INVESTIGATIONS OF NEW SYNTHETIC ROUTES TO FUSED TRICYCLIC HETEROPINES AND RELATED HETEROCYCLES

by

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Thesis presented for the degree of Doctor of Philosophy

University of Edinburgh 1996

DEDICATION

To my parents, Sandy and Mary, to Alan and to Nerys

for their help, support, and encouragement.

CONTENTS

DECLARATION

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

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 1992 and September 1995.

ACKNOWLEDGEMENTS

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I should also like to acknowledge Dr. G. Robertson, Glaxo Research and Development, for his helpful suggestions and interest in the research carried out in collaboration with Glaxo Research and Development.

POSTGRADUATE LECTURE COURSES ATTENDED BETWEEN OCTOBER 1992 AND SEPTEMBER 1995

Royal Society of Chemistry - Perkin Division

Twenty-first Scotitish Regional Meeting (1992), Edinburgh.

Twenty-second Scottish Regional Meeting (1993), Aberdeen.

Twenty-third Scottish Regional Meeting (1994), Dundee.

Organic Research Group Seminars, University of Edinburgh, 1992-93, 1993-94, 1994-95.

Organic Research Group Colloquia, University of Edinburgh, 1992-93, 1993-94, 1994-95.

"Introductory Course in German": 1992; Department of German, University of Edinburgh.

Zeneca Lecture and Symposium, 1994; University of Edinburgh.

"Leads in Medicinal Chemistry and New Strategies for Drug Design"; 1992-1993, 1993-1994, 1994-1995: various lectures from Merck Sharp & Dohme Ltd.

"Chemical Development in the Pharmaceutical Industry"; 1993 and 1994: various lectures from SmithKline Beecham Pharmaceuticals Plc.

"Industrial Applications of Peroxides"; 1994: various lectures from Solvay Interox (Warrington).

"Mass Spectroscopy in Action"; 1993: various lectures from ICI.

"Research and Development in the Pharmaceutical Industry"; 1994: Prof. A McKillop, University of East Anglia.

"Challenges in Development Chemistry"; 1995: various lectures from Zeneca Fine Chemicals (Grangemouth).

ABSTRACT

The subject matter of this thesis is concerned with investigations into the synthesis of tricyclic heteropine systems. In particular Lewis acid-catalysed and carbanion-induced cyclisation reactions of suitably substituted isothiocyanate and carbodiimide derivatives were investigated for the synthesis of dibenzoxazepines, pyridobenzoxazepines, dibenzothiazepines, dibenzodiazepines and benzonaphthoxazepines. These studies were also expanded to investigate the synthesis of benzoxazepinodibenzoxazepines and benzoxazepinobenzonaphthoxazepines via the double-cyclisation of the appropriate bis-isothiocyanate derivatives. The description of the results obtained in these studies is preceded by a review on the use of tricyclic heteropine derivatives as chemotherapeutic agents in the areas of schizophrenia and Alzheimer's disease. The synthetic strategies currently available for the synthesis of tricyclic heteropines are also included in this review. It highlights the need for a flexible, widely applicable route to this class of compound and how the present studies could address this problem.

The syntheses of the appropriate 2-isothiocyanatodiphenyl ether derivatives were readily accomplished, and in most cases their subsequent reaction with a Lewis acid catalyst resulted in the formation of the desired tricyclic heteropine. These compounds were also synthesised in high yield via a carbanion-induced cyclisation involving reaction of appropriate halogen derivatives with butyl lithium, the first examples of intramolecular carbanion addition to a heterocumulene. The attempted transition metal-mediated and radical-induced cyclisation of the isothiocyanate precursors,

however, proved unsuccessful, with no formation of the desired tricyclic heteropine system.

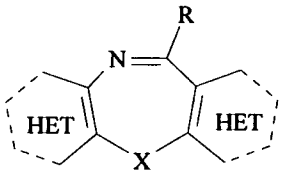
The attempted functionalisation of the tricyclic heteropines, via thiomethylation of the thiolactam moiety and subsequent displacement of the thiomethyl-group, proved unsuccessful. This failure to obtain appropriately amino-functionalised structures prompted investigations into the carbanion-induced cyclisation reactions of carbodiimide precursors.

The synthesis of N-phenyl-N′-(2-phenoxy)phenyl carbodiimides capable of undergoing the carbanion-induced cyclisations was achieved by the novel dehydration of urea derivatives using either phosphoryl chloride-ethyl diisopropylamine, or triphosgene-triethylamine. The desired tricyclic heteropine derivatives were then obtained by the action of butyl lithium on these carbodiimide precursors.

The attempted synthesis of benzoxazepinodibenzoxazepines and benzoxazepinobenzonaphthoxazepines via a double-cyclisation of the appropriate bis-isothiocyanate derivatives proved more complex. In most cases mono-cyclised products were isolated and fully characterised, but materials believed to be the fully cyclised products proved very difficult to purify and therefore could not be fully characterised.

Chapter 1

A Survey of the Biological Activity and Synthesis of Tricyclic Heteropines



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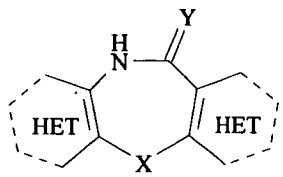


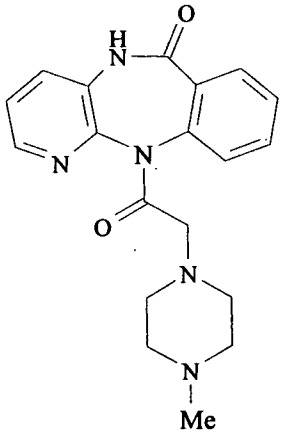
(2)

(X = O,S,NR,CH_2)

(Y = O, S, NR)

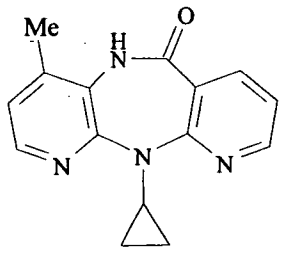
(HET = aromatic or heteroaromatic nucleus)

Scheme 1



.2HCl

(3)



(4)

Scheme 2

1.1 Introduction

The study of tricyclic heteropine derivatives represents an interesting and exciting field of investigation in medicinal chemistry. The following chapter will firstly review the clinical uses and limitations of such heterocycles, then outline the synthetic routes to tricyclic heteropines currently available to the synthetic chemist.

1.2 Biological Background

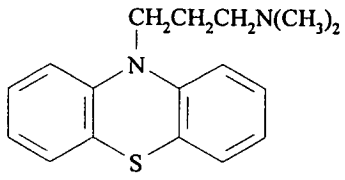
Compounds containing the basic tricyclic heteropine structure [Scheme 1; (1) and (2)] exhibit diverse pharmacological activity and hence have found applications in the understanding and treatment of a number of ailments. These include schizophrenia,[1] Alzheimer's disease[2] and depression[3] as well as asthma,[4] allergies,[5] inflammatory conditions[6] and HIV infection.[7] Tricyclic heteropines have even been used as riot control agents.[8] A slight modification of the tricyclic structure leads to a profound alteration of the activity profile of the compound. Indeed pirenzepine [Scheme 2; (3)] an M_1-selective antimuscarinic compound used in the treatment of peptic ulcers is structurally very similar to nevirepine (4), a potent inhibitor of HIV-1 reverse transcriptase.

Investigations into the treatment of schizophrenia have initiated a large amount of research concerning the use of tricyclic heteropines and their derivatives as neuroleptics agents.[9] More people between the ages of twenty-five and sixty-five who are hospitalised or disabled within the community suffer from this potentially

debilitating condition than any other psychiatric disorder, accounting for around 1% of the total population. There is no known cure for schizophrenia. 30% of schizophrenic patients remain permanently institutionalised, 45% are maintained within society only through the continued use of neuroleptic drugs while the remainder are accounted for by homeless and other untreated cases. However, despite the severity of the conditions it encompasses, the diagnosis of schizophrenia remains in some respects ill-defined. Public knowledge of, and attitude towards such psychiatric disorders is often ill informed. For instance, schizophrenia is still frequently confused with the rare "Jekyll and Hyde" dual personality syndrome. Indeed some people have categorically denied the existence of schizophrenia as a disease, seeing it as a socially defined or induced phenomenon.

In the past, and even now in some parts of the world, man has looked upon the abnormal behaviour associated with schizophrenia as a sign of magical powers or of possession by the devil. Only as recently as 1911 the Swiss psychiatrist Eugene Bleuler first coined the term schizophrenia (Greek: skhizo, split; phren, mind) in an attempt to describe more appropriately the essential elements of the condition, which at that time was thought of as an incurable disease. It is now considered a treatable medical illness.

Schizophrenia is the generic name for a group of disorders characterised by a progressive disintegration of the personality and its relationship with the outside world. Emotional stability and thinking deteriorate with impairment of personal relationships and the ability to cope with everyday life.[10]



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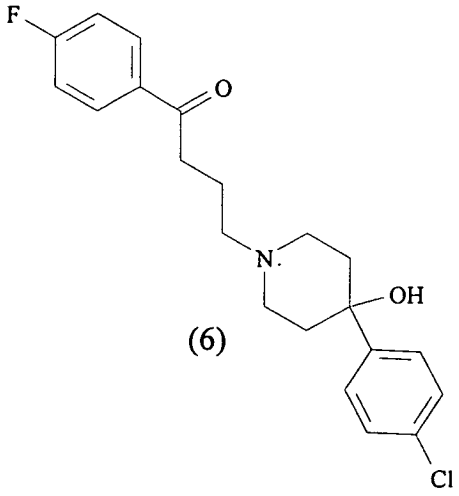

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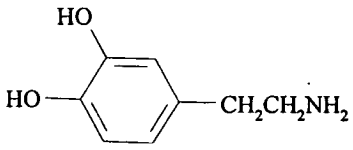

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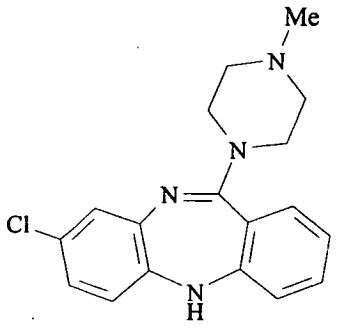

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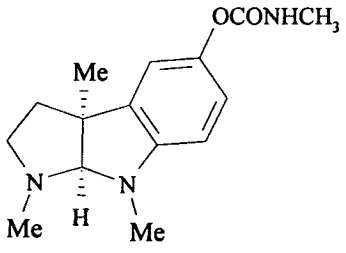


(9)

Scheme 3

The key symptoms of schizophrenia can be divided into two groups which have different underlying causes. The initial, so called positive symptoms, include delusions, hallucinations and thought disorders, while the negative symptoms, which have a later onset, include dementia, loss of emotional response and social withdrawal. It has been suggested that the negative symptoms are a reflection of atrophy of certain brain areas,[11] a hypothesis which is supported by studies using computer tomography. These studies have shown that chronic schizophrenic patients undergo a progressive shrinkage of the brain. There have been many theories concerning the aetiology of schizophrenia, but with the emergence of neuroleptics, chemical theories have come to the fore. It is possible that the gradual degradation of neurons which results in the negative symptoms is caused by a biological abnormality of which the positive symptoms are the outward sign.

The theory initiating the most interest as to the causes of schizophrenia is the so called dopamine hypothesis,[12] which proposes an increased activity of dopamine neurotransmission in the disease. This hypothesis originated in the observation that drugs with dopamine agonist or dopamine-releasing properties, typically amphetamines, can induce a psychosis indistinguishable from paranoid schizophrenia. The direct relationship between the clinical efficacy of antipsychotic drugs and their antagonistic action at dopamine receptors lends further support to the hypothesis. Consequentially, several dopamine D_2 receptor antagonists have been developed as drugs to combat schizophrenia. The first group, the so called typical neuroleptics such as chlorpromazine [Scheme 3; (5)] and more recently haloperidol (6), were successful in a small number of cases, but in general these drugs treated

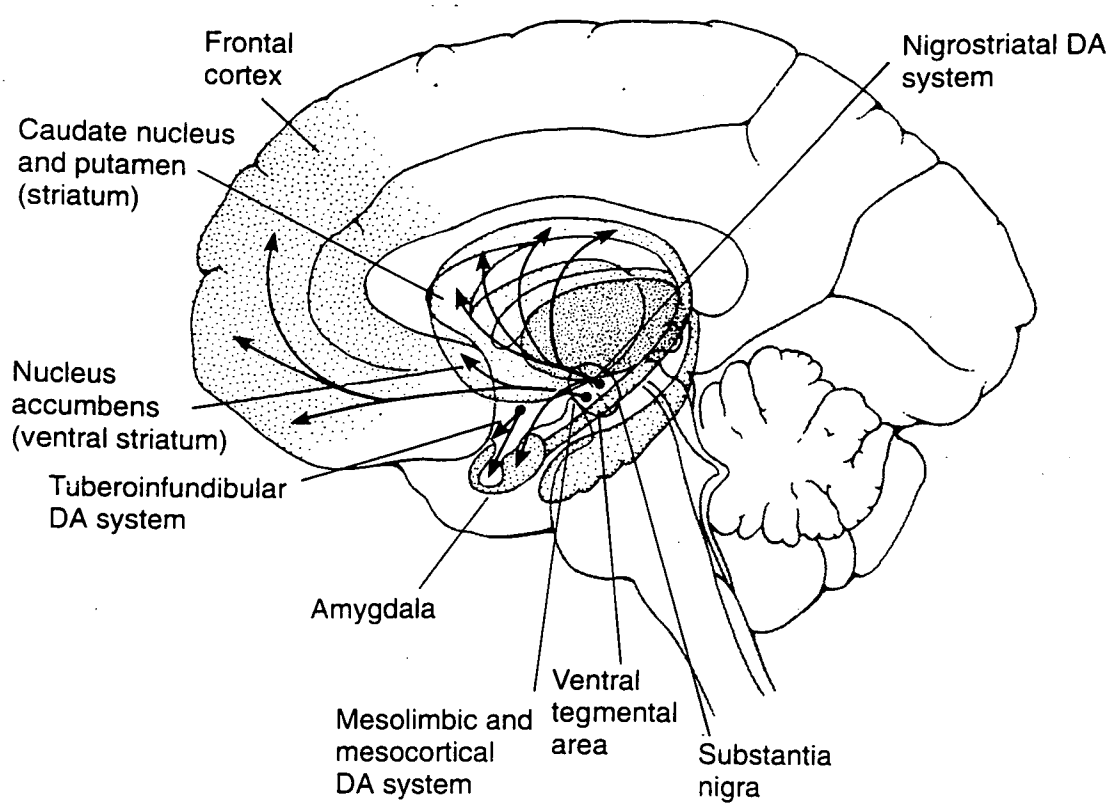

Frontal cortex
Nigrostriatal DA system
Caudate nucleus and putamen (striatum)
Nucleus accumbens (ventral striatum)
Tuberoinfundibular DA system
Amygdala
Ventral tegmental area
Mesolimbic and mesocortical DA system
Substantia nigra

Figure 1

only the positive symptoms of the patient and failed to attenuate the negative symptoms.[13] More importantly however, these drugs were associated with serious neurological side-effects resulting in loss of control of bodily movement.[14] This was due to extrapyramidal side-effects resulting in Parkinsonism-like symptoms and tardive dyskinesia, involuntary body movements such as facial ticks. These side-effects usually only appear after years of drug administration. They are thought to be due to indiscriminate dopamine blockade throughout the brain[15] and persist even after termination of the treatment with the typical neuroleptic drug.

Dopamine (7) is the most common neurotransmitter in the mammalian brain (Figure 1), there being three neuronal pathways controlled by this agent: the nigrostriatal pathway, which is associated with the control of movement; the mesocorticolimbic pathway, extending into the mesolimbic and mesocortical brain regions, associated with emotional states, cognitive function and social behaviour; the tuberoinfundibular pathway which is involved with the secretion of prolactin. These different regions of the brain are reflected in the distribution patterns of the dopamine receptor subtypes.[15]

The dopamine D_2 receptor is heavily localised in the nigrostriatial pathway and has lower levels in various cortical areas. The D_3 receptor is most highly concentrated in the dopaminergic limbic regions and is only found in low levels in the striatum. The D_4 receptor is most highly concentrated in the dopaminergic cortical and limbic areas with lesser amounts in the striatum.

The different distribution of these dopamine receptors presents some interesting aspects. Neuroleptic agents such as haloperidol and chlorpromazine which are most

noted for their production of extrapyramidal side-effects and tardive dyskinesia have highest affinity at the dopamine D_2 receptor. Since the dopamine D_2 receptor is dominant in the striatum, a brain structure which plays an important role in controlling motor behaviour, it has been suggested that D_2 receptor blockade may be linked to these undesirable phenomenon. Based on their tissue distributions, the dopamine D_3 and D_4 receptors would not appear to play a role in the production of extrapyramidal side-effects and consequentially selective antagonists at these two receptors may represent a more desirable class of antipsychotic agents. This hypothesis has been supported by clinical trials.[15]

Haloperidol (6), a typical neuroleptic with a twenty-fold greater affinity for the D_2 receptor compared to the D_4 receptor is known to attenuate only the positive symptoms of schizophrenia and also cause debilitating extrapyramidal side-effects. However, clozapine (8), a so called atypical neuroleptic with a fifteen-fold greater affinity for the D_4 receptor compared to the D_2, not only eliminates the positive symptoms of schizophrenia but also the negative symptoms, upon which the typical neuroleptics have no effect. In addition to this, clozapine does not induce the extrapyramidal side-effects that are the drawback of the typical neuroleptics. This selectivity of clozapine for the dopamine D_4 receptor and the selectivity of the typical neuroleptic haloperidol for the dopamine D_2 receptor, along with the marked differences in the distribution of the dopaminergic receptor subtypes within the brain, is consistent with clozapine's atypical behaviour, its low incidence of extrapyramidal side-effects and haloperidol's propensity to produce extrapyramidal side-effects.

Although the ability of clozapine to differentiate between dopamine receptor subtypes seems to be vital to its atypical behaviour, clozapine has also been shown to have a high affinity for an array of receptors,[16,17] and its atypical behaviour may be a reflection of their cumulative effects.

Clozapine was introduced as a neuroleptic in the 1970s but was withdrawn from use shortly after, following several fatalities due to drug induced agranulocytosis,[18] a disorder of the white blood cells. However, as clozapine treatment was associated with a low incidence of extrapyramidal side-effects, a notable lack of tardive dyskinesia and an efficacy in otherwise unresponsive patients, it has recently been reintroduced in several countries along with regular haematological monitoring of the patient. In addition, there is recent evidence[19] that the coadministration of a radical scavenger, such as ascorbic acid, with clozapine prevents the radical induced agranulocytosis.

Although clozapine represents a great advance in the treatment of schizophrenia, the severe toxic effects have stimulated the search for alternatives. Despite an extensive effort to find a safer drug no alternative has yet been identified which has clinical antypsychotic efficacy combined with the lack of extrapyramidal side-effects and a low risk of inducing any other serious toxic effects. So, within this field, there remains a need for improved antipsychotic agents and hence new and improved synthetic routes to tricyclic heteropine derivatives.

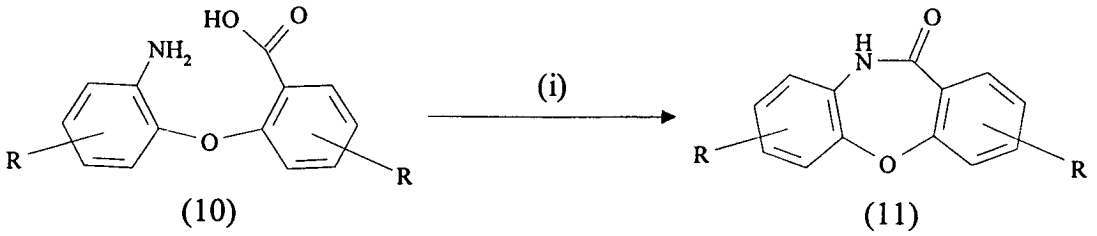
The treatment of Alzheimer's disease, for which no cure is currently available, is a second area in which tricyclic heteropine derivatives can play a major role. Dementia, or Alzheimer's disease, recognised first by Alois Alzheimer, a German

neurologist, in 1907 is unquestionably the most serious psychiatric disorder of old age. It will within the next decade become the largest socio-medical problem yet faced in the western world, and this problem will increase as the proportion of the population over the age of sixty-five rises to more than 20% by the end of the century.

Alzheimer's disease is characterised by a progressive deterioration of cognition, memory, intellect, behaviour and emotion that is irreversible. A definite diagnosis of Alzheimer's disease requires histological examination of the brain, which is usually only performed at post mortem. The affected brain shows a generalised shrinkage, and examination on a microscopic scale, particularly in the areas associated with the memory,[20] shows a loss of neuronal cells and the build-up of plaques and tangles which are the hallmark of Alzheimer's disease. The plaques are extracellular structures consisting of swollen, degenerating nerve structures and a central core of a protein called an amyloid. The neurofibrillary tangles are intracellular structures made up of bundles of abnormal fibres, each of which consist of paired helical filaments and a protein named tau.

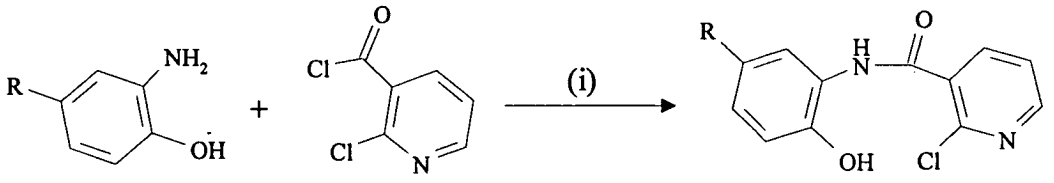
In addition to these neurological changes, there are widespread changes in brain neurotransmitter systems.[21] The best characterised of these changes is a decrease in the amount of the neurotransmitter acetylcholine and the enzymes which are involved in its metabolism. The decrease is seen in the areas of the brain known to be important in the memory function.[20] This suggests that restoration of normal acetylcholine levels within these areas may attenuate the symptoms of Alzheimer's disease. Three types of pharmacological strategies have been utilised to stimulate

cholinergic activity:[22] namely (i) enhancement of acetylcholine synthesis and release from presynaptic neurons, (ii) inhibition of acetylcholine metabolism, (iii) direct stimulation of postsynaptic cholinergic receptors. Strategies (i) and (ii) have some obvious drawbacks. (i) By analogy with the effect of administering L-dopa on Parkinson's disease, cholinergic precursor levels could be enhanced. However, the availability of acetyl coenzyme A rather than that of the precursor choline seems to be the limiting factor for the synthesis of acetylcholine. Furthermore, cholinergic precursors do not readily penetrate the blood-brain barrier. Alternatively an antagonist at the presynaptic M_2 muscarinic receptor could inhibit the negative feed-back mechanism by which the amount of acetyl choline released is controlled, thereby increasing the release of acetylcholine at the nerve terminals.[23] Unfortunately this approach has been precluded by the fact that presynaptic M_2 muscarinic receptors are markedly reduced in cerebral cortices of patients suffering from Alzheimer's disease. (ii) Acetylcholine is enzymatically degraded in the synapse by acetylcholinesterase and thus inhibition of this enzyme should enhance the availability of acetylcholine. Although this approach has produced some positive results in clinical trials with drugs such as physostigmine (9), these compounds are toxic and their beneficial effects are transient. (iii) The most obvious method of enhancing the cholinergic function is to use direct agonists acting at the postsynaptic M_1 receptor which is independent of the presynaptic neuron and the availability of the transmitter. The number of these postsynaptic M_1 receptors is not reduced in Alzheimer's disease,[24] and hence is an attractive target for a therapeutic agent. However, a drug that is an unselective agonist at both M_1 and M_2 muscarinic



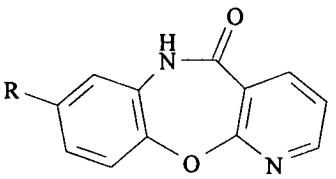
(10) (11)

(i) 180°. (R = H, OMe)



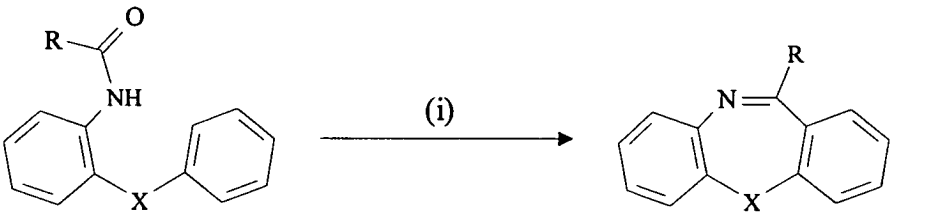
(12) (13) (14)

(ii)



(15)

(i) THF, reflux. (R = H, CH_3, Cl)
(ii) NaOEt, DMF, reflux.



(16) (17)

(i) Polyphosphoric acid, 150°. (X = O,S, NMe, CH_2)
(R = H, Me)

Scheme 4

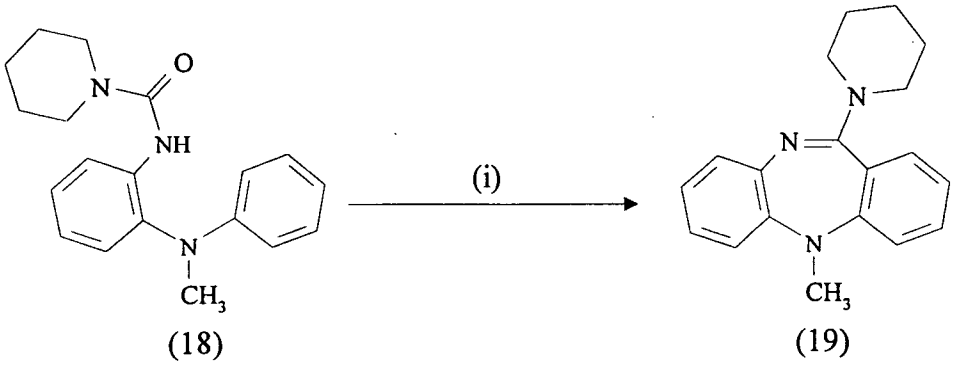
receptors would not only enhance the cholinergic response through the M_1 receptor, it would also inhibit the release of acetylcholine by the activation of the presynaptic M_2 receptors, resulting in a net decrease in acetylcholine release.[23] In addition, M_2 receptors are also important in the heart and gut, where unwanted stimulation of the receptors would lead to adverse side-effects. A better approach would be to find an M_1-selective receptor agonist.

As stated earlier, pirenzepine (3) is an M_1-selective antimuscarinic compound. It does not however have any effect within the central nervous system due to its inability to cross the blood-brain barrier. It is possible therefore that other derivatives of the basic tricyclic heteropine structure would possess the desired properties for use as a drug in the treatment of Alzheimer's disease.

In addition to their uses in the treatment of schizophrenia and Alzheimer's disease, tricyclic heteropines have found uses in a number of other ways. Their ability to act as prostaglandin E_2 antagonists[25] and in the field of HIV research as HIV-1 reverse transcriptase inhibitors[26] has fueled much recent research. There is therefore a need for organic chemists to devise flexible routes to tricyclic heteropine derivatives which can be applied to the synthesis of an array of analogues for biological evaluation.

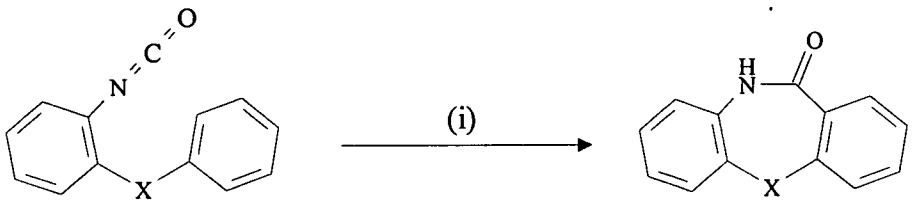
1.3 Synthesis of Tricyclic Heteropines

It is readily apparent from the diverse biological activity of tricyclic heteropines and the further modification of their activity profiles by subtle structural variations, that it



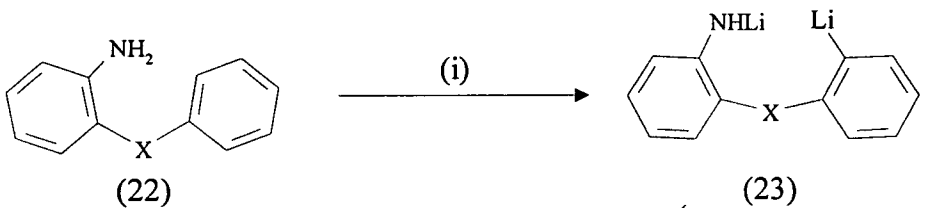
(18) (19)

(i) $POCl_3$, $PhCH_3$, reflux.

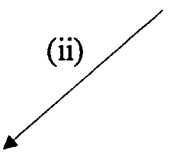


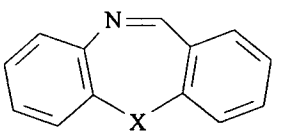
(20) (21)

(i) $AlCl_3$. (X = O,S)



(22) (23)





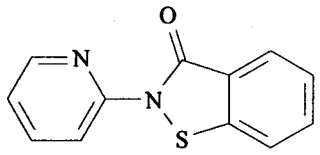
(24)

(i) n-BuLi. (X = O, S, NH)
(ii) $(CH_3)_2NCOH$.

Scheme 5

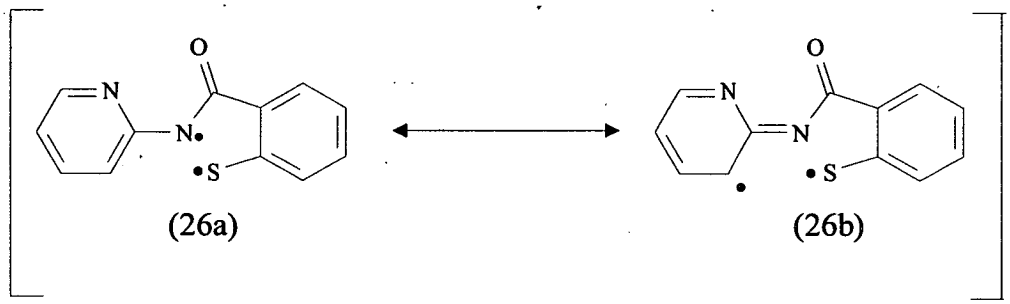
is of prime importance to have readily accessible as large an array of these structures as possible. Therefore, the ability to synthesise and modify tricyclic heteropines in a rational manner is vital in order to provide the necessary candidates for biological screening.

Although a number of tricyclic heteropines have been described in the literature, the available general routes for their construction are relatively few, with the majority of syntheses employing one of three main approaches. The approach most commonly used (Scheme 4) involves the initial formation of the heteroatom bridge between the two aromatic rings, with the ring closure being accomplished by the cyclocondensation of an amine with an aldehyde or ketone function to form an imine, with an amide to give an amidine, or with a carboxylic acid to give the corresponding lactam [e.g. (10) → (11)].[27] In practice this method often results in reductive cyclisation of the appropriate nitro compound[28] and has formed the basis of many synthetic routes to a plethora of heteropine derivatives such as dibenzothiazepines,[29] dibenzodiazepines,[30] pyridobenzoxazepines[31] and thienobenzoxazepines.[32] An alternative strategy (Scheme 4) involves initial construction of the amide or imine link by the condensation of an aromatic amine with an appropriate carbonyl compound [e.g. a carboxylic acid derivative or an aldehyde or ketone; e.g. (12) + (13) → (14) → (15)].[18] This type of cyclocondensation has also been demonstrated using amines and amides.[33] The third major strategy (Scheme 4) involves the ring closure of appropriately functionallised amides [e.g. (16) → (17)].[34] This Bischler-Napieralski type cyclisation has been applied to the synthesis of a variety of systems such as dibenzoxazepines[35] and dibenzothiazepines.[36] This strategy has been further

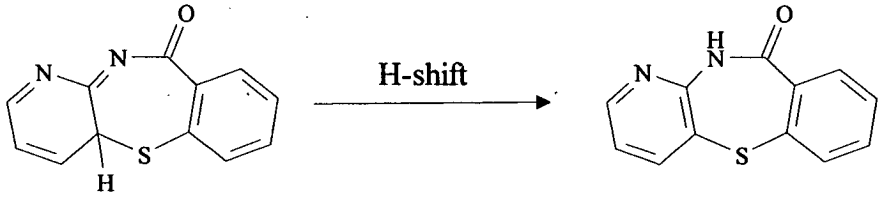


(25)

(i)



(26a) (26b)



(27) (28)

(i) hν.

Scheme 6

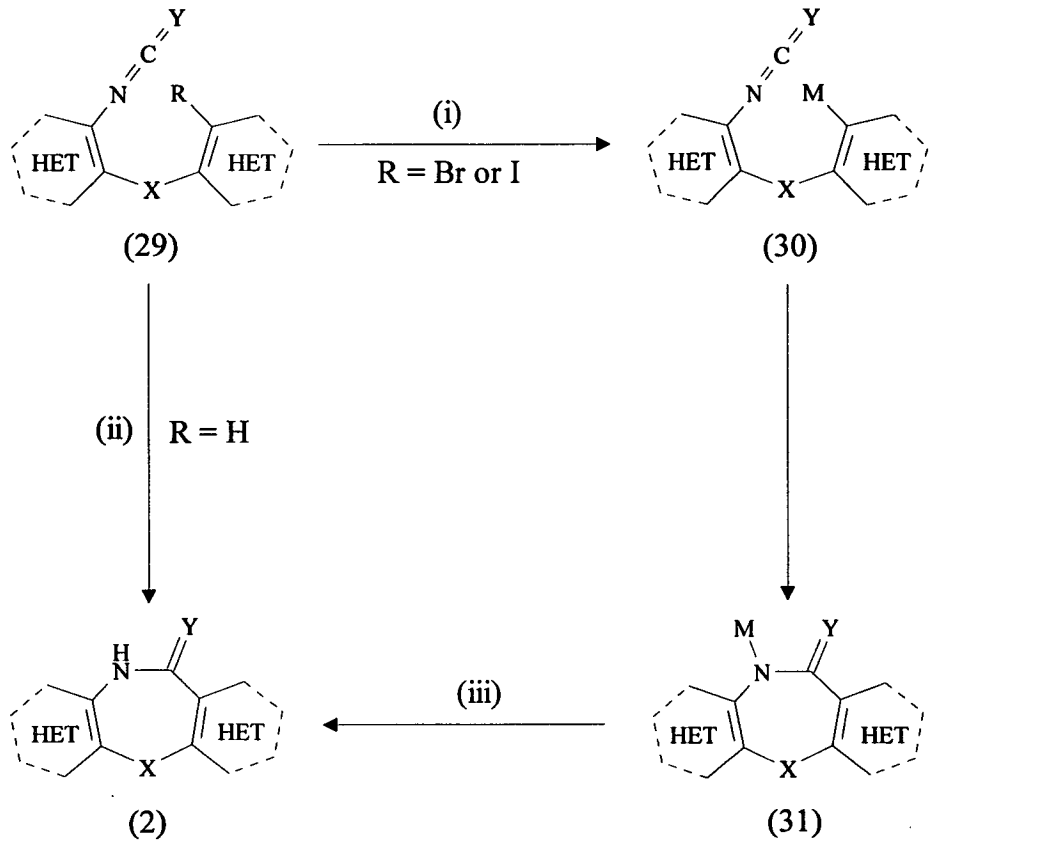
extended (Scheme 5) to the cyclisation of appropriately functionalised urea derivatives [e.g. (18) → (19)].[37] An added advantage of this strategy for the synthesis of tricyclic heteropines is that the functionalisation of the imine bond is already incorporated into the cyclisation precursor. In spite of the obvious advantage of this approach and others employing a similar strategy, they have seldom been cited in the literature. Other infrequently employed approaches include (Scheme 5) Lewis acid catalysed cyclisations of heterocumulene derivatives [e.g. (20) → (21)],[38] carbonyl insertion into diphenylamine dilithio derivatives [e.g. (22) → (23) → (24)][39] and photolysis {Scheme 6; (25) → [(26a) + (26b)] → (27) → (28)}.[40]

The approaches to tricyclic heteropines discussed here, and many more less widely used methods omitted for brevity, have been used to prepare a myriad of tricyclic heteropine derivatives. However they all suffer from certain drawbacks. The most important of these are the harsh reaction conditions, particularly in the ring closure steps where high temperatures and polyphosphoric acid are often employed. The restricted availability of the required starting materials can also limit the synthetic versatility and utility of the aforementioned synthetic methods for the synthesis of the required range of structures.

It was anticipated that a more versatile synthetic strategy for the synthesis of tricyclic heteropines could be developed by the exploitation of heterocumulenes (isocyanates, isothiocyanates, carbodiimides), utilising a number of mild conditions to induce cyclisation such as carbanion-promoted, radical-mediated and transition metal promoted processes. This strategy will be discussed more fully in Chapter 2.

Chapter 2

Studies of Novel Cyclisation Reactions of Heterocumulenes Leading to Tricyclic Heteropine Derivatives



(i) Mg or BuLi.
(ii) Lewis acid.
(iii) [H^+].

(M = Mg or Li)
(X,Y = NR, O, S)
(HET = aromatic or heteroaromatic nucleus)

Scheme 7

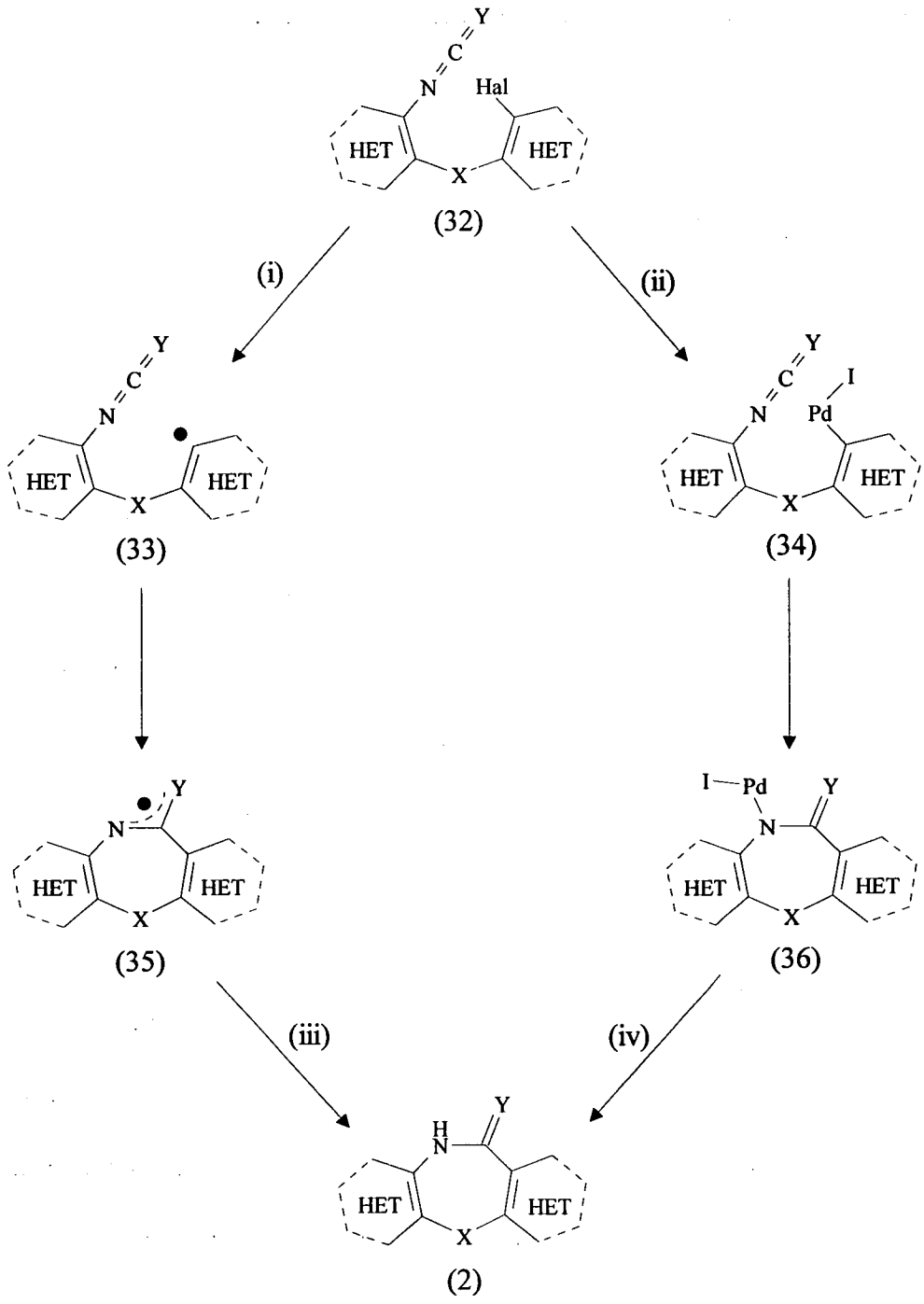
Studies of Novel Cyclisation Reactions of Heterocumulenes Leading to Tricyclic Heteropine Derivatives

2.1 Introduction

The following chapter describes investigations into new, general synthetic approaches to the tricyclic heteropine derivatives (1), dibenzoxazepines, pyridobenzoxazepines, pyrimidobenzoxazepines, dibenzothiazepines and dibenzodiazepines. The stimulus for these investigations was the potential biological activity of such compounds as already discussed in Chapter 1, particularly their potential use as receptor site probes in schizophrenia.

The general synthetic routes to tricyclic heteropines currently available to the synthetic chemist have been outlined in the previous chapter. It was anticipated that the relatively harsh reaction conditions employed in the ring closure steps involved in these routes could be avoided by the use of heterocumulene intermediates. It was thought that the incorporation of a highly reactive isocyanate, isothiocyanate or carbodiimide moiety into the appropriate cyclisation precursor would facilitate cyclisation under a variety of milder conditions.

The first cyclisation method investigated was the Lewis acid catalysed cyclisation of heterocumulenes [Scheme 7; (29) → (2)]. Although there has been previous work in the same area,[41] it was largely limited to the cyclisation reactions of carbodiimides, leading to dibenzoxazepine derivatives [(2); X=O; Y=NR; HET=benzene]. It was hoped that further research on such processes, using a broader range of cyclisation precursors would afford a greater understanding of their uses and limitations.



(i) Bu_3SnH or $Bu_3SnSnBu_3$.
(ii) Pd(0).
(iii) [H•].
(iv) [H].

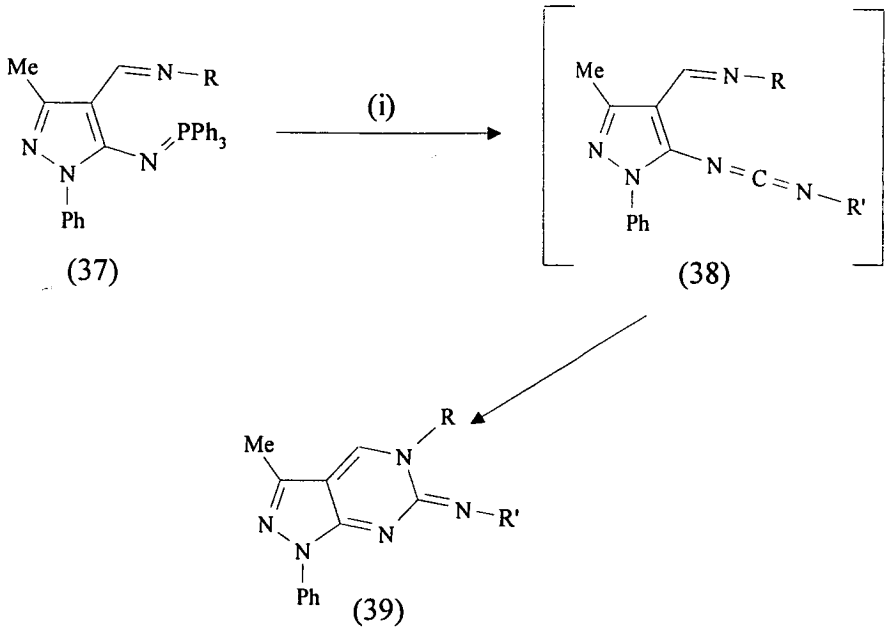
(X,Y = NR, O, S)
(HET = aromatic or heteroaromatic nucleus)

Scheme 8

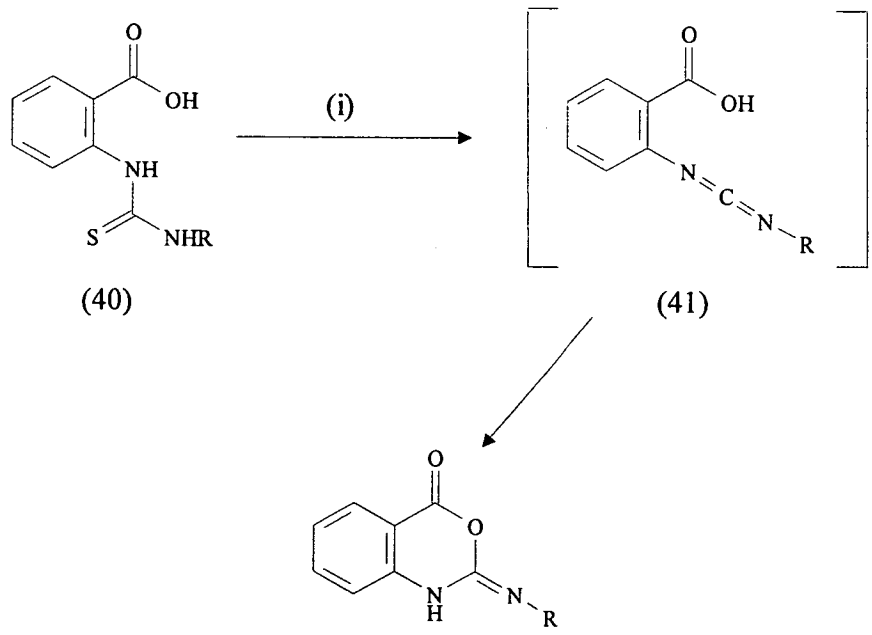
A second, very attractive method of inducing cyclisation of the heterocumulene precursors is by a carbanion-promoted process [i.e.; (29) → (30) → (31) → (2)]. This could be achieved either through a Grignard type addition onto the heterocumulene or by the addition of a lithium salt. Although there are a few examples of addition to heterocumulenes by Grignard[42,43] and organolithium reagents[44] they have all been intermolecular processes. The proposed methodology in the present studies would be the first example of intramolecular addition. Both the Grignard and lithium approaches require a halide substituent attached to the heteroaromatic ring ortho to the ether, sulphide or amine bridge, the introduction of which would not pose a problem. The Grignard and the lithium salt approaches both lend themselves to mild reaction conditions, often at low temperature. In addition, the Grignard and organolithium intermediates both react in a specific manner, affording greater control than is possible using the Lewis acid methodology.

Neither radical addition to heterocumulenes nor transition metal promoted addition to heterocumulenes has been reported in the literature. It was anticipated that the investigation of such processes could also provide novel, flexible routes to tricyclic heteropine derivatives under mild conditions (Scheme 8). The halide substituted heterocumulene derivatives (32) would act as cyclisation precursors in both these processes. The radical mediated cyclisation [i.e. (32) → (33) → (35) → (2)] could be induced by the action of either tributyltin hydride or hexabutylditin, forming an aryl radical (33) which could then add across the heterocumulene to form the tricyclic heteropine derivatives (2).

The transition metal promoted process [i.e. (32) → (34) → (36) → (2)] is analogous to the Heck reaction.[45] The palladium reagent reacts by insertion into the carbon-

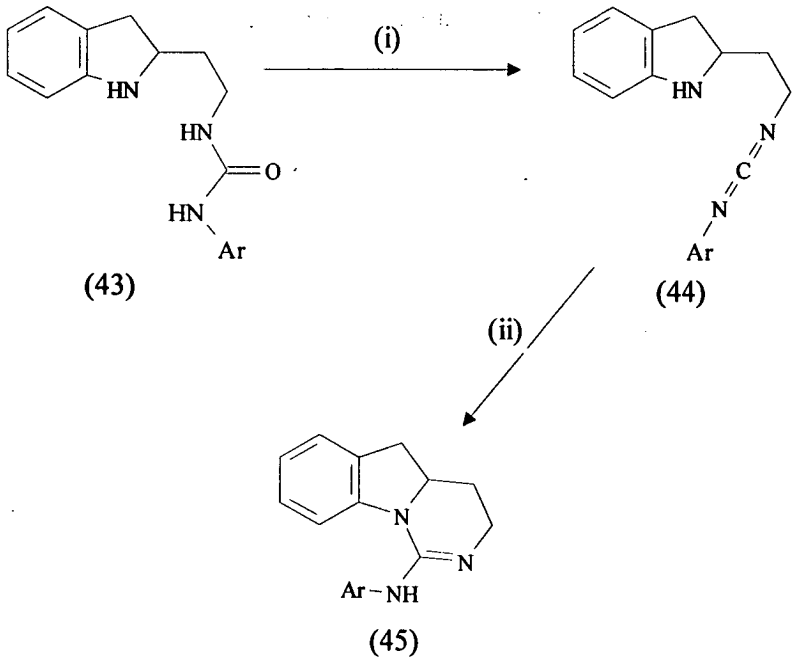


(i) R'N=C=O, DCM, room temp.

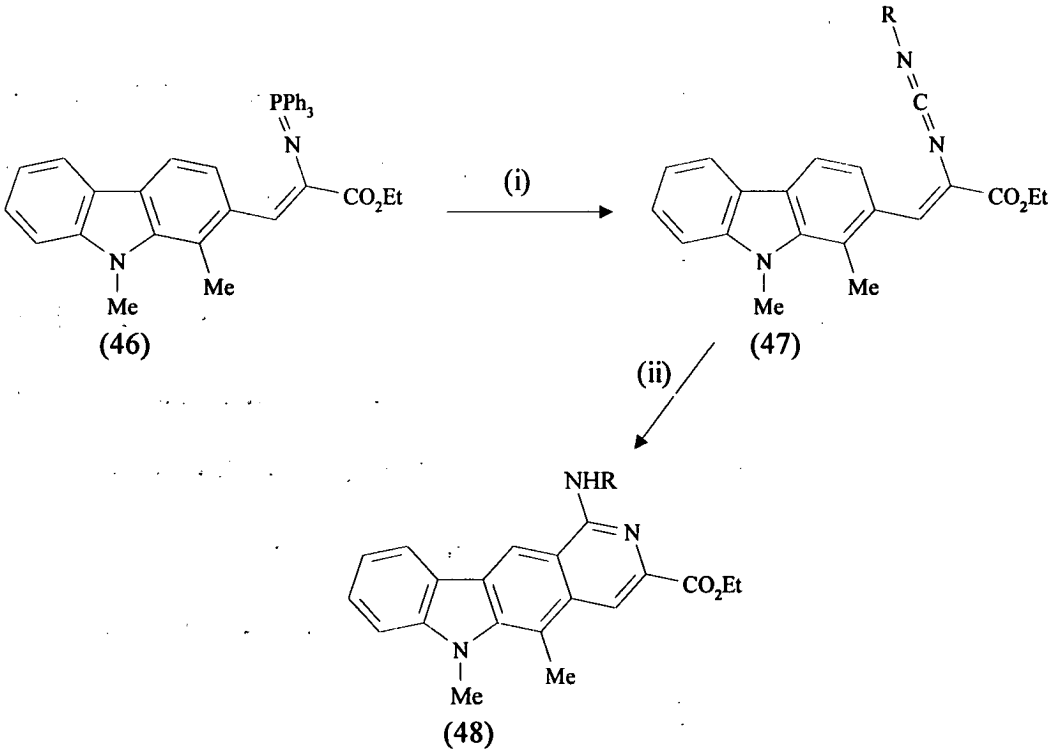


(i) HgO, acetone.

Scheme 9



(i) Ph_3P, Et_3N, CCl_4, CH_2Cl_2, reflux.
(ii) $SnCl_4$, CCl_4, room temp.



(i) RN=C=O, toluene, reflux.
(ii) $PhCH_3$, 160°, sealed tube.

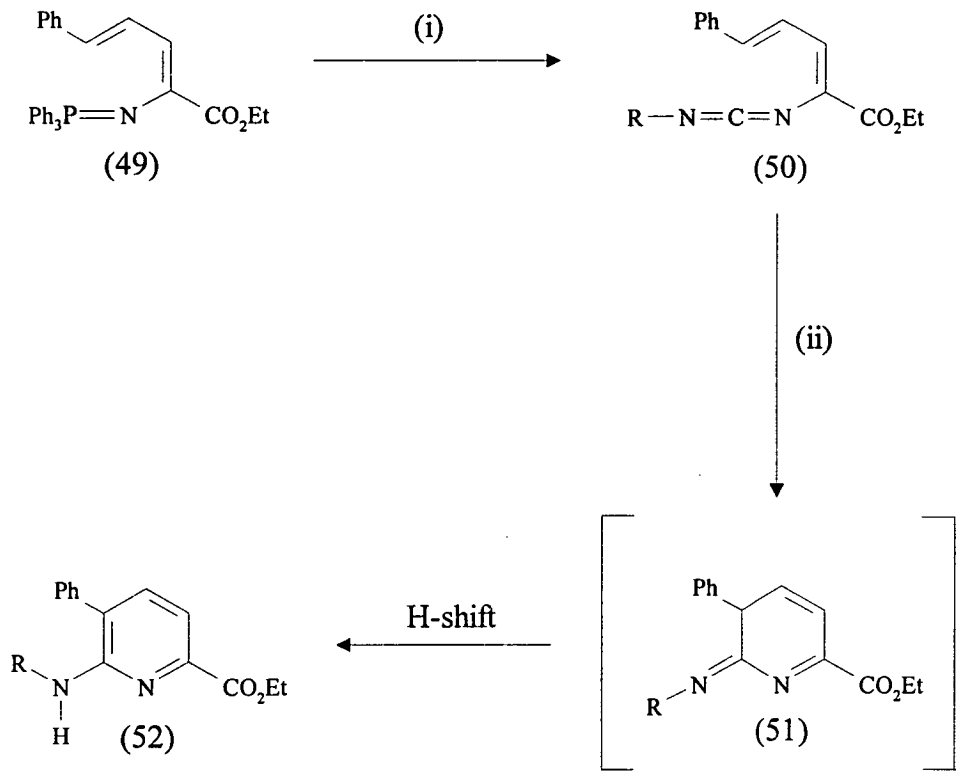
Scheme 10

halogen bond forming an organo-palladium species (34). This reacts intramolecularly with the heterocumulene moiety to form the seven membered ring structure (36) with elimination of the palladium affording the tricyclic heteropine derivatives (2).

The proposed novel routes here described all have potential as versatile strategies for the synthesis of tricyclic heteropines. They would complement existing methodology and provide valuable methods for synthesising compounds of possible biological activity.

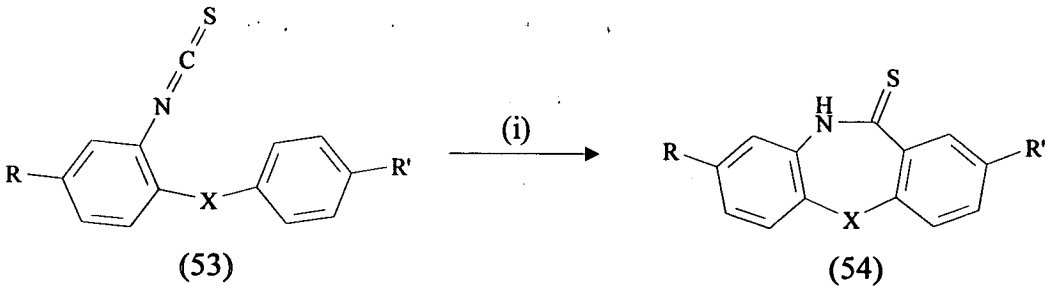
2.2 Cyclisation Reactions of Heterocumulene Derivatives

Although they have seen only limited use in the synthesis of tricyclic heteropines,[41] substituted carbodiimides have been applied as key precursors of many classes of compounds including amidines, guanidines and isoureas.[46] They have also proven valuable intermediates in the synthesis of a variety of heterocyclic systems but their use as direct precursors of heterocyclic systems has been somewhat limited. In this context the carbodiimide functionality is most commonly created and immediately trapped intramolecularly by a nitrogen or oxygen nucleophile (Scheme 9) forming heterocyclic systems such as pyrazolopyrimidines [i.e. (37) → (38) → (39)][47] and benzoxazinones [i.e. (40) → (41) → (42)].[48] Such heterocyclisations have the added advantage that the potentially unstable carbodiimide intermediate need not be isolated. In a few cases (Scheme 10) the carbodiimide intermediate has been isolated and subsequently cyclised, the final ring closure step being initiated either by Lewis acid catalysis [i.e. (43) → (44) → (45)][49] or thermally [i.e. (46) → (47) → (48)][50] to form pyrimidoindole and pyridocarbazole derivatives respectively. Carbodiimides



(i) RN=C=O, toluene.
(ii) Toluene, reflux.

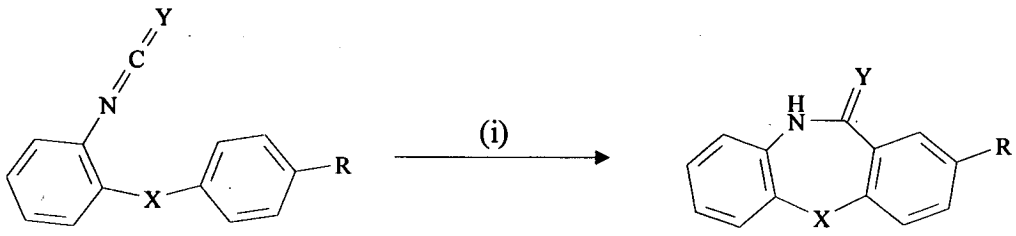
Scheme 11



(53) (54)

(i) $AlCl_3$, 1,2-dichlorobenzene, 100^o.

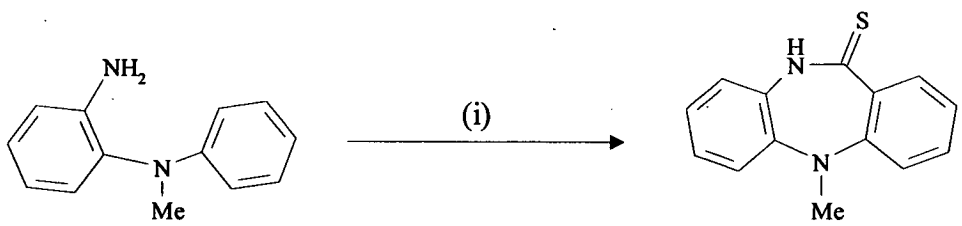
(X=O,S)
(R,R'=H,Cl,Me)



(55) (56)

(i) Polyphosphoric acid or $AlCl_3$.

(X,Y=O,S)
(R,=Me,OMe, SO_2Me)



(57) (58)

(i) $COCl_2$, CS_2, Et_3N, room temp. then $AlCl_3$.

Scheme 12

have also been used as dienophiles (Scheme 11) in the synthesis of highly functionalised pyridine derivatives [i.e. (49) → (50) → (51) → (52)][51] where the carbodiimide, upon heating in toluene, undergoes electrocyclisation, followed by a 1,3-proton shift to give the desired products.

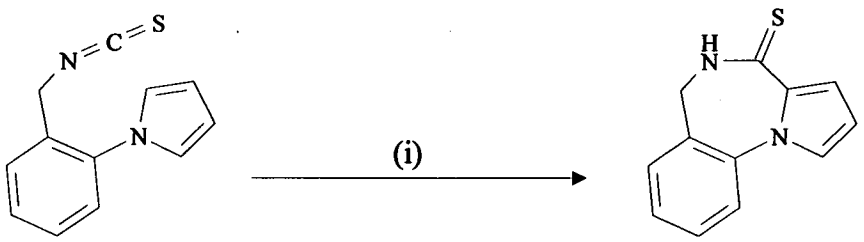
These relatively few examples show how carbodiimides can be used to form complex ring structures difficult to synthesise by alternative methods. However, by synthesising appropriate compounds containing a carbodiimide functionality it was hoped to develop additional methods for inducing cyclisation, thus opening up new routes to a large number of structures of synthetic and pharmacological importance.

Isothiocyanates have been shown to have uses in the synthesis of various classes of compounds such as thioamides and thioureas,[52] which in turn are valuable intermediates in synthetic organic chemistry. Substituted isothiocyanates have also been applied as direct precursors in the synthesis of an array of complex heterocyclic systems. These include systems such as triazines,[53] triazolidines[54] and thiatriazoles,[55] but for brevity only their role in the synthesis of tricyclic heteropine derivatives will be covered in this discussion.

Aluminium trichloride catalysed cyclisation reactions of isothiocyanate derivatives, leading to tricyclic heteropines have been reported by Nagarajam, Kulkani, Venkateswarlu and Shah[56] (Scheme 12). Substituted o-isothiocyanatodiphenyl ethers (53) were converted into the corresponding dibenzoxazepinethiones and dibenzothiazepine thiones (54) by the action of aluminium trichloride. They report that the substituted tricyclic heteropines (54) were obtained in only one isomeric form, which is contrary to findings from related work by Weddel and Tennant.[41] Further examples of cyclisation reactions of o-isothiocyanatodiphenyl ether

derivatives have been reported by Schmutz[57] where the isothiocyanate precursors (55) were cyclised to the corresponding tricyclic heteropines (56) by the action of either aluminium trichloride of polyphosphoric acid. The paper also indicates that deactivating substituents on the benzene ring (e.g. R=SO_2Me) result in considerably lower yields.

Similar reactions have also been reported by Hunziker, Fischer and Schmutz[58]. In this case the treatment of the amine (57) with phosgene, carbon disulphide and triethylamine afforded the isothiocyanate derivative which without isolation was then reacted in situ with aluminium trichloride, affording the desired tricyclic heteropine (58). It was anticipated that the investigations undertaken in the present studies would further develop this concept by studying the Lewis acid catalysed cyclisations of these isothiocyanate precursors in a more detailed and methodical manner.

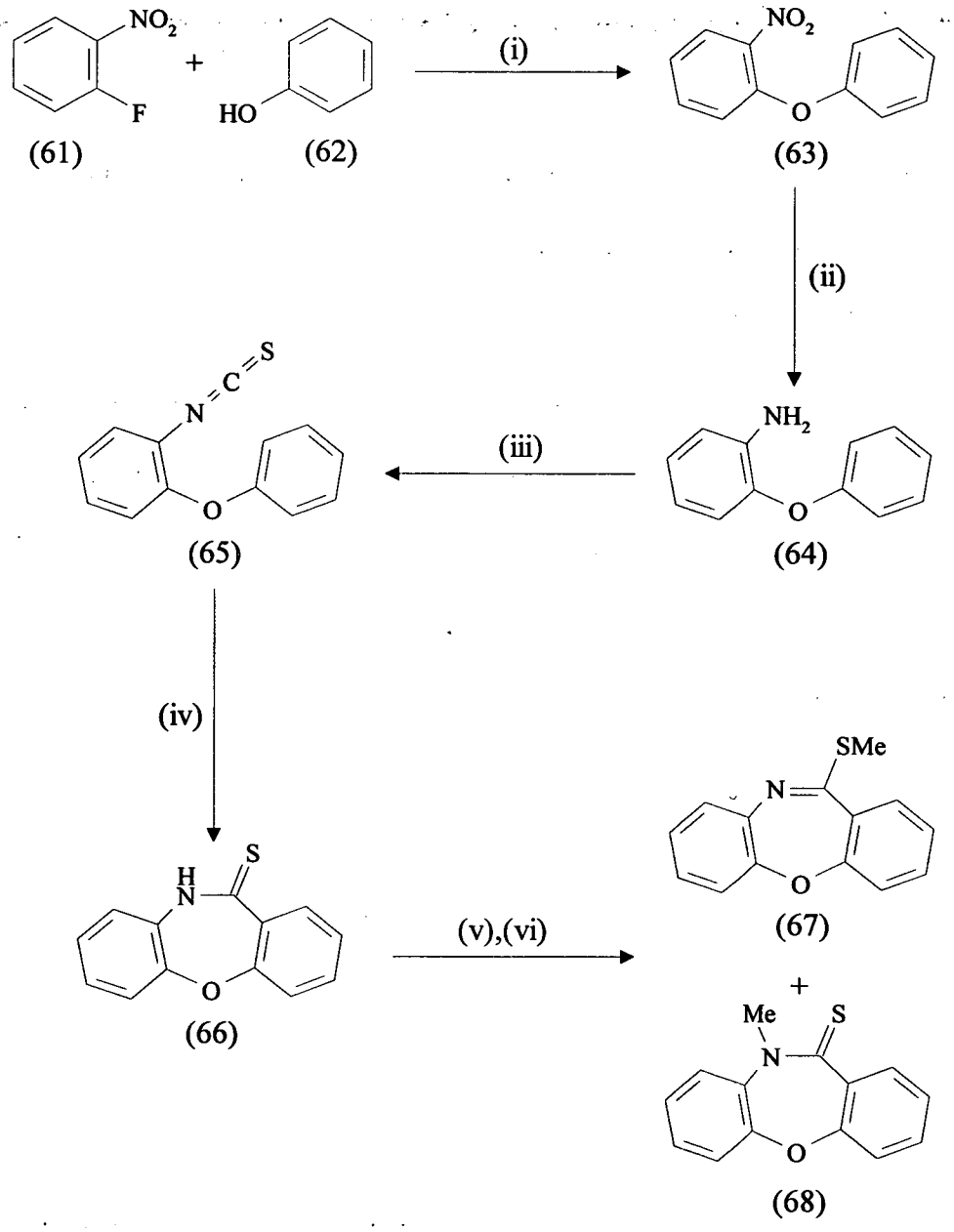


(59) (60)

(i) polyphosphoric acid.

Scheme 13

Isothiocyanate derivatives have also been employed as precursors of tricyclic heteropine derivatives other than dibenz-fused systems. Duceppe and Gauthier[59] reported that 1-(2-isothyocyanato-methylphenyl)pyrrole [Scheme 13; (59)] on



(i) NaH, DMF, 100^{o}.
(ii) H_2, Pd-C, EtOAc, room temp., atmos. press.
(iii) $Cl_2C{=}S$, AcOH, $HCl_{(aq)}$, room temp.
(iv) Lewis acid.
(v) MeI, NaH, DMF, room temp.
(vi) Me_2SO_4, NaH, DMF, room temp.

Scheme 14

treatment with polyphosphoric acid afforded the pyrrolobenzodiazepine (60) in high yield.

These examples highlight the potential use of isothiocyanates in the synthesis of tricyclic heteropines. It was anticipated that the investigations described in this, and the subsequent chapter would exploit this underdeveloped area, leading to the synthesis of an array of compounds of possible biological importance. With this aim in mind, novel methods were investigated to induce the intramolecular cyclisation of heterocumulenes in general and to exploit the untapped potential of this functionality by applying these methods specifically to the problem of the synthesis of tricyclic heteropine derivatives.

2.3 Cyclisations of Heterocumulenes Leading to Dibenz[b,f][1,4]oxazepines, Pyridobenz[2,3-b][1,4]oxazepines and Pyridobenz[2,3-f][1,5]oxazepines

Investigations initially centred on the synthesis of dibenzoxazepine derivatives. Not only did this avoid the use of protecting groups necessary in the synthesis of dibenzodiazepines, but acted as a valuable model when expanding the research to include other tricyclic heteropine systems.

The key starting material for the proposed synthetic approach (Scheme 14) to dibenz[b,f][1,4]oxazepine-11[10H]-thione (66) was the known[60] 2-aminodiphenyl ether (64). The synthesis of the amine was achieved via the sodium hydride catalysed reaction of phenol (62) with 2-fluoronitrobenzene (61) in dimethylformamide at 100°, affording 2-nitrodiphenyl ether (63)[61] in quantitative yield. This was reduced catalytically over palladium-on-charcoal in ethyl acetate at room temperature and

atmospheric pressure to give the desired 2-aminodiphenyl ether (64) in high yield. The amine (64) was subsequently reacted with two equivalents of thiophosgene in an 80% mixture of acetic acid in 2M aqueous hydrochloric acid at room temperature to afford in quantitative yield a pale yellow oil, which gave accurate mass data consistent with the expected molecular formula $C_{13}H_9NOS$, corresponding to the 2-isothiocyanatodiphenyl ether structure (65). The spectroscopic properties of the product were also in accord with this structure.

As previously described, aluminium trichloride has been used to catalyse the cyclisation of 2-isothiocyanatodiphenyl ether derivatives[56,57] to give the corresponding dibenzoxazepines. In this case however the Lewis acid selected was aluminium tribromide, widely accepted as one of the strongest Lewis acids. It must also be noted however, that when an order of Lewis acidity is being assigned to a collection of metal cations the reference ligand must be defined, for a different reference ligand can often lead to a different order of Lewis acidity. The same observation, of course, also applies to orders of Lewis basicity.[62]

The isothiocyanate (65) in dichloromethane was reacted with a solution of aluminium tribromide in dichloromethane at room temperature. This afforded a moderate yield (53%) of a yellow crystalline product which gave analytical and mass spectral data consistent with the expected dibenzoxazepinethione structure (66). The i.r. and ^1H n.m.r. spectroscopic properties of the product were also in accord with this structure. The yield of the cyclised material was increased to 82% by heating the reaction mixture under reflux. At this point it was decided to undertake a study of the effects of changing the Lewis acid on the outcome of this cyclisation step. Related work by Weddel and Tennant[41] showed that the optimum stoichiometry of the Lewis

acid for this type of reaction changed from Lewis acid to Lewis acid, namely: aluminium tribromide, 2 equivalents; aluminium trichloride, 2 equivalents; titanium tetrachloride, 5 equivalents; stannic chloride, 5 equivalents; zinc chloride, 2 equivalents. These ratios of catalyst to reagent were employed throughout the present studies.

Due to the comparative insolubility of aluminium trichloride in dichloromethane it was decided to switch the order of addition of the reagents so that the isothiocyanate was added to the Lewis acid, avoiding having to add the aluminium trichloride as a suspension. This protocol was adopted for all the Lewis acids in the study. It was therefore decided to repeat the reaction of 2-isothiocyanatodiphenyl ether (65) with aluminium tribromide at room temperature, reversing the order of addition. This resulted in an increase in the yield of the dibenzoxazepine to 64%, and the recovery of unreacted isothiocyanate in 4% yield. The yield was further increased by use of aluminium trichloride as catalyst in dichloromethane at room temperature. This afforded a 91% yield of the desired tricyclic heteropine in a much cleaner reaction. The use of zinc chloride as catalyst in dichloromethane at room temperature proved unsuccessful however, with no reaction occurring. Subjecting the same reaction mixture to reflux conditions had no effect on this result, and further increasing the reaction temperature by the use of 1,2-dichloroethane under reflux again resulted in no formation of the desired dibenzoxazepinethione (66). In each of the reactions using zinc chloride as catalyst the isothiocyanate starting material was recovered in quantitative yield. Similarly, the use of stannic chloride as catalyst in dichloromethane at room temperature and under reflux, then in 1,2-dichloroethane

under reflux did not afford the desired tricyclic heteropine derivative (66), with the isothiocyanate starting material again being recovered in quantitative yield.

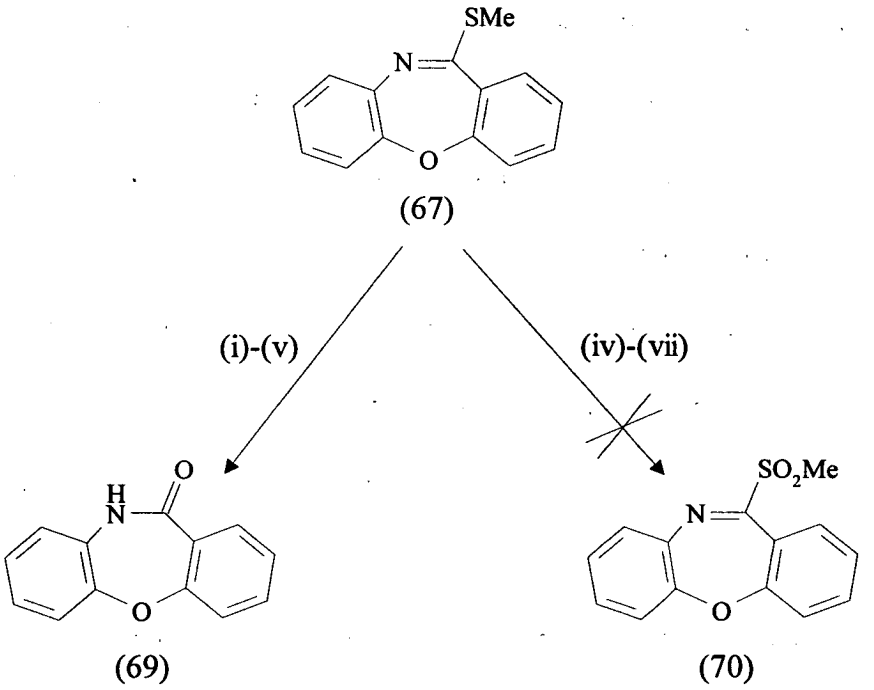
The only non-aluminium-containing Lewis acid in this study that gave any cyclised material was titanium tetrachloride. The titanium tetrachloride catalysed cyclisation of the isothiocyanate (65) in dichloromethane at room temperature gave a mixture which was separated by chromatography to afford only a 12% yield of the desired product (66) and a 77% yield of the unreacted isothiocyanate. Hoping to increase the yield of the cyclised product the reaction was repeated, but with heating under reflux. Unexpectedly, this reaction gave only the unreacted isothiocyanate recovered in quantitative yield. It was therefore decided to repeat the titanium tetrachloride catalysed reaction in dichloromethane at room temperature. This reaction gave a mixture which t.l.c. showed to be similar to that obtained in the first reaction. This mixture was then taken and reacted with a further five equivalents of titanium tetrachloride in dichloromethane under reflux. However, the mixture of starting material (65) and dibenzoxazepinethione (66) was recovered unchanged. If under these conditions the cyclised product (66) had reverted back to the isothiocyanate (65) it could have been proposed that the system was in equilibrium, but this was not the case. Due to there being next to no information on how Lewis acids act as catalysts in this type of process and the types of complexes formed betweem heterocumulenes and Lewis acids, it is difficult to understand how these findings arise. Consequently no explanation can be put forward at present.

The final Lewis acid catalyst investigated in this study was boron trifluorde. Thus, boron trifluoride etherate in dichloromethane was added to the isothiocyanate (65) in dichloromethane at room temperature. Again, these conditions proved unsuccessful

in catalysing the cyclisation reaction, with the unreacted isothiocyanate being recovered in quantitative yield.

With a ready supply of dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) at hand, through the aluminium trichloride catalysed process, it was decided to attempt to thiomethylate the thione (66). It was anticipated that this would allow further functionalisation of the tricyclic structure by displacement of the methylthio group with various nucleophiles.[58,59,63]

The methylthio compound (67) was obtained by the sodium hydride catalysed reaction of the thione (66) with one equivalent of methyl iodide in dimethylformamide at room temperature. These conditions afforded a mixture, from which flash chromatography isolated a 25% yield of a colourless crystalline product which gave analytical and mass spectral data consistent with the methylthiodibenz[b,f][1,4]oxazepine structure (67). The i.r. and ^{1}H n.m.r. spectroscopic properties of the product were also in accord with this structure. The ^{1}H n.m.r. spectrum showed a three-proton singlet at δ2.62 due to the S-methyl substituent, in accord with the expected methylthio structure (67). Chromatography also isolated a yellow oil in low yield (4%), whose analytical and mass spectral data were consistent with the 10-methyldibenz[b,f][1,4]oxazepine-11-thione structure (68), resulting from the competing N-methylation reaction. This structure was further confirmed by the compound's other spectroscopic properties. The ^{1}H n.m.r. spectrum showed the expected three-proton singlet at δ4.04 due to the N-methyl substituent. The yield of the methylthio compound (67) was increased to 50% by repeating the reaction using 4 equivalents of methyl iodide. In an attempt to further increase the yield of this reaction methyl iodide was replaced by dimethyl sulphate as the



(i) Piperidine, NaH, DMF, 100^{O}.

(ii) 2M $HCl_{(aq)}$, EtOH, reflux.

