PYRIDO ANALOGS OF PSYCHOPHARMACOLOGICAL AGENTS

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

in Pharmacy

by

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A C K N O W L E D G M E N T S

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TO MY PARENTS

ABSTRACT

The intramolecular nucleophilic cyclization of 3-pyridylalkylamines onto the 2-position of the pyridine ring was investigated using a wide variety of experimental conditions. The optimum conditions determined for cyclization were pulverized sodium in toluene at reflux for 72 hours. Two bicyclic products, 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine and 1,2,3,4-tetrahydro-1,8-naphthyridine, were prepared in good yield.

Aralkylhydrazines are known to be MAO inhibitors. Only one 3-pyridylalkylhydrazine has been previously reported and tested for MAO inhibition. A series of 3-pyridylalkylhydrazines were prepared and their hydrochloride salts were tested for MAO inhibitory activity in both *in vivo* and *in vitro* methods. All three showed MAO inhibitory activity. In the *in vitro* screen 2-(3-pyridyl)ethylhydrazine was as active as the marketed benzene isostere phenelzine.

1,4-Benzodiazepines are marketed as central nervous system depressants. Only one pyrido[2,3-e]-1,4-diazepine has been reported in the literature. It was not clear if this compound was tested for pharmacological activity. A series of pyrido-[2,3-e]-1,4-diazepines was attempted to be synthesized by repeating the literature synthesis from 2-amino-3-benzoylpyridine. However, problems were encountered and no pyrido[2,3-e]-1,4-diazepine was isolated. Presumably hydrolysis occurred in one of the steps

resulting in the isolation of the starting material.

The novel intramolecular nucleophilic cyclization of 3-pyridylalkylamines was applied in an attempt to prepare pyrido-[2,3-e]-1,4-diazepines. Side chain imines were prepared from nicotinaldehyde with N-methylethylenediamine and ethylenediamine. Cyclization of the N-methylimine and the saturated N-methyl-ethylenediamine derivatives were attempted, but gave discouraging results. The ethylenediamine derivative was also prepared, but once again the cyclization failed to occur. It was planned to prepare 5-phenylpyrido[2,3-e]-1,4-diazepines by using 3-benzoyl-pyridine as starting material. However, since the above route starting with nicotinaldehyde was unsuccessful only the condensation of 3-benzoylpyridine with N-methylethylenediamine is reported in this work. In the attempted cyclization of N-(3-picolyl)ethylenediamine intermediates were suspected and further work in this area will probably result in the formation of the desired ring system.

The use of 2-amino-3-benzoylpyridine for the synthesis of 3-substituted-2-amino-4-phenyl-1,8-naphthyridines was investigated. Two new derivatives were prepared as analogs of the pteridine diuretic, triamterene.

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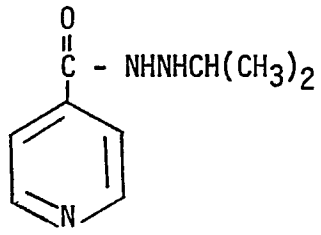
1.0.0.0.0 INTRODUCTION

1.1.0.0.0 Aralkyl monoamine oxidase inhibitors

In 1951 iproniazid (1) was synthesized as a potential chemotherapeutic agent for tuberculosis. It is the isopropyl derivative of isoniazid (2), which is a potent inhibitor of the tubercle bacillus.



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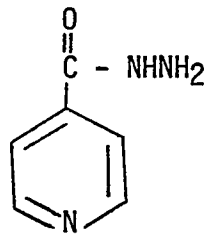

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During clinical studies a mood-elevating effect of iproniazid was noticed. It was found to be less useful than isoniazid in the clinical treatment of tuberculosis, and due to its marked central stimulation its use was discontinued.

Zeller's group[1] discovered that iproniazid, in contrast to isoniazid, was a potent inhibitor of monoamine oxidase (MAO), the enzyme responsible for the metabolic degradation of central excitatory catecholamines such as epinephrine, norepinephrine, dopamine and serotonin. It was found to elevate levels of biogenic amines in the brain, and prevent the fall in amine levels induced by reserpine.

Kline and coworkers[2] tested iproniazid for its anti-depressant properties, and found it to be useful in the treatment of depression. He attributed the clinical antidepressant

effect of iproniazid to MAO inhibition, with a subsequent increase in cerebral serotonin and norepinephrine. He contrasted the antidepressant effect of iproniazid with that of reserpine induced depression, which is correlated with a decrease of serotonin and norepinephrine levels in the brain.

Preincubation of iproniazid with MAO was found to be necessary to obtain maximum *in vitro* inhibition, indicating irreversible binding.[3] It has been suggested that iproniazid is firstly converted into an "active principle", isopropylhydrazine, before it inactivates the enzyme.[4,5] Iproniazid is more active on brain MAO *in vivo* than *in vitro*. This observation supports the previous suggestion, because isopropylhydrazine is a more potent MAO inhibitor than iproniazid.[6]

1.1.1.0.0 Structure-activity relationships of hydrazine MAO inhibitors

The success of iproniazid in the treatment of depression led to the synthesis of a large number of hydrazine derivatives as potential anti-depressive agents, by the early 1960's. A number of comprehensive reviews on the influence of chemical structure of hydrazine derivatives on MAO inhibition are available.[7-11] It should be noted that *in vitro* activity does not always correlate with *in vivo* activity, since some hydrazines with little *in vitro* activity are metabolized *in vivo* to produce powerful MAO inhibitors. Tissue penetration and specificity also contribute to the potency of the compounds.[8,12] In addition, many investigators have used a

variety of *in vitro* techniques, thus structure-activity comparisons are usually difficult.

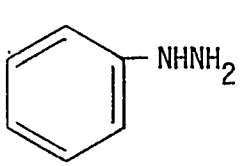
1.1.1.1.0 Alkylhydrazines

Zeller's group[13] discovered that simple alkylhydrazines were as potent *in vitro* MAO inhibitors as iproniazid. A series of substituted alkylhydrazines were tested for *in vitro* MAO inhibition.[7,8] While hydrazine and methylhydrazine were practically devoid of MAO inhibitory activity, the addition of a longer straight or branched alkyl side chain gave potent MAO inhibition. Maximum inhibition was observed with ethyl-, isopropyl- and 2-pentylhydrazine. An increase in the length of the alkyl chain beyond five carbon atoms resulted in a sharp decrease in MAO inhibition. A branched alkyl chain of eight carbon atoms was found to result in a complete loss of enzyme inhibition.

A hydrogen atom on the hydrazine nitrogen bearing the alkyl group is essential for MAO inhibition, and indeed unsymmetrical disubstituted alkylhydrazines are devoid of any significant activity. Symmetrical disubstituted alkylhydrazines are generally less potent *in vitro* inhibitors than the corresponding monoalkyl derivatives.[14] However, they are usually more potent *in vivo* inhibitors. It has been suggested that the disubstituted hydrazines are cleaved metabolically to release a highly active monosubstituted derivative.[7,8]

1.1.1.2.0 Phenylalkyhydrazines

Biel and coworkers[15] investigated the structure-activity relationships of a series of phenylalkylhydrazines for MAO inhibition. In general the relationships noted for alkylhydrazines applied to the phenylalkyl derivatives. The length of the alkane side chain had a great effect on MAO inhibition. Phenylhydrazine (3), which lacks an alkyl side chain, was a very weak inhibitor in vitro and was devoid of MAO inhibitory activity in vivo. Benzylhydrazine (4), which has a methylene side chain, was a potent MAO inhibitor. In fact it was 40 times more potent than iproniazid in vivo. Increasing the methylene chain caused a marked decrease in activity. Phenelzine (5) was only 1/10 as active as benzylhydrazine. A further increase in chain length resulted in a greater decrease in activity. Phenylpropylhydrazine (6) was less than 1/40 as active as benzylhydrazine.



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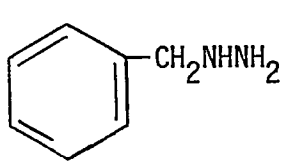

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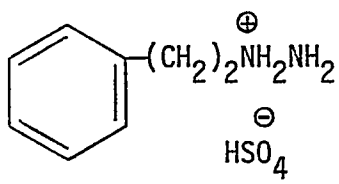

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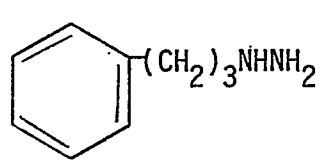

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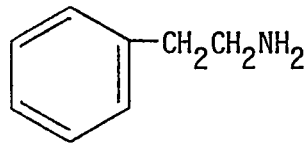
The structure-activity relationships of the phenylalkylhydrazines are closely paralled by a similar relationship in the phenylalkylamine series with respect to sympathomimetic potency. β-Phenethylamine (7), a potent pressor agent, is paralled by its nitrogen isostere, benzylhydrazine (8), which is the most potent phenylalkylhydrazine MAO

inhibitor. In contrast, benzylamine and its nitrogen isostere, phenylhydrazine, are weak with regard to pressor activity and MAO inhibition respectively.[15]



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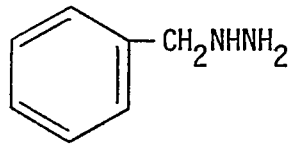
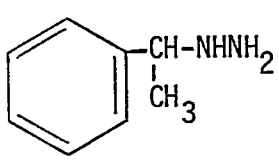


(8)

Branching of the side chain yielded compounds which were potent MAO inhibitors. α-Methylbenzylhydrazine (9) was about 20 times as potent as iproniazid in vivo. Disubstitution on the alkyl side chain resulted in a decrease in activity. Pheniprazine (PIH, JB-516) (10) was about 40 times as potent as iproniazid. It had a high affinity for brain MAO and it produced central stimulant properties, which have been postulated to be due to its similarity in structure to amphetamine (11) rather than MAO inhibition.[15] α-Phenylisopropylhydrazine (12) and α-phenyl sec-butylhydrazine (13) were about 1/2 as potent as pheniprazine. A further increase in the length of the alkyl chain caused a marked decrease in MAO inhibition.[15]



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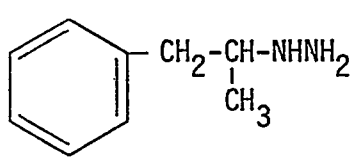

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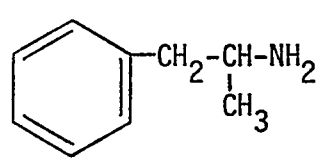

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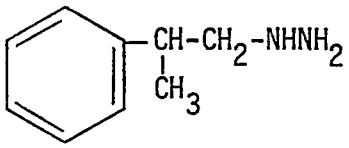

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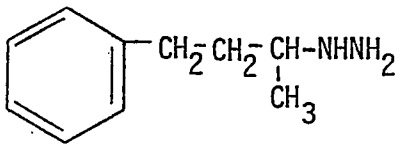

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In general, nuclear substitution, N-acylation or N-alkylation caused a decrease in MAO inhibition. The most potent of the nuclear substituted compounds were the 3,4-methylenedioxy- and 3-chloro- derivatives. They possessed about 1/2 the activity of the unsubstituted compounds.

1.1.1.3.0 Heterocyclic alkylhydrazines

Replacement of the phenyl ring with heterocyclic ring systems such as pyridyl, thienyl, furyl and benzodioxanyl generally caused a sharp drop in MAO inhibition. The thienyl group which is usually considered isosteric with the phenyl ring was the most potent of the heterocyclic derivatives. 2-Thienylmethylhydrazine was 8 times as potent as iproniazid *in vivo*, and produced 60% inhibition *in vitro* as compared to 25% inhibition by iproniazid at 10^{-5}M. 2-Furylmethylhydrazine was inactive, while the benzodioxanylmethyl derivative displayed only slight *in vivo* activity.[15]

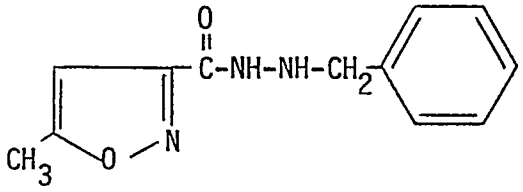
Only a limited amount of research has been carried out with pyridyl derivatives, but it appears that the 3-pyridylalkylhydrazines are the most active. 3-Pyridylmethylhydrazine was 4 times as potent as iproniazid *in vivo*, while 2-pyridylmethylhydrazine was devoid of *in vivo* inhibition. 3-Pyridylmethylhydrazine produced 75% MAO inhibition

in vitro, while 2-pyridylmethylhydrazine gave 15% inhibition at 10^{-5}M. No other 3-pyridylalkylhydrazines are reported in the literature. Kost and coworkers[16-18] have prepared 2- and 4-pyridylethylhydrazine from the corresponding vinyl pyridines. They reported that 2-pyridylethylhydrazine inhibited MAO activity for 5 days.

1.1.2.0.0 Aralkylhydrazine antidepressants in clinical practice

The toxic effects of the hydrazine derivatives,such as hepatotoxicity, impairment of red-green color vision and neurologic damage have led to the removal of iproniazid and pheniprazine from the market.[9] Phenelzine is the only unsubstituted aralkylhydrazine presently marketed as an antidepressant. It is interesting to note that there is individual variation in the rate of metabolism of phenelzine. There are both slow and rapid acetylators in humans, which is also observed with isoniazid. In fact with the rapid acetylators, phenelzine is no more effective than a placebo in the treatment of neurotic depression.[19]

Benzylhydrazine, which is 10 times as potent as phenelzine *in vivo*, has a much lower LD_{50} and is too toxic for clinical use. However, acylation of the terminal nitrogen of benzylhydrazine affected a marked reduction in its toxicity. In fact, isocarboxazid (14), the 5-methylisoxazole-3-carboxylic acid hydrazide of benzylhydrazine has found use as an antidepressant.[8]



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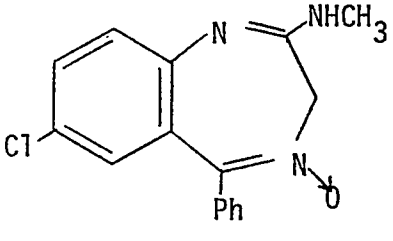
1.2.0.0.0 1,4-Benzodiazepine CNS depressants

The benzodiazepines are one of the most widely prescribed classes of drugs today. These compounds have a broad spectrum of effects on the central nervous system. Chlordiazepoxide (15) and diazepam (16) are used mainly as antianxiety agents. Diazepam has also found use as a centrally acting muscle relaxant. Oxazepam (17) is comparable to chlordiazepoxide but with diminished side effects. Nitrazepam (18) is used primarily as an anticonvulsant, while flurazepam (19) is marketed as a hypnotic. Chlorazepate (20) has recently been introduced as a minor tranquilizer.[20]



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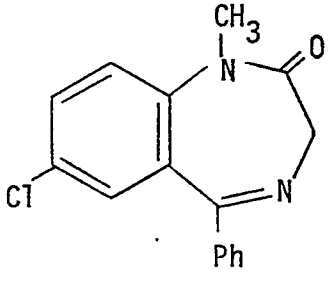

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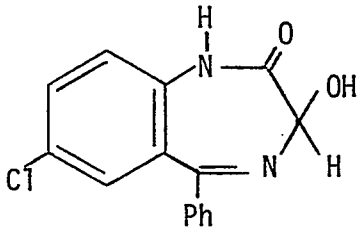

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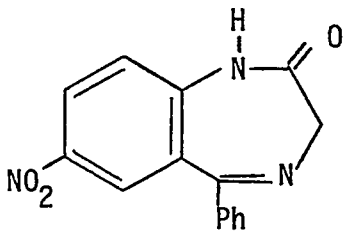

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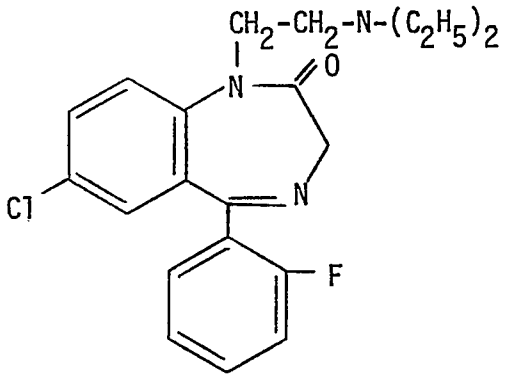

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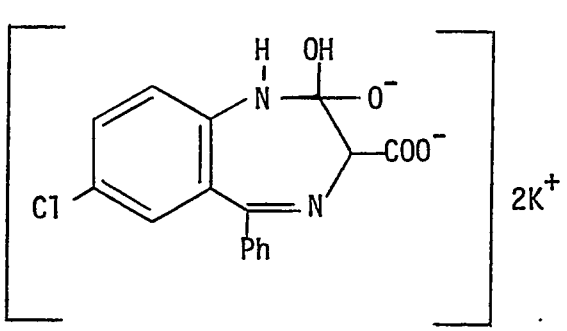

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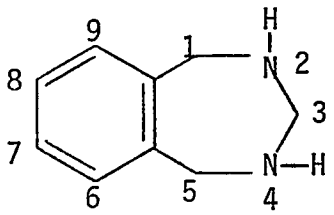
1.2.1.0.0 Nomenclature of benzodiazepines

Benzodiazepines are numbered starting at the position adjacent to the carbocyclic ring, regardless of the position of the nitrogen atoms, which are indicated by prefixed numbers. Benzodiazepine indicates the maximum degree of unsaturation, three double bonds in the seven-membered ring. The odd hydrogen atom is given the lowest possible number and is indicated by the term H. However, priority is given to the position of a ring functional group, which is expressed as a suffix. Thus, compound (21) is named 2,3,4,5-tetrahydro-1H-2,4-benzodiazepine,

while compound (22) is named 1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one.[21]



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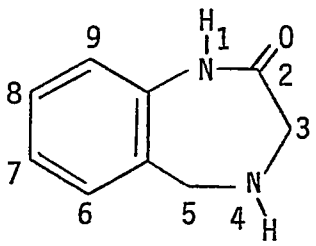

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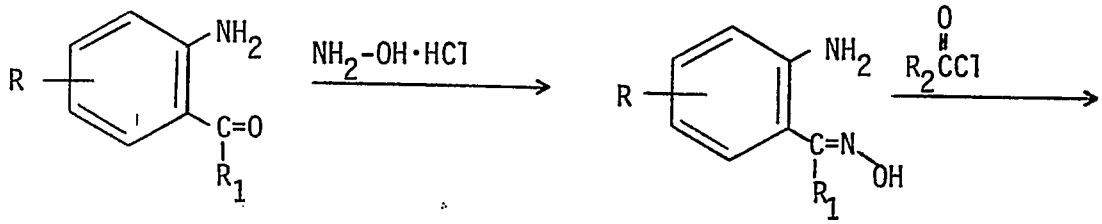
1.2.2.0.0 The development of 1,4-benzodiazepines

Like many of the drugs in use today the benzodiazepine CNS depressants were discovered accidentally rather than by rational drug design. In fact in this case the synthesis of the ring system itself was not planned. In the early 1960's Sternbach and coworkers[22] of Hoffmann-LaRoche attempted to synthesize a series of 3,1,4-benzoxadiazepines as potential pharmacologically active compounds. This series of compounds was to be synthesized by conversion of the corresponding o-aminoketone (23) to the oxime (24), followed by acetylation and treatment with a Beckmann mixture (24 → 26). Treatment of the supposed chloromethylbenzoxadiazepine (26; R_2=CH_2Cl) with amines should have yielded a series of compounds, presumed to be benzoxadiazepines with basic substituents (27).



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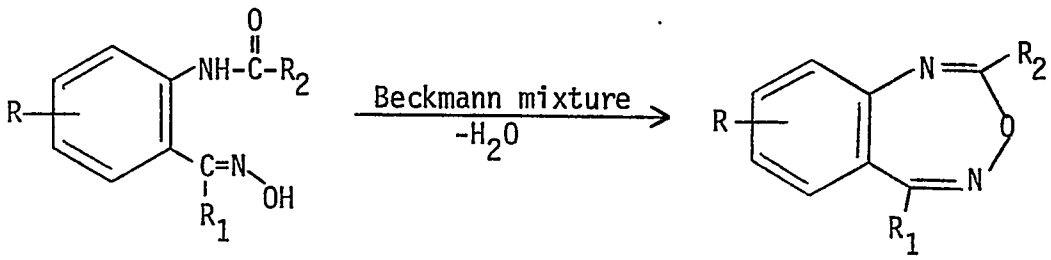

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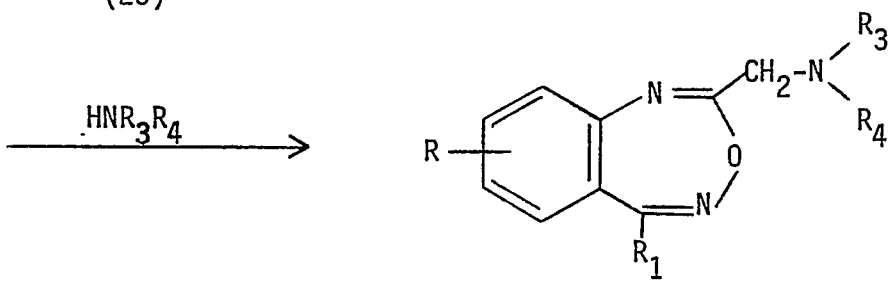
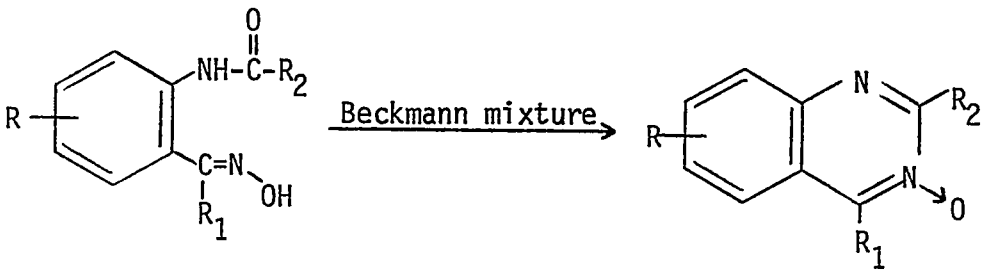


(27)

The workers[22] on further investigation found that the compounds assumed to be benzoxadiazepines (26,27) were, in fact, quinazoline 3-oxides. Thus, treatment of the acetylated derivatives (28; R_2=CH_2Cl, CH_3) with a Beckmann mixture yielded the substituted quinazoline 3-oxides (29). A number of 2-chloromethylquinazoline 3-oxides (29; R_2=CH_2Cl) were prepared and treated with various secondary amines to yield a series of tertiary amines (30), which proved to be pharmacologically inactive.



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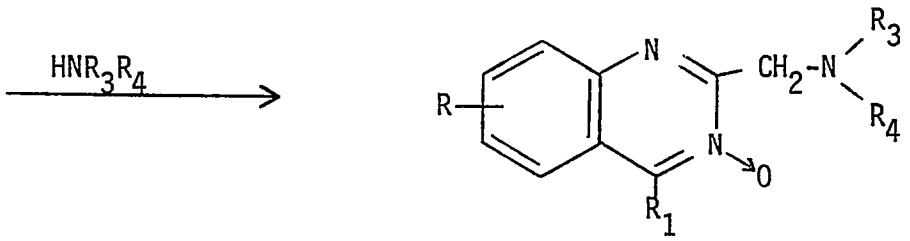

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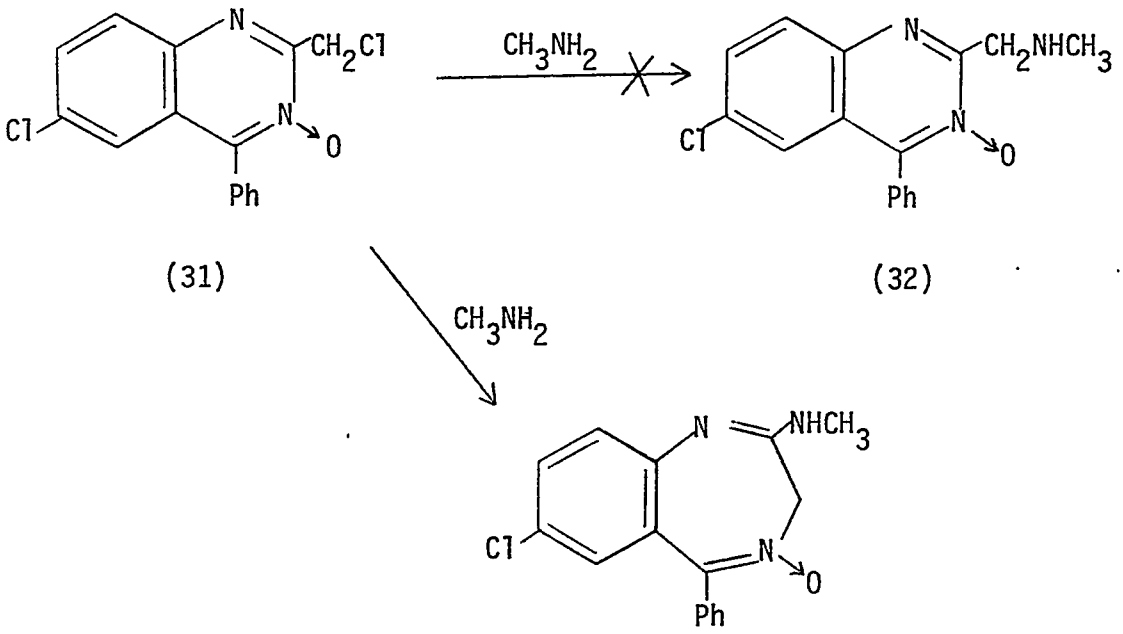
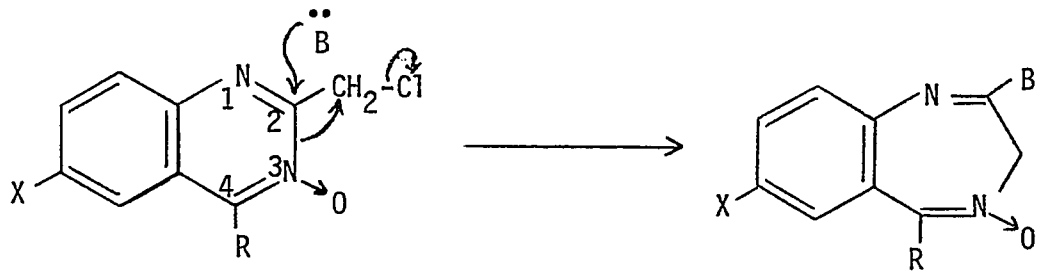
Sternbach et al.[22] then expanded the project to include the reaction of chloromethylquinazoline 3-oxides with primary amines and ammonia. This led to the discovery of chlordiazepoxide. The Hoffmann-LaRoche workers found that treatment of the substituted chloromethyl-quinazoline 3-oxide (31) with methylamine did not yield the expected aminoquinazoline N-oxide (32). Instead, a rearrangement occurred which yielded 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (chlordiazepoxide) (33).



(31) (32) (33)

The 2-position of the quinazoline nucleus (34) carries a partial positive charge due to the inductive effect of the N-oxide group. This effect is reinforced by an electron-withdrawing substituent at the 6-position. One of the suggested mechanisms for the rearrangement involves nucleophilic attack by the base (methylamine) at the 2-position (34→35), rather than replacement of the chlorine atom. This results in a concerted displacement of the halide with simultaneous attack of the 2,3- bonding electrons on the methylene carbon to form a seven membered ring structure (35).[23-25] The N-oxide function is essential for ring enlargement.[26]

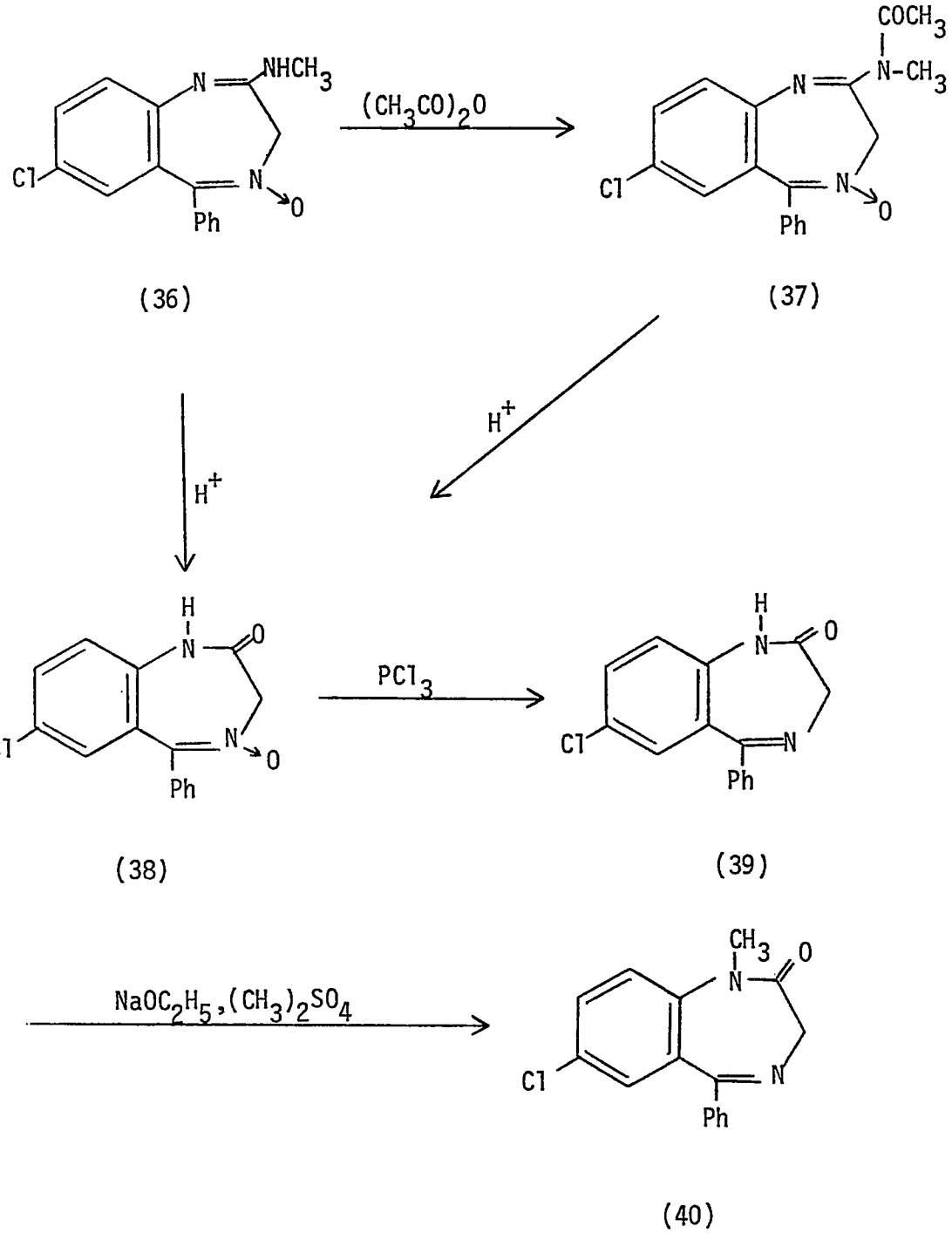


(34) (35)

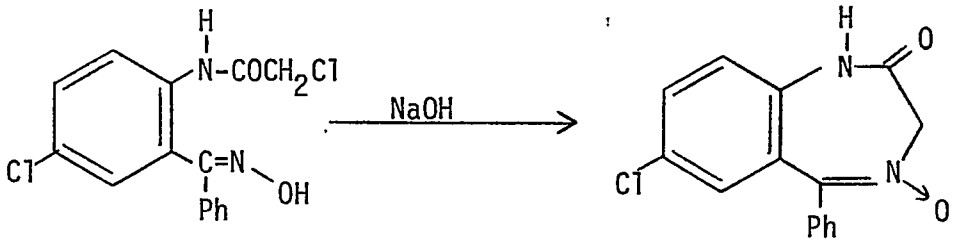
Chlordiazepoxide was found to possess interesting pharmacological properties. A number of related 1,4-benzodiazepines were synthesized *via* the ring enlargement of quinazoline 3-oxides and found to possess a combination of muscle relaxant, tranquilizing and anticonvulsant properties.[26-29]

The Hoffmann-LaRoche workers[22,27,30] synthesized the acetyl derivative (37) of chlordiazepoxide (36) and discovered that it had similar pharmacological properties. This observation suggested that both compounds owed their pharmacological activity to a common degradation product. Stability studies of the acetyl derivative and chlordiazepoxide itself indicated that the substituent at the 2-position was readily removed by acid hydrolysis to yield the 1,4-benzodiazepin-2-one 4-oxide (38), which retained pharmacological activity. Removal of the *N*-oxide function by phosphorus trichloride (38→39) did not alter the pharmacological activity. This work indicated that the basic substituent at the 2-position and the *N*-oxide function of chlordiazepoxide were not required for pharmacological activity, and led to the

synthesis of a wide variety of 1,4-benzodiazepin-2-ones, including diazepam (40).

