Investigations of New Synthetic Routes
to Fused Tricyclic Benzoheteropines

by

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Declaration

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

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1987 and September 1990.

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Postgraduate Lecture Courses

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"Business Management"
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"Modern Methods of N.M.R."
Dr. Sadler (University of Edinburgh)

"Recent Advances in Organic Chemistry"
Prof. R. Ramage (University of Edinburgh)

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Prof. R. Baker (Merk, Sharp and Dohne)

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Abstract

This thesis is concerned with the synthesis of fused tricyclic benzoheteropines by novel Friedel-Crafts type cyclisation reactions involving heterocumulenes.

A general synthetic pathway was developed for the preparation of 1-[2-(3-methoxy-pyrid-3-yl)-3-phenyl carbodiimide prepared in four steps from 2-chloro-3-nitro pyridine and 3-methoxy aniline. Studies were carried out into the optimisation of Lewis acid catalysis conditions for the successful intramolecular cyclisation of this carbodiimide to 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoazepine and 7-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoazepine. The extension of this methodology to the use of other carbodiimides was demonstrated by the preparation of 9-methoxy-6-methylaminopyrido[2,3-b][1,4]benzoazepine from the readily prepared 1-[2-(3-methoxy-pyrid-3-yl)-3-methyl carbodiimide.

Investigations carried out into the cyclisation process showed that an electron donating group on the aromatic ring is essential for directing the successful ring closure to the benzoazepine. It was found that the electronic nature of the carbodiimide had a marked effect on the efficiency of cyclisation process. This was thought to have been due to a change in the electronic nature of the carbodiimide. Thus electron donating groups immediately adjacent to the carbodiimide multiple bond were found to inhibit ring closure. Under the developed cyclisation conditions 9-methoxypyrido[2,3-b][1,4]benzoazepin-6(5H)-one was prepared from the
Friedel-Crafts type ring closure of 2-(3-methoxyphenoxy)pyrid-3-yl isocyanate. Likewise 9-methoxypyrido[2,3-b][1,4]benzoxazepin-6(5H)-thione was prepared from the corresponding isothiocyanate. The generality of the developed methodology to the synthesis of other fused tricyclic oxazepines was demonstrated by the analogous preparation of 3-methoxy-11-phenylamido-dibenz[b,f][1,4]oxazepine and 9-methoxy-6-phenylamino-pyrimido[4,5-b][1,4]benzoxazepine.

Extension of the synthetic strategy to the syntheses of fused tricyclic thiazepines was demonstrated by the synthesis of 9-methoxy-6-(N-phenylamino)pyrido[2,3-b][1,4]-benzothiazepine. As with the synthesis of the oxazepine ring systems the general methodology allowed the preparation of other tricyclic heteropines. Thus 3-methoxy-11-(N-phenylamino)dibenzo[b,f][1,4]thiazepine and 2-(N,N-dimethylamino)-9-methoxy-6-(N-phenylamino)pyrimido[4,5-b][1,4]benzothiazepine were prepared by Lewis acid ring closure of the corresponding carbodiimides.

Analogous to the synthesis of the oxazepine and thiazepine ring systems, studies were also carried into the development of a similar route to tricyclic diazepine derivatives. 1-{2-[N-(3-methoxyphenyl),N-methyl]aminopyrid-3-yl}-3-methoxyphenylcarbodiimide was easily synthesised from 2-chloro-3-nitropyridine and 3-methoxy aniline. This carbodiimide under the established Lewis acid catalysed cyclisation conditions yielded 9-methoxy-11-methyl-11H-pyrido[2,3-b][1,4]benzodiazepine thus further exemplifying the adaptability of the general methodology to the synthesis of a variety of tricyclic heteropines.
Preface

In recent years it has become evident that with the advancement of clinical science and the gradual eradication of many diseases, the world's health problems may be increasingly associated with the diseases of the aged. It has been recognised that the largest single problem of old age is that of mental deterioration, the commonest cause of such deterioration being Alzheimer's disease. First discovered in 1907 much work has been carried out to investigate the cause and possible treatment of Alzheimer's disease. Although some progress has been made towards the treatment of the symptoms of Alzheimer's disease much work has still to be done in the development of useful therapeutic agents for the treatment of this disease.

Certain classes of molecules have been identified as potentially useful therapeutic agents for the treatment of Alzheimer's disease, however progress in this area has to a large extent been curbed by the lack of availability of such compounds.

The following thesis is concerned with the development of new general methods for the synthesis of fused tricyclic benzo heteropines as potential therapeutic agents for the treatment of Alzheimer's disease. By way of introduction, Chapter 1 firstly gives a brief review of Alzheimer's disease and approaches to therapy, and secondly provides a survey of the method of synthesis of fused tricyclic heteropines reported in the literature to date. This is followed in Chapters 2 to 4 by an account of the results obtained in the present studies.
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Bibliography
Chapter One

The Cholinergic Approach
to Alzheimer's Disease and Methods for
the Synthesis of Non-bridgehead Fused
Tricyclic Heteropines as Possible
Therapeutic Agents
The Cholinergic Approach to Alzheimer's Disease and Methods for the Synthesis of Non-bridgehead Fused Tricyclic Heteropine Therapeutic Agents

This introductory chapter is divided into two main sections. The objective of the first of these sections is to provide a brief review of Alzheimer's disease with particular emphasis on the cholinergic approach to the therapy of the disease. The literature relating to the subject of Alzheimer's disease is extensive and covers all aspects of the disease and possible therapies. However as an introduction to the field a review by S. Iversen written with the chemist in mind is recommended.

The second section consists of a survey of methods for the synthesis of non-bridgehead fused tricyclic heteropines which as a class are of interest as therapeutic agents for Alzheimer's disease. No attempt has been made to provide comprehensive coverage of the wide field of tricyclic heteropine synthesis but rather to exemplify the methodologies employed in the synthesis of this type.

1.1 Alzheimer's Disease

The past decade has seen an explosive growth worldwide of research into the problems presented by Alzheimer's disease, adding to a growing awareness that the increasing proportion of elderly people in the world population will be associated with an increase in the prevalence of a wide range of chronic and disabling diseases of old age. Mental
degeneration in later life is the largest single problem of the aged and Alzheimer's disease has become recognised as the commonest cause of such mental deterioration. The scale of the problem has been emphasised by global demographic trends which predict that by the year 2025 there will be one billion people aged 60 and over, corresponding to more than 20 percent of the world's population, with a proportionate increase in the number of people suffering from Alzheimer's disease.

The disease, first described as a clinical entity by Alois Alzheimer in 1907 causes a slowly progressive dementia usually resulting in death approximately seven years after its onset.

The symptoms of the diseased patients range from loss of recent memory in the early stages to severe memory loss, depression and paranoia. Complete mental deterioration follows and death usually occurs from the complications that afflict bed ridden patients. The post mortem examination of Alzheimer's diseased brains show very characteristic pathological changes. Examination of stained sections of the brain reveal a loss of neurons most commonly in those areas of the cortex responsible for higher intellectual function and memory formation. This neural depletion is accompanied by accumulations of twisted filaments known as neurofibrillary tangles and scattered focuses of cellular debris and amyloid tissue known as neuritic plaques. Post mortem examination is still the only definitive method for the diagnosis of Alzheimer's disease. However recent studies by Talamo et al. have found related pathological changes in the tissue of the
sensory epithelium of the nose. This tissue is relatively easy to biopsy by examination with antibodies specific for proteins known to be involved in the neurofibrillary tangles and neuritic plaques that are characteristic of Alzheimer's disease. The development of this technique into a reliable clinical test would be invaluable in providing positive evidence for the disease in the living patient which at present can only be inferred.

The rapid upsurge of scientific interest in Alzheimer's disease over the past ten to fifteen years has been a direct result of studies by three independent research groups that linked characteristic neurochemical deficiencies with the diseased brains of patients suffering from Alzheimer's disease. Neurochemical studies\(^7\) showed that the levels of the enzyme choline acetyltransferase were in some cases reduced by as much as 90 percent. The enzyme choline acetyltransferase catalyses the synthesis of the neurotransmitter acetylcholine within the presynaptic terminal of the neurons known as cholinergic neurons. It is therefore reasoned that the deficiency of this enzyme directly reflects the degradation of cholinergic neurons in diseased brains which in turn leads to poor communication and hence the disease symptoms. Acetylcholine is only one of more than 50 different chemical messengers that are known to contribute to chemical communication in the brain. However most of the research concerned with neurotransmitter depletion in Alzheimer's disease has focused on the cholinergic model. This is not unreasonable since there are firm grounds for selecting cholinergic deficiency as being of critical importance for the
entire disease process. It is clear that Alzheimer’s disease is not a disease of only one neurotransmitter system. However the loss of cholinergic neurons is the most severe, extensive and specific of all the neurological changes. There is increasing evidence that degeneration of the cholinergic system of the hippocampus and cerebral cortex is a direct cause of loss of memory and cognitive function, both of which are symptoms of Alzheimer’s disease.

The cholinergic hypothesis suggests that if the symptoms of Alzheimer’s disease are a direct result of acetylcholine deficiency then the therapeutic objective is the development of a drug which restores the acetylcholine level in the same manner as L-dopa is effective in restoring dopamine levels in Parkinson’s disease.

The most obvious strategy to increase the levels of acetylcholine would be to enhance its synthesis in surviving neurons by providing the enzyme choline acetyltransferase which is the precursor of the neurotransmitter. Clinical trials with choline and lecithin (the major dietary precursor of choline) have been disappointing probably due to successful choline uptake being linked to a high affinity transport system which is completely saturated under normal conditions.

An alternative approach to increasing the availability of acetylcholine is to limit its breakdown. Acetylcholine is broken down by the enzyme acetylcholinesterase, whose inhibition has been clinically studied with limited positive results. Trials with the acetylcholinesterase inhibitors
Scheme 1
(Scheme 1) Tacrine (1) and physostigmine (2) showed only moderate transient improvement in the cognitive function of patients suffering from Alzheimer's disease and therefore have only a narrow therapeutic window.

Alternatively acetylcholine levels may be artificially enhanced by agents which mimic its action. In order to develop drugs to achieve this effectively it is necessary to know more about the specific receptor sites involved. The receptors which are involved in the cholinergic system can be classified into two types, muscarinic and nicotinic based on their distinct physiological responses to the substances muscarine (5) and nicotine (6). The majority of cholinergic receptors in the central nervous system are of the muscarinic type which can be further subclassified into types m₁ and m₂. There is evidence to suggest that the postsynaptic receptors of the cholinergic neurons are of the m₁ type although the exact nature of these receptors remains unknown. Clinical trials have also been carried out with potential muscarinic agonists¹⁰,¹¹ acting as neurotransmitter mimics at the m₁ receptor. The drug arecholine (3) produced some improvement in the learning capacity of patients with Alzheimer's disease but only for a very short duration. Arecholine (3) also caused a high incidence of undesirable side effects further limiting its practical usefulness. The compound oxotremorine (4) proved to be longer acting but was also limited by the problem of side effects. Research is still being carried out to find muscarinic agonists which may be suitable for use as therapeutic agents for Alzheimer's disease.
Scheme 2

[Ar = Benzenoid or Heteroaromatic nucleus]
[X = NR, O, S, CRR']
The cholinergic agonist approach is primarily concerned with postsynaptic agents yet there is another probably more subtle approach to use of acetylcholine mimics. The presynaptic terminal of the cholinergic neuron is known to possess muscarinic receptors of the $m_2$ type. It is thought that the function of these receptors is to provide a feedback mechanism modulating the release of the neurotransmitter into the synapse. It is conceivable that a presynaptic solution to the problem may be achieved by blocking the feedback mechanism so that in the absence of a modulating signal the terminal should release more acetylcholine per firing. This may be achieved by developing muscarinic antagonists which selectively act at the presynaptic ($m_2$) receptors (Scheme 2). The derivative clozapine (7) has shown antipsychotic properties which are thought to be due to its anticholergic effect. A structurally similar compound pirenzepine (8) also shows muscarinic antagonism but in addition exhibits a reasonable degree of selectivity between the $m_1$ and $m_2$ receptor sites. The drug clozapine (7) in clinical trials produced peripheral side effects which were unacceptable for its further use. In contrast pirenzepine (8) has no such side effects but it is not useful for treatment of diseases of the central nervous system due to its inability to cross the blood-brain barrier.

A great deal of research is in progress to define the cause of Alzheimer’s disease and many theories have been postulated. However the cholinergic approach is still probably the closest to finding a solution to
\[
\text{R—C}(\text{NH}_2), \quad \text{N}(12)
\]

(i) heat.

Scheme 3

\[
\begin{align*}
\text{(13)} & \quad \text{NO}_2 \\
\text{(14)} & \quad \text{NH}_2 \\
\text{(15)} & \quad \text{N}(12)
\end{align*}
\]

(i) heat.

Scheme 4

\[
\begin{align*}
\text{MeOH, } 0-5^\circ; \\
\text{SnCl}_2, \text{CH}_3\text{CO}_2\text{H, room temp;}
\end{align*}
\]

(iii) \text{H}_2\text{SO}_4 (20\%), 100-105^\circ.
the problem of therapy, although much work has still to be done to develop suitably selective drugs that do not possess undesirable side effects.

1.2 Methods for the Synthesis of Non-bridgehead Fused Tricyclic Heteropines

The pharmacological activity of the tricyclic heteropine derivatives clozapine (7) and pirenzepine (8) has stimulated numerous studies on the synthesis of novel derivatives. However most of these studies have focused mainly on determining structure activity relationships influenced by the side chain. Synthetic studies involving extensive variation of the tricyclic nucleus of tricyclic heteropines are less numerous. This reflects the current lack of a general strategy for the synthesis of tricyclic heteropines of the types (9) and (10). Ring systems of general types (9) and (10) have largely been synthesised by relatively few distinct routes, the most useful involving the construction of the central seven membered ring last. Methods by which this is achieved fall mainly into three categories depending of the nature of the final ring closure step. Each of these and additional methods involving ring expansion will be discussed in turn.

1.2.1 Tricyclic Heteropine Formation by Intramolecular Amine-Carbonyl Type Condensation Reactions

An early synthesis of the dibenzo[b,e][1,4]diazepine ring system (Scheme 3) by Perkin et al\textsuperscript{13} simply involved heating N-(2-
Scheme 5

(i) DMF, reflux;
(ii) FeSO₄, NH₃, H₂O, reflux.

Scheme 6

(i) HC(OCH₃)₃, room temp;
(ii) Pd–C/H₂, CH₃OH, room temp;
(iii) F₃CCO₂H, dioxane, room temp.
aminophenyl)anthranilic acid (11a) to give the dibenzodiazepinone derivative (12a) via formation of the central seven-membered ring by a simple condensation reaction between the amino and the carbonyl group. This strategy has been widely used for the construction of various tricyclic heteropine ring systems, exemplified by the dibenzoazepine synthesis [(11b)-(12b)] in which the dibenzoazepine (12b) was obtained in very high yield 92%\textsuperscript{14}. Lactam formation of this type typically requires temperatures of around 200\textdegree. However catalysis by phosphoric acid resulted in dibenzothiazepinone formation [(11c)-(12c)] in reasonable yield 60% under less forceful conditions\textsuperscript{15}. Similarly, (Scheme 4) the amino ester (16) undergoes ring-closure to form the pyrimido[4,5-b][1,4]diazapinone (17) in the presence of 20% sulphuric acid\textsuperscript{16}.

In a tricyclic heteropine synthesis akin to that involving amine-carbonyl group condensation as the final ring-closure step (see Scheme 3 before) Brewster\textsuperscript{17} has described a pyrido[2,3-b][1,4]benzoxazepine synthesis (Scheme 5) involving amine carboxaldehyde group condensation as the final ring-closure step. This involved initial intermolecular aromatic substitution of 2-chloro-3-nitropyridine (18) by the potassium phenoxide (19) derived from salicylaldehyde to give the ether (20). Reduction of the latter afforded the pyridobenzoxazepine (22) albeit in low yield (28%) via the presumed intermediacy of the amino aldehyde (21).

Slight changes in the general methodology have been investigated, an example of which is shown (Scheme 6) by Tambute\textsuperscript{18} in which the ring-
(i) n-C\textsubscript{4}H\textsubscript{9}Li, ether, room temp.;  
(ii) HCON(CH\textsubscript{3})\textsubscript{2}.H\textsubscript{2}O, room temp.

Scheme 7

(i) heat;  
(ii) DMF, NaOH, 100°.

Scheme 8
Scheme 9

(i) $H_2SO_4(aq)$, 70°.
closure is achieved in high yield (80%) by intramolecular reaction between the amine and the acetal functionality of (25) in the presence of trifluoroacetic acid.

A more versatile route recently proposed by Narasimhan and Chandrachood\textsuperscript{19} demonstrates (Scheme 7) the preparation of dibenzo[b,f][1,4]oxazapines (29a), dibenzo[b,e][1,4]thiazepines (29b) and dibenzo[b,e][1,4]diazepines (29c) from 2-aminodiphenyl ether (27a), 2-aminodiphenylsulphide (27b) and 2-aminodiphenylamine (27c) in reasonable yields (62-78%). This two step process involves initial lithiation to yield the C,N,-dilithio derivatives (28 a-c) which are then treated with aqueous dimethylformamide to afford the targeted tricyclic heteropines.

1.2.2 Tricyclic Heteropine Formation by Intramolecular Nucleophilic Aromatic Substitution Reactions

Tricyclic heteropine formation involving intramolecular nucleophilic aromatic substitution as the final ring-closure step is illustrated (Scheme 8) by the synthesis of the dibenz[b,f][1,4]oxazepinone (33) reported by Chakrabarti \textit{et al}\textsuperscript{20}. In this tricyclic heteropine synthesis reaction of 2-aminophenol (30) with 2-chloro-4-nitrobenzoyl chloride (31) affords the amide (32) which undergoes ring-closure by intramolecular nucleophilic displacement of the chloro-substituent by the phenoxide function. A variation on this general procedure\textsuperscript{21} (Scheme 9) achieves the final ring-closure by thermal decomposition of the diazonium salt (34). On heating in
(37) \[ \text{EtO} \text{C}_{2}\text{H} \]

(i) \[ \rightarrow \]

(38) \[ \text{EtO} \text{C}_{2}\text{HCl} \]

(ii) \[ \rightarrow \]

(39) \[ \text{EtO} \text{C}_{2}\text{S} \]

(iii) \[ \rightarrow \]

(40) \[ \text{EtO} \text{C}_{2}\text{S} \]

(41) \[ \text{EtO} \text{C}_{2}\text{S} \]

(42) \[ \text{EtO} \text{C}_{2}\text{S} \]

(i) \( \text{SOCl}_2, 100^\circ \)

(ii) \( \text{NH}_2\text{C}_2\text{H}_4(\text{OH})\text{C}_2\text{Cl}_2, \text{room temp} \)

(iii) \( \text{P}_2\text{O}_5-\text{H}_3\text{PO}_4, 120^\circ \)

Scheme 10
Scheme 11

(i) C₆H₆,(C₂H₅)₃N, reflux;
(ii) SnCl₂, CH₃CO₂H, room temp;
(iii) 200°.

Scheme 12

(i) 140°;
(ii) (C₇H₈)₃N, room temp.
the presence of sulphuric acid the methoxy group undergoes a nucleophilic aromatic substitution reaction displacing a molecule of nitrogen. Methane is then lost from the proposed intermediate (35) to form the dibenzoxazepinone (36) in 25% yield.

In a similar manner (Scheme 10) the thieno oxazepinone (42) was synthesised in better yield (64%) from the thiophene (37). In this case the ether linkage was formed by displacement of the ethoxy group of compound (39). This is facilitated by protonation of the thiophene ring with polyphosphoric acid forming the intermediate (40), thus allowing the hydroxy group to perform the nucleophilic displacement of the ethoxy group forming the oxazepinone (42). Feng et al have successfully prepared (Scheme 11) the pyridodiazepinone (47) using similar methodology. This method utilises the properties of the pyridine ring to undergo nucleophilic displacement of chlorine at the 2-position to give the ring closed product (47) again in poor yield (32%).

In extension to other heteroaromatic nuclei this methodology was utilised for the preparation of pyrimidobenzoxazepines (Scheme 12). The first bridge was formed via the formation of an imine bond between the amine group of 2-aminophenol (30) and the acetyl group of the substituted pyrimidine (48). The final ring-closure step again involved the nucleophilic displacement of chloride from the heteroaromatic ring, this time at room temperature under basic conditions to give superior yield (75%) of the tricyclic heteropine (50).
(i) NaH, Cu, DMF, 150–160°;
(ii) Pd–C, H₂, C₂H₅OH, room temp;
(iii) HCO₂H, reflux;
(iv) POCl₃, PPA, 100°.

Scheme 13
(i) PPA, reflux.

Scheme 14

(i) HN\((\text{C}_2\text{H}_4\text{)}_2\text{NCH}_3\), C\(_6\text{H}_6\), reflux;
(ii) POCl\(_3\), reflux.

Scheme 15
Scheme 16

(i) PhCN, 200°C;
(ii) oCl₂C₆H₄, COCl₂, 150°C;
(iii) POC₁₃, C₆H₅NO₂, 220°C;
(iv) AlCl₃, oCl₂C₆H₄, 100°C.
1.2.3 Tricyclic Heteropine Formation by Intramolecular Electrophilic Aromatic Substitution Reactions

In contrast to the relatively limited application of the methodology described before a large number of tricyclic heteropine syntheses involve intramolecular electrophilic aromatic substitution (Friedel-Crafts) type ring-closure in the key ring-forming step. This methodology is illustrated by the synthesis (Scheme 13) of the dibenz[b,f][1,4]oxazepine (56)\textsuperscript{25}. 2-Chloronitrobenzene (51) was reacted with sodium phenoxide to give the nitro compound (53). Reduction followed by formulation yielded the formamide derivative (55) which on treatment with phosphoryl chloride underwent cyclodehydration to form the dibenzoazepine (56) in excellent yield (88%). This general strategy has been extended\textsuperscript{26} (Scheme 14) to the polyphosphoric acid catalysed cyclisation of the acetyl derivatives (57a-c) to the corresponding dibenzoheteropines (58a-c). Hunziker et al\textsuperscript{27} have further demonstrated the versatility of this type of tricyclic heteropine synthesis by the ring-closure (Scheme 15) of the ureas (60a-b) derived from the corresponding isocyanates (59a-b) to the dibenzoazepine (61a) and the dibenzothiazapine (61b) with functionalised side chains. This type of cyclisation has also been applied\textsuperscript{28} to the synthesis (Scheme 16) of the dibenzothiazepine (65) prepared in 40% yield from the amidine (63) which was prepared from the reaction of the benzene sulphonate of 2-aminodiphenyl sulphide (62a) with benzonitrile.
Scheme 17

(i) Zn, NH₄Cl, DME, 40°.
(i) $H^+$. PhCHO. reflux.

Scheme 18

(i) $PCl_5$.
(ii) $P_2O_5-H_3PO_4$. $160^\circ$. 
The amine (62b) also proved to be a convenient starting point for an alternative synthesis\textsuperscript{29} of the thiazepinone (66) involving the Friedel-Crafts type cyclisation of the isocyanate (64) derived by phosgenation of the amine (62b). Recently an interesting variation on this type of synthesis has been illustrated by the synthesis (Scheme 17) of the dibenzodiazepine (70)\textsuperscript{30} involving a novel reductive cyclisation of the benzanilide (67) with zinc and aqueous ammonium chloride. It is proposed that the fused tricyclic system (70) is obtained via intramolecular electrophilic attack of the nitroso group onto the benzene ring directed by the hydroxy functionality. The overall yield of the diazepine (70) was again only moderate (40%).

Hiramitsu and Maki\textsuperscript{31} (Scheme 18) in their synthesis obtained the pyrimido[5,4-f][1,4]benzothiazepine (72) in 64%. The ring closure step is achieved via a Mannich-type cyclisation, thus 1,3-dimethyl-6-(\(\sigma\)-aminophenylthio)-uracil (71) is reacted with benzaldehyde and proceeds through the proposed Schiff's base (73) to the product (72).

1.2.4 **Tricyclic Heteropine Formation Involving Ring Expansion Reactions**

A fourth type of general approach to the synthesis of tricyclic heteropines which has attracted less attention than the more orthodox cyclisation procedures already discussed can be classed under the general heading of ring expansion reactions.
Scheme 20

(i) H$_2$SO$_4$(conc); NaN$_3$, room temp;
(ii) Zn, CH$_3$CO$_2$H, reflux.

Scheme 21

(i) NH$_3$,NaNH$_2$,reflux;
(ii) HCl(aq). room temp.
(i) hν (450W/medium pressure Hg). C₆H₆, room temp.

Scheme 22

(i) NH₂OSO₃NH₄, 30% NH₃-MeOH, room temp.

Scheme 23
Early workers in this area\textsuperscript{32, 33} prepared (Scheme 19) dibenz[b,f][1,4]oxazepinone (75) and dibenz[b,f][1,4]thiazepinone (76) by the phosphorus pentachloride or polyphosphoric acid catalysed Beckmann rearrangements of the xanthone oximes (74a) and thioxanthone oximes (74b) respectively in 38-40\% yield. In a similar manner\textsuperscript{34} (Scheme 20) the reaction of the thioxanthene oxide (77) with hydrazoic acid gave, via a Schmidt reaction, the dibenzo[b,f][1,4]thiazepinone-5-oxide (78) which was reduced to the target thiazepinone (79) in total yield of 44\%. The overall yield of thiazepinone synthesis has been improved to 83\% via a slightly different approach (Scheme 21). The thioxanthene dioxide (80), sodium amide in liquid ammonia method, has proved to be a good substitute for hydrazoic acid in effecting an identical transformation to the dibenzo[b,f][1,4]thiazepinone 5, 5-dioxide (83)\textsuperscript{35}. It has been proposed as a mechanism the intermediate aryne structure (82).

In contrast to the foregoing types of ring expansion the photochemical isomerisation (Scheme 22) of 2-(3-pyridyl)-1,2-benzisothiazol-3(2H)-one (84) resulted in the formation of pyrido[2,3-b][1,4]benzothiazepinone (87) via the presumed\textsuperscript{36} intermediacy of the biradical species (85), albeit in very poor yield (23\%).

Acridines have also shown to be potential precursors to diazepine synthesis. This has been demonstrated\textsuperscript{37} (Scheme 23) by the reaction of the acridine (88) with hydroxylamine-o-sulphonic acid yielding a one step
preparation of the dibenzo[b,e][1,4]diazepine (91) in 71% yield via the proposed aziridine ring formation (90) and subsequent ring expansion.
Chapter Two

Investigations of New Syntheses of Fused Tricyclic Oxazepines Based on Novel Heterocumulene Cyclisation Reactions
(X=Y=NR,OS)
(Ar=Benzenoid or Heteroaromatic nucleus)

Scheme 24
Investigations of New Syntheses of Fused Tricyclic Oxazepines Based on Novel Heterocumulene Cyclisation Reactions

2.1 Introduction

The lack of general methods for the synthesis of tricyclic heteropines, as discussed in Chapter 1, has provided the stimulus for current interest in the development of versatile strategies for the efficient synthesis of heterocyclic structures of the type (9) and (10). The investigations which provide the subject material of the following three chapters of the present thesis had as their primary objective the development of such a general synthetic strategy (Scheme 24) based on novel heterocumulene cyclisation reactions as the key ring-forming step. The proposed general synthetic strategy also involved as key steps condensation reactions of appropriate phosphinimines (iminophosphoranes) (94) for the synthesis of the heterocumulenes (96) required as precursors of the target tricyclic heteropines (97).

The reactions of phosphinimines with carbon dioxide and carbon disulphide to form isocyanates and isothiocyanates respectively are known, as are their reactions with isocyanates to form carbodiimides.

The versatility of the phosphinimines (94) as precursors of heterocumulenes (96) makes them key intermediates in the synthetic strategy. Phosphinimines (94) in turn are readily accessible from azides (95) which react with phosphines with the elimination of gaseous nitrogen. Alternatively triphenylphosphinimines (94) may be synthesised directly from
(98) \( \text{N}=\text{C}=\text{O} \)

(i) or (ii) 

(99) \( \text{H} \text{O} \)

(i) \( \text{AlCl}_3, \text{C}_6\text{H}_6, \text{reflux} \); 
(ii) \( \text{HBF}_6, \text{sulpholane, reflux} \).

Scheme 25

\[ \begin{array}{c}
\text{SO}_2-\text{N}=\text{C}=0 \\
\text{(100)}
\end{array} \]

(i) 

\[ \begin{array}{c}
\text{SO}_2-\text{N}=\text{C}-\text{O}-\text{AlCl}_3 \\
\text{(101)}
\end{array} \]

\[ \begin{array}{c}
\text{SO}_2-\text{N}=\text{C}-0-\text{AlCl}_3 \\
\text{(102)}
\end{array} \]

(i) \( \text{C}_6\text{H}_5\text{OCH}_3, \text{AlCl}_3, \text{C}_6\text{H}_6, \text{reflux} \).

Scheme 26
Scheme 27

(i) $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$, room temp.

Scheme 28

(i) $180^\circ$.
the respective amines (93) by reaction with triphenylphosphine dichloride generated \textit{in situ}.\textsuperscript{40}

The proposed ring-closure of the heterocumulenes (96) to the tricyclic heteropines (97) corresponds to an intramolecular Friedel-Crafts type acylation reaction with formation of a central seven-membered ring. Friedel-Crafts reactions of isocyanates and isothiocyanates were first reported by Leuchart and Schmidt.\textsuperscript{41} These workers found (Scheme 25) that phenyl isocyanate (98) condensed with aromatic hydrocarbons (e.g. benzene) in the presence of aluminium chloride to afford anilides [e.g. (99)] in 50\% yield.

The same reaction was subsequently investigated\textsuperscript{42} using hexafluoroboric acid but afford the corresponding anilides [e.g. (99)] in poorer yield. The mechanism shown in Scheme 26 has been proposed by McFarland and Yao\textsuperscript{43} for the Friedel-Crafts reaction of tosyl isocyanate (100) with anisole (101). These authors propose that the aluminium trichloride forms a complex (101) with the isocyanate which enhances the electrophilic nature of the carbon centre in the latter thus promoting the electrophilic substitution reaction to form the amide (103). This type of Friedel-Crafts process has been successfully applied to a key step in the total synthesis of (±)-lycoricide\textsuperscript{44} (Scheme 27). In this example the six membered lactam (105) is formed by an electrophilic aromatic substitution reaction of the isocyanate group with the adjacent phenyl ring.

By virtue of their close structural relationship to isocyanates, carbodiimides would also be expected to undergo Friedel-Crafts type
Scheme 29

(R = Ph, OC\textsubscript{2}H\textsubscript{5}, or OCH\textsubscript{3}; R' = aryl or alkyl)
(X = O or S)
process. However at the outset of the present studies no example of the participation of a carbodiimide in a Friedel-Crafts type process, either intermolecular or intramolecular had been reported in the literature. Recently however Molina and his coworkers\(^\text{45}\) have described the purely thermal cyclisation (Scheme 28) of the pyrrolylphenyl carbodiimides (106) to the corresponding 4-aminopyrrolo[1,2-a]quinoxalines (107).

The work described here is the development of a general synthetic route to tricyclic heteropines via novel Friedel-Crafts cyclisations involving carbodiimides. The initial approach to the development involved investigations of the preparation of analogous structures to that of the biologically active molecule pirenzepine (8) Although pirenzepine (8) is a diazepine ring system, an initial study was carried out into the synthesis of oxazepines for simplicity. Thus Chapter 2 deals with the general synthesis of oxazepines with the following Chapters, 3 and 4, covering the extension of the synthetic strategy to diazepines and thiazepines respectively.

2.2 **Investigations of Heterocumulene Cyclisation Reactions Leading To Pyrido[2,3-b][1,4]benzoxazepine Derivatives**

The initial objective of the work was the development of a synthetic pathway for the preparation (Scheme 29) of pyrido[2,3-b][1,4]benzoxazepines (114) and pyrido[2,3-b][1,4]benzoxazepinones (115) as outlined via the phosphinimine (111).
(108) + (109) \rightarrow (110)

(i) NaH, DMF, 100°;
(ii) H₂, PdC, C₂H₅OCOCH₃, room temp., atmos. press.
(iii) PhCOCl, (C₂H₅)₃N, DME, room temp.

Scheme 30
Scheme 31

(i) HCl, NaNO₂, 0°, then NaN₃, 0°;
(ii) Ph₃P,(C₂H₅)₃N, Cl₃CCl₃, CH₃CN, reflux;
(iii) Ph₃P, DME, 60°;
(iv) HCl(aq), reflux;
(V) PhNCO, DME, room temp, then SiO₂;
(vi) NaOH(aq) dioxane, room temp;
(vii) HCl(aq), dioxane, room temp.
The initial step in the general synthetic strategy (Scheme 29) involved the synthesis (Scheme 30) of the nitropyridyl either (110). This previously undescribed compound was formed in high yield (89%) by reaction of the sodium salt of 3-methoxyphenol (109) with 2-chloro-3-nitropyridine (108) in a process involving nucleophilic displacement of the chloro-substituent in the latter. The nitropyridine derivative (110) analyzed correctly and showed spectroscopic properties in accord with its assigned structure and on catalytic reduction afforded the expected amine (116) as an oil in essentially quantitative yield. The amine (116) was characterised analytically and spectroscopically and by its acylation with benzoyl chloride yielding the N-benzoyl derivative (117) in high yield (86%).

The amine (116) was next transformed quantitatively (Scheme 31) into the azidopyridine derivative (118) by diazotisation followed by treatment of the resulting diazonium salt with sodium azide. Treatment of the azide (118) with triphenyl phosphine in 1,2-dimethoxyethane at 60° resulted in its transformation in near quantitative yield into the expected phosphinimine derivative (119). In addition to its characterisation by combustion analysis and mass and $^1$H n. m. r. spectroscopy the identity of the phosphinimine (119) was further proven by its hydrolytic conversion into the amine (116) and triphenylphosphine oxide in aqueous hydrochloric acid. The nature of the phosphinimine (119) was also verified by its alternative synthesis directly from the amine (116) using a procedure described by Wainhoff et al.\textsuperscript{40} This involved the \textit{in situ} generation of triphenylphosphine
dichloride and its condensation with the amine (116) with elimination of two equivalents of hydrogen chloride. Although the phosphinimine (119) was obtained in one step from the amine (116) by this method the yield (50%) was poor in comparison to that obtained by the route involving the azide (118).

Although the synthetic route to the phosphinimine (119) involving the azide (118) was higher yielding, investigations were carried out to improve the efficiency of the direct method from the amine (116) employing the conditions described by Wamhoff. It was found that near quantitative yields of the phosphinimine (119) could be produced by repetition of the reaction as described by Wamhoff using a two-fold increase in the amount of triphenylphosphine, hexachloroethane and triethylamine. As a consequence of the use of excess reagents large amounts of triphenylphosphine oxide were produced on workup. The phosphinimine (119) was purified free from triphenylphosphine oxide by flash-column chromatography over silica.

Treatment (Scheme 31) of the phosphinimine (119) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature gave a product which after attempted purification by column chromatography yielded the urea (121) presumably as a result of hydrolysis of the initially formed carbodiimide (120). The urea (121) gave a combustion analysis and mass, i.r. and $^1$H n.m.r. spectra supporting its assigned structure. Attempts were also made to further verify the structure of the urea (121) by its hydrolytic
(i) $\text{H}_2\text{SO}_4\text{(aq), C}_3\text{H}_5\text{CO}_2\text{H, reflux;}$
(ii) $\text{PhN}=\text{C}=0, \text{DME, room temp.}$

Scheme 32
degradation to the amine (116). However attempted hydrolysis by heating under reflux with either 2M aqueous or 20% aqueous potassium hydroxide solutions gave only high yields of the unreacted urea (121). In contrast (Scheme 32) the urea (121) was successfully degraded to the amine (116) by hydrolysis under acidic conditions. The structure of the urea (121) was fully confirmed by its independent synthesis from the amine (116) by reaction with phenyl isocyanate in 1,2-dimethoxyethane at room temperature.

Repetition of the reaction of the phosphinimine (119) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature verified that the urea (121) originated from the initially expected carbodiimide derivative (120). This the crude product showed i.r. absorption at 2140 cm\(^{-1}\) attributable to the heterocumulene moiety present in the carbodiimide (120). However a major drawback of the aza-Wittig reaction of the phosphinimine (119) with phenyl isocyanate was the coformation of triphenylphosphine oxide as by-product. This contaminant could not be removed from the oily carbodiimide (120) by chromatography due to hydrolysis of the latter to the urea (121) as already discussed. Moreover, though carbodiimides as a general class are relatively thermally stable attempted removal of the contaminating triphenylphosphine oxide by preferential distillation of the oily carbodiimide (120) from the crude product resulted in its decomposition. It was found that at best the crude carbodiimide (120) could only be partially freed from contaminating
triphenylphosphine oxide by extraction with diethyl ether leaving the latter largely but not entirely insoluble.

Although the carbodiimide (120) could not be completely purified for full characterisation its identity was verified by its hydrolysis to the urea (121) under both acidic and basic conditions.

Despite the fact that the carbodiimide (120) derived from the phosphinimine (119) was only available in impure form it was decided at this point to investigate its Friedel-Crafts type cyclisation (Scheme 33) to the pyridobenzoxazepine derivative (122). Since boron trifluoride etherate has been extensively used as an efficient mild catalyst for orthodox Friedel-Crafts processes this reagent was initially investigated as a catalyst for the process [(120) -> (122)]. However heating the carbodiimide (120) under reflux with boron trifluoride etherate in methylene chloride failed to afford the ring-closed product (122) but rather only the urea (121) in low yield (19%). The urea product (121) of this reaction presumably arises by hydrolysis of the carbodiimide (120) on workup.

Polyphosphoric acid has found many applications as a catalyst for effecting alkylations and acylations of aromatic systems but suffers from the disadvantage of being relatively viscous at low temperatures. An equivalent alternative reagent consisting of a 10% solution of phosphorous pentoxide in methanesulphonic acid which does not suffer from this disadvantage has been recently developed by Eaton et al. Again however stirring the carbodiimide (120) with Eaton’s reagent at room temperature for 24h in an
attempt to obtain the pyridobenzoxazepine derivative (122) gave instead only a high yield of the urea (121). Conversely repetition of this reaction at 100° gave only a complex mixture from which no identifiable material was obtained.

Aluminium chloride has also been widely used as a Friedel-Crafts catalyst in acylation reactions. In the present studies heating the carbodiimide (120) with 2.2 equivalents of aluminium trichloride in carbon disulphide afforded a readily separable mixture of two isomeric products in low yield. The minor product, isolated in low yield (10%), analysed correctly and gave mass, i.r. and 1H n.m.r. spectra consistent with its formation as either of the pyridobenzoxazepine structures (122) and (123). The formation of this product as the 9-methoxy derivative (122) was supported by NOE enhancement of the signal due to the proton at H-10 by irradiation of the methoxy group and its structure firmly established by x-ray analysis (see Figure 1 and Tables 1 and 2). The structure of the pyridobenzoxazepine derivative (122) was further verified by its reaction with phenyl isocyanate to give the expected urea derivative (124) in high yield (94%). The second isometric product, obtained in somewhat higher yield (18%), is formulated as the 7-methoxy derivative (123) on the basis of its analytical and mass spectral properties.

Although aluminium chloride in carbon disulphide has been used as the standard catalyst-solvent combination for Friedel-Crafts reactions, Sims et al. have reported improved conditions using aluminium chloride in
### Table 1. Bond Lengths (Å) with standard deviations

<table>
<thead>
<tr>
<th>Bond Lengths</th>
<th>Value (Å)</th>
<th>Standard Deviation (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1) - C(2)</td>
<td>1.344</td>
<td>0.009</td>
</tr>
<tr>
<td>N(1) - C(11')</td>
<td>1.320</td>
<td>0.008</td>
</tr>
<tr>
<td>C(2) - C(13)</td>
<td>1.366</td>
<td>0.010</td>
</tr>
<tr>
<td>C(3) - C(4)</td>
<td>1.391</td>
<td>0.009</td>
</tr>
<tr>
<td>C(4) - C(4')</td>
<td>1.391</td>
<td>0.009</td>
</tr>
<tr>
<td>C(4') - N(5)</td>
<td>1.399</td>
<td>0.008</td>
</tr>
<tr>
<td>C(4') - C(11')</td>
<td>1.391</td>
<td>0.009</td>
</tr>
<tr>
<td>N(5) - C(6)</td>
<td>1.304</td>
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<tr>
<td>C(6) - C(6')</td>
<td>1.458</td>
<td>0.013</td>
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<tr>
<td>C(6) - N(61)</td>
<td>1.377</td>
<td>0.010</td>
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<tr>
<td>C(6') - C(7)</td>
<td>1.409</td>
<td>0.010</td>
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<tr>
<td>C(7) - C(8)</td>
<td>1.372</td>
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<tr>
<td>C(8) - C(9)</td>
<td>1.390</td>
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### Table 2. Angles (degrees) with standard deviations

<table>
<thead>
<tr>
<th>Bond Angles</th>
<th>Value (°)</th>
<th>Standard Deviation (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1) - C(11') - C(13)</td>
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<td>0.6</td>
</tr>
<tr>
<td>C(2) - C(11') - C(4')</td>
<td>122.6</td>
<td>0.6</td>
</tr>
<tr>
<td>C(2) - C(3) - C(4)</td>
<td>118.6</td>
<td>0.6</td>
</tr>
<tr>
<td>C(3) - C(4) - C(4')</td>
<td>120.0</td>
<td>0.6</td>
</tr>
<tr>
<td>C(4) - C(4') - N(5)</td>
<td>117.8</td>
<td>0.5</td>
</tr>
<tr>
<td>C(4') - C(11'') - C(11')</td>
<td>116.1</td>
<td>0.6</td>
</tr>
<tr>
<td>N(5) - C(6) - C(6')</td>
<td>112.2</td>
<td>0.6</td>
</tr>
<tr>
<td>C(6) - C(6') - C(7)</td>
<td>114.3</td>
<td>0.5</td>
</tr>
<tr>
<td>C(6') - C(10) - C(10')</td>
<td>121.4</td>
<td>0.5</td>
</tr>
<tr>
<td>C(7) - C(7') - C(8)</td>
<td>117.7</td>
<td>0.5</td>
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<tr>
<td>C(8) - C(9) - C(10)</td>
<td>121.8</td>
<td>0.5</td>
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### Table 3. Torsion angles (degrees) with standard deviations

<table>
<thead>
<tr>
<th>Torsion Angles</th>
<th>Value (°)</th>
<th>Standard Deviation (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(11') - C(13) - C(4')</td>
<td>-0.4</td>
<td>10.9</td>
</tr>
<tr>
<td>C(2) - C(3) - C(4) - C(4')</td>
<td>1.3</td>
<td>10.9</td>
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<td>C(3) - C(4) - C(4') - N(5)</td>
<td>-5.0</td>
<td>9.1</td>
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<tr>
<td>C(4) - C(4') - N(5) - C(6)</td>
<td>-170.6</td>
<td>6.6</td>
</tr>
<tr>
<td>C(5) - C(6) - C(6') - C(7)</td>
<td>37.0</td>
<td>9.0</td>
</tr>
<tr>
<td>C(6) - C(6') - C(7) - C(8)</td>
<td>140.1</td>
<td>7.7</td>
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<tr>
<td>C(7) - C(8) - C(9) - C(10)</td>
<td>113.9</td>
<td>6.6</td>
</tr>
<tr>
<td>C(8) - C(9) - C(10) - C(11')</td>
<td>150.2</td>
<td>6.6</td>
</tr>
<tr>
<td>C(9) - C(10) - C(11') - C(13)</td>
<td>37.0</td>
<td>9.0</td>
</tr>
<tr>
<td>C(10) - C(11') - C(13) - N(1)</td>
<td>4.0</td>
<td>9.0</td>
</tr>
<tr>
<td>C(11') - C(13) - N(1) - C(2)</td>
<td>179.9</td>
<td>6.6</td>
</tr>
<tr>
<td>C(13) - C(11') - N(1) - C(2)</td>
<td>179.9</td>
<td>6.6</td>
</tr>
<tr>
<td>C(11') - C(13) - N(1) - C(2)</td>
<td>-0.4</td>
<td>10.9</td>
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<td>C(13) - C(11') - N(1) - C(2)</td>
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<td>6.6</td>
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<tr>
<td>C(11') - C(13) - N(1) - C(2)</td>
<td>179.9</td>
<td>6.6</td>
</tr>
<tr>
<td>C(13) - C(11') - N(1) - C(2)</td>
<td>-0.4</td>
<td>10.9</td>
</tr>
<tr>
<td>C(11') - C(13) - N(1) - C(2)</td>
<td>179.9</td>
<td>6.6</td>
</tr>
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</table>

### Table 4. Hydrogen Bond Distances (Å) with standard deviations

<table>
<thead>
<tr>
<th>Hydrogen Bond</th>
<th>Distance (Å)</th>
<th>Standard Deviation (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(9) - O(91)</td>
<td>1.426</td>
<td>0.010</td>
</tr>
<tr>
<td>C(9) - O(91)</td>
<td>1.426</td>
<td>0.010</td>
</tr>
<tr>
<td>C(9) - O(91)</td>
<td>1.426</td>
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<tr>
<td>C(9) - O(91)</td>
<td>1.426</td>
<td>0.010</td>
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</tbody>
</table>
Scheme 34

(i) SnCl$_4$, CH$_2$Cl$_2$, room temp;
(ii) SnCl$_4$, CH$_2$Cl$_2$, reflux;
(iii) TiCl$_4$, CH$_2$Cl$_2$, reflux;
(iv) SnCl$_4$, CH$_2$CH$_2$Cl, reflux.
dichloromethane as solvent. However the attempted cyclisation (Scheme 33) of the carbodiimide (120) using aluminium chloride in dichloromethane gave the pyridobenzoxazepine derivative (122) in very poor yield (9%) together with an unresolvable multicomponent mixture which yielded no identifiable material.

There are reports in the literature of successful Friedel-Crafts type acylations being carried out using zinc chloride as the catalyst.\textsuperscript{52} In view of this it was decided to attempt to improve the efficiency of the cyclisation of the carbodiimide (120) by heating the former with zinc chloride under reflux in tetrachloroethane for 24h. However these conditions resulted only in a complex multicomponent mixture whose t.l.c. showed neither of the expected pyridobenzoxazepine products (122) or (123) to be present.

The Lewis acid, stannic chloride, has been demonstrated\textsuperscript{53} to be synthetically useful as a catalyst in Friedel-Crafts type cyclisations and in some instances has been proved to be more effective than aluminium chloride. In the present investigations it was found that the use of stannic chloride as catalyst (Scheme 34) greatly improved the efficiency of the Friedel-Crafts type cyclisation [(120) \rightarrow (122)]. Treatment of the carbodiimide (120) with five equivalents of stannic chloride in methylene chloride at room temperature for 24 h gave a moderately increased yield (36%) of the pyrido[b,f][1,4]benzoxazepine (122) together with a low yield (14%) of the urea (121). Repetition of this reaction at elevated temperature by heating under reflux in methylene chloride had a favourable
effect, the yield of the pyridobenzoxazepine (122) being increased to 49%.
The urea (121) was again formed in low yield (7%) as a by-product in this reaction. Urea formation is assumed to arise from the hydrolysis of unreacted carbodiimide (120) on workup.

As already indicated the carbodiimide (120) used in the foregoing investigations was partially contaminated with triphenylphosphine oxide due to the lack of a suitable method of purification as discussed earlier. The effect of the contaminating triphenylphosphine oxide on the efficiency of the cyclisation of the carbodiimide (120) was not known and might be the reason for the poor to moderate yields of the pyridobenzoxazepine (122) and (123) obtained. In an attempt to quantify the effect of the triphenylphosphine oxide contaminant, the completely unpurified carbodiimide (120) contaminated with one equivalent of triphenylphosphine oxide was heated under reflux in methylene chloride with five equivalents of stannic chloride for 24h. In contrast to the yield of the pyridobenzoxazepine (122) obtained from the reaction of the partially purified starting material (120) the yield in this case decreased to 16% with 16% of urea (121) formation. Although the exact cause of the decreased efficiency of the cyclisation of the heavily contaminated carbodiimide is not known this experiment does illustrate that the presence of the triphenylphosphine oxide contaminant has a detrimental effect on the cyclisation process.

Another variable which could play a role in the optimisation of the reaction conditions is the amount of catalyst employed. The use of five
Variation of the Infrared Absorption of the Carbodiimide Derivative (120) with Molar Equivalents of Stannic Chloride*

(* Measured in methylene chloride)

Figure 2
equivalents of the Lewis acid was based on the number of potential coordination sites in the carbodiimide structure (120).

Repetition of the cyclisation of the partially purified carbodiimide (120) in refluxing methylene chloride using seven equivalents of stannic chloride and a reaction time of 24h gave the pyridobenzoxazepine (122) in the low yield (39%) together with the urea (121) also in low yield (17%). Thus in comparison to the earlier experiment in which five equivalents of stannic chloride had been used, the increase in the amount of catalyst used appears to have a detrimental effect on the yield of pyridobenzoxazepine (122) produced.