(iii) $AcOH_{(aq)}$, reflux.

(iv) 30% H_2O_2(aq), AcOH, 50^{O}.

(v) MCPBA, $CHCl_3$, 50^{O}.

(vi) Oxone, CH_2Cl_2, room temp.

(vii) NaOCl, dioxane, room temp.

Scheme 15

methylating agent. The use of four equivalents of this reagent afforded the desired methylthio compound (67) in 97% yield.

The first attempt to displace the methylthio group in the methylthio compound (67) was made with piperidine in acetonitrile under reflux. This failed to result in any reaction, with the starting material being recovered in high yield. The same result was obtained on refluxing the methylthio compound (67) in neat, excess piperidine. The methylthio compound (67) in 1,2-dimethoxyethane was next treated with the sodium salt of piperidine under reflux (Scheme 15). However, this attempt to increase the reactivity of the nucleophile resulted in no reaction, with the starting material being recovered in quantitative yield. In a further attempt to induce the displacement of the methylthio group of the methylthio compound (67) this reaction was repeated using dimethylformamide as the solvent, thus allowing the reaction temperature to be raised to 100°. This however did not result in the formation of the desired amidine product. The reaction gave a high yield of a pale yellow crystalline compound whose melting point, mass spectral and spectroscopic data was consistent with dibenz[b,f][1,4]oxazepin-11(10H)-one (69).[64] This result was initially thought to be due to a base catalysed hydrolysis of either the methylthio compound (67) or the thione (66) after a demethylation step. To investigate this proposal a solution of the methylthio compound (67) in ethanol was stirred at room temperature with 2M aqueous sodium hydroxide. This resulted in no reaction, giving the methylthio compound (67) as a yellow solid, which t.l.c. showed to contain only a trace of the lactam (69). Similarly, treatment of the thione (66) with 2M aqueous sodium hydroxide at room temperature resulted in no reaction, with the starting material being recovered in quantitative yield.

In a further attempt to displace the methylthio group with piperidine the methylthio compound (67) and the base were stirred in dichloromethane at room temperature in the presence of lead tetraacetate. This, however, resulted in no reaction with the methylthio starting material (67) being recovered in quantitative yield. Similarly, replacing lead tetraacetate with nickel acetonylacetonate proved unsuccessful, with the methylthio starting material again being recovered in quantitative yield.

Other nucleophiles were also used in an attempt to displace the methylthio group. The methylthio compound (67) was first heated under reflux in neat, excess benzylamine. This however did not afford the desired amidine product, the only material obtained being a multicomponent oil, from which no identifiable material could be isolated. Unsuccessful attempts to affect the displacement of the methylthio group were also made using hydrazine. The methylthio compound (67) and excess hydrazine were heated in both refluxing ethanol and dioxane, but in both cases the unreacted starting material was recovered in quantitative yields.

Reports in the literature by Sunay, Talbot and Galullo[65] and in a Belgian patent[66] indicated that the displacement of the methylthio group, proving until now so troublesome, could be circumvented by the direct functionalisation of the lactam (69). These papers showed that dibenzodiazepinone and pyridobenzodiazepinone derivatives could be converted directly into their N-methylpiperazinyl derivatives by the action of a titanium tetrachloride-N-methylpiperazine complex in anisole. In analogy with this work a solution of the thiolactam (66) in anisole was heated at 120^{o} in the presence of titanium tetrachloride and N-methylpiperazine but the only material obtained from this reaction was the thiolactam (66), recovered in high yield. Repetition of this reaction but using the lactam (69) as the substrate again failed to

afford the desired compound, with the unreacted starting material being recovered in quantitative yield.

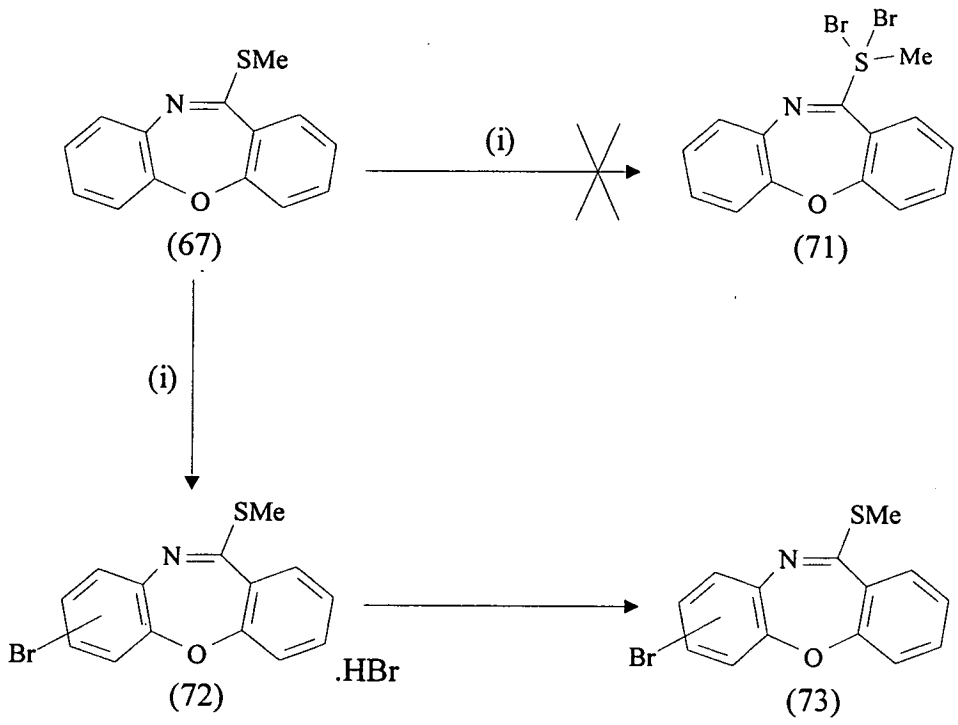
In a final attempt to displace the methylthio group, a solution of the methylthio compound (67) in acetonitrile was treated with tetraethylammonium cyanide and stirred at room temperature. Again this proved unsuccessful, with the starting material being recovered in quantitative yield.

Having failed to achieve the displacement of the methylthio group it was anticipated that a better leaving group would be obtained by the oxidation of the sulphur to the corresponding sulphone (70). Hydrogen peroxide, either alone or associated with various catalysts or solvents such as acetic acid,[67] is the most widely used oxidising agent for the oxidation of organic sulphides to the corresponding sulphoxides and sulphones. Consequently this was the first method employed when attempting to oxidise the sulphur of the methylthio compound (67). The methylthio compound (67) in acetic acid was treated at 50° with a 30% aqueous solution of hydrogen peroxide. Aqueous basic work-up failed to isolate either the sulphoxide or the sulphone, the only material obtained being a moderate yield of the lactam (69) . The next attempt to oxidise the methylthio compound was made using meta-chloroperbenzoic acid (MCPBA),[68,69] which has previously been used to synthesise both sulphoxides and sulphones from a variety of multifunctional heterocyclic thioesters. Treatment of the methylthio compound (67) in chloroform with MCPBA at 50° did not however afford the desire product. Again the lactam (69) was obtained in quantitative yield It was suspected that the formation of the lactam (69) from the methylthio compound (67) was an acid catalysed process. This hypothesis was supported by further investigations into the stability of the thiolactam compound (67) under aqueous acid

conditions. Heating an ethanolic solution of the methylthio compound (67) under reflux with 2M aqueous hydrochloric acid, affording the expected lactam (69) in high yield. Similarly, on heating the methylthio compound (67) under reflux in 70% aqueous acetic acid the lactam (69) was again obtained in high yield. A blank experiment, with the reaction mixture at neutral pH, was also then performed, where the methylthio compound was heated under reflux in aqueous ethanol. In this case the starting material was recovered unchanged in high yield, showing that the previous results were not due to a simple hydrolysis of the methylthio compound, and the presence of acid was crucial to the mechanism.

In an attempt to obtain the lactam (69) directly from the thiolactam (66) an ethanolic solution was treated with 30% aqueous hydrogen peroxide and 2M aqueous sodium hydroxide then heated at 50°. Removal of the solvent allowed the expected lactam (69) to be collected directly, but only in a very poor yield.

In a further attempt to oxidise the methylthio compound (67) it was treated in dichloromethane at room temperature with tetrabutylammonium peroxymonosulphate(Oxone),[70,71] a salt of Caro's acid soluble in organic solvents. Although Oxone has been reported as an effective reagent in the oxidation of organic sulphur compounds these conditions resulted in no reaction, with the starting material being recovered in quantitative yield. Similarly, the treatment of the methylthio compound (67) in dioxane with aqueous sodium hypochlorite,[73] another reagent that has found use in the synthesis of both sulphoxides and sulphones, did not result in the formation of the desired product, with the starting material being recovered unchanged in moderate yield.



(i) Br_2, $CHCl_3$, room temp. or reflux.
(ii) 2M NaOH, EtOH, room temp.

Scheme 16

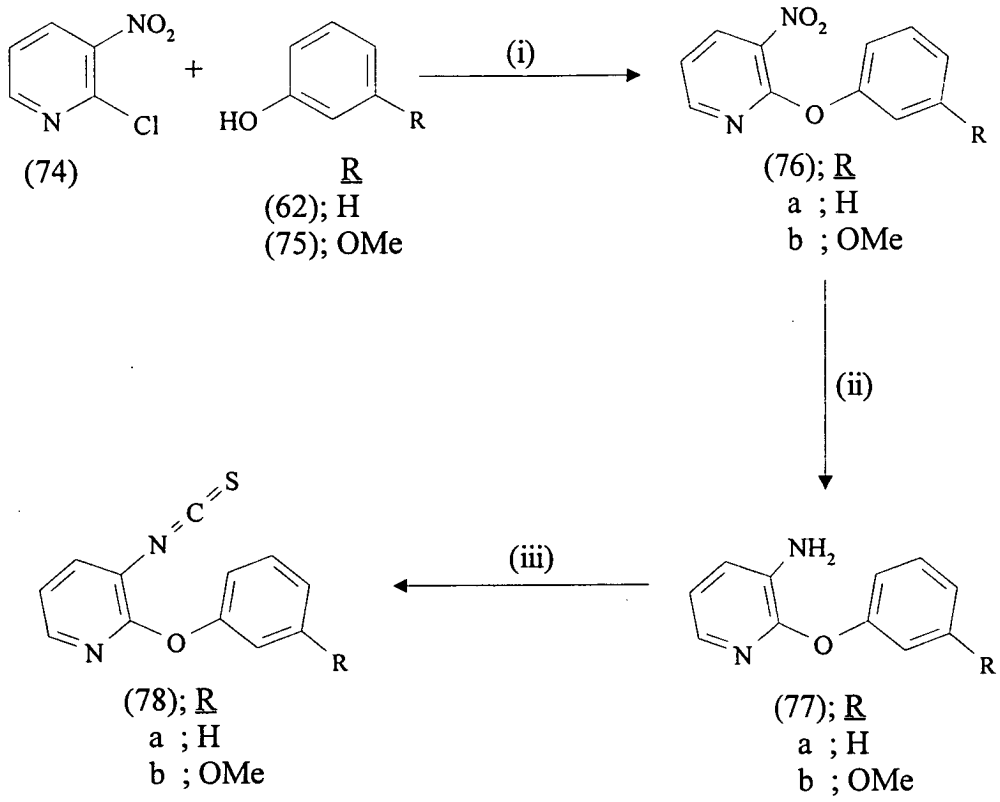
Duceppe and Gauthier[59] reported that a methylthio group of a pyrrolobenzodiazepine could be displaced by preforming the hydroiodide salt of the methylthio compound which was then reacted with the nucleophile. In analogy, a methanolic solution of the methylthio compound (67) was treated with a solution of hydrogen chloride in ether at room temperature. This, however, resulted in no formation of the hydrochloride salt, with the starting material being recovered in high yield.

The oxidation of organic sulphides by molecular halogens was first reported in the literature in 1907.[74] The halogens initially form addition compounds with the organic sulphides which are then readily hydrolysed to the corresponding sulphoxide. A second oxidation step gives the sulphone.[75] Unfortunately, undesirable side reactions sometimes occur, such as halogenation at various positions or cleavage of the carbon-sulphur bond.[76] With this in mind an attempt was made to oxidise the methylthio compound [Scheme 16; (67)] by treating a solution in chloroform at room temperature with one equivalent of bromine. This did not afford the desired product, but gave a yellow solid which t.l.c. showed to be a mixture of unreacted starting material (67) and the lactam (69). This mixture was recovered unchanged on treatment with water at room temperature. The methylthio compound (67) was next treated with one equivalent of bromine and stirred at room temperature for 2.5h, after which time a second equivalent of bromine was added and the mixture stirred for 1.5h at room temperature then heated under reflux for a further 2h. After cooling, the reaction mixture was filtered to afford a yellow crystalline solid in high yield which on crystallisation from toluene afforded analytical data consistent with the hydrobromide salt of a monobrominated derivative of 11-methylthiodibenz[b,f][1,4]oxazepine (72). The mass spectrum of this compound

contained a fragment ion at m/z 320 and 318 corresponding to the loss of hydrogen bromide from the parent molecule. However, the ^{1}H n.m.r. spectrum was ill-defined, giving no additional information as to its exact structure. Changing the amount of bromine used and the length of reflux in its reaction with the methylthio compound (67) did not improve the reaction. With two equivalents of bromine and under reflux fro 9h the hydrobromide (72) was obtained in low yield along with a high yield of the lactam (69). Using three equivalents of bromine and refluxing for 5h, the hydrobromide (72) was isolated in moderate yield, but on subjection to flash chromatography over silica it decomposed, to give only unresolvable multicomponent oils.

To confirm the structure of the hydrobromide salt (72) an ethanolic solution was treated at room temperature with 2M aqueous sodium hydroxide. This afforded in high yield a colourless crystalline solid, which gave accurate mass data consistent with the molecular formula $C_{14}H_{10}BrNOS$ and whose i.r. and ^{1}H n.m.r. spectroscopic properties were consistent with its formulation as a monobrominated methylthio compound (73). The ^{1}H n.m.r. spectrum showed a three-proton singlet at δ2.57 which is characteristic for a methylthio group in this type of compound.

The emphasis on the work in hand was now changed to the Lewis acid catalysed cyclisation reactions of isothiocyanates, leading to pyridobenzoxazepine and pyrimidobenzoxazepine derivatives. As stated earlier, the synthetic routes to these types of structures reported in the literature to date have tended to be very specific and inapplicable in a general sense. It was anticipated that the methodology employed in the present studies would prove to be a general synthetic strategy, leading to a number of compounds of interest for their pharmacological properties.

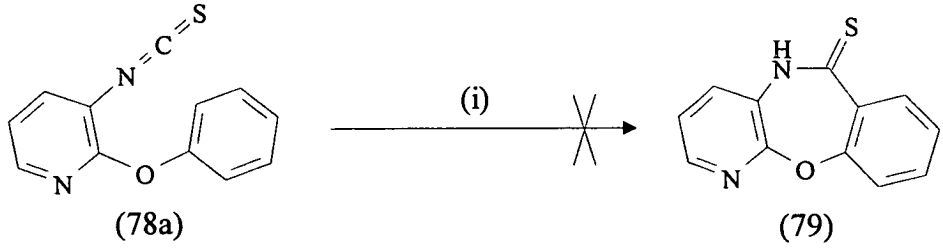


(i) NaH, DMF, 100°.

(ii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.

(iii) $Cl_2C{=}S$, AcOH, $HCl_{(aq)}$, room temp.

Scheme 17



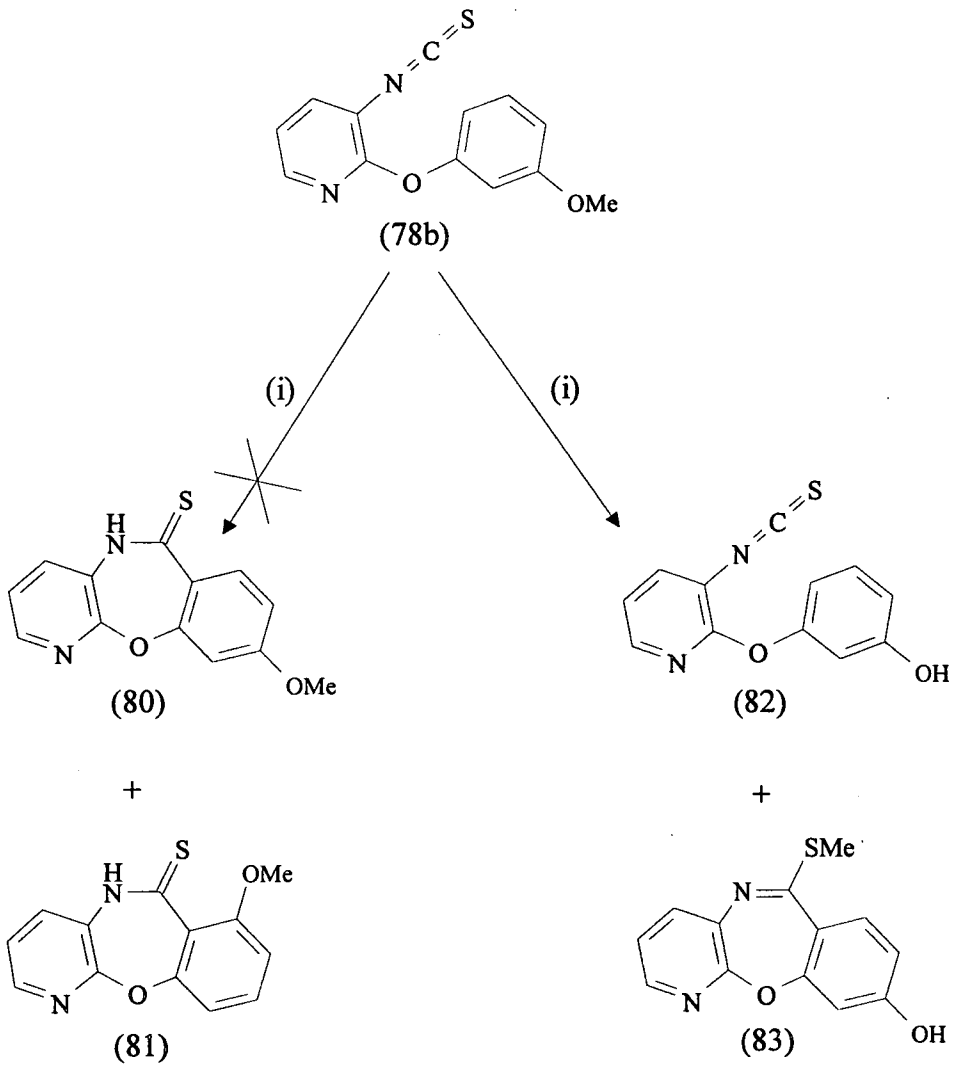
(i) $AlCl_3$, solvent.

Scheme 18

3-Nitro-2-phenoxypyridine [Scheme 17; (76a)][77] was obtained in high yield by the sodium hydride catalysed coupling of 2-chloro-3-nitropyridine (74) with phenol (62). The nitro compound then underwent reduction to 3-amino-2-phenoxypyridine (77a)[77] in good yield by the action of stannous chloride dihydrate and aqueous hydrochloric acid in refluxing tetrahydrofuran. To gain the isothiocyanate precursor a solution of the amine (77a) in aqueous hydrochloric acid and acetic acid was treated with thiophosgene and stirred at room temperature. This afforded the expected isothiocyanate product (78a) in high yield as a colourless compound which gave accurate mass data consistent with the molecular formula $C_{19}H_{14}N_2O$. Its spectroscopic properties were also entirely consistent with the 3-isothiocyanato-2-phenoxypyridine structure (78a).

In an attempt to induce its cyclisation to the pyridobenzoxazepine [Scheme 18; (79)] the isothiocyanate (78a) was added to a suspension of aluminium trichloride in dichloromethane, then stirred at room temperature. This, however, did not result in the formation of the desired pyridobenzoxazepine product (79), the only material recovered being isothiocyanate starting material (78a) in quantitative yield. Similarly, no reaction was observed when the reaction was repeated with heating under reflux. Even on further increasing the reflux temperature by the use of 1,2-dichloroethane as the solvent under reflux, there was no formation of the desired pyridobenzoxazepine product (79), with the only material recovered being impure isothiocyanate starting material (78a).

Weddel and Tennant[41] showed that similar types of Lewis acid catalysed cyclisations could be induced in otherwise unreactive systems by the incorporation of a methoxy substituent on the benzene ring. In anticipation that the activating effect of the



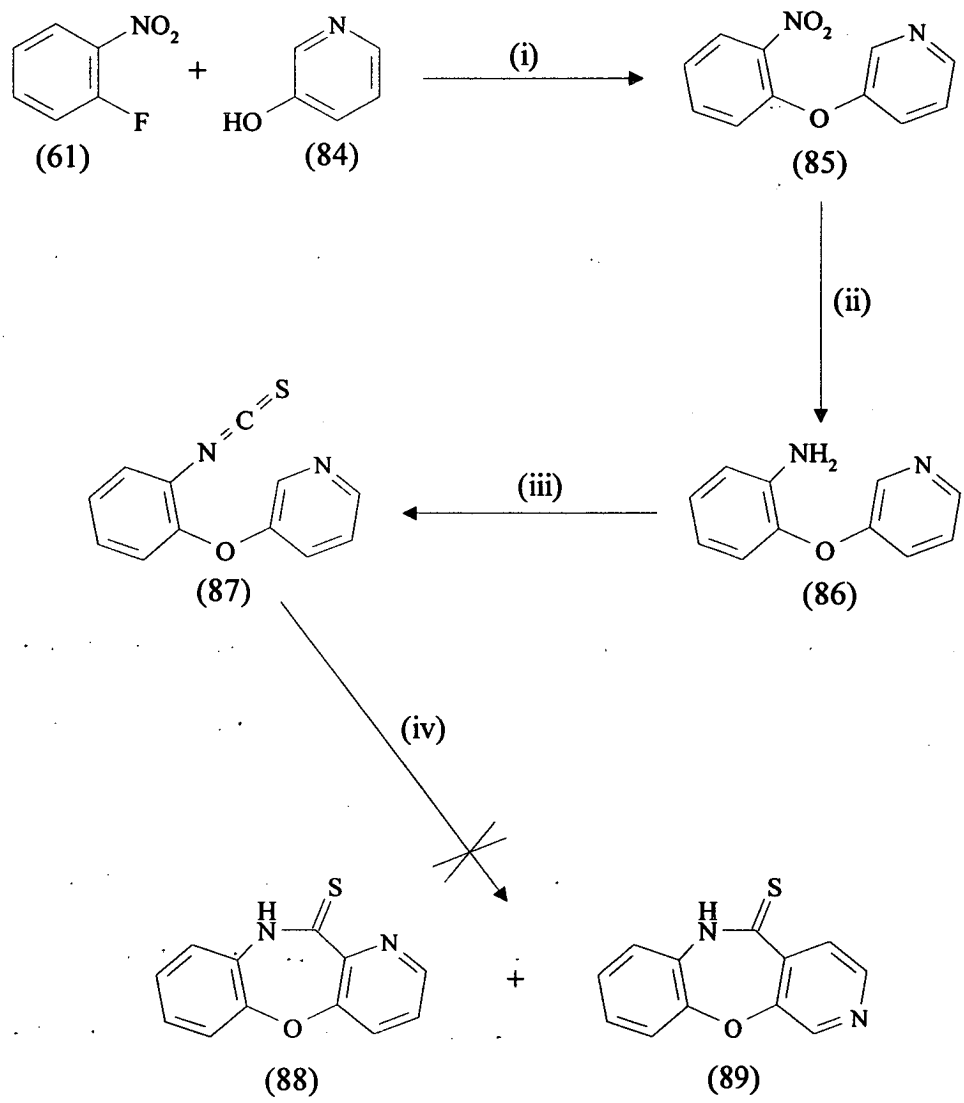
(i) $AlCl_3$, CH_2Cl_2, room temp.

Scheme 19

methoxy-group would be beneficial in the present work it was set about synthesising the appropriate isocyanate precursor (Scheme 17).

3-Amino-2-(3-methoxyphenoxy)nitropyridine (77b) was synthesised in moderate yield as described by Weddel and Tennant[41] and outlined in Scheme17. Subsequent reaction with thiophosgene in an 80% mixture of acetic acid in aqueous hydrochloric acid at room temperature afforded a mixture from which flash chromatography isolated a colourless solid product whose analytical data corresponded to the expected 3-isothiocyanato-2-(3-methoxyphenoxy)pyridine structure (78b). The spectroscopic properties were also consistent with the proposed structure. Thus, its i.r. spectrum showed isothiocyanate absorption at 2045 cm^{-1} and the ^1H n.m.r. spectrum of the product was also entirely consistent with the proposed structure, with a three-proton singlet at δ3.81 corresponding to the methoxy group.

With the appropriate activated precursor in hand it was subjected to the aluminium trichloride catalysed cyclisation conditions (Scheme 19). A solution of the isothiocyanate (78b) in dichloromethane was added to a suspension of aluminium trichloride at room temperature giving a complex mixture. Flash chromatography of this mixture afforded three products. Firstly, unreacted starting material was obtained in 39% yield. A colourless crystalline compound was then isolated in 35% yield, whose mass spectral data showed that it was not the expected product. The accurate mass data was consistent with the molecular formula $C_{12}H_8N_2O_2S$, suggesting that the product was a result of the loss of the methyl group from the starting material. The i.r. and ^1H n.m.r. spectroscopic properties of this product were also consistent with the proposed 2-(2-hydroxyphenoxy)-3-isothiocyanatopyridine structure (82). The i.r. spectrum showed hydroxyl absorption at 3195cm^{-1} and a band at 2078cm^{-1}

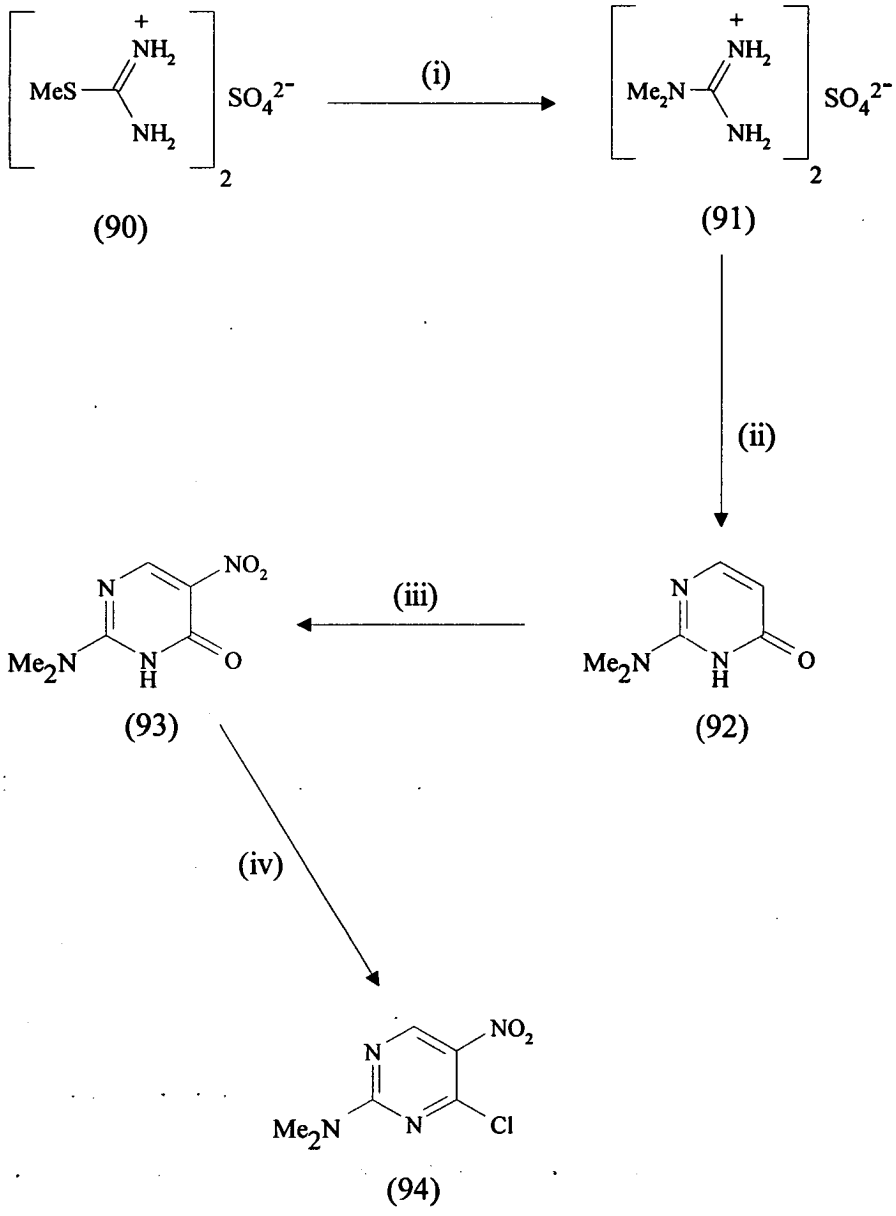


(i) NaH, DMF, 100^{o}.
(ii) H_2, Pd-C, EtOAc, room temp., atmos. press.
(iii) $Cl_2C{=}S$, AcOH, $HCl_{(aq)}$, room temp.
(iv) $AlCl_3$, CH_2Cl_2, room temp.

Scheme 20

corresponding to the isothiocyanate substituent. The third material isolated was a yellow crystalline compound, obtained in 14% yield, whose accurate mass data was consistent with either of the expected pyridobenzoxazepine structures [(80) or (81)]. The ^{1}H n.m.r. spectrum, however, showed the absence of a methoxy group. However, a three-proton singlet at δ2.45 indicated the presence of a methylthio group. The correct structure was established by performing a nuclear Overhauser effect experiment. Irradiation of the hydroxyl proton at δ10.63 resulted in an enhancement of two aromatic protons at δ6.69 and δ6.74. This allowed the compound to be positively identified as the pyridobenzoxazepine structure (83). The i.r. spectrum of the compound was entirely consistent with this proposed structure.

The cleavage of methoxyphenol bonds by aluminium trichloride was first reported in 1892 by Hartmann and Gattermann.[78] The aluminium trichloride and the ether form a complex which liberates methyl chloride to leave a phenoxyaluminium dichloride species. The aluminium complex can then be hydrolysed to afford the phenol.[79] With this knowledge it is then possible to explain the results obtained in the reaction of the isothiocyanate (78b) with aluminium trichloride. The isothiocyanate product (82) is obtained by the demethylation of the starting material (78b) prior to cyclisation. The resulting hydroxy substituted isothiocyanate derivative apparently does not possess the activating effect (see the methoxy compound before) necessary for cyclisation so the reaction terminates at this point. The methylthio compound (83) results from the demethylation of the pyridobenzoxazepinethione (80). The methyl chloride liberated in the demethylation step then acts as a methylating agent resulting in the formation of the methylthio compound (83).



(90) (91) (92) (93) (94)

(i) Me_2NH, H_2O, room temp.

(ii) Malic acid, H_2SO_4, 95°.

(iii) HNO_3, H_2SO_4, 100°.

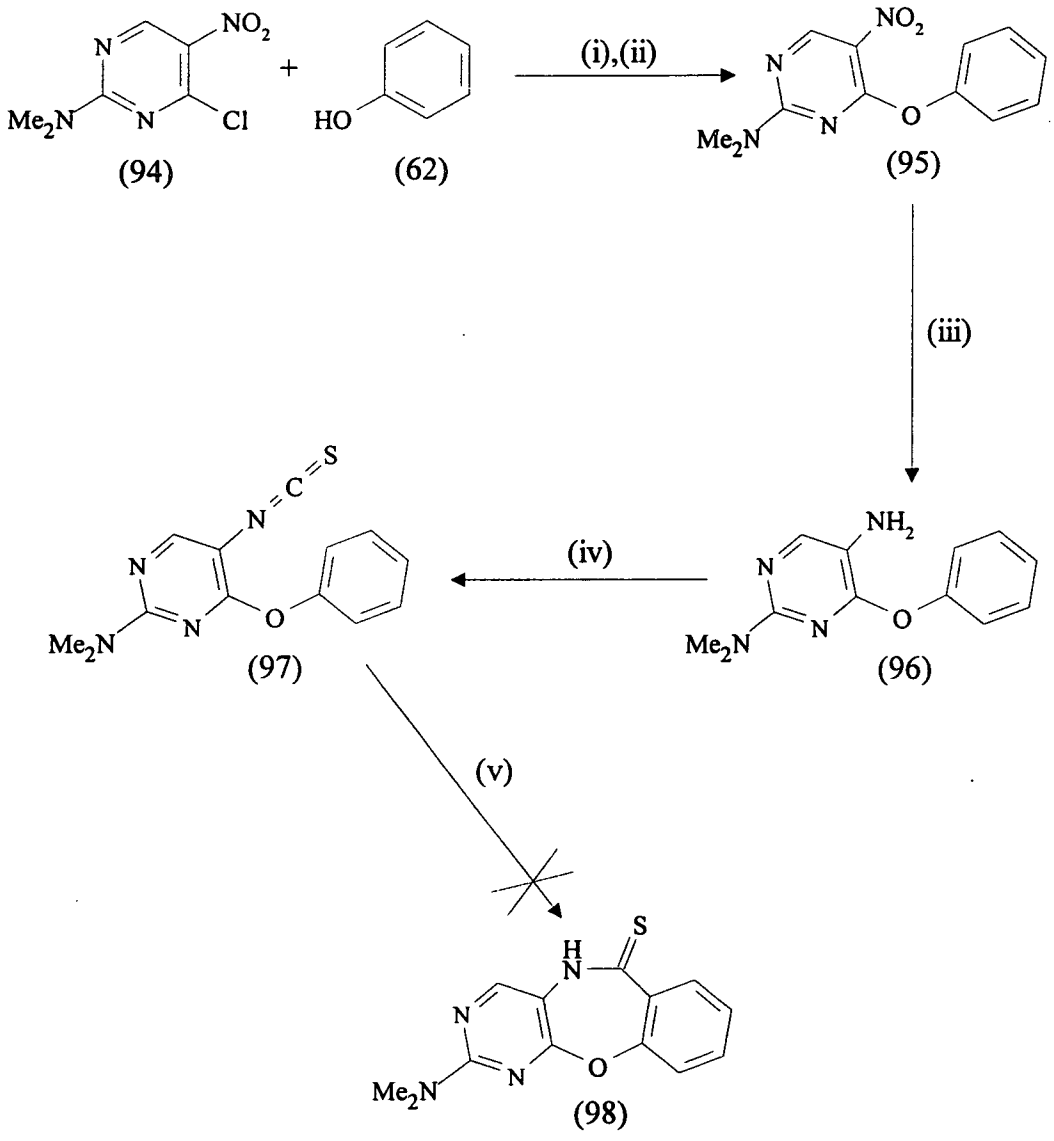
(iv) $POCl_3$, $PhNMe_2$, reflux.

Scheme 21

In an attempt to increase the yield of the cyclised material, the reaction was repeated using 1,2-dichloroethane as the solvent under reflux conditions. Unfortunately these conditions afforded only a good yield of a complex mixture, from which no identifiable material could be isolated.

The synthesis of pyridobenzoxazepine derivatives by the foregoing strategy was further investigated (Scheme 20) by the synthesis of 3-(2-isothiocyanatophenoxy)pyridine (87) and its subsequent subjection to the Lewis acid catalysed cyclisation conditions. It was anticipated that by changing the position of the pyridine nitrogen the reactivity of the isothiocyanate precursor could be favourably altered, allowing formation of the desired tricyclic heteropine system. The synthesis of 3-(2-nitrophenoxy)pyridine (85) and 3-(2-aminophenoxy)pyridine (86) have previously been reported in the literature by Abramovitch et al.[80] In this work the nitro compound (85) was synthesised in 25% yield by the reaction of 2-bromonitrobenzene with the potassium salt of 3-hydroxypyridine at 180°, with subsequent catalytic reduction over Raney nickel to afford the amine (86). In the present studies it was found more convenient to use a sodium hydride catalysed coupling of 2-fluoronitrobenzene (61) and 3-hydroxypyridine (84) in dimethylformamide at 100°. This afforded a 62% yield of the desired nitro product as a brown oil, which was reduced catalytically over palladium-on-charcoal to give the amine (86) in moderate yield (50%).

Reaction of the amine (86) with thiophosgene at room temperature in aqueous hydrochloric acid and acetic acid afforded a brown oil, flash chromatography of which gave a yellow oil whose accurate mass data was were entirely consistent with the expected 3-(2-isothiocyanatophenoxy)pyridine structure (87). Its i.r. and ^1H



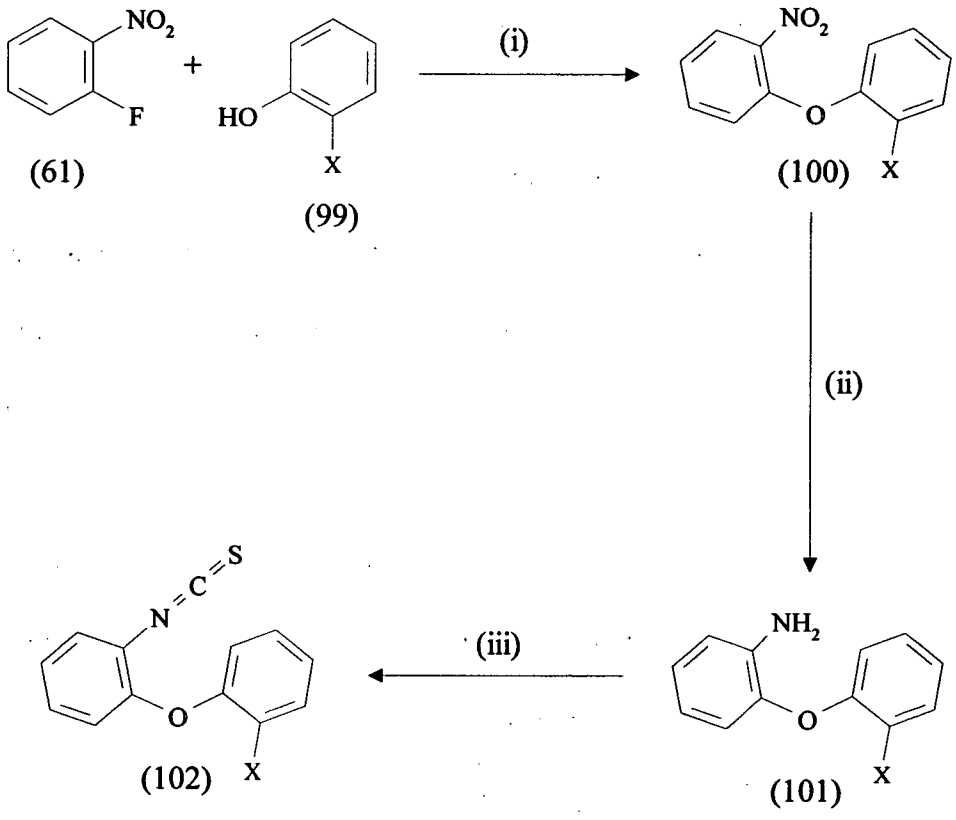
(i) NaH, DME, reflux.
(ii) NaH, DMF, 100^{o}.
(iii) H_2, Pd-C, EtOAc, room temp., atmos. press.
(iv) $Cl_2C{=}S$, AcOH, $HCl_{(aq)}$, reflux.
(v) $AlCl_3$, CH_2Cl_2, room temp. or reflux.

Scheme 22

n.m.r. spectroscopic properties were also consistent with the expected isothiocyanate product (87). In the hope of inducing its cyclisation the isothiocyanate (87) was added to a suspension of aluminium trichloride in dichloromethane at room temperature. However, aqueous base work-up did not afford the pyridobenzoxazepine products (88) and (89). The only material isolated was a yellow oil which was shown by t.l.c. to be a mixture of starting material and baseline material, and was not further investigated.

2-Dimethylamino-4-chloro-5-nitropyrimidine [Scheme 21; (94)] was readily prepared by methods reported in the literature by Overberger and Kogon[81] and by Saunders.[82] Thus, 2-dimethylamino-5-nitro-4-phenoxy pyrimidine (95) was obtained in moderate yield by the sodium hydride catalysed reaction (Scheme 22) of the pyrimidine (94) with phenol (62) in 1,2-dimethoxyethane under reflux. The yield of the nitropyridimidine derivative (95) was improved slightly by repeating the experiment but changing the solvent to dimethylformamide at 100^0. The reduction of the nitropyrimidine (95) with stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux afforded a colourless product whose analytical and mass spectral data were in accord with the expected amine product (96). The product's ^{1}H n.m.r. spectrum was also consistent with the assigned structure (96) with a broad, two-proton signal at δ3.30 due to the exchangeable amine protons and a six-proton singlet at δ2.94 corresponding to the two methyl groups. Its i.r. spectrum was also in accord with the amine structure (96), showing absorption at 3382 and 3295 cm^{-1} due to the primary amino group.

Reaction of the amine (96) with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature afforded in high yield a colourless crystalline product



(i) NaH, DMF, 100°.
(ii) [H].
(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

X
a ; Br
b ; I

Scheme 23

whose analytical and spectroscopic data were in accord with its formulation as the expected isothiocyanate derivative (97). However, all attempts to induce the cyclisation of the isothiocyanate (97) proved unsuccessful. Exposure to aluminium trichloride in dichloromethane, both at room temperature and under reflux failed to catalyse any reaction, with the starting material being recovered in quantitative yield in both cases.

As discussed earlier, it was hoped to apply carbanion induced cyclisations of heterocumulenes to the synthesis of dibenzoxazepine derivatives. It was therefore necessary to synthesise the appropriate halogenated isothiocyanate precursors. The synthesis of 2-bromo-2'nitrodiphenyl ether [Scheme 23; (100a)] has previously been described by Currie and Tennant,[83] as has its reduction to the corresponding amine derivative (101a) using titanium trichloride. Ready access to good yields of the amine (101a) was essential, as this compound was a key intermediate in the synthesis of a number of tricyclic systems. Due to the variable yields obtained when using titanium trichloride as the reducing agent, and the expensive nature of titanium trichloride it was decided to investigate other ways of effecting this reduction.

Reaction of the nitro compound (100a) with nine equivalents of titanium trichloride in aqueous hydrochloric acid and tetrahydrofuran at room temperature afforded the desired amino product (101a) in moderate yield (38%) as a pale yellow oil. However, on repeating this reaction, but in the absence of hydrochloric acid and using only three equivalents of titanium trichloride only a 4% of the desired amino product (101a) was obtained, with unreacted starting material being recovered in high yield. Similarly, the use of ten equivalents of titanium trichloride afforded a complex multicomponent oil containing only a small amount of the desired amine (101a).

These results highlight the need for an alternative method of reducing the nitro compound (100a) to the corresponding amine (101a).

The first reduction method investigated was catalytic reduction. Due to its tendancy to dehalogenate aryl halides the use of palladium-on-charcoal was precluded. Thus the nitro compound (100a) in acetic acid was reduced catalytically over Raney nickel at room temperature and atmospheric pressure. These conditions afforded a good yield of a red oil which t.l.c. showed to be a mixture containing only a small amount of the desired product.

Satoh and Suzuki[84] reported that aromatic nitro groups could be reduced to the corresponding amine derivative in good yields by the action of a sodium borohydride-cobaltous chloride system in hydroxylic solvents under reflux conditions. When the nitro compound (100a) in methanol was treated on a small trial scale with a solution of sodium borohydride in the presence of cobaltous chloride the desired amine (101a) was indeed afforded pure, in high yield. However, on repeating this reaction on a larger scale the only material obtained was a black, multicomponent, viscous oil, from which no identifiable material could be isolated.

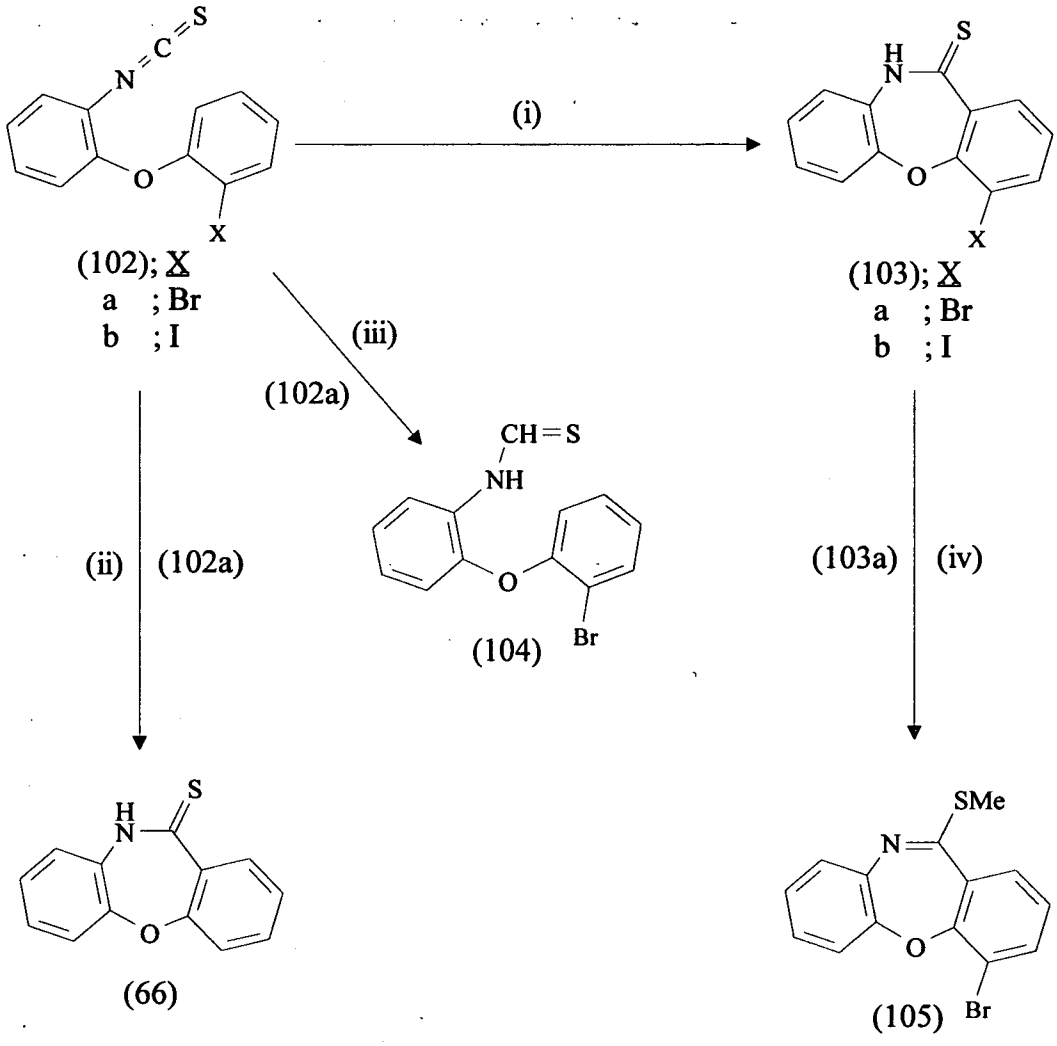
Changing the co-catalyst from cobaltous chloride to palladium-on-charcoal did not improve the outcome. Thus, the reaction of the nitro compound (100a) in dioxane with sodium borohydride in aqueous sodium hydroxide in the presence of palladium-on-charcoal gave a moderate yield of an oil, which was shown bt t.l.c. to contain the desired amine (101a). Repetition of this reaction but using methanol as the solvent afforded only a moderate yield of the desired amine (101a) as a brown oil.

Stannous chloride dihydrate has been known for many years to act as a reducing agent for the conversion of aromatic nitro groups into the corresponding amines.

These conversions have been reported to occur in the presence of either aqueous hydrochloric acid, organic solvents, or in the presence of both. It was decided to apply this methodology to the problem at hand. An ethanolic solution of the nitro compound (100a) was treated with stannous chloride dihydrate and stirred at 70°. These conditions did not result in the formation of the desired amine. The only material obtained was a complex multicomponent mixture, from which no identifiable material could be isolated. However, the use of conditions analogous to those employed when using titanium trichloride gave a more favourable result. Thus, a solution of the nitro compound (100a) in tetrahydrofuran was treated with stannous chloride dihydrate in the presence of aqueous hydrochloric acid at room temperature for 18h to afford the desired amine product (101a) in quantitative yield. It was also shown that the reaction time could be reduced to 1h by heating the mixture under reflux with no significant drop in the yield of the reaction or in the ease of isolating the desired product. These conditions also proved applicable to a wide number of systems, where they consistently gave equally high yields (see later).

With a ready source of the amine (101a) at hand it was converted to the isothiocyanate (102a) by the action of thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature. These conditions gave a quantitative yield of a yellow oil which gave accurate mass data consistent with the molecular formula $C_{13}H_8BrNOS$. Its i.r. and ^1H n.m.r. spectroscopic properties were also consistent with the expected 2-bromo-2'-isothiocyanatodiphenyl ether structure (102a), the i.r. spectrum showing absorbtion at 2103-2029cm^{-1} due to the isothiocyanate group.

Although the isothiocyanate (102a) was intended for investigations of carbanion-induced cyclisations it was also subjected, in passing, to Lewis acid catalysed



(i) $AlCl_3$, CH_2Cl_2, room temp.

(ii) BuLi, THF, -78° - room temp.

(iii) Bu_3SnH, AIBN, toluene, reflux.

(iv) NaH, MeI, DMF, room temp.

Scheme 24

cyclisation conditions (Scheme 24). The use of aluminium trichloride in refluxing dichloromethane afforded a mixture as a yellow solid. Chromatography gave a good yield of a yellow crystalline product whose analytical and mass spectral data was consistent with the expected 4-bromodibenz[b,f][1,4]oxazepine-11(10H)-thione structure (103a). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with the assigned thione structure. However, to further verify the structure (103a) the methylthio derivative was synthesised via a sodium hydride catalysed reaction of the thione (103a) with methyl iodide. This gave an orange semi-solid, which on subjection to flash chromatography over silica afforded a pale brown crystalline product whose analytical and mass spectral data was consistent with its formulation as 4-bromo-11-methylthiodibenz[b,f][1,4]oxazepine (105). Its spectroscopic properties were also in accord with this methylthio structure, the ^{1}H n.m.r. spectrum showing a three-proton singlet at δ2.58 due to the methylthio group.

As outlined in Scheme 7 it was anticipated that tricyclic heteropine derivatives could be synthesised via a carbanion-induced cyclisation of 2-halogeno-2′-isothiocyanatodiphenyl ether derivatives. The first attempts to effect such cyclisations were made using intramolecular Grignard-type addition to the heterocumulene.

On treatment of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) in ether with magnesium metal there was no formation of either the expected tricyclic heteropine derivative (66) or an intermediate organomagnesium species, with the brominated isothiocyanate starting material (102a) being recovered unchanged in quantitative yield. Due to the obvious reluctance to form a Grignard species it was thought that the reaction may be initiated by sonocation. However, on repeating the reaction with

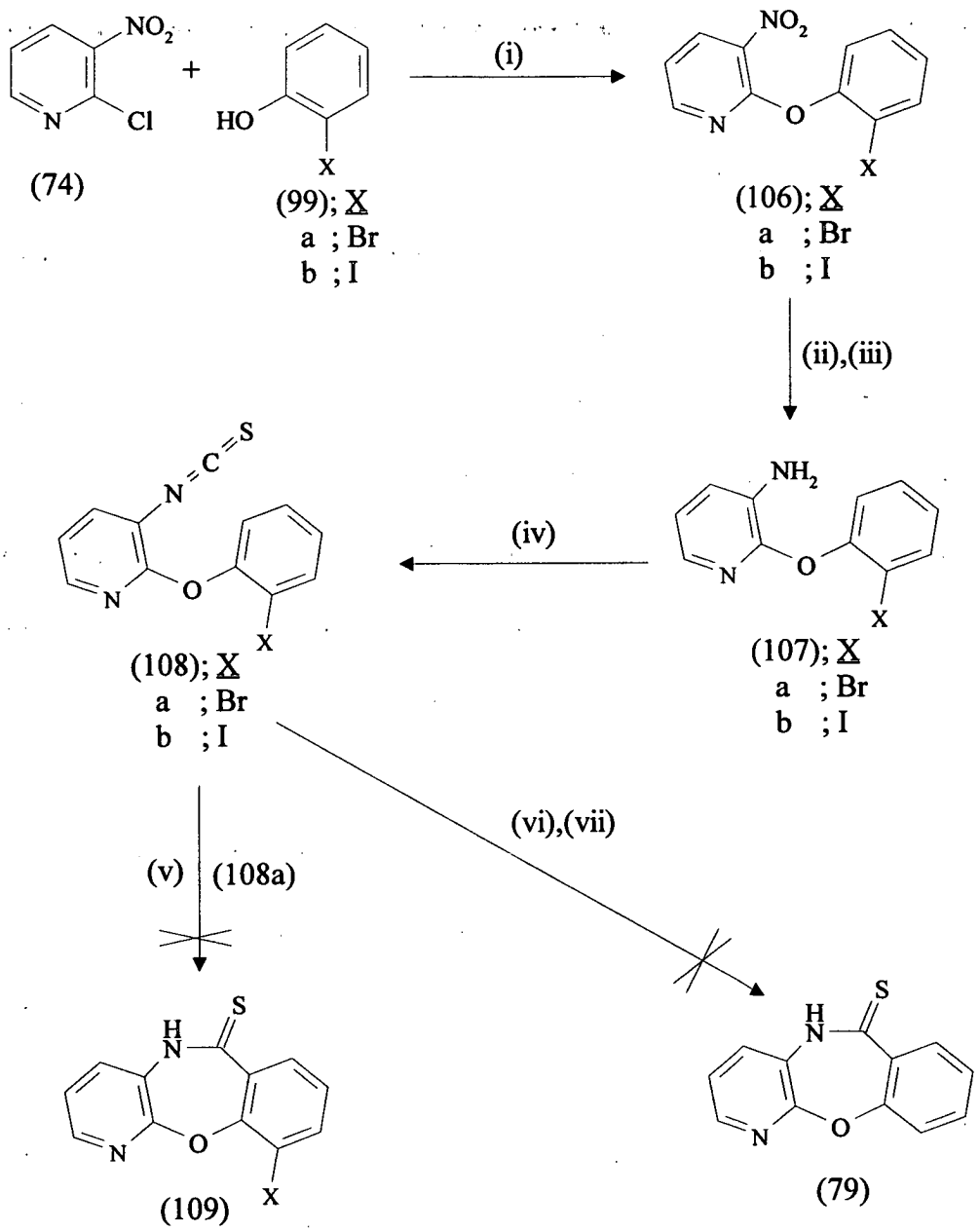
sonocation there was again no formation of the desired product, with the isothiocyanate again being recovered unchanged in quantitative yield.

An alternative method of effecting a carbanion-induced cyclisation was investigated (Scheme 7) in which organolithium intermediates could react intramolecularly with the heterocumulene to form tricyclic heteropine structures. Thus, a solution of the isothiocyanate (102a) in tetrahydrofuran was treated at -78° with one equivalent of n-butyllithium. After 2h the reaction was shown by t.l.c. to be incomplete, so the mixture was warmed to room temperature and stirred for a further 2h. An aqueous work-up afforded a yellow semi-solid which was flash chromatographed to give a low yield (8%) of unreacted starting material (102a) and the desired dibenzoxazepine (66) in 66% yield. This is the first reported example of intramolecular carbanion addition to a heterocumulene. Under the same reaction conditions the effect of changing the amount and type of butyllithium was investigated (Table 1). The results of this investigation showed that when using only one equivalent of butyllithium the highest yield of the dibenzoxazepine (66) (66%) was obtained with n-butyllithium, and that the highest yield in the study (80%) was when using two equivalents of s-butyllithium.

REAGENT	NUMBER OF EQUIVALENTS	RECOVERY OF (102a) / %	YIELD OF (66) / %
n-BuLi	1	8	66
s-BuLi	1	8	48
t-BuLi	1	20	53
s-BuLi	2	6	80
t-BuLi	4	13	29

Table 1

Having proved the usefulness of butyllithium as a mild reagent for the cyclisation of 2-isothiocyanatodiphenyl ether derivatives to give dibenzoxazepine derivatives this



(i) NaH, DMF, 100°.
(ii) $SnCl_2$, $HCl_{(aq)}$, THF, room temp.
(iii) H_2, Ra-Ni, AcOH, room temp., atmos. press.
(iv) $Cl_2C{=}S$, AcOH, $HCl_{(aq)}$, room temp.
(v) $AlBr_3$, CH_2Cl_2, reflux.
(vi) s-BuLi, THF, -78° - room temp.
(vii) Mg, Et_2O, reflux.

Scheme 25

novel methodology was also applied to the synthesis of pyridobenzoxazepine systems (Scheme 25).

2-(2-Bromophenoxy)-3-nitropyridine (106a) was synthesised in high yield as described by Weddel and Tennant.[41] The reduction of the nitro compound (106a) to the corresponding amine (107a) using titanium trichloride was also reported[41] but in the work in hand it was found more convenient to effect the reduction by the use of stannous chloride dihydrate. Thus, treatment of the corresponding 2-(2-halogenophenoxy)-3-nitropyridine derivative (106) in tetrahydrofuran with stannous chloride dihydrate in the presence of aqueous hydrochloric acid at room temperature afforded the desired amine derivative (107) in good yield. It was found that the amount of solvent and acid used in this reaction was crucial to the efficiency of this reduction step. On reducing the volumes of the aqueous hydrochloric acid and tetrahydrofuran by half, the yields also dropped by around a half.

The amine (107a) reacted with thiophosgene in concentrated hydrochloric acid to afford a colourless crystalline product whose analytical and mass spectral data was consistent with the molecular formula $C_{12}H_2BrN_2OS$. The i.r. spectrum of this product was also consistent with the expected 2-(2-bromophenoxy)-3-isothiocyanatopyridine structure (108a), showing absorption at 2111cm^{-1} due to the isothiocyanate substituent.

In the hope of forming the corresponding pyridibenzoxazepine derivative (109) the isothiocyanate (108a) was treated in refluxing dichloromethane with two equivalents of aluminium tribromide. These conditions, however, resulted in the starting material being isolated unchanged in quantitative yield with no evidence for formation of the cyclic product (109),. An explanation of this lack of reactivity may be that the lone-

pair electrons of the pyridine ring nitrogen offer an additional co-ordination site to those available in the diphenyl ether systems. If the Lewis acid was preferentially co-ordinating at this site, rather than at the heterocumulene group, it would not be able to catalyse the desired cyclisation. If this hypothesis was correct, using a larger excess of the Lewis acid may cause cyclisation even in these unreactive systems, by swamping all the co-ordination sites. However, on repeating the reaction using four equivalents of aluminium tribromide the only material obtained was a multicomponent red oil. From this oil chromatography isolated a low yield of the isothiocyanate starting material, but the remainder of the material was composed only of complex oils and gums which yielded no identifiable material.

After these unsuccessful attempts to cyclise the isothiocyanate (108a) using aluminium tribromide the focus of the investigations was returned to the carbanion-induced cyclisations. Thus, the isothiocyanate (108a) in tetrahydrofuran was treated with s-butyllithium at reduced temperature. However, no formation of the desired cyclised product (79) was observed, with chromatography giving low yields of unreacted starting material (108a) and an intractable brown gum.

The synthesis of 2-(2-iodophenoxy)-3-nitropyridine (106b) and 3-amino-2-(2-iodophenoxypyridine (107b) was achieved in good yield as described in the literature.[41] The amine (107b) was then reacted with thiophosgene in aqueous hydrochloric acid at room temperature to give a colourless crystalline product whose analytical and mass spectral data were in agreement with the expected isothiocyanate structure (108b). Its i.r. spectroscopic properties were also in accord with the isothiocyanate structure (108b), the spectrum showing absorption at 2125-2110cm^{-1} due to the isothiocyanate group. The isothiocyanate derivative (108b) was then

treated with magnesium metal in ether, in an attempt to form a Grignard intermediate which could then add across the heterocumulene functionality. However, as in the diphenyl ether case, there was no evidence of the formation of either the cyclised product (79) or an organomagnesium intermediate, only the starting material being recovered in high yield.

In addition to the Lewis acid catalysed and the carbanion induced cyclisations it was anticipated that radical mediated and transition metal promoted processes (Scheme 7) might also effect the cyclisation of appropriately functionalised diphenyl ether derivatives. The key starting material for the proposed investigations into radical mediated cyclisations (Scheme 24) was 2-bromo-2′-isothiocyanatodiphenyl ether (102a), the synthesis of which has already been discussed. The reaction of this isothiocyanate (102a) with tributyltin hydride and azoisobutyronitrile (AIBN) in toluene under reflux did not however afford the desired dibenzoxazepine (66). Instead this reaction afforded a good yield of a cream crystalline product which gave analytical and mass spectral data consistent with the molecular formula $C_{13}H_{10}BrNOS$. The i.r. spectrum of this product showed amine absorption at 3009cm^{-1} and absorption at 1603cm^{-1} due to a thiocarbonyl group. The ^{1}H n.m.r. spectrum contained a one-proton singlet at δ9.92, characteristic of a thioformyl group, and a one-proton resonance due to an exchangeable amine hydrogen. These properties are entirely consistent with the thioformamide structure (104). Although the reductive properties of tributyltin hydride are well documented there has been no reported example of the reduction of an isothiocyanate to a thioformamide. However, unrelated work by Bachi and Denenmark[85] on radical mediated syntheses of thiolactams suggests that the tributyltin hydride may attack the isothiocyanate group

to form a tinthioimidoyl intermediate. This radical intermediate could then abstract a proton to form a thioformamide system. Consequently, it was anticipated that the use of hexabutylditin would be more appropriate, by being less likely to reduce the isothiocyanate. In the event, not only did the hexabutylditin not reduce the isothiocyanate group, it did not catalyse any reaction at all. Irradiation of the isothiocyanate (102a) with a 500W tungsten lamp in the presence of a catalytic amount of hexabutylditin afforded only a good yield of a brown oil, which t.l.c. showed to be a mixture of unreacted starting material and tin residues. Similarly, the use of one equivalent of hexabutylditin with irradiation by a tungsten lamp, or a catalytic amount of hexabutylditin using a 240W mercury vapour photochemical reactor afforded the same intractable oily mixture in each case.

In the hope that iodo analogue would prove more susceptible to radical induced cyclisations of this sort it was set about synthesising the appropriate iodo-substituted isothiocyanate derivative (Scheme 23). The synthesis of 2-iodo-2′-nitrodiphenyl ether (100b) and 2-amino-2′-iododiphenyl ether (101b) has previously been reported in the literature.[83] Howwever, the reducing agent used in the synthesis of the amine (101b), titanium trichloride, was found to give variable results and was very expensive. The use of ten equivalents of titanium trichloride in tetrahydrofuran afforded only a complex mixture, which although t.l.c. showed to contain the desired amine product (101b) in low yield was not further investigated. As the amine (101b) was a key starting material an alternative method for the synthesis of this compound was sought, which would give the desired amine (101b) in high yield. As in the bromine case the use on a small scale of sodium borohydride and cobaltous chloride in methanol initially gave good results, with the desired amine product (101b) being

obtained pure, in high yield. However, repetition on a preparative scale gave only a black oil, from which no identifiable material could be isolated. Again this led to the use of stannous chloride dihydrate as the reducing agent. Thus, treatment of the nitro compound (100b) with stannous chloride dihydrate in tetrahydrofuran and aqueous hydrochloric acid at room temperature for 18h afforded the desired amine product (101b) in high yield. As described in the synthesis of 2-amino-2′-bromodiphenyl ether (101a), this result could be maintained on reducing the reaction time to one hour under reflux. The subsequent reaction of the amine (101b) with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature afforded a high yield of a yellow oil which gave accurate mass data consistent with the molecular formula $C_{13}H_8INOS$. This, together with the observed spectroscopic properties of the product allowed its formulation as 2-iodo-2′-isothiocyanatodiphenyl ether (102b). In particular the i.r. spectrum of this compound showed absorption at 2050-2026cm^{-1}, consistent with an isothiocyanate functionality.

Having now a ready supply of the isothiocyanate precursor (102b) it was decided to subject it in passing to the Lewis acid catalysed cyclisation conditions. A solution of the iodo-isothiocyanate (102b) in dichloromethane was treated with aluminium trichloride and heated under reflux. This afforded in high yield a yellow crystalline product whose analytical data and spectroscopic properties were consistent with those of the desired dibenzoxazepine product (103b), giving another example of a Lewis acid catalysed cyclisation of this type.

In the hope of obtaining the dibenzoxazepine (66) by a radical induced cyclisation of a isothiocyanate precursor, the iodo-isothiocyanate (102b) was treated with a catalytic amount of hexabutylditin in benzene then irradiated with a 500W tungsten

lamp. However, these conditions gave only a high yield of a brown oil, which t.l.c. showed to be a mixture of unreacted starting material and tin residue and was not further investigated. The use of one equivalent of hexabutylditin and using a 240W mercury vapour photochemical reactor again gave a mixture of unreacted starting material and tin residues. Similarly, increasing the amount of hexabutylditin to a 50% excess had no effect on the result, with the reaction affording in high yield a mixture of starting material and tin residues as a brown oil. This apparent lack of reactivity of the isothiocyanates (102) to radical mediated cyclisation prompted investigations into the transition metal promoted cyclisations proposed earlier (Scheme 8).

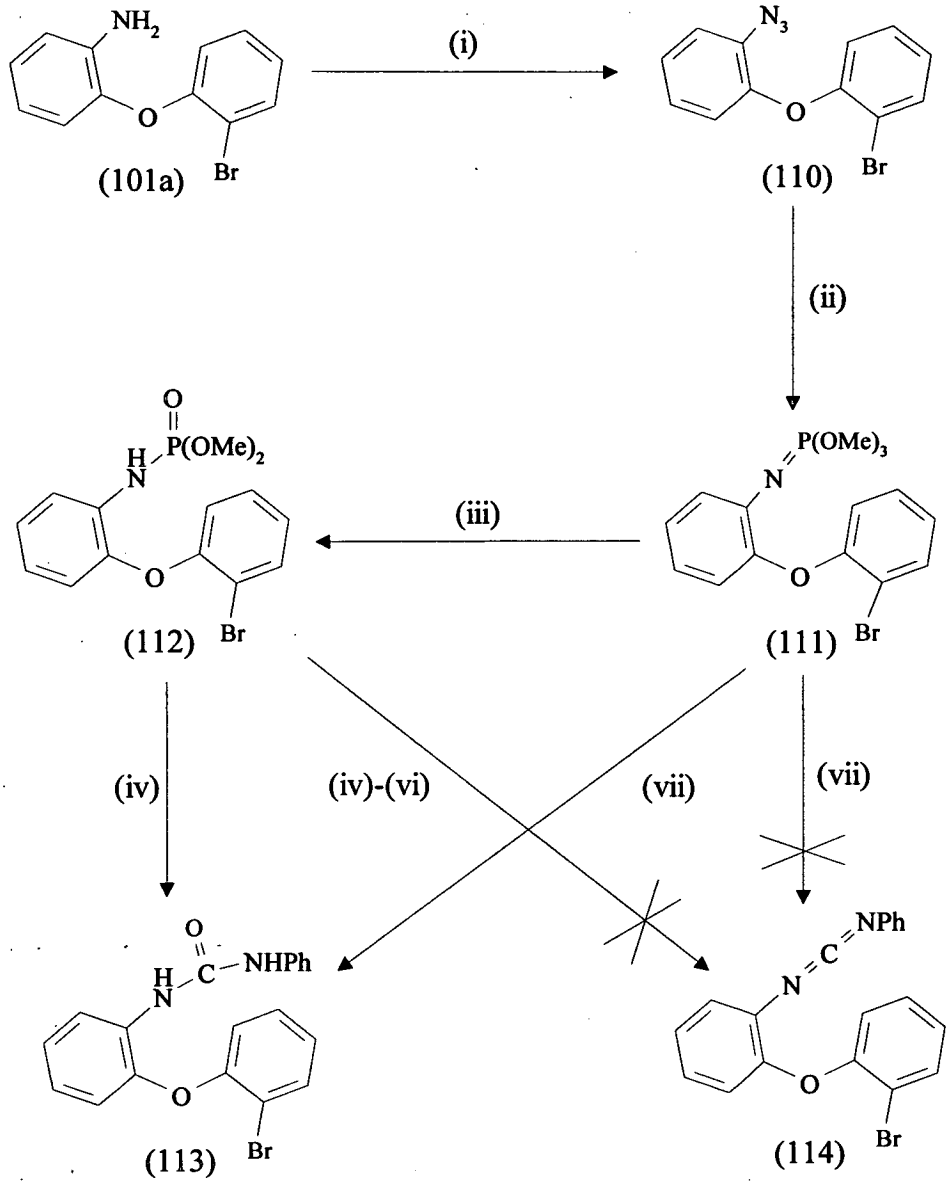
A solution of the isothiocyanate (102b) in acetonitrile was treated under reflux with palladium acetate in the presence of triorthotolylphosphine and triethylamine. These conditions afforded a brown solid which would not run on t.l.c. in any solvent. The i.r. spectrum of this brown solid showed no identifiable bands, and in particular a total lack of absorption due to the isothiocyanate group in the starting material. The melting point and behaviour of this material were unchanged by treatment with aqueous acid or aqueous base, both at room temperature and on warming. Similarly, no change was observed on warming the material in piperidine. On strong roasting, the material left an infusible residue, suggesting the presence of inorganic material. Although the product could not be crystallised it was precipitated from ethyl acetate by hexane. However, this material did not afford any meaningful analytical or spectroscopic data. Since it was thought that this material might be some sort of organo-palladium complex, a solution of the material in dioxane was hydrogenated over palladium-on-charcoal at room temperature and atmospheric pressure for 4h, in the hope of liberating an identifiable organic fragment. This, however, proved

unsuccessful, with the possible palladium species being recovered unchanged. Similarly, on hydrogenating a solution of the suspected palladium species in ethyl acetate over Raney nickel at room temperature and atmospheric pressure for 2h, the material was again recovered unchanged.

The palladium induced cyclisation technique was also attempted with the bromo-isothiocyanate (102a), employing the same reaction conditions. These conditions afforded a brown solid whose chemical and spectroscopic properties were very similar to those resulting from the iodine analogue. The properties of this solid again suggested that it was some sort of organo-palladium complex, but its exact structure could not be ascertained.

Due to the discouraging results from the attempted radical-induced and palladium-mediated cyclisation reactions of the isothiocyanate derivatives (102) these lines of research were not further investigated. Instead, the remainder of the work was centred on expanding the scope of the more promising carbanion-induced cyclisations.

After the unsuccessful attempts to functionalise the tricyclic heteropine structure [Scheme 15; (67)] by displacement of the methylthio group it became increasingly important to find an alternative method of synthesising functionalised tricyclic heteropine systems. It was anticipated that this could readily be achieved by the cyclisation of an appropriately functionalised carbodiimide derivative. In this way, the desired amino functionality could be incorporated into the precursor, circumventing the need for further manipulation. Related work by Weddel and Tennant[41] showed that carbodiimide derivatives would not undergo Lewis acid catalysed cyclisation onto unactivated benzene rings. Therefore it was hoped to



(i) $NaNO_2$, $HCl_{(aq)}$ then $NaN_{3\,(aq)}$, 0^o.
(ii) $P(OMe)_3$, DME, room temp.
(iii) SiO_2.
(iv) PhN=C=O, NaH, DME, 70^o.
(v) PhN=C=O, NaH, DME, room temp.
(vi) PhN=C=O, K_2CO_3, xylene, reflux.
(vii) PhN=C=O, DME, room temp

Scheme 26

overcome this difficulty by employing the novel carbanion-induced cyclisation process described earlier in this chapter. With this aim in mind it was set about synthesising the appropriate carbodiimide derivatives. The synthesis of similar compounds has previously been described by Weddel and Tennant[41] via azide and phosphinimine intermediates,and it was anticipated that the desired compounds could be obtained by using this approach.

The key starting material for the proposed synthetic approach (Scheme 26) to the carbodiimide precursor (144) was the readily available 2-amino-2′-bromodiphenyl ether (101a),[83] the synthesis of which has been described previously (Scheme 23). Reaction of the amine (Scheme 26) with sodium nitrite in aqueous acid at 0^{o} gave the diazonium salt, which was reacted in situ with sodium azide to afford a high yield of a brown crystalline material, which gave analytical and mass spectral data consistent with the expected 2-azido-2′-bromodiphenyl ether (110). Its i.r. amd ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2124-2103 cm^{-1} due to the azide substituent. The azide (110) was converted to the phosphinimine (111) in a Staudinger type reaction,[86] by the action of trimethylphosphite in 1,2-dimethoxyethane at room temperature. These conditions afforded the expected phosphinimine product (111) in high yield as a yellow oil, which showed accurate mass data in accord with the molecular formula $C_{15}H_{17}BrNO_4P$. Its ir. and ^{1}H n.m.r. spectroscopic properties were also consistent with its formulation as the phosphinimine (111). Due to the ease with which it undergoes hydrolysis the phosphinimine (111) was used without further purification in its subsequent transformation to the carbodiimide. Thus, the phosphinimine (111) in 1,2-dimethoxyethane was treated at room temperature with phenyl isocyanate to

afford a red oil which t.l.c. and i.r. spectroscopy showed to contain the desired carbodiimide product (114). Chromatography failed to isolate the pure carbodiimide, but afforded a mixed fraction which t.l.c. showed to contain the desired product. In addition, a colourless crystalline compound was isolated in moderate yield, whose analytical and mass spectral data were in accord with its formulation as N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113). Its i.r. spectrum showed amino absorption at 3411 and 3305cm^{-1} and absorption at 1734cm^{-1} due to a carbonyl group. The product's ^{1}H n.m.r. spectrum was also in accord with the urea structure (113) with two one-proton singlets at δ9.32 and 8.53 due to the amine protons.

The need for a route to carbodiimides giving the desired product without tne need of further purification was the driving force behind the search for alternative methods of synthesising these compounds. Wadsworth and Emmons[88] reported that phosphoramidate anions react with isocyanates in 1,2-dimethoxyethane to afford pure carbodiimides in high yields. In order to exploit this chemistry it was necessary to obtain the appropriate phosphoramidate starting material. This was achieved in high yield by the hydrolysis of the phosphinimine (111) over silica. Thus, flash chromatography of the phosphinimine (111) over silica afforded a colourless crystalline material whose analytical and mass spectral data was consistent with its assigned phosphoramidate structure (112). The product's i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with the expected structure. Its ^{1}H n.m.r. spectrum showed a one-proton singlet at δ5.73 due to the exchangeable amine proton, and a six-proton doublet at δ3.78 due to the two phosphorous methoxy substituents, with a characteristic 11.2Hz coupling to the phosphorous. Not only did this method offer a convenient way of effecting the conversion to the

phosphoramidate, but it acted as an additional purification stage. This allowed the use of pure material in the carbodiimide formation step, something which was not possible using the previous methods.