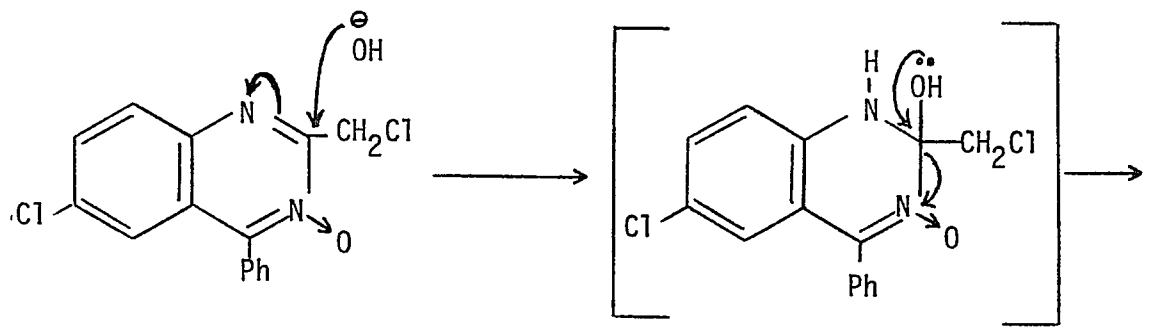


Simpler methods for the synthesis of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (42) have been developed. Treatment of the chloracetyl β-oxime (41) with base yielded the seven-membered ring system.[30]

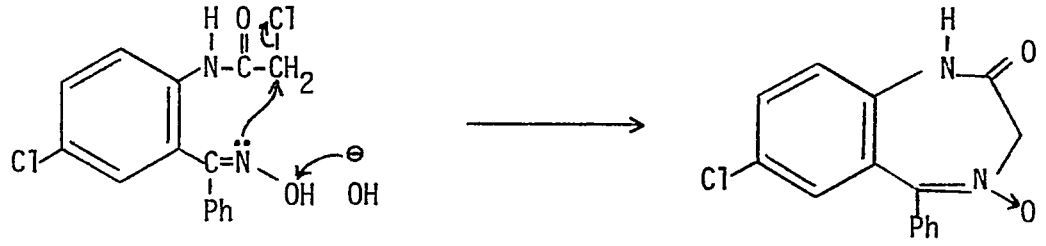


(41) (42)

Treatment of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (43) with alkali resulted in a ring enlargement similar to that for the synthesis of chlordiazepoxide. The suggested mechanism for the rearrangement involved nucleophilic attack by the hydroxyl ion at the 2-position, followed by ring opening to the β-oxime (45), and then an intramolecular alkylation to give the benzodiazepin-2-one 4-oxide (46).[31]

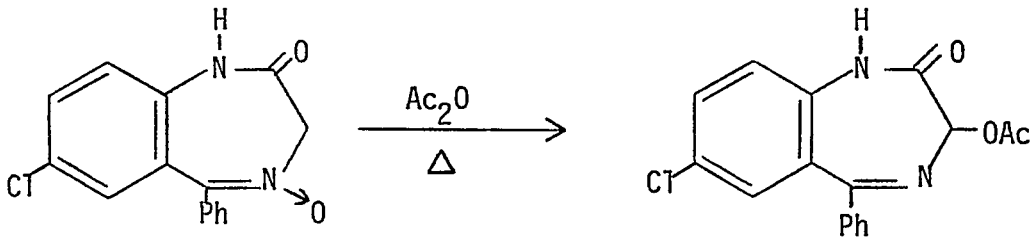


(43) (44)

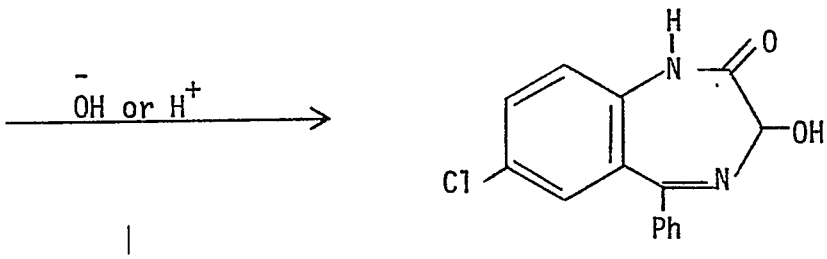


(45) (46)

The benzodiazepin-2-one 4-oxide (47) underwent a Polonovsky rearrangement on treatment with acid chlorides or acid anhydrides to yield the 3-acetoxy derivative (48). Hydrolysis yielded the 3-hydroxy compound (oxazepam) (49) which possessed similar properties to that of chlordiazepoxide.[31]



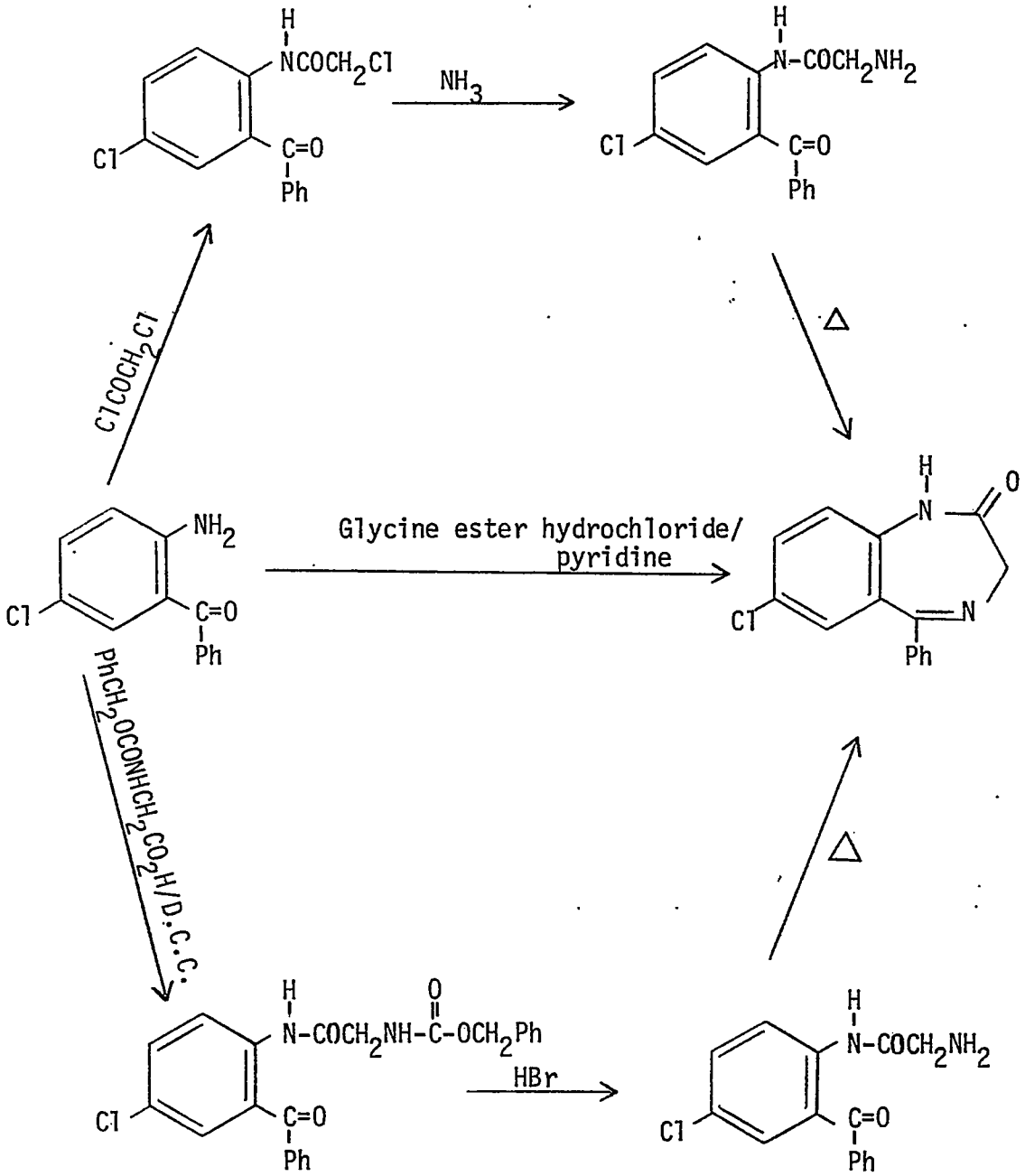
(47) (48)



(49)

As previously mentioned the benzodiazepinone without the N-oxide function was found to possess pronounced muscle relaxant, sedative and anti-convulsant properties. [22,26,27] Since the synthesis previously described involved a number of steps a more direct approach to the synthesis of benzodiazepinones was developed.[31-33] Three general methods are widely used for the synthesis of the 1,3-dihydro-2H-1,4-benzodiazepin-2-ones, using the appropriately substituted 2-aminobenzophenone as starting material (Scheme 1).

Scheme 1. The synthesis of 1,3-dihydro-2H-1,4-benzodiazepin-2-ones

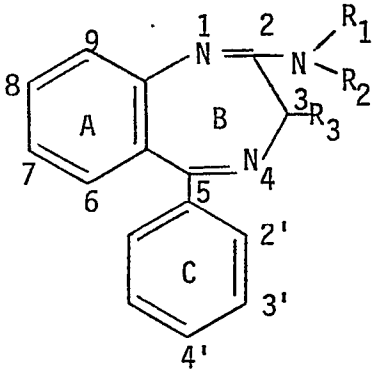


1.2.3.0.0 Structure-activity relationships of the 1,4-benzodiazepines

The ease of synthesis of the 1,4-benzodiazepines has led to the preparation of a large number of analogs. A number of reviews on the structure-activity relationships in the 1,4-benzodiazepine series are available.[20,23,24,34-36] In discussing the structure-activity relationships of the 1,4-benzodiazepines it is convenient to consider the 2-amino-3H-1,4-benzodiazepine 4-oxides and the 1,3-dihydro-2H-1,4-benzodiazepin-2-ones separately.

1.2.3.1.0 2-Amino-3H-1,4-benzodiazepine 4-oxides

This was the first series of the benzodiazepines to be synthesized and tested for pharmacological activity. Structure-activity relationships are usually evaluated by the result of changes in rings A; B and C (50) and compared to chlordiazepoxide (51).



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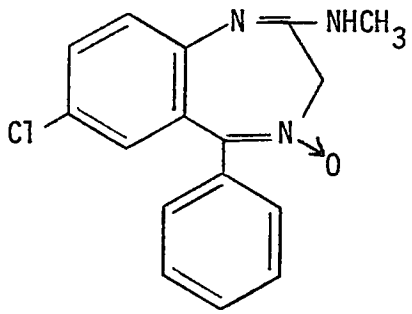


(51)

Substitution on ring A indicated that an electron-withdrawing substituent at the 7-position generally maintained the activity. Replacement of the chlorine group at position 7 by a hydrogen or methyl group lowered activity, while a bromine or nitro group at the 7-position maintained the activity. A trifluoromethyl substituent in position 7 caused an increase in anticonvulsant activity. Substitution at positions in ring A other than position 7 or disubstitution caused a marked decrease in activity.

Structural changes in the methylamino substituent in ring B revealed that replacement of the methyl group by a hydrogen caused a decrease in potency. On the other hand, exchange of the secondary amino hydrogen for a methyl group or an acetyl group did not alter the potency. In general lengthening or branching of the substituents on the exocyclic nitrogen produced less active compounds. Substitution at position 3 of ring B caused a marked decrease in activity. The effect of eliminating the N-oxide function was variable.

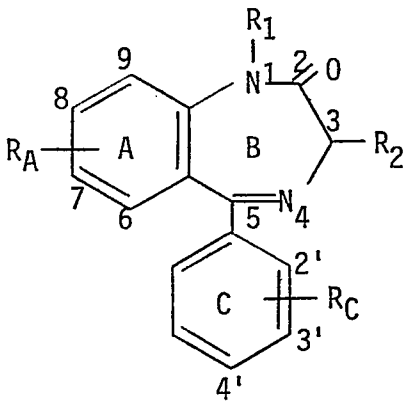
Substitution in ring C generally caused a sharp decrease in activity, with the exception of the 2'-chlorine derivatives which retained the activity. Replacement of the phenyl group at position 5 of ring A by a hydrogen, methyl, cyclohexyl or heterocyclic group greatly reduced the potency.

In conclusion, the structure-activity relationships of the 2-amino-3H-1,4-benzodiazepines may be summarized by emphasizing that although a large number of derivatives have been synthesized, none of them have proven superior to chlordiazepoxide in biological activity.

However, three important generalizations are seen. An increase in the size of the substituent on the methylamino group at position 2 or replacement of the phenyl group at the 5-position caused a marked decrease in potency. An electron-withdrawing substituent at the 7-position was generally required to maintain the activity.

1.2.3.2.0 1,3-Dihydro-2H-1,4-benzodiazepin-2-ones

This series of benzodiazepines has been studied extensively for structure-activity relationships. They are readily accessible by various routes (Scheme 1) and a large number of derivatives have been prepared with structural changes in rings A, B and C (52). Diazepam (53) was the first member of this group to be marketed, and is the prototype for correlations in this series.



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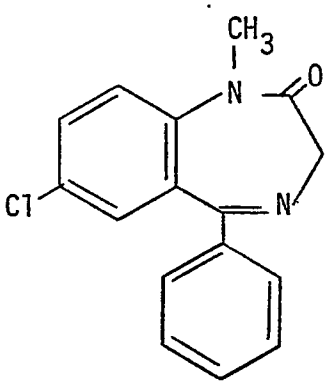


(53)

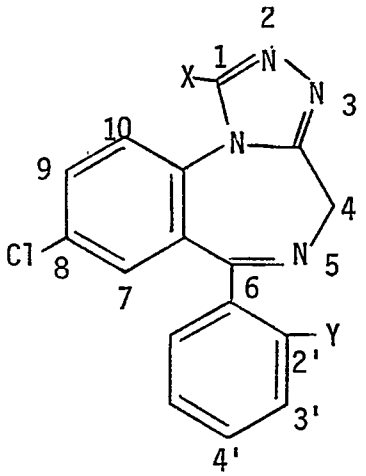
Substitution in ring A (R_A) revealed that an electron-withdrawing substituent at the 7-position generally increased activity. The potency of the derivative generally increased with the strength of the electronic character of the substituent, with the nitro and trifluoromethyl substituted derivatives showing the highest activity. However, larger groups such as phenyl or methylsulfonyl caused a decrease in potency.

Electron-releasing groups at the 7-position generally caused a sharp decrease in activity. Also, compounds which were substituted at positions other than 7, or contained more than one substituent in ring A were much less active. Derivatives which lacked a substituent in ring A displayed only slight activity.

Investigations on the effect of substitution in ring C revealed that the position of substitution (R_C) was most important. Halogen substituents at the 2'-position generally caused an increase in activity. This effect was mainly influenced by the size of the substituent, and generally did not depend on its electronic effects. Introduction of substituents other than halogen at the 2'-position generally resulted in decreased activity. However, a 2'-nitro derivative has been reported to be 5 times more potent than nitrazepam and diazepam in its anti-epileptic properties.[37] Disubstitution by halogens, both in the ortho-positions resulted in compounds of high activity.[20] Substitution at the 3'- or 4'- positions caused a decrease in activity. Replacement of the phenyl group at the 5-position by alkyl groups or heterocycles caused a sharp drop in potency. Only the 5-substituted pyridyl derivatives displayed any activity.

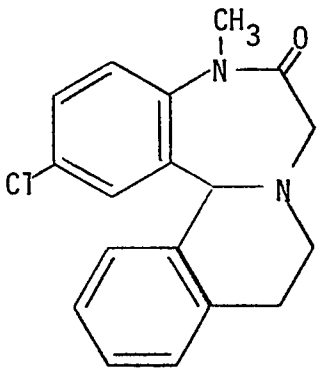
With regard to changes in ring B, it was found that a methyl group in the 1-position increased activity. Substitution by an ethyl, allyl, acetonyl, cyclopropylmethyl or a diethylaminoethyl group in the 1-position did not alter the activity. However, larger substituents in the 1-position generally caused a significant decrease in activity.

The carbonyl group at the 2-position appeared to be necessary for high activity. The 2-thione derivatives were less active than the corresponding carbonyl compounds. Recently triazolobenzodiazepines (54), which have a C=N group at the 2-position, have been reported to possess sedative and antianxiety activity. Structure-activity relationships for a series of these compounds gave similar correlations to those just discussed. Thus, for example, substitution at the 2'-position of the phenyl ring by chlorine or fluorine group increased the activity.[37,38]



(54)

Substitution at the 3-position of the 1,4-benzodiazepinones (52) by alkyl groups resulted in a decrease in activity. However, a hydroxyl group at the 3-position did not alter the activity. Hydrogenation of the 4,5- double bond yielded less active compounds. Compounds have been reported in which bridging between the 4-position of the diazepine ring and its 5-phenyl substituent has occurred.[39] These derivatives (55) were pharmacologically inactive. Other compounds have been prepared which linked either ring A and B, or ring A and C, by an alkyl chain.[20] These compounds were also inactive. However, several derivatives of oxazolazepam (56) have been reported to be more potent anticonvulsants than diazepam.[38]



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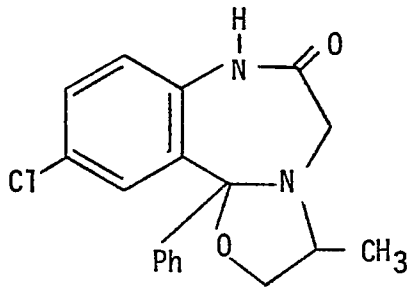
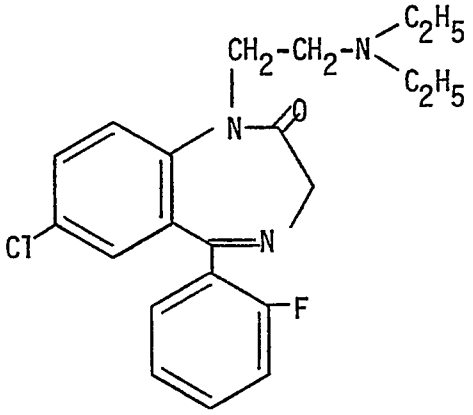


(56)

It is interesting to note that in the 1,4-benzodiazepine series the substitution effects were additive. Methylation of the 1-position, substitution with electron-withdrawing groups at the 7-position, and the introduction of halogens into the 2'-position gave compounds of very high activity. These substitution effects have been utilized to prepare compounds which possess high activity and a large number are presently under thorough clinical investigation.

Flurazepam (57) was recently introduced on the market as a hypnotic. Clonazepam (58) and flunitrazepam (59) were found to be more potent than nitrazepam or diazepam in their antiepileptic activity.[40] Flunitrazepam (59) was also found to be a potent hypnotic, about 20 times more active than flurazepam.[37] Lorazepam (60; X=Cl), an analog of oxazepam (60; X=H), has been reported to possess potent sedative and depressant activity in man.[37] It is possible that some of the new benzodiazepines currently under clinical investigation will be marketed in the near future.



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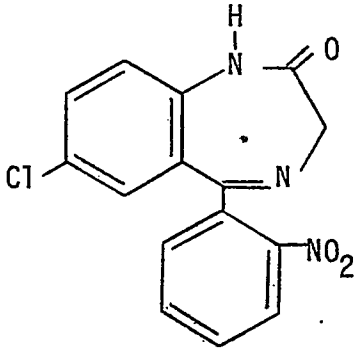

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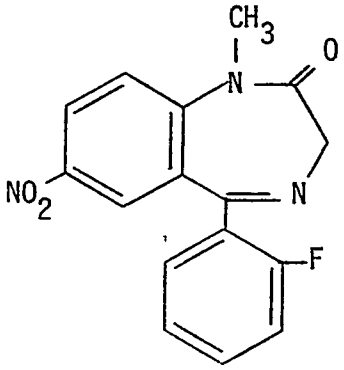

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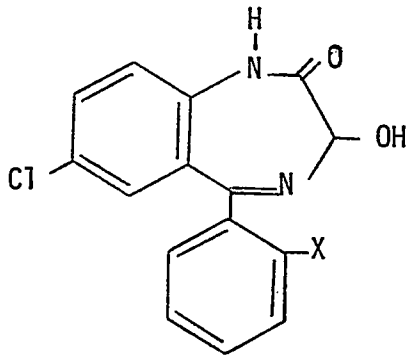
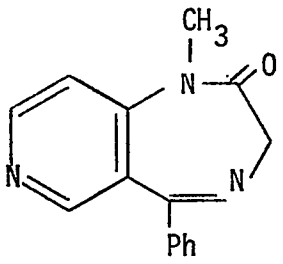


(60)

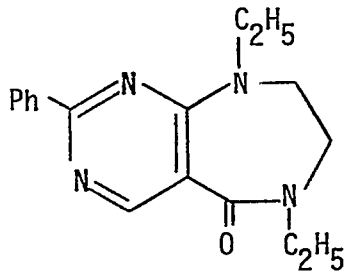
1.2.3.3.0 Heterocyclic 1,4-diazepines

The success of the 1,4-benzodiazepines as central nervous system depressants has led to the more recent synthesis of a number of heterocyclic analogs. Littell and Allen[41,42] prepared a series of pyridodiazepines. One member of the series, 1,3-dihydro-5-phenyl-2H-pyrido-[4,3-e]-1,4-diazepin-2-one (61) was reported to have similar pharmacological properties to those of the benzodiazepines.



(61)

A pyrimidine analog, pyrimido [4,5-e] -1,4-diazepin-5-one (62), has been prepared and reported to possess moderate central nervous system depressant activity accompanied by anticonvulsant effects.[43] The synthesis of a furo [2,3-e]-1,4-diazepine (63) has recently been noted, however no pharmacological investigations have been reported.[44]



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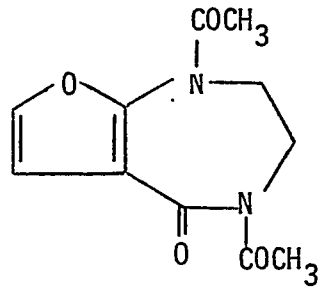
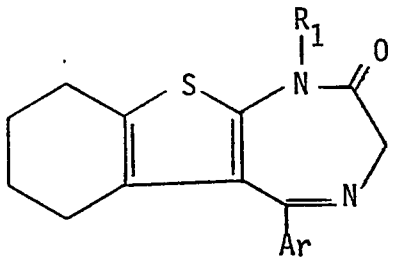


(63)

In 1971 the synthesis of tetrahydrobenzothieno- (64)[45], pyrazolo [3,4-e]- (65)[46] and pyrazolo [4,3-e]- (66)[47] 1,4-diazepin-2-ones were reported in the patent literature. All three heterocyclic diazepinones were reported to be useful anticonvulsant and antianxiety agents.



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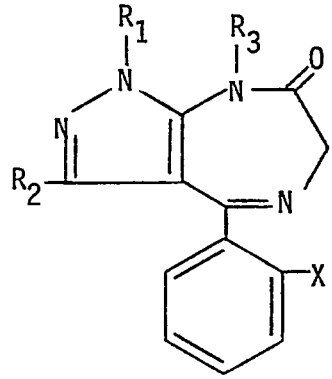

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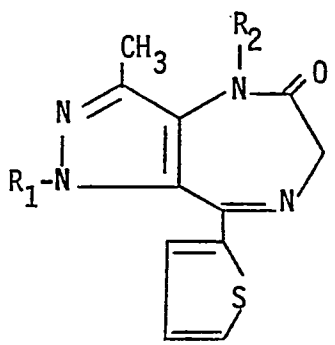
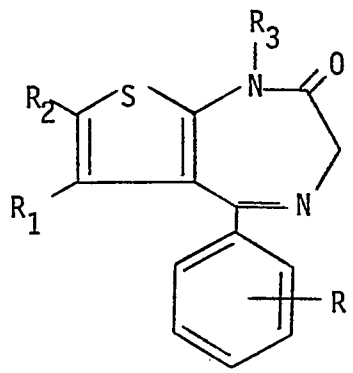


(66)

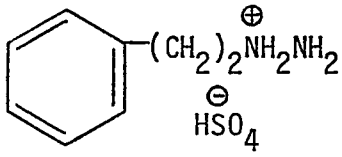
Nakanishi and coworkers[48-50] have recently described the synthesis of a series of thieno [2,3-e]-1,4-diazepin-2-ones (67). They reported that some of the derivatives displayed central nervous system depressant activity at least as great as chlordiazepoxide.



(67)

2.0.0.0.0 OBJECTIVES OF RESEARCH

As previously indicated in section 1.1.1.0.0 many hydrazine derivatives exhibit marked MAO inhibition. Phenelzine (68), an aralkylhydrazine, is marketed as an antidepressant. It was hoped to prepare 3-pyridylalkylhydrazine analogs of phenelzine (69; n=1,2,3) and test them for MAO inhibition by <u>in vivo</u> and <u>in vitro</u> methods. A comparison of the screening results to those of phenelzine should be of interest, as they would give an indication of the effect of the pyridine ring. In pyridines the electronic effects of the aza atom at the 3-position are minimal, but marked at the 2- and 4- positions.



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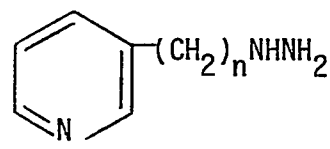
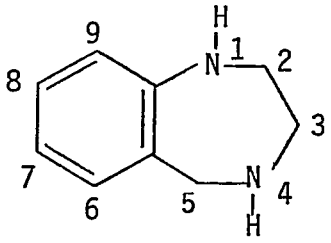


(69)

As previously mentioned in section 1.2.3.0.0 the benzodiazepines (70) which contained an electron-withdrawing substituent at the 7-position displayed good central nervous system depressant activity. The same substituent at the 9-position gave compounds which were much less active. This decrease in activity could be due to a steric effect rather than an electronic effect. The pyrido isosteres (71,72), which contain an aza atom in the ring at the 7- or 9- position should have similar electronic features to the analogous benzodiazepines but lack

any steric effects.



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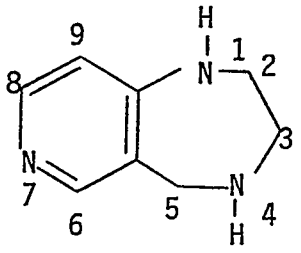

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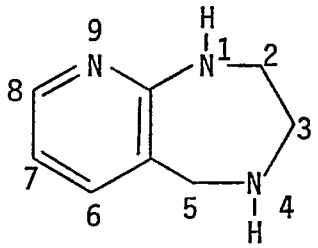
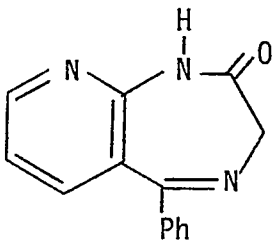


(72)

Littell and Allen[41,42] have prepared a series of pyridodiazepines, which included one pyrido [2,3-e] -1,4-diazepine (73). It was not clear if that compound was tested for pharmacological activity. The authors reported that "representative compounds were tested for central nervous depressant properties". 1,3-Dihydro-1-methyl-5-phenyl-2H-pyrido [4,3-e] -1,4-diazepin-2-one (74), the 7-aza isostere of diazepam (75), was reported to "have pharmacological effects on mice similar to, but less pronounced than diazepam".



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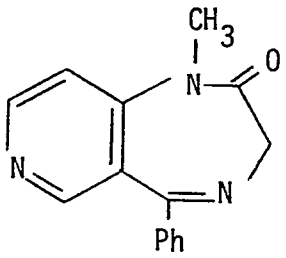

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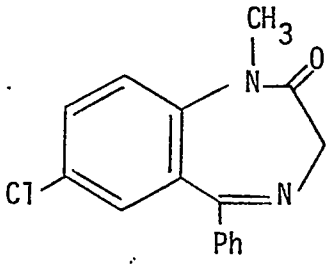
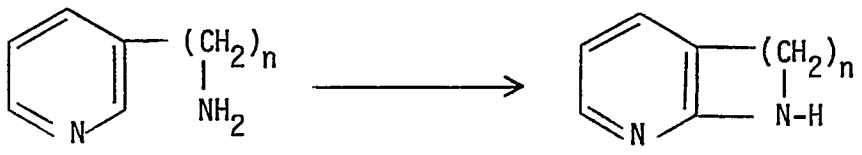


(75)

It was planned to prepare a series of pyrido [2,3-e] -1,4-diazepines, which possess a 9-aza atom, and compare their pharmacological activity to that reported in the literature for the corresponding 9-substituted-1,4-benzodiazepines. This comparison would give an idea as to whether the loss of activity of the 9-substituted benzodiazepines was due to an electronic or steric effect.

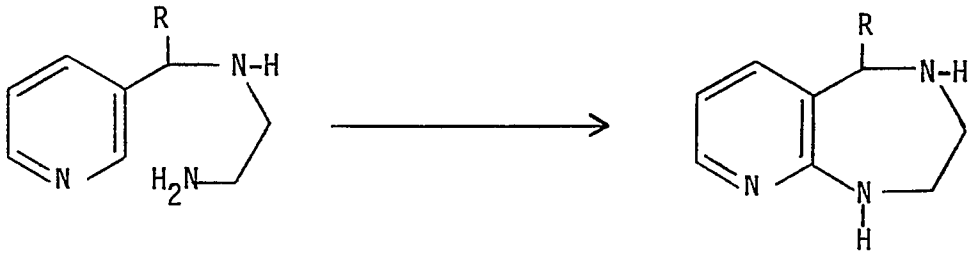
There are only a few reports of intramolecular nucleophilic cyclizations onto the pyridine ring to give bicyclic systems.[51-56] It was of interest to investigate the synthetic potential of intramolecular nucleophilic cyclizations of 3-substituted side chain nucleophiles. It was hoped to prepare suitable 3-pyridylalkylamines

and apply a wide variety of experimental conditions to determine the optimum reaction conditions necessary for cyclization (76→77).



(76) (77)

If the cyclizations proved to be successful the versatility of this reaction would be investigated by applying the optimum conditions to the synthesis of pyrido [2,3-e] -1,4-diazepines (78→79).

