(v) MeCOBr, CH₂Cl₂, -10°.

(vi) MeCOCl, AgBF₄, Cl(CH₂)₂Cl, room temp.

(vii) BrCN, CH₂Cl₂, -10°.

(viii) TiCl₄, CH₂Cl₂, -10°.

(ix) TiCl₄, CH₂Cl₂, reflux.

Scheme 62
Reaction (Scheme 62) of commercially available 1,1'-biphenyl-2-amine (230) with formic acid under reflux gave the known\textsuperscript{136} formamide (231) in almost quantitative yield (98\%). This compound was subsequently converted into the known\textsuperscript{132} isocyanide (232) in high yield (87\%) by dehydration with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. In accord with most literature reports\textsuperscript{132-134} the isocyanide (232) was isolated as an oil, which was found to be unstable towards prolonged storage, contrary to a report by Ugi et al\textsuperscript{n} who erroneously described this compound as a solid melting at 116-118\°.

It was first decided to investigate (Scheme 62) the reactions of the isocyanide (232) with acid halides, with the aim of preparing the α-ketoimidoyl halides (233a) and (233b). The attempted reaction of the isocyanide (232) with acetyl chloride in ether at 0\° was unsuccessful however, giving a near quantitative recovery (99\%) of the unchanged starting material. Repetition of this reaction in refluxing methylene chloride resulted in a 71\% yield of the formamide (231), which presumably arises from hydrolysis of the isocyanide (232) by traces of hydrochloric acid present in the mixture. As acetyl bromide is a more reactive acylating agent than acetyl chloride, its reaction with the isocyanide (232) was next investigated. This reaction gave \(N\)-(1,1'-biphenyl-2-yl)-2-ketopropanamide (237) in 13\% yield as the only characterisable product after chromatography. The isolation of this product does at least indicate that the α-ketoimidoyl bromide (233b) is being formed, but its high reactivity means that its isolation is difficult and becomes almost impossible if chromatography is required. In order to eliminate this problem it was decided to attempt the reaction of the isocyanide (232) with acetyl chloride in the presence of silver tetrafluoroborate. These conditions were chosen in the expectation that silver ion would activate the acid chloride towards reaction with the isocyanide and would also act as a catalyst for ring closure of the
(i) Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, 1,2-dimethoxyethane, reflux.
(ii) H$_2$, 10% Pd-C, EtOAc, room temp.
(iii) 98-100% HCO$_2$H, reflux.
(iv) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60°.
(v) TiCl$_4$, CH$_2$Cl$_2$, -10°.
(vi) TiCl$_4$, CH$_2$Cl$_2$, reflux.

Scheme 63
resulting α-ketoimidoyl chloride to give 6-acetylphenanthridine (234). Thus a solution of the isocyanide (232), acetyl chloride, and silver tetrafluoroborate in 1,2-dichloroethane was stirred at room temperature, but these conditions resulted in a complex mixture which could not be resolved by chromatography.

The reluctance of the isocyanide (232) to react with acid halides once again highlights the differing reactivity of aryl and alkyl isocyanides, with the latter easily undergoing insertion$^{3,32}$ into the C-Cl bond of acid chlorides. On the other hand halogens are known$^3$ to react readily with both aryl and alkyl isocyanides. It was therefore anticipated that cyanogen bromide, as a pseudo-halogen, would react similarly to give the cyanoimidoyl bromide (235), a potentially useful intermediate for cyclisation to give 6-cyanophenanthridine. Unfortunately reaction of the isocyanide (232) with cyanogen bromide in methylene chloride gave only a quantitative recovery of the unchanged starting material (232), with no evidence for the formation of the cyanoimidoyl bromide (235) or any of its possible hydrolysis products.

In view of the disappointing lack of success achieved in the attempted reactions of the isocyanide (232) with acid halides and cyanogen bromide, it was next decided to investigate its direct Lewis acid promoted cyclisation which it was hoped (Scheme 62) would yield phenanthridine (236). In practice, reaction of the isocyanide (232) with five equivalents of titanium tetrachloride in methylene chloride at -10° gave a moderate yield (49%) of the formamide (231). This compound was obtained in similar yield (41%) by conducting the same reaction under reflux. As previously discussed (see Chapter 2; section 2.2) the production of the formamide (231) and the absence of any cyclisation product suggests that coordination of the isocyan group in (232) with the Lewis acid has taken place, but that the adjacent phenyl ring is not sufficiently nucleophilic to effect ring closure. It was thus
decided (Scheme 63) to investigate the cyclisation of the isocyanide (243), which contains a methoxy group in the correct position to provide the activation necessary for ring closure.

The isocyanide (243) was readily synthesised as outlined in Scheme 63. 3-Methoxyphenylboronic acid (239) was prepared in quantitative yield by the previously described reaction of 3-bromoanisole with n-butyllithium and triisopropylborate, and was then employed in a palladium catalysed boronic acid coupling reaction with 2-bromonitrobenzene (238) to give the biphenyl derivative (240) in excellent yield (92%). The nitro compound (240) was then reduced to the corresponding amine (241) in quantitative yield by catalytic hydrogenation, and this was subsequently converted into the formamide (242) in good yield (70%) by heating under reflux in formic acid. Dehydration of the formamide (242) using the established dehydration protocol gave the desired isocyanide (243) in good yield (82%) as a stable, low melting solid which had analytical and spectroscopic characteristics fully in accord with its assigned structure. The considerably greater stability of the isocyanide (243) compared with the parent biphenyl isocyanide (232) supports the generalisation that solid isocyanides tend to be more stable towards storage than liquid isocyanides.

Cyclisation (Scheme 63) of the isocyanide (243) was successfully effected by reaction with five equivalents of titanium tetrachloride in methylene chloride at -10°C and gave the known 9-methoxyphenanthridine (244), although in poor yield (36%). This compound was later obtained in a substantially improved yield (83%) by conducting the same reaction under reflux. The cyclisation of the isocyanide (243) can take place at either of the two activated positions in the adjacent phenyl ring (para or ortho to the methoxy group), giving rise to the two isomeric products, namely the 9-methoxy (244) and 7-methoxyphenanthridines respectively. The product
obtained was found to be exclusively the 9-methoxy isomer (244), this structure assignment being based on the comparison of its melting point with that reported in the literature and on an examination of its proton n.m.r.
spectrum. This contains a one proton doublet (J = 8.1 Hz) centred at δ8.20, a
double doublet (J = 8.2 and 2.4 Hz) centred at δ7.32, and a meta coupled
doublet (J = 2.3 Hz) centred at δ7.91. This splitting pattern in the substituted
ring is consistent only with the 9-methoxyphenanthridine (244) structure. The
observed regioselectivity of the cyclisation [(243)→(244)] is presumed to arise
from steric factors in the coordinated species undergoing cyclisation. It is
reasonable to assume that such a species will involve coordination of titanium
tetrachloride at both the isocyano group and at the ether oxygen atom. The
steric demands of these extremely bulky groups would then dictate that the
preferred conformation of the coordinated intermediate is that which leads to
the 9-methoxyphenanthridine (244).

The formation of the methoxyphenanthridine (244) demonstrates the
need for electronic activation of the attacking phenyl ring for cyclisation to be
successful. The level of activation necessary for cyclisation to give a six-
membered ring is less than that required for cyclisation to give a seven
membered ring however, as the latter was shown (Chapter 2; Section 2.2) to
require activation by two electron donating groups. The greater reactivity of
the biphenyl system towards ring closure is attributable to the closer proximity
of the isocyano group in (243) to the adjacent phenyl ring and the
conformationally more constrained nature of the biphenyl system as a whole.

Although the successful cyclisation of the isocyanide (243) was
pleasing, the absence of any useful functionality in the product (244) was a
slight drawback. It was therefore decided at this stage to investigate the
synthesis of biphenyl isocyanide dihalides and their potential exploitation for
the synthesis of 6-halogenated phenanthridines.
(i) Cl₂, Cl(CH₂)₂Cl, -10°.
(ii) SO₂Cl₂, CH₂Cl₂, -10°.
(iii) SO₂Cl₂, CH₂Cl₂, -10°.
(iv) SO₂Cl₂, CH₂Cl₂, room temp.
(v) SOCl₂, SO₂Cl₂, room temp. then 30°.
Reaction (Scheme 64) of 1,1'-biphenyl-2-isocyanide (232) with a solution of chlorine in 1,2-dichloroethane gave an oil whose i.r. spectrum showed strong bands at 2120 cm\(^{-1}\) and 1680 cm\(^{-1}\), attributable to the isocyanide (232) and the isocyanide dichloride (245) respectively. Despite the formation of the isocyanide dichloride (245) in this reaction, the inconvenience of the procedure in practice prompted its abandonment. Sulphuryl chloride is a commonly used alternative chlorinating agent which is free of the practical difficulties associated with the use of chlorine gas, and it was therefore decided to investigate its reaction with the isocyanide (232). Accordingly the isocyanide (232) was stirred with one equivalent of sulphuryl chloride in methylene chloride at -10\(^\circ\), and these conditions gave the known isocyanide dichloride (245) cleanly in quantitative yield. The isocyanide dichloride (245) was also obtained in quantitative yield (Scheme 64) by reaction of the formamide (231) with thionyl chloride and sulphuryl chloride, a significant improvement on the yield previously reported (72%) for the preparation of (245) by this method. The classical method for the preparation of isocyanide dichlorides is the chlorination of isothiocyanates, and in order to circumvent the inconvenient use of chlorine gas in this procedure it was decided to attempt this reaction using sulphuryl chloride. Unfortunately, this was unsuccessful (Scheme 64) as the attempted reaction of 1,1'-biphenyl-2-isothiocyanate (246) [which was readily prepared in 75% yield by the reaction of 1,1'-biphenyl-2-amine (230) with thiophosgene] with two equivalents of sulphuryl chloride in methylene chloride at -10\(^\circ\) gave only unchanged starting material (71%), while at room temperature a complex mixture was obtained which yielded no identifiable material. On the basis of these experiments, the reaction of the isocyanide (232) with sulphuryl chloride in methylene chloride at -10\(^\circ\) was chosen as the standard method for the preparation of the isocyanide dichloride (245).
(i) NaCN, 1,2-dimethoxyethane, reflux.
(ii) see Table 7.

Scheme 65
As the isocyanide (232) had previously been shown (Scheme 62) to be unreactive towards cyanogen bromide, the displacement (Scheme 65) of one chlorine atom in the isocyanide dichloride (245) by cyanide ion was seen as an alternative route to the analogous cyanoimidoyl chloride (247). Accordingly, the isocyanide dichloride (245) was heated under reflux in DME with four equivalents of sodium cyanide, but these conditions resulted in a complex mixture from which no identifiable product could be isolated.

Further to the failure of the transformation [(245)→(247)] it was next decided (Scheme 65) to study the direct cyclisation of the isocyanide dichloride (245) promoted by various Lewis acids. The results of these investigations are collected in Table 7 (over page). The reaction of the isocyanide dichloride (245) with silver tetrafluoroborate in 1,2-dichloroethane at -10° was first investigated (Table 7, entry 1). These conditions gave the known139 6-chlorophenanthridine (248), although in extremely poor yield, with the remainder of the material forming a complex mixture from which no identifiable product could be obtained. The reaction (Table 7, entry 2) of the isocyanide dichloride (245) with one equivalent of titanium tetrachloride in methylene chloride at -10° disappointingly gave a quantitative recovery of the unchanged starting material, however (Table 7, entry 3) repetition of this reaction under reflux gave the desired 6-chlorophenanthridine (248) in high yield. Increasing the reaction time (Table 7, entry 4) unexpectedly caused a slight reduction in the yield of the cyclised product (248) and a corresponding increase in the amount of unchanged isocyanide dichloride (245). On the other hand (Table 7, entry 5) increasing the excess of titanium tetrachloride to two equivalents gave the chlorophenanthridine (248) in slightly improved yield compared to that obtained using one equivalent under otherwise identical conditions (Table 7, entry 3). With the exception of entries 6 and 7 all the reactions in Table 7 were carried out by treating the isocyanide (232) with
### Table 7: Lewis Acid Promoted Cyclisation Reactions of 1,1′ Biphenyl-2-isocyanide Dichloride (245)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>(245):Lewis Acid Ratio</th>
<th>Solvent</th>
<th>Reaction Temp.(°C)</th>
<th>Time (h)</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(245) (246)</td>
</tr>
<tr>
<td>1</td>
<td>AgBF₄</td>
<td>1:1</td>
<td>Cl(CH₂)₂Cl</td>
<td>-10</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>TiCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>TiCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>TiCl₄</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>6 c</td>
<td>TiCl₄</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>3</td>
<td>86</td>
</tr>
<tr>
<td>7 c</td>
<td>TiCl₄</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>AlCl₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>2</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>AlCl₃</td>
<td>1:5</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>2</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>AlCl₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>room temp.</td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>BCl₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>~10</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

a, complex mixture obtained; b, t.l.c. indicated that the remaining material contained 6-chlorophenanthridine (248) and unchanged starting material (245); c, isocyanide dichloride (245) was prepared from formamide (231) using SOCl₂ and SO₂Cl₂.
sulphuryl chloride then adding the Lewis acid to this mixture. In the case of entries 6 and 7 the isocyanide dichloride (245) was prepared directly from the formamide (231) by reaction with thionyl chloride and sulphuryl chloride. This procedure necessitates isolation of the isocyanide dichloride (245) prior to its reaction with the Lewis acid, and it was feared that exposure of such a reactive compound to the atmosphere may prove detrimental to the final yield. These fears were proved to be unfounded (Table 7, entry 6) by heating the so derived isocyanide dichloride (245) under reflux in methylene chloride with two equivalents of titanium tetrachloride, as these conditions gave the chlorophenanthridine (248) in excellent yield. This yield was further increased (Table 7, entry 7) by increasing the reaction time from 3 to 4h. The application of these optimum conditions (Table 7, entry 7) results in 6-chlorophenanthridine (248) being obtained in excellent overall yield (92%) from 1,1'-biphenyl-2-amine (230).

Although the use of titanium tetrachloride as the Lewis acid gives excellent yields of the chlorophenanthridine (248), it was anticipated that a more powerful Lewis acid would allow the reaction to proceed at lower temperatures. It was therefore decided to investigate the aluminium trichloride promoted cyclisation reactions of the isocyanide dichloride (245). Reaction (Table 7, entry 8) of the isocyanide dichloride (245) with two equivalents of aluminium trichloride in methylene chloride at -10° gave the desired chlorophenanthridine (248) in moderate yield along with a comparable amount of the unchanged isocyanide dichloride (245). The initial results obtained using titanium tetrachloride suggested that two equivalents of the Lewis acid were better than one, and it was therefore anticipated that increasing the excess further might enhance the efficiency of the cyclisation. Accordingly (Table 7, entry 9) the isocyanide dichloride (245) was stirred at -10° with five equivalents of aluminium trichloride, but these conditions offered
no improvement on the yield of the chlorophenanthridine (248) obtained using two equivalents under similar conditions (Table 7, entry 8). The chlorophenanthridine (248) was eventually obtained in high yield (Table 7, entry 10) by reaction of the isocyanide dichloride (245) with two equivalents of aluminium trichloride in methylene chloride at room temperature. This yield is comparable to that obtained using a similar excess of titanium tetrachloride under reflux (see Table 7, entry 6), and clearly demonstrates the relationship between the strength of the Lewis acid and the efficiency of the cyclisation.

It was next decided to attempt cyclisation of the isocyanide dichloride (245) by its reaction (Table 7, entry 11) with two equivalents of boron trichloride in methylene chloride at -10°C, but no cyclisation was observed under these conditions and the starting material (245) was recovered unchanged in quantitative yield. This result is somewhat surprising as boron trichloride has been ranked as one of the strongest of all Lewis acids by i.r. measurements, n.m.r. studies, and molecular orbital calculations, and therefore should promote the cyclisation [(245)→(248)] more effectively than aluminium trichloride. However, the aforementioned Lewis acidity studies have all employed carbonyl compounds as substrates, and it is known that the relative strength of a Lewis acid is highly dependent on the reaction conditions, the solvent, and most importantly on the nature of the Lewis base with which it is interacting. This delicate interplay of variables makes it impossible to compile a universally applicable order of Lewis acid strengths, and accordingly it has been shown that for the benzylation of toluene boron trichloride was 167 times less active than aluminium trichloride. The results obtained in the present study (see Table 7) indicate that for the cyclisation of the isocyanide dichloride (245) aluminium trichloride is a more powerful Lewis acid than titanium tetrachloride which in turn is more powerful than boron trichloride.
(i) Br₂, CH₂Cl₂, -10°.
(ii) Br₂, CH₂Cl₂, room temp.
(iii) piperidine, Et₂O, 0°.
(iv) NaCN, 1,2-dimethoxyethane, reflux.

Scheme 64
Having successfully demonstrated the cyclisation of the isocyanide dichloride (245), attention was next turned (Scheme 66) to the preparation and reactivity of the previously unreported 1,1'-biphenyl-2-isocyanide dibromide (249). This compound, owing to its greater electrophilicity, was expected to undergo cyclisation and displacement reactions more readily than the corresponding isocyanide dichloride (245). Reaction (Scheme 66) of the isocyanide (232) with one equivalent of bromine in methylene chloride at -10° gave the desired isocyanide dibromide (249) in quantitative yield as a low melting, unstable solid. The reaction of isocyanides with bromine is currently the only general method available for the synthesis of isocyanide dibromides, and it was therefore decided to investigate the preparation of the isocyanide dibromide (249) from the corresponding isothiocyanate (246). Unfortunately however, the attempted reactions of the isothiocyanate (246) with two equivalents of bromine in methylene chloride at -10° or at room temperature gave only unchanged starting material (246) in 83% and 100% yields respectively.

The ability of isocyanide dihalides to participate in monosubstitution reactions with various nucleophiles to give the appropriately substituted imidoyl halides is well known. It was therefore decided to investigate the preparation of such intermediates from the isocyanide dibromide (249) with a view to the synthesis of substituted phenanthridines via their cyclisation reactions. Reaction (Scheme 66) of the isocyanide dibromide (249) with piperidine in ether at 0° failed to yield the desired imidoyl bromide (250), but its formation during the reaction was confirmed by the isolation of the urea derivative (251) (61%) as the only product. This product is derived from the initially formed imidoyl bromide (250) by hydrolysis during the work-up. Likewise the reaction of the isocyanide dibromide (249) with one equivalent of sodium cyanide under reflux in DME failed to give the desired cyanoimidoyl
(i) NaN₃, 1,2-dimethoxyethane, room temp.
(ii) AlBr₃, CH₂Cl₂, reflux.
(iii) AlBr₃, Cl(CH₂)₂Cl, reflux.
(iv) AgBF₄, Cl(CH₂)₂Cl, room temp. or reflux.
(v) AgOAc, Cl(CH₂)₂Cl, reflux.
(vi) NaN₃, DMF, 100°.
(vii) Ph₃P, 1,2-dimethoxyethane, room temp. then 50°.
(viii) HCl, H₂O, reflux.
(ix) NaN₃, conc. H₂SO₄, H₂O, AcOH, 0°.

Scheme 67
bromide (235). The only isolated products from this reaction were the unchanged isocyanide dibromide (249) (56%) and the isocyanide (232) (54%). Repetition of this reaction using four equivalents of sodium cyanide was similarly unsuccessful, and surprisingly gave the isocyanide (232) in quantitative yield. This unexpected result can be explained by assuming that the cyanoimidoyl bromide (235) is being formed in the reaction, but its instability towards loss of cyanogen bromide via an α-elimination process generates the isocyanide (232). This proposal is in keeping with a previous attempt (see Scheme 62) to prepare the cyanoimidoyl bromide (235) by reaction of the isocyanide (232) with cyanogen bromide, which returned the starting material (232) unchanged in quantitative yield.

In contrast to the failure of the isocyanide dibromide (249) to furnish the desired substitution products from its reactions with piperidine or cyanide ion, the reaction (Scheme 67) with one equivalent of sodium azide in DME at room temperature gave the bromotetrazole (252) in excellent yield (96%). This compound, which was isolated as a stable, crystalline solid, had analytical and spectroscopic characteristics which were fully in accord with its assigned structure. In addition (Figure 3 and Tables 8 and 9) an X-ray crystal structure was obtained. The X-ray data (Tables 8 and 9) interestingly shows that two distinct molecules are present in the solid state. This phenomenon may be attributable to the steric bulk of the bromotetrazole moiety which restricts rotation about the C1'-C1" bond, and consequently two atropisomers can co-exist.

The chemistry of halotetrazoles has not been widely investigated, and so having successfully obtained the bromotetrazole (252) it was considered of interest to investigate its cyclisation reactions. Ring closure (Scheme 67) to
Figure 3
X-Ray Diffraction Data for 1-(1,1'-Biphenyl-2-yl)-5-bromotetrazole (252)

**Table 2: Bond Lengths (Angstroms) with Standard Deviations**

<table>
<thead>
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<th>Bond</th>
<th>Length (Å)</th>
<th>Standard Deviation (Å)</th>
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<tr>
<td>N(1)-N(2)</td>
<td>1.356(7)</td>
<td>1.329(5)</td>
</tr>
<tr>
<td>N(1)-C(2')</td>
<td>1.445(5)</td>
<td>1.295(6)</td>
</tr>
<tr>
<td>N(3)-N(4)</td>
<td>1.367(7)</td>
<td>1.297(7)</td>
</tr>
<tr>
<td>N(4)-N(5)</td>
<td>1.383(5)</td>
<td>1.395(5)</td>
</tr>
<tr>
<td>C(5)-Br(5)</td>
<td>1.385(6)</td>
<td>1.388(7)</td>
</tr>
<tr>
<td>C(1')-C(1'')</td>
<td>1.378(7)</td>
<td>1.370(7)</td>
</tr>
<tr>
<td>N(1A)-N(1A')</td>
<td>1.380(6)</td>
<td>1.377(7)</td>
</tr>
<tr>
<td>N(2A)-N(2A')</td>
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<td>N(3A)-N(3A')</td>
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<td>N(1A)-C(2')</td>
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<td>N(4A)-C(5A)</td>
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<td>1.366(8)</td>
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<tr>
<td>C(1')-C(1'')</td>
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<td>1.377(7)</td>
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<tr>
<td>C(2')-C(2'')</td>
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<td>1.366(8)</td>
</tr>
<tr>
<td>C(4')-C(5')</td>
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<td>N(1A)-N(2A)</td>
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<td>1.297(7)</td>
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<tr>
<td>N(4A)-N(5A)</td>
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<tr>
<td>C(5A)-Br(5A)</td>
<td>1.385(6)</td>
<td>1.388(7)</td>
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<td>C(1')-C(1'')</td>
<td>1.378(7)</td>
<td>1.370(7)</td>
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<tr>
<td>C(2')-C(2'')</td>
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<td>1.377(7)</td>
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<tr>
<td>C(4')-C(5')</td>
<td>1.380(6)</td>
<td>1.377(7)</td>
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**Table 2: Bond Angles (Degrees) with Standard Deviations**

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<th>Bond</th>
<th>Angle (°)</th>
<th>Standard Deviation (°)</th>
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<td>N(1)-N(1A)-C(2')</td>
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<td>N(2A)-N(2A')-C(3')</td>
<td>113.1(4)</td>
<td>112.8(3)</td>
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<td>N(2A)-N(3A)-N(5A)</td>
<td>110.6(5)</td>
<td>110.5(4)</td>
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<tr>
<td>N(1A)-N(2A)-N(3A)</td>
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<td>110.5(4)</td>
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<tr>
<td>N(1A)-N(3A)-N(5A)</td>
<td>119.2(3)</td>
<td>117.2(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(1'')</td>
<td>123.5(4)</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(3')</td>
<td>133.3(3)</td>
<td>117.2(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(5A)</td>
<td>122.2(4)</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(3A)</td>
<td>112.0(3)</td>
<td>117.2(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(5A')</td>
<td>107.9(4)</td>
<td>120.5(3)</td>
</tr>
<tr>
<td>N(1A)-C(2')-C(3A')</td>
<td>113.1(4)</td>
<td>112.8(3)</td>
</tr>
</tbody>
</table>

![Image of Table 2: Bond Angles (Degrees) with Standard Deviations]
give the tetrazolophenanthridine (253) was first attempted by heating the bromotetrazole (252) under reflux in methylene chloride with two equivalents of aluminium tribromide, however these conditions resulted in a quantitative recovery of the unchanged starting material. Repetition of this reaction using 1,2-dichloroethane as the solvent also failed to give the cyclic product (253), and the unchanged bromotetrazole (252) was isolated in 30% yield as the only product. Evidently the polarisation of the C-Br bond in the bromotetrazole (252) provided by aluminium tribromide is insufficient to induce cyclisation. It was therefore decided to attempt cyclisation using silver ion, which should encourage the formation of a cationic intermediate. Reaction of the bromotetrazole (252) with silver tetrafluoroborate in 1,2-dichloroethane at room temperature disappointingly gave a quantitative recovery of the unchanged starting material, however conducting the reaction under reflux gave the desired tetrazolophenanthridine (253) in moderate yield (52%). Silver acetate proved to be a less effective agent than silver tetrafluoroborate, giving the cyclised product (253) in poor yield (18%) under identical conditions (i.e. heating under reflux in 1,2-dichloroethane) along with a 57% recovery of the unchanged starting material (252).

It is logical to assume that the silver ion promoted cyclisation of the bromotetrazole (252) to give the tetrazolophenanthridine (253) is proceeding through a cationic intermediate. It was anticipated that generation of such an intermediate by an alternative method would also lead to the cyclised product (253), and it was therefore decided to investigate (Scheme 67) the diazotisation and cyclisation of the aminotetrazole (256). This compound was readily prepared from the bromotetrazole (252) as outlined in Scheme 67. Reaction of the bromotetrazole (252) with one equivalent of sodium azide in DMF at 100° gave the azidotetrazole (254) in high yield (87%). This was subsequently converted into the phosphineimine (255) in excellent yield
(i) see Table 10.
(ii) KOH, H₂O, EtOH, reflux.
(iii) NaOEt, EtOH, reflux.

Scheme 69
(94%) by reaction with triphenylphosphine in DME at 60°, and thence into the aminotetrazole (256) (70%) by hydrolysis with aqueous hydrochloric acid under reflux. All of the previously undescribed tetrazole derivatives, (254) to (256), had analytical and spectroscopic properties fully in accord with their assigned structures.

It was pleasing to find that diazotisation of the amino group in the tetrazole derivative (256) with sodium nitrite and sulphuric acid in acetic acid at 0° gave the desired tetrazolophenanthridine (253) in moderate yield (55%), accompanied by a 23% recovery of the unchanged starting material. This yield of the cyclised product (253) is comparable to that obtained by reaction of the bromotetrazole with silver tetrafluoroborate, but was achieved under considerably milder conditions.

In view of the successful preparation and cyclisation of the bromotetrazole (252) it was decided to attempt to extend these reactions to the synthesis and cyclisation of the analogous 5-bromo-1,2,3-triazoles. Thus the isocyanide dibromide (249) was stirred at room temperature in methylene chloride with ethyl diazoacetate and N-ethyldiisopropylamine, but these conditions gave only a 99% recovery of the unchanged isocyanide (232). Heating a neat mixture of the isocyanide dibromide (249) and ethyl diazoacetate at 50° offered no improvement, giving only a complex mixture which proved inseparable by chromatography. As a result of these failures, investigations on the preparation of bromotriazoles from the isocyanide dibromide (249) were terminated.

Attention was next turned (Scheme 68) to the Lewis acid promoted cyclisation reactions of 1,1'-biphenyl-2-isocyanide dibromide (249) itself. The results of these studies are shown in Table 10 (over page). Cyclisation was first attempted (Table 10, entry 1) by reaction of the isocyanide dibromide (249) with silver tetrafluoroborate in 1,2-dichloroethane at -10°, and these
Table 10: Lewis Acid Promoted Transformations of 1,1'-Biphenyl-2-Isocyanide Dibromide (248)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>(249):Lewis Acid Ratio</th>
<th>Solvent</th>
<th>Reaction Temp.(°C)</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(257) (249) (245)</td>
</tr>
<tr>
<td>1</td>
<td>AgBF₄</td>
<td>1:1</td>
<td>Cl(CH₂)₂Cl</td>
<td>-10</td>
<td>60 27 0</td>
</tr>
<tr>
<td>2</td>
<td>TiCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>a 0 0</td>
</tr>
<tr>
<td>3</td>
<td>TiCl₄</td>
<td>1:5</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>a 0 0</td>
</tr>
<tr>
<td>4</td>
<td>AlCl₃</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>a 0 0</td>
</tr>
<tr>
<td>5</td>
<td>SnCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>0 0 100</td>
</tr>
</tbody>
</table>

a, eutectic mixture of 6-chlorophenanthridine (257) and 6-bromophenanthridine (257) obtained; b, 1,1'-biphenyl-2-isocyanide bromochloride (260) obtained (12% yield).
conditions gave a moderate yield of the known\textsuperscript{145} 6-bromophenanthridine (257). This result clearly demonstrates the greater reactivity of the isocyanide dibromide (249) compared to the isocyanide dichloride (245), which gave only a 5% yield of the analogous chlorophenanthridine (248) under identical conditions (see Table 7, entry 1).