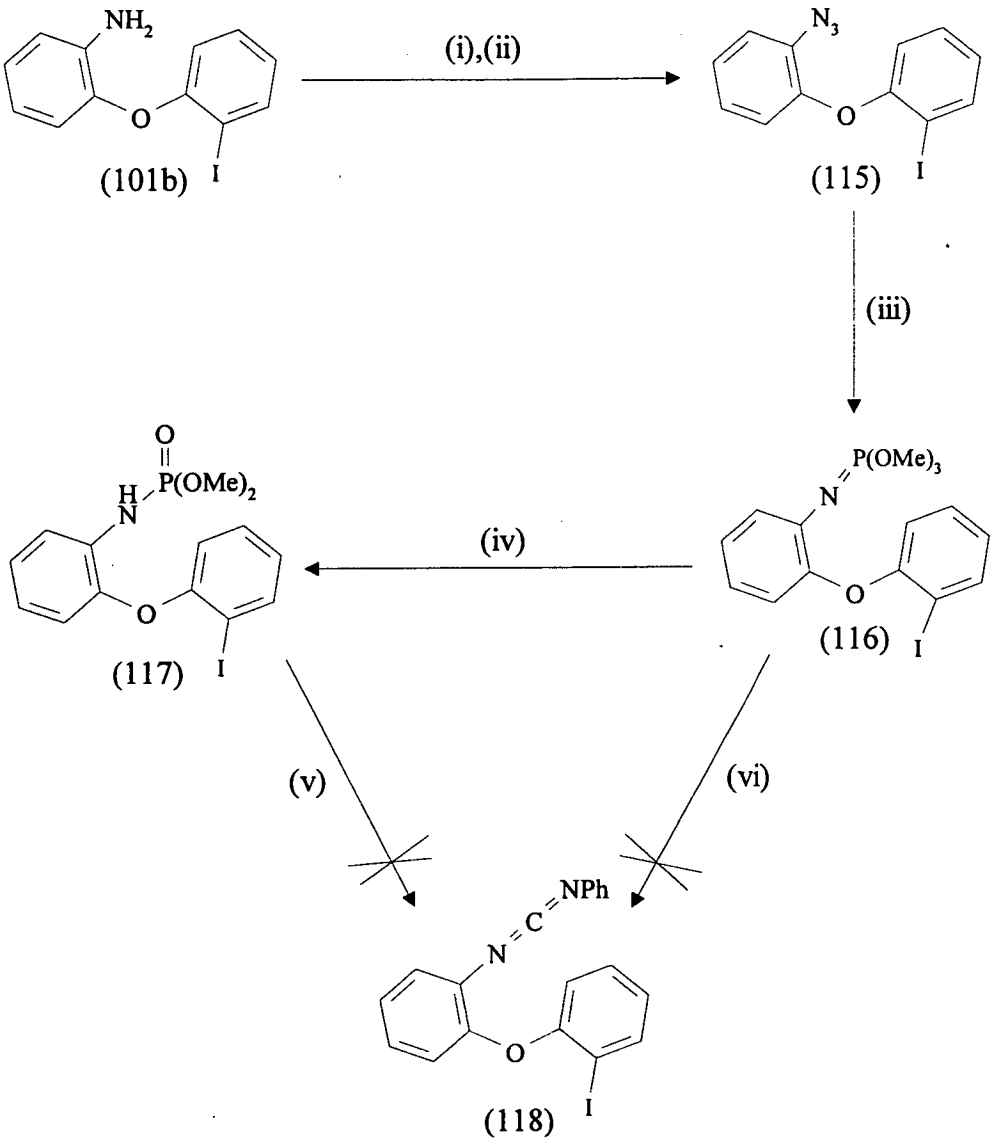
With the phosphoramidate (112) now in hand it was converted to the sodium salt by the action of sodium hydride in 1,2-dimethoxyethane at 70°. The sodium salt was then reacted in situ with phenyl isocyanate at 70° to give a yellow oil which t.l.c. showed to be a mixture of the desired carbodiimide product (114), the urea (113) and N,N'-diphenyl urea. This mixture was subjected to chromatography over silica giving moderate yields of the urea (113) and N,N'-diphenyl urea. There was no evidence of the carbodiimide surviving the chromatography. Repeating the reaction between the phosphoramidate anion and phenyl isocyanate but with stirring at room temperature afforded a complex mixture which, although containing small amounts of the desired product, was not further investigated.

It has also been reported in the literature[89] that the conversion of phosphoramidates to carbodiimides can be effected by reaction with an isocyanate in refluxing xylene in the presence of potassium carbonate. These conditions were reported to give highly pure products, often in quantitative yields. However, on employing these reaction conditions to the problem at hand the result was less than satisfactory. Treatment of the phosphoramidate (112) in refluxing xylene with phenyl isocyanate in the presence of solid anhydrous potassium carbonate afforded a brown oil, which was shown by t.l.c. and i.r. spectroscopy to contain the carbodiimide, but chromatography gave only the urea (113) in moderate yield, and a good yield of phenyl isocyanate. This unsuccessful attempt to form the desired carbodiimide derivative prompted a further search for an alternative route to these systems. It was thought that the initial

method of reacting a phosphinimine with an isocyanate could be adapted to give an alternative route to carbodiimides. Instead of siting the phosphinimine moiety on the diphenyl ether and reacting this with the isocyanate it was proposed that the position of these functional groups could be reversed. A number of isothiocyanate derivatives were already available from previously described investigations and it was anticipated that these could be reacted with phosphinimine derivatives to afford the desired carbodiimides.

In order to test this proposal it was necessary to obtain N-phenyl trimethoxyphosphinimine, the synthesis of which has been described in the literature.[90] This synthesis was achieved in high yield by the conversion of phenyl hydrazine to phenyl azide, and thence to the phenyl phosphinimine. A solution of N-phenyl trimethoxyphosphinimine was then treated under reflux with 2-bromo-2′-isothiocyanatodiphenyl ether (102a) in 1,2-dimethoxyethane. These conditions afforded a red oil which t.l.c. showed to be a complex mixture. Chromatography failed to isolate any of the desired carbodiimide product (114), giving only a good recovery of the isothiocyanate starting material and a small amount of an unidentified yellow oil.

2-Isothiocyanatodiphenyl ether (65) was also subjected to these conditions, giving a complex red oil. From this oil chromatography isolated the isothiocyanate starting material in moderate yield, along with a colourless solid whose mass spectral and spectroscopic data suggested its formulation as N-Phenyl,N′-(2-phenoxy)phenyl urea. The remainder of the material was recovered as a mixed fraction, in which the presence of the desired carbodiimide product was indicated by the correct molecular ion peak in its mass spectrum. Repetition of this reaction, but changing the solvent to



(i) $NaNO_2$, $HCl_{(aq)}$ then $NaN_{3\,(aq)}$, 0^o.

(ii) $NaNO_2$, $HCl_{(aq)}$,AcOH then $NaN_{3\,(aq)}$, 0^o- room temp.

(iii) $P(OMe)_3$, DME, room temp.

(iv) SiO_2.

(v) PhN=C=O, NaH, DME, 70^o.

(vi) PhN=C=O, DME, room temp.

Scheme 27

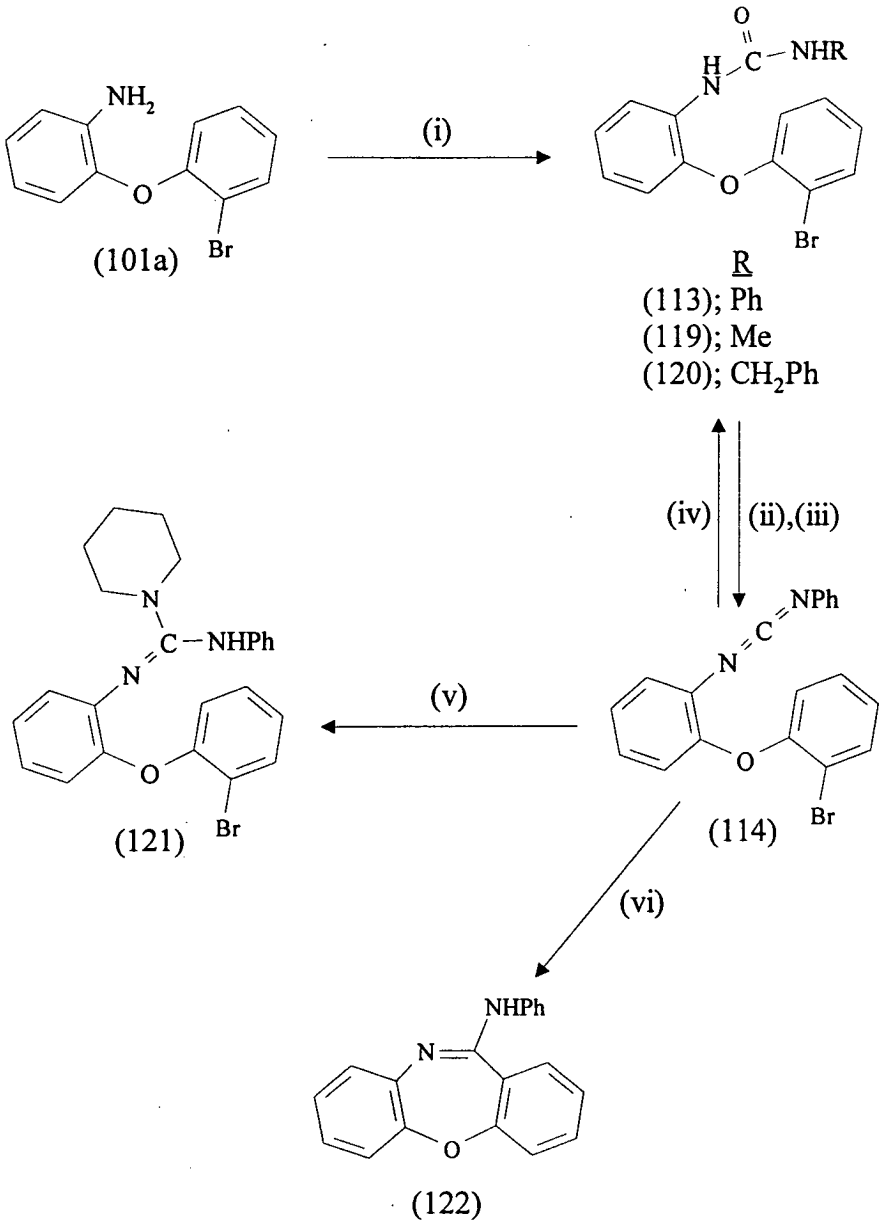
dioxane, did not improve the result. These conditions gave a complex mixture, from which no identifiable material could be isolated.

Attention was next directed to the synthesis of the iodo analogue (Scheme 27). The synthesis of 2-amino-2′-iododiphenyl ether (101b) has been described before in this chapter (Scheme 23). The amine (101b) was treated at low temperature with sodium nitrite in the presence of aqueous hydrochloric acid to form the diazonium salt which was then displaced using sodium azide. This resulted in a good recovery of the starting material and a low yield of a brown oil. This oil gave accurate mass data consistent with the molecular formula $C_{12}H_8IN_3O$. Its spectroscopic properties were also in accord with the expected azide structure (115), its i.r. spectrum containing bands at 2125-2100 cm^{-1} due to the azide substituent. In an attempt to improve the yield of the azide (115) the reaction was repeated using acetic acid as a co-solvent, thereby giving a homogeneous reaction mixture. These conditions gave a good yield of the desired azide product (115). With the azide (115) now in hand it was reacted as before in a Staudinger reaction[86] with trimethylphosphite in 1,2-dimethoxyethane at room temperature. These conditions gave a high yield of a brown oil which had spectroscopic properties consistent with the phosphinimine structure (116). Thus, its ^1H n.m.r. spectrum showed a nine-proton doublet at δ3.59 due to the 11.4Hz coupling of the methoxy protons to the phosphorous. The instability of this compound necessitated its use in subsequent steps without further purification.

In an attempt to obtain the carbodiimide (118) directly, the phosphinimine (116) was treated in 1,2-dimethoxyethane with phenyl isocyanate. However, these conditions afforded only a complex brown oil which was not further investigated. In a similar way to the bromine analogue it was hoped that the iodo-carbodiimide (118) could be

obtained by the reaction of the phosphoramidate salt with the isocyanate. To this end the phosphinimine (116) was flash chromatographed over silica, giving a good yield of a colourless crystalline material, whose analytical and mass spectral data was fully consistent with its formulation as the phosphoramidate (117). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure. The ^{1}H n.m.r. spectrum showed a six-proton doublet at δ3.78 with a 11.4Hz coupling due to the two methoxy groups coupling to the phosphorous. The sodium salt of the phosphoramidate (117) was obtained by the action of sodium hydride in 1,2-dimethoxyethane at 70°. The sodium salt was then reacted in situ with phenyl isocyanate at 70° giving a brown viscous oil, from which no identifiable material could be obtained. On failing to obtain the desired carbodiimide products in a pure form and in high yield an alternative method of synthesising these compounds was sought.

Early methods for the preparation of carbodiimides were based on the dehydrosulphurisation of thioureas by mercury, silver or lead oxides,[48] but the tedious isolation of the carbodiimides from metallic sulphides is an important shortcoming of these methods. Methods of dehydrating ureas by the use of organic sulphur and phosphorus reagents such as p-toluenesulphonyl chloride,[91] triphenylphosphine, carbon tetrachloride and triphenylbromophosphonium bromide[92] overcome these difficulties, but often lead to poor yields of unstable carbodiimides. It was, however, hoped to form the carbodiimides required in the present studies via the dehydration of ureas in a novel way. It was anticipated that the action of phosphoryl chloride and diisopropylethylamine on a urea would effect the dehydration, giving the desired carbodiimide product.



(i) PhN=C=O, dioxane, room temp.

(ii) $POCl_3$, Pr^i_2NEt, $Cl(CH)_2Cl$, reflux.

(iii) $(Cl_3CO)_2C=O$, Et_3N, CH_2Cl_2, reflux.

(iv) $HCl_{(aq)}$, DME, room temp.

(v) Piperidine, Et_2O, room temp.

(vi) s-BuLi or t-BuLi,THF, -78^{o}- room temp.

Scheme 28

Although the urea [Scheme 28; (113)] had previously been obtained as a by-product in reactions it was now necessary to have ready access to this material. The synthesis of the urea (113) was achieved by the direct reaction of the amine (101a) with phenyl isocyanate in dioxane at room temperature. This afforded the desired urea product (113) in high yield as a crystalline solid.

The urea (113) in anhydrous dichloromethane was treated at room temperature with three equivalents of diisopropylethylamine in the presence of a 10% excess of phosphoryl chloride. However, the only material obtained was the urea (113), reisolated in moderate yield.

The order of addition of the reagents was switched, in the hope that the phosphoryl chloride would form an imidoyl chloride intermediate which could then be converted to the carbodiimide by the later addition of diisopropylethylamine. In the event, however, the urea (113) was present as a suspension throughout the reaction, even on heating under reflux for 21h and only the starting material was recovered unchanged in quantitative yield.

It was decided to revert back to the original order of addition, but changing the solvent to dichloroethane to increase the reaction temperature. Thus, the urea (113) was treated in refluxing 1,2-dichloroethane with three equivalents of diisopropylethylamine and a 10% excess of phosphoryl chloride, affording a light brown oil. The oil was extracted with anhydrous ether to give a pale yellow oil which t.l.c. showed to be a mixture of urea (113) and an unknown material. This was separated by flash chromatography over silica to give a low yield of the urea (113) (20%) and a 36% yield of a yellow oil, which gave accurate mass data consistent with the expected carbodiimide product (114). The oil's i.r. spectrum was also in

accord with the carbodiimide structure (114), showing absorption due to the carbodiimide substituent at 2139-2104cm^{-1}. Lengthening the reaction time to 17h increased the yield of the carbodiimide (114) to 75% after chromatography, together with a 13% recovery of the starting material. However, further increasing the reaction time to 24h did not improve the result, with the carbodiimide (114) being isolated in only 68% yield together with a 14% recovery of the urea starting material.

It was also found that altering the number of equivalents of phosphoryl chloride was detrimental to the final outcome of the reaction. Treatment of the urea (113) with three equivalents of diisopropylethylamine and a 50% excess of phosphoryl chloride gave a brown oil, flash chromatography of which gave the desired carbodiimide product (114) in only a 22% yield, together with the urea starting material (113) in 60% yield. Similarly, using a 10% excess of both diisopropylethylamine and phosphoryl chloride resulted in only a 27% yield of the desired carbodiimide product (114) and a 45% recovery of the urea (113).

It was hoped to further confirm the carbodiimide structure (114) by reacting it with methylamine to form a stable guanidine species. However, when the carbodiimide (114) in ethanol was treated with methylamine at room temperature the only material isolated was the urea (113) in low yield. Nonetheless, a solution of the carbodiimide (121) in 1,2-dimethoxyethane, on treatment with 2M aqueous hydrochloric acid at room temperature afforded a high yield of the urea (113). More conclusively, however, on treating an ethereal solution of the carbodiimide (114) with piperidine at room temperature, a colourless solid was obtained in high yield whose analytical and mass spectral data was entirely consistent with the expected guanidine product (121).

The product's i.r. and ^{1}H n.m.r. spectroscopic properties were also in agreement with this structure.

The yield of the dehydration step could not be improved by changing either the base or the chlorinating agent. The use of triethylamine instead of the Hunig base afforded a complex brown gum, from which no identifiable material could be isolated. Similarly, replacing the phosphoryl chloride with thionyl chloride as the chlorinating agent resulted in no reaction, the starting material being recovered in good yield.

As mentioned earlier, ureas can be converted into carbodiimides by the action of triphenylphosphine and carbon tetrachloride. It was decided to investigate this method of dehydration, hoping to further improve the yield of the carbodiimide (114).

The urea (113) was treated in refluxing dichloromethane with triphenylphosphine in the presence of carbontetrachloride and triethylamine. These conditions gave a brown oily semi-solid which was flash chromatographed over silica, giving only a 20% yield of the desired carbodiimide product (114) and a 40% recovery of the urea starting material. In the hope of increasing the yield of carbodiimide (114) the reaction time was increased to 17h. However, the only material obtained under these conditions was a brown oil which t.l.c. showed to be similar to that from the shorter reaction time. The mixture was therefore not further investigated.

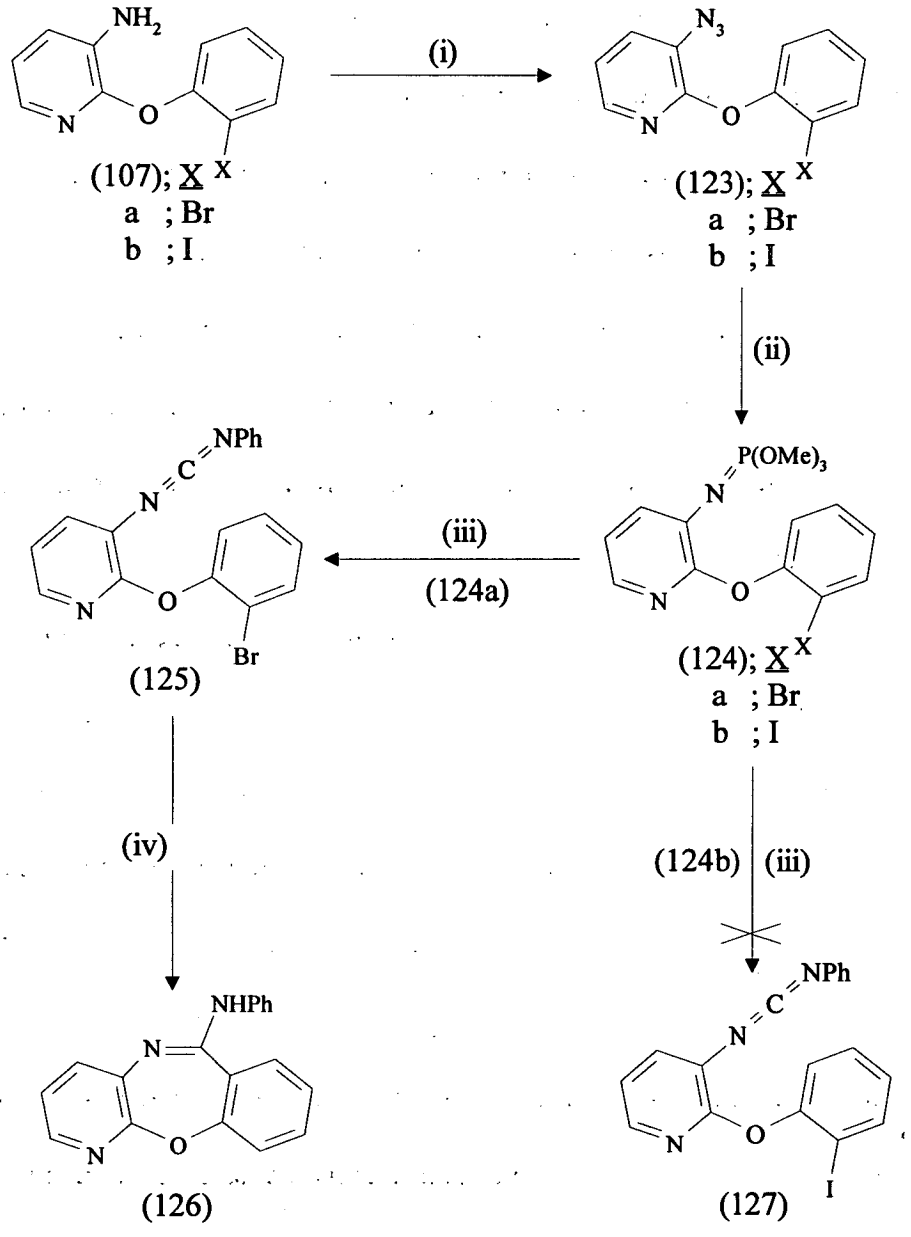
Phosgene has been reported[93] to act as a dehydrating agent of ureas, giving the corresponding carbodiimide. Due to the harmful nature of phosgene it was anticipated that triphosgene[94] could also accomplish this transformation, thereby avoiding the use of the more dangerous phosgene. Thus, the urea (113) was treated in refluxing, anhydrous dichloromethane with a two thirds of an equivalent of

triphosgene in the presence of four equivalents of triethylamine. These conditions gave a brown gum which was extracted with 60-80 light petroleum to afford the desired carbodiimide product (114) in 89% yield.

With the desired carbodiimide (114) now readily available by a choice of routes, the investigations moved on to the investigation of the carbanion induced cyclisation of this compound.

Treatment of the carbodiimide (114) with s-butyllithium in tetrahydrofuran at low temperature afforded a gummy orange oil. Flash chromatography of this oil gave a colourless crystalline product in 35% yield whose analytical and mass spectral data were consistent with its formulation as the dibenzoxazepine (122). Its i.r. and ^{1}H n.m.r. spectroscopic data was also consistent with this structure. On repeating this reaction but using t-butyllithium the desired dibenzoxazepine product (122) was isolated in 47% yield. The yield of the dibenzoxazepine (122) was further increased by limiting the reaction time to 30min at -78°. This afforded the desired dibenzoxazepine (122) in 66% yield.

After this success it was hoped to expand the investigations to include the synthesis and subsequent cyclisation of other carbodiimide derivatives. To this end the amine (101a) was similarly reacted with methyl isocyanate and benzyl isocyanate to afford good yields of the ureas (119) and (120) respectively. These were then subjected to the previously developed dehydration conditions. Unfortunately, on treatment with diisopropylethylamine and phosphoryl chloride in refluxing 1,2-dichloroethane neither the methyl urea (119) nor the benzyl urea (120) afforded any of the desired carbodiimides, the ureas being recovered in high yields in each case. Similarly on application of the triphosgene conditions there was again no formation of the



(i) $NaNO_2$, $HCl_{(aq)}$ then $NaN_{3\,(aq)}$, 0^o.

(ii) $P(OMe)_3$, DME, room temp.

(iii) PhN=C=O, DME, room temp.

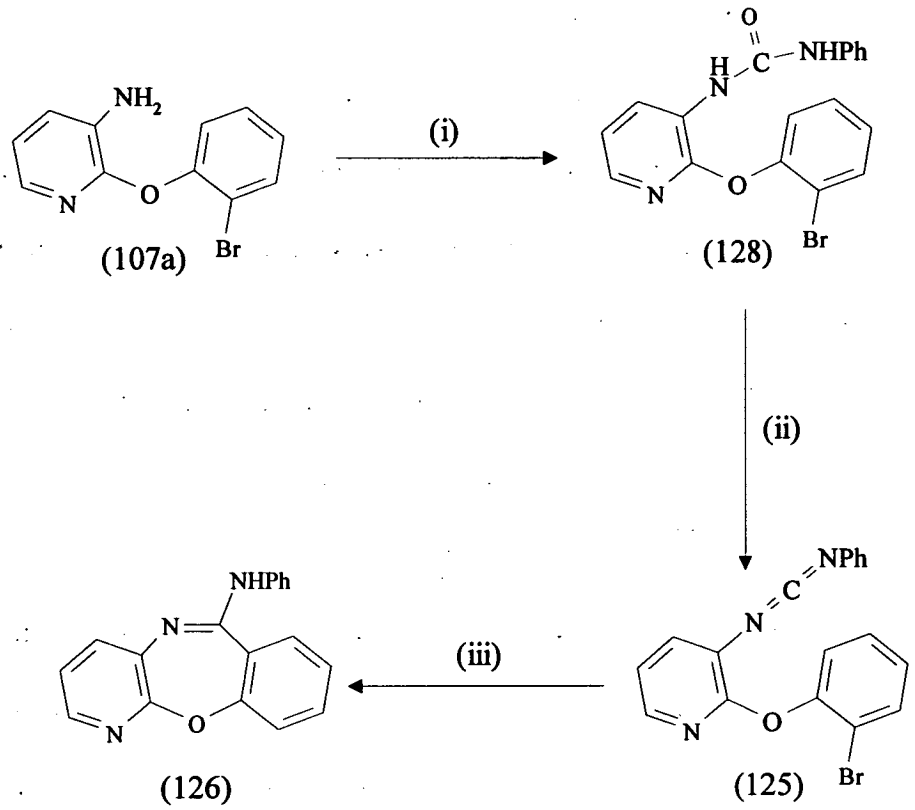
(iv) Mg, Et_2O, reflux.

Scheme 29

carbodiimides. In both cases the urea starting material was recovered in moderate yield. Although this lack of reactivity must be due to some electronic effect, no real explanation can be put forward as to why these alkyl ureas do not behave in the same way as their aryl analogues. Due to lack of time no further attempts were made to obtain the methyl and benzyl carbodiimides using alternative dehydration methods, and the synthetic approach to these compounds was abandoned at this stage.

The aim of the investigation was now changed to focus on the synthesis of pyridobenzoxazepine derivatives via the carbanion-induced cyclisation of carbodiimide precursors.

The synthesis (Scheme 29) of the bromo-carbodiimide derivative (125) and its iodo analogue (126) via their azide (123) and phosphinimine derivatives (124) has been described in the literature by Weddel and Tennant.[41] However, on repeating this work both the bromo and iodo carbodiimide derivatives were obtained only as components of complex mixtures. The reaction of the bromo-phosphinimine (124a) with phenyl isocyanate in 1,2-dimethoxyethane at room temperature afforded a multicomponent orange semi-solid which was triturated with ether to give the desired carbodiimide product (125)[41] in low yield. This was then taken, and in an attempt to effect an intramolecular Grignard addition to the carbodiimide, treated with magnesium in ether and heated under reflux for 3.5h. This reaction afforded a multicomponent orange gum which was flash chromatographed over silica, affording the carbodiimide starting material (125) in moderate yield. Also isolated was a small amount of an unidentified solid and a moderate yield of a colourless crystalline product whose analytical and mass spectral data were consistent with its formulation



(i) PhN=C=O, dioxane, room temp.

(ii) $POCl_3$, Pr^i_2NEt, $Cl(CH)_2Cl$, reflux.

(iii) t-BuLi,THF, -78^o.

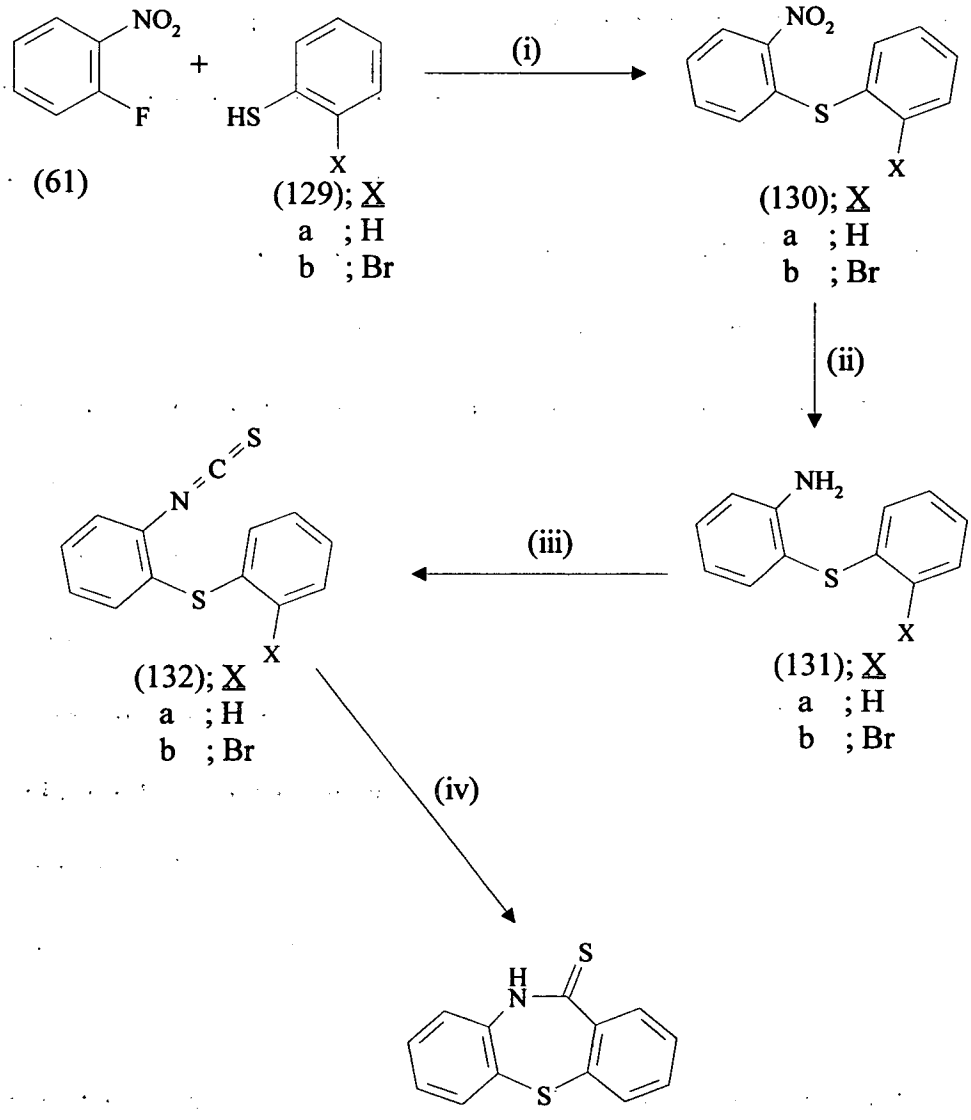
Scheme 30

as the urea [Scheme 30; (128)]. The product's i.r. and ^{1}H n.m.r. spectroscopic data were also in accord with this structure.

The reaction of the iodo-phosphinimine (124b) with phenyl isocyanate in dichloromethane at room temperature afforded an orange oil which both t.l.c. and i.r. spectroscopy showed to contain the desired carbodiimide product (127). However, flash chromatography over silica failed to give any identifiable material.

After successfully developing methods of synthesising diphenyl ether carbodiimide derivatives by the dehydration of the corresponding ureas, it was decided to apply this knowledge to the problem of synthesising phenoxypyridine carbodiimide derivatives. To this end (Scheme 30) the bromo-amine (107a) was reacted with phenyl isocyanate in dioxane at room temperature, giving the expected urea product (128) in high yield. This compound was then taken and treated with diisopropylethylamine and phosphoryl chloride and heated under reflux in 1,2-dichloroethane. These conditions afforded a brown oil which was extracted with 60-80 light petroleum, giving a good yield of the expected carbodiimide product (125).

In the hope of inducing its cyclisation to the pyridobenzoxazepine (126) the carbodiimide (125) was treated with t-butyllithium in tetrahydrofuran at low temperature. Flash chromatography of the resulting complex mixture isolated a light brown crystalline product which gave accurate mass data consistent with the expected pyridobenzoxazepine structure (126). The product's i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with the cyclised product, the i.r. spectrum showing amine absorption at 3034 cm^{-1}.



(i) NaH, DMF, 100°.
(ii) [H].
(iii) $Cl_2C=S$, $HCl_{(aq)}$, AcOH, room temp.
(iv) $AlBr_3$, CH_2Cl_2, room temp.
(v) s-BuLi, THF, -78° - room temp.

Scheme 31

2.4 Cyclisations of Heterocumulenes Leading to Dibenzo[b,f][1,4]thiazepines

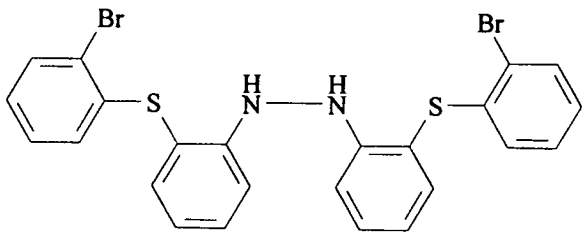
The synthesis of 2-nitrodiphenyl sulphide [Scheme 31; (130a)] has been previously reported by Roberts and Turner[95] but in the present work it was found more convenient to obtain this material via the sodium hydride catalysed reaction of thiophenol (129a) and 2-fluoronitrobenzene (61) in dimethylformamide at 100°. This raised the yield of the desired product (130a) from 59% to 92%. The nitro compound (130a) was then reduced in high yield to the corresponding amine (131a)[96] by the action of stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux. To gain the isothiocyanate precursor (132a) the amine (131a) was reacted with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature. These conditions afforded a yellow oil which gave accurate mass spectral data consistent with the desired isothiocyanate structure (132a). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with the isothiocyanate structure (132a), the i.r. spectrum showing a band at 2059cm^{-1} due to the isothiocyanate substituent.

With the isothiocyanate precursor (132a) in hand it was treated in dichloromethane with aluminium tribromide to afford a complex mixture. This mixture was flash chromatographed, giving a low yield of the isothiocyanate starting material (132a). Chromatography also gave in low yield (23%) a brown crystalline product which gave accurate mass data consistent with the molecular formula $C_{13}H_9NS_2$. Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with the expected dibenzothiazepine structure (133). The yield of the dibenzothiazepine (133) was not improved by heating the reaction under reflux. These conditions gave a complex

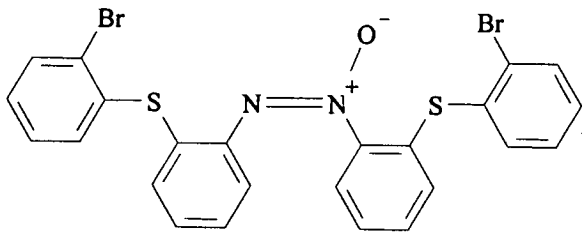
mixture from which flash chromatography over silica isolated only a low yield of the isothiocyanate starting material (132a), the remainder of the material being made up of complex oils and gums from which no identifiable material could be obtained. However, changing the Lewis acid catalyst to aluminium trichloride improved the yield of the reaction. In this case flash chromatography gave the desired dibenzothiazepine (133) in good yield (59%), with a 16% recovery of the isothiocyanate starting material (132a).

Complementary to the Lewis acid catalysed cyclisation reactions of the isothiocyanate derivative (132a) were investigations towards the carbanion-induced cyclisation of the isothiocyanate derivative (132b) to give the dibenzothiazepine derivative (133). It was therefore necessary to synthesise the isothiocyanate precursor, 2-bromo-2′-isothiocyanatodiphenyl sulphide (132b). The sodium hydride catalysed reaction of 2-bromothiophenol (129b) with 2-fluoronitrobenzene (61) afforded 2-bromo-2′-nitodiphenyl sulphide (130b)[97] in high yield. This was then reduced catalytically over Raney nickel in acetic acid at room temperature and atmospheric pressure to give, after flash chromatography, a 61% yield of the desired 2-amino-2′-bromodiphenyl sulphide (131b).[97] The use of dimethylformamide as the solvent in this reduction step afforded a more complex reaction product. In addition to giving the desired amine (131b) in 48% yield chromatography also gave in low yield a cream crystalline product which gave analytical and mass spectral data consistent with the molecular formula $C_{24}H_{18}Br_2N_2S_2$ suggesting the hydrazo structure (134). Its i.r. and ^1H n.m.r. spectroscopic properties were also in accord with this structure. Chromatography also gave in low yield an orange crystalline solid, which gave analytical and mass spectral data consistent with the azoxy

structure (135). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure.



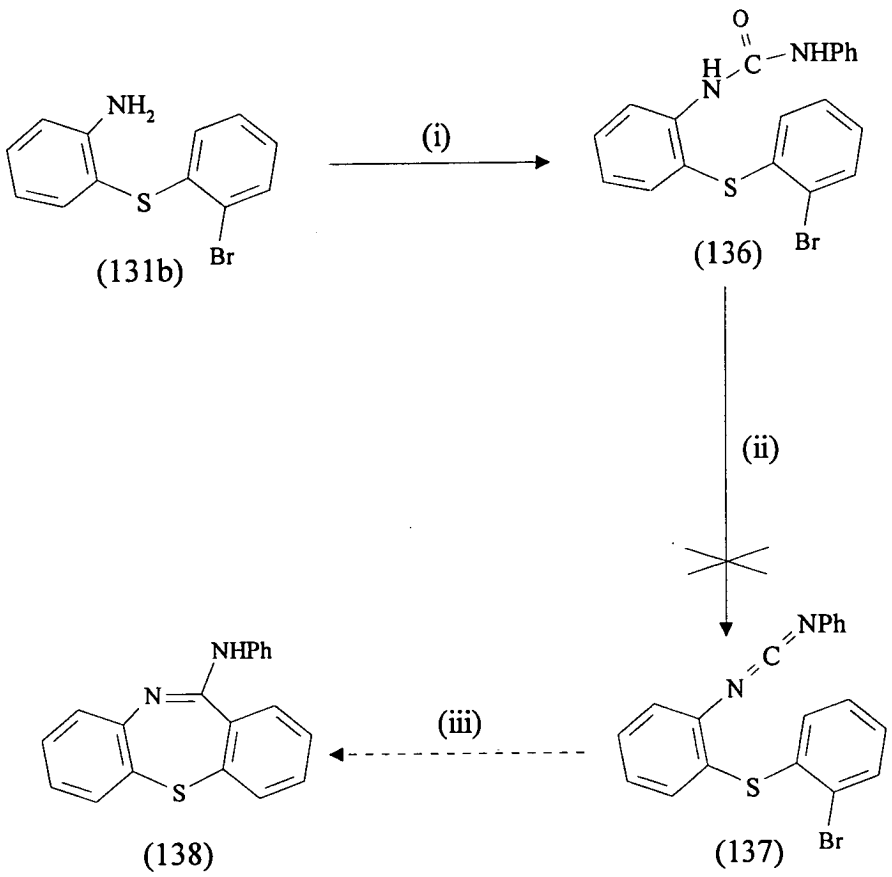
(134)



(135)

The room temperature reaction of the amine (131b) in acetic acid with thiophosgene in the presence of aqueous hydrochloric acid afforded a mixture as a brown oil. Flash chromatography of this oil afforded in good yield a colourless oil which gave analytical and mass spectral data consistent with the expected isothiocyanate structure (132b). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in agreement with this structure, the i.r. spectrum showing absorption at 2047cm^{-1} due to the isothiocyanate group.

With the isothiocyanate precursor now in hand its anticipated carbanion-induced cyclisation to the dibenzothiazepine (133) was next investigated. The isothiocyanate (132b) was treated at low temperature with one equivalent of s-butyllithium to give a complex brown oil, from which no identifiable material could be isolated. However, repetition of the reaction using two equivalents of s-butyllithium afforded a yellow semi-solid, which on trituration with hexane-ether afforded the desired cyclised



(i) PhN=C=O, dioxane, room temp.

(ii) $POCl_3$, Pr^i_2NEt, $Cl(CH)_2Cl$, reflux.

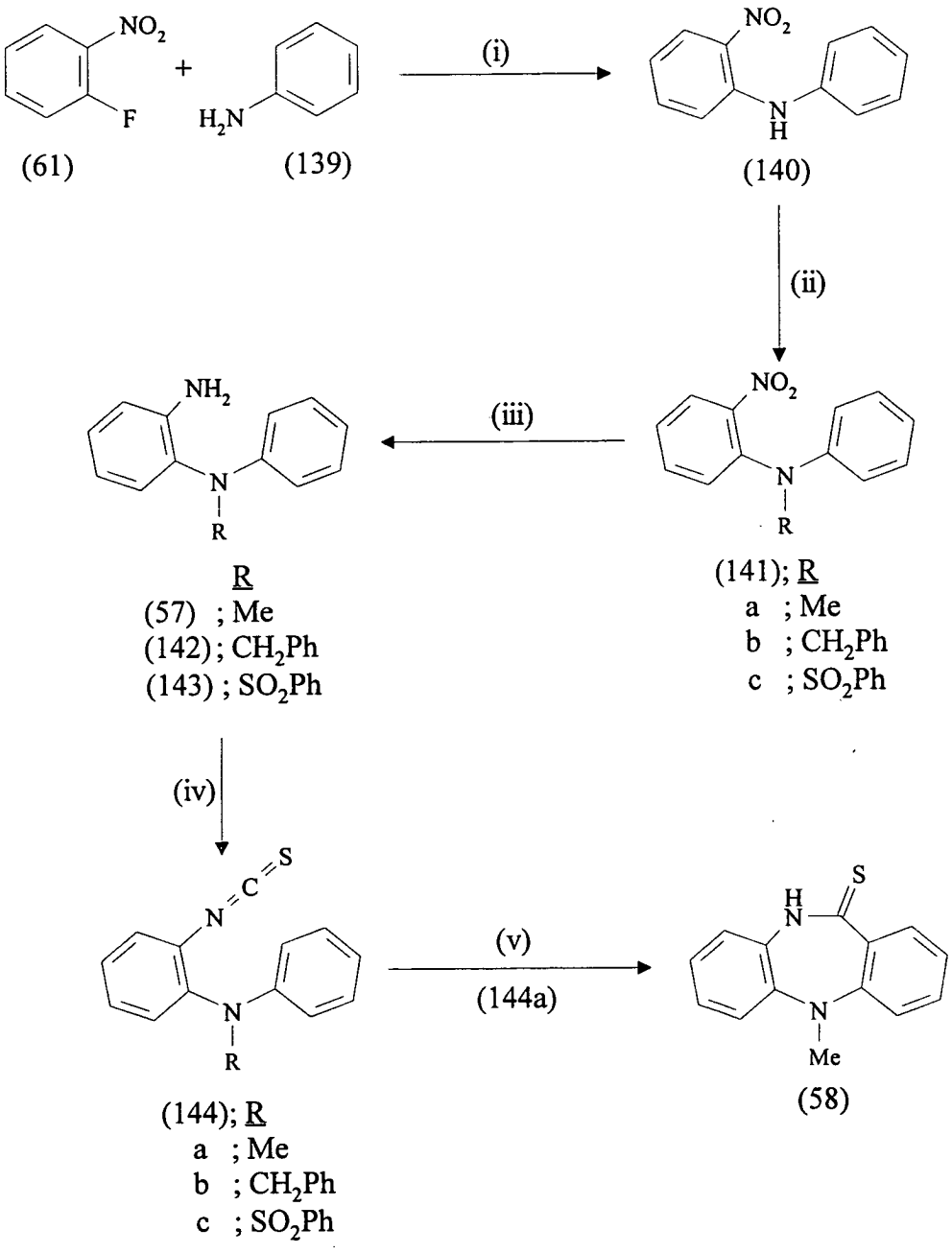
(iii) t-BuLi,THF, -78^O.

Scheme 32

product (133) in moderate yield (46%). The remainder of the material consisted of impure isothiocyanate starting material (132b).

After having demonstrated the carbanion induced cyclisation of 2-isothiocyanatodiphenyl sulphide (132b) to give the dibenzothiazepine (133) it was decided to expand this approach to include the carbanion-induced cyclisations of the analogous carbodiimide derivatives. It was therefore necessary to synthesise (Scheme 32) the appropriate carbodiimide derivative.

The synthesis of 2-amino-2′-bromodiphenyl sulphide (131b) has been described earlier in this chapter (Scheme 31). The amine (131b) was reacted with phenyl isocyanate in dioxane at room temperature giving an orange oil. This oil was subjected to flash chromatography to give a good yield of a colourless crystalline product whose analytical data was consistent with its formulation as the urea (136). Its spectroscopic properties were also in accord with the expected structure. The i.r. spectrum showed absorption at 3303cm^{-1} due to the presence of NH-groups and carbonyl absorption at 1655cm^{-1}. The urea (136) was then treated with diisopropylethylamine and phosphoryl chloride in 1,2-dichloroethane and heated under reflux for 17h, giving a brown oil which i.r. spectroscopy showed to contain the desired carbodiimide. However, chromatography of this oil failed to afford the desired carbodiimide (137), instead giving the urea starting material (136) in moderate yield. Similarly, trituration of the initial brown oil product with 60-80 light petroleum afforded no identifiable material.



(i) KF, 180^{o}.

(ii) Me_2SO_4 or $PhCH_2Br$ or TO_2SCl, NaH, DMF, room temp or 100^{o}.

(iii) $SnCl_2$, $HCl_{(aq)}$, THF, room temp. or reflux.

(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

(v) $AlCl_3$, CH_2Cl_2, room temp.

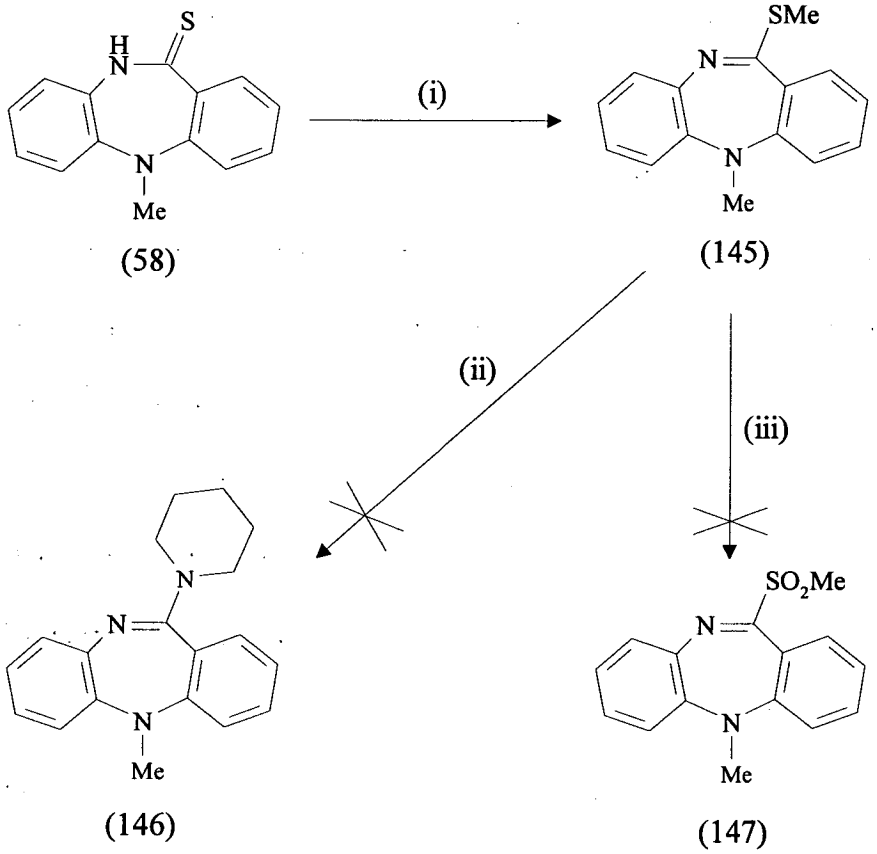
Scheme 33

2.5 Cyclisations of Heterocumulenes Leading to Dibenzo[b,e][1,4]diazepines

To complete these investigations on the synthesis of tricyclic heteropines it was decided to expand the work (Scheme 33) to include the synthesis of dibenzodiazepine systems.

The synthesis of 2-nitrodiphenylamine (140)[98] was achieved in high yield by the potassium fluoride catalysed condensation of 2-fluoronitrobenzene (61) with aniline (139). Due to the nature of the chemistry it was necessary to protect or block the secondary amine group to prevent premature cyclisation of the isothiocyanate precursor to give a benzimidazole system.[58] It was decided to first block the secondary amine group using a methyl group. This was achieved by the sodium hydride catalysed reaction of the nitro compound (140) with dimethyl sulphate in dimethylformamide at room temperature. These conditions afforded the known[99] N-methyl-2-nitrodiphenylamine (141a) in high yield. The reduction of the nitro compound (141a) to the corresponding known[99] amine (57) was then achieved in quantitative yield by the action of stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux.

The reaction of the amine (57) with thiophosgene in aqueous hydrochloric acid and acetic acid afforded a mixture as a brown oil. From this oil flash chromatography gave a yellow oil whose analytical data was consistent with the expected isothiocyanate structure (144a). Its spectroscopic properties were also in agreement with this structure, the i.r. spectrum showing absorption at 2110cm^{-1} due to the isothiocyanate substituent, and the ^{1}H n.m.r. spectrum showing a three-proton singlet at δ3.28 corresponding to the methyl group.



(58) (145) (146) (147)

(i) Me_2SO_4, NaH, DMF, room temp.

(ii) Piperidine, NaH, DMF, 100^{o} or reflux.

(iii) $KMnO_4$, AcOH, room temp.

Scheme 34

With the isothiocyanate precursor (144a) in hand it was decided to subject it to the Lewis acid catalysed cyclisation conditions discussed earlier in this chapter. The isothiocyanate (144a) was added to aluminium trichloride in dichloromethane and stirred at room temperature for 24h. These conditions afforded a yellow crystalline solid whose spectroscopic properties were consistent with its formulation as the known[58] dibenzodiazepine (58).

As described earlier in this chapter it was anticipated that the desired functionalisation of the heteropine ring (Scheme 34) could be achieved by S-methylation of the thione and the subsequent displacement of the methylthio group by a number of nucleophiles. The use of this methodology has been illustrated by Hunziker, Fischer and Schmutz.[58] The thione (58) was converted to the methylthio compound (145)[58] by its sodium hydride catalysed reaction with dimethyl sulphate, giving the desired product in good yield (75%). The methylthio compound (145) was then used in the attempted displacement reactions.

The sodium salt of piperidine in dimethylformamide was treated with the methylthio compound (145) at 100°. However, the only material isolated from this reaction was the methylthio compound (145), recovered in quantitative yield. Repeating this reaction with heating under reflux, however, gave a different result. A complex brown semi-solid was obtained, which on subjection to flash chromatography afforded moderate yields of the methylthio compound (145) and the thione (58). In addition to this, chromatography also gave in moderate yield (53%) a yellow crystalline product whose melting point and spectroscopic properties were consistent with its formulation as 5-methyldibenzo[b,f][1,4]diazepine-11(10H)-one.[100] Due to this apparent unreactivity of the latter group to displacement it was decided to

modify the methylthio leaving group. It was anticipated that oxidation of the sulphur would afford a better leaving group, thereby facilitating easier displacement. To this end a solution of the methylthio compound (145) in acetic acid was treated with aqueous potassium permanganate solution and stirred at room temperature. This did not, however, afford the expected sulphone product (147). Instead, this reaction afforded a complex brown oil which t.l.c. showed to be mainly impure starting material (145). The attempted functionalisation of the thione (58) was not further investigated.

Having demonstrated that the synthetic strategy was compatible with the diphenylamine system the next step was to look at the possible use of protecting-groups for the secondary amine group. The first protecting-group investigated (Scheme 33) was the benzyl group. It was anticipated that this group would be removable reductively after the cyclisation step to allow further functionalisation of the heteropine ring.

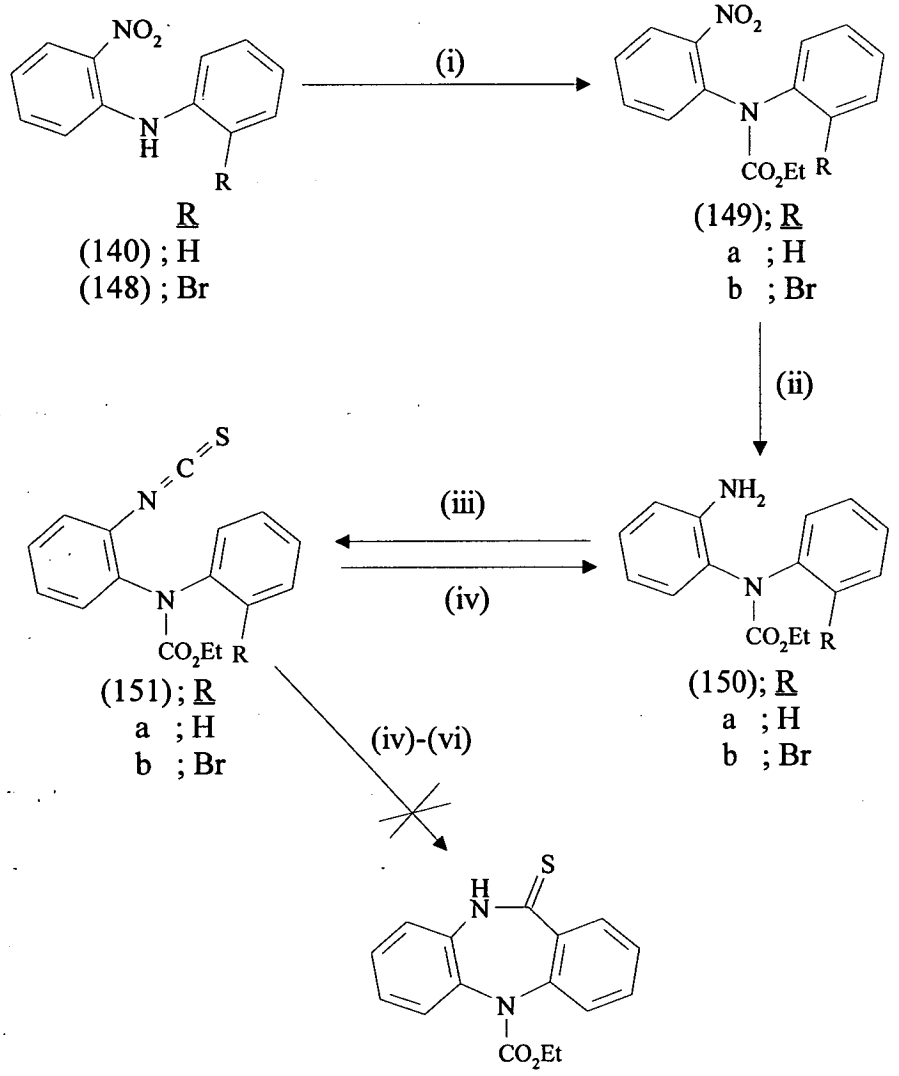
2-Nitrodiphenylamine (140) in dimethylformamide was reacted with benzyl bromide in a sodium hydride catalysed reaction at room temperature. This afforded the known[83] benzyl protected nitrodiphenylamine (141b) in quantitative yield. The benzyl protected nitro compound (141b) was then reduced in high yield to the known[83] corresponding amine (142) by the action of stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran at room temperature for 18h. It was also shown that the reaction time could be reduced to 1h under reflux, with no significant reduction in yield.

The next step was the formation of the isothiocyanate precursor. A suspension of amine (142) in acetic acid was treated at room temperature with thiophosgene in the

presence of aqueous hydrochloric acid. These conditions gave a red oil from which chromatography gave a low yield of a yellow oil whose analytical and mass spectral data was consistent with its formulation as the isothiocyanate (144b). Its i.r. and ^1H n.m.r. spectroscopic properties were also in accord with this structure the i.r. spectrum showing absorption at 2104cm^{-1} due to the isothiocyanate substituent. The reaction was repeated on a homogeneous mixture the amine (142) in acetic acid and aqueous hydrochloric acid, affording a brown oil, chromatography of which gave a moderate yield (24%) of the isothiocyanate (144b) and a 30% recovery of the amine starting material. The yield, however, was not increased by heating the reaction mixture at 50°. Using these conditions only impure starting material was recovered, in high yield.

The low yields of the isothiocyanate (144b) must be due to some adverse effect of the benzyl group. This could involve electronic or, more probably, steric effects. Unfortunately lack of time prevented further investigations into this line of work. The apparent unsuitability of the benzyl group necessitated a search for an alternative protecting group.

The next protecting group investigated was the tosyl group. The synthesis of the appropriate N-protected nitro (141c) and amine derivatives (143) has been previously reported in the literature.[83] The sodium hydride catalysed reaction of 2-nitrodiphenylamine (140) with p-toluenesulphonyl chloride in dimethylformamide at 100° afforded the expected tosyl-protected nitro derivative (141c) in moderate yield. The nitro compound (141c) was then reduced in good yield to the corresponding amine (143) by the action of stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux. The subsequent reaction of the amine (143)



R
(140) ; H
(148) ; Br

(149); R
a ; H
b ; Br

(150); R
a ; H
b ; Br

(151); R
a ; H
b ; Br

(152)

(i) $ClCO_2Et$, NaH, DMF, room temp.
(ii) [H].
(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(iv) $AlBr_3$, CH_2Cl_2, room temp.
(v) $AlCl_3$ or $TiCl_4$ or $SnCl_4$, CH_2Cl_2, room temp or reflux.
(vi) s-BuLi, THF, -78°- room temp.

Scheme 35

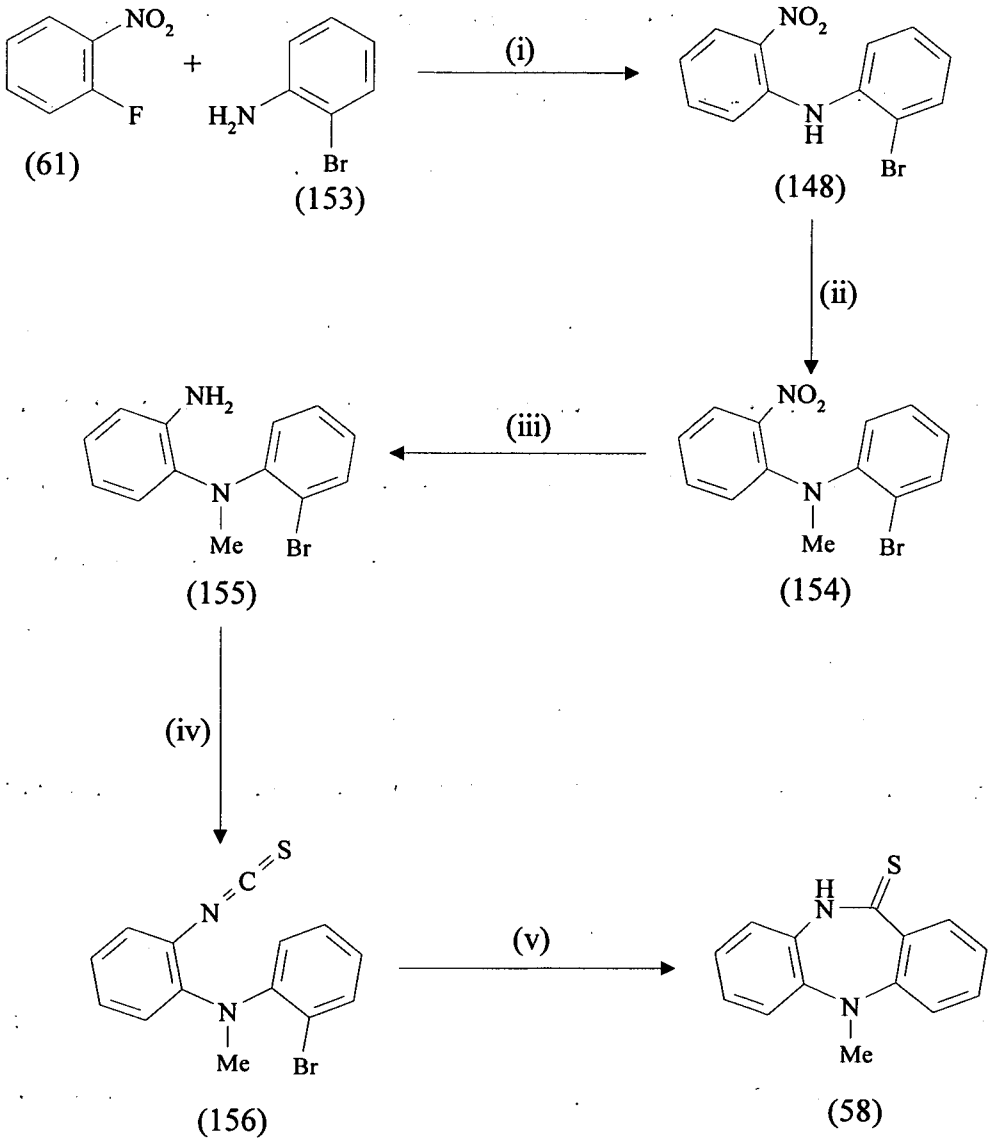
with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature afforded a light brown crystalline product in excellent yield, whose analytical and mass spectral data were consistent with its formulation as the tosyl-protected isothiocyanate (144c). Its other spectroscopic properties were also consistent with this structure, the ^{1}H n.m.r. spectrum showing a three-proton singlet at δ2.42 due to the methyl substituent of the tosyl-group. Also the i.r. spectrum showed absorption at 2114cm^{-1} due to the expected isothiocyanate group.

With the isothiocyanate precursor now readily available the isothiocyanate (144c) was subjected to the Lewis acid catalysed cyclisation conditions. Treatment of the isothiocyanate (144c) in dichloromethane with aluminium trichloride in at room temperature afforded only a complex gum, from which no identifiable material could be isolated. In the hope that a milder Lewis acid might effect a cleaner reaction the aluminium trichloride was replaced as the cayalyst by titanium tetrachloride. However, these conditions also resulted in the formation of a complex gum, from which no identifiable material could be isolated. Again the choice of protecting group seemed incompatible with the synthetic strategy employed, the tosyl group in some way reacting under the acid conditions.

The next protecting group investigated (Scheme 35) was the ethoxycarbonyl group. The synthesis of the appropriately protected nitro compound (149a) and amine (150a) has previously been described by Heckendorn.[101] The sodium hydride catalysed reaction of 2-nitrodiphenylamine (140) with ethyl chloroformate in dimethylformamide afforded a high yield of the desired product (149a). In the present studies it was found more convenient to use palladium-on-charcoal as the catalyst in the hydrogenation step instead of the Raney nickel reported in the

literature.[101] The use of palladium-on-charcoal in ethanol at room temperature and atmospheric pressure afforded a quantitative yield of the desired amine derivative (150a). In order to obtain the isothiocyanate precursor (151a) a solution of the amine (150a) in aqueous hydrochloric acid and acetic acid was stirred at room temperature with thiophosgene. These conditions afforded a quantitative yield of a light brown crystalline product whose analytical data and spectroscopic properties were entirely consistent with its formulation as the isothiocyanate (151a).

In the hope of forming the dibenzodiazepine (152), which could then be deprotected, the Lewis acid catalysed cyclisation of the isothiocyanate (151a) was investigated. The isothiocyanate (151a) was added to aluminium tribromide in dichloromethane and stirred at room temperature to give a quantitative yield of a light brown crystalline product, whose melting point and spectroscopic properties were consistent with its formulation as the ethoxycarbonyl-protected amine derivative (150a). Although the use of Lewis acids for the cleavage of ether bonds is well documented, this is the first reported example of cleavage of an isothiocyanate functionality to give an amine. This hydrolytic action was peculiar to aluminium tribromide. On repeating the reaction using aluminium trichloride as the catalyst the only material isolated was the isothiocyanate starting material (151a) recovered in quantitative yield. Raising the reaction temperature by refluxing in dichloromethane, with aluminium trichloride as catalyst gave only a low recovery of the isothiocyanate (151a) with the remainder of the isolated material consisting of intractable oils. Similarly, the use of titanium tetrachloride in dichloromethane, both at room temperature and under reflux resulted in no formation of the cyclised product (152). In both of these cases the isothiocyanate starting material was recovered unchanged



(i) KF, 180^{o} or NaH, DMF, 100^{o}.
(ii) Me_2SO_4, NaH, DMF, room temp.
(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.
(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(v) s-BuLi, THF, -78^{o}.

Scheme 36

in quantitative yield. This is yet another example of how changing the Lewis acid used in a reaction can drastically alter its outcome. There is very little known of the Lewis acids' role in these reactions and an in-depth study of this aspect is outwith the scope of these investigations. Consequently, without knowing the types of intermediate complex involved in these reactions it is difficult to fully explain the results.

In light of the results from the attempted Lewis acid catalysed cyclisations of the isothiocyanate precursors there was an increasing importance put on the investigation of carbanion-induced cyclisations. To this end it was decided to synthesise the appropriate isothiocyanate precursor [(Scheme 36; (156)]. 2-Fluoronitrobenzene (61) was reacted with 2-bromoaniline (153) in the presence of potassium fluoride at 180°. Unlike the unbrominated case these conditions afforded a complex mixture of starting materials and product. The unreacted bromoaniline (153) was removed from the mixture by the formation of its hydrochloride salt. Unreacted 2-fluoronitrobenzene (61) was next removed from the mixture by distillation leaving a 14% yield of the desired 2-bromo-2′-nitrodiphenylamine (148).[102] In the hope of increasing the yield of 2-bromo-2′-nitrodiphenylamine (148) a solution of 2-fluoronitrobenzene (61) in dimethylformamide was reacted with 2-bromoaniline (153) in a sodium hydride catalysed reaction. This afforded a red oil, from which flash chromatography gave the desired product (148) in 73% yield.

To avoid the complications involved in using the more complex protecting groups, the amine functionality was again blocked using a methyl-group. This was achieved by forming the sodium salt of the amine with sodium hydride in dimethylformamide, and its subsequent room temperature reaction with dimethyl sulphate. These

conditions afforded an orange crystalline solid whose analytical and mass spectral data were fully consistent with the expected methylated product (154). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the ^{1}H n.m.r. spectrum showing a three-proton singlet at δ3.28 due to the methyl blocking-group. The yield of the methylation reaction was raised to 100% by lengthening the reaction time to 24h at room temperature.

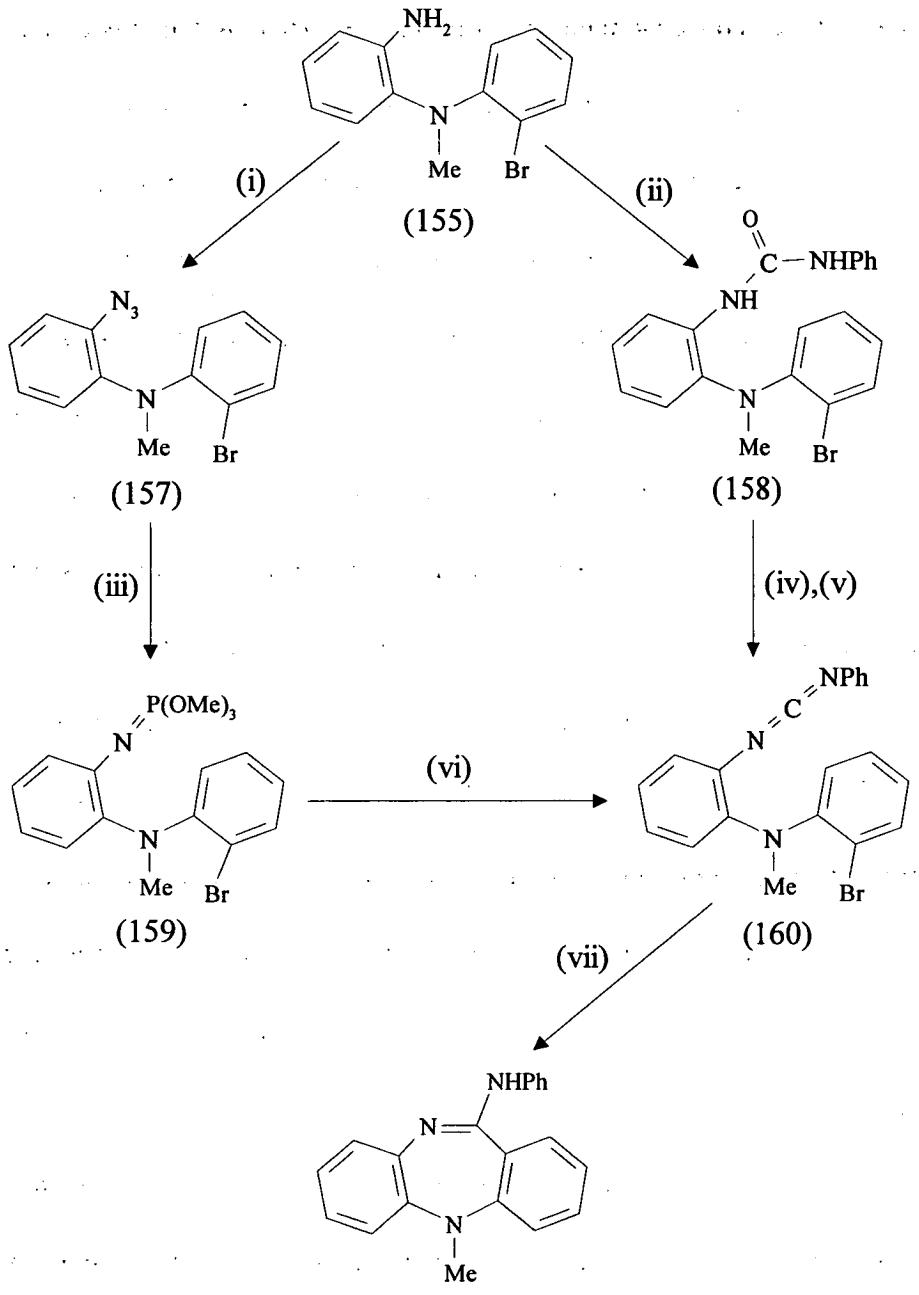
The reduction of the nitro compound (154) to the corresponding amine (155) was achieved in good yield by the action of stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux. These conditions afforded a yellow oil whose analytical data was consistent with its formulation as the amine (155). The spectroscopic properties of this product were also consistent with the assigned amine structure. The ^{1}H n.m.r. showed a two-proton signal at δ3.97 due to the exchangeable amine protons and the i.r. spectrum showed the presence of an amine group with an absorption bands at 3436 and 3345cm^{-1}.

To form the isothiocyanate precursor the amine (155) was dissolved in aqueous hydrochloric acid and acetic acid then treated at room temperature with thiophosgene. These conditions gave a brown oil which after flash chromatography afforded a moderate yield of the expected isothiocyanate product (156) as a yellow oil. The assignment of this structure was entirely consistent with the product's analytical and spectroscopic properties.

With the isothiocyanate precursor (156) now available, its carbanion-induced cyclisation to the dibenxodiazepine (58) was investigated. The isothiocyanate (156) was treated at low temperature with one equivalent of s-butyllithium to give the expected dibenzodiazepine product (58) in quantitative yield. Having demonstrated

that dibenzodiazepines could be synthesised by the carbanion induced cyclisation of the appropriate isothiocyanate derivative, the next step was to investigate the incorporation of an appropriate protecting group into the precursor. Of the protecting groups previously studied the carbamate group was considered the most promising.

2-Bromo-2′-nitrodiphenylamine [Scheme 35; (148)] was reacted with sodium hydride in dimethyl formamide to give the sodium salt of the amine. However, unlike the unbrominated case, treatment of the sodium salt with ethyl chloroformate at room temperature for 30min resulted in no reaction. In the event, the reaction was found to take 34h in total, the desired ethoxycarbonyl protected product (149b) then being obtained in good yield (88%). Its i.r. spectrum was in accord with this structure, showing carbonyl absorption at 1694cm^{-1} and absorption at 1574 and 1345cm^{-1} due to the nitro-group. This material was then used in the subsequent reduction step without further purification. The nitro compound (149b) was reacted with stannous chloride dihydrate in aqueous hydrochloric acid and tetrahydrofuran under reflux. This afforded a high yield of a colourless crystalline material whose accurate mass data and i.r and ^{1}H n.m.r. spectroscopic properties were consistent with its formulation as the amine (150b). The amine was then reacted at room temperature with thiophosgene in aqueous hydrochloric acid and acetic acid to give a moderate yield of a yellow oil whose spectroscopic properties were consistent with its formulation as the isothiocyanate (151b). The isothiocyanate (151b) was then treated at low temperature with s-butyllithium to give a brown semi-solid, from which flash chromatography gave only brown oils which yielded no identifiable material. Due to lack of time this line of work was not further investigated.



(i) $NaNO_2$, $HCl_{(aq)}$ then $NaN_{3\,(aq)}$, 0^{o}.
(ii) PhN=C=O, dioxane, room temp.
(iii) $P(OMe)_3$, DME, room temp.
(iv) $POCl_3$, Pr^i_2NEt, $Cl(CH_2)_2Cl$, reflux.
(v) $(Cl_3CO)_2C=O$, Et_3N, CH_2Cl_2, reflux.
(vi) PhN=C=O, DME, room temp.
(vii) s-BuLi or t-BuLi, THF, -78^{o}- room temp.

Scheme 37

In the light of the results described previously, the focus of the work was next changed to the investigation of the cyclisations of carbodiimide derivatives leading to dibenzodiazepines (Scheme 37). The first method investigated for the synthesis of the appropriate carbodiimides precursors was via the azide and phosphinimine derivatives[41] as described earlier in this chapter. N-Methyl-2-amino-2′-bromodiphenylamine (155) was treated at 0° with aqueous sodium nitrite and the resulting diazonium salt displaced with sodium azide to give a brown oil. This oil was flash chromatographed to give unreacted starting material (155) in low yield, and a 37% yield of a red oil whose analytical and mass spectral data were consistent with its formulation as the azide (157). The product's i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2131cm^{-1} due to the expected azide substituent. The yield of the azide (157) was not markedly improved by lengthening the reaction times for the diazonium salt formation to 30min and for the displacement to 2h. The use of these conditions afforded the azide (157) in 49% yield.

Reaction of the azide (157) with trimethylphosphite in 1,2-dimethoxyethane at room temperature afforded a light brown oil which ^{1}H n.m.r. spectroscopy showed to be a mixture of the desired product (159) and a second phosphorous containing species. Due to the instability of the phosphinimine (159) it could not be isolated in a pure form, so the mixture was used without further purification in the subsequent step. The impure phosphinimine (159) was treated at room temperature with phenyl isocyanate in 1,2-dimethoxyethane. This reaction afforded a red oil which t.l.c. and i.r. spectroscopy showed to be a complex mixture containing the desired carbodiimide product (160). As in the previous step, the inherent instability of the

product prevented further purification, so the material was used in the final butyllithium-induced cyclisation step without further purification. It was hoped that the dibenzodiazepine (161) could be isolated form the resulting mixture. Thus, the impure carbodiimide (160) in tetrahydrofuran was treated with s-butyllithium, affording a multicomponent brown oil, which on flash chromatography afforded only mixed fractions as intractable oils and gums, from which no identifiable material could be isolated.

The inability to purify the phosphinimine (159) and carbodiimide intermediate (160) seemed to a major drawback in this synthetic approach to the desired dibenzodiazepine system. A much purer source of the carbodiimide precursor was essential in order to properly investigate the synthetic utility of the butyllithium-induced cyclisation. It was therefore necessary to adopt another strategy for the synthesis of the carbodiimide precursor, and as described earlier in this chapter the strategy adopted was the dehydration of the appropriate urea derivative.

Thus, the amine (155) was reacted with phenyl isocyanate in dioxane at room temperature giving a high yield of a colourless crystalline material whose analytical and mass spectral data were consistent with those of the expected urea product (158). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing amino absorption at 3336cm^{-1} and absorption at 1658cm^{-1} due to the carbonyl group. The urea (158) was treated as described earlier with diisopropylethylamine and phosphoryl chloride then heated under reflux in 1,2-dichloroethane for 17h. These conditions afforded a brown viscous oil, which on repeated extraction with 60-80 light petroleum afforded a good yield of the desired carbodiimide product (160). As described in the work towards the synthesis of

dibenzoxazepines the dehydration of ureas to give the corresponding carbodiimide derivatives can also be accomplished using triphosgene in the presence of triethylamine. In the hope that this would prove a better approach, the triphosgene methodology was applied to the problem at hand. Thus, a suspension of the urea (158) in dichloromethane was treated with triethylamine and triphosgene then heated under reflux for 4h. These conditions afforded a yellow oil which t.l.c. showed to contain the desired carbodiimide product (160). However, flash chromatography over silica afforded only a 2% yield of the carbodiimide (160) and a 52% recovery of the unreacted urea (158). The remainder of the isolated material consisted of a complex yellow oil which was not further investigated. This result showed that unlike its diphenyl ether analogue (114) the diphenylamine carbodiimide derivative (160) was too unstable to be purified by flash chromatography. Isolation was best achieved by repeated extraction with 60-80 light petroleum, thus preventing hydrolysis to the urea. Treatment of the carbodiimide (160) with one equivalent of t-butyllithium in tetrahydrofuran at low temperature afforded a yellow oil which was flash chromatographed over silica to give the desired dibenzodiazepine (161) in moderate yield as a light brown solid (30%).

2.6 Experimental

General Experimental Details

Infrared spectra were recorded using a Bio-Rad FTS-7 insrument. I.r. bands were strong and sharp unless otherwise specified as br (broad) or w (weak). Solids were measured as suspensions (mulls) in Nujol and liquids as thin films.

