

**STUDIES OF SOME FUSED-RING HETEROCYCLES  
AND  
2,6-DIARYLPYRIDINE DERIVATIVES**

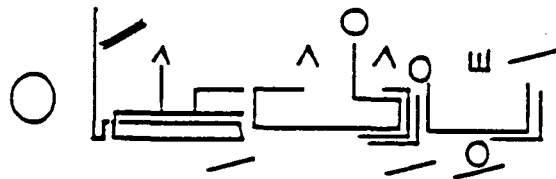
Thesis Submitted for the Degree of Doctor of Philosophy

By  
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(Rabbi zid-nee ilmaa)

O my Lord, increase me in knowledge.

## ABSTRACT

This work reported is divided into two parts: the first part deals with quinoxaline derivatives and includes the preparation and characterisation of novel linear tricyclic quinones 1,4-diazanthracen-9,10-diones, (54) and (55). The reaction of diazaphthoquinones and 1-acetyl-1,3-butadiene are used to produce these quinones through the Diels-Alder reaction.

In addition hexaazapentacyclic 5,6,7,12,13,14-hexaazapentacene was prepared by the reaction of bis(2-chloroquinoxalin-3-yl)sulfide with thioamide and the reaction of the sulfide with amines was investigated. Two different approaches to 6,13-dibutyl-5,6,7,12,13,14-hexaazapentacene are given. Derivatives of the pentacyclic, 6-thia-5,7,12,13,14-pentaazapentacene and the unsubstituted 6,13-dihydro compound are described.

The novel *N*-(2,5-dimethoxy-6-nitrophenyl)guanidine is used to obtain 3-amino-5,6-dimethoxy-1,2,4-benzotriazine-1-oxide and 4,7-dimethoxy-1,2,3-benzotriazole is shown to be second product.

Second part of the work is concerned with the development of a preparative route to 2,6-diphenylpyridines substituted with different groups on the phenyl nuclei. Several approaches were attempted. Finally, success was achieved and a series of compounds having basic chains of different length on the phenyl groups was prepared. One chain in each case had a terminal primary amine. The binding constants of the primary amines and their *N*-acetyl derivatives with DNA were determined using fluorescence spectroscopy.

## ACKNOWLEDGEMENTS

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*TO ARJAN AND TALHA*

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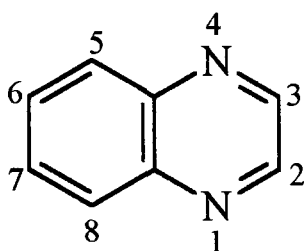
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# CHAPTER: 1

## 1.1 INTRODUCTION

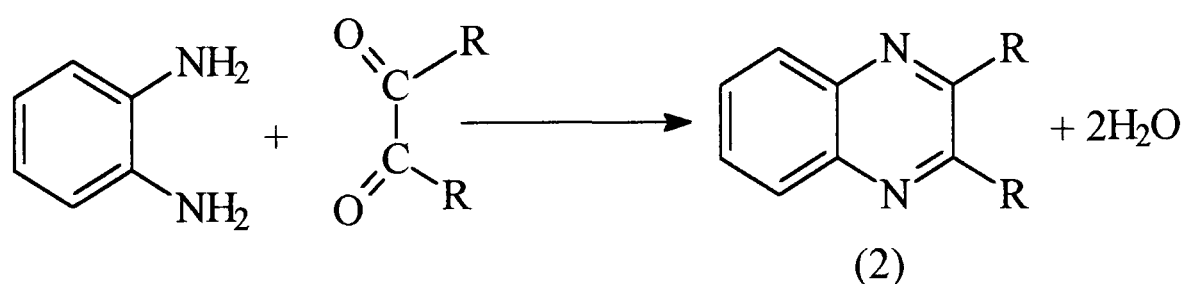
### 1.1.1 Quinoxaline and related compounds.

The approved numbering for the quinoxaline ring system, also known as 1,4-diazanaphthalene, is shown in structure (1).



(1)

The vast majority of quinoxalines are of synthetic origin and with very few exceptions the synthetic method used is to condense an *ortho*-disubstituted benzene with a two-carbon synthon. Thus condensation of *o*-phenylene diamines with  $\alpha$ -dicarbonyl compounds results in quinoxaline (2) (Scheme 1).



Scheme 1

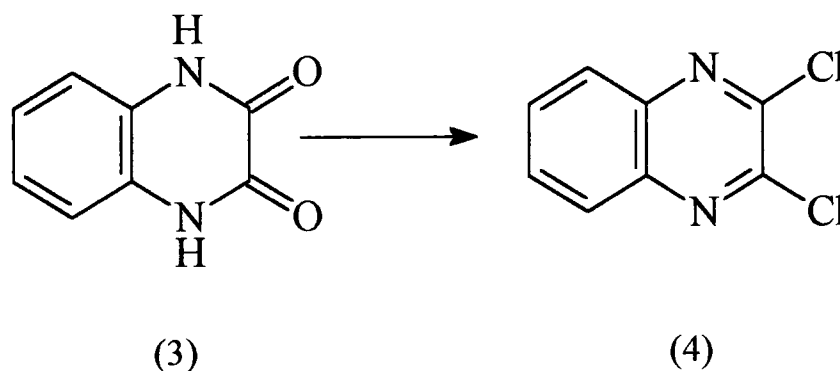
Formation of the bicyclic system generally takes place very smoothly in good yields at a temperature below 100°C and compounds are readily isolated as crystalline solids.<sup>1</sup>



By suitable choice of the 1,2-dicarbonyl component, alkyl and aryl substituted quinoxalines and quinoxalinones have been prepared. Some have shown biological activity.<sup>2</sup>

Quinoxaline itself and many of its simple derivatives do not readily undergo substitution on carbon when treated with electrophilic reagents. However, the parent base is resistant to nitration with fuming nitric acid and concentrated sulfuric acid at 100 °C, but under forcing condition (concentrated nitric acid and oleum) it has been converted into 5,6-dinitroquinoxaline as the major product.<sup>3</sup>

The benzene ring of quinoxalin-2-ones is susceptible to electrophilic substitution and nitration and halogenation occur smoothly in the 7-position when the reactions are carried out in acetic acid solution.<sup>4</sup> Quinoxaline 2,3-dione (3) is readily converted into 2,3-dichloroquinoxaline (4) on treatment with phosphoryl chloride,<sup>5</sup> or with a mixture of phosphoryl chloride and phosphorus pentachloride<sup>6</sup> (Scheme 2).



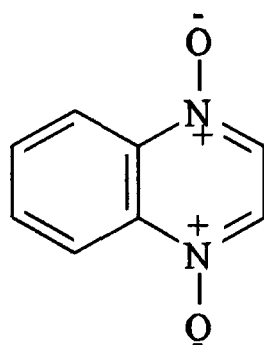
Scheme 2

Many 2-chloro-3-substituted quinoxalines have been prepared from 2,3-dichloroquinoxaline (4) by partial displacement of chlorine<sup>7</sup> and (4) has been converted into a number of polycyclic compounds.

### 1.1.2 Oxidation of quinoxaline.

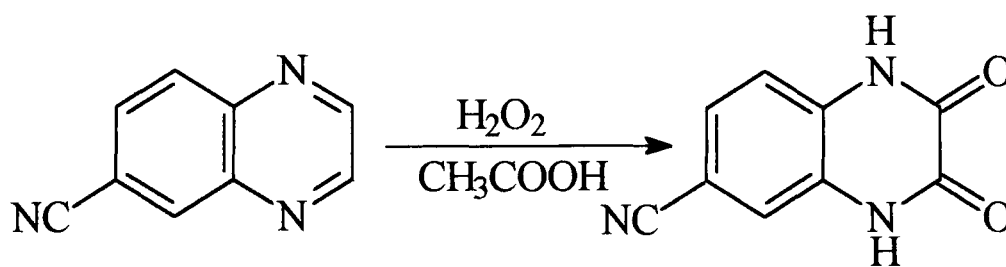
Quinoxaline di-N-oxides with useful antibacterial and growth promoting properties have been synthesized by oxidation of corresponding quinoxalines.

The most convenient reagent for causing *N*-oxidation is 30% aqueous hydrogen peroxide in acetic acid. One equivalent of peracetic acid in acetic acid gives the 1-oxide but with an excess of peracetic acid, quinoxaline 1,4-dioxide (5) is formed.<sup>8</sup>



(5)

5-Substituted quinoxalines generally give 1-oxides which can not be oxidized further into 1,4-dioxides. However, 5-methoxyquinoxaline is an exception in this respect, because it is readily converted into the 1,4-dioxide.<sup>9</sup> Substituents in the 6-position have an unexpected effect. Thus, quinoxalines with electron-donating groups e.g., Me or MeO in this position readily form di-*N*-oxides, but when electron withdrawing groups e.g., NO<sub>2</sub> and CN are present, quinoxaline-2,3-diones (7) are the major products of oxidation<sup>8</sup> (Scheme 3).



(6)

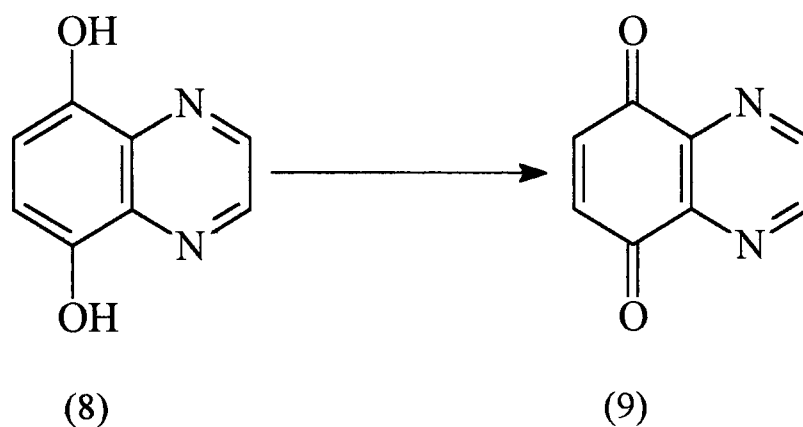
(7)

Scheme 3

Quinoxaline 1,4-dioxides are active against a wide range of bacteria and they have been added to animal feeds both as bactericides and growth promoting agents.<sup>10</sup>

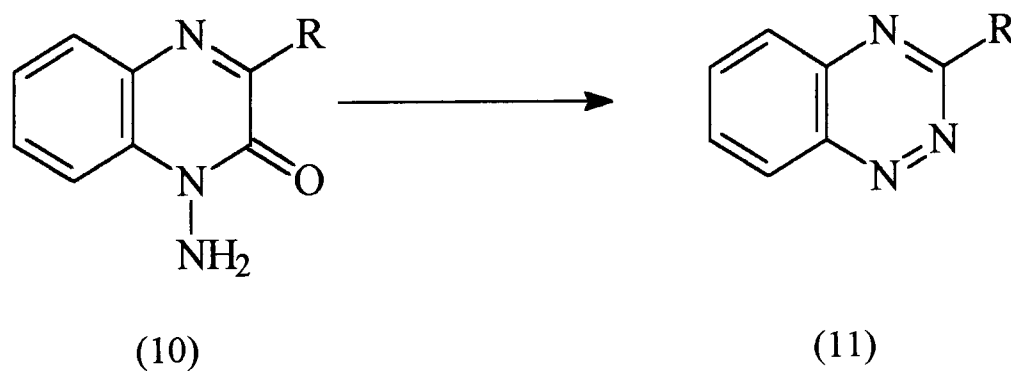
The oxidation of quinoxaline at the 5,8-positions produces quinoxaline 5,8-diones (9).

The parent compound is obtained by silver oxide oxidation of 5,8-dihydroxy quinoxaline (8)<sup>11</sup> (Scheme 4).



Scheme 4

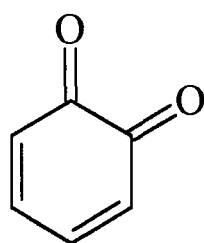
It is also found that oxidation of 1-aminoquinoxaline-2-ones (10) with lead tetraacetate gives benzo-1,2,4-triazines<sup>12</sup> (11) as shown in Scheme 5.



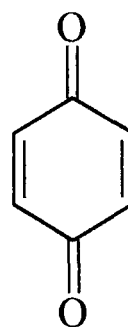
Scheme 5

### 1.1.3 Linear tricyclic quinones.

Compounds derived from benzene and its homologues by the replacement of two atoms of hydrogen with oxygen are known as quinones. Natural quinones are found most commonly in higher plants, fungi and bacteria; the simplest carbocyclic quinones are 1,2-benzoquinone (12) and 1,4-benzoquinone (13).

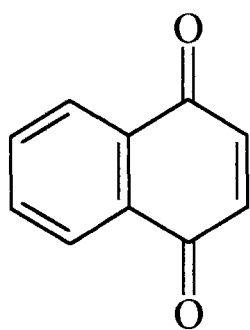


(12)

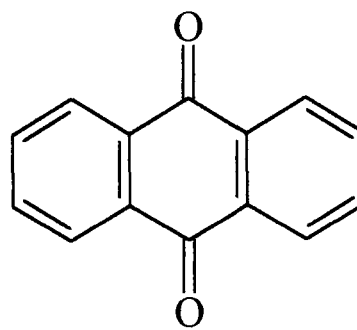


(13)

Next in the series of carbocyclic quinones are naphthoquinones (14) and anthraquinones (15). Compounds containing the quinone nucleus play an important role in numerous biological processes due to their participation in reduction-oxidation changes.<sup>13</sup>

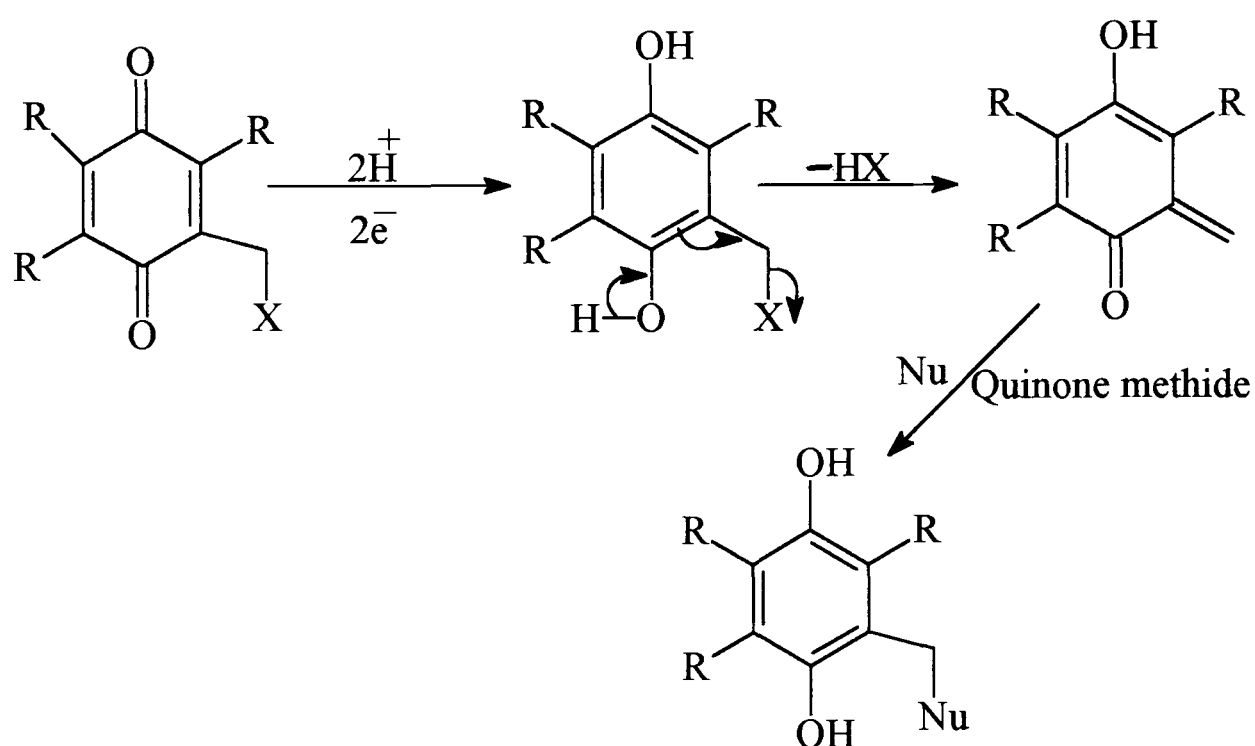


(14)



(15)

Many investigators have now reported a large number of benzo-, naphtho- and anthraquinone derivatives which are appropriately substituted to facilitate quinone methide formation subsequent to an initial reduction to the hydroquinone.<sup>14</sup> The intermediate quinone methide is then viewed as the cytotoxic species in that it reacts with a biologically important nucleophile to form covalently bound adducts. An outline of this is given in Scheme 6.

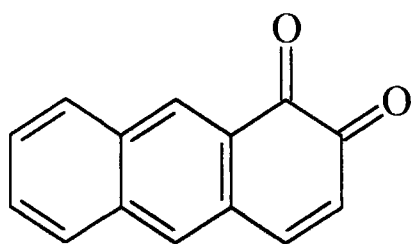


Nu = DNA, protein, carbohydrate.  
X = Cl, OH

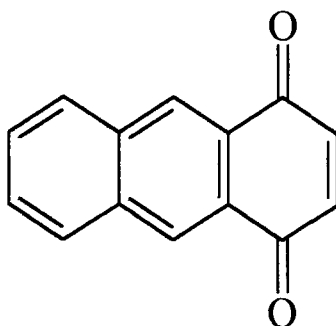
Scheme 6

Some heterocyclic quinones have chemotherapeutic value as antitumour, antibacterial and antifungal agents.<sup>15</sup> The largest group of natural quinones and the most important (biologically) is the anthraquinones.

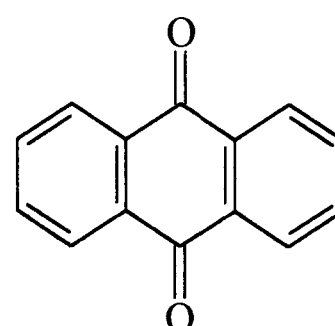
The three unsubstituted anthraquinones are 1,2-, 1,4- and the 9,10-isomers, (16), (17) and (18), respectively.



(16)



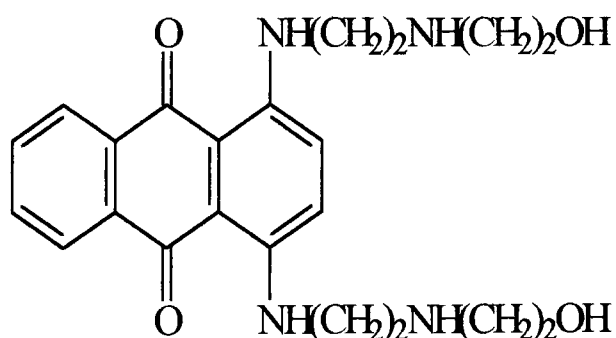
(17)



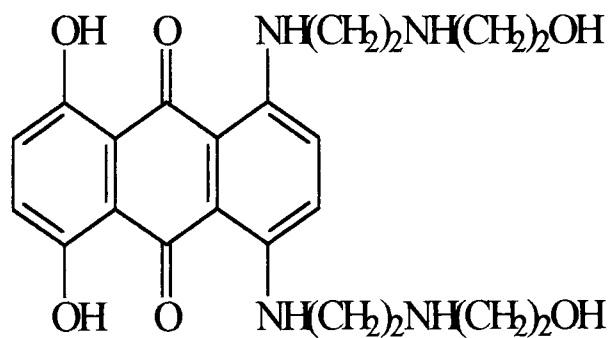
(18)

The parent 9,10-anthraquinone (18) is a substance of great technical importance as an intermediate for the manufacture of anthraquinone dyes and drugs.

Naturally occurring quinones which structurally consist of an anthracene-9,10-dione chromophore include some important antitumour agents such as doxorubicin and the anthracycline antibiotics. The synthetic anthracene-9,10-diones such as mitoxantrone (19) and ametantrone (20) are potent antitumour agents.<sup>16</sup>



(19)



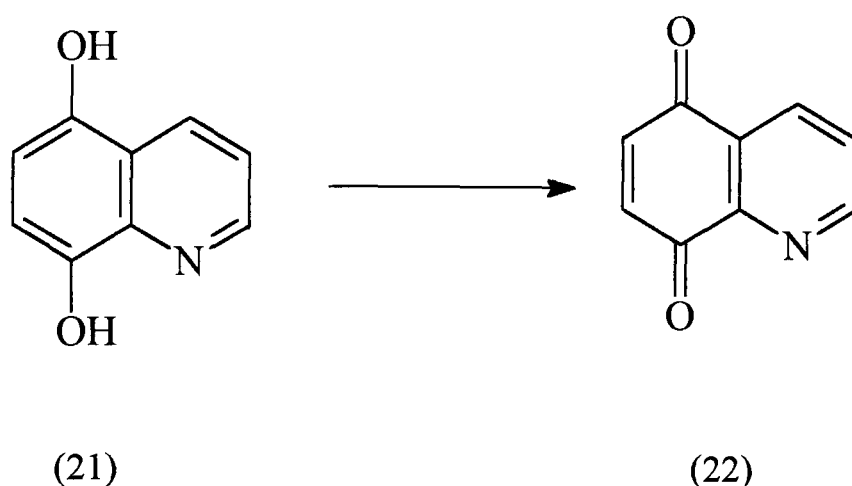
(20)

#### 1.1.4 Preparation of quinones.

Heterocyclic quinones are usually prepared by using one of the following methods :-

- 1) Oxidation of heteroaromatic compounds
- 2) Cyclisation reactions.

An example of an oxidation process is the conversion of 5,8-dihydroxyquinoline (21) into the *p*-quinone (22) by using nitric acid as the oxidant (Scheme 7).



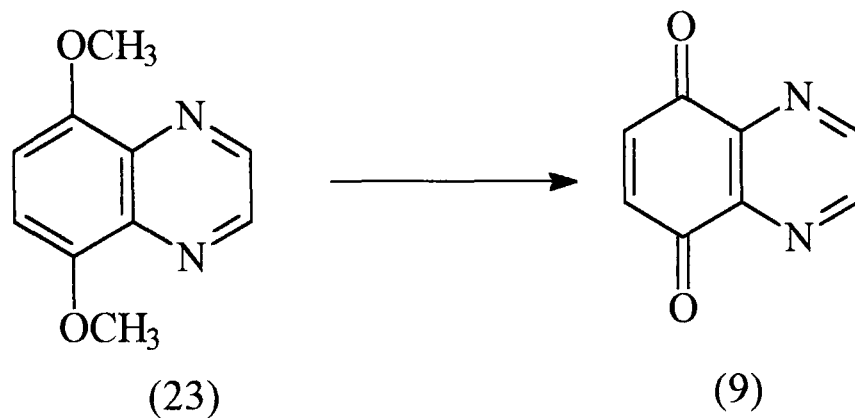
Scheme 7

This reagent can also produce *o*-quinones from the corresponding dimethoxy compounds.<sup>17</sup> A possible disadvantage of using a strong acidic oxidising agent is the formation of byproducts such as nitro derivatives.<sup>18</sup>

Fremy's salt (potassium nitrosodisulphonate) is a widely used oxidising agent in this field, particularly for those aromatic rings which have hydroxy or amino groups, and the oxidation is normally carried out in an aqueous medium.<sup>19</sup>

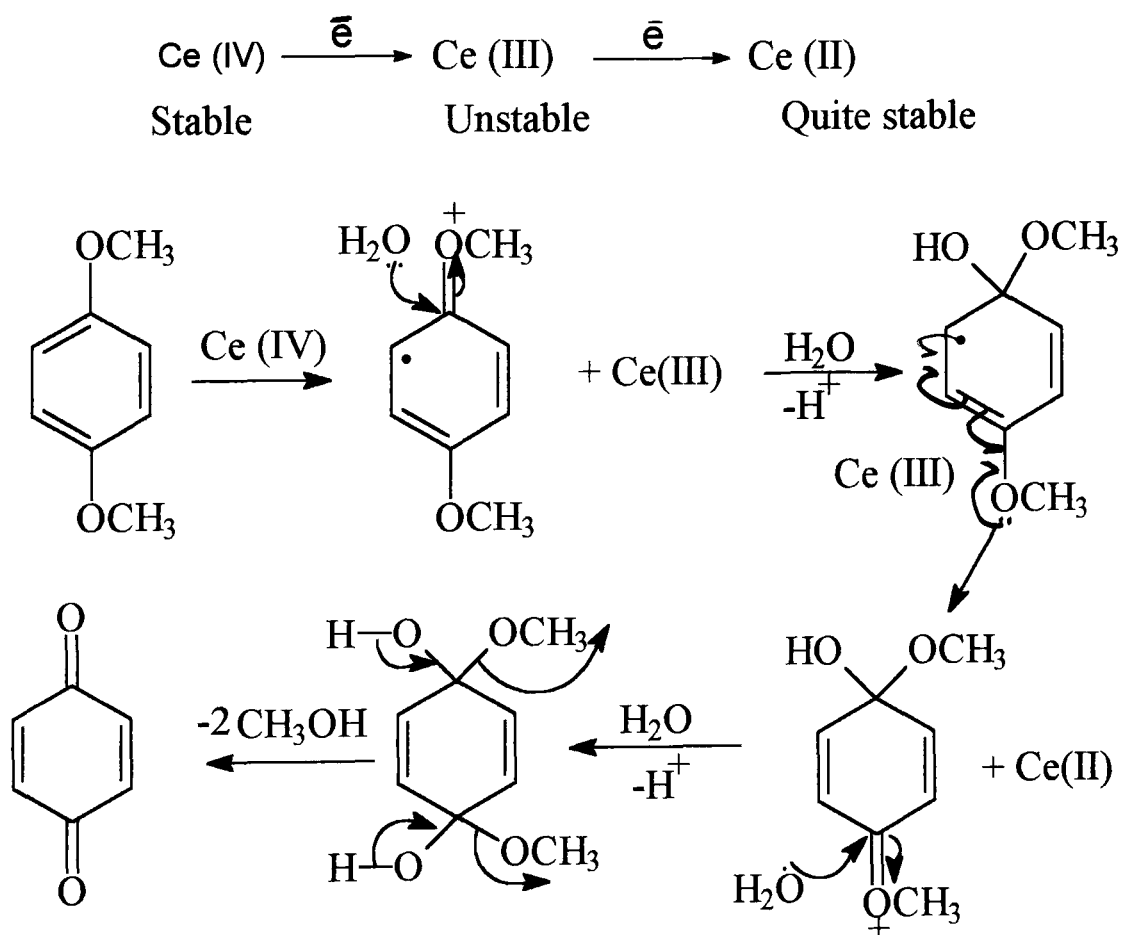
CAN (cerium(IV) ammonium nitrate) is another cheap and multi-electron oxidant, which has been used extensively for the fast and convenient preparation of quinones from dihydroxy- and dimethoxy-quinones.<sup>20</sup>

5,8-Dimethoxyquinoxaline (23) was oxidatively demethylated with CAN in aqueous acetonitrile to afford the corresponding quinoxalin-5,8-dione (9) (Scheme 8).



Scheme 8

### Mechanism

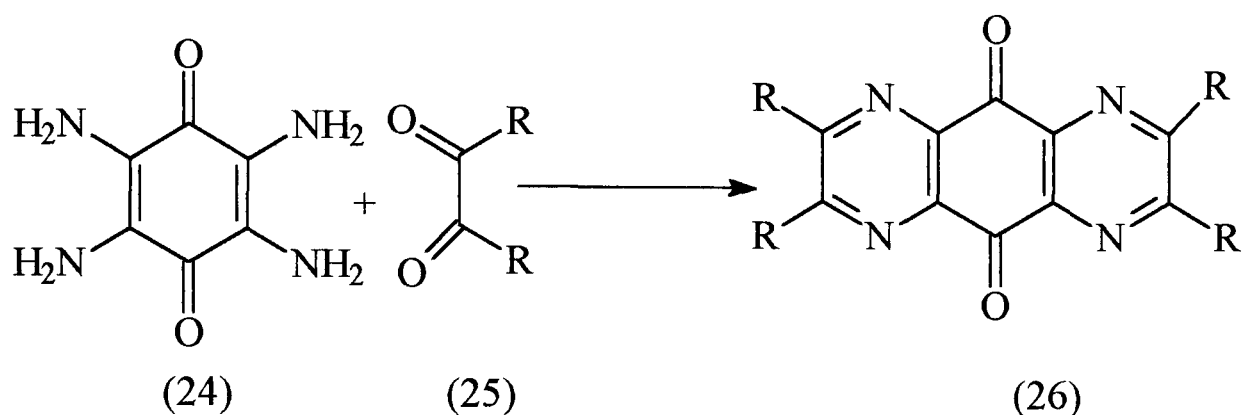


Scheme 9



### 1.1.5 Cyclisation by addition reaction.

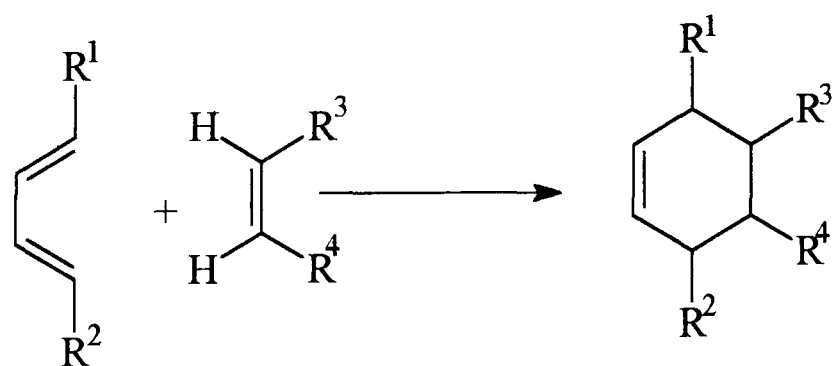
Renault and co-workers<sup>21</sup> have obtained the 5,10-pyrazino[2,3-g]quinoxaline (26) by the condensation of 2,3,5,6-tetraaminobenzoquinone (24) with 1,4-dibromo butanedione (25) (Scheme 10).



Where  $R = \text{CH}_2\text{Br}$

Scheme 10

In the present work, the Diels-Alder reaction is a useful method for the preparation of linear tricyclic quinones. The Diels-Alder reaction is a very useful reaction in organic synthesis.<sup>22</sup> It involves the cycloaddition of an alkene (dienophile) to a conjugated diene. The term cycloaddition refers to the fact that the cyclic compound is produced by an addition between two non-cyclic partners<sup>23</sup> (Scheme 11).



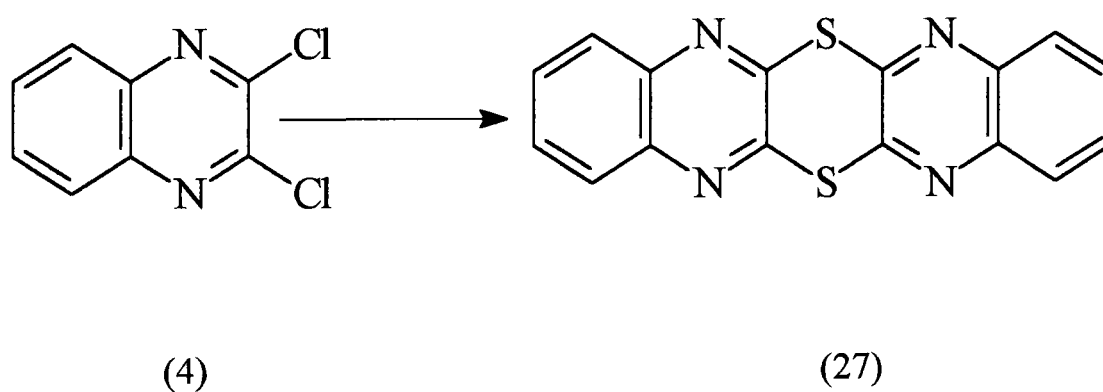
Scheme 11

In the process two  $\pi$  bonds, one in the dienophile and one from the diene are converted to two sigma bonds. A four carbon fragment, the diene, reacts with a two carbon fragment, the dienophile. Therefore, the Diels-Alder reaction is termed a [4+2] cycloaddition process.<sup>24</sup>

### 1.1.6 Fused polycyclic system.

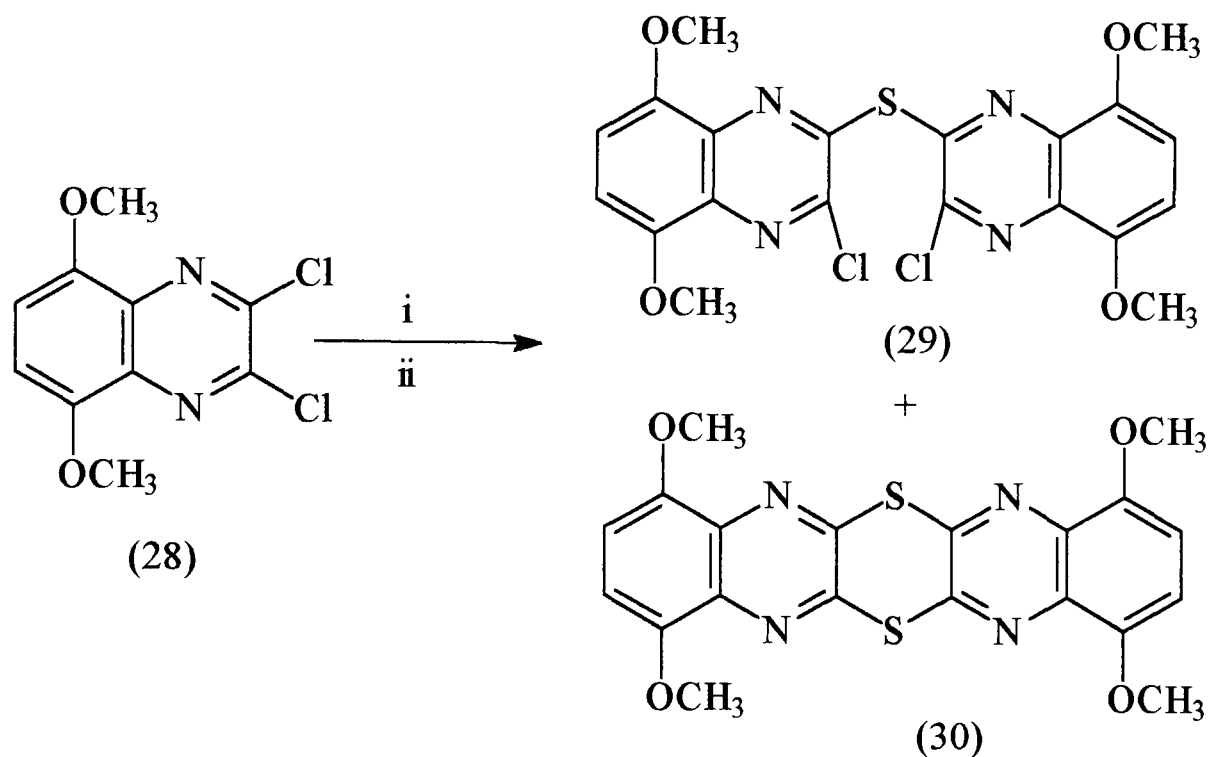
Many reactions which utilise nitrogen, oxygen and sulfur nucleophiles have been carried out on 2,3-dichloroquinoxaline (4) and its benzo substituted derivatives.

When 2,3-dichloroquinoxaline and thiourea are allowed to react in ethanol, 1,4-dithia-1,4-dihydrophenazino[2,3-*b*]quinoxaline (27) is obtained in excellent yield<sup>25</sup> (Scheme 12).



Scheme 12

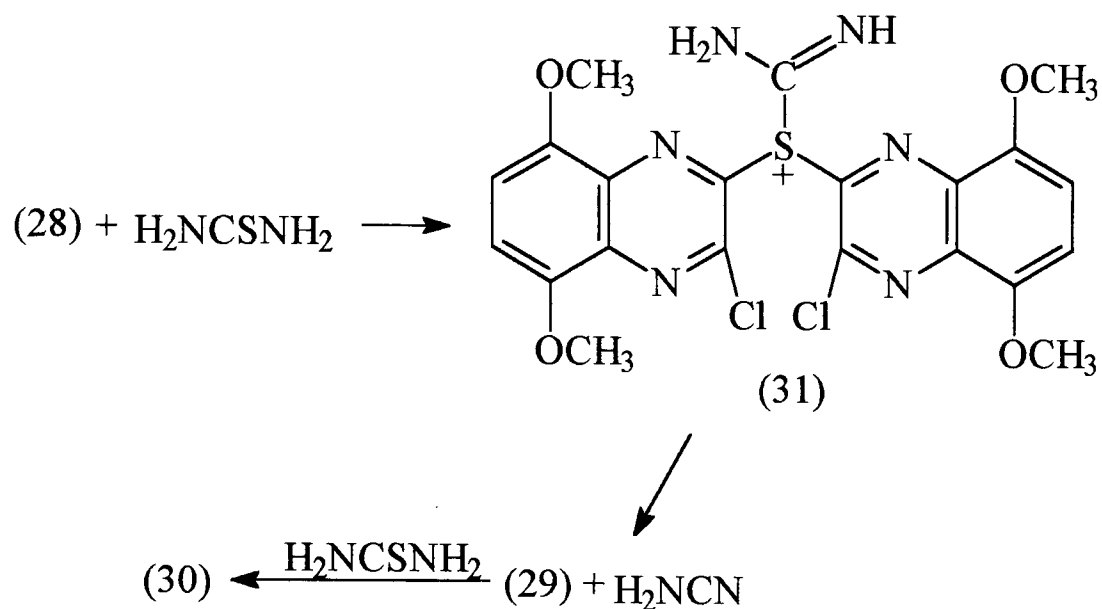
Recently, Parrick and co-workers reported<sup>26</sup> that treatment of 2,3-dichloro-5,8-dimethoxy quinoxaline (28) with an equimolar quantity of thiourea in DMF gave two products (Scheme 13).



Reagents: (i) H<sub>2</sub>NCSNH<sub>2</sub>  
(ii) DMF

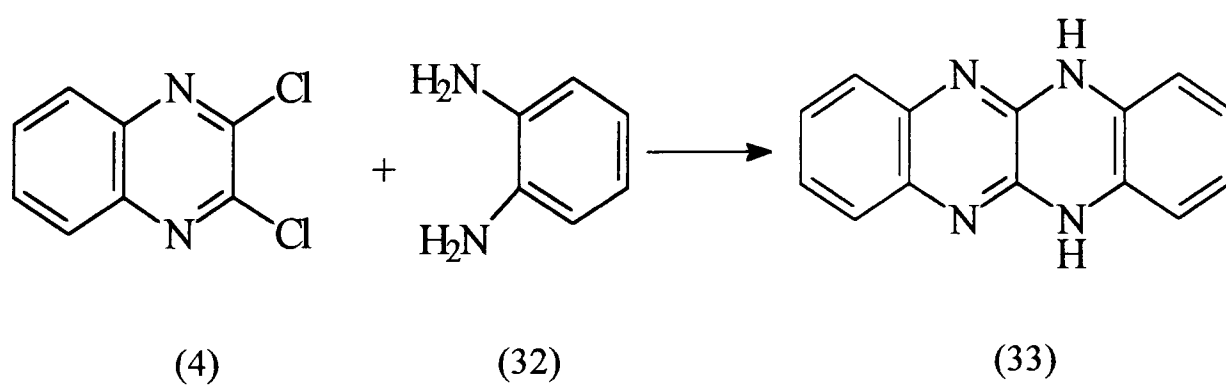
Scheme 13

The bis (2-chloro-5,8-dimethoxyquinoxalin-3-yl)sulfide (29) was an intermediate in the formation of 1,4,8,11-tetramethoxy-6,13-dihydro-5,7,12,14-tetraaza-6,13-dithia penta-cene (30) and bis (2-chloro-5,8-dimethoxyquinoxalin-3-yl)sulfide (29) was thought to be formed from isothiuronium salt (31) (Scheme 14).

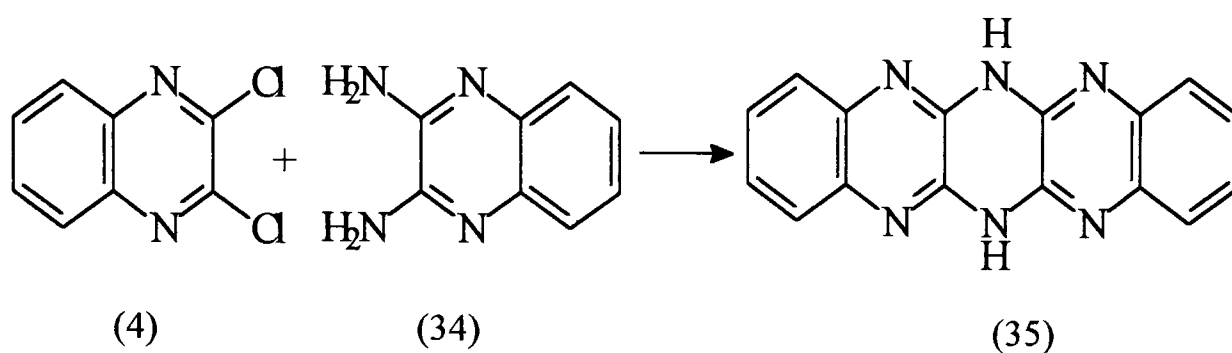


Scheme 14

However 2,3-dichloroquinoxaline (4) has been converted into a number of polycyclic derivatives by reaction with *o*-disubstituted benzenes (32). Thus reaction of (4) with *o*-phenylene diamines (32) and 2,3-diaminoquinoxaline (34) gave the tetraaza-naphthalene (33) (Scheme 15),<sup>27</sup> and fluorubin (35) respectively (Scheme 16).



Scheme 15



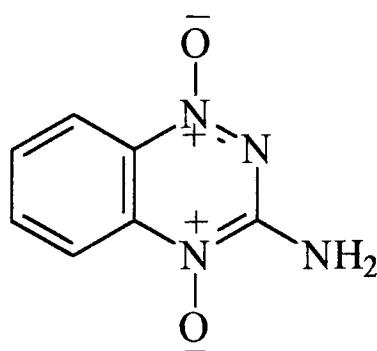
Scheme 16

Fluorubin is a reddish-yellow pigment with an orange red fluorescence. It has been suggested that derivatives of fluorubin are suitable substances for signalling in sea rescue work.<sup>28</sup>

#### 1.1.7 3-Amino-1,2,4-benzotriazine.

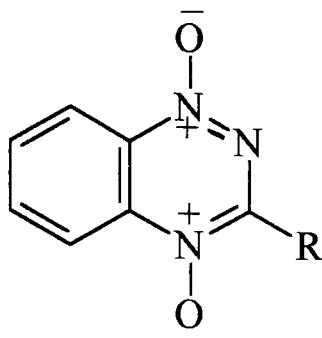
Benzotriazine dioxide can be considered as an azaquinoxaline derivative. The dioxides have shown significant selective toxicity towards hypoxic cells in solid tumours.<sup>29</sup>

The most active compound of the series was found to be 3-amino-1,2,4-benzotriazine-1,4-dioxide (36), SR4233, and this now represents the lead compound in a new class of bioreductively activated anticancer drugs. SR 4233 is in clinical trials.<sup>30</sup>



SR 4233 (36)

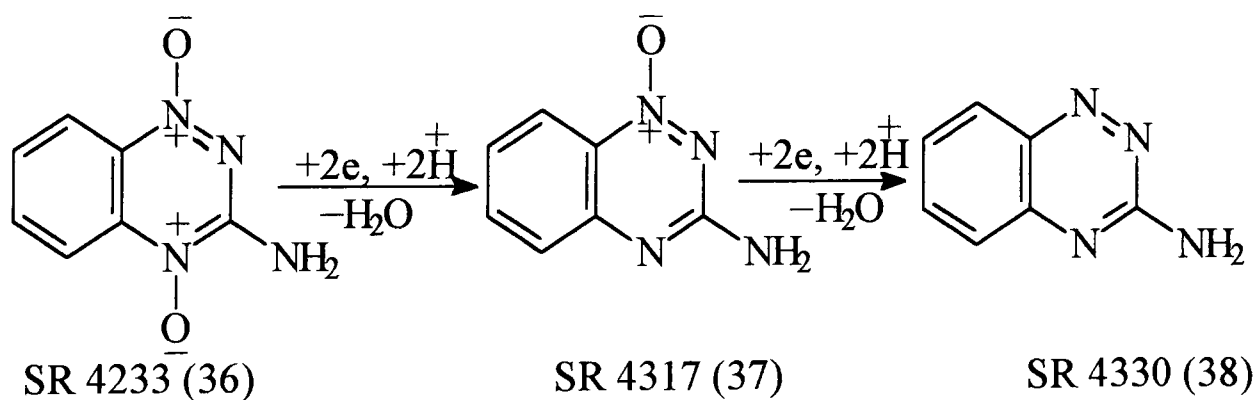
A number of derivatives of 1,2,4-benzotriazine and of its 1,4-dioxides have been reported<sup>31</sup> and tested for anticancer activity. The biological activity is dependent on the substituent.



Where R = NH<sub>2</sub> (SR 4233)  
 CH<sub>3</sub> (SR 4713)  
 CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub> (SR 4941)  
 CH<sub>2</sub>CH<sub>3</sub> (SR 4895)

SR 4941 has almost identical lipophilicity to SR 4233 but is 10 times more soluble in aqueous media, and has excellent hypoxic selectivity.<sup>31</sup>

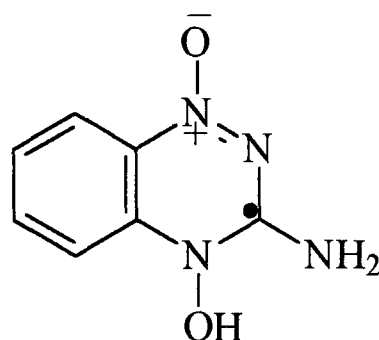
The mode of action of SR 4233 may be due to DNA damage caused by a radical intermediate. 3-Amino-1,2,4-benzotriazine-dioxide and analogues are reduced to radicals which then abstract a hydrogen atom from the sugar of DNA.<sup>32</sup> However the first stable reduced metabolites of SR 4233 are the two electron and four electron reduction products SR 4317 (37) and SR 4330 (38) respectively (Scheme 18) in a hypoxic cell.<sup>33</sup>



Scheme 18

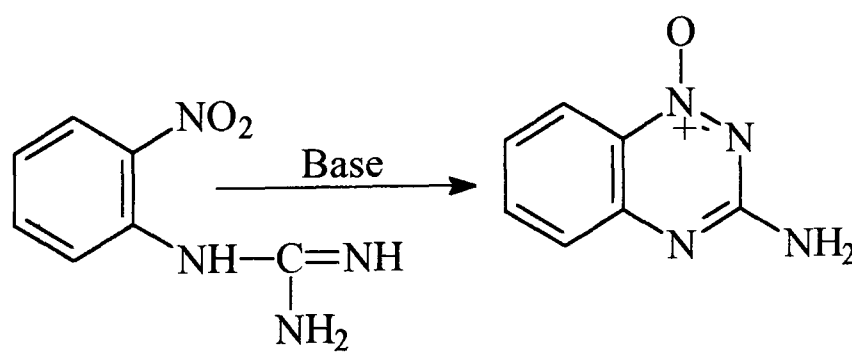
SR 4317 (37) is reported to be not measurably toxic to hypoxic cells at levels significantly greater than those at which SR 4233 (36) is toxic.<sup>34</sup> It was suggested that the damaging species existed at the one electron reduction level. Further studies showed that the one electron reduction product of SR 4233 is an oxidising radical that causes single and double strand breaks in the DNA molecule.<sup>35</sup>

The natural life time of this radical was sufficiently long that it could diffuse over significant distances within hypoxic cells and thus cause oxidative damage of cellular targets. Therefore, it has been suggested that the one electron reduction product (39) is the active species.<sup>35</sup>



(39)

The most convenient preparation of 3-aminobenzo-1,2,4-triazine-1-oxide was reported by Arndt in 1913.<sup>36</sup> and involves the cyclisation of *o*-nitrophenylguanidines (Scheme 19).

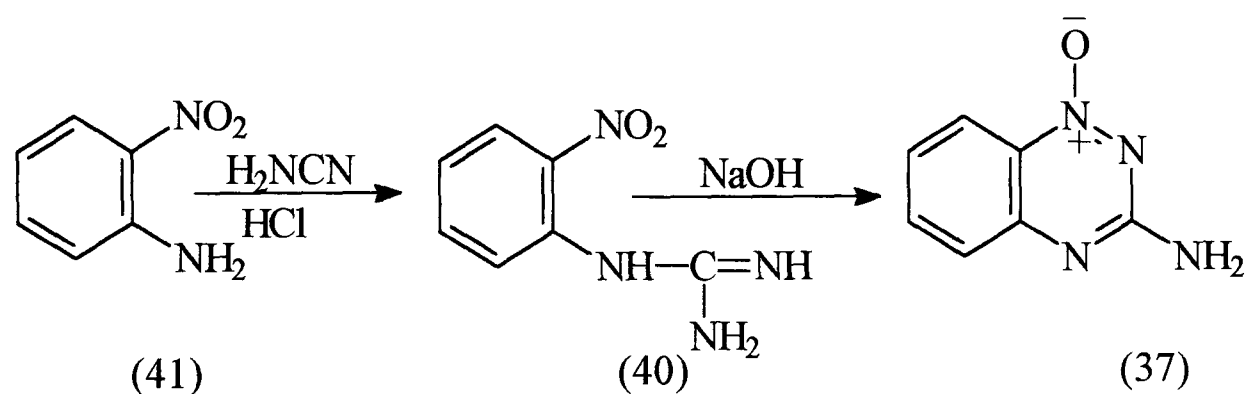


(40)

(37)

Scheme 19

Another method involves the condensation of nitroaniline (41) with cyanamide or mono sodium cyanamide under acidic condition yielding *o*-nitrophenylguanidine (40) which was cyclised directly in alkaline media (Scheme 20) to (37) with a yield of 60%.