Cyclisation was next attempted (Table 10, entry 2) by reaction of the isocyanide dibromide (249) with one equivalent of titanium tetrachloride in methylene chloride at -10°. However, these conditions resulted in halogen exchange between the Lewis acid and the isocyanide dibromide (249), giving a eutectic mixture of the 6-chloro (248) and 6-bromo (257) phenanthridines. In order to try to effect complete halogen exchange (Table 10, entry 3) this reaction was repeated using a five-fold excess of titanium tetrachloride, but again a eutectic mixture of the 6-chloro (248) and 6-bromo (257) phenanthridines was obtained. The E.I. mass spectrum of this mixture, which could not be separated by chromatography or crystallisation, contained characteristic peaks at 259 and 257 (1:1 intensity) corresponding to the bromo product (257), and at 215 and 213 (1:3 intensity) corresponding to the chloro product (248). The combustion analysis of the mixture showed it to be a 2:1 mixture of the bromo (257) and chloro (248) phenanthridines. The eutectic melting temperature was determined by mixing equal portions of (248) and (257) and crystallising the mixture three times, and was found to be 119-120°. This value is intermediate between the melting points of the bromophenanthridine (257) (m.p. 124-125°) and the chlorophenanthridine (248) (m.p. 116-117°). The formulation of this product as a eutectic mixture of the two halophenanthridines (248) and (257) was further confirmed by its reaction with aqueous potassium hydroxide solution under reflux in ethanol to give phenanthridin-6-one\textsuperscript{146} (258), and with sodium ethoxide in refluxing ethanol to give a high yield of 6-ethoxyphenanthridine (259).
A similar halogen exchange reaction was observed (Table 10, entry 4) upon reaction of the isocyanide dibromide (249) with aluminium trichloride in methylene chloride at -10°. This gave a eutectic mixture of the two possible halophenanthridines (248) and (257), although the composition of this mixture is not known as no combustion analysis of the product was obtained. Also obtained from this reaction was a small amount (12%) of the halogen exchange product 1,1'-biphenyl-2-isocyanide bromochloride (260). This compound was isolated as a low melting, unstable solid which proved too unstable for combustion analysis and therefore was characterised by high resolution mass spectrometry.

The reaction (Table 10, entry 5) of the isocyanide dibromide (249) with one equivalent of stannic chloride in methylene chloride at -10° surprisingly gave no cyclised product, and instead caused complete halogen exchange to give a quantitative yield of the isocyanide dichloride (245).

The halogen exchange reactions observed in the present study were not entirely unexpected as such exchange processes have ample precedent in the field of Friedel-Crafts acylation reactions. For example, it is well known\textsuperscript{143,147,148} that halogen scrambling often occurs upon the treatment of an acid halide with a Lewis acid, although the mechanism by which this exchange proceeds is unknown.

Halogen exchange in the isocyanide dibromide (249) was also shown to occur without the aid of a Lewis acid. Thus (Scheme 69) reaction of the
isocyanide dibromide (249) with one equivalent of sulphuryl chloride in methylene chloride at -10° gave a mixture of the isocyanide dichloride (245) and the corresponding bromochloride (260). These two compounds proved to be inseparable by t.l.c. but their presence was confirmed by the E.I. mass spectrum of the mixture. This contained the required molecular ion peaks at 297, 295, and 293, corresponding to the isocyanide bromochloride (260), and at 253, 251, and 249, corresponding to the isocyanide dichloride (245). Unfortunately, the inseparability of the mixture meant that it was impossible to determine the proportions of the two components. Complete halogen exchange was achieved by repetition of the preceding reaction using four equivalents of sulphuryl chloride, which gave the isocyanide dichloride (245) in 96% yield as the only product detectable by mass spectrometry. Reaction of the isocyanide dibromide (249) with four equivalents of benzyltriethylammonium chloride in methylene chloride at -10° also caused halogen exchange, giving a mixture of the isocyanide dichloride (245) and bromochloride (260) as shown by mass spectrometry. An attempt to obtain only the isocyanide bromochloride by using one equivalent of
(i) see Table 11.
(ii) piperidine, MeCN, reflux.
(iii) (PhCH₂NMe₂)⁺OH⁻, dioxane, reflux.
(iv) NaOEt, EtOH, reflux.
(v) NaCN, DMF, 100°.
(vi) NaN₃, DMF, 100°.

Scheme 70
benzyltriethylammonium chloride was unsuccessful, and a mixture of the isocyanide dichloride (245), dibromide (249), and bromochloride (260) was obtained.

It is logical to assume that this halogen exchange is proceeding by nucleophilic substitution of bromine by chlorine. The reverse process would therefore be expected to be less favourable due to the inferior leaving group ability of chlorine. This was confirmed by the reaction (Scheme 69) of the isocyanide dichloride (245) with four equivalents of bromine in methylene chloride at -10°, which gave a mixture of the isocyanide dichloride (245) and the corresponding bromochloride (260). Similarly unsuccessful was the reaction of the isocyanide dichloride (245) with four equivalents of tetrabutylammonium bromide in methylene chloride at -10°, which returned the starting material (245) unchanged in 96% yield. In both cases the E.I. mass spectrum of the product mixture showed no evidence for the presence of the isocyanide dibromide (249).

The results shown in Table 10 indicate that cyclisation reactions involving an isocyanide dihalide-Lewis acid combination in which the halogens are mixed is incompatible with the isolation of a single, pure cyclised product. In view of this (Scheme 70) the cyclisation reactions of the isocyanide dibromide (249) promoted by bromine-based Lewis acids were next investigated. The results of this study are collected in Table 11 (on next page).
Cyclisation was first attempted (Table 11, entry 1) by reaction of the isocyanide dibromide (249) with one equivalent of titanium tetrabromide at -10°, but these conditions resulted in a high recovery of the unchanged dibromide (249). Repetition of this reaction under reflux (Table 11, entry 2) gave a similar result, with no evidence for the formation of the cyclised product (257). In contrast (Table 11, entry 3), the desired bromophenanthridine (257) was obtained in almost quantitative yield upon prolonged heating (24h) of the isocyanide dibromide (249) under reflux in methylene chloride with one equivalent of titanium tetrabromide. An attempt (Table 11, entry 4) to reduce this reaction time by increasing the excess of titanium tetrabromide to two equivalents was unsuccessful, giving a poor yield of the bromophenanthridine (257) along with a good recovery of the unchanged isocyanide dibromide (249). This result indicates that it is the reaction time and temperature which determines the efficiency of this
reaction, and not the Lewis acid excess. Despite the greater reactivity of the isocyanide dibromide group, it is evident that the titanium tetrabromide promoted cyclisation of the isocyanide dibromide (249) is less efficient than the titanium tetrachloride promoted cyclisation of the corresponding dichloride (245) [compare (Table 11, entry 2) and (Table 7, entry 3)]. This observation is readily explained by the fact that titanium tetrachloride is a stronger Lewis acid than titanium tetrabromide, as steric effects in the latter Lewis acid inhibit coordination.\textsuperscript{143}

It was previously shown (see Table 7) that aluminium trichloride is a more effective Lewis acid than titanium tetrachloride for the cyclisation of the isocyanide dichloride (245). It was therefore anticipated that aluminium tribromide would show a similar increase in activity over titanium tetrabromide in the cyclisation of the isocyanide dibromide (249). This is indeed the case as the reaction (Table 11, entry 5) of the isocyanide dibromide (249) with two equivalents of aluminium tribromide in methylene chloride at $-10^\circ$ gave the bromophenanthrine (257) in excellent yield. This reaction is more efficient than the corresponding aluminium trichloride promoted cyclisation of the isocyanide dichloride (245) because, in contrast to the titanium halides, aluminium tribromide is a stronger Lewis acid than aluminium trichloride.\textsuperscript{140,142} This is due to the greater tendency of the chlorine atoms to back-donate to the metal, thereby reducing its electron deficiency.

Boron tribromide is reportedly\textsuperscript{140-142} an extremely strong Lewis acid and it was therefore decided to investigate its applicability to the present cyclisation reaction. Thus (Table 11, entry 6) the isocyanide dibromide (249) was stirred with two equivalents of boron tribromide in methylene chloride at $-10^\circ$, but these conditions surprisingly gave an almost quantitative recovery of the unchanged starting material (249). Likewise (Table 11, entry 7) the use of boron trifluoride under identical conditions gave unchanged isocyanide
dibromide (249) as the only isolated product. It is therefore clear from the results shown in Tables 7 and 11 that the optimum conditions for the cyclisation of biphenyl isocyanide dihalides to phenanthridines combine the more reactive dihalide [the dibromide (249)] with the most powerful Lewis acid (aluminium tribromide).

It is reasonable to assume that the mechanism of this cyclisation reaction is analogous to that of the Friedel-Crafts acylation of aromatic rings with acid halides and Lewis acids. It is likely that this involves initial coordination of the Lewis acid with the nitrogen atom lone pair of the isocyanide dihalide group, although the changes which occur in the molecule subsequent to such coordination are unknown. It has been said\textsuperscript{149} that "the mechanisms of Friedel-Crafts reactions are certainly not well understood and one of the factors of uncertainty is about the nature of the actual electrophilic species". This statement is equally applicable to the Lewis acid promoted cyclisation of isocyanide dihalides. The role of the Lewis acid is to induce sufficient polarisation in the isocyanide dihalide group to render it a more active electrophilic substituting agent, thus lowering the activation energy for cyclisation.

\textbf{Scheme 71}
This polarisation (Scheme 71) may take the form of a relatively weak donor-acceptor complex (263), in which the net effect is a weakening of the carbon-halogen bond. At the other extreme, coordination may lead to a completely ionised species (264) in which the nitrilium cation acts as the electrophilic agent. In the field of Freidel-Crafts acylations with acid chlorides there is ample evidence\textsuperscript{150,151} for the existence in the acylating medium of donor-acceptor complexes and acylium ions, and for the co-existence\textsuperscript{152-154} of both species in a rapidly mobile equilibrium.

The presence of the acylium species is most commonly inferred from its characteristic i.r. absorption at 2200-2300 cm\textsuperscript{-1}, due to a contribution from a carbon-oxygen triple bonded resonance form. On the other hand a donor-acceptor complex is identified by a lowering of the i.r. stretching frequency of the acid chloride carbonyl group by 100-200 cm\textsuperscript{-1}. This is due to electron donation from the carbonyl oxygen atom to the Lewis acid and consequent reduction of the C-O bond order. It was therefore decided to investigate the nature of the intermediate complex in the isocyanide dihalide cyclisation by an i.r. study of the reaction. Thus a solution of the isocyanide dichloride (245) in methylene chloride was treated at room temperature with one equivalent of aluminium trichloride, and the i.r. spectrum of the mixture was immediately recorded. This showed that the C-N double bond absorption, which appears at 1647 cm\textsuperscript{-1} in the free isocyanide dichloride, was still present but was accompanied by new bands in the 1600-1700 cm\textsuperscript{-1} region and a strong band at 1714 cm\textsuperscript{-1}. The band at 1714 cm\textsuperscript{-1} disappeared after 1 h but the remainder of the spectrum was unchanged throughout the course of the reaction (4 h). After the usual work-up this reaction gave a 70% yield of the chlorophenanthridine (248) along with a small amount (20%) of unchanged isocyanide dichloride (245). This experiment offers conflicting evidence in that neither the absorptions at 2000-2300 cm\textsuperscript{-1}, which would indicate a
nitrilium cation, nor a reduction in the C-N double bond frequency, which would indicate a donor-acceptor species, were observed. It is possible that the absorption at 1714 cm\(^{-1}\) corresponds to a species in which the Lewis acid is coordinated to one of the chlorine atoms, which would increase the C-N bond order and its stretching frequency. Such a mode of coordination has been proposed\(^{155}\) for the acetyl chloride-titanium tetrachloride system. It is therefore impossible to derive any definite information from this study concerning the nature of the coordinated intermediates in the cyclisation [(245)→(248)].

Antimony pentahalides are known for their ability to form relatively stable coordination compounds with a variety of donor molecules. It was therefore decided to attempt to isolate the complex involved in the present cyclisation reaction by reaction of the isocyanide dichloride (245) with antimony pentachloride followed by a non-hydrolytic work-up. Reaction of (245) with one equivalent of antimony pentachloride in methylene chloride at -10\(^\circ\) gave a yellow solid which was relatively stable to crystallisation and long term storage. On treatment with aqueous sodium hydroxide solution, this solid gave a quantitative yield of the chlorophenanthridine (248). This confirms that this solid is a complex of the cyclised product (248) and not of the isocyanide dichloride (245). Unfortunately, the structure of this complex could not be unambiguously established as it proved too insoluble to obtain an n.m.r. spectrum and its mass spectrum contained no assignable peaks. The structure of this compound was tentatively assigned as that of a 6-chlorophenanthridine-antimony pentachloride complex (265), although the combustion analysis failed to distinguish between this possibility and an N-protonated chlorophenanthridine with antimony hexachloride as the counterion.
In summary, the preceding reactions have failed to provide any definite mechanistic information on the Lewis acid promoted cyclisation of isocyanide dihalides. The mode of initial coordination, the nature and role of any intermediate complexes, and the nature of the actual electrophilic species therefore remain unknown. Further information could only be obtained by extensive studies on the reaction mechanism, which were out with the scope of the present investigation.

Having obtained the bromophenanthridine (257) it was next decided to investigate its nucleophilic displacement reactions, as shown in Scheme 70. Heating the bromophenanthridine (257) under reflux in acetonitrile with two equivalents of piperidine gave the piperidinophenanthridine derivative (261) in high yield (86%). An attempt to prepare this compound by reaction of the isocyanide dibromide (249) with piperidine and cyclisation of the resulting amidoyl bromide with aluminium tribromide gave the desired product in only 6% yield. Reaction of the bromophenanthridine (257) with aqueous benzyltrimethylammonium hydroxide solution under reflux in dioxane gave phenanthridin-6-one$^{146}$ (258) in almost quantitative yield (97%). The reactivity of the bromine atom in the bromophenanthridine (257) was further demonstrated by its reaction with sodium ethoxide under reflux in ethanol to give a good yield (76%) of 6-ethoxyphenanthridine (259). Preparation of the known$^{156}$ 6-cyanophenanthridine (262) proved to be more difficult than expected. Reaction of the bromophenanthridine (257) with one equivalent of sodium cyanide in DMF at 100° for 1h gave the desired product in very poor yield (20%), along with a good recovery (65%) of the unchanged starting material. The yield of the cyanophenanthridine (262) was only marginally increased (25%) by increasing the reaction time to 22h. Finally, the tetrazolophenanthridine$^{144}$ (253) was obtained in excellent yield (91%) by the reaction of the bromophenanthridine (257) with sodium azide in DMF at 100°.
(i) 98-100% HCO\(_2\)H, reflux.
(ii) Ph\(_3\)P, CCl\(_4\), Et\(_3\)N, Cl(CH\(_2\))\(_2\)Cl, 60°.
(iii) SO\(_2\)Cl\(_2\), CH\(_2\)Cl\(_2\), -10°.
(iv) Br\(_2\), CH\(_2\)Cl\(_2\), -10°.
(v) see Table 12.

Scheme 72
The substituted phenanthridine derivatives (253), (259), and (261) had analytical and spectroscopic characteristics fully in accord with their assigned structures. The low availability of the cyanophenanthridine (262) meant that a combustion analysis could not be obtained and this compound was characterised by comparison of its melting point with the literature value, along with spectroscopic data.

3.3 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF NAPHTHALENE-1-ISOCYANIDE DIHALIDES

The cyclisation of 1-substituted naphthalene derivatives at the peri position to give 1,8 ring-fused naphthalenes is well known.\textsuperscript{157,158} This type of process has been used to prepare a variety of five-, six-, seven-, and eight-membered ring-fused systems of which the six-membered type is by far the most common. The formation of a five-membered carbocyclic ring across the peri positions of naphthalene is demonstrated\textsuperscript{159} by the preparation of acenaphthenone by the polyphosphoric acid catalysed cyclisation of naphthalene-1-acetic acid or by ring closure of the corresponding acid chloride using aluminium trichloride. The synthesis of naphthalene derivatives with peri-fused five-membered heterocyclic rings is somewhat less common, but is illustrated\textsuperscript{160} by the aluminium trichloride promoted cyclisation of naphthalene-1-isothiocyanate to give benz[c,d]indol-2(1H)-thione. In view of these transformations which demonstrate the feasibility of electrophilic ring closure to give five-membered peri-fused heterocyclic naphthalene derivatives, it was decided to investigate (Scheme 72) the preparation of benz[c,d]indole derivatives (270) by the Lewis acid promoted cyclisation of naphthalene-1-isocyanide dihalides (269). It was anticipated that the cyclic products (270) would be synthetically useful as the ring strain present in such
Table 12: Attempted Lewis Acid Promoted Cyclisation Reactions of Naphthalene-1-isocyanide Dihalides (269 a-c)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>X</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Reaction Temp.(°C)</th>
<th>Time (h)</th>
<th>Products(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Cl</td>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>room temp.</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Cl</td>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Cl</td>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>18</td>
<td>- a</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Cl</td>
<td>SbCl₅</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>0.5</td>
<td>- a</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Br</td>
<td>AlBr₃</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Br</td>
<td>AlBr₃</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>- a</td>
</tr>
</tbody>
</table>

a, complex mixture obtained.
structures would enhance the reactivity of the halogen atom towards nucleophilic displacement.

Preparation (Scheme 72) of the known\textsuperscript{161} formamidonaphthalene (267a) was accomplished in excellent yield (92%) by heating commercially available 1-aminonaphthalene (266a) under reflux in formic acid. The formamide (267a) was then converted into the isocyanide\textsuperscript{1} (268a) in 79% yield, after distillation, by dehydration with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. The isocyanide dichloride (269a) was then prepared in quantitative yield by chlorination of the isocyanide (268a) with sulphuryl chloride at -10°, and was characterised by high resolution mass spectrometry. The excellent yield of the isocyanide dichloride (269a) obtained by this method is to be contrasted with the poor yield (20%) reported\textsuperscript{7} by Kühle et al for the preparation of this compound by reaction of the formamide (267a) with thionyl chloride and sulphuryl chloride.

Cyclisation of the isocyanide dichloride (269a) was first attempted (Table 12, entry 1) by reaction with two equivalents of aluminium trichloride in methylene chloride at room temperature. Disappointingly however, these conditions resulted only in a near quantitative recovery of the unchanged isocyanide dichloride (269a). Repetition of this reaction in refluxing methylene chloride (Table 12, entry 2) gave a similar result, while extension of the reaction time (Table 12, entry 3) gave a complex product mixture which yielded no characterisable material. In an effort to elucidate the reasons for these disappointing failures an i.r. study of the reaction of the isocyanide dichloride (269a) with aluminium trichloride at room temperature was undertaken. It was hoped that changes in the absorption frequency of the C-N double bond of the dichloride (269a) in the presence of aluminium trichloride would provide some information regarding the mode of complexation with the Lewis acid. On addition of one equivalent of aluminium
trichloride to a methylene chloride solution of the isocyanide dichloride (269a) the i.r. absorption of the C-N double bond, which appears at 1651 cm\(^{-1}\) in the free isocyanide dichloride (269a), had not shifted from this frequency and remained unchanged, as did the rest of the spectrum. When a second equivalent of aluminium trichloride was added, two new bands at 1715 cm\(^{-1}\) and 1674 cm\(^{-1}\) appeared and the spectrum as a whole changed considerably. Over the next 2h the peaks at 1715 cm\(^{-1}\) and 1674 cm\(^{-1}\) disappeared leaving only one strong absorption at 1644 cm\(^{-1}\), and working up the mixture afforded a 100% recovery of the unchanged isocyanide dichloride (269a). As already discussed, the interpretation of the results of such an i.r. study with any confidence is extremely difficult in the absence of more detailed information. However, it is clear that complexation of aluminium trichloride with the isocyanide dichloride (269a) does not occur until a second equivalent of the Lewis acid has been added. The nature of this complexation is unknown but the absorption at 1715 cm\(^{-1}\) may be due to complexation to one of the chlorine atoms, in a similar fashion to that discussed previously (Section 3.2) in relation to the biphenyl isocyanide dichloride (245). The strong absorption at 1644 cm\(^{-1}\) may be due to a weak interaction of the Lewis acid with the nitrogen atom of the isocyanide dihalide group. At no time during the reaction was there any evidence for the presence of any ionised species.

In view of the fact that complexation of some kind does take place but cyclisation does not, it was decided to attempt to isolate a complex of the isocyanide dichloride (269a) with antimony pentachloride. It was hoped that such a complex would prove characterisable and so provide an insight into the mode of reaction of the isocyanide dichloride (269a) with Lewis acids. Unfortunately however (Table 12, entry 4), the reaction of (269a) with one equivalent of antimony pentachloride in methylene chloride at -10° followed by a non-hydrolytic work-up gave an unstable foam which could not be
identified. After treatment with aqueous sodium bicarbonate solution followed by flash-chromatography this foam afforded the unchanged isocyanide dichloride (269a) in poor yield (16%) as the only identifiable product.

In view of the lack of reaction with the isocyanide dichloride (269a) it was next decided to investigate the Lewis acid promoted cyclisation of the more electrophilic isocyanide dibromide (269b). This compound was prepared (Scheme 72) in quantitative yield by the reaction of the isocyanide (268a) with bromine, and was characterised by high resolution mass spectrometry. Reaction (Table 12, entry 5) of the isocyanide dibromide (269b) with two equivalents of aluminium tribromide in methylene chloride under reflux disappointingly gave the unchanged isocyanide dibromide (269b) in 93% yield as the only identifiable material, with no evidence for the formation of the desired tricyclic product (270b).

The failure of the isocyanide dihalides (269 a and b) to undergo Lewis acid promoted cyclisation at the peri position of the naphthalene ring, even under the most forcing conditions (Table 12, entry 5), is surprising because electrophilic ring closure of this type has been demonstrated\textsuperscript{159} with naphthalene-1-acetic acid and the corresponding acid chloride. An explanation for the failure of these cyclisation reactions may lie in the steric factors at work in the isocyanide dihalides (269a) and (269b). The steric repulsion between a substituent at position 1 of naphthalene and the peri-hydrogen atom at position 8 is well known,\textsuperscript{157} and this interaction can have important effects on the conformation, and hence on the reactivity, of the molecule. For example, a study\textsuperscript{162} of 1-phenynaphthalene has shown that the phenyl and naphthalene rings are non-coplanar due to steric interaction of the phenyl ring with the peri-hydrogen atom. It is probable then that the extremely bulky isocyanide dihalide groups in the compounds (269a) and (269b) are subject to a similar effect which pushes them away from the peri
position and so inhibits cyclisation. This effect will be greatly amplified by coordination of the Lewis acid, which will increase the steric demands of the isocyanide dihalide groups. With the molecule forced into such a conformation cyclisation at the 2-position of the naphthalene ring could potentially take place, but this is not a feasible alternative due to the enormous ring strain which would result in the fused four-membered ring product.

It is known that when two groups are forced into great proximity to each other, reactions can occur which under normal circumstances would not take place. A prime example of this is 1,8-divinylnaphthalene, which has been shown\textsuperscript{163} to undergo intramolecular thermal [2+2] cycloaddition involving the vinyl substituents to give a mixture of naphthobicycloheptene derivatives. Thermal [2+2] cycloaddition reactions of olefins are of course disallowed on orbital symmetry grounds, but the close proximity of the olefinic groups in 1,8-divinylnaphthalene allows the thermal process to occur. It was thus reasoned that by forcing the isocyanide dihalide group close to the peri position cyclisation would be encouraged, and that this effect might be brought about by the placement of a suitable substituent at the 2-position of the naphthalene ring. Therefore (Scheme 72), 2-methylnaphthalene-1-isocyanide dibromide (269c) was chosen as a potentially suitable substrate in this context.

The known amine\textsuperscript{164} (266c), was prepared in quantitative yield by catalytic hydrogenation of commercially available 2-methyl-1-nitronaphthalene, and was converted into the known\textsuperscript{165} formamide (267c) in excellent yield (95%) by reaction with formic acid under reflux. The known\textsuperscript{165} isocyanide (268c) was then prepared in good yield (78%) by dehydration of the formamide (267c) with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. Both the formamide (267c) and the isocyanide (268c) had melting points in good agreement with the literature values and
(i) 98-100% HCO$_2$H, reflux.
(ii) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60°.
(iii) POCl$_3$, i-Pr$_2$NEt, CH$_2$Cl$_2$, room temp.
(iv) Br$_2$, CH$_2$Cl$_2$, -10°.
(v) AlBr$_3$, CH$_2$Cl$_2$, reflux.

Scheme 73
their identities were further confirmed by their analytical and spectroscopic data. Reaction of the isocyanide (268c) with bromine in methylene chloride at -10° gave the isocyanide dibromide (269c) in quantitative yield as an unstable oil which was characterised by high resolution mass spectrometry. Unfortunately however (Table 12, entry 6) reaction of the isocyanide dibromide (269c) with two equivalents of aluminium tribromide under reflux in methylene chloride failed to give the desired bromobenz[c,d]indole derivative (270c), affording instead a moderate recovery of the unchanged starting material (269c) together with a complex mixture which could not be resolved by chromatography. The failure of this reaction suggests that it would be impossible to prepare tricyclic structures such as (270 a-c) by cyclisation of the corresponding isocyanide dihalides. The reason for this may be that the steric demands of the coordinated isocyanide dihalide groups, particularly the dibromides, restrict their approach to the peri position to such an extent that cyclisation is impossible. In addition, the ring strain present in (270 a-c) due to the unsaturation in the five-membered ring may mean that its formation is disfavoured. The possibility exists, however, that 1,8-fused six-, seven-, or eight-membered rings could be prepared by cyclisation of the appropriate naphthylalkyl isocyanide dihalides.

3.4 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF 1,3-DIPHENYL-1H-PYRAZOLE-5-ISOCYANIDE DIBROMIDE

Although a great many aromatic isocyanides have been reported, the literature is almost devoid of references to heteroaromatic isocyanides. Wentrup et al\textsuperscript{66} have reported the preparation of a number of isocyanides of the indole and pyrazole series in extremely high yields (> 90%) by the pyrolysis of appropriately substituted 3-phenyl-4-iminoisoxazol-5-ones.
Despite the high yields obtained, the synthetic utility of this procedure must be called into question due to the high temperatures involved, bearing in mind the susceptibility of isocyanides in general to thermal decomposition and rearrangement. More recently the preparation and chemistry of various 6-isocyno-1,2,3-triazines have been reported by Hashida et al. In view of the scarcity of reports concerning the heteroaromatic isocyanides it was considered of interest to investigate the synthesis and cyclisation reactions of some heteroaromatic isocyanides and isocyanide dihalides.

Initially (Scheme 73) the isocyanopyrazole (273) was selected for study due to its structural similarity to 1,1'-biphenyl-2-isocyanide (232), whose Lewis acid promoted transformations were discussed in Section 3.2. Reaction of the aminopyrazole (271) in refluxing formic acid gave the formamide (272) in high yield (87%). This was subsequently converted into the isocyanide (273) in disappointingly low yield (20%) by dehydration with triphenylphosphine and carbon tetrachloride in the presence of triethylamine, the remainder of the material forming a complex mixture which could not be separated by flash-chromatography or preparative t.l.c. This yield was considerably improved however, to an acceptable 58%, by dehydration of the formamide (272) using phosphoryl chloride in the presence of N-ethyldiisopropylamine.

Reaction of the isocyanide (273) with bromine in methylene chloride at -10° followed by two equivalents of aluminium tribromide in methylene chloride under reflux unfortunately gave only the corresponding isocyanide dibromide (274) in high yield (70%), after chromatography. Due to the instability of the isocyanide dibromide (274) a satisfactory combustion analysis proved unattainable, but its identity was established by its spectroscopic data. The structure of this compound was further confirmed by its alkaline hydrolysis to give a crude product which was shown by t.l.c. and i.r. spectroscopy to be the amine (271). Also obtained, in low yield (5%), from
(i) 98-100% HCO\textsubscript{2}H, reflux.
(ii) Ph\textsubscript{3}P, CCl\textsubscript{4}, Et\textsubscript{3}N, Cl(CH\textsubscript{2})\textsubscript{2}Cl, 60\textdegree.
(iii) POCl\textsubscript{3}, i-Pr\textsubscript{2}NH, CH\textsubscript{2}Cl\textsubscript{2}, 0\textdegree.
(iv) POCl\textsubscript{3}, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, room temp.
(v) (CF\textsubscript{3}SO\textsubscript{2})\textsubscript{2}O, i-Pr\textsubscript{2}NEt, CH\textsubscript{2}Cl\textsubscript{2}, -78\textdegree.
(vi) TiCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, reflux.

Scheme 74
the aluminium dibromide reaction was a yellow solid which was in insufficient quantity for purification beyond flash-chromatography, and whose structure was tentatively assigned as that of the cyclised product (275). This structure assignment is based on the compound's proton n.m.r. spectrum and its E.I. mass spectrum, which showed the expected molecular ion peaks at 325 and 323 in a 1:1 ratio.

The poor yield of the cyclised product (275) is surprising in the light of the high yields achieved with the structurally related biphenyl isocyanide dibromide (249) (see Section 3.2). It is possible that this is due to preferential interaction of the pyrazole nitrogen atoms with the Lewis acid, although the nature of this interaction is not known. Although the low yield and incomplete characterisation of the cyclic product (275) was disappointing, time limitations and the low availability of starting material meant that this reaction was not investigated further.

