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NAME OF AUTHOR/*NOM DE L'AUTEUR* KINFE REDDA

TITLE OF THESIS/*TITRE DE LA THÈSE* SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-IMINOPYRIDINIUM YLIDES AND THEIR 1,2,5,6-TETRAHYDROPYRIDINE REDUCTION PRODUCTS

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NAME OF SUPERVISOR/*NOM DU DIRECTEUR DE THÈSE* Dr. E.E. KNAUS

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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-IMINOPYRIDINIUM YLIDES AND THEIR 1,2,5,6-TETRAHYDROPYRIDINE REDUCTION PRODUCTS

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DIVISION OF MEDICINAL CHEMISTRY, FACULTY OF

PHARMACY AND PHARMACEUTICAL SCIENCES

EDMONTON, ALBERTA

SPRING, 1978

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF N-IMINOPYRIDINIUM YLIDES AND THEIR 1,2,5,6-TETRAHYDROPYRIDINE REDUCTION PRODUCTS" submitted by Kinfe Redda in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

E. E. Knaus
Supervisor

R. T. Coutts

External Examiner

Date December 12, 1977

DEDICATED TO

MY PARENTS

ABSTRACT

Novel N-iminopyridinium ylides 112 were prepared by the reaction of N-(2,4-dinitrophenyl)pyridinium chlorides 109 with alkyl (aryl) carbonyl, methane (benzene) sulfonyl and phenylethyl hydrazines 110. Sodium borohydride reduction of the N-iminopyridinium ylides 112 in 95% ethanol at 0° for 4 hr affords the medicinally important N-amino-1,2,5,6-tetrahydropyridine derivatives 113. Mechanisms for the formation of the pyridinium ylides 112 and 1,2,5,6-tetrahydropyridine analogs 113 are discussed. It is believed that the formation of the 1,2,5,6-tetrahydropyridines 113 proceeds *via* the corresponding 1,2-dihydropyridine intermediates. However, attempts to stop the reduction at the N-amino-1,2-(1,4-)dihydropyridine stage using sodium borohydride in basic media or tetrabutylammonium borohydride in aprotic solvents were not successful suggesting that the dihydropyridines might be very unstable species.

Mass spectral fragmentation patterns of both the N-iminopyridinium ylides 112 and their N-amino-1,2,5,6-tetrahydropyridine 113 reduction products which are very diagnostic are described in detail.

Quaternization of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) using methylchloroformate followed by sodium borohydride reduction in methanol at -65° afforded N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)-carbonylamino]-1,2,5,6-tetrahydropyridine (123a) whereas

reduction in 95% ethanol at 25° gave N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b). On the other hand, quaternization of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) using [illegible] followed by sodium borohydride reduction in methanol at -65° gave rise to N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123c) and N-[1-(1,2,5,6-tetrahydropyridyl)]-C-methoxy-C-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)]azomethine (123d).

n-Butyllithium catalysed reactions of alkyl(pyridylcarbonyl) hydrazines and alkyl nicotinates were employed to prepare structurally related analogs of the alkyl-(pyridylcarbonyl)-N-amino-1,2,5,6-tetrahydropyridines. For example, reaction of N-aminopiperidine with *n*-butyllithium in dry tetrahydrofuran at -65° followed by addition of ethyl nicotinate gives N-(3-pyridylcarbonylamino)piperidine (131a).

A one-step synthesis of the medicinally important derivatives of benzenesulfonamides in which the N^1 sulfonamide nitrogen is part of a 1,2-(1,4-)dihydropyridyl ring system was also developed. For example, reaction of pyridine with benzenesulfonyl chloride (benzenesulfonic anhydride) in methanol (pyridine) in the presence of sodium borohydride affords an isomeric mixture of N-(benzenesulfonyl)-1,2-dihydropyridine (142b) and

N-(benzenesulfonyl)-1,4-dihydropyridine (141b). The product(s) obtained from reduction of N-sulfonylpyridinium salts appears to be dependent upon solvent and temperature. Attack by hydride anion occurs predominantly or exclusively at the 2-position to give N-sulfonyl-1,2-dihydropyridines 142 using methanol as solvent at -65° whereas attack at the 4-position is usually favoured slightly when pyridine is employed as solvent at 25°.