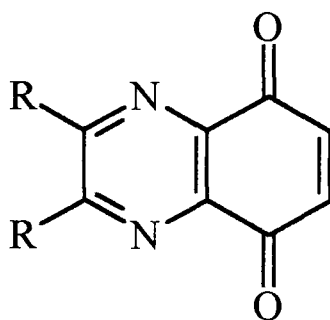
Scheme 20

Oxidation of 3-amino-1,2,4-benzotriazine-1-oxide (37) by hydrogen peroxide in acetic acid at 50 °C affords 3-amino-1,2,4-benzotriazine-1,4-dioxide (36).<sup>37</sup>



## 1.2 RESULTS AND DISCUSSION.

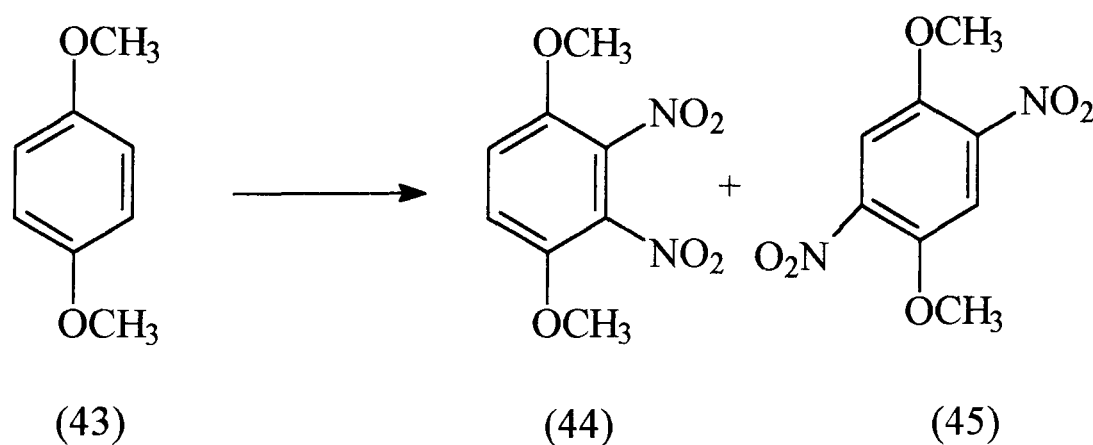
Tricyclic quinones were obtained from quinoxaline-5,8-dione (9) and 2,3-dimethoxy-5,8-dione (42) by the use of the Diels-Alder reaction.



(9) R = H

(42) R = OCH<sub>3</sub>

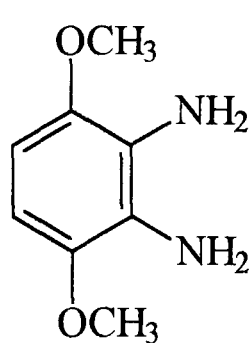
The synthesis of quinoxaline-5,8-dione was accomplished in three steps from 1,4-dimethoxybenzene (43). Nitration of (43) using concentrated nitric acid in glacial acetic acid gave a mixture of 1,4-dimethoxy-2,3-dinitrobenzene (44) and 1,4-dimethoxy-2,5-dinitrobenzene (45) (Scheme 21).<sup>38</sup>



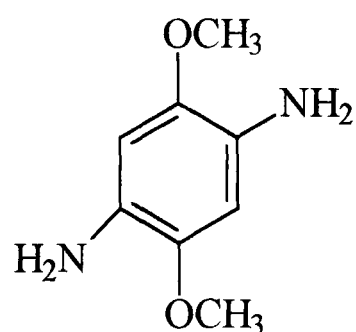
Scheme 21

At this stage it was not necessary to separate the two isomers as 80% of the mixture was 1,4-dimethoxy-2,3-dinitrobenzene (44) and the isomer, 1,4-dimethoxy-2,5-dinitrobenzene (45) cannot produce a quinoxaline in subsequent reactions.

The reduction of the mixture of dinitro isomers (44) and (45) by catalytic hydrogenation over palladium on charcoal at room temperature gave the mixture of 2,3-diamino-1,4-dimethoxybenzene (46) and 2,5-diamino-1,4-dimethoxybenzene (47).<sup>39</sup>

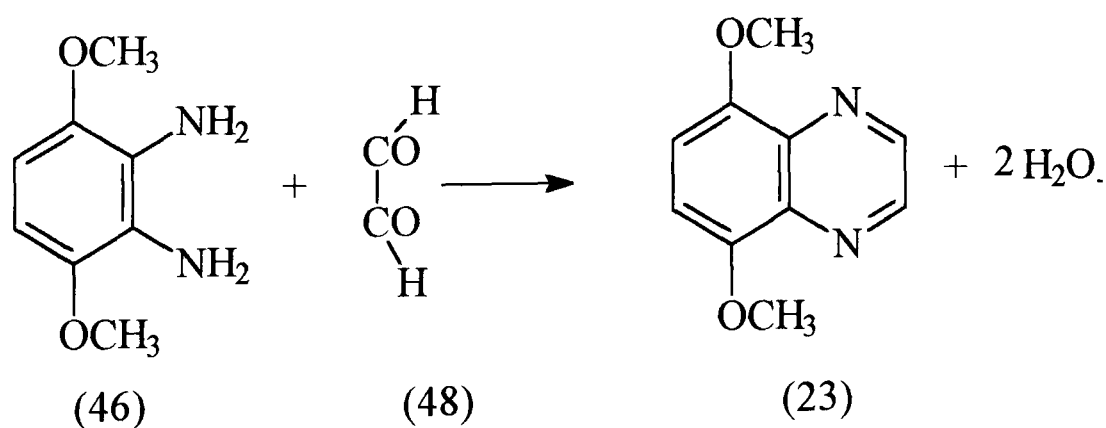


(46)



(47)

The diamines are not stable in air at room temperature so the mixture of diamines (46) and (47) was quickly treated with appropriate dicarbonyl compound when only the *o*-diamine (46) gave the quinoxaline.<sup>40</sup> 5,8-Dimethoxyquinoxaline (23) has been prepared by the condensation of 2,3-diamino-1,4-dimethoxybenzene with the glyoxal-sodium bisulfite adduct (48) (Scheme 22).

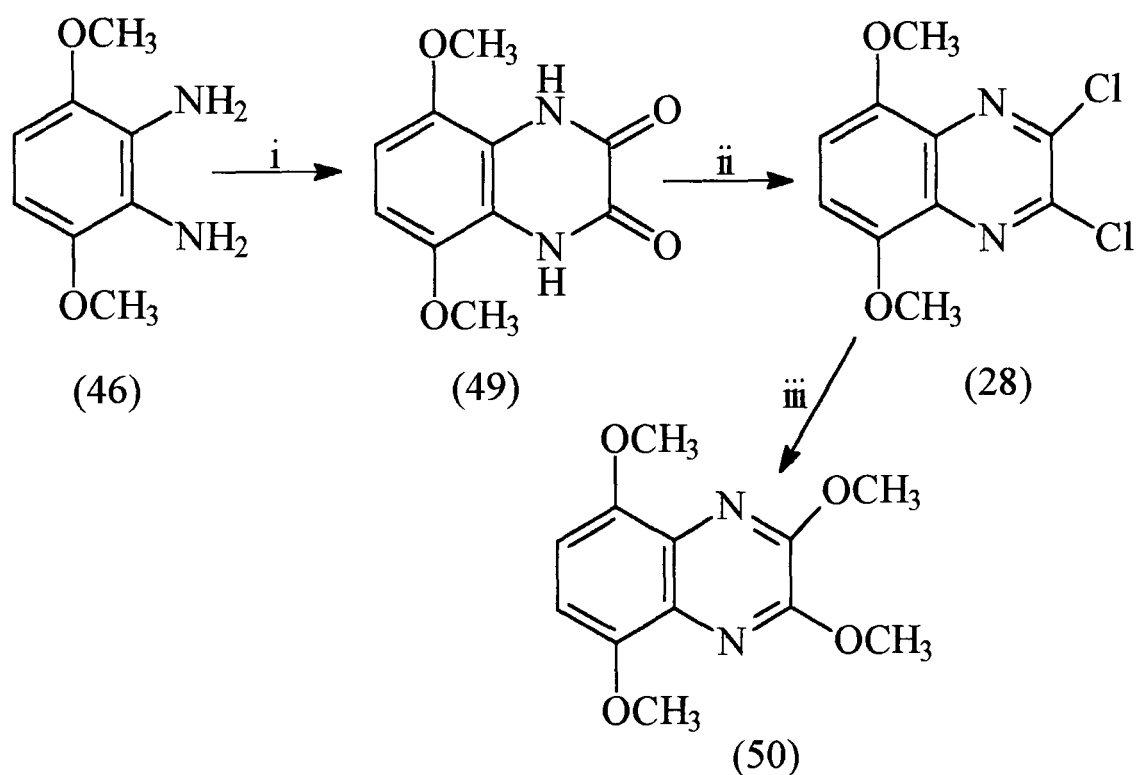


Scheme 22

The 5,8-dimethoxyquinoxaline (23) showed a singlet at 4.03 ppm due to two methoxy groups while the aromatic hydrogens gave rise to two singlets at 6.96 and 8.83 ppm respectively in the  $^1\text{H}$  NMR spectrum.

However 1,4-dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49) is conveniently prepared by boiling a mixture of the *o*-phenylene diamine (46) with oxalic acid dihydrate in 4M hydrochloric acid.<sup>41</sup> In the present work a mixture of the diamino compounds (46) and (47) was refluxed with an excess of diethyl oxalate using an air condenser so that the ethyl alcohol formed by intermolecular condensation was allowed to escape (Scheme 23).<sup>42</sup>

The 1,4-dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49) was purified by repeated dissolution in aqueous sodium hydroxide followed by precipitation by the addition of acetic acid.



Reagents: (i) diethyl oxalate, (ii) phosphoryl chloride,  
(iii) sodium methoxide in methanol

Scheme 23

The useful synthetic application of 1,4-dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49) is the conversion into 2,3-dichloro-5,8-dimethoxyquinoxaline (28) by the treatment with a mixture of phosphoryl chloride and *N, N*-dimethylaniline.<sup>43</sup> The reaction is normally carried out under reflux for periods between 1-4 h in 42% yield. The presence of the two chlorine atoms was confirmed by the appearance of three molecular ion peaks at 262, 260 and 258 daltons, due to the isotopes of chlorine.

Many nucleophilic displacement reactions have been carried out on 2,3-dichloro-5,8-dimethoxyquinoxaline (28). It was expected that (28) would be a useful precursor for the preparation of some 2,3-disubstituted-5,8-dimethoxyquinoxaline derivatives, e.g. 2,3,5,8-tetramethoxyquinoxaline (50), by nucleophilic substitution (Scheme 23).

Treatment of compound (28) with sodium methoxide at reflux for 3 h gave the tetramethoxy compound (50) in 80% yield. The methoxyl groups at the 2-, 3-, 5- and 8-positions produced two singlets at 4.00 and 4.21 ppm whereas the 6- and 7-aromatic protons gave rise to a singlet at 6.86 ppm in the <sup>1</sup>H NMR spectrum. The mass spectrum of (50) showed a molecular ion peak at 250 daltons.

These quinoxalines (23) and (50) were to be used as precursors of quinones. Heterocyclic quinones have been prepared by using the following general methods:-

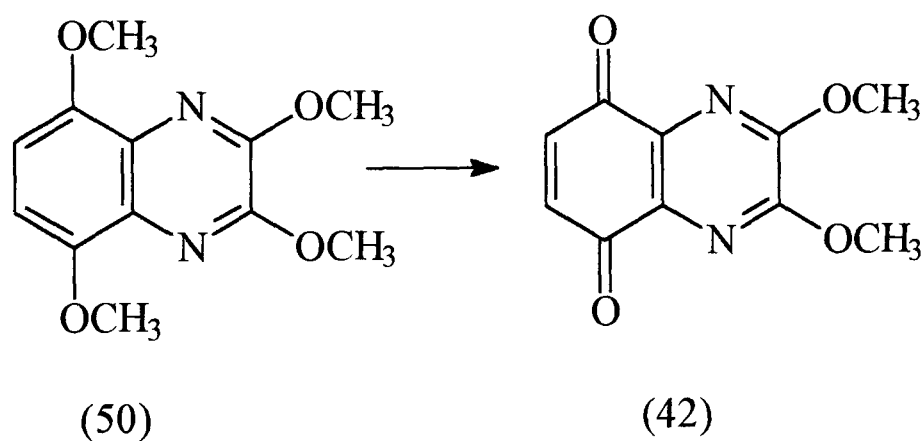
- a. The oxidation of heteroaromatic compounds.
- b. Cyclisation of acyclic intermediates or from addition reactions.

It is probably true to say that most preparations of heterocyclic quinones are through an oxidation process. Various classical strong oxidising agents such as Fremy's salt (potassium nitrosodisulphonate, O-N(SO<sub>3</sub>K)<sub>2</sub>) are particularly effective reagents for oxidation of aromatic rings containing only one hydroxy or amino group.<sup>44</sup>

Nitric acid<sup>17</sup> still finds wide applications and another useful oxidising agent is ceric ammonium nitrate (CAN).<sup>45</sup>

Generally, the formation of quinones from dimethoxyquinoxaline has been achieved by using relatively long routes.<sup>46</sup> In the present work, attempts were made to obtain the different heterocyclic quinones in a single step from the *p*-dimethoxyquinoxaline by using ceric ammonium nitrate (CAN) as an oxidising agent in aqueous acetonitrile medium.<sup>47</sup>

An attempt to prepare diazanaphthaquinones directly from their dimethoxy derivatives (23) and (50) by the action of CAN gave the required quinoxaline-5,8-dione (9) (Scheme 8) and 2,3-dimethoxyquinoxaline-5,8-dione (42) (Scheme 24).



Scheme 24

These compounds (9) and (42) showed strong absorptions at 1678 and 1670  $\text{cm}^{-1}$  respectively due to the carbonyl groups, and the methoxy groups of compound (42) at position 2 and 3 showed a singlet at 4.24 ppm in the  $^1\text{H}$  NMR, whereas the 6- and 7- aromatic protons gave rise to a downfield singlet at 6.99 ppm.

Quinoxaline-5,8-quinones containing electron donating groups, e.g.  $\text{OCH}_3$ ,  $\text{OC}_2\text{H}_5$ , at the 2- and 3- positions are stable at room temperature in the crystalline form and in solution form. The probable reason for the stability of these quinones is the resonance (51)  $\leftrightarrow$  (52) (Fig 1).

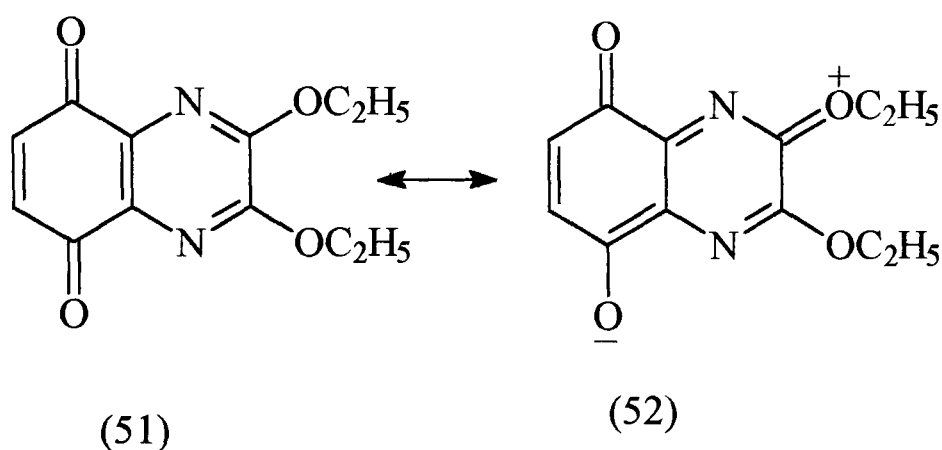
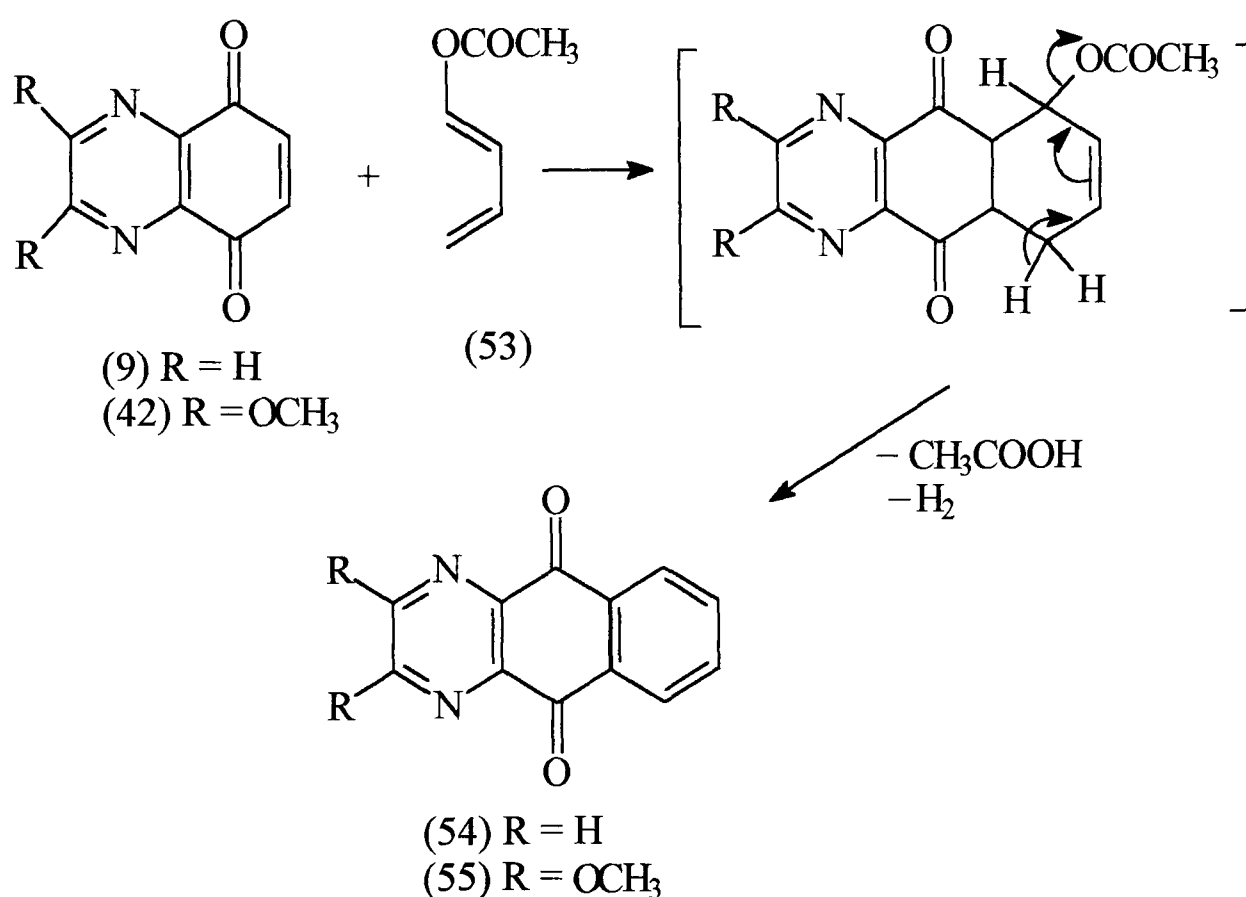


Fig 1: Resonance stabilization of 2,3-diethoxyquinoxaline-5,8-dione.

### 1.2.1 The Diels-Alder reaction.

In the present work we used the Diels-Alder reaction for the synthesis of linear tricyclic quinones. For example the reaction of substituted quinoxaline-5,8-diones (9) and (42) with 1-acetoxy-1,3-butadiene (53) produced the fully aromatized compounds, 1,4-diazaanthracene-9,10-dione (54) and 2,3-dimethoxy-1,4-diazaanthracene-9,10-dione (55) respectively, presumably by the elimination of acetic acid from the initial [4+2]cycloaddition product followed by the oxidative aromatization (Scheme 25).<sup>48</sup>



Scheme 25

The IR spectra of 1,4-diazaanthracene-9,10-dione (54) and 2,3-dimethoxy-1,4-diazaanthracene-9,10-dione (55) showed strong absorptions at 1678 and 1684  $\text{cm}^{-1}$ , respectively, due to the carbonyl groups. The  $^1\text{H}$  NMR spectra of these compounds also showed the symmetrical nature of the molecule produced by the elimination of acetic acid from the intermediate adducts. The  $^1\text{H}$  NMR spectrum of (54) showed two double doublets at 7.97 and 8.26 ppm ( $J = 6.1$  and  $3.6$  Hz) due to the 6-, 7- and 5- and 8-aromatic protons respectively, and a singlet at 9.12 ppm due to the 2- and 3-aromatic protons.

The 2,3-dimethoxy-1,4-diazaanthracene-9,10-dione (55) showed a singlet at 4.29 ppm caused by the 2- and 3-methoxy groups and the 6-, 7- and 5- and 8-aromatic protons gave rise two double doublets at 7.80 and 8.26 ppm ( $J = 5.9$  and  $3.2$  Hz) respectively. The mass spectra of (54) and (55) showed the expected molecular ion peaks in agreement with molecular formulae  $\text{C}_{12}\text{H}_6\text{N}_2\text{O}_2$  and  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$ , respectively.

### 1.2.2 Synthesis of fused-ring heterocyclic compounds

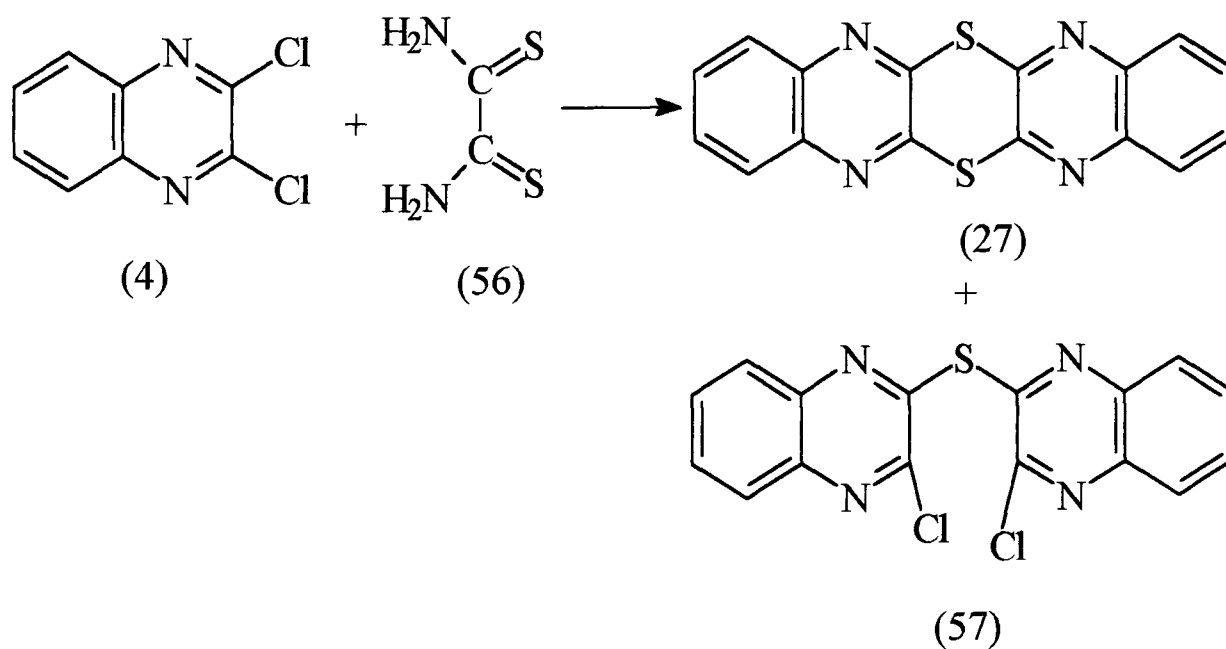
2,3- Dichloroquinoxaline (4) (obtained from 2,3-quinoxalindione by treatment with phosphoryl chloride) and thiourea were allowed to react in a mixture of dimethylformamide and triethylamine in a 1:1 molecular proportion to give the poly cyclic compound 1,4-dithia[2,3-*b*:5,6-*b'*]diquinoxaline (27) in 28% yield (Scheme 12).

It has been reported that this type of polycyclic compound is of current interest as a functional material for electronic, opto-electronic and photonic devices.<sup>49</sup> Matsuota<sup>49</sup> have reported the reaction between 2,3-dichloroquinoxaline and thiourea but gave the wrong structural formula for the product. However the error was corrected.<sup>50</sup>



In the present work, a successful attempt was made to synthesise (27) and the expected intermediate the bis(2-chloroquinoxaline-3-yl)sulfide (57) was isolated. However, the yield of 1,4-dithia[2,3-*b*:5,6-*b'*]diquinoxaline (27) obtained in this work (Scheme 12) was not significantly higher than that reported by Matsuota.<sup>50</sup> Therefore an attempt was made to improve the yield of (27) by the increasing the quantity of thiourea in the reaction.

It was found that the compound (27) can be prepared in excellent yield by using 1:1 molecular quantities of (4) and dithioamide (56), respectively in the mixture of *N,N*-dimethylformamide (DMF) and triethylamine. After completion of the reaction, the compound (27) was separated by filtration directly from the cold reaction due to its high insolubility in several organic solvents, whereas the second, and more soluble compound (57), was separated from the filtrate by the addition of water followed by solvent extraction (Scheme 26).



Scheme 26

The  $^1\text{H}$  NMR spectrum of (57) indicated its unsymmetrical structure by the appearance of two double doublets at 7.86 ppm and 8.05 ppm for aromatic protons due to the attachment of different atoms (sulfur and chlorine) to the heterocycle. The mass spectrum of (57) confirmed the presence of the two chlorine atoms by the presence of three molecular ion peaks which were in accordance with the structural formula.

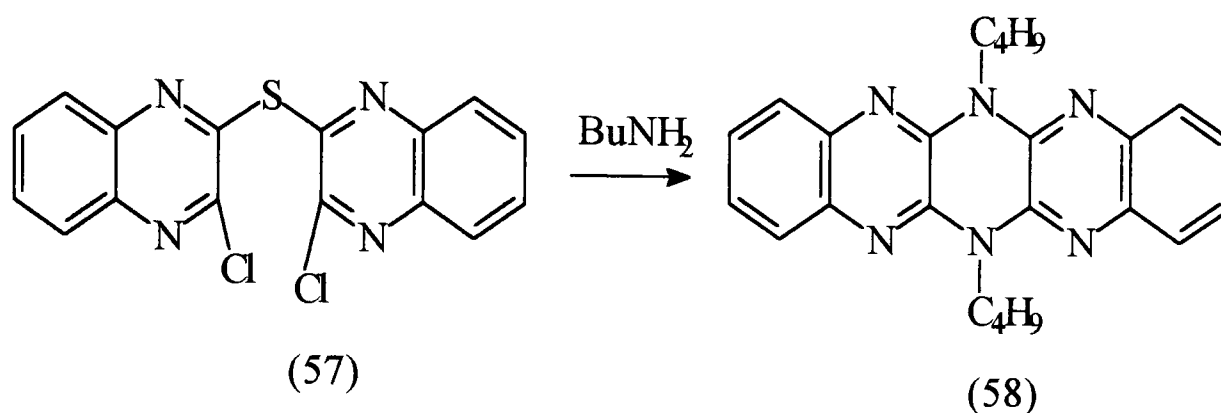
The reaction between 2,3-dichloroquinoxaline (4) and dithioamide (56) seems to be initiated by the nucleophilic attack of sulfur at the 2- and 3-position of the 2,3-dichloroquinoxaline as reported in the literature.<sup>51,52</sup>

### 1.2.3 Reaction of bis(2-chloroquinoxalin-3-yl)sulfide (57) with amines.

It has been reported that florubin (35) is produced when 2,3-dichloroquinoxaline (4) is treated with 2,3-diaminoquinoxaline (34).<sup>27</sup>

However, in the present work a new route for the synthesis of florubin (35) derivatives is reported and the compound (57) was utilised as an intermediate in reactions with several amines, e.g. n-butylamine, benzylamine, aniline, cyanamide, ethylenediamine. These amines make a nucleophilic attack on the carbon atom to which chlorine is attached. The 2- and 3-position of quinoxaline are easily attacked because the electron attracting properties of the ring nitrogen produce a positive charge on the adjacent carbon atom.

When bis(2-chloroquinoxalin-3-yl)sulfide (57) was treated with n-butylamine in anhydrous tetrahydrofuran (THF) at reflux for 6h, the product 6,13-dibutyl-5,6,7,12,13,14-hexaazapentacene (58) was obtained after work-up in 45 % yield (Scheme 27).

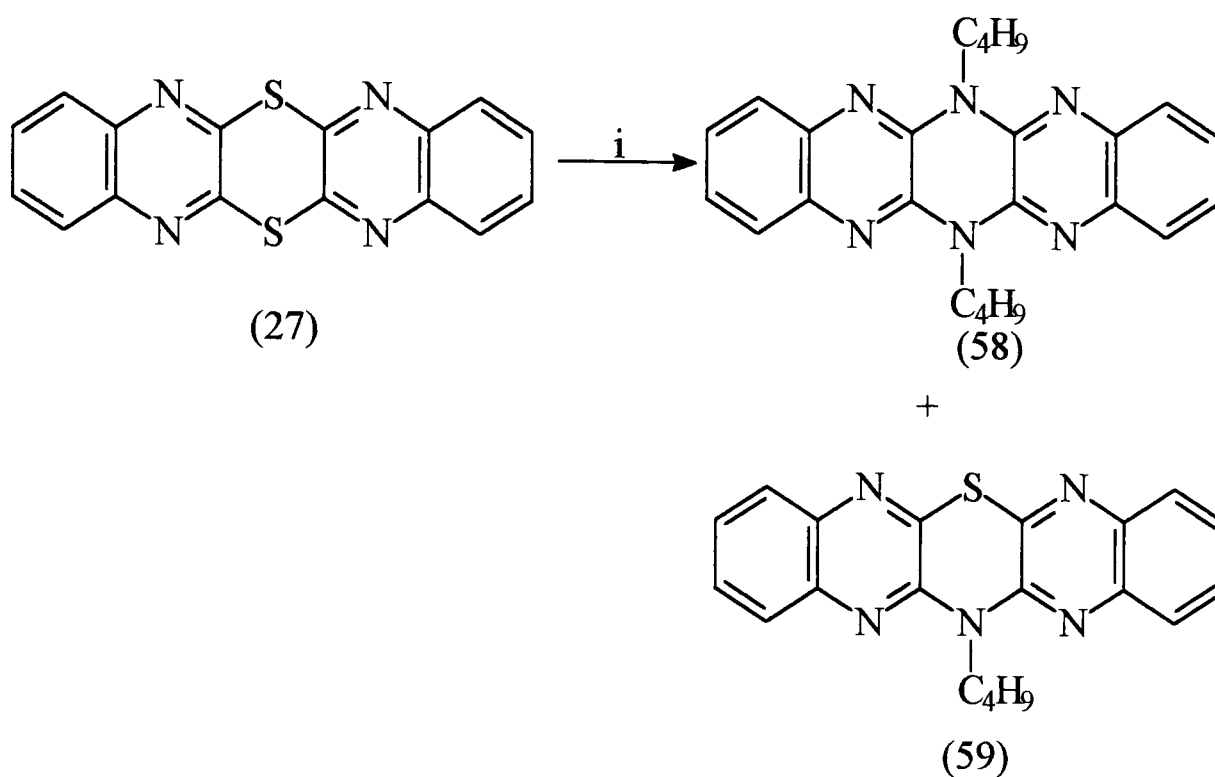


Scheme 27

A symmetrical structure for (58) is indicated by the <sup>1</sup>H NMR spectrum which shows a triplet at 1.03 ppm caused by the 2 x NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> groups, multiplets at 1.54 ppm and 1.78 ppm due to 4 x NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, triplet at 4.45 ppm due to 2 x NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and two double doublets at 7.32 ppm ( J = 6.2 and 2.5 Hz) and 7.57 ppm ( J = 6.2 and 2.5 Hz) corresponding to eight aromatic protons respectively. The mass spectrum of (58) showed a molecular ion peak at 398 daltons, which was in agreement with a molecular formula of C<sub>24</sub>H<sub>26</sub>N<sub>6</sub>.

A successful alternative route to (58) utilizes 1,4-dithia[2,3-*b*:5,6-*b'*]diquinoxaline (27). When (27) was treated with n-butylamine in anhydrous dimethyl sulphoxide (DMSO) the product (58) was obtained in a low yield, but an unexpected product (59) was also isolated by column chromatography.

The first eluted component (11% yield) was characterised as 6,13-dibutyl-5,6,7,12,13,14-hexaazapentacene (58). The second component was characterised as 13-butyl-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (59) (Scheme 28).



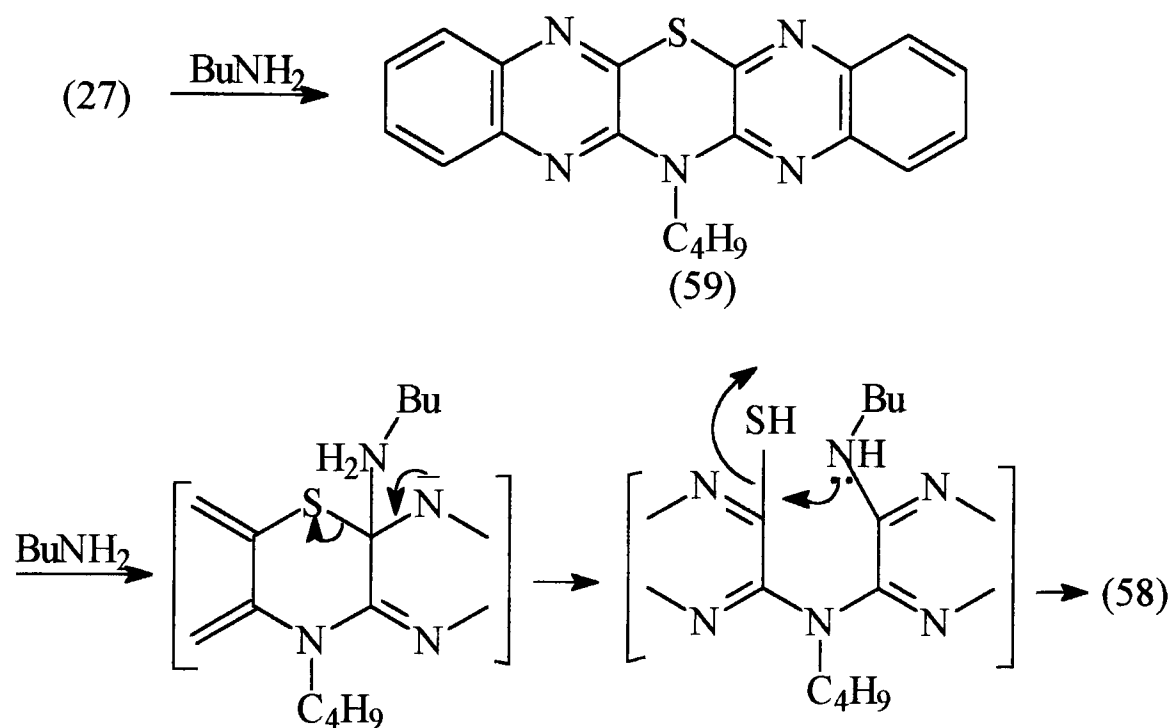
Reagents: (i) n-butylamine, DMSO

Scheme 28

The unsymmetrical structure of (59) was clear from its <sup>1</sup>H NMR spectrum which showed a triplet at 1.05 ppm caused by NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> group, two multiplets at 1.53 and 1.87 ppm respectively due to NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> protons, triplet at 4.54 ppm caused by NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> and two multiplets at 7.52 and 7.71 ppm for aromatic protons due to the attachment of different atoms (sulfur and nitrogen).

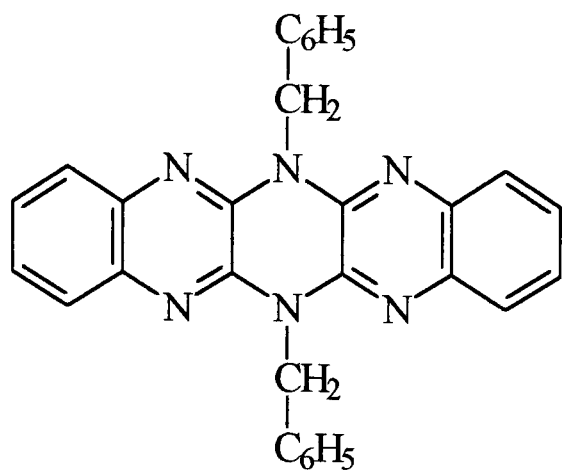
The mass spectrum and the elemental analysis of 13-butyl-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (59) were in agreement with the molecular formula C<sub>20</sub>H<sub>17</sub>N<sub>5</sub>S.

The conversion of (27) to (58) was thought to go through the intermediate (59) which undergoes intermolecular attack by butylamine at the very electron deficient bridge-head atom followed by intramolecular cyclisation with elimination of hydrogen sulfide (Scheme 29).

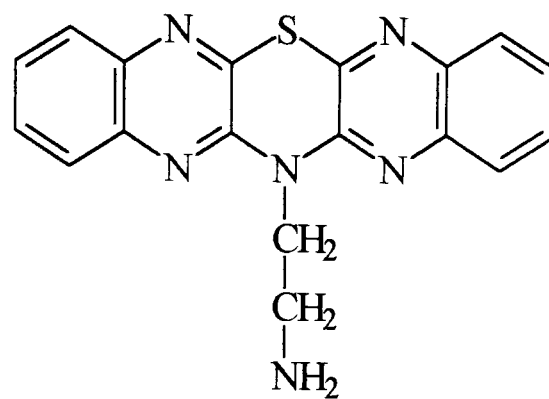


Scheme 29

Several nucleophilic substitution reactions of (57) are also reported in this work. When bis(2-chloroquinoxalin-3-yl)sulfide (57) was separately treated with benzylamine, ethylene diamine and cyanamide in anhydrous THF at reflux for 6h, the products obtained were 6,13-dibenzyl-5,6,7,12,13,14-hexaazapentacene (60), 13-(2-aminoethyl)-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (61) and 6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (62) respectively.



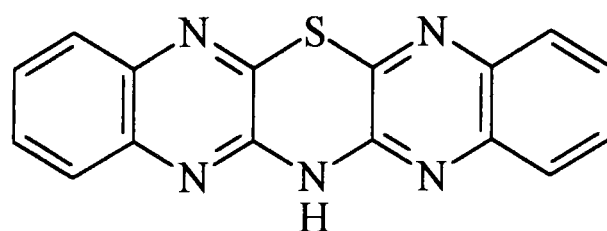
(60)



(61)

These compounds were characterised on the basis of their  $^1\text{H}$  NMR spectra, mass spectra and elemental analyses. However, when aniline was used no reaction occurred. The failure of the reaction was probably due to lower availability of the unshared electron pair on the nitrogen atom, which in this case is delocalised on to the  $\pi$  orbital of the nucleus producing a less nucleophilic amine.

When compound (57) was treated with cyanamide, 6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (62) was unexpectedly obtained in 60% yield. The IR spectrum showed an N-H stretching absorption at  $3446\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR spectrum of (62) shows a multiplet at 7.51 ppm for aromatic protons and an exchangeable singlet at 11.90 ppm due to the N-H group. The above spectral data and the presence of the principal molecular ion peak at 303 daltons in the EI mass spectrum confirmed the molecular formula of  $\text{C}_{16}\text{H}_9\text{N}_5\text{S}$ . The formation of (62) presumably occurred by hydrolysis of the first formed N-cyano compound in the work up process followed by decarboxylation to give (62).



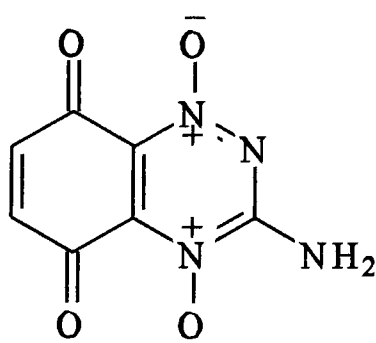
(62)

These compounds (58), (59), (60), (61) and (62) are very sparingly soluble in water, have high melting points and display green fluorescence in ultraviolet light.

#### 1.2.4 3-Amino-5,6-dimethoxy-1,2,4-benzotriazine.

A great number of 1,2,4-benzotriazine derivatives have been investigated for their biological activity, and the increase of interest in this class of compound is related to their noticeable antitumour activity.<sup>30</sup>

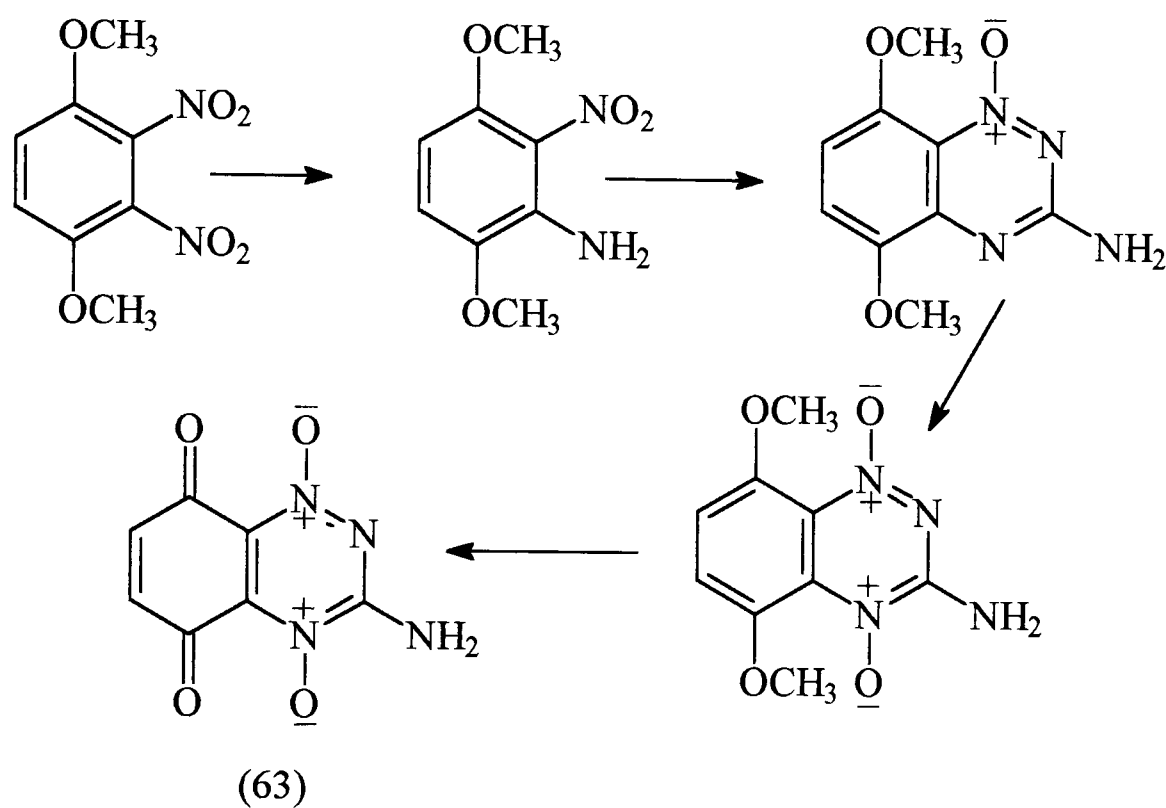
3-Amino-1,2,4-benzotriazine-1,4-dioxide (also known as SR4233 and tirapazamine) (37) shows significant selective toxicity towards hypoxic cells in solid tumours.<sup>32</sup> Thus, our aim was to prepare a 5,8-disubstituted 1,2,4-benzotriazine nucleus in order to attempt the preparation of 5,8-dioxo-1,2,4-benzotriazine-1,4-dioxide (63).



(63)

This compound was of interest because the quinone may not have anticancer activity but would be expected to be reduced in hypoxic cells to give a benzenoid ring and the resultant compound would then be expected to be cytotoxic at the tumour. In this way, it was hoped to obtain a cytotoxic effect more specifically targeted to hypoxic cells.

It was hoped to obtain the benzotriazine quinone (63) from the corresponding 5,8-dimethoxy-1,2,4-benzotriazine-1,4-dioxide (Scheme 30).



Scheme 30

The synthesis of (63) required a series of reactions starting with the nitration of 1,4-dimethoxybenzene (43). As described earlier in this thesis, nitration of 1,4-dimethoxybenzene gives the isomeric, 2,3- and 2,5-dinitro-1,4-dimethoxybenzenes. However, in the present work, separation of these two isomers was achieved using column chromatography.

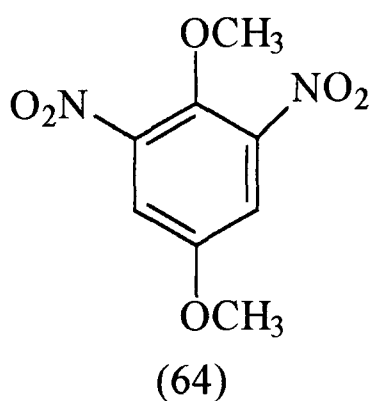


The first isomer eluted was 2,5-dinitro-1,4-dimethoxy isomer (45) possibly due to the 2,3-dinitro isomer (44) being more polar than 2,5-dinitro isomer. Previous work has concluded from results obtained by gas chromatography, that the 2,3-dinitro isomer (mp 180 °C) and 2,5-dinitro isomer (mp 202 °C) are present in the proportion of 88% and 12% respectively.<sup>53</sup>

These isomers were identified in the work reported here by mp. and yield. The 3- and 6- hydrogen atoms of 2,5-dinitro-1,4-dimethoxybenzene (45) showed a singlet at 7.91 ppm in the <sup>1</sup>H NMR spectrum while the 5- and 6-hydrogen atoms of 2,3-dinitro-1,4-dimethoxybenzene (44) displayed a singlet at 7.68 ppm due to its symmetrical structure.

The 2,3-dinitro isomer had mp 186 °C and was present as 80% of the mixture, while the 2,5-dinitro isomer had mp 205 °C and was the remaining 20%.

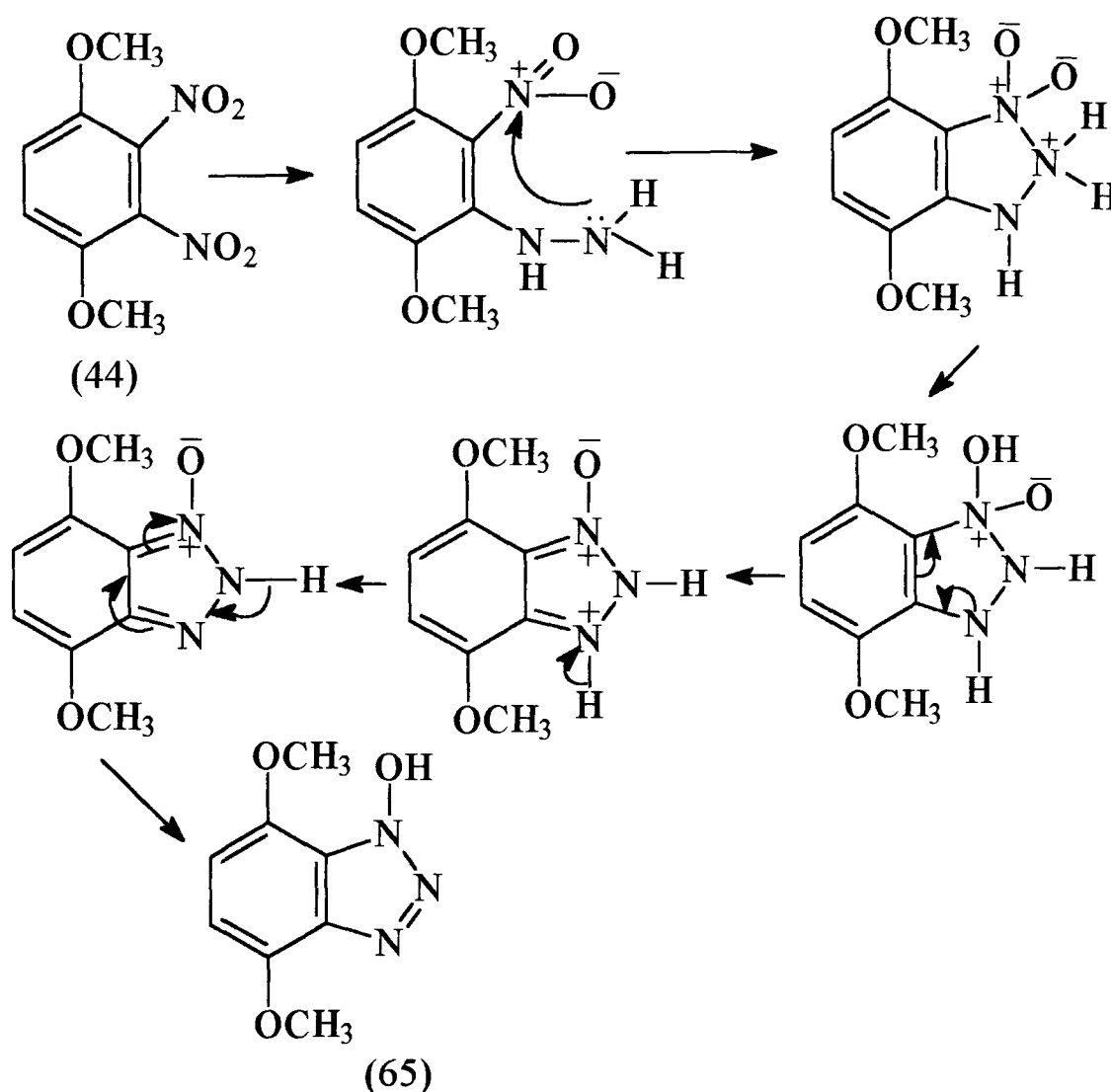
The third isomer, i.e. 1,4-dimethoxy-2,6-dinitrobenzene (64) (mp 109-111 °C), was reported by Burger and Fitchett<sup>54</sup> and had a different melting point from the 2,3- and 2,5-dinitro isomers.



It is easier to reduce both nitro groups of 2,3-dinitro and 2,5-dinitro isomers than to reduce only one nitro group. Several selective reduction methods have been reported and three were tried in this work, e.g. hydrazine hydrate<sup>55</sup>, hydrazine hydrate in the presence of Raney nickel<sup>56</sup>, and sodium dithionite.<sup>57</sup>

The first method tried was the reduction of (44) with hydrazine hydrate in the presence of Raney nickel but only starting material was obtained. The other potentially selective method tried for the reduction of one nitro group in a dinitrodimethoxybenzene (44) was treatment with hydrazine hydrate alone. The unexpected product 1-hydroxy-4,7-dimethoxy-1,2,3-benzotriazole (65) was obtained in excellent yield.