On the assumption that the mechanism of the Lewis acid catalyst cyclisation of the carbodiimide (120) to the pyridobenzoxazepine (122) involves initial complexation between the catalyst and one of the nitrogen atoms of the carbodiimide moiety it was of interest to ascertain how many equivalents of Lewis acid are required before complexation at this site occurs. An infrared spectroscopic study was therefore carried out to try and probe this aspect of the Lewis acid catalyst cyclisation [(120) -> (122)]. The validity of this study was based on the assumption that complexation between the Lewis acid and the carbodiimide substituent would in some way affect its characteristic infrared absorption at 2140cm\(^{-1}\). The graph of the data obtained (Figure 2) shows the absorption of the carbodiimide multiple bond system persisting until five equivalents of stannic chloride have been added. If the decrease in the absorption observed can be ascribed to
complexation between the carbodiimide group and stannic chloride then it can be argued that five equivalents of the Lewis acid is the minimum quantity needed for this to occur. If complexation to the carbodiimide moiety is a prerequisite for cyclisation then it can be inferred that five equivalents of catalyst is also the minimum amount needed to achieve efficient cyclisation.

Having obtained reasonably firm evidence for the optimum amount of catalyst required to promote the cyclisation of the carbodiimide (120), further studies were undertaken to try and improve the yield of the pyridobenzoxazepine (122). Titanium tetrachloride has also been used as the Lewis acid catalyst in Friedel-Craft type cyclisations and it was therefore of interest to know if the use of this catalyst would increase the efficiency of the cyclisation reaction \[(120) \rightarrow (122)\]. In practice heating the carbodiimide (120) under reflux with five equivalents of titanium tetrachloride in methylene chloride afforded a comparable yield (49%) of the pyridobenzoxazepine (122) to that obtained using stannic chloride under the same conditions indicating that the nature of the Lewis acid catalyst has relatively little bearing on the efficiency of the cyclisation. In contrast heating under reflux with five equivalents of stannic chloride in methylene chloride with prolongation of the reaction time to 48h resulted in an increase in the yield of the pyridobenzoxazepine (122) to a more respectable 58%, the urea (121) also being formed in minor amounts (6%). The yield of the pyridobenzoxazepine (122) was only marginally improved upon at
elevated temperature, thus, heating the carbodiimide (120) under reflux with five equivalents of stannic chloride for 24h in the higher boiling solvent 1,2-dichloroethane resulted in its transformation into the pyridobenzoxazepine (122) (59%) together with the urea (121) (8%). Increasing the reaction temperature even further by repetition of the reaction in refluxing 1,1,2,2-tetrachloroethane gave only a complex mixture whose t.l.c showed only the presence of the urea (121), with no indication of the presence of the pyridobenzoxazepine (122).

In conclusion the optimum conditions for achieving the maximum efficiency of the cyclisation [(120) -> (122)] were to heat under reflux with five equivalents of stannic chloride in 1,2-dichloroethane for 24h. However under these conditions the urea (121) was still being formed as a by-product presumably as the result of hydrolysis of the unreacted carbodiimide (120) on workup. Thus there is still scope for the optimisation of the reaction conditions. Reaction temperature and time have been shown to be important and it is possible that further optimisation of these parameters might improve the efficiency of the cyclisation [(120) -> (122)] even further. However it was decided at this stage to direct attention to the investigations of the scope of novel Lewis acid catalysed transformations of the type [(120) -> (122)]. Thus having demonstrated the Lewis acid catalysed Friedel-Crafts type cyclisation of the carbodiimide (120) to the pyridobenzoxazepine (122) in reasonable yield it was of interest to investigate the synthesis of
Scheme 35

(i) CH$_3$N=C=O, DME, room temp.
(ii) SnCl$_4$, CH$_2$Cl$_2$, reflux.
(i) PhCH$_2$N=C=O, DME, room temp;
(ii) SnCl$_4$, Cl(CH$_2$)$_2$Cl, reflux.

Scheme 36
other carbodiimides and their subsequent Lewis acid catalysed cyclisation reactions (Schemes 35 and 36).

Reaction of the phosphinimine (119) with methyl isocyanate in 1,2-dimethoxyethane at room temperature gave the crude carbodiimide (125) in quantitative yield which due to its instability to heat and column chromatography could not be purified and was characterised by its typical infrared absorption at 2160 cm\(^{-1}\). Heating the crude carbodiimide (125) under reflux with five equivalents of stannic chloride in methylene chloride for 24h gave only a low yield (10\%) of a product identified on the basis of its high resolution mass spectrum as the expected pyridobenzoxazepine derivative (126). The inefficiency of this reaction can be attributed to the impure nature of the carbodiimide starting material (125) which was heavily contaminated with difficult to remove triphenylphosphine oxide.

Reaction (Scheme 36) of the phosphinimine (119) with benzylisocyanate in 1,2-dimethoxyethane at room temperature afforded the crude carbodiimide (127) which again due to its instability to heat and column chromatography could only be partially freed from triphenylphosphine by its preferential solubility in ether. It was hoped that cyclisation of the carbodiimide (127) would yield the corresponding pyridobenzoxazepine (128), debenzylation of which would permit the synthesis of the primary amino derivative (130). Exploitation of the amino functionality in the latter would in turn allow synthetic access to analogues of the biologically active tricyclic heteropines pirenzepine (8) and clozapine.
(i) NaH, DMF, 100°C;
(ii) H₂, PdC, C₂H₅OCOCH₃, room temp., atmos. press.;
(iii) Ph₃P, (C₂H₅)₃N, Cl₂CCL₃, CH₃CN, reflux;
(iv) PhN=C=O, DME, room temp.

Scheme 32
Scheme 38

(i) HCl (aq), DME, room temp;
(ii) SnCl$_4$, Cl(CH$_2$)$_2$Cl, reflux;
(iii) n-C$_4$H$_9$Li, THF, room temp.
Scheme 39

(i) PhLi, pentane, 10 °.

Scheme 40

(i) n-C₆H₅Li;
(ii) H₂O.
(7) (see Chapter 1). Unfortunately the attempted stannic chloride cyclisation (Scheme 36) of the partially purified carbodiimide (127) gave only a moderate yield (55%) of the urea (129) with no evidence for the formation of the expected pyridobenzoxazepine (128). The apparent lower reactivity of the benzylcarbodiimide (127) towards cyclisation compared with the phenyl derivative (120) may be due to the lower electrophilicity of the carbodiimide substituent in the former stemming from the net electron-donating effect of the benzyl substituent.

Although the success of the Lewis acid catalysed transformation [(120) -> (122)] clearly demonstrates the feasibility of the tricyclic heteropine synthesis based on intramolecular Friedel-Crafts type processes of carbodiimide it was of interest to know if the electron-donating m-methoxy substituent in the carbodiimide (120) is essential for its successful cyclisation. To this end it was decided to synthesise and investigate the Lewis acid catalysed cyclisation (Schemes 37 and 38) of the des-methoxy carbodiimide (135). Work carried out by Pomet and Miginiac has shown (Scheme 39) that phenyllithium adds across the carbodiimide substituent of diphenyl carbodiimide (139) giving the addition product (140). Hence it was anticipated that even if the carbodiimide derivative (135) failed to undergo Lewis acid catalysed cyclisation its availability would allow the study (Scheme 40) of its conversion into an ortho-lithiated derivative (141) set up for cyclisation to the pyridobenzoxazepine (138) through nucleophilic
addition of the ortho-lithio carbanion across the electrophilic carboximide side-chain.

In pursuit of those objectives (Scheme 37) 2-chloro-3-nitropyridine (108) was condensed with sodium phenolate in dimethylformamide at 100° to afford the known\(^{58}\) 3-nitropyridyl ether (132) in high yield (89%). The nitropyridine derivative (132) in turn was readily reduced catalytically over palladium-on-charcoal to give the known\(^{59}\) amine (133) in 93% yield as a yellow solid which had a melting-point consistent with the literature\(^{59}\) and showed spectroscopic properties in accord with its structure. The amine (133) in turn was directly transformed into the phosphinimine (134) in moderate yield (54%) using the Wamhoff procedure described before. The phosphinimine (134) characteristically underwent an aza-Wittig reaction with phenyl isocyanate to give the expected carbodiimide (135) in near quantitative yield. As in the preparation of the carbodiimide (120), the crude product (135) was heavily contaminated with triphenylphosphine oxide. However in this case the compound was more easily purified by recrystallisation yielding a colourless crystalline solid which analysed correctly and had spectroscopic properties consistent with the proposed carbodiimide structure (135). The identity of the carbodiimide (135) was further verified by its hydrolysis (Scheme 38) with aqueous hydrochloric acid to give the urea (136) in good yield (72%).

It was of interest at this stage to see what effect the absence of the methoxy group would have on the attempted Lewis acid catalysed cyclisation
(Scheme 38) of the carbodiimide (135) to the corresponding pyridobenzoxazepine (138). Thus the carbodiimide (135) was heated under reflux with five equivalents of stannic chloride in 1,2-dichloroethane for 24h. However this reaction gave only a multicomponent mixture which yielded no identifiable material. This result tends to indicate that activation by both the ether oxygen and an electron-donating meta substituent in the phenyl ring is a prerequisite for successful Lewis acid catalysed cyclisation of pyridyl aryl ethers of the type (135) to the corresponding pyridobenzoxazepines [e.g. (138)]. However the lack of formation of the urea (136) expected from hydrolysis of the unreacted carbodiimide (135) on workup is surprising. This result may indicate that under the reaction conditions the carbodiimide (135) may follow reaction pathways other than cyclisation thus accounting for the complex mixture obtained.

In view of the failure of the carbodiimide (135) to undergo Lewis acid catalysed cyclisation it was decided to attempt to promote the cyclisation of this substrate to the pyridobenzoxazepine derivative (138) by lithiation\textsuperscript{57} of the phenyl ring ortho to the ether substituent (Scheme 38). It was anticipated that the resulting carbanion (141) would exhibit enhanced reactivity towards cyclisation by nucleophilic addition to the carbodiimide side chain thus providing an efficient route to the pyridobenzoxazepine derivative (138). In practice however the attempted reaction of the carbodiimide (135) with n-butyllithium in tetrahydrofuran gave a low yield (32%) of a product whose accurate mass analysis and spectroscopic
properties allow its formulation as the amidine derivative (137). This product is derived by simple nucleophilic addition of n-butyllithium across the carbodiimide substituent in the ether. Pornet and Miginiac\textsuperscript{56} have reported the analogous nucleophilic addition of n-butyllithium across the heterocumulene system of diphenylcarbodiimide. n-Butyllithium therefore prefers to add across the carbodiimide substituent rather than form the ortho-lithiated intermediate (141) required for possible subsequent cyclisation. The use of the more hindered sec-butyllithium, would favour ortho-lithiation at the expense of nucleophilic addition across the carbodiimide substituent. However though this reagent was not investigated for the promotion of the cyclisation [(135) \(\rightarrow\) (138)] it was employed in an attempt to effect a related type of cyclisation as described later.

As already demonstrated, one of the factors responsible for the relative inefficiency of the Lewis acid catalysed cyclisation of the carbodiimide (120) to the pyridobenzoxazepine (122), was the presence in the former of contaminating triphenylphosphine oxide which not surprisingly must interfere with the course of the cyclisation. Since the presence of the triphenylphosphine oxide impurity in the carbodiimide (120) was a consequence of the use of the triphenylphosphinimine (119) in its preparation it was of obvious interest to seek an alternative aza-Wittig type process with a more readily removable phosphorus by-product. Studies by Wadsworth and Emmons\textsuperscript{60} have shown (Scheme 41) that carbodiimides are also products of the reactions of isocyanates (144) with readily available
Scheme 42

(i) \((\text{C}_2\text{H}_5\text{O})_2\text{PH}=\text{O}, (\text{C}_2\text{H}_5)_3\text{N}, \text{CCl}_4, \text{toluene, 50}^\circ\);  
(ii) \((\text{C}_2\text{H}_5\text{O})_3\text{P}, \text{DME, room temp};\)  
(iii) \(\text{PhN}=\text{C}=\text{O}, \text{NaH, DME, 70}^\circ\);  
(iv) \(\text{SnCl}_4, \text{Cl(CH}_2\text{)}_2\text{Cl, reflux}.\)
phosphoramidate anions (143). However the phosphorus by-product in this case is a water soluble, and hence readily removable phosphate (146). It was therefore decided to investigate the synthesis and Wadsworth-Emmons reaction (Scheme 42) of the phosphoramidate derivative (148) as an alternate route to the pure carbodiimide (120) for use in more efficient synthesis of the pyridobenzoxazepine (122). Initially attempts (Scheme 42) were made to convert the available amine (116) using a procedure described by Atherton, Openshaw and Todd involving triethylamine catalysed reaction with diethyl phosphite and carbon tetrachloride in toluene at room temperature. However under these conditions the starting amine (116) was recovered largely unchanged. However repetition of this reaction at 50°C while still giving a substantial amount (79%) of the amine (116) also afforded a low yield (17%) of a product which analysed correctly and had mass, i.r. and $^1H$ n. m. r. spectra in accord with the required phosphoramidate (148). An attempt to enhance the yield of the phosphoramidate (148) by carrying out the reaction of the amine (116) with diethyl phosphite and carbon tetrachloride in refluxing toluene in the presence of triethylamine was unsuccessful.

In a more direct approach reaction of the amine (116) with one equivalent of diethyl chlorophosphite in the presence of triethylamine also failed to produce any of the phosphoramidate (148). Atherton et al have reported good yields of the corresponding phosphoramidates by reaction of even weakly basic amines such as aniline with dibenzyl phosphite and carbon
tetrachloride in the presence of triethylamine. However even these conditions failed to give an appreciable amount of the corresponding phosphoramide from the amine (116).

Recent studies by Koziara described a one-pot transformation of alkyl bromides into N-alkylphosphoramidates by initial conversion of the alkyl bromide into the corresponding azide, then reaction of the latter with triethyl phosphite and subsequent hydrolysis of the resulting triethoxyphosphinimine. With the azide (118) already available as described before it was decided to investigate the use of this substrate in a route to the phosphoramide (148) (Scheme 42) based on Koziara's method. In practice reaction of the azide (118) with an equivalent amount of triethyl phosphite gave an oil which on attempted purification by flash-column chromatography over silica gave a high yield of the required phosphoramide (148). The phosphoramide (148) was presumably formed via the triethoxyphosphinimine (147) which was hydrolysed on the silica during chromatography.

Having devised an efficient route to the phosphoramide (148) its conversion into the carbodiimide (120) using the Wadsworth-Emmons procedure was investigated (Scheme 42). Reaction of the phosphoramide anion, generated in situ from the phosphoramide (148) and sodium hydride, with phenyl isocyanate gave a high yield of the carbodiimide (120) which had spectroscopic characteristics similar to the sample obtained previously from the triphenylphosphinimine (119).
However on standing the sample's characteristics carbodiimide infrared absorption at 2140 cm\(^{-1}\) slowly disappeared. This behaviour was not observed with the sample of the carbodiimide (120) obtained from the triphenylphosphinimine (119) which was contaminated with triphenylphosphine oxide. Interestingly however the carbodiimide absorption in the infrared spectrum of the sample of the carbodiimide (120) obtained from the phosphoramidate (148) reappeared when the sample was heated. This type of phenomenon has also been observed by Wadsworth and Emmons\(^{60}\) who postulate that carbodiimide cyclodimerisation may be the cause of the observed changes though no evidence was presented in support of this suggestion. However since the proposal of Wadsworth and Emmons evidence for the tendency of carbodiimides to undergo cyclodimerisation has accumulated.\(^{46,63}\) The mass spectrum of the sample of the carbodiimide (120) obtained from the phosphoramidate (148) is complex but does show the presence of very high molecular ions indicating the possible presence of polymeric material. It is not clear why the sample of the carbodiimide (120) derived from the triphenylphosphinimine (119). It is possible that the presence of contaminating triphenylphosphine oxide in this particular sample of carbodiimide (120) is having a stabilising effect on the latter towards cyclodimerisation though the mechanism for this is not obvious.

An attempt was made to ring close the sample of carbodiimide (120) derived from the phosphoramidate (148) by treatment with five
equivalents of stannic chloride in refluxing 1,2-dichloroethane for 24h. However in contrast to the successful cyclisation achieved previously, the carbodiimide (120) derived from the phosphoramidate (148) did not undergo ring closure to form the expected pyrido[b,f][1,4]benzoxazepine (122). Instead only a complex mixture was obtained which yielded no identifiable material.

In an effort to elucidate the factors responsible for the differences in the behaviour of the sample of the carbodiimide (120) obtained from the diethyl phosphoramidate (148) with that derived from the triphenylphosphinimine (119) it was decided to investigate (Scheme 43) the synthesis and properties of the carbodiimide (120) derived from the dimethyl phosphoramidate (150). To this end the azide (118) was reacted with trimethyl phosphite in 1,2-dimethoxyethane at room temperature and the resulting oily product chromatographed over silica to give the dimethyl phosphoramidate (150) in essentially quantitative yield. The phosphoramidate (150) had analytical and spectroscopic properties fully in agreement with its assigned structure. Conversion of the phosphoramidate (150) into the corresponding anion with sodium hydride followed by reaction with phenyl isocyanate afforded a quantitative yield of the carbodiimide (120). This was identical in all respects to the sample obtained from the diethyl phosphoramidate (148) except that it did not undergo the apparent cyclodimerisation exhibited by the latter. This was clearly evidenced by the persistence of the carbodiimide absorption at 2140 cm⁻¹ in the infrared.
Scheme 43

(i) \((\text{CH}_3\text{O})_3\text{P}\). DME, room temp;
(ii) \(\text{SiO}_2\);
(iii) \(\text{PhN}=\text{C}=\text{O}, \text{NaH, DME, room temp}\);
(iv) \(\text{PhN}=\text{C}=\text{O}, \text{DME, room temp}\).
spectrum of the sample of the carbodiimide (120) obtained from the
dimethyl phosphoramidate (150). The identity of this sample of the
carbodiimide (120) was firmly substantiated by its reaction with aqueous
hydrochloric acid to give the urea (121) identical in all respects to the
sample obtained before.

All of the available evidence indicates that the three samples of
carbodiimide (120) obtained from the triphenylphosphinimine (119) and the
two phosphoramidates (148) and (150) are identical. The contrasting
tendency of the sample of the carbodiimide (120) derived from the diethyl
phosphoramidate (148) to undergo cyclodimerisation may therefore be due
to the catalytic effect of traces of impurities, such as sodium diethyl
phosphate, in the later though this should have been completely removed in
the workup. Pyridine, for example, is known to catalyse the
cyclodimerisation of sulphonylcarbodiimides.

The synthesis (Scheme 43) of the phosphoramidate (150) from the
azide (118) involves the initial formation of the oily
trimethoxyphosphinimine (149) and its conversion, without characterisation,
on chromatography into the isolated product (150). It was therefore of
interest to evaluate the trimethoxyphosphinimine (149) as a more
convenient precursor of the carbodiimide (120). Combustion and spectral
analysis of the initial oily product formed in quantitative yield by reaction of
the azide (118) with trimethyl phosphite showed that it was indeed the
trimethoxyphosphinimine (149). Moreover the trimethoxyphosphinimine (149)
(i) RN=O, DME, room temp;
(ii) 4-RC₆H₄N=C=O, DME, room temp;
(iii) SnCl₂, Cl(CH₂)₂Cl, reflux;
(iv) HCl(aq), DME, room temp.

Scheme 44
underwent a smooth aza-Wittig reaction with phenyl isocyanate giving the pure carbodiimide (120) in high yield (95%) free from any phosphorus by-product which in this case was the water soluble, and therefore readily removable trimethyl phosphate. The pure carbodiimide (120) so obtained was characterised by its acid catalysed conversion into the urea (121) in moderate yield (64%). Some what disappointingly, the cyclisation of the pure carbodiicate (120) by heating under reflux with five equivalents of stannic chloride in 1,2-dichloroethane afforded the pyridobenzoxazepine (122) in only 43% yield. Removal of the contaminating triphenylphosphine oxide (see before) therefore apparently has little effect on improving the efficiency of the Lewis acid catalysed cyclisation of the carbodiimide (120) to the pyridobenzoxazepine (122). The superiority of the trimethoxyphosphinimine (149) as a starting material for the synthesis of the pure carbodiimide (120) prompted its use (Scheme 44) as a precursor of pure samples of the N-alkyl carbodiimides (125) and (127) previously available only in impure form as described before (see Schemes 35 and 36). Reaction of the trimethoxyphosphinimine (149) with benzyl isocyanate gave the pure carbodiimide (127) in quantitative yield. However the attempted stannic chloride cyclisation of the pure sample of the carbodiimide (127) to give corresponding pyridobenzoxazepine (128) was no more successful than using the sample contaminated with triphenylphosphine oxide as described before. The reaction of the trimethoxyphosphinimine (149) with methyl isocyanate gave a crude mixture whose i.r. spectrum showed absorption due
to a carbodiimide species. However attempted purification of the mixture resulted in its decomposition with no identifiable material being isolated.

The essentially unsuccessful attempts (Schemes 35 and 36) at effecting the Lewis acid catalysed cyclisations of the N-alkyl carbodiimides (125) and (127) to the corresponding pyridobenzoxazepines implies that replacement of the N-phenyl group in the carbodiimide moiety by election donating groups inhibits the cyclisation process. To probe this possibly further it was decided to investigate the synthesis and Lewis acid catalysed cyclisation (Scheme 44) of carbodiimides (150) containing respectively an election-withdrawing nitro group and an election-donating methoxy substituent. The nitro-functionalised carbodiimide (150a) was readily obtained by the reaction of the trimethoxyphosphinimine (149) with 4-nitrophenyl isocyanate as a relatively stable colourless crystalline solid. This product was fully characterised analytically and spectroscopically. Unfortunately the nitrophenyl carbodiimide (150a) underwent cyclisation to the corresponding pyridobenzoxazepine (151) in only low yield (18%) using the standard stannic chloride conditions.

The trimethoxyphosphinimine (149) reacted as expected with 4-methoxyphenyl isocyanate giving the carbodiimide (150b) in high yield (93%). However unlike the nitro-derivative (150a) the methoxyphenyl carbodiimide (150b) was an oil and in addition to its combustion and spectral analysis was characterised by its acid catalysed conversion into the urea (152). In contrast to the nitrophenyl carbodiimide (150a) the
Scheme 45

(i) \( n-C_4H_9Li \) or \( Mg \);
(ii) \( (n-C_2H_5)_3SnH \).
attempted stannic chloride catalysed ring-closure of the methoxy derivative (150b) gave only a complex mixture with no evidence for the formation of the corresponding pyridobenzoxazepine derivative. The contrasting successful formation of the pyridobenzoxazepine (151) albeit in low yield from the nitrophenyl carbodiimide (150a) provides some indication that Lewis acid catalysed cyclisation of carbodiimides of the type (150a) to the respective pyridobenzoxazepines is prompted by election-donating substituents.

Because of the success, but relative inefficiency, of Lewis acid catalysed cyclisation reactions of carbodiimides such as (120) to the corresponding pyridobenzoxazepines [e.g. (122)] it was of interest to investigate alternative cyclisation procedures with such substrates involving nucleophilic addition of an election-rich ortho centre in the phenyl moiety across the carbodiimide side-chain (Scheme 45). Two such procedures could be envisaged using the bromo-functionalised carbodiimide derivative (153). Thus metal-halogen exchange or Grignard reaction could be used to convert the bromo compound (153) into ortho-functionalised organometallic intermediates (154) set up for cyclisation through nucleophilic addition across the carbodiimide side-chain. Though intramolecular processes of this type are unknown, intermolecular examples have been described in the literature. Moreover the propensity for metal-halogen exchange [(153) -> (154; X = Li)] to occur at low temperature
(108) 

(156) 

(i) NO₂ 

NO₂ 

(157) 

(108) 

(156) 

(ii) Br 

Br 

(157) 

Br 

Br 

(158) 

(108) 

(156) 

(iii) 

(159) 

(160) 

(iv) 

(160) 

(159) 

(v) 

(153) 

(158) 

(vi), (vii) or (viii) 

(138) 

(i) NaH, DMF, 100°C; 
(ii) H₂, Pd/C, C₂H₄COCH₃, room temp., atmos. press; 
(iii) HCl(aq), NaNO₂, 0°C, then NaN₃, 0°C; 
(iv) (CH₃O)₃P, DME, room temp; 
(v) PhN=C=O, DME, room temp; 
(vi) Mg, (C₂H₄)₂O, room temp; 
(vii) s-C₆H₅Li, THF, room temp; 
(viii) (C₆H₅)₃SnH, AIBN, C₆H₆, reflux. 

Scheme 46
would avoid the butyllithium reagent across the carbodiimide substituent observed before (see Scheme 38).

A second approach (Scheme 45) would involve possible cyclisation of the radical intermediate (155) produced by reaction of the bromo-substituted carbodiimide (153) with tributyltin hydride. Again though intramolecular radical addition reactions of carbodiimides appear to be unknown, intermolecular processes of this type have been reported in the literature.

The bromo-funtionalised carbodiimide (153) required for the investigation of these alternative cyclisation strategies was readily prepared by the standard approach already developed as outlined in Scheme 46. All of the steps in this synthesis went in greater than 90% yield and the bromo-carbodiimide derivative (153) in particular was obtained as a crystalline solid in 92% yield.

Disappointingly treatment of the bromo-carbodiimide (153) with magnesium metal in anhydrous diethyl ether for 65h at room temperature followed by aqueous acidic work up yielded none of the expected cyclised product (138). Only a complex mixture was obtained which yielded no identifiable product. Similarly the treatment of the bromo-carbodiimide (153) with secondary butyllithium at -100° also yielded no identifiable products. The attempted radical ring-closure of compound (153) by reaction with tributyltin hydride was also unsuccessful only an intractable mixture being obtained. Despite the failure of attempts to promote carbanion and
(i) NaH, DMF, 100°.
(ii) H, Raney Ni, CH₃CO₂H, room temp., atmos. press.;
(iii) HCl(aq), NaNO₂, 0°, then NaN₃ 0°;
(iv) (CH₃O)₃P, DME, room temp;
(v) PhN=C=O, CH₂Cl₂, room temp;
(vi) Pd(OOCCH₃), Ph₃P, K₂CO₃, (n-C₄H₉)₄⁺NO₃⁻, CH₃CN, reflux;
(vii) Pd(OOCCH₃), (Tol)₃P, (C₂H₅)₃N, CH₂CN, reflux.

Scheme 47
radical mediated cyclisations of the bromo-carbodiimide (153) under standard conditions it is possible that future more in depth studies of such cyclisation processes will be successful.

One of the more important developments in organic chemistry in recent years has been the use of organopalladium intermediates in a catalytic method for the vinylation of organic halides (Heck Reactions). Although Heck Reactions have been successfully utilised both intermolecularly and intramolecularly for the arylation of a wide variety of alkenes there are no examples to date of the palladium catalysed coupling of an organic halide with a carbodiimide multiple bond system. It was therefore of interest to see if the ring closure of an appropriate carbodiimide derivative to the corresponding pyridobenzoxazepine could be achieved by palladium catalysis. The iodo-carbodiimide starting material (166) required to test this possibility was readily synthesised using the standard approach already developed as outlined in Scheme 47. The only stage of this synthesis which presented some difficulty was that of the catalytic reduction of the nitro-compound (162) to the amine (163). The use of 10% palladium-on-charcoal as the catalyst for this transformation gave only a high recovery (96%) of the unreacted starting-material (162). However the use of Raney nickel as the catalyst achieved the reduction [(162) -> (163)] in quantitative yield. The iodo-carbodiimide (166) was subsequently obtained as a brown gum in 94% yield. Unfortunately the attempted cyclisation of the iodo-carbodiimide (166) by reaction with
(i) Cu, K₂CO₃, DMF, reflux;
(ii) (PhO)₂PON₃,(C₂H₅)₃N, toluene, 100°;
(iii) CO₂(g), DME, room temp;
(iv) SnCl₄, Cl(CH₂)₂Cl, reflux;
(V) C₂H₅OH, DME, room temp.

Scheme 4B
palladium acetate and triphenylphosphine in the presence of potassium carbonate under standard conditions of the Heck Reaction gave only a complex mixture which yielded no characterisable material. Repetition of the reaction using tri-o-tolylphosphine as the complexing ligand and triethylamine as the base also gave only a complex mixture which could not be separated chromatographically. Further work needs to be carried out to thoroughly explore the potential, if any, of the Heck reaction for the heterocyclisation of carbodiimide derivatives.

As discussed briefly before (See Section 2.2) it was also the objective of the present studies to develop general synthetic routes to pyrido[2,3-b][1,4]benzoxazepinones and pyrido[2,3-b][1,4]-benzoxazepinethiones based on intramolecular Friedel-Crafts type reactions involving the Lewis acid catalysed cyclisation of appropriate isocyanates and isothiocyanates (see Scheme 29). The requisite isocyanates (113; $X = 0$) and isothiocyanates (113; $X = S$) are in turn potentially readily accessible by the reaction$^{72}$ of appropriate phosphinimines (111) with carbon dioxide and carbon disulphide respectively. However in the present studies it was found (Scheme 48) that the reaction of the already available phosphinimine (149) with carbon dioxide gave a high yield of an oil which showed i.r absorption attributable to the presence of the required isocyanate (169). However, treatment of the oil with ethanol gave the carbamate derivative (171) only in low yield (8%). Since this result indicated that the isocyanate (169) was present in the oil only to a minor extent, an alternative route to the
isocyanate (169) was sought. Recent studies by Lasne and Ripole\textsuperscript{73} have demonstrated the formation of isocyanates by a modified Curtius reaction involving the reaction of carboxylic acids with diphenylphosphorylazide. It was therefore decided to apply this method to the synthesis (Scheme 48) of the required isocyanate (169). The known\textsuperscript{74} nicotinic acid derivative (168) was therefore prepared in high yield by the reaction of 2-chloronicotinic acid (167) with 3-methoxyphenol (109) and its reaction with diphenylphosphorylazide investigated. This gave a product in good yield (79\%) which gave mass and i.r. spectra in accordance with its formulation as the required isocyanate derivative (169). The i.r. spectrum of the compound was also identical to that of the product obtained before by the reaction of phosphinimine (149) with carbon dioxide.

Having successfully synthesised the isocyanate (169) attention was next directed to the study of its Lewis acid catalysed cyclisation to the pyridobenzoxazepinone derivative (170). The only previously described examples of a Lewis acid catalysed intramolecular Friedel-Crafts type reaction of an isocyanate appears to be that involved in the total synthesis of (±)-Lycorcidine\textsuperscript{44} described before (see Scheme 27). In the case of the isocyanate (169) heating under reflux with five equivalents of stannic chloride in 1,2-dichloroethane gave low yield (16\%) of a product which was characterised spectroscopically as the 9-methoxypyridobenzoxazepinone derivative (170) or its 7-methoxy isomer. This product is assigned the former structure by analogy with the preferential formation of the
Scheme 49

(i) CS$_2$, DME, reflux;
(ii) CH$_2$C=S, HCl(aq), room temp;
(iii) SnCl$_2$, Cl(CH$_2$)$_2$Cl, reflux.
9-methoxypyridobenzoxazepinone (122) observed before. The poor yield of the pyridobenzoaxazepininone (170) obtained in the stannic chloride catalysed cyclisation of the isocyanate (169) was disappointing. However it is possible that the efficiency of this transformation could have been improved had time permitted. Reaction (Scheme 49) of the phosphinimine (119) with carbon disulphide afforded only a poor yield (31%) of the required isothiocyanate (172) the reaction product being heavily contaminated with triphenylphosphine sulphide. However an alternative route to the isothiocyanate (172) was achieved in excellent yield (97%) by reaction of the previously prepared amine (116) with thiophosgene at ambient temperature. Having successfully obtained the desired heterocumulene (172) its transformation into the pyridobenzoxazepinethione (173) was easily achieved, albeit in only 32% yield using stannic chloride as the ring closure catalyst as before. The 9-methoxy formulation (173) for this product rather than the alternative 7-methoxy structure is based on analogy with the pyridobenzoxazepinone structure (170) as discussed before.

While the yields of the pyrido[2,3-b][1,4]benzoxazepine derivatives (122), (170) and (173) achieved in the stannic chloride catalysed cyclisations of the heterocumulene derivatives (120), (169) and (172) were only poor to moderate the success of these unprecedented heterocyclisation reactions demonstrated the potential viability of this new general approach to fused tricyclic oxazepines. This in turn promoted the evaluation of analogous routes to other such structures in which the pyridine nucleus of
Scheme 50

(i) NaH, DMF, 100 °C;
(ii) H₂, PdC, C₂H₅OCOC₂H₅, room temp., atmos. press.;
(iii) HCl(aq), NaNO₂, 0 °C, then NaN₃, 0 °C;
(iv) (CH₃O)₃P, DME, room temp.;
(v) PhN=C=O, DME, room temp.;
(vi) SnCl₄, Cl(CH₂)₂Cl, reflux.
the pyrido [2,3-b][1,4]benzoxazepine ring systems was replaced by other heteroaromatic nuclei.

2.3 **Investigations of Heterocumulene Cyclisation Reactions Leading to Various Fused Tricyclic Oxazepine Derivatives**

Initial investigations under this heading centred on the anticipated synthesis (Scheme 50) of the phenylaminobenzoxazepine (180) by the stannic chloride catalysed cyclisation of the carbodiimide derivative (179). This was readily accessible in good overall yield (Scheme 50) starting from the known\(^\text{75}\) nitrodiphenyl ether (175) and elaborating this compound by the standard strategy developed for pyridyl carbodiimide before. Heating the carbodiimide derivative (179) under reflux with five equivalents of stannic chloride in 1,2-dichloroethane gave the expected dibenoxazepine (180) as the major product (yield 71%) together with a low yield (5%) of a compound whose analytical and spectroscopic properties allow its formulation as the dibenzoxazepinone (181). This product is presumably derived by solvolysis of compound (180) under the reaction conditions. Formation of the dibenzoxazepinone derivative (181) by Lewis acid catalysed cyclisation of the carbodiimide (179) provides some indication for the general scope of such processes. However further work would be required to optimise the reaction conditions for the preparation of dibenzoxazepine derivatives such as (180) or (181) in acceptable yield.
Scheme 51

(i) \((\text{CH}_3)_2\text{NH}, \text{H}_2\text{O}\), room temp;
(ii) 20\%w/w \(\text{SO}_3\text—\text{H}_2\text{SO}_4\), \(\text{HO}_2\text{CCH(OH)CH}_2\text{CO}_2\text{H}\), 95\°;
(iii) \(\text{H}_2\text{SO}_4\), \(\text{HNO}_3\), 100\°;
(iv) \(\text{POCl}_3\), \(\text{PhN(C}_2\text{H}_2)_2\), reflux.
(i) NaH, DMF, 100°C; 
(ii) H₂, PdC, C₂H₅OCOCH₃, room temp., atmos. press.; 
(iii) H₂, PdC, CH₃CO₂H, room temp., atmos. press.; 
(iv) NaBH₄, PdC, NaOH(aq), DME, room temp.; 
(v) PhN=C=O, DME, room temp.

Scheme 52
Scheme 53

(i) HCl(aq), NaNO$_2$, 0°, then NaN$_3$, 0°;
(ii) (CH$_3$O)$_3$P, DME, room temp;
(iii) PhN=C=O, DME, room temp;
(iv) SnCl$_4$, Cl(CH$_2$)$_2$Cl, reflux.
Attention was next turned to the attempted synthesis (Schemes 51 - 53) of the pyrimido[4,3-b][1,4]benzoxazepine ring system by the stannic chloride catalysed cyclisation of an appropriate carbodiimide derivative. The particular carbodiimide (193) whose cyclisation was investigated was chosen for study on the basis of its predicted ease of synthesis (Schemes 51 and 52). This involved the initial preparation of the known76, 77 chloro-nitropyrimidine (187) as outlined in Scheme 51 and its base-catalysed reaction (Scheme 52) with 3-methoxyphenol (109) to give the previously undescribed pyrimidyl ether (188) in high yield (87%). This product was fully characterised analytically and spectroscopically and was further elaborated (Scheme 52 and 53) through the amine (189) to the required carbodiimide (193) using a similar approach to that applied in the synthesis of other structurally related carbodiimides described before. The only problem encountered in the synthesis of the pyrimidyl carbodiimide (193) concerned the reduction of the nitropyrimidine derivative (188) to the amine (189). The latter compound was isolated only in low yield (29%) as a dark brown oil on attempted reduction of the nitropyrimidine derivative (188) with hydrogen over palladium-on-charcoal at room temperature and atmospheric pressure. A substantial amount (58%) of the unreacted starting-material (188) was also recovered under these conditions. The dark oily amine (189) was characterised by its reaction with phenyl isocyanate (Scheme 52) to give a moderate yield (54%) of the solid urea derivative (190) which was fully characterised analytically and spectroscopically.
Repetition of the catalytic reduction of the nitropyrimidine derivative (188) over palladium-on-charcoal in the presence of hydrochloric acid afforded only the unreacted starting material (188) in high yield (95%). Carrying out the catalytic hydrogenation of the nitro-compound (188) over palladium-on-charcoal at elevated pressure (3 atm) also gave only low yield (13%) of the amine (189). On the other hand carrying out the hydrogenation at elevated pressure (3 atm) in glacial acetic acid with extension of the reaction time from two to six hours doubled the yield of the amine (189) to 26%. However it was ultimately found that the best yield (67%) of the amine (189) was obtained by hydrogenation of the nitro-compound (188) over palladium-on-charcoal in glacial acetic at room temperature and atmospheric pressure. The attempted hydride-transfer reduction of the nitropyrimidine derivative (188) using sodiumborohydride in aqueous sodium hydroxide in the presence of palladium-on-charcoal gave only a low yield (23%) of the desired amine (189) the majority of the product being 3-methoxyphenol (109) which presumably arises by reductive cleavage of the ether bridge in the nitropyrimidine derivative (188).

The pyrimidyl carbodiimide (193) was obtained in good overall yield as a dark brown oil which showed the expected i.r. absorption at 2130cm\(^{-1}\) due to the carbodiimide group. Heating the pyrimidyl carbodiimide (193) under reflux with five equivalents of stannic chloride in 1,2-dichloroethane gave low yield (16%) of the expected pyrimidinobenzoxazepine (194) whose structure follows from its analytical
and spectroscopic properties and by analogy with the structurally similar pyridobenzoxazepine derivative (122) obtained before. Restrictions on time prevented the investigation of the improvement of the efficiency of the pyrimidobenzoxazepine synthesis [(193) \to (194)].

2.4 Experimental

General Experimental Details

Infrared spectra were recorded using a Perkin-Elmer 298 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 b (broad); s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, and m=multiplet. $^{13}$C n.m.r. spectra were recorded at 50 Mhz using a Bruker WP-200SY spectrometer and were fully decoupled. Signals were sharp andquat = quaternary carbon atoms and methylene groups were identified by 3\pi/4 DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence spectra.

Electron Impact (EI) 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 4 four circle diffractometer on single crystals grown from the stated crystallisation solvent.

Microanalyses were determined using a Carlo-Erba Strumentazione 1106 elemental analyser. 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% suspension in mineral oil and was washed with anhydrous ether before use. Solvents were of technical grade unless specified light petroleum had b.p. 60-80°. Organic extracts were dried over anhydrous magnesium sulphate prior to filtration and rotary evaporation under reduced pressure. All yields are based on unrecovered starting material.

Wet column flash-chromatography was carried out over silica (Merck type 9385) or alumina (Merck type 1097) and dry column flash-chromatography (t.l.c.) was carried out using polygram sil G/UV_254 or polygram ALOX N/UV_254 precoated plastic sheets.
2- Aryloxy-3-nitropyridines

A stirred suspension of sodium hydride (2.6g; 0.11 mol) in anhydrous dimethylformamide (50.0 ml) was stirred and treated dropwise with cooling (ice-bath) with a solution of the corresponding phenol (0.1 mol) in anhydrous dimethylformamide (25.0 ml) and the mixture was then stirred at room temperature with exclusion of atmospheric moisture for 15 min by which time gas evolution had ceased. A solution of 2-chloro-3-nitropyridine (108) (15.8g, 0.1 mol) was added in one portion and the mixture was stirred and heated at 100° for 1h then worked up as described for the individual reactions below.

(i) The cooled mixture from phenol was diluted with water (10.0 ml) and then stirred at room temperature for 15 min. Evaporation under high vacuum yielded a brown gum which was triturated with water (100 ml) to give 3-nitro-2-phenoxypyridine (132) (89%) which formed brown crystals, m.p. 88-91° (from ethanol) (lit.58, 94°). Extraction of the aqueous mother liquor yielded a dark brown oil (0.85g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

(ii) The cooled mixture from 3-methoxyphenol (109) was diluted with water (10.0 ml) then stirred at room temperature for 15 min. Evaporation under high vacuum yielded a brown gum, which was triturated with water (200 ml) to give the product (110) (89%) which formed yellow needles, m.p. 81-82° (from ethanol), $\nu_{\text{max}}$ 1525 and 1355 (NO$_2$)cm$^{-1}$,
\[ \delta_H(\text{CDCl}_3) \ 8.37 (1H, s, ArH), \ 6.86-6.69 (6H, m, ArH) \] and 3.79 (3H, s, CH\text{3}).

**Found:** C, 58.5; H, 4.1; N, 11.4%; m/z (EI ms), 246(M⁺)

**C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}O\textsubscript{4} requires:** C, 58.5; H, 4.1; N, 11.3%; M, 246

Evaporation of the ethanolic mother liquor gave a brown oil (9.3g) whose t.l.c in methylene chloride-hexane over silica showed it to be a complex mixture which therefore was not further investigated.

(iii) The cooled mixture from 2-bromophenol (156) was diluted with water (10.0 ml) then stirred at room temperature for 15 min.

Evaporation under high vacuum yielded a brown gum, which was triturated with water (40.0 ml) to afford **2-(2-bromophenoxy)-3-nitropyridine (157)** (99%) which formed colourless needles, m.p. 72-73° (from methanol), \nu_{\text{max}} 1520 and 1350 (NO\textsubscript{2}) cm\textsuperscript{-1}, \[ \delta_H((\text{CD}_3)_2\text{SO}) \ 8.62 (1H, dd, J\text{ortho} 8Hz and J\text{meta} 2Hz, ArH), \ 8.41 (1H, dd, J\text{ortho} 5Hz and J\text{meta} 2Hz, ArH), \ 7.76(1H, ddd, J8Hz and J2Hz and J1Hz, ArH) \] and 7.62-7.15 (4H, m, ArH).

**Found:** C, 44.5; H, 2.4; N, 9.5%; m/z (EI ms), 215 (M⁺-Br); m/z (FAB ms), 297, 295 [(M+H)⁺]

**C\textsubscript{11}H\textsubscript{7}BrH\textsubscript{2}O\textsubscript{3} requires:** C, 44.7; H, 2.4; N, 9.5%; M, 295, (M+H), 297, 295

(iv) The cooled mixture from 2-iodophenol (161) was diluted with water (15.0 ml) and stirred at room temperature for 15 min then evaporated under high vacuum. The residue was triturated with water (80.0 ml) and the solid collected to give **2-(2-iodophenoxy)-3-nitropyridine (162)** (98%).
which formed colourless crystals, m.p. 104-105° (from methanol), $v_{\text{max}}$ 1520 and 1345 (NO$_2$) cm$^{-1}$, $\delta_H$(CD$_3$)$_2$SO] 8.62 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 8.40 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.91 (1H, dd, J8Hz and J2Hz, ArH) and 7.51-7.09 (4H, m, ArH).

**Found:** C, 38.5; H, 2.1; N, 8.2%; m/z (EI ms), 342 (M$^+$)

**C$_{11}$H$_7$IN$_2$O$_3$ requires:** C, 38.6; H, 2.1; N, 8.2%; M, 342

Extraction of the aqueous mother liquor yielded a brown oil (3.7g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

### 3-Amino-2-aryloxy-pyridines

A solution of the corresponding 2-aryloxy-3-nitrophyridine derivative (0.04 mol) in ethyl acetate (200-500 ml) was hydrogenated over 10% palladium-on-charcoal (10% by weight) at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. The mixture was filtered through celite and the filtrate was evaporated to give the corresponding 3-amino-2-aryloxy-pyridine derivative.

(i) **3-Amino-2-phenoxy-pyridine (133)** was obtained as a yellow solid (93%) which formed yellow crystals, m.p. 95-102° (lit., $^9$, 100-120°), $v_{\text{max}}$ 3460 and 3320 (NH$_2$) cm$^{-1}$.

(ii) **3-Amino-2-(3-methoxyphenoxy) pyridine (116)** was obtained (97%), which formed off-white crystals, m.p. 74-76° (from toluene), $v_{\text{max}}$ 3420, 3310 and 3200 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.58 (1H, dd Jortho 5Hz and
Jmeta 2Hz, ArH), 7.35-6.61 (6H, m, ArH), 3.77 (3H, s, OCH₃) and 3.77 (2H, s, NH₂) (exch.).

**Found:** C, 66.4; H, 5.6; N, 12.8%; m/z (EI ms), 216(M⁺)

C₁₂H₁₂N₂O₂ requires: C, 66.7; H, 5.6; N, 13.0%; M, 216

(iii) **3-Amino-2-(2-bromophenoxy)pyridine (158)** (99%) was obtained which formed colourless crystals, m.p. 97-100° (from benzene-hexane). vₘₐₓ 3420, 3300 and 3100 (NH) cm⁻¹, δ_H(CDCl₃) 7.68-6.74 (7H, m, ArH) and 3.79 (2H, brs, NH₂ ) (exch.).

**Found:** C, 49.8; H, 3.4; N, 10.5%; m/z (EI ms), 265 (M⁺) and 185 (M⁺-Br)

C₁₁H₉BrN₂O requires: C, 49.8; H, 3.4; N, 10.6%; M, 265

**The Attempted Catalytic Reduction of 2-(2-iodophenoxy)-3-nitropyridine (162) using Hydrogen over Palladium-on-charcoal**

A solution of the nitro compound (162) (6.8g, 0.02 mol) in ethyl acetate (100 ml) was hydrogenated over 5% palladium-on-charcoal (0.68g) at room temperature and atmospheric pressure for 0.5h. No hydrogen uptake was observed and hence glacial acetic acid (0.1 ml) was added and hydrogenation continued for a further 0.5h. After this time no hydrogen absorption was observed.

The mixture was filtered through celite and the filtrate was rotary evaporated to afford unreacted starting material (6.5g, 96%), m.p. 108-110°,
identified by comparison (m.p., i.r. spectrum and t.l.c. in ethyl acetate
hexane (1:1) over silica) with an authentic sample.

3-Amino-2-(2-iodophenoxy)pyridine (163)

A solution of the nitropyridine derivative (162) (6.8g, 0.02 mol) in
glacial acetate acid (100 ml) was hydrogenated over Raney nickel (0.85g) at
room temperature and atmospheric pressure for 12h by which time no
further hydrogen uptake was observed.

The mixture was filtered through celite and the rotary evaporated
to yield 3-amino-2-(2-iodophenoxy)pyridine (163) (6.2g), 100%) as a
yellow solid, m.p. 106-109° (from toluene), $\nu_{\text{max}}$ 3420 and 3305 (NH)cm$^{-1}$,
$\delta_{\text{H}}$(CDCl$_3$) 8.25-7.79 (1H, m, ArH), 7.56-6.75 (6H, m, ArH) and 4.01 (2H,
brs, NH$_2$) (exch.).

**Found:** C, 42.7; H, 2.8; N, 8.8%; m/z (EI ms), 311.9757 (M$^+$)

**C$_{11}$H$_9$IN$_2$O requires:** C, 42.3, H, 2.9, N, 8.9%, M, 311.9761

3-(N-Benzoyl)amino-2-(3-methoxy) phenoxy pyridine (117)

A solution of the amine (116) (0.43g, 0.002 mol) in anhydrous
1,2-dimethoxyethane (5.0 ml) was stirred and cooled to 15° (ice-bath) and
treated dropwise with a solution of triethylamine (0.2g, 0.002 mol) in
anhydrous 1,2-dimethoxyethane (2.5 ml). The mixture was then treated
dropwise at 15° with a solution of benzoyl chloride (0.28g, 0.002 mol) in
anhydrous 1,2-dimethoxyethane (2.5 ml) and the mixture was stirred in the melting ice-bath for 18 h.

The mixture was filtered to remove triethylamine hydrochloride (0.24 g), m.p. 260-263°, identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated yielding a brown oil which was triturated with water (10.0 ml) to give 3-(N-benzoylamino)-2-(3-methoxy)phenoxypyridine (117) (0.55 g, 86%) as a colourless solid, m.p. 104-107° (from toluene), $v_{max}$ 3400 br (NH) and 1665 (CO) cm$^{-1}$, $\delta_{H}(CDCl_3)$ 8.89 (1H, dd, Jortho 8 Hz, and Jmeta 2 Hz, ArH), 8.54 (1H, bs, NH), 8.15-7.81 (3H, m, ArH), 7.61-6.72 (8H, m, ArH) and 3.79 (3H, s, CH$_3$).