A series of selected N-carbonylamino-1,2,5,6-tetrahydropyridines 113 and the structurally related pyridylcarbonyl hydrazine derivatives 131 were subjected to broad spectrum pharmacological screening. Significant analgesic, antiinflammatory, hyperglycemic and hypoglycemic effects were exhibited.

ACKNOWLEDGEMENTS

I would like to express my indebtedness and gratitude to Dr. E. E. Knaus for his advice and guidance throughout this investigation and his valuable suggestions and criticisms in the preparation of this thesis.

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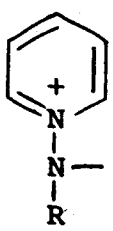
1.0.0.0.0. INTRODUCTION

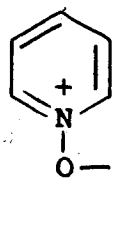
A ylide is formally defined as an internal salt formed by abstraction of a proton from a carbon or nitrogen atom adjacent to a heteroatom bearing a positive charge.[1] Phosphonium and sulfonium ylides have been studied more extensively than nitrogen ylides.[2]

There is a marked difference in stability between nitrogen ylides and those of phosphorus and sulfur which have unoccupied d orbitals available for overlap. Nitrogen is a first row element having occupied 2s and 2p orbitals. The next available unoccupied orbital is the 3s orbital which is at a much higher energy level. In contrast, phosphorus and sulfur, which are second row elements with occupied 3s and 3p orbitals, have as their next available unoccupied orbitals the 3d orbitals which are at only a slightly higher energy level and therefore more available for overlap for an anion adjacent to them.[2] Consequently, the ammonium, pyridinium, quinolinium and the isoquinolinium ylides are considerably less stable and more difficult to prepare.

The N-iminopyridinium ylides 1 are isoelectronic



(1)



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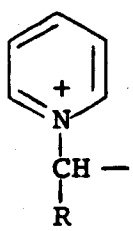
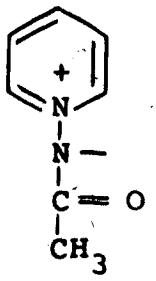


(3)

R = aryl, acyl, sulfonyl

and isosteric with the N-oxides 2 and N-ylides 3. The N-iminopyridinium ylides (1) have received less attention than the N-oxides 2[3,4] and N-ylides 3[5,6] which have been studied extensively and are the subject of several reviews.

Several nomenclatures have been employed in the literature to designate the structure of N-iminopyridinium ylides. For example, structure 4 has been named N-acetylimino pyridinium ylide, pyridine-1-(N-)acetyl-



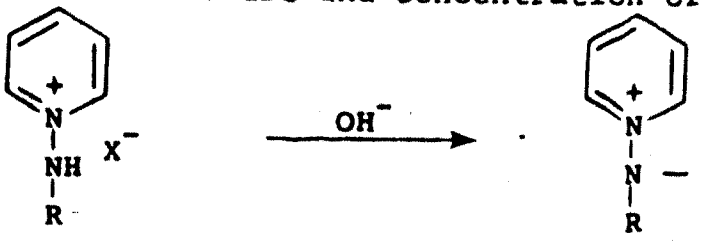
(4)

imide, N-acetyliminopyridinium betaine, N-acetylimino-pyridine, 1-acetylaminopyridinium hydroxide inner salt and acetylpyridinium imine.[7] The N-iminopyridinium ylide nomenclature will be used in this dissertation.