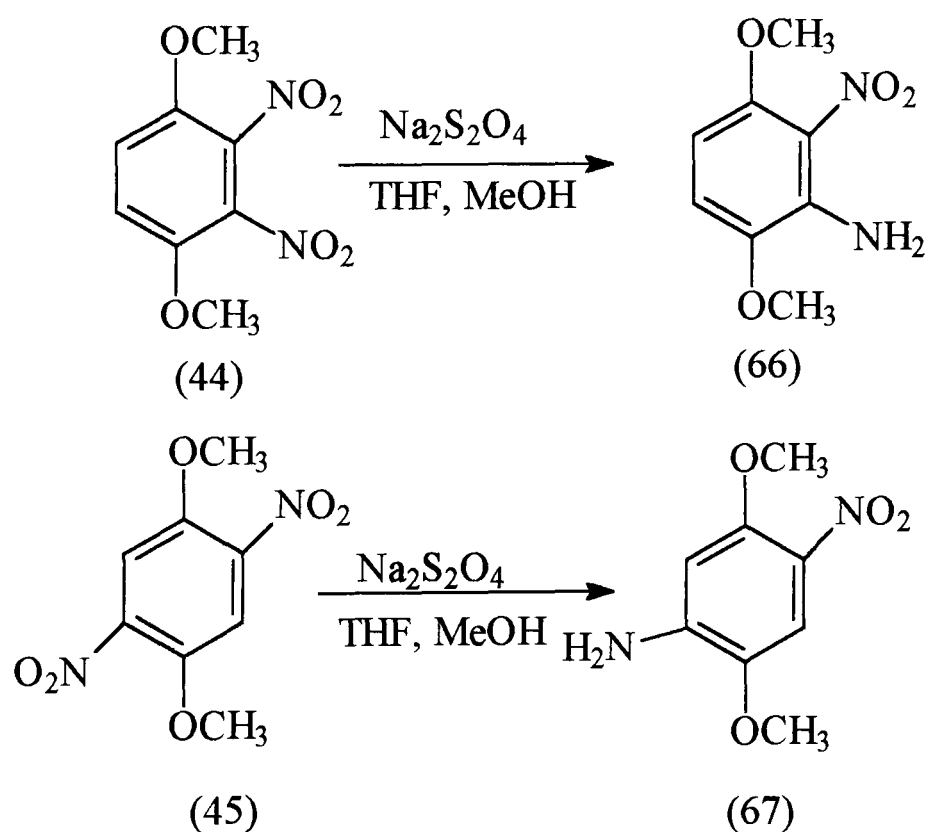
The suggested mechanism for the formation of benzotriazole is that a nitro group of dinitro compound (44) is readily displaced by hydrazine to give the hydrazino derivative. This then undergoes intramolecular cyclisation by nucleophilic attack of the amino group on the adjacent nitrogen followed by elimination of a hydroxyl group to give compound (65) (Scheme 31).



Scheme 31

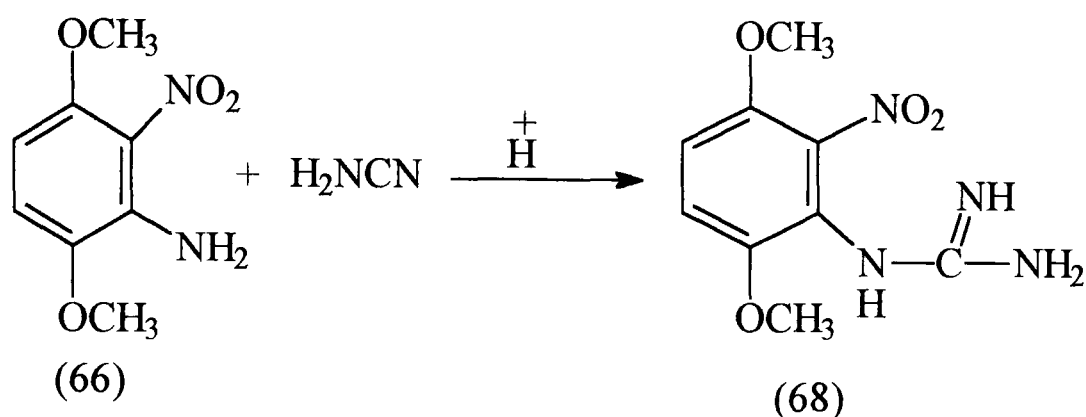
The product was characterised by spectral data and elemental analysis. The  $^1\text{H}$  NMR spectrum showed a singlet at 3.92 ppm for the six protons of the 4- and 7-methoxy groups, a doublet at 6.65 ppm ( $J = 8.0$  Hz) caused by the 6-proton, a doublet at 6.83 ppm ( $J = 8.0$  Hz) due to the 5-proton. In addition the spectrum contained an exchangeable singlet at 13.5 ppm due to OH group. The mass spectrum of (65) showed a molecular ion peak at 195 daltons which was in the agreement with the molecular formula,  $\text{C}_8\text{H}_9\text{N}_3\text{O}_3$ .

Finally, successful partial reduction of 2,3-dinitro-1,4-dimethoxybenzene (44) and 2,5-dinitro-1,4-dimethoxybenzene (45) was carried out by the use of sodium dithionite under alkaline conditions to give 2,5-dimethoxy-6-nitroaniline (66) and 2,5-dimethoxy-4-nitroaniline (67), respectively (Scheme 32). The  $\text{NH}_2$  groups of (66) and (67) gave rise to broad singlets in  $^1\text{H}$  NMR spectra at 3.85 ppm and 4.58 ppm respectively, which disappeared on addition of  $\text{D}_2\text{O}$ .



Scheme 32

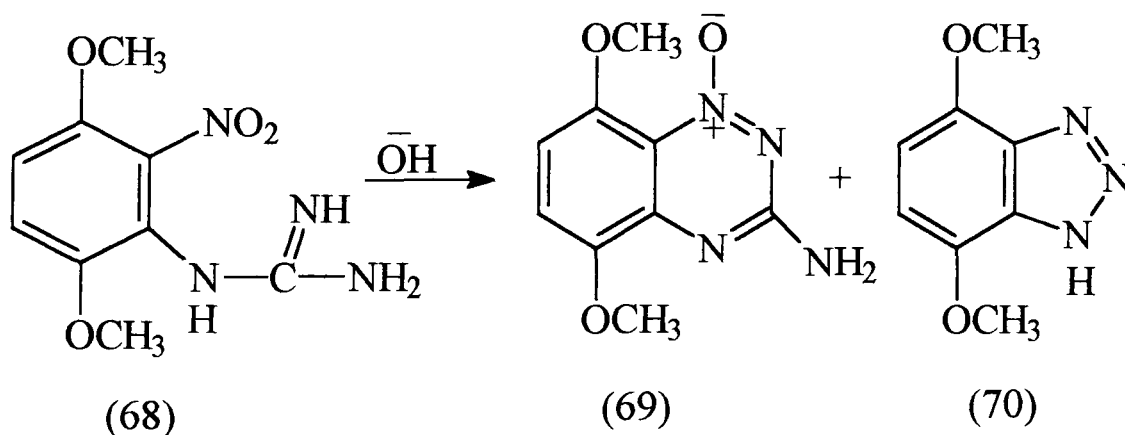
The compound (66) was used as an intermediate for further reactions. Condensation of 2,5-dimethoxy-6-nitroaniline (66) with cyanamide under acidic condition according to the procedure described by Mason and Tennant<sup>58</sup> gave N-(2,5-dimethoxy-6-nitrophenyl)guanidine (68) in 67% yield (Scheme 33).



Scheme 33

The IR spectrum of the product showed NH<sub>2</sub> stretching vibrations at 3400 and 3186 cm<sup>-1</sup>. The molecular ion peak in the mass spectrum of (68) was at 240 daltons which was in agreement with the molecular formula C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub>.

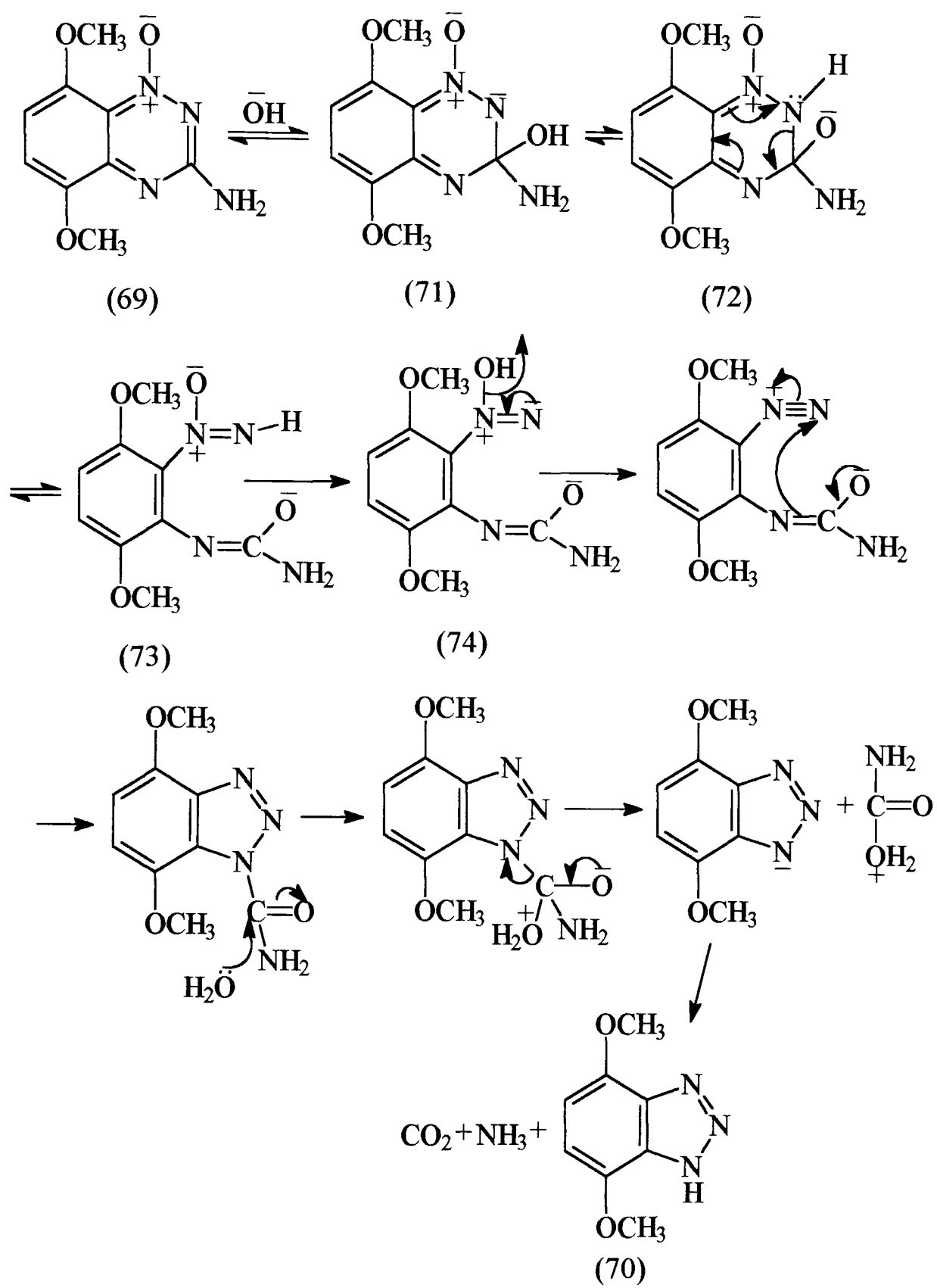
However, when compound (68) was treated with aqueous base it gave 3-amino-5,6-dimethoxy-1,2,4-benzotriazine-1-oxide (69), and the unexpected product 4,7-dimethoxy-1,2,3-benzotriazole (70) (Scheme 34).



Scheme 34

The  $^1\text{H}$  NMR spectrum of (69) showed two singlets caused by the two methoxy groups at 3.83 and 3.81 ppm, a doublet at 6.66 ppm ( $J = 9.0$  Hz) due to an aromatic proton, a doublet at 7.13 ( $J = 8.0$  Hz) caused by an aromatic proton and an exchangeable singlet due to  $\text{NH}_2$  group at 7.11 ppm. The IR spectrum of (69) showed the presence of an  $\text{NH}_2$  stretching vibrations at 3406 and 3286  $\text{cm}^{-1}$ . The molecular ion peak in the mass spectrum of (69) was at 222 daltons which was in agreement with the molecular formula  $\text{C}_9\text{H}_{10}\text{N}_4\text{O}_3$ .

The compound (70) was thought to be formed through a molecular rearrangement caused by the action of excess hot alkali. The rearrangement can be explained as an attack by the hydroxy ion at the 3-position of the triazine ring to form an intermediate (71). The key steps in the proposed mechanism<sup>59</sup> are the formation of azoxy intermediate (73) and its rearrangement to the diazonium hydroxide (74), which then gives rise to the triazole ring (Scheme 35).

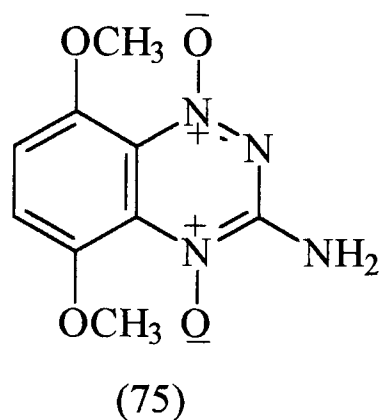


Scheme 35

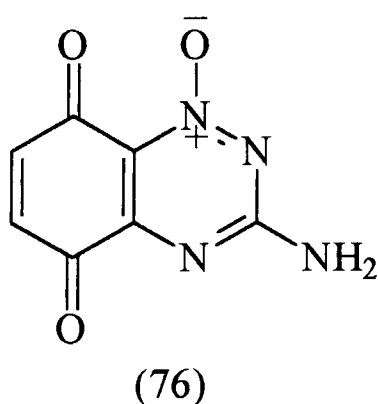
In the present work it was shown that (70) can be formed in high yield from (69) by treatment with strong concentrated solution of sodium ethoxide in ethanol.

The  $^1\text{H}$  NMR spectrum of 4,7-dimethoxy-1,2,3-benzotriazole (70) displays its symmetrical structure shows a singlet due to the 4- and 7-methoxy groups at 3.94 ppm, an exchangeable singlet at 6.21 ppm caused by NH group and a singlet due to 5- and 6-proton at 6.72 ppm.

An attempt was made to oxidise (69) to the corresponding 5,8-dimethoxy-1,2,4-benzotriazine-1,4-dioxide (75) with hydrogen peroxide. However the failure of the reaction was probably due to the steric hindrance caused by the 5-methoxy group.



Compound (69) was treated with CAN in an attempt to obtain the corresponding quinone (76). A colour change from pale yellow to dark brown was observed during the reaction and the IR spectrum of the crude product showed a peak at  $1680\text{ cm}^{-1}$  which is probably due to the quinone carbonyl group. However, the product decomposed at room temperature during the attempted work-up procedure.



# EXPERIMENTAL

## SYNTHESIS

The following abbreviations have been used in the experimental section:

Me (methyl), Et (ethyl), Ph (phenyl), Ar (aromatic), conc. (concentrated), EtOH (ethanol), AcOH (glacial acetic acid), Pd/C (palladium (10%) on charcoal), DCM (dichloromethane), petroleum spirit (petroleum ether, bp. 40-60 °C), DMF (dimethyl formamide), DMSO (dimethyl sulfoxide), DMSO-d<sub>6</sub> (hexadeuterodimethyl sulfoxide), THF (tetrahydrofuran), MeCN (acetonitrile), MeOH (methanol), mp (melting point), bp (boiling point), h (hour), min (minutes) and ether (diethyl ether).

Unless otherwise stated, solutions in organic solvents were dried over anhydrous sodium sulfate.

All melting points were determined using an Electrothermal Digital apparatus and are uncorrected.

Infrared spectra (IR) were recorded using a Perkin Elmer 1600 FTIR and 1420 Ratio Recording IR spectrophotometer in the range of 600-4000 cm<sup>-1</sup> as KBr disc unless otherwise stated.

Proton nuclear magnetic resonance (<sup>1</sup>HNMR) spectroscopy was carried out using a Varian CFT-20 (90 MHz), a Jeol FX 200 (200 MHz) and a Bruker AM 360 (360 MHz) instruments and spectra were recorded for solutions in deuterated solvent relative to tetramethylsilane (internal standard). Resonances are reported in the form: (instrument frequency, solvent); δ = shift in ppm from tetramethylsilane at 0 ppm and the multiplicity of signals as s, singlet; d, doublet; dd, double doublet; q, quartet; t, triplet; m, multiplet; br, broad.



Low resolution electron impact mass spectra were recorded on an AEI MS902 spectrometer. Low resolution fast atom bombardment (FAB) spectra and both EI and FAB accurate mass determinations were provided by the EPSRC Mass Spectrometry Services Centre, Department of Chemistry, University of Wales, Swansea.

Microanalysis were performed by MEDAC Ltd and Natural Resource Management Ltd, on a Carlo Erba 1106 elemental analyser (dynamic combustion system) or on a Control Equipment Corporation Model 240 XA (static combustion system).

Purification by column chromatography were performed on Kieselgel 60 (230-400 mesh ASTM) using redistilled solvents. Columns were generally packed dry and developed under light positive pressure. Thin layer chromatography (TLC) was carried out on commercial silica plates [ Camlab, 0.25 mm with fluorescence indicator UV<sub>254</sub>].

### **2,3- and 2,5-Dinitro-1,4-dimethoxybenzene (44) and (45).**

Nitric acid (18 cm<sup>3</sup>, sp. gravity 1.42) was added to a solution of 1,4-dimethoxybenzene (43) (13.8 g, 100 mmol) in glacial acetic acid (35 cm<sup>3</sup>). After the reaction subsided, more conc. nitric acid (18 cm<sup>3</sup>) was added. The reaction mixture was heated for 5 minutes at 80-90 °C, and then diluted with water (300 cm<sup>3</sup>). A mixture of 2,3- and 2,5-dinitro-1,4-dimethoxybenzene was filtered off and crystallised from glacial acetic acid (18 g), mp 160-164 °C (lit.,<sup>38</sup> mp 155-160 °C).

### **2,3- and 2,5-Diamino-1,4-dimethoxybenzene (46) and (47).**

A mixture of 2,3- and 2,5-dinitro-1,4-dimethoxybenzene (5 g, 25.2 mmol) in absolute ethanol (75 cm<sup>3</sup>) was hydrogenated over palladium charcoal (10%, 300 mg) for 2 days at 50 lb/in<sup>2</sup> in a Parr hydrogenator. The catalyst was filtered off and the solution containing 2,3- and 2,5-diamino-1,4-dimethoxybenzene was immediately used in further reactions.

### **5,8-Dimethoxyquinoxaline (23).**

The solution containing the mixture of 2,3- and 2,5-diamino-1,4-dimethoxybenzene was evaporated *in vacuo* to obtain a deep violet residue which was immediately added to a warm saturated solution of glyoxal sodium bisulfite adduct (6 g) in water (50 cm<sup>3</sup>). The reaction mixture was stirred and heated at 70 °C for 45 min., and then filtered to remove the black residue. The filtrate was basified with sodium hydroxide pellets and filtered again to obtain a blood-red solution, which was extracted with dichloromethane (3 x 100 cm<sup>3</sup>). The extract was then washed with water, dried over anhydrous sodium sulfate and percolated through a column of neutral alumina. The bright yellow eluate was concentrated to afford greenish-yellow crystals of 5,8-dimethoxyquinoxaline (3 g), mp 149-150 °C (lit.,<sup>53</sup> mp 147-148 °C); IR(KBr)  $\nu_{\max}$ /cm<sup>-1</sup> 2234, 1608 (C=N), 1484, 1350,

1268, 1104, 820, 696, 546; <sup>1</sup>HNMR (90 MHz, CDCl<sub>3</sub>) δ 4.03 (6H, s, 5- and 8-OCH<sub>3</sub>), 6.96 (2H, s, 6- and 7-H), 8.83 (2H, s, 2- and 3-H); MS, m/z(r.i.) 192 (27%), 190 (M<sup>+</sup>, 95), 175 (M - CH<sub>3</sub>, 100), 161 (M - 2 x CH<sub>3</sub>, 81), 147 (35), 82 (37).

#### **1,4-Dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49).**

Diethyl oxalate (40 g) in glacial acetic acid (25 cm<sup>3</sup>) was added to a solution of 2,3- and 2,5-diamino-1,4-dimethoxybenzene and refluxed with stirring for 3 h. After cooling the reaction mixture, the resultant crystals were separated by filtration, washed thoroughly with water and finally with acetone, to give light-green, 1,4-dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49). The compound was purified by repeated dissolution in alkali (aqueous NaOH; 2M) followed by precipitation with acetic acid, to give the quinoxaline (49) (3.0 g), mp 322-325 °C (lit.,<sup>60</sup> mp 325-329 °C); IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3052, 1712 (CO), 1530, 1338, 1240, 1118, 852; <sup>1</sup>HNMR (90 MHz, DMSO-d<sub>6</sub>) δ 3.80 (6H, s, 5- and 8-OCH<sub>3</sub>), 6.70 (2H, s, 6- and 7-H), 11.01 (2H, s, 1- and 4-H); MS, m/z(r.i.) 222 (M<sup>+</sup>, 71%), 207 (M - CH<sub>3</sub>, 32), 179 (43), 83 (100).

#### **2,3-Dichloro-5,8-dimethoxyquinoxaline (28).**

1,4-Dihydro-2,3-dioxo-5,8-dimethoxyquinoxaline (49) (1g, 4.5 mmol) was heated under reflux with phosphoryl chloride (10 cm<sup>3</sup>) and *N,N*-dimethylaniline (5 cm<sup>3</sup>) for 4 h. The cool reaction mixture was slowly poured into stirred ice-water (200 cm<sup>3</sup>) and the product was extracted with dichloromethane (3 x 100 cm<sup>3</sup>). The extract was washed with water, dried over anhydrous sodium sulfate, evaporated *in vacuo*, and the greenish-yellow residue was percolated through a neutral alumina column to yield yellow crystals of 2,3-dichloro-5,8-dimethoxyquinoxaline (28), (0.54 g, 42 %), mp 215-216 °C (lit.,<sup>60</sup> mp 215 °C); IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 1598, 1272, 1180, 1104, 824; <sup>1</sup>HNMR (90 MHz, CDCl<sub>3</sub>) δ 7.03 (2H, s, 6- and 7-H), 4.01 (6H, s, 5- and 8-OCH<sub>3</sub>); MS, m/z(r.i.) 262 (5%), 260 (M<sup>+</sup> for <sup>37</sup>Cl + <sup>35</sup>Cl, 50), 258 (M<sup>+</sup> for <sup>35</sup>Cl, 95), 229 (M - 2OCH<sub>3</sub>, 96), 215 (15), 164 (100).

### **2,3,5,8-Tetramethoxyquinoxaline (50).**

A solution of 2,3-dichloro-5,8-dimethoxyquinoxaline (28) (1 g, 3.8 mmol) in methanol (10 cm<sup>3</sup>) was added to a freshly prepared solution of sodium methoxide [obtained by the addition of sodium hydride (0.92 g) to methanol (40 cm<sup>3</sup>)]. The reaction mixture was refluxed for 3 h., and then poured into ice-water (50 cm<sup>3</sup>). The resulting precipitate was filtered off, washed with water, and crystallised from methanol to give 2,3,5,8-tetramethoxyquinoxaline (50) (0.92g, 80%), mp 174-175°C (lit.,<sup>26</sup> mp 174 °C); IR(KBr)  $\nu_{\max}/\text{cm}^{-1}$  2924, 1616, 1466, 1414, 1344, 1236, 1114, 1020, 995, 792; <sup>1</sup>HNMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  4.00 (6H, s, 5- and 8-OCH<sub>3</sub>), 4.21 (6H, s, 2- and 3-OCH<sub>3</sub>), 6.86 (2H, s, 6- and 7-H); MS, m/z(r.i.) 251(14%), 250 (M<sup>+</sup>, 100), 235 (M - CH<sub>3</sub>, 83), 220 (M-CH<sub>3</sub>, 76), 192 (21).

### **GENERAL METHOD OF OXIDATION OF 5,8-DIMETHOXY QUINOXALINES.**

A stirred solution/suspension of appropriate quinoxaline (1 mmol) in a mixture of acetonitrile and water (20 cm<sup>3</sup>, 4:1 v/v) was treated with ceric ammonium nitrate (CAN) (4 mmol) in an ice-bath. The stirring was continued for 3 h., and the mixture was diluted with water (50 cm<sup>3</sup>). The quinone was extracted with dichloromethane (3 x 10 cm<sup>3</sup>) and the extract washed repeatedly with water. The combined extract was dried (anhydrous sodium sulfate), the solid removed, the solvent evaporated *in vacuo*, and the residue crystallised from an appropriate solvent.

### **Quinoxaline-5,8-dione (9).**

5,8-Dimethoxyquinoxaline (23) (0.190 g) yielded the quinoxaline-5,8-dione (9) which was crystallised from ethyl acetate (0.155 g, 97%), mp 172-174 °C (lit.,<sup>61</sup> mp 172 °C); IR(KBr)  $\nu_{\max}/\text{cm}^{-1}$  1678 (CO), 1606, 1482, 1268, 1168, 1102, 962; <sup>1</sup>HNMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  7.27 (2H, s, 2- and 3-H), 9.08 (2H, s, 6- and 7-H); MS, m/z(r.i.) 162 (M<sup>+</sup>, 97%), 160 (M - 2H, 97), 147 (M- CH<sub>3</sub>, 54), 132 (M- 2CH<sub>3</sub>, 42), 130 (100), 104 (26), 83 (31).

### **2,3-Dimethoxyquinoxaline-5,8-dione (42).**

2,3,5,8-Tetramethoxyquinoxaline (50) (0.25 g) gave the 2,3-dimethoxyquinoxaline-5,8-dione which was crystallised from a mixture of ethyl acetate and dichloromethane (9:1) (0.207 g, 94%), mp 229-230 °C (lit.,<sup>61</sup> mp 224 °C); IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 2878, 1670 (CO), 1595, 1484, 1020, 854, 760, 694, 546; <sup>1</sup>HNMR (90 MHz, CDCl<sub>3</sub>)  $\delta$  4.24 (6H, s, 2- and 3-OCH<sub>3</sub>), 6.99 (2H, s, 6- and 7-H); MS, m/z(r.i.) 222 (35%), 221 (16), 220 (M<sup>+</sup>, 100), 206 (40), 189 (M - OCH<sub>3</sub>, 29), 175 (66), 162 (25), 82 (26).

## **REACTION OF DIAZANAPHTHOQUINONES AND 1-ACETOXY-1,3-BUTADIENE.**

### **General Method.**

A mixture of diazanaphthoquinone (1 mmol), 1-acetoxy-1,3-butadiene (1.2 mmol) and anhydrous benzene (20 cm<sup>3</sup>) was refluxed for 2 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in ethanol and refluxed for 2-4 h. On completion of the reaction (monitored by T.L.C.), the solvent was evaporated *in vacuo* and the residue crystallised from ethanol.

### **1,4-Diazaanthracene-9,10-dione (54).**

Quinoxaline-5,8-dione (9) (0.160 g) and 1-acetoxy-1,3-butadiene (0.134 g) afforded 1,4-diazaanthracene-9,10-dione (54) (0.11 g, 54%), mp above 300 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 2924, 1734, 1678 (CO), 1480, 1176, 1062, 939, 843, 697, 567; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  7.97 (2H, dd, *J* = 6.1 and 3.6 Hz, 6- and 7-H), 8.26 (2H, dd, *J* = 6.1 and 3.6 Hz, 5- and 8-H), 9.12 (2H, s, 2- and 3-H); MS, m/z(r.i.) 212 (21%), 211 (12), 210 (M<sup>+</sup>, 100), 186 (92), 182 (92), 154 (16), 104 (19) (Found: C, 68.26; H, 2.81; N, 13.15. C<sub>12</sub>H<sub>6</sub>N<sub>2</sub>O<sub>2</sub> requires C, 68.57; H, 2.85; N, 13.33 %).

### 2,3-Dimethoxy-1,4-diazaanthracene-9,10-dione (55).

2,3-Dimethoxyquinoxaline-5,8-dione (42) (0.22 g) and 1-acetoxy-1,3-butadiene (0.13 g) gave 2,3-dimethoxy-1,4-diazaanthracene-9,10-dione (55) (0.169 g, 63%), mp 274-275 °C; IR(KBr)  $\nu_{\max}/\text{cm}^{-1}$  1736, 1684 (CO), 1624, 1591, 1526, 1402, 1308, 1284, 986, 869, 745, 567, 542;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  4.29 (6H, s, 2- and 3- $\text{OCH}_3$ ), 7.8 (2H, dd,  $J = 5.9$  and 3.2 Hz, 6- and 7-H), 8.32 (2H, dd,  $J = 5.9$  and 3.2 Hz, 5- and 8-H); MS,  $m/z(\text{r.i.})$  270 ( $\text{M}^+$ , 100), 255 ( $\text{M} - \text{CH}_3$ , 15), 240 ( $\text{M} - 2\text{CH}_3$ , 43), 225 (22), 213 (17), 149 (7), 104 (16), 85 (48) (Found: C, 62.12; H, 3.81; N, 10.15.  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_4$  requires C, 62.22; H, 3.73; N, 10.37 %).

### 2,3-Dichloroquinoxaline (4).

2,3-Quinoxalindione (2 g, 12 mmol) was heated under reflux with phosphoryl chloride ( $20 \text{ cm}^3$ ) and *N,N*-dimethylaniline ( $10 \text{ cm}^3$ ) for 3.5 h. The cooled reaction mixture was slowly poured into ice-water and extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate, evaporated *in vacuo*, and the greenish yellow residue was dissolved in dichloromethane and percolated through a neutral alumina column to yield crystals of 2,3-dichloroquinoxaline on evaporation of the solvent (1.5 g, 62%), mp 150-151 °C (lit.,<sup>2</sup> mp 150 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1596, 1272, 1182, 1104, 804;  $^1\text{H NMR}$  (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 (2H, dd,  $J_{7,8} = 6.4$  Hz,  $J_{8,6} = 2.7$  Hz, 8-H), 8.03 (2H, dd,  $J_{5,6} = 6.3$  Hz,  $J_{5,7} = 3.0$  Hz, 5-H); MS,  $m/z$  (r.i.) 202 ( $\text{M}^+$  for  $^{37}\text{Cl}$ , 10 %), 200 ( $\text{M}^+$  for  $^{37}\text{Cl} + ^{35}\text{Cl}$ , 65), 198 ( $\text{M}^+$  for  $^{35}\text{Cl}$ , 100), 165 (29), 163 (91), 102 (72).

### 1,4-Dithia[2,3-*b*:5,6-*b'*]diquinoxaline (27).

A stirred mixture of 2,3-dichloroquinoxaline (4) (1.75 g, 8.8 mmol), thiourea (0.688 g, 8.8 mmol), DMF ( $30 \text{ cm}^3$ ) and triethylamine (1.8 g) was refluxed for 5 h. A yellow precipitate formed during the reaction. The solid was collected and washed with water and then methanol to give the title compound (27) (0.50 g, 28%), mp above 300 °C (lit.,<sup>50</sup>

mp 300 °C); IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 1674, 1552, 1334, 1256, 1102, 894, 782, 592 ;<sup>1</sup>HNMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  7.79 (4H, m, Ar-H), 7.81 (4H, m, Ar-H); MS m/z(r.i.) 320 (M<sup>+</sup>, 100%), 288 (M - S, 4), 276 (5), 214 (5), 85 (23).

### **Bis(2-chloroquinoxalin-3-yl)sulfide (57).**

2,3-Dichloroquinoxaline (4) (0.50 g, 2.5 mmol) and dithioamide (0.16 g, 2.5 mmol), was dissolved in DMF (15 cm<sup>3</sup>) and triethylamine (0.50 g) was added with stirring. The reaction mixture was refluxed for 5h. The yellow product precipitated out during the reaction. After cooling the reaction mixture the compound (27) was collected by filtration and washed with water and methanol (0.32 g, 40 %).

Addition of water to the initial filtrate from the above reaction gave more product. The solid was collected and crystallised from chloroform and petroleum spirit to give *bis(2-chloroquinoxalin-3-yl)sulfide* (57) (0.360 g, 40%) mp 174-176 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 1554, 1526, 1476, 1256, 1174, 1110, 996, 799; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  7.76 (4H, m, 6- and 7 -H), 7.86 (2H, dd,  $J = 7.6$  Hz,  $J = 1.7$  Hz, 5-H), 8.05 (2H, dd,  $J = 7.6$  Hz,  $J = 1.7$  Hz, 8-H); MS, m/z(r.i) 360 (M<sup>+</sup> for <sup>37</sup>Cl + <sup>35</sup>Cl, 1.5%), 358 (M<sup>+</sup> for <sup>35</sup>Cl, 2), 326 (M - S, 17), 324 (M - H<sub>2</sub>S, 84), 323 ( 100), 288 (4), 109 (9) (Found: C, 53.31; H, 2.25; N, 15.74. C<sub>16</sub>H<sub>8</sub>N<sub>4</sub>SCl<sub>2</sub> requires: C, 53.50; H, 2.22; N, 15.60%).

## **REACTION OF BIS(2-CHLOROQUINOXALIN-3-YL)SULFIDE WITH AMINES.**

### **General Method.**

The bis(2-chloroquinoxalin-3-yl)sulfide (57) (0.39 g, 1.1 mmol) and amine (4.4 mmol) were dissolved in anhydrous THF (50 cm<sup>3</sup>) containing anhydrous potassium carbonate (1 g) and refluxed for 6h. After completion of the reaction, the solvent was evaporated *in vacuo*.

### **6,13-Dibutyl-5,6,7,12,13,14-hexaazapentacene (58).**

Bis(2-chloroquinoxalin-3-yl)sulfide (57) and n-butylamine (0.32 g) produced a residue which was dissolved in water, the product was extracted with dichloromethane, dried (anhydrous sodium sulfate) and purified by column chromatography using petroleum ether (bp 40-60 °C) and dichloromethane (90:10) and crystallised from a mixture of dichloromethane and petroleum ether (bp 40- 60 °C) to give *6,13-dibutyl-5,6,7,12,13,14-hexaazapentacene* (0.19 g, 45%); mp 271-271.5 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 1556, 1506, 1456, 1374, 1306, 1136, 760; <sup>1</sup>HNMR (200MHz, CDCl<sub>3</sub>)  $\delta$  1.03 (6H, t, 2 x N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.54 (H, m, 2 x N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 1.78 (4H, m, 2 x N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 4.45 (4H, t, 2 x N-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>), 7.32 (4H, dd,  $J_{1,2} = 6.2$  Hz,  $J_{1,3} = 2.5$  Hz, 2, 3, 9, 10-H), 7.57 (4H, dd,  $J_{8,9} = 6.2$  Hz,  $J_{8,10} = 2.5$  Hz, 1,4, 8, 11-H); MS, m/z(r.i.) 399 (30%), 398 (M<sup>+</sup>, 100), 355 (7), 340 (19), 300 (19), 286 (41), 285 (10), 198 (19), 117 (22) (Found: C, 72.12; H, 6.5; N, 20.90. C<sub>24</sub>H<sub>26</sub>N<sub>6</sub> requires: C, 72.36; H, 6.5; N, 21.10%).

### **6,13-Dibenzyl-5,6,7,12,13,14-hexaazapentacene (60).**

When benzylamine (0.47 g) was used with (57) a solid was filtered off and purified by chromatography using petroleum ether (40-60 °C) and dichloromethane (90:10), to give the *6,13-dibenzyl-5,6,7,12,13,14-hexaazapentacene*, (0.12 g, 36%), mp 367-368 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 2313, 2213, 1504, 1456, 1374, 1232, 1145, 1098, 998, 876, 758, 708, 696, 574, 542; MS m/z(r.i.) 467 (50%), 466 (M<sup>+</sup>, 100), 376 (26), 375 (73), 91 (16) <sup>1</sup>HNMR (200MHz, TFA)  $\delta$  4.91 (4H, m, 2 x N-CH<sub>2</sub>), 7.44 (6H, m, 2 x 3-, 2 x 4-, and 2 x 5-benzylic-H), 7.70 (4H, m, 2 x 2- and 2 x 6-benzylic-H), 7.86 (8H, m, 1-, 2-, 3-, 4-, 8-, 9-, 10- and 11-Ar-H); MS ([FAB; NOBA]): M<sup>+</sup> 466.1906. C<sub>30</sub>H<sub>22</sub>N<sub>6</sub> requires M<sup>+</sup> 466.1896 daltons. (Found: C, 76.52; H, 4.75; N, 17.60. C<sub>30</sub>H<sub>22</sub>N<sub>6</sub> requires: C, 77.23; H, 4.75; N, 18.00%).



**6,13-Dihydro-6-thia-5, 7, 12, 13, 14-pentaazapentacene (62).**

Bis(2-chloroquinoxalin-3-yl)sulfide (57) and cyanamide (0.18 g) yielded a solid which was separated by filtration and crystallised from ethanol to give the *title compound* (62), (0.10 g, 60%), mp above 300 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3446 (NH), 2314, 2213, 1616, 1578, 1478, 1392, 1237, 1198, 1076, 998, 876, 740, 665, 567, 543, 521; <sup>1</sup>HNMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  7.51 (8H, m, 1-, 2-, 3-, 4-, 8-, 9-, 10- and 11-Ar-H), 11.90 (1H, s, exchangeable with D<sub>2</sub>O, 13-H), MS, m/z(r.i.) 304 (18%), 303 (M<sup>+</sup>, 100), 302 (9), 271(4), 128 (10) (Found: C, 63.02; H, 2.91; N, 23.00. C<sub>16</sub>H<sub>9</sub>N<sub>5</sub> S requires: C, 63.36; H, 2.97; N, 23.10%).

**13-(2-Aminoethyl)-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (61).**

Ethylene diamine (0.229 g, 4.4 mmol) in anhydrous THF (50 cm<sup>3</sup>) was added dropwise to the mixture of bis(2-chloroquinoxalin-3-yl)sulfide (57) (0.393 g) in anhydrous THF and potassium carbonate and the mixture refluxed for 6 h. After completion of the reaction, the solvent was evaporated *in vacuo*, and the residue was crystallised with ethanol to yield *13-(2-aminoethyl)-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene* (0.250 g, 65%), mp 258.5-259 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3445 (NH<sub>2</sub>), 3420, 1698, 1468, 1410, 1292, 768; <sup>1</sup>HNMR (200MHz, DMSO-d<sub>6</sub>)  $\delta$  1.22 (2H, s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 3.26 (2H, t, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 4.53 (2H, t, CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 7.62 (8H, m, Ar-H); MS, m/z(r.i.) 346 (M<sup>+</sup>, 7), 330 (M - NH<sub>2</sub>, 7), 329 (23), 328 (21), 218 (9), 317 (34), 305 (13), 303 (100), 73 (31) (Found: C, 62.22; H, 4.02; N, 24.16. C<sub>18</sub>H<sub>14</sub>N<sub>6</sub>S requires: C, 62.42; H, 4.07; N, 24.26%).

**6,13-Dibutyl-5,6,7,12,13-hexaazapentacene (58) and 13-butyl-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (59) from 1,4-dithia[2,3-*b*:5,6-*b*]diquinoxaline (27).** To a solution of 1,4-dithia[2,3-*b*:5,6-*b*]diquinoxaline (27) (0.352 g, 1.1 mmol) in anhydrous dimethyl sulfoxide (40 cm<sup>3</sup>), n-butylamine (0.321 g, 4.4 mmol) was added and the mixture refluxed for 10 h. The solid was collected from the cooled reaction mixture. T.L.C analysis showed two components which were separated by column chromatography using a mixture of petroleum spirit (40-60 °C) and dichloromethane (50:50). The first component eluted was characterised as *6,13-dibutyl-5,6,7,12,13-hexaazapentacene* (58) (0.05 g, 11%) by comparison of its physical data with those of compound (58) obtained earlier. The second component eluted was characterised as *13-butyl-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene* (59) (0.215 g, 54%), mp 221.4-222 °C; IR(KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  1558, 1512, 1464, 1410, 1336, 1292, 1218, 1130, 762; <sup>1</sup>HNMR (200MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.05 (3H, t, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.53 (2H, t, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.87 (2H, t, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.54 (2H, t, NCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 7.52 (4H, m, 2-, 3-, 9-, 10-H), 7.71 (4H, m, 1-, 4-, 8-, 11-H); MS, m/z(r.i.) 360 (13%), 359 (M<sup>+</sup>, 49), 330 (8), 317 (22), 316 (15), 304 (25), 303 (78), 245 (56), 112 (13), 83 (100); MS ([FAB; NOBA]): M<sup>+</sup> 359.1201. C<sub>20</sub>H<sub>17</sub>N<sub>5</sub>S requires M<sup>+</sup> 359.1205 daltons.

**Separation of 2,3- and 2,5-dinitro-1,4-dimethoxybenzene isomers, (44) and (45) respectively.**

These two isomers were separated by column chromatography using a mixture of petroleum spirit (bp 40-60 °C) and ethyl acetate (70:30) as solvent system.

**2,3-Dinitro-1,4-dimethoxybenzene (44).**

This isomer (80% of the total dimethoxybenzenes) had mp 189 °C (lit.,<sup>53</sup> mp 186 °C), IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 2292, 1542, 1494, 1436, 1350 (NO<sub>2</sub>), 1128, 1054, 810 ; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.90 (6H, s, 1- and 4-OCH<sub>3</sub>), 7.68 (2H, s, 5- and 6-H); MS m/z (r.i.) 228 (M<sup>+</sup>, 23%), 227 (M - H, 100), 182 (M - NO<sub>2</sub>, 7), 136 (7), 106 (7), 76 (23).

**2,5-Dinitro-1,4-dimethoxybenzene (45).**

The minor isomer (20%) had mp 205 °C (lit.,<sup>53</sup> mp 202 °C) ; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 2292, 1542, 1494, 1436, 1354 (NO<sub>2</sub>), 1128, 1054, 810; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.90 (6H, s, 1- and 4-OCH<sub>3</sub>), 7.91 (2H, s, 3- and 5-H); MS m/z(r.i.) 228 (M<sup>+</sup>, 23%), 227 (M - H, 100), 136 (7), 106 (7), 76 (23).

**PARTIAL REDUCTION OF 2,3- AND 2,5-DINITRO-1,4-DIMETHOXYBENZENE.**

**(i) Attempted reduction with hydrazine hydrate.**

**1-Hydroxy-4,7-dimethoxy-1,2,3-benzotriazole (65).**

A mixture of 2,3-dinitro-1,4-dimethoxybenzene (44) (5.7 g, 25 mmol) and 60% hydrazine hydrate (3.75 g, 75 mmol) was stirred for 10 min at 28-30 °C. The temperature was then raised to 90 °C during 45 min. and stirring was continued for 18 h at 90<sup>o</sup> C on a water bath. The reaction mixture was neutralized with dilute hydrochloric acid and, after cooling the reaction mixture, the resultant crystals of *1-hydroxy-4,7-dimethoxy-1,2,3-benzo-*

*triazole* (65) were collected and recrystallised from ethanol (4.80 g, 78%), mp 230-231 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3014 (OH), 2362, 2161, 1532, 1234, 1070, 802, 776, 689, 546; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.92 (6H, s, 4- and 6-OCH<sub>3</sub>), 6.65 (1H, d,  $J$  = 8.2 Hz, 6-H), 6.83 (1H, d,  $J$  = 8.0 Hz, 5-H), 13.50 (1H, s, 1-OH); MS,  $m/z$ (r.i.) 195 (M<sup>+</sup>, 65), 180 (M- CH<sub>3</sub>, 12), 179 (100), 165 (11), 136 (6) (Found: C, 49.33; H, 4.74; N, 21.89; C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> requires: C, 49.23; H, 4.61; N, 21.53%).

**(ii) Reduction with sodium dithionite.**

**General Method.**

A freshly prepared solution of sodium dithionite (17.2 mmol) in water (50 cm<sup>3</sup>) was added dropwise to a hot solution of dinitrodimeoxybenzene (2.19 mmol) in a mixture of tetrahydrofuran (11 cm<sup>3</sup>) and methanol (22 cm<sup>3</sup>). The reaction mixture was heated for a few minutes and diluted with water (25 cm<sup>3</sup>) and heating was continued for a further 45 min. Completion of the reaction was monitored by T.L.C. Organic solvents were evaporated off using the rotary evaporator. The aqueous solution was cooled in an ice-bath to give a solid which was purified by column chromatography using a mixture of ethyl acetate and petroleum spirit (bp 40-60 °C) (1:1)

**2,5-Dimethoxy-6-nitroaniline (66).**

1,4-Dimethoxy-2,3-dinitrobenzene (44) (0.50 g) was yielded *2,5-dimethoxy-6-nitroaniline* (66) (0.175 g, 40%); mp 72-74 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3480 (NH<sub>2</sub>), 3348 (NH<sub>2</sub>), 2936, 1618, 1592 (NO<sub>2</sub>), 1522, 1464, 1340 (NO<sub>2</sub>), 1268, 1128, 1098, 998, 867, 776, 675, 543, 521; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.83 (6H, s, 2- and 5-OCH<sub>3</sub>), 3.85 (2H, s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 6.20 (1H, d,  $J$  = 8.7 Hz, 4-H), 6.73 (1H, d,  $J$  = 9.3 Hz, 3-H); MS,  $m/z$ (r.i.) 199 (22%), 198 (M<sup>+</sup>, 96), 183 (100), 182 (M - NH<sub>2</sub>, 19), 152 (M - NO<sub>2</sub>, 19), 122 (55), 107 (15), 105 (9), 98 (21) (Found: C, 48.48; H, 5.03; N, 13.84. C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> requires: C, 48.48; H, 5.05; N, 14.14%).

### **2,5-Dimethoxy-4-nitroaniline (67).**

Reduction of 1,4-dimethoxy-2,5-dinitrobenzene (45) (0.50 g) with sodium dithionite (3 g) in a procedure similar to that described for (66) gave *2,5-dimethoxy-4-nitroaniline* (67) (0.26 g, 60%), mp 156-158 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3470 (NH<sub>2</sub>), 3342 (NH<sub>2</sub>), 1638, 1528 (NO<sub>2</sub>), 1448, 1384 (NO<sub>2</sub>), 1286, 1256, 1038, 987, 886, 774, 654, 543, 521; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.87 (3H, s, 2-OCH<sub>3</sub>), 3.90 (3H, s, 5-OCH<sub>3</sub>), 4.58 (2H, s, exchangeable with D<sub>2</sub>O NH<sub>2</sub>), 6.28 (1H, s, 6-H), 7.57 (1H, s, 3-H); MS, m/z(r.i.) 199 (12%), 198 (M<sup>+</sup>, 100), 183 (66%), 182 (M - NH<sub>2</sub>, 15), 152 (M - NO<sub>2</sub>, 19), 122 (23), 107 (35), 89 (9) (Found: C, 48.48; H, 5.05; N, 13.63. C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub> requires: C, 48.48; H, 5.05; N, 14.14%).

### ***N*-(2,5-Dimethoxy-6-nitrophenyl)guanidine (68), 3-amino-5,8-dimethoxy-1,2,4-benzotriazine-1-oxide (69) and 4,7-dimethoxy-1,2,3-benzotriazole (70).**

A mixture of the 2,5-dimethoxy-6-nitroaniline (66) (0.73 g, 3.7 mmol) and cyanamide (1.5 g, 35 mmol) was fused at 100 °C. The mixture was cooled to room temperature, treated with concentrated hydrochloric acid (2 cm<sup>3</sup>) and warmed briefly at 100 °C until a vigorous reaction occurred. After the reaction had subsided, the mixture was cooled to room temperature and a solution of sodium hydroxide (1.5 g) in water (2 cm<sup>3</sup>) added and warmed at 100 °C for 1 h. A yellow solid separated on cooling and after addition of water the yellow solid was collected and crystallised from aqueous methanol to yield *N*-(2,5-dimethoxy-6-nitrophenyl)guanidine (68), (0.59 g, 67 %), mp 250-251 °C; IR(KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3400 (NH<sub>2</sub>), 3186 (NH<sub>2</sub>), 1670, 1580, 1526, 1488, 1252; <sup>1</sup>HNMR (200 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.68 (3H, s, 5-OCH<sub>3</sub>), 3.74 (3H, s, 8-OCH<sub>3</sub>), 5.09 (2H, s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 6.58 (1H, d, *J* = 9.2 Hz, 6-H), 6.90 (1H, d, *J* = 8.7 Hz, 7-H); MS, m/z(r.i.) 240 (M<sup>+</sup>, 82%), 225 (M - CH<sub>3</sub>, 35), 224 (M - NH<sub>2</sub>, 10), 209 (M - OCH<sub>3</sub>, 18), 198 (M - CH<sub>2</sub>N<sub>2</sub>, 100) (Found: C, 44.90; H, 5.10; N, 23.13. C<sub>9</sub>H<sub>12</sub>N<sub>4</sub>O<sub>4</sub> requires: C, 45.00; H, 5.04; N, 23.33%).

The aqueous layer from which (66) deposited was evaporated, the residue dissolved in ethanol and separated by column chromatography [silica gel, mixture of ethyl acetate and petroleum spirit (bp 40-60 °C) (70:30)] to give *3-amino-5,8-dimethoxy-1,2,4-benzotriazine-1-oxide* (69), (0.16 g, 20%) and followed by *4,7-dimethoxybenzotriazole* (70), (0.07 g, 11 %). The compound (69) was crystallised from methanol and had mp 229-231 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3406 (NH<sub>2</sub>), 3286 (NH<sub>2</sub>), 1622, 1510, 1288, 1070; <sup>1</sup>HNMR (200MHz-DMSO-d<sub>6</sub>)  $\delta$  3.81(3H, s, 5-OCH<sub>3</sub>), 3.83 (3H, s, 8-OCH<sub>3</sub>), 6.66 (1H, d, *J* = 9.0 Hz, 6-H), 7.11 (1H, d, *J* = 8.0 Hz, 7-H), 7.13 (2H, s, exchangeable with D<sub>2</sub>O, 3-NH<sub>2</sub>); MS, *m/z*(r.i.) 236 (35%), 222 (M<sup>+</sup>, 100), 207 (M - CH<sub>3</sub>, 34), 206 (M - H, 25), 205 (33), 177 (10) (Found: C, 48.50; H, 4.59; N, 25.14. C<sub>9</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub> requires: C, 48.65; H, 4.50; N, 25.22%).