3.5 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF 1-BENZYL-4-PHENYL-1H-1,2,3-TRIAZOLE-5-ISOCYANIDE AND 1-BENZYL-4-PHENYL-1H-1,2,3-TRIAZOLE-5-ISOCYANIDE DIHALIDES

As already discussed in Section 3.4, heteroaromatic isocyanides have hitherto been an extremely understudied class of compounds. It was therefore decided to attempt to extend the investigations of Section 3.4 to 1,2,3-triazole isocyanides. It was anticipated (Scheme 74) that cyclisation of the isocyanide (278) might take place to give the bridgehead fused triazole (279) which would then serve as a precursor to functionalised 2,4-benzodiazepines by the well known\textsuperscript{168,169} acid promoted ring scission of such bridgehead fused heterocycles.
Preparation (Scheme 74) of the formamidotriazole (277) was easily accomplished in almost quantitative yield (98%) by heating the readily accessible amine (276) under reflux in formic acid. Unfortunately, subsequent conversion of the formamide (277) into the isocyanide (278) proved to be more difficult than expected. Dehydration of (277) with triphenylphosphine and carbon tetrachloride in the presence of triethylamine gave the desired isocyanide (278) in only 49% yield, while the use of the phosphoryl chloride-diisopropylamine combination surprisingly caused a drop in yield (30%). A modification of this procedure, involving replacement of diisopropylamine with the more basic \(N\)-ethyldiisopropylamine, increased the yield only slightly to a still unsatisfactory 46%. Trifluoromethanesulphonic anhydride in the presence of \(N\)-ethyldiisopropylamine has been reported to be an excellent reagent system for the dehydration of formamides to isocyanides, but application of this reagent combination to the formamide (277) gave only a complex mixture with no evidence for the formation of the isocyanide (278). The low yield of the isocyanotriazole (278), and (see Section 3.4) of the isocyanopyrazole (273), demonstrates that the presence of a heterocyclic ring appears to exert an inhibiting effect on the conversion of formamides to isocyanides. This effect was also apparent in Hashida's unsuccessful attempted preparation of isocyanotriazenes by dehydration of formamidotriazenes with the normally reliable phosgene-triethylamine reagent system. Although the origin of this inhibiting effect is not clear, the consequent problematic preparation of heteroaromatic isocyanides may in part account for the scarcity of literature reports concerning these compounds.

With the isocyanide (278) in hand, its cyclisation was attempted by reaction with five equivalents of titanium tetrachloride under reflux in methylene chloride. Unfortunately, these conditions failed to give the desired
(i) SO$_2$Cl$_2$, CH$_2$Cl$_2$, -10°.
(ii) Br$_2$, CH$_2$Cl$_2$, -10°.
(iii) see Table 13.
(iv) (PhCH$_2$NMe$_3$)$^+$+(OH)$^-$, H$_2$O, dioxane, reflux.

Scheme 75
triazolobenzodiazepine (279), affording instead a good yield (67%) of the formamide (277) as the only product. The formation of the formamide (277) in this reaction suggests that coordination of the Lewis acid to the isocyano group is taking place, but the attacking aromatic ring is not sufficiently nucleophilic to effect ring closure. This is not unexpected in the light of previous work (see Chapter 2, Section 2.2 and Chapter 3, Section 3.2) which showed that activation of the attacking aromatic ring by at least one electron-donating substituent is required for successful cyclisation.

Attention was next turned (Scheme 75) to the cyclisation of the isocyanide dichloride (280a), which was prepared from the isocyanide (278) in quantitative yield by its reaction with sulphuryl chloride in methylene chloride at \(-10^\circ\). Unfortunately however (Table 13, entry 1), the attempted reaction of (280a) with two equivalents of aluminium chloride under reflux in methylene chloride gave only a quantitative recovery of the unchanged isocyanide dichloride (280a), with no evidence of any cyclised product.

The isocyanide dibromide (280b), which is a more potent electrophilic reagent than the corresponding isocyanide dichloride, was prepared in 100% yield by reaction of the isocyanide (278) with bromine at \(-10^\circ\). Disappointingly, reaction (Table 13, entry 2) of the dibromide (280b) with one equivalent of titanium tetrachloride in methylene chloride at \(-10^\circ\) gave only a high recovery of the unchanged isocyanide dibromide (280b), together with a small amount (4%) of the formamide (277). The isocyanide dibromide (280b) obtained from this reaction was characterised by its combustion analysis, high resolution mass spectrometry, and other spectroscopic data. Interestingly, this compound showed no evidence of any halogen exchange between the isocyanide dibromide (280b) and the Lewis acid, as had been observed previously (see Section 3.2) in the reactions of 1,1'-biphenyl-2-isocyanide dibromide (249) with chlorinated Lewis acids.
Table 13: Lewis Acid Promoted Cyclisation Reactions of 1-Benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide Dihalides (280a and b)

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Lewis Acid</th>
<th>(280):Lewis Acid Ratio</th>
<th>Solvent</th>
<th>Reaction Temp.(°C)</th>
<th>Time (h)</th>
<th>Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>AlCl₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>TiCl₄</td>
<td>1:1</td>
<td>CH₂Cl₂</td>
<td>-10</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>AlBr₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>AlBr₃</td>
<td>1:2</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>AlBr₃</td>
<td>1:5</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>4</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>AlBr₃</td>
<td>1:5</td>
<td>CH₂Cl₂</td>
<td>room temp.</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

a, complex mixture obtained.
The use (Table 13, entry 3) of aluminium tribromide as the Lewis acid did give the cyclised product (281b) although only in low yield, together with a good recovery of the unchanged isocyanide dibromide (280b). This reaction may take two courses, involving cyclisation at the phenyl ring of (280b) to give the triazoloisoquinoline derivative (281b) or at the benzyl moiety to give the triazolobenzodiazepine (283), however the combustion analysis and spectroscopic properties of the product failed to distinguish between these two possibilities. A $^{13}$C n.m.r. spectrum would similarly be expected to show very little difference between (281b) and (283), and the product obtained unfortunately was not suitable for single crystal X-ray analysis. The structure of the cyclised product is therefore only tentatively assigned as the isoquinoline derivative (281b). This product should be more easily formed as the attacking phenyl ring is held rigidly in close proximity to the isocyanide dibromide group in (280b). On the other hand, the phenyl ring of the benzyl substituent is not only more remote from the reaction site but has greater flexibility and so is less likely to react, despite the minor activation of this ring by the methylene group. The ease of formation of six-membered compared to seven-membered rings in isocyanide dihalide cyclisations has been demonstrated and discussed previously (see Section 3.2). From a synthetic point of view the seven-membered ring product (283) would be of greater interest due to its potential for further elaboration by acid promoted ring opening of the bridgehead fused 1,2,3-triazole ring, which is not possible in the more stable 4,5-fused triazole structure (281b).

Increasing the reaction time (Table 13, entry 4) failed to improve the yield of the cyclised product (281b), while the use (Table 13, entry 5) of five equivalents of aluminium tribromide in refluxing methylene chloride did increase the yield slightly but at the expense of significant decomposition of the starting material. An attempt (Table 13, entry 6) to circumvent this
decomposition but retain the beneficial effect of the excess Lewis acid by lowering the reaction temperature was unsuccessful, with the cyclised product (281b) being obtained in very poor yield.

Alkaline hydrolysis of the presumed bromoisouquinoline derivative (281b) with aqueous benzyltrimethylammonium hydroxide afforded the corresponding lactam (282) in quantitative yield. The spectroscopic properties of this product also failed to unambiguously establish its identity as the triazoloisouquinoline (282) or the alternative triazolobenzodiazepinone, and unfortunately this compound also was not suitable for single crystal X-ray analysis. Lack of time did not permit the further accumulation of evidence for or against the tentatively assigned structures (281b) and (282) for the cyclised compound and its hydrolysis product respectively.

The reason for the consistently low yield of the cyclised product (281b) is not clear, but may be due to competing complexation of the triazole nitrogen atoms with the Lewis acid. Indeed the absence of any halogen exchange products on reaction of the isocyanide dibromide (280b) with titanium tetrachloride suggests that, at least with one equivalent of Lewis acid, coordination at the isocyanide dibromide group has not occurred. Despite the low yield obtained, the preparation of (281b) represents an unprecedented cyclisation of a heteroaromatic isocyanide dihalide. The potential of this reaction to generate a range of unusual fused heterocycles, which themselves may be further manipulated by displacement of the bromine atom and subsequent exploitation of the reactivity of the heterocyclic ring, suggests that the cyclisation of heteroaromatic isocyanide dihalides would be a fruitful area for future investigations.
3.6 EXPERIMENTAL

General Experimental Details

For general experimental details see Chapter 2, Section 2.9; page 77.

Analytical and Spectroscopic Data

For analytical and mass spectroscopic data see Table 14, page 309.

\( N-(1,1'-\text{Biphenyl-2-yl})\text{formamide} (231) \)

A mixture of 1,1'-biphenyl-2-amine (230) (33.8 g; 0.02 mol) and 98-100% formic acid (200.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

Rotary evaporation of the cooled mixture gave an oil which was dissolved in methylene chloride, and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml). Rotary evaporation of the combined organic extracts gave an oil which solidified to afford \( N-(1,1'-\text{biphenyl-2-yl})\text{formamide} (231) \) as a pink solid (38.5 g; 98%), m.p. 71-74° (lit.,\textsuperscript{136} 75°).

\( 1.1'-\text{Biphenyl-2-isocyanide} (232) \)

A solution of \( N-(1,1'-\text{biphenyl-2-yl})\text{formamide} (231) \) (7.9 g; 0.04 mol) in anhydrous 1,2-dichloroethane (80.0 ml) was treated with carbon tetrachloride (7.4 g; 0.048 mol) followed by triphenylphosphine (12.6 g; 0.048 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (8.1 g; 0.08 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

Rotary evaporation of the cooled mixture gave a semi-solid which was treated with water (30.0 ml) and extracted with methylene chloride to give a semi-solid which was triturated with ether to afford triphenylphosphine oxide
as a cream solid (11.5 g), m.p. 146-149° (lit., 126 152-153°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil (10.8 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave the known 1,1'-biphenyl-2-isocyanide (232) as an orange-brown oil (6.2 g; 87%), \( \nu_{\text{max}} \) 2120 (NC) cm\(^{-1}\).

Elution with methanol gave a dark brown oil (93.8 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to contain mainly triphenylphosphine oxide, and therefore was not further investigated.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Acetyl Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in the appropriate anhydrous solvent (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of acetyl chloride (0.16 g; 0.002 mol) in the appropriate anhydrous solvent (5.0 ml), and the mixture was stirred at -10° or under reflux, under nitrogen, for 7h.

(i) In anhydrous ether at -10°

Rotary evaporation of the mixture gave unchanged 1,1'-biphenyl-2-isocyanide (232) as a brown oil (99%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

(ii) In anhydrous methylene chloride under reflux

The cooled mixture was rotary evaporated to give a brown oil (0.45 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (95:5) gave an intractable brown oil (0.09 g) which was not further investigated.
Elution with hexane-ethyl acetate (8:2) gave N-(1,1'-biphenyl-2-yl)formamide (231) as a light brown solid (0.28 g; 71%), m.p. 67-70° (lit., 75°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable black gum (0.02 g) which was not investigated further.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Acetyl Bromide in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of acetyl bromide (0.25 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 7h.

Rotary evaporation of the mixture gave an oil (0.58 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave N-(1,1'-biphenyl-2-yl)-2-ketopropanamide (237) (0.06 g; 13%) which formed pink needles, m.p. 105-106° (from ethanol), \( \nu_{\text{max}} \) 3360 (NH), 1720 and 1695 (C=O) cm\(^{-1}\), \( \delta_H(\text{CDCl}_3) \) 8.93 (1H, bs, NH), 8.45 (1H, dd, J 6 and 1 Hz, ArH), 7.54-7.19 (8H, m, ArH), and 2.48 (3H, s, CH\(_3\)).

Elution with hexane-ethyl acetate (6:4) through ethyl acetate to methanol gave only a series of multicomponent oils and gums (0.28 g) which were not further investigated.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Acetyl Chloride in the Presence of Silver Tetrafluoroborate

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred under nitrogen, treated
dropwise at room temperature with a solution of acetyl chloride (0.16 g; 0.002 mol) in anhydrous 1,2-dichloroethane (5.0 ml) and the mixture was stirred at room temperature, under nitrogen, for 4h. A solution of silver tetrafluoroborate (0.43 g; 0.0022 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was added dropwise and the mixture was stirred at -10° (ice-salt bath), under nitrogen, for 20h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, and filtered to remove silver residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a gum (0.45 g) which was flash-chromatographed over silica to give no identifiable material.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Cyanogen Bromide in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of cyanogen bromide (0.21 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen for 1h.

Rotary evaporation of the mixture gave unchanged 1,1'-biphenyl-2-isocyanide (232) as a brown oil (0.39 g; 100%) identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Titanium Tetrachloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.72 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was stirred under nitrogen, treated
dropwise at -10 ° (ice-salt bath) with a solution of titanium tetrachloride (3.8 g; 2.2 ml; 0.002 mol) in anhydrous methylene chloride (10.0 ml) and the mixture was stirred at -10° or under reflux, under nitrogen, for 2-24h then worked up as described for the individual reactions below.

(i) At -10° for 2h

The mixture was treated dropwise with 60% w/v aqueous sodium hydroxide solution (3.0 ml; 0.02 mol) then water (10.0 ml), and the mixture was filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.70 g) which was triturated with hexane-ether to give N-(1,1'-biphenyl-2-yl)formamide (231) as a cream solid (0.38 g; 49%), m.p. 65-68° (lit., 136 75°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(ii) Under reflux for 24h

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.04 mol) and extracted with methylene chloride to give an oil (0.60 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave an intractable brown oil which was not investigated further.

Elution with hexane-ethyl acetate (8:2) gave N-(1,1'-biphenyl-2-yl)formamide (231) as a light brown solid (41%), m.p. 65-68° (lit., 136 75°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with methanol gave a brown gum whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture, and was therefore not further investigated.
3-Methoxyphenylboronic Acid (239)

3-Methoxyphenylboronic acid (239) was prepared by the reaction of 3-bromoanisole with n-butyllithium and triisopropylborate as described by Kajimoto et al.\textsuperscript{37} as a colourless solid (yield 100%), and had m.p. 151-154° (lit.,\textsuperscript{137} 159°).

3'-Methoxy-2-nitro-1,1'-biphenyl (240)

A solution of 2-bromonitrobenzene (238) (4.0 g; 0.02 mol) in alumina washed 1,2-dimethoxyethane (40.0 ml) was stirred under nitrogen, treated at room temperature with tetrakistriphenylphosphine palladium (0.69 g; 0.0006 mol) followed by a solution of sodium carbonate (2.1 g; 0.02 mol) in water (10.0 ml) then 3-methoxyphenylboronic acid (239) (4.6 g; 0.03 mol), and the mixture was stirred and heated under reflux, under nitrogen, for 19h.

The cooled mixture was rotary evaporated to one fifth of its original volume, treated with water (40.0 ml), and extracted with methylene chloride to give a waxy solid (6.2 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (95:5) gave 3'-methoxy-2-nitro-1,1'-biphenyl (240) (4.2 g; 92%) which formed yellow plates, m.p. 70-72° (from ethanol), \( \nu_{\text{max}} \) 1525 and 1355 (NO\textsubscript{2}) cm\textsuperscript{-1}, \( \delta_H (\text{CDCl}_3) \) 7.89-7.76(1H, m, ArH), 7.69-7.22(4H, m, ArH), 7.00-6.82(3H, m, ArH), and 3.81(3H, s, OCH\textsubscript{3}).

Final elution with methanol gave a gum (0.70 g) whose t.l.c. in methylene chloride-hexane (1:1) over silica showed it to be a complex mixture, which was not further investigated.

3'-Methoxy-1,1'-biphenyl-2-amine (241)

A solution of 3'-methoxy-2-nitro-1,1'-biphenyl (240) (2.3 g; 0.01 mol) in ethanol (100.0 ml) was hydrogenated over 10% palladium-on-charcoal
(0.23 g) at room temperature and atmospheric pressure for 1 h, during which time hydrogen (774 ml; 0.035 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give an oil. This solidified on cooling to afford 3'-methoxy-1,1'-biphenyl-2-amine (241) (2.0 g; 100%) which formed colourless plates, m.p. 46° (from cyclohexane), $\nu_{\text{max}}$ 3420 and 3340 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.47-6.70 (8H, m, ArH), 3.84 (3H, s, OCH$_3$), and 3.69 (2H, s, NH$_2$) (exch).

$N$-(3'-Methoxy-1,1'-biphenyl-2-yl)formamide (242)

A mixture of 3'-methoxy-1,1'-biphenyl-2-amine (241) (1.4 g; 0.007 mol) and 98-100% formic acid (40.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3 h.

Rotary evaporation of the cooled mixture gave an oil which was dissolved in methylene chloride, and the solution was washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 5.0 ml). Rotary evaporation of the organic layer gave an oil which was triturated with hexane-ether to give $N$-(3-methoxy-1,1'-biphenyl-2-yl)formamide (242) (1.1 g; 70%) which formed colourless plates, m.p. 63-64° (from cyclohexane), $\nu_{\text{max}}$ 3220-3160 (br) (NH) and 1650 (C=O) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.71 (1H, s, NH) (exch), 8.59-8.25 (1H, m, CHO), 7.47-7.15 (5H, m, ArH), 6.99-6.84 (3H, m, ArH), and 3.81 (3H, s, OCH$_3$).

Rotary evaporation of the organic mother liquor gave an oil (0.30 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a mixture containing more of the desired product (242), which was not further investigated.
A solution of $N$-(3-methoxy-1,1'-biphenyl-2-yl)formamide (242) (2.0 g; 0.009 mol) in anhydrous 1,2-dichloroethane (30.0 ml) was treated with carbon tetrachloride (1.7 g; 0.011 mol) followed by triphenylphosphine (2.9 g; 0.011 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (1.8 g; 0.018 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (20.0 ml) and extracted with methylene chloride to give an oil. This was triturated with ether to afford triphenylphosphine oxide as a cream solid (1.9 g), m.p. 147-149° (lit.,126 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil (2.9 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 3-methoxy-1,1'-biphenyl-2-isocyanide (243) (1.6 g; 82%) which formed colourless needles, m.p. 46-47° (from hexane), $\nu_{\text{max}}$ 2110 (NC) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.49-6.89(8H, m, ArH) and 3.84(3H, s, OCH$_3$).

Elution with hexane-ethyl acetate (7:3) gave unchanged $N$-(3-methoxy-1,1'-biphenyl-2-yl)formamide (242) as a brown oil (0.33 g; 17%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] with a sample prepared previously.

Final elution with methanol gave triphenylphosphine oxide as a cream solid (0.89 g), m.p. 144-147° (lit.,126 152-153°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
9-Methoxyphenanthridine (244)

(a) A solution of 3-methoxy-1,1'-biphenyl-2-isocyanide (243) (0.42 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (1.9 g; 1.1 ml; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (77.0 ml; 0.1 mol), stirred at room temperature for 10 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.35 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave a multicomponent oil (0.08 g) which was not investigated further.

Further elution with hexane-ethyl acetate (7:3) gave 9-methoxyphenanthridine (244) (0.15 g; 36%) \( \delta_H(\text{CDCl}_3) 9.18(1\,\text{H}, \text{s}, \text{N=CH}), 8.50(1\,\text{H}, \text{dd}, J 8 \text{ and } 1 \text{ Hz}, \text{ArH}), 8.20(1\,\text{H}, \text{dd}, J 8 \text{ and } 1 \text{ Hz}, \text{ArH}), 7.98(1\,\text{H}, \text{d}, J 9 \text{ Hz}, \text{ArH}), 7.91(1\,\text{H}, \text{d}, J 2\text{Hz}, \text{ArH}), 7.75(1\,\text{H}, \text{dd}, J 8, 7, \text{ and } 1 \text{ Hz}, \text{ArH}), 7.67(1\,\text{H}, \text{dd}, J 8, 7, \text{ and } 1 \text{ Hz}, \text{ArH}), 7.32(1\,\text{H}, \text{dd}, J 9 \text{ and } 2 \text{ Hz}, \text{ArH}), \text{ and } 4.03(3\,\text{H}, \text{s}, \text{OCH}_3)), \) which formed colourless needles, m.p. 84-85° (from cyclohexane), (lit.,\(^{138} 85-86°), \nu_{\text{max}} 1620 (\text{N=C}) \text{ cm}^{-1}, \delta_H(\text{CDCl}_3) 9.16(1\,\text{H}, \text{s}, \text{N=CH}), 8.54-8.42(1\,\text{H}, \text{m}, \text{ArH}), 8.22-7.22(6\,\text{H}, \text{m}, \text{ArH}), \text{ and } 4.03(3\,\text{H}, \text{s}, \text{OCH}_3)).

Final elution with methanol gave an intractable gum (0.04 g) which was not further investigated.

(b) Repetition of the reaction described in (a) above under reflux for 2h gave 9-methoxyphenanthridine (244) as a cream solid (0.35 g; 83%), m.p. 71-
73°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample, prepared in (a) before.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide (232) with Chlorine in 1,2-Dichloroethane

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of chlorine in anhydrous 1,2-dichloroethane (3.9 ml of a 0.56 M solution; 0.0022 mol), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave a dark brown oil (0.40 g) whose t.l.c. in hexane-methylene chloride (1:1) over silica showed it to be a mixture of the unreacted starting material (232) and 1,1'-biphenyl-2-isocyanide dichloride (245), which was not further investigated.

1,1'-Biphenyl-2-isocyanide Dichloride (245)

(a) From 1,1'-biphenyl-2-isocyanide (232)

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a colourless oil (0.54 g; 100%), b.p. 114-117°/0.10-0.05 mmHg (lit.,7,44 172-177°/12 mmHg), \(v_{\text{max}}\) 1670-1640 (br) (N=C) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3)\) 7.52-7.24 (8H, m, ArH) and 7.00-6.88 (1H, m, ArH), m/z (ElMS) 253, 251, and 249 (M\(^+\)).
(b) **From \( N-(1,1'-\text{biphenyl}-2-\text{yl})\text{formamide (231)} \)**

1,1'-Biphenyl-2-isocyanide dichloride (245) was prepared by the reaction of \( N-(1,1'-\text{biphenyl}-2-\text{yl})\text{formamide (231)} \) with thionyl chloride and sulphuryl chloride as described by Kühle *et al.*,\(^{44}\) as a brown oil (yield 100%), \( \nu_{\max} \) 1670-1640 (br) (N=C) cm\(^{-1}\), identical (i.r. spectrum) to a sample prepared in (a) before.

**1,1'-Biphenyl-2-isothiocyanate (246)**

A suspension of 1,1'-biphenyl-2-amine (230) (8.5 g; 0.05 mol) in concentrated hydrochloric acid (250.0 ml) was stirred and treated slowly with water (250.0 ml) then dropwise with thiophosgene (22.8 g; 0.2 mol) and the mixture was stirred at room temperature for 18 h.

The mixture was cooled (ice bath), neutralised with 10 M aqueous sodium hydroxide solution and glacial acetic acid, and extracted with methylene chloride to give an oil (10.0 g) which was distilled to afford 1,1'-biphenyl-2-isothiocyanate (246) as a pale yellow oil (7.9 g; 75%), b.p. 132-135°/0.30-0.20 mmHg (lit.,\(^{134}\) 130-132°/0.25 mmHg), \( \nu_{\max} \) 2111 (N=CS) cm\(^{-1}\).

**The Attempted Reaction of 1,1'-Biphenyl-2-isothiocyanate (246) with Sulphuryl Chloride in Methylene Chloride**

(a) A solution of 1,1'-biphenyl-2-isothiocyanate (246) (0.42 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of sulphuryl chloride (0.54 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h.

Rotary evaporation of the mixture gave an oil (0.51 g) which was flash-chromatographed over silica.
Elution with hexane gave unchanged 1,1'-biphenyl-2-isothiocyanate (246) as a colourless oil (0.30 g; 71%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Elution with hexane-ether (95:5) gave an oil (0.16 g) whose t.l.c. in hexane-ether (2:1) showed it to be a mixture from which no characterisable material was obtained.

(b) Repetition of the reaction described in (a) before using three equivalents of sulphuryl chloride (0.006 mol) at room temperature for 48h gave an oil (0.55 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Sodium Cyanide in 1,2-Dimethoxyethane

A solution of 1,1'-biphenyl-2-isocyanide dichloride (245) (0.52 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with sodium cyanide (0.39 g; 0.008 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 16h.

The cooled mixture was filtered to remove inorganic material and the filtrate was rotary evaporated to give a black gum (0.55 g) whose t.l.c. in hexane-methylene chloride (1:1) over silica showed it to be a complex mixture, from which no identifiable material was obtained.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Silver Tetrafluoroborate in 1,2-Dichloroethane

A solution of 1,1'-biphenyl-2-isocyanide dichloride (245) (3.8 g; 0.015 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of silver...
tetrafluoroborate (3.2 g; 0.0165 mol) in anhydrous 1,2-dichloroethane (50.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (127 ml; 0.165 mol), stirred at room temperature for 15 min, and filtered to remove silver residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (3.2 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 6-chlorophenanthridine (248) (0.15 g; 5%) which formed colourless plates, m.p. 116-117° (from cyclohexane) (lit., 139-117-118°). $\nu_{\text{max}}$ 1610 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.62-8.38 (3H, m, ArH) and 8.14-7.54 (5H, m, ArH).

Elution with hexane-ether (99:1) through ether to methanol gave only a series of multicomponent oils and gums (3.01 g) which were not investigated further.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (248) with One Equivalent of Titanium Tetrachloride in Methylene Chloride at -10°

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of titanium tetrachloride (0.42 g; 0.24 ml; 0.0022 mol) in anhydrous methylene chloride (5.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15
min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a light brown oil (0.50 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

6-Chlorophenantridine (248)

(A) From the Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) With Titanium Tetrachloride in Methylene Chloride

(a) A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1 h. A solution of titanium tetrachloride (0.0022 mol or 0.0044 mol) in anhydrous methylene chloride (5.0 ml) was added dropwise and the mixture was stirred and heated under reflux, under nitrogen, for 2-4 h then worked up as described for the individual reactions below.

(i) Using one equivalent of titanium tetrachloride under reflux for 2 h

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 6-chlorophenantridine (248), which was collected with the aid of a little hexane, as a yellow solid (0.32 g; 74%), m.p. 86-91°C (lit., 139° 117-118°C), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
Rotary evaporation of the hexane mother liquor gave an oil (0.14 g) whose t.l.c. in hexane-ether (2:1) over silica showed it to be a mixture of the desired product (248) and 1,1'-biphenyl-2-isocyanide dichloride (245), which was not further investigated.

(ii) **Using one equivalent of titanium tetrachloride under reflux for 4h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a solid (0.44 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a colourless oil (0.18 g; 36%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Further elution with hexane-ether (95:5) gave 6-chlorophenanthridine (248) as a cream solid (0.22 g; 51%), m.p. 101-105° (lit. 134 117-118°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ether (8:2) gave a cream solid (0.01 g), m.p. 165-171°, which was not further investigated.

(iii) **Using two equivalents of titanium tetrachloride under reflux for 2h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0 ml; 0.044 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy solid (0.51 g) which was flash-chromatographed over silica.
Elution with light petroleum (b.p. 40-60°)-ether (98:2) gave 6-chlorophenanthridine (248) as a cream solid (0.33 g; 77%), m.p. 114-116° (lit.,139 117-118°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a gum (0.04 g) whose t.l.c. in hexane-ether (2:1) over silica showed it to be a multicomponent mixture, which therefore was not further investigated.

(b) A mixture of 1,1'-biphenyl-2-formamide (231) (0.39 g; 0.002 mol) and thionyl chloride (3.0 ml) was stirred under nitrogen and treated dropwise with sulphuryl chloride (0.27 g; 0.002 mol) and the mixture was stirred under nitrogen at room temperature for 2h then at 80° (oil bath) for 15 min.

The cooled mixture was rotary evaporated to give 1,1'-biphenyl-2-isocyanide dichloride (245) as a yellow oil (0.51 g; 100%), identical [t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously. This was dissolved in anhydrous methylene chloride (10.0 ml) and the solution was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (0.76 g; 0.44 ml; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 3-4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy solid which was worked up further as described for the individual reactions below.

(i) From 3h at reflux

The solid product mixture was flash-chromatographed over silica.
Elution with hexane-ether (8:2) gave 6-chlorophenanthridine (248) as a pale yellow solid (0.35 g; 86%), m.p. 108-110° (lit., 139 117-118°) identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.02 g) which was not investigated further.

(ii) From 4h at reflux

The solid product mixture was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave 6-chlorophenanthridine (248) as a colourless solid (0.40 g; 94%), m.p. 111-113° (lit., 139 117-118°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

(B) From the Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Aluminium Trichloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.004-0.01 mol) in anhydrous methylene chloride (15.0-40.0 ml) was added portionwise and the mixture was stirred at -10° or at room temperature, under nitrogen, for 2-4h then worked up as described for the individual reactions below.