1.1.0.0.0. General synthesis of N-iminopyridinium ylides

1.1.1.0.0. Preparation from quaternary pyridinium salts

This synthetic method involves base catalysed deprotonation of an N-aminopyridinium salt 5 to afford the ylide 1. The nature and concentration of the base

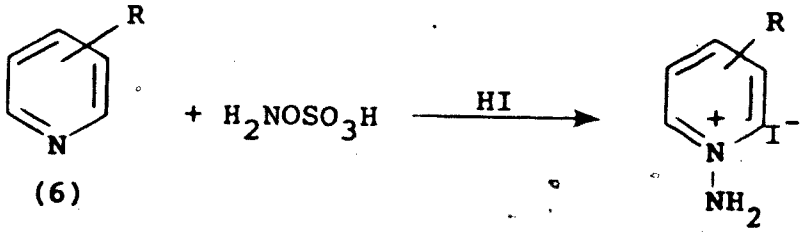


(5) (1)

R = aryl, acyl, sulfonyl

necessary for deprotonation is dependent upon the substituent R. For example, 10% sodium hydroxide solution transforms N-acyl and N-sulfonylamino pyridinium salts to the corresponding ylides.[7]

N-aminopyridinium salts are accessible *via* two different synthetic procedures. Reaction of pyridines 6,



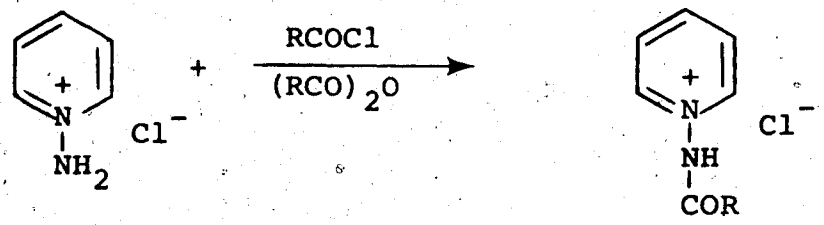
(6) (7)

R = Hydrogen, alkyl, halogen, acetyl

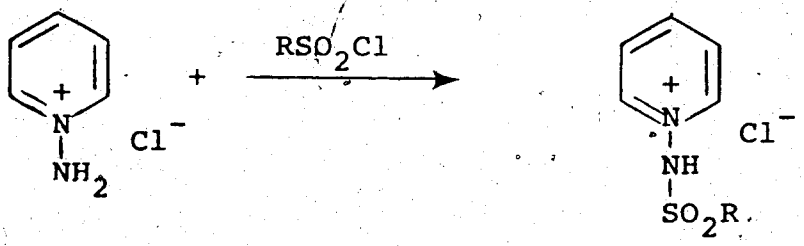
with hydroxylamine-O-sulfonic acid afford N-aminopyridium salts 7 in good yields.[8,9] The corresponding chloride

salts are obtained from the iodide salts 7 by anion exchange column chromatography.[7,9]

Other N-aminopyridinium salts can be prepared from N-aminopyridinium chloride 8. For example, reaction of



(8) (9)