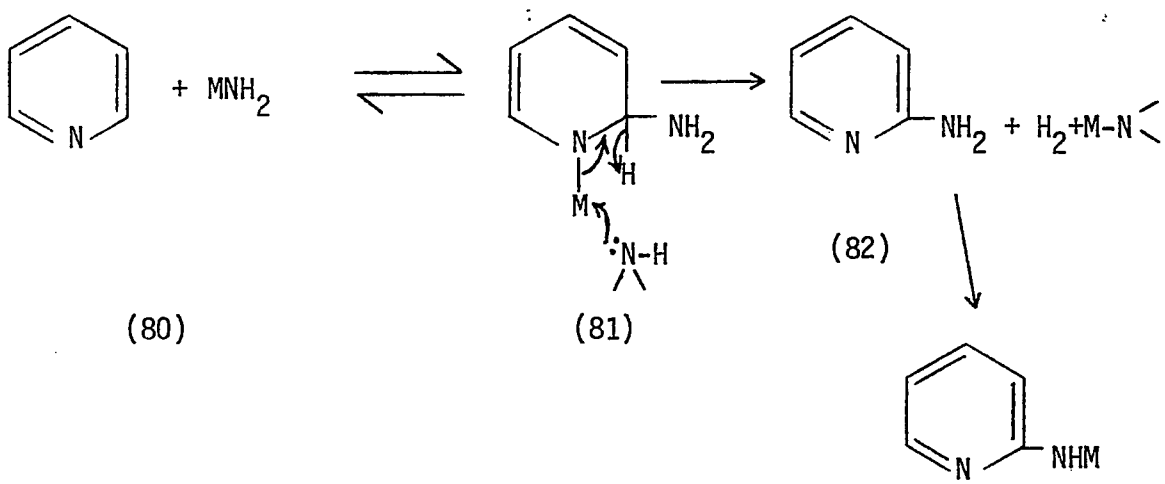


(78) (79)

3.0.0.0.0 DISCUSSION OF THE EXPERIMENTAL WORK

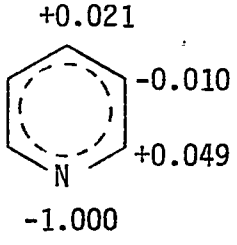
3.1.0.0.0 Intramolecular nucleophilic cyclization of 3-pyridyl-alkylamines

In 1914 Tschitschibabin[57] discovered a reaction where heterocyclic bases such as pyridine react with alkali metal amides to yield amino derivatives. In the amination of pyridine by sodium or potassium amide the addition occurred at the α-position. The γ-derivative was found only when the α-positions were substituted or at much higher temperatures.[58,59] It has been suggested that the overall reaction proceeds by a S_N2 addition-elimination pathway[58,60] (80 ⟶ 83).



(80) (81) (82) (83)

Several suggestions for the preferred orientation at the 2-position have been proposed.[60] The charge distribution on the pyridine nucleus in the ground state[61,62] (84), the statistical factor that there are two α-positions and one γ-position, and the fact that the lone pair of the nitrogen atom readily complexes with cations suggesting the possibility of a cyclic transition state, all favor nucleophilic attack at the 2-position. It has also been suggested that the observed orientation in this reaction depended upon the relative ease of elimination of a hydride ion from the 2- and 4- positions, and not upon the initial mode of addition.[60]



(84)

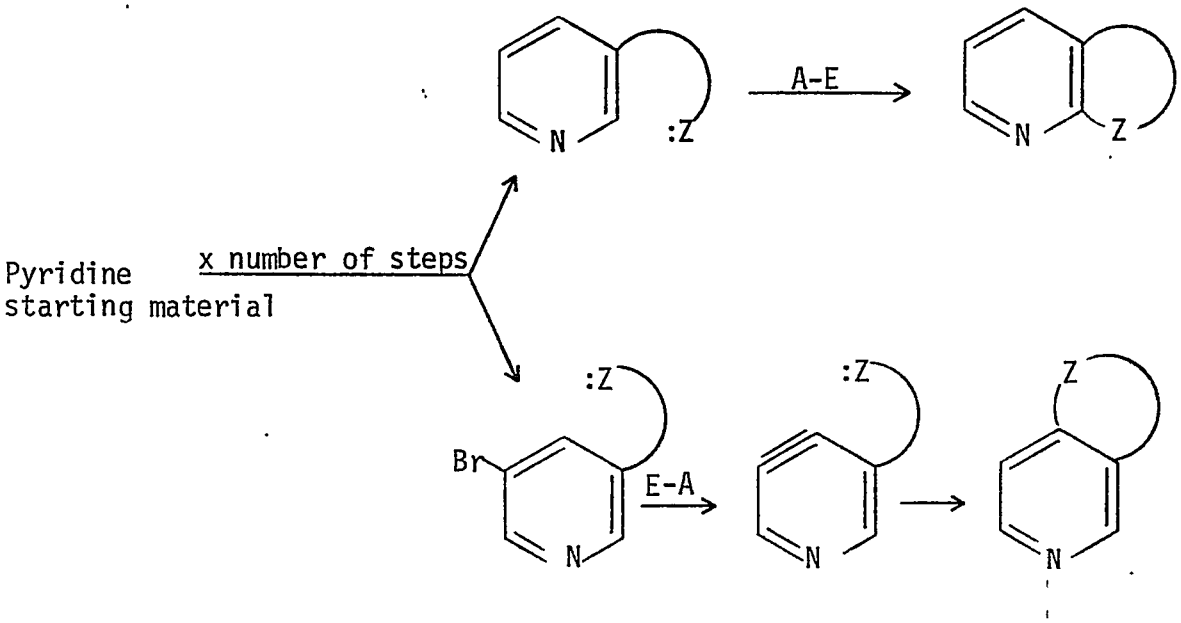
Abramovitch[63] investigated the preferential attack at the 2-position in aminations of 3-substituted pyridines. The preferred orientation did not depend upon the electrical effect of the 3-substituent. He suggested that in the transition state the solvent molecules would tend to orient themselves around the pyridine nitrogen, the leaving group and the attacking nucleophile, thus stabilizing the transition state by solvation. He proposed that in nucleophilic substitutions, involving displacement of a hydride ion, hindrance to solvation in the

transition state may explain the observed preferred attack at the 2-position.

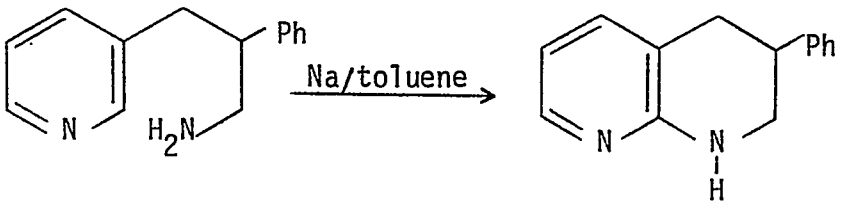
The classical Tschitschibabin reaction is limited to the formation of primary amines as attempts to produce a secondary amine by using substituted alkali amides have been unsuccessful. Kovács and Vajda[64-68] have discovered a Tschitschibabin-type reaction, where a secondary amine can be prepared in good yield by direct nucleophilic substitution. Pyridine and the alkylamine were refluxed together in toluene in the presence of pulverized sodium to yield the 2-pyridylalkylamine. This type of reaction has also been extended to include the preparation of 2-pyridylalkylhydrazines.[69-71]

It would appear that intramolecular nucleophilic cyclization onto the pyridine ring should proceed without difficulty. However, there are few literature references to such cyclizations. Cyclization could occur at either the 2- or 4- positions depending upon the mechanism involved. The Tschitschibabin-type reaction, which proceeds by a S_N2 addition-elimination mechanism, should involve cyclization onto the 2-position. An elimination-addition mechanism, which proceeds through a pyridyne intermediate, would result in cyclization at the 4-position (Scheme 2).

Scheme 2. Mechanisms for intramolecular nucleophilic cyclization onto the pyridine ring

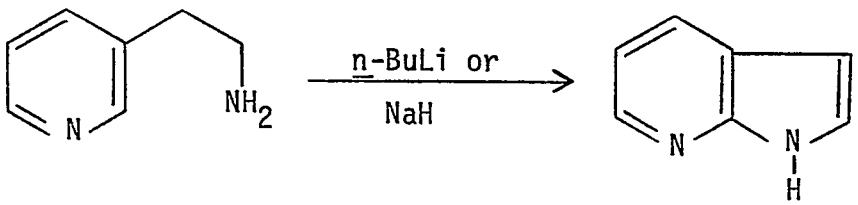


In 1966 the first reference to intramolecular nucleophilic cyclization of substituted pyridines onto the pyridine ring was reported. 2-Phenyl-3-(3-pyridyl)propylamine (85) was cyclized to 1,2,3,4-tetrahydro-3-phenyl-1,8-naphthyridine (86) in good yield using sodium in toluene.[51,52]



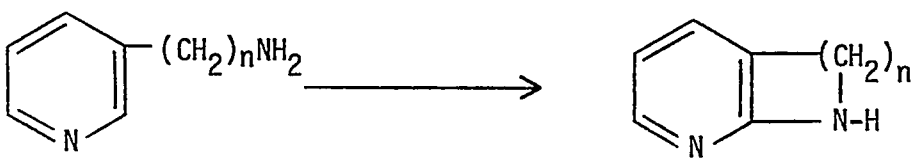
(85) (86)

2-(3-Pyridyl)ethylamine (87) has been cyclized to yield 1H-pyrrolo [2,3-b] pyridine (88) in trace amounts when treated with n-butyllithium in dioxane[53] or sodium hydride in toluene.[54] Kauffmann [55,56] has recently reported two cyclizations onto the 4-position of the pyridine ring via an elimination-addition pathway.



(87) (88)

It appeared to be essential to first determine the optimum conditions necessary for achieving the addition-elimination cyclization before the versatility of this reaction could be investigated. Therefore, 3-pyridylalkylamines with saturated side chains free of substituents were planned to be synthesized and a wide variety of cyclization conditions were to be applied to one. It was hoped to synthesize two previously unreported amines, 4-(3-pyridyl)butylamine (89;n=4) and 3-(3-pyridyl)propylamine (89;n=3) and to attempt their cyclization to 6,7,8,9-tetrahydro-5H-pyrido [2,3-b] azepine (90;n=4), and 1,2,3,4-tetrahydro-1,8-naphthyridine (90;n=3), respectively.

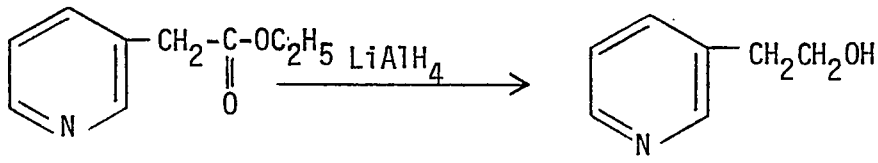


(89) (90)

3.1.1.0.0 Preparation of the 3-(3-pyridyl)alkylamines

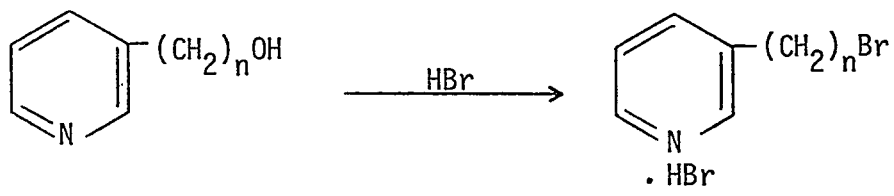
Suitable starting materials for the desired side chain amines appeared to be 3-(3-pyridyl)propan-1-ol and 2-(3-pyridyl) ethanol (92). The former was commercially available, while the latter was prepared by lithium aluminum hydride reduction of ethyl 3-pyridylacetate (91) by modifying the procedure described by Barnden.[72] Ethyl 3-pyridyl-

acetate was reduced instead of methyl 3-pyridylacetate.



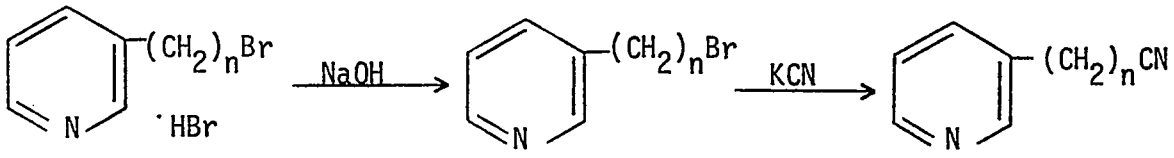
(91) (92)

Treatment of the corresponding alcohols, 3-(3-pyridyl)propan-1-ol (93;n=3) and 2-(3-pyridyl)ethanol (93;n=2), with 48% hydrobromic acid using the general method of Hurst[73] gave the previously unreported compounds, 3-(3-bromopropyl)pyridine hydrobromide (94;n=3) and 3-(2-bromoethyl)pyridine hydrobromide (94;n=2) in good yields. The infrared spectra of the hydrobromides contained a broad band from 2800-2500 cm^{-1}, which confirmed the presence of a salt. The hydrobromides were stable solids which could be stored without decomposition.



(93) (94)

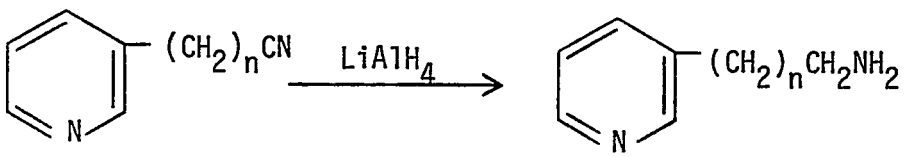
The free bromides (96;n=2,3) were obtained by basification of an aqueous solution of the hydrobromide (95;n=2,3) and extraction into chloroform. The free bases were unstable oils which rapidly underwent intermolecular quaternization and therefore were used immediately upon being obtained. Treatment of the free bromides with potassium cyanide applying the method used by Hurst[73], gave 3-(3-pyridyl)butyronitrile (97;n=3) and 2-(3-pyridyl)propionitrile (97;n=2) in good yields. The products distilled as colorless oils and had the characteristic odor of nitriles. The infrared spectra contained a sharp band at 2235 cm^{-1} which confirmed the presence of a nitrile.



(95) (96) (97)

The 3-(3-pyridyl) alkylamines (99;n=2,3) were prepared by treatment of the corresponding nitriles (98;n=2,3) with a two-fold excess of lithium aluminum hydride according to the general methods described in the literature.[74,75] The products distilled as colorless oils with a characteristic odor, and gave a positive Rimini's test for primary aliphatic amines. The infrared spectra displayed two bands at 3360 and 3290 cm^{-1}, indicating the presence of a primary amine. Also, the nmr spectra contained an additional methylene group in the

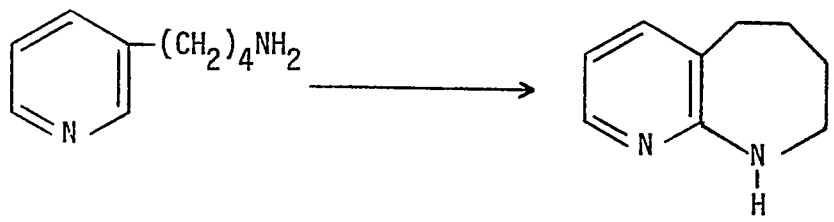
aliphatic region, and a singlet containing two protons that exchanged readily with deuterium oxide, which confirmed that reduction to the primary aliphatic amine had occurred.



(98) (99)

3.1.2.0.0 Cyclization of the 3-(3-pyridyl)alkylamines

The cyclization of 4-(3-pyridyl)butylamine (100) to the previously unreported, 6,7,8,9-tetrahydro-5H-pyrido [2,3-b] azepine (101) was investigated using a wide variety of experimental conditions. Initially it was attempted to monitor the course of the reaction using nmr spectroscopy by following the disappearance of the pyridine α-proton and the formation of a simplified aromatic ABX system. However, the two-phase nature of the reaction mixture and the complexity of the spectra before work-up made this impossible. Therefore, after work-up a glc analysis of each reaction for the primary amine (100) and the cyclized product (101) was carried out.



(100) (101)

A mixture of 0.004 moles of the primary amine, the particular alkali metal reagent and the particular solvent were heated under reflux for the recorded time, as shown in Table 1. The crude products were analyzed by glc using pure samples of the starting material and product as internal standards to determine the actual yields.

The quantitative work gave a number of interesting observations. Firstly, regarding reagents, the highest yields of the cyclic product were obtained with sodium suspension (Table 1, No. 4), sodium hydride (No. 18), potassium hydride (No. 21) and sodium amide (No. 22) in boiling toluene. Also in this solvent fair yields were obtained with potassium suspension (No. 11) and n-butyllithium (No. 15). Despite the exothermic nature of the reactions at room temperature when lithium reagents were added to the reaction mixtures, generally only trace amounts of the cyclic product were obtained, except in the case of n-butyllithium (No. 15). In fact most reactions with lithium reagents generally yielded mainly unidentified products.

TABLE I

Cyclization of 4-(3-pyridyl)butylamine (100) to 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine (101)

No.	Reagent	Molar ratio	Solvent	Reflux time (hr.)	Crude[a] (%)	101[b] (%)	100[b] (%)	Unidentified products[a] (%)
1	Na	2:1	Toluene	6	98.3	0	38.8	59.5
2	Na	2:1	Toluene	24	98.3	12.7	14.2	71.5
3	Na	2:1	Toluene	48	76.7	57.4	0	20.1
4	Na	2:1	Toluene	72	88.3	86.5	0	3.0
5	Na	1:1	Toluene	72	91.7	16.6	12.7	52.6
6	Na	4:1	Toluene	24	93.3	19.3	7.4	67.0
7	Li	2:1	Dioxane	24	91.7	0	19.2	72.5
8	Li	2:1	Dioxane	72	95.0	0	5.9	89.1
9	Li	2:1	Toluene	72	86.7	0.9	40.4	45.4
10	Li	2:1	Xylene	72	98.3	0.7	0	97.6
11	K	2:1	Toluene	72	96.7	7.7	2.3	86.7
12[c]	Na salt	1:1	Toluene	72	94.2	21.6	10.6	62.6

No.	Reagent	Molar ratio	Solvent	Reflux time (hr.)	Crude[a] (%)	101[b] (%)	100[b] (%)	Unidentified products[a] (%)
13[c]	Li salt	1:1	Toluene	72	70.9	0	57.6	13.3
14	n-BuLi	2:1	Dioxane	24	65.0	0.1	14.5	50.4
15	n-BuLi	2:1	Toluene	72	98.3	10.3	0	88.2
16	n-BuLi	2:1	Xylene	72	99.2	4.1	0	95.1
17	NaH	2:1	Dioxane	72	98.3	0	23.4	74.9
18	NaH	2:1	Toluene	54	93.3	65.5	0	28.7
19	LiH	2:1	Toluene	72	71.7	0	51.3	20.4
20	LiH	2:1	Xylene	72	94.7	0.9	1.6	92.2
21	KH	2:1	Toluene	72	99.2	54.1	0	45.8
22	$NaNH_2$	2:1	Toluene	72	95.8	45.0	4.9	46.0
23	$LiNH_2$	2:1	Toluene	72	96.7	0	19.5	77.2
24	$LiNH_2$	2:1	Xylene	72	96.7	0	1.6	95.1

[a] Calculation based on starting material

[b] Determined by glc

[c] Salts prepared in ether before reaction undertaken

The reactions carried out with a slight excess of sodium in toluene for different periods of time (No. 1,2,3 and 4) indicated the slow nature of the cyclization. The optimum period of time for cyclization appeared to be 72 hours. The decrease in starting material and the unidentified products as the amount of cyclization product increased suggested that these unidentified products were in most cases intermediates in the cyclization, rather than decomposition products. Unfortunately these chloroform soluble products could not be separated and were not recorded on the chromatographs.

The effect of the reflux temperature was illustrated by, for example, the reactions carried out with n-butyllithium (No. 14, 15, and 16) and with sodium hydride (No. 17 and 18) in different solvents. The highest yields of the cyclized product were generally obtained when toluene (bp 110^{o}) was used as the solvent. Reactions in which dioxane (bp 101^{o}) was the solvent often gave high recoveries of the starting material (e.g. No. 7, 14, and 17). Decomposition was suspected in some cases where xylene (bp 144^{o}) was used as the solvent, as in these cases only trace amounts of starting material or cyclic product were recovered (e.g. No. 10, 20 and 24).

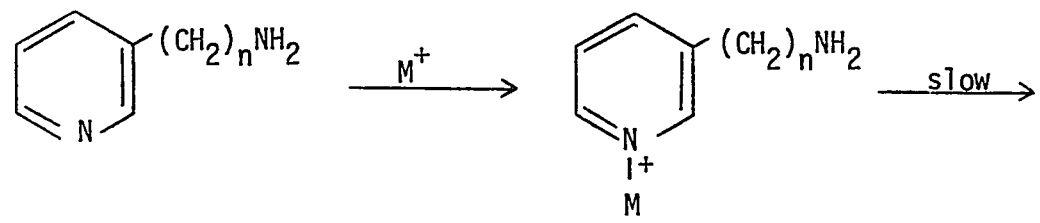
The necessity for a slight excess of the alkali metal reagent was evident by a comparison with an analogous reaction involving an equimolar ratio of reagent to starting material (No. 4 and 5). This was further illustrated by the comparatively low yields of the cyclic product obtained in reactions where the alkali metal salts of the starting material (No. 12 and 13) were used in the absence of excess

reagent. A slight excess, a 2:1 ratio (No. 2), appeared to be the optimum ratio, as a further increase in the ratio of reagent to starting material (4:1) did not cause a very significant increase in the amount of cyclized product (No. 6).

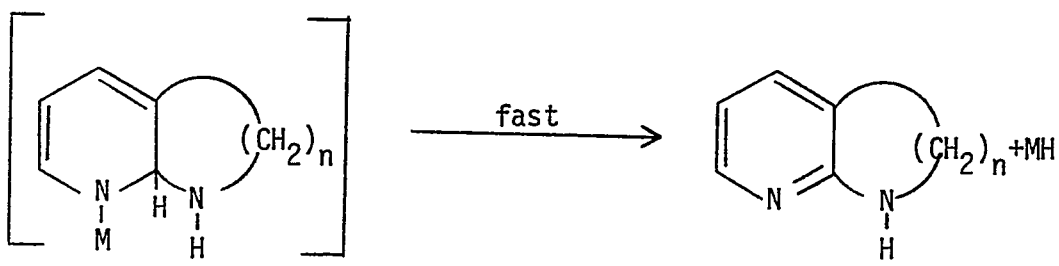
This cyclization appeared to be analogous with the Tschitschibabin reaction of alkali metal amides.[60,63] The experimental evidence suggested a similar S_N2 type addition-elimination mechanism to the Tschitschibabin reaction and the related synthesis of 2-pyridylalkylamines. Kovács and Vajda[66] have suggested that the reaction of the substituted amine, sodium and pyridine to yield the 2-pyridylalkylamines is started initially by a radical mechanism. The sodium cations thus produced increase the polarization of pyridine and thereby enhance the nucleophilic addition and also the cleavage of the hydride ion during rearomatization.

Therefore, the proposed mechanism in this work which is in agreement with that of Kovács[66] and Abramovitch[60], would involve rapid formation of the alkali metal-pyridine complex initially (102⟶103).This complex was rapidly formed and was exothermic at room temperature with lithium reagents, while it formed rapidly on warming with potassium and sodium reagents. These results agreed with Abramovitch[76] who has stated that in the amination of pyridine the addition step of lithium compounds was exothermic at room temperature, while the amination with potassium or sodium amide proceeded at an appreciably higher temperature. The next step would be the rate-determining addition of the side chain to the 2-position of the

pyridine ring (103⟶104) which would be followed by rapid hydride elimination (104⟶105). The experimental evidence indicated that these latter steps proceeded well with sodium and potassium, but not with lithium. This was not surprising as Giam[77] has reported that lithium amides gave poor yields of aminopyridines in the Tschitschibabin reaction.



(102) (103)



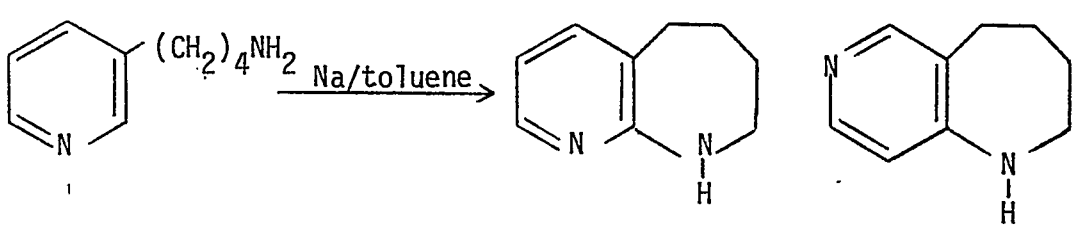
(104) (105)

The optimum conditions found in the quantitative analyses were applied to investigate the preparative capability of the cyclization of 4-(3-pyridyl)butylamine (106) and 3-(3-pyridyl)propylamine. These 3-pyridylalkylamines were treated with a slight excess of sodium in

boiling toluene for 72 hours to give good yields of 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]azepine (107), a new ring system, and 1,2,3,4-tetrahydro-1,8-naphthyridine, respectively. Both products were stable and were purified by vacuum distillation to yield colorless oils, which solidified upon cooling.

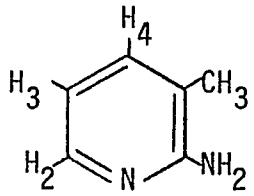
The azepine (107) showed an absorption at 3265 cm^{-1} in the infrared spectrum, which is characteristic of a N-H stretching vibration. It also gave a positive Lieberman's test, and a negative Rimini's test, indicating the presence of a secondary amine. Mass spectrometry indicated that cyclization had occurred as the parent ion was two mass units lighter than the 3-pyridylalkylamine starting material.

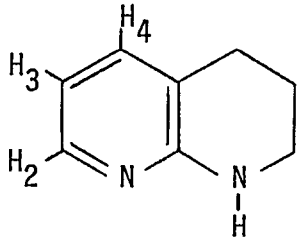
However, cyclization could have occurred at the 4-position to yield 6,7,8,9-tetrahydro-5H-pyrido[4,3-b]azepine (108). The pyrido-[2,3-b]azepine structure was confirmed by nmr spectroscopy (Table 2). The spectrum of the cyclized product contained two meta split doublets and a doublet of doublets in the aromatic proton region, which is similar to that recorded for 2-amino-3-picoline.[78] If the cyclization had occurred in the 4-position the spectrum would have resembled that for 4-amino-3-picoline, which shows two doublets and a singlet.

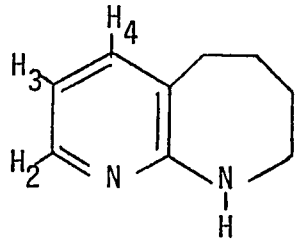


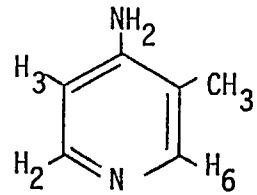
(106) (107) (108)

Table 2. Nmr Spectra of the aromatic region of the cyclic products of nucleophilic cyclization and 2- and 4-amino-3-picoline[a]









Compound	Chemical Shifts (δ)				Coupling Constants J (cps)		
	H-2	H-3	H-4	H-6	J2,3	J2,4	J3,4
2-Amino-3-picoline[b]	7.98 dofd	6.53 dofd	7.18 dofd	----	5.1	1.8	7.2
1,2,3,4-Tetrahydro-1,8-naphthyridine[c]	7.97 dofd	6.67 dofd	7.27 dofd	----	4.5	1.8	7.8
6,7,8,9-Tetrahydro-5H-pyrido[2,3-b]azepine	7.97 dofd	6.66 dofd	7.30 dofd	----	4.8	1.9	8.0
4-Amino-3-picoline[b]	8.08 d	6.52 d	----	8.08 s	5.5	---	---

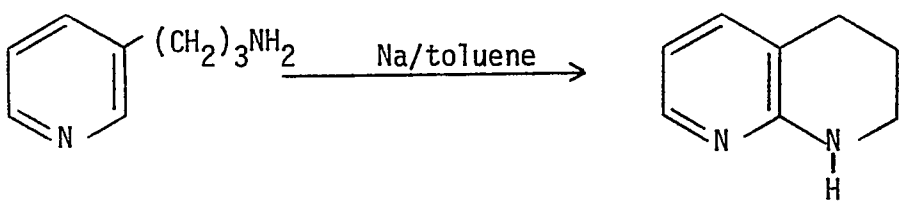
[a]For ease of comparison 2-amino-3-picoline, 1,2,3,4-tetrahydro-1,8-naphthyridine and 4-amino-3-picoline are numbered non-systematically as shown. Measurements were taken in deuterochloroform using tetramethylsilane as internal reference.

[b]Lit.,[78]

[c]These assignments are in agreement with those of Armarego[79]

Suffixes: d = doublet, dofd = doublet of doublets, s = singlet

1,2,3,4-Tetrahydro-1,8-naphthyridine (110) had previously been reported in the literature.[79] It was synthesized by Armarego by reduction of the parent unsaturated ring system. The product obtained from the cyclization of 3-(3-pyridyl)propylamine (109) was found to be identical to an authentic sample with respect to its melting point, glc retention time, mass spectrum, nmr and infrared spectrum[a]. The nmr spectrum also indicated that cyclization has occurred at the 2-position as it resembled the spectrum of 2-amino-3-picoline (Table 2).



(109) (110)

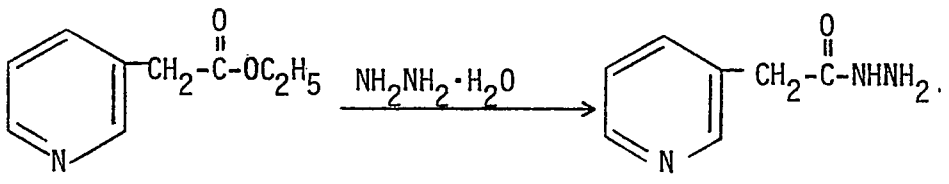
a. Reference sample obtained from Dr. W.L.F. Armarego, The Australian National University, Canberra.

3.2.0.0.0 The preparation of 3-pyridylalkylhydrazines

As previously mentioned in section 1.1.1.3.0 the replacement of the phenyl ring in phenylalkylhydrazines resulted in a decrease in MAO inhibitory activity. In the ground state the electronic effects of the pyridine nitrogen would be the least at the 3-position. Only one 3-pyridylalkylhydrazine has been prepared and tested for MAO inhibition.[15] It was planned to prepare a series of 3-pyridylalkylhydrazines and compare their MAO inhibitory activity to phenelzine and the 2- and 4-pyridylethylhydrazines prepared by Kost and coworkers.[17,18]

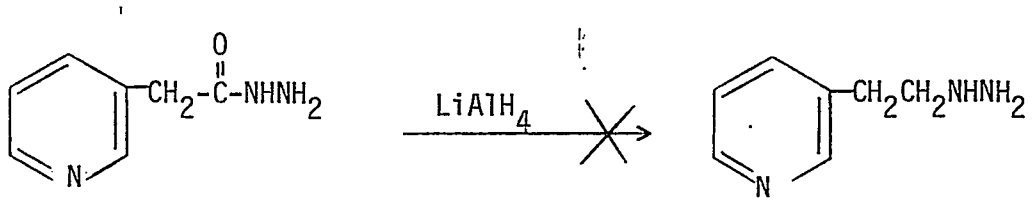
3.2.1.0.0 From ethyl 3-pyridylacetate

3-Pyridylacetic acid hydrazide (112) was obtained in good yield from the condensation of ethyl 3-pyridylacetate (111) and hydrazine hydrate according to the general method described by Hickinbottom.[80] Excess hydrazine hydrate was used to prevent the formation of symmetrically disubstituted hydrazides.



(111) (112)

Reduction of the hydrazide (113) to 2-(3-pyridyl)ethylhydrazine (114) was attempted using lithium aluminum hydride by the general methods described in the literature.[81,82] However, upon work-up only starting material was recovered. Hinman[83,84] has reported that acylhydrazines, which have a hydrogen on the acyl substituted nitrogen are reduced very slowly or not at all. He attributed the slowness of the reaction to the formation of an unreactive complex of the functional group with some form of the reducing agent, $-C(=O\rightarrow AlH_3)=N-$, which resisted attack by lithium aluminum hydride. Huisgen and coworkers[85] have also reported difficulty in reducing the -CONH- grouping.