**Found:** C, 70.7; H, 5.0; N, 8.4%; m/z (EI ms), 320.1161 (M$^+$)

**C$_{19}$H$_{16}$N$_2$O$_3$ requires:** C, 71.3; H, 5.0; N, 8.8%; M, 320 1161

2-Aryloxy-3-azidopyridines

A solution of corresponding 3-amino-2-aryloxypyridine (0.02 mol) in 5M aqueous hydrochloric acid (50.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (1.5 g, 0.022 mol) in water (10.0 ml) at such a rate that the reaction temperature was <5°. After stirring with a solution of sodium azide (1.9 g, 0.03 mol) in water (10.0 ml) at such a rate that the reaction temperature was <5°, and the mixture was stirred in the melting ice-bath for 0.5 h, then worked up as described for the individual reactions below.
(i) Filtration gave the **3-azido-2-(3-methoxyphenoxy)pyridine** (118) (100%) which formed light brown crystals, m.p. 65-67° (from hexane), $v_{\text{max}}$ 2110 (N$_3$)cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.91 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.41-6.66 (6H, m, ArH) and 3.79 (3H, s, CH$_3$).

**Found:** C, 59.4; H, 4.1; N, 22.8%; m/z (EI ms), 242 (M$^+$)

**C$_{11}$H$_{10}$N$_4$O$_2$ requires:** C, 59.5; H, 4.1; N, 23.1%; M, 242

(ii) Filtration of the mixture yielded **3-azido-2-(2-bromophenoxy)pyridine** (159) (96%) which formed light brown crystals, m.p. 72-74° (from hexane), $v_{\text{max}}$ 2103 (N$_3$)cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.86 (1H, dd, Jortho 5Hz, Jmeta 2Hz, ArH), 7.65 (1H, dd, Jortho 8Hz, Jmeta 1Hz, ArH) and 7.43-6.96 (5H, m, ArH).

**Found:** C, 45.6; H, 2.4; N, 19.1%; m/z (FAB ms), 292 [(M+H)$^+$] 

**C$_{11}$H$_7$BrN$_4$O requires:** C, 45.4; H, 2.4; N, 19.2%; (M+H), 292

(iii) Filtration of the mixture yielded **3-azido-2-(2-iodophenoxy)pyridine** (164) (92%) which formed cream coloured needles, m.p. 62-63° (from hexane), $v_{\text{max}}$ 2100 (N$_3$)cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.92-7.80 (2H, m, ArH) and 7.51-6.86 (5H, m, ArH).

**Found:** C, 38.4; H, 2.0; N, 16.3%; m/z (EI ms), 388.9686 (M$^+$)

**C$_{11}$H$_7$I$_2$N$_4$O requires:** C, 39.1; H, 2.1; N, 16.6%; M, 338.9700

Extraction of the filtrate with methylene chloride yielded a brown gum (0.50g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

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N-(2-phenoxypyrid-3-yl)triphenyl phosphinimine (134)

A solution of the amine (133) (1.5g, 0.008 mol) in anhydrous acetonitrile (40.0 ml) was stirred under nitrogen and treated with triphenylphosphine (4.6g, 0.018 mol) then hexachloroethane (3.8g, 0.0016 mol) and the mixture was stirred under nitrogen and heated under reflux for 18h.

Filtration of the cooled reaction mixture yielded triethylamine hydrochloride (3.0g), m.p. 257-259°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The filtrate was evaporated and the residue was treated with water (40.0 ml) and extracted with methylene chloride to give a brown gum (6.5g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:4) yielded unreacted triphenylphosphine (0.28g), m.p. 68-71°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (3:7) gave a red oil (0.068g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

Further elution with ethyl acetate-hexane (7:3) yielded N-(2-phenoxypyrid-3-yl)triphenyl phosphinimine (134) (1.9g, 54%) which formed colourless crystals, m.p. 147-149° (from ethyl acetate), δ_H(CDCl_3) 7.72-6.62 (m, ArH).

**Found:** C, 78.1; H, 5.3; N, 6.3%; m/z (El ms), 447 (M^+)
Further elution with ethyl acetate-hexane (7:3) afforded triphenylphosphine oxide (0.92g, 41%) as a colourless solid, m.p. 142-144°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with methanol gave a second crop of triphenylphosphine oxide (1.1g, 49%) as a gummy brown solid, identified by comparison (t.l.c. in ethyl acetate-hexane (1.1) over silica) with an authentic sample.

**N\text{2-}-(3-\text{O ethoxyphenoxy})\text{pyrid-3-yl}\text{triphenyl phosphinimine (119)}**

(a) A solution of the amine (116) (0.43g, 0.002 mol) in anhydrous acetonitrile (40.0 ml) was stirred under nitrogen and treated with triphenyl phosphine (1.2g, 0.0044 mol), followed by triethylamine (0.80g, 0.008 mol) and then hexachloroethane (0.95g, 0.004 mol). The mixture was then heated under reflux for 18h in an atmosphere of nitrogen.

Filtration of the cooled mixture yielded triethylamine hydrochloride (0.46g), m.p. 255-258° identified by comparison (m.p. and i.r. spectrum) with an authentic sample. Evaporation of the filtrate yielded with water (10.0 ml) and extracted with methylene chloride to give a yellow oil (1.6g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (6:4) gave the **iminophosphorane (119)** (0.94g, 99%) as colourless crystals, m.p. 117-
118.5° (from acetonitrile), $\delta_H^{1}$(CDCl$_3$) 7.82-6.13 (22H, m, ArH) and 3.65 (3H, s, CH$_3$).

**Found:** C, 75.7; H, 5.2; N, 6.0%; m/z (El ms), 476 (M$^+$)

**C$_{30}$H$_{25}$N$_2$OP requires:** C, 75.6; H, 5.3; N, 5.9%; M, 476

Elution with methanol gave triphenylphosphine oxide (0.46g) as a light brown solid, m.p. 142-149°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ammonia-methanol (1:9) gave only a brown oil (0.0 64g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which was not further investigated.

(b) A solution of 3-amino-2-(3-methoxyphenoxy) pyridine (116) (1.1g; 0.005 mol) in anhydrous acetonitrile (40.0 ml) was stirred under nitrogen and treated with triphenyl phosphine (1.5g ; 0.006 mol) followed by triethylamine (1.0g; 0.01 mol) then hexachloroethane (1.2g; 0.005 mol), and the mixture was heated under reflux for 18h.

Filtration of the cooled mixture yielded triethylamine hydrochloride (0.77g), m.p. 254-257°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the filtrate yielded an oil which was treated with water (20.0 ml) and extracted with ethyl acetate to give a purple oil (2.7g) which was flash-chromatographed over silica. Elution with hexane-ethyl acetate (7:3) yielded unreacted triphenyl phosphine (0.19g; 13%), m.p. 64-
67°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (6:4) yielded \textbf{N-12-(3-methoxyphenoxy)pyrid-3-yl} triphenylphosphinimine (119) (1.2g; 50\%) as a colourless solid, m.p. 111-115°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Further elution with methanol yielded triphenylphosphine oxide (0.46g), m.p. 146-148°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared in (a) before.

(c) A solution of the azide (118) (0.48g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was stirred and treated with a solution of triphenylphosphine (0.52g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture stirred at room temperature for 0.5h then at 60° for a further 0.5h.

The mixture was cooled and evaporated to afford the \textbf{iminophosphorane (119)} (0.95g; 99\%) which formed a colourless crystalline solid, m.p. 117-119° (from acetonitrile), identical (m.p. and i.r. spectrum) with a sample prepared in (a) before.
The Acid - Catalysed Hydrolysis of N-[2-(3-Methoxyphenoxy)pyrid-3-yl] triphenylphosphinimine (119) with 2M Hydrochloric Acid

N-[2-(3-Methoxyphenoxy)pyrid-2-yl]triphenylphosphinimine (119) (0.95g; 0.002 mol) was treated with 2M hydrochloric acid (10.0 ml) and the mixture was heated under reflux for 24h.

The mixture was evaporated and extracted with methylene chloride to yield an oil (0.87g) which was triturated with diethyl ether to afford triphenylphosphine oxide (0.19g; 34%), m.p. 141-145\degree, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the diethyl ether mother liquor gave an intractable oil (0.20g) which yielded no identifiable material. The aqueous mother liquor was made basic with 2M sodium hydroxide solution and extracted with ethyl acetate to afford

3-amino-2-(3-methoxyphenoxy) pyridine (116) (0.096g; 25%) as a gummy solid, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample.

N-(2-Aryloxypyrid-3-yl)trimethoxyphosphinimines

Solutions of the corresponding 3-azido-2-aryloxypyridine derivative (0.008 mol) in anhydrous 1,2-dimethoxyethane (40.0 ml) and trimethyl phosphite (1.2g; 0.0 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) were mixed and the mixture was stirred at room temperature for 4h then worked up as described for the individual reactions below.

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(i) The mixture from 3-azido-2-(3-methoxyphenoxy)pyridine (118) was evaporated with removal of the excess of trimethyl phosphite as an azeotrope with anhydrous toluene to afford \( N-[2-(3\text{-methoxyphenoxy})\text{pyrid-3-yl}] \) trimethoxyphosphinimine (149) 100% as a brown oil, 
\[
\delta_H(\text{CDCl}_3) \ 7.68 \ (1\text{H}, \text{m, ArH}), \ 7.30-7.20 \ (2\text{H}, \text{m, ArH}), \ 6.91-6.85 \ (1\text{H}, \text{m, ArH}), \ 6.69-6.63 \ (3\text{H}, \text{m, ArH}), \ 3.77 \ (3\text{H}, \ 3\text{CH}_3) \ \text{and} \ 3.74 \ (9\text{H}, \text{d, J11HZ, 3xCH}_3).
\]
Found: C, 53.4; H, 5.9; N, 8.5%; m/z (EI ms), 338 (M⁺)

\( C_{15}H_{19}N_2O_5P \) requires: C, 53.3; H; 5.7%; N, 8.3%; M, 338

(ii) The mixture from 3-azido-2-(2-bromophenoxy)pyridine (159) was evaporated with removal of the excess of trimethylphosphite as an azeotrope with toluene to give \( N-[2-(2\text{-bromophenoxy})\text{pyrid-3-yl}] \) trimethoxyphosphinimine (160) (92%) which formed light brown crystals, m.p. 134-137° (from ethyl acetate-hexane), 
\[
\delta_H[(\text{CD}_3)_2\text{SO}] \ 7.70 \ (1\text{H}, \text{d, J8HZ, ArH}), \ 7.50-6.93 \ (6\text{H}, \text{m, ArH}) \ \text{and} \ 3.74 \ (9\text{H}, \text{d, J12Hz 3xCH}_3).
\]
Found: C, 43.3; H, 4.1; N, 7.2%; m/z (EI ms) 388 and 386 (M⁺)

\( C_{14}H_{16}BrN_2O_4P \) requires: C, 43.4; H, 4.2; N, 7.2%; M, 387

(iii) The mixture from 3-azido-2(2-iodophenoxy) pyridine (164) was evaporated with removal of the excess of trimethyl phosphite as an azeotrope with toluene to give a brown solid which was triturated with ethyl acetate to afford \( N-[2-(2\text{-iodophenoxy})\text{pyrid-3-yl}] \) trimethoxyphosphinimine (165) (72%) as a colourless solid, m.p. 158-161°
(decomp.), $\delta_H(\text{CDCl}_3)$ 7.84 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.61
(1H, m, ArH), 7.34-7.25 (2H, m, ArH), 6.96-6.83 (3H, m, ArH) and 3.78
(9H, d, J12Hz, 3xCH$_3$).

**Found:** C, 38.4; H, 3.7; N, 6.3%; m/z (EI ms), 434 (M$^+$)

C$_{14}$H$_{16}$IN$_2$O$_4$P **requires:** C, 38.7; H, 3.7; N, 6.5%; M, 434

Evaporation of the ethyl acetate mother liquor yielded an
intractable gum which was not further investigated.

**The Attempted Reaction of 3-Amino-2-(3-methoxyphenoxy)pyridine**

(116) **with Diethyl Phosphite**

(a) A solution of 3-amino-2-(3-methoxyphenoxy)pyridine (116)
(0.43g; 0.002 mol) was added dropwise with cooling (ice-bath) to a solution
of diethyl phosphite (0.27g; 0.002 mol) in toluene (5.0 ml). The mixture was
then stirred at room temperature for 24h.

The mixture was treated with water (10.0 ml) stirred for 15 min
then extracted with methylene chloride to yield a brown oil (0.59g) whose
t.l.c in ethyl acetate-hexane (1:1) over silica showed it to consist mainly of
unreacted starting material. The oil was not further investigated.

(b) The reaction described in (a) before was repeated with stirring
at 50° for 24h.

The cooled mixture was diluted with water (10.0 ml) and extracted
with methylene chloride to afford a brown oil (0.66g) which was flash-
chromatographed over silica.
Elution with ethyl acetate-hexane (2:3) gave unreacted starting material (116) (0.34g; 79%), m.p. 76-79°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Further elution with ethyl acetate-hexane (3:2) yielded diethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl] phosphoramidate (148) (0.12g; 17%) as a colourless solid, m.p. 81-84°, identical (m.p. and i.r. spectrum) to a sample prepared later.

Final elution with methanol gave only an intractable brown gum (0.30g) which was not further investigated.

(c) The reaction described in (a) before was repeated but with heating under reflux for 24h.

The cooled mixture was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown oil (0.41g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to consist largely of unreacted starting material. The oil was not further investigated.

**The Attempted Reaction of 3-Amino-2-(3-methoxyphenoxy)pyridine (116) with Diethyl Chlorophosphate.**

A solution of 3-amino-2-(3-methoxyphenoxy)pyridine (116) (0.43g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred under nitrogen and treated successively with diethyl chlorophosphate (0.35g; 0.002 mol) then triethylamine (0.20g; 0.002 mol). The mixture was then heated under reflux for 3h.
The mixture was rotary evaporated and residue was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown oil (0.59g) whose t.l.c. in ethyl acetate-hexane (1.1) over silica showed to consist largely of unreacted starting material. The oil was not further investigated.

**Diethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl] phosphoramidate (148)**

Solutions of 3-azido-2-(3-methoxyphenoxy)pyridine (118) (2.2g; 0.009 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) and triethyl phosphate (1.5g; 0.009 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) were mixed and the mixture stirred at room temperature for 18h. After this time further triethyl phosphate (0.37g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was added and stirring continued at room temperature for 1h.

The mixture was rotary evaporated yielding an oil (3.8g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded **3-amino-2-(3-methoxyphenoxy) pyridine (116)** (0.077g; 4%), m.p. 70-73°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate-hexane (3:2) afforded **diethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl] phosphoramidate (148)** (3.1g; 96%) which formed colourless crystals, m.p. 88-89° (from toluene-hexane), νmax 3140 (NH)cm⁻¹, δH(CDCl₃) 7.77-6.63 (7H, m, ArH), 5.70 (1H, d, J10Hz, 6H, ArCH₂, 1H, ArN), 4.24 (2H, q, J7Hz, CH₂), 3.67 (3H, s, OCH₃).
NH), 4.17 (4H, dq, J7Hz and J1Hz, 2xCH₂), 3.78 (3H, s, CH₃) and 1.34 (6H, dt, J7Hz and J1Hz, 2xCH₃).

**Found:** C, 54.4; H, 6.1; N, 7.9%; m/z (FAB ms), 353 [(M+H)⁺]

C₁₆H₂₁N₂O₅-P requires: C, 54.5; H, 5.9; N, 7.9%; (M+H), 353

Final elution with methanol gave only an intractable brown gum (0.11g) which was not further investigated.

**Dimethyl N- [2-(3-Methoxyphenoxy)pyrid-3-yl] phosphoramidate (150)**

Solutions of 3-azido-2-(3-methoxyphenoxy) pyridine (118) (2.4g; 0.01 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) and trimethyl phosphite (1.4g; 0.013 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) were mixed and the mixture was stirred at room temperature for 18h.

The mixture was rotary evaporated under high vacuum with azeotropic removal of the excess of trimethyl phosphite using toluene to afford a brown oil (3.4g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) yielded a multicomponent gum (0.051g) which was not further investigated.

Further elution with hexane-ethyl acetate (1:1) afforded **dimethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl] phosphoramidate (150)** (3.2g; 99%) as a colourless crystalline solid, m.p. 89-91° (from toluene), ν_max 3190 (NH) cm⁻¹, δ_H (CDCl₃) 7.74 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.54 (2H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.27-6.63 (4H, m, ArH).
ArH), 5.73 (1H, bd, J9Hz, NH), 3.80 (6H, d, J11Hz, 2xCH₃) and 3.77 (3H, s, CH₃).

**Found:** C, 52.2; H, 5.3; N, 8.7%; m/z (EI ms), 324 (M⁺)

**C₁₄H₁₁N₂O₃P requires:** C, 51.9; H, 5.3; N, 8.6%; M, 324

Further elution with methanol yielded only a small amount of a brown gum (0.087g) which was not further investigated.

**The Attempted Reaction of 3-Amino-2-(3-methoxyphenoxy) pyridine (116) with Dibenzy1 Phosphite**

A mixture of dibenzyl phosphite (0.52g; 0.002 mol), triethylamine (0.20g; 0.002 mol) and carbon tetrachloride (0.77g; 0.005 mol) in toluene (10.0 ml) was stirred and treated dropwise with cooling (ice-bath) with a solution of 3-amino-2-(3-methoxyphenoxy) pyridine (116) (0.43g; 0.002 mol) in toluene (10.0 ml). The resulting mixture was then stirred at room temperature for 24h.

The mixture was diluted with water (10.0 ml) and extracted with methylene chloride to afford a brown oil (0.79g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave unreacted starting material (116) (0.33g; 76%), m.p. 54-59°, identified by comparison (m.p. and i.r. spectrum and t.l.c. in ethyl acetate-hexane (2:3) over silica) with an authentic sample.
Further elution with methanol gave only an intractable gum (0.10g) which was not further investigated.

1-(2-Aryloxypyrid-3-yl)-3-phenylcarbodiimides

Solutions of the corresponding phosphinimine (0.005 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) and the corresponding isocyanate (0.005 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) were mixed and stirred at room temperature with the exclusion of atmospheric moisture for 4-18h then worked up as described for the individual reactions below.

(i) The mixture from N-(2-phenoxy pyrid -3-yl) triphenyl-phosphinimine (134) and phenylisocyanate was evaporated to give an oily solid which was triturated with anhydrous diethyl ether to yield triphenylphosphine oxide (86%), m.p. 138-147°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the diethyl ether mother liquor gave 1-(2-phenoxy pyrid-3-yl)-3-phenylcarbodiimide (135) (98%) as colourless crystals, m.p. 63-65° (from benzene-hexane), \( \delta \) \( H(CDCl_3) \) 7.92 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH) and 7.80-6.87 (12H, m, ArH).

Found: m/z (El ms), 287.1055 (M)

18113N30 requires: M, 287.1059

(ii) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]triph enylphosphinimine (119) and phenyl isocyanate was evaporated to
give a gummy solid which was triturated with anhydrous diethyl ether to afford triphenylphosphine oxide (63%), m.p 139-143°, identified by comparison (m.p and i.r. spectrum) with an authentic sample.

Evaporation of the diethyl ether mother liquor afford the impure carbodiimide (120) (100%) \( \nu_{\text{max}} \) 2140 (N=C=N) cm\(^{-1} \), contaminated with triphenyl phosphine oxide. The carbodiimide (120) was used without further purification due to its instability to distillation or flash-chromatography.

(iii) The mixture from \( N\)-[\( 2\)-\( (3\)-methoxyphenoxy)pyrid-3-yl]triphenylphosphinimine (119) and phenyl isocyanate was evaporated to give a gummy solid which was flash-chromatographed over silica. Elution with methylene chloride-hexane (3:2) yielded a series of intractable oils with were not further investigated.

Further elution with methylene chloride-hexane (4:1) gave the carbodiimide (120) (17%) as a yellow oil, \( \nu_{\text{max}} \) 2140 (N=C=N) cm\(^{-1} \).

Further elution with ethyl acetate yielded \( 1\)\( -[2\)-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) as a monohydrate (85%) which formed colourless crystals, m.p. 75-79° (from ethyl acetate-light petroleum), identical (i.r. spectrum) with an authentic sample prepared later.

**Found:** C, 64.4; H, 5.2; N, 11.8%; m/z (EI ms), 335 (M\(^+\)-H\(_2\)O)

**C\(_{19}\)H\(_{17}\)N\(_3\)O\(_3\)H\(_2\)O requires:** C, 64.6; H, 5.4; N, 11.9%; M, 355
Further elution with methanol gave triphenylphosphine oxide (98%), m.p 149-135°, identical (m.p and i.r. spectrum) to an authentic sample.

(iv) the mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]trimethoxyphosphinimine (149) and phenyl isocyanate was evaporated to give a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated to afford 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenyl carbodiimide (120) (95%) as a brown oil, $v_{\text{max}}$ 2140 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.99-7.87 (1H, m, ArH), 7.51-6.59 (11H, m, ArH) and 3.71 (3H, s, CH$_3$).

**Found:** C, 71.2; H, 4.9; N, 13.0%; m/z (FAB ms), 318.1242 [(M+H)$^+$]

$\textbf{C}_{19}\textbf{H}_{15}\textbf{N}_3\textbf{O}_2$ **requires:** C, 71.9, H, 4.8; N; 13.2%; (M+H)$^+$, 318.1242

(v) The mixture from N-[2-(2-bromophenoxy)pyrid-3-yl]-trimethoxyphosphinimine (160) and phenyl isocyanate was evaporated to give an orange oil which was dissolved in diethyl ether (150.0 ml) and the solution washed with water and evaporated to afford the carbodiimide (153) (98%) as a light brown solid, m.p. 70-73° (from hexane - toluene) $v_{\text{max}}$ 2140 and 2094 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.90-7.85 (1H, m, ArH) and 7.64-6.93 (11H, m, ArH).

**Found:** m/z (EI ms), 367.0110 and 365.0135 (M$^+$)

$\textbf{C}_{18}\textbf{H}_{12}\textbf{BrN}_3\textbf{O}$ **requires:** M, 367.0145 and 365.0164

(vi) The mixture from N-[2-(2-iodophenoxy)pyrid-3-yl]trimethoxy phosphinamine (165) and phenyl isocyanate was evaporated to give a gum
which was dissolved in diethyl ether (20.0 ml) and the solution washed with water (5.0 ml) and evaporated to afford the carbodiimide (166) (94%) as a brown gum, $v_{\text{max}}$ 2120 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.91-7.74 (1H, m, ArH) and 7.58-6.83 (8H, m, ArH).

**Found:** C, 52.5; H, 3.0; N, 10.1%; m/z (FAB ms), 414[(M+H)$^+$]

$	ext{C}_{18}\text{H}_{12}\text{IN}_3\text{O}$ requires: C, 52.3; H, 2.9; N, 10.2%; (M+H), 414

(vii) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]trimethoxy phosphinimine (149) and 4-nitrophenyl isocyanate was evaporated to give a gummy solid which was dissolved in methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated to afford 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-(4-nitrophenyl)-carbodiimide (150a) (100%) which formed cream coloured microcrystals, m.p. 125-127° (from toluene), $v_{\text{max}}$ 2110 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.17-7.95 (3H, m, ArH), 7.54-6.64 (8H, m, ArH) and 3.74 (3H, s, CH$_3$).

**Found:** C, 62.9; H, 3.8; N, 15.2%; m/z (EI ms), 362 (M$^+$)

$	ext{C}_{19}\text{H}_{14}\text{N}_4\text{O}_4$ requires: C, 62.9; H, 3.9; N, 15.5%; M, 362

(viii) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]triphenyl phosphinimine (119) and 4-methoxyphenyl isocyanate was evaporated yielding a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated to afford impure 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-(4-methoxyphenyl)-
carbodiimide (150b) (100%) contaminated with triphenylphosphine oxide, identified by comparison (i.r. spectrum) with a sample prepared earlier.

(ix) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl] trimethoxy phosphinimine (149) and 4-methoxyphenyl isocyanate was evaporated to give a gum which was dissolved in methylene chloride (20.0 ml), and the solution washed with water (20.0 ml) and evaporated to give 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-(4-methoxyphenyl)-
carbodiimide (150b) (93%) as a brown oil, $v_{\text{max}}$ 2130 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.97-7.87 (1H, m, ArH), 7.44 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.36-6.61 (9H, m, ArH), 3.75 (3H, s, CH$_3$) and 3.71 (3H, s, CH$_3$).

Found: m/z (FAB ms), 348.1348 [(M+H)$^+$]

C$_{20}$H$_{17}$N$_3$O$_3$ requires (M+H), 348.1348

(x) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl] triphenyl phosphinimine (119) and methyl isocyanate was evaporated giving impure carbodiimide (125) (100%) as an oil, $v_{\text{max}}$ 2160 (N=C=N) cm$^{-1}$, contaminated with triphenylphosphine oxide. The carbodiimide (125) was used without further purification due to its instability to distillation or flash-chromatography.

(xi) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl] trimethoxy phosphinimine (149) and methyl isocyanate was evaporated to give a gum. This was dissolved in methylene chloride (20.0 ml) and the solution washed with water (10.0 ml) and evaporated to give a brown oil
whose $^1$H n.m.r. spectrum showed it to be mainly the unreacted starting material (149).

The oil was redissolved in anhydrous 1,2-dimethoxyethane (20.0 ml) mixed with a solution of methyl isocyanate (1.2 g; 0.02 ml) in anhydrous 1,2-dimethoxyethane (20.0 ml) and the mixture stirred at room temperature for a further 4 h.

The mixture was evaporated and the residual gum was dissolved in methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated yielding a brown oil (0.42 g) whose i.r. spectrum showed the presence of the expected carbodiimide (125), $v_{\text{max}}$ 2150 (N=C=N) cm$^{-1}$.

On attempting further purification the oil decomposed as indicated by the loss of the band at 2150 cm$^{-1}$ in the i.r. spectrum of the sample.

(xii) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]triphenylphosphine (119) and benzyl isocyanate was evaporated to give a gummy solid which was triturated with anhydrous diethyl ether to give triphenylphosphine oxide (54%), m.p. 134-144°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the diethyl ether mother liquor yielded the crude carbodiimide (127) (0.87 g) as a brown oil contaminated with triphenylphosphine oxide, $v_{\text{max}}$ 2140 (N=C=N) cm$^{-1}$ identified by comparison (i.r. spectrum) with a sample prepared later.

(xiii) The mixture from N-[2-(3-methoxyphenoxy)pyrid-3-yl]trimethoxy phosphinimine (149) and benzyl isocyanate was evaporated to
give a gum. This was dissolved in methylene chloride (20.0 ml) the solution washed with water (20.0 ml) and evaporated to afford 1-{2-(3-
methoxyphenoxy)pyrid-3-yl}-3-benzylcarbodiimide (127) (100%) as a brown oil, \( \nu_{\text{max}} \) 2140 (N=C=N) cm\(^{-1}\).

**Found:** m/z (FAB ms), 332.1399 [(M+H)\(^+\)]

\( \text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2 \text{ requires: } \text{(M+H)}; \text{ 332.1399} \)

**Attempted Hydrolysis of 1-{2-(3-methoxyphenoxy)pyrid-3-yl]-3-
phenylurea (121) using Aqueous Sodium Hydroxide**

(a) A solution of the urea (121) (0.33g; 0.001 mol) in ethanol (10.0 ml) was treated with 2M aqueous sodium hydroxide solution (2.5 ml) and the mixture was heated under reflux for 1h.

The cooled mixture was rotary evaporated and the residue was treated with water (10.0 ml). Filtration afforded the unreacted urea (121) (0.27g, 82%) as a waxy solid m.p. 104-110° identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample prepared before.

(b) A solution of the urea (121) (0.33g, 0.001 mol) in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide solution (2.5 ml) and the mixture was heated under reflux for 1h.

The cooled mixture was rotary evaporated and the residue was treated with water (5.0 ml) and filtered to yield the unreacted starting material (121) (0.31g, 94%), m.p. 106-109°, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample prepared before.

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spectrum and t.l.c. in ethyl acetate-hexane (2:3) over silica) with an authentic sample prepared before.

(c) A solution of the urea (121) (0.33g; 0.001 mol) in glacial acetate acid (5.0 ml) was treated with 20% w/v aqueous sulphuric acid solution (2.5 ml) and the mixture was heated under reflux for 1h.

The cooled mixture was rotary evaporated to one half its original volume under high vacuum. Water (10.0 ml) was added and the mixture was extracted with methylene chloride to afford a brown oil (0.26g) which was dissolved in methylene chloride and the solution was washed with 2M aqueous hydrochloric acid (5.0 ml) and evaporated yielding unreacted starting material (121) (0.15g; 45%) as a brown gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:7) over silica) with an authentic sample.

The acidic aqueous mother liquor was basified with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to yield 3-amino-2-(3-methoxyphenoxy)pyridine (116) (0.029g; 13%), m.p. 71-73°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

1-[2-(3-Methoxyphenoxy)pyrid-3-yl] 3-phenylurea (121)

Solutions of 3-amino-2-(3-methoxyphenoxy)pyridine (116) (0.43g; 0.002 mol) in anhydrous 1, 4-dioxane (10.0 ml) and phenyl isocyanate (0.24g, 0.002 mol) in anhydrous 1, 4-dioxane (5.0 ml) were mixed and the mixture was stirred at room temperature for 2h.

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Evaporation of the mixture gave a brown oil (0.59g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:4) gave unreacted amino pyridine (116) (0.07g, 16%), m.p. 76-79°, identical (m.p. and i.r. spectrum) to an authentic sample. Further elution with ethyl acetate-hexane (1:4) yielded a yellow oil (0.27g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be largely starting material (116).

Further elution with ethyl acetate-hexane (1:4) afforded 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) (0.15g; 22%) which formed light brown crystals of a monohydrate, m.p. 62-66° (from toluene), \( \nu_{\text{max}} \) 3500 (NH) and 1690 (CO) cm\(^{-1}\); \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.57 (1H, dd, J\text{ortho} 8Hz and J\text{meta} 2Hz, ArH) 7.56-6.46 (11H, m, ArH) 3.90 (2H, brs, 2xNH)(exch.) and 3.67 (3H, d, J3Hz, CH\(_3\)).

**Found:** C, 64.1; H, 5.3; N, 11.7%; m/z (FAB ms), 336 [(M+H)-H\(_2\)O]

**C\(_{19}\)H\(_{17}\)N\(_3\)O\(_3\) . H\(_2\)O requires:** C, 64.6; H, 5.4; N, 11.9%; M, 353

Further elution with methanol gave only a small quantity of brown gum (0.021g) which was not further investigated.
The Attempted Reaction of Diethyl N-[2-(3-Methoxyphenoxy)pyrid-3-yl] phosphoramidate (148) with Phenyl Isocyanate in the presence of Sodium Hydride

A suspension of sodium hydride (0.048g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (2.5 ml) was stirred under nitrogen and treated dropwise with a solution of diethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl]phosphoramidate (148) (0.07g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml). After the initial hydrogen evolution had ceased the mixture was heated at 70° for 0.5h. The mixture was then cooled to room temperature and treated dropwise with stirring with a solution of phenyl isocyanate (0.24g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (2.5 ml). The mixture was then heated at 70° for 0.5h.

The mixture was cooled and evaporated to yield a gum which was treated with water (10.0 ml) and extracted with diethyl ether to afford the carbodiimide (120) as a yellow gum (0.05g), \(\nu_{\text{max}}\) 2140 (N=C=N) cm\(^{-1}\); \(\delta_H(\text{CDCl}_3)\), complex, identical (i.r. spectrum) to an authentic sample prepared before. On standing the gum slowly solidified to give an unidentified solid whose i.r. spectrum lacked absorption due to a carbodiimide group. Heating the solid past its melting point gave an oil, \(\nu_{\text{max}}\) 2140 (N=C=N) cm\(^{-1}\), identical (i.r. spectrum) to the carbodiimide (120) obtained before.
The Reaction of Dimethyl N-[2-(3-methoxyphenoxy)pyrid-3-yl]-
phosphoramidate (150) with phenyl isocyanate in the presence of
Sodium Hydride

A suspension of sodium hydride (0.096g; 0.004 mol) in anhydrous
1,2-dimethoxyethane (5.0 ml) was stirred under nitrogen and treated
dropwise with a solution of dimethyl N-[2-(3-methoxyphenoxy)pyrid-3-
yl]phosphoramidate (150) (1.3g; 0.004 mol) in anhydrous
1,2-dimethoxyethane (10.0 ml). After the initial hydrogen evolution had
ceased the mixture was heated at 70° for 0.5h, then cooled to room
temperature and treated dropwise with stirring with a solution of phenyl
isocyanate (0.48g, 0.004 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and
then heated at 70° for a further 0.5h.

The mixture was cooled and evaporated yielding a gum which was
treated with water (20.0 ml) and extracted with diethyl ether to afford the
carbodiimide (120) (1.3g, 100%), ν\text{max} 2140 (N=C=N)cm\-1, identical (i.r.
spectrum) to an authentic sample prepared from diethyl N-[2-(3-
methoxyphenoxy)pyrid-3-yl]phosphoramidate (148) before.

1-(2-Phenoxypyrid-3-yl)-3-phenylurea (136)

A solution of the impure carbodiimide (120) (1.3g; 0.002 mol)
contaminated with triphenylphosphine oxide in 1,2-dimethoxyethane
(10.0 ml) was treated with 2M hydrochloric acid (5.0 ml) and the mixture
was stirred at room temperature for 5h.
The mixture was rotary evaporated yielding a gum. This was treated with water (10.0 ml) and extracted with methylene chloride to afford a gum (1.2g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:1) yielded 1-(2-phenoxypyrid-3-yl)-3-phenylurea (136) (0.44g; 72%) as a colourless solid, m.p. 156-158° (from toluene); \( \nu_{\text{max}} \) 3300 (NH) and 1655 (CO) cm\(^{-1} \), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.56 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH) and 7.72-6.89 (14H, m, 2xNH+ArH). Found: C, 71.3; H, 5.1; N, 13.5%; m/z (EI ms), 305.1167(M\(^+\))

\( \text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_2 \) requires: C, 70.8; H, 4.9; N, 13.8%; M, 305.1164

1-[2-(3-Methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121)

(a) A solution of the impure carbodiimide (120) (2.0g; 0.005 mol) contaminated with triphenylphosphine oxide in 1, 4-dioxane (15.0 ml) was treated with 2M hydrochloric acid (5.0 ml) and the mixture was stirred at room temperature for 1h.

The mixture was evaporated under high vacuum yielding a gum which was treated with water (10.0 ml) and extracted with methylene chloride to afford an oil (2.1g) whose i.r. spectrum showed the presence of unreacted starting material (120). The oil was redissolved in 1, 4-dioxane (15.0 ml) and the solution treated with 2M of hydrochloric acid (5.0 ml) and the mixture was then stirred at room temperature for a further 4h.

The mixture was evaporated under high vacuum and the residue was treated with water (10.0 ml) and filtered to remove a small amount of
an unidentified solid. Extraction of the filtrate with methylene chloride yielded the impure urea (121) (1.7g, 100%) as an oil, identified by comparison (i.r. spectrum) with a sample obtained before. The t.l.c. of the impure urea (121) in ethyl acetate (2:3) over silica showed the presence of contaminating triphenylphosphine oxide.

(b) A solution of the carbodiimide (120) (0.95g; 0.003 mol) in 1, 4-dioxane (9.0 ml) was treated with 2M hydrochloric acid (3.0 ml; 0.006 mol) and the mixture was stirred at room temperature for 0.5h.

The mixture was rotary evaporated under high vacuum yielding a gum. This was treated with water (10.0 ml) and filtered to give a colourless solid (0.81g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:4) yielded 1-(2-(3-methoxyphenoxy)pyrid-3-yl)-3-phenylurea (121) (0.20g; 20%) as a gummy solid, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-light petroleum (b.p. 40-60°) (2:3) over silica) with a sample prepared before.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) through ethyl acetate to methanol afforded a series of intractable gums (total 0.55g) which yielded no further identifiable material.

(c) A solution of the carbodiimide (120) 0.43g; 0.0013 mol) in 1,2-dimethoxyethane (10.0 ml) was treated with 2M hydrochloric acid (5.0 ml) and the mixture was stirred at room temperature for 5h.
The mixture was rotary evaporated yielding a gum. This was treated with water (10.0 ml) and extracted with methylene chloride to afford a gum (0.45g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:1) yielded the urea (121) (0.28g, 64%) as a yellow gum, identified by comparison (i.r. spectrum) with a sample obtained before.

(d) A solution of the impure carbodiimide (120) (1.9g; 0.005 mol) in 1,4-dioxane (15.0 ml) was treated with 2M sodium hydroxide solution (2.5 ml) and the mixture was stirred at room temperature for 1h.

The mixture was evaporated yielding a yellow gum which was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown gum (1.5g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded the urea (121) (0.37g; 23%), m.p. 100-108°, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with a sample obtained before.

Further elution with ethyl acetate gave only an intractable foam (0.43g) which yielded no identifiable material.

Final elution with methanol yielded triphenylphosphine oxide (0.31g; 22%), m.p. 146-149°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.
1-[2-(3-Methoxyphenoxy)pyrid-3-yl]-3-(4-methoxyphenyl) urea (152)

A solution of the carbodiimide (150b) (1.9g; 0.0044 mol) in 1,2-dimethoxyethane (15.0 ml) was treated with 2M hydrochloric acid (5.0 ml, 0.01 mol) and the mixture was stirred at room temperature for 17h.

The mixture was rotary evaporated under reduced pressure and the residue was treated with water (10.0 ml) and extracted with methylene chloride to afford a gum (1.9g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) yielded a small amount of gum which was not further investigated.

Further elution with ethyl acetate-hexane (2:3) yielded 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-(4-methoxyphenyl)urea (152) (0.99g; 68%) as a colourless foam. νmax 3330 (NH) and 1700 (CO) cm⁻¹, δH(CDCl₃) 8.59-8.45 (1H, m, ArH), 7.73-6.42 (10H, m, ArH), 3.72 (3H, s, CH₃) and 3.61 (3H, s, CH₃).

**Found:** C, 65.2; H, 5.0; N, 11.3%; m/z (FAB ms), 366.1454 [(M+H)⁺]

**C₂₀H₁₉N₃O₄ requires:** C, 65.8; H, 5.2; N, 11.5%; (M+H), 366.1454

Further elution with ethyl acetate-hexane (1:1) through ethyl acetate to methanol gave only a series of gums total (0.5g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent mixtures which therefore were no further investigated.

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The Attempted Boron Trifluoride-Etherate Catalysed Ring-closure of 1-(2-(3-methoxyphenoxy)pyrid-3-yl)-3-phenylcarbodiimide (120)

A solution of the impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.82g; 0.002 mol) in anhydrous methylene chloride (10.0 mol) was stirred and cooled to 0°C (ice-salt bath) and treated dropwise with a solution of boron trifluoride etherate (1.4g; 0.01 mol) in methylene chloride (5.0 ml). The mixture was then heated under reflux for 24h.

The mixture was cooled, treated with ice (10.0g) and stirred at room temperature for 0.5h then extracted with methylene chloride yielding a brown oil (0.95g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) yielded 1-(2-(3-methoxyphenoxy)pyrid-3-yl)-3-phenylurea (121) (0.13g; 19%), as a colourless gum; identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:7) over silica) with an authentic sample obtained before.

Further elution with ethyl acetate-hexane (2:3) through ethyl acetate to methanol gave only a series of intractable gums (total 0.48g) which yielded no identifiable material.

Phosphorus pentoxide-methanesulphonic acid (Eaton’s Reagent)

Eaton’s Reagent was prepared by the dissolution of phosphorus pentoxide in methanesulphonic acid at room temperature as described by Eaton, Carlson, and Lee.49
The Attempted Acid Catalysed Ring Closure of 1-[2-(3-Methoxyphenoxy)pyrid-3-yl]-3-phenylcarbodiimide (120) using Eaton's Reagent

(a) The impure carbodiimide (120) (1.6 g; 0.005 mol) (contaminated with triphenylphosphine oxide) was stirred and cooled to 5-10° (ice-bath) then treated dropwise with Eaton's Reagent (7.5 g) and the mixture then stirred at room temperature for 24 h.

The mixture was added slowly to water (25.0 ml) and extracted with methylene chloride to afford an oil (1.7 g). This was treated with 10% w/v aqueous sodium hydrogen carbonate solution (20.0 ml) and extracted with methylene chloride yielding 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) as a gum (1.5 g; 80%), identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane 3:2) over silica) with an authentic sample.

(b) Repetition of the procedure described in (a) but with stirring of the mixture at 100° for 24 h. The mixture was cooled and added dropwise with stirring to water (25.0 ml) then extracted with methylene chloride yielding a gum (1.5 g). This was treated with 10% w/v aqueous sodium hydrogen carbonate solution (20.0 ml) and extracted with methylene chloride to afford a gum (1.3 g) whose t.l.c. in ethyl acetate-hexane 3:2) over silica showed it to be a multicomponent mixture which yielded no identifiable material.
The original aqueous mother liquor was neutralised with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride to yield a gum (0.4g) whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be a multicomponent mixture which yielded no identifiable material.

**9-Methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) and 7-Methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (123)**

(a) A solution of the impure carbodiimide (120) (1.8g; 0.005 mol) (contaminated with triphenylphosphine oxide) in carbon disulphide (10.0 ml) was added dropwise to a stirred suspension of aluminium trichloride (1.4g; 0.011 mol) in carbon disulphide (10.0 ml) and the mixture was then heated under reflux for 2h.

The mixture was cooled to 0° (ice-salt bath) then treated with 0.2M aqueous hydrochloric acid (5.0 ml) and stirred at room temperature for 1h. The mixture was then diluted with water (10.0 ml) and extracted with methylene chloride to afford a yellow foam (1.7g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:9) through to ethyl acetate-hexane (1:1) yielded a series of intractable gums (total 0.13g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (1:1) afforded **9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122)** (0.16g;
10%) as a colourless solid, m.p 182-184° (from toluene), $\nu_{\text{max}}$ 2250
(NH)$\text{cm}^{-1}$, $\delta_H$(CDCl$_3$) 7.93 (1H, dd, J ortho 5Hz, J meta 2Hz, ArH), 7.68
(2H, d, J8Hz, ArH), 7.57 (1H, d, J7Hz, ArH), 7.39 (1H, d, J8Hz, ArH)
7.38-7.31 (2H, m, ArH) 7.12-7.05 (2H, m, ArH), 6.93 (1H, d, J2Hz, H-10)
(enhanced 6% by irradiation of CH$_3$O), 3.70 (3H, s, CH$_3$), $\delta_C$ (CDCl$_3$
163.6 (quat), 160.1 (quat), 155.9 (quat), 154.5 (quat), 141.7 (art), 139.7
(quat), 135.5 (CH), 135.3 (quat), 128.6 (CH), 127.9 (CH), 123.2 (CH), 122.2
(CH), 120.5 (CH), 117.2 (quat), 112.3 (CH), 106.2 (CH) and 55.4 (CH$_3$

**Found:** C, 71.6; H, 4.7; N, 13.3%; $m/z$ (EI MS), 317 (M$^+$)

**C$_{19}$H$_{15}$N$_3$O$_2$ requires:** C, 71.9; H, 4.7; N, 13.3%; M, 317

Further elution with ethyl acetate-hexane (1:1) yielded a colourless solid (0.15g), m.p. 200-230°, whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be an unresolvable mixture of the isometric pyridobenzoxazepinies (122) and (123).

Further elution with ethyl acetate-hexane (1:1) yielded **7-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine** (123) (0.29g; 18%) as a colourless solid, m.p. 113-114°.

**Found:** C, 71.6; H, 4.8; N, 13.2%; $m/z$ (EI ms), 317 (M$^+$)

**C$_{19}$H$_{15}$N$_3$O$_2$ requires:** C, 71.9; H, 4.7; N, 13.3%; M, 317

Further elution with ethyl acetate-hexane (1:1) through ethyl acetate to methanol yielded only a series of intractable gums (total 0.71g) which yielded no identifiable material.
(b) A solution of the impure carbodiimide (120) (1.8g; 0.005 mol) (contaminated with triphenylphosphine oxide) in methylene chloride (10.0 ml) was added dropwise to a stirred suspension of aluminium trichloride (2.3g; 0.018 mol) in methylene chloride (10.0 ml) and then the mixture was stirred and heated under reflux for 2h.

The mixture was cooled to 0º (ice-salt bath) and treated with 0.2M aqueous hydrochloric acid (5.0 ml) then stirred at room temperature for 1h. Concentrated hydrochloric acid (1.0 ml) was added and the mixture was stirred for a further 17h at room temperature.

The mixture was filtered to remove inorganic material and the filtrate was extracted with methylene chloride to afford a yellow foam (0.98g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) through to ethyl acetate-hexane (1:1) gave a series of intractable gums (total 0.13g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (3:2) afford impure 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.14g; 9%) m.p. 66-67º identified by comparison (i.r spectrum and t.l.c in ethyl acetate-hexane (3:2) over silica) with a sample obtained before.

Further elution with ethyl acetate yielded triphenylphosphine oxide (0.27g), m.p. 144-147º identified by comparison (m.p. and i.r. spectrum) with an authentic sample.
Further elution with ethyl acetate through to methanol yielded only a series of intractable gums (total 0.34g) which were not further investigated.

(c) A stirred solution of the impure carbodiimide (120) (1.9g; 0.005 mol) (contaminated with triphenylphosphine oxide) in methylene chloride (10.0 ml) was stirred and cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (6.5g; 0.025 mol) in anhydrous methylene chloride. The mixture was then stirred at room temperature for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 2M aqueous sodium hydroxide solution (50.0 ml). The mixture was treated with methylene chloride resulting in a three phase system which was filtered to remove inorganic material. The two phase filtrate was separated and the aqueous phase further extracted with methylene chloride. Evaporation of the combined methylene chloride extracts afforded an oil (1.6g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave only a small amount of oil which was not further investigated.

Further elution with ethyl acetate-hexane (3:7) yielded 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) (0.24g; 14%) as a colourless gum, identified by comparison (i.r. spectrum and t.l.c in ethyl acetate-hexane (3:2) over silica) with a sample prepared before.
Further elution with ethyl acetate-hexane (2:3) yielded a small amount of gum which was not further investigated.

Further elution with ethyl acetate-hexane (2:3) afforded \textbf{9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122)} (0.51g; 36%), m.p. 176-179° identical (m.p. and i.r spectrum) to a sample obtained before.

Further elution with ethyl acetate gave an intractable gum (0.12g) which was not further investigated.

Further elution with methanol afforded triphenylphosphine oxide (0.38g) as a gummy solid, identified by comparison [i.r. spectrum and t.l.c in ethyl acetate-hexane (3:2) over silica] with an authentic sample.

(d) The procedure described before in (a) was repeated but with heating of the mixture under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 2M aqueous sodium hydroxide solution (50.0 ml). Methylene chloride (35.0 ml) was added and the mixture was stirred at room temperature for 0.5h giving a three phase system. This was filtered to remove inorganic material and the two phase filtrate was separated and the aqueous phase further extracted with methylene chloride. Evaporation of the combined methylene chloride extracts gave a gum (1.3g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave a small amount of a gum which was not further investigated.
Further elution with ethyl acetate-hexane (3:7) afforded 1-(2-(3-methoxyphenoxy)pyrid-3-yl)-3-phenylurea (121) (0.12g; 7%) as a yellow gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:2) over silica) with a sample prepared before.

Further elution with ethyl acetate-hexane (2:3) yielded 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.78g; 49%) m.p. 177-179° identical (m.p. and i.r. spectrum) to a sample obtained before.

Further elution with methanol yielded triphenyphosphine oxide, m.p. 124-130° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(e) A stirred solution of the impure carbodiimide (120) (contaminated with triphenyphosphine oxide) (0.80g; 0.002 mol) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (2.6g; 0.01 mol) in anhydrous methylene chloride (5.0 ml). The mixture was then heated under reflux for 48h.

The stirred mixture was cooled to 0° (ice-salt bath) and treated dropwise with 15M aqueous sodium hydroxide solution (67.8 ml; 0.1 mol). The mixture was stirred and allowed to warm to room temperature over 15 min then diluted with water (20.0 ml) and the mixture extracted with methylene chloride to give a gum (0.66g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) yielded 1-(2-(3-methoxyphenoxy)pyrid-3-yl)-3-phenylurea (121) (0.042g; 6%) as a yellow
gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample obtained before.

Further elution with ethyl acetate-hexane (3:2) gave 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.37; 58%) m.p. 176-181° identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate yielded triphenylphosphine oxide (0.12g), m.p. 142-145°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Final elution with methanol gave only an intractable brown gum (0.074g) which yielded no identifiable material.

(f) A stirred solution of the crude impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.67g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (3.7g; 0.014 ml) in anhydrous methylene chloride (5.0 ml). The mixture was heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 2M aqueous sodium hydroxide solution (50.0 ml). Further methylene chloride (35.0 ml) was added and the mixture was stirred and allowed to warm to room temperature over 1h.

Extraction with methylene chloride yielded a brown oil (0.71g) which was flash-chromatographed over silica. Elution with ethyl acetate-
hexane (3:7) yielded **1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121)** (0.11g; 17%) as a colourless gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:2) over silica) with an authentic sample.