The *4,7-dimethoxy-1,2,3-benzotriazole* (70) had mp 154-156 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3415, 1560, 1540, 1455, 1289, 1004, 804; <sup>1</sup>HNMR (200 MHz-DMSO-d<sub>6</sub>)  $\delta$  3.94 (6H, s, 4- and 7-OCH<sub>3</sub>), 6.21(1H, s, exchangeable with D<sub>2</sub>O), 6.72 (2H, s, 5- and 6-H); MS, *m/z*(r.i.) 180 (11%), 179 (M<sup>+</sup>, 100), 164 (M- NH, 5), 149 (M- 2CH<sub>3</sub>, 24), 136 (16), 57 (10) (Found: C, 53.30; H, 5.02; N, 23.08. C<sub>8</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub> requires: C, 53.63; H, 5.06; N, 23.46%).

### **3-Amino-5,8-dimethoxy-1,2,4-benzotriazine-1-oxide (69) and 4,7-dimethoxy- 1,2,3-benzotriazole (70).**

N-(2,5-dimethoxy-6-nitrophenyl)guanidine (68) (0.50 g) was dissolved in aqueous sodium hydroxide (1.5 g) and warmed at 100 °C for 1h. The aqueous layer was evaporated and solid was collected and purified by column chromatography using mixture of ethyl acetate and petroleum spirit (bp 40-60 °C) (70:30)] to give (69), (0.30 g, 60%) and (70), (0.10 g, 20%). The structures were confirmed by IR and <sup>1</sup>H NMR spectroscopy, mass spectrometry and elemental analysis and the compounds were shown to be identical to those obtained earlier.

**Attempted preparation of 3-amino-1,2,4-benzotriazine-1,4-dioxide (75).**

A suspension of the 1-oxide (69) (0.005 mole) in acetic acid (25 cm<sup>3</sup>) was stirred and heated at 45-50 °C for 20-60 h with 30% aqueous hydrogen peroxide (12 cm<sup>3</sup>), but only starting material was obtained.

**Attempted preparation of 3-amino-1,2,4-benzotriazine-1-oxide-5,8-quinone (76).**

To a stirred solution of 3-amino-5,8-dimethoxy-1,2,3-benzotriazine-1-oxide (69) (0.10 g) in a mixture of acetonitrile and water (10 cm<sup>3</sup>, 4:1 v/v) was added portionwise ceric ammonium nitrate (0.96 g, 4 mmol) while the mixture was cooled in an ice-bath. The stirring was continued for 15-20 min at 0 °C and then the mixture was diluted with water (50 cm<sup>3</sup>). The reaction mixture slowly changed colour at room temperature. The mixture was extracted with dichloromethane and the solvent evaporated *in vacuo* to give a dark brown residue which was crystallised from ethyl acetate, the product had mp above 330 °C but the IR and <sup>1</sup>HNMR spectra were complicated, perhaps due to the decomposition of the expected product.

## CHAPTER: 2

### 2.1 INTRODUCTION

#### 2.1.1 Bleomycin (BLM).

The naturally occurring glycopeptide bleomycin exhibits both antibiotic and antitumour properties and was originally isolated from *Streptomyces verticillus* in 1966.<sup>62</sup> There are apparently several modes of action by which bleomycin (BLM) exerts its antitumour activity. One firmly established mechanism involves interaction with DNA in the presence of a metal ion cofactor and subsequent degradation of the double helix.<sup>63,64</sup>

BLM is used in the treatment of several types of cancer including squamous cell carcinomas of skin, head, neck and tumours of the testis. The clinically used mixture of BLM, known as Blenoxane, consists mainly of BLM congeners A<sub>2</sub> and B<sub>2</sub>, which differ only in their C-terminal groups (Fig 2). Structurally, BLM is a linear hexapeptide consisting of both common and uncommon amino acids and it also contains a disaccharide bonded through a glycoside linkage to an amino acid side chain.

Previous studies have shown that the bleomycin molecule consists of two distinct and relatively independent regions. One region is localized around the bithiazole containing moiety and the cationic terminus and is responsible for the association with DNA, the other region is comprised of the pyrimidine group which contains the metal binding site.<sup>65,66,67</sup>



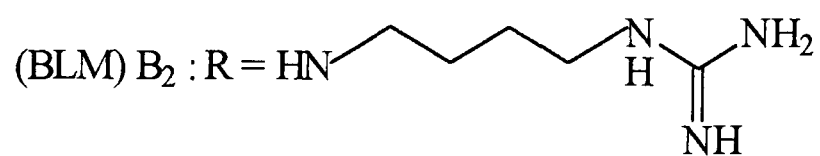
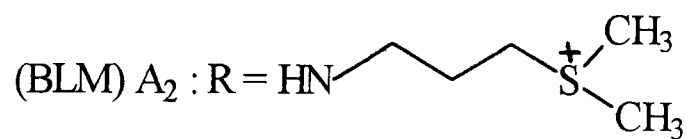
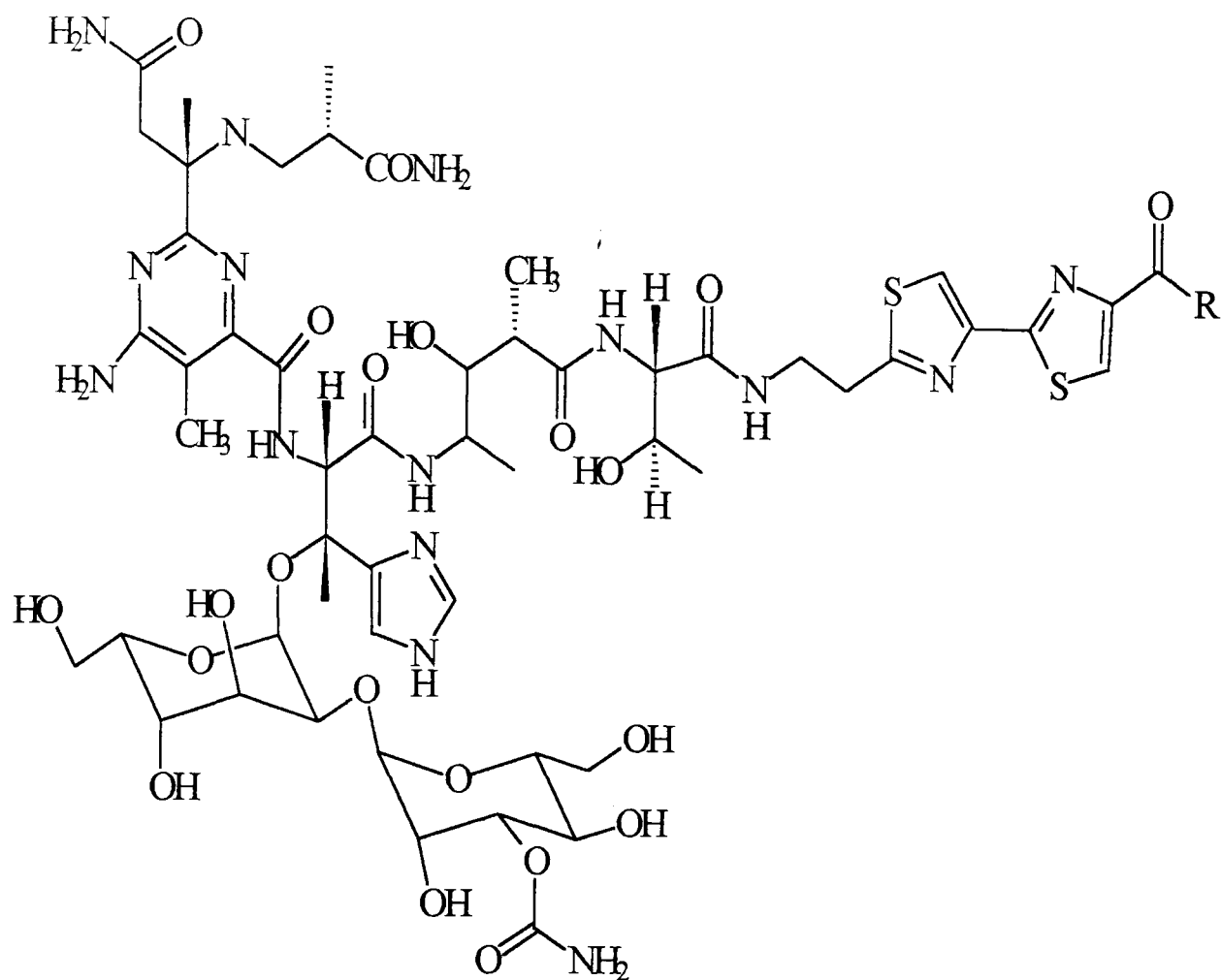


Fig 2: Structure of bleomycins.

Several metal complexes of bleomycin are known to bind with and cause degradation of DNA.<sup>68</sup>

The proposed mechanism of oxygen activation by Fe (II)-BLM is shown in Fig 3. The ferrous complex is activated in the presence of molecular oxygen, binds with DNA and causes degradation of the DNA.<sup>69</sup>

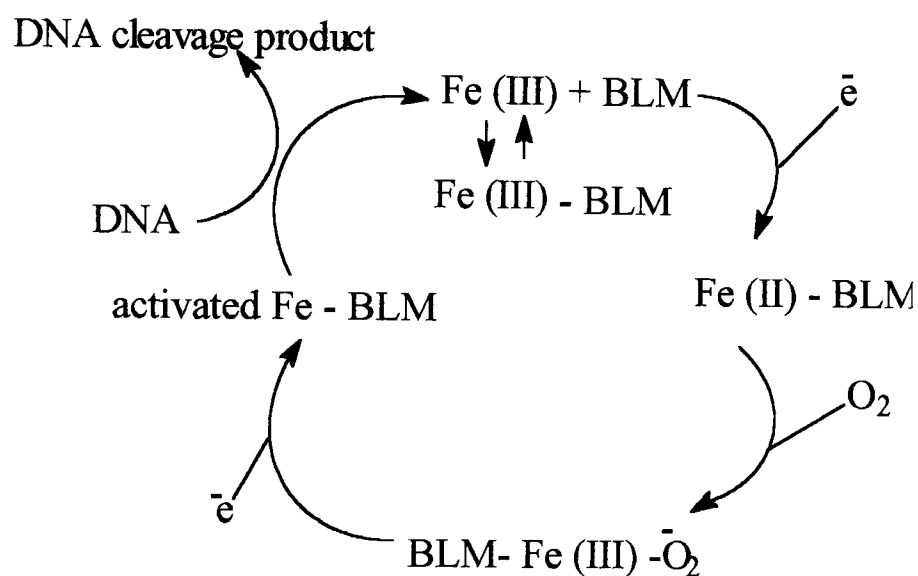


Fig 3: Fe (II)-BLM complex

The Fe (II) centre binds oxygen and undergoes one electron reduction and protonation to form the Fe (III)- hydroperoxide. This hydroperoxide undergoes heterolytic O-O bond scission to produce the putative perferryl species, which abstracts the 4'-H from deoxyribose to initiate DNA damage.<sup>62</sup>

Chemotherapy with increased doses of bleomycin, or even small doses applied frequently, are not acceptable because of severe cumulative pulmonary toxicity but the drug continues to interest oncologists because of its remarkable lack of bone marrow toxicity. However, because of pulmonary toxicity, BLM is used clinically in low doses mainly in synergistic combinations with other anticancer agents, e.g cisplatin, mitomycin and methotrexate.<sup>70</sup>

Another approach to improving chemotherapy based on BLM is to find compounds (amplifiers) that alone do not have significant activity or toxicity but which enhance the activity of the drug (or which act directly at the DNA level and have focused on the BLM reaction). Amplifiers of the cytotoxic effect of bleomycin may in general:-

- I. Increase the intracellular level of the drug.<sup>71</sup>
- II. Inhibit DNA repair or synthesis.<sup>72</sup>
- III. Bind with DNA and by so doing stimulate directly drug-induced DNA fragmentation.<sup>73</sup>

A number of unfused aromatic cations have been found to bind to DNA by intercalation and to amplify the bleomycin catalysed cleavage of DNA.

These compounds which bind to DNA interact with the duplex through three primary modes. (Fig 4)

- I. Electrostatic interactions with the anionic sugar-phosphate backbone of DNA.
- II. Intercalation..
- III. Interaction in the DNA major and minor groove.

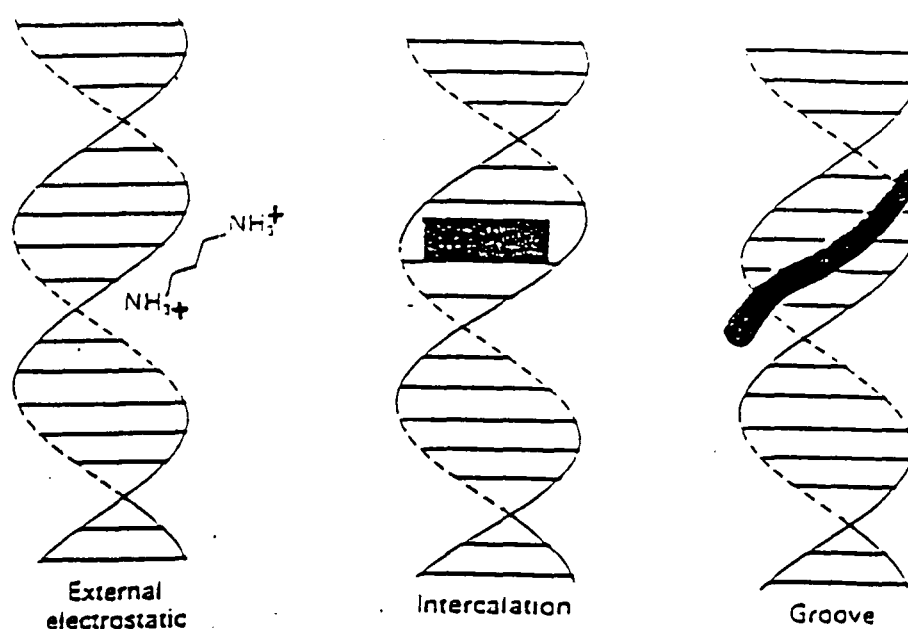


Fig 4: The three primary binding modes of DNA.

### 2.1.2 Structure of DNA.

The double helical structure of DNA was first described by Watson and Crick in 1953. The DNA molecule consists of two antiparallel strands of bases, adenine (A) and thymine (T), guanine (G) and cytosine (C), supported on a sugar phosphate backbone (Fig 5).

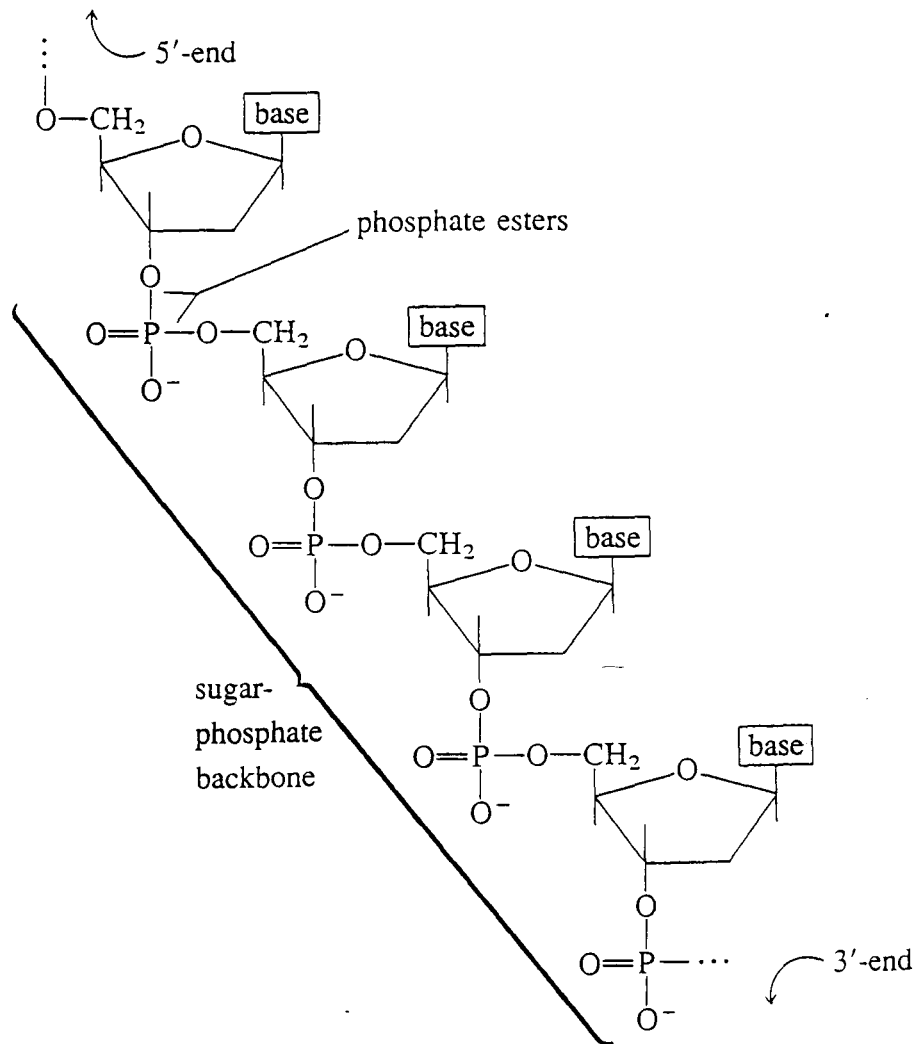


Fig 5: General structure of DNA; Base = A, T, G and C.

The bases form specific hydrogen bonded pairs. Adenine associates with thymine (AT) on the opposite strand, and guanine associates with cytosine (GC).

The distance between each successive base-pair is 3.4 Å. This gives rise to two well defined channels on the exterior of the double helix. These channels are unequal in size and known as major and minor grooves which are approximately equally deep but with very different widths, whereas the minor groove is narrow, the major groove is much more open (Fig 6).

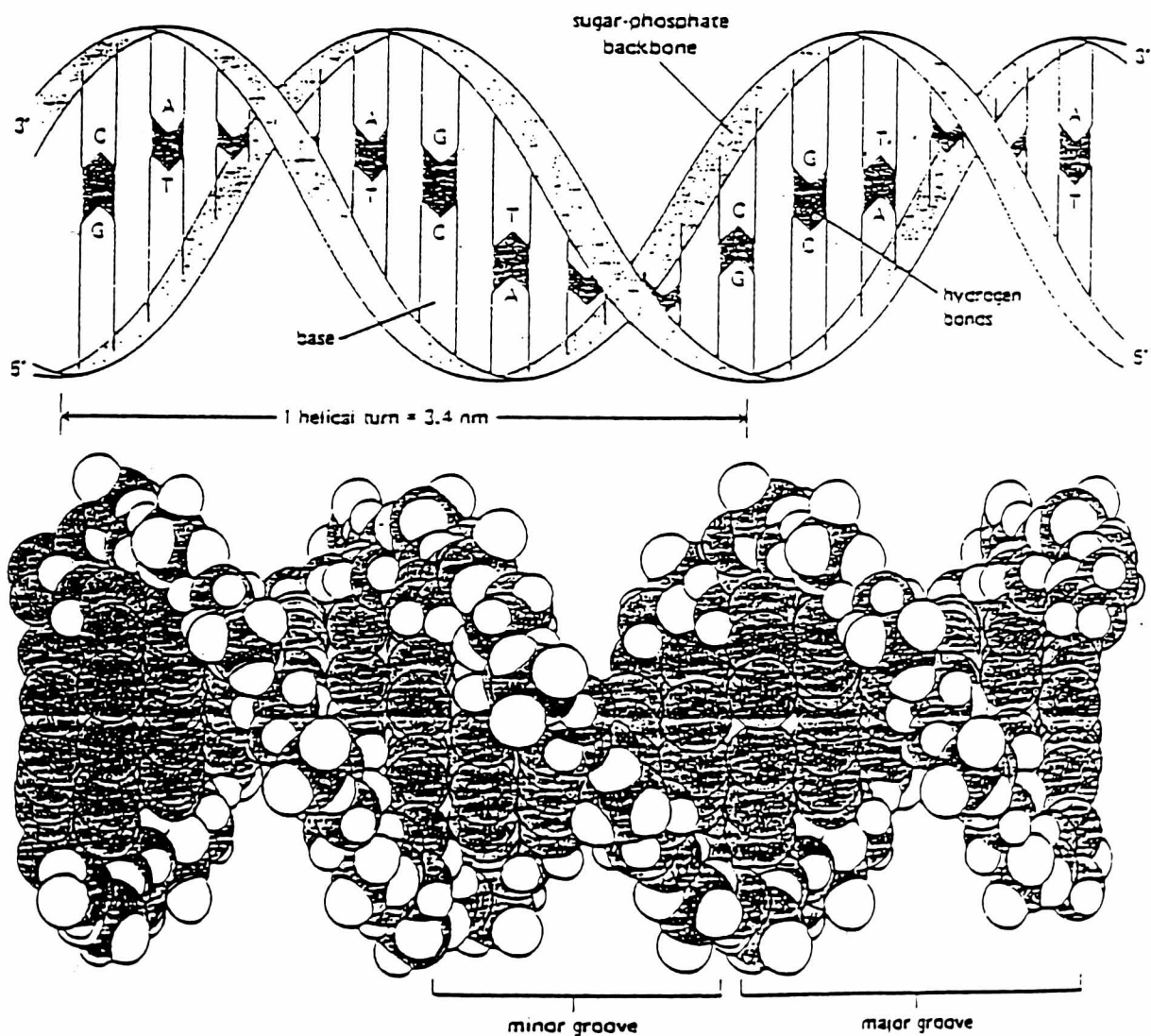
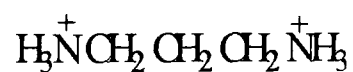


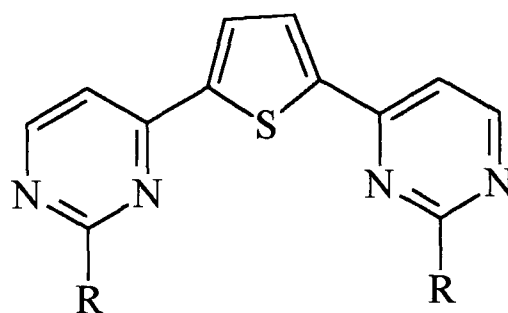
Fig 6: DNA double helix.

### 2.1.3 External electrostatic interactions.

Nucleic acids are highly charged polyelectrolytes whose anionic phosphate groups strongly affect their structure and interactions. Therefore cations of organic amines such as 1,3-diaminopropane and unfused aromatic intercalators interact strongly with DNA.<sup>74</sup>



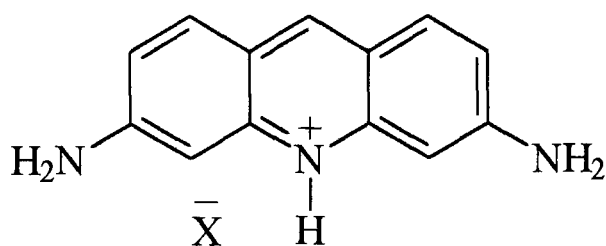
1,3-Diaminopropane



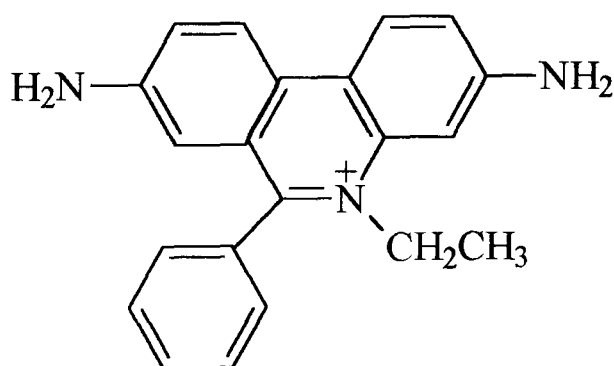
Unfused aromatic intercalator.

### 2.1.4 Intercalation.

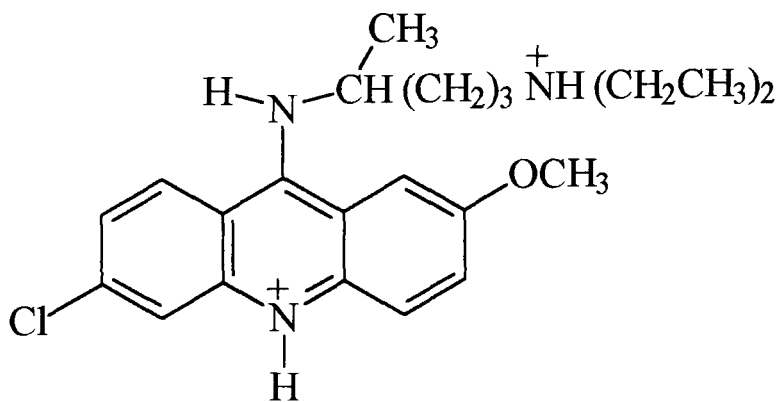
Some planar molecules, usually having two to four fused aromatic rings and a positive charge which is needed for activity<sup>75</sup> on the ring or on a substituent, e.g. proflavine (77), ethidium (78) and quinacrine (79) (generally known as classical intercalators), are capable of insertion between the base pairs of duplex DNA. They bind only to double stranded DNA and insertion between base pairs causes the helix to lengthen<sup>76,77,78,79,80,81</sup> (Fig 7).



Proflavine (77)



Ethidium (78)



Quinacrine (79)

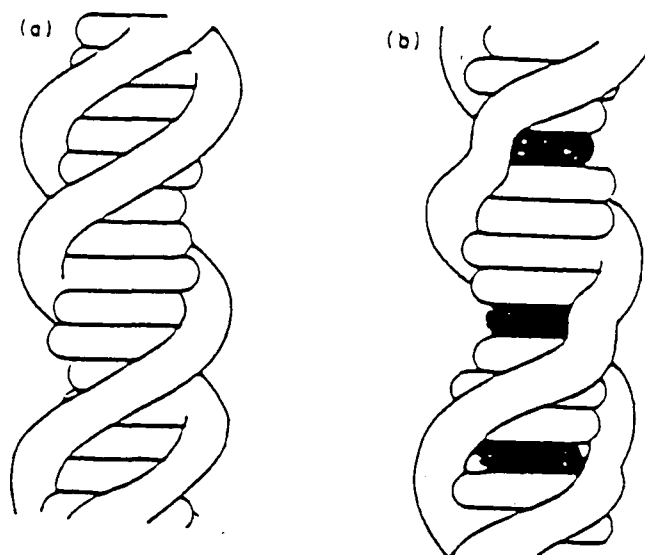
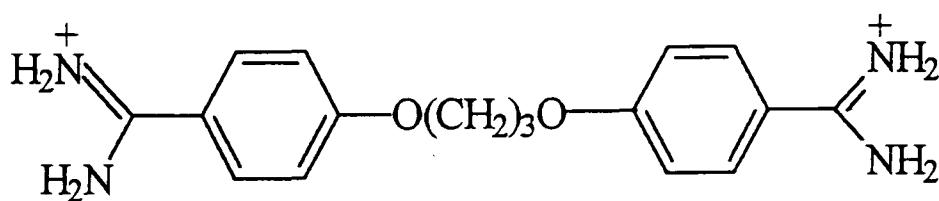


Fig 7: The intercalation model: (a) representation of DNA  
 (b) same molecule containing intercalated drug molecules.

### 2.1.5 Groove binding molecules.

Many unfused aromatic compounds with terminal basic functions exhibit binding specificity primarily through groove interactions. These types of molecules bind covalently to guanine in the major groove through hydrogen-bonding. However, the compounds that bind noncovalently in the minor groove of DNA are long, flexible molecules with one or two positively charged end groups,<sup>82</sup> e.g. pentamidine (80).



Pentamidine (80)



For groove binding the surface of the ligand must be helically concave to complement the curvature of the groove surface. Typical groove binding molecules contain an unfused aromatic system with terminal basic functions. Torsional freedom between aromatic rings allows the molecules to form a non-planar shape which closely matches the helical curvature of the minor groove.

### **2.2.1 Bleomycin amplifiers.**

As described before in this thesis (2.1.1), BLM can only be used clinically in low doses due to pulmonary toxicity but it may be possible to enhance the activity of BLM by giving the patient compounds that alone may have no activity or toxicity but that amplify the action of BLM. The mechanism of amplification is not fully understood.

Previous studies by Povirk and co-workers<sup>83</sup> have suggested that the region of bleomycin molecule containing the bithiazole moiety is important for interaction with DNA. Therefore a number of chemically prepared bithiazole derivatives were tested for their ability to inhibit the interaction of bleomycin with DNA. This work showed that the bithiazole moiety plays an important role in the binding of BLM to DNA.<sup>84</sup>

The best amplifiers of bleomycin cytotoxicity are composed of at least two fused or unfused conjugated aromatic rings which are cationic or can acquire a positive charge by protonation of a nitrogen. Generally, an anionic or potential anionic centre decreases the activity of the molecule. Since these factors affect the interaction of an aromatic molecule with DNA in the same way, then binding of an amplifier molecule to DNA must be essential for amplification.<sup>85</sup>

A number of unfused aromatic cations such as the compound shown in Fig 8 have been found to enhance the degradation of DNA by bleomycin. These compounds do not necessarily have biological activity of their own and have thus been termed amplifiers to distinguish their effects from drug synergism. It was found that these compounds are DNA intercalators.<sup>86,87,88</sup>

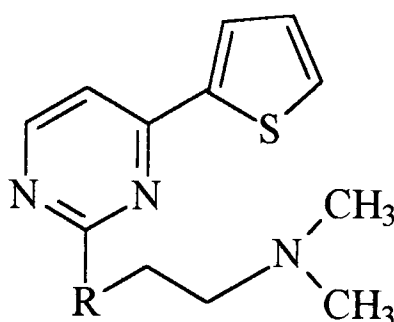


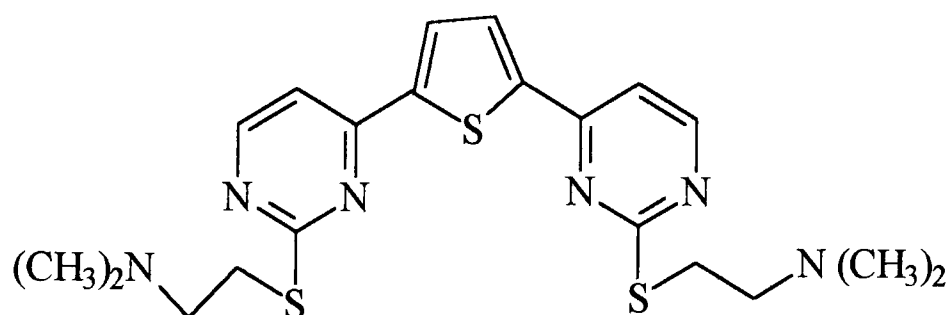
Fig 8: Unfused heteropolyaromatic intercalator molecules: R = S or NH

These types of compounds increase the rate of DNA degradation by bleomycin and have a conformationally flexible, unfused polyaromatic system and a cationic side chain (protonated in water) in the molecule. These are desirable features for amplifiers because the unfused ring systems are better amplifiers than rigid, planar intercalators. This may be due to the torsional conformational freedom in the unfused molecules which causes more extensive lengthening of DNA and breathing of DNA base pairs in the intercalation complex than fused systems of similar molecular area.<sup>89,90,91</sup>

This class of compound shows promise for development as amplifiers of the BLM-type drugs and several mono-, di- and tri-cationic compounds have been synthesized. The electrostatic interaction of these cationic groups with the anionic DNA backbone enhances groove binding or intercalation of the aromatic portion of the molecule by increasing the overall stability of the amplifier-DNA complex.<sup>92</sup>

Previous studies have shown that compounds binding with DNA by this dual mode also show increased bleomycin amplification in comparison to the activity of both noncationic aromatic derivatives and nonaromatic polycationic amines.<sup>93</sup>

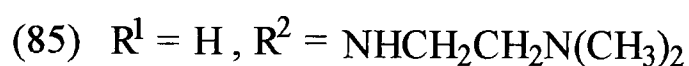
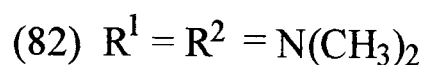
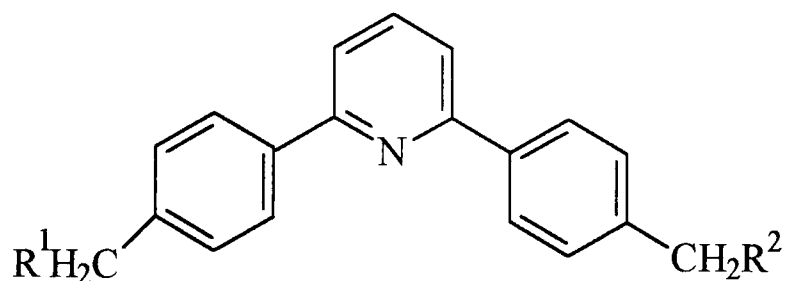
It has been observed that unfused aromatic ring compounds with a terminal basic function bind to DNA in one of the grooves and amplify the degradation of DNA by bleomycin. The dipyrimidinylthiophene (81) is the best amplifier of bleomycin *in vitro* found so far and exhibits the greatest amplification activity at high concentration. Its DNA binding constant ( $13 \times 10^6 \text{ M}^{-1}$ ) exceeds that of BLM ( $10^5 \text{ M}^{-1}$ ).<sup>89</sup>



(81)

Compound (81) and similar unfused intercalators have tertiary amine side chains which are cationic in water. This is an important feature because it not only increases the solubility of the compound but also increases the DNA binding constant through electrostatic interaction with the anionic DNA backbone while the positively polarized aromatic system intercalates with DNA base pairs.<sup>94</sup>

Studies have shown that the tricyclic unfused compounds, e.g 82-85, intercalate strongly with DNA and are better amplifiers than ethidium (a classical intercalator). They cause more lengthening of DNA at low concentration and protonation of the basic amino side chain depends on the separation of the adjacent amino groups.<sup>89</sup>



For both the amino functions to be protonated in an aliphatic diamine at pH 7 the nitrogen atoms must be separated by at least three methylene groups. Thus compounds (81), (82), and (83) are dicationic while (84) is tetra- and (85) is mono-cationic.

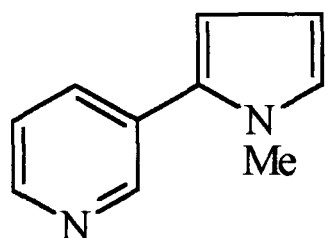
The length of the cationic side chain is also important in another way. Here a short cationic side chain is favourable since the cation binds in close proximity to the DNA phosphate backbone which positions the aromatic system favourably for intercalation.<sup>95</sup> Only the molecules which have the aromatic system polarised extensively in the direction of the side chain, so that the intercalating part constitutes a positive part of the dipole, show strong intercalative binding with DNA.<sup>96</sup>

Therefore, for intercalation to occur the polarity of the unfused rings is of primary importance. The cationic side chain of the amplifier interacts electrostatically with the anionic DNA phosphate backbone while the positively polarised aromatic system intercalates with the DNA base pairs.<sup>97</sup>

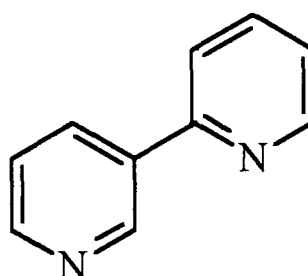
## 2.2 Chemistry of 2,6-diarylpyridines and related compounds.

The pyridine nucleus is a major components of a variety of natural products and drugs<sup>98</sup> and a very small number of substituted pyridine compounds are found in nature mostly in enzymes and alkaloids. Some are obtained by degradation of complex natural materials such as coal, shale and various alkaloids.

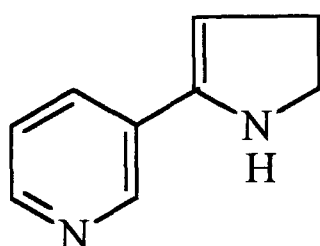
The substituted pyridines e.g. nicotyrine (86), 2,3-bipyridine (87), myosmine (88), nicotine (89) and nicotelline (90) were obtained from alkaloids by fractional extraction.<sup>99</sup>



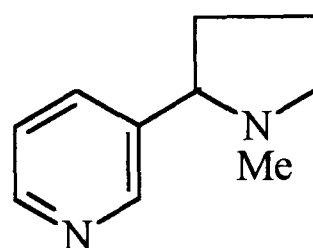
Nicotyrine (86)



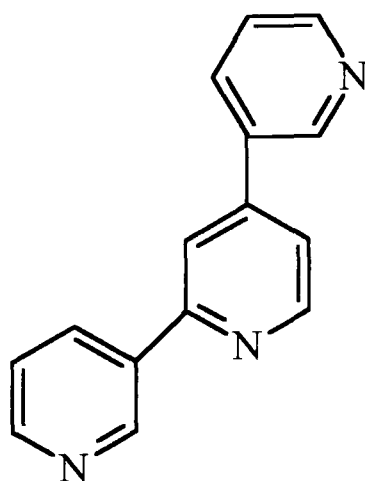
2,3-Bipyridine (87)



Myosmine (88)



Nicotine (89)

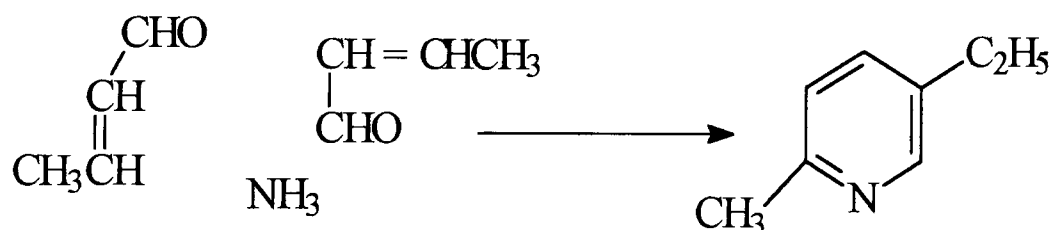


Nicotelline (90)

There are few methods reported in literature for the synthesis of 2,6-diarylpyridines. These methods generally involve complex reaction processes and result in low yields of the product. However, the condensation of aldehydes, ketones,  $\alpha,\beta$ -unsaturated carbonyl compounds or various derivatives of such compounds with ammonia or its derivatives to form substituted pyridines is the one of the oldest organic reactions.<sup>100</sup>

This reaction was studied extensively by Chichibabin and his co-workers<sup>101</sup> and can be regarded as an aldol condensation, generally in conjunction with a Michael type reaction and ring closures involving ammonia.

Two general methods were used for the preparation of substituted pyridines. The first method required the reaction of carbonyl compounds with an aldehyde-ammonia in a sealed tube. The second method involved the passing of ammonia and the carbonyl compound together in the vapour phase over a catalyst such as alumina. However, these methods gave low yields of pyridines<sup>102</sup> (Scheme 36).



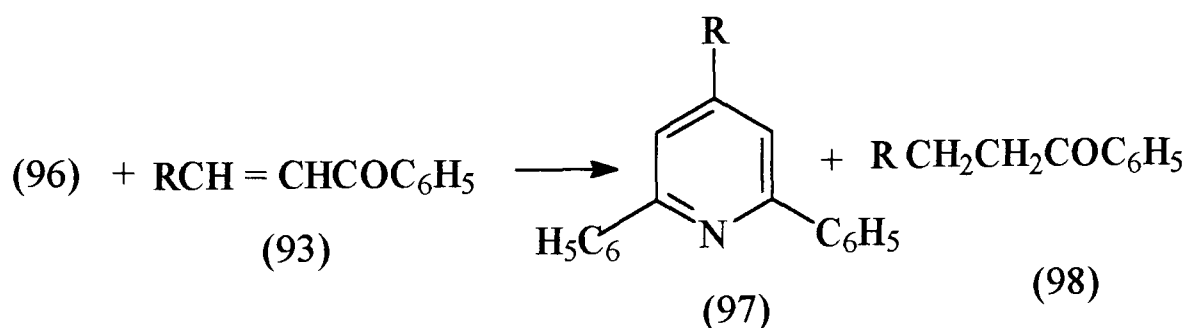
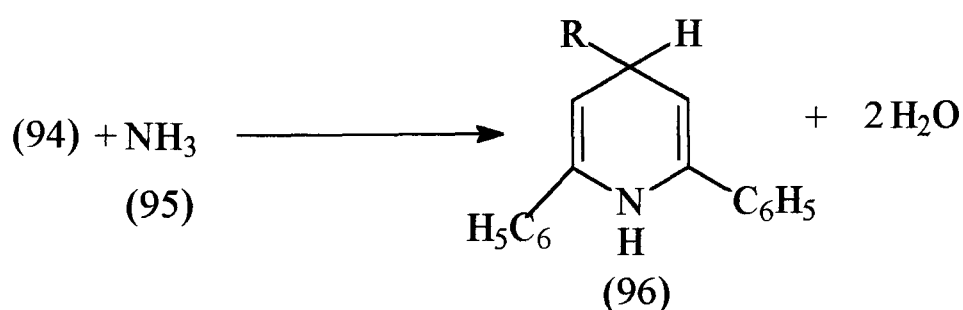
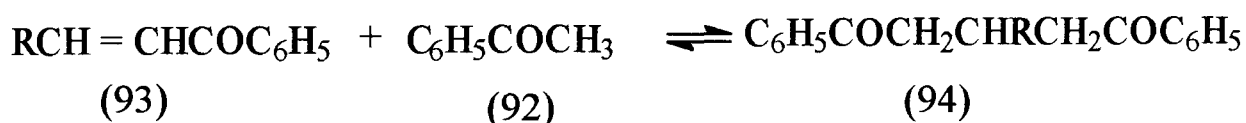
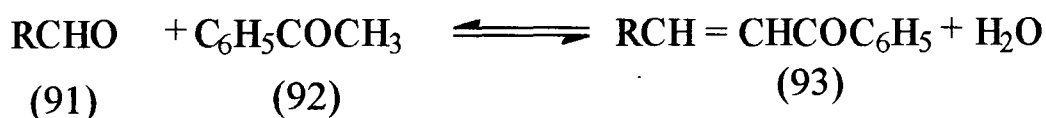
Scheme 36

Frank and Seven<sup>102</sup> reported the yield is not higher than 20%, and high temperature, sealed tubes or vapour phase reaction over heated catalysts were necessary. While Frank and Seven modified the synthesis by employing aqueous ammonia and catalytic amounts of ammonium acetate the reaction still required the use of a steel autoclave at a temperature of 250 °C with pressures up to 1450 p.s.i.

However, because of the formation of mixtures of pyridines and of various byproducts, the method has had a poor reputation for synthetic purposes.<sup>103</sup>

Weiss improved the procedure by causing the reaction of aromatic aldehydes with aryl methyl ketones in glacial acetic acid in the presence of ammonium acetate. He found that the carbon atom of the formyl group occurs at the 4-position of the pyridine with methyl group carbon atoms occurring at position 3 and 5 in the pyridine nucleus.<sup>101</sup>

The reaction is thought to proceed by initial condensation of the aldehyde (91) with an aryl methyl ketone, e.g. acetophenone (92) to form an aldol condensation product (93) and this is followed by a Michael type addition reaction to form a 1,5-diketone (94). (Scheme 37).



Scheme 37



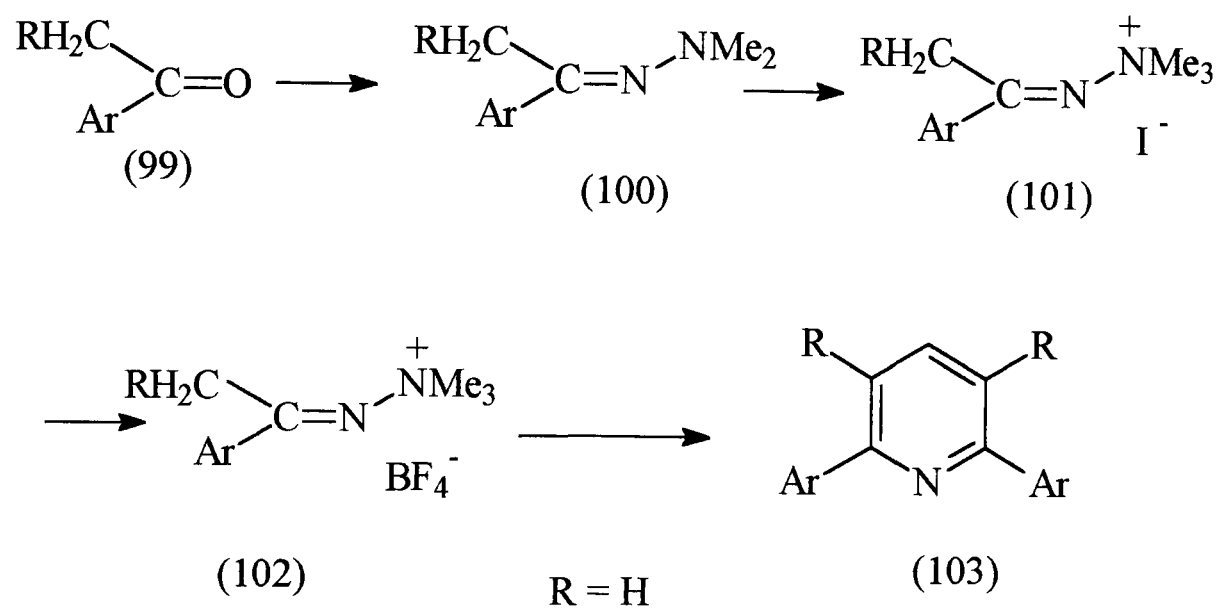
The diketone then condenses with ammonia (95) to form a 1,4-dihydropyridine (96) which, in turn is dehydrogenated to a pyridine (97) (Scheme 37). The aldol and Michael reaction steps are reversible. However, the yield from these reactions is very low.

Another route to the difficultly accessible 2,6-diphenylpyridines and fused ring pyridines is by pyrolysis of  $\alpha$ -methylene ketone *N,N,N*-trimethylhydrazonium fluoroborates. This has been reported to be the best method for the synthesis of 2,6-diarylpyridines.<sup>104</sup>

In this process the ketone (99) reacts directly with anhydrous *N,N*-dimethylhydrazine to give excellent yields of the corresponding *N,N*-dimethylhydrazone (100).<sup>105</sup> Treatment of (100) with alcoholic methyl iodide produces the *N,N,N*-trimethylhydrazonium iodide (101) which can be easily converted into the corresponding *N,N,N*-trimethylhydrazonium fluoroborate (102).<sup>106</sup>

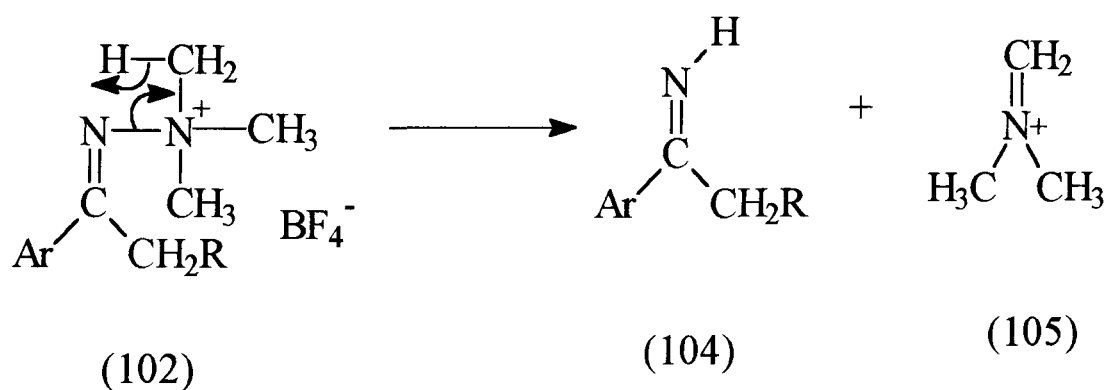
Pyrolysis of *N,N,N*-trimethylhydrazonium fluoroborate (102) at 200°C under a slow stream of nitrogen affords a substituted pyridine (103) (Scheme 38). This method has the disadvantage of providing only symmetrically substituted pyridines and usually in low yield.

The pyrolysis conditions for most fluoroborates can be varied considerably with little effects on the overall yield of the pyridine products.



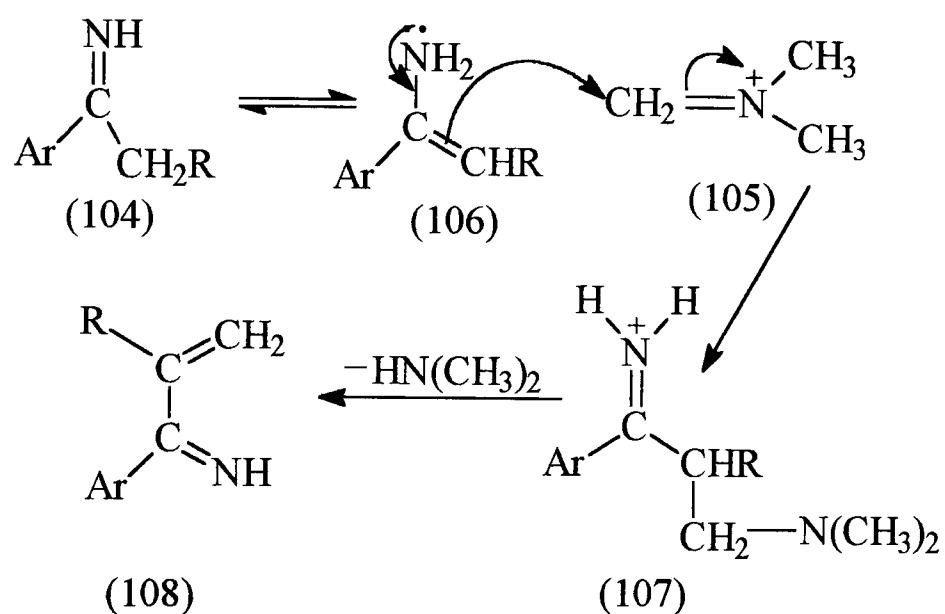
Scheme 38

The suggested mechanism<sup>107</sup> (Scheme 39) for the formation of (103) is that the *N,N,N*-trimethylhydrazone cation (102) undergoes simple N-N cleavage as the most likely thermal process, independent of interaction with the anion, to produce the imine (104) and the dimethylmethyleneammonium cation (105) by migration of hydrogen.