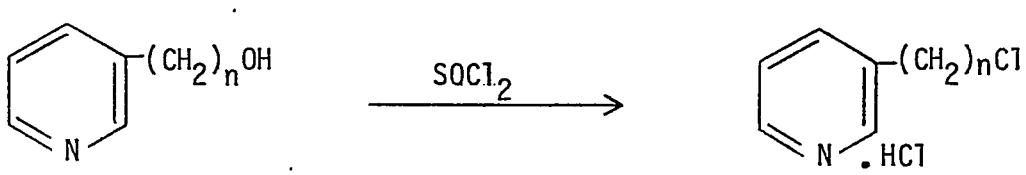
(113) (114)

3.2.2.0.0 From 3-pyridylalkylchlorides

A search of the literature indicated that another general method for the preparation of aralkylhydrazines was the reaction of hydrazine with an aralkylhalide.[15,86,87] It is known that the order of reactivity of alkylhalides increases from chlorine to iodine.[88] The reaction of unsubstituted hydrazines with alkyliodides was reported

to be difficult to stop at the monoalkylhydrazine stage.[89] Therefore it was decided to prepare the 3-pyridylalkylchlorides, which would be less reactive than the corresponding 3-pyridylalkylbromides in order to assist in the prevention of the formation of the N,N'-dialkylhydrazines.

The 3-pyridylalkylchlorides were prepared from the corresponding alcohols with the exception of 3-picolyl chloride (116;n=1), which was commercially available. 3-Pyridylethanol (115;n=2) was prepared from ethyl 3-pyridylacetate as described in section 3.1.1.0.0. The alcohols (115;n=2,3) were treated with excess thionyl chloride and heated at reflux according to the general literature methods to yield the hitherto unreported hydrochlorides (116;n=2,3).[90-92] The infrared spectra of the hydrochlorides contained a broad band from 2800-2450 cm^{-1}, which confirmed the presence of a salt. The hydrochlorides were stable solids which could be stored without decomposition.



(115) (116)

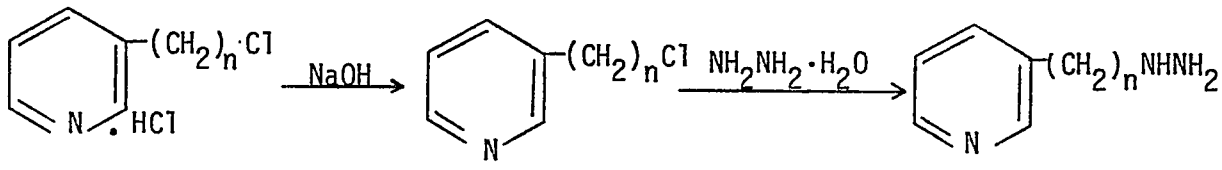
The free chlorides (118;n=1,2,3) were obtained upon basification of an aqueous solution of the hydrochlorides (117;n=1,2,3) and subsequent extraction into chloroform. They were unstable oils which

rapidly underwent intermolecular quaternization, and therefore were used immediately. Initially, the free chloride was added dropwise to a solution of excess hydrazine in ethanol at room temperature and then heated at reflux for 3 hours according to the general procedures described in the literature.[93,94] However, results proved to be discouraging.

The reaction was then carried out with vigorous stirring without solvent using the method of Kost and coworkers.[95] A large excess of hydrazine was used and the free chloride was added dropwise with vigorous stirring to the hydrazine hydrate at 90^{o} to prevent the formation of polyalkylation products.[15,96] Upon cooling, the mixture was extracted continuously with ether overnight and distilled to give the previously unreported (119a;n=2,3) and known (119a;n=1) hydrazines. The infrared spectra of the hydrazines contained a broad band from 3400-3250 cm^{-1} which is characteristic of hydrogen-bonded N-H stretching. The nmr spectra of the hydrazines contained a 3 proton singlet, which was readily replaced by deuterium oxide, indicating the presence of the hydrazine group.

The hydrazines were unstable compounds and slowly decomposed even upon storage in the cold. Kost and coworkers[16] have reported that 2-pyridylethylhydrazine was an unstable compound. Quotable elemental analysis figures could not be obtained for the hydrazines due to their instability. Therefore, the p-nitrophenylhydrazone (119b;n=2,3) and dipicrate (119c;n=2,3) derivatives were prepared and gave quotable analysis figures. In order to test the hydrazines for

MAO inhibition a stable water-soluble derivative was required. Thus the hydrochloride salts (119d;n=1,2,3) were prepared.



(117) (118) (119)

a; free base

b; p-nitrobenzaldehyde derivative

c; dipicrate derivative

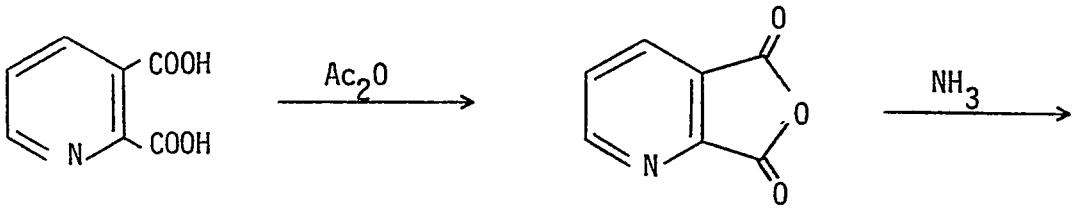
d; hydrochloride salt

3.3.0.0.0 The attempted preparation of pyrido [2,3-e]-1,4-diazepines

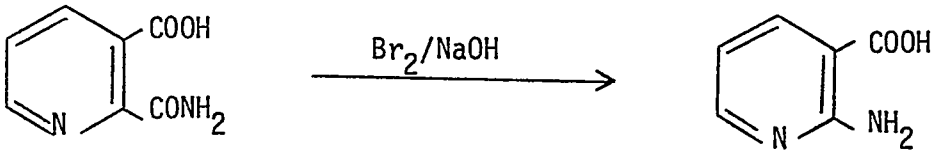
There is only one literature reference[41] and its related patent,[42] for the synthesis of pyrido isosteres of the 1,4-benzodiazepines. One pyrido [2,3-e]-1,4-diazepine was prepared, but it was not clear if it was tested for central nervous system depressant properties. It was planned to investigate the literature synthesis and also attempt to apply the novel intramolecular nucleophilic cyclization reaction (section 3.1.0.0.0) for the synthesis of a number of pyrido [2,3-e]-1,4-diazepines.

3.3.1.0.0 From 2-amino-3-benzoylpyridine

2-Aminonicotinic acid (123) was prepared from commercially available quinolinic acid (120) using the method of Mann and Reid[97] (120⟶123).



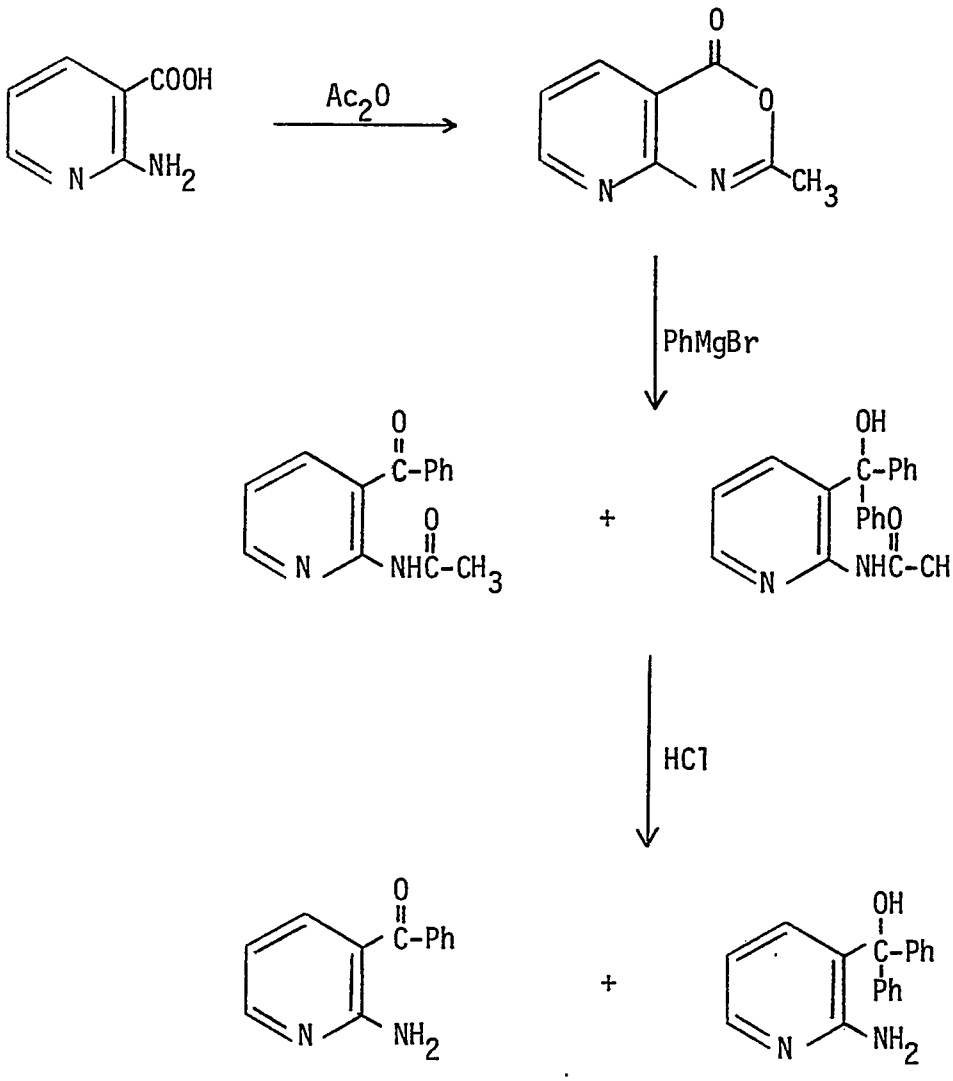
(120) (121)



(122) (123)

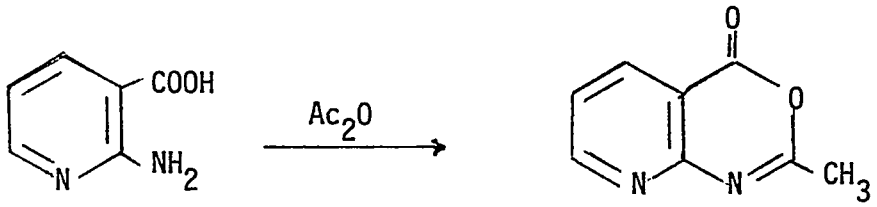
Littell and Allen[41,42] have prepared 2-amino-3-benzoylpyridine from 2-aminonicotinic acid <u>via</u> a Grignard synthesis (Scheme 3).

Scheme 3. Literature synthesis of 2-amino-3-benzoylpyridine



The Grignard reaction gave poor yields and it was hoped to repeat the synthesis and improve the yield of the ketone.

In the present work 2-aminonicotinic acid (124) was refluxed with acetic anhydride to give 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (125) in good yield. This latter compound was unstable as it was hydrolyzed by moisture. Ismail and Wibberley[98] have also reported that pyridoxazinones were rapidly hydrolyzed by moisture. Therefore, the product (125) was used as soon as possible after it was prepared.

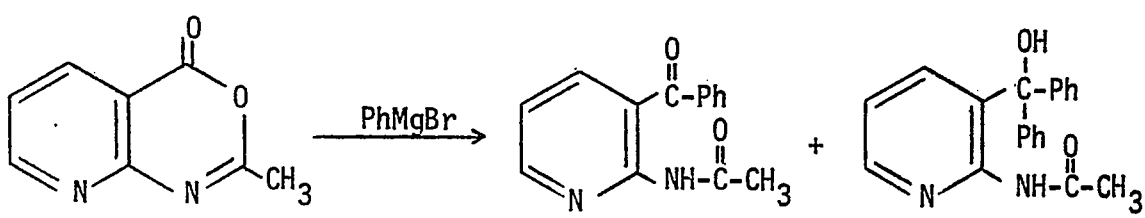


(124) (125)

Littell and Allen[41,42] reported a yield of 27% of the ketone (127) and 58% of the carbinol (128) in the Grignard reaction of the pyridoxazin-4-one (126) with phenylmagnesium bromide. Lothrop and Goodwin[99] found that if a benzoxazin-4-one was added to the Grignard reagent the corresponding carbinol would be the only product formed. However, on inverse addition the o-acetamidobenzophenone would be formed in about a 30% yield. Sternbach et al[100] and Lednicer and Emmert[101] have also reported a similar Grignard reaction with benzoxazinones. Upon the addition of the Grignard reagent, the acetamidoketones were formed in 20-30% yields, along with small amounts of

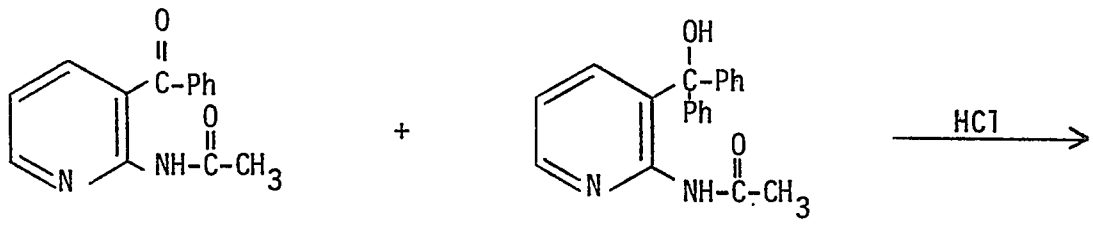
the carbinols.

Littell and Allen[41,42] used a slight excess of the Grignard reagent, which may have been responsible for the large amount of the carbinol formed. It was hoped that by adding an equimolar ratio of the Grignard reagent to the pyridoxazin-4-one (126) dropwise over a long period of time with vigorous stirring, the amount of carbinol (128) formed would be limited. After work-up a white solid was obtained which showed the presence of two components with relative peak areas of 67:33% on glc analysis. The mixture was purified by column chromatography according to the literature procedure.[41,42] It was shown by mass spectrometry that the major component detected in the glc analysis was the carbinol (128), while the minor component was the ketone (127). The 25-30% yields of the ketone obtained were similar to those reported in the literature for the reaction of benzoxazinones with Grignard reagents.[100,101]

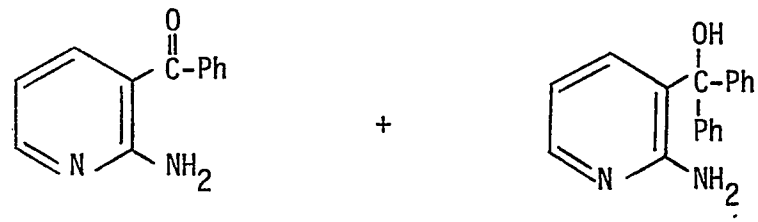


(126) (127) (128)

The recommended literature method which employed column chromatography proved to be very time consuming, because of the large scale of the reaction. It was found that by proceeding directly to the hydrolysis of the mixture of the acetamido-compounds, purification could be achieved by fractional recrystallization making bulk synthesis a reality. The mixture of the ketone (129) and carbinol (130) was treated with hydrochloric acid to yield a mixture of the deacetylated compounds (131 and 132). Fractional recrystallization was attempted using a dichloromethane-hexane solvent mixture as the literature suggested.[41] However, water proved to be a better solvent to separate the mixture and purify 2-amino-3-benzoylpyridine (131).



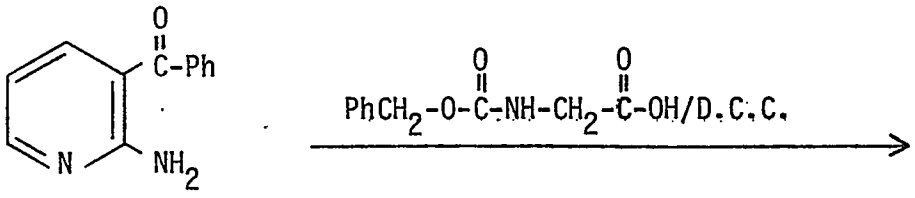
(129) (130)



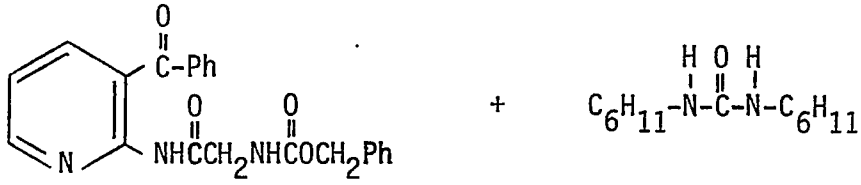
(131) (132)

As previously indicated (Scheme 1), three main routes were employed for the synthesis of the 1,4-benzodiazepines. One of these routes utilized a halogenated compound, chloracetylchloride. Littell and Allen[41] reported that the desired pyridodiazepines were not obtained using this reagent. A quaternary pyridinium compound was probably formed rather than the desired N-acylated product.[102] They also obtained discouraging results with glycine ester hydrochloride. However, the third route, which involved the use of a protected amino acid derivative, proved to be successful. They prepared a series of pyrido-1,4-diazepinones, which included one pyrido[2,3-e]-1,4-diazepine. It was planned to repeat this synthesis and to expand it to further derivatives.

2-Amino-3-benzoylpyridine (133) was treated with carbobenzyloxy-glycine in the presence of N,N'-dicyclohexylcarbodiimide (D.C.C.) as described by Littell and Allen[41,42] to supposedly yield 2-(α-carbobenzoxamidoacetamido)-3-benzoylpyridine (134) and N,N'-dicyclohexylurea (135). The crude condensation product was not characterized, but carried through to the hydrolysis and cyclization stages without purification.

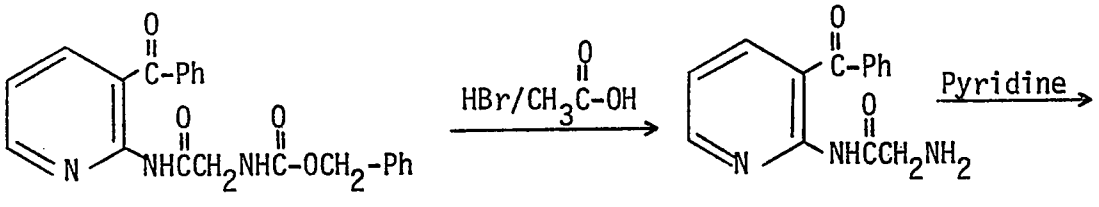


(133)

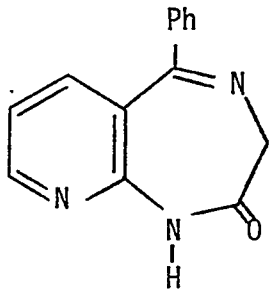


(134) (135)

Acidic hydrolysis of the supposed carbobenzoxamidoacetamido-compound (136) was carried out with hydrogen bromide in acetic acid to give the assumed aminoacetamido-compound (137), which was treated under the cyclization conditions without characterization according to the literature procedure.[41,42] Examination of the ultimate product by mass spectrometry and infrared spectroscopy indicated that the material obtained from the cyclization step was actually the original starting material, 2-amino-3-benzoylpyridine (133). The mass spectrum did not show any sign of a peak at m/e 237, which corresponds to the parent ion of 1,3-dihydro-5-phenyl-2H-pyrido [2,3-e]-1,4-diazepin-2-one (138). Therefore it appeared that the cyclization step (137⟶ 138) had probably not occurred at all.



(136) (137)



(138)

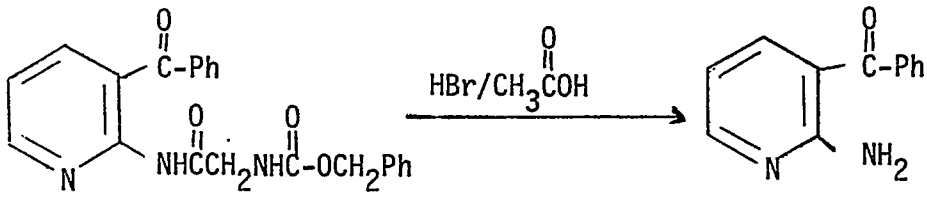
Sheehan and Hess[103] discovered that condensations between a free carboxyl function and a free amino group could be achieved in the presence of D.C.C. to form an amide linkage for the synthesis of amino acids. The co-product, N,N'-dicyclohexylurea, formed was insoluble in most solvents and easily separated. Buzas and coworkers[104-106] extended this reaction to include the formation of amides from aromatic amines and aliphatic and aromatic acids. Sternbach's group[32] and Stempel and Landgraf[33] have applied this method to the preparation of intermediates in the synthesis of benzodiazepines.

Due to the failure of the overall reaction sequence (133⟶138) it was decided to investigate the condensation reaction. The precipitate formed was weighed and examined by mass spectrometry. A quantitative yield of the urea was formed and the mass spectrum showed a parent ion at m/e 224, indicating that the initial condensation (133⟶134)had probably occurred with the formation of N,N'-dicyclohexylurea.

It is unlikely that the cyclization step (137⟶138) would have failed. Therefore it would appear that the reaction sequence did not

occur as according to Littell and Allen during the hydrolysis stage (136⟶137). Precautions were taken to keep the acetous hydrobromic acid dry and thus prevent any excessive hydrolysis due to moisture.

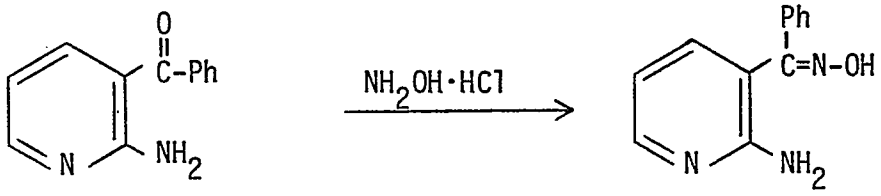
Ishai and Berger[107] have hydrolyzed amide linkages with hydrobromic acid in acetic acid. Stempel and Landgraf[33] used 20% hydrobromic acid in acetic acid to remove the protective carbobenzoxy group in the synthesis of benzodiazepines. Littell and Allen[41,42] removed the protective group using a saturated solution of hydrogen bromide in acetic acid. Standard strengths of the acidic solutions were not prepared and the saturated solution of hydrogen bromide in acetic acid employed in the hydrolysis reaction may have been too strong. If this was the case, hydrolysis of both amide linkages in 2-(α-carbobenzoxamidoacetamido)-3-benzoylpyridine (139) may have occurred yielding the starting material, 2-amino-3-benzoylpyridine (140).



(139) (140)

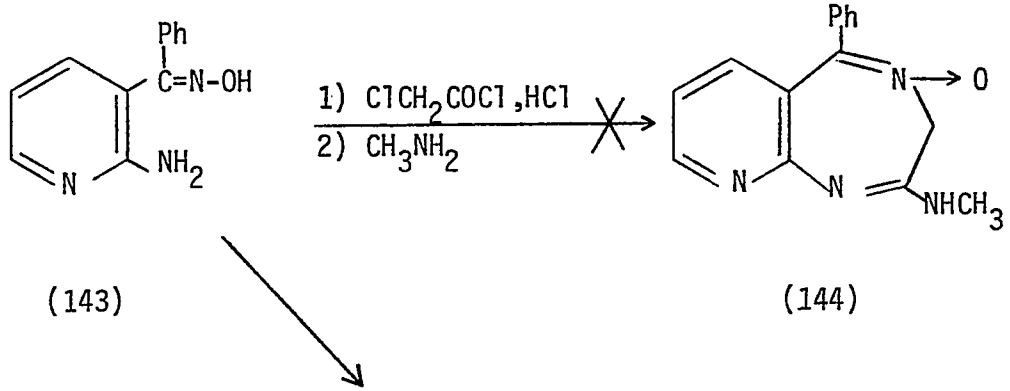
Littell and Allen[42] also reported the synthesis of a pyrido-[3,4-e]diazepine 4-oxide from an oxime by an analogous reaction to the one described by Sternbach and Reeder[30] for the synthesis of chlordiazepoxide. They gave no indication of the yield or problems associated with the reaction. At first sight it would appear that difficulties would be encountered in this type of synthesis. Bell and coworkers[108] stated that the drawback to this method was the difficulty in obtaining the desired β-oxime, since the predominant form resulting from oximation and acylation of the corresponding o-aminoketone is the α-oxime. Littell and Allen[42] prepared the oxime of 3-amino-4-benzoylpyridine in good yield, but gave no indication as to whether or not a mixture of isomers was obtained.

In the present work 2-amino-3-benzoylpyridine (141) was treated with hydroxylamine hydrochloride according to the procedure of Littell and Allen[42] to give the oxime (142) in good yield. Neither glc nor tlc analysis of the recrystallized oxime was carried out to see if a mixture of isomers had been formed.

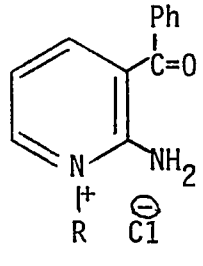


(141) (142)

The preparation of 2-methylamino-5-phenyl-3H-pyrido[2,3-e]-1,4-diazepine 4-oxide (144) was attempted by treating the oxime (143) with chloroacetylchloride, hydrogen chloride and methylamine according to the procedure of Littell and Allen[42]. After work-up a water-soluble yellowish-white solid was obtained whose infrared spectrum indicated the presence of a quaternary nitrogen by a broad band in the region of 2850-2350 cm^{-1}. The mass spectrum showed a parent peak at m/e 198, which corresponds to 2-amino-3-benzoylpyridine. The experimental evidence would seem to indicate that the oxime had decomposed to 2-amino-3-benzoylpyridine and that the chloroacetyl-chloride had formed a quaternary pyridinium salt (145) rather than the desired acylation product. It has been reported that benzophenone oxime readily decomposes to benzophenone.[109]



(143) (144)



(145)

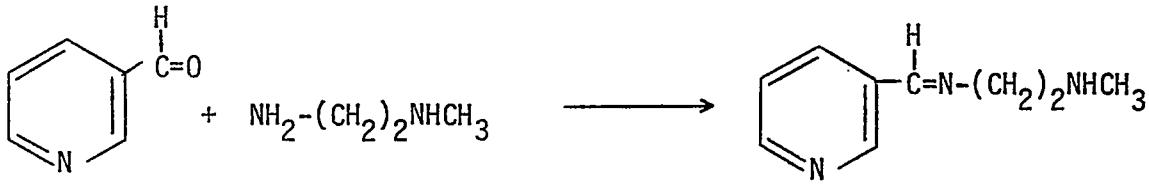
3.3.2.0.0 *Via* intramolecular nucleophilic cyclization

The second route for the synthesis of pyrido[2,3-*e*]-1,4-diazepines involved an extension of the investigatory intramolecular nucleophilic cyclization discussed in section 3.1.2.0.0. It was ultimately planned to prepare suitable imines from 3-benzoylpyridine and then attempt to cyclize them to pyrido[2,3-*e*]-1,4-diazepines. It was decided to firstly investigate the synthetic potential of the cyclization starting with nicotinaldehyde, and then apply the optimum conditions to the 3-benzoylpyridine derivatives.

3.3.2.1.0 From nicotinaldehyde

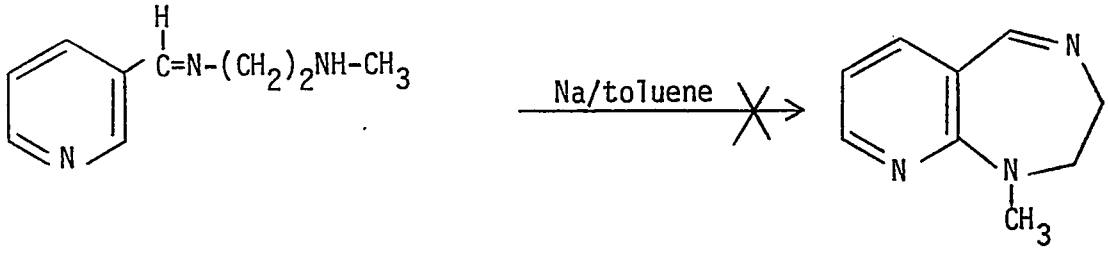
It is well known that when aldehydes or ketones are heated with primary amines, imines are formed. The reaction is reversible and reaches an equilibrium before the reaction is complete. Usually the water formed in the reaction is removed by azeotropic distillation with benzene using a Dean-Stark trap.[110-118]

Nicotinaldehyde (146) was refluxed with *N*-methylethylenediamine (147) to give *N*-methyl-*N*'-(3-picolylidene)ethylenediamine (148) in good yield. In this and all subsequent analogous condensations a Dean-Stark trap was used. The product distilled as a colorless oil and its infrared spectrum contained a band at 3310 cm^{-1} which is characteristic of a secondary amine. The nmr spectrum of the product contained a one proton singlet, which was replaced readily by deuterium oxide, confirming that the condensation had occurred.



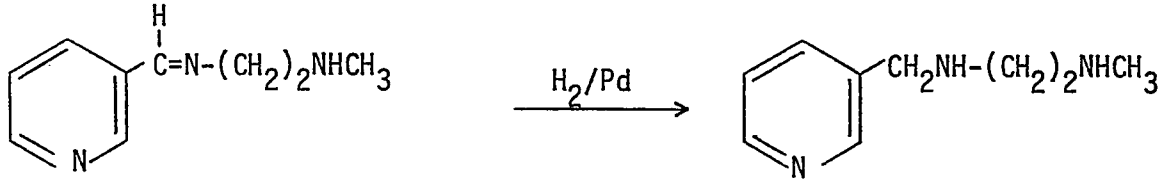
(146) (147) (148)

Cyclization was attempted using the optimum conditions determined in section 3.1.2.0.0. The imine (149) was refluxed in toluene in the presence of pulverized sodium for 72 hours. After work-up a poor yield of a black tar was isolated, which decomposed further on attempted distillation. There was not any indication that the cyclic product, 2,3-dihydro-1-methyl-1H-pyrido[2,3-e]-1,4-diazepine (150), had formed. The apparent decomposition may have been due to the presence of the double bond and the forcing conditions used in the attempted cyclization. It has been reported that metallic sodium reacted with imines to form disodium derivatives.[119] The rigid structure of the side chain, due to the double bond, may have also prevented the cyclization.



(149) (150)

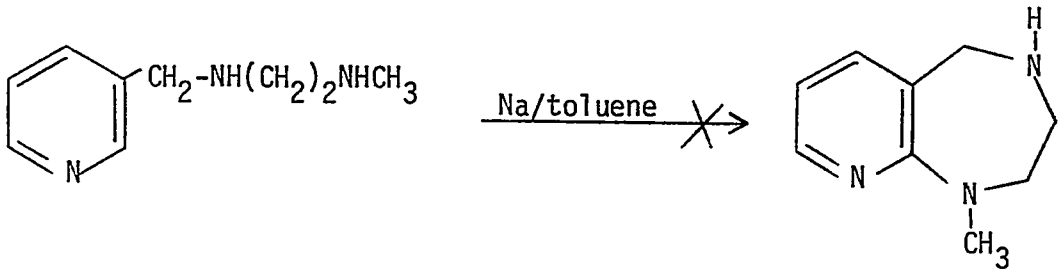
It was therefore decided to reduce the double bond of the imine before attempting the cyclization. Imines have been reduced by a wide variety of reagents.[120-123] The reduction of N-methyl-N'-(3-picolylidene)ethylenediamine (151) was attempted first by using lithium aluminum hydride according to the method described by Billman and Tai.[116] However upon work-up the infrared and mass spectra of the product indicated that reduction had not occurred. N-Methyl-N'-(3-picolyl)ethylenediamine (152) was obtained by catalytic hydrogenation using palladium on charcoal according to the general procedure of Elslager and coworkers.[124] The product distilled as a colorless oil and its nmr spectrum contained a two proton singlet, which was readily replaced by deuterium oxide. The mass spectrum of the product showed a parent peak at two mass units higher than the imine which confirmed that reduction had occurred.