Further elution with ethyl acetate-hexane (2:3) afforded **9-methoxy-6-phenylaminopyridolo[2,3-b][1,4]benzoxazepine (122)** (0.25g; 39%) m.p. 172-175°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol gave only an intractable brown oil (0.33g) which yielded no identifiable material.

(g) A stirred solution of the impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.84g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was cooled to 0° (ice-salt bath) then treated dropwise with a solution of stannic chloride (2.6g; 0.01 mol) in anhydrous 1,2-dichloroethane (5.0 ml) and the mixture was heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated with 15M aqueous sodium hydroxide solution (6.8 ml; 0.1 mol) and allowed to warm to room temperature with stirring over 15 min. The mixture was diluted with water and extracted with methylene chloride to give a gum (0.82g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) yielded a series of intractable gums (total 0.042g) which were not further investigated.
Further elution with ethyl acetate-hexane (3:7) yielded 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) (0.051g; 8%) as a gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample.

Further elution with ethyl acetate-hexane (3:2) yielded 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.37g; 59%), m.p. 178-180°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate-hexane (7:3) yielded only intractable gums (total 0.0037g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (7:3) gave triphenylphosphine oxide (0.16g) identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate through to methanol gave only a series of intractable gums (total 0.17g) which were not further investigated.

(h) A stirred solution of the pure carbodiimide (120) (1.2g; 0.0036 ml) in anhydrous 1,2-dichloroethane (20.0 ml) was cooled to 0° (ice-salt bath) then treated dropwise with a solution of stannic chloride (4.7g; 0.018 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture was heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 15M aqueous sodium hydroxide solution (13.3 ml, 0.2 mol) and allowed to warm to room temperature with stirring over 15
min. The mixture was diluted with water (40.0 ml) and extracted with methylene chloride to afford a gum (1.1g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:4) gave a series of intractable gums (total 0.075g) which were not further investigated.

Further elution with ethyl acetate-hexane (1:4) gave 1-[2(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121) (0.03g; 2%) as a yellow gum, identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (2:3) gave 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.49g; 43%), m.p. 170-174° identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate-hexane through to methanol yielded a series of intractable gums (total 0.46g) which yielded no identifiable material.

(i) A solution of the impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (1.9g; 0.005 mol) in anhydrous 1, 1, 2, 2,-tetrachloroethane (10.0 ml) was stirred and cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (6.5g; 0.025 mol) in anhydrous 1, 1, 2, 2-tetrachloroethane (5.0 ml). The mixture was then heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt-bath) then treated dropwise with 2M aqueous sodium hydroxide solution (55.0 ml).
Methylene chloride (50.0 ml) was added and the mixture was stirred at room temperature for 2h giving a three phase mixture which was filtered to remove inorganic material. The two phase filtrate was separated and the aqueous layer was further extracted with methylene chloride. Evaporation of the combined methylene chloride extracts yielded an oil (1.8g) whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be a complex mixture consisting mainly of 1-12-(3-methoxyphenoxypyrind-3-yl)-3-phenyl urea (121) and triphenylphosphine oxide. The oil was not further investigated.

(j) A solution of the impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.73g, 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred under nitrogen and cooled to 0° (ice-salt bath) then treated dropwise with titanium tetrachloride (1.9g; 0.01 mol) in anhydrous methylene chloride (5.0 ml). The mixture was then heated under reflux for 24h.

The reaction mixture was stirred and cooled to 0° (ice-salt bath) then treated with 60% w/v aqueous sodium hydroxide solution (6.8 ml, 0.1 mol). The stirred mixture was allowed to warm to room temperature over 15 min then treated with water (20.0 ml) and the resulting two phase mixture extracted with methylene chloride to afford an oil (0.68g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded 9-methoxy-6-phenylaminopyrido[2,3-b][1,4]benzoxazepine (122) (0.31g; 49%), m.p.
176-179°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate gave a gum whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Final elution with methanol yielded triphenylphosphine oxide (0.058g) as a gummy solid, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:2) over silica) with an authentic sample.

**1,3-Diphenyl-1-[9-methoxypyrido[2,3-b][1,4]benzoazepin-6-yl] urea (124)**

Solutions of the pyridobenzoxazepine derivative (122) (0.63g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and phenyl isocyanate (0.24g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) were mixed and the mixture was stirred at room temperature for 2h.

Evaporation of the mixture yielded **1,3-diphenyl-1-[9-methoxypyrido[2,3-b][1,4]benzoazepin-6-yl] urea (124)** (0.82g; 94%) as a colourless solid, m.p. 174-180° (from hexane-toluene), $\nu_{\text{max}}$ 1695 (CO)cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.17-6.41 (16H, m, ArH), 5.60 (1H, brs, NH) (exch.) and 3.79 (3H, s, CH$_3$).

**Found:** C, 72.0; H, 4.2; N, 12.8%; m/z (FAB ms), 437.1614 [(M+H)$^+$]

**C$_{26}$H$_{20}$N$_{4}O_3$ requires:** C, 71.6; H, 4.6; N, 12.8%; (M+H), 437.1614
The Study of the Reaction of 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenyl carbodiimide (120) with Stannic Chloride Using Infra red Spectroscopy

The impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.001 mol) was dissolved in methylene chloride (20.0 ml) and the i.r. spectrum of the resulting solution recorded. The solution was then treated with stannic chloride (0.26g; 0.001 mol) and the mixture stirred at room temperature for 5 min. The i.r. spectrum of the mixture was recorded and stirring continued for a further 25 min at room temperature after which time the i.r. spectrum of the mixture was again recorded. A further equivalent of stannic chloride (0.26g; 0.001 mol) was added and i.r. spectra of the mixture recorded at the same time intervals as before.

The above procedure was repeated until five equivalents of stannic chloride had been added. The variation in intensity of the i.r. absorption band at 2140 cm\(^{-1}\) due to the carbodiimide group (N=C=N) as a function of the amount of stannic chloride added is illustrated by the graph shown in Figure 2 (Section 2.2).
**The Stannic Chloride Catalysed Ring Closure of 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylcarbodiimide (120) in the Presence of Triphenylphosphine Oxide**

A solution of the impure carbodiimide (120) (contaminated with triphenylphosphine oxide) (0.63g; 0.002 mol) and triphenylphosphine oxide (0.56g; 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred and cooled to 0°C (ice-salt bath) then treated drop wise with 15M aqueous sodium hydroxide solution (6.8 ml; 0.1 mol). The stirred mixture was allowed to warm to room temperature over 15 min then extracted with methylene chloride to give a gum (1.1g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave **1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylurea (121)** (0.11g; 16%) as a colourless gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:2) over silica) with an authentic sample obtained before.

Further elution with ethyl acetate-hexane (3:2) afforded the impure **pyrido oxazepine (122)** (0.099g; 16%) as a gummy solid, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (3:2) over silica) with an authentic sample obtained before.

Further elution with ethyl acetate gave triphenylphosphine oxide (0.27g; 48%), m.p. 139-145°C, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.
The Attempted Stannic Chloride Catalysed Ring Closure of 1-[2-(3-Methoxyphenoxy)pyrid-3-yl]-3-phenylcarbodiimide (120) Derived from Diethyl N-[2-(methoxyphenoxy)pyrid-3-yl] phosphoramidate (148)

A solution of the carbodiimide (120) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of stannic chloride (2.6g; 1.2 ml; 0.01 mol) in anhydrous 1,2-dichloroethane (5.0 ml) and the mixture heated under reflux for 24h.

The mixture was cooled to 0° (ice-salt bath) then treated dropwise with stirring with 15M aqueous sodium hydroxide solution (6.8 ml; 0.1 mol) and the mixture allowed to warm to room temperature while stirring for 15 min. After this time water (20.0 ml) was added and the mixture extracted with methylene chloride to afford a gum (0.56g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) through ethyl acetate to methanol gave only a series of intractable gums (total 0.43g) whose t.l.c. in ethyl acetate (1:1) over silica showed them to be unresolvable multicomponent mixtures which were not further investigated.
The Attempted Zinc Chloride Catalysed Ring Closure of 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-phenylcarbodiimide (120) in 1,1,2,3-Tetrachloroethane

A stirred solution of the impure carbodiimide (120) (contaminated by triphenylphosphine oxide) (1.9g; 0.005 mol) in anhydrous 1, 1, 2, 2-tetrachloroethane (25.0 ml) was treated with zinc chloride (0.15g; 0.001 mol) and the mixture was stirred and heated under reflux for 17h.

The mixture was cooled and evaporated under high vacuum yielding a brown oil (3.0g) whose i.r. spectrum showed the presence of unreacted starting material. The oil was redissolved in 1, 1, 2, 2-tetrachloroethane (25.0 ml) and treated with a further aliquot of zinc chloride (3.4g; 0.025 mol) then heating under reflux continued for a further 2h.

The mixture was stirred and cooled to 0° (ice salt bath) then treated dropwise with 2M aqueous sodium hydroxide solution (25.0 ml). The mixture was stirred at room temperature for 30 min then extracted with methylene chloride yielding a gum (2.5g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture containing urea (121) and triphenylphosphine oxide with none of the expected pyridobenzoxazepine (122) present. The gum was not further investigated.
The Attempted Stannic Chloride Catalysed Ring-Closure of 1-[2-(3-methoxyphenoxy)pyrid-3-yl]-3-(4-methoxyphenyl)carbodiimide (150b)

A solution of the carbodiimide (150b) (1.8g; 0.0047 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred and treated dropwise at room temperature with stannic chloride (6.1g; 0.024 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture was stirred and heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 15M aqueous sodium hydroxide solution (16.0 ml; 0.24 mol). The mixture was stirred and allowed to warm to room temperature over 15 min, then diluted with water (47.0 ml) and the resulting mixture extracted with methylene chloride to afford a gum (1.5g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which was not further investigated.

9-methoxy-6-(4-nitrophenylamino)pyrido[2,3-b][1,4]benzoxazepine (151)

A solution of the carbodiimide (150a) (1.7g; 0.0047 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred and treated dropwise with a solution of stannic chloride (6.1g; 0.024 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture stirred and heated under reflux for 24h.
The mixture was cooled to 0°C (ice-salt bath) and treated dropwise with stirring with 15M aqueous sodium hydroxide solution (16.0 ml; 0.24 mol) then allowed to warm to room temperature with stirring over 15 min. The mixture was diluted with water (47.0 ml) and extracted with methylene chloride to afford a gum (1.4g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:4) through to ethyl acetate-hexane (3:7) yielded a series of intractable gums (total 0.25g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (3:7) yielded a gummy solid (0.37g) which was triturated with diethyl ether to give 9-methoxy-6-(4-nitrophenylamino)pyrido[2,3-b][1,4]benzoxazepine (151) (0.29g; 18%) as a yellow solid, m.p. 126-129°C (from glacial acetic acid), νmax 2390 (NH) and 1505 and 1330 (NO2) cm⁻¹, δH[(CD3)2SO] 10.65 (1H, bs, NH) (exch.), 8.22-6.93 (10H, m, ArH) and 3.85 (3H, s, CH3).

**Found:** m/z (FAB) ms), 343.1094 [(M+H)+]

C_{19}H_{14}N_{4}O_{4} requires: (M+H), 363.1093

Further elution with ethyl acetate-hexane (3:7) through ethyl acetate to methanol gave only a series of intractable gums (total 0.23g) whose t.l.c. in ethyl acetate-hexane (1:1) showed them to be multicomponent mixtures which were not further investigated.
9-Methoxy-6-methylaminopyrido[2,3-b][1,4]benzoazepine (126)

A stirred solution of the impure carbodimide (125) (contaminated with triphenylphosphine oxide) (2.5g; 0.005 mol) in anhydrous methylene chloride (10.0 ml) was cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (6.5g; 0.025 mol) in methylene chloride (5.0 ml). The mixture was then heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 2M aqueous sodium hydroxide solution (50.0 ml). The resulting mixture was stirred at room temperature for 0.5h then filtered to remove inorganic material and the filtrate extracted with methylene chloride yielding a brown gum which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) through acetate-hexane (1:1) yielded only a series of intractable gums which yielded no identifiable material.

Further elution with ethyl acetate-hexane (1:1) gave 9-methoxy-6-methylaminopyrido[2,3-b][1,4]benzoazepine (126) (0.13g; 10%) as a light brown gum.

**Found**: m/z (FAB ms), 256.1086 [(M+H)]+

**C_{14}H_{13}N_{3}O_2** requires: (M+H), 256.1086

Further elution with ethyl acetate afforded triphenylphosphine oxide (0.71g), m.p. 135-143°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.
Final elution with methanol gave a gum (0.13g) whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be a multicomponent mixture which was not further investigated.
The Attempted Stannic Chloride Catalysed Ring Closure of 1-Benzyl-3-[2-(3-methoxyphenoxy)pyrid-3-yl] carbodiimide (127)

A solution of the impure carbodiimide (127) (contaminated with triphenylphosphine oxide) (0.87 g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of stannic chloride (2.6 g; 0.01 mol) in anhydrous 1,2-dichloroethane (5.0 ml) and the mixture heated under reflux for 24 h.

The mixture was stirred and cooled to 0° (ice-salt bath) then treated dropwise with 15M aqueous sodium hydroxide solution (6.8 ml; 0.1 mol) and the mixture allowed to warm to room temperature with stirring over 15 min. The mixture was diluted with water (20.0 ml) and extracted with methylene chloride to give a gum (0.75 g) which was flash chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded only intractable gums (total 0.028 g) which were not further investigated.

Further elution with ethyl acetate-hexane (2:3) yielded 1-benzyl-3-[2-(3-methoxyphenoxy)pyrid-3-yl] urea (129) (0.39 g; 55%) as a pale green gum, $\nu_{\text{max}}$ 3436 (NH) and 1609 (CO) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.90 (1H, dd, Jortho 5 Hz and Jmeta 2 Hz, ArH), 7.54-7.26 (8H, m, ArH), 7.10 (1H, dd, Jortho 8 Hz and Jortho 5 Hz, ArH), 6.95 (1H, d, Jmeta 2 Hz, ArH), 6.72 (1H, dd, Jortho 9 Hz and Jmeta 2 Hz, ArH), 5.30 (1H, s, NH), 5.10 (1H, m, NH), 4.75 (1H, s, CH), 4.72 (1H, s, CH) and 3.81 (3H, s, CH$_3$).
**Found:** C, 68.6; H, 5.2; N, 11.7%; m/z (El ms), 331 (M⁺-H₂O)

**C₂₀H₁₉N₃O₃ requires:** C, 68.7; H, 5.4; N, 12.0%; M, 349

Further elution with methanol gave only an intractable gum (0.29g) which was not further investigated.

**The Attempted Stannic Chloride Catalysed Ring-Closure of 1-(2-phenoxypyrid-3-yl)-3-phenylcarbodiimide (135)**

A solution of the impure carbodiimide (135) (contaminated with triphenylphosphine oxide) (0.57g; 0.002 mol) in anhydrous 1,2-dichloroethane (10.0 ml) was stirred and cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (2.6g; 0.01 mol) in 1,2-dichloroethane (5.0 ml). The mixture was then heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) and treated dropwise with 15M aqueous sodium hydroxide solution (6.8 ml; 0.1 mol) and the mixture was allowed to warm to room temperature with stirring over 15 min. The mixture was diluted with water (20.0 ml) and extracted with methylene chloride to afford an oil (0.51g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.
The Attempted Lithiative Ring Closure of 1-(2-phenoxy-pyrid-3-yl)-3-phenyl carbodiimide (135)

A solution of the carbodiimide (135) (1.4g; 0.005 mol) in anhydrous tetrahydrofuran (10.0 ml) was stirred, cooled to -25° (solid CO₂-acetone bath) and treated dropwise with a 1.43M solution of butyl lithium in hexanes (3.5 ml; 0.005 mol) over 10 min. The mixture was then stirred under nitrogen and allowed to warm to room temperature over 18h.

The mixture was stirred and treated with saturated ammonium chloride solution (10.0 ml) then extracted with tetrahydrofuran to give a brown gum (1.5g) which was flash chromatographed over silica.

Elution with diethyl ether-hexane (1:1) gave 2-butyl-1-(2-phenoxy-pyrid-3-yl)-3-phenylformamidine (137) (0.56g; 32%) which was purified by bulb-to-bulb distillation, b.p. 210-230° / 0.04 mm Hg, νmax 3440 (NH)cm⁻¹, δH(CDCI₃) 9.78 (1H, bs, NH), 7.74 (1H, dd, Jmeta 5Hz, Jortho 2Hz, ArH), 7.50-6.88 (12 H, m, ArH), 2.35-2.25 (2H, m, CH₂), 1.68-1.16 (4H, m, 2xCH₂) and 0.89-0.73 (3H, m, CH₃).

Found: m/z (EI ms), 345.1832 (M⁺)

C₂₂H₂₃N₃O requires: M, 345.1841

Further elution with ethyl acetate-hexane (1:1) through ethyl acetate to methanol gave only a series of intractable gums (total 1.0g) which were not further investigated.
The Attempted Magnesium Catalysed Ring Closure Of 1-[2-(2-Bromophenoxy)pyrid-3-yl]-3-phenylcarbodiimide (153)

A solution of the carbodiimide (153) (0.55g; 0.0015 mol) in anhydrous diethyl ether (10.0 ml) was treated with magnesium turnings (0.037g; 0.0015 mol) and dibromoethane (0.1 ml) and the mixture was stirred at room temperature for 65h.

After this time the solution i.r. spectrum of the mixture showed the presence of starting material. A few crystals of iodine were added and stirring was continued at room temperature for a further 24h.

The mixture was stirred and treated with 2M aqueous hydrochloric acid (5.0 ml; 0.01 mol) then stirred at room temperature for 1 hour and extracted with methylene chloride to afford a brown oil (0.44g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

The Attempted Reaction of 1-(2-(2-Bromophenoxy)pyrid-3-yl)-3-phenylcarbodiimide (153) with Sec-Butyllithium in Hexane

A solution of the carbodiimide (153) (1.8g; 0.005 mol) in anhydrous tetrahydrofuran (25.0 ml) was stirred under nitrogen and cooled to -100° (ethanol-liquid nitrogen slush bath) then treated dropwise with a 1.0M solution of sec-butyllithium in hexane (4.9 ml; 0.005 mol) at -100° and the mixture then allowed to warm to room temperature. Stirring was continued at room temperature for 18h.
The mixture was treated with stirring with saturated ammonium chloride solution (25.0 ml) and extracted with tetrahydrofuran to afford an orange gum (1.8g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (4:6) through to methanol gave only a series of intractable gums which yielded no identifiable material.

**The Attempted Tributyltinhydride Mediated Radical Ring Closure of 1-(2-(2-Bromophenoxy)pyrid-3-yl)-3-phenylcarbodiimide (153)**

A suspension of azoisobutyronitrile (0.0075g; 0.04 mmol) in anhydrous benzene (10.0 ml) was stirred under nitrogen and treated at room temperature with a solution of the carbodiimide (153) (0.73g; 0.002 mol) in anhydrous benzene (5.0 ml) and the resulting mixture was heated under reflux and treated dropwise over 1h with a solution of tributyltin hydride (1.5g; 0.005 mol) in anhydrous benzene (10.0 ml). Heating under reflux was then continued for a further 3h.

The mixture was cooled and evaporated and the residue extracted with boiling hexane to afford a gum (0.40g) which was flash-chromatographed over silica.

Elution with diethyl ether-hexane (3:7) through diethyl ether to methanol gave only a series of intractable gums (total 0.29g) which yielded no identifiable material.
The Attempted Palladium Acetate Catalysed Ring-Closure of 1-(2-(2-Iodophenoxy)pyrid-3-yl)-3-phenyl carbodiimide (166)

(a) A solution of the carbodiimide (166) (0.75g; 0.0018 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated successively with palladium acetate (0.045g; 0.2 mmol), triphenyl phosphate (0.11g; 0.4 mmol), anhydrous potassium carbonate (0.28g; 0.002 mol) and tetrabutyl ammonium chloride (0.56g; 0.002 mol) and the mixture was stirred and heated under reflux for 1 hour.

The mixture was cooled and diluted with water (10.0 ml) the extracted with methylene chloride to afford a gum (1.4g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:4) through ethyl acetate to methanol yielded only a series of gums (total 1.0g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent which were not further investigated.

(b) A solution of the carbodiimide (166) (0.82g; 0.002 mol) in anhydrous acetonitrile (10.0 ml) was stirred under nitrogen and treated successively at room temperature with palladium acetate (0.045g; 0.2 mmol), tri-o-tolylphosphine (0.12g; 0.4 mmol) and triethylamine (0.81g; 0.008 mol) and the mixture was stirred and heated under reflux under nitrogen for 18h.

The mixture was cooled, diluted with water (10.0 ml) and extracted with methylene chloride to afford a gum (0.90g) whose t.l.c. in ethyl acetate-
hexane (1:1) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(c) A solution of the carbodiimide (166) (0.83g; 0.002 mol) in anhydrous acetonitrile (10.0 ml) was stirred under nitrogen and treated successively at room temperature with palladium acetate (0.45g; 0.002 mol), tri-o-tolylphosphine (1.2g; 0.004 mol) and triethylamine and the mixture was stirred and heated under reflux nitrogen for 17h.

The mixture was cooled, diluted with water (10.0 ml) and extracted with methylene chloride to afford a gummy solid (2.4g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which yielded no identifiable material.

The Reaction of N-(2-(3-Methoxyphenoxy)pyrid-3-yl)trimethoxyphosphinimine (149) with Carbon Dioxide

A solution of the phosphinimine (149) (1.3g; 0.004 mol) in anhydrous 1,2-dimethoxyethane (15.0 ml) was stirred and treated with carbon dioxide gas at room temperature for 5h. The mixture was then evaporated to yield an oil (1.2g) whose i.r. spectrum showed isocyanate absorption, $v_{\text{max}}$ 2140 (N=C=O) cm$^{-1}$. The oil was dissolved in ethanol (5.0 ml; 0.01 mol) and the solution stirred at room temperature for 1h.

Evaporation of the mixture yielded an oil (1.3g) which was flash-chromatographed over silica.
Elution with ethyl acetate-hexane (1:4) afforded \((\text{ethoxycarbonylamino})-2-3\text{-methoxyphenoxy})\text{pyridine (171)}\) (0.09g; 8%) as a yellow gum, \(v_{\text{max}}\) 3438 and 3329 (NH) and 1734 (CO)\text{cm}^{-1},

\[\delta_{\text{H}}(\text{CDCl}_3)\text{SO}]\]

9.15 (1H, S, NH), 8.13 (1H, dd Jortho 8Hz and Jmeta 2Hz, ArH), 7.84 (1H, dd Jortho 5Hz and Jmeta 2Hz, ArH), 7.35-7.27 (2H, m, ArH), 7.14 (1H, dd, Jortho 8Hz and Jortho 5Hz, ArH), 6.83-6.68 (2H, m, ArH), 4.16 (2H, q, J7Hz, CH\(_2\)), 3.77(3H, s, CH\(_3\)) and 1.26 (3H, t, J7Hz, CH\(_3\)).

**Found:** C, 62.8; H, 5.7; N, 9.7%; m/z (EI ms), 288, (M\(^+\))

**C\(_{15}\)H\(_{16}\)N\(_2\)O\(_4\) requires** C, 62.5; H, 5.6; N, 9.7%; M, 288

Further elution with ethyl acetate-hexane (1:4) through to ethyl acetate-hexane (1:1) yielded only a series of gums (total 0.90g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent mixtures which were not further investigated.

**2-(3-Methoxyphenoxy)pyridine-3-carboxylic Acid (168)**

A solution of 2-chloropyridine-3-carboxylic acid (167) (7.9g; 0.05 mol) and 3-methoxyphenol (109) (6.2g; 0.05 mol) in dimethylformamide (50.0 ml) was treated with anhydrous potassium carbonate (12.0g) and copper bronze (0.1g) and the mixture was stirred and heated under reflux for 17h.

The mixture was cooled and evaporated under high vacuum and the residue treated with water (30.0 ml). The resulting mixture was clarified
with charcoal, acidified with 2M aqueous hydrochloric acid and filtered to afford **2-(3-methoxyphenoxy)pyridine-3-carboxylic acid (168)** (8.9g; 73%) as a colourless solid, m.p. 167-168° (from ethanol), \( v_{\text{max}} \) 3100 - 2500 br (OH) and 1690 (CO) cm\(^{-1}\), \( \delta_H \) 8.49 (1H, dd, \( J_{\text{ortho}} \) 8Hz and \( J_{\text{meta}} \) 2Hz, ArH), 8.33 (1H, dd, \( J_{\text{ortho}} \) 5Hz and \( J_{\text{meta}} \) 2Hz, ArH), 7.38-7.13 (2H, m, ArH), 6.86-6.73 (3H, m, ArH) and 3.80 (3H, s, CH\(_3\)).

**Found:** C, 63.9; H, 4.4; N, 5.9%; m/z (EI ms), 245 (M\(^+\))

**C\(_{13}\)H\(_{11}\)NO\(_4\) requires:** C, 63.7; H, 4.5; N, 5.7%; M, 245

The aqueous acidic mother liquor was extracted with methylene chloride to afford a red oil whose t.l.c. in ethyl acetate-hexane (3:2) over silica showed it to be a multicomponent mixture which therefore was not further investigated.

**2-(3-Methoxyphenoxy)pyrid-3-yl Isocyanate (169)**

A suspension of 2-(3-Methoxyphenoxy)pyridine-3-carboxylic acid (168) (2.5g; 0.01 mol) in anhydrous toluene (50.0 ml) was stirred under nitrogen and treated with triethylamine (1.1g; 0.011 mol) followed by diphenylphosphorylazide (2.75g; 0.01 mol). The mixture was then heated at 100° under nitrogen for 3h.

The mixture was cooled and evaporated and the resulting residue was extracted with boiling hexane leaving an intractable gum which was not further investigated. Evaporation of the hexane extract yielded impure **2-(3-**
Methoxyphenoxy)pyrid-3-yl isocyanate (169) (1.9g; 79%) as a yellow oil, 
\[ \nu_{\text{max}} 2250 \text{ (N=C=O) cm}^{-1} \]

**Found:** m/z (El ms), 242-0693 (M⁺)

**C₁₃H₁₀N₃O₃ requires:** M, 242.0691

9-Methoxypyrido[2,3-b][1,4]benzoxazepin-6(5H)-one (170)

A solution of the pyridyl isocyanate (169) in anhydrous 1,2-dichloroethane (35.0 ml) was cooled 0-10° (ice-bath) and treated dropwise with stirring with a solution of stannic chloride (9.1g; 0.035 mol) in anhydrous 1,2-dichloroethane (18.0 ml). The mixture was then stirred and heated under reflux for 24h.

The mixture was cooled to 0-10° (ice bath) and treated dropwise with stirring with 15M aqueous sodium hydroxide solution (24.5 ml; 0.37 mol). The mixture was then allowed to warm to room temperature with stirring over 1 hour. The mixture was treated with water (70.0 ml) followed by methylene chloride to give a three phase mixture which was filtered to remove inorganic material. Evaporation of the methylene chloride extract afforded a gum (0.54g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:9) yielded a yellow oil (0.19g) whose t.l.c. in ethyl acetate-hexane (1:1) showed it to be a complex mixture which was not further investigated.
Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) afforded \textit{9-Methoxypyridolo[2,3-b][1,4]benzoxazepin-6(5H)-one} (170) (0.27g; 16%) as a colourless solid, m.p. 180-190° (from ethyl acetate), \(v_{\text{max}}\) 3280 (NH) and 1705 (CO) cm\(^{-1}\), \[\delta\text{H}(\text{CD}_3\text{SO})\] 8.54 (1H, dd, J\text{ortho} 8Hz, J\text{meta} 2Hz, ArH), 7.69 (1H, dd, J\text{ortho} 5Hz, J\text{meta} 2Hz, ArH), 7.41 - 6.61 (4H, m, ArH), and 3.72 (3H, s, CH\(_3\)).

\textbf{Found}: m/z (EI ms), 242.0691 (M\(^+\))

\textbf{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3 \text{requires}: \text{M}, 242.0691

Further elution with ethyl acetate-light petroleum (b.p. 40 - 60°) (3:2) through ethyl acetate to methanol gave only a series of intractable gums whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be complex mixtures which therefore were not further investigated.

\textbf{2-(3-Methoxyphenoxy)pyrid-3-yl Isothiocyanate (172)}

(a) A solution of 3-amino-2-(3-methoxyphenoxy)pyridine (116) (2.2g; 0.01 mol) in concentrated hydrochloric acid (50.0 ml) was diluted with water (50.0 ml) and treated dropwise with stirring with thiophosgene (2.3g; 0.02 mol). The mixture was then stirred at room temperature for 24h.

The mixture was extracted with methylene chloride to afford an oil (2.6g) which was flash chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) yielded \textbf{2-(3-Methoxyphenoxy)pyrid-3-yl Isothiocyanate (172)} (2.5g; 97%) as a colourless solid, m.p. 49-51° (from hexane), \(v_{\text{max}}\) 2040 (N=C=S) cm\(^{-1}\),
$\delta_H(\text{CDCl}_3)$ 8.01 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.48 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.45-7.25 (1H, m, ArH), 6.99-6.97 (1H, m, ArH), 6.96-6.75 (3H, m, ArH) and 3.81 (3H, s, CH$_3$).

**Found:** C, 59.9; H, 3.8; N, 10.7%; m/z (EI ms), 258.0461 (M$^+$)

**C$_{13}$H$_{10}$N$_2$O$_2$S requires:** C, 60.5; H, 3.9; N, 10.9%; M, 258.0463

Further elution with methanol gave only an intractable gum (0.26g) which was not further investigated.

(b) A solution of the phosphinimine (119) (2.9g; 0.006 mol) in anhydrous 1, 2 dimethoxyethane (30.0 ml) was treated with carbon disulphide (1.8g; 0.024 mol) and the mixture was heated under reflux for 2h.

The mixture was evaporated yielding a gummy solid (3.6g) which was flash-chromatographed over silica.

Elution with methylene chloride-hexane (1:1) yielded triphenylphosphine sulphide (1.3g; 74%), m.p. 159-163 identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methylene chloride-hexane (1:1) yielded a colourless gummy solid (0.21g), whose t.l.c. in methylene chloride-hexane (4:1) over silica showed it to be a mixture containing triphenylphosphine sulphide and the isothiocyanate (172) product.

Further elution with methylene chloride-hexane (4:1) gave impure 2-(3-methoxyphenoxy)pyrid-3-ylisothiocyanate (172) (0.46g; 31%) as an oil, identified by comparison (i.r. spectrum) with a sample obtained before.
Further elution with methanol yielded an intractable oil (0.97g) which was shown by t.l.c. in ethyl acetate-hexane (7:3) over silica to be a multicomponent mixture which therefore was not further investigated.

**9-Methoxypyrido [2,3-b][1,4]benzoxazepin-6(5H)-thione (173)**

A solution of the isothiocyanate (172) (2.6g; 0.01 mol) in anhydrous 1,2-dichloroethane (50.0 ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (13.0g; 0.05 mol) in anhydrous 1,2-dichloroethane (25.0 ml) and the mixture was heated under reflux for 24h.

The mixture was cooled to 0° (ice-salt bath) and treated dropwise with stirring with 15M aqueous sodium hydroxide solution then allowed to warm to room temperature with stirring over 15 minutes. The mixture was diluted with water (100 ml) and extracted with methylene chloride to give a gummy solid (1.5g) which was triturated with diethyl ether to afford 9-methoxypyrado[2,3-b][1,4]benzoxazepine-6(5H)-thione (173) (0.82g; 32%) as a yellow solid, m.p. 272-273° (from dimethylformamide), \( \nu_{\text{max}} \) 3150 (NH)cm\(^{-1}\), \( \delta_{\text{H}}[(\text{CD}_3)_2\text{SO}] \) 12.40 (1H, s, NH) (exch.), 8.18-7.94 (2H, m, ArH), 7.76 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.36 (1H, dd, Jortho 8Hz and Jortho 5Hz, ArH), 6.96-6.81 (2H, m, ArH) and 3.84 (3H, s, CH\(_3\)).

**Found:** C, 60.9; H, 3.9; N, 11.1%; m/z (EI ms), 258.0464 (M\(^+\))

**C\(_{13}\)H\(_{10}\)N\(_2\)O\(_2\)S requires:** C, 60.5; H 3.9; N 10.9%; M, 258.0463
Evaporation of the diethylether washings yielded a gum (0.37g) whose t.l.c. in ethyl acetate hexane (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

1-(3-Methoxyphenoxo)-2-nitrobenzene (175)

A stirred suspension of sodium hydride (10.6g; 0.44 mol) in anhydrous dimethylformamide (50.0 ml) was treated dropwise, with cooling (ice-bath) with a solution of 3-methoxyphenol (109) (49.6g; 0.4 mol) in anhydrous dimethylformamide (50.0 ml) and the mixture was stirred at room temperature for 15 minutes. A solution of 1-chloro-2-nitrobenzene (174) (63.0g; 0.4 mol) in anhydrous dimethylformamide (100 ml) was then added in one portion and the mixture stirred at 100° for 1h.

The cooled mixture was treated with water (40.0 ml) and stirred at room temperature for 15 minutes. Evaporation under high vacuum yielded a brown gum which was treated with water (400 ml) and extracted with methylene chloride to give a gummy solid (96.5g) which was triturated with methanol yielding a light brown solid (76.3g). This was purified by recrystallisation to give 1-(3-methoxyphenoxo)-2-nitrobenzene (175) (52.4g; 53%) as a colourless crystalline solid, m.p. 54-57° (from diethyl ether-hexane) (lit.75, 56-57°).

Evaporation of the methanolic mother liquor gave an intractable brown oil (19.5g) which yielded no identifiable material.
Evaporation of the diethyl ether-hexane mother liquor yielded a brown gummy solid (9.4g) whose t.l.c. in methylene chloride-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

1-Amino-2-(3-methoxyphenoxy) benzene (176)

A solution of 1-(3-methoxyphenoxy)-2-nitrobenzene (175) (24.5g; 0.1 mol) in ethyl acetate (100 ml) was hydrogenated over 10% palladium-on-charcoal (2.4g) at room temperature and atmospheric pressure for 6h. The catalyst was removed by filtration through celite and the filtrate was rotary evaporated to afford 1-amino-2-(3-methoxyphenoxy) benzene (176) (21.4g; 99%) as a brown oil, ν<sub>max</sub> 3470 and 3380 (NH<sub>2</sub>) cm<sup>-1</sup>, δ<sub>H</sub>(CDCl<sub>3</sub>) 7.25-7.15 (1H, m, ArH), 7.03-6.52 (7H, m, ArH), 3.80 (2H, s, NH) (exch.) and 3.77 (3H, s, CH<sub>3</sub>).

Found: C, 72.2; H, 6.2; N, 7.1%; m/z (FAB ms), 215.0947 (M<sup>+</sup>)

C<sub>13</sub>H<sub>13</sub>N<sub>2</sub> requires: C, 72.6; H, 6.0; N, 6.5%; M, 215.0947

1-Azido-3-(3-methoxyphenoxy) benzene (177)

A solution of the amine (176) (20.8g; 0.097 mol) in 5M aqueous hydrochloric acid (243 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (7.4g; 0.11 mol) in water (48.5 ml) then stirred at 0-5° for 5 min to ensure complete diazotiation. The resulting diazonium solution was then treated dropwise with stirring at 0-5°
(ice-salt bath) with a solution of sodium azide (9.4g; 0.15 mol) in water (48.5 ml) and the reaction mixture then stirred in the melting ice-bath for 0.5h.

Extraction of the reaction mixture with methylene chloride yielded 1-azido-2-(3-methoxyphenoxy) benzene (177) (20.7g; 89%) as a dark brown oil, $\nu_{\text{max}}$ 2110 (N$_3$) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.31-6.97 (5H, m, ArH), 6.71-6.46 (3H, m, ArH) and 3.77 (3H, s, CH$_3$).

**Found:** m/z (EI ms), 241.0854 (M$^+$)

**C$_{13}$H$_{11}$N$_3$O$_2$ requires:** M, 241.0851

**N-2-(3-Methoxyphenoxy)phenyltrimethoxy phosphinimine (178)**

A solution of the azide (177) (19.3g; 0.08 mol) in anhydrous 1,2-dimethoxyethane (250 ml) was treated with a solution of trimethyl phosphite (12.4g; 0.1 mol) in anhydrous 1,2-dimethoxyethane (150 ml) and the mixture was stirred at room temperature for 4h.

The mixture was evaporated under a high vacuum with removal of the excess trimethyl phosphite as an azeotrope with toluene yielding N-2-(3-methoxyphenoxy)phenyltrimethoxy phosphinimine (178) (27.1g; 100%) as a dark brown oil, $\delta_H$(CDCl$_3$) 7.24-6.42 (8H, m, ArH), 3.72 (3H, s, CH$_3$) and 3.59 (9H, d, J11Hz, 3 x CH$_3$).

**Found:** m/z (EI ms), 337.1084 (M$^+$)

**C$_{16}$H$_{20}$N$_5$O$_5$P requires:** M, 337.1079
1-[2-(3-Methoxyphenoxy)phenyl]-3-phenyl carbodiimide (179)

A solution of the iminophosphorane (178) (6.7g; 0.02 mol) in anhydrous 1,2-dimethoxyethane (100 ml) was treated with a solution of phenyl isocyanate (2.4g; 0.02 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) and the mixture was stirred at room temperature for 4h.

Evaporation of the reaction mixture gave a brown oil which was dissolved in diethyl ether (100 ml) and the solution washed with water (100 ml) and evaporated to afford 1-[2-(3-methoxyphenoxy)phenyl]-3-phenyl carbodiimide (179) (6.1g; 97%) as a dark brown oil, \( \nu_{\text{max}} \) 2120 cm\(^{-1}\), \( \delta_H(\text{CDCl}_3) \) 7.35-6.90 (10H, m, ArH), 6.64-6.35 (3H, m, ArH) and 3.66 (3H, d, J2Hz, CH\(_3\)).

Found: C, 75.7; H, 5.3; N, 8.7%; m/z (FAB ms), 317 [(M+H)]^+

\( \text{C}_{20}\text{H}_{16}\text{N}_{2}\text{O}_{2} \) requires: C, 75.9; H, 5.1; N, 8.9% ; (M+H), 317

The Stannic Chloride Catalysed Ring-Closure of 1-[2-(3-Methoxy)phenyl]-3-phenyl carbodiimide (179)

A solution of the carbodiimide (179) (5.9g; 0.018 mol) in anhydrous 1,2-dichloroethane (90.0 ml) was cooled to 0° (ice-salt bath) and treated dropwise with stirring with a solution of stannic chloride (23.4g; 0.09 mol) in anhydrous 1,2-dichloroethane and the mixture was then heated under reflux for 24h.
The mixture was cooled to 0° (ice-salt bath) and treated dropwise with 15m aqueous sodium hydroxide solution (62.0 ml; 0.93 mol). The mixture was then stirred and allowed to warm to room temperature over 15 min. The mixture was diluted with water (180 ml) and extracted with methylene chloride to afford a brown oil (6.3g) which was flash-chromatographed over silica.

Initial elution with ethyl acetate-light petroleum (b.p. 40-60°) gave a series of intractable gums (total 7.0g) which yielded no identifiable material.

Further elution with ethyl acetate-light petroleum (b.p 40-60°) (1:9) afforded 3-methoxy-11-phenylaminodibenz[b,f][1,4]oxazepine (180) (4.1g; 71%) as a yellow gum, $\nu_{\text{max}}$ 3420 and 3380 (NH) and 1725 (CO)cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.59-6.65 (13H, m, ArH and NH), and 3.82 (3H, s, CH$_3$).

**Found:** C, 75.7; H, 5.2; N, 8.8%; m/z (FAB ms), 317 [(M+H)$^+$]

C$_{20}$H$_{16}$N$_2$O$_2$ requires: C, 75.9 ;H,5.1 ;N, 8.9%; (M+H), 317

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) yielded diphenyl urea (0.25g) as colourless needles, m.p. 244°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) afforded 3-methoxydibenz[b,f][1,4]oxazepin-11(10H)-one (181) (0.21g; 5%) as a colourless solid, m.p. 186-187° (from toluene), $\nu_{\text{max}}$ 3170 (NH) and 1670 (CO)cm-1, $\delta_H$(CDCl$_3$) 8.94 (1H, bs, NH), 7.96-7.84 (1H, m,
ArH), 7.24-7.05 (4H, m, ArH), 6.83-6.71 (2H, m, ArH) and 3.84 (3H, s, CH$_3$).

**Found:** C, 69.6; H, 4.5; N, 5.8%; m/z (EI ms), 241 (M$^+$)

C$_{14}$H$_{11}$NO$_3$ requires: C, 69.7; H, 4.6; N, 5.8%; M, 241

Further elution with ethyl acetate through to methanol gave only a series of intractable brown gums (total 0.40g) which were not further investigated.

**N, N-Dimethylguanidinium sulphate (184)**

A stirred suspension of S-methyl isothiourea sulphate (268g; 0.96 mol) in water (320 ml) was treated dropwise with 40% aqueous dimethylamine solution (230g; 2.0 mol) resulting in the liberation of methanethiol. Once gas evolution had subsided the mixture was heated under reflux for 5 min.

The mixture was concentrated under high vacuum until a white precipitate formed and after cooling at 0$^\circ$ (ice-salt bath) for 1h the solid was collected and combined with a second crop obtained by further concentration of the mother liquor to give **N, N-dimethylguanidinium sulphate (184)** (206.5g; 78%) as a colourless solid, m.p. 285-286° (decomp) (lit.$^7$6, 285-288° decomp.), identical (m.p. and i.r. spectrum) to an authentic sample.
2-(N, N-Dimethylamino) pyrimidin-4(3H)-one (185)

Malic acid (61.6g; 0.46 mol) was added in portions at 0° (ice-salt bath) with stirring over 35 min to 20% oleum (288 ml) and the mixture was stirred at 0° for 20 min then treated with N, N-Dimethyl guanidinium sulphate (184) (62.6g; 0.23 mol) in portions over 25 min at 0°. The mixture was allowed to warm to room temperature over 3h and then heated at 95° for a further 3h.

The mixture was cooled and poured onto ice (805g) and the resulting solution was basified with concentrated ammonia solution then stored in a refrigerator for 17h. Filtration yielded 2-(N, N-dimethylamino) pyrimidin-4(3H)-one (185) (66.1g; 100%) as a colourless solid, m.p. 176-179° (lit. 175-176°), identified by comparison (i.r. and t.l.c. in ethyl acetate-methanol (9:1) over silica) with an authentic sample.

2-Dimethylamino-5-nitropyrimidine-6(1H)-one (186)

A mixture of fuming nitric acid (d=1.52) (50.0 ml) and concentrated sulphuric acid (50.0 ml) was stirred and cooled to 10° (ice-water bath) then treated in portions with 2-dimethylaminopyridin-6(1H)-one (185) (61.2g; 0.44 mol) at such a rate that the reaction temperature did not exceed 70°. The mixture was then stirred and heated at 100° for 4h.

The mixture was cooled, poured onto ice and filtered to afford
2-dimethylamino-5-nitropyrimidin-6(1H)-one (186) (65.5g; 81%) as a
colourless solid, m.p. 284-286° (lit.\textsuperscript{76}, 302-305°), identified by comparison
(m.p. and i.r. spectrum) with an authentic sample.

4-Chloro-2-dimethylamino-5-nitropyrimidine (187)

2-Dimethylamino-5-nitropyrimidin-6(1H)-one (186) (23.9g;
0.13 mol) was mixed with phosphoryl chloride (214.5g; 1.4 mol). N, N-
dimethylaniline (27.7g; 0.19 mol) was added and the mixture was heated
under reflux for 1.5h.

The mixture was cooled and evaporated under reduced pressure
giving a brown gum which was treated with ice (400g) and diethyl ether
(400 ml) followed by filtration afforded 4-Chloro-2-dimethylamino-5-
nitropyrimidine (187) (23.2g; 88%) as a light brown solid, m.p. 140-144°
(lit.\textsuperscript{76}, 140-144°), identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ether layer afforded only an intractable gummy
solid (2.5g) which was not further investigated.

2-Dimethylamino-4-(3-methoxyphenoxy)-5-nitropyrimidine (188)

A stirred suspension of sodium hydride (1.1g; 0.044 mol) in
anhydrous dimethylformamide (20.0 ml) was treated dropwise at room
temperature with a solution of 3-methoxy phenol (109) (4.9g; 0.04 mol) in
anhydrous dimethylformamide (20.0 ml) and the mixture was stirred at
room temperature with exclusion of atmospheric moisture for 15 min. A
solution of the chloro-nitopyrimidine (187) (8.1g; 0.04 mol) in anhydrous dimethyl formamide (50.0 ml) was then added in one portion and the mixture was stirred and heated at 100° with exclusion of atmospheric moisture for 1h.

The mixture was cooled and treated with water (4.0 ml) then stirred at room temperature for 15 min. Evaporation under high vacuum yielded a gum which was treated with water (102 ml) to give 2-dimethylamino-4-(3-methoxyphenoxy)-5-nitropyrimidine (188) (10.7g; 87%) which formed colourless needles, m.p. 124-126° (from ethanol), δ_H(CDC_3) 9.06 (1H, s, ArH), 7.28-7.18(1H, m, ArH), 6.84-6.69 (3H, m, ArH), 3.79 (3H, s, CH_3), 3.21 (3H, s, CH_3) and 2.89 (3H, s, CH_3).

**Found:** C, 54.0, H, 4.9; N, 19.6%; m/z (EI ms), 290 (M⁺)

**C_{13}H_{14}N_{4}O_{4} requires:** C, 53.8; H, 4.8; N, 19.3%, M, 290

5-Amino-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (189)

(a) A solution of the nitopyrimidine derivative (188) (0.58g; 0.002 mol) in glacial acetic acid (30.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.058g) at room temperature and atmospheric pressure for 2h by which time hydrogen absorption had ceased.

The mixture was filtered through celite and the filtrate was evaporated to yield a gum (0.56g) which was flash-chromatographed over silica.
Elution with ethyl acetate-hexane (7:3) yielded **5-amino-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (189)** (0.37g; 67%) which formed off-white microcrystals, m.p. 53-55° (from hexane-toluene), ν\text{max} 3410, 3320 and 3190 (NH) cm\(^{-1}\), δ\text{H}(CDCl\(_3\)) 7.86 (1H, s, ArH), 7.30-7.22 (1H, m, ArH), 6.81-6.72 (3H, m, ArH), 3.79 (3H, s, CH\(_3\)) and 2.93 (6H, s, 2xCH\(_3\)).

**Found:** C, 60.5; H, 6.5; N, 22.0%; m/z (EI ms), 260.1279 (M\(^+\))

**C\(_{13}\)H\(_{16}\)N\(_4\)O\(_2\)** requires: C, 60.0; H, 6.2; N, 21.5%; M, 260.1273

Further elution with ethyl acetate-hexane (7:3) through ethyl acetate to methanol gave only a series of intractable gums (total 0.17g) which were not further investigated.

(b) A solution of the nitropyrimidine derivative (188) (0.62g; 0.002 mol) in ethyl acetate (20.0 ml) was hydrogenated over 5% palladium-on-charcoal (0.062g) at room temperature and atmospheric pressure for 3h by which time no hydrogen had been absorbed. Glacial acetic acid (0.1 ml) was added and hydrogenation continued for a further 3h.

The mixture was filtered through celite and the filtrate was evaporated to afford a gummy solid (0.58g) which was triturated with diethyl ether to give the unreacted starting material (188) (0.36g; 58%), m.p. 120-123°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the diethyl ether mother liquor yielded **5-amino-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (189)** (0.16, 29%) as a
brown oil, identified by comparison (i.r. spectrum) with a sample prepared before.

(c) 2-dimethylamino-4-(3-methoxyphenylamino)-5-nitropyrimidine (188) (0.58g; 0.002 mol) in ethyl acetate (80.0 ml) containing concentrated hydrochloric acid (0.1 ml) was hydrogenated over 5% palladium-on-charcoal (0.058g) at room temperature and atmospheric pressure for 2h.

The mixture was filtered through celite and the filtrate was evaporated to give the unreacted starting material (188) (0.55g; 95%), m.p. 127-129°, identified by comparison (m.p., i.r. spectrum and t.l.c. in methylene chloride over silica) with an authentic sample.

(d) A solution of the nitropyrimidine derivative (188) (1.2g; 0.004 mol) in ethyl acetate (200 ml) was hydrogenated over 5% palladium-on-charcoal (0.12g) at room temperature and 3 atmospheres pressure for 6h.

The mixture was filtered through celite and the filtrate was evaporated to give a sticky yellow solid (1.1g). This was dissolved in methylene chloride (10.0 ml) and the solution washed with 2M aqueous hydrochloric acid (10.0 ml) and evaporated to afford the unreacted starting material (188) (0.76, 66%), m.p. 121-127°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The acidic aqueous mother liquor was basified with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to afford 5-amino-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (189)
(0.27g, 26%) as a dark brown oil, identified by comparison (i.r. spectrum) with a sample prepared before.

(e) A solution of the nitropyrimidine derivative (188) (1.2g; 0.004 mol) in ethyl acetate (100 ml) was hydrogenated over 5% palladium-on-charcoal (0.12g) at room temperature and 3 atmospheres of pressure for 2h.