Scheme 39

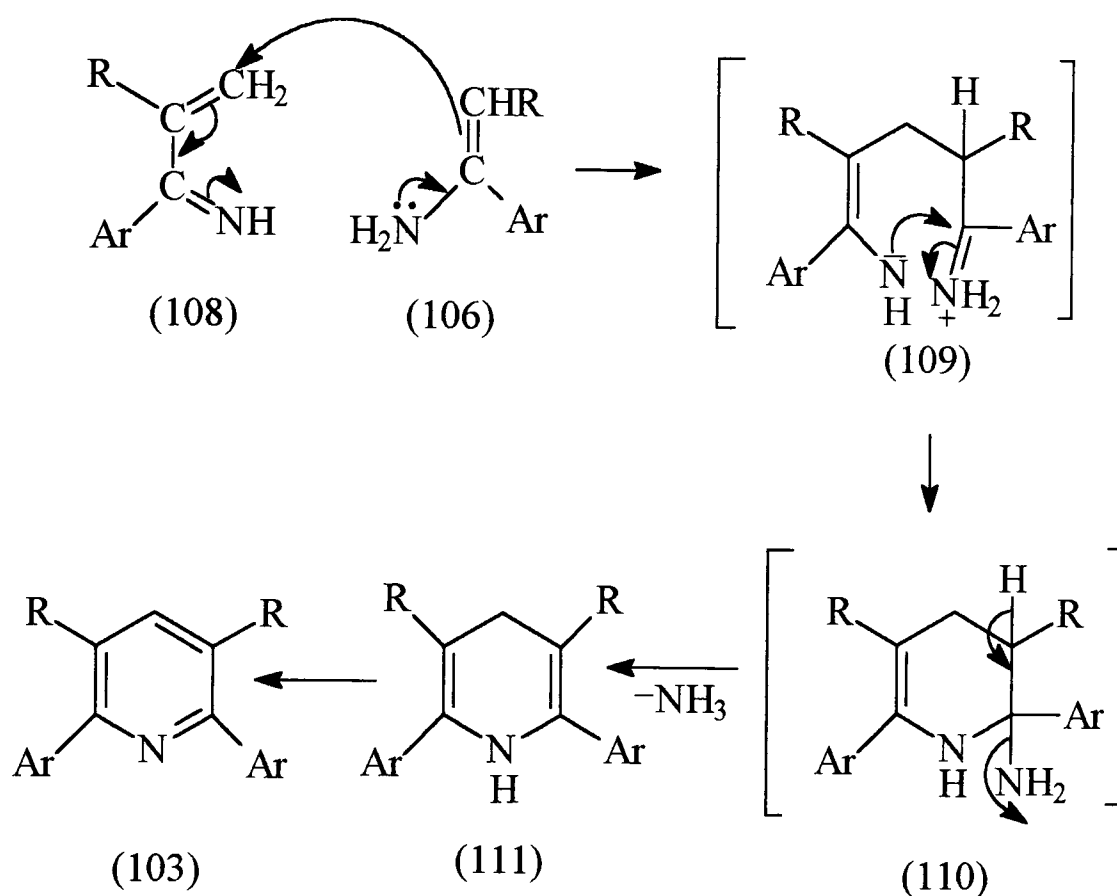
The imine (104) is sufficiently stable to undergo subsequent tautomerism and reacts as the enamine. Thus, tautomerism of (104) to  $\alpha$ -aminostyrene (106) followed by electrophilic alkylation of the resulting enamine with the dimethylmethyleneammonium cation (Mannich reagent) (105) gives  $\beta$ -dimethylaminopropiophenone iminium ion (107) (Scheme 40).



Scheme 40

Under pyrolysis conditions the iminium ion (107) loses dimethylamine to give the diene (108) which is one of the reactive intermediates (Scheme 40).

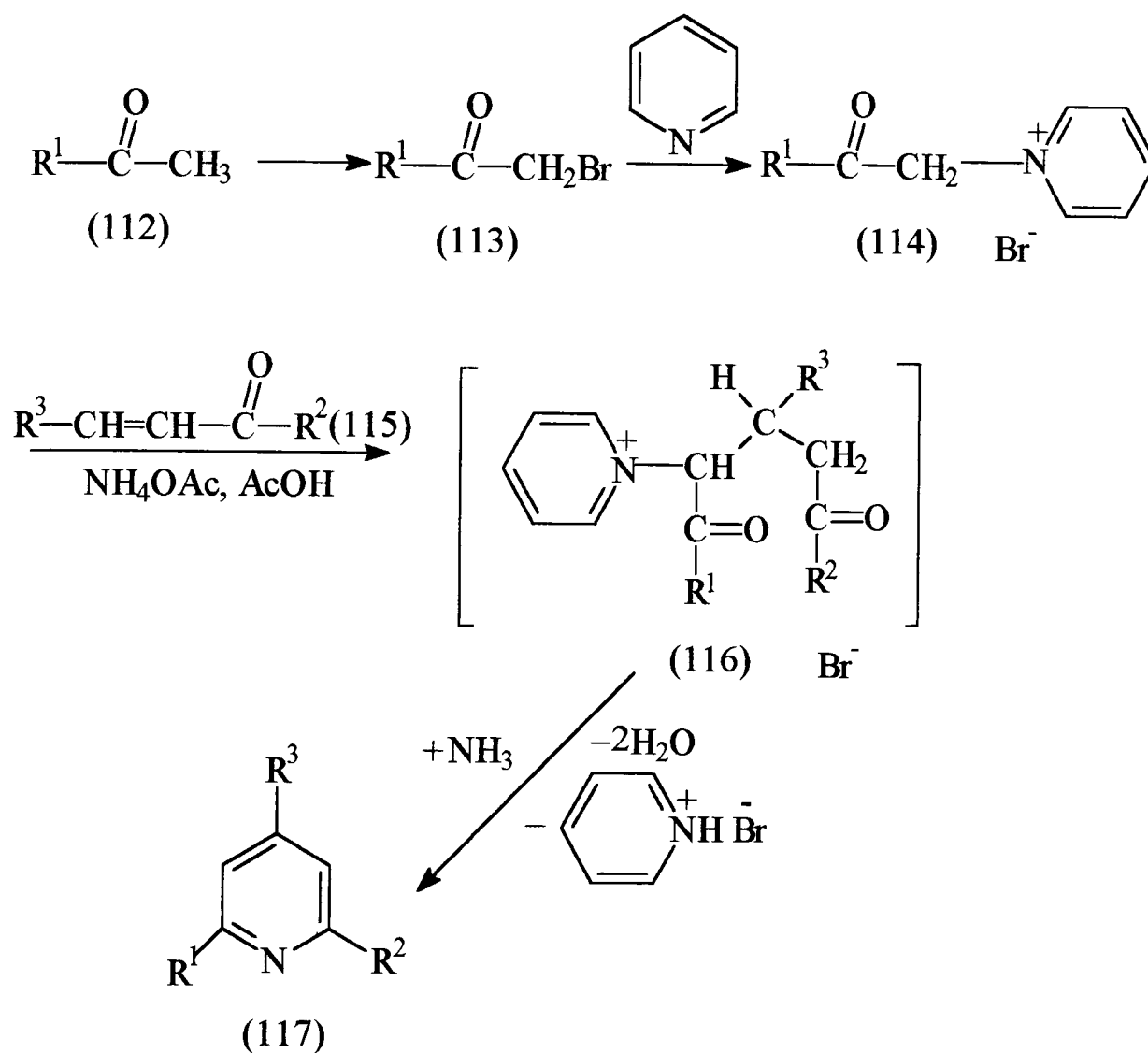
After the formation of these fragments, the reaction of the electron rich  $\beta$ -carbon of the enamine (106) with (108) by a Michael addition gives the intermediate (109) which, after elimination of ammonia gives the dihydropyridine (111). Aromatization of the pyridine nucleus can occur by transfer of hydrogen to molecules with isolated double bonds<sup>108</sup> or by loss of molecular hydrogen<sup>109</sup> (Scheme 41).



Scheme 41

Some of the best methods for the preparation of diarylpyridines were reported by Krohnke. In 1961 he described<sup>110</sup> a route to some substituted pyridines. In this method the methyl ketone (112) is brominated to give a bromomethyl ketone (113) which reacts with anhydrous pyridine to produce the pyridinium salt (114). The pyridinium salt then can be treated with ammonium acetate in glacial acetic acid, or with an unsaturated ketone (115) in water, or with a Mannich base<sup>111</sup> to give the 1,5-diketone (116) intermediate via Michael addition reaction.

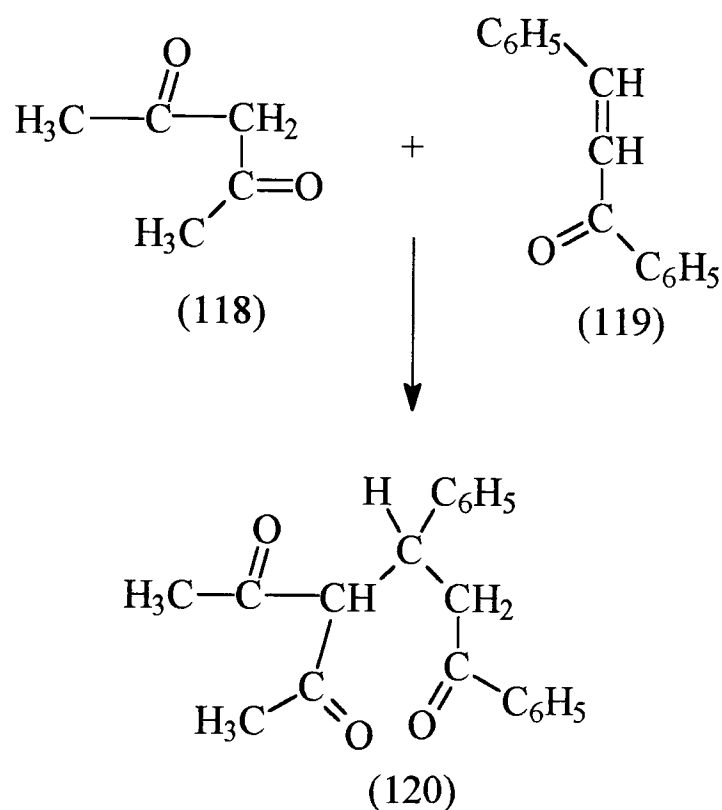
The 1,5-diketone (116) which is rarely isolated, undergoes ring closure on treatment with ammonium acetate to produce substituted pyridines (117) (Scheme 42) which may be 2,6-diarylpyridines.



Scheme 42

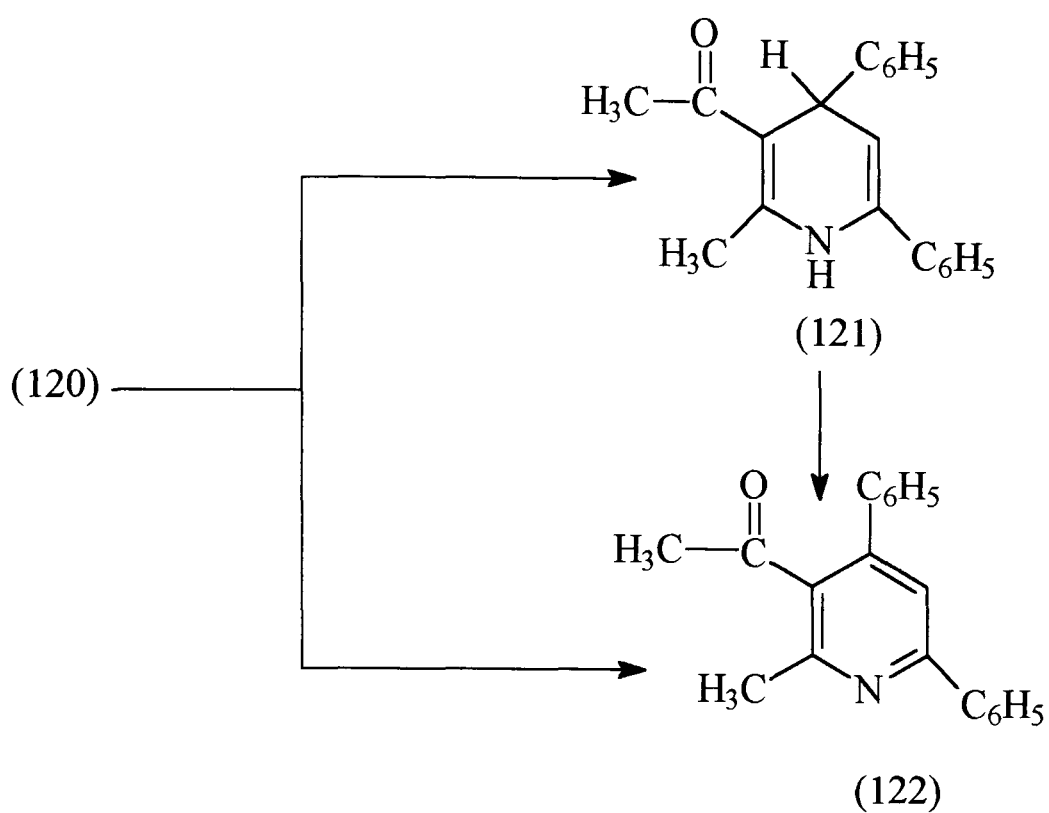
This method has some advantages over the previously described routes. The reaction proceeds at reflux temperature and the yield of 2,6-diarylpyridine is generally greater than can be obtained by the previously described routes. Secondly the synthesis of bis-, ter- and up to septa-pyridines can be achieved starting from the pyridinium salts and unsaturated ketone (or Mannich bases) under mild conditions.

Krohnke (1968) has shown 1,3-dicarbonyl compounds may be used instead of pyridinium salts for the synthesis of pyridines. When acetylacetone (118) reacts with 1,3-diphenyl-1-oxoprop-2-ene (119) in ethanol containing sodium hydroxide to form the 1,5-diketone (120) and in this case the (120) can be isolated.<sup>112</sup> (Scheme 43)



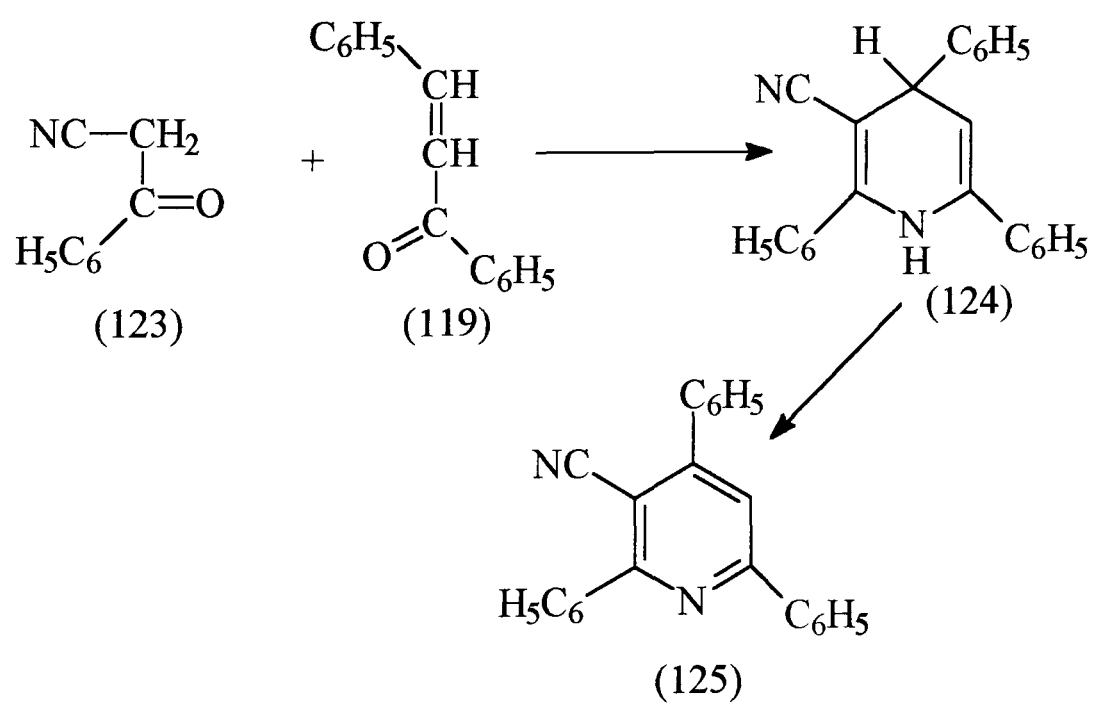
Scheme 43

Treatment of (120) with ammonium acetate in methanol gives the 1,4-dihydropyridine (121),<sup>113</sup> which can be dehydrogenated by the treatment with sodium nitrite in glacial acetic acid to give pyridine (122). The substituted pyridine (122) can also be obtained directly from (120) by treatment with ammonium acetate and ferric chloride in glacial acetic acid (Scheme 44).



Scheme 44

An alternative to 1,3-diketone (118) an aryl cyanomethyl ketone (123) can also be used to form dihydropyridine (124) with ammonium acetate in glacial acetic acid. The (124) was dehydrogenated by the treatment with sodium nitrite in glacial acetic acid to produce 2,4,6-triphenyl-5-cyanopyridine (125) (Scheme 45).<sup>114</sup>



Scheme 45





The trifluoromethyl-substituted  $\beta$ -diketones (129) can be prepared by condensation of ethyl trifluoroacetate with methyl ketones in the presence of potassium t-butoxide in good yield.<sup>116</sup> Trifluoromethyl-substituted  $\beta$ -diketones (129) are present as keto-enol tautomers (129 and 130) in solution. (Fig 10)

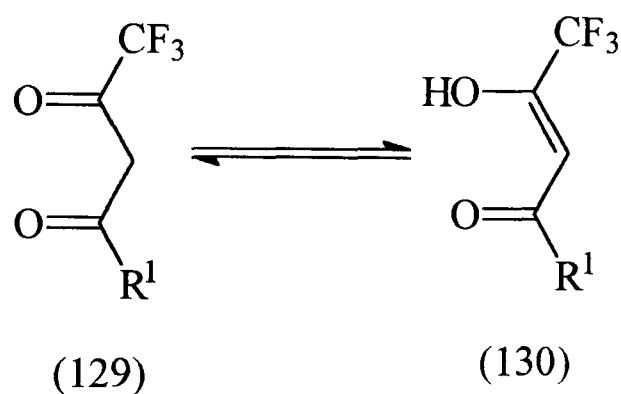
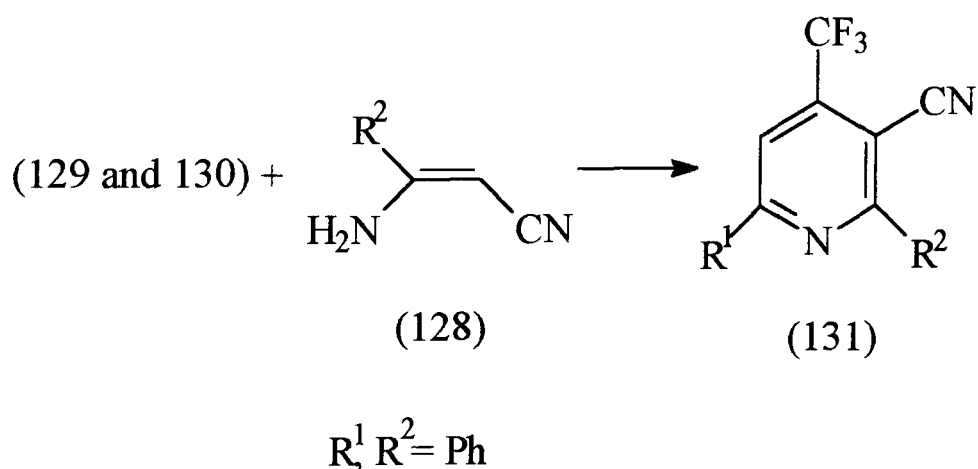


Fig 10: Keto-enol tautomers of trifluoromethyl-substituted  $\beta$ -diketone

Reaction of trifluoromethyl-substituted  $\beta$ -diketones (129) and  $\beta$ -amino- $\beta$ -aryl acrylonitrile (128) in ethanol at reflux for 8 hours gave the 2,6-diaryl-3-cyano-4-(trifluoromethyl)pyridine (131) in 53% yield (Scheme 47).



Scheme 47

Use of 1-propanol as a solvent produced an increase in the amount of by-products and reduced the yield of (131) to 48%. To obtain a high yield of the product it was crucial to use two equivalents of  $\beta$ -amino- $\beta$ -aryl acrylonitrile (128) for a prolonged reaction time (24 hour).<sup>115</sup>

If the compound (129) bears a 4-methoxyphenyl group adjacent to the carbonyl carbon the product is the corresponding pyridine in low yield. However, the nitrile compound (128) having a 4-methoxyphenyl group at  $\beta$ -carbon afforded high yields of the pyridine product. On the basis of these results it was concluded that for the high yields of the substituted pyridines, it is necessary to use  $\beta$ -diketones having an electron-withdrawing group and also an enaminonitrile containing an electron-releasing group.

## 2.3 RESULTS AND DISCUSSION.

The aim of present work was to synthesize a DNA binder which was to be incorporated into an analogue of bleomycin A<sub>2</sub>. Previous studies have shown that in the bleomycin molecule the presence of a bithiazole nucleus, which contains a cationic substituent, is responsible for the association with DNA.<sup>117,118</sup> Several polyheteroaromatic compounds with flexible substituents containing cationic groups have been prepared and their binding with DNA studied. Also their effects on the bleomycin mediated degradation of double strand DNA have been investigated.<sup>119</sup>

It has been shown<sup>120</sup> that unfused polycyclic systems are better amplifiers of bleomycin cytotoxicity than fused classical intercalators. The effective unfused aromatic compounds have a conformationally flexible side chain and a cationic region e.g. (81), (82) and (83). This class of compound shows promise for development as amplifiers of the biological effects of bleomycin type drugs.<sup>121,122,123</sup>

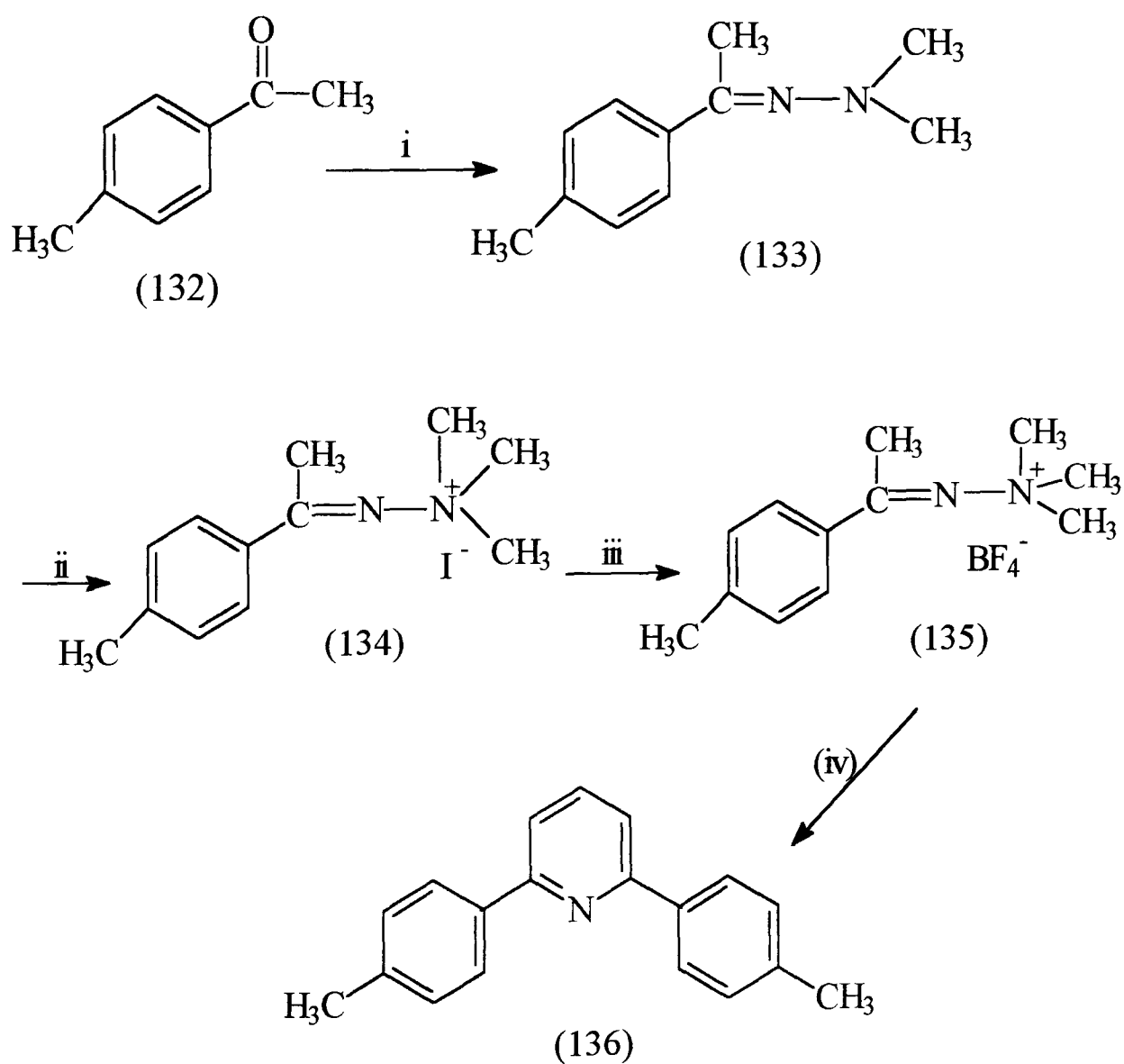
Therefore, the intention in the present work was to prepare and characterise some novel unfused tricyclic molecules which contain a terminal and potentially cationic substituent, which can bind with DNA.

### 2.3.1 2,6-Bis(4-methylphenyl)pyridine (136).

The first route attempted for the preparation of 2,6-bis(4-methylphenyl)pyridine (136) was by pyrolysis of a ketone *N,N,N*-trimethylhydrazonium tetrafluoroborate, (see Introduction for a general discussion of the reaction). The key step in the synthesis of 2,6-bis(4-methylphenyl)pyridine was the conversion of 4-methylacetophenone (132) into 4-methyl acetophenone *N,N*-dimethylhydrazone (133) by reaction with anhydrous *N,N*-dimethylhydrazine in glacial acetic acid and absolute ethanol. After the usual work-up procedure, a yellow oil was obtained which was purified by distillation to give 4-methylacetophenone *N,N*-dimethylhydrazone in 80% yield.

The  $^1\text{H}$  NMR spectrum of (133) showed a singlet at 2.35 ppm caused by the two C-methyl groups, a singlet at 2.58 ppm was due to two *N*-methyl groups and two doublets at 7.61 ppm and 7.64 ppm were due to the aromatic protons.

When 4-methylacetophenone *N,N*-dimethylhydrazone was treated with methyl iodide the product was 4-methylacetophenone *N,N,N*-trimethylhydrazonium iodide (134) (Scheme 48).



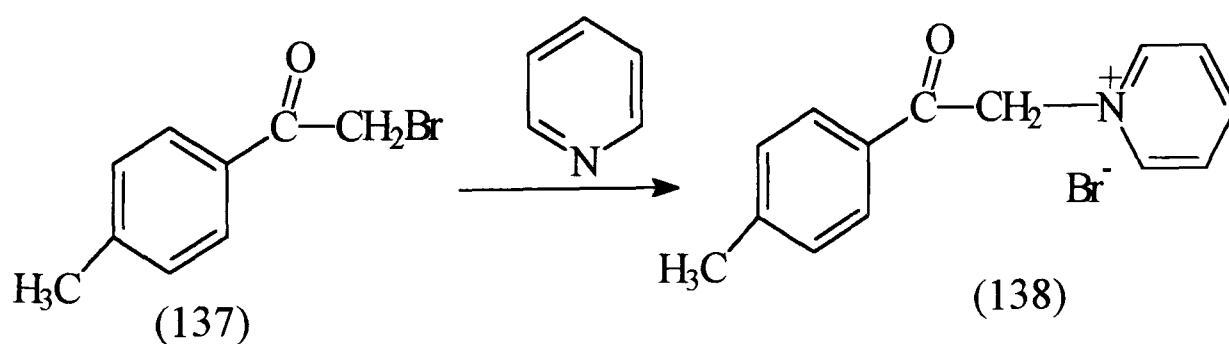
Reagent: (i)  $\text{Me}_2\text{NNH}_2$ , AcOH, EtOH; (ii) MeI;  
 (iii)  $\text{NaBF}_4$ ; (iv) Isopropylbenzene.

Scheme 48

A hot aqueous solution of (134) was treated with aqueous sodium fluoroborate to give a precipitate of the fluoroborate (135). When (135) was slowly heated in isopropyl- benzene (cumene), the exothermic reaction caused the solution to reflux. The crude product was obtained as a solid from the reaction mixture and purified to give a disappointingly low yield (17%) of 2,6-bis(4-methylphenyl)pyridine (136).

The two methyl groups of (136) gave rise to a singlet at 2.41 ppm in the  $^1\text{H}$  NMR spectrum, while the four benzene ring protons at positions of 3- and 5- gave multiplets at 7.41 ppm. The 3- and 5-protons of the pyridine nucleus gave multiplets at 7.62 ppm and a triplet at 7.83 ppm was caused by the 4-proton of pyridine ring. The resonances at 8.10 ppm were due to the four 2- and 6-protons of the carbocyclic systems. The mass spectrum of (136) showed the expected molecular ion peak at 259 daltons.

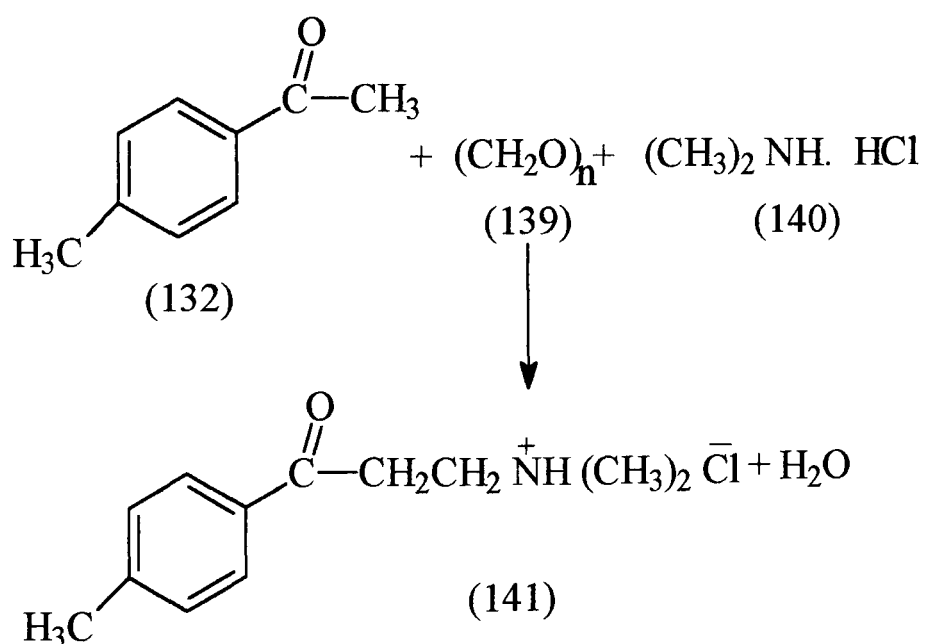
An alternative approach to 2,6-diarylpyridine was reported by Krohnke<sup>110</sup> (see introduction p.77). This route was investigated in an attempt to increase the yield of (136). The initial step in the synthesis of 2,6-bis(4-methyl phenyl)pyridine by this method was the conversion of 4-methylphenacyl bromide (137) into 1-(4-methylphenacyl) pyridinium bromide (138) (Scheme 49).



Scheme 49

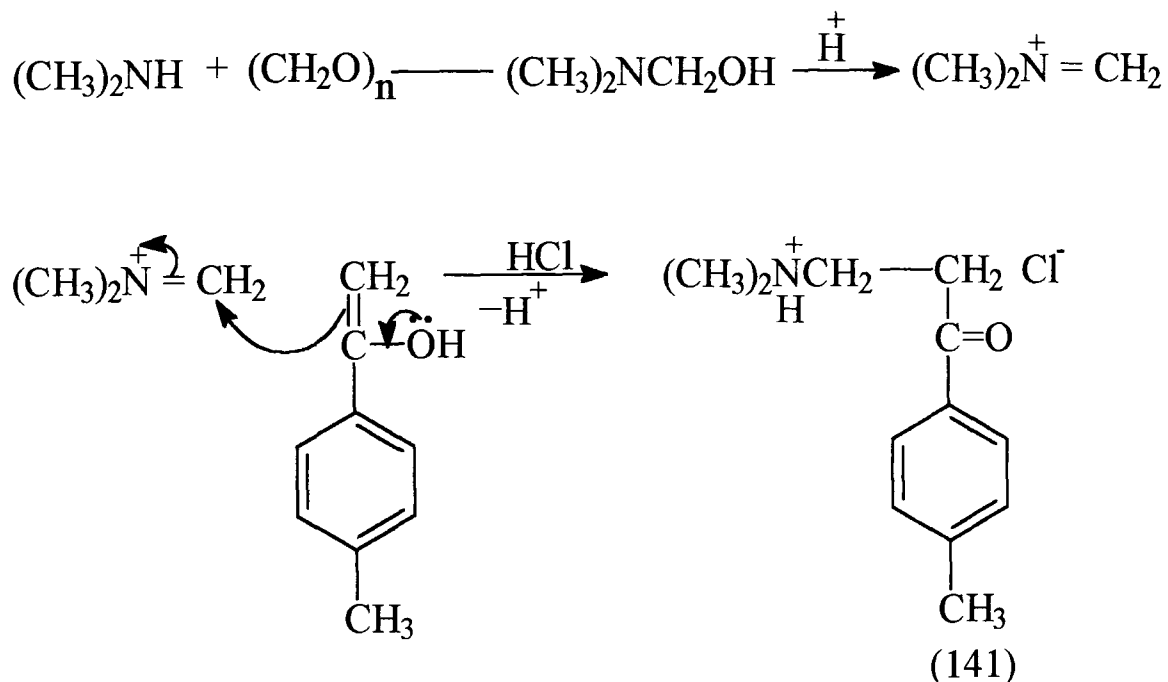
The IR spectrum of 1-(4-methylphenacyl)pyridinium bromide (138) showed the expected carbonyl stretching absorption at  $1688\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR spectrum showed singlets at 2.42 ppm and 6.47 ppm caused by the methyl and methylene groups respectively. The protons on the aromatic nucleus of the tolyl group gave rise to two doublets at 7.41 ppm ( $J = 7.4\text{ Hz}$ ) and 7.92 ppm ( $J = 7.4\text{ Hz}$ ). The 3- and 5-protons of the pyridine ring gave a triplet at 8.27 ppm, a multiplet at 8.73 was due to the 4-proton, and the 2- and 6-protons caused a triplet at 9.01 ppm.

1-(4-Methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) was prepared by the Mannich reaction.<sup>124</sup> Heating a mixture of 4-methylacetophenone (132), paraformaldehyde (139) and dimethylamine hydrochloride (140) in absolute ethanol gave the tertiary amine hydrochloride (141) in good yield (Scheme 50).



Scheme 50

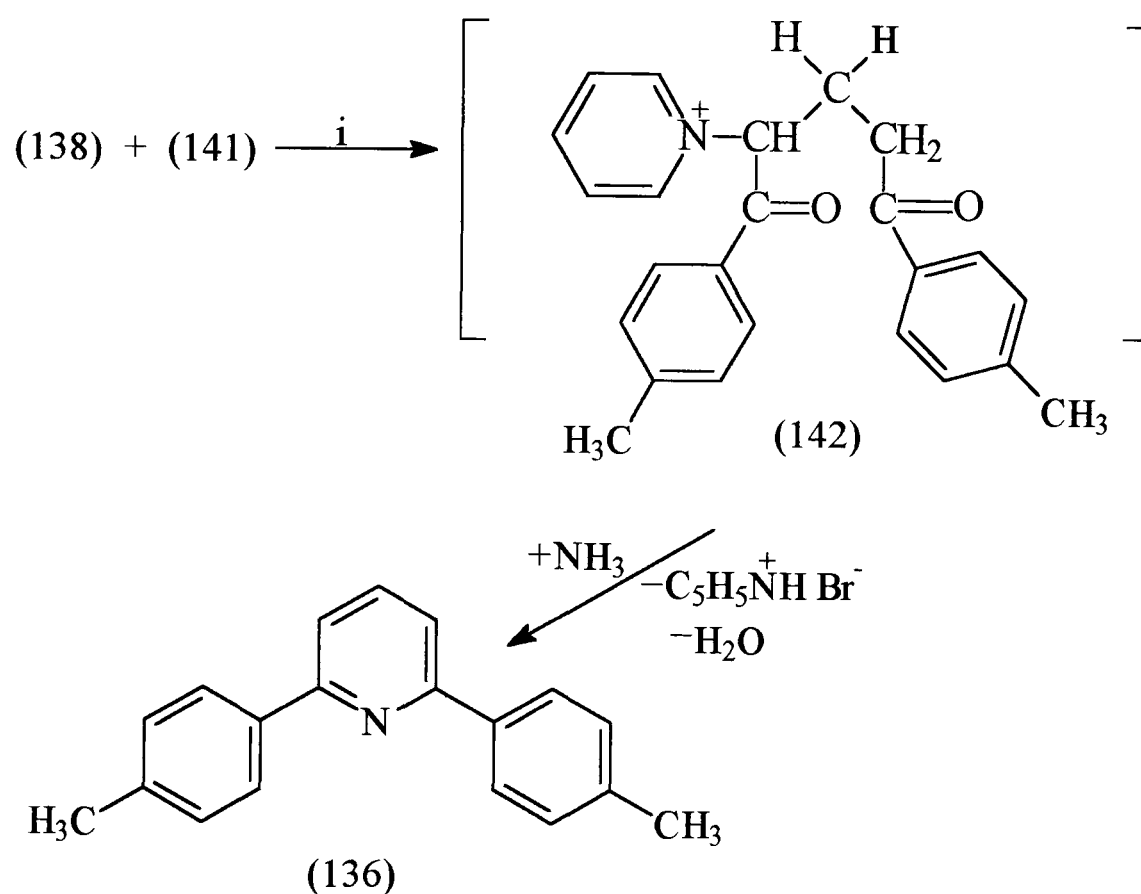
The mechanism of this reaction may involve the intermediate formation of dimethylaminomethanol which, under the influence of acid was converted into a reactive methylene ammonium salt. Reaction of the ammonium salt with 4-methylacetophenone gave 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (Scheme 51).



Scheme 51

The  $^1\text{H}$  NMR spectrum of (141) showed a singlet at 2.43 ppm due to the  $\text{C}-\text{CH}_3$  group, a singlet due to resonance by  $\text{N}-(\text{CH}_3)_2$  at 2.87 ppm and two triplets at 3.54 and 3.73 ppm due to the methylene protons. Two doublets at 7.26 and 7.87 ppm were caused by four aromatic protons and a singlet at 13.01 ppm was due to the NH group. IR spectrum of 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) showed a peak at  $1674\text{ cm}^{-1}$  due to the carbonyl group.

When compounds (138) and (141) were refluxed with ammonium acetate in glacial acetic acid a Michael addition reaction occurred to give (142) which then underwent ring closure on treatment with ammonium acetate to give 2,6-bis(4-methylphenyl)pyridine (136) in 35% yield (Scheme 52).



Reagents: (i) ammonium acetate, glacial acetic acid.

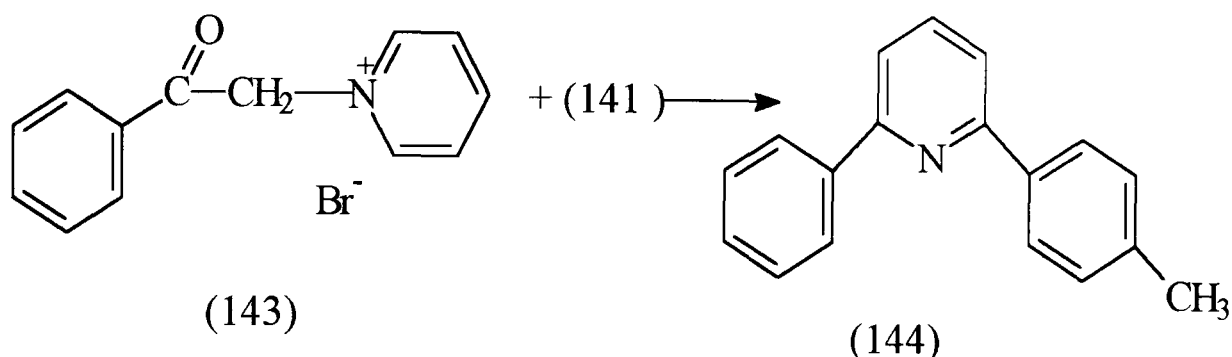
Scheme 52

Spectral data for (136) were in good agreement with its structure and the yield was improved to 67% by using methanol as a solvent instead of glacial acetic acid.



### 2.3.2 2-Phenyl-6-(4-tolyl)pyridine (144).

The 2-phenyl-6-(4-tolyl)pyridine (144) was synthesised according to (Scheme 53). The precursor (phenylacetylpyridinium bromide) (143) was prepared by treating phenacyl bromide with dry pyridine.

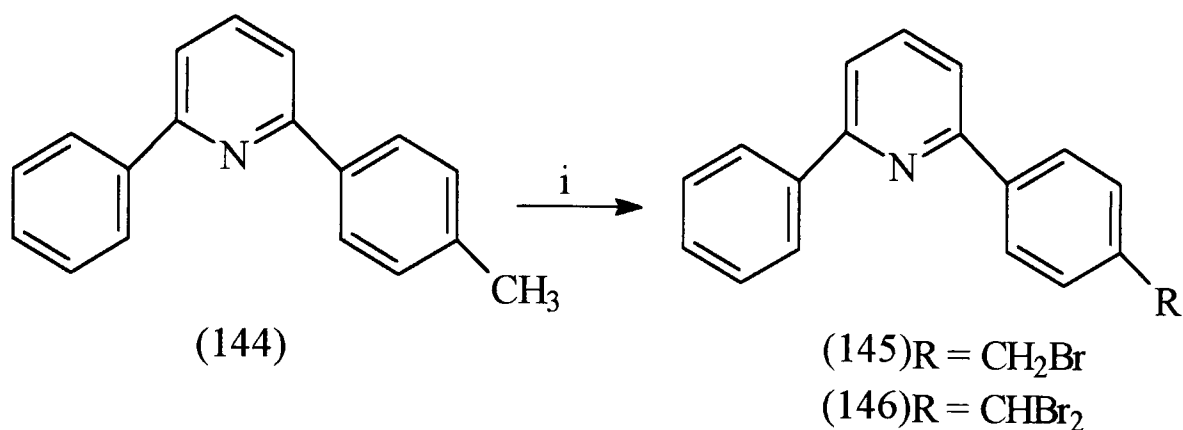


Scheme 53

Compounds (143) and 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) were treated with ammonium acetate in methanol to produce 2-phenyl-6-(4-tolyl)pyridine (144) in 67% yield.

The  $^1\text{H}$  NMR spectrum of 2-phenyl-6-(4-tolyl)pyridine (144) showed a singlet at 2.41 ppm caused by the C-CH<sub>3</sub> group, a doublet at 7.29 ppm due to 3- and 5-protons of the tolyl nucleus and multiplets at 7.42-7.49 ppm due to the three aromatic protons. The 3- and 5-protons of the pyridine nucleus gave rise to a doublet at 7.66 ppm, a triplet at 7.79 ppm was caused by the 4-proton of the pyridine ring and two doublets at 8.05 ppm and 8.15 ppm were due to four protons adjacent to pyridine on the carbocyclic systems.

Bromination of 2-phenyl-6-(4-tolyl)pyridine (144) with *N*-bromosuccinimide (NBS) in carbon tetrachloride (CCl<sub>4</sub>) using benzoyl peroxide as an initiator gave a complex mixture from which 2-([4-bromomethyl]phenyl)-6-phenylpyridine (145) was isolated in 60% yield by column chromatography (Scheme 54).



Reagents: (i) NBS, CCl<sub>4</sub>

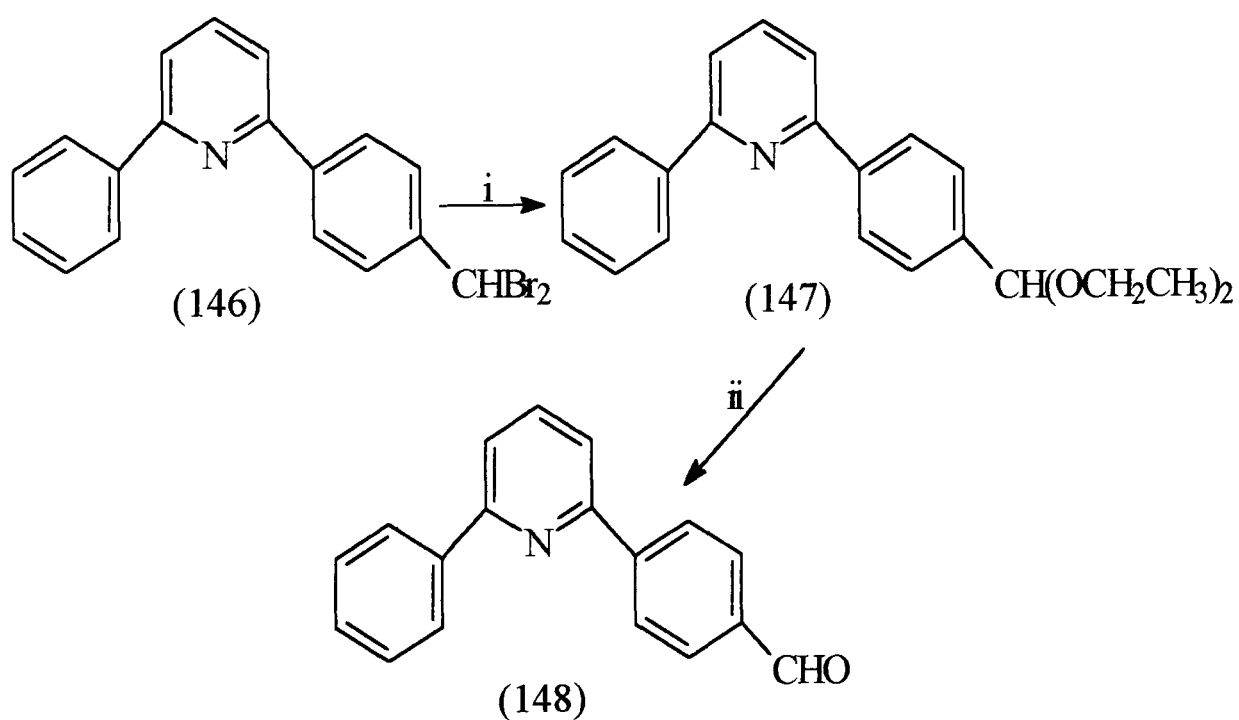
Scheme 54

2-(4-[Bromomethyl]phenyl)-6-phenylpyridine (145) was characterised by its <sup>1</sup>H NMR spectrum which had a singlet at 4.56 ppm due to the methylene group, as well as other expected peaks (see Experimental section). The mass spectrum showed the presence of molecular ions at 325 and 323 daltons in the relative abundance ratio 1:1 due to the <sup>81</sup>Br and <sup>79</sup>Br isotopes respectively.

Treatment of (145) with *n*-butylamine in tetrahydrofuran (THF) to form a secondary amine as described by Streckowski and co-workers<sup>92</sup> was unsuccessful and resulted in the recovery of the starting material. A similar result was obtained when anhydrous ethanol was used as a solvent and the reaction mixture refluxed overnight.

To overcome the problem associated with monobromomethyl derivative (145) an alternative approach was tried in which the 2-phenyl-6-(4-tolyl)pyridine was converted into 2-(4-[dibromomethylphenyl])-6-phenylpyridine (146) by using 2 molecular equivalents of *N*-bromosuccinimide (Scheme 54).

The  $^1\text{H}$  NMR spectrum of (146) showed a singlet at 6.71 ppm due to the  $\text{CHBr}_2$ . Treatment of (146) with sodium ethoxide (sodium dissolved in ethanol) in anhydrous ethanol at reflux afforded 2-(4-[diethoxymethyl]phenyl)-6-phenylpyridine (147) in 47% yield and the hydrolysis of (147) with hydrochloric acid (3M) gave a complex mixture from which 2-(4-formylphenyl)-6-phenylpyridine (148) was isolated in only 19% yield by column chromatography (Scheme 55).

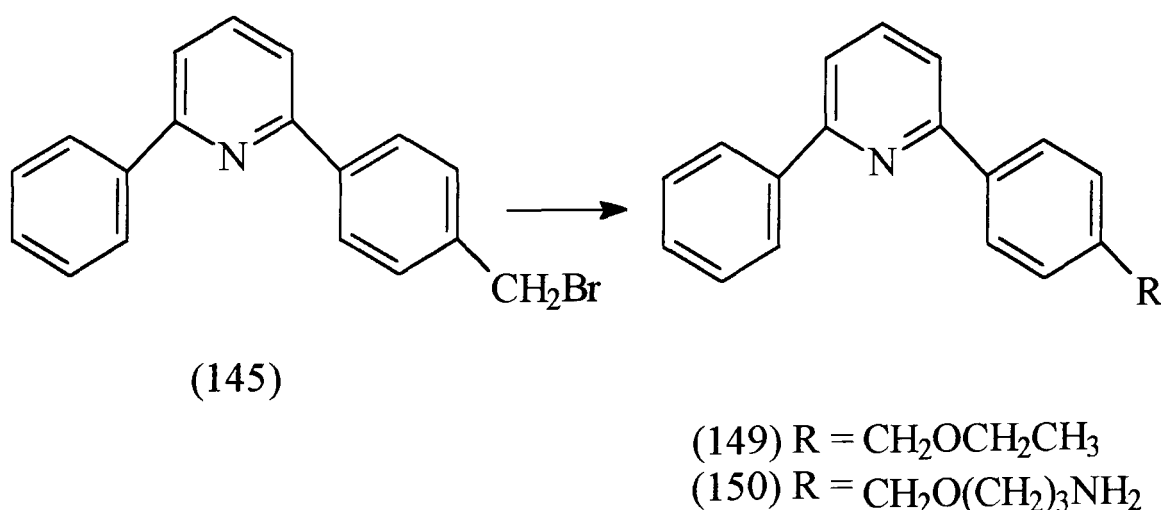


Reagents: (i) NaOEt, EtOH; (ii) aq. HCl

Scheme 55

2-(4-Formylphenyl)-6-phenylpyridine (148) was characterised by its IR spectrum which showed the presence of a C=O group by a signal at  $1704\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum showed multiplets at 7.43 ppm due to the five benzene ring protons and multiplet at 7.62 ppm caused by the 3- and 5-protons of pyridine nucleus, a triplet at 7.81 ppm caused by the 4-proton of pyridine. Four aromatic protons gave rise to a multiplet at 8.10 ppm and a singlet at 10.04 ppm due to the CHO group. The unsatisfactory yield of (148) made this route unattractive for further reactions but it showed that the nucleophilic displacement reaction did not take place under mild conditions.