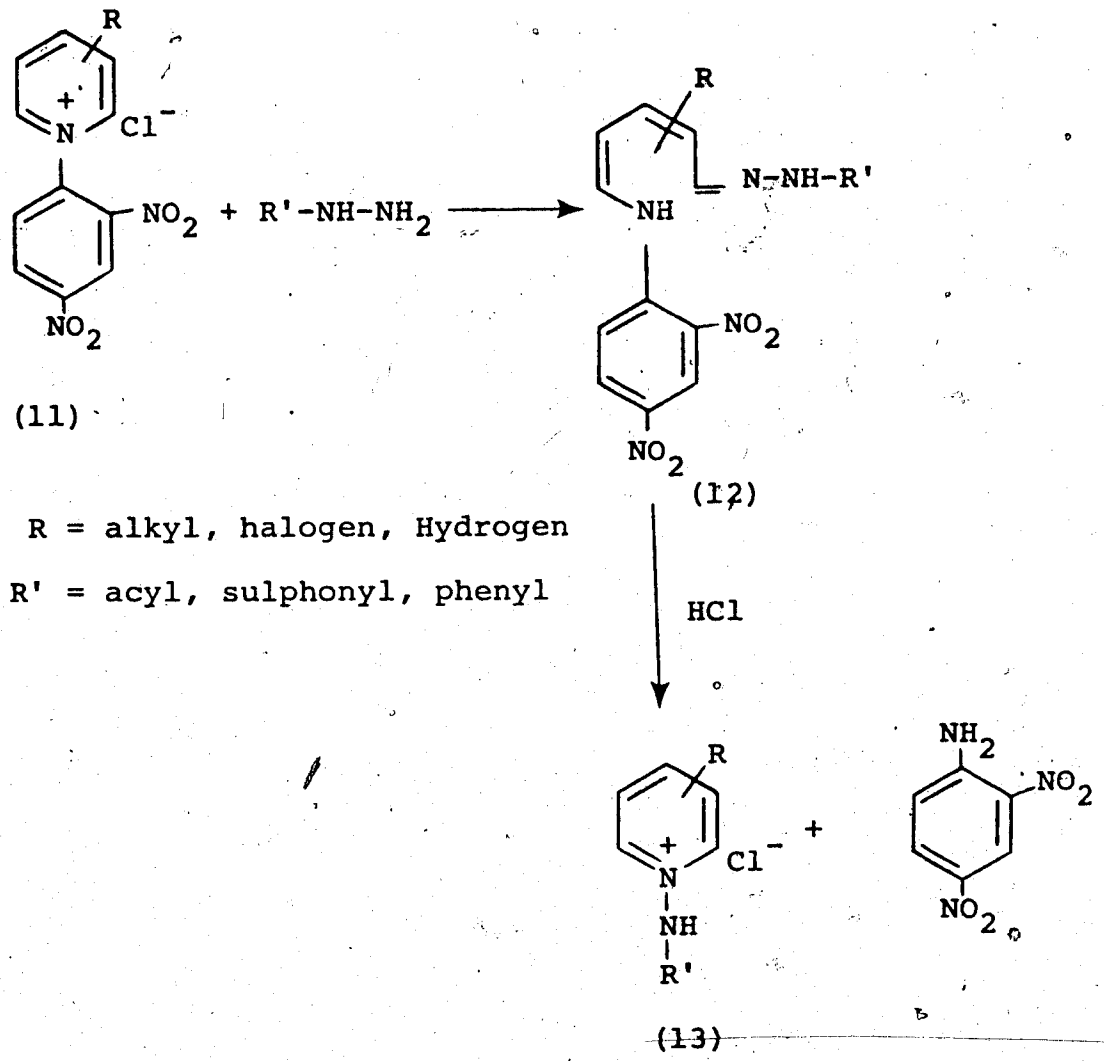


(8) (10)

R = alkyl, phenyl

N-aminopyridinium chloride (8) with an acid chloride or acid anhydride affords 9 and with sulfonyl chloride gives rise to 10.[10,11]

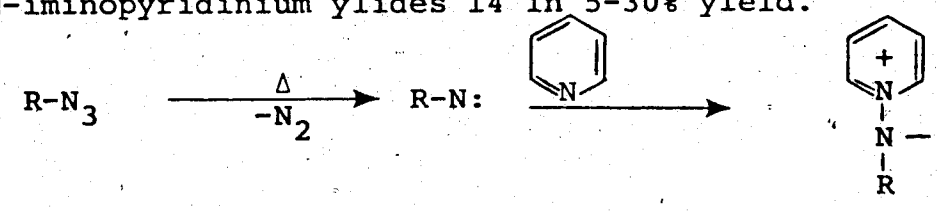
Alternatively, N-(2,4-dinitrophenyl)pyridinium chlorides 11, commonly referred to as "Zincke salts"[12,13] are excellent precursors for the synthesis of N-amino-pyridinium salts. Reaction of Zincke salts 11 with hydrazines afford 5-(2,4-dinitroanilino)-2,4-pentadienal hydrazones 12.