The mixture was filtered through celite and the filtrate was evaporated to yield a solid (1.1g) which was dissolved in methylene chloride (10.0 ml) and the solution, washed with 2M aqueous hydrochloric acid and evaporated to give the unreacted starting material (188) (0.77g; 66%), m.p. 122-124°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The acidic aqueous mother liquor was made basic with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to afford impure **5-amino-2-dimethylamino-4-(3-methoxyphenoxy)pyrimidine (189)** (0.14g; 13%) as a brown oil, identified by comparison (i.r. spectrum) with a sample prepared before.

(f) A solution of the nitropyrimidine derivative (188) (0.87g; 0.003 mol) in 1,2-dimethoxyethane (50.0 ml) was treated with 0.5M aqueous sodium hydroxide solution (5.0 ml, 0.002 mol) and 5% palladium-on-charcoal and the resulting suspension was stirred under nitrogen and treated dropwise with a solution of sodium borohydride (0.23g; 0.006 mol) in water
(2.5 ml) over 10 min. The mixture was then stirred at room temperature under nitrogen for a further 15 min.

The mixture was filtered through celite and the filtrate was rotary evaporated to give a yellow gum which was treated with water (10.0 ml) and the mixture acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to afford 3-methoxyphenol (109) (0.31g; 85%) as a brown oil, identified by comparison (i.r. spectrum) with an authentic sample.

The acidic aqueous mother liquor was basified with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to give crude 5-amino-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (189) (0.18g; 23%) as a brown oil, identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

1-[2-Dimethylamino-4-(3-methoxyphenoxy)pyrimidin-5-yl]-3-phenyl urea (190)

The crude aminopyrimidine derivative (189) (0.14g; 0.5 mol) was dissolved in anhydrous diethyl ether (10.0 ml) and treated with stirring with phenyl isocyanate (0.6 ml, 5.0 mmol). The mixture was stirred at room temperature for 1h then filtered to afford 1-[2-dimethylamino-4-(3-methoxyphenoxy)pyrimidin-5-yl]-3-phenyl urea (190) (0.11g; 54%), which formed colourless crystals, m.p.175-176° (from ethanol), $\nu_{max}$ 3320 (NH) and 1645 (CO)cm$^{-1}$, $\delta_H[(CD_2)_{2}SO]$ 8.96 (1H, s, NH) (exch.), 8.63
(1H, s, ArH), 8.01(1H, s, NH) (exch.) 7.53-6.74(9H, m, ArH), 3.76 (3H, s, CH₃), and 2.91 (6H; H, s, 2xCH₃).

**Found:** C, 63.3; H, 5.6; N, 18.5%; m/z (EI ms), 379.1634 (M⁺)

**C₂₀H₂₁N₅O₃ requires:** C, 63.3; H, 5.5; N, 18.5%; M, 379.1644

Evaporation of the mother liquor yielded only an intractable gum (0.049g) which was not further investigated.

**5-Azido-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (191)**

A solution of the aminopyrimidine derivative (189) (5.6g; 0.02 mol) in 5M aqueous hydrochloric acid (50.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise at 0-5° with a solution of sodium nitrite (1.5g; 0.022 mol) in water (10.0 ml). The resulting diazonium salt solution was stirred at 0-5° for a further 5 min then treated dropwise with a solution of sodium azide (0.9g; 0.03 mol) in water (10.0 ml) at 0-5°. The mixture was stirred in the melting ice-bath for 0-5h then allowed to warm to room temperature over a further 0-5h.

The mixture was made alkaline by the addition of 2M aqueous sodium hydroxide solution and then extracted with methylene chloride to give a dark brown gummy solid (4.6g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (45:55) afforded **5-azido-2-dimethylamino-4-(3-methoxyphenoxy) pyrimidine (191)** (3.9g; 64%) as a light brown solid, m.p. 66-98° (from hexane), ν_max 2140 and 2120 (N₃)cm⁻¹.
\( \delta_H(\text{CDCl}_3) \) 7.92 (1H, s, ArH), 7.37-7.15 (1H m, ArH), 6.85-6.67 (3H, m ArH), 3.78 (3H, s, CH\(_3\)) and 2.96 (6H, s, 2xCH\(_3\)).

**Found:** C, 56.5; H 5.2 ; N, 24.3%; m/z (EI ms), 258 (M\(^+\)-N\(_2\))

C\(_{13}\)H\(_{14}\)N\(_6\)O\(_2\) requires: C, 54.5; H, 4.9; N, 29.5%; M, 286

Further elution with ethyl acetate-hexane (45:55) through ethyl acetate to methanol gave only a series of unresolvable gums (total 0.51g) which were not further investigated.

**N-[12-Dimethylamino-4-(3-methoxy phenoxy)pyrimidin-5-yl]trimethoxy phosphinimine (192)**

A solution of the azide (191) (0.61g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with a solution of trimethyl phosphite (0.31g; 0.0025 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 5h.

The mixture was rotary evaporated to give and oil which was azeotroped with toluene to remove the excess of trimethyl phosphite giving

**N-[2-dimethylamino-4-(3-methoxyphenoxy)pyrimidin-5-yl]trimethoxyphosphinimine (192)** (0.78g; 100%) as a dark brown oil,

\( \delta_H(\text{CDCl}_3) \) 8.13-7.93 (1H, m, ArH) 7.24-7.12 (1H, m, ArH), 6.81-6.70 (3H, m, ArH), 3.77 (3H, s, CH\(_3\)) 3.75 (9H, d, 5 11 Hz, 3xCH\(_3\)) 2.94 (3H, s, CH\(_3\)) and 2.93 (3H, s, CH\(_3\)).

**Found:** C, 50.1; H, 6.2; N, 14.7%, m/z (EI ms), m, 382 (M\(^+\))
1-[2-Dimethyamino-4-(3-methoxyphenoxy) pyrimidin-5-yl] phenylcarbodimide (193)

A solution of the iminophosphorane (192) (1.9 g; 0.005 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) was treated with a solution of phenyl isocyanate (0.59 g; 0.005 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 4 h.

The mixture was rotary evaporated to give a brown oil which was dissolved in a methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated to give 1-[2-dimethylamino-4-(3-methoxyphenoxy)pyrimidin-5-yl]-3-phenylcarbodimide (193) (1.9 g; 100%) as a brown oil, \( v_{\text{max}} \) 2130 (N=C=N) cm\(^{-1}\).

Found: m/z (EI ms) M, 361.1531 (M\(^+\))

\( \text{C}_{20}\text{H}_{19}\text{N}_{5}\text{O}_{2} \) requires: M, 361.1539

9-Methoxy-6-phenylaminopyrimido[4,5-b][1,4]benzoxazepine (194)

A solution of the carbodiimide (193) (1.4 g; 0.004 mol) in anhydrous 1,2-dichloroethene (250 ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (5.2 g; 0.02 mol) in anhydrous 1,2-dichloroethene (12.0 ml) and the mixture then stirred and heated under reflux for 24 h.

The mixture was cooled and treated dropwise with stirring at 0-10\(^\circ\) (ice-bath) with 15 m aqueous sodium hydroxide solution (13.6 ml; 0.20 mol)
then stirred at 0-10° for 15 min. Water (40.0 ml) was added and the mixture was extracted with methylene chloride to give a brown gum (1.4g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave a series of yellow gums (total 0.048g) whose t.l.c. in ethyl acetate-hexane (1:1) showed them to be unresolvable complex mixtures which were not further investigated.

Further elution with ethyl acetate-hexane (35:65) yielded the pyrimidino oxazepine (194) (0.23g; 16%) which formed yellow crystals, m.p. 232-233° (from dimethylformamide-water), \( \nu_{\text{max}} \) 3260 (NH) cm\(^{-1}\)

\[ \delta_\text{H}[\text{(CD}_3\text{)}_2\text{SO}] \] 9.13 (1H, s, NH), 8.23 (1H, s, ArH), 7.95-6.86 (8H, m, ArH), 3.84 (3H, s, CH\text{3}) and 3.08 (6H, s, 2xCH\text{3}).

**Found:** C, 66.6; H, 5.3; N, 19.3%; m/z (FAB ms), 362 [(M+H)\(^+\)]

\( \text{C}_{20}\text{H}_{19}\text{N}_5\text{O}_2 \) **requires:** C, 66.5; H, 5.3, N, 19.4%, M, 361

Further elution with ethyl acetate-hexane (2:3) through ethyl acetate to methanol gave only a series of gums (total 0.5g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent gums which were not further investigated.
Chapter 3

Investigations of New Syntheses of

Fused Tricyclic Thiazepines

Based on

Novel Heterocumulene Cyclisation Reactions
Investigations of New Syntheses of Fused Tricyclic Thiazepines Based on Novel Heterocumulene Cyclisation Reactions

3.1 Introduction

As demonstrated in Chapter 2 the Lewis acid catalysed, intramolecular Friedel-Crafts type cyclisation reaction of ortho aryloxyphenyl heterocumulenes (carbodiimides, isocyanates, and isothiocyanates) represent a new strategy for the general synthesis of fused tricyclic oxazepines. Such molecules are members of the structural class of tricyclic heteropines which as discussed in Chapter 1 are of general interest because of their neuroleptic activity and in particular because of their potential application as agents for the treatment of psychotic disorders such as schizophrenia and Alzheimer's Disease. For these reasons it was of interest to know if the general strategy for the synthesis of fused tricyclic oxazepines could be extended to the corresponding sulphur analogues, fused tricyclic thiazepines, moreover it was possible that these types of heterocycle might be accessible in higher yield than their oxygen counterparts (see Chapter 2). The investigation of the Lewis acid catalysed cyclisation of appropriate heterocumulenes as a strategy for the general synthesis of fused tricyclic thiazepines provides the subject material of the following chapter.
Scheme 54

(i) NaH, DME, 100;
(ii) $H_2$, PdC, THF, room temp, atmos. press.
(iii) $Na_2S_2O_4$, $CH_3CO_2H$, reflux;
(i) NaNO₂, HCl(aq), 0°C, then NaN₃, 0°C;
(ii) (CH₃O)₃P, DME, room temp;
(iii) PhN=C=O, DME, room temp;
(iv) HCl, H₂O, DME, room temp;
(v) SnCl₄, Cl(CH₂)₂Cl, reflux.

Scheme 55
3.2 Investigations of Heterocumulene Cyclisation Reactions Leading to Pyrido[2,3-b][1,4]benzothiazepine Derivatives

Initial studies under this heading centred on the synthesis (Schemes 54 and 55) of the arylthiopyridyl carbodiimide (201) and the investigations of its Lewis acid catalysed cyclisation to the pyridobenzothiazepine derivative (203). Synthesis of the required carbodiimide derivative (201) was accomplished by a reaction sequence (Scheme 54 and 55) analogous to that used for the oxygen analogue (see Chapter 2, Section 2.2). The required arylthionitropyridine starting-material (196) was readily accessible by the sodium hydride catalysed condensation of 3-methoxythiophenol (195) with 2-chloro-3-nitropyridine (108). However the next step involving the reduction of the nitro-compound (196) to the amine (197) was not quite so straightforward. Initially an attempt was made to effect this reduction by heating under reflux with sodium dithionite in acetic acid. However these conditions afforded the required amine (197) only in low yield (6%) plus its acetyl derivative (198)(7%) together with a substantial amount (51%) of the unreacted nitro-compound (196). The attempted hydrogenation of the nitropyridine derivative (196) using Raney nickel as catalyst was even less successful, the starting-material being recovered unchanged in quantitative yield. However the amine (197) was eventually obtained in high yield (84%) by catalytic hydrogenation of the nitropyridine derivative (196) in tetrahydrofuran over palladium-on-charcoal.
The transformation of the amine (197) through the azide (199) and the trimethoxyphosphinimine (200) into the pyridyl carbodiimide (201) proceeded in a straightforward manner giving the latter product in good overall yield. The compound (201) exhibited characteristic carbodiimide absorption at 2135cm\(^{-1}\) in its i.r. spectrum and was further characterised by its conversion (Scheme 55) into the corresponding urea derivative (202) albeit in low yield (31%).

Having successfully synthesised the target arylthiopyridyl carbodiimide (201) attention was next turned to the study of its Lewis acid catalysed cyclisation (Scheme 55) to the pyridobenzothiazepine derivative (203). In practice, heating the carbodiimide derivative (201) under reflux with five equivalents of stannic chloride in 1,2-dichloroethane for 24h, gave a readily separable mixture of two products. The product forming in major amount (40%) showed analytical and spectroscopic properties which allow its formulation either as the expected pyridobenzothiazepine derivative (203) or its 7-methoxy analogue. However the formulation of the product as the 9-methoxy derivative (203) follows from an NOE experiment which demonstrated enhancement of the signal due to H-10 in the \(^1\)H n. m. r. spectrum of the compound by irradiation of the protons of the methyl substituent. The minor product (yield 12%) gave accurate mass measurement consistent with the molecular formula \(\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_2\text{S}\). This together with the presence of absorption due to a carbonyl group in its i.r. spectrum demonstrates the minor product to be the lactam derivative (204).
Scheme 56

(i) NaH, DMF, 100°C;
(ii) 15%w/v TiCl₃(aq), THF, room temp;
(iii) NaNO₂, HCl(aq), 0°C, then NaN₂, 0°C;
(iv) (CH₃O)₃P, DME, room temp;
(v) PhN=C=O, DME, room temp;
(vi) SnCl₄, Cl(CH₂)₂Cl, reflux.

(1) NaH, DMF, 100°C;
(2) 15%w/v TiCl₃(aq), THF, room temp;
(3) NaNO₂, HCl(aq), 0°C, then NaN₂, 0°C;
(4) (CH₃O)₃P, DME, room temp;
(5) PhN=C=O, DME, room temp;
(6) SnCl₄, Cl(CH₂)₂Cl, reflux.
rather than the 7-methoxy isomer based on the presumption that it is derived by hydrolysis of the major amino product (203) of established structure.

3.3 Investigations of Heterocumulene Cyclisation Reactions Leading to Various Fused Benzothiazepine Derivatives

The successful stannic chloride catalysed cyclisation of the carbodiimide (201) to the pyrido[2,3-b][1,4]benzothiazepine derivatives (203) and (204) exemplifies a novel, moderately efficient route to the pyrido[2,3-b][1,4]benzothiazepine ring system. In view of this it was decided to attempt to extend this type of cyclisation to the synthesis of derivatives of other fused tricyclic benzothiazepine ring systems. Effort was therefore first directed to the synthesis (Scheme 56) of the arylthiophenyl carbodiimide (209) as a potential precursor of the dibenzothiazepine derivative (210).

Synthesis of the required carbodiimide starting-material (209) followed a route (Scheme 56) akin to that exploited for the synthesis of carbodiimides described earlier. This involved the initial sodium hydride catalysed condensation of 2-nitrochlorobenzene (174) with 3-methoxythiophenol (195) to give the thioether (205) in essentially quantitative yield. Because of the presence of the thioether substituent which was liable to inhibit catalytic reduction by catalyst poisoning, titanium trichloride was chosen as the reducing agent for effecting the conversion of the nitro compound (205) into the amine (206). Initially, using a
stoichiometric amount of titanium trichloride gave only a low yield (30%) of the required amine (206) together with a large amount (70%) of the unreacted starting-material (205). However the use of excess titanium trichloride resulted in the conversion of the nitro compound (205) into the amine (206) in 97% yield.

Each of the steps in the subsequent conversion (Scheme 56) of the amine (206) through the azide (207) and phosphinimine (208) into the carbodiimide (209) proceeded efficiently giving the latter in high overall yield. The carbodiimide (209) was obtained as a dark brown oil whose i.r. spectrum showed an intense absorption band at 2110 cm⁻¹ characteristic of the carbodiimide substituent.

With the carbodiimide (209) readily available its tendency to undergo Lewis acid catalysed cyclisation was next investigated. Interestingly, heating the carbodiimide (209) under reflux with five equivalents of stannic chloride in 1,2-dichloroethane afforded the expected dibenzothiazepine (210) in 79% yield. This product was identified on the basis of its analytical and spectroscopic properties. The high yield of the dibenzothiazepine (210) demonstrates that Lewis acid catalysed heterocyclisation can be a very efficient process for the synthesis of fused tricyclic benzoheteropines.

Having shown that Lewis acid catalysed cyclisation of appropriate carbodiimide precursors provides a new approach to the synthesis of fused tricyclic benzoheteropines it was next decided to attempt to further extend this strategy to pyrimido[4,5-b][1,4]benzothiazepine ring system (Schemes 57
(i) NaH. DMF, 100°C;
(ii) H₂. PdC. CH₃CO₂H. room temp. atmos. press;
(iii) TiCl₃, HCl(aq). CH₃CO₂H. room temp;
(iv) 15%w/v TiCl₃(aq). THF. room temp.

Scheme 57
(i) NaNO₂, HCl(aq), 0°, then NaN₃, 0°;
(ii) (CH₃O)₃P, DME, room temp;
(iii) PhN=C=O, DME, room temp;
(iv) SnCl₄, Cl(CH₂)₂Cl, reflux.

Scheme 58
and 58). The key precursor in this case was the carbodiimide derivative (216) which was anticipated to be readily accessibly by the well established route used before from the amine (213) through the azide (214) and the phosphinimine (215).

The nitro precursor (211) of the amine (213) was readily obtained in high yield (98%) by the sodium hydride catalysed condensation of the known76,77 chioro-nitropyrimidine derivative (187) with 3-methoxythiophenol (195). Reduction of the nitropyrimidine derivative (211) to the amine (213) was initially attempted by catalytic hydrogenation over palladium-on-charcoal. However reduction under these conditions was very sluggish and gave the amine (213) in only 14% yield together with a significant amount (42%) of the unreacted starting-material (211).

Attempted catalytic hydrogenation of the nitro compound (211) over Raney nickel was even less successful, the starting-material (211) being recovered unchanged under these conditions in essentially quantitative yield. The use of sodium dithionite as the reducing agent was also unsuccessful. Heating the nitro compound (211) with this reagent under reflux in glacial acetic acid gave only a complex mixture which yielded no identifiable material. The use of titanium trichloride as the reducing agent for effecting the transformation [(211) -> (213)] was only marginally more successful. Treatment of the nitro compound (211) with this reagent in aqueous hydrochloric acid-glacial acetic acid gave the amine (213) in low yield (16%) together with two other products identified analytically and/or
spectroscopically as the acetamido derivative (212) (yield 22%) and methoxythiophenol (195) (yield 8%). The latter product most probably arises as the result of reductive cleavage of the thioether substituent in the starting nitro compound (211). The \textit{in situ} acetylation of the amine (213) indicated by the isolation of the acetamido product (212) was readily suppressed by carrying out the reduction with titanium trichloride in tetrahydrofuran rather than glacial acetic acid as the solvent. However under these modified conditions the yield of the amine (213) was at best only 34%.

Despite the inefficiency of the reduction step [(211) -> (213)] it was decided to proceed with the conversion of the amine (213) into the required carbodiimide starting material (216) through the intermediacy of the azide (214) and the phosphinimine (215) (Scheme 58). Each of these stages of the synthesis proceeded smoothly and in high yield giving the carbodiimide (216) as a dark brown oil which showed characteristic i.r. carbodiimide absorption at 2130cm$^{-1}$.

Rather disappointingly heating the carbodiimide (216) under reflux with five equivalents of stannic chloride in 1,2-dichloroethane gave the expected pyrimidobenzothiazepine derivative (217) in only 12% yield. The product (217) had analytical and spectroscopic properties fully in accord with its assigned structure which was firmly established by x-ray analysis (see Figure 3 and Tables 3 and 4). The reaction of the carbodiimide (216) with stannic chloride also afforded two other products one of which was obtained
Table 3. Bond Lengths (Å) with standard deviations

<table>
<thead>
<tr>
<th>Bond Lengths</th>
<th>Standard Deviation</th>
</tr>
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<tbody>
<tr>
<td>N(1) - C(2)</td>
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</tr>
<tr>
<td>N(1) - C(11a)</td>
<td>1.323(8)</td>
</tr>
<tr>
<td>C(2) - N(3)</td>
<td>1.365(10)</td>
</tr>
<tr>
<td>C(2) - N(21)</td>
<td>1.351(10)</td>
</tr>
<tr>
<td>N(3) - C(4)</td>
<td>1.328(10)</td>
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<tr>
<td>C(4) - C(4a)</td>
<td>1.399(10)</td>
</tr>
<tr>
<td>C(4a) - N(5)</td>
<td>1.405(9)</td>
</tr>
<tr>
<td>N(5) - C(6)</td>
<td>1.286(9)</td>
</tr>
<tr>
<td>C(6) - C(6a)</td>
<td>1.494(10)</td>
</tr>
<tr>
<td>C(6a) - N(61)</td>
<td>1.373(9)</td>
</tr>
<tr>
<td>N(61) - C(61)</td>
<td>1.385(10)</td>
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Table 4. Angles (degrees) with standard deviations

<table>
<thead>
<tr>
<th>Angle (degrees)</th>
<th>Standard Deviation</th>
</tr>
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<tbody>
<tr>
<td>C(2) - N(1) - C(11a)</td>
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</tr>
<tr>
<td>N(1) - C(2) - N(3)</td>
<td>124.9(6)</td>
</tr>
<tr>
<td>N(1) - C(2) - N(21)</td>
<td>118.7(6)</td>
</tr>
<tr>
<td>N(3) - C(2) - N(21)</td>
<td>116.3(6)</td>
</tr>
<tr>
<td>C(2) - N(3) - C(4)</td>
<td>115.7(6)</td>
</tr>
<tr>
<td>N(3) - C(4) - C(4a)</td>
<td>124.3(7)</td>
</tr>
<tr>
<td>C(4) - C(4a) - N(5)</td>
<td>117.3(6)</td>
</tr>
<tr>
<td>C(4) - C(4a) - C(11a)</td>
<td>114.2(6)</td>
</tr>
<tr>
<td>N(5) - C(4a) - C(11a)</td>
<td>127.8(6)</td>
</tr>
<tr>
<td>C(4a) - N(5) - C(6)</td>
<td>121.7(6)</td>
</tr>
<tr>
<td>N(5) - C(6) - C(6a)</td>
<td>126.8(6)</td>
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<tr>
<td>C(7) - C(8) - C(9)</td>
<td>118.6(8)</td>
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Torsion angles (degrees) with standard deviation

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<th>Torsion Angles</th>
<th>Standard Deviation</th>
</tr>
</thead>
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<tr>
<td>C(11a) - N(1) - C(2) - N(3)</td>
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</tr>
<tr>
<td>C(11a) - N(1) - C(2) - N(21)</td>
<td>178.2(6)</td>
</tr>
<tr>
<td>C(2) - N(1) - C(11a) - C(4a)</td>
<td>3.0(10)</td>
</tr>
<tr>
<td>C(2) - N(1) - C(11a) - S(11)</td>
<td>-175.2(5)</td>
</tr>
<tr>
<td>N(1) - C(2) - N(3) - C(4)</td>
<td>1.8(11)</td>
</tr>
<tr>
<td>N(21) - C(2) - N(3) - C(4)</td>
<td>-179.2(7)</td>
</tr>
<tr>
<td>N(1) - C(2) - N(21) - C(22)</td>
<td>175.4(7)</td>
</tr>
<tr>
<td>N(1) - C(2) - N(21) - C(23)</td>
<td>-3.1(10)</td>
</tr>
<tr>
<td>N(3) - C(2) - N(21) - C(22)</td>
<td>-3.6(10)</td>
</tr>
<tr>
<td>N(3) - C(2) - N(21) - C(23)</td>
<td>177.8(7)</td>
</tr>
<tr>
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in 23% yield and shown by comparison with an authentic sample to be identical to 3-methoxythiophenol (195). The other product, obtained in low yield (13%) was a high-melting solid whose analytical and spectroscopic properties allow its formulation as the pyrimidobenzothiazepinone derivative (218).

Though the poor yields of the corresponding fused tricyclic benzothiazepines obtained from the stannic chloride catalysed cyclisations of the carbodiimides (201) and (216) were disappointing the efficiency of the dibenzothiazepine synthesis [(209) -> (210)] indicates that such heterocyclisations can be synthetically viable.

3.2 Experimental

2-((3-Methoxyphenylthio)-3-nitropyridine (196)

A stirred suspension of sodium hydride (1.3g; 0.055 mol) in anhydrous dimethylformamide (5.0 ml) was cooled to 5-10° (ice bath) and treated dropwise with a solution of 3-methoxythiophenol (195) (7.0g; 0.05 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-chloro-3-nitropyridine (108) (7.9g; 0.05 mol) was then added in one portion and the mixture was stirred and heated at 100° for 1h.

The mixture was cooled and treated with water (5.0 ml) and then stirred at room temperature for 15 min. The mixture was evaporated and the residue was treated with water (40.0 ml) and filtered to give 2-(2-
(196), (13.1g; 100%) as a yellow solid, m.p. 89-90° (from methanol), $\nu_{\text{max}}$ 1520 and 1335 (NO$_2$) cm$^{-1}$

$\delta_H([\text{CD}_3]_2\text{SO})$ 8.67-8.54 (2H, m, ArH), 7.51-7.01 (5H, m, ArH) and 3.77 (3H, s, CH$_3$).

**Found:** C, 54.9; H, 3.9; N, 10.7%; m/z (El ms), 262(M$^+$)

C$_{12}$H$_{10}$N$_2$O$_3$S requires: C, 55.0; H, 3.8; N, 10.7%; M, 262

**3-Amino-2-(-3-methoxyphenylthio)pyridine (197)**

(a) A solution of the nitropyridine derivative (196) (0.52g; 0.002 mol) in anhydrous tetrahydrofuran (20.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.052g) at room temperature and atmospheric pressure for 3h. Further 10% palladium-on-charcoal catalyst (0.25g) was added and hydrogenation of the mixture continued at room temperature and atmospheric pressure for a further 2h.

The mixture was filtered through celite and the filtrate evaporated to yield a yellow solid (0.43g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave **3-amino-2-(3-methoxyphenylthio)pyridine (197)** (0.39g; 84%) as a cream coloured solid, m.p. 72-73° (from hexane-toluene), $\nu_{\text{max}}$ 3433, 3274 and 3135 (NH) cm$^{-1}$, $\delta_H(\text{CDCl}_3)$ 8.11 (1H, dd, Jortho 4Hz and Jmeta 2Hz, ArH), 7.27-6.71 (6H, m, ArH), 4.26 (2H, bs, NH) and 3.73 (3H, s, CH$_3$).

**Found:** C, 61.9; H, 5.2; N, 12.0%; m/z (El ms), 232(M$^+$)
**C_{12}H_{12}N_{2}OS requires**: C, 62.0; H, 5.2; N, 12.1%; M, 232

Further elution with ethyl acetate through to methanol gave only a series of intractable gums (total 0.04g) which were not further investigated.

(b) A solution of the nitropyridine derivative (196) (0.52; 0.002 mol) in glacial acetic acid (15.0 ml) was treated with sodium dithionite (0.52g) and the mixture was heated under reflux for 1h. The mixture was then treated with a second portion of sodium dithionite (0.52g) and heating under reflux continued for a further 1h.

The mixture was rotary evaporated under high vacuum to give a yellow gum which was treated with water (10.0 ml) and extracted with methane chloride to yield a gummy yellow solid (0.49g), m.p. 60-68°C, whose t.l.c in ethyl acetate-light petroleum (b.p. 60-80°C) (1:1) over silica showed it to be a mixture containing starting material (196). The solid was redissolved in glacial acetic acid (15.0 ml) and the previous procedure repeated with two further portions of sodium dithionite (0.52g).

The mixture was rotary evaporated under high vacuum to give a yellow gum which was treated with water (10.0 ml) and extracted with methylene chloride to give a gummy solid (0.46g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) afforded unreacted starting material (196), (0.24g; 51%), m.p. 84-90°C, identical (m.p. and i.r. spectrum) to an authentic sample.
Further elution with ethyl acetate-hexane (3:7) yielded 3-amino-2-
(3-methoxyphenylthio)pyridine (197) as a gum (0.03g; 6%), identified by
comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate-hexane (3:7) gave 3-N-acetamide-
2(3-methoxyphenylthio)pyridine (198) (0.04g; 7%) as a gum, \( \nu_{\text{max}} \) 3250
(NH) and 1670 (CO) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.53 (1H, d, J 8Hz, ArH) 8.25-8.21
(1H, m, ArH), 7.95-7.83 (1H, m, ArH), 7.30-7.10 (2H, m, ArH), 7.10-6.70
(3H, m, ArH), 3.66 (3H, s, CH\(_3\)) and 2.04 (3H, s, CH\(_3\)).

**Found:** m/z (FAB ms), 275.0854 [(M+H)]

\( \text{C}_{14}\text{H}_{15}\text{N}_{2}\text{O}_{2}\text{S} \) requires: (M+H), 275.0854

Further elution with methanol gave only a small amount of
intractable gum (0.01g) which was not further investigated.

**The Attempted Catalytic Reduction of 2-(3-Methoxyphenylthio)-3-
nitropyridine (196) Using Hydrogen over Raney Nickel**

A solution of the nitropyridine derivative (196) (5.2g; 0.02 mol) in
glacial acetic acid (150 ml) was hydrogenated over Raney nickel (0.66g of a
50% slurry in water) at room temperature and atmospheric pressure for 1h.

The mixture was filtered through celite and the filtrate was
evaporated to give a yellow solid (6.1g), m.p. 89-95° whose i.r. spectrum and
t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a mixture
mainly containing the starting material (196) which was therefore not further investigated.

3-Azido-2(3-methoxyphenylthio)pyridine (199)

A solution of the amine (197), (0.93g; 0.004 mol) in 5M aqueous hydrochloric acid (10.0 ml) was stirred and cooled to 0° (ice-salt bath) and then treated dropwise with a solution of sodium nitrate (0.30g; 0.0044 mol) in water (2.0 ml) at such a rate that the reaction temperature was <5 °. After stirring at <5 ° for 5 min the resulting diazonium salt solution was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium azide (0.39g; 0.006 mol) in water (2.0 ml) at such a rate that the reaction temperature was <5 °. The reaction mixture was then stirred in the melting ice-salt bath for 0.5 h.

The mixture was basified with 2M aqueous sodium hydroxide and the precipitated solid was collected and washed with water to afford 3-azido-2-(3-methoxyphenylthio)pyridine (199). (0.98g, 95%) which formed cream coloured crystals m.p. 77-79° (from hexane). νmax 2143 and 2109 (N3)cm⁻¹, 8H(CDCl3) 8.13 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.40-6.82 (6H, m, ArH) and 3.72 (3H, s, CH3).

**Found:** C, 56.5; H, 3.9; N, 22.2%; m/z (EI ms), 258.0566 (M⁺)

**C12H10N4OS requires:** C, 55.8; H, 3.9; N, 21.7%; M, 258.0575
N-[2-(3-Methoxyphenylthio)pyrid-2-yl]trimethoxyphosinimine (200)

A solution of the azide (199) (0.52g; 0.002 mol) in anhydrous 1,2-dimethoxyethane ethane (10.0 ml) was treated with a solution of trimethyl phosphate (0.25g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 4h.

The mixture was rotary evaporated with removal of the excess of trimethyl phosphate as an azeotrope with toluene to give N-2-(3-methoxyphenylthio)pyrid-2-yltrimethoxyphosinimine (200) as a colourless solid (0.71g, 100%) m.p. 74-76° (from benzene/hexane), \[ \delta_h(CDCl_3) \] 7.88-7.79 (1H, m, ArH), 7.34-6.78 (6H, m, ArH), 3.82 (9H, d, J11Hz, 3 x CH) and 3.77 (3H, s, CH3).

**Found:** C, 51.3; H, 5.4; N, 7.9%; m/z (EI ms) 354.0799 (M⁺)

**C15H19N2O4PS requires:** C, 50.9; H, 5.4; N, 7.9%; M, 354.0803

1-N-2-(3-Methoxyphenylthio)pyrid-2-yl-3-N-phenyl carbodiimide (201)

A solution of the phosphinimine (200) (0.35g; 0.001 mol) in anhydrous 1,2 dimethoxyethane (5.0 ml) was treated with a solution of phenyl isocyanate (0.12g; 0.001 mol) in anhydrous 1,2-dimethoxyethane (2.5 ml) and the mixture was stirred at room temperature for 4h.

The mixture was rotary evaporated to give a yellow oil (0.83g) which was dissolved in methylene chloride (10.0 ml) and the solution washed with water (10.0 ml) and rotary evaporated to give 1-N-2-(3-
methoxyphenylthio)pyrid-2-yl-3-N-phenyl carbodiimide (201) (0.33g; 100%) as a light brown oil, $\nu_{\text{max}}$ 2135(N=C=N) cm$^{-1}$, which decomposed on attempted purification by distillation.

**The Hydrolysis of 1-N-2-(3-Methoxyphenylthio)pyrid-2-yl-N-phenyl carbodiimide (201) Using Aqueous Hydrochloric Acid**

The carbodiimide (201) (0.33g; 0.001 mol) was dissolved in 1,2-dimethoxyethane (10.0 ml) and the solution was treated with 2M aqueous hydrochloric acid (5.0 ml; 0.01 mol). The mixture was then stirred at room temperature for 17h.

The mixture was rotary evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to yield a yellow gum (0.34g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:4) yielded only a series of gums (total 0.027g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent mixtures which therefore were not further investigated.

Further elution with ethyl acetate-light petroleum ether (b.p. 40-60°) (1:4) afforded 1-N-2-(3-methoxyphenylthio)pyrid-2-yl-3-N-phenyl urea (202) (0.11g; 31%) as a colourless solid, m.p. 163-165° (from ethyl acetate), $\nu_{\text{max}}$ 3510 and 3310 (NH) and 1690 (CO) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.57 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 8.21 (1H, dd, Jortho 5Hz and Jmeta 2Hz, Jortho 8Hz and Jmeta 2Hz, ArH).
ArH), 7.66 (bs, NH) (exch.), 7.34-7.00 (7H, m, ArH), 6.74-6.57 (3H, m, ArH) and 3.66 (3H, s, CH₃).

**Found:** C, 65.3; H, 4.8; N, 11.6%, m/z (EI ms), 351.1045 (M⁺)

**C₁₉H₁₇N₃O₂ S requires:** C, 65.3; H, 4.8; N, 12.0%; M, 351.1041

Further elution with methanol yielded only a gum (0.11g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a multicomponent mixture which therefore was not further investigated.

**The Stannic Chloride Catalysed Ring Closure of 1-N-2-(3-Methoxyphenylthio)pyrid-2-yl-3-N-phenyl Carbodiimide (201)**

A solution of the carbodiimide (201) (1.3g, 0.004 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred and treated dropwise at room temperature with a solution of stannic chloride (5.2g, 0.02 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture was then heated under reflux for 24h.

The mixture was cooled to 5-10° (ice bath) and treated dropwise with 15M aqueous sodium hydroxide solution (13.6 ml; 0.2 mol) and the mixture stirred at room temperature for 15 min. Water (40.0 ml) was added and the mixture extracted with methylene chloride to give a gummy orange solid (1.8g) which was triturated with diethyl ether to give a light brown solid (0.65g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (1:1) yielded 9-methoxy-6-(N-phenylamino)-pyrido[2,3-b][1,4]benzothiazepine (203) (0.52g, 40%) as
a colourless solid, m.p. 231-232° (from dimethylformamide-water), \( v_{\text{max}} \)
\[ 3270 \text{ (NH) cm}^{-1}, \delta^H [(CD_3)_2SO] 9.42 (1H, s, NH), 8.06 (1H, dd, J\text{ortho} 5\text{Hz Jmeta} 2\text{Hz, H-2}), 7.93-7.91 (2H, m, ArH), 7.59 (1H, d, J\text{ortho} 9\text{Hz, H-7}) \]
(enhanced 13% by irradiation of NH), 7.47 (1H, dd, J\text{ortho} 8\text{Hz Jmeta} 2\text{Hz, H-4}), 7.34-7.30 (2H, m, ArH), 7.28, (1H, dd, J\text{ortho} 8\text{Hz Jmeta} 5\text{Hz, H-3}), 7.14 (1H, d, Jmeta 3H, H-10) (enhanced 10% by irradiation of CH_3O),
7.08 (1H, d, Jmeta 3H, H-8) (enhanced 22% by irradiation of CH_3O), 7.06-7.01 (1H, m, ArH), and 3.81 (3H, s, CH_3).

**Found:** C, 67.8; H, 4.6; N, 12.6%; m/z (EI ms), 333.0939 (M⁺)

**C_{19}H_{15}N_{3}O_{2}S** requires: C, 68.5; H, 4.5; N, 12.6%; M, 333.0936

Further elution with ethyl acetate-hexane (3:2) yielded **9-methoxy [2,3-b][1,4]benzothiazepin-6(5H)-one (204)** (0.12g, 12%) as a colourless solid, m.p. 300°(dec), \( v_{\text{max}} \) 1665 (C=O)cm\(^{-1}\).

**Found:** m/z (FAB ms) 259.0541 [(M+H)⁺]

**C_{13}H_{11}N_{2}O_{2}S** requires: M, 259.0541

**1-(3-Methoxyphenylthio)-2-nitrobenzene (205)**

A stirred suspension of sodium hydride (1.3g; 0.055 mol) in anhydrous dimethylformamide (5.0 ml) was treated dropwise at 5-10° (ice bath) with a solution of 3-methoxythiophenol (195) (7.0g, 0.05 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 15 min. A solution of 2-chloronitrobenzene (174)
(7.9g; 0.05 mol) in anhydrous dimethylformamide (15.0 ml) was added in one portion and the mixture was stirred and heated at 100° for 1h.

The mixture was cooled and treated with water (5.0 ml) then stirred at room temperature for 15 min. The mixture was rotary evaporated under high vacuum to give a gum which was treated with water (40.0 ml) to yield 1-(3-methoxyphenylthio)-2-nitrobenzene (205) (12.9g; 99%) as a yellow solid, m.p. 118-121° (from ethyl acetate), δ_H[(CD3)2SO] 8.22 (1H, dd, Jortho 8Hz, Jmeta 2Hz, ArH), 7.69-6.88 (7H, m, ArH) and 3.78 (3H, s, CH3).

Found: m/z (EI ms), 261.0463(M)

C_{13}H_{11}NO_{3}S requires: M, 261.0460

1-Amino-2-(3-methoxyphenylthio)benzene (206)

(a) A solution of the nitro benzene derivative (205) (2.6g, 0.01 mol) in tetrahydrofuran (230 ml) was stirred at room temperature under an atmosphere of nitrogen and treated dropwise with a 15% w/v solution of titanium trichloride in aqueous hydrochloric acid (120 ml). The mixture was then stirred at room temperature under nitrogen for 17h.

The mixture was rotary evaporated and the residue was basified with 50% w/v aqueous sodium hydroxide solution and then extracted with methylene chloride to afford 1-amino-2-(3-methoxyphenylthio) benzene (206) (2.3g; 97%) as a yellow oil, v_{max} 3470 and 3370(NH)cm\(^{-1}\).
δ_H(CDCl₃) 7.51-6.59 (8H, m, ArH), 4.16 (2H, bs, NH₂) (exch.) and 3.71 (3H, s, CH₃).

**Found:** C, 67.8; H, 5.8; N, 6.0%; m/z (EI ms), 231

C₁₃H₁₃NOS requires: C, 67.5; H, 5.6; N, 6.1%; M, 231

The amine (206) was further characterised as its hydrochloride obtained by treatment of the amine (206) (0.22g; 0.0008 mol) with 2M aqueous hydrochloric acid (2.0 ml) as a colourless solid (0.21g; 93%), m.p. 126-132° (from ethanol), v_max 2500br (NH), δ_H[(CD₃)₂SO] 7.73 (3H, bs, +NH₃), 7.44-6.70 (8H, m, ArH) and 3.69 (3H, s, CH₃).

**Found:** C, 58.9; H, 5.4; N, 5.2%; m/z (EI ms), 231.0724(M⁺)

C₁₃H₁₄ClNOS requires: C, 58.4; H, 5.2; N, 5.2%; M, 231.0719

(b) A solution of the nitrobenzene derivative (205) (2.6g; 0.01 mol) in tetrahydrofuran (230 ml) was stirred at room temperature under nitrogen and treated dropwise with a 15% w/v solution of titanium trichloride in aqueous hydrochloric acid (26.0 ml). The mixture was stirred at room temperature under nitrogen for 17h

The mixture was rotary evaporated and the residue was basified with 50% w/v aqueous sodium hydroxide solution and then extracted with methylene chloride to afford a gummy yellow solid (2.1g) whose ¹H.n.m.r. spectrum showed a mixture of the product amine (206) (30%) and unreacted starting material (70%) which was not further investigated.

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1-Azido-2-(3-methoxyphenylthio) benzene (207)

A solution of the amine (206) (4.8g; 0.021 mol) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (1.6g; 0.023 mol) in water (10.5 ml) at such a rate that the reaction temperature was 0-5°. The resulting diazonium solution was stirred at 0-5° for 15 min then treated dropwise with stirring at 0-5° with a solution of sodium azide (2.0g; 0.03 mol) in water (10.5 ml). The mixture was then stirred in the melting ice-bath for 0.5h.

The mixture was extracted with methylene chloride and the resulting three phase mixture was filtered to afford the hydrochloride of the unreacted starting material (206) as a colourless solid (0.58g; 10%), m.p. 157-159°, identified by comparison (m.p. and i.r. spectrum) with a sample obtained previously.

Evaporation of the methylene chloride phase yielding a brown oil (4.4g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:9) gave the product azide (207) (3.8g; 70%) which formed colourless crystals, m.p. 43-44° (from hexane), $\nu_{\text{max}}$ 2100 (N$_3$)cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.32-6.74 (8H, m, ArH) and 3.75 (3H, s, CH$_3$).

**Found:** C, 60.8; H, 4.3; N, 16.4%; m/z (EI ms), 257 (M$^+$)

**C$_{13}$H$_{11}$N$_3$OS requires:** C, 60.7; H, 4.3; N, 16.3%; M, 257
Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:9) through ethyl acetate to methanol gave only intractable gums (total 0.66g) which yielded no identifiable material.

**N-[2-(3-Methoxyphenylthio)phenyl]trimethoxyphosphinimine (208)**

Solutions of the azide (207) (2.6g; 0.01 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) and trimethyl phosphite (1.6g; 0.013 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) were mixed and the mixture was stirred at room temperature for 4h.

The mixture was rotary evaporated under high vacuum, with removal of the excess trimethyl phosphite as an azeotrope with toluene yielding **N-[2-(3-methoxyphenylthio)phenyl]trimethoxyphosphinimine (208)** (3.4g; 97%) as a dark brown oil, $\delta_\text{H}$(CDCl$_3$) 7.19-6.66 (8H, m, ArH), 3.74 (9H, d, J11Hz, 3XCH$_3$) and 3.73 (3H, s, CH$_3$).

**Found:** m/z (El ms), 353.0848 (M$^+$)

**C$_{16}$H$_{20}$NO$_4$PS requires:** M, 353.0851

**1-N-2-(3-Methoxyphenylthio)phenyl-3-N-phenyl carbodiimide (209)**

Solutions of the iminophosphorane (208) (3.2g; 0.009 mol) in anhydrous 1,2-dimethoxyethane (45.0 ml) and phenyl isocyanate (1.1g; 0.009 mol) in anhydrous 1,2-dimethoxyethane (22.5 ml) were mixed and the mixture was stirred at room temperature for 4h.
The mixture was evaporated to give a brown oil which was dissolved in diethyl ether (45.0 ml) and the solution washed with water (50.0 ml) and evaporated to give 1-N-2-(3-methoxyphenylthio)phenyl-3-N-phenyl carbodiimide (209) (2.8 g; 94%) as a dark brown oil, $v_{\text{max}}$ 2110 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.43-6.70 (13H, m, ArH), 3.71 (3H, s, CH$_3$) and 3.69 (3H, s, CH$_3$).

**Found:** C, 72.1; H, 5.3; N, 7.8%; m/z (EI ms), 332.0991 (M$^+$)

**C$_{20}$H$_{16}$N$_2$O$_3$ requires:** C, 72.3; H, 4.8; N, 8.4%; M, 332.0983

**3-methoxy-11-(N-phenylamino)dibenzo[bf][1,4]thiazepine (210)**

A solution of the carbodiimide (209) (1.3 g; 0.004 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred and cooled to 0$^\circ$ (ice-salt bath) and treated dropwise with a solution of stannic chloride (5.2 g; 0.02 mol) in anhydrous 1,2-dichloroethane (10.0 ml) and the mixture was then stirred and heated under reflux for 24 h.

After this time the mixture was cooled to 0$^\circ$ (ice-salt bath) and treated dropwise with stirring with 15 M sodium hydroxide solution (13.8 ml; 0.21 mol) and the mixture allowed to warm to room temperature while stirring for 15 min. Water (40.0 ml) was added and the mixture was extracted with methylene chloride to afford an oil (1.6 g) which was flash-chromatographed over silica.
Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:9) gave only a series of intractable oils (total 0.46g) which yielded no identifiable material.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) yielded the dibenz[b,f][1,4]thiazepine derivative (210) (1.1g; 79%) which formed colourless crystals, m.p. 123-127° (from hexane-toluene), $v_{\text{max}}$ 3380 (NH) and 1630 (N=C) cm$^{-1}$, $\delta_H$ (CDCl$_3$) 7.69-6.74 (12H, m, ArH) and 3.79 (3H, s, CH$_3$).

**Found:** C, 72.7; H, 4.9; N, 2.3%; m/z (EI ms), 332.0977 (M$^+$)

**C$_{20}$H$_{16}$N$_2$OS requires:** C, 72.3; H, 4.8; N, 2.4%; M, 332.0983

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) through to methanol yielded only a series of gums (total 0.37g) whose t.l.c. in ethyl acetate-light petroleum (b.p. 40-60°) (3:7) over silica showed them to be multicomponent mixtures which therefore were not further investigated.

**2-Dimethylamino-4-(methoxyphenylthio)-5 nitopyrimidine (211)**

A stirred suspension of sodium hydride (1.3, 0.055 mol) in anhydrous dimethylformamide (5.0 ml) was treated dropwise at 5-10° (ice-bath) with a solution of 3-methoxythiophenol (195) (7.0g; 0.05 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature for 15 minutes. A solution of the chloro-nitro pyrimidine (187)
(10.1g; 0.05 mol) in anhydrous dimethylformamide (50.0 ml) was added in one portion and the mixture was stirred at 100° for 1h.

The mixture was cooled and treated with water (5.0 ml) then stirred at room temperature for 15 minutes. The mixture was rotary evaporated under high vacuum to yield a brown gum which was treated with water (40.0 ml) to give 2-dimethylamino-4-(3-methoxyphenylthio)-5-nitropyridine (211) (15.0g; 98%) as yellow crystals, m.p. 157-158° (from dimethylformamide), $\nu_{max}$ 1520 and 1350 (NO$_2$)cm$^{-1}$, $\delta_{H}$ (CD$_3$)$_2$SO 9.01 (1H, s, ArH), 7.52-7.03 (4H, m, ArH), 3.77 (3H, s, CH$_3$), 3.13 (3H, s, CH$_3$) and 2.68 (3H, s, CH$_3$).

**Found:** C, 50.8; H, 4.6; N, 18.6%; m/z (EI ms), 306 (M$^+$)

C$_{13}$H$_{14}$N$_4$O$_3$S requires: C, 50.9; H, 4.6; N, 18.3%; M, 306

**5-Amino-2-dimethylamino-4-(3-methoxyphenylthio)pyrimidine (213)**

(a) A solution of the nitropyrimidine (211) (0.61g; 0.002 mol) in glacial acetic acid (40.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.06g) at room temperature and atmospheric pressure for 0.5h. After this time no hydrogen absorption was observed. Hydrogenation was continued for a further 4h with further portions of 10% palladium-on-charcoal (0.06g) being added at hourly intervals. After this time the t.l.c. of the reaction mixture in ethyl acetate-hexane (1:1) over silica showed the presence of starting material. Further 10% palladium-on-charcoal (0.30g) was added and the mixture was hydrogenated for a further 4h.
The mixture was filtered through celite and the filtrate was evaporated to give a gum (0.52g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:7) gave unreacted starting material (211) (0.26g; 42%), m.p. 150-154, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate-hexane (3:7) yielded 5-amino-2-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (213) (0.08g; 14%) which was purified by Kugelrhor distillation yielding a yellow oil, b.p. 210-240°/0.2mm Hg, ν\text{max} 3400, 3320 and 3200 (NH)cm\(^{-1}\), δ\(_H\)(CDCl\(_3\)) 7.77 (1H, s, ArH), 7.39-6.83 (4H, m, ArH) 3.79 (3H, s, CH\(_3\)), 3.12 (2H, bs, NH\(_2\)) (exch.) and 2.91 (6H, s, 2xCH\(_3\)).

**Found:** m/z (EI ms), 276.1046 (M\(^+\))

\(\text{C}_{13}\text{H}_{16}\text{N}_{4}\text{OS}\) requires: M, 276.1044

Further elution with ethyl acetate-hexane (3:7) through ethyl acetate to methanol yielded only a series of gums (total 0.059g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed them to be multicomponent mixtures which were not further investigated.