(i) Using two equivalents of aluminium trichloride at -10° for 2h

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary
evaporation of the combined organic extracts gave an oil (0.48 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a yellow oil (0.19 g; 38%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-chlorophenanthridine (248) as a colourless solid (0.24 g; 56%), m.p. 106-109° (lit.,\textsuperscript{139} 117-118°), identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

(ii) Using five equivalents of aluminium trichloride at -10° for 2h

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (77.0 ml; 0.1 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.48 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a yellow oil (0.15 g; 30%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-chlorophenanthridine (248) as a cream solid (0.25 g; 58%), m.p. 108-110° (lit.,\textsuperscript{139} 117-118°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(iii) Using two equivalents of aluminium trichloride at room temperature for 4h

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary
evaporation of the combined organic extracts gave a waxy solid (0.45 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a colourless oil (0.08 g; 16%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-chlorophenanthridine (248) as a cream solid (0.36 g; 84%), m.p. 114-115° (lit.,139 117-118°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Aluminium Trichloride in Methylene Chloride Monitored by Infrared Spectroscopy

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.18 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.14 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A portion of the mixture was then removed and its i.r. spectrum was recorded. A suspension of anhydrous aluminium trichloride (0.13 g; 0.001 mol) in anhydrous methylene chloride (10.0 ml) was added portionwise at room temperature, and a portion of the mixture was immediately removed and its i.r. spectrum was recorded. The mixture was then stirred at room temperature, under nitrogen, for 4h during which time portions of the mixture were removed and their i.r. spectra recorded after 15, 60, 120, 180, and 240 min.

Finally, the mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (8.0 ml; 0.01 mol) stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary
evaporation of the combined organic extracts gave an oil (0.23 g) which was
flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide
dichloride (245) as a yellow oil (0.05 g; 20%), identical [i.r. spectrum and t.l.c.
in hexane-ether (2:1) over silica] to a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-chlorophenanthridine (248) as
a cream solid (0.15 g; 70%), M.P. 107-109° (lit.,\textsuperscript{139} 117-118°), identified by
comparison (m.p. and i.r. spectrum) with a sample prepared previously.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245)
with Boron Trichloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.18 g; 0.001 mol) in
anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated
dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.14 g;
0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was
stirred at -10°, under nitrogen, for 1h. A solution of boron trichloride in
anhydrous methylene chloride (2.0 ml of a 1.0 M solution; 0.002 mol) in
anhydrous methylene chloride (8.0 ml) was added dropwise and the mixture
was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen
carbonate solution (16.0 ml; 0.02 mol), stirred at room temperature for 15 min,
and extracted with methylene chloride to give 1,1'-biphenyl-2-isocyanide
dichloride (245) as a yellow oil (0.26 g; 100%), identical [i.r. spectrum and
t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.
The Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Antimony Pentachloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.18 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.14 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of antimony pentachloride (0.30 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 0.5h.

Filtration of the mixture gave a solid which was tentatively identified as 6-chlorophenanthridine-antimony pentachloride complex (265) (0.40 g; 80%) which formed yellow plates, m.p. 227-232 (from acetonitrile), $\nu_{\text{max}}$ 1639 (N=C) cm$^{-1}$.

Rotary evaporation of the methylene chloride mother liquor gave an intractable brown gum (0.01 g) which was not investigated further.

A portion of the 6-chlorophenanthridine-antimony pentachloride complex (265) (0.10 g; 0.002 mol) was treated with 2 M aqueous sodium hydroxide solution (2.0 ml) and the mixture was warmed gently then treated with methylene chloride and filtered to remove an unidentified colourless solid (0.006 g), m.p. > 350°.

Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 6-chlorophenanthridine (248) as a pale brown solid (0.05 g; 86%), m.p. 108-110° (lit.,$^{139}$ 117-118°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
1,1'-Biphenyl-2-isocyanide Dibromide (249)

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.90 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.80 g; 0.005 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave 1,1'-biphenyl-2-isocyanide dibromide (249) as a brown oil (1.7 g; 100%), b.p. 175-180°/0.08-0.05 mm Hg. This solidified to give a cream solid which formed colourless needles, m.p. 53-54° [from petroleum ether (b.p. 60-80°)], νmax 1680 (N≡C) cm⁻¹, δH(CDCl₃) 7.44-7.24(8H, m, ArH) and 6.96-6.84(1H, m, ArH).

The Attempted Reaction of 1,1'-Biphenyl-2-isothiocyanate (246) with Bromine in Methylene Chloride

A solution of 1,1'-biphenyl-2-isothiocyanate (246) (0.42 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10° or at room temperature, under nitrogen, for 1-24h then worked up as described for the individual reactions below.

(i) At -10° for 1h

Rotary evaporation of the mixture gave unchanged 1,1'-biphenyl-2-isothiocyanate (246) as a yellow oil (0.35 g; 83%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

(ii) At room temperature for 24h

Rotary evaporation of the mixture gave unchanged 1,1'-biphenyl-2-isothiocyanate (246) as an orange oil (0.43 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.
The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Piperidine in Ether

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (1.7 g; 0.005 mol) in anhydrous ether (10.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of piperidine (0.85 g; 0.01 mol) in anhydrous ether (10.0 ml), and the mixture was stirred at 0°, under nitrogen, for 0.5h.

The mixture was treated with anhydrous ether (10.0 ml) and filtered to give piperidine hydrobromide as a colourless solid (0.79 g), m.p. 232-234° (lit., 170° 235°).

Rotary evaporation of the ethereal mother liquor gave an oil (1.8 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (6:4) gave N-(1,1'-biphenyl-2-yl)carbamoylpiperidine (251) (0.86 g; 61%) which formed colourless plates, m.p. 85-86° (from cyclohexane), \(v_{\text{max}} 3280 \text{ (NH)} \) and 1630 (C=O) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3) 8.11(1H, \text{ dd, J 8 and 1 Hz, ArH}), 7.44-7.00(8H, \text{ m, ArH}), 6.49(1H, \text{ bs, NH}), 3.25-3.17(4H, \text{ m, 2xCH}_2), \) and 1.50-1.40(6H, m, 3xCH\(_2\)).

Final elution with methanol gave an intractable orange foam (0.90 g) which was not investigated further.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Sodium Cyanide in 1,2-Dimethoxyethane

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (0.68 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with sodium cyanide (0.004-0.008 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 13-16h then worked up as described for the individual reactions below.
Using two equivalents of sodium cyanide

After 13h the cooled mixture was filtered to remove inorganic material and the filtrate was rotary evaporated to give an oil (0.55 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave unchanged 1,1'-biphenyl-2-isocyanide dibromide (249) as a colourless oil (0.30 g; 46%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Further elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide (232) as a yellow oil (0.19 g; 54%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

Final elution with methanol gave an intractable dark brown gum (0.02 g) which was not further investigated.

Using four equivalents of sodium cyanide

After 16h the cooled mixture was filtered to remove inorganic material and the filtrate was rotary evaporated to give 1,1'-biphenyl-2-isocyanide (232) as a brown oil (100%), identical [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (3.4 g; 0.01 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) was treated portionwise with sodium azide (0.65 g; 0.01 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 24h.

Rotary evaporation of the mixture gave a semi-solid. This was treated with water (20.0 ml) and extracted with methylene chloride to give 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) (2.9 g; 96%) which formed colourless
plates, m.p. 118-119° (decomp.) (from toluene), δ_H(CDCl_3) 7.75-7.01(9H, m, ArH).

5-Azido-1-(1,1'-biphenyl-2-yl)tetrazole (254)

A solution of 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) (6.0 g; 0.02 mol) in anhydrous dimethylformamide (50.0 ml) was treated with sodium azide (1.3 g; 0.02 mol) and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (50.0 ml) and extracted with methylene chloride to give an oil (7.1 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 5-azido-1-(1,1'-biphenyl-2-yl)tetrazole (254) (4.6 g; 87%) which formed pale yellow plates, m.p. 64-65° (from ethanol), ν_max 2154 (N_3) cm^{-1}, δ_H(CDCl_3) 7.64-7.02(9H, m, ArH).

Final elution with methanol gave an intractable brown gum (0.50 g) which was not investigated further.

1-(1,1'-Biphenyl-2-yl)-5-triphenylphosphineiminotetrazole (255)

A solution of 5-azido-1-(1,1'-biphenyl-2-yl)tetrazole (254) (3.9 g; 0.015 mol) in anhydrous 1,2-dimethoxyethane (40.0 ml) was treated in one portion with a solution of triphenylphosphine (3.9 g; 0.015 mol) in anhydrous 1,2-dimethoxyethane (40.0 ml) and the mixture was stirred, with exclusion of atmospheric moisture, at room temperature for 0.5h then at 60° (oil bath) for 0.5h.

The mixture was cooled (ice bath) and filtered to give a colourless solid. This was combined with further material, obtained by rotary evaporation of the organic mother liquor and trituration of the resulting residue with ether, to afford 1-(1,1'-biphenyl-2-yl)-5-triphenylphosphineiminotetrazole
(255) (7.0 g; 94%) which formed colourless crystals, m.p. 236-238° (from glacial acetic acid), $d_H[(CD_3)_2SO]$ 8.42-7.75(7H, m, ArH), 7.67-7.39(8H, m, ArH), and 6.90-6.63(9H, m, ArH).

Rotary evaporation of the ethereal mother liquor gave an intractable orange oil (0.40 g) which was not further investigated.

5-Amino-1-(1,1'-biphenyl-2-yl)tetrazole (256)

A suspension of 1-(1,1'-biphenyl-2-yl)-5-triphenylphosphineiminotetrazole (255) (4.0 g; 0.008 mol) in 2 M aqueous hydrochloric acid solution (40.0 ml) was stirred and heated under reflux for 24h.

The cooled mixture was made basic with 2 M aqueous sodium hydroxide solution and extracted with methylene chloride to give a waxy solid (4.2 g) which was flash-chromatographed over alumina.

Elution with hexane-ethyl acetate (2:8) gave triphenylphosphine oxide as a cream solid (2.0 g; 90%), m.p. 148-150 (lit., 126 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate-methanol (95:5) gave 5-amino-1-(1,1'-biphenyl-2-yl)tetrazole (256) (1.3 g; 70%) which formed colourless plates, m.p. 168-170° (from toluene), $v_{max}$ 3318 and 3148 (NH) cm$^{-1}$, $d_H$(CDCl$_3$) 7.62-7.35(4H, m, ArH), 7.33-7.04(5H, m, ArH), and 4.85(2H, bs, NH$_2$) (exch).

Final elution with methanol gave an intractable brown semi-solid (0.10 g) which was not investigated further.

The Attempted Reaction of 1-(1,1'-Biphenyl-2-yl)-5-bromotetrazole (252) with Aluminium Tribromide

A solution of 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) (0.30 g; 0.001 mol) in the appropriate anhydrous solvent (10.0 ml) was stirred under
nitrogen, treated dropwise at 0° (ice bath) with a solution of aluminium tribromide (0.53 g; 0.002 mol) in the appropriate anhydrous solvent (10.0 ml) and the mixture was stirred and heated under reflux, under nitrogen, for 4 h then worked up as described for the individual reactions below.

(i) **In anhydrous methylene chloride**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which solidified on cooling to afford unchanged 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) as a light brown solid (0.30 g; 100%), m.p. 110-114° (decomp.), identified by comparison (m.p. and i.r. spectrum) to a sample prepared previously.

(ii) **In anhydrous 1,2-dichloroethane**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.30 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unchanged 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) as a cream solid (0.09 g; 30%), m.p. 109-111° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) through ethyl acetate to methanol gave only a series of multicomponent mixtures (0.10 g) which were not further investigated.
The Attempted Reaction of 1-(1,1'-Biphenyl-2-yl)-5-bromotetrazole (252) with Silver Tetrafluoroborate in 1,2-Dichloroethane

A solution of 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) (0.60 g; 0.002 mol) in anhydrous 1,2-dichloroethane (5.0 ml) was stirred under nitrogen, treated dropwise at room temperature with a solution of silver tetrafluoroborate (0.43 g; 0.0022 mol) in anhydrous 1,2-dichloroethane (15.0 ml), and the mixture was stirred at room temperature, under nitrogen, for 1h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol) and extracted with methylene chloride to give an oil (0.63 g) which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave unchanged 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) as a cream solid (0.56 g; 96%), m.p. 114-116° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Tetrazolo[1,5-e]phenanthridine (263)

(a) From 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252)

A solution of 1-(1,1'-biphenyl-2-yl)-5-bromotetrazole (252) (0.60 g; 0.002 mol) in anhydrous 1,2-dichloroethane (5.0 ml) was stirred under nitrogen, treated dropwise at room temperature with a solution of silver tetrafluoroborate or silver acetate (0.0022 mol) in anhydrous 1,2-dichloroethane (20.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 5h then worked up as described for the individual reactions below.

(i) Using silver tetrafluoroborate

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol) and extracted with methylene chloride to give a solid, which was washed with ether. This was
combined with further material obtained by rotary evaporation of the ethereal
mother liquor and flash-chromatography of the residue in hexane-ethyl
acetate (7:3) over silica to afford tetrazolo[1,5-e]phenanthridine (253) (0.23 g;
52%) which formed colourless needles, m.p. 232-223° (from methanol)
(lit., 144 234-236°), ν max 1610 (Ar) cm -1, δ H[(CD 3 ) 2 SO] 8.84-8.49(4H, m, ArH)
and 8.00-7.69(4H, m, ArH).

Elution with hexane-ethyl acetate (9:1) gave unchanged 1-(1,1'-
biphenyl-2-yl)-5-bromotetrazole (252) as a light brown solid (0.09 g; 15%),
m.p. 115-117° (decomp.), identical (m.p. and i.r. spectrum) to a sample
prepared previously.

Final elution with methanol gave an intractable brown gum (0.04 g)
which was not investigated further.

(ii) Using silver acetate

The cooled mixture was poured into 10% w/v aqueous sodium
hydrogen carbonate solution (17.0 ml; 0.022 mol) and filtered to remove silver
residues. Separation of the filtrate, extraction of the aqueous layer with
methylene chloride, and rotary evaporation of the combined organic extracts
gave a gum (0.59 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unchanged 1-(1,1'-
biphenyl-2-yl)-5-bromotetrazole (252) as a brown solid (0.34 g; 57%), m.p.
114-117° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared
previously.

Elution with hexane-ethyl acetate (6:4) gave tetrazolo[1,5-
e]phenanthridine (253) as a cream solid (0.08 g; 18%), m.p. 227-230° (lit., 144
234-236°), identified by comparison (m.p. and i.r. spectrum) with a sample
prepared previously.

Final elution with methanol gave an intractable brown gum (0.04 g)
which was not investigated further.
(b) From 5-amino-1-(1,1'-biphenyl-2-yl)tetrazole (256)

A solution of 5-amino-1-(1,1'-biphenyl-2-yl)tetrazole (256) (0.47 g; 0.002 mol) in glacial acetic acid (5.0 ml) was stirred and treated dropwise at <30° (ice-water bath) with concentrated sulphuric acid (1.6 ml). The mixture was then cooled to 0° (ice bath) and treated dropwise with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml) and the mixture was stirred at 0° for 2h.

Water (5.0 ml) was added then the mixture was rotary evaporated to half its original volume and extracted with methylene chloride. The organic extracts were washed four times with 10% w/v aqueous sodium hydrogen carbonate solution (4 x 10.0 ml) and rotary evaporated to give a semi-solid (0.42 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave tetrazolo[1,5-e]phenanthridine (253) as a cream solid (0.24 g; 55%), m.p. 226-229° (lit., 144 234-236°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (6:4) gave unchanged 5-amino-1-(1,1'-biphenyl-2-yl)tetrazole (256) as a cream solid (0.11 g; 23%), m.p. 161-163°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.01 g) which was not investigated further.

(c) From 6-bromophenanthridine (257)

A solution of 6-bromophenanthridine (257) (0.26 g; 0.001 mol) in anhydrous dimethylformamide (2.5 ml) was added to a stirred suspension of sodium azide (0.07 g; 0.001 mol) in anhydrous dimethylformamide (2.5 ml) and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.
The cooled mixture was rotary evaporated to give a solid which was treated with water (5.0 ml) and filtered to afford tetrazolo[1,5-e]phenanthridine (253) as a light brown solid (0.20 g; 91%), m.p. 214-218° (lit., 144 234-236°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

**Ethyl Diazooacetate**

A sample of ethyl diazoacetate was kindly provided by Miss Amanda Davison, Department of Chemistry, University of Edinburgh.

**The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Ethyl Diazooacetate**

(i) **At room temperature**

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of ethyl diazoacetate (0.23 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at room temperature, under nitrogen, for 24h. N-Ethylidiosopropylamine (0.26 g; 0.002 mol) was added and stirring was continued at room temperature, with exclusion of atmospheric moisture, for a further 5h after which time a further portion of N-ethylidiosopropylamine (0.26 g; 0.002 mol) was added. The mixture was then stirred at room temperature, with exclusion of atmospheric moisture, for a further 19h.

Rotary evaporation of the mixture gave a semi-solid. This was tritutated with ether to give a cream solid (0.52 g), m.p. 94-96°, which was not further investigated.
Rotary evaporation of the ethereal mother liquor gave an oil (0.81 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave unchanged 1,1'-biphenyl-2-isocyanide (232) as a brown-yellow oil (0.34 g; 99%), identical [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.

Further elution with hexane-ether (99:1) gave unreacted ethyl diazoacetate as a yellow oil (0.14 g; 64%), identical [i.r. spectrum and t.l.c. in hexane ether (1:1) over silica] to an authentic sample.

Final elution with methanol gave an intractable brown gum (0.03 g) which was not further investigated.

(ii) At 50°

A mixture of 1,1'-biphenyl-2-isocyanide dibromide (249) (0.68 g; 0.002 mol) and ethyl diazoacetate (0.46 g; 0.004 mol) was stirred and heated at 50° (oil bath), with exclusion of atmospheric moisture, for 17h.

The cooled mixture was rotary evaporated to give an oil (0.94 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) through ether to methanol gave only a series of multicomponent oils and gums (0.48 g) which were not investigated further.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Titanium Tetrachloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.72 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of titanium tetrachloride (0.004-0.02 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and
the mixture was stirred at -10°, under nitrogen, for 2h then worked up as described for the individual reactions below.

(i) Using five equivalents of titanium tetrachloride

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (154 ml; 0.2 mol), stirred at room temperature for 15 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a 2:1 mixture of 6-bromophenanthridine (257) and 6-chlorophenanthridine (248) (100%) which formed colourless plates, m.p. 121-122° (from cyclohexane), ν_max 1670 (N=C) cm⁻¹, δ_H(CDCl₃) 8.60-8.34 (3H, m, ArH) and 8.14-7.24 (5H, m, ArH).

Found: C, 64.9; H, 3.5; N, 5.8%; m/z (ElMS) 259 and 257, 215 and 213 (M⁺).

2C_{13}H_{16}Br:C_{13}H_{16}NCl requires: C, 64.7; H, 3.2; N, 5.8%; M, 259 and 257, 215 and 213.

This was identical with a sample prepared by combining 6-bromophenanthridine (257) (0.05 g) and 6-chlorophenanthridine (248) (0.05 g) and crystallisation of the mixture three times from cyclohexane to give a white solid, m.p. 119-120°.

(ii) Using one equivalent of titanium tetrachloride

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a brown solid (0.90 g) which was crystallised from cyclohexane to give a eutectic mixture of 6-bromophenanthridine (257) and 6-chlorophenanthridine (248) as a cream solid (0.54 g), m.p. 104-107°,
identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

**The Reaction of the Mixture of 6-Bromophenanthridine (257) and 6-Chlorophenanthridine (248) with Ethanolic Potassium Hydroxide**

A solution of the mixture of 6-bromophenanthridine (257) and 6-chlorophenanthridine (248) (0.52 g) in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide solution (5.0 ml) and the mixture was stirred and heated under reflux for 2 h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (5.0 ml) and extracted with methylene chloride to give an oil (0.44 g) which was triturated with ether to afford phenanthridin-6(5H)-one (258) as a colourless solid (0.04 g), m.p. 255-262° (lit.,146 293-294°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil. This was triturated with hexane to give a cream solid which was combined with further material, obtained by rotary evaporation of the hexane mother liquor and flash-chromatography of the resulting residue in hexane-ethyl acetate (9:1) over silica, to afford 6-ethoxyphenanthridine (259) (0.18 g) which formed colourless needles, m.p. 57-58° (from ethanol), \( \nu_{\text{max}} \) 1620 (N=C) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.54-8.32(3H, m, ArH), 7.94-7.34(5H, m, ArH), 4.20(2H, q, J 7 Hz, CH\(_2\)), and 1.54(3H, t, J 7 Hz, CH\(_3\)).

**The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (248) with Aluminium Trichloride in Methylene Chloride**

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol)
in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (15.0 ml) was added portionwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy solid (0.54 g) which was flash-chromatographed over silica.

Elution with light petroleum (b.p. 40-60°)-ether (98:2) gave 1,1'-biphenyl-2-isocyanide bromochloride (260) as a pale yellow solid (0.07 g; 12%), m.p. 35-39°.

Elution with light petroleum (b.p. 40-60°)-ether (98:2) gave a mixture of 6-bromophenanthridine (257) and 6-chlorophenanthridine (248) as a cream solid (0.38 g), m.p. 121-123°, m/z (ElMS) 259 and 257 (M⁺), 215 and 213 (M⁺), identified by comparison (m.p., i.r. and mass spectra) with a sample prepared previously.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Stannic Chloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of stannic chloride (0.52 g; 0.24 ml; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.
The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 15 min, and filtered to remove tin residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a brown oil (0.58 g; 100%), b.p. 120-124°/0.10-0.05 mmHg (lit., 172-177°/12 mmHg), m/z (ElMS) 253, 251, and 249 (M⁺), identical [i.r. and mass spectra, and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Sulphuryl Chloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (0.68 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.002-0.008 mol) in anhydrous methylene chloride (5.0-10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h then worked up as described for the individual reactions below.

(i) Using one equivalent of sulphuryl chloride

Rotary evaporation of the mixture gave a mixture of 1,1'-biphenyl-2-isocyanide dichloride (245) and 1,1'-biphenyl-2-isocyanide bromochloride (260) as a brown oil (0.58 g), ν_max 1660-1640 (br) (N=C) cm⁻¹, m/z (ElMS) 297, 295, and 293 (M⁺), 253, 251, and 249 (M⁺).

(ii) Using four equivalents of sulphuryl chloride

Rotary evaporation of the mixture gave 1,1'-biphenyl-2-isocyanide dichloride (245) as a brown oil (0.24 g; 96%), ν_max 1660 (N=C) cm⁻¹, m/z (ElMS) 253, 251, and 249 (M⁺), identical [i.r. and mass spectra, and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.
The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Benzyldiethylammonium Chloride in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (0.34 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of benzyldiethylammonium chloride (0.001-0.004 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) Using four equivalents of benzyldiethylammonium chloride

Rotary evaporation of the mixture gave a colourless solid (0.92 g), m.p. 180-181° (decomp.), which was collected with the aid of a little ether and was not investigated further.

Rotary evaporation of the ethereal mother liquor gave a mixture of 1,1'-biphenyl-2-isocyanide dichloride (245) and 1,1'-biphenyl-2-isocyanide bromochloride (260), as a yellow oil (0.27 g), $\nu_{\text{max}}$ 1660-1640 (br) (N=C) cm$^{-1}$, m/z (ElMS) 297, 295, and 293 ($M^+$), 253, 251, and 249 ($M^+$).

(ii) Using one equivalent of benzyldiethylammonium chloride

Rotary evaporation of the mixture gave a semi-solid which was washed with ether to afford a pale yellow solid (0.26 g), m.p. 180-185° (decomp.), which was not investigated further.

Rotary evaporation of the ethereal mother liquor gave a mixture of 1,1'-biphenyl-2-isocyanide dichloride (245), 1,1'-biphenyl-2-isocyanide bromochloride (260), and unchanged 1,1'-biphenyl-2-isocyanide dibromide (249) as a dull yellow oil (0.27 g), $\nu_{\text{max}}$ 1700-1640 (br) (N=C) cm$^{-1}$, m/z (ElMS) 341, 339, and 337 ($M^+$), 297, 295, and 293 ($M^+$), and 253, 251, and 249 ($M^+$).
The Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Bromine in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide dichloride (245) (0.24 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave a mixture of 1,1'-biphenyl-2-isocyanide bromochloride (260) and unchanged 1,1'-biphenyl-2-isocyanide dichloride (245) as a yellow-brown oil (0.25 g), \( \nu_{\text{max}} \) 1660 and 1640 (N=C) cm\(^{-1}\), m/z (EIMS) 297, 295, and 293 (M\(^+\)), 253, 251, and 249 (M\(^+\)).

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dichloride (245) with Tetra-n-butylammonium Bromide in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide dichloride (245) (0.25 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (solid CO\(_2\)-ethylene glycol bath) with a solution of tetra-n-butylammonium bromide (1.3 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h.

Rotary evaporation of the mixture gave a semi-solid which was washed with ether to afford unchanged tetra-n-butylammonium bromide as a colourless solid (1.2 g; 92%), m.p. 97-100°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Rotary evaporation of the ethereal mother liquor gave unchanged 1,1'-biphenyl-2-isocyanide dichloride (245) as a yellow oil (0.24 g; 96%), \( \nu_{\text{max}} \) 1660 (N=C) cm\(^{-1}\), m/z (EIMS) 253, 251, and 249 (M\(^+\)), identical [i.r. and mass
spectra, and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with One Equivalent of Titanium Tetrabromide in Methylene Chloride

(a) **At -10°**

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.54 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of titanium tetrabromide (1.2 g; 0.0033 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (26.0 ml; 0.033 mol), stirred at room temperature for 15 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil. This slowly solidified to afford 1,1'-biphenyl-2-isocyanide dibromide (249) as a light brown solid (0.88 g; 87%), m.p. 42-45°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(ii) **Under reflux**

Repetition of the reaction described in (a) before under reflux for 2h gave 1,1'-biphenyl-2-isocyanide dibromide (249) as a pale brown solid (85%), m.p. 41-44°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
6-Bromophenanthridine (257)

(a) From the Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Silver Tetrafluoroborate in 1,2-Dichloroethane

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous 1,2-dichloroethane (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of silver tetrafluoroborate (0.43 g; 0.0022 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, and filtered to remove silver residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a semi-solid (0.61 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dibromide (249) as a colourless oil (0.18 g; 27%), identified by comparison (i.r. and mass spectra) to a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-bromophenanthridine (257) (0.31 g; 60%) which formed colourless plates, m.p. 124-125° (from cyclohexane) (lit.,145 123-124°). $\nu_{\text{max}}$ 1610 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.56-8.32(3H, m, ArH) and 8.15-7.54(5H, m, ArH).

(b) From the Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Titanium Tetrabromide in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol)
in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of titanium tetrabromide (0.0022-0.0044 mol) in anhydrous methylene chloride (5.0-10.0 ml) was added dropwise and the mixture was stirred and heated under reflux, under nitrogen, for 4-24h then worked up as described for the individual reactions below.

(i) **Using one equivalent of titanium tetrabromide for 24h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.022 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy solid (0.54 g) which was flash-chromatographed over silica.

Elution with hexane-ether (97.5:2.5) gave 6-bromophenanthridine (257) as a cream solid (0.48 g; 93%), m.p. 113-116° (lit., 123-124°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(ii) **Using two equivalents of titanium tetrabromide for 4h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0 ml; 0.044 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.63 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dibromide (249) as a colourless oil (0.46 g; 68%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] with a sample prepared previously.
Further elution with hexane-ether (99:1) gave 6-bromophenanthrindine (257) as a cream solid (0.09 g; 17%), m.p. 121-123° (lit.,\textsuperscript{145} 123-124°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

(c) From the Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Aluminium Tribromide in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.36 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy solid (0.54 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave 1,1'-biphenyl-2-isocyanide dibromide (249) as a yellow oil (0.10 g; 15%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] with a sample prepared previously.

Elution with hexane-ether (98:2) gave 6-bromophenantrindine (257) as a pale yellow solid (0.41 g; 80%), m.p. 116-119° (lit.,\textsuperscript{145} 123-124°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
The Attempted Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Boron Trihalides in Methylene Chloride

A solution of 1,1'-biphenyl-2-isocyanide (232) (0.18 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.16 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10° under nitrogen, for 1 h. A solution of boron tribromide (0.0022 mol) or boron trifluoride etherate (0.0011 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at -10° under nitrogen, for 2 h then worked up as described for the individual reactions below.

(i) Using boron tribromide

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (16.0 ml; 0.022 mol), stirred at room temperature for 15 min, and extracted with methylene chloride to give 1,1'-biphenyl-2-isocyanide dibromide (249) as a yellow-brown oil (0.33 g; 97%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

(ii) Using boron trifluoride etherate

The mixture was treated with ice (2.5 g), stirred at room temperature for 1 h, and extracted with methylene chloride to give 1,1'-biphenyl-2-isocyanide dibromide (249) as a black oil (100%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

The Reaction of 1,1'-Biphenyl-2-isocyanide Dibromide (249) with Piperidine then Aluminium Tribromide

A solution of 1,1'-biphenyl-2-isocyanide dibromide (249) (1.4 g; 0.004 mol) in anhydrous ether (20.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of piperidine (0.68 g; 0.008 mol) in
anhydrous ether (10.0 ml), and the mixture was stirred at 0°, under nitrogen, for 1h.