Subsequent ring cyclization of 12 together with elimination of 2,4-dinitroaniline yield pyridinium salts 13.[13,14]

1.1.2.0.0. Preparation from azides and pyridines

The reaction of sulfonyl, acyl and cyanogen azides with pyridines using thermolysis conditions gives rise to N-iminopyridinium ylides 14 in 5-30% yield.[7,15]



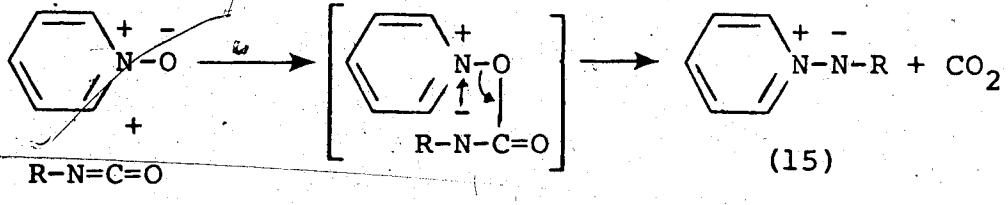
R = $ArSO_2$-, Ac-, CN-

(14)

The initial reactions reported by Curtius and coworkers[16,17] involved heating an aromatic sulfonyl azide in pyridine. Although the structures of the various N-iminopyridinium ylides prepared in this way were not clearly recognized at that time, sulfonyl nitrenes were formulated as reaction intermediates. The thermolysis and photolysis of azides in the presence of pyridines has now been developed into a general method of preparing N-iminopyridinium ylides.[15]

1.1.3.0.0. Preparation from isocyanates and pyridine-1-oxides

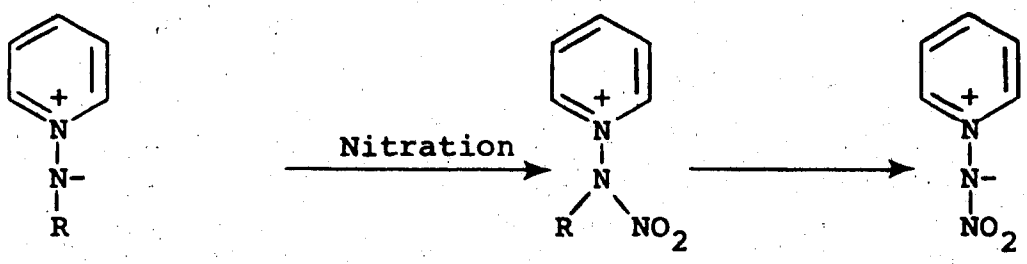
Pyridine-1-oxides react with isocyanates to furnish N-iminopyridinium ylides 15 in moderate yields.[18]



(15)

1.1.4.0.0. Preparation from other N-iminopyridinium ylides

The imino group of pyridinium ylides is a nucleophilic reaction center which undergoes reaction with electrophiles to yield other pyridinium ylides such as 16.



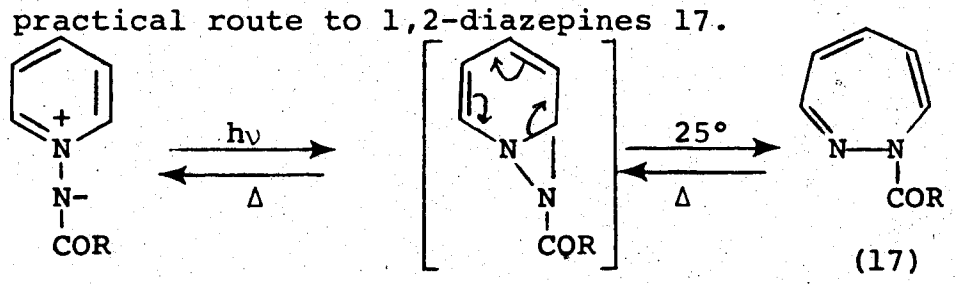
(1) (16)

R = Ac-, $ArSO_2$

In this way, N-iminosulfonyl or N-iminocarbonyl-pyridinium ylides undergo nitration at the imino group in the presence of acetic acid - acetic anhydride solvent.[11]

1.1.5.0.0. Preparation from diazepines by rearrangement

Studies by Sasaki and coworkers[19] and others[20] have shown that photolysis of N-acyliminopyridinium ylides is a practical route to 1,2-diazepines 17.