(b) A solution of the nitropyrimidine (211) (5.8g; 0.019 mol) in glacial acetic acid (380 ml) was stirred under nitrogen and treated dropwise at room temperature with a 15% w/v solution of titanium trichloride in aqueous hydrochloric acid (219 ml). The resulting mixture was then stirred at room temperature under nitrogen for 17h.
The mixture was concentrated under high vacuum and the concentration (100 ml) was basified with 50% w/v aqueous sodium hydroxide solution. Water (95.0 ml) was added and the mixture was extracted with methylene chloride to afford a brown gum which was combined with a second crop of oil obtained by stirring the basic solution at room temperature for 19h followed by further extraction with methylene chloride (total 3.1g) and flash-chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded 3-methoxythiophenol (195) (0.22g; 8%) as a yellow oil, identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (1:1) yielded 5-amino-2-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (213) (0.82g; 16%) as a brown oil, identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

Further elution with ethyl acetate-hexane (7:3) afforded 5-acetamido-2-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (212) (1.3g; 22%) as a colourless solid, m.p. 121-123° (from benzene-hexane), v_max 3250 (NH)cm⁻¹, δ_H(CDCl₃) 8.17 (1H, s, ArH), 7.33-7.04 (5H, m, ArH + NH), 3.78 (3H, s, CH₃), 2.90 (6H, 2xCH₃) and 2.14 (3H, s, CH₃).

**Found:** C, 57.0; H, 5.8; N, 17.8%; m/z (EI ms), 318.1144 (M⁺)

**C₁₅H₁₈N₄O₂S requires:** C, 56.6; H, 5.7; N, 17.6%; M, 318.1150
Further elution with ethyl acetate through to methanol yielded a series of intractable gums (total 0.22g) which were not further investigated.

(c) A solution of the nitropyrimidine (211) (0.61g; 0.002 mol) in tetrahydrofuran (50.0 ml) was stirred under nitrogen and treated dropwise at room temperature with a 15% w/v solution of titanium trichloride in aqueous hydrochloric acid (23.0 ml). The resulting mixture was then stirred at room temperature under nitrogen for 17h.

The mixture was evaporated under reduced pressure and the residue was basified with 50% w/v aqueous sodium hydroxide solution. Water (10.0 ml) was added and the mixture was extracted with methylene chloride to afford an oil which was combined with a second oil obtained by stirring the basic aqueous mother liquor at room temperature for 17h followed by further extraction with methylene chloride, total (0.52g) and flash-chromatographed over silica.

Elution with ethyl acetate-hexane (2:3) yielded 3-methoxythiophenol (195) (0.14g; 50%) as an oil, identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (2:3) gave 5-amino-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (213) (0.19g; 34%) as a brown oil identified by comparison (i.r. spectrum) with a sample prepared in (a) before.

Further elution with ethyl acetate through to methanol yielded only a series of gums (total 0.089g) whose t.l.c. in ethyl acetate-hexane (7:3) over
silica showed them to be multicomponent mixtures which therefore were not further investigated.

The attempted catalytic hydrogenation of 2-Dimethylamino-5-nitro-4-(3-methoxyphenylthio) pyrimidine (211) over Raney Nickel

A solution of nitropyrimidine (211) (0.61g; 0.002 mol) in glacial acetic acid (40.0 ml) was hydrogenated over Raney nickel (0.07g) at room temperature and atmospheric pressure for 1h.

The mixture was filtered through celite and the filtrate was rotary evaporated under high vacuum to give the unreacted starting material (211) (0.6g; quant.), m.p. 175°-180° identified by comparison (i.r. spectrum and t.l.c. in the ethyl acetate-hexane (1:1) over silica) with an authentic sample.

The attempted reduction of 2-Dimethylamino-5 nitro-4-(3-methoxyphenylthio) pyrimidine (211) using Sodium Dithionate in Acetic Acid

A solution of the nitro pyrimidine (211), (0.61g; 0.002 mol) in glacial acetic acid (40.0 ml) was treated with sodium dithionite (0.61g) and the mixture was heated under reflux for 1h after which time a further portion of sodium dithionite (0.61g) was added, and heating under reflux was continued for a further 1h.

The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (0.75g) which
contained unreacted starting material as demonstrated by comparison (t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample. The mixture was re-dissolved in glacial acetic acid (40.0 ml), treated with further sodium dithionate (0.61g) and the mixture heated under reflux for 1hr.

The mixture was rotary evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to give a brown gum (0.63g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

5-Azido-2-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (214)

A solution of the amine (213) (2.5g; 0.009 ml) in 5M hydrochloric acid (22.5 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (0.68g; 0.0099 mol) in water (4.5 ml) at 0-5°. After stirring at 0-5° for 5 min, the diazonium solution was treated dropwise at 0-5° with a solution of sodium azide (0.88g; 0.014 mol) in water (4.5 ml) and the mixture was then stirred in the melting ice bath for 0-5h.

The mixture was basified with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to give 5-azido-2-dimethylamino-4-(3-methoxyphenylthio) pyrimidine (214) (2.4g; 88%) as a dark brown oil, \( \nu_{\text{max}} \) 2110 (NH\(_3\)) cm\(^{-1}\), which could not be purified for further characterisation.
N-[2-Dimethylamino-4-(3-methoxyphenylthio)pyrimidin-5-yl])

trimethoxyphosphinimine (215)

A solution of the azide (214) (2.1g; 0.007 mol) in anhydrous 1,2-dimethoxyethane (35 ml) was treated with a solution of trimethylphosphite (1.1g; 0.009 mol) in anhydrous 1,2-dimethoxyethane (17.5 ml) and the mixture was stirred at room temperature for 4h.

The mixture was rotary evaporated under high vacuum with removal of the excess trimethylphosphite to yield N-[2-dimethylamino-4-(3-methoxyphenylthio)pyrimidin-5-yl])trimethoxyphosphinimine (215) (2.7g; 97%) as a dark brown oil, δH(CDCl3) 8.0 (1H, s, ArH) 7.99-6.96 (9H, m, ArH), 3.78 (9H, d, J11Hz, 3xCH3) and 3.71 (3H, s, CH3).

Found: m/z (FAB ms), 399.1256 [(M+H)+]

C16H23N404PS requires: (M+H), 399.1256

1-N-[2-Dimethylamino-4-(3-methoxyphenylthio)pyrimidin-5-yl]-3-N-phenyl carbodiimide (216)

A solution of the iminophosphorane (215) (2.4g; 0.006 ml) in anhydrous 1,2-dimethoxyethane (30.0 ml) was stirred and treated at room temperature with a solution of phenylisocyanate (0.71g; 0.006 mol) in anhydrous 1,2-dimethoxyethane (15 ml) and the mixture was stirred at room temperature for 4h.
The mixture was rotary evaporated and the brown oil obtained was dissolved in diethylether (30.0 ml), and the solution washed with water (30.0 ml) and evaporated to yield 1-N-[2-dimethylamino-4-(3-methoxyphenylthio)pyrimidin-5-yl]-3-N-phenylcarbodiimide (216) (2.2g; 97%) as a dark brown oil, $\nu_{\text{max}}$ 2130 (N=C=N) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.94 (1H, s, ArH), 7.39-6.87 (9H, m, ArH), 3.78 (3H, s, CH$_3$) and 2.98 (6H, s, 2xCH$_3$).

**Found:** m/z (FAB ms), 378.1389 [(M+H)$^+$]

C$_{20}$H$_{19}$N$_5$OS requires: (M+H), 378.1389

**The Stannic Chloride Catalysed Ring Closure of 1-N-[2-Dimethylamino-4-(3-methoxyphenylthio)pyrimidin-5-yl]-3-N-phenylcarbodiimide (216)**

A solution of the carbodiimide (216) (1.3g, 0.004 mol) in anhydrous 1,2-dichloroethane (20.0 ml) was stirred and cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (6.5g, 0.025 mol) in anhydrous 1,2-dichloroethane (12.5 ml). The mixture was then heated under reflux for 24h.

The mixture was stirred, cooled to 0° and treated dropwise with 15M sodium hydroxide solution (17.5 ml; 0.26 mol) and the mixture allowed to warm to room temperature while stirring for 15 min. Water (50.0 ml)
was added and the mixture was extracted with methylene chloride to afford a gum (2.1g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:4) gave 3-methoxythiophenol (195) (0.16g; 23%) as an oil, identical (i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:4) yielded a gum (0.05g) whose t.l.c. in ethyl acetate-light petroleum (b.p. 40-60°) (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (3:7) afforded 2-(N,N-dimethylamino)-9-methoxy-6-(N-phenylamino) pyrimido[4,5-b][1,4]benzothiazepine (217) (0.23g; 12%) which formed cream coloured crystals, m.p.180-182° (from toluene-hexane), v_max 2260 (NH) and 1620 (C=N)cm⁻¹, δ_H (CDCl₃) 8.19 (1H, s, ArH), 7.58-7.55 (1H, m, ArH), 7.43 (1H, d, J9Hz, ArH), 7.43-6.99 (5H, m, ArH), 6.99-6.81 (1H, m, ArH), 6.68 (1H, bs, NH), 3.81 (3H, s, CH₃) and 3.14 (6H, s, 2xCH₃). Found: C, 63.9; H, 5.0; N, 17.6%; m/z (EI ms), 377.1306 (M⁺)

C_{20}H_{19}N_{5}O_{5}S requires: C, 63.7; H, 5.0; N, 18.6%; M, 377.1310

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:1) yielded a gum (0.10g) whose t.l.c. in ethyl acetate-light petroleum (b.p. 40-60°) (1:1) showed it to be a multicomponent mixture which was not further investigated.
Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:1) gave 2-(N, N-dimethylamino)-9-methoxypyrimido[4,5-b][1,4]
benzothiazepin-6(5H)-one (218) (0.20g; 13%) which formed cream coloured crystals, m.p. 314-315° (from acetic acid), ν_max 1660 (C=O)cm⁻¹, δ_H[(CD₃)₂SO] 10.11 (1H, s, NH), 8.18 (1H, s, ArH), 7.68 (1H, d, J8Hz, ArH), 7.12-7.01 (2H, m, ArH), 3.82 (3H, s, CH₃) and 3.08 (6H, s, 2xCH₃). Found: m/z (EI ms), 302.0835 (M⁺)

C₁₄H₁₄N₄O₂S requires: M, 302.0837

Further elution with ethyl acetate through to methanol yielded only a series of intractable gums (total 0.81g) whose t.l.c. in ethyl acetate-hexane (1:1) showed them to be complex mixtures which are not further investigated.
Chapter 4

Investigations of New Syntheses of

Fused Tricyclic Diazepines

Based On

Novel Heterocumulene Cyclisation Reactions
Investigations of New Syntheses of Fused Tricyclic Diazepines Based On Novel Heterocumulene Cyclisation Reactions

4.1 Introduction

In Chapters 2 and 3 it was shown that in certain instances Lewis acid catalysed cyclisations can be exploited for the construction of fused tricyclic benzoxazepines and benzothiazepines. Although these studies demonstrate the viability of such heterocyclisations for the synthesis of fused tricyclic heteropines they fall short of the broader objective set out in Chapter 1. This was to develop a viable general route to biologically active analogues of the known neuroleptic agents (Scheme 2), clozapine (7) and pirenzepine (8). Since these compounds are in fact fused tricyclic benzodiazepines an obvious extension of the investigations described in Chapters 2 and 3 was to attempt to harness Lewis acid catalysed heterocumulene cyclisation for the synthesis of these particular types of fused tricyclic heteropines. In so doing it was recognised that compared with the synthesis of fused tricyclic benzoxazepines and benzothiazepines described in Chapters 2 and 3 that of structurally related fused tricyclic benzodiazepines had to take into account both N(11)-unsubstituted as well as substituted structures.
(i) (n-C₄H₉)₂O, heat;
(ii) H₂, PdC, C₂H₅OCOCH₃, room temp., atmos. press;
(iii) NaNO₂, HCl(aq), 0°C;
(iv) Ph₃P, Cl₂CCCl₂(C₂H₅)₃N.CH₃CN, heat;
(v) HCl(aq), heat;
(vi) HCl(aq), room temp.

Scheme 59
4.2 Investigations of Heterocumulene Cyclisation Reactions Leading to Pyrido[2,3-b][1,4]benzodiazepine Derivatives

Initial studies under this heading by analogy with the general synthetic strategy described before in Chapters 2 and 3, centred on the synthesis (Scheme 59) of the phosphinimine derivative (223). It was intended to see if this compound, like the other phosphinimines described before in Chapters 2 and 3, would react with phenyl isocyanate to afford an isolable carbodiimide. However it was also realised that due to the presence of the free NH-group the latter might undergo spontaneous heterocyclisation. Initially it was intended to synthesise the phosphinimine (223) from the amine (221) by azido-dediazoniation followed by reaction of the resulting azide with triphenylphosphine. In practice the known\textsuperscript{78} nitropyridine derivative (220) was readily prepared in high yield (81\%) by reaction (Scheme 59) of 2-chloro-3-nitropyridine (108) with 3-methoxyaniline (219) in refluxing di-n-butyl ether. Subsequent catalytic reduction of the nitro compound (220) in ethanol over palladium-on-charcoal afforded the required amine (221) in 70\% yield. However simple replacement of ethanol by ethyl acetate as the solvent in this reduction raised the yield of the amine (221) to (83\%). Diazotisation of the amine (221), followed by treatment of the resulting diazonium solution with sodium azide yielded not the expected azide but rather a high yield (79\%) of a product identified as the triazolopyridine derivative (222) on the basis of its combustion analysis and mass, i.r. and $^1$H n.m.r. spectral properties.
(i) 4-RC₆H₄N=C=O, DME or dioxane, room temp. or reflux.

*Scheme 60*

(i) CH₃N=C=O, DME, room temp.

*Scheme 61*
Formation of this product is readily explained in terms of spontaneous heterocyclisation involving intramolecular coupling between the diazonium group and the nitrogen centre in the amino side-chain. Heterocyclisation reactions of this type are already well known in the literature. In accord with this mode of formation of the triazolopyridine derivative (222), the same product was formed in 88% yield by diazotisation of the amine (221) in the absence of azide ion.

Since the spontaneous heterocyclisation of the amine (221) on diazotisation precluded its conversion into the corresponding azide and hence into the phosphinimine (223) an alternative route to the latter had to be sought. The Wanthoff method has already been used elsewhere in this thesis (see Chapter 2, Section 2.2). Application of this method to the amine (221) resulted in the formation of the required phosphinimine (223) in good yield (79%). This compound was identified on the basis of its analytical and spectroscopic properties and its reconversion in aqueous hydrochloric acid through the phosphonium salt (224) into the parent amine (221).

With the phosphinimine derivative (223) readily available attention was next directed to its conversion (Scheme 60) into the carbodiimide (225a) by reaction with phenyl isocyanate. In practice, reaction of the phosphinimine (223) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature gave not the carbodiimide but rather a moderate yield (67%) of a product whose i.r. spectrum lacked absorption due to a carbodiimide group but contained an NH band at 3340 cm⁻¹. On the basis of this and its
combustion analysis and spectroscopic properties, the compound is formulated as the imidazo [4,5-b]pyridine derivative (226a). This product is obviously the outcome of the formation and spontaneous heterocyclisation of the expected carbodiimide derivative (225a). Since this represents a potentially useful route to derivatives of the imidazo [4,5-b]pyridine ring system, it was decided to briefly evaluate the scope of such heterocyclisation reactions (Scheme 60 and 61). It was found that the phosphinimine (223) reacted readily with aryl isocyanates containing electron-withdrawing para-substituents (nitro and chloro) at room temperature to give the corresponding imidazopyridine derivatives (226b and c) in ca 60% yield. In marked contrast the attempted reaction of the phosphinimine (223) with aryl isocyanates containing electron-donating para-substituents (methoxy and methyl) at room temperature did not go to completion and heating under reflux had to be employed to obtain the respective imidazopyridine derivatives (226d and e) in good yield 65-70%. These substituent effects demonstrate that initial condensation of the phosphinimine (223) with aryl isocyanate to give the corresponding carbodiimides (225a-d) is rapid and that subsequent heterocyclisation of the latter to the imidazopyridines (226a-d) is rate determining. Thus since the final heterocyclisation step [(225) -> (226)] involves electrophilic addition of the arylamino substituent to the ortho carbodiimide side-chain it will be facilitated by electron-withdrawing terminal N-aryl groups. The same effect was observed in the reaction of the phosphinimine (223) (Scheme 61) with methyl isocyanate which due to the
Scheme 62

(i) CH$_3$CO$_2$H, heat;
(ii) NaH, DMF, room temp. or 50°;
(iii) (CH$_3$CO)$_2$O, H$_2$SO$_4$(conc.); heat;
(iv) CH$_3$COCl, CH$_3$CO$_2$H, reflux.

Scheme 63

(i) H$_2$PdC, CH$_3$CO$_2$OH, room temp. atmosp. press;
(ii) SnCl$_4$, C$_2$H$_5$OH, 70°;
(iii) Na$_2$S$_2$O$_4$, C$_2$H$_5$OH, H$_2$O, reflux.
relative unreactivity of the intermediate N-methyl carbodiimide (227) required heating under reflux to achieve the formation of the methylamino-imidazopyridine (228) in good yield (75%).

The spontaneous cyclisation of pyridyl carbodiimides containing ortho N-unsubstituted methoxyphenylamino side-chains to the corresponding imidazopyridine derivatives necessitated the investigation of the synthesis and cyclisation of N-protected derivatives of the former substrates. Initial attempts (Scheme 62) to synthesise the N-acetyl nitropyridine derivative (230) with a view to its conversion via the amine into the corresponding carbodiimide were however unsuccessful. Thus the attempted sodium hydride catalysed condensation of the known \textsuperscript{80} N-acetyl 3-methoxyaniline (229) with 2-chloro-3-nitropyridine (108) both at room temperature or 50° gave only the unreacted starting materials. The failure of this route to give the required N-acetyl derivative (230) prompted an alternative synthetic approach (Scheme 62) involving acetylation of the already available methoxyphenylamino-nitropyridine derivative (220). Initially however, attempted acetylation by heating with acetic anhydride gave only a high recovery (75%) of the unreacted starting material. Attempted catalysis of the reaction of the amino compound (220) with acetic anhydride using concentrated sulphuric acid was also unsuccessful at room temperature or 100°. However heating the amino compound (220) under reflux with acetic anhydride in the presence of concentrated sulphuric acid gave the required N-acetyl derivative (230) though only in moderate yield (43%). Acetylation
Scheme 64

(i) TSO₂Cl, NaOOCOCH₃, C₂H₅OH, heat;
(ii) NaH, DMF, 100°;
(iii) NaH, TSO₂Cl, DMF, room temp.

(T = 4-CH₃C₆H₄)
of the amino compound (220) by heating with a mixture of acetyl chloride and acetic acid under reflux for 6h also gave the N-acetyl derivative (230) though in even lower yield (31%). However the use of these conditions but with an increase in the reaction time to 13h raised the yield of the N-acetyl derivative (230) to 56%. A further attempt to improve on this yield of the N-acetyl derivative (230) involving the sodium hydride catalysed condensation of the amino compound (220) with acetyl chloride gave only a good yield (67%) of the unreacted starting material (220).

Having synthesised the N-acetyl derivative (230) in moderate yield attention was next turned (Scheme 63) to its reduction to the corresponding amine (231). However the attempted catalytic reduction of the nitro compound (230) gave only intractable gums which yielded no identifiable material. Likewise attempted reduction using stannous chloride afforded only a multicomponent mixture. In contrast heating the nitro compound (230) with sodium dithionite in aqueous ethanol resulted in reductive cyclisation to the imidazopyridine derivative (232) in moderate yield (53%). The imidazopyridine product (232) gave mass, i.r. and $^1$H n.m.r. spectra which fully support its assigned structure. The formation of the imidazopyridine derivative (232) by dithionite reduction of the nitro-compound (230) is presumably the result of the intermediate formation and spontaneous cyclodehydration of the required amine (231). In view of this it was decided to investigate (Scheme 64) the N-tosyl derivative (234) as a source of an amine incapable of spontaneous heterocyclisation and hence
Scheme 65
appropriate for further elaboration to a carbodiimide derivative set up for Lewis acid catalysed cyclisation. Initially an attempt was made (Scheme 64) to synthesise the required N-tosyl derivative (234) by sodium hydride catalysed condensation of 2-chloro-3-nitropyridine (108) with the known N-tosyl 3-methoxyaniline (233). However this approach was unsuccessful with the unreacted starting-materials (108) and (233) being recovered unchanged in good yield. However the required N-tosyl derivative (234) was observed in low yield (33%) by the sodium hydride catalysed condensation of the methoxyphenylamino-nitropyridine (220) with tosyl chloride in dimethylformamide at room temperature. Repetition of this reaction at elevated temperature in an attempt to improve the yield actually afforded the N-tosyl derivative (234) in only 27% yield. A further attempt to improve the yield of the N-tosyl derivative (234) by the sodium hydride catalysed condensation of the amino-compound (220) with tosyl chloride in refluxing diglyme gave only a moderate yield of the unreacted starting-material (220). Since the N-tosyl derivative (234) was only accessible in low yield it was decided to investigate other N-substituted methoxyphenylamino-nitropyridine derivatives as starting-materials for the synthesis of carbodiimides appropriate for Lewis acid catalysed cyclisation to the corresponding pyridobenzodiazepine derivatives.

Initially attention was centred on the synthesis (Scheme 65) of the N-methyl methoxyphenylaminopyridyldicarbodiimide (238) with a view to investigation of its Lewis acid catalysed cyclisation to the
N-methylpyridobenzodiazepine derivative (240). Thus sodium catalysed methylation of the amine (220) with methyl iodide proceeded smoothly giving the N-methyl derivative (235) in good yield (68%). Catalytic reduction of the nitro compound (235) to the amine (236) also proceeded in high yield (100%). The amine (236) was next converted into the triphenylphosphinimine (237) using the procedure described by Wamhoff\(^4\) involving the reaction with triphenylphosphine and hexachloroethane in the presence of triethylamine. The triphenylphosphinimine (237) was obtained in good yield (82%) and reacted as expected with phenyl isocyanate in 1,2-dichloroethane at room temperature giving the expected carbodiimide derivative (238). The latter was obtained as an unstable oil which could not be entirely freed from contaminating triphenylphosphine oxide but showed characteristic i.r. absorption at 2140\(\text{cm}^{-1}\) due to the carbodiimide substituent. The attempted characterisation of the impure carbodiimide (238) by alkaline hydrolysis to the urea (239) gave only a multicomponent gum which yielded no identifiable material.

Despite the presence of contaminating triphenylphosphine oxide in the carbodiimide (238) it was decided to attempt its Lewis acid catalysed cyclisation (Scheme 65) to the pyridobenzodiazepine derivative (240). Heating the impure carbodiimide (238) under reflux with five equivalents of stannic chloride in methylene chloride gave after chromatography of the reaction mixture a good yield (59%) of the product which gave an accurate mass analysis consistent with the pyridobenzodiazepine structure (240). This
(i) NaN\textsubscript{3}, HCl(aq), 0\textdegree\textsuperscript{o} then NaN\textsubscript{3}, 0\textdegree\textsuperscript{o};
(ii) (CH\textsubscript{2}O\textsubscript{3})\textsubscript{3}P, DME, room temp;
(iii) PhN=C=O, DME, room temp;
(iv) SnCl\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, reflux.

Scheme 66
(i) NaNO₂, HCl(aq), 0°;  
(ii) hv, toluene.

Scheme 67

(i) PhCH=O, PhCH₂OH, KOH, reflux;  
(ii) (n-C₅H₁₀)₂O, heat;  
(iii) NaH, PhCH₂Br, DMF, room temp.

Scheme 68
structure for the product was verified by i.r. and $^1$H n.m.r. and $^{13}$H n.m.r. spectra. The 9-methoxy orientation (240) for this product rather than the alternative 7-methoxy structure was assigned by analogy with structurally related pyridobenzoxazepine derivatives described in Chapter 2.

Because of the difficulty of freeing the carbodiimide (238) derived by the aza-Wittig reaction of the triphenylphosphinimine (237) with phenyl isocyanate from contaminating triphenylphosphinoxide, it was decided as in the case of pyridobenzoxazepine synthesis (see Chapter 2, Section 2.2) to attempt to exploit (Scheme 66) the trimethoxyphosphinimine derivative (242) since the synthesis of the trimethoxyphosphinimine (242) involved azido-dediazoniation of the diazonium salt derived from the amine (236) it was decided to initially investigate the behaviour of the latter towards simple diazotisation (Scheme 67). In practice treatment of the amine (236) with sodium nitrite in hydrochloric acid at 0° afforded a good yield (73%) of a product which analysed correctly and showed spectroscopic properties consistent with its formulation as the pyridotriazepine structure (243). The formulation of this product as the 9-methoxy derivative (243) rather than the corresponding 7-methoxy derivative is based on analogy with the pyridobenzotriazepine derivative (240). Formation of the pyridobenzotriazepine (243) by diazotisation of the amine (236) is readily explained in terms of the formation of the corresponding diazonium salt and its cyclisation by intramolecular coupling at the para position to the methoxy group in the phenyl ring. A similar heterocyclisation reaction has been
reported in the literature. With the pyridobenzotriazepine derivative (243) readily accessible a speculative attempt was made (Scheme 67) to effect its photo ring-contraction with loss of nitrogen to afford the pyridoindole derivative (244). However the pyridobenzotriazepine derivative (243) was recovered unchanged in high yield (92%) after irradiation at 254nm for 28h.

Despite the demonstration that diazotisation of the amine (236) results in the formation of the benzotriazepine (243) it was decided to proceed with the synthesis (Scheme 66) of the azide (241) required as the precursor of the trimethoxyphosphinimine derivative (242). Thus diazotisation of the amine (236) followed by treatment of the resulting diazonium salt solution with sodium azide gave the expected azide (241) in good yield (67%). The azide (241) in turn reacted smoothly with trimethyl phosphate in 1,2-dimethoxyethane at room temperature to give the trimethoxyphosphinimine (242) in high yield (89%). Reaction of the trimethoxyphosphinimine (242) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature afforded the pure carbodiimide (238) uncontaminated with any phosphorus by-product in quantitative yield. Heating the pure carbodiimide (238) under reflux with 5 equivalents of stannic chloride in 1,2-dichloroethane afforded the pyridobenzodiazepine derivative (240) in moderate yield (54%) identical in all respects with sample obtained before.
(i) H₂, Pd, THF, room temp., atmos. press;
(ii) NaNO₂, HCl(aq), 0°, then NaN₃, 0°;
(iii) (CH₃O)₃P, DME, room temp;
(iv) PhN=O, DME, room temp;
(v) SnCl₄, Cl(CH₂)₂Cl, reflux.

Scheme 69
Having shown that the N-substituted methoxy phenylaminopyridyl carbodiimide (238) is readily synthesised and undergoes stannic chloride catalysed cyclisation to the pyridobenzodiazepine derivative (240) in reasonable yield, attention was next turned to the synthesis (Schemes 68 and 69) of the N-benzyl carbodiimide (250) and the investigation of its stannic chloride catalysed cyclisation to a pyridobenzodiazepine derivative amenable to debenzylation to the corresponding N-unsubstituted compound. Initially an attempt (Scheme 68) was made to synthesis the key N-benzyl nitopyridine starting-material (246) by condensation of 2-chloro-3-nitropyridine (108) with the known N-benzyl-3-methoxyaniline (245) in refluxing di-n-butyl ether. However, this reaction gave only good recoveries of the unreacted starting-materials. In addition the attempted sodium hydride catalysed condensation (Scheme 68) of the methoxyphenylaminopyridine (220) with benzyl chloride also afforded only a high recovery (79%) of the unreacted starting-material (220). In contrast the replacement of benzyl chloride by benzyl bromide in this reaction afforded an excellent yield (96%) of the required N-benzyl derivative (246) which showed analytical and spectroscopic properties fully in accord with its assigned structure.

Having successfully obtained the N-benzyl nitopyridine derivative (246) attention was directed (Scheme 69) to its reduction to the amine (247). Catalytic reduction of the nitro compound (246) gave the required amine (247) in moderate yield (64%). Attempts to improve the yield of the
Scheme 70

(i) CX₂, solvent.

**Scheme 70**

N \text{PR}_3

\begin{align*}
\text{(252)} & \quad \text{N} - \text{C} = \text{X} \\
\text{(253)} & \quad \text{N} - \text{C} = \text{X} \\
\text{(254)} & \quad \text{N} - \text{C} = \text{X}
\end{align*}

\text{a; O} \\
\text{b; S}
amine (247) using reducing agents such as sodium dithionite or titanium trichloride either gave even lower yields of the amine (247) or either unreacted starting-material (246) or intractable product mixtures.

The subsequent conversion (Scheme 69) of the amine (247) into the required carbodiimide (250) through the azide (248) and the trimethoxyphosphinimine (249) proceeded as expected in good overall yield. Disappointingly the attempted stannic chloride catalysed cyclisation of the carbodiimide (250) to the pyridobenzodiazepine derivative gave instead only a low yield of the urea derivative (251). The reason for the contrasting behaviour of the N-benzyl carbodiimide (250) compared with the N-methyl compound (238) in terms of the pyridobenzodiazepine formation is not clear. Unfortunately lack of time prevented the further investigation of the reason or reasons for this contrast in behaviour.

In Chapter 2 it was demonstrated (see Section 2.2, Schemes 48 and 49), that the Lewis acid-catalysed cyclisation of appropriate isocyanate and isothiocyanate derivatives provided a useful synthetic route to tricyclic fused oxazepinones and thiazepinones. It was therefore of interest to know if the Lewis acid catalysed cyclisation of appropriate isocyanate and isothiocyanate derivatives could also be harnessed to the synthesis of the corresponding fused tricyclic diazepinone and diazepinethione derivatives. The synthetic strategy initially envisaged in the case of pyridobenzodiazepinones and pyridobenzodiazepinethiones is illustrated in general in Scheme 70. This entailed the reaction of appropriate phosphinimine derivatives (252) with
Scheme 71

(i) CO₂, DME, reflux;
(ii) CS₂, DME, reflux.
Scheme 72
carbon dioxide or carbon disulphide to give the corresponding isocyanates (253; \(X=O\)) or isothiocyanates (253; \(X=S\)) followed by the Lewis acid catalysed cyclisation of the latter to the respective pyridobenzoxazepinones (254a; \(X=O\)) or pyridobezoxazepinethiones (254; \(X=S\)). In practice however (Scheme 71) the attempted reaction of the triphenyphosphinimine derivative (223) prepared before, with carbon dioxide failed to give the expected isocyanate (255) instead this reaction gave only a high recovery (98%) of the unreacted starting-material (223). The attempted reaction (Scheme 71) of the triphenyphosphinimine derivative (223) with carbon disulphide likewise failed to afford the required isothiocyanate derivative (256). The product of this reaction, obtained moderate yield (56%) together with unreacted starting-material (34%), analysed correctly for the isothiocyanate derivative (256) but lacked i.r. absorption due to isothiocyanate substitution. On this basis it is formulated as the imidazopyridinethione derivative (257). Formation of the latter by reaction of the triphenylyphosphinimine derivative (223) with carbon disulphide is readily explained in terms of the intermediate formation and spontaneous cyclisation of the isothiocyanate derivative (256).

Having failed to obtain the required isocyanate derivative (255) directly by reaction of the triphenylyphosphinimine derivative (223) with carbon disulphide it was decided to pursue the alternative synthetic strategy generalised in Scheme 72. This involved the synthesis of a nicotinic ester derivative (259) and its elaboration through the hydrazide (260) and acyl
(i) 3-CH₃OC₆H₄NHCH₂Ph, diglyme, 140°C;  
(ii) 3-CH₃OC₆H₄NH₂, diglyme, 140°C;  
(iii) CH₃OH, HCl(g), reflux;  
(iv) NaH, PhCH₂Cl, DMF, room temp.
(i) $\text{NH}_2\text{NH}_2$, CH$_3$OH, reflux;
(ii) NaOH(aq), C$_2$H$_5$OH, reflux;
(iii) SOCl$_2$, room temp. or reflux.

Scheme 74
azide (261) to the required isocyanate (262). In practice the attempted synthesis (Scheme 73) of the N-benzyl nicotinic ester (266) through reaction of 2-chloronicotinic acid (167) with N-(3-methoxyphenyl)benzylamine followed by esterification, failed at the first stage. Thus, heating the acid (167) with the N-benzyl-3-methoxyaniline (245) under reflux in diglyme gave only good recoveries of both unreacted starting-materials. In contrast the analogous reaction of 2-chloronicotinic acid (167) with 3-methoxy aniline (219) gave an excellent yield (91%) of the expected product (265) which analysed correctly and showed spectroscopic properties which fully support its structure. Esterification of the carboxylic acid (265) afforded the ester (267) in moderate yield (52%) and subsequent benzylation afforded the N-benzyl derivative (266) in excellent yield (89%). Disappointingly however the attempted conversion (Scheme 74) of the ester (266) into the hydrazide (268) by reaction with hydrazine afforded only a high recovery (91%) of the unreacted starting material. In an alternative approach (Scheme 74) to the required hydrazide (268), the ester (266) was hydrolysed to the acid (264) in good yield (61%) with a view to its conversion into the acid chloride (269) and hence hydrazide (268) failed at the acid chloride stage. Thus the attempted reaction of the carboxylic acid (264) with thionyl chloride at room temperature or even under reflux gave only intractable gums which yielded no identifiable material. Due to constraints on time investigations of the synthesis of potential heterocumulene precursors of pyridobenzodiazepinone and pyridobenzodiazepinethione derivatives were terminated at this point.
Scheme 75

(i) KF, 180°C;
(ii) NaH, PhCH₂Br, DMF, room temp;
(iii) H₂, Pd-C, C₂H₅OCOCH₃, room temp. atmos. press;
(iv) NaNO₂, HCl(aq), 0°C then NaN₃, 0°C;
(v) (CH₃O)₃P, DME, room temp.
4.3 Investigations of Heterocumulene Cyclisation Reactions

Leading to Various Fused Tricyclic Diazepine Derivatives

In the foregoing section (Schemes 65 and 66) it was demonstrated that the stannic chloride catalysed cyclisation of the carbodiimide derivative (238) affords the pyridobenzodiazepine (240) in moderate yield. It was therefore of interest to know if the analogous carbodiimide cyclisation reactions could be exploited for the synthesis of derivatives of other fused tricyclic benzodiazepine ring systems. With this objective in mind it was initially decided to investigate the application of Lewis acid catalysed carbodiimide cyclisation to the synthesis of the dibenzo[b,e][1,4]diazepine ring system. To this end (Scheme 75) an attempt was made to synthesise the carbodiimide (276) with the intention of effecting its stannic chloride catalysed cyclisation to the corresponding dibenzodiazepine derivative. The thermal condensation of 2-fluoronitrobenzene (270) with 3-methoxyaniline (219) in the presence of potassium fluoride proceeded in good yield (73%) to give the known nitrodiphenylamine derivative (271). Sodium hydride catalysed benzylation of the latter also occurred smoothly giving high yield (83%) of the expected N-benzyl derivative (272). Catalytic hydrogenation of the latter afforded an excellent yield (99%) of the required amine (273), diazotisation and azo-dediazonation of which gave the gummy azide (274) in good yield (81%), unfortunately the attempted reaction of the azide (274) with trimethyl phosphite gave only an intractable foam rather than the expected trimethoxy phosphinimine derivative (275) required as precursor of
\[ \text{(i) } \text{C}_2\text{H}_5\text{OH, reflux;} \]
\[ \text{(ii) } \text{H}_2, \text{PdC, CH}_3\text{CO}_2\text{H, room temp., atmos. press;} \]
\[ \text{(iii) } \text{NaNO}_2, \text{HCl(aq), } 0^\circ; \]
\[ \text{(iv) } \text{Ph}_3\text{P, Cl}_3\text{CCl}_3, (\text{C}_2\text{H}_5)_3\text{N, CH}_3\text{CN, reflux;} \]
\[ \text{(v) } \text{PhN=C=O, 1,4-dioxane, reflux.} \]

\textbf{Scheme 76}
the carbodiimide (276). The failure to obtain the trimethoxyphosphinimine derivative (275) prevented the further investigation of the synthesis of the carbodiimide (276) and hence its stannic chloride cyclisation to the corresponding dibenzodiazepine derivative.

Despite the lack of success in demonstrating the stannic chloride catalysed cyclisation of an appropriate carbodiimide derivative, it was decided to attempt to extend Lewis acid catalysed carbodiimide cyclisation to the synthesis of derivatives of the pyrimido[4,5-b][1,4]benzodiazepine ring system. Initial studies in this context were directed towards of an N-unsubstituted pyrimidobenzodiazepine derivative. Thus (Scheme 76) the known\textsuperscript{76} and readily synthesised chloronitropyrimidine derivative (187) condensed readily with 3-methoxyaniline (219) to afford the expected methoxy-phenylaminopyrimidine derivative (277) in high yield (94%). Catalytic reduction of the nitropyrimidine derivative (277) also occurred readily to give the corresponding amine (278) in good yield (77%). The conversion of the amine (278) into the corresponding azide and then appropriate phosphinimine derivative was precluded by the behaviour of the amine (278) towards diazotisation (Scheme 76). This reaction gave good yield (83%) of a product which is assigned the triazolopyrimidine structure (279) on the basis of its analytical and spectroscopic properties.

In an alternative approach (Scheme 76) reactions of the amine (278) with triphenylphosphine and carbontetrachloroethane affected its conversion into the triphenylphosphinimine derivative (280) in moderate
(i) NaH, PhCH₂Br, DMF, room temp;
(ii) 15% w/v TiCl₃(aq), THF, room temp;
(iii) NaNO₂, HCl(aq), 0°, then NaN₃, 0°;
(iv) (CH₃O)₃P, DME, room temp;
(v) PhN=C=O, DME, room temp;
(vi) SnCl₄Cl(CH₂)₂Cl, reflux.

Scheme 77
yield (59%). However reaction of the triphenylphosphinimine derivative (280) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature afforded not the expected carbodiimide (281) but rather the product of its spontaneous cyclisation, the imidazopyrimidine derivative (282). The structure of the latter compound was fully substantiated by its analytical and spectroscopic properties.

Because of the instability of the N-unsubstituted carbodiimide (281) to spontaneous cyclisation to the imidazopyrimidine derivative (282) it was necessary to synthesise (Scheme 77) an N-sustituted carbodiimide (287) in order to investigate the possibility of the Lewis acid catalysed cyclisation of an arylaminopyrimidylcabrodiimide (287) to the corresponding pyrimido[4,5-b][1,4]benzodiazepine. Initially the attempted sodium hydride catalysed benzylation of the methoxyphenylaminopyrimidine (277) using benzyl chloride or one equivalent or benzyl bromide gave either none of the required N-benzyl derivative (283) or a mixture of the latter and unreacted starting-material. However the sodium hydride catalysed reaction of the amino compound (277) with excess of benzyl bromide afforded the required N-benzyl derivative (283) in high yield (91%).

The attempted conversion of the nitropyrimidine (283) into the amine (284) by catalytic hydrogenation gave only a high recovery (89%) of the unreacted starting-material (283). However the amine (284) was obtained in moderate yield (61%) by reduction of the nitropyrimidine
derivative (283) with excess of titanium trichloride in aqueous tetrahydrofuran at room temperature.

The amine (284) was converted under standard conditions in good yield (76-85%) into the azide (285) and then the trimethoxyphosphinimine derivative (286). Reaction of the latter compound with phenyl isocyanate in 1,2-dimethoxyethane at room temperature gave the required carbodiimide (287) as a brown gum in quantitative yield. Disappointingly the attempted stannic chloride catalysed cyclisation of the carbodiimide (287) failed to afford the corresponding pyrimidinobenzodiazepine derivative but rather a low yield (16%) of a product identified on the basis of its analytical and spectroscopic properties as the urea derivative (288). This product is presumably derived by simple hydrolysis of the unreacted carbodiimide (287) on workup.

Due to constraints on time the foregoing studies were terminated at this stage.
4.4 Experimental

2-(3-methoxyphenyl)amino-3-nitropyridine (220)

A solution of 2-chloro-3-nitropyridine (108) (15.8g; 0.1 mol) in di-
n-butyl ether (50.0 ml) was treated with 3-methoxyaniline (219) (3.9g; 0.3 mol) and the mixture was heated under reflux for 3h.

The mixture was evaporated under high vacuum and the residue was dissolved in methylenechloride (100 ml) and the solution washed with 2M aqueous hydrochloric acid (150 ml). Evaporation of the methylene chloride extract gave a gummy brown solid (25.2g) which was triturated with methanol yielding 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (19.9g; 81%) as a red solid, m.p 93-96 (from methanol) (lit., 78 99-100°).

Evaporation of the methanolic mother liquor afforded a dark brown gum (4.9g) whose t.l.c in ethyl acetate-hexane (4:6) over silica showed it to be a complex mixture which was not further investigated.

3-Amino-2-N-(3-methoxyphenyl)amino pyridine (221)

(a) A solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (0.49g; 0.002 mol) in the minimum quantity of ethanol (10.0 ml) was hydrogenated over 5% palladium-on-charcoal (0.049g) at room temperature and atmospheric pressure for up to 1h by which time the absorption of the hydrogen had ceased.

The mixture was filtered through celite and the filtrate was evaporated to give a light brown solid (0.35g) which was crystallised to
afford 3-amino-2-N-(3-methoxyphenyl)aminopyridine (221) (0.30g; 70%) as light brown crystals, m.p. 99-102° (from toluene), \( \nu_{\text{max}} \) 3350, 3220, and 3125 (NH) cm\(^{-1}\), \( \delta \) (CDCl\(_3\)) 7.85 (1H, dd, J\(_{\text{ortho}}\) 5Hz and J\(_{\text{meta}}\) 1Hz, ArH), 6.50 (1H, td, J\(_{\text{ortho}}\) 8Hz and J\(_{\text{meta}}\) 1Hz, ArH), 4.60 (2H, s, NH\(_2\)) (exch.) and 3.77 (3H, s, CH\(_3\))

**Found:** C, 66.7; H, 6.1; N, 19.2%; m/z (EI ms), 215 (M\(^+\))

**C\(_{12}\)H\(_{13}\)N\(_3\)O requires:** C, 66.9; H, 6.1; N, 19.5%; M, 215

(b) A solution of the nitro-compound (220) (12.3g; 0.0025 mol) in ethyl acetate (300 ml) was hydrogenated over 10% palladium-on-charcoal at room temperature at atmospheric pressure for 4h by which time the absorption of hydrogen had ceased.

The mixture was filtered through celite and the filtrate was evaporated to give a gummy solid (12.7g) which was triturated with diethyl ether to afford 2-(3-methoxyphenyl)amino-3-amino pyridine (221) (8.9g; 83%), identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Evaporation of the diethyl ether mother liquor yielded on intractable brown gum (1.3g) which yielding no further identifiable material.

3-(3-Methoxyphenyl)-3H-1,2,3-triazolo[4,5-b]pyridine (222)

(a) A suspension of 3-amino-2-(3-methoxyphenyl) aminopyridine (221) (0.22g; 0.001 mol) in concentrated H\(_2\)SO\(_4\) (6.0 ml) was stirred, cooled to 0° (ice-salt bath) and treated dropwise with a solution of sodium nitrite
(0.60g; 0.009 mol) in water (6.0 ml) at such a rate that the reaction temperature was <5 °. The mixture was stirred at <5 ° for 15 min then treated at 0° with stirring with a solution of sodium azide (0.07g; 0.001 mol) in water (1.5 ml) and the mixture was stirred at 10° for 0.5h.

The mixture was poured onto ice (5.0g) and filtered yielding 3-(3-methoxyphenyl)-3H-1,2,3-triazolo[4,5-b] pyridine (222) (0.18g, 79%) as a colourless solid, m.p. 82° (from hexane), δ_H(CDCl_3) 8.75 (1H, dd, J ortho 5Hz and J meta 2Hz, ArH), 8.44 (1H, dd, J ortho 8Hz and J meta 2Hz, ArH), 7.99-7.84 (2H, m, ArH), 7.59-7.24 (2H, m, ArH), 7.06-6.91 (1H, m, ArH) and 3.90 (3H, s, CH_3).

Found: C, 63.7; H, 4.5; N, 25.0%; m/z (EI ms), 226 (M⁺)

C_{12}H_{10}N_{4}O requires: C, 63.4; H, 4.8; N, 24.7%; M, 226

(b) A stirred solution of 2-(3-methoxyphenyl)amino-3-aminopyridine (221) (1.3g; 0.006 mol) in 5M hydrochloric acid (15.0 ml) was cooled to 0° (ice-salt-bath) and treated dropwise with a solution of sodium nitrite (0.46g; 0.0066 mol) in water (3.0 ml) at 0-5°. Further 5M aqueous hydrochloric acid (15.0 ml) was added and the mixture was stirred in the melting ice-bath for 0.5h.

The mixture was filtered to yield 3-(3-methoxyphenyl)-3-H-1,2,3-triazolo [4,5-b] pyridine (222) (1.2g; 88%), m.p. 78.81°, identical (m.p. and i.r. spectrum) to the sample prepared in (a) before.
N-{2-[N-(3-Methoxyphenyl)amino]pyrid-3-yl} triphenylphosphinimine (223)

A solution of the amine (221) (2.2g; 0.01 mol) in anhydrous acetonitrile (100 ml) was stirred under nitrogen and treated with triphenylphosphine (3.1g; 0.012 mol) followed by triethylamine (20g; 0.02 mol) then hexachloroethane (2.4g; 0.01 mol) and the mixture was heated under reflux under an atmosphere of nitrogen for 18h.

The mixture was cooled and evaporated and the residue was treated with water (40.0 ml) and extracted with ethyl acetate to give a brown gum (5.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (65:35) gave unreacted triphenylphosphine (0.33g; 10%), m.p. 66-70° identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (65:35) yielded an intractable red oil (0.031g) which was not further investigated.

Further elution with hexane-ethyl acetate (65:35) afforded N-{2-[N-(3-methoxyphenyl)amino]pyrid-3-yl}triphenylphosphinimine (223) (3.7g; 79%) which formed colourless crystals, m.p. 125-127° (from ethyl acetate-hexane), νmax 3360 (NH) cm⁻¹, δH(CDCl₃) 8.57 (1H, s, NH) (exch.), 7.87-7.16 (19H, m, ArH), 6.53-6.19 (3H, m, ArH) and 3.83 (3H, s, CH₃).

Found: C, 75.9, H, 5.5, N, 8.8%, m/z No parent ion

C₃₀H₂₆N₃OP requires: C, 75.8; H, 5.5; N, 8.8%; M, 475
Further elution with ethyl acetate-hexane (1:1) through to ethyl acetate gave only a series of intractable oils (total 0.71g) which yielded no identifiable material.

Further elution with methanol afforded triphenylphosphine oxide (0.68g) as a gummy brown solid, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample.

Further elution with ethanol gave only an intractable oil (0.067g) which was not further investigated.

The Attempted Hydrolysis of N-[2-][N-(3-Methoxyphenyl)]amino pyrid-3-yl]triphenylphosphinimine (223) Using Aqueous Hydrochloric Acid

The phosphinimine (223) (0.51g; 0.001 mol) was treated with 2M aqueous hydrochloric acid (5.0 ml) and the mixture was stirred at room temperature for 1h.

The mixture was neutralised by the addition of 2M aqueous sodium hydroxide solution and extracted with methylene chloride to afford a brown gum (0.48g) which was triturated with ethyl acetate-hexane to yield N-[2-[N-(3-Methoxyphenyl)]amino triphenylphosphonium chloride (224) (0.21g; 41%) as a colourless solid, m.p. 195-197° (from acetonitrile),

δ_H(CDCl_3) 8.95 (1H, bs, NH) 7.86-6.39 (23H, m, ArH + NH) and 3.85 (3H, s, CH3).

Found: C, 70.5; H, 5.3; N, 8.5%; m/z (FAB ms), 476 (M+-Cl)
C_{30}H_{27}ClN_3OP requires:  C, 70.5;  H, 5.3;  N, 8.2%;  M, 511.5

Evaporation of the hexane-ethyl acetate mother liquor yielded the unreacted starting-material (223) (0.20g; 39%), m.p. 116-121°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

The Hydrolysis of \(N\-{2-[N-(3-Methoxyphenyl)]aminopyrid-3-y1}\)triphenylphosphinimine (223) Using Aqueous Hydrochloric Acid

The phosphinimine (223) (0.95g; 0.0002 mol) was treated with 2M aqueous hydrochloric acid (10.0 ml) and the mixture was heated under reflux for 24h.

The mixture was cooled and filtered to remove triphenylphosphine oxide (0.57g; 98%), m.p. 150-153°, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous acidic filtrate was made basic by the addition of 2M aqueous sodium hydroxide solution and extracted with methylene chloride to afford \(3\text{-amino-2-(3-Methoxyphenyl)aminopyridine (221)}\) (0.33g; 77%), m.p. 99-103°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

2-Arylamino-3-(3-methoxyphenyl)-3H-imidazo[4,5-b]pyridines

Solutions of \(N\-{2-[N-(3-Methoxyphenyl)]aminopyrid-3-y1}\)triphenylphosphinimine (223) (0.002 mol) in anhydrous
1,2-dimethoxyethane (10.0 ml) and the respective isocyanate derivative (0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) were mixed and the mixture was stirred at room temperature for 4-24h, then worked up as indicated for the individual reactions below.