^{1}H n.m.r. spectra were measured in the stated solvents at 80MHz using a Bruker WP-80SY instrument, at 200MHz using Bruker WP-200SY or Bruker AC-200 instruments, at 250MHz using a Bruker AC-250 instrument, or at 360Mhz using a Bruker WH-360 instrument. Signals were sharp singlets unless otherwise specified as b (broad); s singlet, d = doublet, dd = doublet doublet, t = triplet, q = quartet and m = multiplet. ^{13}C n.m.r. spectra were measured in the stated solvent using Bruker AC-200 or Bruker AC-250 instruments. Quaternary carbon atoms and methylene groups were identified by 3/4 DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence spectra.

Electron impact (EI) mass spectra were recorded at 70eV on a Kratos MS-50TC instrument. Fast Atom Bombardment (FAB) mass spectra were recorded at 70eV on a Kratos MS-50TC instrument for matrices in thioglycerol.

Elemental analyses were determined using a Perkin-Elmer 2400 elemental analyser. Routine melting points (m.p.) were carried out using a Gallencamp apparatus and are uncorrected. Melting points of analytical samples were determined on a Koffler hot-stage and are uncorrected.

Unless specified, all reagents were laboratory grade. Sodium hydride was a 60% or 80% suspension in mineral oil and was washed with anhydrous diethyl ether before use.

Solvents were of technical grade unless otherwise stated. Anhydrous solvents were prepared as follows: xylene was distilled and stored over sodium wire; diethyl ether, benzene and toluene were stored over sodium wire; dichloromethane, chloroform, dimethylformamide, methanol and acetonitrile were distilled and stored over anhydrous 4A molecular sieves; 1,2-dimethoxyethane and 1,4-dioxane were distilled

from calcium hydride and stored over anhydrous 4A molecular sieves; tetrahydrofuran was distilled from sodium and benzophenone immediately prior to use.

All organic extracts were dried over anhydrous magnesium sulphate prior to evaporation under reduced pressure. Atmospheric moisture was excluded from reaction mixture using a guard tube containing self-indicating silica gel (Fisons 6-16 mesh).

Wet column flash chromatography was carried out at 5-7 p.s.i. (air line) over silica (Merck Kieselgel 60, 230-400 mesh) or alumina (Merck Aluminiumoxid 90, 70-230 mesh, activity III). Thin layer chromatography (t.l.c.) was carried out using Polygram Sil' G/UV_{254} or ALOXN/UV_{254} precoated sheets.

2-Nitrodiphenyl Ether (63)

A vigorously stirred suspension of sodium hydride (3.9g; 0.17mol) in anhydrous dimethylformamide (60.0ml) was treated dropwise at 0-10° (ice bath) with a solution of phenol (62) (14.1g; 0.15mol) in anhydrous dimethylformamide (30.0ml) and the mixture was stirred at room temperature, with exclusion of atmospheric moisture, for 15min. A solution of 2-fluoronitrobenzene (61) (21.2g; 0.2mol) in anhydrous dimethylformamide (90.0ml) was then added in one portion and the mixture was stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The mixture was treated with water (40.0ml) and rotary evaporated to give a yellow residue which was treated with water (200ml) and extracted three times with ethyl acetate (3 x 100ml) to afford 2-nitrodiphenyl ether (63) as a yellow oil (32.3g; 100%), ν_{max} 1531 and 1354 (NO_2) cm^{-1}.[61]

2-Aminodiphenyl Ether (64)

A solution of 2-nitrodiphenyl ether (63) (32.3g; 0.015mol) in ethanol (75.0ml) was hydrogenated over 10% palladium-on-charcoal (3.2g) at room temperature and atmospheric pressure for 6h, during which time 10200ml hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give 2-aminodiphenyl ether (64) as a light brown oil (27.1g; 98%), ν_{max} 3621, 3461 and 3398 (NH_2) cm^{-1}.[60]

2-Isothiocyanatodiphenyl Ether (65)

A solution of 2-aminodiphenyl ether (64) (11.1g; 0.06mol) in glacial acetic acid (90.0ml) was stirred and treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (30.0ml) then dropwise at room temperature with a solution of thiophosgene (13.8g; 0.12mol) in glacial acetic acid (30.0ml).The mixture was then stirred at room temperature for 2h.

The mixture was treated with water (120ml) and extracted three times with dichloromethane (3 x 120ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 120ml) then rotary evaporated to give 2-isothiocyanatodiphenyl ether (65) as a brown oil (13.6g; 100%), ν_{max} 2052 and 2026 (N=C=S) cm^{-1};

Found: m/z (EI HRMS), 227.0408 (M^+),

$C_{13}H_9NOS$ requires: M, 227.0405.

Lewis Acid Catalysed Cyclisations of 2-Isothiocyanatodiphenyl Ether (65)

(a) A stirred solution of 2-isothiocyanatodiphenyl ether (65) (2.3g; 0.01mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of aluminium tribromide (5.5g; 0.02mol) in anhydrous dichloromethane (25.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford a yellow solid (4.5g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded a mixed fraction as an orange oil (0.13g) which was not further investigated.

Further elution with hexane-ether (95:5) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (1.2g; 53%), m.p. 172-178°, which formed yellow crystals, m.p. 195-198° (from hexane-toluene), ν_{max} 3156 (NH) cm^{-1}, δ_H ($CDCl_3$) 10.41 (1H, bs, NH) (exch) 8.20 (1H, ddd J 7.9, 1.8 and 0.5Hz, ArH) 7.49 (1H, dt J 7.9 and 1.8Hz, ArH) and 7.29-7.12 (6H, m, ArH);

Found: C, 68.8; H, 4.3; N, 6.2%; m/z (EI ms), 227 (M^+),

$C_{13}H_9NOS$ requires: C, 68.7; H, 4.0; N, 6.2%; M, 227.

Further elution with methanol afforded a brown intractable solid (0.11g), m.p. 155-162°, which was not further investigated.

(b) The reaction was repeated as described in (a) before, but on a 0.02 molar scale and with heating under reflux for 4h. to give a yellow solid (4.5g) which was flash

chromatographed over silica. Elution with hexane-ether (90:10) afforded a mixed fraction as a red oil (0.28g) which was not further investgated.

Further elution with hexane-ether (50:50) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (2.1g; 46%), m.p. 195-198°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded a mixed fraction as a yellow gum (0.22g) which was not further investigated.

Further elution with ether afforded a second crop of dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (1.7g; 36%), m.p. 178-183°, identified by comparison (melting point and i.r. spectrum) with the first crop.

(c) A stirred suspension of aluminium tribromide (2.7g; 0.01mol) in anhydrous dichloromethane (10.0ml) under nitrogen was treated dropwise at -10° (ice-acetone bath) with a solution of 2-isothiocyanatodiphenyl ether (65) (1.1g; 0.005mol) in anhydrous dichloromethane (15.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford a yellow solid (1.1g), m.p. 153-161°, which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded 2-isothiocyanatodiphenyl ether (65) as a pale yellow oil (0.18g; 16%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.16g) which was not further investigated.

Further elution with hexane-ether (95:5) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.70g; 76%), m.p. 193-197°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(d) Repetition of the reaction described in (c) before, but on a 0.04 molar scale and using aluminium trichloride (0.008mol) as the catalyst afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as an orange solid (8.2g; 76%), m.p. 182-187°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(e) Repetition of the reaction described in (c) before, but on a 0.002 molar scale and using zinc dichloride (0.004mol) as the catalyst afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (0.45g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(f) Repetition of the reaction described in (e) before, but with heating under reflux for 4h afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (0.45g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(g) Repetition of the reaction described in (e) before but using 1,2-dichloroethane as the sovent and heating under reflux for 4h afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (0.45g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(h) A stirred solution of 2-isothiocyanatodiphenyl ether (65) (1.1g; 0.005mol) in anhydrous dichloromethane (15.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of stannic chloride (6.5g; 0.025mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (1.1g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(i) Repetition of the reaction described in (h) before, but with heating under reflux for 4h afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (1.1g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(j) Repetition of the reaction described in (h) before, but using 1,2-dichloroethane as the sovent and heating under reflux for 4h afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (1.1g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(k) A stirred solution of 2-isothiocyanatodiphenyl ether (65) (1.1g; 0.005mol) in anhydrous dichloromethane (15.0ml) under nitrogen was treated dropwise at -10° (ice-acetone bath) with a solution of titanium tetrachloride (4.8g; 0.025mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford a yellow semi-solid (1.1g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded 2-isothiocyanatodiphenyl ether (65) as a pale yellow oil (0.85g; 77%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (95:5) afforded dibenz[b,f][1,4]oxazepine-11(10)-thione (66) as a yellow solid (0.13g; 12%), m.p. 175-182°, identified by comparison (i.r. spectrum) with to an authentic sample prepared before.

Further elution with methanol afforded a brown oil (0.081g) which was not further investigated.

(l) Repetition of the reaction described afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a yellow oil (1.1g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(m) Repetition of the reaction described in (l) before, but using mixture of 2-isothiocyanatodiphenyl ether (65) and dibenz[b,f][1,4]oxazepine-11(10)-thione (66) resulting from the reaction described in (k) before, afforded a brown oily semi-solid which t.l.c. in hexane-ether over silica showed to be a mixture of 2-isothiocyanatodiphenyl ether starting material (65) and the dibenz[b,f][1,4]oxazepine-11(10)-thione (66) (1.1g; 100%). The mixture was not further investigated.

(n) A stirred solution of boron trifluoride etherate (0.57g; 0.004mol) in anhydrous dichloromethane (10.0ml) under nitrogen was treated dropwise at -10° (ice-acetone bath) with a solution of 2-isothiocyanatodiphenyl ether (65) (0.45g; 0.002mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The stirred mixture was cooled in an ice bath, treated with ice (10.0g) then stirred in the melting ice bath for 1h. The mixture was extracted three times with dichloromethane (3 x 10.0ml) to afford unreacted 2-isothiocyanatodiphenyl ether (65) as a brown oil (0.45g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

11-Methylthiodibenz[b,f][1,4]oxazepine (67)

(a) A vigorously stirred suspension of sodium hydride (0.22g; 0.0088mol) in anhydrous dimethylformamide (10.0ml) was treated in one portion at room temperature with a solution of dibenz[b,f][1,4]oxazepine-11(10)-thione (66) (1.8g; 0.008mol) in anhydrous dimethylformamide (20.0ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min. A solution of methyl iodide (1.1g; 0.008mol) in anhydrous dimethylformamide (10.0ml) was added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with water (10.0ml) and stirred at room temperature for 10min. Rotary evaporation gave a red oily residue which was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 20.0ml) to give an orange oil (1.6g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a pale yellow solid (0.49g; 25%), m.p. 83-84° (from ethanol), δ_H ($CDCl_3$) 7.72 (1H, dt J 5.8 and 0.7Hz, ArH), 7.49-7.11 (7H, m, ArH) and 2.62 (3H, s, SCH_3);

Found: C, 69.4; H, 4.7; N, 5.7%; m/z (EI ms), 241 (M^+) and 194 (M^+-SCH_3),

$C_{14}H_{11}NOS$ requires: C, 69.7; H, 4.6; N, 5.8%; M, 241.

Further elution with hexane-ether (80:20) afforded 10-methyldibenz[b,f][1,4]oxazepine-11-thione (68) as a yellow oil (0.12g; 12%), δ_H 8.10 (1H, dd J 7.8 and 1.7Hz, ArH), 7.40-7.06 (7H, m, ArH) and 4.04 (3H, s, NCH_3);

Found: C, 69.6; H, 4.8; N, 5.5%; m/z (EI ms), 241 (M^+),

$C_{14}H_{11}NOS$ requires: C, 69.7; H, 4.6; N, 5.8%; M, 241.

Further elution with ether through methanol afforded only complex oils (0.49g) which were not further investigated.

(b) Repetition of the reaction described in (a) before, but on a 0.01 molar scale and using four equivalents of methyl iodide (0.08mol) gave a yellow gummy residue which was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 30.0ml) to give a red oil (4.3g) which was flash chromatographed over alumina.

Elution with hexane-ether (99:1) afforded 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a pale yellow solid (1.2g; 50%), m.p. 78-81°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (98:2) through ether afforded no material and elution with methanol afforded only a complex oil (1.0g) which was not further investigated.

(c) Repetition of the reaction described in (a) before, but on a 0.015 molar scale and using four equivalents dimethylsulphate (0.06mol) as the methylating agent gave 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a brown solid (3.5g; 97%), m.p. 81-85°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine in Anhydrous Acetonitrile Under Reflux.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.46g; 0.002mol) in anhydrous acetonitrile (10.0ml) was treated at room temperature with piperidine (0.19g; 0.0022mol) then stirred and heated under reflux, with the exclusion of atmospheric moisture, for 24h.

The mixture was rotary evaporated, affording a red oil which was treated with water (10.0ml) to giving 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a light brown solid (0.43g; 94%), m.p. 79-84°, identical (melting point and i.r. spectrum) to an authentic sample prepare before.

The Attempted Reaction of the 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine Under Reflux.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in piperidine (5.0ml) was heated under reflux for 24h.

The mixture was allowed to cool to room temperature then was rotary evaporated to give 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a light brown solid (0.24g;

100%), m.p. 78-82°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The Attempted Sodium Hydride Catalysed Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine in Anhydrous 1,2-Dimethoxyethane Under Reflux.

A vigorously stirred suspension of sodium hydride in anhydrous 1,2-dimethoxyethane (5.0ml) was treated dropwise at 0-5° with a solution of piperidine (0.17g; 0.002mol) in anhydrous 1,2-dimethoxyethane (5.0ml) then stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. The mixture was treated with a solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.46g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) then stirred and heated under reflux for 1h.

The cooled mixture was treated with water (5.0ml) then stirred at room temperature for 15min. Rotary evaporation gave a brown residue which was treated with water (20.0ml) then extracted three times with dichloromethane (3 x 10.0ml) to afford 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a brown solid (0.46g; 100%), m.p. 79-85°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The Sodium Hydride catalysed Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine in Dimethylformamide at 100°.

A vigorously stirred suspension of sodium hydride (0.053g; 0.0022mol) in anhydrous dimethylformamide (5.0ml) was treated dropwise at 0-5° (ice bath) with a solution of

piperidine (0.17g; 0.002mol) in anhydrous dimethylformamide (5.0ml) and the mixture was stirred at room temperature with exclusion of atmospheric moisture for 15min. A solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.46g; 0.002mol) in anhydrous dimethylformamide (10.0ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was allowed to cool to room temperature, treated with water (5.0ml) and stirred at room temperature for 15min. Rotary evaporation gave a yellow oily residue which was treated with water, affording dibenz[b,f][1,4]oxazepin-11(10H)-one (69) as a pale yellow solid (0.39g; 93%), m.p. 215-216° (from ethanol) (lit.[64], 213-215°), δ_H ($CDCl_3$) 8.62 (1H, bs, NH) (exch), 7.74 (1H, dd J 8.1 and 2.0Hz, ArH), 7.63-7.41 (1H, m, ArH) and 7.34-7.04 (6H, m, ArH);

Found: m/z (EI HRMS), 211.0645 (M^+),

$C_{13}H_9NO_2$ requires: M, 211.0633.

Extraction of the filtrate with dichloromethane (3 x 5.0ml) afforded no identifiable material.

The Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Sodium Hydroxide in Aqueous Ethanol.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in ethanol (7.5ml) was treated with 2M aqueous sodium hydroxide solution (2.5ml) and the mixture was stirred at room temperature for 17h.

The mixture was adjusted to pH 1 by the addition of 2M aqueous hydrochloric acid then extracted three times with dichloromethane (3 x 10.0ml) to afford a pale yellow

gum (0.24g), whose i.r. and t.l.c. in hexane-ether over silica showed it to be mainly unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) plus a small amount of the dibenz[b,f][1,4]oxazepin-11(10H)-one (69). The mixture was not further investigated.

The Attempted Reaction of Dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) with Sodium Hydroxide in Aqueous Ethanol.

A stirred solution of dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) (0.22g; 0.001mol) in ethanol (7.5ml) was treated with 2M aqueous sodium hydroxide solution (2.5ml) and the resulting suspension was stirred at room temperature for 15min..

The mixture was adjusted to pH 1 by the addition of 2M aqueous hydrochloric acid then extracted three times with dichloromethane (3 x 10.0ml) to afford unreacted dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.22g; 100%), m.p. 183-185°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The Attempted Lead Tetra-acetate Catalysed Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine in Dichloromethane at Room Temperature.

A solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in dichloromethane (2.5ml) was treated in one portion with lead tetra-acetate (0.44g; 0.001mol) then dropwise with a solution of piperidine (0.085g; 0.001mol) in dichloromethane (2.5ml). The mixture was then stirred at room temperature for 65h.

The mixture was treated with water (5.0ml) then extracted three times with dichloromethane (3 x 5.0ml) to afford impure unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a brown gum (0.27g; 100%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Attempted Nickel Acetylacetonate Catalysed Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Piperidine in Dichloromethane at Room Temperature.

A solution of the 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in dichloromethane (2.5ml) was treated in one portion with nickel acetylacetonate (0.26g; 0.001mol) then dropwise with a solution of piperidine (0.085g; 0.001mol) in dichloromethane (2.5ml). The mixture was then stirred at room temperature for 65h.

The mixture was treated with water (5.0ml) then extracted three times with dichloromethane (3 x 5.0ml) to afford impure unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a brown gum (0.25g; 100%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Benzylamine at Room Temperature.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in benzylamine (0.21g; 0.002mol) was heated at 150-160^{o} (oil bath) for 4h.

The mixture was allowed to cool to room temperature giving a brown viscous oil (0.46g) which was flash chromatographed over 2% triethylamine doped silica.

Elution with hexane-ether (80:20) through to methanol afforded only unidentifiable yellow oils (0.28g) which were not further investigated.

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Hydrazine.

(a) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in ethanol (10.0ml) was treated with 100% hydrazine hydrate (0.13g; 0.004mol) and the mixture was then heated under reflux for 0.5h.

Rotary evaporation of the cooled solution gave a yellow residue which was treated with water (10.0ml) then extracted three times with dichloromethane (3 x 10.0ml) to afford unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a yellow solid (0.48g; 100%), m.p. 83-86°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but using a tenfold excess of 100% hydrazine hydrate under reflux in dioxane for 1h afforded 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a yellow solid (0.48g; 100%), m.p. 82-86°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The Attempted Lewis Acid Catalysed Reactions of Dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) and Dibenz[b,f][1,4]oxazepine-11(10H)-one (69) with N-Methylpiperazine in Anisole at 120°.

(a) A stirred suspension of dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) (0.24g; 0.001mol) in N-methylpiperazine (1.0ml) was treated in one portion with a solution of titanium tetrachloride (0.12ml; 0.0011mol) in anhydrous anisole (0.5ml) then heated at 120° for 2h.

The cooled mixture was treated with water (5.0ml) then extracted three times with dichloromethane (3 x 5.0ml) to afford a brown semi-solid (0.51g) which was triturated with hexane-ether to remove the N-methylpiperazine, leaving unreacted dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a light brown solid (0.21g; 90%) m.p. 184-190°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but with dibenz[b,f][1,4]ozaxepin-11(10H)-one (69) afforded the unreacted starting material a a light brown solid (0.19g; 90%), m.p. 207-211° (lit.[64], 213-215°).

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Tetraethylammonium Cyanide in Acetonitrile at Room Temperature.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.46g; 0.002mol) in anhydrous acetonitrile (10.0ml) was treated at room temperature in several portions with a solution of tetraethylammonium cyanide (0.62g; 0.004mol) in

anhydrous acetonitrile (5.0ml) and the mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 24h.

Rotary evaporation of the mixture afforded a red solid which was treated with 2M aqueous hydrochloric acid (5.0ml) then extracted three times with dichloromethane (3 x 5.0ml) to afford 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a yellow solid (0.47g;100%), m.p. 82-87°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Dibenz[b,f][1,4]oxazepin-11(10H)-one (69)

(a) A solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in ethanol (5.0ml) was treated with 2M aqueous hydrochloric acid (1.3ml) then heated under reflux for 1h.

Rotary evaporation of the cooled solution afforded a cream residue which was treated with water (5.0ml) and extracted three times with dichloromethane (3 x 5.0ml) to afford dibenz[b,f][1,4]oxazepin-11(10H)-one (69) as a pale yellow solid (0.20g; 95%), m.p. 209-213° (lit.[64], 213-215°).

(b) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in 70% aqueous acetic acid (5.0ml) was heated under reflux for 1h.

Rotary evaporation of the cooled solution afforded dibenz[b,f][1,4]oxazepin-11(10H)-one (69) as a light brown solid (0.21g; 100%), m.p. 203-209° (lit.[64], 213-215°).

(c) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in glacial acetic acid (5.0ml) was treated at room temperature with an aqueous solution of 30% w/v hydrogen peroxide (2.5ml) and the mixture then heated at 50° (oil bath) for 24h.

The mixture was allowed to cool to room temperature, concentrated to one half of the original volume by rotary evaporation then diluted with water (2.5ml). The solution was basified by the addition of 10% w/v aqueous sodium hydrogen carbonate solution then extracted three times with dichloromethane (3 x 5.0ml) to afford dibenz[b,f][1,4]oxazepin-11(10H)-one (69) as a pale yellow solid (0.10g; 48%), m.p. 201-209° (lit.[64], 213-215°).

(d) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in chloroform (5.0ml) was treated dropwise at room temperature with a solution of 50-55% w/w meta-chloroperbenzoic acid (0.26g; 0.0015mol) in chloroform (5.0ml) and the mixture then heated at 50° (oil bath) for 17h.

The mixture was allowed to cool to room temperature, washed twice with 10% w/v aqueous sodium hydrogen carbonate solution (2 x 5.0ml) then rotary evaporated to give the dibenz[b,f][1,4]oxazepin-11(10H)-one (69) as a pale yellow solid (0.21g; 100%), m.p. 207-212° (lit.[64], 213-215°).

(e) A solution of dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) (0.45g; 0.002mol) in ethanol (10.0ml) was stirred and treated at room temperature with 5M aqueous sodium hydroxide solution (5.0ml) followed by a single portion of 30% w/v aqueous

hydrogen peroxide solution (2.5ml). The mixture was then stirred at room temperature for 1h, then at 50° (oil bath) for a further 3h.

The mixture was cooled and concentrated by rotary evaporation to remove the ethanol, keeping the temperature below 50°. The resulting suspension was acidified with concentrated hydrochloric acid then neutralised with solid sodium acetate. This gave a suspension of the dibenz[b,f][1,4]oxazepin-11(10H)-one (69) which was collected as a colourless solid (0.030g; 7%), m.p. 212-216°, (lit.[64], 213-215°).

Extraction of the aqueous filtrate with dichloromethane (3 x 15.0ml) afforded no identifiable material.

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) With Aqueous Ethanol.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in ethanol (5.0ml) was treated with water (1.3ml) then heated under reflux for 1h.

The cooled solution was rotary evaporated, the residue was treated with water (5.0ml) then extracted with dichloromethane (3 x 5.0ml) to afford impure unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a brown oil (0.20g; 83%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Attempted Oxidation of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) With Tetrabutylammonium Peroxymonosulphate in Dichloromethane at Room Temperature.

A solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in dichloromethane(5.0ml) was treated at room temperature with tetrabutylammonium

peroxymonosulphate (0.24g; 0.001mol) and stirred at room temperature for 2h. A second portion of tetrabutylammonium peroxymonosulphate (0.24g; 0.001mol) was then added and the mixture was stirred at room temperature for 1h, then under reflux for a further 3h.

The mixture was allowed to cool to room temperature, washed twice with 2M aqueous hydrochloric acid (10.0ml) then rotary evaporated to give unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a yellow solid (0.24g; 100%), m.p. 80-85°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The Attempted Oxidation of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) With Aqueous Sodium Hypochlorite in Dioxane at Room Temperature.

A solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in dioxane (10.0ml) was treated dropwise with an aqueous solution of sodium hypochlorite (14% available chlorine) (6.0ml) and the mixture then stirred at room temperature for 0.5h.

The mixture was concentrated by rotary evaporation to remove the dioxane, diluted with water (10.0ml) and extracted three times with dichloromethane (3 x 10.0ml) to give a yellow oil which on cooling gave unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.20g; 42%), as a cream solid, m.p. 79-83°, identical (melting point and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) with Hydrogen chloride in Ether at Room Temperature.

A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.24g; 0.001mol) in methanol (15.0ml) was treated with a 1.0M solution of hydrogen chloride in ether (10.0ml) and the mixture then stirred at room temperature for 30min.

The mixture was concentrated by rotary evaporation to remove the methanol then diluted with ether in an unsuccessful attempt to precipitate the hydrochloride salt. T.l.c. in hexane-ether over silica showed the resulting mixture to contain largely starting material. Basification with 2M aqueous sodium hydroxide solution, then extractionwith ether (3 x 5.0ml) afforded unreacted 11-methylthiodibenz[b,f][1,4]oxazepine (67) as a light brown solid (0.23g; 96%), m.p. 78-83°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Reactions of 11-Methylthiodibenz[b,f][1,4]oxazepine (67) With Bromine.

(a) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in anhydrous $CHCl_3$ (7.5ml) was treated dropwise with a solution of bromine (0.32g; 0.002mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture then stirred at room temperature for 15min.

The mixture was diluted with anhydrous ether (20.0ml) and filtered to remove a gummy yellow solid.. The ether filtrate was rotary evaporated to give a light brown solid (0.27g), m.p. 159-164°, whose t.l.c. in hexane-ether over silica showed it to be a mixture of the starting material (67) and dibenz[b,f][1,4]oxazepine-11(10H)-thione (69), which was not further investigated.

The gummy yellow solid was added to water (10.0ml) and the mixture warmed gently to give a colourless solid (0.17g), m.p. 141-145°, whose t.l.c. in hexane-ether over silica showed it to be a mixture of the starting material (67) and dibenz[b,f][1,4]oxazepine-11(10H)-thione (69), which was not further investigated.

Extraction of the aqueous mother liquor with dichloromethane (3 x 10.0ml) gave no further identifiable material.

(b) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in anhydrous $CHCl_3$ (7.5ml) was treated dropwise with a solution of bromine (0.32g; 0.002mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture stirred at room temperature for 2.5h. The mixture was then treated with a second portion of bromine (0.32g; 0.002mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture stirred at room temperature for 1.5h, followed by a further 2h under reflux.

The mixture was filtered to remove the hydrobromide salt of a mono-brominated derivative of 11-methylthiodibenz[b,f][1,4]oxazepine (72) (0.62g; 94%), which formed yellow microcrystals, m.p. 283-285° (from toluene);

Found: C, 41.9; H, 2.5; N, 3.5%; m/z (FAB ms), 322 and 320 (MH^+- HBr),

$C_{14}H_{11}Br_2NOS$ requires: C, 42.4; H, 2.4; N, 3.4%; M, 401.

The filtrate was rotary evaporated to give a brown gum (0.14g) which was not further investigated.

(c) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in anhydrous $CHCl_3$ (7.5ml) was treated dropwise with a solution of bromine (0.32g;

0.002mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture then stirred and heated under reflux for 4h.

The mixture was rotary evaporated to give a yellow semi-solid (1.2g) which was dissolved in anhydrous $CHCl_3$ (7.5ml), treated dropwise with a solution of bromine (0.32g; 0.002mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture was then stirred and heated under reflux for a further 5h.

The mixture was filtered to obtain the hydrobromide salt (72) as a yellow solid (0.65g), m.p. 293-298°, whose i.r. spectrum was identical to the material obtained in (b) before. The filtrate was rotary evaporated to give an intractable red-brown semi-solid (0.91g) which was not further investigated.

(d) A stirred solution of 11-methylthiodibenz[b,f][1,4]oxazepine (67) (0.48g; 0.002mol) in anhydrous $CHCl_3$ (7.5ml) was treated dropwise with a solution of bromine (0.64g; 0.004mol) in anhydrous $CHCl_3$ (2.5ml) and the mixture then stirred and heated under reflux for 4h. The mixture was then treated dropwise with a second portion of bromine (0.32g; 0.002mol) in anhydrous $CHCl_3$ (2.5ml) and heating under reflux continued for a further 1h.

The mixture was rotary evaporated to give a red-brown solid (1.1g), m.p. 143-150°, which was flash chromatographed over silica.

Elution with hexane-dichloromethane (95:5) through dichloromethane to methanol afforded only mixed fractions as dark brown oils (1.2g), which were not further investigated.

Reaction of the Hydrobromide Salt (72) with Aqueous Sodium Hydroxide at Room Temperature.

A solution of the hydrobromide salt (72) (0.35g; 0.001mol) in ethanol (7.5ml) was treated in a single portion with 2M aqueous sodium hydroxide solution(2.5ml). The resulting suspension was then stirred at room temperature for 30min.

The mixture was concentrated by rotary evaporation to remove the ethanol and the residue diluted with water (5.0ml). The mixture was filtered to remove the brominated methylthio compound (73) as a colourless solid (0.19g), m.p. 102-110°, which formed colourless microcrystals, m.p. 130-131° (from ethanol), δ_H 7.68-7.02 (7H, m, ArH), and 2.57 (3H, s, SCH_3);

Found: m/z (EI HRMS), 320.9636 and 318.9664 (M^+),

$C_{14}H_{10}BrNOS$ requires: M, 320.9647 and 318.9667.

Acidification of the filtrate with 2M aqueous hydrochloric acid and extraction with dichloromethane (3 x 5.0ml) gave no further identifiable material.

3 Nitro-2-aryloxypyridine Derivatives (76)

A vigorously stirred suspension of sodium hydride (1.3g; 0.055mol) in anhydrous dimethylformamide (25.0ml) was treated dropwise at 0-10° (ice bath) with a solution of the corresponding hydroxybenzene derivative (0.05mol) in anhydrous dimethylformamide (12.5ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture for 15min. A solution of 2-chloro-3-nitropyridine (74) (7.9g; 0.05mol) in anhydrous dimethylformamide (12.5ml) was added in one portion and the mixture was then stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (5.0ml) then rotary evaporated, and the residue worked up as described for the individual reactions below.

(i) The reaction with phenol (62) afforded a brown residue which was triturated with water (50.0ml) to give 3-nitro-2-phenoxypyridine (76a) as a dark brown solid (93%), m.p. 89-94° (lit.[77], 94°).

(ii) The reaction with 3-methoxyphenol (75) afforded a brown residue which was treated with water (50.0ml) and extracted with dichloromethane (3 x 150ml) to give a dark brown semi-solid (12.7g) which was crystallised from ethanol to give a dark brown solid (9.5g), m.p. 60-66°. This was flash chromatographed over silica.

Elution with ethyl acetate afforded 2-(3-methoxyphenoxy)-3-nitropyridine (76b) as a yellow solid (8.1g; 66%), m.p. 85-88 (lit.[41], 81-82°).

Further elution with methanol afforded a brown gum (1.2g) which was not further investigated.

Rotary evaporation of the ethanolic mother liquor afforded a mixed fraction as a dark brown oil (3.1g) which was not further investigated.

3-Amino-2-aryloxypyridine Derivatives (77)

A stirred solution of the corresponding 3-nitro-2-aryloxypyridine derivative (76) (0.02mol) in tetrahydrofuran (200ml) was treated with a solution of stannous chloride dihydrate (20.0g; 0.088mol) in 2M aqueous hydrochloric acid (200ml) and the mixture heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution then concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was extracted three times with ether (3 x 200ml) and the combined organic extracts rotary evaporated to afford the 3-amino-2-aryloxypyridine derivative.

(i) Reduction of 3-nitro-2-phenoxypyridine (76a) afforded 3-amino-2-phenoxypyridine (77a) as a pale brown solid (73%), m.p. 96-102° (lit.[77], 100-102°).

(ii) Reduction of 2-(3-methoxyphenoxy)-3-nitropyridine (76b) afforded a brown oil (4.4g) which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded 3-amino-2-(3-methoxyphenoxy)pyridine (77b) as a pale brown solid (95%), m.p. 71-76° (lit.[41], 74-76°).

3-Isothiocyanato-2-aryloxypyridine Derivatives (78)

A stirred solution of the corresponding 3-amino-2-aryloxypyridine derivative (77) (0.01mol) in glacial acetic acid (30.0ml) was treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (10.0ml) then dropwise at room temperature with a solution of thiophosgene (2.3g; 0.02mol) in glacial acetic acid (10.0ml).The mixture was then stirred at room temperature for 2h.

The mixture was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 80.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 40.0ml) then rotary evaporated to give the crude reaction product as a brown oil.

(i) The red-brown oil from 3-amino-2-phenoxypyridine (77a) was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a mixed fraction as a pale yellow oil (0.081g) which was not further investigated.

Further elution with hexane-ether (98:2) afforded 3-isothiocyanato-2-phenoxypyridine (78a) as a colourless solid (2.1g; 91%), m.p. 69-71° (from ethanol), ν_{max} 2019 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.99 (1H, dd J 5.0 and 1.7Hz, ArH), 7.50-7.38 (3H, m, ArH), 7.29-7.17 (3H, m, ArH) and 7.01-6.95 (1H, m, ArH);

Found: C, 62.6; H, 3.7; N, 12.3%; m/z (EI HRMS), 228.0352 (M^+),

$C_{12}H_8N_2OS$ requires: C, 63.2; H, 3.5; N, 12.3%; M, 228.0357.

Further elution with methanol afforded an intractable brown gum (0.11g) which was not further investigated.

(ii) The brown oil from 3-amino-2-(3-methoxyphenoxy)pyridine (77b) was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a yellow oil (0.18g) which was not further investigated.

Further elution with hexane-ether (98:2) afforded 3-isothiocyanato-2-(3-methoxyphenoxy)pyridine (78b) as a colourless solid (1.5g; 78%), m.p. 51-53° (from ethanol), ν_{max} 2045 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 8.00 (1H, dd J 5.0 and 2.8Hz, ArH), 7.47 (1H, dd J 7.8 and 1.8Hz, ArH), 7.37-7.25 (1H, m, ArH), 6.96 (1H, dd J 5.0 and 2.8Hz, ArH), 6.82 - 6.75 (3H, m, ArH) and 3.81 (3H, s, OCH_3);

Found: C, 60.3; H, 4.0; N, 10.8%; m/z (EI ms), 258 (M^+),

$C_{13}H_{10}N_2O_2S$ requires: C, 60.5; H, 3.9; N, 10.9%; M, 258.

Further elution with methanol afforded an intractable brown gum (0.11g) which was not further investigated.

Attemped Lewis Acid Catalysed Cyclisation Reactions of 3-Isothiocyanato-2-phenoxypyridine (78a)

(a) A suspension of aluminium trichloride (1.3g; 0.01mol) in anhydrous dichloromethane (20.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution 3-isothiocyanato-2-phenoxypyridine (78a) (1.2g; 0.005mol) in anhydrous dichloromethane (10.0ml) and the mixture then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (77.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to give unreacted 3-isothiocyanato-2-phenoxypyridine (78a) as a pale yellow solid (1.3g; 100%), m.p. 60-67°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but with heating under reflux for 4h, afforded unreacted 3-isothiocyanato-2-phenoxypyridine (78a) as a pale yellow solid (1.3g; 100%), m.p. 60-67°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(c) Repetition of the reaction described in (a) before, but using 1,2-dichloroethane as the solvent and with heating under reflux for 4h afforded unreacted 3-isothiocyanato-2-

phenoxypyridine (78a) as a pale yellow oil (1.3g; 100%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Attempted Lewis Acid Catalysed Cyclisation Reactions of 3-Isothiocyanato-2-(3-methoxyphenoxy)pyridine (78b)

(a) A stirred suspension of aluminium trichloride (1.0g; 0.008mol) in anhydrous dichloromethane (16.0ml) under nitrogen was treated dropwise at -10° (ice-acetone bath) with a solution of 3-isothiocyanato-2-(3-methoxyphenoxy)pyridine (78b) (1.0g; 0.004mol) in anhydrous dichloromethane (8.0ml) then heated under reflux for 17h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (62.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 40.0ml) to afford a yellow solid (0.93g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded 3-isothiocyanato-2-(3-methoxyphenoxy)pyridine (78b) as a cream solid (0.30g; 30%), m.p. 52-55°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (70:30) afforded 2-(3-hydroxyphenoxy)-3-isothiocyanatopyridine (82) as a colourless solid which formed colourless needles (0.35g; 36%), m.p. 166-169° (from hexane-ethanol), ν_{max} 3145 (OH) and 2078 (N=C=S) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.85 (1H, s, OH) (exch), 8.07 (1H, dd J 4.8 and 1.5Hz, ArH), 7.87 (1H, dd J 7.7 and 1.5Hz, ArH), 7.31-7.15 (2H, m, ArH) and 6.68-6.57 (3H, m, ArH);

Found: C, 58.4; H, 3.6; N, 11.5%; m/z (EI HRMS), 244.0314 (M^+),

$C_{12}H_8N_2O_2S$ requires: C, 59.0; H, 3.3; N, 11.5%; M, 244.0307.

Further elution with hexane-ether (25:75) afforded 9-hydroxy-6-methylthiopyrido[2,3-b][1,4]benzoxazepine (83) as a pale yellow solid (0.15g; 15%), m.p. 257-260° (from hexane-ethanol), δ_H 10.60 (1H, s, OH) (exch), 8.06-7.86 (1H, m, ArH), 7.68-7.07 (3H, m, ArH), 6.70-6.64 (2H, m, ArH) and 2.51(3H, s, SCH_3);

Found: C, 60.5; H, 4.1; N, 10.4%; m/z (EI HRMS), 258.0467 (M^+),

$C_{13}H_{10}N_2O_2S$ requires: C, 60.5; H, 3.9; N, 10.9%; M, 258.0463.

Further elution with methanol afforded an intractable brown gum (0.031g) which was not further investigated.

(b) Repetition of the reaction described in (a) before, but using 1,2-dichloroethane as the solvent and with heating under reflux for 4h afforded a yellow solid (0.15g), m.p. 195-202°, which was shown (t.l.c. in hexane-ether over silica) to be a complex mixture, and was not further investigated.

The aqueous mother liquor was adjusted to pH 1 by the addition of 2M aqueous hydrochloric acid, then extracted three times with dichloromethane (3 x 40.0ml) to afford a yellow solid (0.23g), m.p. 217-223°, which was shown (t.l.c. in hexane-ether over silica) to be a complex mixture, and was not further investigated.

3-(2-Nitrophenoxy)-pyridine (85)

A vigorously stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was treated in several portions at 0-10° (ice bath) with a solution of 3-hydroxypyridine (84) (9.5g; 0.1mol) in anhydrous dimethylformamide

(25.0ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15min. A solution of 2-fluoronitrobenzene (61) (14.1g; 0.1mol) in anhydrous dimethylformamide (25.0ml) was then added in one portion and the mixture was stirred 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (12.5ml) and rotary evaporated to give a brown residue which was treated with water (12.5ml) and extracted three times with dichloromethane (3 x 20.0ml). Rotary evaporation of the combined dichloromethane extracts gave a dark brown oil (18.3g) which was distilled, affording 3-(2-nitrophenoxy)pyridine (85) as a brown oil (13.4g; 62%), b.p. 130°/0.1mmHg (lit.[80], 148-152°/0.42mmHg)

3-(2-Aminophenoxy)pyridine (86)

A solution of 3-(2-nitrophenoxy)pyridine (85) (13.0g; 0.06mol) in ethyl acetate (75.0ml) was hydrogenated over 10% palladium on charcoal (0.13g) at room temperature and atmospheric pressure for 27h during which time 4103ml of hydrogen had been absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give a red-brown oil (11.1g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (90:10) through (85:15) afforded only small amounts of mixed fractions as oils (0.74g) which were not further investigated.

Further elution with hexane-ethyl acetate (85:15) afforded the known[80] 3-(2-aminophenoxy)pyridine (86) as a red oil (5.3g; 50%) which was used without further purification.

Further elution with methanol afforded a dark brown intractable oil (4.6g) which was not further investigated.

3-(2-Isothiocyanatophenoxy)pyridine (87)

A stirred solution of 3-(2-aminophenoxy)pyridine (86) (0.93g; 0.005mol) in glacial acetic acid (7.5ml) was treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (2.5ml) then dropwise at room temperature with a solution of thiophosgene (1.2g; 0.01mol) in glacial acetic acid (2.5ml). The mixture was then stirred at room temperature for 2h.

The mixture was treated with water (10.0ml) and extracted three times with dichloromethane (3 x 20.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0ml) then rotary evaporated to give a brown oil (2.0g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a yellow oil (0.034g) which was not further investigated.

Further elution with hexane-ether (3:1) afforded 3-(2-isothiocyanatophenoxy)pyridine (87) as a yellow oil (0.72g; 63%), b.p. 105°/0.2mmHg, ν_{max} 2051 and 2030 (N=C=S)cm^{-1}, δ_H [$(CD_3)_2SO$] 8.43-8.35 (2H, m, ArH), 7.31-7.22 (5H, m, ArH) and 7.19-6.89 (1H, m, ArH);

Found: C, 63.2; H, 4.1; N, 12.6%; m/z (EI HRMS), 228.0355 (M^+),

$C_{12}H_8N_2OS$ requires: C, 63.2; H, 3.5; N, 12.3%; M, 228.0357.

Further elution with methanol afforded an intractable brown gum (0.28g) which was not further investigated.

The Attempted Aluminium Trichloride Catalysed Cyclisation of 3-(2-Isothiocyanatophenoxy)pyridine (87) in Dichloromethane at Room Temperature.

A suspension of aluminium trichloride (0.27g; 0.002mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of 3-(2-isothiocyanatophenoxy)pyridine (87) (0.23g; 0.001mol) in anhydrous dichloromethane (5.0ml) and the mixture then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (40.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford a yellow solid (0.14g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of starting material and baseline material, and was not further investigated.

2-(N,N-Dimethylamino)-5-nitropyrimid-4(3H)-one (93)

2-(N,N-Dimethylamino)-5-nitropyrimid-4(3H)-one (93) was prepared (yield 68%) as described by Overberger and Kogon,[81] and had m.p. 298-304° with decomp. (lit.[81], 303-305° with decomp.).

2-(N,N-Dimethylamino)-4-chloro-5-nitropyrimidine (94)

2-(N,N-Dimethylamino)-4-chloro-5-nitropyrimidine (94) was prepared (yield 83%) by the reaction 2-(N,N-dimethylamino)-5-nitropyrimid-4(3H)-one (93) with phosphoryl chloride in the presence of N,N-dimethylamine as described by Saunders,[82] and had m.p. 142-147° (lit.[82], 143-145°).

2-(N,N-Dimethylamino)-5-nitro-4-phenoxypyrimidine (95)

(a) A vigorously stirred suspension of sodium hydride (0.26g; 0.011mol) in anhydrous 1,2-dimethoxyethane (2.0ml) was treated dropwise at 0-10° (ice bath) with a solution of phenol (62) (0.94g; 0.01mol) in anhydrous 1,2-dimethoxyethane (4.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 2-(N,N-dimethylamino)-4-chloro-5-nitropyrimidine (94) (2.0g; 0.01mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was added in one portion and the mixture stirred and heated under reflux, with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (5.0ml) and rotary evaporated to give a gummy brown residue which was triturated with water to give 2-(N,N-dimethylamino)-5-nitro-4-phenoxypyrimidine (95) as a light brown solid (1.1g; 42%), which formed pale yellow needles, m.p. 130-136° (from ethanol), ν_{max} 1545 and 1327 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 9.06 (1H, s, ArH), 7.49-7.07 (5H, m, ArH), 3.21 (3H, s, NCH_3), and 2.86 (3H, s, NCH_3);

Found: C, 55.0; H, 4.8; N, 21.4%; m/z (EI ms), 260 (M^+),

$C_{12}H_{12}N_4O_3$ requires: C, 55.3; H, 4.6; N, 21.5%; M, 260.

The aqueous fraction was adjusted to pH 1 by the addition of concentrated hydrochloric acid and extracted three times with dichloromethane (3 x 30.0ml). Rotary evaporation of the combined dichloromethane fractions afforded a yellow oil (0.41g) which was not further investigated.

(b) A vigorously stirred suspension of sodium hydride (0.26g; 0.011mol) in anhydrous dimethylformamide (2.0ml) was treated dropwise at 0-10° (ice bath) with a solution of phenol (62) (0.94g; 0.01mol) in anhydrous dimethylformamide (4.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 2-(N,N-dimethylamino)-4-chloro-5-nitropyrimidine (94) (2.0g; 0.01mol) in anhydrous dimethylformamide (8.0ml) was added in one portion and the mixture was stirred and heated at 100°, with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (4.0ml) and rotary evaporated to give a red-brown solid which was treated with water (50.0ml) and extracted three times with dichloromethane (3 x 50.0ml) to give an orange semi-solid (3.0g) which was triturated with hexane-ether to give 2-(N,N-dimethylamino)-5-nitro-4-phenoxypyrimidine (95) as a yellow solid (1.4g; 54%),m.p. 127-132°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The aqueous fraction was adjusted to pH 1 by the addition of concentrated hydrochloric acid and extracted three times with dichloromethane (3 x 30.0ml). Rotary evaporation of the combined dichloromethane fractions afforded a yellow oil (0.41g) which was not further investigated.

The hexane-ether fraction was rotary evaporated to give a dark red oil (0.61g) which was not further investigated.

The aqueous mother liquor was acidified with 2M aqueous sulphuric acid, neutralised with sodium acetate then extracted twice with dichloromethane (2 x 15.0ml) to give no further identifiable material.

5-Amino-2-(N,N-dimethylamino)-4-phenoxypyrimidine (96)

A stirred solution of 2-(N,N-dimethylamino)-5-nitro-4-phenoxypyrimidine (95) (0.52g; 0.002mol) in tetrahydrofuran (20.0ml) was treated with a solution of stannous chloride dihydrate (2.0g; 0.0088mol) in 2M aqueous hydrochloric acid (20.0ml) and the mixture was heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was then extracted three times with ether (3 x 20.0ml) and the combined organic extracts rotary evaporated to give 5-amino-2-(N,N-dimethylamino)-4-phenoxypyrimidine (96) as a purple solid (0.46g; 100%), which formed colourless crystals, m.p. 82° (from hexane), ν_{max} 3382 and 3295 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 7.87 (1H, s, ArH), 7.31-7.14 (5H, m, ArH), 3.30 (2H, bs, NH_2) (exch), and 2.94 (6H, s, $N(CH_3)_2$);

Found: C, 62.7; H, 6.4; N, 24.5%; m/z (EI ms), 230 (M^+),

$C_{12}H_{14}N_4O$ requires: C, 62.6; H, 6.1; N, 24.3%; M, 230.

2-(N,N-Dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97)

A stirred solution of 5-amino-2-(N,N-dimethylamino)-4-phenoxypyrimidine (96) (0.92g; 0.004mol) in glacial acetic acid (15.0ml) was treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (5.0ml) then dropwise at room temperature with a solution of thiophosgene (0.96g; 0.008mol) in glacial acetic acid (5.0ml). and the mixture was then stirred at room temperature for 4h.

The mixture was treated with water (20.0ml) and extracted three times with dichloromethane (3 x 20.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml) then rotary evaporated to give 2-(N,N-dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97) as a light brown solid (1.0g; 92%), which formed colourless needles, m.p. 103-105° (from hexane), ν_{max} 2133 (N=C=S)cm^{-1}, δ_H ($CDCl_3$) 8.07 (1H, s, ArH), 7.43-6.98 (5H, m, ArH), and 2.97 (6H, s, $N(CH_3)_2$);

Found: C, 57.0; H, 4.5; N, 20.4%; m/z (EI ms), 272 (M^+),

$C_{13}H_{12}N_4OS$ requires: C, 57.3; H, 4.4; N, 20.6%; M, 272.

Attempted Aluminium Trichloride Catalysed Cyclisations of 2-(N,N-Dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97)

(a) A stirred suspension of aluminium trichloride (0.53g; 0.004mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of 2-(N,N-dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97) (0.54g; 0.002mol) in anhydrous dichloromethane (5.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford unreacted 2-(N,N-dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97) as a light brown solid (0.53g; 100%), m.p. 94-101°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) A stirred suspension of aluminium trichloride (0.53g; 0.004mol) in anhydrous 1,2-dichloroethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of 2-(N,N-dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97) (0.54g; 0.002mol) in anhydrous 1,2-dichloroethane (5.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford 2-(N,N-dimethylamino)-5-isothiocyanato-4-phenoxypyrimidine (97) as a light brown solid (0.53g; 100%), m.p. 93-101°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

2-Bromo-2′-nitrodiphenyl Ether (100a)

2-Bromo-2′-nitrodiphenyl ether (100a) was prepared (yield 94%) by the sodium hydride catalysed reaction of 2-bromophenol (99a) with 2-fluoronitrobenzene (61) as described by Currie and Tennant,[83] and had m.p. 39-43° (lit.[83], 45-46°).

2-Amino-2′-bromodiphenyl Ether (101a)

(a) A solution of 2-bromo-2′-nitrodiphenyl ether (101a) (5.9g; 0.02mol) in tetrahydrofuran (200ml) under nitrogen was stirred and treated with concentrated hydrochloric acid (10.0ml) followed by 15% w/v aqueous titanium trichloride solution (186ml; 0.18mol) added in three portions. The mixture was then stirred under nitrogen at room temperature for 4h.

The mixture was rotary evaporated to give a purple oily liquid which was stirred and cooled in an ice bath then basified by the dropwise addition of 50% w/v aqueous sodium hydroxide solution (400ml). The mixture was then diluted with water (20.0ml) and extracted three times with dichloromethane (3 x 200ml) to give 2-amino-2′-bromodiphenyl ether (101a) as a pale yellow oil (2.0g; 38%), ν_{max} 3469 and 3376 (NH_2) cm^{-1}.[83]

The aqueous mother liquor was stirred in air for three hours, by which time the original purple colour had disappeared. Inorganic residues were removed by filtration, and the filtrate was extracted three times with dichloromethane (3 x 100ml) to give further 2-amino-2′-bromodiphenyl ether (101a) as a red oil (0.31g; 6%) which was identified by comparison (i.r. spectrum) with an authentic sample prepared previously.

(b) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (5.9g; 0.02mol) in tetrahydrofuran (200ml) was stirred under nitrogen and treated with 15% w/v aqueous titanium trichloride solution (62.0ml; 0.06mol) added in several portions. The mixture was then stirred at room temperature for 19h.

The mixture was rotary evaporated to give a purple oily liquid which was stirred and cooled in an ice bath, then basified by the dropwise addition of 50% w/v aqueous sodium hydroxide solution. The mixture was then diluted with water (20.0ml) and extracted three times with dichloromethane (3 x 200ml) to give a pale yellow oil (5.0g).

The aqueous mother liquor was stirred in air for 2h, by which time the original purple colour had disappeared. Inorganic residues were removed by filtration and the filtrate then extracted three times with dichloromethane (3 x 100ml) to give a red oil (0.2g).

Both oils were combined and dissolved in dichloromethane (50.0ml) and the solution was washed twice with 2M aqueous hydrochloric acid (2 x 10.0ml). The dichloromethane extract was rotary evaporated to give unreacted 2-bromo-2′-nitrodiphenyl ether (100a) as a light brown oil (5.0g; 95%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The combined aqueous acid fractions were basified with 2M aqueous sodium hydroxide solution then extracted three times with dichloromethane (3 x 75.0ml) to give the amine (101a) as a light brown oil (0.20g; 4%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(c) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (11.8g; 0.04mol) in tetrahydrofuran (400ml) under nitrogen was stirred and treated with several portions of 15% w/v aqueous titanium trichloride solution (460ml; 0.4mol). The mixture was then stirred at room temperature for 5h.

The mixture was rotary evaporated to give a purple oily liquid which was stirred and cooled in an ice bath then basified by the dropwise addition of 50% w/v aqueous

sodium hydroxide (150ml). The mixture was diluted with water (40.0ml) and extracted three times with dichloromethane (3 x 400ml) to give the amine (101a) as a pale yellow oil (7.5g; 71%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The aqueous mother liquor was stirred in air for 2h, by which time the original purple colour had disappeared. Inorganic residues were removed by filtration and the filtrate then extracted three times with dichloromethane (3 x 100ml) to give a pale yellow oil (0.10g) which was not further investigated.

(d) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (2.6g; 0.01mol) in glacial acetic acid (40.0ml) was hydrogenated over Raney nickel catalyst (0.5ml of a 50% slurry in water) at room temperature and atmospheric pressure. After 2h only 25% of the hydrogen required for complete conversion of the starting material had been absorbed and the uptake of hydrogen had virtually ceased. A second portion of Raney nickel catalyst (0.5ml of a 50% slurry in water) was therefore added and the hydrogenation continued for a further 8h. until the required amount of hydrogen had been absorbed.

The catalyst was removed by filtration through a celite pad, and the filtrate was rotary evaporated to give a red oil (1.8g) whose i.r. spectrum and t.l.c. in hexane-ether over silica showed it to be a mixture of the 2-bromo-2′-nitrodiphenyl ether (100a) and the desired 2-amino-2′-bromodiphenyl ether product (101a) which was not further investigated

(e) A stirred mixture of 2-bromo-2′-nitrodiphenyl ether (100a) (2.9g; 0.01mol) and cobalt dichloride hexahydrate (4.8g; 0.02mol) in methanol (60.0ml) was treated in several portions at room temperature with sodium borohydride (3.8g; 0.1mol) then stirred at 40° (water bath) for 1h. The mixture was then treated with 3M aqueous hydrochloric acid (20.0ml) and heated under reflux for 1h.

The resulting suspension was rotary evaporated to give a brown residue which was basified with concentrated aqueous ammonia solution. The mixture was then treated with ether (50.0ml) and the insoluble inorganic material removed by filtration. The two phase filtrate was separated and the aqueous phase extracted a further three times with ether (3 x 20.0ml). The combined ether fractions were rotary evaporated to give 2-amino-2′-bromodiphenyl ether (101a) as a brown solid (2.2g; 83%), m.p. 49-54° (lit.[83], 55-56°) identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(f) Repetition of the reaction described in (e) before, on a 0.08mol scale afforded a complex black oil (19.2g), possibly containing the desired product, which was not further investigated.

(g) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (1.5g; 0.005mol) in 1,4-dioxane (12.5ml) was treated with 2% w/v aqueous sodium hydroxide solution (5.0ml) then with 10% palladium-on-charcoal (0.02g). The mixture was stirred and treated dropwise with a solution of sodium borohydride (0.38g; 0.01mol) in water (2.5ml) then stirred at room temperature for 20h.

The catalyst was removed by filtration through celite and the filtrate was rotary evaporated to give a red gum (1.1g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded 2-bromo-2′-nitrodiphenyl ether (100a) as a red oil (0.10g; 7%) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (98:2) then methanol afforded 2-amino-2′-bromodiphenyl ether (101a) as a red oil (0.98g; 69%) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(h) A suspension of 10% palladium-on-charcoal (0.025g) in water (5.0ml) was stirred and treated with a solution of sodium borohydride (0.35g; 0.01mol) in water (7.5ml). The mixture was then treated dropwise with a solution of 2-bromo-2′-nitrodiphenyl ether (100a) (1.5g; 0.005mol) in methanol (25.0ml) and the mixture stirred at room temperature for 10 min.

The catalyst was removed by filtration through celite and the filtrate concentrated by rotary evaporation to remove the methanol. The basic aqueous residue was diluted with water (12.5ml), and extracted three times with dichloromethane (3 x 25.0ml) to give 2-amino-2′-bromodiphenyl ether (101a) as a brown oil (0.96g; 66%) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(i) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (1.5g; 0.005mol) in ethanol (40.0ml) was treated with stannous chloride dihydrate (4.8g; 0.25mol) and the mixture was stirred under nitrogen and heated at 70° (oil bath) for 30min.

The mixture was poured onto ice (10.0g) and the resulting suspension was adjusted to pH 8 by the addition of 10% w/v aqueous sodium hydrogen carbonate solution. The insoluble inorganic material was removed by filtration and the filtrate was extracted with three times dichloromethane (3 x 30.0ml) to give a brown oil (0.14g) whose t.l.c. in hexane-ether over silica showed it to be a multicomponent mixture which was not further investigated.

The aqueous mother liquor was adjusted to pH 14 by the addition of 50% w/v aqueous sodium hydroxide solution and extracted three times with dichloromethane (3 x 50.0ml) to give a light brown oil (1.6g) whose t.l.c. in hexane-ether over silica showed it to be a multicomponent mixture which was not further investigated.

(j) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (5.9g; 0.02mol) in tetrahydrofuran (200ml) was treated with a solution of stannous chloride dihydrate (20.0g; 0.089mol) in 2M aqueous hydrochloric acid (200ml) and the mixture was stirred at room temperature for 18h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution and the mixture was concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 100ml) give 2-amino-2′-bromodiphenyl ether (101a) as a pale brown solid (4.6g; 87%), m.p. 51-56°, (lit.[83], 55-56°) identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(k) A solution of 2-bromo-2′-nitrodiphenyl ether (100a) (32.3g; 0.11mol) in tetrahydrofuran (550ml) was treated with a solution of stannous chloride dihydrate

(110g; 0.49mol) in 2M aqueous hydrochloric acid (550ml) and the mixture was stirred and heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 550ml) to give 2-amino-2′-bromodiphenyl ether (101a) as a light brown solid (27.3g; 94%), m.p. 54-57° (lit.[83], 55-56°), identical (melting point and i.r. spectrum) to an authentic sample prepared before.

2-Bromo-2′-isothiocyanatodiphenyl Ether. (102a)

A solution of 2-amino-2′-bromodiphenyl ether (101a) (5.3g; 0.02mol) in glacial acetic acid (50.0ml) was stirred and treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (15.0ml) then dropwise at room temperature with a solution of thiophosgene (4.6g; 0.04mol) in glacial acetic acid (10.0ml) and the mixture was then stirred at room temperature for 2h.

The mixture was treated with water (80.0ml) and extracted three times with dichloromethane (3 x 160ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 80.0ml) then rotary evaporated to give 2-bromo-2′-isothiocyanatodiphenyl ether (102a) as a red oil (6.1g; 100%), ν_{max} 2103 and 2029 (N=C=S) cm^{-1};

Found: m/z (EI HRMS), 304.9531 and 306.9507 (M^+),

$C_{13}H_8BrNOS$ requires: M, 304.9511 and 306.9491.

4-Bromodibenz[b,f][1,4]oxazepine-11(10H)-thione (103a)

A stirred solution of 2-bromo-2'-isothiocyanatodiphenyl ether (102a) (3.1g; 0.01mol) in anhydrous dichloromethane (50.0ml) under nitrogen was treated dropwise at -10° (ice-acetone bath) with a solution of aluminium tribromide (5.5g; 0.02mol) in anhydrous dichloromethane (50.0ml) then stirred and heated under reflux for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (170ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to afford an orange solid (2.9g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded a mixed fraction as a red oil (0.51g) which was not further investigated.

Further elution with hexane-ether (50:50) afforded 4-bromodibenz[b,f][1,4]oxazepine-11(10H)-thione (103a) as a yellow solid (1.7g; 56%), m.p. 212-214° (from methanol-dimethylformamide), ν_{max} 3150 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.81 (1H, s, NH) (exch) and 7.99-7.01 (7H, m, ArH);

Found: C, 50.9; H, 2.9; N, 4.4%; m/z (EI ms), 307 and 305 (M^+),

$C_{13}H_8BrNOS$ requires: C, 51.0; H, 2.6; N, 4.6%; M, 307 and 305.

Further elution with methanol gave an intractable black gum (0.21g) which was not further investigated.

4-Bromo-11-methylthiodibenz[b,f][1,4]oxazepine (105)

A vigorously stirred suspension of sodium hydride (0.11g; 0.0044mol) in anhydrous dimethylformamide (5.0ml) was treated in one portion at room temperature with a solution of 4-bromodibenz[b,f][1,4]oxazepine-11(10H)-thione (103a) (1.2g;

0.004mol) in anhydrous dimethylformamide (10.0ml) and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15min. A solution of methyl iodide (0.56g; 0.004mol) in anhydrous dimethylformamide (5.0ml) was added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with water (5.0ml) and stirred at room temperature for 10min. Rotary evaporation gave a red oily residue which was treated with water (20.0ml) and extracted three times with dichloromethane (3 x 20.0ml) to give an orange semi-solid (1.2g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded 4-bromo-11-methylthiodibenz-[b,f][1,4]oxazepine (105) as a yellow solid (0.75g; 59%), m.p. 192-195° (from AcOH), δ_H 7.92 (1H, dd J 8.0 and 1.4Hz, ArH), 7.69 (1H, dd J 7.8 and 1.4Hz, ArH), 7.38 (1H, dt J 3.5, 3.5 and 2.4Hz, ArH), 7.32-7.22 (4H, m, ArH) and 2.58 (3H, s, SCH_3);

Found: C, 52.2; H, 3.2; N, 4.3%; m/z (EI ms), 321 and 319 (M^+)

240 (M^+ - Br) and 193 (M^+ - SCH_3 - Br),

$C_{14}H_{10}BrNOS$ requires: C, 52.5; H, 3.1; N, 4.1%; M, 320.

Further elution with ether through methanol afforded only a complex oils and gums (0.49g) which were not further investigated.

The Attempted Reaction of 2-Bromo-2′-isothiocyanatodiphenyl Ether (102a) With Magnesium in Refluxing Ether.

(a) A stirred solution of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) (0.61g; 0.002mol) in anhydrous ether (20.0ml) was treated with magnesium turnings

(0.048g; 0.002mol) and a single crystal of iodine. The mixture was stirred at room temperature for 2h, then stirred and heated under reflux for a further 24h.

The mixture was allowed to cool to room temperature, treated with a single portion of saturated aqueous ammonium chloride solution (5.0ml) then stirred for 15min at room temperature. The mixture was extracted twice with ether (2 x 5.0ml) to give 2-bromo-2′-isothiocyanatodiphenylether (102a) as a brown oil (0.61g; 100%) identical (i.r. spectrum) to an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but with sonocation afforded 2-bromo-2′-isothiocyanatodiphenyl ether (102a) as a brown oil (0.61g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

Dibenz[b,f][1,4]oxazepin-11(10H)-thione (66)

(a) A stirred solution of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) (0.15g; 0.0005mol) in anhydrous tetrahydrofuran (5.0ml) was treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.6M solution of n-butyllithium in hexane (0.31ml; 0.0005mol). The mixture was stirred at -78° (dry ice-acetone bath) for 2h, allowed to warm to room temperature, then stirred for a further 2h. at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (5.0ml) then extracted three times with ether (3 x 5.0ml) to give a yellow semi-solid (0.16g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.012g) which t.l.c. in hexane-ether over silica showed it to contain 2-bromo-2′-isothiocyanatodiphenyl ether (102a).

Further elution with hexane-ether (90:10) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.10g; 66%), m.p. 191-196°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable brown gum (0.041g) which was not further investigated.

(b) The reaction was carried out as described in (a) before, but using a 1.3M solution of s-butyllithium in cyclohexane.

The mixture was treated with a saturated aqueous solution of ammonium chloride (5.0ml) then extracted three times with ether (3 x 5.0ml) to give a yellow gum (0.29g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.023g) which t.l.c. in hexane-ether over silica showed it to contain 2-bromo-2′-isothiocyanatodiphenyl ether (102a).

Further elution with hexane-ether (90:10) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (48%), m.p. 173-181, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable yellow gum (0.14g) which was not further investigated.

(c) The reaction was carried out as described in (a) before, but using a 1.7M solution of t-butyllithium in pentane.

The mixture was treated with a saturated aqueous solution of ammonium chloride (5.0ml) then extracted three times with ether (3 x 5.0ml) to give a brown oil (0.14g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.030g) whose t.l.c. in hexane-ether over silica showed it to contain 2-bromo-2′-isothiocyanatodiphenyl ether (102a).

Further elution with hexane-ether (90:10) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.080g; 53%), m.p. 189-195°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable brown gum (0.030g) which was not further investigated.

(d) The reaction was carried out as described in (a) before, but using 2.2 equivalents of a 1.3M solution of s-butyllithium in cyclohexane.

The mixture was treated with a saturated aqueous solution of ammonium chloride (5.0ml) then extracted three times with ether (3 x 5.0ml) to give a yellow gum (0.18g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.009g) whose t.l.c. in hexane-ether over silica showed it to contain 2-bromo-2′-isothiocyanatodiphenyl ether (102a).

Further elution with hexane-ether (90:10) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.12g; 80%), m.p. 191-196°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable yellow gum (0.039g) which was not further investigated.

(e) The reaction was carried out as described in (a) before, but using 4.4 equivalents of a 1.7M solution of t-butyllithium in pentane.

The mixture was treated with a saturated aqueous solution of ammonium chloride (5.0ml) then extracted three times with ether (3 x 5.0ml) to give a brown oil (0.13g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a yellow oil (0.021g) whose t.l.c. in hexane-ether over silica showed it to contain 2-bromo-2′-isothiocyanatodiphenyl ether starting material (102a).

Further elution with hexane-ether (90:10) afforded dibenz[b,f][1,4]oxazepine-11(10H)-thione (66) as a yellow solid (0.043g; 45%), m.p. 189-194°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable brown gum (0.060g) which was not further investigated.

The Sodium Hydride Catalysed Reaction of 2-Chloro-3-nitropyridine (74) with Phenol Derivatives (99) in Dimethylformamide at 100°.

A vigorously stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (10.0ml) was treated dropwise at 0-10° (ice bath) with a solution of the phenol derivative (99) (0.1mol) in anhydrous dimethylformamide (20.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture for 15min. A solution of 2-chloro-3-nitropyridine (74) (15.8g; 0.1mol) in anhydrous dimethylformamide (20.0ml) was added in one portion and the mixture stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (20.0ml), rotary evaporated and the residue treated with water (80.0ml) to give the product.

(i) 2-Bromophenol (99a) afforded the known[41] 2-(2-bromophenoxy)-3-nitropyridine (106a) as a light brown solid (34.1g; 99%), m.p. 68-70° (lit.[41], 72-73°).

(ii) 2-Iodophenol (99b) afforded the known[41] 2-(2-iodophenoxy)-3-nitropyridine (106b) as a light brown solid (29.5g; 100%), m.p. 99-104° (lit.[41], 104-105°).

The aqueous filtrate was extracted three times with dichloromethane (3 x 75.0ml) to afford a mixed fraction as a yellow oil (3.6g) which was not further investigated. The aqueous fraction was adjusted to pH 1 by the addition of 2M aqueous hydrochloric acid then extracted three times with dichloromethane (3 x 75.0ml) to afford a red oil (0.26g) which was not further investigated

Reduction of 3-Aryloxy-2-nitropyridine Derivatives (106) Using Stannous Chloride in Tetrahydrofuran in the presence of Aqueous Hydrochloric Acid.

(a) A solution of the 2-aryloxy-3-nitropyridine (106) (0.1mol) in tetrahydrofuran (1000ml) was treated with a solution of stannous chloride dihydrate (100g; 0.44mol) in 2M aqueous hydrochloric acid (1000ml) and the mixture was stirred at room temperature for 18h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution then concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 500ml) to afford the amine product.

(i) Reduction of 2-(2-bromophenoxy)-3-nitropyridine (106a) gave a brown solid (22.6g) which was recrystallised from hexane-benzene, to afford the known[41] 3-amino-2-(2-bromophenoxy)pyridine (107a) as a brown solid (58%), m.p. 97-100° (lit.[41], 97-100°).

Rotary evaporation of the hexane-benzene mother liquor afforded a dark brown semi-solid (5.4g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (3:1) afforded a yellow semi-solid (2.0g) which was triturated with ether to give 3-amino-2-(2-bromophenoxy)pyridine (107a) as a colourless solid (1%), m.p. 98-103°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Further elution with methanol afforded a dark brown semi-solid (2.4g) which was triturated with ether to give a second crop of 3-amino-2-(2-bromophenoxy)pyridine

(107a) as a brown solid (3%), m.p. 99-103°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(ii) Reduction of 2-(2-iodophenoxy)-3-nitropyridine (106b) gave a dark brown solid (25.0g) which was crystallised from benzene, giving the known[41] 3-amino-2-(2-iodophenoxy)-pyridine (107b) as a grey solid (56%), m.p. 95-100° (lit.[41], 97-100°).

Rotary evaporation of the hexane-benzene mother liquor afforded a dark brown semi-solid (9.9g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (85:15) afforded a second crop of 3-amino-2-(2-iodophenoxy)pyridine (107b) as a colourless solid (29%), m.p. 98-103°, identical (i.r. spectrum) to the first crop.

Further elution with methanol afforded a dark brown gummy solid (0.7g) which was not further investigated.

(b) The reaction described in (a) before was repeated but using half of the volumes of tetrahydrofuran and 2M aqueous hydrochloric acid.

(i) Reduction of 2-(2-bromophenoxy)-3-nitropyridine (106a) gave a dark brown solid (0.51g) which was recrystallised from hexane-benzene, giving 3-amino-2-(2-bromophenoxy)-pyridine (107a) as a grey solid (32%), m.p. 100-105° (lit.[41], 97-100°).

Rotary evaporation of the hexane-benzene mother liquor afforded a second crop of 3-amino-2-(2-bromophenoxy)pyridine (107a) as a dark brown solid (25%), m.p. 87-

91°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(ii) Reduction of 2-(2-iodophenoxy)-3-nitropyridine (106b) gave a light brown solid (0.59g) which was recrystallised from benzene, giving 3-amino-2-(2-iodophenoxy)pyridine (107b) as a colourless solid (53%), m.p. 104-107° (lit.[41], 106 - 109°).

Rotary evaporation of the benzene mother liquor afforded a second crop of 3-amino-2-(2-iodophenoxy)pyridine (107b) as a dark brown solid (24%), m.p. 87-91°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

3-Amino-2-(2-iodophenoxy)pyridine (107b)

A solution of 2-(2-iodophenoxy)-3-nitropyridine (106b) (8.5g; 0.025mol) in glacial acetic acid (125ml) was hydrogenated over Raney nickel catalyst (1.3ml of a 50% slurry in water) at room temperature and atmospheric pressure for 7h during which time 1780ml of hydrogen had been absorbed.

The catalyst was removed by filtration through celite, and the filtrate rotary evaporated to give a dark brown solid which was dissolved in dichloromethane (20.0ml) and washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 10.0ml). Rotary evaporation of the combined dichloromethane extracts afforded a dark brown solid (7.3g) which was recrystallised from toluene to give 3-amino-2-(2-iodophenoxy)pyridine (107b) as a dark brown solid (5.0g; 64%), m.p. 105-108° (lit.[41], 106-109°).

Rotary evaporation of the toluene mother liquor afforded a second crop of 3-amino-2-(2-iodophenoxy)pyridine (107b) as a dark brown solid (1.5g; 19%), m.p. 100 - 103° identified by comparison (i.r. spectrum) with an authentic sample prepared before.

2-Aryloxy-3-isothiocyanatopyridine Derivatives (108)

A solution of the 3-amino-2-aryloxypyridine derivative (107) (0.02mol) in concentrated hydrochloric acid (40.0ml) was diluted with water (40.0ml), treated dropwise at room temperature with thiophosgene (2.3g; 0.02mol) and the mixture was stirred at room temperature for 24h, then worked up as described for the individual reactions below.

(i) The mixture from the reaction of 3-amino-2-(2-bromophenoxy)pyridine (107a) was extracted three times with dichloromethane (3 x 50.0ml) to afford 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) as a colourless solid (100%), m.p. 108-110° (from ethanol), ν_{max} 2111 (N=C=S)cm^{-1}, δ_H ($CDCl_3$) 7.95 (1H, dd J 5.0 and 1.7Hz, ArH), 7.65 (1H, dd J 7.9 and 1.7 Hz, ArH), 7.52-7.11 (4H, m, ArH) and 6.98 (1H, dd J 7.9 and 5.0Hz, ArH);

Found: C, 46.6; H, 2.4; N, 9.0%; m/z (EI ms), 308 and 306 (M^+),

$C_{12}H_7BrN_2OS$ requires: C, 46.9; H, 2.3; N, 9.1%; M, 307.

(ii) The mixture from the reaction of 3-amino-2-(2-iodophenoxy)pyridine (107b) was filtered to give 2-(2-iodophenoxy)-3-isothiocyanatopyridine (108b) as a light brown

solid (1.6g; 90%), m.p. 118-122° (from ethyl acetate), ν_{max} 2125 and 2110 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.97-6.95 (8H, m, ArH);

Found: C, 40.3; H, 2.1; N, 7.8%; m/z (FAB HRMS), 354.9413 (MH^+), $C_{12}H_7IN_2OS$ requires: C, 40.6; H, 2.0; N, 7.9%; M, 354.9402.

The filtrate was adjusted to pH 7 by the addition of 10M aqueous sodium hydroxide solution then extracted three times with dichloromethane to afford a second crop of 2-(2-iodophenoxy)-3-isothiocyanatopyridine (108b) as a brown solid (0.11g; 6%), m.p. 109-112°, identified by comparison (melting point and i.r. spectrum) with the first crop.

Attempted Aluminium Tribromide Catalysed Cyclisations of 2-(2-Bromophenoxy)-3-isothiocyanatopyridine (108a).

(a) A stirred solution of 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) (0.61g; 0.002mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of aluminium tribromide (1.1g; 0.004mol) in anhydrous dichloromethane (10.0ml) and the mixture then heated under reflux for 4h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml) and stirred at room temperature for 15min. Inorganic material was removed by filtration and the filtrate was extracted three times with dichloromethane (3 x 10.0ml) to afford 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) as an orange oil (0.61g; 100%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but using four equivalents of aluminium tribromide afforded a red oil (1.0g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (98:2) afforded ureacted 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) as a cream solid (0.031g; 5%), m.p. 105-108° identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ethyl acetate (97:3) through ethyl acetate to methanol afforded mixed fractions as oils and gums (0.58g) which were not further investigated.

The Attemped Secondary-Butyllithium Catalysed Cyclisation of 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) in Tetrahydrofuran.

A solution of 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) (1.2g; 0.004mol) in anhydrous tetrahydrofuran (20.0ml) was stirred and treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.1M solution of sec-BuLi in cyclohexane (3.6ml; 0.004mol). The mixture was then stirred at -78° (dry ice-acetone bath) for 2h, allowed to warm up to room temperature, then stirred for a further 2h. at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (40.0ml) then extracted three times with ether (3 x 40.0ml) to give a brown oil (1.2g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded impure unreacted 2-(2-bromophenoxy)-3-isothiocyanatopyridine (108a) as a yellow oil (0.25g; 21%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable brown gum (0.65g) which was not further investigated.

The Attempted Cyclisation of 2-(2-Iodophenoxy)-3-isothiocyanatopyridine (108b) Using Magnesium in Diethyl Ether.

A stirred solution of 2-(2-iodophenoxy)-3-isothiocyanatopyridine (108b) (0.71g; 0.002mol) in anhydrous ether (20.0ml) was treated with magnesium turnings (0.048g; 0.002mol) and a single crystal of iodine. The mixture was stirred at 45° (water bath) for 1h, then heated under reflux for a further 3.5h.

The mixture was allowed to cool to room temperature, treated with a single portion of 2M aqueous hydrochloric acid (5.0ml) then stirred at room temperature for 1h. The mixture was extracted three times with ether (3 x 10.0ml) to afford 2-(2-iodophenoxy)-3-isothiocyanatopyridine (108b) as a light brown solid (0.65g; 92%), m.p. 115-120°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The Attempted Tributyltin Hydride Catalysed Cyclisation of 2-Bromo-2'-isothiocyanatodiphenyl Ether (102a).

A stirred suspension of azoisobutyronitrile (0.033g; 0.0002mol) in anhydrous toluene (5.0ml) under nitrogen was treated with 2-bromo-2'-isothiocyanatodiphenyl ether (102a) (0.31g; 0.001mol) in anhydrous toluene (2.5ml) added in one portion. The resulting mixture was heated under reflux and treated dropwise over 1h with a solution of tributyltin hydride (0.75g; 0.025mol) in anhydrous toluene (5.0ml) then the mixture stirred and heated under reflux for a further 3h.

The mixture was allowed to cool to room temperature, treated with a solution of potassium fluoride (0.22g; 0.0038mol) in water (5.0ml) and stirred at room temperature for 15min. The mixture was extracted three times with ether (3 x 5.0ml) to afford a brown oil (0.51g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded a mixed fraction as a yellow oil (0.011g) whose t.l.c. in hexane-ether over silica showed it to contain unreacted 2-bromo-2′-isothiocyanatodiphenyl ether (102a).