(151) (152)

Cyclization of N-methyl-N'-(3-picolyl)ethylenediamine (153) was attempted using the conditions previously described. Upon work-up a black tar was isolated in poor yield which appeared to decompose further on attempted distillation. Again the cyclic product,

2,3,4,5-tetrahydro-1-methyl-1H-pyrido [2,3-e]-1,4-diazepine (154) was not detected. It is worthy of note that attempts at nucleophilic substitution by secondary amines in the Tschitschibabin reaction have been unsuccessful.[58,66]

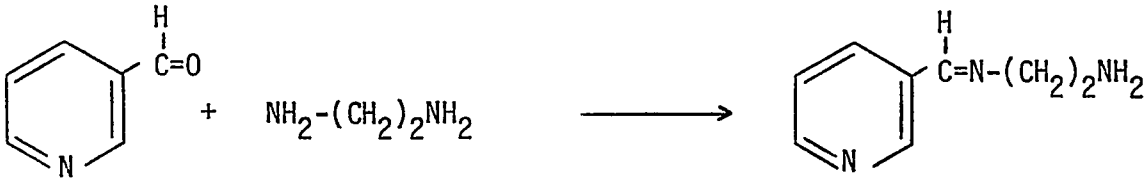


(153) (154)

Therefore the next approach was to attempt to synthesize the imine from nicotinaldehyde and ethylenediamine, which would contain a terminal primary amine group. The presence of the two primary amine groups in ethylenediamine posed a potential problem. It is known that bases such as hydrazine, with two primary amino groups, will react with two molecules of carbonyl compounds to form azines rather than the monosubstituted imines.[125-127] To overcome this difficulty a large excess of hydrazine has been used.[128] Thus a solution of nicotinaldehyde was added dropwise to a solution of a large excess of ethylenediamine and heated under reflux. A good yield of an unidentified oil was obtained, however, the product could not be distilled without decomposition. In general, the formation of imines is acid catalyzed and occurs at a maximum rate at pH 4.[129] The

large excess of ethylenediamine which would have increased the pH could have slowed the reaction down.

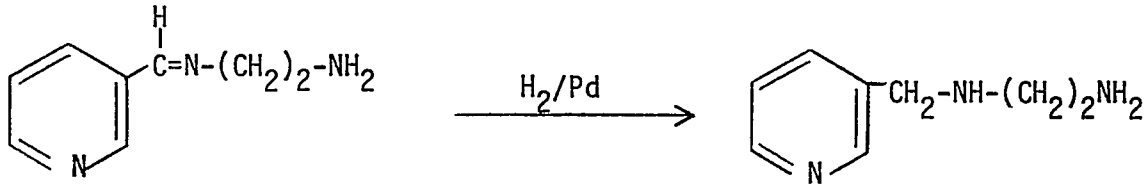
When the N-methyl derivative (148) was prepared, equimolar ratios of the amine to aldehyde were used. It was therefore decided to attempt to synthesize N-(3-picolylidene)ethylenediamine (157) by using equimolar ratios of reactants. A solution of nicotinaldehyde (155) was cautiously added dropwise to a solution of ethylenediamine (156) with vigorous stirring and then heated to reflux. Distillation gave the desired imine as a colorless oil in good yield. A small amount of residue which remained after distillation was probably the azine. The infrared spectrum of the distilled product contained two absorption bands at 3360 and 3280 cm^{-1}, which is characteristic of a primary amine. Mass spectrometry confirmed that the imine had been formed.



(155) (156) (157)

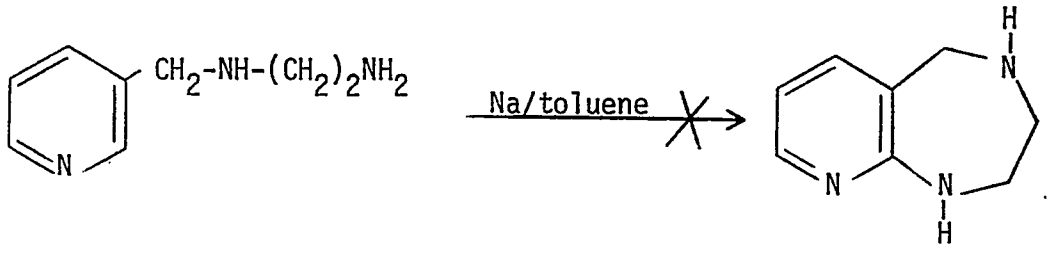
N-(3-Picolylidene)ethylenediamine (158) was reduced by catalytic hydrogenation to N-(3-picolyl)ethylenediamine (159) using palladium on charcoal according to the general method of Elslager and coworkers.[124] The product distilled as a colorless oil in good yield. The infrared spectrum of the product contained two absorption bands at 3340 and

3265 cm^{-1}, which is characteristic of a primary amine. The mass spectrum of the product confirmed that reduction had occurred, as the parent ion was two mass units higher than the imine starting material.



(158) (159)

Cyclization of N-(3-picolyl)ethylenediamine (160) was attempted using the conditions previously described. Upon work-up a good yield of a dark brown oil was obtained. Distillation gave a small amount of an oil, which was identified as starting material by mass spectrometry. It appeared that cyclization had not occurred as there was not a peak at m/e 149, which corresponds to 2,3,4,5-tetrahydro-1H-pyrido[2,3-e]-1,4-diazepine (161). Since there was a good recovery of crude product and the starting material was definitely present in this, perhaps this reaction is worthy of further investigation. The reaction conditions employed used a 2:1 ratio of sodium to the side chain diamine. It may be possible that a higher ratio of sodium to the diamine is required to achieve the cyclization.



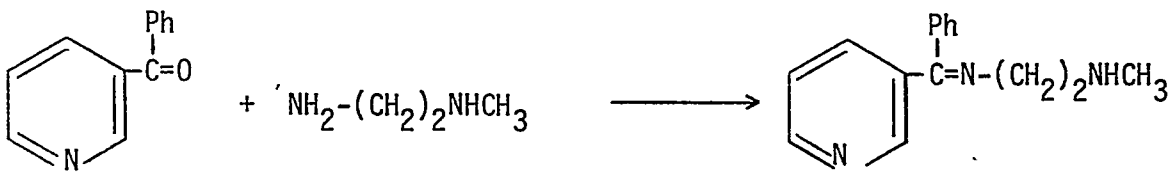
(160) (161)

3.3.2.2.0 From 3-benzoylpyridine

Since all active benzodiazepines contain a phenyl group at the 5-position it was planned to prepare analogous 3-picolylethylenediamines from 3-benzoylpyridine. Originally it was hoped to apply the optimum cyclization conditions determined in section 3.3.2.1.0 to the picolylethylenediamines in an attempt to prepare 5-phenylpyrido[2,3-e]-1,4-diazepines. However, since in the work to date these cyclizations have failed to yield any detected bicyclic products only the attempted synthesis of the side chain imines are reported here.

The preparation of N-methyl-N'-α-(3-pyridyl)benzylidene ethylenediamine (164) was firstly attempted by refluxing 3-benzoylpyridine (162) with N-methylethylenediamine (163). Distillation gave an oil which was identified as 3-benzoylpyridine, the starting material. It has been reported that the analogous reaction of benzophenones was relatively slow and was best carried out in the presence of a fairly strong acid, such as zinc chloride or 40% hydrobromic acid.[116] Thus the reaction was repeated using hydrobromic acid as a catalyst. The

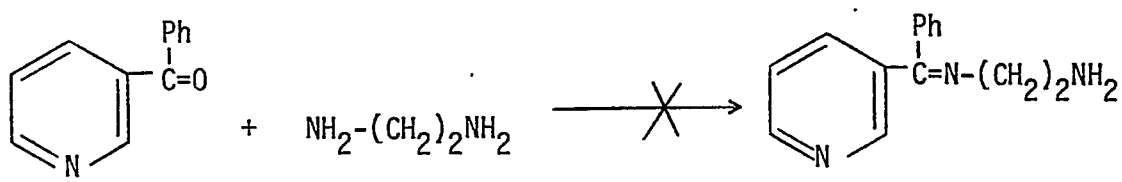
product distilled as a colorless oil and its infrared spectrum contained a band at 3310 cm^{-1}, which is characteristic of a secondary amine. The infrared spectrum of the product was very similar to that of N-methyl-N'-(3-picolylidene)ethylenediamine, which lacks the phenyl group. Mass spectrometry confirmed that the imine had been formed.



(162) (163) (164)

Neither reduction nor cyclization of N-methyl-N'-α-(3-pyridyl)-benzylidene ethylenediamine was attempted due to the lack of success of cyclization with N-methyl-N'-(3-picolyl)ethylenediamine.

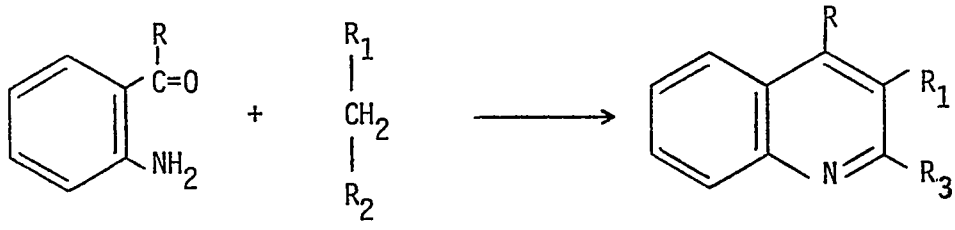
An attempt at preparing N-α-(3-pyridyl)benzylidene ethylenediamine (167) from 3-benzoylpyridine (165) and ethylenediamine (166) with hydrobromic acid as a catalyst was unsuccessful.



(165) (166) (167)

3.4.0.0.0 Preparation of 2,3-disubstituted-4-phenyl-1,8-naphthyridines from 2-amino-3-benzoylpyridine

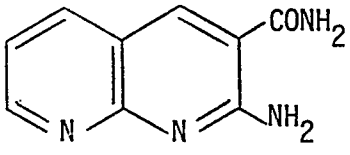
The previously discussed attempted synthesis of pyrido[2,3-e]-1,4-diazepines from 2-amino-3-benzoylpyridine (section 3.3.1.0.0) was of interest in our laboratories for a number of reasons. Firstly, the failure of this synthesis in our hands could be attributed to the lack of nucleophilic activity of the carbonyl group, or the steric hindrance of a diaryl ketone. Quinolines (170) are readily synthesized by the Friedländer method from o-amino aromatic carbonyl compounds (168) and a methylene compound (169) containing an α-group capable of reacting with amines.[130-136] If such syntheses were attempted it could throw light on the present problem.



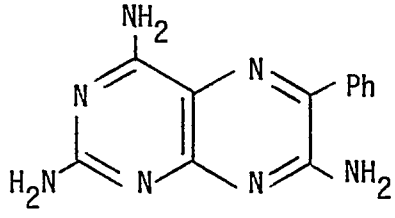
(168) (169) (170)

Secondly, other workers in our laboratories have been synthesizing 1,6- and 1,8-naphthyridines by the Friedländer synthesis and this experience could be applied to the present work. There are few reports to the synthesis of naphthyridines by the Friedländer method and all refer to o-aminoarylaldehydes.[137,138] None refer to o-aminodiarylketones.

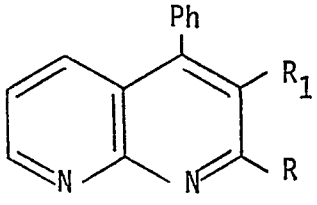
Lastly, these naphthyridines have been synthesized as analogs of the pteridine diuretics.[139] Many have been found to be active in a rat saline-loaded screen.[140] The most interesting compound to date is 2-amino-1,8-naphthyridine-3-carboxamide (171) which is far more potent in rats than triamterene (172), the most active pteridine diuretic which is marketed. It came of interest to see whether or not steric hindrance at the 7-position would effect activity. Thus at present two series of compounds, 4-phenyl-(173) and 7-phenyl-(174) 2,3-disubstituted-1,8-naphthyridines, are being synthesized and their activities compared. The present investigation should thus be of assistance in this program, particularly if the analog of (171) could be prepared (173;R=NH_2, R_1=$CONH_2$).



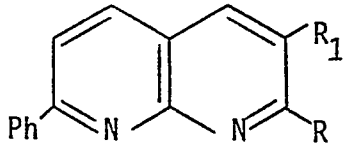
(171)



(172)



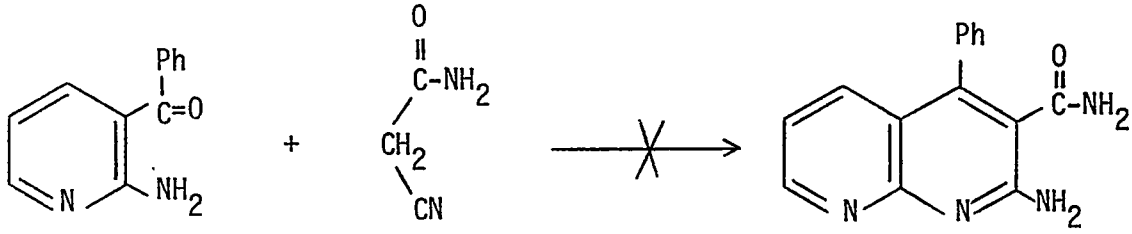
(173)



(174)

3.4.1.0.0 From 2-amino-3-benzoylpyridine and cyanoacetamide

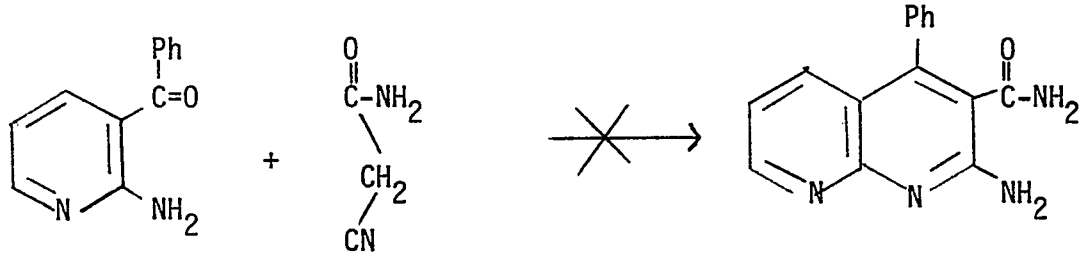
The synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carboxamide (177) was attempted first by using the general procedure described by Hawes and Gorecki.[138] 2-Amino-3-benzoylpyridine (175) and cyanoacetamide (176) were heated at reflux in alcohol using piperidine as a base catalyst. However, upon work-up only starting material was recovered. The same result was obtained when sodium hydroxide or sodium methoxide were used as base catalysts. The lack of success of this reaction was probably due to steric hindrance of the diaryl ketone, since the methylene group of cyanoacetamide is activated.



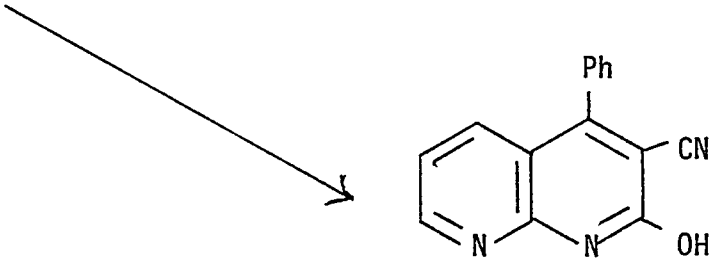
(175) (176) (177)

Campaigne and Randau[136] have prepared quinolines from o-amino-benzophenones via the Friedländer synthesis using pyridine as the solvent. Thus in an attempt to prepare 2-amino-4-phenyl-1,8-naphthyridine-3-carboxamide (180), 2-amino-3-benzoylpyridine (178) and cyanoacetamide (179) were heated under reflux in pyridine for 48 hours. Upon work-up a brown solid was obtained whose infrared spectrum contained a sharp band at 2240 cm^{-1}, which is characteristic of a

nitrile, and a broad band from 1690-1610 cm^{-1}. The latter absorption band was probably due to a naphthyrid-2-one. It is known that 2-hydroxypyridines exist in the tautomeric pyridone form.[141] The mass spectrum of the product indicated that the 2-hydroxy compound had been formed, as the parent ion was at m/e 247, which corresponds to 3-cyano-2-hydroxy-4-phenyl-1,8-naphthyridine (181). A major fragment ion occurred at m/e 219, which would suggest a loss of C=O from the naphthyrid-2-one compound, thus confirming that 3-cyano-2-hydroxy-4-phenyl-1,8-naphthyridine had been formed.



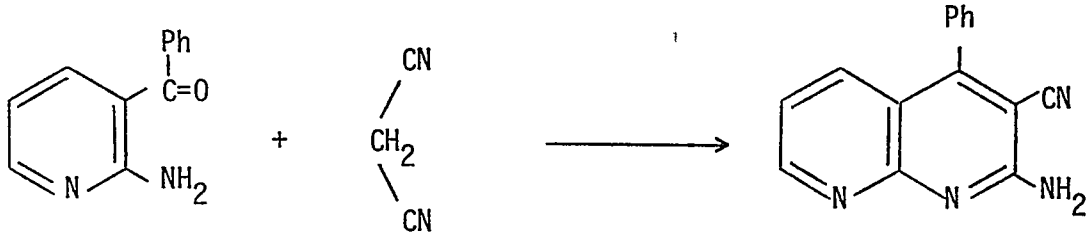
(178) (179) (180)



(181)

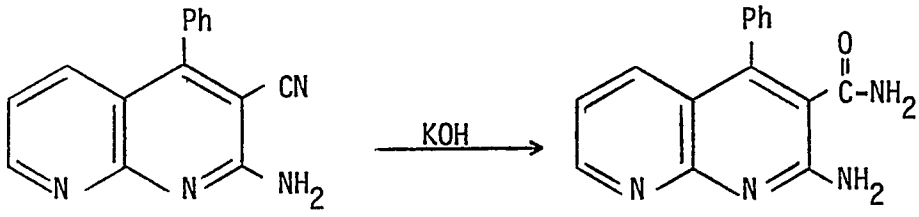
3.4.2.0.0 From 2-amino-3-benzoylpyridine and malononitrile

Due to the lack of success with cyanoacetamide as the α-methylene compound, it was decided to use malononitrile and attempt to prepare the nitrile (184), which could then be hydrolyzed to the corresponding amide by the general method of Campaigne and Randau.[136] Thus 2-amino-3-benzoylpyridine (182) and malononitrile (183) were heated under reflux in pyridine for 24 hours. Upon work-up a brown solid was obtained. The infrared spectrum of the product contained two absorption bands at 3420 and 3320 cm^{-1}, which indicated the presence of a primary amino group. The spectrum also contained a sharp band at 2230 cm^{-1}, which is characteristic of a nitrile. The mass spectrum contained a parent ion at m/e 246, which corresponds to 2-amino-3-cyano-4-phenyl-1,8-naphthyridine (184), confirming that the desired reaction had occurred.



(182) (183) (184)

2-Amino-3-cyano-4-phenyl-1,8-naphthyridine (185) and potassium hydroxide were heated under reflux in alcohol for one hour to yield a brown solid after work-up. The infrared spectrum of the product contained two bands at 3350 and 3290 cm^{-1}, indicating the presence of a primary amine. The spectrum also contained an absorption band at 1675 cm^{-1}, indicating the presence of an amide. There was not an absorption band at 2230 cm^{-1}, indicating that hydrolysis of the nitrile had occurred. The mass spectrum of the product contained a parent ion at m/e 264, which corresponds to 2-amino-4-phenyl-1,8-naphthyridine-3-carboxamide (186), confirming that the desired degree of hydrolysis had occurred.

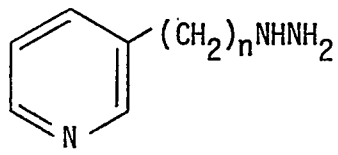


(185) (186)

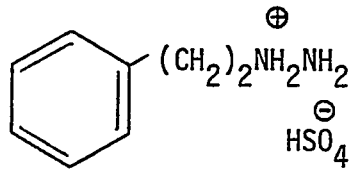
4.0.0.0.0 PHARMACOLOGICAL SCREENING OF MAO INHIBITORS

4.1.0.0.0 *In vivo* testing

An *in vivo* study of the MAO inhibition of the hydrochloride salts of HLD 18 (187; n=3), HLD 21 (187; n=2) and HLD 29 (187; n=1), using phenelzine (188) as a reference compound, was carried out by Dr. D.D. Johnson and Mr. W. Wilcox, Department of Pharmacology, University of Saskatchewan, Saskatoon, Saskatchewan.



(187)



(188)

4.1.1.0.0 Hexobarbital sleeping time prolongation

The procedure employed was exactly the same as that reported by Eltherington and Horita.[142] Groups of 10 mice were pretreated with one of the inhibitors (100 mg/kg). HLD 29 was found to be much more toxic than the other inhibitors at this dose. In fact, its LD_{50} was found to be between 50 and 75 mg/kg. Therefore the mice being treated with HLD 29 were given 32.12 mg/kg (20 m moles) and compared to phenelzine (46.45 mg/kg, 20 m moles). At various time

intervals after the inhibitor, the groups of mice each received 100 mg/kg of hexobarbital. All injections were made intraperitoneally. The control mice received 100 mg/kg of hexobarbital alone. The sleeping times were measured by the period of absence of the righting reflex. The mean percentage sleeping times, as compared to the control, are recorded in tables 3 and 4, while these results are depicted in figures 1 and 2. The raw data is recorded in the appendix (6.2.1.0.0).

Table 3. Mean % control of hexobarbital sleeping time of HLD 18, HLD 21 and phenelzine

Time in hours after MAO inhibitor	Phenelzine (100 mg/kg)	HLD 21 (100 mg/kg)	HLD 18 (100 mg/kg)
½	702.5	246.7	315.6
2	699.4	120.2	115.6
4	485.7	97.5	112.8
16	298.8	99.4	94.4
24	239.7	108.4	97.5
48	150.8	103.2	116.8

Table 4. Mean % control of hexobarbital sleeping time of HLD 29 and phenelzine

Time in hours after MAO inhibitor	Phenelzine (46.45 mg/kg)	HLD 29 (32.12 mg/kg)
½	414.8	122.2
2	370.8	153.8
4	316.2	119.4
16	222.5	101.1
24	116.5	109.2
48	96.1	121.1

Figure 1. Effect of HLD 18, HLD 21 and phenelzine on the hexobarbital sleeping time

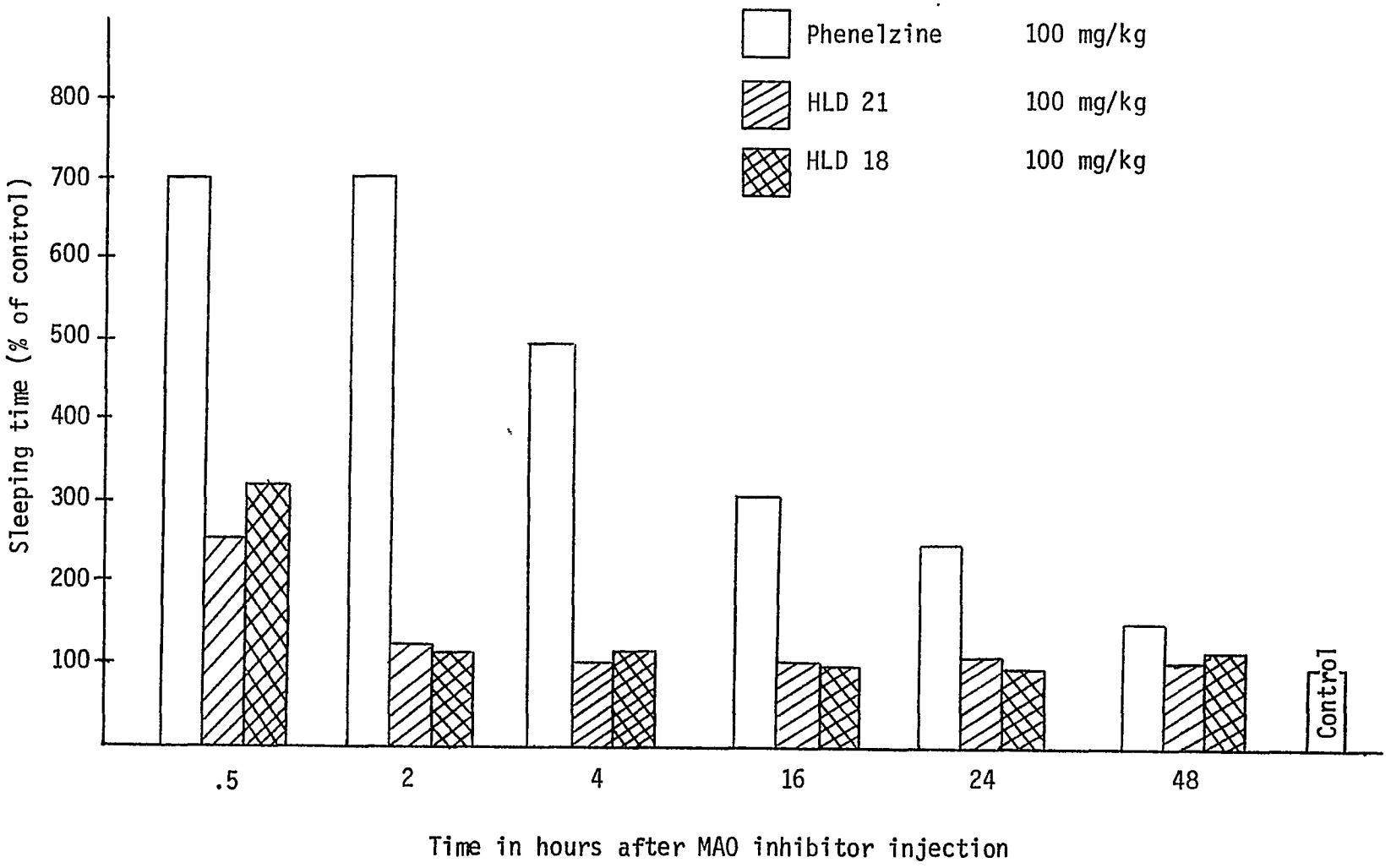
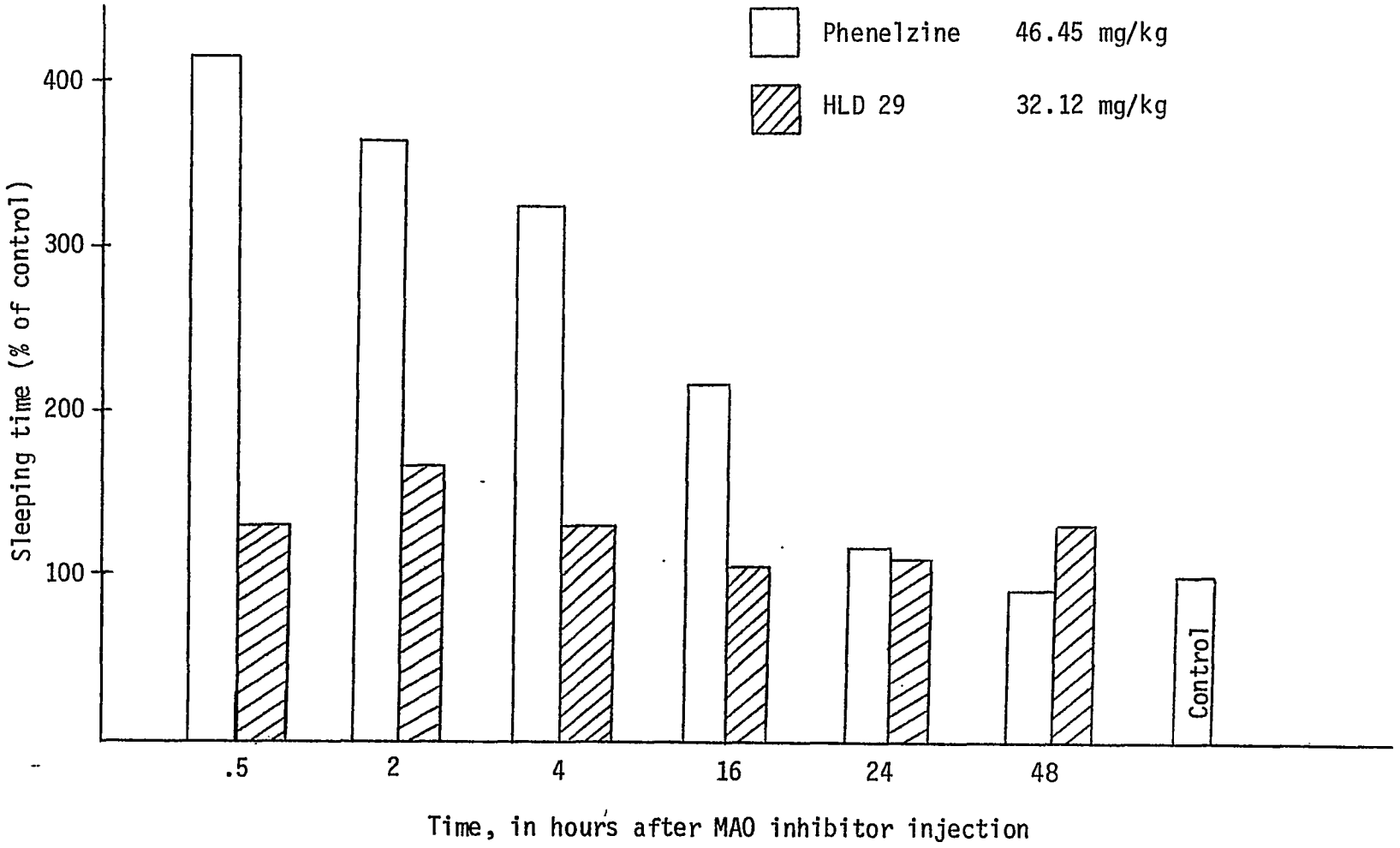


Figure 2. Effect of HLD 29 and phenelzine on the hexobarbital sleeping time



From the screening results it appeared that HLD 18, 21 and 29 were far less potent than phenelzine in prolonging the hexobarbital sleeping time. However, the potentiation of barbituate sleeping time is not a specific test for MAO inhibition. Therefore a more specific MAO inhibition screen was required.

4.1.2.0.0 Reserpine reversal

It is known that reserpine causes a sedation or tranquilizing effect; however, if a MAO inhibitor is given before reserpine, excitation rather than sedation occurs.

The procedure employed was the same as that reported by Eltherington and Horita[142], except that an actophotometer was used to measure the motor activity of the mice instead of visual observation. Groups of 5 mice were pretreated with 100 mg/kg of HLD 21, HLD 18 or phenelzine. This was followed by reserpine (5 mg/kg) at the various time intervals indicated in Table 5. The mice pretreated with HLD 29 received 32.12 mg/kg and were compared to phenelzine (46.45 mg/kg). The mice then received reserpine (5 mg/kg) at the time intervals indicated in Table 6. In both experiments the control mice received reserpine (5 mg/kg) alone. For all recordings the mice were placed in an actophotometer for a ½ hour duration to measure motor activity. The results are depicted in figures 3 and 4 and the raw data is recorded in the appendix (6.2.2.0.0).