(i) The mixture from phenyl isocyanate was rotary evaporated to give a gummy solid which was triturated with ethyl acetate to afford 3-(3-methoxyphenyl)-2-(N-phenylamino)-3H-imidazo[4,5-b]pyridine (226a) (67%) as a colourless solid, m.p. 183-185° (from benzene), $v_{\text{max}}$ 3340 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.09 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.82 (1H, dd, Jortho 8Hz and Jmeta 2Hz, ArH), 7.63-6.97 (10H, M, ArH) and 3.82 (3H, s, OCH$_3$), $\delta_c$ (CDCl$_3$) 161.1 (quat.), 149.6 (quat.), 147.7 (quat.), 140.9 (CH), 138.3 (quat.), 134.7 (quat.), 133.8 (quat.), 131.1 (CH), 129.1 (CH), 123.5 (CH), 123.0 (CH), 119.5 (CH), 118.8 (CH), 118.3 (CH), 115.3 (CH), 113.3 (CH) and 55.54 (CH$_3$).

**Found:** C, 72.0; H, 5.1; N, 17.4%; m/z (EI ms)), 316 (M$^+$)

**C$_{19}$H$_{16}$N$_4$O requires:** C, 72.2; H, 5.1; N, 17.7%; M, 316

The ethyl acetate was evaporated yielding an oil whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

(ii) The mixture from 4-methylphenyl isocyanate was evaporated to yield a brown oil whose i.r. spectrum showed that the reaction had not gone to completion. The oil was redissolved in anhydrous
1,2-dimethoxyethane (10.0 ml) and the mixture was heated under reflux for 17h.

The cooled mixture was evaporated to yield a brown gum (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) yielded a series of intractable gums (total 0.26g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (1:1) afforded 3-(3-methoxyphenyl)-2-(4-methylphenylamino)-3H-imidazo[4,5-b]pyridine (226d) (65%) as a colourless solid m.p. 121-122° (from methanol), \( \nu_{\text{max}} \) 3250 (NH)cm\(^{-1}\), \( \delta_{\text{H}}[(\text{CD}_3)_2\text{SO}] \) 8.65 (1H, s, NH), 7.95 (1H, dd, J\text{ortho} 5Hz and J\text{meta} 2Hz, ArH), 7.79-7.04 (10H, m, ArH), 3.83 (3H, s, CH\(_3\)) and 2.27 (3H, s, CH\(_3\)).

**Found:** m/z (EI ms), 330.1482 (M\(^+\))

**C\(_{20}\)H\(_{18}\)N\(_4\)O requires:** M, 330.1481

Further elution with ethyl acetate yielded 1-{2-[N-(3-Methoxyphenyl)amino]pyrid-3-yl]-3-(4-methylphenyl)urea (14%) as a colourless solid, m.p. 186-190°. \( \nu_{\text{max}} \) 1700 (CO)cm\(^{-1}\).

**Found:** m/z (EI ms), 240 (M\(^+\))

**C\(_{20}\)H\(_{20}\)N\(_4\)O\(_2\) requires:** M, 240

Further elution with ethyl acetate gave triphenylphosphine oxide (72%), m.p. 152-154°, identical (m.p. and i.r. spectrum) to an authentic
sample. Further elution with methanol gave only an intractable gum (0.06g) which was not further investigated.

(iii) The mixture from 4-methoxyphenyl isocyanate was evaporated to yield a brown oil whose i.r. spectrum showed that the reaction had not gone to completion. The oil was therefore redissolved in anhydrous 1,2-dimethoxyethane (15.0 ml) and the mixture heated under reflux for 21h. Evaporation of the mixture yielded a brown oil whose i.r. spectrum again showed that the reaction had not gone to completion. The oil was dissolved in anhydrous 1,4-dioxane (15.0 ml) and the mixture heated under reflux for 17h.

The mixture was cooled and evaporated yielding a gummy solid which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) afforded 2-(3-

**Methoxyphenylamino)-3-methoxyphenyl-3H-imidzo[4,5-b]pyridine**

(226e) (71%) which formed colourless crystals, m.p. 160-161° (from ethyl acetate). $v_{\text{max}}$ 3280 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.04 (1H, dd, Jortho 5Hz and Jmeta 1Hz, ArH), 7.76 (1H, dd, Jortho 8Hz and Jmeta 1Hz, ArH), 7.56-7.47 (3H, m, ArH) 7.25-6.87 (6H, M, ArH), 6.40 (1H, brs, NH) (exch.), 3.84 (3H, s, CH$_3$) and 3.79 (3H, s, CH$_3$).

**Found:** C, 69.2; H, 5.3; N, 16.0% m/z (EI ms), 346 (M$^+$)

**C$_{20}$H$_{18}$N$_4$O$_2$ requires:** C, 69.4; H, 5.2; N, 16.2%; M, 346

Further elution with ethyl acetate-hexane (1:1) yielded an intractable brown gum which was not further investigated.
Further elution with ethyl acetate gave triphenylphosphine oxide (61%), m.p. 148-150°, identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with methanol yielded only an intractable brown gum which gave no identifiable material.

(iv) Evaporation of the mixture from p-chlorophenyl isocyanate yielded a gummy solid which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) yielded a small amount of an intractable yellow gum which was not further investigated.

Further elution with hexane-ethyl acetate (4:1) gave a yellow gum which was further purified by preparative t.l.c. in hexane-ethyl acetate (3:2) over silica yielding a solid which was combined with a second crop obtained by further elution with hexane-ethyl acetate (7:3) to give 2-(4-chlorophenylamino)-3-(3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine (226c) (60%) which formed colourless crystals, m.p. 186-189° (from ethyl acetate), δH 8.08 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.86-7.02 (10H, m, ArH), 8.50 (1H, brs, NH) (exch.) and 3.84 (3H, s, CH3).

**Found:** C, 65.0; H, 4.3; N, 15.8%; m/z (EI ms), 352 and 350 (M+)

**C19H15ClN4O requires:** C, 65.1; H, 4.3; N, 16.0%; M, 350.5 and 352

Further elution with ethyl acetate through to methanol yielded triphenylphosphine oxide (83%), m.p. 136-140°, identified by comparison m.p. and i.r. spectrum with an authentic sample.
(v) Filtration of the mixture from 4-nitrophenyl isocyanate afforded a solid which was combined with a second crop obtained by evaporating the filtrate and triturating the yellow gum obtained with methanol to yield 3-(3-methoxyphenyl)-2-(4-nitrophenylamino)-3H-imidazo[4,5-b]pyridine (226b) (62%) which formed yellow crystals, m.p. 275-276° (from acetic acid), $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$ 9.66 (1H, brs, NH) (exch.), 8.29-7.09 (11H, m, ArH) and 3.82 (3H, s, CH$_3$).

**Found:** C, 62.7; H, 4.2; N, 19.1%; m/z (EI ms) 361.1162 (M$^+$)

**C$_{19}$H$_{15}$N$_5$O$_3$ requires:** C, 63.2; H, 4.2; N, 19.4%; M, 361.1175

Evaporation of the methanolic mother liquor yielded a yellow gum whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a complex mixture which therefore was not further investigated.

3-(3-Methoxyphenyl)-2-(N-methylamino)-3H-imidazo[4,5-b]pyridine (228)

Solutions of the phosphinimine (223) (0.95g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and methyl isocyanate (0.11g; 0.002 mol) in 1,2-dimethoxyethane (5.0 ml) were mixed and the mixture was stirred at room temperature for 1h then under reflux for 3h.

The mixture was then cooled and treated with a further portion of methyl isocyanate (0.33g; 0.006 mol) and heating under reflux continued for a further 1h.
The mixture was evaporated yielding a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with ethyl acetate-hexane (3:2) through to ethyl acetate-hexane (7:3) yielded only a series of intractable gums (total 0.28g) whose t.l.c. in ethyl acetate-hexane (7:3) over silica showed them to be multicomponent mixtures which were not further investigated.

Further elution with ethyl acetate-hexane (7:3) through to ethyl acetate-hexane (9:1) yielded triphenphosphine oxide (0.39g; 70%), m.p. 147-151°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane (9:1) afforded 3-(3-methoxyphenyl)-2-(N-methylammino)-3H-imidazo[4,5-b] pyridine (228) (0.38g, 75%) which formed colourless crystals, m.p. 148-149° (from hexane-toluene), v_max 3230 (NH)cm⁻¹, δ_H(CDCl₃) 7.97 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.74-6.94 (6H, m, ArH), 3.81 (3H, s, CH₃), 3.11 (3H, d, J5Hz, CH₃) and 2.23 (1H, bs, NH) (exch.).

Found: C, 65.9; H, 5.6; N, 22.0%; m/z (EI ms), 254 (M⁺)

C₁₄H₁₄N₄O requires: C, 66.1; H, 5.5; N, 22.1%; M, 254

Further elution with ethyl acetate-hexane (9:1) through ethyl acetate to methanol gave only a series of intractable gums which yielded no identifiable material.
N-Toluene-4-sulphonyl 3-methoxy aniline (233)

A solution of 3-methoxyaniline (219) (12.3g; 0.1 mol) and toluene-4-sulphonyl chloride (19.1g; 0.1 mol) in ethanol (500 ml) was treated with fused sodium acetate (9.0g; 0.11 mol) and the mixture heated under reflux for 1h.

The mixture was cooled and evaporated and the resulting residue treated with water (100 ml) and extracted with diethyl ether. The ether extract was washed with 2M aqueous hydrochloric acid (100 ml) then with water (100 ml) and evaporated yielding a pale yellow oil (26.5g). The oil was dissolved in 2M aqueous sodium hydroxide solution (55.0 ml) and the solution washed with methylene chloride then acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to afford the known\textsuperscript{81} N-Toluene-4-sulphonyl 3-methoxyaniline (233) (17.9; 65%) as a yellow oil, \( \nu_{\text{max}} \) 3260 (NH)cm\(^{-1}\), \( \delta_{\text{H}}\) (CDCl\(_3\)) 7.74-7.61 (5H, m, ArH), 6.96 (1H, brs, NH) (exch.), 6.71-6.52 (3H, m, ArH), 3.71 (3H, s, CH\(_3\)) and 2.35 (3H, s, CH\(_3\)).

**Found:** C, 60.5 ; H, 5.4; N, 5.2%; m/z (FAB ms), 278 [(M+H)+]

**Calc. for C\(_{14}\)H\(_{15}\)NO\(_3\)S:** C, 60.6; H, 5.4; N, 5.1%; M, 277

The Attempted Reaction of 2-Chloro-3-nitropyridine (108) with N-Toluene-4-sulphonyl 3-methoxyaniline (233)

A stirred suspension of sodium hydride (0.13g; 0.0055 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room
temperature with a solution of N-toluene-4-sulphonyl 3-methoxyaniline (233) (1:4g; 0.005 mol) in anhydrous dimethyl formamide (2.5 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of 2-chloro-3-nitropyridine (108), (0.80g; 0.005 mol) in anhydrous dimethylformide (5.0 ml) was added and the mixture was then stirred at 100° (oil bath) for 1h.

The mixture was cooled and treated with water (2.0 ml) and the mixture was stirred at room temperature for 15 min. Evaporation of the mixture yielded a brown oil which was treated with water (10.0 ml) and extracted with methylene chloride to give an oil (1.3g).

Trituration of the oil with diethyl ether yielded unreacted 2-chloro-3-nitropyridine (108) (0.22g; 28%) as a gummy solid identified by comparison (i.r. spectrum) with an authentic sample.

Evaporation of the ether washings yielded only a brown oil (0.95g) (whose t.l.c. in diethyl ether-hexane (1:1) over silica) showed it to be a complex mixture which was not further investigated.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with ethyl acetate to afford unreactable N-toluene-4-sulphonyl 3-methoxy aniline (233) identified by comparison (i.r. spectrum and t.l.c. in hexane-ethyl acetate (3:2) over silica) with an authentic sample.
The Attempted Reaction of 2-Chloro-3-nitropyridine (108) with N-
Toluene-4-sulphonyl 3-methoxyaniline (233)

A stirred suspension of sodium hydride (2.4g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) was treated at room temperature with a solution of N-toluene-4-sulphonyl 3-methoxyaniline (233) (2.8g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of 2-chloro-3-nitropyridine (108) (1.6g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) was then added and the mixture stirred at room temperature with exclusion of atmospheric moisture for 22h.

The mixture was cooled and treated with water (1.0 ml) and the mixture evaporated to yield a brown oil (4.7 g) which was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown gummy solid (1.7 g). Trituration of the solid with ethanol gave unreacted 2-chloro-3-nitropyridine (108) (0.42 g; 26%), m.p. 98-101° identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic washings gave only an intractable solid (1.1g) which yielded no identifiable material.

The aqueous mother liquor was acidified with 2M aqueous hydrochloric acid and extracted with methylene chloride to afford a red oil (1.2g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) yielded unreacted
**N-toluene-4-sulphonyl 3-methoxyaniline (233)** (1.1 g; 39%), identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with ethyl acetate-hexane through ethyl acetate to methanol gave only a series of multicomponent gums (total 0.28g) which yielded no identifiable material.

**The Attempted Reaction of 2-(3-Methoxyphenyl) amino-3-nitropyridine (220) with Toluene-4-sulphonyl chloride in diglyme**

A stirred suspension of sodium hydride (0.055g; 0.0023 mol) in anhydrous diglyme (2.5 ml) was treated at room temperature with a solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (0.49g; 0.002 mol) in diglyme (5.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15 min. A solution of toluene-4-sulphonyl chloride (0.38g; 0.002 mol) in anhydrous diglyme (2.5 ml) was added and the mixture was heated under reflux with exclusion of atmospheric moisture for 1h.

The mixture was cooled and treated with water (10.0 ml) and extracted with methylene chloride to afford a gummy solid (0.91 g). Trituration of the solid with diethyl ether gave unreacted 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (0.29g; 59%), m.p. 84-88°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.
Evaporation of the ether mother liquor gave a gummy red solid (0.31g) whose t.l.c. in ethyl acetate-hexane (2:3) over silica showed it to be impure starting material (220) which was not further investigated.

2-[N-(3-Methoxyphenyl), N-(toluene-4-sulphonyl)amino-3-nitropyridine (234)

(a) A stirred suspension of sodium hydride (0.055g; 0.0023 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room temperature with a solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (0.49g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of toluene-4-sulphonyl chloride (0.38g; 0.002 mol) in anhydrous dimethylformamide (2.5 ml) was then added and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 17h.

The mixture was diluted with water (2.0 ml) and stirred at room temperature for 15 min. Evaporation of the mixture yielded a brown oil which was treated with water (10.0 ml) and extracted with methylene chloride yielding a brown oil (1.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave unreacted 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (0.24g; 49%), m.p. 94-96°.
identified by comparison (m.p. and i.r. spectrum) an authentic sample prepared before.

Further elution with hexane-ethyl acetate (7:3) gave an intractable oil (0.061g) which yielded no identifiable material.

Further elution with hexane-ethyl acetate (7:3) afforded 2-[N-(3-methoxyphenyl) N(toluene-4-sulphonyl)amino-3-nitropyridine (234)] (0.26g; 33%) which formed colourless crystals m.p. 129-131° (from toluene-hexane), \( \nu_{\text{max}} \) 1535 and 1350 (NO\(_2\)) cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 8.62 (1H, dd, J\(\text{ortho} \) 5Hz and J\(\text{meta} \) 2Hz, ArH), 8.20 (1H, dd, J\(\text{ortho} \) 8Hz and J\(\text{meta} \) 2Hz, ArH), 7.61-6.77 (9H, m, ArH), 3.72 (3H, s, CH\(_3\)) and 2.40 (3H, s, CH\(_3\)).

**Found:** C, 57.5; H, 4.3; N, 10.4%; m/z (FAB ms), 400 [(M+H)+]

**C\(_{19}\)H\(_{17}\)N\(_3\)O\(_5\)S requires:** C, 57.2; H, 4.3; N, 10.5%; M, 399

Further elution with ethyl acetate-hexane through ethyl acetate to methanol yielded only a series of intractable gums (total 0.20g) which were not further investigated.

(b) The reaction described before in (a) before was repeated but with stirring of the mixture at 100° for 1h.

The mixture was cooled, diluted with water (2.0 ml) and stirred at room temperature for 15 min. Evaporation of the mixture yielded a brown oil which was treated with water (10.0 ml) and extracted with methylene chloride to give a brown oil (0.72g) whose t.l.c. in hexane-ethyl acetate (3:2) over silica showed the presence of unreacted starting material (220). The oil was redissolved in anhydrous dimethylformamide (5.0 ml) and the solution
was added to a stirred suspension of sodium hydride (0.036g; 0.0015 mol) in anhydrous dimethylformamide (2.5 ml). The mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15 min and then treated with a solution of toluene-4-sulphonyl chloride (0.28g; 0.0015 mol) in anhydrous dimethylformamide (2.5 ml) and the mixture stirred at 100° (oil bath) for 1h.

The mixture was cooled and diluted with water (2.0 ml) and the mixture stirred at room temperature for 15 min. Evaporation of the mixture yielded a brown gum which was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown oil (0.68g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) yielded unreacted 2-(3-methoxyphenylamino)-3 nitropyridine (220) (0.097g; 20%), m.p. 99-101°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ethyl acetate (4:1) yielded an intractable red oil (0.039g) which yielded no identifiable material.

Further elution with ethyl acetate-hexane (2:3) afforded 2-[N-(3-methoxyphenyl), N-toluene-4-sulphonyl]amino-3-nitropyridine (234) (0.21g; 27%), m.p. 111-114°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate through to methanol yielded only a series of brown gums (total 0.24g) which yielded no identifiable material.
N-Acetyl 3-methoxyaniline (229)

3-Methoxyaniline (219) (12.3g; 0.1 mol) was treated with glacial acetic acid (50.0 ml) and the mixture heated under reflux for 3h. The mixture was cooled and evaporated yielding a brown oil (17.1g) which was triturated with light petroleum (b.p. 40-60°) to afford the known N-acetyl 3-methoxyaniline (229) (16.0g; 97%) as a colourless solid, m.p. 79-81° (lit. 80, 81°)

Attempted Reactions of 2-Chloro-3-nitro pyridine (108) with N-Acetyl 3-Methoxyaniline (229)

(a) A stirred suspension of sodium hydride (0.24g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) was treated dropwise at room temperature with a solution of N-Acetyl 3-methoxyaniline (229) (1.7g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of 2-chloro-3-nitropyridine (108) (1.6g; 0.01 mol) in anhydrous dimethylformamide (5.0 ml) was added and the mixture stirred at room temperature for 16h.

Evaporation of the mixture under high vacuum gave an oil which was treated with water (10.0 ml) and extracted with methylene chloride (240 ml) to afford a dark brown oil (2.6g) whose t.l.c. in hexane-ethyl acetate (3:2) over silica showed it to be only a mixture of the two starting materials which therefore was not further investigated.
(b) Repetition of the reaction described in (a) but with stirring at 50° (oil bath) for 20h, gave a mixture which was cooled and evaporated under high vacuum yielding a brown oil which was treated with water (10.0 ml) and extracted with methylene chloride to afford a brown oil (3.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (2:1) yielded unreacted 2-chloro-3-nitropyridine (108) (0.52g; 32%), m.p. 91-96°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (3:2) yielded only a small amount of a multicomponent oil (0.08g) which was not further investigated.

Further elution with ethyl acetate-hexane (3:2) gave unreacted N-acetyl 3-methoxyaniline (229) (1.4g; 88%), m.p. 74-79°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Final elution with ethyl acetate-hexane (4:1) through ethyl acetate to methanol gave only a series of intractable gums (total 0.48g) which yielded no identifiable material.

**Attempted Acetylation Reactions of 2-(3-methoxyphenyl)amino-3-nitropyridine (220)**

(a) 2-(3-Methoxyphenyl)amino-3-nitropyridine (220) (1.2g; 0.005 mol) was treated with acetic anhydride (5.0 ml) and the mixture was heated under reflux for 3h.
The mixture was cooled and evaporated under high vacuum yielding a gummy red solid (1.2g) which was triturated with diethyl ether to afford the unreacted starting material (220) (0.90g; 75%), m.p. 92-94°, identified by comparison (m.p. and i.r. spectrum) to an authentic sample prepared before.

Evaporation of the ether mother liquor gave only a small amount of a gummy red solid (0.033g) which was not further investigated.

(b) 2-(3-Methoxyphenylamino)-3-nitro pyridine (220) (1.2g; 0.005 mol) was treated with acetic anhydride (10.0 ml) and concentrated sulphuric acid (0.1 ml) and the mixture was stirred at room temperature for 1h. Water (20.0 ml) was added and the mixture was then stirred at room temperature for a further 1h.

Filtration afforded the unreacted starting material (220) (1.1g; 91%) m.p. 98-101°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

(c) repetition of the reaction described in (a) but with stirring and heating at 100° (oil bath) for 1h followed by dilution with water (20.0 ml) and the mixture stirred at room temperature for a further 1h, gave after filtration the unreacted starting material (220) (0.66g; 55%), m.p. 81-85°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride afforded a brown oil (0.46g) whose t.l.c. in hexane-ethyl acetate (3:2) over
silica showed it to be a multicomponent mixture which was not further investigated.

(d) A stirred suspension of sodium hydride (0.14g; 0.0055 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room temperature with a solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (1.2g; 0.0055 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15 min. A solution of acetyl chloride (0.39g; 0.005 mol) in anhydrous dimethylformamide (2.5 ml) was added and the mixture was then stirred at room temperature with exclusion of atmospheric moisture for 17h.

The mixture was treated with water (20.0 ml) and filtered to afford the unreacted starting material (220) (0.80g; 67%) m.p. 86-89°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride gave an intractable oil which yielded no identifiable material.

2-[N-Acetyl, N-(3-methoxyphenyl)] amino-3-nitropyridine (230)

(a) 2-(3-methoxyphenylamino)-3-nitropyridine (220) (1.2g; 0.005 mol) was treated with acetic anhydride (10.0 ml) and concentrated sulphuric acid (0.1 ml) and the mixture was heated under reflux for 1h.

The mixture was then cooled and diluted with water (60.0 ml) then extracted with methylene chloride. The combined methylene chloride
extracts were washed with water (2 x 50.0 ml) and evaporated to give a brown oil (2.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (2:1) yielded 2-[N-acetyl, N-(3-methoxyphenyl)amino-3-nitropyridine (230) (0.61g; 43%) as a colourless solid, m.p. 104-106° (from hexane-ethyl acetate), v_{max} 1680 (CO) and 1520 and 1355 (NO2)cm\(^{-1}\), δ_H(CDCl_3) 8.60 (1H, dd, J_{ortho} 5Hz and J_{meta} 2Hz, ArH), 7.42-6.93 (6H, m, ArH), 3.83 (3H, s, CH_3) and 2.06 (3H, s, CH_3).

*Found:* C, 58.3; H, 4.5; N, 14.5%; m/z (EI ms), 287 (M^+)

C_{14}H_{13}N_3O_4 *requires:* C, 58.5; H, 4.5; N, 14.6%; M, 287

Further elution with hexane-ethyl acetate gave only a series of intractable oils (total 0.41 g) which were not further investigated.

(b) A solution of 2-(3-Methoxyphenylamino-3-nitropyridine (220) (0.98 g; 0.004 mol) in glacial acetic acid (5.0 ml) and the mixture was heated under reflux for 6h.

The mixture was cooled and evaporated under high vacuum yielding a gummy solid (1.0g) whose t.l.c. in hexane-ethyl acetate (3:2) over silica showed the presence unreacted starting material (220). The solid was redissolved in glacial acetic acid (5.0 ml) and the solution treated with acetyl chloride (7.5 ml) then the mixture was heated under reflux for 6h.

The mixture was cooled and evaporated under high vacuum yielding an oil (1.3g) which was flash-chromatographed over silica.
Elution with hexane-ethyl acetate (3:2) gave unreacted starting material (220) (0.24g; 25%), m.p. 93-95°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ethyl acetate (3:2) yielded 2-\[^{N-}\text{acetyl,}
\]
\[
\text{N-}(3\text{-methoxyphenyl})\text{amino-3-nitropyridine (230) (0.64g; 565), m.p. 103-104°, identical (m.p. and i.r. spectrum) to a sample prepared before.}
\]

Further elution with hexane ethyl acetate (3:2) through ethyl acetate to methanol gave only a series of intractable gums (total 0.14g) which yielded no identifiable material.

(c) A solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (7.4g; 0.03 mol) in glacial acetic acid (75.0 ml) was mixed with acetyl chloride (113 ml) and the mixture was heated under reflux for 6h.

The mixture was cooled and evaporated under high vacuum yielding a gummy solid (8.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:2) yielded an intractable red oil (0.11g) which was not further investigated.

Further elution with hexane ethyl acetate (3:2) gave the unreacted starting material (220) (3.9g; 53%), m.p. 96-100°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with hexane-ethyl acetate (3:2) gave a gum (0.32g) whose t.l.c. in hexane-ethyl acetate (3:2) showed it to be a complex mixture which therefore was not further investigated.

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Further elution with hexane-ethyl acetate (3:2) yielded 2-[N-acetyl, N-(3- methoxyphenyl)]amino-3-nitropyridine (230) (3.1g; 315), m.p. 90-98°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

Further elution with ethyl-acetate through to methanol yielded only a small amount of an intractable brown gum (0.064g) which was not further investigated.

**Attempted Reduction Reactions of 2-[N-Acetyl,N-2-(3-methoxyphenol)]amino-3-nitropyridine (230)**

(a) **Using Catalytic Hydrogenation**

A solution of 2-[N-acetyl,N-2-(3-methoxyphenol)]amino-3-nitropyridine (230) (0.29g; 0.001 mol) in ethanol (100 ml) was hydrogenated over 5% palladium-on-charcoal (0.029g) at room temperature and atmospheric pressure for 4h by which time the absorption of hydrogen had ceased.

The mixture was filtered through celite and the filtrate was evaporated to yield a brown oil (0.29g). This was dissolved in methylene chloride (5.0 ml) and the solution washed with 2M aqueous hydrochloric acid (7.5 ml) and evaporated to give an intractable gummy solid (0.051g) which yielded no identifiable material.
The acid aqueous mother liquor was neutralised with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to afford a brown gum (0.19g) which yielded no identifiable material.

(b) Using Stannous Chloride in Ethanol

A solution of 2-[N-acetyl, N-2-(3-methoxyphenol)]amino-3-nitropyridine (230) (0.57g; 0.002 mol) in ethanol (5.0 ml) was treated with stannous chloride (1.9g; 0.01 mol) and the mixture was stirred under an atmosphere of nitrogen at 70° (oil bath) for 30 min.

The mixture was cooled and poured onto ice (10.0g) and the resulting solution was made basic by the addition of 10% w/v aqueous sodium hydrogen carbonate solution (13.0 ml). The mixture was then extracted with ethyl acetate and the extract washed with brine (200 ml) and evaporated to give an oil (0.15g) whose t.l.c. in ethyl acetate-methanol (9:1) over silica showed it to be a multicomponent mixture which was not further investigated.

3-(3-Methoxyphenyl)-2-methyl-3H-imidazo[4,5-b]pyridine (232)

A solution of 2-[N-acetyl,N-2-3-methoxyphenol)]amino-3-nitropyridine (230) (0.57g; 0.002 mol) in 70% v/v aqueous ethanol was treated with sodium dithionite (0.57g) and the mixture heated under reflux for 1h. The mixture was then treated with a second portion of sodium dithionite (0.57g) and heating under reflux continued for a further 1h.
The mixture was cooled and evaporated yielding a yellow gum. This was treated with water (5.0 ml) and extracted with methylene chloride to afford a yellow oil (0.40 g) which was flash chromatographed over silica.

Elution with ethyl acetate yielded the imidazopyridine derivative (232) (0.25 g; 52%) which formed light brown crystals, m.p. 110-112° (from cyclohexane), $\nu_{\text{max}}$ 1616 (C=N) cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 8.34 (1 H, dd, Jortho 5 Hz and Jmeta 2 Hz, ArH), 8.01 (1 H, dd, Jortho 8 Hz and Jmeta 2 Hz, ArH), 7.57-6.89 (5 H, m, ArH), 3.82 (3 H, s, CH$_3$) and 2.58 (3 H, s, CH$_3$).

**Found:** m/z (EI ms), 239.1056 (M$^+$)

C$_{14}$H$_{13}$N$_3$O requires: M, 259 1059

Further elution with ethyl acetate methanol (9:1) through to methanol gave only intractable gums (total 0.01 g) which were not further investigated.

**N- Benzyl 3-Methoxyaniline (245)**

3-Methoxyaniline (219) (41.0 g; 0.33 mol), benzyl alcohol (45.0 g; 0.42 mol) and potassium hydroxide (3.0 g) were mixed and the mixture heated under reflux. Benzaldehyde (0.7 g; 0.0066 mol) diluted with benzyl alcohol (4.7 ml) was added to the boiling mixture in three portions, the first when the temperature had stabilised at 220° and the other two portions added at ten minute intervals thereafter. The mixture was then heated under reflux for 20 min.
The mixture was cooled and treated with water (80.0 ml) and extracted with diethyl ether. The ether extract was washed with water (300 ml) and evaporated yielding a dark brown oil (75.5 g). The oil was purified by distillation to afford the known[^2] **N-benzyl-3-methoxyaniline** (245) (47.1 g; 67%) as a pale orange oil, b.p. 168-202°/1.0 mm Hg, $v_{\text{max}}$ 3420 (NH) cm$^{-1}$.

**The Attempted Reaction of 2-Chloro-3-nitropyridine (108) with N-Benzyl-3-methoxyaniline (245)**

The mixture was cooled and the supernatant liquor was decanted from a small amount of brown residue and evaporated under high vacuum yielding a red oil (5.5 g) which was flash-chromatographed over silica.

Elution with hexane-diethyl ether (2:1) gave unreacted N-benzyl-3-methoxyaniline (245) as an orange oil (2.8 g; 66%), identified by comparison (i.r. spectrum and t.l.c. in diethyl ether-hexane (1:1) over silica) with an authentic sample.

Further elution with hexane-diethyl ether (2:1) yielded a red gummy solid (2.1 g) which was triturated with diethyl ether to give unreacted 2-chloro-3-nitropyridine (108) (0.56 g; 35%), m.p. 79-83°, identified by comparison (m.p. and i.r. spectrum), with an authentic sample. Evaporation of the ether washings gave a red oil (0.97 g) which yielded no identifiable material.
Further elution with diethyl ether hexane through ether and ethyl acetate to methanol only gave a series of intractable tars (total 0.46g) which were not further investigated.

**The Attempted Benzylation of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) with Benzyl Chloride.**

A stirred suspension of sodium hydride (0.14g; 0.0055 mol) in anhydrous dimethyl formamide (2.5 ml) was treated dropwise at room temperature with a solution of 2-(3-methoxyphenyl)amino-3-nitropyridine (220) (1.2g; 0.005 mol) in anhydrous dimethylformamide (10.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of benzyl chloride (0.63g; 0.005 ml) in anhydrous dimethylformamide (2.5 ml) was added in one portion and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 17h.

The mixture was diluted with water (20.0 ml) and extracted with methylene chloride to give a red oil (1.9g) which was triturated with methanol to yield unreacted starting material (220) (0.95g; 79%), m.p. 89-94° identified by comparison (m.p., i.r. spectrum and t.l.c. in hexane acetate (2:3) over silica) with an authentic sample.

Evaporation of the methanol washings yielded a red oil (0.96g) whose t.l.c. in hexane-ethyl acetate (3:2) over silica showed it to be a
mixture containing mainly unreacted starting material. The oil was not further investigated.

2-[N-Benzyl,N-(3-methoxyphenyl)]amino 3-nitropyridine (246)

A stirred suspension of sodium hydride (0.0559 g; 0.0023 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room temperature with a solution of 2-[N-Benzyl, N-(3-methoxyphenyl)]amino 3-nitropyridine (220) (0.49 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of benzyl bromide (0.34 g; 0.002 mol) in anhydrous dimethylformamide (2.5 ml) was added in one portion and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 17 h.

Water (2.0 ml) was added and the mixture was stirred at room temperature for 15 min. The mixture was evaporated and the residue was treated with water (10.0 ml) and extracted with methylene chloride to afford 2-[N-Benzyl,N-(3-methoxyphenyl)]amino 3-nitropyridine (246) (0.64 g, 96%) which formed yellow crystals, mp. 117-118° (from methanol), ν_max 1510 and 1380 (NO_2) cm⁻¹, δ_H (CDCl_3) 8.40 (1H, dd, Jortho 5 Hz and Jmeta 2 Hz, ArH), 7.99 (1H, dd, Jortho 8 Hz, ArH), 7.45-7.10 (6H, m, ArH), 6.86 (1H, dd, Jortho 8 Hz and Jortho 5 Hz, ArH), 6.64-6.56 (3H, m, ArH), 5.41 (2H, s, CH_2) and 3.70 (3H, s, CH_3).

Found: C, 68.8, H, 5.2; N, 12.6%; m/z (EI ms), 335.1270 (M⁺)
$C_{19}H_{17}N_3O_3$ requires: C, 68.1; H, 5.1; N, 12.5%; M, 335.1270

2-[N-(3-Methoxyphenyl),N-methyl]amino-3-nitropyridine (235)

A stirred suspension of sodium hydride (1.1g; 0.044 mol) in anhydrous dimethylformamide (20.0 ml) was treated dropwise at room temperature with a solution of 2-(3-methoxyphenylamino)-3-nitropyridine (220) (9.8g; 0.04 mol) in anhydrous dimethylformamide (80.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15 min. A solution of iodomethane (5.7g; 0.04 mol) in anhydrous dimethylformamide (20.0 ml) was added in one portion and the mixture stirred at room temperature with the exclusion of atmospheric moisture for 17h.

The mixture was treated with water (10.0 ml) and the mixture stirred at room temperature for 15 min. The mixture was evaporated, and the residue was treated with water (100 ml) and extracted with methylene chloride to give a dark brown oil (11.3g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a red oil (8.5g) which was purified by Kugelrohr distillation to afford 2-[N-(3-methoxyphenyl),N-methyl]amino-3-nitropyridine (235) (7.1g; 68%) as a red oil, b.p. 140-150°/0.03 min Hg, $\nu$ max 1520 and 1340 (NO$_2$)cm$^{-1}$, 8H 8.48 (1H, dd, Jortho 5Hz, Jmeta Hz, ArH), 7.95 (1H, dd, Jortho 8Hz, Jmeta Hz, ArH), 7.28-6.53 (5H, m, ArH), 3.73 (3H, s, CH$_3$) and 3.58 (3H, s, CH$_3$)
**Found**: C, 60.4; H, 5.1; N 16.1%; m/z (EI ms), 259 (M⁺)

**C₁₃H₁₃N₃O₃ requires**: C, 60.2; H, 5.0; N, 16.2%; M, 259

Further elution through ethyl acetate to methanol-ammonia (9:1) gave only a series of intractable gums (total 1.0g) which were not further investigated.

**Attempted Reduction Reactions of 2-[N-Benzyl, N -(3-methoxyphenyl)] amino-3-nitropyridine (235)**

(a) **Using Sodium Dithionite in Acetic Acid**

A solution of the nitropyridine derivative (246) (0.67g; 0.002 mol) in glacial acetic (10.0 ml) was treated with sodium dithionite (0.67g) and the mixture was heated under reflux for 1h. The mixture was then treated with a second portion of sodium dithionite (0.67g) and heating under reflux continued for a further 1h.

The mixture was rotary evaporated under high vacuum to give a yellow gum which was treated with water (5.0 ml) and extracted with methylene chloride to yield a dark brown oil (0.71g) whose t.l.c. in ethyl acetate-hexane (1:1) over silica showed it to be a multicomponent mixture. The oil was dissolved in methylene chloride (10.0 ml) and the solution was washed with 2M aqueous hydrochloric acid (5.0 ml) and evaporated giving an intractable gum (0.59g) which yielded no identifiable material.
The acidic aqueous mother liquor was basified with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to give a brown gum (0.011g) which also yielded no identifiable material.

(b) **Using Titanium Trichloride in Aqueous Hydrochloric Acid**

(i) A solution of the nitopyridine derivative (246) (0.67g; 0.002 mol) in 1,2-dimethoxyethane (10.0 ml) was stirred under nitrogen and treated dropwise at room temperature with a 15% w/w solution of titanium trichloride in aqueous hydrochloric acid (6.9 ml; 1.2g; 0.008 mol). The mixture was then stirred at room temperature for 1h.

The mixture was concentrated under reduced pressure and the residue was neutralised with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride to afford a dark brown oil (0.64g) which was flash-chromatographed over silica.

Elution with hexane ethyl acetate (7:3) yielded the unreacted starting material (246) (0.29g; 435) as a red oil, identified by comparison (i.r. spectra and t.l.c. in hexane-ethyl acetate (1:1)) with an authentic sample.

Further elution with ethyl acetate-hexane (3:2) through ethyl acetate to methanol gave only a series of intractable gums (total 0.24g) whose i.r. spectrum showed the presence of the amine (247) by comparison with a sample prepared before. The gums were not further investigated.

(ii) The procedure described in (i) was repeated except using 15% w/w titanium trichloride in aqueous hydrochloric acid (20.0 ml; 3.5g; 0.023 mol).
The mixture was filtered to yield the unreacted starting material (246) (0.025g; 4%), m.p. 113-116°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Evaporation of the filtrate under high vacuum gave only a gum (0.47g) whose t.l.c. in hexane-ethyl acetate (1:1) over silica showed it to be a multicomponent mixture which was not further investigated.

3-Amino-2-[N-benzyl, N-(3-methoxyphenyl)]aminopyridine (247)

A solution of the nitropyridine derivative (246) (28.5g, 0.085 mol) in tetrahydrofuran (400 ml) was hydrogenated over 10% palladium-on-charcoal (2.8g) at room temperature and atmospheric pressure for 4h by which time the absorption of hydrogen had ceased.

The mixture was filtered through celite and filtrate was evaporated to yield a brown gum (25.9g) which was triturated with diethyl ether to afford 3-amino-2-[N-benzyl, N-(3-methoxyphenyl)] aminopyridine (247) (16.5g;64%) as a colourless solid, m.p. 84-85° (from ethyl acetate-hexane), $v_{\text{max}}$ 3419, 3272 and 3151 (NH$_2$)cm$^{-1}$, $\delta_{\text{H}}$(CDCl$_3$) 7.94 (1H, dd, $J_{\text{ortho}}$ 5Hz and $J_{\text{meta}}$ 2Hz, ArH), 7.41-6.92 (8H, m, ArH), 6.45-6.29 (3H, m, ArH), 5.17 (2H, s, CH$_2$), 3.68 (3H, s, CH$_3$) and 3.66 (2H, bs, NH$_2$).

Found: C, 74.7; H, 6.3; N, 13.8%; m/z (EI ms), 305 (M$^+$)

C$_{19}$H$_{19}$N$_3$O requires: C, 74.5; H, 6.2; N, 13.6%; M, 305

Evaporation of the diethyl ether mother liquor gave an intractable brown oil (7.8g) which yielded no identifiable material.
3-Amino-2-[N-(3-Methoxyphenyl), N-methyl] aminopyridine (236)

A solution of 2-[N-(3-methoxyphenyl),N-methyl]amino-3-nitopyridine (235) (1.3g, 0.005 mol) in ethanol (20.0 ml) was hydrogenated over 5% palladium-on-charcoal (0.13g) at room temperature and atmospheric pressure for 6h by which time the absorption of hydrogen had ceased.

The mixture was filtered through celite and the filtrate was evaporated to afford 3-amino-2-[N-(3-methoxyphenyl), N-methyl] aminopyridine (236) (1.2g, 100%) as a grey solid, m.p. 76-77° (from ethyl acetate-hexane), $\nu_{\text{max}}$ 3380, 3280 and 3160 (NH) cm$^{-1}$, $\delta_H$(CDCl$_3$) 7.94 (1H, dd, Jortho 41 Hz and Jmeta 3Hz, ArH), 7.24-6.95 (3H, m, ArH), 6.49-6.28 (3H, m, ArH), 3.73 (3H, s, CH$_3$), 3.34 (3H, s, CH$_3$) and 3.55-2.90 (2H, bs, NH$_2$) (exch.).

**Found**: C, 68.6; H, 6.8; N, 18.5%; m/z (EI ms), 229.1211 (M$^+$)

$\text{C}_{13}\text{H}_{15}\text{N}_3\text{O}$ requires: C, 68.1; H, 6.5; N, 18.3%; M, 229.1215

9-Methoxy-11-methyl-11H-pyrido[2,3-c][1,2,5]benzotriazepine (243)

A solution of the amine (236) (0.92g, 0.004 mol) in 5M aqueous hydrochloric acid (2.2 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (0.30g, 0.0044 mol) in water (1.0 ml) at 0-5°. After stirring at 0-5° for 15 min the diazonium solution was treated with a solution of sodium acetate (1.6g, 0.02 mol) in water (20 ml) at 0-5°. The diazonium solution was then treated with a solution of sodium acetate (1.6g, 0.02 mol) in water (20 ml) at 0-5°. The diazonium solution was then treated with a solution of sodium acetate (1.6g, 0.02 mol) in water (20 ml) at 0-5°.
water (2.0 ml) and the mixture was then stirred in the melting ice-bath for 2h.

Filtration of the mixture gave an orange solid (0.88g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (2:1) afforded **9-methoxy-11-methyl-11H-pyrido[2,3-c][1,2,5]benzotriazepine (243)** (0.8g, 73%), which formed orange needles, m.p. 103-105° (from hexane-toluene), δ_H(CDCl_3) 8.11 (1H, dd, Jortho 5Hz, Jmeta 2Hz, ArH), 7.79 (1H, dd, Jortho 8Hz, Jmeta 2Hz, ArH), 7.50 (1H, d, Jortho 9Hz, ArH), 7.02 (1H, dd, Jortho 8Hz, Jmeta 5Hz, ArH), 6.61 (1H, dd, Jortho 9Hz, Jmeta 3Hz, ArH), 6.28 (1H, d, Jmeta 3Hz, ArH), 3.79 (3H, s, CH_3), and 3.13 (3H, s, CH_3), δ_c (CDCl_3) 162.8 (quat.), 154.8 (quat.), 148.7 (CH), 147.3 (quat.), 139.7 (quat.), 138.7 (CH), 133.4 (CH), 119.5 (CH), 108.1 (CH), 104.7 (CH), 55.4 (CH_3), and 34.4 (CH_3).

**Found:** C, 65.0; H, 5.0; N, 23.5%; m/z (EI ms), 240 (M^+)  

**C_{13}H_{12}N_4O** requires: C, 65.0; H, 5.0; N, 23.3%; M, 240

Further elution with hexane-ethyl acetate (2:1) through ethyl acetate to methanol gave only small amounts of gums which were not further investigated.
The Attempted Photolysis of 9-Methoxy-11-methyl-11-H-pyrido[2,3-c]
[1,2,5]benzo triazepine (243)

A solution of the triazepine derivative (243) (0.48g, 0.002 mol) in toluene (150 ml) was irradiated with mercury lamp (125W) for 28h. After this time the t.l.c. of the reaction solution in ethyl acetate-hexane (1:1) over silica showed only the presence of the unreacted starting material (243). The solution was then further irradiated with a mercury lamp (440W) for 10h.

The mixture was evaporated to give the unreacted starting material (243) (0.44g, 92%) as a red gum, identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample prepared before.

2-[N-Alkyl,N-(3-methoxyphenyl)]amino-3-azidopyridines

A suspension or solution of the corresponding aminopyridine derivative (0.02 mol) in 5M aqueous hydrochloric acid (50.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (1.5g, 0.022 mol) in water (10.0 ml) at 0-5°. After stirring at 0-5° for 30 min the resulting diazonium solution was treated dropwise with stirring with a solution of sodium azide (1.9g, 0.03 mol) in water (10.0 mol) at 0-5° and the mixture was stirred in the melting ice bath for 0.5h then worked up as described for the individual reactions below.
(i) The mixture from 3-amino-2-[N-benzyl,N-(3-methoxyphenyl)]
amino pyridine (247) was made basic by the addition of 2M aqueous sodium
hydroxide solution and extracted with methylene chloride to afford a brown
oil (6.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) yielded 3-azido-2-[N-
benzyl,N-(3-methoxyphenyl)]aminopyridine (248) (5.2g, 79%)
as a brown oil, \( \nu_{\text{max}} \) 2100 (N\(_3\)) cm\(^{-1}\), \( \delta_H (\text{CDCl}_3) \) 8.18 (1H, dd, Jorth 5Hz and
Jmeta 2Hz, ArH) 7.48-6.92 (8H, m, ArH), 6.56-6.34 (3H, m, ArH), 5.19 (2H,
s, CH\(_2\)) and 3.69 (3H, s, CH\(_3\)).

\textbf{Found:} m/z (EI ms), 331.1434 (M\(^+\))

\textbf{C}_{19}H_{17}N_5O \textbf{requires:} M, 331.1433

(ii) The mixture from 3-amino-2-[N-(3-methoxypenyl),N-methyl]
amino pyridine (236) was basified by the addition of 2M aqueous sodium
hydroxide solution and extracted with methylene chloride to give a dark
brown oil (2.6g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (3:1) yielded 3-azido-2-[N-(3-
methoxyphenyl),N-methyl]aminopyridine (241) (1.7g, 67%) as a brown
oil, \( \nu_{\text{max}} \) 2110 (N\(_3\)) cm\(^{-1}\), \( \delta_H \) 8.20 (1H, dd; Jorth 5Hz and Jmeta 2Hz, ArH),
7.39-6.93 (3H, m, ArH), 6.58-6.36 (3H, m, ArH), 3.74 (3H, s, CH\(_3\)) and 3.37
(3H, s, CH\(_3\)).

\textbf{Found:} C, 59.5; H, 4.9; N, 26.0%; m/z (EI ms), 227 (M\(^+\)-N\(_2\))

\textbf{C}_{13}H_{13}N_5O \textbf{requires:} C, 61.2; H, 5.1; N, 27.5%; M, 255
Further elution with hexane-ethyl acetate (3:1) through ethyl acetate to methanol gave only intractable oils (total 0.68g) which were not further investigated.

**N-{2-[N-alkyl,N-(3-methoxyphenyl)]aminopyrid-3-yl}\trimethoxyphosphinimines**

Solutions of the corresponding azide (0.015 mol) in anhydrous 1,2-dimethoxyethane (75.0 ml) and trimethyl phosphite (2.4g, 0.019 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) were mixed and the mixture stirred at room temperature for 4h then worked up as described for individual reactions below.

(i) The mixture from 3-azido-2-[N-benzyl,N-(3-methoxyphenyl)]aminopyridine (248) was rotary evaporated under high vacuum, with removal of the excess of trimethyl phosphite as an azeotrope with toluene yielding **N-2-[N-benzyl,N-(3-methoxyphenyl)]aminopyrid-3-yl\trimethoxyphosphinimine (249)** (6.3g, 98%) as a brown oil, $\delta_H$(CDCl$_3$)

7.92 (1H, dd, Jmeta 2Hz and Jmeta 1Hz, ArH), 7.87-6.78 (8H, m, ArH), 6.38-6.18 (3H, m, ArH), 5.26 (2H, s, CH$_2$), 3.61 (3H, s, CH$_3$) and 3.50 (9H, d, J11Hz, 3xCH$_3$).

**Found**: m/z (El ms), 427.1651 (M$^+$)

C$_{22}$H$_{26}$N$_3$O$_4$P requires: M, 427.1661

(ii) The mixture from 3-azido-2-[N-methyl,N-(3-methoxyphenyl)]aminopyridine (241) was rotary evaporated under high
vacuum with removal of the excess of trimethyl phosphite as an azeotrope with toluene yielding \textbf{N-2-\{N-3-methoxyphenyl, N-methyl\}aminopyrid-3-yl}trimethoxyphosphinimine (242) (2.1g, 89\%) as a dark brown oil, \\ \(\delta_H^{}(\text{CDCl}_3)\) 7.91 (1H, dd, J\text{ortho} 5\text{Hz} and J\text{meta} 2\text{Hz}, \text{ArH}), 7.25-6.87 (3H, m, ArH), 6.37-6.24 (3H, m, ArH) 3.66 (3H, s, CH\text{3}), 3.47 (9H, d, J11Hz, 3xCH\text{3}) and 3.37 (3H, s, CH\text{3}). \\ \textbf{Found:} \ m/z \ (Ei \ ms), 351.1346 (M+) \\ \textbf{C}_{16}\text{H}_{22}\text{N}_{3}\text{O}_{4} \textbf{requires:} \ M, 351.1348 \\

\textbf{N-2-\{N-(3-Methoxyphenyl), N-methyl\}aminopyrid-3-yl}triphenylphosphinimine (237) \\ 
A solution of the amine (236) (2.3g, 0.01 mol) in anhydrous acetonitrile (200 ml) was stirred under nitrogen and treated at room temperature with triphenylphosphine (5.8g, 0.022 mol) followed by triethylamine (4.1g, 0.04 mol) then hexachloroethane (4.8g, 0.02 mol) and the mixture heated under reflux in an atmosphere of nitrogen for 18h.