Filtration of the mixture gave piperidine hydrobromide as a colourless solid (0.54 g), m.p. 235-239° (lit., 170-235°).

Rotary evaporation of the ethereal mother liquor gave a brown oil (1.4 g) which was dissolved in anhydrous methylene chloride (20.0 ml). The resulting solution was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of aluminium tribromide (2.1 g; 0.008 mol) in anhydrous methylene chloride (20.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 3h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (1.4 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 6-piperidinophenanthridine (261) (0.06 g; 6%) which formed colourless plates, m.p. 91-92° (from ethanol), $\nu_{\text{max}}$ 1610 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.58-7.24(8H, m, ArH), 3.45-3.38(4H, m, 2xCH$_2$), and 1.91-1.78(6H, m, 3xCH$_2$).

Elution with hexane-ether (6:4) gave N-(1,1'-biphenyl-2-yl)carbamoylpiperidine (251) as a cream solid (0.31 g; 28%), m.p. 81-83°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.33 g) which was not investigated further.
6-Piperidinophenanthridine (261)

A solution of 6-bromophenanthridine (257) (0.26 g; 0.001 mol) in anhydrous acetonitrile (5.0 ml) was treated with piperidine (0.17 g; 0.002 mol) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 24 h.

The cooled mixture was rotary evaporated to give a waxy solid. This was treated with water (5.0 ml) and extracted with methylene chloride to give a semi-solid (0.30 g) which was flash-chromatographed over silica. Elution with hexane-ether (9:1) gave 6-piperidinophenanthridine (261) as a cream solid (0.21 g; 81%), m.p. 77-79°C, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Phenanthridin-6(5H)-one (258)

A solution of 6-bromophenanthridine (257) (0.26 g; 0.001 mol) in dioxane (5.0 ml) was treated in one portion with 40% w/v aqueous benzyltrimethylammonium hydroxide solution (1.7 ml; 0.004 mol) and the mixture was stirred and heated under reflux for 2 h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (5.0 ml) and the mixture was acidified with 2 M aqueous hydrochloric acid solution then filtered to give phenanthridin-6(5H)-one (258) (0.19 g; 97%), m.p. 286-289°C (lit., 146 293-294°C), identified by comparison (m.p. and i.r. spectrum) with a commercially available sample.

6-Ethoxyphenanthridine (259)

(a) A solution of sodium (0.18 g; 0.008 mol) in anhydrous ethanol (10.0 ml) was stirred and treated portionwise with a mixture of 6-bromophenanthridine (257) and 6-chlorophenanthridine (248) (0.52 g) and the mixture was stirred and heated under reflux, with exclusion of atmospheric moisture, for 2 h.
The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.50 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (95:5) gave 6-ethoxyphenanthridine (259) as a light brown solid (0.43 g), m.p. 45-48°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with methanol gave an intractable brown gum (0.01 g) which was not investigated further.

(b) Repetition of the reaction described in (a) above using a pure sample of 6-bromophenanthridine (257) (0.002 mol) gave 6-ethoxyphenanthridine (259) as a pale yellow solid (76%), m.p. 52-54°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

6-Cyanophenanthridine (262)

A solution of 6-bromophenanthridine (257) (0.26 g; 0.001 mol) in anhydrous dimethylformamide (2.5 ml) was added in one portion to a stirred suspension of sodium cyanide (0.05 g; 0.001 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1-22h then worked up as described for the individual reactions below.

(i) Using a reaction time of 1h

The cooled mixture was rotary evaporated to give a solid. This was treated with water (5.0 ml) and extracted with methylene chloride to give a solid (0.25 g) which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave unchanged 6-bromophenanthridine (257) as a cream solid (0.17 g; 65%), m.p. 118-119° (lit., 123-124°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.
Elution with hexane-ether (98:2) also gave 6-cyanophenanthridine (262) (0.04 g; 20%) which formed colourless needles, m.p. 132-133° (from ethanol) (lit.,\textsuperscript{156} 136-137°), $\nu_{\text{max}}$ 2230 (w) (CN) cm\textsuperscript{-1}, $\delta_H$(CDCl$_3$) 8.75-7.25(8H, m, ArH).

(ii) Using a reaction time of 22h

The cooled mixture was rotary evaporated to give a solid which was treated with water (5.0 ml) and extracted with methylene chloride to give a waxy solid (0.25 g) which was flash-chromatographed over silica.

Elution with hexane-ether (99:1) gave unchanged 6-bromophenanthridine (257) as a pale yellow solid (0.16 g; 62%), m.p. 119-120° (lit.,\textsuperscript{145} 123-124°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Further elution with hexane-ether (99:1) gave 6-cyanophenanthridine (262) as a yellow solid (0.05 g; 25%), m.p. 125-127° (lit.,\textsuperscript{156} 136-137°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

1-Amino-2-methynaphthalene (266c)

A solution of 2-methyl-1-nitronaphthalene (7.5 g; 0.04 mol) in ethyl acetate (75.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.75 g) at room temperature and atmospheric pressure for 4h, during which time hydrogen (2910 ml; 0.13 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give the known\textsuperscript{164} 1-amino-2-methynaphthalene (266c) as a brown-orange oil (6.4 g; 100%), $\nu_{\text{max}}$ 3465, 3385, and 3244 (NH) cm\textsuperscript{-1}. 
**N-(Naphthalen-1-yl)formamide Derivatives (267a) and (267c)**

A mixture of the corresponding 1-aminonaphthalene (0.04 mol) and 98-100% formic acid (60.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3 h then worked up as described for the individual reactions below.

(i) **N-(Naphthalen-1-yl)formamide (267a)**

The cooled mixture from 1-aminonaphthalene (266a) was rotary evaporated to give a waxy solid which was dissolved in methylene chloride, and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 × 5.0 ml). Rotary evaporation of the organic layer gave N-(naphthalen-1-yl)formamide (267a) as a purple solid (92%), m.p. 134-136° (lit., \(^{161}138-139°\)).

(ii) **N-(2-methylnaphthalen-1-yl)formamide (267c)**

The cooled mixture from 1-amino-2-methylnaphthalene (266c) was rotary evaporated to give N-(2-methylnaphthalen-1-yl)formamide (267c) (7.0 g; 95%) which formed colourless needles, m.p. 174-175° (from ethanol) (lit., \(^{165}175-176°\)), \(\nu_{\text{max}}\) 3214 (NH) and 1655 (C=O) cm\(^{-1}\), \(\delta_{\text{H}}(\text{CDCl}_3)\) 8.56-7.24 (8H, m, NH, CHO, and 6xArH) and 2.49 (3H, s, CH\(_3\)).

**Naphthalene-1-isocyanide Derivatives (268a) and (268c)**

A solution of the corresponding N-(naphthalen-1-yl)formamide derivative (267a) or (267c) (0.01 mol) in anhydrous 1,2-dichloroethane (30.0 ml) was treated with carbon tetrachloride (1.9 g; 0.012 mol) followed by triphenylphosphine (3.1 g; 0.012 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (2.0 g; 0.02 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5 h then worked up as described for the individual reactions below.
(i) Naphthalene-1-isocyanide (268a)

The cooled mixture from N-(naphthalen-1-yl)formamide (267a) was rotary evaporated to give a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a purple oil which was distilled to give naphthalene-1-isocyanide (268a) as a green oil (79%), b.p. 141-152°/0.20-0.05 mmHg (lit.,¹ 90-95°/0.005 mmHg), νmax 2118 (NC) cm⁻¹.

Elution with hexane-ethyl acetate (7:3) gave unchanged N-(naphthalen-1-yl)formamide (267a) as a cream solid (9%), m.p. 136-138° (lit.,¹ 161 138-139°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a waxy purple solid (6.8 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to contain mainly triphenylphosphine oxide, and therefore was not further investigated.

(ii) 2-Methylnaphthalene-1-isocyanide (268c)

The cooled mixture from N-(2-methylnaphthalen-1-yl)formamide (267c) was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 2-methylnaphthalene-1-isocyanide (268c) (1.3 g; 78%) which formed cream plates, m.p. 52-53° (from hexane) (lit.,¹ 65 55-56°), νmax 2110 (NC) cm⁻¹, δH(CDCl₃) 8.20-7.24(6H, m, ArH).

Final elution with methanol gave a brown semi-solid (3.5 g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture, which was not further investigated.
Naphthalene-1-isocyanide Dihalide Derivatives (269a-c)

A solution of the corresponding naphthalene-1-isocyanide derivative (0.0005 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride or bromine (0.0005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) Naphthalene-1-isocyanide Dichloride (269a)

The mixture from naphthalene-1-isocyanide (268a) and sulphuryl chloride was rotary evaporated to give the known naphthalene-1-isocyanide dichloride (269a) as a green oil (0.11 g; 100%), $\nu_{\text{max}}$ 1650 (N=C) cm$^{-1}$.

(ii) Naphthalene-1-isocyanide Dibromide (269b)

The mixture from naphthalene-1-isocyanide (268a) and bromine was rotary evaporated to give naphthalene-1-isocyanide dibromide (269b) as a purple oil (100%), $\nu_{\text{max}}$ 1674 (N=C) cm$^{-1}$.

(iii) 2-Methylnaphthalene-1-isocyanide Dibromide (269c)

The mixture from 2-methylnaphthalene-1-isocyanide (268c) and bromine was rotary evaporated to give 2-methylnaphthalene-1-isocyanide dibromide (269c) as a pale brown oil (0.16 g; 100%), $\nu_{\text{max}}$ 1681 (N=C) cm$^{-1}$.

The Attempted Reaction of Naphthalene-1-isocyanide Dichloride (269a) with Aluminium Trichloride in Methylene Chloride

A solution of naphthalene-1-isocyanide (268a) (0.31 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.53 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was
added portionwise and the mixture was stirred at room temperature or under reflux, under nitrogen, for 4-18h then worked up as described for the individual reactions below.

(i) **At room temperature for 4h**

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride and ethyl acetate, and rotary evaporation of the combined organic extracts gave naphthalene-1-isocyanide dichloride (269a) as a brown oil (0.43 g; 96%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

(ii) **Under reflux for 4h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave naphthalene-1-isocyanide dichloride (269a) as a brown oil (0.40 g; 89%), identified by comparison [i.r. spectrum and t.l.c. in hexane-methylene chloride (2:1) over silica] with a sample prepared previously.

(iii) **Under reflux for 18h**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a gum. This was triturated with ether to afford a brown solid, m.p. 118-225° (decomp.), whose t.l.c. in
hexane-ether (2:1) over silica showed it to be a mixture, and was therefore not further investigated.

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

Elution with hexane-ether (99:1) through ether to methanol gave only a series of intractable mixtures which were not investigated further.

The Reaction of Naphthalene-1-isocyanide Dichloride (268a) with Aluminium Trichloride in Methylene Chloride Monitored by Infrared Spectroscopy

A solution of naphthalene-1-isocyanide (268a) (0.15 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.14 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then a sample was removed and its i.r. spectrum was recorded. A suspension of anhydrous aluminium trichloride (0.13 g; 0.01 mol) in anhydrous methylene chloride (10.0 ml) was added portionwise at room temperature, and a sample of the mixture was removed and its i.r. spectrum was recorded. The mixture was stirred at room temperature, under nitrogen, and portions of the mixture were removed and their i.r. spectra were recorded after 1.5 and 2h. A further portion of anhydrous aluminium trichloride (0.13 g; 0.001 mol) in anhydrous methylene chloride (10.0 ml) was added portionwise and a sample of the mixture was immediately removed and its i.r. spectrum was recorded. The mixture was stirred at room temperature, under nitrogen, and portions of the mixture were removed and their i.r. spectra were then recorded after 20 min, 1h, and 2h.

The mixture was treated with 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol), stirred at room temperature for 15 min,
then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave naphthalene-1-isocyanide dichloride (269a) as a brown oil (0.24 g; 100%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

The Attempted Reaction of Naphthalene-1-isocyanide Dichloride (269a) with Antimony Pentachloride in Methylene Chloride

A solution of naphthalene-1-isocyanide (268a) (0.31 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1 h. A solution of antimony pentachloride (0.60 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at -10°C, under nitrogen, for 0.5 h.

Rotary evaporation of the mixture gave an intractable brown foam (1.1 g). This was dissolved in methylene chloride and the solution was treated with 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml; 0.02 mol) and stirred at room temperature for 15 min, then filtered to remove antimony residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.50 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave naphthalene-1-isocyanide dichloride (269a) as an orange-brown oil (0.07 g; 16%), identical (i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica) to a sample prepared previously.
Elution with hexane-ether (9:1) through ether to methanol gave only a series of multicomponent mixtures (0.06 g) which were not investigated further.

The Attempted Reaction of Naphthalene-1-isocyanide Dibromide Derivatives (268b) and (268c) with Aluminium Tribromide

A solution of the appropriate naphthalene-1-isocyanide derivative (268a) or (268c) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h then worked up as described for the individual reactions below.

(i) From naphthalene-1-isocyanide dibromide (269b)

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave naphthalene-1-isocyanide dibromide (296b) as a brown oil (0.58 g; 93%), identical [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.

(ii) From 2-methylnaphthalene-1-isocyanide dibromide (269c)

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary
evaporation of the combined organic extracts gave an oil which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave unchanged 2-methylnaphthalene-1-isocyanide dibromide (269c) as a brown oil (62%), identified by comparison [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] with a sample prepared previously.

Elution with hexane-ether (7:3) through ether to methanol gave only a series of complex gums, which were not further investigated.

5-Amino-1,3-diphenyl-1H-pyrazole (271)

A sample of 5-amino-1,3-diphenyl-1H-pyrazole (271) was kindly provided by Dr. Ronald Torano, Department of Chemistry, University of Edinburgh.

N-(1,3-Diphenyl-1H-pyrazol-5-yl)formamide (272)

A mixture of 5-amino-1,3-diphenyl-1H-pyrazole (271) (1.6 g; 0.007 mol) and 98-100% formic acid (40.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0 ml). Rotary evaporation of the organic layer gave N-(1,3-diphenyl-1H-pyrazol-5-yl)formamide (272) (1.6 g; 87%) which formed colourless plates, m.p. 140-141° (from ethanol), $\nu_{\text{max}}$ 3225 (NH) and 1665 (C=O) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.46-8.26(1H, m, CHO) and 7.89-7.08(11H, m, ArH).
1,3-Diphenyl-1H-pyrazole-5-isocyanide (273)

(a) A solution of N-(1,3-diphenyl-1H-pyrazol-5-yl)formamide (272) (0.79 g; 0.003 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was treated with carbon tetrachloride (0.55 g; 0.0036 mol) followed by triphenylphosphine (0.94 g; 0.0036 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (0.61 g; 0.006 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (2.6 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave 1,3-diphenyl-1H-pyrazole-5-isocyanide (273) (0.15 g; 20%) which formed brown plates, m.p. 92-94° (from hexane), $\nu_{\text{max}}$ 2118 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.97-6.51(11H, m, ArH).

Elution with hexane-ether (7:3) through ether to methanol gave only a series of intractable oils (0.78 g) which were not investigated further.

(b) A solution of N-(1,3-diphenyl-1H-pyrazol-5-yl)formamide (272) (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was treated with N-ethyldiisopropylamine (1.4 g; 0.011 mol) then dropwise at 0° (ice bath) with phosphoryl chloride (0.75 g; 0.0044 mol) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 4h.

The mixture was treated with 2 M aqueous sodium carbonate solution (4.4 ml), stirred at room temperature for 1h, then treated with water (20.0 ml) and extracted with methylene chloride. The combined organic extracts were washed three times with water (3 x 5.0 ml) and rotary evaporated to give an oil (1.9 g) which was flash-chromatographed over silica.

Elution with hexane-ether (95:5) gave 1,3-diphenyl-1H-pyrazole-5-isocyanide (273) as a cream solid (0.57 g; 58%), m.p. 90-92°, identical (m.p. and i.r. spectrum) to a sample prepared previously.
Elution with hexane-ether (7:3) through ether to methanol gave only a series of intractable mixtures (0.44 g) which were not investigated further.

**The Attempted Reaction of 1,3-Diphenyl-1H-pyrazole-5-isocyanide Dibromide (274) with Aluminium Tribromide in Methylene Chloride**

A solution of 1,3-diphenyl-1H-pyrazole-5-isocyanide (273) (0.49 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added dropwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.71 g) which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave 1,3-diphenyl-1H-pyrazole-5-isocyanide dibromide (274) (0.57 g; 70%) which formed light brown plates, m.p. 101-103° (from ethanol), $\nu_{\text{max}}$ 1647 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.00-7.01(11H, m, ArH).

Elution with hexane-ether (97:3) gave a yellow solid tentatively identified as 5-bromo-2-phenylpyrazolo[1,5-a]quinazoline (275) (0.03 g; 5%), m.p. 132-134°, $\delta_{\text{H}}$(CDCl$_3$) 8.59-7.34(10H, m, ArH), m/z (ElIMS) 325 and 323 (M$^+$).
Elution with methanol gave an intractable brown gum (0.01 g) which was not investigated further.

**The Reaction of 1,3-Diphenyl-1H-pyrazole-5-isocyanide Dibromide (274) with Aqueous Sodium Hydroxide Solution in Dioxane**

A solution of 1,3-diphenyl-1H-pyrazole-5-isocyanide dibromide (274) (0.10 g) in dioxane (2.0 ml) was treated with 2 M aqueous sodium hydroxide solution (2.0 ml) and the mixture was stirred at room temperature for 6h. The mixture was then extracted with methylene chloride to give an oil (0.08 g) whose t.l.c. in hexane-ether (1:1) over silica showed it to contain mainly 5-amino-1,3-diphenyl-1H-pyrazole (271).

**5-Amino-1-benzyl-4-phenyl-1H,2,3-triazole (276)**

A sample of 5-amino-1-benzyl-4-phenyl-1H,2,3-triazole (276) was kindly provided by Mr. John Wastle, Department of Chemistry, University of Edinburgh.

**N-(1-Benzyl-4-phenyl-1H,2,3-triazol-5-yl)formamide (277)**

A mixture of 5-amino-1-benzyl-4-phenyl-1H,2,3-triazole (276) (10.0 g; 0.04 mol) and 98-100% formic acid (100.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h. The cooled mixture was rotary evaporated to give N-(1-benzyl-4-phenyl-1H,2,3-triazol-5-yl)formamide (277) (10.8 g; 98%) which formed colourless plates, m.p. 170-171° (from ethanol), \( \nu_{\text{max}} \) 3200 (NH) and 1700 (C=O) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.34(1H, s, CHO), 7.78-7.76(2H, m, ArH), 7.46-7.26(8H, m, ArH), and 5.52(2H, s, CH\_2).
1-Benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278)
(a) A solution of \(N\)-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) (2.0 g; 0.007 mol) in anhydrous 1,2-dichloroethane (40.0 ml) was treated with carbon tetrachloride (1.3 g; 0.0084 mol) followed by triphenylphosphine (2.2 g; 0.0084 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (1.4 g; 0.014 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (20.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.09 g; 49%) which formed light brown plates, m.p. 107-108° (decomp.) (from cyclohexane), \(\nu_{\text{max}}\) 2110 (N=C) cm\(^{-1}\), \(\delta_H(\text{CDCl}_3)\) 8.02-7.89(2H, m, ArH), 7.54-7.24(8H, m, ArH), and 5.59(2H, s, CH\(_2\)).

Elution with hexane-ethyl acetate (1:1) to hexane-ethyl acetate (4:6) gave a series of multicomponent gums (1.1 g) which were not further investigated.

Final elution with methanol gave triphenylphosphine oxide as a brown solid (1.7 g), m.p. 147-151° (lit.,\(^{126}\) 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A suspension of \(N\)-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) (1.4 g; 0.005 mol) in anhydrous methylene chloride (20.0 ml) was stirred and treated dropwise at 0° (ice bath) with diisopropylamine (1.4 g; 0.014 mol) then dropwise with phosphoryl chloride (0.84 g; 0.0055 mol) and the mixture was stirred at 0° (ice bath), with exclusion of atmospheric moisture, for 4h.
The mixture was treated dropwise with 2 M aqueous sodium carbonate solution (5.5 ml), stirred at room temperature for 15 min, and extracted with methylene chloride. The combined organic extracts were washed three times with water (3 x 5.0 ml) and rotary evaporated to give a semi-solid (1.3 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) as a cream solid (0.36 g; 30%), m.p. 101-103° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) through ethyl acetate to methanol gave a series of intractable oils and gums (0.72 g) which were not further investigated.

(c) Repetition of the reaction described in (b) before using N-ethyldiisopropylamine as the base at room temperature gave 1-benzyl-1-phenyl-1H,2,3-triazole-5-isocyanide (278) as a yellow solid (46%), m.p. 103-104° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared previously.

The Attempted Reaction of N-(1-Benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) with Trifluoromethanesulphonic Anhydride in Methylene Chloride

A suspension of N-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) (1.4 g; 0.005 mol) in anhydrous methylene chloride (40.0 ml) was stirred under nitrogen, treated dropwise at -78° (solid CO₂-acetone bath) with N-ethyldiisopropylamine (3.9 g; 0.03 mol) followed by trifluoromethanesulphonic anhydride (2.1 g; 0.0075 mol), and the mixture was stirred at -78°, under nitrogen, for 20 min.
The mixture was treated with 10% w/v aqueous sodium hydrogen carbonate solution (6.0 ml; 0.0075 mol), allowed to warm to room temperature, and extracted with methylene chloride. The organic extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (6.0 ml; 0.0075 mol) and rotary evaporated to give an intractable brown-black semi-solid (5.3 g) from which no identifiable material was obtained.

The Attempted Reaction of 1-Benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) with Titanium Tetrachloride in Methylene Chloride

A solution of 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.39 g; 0.0015 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (1.4 g; 0.83 ml; 0.0075 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred and heated under reflux, under nitrogen, for 2h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (58.0 ml; 0.075 mol), stirred at room temperature for 15 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.44 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave a solid which was combined with further material, obtained by elution with hexane-ethyl acetate (6:4), to afford N-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) as an orange solid (0.28 g; 67%), m.p. 165-168°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.02 g) which was not further investigated.
A solution of 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.13 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.068 g; 0.0005 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. Rotary evaporation of the mixture gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dichloride (280a) as a viscous yellow oil (0.17 g; 100%), $\nu_{\text{max}}$ 1640 (N=C) cm$^{-1}$.

The Attempted Reaction of 1-Benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide Dichloride (280a) with Aluminium Trichloride in Methylene Chloride

A solution of 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.26 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.14 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (15.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h. The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (16.0 ml; 0.02 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dichloride (280a) as a brown-red oil (0.36 g;
100%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to a sample prepared previously.

**The Attempted Reaction of 1-Benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide Dibromide (280b) with Titanium Tetrachloride in Methylene Chloride**

A solution of 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.78 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of titanium tetrachloride (0.57 g; 0.33 ml; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred at -10°, under nitrogen, for 2 h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (23.0 ml; 0.03 mol), stirred at room temperature for 15 min, and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (1.2 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (8:2) gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dibromide (280b) (1.1 g; 87%) which formed colourless plates, m.p. 62-63° (from diethyl ether), $\nu_{\text{max}}$ 1640 (N=C) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.69-7.24 (10H, m, ArH) and 5.40 (2H, s, CH$_2$).

Elution with hexane-ethyl acetate (4:6) gave N-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)formamide (277) as a cream solid (0.03 g; 4%), m.p. 169-171°, identical (m.p. and i.r. spectrum) to a sample prepared previously.
A solution of 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide (278) (0.52 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, and filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dibromide (280b) as a yellow solid (64%), m.p. 59-61°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-ether (7:3) gave 3-benzyl-5-bromo-1H-[1,2,3]triazolo[4,5-c]isoquinoline (281b) (30%) which formed yellow crystals, m.p. 182-184° (from ethanol), \( \nu_{\text{max}} \) 1604 (N=C) cm\(^{-1}\), \( \delta_H (\text{CDCl}_3) \) 8.13-7.96 (3H, m, ArH), 7.63-7.24 (6H, m, ArH), and 5.48 (2H, s, CH\(_2\)).

Final elution with methanol gave an intractable brown gum which was not investigated further.

(b) Repetition of the reaction described in (a) before under reflux for 17h followed by flash-chromatography of the product in hexane-ether over silica gave 1-benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dibromide (280b) as a yellow solid (0.58 g; 78%), m.p. 57-59°, identified by comparison (m.p. and i.r.
spectrum) with a sample prepared previously, followed by 3-benzyl-5-bromo-
1H-[1,2,3]triazolo[4,5-c]isoquinoline (281b) as a yellow solid (0.15 g; 24%),
m.p. 178-180°, identical (m.p. and i.r. spectrum) to a sample prepared
previously.

(c) Repetition of the reaction described in (a) before using five equivalents
(0.01 mol) of aluminium tribromide followed by flash-chromatography of the
product in hexane-ether over silica gave 3-benzyl-5-bromo-1H-
[1,2,3]triazolo[4,5-c]isoquinoline (281b) as a yellow solid (0.25 g; 37%), m.p. 172-175°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(d) Repetition of the reaction described in (a) before using five equivalents
of aluminium tribromide (0.01 mol) at room temperature for 4h followed by
flash-chromatography of the product in hexane-ether over silica gave 1-
benzyl-4-phenyl-1H-1,2,3-triazole-5-isocyanide dibromide (280b) as a yellow
solid (0.66 g; 79%), m.p. 56-59°, identified by comparison (m.p. and i.r.
spectrum) with a sample prepared previously, followed by 3-benzyl-5-bromo-
1H-[1,2,3] triazolo[4,5-c]isoquinoline (281b) as a yellow solid (0.08 g; 12%),
m.p. 176-179°, identified by comparison (m.p. and i.r. spectrum) with a
sample prepared previously.

3-Benzyl-1H-[1,2,3]triazolo[4,5-c]isoquinolin-5(4H)-one (282)

A solution of 3-benzyl-5-bromo-1H-[1,2,3]triazolo[4,5-c]isoquinoline
(281b) (0.34 g; 0.001 mol) in dioxane (5.0 ml) was treated with 40% w/v
aqueous benzyltrimethylammonium hydroxide solution (1.7 ml; 0.004 mol)
and the mixture was stirred and heated under reflux for 2h.

The cooled mixture was rotary evaporated to give a gum which was
treated with water (5.0 ml) and the mixture was acidified with 2 M aqueous
hydrochloric acid solution. Filtration afforded 3-benzyl-1H-[1,2,3]triazolo[4,5-
c)isoquinolin-5(4H)-one (282) which formed light brown plates, m.p. 286-289° [from glacial acetic acid-water (2:1)], $\nu_{\text{max}}$ 3403-3129 (br) (NH) and 1667 (C=O) cm$^{-1}$, $\delta_{\text{H}}[(\text{CD}_3)\text{SO}]$ 11.12(1H, bs, NH) (exch), 7.97.32(9H, m, ArH), and 5.76(2H, s, CH$_2$).
Table 14: Analytical and Mass Spectroscopic Data

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*a*, molecular ions obtained by Electron Impact mass spectroscopy or, for values in parentheses, obtained by Fast Atom Bombardment mass spectroscopy.
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* a, molecular ions obtained by Electron Impact mass spectroscopy or, for values in parentheses, obtained by Fast Atom Bombardment mass spectroscopy.
Table 14 (continued): Analytical and Mass Spectroscopic Data

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a, molecular ions obtained by Electron Impact mass spectroscopy or, for values in parentheses, obtained by Fast Atom Bombardment mass spectroscopy.
CHAPTER 4

INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF ALKENYLARYL ISOCYANIDES AND ARALKYL ISOCYANIDES AND THEIR DIHALIDE DERIVATIVES
(i) Lewis Acid.

(Ar = Aromatic or heteroaromatic nucleus)
(R = H, Cl, Br)

Scheme 76
4.1 INTRODUCTION

Chapters 2 and 3 of this thesis have described investigations on the synthesis of five-, six- and seven-membered rings by the Lewis acid promoted cyclisation reactions of isocyanides and isocyanide dihalides with proximate aromatic rings, processes which can be regarded as being analogous to the intramolecular Friedel-Crafts acylation of aromatic rings. However, the Friedel-Crafts acylation of olefins is also a well known reaction and it was anticipated that this analogy could be extended to the reaction of isocyanides and isocyanide dihalides with carbon-carbon double bonds, as outlined in Scheme 76. It was envisaged that from the appropriate cis- or trans- isocyanodiarlylalkene starting materials (284) the 3-substituted indole derivatives (286; R = H) or 3-substituted quinoline derivatives (287; R = H) could be obtained depending on which terminus of the olefinic bond is the preferred site for reaction. In addition it was anticipated that the tricyclic azocine derivatives (288; R = H) might be accessible by cyclisation of the cis-isocyanodiarlylalkenes (284), although such a cyclisation of the trans- isomers can be ruled out on steric grounds. Similarly the synthetically useful 2-halogenoindole (286; R = Cl, Br), 2-halogenoquinoline (287; R = Cl,Br), and 6-halogenoazocine (288; R = Cl, Br) derivatives could be anticipated as possible products of the cyclisation of the appropriate diarylalkyl isocyanide dihalides (285) (X = Cl,Br).