Further elution afforded the thioformamide (104) as a yellow solid (0.22g; 77%), m.p. 137-139° (from ethanol-hexane), ν_{max} 3009 (NH) and 1603 (CS) cm^{-1}, δ_H ($CDCl_3$) 9.92 (1H, d J 15.0Hz, CSH), 9.70 (1H, bs, NH), 7.66 (1H, dd J 7.9 and 1.5 Hz, ArH), 7.40-7.29 (2H, m, ArH), 7.25-7.02 (4H, m, ArH) and 6.89-6.64 (1H, m, ArH);

Found: C, 50.4; H, 3.6; N, 4.6%; m/z (EI ms), 309 and 307 (M^+),

$C_{13}H_8INOS$ requires: C, 50.7; H, 3.3; N, 4.6%; M, 308.

Further elution with methanol afforded an intractable brown gum (0.24g) which was not further investigated.

The Attempted Hexabutylditin Catalysed Cyclisation of 2-Bromo-2′-isothiocyanatodiphenyl ether (102a).

(a) A stirred solution of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) (0.61g; 0.002mol) in anhydrous benzene (7.5ml) and treated with a solution of hexabutylditin (0.12g; 0.0002mol) in anhydrous benzene (2.5ml). The mixture was then purged with nitrogen, heated under reflux and irradiated with a 500W tungsten lamp for 4h.

Rotary evaporation of the mixture afforded a brown oil (0.75g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-bromo-2′-isothiocyanatodiphenyl ether (102a) and tin residues.

(b) Repetition of the reaction described in (a) before, but using 1 equivalent of hexabutylditin, afforded a brown oil (0.74g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-bromo-2′-isothiocyanatodiphenyl ether (102a) and tin residues.

(c) Repetition of the reaction described in (a) before, but using 1 equivalent of hexabutylditin and irradiating through Pyrex jacket with a 240W mercury vapour lamp in a Hanovia photochemical reactor, afforded a brown oil (0.74g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-bromo-2′-isothiocyanatodiphenyl ether (102a) and tin residues.

2-Iodo-2′-nitrodiphenyl Ether (100b)

2-Iodo-2′-nitrodiphenyl ether (100b) was prepared (yield 99%) by the sodium hydride catalysed reaction of 2-iodophenol (99b) and 2-fluoronitrobenzene (61) in dimethylformamide as described by Currie and Tennant[83], and had m.p. 61-64° (lit.[83], 65-66°).

2-Amino-2′-iododiphenyl Ether (101b)

(a) A stirred solution of 2-iodo-2′-nitrodiphenyl ether (100b)(13.6g; 0.04mol) in tetrahydrofuran (500ml) under nitrogen was treated in several portions with 15% w/v

aqueous titanium trichloride solution (460ml; 0.4mol). The mixture was then stirred under nitrogen at room temperature for 5h.

The mixture was rotary evaporated to give a purple oily liquid which was stirred and cooled in an ice bath, then basified by the dropwise addition of 50% w/v aqueous sodium hydroxide solution. The mixture was diluted with water (40.0ml) and extracted three times with dichloromethane (3 x 200ml) to give 2-amino-2′-iododiphenyl ether (101b) as a pale yellow solid (9.2g; 74%), m.p. 75-79° (lit.[83], 84°).

The aqueous mother liquor was stirred in air for 24h, by which time the original purple colour had disappeared. Inorganic residues were removed by filtration and the filtrate was extracted three times with dichloromethane (3 x 20.0ml) to give a pale yellow oil (0.10g) which was not further investigated.

(b) A stirred mixture of 2-iodo-2′-nitrodiphenyl ether (100b) (3.4g; 0.01mol) and cobalt dichloride hexahydrate (4.8g; 0.02mol) in methanol (60.0ml) was treated with sodium borohydride (3.8g; 0.1mol) added in several portions at room temperature then stirred at 40° (water bath) for 1h. The mixture was treated with 3M aqueous hydrochloric acid (20.0ml) and heated under reflux for 1h.

The resulting suspension was rotary evaporated to give a brown residue which was basified with concentrated aqueous ammonia solution. The mixture was then treated with ether (50.0ml) and the insoluble inorganic material removed by filtration. The two phase filtrate was separated and the aqueous phase extracted a further three times with ether (3 x 20.0ml). The combined ether fractions were rotary evaporated to give 2-amino-2′-iododiphenyl ether (101b) as a brown solid (1.6g; 51%), m.p. 58-61°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(c) Repetition of the reaction described in (b) before, on a 0.04mol scale afforded a complex black oil (19.2g), possibly containing the desired product, which was not further investigated.

(d) A solution of 2-iodo-2′-nitrodiphenyl ether (100b) (0.68g; 0.002mol) in tetrahydrofuran (20.0ml) was treated with a solution of stannous chloride dihydrate (2.0g; 0.0089mol) in 2M aqueous hydrochloric acid (20.0ml) and the mixture was stirred at room temperature for 18h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was extracted three times with ether (3 x 30.0ml) to give 2-amino-2′-iododiphenyl ether (101b) as a pink solid (0.60g; 96%), m.p 80-84° (lit.[83], 84°), identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(e) A stirred solution of 2-iodo-2′-nitrodiphenyl ether (100b) (20.0g; 0.06mol) in tetrahydrofuran (600ml) was treated with a solution of stannous chloride dihydrate (60.0g; 0.27mol) in 2M aqueous hydrochloric acid (600ml) and the mixture was heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was then extracted three times with ether (3 x 600ml) to give 2-amino-2′-iododiphenyl ether (101b) as a light brown solid

(18.0g; 96%), m.p. 76-82° (lit.[83], 84°), identical (melting point and i.r. spectrum) to an authentic sample prepared before.

2-Iodo-2′-isothiocyanatodiphenyl Ether (102b)

A stirred solution of 2-amino-2′-iododiphenyl ether (101b) (3.1g; 0.01mol) in glacial acetic acid (25.0ml) was treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (7.5ml) then dropwise at room temperature with a solution of thiophosgene (2.3g; 0.02mol) in glacial acetic acid (5.0ml). The mixture was then stirred at room temperature for 2h.

The mixture was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 80.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 40.0ml) then rotary evaporated to give 2-iodo-2'-isothiocyanatodiphenyl ether (102b) as a brown oil (3.0g; 85%), ν_{max} 2150 and 2026 (N=C=S) cm^{-1};

Found: m/z (EI ms), 352.9374 (M^+),

$C_{13}H_8INOS$ requires: M, 352.9373.

4-Iododibenz[b,f][1,4]oxazepine-11(10H)-thione (103b)

A stirred solution of 2-iodo-2′-isothiocyanatodiphenyl ether (102b) (0.71g; 0.002mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of aluminium tribromide (1.1g; 0.004mol) in anhydrous dichloromethane (10.0ml) then stirred and heated under reflux for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 10.0ml00 to afford an orange solid (0.71g), m.p. 167-170°. This was crystallised from acetic acid to give 4-iododibenz[b,f][1,4]oxazepine-11(10H)-thione (103b) as a brown solid (0.57g; 80%), which formed yellow cubes, m.p. 207-210° (from acetic acid), ν_{max} 3164 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.77 (1H, s, NH) and 8.05-7.97 (2H, m, ArH), 7.60 (1H, dd J 7.9 and 2.0Hz, ArH), 7.57-7.11 (3H, m, ArH) and 7.04 (1H, t J 7.9Hz, ArH);

Found: C, 44.3; H, 2.3; N, 4.0%; m/z (EI ms), 357 (M^+),

$C_{13}H_8INOS$ requires: C, 44.2; H, 2.3; N, 4.0%; M, 307 and 357.

Attempted Hexabutylditin Catalysed Cyclisation of 2-Iodo-2′-isothiocyanatodiphenyl Ether (102b).

(a) A stirred solution of 2-iodo-2′-isothiocyanatodiphenyl ether (102b) (0.71g; 0.002mol) in anhydrous benzene (7.5ml) was treated with a solution of hexabutylditin (0.12g; 0.0002mol) in anhydrous benzene (2.5ml) and the mixture was then purged with nitrogen, heated under reflux and irradiated with a 500W tungsten lamp for 4h.

Rotary evaporation of the mixture afforded a brown oil (0.81g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-iodo-2′-isothiocyanatodiphenyl ether (102b) and tin residues.

(b) Repetition of the reaction described in (a) before, but using 1 equivalent of hexabutylditin and irradiating through quartz with a 240W mercury vapour lamp in a

Hanovia photochemical reactor afforded a brown oil (2.4g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-iodo-2′-isothiocyanatodiphenyl ether (102b) and tin residues.

(c) Repetition of the reaction described in (a) before, but using 1.5 equivalents of hexabutylditin and irradiatingthrough Pyrex with a 240W mercury vapour lamp in a Hanovia photochemical reactor afforded a brown oil (2.3g) which was shown (t.l.c. in hexane-ether over silica) to be a mixture of unreacted 2-iodo-2′-isothiocyanatodiphenyl ether (102b) and tin residues.

The Attempted Palladium Acetate Catalysed Cyclisation of 2-Iodo-2′-isothiocyanatodiphenyl Ether (102b) in the Presence of Tri-ortho-tolylphosphine and Triethylamine in Refluxing Acetonitrile.

A solution of 2-iodo-2′-isothiocyanatodiphenyl ether (102b) (0.71g; 0.002mol) in anhydrous acetonitrile (10.0ml) was stirred under nitrogen and treated with $(o\text{-tol})_3P$ (1.2g; 0.004mol) and triethylamine (0.52g; 0.012mol) then deoxygenated by bubbling nitrogen through the solution for 10min. The mixture was then treated with palladium (II) acetate (0.45g; 0.002mol) and stirred and heated under reflux for 3h. The cooled mixture was treated with 2M aqueous hydrochloric acid (10.0ml), stirred and adjusted to pH 6 by the addition of potassium carbonate then extracted three times with dichloromethane (3 x 5.0ml). The combined dichloromethane extracts were dried and rotary evaporated to give a dark brown gum (2.4g) which was triturated with ether to afford a brown solid, (1.4g), m.p. 166-172°, which left an infusible residue on strong roasting and was therefore believed to be a palladium

complex. The material was treated with 2M aqueous hydrochloric acid (5.0ml) and warmed to 40°, but was recovered unchanged (melting point and i.r. spectrum).

The possible palladium complex was then treated with piperidine (0.50ml) and warmed to 100°, but on re-isolation the material was found to be unchanged (melting point and i.r. spectrum).

Rotary evaporation of the ether mother liquor afforded a brown semi-solid (0.54g) which was not further investigated.

Attempted Reduction of the Proposed Palladium Complex.

(a) A solution of the possible palladium complex (0.50g; ~0.001mol) in dioxane (40.0ml) was hydrogenated over 10% palladium-on-charcoal (3.2g) at room temperature and atmospheric pressure for 4h, during which time 135ml hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give the unreacted starting material as a gummy brown solid (0.53g) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a) before, but using Raney nickel catalyst in ethyl acetate afforded the unreacted starting material as a brown gum (0.45g), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Attempted Palladium Acetate Catalysed Cyclisation of 2-Bromo-2′-isothiocyanatodiphenyl Ether (102a) in the Presence of Triorthotolyl Phosphine and Triethylamine in Refluxing Acetonitrile.

A solution of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) (0.15g; 0.0005mol) in anhydrous acetonitrile (10.0ml) was stirred under nitrogen and treated with $(o\text{-tol})_3P$ (0.15g; 0.0005mol) and triethylamine (0.15g; 0.0015mol) then deoxygenated by bubbling nitrogen through the solution for 10min. The mixture was then treated with palladium (II) acetate (0.056g; 0.00025mol) and stirred and heated under reflux for 3h.

The cooled mixture was treated with 2M aqueous hydrochloric acid (5.0ml), stirred and adjusted to pH 6 by the addition of potassium carbonate then extracted three times with dichloromethane (3 x 5.0ml). The combined dichloromethane extracts were washed twice with water (2 x 5.0ml), then dried and rotary evaporated to give a dark brown gum (0.21g) which was triturated with ether to afford a brown solid, (0.050g), m.p. 194-196°, which left an infusible residue on strong roasting. Rotary evaporation of the ether mother liquor afforded a brown gum (0.14g) which was not further investigated.

2-Azido-2′-bromodiphenyl Ether (110)

2-Amino-2′-bromodiphenyl ether (101a) (10.4g; 0.04mol) was treated with 5M aqueous hydrochloric acid (200ml) and the mixture was warmed gently to form a suspension of 2-amino-2′-bromodiphenylether hydrochloride. This was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (3.1g; 0.044mol) in water (20.0ml), then stirred at 0° for a further 10 min. A solution of

sodium azide (3.9g; 0.06mol) in water (20.0ml) was then added dropwise at 0° and the resulting mixture stirred in the melting ice bath for 30 min.

The mixture was extracted three times with dichloromethane (3 x 100ml) to afford a brown oil which was combined with further material obtained by basification of the aqueous mother liquor with 5M aquous sodiumhydroxide and extraction three times with dichloromethane (3 x 200ml) to 2-azido-2′-bromodiphenyl ether (110) as a brown oil (11.3g; 97%), ν_{max} 2124 and 2103 (N_3) cm^{-1}, δ_H ($CDCl_3$) 7.62 (1H, dd J 1.7 and 7.6Hz, ArH) and 7.59-6.75 (7H, m, ArH);

Found: C, 50.1; H, 2.9; N, 14.4%; m/z (EI ms), 291 and 289(M^+),

$C_{12}H_8BrN_3O$ requires: C, 49.7; H, 2.8; N, 14.5%; M, 291 and 289.

2-Azido-2′-iododiphenyl Ether (115)

(a) 2-Amino-2′-iododiphenyl ether (101b) (3.1g; 0.01mol) was treated with 5M aqueous hydrochloric acid (50.0ml) and warmed gently to form a suspension of 2-amino-2′-iododiphenyl ether hydrochloride. This was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.77g; 0.011mol) in water (5.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. The diazonium solution was decanted from the flask, leaving a dark brown solid, which was treated with 2M aqueous sodium hydroxide solution (30.0ml) to afford unreacted 2-amino-2′-iododiphenyl ether (101b) as a dark brown solid (1.5g; 50%), m.p., 77-83°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The diazonium solution was then treated dropwise with stirring at 0° with a solution of sodium azide (0.98g; 0.015mol) in water (5.0ml), at such a rate that the reaction temperature was <5°. The mixture was then stirred in the melting ice bath for 30 min. The mixture was extracted with ether (3 x 50.0ml) to afford 2-azido-2′-iododiphenyl ether (115) as a brown oil (0.70g; 20%), ν_{max} 2125 and 2100 (N_3) cm^{-1};

Found: m/z (EI HRMS), 336.9729 (M^+),

$C_{12}H_8IN_3O$ requires: M, 336.9714.

(b) 2-Amino-2′-iododiphenyl ether (101b) (3.1g; 0.01mol) was dissolved in glacial acetic acid (50.0ml), and treated the solution with 5M aqueous hydrochloric acid (25.0ml). This mixture was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.77g; 0.011mol) in water (5.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. The diazonium solution was treated dropwise at 0° with a solution of sodium azide (0.98g; 0.015mol) in water (5.0ml), then stirred in the melting ice bath for 30 min.

The mixture was concentrated to one quarter of the original volume, trated with ether (100ml), then washed with 10% w/v aqueous sodium hydrogen carbonate (3 x 60.0ml). Rotary evaporation of the ether fraction afforded a red oil (2.5g) which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (95:5) afforded unreacted 2-amino-2′-iododiphenyl ether (115) as a brown oil (2.4g; 71%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded a dark brown solid (0.025g) which was not further investigated.

Reaction of 2-Azido-2′-halogenodiphenyl Ether Derivatives with Trimethylphosphite in 1,2-Dimethoxyethane.

A stirred solution of the 2-azido-2′-halogenodiphenyl ether derivative (0.015mol) in anhydrous 1,2-dimethoxyethane (75.0ml) was treated at room temperature with a solution of trimethylphosphite (2.4g; 0.019mol) in anhydrous 1,2-dimethoxyethane (37.5ml) added in one portion. The mixture was then stirred at room temperature with the exclusion of atmospheric moisture for 17h, then rotary evaporated to afford the phosphinimine product.

(i) 2-Azido-2′-bromodiphenyl ether (110) afforded the phosphinimine (111) as a light brown oil (95%), δ_H ($CDCl_3$) 7.53 (1H, dd J 7.6 and 1.7 Hz, ArH), 7.19-6.59 (7H, m, ArH) and 3.58 (9H, d J 11.4Hz, $N=P(OCH_3)_3$);

Found: m/z (EI HRMS), 387.0076 and 385.0087 (M^+),

$C_{15}H_{17}BrNO_4P$ requires: M, 387.0059 and 385.0079.

(ii) 2-Azido-2′-iododiphenyl ether (115) afforded the phosphinimine (116) as a light brown oil (92%), δ_H ($CDCl_3$) 7.59 (1H, dd J 7.7 and 1.6Hz, ArH), 7.18 - 6.57 (7H, m, ArH) and 3.61 (9H, d J 11.4Hz, $N=P(OCH_3)_3$).

Reaction of Phosphinimine Derivatives with Phenyl Isocyanate in 1,2-Dimethoxyethane.

A stirred solution of the corresponding phosphinimine derivative (0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was treated at room temperature with a solution of phenyl isocyanate (0.26g; 0.0022mol) in anhydrous 1,2-dimethoxyethane

(10.0ml). The mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 4h, then worked up as described for the individual reactions below

(a)(i)Rotary evaporation of the mixture from the phosphinimine (111) afforded a red oil which was dissolved in ether (12.5ml) and the solution washed three times with water (3 x 10.0ml). Rotary evaporation of the combined ether extracts afforded a red oil (0.67g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a mixed fraction as a brown oil (0.16g) which had a band in the i.r. spectrum consistent with the desired carbodiimide product (114), ν_{max} 2143 (N=C=N) cm^{-1}.

Further elution with hexane-ether (90:10) afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) as a cream solid (0.27g; 35%), m.p. 175-178° (from ethanol), ν_{max} 3411 and 3305 (NH_2) and 1734 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.32 (1H, bs, NH) (exch), 8.53 (1H, bs, NH) (exch), 8.29 (1H, dd J 8.1and 1.5Hz, ArH), 7.79 (1H, dd J 7.8 and 1.5Hz, ArH), 7.48 -6.86 (10H, m, ArH) and 6.59 (1H, dd J 8.1 and 1.4Hz, ArH)

Found: C, 59.3; H, 3.7; N, 7.3%; m/z (EI ms), 384 and 382(M^+),

$C_{19}H_{15}BrN_2O_2$ requires: C, 59.5; H, 3.9; N, 7.3%; M, 383.

Further elution with methanol afforded impure diphenyl urea as a light brown solid (0.24g), m.p., 194-198° (lit.[103], 239-241°).

(b) Repetition of the reaction described in (a) before, but using 1 equivalent of phenyl isocyanate (0.002mol) afforded a red oil which was dissolved in ether (12.5ml) and

the solution washed three times with water (3 x 10.0ml). Rotary evaporation of the combined ether extracts afforded a brown oil (0.74g) which had a band in the i.r. spectrum consistent with the desired carbodiimide product (114), ν_{max} 2143 (N=C=N) cm^{-1}.

(ii) Rotary evaporation of the mixture from the phosphinimine (116) afforded a red oil which was dissolved in ether (25.0ml) and the solution washed three times with water (3 x 20.0ml). Rotary evaporation of the combined ether extracts afforded a complex red oil (0.67g) which was not further investigated.

Dimethoxy N-[2-(2-Halogenophenoxy)phenyl]phosphoramidates

The corresponding phosphinimine (0.0055mol) was flash chromatographed over silica.

Elution with ether afforded the desired phosphoramidate product.

Further elution with methanol afforded intractable brown gums which were not further investigated.

(i) The bromo-phosphinimine (111) gave the phosphoramidate (112) which formed colourless cubes (97%), m.p. 94-95° (from hexane-toluene), ν_{max} 3140 (NH) cm^{-1}, δ_H ($CDCl_3$) 7.62 (1H, dd J 7.9 and 1.5Hz, ArH), 7.32-7.21 (2H, m, ArH), 7.08-6.83 (4H, m, ArH), 6.72-6.67 (1H, m, ArH), 5.73 (1H, d J 9.6Hz, NH) and 3.78 (6H, d J 11.4Hz, $-PO(OCH_3)_2$);

Found: C,45.4; H, 4.2; N, 3.6%; m/z (EI ms), 372 (M^+),

$C_{14}H_{15}BrNO_4P$ requires: C,45.2; H, 4.0; N, 3.8%; M, 372.

(ii) The iodo-phosphinimine (116) gave the phosphoramidate (117) which formed colourless cubes (82%), m.p. 111-114° (from toluene), ν_{max} 3127 (NH) cm^{-1}, δ_H ($CDCl_3$) 7.85 (1H, dd J 7.8 and 1.5Hz, ArH), 7.33-7.25 (2H, m, ArH), 7.04 (1H, dt J 8.0, 8.0 and 1.5Hz, ArH), 6.91-6.84 (3H, m, ArH), 6.69 (1H, dt J 8.0, 1.5 and 1.5Hz, ArH), 5.69 (1H, d J 9.6Hz, NH) and 3.78 (6H, d J 11.4Hz, $-PO(OCH_3)_2$);

Found: C, 40.1; H, 3.6; N, 3.4%; m/z (EI ms), 419 (M^+),

$C_{14}H_{15}INO_4P$ requires: C, 40.1; H, 3.6; N, 3.3%; M, 419.

Attempted Sodium Hydride Catalysed Reactions of the Bromo-phosphoramidate (112) with Phenyl Isocyanate.

(a) A suspension of sodium hydride (0.096; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml)was vigorously stirred under nitrogen and treated dropwise at room temperature with a solution of the bromo-phosphoramidate (112) (1.5g; 0.004mol) in anhydrous 1,2-dimethoxyethane (10.0ml). After the gas evolution had ceased, the mixture was heated at 70° (oil bath) for 0.5h then cooled to room temperature. The mixture was treated dropwise with a solution of phenyl isocyanate (0.48g; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) then stirred and heated at 70° (oil bath) for a further 0.5h.

The cooled mixture was rotary evaporated giving a brown gum which was treated with water (20.0ml) and extracted three times with ether (3 x 10.0ml) to afford a yellow-brown oil (1.5g) which was flash chromatographed over silica.

Elution with hexane afforded a multicomponent yellow oil (0.15g) which was not further investigated.

Elution with hexane-ether (95:5) afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) as a colourless solid (0.46g; 30%), m.p. 175-178°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Further elution with methanol afforded impure diphenyl urea as a light brown oil (0.65g), identified by comparison (i.r. spectrum) with an authentic sample.

(b) A suspension of sodium hydride (0.096; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was vigorously stirred under nitrogen was stirred and treated dropwise at room temperature with a solution of the bromo-phosphoramidate (112) (1.5g; 0.004mol) in anhydrous 1,2-dimethoxyethane (10.0ml). After the gas evolution had ceased, the mixture was heated at 70° (oil bath) for 0.5h then cooled to room temperature. The mixture was treated dropwise with a solution of phenyl isocyanate (0.48g; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) then stirred at room temperature for a further 3h.

The mixture was rotary evaporated to give cream gum which was treated with water (20.0ml) and extracted three times with ether (3 x 10.0ml) to afford a pale yellow glass (1.1g), m.p. 73-80°, which was shown by t.l.c. in hexane-ether over silica to be a complex mixture and therefore was not further investigated.

(c) A stirred solution of the bromo-phosphoramidate (112) (0.74g; 0.002mol) in anhydrous xylene (10.0ml) was treated with anhydrous potassium carbonate (1.1g; 0.008mol) and phenyl isocyanate (0.26g; 0.0022mol) and the mixture heated under reflux for 7h.

The cooled mixture was filtered to remove inorganic material then rotary evaporated to give a brown oil (0.61g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.22g; 29%), as a colourless solid, m.p. 171-176°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (80:20) afforded diphenyl urea (0.31g; 69%), as a colourless solid, m.p. 233-239°, (lit.[103], 239-241°).

Further elution with ether afforded a brown oil (0.051g) which was not further investigated.

The Attempted Sodium Hydride Catalysed Reaction of the Iodo-phosphoramidate (117) with Phenyl Isocyanate.

A suspension of sodium hydride (0.096; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) was vigorously stirred under nitrogen and treated dropwise at room temperature with a solution of the iodo-phosphoramidate (117) (1.7g; 0.004mol) in anhydrous 1,2-dimethoxyethane (10.0ml). After the gas evolution had ceased, the mixture was heated at 70° (oil bath) for 0.5h then cooled to room temperature. The mixture was treated dropwise with a solution of phenyl isocyanate (0.48g; 0.004mol) in anhydrous 1,2-dimethoxyethane (5.0ml) then stirred and heated at 70° (oil bath) for a further 0.5h.

The cooled mixture was rotary evaporated giving a brown gum was treated with water (20.0ml) and extracted three times with ether (3 x 10.0ml) to afford a brown viscous gum (1.5g) which was flash chromatographed over silica.

Elution with hexane through ether and methanol afforded only mixed fractions as brown oils (0.48g) which were not further investigated.

Phenyl Azide

Phenyl azide was prepared (yield 100%) by the reaction of phenyl hydrazine with aqueous sodium nitrite as described by Lindsey and Allen,[90a] ν_{max} 2126 and 2093 (N_3) cm^{-1}.[90a]

N-Phenyl trimethoxyphosphinimine

N-Phenyl trimethoxyphosphinimine was prepared (yield 99%) by the reaction of phenyl azide with trimethylphosphite as described by Wiegrabe and Bock,[90b] δ_H ($CDCl_3^3$) 7.16-6.78 (5H, m, ArH) and 3.78 (9H, d J 7.3Hz, $N=P(OCH_3)_3$).[90b]

The Attempted Reaction of 2-Bromo-2′-isothiocyanatodiphenyl Ether (102a) with N-Phenyl trimethoxyphosphinimine

A stirred solution of N-Phenyl trimethoxyphosphinimine (0.43g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) was treated with a solution of 2-bromo-2′-isothiocyanatodiphenyl ether (102a) (0.61g; 0.002mol) in anhydrous 1,2-dimethoxyethane (10.0ml) added in one portion. The mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 4.5h then under reflux for a further 15.5h.

The mixture was rotary evaporated to give a red oil which was dissolved in ether (12.5ml) then washed three times with water (3 x 10.0ml). Rotary evaporation of the ether extract gave a red oil (0.86g) which was flash chromatographed over silica.

Elution with hexane afforded unreacted 2-bromo-2′-isothiocyanatodiphenyl ether (102a) as a yellow oil (0.22g; 50%) identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane afforded an unidentified yellow oil (0.11g).

Further elution with hexane through ether to methanol afforded only small amounts of unidentifiable oils (0.11g) which were not further investigated.

The Attempted Reaction of 2-Isothiocyanatodiphenyl Ether (65) with N-Phenyl trimethoxyphosphinimine

(a) A stirred solution of N-Phenyl trimethoxyphosphinimine (1.1g; 0.005mol) in anhydrous 1,2-dimethoxyethane (25.0ml) was treated with a solution of 2-isothiocyanatodiphenyl ether (65) (1.1g; 0.005mol) in anhydrous 1,2-dimethoxyethane (25.0ml) added in one portion The mixture was then stirred under reflux, with the exclusion of atmospheric moisture, for 17h.

The mixture was rotary evaporated to give a red oil which was dissolved in ether (30.0ml) then washed three times with water (3 x 10.0ml). Rotary evaporation of the ether extract gave a red oil (1.7g) which was flash chromatographed over silica.

Elution with hexane afforded unreacted 2-isothiocyanatodiphenyl ether (65) as a pale yellow oil (0.27g; 25%) identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane afforded a pale yellow oil (0.089g) which had a molecular ion peak in the mass spectrum corresponding to the desired carbodiimide product.

Further elution with ether afforded N-phenyl,N′-(2-phenoxy)phenyl urea as a colourless solid (0.28g; 17%), m.p. 169-171° (from glacial acetic acid), ν_{max} 3318 (NH) and 1649 (CO) cm^{-1}, δ_H ($CDCl_3$) 9.30 (1H, bs, NH) (exch), 8.49 (1H, bs, NH) (exch) and 7.49-6.77 (14H, m, ArH);

Found: C,74.8; H, 5.3; N, 8.9%; m/z (EI ms), 304 (M^+),

$C_{19}H_{16}N_2O_2$ requires: C, 75.0; H, 5.3; N, 9.2%; M, 304.

Further elution with ether through to methanol afforded only multicomponent oils (0.80g) which were not further investigated.

(b) Repetition of the reaction described in (a) before, but refluxing in 1,4-dioxane for 19h gave a red oil which was dissolved in dichloromethane (20.0ml) and the solution washed three times with water (3 x 10.0ml). Rotary evaporation of the dichloromethane extract gave a red oil (1.4g) which decomposed on attempted purification by distillation.

N-Phenyl,N′-[2-(2-bromophenoxy)]phenyl Urea (113)

A solution of 2-amino-2′-bromodiphenyl ether (101a) in anhydrous dioxane (62.5ml) was treated with a solution of phenyl isocyanate (3.0g; 0.025mol) in anhydrous dioxane (62.5ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 2h.

The mixture was rotary evaporated to give a light brown solid (10.1g), m.p. 161-168°, which was crystallised from ethanol to give N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (6.7g; 70%), as a cream solid, m.p. 170-176°,

identified bt comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The ethanolic filtrate was rotary evaporated to give a dark brown semi-solid (2.2g) which was flash chromatographed over silica.

Elution with hexane-ether (50:50) afforded a second crop N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (1.0g; 10%), as a cream solid, m.p. 167-173°, identified by comparison (melting point and i.r. spectrum) with the first crop.

Further elution with methanol afforded a dark brown intractable gum (1.1g) which was not further investigated.

Reactions of N-Phenyl,N′-[2-(2-bromophenoxy)]phenyl Urea (113) with Phosphoryl Chloride in the presence of Diisopropylethylamine.

(a) A suspension of N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) in anhydrous dichloromethane (10.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) and cooled to 0° (ice-salt bath). The mixture was treated dropwisewith stirring with phosphoryl chloride (0.68g; 0.0044mol) at such a rate that the reaction temperature was 0-5° then stirred at room temperature for 17h.

The mixture was treated dropwise with 1M aqueous sodium carbonate solution (5.0ml) then stirred for at room temperature 1h. The mixture was treated with water (2.5ml) and the suspended N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) was collected as a colourless solid (0.35g; 45%), m.p. 170-175°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before. The two phase filtrate was separated and the organic layer was washed twice with water (2 x

2.5ml) then rotary evaporated to give a light brown semi-solid (0.13g) whose t.l.c. in hexane-ether over silica showed it to be impure N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113).

(b) Repetition of the reaction as described in (a) before, but using 1.1 equivalents of phosphoryl chloride, heating under reflux for 1h, then adding 3 equivalents of diisopropylethylamine and heating under reflux for a further 21h.

The cooled solution was rotary evaporated to give a brown oil (1.7g) whose t.l.c. in hexane-ether over silica showed it to be a mixture of baseline material and N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113). The oil was stirred with 2M aqueous hydrochloric acid for 15min at room temperature and the insoluble N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) collected as a cream solid, (0.77g, 100%), m.p. 173-178°. identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(c) Repetition of the reaction as described in (a) before, but using 1.1 equivalents of phosphoryl chloride, and heating under reflux in anhydrous 1,2-dichloroethane for 4h.

The cooled solution was rotary evaporated to give a brown oil (1.5g) which was washed three times with anhydrous ether (3 x 10.0ml). The combined ethereal extracts were rotary evaporated to give a pale yellow solid (0.33g) whose t.l.c. in hexane-ether over silica showed it to be a mixture of baseline material, N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) and a third product.

The residual brown oil (0.95g) was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (114) as a pale yellow solid, (0.26g; 36%), which formed colourless crystals (from hexane),m.p. 81-84°, ν_{max} 2143 and 2107 (N=C=N) cm^{-1}, δ_H ($CDCl_3$) 7.52 (1H, dd J 7.9 and 1.6Hz, ArH) and 7.31-6.75 (12H, m, ArH);

Found: m/z (FAB HRMS), 367.0285 and 365.0294 (MH^+)

$C_{19}H_{12}BrN_2O$ requires: M, 3670270 and 365.0290.

Further elution with methanol afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.15 g; 20%) as a colourless solid, m.p. 169-175°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(d) Repetition of the reaction as described in (c) before, but with heating under reflux for 17h.

The cooled solution was rotary evaporated to give a light brown oil (2.1g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (114) as a pale yellow oil, (0.55g; 75%), identified by comparison (i.r. spectrum) with an authentic sample prepared in (c) before.

Further elution with hexane-ether (50:50) afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.10g; 13%) as a colourless solid, m.p. 170-177°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded a yellow oil (0.23g), whose t.l.c. in hexane-ether over silica showed it to be baseline material, which was not further investigated.

(e) Repetition of the reaction as described in (c) before, but with heating under reflux for 24h.

The cooled solution was rotary evaporated to give a light brown oil (9.9g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (114) as a pale yellow oil, (2.5g; 68%), identified by comparison (i.r. spectrum) with an authentic sample prepared in (c) before.

Further elution with hexane-ether (50:50) afforded N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.53g; 14%) as a colourless solid, m.p. 170-175°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded a yellow oil (5.3g), whose t.l.c. in hexane-ether over silica showed it to be baseline material, which was not further investigated.

(f) Repetition of the reaction as described in (a) before, but using 1.5 equivalents of phosphoryl chloride and heating under reflux in anhydrous 1,2-dichloroethane for 24h.

The cooled solution was rotary evaporated to give a light brown oil (2.2g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (114) as a pale yellow oil, (22%), identified by comparison (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (14%) as a colourless solid, m.p. 171-176°, identified by comparisonl (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an orange oil, whose t.l.c. in hexane-ether over silica showed it to be baseline material, which was not further investigated.

(g) Repetition of the reaction as described in (a) before, but using 1.1 equivalents of phosphoryl chloride, 1.1 equivalents of diisopropylethylamine and heating under reflux in anhydrous 1,2-dichloroethane for 17h.

The cooled solution was rotary evaporated to give a light brown oil (0.90g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (114) as a yellow oil, (0.20g; 27%), identified by comparison (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.33g; 45%) as a cream solid, m.p. 168-173°, identfied by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an orange oil (0.27g), whose t.l.c. in hexane-ether over silica showed it to be baseline material, which was not further investigated.

The Attempted Reaction of N-Phenyl,N′-[2-(2-bromophenoxy)]phenyl Urea (113) with Phosphoryl Chloride in the presence of Diisopropylethylamine and Subsequent Reaction with Methylamine.

A suspension of N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) in anhydrous dichloromethane (10.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) then cooled to 0° (ice-salt bath). The mixture was treated dropwise with phosphoryl chloride (0.68g; 0.0044mol) at such a rate that the reaction temperature was 0-5°, then heated under reflux for 17h.

The cooled solution was rotary evaporated to give a brown oil (1.3g) which was washed twice with anhydrous ether (2 x 10.0ml). The combined ethereal extracts were rotary evaporated to give a cream semi-solid (0.25g) whose t.l.c. in hexane-ether over silica showed it to be a mixture of baseline material and N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113).

The residual brown oil (1.1g) was dissolved in anhydrous ethanol (4.0ml) treated with 33% methylamine in ethanol (1.0ml; 0.014mol) and the mixture stirred at room temperature for 1h. The insoluble N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.18g; 25%) was collected as a colourless solid, m.p. 175-179°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The ethanolic filtrate was rotary evaporated to give a light brown semi-solid (0.91g) whose t.l.c. in hexane-ether over silica showed it to be a mixture of baseline material and N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113).

N-Phenyl,N′-[2-(2-bromophenoxy)]phenyl Urea (113)

A solution of the carbodiimide (114) (0.73g; 0.002mol) in 1,2-dimethoxyethane (7.5ml) was treated with 2M aqueous hydrochloric acid (2.5ml) and the mixture stirred at room temperature for 17h.

The mixture was concentrated by rotary evaporation to remove the 1,2-dimethoxyethane, diluted with water (5.0ml) then extracted three times with dichloromethane (3 x 10.0ml) to give N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.63g; 82%) as a colourless solid, m.p. 171-176°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

1-{N-[2-(2-Bromophenoxy)phenyl]imino-N-phenylcarbanoyl}piperidine (121)

A solution of N-phenyl,N′-[2-(2-bromophenoxy)]phenyl carbodiimide (114) (0.37g; 0.001mol) in anhydrous ether (7.5ml) was treated with a solution of piperidine (0.085g; 0.001mol) in anhydrous ether (2.5ml) added in a single portion and the mixture then stirred at room temperature, with the exclusion of atmospheric moisture, for 0.5h.

The mixture was rotary evaporated to give a yellow oil which solidified on standing to give 1-{N-[2-(2-bromophenoxy)phenyl]imino-N-phenylcarbanoyl}piperidine (121) as a cream solid (0.43g; 96%), which formed colourless cubes, m.p. 102-103°

(from 40-60° light petroleum-ethanol), ν_{max} 3393 (NH) cm^{-1}, δ_H ($CDCl_3$) 7.56-6.66 (13H, m, ArH), 5.81 (1H, bs, NH) (exch), 3.20 (4H, bs, CH_2) and 1.49 (6H, bs, CH_2);

Found: C, 64.3; H, 5.3; N, 9.3%; m/z (EI ms), 450 (M^+),

$C_{14}H_{12}N_2S$ requires: C, 64.0; H, 5.3; N, 9.3%; M, 450.

The Attempted Reaction of N-Phenyl,N'-[2-(2-bromophenoxy)]phenyl Urea (113) with Phosphoryl chloride in the presence of Triethylamine.

A suspension of N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred under nitrogen was treated with a single portion of triethylamine (0.61g; 0.006mol) then cooled to 0° (ice-salt bath). The mixture was stirred and treated dropwise with phosphoryl chloride (0.34g; 0.0022mol) at such a rate that the reaction temperature was 0-5°, then heated under reflux for 17h.

The cooled solution was filtered to remove triethylamine hydrochloride (0.26g) as a colourless solid, m.p. 243-251°, (lit.[104], 261°). Rotary evaporation of the filtrate afforded a light brown gum (1.6g) whose t.l.c. in hexane-ether over silica showed it to be a complex mixture containing both starting material and the carbodiimide product which was not further investigated.

The Attempted Reaction of N-Phenyl,N'-[2-(2-bromophenoxy)]phenyl Urea (113) with Carbon Tetrachloride and Triphenyl Phosphine in the presence of Triethylamine.

(a) A solution triphenyl phosphine (0.58g; 0.0022mol), carbon tetrachloride (0.30g; 0.002mol) and triethylamine (0.20g; 0.002mol) in anhydrous dichloromethane

(10.0ml) was stirred under nitrogen and treated with N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) added in a single portion and the mixture heated under reflux for 2.5h.

The cooled solution was rotary evaporated to give a brown oily semi-solid (1.9g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded the desired carbodiimide product (114) as a yellow oil, (0.15g; 20%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded unreacted N-phenyl,N′-[2-(2-bromophenoxy)]phenyl urea (113) (0.33g; 45%) as a colourless solid, m.p. 170-176°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded an intractable brown oil (0.73g), which was not further investigated.

(b) Repetition of the reaction as described in (a) before but using 1,2-dichloroethane as solvent and heating under reflux for 17h gave a mixture which was cooled and filtered to remove triethylamine hydrochloride (0.091g) as a colourless solid, m.p. 254-259°, (lit.[104], 261°). The filtrate was rotary evaporated to give a brown oil (1.4g) whose t.l.c. in hexane-ether over silica showed it to be a complex mixture containing both starting material and the carbodiimide product (114), which therefore was not further investigated.

The Attempted Reaction of N-Phenyl,N'-[2-(2-bromophenoxy)]phenyl Urea (113) with Thionyl chloride in the presence of Diisopropylethylamine.

A suspension of N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) in anhydrous 1,2-dichloroethane (8.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) then cooled to 0° (ice-salt bath). The mixture was treated dropwise with thionyl chloride (0.26g; 0.0022mol) at such a rate that the reaction temperature was 0-5°, then heated under reflux for 17h.

The cooled solution was rotary evaporated to give a dark brown oil (1.9g) whose t.l.c. in hexane-ether over silica showed it to be impure starting material (113), and therefore was not further investigated.

N-Phenyl,N'-[2-(2-bromophenoxy)]phenyl Carbodiimide (114)

A suspension of N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.77g; 0.002mol) in anhydrous dichloromethane (15.0ml) was stirred under nitrogen and cooled to 0° (ice-salt bath) then treated with a solution of triethylamine (0.40g; 0.004mol) in anhydrous dichloromethane (2.5ml) added in a single portion. A solution of triphosgene (0.20g; 0.00066mol) in anhydrous dichloromethane (2.5ml) was then added in one portion and the mixture was stirred under reflux for 1.5h. A second portion of triethylamine (0.40g; 0.004mol) in anhydrous dichloromethane (2.5ml) was added, followed by a second portion of triphosgene (0.20g; 0.00066mol) in anhydrous dichloromethane (2.5ml) and the mixture heated under reflux for a further 2.5h.

The cooled solution was rotary evaporated to give a brown semi-solid (1.3g) which was triturated with anhydrous ether to give a cream solid. The solid was washed with water to remove triethylamine hydrochloride leaving N-phenyl,N'-[2-(2-bromophenoxy)]phenyl urea (113) (0.030g; 4%), m.p. 159-165°, identified by comparison (melting point and i.r. spectrum) to an authentic sample prepared before. Rotary evaporation of the ether fraction afforded a brown gum (0.88g) which was extracted three times with anhydrous 60-80° light petroleum (3 x 10.0ml) leaving a mixed fraction as a cream solid (0.22g), m.p. 159-167°, which was not investigated further. The combined light petroleum extracts were rotary evaporated to give the desired carbodiimide product (114) as a yellow oil, (0.65g; 89%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Butyllithium Catalysed Cyclisations of N-Phenyl,N'-[2-(2-bromophenoxy)]phenyl Carbodiimide (114).

(a) A solution of N-phenyl,N'-[2-(2-bromophenoxy)]phenyl carbodiimide (114) (0.74g; 0.002mol) in anhydrous tetrahydrofuran (10.0ml) was stirred under nitrogen and treated dropwise at -78° (dry ice-acetone bath) with a 1.1M solution of s-butyllithium in cyclohexane (1.8ml; 0.002mol). The mixture was then stirred under nitrogen, at -78° (dry ice-acetone bath) for 2h, allowed to warm to room temperature, then stirred for a further 2h at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (20.0ml) then extracted three times with ether (3 x 20.0ml) to give a gummy orange oil (0.64g) which was flash chromatographed over silica.

Elution with hexane-ether (96:4) afforded an unidentified yellow oil (0.19g).

Further elution with hexane-ether (70:30) afforded the dibenzoxazepine (122) (0.20g; 35%) as a colourless solid, m.p. 124-130°, which formed colourless cubes, m.p. 134-135° (from ethanol),ν_{max} 3274 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.34 (1H, bs, NH) (exch), 8.01 (2H, dd J 7.6 and 8.6Hz, ArH), 7.74-7.55 (4H, m, ArH), 7.40-7.29 (3H, m, ArH), and 7.18-6.96 (4H, m, ArH);

Found: C, 79.4; H, 5.2; N, 9.8 %; m/z (EI ms), 286 (MH^+),

$C_{19}H_{14}N_2O$ requires: C, 79.7; H, 4.9; N, 9.8%; M, 286.

Final elution with methanol afforded an intractable orange gum (0.31g) which was not further investigated.

(b) A solution of N-phenyl,N'-[2-(2-bromophenoxy)]phenyl carbodiimide (114) (0.74g; 0.002mol) in anhydrous tetrahydrofuran (10.0ml) was stirred under nitrogen and treated dropwise at -78° (dry ice-acetone bath) with a 1.7M solution of t-butyllithium in pentane (1.2ml; 0.002mol). The mixture was then stirred under nitrogen, at -78° (dry ice-acetone bath) for 2h, allowed to warm to room temperature, then stirred for a further 2h at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (20.0ml) then extracted three times with ether (3 x 10.0ml) to give a brown gum (0.92g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded the dibenzoxazepine (122) (0.27g; 47%) as a light brown solid, m.p. 129-134°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (90:10) through to methanol afforded mixed fractions as oils and gums (0.37g) which were not further investigated.

(c) A solution of N-phenyl,N′-[2-(2-bromophenoxy)]phenyl carbodiimide (114) (0.37g; 0.001mol) in anhydrous tetrahydrofuran (5.0ml) was stirred under nitrogen and treated dropwise at -78° (dry ice-acetone bath) with a 1.4M solution of t-butyllithium in pentane (0.71ml; 0.001mol). The mixture was then stirred under nitrogen, at -78° (dry ice-acetone bath) for 30min.

The mixture was treated with a saturated aqueous solution of ammonium chloride (10.0ml) then extracted three times with ether (3 x 5.0ml) to give a yellow oil (0.38g) which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded the dibenzoxazepine (122) (0.19g; 66%) as a light brown solid, m.p. 127-134°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded only a small amount ofbrown oil (0.043g) which was not further investigated.

N-Methyl,N′-[2-(2-bromophenoxy)]phenyl Urea (119)

A solution of 2-amino-2′-bromodiphenyl ether (101a) (1.3g; 0.005mol) in anhydrous dioxane (12.5ml) was treated in with a solution of methyl isocyanate (0.29g; 0.005mol) in anhydrous dioxane (12.5ml) added in one portion and the mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 4h.

A second portion of methyl isocyanate (0.15g; 0.0025mol) in anhydrous dioxane (6.0ml) was added and the mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for a further 18h.

The mixture was rotary evaporated to give a brown gum (1.5g), whose t.l.c. in hexane-ether showed it to be a mixture of starting materials and one other

component. The mixture was therefore treated with a third portion of methyl isocyanate (0.29g; 0.005mol) in anhydrous dioxane (12.5ml) and the mixture then stirred at room temperature, with the exclusion of atmospheric moisture, for a further 24h.

The mixture was rotary evaporated to give a brown oil (1.9g) which was flash chromatographed over silica

Elution with hexane-ether (90:10) afforded unreacted 2-amino-2′-bromodiphenyl ether (101a) (0.10g; 8%), as a light brown solid, m.p. 48-53°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded N-methyl,N′-[2-(2-bromophenoxy)]phenyl urea (119) as a light brown solid (1.1g; 69%), which formed colourless cubes, m.p. 124-125° (from hexane-toluene),ν_{max} 3314 (NH) and 1685 (CO) cm^{-1}, δ_H ($CDCl_3$) 8.13 (1H, dd J and 8.1 and 1.6Hz, ArH), 7.59 (1H, dd J 7.9 and 1.6Hz, ArH), 7.26-6.86 (5H, m, ArH), 6.72 (1H, dd J 8.1 and 1.5Hz, ArH), 4.98 (1H, d J 4.7Hz, NHMe) (exch) and 2.78 (3H, d J 4.6Hz, NCH_3);

Found: C, 52.4; H, 4.0; N, 8.4 %; m/z (FAB ms), 323 and 321 (MH^+),

$C_{14}H_{13}BrN_2O_2$ requires: C, 52.3; H, 4.1; N, 8.7%; M, 321.

Further elution with methanol afforded a dark brown intractable gum (0.37g) which was not further investigated.

N-Benzyl N′-[2-(2-bromophenoxy)]phenyl Urea (120)

A solution of 2-amino-2′-bromodiphenyl ether (101a) (1.3g; 0.005mol) in anhydrous dioxane (12.5ml) was treated with a solution of benzyl isocyanate (0.67g; 0.005mol) in anhydrous dioxane (12.5ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 4h. A second portion of benzyl isocyanate (0.67g; 0.005mol) in anhydrous dioxane (12.5ml) was added and the mixture was then stirred and heated under reflux, with the exclusion of atmospheric moisture, for a further 17h.

The cooled mixture was rotary evaporated to give a brown oil (2.7g), which was flash chromatographed over silica.

Elution with hexane-ether (60:40) afforded N-benzyl,N′-[2-(2-bromophenoxy)]phenyl urea (120) as a light brown solid (0.91g; 47%), which formed colourless needles, m.p. 138-139° (from ethanol), ν_{max} 3293 (NH) and 1692 (CO) cm^{-1}, δ_H ($CDCl_3$) 8.17 (1H, dd J 8.1 and 1.6Hz, ArH), 7.57 (1H, dd J 7.9 and 1.6Hz, ArH), 7.36-6.83 (10H, m, ArH), 6.68 (1H, dd J 1.5 and 8.1Hz, ArH), 5.41 (1H, t J 5.6 and 5.6Hz, $NHCH_2$) (exch) and 4.35 (2H, d J 5.7Hz, CH_2);

Found: C, 60.1; H, 4.3; N, 6.8 %; m/z (FAB HRMS), 3990543 and 397.0565 (MH^+),

$C_{20}H_{17}BrN_2O_2$ requires: C, 60.5; H, 4.3; N, 7.1%; M, 399.0533 and 397.0552.

Further elution with hexane-ether (60:40) afforded a mixed fraction as a dark brown gum (0.37g) which was not further investigated.

Further elution with methanol afforded 1,3-dibenzyl urea as a brown solid (0.84g; 50%), which formed colourless needles, m.p. 170-172° (from ethanol), ν_{max} 3319

(NH) and 1612 (CO) cm^{-1}, δ_H ($CDCl_3$) 7.36-7.18 (10H, m, ArH), 6.44 (2H, t J 6.0 Hz, NH) and 4.23 (4H, d J 6.0Hz, CH_2);

Found: C, 74.9; H, 6.4; N, 11.6 %; m/z (FAB ms), 241 (MH^+),

$C_{15}H_{12}N_2O$ requires: C, 75.0; H, 6.7; N, 11.7%; M, 240.

The Attempted Reaction of 1-Alkyl-3-arylcarbodiimides with Phosphoryl Chloride in the presence of Diisopropylethylamine.

A suspension of the corresponding urea (0.002mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) and cooled to 0° (ice-salt bath). The mixture was treated dropwise with phosphoryl chloride (0.0022mol) at such a rate that the reaction temperature was 0-5°, then heated under reflux for 17h.

The cooled solution was then rotary evaporated and the residue worked up as described for the individual reactions below.

(i) The reaction with N-methyl,N'-[2-(2-bromophenoxy)]phenyl urea (119) afforded a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (50:50) gave unreacted N-methyl,N'-[2-(2-bromophenoxy)]phenyl urea (119) (99%) as a colourless solid, m.p. 119-125°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded only baseline material which was not further investigated.

(ii) The reaction with N-benzyl,N′-[2-(2-bromophenoxy)]phenyl urea (120) afforded a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (50:50) gave unreacted N-benzyl,N′-[2-(2-bromophenoxy)]phenyl urea (120) (100%) as a colourless solid, m.p. 128-135°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol afforded only baseline material which was not further investigated.

The Attempted Reaction of 1-Alkyl-3-arylcarbodiimides with Triphosgene in the presence of Triethylamine.

A suspension of the corresponding urea (0.002mol) in anhydrous dichloromethane (15.0ml) was stirred under nitrogen and cooled to 0° (ice-salt bath) then treated with a solution of triethylamine (0.004mol) in anhydrous dichloromethane (2.5ml) added in one portion. A solution of triphosgene (0.00066mol) in anhydrous dichloromethane (2.5ml) was then added in one portion and the mixture stirred under reflux for 2h. A second portion of triphosgene (0.00066mol) in anhydrous dichloromethane (2.5ml) was added and the mixture heated under reflux for a further 2h.

(i) The reaction with N-methyl,N′-[2-(2-bromophenoxy)]phenyl urea (119) afforded a yellow semi-solid which was triturated with anhydrous ether to give triethylamine hydrochloride as a cream solid, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The ethereal mother liquor was rotary evaporated to give N-methyl,N′-[2-(2-bromophenoxy)]phenyl urea (119) (70%) as a brown oil, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(ii) The reaction with N-benzyl,N′-[2-(2-bromophenoxy)]phenyl urea (120) afforded a yellow semi-solid which was triturated with anhydrous ether to give triethylamine hydrochloride as a cream solid, identified by comparison (i.r. spectrum) with an authentic sample prepare before.

The ethereal mother liquor was rotary evaporated to give N-benzyl,N′-[2-(2-bromophenoxy)]phenyl urea (120) (58%) as a brown oil, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

3-Azido-2-(2-bromophenoxy)pyridine (123a)

A stirred solution of 3-amino-2-(2-bromophenoxy)pyridine (107a) (3.0g; 0.01mol) in 5M aqueous hydrochloric acid (35.0ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.83g; 0.012mol) in water (7.5ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. A solution of sodium azide (2.1g; 0.033mol) in water (12.0ml) was added dropwise at such a rate that the reaction temperature was <5°, and the mixture then stirred in the melting ice bath for 1h.

The precipitated solid was collected to give the known[41] 3-azido-2-(2-bromophenoxy)pyridine (123a) (2.9g; 91%), as an orange solid, m.p. 70-73°, (lit.[41], 72-74°), ν_{max} 2124 and 2103 (N_3) cm^{-1}.

3-Azido-2-(2-iodophenoxy)pyridine (123b)

3-Amino-2-(2-iodophenoxy)pyridine (107b) (6.3g; 0.02mol) was treated with 5M aqueous hydrochloric acid (200ml) and the mixture warmed gently to form a suspension of 3-amino-2-(2-iodophenoxy)-pyridine hydrochloride. This was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (1.6g; 0.022mol) in water (15.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. A solution of sodium azide (2.0g; 0.03mol) in water (15.0ml) was added dropwise at such a rate that the reaction temperature was <5°, and the mixture then stirred in the melting ice bath for 17h.

The precipitated solid was collected to to give the known[41] 3-azido-2-(2-iodophenoxy)pyridine (123b) (5.3g; 78%), as light brown solid, m.p. 65-72°, (lit.[41], 74-78°), ν_{max} 2125 and 2100 (N_3) cm^{-1}.

The aqueous mother liquor was adjusted to pH 14 by the addition of 2M aqueous sodium hydroxide solution and extracted three times with dichloromethane (3 x 150ml) to afford a mixed fraction as a gummy red solid (1.0g) which was not investigated further.

N-[2-(2-Halogenophenoxy)pyrid-3-yl]trimethoxyphosphinimines.

A solution of the corresponding 3-azido-2-aryloxypyridine derivative (123) (0.01mol) in anhydrous 1,2-dimethoxyethane (50.0ml) was stirred and treated at room temperature with a solution of trimethylphosphite (0.013mol) in anhydrous 1,2-dimethoxyethane (25.0ml) added in one portion. The mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h then worked up as described for the individual reactions below.

(i) The mixture from the reaction with 3-azido-2-(2-bromophenoxy)pyridine (123a) was rotary evaporated to give the known[41] phosphinimine derivative (124a) (75%), as a light brown solid, 129-136° (lit.[41], 134-137°), δ_H ($CDCl_3$) 7.62-7.53 (2H, m, ArH), 7.32-7.23 (2H, m, ArH), 7.05-6.98 (2H, m, ArH) 6.90-6.83 (1H, m, ArH) and 3.77 (9H, d J 11.5Hz, $N=P(OCH_3)_3$).

(ii) The mixture from the reaction with 3-azido-2-(2-iodophenoxy)pyridine (123b) was filtered to give the known[41] phosphinimine derivative (124b) (94%), as a colourless solid, 153-158° (lit.[41], 154-159°), δ_H ($CDCl_3$) 7.82 (1H, dd J 7.9 and 1.6Hz, ArH), 7.6 (1H, dd J 2.7 and 1.2Hz, ArH), 7.59-7.23 (2H, m, ArH) 6.94-6.83 (3H, m, ArH) and 3.75 (9H, d J 11.4Hz, $N=P(OCH_3)_3$).

The Reaction the of Phosphinimine Derivatives with Phenyl Isocyanate.

(a) A solution of the corresponding phosphinimine derivative (124a) (1.5g; 0.004mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was stirred at room temperature and treated with a solution of phenyl isocyanate (0.52g; 0.0044mol) in anhydrous 1,2-dimethoxyethane (10.0ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 4h.

Rotary evaporation of the mixture afforded a red oil which was dissolved in ether (25.0ml) and the solution washed three times with water (3 x 10.0ml). Rotary evaporation of the combined ether extracts afforded a waxy orange solid (1.0g) which was triturated with ether to afford the carbodiimide product (125) as a colourless solid (0.63g; 43%), which formed colourless cubes, m.p. 84-86° (from

hexane-toluene), ν_{max} 2139 and 2090 (N=C=N) cm^{-1}, δ_H ($CDCl_3$) 7.89-7.79 (1H, m, ArH), and 7.55-6.91 (11H, m, ArH);

Found: C, 58.7; H, 3.4; N, 11.4%; m/z (FAB ms), 368 and 366 (MH^+)

$C_{18}H_{12}BrN_2O$ requires: C, 59.0; H, 3.4; N, 11.5%; M, 383.

Rotary evaporation of the ether mother liquor afforded a mixed fraction as an orange semi-solid (0.24g), which was not further investigated.

(b) A solution of the corresponding phosphinimine derivative (124b) (1.7g; 0.004mol) in anhydrous dichloromethane (20.0ml) was stirred at room temperature and treated with a solution of phenyl isocyanate (0.52g; 0.0044mol) in anhydrous dichloromethane (10.0ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 23h.

Rotary evaporation of the mixture afforded a red oil which was dissolved in ether (20.0ml) and the solution washed three times with water (3 x 10.0ml). Rotary evaporation of the ether layer afforded a colourless waxy solid (1.3g) whose t.l.c. in hexane-ether over silica showed it to be an unresolvable mixture which therefore was not further investigated.

N-Phenyl,N'-[2-(2-bromophenoxy)]pyridyl Urea (128)

A solution of 3-amino-2-(2-bromophenoxy)pyridine (107a) (10.6g; 0.04mol) in anhydrous dioxane (100ml) was treated with a solution of phenyl isocyanate (4.8g; 0.04mol) in anhydrous dioxane (100ml) added in one portion and the mixture then stirred at room temperature for 2h.

Rotary evaporation gave a gummy brown solid (20.1g), which was triturated with hexane-ether to give N-phenyl,N′-[2-(2-bromophenoxy)]pyridyl urea (128) as a brown solid, (12.5g; 81%), which formed grey microcrystals, m.p. 191-194° (from toluene), ν_{max} 3332 (NH) and 1660 (C=0) cm^{-1}, δ_H ($CDCl_3$) 9.41 (1H, bs, NH) (exch), 8.76 (1H, bs, NH) (exch), 8.59 (1H, dd J 8.0 and 1.5Hz, ArH), 7.75 (1H, dd J 9.0 and 1.3Hz, ArH), 7.63 (1H, dd J 4.8 and 1.5Hz, ArH), 7.50-7.21 (7H, m, ArH) and 7.11-7.03 (2H, m, ArH);

Found: C, 56.6; H, 3.8; N, 10.7%; m/z (FAB ms), 385 and 383(MH^+)

$C_{18}H_{14}BrN_3O_2$ requires: C, 56.3; H, 3.7; N, 10.9%; M, 384.

Rotary evaporation of the hexane-ether fraction afforded a brown gum (5.1g) which was not further investigated.

N-Phenyl,N′-[2-(2-bromophenoxy)]pyridyl Carbodiimide (125)

A suspension of N-phenyl,N′-[2-(2-bromophenoxy)]pyridyl urea (128) (0.77g; 0.002mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) and cooled to 0° (ice-salt bath). The mixture was then treated dropwise with stirring with phosphoryl chloride (0.34g; 0.0022mol) at such a rate that the reaction temperature was 0-5°, then heated under reflux for 17h.

The cooled solution was rotary evaporated to give a dark brown oil (1.6g) which was extracted six times with anhydrous 60-80° light petroleum (6 x 10.0ml) leaving a dark brown gum (1.1g), which was not further investigated. The combined petroleum extracts were rotary evaporated to give N-phenyl,N′-[2-(2-bromophenoxy)]pyridyl

carbodiimide (125) (0.57g; 78%) as a pale yellow solid m.p. 78-81° (from hexane), identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before, ν_{max} 2139 and 2090 (N=C=N) cm^{-1}.

The Attempted Magnesium Catalysed Cyclisation of N-Phenyl,N'-[2-(2-bromophenoxy)]pyridyl Carbodiimide (125).

A solution of N-phenyl,N'-[2-(2-bromophenoxy)]pyridyl carbodiimide (125) (0.67g; 0.002mol) in anhydrous ether (20.0ml) was stirred and treated with magnesium turnings (0.048g; 0.002mol) and a single crystal of iodine. The mixture was stirred and heated to 45° for 1h, then under reflux for a further 3.5h.

The mixture was allowed to cool to room temperature, treated with 2M aqueous hydrochloric acid solution (5.0ml) added in one portion then stirred for 1h at room temperature. The mixture was extracted three times with dichloromethane (3 x 5.0ml) to give an orange-red gum (0.73g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded unreacted N-phenyl,N'-[2-(2-bromophenoxy)]pyridyl carbodiimide (125) (0.34g; 49%) as a waxy colourless solid, which was identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (90:10) afforded a mixed fraction (0.040g) as a waxy colourless solid, which was not further investigated.

Further elution with hexane-ether (85:15) afforded N-phenyl,N'-[2-(2-bromophenoxy)]pyridyl urea (128) (0.29g; 43%), m.p. 138-146°, which was identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded a brown foam (0.050g) which was not further investigated.

6-N-Phenylaminopyrido[2,3-b][1,4]benzoxazepine (126).

A solution of N-phenyl,N'-[2-(2-bromophenoxy)]pyridyl carbodiimide (125) (1.8g; 0.005mol) in anhydrous tetrahydrofuran (25.0ml) was stirred and treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.4M solution of t-butyllithium in pentane (3.6ml; 0.005mol). The mixture was then stirred at -78° (dry ice acetone bath) for 30min.

The mixture was treated with a saturated aqueous solution of ammonium chloride (50.0ml) then extracted three times with ether (3 x 36.0ml) to give an orange oil (1.6g) which was flash chromatographed over silica.

Elution with hexane-ether (70:30) afforded the pyridobenzoxazepine (126) a brown solid (0.22g), which formed light brown crystals, m.p.173-176° (from acetic acid), ν_{max} 3034 (NH) cm^{-1}, δ_H [$(CD_3)_2S=O$] 7.93-6.65 (12H, m, ArH);

Found: m/z (EI HRMS), 288.1134 (M^+),

$C_{18}H_{13}N_3O$ requires: M, 288.1137.

Elution with hexane-ether (60:40) through ether to methanol afforded only oils and gums (1.1g) which yielded no identifiable material.

2-Nitrodiphenyl sulphide (130a)

A suspension of sodium hydride (2.3g; 0.11mol) in anhydrous dimethylformamide (20.0ml) was vigorously stirred and treated at 0-10° (ice bath) with a solution of thiophenol (129a) (11.0g; 0.1mol) in anhydrous dimethylformamide (15.0ml) added in several portions. The mixture was then stirred at room temperature with the

exclusion of atmospheric moisture for 15min. A solution of 2-fluoronitrobenzene (61) (14.1g; 0.1mol) in anhydrous dimethylformamide (15.0ml) was then added in one portion and the mixture was stirred 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The mixture was treated with water (50.0ml) and rotary evaporated to give a brown residue which was treated with water (100ml) and extracted three times with dichloromethane (3 x 100ml) to give the known[95] 2-nitrodiphenyl sulphide (130a) as a yellow solid (21.2g; 92%), m.p. 69-74° (lit.[95], 77°).

2-Aminodiphenyl sulphide (131a)

A solution of 2-nitrodiphenyl sulphide (130a) (23.1g; 0.1mol) in tetrahydrofuran (1000ml) was stirred and treated with a solution of stannous chloride dihydrate (1000g) in 2M aqueous hydrochloric acid (1000ml) added in one portion and the mixture heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was then extracted three times with ether (3 x 750ml) to give a brown oil (16.1g) which was bulb-to-bulb distilled to give the known[96] 2-aminodiphenyl sulphide (131a) as a yellow oil (15.6g; 78%), ν_{max} 3466 and 3370 (NH_2) cm^{-1}.

2-Isothiocyanatodiphenyl sulphide (132a)

A solution of 2-aminodiphenyl sulphide (131a) (8.0g; 0.04mol) in glacial acetic acid (180ml) was stirred and treated with a 1:1 mixture of concentrated hydrochloric acid

and water (60.0ml) added in one portion then dropwise at room temperature with a solution of thiophosgene (9.6g; 0.08mol) in glacial acetic acid (20.0ml). The mixture was then stirred at room temperature for 2h.

The mixture was treated with water (180ml) and extracted three times with dichloromethane (3 x 360ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 180ml) then rotary evaporated to give 2-isothiocyanatodiphenyl sulphide (132a) as a yellow oil (8.7g; 100%), ν_{max} 2059 (N=C=S) cm^{-1};

Found: m/z (EI HRMS), 243.0181 (M^+),

$C_{13}H_9NS_2$ requires: M, 243.0176.

Lewis Acid Catalysed Cyclisations of 2-Isothiocyanatodiphenyl sulphide (132a)

(a) A solution of 2-isothiocyanatodiphenyl sulphide (132a) (1.2g; 0.005mol) in anhydrous dichloromethane (5.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of aluminium tribromide (2.7g; 0.01mol) in anhydrous dichloromethane (12.5ml) then stirred at room temperature for 24h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (45.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 25.0ml) to afford an orange semi-solid (1.4g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) through to hexane-ether (95:5) afforded mixed fractions as red oils whose i.r. and. t.l.c. in hexane-ether over silica showed them to consist mainly of 2-isothiocyanatodiphenyl sulphide (132a).

Further elution with hexane-ether (95:5) afforded dibenzo[b,f][1,4]thiazepine-11(10H)-thione (133) as a yellow solid (0.28g; 23%), m.p. 235-242° (from acetic acid), ν_{max} 3136 (NH) and 1585 (CS) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.80 (1H, bs, NH) (exch), 7.92-7.77 (1H, m, ArH) and 7.64-7.11 (7H, m, ArH);

Found: m/z (EI HRMS), 243.0181 (M^+),

$C_{13}H_9NS_2$ requires: M, 243.0176.

Further elution with methanol gave only an intractable black solid (0.066g), m.p. 140-150° (slow decomposition) which was not further investigated.

(b) The reaction was repeated as described in (a) before, but with heating under reflux for 21h.

The cooled mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (40.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 25.0ml) to afford a dark brown viscous oil (1.6g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a viscous orange oil (0.30g), whose i.r. and. t.l.c. in hexane-ether over silica showed it to be mainly unreacted 2-isothiocyanatodiphenyl sulphide (132a).

Further elution with hexane-ether (95:5) through to methanol afforded only mixed fractions as a red oils and gums (0.84g) which were not further investigated.

(c) A suspension of aluminium trichloride (1.3g; 0.01mol) in anhydrous dichloromethane (50.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of 2-isothiocyanatodiphenyl sulphide (132a) (1.2g;

0.005mol) in anhydrous dichloromethane (25.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (80.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 75.0ml) to afford a yellow solid (1.1g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded unreacted 2-isothiocyanatodiphenyl sulphide (132a) as a brown oil (0.19g; 15%) identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (90:10) afforded dibenzo[b,f][1,4]thiazepine-11(10H)-thione (133) as a yellow solid (0.71g; 59%), m.p. 204-210°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with methanol gave only a small amount of an intractable brown oil (0.080g) which was not further investigated.

2-Bromo-2′-nitrodiphenyl sulphide (130b)

A suspension of sodium hydride (2.4g; 0.11mol) in anhydrous dimethylformamide (20.0ml) was vigorously stirred and treated at 0-10° (ice bath) with a solution of 2-bromothiophenol (129b) (18.9g; 0.1mol) in anhydrous dimethylformamide (15.0ml) added in several portions then stirred at room temperature with the exclusion of atmospheric moisture for 15min. A solution of 2-fluoronitrobenzene (61) (14.1g; 0.1mol) in anhydrous dimethylformamide (15.0ml) was added in one portion and the

mixture was stirred at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (50.0ml) affording the known[97] 2-bromo-2′-nitrodiphenyl sulphide (130b) as a yellow solid (28.8g; 92%), m.p. 109-116° (lit.[97], 116-117°).

The Catalytic Reduction of 2-Bromo-2′-nitrodiphenyl Sulphide (130b) over Raney Nickel

(a) A solution of 2-bromo-2′-nitrodiphenyl sulphide (130b) (6.2g; 0.02mol) in glacial acetic acid (350ml) was hydrogenated over Raney nickel catalyst (3.1ml of a 50% slurry in water) at room temperature and atmospheric pressure for 10h during which time 1436ml of hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give a green glass which was treated with 10% aqueous sodium hydrogen carbonate solution (200ml). The mixture was filtered to remove inorganic material then extracted twice with dichloromethane (2 x 200ml) to afford a yellow-brown oil (5.3g) which was flash chromatographed over silica.

Elution with hexane-dichloromethane (80:20) afforded the known[97] 2-amino-2′-bromodiphenyl sulphide (131b) as a pale yellow solid (3.4g; 61%), m.p. 61-65° (lit.[97], 62-63°).

Final elution with methanol afforded only an intractable brown gum (1.6g) which was not further investigated.

(b) A solution of 2-bromo-2′-nitrodiphenyl sulphide (130b) (21.7g; 0.07mol) in dimethylformamide (140ml) was hydrogenated over Raney nickel catalyst (11.6ml of a 50% slurry in water) at room temperature and atmospheric pressure for 13h during which time 5100ml of hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give a brown oil which was treated with water (200ml) then extracted three times with dichloromethane (3 x 200ml) to afford a brown oil (19.6g) which was flash chromatographed over silica.

Elution with hexane-dichloromethane (95:5) afforded a brown oil (19.2g) whose t.l.c. in hexane-dichloromethane over silica showed it to be a mixed fraction containing unreacted starting material (130b) and 2-amino-2′-bromodiphenyl sulphide (131b).

Further elution with dichloromethane through to methanol afforded only intractable brown oils (0.33g) which were not further investigated.

The initial mixed fraction was dissolved in dimethylformamide (100ml) and hydrogenated over Raney nickel catalyst (11.6ml of a 50% slurry in water) at room temperature and atmospheric pressure for 6h during which time 2123ml of hydrogen was absorbed and uptake had ceased.

The catalyst was removed by filtration through celite, and the filtrate rotary evaporated to give a brown oil which was treated with water (200ml) then extracted three times with dichloromethane (3 x 200ml) to afford a brown oil (14.3g) which was flash chromatographed over silica.

Elution with hexane-dichloromethane (90:10) afforded the hydrazo compound (134) (0.60g) as a yellow solid, m.p. 141-146°, which formed cream needles, m.p. 192-195°

(from dimethylformamide-acetic acid), ν_{max} 3331 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.64-7.06 (10H, m, ArH), 7.53 (2H, bs, NH) (exch) and 6.83-6.59 (6H, m, ArH);

Found: C, 51.5; H, 3.2; N, 4.9%; m/z (EI ms), 558 (M^+),

$C_{24}H_{18}Br_2N_2S_2$ requires: C,51.6; H, 3.4; N, 5.0%; M, 558.

Further elution with hexane-dichloromethane (90:10) afforded a mixed fraction as a red oil (2.0g), which was not further investigated.

Further elution with hexane-dichloromethane (90:10) afforded 2-amino-2'-bromodiphenyl sulphide (131b) as a red oil (9.5g; 48%), ν_{max} 3470, 3371 and 3057 (NH_2) cm^{-1}, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded only an intractable brown gum (1.7g) which was not further investigated.

The celite pad was refluxed in dimethylformamide and the mixture was hot filtered. The filtrate was rotary evaporated to give red oil (2.7g) which was flash chromatographed over silica.

Elution with hexane-dichloromethane (90:10) afforded the hydrazo compound (134) (0.18g) as a red solid, m.p. 139-144°, identified by comparison (melting point and i.r. spectrum) with the first crop.

Further elution with hexane-dichloromethane (80:20) afforded the azoxy compound (135) as a yellow solid (2.5g), m.p. 128-132°, which formed orange plates, m.p. 137-138° (from acetic acid), δ_H [$(CD_3)_2SO$] 8.04-6.99 (16H, m, ArH);

Found: C, 50.6; H, 3.1; N, 4.8%; m/z (EI ms), 572 (M^+),

$C_{24}H_{16}Br_2N_2S_2$ requires: C, 50.4; H, 2.8; N, 4.9%; M, 572.

Final elution with methanol afforded only a small amount of a brown gum (0.032g) which was not further investigated.

2-Bromo-2′-isothiocyanatodiphenyl sulphide (132b)

A solution of 2-amino-2′-bromodiphenyl sulphide (131b) (2.8g; 0.01mol) in glacial acetic acid (30.0ml) was stirred and treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (10.0ml) added in one portion then dropwise at room temperature with a solution of thiophosgene (2.3g; 0.02mol) in glacial acetic acid (10.0ml). The mixture was then stirred at room temperature for 2h. The mixture was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 80.0ml). The combined dichloromethane extracts were washed with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 40.0ml) then rotary evaporated to give a brown oil (2.6g) which was flash chromatographed over silica. Elution with hexane-dichloromethane (99:1) afforded 2-bromo-2′-isothiocyanatodiphenyl sulphide (132b) as a yellow oil (2.2g; 68%), b.p. 212°/1.6mmHg, ν_{max} 2047 (N=C=S)cm^{-1};

Found: C, 48.7; H, 2.6; N, 4.0%; m/z (EI ms), 323 and 321 (M^+), 242 (M^+-Br),

$C_{13}H_8BrNS_2$ requires: C, 48.5; H, 2.5; N, 4.4%; M, 322.

Further elution with hexane-dichloromethane (1:1) through to methanol afforded only intractable gums and oils (0.23g) which were not further investigated.

s-Butyllithium Catalysed Cyclisation Reactions of 2-Bromo-2'-isothiocyanatodiphenyl Sulphide (132b).

(a) A solution of 2-bromo-2'-isothiocyanatodiphenyl sulphide (132b) (0.64g; 0.002mol) in anhydrous tetrahydrofuran (10.0ml) was stirred and treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.1M solution of s-butyllithium in cyclohexane (1.8ml; 0.002mol). The mixture was then stirred, at -78° (dry ice-acetone bath) under nitrogen for 2h, allowed to warm to room temperature, then stirred for a further 2h at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (20.0ml) then extracted three times with ether (3 x 20.0ml) to give a brown oil (0.67g) which was triturated with hexane-ether to give dibenzo[b,f][1,4]thiazepine-11(10H)-thione (133) (0.056g; 12%), as a yellow solid, m.p. 235-242°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

The hexane-ether washings were rotary evaporated to give a brown oil (0.56g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) through ether to methanol afforded only mixed fractions as oils (0.27g) which were not further investigated.

(b) Repetition of the reaction described in (a) before, but using a 0.93M solution of s-butyllithium in cyclohexane (4.3ml; 0.004mol) gave a yellow semi-solid (0.56g) which was triturated with hexane-ether to give dibenzo[b,f][1,4]thiazepine-11(10H)-thione (133) (0.22g; 45%), as a yellow solid, m.p. 210-213°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The hexane-ether washings were rotary evaporated to give a brown oil (0.30g), which was shown by t.l.c. in hexane-ether over silica to be impure isothiocyanate starting material (132b) and therefore was not further investigated.

N-[2-(2-Bromothiophenoxy)phenyl]-N'-phenyl urea (136)

A solution of 2-amino-2'-bromodiphenyl sulphide (131b) (5.6g; 0.02mol) in anhydrous 1,4-dioxane (50.0ml) was stirred and treated with a solution of phenyl isocyanate (2.4g; 0.02mol) in anhydrous 1,4-dioxane (50.0ml) added in one portion then stirred at room temperature for 2h.

The mixture was rotary evaporated to give an orange oil (7.4g), which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded a mixed fraction as a yellow oil (0.52g), which was not investigated further.

Further elution with hexane-ether (70:30) afforded unreacted 2-amino-2'-bromodiphenyl sulphide (131b) as a red oil (1.7g; 30%), identical (i.r. spectrum) to an authentic sample prepared before.

Elution with hexane-ether (25:75) afforded the urea product (136) as a pale yellow solid, (5.1g; 64%), which formed colourless cubes, m.p. 144-146° (from hexane-ethanol), ν_{max} 3303 (NH) and 1655 (C=0) cm^{-1}, δ_H ($CDCl_3$) 8.38 (1H, dd J 8.4 and 1.3Hz, ArH), 7.78 (1H, s, ArH), 7.54-7.40 (2H, m, ArH), 7.33-6.91 (8H, m, ArH), and 6.49 (1H, dd J 7.8 and 1.8Hz, ArH);

Found: C, 57.2; H, 4.1; N, 7.1%; m/z (EI ms), 400 and 398 (M^+),

$C_{19}H_{15}BrN_2OS$ requires: C, 57.1; H, 3.8; N, 7.0%; M, 399.