The successful nucleophilic displacement of both bromine atoms in 2-(4-[di bromomethylphenyl])-6-phenylpyridine (146) encouraged us to try this method with compound (145). This gave an excellent yield of 2-(4-[ethoxymethyl]phenyl)-6-phenylpyridine (149) (Scheme 56) and the product was characterised by its  $^1\text{H}$  NMR spectrum which showed the appearance of extra triplet at 1.12 ppm caused by  $\text{CH}_3$  group and quartet due to the  $\text{CH}_2\text{OCH}_2\text{CH}_3$  at 3.42 ppm.



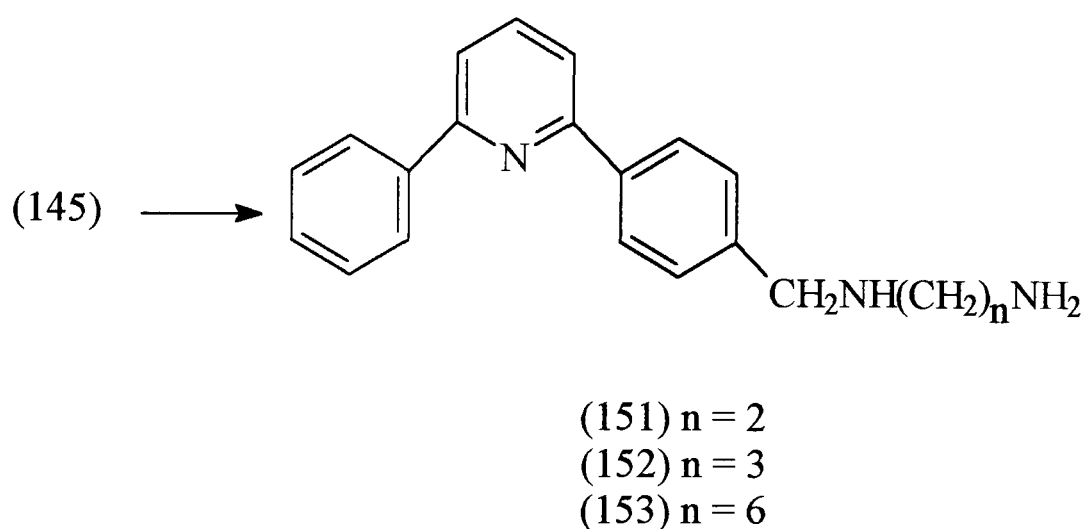
Scheme 56

These results seem to indicate that the nucleophilic displacement reaction of 2-(4-[bromomethyl]phenyl)-6-phenylpyridine (145) required more vigorous reaction conditions than were tried earlier. When 2-(4-[bromomethyl]phenyl)-6-phenylpyridine (145) was treated with 3-aminopropanol in the presence of anhydrous potassium carbonate the product was 2-(4-[3-aminopropoxymethyl] phenyl)-6-phenylpyridine (150) (Scheme 56).

Separation of this highly polar product from impurities was achieved by column chromatography by using a mixed solvent system (chloroform, methanol and ammonia). The structure of (4-[3-aminopropoxymethyl]phenyl)-6-phenylpyridine (150) was confirmed by IR spectrum which showed absorptions at 3320 and 3210  $\text{cm}^{-1}$  due to the  $\text{NH}_2$  stretching vibration. The  $^1\text{H}$  NMR spectrum exhibited two multiplets at 1.73 ppm and 2.91 ppm due to the  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$  and a triplet at 3.83 ppm was caused by  $\text{OCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ . The benzylic  $\text{CH}_2$  gave rise to a singlet at 3.86 ppm, the  $\text{NH}_2$  group gave a singlet at 2.42 ppm, which was exchangeable with  $\text{D}_2\text{O}$  and five aromatic protons gave rise to a multiplet at 7.48 ppm. A multiplet at 7.67 ppm was caused by 3- and 5-protons of pyridine nucleus, a triplet at 7.79 ppm due to the 4-proton of pyridine ring and a multiplet at 8.13 ppm was caused by four protons of carbocyclic systems.

### 2.3.3 Substitution reaction of amines with 2-(4-[bromomethyl]phenyl)-6-phenylpyridine (145).

When 2-(4-[bromomethyl]phenyl)-6-phenylpyridine (145) was separately dissolved in ethylenediamine, 1,3-diaminopropane and 1,6-diaminohexane containing anhydrous potassium carbonate and refluxed for several hours the product were 2-(4-[4-amino-2-azabutyl]phenyl)-6-phenylpyridine (151), 2-(4-[5-amino-2-azapentyl]phenyl)-6-phenylpyridine (152) and 2-(4-[8-amino-2-azaocetyl]phenyl)-6-phenylpyridine (153), respectively (Scheme 57).

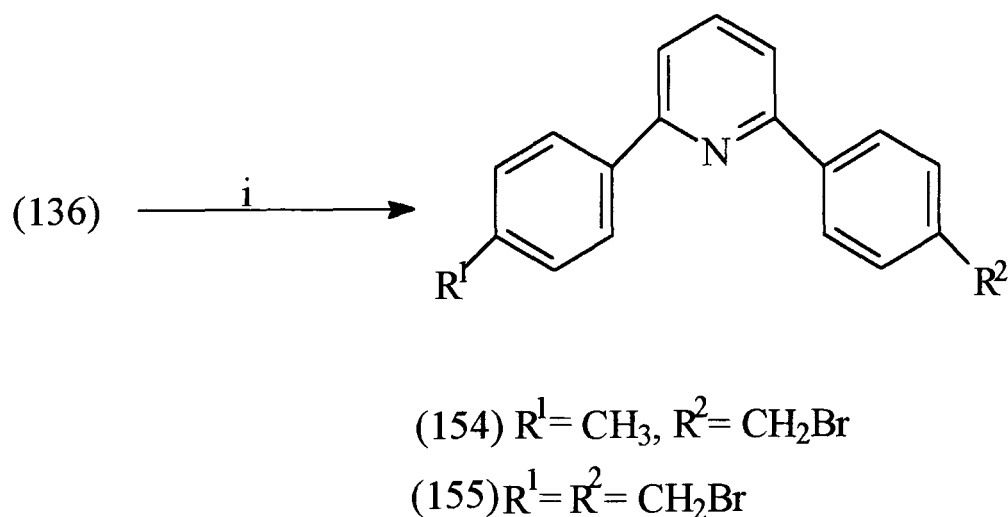


Scheme 57

The IR spectrum of (151) showed absorptions at 3420, 3330 and 3240  $\text{cm}^{-1}$  due to  $\text{NH}_2$  and  $\text{NH}$  stretching vibrations. The  $^1\text{H}$  NMR spectrum showed a broad singlet due to the  $\text{NHCH}_2\text{CH}_2\text{NH}_2$  groups at 1.66 ppm, the two adjacent methylene groups gave rise to triplets at 2.73 and 2.83 ppm and a singlet at 3.87 ppm was caused by aromatic methylene group. Accurate mass measurement of the molecular ion peak agreed with that expected for the molecular formula.

Compounds (152) and (153) were also characterised on the basis of their  $^1\text{H}$  NMR and IR spectra and accurate mass determination on the molecular ion.

Bromination of 2,6-bis(4-methylphenyl)pyridine (136) with an equimolecular quantity of the *N*-bromosuccinimide in carbon tetrachloride ( $\text{CCl}_4$ ) containing benzoyl peroxide gave a mixture of (136), 2-(4-[bromomethyl]phenyl)-6-(4-tolyl)pyridine (154) and 2,6-bis(4-[bromomethyl]phenyl)pyridine (155) (Scheme 58). Separation of the products was achieved by column chromatography and they were purified by crystallisation.

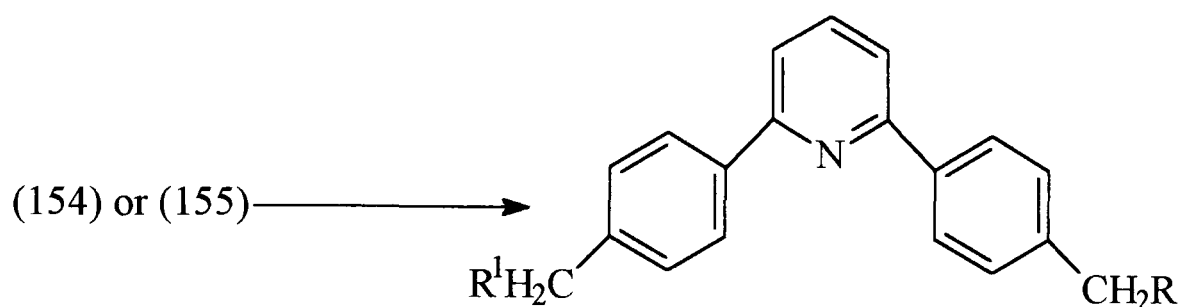


Reagents: (i) NBS,  $\text{CCl}_4$

Scheme 58

The  $^1\text{H}$  NMR spectrum of 2-(4-[bromomethyl]phenyl)-6-(4-tolyl)pyridine (154) showed two singlets at 2.42 and 4.55 ppm due to the aromatic methyl and methylene groups, two doublets at 7.31 and 7.52 ppm were caused by 2 x 3- and 5-protons of carbocyclic rings. A multiplet at 7.67 ppm was due to the 3- and 5-protons of pyridine nucleus and a triplet at 7.83 ppm was caused by the 4-proton of the pyridine ring. Four aromatic protons gave rise to two doublets at 8.05 and 8.13 ppm.

The nucleophilic displacement reactions of bromine in (154) and (155) with 1,6-aminohexane at reflux afforded 2-(4-[8-amino-2-azaocetyl]phenyl)-6-(4-methylphenyl)pyridine (156) and 2,6-bis(4-[8-amino-2-azaocetyl]phenyl)pyridine (157), respectively (Scheme 59).



(156)  $R^1 = CH_3$ ,  $R^2 = NH(CH_2)_6NH_2$

(157)  $R^1 = R^2 = NH(CH_2)_6NH_2$

(158)  $R^1 = H$ ,  $R^2 = S(CH_2)_2N(CH_3)_2$

Reagents: for (156) and (157),  $H_2N(CH_2)_6NH_2$ ;

(158),  $HS(CH_2)_2N(CH_3)_2 HCl$

Scheme 59

Compounds (156) and (157) were characterised through their IR and  $^1H$  NMR spectra and by accurate mass measurement of the molecular ion. The IR spectrum of compound (156) showed peaks at 3330 and 3210  $cm^{-1}$  attributed to the  $NH_2$  group and at 3420  $cm^{-1}$  due to the NH group. The  $^1H$  NMR spectrum of (156) showed multiplets at 1.23-1.54 ppm caused by the four adjacent methylene groups in  $NHCH_2CH_2CH_2CH_2CH_2CH_2NH_2$ , the  $NH_2$  and NH groups gave rise to a broad singlet at 1.88 ppm and there was singlet at 2.42 ppm due to the  $CH_3$  group. The terminal methylene groups in  $NHCH_2CH_2CH_2CH_2CH_2NH_2$  gave rise to a multiplet at 2.66 ppm and the benzylic  $CH_2$  group gave a singlet at 3.85 ppm. In addition, the spectrum showed the presence of all the expected aromatic protons.

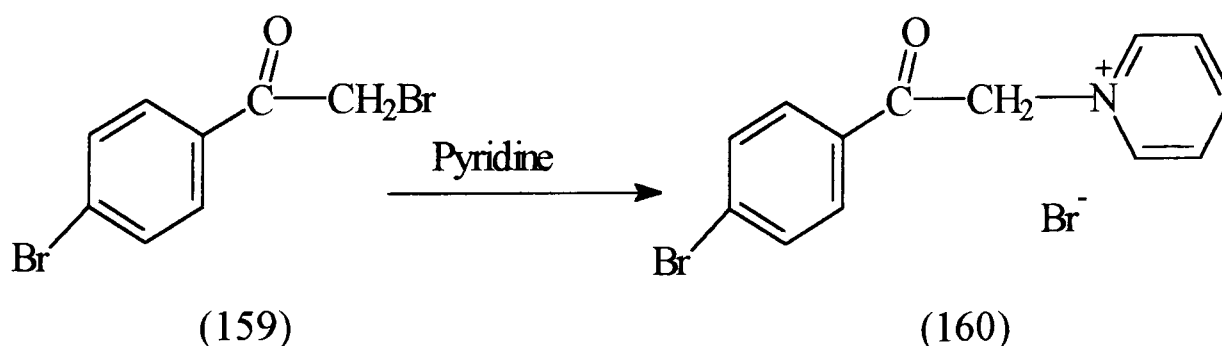


2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-methylphenyl)pyridine (158) was prepared by a reaction of (154) with 2-(dimethylamino)ethanethiol hydrochloride in ethanolic sodium ethoxide solution with added base to abstract protons from 2-(dimethyl amino)ethanethiol hydrochloride to generate a negative charge on sulfur and to scavenge the HBr liberated during the reaction (Scheme 59).

The  $^1\text{H}$  NMR spectrum of 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-methylphenyl) pyridine (158) showed a singlet at 2.21 ppm and 2.43 ppm due to the  $\text{N}(\text{CH}_3)_2$  and  $\text{CH}_3$  aryl substituent respectively. The multiplet at 2.51 ppm was due to two  $\text{CH}_2$  groups.

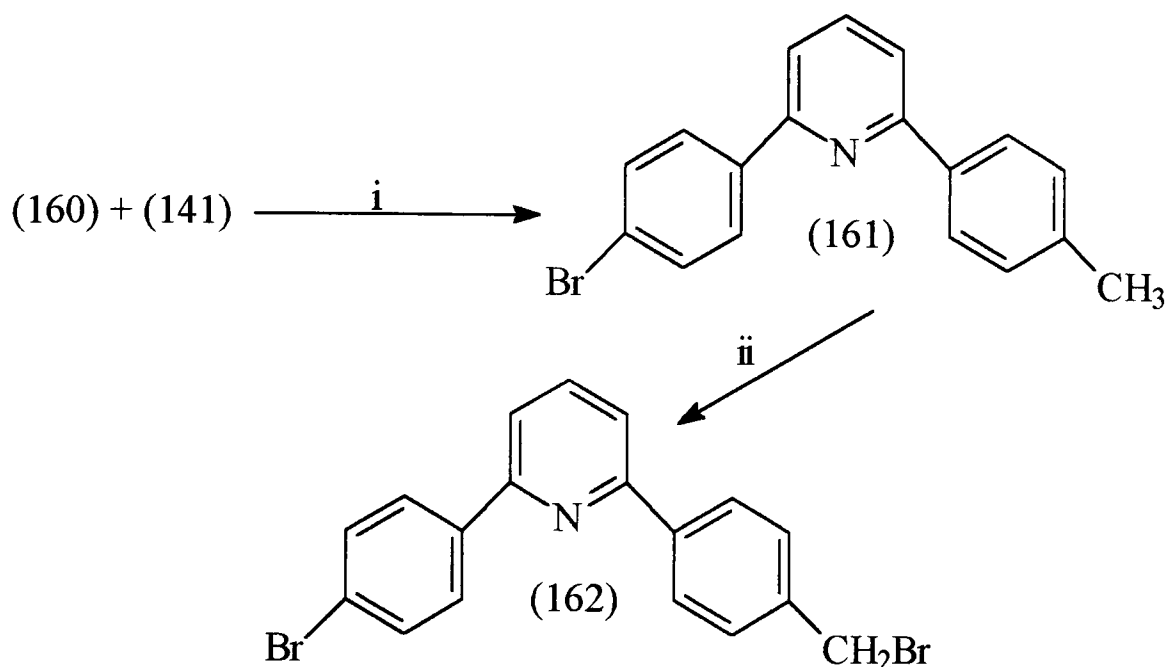
After obtaining diarylpyridines having one basic side chain it was of interest to prepare compounds having two different terminal cationic side chains that might be expected to show strong interaction with DNA.

In addition we investigated the preparation of this type of compound in a series of reactions starting with the synthesis of 1-(4-bromophenacyl)pyridinium bromide (160). The compound (160) was obtained in quantitative yield by reaction of commercially available 4-bromophenacyl bromide (159) with dry pyridine (Scheme 60).



Scheme 60

The reaction of 1-(4-bromophenacyl)pyridinium bromide (160) with 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) and cyclisation with ammonium acetate yielded 2-(4-bromophenyl)-6-(4-tolyl)pyridine (161) (Scheme 61).



Reagents: (i) ammonium acetate, methanol; (ii) NBS,  $\text{CCl}_4$

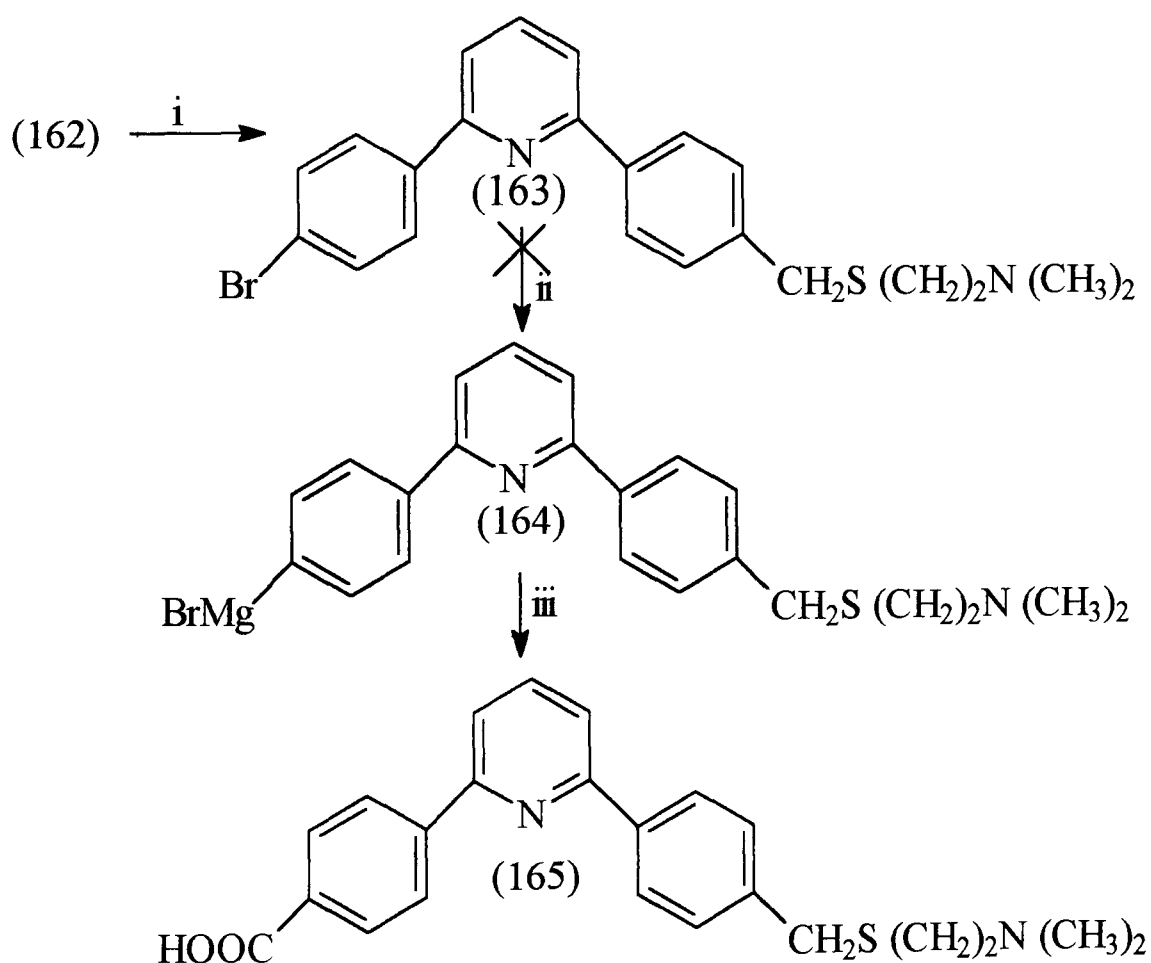
Scheme 61

The compound (161) was characterised by its  $^1\text{H}$  NMR spectrum, which showed a singlet at 2.42 ppm due to the methyl group, a doublet at 7.31 ppm was caused by the 3- and 5-protons of tolyl ring and a multiplet at 7.61 ppm was due to five protons of carbocyclic and pyridine rings. Two doublets at 8.02 and 8.08 ppm due to four aromatic protons.

The second stage involved the bromination of 2-(4-bromophenyl)-6-(4-tolyl)pyridine (161) with *N*-bromosuccinimide in the presence of benzoyl peroxide to give 2-(4-[bromo methyl]phenyl)-6-(4-bromophenyl)pyridine (162) in 50% yield (Scheme 61).

Evidence for the two bromine atoms in (162) was obtained by the appearance of three molecular ion peaks at 405, 403 and 401 daltons due to the isotopes of bromine. Apart from all the expected peaks associated with carbocyclic ring and pyridine nucleus, the  $^1\text{H}$  NMR spectrum showed a singlet at 4.55 ppm due to the bromomethyl group.

The nucleophilic displacement reaction of the alkyl bromide from (162) was carried out with 2-(dimethylamino)ethanethiol hydrochloride in the presence of sodium ethoxide to give 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-bromophenyl)pyridine (163) (Scheme 62), which was purified by column chromatography.



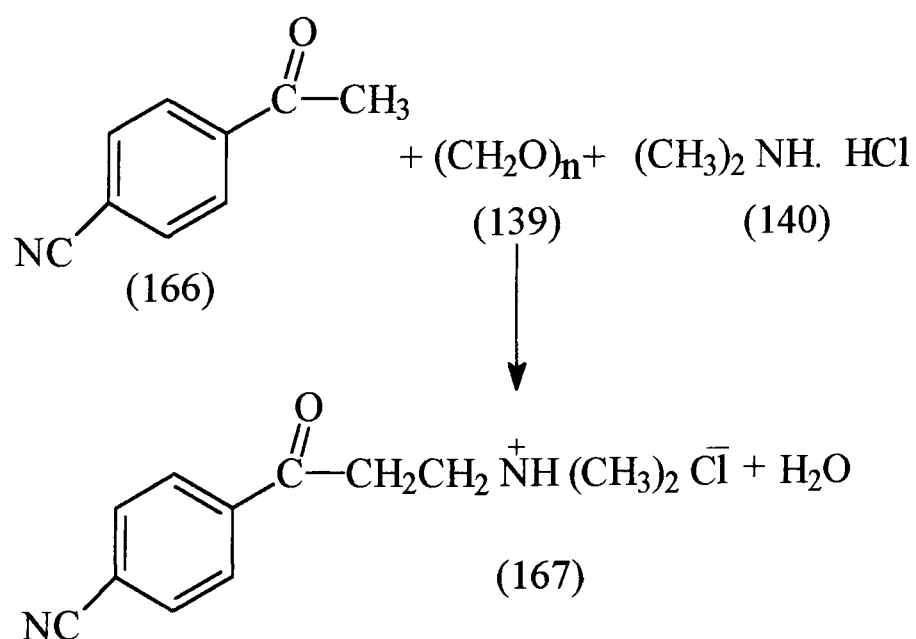
Reagents: (i) NaOEt, HS(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>; (iii) Mg, Et<sub>2</sub>O

Scheme 62

The mass spectrum of (163) showed the presence of molecular ions at 428 and 426 daltons in the relative abundance ratio 1:1 due to the  $^{81}\text{Br}$  and  $^{79}\text{Br}$  isotopes respectively. The  $^1\text{H}$  NMR spectrum showed all expected peaks in the aromatic region including a singlet at 2.36 ppm which was caused by  $\text{N}(\text{CH}_3)_2$  and multiplets at 2.40-2.79 due to the two methylene groups. The benzylic methylene gave rise to a singlet at 3.70 ppm.

An attempt to prepare the carboxylic acid (165) by the formation of a Grignard reagent (164) and its reaction with carbon dioxide was unsuccessful and failed to afford the required compound (165) (Scheme 62).

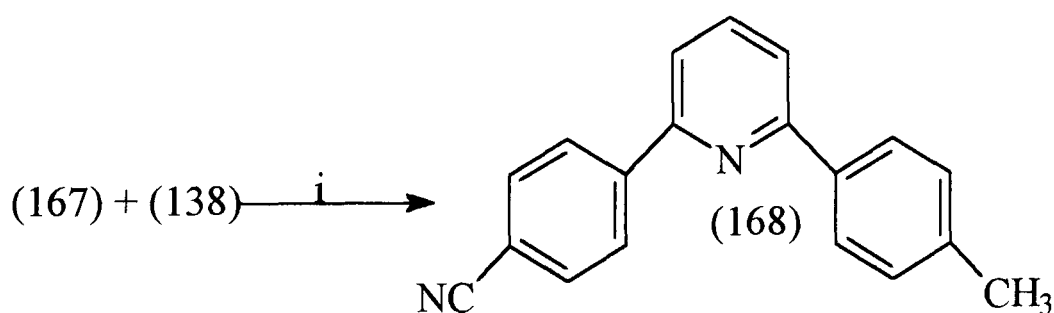
An alternative approach to the target acid (165) required the preparation of 1-(4-cyanophenyl)-3-(dimethylamino)propane-1-one hydrochloride (167) as the first step. The treatment of 4-cyanoacetophenone (166) with paraformaldehyde (139) and dimethylamine hydrochloride (140) in absolute ethanol containing concentrated hydrochloric acid gave the desired (167) in satisfactory yield (Scheme 63).



Scheme 63

The IR spectrum of (167) indicated the presence of both carbonyl and cyanide groups by the appearance of sharp peaks at  $1688\text{ cm}^{-1}$  and  $2226\text{ cm}^{-1}$  respectively. The  $^1\text{H}$  NMR spectroscopy provided evidence of the proposed structure. A singlet at 2.86 ppm was caused by two  $\text{N}(\text{CH}_3)_2$  groups, two triplets at 3.45 ppm and 3.72 ppm were due to two  $\text{CH}_2$  groups and the aromatic protons gave rise to two doublets at 8.09 ppm and 8.17 ppm. The elemental analysis agreed with the molecular formula  $\text{C}_{12}\text{H}_{15}\text{N}_2\text{OCl}$ .

The cyclisation of 1-(4-cyanophenyl)-3-(dimethylamino)propan-1-one hydrochloride (167) and 1-(4-methylphenyl)pyridinium bromide (138) with ammonium acetate in methanol proceeded well and the 2-(4-cyanophenyl)-6-(4-tolyl)pyridine (168) was separated upon cooling the reaction mixture at room temperature (Scheme 64).



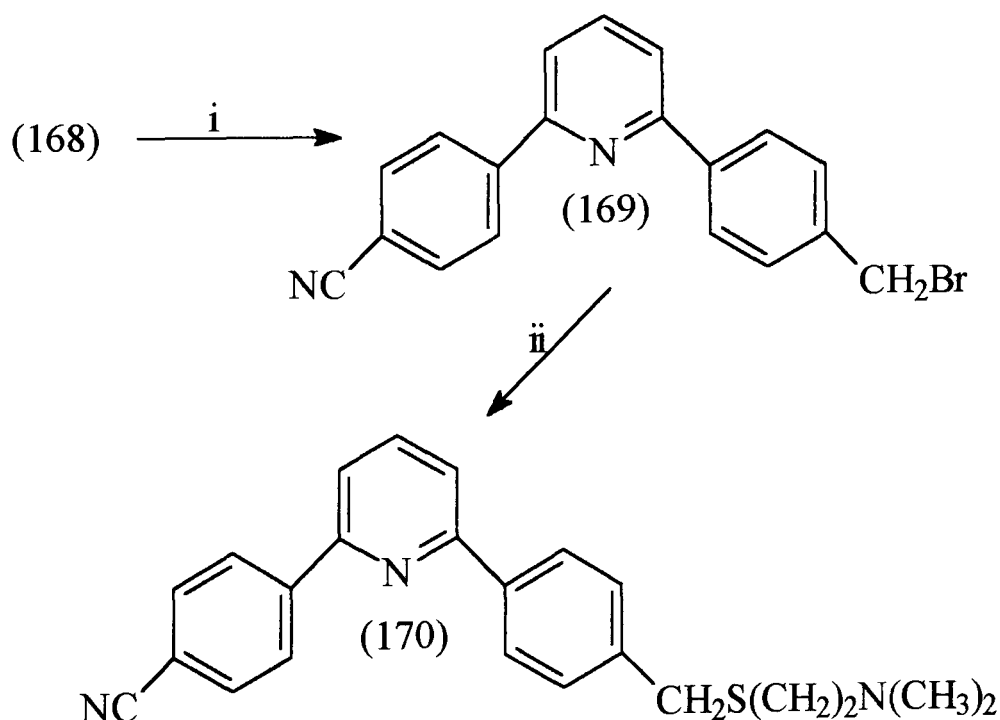
Reagents: (i) ammonium acetate, methanol

Scheme 64

The structure of the compound (168) was shown by its  $^1\text{H}$  NMR spectrum which had a singlet at 2.42 ppm due to the methyl group, a doublet at 7.31 was caused by the 3- and 5-protons of carbocyclic ring and a multiplet at 7.77 ppm was due to the five protons of carbocyclic and pyridine rings. Four aromatic protons gave rise to two doublets at 8.02 and 8.23 ppm. The IR spectrum of (168) showed the presence of a

CN group by a signal at  $2230\text{ cm}^{-1}$ . The elemental analysis and mass spectrum of 2-(4-cyanophenyl)-6-(4-tolyl)pyridine (168) were in accordance with the structural and molecular formula.

The 2-(4-[bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169) was prepared from (168) by reaction with a mixture of N-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride at reflux (Scheme 65). The product was purified by column chromatography and the structure was confirmed by the  $^1\text{H}$  NMR spectrum, which showed a singlet at 4.56 ppm caused by the bromomethyl group. The aromatic protons were present as expected. The mass spectrum showed the presence of molecular ions at 350 and 348 daltons in the relative abundance ratio 1:1 due to the  $^{81}\text{Br}$  and  $^{79}\text{Br}$  isotopes, respectively.



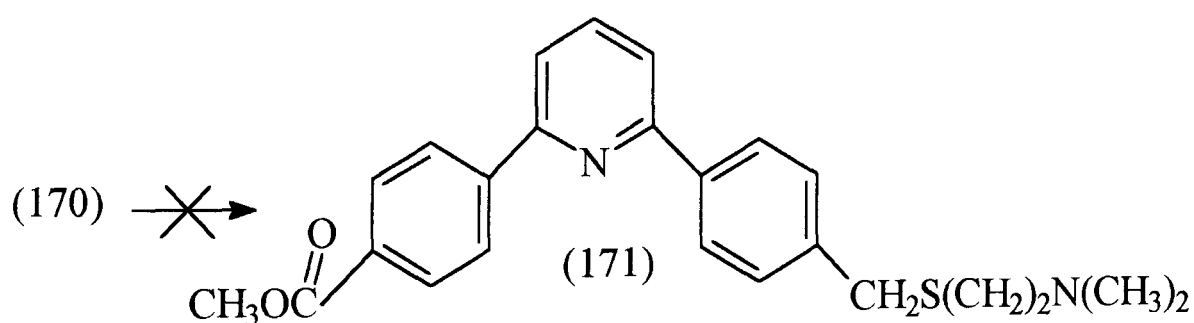
Reagents: (i) NBS,  $\text{CCl}_4$ ; (ii) NaOEt,  $\text{HS}(\text{CH}_2)_2\overset{+}{\text{N}}(\text{CH}_3)_2\text{HCl}^-$

Scheme 65

The reaction of 2-(4-[bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169) with 2-(dimethylamino)ethanethiol hydrochloride containing ethanolic sodium ethoxide (prepared from sodium metal and absolute ethanol) yielded the corresponding sulfide derivative, 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-cyanophenyl)pyridine (170) (Scheme 65).

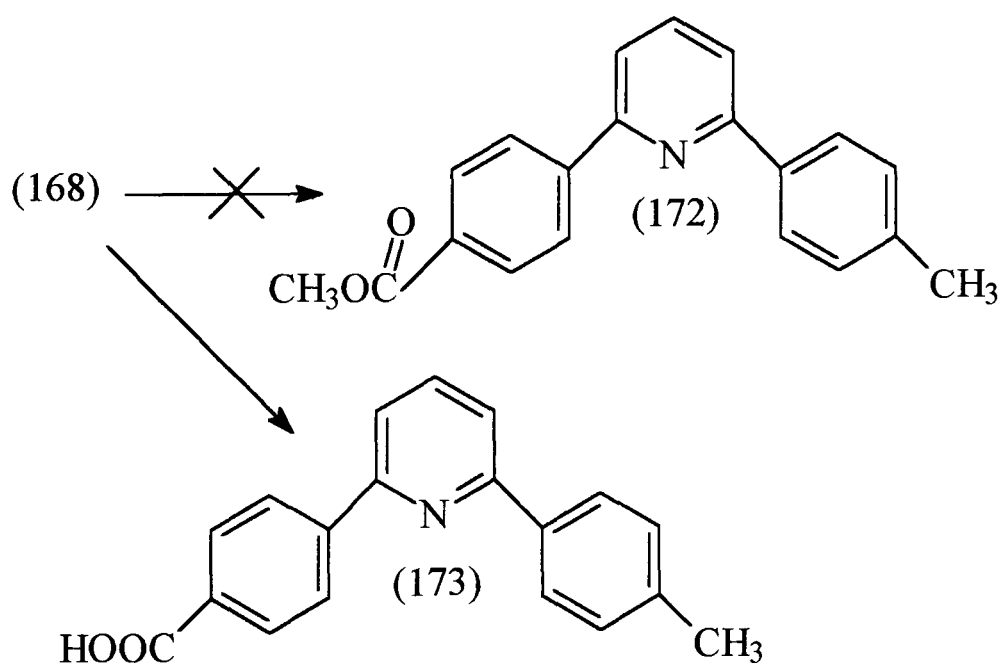
The compound (170) was characterised by its  $^1\text{H}$  NMR spectrum which, in addition to other expected peaks, showed the presence of a singlet at 2.21 ppm due to  $\text{N}(\text{CH}_3)_2$ . Multiplets at 2.48-2.57 ppm were caused by two  $\text{CH}_2$  groups and the benzylic  $\text{CH}_2$  gave rise to a singlet at 3.79 ppm. The accurate mass measurement on the molecular ion was in accord with the molecular formula. When the reaction was repeated it was found to be difficult to isolate the product in a pure state. At least two components were present in the mixture as shown by TLC.

An attempt to obtain 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-[methoxycarbonyl]phenyl)pyridine (171) by hydrolysis of the cyano group of impure 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-cyanophenyl)pyridine (170) in dry methanol by passing dry hydrogen chloride gas, failed and starting material was obtained (Scheme 66).



Scheme 66

When an attempt was made to convert the less complex cyano compound, 2-(4-cyanophenyl)-6-(4-tolyl)pyridine (168) into the corresponding ester (172) by treatment with acidified methanol a product was obtained which showed a broad OH absorption at  $3210\text{ cm}^{-1}$  and a carbonyl absorption at  $1682\text{ cm}^{-1}$ . The  $^1\text{H}$  NMR spectrum showed a singlet at 2.35 ppm assigned to the  $\text{CH}_3$  groups, a broad singlet at 5.16 ppm due to OH and a doublet at 7.32 ppm due to two aromatic protons. The three protons of the pyridine nucleus and two protons of the carbocyclic ring gave rise to a multiplet at 7.94 ppm and two doublets at 8.11 and 8.14 ppm were caused by four aromatic protons. The elemental analysis and mass spectrum data were in agreement with molecular formula  $\text{C}_{19}\text{H}_{15}\text{NO}_2$  and the compound was hence thought to be 4-(2-[6-{4-tolyl}pyridyl])benzoic acid (173) (Scheme 67).

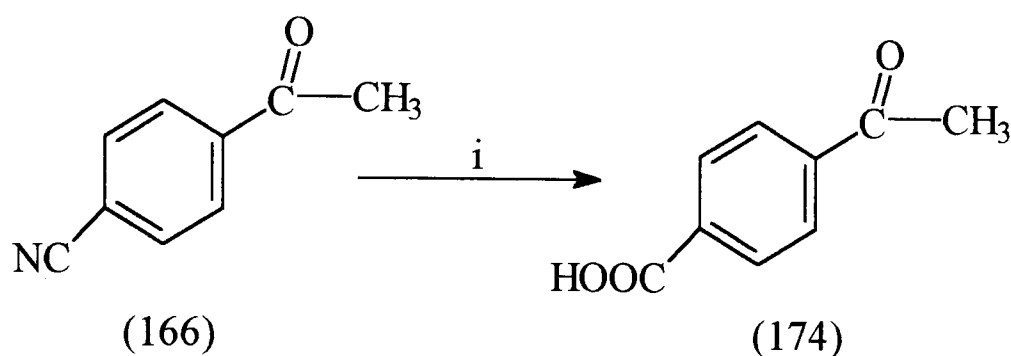


Scheme 67

The formation of (173) probably occurred by hydrolysis of the first formed corresponding ester (172). The overall yield of 4-(2-[6-(4-tolyl)pyridyl])benzoic acid (173) was low.



In order to obtain higher yields of (173) an alternative route was tried by causing hydrolysis of 4-cyanoacetophenone (166) with aqueous sodium hydroxide and subsequent acidification to yield 4-acetylbenzoic acid (174) (Scheme 68).

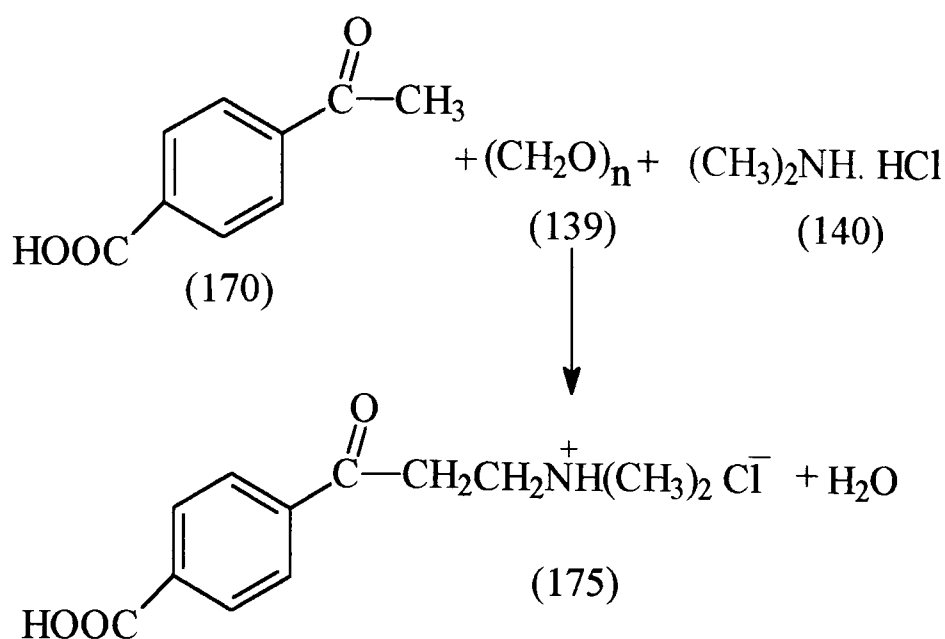


Reagents: (i) NaOH, EtOH and then aq. HCl

Scheme 68

The IR spectrum showed the disappearance of the peak due to the cyano group and the appearance of C=O absorption at  $1684\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR spectrum showed the presence of two singlets at 2.61 and 8.09 ppm due to methyl group and aromatic protons. An exchangeable singlet at 11.0 was caused by OH group. The compound (174) was used as a the starting material for the next stage of the reaction series.

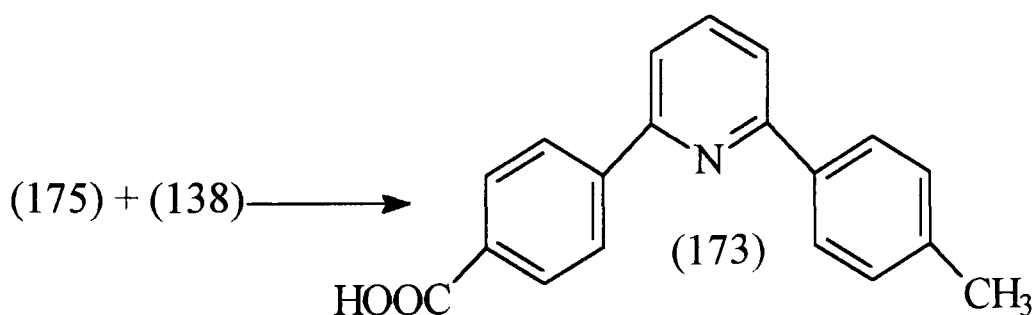
When the mixture of 4-acetylbenzoic acid, paraformaldehyde (139) and dimethylamine hydrochloride (140) were refluxed in ethanol, the required 4-(3-dimethylamino propanoyl)benzoic acid hydrochloride (175) was obtained (Scheme 69).



Scheme 69

The IR spectrum of (175) showed the expected stretching vibration at  $1650 \text{ cm}^{-1}$  due to the C=O group and a broad absorption at  $3431 \text{ cm}^{-1}$  due to OH group. The  $^1\text{H}$  NMR spectrum showed the presence of a singlet at 2.86 ppm due to the  $\text{N}(\text{CH}_3)_2$  group, a multiplet at 3.45-3.61 ppm was caused by the two  $\text{CH}_2$  groups and a singlet at 8.19 ppm due to the four aromatic protons. The NH and OH groups gave rise to exchangeable broad singlets at 9.18 ppm and 11.0 ppm, respectively.

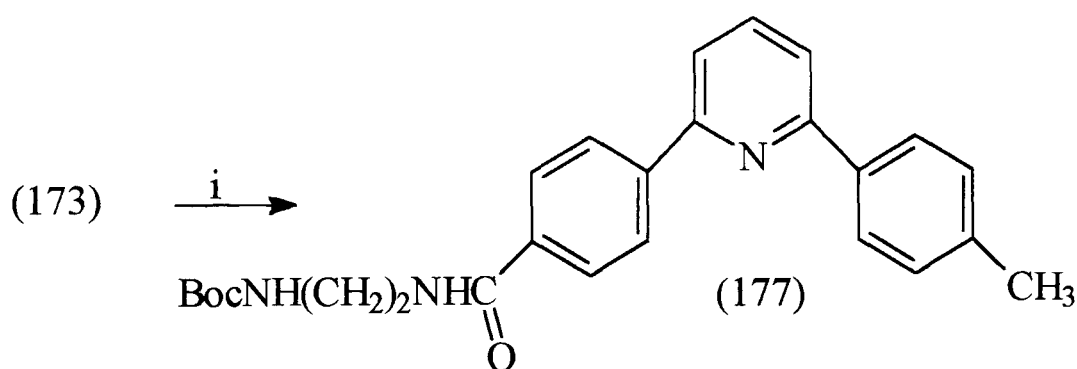
The Krohnke cyclization of (175) and 1-(4-methylphenacyl)pyridinium bromide (138) in the presence of ammonium acetate in methanol gave 4-(2-[6-(4-tolyl)pyridyl])benzoic acid (173) in high yield (Scheme 70).



Scheme 70

The physical data of the product were identical with the compound obtained earlier in this work.

The next step was the preparation of an amide from the substituted benzoic acid. The acid (173) was treated with protected 2-(tert-butoxycarbonylamino)ethylamine (176) (prepared by the reaction of 1,2-diaminoethane with di-tert-butyl dicarbonate in dichloromethane)<sup>63</sup> in the presence of 1-[(3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBT) in DMF to give the desired *N*-(2-[tert-butoxycarbonylamino]ethyl)-4-(2-[6-(4-tolyl)pyridyl])benzamide (177) (Scheme 71).



Reagents: (i) NH<sub>2</sub>(CH<sub>2</sub>)<sub>2</sub>NHBoc, EDCI, HOBT, DMF

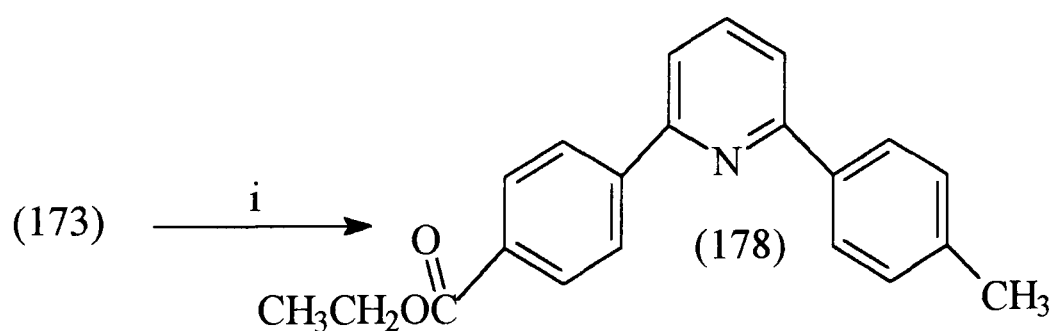
Scheme 71

Compound (177) was characterised by comparison of its IR spectrum with that of (173) which showed the disappearance of a broad peak at 3055 cm<sup>-1</sup> due to the OH group of (173) and the appearance of a peak at 3342 cm<sup>-1</sup> due to the NH group. The comparison between the <sup>1</sup>H NMR spectra of (173) and (177) also showed the disappearance of a peak due to the OH group in (173) but showed extra peak at 1.34

ppm (due to the three methyl groups of  $C(CH_3)_3$ ), a singlet at 2.38 ppm due to the methyl group and a multiplet at 3.14-3.36 ppm was caused by four methylene protons. The two NH groups gave rise to exchangeable singlets at 6.81 ppm and 8.42 ppm.

An attempt to brominate (177) with *N*-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride failed to produce any product and only starting material was detected by analytical t.l.c. This was due to the insolubility of compound (177) in organic solvents.

It was then decided to convert the carboxylic acid group of (173) into the corresponding ester. Esterification of 4-(2-[6-{4-tolyl}pyridyl])benzoic acid (173) was achieved by dissolving it in ethanol containing few drops of concentrated sulfuric acid at reflux to give ethyl 4-(2-[6-{4-tolyl}pyridyl])benzoate (178) (Scheme 72).

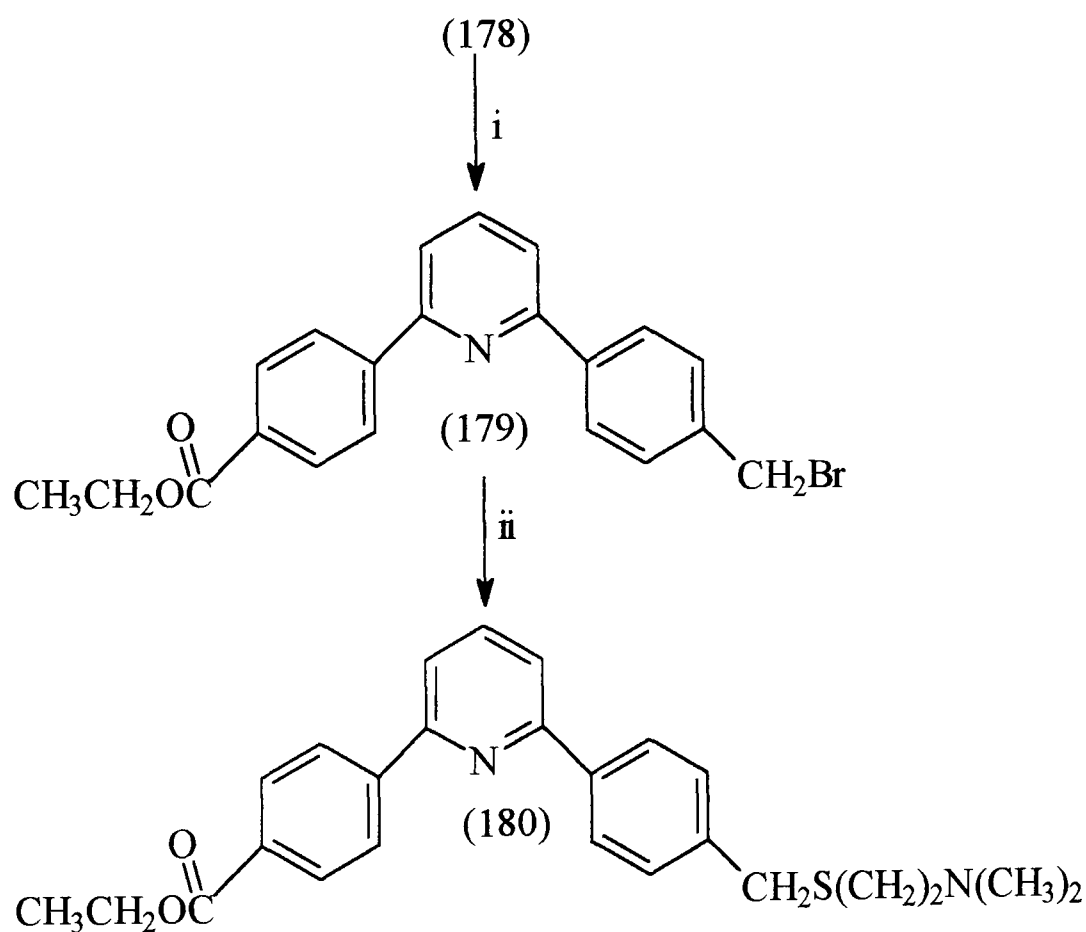


Reagents: (i)  $H_2SO_4$ , EtOH

Scheme 72

The compound (178) showed a triplet at 1.45 ppm due to the methyl group and a quartet at 4.42 ppm caused by the methylene protons in the  $^1H$  NMR spectrum as well as other expected absorptions. The IR spectrum showed the presence of a carbonyl group by the appearance of a sharp peak at  $1686\text{ cm}^{-1}$ .