A further extension of the present studies on the cyclisation reactions of isocyanides and isocyanide dihalides involved the application of such processes to aralkyl derivatives, which it was hoped would allow access to a
(i) (Ph₃PCH₂Ph)⁺Cl⁻, NaOMe, MeOH, reflux.
(ii) 15% aq. TiCl₃, tetrahydrofuran, room temp.

Scheme 77
A wide range of benzo-fused heterocycles containing varying degrees of saturation in the newly formed heterocyclic ring. Such processes would not only be of interest in terms of their potential for the synthesis of a wide variety of otherwise difficultly accessible heterocycles but also in terms of the reactivity towards electrophilic cyclisation of the aralkyl derivatives in comparison with their aromatic counterparts.

4.2 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETERO CYCLISATION REACTIONS OF 2-(2-PHENYLETHENYL)PHENYL ISOCYANIDES AND 2-(2-PHENYLETHENYL)PHENYL ISOCYANIDE DIHALIDES AND RELATED COMPOUNDS

The most readily available substrate for investigations on the Lewis acid promoted intramolecular reactions of isocyanide and isocyanide dihalide substituents with carbon-carbon double bonds is (Scheme 76) 2-(phenylethenyl)phenyl isocyanide (284; Ar = benzene). The aim of these investigations is the evaluation of the potential for such reactivity and ultimately its exploitation to provide a synthetic route to unusual and synthetically useful heterocycles.

The Wittig reaction (Scheme 77) of 2-nitrobenzaldehyde (289) with benzyltriphenylphosphonium chloride in the presence of sodium methoxide, as previously described\textsuperscript{171} by Dwyer, gave the nitrostilbene (290) in excellent yield (96%) as an inseparable mixture of cis- and trans- isomers. Selective reduction of the nitro group in (290) with a ten-fold excess of titanium trichloride at room temperature, as previously described,\textsuperscript{171} gave 2-aminostilbene (68%) as a 1:1 mixture of trans- (291) and cis- (292) isomers which was readily separated by careful flash-chromatography. Initially, it was decided to investigate the trans-isocyanide (294), and this compound was
(i) 98-100% HCO₂H, reflux.
(ii) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(iii) TiCl₄, CH₂Cl₂, -10°.
(iv) TiCl₄, CH₂Cl₂, reflux.
(v) SnCl₄, CH₂Cl₂, -10°.
(vi) SnCl₄, CH₂Cl₂, -78°.
(vii) SO₂Cl₂, CH₂Cl₂, -10°.
(viii) Br₂, CH₂Cl₂, -10°.
(ix) TiCl₄, CH₂Cl₂, reflux.
(x) ZnCl₂, CH₂Cl₂, reflux
(xi) AlBr₃, CH₂Cl₂, reflux.

Scheme 75
prepared as shown in Scheme 78. Reaction of the trans-aminostilbene (291) with refluxing formic acid gave the formamide (293) in high yield (94%) and this was subsequently converted into the isocyanide (294) (73%) by dehydration with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. This compound was isolated as an extremely soluble, low-melting solid whose analytical and spectroscopic properties were fully confirmative of its assigned structure. The Lewis acid promoted cyclisation reactions of the isocyanide (284) were then investigated in the expectation of its conversion into the substituted indole (296a) or quinoline (297a) derivatives. Reaction of the isocyanide (294) with five equivalents of titanium tetrachloride in methylene chloride at -10°C disappointingly failed to yield either of the two possible cyclised products (296a) or (297a). Instead, only a good yield (85%) of the formamide (293) was obtained. Repetition of this reaction under reflux in methylene chloride likewise gave the formamide (293) in high yield (81%) together with a small amount (0.06 g) of a solid product which, due to its extremely low yield, could not be identified.

The isolation of the formamide (293) as the only product of the attempted Lewis acid promoted cyclisation of the trans-isocyanide (294) suggests that complexation of the titanium tetrachloride to the isocyano group in (294) is occurring and that the failure of the reaction is due to the inability of the double bond to effect ring closure. In accord with this suggestion, exposure of the isocyanide (294) to the hydrolytic conditions which prevail in the work-up (i.e. saturated aqueous sodium bicarbonate solution at room temperature) returned the starting material (294) unchanged in 95% yield, confirming that the formamide (293) must be formed by the hydrolysis of the coordinated rather than the free isocyanide. Attempts to overcome this lack of reactivity by increasing the electrophilicity of the coordinated species by the reaction of the isocyanide (294) with the stronger Lewis acid stannic chloride
in methylene chloride either at -10° or at -78° were unsuccessful. These reactions gave high yields of polymeric products which proved to be unresolvable by t.l.c. or flash-chromatography and which could not be crystallised.

In view of the inability of the isocyanide (294) to furnish any cyclised products on reaction with Lewis acids, attention was next turned to its more reactive isocyanide dihalide derivatives. Thus (Scheme 78) reaction of the isocyanide (294) with sulphuryl chloride in methylene chloride at -10° gave the isocyanide dichloride (295a) (100%) as an unstable oil which was characterised by high resolution mass spectrometry. The proton n.m.r. spectrum of this compound showed the correct number of aromatic and olefinic protons, indicating that no chlorination of the double bond had occurred. Unfortunately however, reaction of the isocyanide dichloride (295a) with two equivalents of titanium tetrachloride in refluxing methylene chloride failed to furnish the hoped for ring closed products (296b) or (297b), giving instead an intractable gum which was not further investigated. It was reasoned that the use of a weaker Lewis acid might avoid the decomposition associated with titanium tetrachloride, and indeed reaction of the isocyanide dichloride (295a) with two equivalents of zinc chloride in refluxing methylene chloride proceeded much more cleanly. Unfortunately however, no cyclisation was observed and the only product isolated was the unchanged isocyanide dichloride (295a), in near quantitative yield (96%).

Due to the lack of cyclisation observed with the isocyanide dichloride (295a) the more electrophilic isocyanide dibromide (295b) was next investigated. This compound was prepared in quantitative yield by the reaction of the isocyanide (294) with bromine in methylene chloride at -10°, and its proton n.m.r. spectrum indicated that no competing bromination of the double bond had taken place during the reaction. Unfortunately, reaction of
Scheme 79

(i) 98-100% HCO₂H, reflux.
(ii) Ph₃P, CCl₄, Br₃N, Cl(CH₂)₂Cl, 60°.
(iii) TiCl₄, CH₂Cl₂, -10°.
(iv) Br₂, CH₂Cl₂, -10°.
(v) SO₂Cl₂, CH₂Cl₂, -10°.
(vi) AlBr₃, CH₂Cl₂, reflux.
(vii) ZnCl₂, CH₂Cl₂, reflux.
(viii) NaOH, H₂O, 1,2-dimethoxyethane, reflux.
(ix) piperidine, NaH, DMF, 100°.
the isocyanide dibromide (295b) with two equivalents of aluminium tribromide under reflux in methylene chloride gave only an intractable foam from which no identifiable material could be obtained.

The failure of the isocyanide (294) or either of the isocyanide dihalides (295a) or (295b) to undergo cyclisation to any of the possible cyclic products (296 a-c) or (297 a-c) on treatment with Lewis acids may be attributed to one or other of two factors; either the double bond in the isocyanide (294) and the isocyanide dihalides (295a) and (295b) is not sufficiently nucleophilic to effect ring closure, or steric factors in the coordinated intermediates may be inhibiting cyclisation. However, these possible inhibitory factors could only be demonstrated and circumvented by further studies involving the investigation of substrates containing more highly activated and less sterically encumbered double bonds respectively.

The anticipated potential (Scheme 79) of the cis-(phenylethenyl)phenyl isocyanide (299) and the corresponding isocyanide dihalides (301a) and (301b) to furnish the dibenz[b,f]azocine derivatives (300) and (302 a and b), in addition to the indole (296 a-c) and quinoline (297 a-c) derivatives, stimulated the investigation of their Lewis acid promoted cyclisation reactions. Reaction (Scheme 79) of the cis-aminostilbene (292) with formic acid under reflux gave the formamide (298) in high yield (81%), and this was converted into the isocyanide (299) in similarly good yield (86%) by the standard dehydration protocol. The latter compound was isolated as an oil which was found to be stable to distillation but prone to decomposition upon prolonged storage.

Reaction of the isocyanide (299) with five equivalents of titanium tetrachloride in methylene chloride at -10° failed to give the anticipated dibenzazocine (300) or either of the indole (296a) or quinoline (297a) derivatives. Instead this reaction afforded a poor yield (38%) of the formamide
with the remainder of the material making up a complex mixture which could not be separated by flash-chromatography or preparative t.l.c. The failure of the isocyanide (299) to undergo cyclisation at the aromatic ring is disappointing but perhaps not surprising in view of the lack of any activation of this ring by electron-donating groups. The lack of any cyclised products derived from reaction of the isocyanide (299) at the double bond indicates that this bond is either not sufficiently nucleophilic or cannot effect ring closure due to steric factors.

Attention was next turned to the cis-isocyanide dibromide (301a), which was prepared in quantitative yield by the low temperature reaction of the isocyanide (299) with one equivalent of bromine in methylene chloride, and was characterised by high resolution mass spectrometry. The proton n.m.r. spectrum of this product showed two one proton doublets centred at δ6.68 and δ6.39 corresponding to the protons of the olefinic side-chain, thus confirming that no bromination of the double bond had occurred. Disappointingly however, reaction of the isocyanide dibromide (301a) with two equivalents of aluminium tribromide under reflux in methylene chloride gave only a complex mixture which proved inseparable by chromatography and which showed no evidence for the formation of any cyclised products.

It was suspected that the failure of the isocyanide dibromide (301a) to undergo cyclisation was due to the extremely strong Lewis acid employed, which may be causing unwanted side reactions by interaction with the C-C double bond. It was therefore anticipated that the use of a weaker Lewis acid would circumvent this problem. Accordingly, reaction of the isocyanide (299) with sulphuryl chloride gave the isocyanide dichloride (301b) in quantitative yield, and it was pleasing to find that on reaction of this substrate with two equivalents of zinc chloride in refluxing methylene chloride the chlorodibenzazocine (302b) was produced in excellent yield (88%), together
with a small amount (0.03 g) of a high melting solid which remains unidentified. The dibenzazocine derivative (302b) was found to be rather moisture sensitive and consequently a satisfactory combustion analysis could not be obtained for this product. However, the structure of the dibenzazocine (302b) was confirmed by high resolution mass spectrometry and by its proton n.m.r. spectrum. The latter showed a distorted pair of one proton doublets centred at δ6.84 and δ6.76 respectively, corresponding to an AB system attributable to the protons at positions 11 and 12.

The sensitivity of the chlorodibenzazocine (302b) to atmospheric moisture suggested that the chlorine atom in this compound would prove reactive towards nucleophilic displacement. This was confirmed by its hydrolysis to the known dibenzazocinone (303) in high yield (79%) in aqueous sodium hydroxide solution. The successful preparation of the dibenzazocinone (303) further confirms the assigned structure of the chlorodibenzazocine (302b). Introduction of an amino substituent at the 6-position was attempted by the reaction of the chlorodibenzazocine (302b) with sodium piperidide in DMF at 100°. Unfortunately however, this reaction failed to produce the desired amino product (304) and gave only a 72% yield of the dibenzazocinone (303), whose formation is attributed to traces of water present in the piperidine which was not purified or dried prior to use.

The isolation of the chlorodibenzazocine (302b) in such a high yield is a pleasing result as dibenz[b,f]azocines in general are not readily accessible by other means. The most commonly used route to this ring system is the Beckmann rearrangement of dibenzocyclohepten-5-one oxime derivatives using polyphosphoric acid or phosphorus pentachloride. In addition, 6-substituted dibenz[b,f]azocines can be prepared, although in low yields, by the photolysis or thermolysis of appropriately substituted 5-azidodibenzocycloheptene derivatives via a Schmidt type ring expansion.
process. It is apparent however, that the Lewis acid promoted cyclisation of
the isocyanide dichloride (291b) to give the chlorodibenzazocine (302b) is
superior to either of these procedures in terms of its simplicity, anticipated
general applicability, and the direct production of a synthetically useful
product. The development of a synthetic route to dibenzazocines in general
would be of value as many of these compounds are of considerable interest
due to their biological activity\textsuperscript{178,179} and their ability to furnish stable 10\pi
electron dianions.\textsuperscript{180}

The failure of the zinc chloride promoted reaction of the isocyanide
dichloride (301b) to produce either of the other two possible cyclisation
products, the chloroindole (296b) or the chloroquinoline (297b), was slightly
surprising in light of an analogous reaction reported by Hunziker et al.\textsuperscript{181} This
involved the aluminium trichloride promoted cyclisation of cis-2(2-
phenylethenyl)phenyl isocyanate to give 3-benzylidene indolone, by reaction
of the isocyanate group with the olefinic bond. However, the greater steric
demands of the isocyanide dichloride group compared to the isocyanate
group may inhibit cyclisation of the former by restricting its approach to the
already crowded double bond. It would appear that, at least in the case of cis-
and trans-2(2-phenylethenyl)phenyl isocyanides and the corresponding
isocyanide dihalides, Lewis acid promoted interaction with a C-C double bond
does not occur readily, although further work will be necessary to assess the
potential of this type of cyclisation in other substrates.

Although Hunziker et al.\textsuperscript{81} failed to prepare the dibenzazocinone (303)
by cyclisation of cis-2(2-phenylethenyl)phenyl isocyanate, they did
successfully achieve the aluminium trichloride promoted cyclisation of 2(2-
phenylethyl)phenyl isocyanate to give 11,12-dihydrodibenz[b,f]azocinone.
This observation, taken in conjunction with the successful preparation of the
chlorodibenzazocine (302b) by the Lewis acid promoted cyclisation of the cis-
(i) H₂, 10% Pd·C, EtOH, room temp.
(ii) 98-100% HCO₂H, reflux.
(iii) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(iv) Br₂, CH₂Cl₂, -10°.
(v) SO₂Cl₂, CH₂Cl₂, -10°.
(vi) AlBr₃, CH₂Cl₂, reflux (X = Br).
(vii) AlCl₃, CH₂Cl₂, reflux (X = Cl).
(viii) AlBr₃, piperidine, CH₂Cl₂, reflux.

Scheme 50
isocyanide dichloride (301b) immediately suggested (Scheme 80) that the corresponding 6-halogenodihydridobenzazocines (309a) and (309b) might be accessible by cyclisation of the 2-(2-phenylethyl)phenyl isocyanide dihalide derivatives (308a) and (308b).

The preparation of the required isocyanide (307) is outlined in Scheme 80. Reduction of both the nitro group and the double bond in the nitrostilbene (290) by catalytic hydrogenation gave the aminodiphenylethane (305) in quantitative yield. Reaction of this compound with refluxing formic acid afforded the formamide (306) also in excellent yield (98%), and this was subsequently converted into the isocyanide (307) (81%) by dehydration with triphenylphosphine and carbon tetrachloride in the presence of triethylamine. Reaction of the isocyanide (307) with bromine in methylene chloride at -10° then gave the desired isocyanide dibromide (308a) in quantitative yield. Cyclisation of the isocyanide dibromide (308a) was first attempted by its reaction with two equivalents of aluminium tribromide under reflux in methylene chloride, but these conditions failed to give the anticipated bromodihydridobenzazocine (309a) and instead afforded a moderate yield (46%) of the known dihydridobenzazocinone (311). The disappointingly low yield of this product is probably due to loss of material during chromatography, as the lactam (311) is invisible on t.l.c. even after staining of the plate with iodine. The azocinone (311) is clearly arising from the hydrolysis of the expected initial bromo product (309a) during work-up with aqueous alkali. It was therefore decided to attempt to trap the bromoazocine (309a) with a nucleophilic reagent prior to the hydrolytic work-up. Thus the cyclisation reaction mixture was treated with an excess of anhydrous ethanol and this mixture was heated under reflux for 2h before treatment with aqueous sodium bicarbonate solution. Unfortunately, these conditions failed to give the desired ethoxyazocine derivative (309c), affording instead a poor yield (15%)
of the azocinone (311) together with a complex mixture which proved inseparable by chromatography. More successful however was the reaction of the isocyanide dibromide (308a) with aluminium tribromide followed by an excess of piperidine. These conditions gave the 6-piperidinoazocine (310) in an overall yield of 61% for the one-pot three-step reaction. The structure of this compound was fully confirmed by its analytical and spectroscopic properties. An attempt to extend this type of procedure to the preparation of the 6-cyanodibenzazocine derivative (309d) by quenching the reaction mixture with an excess of tetraethylammonium cyanide was unsuccessful, giving only a complex mixture from which no identifiable material could be obtained.

As a result of the inability to isolate the bromoazocine (309a) and the difficulty encountered in trapping this compound with nucleophilic reagents, it was decided to investigate the cyclisation of the isocyanide dichloride (308b). It was hoped that the chloroazocine product (309b), as a result of its lower reactivity towards nucleophilic displacement, would be stable to the hydrolytic work-up conditions. Thus (Scheme 80) reaction of the isocyanide (307) with one equivalent of sulphuryl chloride in methylene chloride at -10°C predictably gave the isocyanide dichloride (308b) in quantitative yield. Reaction of this compound with two equivalents of aluminium trichloride under reflux in methylene chloride failed to give the chlorodibenzazocine (309b), and again only the azocinone (311) (56% crude yield) was obtained.

The successful cyclisation of the phenylethyl isocyanide dibromide (308a) using aluminium tribromide contrasts with the failure of the phenylethenyl isocyanide dibromides (295b) and (301a) to react under similar conditions, and this suggests that the C-C double bond may be exerting an inhibitory effect on the reaction. Although the origin of this inhibitory effect is not clear it may be due to interaction of the double bond with the Lewis acid...
(i) NaH, PhCH=CHCH₂Br, DMF, 100°.
(ii) 15% aq. TiCl₃, tetrahydrofuran, room temp.
(iii) Na₂SO₄, EtOH, H₂O, reflux.
(iv) NaH, PhCH=CHCH₂Br, DMF, 100°.
(v) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°.
(vi) TiCl₄, CH₂Cl₂, -10°.

Scheme 31
or steric constraints imposed on the molecule by the presence of the double bond.

Although neither of the 6-halogenodihydrodibenzazocines (309a) or (309b) could be isolated, it is probable that quenching of the cyclisation reaction with the appropriate nucleophiles could provide access to a variety of 6-substituted dihydrodibenzazocines, in an analogous manner to the preparation of the 6-piperidino derivative (310). In addition, the cyclisation of 2-(2-phenylethyl)phenyl isocyanide dihalide derivatives should allow access to a range of ring substituted dihydrodibenzazocines and of heteroaromatic dihydrodibenzazocine derivatives by variation of the nature and substitution of the aromatic rings in the starting materials. The extension of the scope of the cyclisation of 2-(2-phenylethyl)phenyl isocyanide dihalide derivatives would be of considerable interest because, as previously discussed, the available general routes to the dibenz[b,f]azocine ring system are relatively few. 11,12-Dihydrodibenz[b,f]azocines, like their unsaturated counterparts, are generally prepared the Beckmann rearrangement of the corresponding dibenzocycloheptan-5-one oxime derivatives. The 11,12-dihydrodibenzazocines in general are of considerable interest as many of their 5,6-dihydro derivatives have shown promising biological activity as anticonvulsant, antihypertensive, psychotropic, analgesic and antiallergic agents.

4.3 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF 2-{1-PHENYLPROP-1-EN-3-YLOXYPHENYL} ISOXYANIDE AND 2-{1-PHENYLPROP-1-EN-3-YLOXYPHENYL} ISOXYANIDE DIHALIDES
It was next decided to investigate possible cyclisation reactions of isocyanides and isocyanide dihalides involving an allylic double bond. It was hoped that the latter might be more reactive than a normal olefinic bond and, due to its greater conformational freedom, would be free of the steric constraints which apply to the alkenylaryl structures described in Section 4.2. In this context (Scheme 81) the propenyloxyphenyl isocyanide (317) was chosen for study.

Reaction (Scheme 81) of the anion of 2-nitrophenol (312) with cinnamyl bromide in DMF at 100° gave the known nitrophenyl allyl ether (313) in excellent yield (95%), a considerable improvement on the published yield (73%) of this compound. Unfortunately, reduction of the nitro compound (313) to the corresponding amine (314) proved to be unexpectedly troublesome. Thus the attempted reduction of the nitro compound (313) with ten equivalents of titanium trichloride in aqueous THF at room temperature gave a multicomponent mixture which could not be separated by flash-chromatography. Correspondingly, reduction with sodium dithionite in aqueous ethanol under reflux gave only a poor yield (22%) of the desired amine (314) together with the unchanged starting material (313), isolated in 20% yield. The amine (314) has been reported previously as the product of the prolonged heating of the nitro compound (313) under reflux with iron in acetic acid. However, the severity and low yields of these conditions coupled with the difficulty encountered using titanium trichloride or sodium dithionite as the reducing agent prompted the search for an alternative strategy for the preparation of the isocyanide (317). Accordingly, 2-formamidophenol (315) was prepared in 76% yield by the reaction of 2-aminophenol with formic acid as described by Bamberger, and was reacted with cinnamyl bromide in the presence of one equivalent of sodium hydride to give the formamidophenyl allyl ether (316) in high yield (81%). The previously undescribed isocyanide...
(i) Br₂, CH₂Cl₂, -10°C.
(ii) SO₂Cl₂, CH₂Cl₂, -10°C.
(iii) TiBr₄, CH₂Cl₂, reflux.
(iv) AlCl₃, CH₂Cl₂, room temp.
(v) TiCl₄, CH₂Cl₂, reflux.
(vi) TiCl₄, CH₂Cl₂, -10°C.
(vii) ZnCl₂, CH₂Cl₂, reflux.

Scheme S2
(317) was then obtained in good yield (76%), accompanied by a small amount of the unchanged starting material (316) (18%), by dehydration of the formamide (316) using triphenylphosphine and carbon tetrachloride in the presence of triethylamine.

The cyclisation of the isocyanide (317) could potentially lead to three products derived respectively from reaction with either terminus of the double bond or with the phenyl ring. The possibility of cyclisation involving the phenyl ring was discounted on the basis of the lack of electronic activation of this ring coupled with the difficulty of ring closure to give a 10-membered ring. Cyclisation involving the terminus of the C-C double bond closest to the ether oxygen atom was considered the most likely mode of reaction due to the formation of a stabilised benzylic cation upon cyclisation. The 1,5-benzoxazepine (319) was therefore anticipated as the reaction product, derived by ring closure followed by allylic rearrangement of the initially formed product (318). Disappointingly however, reaction of the isocyanide (317) with five equivalents of titanium tetrachloride in methylene chloride at -10\(^\circ\) gave only a complex mixture, flash-chromatography of which failed to yield any identifiable product. This result, in conjunction with the results described in Section 4.2 suggests that, at least with titanium tetrachloride as the Lewis acid, C-C double bonds in general are not sufficiently nucleophilic to participate in ring closure with coordinated isocyanides.

As a result of the failure to achieve the Lewis acid promoted cyclisation of the propenyloxyphenyl isocyanide (317) attention was next turned to the study of the analogous cyclisation reactions of the corresponding isocyanide dihalides. Thus (Scheme 82) reaction of the isocyanide (317) with one equivalent of bromine in methylene chloride at -10\(^\circ\) gave the isocyanide dibromide (320a) in quantitative yield as an unstable oil which was characterised by proton n.m.r. spectroscopy. This spectrum showed two one
proton double triplets centred at δ6.77 and δ6.35 corresponding to the two olefinic protons, and a two proton doublet at δ4.73 attributable to the allylic methylene group. These spectroscopic features confirmed that no bromination had occurred at the double bond or at the allylic position. Unfortunately, no molecular ion corresponding to the isocyanide dibromide (320a) could be detected under electron impact or fast atom bombardment mass spectroscopy conditions. Disappointingly however, the attempted reaction of the isocyanide dibromide (320a) with two equivalents of titanium tetrabromide in refluxing methylene chloride gave only a multicomponent oil which could not be resolved by flash-chromatography, with no evidence for the presence of the desired bromobenzoxazepine (321a).

It was suspected that the complex product mixture obtained in the attempted Lewis acid promoted cyclisation of the isocyanide dibromide (320a) may be due to competing complexation of the Lewis acid with the double bond or with the ether oxygen atom, and the consequent promotion of side reactions. Accordingly, the Lewis acid promoted cyclisation of the less reactive isocyanide dichloride (320b) was next investigated. Reaction (Scheme 82) of the isocyanide (317) with sulphuryl chloride in methylene chloride at -10°C gave the isocyanide dichloride (320b) in near quantitative yield (93%), and this product was readily characterised by high resolution mass spectrometry and its proton n.m.r. spectrum. The latter indicated that no chlorination had occurred at the double bond or at the allylic position. Reaction of the isocyanide dichloride (320b) with two equivalents of aluminium trichloride in methylene chloride at room temperature gave a complex mixture, flash-chromatography of which afforded only small amounts (0.03 g and 0.07 g) of two solid products which could not be crystallised and so remain unidentified. An attempt to circumvent the side reactions encountered using aluminium trichloride by reaction of the isocyanide
dichloride (320b) with the weaker Lewis acid titanium tetrachloride in refluxing methylene chloride was unsuccessful, giving, after chromatography, only small amounts (0.01 g and 0.06 g) of two unidentified solids. Carrying out the same reaction at -10°C resulted in no improvement. In a final attempt to prepare the chlorobenzoxazepine (321b) the isocyanide dichloride (320b) was heated under reflux in methylene chloride with two equivalents of zinc chloride, however this reaction likewise gave only an unresolvable mixture which showed no evidence for the presence of any cyclised products.

The foregoing results indicate that cyclisation reactions of isocyanides and isocyanide dihalides involving C-C double bonds are substantially more difficult than the corresponding reactions with aromatic rings. The failure of the allyloxyphenyl isocyanide (317) and allyloxyphenyl isocyanide dihalides (320a) and (320b) to undergo Lewis acid promoted cyclisation cannot however be taken as an indication that reaction with C-C double bonds in general is impossible, particularly in view of the potential interference by the allylic system. Further studies with less sensitive systems and more highly activated double bonds (e.g. enol ethers) will be necessary to provide a fuller understanding of the potential, or otherwise, of this type of cyclisation reaction.

4.4 INVESTIGATIONS OF THE LEWIS ACID PROMOTED HETEROCYCLISATION REACTIONS OF ARALKYL ISOCYANIDES AND ARALKYL ISOCYANIDE DIHALIDES

Although alkyl isocyanides have been the most thoroughly investigated of all isocyanides, there is no precedent for the Lewis acid promoted cyclisation of these compounds or their corresponding isocyanide dihalides. It was therefore of interest to attempt to extend the investigations of such cyclisation reactions to aralkyl isocyanides with a view to the preparation of
(i) 98-100% HCO$_2$H, reflux.
(ii) Ph$_3$P, CCl$_4$, Et$_3$N, Cl(CH$_2$)$_2$Cl, 60°.
(iii) TiCl$_4$, CH$_2$Cl$_2$, -10°.
(iv) TiCl$_4$, CH$_2$Cl$_2$, reflux.
(v) SO$_2$Cl$_2$, CH$_2$Cl$_2$, -10°.
(vi) Br$_2$, CH$_2$Cl$_2$, -10°.
(vii) AlCl$_3$, CH$_2$Cl$_2$, room temp. (X = Cl).
(viii) AlCl$_3$, CH$_2$Cl$_2$, reflux (X = Cl).
(ix) AlBr$_3$, CH$_2$Cl$_2$, reflux (X = Br).

Scheme 85
heterocycles containing a greater degree of unsaturation than could be attained by cyclisation of the purely aryl isocyanides. Such an investigation would not only greatly increase the scope of such cyclisation reactions but would also be expected to yield further information regarding the reactivity differences between alkyl and aryl isocyanides.

The first substrate chosen for study (Scheme 83) was 3-methoxybenzyl isocyanide (324), whose Lewis acid promoted cyclisation it was hoped would lead to 5-methoxyisoindole (326), derived from the first formed 5-methoxyisoindolenine (325) by tautomerisation. The development of a synthetic route to isoindoles is of considerable interest as the chemistry of these unusual and interesting compounds has yet to be fully investigated, largely due to the lack of suitable synthetic methods for isoindoles in general. Although a number of synthetic routes to isoindoles are currently available most of them rely on rather harsh and hence impractical reaction conditions, and in addition they are generally only applicable to the preparation of N-substituted isoindoles. It was therefore anticipated that the Lewis acid promoted cyclisation of appropriately substituted benzyl isocyanides could provide a versatile synthetic route to nuclear substituted isoindoles.