Table 5. Mean motor activity of HLD 18, HLD 21 and phenelzine (% of control) in reserpine reversal screen

Time in hours after MAO inhibitor	Phenelzine (100 mg/kg)	HLD 21 (100 mg/kg)	HLD 18 (100 mg/kg)
½	52.9	57.8	60.5
2	107.0	49.9	96.6
4	152.5	86.2	168.2
16	113.1	139.0	133.6
24	112.4	134.0	141.5
48	121.4	133.9	151.3

Table 6. Mean motor activity of HLD 29 and phenelzine (% of control) in reserpine reversal screen

Time in hours after MAO inhibitor	Phenelzine (46.45 mg/kg)	HLD 29 (32.12 mg/kg)
½	71.9	73.4
2	113.1	60.6
4	106.9	75.5
16	176.6	116.4
24	109.5	136.5
48	95.8	105.8

Figure 3. Reserpine reversal of HLD 18, HLD 21 and phenelzine

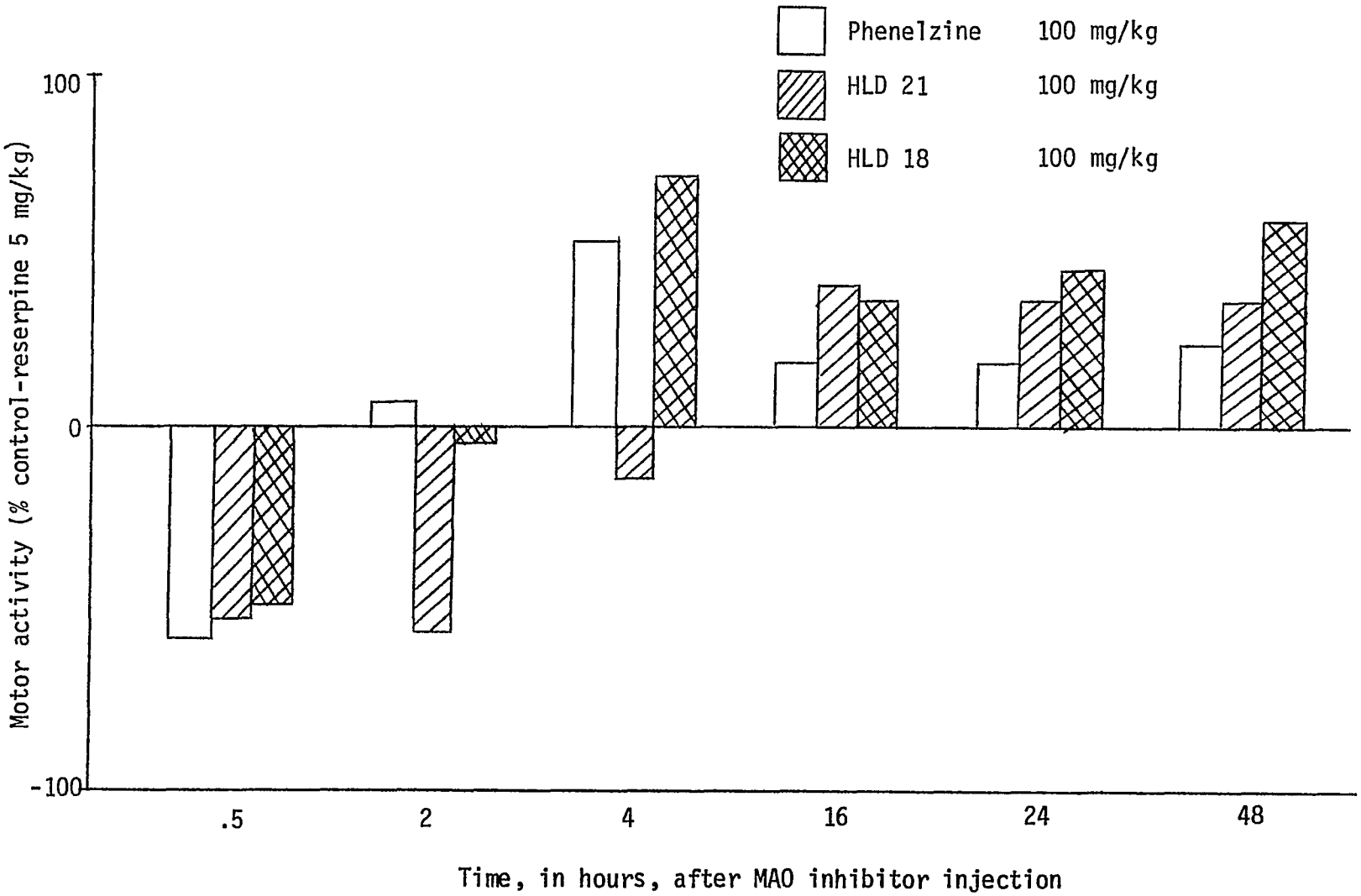
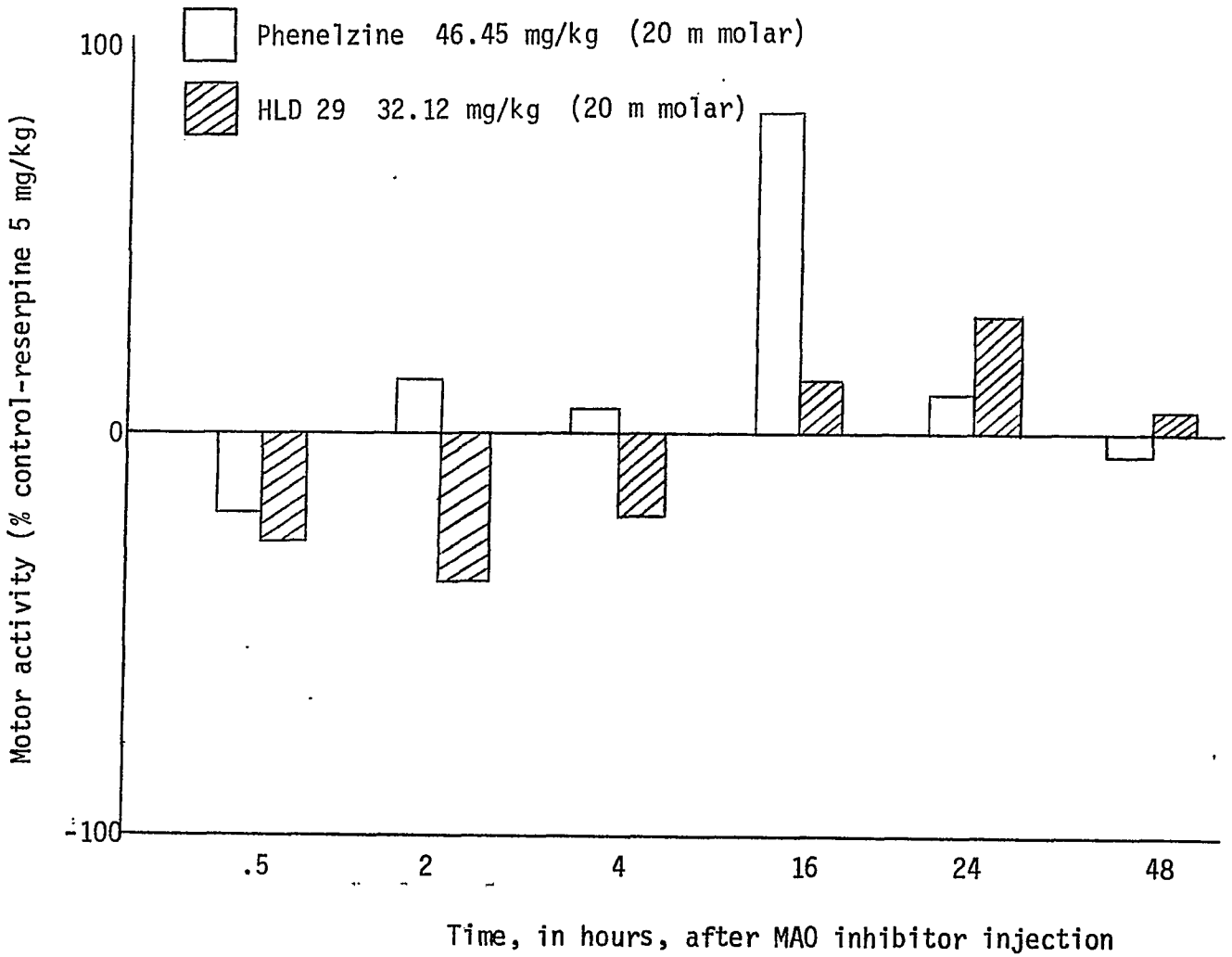


Figure 4. Reserpine reversal of HLD 29 and phenelzine



From these experiments it appeared that all three pyridine compounds were MAO inhibitors, as the results could be depicted by classical reserpine reversal diagrams (figures 3 and 4). HLD 21 and HLD 29 had a longer latency than phenelzine and HLD 18. HLD 29, 21 and 18 had a longer duration of action than phenelzine.

4.2.0.0.0 *In vitro* testing

An even more specific screen was required in which there were no problems of variations in body distribution of the compounds. Thus an *in vitro* study of MAO inhibition of the hydrochloride salts of HLD 18, HLD 21, HLD 29 and phenelzine was carried out by Dr. J. Wood and Mrs. J. Bettany, Department of Biochemistry, University of Saskatchewan, Saskatoon, Saskatchewan.

The procedure employed was similar to that reported by McCaman and coworkers[143], using serotonin creatinine sulfate labelled with ^{14}C in the 3'-position. A 1.2×10^{-3} molar solution of each compound was made up in deionized water, to give a final concentration of 10^{-4} moles in the incubation mixture. The mice were decapitated and the heads kept in liquid nitrogen until required. The brains were homogenized in 1.25% Triton X-100 to give a 10% homogenate. 10λ Buffer substrate which contained the radioactive serotonin creatinine sulfate, 1λ homogenate and 1λ test solution were incubated together for 15 minutes at 38^{0}. The reaction products were extracted into ethyl acetate. After a backwash with dilute acid, the radioactivity

of the metabolized serotonin was determined with a scintillation counter. A control was carried through the procedure without the test solution. The results are recorded in Table 7.

Table 7. MAO inhibition *in vitro* results for HLD 18, HLD 21, HLD 29 and phenelzine

	MAO activity (μ moles/g/hr.)				
	Control	HLD 18	HLD 21	HLD 29	Phenelzine
Trial 1	6.21	1.13	0.26	2.62	0.23
Trial 2	7.37	1.42	0.27	3.38	0.29
Trial 3	5.60	0.64	0.38	3.99	0.33
Trial 4	7.00	0.57	0.27	2.72	0.24
$\bar{X}$	6.55	0.94	0.29	3.18	0.27
S.E.	0.40	0.20	0.02	0.32	0.02
% inhibition		85%	95%	51%	95%

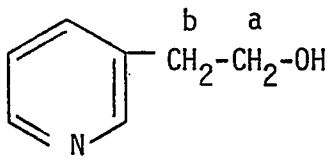
From the results, it can be seen that HLD 21 was equal in potency to phenelzine. HLD 18 was slightly less active, while HLD 29 was approximately ½ as active as phenelzine. Both HLD 21 and phenelzine have an ethylene side chain. The high potency of benzylhydrazine was not evident in its pyridine analog (HLD 29) *in vitro*, although as previously discussed (4.1.1.0.0) the latter significantly displayed high toxic effects *in vivo*.

5.0.0.0.0 DESCRIPTION OF THE EXPERIMENTAL WORK

The preparation of the anhydrous solvents, reagents and the instruments utilized to determine the physical characteristics of the compounds are described in the appendix (section 6.1.0.0.0).

5.1.0.0.0 Preparation of 3-pyridylalkylamines

5.1.1.0.0 Preparation of 2-(3-pyridyl)ethanol (92)



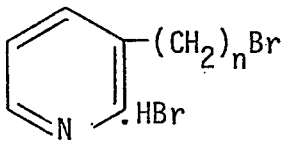
The method of Barnden et al.[72] was followed but ethyl 3-pyridylacetate was used instead of methyl 3-pyridylacetate. A slurry of lithium aluminum hydride (9.5 g, 0.25 mole) in anhydrous ether (450 ml) was added dropwise with vigorous stirring to a solution of ethyl 3-pyridylacetate (91) (82.5 g, 0.5 mole) in anhydrous ether (1200 ml) and the reaction mixture was stirred for 1 hour. The excess reducing agent was decomposed with a minimum amount of a saturated sodium potassium tartrate solution. The solution was extracted with chloroform (3 x 150 ml), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil. The oil was distilled in vacuo to yield the title alcohol (92) (43.8 g, 71.2%) as a color-

less oil: bp 130-132°/0.3 mm (lit.[72], 148°/15 mm); ir (neat) 3450-3200 cm^{-1} (OH hydrogen bonded); nmr ($CDCl_3$) δ8.33 (m, 2, $J_{6,4}$=2.0 Hz, $J_{6,5}$=5.0 Hz, C_6-H and C_2-H), 7.63 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.23 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 5.36 (s, 1, -OH, exchanges readily with D_2O), 3.91 (t, 2, $J_{a,b}$=6.5 Hz, CH_2-OH) and 2.83 ppm (t, $J_{b,a}$=6.5 Hz, -CH_2-CH_2-OH); mass spectrum m/e (rel intensity) 124(6), 123 (M^+, 42), 94(7), 93 (100), 92(47), 80(3), 78(3), 65(6), 64(12), 63(32), 62(5), 61(10), 60(4), 53(3), 52(5), 51(10), 50(6), 41(4), 40(4), 39(38), 38(8), 37(3), 31(15) and 29(5).

Anal. Calcd for C_7H_9NO: C, 68.29; H, 7.37; N, 11.38. Found: C, 68.13; H, 7.30; N, 11.20.

5.1.2.0.0 Preparation of 3-pyridylalkylbromides hydrobromides

5.1.2.1.0 3-(3-Bromopropyl)pyridine hydrobromide (94; n=3)

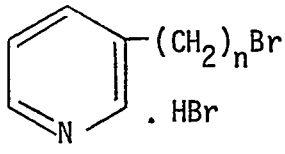


A mixture of 3-(3-pyridyl)propan-1-ol (93; n=3) (58.5 g, 0.4 mole) and 48.3% hydrobromic acid (548 ml) was heated under reflux for 9 hours. The reaction mixture was evaporated in vacuo, cooled, and acetone (120 ml) was added. The precipitate was collected and

recrystallized from acetone to yield the hydrobromide (94; n=3) (69.5 g, 62%) as tan crystals: mp 107-109°; ir (KBr) 2800-2500 cm^{-1} ($\overset{+}{=}NH$); nmr ($CDCl_3$) δ12.78 (s, 1, H-Br, exchanges readily with D_2O), 9.08 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.5 Hz, C_6-H and C_2-H), 8.68 (dofd, 1, $J_{4,6}$=2.0 Hz and $J_{4,5}$=8.5 Hz, C_4-H), 8.29 (dofd, 1, $J_{5,6}$=5.5 Hz and $J_{5,4}$=8.5 Hz, C_5-H), 3.67 (t, 2, $-CH_2Br$), 3,34 (m, 2, $-CH_2-(CH_2)_2Br$) and 2.50 ppm (m, 2, $-CH_2-CH_2Br$); mass spectrum m/e (rel intensity) 202(3), 201(27), 200(M^+,3), 199(31), 120(3), 119(7), 118(10), 117(3), 106(4), 105(3), 93(10.5), 92(100), 91(5), 82(6), 81(3), 80(6), 79(3), 77(5), 66(3), 65(25), 64(4), 63(7), 52(4), 51(9), 50(4), 41(4), 39(25), 38(5), 36(3), 28(6) and 27(9).

Anal. Calcd for $C_8H_{11}Br_2N$: C, 34.19; H, 3.95; Br, 56.88; N, 4.99. Found: C, 34.36; H, 3.90; Br, 57.04; N, 5.14.

5.1.2.2.0 3-(2-Bromoethyl)pyridine hydrobromide (94; n=2)



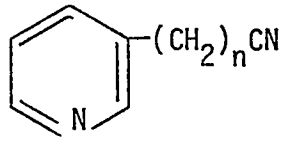
2-(3-Pyridyl)ethanol (93; n=2) (39.6 g, 0.3 mole) was treated by the method described in section 5.1.2.1.0 to yield the hydrobromide (94; n=2) (46.2 g, 75%) as tan crystals: mp 124-125°; ir (KBr) 2800-2400 cm^{-1} ($\overset{+}{=}NH$); nmr ($CDCl_3$) δ11.75 (s, 1, H-Br, exchanges readily with D_2O), 9.05 (m, 2, $J_{6,4}$=1.5 Hz and $J_{6,5}$=5.0 Hz, C_6-H and C_2-H),

8.65 (dofd, 1, $\underline{J}_{4,6}$=1.5 Hz and $\underline{J}_{4,5}$=8.0 Hz, C_4-$\underline{H}$), 8.18 (dofd, 1, $\underline{J}_{5,6}$=5.0 Hz and $\underline{J}_{5,4}$=8.0 Hz, C_5-$\underline{H}$) and 3.72 ppm (m, 4, -($C\underline{H}_2$)$_2$-Br); mass spectrum m/e (rel intensity) 188(3), 187(41), 186(M^+,3), 185(41), 173(2.5), 172(3), 171(3), 155(3), 127(3), 122(8), 107(4), 106(52), 105(36), 104(16), 93(9), 92(100), 91(3), 79(9), 78(20), 77(24), 76(4), 75(3), 74(3), 66(3), 65(31), 64(4), 63(9), 62(3), 53(6), 52(17), 51 (33), 50(19), 39(27), 38(10), 37(4), 27(11) and 26(5).

Anal. Calcd for $C_7H_9Br_2N$: C, 31.49; H, 3.40; Br, 59.85; N, 5.25. Found: C, 31.50; H, 3.80; Br, 60.20; N, 5.37.

5.1.3.0.0 Preparation of 3-pyridylalkylnitriles

5.1.3.1.0 3-(3-Pyridyl)butyronitrile (97; n=3)

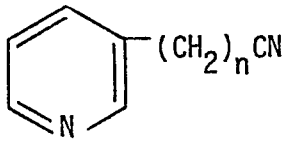


A solution of 3-(3-bromopropyl)pyridine hydrobromide (95; n=3) (56.2 g, 0.2 mole) in water (500 ml), overlayed with chloroform (200 ml), was treated with 50% sodium hydroxide (40 ml). The free base (96; n=3) was extracted with chloroform (3 x 200 ml), dried ($MgSO_4$), and evaporated in vacuo to dryness at low temperature. The viscous oil was immediately dissolved in ethanol (200 ml) and a solution of potassium cyanide (14.3 g) in water (160 ml) was added dropwise with stirring. The solution was heated under reflux for

3 hours. Water (400 ml) was added and the solution extracted with chloroform (3 x 100 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield a black oil, which on distillation in vacuo yielded the title nitrile (97; n=3) (21.1 g, 72.6%) as a colorless oil: bp 146-148°/0.2 mm; ir (neat) 2230 cm^{-1} (C≡N); nmr ($CDCl_3$) δ8.50 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 7.53 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.23 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 2.80 (t, 2, -CH_2-CN), 2.36 (m, 2, -CH_2-$(CH_2)_2$-CN) and 2.03 ppm (m, 2, -CH_2 -CH_2-CN); mass spectrum m/e (rel intensity) 147(7), 146(M^+,41), 119(6), 118(27), 107(4), 106(39), 105(7), 104(5), 93(18), 92(100), 91(3), 79(4), 78(7), 77(6), 66(4), 65(32), 64(5), 63(9), 62(3), 54(4), 53(4), 52(9), 51(17), 50(8), 41(7), 40(4), 39(35) and 38(7).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.18. Found: C, 73.91; H, 7.05; N, 18.93.

5.1.3.2.0 2-(3-Pyridyl)propionitrile (97; n=2)



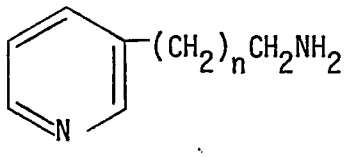
3-(2-Bromoethyl)pyridine hydrobromide (95; n=2) (66.75 g, 0.25 mole) was treated by the method described in section 5.1.3.1.0 to yield the nitrile (97; n=2) (18.8g, 57%) as a colorless oil: bp

150-152°/0.9 mm; ir (neat) 2240 cm^{-1} (C≡N); nmr ($CDCl_3$) δ8.83 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=4.8 Hz, C_6-H and C_2-H), 7.63 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.33 (dofd, 1, $J_{5,6}$=4.8 Hz and $J_{5,4}$=8.0 Hz, C_5-H) and 2.83 ppm (m, 4, -(CH_2)$_2$-CN); mass spectrum m/e (rel intensity) 133(3.5), 132(M^+, 27), 131(3), 106(4.5), 105(19), 104(13), 93(11.5), 92(100), 79(5.5), 78(9.5), 77(7), 76(4.5), 75(3), 66(3), 65(31), 64(4), 63(8), 62(3), 59(3), 52(11), 51(19.5), 50(18), 41(3), 40(3), 39(28), 38(8), 37(3), 31(4), 30(3), 27(7) and 26(5).

Anal. Calcd.for $C_8H_8N_2$: C, 72.70;H, 6.10; N, 21.20. Found: C, 72.57; H, 6.15; N, 20.99.

5.1.4.0.0 Preparation of 3-pyridylalkylamines

5.1.4.1.0 4-(3-Pyridyl)butylamine (99; n=3)

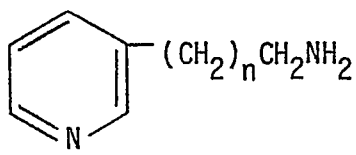


A solution of 3-(3-pyridyl)butyronitrile (98; n=3) (17.5 g, 0.12 mole) in anhydrous ether (240 ml) was added dropwise with vigorous stirring to a cooled (0°) slurry of lithium aluminum hydride (7.6 g, 0.2 mole) in anhydrous ether (80 ml). The mixture was stirred at room temperature for a further 2 hours. The excess reducing agent was decomposed with a minimum amount of water and the ether-insoluble residue was removed by filtration and washed several times

with hot benzene (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow oil, which on distillation in vacuo yielded the title amine (99; n=3) (12.2 g, 66%) as a colorless oil: bp 128-129°/0.3 mm; ir (neat)3360 and 3290 (N-H stretching) and 1570 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.43 (m, 2, $J_{6,4}$=2.4 Hz and $J_{6,5}$=4.9 Hz, C_6-H and C_2-H), 7.50 (ddd, 1, $J_{4,6}$=2.4 Hz, $J_{4,5}$=8.0 Hz, and $J_{4,2}$=2.0 Hz, C_4-H), 7.20 (dofd, 1, $J_{5,6}$=4.9 Hz, and $J_{5,4}$=8.0 Hz, C_5-H), 2.67 (m, 4, $-(CH_2)_2-NH_2$),1.57 (m, 4, $-(CH_2)_2-(CH_2)_2-NH_2$) and 1.20 ppm (s, 2,- NH_2, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 151(1), 150(M^+, 6), 149(4), 133(17), 121(6), 120(8), 119(9), 118(8), 107(22), 106(26), 105(6), 94(13), 93(100), 92(13), 91(14), 90(3), 80(4), 79(3), 78(4), 77(4), 66(3), 65(18), 63(4), 56(3), 52(3), 51(7), 50(3), 45(6), 44(11), 43(3), 42(3), 41(4), 39(24), 30(93) and 27(5).

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.40; N, 18.65. Found: C, 71.97; H, 9.20; N, 18.32.

5.1.4.2.0 3-(3-Pyridyl)propylamine (99; n=2)



2-(3-Pyridyl)propionitrile (98; n=2) (19.8 g, 0.15 mole) was treated by the method described in section 5.1.4.1.0 to yield the title amine (99; n=2) (11.65 g, 52%) as a colorless oil: bp 130-132°/0.6 mm; ir (neat) 3365 and 3295 (N-H stretching) and 1580 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.48 (m, 2, $J_{6,4}$=2.5 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 7.53 (ddd, 1, $J_{4,6}$=2.5 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.17 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 2.70 (m, 4, $-(CH_2)_2-NH_2$), 1.88 (m, 2, $-CH_2-(CH_2)_2-NH_2$) and 1.48 ppm (s, 2, $-NH_2$, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 137(4), 136 (M^+,20), 135(5), 120(4), 119(50), 118(22), 108(3), 107(37), 106(60), 105(3), 104(4),94(4), 93(20), 92(15), 91(4), 80(5), 79(22), 78(8), 77(8), 65(14), 64(3), 63(4), 53(5), 52(6), 51(15), 50(7), 43(5), 42(5), 41(3), 39(22), 38(4), 31(3), 30(100) and 27(5).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.54; H, 8.88; N, 20.57. Found: C, 70.52; H, 8.82; N, 20.28.

5.2.0.0.0 Cyclization of the 3-(3-pyridyl)alkylamines

5.2.1.0.0 Quantitative determination of cyclization

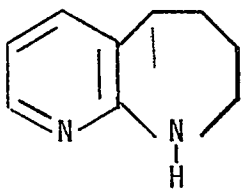
A mixture of 4-(3-pyridyl)butylamine (100) (0.6 g, 0.004 mole), the particular alkali metal reagent in the appropriate amount, and the particular solvent (5 ml) were heated under reflux for the recorded time, as shown in Table 1. In the case of the salts (Table 1, No. 12 and 13), they were prepared quantitatively in advance and added to the

reaction mixture with no additional quantities of reagent added. The sodium salt (No. 12) was prepared with sodium amide in ether under reflux, while the lithium salt (No. 13) was prepared using n-butyllithium in ether at 0^{o}.

In each case the excess base reagent was decomposed in an ice bath by the cautious addition of water (4 ml). Additional water (15 ml) was added and the mixture extracted with chloroform (4 x 10 ml). The combined extracts were dried ($MgSO_4$) and evaporated to yield dark oils. The crude percentage yield recorded in Table 1 was calculated in terms of starting material.

The extracts were analyzed by glc (appendix 6.1.0.0.0) using analytically pure samples of 4-(3-pyridyl)butylamine (100) and 6,7,8, 9-tetrahydro-5H-pyrido [2,3-b] azepine (101), which have significantly different retention times. The actual yields of the starting material and cyclic product were calculated using internal standards and are recorded in Table 1. The yield of unidentified products was calculated in terms of starting material by subtracting the actual recovery of starting material and the corrected yield of cyclic product from the crude percentage yield.

5.2.2.0.0 Preparation of 6,7,8,9-tetrahydro-5H-pyrido [2,3-b] azepine (107)



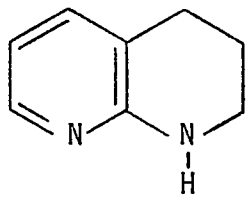
A mixture of 4-(3-pyridyl)butylamine (106) (4.5 g, 0.03 mole), sodium suspension (1.38 g, 0.06 mole) and anhydrous toluene (30 ml) was heated under reflux with stirring for 72 hours. The excess sodium was decomposed by the cautious addition of water (30 ml) with stirring to the cooled (0^{o}) mixture. After the addition of water (30 ml) the mixture was extracted with chloroform (4 x 75 ml), dried ($MgSO_4$), and evaporated _in vacuo_ to yield a dark brown oil. The oil was distilled _in vacuo_ to yield the title _azepine_ (107) (1.55 g, 35%) as a colorless oil which solidified upon cooling: bp 125-127^{o}/2 mm; ir (neat) 3265 cm^{-1} (N-H stretching); nmr ($CDCl_3$) δ7.97 (dofd, 1, $J_{2,4}$=1.9 Hz and $J_{2,3}$=4.8 Hz, C_2-H), 7.30 (dofd, 1, $J_{4,2}$=1.9 Hz and $J_{4,3}$=8.0 Hz, C_4-H), 6.66 (dofd, 1, $J_{3,2}$=4.8 Hz and $J_{3,4}$=8.0 Hz, C_3-H), 5.00 (s, 1, -NH-, exchanges readily with D_2O), 3.17 (m, 2, -CH_2-NH-), 2.70 (m, 2, -CH_2-$(CH_2)_3$NH-) and 1.77 ppm (m, 4, -$(CH_2)_2$-CH_2-NH-); mass spectrum m/e (rel intensity) 149(10), 148(M^+,100), 147(41), 146(4), 145(4), 133(14), 132(4), 131(6), 121(3), 120(35), 119(55), 118(10), 117(4), 94(4), 93(44), 92(7), 91(5), 78(5), 77(4), 66(6), 65(9), 64(5), 63(4), 53(3), 52(5), 51(6), 41(4), 39(9) and 30(4).

Anal. Calcd for $C_9H_{12}N_2$: C, 72.93; H, 8.16; N, 18.91. Found: C, 72.76; H, 8.02; N, 18.73.

Purification of the crude 6,7,8,9-tetrahydro-5H-pyrido[2,3-b]-azepine (107) was originally attempted using preparative glc (appendix 6.1.0.0.0). However, mechanical difficulties were encountered with the preparative attachments and the attempts at purification proved

to be unsuccessful.

5.2.3.0.0 Preparation of 1,2,3,4-tetrahydro-1,8-naphthyridine (110)

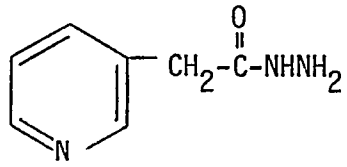


3-(Pyridyl)propylamine (109) (1.36 g, 0.01 mole) was treated by the method described in section 5.2.2.0.0 to yield the title naphthyridine (110) (0.4 g, 30%) as a colorless oil, bp 115-117°/2.5 mm (lit.[79], 96°/0.6 mm; 100°/0.8 mm) which solidified on cooling: mp 58-59°(mixed mp with authentic sample[79] not depressed); ir (neat) 3245 cm^{-1} (N-H stretching) (identical to authentic sample[79]); glc retention time, 4.75 minutes (identical to authentic sample[79]); nmr ($CDCl_3$) δ7.97 (dofd, 1, $J_{7,5}$=1.8 Hz and $J_{7,6}$=4.5 Hz, C_7-H), 7.27 (dofd, 1, $J_{5,7}$=1.8 Hz and $J_{5,6}$=7.8 Hz, C_5-H), 6.67 (dofd, 1, $J_{6,7}$= 4.5 Hz and $J_{6,5}$=7.8 Hz, C_6-H), 4.70 (s, 1, -NH-, exchanges readily with D_2O), 2.53 (t, 2, -CH_2-NH-), 1.77 (t, 2, -CH_2-$(CH_2)_2$-NH-) and 1.00 (m, 2, -CH_2-CH_2-NH-); mass spectrum m/e (rel intensity) 135(8), 134(M^+,92), 133(100), 132(5), 131(8), 119(19), 118(5), 116(4), 107(7), 106(19), 105(5), 104(7), 93(4), 92(5), 80(3), 79(17), 78(13), 77(10), 76(3), 67(3), 66(7), 65(6), 64(31), 63(4), 53(5), 52(10), 51(15), 50(5), 39(10) and 38(3).

5.3.0.0.0 Preparation of 3-pyridylalkylhydrazines

5.3.1.0.0 From ethyl 3-pyridylacetate

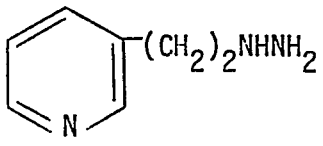
5.3.1.1.0 3-Pyridylacetic acid hydrazide (112)



Ethyl 3-pyridylacetate (111) (16.5 g, 0.1 mole) was slowly added dropwise with vigorous stirring to a solution of hydrazine hydrate (7.5g, 0.15 mole) in ethanol (75 ml) and the reaction mixture was heated under reflux for 5 hours. Evaporation of the ethanol under reduced pressure afforded the crude product which was collected by filtration and recrystallized from ethyl acetate to yield the title hydrazide (112) (13.5 g, 89.5%) as white crystals: mp 122.5-124.5°; ir (KBr) 3320 and 3220 (N-H stretching), 1670-1650 (-C-NH-) and 1620 (N-H bending); nmr (DMSO-d_6) δ8.60 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H and C_2-H), 7.80 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.46 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H) and 3.57 ppm (s, 2, CH_2-C-); mass spectrum m/e (rel intensity) 152(3), 151 (M^+,22), 121(8), 120(100), 119(5), 118(3), 93(22), 92(68), 91(6), 66(5), 65(35), 64(6), 63(7), 39(30) and 31(10).