The mixture was cooled and filtered to yield triethylamine hydrochloride (2.6g), m.p. 255-259\textdegree, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The filtrate was evaporated and the residue was treated with water (50.0 ml) and extracted with ethyl acetate to give a dark brown oil (8.1g) which was flash-chromatographed over silica.
Elution with hexane-ethyl acetate (9:1) gave triphenyl phosphine (0.42g), m.p. 75-78°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with hexane-ethyl acetate (3:2) gave unreacted starting material (236) (0.22g, 10%) as a light brown oil, identical by comparison (i.r. spectrum) with an authentic sample.

Further elution hexane-ethyl acetate (1:1) yielded N-{2-[N-(3-methoxyphenyl),N-methyl]aminopyrid-3-yl}triphenylphosphinimine (237) (4.0g, 82%) which formed colourless crystals, m.p. 139-141° (from toluene-hexane), δ\textsubscript{H} 7.82-7.77 (1H, dd, J\textsubscript{ortho} 4Hz and J\textsubscript{meta} 2Hz, ArH) 7.58-6.22 (21H, m, ArH), 3.63 (3H, 3, CH\textsubscript{3}) and 3.44 (3H, s, CH\textsubscript{3}).

**Found:** C, 76.5; H, 5.6; N, 8.5%; m/z (EI ms) 489.1965 (M\textsuperscript{+})

**C\textsubscript{31}H\textsubscript{28}N\textsubscript{3}OP requires:** C, 76.1; H, 5.7; N, 8.6%; (M+H), 489.1970

Further elution with ethyl acetate through to methanol gave triphenyl phosphine oxide (2.3g) as a pale yellow solid, m.p. 144-149°, identical (m.p. and i.r. spectrum) to an authentic sample.

1-{2-[N-Benzyl, N-(3-methoxyphenyl)] amino pyrid-3-yl]-3-phenylcarbodiimide (250)

Solutions of the phosphinimine (249) (5.9g, 0.014 mol) in anhydrous 1,2-dimethoxyethane (70.0 mol) and phenyl isocyanate (1.7g, 0.014 mol) in anhydrous 1,2-dimethoxyethane (35.0 ml) were mixed and the

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mixture was stirred at room temperature for 4h. Evaporation of the mixture gave a brown oil which was dissolved in diethyl ether (70.0 ml) and the solution washed with water (70.0 ml) and evaporated to afford 1-(2-[N-benzyl,N-(3-methoxyphenyl)aminopyrid-3-yl]-3-phenylcarbodiimide (250) (5.4g, 95%) as a brown oil, $v_{\text{max}}$ 2120 (N=C=N)cm$^{-1}$, $\delta_H$(CDCl$_3$) 8.24 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.55-6.72 (14H, m, ArH), 6.45-6.29 (2H, m, ArH), 5.22 (2H, s, CH$_3$) and 3.57 (3H, s, CH$_3$).

**Found:** C, 76.4; H, 5.7; N, 13.1%; m/z (EI ms), 406.1795 (M+)

C$_{26}$H$_{22}$N$_4$O requires: C, 76.8; H, 5.4; N, 13.8%; M, 406.1794

1-(2-[N-(3-methoxyphenyl), N-methyl]amino pyrid-3-yl]-3-phenylcarbodiimide (238)

(a) A solution of the phosphinimine (242) (1.7g, 0.005 mol) in anhydrous 1,2-dimethoxyethane (25.0 ml) was treated with a solution of phenyl isocyanate (0.59g, 0.005 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 17h.

The mixture was evaporated to give a brown oil which was dissolved in methylene chloride (20.0 ml) and the solution washed with water (20.0 ml) and evaporated to yield 1-(2-[N-(3-methoxyphenyl), N-methyl]aminopyrid-3-yl]-3-phenylcarbodiimide (238) (1.8g, 100%), $v_{\text{max}}$ 2140 (N=C=N)cm$^{-1}$, $\delta_H$(CDCl$_3$), 7.47-6.26 (12H, m, ArH), 3.64 (3H, s, CH$_3$), and 3.35 (3H, s, CH$_3$), which could not be purified for combustion.
and mass spectral analysis and was therefore used without further purification.

(b) A solution of the phosphinimine (237) (0.98g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with a solution of phenyl isocyanate (0.24g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) and the mixture was stirred at room temperature for 4h.

The mixture was evaporated to give an oily solid (1.4g) which was triturated with anhydrous diethyl ether to yield triphenylphosphinimine oxide (0.33g, 59%), m.p. 154-156°, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ether mother liquor gave 1-[2-N-(3-methoxyphenyl)N-methylaminopyrid-3-yl]-3-phenyl carbodiimide (238) as a brown oil (0.92g, 100%), identified by comparison (i.r spectrum) with a sample prepared in (a) before.

The Attempted Reaction Of 1-[2-N-(3-methoxyphenyl)N-methyl)aminopyrid-3-yl]-3-phenyl carbodiimide (238) with Aqueous Sodium Hydroxide

A solution of the carbodiimide (238) (0.92g) in 1, 4 dioxane (15.0 ml) was treated with 2M aqueous sodium hydroxide solution (2.5 ml) and the mixture was stirred at room temperature for 1h.

The mixture was rotary evaporated under high vacuum to give a gum which was treated with water (10.0 ml) and extracted with methylene
chloride to afford an intractable gum (0.88g) whose t.l.c. in ethyl acetate-
hexane (1:1) over silica showed it to be a multicomponent mixture which
was not further investigated.

The Attempted Stannic Chloride Catalysed Ring Closure Of 1-{2-[N-
Benzy1,N-(3-methoxyphenyl)amino]pyrid-3-yl}-3-phenylcarbodiimide
(250)

A solution of the carbodiimide (250) (4.9g, 0.012 mol) in anhydrous
1,2 dichloroethane (60.0 ml) was cooled to 0° (ice-salt bath) and treated
dropwise with a solution of stannic chloride (15.6g, 0.06 mol) in anhydrous
1,2 dichloroethane (30.0 ml) and the mixture was then heated under reflux
for 24h.

The mixture was cooled to 0° (ice-salt bath) and treated dropwise
with 15M aqueous sodium hydroxide solution (41.0 ml, 0.62 mol) and then
allowed to warm to room temperature while stirring over 1h. Water
(120 ml) was added and the mixture was extracted with methylene chloride
to afford a gum (4.9g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (4:1) gave a series of intractable
gums total (0.31g) which were not further investigated.

Further elution with hexane-ethyl acetate (4:1) yielded 1-{2-[N-
benzy1,N-(3-methoxyphenyl)amino]pyrid-3-yl}-3-phenylurea (251) (1.8g,
35%) as a yellow gum, \( v_{\text{max}} \) 3380 and 3360 (NH) and 1730 (CO)cm\(^{-1}\).
δ_H(CDCl₃) 7.99-7.91 (1H, m, ArH) 7.66-6.43 (16H, m, ArH), 5.12 (1H, brs, CH₂), 4.98 (1H, brs, CH₂) and 3.71 (3H, s, CH₃).

**Found:** C, 73.7; H, 5.8; N, 13.5%; m/z (EI ms), 424 (M⁺)

**C₂₆H₂₄N₄O₂ requires:** C, 73.6; H, 5.7; N, 13.2%; M, 424

Further elution with hexane-ethyl acetate (4:1) through to methanol gave only a series of intractable gums (total 1.7g) which yielded no identifiable material.

**9-Methoxy-11-methyl-11H-pyrido[2,3-b][1,4] benzodiazepine (240)**

(a) A solution of the carbodiimide (238) (0.87g, 0.002 mol) in anhydrous methylene chloride (10.0 ml) was stirred and treated dropwise at 0-5° (ice bath) with exclusion of atmospheric moisture with a solution of stannic chloride (2.6g, 0.01 mol) in anhydrous methylene chloride (5.0 ml). The mixture was then heated under reflux for 24h.

The mixture was cooled and treated dropwise with stirring, with 15M aqueous sodium hydroxide solution (6.8 ml, 0.1 mol) and then stirred for 15 min. Water (20.0 ml) was added and the mixture extracted with methylene chloride to give a yellow gum (0.79g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) yielded the **diazepine derivative (240)** (0.39g, 59%) as a pale yellow solid, m.p. 141-143° (from toluene-hexane), νₘₐₓ 3390 (NH) and 1630 (N=C) cm⁻¹, δ_H(CDCl₃), 7.95 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH), 7.73-7.61 (2H, m, ArH), 7.46-
6.85 (6H, m, ArH), 6.66-6.51 (2H, m, ArH), 3.80 (3H, s, CH₃), and 3.29 (3H, s, CH₃). δc (CDCl₃) 162.9 (quat.), 156.8 (quat.), 156.4 (quat.), 133.6 (CH), 128.6 (CH), 128.1 (CH), 122.8 (CH), 120.1 (CH), 119.8 (CH), 119.6 (quat), 108.3 (CH), 104.4 (CH), 55.3 (CH₂) and 35.7 (CH₃).

**Found:** m/z (FAB ms), 331.1559 [M+H⁺]

**C₂₀H₁₈N₄O requires:** (M+H), 331.1559

Further elution with hexane-ethyl acetate (7:3) through ethyl acetate to methanol gave only a series of intractable gums (total 0.48g) which yielded no further identifiable material.

(b) A solution of carbodiimide (238) (1.6g; 0.005 mol) in anhydrous 1,2-dichloroethane (250 ml) was stirred and treated dropwise at room temperature with exclusion of atmospheric moisture with a solution of stannic chloride (6.5g; 0.025 mol) in anhydrous 1,2-dichloroethane (12.0 ml) and the mixture then heated under reflux for 24h.

The mixture was cooled (ice bath) and treated dropwise with stirring, with 15M aqueous sodium hydroxide solution (17.0 ml; 0.26 mol) and stirred for 15 min, water (50.0 ml) was added and the mixture extracted with methylene chloride to give a brown oil (1.7g) which was flash-chromatographed over silica.

Further elution with hexane-ethyl acetate (4:1) gave only a series of intractable gums (total 0.076g) which were not further investigated.

Further elution with hexane-ethyl acetate (7:3) yielded **9-methoxy-11-methyl-11H-pyrido[2,3-b][1,4]benzodiazepine (240)** (0.90g; 54%),
m.p. 128-134°, identified by comparison (m.p. and i.r. spectrum) with a sample obtained in (a) before.

Further elution with ethyl acetate through to methanol yielded only a series of intractable oils (total 0.45g) which were not further investigated.

The Attempted Reaction of N-{2-\(N\)-(3-methoxyphenyl)aminolpyrid-3-yl}triphenylphosphinimine (233) with Carbon Dioxide

A solution of phosphinimine (223) (0.93g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was stirred and treated with a stream of carbon dioxide at room temperature for 1h and then under reflux for 5h.

The mixture was cooled and evaporated to afford the unreacted starting material (223) (0.91g; 98%), m.p. 109-115°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

The Attempted Reaction of 2-Chloronicotinic Acid (167) with N-Benzyl-3-methoxy aniline (245)

2-Chloronicotinic acid (167) (0.79g; 0.005 mol) and N-benzyl-3-methoxy aniline (245) (2.1g, 0.01 mol) were dissolved in 1,2-dimethoxyethane (15.0 ml) and the mixture was heated at 140° (oil bath) for 3h.

The mixture was cooled and rotary evaporated under high vacuum yielding a red oil (4.1g) which was triturated with methylene chloride to give
unreacted 2-chloronicotinic acid (167) (0.49; 62%), m.p. >185 ° (decomp), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Evaporation of the methylene chloride mother liquor gave a red oil (2.6g) which was redissolved in methylene chloride (10.0 ml) and the solution washed with 10% w/v aqueous sodium hydrogen carbonate solution (15.0 ml) and evaporated yielding unreacted N-benzyl-3-methoxy aniline (245) (1.7g; 80%), identified by comparison (i.r. spectrum) with an authentic sample.

The aqueous sodium hydrogen carbonate washings were neutralised by the addition of glacial acetic acid and extracted with methylene chloride to afford only a negligible amount of a brown oil (0.092g) which was not further investigated.

2-(3-Methoxyphenyl)aminopyridine-3-carboxylic Acid (265)

2-Chloronicotinic acid (167) (15.7g, 0.1 mol) and 3-methoxyaniline (219) (24.6g; 0.2 mol) were dissolved in diethylene glycol dimethyl ether (125 ml) and the mixture as heated at 140° (oil bath) for 3h.

The mixture was cooled and rotary evaporated under high vacuum yielding a dark brown oil (58.1g) the oil was treated with 2M aqueous sodium hydroxide solution (110 ml) and extracted with methylene chloride yielding a brown foam (26.3g). Trituration of the foam with diethyl ether afforded 2-(3-methoxyphenyl)aminopyridine-3-carboxylic acid (265) (22.2g; 91%) as a colourless solid, m.p. 160-162° (from toluene). $\nu_{\text{max}}$ 3280
(NH) 3100-2200br (OH) and 1675 (CO) cm\(^{-1}\), \(\delta_{H}(\text{CDCl}_3)\) 8.42-8.21 (2H, m, ArH), 7.43-7.41 (1H, m, ArH) 7.24-7.17 (2H, m, ArH), 6.81-6.54 (2H, m, ArH) 4.59 (1H, s, NH) (exch, ) and 3.81 (3H, s, CH\(_3\)).

**Found:** C, 63.8; H, 4.9; N, 11.3%; m/z (EI ms) 244 (M\(^{+}\))

\(\text{C}_{13}\text{H}_{12}\text{N}_{2}\text{O}_{3}\) requires C, 63.9; H, 4.9; N, 11.5%; M, 244

Evaporation of the ether mother liquor yielded a second crop of impure product (274) (1.4g; 6%) as a yellow solid, m.p. 125-134\(^\circ\), identified by comparison (m.p. and i.r. spectrum) with an authentic sample obtained before.

**Methyl 2-(3-methoxyphenyl)aminopyridine-3-carboxylate (267)**

A stirred suspension of 2-(3-methoxyphenyl)aminopyridine-3-carboxylic acid (265) (12.2g; 0.05 mol) in methanol was cooled to 0\(^\circ\) (ice-salt bath) and treated with a slow steam of hydrogen chloride until the solution was saturated. The mixture was then heated under reflux for 4h.

The mixture was cooled and rotary evaporated yielding a brown oil (29.9g) which was treated with 10% w/v aqueous sodium hydrogen carbonate solution (200 ml) and extracted with ethyl acetate yielding an oil (13.4g). The oil was triturated with diethyl ether to give the hydrochloride of the starting material (274) (3.4g, 23%) m.p.130-133\(^\circ\) (decomp) which was converted by treatment with 2M aqueous sodium hydroxide solution followed by neutralisation with aqueous hydrochloric acid and extraction with methylene chloride into the starting material (274) (1.7g; 13%) as a
yellow gum, identified by comparison (i.r. spectrum) with an authentic sample.

The diethyl ether mother liquor was evaporated to give a yellow oil (8.1g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (1:1) afforded methyl 2(3-methoxyphenyl)aminopyridone-3-carbonylate (267) (6.7g; 52%) which formed colourless crystals, m.p. 45-47° [from light petroleum (b.p. 40-60°)], ν\text{max} 3330 (NH) and 1690 (CO) cm\(^{-1}\), δ\text{H}(\text{CDCl}_3) 10.18 (1H, s, NH), 8.33 (1H, dd, J\text{ortho} 5Hz and J\text{meta} 2Hz, ArH), 8.13 (1H, dd, J\text{ortho} 9Hz and J\text{meta} 2Hz, ArH) 7.50 (1H, m, ArH), 7.24-7.18 (5H, m, ArH), 6.71-6.55 (2H, m, ArH), 3.84 (3H, s, CH\text{3}).

**Found:** C, 64.9; H, 5.4; N, 11.0%; m/z (EI ms), 258 (M\text{+})

**C\text{14}H\text{14}N\text{2}O\text{3} requires:** C, 65.1; H, 5.4; N, 10.9%; M, 258

Further elution with ethyl acetate-hexane (1:1) through to methanol gave only a series of intractable gums (total 1.1g) which were not further investigated.

The aqueous sodium hydrogen carbonate washings were neutralised by the addition of glacial acetic acid and the resulting solution extracted with ethyl acetate to afford unreacted starting material (274) (1.0g, 8%), m.p. 144-147°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.
**Methyl 2-[[N-Benzyl-(3-methoxyphenyl)aminolpyridine-3-carboxylate**  
(266)

A stirred suspension of sodium hydride (0.20g; 0.0083 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room temperature with a solution of methyl 2-(3-methoxyphenyl)aminopyridine-3-carboxylate (276) (2.1g; 0.008 mol) in anhydrous dimethylformamide (15.0 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 1.5h. A solution of benzyl chloride (1.0g; 0.008 mol) in anhydrous dimethylformamide (2.5 ml) was added in one portion and the mixture stirred at room temperature with the exclusion of atmospheric moisture for 17h.

The mixture was treated with water (5.0 ml) and stirred at room temperature for 2h. The mixture was then evaporated yielding a yellow gum which was treated with water (40.0 ml) and extracted with methylene chloride to afford **methyl 2-[[N-benzyl(3-methoxyphenyl)aminolpyridine-3-carboxylate** (266) (2.5g; 89%) as a yellow oil, b.p. 220-225° 0.02mmHg, $\nu_{\text{max}}$ 1720 (CO)cm$^{-1}$; $\delta_{\text{H}}$(CDCl$_3$) 8.32 (1H, dd, Jortho 5Hz and Jmeta 2Hz ArH) 7.80(1H, dd, Jortho 8Hz and Jmeta 2Hz ArH) 7.57-6.49 (10H, m, ArH) 5.46 (2H, s, CH$_2$), 3.66 (3H, s, CH$_3$) and 3.35 (3H, s, CH$_3$).

**Found:** C, 73.5; H, 6.0; N, 8.4%; m/z, (EI ms), 348 (M$^+$)  
**C$_{21}$H$_{20}$N$_2$O$_3$ requires:** C, 72.4; H, 5.8; N, 8.1%; M, 348

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The Attempted Reaction of Methyl 2-[N-Benzyl-(3-methoxyphenyl)-aminopyridine-3-carboxylate (266) with Hydrazine Hydrate

A solution of methyl 2-[N-benzyl-(3-methoxyphenyl)]aminopyridine-3-carboxylate (266) (0.69g; 0.002 mol) was treated with hydrazine hydrate (0.10g; 0.002 mol) and the mixture was heated under reflux for 6h.

The mixture was cooled and rotary evaporated to afford the unreacted starting material (275) (0.63g; 91%) as a yellow oil identified by comparison (i.r. spectrum and t.l.c. in ethyl acetate-hexane (1:1) over silica) with an authentic sample prepared before.

2-[N-Benzyl-(3-methoxyphenyl)aminopyridine-3-carboxylic Acid (264)

A solution of methyl N-benzyl-2-(3-methoxyphenyl)aminopyridine-3-carboxylate (266) (0.69g; 0.002 mol) in ethanol (0.5 ml) was treated with 2M aqueous sodium hydroxide solution (2.5 ml) and the mixture was heated under reflux for 2h.

The mixture was cooled and rotary evaporated and the residue was treated with water (5.0 ml) and the resulting basic solution neutralised by the addition of concentrated hydrochloric acid. Filtration afforded 2-[N-benzyl-(3-methoxyphenyl)aminopyridine-3-carboxylic acid (264) (0.41g; 61%) as a colourless solid m.p. 165-167° (from hexane-toluene), \( \nu_{\text{max}} \) 3100-2200 br (OH) and 1700 (CO)cm\(^{-1}\), \( \delta_H(\text{CDCl}_3) \) 9.18 (1H, s, OH) (exch.), 8.43 (1H, dd, Jortho 5Hz and Jmeta 2Hz, ArH). 8.04 (1H, dd,
Jortho 8Hz and Jmeta 2Hz, ArH). 7.43-6.90 (8H, m, ArH), 6.68-6.45 (2H, m, ArH), 5.22 (2H, s, OH₂) and 3.64 (3H, s, CH₃).

**Found:** C, 72.4; H, 5.5; N, 8.3%; m/z (EI ms), 334.1318 (M⁺)

**C₂₀H₁₈N₂O₃ requires:** C, 71.9; H, 5.4; N, 8.4%; M, 334, 1317

Extraction of the aqueous mother liquor with ethyl acetate yielded only a small amount of a yellow oil (0.090g) which afforded no identifiable material.

The Attempted Reaction of 2-[N-benzyl-(3-methoxyphenyl)-amino]pyridine-3-carboxylic Acid (264) with thionyl chloride

(a) 2-[N-Benzyl-(3-methoxyphenyl)amino]pyridine-3-carboxylate (264) (0.33g, 0.001 mol) was treated with thionyl chloride (2.5 ml; 0.034 mol) and the mixture was heated under reflux for 0.5h.

The mixture was cooled and rotary evaporated yielding a dark brown gum (0.50g) which afforded no identifiable material.

(b) Repetition of the reaction described in (a) except using thionyl chloride (0.5 ml; 0.068 mol) and the mixture was stirred at room temperature for 0.5h, gave after rotary evaporation of the mixture under high vacuum an orange intractable gum (0.62g) which yielded no identifiable material.
The reaction of \( N\{-2\{N-(3\text{-methoxyphenyl)amino}\text{pyrid-3-yl}\}\text{-triphenylphosphinimine (223)} \) with Carbon Disulphide

A solution of the phosphinimine (223) (0.93; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with carbon disulphide (0.15g 0.002 mol) and the mixture was stirred at room temperature for 1h then heated under reflux for 5h.

The mixture was cooled and filtered to yield \( 3\{-3\text{-methoxyphenyl}\}-3H\text{-imidazo[45-b]pyridine-2(1H)-thione (257) } \) (0.057g; 11%) as a colourless solid, m.p. 267-269° (from acetonitrile-methanol),

\[
\delta_H[(\text{CD}_3)_2\text{SO}]: 8.10 (1H, dd, J_{ortho} 5Hz and J_{meta} 2Hz, \text{ArH}), 7.66-7.01 (7H, m, \text{ArH + SH}) \text{ and } 3.79 (3H, s, \text{CH}_3).
\]

**Found:** C, 61.1; H, 4.4; N, 16.5%; m/z (El ms), 257.0627 (M)

\( \text{C}_{13}\text{H}_{11}\text{N}_3\text{OS} \text{ requires:} \) C, 60.7; H, 4.3; N, 16.3%; M, 257.0623

Evaporation of the filtrate yielded an orange solid (0.95g) which was flash-chromatographed over silica.

Elution with hexane-ethyl acetate (7:3) gave triphenylphosphine sulphide (0.30g; 51%), m.p. 151-154°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with hexane-ethyl acetate (65:35) yielded unreacted starting material (223) (0.32g; 34%), m.p. 107-110°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.
Further elution with ethyl acetate afforded a second crop of 3-(3-methoxyphenyl)-3H-imidazo[4,5-b]pyridine-2(1H)-thione (257) (0.23g; 45%), m.p. 255-259°, identified by comparison (m.p. and i.r. spectrum) with a sample obtained before.

Further elution with methanol yielded only an intractable gum (0.016g) which was not further investigated.

1-(3-Methoxyphenylamino)-2-nitrobenzene (271)

2-Fluoronitrobenzene (270) (14.1g; 0.1 mol) was mixed with 3-methoxyaniline (219) (24.6g; 0.2 mol) and anhydrous potassium fluoride (6.0g; 0.1 mol) and the mixture was heated at 180° (oil bath) for 48h.

The mixture was cooled and treated with methylene chloride (200 ml) then washed with water (250 ml), 2M aqueous hydrochloric acid (400 ml) and water (400 ml). Evaporation of the methylene chloride phase yielded a dark brown oil (26.0g) which was extracted with excess of boiling hexane leaving a dark brown gum whose t.l.c. in methylene chloride-light petroleum (b.p. 40-60°) (3:2) over silica showed it to be a multicomponent mixture which was not further investigated.

Evaporation of the hexane extract afforded the known\textsuperscript{83} 2-(3-methoxyphenylamino)-2-nitrobenzene (271) (18.0g, 73%) as a red solid, m.p. 55-57° (from hexane) (lit\textsuperscript{83}, 56-57°)

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1-N-Bezyl-N-3-methoxyphenyl)amino-2-nitrobenzene (272)

A stirred suspension of sodium hydride (1.6g; 0.066 mol) in anhydrous dimethylformamide (75.0 ml) was treated dropwise at room temperature with a solution of the amine (271) (14.7g, 0.06 mol) in anhydrous dimethylformamide (150 ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of benzyl bromide (10.3g 0.06 mol) in anhydrous dimethylformamide (750 ml) was added and the mixture was then stirred at room temperature for 17h.

The mixture was diluted with water (30.0 ml) and was stirred at room temperature for 15 min. The mixture was then evaporated under high vacuum yielding a gum which was treated with water (180 ml) and extracted with methylene chloride to afford a red oil (21.7g) Trituration of the oil with methanol yielded 1-(N-benzyl-N-3-methoxyphenyl)amino-2-nitrobenzene (272) (16.6g; 83%) which formed red crystals, m.p. 84-85° (from methanol), νmax 1520 and 1360 (NO2) cm⁻¹, δH(CDCl3) 7.89 (1H, dd, Jortho 2Hz and Jmeta 1Hz, ArH), 7.80-6.94 (9H, m, ArH), 6.46-6.25 (3H, m, ArH), 4.93 (2H, s, CH2) and 3.67 (3H, s, CH3).

Found: C, 72.2; H, 5.4; N, 8.3%; m/z (EI ms), 334 (M+)

C20H18N2O3 requires: C, 71.9; H, 5.4; N, 8.4%; M, 334

Evaporation of the methanolic mother liquor yielded a red oil (3.3g) whose t.l.c. in diethyl ether-light petroleum (b.p. 40-60°) over silica
showed it to be a multicomponent mixture which yielded no identifiable material.

1-Amino-2-(N-benzyl-N-3-methoxyphenyl)aminobenzene (273)

A solution of the nitrobenzene derivative (272) (16.7g; 0.05 mol) in ethyl acetate (250 ml) was hydrogenated over 10% palladium-on-charcoal (1.7g) at room temperature and atmospheric pressure for 4h.

The mixture was filtered through celite and the filtrate was evaporated to afford 1-amino-2-[N-benzyl-N-(3-methoxyphenyl)amino benzene (273) (15.1g; 99%) as a light brown solid, m.p. 75-77° (from benzene-hexane), v_max 3450 and 3360 (NH) and 1620 (NH def)cm⁻¹, δ_H(CDCl₃) 7.39-6.62 (10H, m, ArH), 6.38-6.20 (3H, m, ArH), 4.82 (2H, s, CH₂), 3.68 (2H, s, NH₂)(exch) and 3.67 (3H, s, CH₃).

Found: C, 78.8; H, 6.7; N, 9.1%; m/z (EI ms), 304 (M⁺)

C₂₀H₂₀N₂O requires: C, 78.9; H, 6.6; N, 9.2%; M, 304

1-Azido-2-[N-benzyl-N(3-methoxyphenyl)amino benzene (274)

A solution of the amine (273) (1.8g 0.006 mol) in glacial acetic acid (15.0 ml) was stirred and cooled (water bath) then treated dropwise with concentrated sulphuric acid (4.5 ml). The mixture was further cooled to 0° (ice-salt bath) and treated dropwise with stirring at 0-5° with a solution of sodium nitrite (0.46g; 0.0066 mol) in water (3.0 ml). The resulting diazonium slurry was stirred at 0-5° for 10 min then treated dropwise with a
solution of sodium azide (0.78g, 0.012 mol) in water (3.0 ml) and the mixture stirred in the melting ice bath for 0.5h.

The mixture was diluted with water (25.0 ml) extracted with methylene chloride and the extract washed with 10% w/v aqueous sodium hydrogen carbonate solution (20.0 ml) and evaporated yielding 1-azido-2-[N-benzyl-N-(3-methoxyphenyl)aminobenzene (274) (1.6g; 81%) as a brown gum, \( v_{\text{max}} \) 2120 (N\(_3\))cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.41-7.0 (10H, m, ArH), 6.81-6.74 (1H, m, ArH), 6.33-6.14 (2H, m, ArH), 4.83 (2H, s, CH\(_2\)) and 3.67 (3H, s, CH\(_3\)).

**Found:** m/z (EI ms), 330.1478 (M\(^+\))

**C\(_{20}\)H\(_{18}\)N\(_4\)O** requires: M, 330.1478

Which due to its instability towards chromatography over silica was used without further purification.

**The Attempted Reaction of 1-Azido-2-[N-benzyl-N-(3-methoxyphenyl)aminobenzene (274) with Trimethyl phosphite.**

Solutions of the crude azide (274) (1.3g; 0.004 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) and trimethylphosphite (0.62g; 0.005 mol) in 1,2-dimethoxyethane (10.0 ml) were mixed and the mixture was stirred at room temperature for 4h.

The mixture was evaporated under high vacuum with removal of the excess of trimethyl phosphite as an azeotrope with toluene yielding a dark brown intractable gum (1.4g) which yielded no identifiable material.
2-(N, N-Dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (277)

A solution of the chloro-nitro pyrimidine (187) (5.1g; 0.025 mol) in ethanol (300 ml) was treated with 3-methoxyaniline (219) (6.2; 0.05 mol) and the mixture was heated under reflux for 3h.

The mixture was cooled and filtered to afford 2-(N, N-dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (286) (0.8g; 94%) which formed yellow needles, m.p. 158-159° (from ethyl acetate), νmax 3310 (NH) and 1560 and 1370 (N=O) cm⁻¹, δH 10.36 (1H, s, NH), 9.07 (1H, s, ArH), 7.39-7.15 (3H, m, ArH), 6.77-6.63 (1H, m, ArH), 3.80 (3H, s, CH₃), 3.29 (3H, s, CH₃) and 3.23 (3H, s, CH₃).

Found: m/z (EI ms), 289.1165 (M⁺)

C₁₃H₁₅N₅O₃ requires: M, 289.1175

Evaporation of the ethanolic mother liquor yielded a gummy brown solid (4.7g) whose i.r. spectrum showed it to be mainly 3-methoxyaniline hydrochloride by comparison with an authentic sample.

5-Amino-2-(N, N-dimethylamino)-4-(3-methoxyphenyl)amino-pyrimidine (278)

A solution of the nitropyrimidine derivative (277) (5.8g; 0.002 mol) in glacial acetic acid (500 ml) was hydrogenated over 5% palladium-on-
charcoal (0.57g) at room temperature and atmospheric pressure for 1h by which time no further hydrogen absorption was observed.

The mixture was filtered through celite and the filtrate was evaporated to yield a dark brown oil (8.0g) which was flash-chromatographed over alumina.

Elution with ethyl acetate-hexane (4:1) yielded a dark brown gum (0.13g) whose t.l.c. in ethyl acetate over alumina showed it to be an unresolvable mixture which was not further investigated.

Further elution with ethyl acetate-hexane (4:1) gave 5-amino-2-(N, N-dimethylamino)-4-(3-methoxyphenyl)aminopyrimidine (278) (4.0g; 77%) which formed off-white crystals, m.p 130-134° (from toluene), \( \nu_{\text{max}} \) 3380, 3340 and 3260 (NH\(_2\))cm\(^{-1}\), \( \delta_{H}(\text{CDCl}_3) \) 7.75 (1H, s, ArH), 7.63-7.54 (1H, m, ArH), 7.59 (1H, brs, NH) (exch.), 7.30-6.99 (2H, m, ArH), 6.63-6.48 (1H, m, ArH), 3.80 (3H, s, CH\(_3\)), 3.14 (6H, s, 2xCH\(_3\)) and 2.46 (2H, brs, NH\(_2\)) (exch).

**Found:** C, 61.7; H, 6.9; N, 27.4%; m/z (El ms), 259.1436 (M\(^+\))

**C\(_{13}\)H\(_{17}\)N\(_5\)O requires:** C, 60.2; H, 6.6; N, 27.0%; M, 259.1433

Further elution with ethyl acetate-hexane (4:1) through to methanol gave only a series of intractable gums (total 0.94g) which were not further investigated.
5-(N,N-Dimethylamino)-3-(3-methoxyphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine (279)

A solution of the aminopyrimidine derivative (278) (0.52g; 0.002 mol) in 5M aqueous hydrochloric acid (5.0 ml) was stirred and cooled to 0° (ice-salt bath) then treated dropwise with a solution of sodium nitrite (0.15g; 0.0022 mol) in water (1.0 ml) at 0-5°. Further water (5.0 ml) was added and the mixture was stirred in the melting ice-bath for 0.5h.

After this time the reaction mixture containing a purple solid was extracted to afford 5-(N,N-dimethylamino)-3-(3-methoxyphenyl)-3H-1,2,3-triazolo[4,5-d]pyrimidine (279) (0.45g; 83%) which formed lime green crystals, m.p 120-121° (from ethanol), δH(CDCl₃) 9.10 (1H, s, ArH), 7.95-7.82 (2H, m, ArH), 7.52-7.24 (1H, m, ArH), 6.98-6.84 (1H, m, ArH), 3.88(3H, s, CH₃) and 3.31 (6H, s, 2xCH₃).

**Found:** C, 58.2; H, 5.3; N, 31.2%; m/z(EI ms), 270.1232 (M⁺)

**C₁₃H₁₄N₆O requires:** C, 57.8; H, 5.2; N, 31.1%; M, 270.1229

N-{2-Dimethylamino-4-[N-(3-methoxyphenyl)amino]pyrimidin-5-yl}-triphenylphosphinimine (280)

A solution of the amine (278) (2.1g; 0.008 mol) in anhydrous acetonitrile (80.0 ml) was stirred under nitrogen and treated at room temperature with triphenylphosphine (2.5g; 0.0096 mol), followed by
triethylamine (1.6g; 0.016 mol) and hexachloroethane (1.9; 0.008 mol). The mixture was then heated under reflux under nitrogen for 18h.

The cooled mixture was filtered to remove triethylamine hydrochloride (0.92g; 42%), m.p. 258-260° identical (m.p. and i.r. spectrum) to an authentic sample. Evaporation of the filtrate yielded a brown gum which was treated with water (32.0 ml) and extracted with methylene chloride to give a brown gum (5.3g) which was then flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (9:1) gave unreacted triphenylphosphine (0.34g), m.p. 75-77°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate gave a gummy solid which was washed with diethyl ether to give N-(2-dimethylamino-4-[N-(3-methoxyphenyl)amino]pyrimidin-5-yl)triphenylphosphinimine (280) (2.4g; 59%) which formed yellow crystals, m.p. 95-98° (from ethyl acetate), $v_{\text{max}} = 3220 \text{ (NH) cm}^{-1}$, $\delta_H(\text{CDCl}_3) = 8.56 (1H, s, NH) \text{ (exch.)}, 7.85-7.08 (19H, m, ArH), 7.51 (1H, m, ArH), 3.82 (3H, s, CH$_3$) \text{ and } 3.09 (6H, s, 2xCH$_3$).

Found: C, 70.7; H, 6.1; N, 12.5%; m/z (FAB ms), 520 [(M+H)$^+$]

C$_{31}$H$_{30}$N$_5$OP requires: C, 71.7; H, 5.8; N, 13.5%; M, 519

Evaporation of the diethyl ether mother liquor yielded an intractable brown gum (0.35g) whose t.l.c. in ethyl acetate over silica showed it to be a multicomponent mixture which therefore was not further investigated.
Further elution with methanol gave a red foam (1.1g) whose t.l.c. in ethyl acetate over silica showed it to be a complex mixture which was not further investigated.

5-(N, N-Dimethylamino)-3-(3-methoxyphenyl)-2-(N-phenylamino)-3H-imidazo[4,5-d] pyrimidine (282)

A solution of the phosphinimine (280) (1.0g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was mixed with a solution of phenyl isocyanate (0.24g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) and the mixture was stirred at room temperature for 21h.

The mixture was rotary evaporated yielding a gummy solid (1.3g) whose i.r. spectrum showed the presence of unreacted starting material (289). The solid was redissolved in anhydrous 1,2-dimethoxyethane (20.0 ml) and the solution heated under reflux for 17h. The mixture was cooled and rotary evaporated yielding a gummy solid (1.2g) whose i.r. spectrum showed the presence of unreacted starting material (280). The solid was redissolved in anhydrous 1,4-dioxane (20.0 ml) and the mixture was heated under reflux for 17h.

The mixture was rotary evaporated under high vacuum yielding a solid (1.2g) which was flash-chromatographed over silica.

Elution with light petroleum (b.p 40-60°) ethyl acetate (4:1) yielded an intractable gum (0.12g) which was not further investigated.
Further elution with light petroleum (b.p. 40-60°) ethyl acetate (3:2) afforded 5-(N, N-dimethylamino-3-(3-methoxyphenyl)-2-(N-phenylamino-3-H-imidazo[4,5-d]pyrimidine (282). (0.52g; 72%) which formed colourless crystals, m.p. 210-212° (from acetic acid-water), $v_{\text{max}}$ 3380 (NH) cm$^{-1}$, $\delta_{H} 8.62$ (1H, brs, NH(exch.)), 8.38 (1H, s, ArH), 7.84-6.94 (9H, m, ArH), 3.82 (3H, s, OCH$_3$), and 3.04 (6H, s, NMe$_2$).

**Found:** C, 66.4; H, 5.6; N, 23.3%; m/z(EI ms), 360(M$^+$)

C$_{20}$H$_{20}$N$_6$O requires: C, 66.7; H, 5.6; N, 23.3%; M, 360

Further elution with ethyl acetate yielded triphenylphosphine oxide (0.35g), m.p. 135-138°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

Further elution with methanol gave only an intractable brown gum (0.21g) which was not further investigated.

**The Attempted Benzylation of 2-(N, N-Dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (277) with Benzyl Chloride**

A stirred suspension of sodium hydride (0.053g; 0.0022 mol) in anhydrous dimethylformamide (2.5 ml) was treated dropwise at room temperature with a solution of 2-(N, N dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (277) (0.58g; 0.002 mol) in anhydrous dimethylformamide (20.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15 min.
A solution of benzyl chloride (0.25g; 0.002 mol) in anhydrous dimethylformamide was added in one portion and the mixture stirred at room temperature with exclusion of atmospheric moisture for 17h.

The mixture was treated with water (2.0 ml) and stirred at room temperature for 15 min then evaporated under high vacuum to yield a red gum which was treated with water (10.0 ml) to give unreacted starting material (277) (0.56g; 97%), m.p. 149-154°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride yielded only a small amount of a brown oil (0.08g) which was not further investigated.

4-[N-Benzyl, N-(3-methoxyphenyl)]amino-2-(N, N-dimethylamino)-5-nitropyrimidine (283)

(a) A stirred suspension of sodium hydride (0.053g; 0.0022 mol) in anhydrous dimethylformamide (5.0 ml) was treated dropwise at room temperature with a solution of 2-(N, N-dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (277) (0.58g; 0.002 mol) in anhydrous dimethylformamide (30.0 ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 17h.

The mixture was treated with water (2.0 ml) and stirred at room temperature for 0.5h. Evaporation under high vacuum yielded a gum which was treated with water (10.0 ml) and extracted with methylene chloride to
afford a yellow solid (0.79g), m.p. 133-138° whose $^1$H n.m.r. spectrum showed it to be a (7:3) mixture of 4-[N-benzyl, N-(3-methoxyphenyl)]amino-2-(N, N-dimethylamino)-5-nitropyrimidine (283) and unreacted starting material (277) which was not further investigated.

(b) A stirred suspension of sodium hydride (0.89g; 0.037 mol) in anhydrous dimethylformamide (85.0 ml) was treated dropwise at room temperature with a solution of 2(N, N-dimethylamino)-4-(3-methoxyphenyl)amino-5-nitropyrimidine (277) (9.8g; 0.034 mol) in anhydrous dimethylformamide (510 ml) and the mixture stirred at room temperature with exclusion of atmospheric moisture for 15 min. A solution of benzyl bromide (8.7g; 0.051 mol) in anhydrous dimethylformamide (85.0 ml) was added and the mixture stirred at room temperature with exclusion of atmospheric moisture for 17h.

The mixture was treated with water (37.0 ml) and stirred at room temperature for 15 min. Evaporation under high vacuum yielded a brown gum which was treated with water (185 ml) and extracted with methylene chloride to give a gummy yellow solid (19.5g) which was triturated with diethyl ether to afford 4-[N-benzyl, N-(3-methoxyphenyl)]amino-2-(N, N-dimethylamino)-5-nitropyrimidine (283) (11.7g; 91%) as a yellow solid, m.p. 144-146° (from acetic acid), $\delta_H[(CD_3)_2SO]$ 8.69 (1H, s, ArH), 7.38-7.07 (6H, m, ArH), 6.74-6.64(3H, m, ArH), 5.36 (2H, s, CH$_2$), 3.67 (3H, s, CH$_3$) and 3.38 (6H, brd, J5Hz, 2xCH$_3$).
Found: C, 63.4; H, 5.6; N, 18.5%; m/z (EI ms), 379 (M+)

$\text{C}_{20}\text{H}_{21}\text{N}_5\text{O}_3$ requires: C, 63.3; H, 5.5; N, 18.5%; M, 379

Evaporation of the diethyl ether mother liquor yielded on intractable dark brown oil (3.4g) which was not further investigated.

The Attempted Catalytic Hydrogenation of 4-([N-Benzyl, N-([3-methoxyphenyl]amino-2-N, N-dimethylamino)-5-nitropyrimidine (283)

A solution of the nitropyrimidine (283) (0.76g; 0.002 mol) in tetrahydrofuran (50.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.076g) at room temperature and atmospheric pressure for 1h, by which time no absorption of hydrogen had occurred.

The mixture was filtered through celite and the filtrate was evaporated to give a gummy solid (0.78g) which was triturated with diethyl ether to afford the unreacted starting material (283) (0.68g; 89%), m.p. 134-141°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

5-Amino-4-([N-Benzyl, N-([3-methoxyphenyl]amino-2-N, N-dimethylaminopyrimidine (284)

A solution of the nitropyrimidine derivative (283) (9.1g; 0.024 mol) in tetrahydrofuran (552 ml) was stirred under nitrogen and treated
dropwise at room temperature with 15% w/v aqueous titanium trichloride solution (206 ml; 0.24 mol). The mixture was then stirred under nitrogen at room temperature for 17h.

The mixture was concentrated by rotary evaporation to remove the tetrahydrofuran and the residue was made basic with 50% w/v aqueous sodium hydroxide solution. Water (120 ml) was added and the mixture was extracted with methylene chloride to afford a brown oil (7.3g) which was flash-chromatographed over silica.

Elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:1) gave a series of intractable gums (0.78g) which were not further investigated.

Further elution with ethyl acetate-light petroleum (b.p. 40-60°) (1:1) yielded 5-amino-4-[N-benzyl, N-(3-methoxyphenyl)]amino-2,N,N-dimethylaminopyrimidine (284) (5.1g; 61%) as a yellow oil which was purified by Kugelrohr distillation, b.p. 240-250°/0.01mm Hg, \( \nu_{\text{max}} \) 3410, 3330 and 3100(NH)cm\(^{-1}\), \( \delta_{\text{H}}(\text{CDCl}_3) \) 7.69 (1H, s, ArH), 7.27-7.24 (6H, m, ArH), 6.60-6.38 (3H, m, ArH), 5.23 (2H, s, CH\(_2\)), 3.69 (3H, s, CH\(_3\)), 3.40 (2H, brs, NH\(_2\)) (exch) and 3.08 (6H, s, 2xCH\(_3\)).

**Found:** m/z (EI ms), 349.1903 (M\(^+\))

**C\(_{20}\)H\(_{23}\)N\(_5\)O requires:** M, 349.1900

Further elution with ethyl acetate through to methanol yielded only a series of intractable gums (1.5g) which yielded no identifiable material.
5-Azido-4-[N-benzyl, N-(3-methoxyphenyl)]amino-2-N, N-
dimethylaminopyrimidine (285)

A suspension of the aminopyrimidine derivative (284) (2.4g; 0.007 mol) in 5M aqueous hydrochloric acid (17.5 ml) was stirred and cooled to 0°(ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.53g; 0.0077 mol) in water (3.5 ml) such that the reaction temperature was 0-5°. The resulting mixture was stirred at 0-5° for 15 min and then treated dropwise with a solution of sodium azide (0.68g; 0.011 mol) in water (3.5 ml) such that the reaction temperature was 0-5°. The mixture was stirred in the melting ice-bath for 0.5h then filtered to afford a grey solid (0.30g), m.p. 234-235°; which was treated with 2M aqueous sodium hydroxide solution and extracted with methylene chloride to yield unreacted starting material (284)(0.26g; 11%) as a gum, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The aqueous filtrate was extracted several times with methylene chloride and the combined extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (20.0 ml) and evaporated to afford 5-azido-4-[N-benzyl, N-(3-methoxyphenyl)]amino-2-N, N-
dimethylaminopyrimidine (285). $v_{\text{max}}$ 2110 (N$_3$) cm$^{-1}$

**Found:** C, 65.5; H, 5.8; N, 19.2%;

**C$_{20}$H$_{21}$N$_{2}$O requires:** C, 64.0; H, 5.6; N, 26.1%
N-{2-Dimethylamino-4-[N-benzyl, N-(3-methoxyphenyl)aminopyrimidin-5-yl]triphenylphosphinimine (286)

Solutions of the crude azidopyrimidine derivative (285) (1.5g; 0.004 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) and trimethylphosphite (0.62g; 0.005 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) were mixed and the mixture was stirred at room temperature for 4h.

The mixture was rotary evaporated under high vacuum with removal of the excess trimethyl phosphite as an azeotrope with toluene to give N-{2-dimethylamino-4-[N-benzyl, N-(3-methoxyphenyl)aminopyrimidin-5-yl]triphenylphosphinimine (286) (1.6g; 85%), $\delta_H$(CDCl$_3$) 7.97 (1H, s, ArH), 7.35-7.16 (6H, m, ArH), 6.68-6.57 (3H, m, ArH), 5.18 (2H, s, CH$_2$), 3.69(3H, s, CH$_3$), 3.57 (9H, d, J11Hz, 3xCH$_3$) and 3.08 (6H, s, 2xCH$_3$).

**Found:** m/z (EI ms), 471.2031 (M$^+$)

**C$_{23}$H$_{30}$N$_5$O$_4$P requires:** M, 471.2035

1{4-[N-Benzyl, N-(3-methoxyphenyl)amino-2-dimethylaminopyrimidin-5-yl]-3-phenylcarbodiimide (287)

Solutions of crude phosphinimine (286) (1.4g; 0.003 mol) in anhydrous 1,2-dimethoxyethane (15.0 ml) and phenyl isocyanate (0.36g;
0.003 mol) in anhydrous 1,2-dimethoxyethane (7.5 ml) were mixed and the mixture was stirred at room temperature for 4h.

The reaction mixture was rotary evaporated under reduced pressure yielding a gum which was dissolved in methylene chloride (30.0 ml), washed with water (30.0 ml) and evaporated to afford 1-{4-[\text{N-benzyl, N-(3-methoxyphenyl)]amino-2-dimethylaminopyrimidin-5-yl}}-3-phenylcarbodiimide (287) (1.6g; quant) as a brown gum, $v_{\text{max}}$ 2140 cm$^{-1}$.

Found: m/z (EI ms), 450.2182 (M$^+$)

C$_{27}$H$_{26}$N$_6$O requires: M, 450.2168

The Attempted Stannic Chloride Catalysed Ring Closure of 1-{4-[\text{N-benzyl, N-(3-methoxyphenyl)]amino-2-dimethylaminopyrimidin-5-yl}}-3-phenylcarbodiimide (287)

A solution of carbodiimide (287) (1.4g; 0.003 mol) in anhydrous 1,2-dichloroethane (15.0 ml) was stirred and cooled to 0° (ice-salt bath) and treated dropwise with a solution of stannic chloride (3.9g; 0.015 mol) in anhydrous 1,2-dichloroethane(7.5 ml). The mixture was then stirred and heated under reflux for 24h.

The mixture was stirred and cooled to 0° (ice-salt bath) and treated dropwise with 15M aqueous sodium hydroxide solution (10.4 ml; 0.16 mol). The mixture was then stirred and allowed to warm to room temperature over 15 min. Water (30.0 ml) was added and the mixture
extracted with methylene chloride to afford a brown oil (1.7g) which was flash-chromatographed over silica.

Elution with light petroleum (b.p. 40-60°) ethyl acetate (7:3) gave a small amount of an unidentified solid.

Further elution with ethyl acetate-light petroleum (b.p.40-60°C) (1:1) gave only a series of intractable gums (total 0.32g) which were not further investigated.

Further elution with ethyl acetate yielded 1-{4-[N-benzyl, N-(3-methoxyphenyl)]amino-2-dimethylaminopyrimidin-5-yl}-3-phenylurea (288) (0.23g; 16%) as a colourless solid, m.p. 211-213° (from ethanol), $v_{\text{max}}$ 3260 (NH) and 1620 (CO)cm$^{-1}$.

**Found:** C, 69.4; H, 5.9; N, 17.8%; m/z (FAB ms), 469 [(M+H)$^+$]

**C$_{27}$H$_{26}$N$_6$O requires:** C, 69.2; H, 5.9; N, 17.9%; M, 468

Further elution with methanol afforded an intractable brown gum (0.36g) which yielded no identifiable material.
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