Reaction (Scheme 83) of commercially available 3-methoxybenzylamine (322) with formic acid under reflux gave the formamide (323) in lower than expected yield (52%). In contrast, the subsequent dehydration of the formamide (323) with triphenylphosphine and carbon tetrachloride in the presence of triethylamine proceeded more efficiently to give the isocyanide (324) in good yield (82%). Despite being stable to distillation the isocyanide (324) was found to darken within minutes of isolation at room temperature, and consequently had to be characterised by high resolution mass spectrometry rather than combustion analysis. It was also found that the isocyanide (324) had an extremely penetrating, foul odour
which was not observed to nearly the same extent with the aromatic isocyanides described in Chapters 2 and 3. This undesirable feature appears to be characteristic of alkyl isocyanides and may be related to their volatility. Reaction of the isocyanide (324) with five equivalents of titanium tetrachloride in methylene chloride at -10° failed to give the desired isoindole (326). Instead this reaction gave a good yield (74%) of the formamide (323) as the only identifiable product. Similarly, the formamide (323) was obtained as the only product (77%) when the reaction was conducted under prolonged reflux in methylene chloride. It was not expected that the isoindole (326) would itself be isolated as the reaction product due to the well known instability of these compounds towards self-condensation and autoxidation. However, the isolation of the formamide (323) as the sole reaction product indicates that cyclisation has not occurred at all. The reason for this is not known, but is probably due to one or more of three factors. Firstly, the activation of the aromatic ring provided by the methoxy group may be insufficient to permit cyclisation. Also, in the isocyanide-titanium tetrachloride complex the N-C-Ti moiety is likely to be linear and so the strain involved in the cyclisation of such a species to give a five-membered ring may be too great. Finally, alkyl isocyanides may have a reduced electrophilicity compared to the aryl isocyanides as they cannot delocalise the negative charge of the isocyano carbon atom into an aromatic ring, and so nucleophilic attack on these compounds becomes more difficult. In view of these factors, attention was next turned to the corresponding isocyanide dihalides, the use of which was expected to have two distinct advantages over the isocyanides. Firstly, being more reactive the isocyanide dihalides should cyclise more readily and require less activation of the aromatic ring. Secondly, the 2-halogenoisouindole products should be more stable than the corresponding 2-unsubstituted compounds derived from isocyanides, as electron withdrawing groups at
positions 1 and 3 are known to stabilise the isoindole system.

In practice (Scheme 83), reaction of the isocyanide (324) with one equivalent of sulphuryl chloride in methylene chloride at -10°C gave the isocyanide dichloride (327a) in quantitative yield. Disappointingly however, attempted reaction of this compound with two equivalents of aluminium trichloride in methylene chloride at room temperature gave only a high recovery (94%) of the unchanged isocyanide dichloride (327a). Likewise reaction of the isocyanide dichloride (327a) with aluminium trichloride in refluxing methylene chloride failed to give the desired chloroisooindole (328b), and again the unreacted starting material (327a) was obtained in 94% yield. In an attempt to overcome the lack of reactivity of the isocyanide dichloride (327a), attention was next turned to the corresponding isocyanide dibromide (327b) which was prepared in quantitative yield by the low temperature reaction of the isocyanide (324) with one equivalent of bromine. Disappointingly however, attempted reaction of the isocyanide dibromide (327b) with two equivalents of aluminium tribromide under reflux in methylene chloride gave only an 81% recovery of the crude isocyanide dibromide (327b), with no evidence for the presence of the desired bromoisooindole (328b).

The lack of formation of any cyclised product from the foregoing reactions was disappointing and may be due to either insufficient activation of the aromatic ring or excessive strain involved in the formation of a five-membered ring. It would therefore be of interest to investigate the cyclisation reactions of benzyl isocyanides containing a more highly activated aromatic ring to determine which of these two factors governs the course of cyclisation. In any case it would be necessary to trap any isoindole product formed, probably by a Diels-Alder reaction with a dienophile such as maleic anhydride, as the isoindole itself would be too unstable for direct isolation and characterisation.
(i) 98-100% HCO₂H, reflux. 
(ii) Ph₃P, CCl₄, Et₃N, Cl(CH₂)₂Cl, 60°. a; Cl 
(iii) SO₂Cl₂, CH₂Cl₂, -10°. b; Br 
(iv) Br₂, CH₂Cl₂, -10°. 
(v) AlCl₃, CH₂Cl₂, reflux (X = Cl). 
(vi) AlBr₃, CH₂Cl₂, reflux (X = Br). 
(vii) AlBr₃, CH₂Cl₂, reflux then NaHCO₃, H₂O, CH₂Cl₂, reflux (X = Br). 
(viii) AlBr₃, CH₂Cl₂, reflux then Et₂NH, CH₂Cl₂, reflux (X = Br).
If the failure of the attempted Lewis acid promoted cyclisation reactions of benzyl isocyanides and benzyl isocyanide dihalides is due to the strain involved in the formation of a five-membered ring, then extension of the aliphatic carbon chain by one carbon atom would give a less sterically constrained substrate which should form a less strained six-membered ring. On the basis of this suggestion it was decided (Scheme 84) to investigate the Lewis acid promoted cyclisation of the \( \beta \)-phenylethyl isocyanide dihalides (332a) and (332b) in the expectation that these reactions would furnish the 1-halogenodihydroisoquinolines (333a) and (333b). It is evident that these compounds could be readily prepared by alternative routes, but the principal aim here was to assess the factors controlling the Lewis acid promoted cyclisation reactions of aralkyl isocyanide dihalides rather than the development of a synthetic route to 1-halogenodihydroisoquinolines. In view of their structural relationship to the benzyl isocyanide (324) previously discussed, the \( \beta \)-phenylethyl isocyanide dihalides (332a) and (332b) were deemed to be suitable substrates for this purpose. In a closely related procedure, substituted dihydroisoquinolines have been prepared by the chlorination of \( N \)-(2-phenylethyl)formamide and the corresponding C-substituted amides and the resulting imidoyl chlorides subjected to Lewis acid mediated cyclisation. Accordingly it was believed that cyclisation of the corresponding isocyanide dichloride (332a) could be effected with a Lewis acid to afford 1-chlorodihydroisoquinoline (333a).

In practice (Scheme 84) reaction of commercially available 2-phenylethylamine (329) with formic acid under reflux gave the known formamide (330) in low yield (42%), together with an 11% recovery of the amine (329). Dehydration of the formamide (330) with triphenylphosphine and carbon tetrachloride in the presence of triethylamine gave the desired isocyanide (331) in high yield (84%) as an unstable oil, which was
characterised by high resolution mass spectrometry along with its proton n.m.r. and i.r. spectra. As with the previously discussed methoxybenzyl isocyanide (324), this compound had an extremely strong, vile odour which made its isolation unpleasant and inconvenient in practice.

Chlorination of the isocyanide (331) using sulphuryl chloride at low temperature gave the isocyanide dichloride (332a) in quantitative yield and, on reaction with two equivalents of aluminium trichloride in refluxing methylene chloride, this afforded a low yield (36%) of the dihydroisoquinolone (334) as the only identifiable product. In contrast to early literature reports\textsuperscript{191,192} which describe this compound as a solid (m.p. 70-73\textdegree) it was isolated as a viscous oil after distillation, in keeping with a report by Lansbury et al\textsuperscript{193} who also could not obtain a crystalline sample of the dihydroisoquinolone (334). This product was characterised by high resolution mass spectrometry and by its proton n.m.r. spectrum. The latter shows a one proton singlet at 67.60-7.23 which disappears on shaking with deuterium oxide, thus allowing its assignment to the \(\text{N-H}\) proton. Also present was a triple doublet (\(J = 6\) and 3Hz) centred at 63.61 and a triplet (\(J = 6\text{Hz}\)) centred at 63.02 corresponding to the methylene groups at positions 3 and 4 respectively. On shaking with deuterium oxide the 3Hz coupling is removed leaving a triplet (\(J = 6\text{Hz}\)) centred at 63.60, thereby confirming the structure of the lactam (334).

As a result of the low yield of the lactam (334) obtained by cyclisation of the isocyanide dichloride (332a) attention was switched to the cyclisation of the corresponding isocyanide dibromide (332b), which was readily prepared in 97% yield by the reaction of the isocyanide (331) with bromine in methylene chloride at -10\textdegree. Reaction of the isocyanide dibromide (332b) with two equivalents of aluminium tribromide in refluxing methylene chloride gave an oil which yielded a waxy solid on distillation and was suspected to be the
bromodihydroisoquinoline (333b). Unfortunately however, due to its unreliable i.r., proton n.m.r., and mass spectra, this compound could not be unambiguously identified. Also obtained from this reaction was a second oil which was suspected to be the dihydroisoquinoline (334) but again, due to dubious spectroscopic data, a firm identification could not be made.

The lactam (334) is clearly arising by hydrolysis of the initially formed 2-halogenodihydroisoquinolines (333a) and (333b) during the aqueous alkaline work-up. It was therefore decided to attempt to obtain a true measure of the yield of the cyclisation by converting all of the initially formed bromo product (333b) into the lactam (334) by deliberate hydrolysis. Thus, reaction of the isocyanide dibromide (332b) with two equivalents of aluminium tribromide in methylene chloride under reflux gave a crude product mixture which was dissolved in methylene chloride and heated under reflux with an excess of saturated aqueous sodium bicarbonate solution. Unfortunately however, this procedure yielded only a complex oily mixture which could not be resolved by flash-chromatography, and showed no evidence for the presence of the lactam (334). In an alternative procedure the cyclisation reaction mixture was quenched with an excess of diethylamine in the hope that the bromo product (333b) would be converted into the corresponding 1-diethylamino-3,4-dihydroisoquinoline. Surprisingly however, the anticipated diethylamino product was not produced and the only product was the hitherto elusive bromodihydroisoquinoline (333b), obtained in low yield (32%) after chromatography then distillation. Due to its semi-solid nature and instability towards moisture a combustion analysis of this product was not obtained and its identity is based only on its mass and proton n.m.r. spectra. The former showed the two characteristic molecular ion peaks at 211 and 209 in a 1:1 ratio, whereas the latter contained a pair of two proton triplets at 83.64 and 83.02 corresponding to the methylene protons at positions 3 and 4.
respectively, with no evidence of an NH proton thus ruling out the presence of any hydrolysed species. This was not the case with the compound’s i.r. spectrum which contained a broad absorption at 3396 cm\(^{-1}\), indicating partial hydrolysis of the bromo compound (333b) by atmospheric moisture.

Although the formation of the bromodihydroisoquinoline (333b) was pleasing, the low yield was something of a disappointment. The reason for this low yield is unclear at present but may be due to one or more of three factors. Firstly, the flexibility of the side chain bearing the isocyano group may have an inhibitory effect on the reaction, or the absence of any electronic activation of the aromatic ring may make cyclisation difficult. In addition the reduced electrophilicity of the alkyl isocyanides may be a factor, and indeed the difficulty encountered in achieving efficient cyclisation of the \(\beta\)-phenylethyl isocyanide dihalides (332a) and (332b) compared to the facile cyclisation of the aromatic isocyanides described in Chapters 2 and 3 appears to confirm the difference in reactivity between the two classes of isocyanide. The successful cyclisation of the \(\beta\)-phenylethyl isocyanide dihalides (332a) and (332b) does at least demonstrate that the inability of the benzyl isocyanide (324) to cyclise to a five-membered ring is to a significant extent due to the strain involved in the formation of a ring of this size rather than the insufficient activation of the aromatic ring.

### 4.5 Experimental

#### General Experimental Details

For general experimental details, see Chapter 2; Section 2.9, page77.

#### Analytical and Mass Spectroscopic Data

For analytical and mass spectroscopic data, see Table 15, page 368.
Benzyltriphenylphosphonium Chloride

Benzyltriphenylphosphonium chloride was prepared by the reaction of benzyl chloride with triphenylphosphine as described by Dwyer,\textsuperscript{171} as a colourless solid (yield 96%), and had m.p. 330-333°C (lit.,\textsuperscript{194} 343-345°C).

1-Nitro-2-(2-phenylethenyl)benzene (290)

1-Nitro-2-(2-phenylethenyl)benzene (290) was prepared by the reaction of 2-nitrobenzaldehyde (289) with benzyltriphenylphosphonium chloride in the presence of sodium methoxide as described by Dwyer,\textsuperscript{171} as a yellow solid (yield 96%), and had m.p. 41-45°C (lit.,\textsuperscript{171} 49-61°C).

cis- and trans-1-Amino-2-(2-phenylethenyl)benzenes (291) and (292)

Reduction of 1-nitro-2-(2-phenylethenyl)benzene (290) with 15% w/w aqueous titanium trichloride solution as described by Dwyer,\textsuperscript{171} gave cis-1-amino-2-(2-phenylethenyl)benzene (292) as a yellow oil (yield 34%) and trans-1-amino-2-(2-phenylethenyl)benzene (291) as a colourless solid (yield 34%) which had m.p. 98-101°C (lit.,\textsuperscript{195} 101.5-102.5°C).

\(N\)-[2-(2-Phenylethenyl)phenyl]formamides (293) and (294)

A mixture of the corresponding 1-amino-2-(2-phenylethenyl)benzene (291) or (292) (3.9 g; 0.02 mol) and 98-100% formic acid was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h then worked up as described for the individual reactions below.

(i) \(trans-N\)-[2-(2-Phenylethenyl)phenyl]formamide (293)

The cooled mixture from \(trans\)-1-amino-2-(2-phenylethenyl)benzene (291) was rotary evaporated to give \(trans-N\)-[2-(2-phenylethenyl)phenyl]formamide (293) (4.2 g; 94%) which formed colourless plates, m.p. 138-139°C (from ethanol), \(v_{max}\) 3150 (NH) and 1690 (C=O) cm\(^{-1}\),
δ_H(CDCl_3) 8.43(1H, s, CHO), 8.30-8.00(1H, bs, NH)(exch), and 7.69-7.03 (11H, m, ArH and HC=CH).

(ii) cis-N-[2-(2-Phenylethenyl)phenyl]formamide (298)

The cooled mixture from cis-1-amino-2-(2-phenylethenyl)benzene (292) was rotary evaporated to give an oil which was dissolved in methylene chloride and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0ml). Rotary evaporation of the organic layer gave an oil which solidified on cooling to afford cis-N-[2-(2-phenylethenyl)phenyl]formamide (298) (3.6 g; 81%) which formed colourless needles, m.p. 96-97°C [from hexane-ethyl acetate (5:1)], v_max 3160 (NH) and 1680 (C=O) cm⁻¹, δ_H(CDCl_3) 8.47-8.15(1H, m, CHO), 7.39-7.06(9H, m, ArH), 6.77(1H, dd, J 12 and 2 Hz, alkene CH) and 6.53(1H, dd, J 12 and 2 Hz, alkene CH).

2-(2-Phenylethenyl)phenyl isocyanides (294) and (299)

A solution of the corresponding N-[2-(2-phenylethenyl)phenyl]formamide (293) or (298) (1.1 g; 0.005 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was treated with carbon tetrachloride (0.92 g; 0.006 mol) followed by triphenylphosphine (1.6 g; 0.006 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (1.0 g; 0.01 mol) was added and the mixture was stirred and heated at 60°C (oil bath), with exclusion of atmospheric moisture, for 2.5 h then worked up as described for the individual reactions described below.

(i) trans-2-(2-Phenylethenyl)phenyl isocyanide (294)

The cooled mixture from trans-N-[2-(2-phenylethenyl)phenyl]formamide (293) was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give a semi-solid which was triturated with ether to afford
triphenylphosphine oxide as a cream solid, m.p. 152-154° (lit., 126 152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave trans-2-(2-phenylethenyl)phenyl isocyanide (294) (73%) which formed colourless needles, m.p. 44-45° [from hexane-pentane (2:1)], νmax 2110 (N=C) cm⁻¹, δH(CDCI₃) 7.79-7.05(11H, m, ArH and HC=CH).

Final elution with methanol gave a brown gum whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

(ii) cis-2-(2-Phenylethenyl)phenyl isocyanide (299)

The cooled mixture from cis-N-[2-(2-phenylethenyl)phenyl]formamide (298) was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave cis-2-(2-phenylethenyl)phenyl isocyanide (298) (0.89 g; 86%) as an unstable yellow oil, b.p 100-110°/0.10-0.05 mmHg, νmax 2110 (N=C) cm⁻¹, δH(CDCI₃) 7.39-7.05(9H, m, ArH), 6.83(1H, d, J 12 Hz, alkene CH), and 6.67(1H, d, J 12 Hz, alkene CH).

Final elution with methanol gave a brown semi-solid whose t.l.c. in ether over silica showed it to be a complex mixture which therefore was not further investigated.

The Attempted Reaction of trans-2-(2-Phenylethenyl)phenyl isocyanide (294) with Titanium Tetrachloride in Methylene Chloride

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.41g;
0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at 0° (ice bath) with a solution of titanium tetrachloride (1.9 g; 1.1 ml; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10° or under reflux, under nitrogen, for 2-23h then worked up as described for the individual reactions below.

(i)  At -10° for 2h

The mixture was treated dropwise with 60% w/v aqueous sodium hydroxide solution (3.3 ml; 0.05 mol), diluted with water (20.0 ml), and filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave trans-N-[2-(2-phenylethenyl)phenyl]formamide (293) as a yellow-orange solid (85%), m.p. 125-128°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

(ii) Under reflux for 23h

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (9.0 ml; 0.01 mol) and extracted with methylene chloride to give a solid (0.46 g) which was flash-chromatographed over silica. Elution with hexane-ethyl acetate (9:1) gave a yellow solid (0.006 g), m.p. 75-81°, which was not investigated further.

Elution with hexane-ethyl acetate (7:3) gave trans-N-[2-(2-phenylethenyl)phenyl]formamide (293) as a yellow solid (0.36 g; 81%), m.p. 135-137°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave an intractable brown solid (0.10 g) which was not investigated further.
The Attempted Reaction of trans-2-(2-Phenylethenyl)phenyl isocyanide (294) with Aqueous Sodium Hydrogen Carbonate Solution

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.21 g; 0.001 mol) in anhydrous methylene chloride (10.0 ml) was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol) and the mixture was stirred at room temperature for 10 min.

The mixture was separated and the aqueous layer was extracted with methylene chloride to give unchanged trans-2-(2-phenylethenyl)phenyl isocyanide (294) as a light brown solid (0.20 g; 95%), m.p. 40-43°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

The Attempted Reaction of trans-2-(2-Phenylethenyl)phenyl isocyanide (294) with Stannic Chloride in Methylene Chloride

(a) With a reaction temperature of -10°

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.41 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of stannic chloride (2.6 g; 1.2 ml; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (61.0 ml; 0.08 mol), stirred at room temperature for 10 min, then filtered to remove tin residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a dark brown polymeric solid (0.38 g), m.p. 105-138°, whose t.l.c. in ether over silica showed it to be a complex mixture which was not investigated further.

(b) With a reaction temperature of -78°

Repetition of the reaction described in (a) before at -78° (solid CO₂-acetone bath) similarly gave a brown polymeric solid (0.46 g), m.p. 85-98°,
flash-chromatography of which over silica gave no identifiable material.

2-(2-Phenylethenyl)phenyl Isocyanide Dihalides (295a and b) and (301a and b)

A solution of the corresponding 2-(2-phenylethenyl)phenyl isocyanide (294) or (299) (0.20 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of sulphuryl chloride or bromine (0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) trans-2-(2-Phenylethenyl)phenyl Isocyanide Dichloride (295a)

The mixture from trans-2-(2-phenylethenyl)phenyl isocyanide (294) and sulphuryl chloride was rotary evaporated to give trans-2-(2-phenylethenyl)phenyl isocyanide dichloride (295a) as an orange oil (0.28 g; 100%), $\nu_{\text{max}}$ 1656 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.75-6.84(11H, m, ArH and HC=CH).

(ii) trans-2-(2-Phenylethenyl)phenyl Isocyanide Dibromide (295b)

The mixture from trans-2-(2-phenylethenyl)phenyl isocyanide (294) and bromine was rotary evaporated to give trans-2-(2-phenylethenyl)phenyl isocyanide dibromide (295b) as a brown oil (0.37 g; 100%), $\nu_{\text{max}}$ 1687 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.73-6.85(11H, m, ArH and HC=CH).

(iii) cis-2-(2-Phenylethenyl)phenyl Isocyanide Dibromide (301a)

The mixture from cis-2-(2-phenylethenyl)phenyl isocyanide (299) and bromine was rotary evaporated to give cis-2-(2-phenylethenyl)phenyl isocyanide dibromide (301a) as a brown oil (0.37 g; 100%), $\nu_{\text{max}}$ 1690 (N=C) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.47-6.84(9H, m, ArH ), 6.68(1H, d, J 12 Hz, alkene CH), and 6.39(1H, d, J 12 Hz, alkene CH).

(iv) cis-2-(2-Phenylethenyl)phenyl Isocyanide Dichloride (301b)

The mixture from cis-2-(2-phenylethenyl)phenyl isocyanide (299) and
sulphuryl chloride was rotary evaporated to give cis-2-(2-phenylethenyl)phenyl isocyanide dichloride (301b) as a dark brown oil (0.28 g; 100%), \( \nu_{\text{max}} \) 1652 (N=C) cm\(^{-1}\), \( \delta_{\text{p}}(\text{CDCl}_3) \) 7.44-6.86 (9H, m, ArH), 6.61 (1H, d, J 12 Hz, alkene CH), and 6.44 (1H, d, J 12 Hz, alkene CH).

The Attempted Reaction of trans-2-(2-Phenylethenyl)phenyl Isocyanide Dichloride (295a) with Titanium Tetrachloride in Methylene Chloride

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.41 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10\(^\circ\) (ice-acetone bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10\(^\circ\), under nitrogen, for 1h. A solution of titanium tetrachloride (0.76 g; 0.44 ml; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred and heated under reflux, under nitrogen, for 2h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a brown gum (0.55 g) whose t.l.c. in hexane-ether (2:1) over silica showed it to be a complex mixture, which therefore was not further investigated.

The Attempted Reaction of trans-2-(2-Phenylethenyl)phenyl Isocyanide Dichloride (295a) with Zinc Chloride in Methylene Chloride

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.41g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10\(^\circ\) (ice-acetone bath) with a solution of
sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of powdered zinc chloride (0.54 g; 0.004 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 22h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave unchanged trans-2-(2-phenylethenyl)phenyl isocyanide dichloride (295a) as a red-brown oil (0.53 g; 96%), identical [i.r. spectrum and t.l.c. in hexane-ether (2:1) over silica] to a sample prepared previously.

The Attempted Reaction of 2-(2-Phenylethenyl)phenyl isocyanide Dibromides (295b) and (301a) with Aluminium Tribromide in Methylene Chloride

(a) Using trans-2-(2-phenylethenyl)phenyl isocyanide dibromide (295b)

A solution of trans-2-(2-phenylethenyl)phenyl isocyanide (294) (0.82 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (2.1 g; 0.008 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature
for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a dark brown foam (0.74 g) whose t.l.c. in hexane-ether (2:1) over silica showed it to be a multicomponent mixture, which therefore was not further investigated.

(b) Using cis-2-(2-phenylethenyl)phenyl isocyanide dibromide (301a)

Repetition of the reaction described in (a) before using cis-2-(2-phenylethenyl)phenyl isocyanide dibromide (301a) and decreasing the reflux time to 1h gave a dark brown gum (0.61 g), flash-chromatography of which gave no identifiable material.

The Attempted Reaction of cis-2-(2-Phenylethenyl)phenyl Isocyanide (299) with Titanium Tetrachloride in Methylene Chloride

A solution of cis-2-(2-phenylethenyl)phenyl isocyanide (299) (0.41g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of titanium tetrachloride (1.9 g; 1.1 ml; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, then filtered to remove titanium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.44 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave unchanged cis-2-(2-phenylethenyl)phenyl isocyanide (299) as an orange-brown oil (0.06 g; 15%), identical [i.r.spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to a sample prepared previously.
Elution with hexane-ethyl acetate (9:1) then hexane-ethyl acetate (8:2) gave two complex oils (0.14 g) which were not further investigated.

Further elution with hexane-ethyl acetate (8:2) gave cis-N-[2-(2-phenylethenyl)phenyl]formamide (298) as a cream solid (0.17 g; 38%), m.p. 94-96°C, identical (m.p. and i.r. spectrum) to a sample prepared previously.

6-Chlorodibenz[b,f]azocine (302b)

A solution of cis-2-(2-phenylethenyl)phenyl isocyanide (299) (0.41 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-acetone bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1h. A suspension of powdered zinc chloride (0.54 g; 0.004 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 22h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.60 g) which was flash-chromatographed over silica.

Elution with hexane-ether (98:2) gave 6-chlorodibenz[b,f]azocine (302b) (0.42 g; 88%) which formed colourless plates, m.p. 96-98°C (from cyclohexane), \( \nu_{\text{max}} \) 1669 (N=C) cm\(^{-1}\), \( \delta_{\text{H}} \) (CDCl\(_3\)) 7.54-6.93(8H, m, ArH), 6.84(1H, d, J 12 Hz, alkene CH), and 6.76(1H, d, J 12 Hz, alkene CH).

Elution with hexane-ether (1:1) through ether to methanol gave a series of intractable mixtures (0.07 g) which were not investigated further.
A solution of 6-chlorodibenz[b,f]azocine (302b) (0.18 g; 0.00075 mol) in 1,2-dimethoxyethane (5.0 ml) was treated with 2 M aqueous sodium hydroxide solution (1.0 ml) and the mixture was stirred and heated under reflux for 3 h.

The cooled mixture was rotary evaporated to give a semi-solid which was treated with water (2.0 ml) then the mixture was acidified with 2 M aqueous hydrochloric acid solution and extracted with methylene chloride. Rotary evaporation of the organic extract gave dibenz[b,f]azocin-6(5H)-one (303) (0.13 g; 79%) which formed colourless plates, m.p. 265-266 °C (from glacial acetic acid) (lit., 174-263-264 °C), \( \delta_{\text{H}}[(\text{CD}_3)_2\text{SO}] \) 9.84(1H, s, NH), 7.34-7.08(8H, m, ArH), 7.00(1H, d, J 12 Hz, alkene CH), and 6.89(1H, d, J 12 Hz, alkene CH).

The Attempted Reaction of 6-Chlorodibenz[b,f]azocine (302b) with Sodium Piperidine in Dimethylformamide

A suspension of sodium hydride (0.026 g; 0.0011 mol) in anhydrous dimethylformamide (2.0 ml) was stirred and treated dropwise at 0 °C (ice bath) with a solution of piperidine (0.085 g; 0.001 mol) in anhydrous dimethylformamide (2.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 6-chlorodibenz[b,f]azocine (302b) (0.12 g; 0.0005 mol) in anhydrous dimethylformamide (2.0 ml) was added in one portion and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 2 h then at 100 °C (oil bath) for 3 h.

The cooled mixture was treated with water (2.0 ml) and rotary evaporated to give a solid which was treated with water (5.0 ml) and extracted with methylene chloride to give dibenz[b,f]azocin-6(5H)-one (303).
as a pale yellow solid (0.08 g; 72%), m.p. 249-253° (lit.,174 263-264°), identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

1-Amino-2-(2-phenylethyl)benzene (305)

A solution of 1-nitro-2-(2-phenylethyl)benzene (290) (11.3 g; 0.05 mol) in ethanol (250 ml) was hydrogenated over 10% palladium-on-charcoal (1.1 g) at room temperature and atmospheric pressure for 2 h, during which time hydrogen (4960 ml; 0.22 mol) was absorbed.

The mixture was filtered through celite and the filtrate was rotary evaporated to give 1-amino-2-(2-phenylethyl)benzene (305) as a brown oil (9.8 g; 100%), \( \nu_{\max} \) 3449, 3372, and 3217 (NH) cm\(^{-1}\).

N-[2-(2-Phenylethyl)phenyl]formamide (306)

A mixture of 1-amino-2-(2-phenylethyl)benzene (305) (4.9 g; 0.025 mol) and 98-100% formic acid (50.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3 h.

The cooled mixture was rotary evaporated to give \( N-[2-(2-\text{phenylethyl})\text{phenyl}]\text{formamide} \) (306) (5.5 g; 98%) which formed colourless needles, m.p. 104-105° (from cyclohexane), \( \nu_{\max} \) 3138 (NH) and 1701 (C=O) cm\(^{-1}\), \( \delta_H(CDCl_3) \) 8.31-8.16 (1H, m, CHO), 7.65 (1H, s, NH)(exch), 7.33-7.02 (9H, m, ArH), and 2.90 (4H, m, 2xCH\(_2\)).

2-(2-Phenylethyl)phenyl isocyanide (307)

A solution of \( N-[2-(2-\text{phenylethyl})\text{phenyl}]\text{formamide} \) (306) (2.3 g; 0.01 mol) in anhydrous 1,2-dichloroethane (30.0 ml) was treated with carbon tetrachloride (1.8 g; 0.012 mol) followed by triphenylphosphine (3.1 g; 0.012 mol) and the mixture was stirred at room temperature for 15 min.
Triethylamine (2.0 g; 0.02 mol) was added and the mixture was stirred and heated at 60°C (oil bath), with exclusion of atmospheric moisture, for 2.5 h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (15.0 ml) and extracted with methylene chloride to give an oil (7.1 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) gave 2-(2-phenylethyl)phenyl isocyanide (307) as an orange oil (1.7 g; 81%), $\nu_{\text{max}}$ 2119 (NC) cm$^{-1}$.

Elution with hexane-ether (8:2) gave unchanged N-[2-(2-phenylethyl)phenyl]formamide (306) as a colourless solid (0.27 g; 12%), m.p. 100-102°C, identical (m.p. and i.r. spectrum) to a sample prepared previously.