Anal. Calcd for $C_7H_9N_3O$: C, 55.64; H, 5.95; N, 27.81. Found: C, 55.75; H, 5.95; N, 27.71.

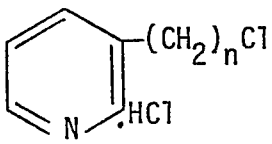
5.3.1.2.0 Attempted preparation of 2-(3-pyridyl)ethylhydrazine (112)



A solution of 3-pyridylacetic acid hydrazide (113) (1.51 g, 0.01 mole) in anhydrous tetrahydrofuran (35 ml) was added dropwise to a slurry of lithium aluminum hydride (1.14 g, 0.06 mole) in anhydrous tetrahydrofuran (35 ml) with vigorous stirring. The reaction mixture was heated under reflux for 5 hours. Upon cooling to 0^{o} the mixture was treated with water (1.5 ml), 15% sodium hydroxide (1.5 ml) and finally water (4.5 ml) to decompose the excess reducing agent. The white precipitate was filtered, washed with tetrahydrofuran and the combined extracts were dried ($MgSO_4$) and evaporated to yield a yellow solid, which was identified as unreduced 3-pyridylacetic acid hydrazide (60% recovery).

5.3.2.0.0 Preparation of 3-pyridylalkylchlorides hydrochlorides

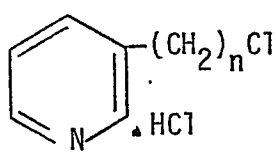
5.3.2.1.0 3-(3-Chloropropyl)pyridine hydrochloride (116; n=3)



Thionyl chloride (50 ml) was added dropwise to a cooled (0^{o}) solution of 3-(3-pyridyl)propan-1-ol (115; n=3) (13.7 g, 0.1 mole) in anhydrous ether (400 ml) with vigorous stirring. The reaction mixture was heated under reflux with stirring for an additional 6 hours. The supernatant liquid was decanted and the solid triturated and washed several times with anhydrous ether to yield a light brown solid. Recrystallization from acetone gave the title hydrochloride (116; n=3) (18.5 g, 96.3%) as white crystals: mp 128-130^{o}; ir (KBr) 2800-2400 cm^{-1} ($=\overset{+}{N}-H$); nmr ($CDCl_3$) δ8.94 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$= 5.0 Hz, C_6-H and C_2-H), 8.48 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz, and $J_{4,2}$=2.0 Hz, C_4-H), 8.05 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 3.70 (t, 2, -CH_2-Cl), 3.16 (t, 2, -CH_2-$(CH_2)_2$Cl) and 2.27 ppm (m, 2, -CH_2-CH_2Cl); mass spectrum m/e (rel intensity) 157(11), 156(3), 155(M^+,36), 127(7), 120(3), 119(9), 118(9), 106(8), 93(12), 92(100), 66(3), 65(22), 63(4), 52(3), 51(5), 50(3), 41(3), 39(18), 38(8), and 36(25).

Anal. Calcd for $C_8H_{11}Cl_2N$: C, 50.02; H, 5.77; Cl, 36.92; N, 7.29. Found: C, 49.99; H, 5.50; Cl, 37.04; N, 7.12.

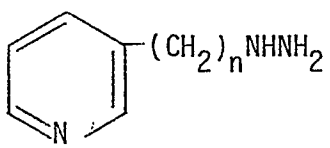
5.3.2.2.0 3-(2-Chloroethyl)pyridine hydrochloride (116; n=2)



2-(3-Pyridyl)ethanol (115; n=2) (12.3 g, 0.1 mole) was treated by the method described in section 5.3.2.1.0 to yield the title hydrochloride (116; n=2) (16 g, 88.5%) as white crystals: mp 150.5-151.5°; ir (KBr) 2800-2450 cm^{-1} ($=\overset{+}{N}H$); nmr ($CDCl_3$) δ8.97 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H and C_2-H), 8.54 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 8.07 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 3.93 (t, 2, $-CH_2-Cl$) and 3.43 ppm (t, 2, $-CH_2-CH_2-Cl$); mass spectrum m/e (rel intensity) 143(11), 142(3), 141 (M^+,32), 105(6), 104(4), 93(7), 92(100), 78(4), 77(4), 65(19), 52(5), 51(10), 50(4), 39(9), 38(8), and 36(25).

Anal. Calcd for $C_7H_9Cl_2N$: C, 47.16; H, 5.10; Cl, 39.83; N, 7.87. Found: C, 47.51; H, 5.01; Cl, 39.73; N, 7.62.

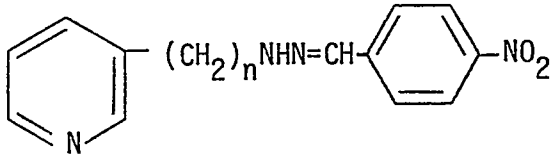
5.3.2.3.0 3-(3-Pyridyl)propylhydrazine (119a;n=3)



A solution of 3-(3-chloropropyl)pyridine hydrochloride (117; n=3) (38.4 g, 0.2 mole) in water (300 ml), overlayed with chloroform (200 ml), was treated with 50% NaOH (40 ml). The free base (118; n=3) was extracted with chloroform (3 x 200 ml) and dried ($MgSO_4$). The chloroform was removed under reduced pressure at a low temperature to yield a viscous yellow oil which was slowly added, dropwise with

vigorous stirring, to hydrazine hydrate at 90° (100 g, 2.0 mole). The reaction mixture was heated under reflux for 8 hours and then extracted continuously with ether for 24 hours. The ether was removed under reduced pressure to yield a yellow oil, which upon distillation *in vacuo* gave the title *hydrazine* (119a; n=3) (20.5 g, 67.4%) as a colorless oil, which was unstable even upon storage in the cold: bp 108-110°/0.4 mm; ir (neat)3400-3240 (N-H stretching, hydrogen bonded) and 1570 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.37 (m, 2, $J_{6,4}$= 2.0 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 7.43 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=7.5 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.10 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=7.5 Hz, C_5-H), 3.70 (s,3, -NH-NH_2, exchanges readily with D_2O), 2.70 (m, 4, -(CH_2)$_2$-$NHNH_2$) and 1.77 ppm (m, 2, -CH_2-(CH_2)$_2$-$NHNH_2$); mass spectrum m/e (rel intensity) 152(4), 151(M^+, 30), 136(3), 135(5), 132(5), 121(5), 120(7), 119(12), 118(13), 108(3), 107(45), 106(100), 105(5), 104(4), 94(4), 93(4), 92(39), 91(4), 80(4), 79(15), 78(5), 77(5), 65(15), 63(3), 59(6), 52(5), 51(7), 45(51), 41(3) and 39(13).

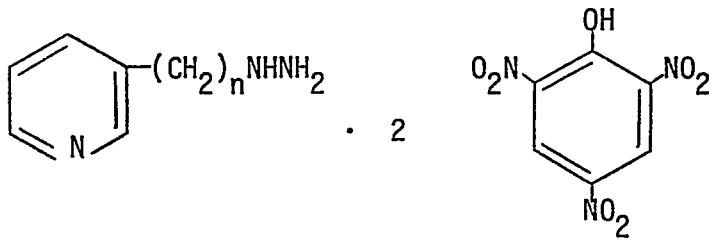
5.3.2.3.1 p-Nitrobenzylidene 3-(3-pyridyl)propylhydrazine (119b; n=3)



A solution of 3-(3-pyridyl)propylhydrazine (119a; n=3) (1.51 g, 0.01 mole) in methanol (2.5 ml) was slowly added to a hot solution of p-nitrobenzaldehyde (1.51 g, 0.01 mole) in methanol (10 ml) with stirring. Upon cooling (0^{o}), bright yellow needles were formed which were collected by filtration and recrystallized from methanol to yield the title hydrazine (119b; n=3) (2.25 g, 79.6%) as yellow needles: mp 121-123^{o}; ir (KBr) 3220 (N-H stretching), 1500 and 1320 cm^{-1} (NO_2 stretching); nmr ($CDCl_3$) δ8.52 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.5 Hz, C_6-H and C_2-H), 8.19 (d, 2, benzene H), 7.59 (d, 2, benzene H), 7.55 (m, 1, C_4-H), 7.52 (s, 1, -N=CH-), 7.25 (dofd, 1, $J_{5,6}$=5.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 2.93 (t, 2, $-CH_2$-NH-), 2.47 (m, 2, $-CH_2-(CH_2)_2NH-$) and 1.67 ppm (m, 2, $-CH_2-CH_2$-NH-); mass spectrum m/e (rel intensity) 285(6), 284(M^+,34), 283(7), 181(4), 179(4), 178(38), 164(4), 162(7), 161(3), 151(5), 150(11), 149(9), 137(3), 136(3), 135(8), 134(4), 133(4), 132(8), 131(7), 122(3), 121(5), 120(14), 119(24), 118(24), 117(5), 108(9), 107(89), 106(87), 105(18), 104(12), 103(23), 94(4), 93(19), 92(40), 91(10), 90(5), 89(14), 79(6), 78(22), 77(11), 76(15), 75(25), 74(10), 73(4), 66(4), 65(29), 64(9), 63(14), 55(3), 53(5), 52(7), 51(15), 50(14), 44(3), 43(33), 42(3), 41(6), 39(27), 32(24), 31(43), 30(100) and 29(27).

Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.19; H, 5.72; N, 19.58.

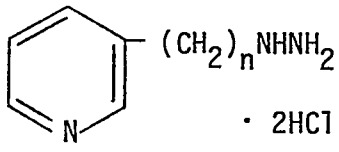
5.3.2.3.2 3-(3-Pyridyl)propylhydrazine dipicrate (119c; n=3)



A solution of 3-(3-pyridyl)propylhydrazine (119a; n=3) (1.51 g, 0.01 mole) in methanol (2.5 ml) was gradually added to a saturated ethereal solution of picric acid (4.58 g, 0.02 mole) with stirring. Upon cooling (0^{o}), yellow crystals were formed which were collected by filtration and recrystallized from methanol to yield the title dipicrate (119c; n=3) (4.75 g, 78%); mp 153-155^{o}d; ir (KBr) 3350 and 3280 (N-H stretching) and 2850-2500 cm^{-1} ($\overset{+}{=}NH$); mass spectrum m/e (rel intensity) 230 (6), 229(100), 219(4), 199(8), 151(M^{+},5), 136 (3), 120(3), 119(4), 118(5), 107(19), 106(64), 93(19), 92(14), 91(23), 90(7), 80(6), 79(6), 78(5), 77(5), 69(3), 66(4), 65(7), 64(4), 63(10), 62(31), 61(10), 53(15), 52(4), 51(8), 50(12), 46(3), 45(27), 39(10), 38(3), 37(3), 31(3) and 30(45).

Anal. Calcd for $C_{20}H_{19}N_9O_{14}$: C, 39.41; H, 3.14; N, 20.68. Found: C, 39.53; H, 3.19; N, 20.48.

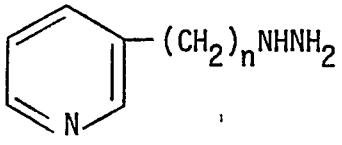
5.3.2.3.3 3-(3-Pyridyl)propylhydrazine dihydrochloride (119d; n=3)



Dry hydrogen chloride gas was slowly bubbled through a cooled (0^{o}) solution of 3-(3-pyridyl)propylhydrazine (119a; n=3) (4.5 g, 0.03 mole) in isopropanol (10 ml) with vigorous stirring. Upon cooling for 24 hours white crystals formed, which were collected by filtration, washed with Skelly-F and recrystallized from isopropanol to yield the title dihydrochloride (119d; n=3) (4.9 g, 73.1%): mp $129-130^{o}$; ir (KBr)3260 and 3160 (N-H stretching), 2900-2500 ($=\overset{+}{N}-H$) and 1560 cm^{-1} (N-H bending); nmr (D_2O) δ8.97 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$= 5.0 Hz, C_6-H and C_2-H), 8.83 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.5 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 8.30 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.5 Hz, C_5-H), 3.37 (m, 4, $-(CH_2)_2-NH-$) and 2.37 ppm (m, 2, $-CH_2-(CH_2)_2-NH-$); mass spectrum m/e (rel intensity) 152(4), 151(M^+,3), 135(4), 120(4), 118(4), 108(3), 107(30), 106(100), 95(4), 94(30), 93(10), 80(4), 79(12), 78(61), 77(5), 65(4), 53(4), 52(5), 51(8), 45(65), 41(3), 39(16), 38(24), 37(7), 36(72), 35(12), 31(6) and 30(5).

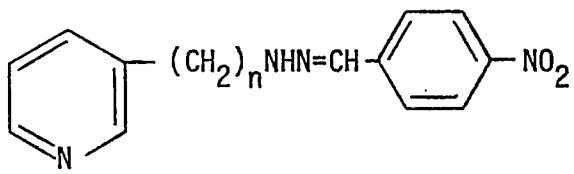
Anal. Calcd for $C_8H_{15}Cl_2N_3$: C, 42.86; H, 6.75; Cl, 31.63; N, 18.75. Found: C, 42.58; H, 7.00; Cl, 31.35; N, 18.42.

5.3.2.4.0 2-(3-Pyridyl)ethylhydrazine (119a; n=2)



3-(2-Chloroethyl)pyridine hydrochloride (117; n=2) (17.8 g, 0.1 mole) was treated by the method described in section 5.3.2.3.0 to yield the title hydrazine (119a; n=2) (8.23 g, 60%) as a colorless oil which was unstable even upon storage in the cold: bp 102-104°/ 0.45 mm; ir (neat) 3340-3220 (N-H stretching, hydrogen bonded) and 1580 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.73 (m,2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 7.83 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=7.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.46 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=7.0 Hz, C_5-H), 3.63 (s, 3, -NH-NH_2, exchanges readily with D_2O) and 3.18 ppm (m, 4, -(CH_2-$NHNH_2$); mass spectrum m/e (rel intensity) 138(4), 137 (M^+,3), 106(4), 94(7), 93(100), 92(9), 78(4), 77(5), 67(3), 66(4), 65(10), 64(3), 63(4), 44(3), 43(4), 39(19), 38(7), 36(20), 33(5), 31(4), and 30(3).

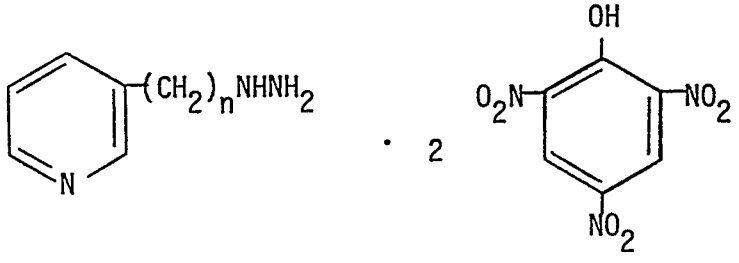
5.3.2.4.1 p-Nitrobenzylidene 2-(3-pyridyl)ethylhydrazine (119b;n=2)



2-(3-Pyridyl)ethylhydrazine (119a; n=2) (1.37 g, 0.01 mole) was treated by the method described in section 5.3.2.3.1 to yield the title hydrazine (119b; n=2) (2.1 g, 77%) as yellow needles: mp 138-139°; ir (KBr) 3190 (N-H stretching), 1490 and 1340 cm^{-1} (NO_2 stretching); nmr ($CDCl_3$) δ8.44 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.5 Hz, C_6-H and C_2-H), 8.18 (d, 2, benzene H), 7.64 (d, 2, benzene H), 7.61 (m, 1, C_4-H), 7.58 (s, 1, -N=CH-), 7.29 (dofd, 1, $J_{5,6}$=5.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 3.20 (t, 2, $-CH_2$-NH-) and 2.63 ppm (t, 2, $-CH_2-CH_2$-NH-); mass spectrum m/e (rel intensity) 271(6), 270(M^+,7), 178(21), 149(4), 132(4), 131(3), 106(5), 103(10), 94(9), 93(100), 92(6), 89(3), 78(3), 77(4), 76(10), 75(4), 65(6), 64(3), 63(4), 51(4), 50(4), 39(8), 36(5), 32(4) and 30(38).

Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.40; H, 5.29; N, 20.35.

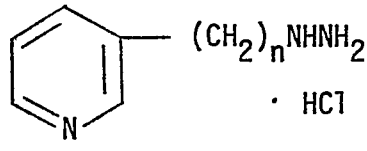
5.3.2.4.2 2-(3-Pyridyl)ethylhydrazine dipicrate (119c; n=2)



2-(3-Pyridyl)ethylhydrazine (119a; n=2) (1.37 g, 0.01 mole) was treated by the method described in section 5.3.2.3.2 to yield the title dipicrate (119c; n=2) (4.5 g, 75%) as yellow needles; mp 162-163°d; ir (KBr) 3330 and 3250 (N-H stretching) and 2900-2500 cm^{-1} ($=\overset{+}{N}H$); mass spectrum m/e (rel intensity) 230(10), 229(100), 199(10), 171(3), 152(3), 137(M^+,3), 136(4), 107(4), 106(11), 105(4), 94(5), 93(84), 92(8), 91(31), 90(5), 80(8), 79(4), 78(6), 77(6), 76(3), 69(4), 66(4), 65(5), 64(5), 63(14), 62(35), 61(10), 59(5), 53(18), 52(4), 51(12), 50(14), 46(3), 45(47), 44(3), 39(12), 38(4), 37(4), 32(6), 31(3) and 30(57).

Anal. Calcd for $C_{19}H_{17}N_9O_{14}$; C, 38.33; H, 2.88; N, 21.17. Found: C, 38.28; H, 2.93; N, 21.02.

5.3.2.4.3 2-(3-Pyridyl)ethylhydrazine hydrochloride (119d; n=2)

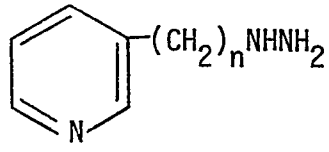


2-(3-Pyridyl)ethylhydrazine (119a; n=2) (4.11 g, 0.03 mole) was treated by the method described in section 5.3.2.3.3 to yield the title hydrochloride (119d; n=2) (4.73 g, 75%) as white crystals: mp 127-128°; ir (KBr) 3250 and 3140 (N-H stretching), 2800-2500 ($=\overset{+}{N}H$) and 1580 cm^{-1} (N-H bending); nmr (D_2O) δ8.70 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 8.13 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$= 2.0 Hz, C_4-H), 7.70 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H) and

3.27 ppm (m, 4, -($\underline{CH_2}$)$_2$-NH); mass spectrum m/e (rel intensity) 137 (M^+,3), 118(3), 116(5), 94(7), 93(100), 92(7), 77(4), 76(3), 66(3), 65(5), 51(3), 45(46), 39(7), 38(27), 37(4), 36(79) and 35(9).

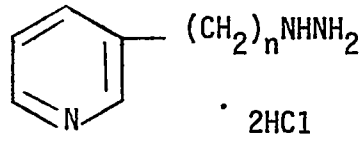
Anal. Calcd for $C_7H_{12}ClN_3$: C, 48.41; H, 6.96; Cl, 20.42; N, 24.20. Found: C, 48.18; H, 6.86; Cl, 20.24; N, 24.45.

5.3.2.5.0 3-Picolylhydrazine (119a; n=1)



3-Picolyl chloride hydrochloride (117; n=1) (16.4 g, 0.1 mole) was treated by the method described in section 5.3.2.3.0 to yield the title hydrazine (119a; n=1) (8.64 g, 70.2%) as a colorless oil which was unstable even upon storage in the cold: bp 124-126°/4.5 mm (lit.[144], 96-100°/0.5-1mm);ir (neat) 3380-3230 (N-H stretching, hydrogen bonded) and 1575 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.63 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H and C_2-H), 7.77 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.33 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 3.97 (s, 2, -CH_2-NH-) and 3.50 ppm (s, 3, -NH-NH_2, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 124(7), 123 (M^+, 86), 121(4), 106(4), 105(3), 94(7), 93(100), 92(51),80(4), 79(5), 78(5), 66(7), 65(30), 63(4), 52(4), 51(5), 50(3), 45(3), 39(12) and 31(5).

5.3.2.5.1 3-Picolylhydrazine dihydrochloride (119; n=1)

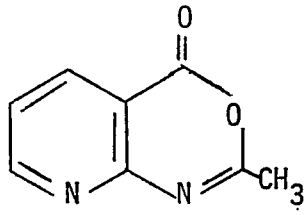


3-Picolylhydrazine (119a; n=1) (3.69 g, 0.03 mole) was treated by the method described in section 5.3.2.3.3 to yield the title dihydrochloride (119d; n=1) (4.47 g, 76%) as white crystals: mp 179-180° (lit.[145], 184-186°); ir (KBr) 3270 and 3150 (N-H stretching), 2850-2500 ($=\overset{+}{N}H$) and 1570 cm^{-1} (N-H bending); nmr (D_2O) δ8.87 (m,2, $\underline{J}_{6,4}$=2.0 Hz and $\underline{J}_{6,5}$=5.5 Hz, C_6-$\underline{H}$ and C_2-$\underline{H}$), 8.43 (ddd, 1, $\underline{J}_{4,6}$=2.0 Hz, $\underline{J}_{4,5}$=8.0 Hz and $\underline{J}_{4,2}$=2.0 Hz, C_4-$\underline{H}$), 7.90 (dofd, 1, $\underline{J}_{5,6}$=5.5 Hz and $\underline{J}_{5,4}$=8.0 Hz, C_5-$\underline{H}$) and 4.37 ppm (s, 2, -$C\underline{H}_2$-NH-); mass spectrum m/e (rel intensity) 123(M^+,21), 94(5), 93(64), 92(34), 80(3), 79(3), 78(5), 67(3), 66(7), 65(35), 63(5), 52(6), 51(10), 50(5), 45(7), 39(38), 38(35), 37(5), 36(100), 35(14) and 31(21).

5.4.0.0.0 Attempted preparation of pyrido[2,3-e] -1,4-diazepines

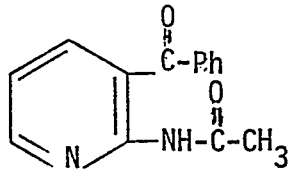
5.4.1.0.0 From 2-amino-3-benzoylpyridine

5.4.1.1.0 Preparation of 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (125)



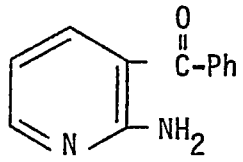
This compound was prepared by a modification of the method of Littell and Allen.[41,42] A solution of 2-aminonicotinic acid (124) (138 g, 1.0 mole) in acetic anhydride (1200 ml) was heated under reflux for 2.5 hours. The excess acetic anhydride was removed under reduced pressure and the brown residue was collected by filtration and recrystallized from benzene to yield the title oxazin-4-one (125) (117 g, 72.2%) as brown crystals: mp 138-140°(lit.[41], 136-140°); mass spectrum m/e (rel intensity) 163(11), 162(M^+,100), 148(8), 147(88), 120(16), 119(39), 118(37), 93(14), 92(19), 91(24), 78(7), 77(11), 76(7), 75(4), 66(3), 65(7), 64(13), 63(5), 53(4), 52(4), 51(9), 50(15), 44(3), 43(67), 42(5), 41(5), 40(6), 39(9), 38(10) and 37(9). The product was unstable and was used without delay for the synthesis of 2-acetamido-3-benzoylpyridine.

5.4.1.2.0 Preparation of 2-acetamido-3-benzoylpyridine (127)



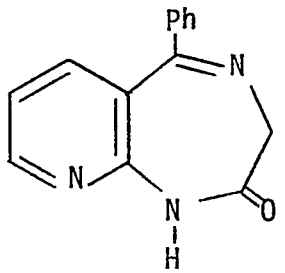
This compound was prepared by a modification of the procedure of Littell and Allen.[41,42] Phenylmagnesium bromide 3M in ether (18.5 ml, 0.5 mole) was added dropwise with vigorous stirring to a cooled (0^{o}) suspension of 2-methyl-4H-pyrido[2,3-d][1,3]oxazin-4-one (126) (81 g, 0.5 mole) in anhydrous benzene (1100 ml) and anhydrous ether (550 ml) over a 3 hour period. The mixture was allowed to warm to room temperature and was stirred overnight. Upon cooling to 0^{o}, 2N hydrochloric acid (550 ml) was added dropwise with stirring. The mixture was diluted with ethyl acetate (200 ml), neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (4 x 150 ml). The organic layer was washed with 2N sodium hydroxide and saturated saline (3 x 100 ml), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid (84.3 g, 72.5%, calculated as product). Glc analysis indicated the presence of two components with relative peak area ratios of 67:33%. The crude mixture was chromatographed on a 4.5 x 60 cm silica gel column using ether-dichloromethane (1:1) according to the literature procedure.[42] Mass spectrometry showed that the major component was 2-acetamido-α,α-diphenyl-3-pyridinemethanol (128), m/e 318 (M^{+},15%), while the minor component was the title compound (127), m/e 240 (M^{+},34%). The literature method[42] of column chromatography proved to be very time consuming and impractical due to the large scale of the reaction, therefore the title compound was not purified further.

5.4.1.3.0 Preparation of 2-amino-3-benzoylpyridine (131)



This compound was prepared by modifying the procedure of Littell and Allen.[41,42] A solution of the crude mixture of 2-acetamido-3-benzoylpyridine (129) and 2-acetamido-α,α-diphenyl-3-pyridinemethanol (130) (9.6g, 0.04 mole) in ethanol (140 ml) and 6N hydrochloric acid were heated at reflux for 2 hours. The solution was cooled (0°), diluted with water (50 ml) and neutralized with ammonium hydroxide. The solid was collected by filtration and recrystallized from water to yield the title compound (131) (2.65 g, 33.4%) as yellow plates: mp 147-148° (lit.[41], 145-148°); ir (KBr) 3420 and 3365 (N-H stretching), 1650-1620 ($-\overset{O}{\overset{\|}{C}}-NH_2$) and 1580 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.43 (dofd, 1, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H), 7.87 (dofd, 1, $J_{4,6}$= 2.0 Hz and $J_{4,5}$=8.0 Hz, C_4-H), 7.63 (m, 5, benzene 5H) and 6.67 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H); mass spectrum m/e (rel intensity) 199(16), 198(M^+,100), 197(79), 196(3), 181(5), 170(6), 169(42), 168(6), 167(3), 121(28), 115(3), 106(3), 105(27), 93(18), 85(5), 78(5), 77(38), 76(3), 66(8), 51(11), 50(4) and 39(9).

5.4.1.3.1 Attempted preparation of 1,3-dihydro-5-phenyl-2H-pyrido-[2,3-e]-1,4-diazepin-2-one (138)

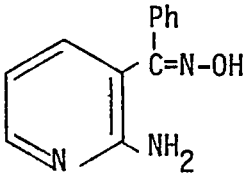


The preparation of this compound was attempted by modifying the work of Littell and Allen.[41,42] A solution of N,N'-dicyclohexyl-carbodiimide (0.907 g, 0.0044 mole) in dichloromethane (4 ml) was added to a cooled (0^{o}) solution of 2-amino-3-benzoylpyridine (133) (0.792 g, 0.004 mole) and carbobenzyloxyglycine (0.92g, 0.0044 mole) in tetrahydrofuran (10 ml) and dichloromethane (4 ml) with stirring. The mixture was stirred at 0^{o} for 3 hours and at room temperature for a further 10 hours, after which additional carbobenzyloxyglycine (0.6 g) and N,N'-dicyclohexylcarbodiimide (0.6 g) was added and the mixture stirred overnight. The mixture was filtered to remove the N,N'-dicyclohexylurea (0.89 g), evaporated under reduced pressure, dissolved in ethyl acetate, and washed with saturated saline and evaporated under reduced pressure to yield an oil, which was supposedly 2-(α-carbobenzoxamidoacetamido)-3-benzoylpyridine (134).

The above oil was dissolved in a saturated solution of hydrogen bromide in acetic acid (6 ml) and stirred at room temperature for 1 hour. Upon the addition of ether a white solid precipitated which

was collected by filtration and immediately dissolved in 80% aqueous methanol (12 ml), and neutralized with ammonium hydroxide. The solvents were removed under reduced pressure to yield a yellow oil, which was heated under reflux in pyridine for 3 hours. Upon evaporation of the solvent the residue was dissolved in ethyl acetate and water. The organic layer was dried ($MgSO_4$) and evaporated to yield a yellow solid, which was found to be 2-amino-3-benzoylpyridine (133), since the product was identical with an authentic sample (mp 147-148°, mass spectrum m/e 198 (M^+,100) and infrared spectrum, 3420 and 3365 (N-H stretching), 1650-1620 ($-\overset{O}{\overset{\|}{C}}-NH_2$) and 1580 cm^{-1} (N-H bending)).

5.4.1.4.0 Preparation of 2-amino-3-benzoylpyridine oxime (142)

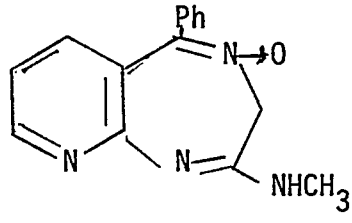


A solution of 2-amino-3-benzoylpyridine (141) (0.99 g, 0.005 mole) and hydroxylamine hydrochloride (0.91 g, 0.013 mole) in ethanol (25 ml) was heated under reflux for 18 hours during which time 15 ml of solvent was distilled. Upon cooling to room temperature, benzene (2 ml) was added, and the mixture was neutralized with dilute potassium carbonate solution. The precipitate was collected and recrystallized from acetone to yield the title oxime (142) (0.56 g, 52.9%) as white needles: mp 207-209°; ir (KBr) 3490 (OH stretching),

3340 and 3210 (N-H stretching) and 1570 cm^{-1} (N-H bending); nmr (DMSO-d_6) δ8.17 (dofd, 1, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H), 7.53 (s, 5, benzene 5H), 7.37 (dofd, 1, $J_{4,6}$=2.0 Hz and $J_{4,5}$=7.5 Hz, C_4-H), 6.80 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=7.5 Hz, C_5-H), and 5.43 ppm (s, 2, $-NH_2$, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 214(12), 213(M^+,100), 212(42), 211(3), 197(17), 196(41), 195(9), 194(13), 183(8), 182(16), 181(21), 169(5), 168(13), 167(3), 166(4), 154(4), 141(3), 140(7), 139(5), 128(4), 127(4), 119(3), 115(4), 114(3), 105(3), 104(7), 103(5), 98(3), 97(3), 94(16), 93(18), 92(6), 91(9), 78(8), 77(26), 76(5), 75(4), 67(5), 66(18), 65(6), 64(4), 63(4), 58(4), 52(5), 51(20), 50(6), 43(12), 41(3), 40(3), 39(12) and 38(4).

Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.61; H, 5.16; N, 19.72. Found: C, 67.28; H, 5.26; N, 19.69.

5.4.1.4.1 Attempted preparation of 2-methylamino-5-phenyl-3H-pyrido[2,3-e]-1,4-diazepine 4-oxide (144)

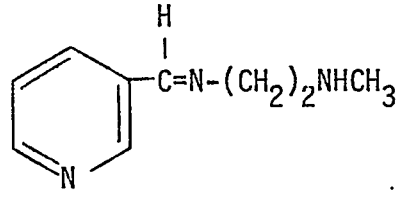


Chloracetylchloride (0.3 g, 0.0027 mole) was added to a solution of 2-amino-3-benzoylpyridine (143) (0.426 g, 0.002 mole) in acetic acid (4 ml) and allowed to stand at room temperature for 72 hours.