The Attempted Reaction of N-[2-(2-Bromothiophenoxy)phenyl]-N'-phenyl urea(136) with Diisopropylethylamine in the presence of Phosphoryl Chloride.

(a) A suspension of the urea (136) (0.80g; 0.002mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred under nitrogen and treated with a single portion of diisopropylethylamine (0.77g; 0.006mol) and cooled to 0° (ice-salt bath). The mixture was treated dropwise with phosphoryl chloride (0.46g; 0.003mol) at such a rate that the reaction temperature was 0-5° then heated under reflux for 17h.

The cooled mixture was rotary evaporated to give a brown oil (2.1g) which was flash chromatographed over silica.

Elution with hexane-ether (50:50) afforded the urea starting material (136) (0.51g; 60%) as a colourless solid, m.p. 136-142°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded an orange oil (0.50g), whose t.l.c. in hexane-ether over silica showed it to be baseline material which was not further investigated.

(b) Repetition of the reaction as described in (a) before but using 1.1 equivalents of phosphoryl chloride (0.0022mol) gave a brown oil (1.8g) which was extracted five times with 60-80° light petroleum, leaving a brown gum (0.91g), whose t.l.c. in hexane-ether over silica showed it to be mainly the urea starting material (136) and baseline material, and was not further investigated.

The combined petroleum extracts were rotary evaporated to give an unidentified light brown oil (0.93g).

2-Nitrodiphenylamine (140)

A mixture of 2-fluoronitrobenzene (61) (28.2g; 0.2mol), aniline (139) (37.2g; 0.4mol) and anhydrous potassium fluoride (11.6g; 0.2mol) was stirred vigorously and heated at 180° (oil bath), with the exclusion of atmospheric moisture, for 48h.

The resulting orange-red semi-solid was treated with water (500ml) and extracted three times with dichloromethane (3 x 200ml). The combined dichloromethane extracts were washed twice with 2M aqueous hydrochloric acid (2 x 400ml), twice with of water (2 x 400ml) and the combined aqueous fractions were then extracted a further twice with dichloromethane (2 x 100ml). Rotary evaporation of the total combined dichloromethane extracts gave the known[98] 2-nitrodiphenylamine (140) as a red crystalline solid (42.3g; 99%), m.p. 74-75° (lit.[98], 75°).

N-Methyl 2-nitrodiphenylamine (141)

A vigorously stirred suspension of sodium hydride (5.4g; 0.22mol) in anhydrous dimethylformamide (200ml) was treated at room temperature with a solution of 2-nitrodiphenylamine (140) (42.0g; 0.2mol) in anhydrous dimethylformamide (400ml) added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture for, 15min. A solution of dimethyl sulphate (100g; 0.8mol) in anhydrous dimethylformamide (400ml) was added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The mixture was treated with concentrated ammonia (40.0ml) and water (80.0ml) and stirred at room temperature for 2h. Rotary evaporation gave a red oily residue which was treated with water (100ml) and extracted three times dichloromethane (3 x

50.0ml) to give the known[99] N-methyl 2-nitrodiphenylamine (141a) as a red oil (43.0g; 94%), ν_{max} 1524 and 1356 (NO_2) cm^{-1}.[99]

N-Benzyl 2-nitrodiphenylamine (141b)

A vigorously stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (50.0ml) was treated at 0-10° (ice bath) with a solution of 2-nitrodiphenylamine (140) (21.4g; 0.1mol) in anhydrous dimethylformamide (100ml) added in several portions and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of benzyl bromide (17.0g; 0.1mol) in anhydrous dimethylformamide (50.0ml) was added in several portions and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 20h.

The resulting mixture was diluted with water (100ml) and rotary evaporated to give a brown residue which was treated with water (600ml) and extracted three times with dichloromethane (3 x 200ml) to give the known[83] N-benzyl 2-nitrodiphenylamine (141b) as an orange-red solid (30.8g; 100%), m.p. 105-108° (lit.[83], 106-108°).

N-(4-Toluenesulphonyl) 2-nitrodiphenylamine (141c)

A vigorously stirred suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (40.0ml) was treated dropwise at 0-10° (ice bath) with a solution of 2-nitrodiphenylamine (140) (21.4g; 0.1mol) in anhydrous dimethylformamide (100ml) and the mixture stirred at room temperature with the exclusion of atmospheric moisture for 15 min. A solution of 4-toluenesulphonyl chloride (38.2g; 0.2mol) in anhydrous dimethylformamide (100ml) was then added in one portion and

the mixture was stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 24h.

The resulting mixture was treated with water (100ml) and rotary evaporated to give a brown residue which was treated with water (200ml) and extracted three times with dichloromethane (3 x 200ml) to give a dark brown oil (38.0g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded unreacted 2-nitrodiphenylamine (140) as a red solid (6.0g; 28%), m.p. 73-77°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (85:15) afforded a mixed fraction as an orange solid (2.9g) which was not further investigated.

Further elution with hexane-ether (75:25) afforded the known[83] N-(4-toluenesulphonyl) 2-nitrodiphenylamine (141c) as a brown solid (13.2g; 50%), m.p. 120-125° (lit.[83], 123-125°).

N-Ethoxycarbonyl 2-nitrodiphenylamine (149a)

A vigorously stirred suspension of sodium hydride (1.3g; 0.055mol) in anhydrous dimethylformamide (25.0ml) was treated at 0-10° (ice bath) with a solution of 2-nitrodiphenylamine (140) (10.7g; 0.05mol) in anhydrous dimethylformamide (50.0ml) added in several portions and the mixture stirred at room temperature with the exclusion of atmospheric moisture for 3h. A solution of ethyl chloroformate (6.0g; 0.055mol) in anhydrous dimethylformamide (25.0ml) was added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min.

The resulting mixture was treated with water (15.0ml) and rotary evaporated to give a brown residue which was treated with water (100ml) and extracted four times with dichloromethane (4 x 25.0ml) to give a dark brown oil (16.1g) which was flash chromatographed over silica.

Elution with hexane-ether (97:3) afforded unreacted 2-nitrodiphenylamine (140) as a red solid (1.5g; 14%), m.p. 71-76°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (70:30) afforded the known[101] N-ethoxycarbonyl 2-nitrodiphenylamine (149a) as a pale yellow solid (11.4g; 93%), m.p. 51-58° (lit.[101], 56-58°).

2-Aminodiphenylamine Derivatives

(a) A stirred solution of the 2-nitrodiphenylamine derivative (0.1mol) in tetrahydrofuran (500ml) was treated with a solution of stannous chloride dihydrate (100g; 0.44mol) in 2M aqueous hydrochloric acid (500ml) and the mixture was heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution, then concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was extracted three times with ether (3 x 500ml) and the combined organic extracts were rotary evaporated to give the 2-aminodiphenylamine derivative.

(i) N-Methyl 2-nitrodiphenylamine (141a) afforded the known[99] N-methyl 2-aminodiphenylamine (57) as a brown oil (96%), ν_{max} 3461, 3368 and 3026 (NH_2) cm^{-1}.[99]

(ii) N-Benzyl 2-nitrodiphenylamine (141b) afforded the known[83] N-benzyl 2-aminodiphenylamine (142) as a yellow solid (100%), m.p. 117-119° (lit.[83], 118-119°).

(iii)N-(4-Toluenesulphonyl) 2-nitrodiphenylamine (141c) afforded the known[83] N-(4-toluenesulphonyl) 2-aminodiphenylamine (143) as a pink solid (1.3g; 78%), m.p. 129-135° (lit.[83], 137-138°).

(b) Repetition of the reaction described in (a)(ii) before, but with stirring at room temperature for 18h afforded an orange solid which was crystallised from ethanol to afford N-benzyl 2-aminodiphenylamine (142) as a yellow solid (10.0g; 91%), m.p. 117-119° (lit.[83], 118-119°).

Rotary evaporation of the ethanolic filtrate gave a mixed fraction as a red semi-solid (0.81g) which was not further investigated.

N-Ethoxycarbonyl 2-aminodiphenylamine (150a)

A solution of N-ethoxycarbonyl 2-nitrodiphenylamine (149a) (4.3g; 0.015mol) in ethanol (75.0ml) was hydrogenated over 10% palladium-on-charcoal (0.43g) at room temperature and atmospheric pressure for 1h during which time 1174ml of hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate rotary evaporated to give the known[101] N-ethoxycarbonyl 2-aminodiphenylamine (150a) as a pale yellow solid (3.8g; 100%), m.p. 86-90° (lit.[101], 87-90°).

2-Isothiocyanatodiphenylamine Derivatives

(a) A solution of the corresponding 2-aminodiphenylamine derivative (0.05mol) in glacial acetic acid (170ml) was stirred and treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (50.0ml). The mixture was treated dropwise at room temperature with a solution of thiophosgene (11.5g; 0.1mol) in glacial acetic acid (30.0ml) and the mixture then stirred at room temperature for 2h. The mixture was diluted with water (200ml) and extracted three times with dichloromethane (3 x 400ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 100ml) then dried and rotary evaporated and the residue further worked up as described for the individual reactions below.

(i) N-Methyl 2-aminodiphenylamine (57) afforded a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded the isothiocyanate (144a) as a yellow oil (82%), ν_{max} 2110 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.45-6.65 (9H, m, ArH) and 3.28 (3H, s, CH_3);

Found: C, 69.8; H, 5.1; N, 11.4%; m/z (Thermospray ms), 241 (MH^+),

$C_{14}H_{12}N_2S$ requires: C, 70.0; H, 5.0; N, 11.7%; M, 240.

Further elution with methanol gave an intractable black gum (2.1g) which was not further investigated.

(ii) N-Benzyl 2-aminodiphenylamine (142) gave a brown oil which was flash chromatographed over silica.

Elution with hexane-ethyl acetate (99:1) gave N-benzyl 2-isothiocyanatodiphenylamine (144b) as an orange oil (14%), b.p. 178°/0.15mmHg, ν_{max} 2138 and 2105 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.82 (1H, dt J 8.0, 0.8 and 0.8Hz, ArH), 7.61-7.12 (13H, m, ArH) and 4.67 (2H, s, CH_2);

Found: C, 75.5; H, 5.2; N, 8.6%; m/z (EI ms), 316 (M^+),

$C_{20}H_{16}N_2S$ requires: C, 75.9; H, 5.1; N, 8.9%; M, 316.

Elution with hexane-ethyl acetate (70:30) gave N-benzyl 2-aminodiphenylamine (142) as an orange solid (30%), m.p. 116-118°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Final elution with hexane-ethyl acetate (60:40) through to methanol gave only mixed fractions (1.3g) which afforded no identifiable material.

(iii) N-(4-Toluenesulphonyl) 2-aminodiphenylamine (143) gave the isothiocyanate (144c) as a pale green solid, (0.80g; 100%), which formed light brown crystals, m.p. 98-99° (from ethanol), ν_{max} 2114 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.65-7.21 (13H, m, ArH) and 2.42 (3H, s, CH_3);

Found: C, 63.1; H, 4.1; N, 7.6%; m/z (thermospray ms), 398 (MNH_4^+) and 381 (MH^+),

$C_{20}H_{16}N_2O_2S_2$ requires: C, 63.1; H, 4.2; N, 7.4%; M, 380.

(iv)N-Ethoxycarbonyl 2-aminodiphenylamine (150a) gave the isothiocyanate (151a) as a light brown solid (3.0g; 100%), which formed light brown cubes, m.p. 56-57° (from ethanol), ν_{max} 2070 (N=C=S) and 1713 (CO) cm^{-1}, δ_H ($CDCl_3$) 7.38-7.16 (9H, m, ArH), 4.26 (2H, q J 7.0Hz, CH_2) and 1.26 (3H, t J 7.1 Hz, CH_3);

Found: C, 64.0; H, 4.8; N, 9.2%; m/z (EI HRMS), 298.0784 (M^+),

$C_{16}H_{14}N_2O_2S$ requires: C, 64,4; H, 4.7; N, 9.4%; M, 298.0776.

(b) A solution of N-benzyl 2-aminodiphenylamine (142) (2.7g; 0.01mol) in glacial acetic acid (40.0ml) was stirred and treated with a 1:1 mixture of concentrated hydrochloric acid and water (5.0ml) added in one portion. The resulting mixture was treated dropwise at room temperature with a solution of thiophosgene (2.3g; 0.02mol) in glacial acetic acid (5.0ml) and the mixture then stirred at room temperature for 24h. The mixture was diluted with water (20.0ml) and extracted three times with dichloromethane (3 x 20.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml) then dried and rotary evaporated to give a red oil (2.1g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) gave an unidentified orange oil (0.37g) which was not further investigated.

Further elution with hexane-ether (99:1) afforded N-benzyl 2-isothiocyanatodiphenylamine (144b) as a yellow oil (0.75g; 24%), identified by comparison (i.r. spectrum and t.l.c. in hexane-ether over silica) with an authentic sample prepared before.

Further elution with ether through to methanol gave only mixed fractions as oils (0.36g) which afforded no identifiable material.

(c) Repetition of the reaction described in (a)(ii) before but with heating at 50° for 2h afforded a dark red solution which was diluted with water (20.0ml) then extracted three times with dichloromethane (3 x 40.0ml). The combined organic extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml) then dried and rotary evaporated to give impure N-benzyl 2-aminodiphenylamine (144b) as a red oil (2.2g) identified by comparison (i.r. spectrum and t.l.c. in hexane-ether over silica) with an authentic sample prepared before.

5-Methyldibenzo[b,f][1,4]diazepine-11(10H)-thione (58)

A stirred suspension of aluminium trichloride (5.2g; 0.04mol) in anhydrous dichloromethane (80.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-methyl 2-isothiocyanatodiphenylamine (144a) (4.8g; 0.02mol) in anhydrous dichloromethane (40.0ml) and the mixture was then stirred at room temperature for 24h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (140ml), stirred at room temperature for 15min then extracted four times with dichloromethane (4 x 120ml) to afford the known[58] dibenzodiazepinethione (58) (4.7g; 97%) which formed yellow crystals, m.p. 219-222° (lit.[58], 215-216°), ν_{max} 3355 (NH) cm^{-1}, δ_H ($CDCl_3$) 10.05 (1H, bs, NH), 8.60-6.95 (8H, m, ArH) and 3.30 (3H, s, CH_3);

Found: m/z (EI HRMS), 240.0710,

$C_{14}H_{12}N_2S$ requires: M, 240.0721.

5-Methyl-11-methylthiodibenz[b,f][1,4]diazepine (145)

A vigorously stirred suspension of sodium hydride (0.12g; 0.0055mol) in anhydrous dimethylformamide (10.0ml) was treated at room temperature with a solution of 5-methyldibenzo[b,f][1,4]diazepine-11(10H)-thione (58) (1.2g; 0.005mol) in anhydrous dimethylformamide (10.0ml) added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of dimethyl sulphate (2.5g; 0.02mol) in anhydrous dimethylformamide (5.0ml) was added in one portion and the mixture then stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with concentrated ammonia (15.0ml) and water (15.0ml) and stirred at room temperature for 2h. Rotary evaporation gave a red oily residue which was treated with water (20.0ml) and extracted three times with ethyl acetate (3 x 25.0ml) to give a yellow solid (1.2g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded the known[58] 5-methyl-11-methylthiodibenz- [b,f][1,4]diazepine (145) as a yellow solid (0.95g; 75%), which formed yellow crystals, m.p. 127-129° (lit.[58], 125-126°), δ_H ($CDCl_3$) 7.57 (1H, dd J 7.6 and 1.5Hz, ArH), 7.36 (1H, dt J 6.8, 6.8 and 0.7Hz, ArH), 7.32-7.31 (1H, m, ArH), 7.18-6.91 (5H, m, ArH), 3.22 (3H, s, NCH_3) and 2.56 (3H, s, SCH_3);

Found: m/z (EI HRMS), 254.0881,

$C_{15}H_{14}N_2S$ requires: M, 254.0979.

Further elution with hexane-ether (95:5) through methanol afforded only complex yellow gums (0.14g) which were not further investigated.

The Attempted Sodium Hydride Catalysed Reaction of 5-Methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) with Piperidine.

(a) A vigorously stirred suspension of sodium hydride (0.027g; 0.0011mol) in anhydrous dimethylformamide (2.5ml) was treated dropwise at 0-5° (ice bath) with a solution of piperidine (0.085g; 0.001mol) in anhydrous dimethylformamide (2.5ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 5-methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) (0.25g; 0.001mol) in anhydrous dimethylformamide (5.0ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was allowed to cool to room temperature then was treated with water (5.0ml) and stirred at room temperature for 15min. Rotary evaporation gave a red oily residue which was treated with water (10.0ml) and extracted three times with ethyl acetate (3 x 10.0ml) to give unreacted 5-methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) as a yellow solid (0.27g; 100%), m.p. 123-127°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) The reaction was repeated as described in (a) before, but with heating under reflux for 1h.

The resulting mixture was allowed to cool to room temperature then was treated with water (5.0ml) and stirred at room temperature for 15min. Rotary evaporation gave a yellow solid residue which was treated with water (10.0ml) and extracted three times with dichloromethane (3 x 10.0ml) to give a brown semi-solid which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded unreacted 5-methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) as a yellow solid (15%), m.p. 125-128°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (95:5) afforded 5-methyldibenzo[b,f][1,4]diazepine-11(10H)-thione (58) as a yellow solid (27%), m.p. 221-226°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (50:50) afforded the known[100] 5-methyldibenzo[b,f][1,4]diazepine-11(10H)-one as a yellow solid (53%), which formed pale yellow crystals, m.p. 214-217° (from ethanol-hexane), (lit.[100], 217-218°), ν_{max} 3166 (NH) and 1651 (C=O) cm^{-1}, δ_H ($CDCl_3$) 9.14 (1H, bs, NH) (exch), 7.86(1H, dd J 8.1 and 1.7Hz, ArH), 7.47-7.39 (1H, m, ArH), 7.16-6.98 (6H, m, ArH) and 3.34 (3H, s, CH_3);

Found: m/z (EI HRMS), 224.0946,

$C_{14}H_{12}N_2O$ requires: M, 224.0950.

Further elution with methanol afforded a yellow oil (0.011g) which was not further investigated.

The Attempted Oxidation of 5-Methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) with Potassium Permanganate in Acetic Acid.

A solution of 5-methyl-11-methylthiodibenz[b,f][1,4]diazepine (145) (0.25g; 0.001mol) in acetic acid (2.5ml) was cooled to 25° (ice-water bath) and treated over a 10min period with a warm solution of potassium permanganate (0.32g; 0.002mol) in water (1.2ml). The mixture was then stirred at room temperature for 50min.

The mixture was treated with a saturated aqueous solution of sodium bisulphate (0.25ml), adjusted to pH 8 by the addition of 20% aqueous ammonia then treated with ethyl acetate (10.0ml). Inorganic material was removed by filtration, the two phase filtrate separated and extracted a further twice with ethyl acetate (2 x 10.0ml). The combined organic extracts were rotary evaporated to give a brown oil (0.16g) whose t.l.c. in hexane-ether over silica showed it to be a complex mixture containing mainly unreacted starting material, and therefore was not further investigated.

Attempted Lewis Acid Catalysed Cyclisation Reactions of N-(4-Toluenesulphonyl) 2-isothiocyanatodiphenylamine (144c).

(a) Using aluminium trichloride as the catalyst.

A stirred suspension of aluminium trichloride (0.27g; 0.002mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-(4-toluenesulphonyl) 2-isothiocyanatodiphenylamine (144c) (0.38g; 0.001mol) in anhydrous dichloromethane (5.0ml) and the mixture was then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with

dichloromethane (3 x 30.0ml) to afford an intractable complex brown gum (0.32g) which yielded no identifiable material.

(b) Using titanium tetrachloride as the catalyst.

A stirred solution of titanium tetrachloride (0.27g; 0.002mol) in anhydrous dichloromethane (10.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-(4-toluenesulphonyl) 2-isothiocyanatodiphenylamine (144c) (0.38g; 0.001mol) in anhydrous dichloromethane (5.0ml) and the mixture was then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 40.0ml) to afford an intractable complex brown gum (0.32g) which yielded no identifiable material.

Attempted Lewis Acid Catalysed Cyclisation Reactions of N-Ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a).

(a) Using aluminium tribromide as the catalyst.

A stirred suspension of aluminium tribromide (1.1g; 0.004mol) in anhydrous dichloromethane (4.0ml) was treated dropwise at -10° (ice - acetone bath) under nitrogen with a solution of N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) (0.60g; 0.002mol) in anhydrous dichloromethane (6.0ml) and the mixture was then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with

dichloromethane (3 x 50.0ml) to afford unreacted N-ethoxycarbonyl 2-aminodiphenylamine (150a) as a light brown solid (0.56g; 100%), m.p. 88-91°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(b) Using aluminium trichloride as the catalyst.

(i) A stirred suspension of aluminium trichloride (0.53g; 0.004mol) in anhydrous dichloromethane (20.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) (0.60g; 0.002mol) in anhydrous dichloromethane (10.0ml) and the mixture was then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 30.0ml) to afford unreacted N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) as a brown oil (0.60g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(ii) Repetition of the reaction described in (b) before but with heating under reflux for 4h afforded a brown oil (0.60g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a complex brown oil (0.080g) followed by unreacted N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) as a yellow oil (0.16g; 26%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with ether afforded only an intractable brown oil (0.27g) which was not further investigated.

(c) Using titanium tetrachloride as the catalyst.

A stirred solution of titanium tetrachloride (1.9g; 0.01mol) in anhydrous dichloromethane (6.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) (0.60g; 0.002mol) in anhydrous dichloromethane (6.0ml) and the mixture was then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 30.0ml) to afford unreacted N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) as a brown oil (0.60g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(d) Using stannic chloride as the catalyst.

A stirred solution of stannic chloride (1.3g; 0.01mol) in anhydrous dichloromethane (20.0ml) was treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) (0.60g; 0.002mol) in anhydrous dichloromethane (10.0ml) and the mixture was then stirred and heated under reflux for 4h.

The mixture was cooled and poured into 10% w/v aqueous sodium hydrogen carbonate solution (34.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 30.0ml) to afford unreacted N-ethoxycarbonyl 2-isothiocyanatodiphenylamine (151a) as a brown oil (0.60g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

2-Bromo-2′-nitrodiphenylamine (148)

(a) A mixture of 2-fluoronitrobenzene (61) (28.2g; 0.2mol), 2-bromoaniline (153) (37.2g; 0.4mol) and anhydrous potassium fluoride (11.6g; 0.2mol) was stirred vigorously and heated at 180° (oil bath), with the exclusion of atmospheric moisture, for 48h.

The mixture was treated with water (175ml) and extracted three times with dichloromethane (3 x 70.0ml) to give a red oil (32.1g) which was treated with 2M aqueous hydrochloric acid (70.0ml) and ether (100ml). The precipitated 2-bromoaniline hydrochloride (14.5g) was removed by filtration and the two phase filtrate was separated and the aqueous layer was extracted a further twice with ether (2 x 100ml). Rotary evaporation of the combined organic fractions gave a red oil (14.7g) which was distilled to remove unreacted 2-fluoronitrobenzene (61) (8.7g) leaving a red oil which solidified on cooling to give the known[102] 2-bromo-2′-nitrodiphenylamine (148) as a red solid (5.1g; 14%), m.p. 95-101° (lit.[102], 105-106°).

(b) A vigorously stirred suspension of sodium hydride (1.1g; 0.044mol) in anhydrous dimethylformamide (8.0ml) was treated dropwise at 0-10° (ice bath) with a solution of 2-bromoaniline (153) (6.9g; 0.04mol) in anhydrous dimethylformamide (6.0ml) and the mixture was stirred at room temperature with, the exclusion of atmospheric moisture, for 15min. A solution of 2-fluoronitrobenzene (61) (2.8g; 0.02mol) in anhydrous dimethylformamide (6.0ml) was added in one portion and the mixture was stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (10.0ml) and stirred at room temperature for 15min. Rotary evaporation gave a dark brown residue which was treated with water (50.0ml) and extracted three times with dichloromethane (3 x 100ml) to give a red oil (9.5g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) gave the known[102] 2-bromo-2′-nitrodiphenylamine (148) as a red solid (3.9g; 67%), m.p. 95-101° (lit.[102], 105-106°).

Further elution with hexane-ether (95:5) gave a mixed fraction as a red oil (2.4g) which was triturated with ether to give a second crop of 2-bromo-2′-nitrodiphenylamine (148) as a red solid (0.35g; 6%), m.p. 101-106°, identical (melting point and i.r. spectrum) to the first crop. The ether washings were rotary evaporated to give a mixed fraction as a red oil (1.9g) which was not further investigated.

Final elution with methanol afforded a brown oil (1.9g) which afforded no identifiable material, and was not further investigated.

N-Methyl 2-bromo-2′-nitrodiphenylamine (154)

(a) A vigorously stirred suspension of sodium hydride (0.14g; 0.0044mol) in anhydrous dimethylformamide (4.0ml) was treated in one portion at room temperature with a solution of 2-bromo-2′-nitrodiphenylamine (148) (1.2g; 0.004mol) in anhydrous dimethylformamide (8.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of dimethyl sulphate (2.0g; 0.016mol) in anhydrous dimethylformamide (8.0ml) was added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with concentrated ammonia (8.0ml) and water (16.0ml) and stirred at room temperature for 2h. Rotary evaporation gave an orange semi-solid which was triturated with water, affording an orange solid which was recrystallised from ethanol to give N-methyl 2-bromo-2′-nitrodiphenylamine (154) as orange needles (0.88g; 91%), m.p. 93-94° (from EtOH), ν_{max} 1574 and 1345 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 7.69-6.93 (8H, m, ArH) and 3.28 (3H, s, CH_3);

Found: C, 50.8; H, 3.6; N, 9.1%; m/z (EI ms), 308 and 306 (M^+),

$C_{13}H_{11}BrN_2O$ requires: C, 50.9; H, 3.6; N, 9.1%; M, 307.

(b) Repetition of the reaction described in (a) before, but with stirring at room temperature for 24h gave N-methyl 2-bromo-2′-nitrodiphenylamine (154) as an orange solid (2.9g; 100%), m.p. 81-87°, identified by comparison (melting point and i.r. spectrum) with authentic sample prepared before.

The Sodium Hydride Catalysed Reaction of 2-Bromo-2′-nitrodiphenylamine (148) with Ethyl Chloroformate.

(a) A vigorously stirred suspension of sodium hydride (0.52g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was treated at 0-10° (ice bath) with a solution of 2-bromo-2′-nitrodiphenylamine (148) (5.9g; 0.02mol) in anhydrous dimethylformamide (20.0ml) added in several portions and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of ethyl chloroformate (2.4g; 0.022mol) in anhydrous dimethylformamide (10.0ml) was added in one portion and the mixture then stirred at room temperature, with the exclusion of atmospheric moisture, for 30min.

The resulting mixture was diluted with water (6.0ml) and rotary evaporated to give a red-brown residue which was treated with water (40.0ml) and extracted three times with dichloromethane (3 x 50.0ml) to give a red oily solid (6.9g) which was triturated with hexane-ether to give unreacted 2-bromo-2′-nitrodiphenylamine (148) as a red solid (4.9g; 83%), m.p. 104-108°, identical (melting point and i.r. spectrum) to an authentic sample prepared before. The hexane-ether mother liquor was rotary evaporated to afford a red oil (1.9g) which was shown (t.l.c. in hexane-ether over silica and i.r. spectrum) to be mainly impure starting material, and was not further investigated.

(b) Repetition of the reaction described in (a) before but with stirring at room temperature for 34h gave a brown oil (7.8g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) gave unreacted 2-bromo-2′-nitrodiphenylamine (148) as a red solid (0.19g; 3%), m.p. 99-105°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (90:10) yielded N-ethoxycarbonyl 2-bromo-2′-nitrodiphenylamine (149b) as a yellow solid (5.8g; 79%), m.p., 76-84°, ν_{max} 1729 (CO) and 1526 and 1326 (NO_2) cm^{-1}.

Final elution with methanol yielded an intractable brown gum (1.3g) which was not further investigated.

2-Amino-2′-bromodiphenylamine Derivatives

A stirred solution of the corresponding 2-bromo-2′-nitrodiphenylamine derivative (0.05mol) in tetrahydrofuran (500ml) was treated with a solution of stannous chloride dihydrate (50.0g; 0.22mol) in 2M aqueous hydrochloric acid (500ml) and the mixture was heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution, then concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 250ml). The combined ether extracts were then rotary evaporated to give a residue which was worked up as described for the idividual reactions below.

(i) The reaction with N-Methyl 2-bromo-2′nitro-diphenylamine (154) afforded a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded N-methyl 2-amino-2′-bromodiphenylamine (155) as yellow oil (75%), b.p. 109°/0.2mmHg, ν_{max} 3436 and 3345 (NH_2) cm^{-1}, $\delta_H(CDCl_3)$ 7.54 (1H, dd J 7.9 and 1.6Hz, ArH), 7.33-7.15 (2H, m, ArH), 7.02-6.89 (2H, m, ArH), 6.82-6.66 (3H, m, ArH), 3.97 (2H, bs, NH_2) (exch) and 3.28(3H, s, NCH_3);

Found: C, 56.4; H, 4.8; N, 10.1%; m/z (EI ms), 278 and 276 (M^+),

$C_{13}H_{13}BrN_2O$ requires: C, 56.3; H, 4.7; N, 10.1%; M, 277.

Further elution with ether through to methanol yielded only intractable brown oils which were not further investigated.

(ii) N-Ethoxycarbonyl 2-bromo-2′-nitrodiphenylamine (149b) afforded N-ethoxycarbonyl 2-amino-2′-bromodiphenylamine (150b) as colourless cubes (5.4g; 88%), m.p. 125-127° (from EtOH), ν_{max} 3455 and 3328 (NH_2) and 1694 (CO) cm^{-1}, δ_H ($CDCl_3$) 7.63 (1H, dd J 7.9 and 1.4Hz, ArH), 7.34-7.03 (5H, m, ArH), 6.78-6.68 (2H, m, ArH), 4.25 (2H, bs, CH_2), 3.72 (2H, bs, NH_2) (exch), and 1.28 (3H, t J 7.1 and 7.1Hz, CH_3);

Found: m/z (EI HRMS), 336.0298 and 334.0315 (M^+),

$C_{15}H_{15}BrN_2O_2$ requires: M, 336.0298 and 334.0317.

2-Bromo-2′-isothiocyanatodiphenylamine Derivatives

A solution of the corresponding 2-amino-2′-bromodiphenylamine derivative (0.005mol) in glacial acetic acid (15.0ml) was stirred and treated with a 1:1 mixture of concentrated hydrochloric acid and water (5.0ml) added in one portion. The mixture was treated dropwise at room temperature with a solution of thiophosgene (0.1mol) in glacial acetic acid (5.0ml) and the mixture then stirred at room temperature for 2h.

(i) The mixture from the reaction with N-methyl 2-amino-2′-bromodiphenylamine (155) was diluted with water (20.0ml) and extracted three times with dichloromethane (3 x 40.0ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml) then dried and rotary evaporated to give a red-brown oil which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded N-methyl 2-bromo-2′-isothiocyanatodiphenylamine (156) as an orange oil (35%), ν_{max} 2121 (N=C=S) cm^{-1}, δ_H ($CDCl_3$) 7.62-6.91 (8H, m, ArH) and 3.23 (3H, s, CH_3);

Found: C, 52.5; H, 3.6; N, 8.9%; m/z (EI ms), 320 and 318 (M^+),

$C_{14}H_8BrN_2S$ requires: C, 52.7; H, 2.5; N, 8.8%; M, 319.

Further elution with hexane-ether (50:50) afforded unreacted N-methyl 2-bromo-2′-aminodiphenylamine (155) as a brown oil (11%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with methanol gave an intractable black gum (0.21g) which was not further investigated.

(i) The mixture from the reaction with N-ethoxycarbonyl 2-amino-2′-bromodiphenylamine (150b) was diluted with water (4.0ml) and a suspended solid collected (0.26g). The colourless solid was treated with 10% w/v aqueous sodium hydrogen carbonate solution (10.0ml) and the mixture extracted three times with dichloromethane (3 x 5.0ml) to give N-ethoxycarbonyl 2-amino-2′-bromodiphenylamine (150b) as a brown oil (0.14g; 27%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The aqueous mother liquor was extracted three times with dichloromethane (3 x 8.0ml) and the combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 20.0ml). Rotary evaporation of the dichloromethane extract gave give a brown oil (0.27g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded N-ethoxycarbonyl 2-bromo-2′-isothiocyanatodiphenylamine (151b) as a yellow oil (0.12g; 37%), ν_{max} 2072 (N=C=S) and 1725 (CO) cm^{-1}, δ_H ($CDCl_3$) 7.68-7.10 (8H, m, ArH), 4.28 (2H, q J 7.0Hz, CH_2) and 1.27 (3H, t J 7.1 and 7.1Hz, CH_3);

Found: C, 50.8; H, 3.5; N, 7.4%; m/z (EI ms), 378 and 376 (M^+),

$C_{16}H_{13}BrN_2O_2S$ requires: C, 50.9; H, 3.9; N, 6.8%; M, 377.

Elution with hexane-ether (50:50) afforded a mixed fraction as a yellow oil (0.10g) which was not investigated further.

S-Butyllithium Catalysed Cyclisation Reactions of 2-Bromo-2′-isothiocyanatodiphenylamine Derivatives.

A solution of the 2-bromo-2′-isothiocyanatodiphenylamine derivative (0.001mol) in anhydrous tetrahydrofuran (5.0ml) was stirred and treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.1M solution of s-butyllithium in cyclohexane (0.001mol). The mixture was then stirred under nitrogen, at -78° (dry ice-acetone bath) for 2h, allowed to warm to room temperature, then stirred for a further 2h at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (10.0ml) then extracted three times with ether (3 x 10.0ml) to give the product.

(i) N-Methyl 2-bromo-2′-isothiocyanatodiphenylamine (156) afforded 5-methyldibenzo[b,f][1,4]diazepine-11(10H)-thione (58) (0.24g; 100%), as a yellow solid m.p., 212-218°, identical (melting point and i.r. spectrum) to an authentic sample prepared before.

(ii) N-Ethoxycarbonyl 2-bromo-2′-isothiocyanatodiphenylamine (151b) afforded a dark brown semi-solid (0.22g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) through ether to methanol afforded only unidentified oils and gums (0.18g) which were not further investigated.

N-Methyl 2-azido-2′-bromodiphenylamine (157)

(a) N-Methyl 2-amino-2′-bromodiphenylamine (155) (2.8g; 0.01mol) was treated with 5M aqueous hydrochloric acid (50.0ml) and the mixture warmed gently to form a suspension of N-methyl 2-amino-2′-bromodiphenylamine hydrochloride. This was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.76g; 0.011mol) in water (5.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. A solution of sodium azide (0.98g; 0.015mol) in water (5.0ml) was added dropwise at such a rate that the reaction temperature was <5°, and the mixture then stirred in the melting ice bath for 30 min.

The mixture was extracted three times with dichloromethane (3 x 50.0ml) to afford a brown oil which was combined with a second oil otained by basifying the mother liquor to pH 14 by the addition of 5M aqueous sodium hydroxide and extraction three times with dichloromethane (3 x 50.0ml) total (3.1g) and flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded N-methyl 2-azido-2′-bromodiphenylamine (157) as a pale yellow solid (1.1g; 39%), m.p., 96-98° (from hexane-ethanol), ν_{max} 2131 (N_3) cm^{-1}, δ_H ($CDCl_3$) 7.54 (1H, dd J 7.8 and 1.3Hz, ArH), 7.31-6.82 (7H, m, ArH) and 3.20 (3H, s, CH_3);

Found: C, 52.5; H, 3.9; N, 18.3%; m/z (EI ms), 303(M^+),

$C_{13}H_{11}BrN_4$ requires: C, 51.5; H, 3.6; N, 18.5%; M, 303.

Further elution with hexane-ether (95:5) afforded unreacted N-methyl 2-amino-2′-bromodiphenylamine (155) as a red oil (0.20g; 7%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (90:10) through to methanol afforded intractable gums (1.2g) that were not further investigated.

(b) N-Methyl 2-amino-2′-bromodiphenylamine (155) (2.8g; 0.01mol) was treated with 5M aqueous hydrochloric acid (50.0ml) and the mixture warmed gently to form a suspension of N-methyl 2-amino-2′-bromodiphenylamine hydrochloride. This was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.76g; 0.011mol) in water (5.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 30 min. A solution of sodium azide (0.98g; 0.015mol) in water (5.0ml) was added dropwise at such a rate that the reaction temperature was <5°, and the mixture then stirred in the melting ice bath for 2 h.

The mixture was extracted three times with dichloromethane (3 x 50.0ml) to afford a brown oil which was combined with a second oil otained by basifying the mother liquor to pH 14 by the addition of 5M aqueous sodium hydroxide and extraction three times with dichloromethane (3 x 50.0ml) total (3.5g) and flash chromatographed over silica.

Elution with hexane afforded N-methyl 2-azido-2′-bromodiphenylamine (157) as a yellow solid (1.2g; 40%), m.p., 92-95°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane through to methanol afforded intractable gums (1.4g) that were not further investigated.

The Reaction of N-Methyl 2-Azido-2′-bromodiphenylamine (157) with Trimethylphosphite.

A stirred solution of N-methyl 2-azido-2′-bromodiphenylamine (157) (1.5g; 0.005mol) in anhydrous 1,2-dimethoxyethane (25.0ml) was treated at room temperature with a solution of trimethylphosphite (0.77g; 0.006mol) in anhydrous 1,2-dimethoxyethane (12.5ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The reaction mixture was rotary evaporated to give a light brown oil (1.9g) which showed signals in its ^{1}H n.m.r. spectrum corresponding to the desired phosphinimine product (159), but also a second phosphorous containing contaminant.

1-[2-(N-2-Bromophenyl-N-methyl)amino]phenyl-3-phenyl carbodiimide (160)

The brown oil containing the phosphinimine (159) (1.4g; 0.0036mol) was dissolved in anhydrous 1,2-dimethoxyethane (20.0ml) and the stirred solution was treated at room temperature with a solution of phenyl isocyanate (0.43g; 0.0036mol) in anhydrous 1,2-dimethoxyethane (20.0ml) added in one portion. The mixture was then stirred at room temperature, with the exclusion of atmospheric moisture, for 4h.

Rotary evaporation of the mixture afforded a red oil which was dissolved in ether (25.0ml) and washed with water (3 x 20.0ml). Rotary evaporation of the ether extract afforded the impure carbodiimide (160) as a red oil (1.3g), ν_{max} 2131 and 2099 (N=C=N) cm^{-1}.

1-[2-(N-2-Bromophenyl-N-methyl)amino]phenyl-3-phenyl urea (158)

A solution of N-methyl 2-amino-2′-bromodiphenylamine (155) (4.7g; 0.017mol) in anhydrous dioxane (40.0ml) was treated with a solution of phenyl isocyanate (2.0g; 0.017mol) in anhydrous dioxane (40.0ml) added in one portion then stirred at room temperature for 2h.

Rotary evaporation gave a cream solid (6.1g), m.p. 189-196°, whose t.l.c. in hexane-ether over silica showed it to be a mixture of starting material and one other product. The solid was redissolved in anhydrous dioxane (40.0ml) and treated with a solution of phenyl isocyanate (1.0g; 0.0085mol) in anhydrous dioxane (40.0ml) added in one portion then stirred at room temperature for a further 1h.

The mixture was rotary evaporated to give a colourless solid (7.2g), m.p. 153-160°, which was flash chromatographed over silica.

Elution with hexane-ether (50:50) afforded the urea product (158) as a colourless solid, (6.6g; 98%), which formed colourless needles, m.p. 207-210° (from acetic acid), ν_{max} 3336 (NH) and 1658 (C=0) cm^{-1}, δ_H ($CDCl_3$) 9.57 (1H, bs, NH) (exch), 8.51 (1H, bs, NH) (exch), 8.24 (1H, d J 8.2Hz, ArH), 7.53-6.79 (11H, m, ArH), 6.50 (1H, d J 7.8 Hz, ArH) and 3.37 (3H, s, NCH_3);

Found: C, 60.3; H, 4.6; N, 10.4%; m/z (FAB ms), 398 and 396 (MH^+),

$C_{20}H_{18}BrN_3O$ requires: C, 60.6; H, 4.6; N, 10.6%; M, 396.

Final elution with methanol afforded a brown gum (0.41g) which was not further investigated.

1-[2-(N-2-Bromophenyl-N-methyl)amino]phenyl-3-phenyl carbodiimide (160)

(a) A stirred suspension of 1-[2-(N-2-bromophenyl-N-methyl)amino]phenyl-3-phenyl urea (158) (1.6g; 0.004mol) in anhydrous 1,2-dichloroethane (20.0ml) under nitrogen was treated with diisopropylethylamine (1.6g; 0.012mol) added in one portion and cooled to 0° (ice-salt bath). The mixture was treated dropwise with phosphoryl chloride (0.68g; 0.0044mol) at such a rate that the reaction temperature was 0-5° then heated under reflux for 17h.

The cooled mixture was rotary evaporated to give a brown oil (3.9g) which was extracted three times with 60-80° light petroleum, leaving a brown gum (3.0g) whose t.l.c. in hexane-ether over silica showed it to be impure urea starting material (158). Rotary evaporation of the combined petroleum extracts afforded the desired carbodiimide product (160) as a yellow oil (0.89g; 59%), ν_{max} 2131 and 2099 (N=C=N) cm^{-1}, δ_H 7.50 (1H, dd J 7.9 and 1.6Hz, ArH), 7.33-6.77 (12H, m, ArH) and 3.17 (3H, s, NCH_3);

Found: m/z (EI HRMS) 379.0488 and 377.0521 (M^+),

$C_{20}H_{16}N_3Br$ requires: M, 379.0508 and 379.0368.

(b) A stirred suspension of the urea (158) (0.79g; 0.002mol) in anhydrous dichloromethane (15.0ml) was cooled to 0° (ice-salt bath) under nitrogen and treated with a solution of triethylamine (0.40g; 0.004mol) in anhydrous dichloromethane (2.5ml) added in one portion. A single portion of a solution of triphosgene (0.20g; 0.00066mol) in anhydrous dichloromethane (2.5ml) was then added in one portion and the mixture stirred under reflux for 2h. A second portion of a solution of

triphosgene (0.20g; 0.00066mol) in anhydrous dichloromethane (2.5ml) was then added and the mixture heated under reflux for a further 2h.

The cooled solution was rotary evaporated to give a yellow semi-solid (1.3g) which was triturated with anhydrous ether to give triethylamine hydrochloride (0.39g) as a cream solid, m.p. 250-258°, (lit.[104], 261°). Rotary evaporation of the ether filtrate afforded a yellow oil (0.69g) which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded the desired carbodiimide product (160) as a yellow oil (0.010g; 2%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (60:40) afforded the urea starting material (158) as a colourless solid (0.41g; 52%), m.p. 195-199°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded an intractable yellow oil (0.23g) which was not further investigated.

5-Methyl-11-phenylaminodibenzo[b,f][1,4]diazepine (161)

A solution of the carbodiimide (160) (1.3g; 0.0034mol) in anhydrous tetrahydrofuran (18.0ml) was stirred and treated dropwise at -78° (dry ice-acetone bath) under nitrogen with a 1.1M solution of s-butyllithium in cyclohexane (3.1ml; 0.0034mol). The mixture was then stirred under nitrogen, at -78° (dry ice-acetone bath) for 2h, allowed to warm to room temperature, then stirred for a further 2h at room temperature.

The mixture was treated with a saturated aqueous solution of ammonium chloride (36.0ml) then extracted three times with ether (3 x 36.0ml) to give a dark brown oil (0.98g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired dibenzodiazepine (161) as a light brown solid (1.8g; 30%), which formed cream crystals, m.p. 127-130° (from acetic acid), ν_{max} 3314 (NH) cm^{-1}, δ_H ($CDCl_3$) 8.21 (1H, bs, NH) (exch), 7.69-6.54 (13H, m, ArH) 3.32 (3H, s, NCH_3);

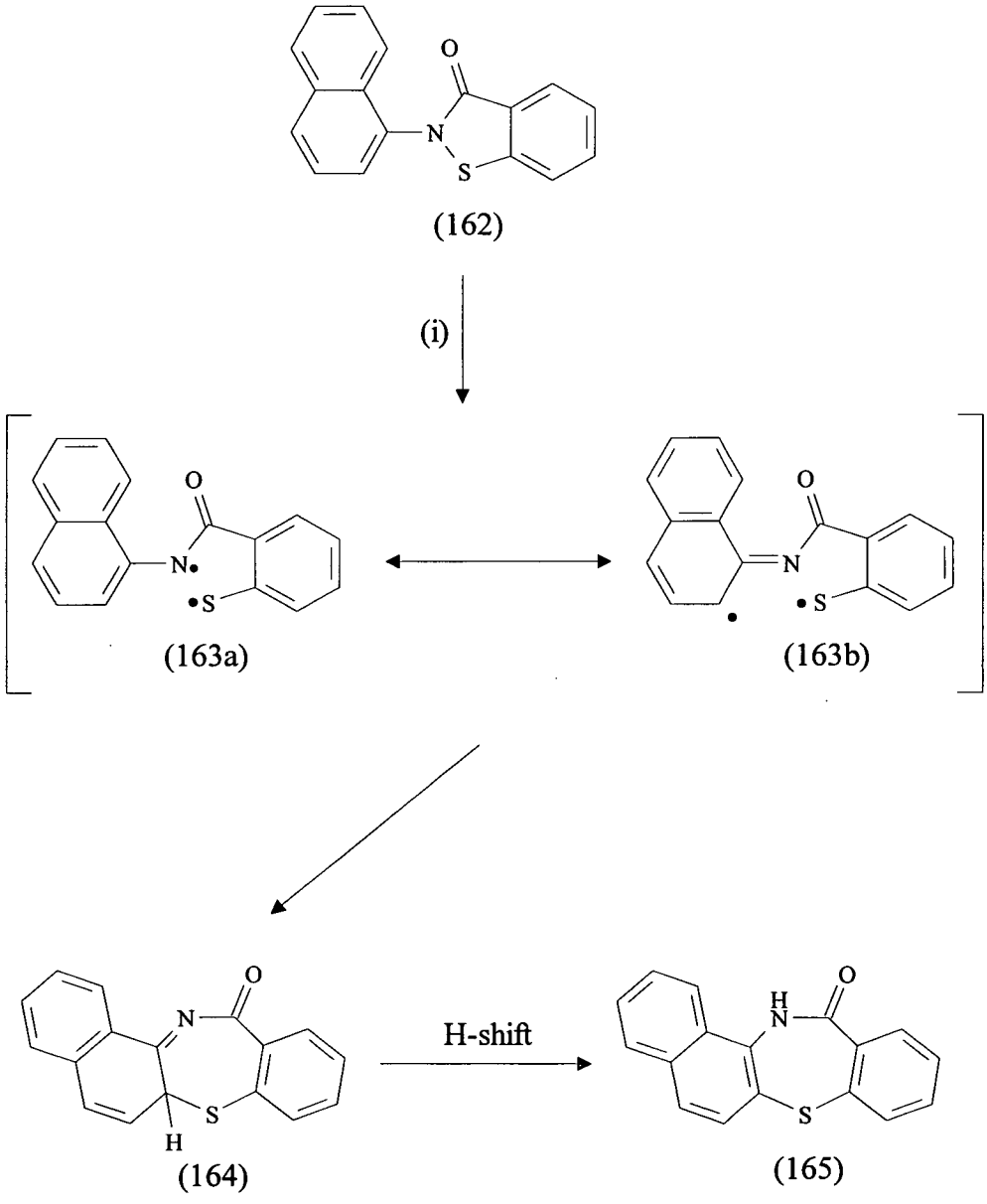
Found: m/z (EI HRMS), 299.1414 (M^+),

$C_{20}H_{17}N_3$ requires: M, 229.1423.

Further elution with hexane-ether (60:40) through to methanol afforded only unidentified oils and gums (0.27g).

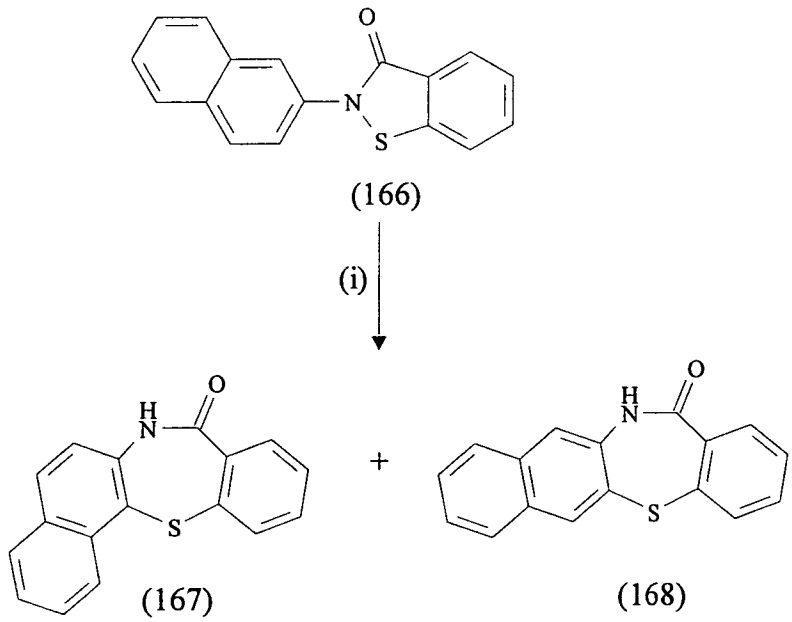
Chapter 3

Studies of Novel Cyclisation Reactions of Heterocumulenes Leading to Polycyclic Heteropine Derivatives



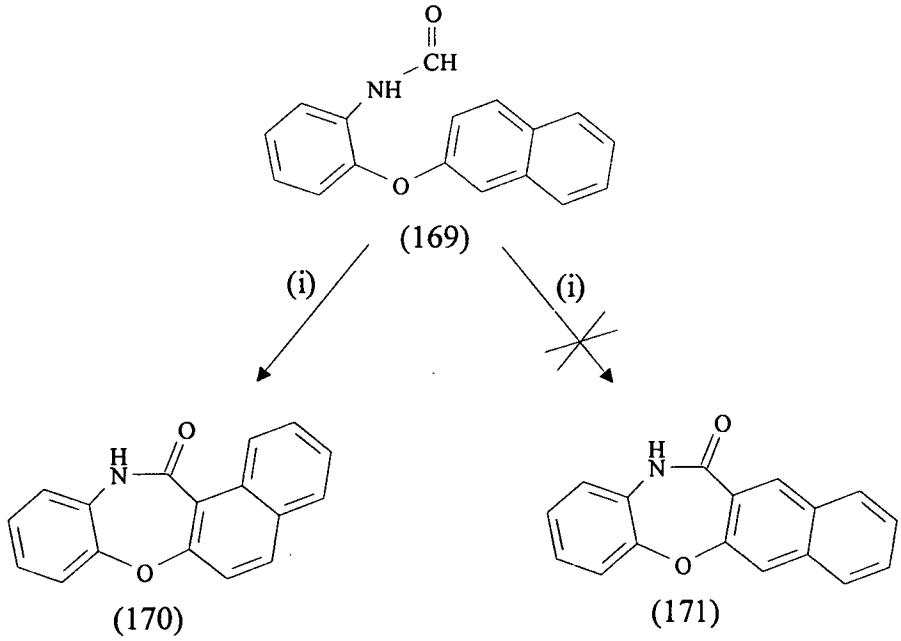
(i) hν.

Scheme 38



(i) hν.

Scheme 39



(i) Polyphosphoric acid.

Scheme 40

Studies of Novel Cyclisation Reactions of Heterocumulenes Leading to Polycyclic Heteropine Derivatives

3.1 Introduction.

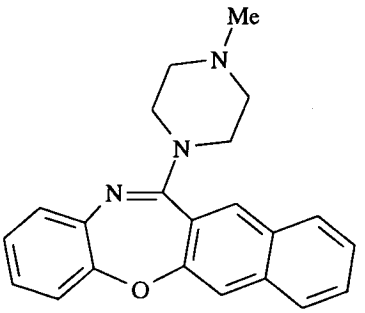
The following chapter describes how the investigations towards the synthesis of dibenzoxazepine derivatives, described in Chapter 2 were expanded to encompass the synthesis of a number of polycyclic oxazepine derivatives, namely; benzonaphthoxazepines, benzoxazepinodibenzoxazepines and benzoxazepinobenzonaphthoxazepines. To date, there has been very little research in this area, with only a few reported syntheses of benzonaphthoxazepine structures described in the literature.

As an extension of their work towards pyridobenzoxazepines[40] Kamigata et al reported[105] the synthesis of benzonaphthoxazepines via a photochemical transformation of 2-naphthyl-1,2-benzisothiazolinones. The irradiation of 2-(1-naphthyl)-1,2-benzisothiazol-3(2H)-one [Scheme 38; (162)] with a 450W Hanovia medium pressure mercury lamp through a Pyrex filter afforded a single product which was identified as benzo[f]naphtho[2,1-b][1,4]thiazepin-12(13H)-one (165).

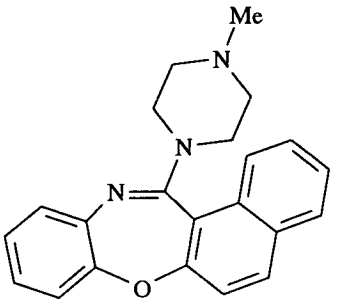
Similarly, (Scheme 39) the reaction of 2-(2-naphthyl)-1,2-benzisothiazol-3(2H)-one (166) resulted in the formation of the two benzonaphthoxazepine structures (167) and (168). The product ratio of (167) and(168) was 2:1 showing that the thiyl radical attacks the α-position of the naphthalene ring two times faster than the β-position. This in accord with the known relative reactivity of the α- and β-positions of naphthalene.[106]

By similarly extending a known route to dibenzoxazepine derivatives (Scheme 40) Wardrop, Sainsbury, Harrison and Inch[107] synthesised the benzonaphthoxazepine system (170) via the polyphosphoric acid catalysed reaction of N-[2-(2-naphthoxy)phenyl]formamide (169). The ring closure of the formamide (169) afforded only the angular system (170) rather than the isomeric linear structure (171). This bias is in agreement with the expected results. The Bischler-Napieralski reaction occurs by electrophilic substitution, and naphthalene usually undergoes electrophilic substitution preferentially in the α-position.

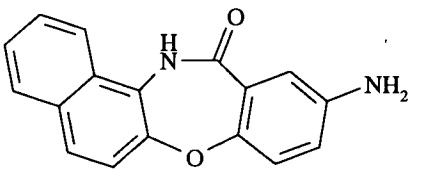
Although other, similar structures (Scheme 41) have been reported in the literature[108] this area has never been studied in any depth. Therefore, it was hoped that



(172)



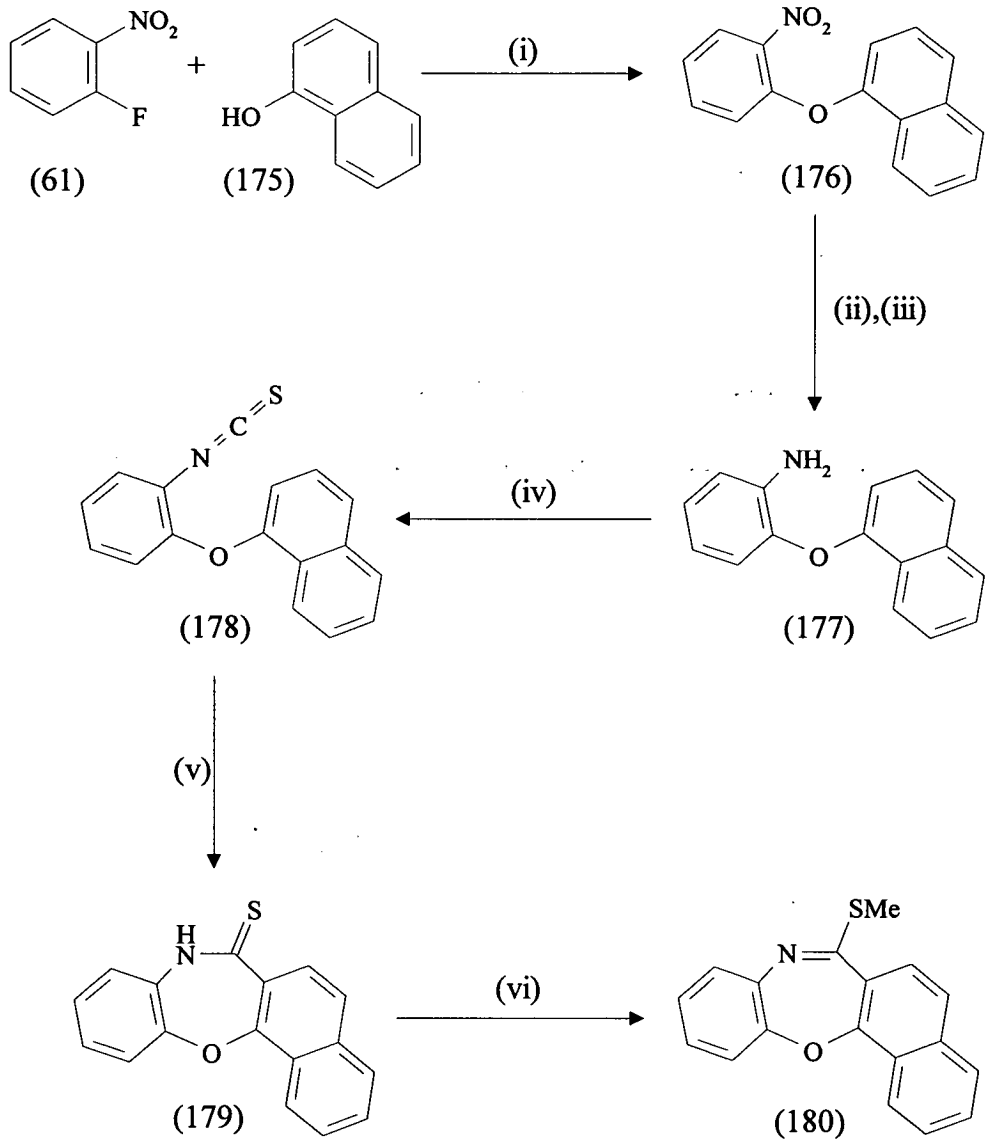
(173)



(174)

Scheme 41

the knowledge gained in the studies of the synthesis of dibenzoxazepines could be exploited to afford a large number of benzonaphthoxazepine,



(i) NaH, DMF, 100°.
(ii) H_2, Pd-C, DME, room temp., atmos. press.
(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.
(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(v) $AlBr_3$ or $AlCl_3$, CH_2Cl_2, room temp.
(vi) Me_2SO_4, NaH, DMF, room temp.

Scheme 42

benzoxazepinodibenzoxazepine and benzoxazepinobenzonaphthoxazepine structures whose chemical, physical and biological properties could then be assessed.

3.2 Cyclisations of Heterocumulenes Leading to Benzo[b]naphth[2,1-f][1,4]oxazepines and Benzo[b]naphth[1,2-f][1,4]oxazepines.

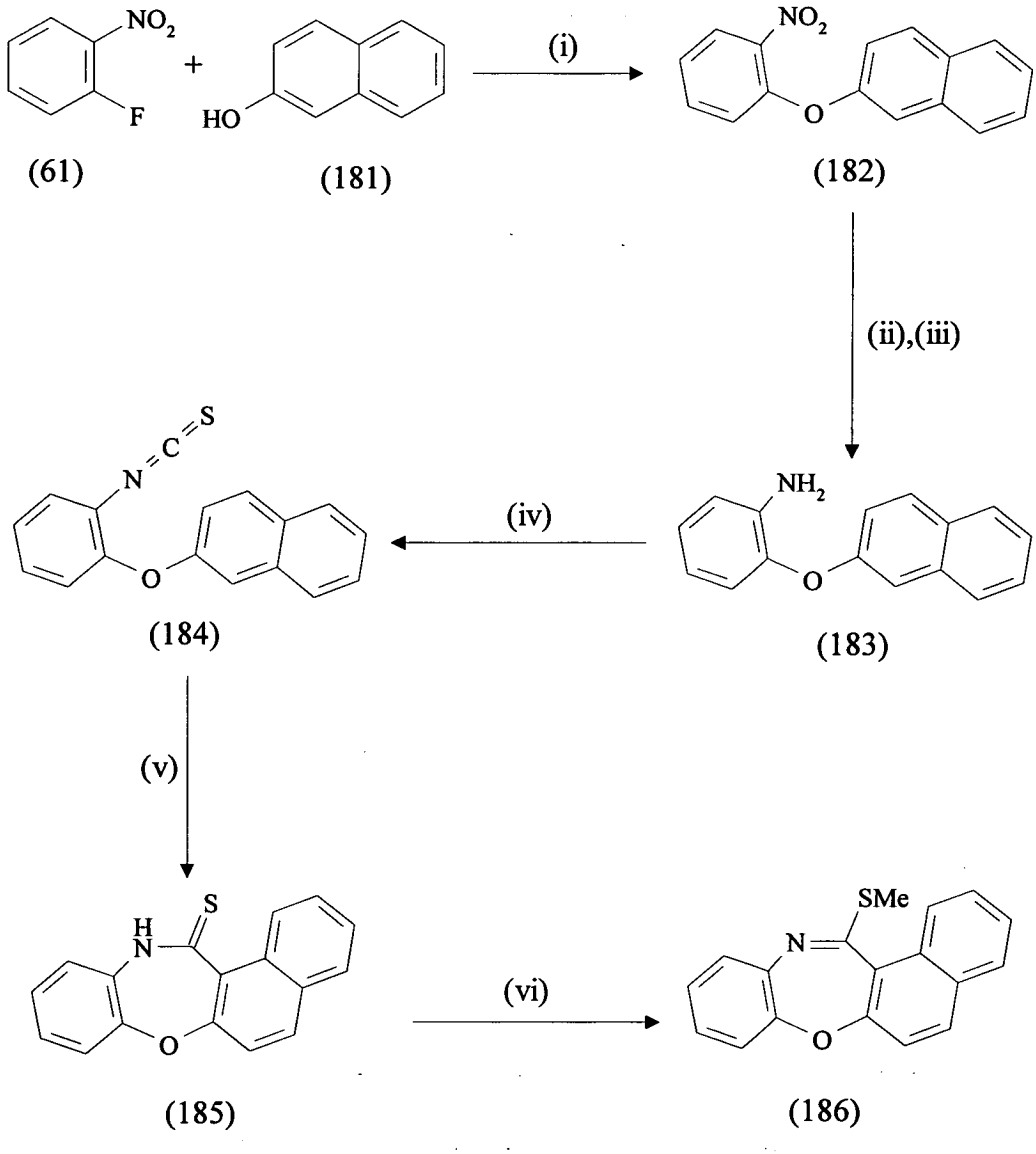
Investigations initially centred on the synthesis of benzonaphthoxazepine derivatives, the simplest of the three proposed polycyclic systems. To this end it was set about synthesising the appropriate isothiocyanate precursors for the investigation of its Lewis acid catalysed cyclisation. α-Naphthol [Scheme 42; (175)] was coupled to 2-fluoronitrobenzene (61) in a sodium hydride catalysed reaction in dimethylformamide. These conditions afforded 2-(1-naphthoxy)nitrobenzene (176) as a crystalline solid in quantitative yield. The nitro compound (176) was then reduced catalytically in 1,2-dimethoxyethane over palladium-on-charcoal to give a quantitative yield of the expected amine (177) as a yellow oil. The assignment of both the nitro (176) and amine structures (177) was entirely consistent with their analytical and spectroscopic data. The reduction of the nitro compound (176) was also demonstrated using stannous chloride dihydrate in refluxing tetrahydrofuran in the presence of aqueous hydrochloric acid, giving a quantitative yield of the desired amine (177).

The amine (177) was next reacted with thiophosgene to afford a quantitative yield of a yellow oil whose analytical and mass spectral data were consistent with the expected isothiocyanate structure (178). The compound's i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2029cm^{-1} due to the isothiocyanate substituent.

With the isothiocyanate precursor now in hand it was subjected to the aluminium tribromide catalysed cyclisation conditions. Thus, a solution of the isothiocyanate (178) in dichloromethane was treated at room temperature with two equivalents of aluminium tribromide. These conditions afforded an oily mixture, from which flash chromatography isolated in 50% yield a yellow crystalline solid whose analytical data was consistent with its formulation as the benzonaphthoxazepinethione (179). Its spectroscopic properties were also consistent with this structure. The i.r. spectrum showed an amine absorption at 3154 and 3105cm^{-1}. The ^{1}H n.m.r. spectrum showed a one-proton singlet at δ12.85 due to the exchangeable thiolactam hydrogen, and in the ^{13}C n.m.r. spectrum there were seven quaternary carbons and ten primary carbons, as would be expected in the benzonaphthoxazepine product (179).

The yield of this cyclisation reaction was increased by swapping the order of addition of the reagents. On adding the isothiocyanate (178) to the aluminium tribromide yield of the cyclised product (179) was raised to 79%. A further increase was observed on changing the Lewis acid to aluminium trichloride, affording a quantitative yield of the desired benzonaphthoxazepine (179).

It was hoped the benzonaphthoxazepine structure (179) could be further verified by the synthesis of its methylthio derivative (180). This was achieved in good yield by the sodium hydride catalysed reaction of the thione (179) with dimethyl sulphate in dimethylformamide at room temperature. Flash chromatography of the resulting mixture gave a cream solid in good yield, whose analytical and mass spectral data was consistent with the expected methylthio structure (180). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the ^{1}H n.m.r. spectrum showing a three-proton singlet at δ2.50, characteristic of a methylthio-



(i) NaH, DMF, 100°.
(ii) H_2, Pd-C, DME, room temp., atmos. press.
(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.
(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(v) $AlBr_3$ or $AlCl_3$, CH_2Cl_2, room temp.
(vi) Me_2SO_4, NaH, DMF, room temp.

Scheme 43

group. In addition to the desired S-methylated product flash chromatography also gave a yellow solid in low yield, whose analytical, mass spectral and ^{1}H n.m.r. spectroscopic properties were consistent with its formulation as 8-methylbenzo[b]naphth[2,1-f][1,4]oxazepine, the ^{1}H n.m.r. showing a three-proton singlet at δ4.11 due to the N-methyl group. This product resulted from the competing N-methylation reaction.

After this success attention was next turned to the synthesis of the isomeric benzonaphthoxazepines (Scheme 43). The use of β-naphthol (181) in the initial sodium hydride catalysed coupling reaction could result in the formation of two possible products in the subsequent Lewis acid catalysed cyclisation step, a linear product resulting from attack at the β-position, or an angled product as a result of the favoured attack at the α-position.

The sodium hydride catalysed reaction of β-naphthol (181) with 2-fluoronitrobenzene (61) in dimethylformamide afforded the known[109] 2-(2-naphthoxy)nitrobenzene (182) as a cream solid in quantitative yield. Its catalytic reduction over palladium-on-charcoal in 1,2-dimethoxyethane afforded the known[109] 2-(2-naphthoxy)aniline (183) as a cream solid in quantitative yield. The reduction of the nitro compound (182) was also demonstrated using stannous chloride dihydrate and aqueous hydrochloric acid in refluxing tetrahydrofuran, giving a good yield of the desired amine (183).

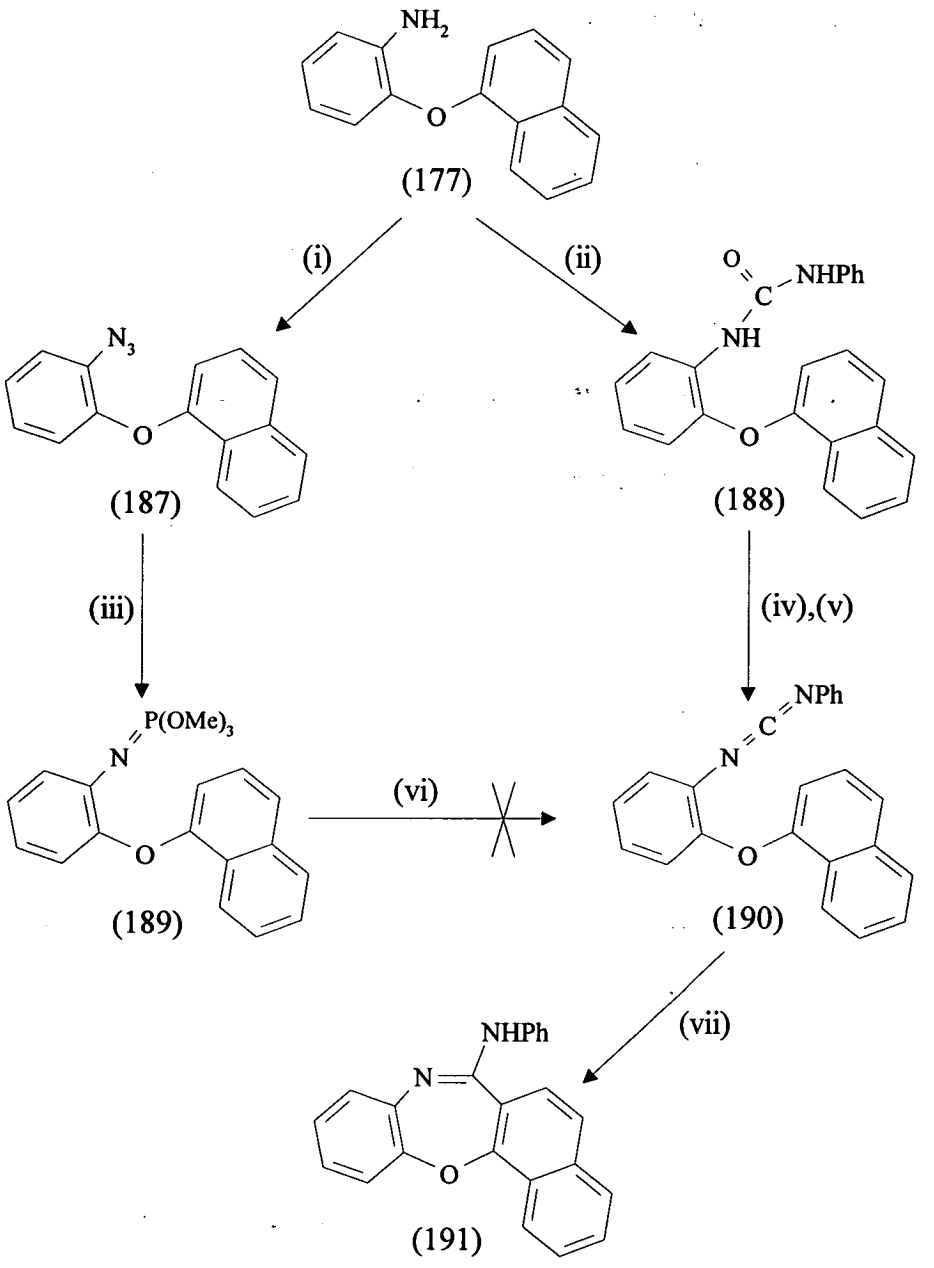
In order to obtain the isothiocyanate precursor (184) the amine (183) was reacted with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature. These conditions afforded a colourless oil whose analytical data and spectroscopic properties were consistent with its formulation as 2-(2-

isothiocyanatophenoxy)naphthalene (184). The i.r. spectrum showed absorption at 2086cm^{-1} due to the isothiocyanate substituent.

In an attempt to induce its cyclisation to the resulting benzonaphthoxazepine the isothiocyanate (184) in dichloromethane was treated with aluminium tribromide to give a brown solid in 93% yield, whose analytical and mass spectral data were consistent with the expected benzonaphthoxazepine structure. Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with the cyclised product. The ^{1}H n.m.r. spectrum also allowed positive assignment of the angular structure (185). The two naphthalene hydrogens on the side fused to the oxazepine ring were identified by spin decoupling experiments, and the coupling between these protons shown to be 9Hz. In the linear system this coupling would be much smaller, somewhere in the region of 0-1Hz.

On reversing the order of addition of the reagents the aluminium tribromide catalysed cyclisation afforded only a 66% yield of the cyclised product (185). However, if in addition to changing the order of addition of the reagents the Lewis acid catalyst was changed to aluminium trichloride a quantitative yield of the benzonaphthoxazepine (185) was obtained.

In a further attempt to verify its structure the benzonaphthoxazepine (185) was converted to its methylthio derivative (186) by its sodium hydride catalysed reaction with dimethyl sulphate. The resulting brown oil was flash chromatographed over silica to give a cream solid in good yield whose analytical and spectroscopic properties were entirely consistent with the expected methylthio product (186). The ^{1}H n.m.r. spectrum showed a three proton singlet at δ2.50, characteristic of a methylthio-group. Flash chromatography also isolated a small amount of an orange oil, whose t.l.c., i.r.



(i) $NaNO_2$, $HCl_{(aq)}$ then NaN_3, 0^o.
(ii) PhN=C=O, dioxane, room temp.
(iii) $(MeO)_3P$, DME room temp.
(iv) $POCl_3$, Pr^i_2NEt, $Cl(CH_2)_2Cl$, reflux.
(v) $(Cl_3CO)_2C=O$, Et_3N, CH_2Cl_2, reflux.
(vi) PhN=C=O, DME, room temp or reflux.
(vii) $SnCl_4$, $Cl(CH_2)_2Cl$, reflux.

Scheme 44

spectrum and mass spectral properties suggested that it was 12-methylbenzo[b]naphth[1,2-f]-1,4]oxazepine, resulting from the competing N-methylation reaction.

After successfully cyclising the isothiocyanate derivatives (178) and (184) it was next decided to look at the Lewis acid catalysed cyclisation of their carbodiimide analogues. As discussed in Chapter 2, Weddel and Tennant[41] showed that diphenyl ether carbodiimide derivatives require activation by an electron-donating group before they will undergo Lewis acid catalysed cyclisation to give dibenzoxazepine derivatives. It was anticipated that the more reactive naphthalene ring would allow these systems to undergo Lewis acid catalysed cyclisations without further activation, and to this end it was set about synthesising the appropriate carbodiimide derivatives.

The amine [Scheme 44; (177)], the synthesis of which has been discussed previously, was converted to the corresponding azide (187) by reaction with sodium nitrite to give the diazonium salt, and its subsequent displacement with sodium azide in aqueous solution at 0°. These conditions afforded in quantitative yield a light brown oil whose analytical and mass spectral data were consistent with the expected azide product (187). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2116cm^{-1} due to the azide substituent.

Treatment of the azide (187) with trimethylphosphite in 1,2-dimethoxyethane gave a high yield of a brown oil whose accurate mass data and ^{1}H n.m.r. spectrum were consistent with the expected phosphinimine product (189), showing a nine-proton doublet at δ3.47 due to the 11.4Hz coupling between the phosphorous and the protons of the three methyl-groups. The instability of this compound prevented

addition purification and hence a more rigorous characterisation by other analytical methods.