(17)

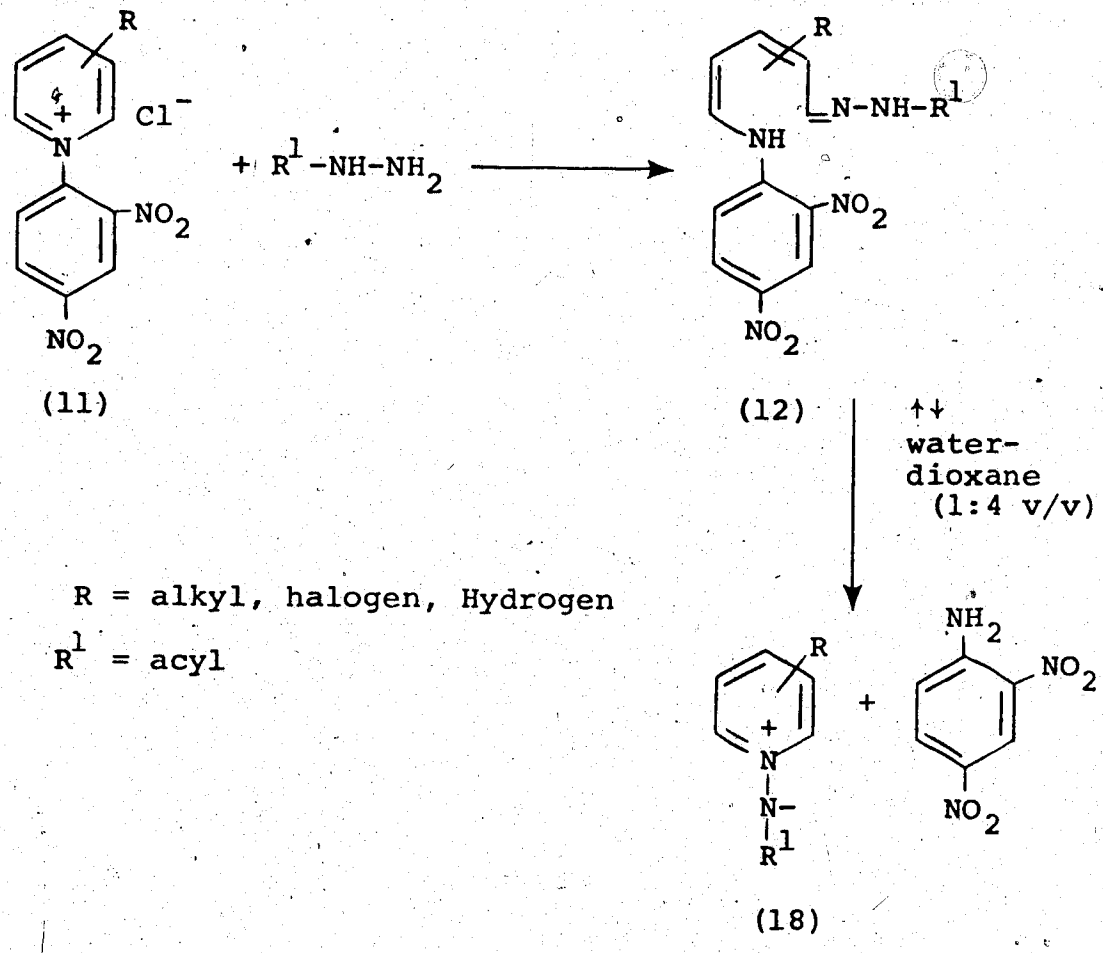
R = -Ph, -OEt

On the other hand, selected diazepines like 17 (R = -Ph, -OEt) undergo the reverse reaction at higher temperatures.[7] At room temperature the equilibrium between diazepine and diaziridine is exclusively on the side of the diazepine whereas at 170°C the equilibrium lies in the direction of the N-iminopyridinium ylide.