The solution was saturated with hydrogen chloride gas and evaporated. The residue was dissolved in dichloromethane (10 ml), washed with dilute potassium carbonate solution, dried ($MgSO_4$) and evaporated to yield a yellow oil. The oil was dissolved in a 30% solution of methylamine in methanol (5 ml) and allowed to stand at room temperature for 18 hours. The solution was concentrated, acidified with cold hydrochloric acid and washed with ether. The aqueous layer was separated, neutralized and extracted with dichloromethane. The organic layer was dried ($MgSO_4$) and evaporated to yield a yellow solid (0.425 g): mp 190-191°; ir (KBr) 2850-2350 cm^{-1} ($\overset{+}{=}NH$); mass spectrum m/e (rel intensity) 198 (M^+,100). The spectroscopic evidence appeared to indicate that the product was probably a pyridinium salt of 2-amino-3-benzoylpyridine (145).

5.4.2.0.0 From nicotinaldehyde

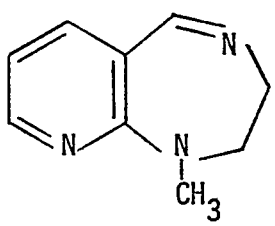
5.4.2.1.0 Preparation of N-methyl-N'-(3-picolylidene)ethylenediamine (148)



In a flask equipped with a Dean-Stark water trap, a solution of nicotinaldehyde (146) (16.05g, 0.15 mole) and N-methylethylenediamine (147) (11.12 g, 0.15 mole) in anhydrous benzene (150 ml) was heated under reflux for 3 hours, at which time 2.7 ml (0.15 mole) of water had been collected. The solvent was removed under reduced pressure to yield a yellow oil, which was distilled *in vacuo* to yield the title diamine (148) (20.4 g, 83.4%) as a colorless oil: bp 108-110°/0.7 mm; ir (neat) 3310 cm^{-1} (N-H stretching); nmr ($CDCl_3$) δ8.70 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=5.0 Hz, C_6-H and C_2-H), 7.87 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.30 (dofd, 1, $J_{5,6}$=5.0 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 4.00 (s, 1, -CH=N-), 3.23 (m, 4, -(CH_2)$_2$-NH), 2.25 (s, 3, -NH-CH_3) and 1.93 ppm (s, 1, -NH-, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 164(2), 163(M^+,9), 162(10), 133(5), 121(7), 120(82), 119(35), 118(4), 105(4), 93(5), 92(7), 85(18), 78(6), 65(6), 64(4), 63(4), 59(11), 58(5), 57(3), 56(4), 52(3), 51(5), 45(3), 44(100), 43(4), 42(11), 41(4), 37(5), 31(3), 30(6) and 27(7).

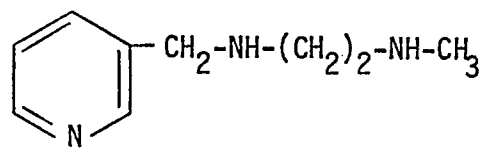
Anal. Calcd for $C_9H_{13}N_3$: C, 66.26; H, 7.97; N, 25.77. Found: C, 66.09; H, 8.13; N, 25.53.

5.4.2.1.1 Attempted preparation of 2,3-dihydro-1-methyl-1H-pyrido[2,3-e]-1,4-diazepine (150)



N-Methyl-N'-(3-picolylidene)ethylenediamine (149) (1.63 g. 0.01 mole) and sodium metal (0.46 g, 0.02 mole) were treated as described in section 5.2.2.0.0 to yield a black tar (0.200 g), which decomposed upon attempted distillation in vacuo.

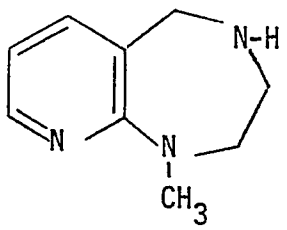
5.4.2.2.0 Preparation of N-methyl-N'-(3-picolyl)ethylenediamine (152)



N-Methyl-N'-(3-picolylidene)ethylenediamine (151) (6.52 g, 0.04 mole), 10% palladium on charcoal (0.652 g) and methanol (250 ml) were shaken together in the presence of hydrogen at 3.0 atmospheres for 4 hours. The mixture was filtered through celite and the filtrate concentrated and distilled in vacuo to yield the title diamine (152) (5.0 g, 75.8%) as a colorless oil: bp 108-110^{o}/0.7 mm; ir (neat) 3300 (N-H stretching) and 1575 cm^{-1} (N-H bending); nmr ($CDCl_3$) δ8.61 (m, 2, $J_{6,4}$=2.0 Hz and $J_{6,5}$=4.5 Hz, C_6-H and C_2-H), 7.77 (ddd, 1, $J_{4,6}$=2.0 Hz, $J_{4,5}$=8.0 Hz and $J_{4,2}$=2.0 Hz, C_4-H), 7.30 (dofd, 1, $J_{5,6}$=4.5 Hz and $J_{5,4}$=8.0 Hz, C_5-H), 3.85 (s, 2, -CH_2-NH-$(CH_2)_2$-), 2.75 (s, 4, -$(CH_2)_2$-NH-), 2.43 (s, 3, -NH-CH_3) and 1.50 ppm (s, 2, -NH-$(CH_2)_2$-NH-, exchanges readily with D_2O); mass spectrum m/e (rel intensity) 166(3), 165(M^+,5), 123(3), 122(25), 121(40), 107(4), 94(8), 93(100), 92(66), 80(3), 66(3), 65(18), 64(3), 63(3), 58(4),

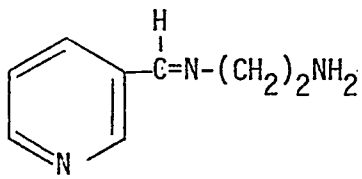
57(3), 56(3), 52(4), 51(4), 45(3), 44(64), 43(4), 42(8), 41(3) and 39(13).

5.4.2.2.1 Attempted preparation of 2,3,4,5-tetrahydro-1-methyl-1H-pyrido[2,3-e]-1,4-diazepine (154)



N-Methyl-N-(3-picolyl)ethylenediamine (153) (1.65 g, 0.01 mole) and sodium metal (0.46 g, 0.02 mole) were treated as described in section 5.2.2.0.0 to yield a black tar (0.210 g) which decomposed upon attempted distillation.

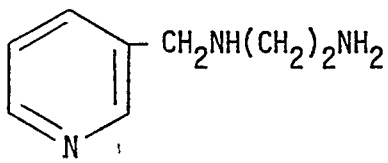
5.4.2.3.0 Preparation of N-(3-picolylidene)ethylenediamine (157)



In a flask equipped with a Dean-Stark water trap, a solution of nicotinaldehyde (155) (5.35 g, 0.05 mole) in anhydrous benzene (50 ml), was added dropwise with stirring to a solution of ethylenediamine (156) (3 g, 0.05 mole) in anhydrous benzene (50 ml). The

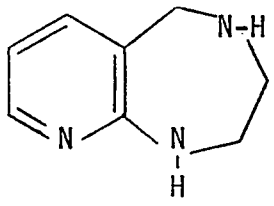
solution was heated under reflux for 3 hours during which time 0.9 ml (o.05 mole) of water was collected. The solvent was removed under reduced pressure to yield a yellow oil, which was distilled *in vacuo* to yield the title *diamine* (157)(5.3 g, 71.1%) as a colorless oil: bp 118-120°/1.4 mm; ir (neat) 3360 and 3280 (N-H stretching) and 1580 cm^{-1} (N-H bending); mass spectrum *m/e* (rel intensity) 149(M^+, 1), 148(4), 120(7), 119(17), 93(4), 92(6), 71(3), 65(4), 63(3), 60(6), 59(3), 51(4), 45(6), 44(4), 43(8), 42(8), 41(5), 39(3) and 30(100).

5.4.2.4.0 Preparation of *N*-(3-picolyl)ethylenediamine (159)



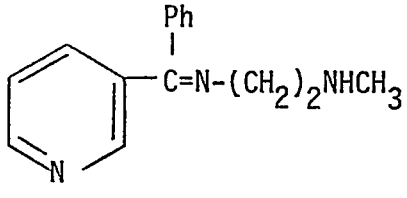
N-(3-Picolylidene)ethylenediamine (158) (4.47 g, 0.03 mole) and 10% palladium on charcoal (0.45 g) were treated as described in section 5.4.2.2.0 to yield the title *diamine* (159)(3.3 g, 72.8%) as a colorless oil: bp 106-108°/0.5 mm; ir (neat) 3340 and 3265 (N-H stretching) and 1575 cm^{-1} (N-H bending); mass spectrum m/e (rel intensity) 152(5), 151(M^+, 29), 122(18), 121(56), 119(3), 107(4), 94(3), 93(37), 92(100), 65(14), 44(4), 39(7), and 30(10).

5.4.2.4.1 Attempted preparation of 2,3,4,5-tetrahydro-1H-pyrido-[2,3-e]-1,4-diazepine (161)



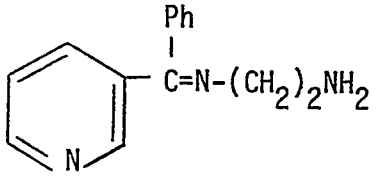
N-(3-Picolyl)ethylenediamine (160) (1.51 g, 0.01 mole) and sodium metal (0.46 g, 0.02 mole) were treated as described in 5.2.2.0.0 to yield a dark brown oil (1.30g). Distillation in vacuo gave an oil (0.020 g),which was identical to the starting material: bp 114-116/0.9 mm; ir (neat) 3340 and 3265 (N-H stretching) and 1575 cm^{-1} (N-H bending); mass spectrum m/e (rel intensity) 152(3), 151(M^+,12), 122(8), 121(38), 119(3), 107(5), 94(3), 93(37), 92(100), 65(16), 44(3), 39(8) and 30(15).

5.4.2.5.0 Preparation of N-methyl-N'-α-(3-pyridyl) benzylidene ethylenediamine (164)



In a flask equipped with a Dean-Stark water trap, a solution of 3-benzoylpyridine (162) (4.58 g, 0.025 mole), N-methylethylenediamine (163) (1.85g, 0.025 mole) and 48% hydrobromic acid (1.5 ml) in anhydrous benzene (40 ml) was heated under reflux for 6 hours, during which time 1.95 ml of water was collected. The benzene was removed under reduced pressure to yield a yellow oil, which was distilled *in vacuo* to yield the title diamine (164) (3.7 g, 62%) as a yellow oil: bp 146-148°/0.9 mm; ir (neat) 3310 cm^{-1} (N-H stretching); mass spectrum m/e (rel intensity) 239 (M^+,1), 200(4), 196(4), 195(4), 187(4), 186(27), 185(14), 184(18), 183(100), 182(15), 155(5), 154(5), 127(3), 122(3), 121(6), 106(17), 105(68), 93(13), 92(8), 79(6), 78(76), 77(58), 76(66), 75(3), 74(4), 65(4), 63(3), 52(11), 51(38), 50(15), 44(5), 42(5), and 39(8).

5.4.2.6.0 Attempted preparation of N-α-(3-pyridyl)benzylidene ethylenediamine (167)

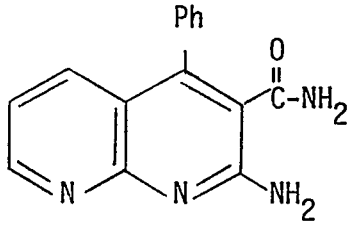


In a flask equipped with a Dean-Stark water trap, a solution of 3-benzoylpyridine (165) (1.83, 0.01 mole) in anhydrous benzene (50 ml), was added dropwise with stirring to a solution of ethylenediamine (0.6 g, 0.01 mole) in anhydrous benzene (50 ml). 48% Hydrobromic acid (0.6 ml) was added and the solution was heated under reflux for

5 hours, during which time 0.2 ml of water (0.01 mole) was collected. The benzene was removed under reduced pressure to yield a yellow oil (1.8g) which decomposed upon attempted distillation.

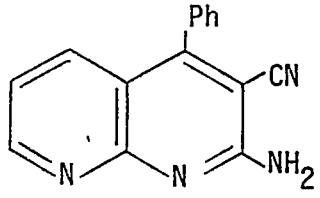
5.5.0.0.0 Preparation of 2,3-disubstituted-4-phenyl-1,8-naphthyridines

5.5.1.0.0 Attempted preparation of 2-amino-4-phenyl-1,8-naphthyridine-3-carboxamide (180)



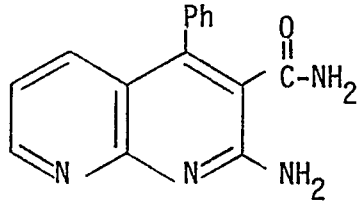
2-Amino-3-benzoylpyridine (178) (0.396 g, 0.002 mole), cyanoacetamide (179) (0.336 g, 0.004 mole) and pyridine (15 ml) were heated under reflux for 48 hours. The pyridine was removed under reduced pressure to give a brown solid: mp 290-292°d;ir (KBr)2240 (C≡N) and 1690-1610 cm^{-1} (-C=O); mass spectrum m/e (rel intensity) 248 (16), 247(M^+, 100), 246(21), 228(7), 227(6), 220(8), 219(45), 218(6), 217(3), 203 (4), 202(3), 201(3), 198(3), 197(3), 192(3), 191(6), 181(4), 176(4), 167(3),166(3), 165(5), 164(8), 151(3), 139(3), 127(8), 126(5), 125(6), 114(5), 102(3), 101(5), 100(7), 96(9), 88(6), 87(4), 79(8), 77(10), 76(3), 75(6), 63(5), 52(7), 51(11), 50(7) and 39(6). This isolated compound was not analyzed, but the spectroscopic evidence indicated that the product was probably 3-cyano-2-hydroxy-4-phenyl-1,8-naphthyridine (181).

5.5.2.0.0 Preparation of 2-amino-3-cyano-4-phenyl-1,8-naphthyridine (184)



2-Amino-3-benzoylpyridine (182) (1.98 g, 0.01 mole), malononitrile (183) (1.32g, 0.02 mole) and pyridine (15 ml) were heated under reflux with stirring for 24 hours. The pyridine was evaporated under reduced pressure to yield a brown solid, which was washed with water (10 ml) and recrystallized from isopropanol to yield the title naphthyridine (184) (0.82 g, 33.3%) as yellow crystals: mp 293-295^{o}; ir (KBr) 3420 and 3320 (N-H stretching), 2230 (C≡N) and 1580 cm^{-1} (N-H bending); mass spectrum m/e (rel intensity) 247(10), 246 (M^{+},100), 245(34), 244(3), 220(7), 219(35), 218(5), 217(3), 203(5), 192(4), 191(6), 176(3), 166(3), 165(4), 164(5), 127(3), 123(4), 96(4) and 51(4).

5.5.3.0.0 Preparation of 2-amino-4-phenyl-1,8-naphthyridine-3-carboxamide (186)



2-Amino-3-cyano-4-phenyl-1,8-naphthyridine (185) (0.492 g, 0.002 mole), potassium hydroxide (0.984 g), water (1 ml) and alcohol (10 ml) were heated under reflux for 1 hour. The solvents were removed under reduced pressure to give a brown solid, which was recrystallized from isopropanol to yield the title carboxamide (186) (0.4 g, 75.6%) as brown crystals: mp 336-337°; ir (KBr) 3420 and 3350 (N-H stretching), 1675-1655 ($-\overset{O}{\overset{\|}{C}}-NH_2$) and 1560 cm^{-1} (N-H bending); mass spectrum m/e (rel intensity) 265(15), 264 (M^+,82) 263(43), 248(8), 247(38), 246(15), 245(7), 221(7), 220(42), 219(13), 218(5), 208(9), 203(5), 199(17), 198(100), 197(68), 193(7), 192(27), 191(7), 181(4), 179(3), 178(3), 170(4), 169(36), 168(3), 167(3), 166(4), 165(4), 151(3), 150(5), 139(3), 132(8), 131(3), 123(3), 121(37), 105(36), 96(4), 93(20), 85(4), 78(4), 77(48), 76(4), 75(3), 66(10), 63(3), 51(15), 50(3), 44(42) and 39(14). The spectra of this product and that isolated from the reaction between 2-amino-3-benzoylpyridine and cyanoacetamide (section 5.5.1.0.0) were completely different.

6.0.0.0.0 APPENDIX

6.1.0.0.0 Instruments, solvents and reagents

Melting points

Melting points were determined on a Gallenkamp MF-370 apparatus, and also with a Mettler FP-1 automatic, digital melting point apparatus. All melting points are uncorrected.

Nmr spectra

Nmr spectra were run on a Varian T-60 spectrometer. Tetramethylsilane (TMS) provided the internal standard with deuterochloroform as solvent, while sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as the internal standard when deuterium oxide or dimethyl-d_6-sulphoxide was the solvent. The spinning rate of the probe was kept at 45-60 rps, while a sweep time of 250 seconds was used for determining the spectra. The abbreviations utilized are: s (singlet), d (doublet), dofd (doublet of doublets),ddd (doublet of doublet of doublets),t (triplet) and m (multiplet). Chemical shifts of the protons are described by δ (ppm) values downfield from the internal standard. All peaks are recorded in the experimental section and note is made of any protons rapidly exchanging with deuterium oxide.

Infrared spectra

Infrared absorption spectra were recorded on a Unicam SP-200 G spectrophotometer previously calibrated with polystyrene, as potassium bromide discs or as a smear employing sodium chloride discs. Only

diagnostic peaks are assigned in the experimental section.

Mass spectra

Mass spectra were determined on an AEI MS-12 single focusing mass spectrometer equipped with a heated inlet system operating near or at the melting point of the compound concerned. Samples were introduced by the direct probe technique and the spectrometer was routinely operated with an electron beam energy of 70 eV. The spectra were run by Mr. D.R. Bain of the Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan. All peaks greater than 3% of the base peak are recorded in the experimental section.

Elemental analyses

Elemental analyses were performed by Dr. F.B. Strauss, Microanalytical Laboratories, Oxford, England, and by Mr. R.M. Smith of the College of Pharmacy, University of Saskatchewan, Saskatoon, Saskatchewan. Mr. Smith used a Coleman Model 33 carbon-hydrogen analyzer.

Gas-liquid chromatography

Solutions (1% w/v) of compounds in chloroform (analytical grade) were analyzed with a Hewlett-Packard 5750 B research chromatograph equipped with a flame ionization detector. The analyses were performed isothermally at 107^{o} on a 6 foot aluminum column (0.125" o.d.) packed with silicone gum UC W-98 (10%) on Diatoport S (80-100 mesh) using nitrogen as the carrier (3.6 l/h). The detector temperature was held $30\text{-}35^{o}$ above the oven temperature during isothermal operation.

Preparative gas liquid chromatography was also performed on the Hewlett-Packard 5750 B research instrument. The aluminum columns (6 ft. x 0.375"o.d.) were packed with 10% SE 30 adsorbed onto acid-washed silanized Chromosorb W (100-120 mesh).

Column chromatography

Column chromatography was performed using silica gel, 60-120 mesh, BDH Chemicals Ltd., Poole, England.

Anhydrous ether

This solvent was prepared by drying commercial anhydrous ether over anhydrous magnesium sulfate for 2 days. The ether was filtered into a dry bottle and sodium wire added. The container was stoppered with a calcium chloride drying tube. After another 2 days, the solvent was ready for use.

Anhydrous benzene

A commercial grade of benzene was first dried over anhydrous calcium chloride, filtered and then stored over sodium wire in a dry bottle.

Anhydrous dioxane, toluene and xylene

A commercial grade of dioxane, toluene or xylene was dried over anhydrous magnesium sulfate, filtered and then stored over sodium wire in a dry bottle.

Anhydrous tetrahydrofuran

This solvent was prepared by adding lithium aluminum hydride powder to a stirring solution of tetrahydrofuran. After refluxing with stirring for 6 hours the tetrahydrofuran was separated from the lithium aluminum hydride by filtration. Distillation of the

tetrahydrofuran in the presence of a reducing agent ($FeSO_4$) gave pure anhydrous tetrahydrofuran.

n-Butyllithium, sodium hydride, potassium hydride and phenylmagnesium bromide

A 22% solution of n-butyllithium in hexane, a 57% oil dispersion of sodium hydride, a 50% oil dispersion of potassium hydride and phenylmagnesium bromide (3 molar in ether) were obtained commercially from Alfa Inorganics, Beverly, Massachusetts.

Pulverized sodium

The required amount of freshly cut sodium was quickly placed in a reaction flask, containing anhydrous xylene, fitted with a condenser and magnetic stirrer. The xylene was heated until the sodium melted and then stirred for 10 minutes. The flask was slowly cooled with stirring to 60^{o}. The xylene was decanted and the anhydrous solvent (dioxane, toluene or xylene) added. The suspension was stirred, the solvent decanted and replaced with the required amount of anhydrous solvent.

Drying procedure

Organic extracts were dried over anhydrous magnesium sulfate for 30 minutes. After filtration, the solvent was evaporated on a rotary film evaporator.

When anhydrous conditions were required, the reaction vessel was guarded by a calcium chloride drying tube.

6.2.0.0.0 Pharmacological data

6.2.1.0.0 Hexobarbital sleeping time prolongation

6.2.1.1.0 Phenelzine 100 mg/kg, hexobarbital 100 mg/kg

	Sleeping time, in minutes					
mouse	½ hour	2 hours	4 hours	16 hours	24 hours	48 hours
1	223	252	195	82	91	77
2	376	262	143	111	75	44
3	222	179	147	110	63	28
4	413	251	151	108	81	24
5	135	199	141	70	80	19
6	286	215	101	100	57	68
7	137	225	164	117	75	35
8	164	207	188	122	103	43
9	130	189	170	90	67	33
10	169	266	*	49	*	36
mean	225.2	224.5	155.9	95.9	76.9	48.4

* mouse found dead

6.2.1.2.0 HLD 18 100 mg/kg, hexobarbital 100 mg/kg

mouse	Sleeping time, in minutes					
	½ hour	2 hours	4 hours	16 hours	24 hours	48 hours
1	69	27	31	48	46	26
2	170	31	31	35	25	28
3	113	21	17	45	23	32
4	96	36	25	20	43	46
5	91	48	43	20	43	45
6	85	49	22	30	30	42
7	124	33	50	19	19	55
8	87	49	55	33	35	30
9	82	41	50	20	18	39
10	96	36	38	33	*	32
mean	101.3	37.1	36.2	30.3	31.3	37.5

* mouse injected improperly

6.2.1.3.0 HLD 21 100 mg/kg, hexobarbital 100 mg/kg

mouse	Sleeping time, in minutes					
	½ hour	2 hours	4 hours	16 hours	24 hours	48 hours
1	74	30	45	26	40	23
2	79	37	49	20	31	24
3	47	42	33	42	75	48
4	102	20	28	48	22	47
5	62	41	46	22	17	34
6	64	45	40	45	33	24
7	93	55	24	24	25	40
8	90	37	23	42	32	25
9	79	40	13	50	31	*
10	102	39	12	*	42	*
mean	72.2	38.6	31.3	31.9	34.8	33.1

* .mouse found dead

6.2.1.4.0 Hexobarbital 100 mg/kg (control)

mouse	Sleeping time, in minutes
1	33
2	37
3	41.3
4	35.5
5	36.8
6	40.3
7	24
8	28.5
9	26
10	24
11	33.2
12	21.3
13	34.8
14	49
15	36
16	27
17	26
18	27
19	29
mean	32.1

6.2.1.5.0 Toxicity study of HLD 29

Dose: 100 mg/kg

weight of mouse/gm	Time of injection	
42	9.20 a.m.	
32	9.20 a.m.	
44	9.20 a.m.	All died by 10.30 a.m.
33	9.20 a.m.	
34	9.20 a.m.	

Dose: 75 mg/kg

weight of mouse/gm	Time of injection	
37	10.30 a.m.	
30	10.30 a.m.	
37	10.30 a.m.	4/5 died by 11.30 a.m.
37	10.30 a.m.	
34	10.30 a.m.	

Dose: 50 mg/kg

weight of mouse/gm	Time of injection	
38	1.30 p.m.	
32	1.30 p.m.	
28	1.30 p.m.	1/5 died by 4.00 p.m.
35	1.30 p.m.	
36	1.30 p.m.	

6.2.1.6.0 Phenelzine 46.45 mg/kg, hexobarbital 100 mg/kg

mouse	Sleeping time, in minutes					
	½ hour	2 hours	4 hours	16 hours	24 hours	48 hours
1	117	91	79	54	37	30
2	117	*	75	54	36	30
3	140	130	114	63	39	30
4	70	70	95	62	34	28
5	118	155	113	70	35	33
6	137	71	*	68	30	20
7	139	89	79	54	28	19
8	112	145	84	78	30	40
9	92	134	87	62	31	21
10	136	65	82	67	31	22
mean	117.8	105.3	89.8	63.2	33.1	27.3

* mouse gave abnormal response

6.2.1.7.0 HLD 29 32.12 mg/kg, hexobarbital 100 mg/kg

mouse	Sleeping time, in minutes					
	½ hour	2 hours	4 hours	16 hours	24 hours	48 hours
1	29	38	42	24	34	37
2	41	38	45	25	23	36
3	32	39	23	23	35	35
4	27	47	39	45	26	35
5	47	57	24	33	19	17
6	*	27	33	23	57	32
7	40	43	34	20	24	30
8	32	67	33	29	34	63
9	33	41	42	25	27	30
10	31	40	34	40	*	29
mean	34.7	43.7	33.9	28.7	31.0	34.4

* mouse found dead

6.2.1.8.0 Hexobarbital 100 mg/kg (control)

mouse	Sleeping time, in minutes
1	59
2	21
3	45
4	32
5	23
6	21
7	19
8	33
9	28
10	27
11	26
12	25
13	33
14	23
15	40
16	17
17	22
18	28
19	24
20	22
mean	28.4

6.2.2.0.0 Reserpine reversal

6.2.2.1.0 Phenelzine (100 mg/kg), HLD 21 (100 mg/kg) and HLD 18 (100 mg/kg)

Time in hours after MAO inhibitor	Actophotometer count (½ hour duration)			
	Phenelzine 100 mg/kg and Reserpine 5 mg/kg	HLD 21 100 mg/kg and Reserpine 5 mg/kg	HLD 18 100 mg/kg and Reserpine 5 mg/kg	Reserpine 5 mg/kg
½	1043	1139	1192	
2	2110	984	1905	
4	3006	1700	3315	
16	2230	2735	2634	
24	2215	2641	2790	
48	2393	2639	2982	
control 1				1662
control 2				1922
control 3				2330
mean control				1931

6.2.2.2:0 Phenelzine (46.45 mg/kg) and HLD 29 (32.12 mg/kg)

Time in hours after MAO inhibitor	Actophotometer count (½ hour duration)		
	Phenelzine 46.45 mg/kg and Reserpine 5 mg/kg	HLD 29 32.12 mg/kg and Reserpine 5 mg/kg	Reserpine 5 mg/kg
½	2004	2045	
2	3151	1689	
4	2979	2105	
16	4921	3245	
24	3051	3805	
48	2669	2948	
control 1			2828
control 2			2747
mean control			2788

6.3.0.0.0 Compound index

6.3.1.0.0 Compounds previously reported in the literature

Formula	Compound	Reference
$C_6H_9N_3$	3-Picolylhydrazine (119a; n=1)	lit.[144]
$C_6H_{11}Cl_2N_3$	3-Picolylhydrazine dihydrochloride (119d; n=1)	lit.[145]
C_7H_9NO	2-(3-Pyridyl)ethanol (92)	lit.[72]
$C_8H_6N_2O_2$	2-Methyl-4H-pyrido [2,3-d][1,3]-oxazin-4-one (125)	lit.[41,42]
$C_8H_{10}N_2$	1,2,3,4-Tetrahydro-1,8-naphthyridine (110)	lit.[79]
$C_{12}H_{10}N_2O$	2-Amino-3-benzoylpyridine (131)	lit.[41,42]
$C_{14}H_{12}N_2O_2$	2-Acetamido-3-benzoylpyridine (127)	lit.[41,42]

6.3.2.0.0 New compounds identified with the aid of elemental analysis

Formula	Compound	Analysed for
$C_7H_9Br_2N$	3-(3-Bromoethyl)pyridine hydrobromide (94; n=2)	C,H,Br,N
$C_7H_9Cl_2N$	3-(2-Chloroethyl)pyridine hydrochloride (116; n=2)	C,H,Cl,N
$C_7H_9N_3O$	3-Pyridylacetic acid hydrazide (112)	C,H,N
$C_7H_{12}ClN_3$	2-(3-Pyridyl)ethylhydrazine hydrochloride (119d; n=2)	C,H,Cl,N

$C_8H_8N_2$	2-(3-Pyridyl)propionitrile (97; n=2)	C,H,N
$C_8H_{11}Br_2N$	3-(3-Bromopropyl)pyridine hydrobromide (94; n=3)	C,H,Br,N
$C_8H_{11}Cl_2N$	3-(3-Chloropropyl)pyridine hydrochloride (116; n=3)	C,H,Cl,N
$C_8H_{12}N_2$	3-(3-Pyridyl)propylamine (99; n=2)	C,H,N
$C_8H_{15}Cl_2N_3$	3-(3-Pyridyl)propylhydrazine dihydrochloride (119d; n=3)	C,H,Cl,N
$C_9H_{10}N_2$	3-(3-Pyridyl)butyronitrile (97; n=3)	C,H,N
$C_9H_{12}N_2$	6,7,8,9-Tetrahydro-5H-pyrido-[2,3-b]azepine (107)	C,H,N
$C_9H_{13}N_3$	N-Methyl-N'-(3-picolylidene)-ethylenediamine (148)	C,H,N
$C_9H_{14}N_2$	4-(3-Pyridyl)butylamine (99; n=3)	C,H,N
$C_{12}H_{11}N_3O$	2-Amino-3-benzoylpyridine oxime (142)	C,H,N
$C_{14}H_{14}N_4O_2$	p-Nitrobenzylidene 2-(3-pyridyl)-ethylhydrazine (119b; n=2)	C,H,N
$C_{15}H_{16}N_4O_2$	p-Nitrobenzylidene 3-(3-pyridyl)-propylhydrazine (119b; n=3)	C,H,N
$C_{19}H_{17}N_9O_{14}$	2-(3-Pyridyl)ethylhydrazine dipicrate (119c; n=2)	C,H,N
$C_{20}H_{19}N_9O_{14}$	3-(3-Pyridyl)propylhydrazine dipicrate (119c; n=3)	C,H,N

6.3.3.0.0 New compounds identified by spectroscopic methods only

Formula	Compound	Spectra
$C_7H_{11}N_3$	2-(3-Pyridyl)ethylhydrazine (119a; n=2)	ir, nmr, ms
$C_8H_{11}N_3$	N-(3-Picolylidene)ethylenediamine (157)	ir,ms
$C_8H_{13}N_3$	N-(3-Picolyl)ethylenediamine (159)	ir,ms
$C_8H_{13}N_3$	3-(3-Pyridyl)propylhydrazine (119a; n=3)	ir,nmr,ms
$C_9H_{15}N_3$	N-Methyl-N'-(3-picolyl)ethylene-diamine (152)	ir,nmr,ms
$C_{15}H_9N_3O$	3-Cyano-2-hydroxy-4-phenyl-1,8-naphthyridine (181)	ir,ms
$C_{15}H_{10}N_4$	2-Amino-3-cyano-4-phenyl-1,8-naphthyridine (184)	ir,ms
$C_{15}H_{12}N_4O$	2-Amino-4-phenyl-1,8-naphthyridine-3-carboxamide (186)	ir,ms
$C_{15}H_{18}N_3$	N-Methyl-N'-α-(3-pyridyl)-benzylidene ethylenediamine (164)	ir,ms

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