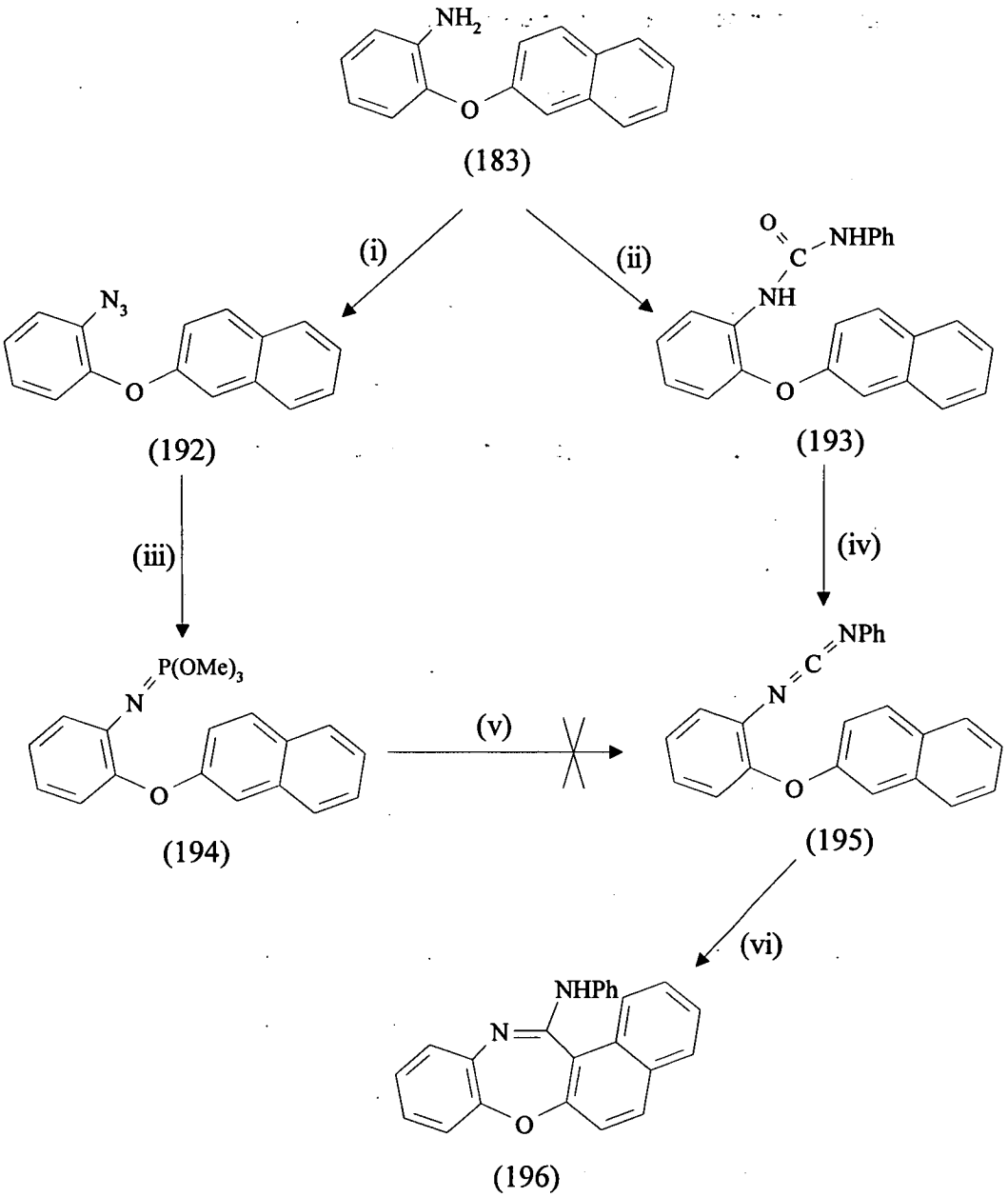
In the hope of forming the carbodiimide precursor (190) directly a solution of the phosphinimine (189) in 1,2-dimethoxyethane was treated with phenyl isocyanate at room temperature. These conditions gave a complex brown oil, from which flash chromatography isolated a 80% yield of phenyl isocyanate. The remainder of the material was recovered as complex oils. This finding suggested that since there had been next to no reaction between the isocyanate and the phosphinimine, and an increase in the reaction temperature might promote the formation of the carbodiimide (190). However, on repeating the reaction with heating under reflux the only materials isolated by flash chromatography were complex oils, from which no identifiable material could be obtained.

The failure to obtain the desired carbodiimide product through this route prompted the search for an alternative methodology. As in the diphenyl ether case (Chapter 2) the method chosen was via the urea, which could then be dehydrated to give the desired carbodiimide product. With this aim in mind the amine (177) was reacted with phenyl isocyanate in dioxane at room temperature to give a good yield of a colourless crystalline product whose analytical and mass spectral data were entirely consistent with the expected urea product (188). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in agreement with its formulation as this structure.

Previous work towards the synthesis of carbodiimide derivatives (Chapter 2) resulted in the development of two methods of obtaining carbodiimides by the dehydration of urea derivatives. Both of these were now applied to the problem at hand. Treatment of the urea (188) with diisopropylethylamine and phosphoryl chloride in refluxing 1,2-

dichloromethane gave a brown multicomponent oil. Flash chromatography of this oil gave a brown oil in good yield (64%) which gave accurate mass data consistent with the molecular formula $C_{23}H_{16}N_2O$. Its i.r. and ^1H n.m.r. spectroscopic properties were also in accord with the expected carbodiimide product (190). Thus, the i.r. spectrum of this material showed multiple-bond absorption at 2139-2104cm^{-1}. Similarly, treatment of the urea with one third of an equivalent of triphosgene in refluxing dichloromethane also afforded a good yield (54%) of the desired carbodiimide product (190), isolated by flash chromatography over silica. The urea starting material (188) was also recovered in low yield (20%). This result was not improved by repeating the reaction but doubling the amount of triphosgene used. These conditions gave only a 30% yield of the carbodiimide (190) and a 31% recovery of the urea starting material (188).

With a ready supply of the carbodiimide precursor (190) now in hand it was subjected to the Lewis acid catalysed cyclisation conditions. As discussed in Chapter 2, Weddel and Tennant[41] reported that the optimum Lewis acid catalyst for the cyclisation of carbodiimides of this type was stannic chloride. Thus, a solution of the carbodiimide in 1,2-dichloroethane was treated with four equivalents of stannic chloride then heated under reflux. These conditions afforded a brown oil from which flash chromatography gave in moderate yield (43%) a colourless solid whose analytical and mass spectral data was in accord with the expected benzonaphthoxazepine structure (191). Its i.r. and ^1H n.m.r. spectroscopic properties were also in agreement with the benzonaphthoxazepine structure. This result illustrates the naphthalene ring's higher reactivity to this type of reaction compared to a phenyl ring. the less reactive phenyl ring requiring additional activation by an electron donating group.



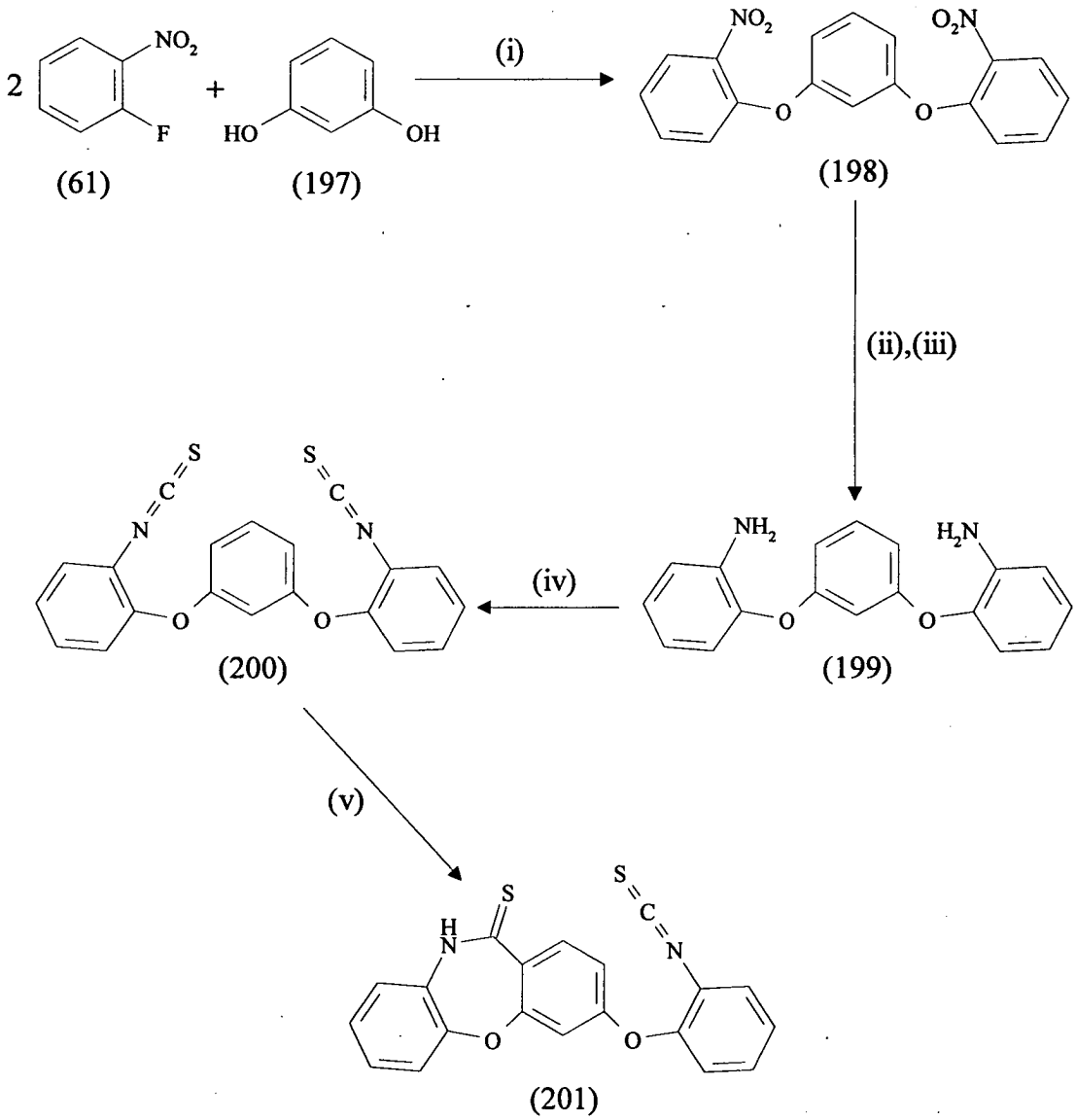
(i) $NaNO_2$, $HCl_{(aq)}$ then NaN_3, 0^o.
(ii) PhN=C=O, dioxane, room temp.
(iii) $(MeO)_3P$, DME room temp.
(iv) $POCl_3$, Pr^i_2NEt, $Cl(CH_2)_2Cl$, reflux.
(v) PhN=C=O, DME, room temp or reflux.
(vi) $SnCl_4$, $Cl(CH_2)_2Cl$, reflux.

Scheme 45

Attention was next turned to the isomeric series of compounds (Scheme 45). As in the previous case the azide (192) was obtained by the diazotization of the amine (183) and its subsequent displacement by sodium azide. These conditions gave a quantitative yield of a brown oil whose analytical and mass spectral data was consistent with the expected azide product (192). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure. The azide (192) in 1,2-dimethoxyethane was then treated at room temperature with trimethylphosphite to afford a quantitative yield of a brown oil which gave accurate mass data consistent with the molecular formula $C_{19}H_{20}NO_4P$. Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with the expected phosphinimine product (194). In the hope of forming the carbodiimide (190) directly, the phosphinimine (194) was treated with phenyl isocyanate in 1,2-dimethoxyethane at room temperature. This gave a complex red oil which was flash chromatographed over silica to give 1,3-diphenyl urea[103] in moderate yield. The remainder of the material was recovered as complex oils and gums, from which no identifiable material could be obtained. Repetition of this reaction, but with heating under reflux, again afforded a complex mixture, but this mixture was taken, and as a solution in 1,2-dimethoxyethane, treated with 2M aqueous hydrochloric acid. The resulting brown oil was flash chromatographed over silicate give the urea (193) in low yield (22%) and 1,3-diphenyl urea.[103] Although the isolation of the urea (193) indicated that there was some initial formation of the desired carbodiimide (195) the inability to obtain the compound in a pure form prompted the switch to an alternative methodology. Again, the methodology chosen for the synthesis of the desired carbodiimide derivative was via the dehydration of the appropriate urea derivative.

The amine (183) in dioxane was treated with phenyl isocyanate to give a good yield of a colourless crystalline product whose analytical and mass spectral data were consistent with the expected urea product (193). Its i.r. and ^1H n.m.r. spectroscopic properties were also in accord with this structure. A solution of the urea (193) in 1,2-dimethoxyethane was treated with diisopropylethylamine and phosphoryl chloride then heated under reflux. These conditions gave a brown gum, from which a colourless solid was isolated in good yield (71%) by extraction with 60-80 light petroleum. This solid gave accurate mass data consistent with the molecular formula $C_{23}H_{16}N_2O$. Its i.r. and ^1H n.m.r. spectroscopic properties were also in accord with the expected carbodiimide product (195), the i.r. spectrum showing absorption at 2142-2104cm^{-1} due to the carbodiimide substituent.

With the carbodiimide precursor (195) in hand it was subjected to the stannic chloride catalysed cyclisation conditions in refluxing 1,2-dichloroethane. These conditions gave a brown oil, from which flash chromatography gave a colourless solid in good yield (71%) whose spectroscopic properties were in accord with the expected benzonaphthoxazepine structure The ^1H n.m.r. spectrum also allowed positive assignment of the angular structure (196). The two naphthalene hydrogens on the side fused to the oxazepine ring were identified by correlation spectroscopy (COSY) experiments, and the coupling between these protons shown to be 8.7Hz. In the linear system this coupling would be much smaller, somewhere in the region of 0-1Hz.



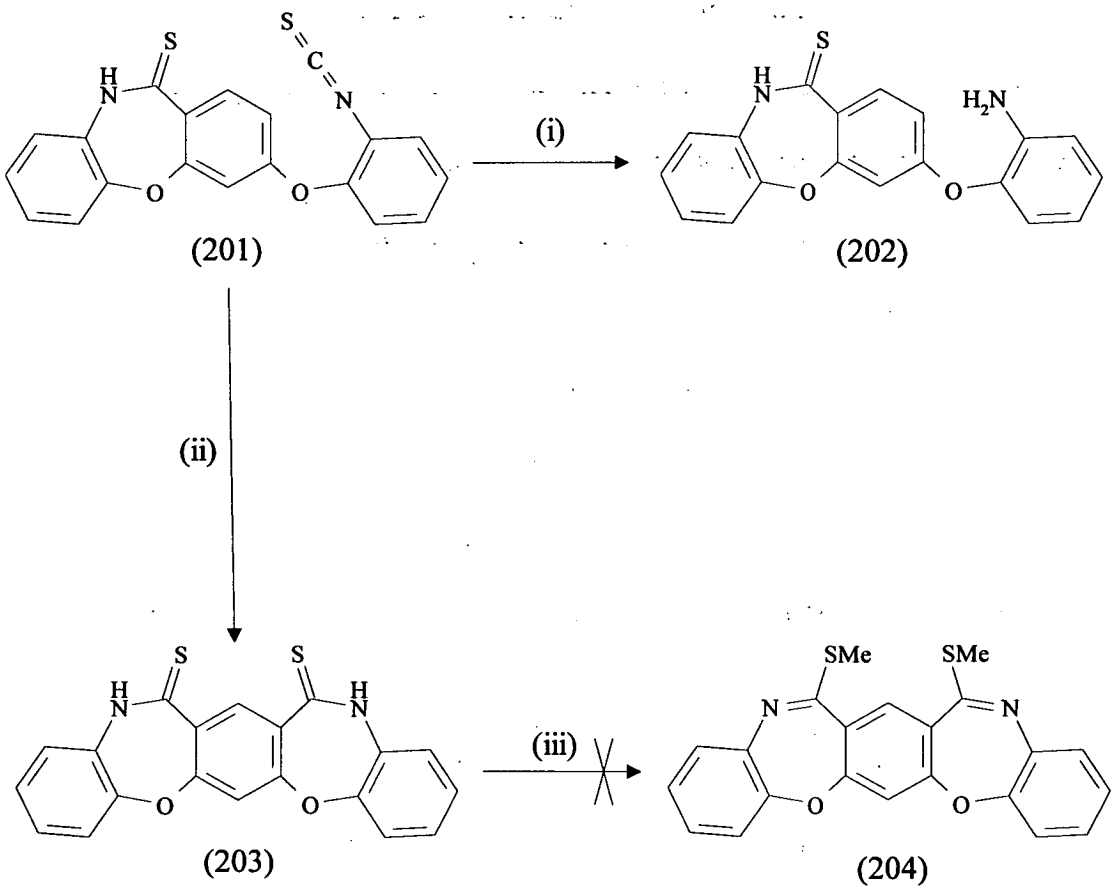
(i) NaH, DMF, 100^{o}.
(ii) H_2, Pd-C, DME, room temp., atmos press.
(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.
(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(v) $AlBr_3$ or $AlCl_3$, CH_2Cl_2, room temp. or -78^{o}- -10^{o}.

Scheme 46

3.3 Cyclisations of Heterocumulenes Leading to [1,5]Benzoxazepino-dibenz[b,f][1,4]oxazepines and [1,5]Benzoxazepinodibenz[b,e][1,4]oxazepines.

There are three dihydroxybenzene isomers which could be used in the synthesis of the desired isothiocyanate precursors. In the present investigations resorcinol (197) was chosen first. The substitution pattern of the hydroxyl groups in resorcinol allows both oxygen atoms to donate electrons in such a way as to doubly-activate certain positions on the benzene ring to the proposed Lewis acid catalysed ring closure step. This double activation does not occur when using either quinol (205) or catechol (212). Thus, resorcinol [Scheme 46; (197)] was reacted with two equivalents of 2-fluoronitrobenzene (61) in a sodium hydride catalysed reaction in dimethylformamide to afford in high yield the known[110] 1,3-bis-(2-nitrophenoxy)benzene (198) as a yellow crystalline solid. The nitro compound (198) was reduced catalytically over palladium-on-charcoal in 1,2-dimethoxyethane to give a high yield (98%) of a colourless crystalline solid whose analytical and mass spectral data was consistent with the expected amine product (199). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing amine absorption at 3416 and 3331cm^{-1}. The ^{1}H n.m.r. spectrum showed a broad four-proton signal at δ3.70 due to the exchangeable amine protons. The bis-nitro compound (198) was also reduced to the corresponding amine (199) in high yield (86%) by stannous chloride dihydrate in refluxing tetrahydrofuran in the presence of aqueous hydrochloric acid.

In order to gain the bis-isothiocyanate precursor the amine (199) was treated at room temperature with thiophosgene in aqueous hydrochloric acid and acetic acid. These conditions afforded a quantitative yield of a pale yellow oil, which gave analytical and



(i) 2M $NaOH_{(aq)}$, DME , reflux.
(ii) $AlCl_3$, CH_2Cl_2, reflux.
(iii) Me_2SO_4, NaH, DMF, room temp.

Scheme 47

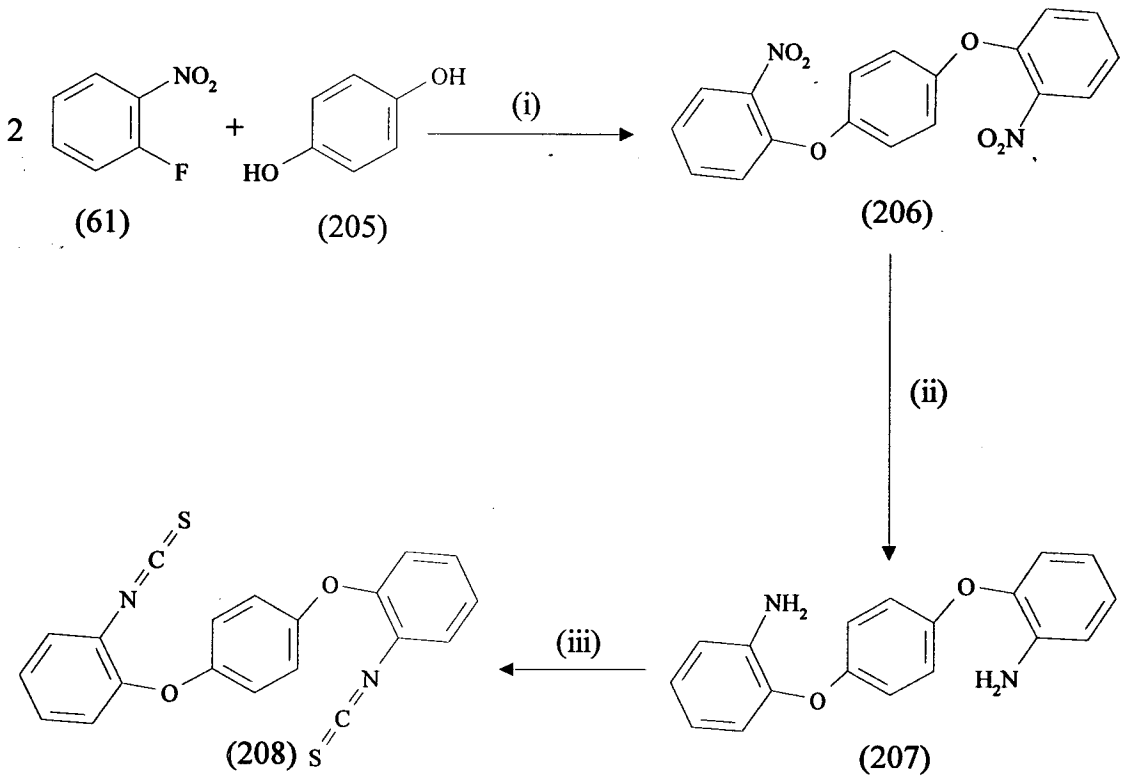
mass spectral data in accord with the expected 1,3-bis-(2-isothiocyanatophenoxy)benzene (200). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with this compound, the i.r. spectrum showing absorption at 2033cm^{-1} due to the isothiocyanate substituents.

With the bis-isothiocyanate (200) now in hand it was hoped that its treatment with a Lewis acid catalyst would result in the formation of a doubly-cyclised species. To this end a solution of the bis-isothiocyanate (200) in dichloromethane was treated with four equivalents of aluminium tribromide at room temperature. These conditions afforded a yellow multicomponent glass from which flash chromatography isolated a yellow crystalline product in low yield, whose analytical and mass spectral data were consistent with the expected product. However, the i.r. and ^{1}H n.m.r. spectroscopic properties of this compound identified it as the mono-cyclised species (201). The i.r. spectrum contained amine absorption at 3154cm^{-1} and absorption at 2029cm^{-1} from the isothiocyanate group. The ^{1}H n.m.r. spectrum showed the presence of the exchangeable amine hydrogen, with a broad one-proton signal at δ12.72. The ^{1}H n.m.r. spectrum also allowed positive assignment of the monocyclic structure (201). The three hydrogens of the substituted benzene ring were identified as an 8.9Hz double at δ8.07, a 2.5Hz doublet at δ6.95 and a doublet of doublets at δ6.87 with couplings of 8.9 and 2.5Hz, which is consistent with only the 3-substituted dibenzoxazepine (201). In the hope of gaining further verification of the structure of the mono-cyclised compound (201) (Scheme 47) an attempt was made to cleave the isothiocyanate substituent with aqueous base to give the corresponding amine. The mono-cyclised compound (201) in 1,2-dimethoxyethane was treated with 2M aqueous sodium hydroxide and heated under reflux. These conditions gave a yellow solid

which was flash chromatographed over silica to give a moderate yield of a yellow glass, which decomposed on attempted crystallisation from acetic acid and dimethylformamide. Its assignment as the amine (202) was, however, supported by its i.r. spectrum, which showed the presence of an amine group with absorption at 3458, 3334 and 3153cm^{-1} and the total lack of isothiocyanate absorption.

Further verification of the structure of the mono-cyclised species (201) was sought by the S-methylation of the thione moiety. However, the sodium hydride catalysed reaction of the mono-cyclised compound (201) with dimethyl sulphate in dimethylformamide at room temperature afforded a dark brown gum, from which flash chromatography gave only intractable oils and gums.

The cyclisation step was repeated (Scheme 46) using aluminium trichloride as the Lewis acid catalyst. These conditions afforded the mono-cyclised species (201) in moderate yield in a much cleaner reaction. The only other material present was a small amount of an intractable brown solid which remained on the baseline on t.l.c. on both silica and alumina. Although this baseline material could not be purified it was suspected that it was either the bis-cyclised material, resulting from the further reaction of the mono-cyclised species (201) or a complex polymeric species. Instead of trying to force a double cyclisation of the bis-isothiocyanate (200) it was thought that isolation of the mono-cyclised species (201) followed by a second, separate, Lewis acid catalysed reaction would allow a more detailed study of the reaction. In order to be able to study this second step it was necessary to purposely limit the initial reaction of the bis-isothiocyanate (199) to only a mono-cyclisation. This was achieved by using only two equivalents of aluminium trichloride and reducing the reaction temperature to -78°, in the hope of suppressing the formation of the suspected



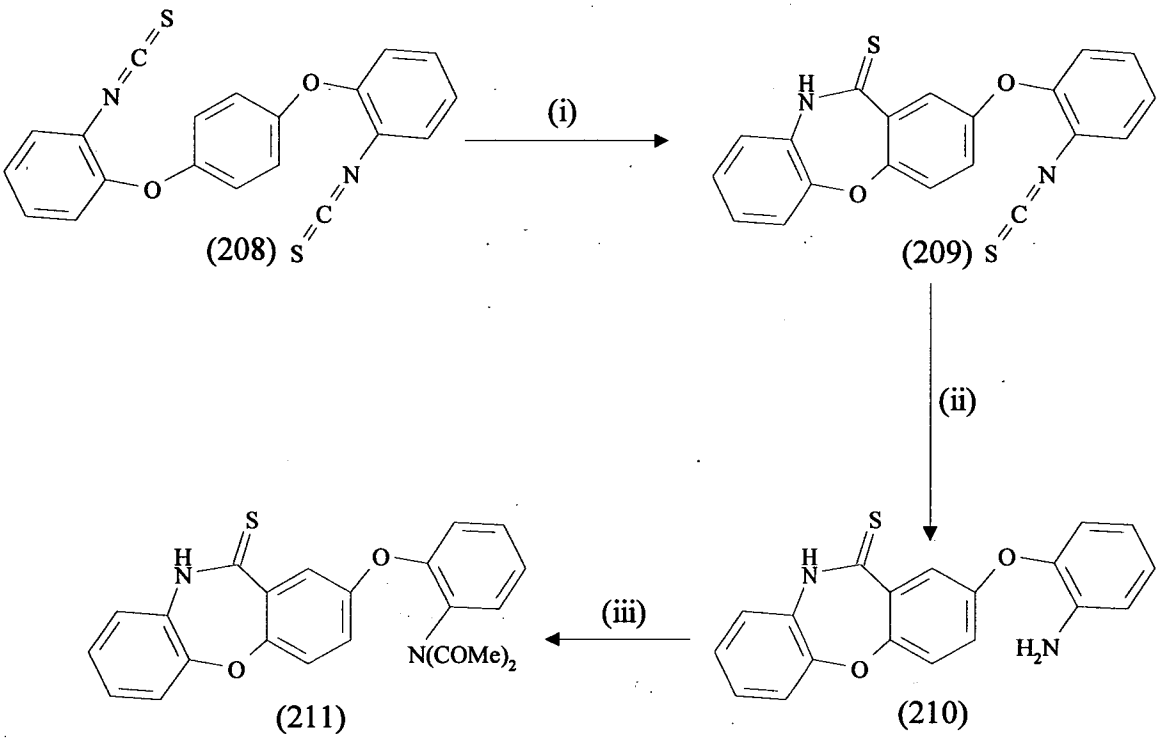
(i) NaH, DMF, 100^{o}.
(ii) H_2, Pd-C, DME, room temp., atmos press.
(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.
(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

Scheme 48

doubly-cyclised material. These conditions, however, afforded only a moderate yield of the mono-cyclised species (201) with the remainder of the mass again being made-up by the intractable brown baseline material.

In order to affect the second cyclisation the mono-cyclised compound (201) was again treated with two equivalents of aluminium trichloride in dichloromethane, but this time the mixture was heated under reflux. These conditions afforded a high yield of an intractable orange solid which, like the baseline material obtained before, would not run on t.l.c. on silica or alumina. This material proved very difficult to crystallise, but it was eventually purified by precipitation from dimethyl formamide with water, followed by repeated crystallisation from a dimethylformamide-acetonitrile mixture. The resulting yellow crystalline product gave analytical and mass spectral data consistent with a doubly-cyclised product (203). ^{1}H n.m.r. proved unsuccessful in identifying which of the two possible isomers was obtained, and X-ray diffraction was precluded by the inability to obtain high quality crystals. In the hope that the bis-methylthio compound (204) would be easier to handle, hence allowing a more rigorous characterisation of its structure, an attempt was made to S-methylate the proposed bis-cyclised compound (203) in a sodium hydride catalysed reaction with dimethyl sulphate. These conditions, however, afforded only an intractable solid which could not be purified, and hence yielded no further information as to the structure of the suspected bis-cyclised species (203).

After these successful investigations into the meta-substituted series it was decided to expand the investigations to encompass the two isomeric systems. The first to be studied was the para-substituted system (Scheme 48). The sodium hydride catalysed reaction of quinol (205) with two equivalents of 2-fluoronitrobenzene (61) in



(i) $AlBr_3$ or $AlCl_3$, CH_2Cl_2, room temp. or room temp. then reflux.
(ii) 2M $NaOH_{(aq)}$, EtOH, reflux.
(iii) Ac_2O, reflux.

Scheme 49

dimethylformamide afforded the known[111] 1,4-bis-(2-nitrophenoxy)benzene (206) in high yield as a cream crystalline solid. The bis-nitro compound (206) was reduced catalytically in 1,2-dimethoxyethane over palladium-on-charcoal to give a quantitative yield of a light brown crystalline product whose accurate mass data and spectroscopic properties were entirely consistent with the expected 1,4-bis-(2-aminophenoxy)benzene (207). The i.r. spectrum showed amine absorption at 3430 and 3351cm^{-1}. The ^{1}H n.m.r. spectrum contained a broad four-proton signal at δ3.56 due to the exchangeable amine hydrogens. The nitro-compound (206) was also reduced in high yield to the corresponding amine (207) by the use of stannous chloride dihydrate and aqueous hydrochloric acid in refluxing tetrahydrofuran.

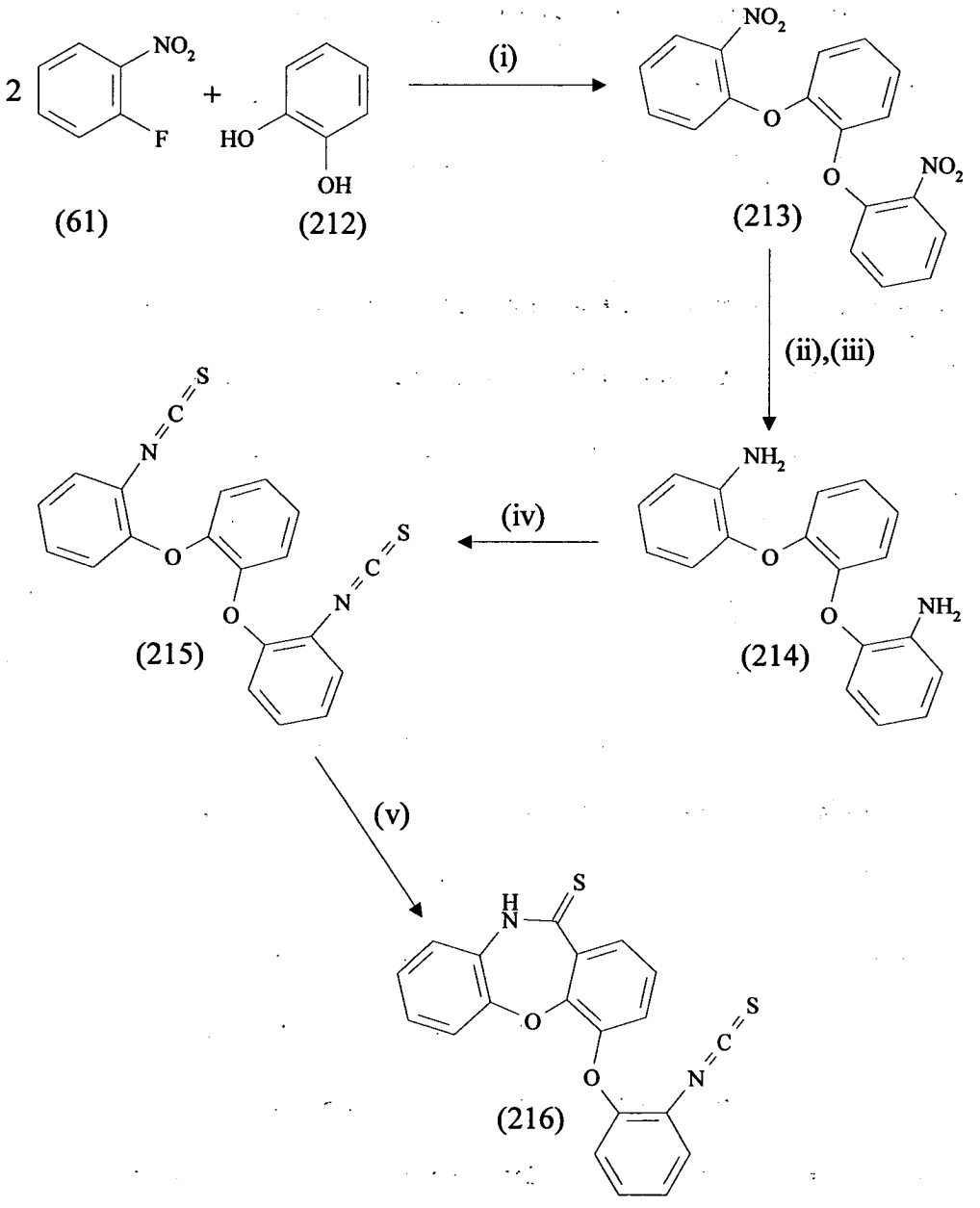
The amine (207) was next treated with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature for 2h. These conditions afforded a good yield of a light brown crystalline product whose analytical and mass spectral data were entirely consistent with the expected bis-isothiocyanate product (208). The product's i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2066cm^{-1} due to the isothiocyanate substituents. The yield of 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) was increased to quantitative levels by increasing the reaction time to 4h at room temperature.

With the bis-isothiocyanate precursor (208) in hand its Lewis acid catalysed cyclisation could now be investigated (Scheme 49). A solution of the bis-isothiocyanate in dichloromethane was treated at room temperature with four equivalents of aluminium tribromide, in the hope of inducing a double cyclisation. These conditions afforded a brown oil, which was flash chromatographed over silica to give the isothiocyanate starting material (208) in low yield. Flash chromatography

also gave in moderate yield (47%) a yellow crystalline product whose analytical and mass spectral data were consistent with a fully cyclised product. However, as in the meta-substituted series, i.r. and ^{1}H n.m.r. spectroscopy proved the product to be the mono-cyclised species (209). The i.r. spectrum had amine absorption at 3163cm^{-1} and multiple bond absorption at 2115-2055cm^{-1}. The ^{1}H n.m.r. spectrum contained a one-proton singlet at δ10.41 due to the hydrogen of the thiolactam moiety. In an attempt to verify the structure of the mono-cyclised species (209) by hydrolysis of the isothiocyanate-group the mono-cyclised species was treated with 2M aqueous sodium hydroxide in ethanol and heated under reflux. These conditions gave a good yield of a yellow crystalline product whose accurate mass data and spectroscopic properties were in accord with the expected amine product (210). The i.r. spectrum had amine absorption at 3462 and 3335cm^{-1} in addition to absorption at 3158cm^{-1} from the thiolactam moiety. The ^{1}H n.m.r. showed a one-proton singlet at δ10.67 from the thiolactam proton and a broad two-proton signal at δ3.46 due to the amine substituent. It was next decided to acylate this amine (210), hoping to further verify its structure. This transformation was achieved by refluxing the amine (210) in excess acetic anhydride for 3h. Aqueous work-up afforded a yellow crystalline solid in good yield which gave accurate mass data consistent with the molecular formula $C_{23}H_{18}N_2O_4S$. I.r. and ^{1}H n.m.r. spectroscopic data indicated that the amine had in fact undergone a double acylation. The ^{1}H n.m.r. spectrum showed a six-proton singlet at δ2.28 due to the two methyl-groups. Although this double acylation was not intentional the formation of the doubly acylated derivative (211) did serve to confirm the structure of the mono-cyclised species (209). However, in the hope of forming the thiourea derivative, and hence obtain further proof of its structure a solution of the

mono-cyclised compound (209) in dioxane was treated with aniline. Unfortunately, these conditions afforded only a dark brown gum, flash chromatography of which gave only a low yield of the unreacted mono-cyclised starting material (209), with the remainder of the material being recovered as intractable brown oils.

In the hope of improving the cyclisation step the Lewis acid catalyst was changed to aluminium trichloride. The bis-isothiocyanate (208) in dichloromethane was treated with four equivalents of aluminium trichloride and stirred at room temperature for 4h. These conditions gave a gummy brown solid which t.l.c. over silica showed to be a mixture of unreacted bis-isothiocyanate starting material (208) and mono-cyclised material (209). In the hope of pushing the reaction to completion this gummy solid was redissolved in dichloromethane, treated with another four equivalents of aluminium trichloride and the resulting mixture heated under reflux for a further 4h. These conditions gave the mono-cyclised compound (209) as a yellow solid, in 71% yield. In an attempt to simplify the synthesis of the mono-cyclised compound (209) the material was not isolated between stirring at room temperature and heating under reflux. Thus, the bis-isothiocyanate starting material (208) in dichloromethane was treated with four equivalents of aluminium trichloride, stirred at room temperature for 4h, then heated under reflux for a further 4h. However, these conditions afforded only a brown glassy solid, from which flash chromatography gave only an intractable brown solid. This solid could not be crystallised and would not run on t.l.c. on silica or alumina. Although, as in the meta-substituted case, this baseline material was suspected of being either a doubly-cyclised product or a polymeric material no characterisation was possible due to its intractable nature.



(i) NaH, DMF, 100^{o}.

(ii) H_2, Pd-C, DME, room temp., atmos press.

(iii) $SnCl_2$, $HCl_{(aq)}$, THF, reflux.

(iv) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

(v) $AlCl_3$, CH_2Cl_2, room temp. or -78^{o}- -10^{o}.

Scheme 50

It was also shown that using only two equivalents of aluminium trichloride the bis-isothiocyanate (208) could be purposely only mono-cyclised to give the desired mono-cyclised product (209) in moderate yield, with no formation of the intractable baseline material. Unfortunately, further investigation into the conversion of the mono-cyclised into the doubly-cyclised species was not possible due to lack of material.

Attention was next turned to the third and last isomeric series in this study. Catechol (212) was reacted in a sodium hydride catalysed reaction with two equivalents of 2-fluoronitrobenzene (61) in dimethylformamide at 100°. These conditions afforded a quantitative yield of a cream crystalline product whose analytical and spectroscopic properties were in total agreement with the expected 1,2-bis-(2-nitrophenoxy)benzene (213). The bis-nitro-compound in 1,2-dimethoxyethane was then hydrogenated over palladium-on-charcoal to give an excellent yield of a light brown crystalline solid whose analytical and mass spectral data were consistent with the desired amine product (214). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure. The i.r. spectrum showed absorption at 3392 and 3274cm^{-1} due to the amine-group, and the ^{1}H n.m.r. contained a broad four-proton signal at δ6.69 due to the exchangeable amine protons. The reduction of the nitro compound (213) to the corresponding amine (214) was also demonstrated by the action of stannous chloride dihydrate in refluxing tetrahydrofuran in the presence of aqueous hydrochloric acid. In this case, however, flash chromatography of the initial brown oil product afforded only a 52% yield of the desired amine (214), with the remainder of the mass being made up by an intractable tar.

The amine (214) was next reacted with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature to give a light brown crystalline product in quantitative yield whose analytical and mass spectral data was entirely consistent with the expected 1,2-bis-(2-isothiocyanatophenoxy)benzene (215). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2085cm^{-1} due to the two isothiocyanate substituents. With this bis-isothiocyanate (215) now in hand its Lewis acid catalysed cyclisation was next investigated.

A solution of the bis-isothiocyanate (215) in dichloromethane was treated with four equivalents of aluminium tribromide at room temperature. However, this resulted in no reaction, with the bis-isothiocyanate starting material (215) being recovered in high yield. However, on repeating this reaction but with heating under reflux, an intractable orange solid was obtained in high yield which would not run on t.l.c. on silica or alumina. As in the cases of the two isomeric systems this baseline material was suspected of being either the bis-cyclised compound or a polymeric species. Unfortunately, due to its intractable nature purification, and hence structural assignment, were not possible. The sample decomposed on attempted crystallisation. Chemical methods also proved unsuccessful in effecting a change in the solid. Treatment with both aqueous sodium hydroxide and hydrochloric acid left the material unchanged. In anticipation of getting a cleaner reaction the Lewis acid catalyst was changed to aluminium trichloride. The use of four equivalents of aluminium trichloride in dichloromethane at room temperature for 4h afforded a brown solid. T.l.c. of this solid showed it to be a complex mixture containing starting material (215), baseline material and a third component thought to be the mono-

cyclised species. In the hope of consuming all the bis-isothiocyanate starting material (215), and thereby improve the yield of the mono-cyclised species, this mixture was redissolved in dichloromethane, treated with another four equivalents of aluminium trichloride and heated under reflux for 4h. However, the only material isolated was a good yield of a brown solid which was shown not to run on t.l.c. This baseline material, having no isothiocyanate absorption band in the i.r. spectrum, had the same chemical and physical properties as the baseline material obtained earlier from the aluminium tribromide catalysed reaction. This material was suspected of being either doubly-cyclised product or polymeric material but characterisation was prevented by its intractable nature.

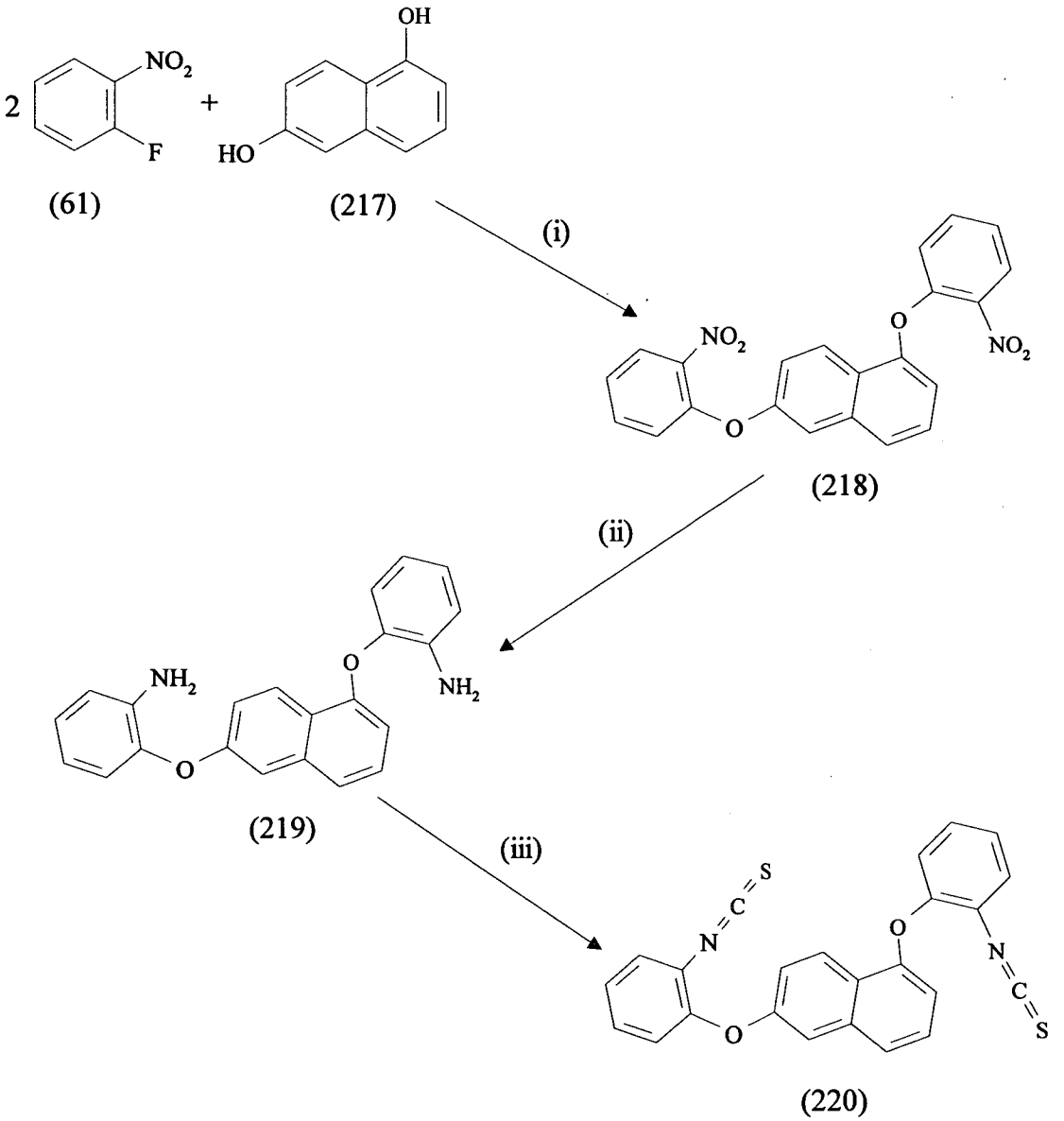
The room temperature reaction of the bis-isothiocyanate (215) with aluminium trichloride was repeated in the hope isolating some of the proposed mono-cyclised material by flash chromatography of the resulting complex mixture. However, this proved impossible, with the reaction giving a complex mixture from which no identifiable material could be isolated. Extending the reaction time to 24h at room temperature did however afford a mixture from which flash chromatography gave a low yield (8%) of unreacted bis-isothiocyanate starting material (215), along with a moderate yield (46%) of a yellow crystalline product whose analytical and mass spectral data were entirely consistent with the mono-cyclised species (216). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing amine absorption at 3356cm^{-1} from the thiolactam moiety, and an absorption at 2042cm^{-1} due to the isothiocyanate substituent. The remainder of the mass from this reaction was made up by baseline material. The result from this reaction seemed to show that like its isomeric structures (200) and (208) the bis-

isothiocyanate (215) undergoes mono-cyclisation at low temperature, with a limited conversion to the doubly-cyclised species. This second cyclisation occurs much more readily at higher temperatures, so if the mono-cyclised species are to be targeted lower temperature reactions must be used.

So that the second cyclisation step could be investigated it was necessary to obtain a reasonable quantity of the mono-cyclised material (216). It was anticipated that the reaction of the bis-isothiocyanate (215) with only two equivalents of aluminium trichloride in dichloromethane at room temperature for 24h would prove a viable route to the mono-cyclised product (216). Unfortunately, these conditions afforded none of the desired mono-cyclised compound (216), with the isothiocyanate starting material (215) being recovered in good yield. Lack of time prevented further investigation of this reaction and hence lack of material prevented the investigation of the second cyclisation step.

3.4 Cyclisations of Heterocumulenes Leading to [1,5]Benzoxazepino-benzo[b]naphth[1,4]oxazepines

After the limited success of the investigations towards the synthesis of benzoxazepinodibenzoxazepines it was anticipated that by replacing the central benzene with the more reactive naphthalene ring the chances of observing a double-cyclisation would be improved. Of the possible ten dihydroxynaphthalene isomers the four with both hydroxly-groups on the same ring were immediately discounted. It was hoped that by keeping the substituents on opposite ends of the naphthalene system the appropriate heterocumulene substrates would cyclise as if they were part of two

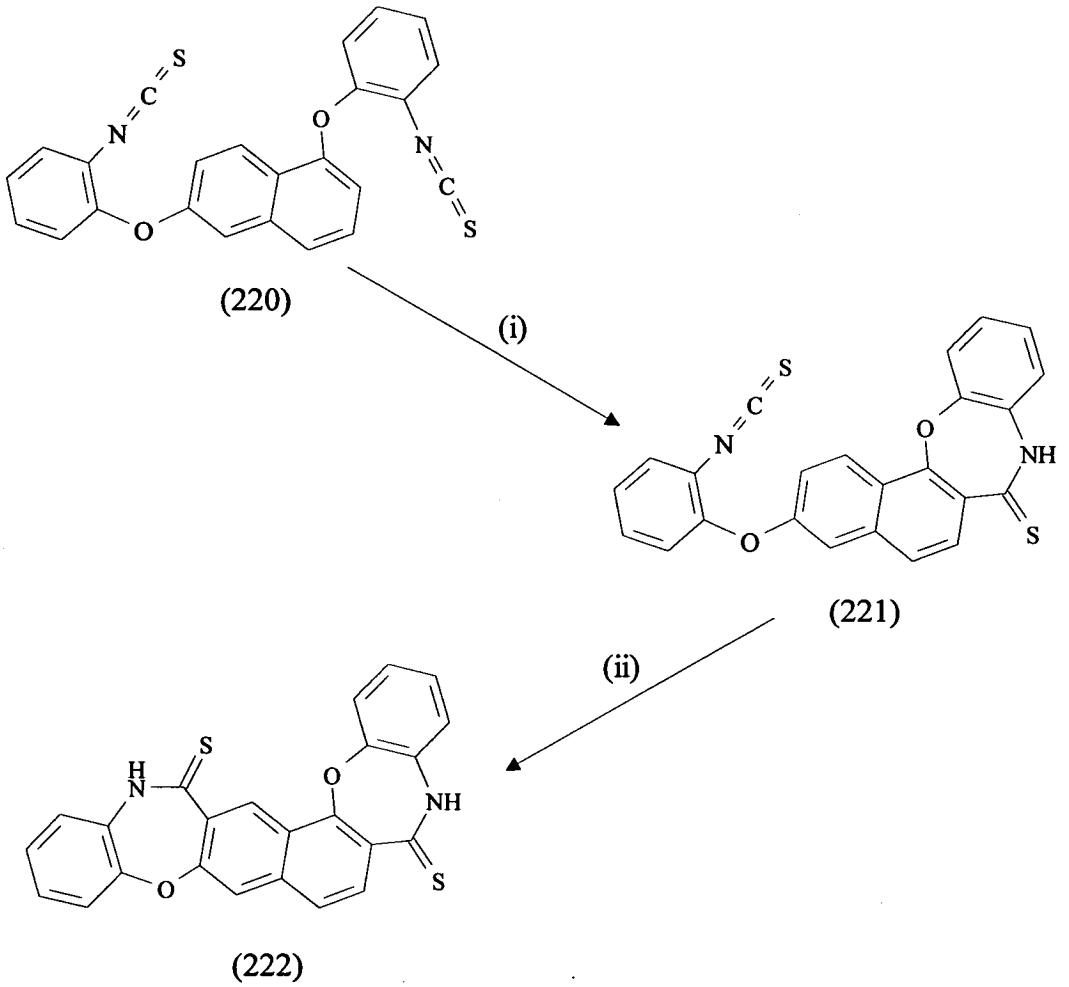


(i) NaH, DMF, 100^{o}.
(ii) H_2, Pd-C, AcOH or DMF, room temp., atmos. press.
(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

Scheme 51

discrete systems. Of the remaining six isomers only four were used in the present studies, the 1,7- and the 1,8-substituted compounds not being commercially available. Both the 1,6- and the 2,7-substituted systems contained sites which were doubly-activated to the Lewis acid catalysed reactions as described earlier in this chapter. In the 1,5- and the 2,6-substituted systems these sites are only singly-activated.

The first series investigated (Scheme 51) was that derived from 1,6-dihydroxynaphthalene (217). 1,6-Dihydroxynaphthalene (217) was coupled to two equivalents of 2-fluoronitrobenzene (61) by a sodium catalysed reaction in dimethylformamide. These conditions gave a good yield of a light brown crystalline product whose analytical and mass spectral data were consistent with the expected 1,6-bis-(2-nitrophenoxy)naphthalene (218). The bis-nitro compound (218) was hydrogenated in acetic acid at room temperature and atmospheric pressure over palladium-on-charcoal to give a dark brown viscous oil, from which flash chromatography gave in 75% yield a colourless crystalline solid, whose analytical and mass spectral data were consistent with the expected amine product (219). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing amine absorption at 3437 and 3352cm^{-1} and the ^{1}H n.m.r. containing a broad four-proton signal at δ3.65 due to the two amine groups. The yield of this reduction step was increased to 90% by changing the solvent to dimethylformamide. To obtain the bis-isothiocyanate precursor (220) the amine (219) was treated with thiophosgene in acetic acid in the presence of aqueous hydrochloric acid at room temperature. These conditions afforded a brown oil which was flash chromatographed over silica. This allowed the isolation in good yield (72%) of a colourless solid whose analytical and mass spectral data was consistent with its



(i) $AlCl_3$, CH_2Cl_2, room temp.

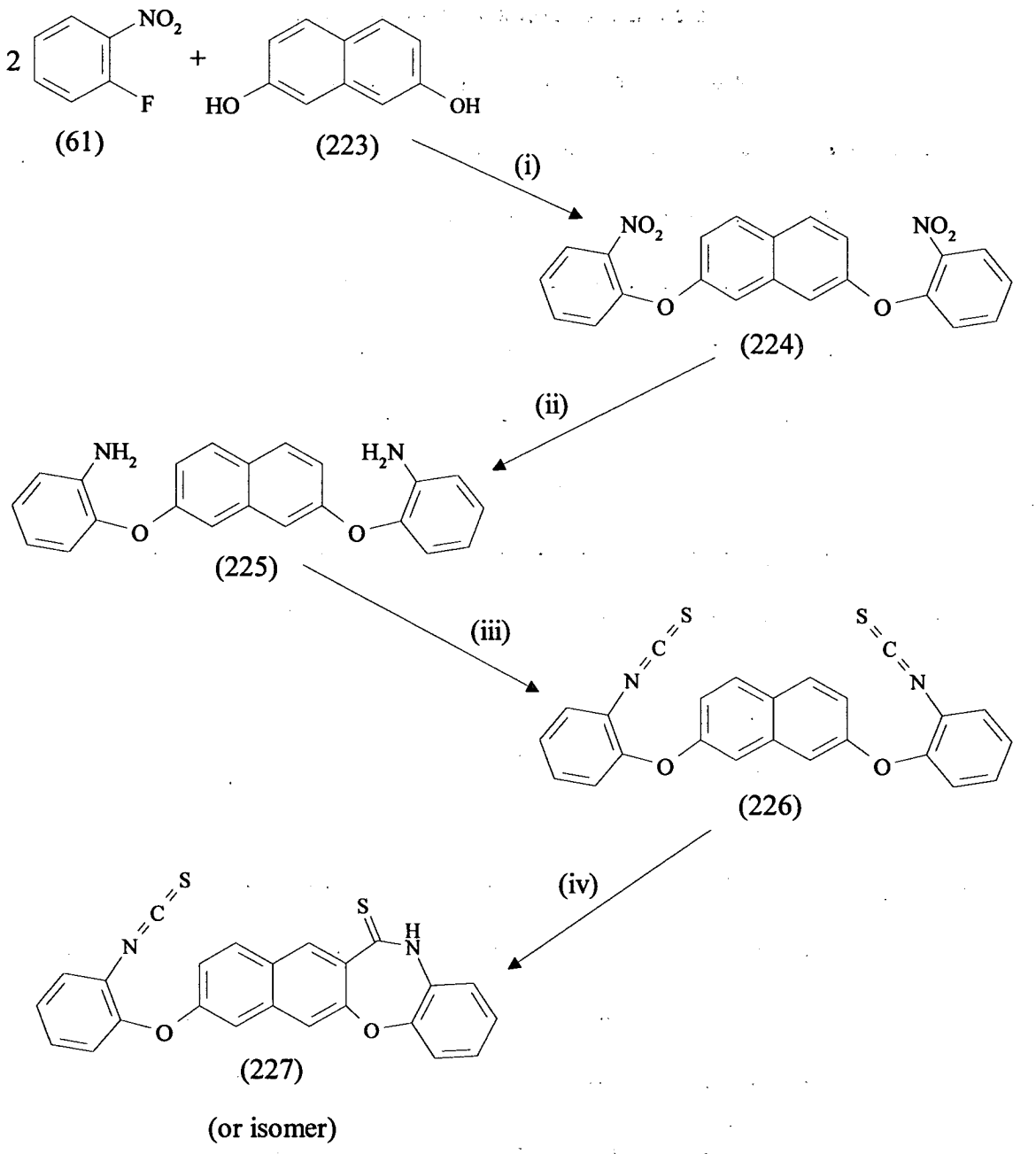
(ii) $AlCl_3$, CH_2Cl_2 or $Cl(CH_2)_2Cl$, reflux.

Scheme 52

formulation as 1,6-bis-(2-isothiocyanatophenoxy)naphthalene (220). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with this structure, the i.r. spectrum showing isothiocyanate absorption at 2061cm^{-1}. Flash chromatography also gave the amine starting material (219) in low yield.

With a good supply of the bis-isothiocyanate precursor (219) now in hand its Lewis acid catalysed cyclisations were investigated (Scheme 52). A solution of the bis-isothiocyanate (220) in dichloromethane was treated at room temperature with four equivalents of aluminium trichloride. These conditions gave a yellow solid, from which flash chromatography gave a yellow crystalline product in 67% yield whose analytical and mass spectral data were consistent with the doubly-cyclised product. However, i.r. spectroscopy showed the presence of an isothiocyanate substituent at 2033cm^{-1} in addition to the expected amine absorption at 3154 and 3105cm^{-1}. This spectroscopic data was entirely consistent with a mono-cyclised species, of which there were three possible isomeric structures. The correct isomer was identified using ^{1}H n.m.r. spectroscopy as 3-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221). The yield of this mono-cyclised compound (221) was increased by repeating the reaction using only two equivalents of aluminium trichloride, giving a 93% yield of the desired product (221).

As further verification of its structure an attempt was made to S-methylate the thiolactam moiety of the mono-cyclised species (221) in a sodium hydride catalysed reaction with dimethyl sulphate. These conditions afforded a complex mixture as a brown oil from which flash chromatographed over silica gave only intractable oils and gums which were not further investigated.



(i) NaH, DMF, 100°.
(ii) H_2, Pd-C, DMF, room temp., atmos. press.
(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(iv) $AlCl_3$, CH_2Cl_2, room temp.

Scheme 53

In the hope of fully cyclising the system a solution of the mono-cyclised compound (221) in dichloromethane was treated with a further two equivalents of aluminium trichloride then heated under reflux. These conditions gave a mixture of starting material (221) and one other component. Flash chromatography and crystallisation proved unsuccessful in separating this mixture. It was thought that using 1,2-dichloroethane, and thereby raising the reflux temperature of the solvent, the reaction would be pushed all the way through to completion, avoiding the difficulties of isolating the product from a complex mixture. These conditions did result in the consumption of all the starting material (221), affording an intractable light brown solid which stuck to the baseline on t.l.c. on silica and decomposed before melting. Although this compound gave accurate mass data and i.r. spectroscopic data consistent with a fully cyclised product its intractable nature prevented it from being fully identified.

Attention was next turned to the 2,7-substituted system (Scheme 53). A good yield of 2,7-bis-(2-nitrophenoxy)naphthalene (224) was obtained by the sodium hydride catalysed reaction of 2,7-dihydroxynaphthalene (223) with two equivalents of 2-fluoronitrobenzene (61). The bis-nitro compound (224) in dimethylformamide was reduced catalytically over palladium-on-charcoal to give a good yield of the desired bis-amine (225). Both the nitro compound (224) and the amine (225) gave analytical and spectroscopic data entirely consistent with their formulation as these products.

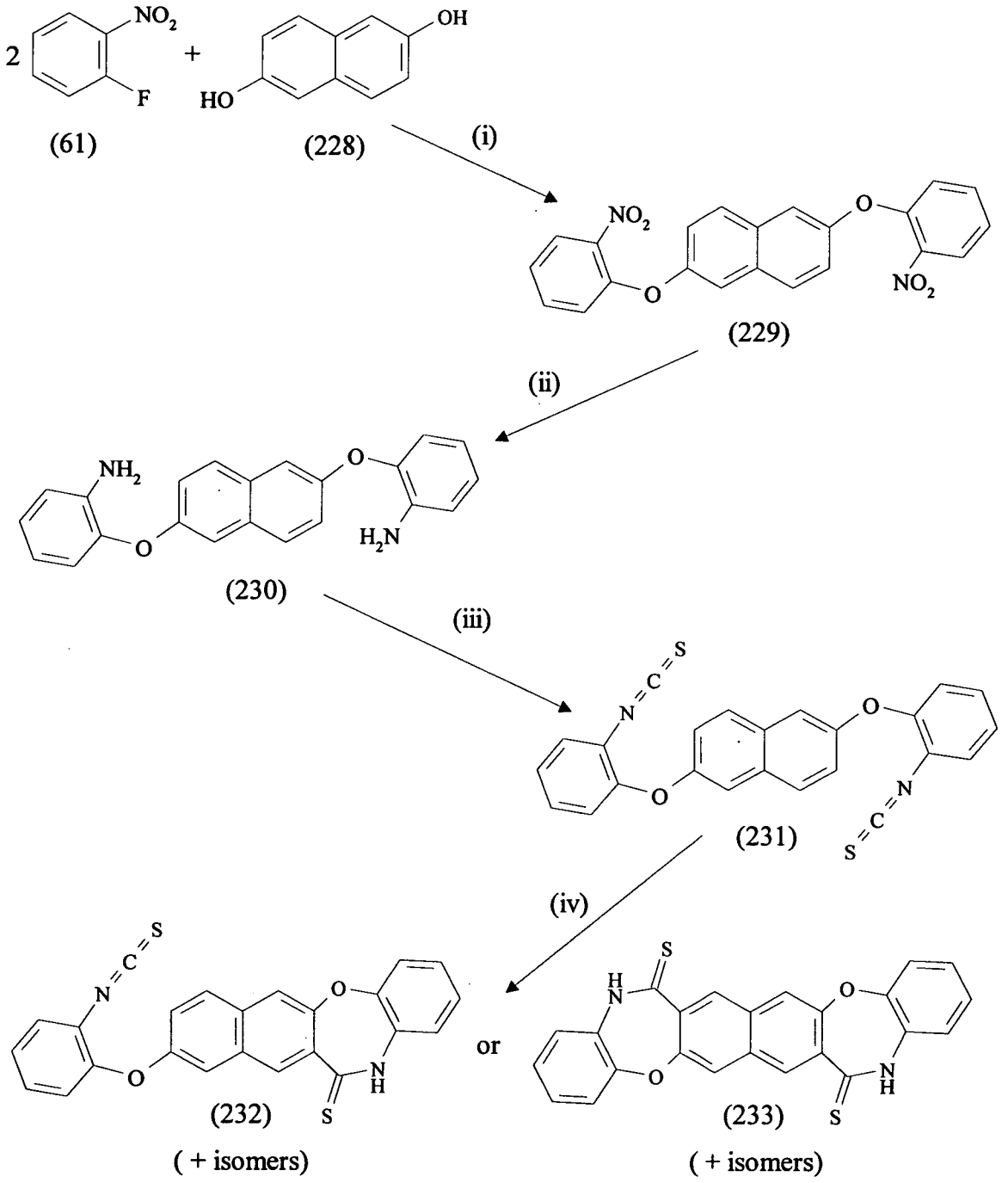
To obtain the bis-isothiocyanate precursor (226) the bis-amine (225) was treated with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature. These conditions afforded a red oil, from which flash chromatography gave a good yield of a light brown crystalline product whose analytical and mass spectral data were

consistent with the desired bis-isothiocyanate product (226). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in accord with this structure, the i.r. spectrum showing absorption at 2117 and 2082cm^{-1} due to the isothiocyanate substituents.

In the hope of forming a doubly-cyclised product a solution of the bis-isothiocyanate (226) in dichloromethane was treated at room temperature with four equivalents of aluminium trichloride. These conditions afforded a complex mixture as a yellow solid from which flash chromatography over silica gave a brown crystalline solid in moderate yield (33%) whose accurate mass data and i.r. and ^{1}H n.m.r. spectroscopic properties suggested that it was one of the mono-cyclised compounds (227). The i.r. spectrum showed isothiocyanate absorption at 2033cm^{-1}. The ^{1}H n.m.r. contained a one-proton singlet at δ13.25 due to the amine hydrogen of the thiolactam moiety. ^{1}H n.m.r. spectroscopy was, however, unsuccessful in identifying which of the two possible isomeric structures had actually been formed.

In an attempt to force the formation of a doubly cyclised product by raising the reaction temperature the bis-isothiocyanate (226) in 1,2-dichloroethane was treated with four equivalents of aluminium trichloride and heated under reflux for 4h. However, the only material isolated from the resulting mixture was a small amount of an intractable orange glass which could not be identified. The remainder of the material was recovered as mixed fractions.

In an attempt to purposely form the mono-cyclised compound (227) a solution of the bis-isothiocyanate (226) in dichloromethane was treated at room temperature with only two equivalents of aluminium trichloride. Unfortunately, these conditions again afforded a mixture of two components inseparable by chromatographic or chemical



(i) NaH, DMF, 100^{o}.

(ii) H_2, Pd-C, DMF, room temp., atmos. press.

(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.

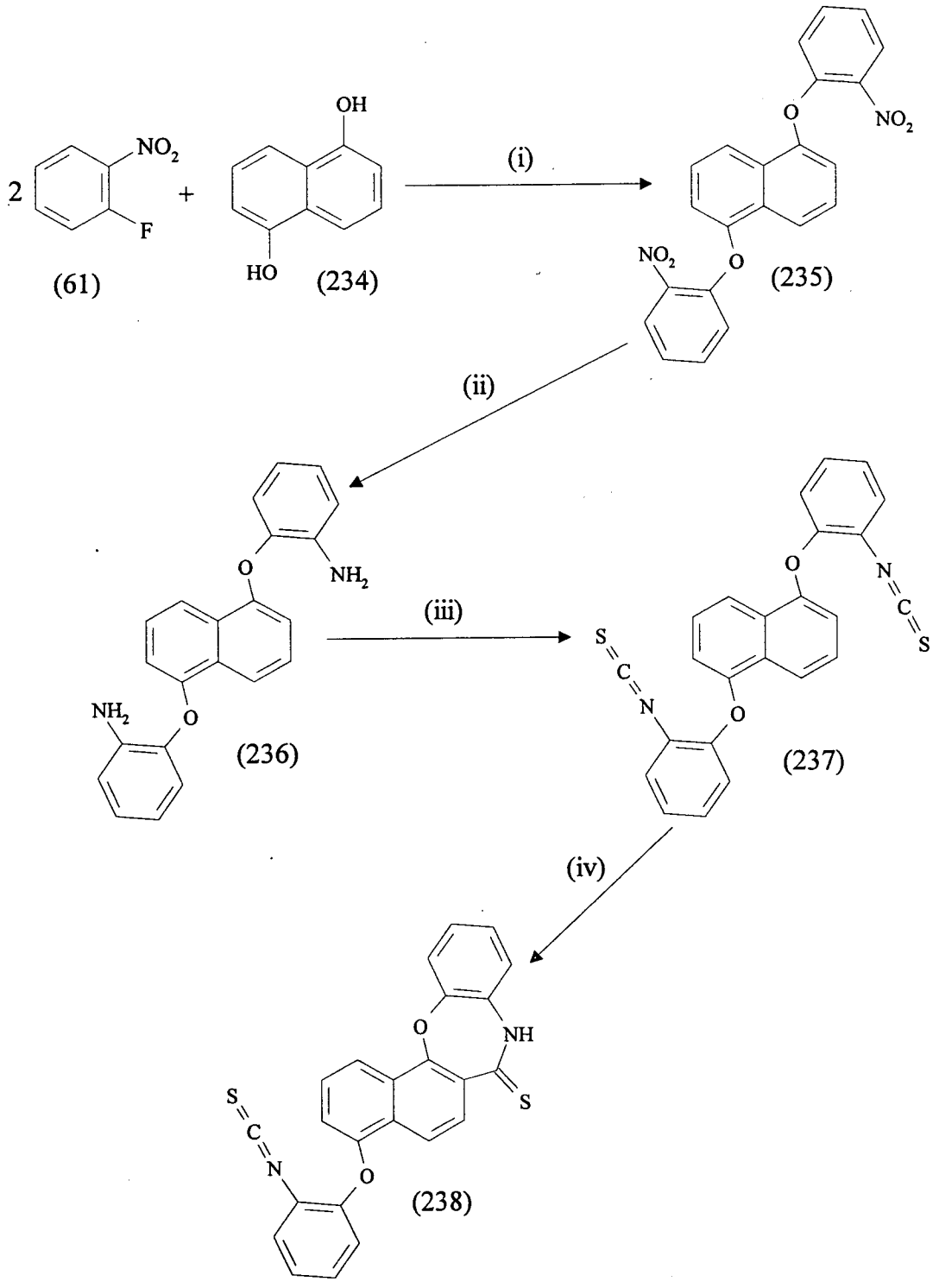
(iv) $AlCl_3$, CH_2Cl_2, room temp. or room temp. then reflux.

Scheme 54

methods. Due to lack of time and material these investigations were not pursued further.

The next system to be investigated (Scheme 54) was that derived from 2,6-dihydroxynaphthalene (228). The sodium hydride catalysed reaction of 2,6-dihydroxynaphthalene (228) with two equivalents of 2-fluoronitrobenzene (61) in dimethylformamide afforded a good yield of a yellow crystalline product, whose analytical and mass spectral data were consistent with its formulation as 2,6-bis-(2-nitrophenoxy)naphthalene (229). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also in agreement with this structure, the i.r. spectrum having nitro-absorption at 1518 and 1350cm^{-1}. The bis-nitro compound (229) in 1,2-dimethoxyethane was next hydrogenated over palladium-on-charcoal to give a good yield of the amine (230) as a pale brown crystalline product. The assignment of the amine structure (230) to this product was backed up by analytical and mass spectral data consistent with the molecular formula $C_{22}H_{18}N_2O_2$. Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with this amine structure. The i.r. spectrum showed amine absorption at 3441 and 3358cm^{-1}. The ^{1}H n.m.r. showed a four proton singlet at δ4.95 due to the two amine-groups. Further reaction of the amine (230) with thiophosgene in aqueous hydrochloric acid and acetic acid at room temperature afforded a moderate yield of a light brown solid, whose analytical and mass spectral data were consistent with the expected bis-isothiocyanate structure (231). This structure was further confirmed by its i.r. spectrum, which showed absorption at 2064cm^{-1} due to the two isothiocyanate substituents.

The bis-isothiocyanate (231) in dichloromethane was reacted with four equivalents of aluminium trichloride at room temperature in the hope of inducing a double



(i) NaH, DMF, 100°.
(ii) H_2, Pd-C, DMF, room temp., atmos. press.
(iii) $Cl_2C{=}S$, $HCl_{(aq)}$, AcOH, room temp.
(iv) $AlCl_3$, CH_2Cl_2, room temp.

Scheme 55

cyclisation. These conditions afforded a red solid from which flash chromatography gave a moderate yield of a light brown solid which gave accurate mass data consistent with the molecular formula $C_{24}H_{14}N_2O_2S_2$ and whose spectroscopic properties suggested that it was a mono-cyclised species (232). The i.r. spectrum showed the presence of an isothiocyanate substituent with absorption at 2031cm^{-1} and an amine absorption at 3149cm^{-1}. Unfortunately, ^{1}H n.m.r. spectroscopy proved unsuccessful in identifying which of the two isomeric mono-cyclised compounds was obtained. Raising the reaction temperature by the use of 1,2-dichloroethane as solvent under reflux resulted in no formation of the mono-cyclised species (232). Instead, These conditions afforded a moderate yield of a brown solid whose accurate mass data and i.r. spectroscopic properties suggested that it was a doubly-cyclised species (233). The i.r. spectrum showed amine absorption at 3121cm^{-1} with a total lack of isothiocyanate absorption. The intractable nature of this material, however, prevented further verification of its structure.

In the hope of improving the route to the mono-cyclised compound (232) the bis-isothiocyanate (231) was treated at room temperature with only two equivalents of aluminium trichloride. These conditions afforded a brown solid from which flash chromatography gave only a low yield of the desired product (232). The remainder of the material was recovered as complex oils and gums. Lack of time prevented further investigations into this line of study.

The last system to be studied (Scheme 55) was that resulting from the functionalisation of 1,5-dihydroxynaphthalene (234). The sodium hydride catalysed reaction of 1,5-dihydroxynaphthalene (234) with two equivalents of 2-fluoronitrobenzene (61) in dimethylformamide gave a 71% yield of a pale yellow solid

whose analytical and spectroscopic properties were consistent with its formulation as 1,5-bis-(2-nitrophenoxy)naphthalene (235). The bis-nitro compound (235) was hydrogenated at room temperature and atmospheric pressure in dimethylformamide to give a quantitative yield of a grey crystalline product whose analytical and mass spectral data were in accord with the expected bis-amine structure (236). Its i.r. and ^{1}H n.m.r. spectroscopic properties were also consistent with this structure. The i.r. spectrum had amine absorption at 3429 and 3351cm^{-1} and the ^{1}H n.m.r. spectrum contained a broad four-proton signal at δ4.98 due to the two amine substituents. Reaction of the amine (236) with thiophosgene in aqueous hydrochloric acid and acetic acid again afforded a quantitative yield of the desired product as a light brown crystalline solid. Analytical and mass spectral data from this solid were consistent with the bis-isothiocyanate structure (237), as were its i.r. and ^{1}H n.m.r. spectroscopic properties. The i.r. spectrum showed absorption at 2068cm^{-1} due to the two isothiocyanate substituents.

In the hope of forming the bis-cyclised species a solution of the bis-isothiocyanate (237) in dichloromethane was treated at room temperature with four equivalents of aluminium trichloride. These conditions afforded a complex mixture, from which flash chromatography gave a moderate yield of a yellow crystalline material whose spectroscopic properties suggested that it was the mono-cyclised compound (238). The mass spectrum had a molecular ion peak at m\e 426. In addition to isothiocyanate absorption at 2103-2026cm^{-1} the i.r. spectrum also showed absorption at 3110cm^{-1} suggesting an amine substituent.

In an attempt to force a double cyclisation of the bis-isothiocyanate (237) the aluminium trichloride catalysed reaction was repeated, but using 1,2-dichloroethane as

the solvent and with stirring at room temperature for 4h then at reflux for 3h. However, the only material obtained from this reaction was an intractable brown solid. Although this was suspected of being either the doubly-cyclised compound or a complex polymeric material it could not be identified by the usual analytical and spectroscopic techniques.

In an attempt to purposely mono-cyclise the bis-isothiocyanate (237), and hence gain a better route to the mono-cyclised compound (238) the bis-isothiocyanate (237) was treated at room temperature in dichloromethane with only two equivalents of aluminium trichloride. These conditions afforded a dark brown gum, from which the desired mono-cyclised product (238) was isolated in good yield by trituration with ether. The remainder of the material was recovered as a complex brown gum, from which no further identifiable material could be obtained.

The intractable nature of the proposed polycyclic species encountered throughout these studies prevented a more thorough assignment of their structure. Unfortunately lack of time, and often material, prevented the further work required to accomplish this goal.

3.5 Experimental.

General Experimental Details

General experimental details are as described in Chapter 2, page 74.

The Reaction of 2-Fluoronitrobenzene with Hydroxynaphthalene Derivatives in Dimethylformamide at 100°.

A suspension of sodium hydride (10.4g; 0.44mol) in anhydrous dimethylformamide (160ml) was vigorously stirred and treated dropwise at 0-10° (ice bath) with a solution of the corresponding hydroxynaphthalene derivative (0.4mol) in anhydrous dimethylformamide (80.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 2-fluoronitrobenzene (61) (62.0g; 0.4mol) in anhydrous dimethylformamide (240ml) was added in one portion and the mixture stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (120ml) and rotary evaporated to give a green residue which was treated with water (800ml) and extracted three times with ether (3 x 1000ml) to give the product.

(i) 1-Hydroxynaphthalene (175) gave 1-(2-nitrophenoxy)naphthalene (176) as a yellow solid (100%), which formed cream crystals, m.p. 46-47° (from ethanol), ν_{max} 1517 and 1340 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.12 (1H, dd J 6.8 and 4.2Hz, ArH), 7.99 (1H, dd J 8.4 and 1.8Hz, ArH), 7.90 (1H, dd J 6.8 and 2.6Hz, ArH), 7.71 (1H, d J 8.4Hz, ArH), 7.59-7.38 (4H, m, ArH), 7.25-7.13 (1H, m, ArH), 7.03 (1H, d J 7.5Hz, ArH) and 6.89 (1H, dd J 8.4 and 1.1Hz, ArH);

Found: C, 72.6; H, 4.0; N, 5.1%; m/z (EI ms), 265 (M^+),

$C_{16}H_{11}NO_3$ requires: C, 72.7; H, 4.2; N, 5.3%; M, 265.

(ii) 2-Hydroxynaphthalene (181) gave the known[109] 2-(2-nitrophenoxy)naphthalene (182) as a yellow solid (100%), m.p. 45-49° (crude), (lit.[109], 58-60°).