Final elution with methanol gave a complex brown gum (3.3 g) which was not investigated further.

2-(2-Phenylethyl)phenyl isocyanide Dihalides (308a) and (308b)

A solution of 2-(2-phenylethyl)phenyl isocyanide (307) (0.21 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of bromine or sulphuryl chloride (0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1 h then worked up as described for the individual reactions below.

(i) 2-(2-Phenylethyl)phenyl Isocyanide Dibromide (308a)

The mixture from reaction with bromine was rotary evaporated to give 2-(2-phenylethyl)phenyl isocyanide dibromide (308a) as a yellow oil (0.37 g; 100%), $\nu_{\text{max}}$ 1687 (N=C) cm$^{-1}$.

(ii) 2-(2-Phenylethyl)phenyl Isocyanide Dichloride (308b)

The mixture from reaction with sulphuryl chloride was rotary evaporated to give 2-(2-phenylethyl)phenyl isocyanide dichloride (308b) as a yellow oil (0.28 g; 100%), $\nu_{\text{max}}$ 1656 (N=C) cm$^{-1}$. 
**11.12-Dihydrodibenz[b,f]azocin-6(5H)-one (311)**

(a) A solution of 2-(2-phenylethyl)phenyl isocyanide (307) (0.83 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.64 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (2.1 g; 0.008 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a gum (1.2 g) which was flash-chromatographed over silica.

Elution with ether-ethyl acetate (6:4) gave 11,12-dihydrodibenz[b,f]azocin-6(5H)-one (311) (0.41 g; 46%) which formed colourless plates, m.p. 241-243° (from toluene) (lit., 182 240-243°), $\nu_{\text{max}}$ 3156(NH) and 1640 (C=O) cm$^{-1}$, $\delta_{n}[(CD_{3})_{2}SO]$ 9.79(1H, s, NH)(exch), 7.20-6.91(8H, m, ArH), and 3.34-3.33(4H, m, 2xCH$_{2}$).

Final elution with methanol gave an intractable brown gum (0.10 g) which was not investigated further.

(b) A solution of 2-(2-phenylethyl)phenyl isocyanide (307) (0.41 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of
anhydrous aluminium trichloride (0.53 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2 h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave crude 11,12-dihyrodibenz[b,f]azocin-6(5H)-one (311) as a yellow-orange oil (0.25 g; 56%), identified by comparison (i.r. spectrum and t.l.c. in ether over silica) with a sample prepared previously. No attempt was made to purify the crude product.

The Attempted Reaction of 2-(2-Phenylethyl)phenyl Isocyanide Dibromide (308a) with Aluminium Tribromide followed by Ethanol or Tetraethylammonium Cyanide

A solution of 2-(2-phenylethyl)phenyl isocyanide (307) (0.62 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10 °C (ice-acetone bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10 °C, under nitrogen, for 1 h. A solution of aluminium tribromide (1.6 g; 0.006 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2 h then quenched with ethanol or tetraethylammonium cyanide and worked up as described for the individual reactions below.

(i) Quenching with ethanol

The cooled mixture was treated portionwise with anhydrous ethanol (5.0 ml), and the mixture was stirred and heated under reflux, under nitrogen,
for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a gum (0.80 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) gave 11,12-dihydrodibenz[b,f]azocin-6(5H)-one (311) as a yellow solid (0.10 g; 15%), m.p. 236-239° (lit., 182 240-243°), identified by comparison (m.p. and i.r. spectrum with a sample prepared previously.

Elution with hexane-ethyl acetate (2:8) through ethyl acetate to methanol gave only multicomponent gums (0.45 g) which were not further investigated.

(ii) Quenching with tetraethylammonium cyanide

The cooled mixture was treated portionwise with a solution of tetraethylammonium cyanide (7.5 g; 0.048 mol) in anhydrous methylene chloride (30.0 ml) and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an intractable black gum (1.3 g) from which no identifiable material was obtained.

6-Piperidino-11,12-dihydrodibenz[b,f]azocine (310)

A solution of 2-(2-phenylethyl)phenyl isocyanide (307) (0.41g; 0.002
mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-acetone bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 2h. Piperidine (3.0 g; 0.035 mol) was then added in one portion and the mixture was stirred and heated under reflux, under nitrogen, for 4h. The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a semi-solid (1.6 g) which was flash-chromatographed over alumina.

Elution with hexane-ether (8:2) gave 6-piperidino-11,12-dihydrodibenz[b,f]azocine (310) (0.35 g; 61%) which formed pale yellow plates, m.p. 93-94° (from hexane), \( \nu_{\text{max}} \) 1609 (N=C) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.07-6.87(8H, m, ArH), 6.69-6.64(4H, m, 2xCH\(_2\)), 3.28-3.11(6H, m, 3xCH\(_2\)), and 2.89-2.67(4H, m, 2xCH\(_2\)).

Final elution with methanol gave an intractable brown gum (0.06g) which was not investigated further.

3-(2-Nitrophenoxyl)-1-phenylpropene (313)

A suspension of sodium hydride (2.7 g; 0.11 mol) in anhydrous dimethylformamide (12.5 ml) was stirred and treated dropwise at 0° (ice bath) with a solution of 2-nitrophenol (312) (13.9 g; 0.1 mol) in anhydrous dimethylformamide (12.5 ml) and the mixture was stirred at room temperature for 15 min. A solution of cinnamyl bromide (19.7 g; 0.1 mol) in anhydrous
dimethylformamide (25.0 ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with exclusion of atmospheric moisture, for 1h.

The cooled mixture was treated with water (25.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (100.0 ml) and extracted with methylene chloride to give an oil which solidified on cooling to afford 3-(2-nitrophenoxy)-1-phenylpropene (313) as a yellow solid (24.2 g; 95%), m.p. 63-66° (lit.,\(^{185}\) 72-73°).

The Attempted Reduction of 3-(2-Nitrophenoxy)-1-phenylpropene (313) with Titanium Trichloride in Aqueous Tetrahydrofuran

A solution of 3-(2-nitrophenoxy)-1-phenylpropene (313) (2.6 g; 0.01 mol) in tetrahydrofuran (100.0 ml) was stirred under nitrogen and treated in one portion with 15% w/v aqueous titanium trichloride solution (115.0 ml; 0.1 mol) and the mixture was stirred at room temperature, under nitrogen, for 20h.

Rotary evaporation of the mixture gave an oil. This was made basic with 50% w/v aqueous sodium hydroxide solution, diluted with water (100.0 ml), and extracted with methylene chloride to give an oil (1.5 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (98:2) through ethyl acetate to methanol gave only a series of multicomponent oils (1.5 g) from which no identifiable material was obtained.

3-(2-Aminophenoxy)-1-phenylpropene (314)

A solution of 3-(2-nitrophenoxy)-1-phenylpropene (313) (0.51 g; 0.002 mol) in 70% v/v aqueous ethanol (20.0 ml) was treated with sodium dithionite (0.51 g) and the mixture was stirred and heated under reflux for 1h. A further
portion of sodium dithionite (0.51 g) was added and stirring and heating under reflux were continued for a further 1h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.48 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (6:4) gave unchanged 3-(2-nitrophenoxy)-1-phenylpropene (313) as a yellow solid (0.10 g; 20%), m.p. 69-71° (lit.,185 72-73°), identical (m.p. and i.r. spectrum) to a sample prepared previously.

Elution with hexane-methylene chloride (2:8) gave 3-(2-aminophenoxy)-1-phenylpropene (314) as a colourless solid (0.10 g; 22%), m.p. 73-75° (lit.,186 75-76°).

Elution with methylene chloride-ethyl acetate (8:2) gave an intractable brown gum (0.07 g) which was not further investigated.

2-Formamidophenol (315)

2-Formamidophenol (315) was prepared by the reaction of 2-aminophenol with formic acid as described by Bamberger,187 as a brown solid (yield 76%), and had m.p. 121-125° (lit.,187 129-130°).

N-[2-(1-Phenylprop-1-en-3-yl)oxy]phenylformamide (316)

A suspension of sodium hydride (1.2 g; 0.05 mol) in anhydrous dimethylformamide (20.0 ml) was stirred and treated dropwise at -10° (ice-salt bath) with a solution of 2-formamidophenol (315) (6.9 g; 0.05 mol) in anhydrous dimethylformamide (75.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of cinnamyl bromide (9.9 g; 0.05 mol) in anhydrous dimethylformamide (20.0 ml) was added portionwise and the mixture was stirred and heated at 100° (oil bath), with exclusion of
The cooled mixture was treated with water (40.0 ml), stirred at room temperature for 15 min, then rotary evaporated to give an oil. This was treated with water (50.0 ml) and extracted with methylene chloride to give a semi-solid which was triturated with ether to afford a light brown solid. This was combined with further material, obtained by rotary evaporation of the ethereal mother liquor and flash-chromatography of the resulting residue in hexane-ethyl acetate (7:3) over silica, to afford N-[2-(1-phenylprop-1-en-3-yl)oxy]phenylformamide (316) (10.3 g; 81%) which formed colorless plates, m.p. 99-101° (from ethanol), $\nu_{\text{max}}$ 3340-3100 (br) (NH) and 1665 (C=O) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.45-8.32(1H, m, CHO), 8.00-7.60(1H, bs, NH), 7.48-6.84 (9H, m, ArH), 6.64-6.28(2H, m, HC=CH) and 4.73(2H, d, J 5 Hz, CH$_2$).

2-(1-Phenylprop-1-en-3-yl)oxyphenyl isocyanide (317)

A solution of N-[2-(1-phenylprop-1-en-3-yl)oxy]phenylformamide (316) (1.3 g; 0.005 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was treated with carbon tetrachloride (0.92 g; 0.006 mol) followed by triphenylphosphine (1.6g; 0.006 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (1.0 g; 0.01 mol) was added and the mixture was stirred and heated at 60° (oil bath) with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (4.0 g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) (0.89 g; 76%) which formed colourless crystals, m.p. 88-89° (from cyclohexane), $\nu_{\text{max}}$ 2110 (NC) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.45-7.22 (7H, m, ArH), 7.02-6.90(2H, m, ArH), 6.79(1H, d, J 16 Hz, alkene CH), 6.41 (1H, dt, J 16 and 6 Hz, alkene CH), and 4.81 (2H, dd, J 6Hz, CH$_2$).
Elution with hexane-ethyl acetate (7:3) gave unchanged $N$-[2-(1-phenylprop-1-en-3-yl)oxy]phenylformamide (316) as a brown solid (0.24 g; 18%), m.p. 94-97°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave triphenylphosphine oxide as a cream solid (1.4 g), m.p. 141-144° (lit. 126 152-153°), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of 2-(1-Phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) with Titanium Tetrachloride in Methylene Chloride

A solution of 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) (0.47 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (1.9 g; 1.1 ml; 0.01 mol) in anhydrous methylene chloride (10.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (9.0 ml; 0.01 mol) and extracted with methylene chloride to give a waxy solid (0.50 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) through ethyl acetate to methanol gave only a series of intractable gums and solids (0.28 g) from which no identifiable material was obtained.

2-(1-Phenylprop-1-en-3-yl)oxyphenyl isocyanide Dihalides (320a) and (320b)

A solution of 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) (0.47 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine or sulphuryl chloride (0.002 mol) in anhydrous methylene chloride.
(5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h then worked up as described for the individual reactions below.

(i) **2-(1-Phenylprop-1-en-3-yl)oxyphenyl Isocyanide Dibromide (320a)**

The mixture from reaction with bromine was rotary evaporated to give an oil which was flash-chromatographed over silica.

Elution with hexane-ether (8:2) gave 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide dibromide (320a) as a pale yellow oil (0.80 g; 100%), $\nu_{\text{max}} 1690 (\text{N=C}) \text{ cm}^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.52-6.93(9H, m, ArH), 6.77(1H, dt, J 16 and 1 Hz, alkene CH), 6.35(1H, dt, J 16 and 5 Hz, alkene CH), and 4.73(2H, dd, J 5 and 1 Hz, CH$_2$).

(ii) **2-(1-Phenylprop-1-en-3-yl)oxyphenyl Isocyanide Dichloride (320b)**

The mixture from reaction with sulphuryl chloride was rotary evaporated to give 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide dichloride (320b) (0.57 g; 93%) which formed grey needles, m.p. 63-64° (from hexane), $\nu_{\text{max}} 1660 (\text{N=C}) \text{ cm}^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.49-6.82(9H, m, ArH), 6.75(1H, dt, J 16 and 1 Hz, alkene CH), 6.35(1H, dt, J 16 and 5 Hz, alkene CH), and 4.73(2H, dd, J 5 and 1 Hz, CH$_2$).

The Attempted Reaction of 2-(1-Phenylprop-1-en-3-yl)oxyphenyl Isocyanide Dibromide (320a) with Titanium Tetrabromide in Methylene Chloride

A solution of 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) (0.47 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (solid CO$_2$-ethylene glycol bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A solution of titanium tetrabromide (1.5 g; 0.004 mol) in anhydrous methylene chloride (10.0 ml) was added dropwise and the mixture was stirred and heated under
reflux, under nitrogen, for 24h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.88 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (95:5) through ethyl acetate to methanol gave only a series of multicomponent oils, gums, and solids (0.63g) from which no identifiable material was obtained.

The Attempted Reaction of 2-(1-Phenylprop-1-en-3-yI)oxyphenyl isocyanide Dichloride (320b) with Aluminium Trichloride or Zinc Chloride in Methylen Chloride

A solution of 2-(1-phenylprop-1-en-3-yI)oxyphenyl isocyanide (317) (0.47 g; 0.002 mol) in anhydrous methylene chloride (5.0ml) was stirred under nitrogen, treated dropwise at -10° (ice-saltbath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride or powdered zinc chloride (0.004 mol) in anhydrous methylene chloride (20.0-30.0 ml) was added portionwise and the mixture was stirred at room temperature or under reflux, under nitrogen, for 4-22h then worked up as described for the individual reactions below.

(i) Using aluminium trichloride

After 4h at room temperature the mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene
chloride, and rotary evaporation of the combined organic extracts gave an oil (0.43 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) through ether to methanol gave only a series of intractable oils and solids (0.14 g) from which no identifiable material was obtained.

(ii) Using zinc chloride

After 22 h at reflux the cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove zinc residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.62 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) through ether to methanol gave only a series of multicomponent oils and gums (0.42 g) from which no identifiable material was obtained.

The Attempted Reaction of 2-(1-Phenylprop-1-en-3-yl)oxyphenyl Isocyanide Dichloride (320b) with Titanium Tetrachloride in Methylene Chloride

(a) Under reflux for 4 h

A solution of 2-(1-phenylprop-1-en-3-yl)oxyphenyl isocyanide (317) (0.47 g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10°C (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°C, under nitrogen, for 1 h. A solution of titanium tetrachloride (0.76 g; 0.44 ml; 0.004 mol) in anhydrous methylene chloride (5.0 ml) was added dropwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h.
The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.64 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave a yellow solid (0.01 g), which was not investigated further.

Elution with hexane-ethyl acetate (9:1) also gave a yellow solid (0.06 g), m.p. 112-125°, which formed colourless plates, m.p. 136-138° (from cyclohexane), νmax 3300-3100, 1775, and 1735 cm⁻¹.

Final elution with methanol gave an intractable brown gum (0.02 g) which was not investigated further.

(b) At -10° for 2h

Repetition of the reaction described in (a) before at -10° for 1h then for 2h after addition of the titanium tetrachloride was complete gave an oil (0.70g), flash-chromatography of which over silica gave only a series of complex mixtures from which no identifiable material was obtained.

\(N\)-(3-Methoxybenzyl)formamide (323)

A mixture of 3-methoxybenzylamine (322) (13.7 g; 0.1 mol) and 98-100% formic acid (50.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride, and the solution was washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0ml) and rotary evaporated to give an oil. This solidified on cooling to afford \(N\)-(3-methoxybenzyl)formamide (323) (8.5 g; 52%) which formed colourless plates,
m.p. 43-44° (from diethyl ether), $\nu_{\text{max}}$ 3360 (NH) and 1670-1650 (br) (C=O) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.21(1H, s, CHO), 7.34-7.12(1H, m, ArH), 6.88-6.71(3H, m, ArH), 6.25-5.63(1H, bs, NH)(exch), 4.41(2H, d, J 6 Hz, CH$_2$), and 3.76(3H, s, OCH$_3$).

3-Methoxybenzyl isocyanide (324)

A solution of N-(3-methoxybenzyl)formamide (323) (1.7 g; 0.01 mol) in anhydrous 1,2-dichloroethane (25.0 ml) was treated with carbon tetrachloride (1.9 g; 0.012 mol) followed by triphenylphosphine (3.1 g; 0.012 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (2.0 g; 0.02 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (10.0 ml) and extracted with methylene chloride to give a semi-solid (5.7 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 3-methoxybenzyl isocyanide (324) as a colourless oil (1.2 g; 82%), b.p. 68-72°/0.10-0.05 mmHg, $\nu_{\text{max}}$ 2145 (NC) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.35-7.25(1H, m, ArH), 6.93-6.86(3H, m, ArH), 4.61(2H, s, CH$_2$), and 3.82(3H, s, OCH$_3$).

Final elution with methanol gave a viscous brown oil (3.5 g) whose t.l.c. in ether over silica showed it to be a mixture of the unreacted starting material (323) and triphenylphosphine oxide, which was not investigated further.

The Attempted Reaction of 3-Methoxybenzyl isocyanide (324) with Titanium Tetrachloride in Methylene Chloride

(a) At -10° for 2h

A solution of 3-methoxybenzyl isocyanide (324) (0.59 g; 0.004 mol) in
anhydrous methylene chloride (10.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of titanium tetrachloride (3.8 g; 2.2 ml; 0.02 mol) in anhydrous methylene chloride (15.0 ml), and the mixture was stirred at -10°, under nitrogen, for 2h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (17.0 ml; 0.01 mol), stirred at room temperature for 15 min, and extracted with methylene chloride to give an oil (0.60 g) which was distilled to afford 4-(3-methoxybenzyl)formamide (323) as a yellow solid (0.49 g; 74%), m.p. 38-41°, identical (m.p. and i.r. spectrum) to a sample prepared previously.

(b) Under reflux for 24h

Repetition of the reaction described in (a) before under reflux for 24h gave an oil which was distilled to afford 4-(3-methoxybenzyl)formamide (323) as a yellow solid (77%), m.p. 37-40°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared previously.

3-Methoxybenzyl Isocyanide Dihalides (327a) and (327b)

A solution of 3-methoxybenzyl isocyanide (324) (0.15 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride or bromine (0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h then worked up as described for the individual reactions below.

(i) 3-Methoxybenzyl Isocyanide Dichloride (327a)

The mixture from reaction with sulphuryl chloride was rotary evaporated to give 3-methoxybenzyl isocyanide dichloride (327a) as a yellow oil (100%), v_max 1650 (N=C) cm⁻¹, m/z (ElMS) 221, 219, and 217 (M⁺).

(ii) 3-Methoxybenzyl Isocyanide Dibromide (327b)
The mixture from reaction with bromine was rotary evaporated to give 3-methoxybenzyl isocyanide dibromide (327b) as a brown oil (100%), $\nu_{\text{max}}$ 1676 (N=C) cm$^{-1}$.

**The Attempted Reaction of 3-Methoxybenzyl Isocyanide Dichloride (327a) with Aluminium Trichloride in Methylene Chloride**

(a) **At room temperature for 4h**

A solution of 3-methoxybenzyl isocyanide (324) (0.29 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.27 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10° under nitrogen, for 1h. A suspension of anhydrous aluminium trichloride (0.53 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred at room temperature, under nitrogen, for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave 3-methoxybenzyl isocyanide dichloride (327a) as a brown oil (0.41 g; 94%), identical [i.r. spectrum and t.l.c. in hexane-ether (1:1) over silica] to a sample prepared previously.

(b) **Under reflux for 4h**

Repetition of the reaction described in (a) before under reflux for 4h gave 3-methoxybenzyl isocyanide dichloride (327a) as a dark brown oil (0.41g; 94%), identified by comparison [i.r. spectrum and t.l.c. in hexane-methylene chloride (1:2) over silica] with a sample prepared previously.
The Attempted Reaction of 3-Methoxybenzyl Isocyanide Dibromide (327b) with Aluminium Tribromide in Methylene Chloride

A solution of 3-methoxybenzyl isocyanide (324) (0.29 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10\textdegree\ (ice-salt bath) with a solution of bromine (0.32 g; 0.002 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10\textdegree, under nitrogen, for 1h. A solution of aluminium tribromide (1.1 g; 0.004 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0 ml; 0.04 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave crude 3-methoxybenzyl isocyanide dibromide (327b) as a brown oil (0.50 g; 81%), identified by comparison (i.r. spectrum) with a sample prepared previously, which decomposed on attempted distillation.

\textit{N-(2-Phenylethyl)}formamide (330)

A mixture of 2-phenylethylamine (329) (48.4 g; 0.4 mol) and 98-100% formic acid (300.0 ml) was stirred and heated under reflux, with exclusion of atmospheric moisture, for 3h.

The cooled mixture was rotary evaporated to give an oil which was dissolved in methylene chloride. The solution was washed three times with 10% aqueous sodium hydrogen carbonate solution (3 x 40.0 ml) and rotary evaporated to afford \textit{N-(2-phenylethyl)}formamide (330) as a colourless oil (25.2 g; 42%), b.p. 150-152\textdegree/4.0-3.5 mmHg (lit.,\textsuperscript{190} 205\textdegree/15 mmHg).
The aqueous mother liquor was made basic with 2 M aqueous sodium hydroxide solution and extracted with methylene chloride to give unchanged 2-phenylethylamine (329) as a yellow oil (5.5 g; 11%), identical [i.r. spectrum and t.l.c. in hexane-ethyl acetate (1:1) over silica] to an authentic sample.

2-Phenylethyl Isocyanide (331)

A solution of N-(2-phenylethyl)formamide (330) (3.0 g; 0.02 mol) in anhydrous 1,2-dichloroethane (30.0 ml) was treated with carbon tetrachloride (3.7 g; 0.024 mol) followed by triphenylphosphine (6.3 g; 0.024 mol) and the mixture was stirred at room temperature for 15 min. Triethylamine (4.0 g; 0.04 mol) was added and the mixture was stirred and heated at 60° (oil bath), with exclusion of atmospheric moisture, for 2.5h.

The cooled mixture was rotary evaporated to give a semi-solid. This was treated with water (25.0 ml) and extracted with methylene chloride to give a semi-solid (10.0 g) which was trituated with ether to afford triphenylphosphine oxide as a pale brown solid (5.2g), m.p. 147-149° (lit. 126
152-153°), identical (m.p. and i.r. spectrum) to an authentic sample.

Rotary evaporation of the ethereal mother liquor gave an oil (4.5 g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (9:1) gave 2-phenylethyl isocyanide (331) as a yellow oil (2.2 g; 84%), \( \nu_{\text{max}} \) 2145 (NC) cm\(^{-1}\), \( \delta_H (\text{CDCl}_3) \) 7.42-7.15(5H, m, ArH), 3.71-3.48(2H, m, CH\(_2\)), and 3.08-2.03(2H, m, CH\(_2\)).

The methanolic eluate was run into an excess of 2 M aqueous hydrochloric acid solution and left for several days prior to disposal.

2-Phenylethyl Isocyanide Dihalides (332a) and (332b)

A solution of 2-phenylethyl isocyanide (331) (0.13 g; 0.001 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated
dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride or bromine (0.001 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10° under nitrogen, for 1 h then worked up as described for the individual reactions below.

(i) 2-Pheny1ethyl Isocyanide Dichloride (332a)

The mixture from reaction with sulphuryl chloride was rotary evaporated to give 2-phenylethyl isocyanide dichloride (332a) as a colourless oil (0.20 g; 100%), $\nu_{\text{max}}$ 1654 (N=C) cm$^{-1}$.

(ii) 2-Pheny1ethyl Isocyanide Dibromide (332b)

The mixture from reaction with bromine was rotary evaporated to give 2-phenylethyl isocyanide dibromide (332b) as a yellow oil (0.28 g; 97%), $\nu_{\text{max}}$ 1678 (N=C) cm$^{-1}$.

3.4-Dihydroisoquinolin-1(2H)-one (334)

A solution of 2-phenylethyl isocyanide (331) (0.52 g; 0.004 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of sulphuryl chloride (0.54 g; 0.004 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1 h. A suspension of anhydrous aluminium trichloride (1.1 g; 0.008 mol) in anhydrous methylene chloride (30.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4 h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0 ml; 0.08 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil (0.60 g) which was flash-chromatographed over silica.
Elution with hexane-ether (9:1) gave an intractable yellow oil (0.06 g) which was not further investigated.

Elution with hexane-ether (2:8) gave the known\textsuperscript{193} 3,4-
dihydroisoquinolin-1(2H)-one (334) as a yellow oil (0.21 g; 36%), b.p. 159-
165°/1.5-1.0 mmHg, $\nu_{\text{max}}$ 3247 (NH) and 1667 (C=O) cm\textsuperscript{-1}, $\delta_{\text{H}}$(CDCl\textsubscript{3}) 8.09
(1H, dd, J 7 and 1 Hz, ArH), 7.60-7.23(4H, m, NH and 3xArH), 3.61(2H, td, J
7 and 3 Hz, CH\textsubscript{2}), and 3.02(2H, t, J 7 Hz, CH\textsubscript{2}).

Final elution with methanol gave an intractable brown gum (0.09 g) which was not investigated further.

**Reactions of 2-Phenylethyl isocyanide Di bromide (332b) with Aluminium Tribromide in Methylene Chloride**

A solution of 2-phenylethyl isocyanide (331) (0.39 g; 0.003 mol) in anhydrous methylene chloride (5.0 ml) was stirred under nitrogen, treated dropwise at -10° (ice-salt bath) with a solution of bromine (0.48 g; 0.003 mol) in anhydrous methylene chloride (5.0 ml), and the mixture was stirred at -10°, under nitrogen, for 1h. A solution of aluminium tribromide (1.6 g; 0.006 mol) in anhydrous methylene chloride (20.0 ml) was added portionwise and the mixture was stirred and heated under reflux, under nitrogen, for 4h then worked up as described for the individual reactions below.

(i) **With subsequent reaction with diethylamine**

The cooled mixture was treated portionwise with diethylamine (2.2 g; 0.03 mol) then stirred and heated under reflux, under nitrogen, for 0.5h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave an oil which was flash-
chromatographed over silica.

Elution with hexane-ether (95:5) gave a yellow oil which was distilled to afford 1-bromo-3,4-dihydroisoquinoline (333b) as a waxy colourless solid (32%), b.p 121-126°/1.5-1.0 mmHg, \( \nu_{\text{max}} \) 3396 (NH) and 1623 (C=N) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.04 (1H, dd, J 8 and 1 Hz, ArH), 7.54-7.22 (3H, m, ArH), 3.64 (2H, t, J 7 Hz, CH\(_2\)), and 3.02 (2H, t, J 7 Hz, CH\(_2\)), m/z (ElIMS) 211,209 (M\(^+\)).

Elution with hexane-ether (1:1) through ether to methanol gave only a series of complex mixtures which were not investigated further.

(ii) **Using the standard work-up procedure**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. Separation of the filtrate, extraction of the aqueous layer with methylene chloride, and rotary evaporation of the combined organic extracts gave a waxy colourless solid (0.17 g; 27%), b.p. 192-199°/1.5-1.0 mmHg, tentatively identified as 1-bromo-3,4-dihydroisoquinoline (333b), identified by comparison (i.r and proton n.m.r. spectra) to a sample prepared previously.

Elution with hexane-ethyl acetate (1:1) gave a viscous brown oil which was distilled to afford a colourless glass (0.09 g; 20%), b.p. 215-220°/1.5-1.0 mmHg, tentatively identified as 3,4-dihydroisoquinolin-1(2H)-one (334), identified by comparison (i.r. spectrum) with a sample prepared previously.

Final elution with methanol gave an intractable brown gum (0.02 g) which was not investigated further.

(iii) **With subsequent reaction with aqueous sodium hydrogen carbonate**

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol), stirred at room temperature for 15 min, then filtered to remove aluminium residues. The mixture was separated, the aqueous layer was extracted with methylene chloride, and the
organic extracts were treated with 10% w/v aqueous sodium hydrogen carbonate solution (46.0 ml; 0.06 mol). The mixture was then stirred and heated under reflux for 1h.

The cooled mixture was separated, the aqueous layer was extracted with methylene chloride, and the combined organic extracts were rotary evaporated to give an oil (0.65 g) which was flash-chromatographed over silica.

Elution with hexane-ether (9:1) through ether to methanol gave only a series of multicomponent oils and gums (0.31 g) from which no identifiable material was obtained.
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<td>H%</td>
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*α*, molecular ions detected by Electron Impact mass spectroscopy or, for values in parentheses, detected by Fast Atom Bombardment mass spectroscopy.
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a, molecular ions detected by Electron Impact mass spectroscopy or, for values in parentheses, detected by Fast Atom Bombardment mass spectroscopy.
### Table 15 (contd.1): Analytical and Mass Spectroscopic Data

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a. Molecular ions detected by Electron Impact mass spectroscopy or, for values in parentheses, detected by Fast Atom Bombardment mass spectroscopy.
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