Ethyl 4-(2-[6-{4-bromomethylphenyl}]pyridyl)benzoate (179) was made by a reaction of compound (178) with NBS and benzoyl peroxide in carbon tetrachloride (Scheme 73). The  $^1\text{H}$  NMR spectrum of (179) showed the disappearance of a peak at 2.42 ppm due to the aromatic methyl group and the appearance of a peak due to two protons as a singlet at 4.57 ppm due to the bromomethyl group. The mass spectrum and elemental analysis data indicated the molecular formula to be  $\text{C}_{12}\text{H}_{18}\text{NO}_2\text{Br}$ .



Reagents: (i) NBS,  $\text{CCl}_4$ ; (ii)  $\text{EtOH}$ ,  $\text{HS}(\text{CH}_2)_2\text{N}^+(\text{CH}_3)_2\text{HCl}^-$

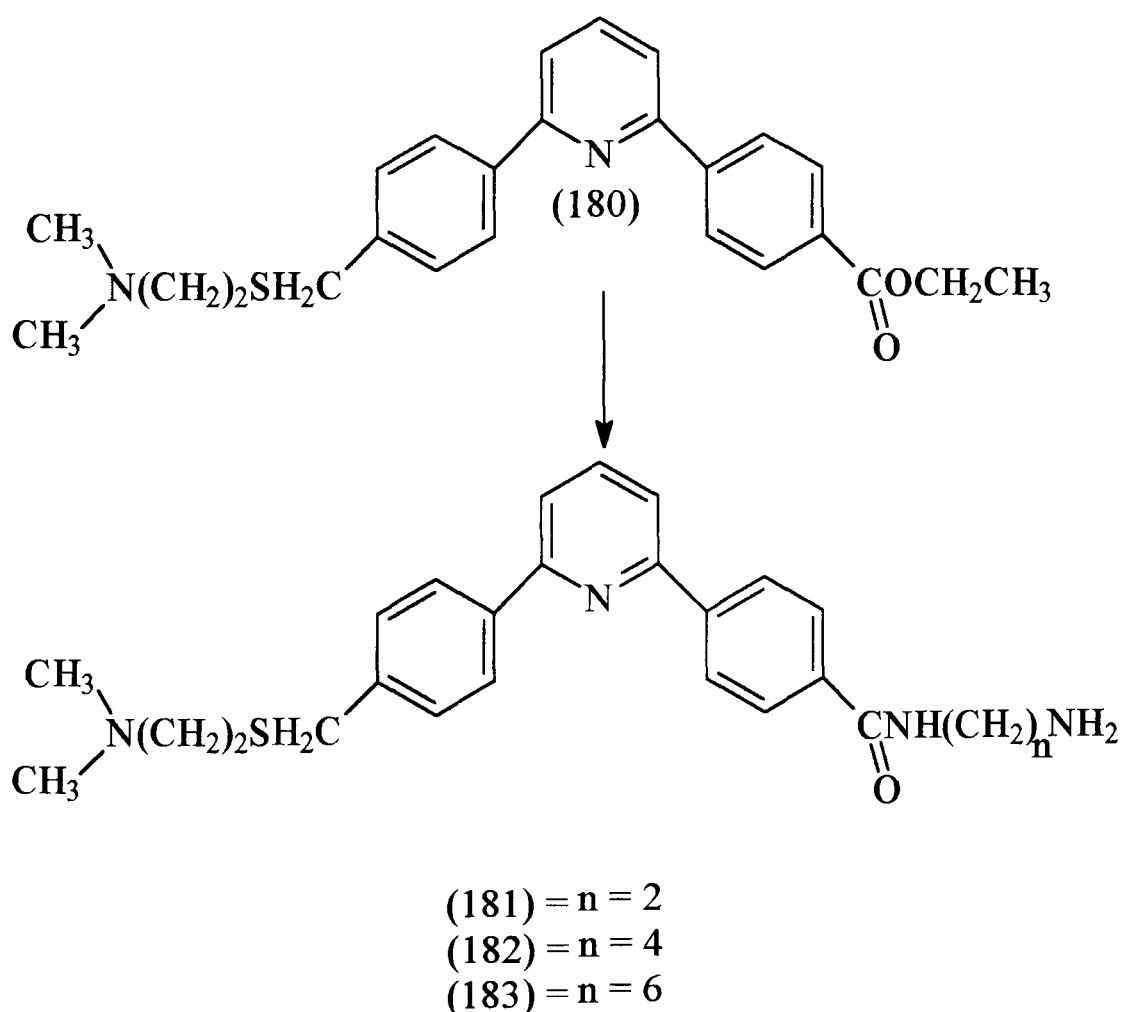
Scheme 73

The nucleophilic displacement reaction of the alkyl bromide group in (179) was carried out with 2-(dimethylamino)ethanethiol hydrochloride in the presence of sodium ethoxide in ethanol. The crude product was purified by column chromatography to give colourless crystals of ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]-pyridyl)benzoate (180) (Scheme 73).

The structure of compound (180) was shown by its  $^1\text{H}$  NMR spectrum which had a triplet at 1.43 ppm due to the ester  $\text{CH}_3$  group and a singlet at 2.24 ppm due to the of a  $\text{N}(\text{CH}_3)_2$  group. The multiplet at 2.49-2.58 ppm was caused by the two  $\text{CH}_2$  groups, a singlet at 3.80 ppm was assigned to the benzylic  $\text{CH}_2$  and a quartet was observed at 4.4 ppm due to the  $\text{OCH}_2$  group in addition to other expected resonances for the protons of the carbocycles and pyridine protons. The accurate mass data for the molecular ion were in accordance with the molecular formula.

### 2.3.4 Aminolysis of ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180).

The nucleophilic displacement reaction of ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180) separately with ethylene diamine, 1,4-diaminobutane and 1,6-diaminohexane in the presence of anhydrous potassium carbonate produces *N*-(2-aminoethyl)- (181), *N*-(4-aminobutyl)- (182) and *N*-(6-aminohexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl) benzamide (183) respectively (Scheme 74). These highly polar compounds were purified by column chromatography.



Scheme 74

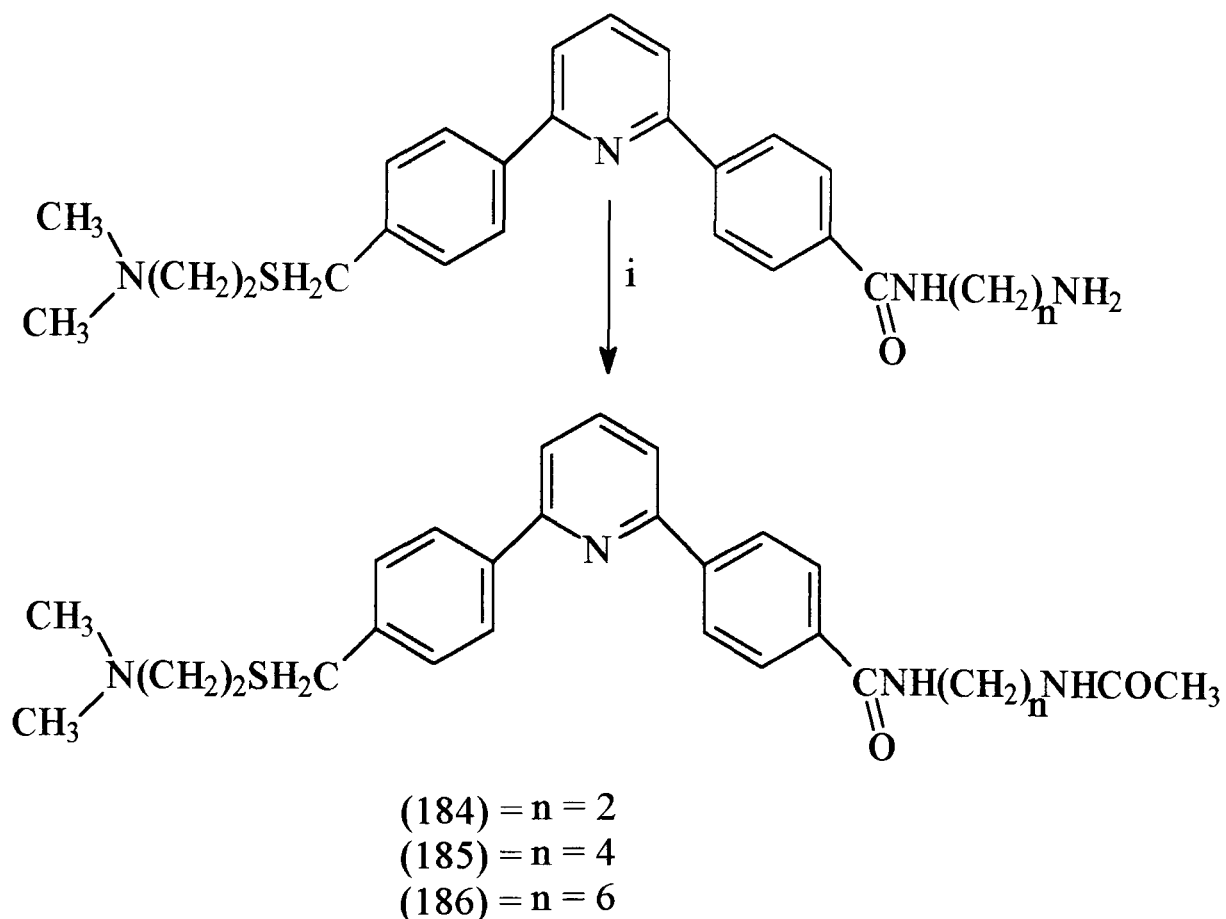
The IR spectrum of (181) exhibits a carbonyl stretching absorption at 1718  $\text{cm}^{-1}$  due to the amide group and NH and  $\text{NH}_2$  stretching vibration at 3340, 3320  $\text{cm}^{-1}$  and 3212  $\text{cm}^{-1}$ . Comparison of the  $^1\text{H}$  NMR spectra of (180) and (181) showed the expected disappearance of a triplet and a quartet at 1.43 and 4.42 ppm due to the ethyl group in (180) and the appearance of multiplets at 2.71-3.17 ppm due to two vicinal methylene groups adjacent to NH and  $\text{NH}_2$  groups. The NH and  $\text{NH}_2$  groups gave rise to a triplet and singlet at 3.29 ppm and 8.55 ppm, respectively. These data and accurate mass measurement on the molecular ion are in accord with the assigned structural formula.

Compounds (182) and (183) were also characterised by their IR spectra,  $^1\text{H}$  NMR spectra and by accurate mass measurement on their molecular ions.

### 2.3.5 Synthesis of the acetyl derivatives of (181), (182) and (183).

When the amines (181), (182) and (183) were separately reacted with glacial acetic acid and acetic anhydride the products were *N*-(2-[acetamido]ethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (184) and the corresponding *N*-(4-[acetamido]butyl)- and *N*-(6-[acetamido]hexyl)- amides (185) and (186) respectively, in quantitative yield (Scheme 75).





Reagents: (i) glacial acetic acid, acetic anhydride

Scheme 75

Compound (184) was characterised by its IR spectrum which showed a peak at 3282  $\text{cm}^{-1}$  due to the NH stretching vibration. The carbonyl stretching frequencies were observed at 1675  $\text{cm}^{-1}$  and 1628  $\text{cm}^{-1}$  and assigned to the amide groups.

All the expected peaks associated with the carbocyclic system and the pyridine nucleus were present in the  $^1\text{H}$  NMR spectrum of (184). There was also a singlet at 1.82 ppm due to the methyl group and a singlet at 2.10 ppm caused by the  $\text{N}(\text{CH}_3)_2$  group. The resonance at 2.48-2.50 ppm was due to the two methylene groups, multiplets at 3.29-3.39 were caused by two methylene groups adjacent to nitrogen and a singlet at 3.82 ppm was due to the benzylic methylene group. The NH and  $\text{NH}_2$  groups gave rise to two triplets at 8.10 ppm and 8.71 ppm. Mass spectral data and accurate mass measurement on the molecular ion were in agreement with the molecular formula  $\text{C}_{27}\text{H}_{32}\text{N}_4\text{O}_2\text{S}$ .

Compounds (185) and (186) were also characterised by their IR,  $^1\text{H}$  NMR spectra and accurate mass measurements.

## EXPERIMENTAL

### **4-Methylacetophenone *N,N*-dimethylhydrazone (133).**

A mixture of 4-methylacetophenone (132) (13.3 g, 100 mmol), anhydrous *N,N*-dimethylhydrazine (18.0 g, 300 mmol), absolute ethanol (20 cm<sup>3</sup>) and glacial acetic acid (1-2 cm<sup>3</sup>) was heated at reflux for 24 h. During this period the colourless solution became bright yellow. The volatile reactants and solvent were removed under reduced pressure and the residual oil fractionally distilled through a 10 cm Vigreux column to give the hydrazone (13.9 g, 80%) bp 64-65 °C (0.5 mm Hg) (lit.,<sup>105</sup> bp 55-56 °C (0.5 mm Hg)); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2952, 1604, 1510, 1486, 1458, 1358, 816; <sup>1</sup>HNMR (360 MHz, CCl<sub>4</sub>)  $\delta$  2.35 (6H, s, 2 x CH<sub>3</sub>) 2.58 (6H, s, 2 x CH<sub>3</sub>), 7.61 (2H, d, *J* = 6.3 Hz, Ar-H), 7.64 (2H, d, *J* = 6.3 Hz, Ar-H); MS, *m/z* (r.i.) 177 (26%), 176 (M<sup>+</sup>, 100), 161 (M- CH<sub>3</sub>, 30), 146 (M- 2 x CH<sub>3</sub>, 32), 132 (14).

### **4-Methylacetophenone *N,N,N*-trimethylhydrazonium iodide (134).**

4-Methylacetophenone *N,N*-dimethylhydrazone (133) (5.0 g, 28 mmol) and excess methyl iodide in anhydrous methanol (25 cm<sup>3</sup>) were refluxed under nitrogen for 6 h. After cooling the solution, cold anhydrous ether was added, the precipitate collected and crystallised from a mixture of absolute ethanol and ethyl acetate to give the methiodide (134) (8.08 g, 90%), mp 160-162 °C (lit.,<sup>105</sup> mp. 159-160 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1596, 1470, 1404, 1364, 1288, 1238, 942, 813; <sup>1</sup>HNMR (360 MHz, D<sub>2</sub>O)  $\delta$  2.41 (3H, s, Ar-CH<sub>3</sub>), 2.80 (3H, s, C-CH<sub>3</sub>), 3.65 (9H, s, N(CH<sub>3</sub>)<sub>3</sub>), 7.35 (2H, d, *J* = 6.3 Hz, Ar-H), 7.73 (2H, d, *J* = 6.3 Hz, Ar-H).

**4-Methylacetophenone *N,N,N*-trimethylhydrazonium tetrafluoroborate (135).**

A hot aqueous solution of sodium fluoroborate (2.0 g) was slowly added to a refluxing solution of 4-methylacetophenone *N,N,N*-trimethylhydrazonium iodide (134) (2.0 g, 6.2 mmol) dissolved in the minimum volume of water to ensure complete dissolution. The mixture was then cooled to room temperature, the crystals were filtered off and dried *in vacuo*, (1.64 g, 96%), mp 160-162 °C (lit.,<sup>105</sup> mp 159-160 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1604, 1562, 1478, 1370, 1288, 1060, 1030, 826, 696; <sup>1</sup>HNMR (360 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  2.41 (3H, s, Ar-CH<sub>3</sub>), 2.81 (3H, s, C-CH<sub>3</sub>), 3.65 (9H, s, N(CH<sub>3</sub>)<sub>3</sub>), 7.35 (2H, d, *J* = 6.3 Hz, Ar-H), 7.76 (2H, d, *J* = 6.3 Hz, Ar-H).

**2,6-Bis(4-methylphenyl)pyridine (136).**

4-Methylacetophenone *N,N,N*-trimethylhydrazonium tetrafluoroborate (1.0 g, 3.6 mmol) in cumene (2.0 g) was slowly heated to about 150 °C. The exothermicity of the reaction then caused the solution to reflux. The mixture was refluxed for a further 1 h. After cooling the liquid was decanted and concentrated *in vacuo*. The crude product was purified by column chromatography using a mixture of petroleum spirit (bp 40-60 °C) and ethyl acetate (98:2) to give the title compound (0.16 g, 17%), mp 160-162 °C (lit.,<sup>106</sup> mp. 165-166 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1922, 1896, 1588, 1510, 1304, 1148, 1114, 1042, 1014, 990, 950, 860, 836, 794, 744, 722, 666; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  2.41 (6H, s, 2 x CH<sub>3</sub>), 7.41 (4H, m, 2 x 3- and 2 x 5-tolyl-H), 7.62 (2H, m, 3- and 5-py-H), 7.83 (1H, t, 4-py-H), 8.03 (4H, m, 2 x 2- and 2 x 6-tolyl-H); MS, *m/z* (r.i.) 260 (59%), 259 (M<sup>+</sup>, 100), 258 (M - H, 26), 257 (6), 244 (M - CH<sub>3</sub>, 6), 196 (21), 181 (6), 119 (8), 117 (41), 109 (32), 105 (10), 104 (8), 98 (12), 76 (4).

## GENERAL METHOD FOR PREPARATION OF MANNICH BASES (141), (167) AND (175).

A mixture of dry dimethylamine hydrochloride (140) (13.2 g, 163 mmol), paraformaldehyde (5.0 g, 166 mmol), the appropriate acetophenone (125 mmol) and absolute ethanol (20 cm<sup>3</sup>) to which concentrated hydrochloric acid (1-2 drops) has been added was refluxed for 2 h. The reaction mixture usually became homogenous but any remaining solid was filtered off. Acetone (100 cm<sup>3</sup>) was added to the warm liquid and the product left in a refrigerator overnight. The crystals were filtered and washed with acetone.

### 1-(4-Methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141).

The product (141) from 4-methylacetophenone (16.75 g, 0.125 mol) was crystallised from a mixture of chloroform and petroleum spirit (bp 40-60 °C) to give colourless crystals of *1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride* (141) (20.0 g, 70%), mp 161-162 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2438, 1674 (C=O), 1602, 1338, 1306, 1226, 1180, 1076, 1008, 962, 850, 786, 722; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  2.43 (6H, s, 2 x Ar-CH<sub>3</sub>), 2.87 (6H, s, 2 x CH<sub>3</sub>), 3.54 (2H, t, *J* = 6.5 Hz, CH<sub>2</sub>), 3.73 (2H, t, *J* = 6.5 Hz, CH<sub>2</sub>), 7.26 (2H, d, *J* = 7.8 Hz, Ar-H), 7.87 (2H, d, *J* = 7.8 Hz, Ar-H), 13.01 (1H, broad signal, exchangeable with D<sub>2</sub>O, NH) MS, *m/z* (r.i.) 191 (M<sup>+</sup> for C<sub>12</sub>H<sub>17</sub>N, 19%), 146 (M - NH(CH<sub>3</sub>)<sub>2</sub>, 75), 131 (M - NH(CH<sub>3</sub>)<sub>2</sub>-CH<sub>3</sub>, 45), 120 (58), 119 (89), 118 (39), 117 (30), 115 (24), 91 (89), 89 (52), 72 (49), 58 (100) (Found: C, 63.21; H, 7.99; N, 6.13. C<sub>12</sub>H<sub>18</sub>ClNO requires: C, 63.29; H, 7.91; N, 6.15%).

**1-(4-Cyanophenyl)-3-(dimethylamino)propan-1-one hydrochloride (167).**

4-Cyanoacetophenone (166) (18.1 g, 125 mmol) yielded a product crystallised from a mixture of chloroform and petroleum spirit (bp 40-60 °C) to give yellow *1-(4-cyanophenyl)-3-(dimethylamino)propan-1-one hydrochloride* (167) (19.26 g, 76%), mp 159-160 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2556, 2370, 2226 (CN), 1688 (C=O), 1480, 1382, 1332, 1220, 962, 858, 786, 730, 578;  $^1\text{H NMR}$  (360 MHz, DMSO- $d_6$ )  $\delta$  2.86 (6H, s, 2 x CH<sub>3</sub>), 3.45 (2H, t,  $J = 6.5$  Hz, CH<sub>2</sub>), 3.72 (2H, t,  $J = 6.5$  Hz, CH<sub>2</sub>), 8.09 (2H, d,  $J = 8.1$  Hz, Ar-H), 8.17 (2H, d,  $J = 8.1$  Hz, Ar-H), 10.5 (1H, broad signal, exchangeable with D<sub>2</sub>O, NH); MS,  $m/z$  (r.i.) 202 (M<sup>+</sup> for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O, 19%), 185 (4), 159 (4), 158 (24), 157 (M -NH(CH<sub>3</sub>)<sub>3</sub>, 94), 156 (11), 149 (12), 131 (45), 130 (100), 129 (43), 102 (26) (Found: C, 60.43; H, 6.28; N, 11.58. C<sub>12</sub>H<sub>15</sub>Cl N<sub>2</sub>O requires: C, 60.37; H, 6.28; N, 11.74%).

**4-(3-Dimethylaminopropanoyl)benzoic acid hydrochloride (175).**

4-Acetylbenzoic acid (170) (20.5 g, 125 mmol) afforded the pale yellow *Mannich base hydrochloride* (175) (20.2 g, 62.%), mp 190-191 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3431 (OH), 2944, 1665 (C=O), 1540, 1412, 1323, 1289, 1215, 962, 858, 786, 730, 578;  $^1\text{H NMR}$  (360 MHz, DMSO- $d_6$ )  $\delta$  2.86 (6H, s, 2 x CH<sub>3</sub>), 3.45-3.61 (4H, m, 2 x CH<sub>2</sub>), 8.19 (4H, s, Ar-H), 9.18 (1H, broad signal, exchangeable with D<sub>2</sub>O, NH), 11.0 (1H, broad signal, exchangeable with D<sub>2</sub>O, OH); MS,  $m/z$  (r.i.) 204 (M<sup>+</sup> for (C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>) -OH, 12%), 177 (M<sup>+</sup> for (C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>)-CO<sub>2</sub>, 23), 176 (96), 159 (16), 149 (100), 148 (12), 45 (46), 44 (75) (Found: C, 55.50; H, 6.26; N, 5.53. C<sub>12</sub>H<sub>16</sub>Cl NO<sub>3</sub> requires: C, 55.90; H, 6.21; N, 5.43%).

## GENERAL METHOD FOR PREPARATION OF PYRIDINIUM BROMIDE (138), (143) AND (160).

The appropriate phenacyl bromide (4.7 mmol) was added to dry pyridine (10 cm<sup>3</sup>) and stirred for 30 min at room temperature. The solid was filtered off and crystallised from mixture of methanol and diethyl ether.

### 1-(4-Methylphenacyl)pyridinium bromide (138).

4-Methylphenacyl bromide (137) (1.0 g) yielded the *title compound* (1.20 g, 87 %), mp 212-213 °C, IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2286, 1688 (CO), 1634, 1592, 1342, 1218, 1152, 994, 754, 722, 682; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.45 (3H, s, Ar-CH<sub>3</sub>), 6.45 (2H, s, CH<sub>2</sub>), 7.41 (2H, d,  $J = 7.4$  Hz, 3- and 5- Ar-H), 7.92 (2H, d,  $J = 7.4$  Hz, 2- and 6-Ar-H), 8.27 (2H, t, 3- and 5-py-H), 8.73 (1H, m, 4-py-H), 9.01 (2H, m, 2- and 6-py-H) (Found: C, 54.52; H, 5.02; N, 4.42. C<sub>14</sub>H<sub>14</sub>Br NO requires: C, 54.98; H, 4.81; N, 4.81 %).

### Phenylacetylpyridinium bromide (143).

Phenacyl bromide (0.93 g) gave colourless phenylacetylpyridinium bromide (143) (1.21 g, 93%), mp. 201-202 °C, IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2272, 1688 (CO), 1618, 1576, 1342, 1218, 1145, 1154, 1045, 1023, 1018, 1005, 996, 886, 845, 823, 756, 745, 732, 722, 682, 645, 606; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  6.54 (2H, s, CH<sub>2</sub>), 7.67 (2H, m, 3- and 5-Ar-H), 7.80 (1H, m, 4-Py-H), 8.07 (2H, m, 3- and 5-Ar-H), 8.29 (2H, m, 2- and 6-Ar-H), 8.70 (1H, m, 4-py-H), 9.05 (2H, m, 2- and 6-py-H) (Found: C, 88.10; H, 6.08; N, 5.65. C<sub>13</sub>H<sub>12</sub>Br NO requires: C, 88.16; H, 6.12; N, 5.71 %).

### **1-(4-Bromophenacyl)pyridinium bromide (160).**

4-Bromophenacyl bromide (159) (1.3 g) yielded a solid which was crystallised to give colourless *4-bromophenacylpyridinium bromide* (160) (1.45 g, 87%), mp 251-251.5 °C, IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2722, 2369, 1868, 1718, 1694 (CO), 1635, 1558, 1506, 1490, 1308, 1180, 1070, 988, 816, 722, 682, 599;  $^1\text{HNMR}$  (360 MHz, DMSO- $d_6$ )  $\delta$  6.53 (2H, s, CH<sub>2</sub>), 7.90 (2H, d,  $J = 7.2$  Hz, 3- and 5-Ar-2H), 8.00 (2H, m, 3- and 5-py-H), 8.32 (2H, d,  $J = 7.2$  Hz, 2- and 6-Ar-H), 8.74 (1H, m, 4-py-H), 9.02 (2H, d,  $J = 7.2$  Hz, 2- and 6-py-H) (Found: C, 43.89; H, 3.02; N, 3.54. C<sub>13</sub>H<sub>11</sub>Br<sub>2</sub>NO requires: C, 43.94; H, 3.09; N, 3.94 %).

## **GENERAL METHOD FOR PREPARATION OF THE 2,6-DIARYL PYRIDINES (136), (144), (161), (168) AND (173).**

### General method using methanol as solvent

A mixture of the appropriate pyridinium salt (6 mmol), the Mannich base (6 mmol) and ammonium acetate (4 g) in methanol (20 cm<sup>3</sup>) was refluxed for 4 h. The reaction mixture was cooled and maintained at 0 °C for 24 h. The precipitate was filtered off and purified.

### **2,6-Bis(4-methylphenyl)pyridine (136).**

The pyridinium salt (138) (1.74g), 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) (1.36 g) and ammonium acetate (4 g) afforded a product which was purified by column chromatography (chloroform:petroleum spirit, 50:50) and crystallised from a mixture of chloroform and petroleum spirit to give the 2,6-bis(4-methylphenyl)pyridine (1.12 g, 72 %), mp 160-162 °C (lit.,<sup>106</sup> mp 165-166° C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1922, 1896, 1588, 1510, 1304, 1148, 1114, 1042, 1014, 990, 950,



860, 836, 794, 744, 722, 666; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>) δ 2.41 (6H, s, 2 x CH<sub>3</sub>), 7.41 (4H, m, 2 x 3- and 5-tolyl-H), 7.68 (2H, m, 3- and 5-py-H), 7.81 (1H, t, for 4-py-H), 8.03 (4H, m, 2 x 2- and 2 x 6-tolyl-H); MS, m/z (r.i.) 260 (34%), 259 (M<sup>+</sup>, 100), 258 (M- H, 26), 257 (6), 244 (M- CH<sub>3</sub>, 6), 196 (21), 181 (6), 119 (8).

### **2-Phenyl-6-(4-tolyl)pyridine (144).**

A mixture of the pyridinium salt (143) (1.66 g), 1-(4-methylphenyl)-3-(dimethyl amino)propan-1-one hydrochloride (141) (1.36 g) and ammonium acetate (4 g) in methanol (20 cm<sup>3</sup>) gave a product which was purified by column chromatography (chloroform : petroleum spirit, 50:50) to give the *2-phenyl-6-(4-tolyl)pyridine* (144) (0.98 g, 67 %), mp 90-93 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2360, 1566, 1306, 1156, 996, 804, 760, 722, 692 ; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>) δ 2.41 (3H, s, CH<sub>3</sub>), 7.29 (2H, d, *J* = 8 Hz, 3- and 5-tolyl-H), 7.42 (1H, m, 4- Ph-H), 7.49 (2H, m, 3- and 5-Ph -H), 7.66 (2H, d, *J* = 9 Hz, 3- and 5-py-H), 7.79 (1H, t, 4-py-H), 8.05 (2H, d, *J* = 8 Hz, 2- and 6-tolyl-H), 8.15 (2H, d, *J* = 6Hz, 3Hz, 2- and 6- Ph-H); MS, m/z (r.i.) 246 (M<sup>+</sup> +1, 69%), 245 (M<sup>+</sup>, 100), 244 (M- H, 95), 243 (36), 242 (30), 241(22), 230 (M- CH<sub>3</sub>, 35), 229 (20), 228 (25), 215 (11), 202 (20), 167 (10) (Found: C, 88.10; H, 6.08; N, 5.45. C<sub>18</sub>H<sub>15</sub>N requires: C, 88.16; H, 6.12; N, 5.71 %).

### **2-(4-Bromophenyl)-6-(4-tolyl)pyridine (161).**

A mixture of the pyridinium salt (160) (2.13 g), 1-(4-methylphenyl)-3-(dimethyl amino)propan-1-one hydrochloride (1.36 g) and ammonium acetate (4 g) yielded a product which was purified by column chromatography (diethyl ether : petroleum spirit, 10:90) and crystallised from a mixture of chloroform and petroleum spirit to give the colourless *2-(4-bromophenyl)-6-(4-tolyl)pyridine*, (1.0 g, 57 %), mp 194-195 °C;

IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2724, 1854, 1734, 1654, 1632, 1592, 1543, 1523, 1443, 1423, 1414, 1376, 1323, 1303, 1274, 1265, 1234, 1114, 1014, 996, 986, 842, 830, 796, 758, 722, 684, 554;  $^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  2.42 (3H, s,  $\text{CH}_3$ ), 7.31 (2H, d,  $J = 7.8$  Hz, 3- and 5-tolyl-H), 7.61 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.02 (2H, d,  $J = 8.0$  Hz, 2- and 6-tolyl-H), 8.08 (2H, d,  $J = 8.0$  Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 325 ( $\text{M}^+$  for  $^{81}\text{Br}$ , 44), 324 (7), 323 ( $\text{M}^+$  for  $^{79}\text{Br}$ , 75), 322 (100), 321(43), 308(5%), 244 ( $\text{M}^- \text{Br}$ , 31), 243 (15), 242 (15), 241(91), 230 (7), 149 (10), 122 (11), 84 (41) (Found: C, 66.56; H, 4.12; N, 4.21.  $\text{C}_{18}\text{H}_{14}\text{Br N}$  requires: C, 66.87; H, 4.33; N, 4.33%).

### **2-(4-Cyanophenyl)-6-(4-tolyl)pyridine (168).**

The pyridinium salt (138) (1.74 g), 1-(4-cyanophenyl)-3-(dimethylamino)propan-1-one hydrochloride (167) (1.43 g) and ammonium acetate (4 g) gave a product which was purified by column chromatography (chloroform:petroleum spirit, 90:10) and then crystallised from a mixture of chloroform and petroleum spirit to give the colourless *2-(4-cyanophenyl)-6-(4-tolyl)pyridine* (168) (1.50 g, 93%), mp 161-162 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2360, 2230 (CN), 1942, 1654, 1633, 1588, 1558, 1540, 1432, 1407, 1308, 1237, 1213, 1188, 1165, 1114, 1016, 988, 866, 800, 744, 758, 722, 668, 654, 608, 598, 554.505;  $^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  2.42 (3H, s,  $\text{CH}_3$ ), 7.31 (2H, d,  $J = 7.8$  Hz, 3- and 5-tolyl-H), 7.77 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.02 (2H, d,  $J = 7.8$  Hz, 2- and 6-tolyl-H), 8.23 (2H, d,  $J = 7.8$  Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 271 (25%), 270 ( $\text{M}^+$ , 100), 268 (8), 267 (7), 266 (6), 208 (9), 156 (54), 149 (35), 135 (7), 134 (10), 133 (6), 128 (9), 126 (8), 121 (7), 120 (9), 113 (45), 105 (7), 99 (10), 97 (13), 86 (10) (Found: C, 84.31; H, 5.10; N, 10.28.  $\text{C}_{19}\text{H}_{14}\text{N}_2$  requires: C, 84.44; H, 5.18; N, 10.37%).

#### **4-(2-[6-{4-Tolyl}pyridyl])benzoic acid (173).**

The pyridinium salt (138) (1.74 g), 4-(3-dimethylaminopropanoyl)benzoic acid hydrochloride (175) (1.54 g) and ammonium acetate (4 g) gave a product which was purified by crystallisation from methanol (decolourising charcoal) to give the *4*-(2-[6-{4-tolyl}pyridyl])benzoic acid (173) (0.90 g, 52 %), mp 287-287.5 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3055 (OH), 1579, 1560, 1406, 1343, 1234, 1209, 1116, 1098, 1010, 996, 987, 866, 800, 744, 758, 722, 667, 654, 556, 543, 523, 511, 510, 506, 504;  $^1\text{H NMR}$  (360 MHz, DMSO- $d_6$ )  $\delta$  2.35 (3H, s, CH<sub>3</sub>), 5.16 (1H, broad signal, exchangeable with D<sub>2</sub>O, OH), 7.32 (2H, d,  $J$  = 7.8 Hz, 3- and 5-tolyl-H), 7.99 (5H, m, 3- and 5-Ar-H, 3-, 4- and 5-py-H), 8.11 (2H, d,  $J$  = 7.8 Hz, 2- and 6-tolyl-H), 8.14 (2H, d,  $J$  = 7.8 Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 290 (M+1, 17%), 289 (M<sup>+</sup>, 100), 288 (24), 259 (6), 245 (6), 244 (M - CO<sub>2</sub>H, 23), 243 (12), 242 (11), 228 (11), 223 (6), 215 (6), 196 (9), 186 (54), 149 (8), 130 (32), 96 (23), 64 (17) (Found: C, 78.64; H, 5.31; N, 4.52. C<sub>19</sub>H<sub>15</sub>NO<sub>2</sub> requires: C, 78.89; H, 5.19; N, 4.84%).

#### **2-Phenyl-6-(4-tolyl)pyridine (144)**

Second method using glacial acetic acid as the solvent.

A mixture of the pyridinium salt (143) (1.66 g, 6 mmol), 1-(4-methylphenyl)-3-(dimethylamino)propan-1-one hydrochloride (141) (1.36 g, 6 mmol) and ammonium acetate (4 g) in glacial acetic acid was heated at 80 °C for 2 h. The mixture was treated with water (20 cm<sup>3</sup>), the precipitate was filtered off and purified by column chromatography (chloroform : petroleum spirit, 50:50) the product was crystallised from a mixture of chloroform and petroleum spirit to give the colourless *2-phenyl-6-(4-tolyl)pyridine*, (0.210 g, 35 %), having physical data identical to that reported on (p. 122).

**Ethyl 4-(2-[6-{4-tolyl}pyridyl])benzoate (178).**

A mixture of 4-(2-[6-{4-tolyl}pyridyl])benzoic acid (173) ( 20.0 g, 70 mmol), absolute ethanol (25 cm<sup>3</sup>) and concentrated sulfuric acid ( 10 cm<sup>3</sup>) was refluxed for 1 h. The reaction mixture was allowed to reach room temperature and then extracted with dichloromethane. The extract was washed with water and then with sodium bicarbonate solution (5%), dried, filtered, concentrated *in vacuo* and the solid purified by column chromatography (ethyl acetate: petroleum spirit, 50:50) to give *ethyl 4-(2-[6-{4-tolyl}pyridyl])benzoate* (178) (16.70 g, 76 %), mp 113-114 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1686 (CO), 1638, 1588, 1534, 1448, 1366, 1328, 1282, 1252, 1166, 1089, 1065, 970, 996, 860, 770, 630, 545, 534, 520, 518; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.45 (3H, t, CH<sub>3</sub>), 2.43 (3H, s, Ar-CH<sub>3</sub>) 4.42 (2H, q, CH<sub>2</sub>), 7.33 (2H, d, *J* = 7.9 Hz, 3- and 5-tolyl-H), 7.79 (2H, d, *J* = 7.8 Hz, 3- and 5-py-H), 7.81 (1H, t, 4-py-H), 8.04 (2H, d, *J* = 7.9 Hz, 3- and 5-Ar-H), 8.15-8.21 (4H, m, 2 x 2- and 6-Ar and tolyl-H); MS, *m/z* (r.i.) 318 (M+1, 82%), 317 (M<sup>+</sup>, 96), 316 (31), 290 (20), 289 (M- C<sub>2</sub>H<sub>4</sub>, 76), 288 (20), 274 (12), 273 (76), 272 (100), 264 (18), 254 (45), 245 (43), 244 (M- CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, 92), 242 (29), 229 (16), 187 (12), 156 (12), 149 (18), 132 (9). 123 (23), 109 (10), 65 (14), 58 (18), 57 (13) (Found: C, 79.29; H, 5.95; N, 4.40. C<sub>21</sub>H<sub>19</sub>NO<sub>2</sub> requires: C, 79.49; H, 5.99; N, 4.41%).

## GENERAL METHOD FOR THE MONO-BROMINATION OF METHYL SUBSTITUTED 2,6-DIARYLPYRIDINES.

A mixture of 2,6-diarylpyridine (2.5 mmol), *N*-bromosuccinimide (0.45 g, 2.5 mmol), benzoyl peroxide (15 mg) and carbon tetrachloride (15 cm<sup>3</sup>) was refluxed, the reaction mixture was cooled and the solid filtered off. The filtrate was evaporated under reduced pressure and the residue purified.

### 2-([4-Bromomethyl]phenyl)-6-phenylpyridine (145).

After refluxing the mixture of 2-phenyl-6-*p*-tolylpyridine (144) (0.60 g), NBS, benzoyl peroxide and carbon tetrachloride for 10 h, yielded 2-([4-bromomethyl]phenyl)-6-phenylpyridine (145) which was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) (0.48 g, 60%), mp 91-92 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1596, 1570, 1444, 1423, 1314, 1226, 1156, 1072, 1016, 986, 844, 790, 762, 696; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  4.56 (2H, s, CH<sub>2</sub>Br), 7.50 (5H, m, 3-, 4- and 5-Ph, 3- and 5-tolyl-H), 7.68 (2H, m, 3- and 5-py-H), 7.80 (1H, t, 4-py-H), 8.12 (4H, d, *J* = 4 Hz, 2- and 6-Ph, 2- and 6-tolyl-H); MS, *m/z* (r.i) 326 (5%), 325 (M<sup>+</sup> for <sup>81</sup>Br, 29), 324 (7), 323 (M<sup>+</sup> for <sup>79</sup>Br, 29), 259 (12), 246 (21), 245 (79), 244 (M- Br, 100), 243 (31), 242 (36), 241(27), 230 (7), 215 (10), 122 (11), 84 (41) (Found: C, 66.56; H, 4.21; N, 4.08. C<sub>18</sub>H<sub>14</sub>Br N requires: C, 66.87; H, 4.33; N, 4.33%).

### 2-(4-[Bromomethyl]phenyl)-6-(4-tolyl)pyridine (154).

A mixture of 2,6-bis(4-methylphenyl)pyridine (136) (0.647 g), *N*-bromosuccinimide, benzoyl peroxide in carbon tetrachloride was refluxed for 18 h to afford a crude product which was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) to give colourless 2-(4-[bromomethyl]phenyl)-6-(4-tolyl)pyridine (154) (0.180 g, 28%), mp 60-61 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1734, 1588, 1510, 1432, 1308, 1226, 1204, 1114, 1014, 966, 864, 769, 744, 668, 602; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)

$\delta$  2.42 (3H, s, CH<sub>3</sub>), 4.55 (2H, s, CH<sub>2</sub>Br), 7.31 (2H, d,  $J = 8$  Hz, 3- and 5-tolyl), 7.52 (2H, d,  $J = 8$  Hz, 3- and 5-Ar-H), 7.67 (2H, m, 3- and 5-py-H), 7.83 (1H, t, 4-py-H), 8.05 (2H, d,  $J = 8.2$  Hz, 2- and 6-tolyl-H), 8.13 (2H, d,  $J = 8.2$  Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 339 (M<sup>+</sup> for <sup>81</sup>Br, 31%), 337 (M<sup>+</sup> for <sup>79</sup>Br, 32), 293 (12), 260 (9), 259 (53), 258 (100), 257 (12), 168 (9), 145 (12), 134 (6), 130 (9), 129 (11), 109 (7), 84 (19), 82 (28) (Found: C, 67.32; H, 4.64; N, 4.10 .C<sub>19</sub>H<sub>16</sub>BrN requires: C, 67.65; H, 4.74; N, 4.15 %).

### **2,6-Bis(4-[bromomethyl]phenyl)pyridine (155).**

The mixture containing 2,6-bis(4-methylphenyl)pyridine (136) (0.647 g), *N*-bromosuccinimide, benzoyl peroxide and carbon tetrachloride was refluxed for 18 h to afford colourless 2,6-bis(4-[bromomethyl]phenyl)pyridine (0.280 g, 35%), mp 152-153 °C (lit.,<sup>92</sup> mp. 150-153 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1588, 1568, 1508, 1444, 1432, 1353, 1323, 1314, 1270, 1228, 1202, 1143, 1121, 1104, 1014, 1010, 990, 852, 798, 730, 672, 600; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  4.55 (4H, s, 2 x CH<sub>2</sub>Br), 7.49 (4H, m, 3- and 5-Ar-H), 7.66 (2H, m, 3- and 5-py-H), 7.81 (1H, t, 4-py-H), 8.10 (4H, m, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 419 (M<sup>+</sup> for <sup>81</sup>Br, 19%), 417 (M<sup>+</sup> for <sup>81</sup>Br and <sup>79</sup>Br, 34), 415 (M<sup>+</sup> for <sup>79</sup>Br, 18), 338 (M- <sup>81</sup>Br, 100), 336 (M- <sup>79</sup>Br, 90), 292 (26), 272 (21), 259 (20), 258 (49), 257 (44), 124 (8), 113 (21), 98 (6), 95 (5), 85 (37), 54 (7).

### **2-(4-[Bromomethyl]phenyl)-6-(4-bromophenyl)pyridine (162).**

A mixture containing 2-(4-bromophenyl)-6-(4-tolyl)pyridine (161) (0.807 g), *N*-bromosuccinimide, benzoyl peroxide and carbon tetrachloride was refluxed for 4 h to afford the crude product which was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) to give the *title compound* (162) (0.50 g, 50%), mp

177-178 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1718, 1560, 1510, 1480, 1443, 1382, 1362, 1220, 1204, 1123, 1098, 962, 858, 769, 744, 668, 602;  $^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  4.55 (2H, s,  $\text{CH}_2\text{Br}$ ), 7.61 (2H, d,  $J = 8$  Hz, 3- and 5-Ar-H), 7.62 (4H, m, 2 x 3- and 5-Ar- and py-H), 7.81 (1H, t, 4-py-H), 8.02 (2H, d,  $J = 8$  Hz, 2- and 6-Ar-H), 8.08 (2H, d,  $J = 8$  Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 405 ( $\text{M}^+$  for  $^{81}\text{Br}$ , 5%), 403 ( $\text{M}^+$  for  $^{81}\text{Br}$  and  $^{79}\text{Br}$ , 11), 401 ( $\text{M}^+$  for  $^{79}\text{Br}$ , 5), 359 (23), 356 (16), 343 (18), 342 (35), 341 (60), 338 (34), 325 ( $\text{M}^-$   $^{79}\text{Br}$ , 95), 323 ( $\text{M}^-$   $^{81}\text{Br}$ , 100), 322 (92), 308 (4), 296 (7), 264 (19), 261 (33), 244 (38), 242 (33), 123 (9), 115 (21), 98 (6), 88 (12), 67 (6), 54 (6) (Found: C, 53.59; H, 3.61; N, 3.42.  $\text{C}_{18}\text{H}_{13}\text{Br}_2\text{N}$  requires: C, 53.86; H, 3.24; N, 3.49%).

### **2-(4-[Bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169).**

Application of the general method to 2-(4-cyanophenyl)-6-(4-tolylpyridine) (168) (0.675 g) yielded a product which was purified by column chromatography (petroleum spirit and diethyl ether, 70:30) to give colourless 2-([4-bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169) (0.49 g, 56%), mp 157-158 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2226 (CN), 1696, 1288, 1228, 1114, 1014, 936, 866, 843, 798, 726, 669, 645, 643, 632, 608, 591;  $^1\text{H NMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  4.56 (2H, s,  $\text{CH}_2\text{Br}$ ), 7.39 (2H, d,  $J = 7.4$  Hz, 3- and 5-Ar -H), 7.79 (5H, m, 3- and 5-Ar- and 3-,4-,5- py-H), 8.10 (2H, d,  $J = 7.4$  Hz, 2- and 6-Ar-H), 8.21 (2H, d,  $J = 7.4$  Hz, 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 350 ( $\text{M}^+$  for  $^{81}\text{Br}$ , 7%), 348 ( $\text{M}^+$  for  $^{79}\text{Br}$ , 7), 271 ( $\text{M}^-$   $^{79}\text{Br}$ , 16), 270 (81), 269 ( $\text{M}^-$   $^{81}\text{Br}$ , 100), 268 (10), 267 (12), 266 (9), 167 (5), 158 (9), 154 (12), 149 (21), 144 (9), 134 (7), 129 (5), 127 (5), 113 (7) (Found: C, 65.29; H, 4.01; N, 7.99.  $\text{C}_{19}\text{H}_{13}\text{Br N}_2$  requires: C, 65.51; H, 3.73; N, 8.04 %).

**Ethyl 4-(2-[6-{4-bromomethylphenyl}]pyridyl)benzoate (179).**

A mixture of ethyl 4-(2-[6-{4-tolyl}pyridyl])benzoate (178) (0.79 g), *N*-bromosuccinimide, benzoyl peroxide in carbon tetrachloride refluxed for 1.5 h afforded colourless *ethyl 4-(2-[6-{4-bromomethylphenyl}]pyridyl)benzoate* (179) which was purified by column chromatography (petroleum spirit and diethyl ether, 80:20) (0.49 g, 50%), mp 104-104.5 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2934, 1716 (CO), 1698, 1608, 1598, 1560, 1450, 1388, 1368, 1312, 1280, 1226, 1180, 1110, 1016, 998, 968, 956, 870, 865, 808, 772, 744, 650, 543, 542, 540;  $^1\text{HNMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  1.42 (3H, t,  $\text{CH}_3$ ), 4.40 (2H, q,  $\text{CH}_2$ ) 4.57 (2H, s,  $\text{CH}_2\text{Br}$ ), 7.53 (2H, d,  $J = 8.0$  Hz, 3- and 5-Ar-H), 7.69 (2H, m, 3- and 5-py-H), 7.85 (1H, t, 4-py-H), 8.12 (2H, d,  $J = 8.0$  Hz, 3- and 5-Ar-H), 8.21 (4H, m, 2 x 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 316 (M- HBr, 19%), 277 (6), 270 (5), 262 (100), 213 (9), 198 (16), 158 (14), 154 (21), 150 (2), 149 (6), 141(19), 136 (13), 122 (5), 106 (6), 105 (12), 77 (8) (Found: C, 63.70; H, 4.50; N, 3.50.  $\text{C}_{21}\text{H}_{18}\text{BrNO}_2$  requires: C, 63.79; H, 4.55; N, 3.54 %).

**2-(4-[Dibromomethylphenyl])-6-phenylpyridine (146).**

A mixture of 2-phenyl-6-(4-tolyl)pyridine (144) (0.60 g), *N*-bromosuccinimide (0.80 g), benzoyl peroxide (20 mg) and carbon tetrachloride (15  $\text{cm}^3$ ) was refluxed for 18 h and then the reaction mixture was cooled and filtered. The filtrate was evaporated under reduced pressure and residue was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) to give the *title compound* (146) (0.46 g, 47%), mp 146-147 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1586, 1566, 1444, 1434, 1316, 1232, 1212, 1184, 1165, 1072, 1040, 996, 987, 964, 954, 850, 814, 812, 766, 756, 736, 696, 654, 632, 618, 612, 546, 532, 512, 510;  $^1\text{HNMR}$  (360 MHz,  $\text{CDCl}_3$ )  $\delta$  6.71 (1H, s,  $\text{CHBr}_2$ ), 7.45 (3H, m, 3-, 4- and 5-Ph-H), 7.67 (4H, m, 3- and 5-py-H), 7.81 (1H, t, 4-py-H), 8.13 (4H, m, 2 x 2- and 6-Ar and py-H); MS,  $m/z$  (r.i.) 404 ( $\text{M}^+$  for  $^{81}\text{Br}$ ,



11%), 402 ( $M^+$  for  $^{81}\text{Br}$  and  $^{79}\text{Br}$ , 21), 400 ( $M^+$  for  $^{79}\text{Br}$ , 10), 324 (39), 323 ( $M - \text{Br}$ , 100), 321(88), 258 (39), 256 (15), 245 (9), 244 (11), 230 (20), 210 (12), 116 (23), 106 (8), 98 (5), 96 (13), 86 (7), 84 (41) (Found: C, 53.69; H, 3.33; N, 3.33.  $\text{C}_{18}\text{H}_{13}\text{Br}_2\text{N}$  requires: C, 53.86; H, 3.24; N, 3.49%).