(2-Aminophenoxy)naphthalene Derivatives.

(a) A solution of the corresponding (2-nitrophenoxy)naphthalene derivative (0.2mol) in 1,2-dimethoxyethane (200ml) was hydrogenated over 10% palladium-on-charcoal (5.2g) at room temperature and atmospheric pressure for 5h, during which time 14000ml hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate rotary evaporated to give the desired amine product.

(i) Reduction of 1-(2-nitrophenoxy)naphthalene (176) gave 1-(2-aminophenoxy)naphthalene (177) as a light brown oil (100%), b.p. 160°/0.6mmHg, ν_{max} 3467 and 3377 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 8.37-8.33 (1H, m, ArH), 7.92-7.84 (1H, m, ArH), 7.59-7.49 (3H, m, ArH), 7.31 (1H, q J 8.0Hz, ArH), 7.03 (1H, dt J 8.0 and 1.5Hz, ArH), 6.92-6.69 (4H, m, ArH) and 3.74 (2H, bs, NH_2) (exch);

Found: C, 81.5; H, 5.5; N, 6.0%; m/z (EI ms), 235 (M^+),

$C_{16}H_{13}NO$ requires: C, 81.7; H, 5.5; N, 6.0%; M, 235.

(ii) Reduction of 2-(2-nitrophenoxy)naphthalene (182) gave the known[109] 2-(2-aminophenoxy)naphthalene (183) as a light brown solid (100%), which formed cream microcrystals, m.p. 78-79° (from hexane-ethanol), (lit.[109], 81-82°).

(b) A solution of the (2-nitrophenoxy)naphthalene derivative (0.004mol) in tetrahydrofuran (40.0ml) was treated with a solution of stannous chloride dihydrate (0.018mol) in 2M aqueous hydrochloric acid (40.0ml) and the mixture then stirred under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% w/v aqueous sodium hydroxide solution, then concentrated by rotary evaporation to remove the tetrahydrofuran. The resulting aqueous residue was then extracted three times with ether (3 x 50.0ml) and the combined organic extracts rotary evaporated to give a residue which was worked up as described for the individual reactions below.

(i) Reduction of 1-(2-nitrophenoxy)naphthalene (176) gave 1-(2-aminophenoxy)naphthalene (177) as a red oil (1.0g; 100%), identical (i.r. spectrum) to an authentic sample prepared before.

(ii) Reduction of 2-(2-nitrophenoxy)naphthalene (182) gave a pink solid (0.87g) which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded a mixed fraction as a cream solid (0.71g) which was crystallised from hexane-ethanol to afford 2-(2-aminophenoxy)naphthalene (183) as a light brown solid (91%), m.p. 65-69°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The hexane-ethanol mother liquor was rotary evaporated to give a mixed fraction as a brown semi-solid (0.10g), which was not further investigated.

Further elution with methanol afforded a brown gum (0.055g) which was not further investigated.

(2-Isothiocyanatophenoxy)naphthalene Derivatives.

A solution of the corresponding (2-aminophenoxy)naphthalene derivative (0.04mol) in glacial acetic acid (131ml) was stirred and treated in one portion with a 1:1 mixture of concentrated hydrochloric acid and water (37.5ml). The mixture was then treated dropwise at room temperature with a solution of thiophosgene (92.0g; 0.8mol) in glacial acetic acid (19.0ml) and the mixture stirred at room temperature for 4h.

The mixture was diluted with water (150ml) and extracted three times with dichloromethane (3 x 300ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 150ml) then dried and rotary evaporated to give the desired isothiocyanate products.

(i) 1-(2-Aminophenoxy)naphthalene (177) afforded 1-(2-isothiocyanatophenoxy)naphthalene (178) as a brown oil (100%), b.p. 204°/0.1mmHg, ν_{max} 2029 (NCS) cm^{-1}, δ_H ($CDCl_3$) 8.23-8.15 (1H, m, ArH), 7.94-7.86 (1H, m, ArH), 7.68 (1H, d J 8.3Hz, ArH), 7.60-7.58 (2H, m, ArH), 7.41 (1H, t J 7.9Hz, ArH), 7.27 (1H, dd J 7.5 and 1.8Hz, ArH), 7.20-7.02 (2H, m, ArH), 6.95 (1H, dd J 7.5 and 1.0Hz, ArH) and 6.86 (1H, dd J 7.5 and 1.8Hz, ArH);

Found: C, 73.0; H, 3.9; N, 5.2%; m/z (EI HRMS), 277.0568 (M^+),

$C_{17}H_{11}NOS$ requires: C, 73.6; H, 4.0; N, 5.1%; M, 277.0561.

(ii) 2-(2-Aminophenoxy)naphthalene (183) afforded 2-(2-isothiocyanatophenoxy)naphthalene (184) as a brown solid (100%), which formed light brown crystals, m.p. 38-41° (from ethanol), ν_{max} 2028 (NCS) cm^{-1}, δ_H ($CDCl_3$) 7.92-7.81 (2H, m, ArH), 7.77-7.69 (1H, m, ArH), 7.51-7.38 (2H, m, ArH), 7.32-7.17

(4H, m, ArH), 7.11 (1H, dd J 7.5 and 1.6Hz, ArH) and 6.99 (1H, dd J 7.5 and 1.6Hz, ArH);

Found: C, 73.8; H, 4.3; N, 4.9%; m/z (EI ms), 277 (M^+),

$C_{17}H_{11}NOS$ requires: C, 73.6; H, 4.0; N, 5.1%; M, 277.

Lewis Acid Catalysed Cyclisations of (2-Isothiocyanatophenoxy)naphthalene Derivatives.

(a) A solution of the corresponding (2-isothiocyanatophenoxy)naphthalene derivative (0.005mol) in anhydrous dichloromethane (10.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of aluminium tribromide (2.67g; 0.01mol) in anhydrous dichloromethane (25.0ml) and the mixture then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml) then stirred at room temperature for 15min. The mixture was extracted three times with dichloromethane (3 x 50.0ml) to give a residue which was worked up as described for the individual reactions below.

(i) 1-(2-Isothiocyanatophenoxy)naphthalene (178) afforded a light brown oily solid (1.3g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded a mixed fraction as a brown oil (0.22g) which was not further investigated.

Further elution with hexane-ether (85:15) afforded benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (179) as a yellow solid (43%), which formed yellow cubes, m.p. 258-261° (from toluene), ν_{max} 3154 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.85 (1H, bs, NH) (exch), 8.67 (1H, t J 4.3Hz, ArH), 8.05-7.94 (2H, m, ArH), 7.79-7.48 (4H,

m, ArH) and 7.37-7.13 (3H, m, ArH), δ_C [$(CD_3)_2SO$] 196.3 (quat), 153.0 (quat), 152.7 (quat), 136.3 (quat), 132.6 (quat), 129.2 (CH), 129.1 (CH), 127.9 (2CH), 127.3 (CH), 126.4 (CH), 126.3 (quat), 125.4 (quat), 124.5 (CH), 123.3 (CH), 122.5 (CH) and 121.5 (CH);

Found: C, 73.6; H, 4.2; N, 4.9%; m/z (EI ms), 277 (M^+),

$C_{17}H_{11}NOS$ requires: C, 73.6; H, 4.0; N, 5.1%; M, 277.

Further elution with methanol afforded an unidentified brown solid (0.15g) which was not further investigated.

(ii) 2-(2-Isothiocyanatophenoxy)naphthalene (184) afforded benzo[b]naphth[1,2-f][1,4]oxazepine-13(12H)-thione (185) as a brown solid (93%), which formed brown crystals, m.p. 258-261° (from toluene), ν_{max} 3141 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.85 (1H, bs, NH) (exch), 8.68 (1H, t J 4.1Hz, ArH), 8.05-7.97 (2H, m, ArH), 7.80-7.60 (4H, m, ArH) and 7.37-7.14 (3H, m, ArH), δ_C [$(CD_3)_2SO$] 156.0 (quat), 155.0 (quat), 133.4 (CH), 132.3 (quat), 131.8 (quat), 131.7 (quat), 129.0 (quat), 128.2 (CH), 127.4 (CH), 126.9 (CH), 126.5 (CH), 126.3 (CH), 125.8 (CH), 125.4 (quat), 122.7 (CH), 121.1)CH) and 119.9 (CH);

Found: C, 73.8; H, 4.4; N, 5.0%; m/z (EI ms), 277 (M^+),

$C_{17}H_{11}NOS$ requires: C, 73.6; H, 4.0; N, 5.1%; M, 277.

(b) A suspension of aluminium tribromide (2.7g; 0.01mol) in anhydrous dichloromethane (25.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of the corresponding (2-isothiocyanatophenoxy)naphthalene derivative

(0.005mol) in anhydrous dichloromethane (10.0ml) and the mixture then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (85.0ml) then stirred at room temperature for 15min. The mixture was then extracted three times with dichloromethane (3 x 100ml) to give a solid which was flash chromatographed.

Elution with hexane-ether (60:40) afforded mixed fractions which were not further investigated.

Further elution with hexane-ether (40:60) afforded the desired product.

(i) 1-(2-Isothiocyanatophenoxy)naphthalene (178) afforded benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (179) as a yellow solid (79%), m.p. 255-260°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(ii) The reaction with 2-(2-isothiocyanatophenoxy)naphthalene (184) afforded benzo[b]naphth[1,2-f][1,4]oxazepine-13(12H)-thione (185) as a yellow solid (66%), m.p. 253-260°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(c) The reaction was repeated as described in (b) before, but using aluminium trichloride (8.0g; 0.06mol) as the catalyst.

(i) 1-(2-Isothiocyanatophenoxy)naphthalene (178) afforded benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (179) as a yellow solid (95%), m.p. 255-262°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(ii) 2-(2-Isothiocyanatophenoxy)naphthalene (184) afforded benzo[b]naphth[1,2-f][1,4]oxazepine-13(12H)-thione (185) as a yellow solid (100%), m.p. 257-266°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Methylthiobenzo[b]naphth[1,4]oxazepine Derivatives.

A suspension of sodium hydride (0.026g; 0.0011mol) in anhydrous dimethylformamide (10.0ml) was vigorously stirred and treated at room temperature with a solution of the corresponding benzonaphthoxazepinethione derivative (0.01mol) in anhydrous dimethylformamide (30.0ml) added in one portion and the mixture was stirred at room temperature with the exclusion of atmospheric moisture for 15min. A solution of dimethyl sulphate (5.0g; 0.04mol) in anhydrous dimethylformamide (10.0ml) was then added in one portion and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with water (20.0ml) and stirred at room temperature for 10min. Rotary evaporation gave a brown solid residue which was treated with water (40.0ml) giving a brown gummy solid which was flash chromatographed over silica as described for the individual reactions below.

(i) In the reaction with benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (179), elution with hexane-ether (99:1) afforded 7-methylthiobenzo[b]naphth[2,1-f][1,4]oxazepine (180) as a yellow solid (68%), which formed cream microcrystals, m.p. 182-184° (from acetic acid), δ_H 8.52 (1H, d J 8.0Hz, ArH), 8.14 (1H, d J 8.9Hz, ArH), 7.98 (1H, d J 3.6Hz, ArH), 7.64-7.49 (3H, m, ArH), 7.30-7.10 (4H, m, ArH) and 2.50 (3H, s, SCH_3);

Found: C, 73.8; H, 4.5; N, 4.7%; m/z (EI ms), 291.0710 (M^+),

$C_{18}H_{13}NOS$ requires: C, 74.2; H, 4.1; N, 4.8%; M, 291.0718.

Further elution with hexane-ether (99:1) afforded 8-methylbenzo[b]naphth[2,1-f][1,4]oxazepine-7-thione as a yellow solid (3%), which formed cream microcrystals, m.p. 182-184° (from acetic acid), δ_H 8.56-8.51 (1H, m, ArH), 8.09 (1H, d J 8.8Hz, ArH), 7.92-7.11 (8H, m, ArH), and 4.11 (3H, s, NCH_3);

Found: C, 73.5; H, 4.5; N, 4.7%; m/z (EI ms), 291.0717 (M^+),

$C_{18}H_{13}NOS$ requires: C, 74.2; H, 4.1; N, 4.8%; M, 291.0718.

Final elution with methanol afforded a brown gum (0.20g) which was not further investigated.

(ii) In the reaction with benzo[b]naphth[1,2-f][1,4]oxazepine-13(12H)-thione (185), elution with hexane-ether (88:12) afforded 13-methylthiobenzo[b]naphth[1,2-f][1,4]oxazepine (186) as a yellow solid (76%), which formed cream microcrystals, m.p. 172-173° (from acetic acid), δ_H 8.52 (1H, d J 8.0Hz, ArH), 8.14 (1H, d J 8.9Hz, ArH), 7.98 (1H, d J 3.6Hz, ArH), 7.64-7.49 (3H, m, ArH), 7.30-7.10 (4H, m, ArH) and 2.50 (3H, s, SCH_3);

Found: C, 73.9; H, 4.3; N, 4.6%; m/z (EI ms), 291 (M^+),

$C_{18}H_{13}NOS$ requires: C, 74.2; H, 4.1; N, 4.8%; M, 291.

Further elution with hexane-ether (99:1) afforded 12-methylbenzo[b]naphth[1,2-f][1,4]oxazepine-13-thione as an orange oil (14%), (FAB ms) 292 (MH^+), which decomposed on attempted distillation.

Final elution with methanol afforded a brown gum (0.21g) which was not further investigated.

(2-Azidophenoxy)naphthalene Derivatives.

The corresponding (2-aminophenoxy)naphthalene derivative (0.05mol) was treated with 5M aqueous hydrochloric acid (125ml) and warmed gently to form a suspension of hydrochloride salt. This mixture was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (3.8g; 0.055mol) in water (25.0ml) at such a rate that the reaction temperature was <5°, then stirred at 0° for 10 min. A solution of sodium azide (4.9g; 0.075mol) in water (25.0ml) was added dropwise at such a rate that the reaction temperature was <5°, and the mixture then stirred in the melting ice bath for 30 min.

The mixture was extracted three times with dichloromethane (3 x 125ml) to afford the desired azide product.

(i) 1-(2-Aminophenoxy)naphthalene (177) afforded 1-(2-azidophenoxy)naphthalene (187) as a light brown oil (100%), ν_{max} 2116 (N_3) cm^{-1}, δ_H ($CDCl_3$) 8.33-8.26 (1H, m, ArH), 7.93-7.87 (1H, m, ArH), 7.65-7.52 (3H, m, ArH), 7.40-7.34 (1H, m, ArH),

7.25-7.06 (3H, m, ArH), 6.97-6.93 (1H, m, ArH) and 6.82 (1H, dd J 7.6 and 1.0Hz, ArH);

Found: C, 73.9; H, 4.0; N, 16.0%; m/z (EI ms), 261(M^+),

$C_{16}H_{11}N_3O$ requires: C, 73.6; H, 4.2; N, 16.1%; M, 261.

(ii) 2-(2-Aminophenoxy)naphthalene (183) afforded 2-(2-azidophenoxy)naphthalene (192) as a light brown oil (100%), ν_{max} 2122 (N_3) cm^{-1}, δ_H ($CDCl_3$) 7.88-7.83 (2H, m, ArH), 7.73-7.69 (1H, m, ArH), 7.51-7.39 (2H, m, ArH) and 7.33-7.04 (6H, m, ArH);

Found: C, 74.1; H, 4.2; N, 16.1%; m/z (EI ms), 261.0901 (M^+),

$C_{16}H_{11}N_3O$ requires: C, 73.6; H, 4.2; N, 16.1%; M, 261.0902.

N-(2-Naphthoxy)phenyl Trimethoxyphosphinimine Derivatives

A solution of the corresponding (2-azidophenoxy)naphthalene derivative (0.015mol) in anhydrous 1,2-dimethoxyethane (75.0ml) was stirred and treated at room temperature with a solution of trimethylphosphite (2.4g; 0.019mol) in anhydrous 1,2-dimethoxyethane (37.5ml) added in one portion and the mixture then stirred at room temperature with the exclusion of atmospheric moisture for 17h.

Rotary evaporation of the resulting mixture gave the desired product.

(i) 1-(2-azidophenoxy)naphthalene (187) afforded the phosphinimine (189) as a brown oil (95%), δ_H ($CDCl_3$) 8.47-6.66 (11H, m, ArH) and 3.47 (9H, d J 11.4Hz, $N=P(OCH_3)_3$);

Found: m/z (FAB HRMS), 358.1190 (MH^+),

$C_{19}H_{20}NO_4P$ requires: MH, 358.1208.

(ii) 2-(2-azidophenoxy)naphthalene (192 afforded the phosphinimine (194) as a brown oil (100%), δ_H ($CDCl_3$) 7.75 (2H, d J 8.8Hz, ArH), 7.60 (1H, d J 7.9Hz, ArH), 7.41-7.24 (4H, m, ArH), 7.11-7.01 (3H, m, ArH), 6.87-6.81 (1H, m, ArH) and 3.53 (9H, d J 11.5Hz, $N=P(OCH_3)_3$);

Found: m/z (FAB HRMS), 358.1199 (MH^+),

$C_{19}H_{20}NO_4P$ requires: MH, 358.1208.

The Reaction of N-(2-Naphthoxy)phenyl Trimethoxyphosphinimine Derivatives with Phenyl Isocyanate.

(a) A solution of the corresponding phosphinimine derivative (0.004mol) in anhydrous 1,2-dimethoxyethane (20.0ml) was treated in one portion at room temperature with a solution of phenyl isocyanate (5.2g; 0.0044mol) in anhydrous 1,2-dimethoxyethane (10.0ml) and the mixture then stirred at room temperature, with the exclusion of atmospheric moisture, for 4h.

The resulting mixtures were worked up as described for the individual reactions below.

(i) The mixture from the reaction with N-[2-(1-naphthoxy)]phenyl trimethoxyphosphinimine (189) was rotary evaporated to afford a red oil which was dissolved in ether (25.0ml) and washed three times with water (3 x 5.0ml). Rotary

evaporation of the ether layer afforded a brown oil (1.4g) which was flash chromatographed over silica.

Elution with hexane afforded phenyl isocyanate (82%) as a colourless oil, identified by comparison (i.r. spectrum) with an authentic sample.

Further elution with hexane-ether (99:1) through to methanol afforded mixed fractions as oils (0.99g) whose t.l.c. in hexane-ether over silica showed them to contain N-phenyl,N′-[2-(1-naphthoxy)]phenyl urea (188) and were therefore not further investigated.

(ii) The mixture from the reaction with N-[2-(2-naphthoxy)]phenyl trimethoxyphosphinimine (194) was rotary evaporated to afford a brown oil (1.1g) which was flash chromatographed over alumina.

Elution with hexane-ether (50:50) afforded a mixed fraction (0.53g) as a brown oil which was not further investigated.

Further elution with ether through to methanol afforded as a brown oil (0.51g) whose t.l.c. and i.r. spectrum showed it to be impure 1,3-diphenyl urea and was therefore not further investigated.

(b) The reaction was repeated as described in (a) before, but with heating under reflux for 4h, and worked up as described for the individual reactions below.

(i) The mixture from the reaction of N-[2-(1-naphthoxy)]phenyl trimethoxyphosphinimine (189) was rotary evaporated to afford a brown oil (1.3g) which was flash chromatographed over silica.

Elution with hexane through to methanol afforded only mixed fractions (1.3g) as oils which was not further investigated.

(ii) The mixture from the reaction of N-[2-(1-naphthoxy)]phenyl trimethoxyphosphinimine (194) was rotary evaporated to afford a red oil which was dissolved in ether (25.0ml) and washed three times with water (3 x 5.0ml). Rotary evaporation of the ether layer afforded a brown oil (1.4g) whose i.r. spectrum and t.l.c. in hexane-ether over silica showed it to contain the desired carbodiimide product (195), ν_{max} 2139 (N=C=N) cm^{-1}, which was used unpurified in the subsequent reaction.

N-Phenyl-N′-[2-(2-naphthoxy)]phenyl urea (193)

A solution of the crude carbodiimide (195) (1.4g; 0.004mol) in anhydrous 1,2-dimethoxyethane (15.0ml) was treated with 2M aqueous hydrochloric acid (5.0ml) and stirred at room temperature for 17h.

The mixture was concentrated by rotary evaporation to remove the 1,2-dimethoxyethane and the resulting residue treated with water (10.0ml) then extracted three times with dichloromethane (3 x 5.0ml) to give a brown oil (1.5g) which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded impure 1,3-diphenyl urea (0.27g) as a brown gum, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (90:10) afforded N-phenyl,N′-[2-(2-naphthoxy)]phenyl urea (193) (0.30g) as a light brown gum, which was identified by comparison (i.r. spectrum) with an authentic sample.

Final elution with methanol afforded an intractable brown gum which was not further investigated.

N-Phenyl,N′-(2-naphthoxy)phenyl Urea Derivatives

A solution of the corresponding (2-aminophenoxy)naphthalene derivative (0.04mol) in anhydrous dioxane (100ml) was treated with a solution of phenyl isocyanate (4.8g; 0.04mol) in anhydrous dioxane (40.0ml) added in one portion and the mixture then stirred at room temperature for 2h.

Rotary evaporation of the resulting mixture gave a dark brown oil which was flash chromatographed over silica as described for the individual reactions below.

(i) In the reaction with 1-(2-aminophenoxy)naphthalene (177), elution with hexane-ether (40:60) afforded N-phenyl,N′-[2-(1-naphthoxy)]phenyl urea (188) as a colourless solid, (81%), m.p. 178-179° (from hexane-ethanol), ν_{max} 3318 (NH) and 1650 (C=0) cm^{-1}, δ_H ($CDCl_3$) 8.28 (1H, dd J 8.1 and 1.5Hz, ArH), 8.10 (1H, d J 7.1Hz, ArH), 7.85 (1H, dd J 8.1 and 1.5 Hz, ArH), 7.95-7.40 (3H, m, ArH), 7.33-7.25 (2H, m, ArH) and 7.17-6.73 (8H, m, ArH);

Found: C, 78.0; H, 5.2; N, 7.6%; m/z (EI ms), 354 (M^+),

$C_{23}H_{18}N_2O_2$ requires: C, 78.0; H, 5.1; N, 7.9%; M, 354.

Final elution with methanol afforded a brown gum (2.9g) which was not further investigated.

(ii) In the reaction with 2-(2-aminophenoxy)naphthalene (183), elution with hexane-ether (70:30) afforded a mixed fraction as a red gum (1.6g) which was not further investigated.

Further elution with hexane-ether (70:30) afforded N-phenyl,N′-[2-(2-naphthoxy)]phenyl urea (193) as a light brown solid, (68%), which formed colourless microcrystals, m.p. 145-148° (from acetic acid), ν_{max} 3315 (NH) and 1658 (C=0) cm^{-1}, δ_H ($CDCl_3$) 9.27 (1H, bs, NH) (exch), 8.55 (1H, bs, NH) (exch), 8.34 (1H, d J 6.1Hz, ArH), 8.02-7.82 (3H, m, ArH), and 7.46-6.93 (12H, m, ArH);

Found: C, 77.7; H, 5.0; N, 7.8%; m/z (FAB ms), 355 (MH^+),

$C_{23}H_{18}N_2O_2$ requires: C, 78.0; H, 5.1; N, 7.9%; M, 354.

Further elution with methanol afforded a brown gum (0.51g) which was not further investigated.

N-Phenyl,N′-[2-(1-naphthoxy)]phenyl Carbodiimide (190)

(a) A suspension of N-phenyl-N′-[2-(1-naphthoxy)]phenyl urea (188) (1.6g; 0.004mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred and treated under nitrogen with a solution of diisopropylethylamine (0.77g; 0.006mol) added in one portion and cooled to 0° (ice-salt bath). The mixture was then treated dropwise with phosphoryl chloride (0.34g; 0.0022mol) at such a rate that the reaction temperature was 0-5° then heated under reflux for 17h.

The cooled mixture was rotary evaporated to give a brown oil (1.7g) which was extracted three times with 60-80° light petroleum (6 x 10.0ml), leaving a brown gum (3.0g) whose t.l.c. in hexane-ether over silica showed it to contain impure urea

starting material (188). Rotary evaporation of the combined petroleum extracts afforded a brown oil (0.50g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (190) as a yellow oil (0.43g; 64%), ν_{max} 2139 and 2104 (NCN) cm^{-1}, δ_H ($CDCl_3$) 8.15 (1H, dd J 8.4 and 1.3Hz, ArH), 7.77 (1H, dd J 8.8 and 1.3Hz, ArH), 7.54 (1H, d 8.4Hz, ArH), and 7.47-6.78 (13H, m, ArH);

Found: m/z (El ms) 336.1262 (M^+),

$C_{23}H_{16}N_2O$ requires: M, 336.1263.

Further elution with hexane-ether (50:50) afforded N-phenyl-N′-[2-(1-naphthoxy)]phenyl urea (188) (0.055g; 8%) as a cream solid, m.p. 168-173°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) A suspension of N-phenyl-N′-[2-(1-naphthoxy)]phenyl urea (188) (0.71g; 0.002mol) in anhydrous dichloromethane (15.0ml) was stirred and cooled to 0° (ice-salt bath) under nitrogen and treated with a solution of triethylamine (0.40g; 0.004mol) in anhydrous dichloromethane (2.5ml) added in one portion. A solution of triphosgene (0.20g; 0.00066mol) in anhydrous dichloromethane (2.5ml) was then added in one portion and the resulting mixture stirred under reflux for 1.5h.

The cooled solution was rotary evaporated to give a brown gummy solid (1.3g) which was triturated with anhydrous ether to give triethylamine hydrochloride (0.37g) as a cream solid, identified by comparison (i.r. spectrum) with an authentic sample prepared before. Rotary evaporation of the ether mother liquor afforded a yellow oil (0.76g) which was triturated with anhydrous 60-80° light petroleum to give N-phenyl-

N′-[2-(1-naphthoxy)]phenyl urea (188) as a light brown solid (0.38g), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Rotary evaporation of the petroleum extracts gave a brown oil (0.68g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (190) as a yellow oil (0.36g; 54%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with ether afforded impure urea starting material (188) as a brown oil (0.13g), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(c) A suspension of N-phenyl-N′-[2-(1-naphthoxy)]phenyl urea (188) (0.71g; 0.002mol) in anhydrous dichloromethane (15.0ml) was stirred and cooled to 0° (ice-salt bath) under nitrogen and treated with a solution of triethylamine (0.40g; 0.004mol) in anhydrous dichloromethane (2.5ml) added in one portion. A solution of triphosgene (0.40g; 0.0013mol) in anhydrous dichloromethane (2.5ml) was then added in one portion and the mixture then stirred under reflux for 1.5h.

The cooled solution was rotary evaporated to give a brown gummy solid (1.5g) which was triturated with anhydrous ether to give triethylamine hydrochloride (0.63g) as a cream solid, identified by comparison (i.r. spectrum) with an authentic sample prepared before. Rotary evaporation of the ether mother liquor afforded a yellow oil (0.75g) which was triturated with anhydrous 60-80° light petroleum to give impure urea starting material (188) as a light brown gum (0.21g), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Rotary evaporation of the petroleum extracts gave a brown oil (0.40g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded the desired carbodiimide product (190) as a yellow oil (0.20g; 30%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with ether afforded urea starting material (188) as a brown solid (0.12g), m.p. 172-177°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

N-Phenyl-N′-[2-(2-naphthoxy)]phenyl Carbodiimide (195)

A stirred suspension of N-phenyl-N′-[2-(2-naphthoxy)]phenyl urea (193) (1.8g; 0.005mol) in anhydrous 1,2-dichloroethane (10.0ml) was treated under nitrogen with a single portion of diisopropylethylamine (0.19g; 0.015mol) and cooled to 0° (ice-salt bath). The mixture was treated dropwise with phosphoryl chloride (0.85g; 0.0055mol) at such a rate that the reaction temperature was 0-5° then heated under reflux for 17h. The cooled mixture was rotary evaporated to give a brown oil (4.7g) which was extracted three times with 60-80° light petroleum (6 x 25.0ml), leaving a brown gum (3.6g) whose t.l.c. in hexane-ether over silica showed it to contain impure urea starting material (193). Rotary evaporation of the combined petrol extracts afforded the desired carbodiimide product (195) as a cream solid (1.2g; 71%), ν_{max} 2142 and 2104 (N=C=N) cm^{-1}, δ_H ($CDCl_3$) 7.79-6.94 (16H, m, ArH);

Found: m/z (EI ms) 336.1259 (M^+),

$C_{23}H_{16}N_2O$ requires: M, 336.1263.

The Stannic Chloride Catalysed Cyclisations of N-Phenyl,N′-(2-naphthoxy)phenyl Carbodiimide Derivatives.

A solution of the corresponding carbodiimide derivative (0.002mol) in anhydrous 1,2-dichloroethane (10.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of stannic chloride (2.6g; 0.01mol) in anhydrous 1,2-dichloroethane (5.0ml) then heated under reflux for 24h.

The mixture was cooled to 0° (ice-salt bath), treated with 15M aqueous sodium hydroxide solution (6.8ml) and stirred at room temperature for 15min. The mixture was then diluted with water (20.0ml) and extracted three times with dichloromethane (3 x 10.0ml). Rotary evaporation of the combined dichloromethane extracts gave a brown oil (0.68g) which was flash chromatographed over silica as described for the individual reactions below.

(i) In the reaction with N-phenyl-N′-[2-(1-naphthoxy)]phenyl carbodiimide (190), elution with hexane-ether (85:15) afforded the dibenzoxazepine (191) as a light brown solid (43%), which formed colourless crystals, m.p. 192-184° (from ethanol), ν_{max} 3176 (NH) cm^{-1}, δ_H ($CDCl_3$) 8.64 (1H, d J 7.9Hz, ArH), 7.84 (1H, d J 7.9Hz, ArH) 7.72-7.00 (13H, m, ArH) and 6.77 (1H, bs, NH) (exch);

Found: C, 81.5; H, 4.8; N, 8.2%; m/z (EI ms) 336.1254 (M^+),

$C_{23}H_{16}N_2O$ requires: C, 82.1; H, 4.8; N, 8.3%; M, 336.1263.

Further elution with methanol afforded a dark brown gum (0.27g) which was not further investigated.

(ii) In the reaction with N-phenyl-N′-[2-(2-naphthoxy)]phenyl carbodiimide (195), elution with hexane-ether (70:30) afforded the dibenzoxazepine (196) as a light brown solid

(71%), which formed colourless crystals, m.p. 149-152° (from 1,4-dioxane), ν_{max} 3389 (NH) cm^{-1}, δ_H ($CDCl_3$) 9.65 (1H, bs, NH) (exch), 8.15 (1H, d J 9.8Hz, ArH), 8.12-7.98 (2H, m, ArH) and 7.70-6.89 (12H, m, ArH);

Found: m/z (EI HRMS) 336.1250 (M^+),

$C_{23}H_{16}N_2O$ requires: M, 336.1263.

Further elution with methanol afforded a dark brown gum (0.18) which was not further investigated.

Bis-(2-nitrophenoxy)benzene Derivatives.

A suspension of sodium hydride (2.6g; 0.11mol) in anhydrous dimethylformamide (40.0ml) was vigorously stirred and treated dropwise at 0-10° (ice bath) with a solution of the corresponding bis-hydroxynaphthalene derivative (0.05mol) in anhydrous dimethylformamide (20.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 2-fluoronitrobenzene (61) (14.1g; 0.1mol) in anhydrous dimethylformamide (60.0ml) was added in one portion and the mixture stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (30.0ml) and rotary evaporated to give a residue which was worked up as described for the individual reactions below.

(i) Catechol (212) gave a brown residue which was triturated with water (200ml) to give 1,2-bis-(2-nitrophenoxy)benzene (213) as a light brown solid (100%), which formed light brown needles, m.p. 108-110° (from ethanol), ν_{max} 1521 and 1349 (NO_2) cm^{-1},

δ_H ($CDCl_3$) 7.86 (2H, dd J 8.2 and 1.8Hz, ArH), 7.53-7.44 (2H, m, ArH), 7.33-7.11 (6H, m, ArH) and 6.93 (2H, dd J 8.2 and 1.2Hz, ArH);

Found: C, 61.7; H, 3.5; N, 7.9%; m/z (EI ms), 352 (M^+),

$C_{18}H_{12}N_2O_6$ requires: C, 61.4; H, 3.4; N, 8.0%; M, 352.

(ii) Resorcinol (197) gave a yellow residue which was treated with water (200ml) then extracted four times with dichloromethane (4 x 250ml) to give 1,3-bis-(2-nitrophenoxy)benzene (198) as a yellow solid (94%), which formed light brown needles, m.p. 88-89° (from ethanol), ν_{max} 1524 and 1347 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 7.94 (2H, dd J 8.4 and 1.7Hz, ArH), 7.59-7.51 (2H, m, ArH), 7.34 (1H, t J 8.4Hz, ArH), 7.28-7.19 (2H, m, ArH), 7.08 (2H, dd J 8.2 and 1.0Hz, ArH), 6.82 (2H, dd J 8.2 and 2.3Hz, ArH) and 6.71 (1H, t J 2.3Hz, ArH);

Found: C, 61.5; H, 3.1; N, 7.7%; m/z (EI ms), 352 (M^+),

$C_{18}H_{12}N_2O_6$ requires: C, 61.4; H, 3.4; N, 8.0%; M, 352.

(iii) Quinol (205)gave a yellow residue which was triturated with water (200ml) to give 1,4-bis-(2-nitrophenoxy)benzene (206) as a light brown solid (89%), which formed light brown cubes, m.p. 39-43° (from acetic acid), ν_{max} 1520 and 1343 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 7.94 (2H, dd J 8.1 and 1.7Hz, ArH), 7.56-7.48 (2H, m, ArH), 7.25-7.16 (2H, m, ArH) and 7.06-6.99 (6H, m, ArH);

Found: C, 61.2; H, 3.3; N, 7.8%; m/z (EI ms), 352 (M^+),

$C_{18}H_{12}N_2O_6$ requires: C, 61.4; H, 3.4; N, 8.0%; M, 352.

Extraction of the aqueous mother liquor three times with dichloromethane (3 x 100ml) gave no identifiable material.

The aqueous mother liquor was adjusted to pH 1 by the addition of concentrated aqueous hydrochloric acid then extracted three times with dichloromethane (3 x 100ml) to give no identifiable material.

Bis-(2-aminophenoxy)benzene Derivatives.

(a) A solution of the corresponding bis-(2-nitrophenoxy)benzene derivative (0.05mol) in 1,2-dimethoxyethane (100ml) was hydrogenated over 10% palladium-on-charcoal (1.8g) at room temperature and atmospheric pressure for 28h, during which time 6840ml hydrogen was absorbed.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give the desired amine product.

(i) 1,2-Bis-(2-nitrophenoxy)benzene (213) afforded 1,2-bis-(2-aminophenoxy)benzene (214) as a brown solid (99%), which formed light brown cubes, m.p. 108-109° (from ethanol), ν_{max} 3392 and 3274 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 7.06-6.62 (12H, m, ArH) and 3.69 (4H, bs, NH_2) (exch);

Found: C, 73.5; H, 5.5; N, 9.4%; m/z (EI HRMS), 292.1199 (M^+),

$C_{18}H_{16}N_2O_2$ requires: C, 74.0; H, 5.5; N, 9.6%; M, 292.1212.

(ii) 1,3-Bis-(2-nitrophenoxy)benzene (198) afforded 1,3-bis-(2-aminophenoxy)benzene (199) as a light brown solid (91%), which formed colourless crystals, m.p. 67-68° (from hexane-ethanol), ν_{max} 3416 and 3331 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 7.18 (1H, t J 8.1Hz, ArH), 7.03-6.59 (11H, m, ArH) and 3.70 (4H, bs, NH_2) (exch);

Found: C, 74.0; H, 5.7; N, 9.5%; m/z (EI ms), 292 (M^+),

$C_{18}H_{16}N_2O_2$ requires: C, 74.0; H, 5.5; N, 9.6%; M, 292.

(iii) 1,4-Bis-(2-nitrophenoxy)benzene (206) afforded 1,4-bis-(2-nitrophenoxy)benzene (207) as a light brown solid (100%), which formed light brown crystals, m.p. 94-95° (from ethanol), ν_{max} 3430 and 3351 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 7.04-6.99 (2H, m, ArH), 6.96-6.92 (4H, m, ArH), 6.85-6.79 (4H, m, ArH), 6.77-6.65 (2H, m, ArH) and 3.56 (4H, bs, NH_2) (exch);

Found: m/z (EI ms), 292.1214 (M^+),

$C_{18}H_{16}N_2O_2$ requires: M, 292.1212.

(b) A solution of the corresponding bis-(2-nitrophenoxy)benzene derivative (0.005mol) in tetrahydrofuran (50.0ml) was treated with a solution of stannous chloride dihydrate (5.0g; 0.022mol) in 2M aqueous hydrochloric acid (50.0ml) and the mixture stirred and heated under reflux for 1h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 50.0ml) to give a residue which was worked up as described for the individual reactions below.

(i) 1,2-bis-(2-nitrophenoxy)benzene (213) gave a dark brown oil (1.6g), which was flash chromatographed over silica.

Elution with dichloromethane afforded 1,2-bis-(2-aminophenoxy)benzene (214) as a red-brown oil (58%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution afforded a purple tar (0.40g) which was not further investigated.

(ii) 1,3-Bis-(2-nitrophenoxy)benzene (198) gave 1,3-bis-(2-aminophenoxy)benzene (199) as a dark brown oil (86%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(iii) 1,4-Bis-(2-nitrophenoxy)benzene (206) gave a dark brown oil (0.59g), which was shown by t.l.c. in hexane-ether over silica to be a mixture of 1,4-bis-(2-aminophenoxy)benzene (207) and starting material.

The oil was dissolved in tetrahydrofuran (20.0ml) was treated with a solution of stannous chloride dihydrate (2.0g; 0.009mol) in 2M aqueous hydrochloric acid (20.0ml) and the mixture was stirred and heated under reflux for a further 1h.

The mixture was adjusted to pH 14 by the addition of 30% aqueous sodium hydroxide solution and concentrated by rotary evaporation to remove the tetrahydrofuran. The aqueous residue was then extracted three times with ether (3 x 25.0ml) and the combined organic extracts rotary evaporated to give 1,4-bis-(2-aminophenoxy)benzene (207) as a dark brown oil (92%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Bis-(2-isothiocyanatophenoxy)benzene Derivatives.

(a) A solution of the corresponding bis-(2-aminophenoxy)benzene derivative (0.01mol) in glacial acetic acid (45.0ml) was stirred and treated with a 1:1 mixture of concentrated hydrochloric acid and water (12.5ml) added in one portion, then dropwise at room temperature with a solution of thiophosgene (4.6g; 0.04mol) in glacial acetic acid (5.0ml). The mixture then stirred at room temperature for 2h.

The mixture was diluted with water (50.0ml) and extracted three times with dichloromethane (3 x 100ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 50.0ml) then rotary evaporated to give the desired isothiocyanate product.

(i) 1,2-Bis-(2-aminophenoxy)benzene (214) afforded 1,2-bis-(2-isothiocyanatophenoxy)benzene (215) as a light brown solid (100%), which formed light brown cubes, m.p. 125-130° (from ethanol), ν_{max} 2085 (NCS) cm^{-1}, δ_H ($CDCl_3$) 7.28-6.99 (10H, m, ArH) and 6.81 (2H, dd J 8.2 and 1.4Hz, ArH);

Found: C, 63.5; H, 3.1; N, 7.3%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

(ii) 1,3-Bis-(2-aminophenoxy)benzene (199) afforded 1,3-bis-(2-isothiocyanatophenoxy)benzene (200) as a light yellow oil (100%), b.p. 224° /0.2mmHg, ν_{max} 2033 (NCS) cm^{-1}, δ_H ($CDCl_3$) 7.35-7.19 (5H, m, ArH), 7.13-7.00 (4H, m, ArH) and 6.77-6.67 (3H, m, ArH);

Found: C, 63.7; H, 3.0; N, 7.4%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

(iii) 1,4-bis-(2-aminophenoxy)benzene (207) afforded 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) as a light brown solid (57%), which formed light brown crystals, m.p. 131-133° (from ethyl acetate), ν_{max} 2066 (NCS) cm^{-1}, δ_H ($CDCl_3$) 7.23-7.17 (4H, m, ArH), 7.10-7.02 (6H, m, ArH) and 6.96-6.91 (2H, m, ArH);

Found: C, 63.5; H, 2.8; N, 7.2%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

(b) Repetition of the reaction described in (a)(iii) before, but with stirring at room temperature for 4h afforded 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) as a light brown solid (100%), m.p. 125-130°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Aluminium Tribromide Catalysed Cyclisations of Bis-(2-isothiocyanatophenoxy)benzene Derivatives.

(a) A suspension of aluminium tribromide (5.3g; 0.02mol) in anhydrous dichloromethane (25.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of the bis-(2-isothiocyanatophenoxy)benzene derivative (0.005mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml). The combined dichloromethane extracts were then rotary evaporated, and the resulting residue was worked up as described for the individual reactions below.

(i) 1,2-Bis-(2-isothiocyanatophenoxy)benzene (215) afforded impure unreacted 1,2-bis-(2-isothiocyanatophenoxy)benzene (215) as a brown oil (95%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(ii) 1,3-Bis-(2-isothiocyanatophenoxy)benzene (200) afforded a glassy yellow solid which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded 1,3-bis-(2-isothiocyanatophenoxy)benzene (200) as a brown oil (5%), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (85:15) afforded 3-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201) as a yellow solid (18%), m.p. 182-185° (from acetic acid),ν_{max} 3154 (NH) and 2029 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.72 (1H, bs, NH) (exch), 8.06 (1H, d J 8.8Hz, ArH), 7.99-7.11 (8H, m, ArH) and 6.97-6.75 (2H, m, ArH);

Found: C, 63.7; H, 3.2; N, 7.3%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

Further elution with hexane-ether (80:20) through ether to methanol afforded only intractable glasses which were not further investigated.

(b) Repetition of the reaction described in (a)(i) before, but with 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) and stirring at room temperature for only 2h afforded a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (99:1) afforded 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) as a yellow solid (5%), m.p. 127-129°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (90:10) afforded 2-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (209) as a yellow solid (47%), m.p. 155-157° (from toluene), ν_{max} 3163 (NH) and 2115 and 2055 (NCS) cm^{-1}, δ_H ($CDCl_3$) 10.41 (1H, bs, NH) (exch), 7.83 (1H, t J 1.7Hz, ArH) and 7.28-6.89 (10H, m, ArH);

Found: C, 64.0; H, 3.3; N, 7.3%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

Further elution with hexane-ether (80:20) through ether to methanol afforded only intractable oils which were not further investigated.

(c) Repetition of the reaction as described in (a)(i), but with heating under reflux for 4h, afforded an intractable unidentified orange solid.

Aluminium Trichloride Catalysed Cyclisations of Bis-(2-isothiocyanatophenoxy)benzene Derivatives.

(a) A suspension of aluminium trichloride (2.7g; 0.02mol) in anhydrous dichloromethane (25.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of the corresponding bis-(2-isothiocyanatophenoxy)benzene derivative (0.005mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to give a residue which was worked up as described for the individual reactions below.

(i) 1,2-Bis-(2-isothiocyanatophenoxy)benzene (215) afforded a yellow multicomponent oil which was not further investigated.

(ii) 1,3-Bis-(2-isothiocyanatophenoxy)benzene (200) afforded a yellow glassy solid which was crystallised from acetic acid to give 3-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201) as a yellow solid (53%), m.p. 179-184°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before. The acetic acid mother liquor was evaporated to give a second crop of 3-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201) as a yellow solid, m.p. 163-179°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(b) Repetition of the reaction described in (a)(i) before, but with stirring at room temperature for 24h, afforded a yellow solid which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded 1,2-bis-(2-isothiocyanatophenoxy)benzene (215) as a yellow solid (31%), m.p. 52-59°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (90:10) afforded 4-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (216) as a yellow solid (27%), m.p. 209-210° (from toluene),ν_{max} 3356 (NH) and 2042 (NCS) cm^{-1}, δ_H ($CDCl_3$) 10.13 (1H, bs, NH) (exch), 8.02 (1H, dd J 7.2 and 2.4Hz, ArH), 7.33-7.02 (9H, m, ArH) and 6.75 (1H, dd J 8.1 and 1.5Hz, ArH);

Found: C, 63.7; H, 3.4; N, 7.2%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

Further elution with ether afforded an intractable brown solid which was not further investigated.

(c) A suspension of aluminium trichloride (1.1g; 0.008mol) in anhydrous dichloromethane (20.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of the corresponding bis-(2-isothiocyanatophenoxy)benzene derivative (0.002mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate (85.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to give a residue which was then recycled through the process above, but with heating under reflux for 4h to give a brown solid (0.56g), m.p. 171-179°, which on strong roasting left an infusible residue. This material could not be crystallised and was recovered unchanged on treatment with aqueous acid and base.

(ii) Repetition of the reaction described in (c)(i) before, but using 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) afforded 2-(2-

isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (209) as a yellow solid (71%), m.p. 155-157°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

(iii) Repetition of the reaction described in (c)(i) before, but with stirring at room temperature for 4h, followed directly by heating under reflux for a further 4h, thereby missing out the first isolation procedure gave an intractable brown glass which was shown by t.l.c. not to run on silica or alumina. This solid could not be crystallised or purified by any other means, and was therefore not further investigated.

(d) The reaction was repeated as described in (a)(i) before, but using only two equivalents of aluminium trichloride (0.01mol) and stirring at room temperature for 24h, and the resulting mixture then worked up as described for the individual reactions below

(i) 1,2-bis-(2-isothiocyanatophenoxy)benzene (215) afforded an orange gum (83%), whose i.r. spectrum identified it to be impure 1,2-bis-(2-isothiocyanatophenoxy)benzene starting material (215).

(ii) Repetition of the reaction described in (d)(i) before, but using 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) afforded a red glass which was flash chromatographed over silica.

Elution with hexane-ether (85:15) afforded unreacted 1,4-bis-(2-isothiocyanatophenoxy)benzene (208) as light brown solid (8%), m.p. 119-127°,

identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (70:30) afforded 2-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (209) as a yellow solid (46%), m.p. 155-160°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded an intractable yellow solid, m.p. >360°, which could not be crystallised, and was recovered unchanged from 2M aqueous hydrochloric acid and 2M aqueous sodium hydroxide.

(e) Repetition of the reaction described in (d)(i) before, but using 1,2-bis-(2-isothiocyanatophenoxy)benzene (215) and with stirring at -78° for 1h and at -10° for a further 2h gave a yellow solid which was crystallised from acetic acid to give 4-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (216) as a yellow solid (46%), m.p. 181-186°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

Rotary evaporation of the acetic acid mother liquor gave a brown gum which was not further investigated.

3-(2-Aminophenoxy)dibenzoxazepine-11(10H)-thione (202)

A solution of 3-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201) (0.38g; 0.001mol) in 1,2-dimethoxyethane (5.0ml) was treated with 2M aqueous sodium hydroxide solution (2.5ml) and the mixture then stirred under reflux for 1h.

The mixture was concentrated by rotary evaporation to remove the 1,2-dimethoxyethane and the resulting aqueous residue extracted three times with dichloromethane (3 x 5.0ml) to give a yellow solid (0.29g) which was flash chromatographed over silica.

Elution with hexane-ether (70:30) afforded 3-(2-aminophenoxy)dibenzoxazepine-11(10H)-thione (202) as a yellow glass (0.13g; 43%), m.p. 81-86°, ν_{max} 3458, 3334 and 3153 (NH_2) cm^{-1}, which decomposed on attempted purification by crystallisation.

Further elution with hexane-ether (50:50) through methanol afforded only small amounts of complex gums.

Aluminium Trichloride Catalysed Cyclisation of 3-(2-Isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201).

A suspension of aluminium trichloride (0.52g; 0.004mol) in anhydrous dichloromethane (10.0ml) was stirred and cooled to -10° (ice-acetone bath) under nitrogen and treated dropwise with a solution of 3-(2-aminophenoxy)dibenzoxazepine-11(10H)-thione (201) (0.75g; 0.002mol) in anhydrous dichloromethane (10.0ml). The mixture was then stirred at room temperature for 24h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate (30.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 50.0ml) to give the doubly-cyclised compound (203) as a yellow solid (97%), m.p. 146-149° (from dimethylformamide-acetonitrile),ν_{max} 3356 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.8-6.7 (12H, m, ArH);

Found: C, 63.5; H, 3.3; N, 7.2%; m/z (EI ms), 376 (M^+),

$C_{20}H_{12}N_2O_2S_2$ requires: C, 63.8; H, 3.2; N, 7.4%; M, 376.

The Sodium Hydride Catalysed Reaction of the [1,5]Benzoxazepinodibenz[b,f][1,4]oxazepine Derivative (203) with Dimethyl sulphate.

A suspension of sodium hydride (0.052g; 0.0022mol) in anhydrous dimethylformamide (4.0ml) was vigorously stirred and treated dropwise at 0-10° (ice bath) with a solution of the bis-thiolactam (203) (0.38g; 0.001mol) in anhydrous dimethylformamide (4.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of dimethyl sulphate (1.0g; 0.008mol) in anhydrous dimethylformamide (2.0ml) was added and the mixture stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with a 1:1 mixture of concentrated ammonia and water (12.0ml) then stirred for 24h at room temperature. Rotary evaporation gave an orange solid which was treated with water (10.0ml) to give an orange solid (0.27g), m.p. 130-137°, which was shown not to run on t.l.c. on silica or alumina. The solid could not be purified by crystallisation or chromatography, and hence could not be characterised.

The Attempted Thiomethylation of 3-(2-Isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (201).

A suspension of sodium hydride (0.052g; 0.0022mol) in anhydrous dimethylformamide (4.0ml) was vigorously stirred and treated dropwise at 0-10° (ice

bath) with a solution of the thiolactam (201) (0.75g; 0.002mol) in anhydrous dimethylformamide (4.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of dimethyl sulphate (0.59g; 0.004mol) in anhydrous dimethylformamide (2.0ml) was added and the mixture stirred at room temperature, with the exclusion of atmospheric moisture, for 17h.

The resulting mixture was treated with water (4.0ml) then stirred for 24h at room temperature. Rotary evaporation gave an orange solid which was treated with water (8.0ml) to give an brown gum (0.79g) which was flash chromatographed over silica. Elution with hexane-ether (90:10) through to methanol afforded only small amounts of unidentified oils and gums which were not further investigated.

2-(2-Aminophenoxy)dibenzoxazepine-11(10H)-thione (210)

A solution of 2-(2-isothiocyanatophenoxy)dibenzoxazepine-11(10H)-thione (209) (0.38g; 0.001mol) in ethanol (5.0ml) was treated with 2M aqueous sodium hydroxide solution (2.5ml). The mixture was then stirred under reflux for 1h.

The mixture was concentrated by rotary evaporation to remove the ethanol and the resulting aqueous residue was extracted three times with dichloromethane (3 x 5.0ml) to afford 2-(2-aminophenoxy)dibenzoxazepine-11(10H)-thione (210) as yellow solid (0.29g; 76%), m.p. 83-84° (from hexane-ethanol), ν_{max} 3464 and 3335 (NH_2) and 3153 (NH) cm^{-1}, δ_H ($CDCl_3$) 10.20 (1H, bs, NH) (exch), 7.81 (1H, d J 2.8Hz, ArH), 7.50-6.64 (10H, m, ArH) and 3.53 (2H, bs, NH) (exch);

Found: m/z (EI ms), 334.0788 (M^+),

$C_{19}H_{14}N_2O_2S$ requires: M, 334.0776.

2-(2-N,N-Diacylaminophenoxy)dibenz[b,f][1,4]oxazepine-11(10H)-thione (211)

A solution of 2-(2-aminophenoxy)dibenz[b,f][1,4]oxazepine-11(10H)-thione (210) (0.17g; 0.0005mol) was treated with acetic anhydride (5.0ml) then heated under reflux, with exclusion of atmospheric moisture, for 3h.

Rotary evaporation gave an orange gum (0.19g) which was triturated with water to give the diacyl derivative (211) as a yellow solid (0.16g; 66%), m.p. 93-95° (from hexane-toluene), ν_{max} 3132 (NH) and 1712 (CO) cm^{-1}, δ_H ($CDCl_3$) 10.48 (1H, bs, NH) (exch), 7.87-6.76 (11H, m, ArH) and 2.28 (6H, s, CH_3);

Found: m/z (FAB HRMS), 419.1071 (MH^+),

$C_{23}H_{18}N_2O_4S$ requires: MH, 419.1066

The Attempted Reaction of 2-(2-Isothiocyanatophenoxy)dibenz[b,f][1,4]oxazepine-11(10H)-thione (209) with Aniline.

A solution of 2-(2-isothiocyanatophenoxy)dibenz[b,f][1,4]oxazepine-11(10H)-thione (209) (0.38g; 0.001mol) in anhydrous dioxane (10.0ml) was stirred and treated at room temperature with a solution of aniline (0.095g; 0.001mol) in anhydrous dioxane (5.0ml). The mixture was stirred at room temperature for 2h then heated under reflux for a further 2h.

Rotary evaporation of the resulting mixture gave a brown gum (0.39g) which was flash chromatographed over silica.

Elution with hexane-ether (65:35) afforded 2-(2-isothiocyanatophenoxy)dibenz[b,f][1,4]oxazepine-11(10H)-thione (209) as a yellow glass (0.12g; 31%), m.p. 93-98°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (50:50) through ether to methanol afforded only complex mixtures as brown oils (0.20g) which were not further investigated.

Bis-(2-nitrophenoxy)naphthalene Derivatives.

A suspension of sodium hydride (5.3g; 0.22mol) in anhydrous dimethylformamide (100ml) was vigorously stirred and treated dropwise at 0-10° (ice bath) with a solution of the corresponding dihydroxynaphthalene derivative (0.1mol) in anhydrous dimethylformamide (50.0ml) and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of 2-fluoronitrobenzene (61) (28.2g; 0.2mol) in anhydrous dimethylformamide (50.0ml) was added in one portion and the mixture stirred and heated at 100° (oil bath), with the exclusion of atmospheric moisture, for 1h.

The resulting mixture was treated with water (60.0ml) and rotary evaporated to give a residue which was worked up as described for the individual reactions below.

(i) 1,5-Dihydroxynaphthalene (234) gave a dark brown residue which was treated with water (250ml) and extracted three times with ethyl acetate (3 x 500ml) to give a light brown solid. This was crystallised from dimethylformamide to afford 1,5-bis-(2-nitrophenoxy)naphthalene (235) as a brown solid (57%), which formed pale yellow crystals, m.p. 195-196° (from dimethylformamide), ν_{max} 1519 and 1347 (NO_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.15 (2H, dd J 8.2 and 1.7Hz, ArH), 7.95 (2H, d J 8.2Hz, ArH), 7.75-7.38 (6H, m, ArH) and 7.19-7.17 (4H, m, ArH);

Found: C, 65.3; H, 3.6; N, 6.9%; m/z (EI ms), 402 (M^+),

$C_{22}H_{14}N_2O_6$ requires: C, 65.6; H, 3.5; N, 7.0%; M, 402.

The dimethylformamide mother liquor was rotary evaporated to give a dark brown solid, m.p. 184-190°, which was not further investigated.

The aqueous mother liquor was adjusted to pH 2 by the addition of 2M aqueous hydrochloric acid then extracted three times with dichloromethane (3 x 500ml) to give a dark brown oil (13.1g) which was flash chromatographed over silica.

Elution with hexane-ether (95:5) afforded a mixed fraction as a red oil (2.0g) which was not further investigated.

Further elution with hexane-ether (90:10) afforded 1,5-bis-(2-nitrophenoxy)-naphthalene (234) as a pale yellow solid (5%), m.p. 189-195° identified by comparison (melting point and i.r. spectrum) with the first crop.

Further elution with ether through to methanol afforded mixed fractions as brown gums which were not further investigated.

(ii) 1,6-Dihydroxynaphthalene (217) gave a dark brown residue which was treated with water (250ml) and extracted three times with ethyl acetate (3 x 500ml) to give a yellow solid. This was crystallised from acetic acid to afford 1,6-bis-(2-nitrophenoxy)naphthalene (218) as a brown solid (75%), which formed light brown crystals, m.p. 127-128° (from acetic acid), ν_{max} 1519 and 1339 (NO_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.18-8.11 (3H, m, ArH), 7.79-7.64 (3H, m, ArH), 7.57-7.29 (6H, m, ArH), 7.13 (1H, dd J 8.3 and 0.9Hz, ArH) and 6.98 (1H, d J 7.1Hz, ArH);

Found: C, 65.4; H, 3.6; N, 6.8%; m/z (EI ms), 402 (M^+),

$C_{22}H_{14}N_2O_6$ requires: C, 65.7; H, 3.5; N, 7.0%; M, 402.

The acetic acid mother liquor was rotary evaporated to give a red brown oil which was not further investigated.

(iii) 2,6-Dihydroxynaphthalene (228) gave a dark brown residue which was triturated with water (375ml) to give a yellow solid, m.p. 140-146°. This was crystallised from acetic acid to give 2,6-bis-(2-nitrophenoxy)naphthalene (229) as a yellow solid (80%), which formed yellow needles, m.p. 160-161° (from acetic acid), ν_{max} 1518 and 1350 (NO_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.11 (2H, dd J 8.1 and 1.7Hz, ArH), 7.96 (2H, d J 8.1Hz, ArH), 7.72 (2H, dt J 1.7 and 7.6Hz, ArH), 7.55 (2H, d J 2.5Hz, ArH) and 7.45-7.31 (4H, m, ArH) and 7.23 (2H, dd J 1.0 and 7.6Hz, ArH);

Found: C, 66.1; H, 3.5; N, 7.0%; m/z (EI HRMS), 402.0857 (M^+),

$C_{22}H_{14}N_2O_6$ requires: C, 65.7; H, 3.5; N, 7.0%; M, 402.0852.

Rotary evaporation of the acetic acid filtrate gave a second crop of 2,6-bis-(2-nitrophenoxy)naphthalene (229) as a brown solid, m.p. 138-145°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The aqueous mother liquor was extracted three times with dichloromethane (3 x 200ml) to give a brown oil which was not further investigated.

(iv) 2,7-Dihydroxynaphthalene (223) gave a dark brown residue which was treated with water (500ml) and extracted three times with ethyl acetate (3 x 500ml) to give a brown oil, which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded a mixed fraction as a red oil which was not further investigated.

Further elution with ether afforded 2,7-bis-(2-nitrophenoxy)naphthalene (224) as a yellow solid (71%), m.p. 90-96°, which formed yellow needles, m.p. 107-110° (from ethanol), ν_{max} 1521 and 1350 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 7.97 (2H, dd J 8.2 and 1.7Hz,

ArH), 7.85 (2H, d J 8.7Hz, ArH), 7.53 (2H, dt J 9.0, 9.0 and 1.6Hz, ArH) and 7.42-7.07 (8H, m, ArH);

Found: C, 65.2; H, 3.7; N, 6.9%; m/z (EI ms), 402.0857 (M^+),

$C_{22}H_{14}N_2O_6$ requires: C, 65.7; H, 3.5; N, 7.0%; M, 402.0852.

Further elution with methanol afforded a brown gum which was not further investigated.

The aqueous mother liquor was adjusted to pH 1 by the addition of 2M aqueous hydrochloric acid and extracted three times with dichloromethane (3 x 100ml) to give no identifiable material.

Bis-(2-aminophenoxy)naphthalene Derivatives.

(a) A solution of the corresponding bis-(2-nitrophenoxy)naphthalene derivative (0.02mol) in dimethylformamide (150ml) was hydrogenated over 10% palladium-on-charcoal (0.80g) until hydrogen uptake had ceased.

The catalyst was removed by filtration through celite, and the filtrate was rotary evaporated to give a residue which was worked up as described for the individual reactions below.

(i) 1,5-bis-(2-nitrophenoxy)naphthalene (235) gave 1,5-bis-(2-aminophenoxy)naphthalene (236) as a light brown solid (100%), m.p. 152-158°, which formed grey crystals, m.p. 165-168° (from acetic acid), ν_{max} 3429 and 3351 (NH_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.94 (2H, d J 8.3Hz, ArH), 7.43 (2H, t J 4.0Hz, ArH), 6.99-6.52 (10H, m, ArH) and 4.98 (4H, bs, NH_2) (exch);

Found: C, 77.4; H, 5.2; N, 8.0%; m/z (EI ms), 342 (M^+),

$C_{22}H_{18}N_2O_2$ requires: C, 77.2; H, 5.3; N, 8.2%; M, 342.

(ii) 1,6-Bis-(2-nitrophenoxy)naphthalene (218) gave a dark brown viscous oil which was treated with water (50.0ml) and extracted three times with dichloromethane (3 x 10.0ml) to give a dark brown oil which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded 1,6-bis-(2-aminophenoxy)naphthalene (219) as a pale yellow solid (90%), m.p. 115-123°, which formed colourless crystals, m.p. 117-119° (from hexane-ethanol), ν_{max} 3437 and 3352 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 8.33 (1H, d J 9.1Hz, ArH), 7.39-7.22 (3H, m, ArH), 7.10-6.67 (10H, m, ArH) and 3.65 (4H, bs, NH_2) (exch);

Found: C, 76.8; H, 5.3; N, 8.2%; m/z (EI ms), 342 (M^+),

$C_{22}H_{18}N_2O_2$ requires: C, 77.2; H, 5.3; N, 8.2%; M, 342.

Further elution with hexane-ether (50:50) through methanol afforded only small amounts of intractable gums which were not further investigated.

(iii) 2,6-Bis-(2-nitrophenoxy)naphthalene (229) gave a light brown solid, m.p. 203-210°, which was crystallised from acetic acid to give 2,6-bis-(2-aminophenoxy)naphthalene (230) as a light brown solid (74%), which formed cream cubes, m.p. 215-218° (from acetic acid), ν_{max} 3441 and 3358 (NH_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.76 (2H, d J 8.8Hz, ArH), 7.24-7.15 (4H, m, ArH), 6.99-6.81 (6H, m, ArH), 6.61-6.52 (2H, m, ArH) and 4.95 (4H, bs, NH_2) (exch);

Found: C, 77.2; H, 5.1; N, 8.1%; m/z (EI ms), 342 (M^+),

$C_{22}H_{18}N_2O_2$ requires: C, 77.2; H, 5.3; N, 8.2%; M, 342.

The acetic acid filtrate was rotary evaporated to give a red oil (1.6g) which was not further investigated.

(iv) 2,7-Bis-(2-nitrophenoxy)naphthalene (224) gave a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (50:50) afforded 2,7-bis-(2-aminophenoxy)naphthalene (225) as a light brown solid (99%), which formed cream cubes, m.p. 80-82° (from ethanol), ν_{max} 3364, 3377 and 3203 (NH_2) cm^{-1}, δ_H ($CDCl_3$) 7.78-7.62 (2H, m ArH), 7.25-6.70 (12H, m, ArH) and 3.78 (4H, bs, NH_2) (exch);

Found: C, 77.9; H, 5.3; N, 8.0%; m/z (EI ms), 342.1368 (M^+),

$C_{22}H_{18}N_2O_2$ requires: C, 77.2; H, 5.3; N, 8.2%; M, 342.1368.

Further elution with methanol afforded a brown oil which was not further investigated.

(b) Repetition of the reaction described in (a)(ii) before, but using acetic acid as the solvent, gave a dark brown viscous oil which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded 1,6-bis-(2-aminophenoxy)naphthalene (219) as a pale yellow solid (75%), m.p. 117-119°, identical (melting point i.r. spectrum) to an authentic sample prepared before.

Further elution with hexane-ether (80:20) through ether to methanol afforded only mixed fractions as oils which were not further investigated.

Bis-(2-isothiocyanatophenoxy)naphthalene Derivatives

A solution of the corresponding bis-(2-aminophenoxy)naphthalene derivative (0.01mol) in glacial acetic acid (60.0ml) was stirred and treated with a 1:1 mixture of concentrated hydrochloric acid and water (20.0ml) then dropwise at room temperature with a solution of thiophosgene (4.8g; 0.04mol) in glacial acetic acid (20.0ml) and the mixture then stirred at room temperature for 4h.

The mixture was diluted with water (100ml) and extracted three times with dichloromethane (3 x 200ml). The combined dichloromethane extracts were washed three times with 10% w/v aqueous sodium hydrogen carbonate solution (3 x 100ml) then rotary evaporated to give a residue which was worked up as described for the individual reactions below.

(i) 1,5-Bis-(2-aminophenoxy)naphthalene (236) gave 1,5-bis-(2-isothiocyanatophenoxy)naphthalene (237) as a light brown solid (100%), m.p. 175-178° (from 1,2-dimethoxyethane), ν_{max} 2111 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.96 (2H, d J 8.5Hz, ArH), 7.60-7.52 (4H, m, ArH), 7.42-7.22 (4H, m, ArH) and 7.10 (4H, m, ArH);

Found: C, 67.4; H, 3.5; N, 6.4%; m/z (EI ms), 426 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: C, 67.6; H, 3.3; N, 6.6%; M, 426.

(ii) 1,6-Bis-(2-aminophenoxy)naphthalene (219) gave a brown oil which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded 1,6-bis-(2-isothiocyanatophenoxy)naphthalene (220) as a light brown solid (72%), forming

colourless crystals, m.p. 88-90° (from acetic acid), ν_{max} 2061 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.19 (1H, d J 9.1Hz, ArH), 7.68 (1H, d J 8.3Hz, ArH), 7.54-7.18 (10H, m, ArH), 7.03 (1H, dd J 8.3 and 1.4Hz, ArH) and 6.87 (1H, dd J 0.7 and 7.6Hz, ArH);

Found: C, 67.7; H, 3.4; N, 6.6%; m/z (EI ms), 426 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: C, 67.6; H, 3.3; N, 6.6%; M, 426.

Further elution with hexane-ether (90:10) afforded a red oil which was not further investigated.

Further elution with hexane-ether (80:20) afforded 1,6-bis-(2-aminophenoxy)naphthalene (220) as a red oil (11%), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Final elution with methanol afforded a brown gum which was not further investigated.

(iii) 2,6-Bis-(2-aminophenoxy)naphthalene (230) gave a light brown solid which was flash chromatographed over silica.

Elution with hexane-ether (98:2) afforded 2,6-bis-(2-isothiocyanatophenoxy)naphthalene (231) as a light brown solid (47%), which formed cream crystals, m.p. 170-172° (from 1,2-dimethoxyethane), ν_{max} 2064 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.95 (2H, d J 8.8Hz, ArH) and 7.54-7.11 (12H, m, ArH);

Found: C, 67.5; H, 3.5; N, 6.4%; m/z (EI ms), 426 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: C, 67.6; H, 3.3; N, 6.6%; M, 426.

Further elution with ether afforded a brown oil which was not further investigated.

(iv) 2,7-Bis-(2-aminophenoxy)naphthalene (225) gave a red oil which was flash chromatographed over silica.

Elution with hexane afforded a waxy yellow solid, m.p. 73-79°, which decomposed on attempted crystallisation.

Further elution with hexane afforded 2,7-bis-(2-isothiocyanatophenoxy)naphthalene (226) as a light brown solid (78%), which formed cream cubes, m.p. 108-109° (from ethanol), ν_{max} 2117 and 2082 (NCS) cm^{-1}, δ_H ($CDCl_3$) 7.84 (2H, d J 8.9Hz, ArH) and 7.29-7.00 (12H, m, ArH);

Found: C, 67.8; H, 3.3; N, 6.4%; m/z (EI ms), 426 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: C, 67.6; H, 3.3; N, 6.6%; M, 426.

Further elution with hexane-ether (98:2) through to methanol afforded brown oils which were not further investigated.

Aluminium Trichloride Catalysed Cyclisations of Bis-(2-Isothiocyanatophenoxy)naphthalene Derivatives.

(a) A suspension of aluminium trichloride (1.1g; 0.008mol) in anhydrous dichloromethane (25.0ml) was stirred and treated dropwise at -10° (ice-acetone bath) under nitrogen with a solution of the corresponding bis-(2-isothiocyanatophenoxy)naphthalene derivative (0.002mol) in anhydrous dichloromethane (10.0ml) then stirred at room temperature for 4h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (77.0ml), stirred at room temperature for 15min then extracted three times with dichloromethane (3 x 100ml) to give a residue which was worked up as described for the individual reactions below.

(i) 1,5-Bis-(2-isothiocyanatophenoxy)naphthalene (237) gave a brown solid which was flash chromatographed over silica.

Elution with hexane-ether (60:40) afforded 4-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (238) as a yellow crystalline solid (58%), m.p. 253-255° (from dimethylformamide-acetic acid), ν_{max} 3110 (NH) and 2103 and 2026 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.49 (1H, d J 8.7Hz, ArH) and 8.22-6.84 (12H, m, ArH);

Found: m/z (FAB HRMS), 427.0585 (MH^+),

$C_{24}H_{14}N_2O_2S_2$ requires: MH, 427.0575

Further elution with methanol afforded an intractable brown oil which was not further investigated.

(ii) 1,6-Bis-(2-isothiocyanatophenoxy)naphthalene (220) gave a yellow solid which was flash chromatographed over silica.

Elution with hexane-ether (90:10) afforded 3-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221) as a yellow solid (67%), m.p. 178-180° (from acetic acid), ν_{max} 3154 and 3105 (NH) and 2033 (NCS) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.85 (1H, bs, NH) (exch), 8.73 (1H, d J 8.2Hz, ArH), 8.01 (1H, d J 8.8Hz, ArH) and 7.70-7.21 (11H, m, ArH);

Found: C, 67.7; H, 3.5; N, 6.4%; m/z (EI ms), 426 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: C, 67.6; H, 3.3; N, 6.6%; M, 426 .

Further elution with hexane-ether (50:50) through to methanol afforded only complex mixtures which were not further investigated.

(iii) 2,6-Bis-(2-isothiocyanatophenoxy)naphthalene (231) gave a red solid which was flash chromatographed over silica.

Elution with hexane-ether (85:15) afforded the (2-isothiocyanatophenoxy)benzo[b]naphth[1,4]oxazepinethione derivative (232) as a yellow solid (60%), m.p. 240-243° (from acetic acid), ν_{max} 3149 (NH) and 2031 (NCS) cm^{-1};

Found: m/z (FAB HRMS), 427.0585 (MH^+),

$C_{24}H_{14}N_2O_2S_2$ requires: MH, 427.0575 .

Further elution with hexane-ether (40:60) through to methanol afforded only complex mixtures which were not further investigated.

(iv) 2,7-Bis-(2-isothiocyanatophenoxy)naphthalene (226) gave a yellow solid which was flash chromatographed over silica.

Elution with hexane-ether (50:50) afforded the (2-isothiocyanatophenoxy)benzo[b]naphth[1,4]oxazepinethione derivative (227) as a brown solid (33%), m.p. 279-282° (from acetic acid), ν_{max} 3154 (NH) and 2023 (NCS) cm^{-1}, δ_H ($CDCl_3$) 13.25 (1H, bs, NH) (exch) and 8.46-7.19 (13H, m, ArH);

Found: m/z (EI ms), 426.0498 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: M, 426.0497.

Further elution with hexane-ether (50:50) through to methanol afforded only small amounts of unidentified material which were not further investigated.

(b) The reaction was repeated as described in (a) before, but using 1,2-dichloroethane as the solvent and stirring at room temperature for 4h followed by heating under reflux

for a further 3h. The resulting mixture was then worked up as described for the individual reactions below

(i) 1,5-Bis-(2-isothiocyanatophenoxy)naphthalene (237) afforded an intractable brown foam, which was not further investigated.

(ii) Repetition of the reaction described in (b)(i) before, but using 2,6-bis-(2-isothiocyanatophenoxy)naphthalene (231) and stirring at room temperature for 4h followed by heating under reflux for a further 2h, afforded the doubly-cyclised material (233) as a brown solid (56%), m.p. 219-222° (from dimethylformamide), ν_{max} 3121 (NH) cm^{-1};

Found: m/z (EI ms), 426.0498 (M^+),

$C_{24}H_{14}N_2O_2S_2$ requires: M, 426.0497.

(iii) Repetition of the reaction described in (b)(i) before, but using 2,7-bis-(2-isothiocyanatophenoxy)naphthalene (226) and stirring at room temperature for 4h followed by heating under reflux for a further 19h, afforded an orange solid which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded a mixed fraction as a yellow solid, m.p. >360°, which was not further investigated.

Final elution with methanol afforded an unidentified orange glass, which afforded no collectable material on trituration and was therefore not further investigated.

(c) Repetition of the reaction described in (a)(i) before, but using only two equivalents of aluminium trichloride (0.004mol) and stirring for 15min at room temperature, afforded a residue which was worked up as described for the individual reactions below.

(i) 1,5-Bis-(2-isothiocyanatophenoxy)naphthalene (226) gave a dark brown gum which was triturated with ether to give 4-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (238) as a yellow solid (76%), m.p. 210-216°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The ether washings were rotary evaporated to give a brown gum which was not further investigated.

(ii) 1,6-Bis-(2-isothiocyanatophenoxy)naphthalene (220) gave a yellow solid, m.p. 167-172°, which was crystallised from acetic acid to give 3-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221) as a yellow solid (93%), m.p. 174-178°, identified by comparison (melting point and i.r. spectrum) with an authentic sample prepared before.

The acetic acid mother liquor was rotary evaporated to give a brown gum which was not further investigated.

(iii) 2,6-Bis-(2-isothiocyanatophenoxy)naphthalene (231) gave a brown solid which was flash chromatographed over silica.

Elution with hexane-ether (85:15) afforded the (2-isothiocyanatophenoxy)benzo[b]naphth[1,4]oxazepinethione derivative (232) as an orange solid (12%), m.p. 197-206°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with hexane-ether (40:60) through to methanol afforded only complex mixtures which were not further investigated.

(iv) 2,7-Bis-(2-isothiocyanatophenoxy)naphthalene (226) gave an orange solid which was flash chromatographed over silica.

Elution with hexane-ether (80:20) afforded an inseparable mixture as an orange solid, m.p. 186-191°, which was not further investigated.

Further elution with methanol afforded no identifiable material.

Attempted Aluminium Trichloride Catalysed Reactions of 3-(2-Isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221).

(a) A suspension of aluminium trichloride (0.54g; 0.004mol) in anhydrous dichloromethane (20.0ml) was stirred and cooled to -10° (ice-acetone bath) under nitrogen and treated dropwise with a solution of 3-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221) (0.85g; 0.002mol) in anhydrous dichloromethane (10.0ml). The resulting mixture was stirred at room temperature for 1h then heated under reflux for a further 24h.

The mixture was poured into 10% w/v aqueous sodium hydrogen carbonate solution (31.0ml), stirred at room temperature for 15min then extracted three times with ethyl

acetate (3 x 50.0ml) to give a yellow solid (0.81g) which was flash chromatographed over silica.

Elution with hexane-ether (60:40) through to methanol afforded only mixed fractions (0.51g) from which no identifiable material could be isolated.

(b) Repetition of the reaction described in (a) before, but using 1,2-dichloroethane as the solvent and heating under reflux for 24h, afforded a doubly-cyclised product as a light brown solid, (0.42g), m.p. 234-237° (from dimethylformamide-toluene), identified by comparison (i.r. spectrum) with an authentic sample prepared before, ν_{max} 3155 and 3106 (NH) cm^{-1};

Found: m/z (FAB HRMS), 427.0568,

$C_{24}H_{14}N_2O_2S_2$ requires: MH, 427.0575.

The Attempted Sodium Hydride Catalysed Reaction of 3-(2-Isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221) with Dimethyl sulphate.

A suspension of sodium hydride (0.026g; 0.0011mol) in anhydrous dimethylformamide (1.0ml) was vigorously stirred and treated at room temperature with a solution of 3-(2-isothiocyanatophenoxy)benzo[b]naphth[2,1-f][1,4]oxazepine-7(8H)-thione (221) in anhydrous dimethylformamide (2.0ml) added in one portion, and the mixture was stirred at room temperature, with the exclusion of atmospheric moisture, for 15min. A solution of dimethyl sulphate (0.59g; 0.004mol) in anhydrous

dimethylformamide (2.0ml) was added in one portion and the mixture stirred at room temperature, with the exclusion of atmospheric moisture. for 17h.

The resulting mixture was treated with water (10.0ml) and rotary evaporated to give a yellow oily residue. This residue was treated with water and extracted three times with dichloromethane (3 x 10.0ml) to give a brown oil (0.36g) which was flash chromatographed over silica.

Elution with hexane-ether through to methanol afforded only intractable gums (total 0.35g) which were not further investigated.

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