### **2-(4-[Diethoxymethyl]phenyl)-6-phenylpyridine (147).**

2-(4-[Dibromomethyl]phenyl)-6-phenylpyridine (146) (0.35 g, .86 mmol) was dissolved in dry ethanol (10  $\text{cm}^3$ ) and added dropwise to a solution of sodium ethoxide (sodium metal (0.20 g) dissolved in ethanol (20  $\text{cm}^3$ )). The reaction mixture was refluxed for 30 minutes, cooled and the solvent was evaporated *in vacuo*. The residue was dissolved in water and extracted with chloroform. The extract was dried, evaporated and the residue was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) to give the *acetal* (147) (0.46 g, 47%), mp 46-47 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  2268, 2161, 1867, 1586, 1566, 1316, 1232, 1184, 1115, 1072, 1040, 998, 996, 850, 814, 766, 736, 696;  $^1\text{H}$ NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (6H, m, 2 x  $\text{CH}_3$ ), 3.53- 3.70 (4H, m, 2 x  $\text{CH}_2$ ), 5.58 (1H, s, CH), 7.46 (4H, m, 2 x 3- and 5-Ar-H), 7.59 (1H, m, 4-Ar-H), 7.70 (2H, m, 3- and 5-py-H), 7.81(1H, t, 4-py-H), 8.14 (4H, m, 2 x 2- and 6-Ar-H); MS,  $m/z$  (r.i.) 334 ( $M^+ + \text{H}$ , 8), 333 ( $M^+$ , 7), 289 ( $M - \text{C}_2\text{H}_4\text{O}$ , 70), 288 ( $M^+ - \text{OCH}_2\text{CH}_3$ , 94), 260 (100), 249 (48), 248 (10), 232 (47), 230 (10), 127 (10), 110 (12), 98 (10), 97 (10), 84 (41) (Found: C, 79.17; H, 6.84; N, 4.18.  $\text{C}_{22}\text{H}_{23}\text{NO}_2$  requires: C, 79.27; H, 6.90; N, 4.20%).

### **2-(4-Formylphenyl)-6-phenylpyridine (148).**

2-(4-[Diethoxymethyl]phenyl)-6-phenylpyridine (147) (0.20 g, 0.77 mmol) was hydrolysed with boiling 3M hydrochloric acid (5  $\text{cm}^3$ ) for 2h. The reaction mixture was neutralized with aqueous sodium hydroxide and extracted with chloroform. The extract was evaporated and the residue purified by column chromatography (chloroform) to give the *aldehyde* (148) (0.03 g, 19%), mp 46-47 °C; IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$  1704 (CO),

1606, 1564, 1434, 1423, 1323, 1304, 1268, 1210, 1202, 1160, 1096, 1022, 986, 969, 846, 808, 814, 760, 736, 696; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>) δ 7.43 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.62 (2H, m, 3- and 5-py-H), 7.81 (1H, t, 4-py-H), 8.25 (4H, m, 2 x 2- and 2 x 6-Ar-H), 10.04 (1H, s, CHO); MS, m/z (r.i) 260 (M<sup>+</sup>, 44%), 259 (M<sup>+</sup>, 100), 245 (65), 244 (40), 233 (M-CHO, 10), 232 (35), 231 (15), 230 (37), 230 (37), 228 (17), 198 (9), 188 (12), 178 (14), 169 (13), 167 (11), 154 (15), 114 (7), 84 (41), 54 (9) (Found: C, 83.18; H, 4.92; N, 5.21. C<sub>18</sub>H<sub>13</sub>NO requires: C, 83.30; H, 5.01; N, 5.40%).

**2-(4-[Ethoxymethyl]phenyl)-6-phenylpyridine (149).**

2-([4-Bromomethyl]phenyl)-6-phenylpyridine (145) (0.30 g, 0.92 mmol) was dissolved in dry ethanol (10 cm<sup>3</sup>) and added dropwise to a solution of sodium ethoxide (sodium metal (0.2 g) dissolved in ethanol (20 cm<sup>3</sup>)). The reaction mixture was refluxed for 30 min., cooled and the solvent evaporated *in vacuo*. The residue was dissolved in water and extracted with chloroform. The extract was dried, evaporated and the residue was purified by column chromatography (petroleum spirit and diethyl ether, 90:10) to give the *title compound* (149) (0.268 g, 93%), mp 41-41.5 °C; IR (KBr) ν<sub>max</sub>/cm<sup>-1</sup> 2112, 1897, 1650, 1544, 1499, 1320, 1280, 1144, 1092, 962, 943, 866, 865, 832, 776, 745, 642, 632, 612, 606, 568, 543; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>) δ 1.12 (3H, t, CH<sub>3</sub>), 3.42 (2H, q, CH<sub>2</sub>), 4.61 (2H, s, Ar-CH<sub>2</sub>), 7.47 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.61 (2H, m, 3- and 5-py-H), 7.82 (1H, t, 4-py-H), 8.10 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, m/z (r.i.) 290 (M<sup>+</sup>+H, 25%), 289 (M<sup>+</sup>, 88), 260 (M-CH<sub>2</sub>CH<sub>3</sub>, 87), 246 (M- OCH<sub>2</sub>CH<sub>3</sub>, 24), 245 (100), 244 (95), 242 (23), 232 (86), 230 (13), 198 (8), 176 (14), 154 (12), 149 (22), 98 (12), 96 (13), 88 (6), 86 (12), 56 (6), 54 (12) (Found (FAB;NOBA): M<sup>+</sup>, 289.1467 daltons. C<sub>20</sub>H<sub>19</sub>NO requires M, 289.1461).

#### **4-Acetylbenzoic acid (174).**

A mixture of 4-acetylbenzotrile (166) (0.98 g, 6.8 mmol), methanol (20 cm<sup>3</sup>) and sodium hydroxide solution (3M, 10 cm<sup>3</sup>) was refluxed for 1.5 h. The solution was cooled and acidified to pH 1 by dropwise addition of concentrated hydrochloric acid. The precipitate was filtered off, washed with water and dried to give the acid (1.08 g, 97%), mp 209-210 °C (lit.,<sup>125</sup> mp 208-210 °C); IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3444, 1684 (CO), 1500, 1437, 1283, 937, 815, 815, 642; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.62 (3H, s, CH<sub>3</sub>), 8.04 (4H, s, Ar-H), 11.0 (1H, br.s, exchangeable with D<sub>2</sub>O, OH); MS, m/z (r.i.) 165 (M<sup>+</sup>+1, 5%), 164 (M<sup>+</sup>, 49), 150 (33), 149 (M-CH<sub>3</sub>, 100), 130 (21), 122 (9), 121 (84), 93 (5), 65 (22), 43 (13).

#### **Attempted preparation of 2-(4-[methoxycarbonyl]phenyl)-6-(4-tolyl)pyridine (172).**

Dry hydrogen chloride was passed into an ice-cold solution of 2-(4-cyanophenyl)-6-(4-tolyl)pyridine (168) (0.27 g, 1 mmol) in dry methanol (300 cm<sup>3</sup>) until the solution was saturated. After 1 h the solution was allowed to reach room temperature and ice-cold water (300 cm<sup>3</sup>) was added, the solvent evaporated, and the crude product was solidified by adding acetone and petroleum spirit. The solid was filtered off and crystallised from methanol to give the unexpected *4(2-[6-{4-tolyl}]benzoic acid (173)* (0.25 g, 23%), mp 287-287.5 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3055 (OH), 1579, 1560, 1406, 1234, 1209, 1116, 1098, 1010, 996, 987, 866, 800, 744, 758, 722, 667, 654, 556, 543; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.35 (3H, s, CH<sub>3</sub>), 5.16 (1H, broad signal, exchangeable with D<sub>2</sub>O, OH), 7.32 (2H, d, *J* = 7.8 Hz, 3- and 5-tolyl-H), 7.99 (5H, m, 3- and 5-Ar-H, 3-, 4- and 5-py-H), 8.15 (2H, d, *J* = 7.8 Hz, 2- and 6-tolyl-H), 8.20 (2H, d, *J* = 7.8 Hz, 2- and 6-Ar-H).

### 2-(4-[3-Aminopropoxymethyl]phenyl)-6-phenylpyridine (150) .

A mixture of 2-([4-bromomethyl]phenyl)-6-phenylpyridine (145) (0.5 g, 1.6 mmol), anhydrous potassium carbonate (0.22 g) and 3-aminopropanol (5 cm<sup>3</sup>) was refluxed for 2 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and the product was purified by column chromatography (chloroform: methanol: aq. ammonia (d 0.88), 90:8:2) to give the 2-(4-[3-aminopropoxymethyl]phenyl)-6-phenylpyridine (150) (0.30 g, 61%), mp 82-83 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3320 (NH<sub>2</sub>), 3210 (NH<sub>2</sub>), 1891, 1756, 1650, 1567, 1543, 1443, 1378, 1323, 1278, 1198, 1144, 1096, 1056, 969, 963, 866, 632, 543, 522, 501; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.73 (2H, m, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 2.42 (2H, br.s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 2.91 (2H, m, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 3.83 (2H, t, *J* = 5.2 Hz, CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-NH<sub>2</sub>), 3.86 (2H, s, Ar-CH<sub>2</sub>), 7.48 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.67 (2H, m, 3- and 5-py-H), 7.79 (1H, t, 4-py-H), 8.13 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, *m/z*(r.i.) 319 (M<sup>+</sup>+H, 29%), 318 (M<sup>+</sup>, 41), 273 (15), 260 (M-(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>, 30), 259 (32), 245 (24), 244 (67), 242 (23), 232 (51), 231 (13), 212 (9), 123 (9), 109 (13), 98 (15), 87 (10), 85 (64), 83 (100) (Found: (EI): M<sup>+</sup>, 318.1732 daltons. C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O requires M, 318.1725).

## GENERAL METHOD FOR AMINOLYSIS OF 2-(4-[BROMOMETHYL]PHENYL)-6-PHENYLPYRIDINE.

A mixture of the appropriate 2-(4-[bromomethyl]phenyl)-6-arylpyridine (145) (1.6 mmol) and anhydrous potassium carbonate (0.22 g) was dissolved in an excess of a diamine under a nitrogen atmosphere. The mixture was refluxed for 2 h unless stated otherwise. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo*. The resulting oil was distilled to remove the excess of diamine and the crude product purified by column chromatography on silica gel using a mixture of chloroform and methanol (85:15) containing conc. aqueous ammonia (3-5 drops) unless otherwise stated.

### 2-(4-[4-Amino-2-azabutyl]phenyl)-6-phenylpyridine (151).

2-(4-[Bromomethyl]phenyl)-6-phenylpyridine (145) (0.50 g), anhydrous potassium carbonate and ethylene diamine (5 cm<sup>3</sup>) gave the 2-(4-[4-amino-2-azabutyl]phenyl)-6-phenylpyridine (151) (0.25 g, 53%), mp 69-70 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3420 (NH), 3330 (NH<sub>2</sub>), 3240 (NH<sub>2</sub>), 1654, 1616, 1570, 1543, 1448, 1412, 1386, 1323, 1114, 1098, 1043, 1021, 996, 986, 760, 696, 543, 520; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.66 (3H, br.s, exchangeable with D<sub>2</sub>O, NH and NH<sub>2</sub>), 2.73 (2H, t, *J* = 5.6 Hz, CH<sub>2</sub>), 2.83 (2H, t, *J* = 5.6 Hz, CH<sub>2</sub>), 3.87 (2H, s, Ar-CH<sub>2</sub>), 7.43 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.65 (2H, m, 3- and 5-py-H), 7.80 (1H, t, 4-py-H), 8.12 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, *m/z*(r.i.) 304 (M<sup>+</sup>+H, 22%), 303 (M<sup>+</sup>, 100), 273 (M- CH<sub>2</sub>NH<sub>2</sub>, 22), 245 (42), 244 (94), 243 (9), 241(6), 122 (5), 111 (13), 109 (6), 98 (12), 96 (14), 85 (16), 83 (25), 56 (14) (Found: (EI): M<sup>+</sup>, 303.1735 daltons. C<sub>20</sub>H<sub>21</sub>N<sub>3</sub> requires M, 303.1728).

**2-(4-[5-Amino-2-azapentyl]phenyl)-6-phenylpyridine (152).**

2-(4-[Bromomethyl]phenyl)-6-phenylpyridine (0.50 g), anhydrous potassium carbonate and 1,3-diaminopropane (5 cm<sup>3</sup>) yielded the 2-(4-[5-amino-2-azapentyl]phenyl)-6-phenylpyridine (152) (0.25 g, 52%), mp 69-70 °C; IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup> 3420 (NH), 3330 (NH<sub>2</sub>), 3210 (NH<sub>2</sub>), 1654, 1570, 1448, 1386, 1234, 1123, 1114, 1098, 1032, 996, 986, 760, 696, 543, 521; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.71 (2H, m, CH<sub>2</sub>), 1.96 (3H, br.s, exchangeable with D<sub>2</sub>O, NH and NH<sub>2</sub>), 2.73 (2H, m, 2 x CH<sub>2</sub>), 3.87 (2H, s, Ar-CH<sub>2</sub>), 7.43 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.67 (2H, m, 3- and 5-py-H), 7.80 (1H, t, 4-py-H), 8.10 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, m/z (r.i.) 318 (M<sup>+</sup>+H, 18%), 317 (M<sup>+</sup>, 76), 260 (20), 259 (M-(CH<sub>2</sub>)<sub>3</sub> NH<sub>2</sub>, 57), 246 (21), 245 (100), 242 (43), 232 (19), 122 (5), 121 (32), 113 (12), 109 (9), 105 (13), 103 (7), 98 (43), 96 (12), 89 (7), 85 (16), 83(25) (Found (EI): M<sup>+</sup>, 317.1892 daltons. C<sub>21</sub>H<sub>23</sub>N<sub>3</sub> requires M, 317.2884).

**2-(4-[8-Amino-2-azaooctyl]phenyl)-6-phenylpyridine (153).**

2-(4-[Bromomethyl]phenyl)-6-phenylpyridine (145) (0.50 g), anhydrous potassium carbonate and an excess of 1,6-diaminohexane (5 cm<sup>3</sup>) afforded the *title compound* (153) (0.23 g, 43%), mp 88-89 °C; IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup> 3420 (NH), 3330 (NH<sub>2</sub>), 3220 (NH<sub>2</sub>), 1654, 1570, 1448, 1442, 1386, 1232, 1212, 1114, 1098, 1043, 1021, 986, 987, 886, 885, 760, 696; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.32 (8H, m, 4 x CH<sub>2</sub>), 1.56 (3H, br.s, exchangeable with D<sub>2</sub>O, NH and NH<sub>2</sub>), 2.64 (4H, m, 2 x CH<sub>2</sub>), 3.84 (2H, s, Ar-CH<sub>2</sub>), 7.49 (5H, m, 2 x 3-, 2 x 5- and 4-Ar-H), 7.68 (2H, m, 3- and 5-py-H), 7.80 (1H, t, 4-py-H), 8.13 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, m/z (r.i.) 360 (M<sup>+</sup>+1, 17%), 359 (M<sup>+</sup>, 55), 240 (17), 329 (10), 273 (M-(CH<sub>2</sub>)<sub>5</sub> NH<sub>2</sub>, 22), 266 (14), 259 (44), 246 (20%), 245 (100), 244 (52), 232 (8), 165 (13), 143 (12), 129 (10), 105 (14), 98 (9), 96 (8), 89 (12), 85 (13), 84 (30) (Found: (EI): M<sup>+</sup>, 359.2361 daltons. C<sub>24</sub>H<sub>29</sub>N<sub>3</sub> requires M, 359.2361).

**2-(4-[8-Amino-2-azaocetyl]phenyl)-6-(4-methylphenyl)pyridine (156)**

2-(4-[Bromomethyl]phenyl)-6-(4-methylphenyl)pyridine (154) (0.53 g), anhydrous potassium carbonate and an excess of 1,6-diaminohexane (5 cm<sup>3</sup>) gave 2-(4-[8-amino-2-azaocetyl]phenyl)-6-(4-methylphenyl)pyridine (156) (0.27 g, 45%), mp 98-99 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3420 (NH), 3330 (NH<sub>2</sub>), 3210 (NH<sub>2</sub>), 1876, 1765, 1686, 1654, 1570, 1560, 1448, 1423, 1386, 1323, 1234, 1212, 1114, 1098, 1045, 1021, 986, 886, 843, 760, 696; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.23-1.52 (8H, m, 4 x CH<sub>2</sub>), 1.88 (3H, s, exchangeable with D<sub>2</sub>O, NH and NH<sub>2</sub>), 2.42 (3H, s, Ar-CH<sub>3</sub>), 2.66 (4H, m, 2 x CH<sub>2</sub>), 3.85 (2H, s, Ar-CH<sub>2</sub>), 7.29-7.31 (2H, m, 3- and 5-tolyl-H), 7.45 (2H, m, 3- and 5-Ar-H), 7.67 (2H, d,  $J = 7.6$  Hz, py-H), 7.77 (1H, t, 4-py-H), 8.01-8.18 (4H, m, 2- and 6-tolyl, 2- and 6-Ar-H); MS,  $m/z(\text{r.i.})$  374 (M<sup>+</sup>+1, 13%), 373 (M<sup>+</sup>, 60), 354 (42), 287 (25), 258 (M- NH(CH<sub>2</sub>)<sub>6</sub> NH<sub>2</sub>, 55), 191 (39), 149 (28), 148 (37), 134 (26), 129 (100), 112 (34), 86 (45) (Found: (EI): M<sup>+</sup>, 373.2499 daltons. C<sub>25</sub>H<sub>31</sub>N<sub>3</sub> requires M, 373.2508).

**2,6-Bis(4-[8-amino-2-azaocetyl]phenyl)pyridine (157).**

A mixture of 2,6-bis([4-bromomethyl]phenyl)pyridine (155) (0.66 g), anhydrous potassium carbonate and an excess of 1,6-diaminohexane (5 cm<sup>3</sup>) afforded the crude product which was purified by column chromatography (methanol: aq. ammonia, 85:15) to give the 2,6-bis(4-[8-amino-2-azaocetyl]phenyl)pyridine (157) (0.20 g, 26%), mp 147-148 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3420 (NH), 3330 (NH<sub>2</sub>), 3320 (NH<sub>2</sub>), 1654, 1570, 1448, 1386, 1234, 1212, 1114, 1098, 1065, 998, 986, 886, 884, 760, 696, 543; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.44 (6H, s, exchangeable with D<sub>2</sub>O, 2 x NH and 2 x NH<sub>2</sub>), 1.34-1.56 (16H, m, 8 x CH<sub>2</sub>), 2.67 (8H, m, 4 x CH<sub>2</sub>), 3.91 (4H, s, 2 x Ar-CH<sub>2</sub>), 7.44 (4H, m, 2 x 3- and 2 x 5-Ar-H), 7.65 (2H, m, 3- and 5-py-H), 7.81 (1H, t, 4-py-H), 8.11 (4H, m, 2 x 2- and 2 x 6-Ar-H) (Found: (EI): M<sup>+</sup>, 488.3746 daltons. C<sub>31</sub>H<sub>45</sub>N<sub>5</sub> requires M, 487.3660).

## GENERAL METHOD FOR THE PREPARATION OF SULFIDES FROM 2-(4-BROMOMETHYL]PHENYL)-6-ARYLPYRIDINE.

Metallic sodium (1.19 g, 52 mmol) was reacted with anhydrous ethanol (100 cm<sup>3</sup>) and resultant solution of sodium ethoxide was treated with 2-(dimethylamino)ethanethiol hydrochloride (3.68 g, 26 mmol). The mixture was stirred for 10 min. at 25 °C then treated with the appropriate 2-(4-[bromomethyl]phenyl)-6-arylpyridine (24 mmol) and stirred for 2 h at reflux. The solid was filtered off and the filtrate evaporated. The crude product was purified by chromatography on silica gel with a mixture of chloroform and methanol (98:2) unless otherwise stated.

### 2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-methylphenyl)pyridine (158).

The product from 2-(4-[bromomethyl]phenyl)-6-(4-tolyl)pyridine (154) (8.0 g) and 2-(dimethylamino)ethanethiol hydrochloride (3.68 g) gave the colourless *title compound* (158) (7.0 g, 81%), mp 54-55 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2234, 1643, 1570, 1560, 1432, 1414, 1343, 1245, 1209, 1167, 1078, 1067, 1008, 996, 994, 887, 883, 796, 668, 662, 592, 569; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  2.21 (6H, s, 2 x CH<sub>3</sub>), 2.43 (3H, s, CH<sub>3</sub>), 2.51 (4H, m, 2 x CH<sub>2</sub>), 3.74 (2H, s, Ar-CH<sub>2</sub>), 7.30 (2H, d,  $J = 8$  Hz, 3- and 5-tolyl-H), 7.44 (2H, d,  $J = 8$  Hz, 3- and 5-Ar-H), 7.65 (2H, m, 3- and 5-py-H), 7.78 (1H, t, 4-py-H), 8.04 (2H, d,  $J = 8$  Hz, 2- and 6-tolyl-H), 8.09 (2H, d,  $J = 8$  Hz, 2- and 6-Ar-H); MS,  $m/z(\text{r.i.})$  363 ( $M^+ + 1$ , 6%), 362 ( $M^+$ , 18), 302 (9), 290 ( $M - (\text{CH}_3)_2$ , 7), 273 (7), 260 (20), 259 (100), 258 (34), 222 (45), 122 (5), 123 (13), 112 (9), 98 (5), 87 (95), 85 (16), 83 (25) (Found: (EI):  $M^+$ , 362.1892 daltons. C<sub>23</sub>H<sub>26</sub>N<sub>2</sub>S requires  $M$ , 362.1808).



**2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-bromophenyl)pyridine (163).**

The 2-(4-[bromomethyl]phenyl)-6-(4-bromophenyl)pyridine (162) (9.9 g) and 2-(dimethyl amino)ethanethiol hydrochloride yielded 2-(4-[4-dimethylamino-2-thiabutyl]phenyl)-6-(4-bromophenyl)pyridine (163) (6.6 g, 62%), mp 82.7-83 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  1590, 1560, 1434, 1423, 1368, 1324, 1289, 1267, 1234, 1166, 1070, 1006, 998, 968, 886, 798, 745, 723, 689, 678, 662, 654, 592, 543, 520, 512, 518, 512;  $^1\text{H}$ NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  2.36 (6H, s, 2 x  $\text{CH}_3$ ), 2.40-2.79 (4H, m, 2 x  $\text{CH}_2$ ), 3.70 (2H, s, Ar- $\text{CH}_2$ ), 7.46 (2H, d,  $J = 8$  Hz, 3- and 5-Ar-H), 7.66 (4H, m, 3- and 5-py, 3- and 5-Ar-H), 7.81 (1H, t, 4-py-H), 8.07 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, m/z (r.i.) 428 ( $\text{M}^+$  for  $^{81}\text{Br}$ , 9%), 426 ( $\text{M}^+$  for  $^{79}\text{Br}$ , 9), 368 (M-  $\text{CH}_2\text{N}(\text{CH}_3)_2$ , 8), 357 (16), 356 (14), 354 (8), 326 (19), 325 (98), 324 (63), 223 (9), 212 (13), 112 (14), 109 (3), 98 (43), 83 (25) (Found: (EI):  $\text{M}^+$ , 426.0765 daltons.  $\text{C}_{22}\text{H}_{23}\text{BrN}_2\text{S}$  requires M, 426.0809).

**2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-cyanophenyl)pyridine (170).**

The 2-(4-[bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169) (8.35 g) and 2-(dimethyl amino)ethanethiol hydrochloride afforded the *tertiary amine* (170) (4.8 g, 54%), mp 53-54 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  2362, 2226 (CN), 1558, 1506, 1376, 1270, 1164, 1016, 1009, 1005, 998, 987, 867, 845, 798, 765, 669, 662, 592, 547, 542, 521, 511;  $^1\text{H}$ NMR (360 MHz,  $\text{CDCl}_3$ )  $\delta$  2.21 (6H, s, 2 x  $\text{CH}_3$ ), 2.48- 2.57 (4H, m, 2 x  $\text{CH}_2$ ), 3.79 (2H, s, Ar- $\text{CH}_2$ ), 7.44 (2H, d,  $J = 8$  Hz, 3- and 5-Ar-H), 7.72 (4H, m, 3- and 5-py, 3- and 5-Ar-H), 7.86 (1H, t, 4-py-H), 8.07 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, m/z (r.i.) 373 ( $\text{M}^+$ , 6%), 328 (6), 313 (7), 271(15), 270 (64), 269 (M-  $\text{S}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$ , 36), 268 (5), 268 (5), 267 (6), 123 (9), 115 (13), 109 (65), 105 (8), 104 (9), 98 (7), 87 (15), 71(5), 66 (9), 65 (13), 59 (4), 58 (100) (Found: (EI):  $\text{M}^+$ , 373.1604 daltons.  $\text{C}_{23}\text{H}_{23}\text{N}_3\text{S}$  requires M, 373.1613).

**Ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180).**

The ethyl 4-(2-[6-{4-bromomethylphenyl}]pyridyl)benzoate (179) (9.48 g) and 2-(dimethylamino)ethanethiol hydrochloride gave a product which was purified by chromatography (chloroform:methanol, 96:4) afforded *ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate* (180) (0.25 g, 70%), mp 36-36.5 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 1686, 1555, 1505, 1443, 1414, 1324, 1311, 1270, 1115, 1050, 998, 976, 945, 879, 866, 798, 665, 663, 598, 573, 565, 530 ; <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.43 (3H, t, CH<sub>3</sub>), 2.24 (6H, s, 2 x CH<sub>3</sub>), 2.49- 2.58 (4H, m, 2 x CH<sub>2</sub>), 3.80 (2H, s, Ar-CH<sub>2</sub>), 4.42 (2H, q, CH<sub>2</sub>), 7.42 (2H, d, *J* = 6.7 Hz, 3- and 5-Ar-H), 7.73 (2H, m, 3- and 5-Ar-H), 7.84 (1H, t, 4-py-H), 8.09 (2H, m, 3- and 5-py-H), 8.21 (4H, m, 2 x 2- and 2 x 6-Ar-H); MS, *m/z* (r.i.) 317 (15%), 316 (M- S(CH<sub>2</sub>)<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub>, 8), 149 (8), 122 (14), 105 (22), 103 (19), 83 (8), 77 (9), 73 (9), 70 (39), 58 (100), 56 (33), 45 (49), 42 (32) (Found: (EI): M<sup>+</sup>, 421.1951 daltons. C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S requires M, 421.1940).

**2-([*Tert*-Butoxycarbonylamino]ethyl)amine (176).**

To an ice-cooled solution of 1,2-diaminoethane (5 cm<sup>3</sup>, 0.075 mol) in dichloromethane (40 cm<sup>3</sup>) was added di-*tert*-butyldicarbonate (5.45 g, 0.025 mol) in dichloromethane (20 cm<sup>3</sup>) over 20 min. After being stirred at ambient temperature overnight, the suspension was filtered and the filtrate concentrated, the residue was connected to a vacuum pump to remove the excess amine and to leave 2-(*tert*-butoxycarbonylamino]ethyl)amine (3.84 g, 96%)<sup>63</sup> <sup>1</sup>HNMR (360 MHz, CDCl<sub>3</sub>)  $\delta$  1.24 (2H, s, NH<sub>2</sub>), 1.46 (9H, s, Boc), 2.73 (2H, m, CH<sub>2</sub>), 3.13 (2H, s, CH<sub>2</sub>), 5.02 (1H, s, NH); MS, *m/z* (r.i.) 160 (M<sup>+</sup>, 4%), 143 (M<sup>+</sup>- NH<sub>3</sub>, 17), 115 (M<sup>+</sup>- C(CH<sub>3</sub>)<sub>3</sub>, 100), 98 (16).

**N-(2-[*Tert*-Butoxycarbonylamino]ethyl)-4-(2-[6-{4-tolyl}pyridyl])benzamide (177).**

A mixture of the 4-(2-[6-{4-tolyl}phenyl]pyridyl)benzoic acid (173) (0.367 g, 1.27 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) (0.29 g, 1.52 mmol) and 1-hydroxybenzotriazole (HOBT) (0.22 g, 1.65 mmol) in anhydrous DMF (10 cm<sup>3</sup>) was stirred at room temperature for 30 min and to this solution was added the protected amine (0.212 g, 1.33 mmol). After the mixture had been stirred overnight the solid was filtered off and the filtrate removed *in vacuo*. The residue was treated with ethyl acetate, the suspension was filtered, the filtrate concentrated and the product purified by chromatography (ethyl acetate; petroleum spirit 60:40) to give colourless *N*-(2-[*tert*-butoxycarbonylamino]ethyl)-4-(2-[6-{4-tolyl}pyridyl])benzamide (177) (0.370 g, 68%) mp 198-198.5 °C; IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$  3342 (NH), 1686 (CO), 1635, 1588, 1534, 1448, 1388, 1366, 1322, 1252, 1166, 970, 860, 802, 770, 630; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.34 (9H, s, 3 x CH<sub>3</sub>), 2.38 (3H, s, Ar-CH<sub>3</sub>), 3.14-3.36 (4H, m, 2 x CH<sub>2</sub>), 6.81 (1H, s, exchangeable with D<sub>2</sub>O, NH), 7.32 (2H, d, *J* = 7.8 Hz, 3- and 5-Ar-H), 7.92 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.24 (2H, d, *J* = 8 Hz, 2- and 6-tolyl-H), 8.28 (2H, d, *J* = 8 Hz, 2- and 6-Ar-H), 8.42 (1H, s, exchangeable with D<sub>2</sub>O, NH); MS, *m/z* (r.i.) 316 (9%), 315 (M<sup>+</sup> - NH(Boc), 7), 314 (34), 313 (100), 312 (49), 311 (15), 302 (15), 301 (12), 289 (17), 285 (32), 284 (98), 273 (12), 272 (24), 245 (19), 244 (22), 221 (9), 142 (20) (Found: C, 72.12; H, 6.51; N, 9.62. C<sub>26</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub> requires C, 72.38; H, 6.72; N, 9.74 %).

**GENERAL METHOD FOR AMINOLYSIS OF ETHYL 4-(2-[6-{4-(2-[DIMETHYLAMINO]ETHYL)THIOMETHYL}PHENYL]PYRIDYL)BENZOATE (180).**

The ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180) (1.6 mmol), anhydrous potassium carbonate (1.6 mmol) and an excess of amine (5 cm<sup>3</sup>) were refluxed under a nitrogen atmosphere for 8 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo*, the excess of amine removed by distillation and the crude product was purified by column chromatography with a mixture of methanol, chloroform and conc. aqueous ammonia (90:5:5) unless otherwise stated and then crystallised from methanol.

***N*-(2-Aminoethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (181).**

The ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180) (0.67 g) and 1,2-diaminoethane afforded a product which was purified by column chromatography (methanol:chloroform: aq. ammonia, 92:8:2) to give the *title compound* (181) (0.48 g, 70%), mp 103-104 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3340 (NH), 3320 (NH<sub>2</sub>), 3212 (NH<sub>2</sub>), 1734, 1718 (CO), 1686, 1628, 1586, 1540, 1320, 1164, 1014, 808, 768, 754, 696, 632, 587, 542, 512; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.11 (6H, s, 2 x CH<sub>3</sub>), 2.42-2.54 (4H, m, 2 x CH<sub>2</sub>), 2.71-3.17 (4H, m, 2 x CH<sub>2</sub>), 3.29 (2H, br.s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.48 (2H, d, *J* = 8.0 Hz, 3- and 5-Ar-H), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.18 (2H, d, *J* = 8.0 Hz, 2- and 6-Ar-H), 8.30 (2H, d, *J* = 8.0 Hz, 2- and 6-Ar-H), 8.55 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (*r.i.*) 435 (M<sup>+</sup>+1, 53%), 413 (75), 391 (39), 301 (12), 287 (9), 243 (27), 234 (12), 194 (23), 189 (10), 176 (45), 167 (26), 154 (16), 149 (100), 141 (20), 132 (42), 123 (47), 118 (19), 109 (12), 98 (9), 87 (43) (Found: C, 69.01; H, 6.41; N, 13.08. C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>SO requires: C, 69.09; H, 6.95; N, 12.89%).

***N*-(4-Aminobutyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (182).**

The ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180) and 1,4-diaminobutane afforded a product which was twice triturated with diethylether (2 x 10 cm<sup>3</sup>) to give colourless *N*-(4-aminobutyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (182) (0.30 g, 41%), mp 155-156 °C; IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup> 3340 (NH), 3300 (NH<sub>2</sub>), 3200 (NH<sub>2</sub>), 2938, 1718 (CO), 1686, 1628, 1588, 1540, 1450, 1442, 1320, 1239, 1164, 1123, 1014, 808, 768, 632, 589, 543, 511, 510; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.40-1.62 (4H, m, for 2 x CH<sub>2</sub>), 2.10 (6H, s, 2 x CH<sub>3</sub>), 2.29-2.40 (4H, m, 2 x CH<sub>2</sub>), 2.51-3.21 (4H, m, 2 x CH<sub>2</sub>), 3.39 (2H, br.s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.47 (2H, d, *J* = 8.2 Hz, 3- and 5-Ar-H), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.18 (2H, d, *J* = 8.2 Hz, 2- and 6-Ar-H), 8.31 (2H, d, *J* = 8.2 Hz, 2- and 6-Ar-H), 8.65 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (r.i.) 463 (M<sup>+</sup>+1, 100%), 413 (9), 391 (12), 358 (33), 272 (14), 243 (24), 212 (9), 149 (32), 144 (12), 123 (25), 107 (45) (Found: C, 69.51; H, 7.15; N, 11.92. C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>OS requires: C, 70.09; H, 7.40; N, 12.10%).

***N*-(6-Aminohexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (183).**

The ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzoate (180) and 1,6-diaminohexane yielded a product which was crystallised from a mixture of methanol and diethyl ether to give colourless *N*-(6-aminohexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (183) (0.30 g, 38%), mp 143-144 °C; IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup> 3400 (NH), 3321 (NH<sub>2</sub>), 3200 (NH<sub>2</sub>), 2923, 1719 (CO), 1696, 1628, 1567, 1540, 1486, 1420, 1220, 1154, 1014, 968, 867, 816,

789,768, 632, 580, 565; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>) δ 1.32-1.54 (8H, m, for 2 x CH<sub>2</sub>), 2.10 (6H, s, 2 x CH<sub>3</sub>), 2.39-2.50 (4H, m, 2 x CH<sub>2</sub>), 2.90-3.28 (4H, m, 2 x CH<sub>2</sub>), 3.29 (2H, br.s, exchangeable with D<sub>2</sub>O, NH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.48 (2H, d, *J* = 8.1 Hz, 3- and 5-Ar-H), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.19 (2H, d, *J* = 8.1 Hz, 2- and 6-Ar-H), 8.30 (2H, d, *J* = 8. Hz, 2- and 6-Ar-H), 8.57 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (*r.i.*) 491 (M<sup>+</sup>+1, 100%), 419 (5), 387 (24), 315 (16), 272 (15), 243 (17), 212 (9), 183 (7), 176 (12), 161 (14), 149 (15), 132 (15), 123 (47), 117 (93), 107 (21), 98 (7), 88 (12) (Found: C, 70.53; H, 7.47; N, 10.86. C<sub>29</sub>H<sub>38</sub>N<sub>4</sub>SO requires: C, 70.98; H, 7.80; N, 11.41%).

#### GENERAL METHOD FOR ACETYLATION OF THE AMINES.

Acetic anhydride (0.012 g, 1 mmol) was added to a mixture of the appropriate amine (1 mmol) in glacial acetic acid at room temperature and then the reaction mixture was refluxed for 1 h. The solvent was evaporated *in vacuo* and the crude product was purified by chromatography using methanol as eluent. The acetamide was crystallised from a mixture of methanol and diethyl ether.

#### ***N*-(2-[Acetamido]ethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (184).**

The *N*-(2-aminoethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (181) (0.434 g), glacial acetic acid and acetic anhydride yielded pale yellow *N*-(2-[acetamino]ethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (184) (0.406 g, 85%), mp 192-193 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3282 (NH), 2923, 1675 (amide CO), 1628, 1560, 1540, 1408, 1323, 1290, 1129, 1016, 968, 886, 768, 632, 589, 540, 521; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>) δ 1.82

(3H, s, CH<sub>3</sub>), 2.10 (6H, s, 2 x CH<sub>3</sub>), 2.48-2.50 (4H, m, 2 x CH<sub>2</sub>), 3.29-3.39 (4H, m, 2 x CH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.48 (2H, d, *J* = 7.8 Hz, 3- and 5-Ar-H), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.10 (1H, t, exchangeable with D<sub>2</sub>O, NH), 8.17 (2H, d, *J* = 7.8 Hz, 2- and 6-Ar-H), 8.31 (2H, d, *J* = 7.8 Hz, 2 and 6-Ar-H), 8.71 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (r.i.) 477 (M<sup>+</sup>+1, 100%), 461 (12), 413 (18), 391 (22), 373 (29), 349 (10), 273 (12), 259 (17), 243 (20), 192 (10), 149 (30), 132 (9), 123 (35), 122 (12), 107 (54) (Found: C, 68.36; H, 6.48 ; N, 11.24 C<sub>27</sub>H<sub>32</sub>N<sub>4</sub>O<sub>2</sub>S requires: C, 68.06; H, 6.72; N, 11.76%).

***N*-(2-[Acetamido]butyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (185).**

The *N*-(6-aminobutyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (182) (0.462 g), glacial acetic acid and acetic anhydride gave the *title compound* (185) (0.25 g, 50%), mp 178.9-179 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3290 (NH), 2923, 1632 (amide CO), 1558, 1540, 1450, 1372, 1330, 1288, 1230, 1164, 1128, 1044, 1016, 926, 862, 810, 756, 745, 696, 606, 520; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.47-1.56 (4H, m, for 2 x CH<sub>2</sub>), 1.81 (3H, s, CH<sub>3</sub>), 2.11 (6H, s, 2 x CH<sub>3</sub>), 2.34-2.51 (4H, m, 2 x CH<sub>2</sub>), 3.07-3.32 (4H, m, 2 x CH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.48 (2H, d, *J* = 8.0 Hz, 3- and 5-Ar-H), 7.81 (1H, t, exchangeable with D<sub>2</sub>O, NH), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.18 (2H, d, *J* = 8.0 Hz, 2- and 6-Ar-H), 8.30 (2H, d, *J* = 8.0 Hz, 2- and 6-Ar-H), 8.61 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (r.i.) 505 (M<sup>+</sup>+1, 85%), 490 (6), 413 (22), 400 (15), 391 (32), 273 (16), 259 (18), 243 (15), 191 (14), 166 (32), 149 (56), 140 (22), 128 (20), 123 (68), 107 (100) (Found: C, 69.29; H, 7.10; N, 11.31 C<sub>29</sub>H<sub>36</sub>N<sub>4</sub>O<sub>2</sub>S requires: C, 69.04; H, 6.86; N, 11.11%).

***N*-(2-[Acetamido]hexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (186).**

The *N*-(6-aminohexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (183) (0.49 g), glacial acetic acid and acetic anhydride gave *N*-(2-[acetamido]hexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (186) (0.29 g, 55%), mp 150-150.5 °C; IR (KBr)  $\nu_{\max}$  /cm<sup>-1</sup> 3290 (NH), 2923, 1660 (amide CO), 1550, 1540, 1480, 1320, 1260, 1150, 1124, 1041, 1081, 928, 850, 756, 745, 696, 606, 568, 520; <sup>1</sup>HNMR (360 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.32-1.55 (8H, m, 4 x CH<sub>2</sub>), 1.84 (3H, s, CH<sub>3</sub>), 2.15 (6H, s, 2 x CH<sub>3</sub>), 2.38-2.51 (4H, m, 2 x CH<sub>2</sub>), 3.01-3.30 (4H, m, 2 x CH<sub>2</sub>), 3.82 (2H, s, Ar-CH<sub>2</sub>), 7.48 (2H, d, *J* = 8.1 Hz, 3- and 5-Ar-H), 7.83 (1H, t, exchangeable with D<sub>2</sub>O, NH), 7.98 (5H, m, 3- and 5-Ar, 3-, 4- and 5-py-H), 8.19 (2H, d, *J* = 8.1 Hz, 2- and 6-Ar-H), 8.29 (2H, d, *J* = 8.1 Hz, 2- and 6-Ar-H), 8.60 (1H, t, exchangeable with D<sub>2</sub>O, NH); MS (FAB;NOBA) (*r.i.*) 533 (M<sup>++1</sup>, 100%), 429 (16), 413 (15), 391 (16), 259 (11), 243 (14), 201 (14), 149 (25), 120 (23), 107 (42) (Found: C, 69.61; H, 7.22 ; N, 9.86 C<sub>31</sub>H<sub>40</sub>N<sub>4</sub>O<sub>2</sub>S requires: C, 69.92; H, 7.51; N, 10.52%).



## Physico-Chemical Measurement

### DNA Binding constant.

The interaction of drugs with nucleic acid can be measured by the loss of the ethidium fluorophore, which occurs upon binding of the compounds. Ethidium binds with nucleic acid through intercalation and this causes a large fluorescence enhancement (~25 fold) due to the immersion of the ethidium in the hydrophobic region of the nucleic acid and the isolation of the fluorophore from water.<sup>126,127</sup>

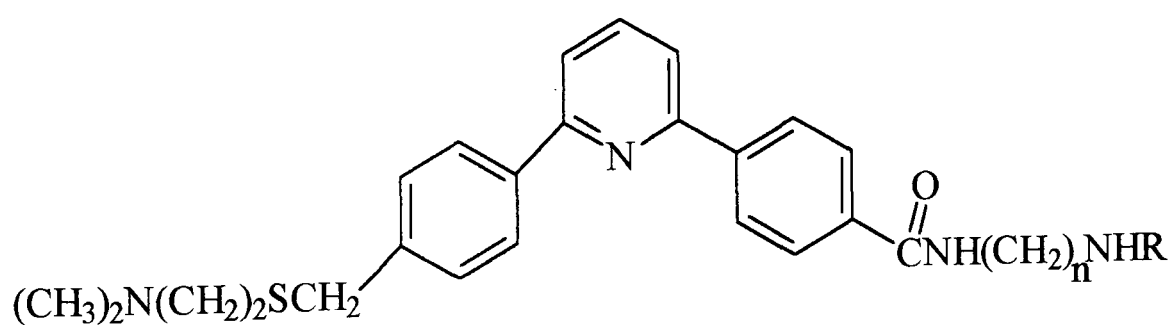
If another drug which binds with DNA is added to a solution of DNA saturated with ethidium and if this drug binds more strongly to DNA than ethidium, then displacement of some ethidium from DNA occurs and the fluorescence decreases.

The DNA binding constant of the drugs can be estimated by the decrease in fluorescence of ethidium as a function of the concentration of the added drug. The drug concentration which produces 50% inhibition of fluorescence is approximately inversely proportional to the binding constant which was determined in this work from a plot of percentage fluorescence against drug concentration measured at pH 7.5.

The binding constant of ethidium is  $10^7 \text{ M}^{-1}$  when the concentration of ethidium is  $8 \mu\text{m}$ . Therefore the binding constant can be calculated by dividing the product of ethidium bromide concentration and ethidium bromide binding constant by the concentration producing 50% loss in fluorescence. The measured fluorescence was corrected in all cases by subtracting the blank value, which is the fluorescence of ethidium bromide alone in buffer. The fluorescence of 100% was then the value for DNA saturated with ethidium bromide. The calculated binding constants are shown in Table 1.

DNA Binding Drugs	Concentration of Drugs X/ $\mu$ M	DNA Binding Constant at pH 7.5/ $M^{-1}$
181	23.82575	$3.3 \times 10^6$
182	25.75277	$3.1 \times 10^6$
183	17.65464	$4.5 \times 10^6$
184	233.6548	$3.4 \times 10^5$
185	187.9639	$4.3 \times 10^5$
186	75.18557	$1.1 \times 10^6$

Table 1: Binding constants of the novel compounds.



(181)  $n = 2, R = H$

(184)  $n = 2, R = COCH_3$

(182)  $n = 4, R = H$

(185)  $n = 4, R = COCH_3$

(183)  $n = 6, R = H$

(186)  $n = 6, R = COCH_3$

It has been reported <sup>86</sup> that tricyclic unfused polyaromatic systems with a cationic side chain are better amplifiers (binding constant,  $K=13 \times 10^6 \text{ M}^{-1}$ ) than classical intercalators ( $10^7\text{-}10^5 \text{ M}^{-1}$ ) at low concentration.

The electrostatic interaction of these cationic groups with the anionic DNA chain enhances groove binding or intercalation of the aromatic portion of the molecule. This is due to the stability of the molecule-DNA complex.<sup>128</sup> Several other unfused compounds with alkylthio or alkylamino linkages and with cationic side chains were tested. The thio substituted derivatives were found to bind more strongly than the amino analogue.<sup>129</sup>

In the present work, the novel amines (**181-183**) were found to bind to DNA and the different cationic side chains produced only a very small difference in the binding strengths (Table 1). The compounds having the longest cationic side chain and including a sulfur atom bind more strongly than the other DNA binders. The lower the values of the drug concentration, the greater the interaction with DNA. These compounds have been coupled through an amide link with analogues of the metal-binding part of the bleomycin structure, it was therefore of interest to study the DNA binding of the compounds after they had been converted from amines to amides and the acetyl derivatives (**184-186**) were studied. An order of magnitude decrease in the binding constant in going from the amine to the amide occurred, except in the case of (**183**) and (**186**) where the difference was less.

## Experimental

All the experiments were carried out using 10 mM TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid) and 0.5 mM EDTA (ethylenediaminetetraacetic acid) at pH 7.5 containing 9.92  $\mu$ M DNA.

The fluorescence measurement was carried out on a Perkin-Elmer LS50B luminescence spectrometer at excitation and emission wave lengths of 525 and 600 nm respectively. The effect of the drug in quenching the ethidium-DNA fluorescence was then measured by the addition of consecutive amounts (3  $\mu$ Ls) of a solution of the drug (concentration within the range 0.1  $\mu$ M to 100  $\mu$ M), leaving 5 min intervals between the addition of the drug and the measurement of the new fluorescence. Increasing amounts of the drug were added until the fluorescence was quenched by over 50 %. All fluorescence readings were corrected by subtraction of the blank value (that fluorescence recorded for ethidium bromide in buffer alone).

## CONCLUSION

The study of certain hexaazapentacenes has shown that these compounds can be obtained from 1,4-dithia[2,3-b:5,6-b]diquinoxalines and bis(2-chloroquinoxalin-3-yl)sulfides by using different reaction conditions. The 3-amino-5,6-dimethoxy-1,2,4-benzotriazine-1-oxide resisted attempts to cause further *N*-oxidation, probably due to steric hindrance.

Several routes for the synthesis of 2,6-diphenylpyridines carrying different substituents at the 4 and 4' positions of the phenyl nuclei have been investigated. A successful method for the preparation of 2,6-diphenylpyridines carrying a dimethylaminoalkyl group on one phenyl nucleus and a primary alkylamine substituent on the other phenyl ring has been developed. The binding of these compounds and the acetyl derivatives of the amines with DNA was studied.

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## APPENDIX

### List of Novel Compounds

- 2,3-Dimethoxy-1,4-diazaanthracene-9,10-dione (55)
- Bis(2-chloroquinoxalin-3-yl)sulfide (57)
- 6,13-Dibutyl-5,6,7,12,13,14-hexaazapentacene (58)
- 13-Butyl-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (59)
- 6,13-Dibenzyl-5,6,7,12,13,14-hexaazapentacene (60)
- 13-(2-Aminoethyl)-6,13-dihydro-6-thia-5,7,12,13,14-pentaazapentacene (61)
- 6,13-Dihydro-6-thia-5,7,12,13,14-pentaazapentacene (62)
- 1-Hydroxy-4,7-dimethoxy-1,2,3-benzotriazole (65)
- 2,5-Dimethoxy-6-nitroaniline (66)
- 2,5-Dimethoxy-4-nitroaniline (67)
- N-(2,5-dimethoxy-6-nitrophenyl)guanidine (68)
- 3-Amino-5,6-dimethoxy-1,2,4-benzotriazine-1-oxide (69)
- 4,7-Dimethoxy-1,2,3-benzotriazole (70)
- 1-(4-Methylphenyl)-3-(dimethylamino)propane-1-one hydrochloride (141)
- 1-(4-Cyanophenyl)-3-(dimethylamino)propane-1-one hydrochloride (167)
- 4-(3-dimethylaminopropanoyl)benzoic acid hydrochloride (175)
- 1-(4-Methylphenacyl)pyridinium bromide (138)
- Phenacylpyridinium bromide (143)
- 1-(4-Bromophenacyl)pyridinium bromide (160)
- 2-Phenyl-6-(4-tolyl)pyridine (144)
- 2-(4-Bromophenyl)-6-(4-tolyl)pyridine (161)
- 2-(4-Cyanophenyl)-6-(4-tolyl)pyridine (168)

4-(2-[6-{4-Tolyl}pyridyl])benzoic acid (173)  
Ethyl 4-(2-[6-{4-tolyl}pyridyl])benzoate (178)  
2-(4-[Bromomethyl]phenyl)-6-phenylpyridine (145)  
2-(4-[Bromomethyl]phenyl)-6-(4-tolyl)pyridine (154)  
2-(4-[Bromomethyl]phenyl)-6-(4-bromophenyl)pyridine (162)  
2-(4-[Bromomethyl]phenyl)-6-(4-cyanophenyl)pyridine (169)  
Ethyl 4-(2-[6-{4-bromomethylphenyl}]pyridyl)benzoate (179)  
2-(4-[Dibromomethylphenyl])-6-phenylpyridine (146)  
2-(4-[Diethoxymethyl]phenyl)-6-phenylpyridine (147)  
2-(4-Formylphenyl)-6-phenylpyridine (148)  
2-(4-[Ethoxymethyl]phenyl)-6-phenylpyridine (149)  
2-(4-[3-Aminopropoxymethyl]phenyl)-6-phenylpyridine (150)  
2-(4-[4-Amino-2-azabutyl]phenyl)-6-phenylpyridine (151)  
2-(4-[5-Amino-2-azapentyl]phenyl)-6-phenylpyridine (152)  
2-(4-[8-Amino-2-azaocetyl]phenyl)-6-phenylpyridine (153)  
2-(4-[8-Amino-2-azaocetyl]phenyl)-6-(4-methylphenyl)pyridine (156)  
2,6-Bis(4-[8-amino-2-azaocetyl]phenyl)pyridine (157)  
2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-methylphenyl)pyridine  
(158)  
2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-bromophenyl)pyridine  
(163)  
2-(4-[4-Dimethylamino-2-thiabutyl]phenyl)-6-(4-cyanophenyl)pyridine  
(170)  
Ethyl 4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)  
benzoate (180)  
N-(2-[Tert-Butoxycarbonylamino]ethyl)-4-(2-[6-{4-tolyl}pyridyl])  
benzamide (177)

N-(2-Aminoethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (181)

N-(4-Aminobutyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (182)

N-(6-Aminoethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (183)

N-(2-[Acetamido]ethyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (184)

N-(2-[Acetamido]butyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (185)

N-(2-[Acetamido]hexyl)-4-(2-[6-{4-(2-[dimethylamino]ethyl)thiomethyl}phenyl]pyridyl)benzamide (186)