1.1.6.0.0. Preparation from Zincke salts and hydrazines

This reaction is similar to that described for the preparation of quaternary pyridinium salts under Section 1.1.1.0.0. In this case cyclization of the intermediate 12 is effected at reflux using a water-dioxane (1:4 v/v) mixture rather than hydrochloric acid.

N-(2,4-dinitrophenyl)pyridinium chlorides 11 react with alkyl, aryl and arylcarbonyl hydrazines to afford



the ring opened intermediate 12. Treatment of 12 with a water-dioxane (1:4 v/v) mixture at 100° results in the elimination of 2,4-dinitroaniline and the formation of the ring closure product N-iminopyridinium ylide 18.[13]

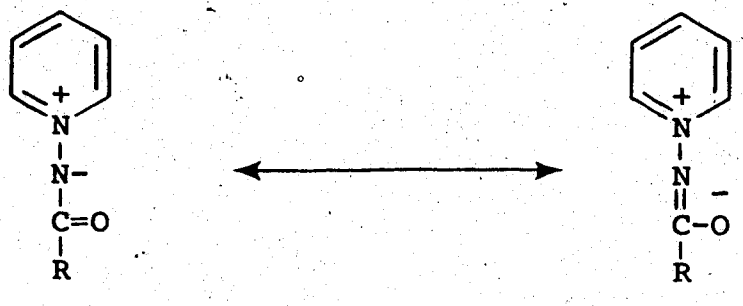
1.2.0.0.0 Physical properties of N-iminopyridinium ylides

1.2.1.0.0. Solubility

N-Iminopyridinium ylides are usually crystalline solids which are soluble in water. The resulting solutions are neutral (pH 6.9-7.2) and have low conductivity.[15,21] Most N-iminopyridinium ylides are soluble in polar organic solvents such as methanol, ethanol, chloroform and methylene chloride but are sparingly soluble in ether, benzene and other non-polar organic solvents.

1.2.2.0.0. Infrared spectra

The group of N-iminopyridinium ylides which have received the greatest attention are the acyl and sulfonyl derivatives. The infrared spectra of the acyliminopyridinium ylides show a strong absorption at the 1555-1600 cm^{-1} region which is assigned to the stretching frequency of the resonating carbonyl group (19-20).[15,22,23] The carbonyl group in the corresponding pyridinium salts

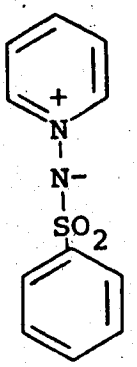


(19) (20)

R = alkyl, Aryl

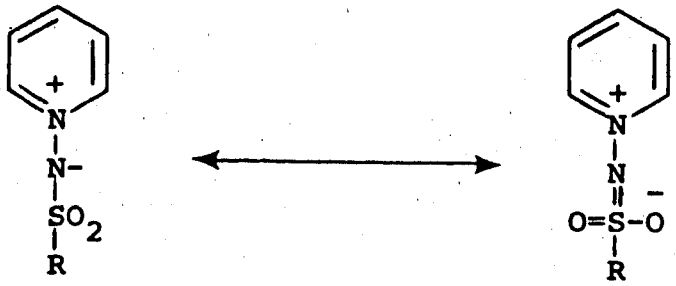
which absorbs at about 1700 cm^{-1} is shifted to a lower wave number in the ylides indicating that the resonance form 20 makes a greater contribution in the ylide structure. In general, if R is an electron donating group which would favour the resonance structure 20 the absorption is shifted to lower wave number (lower frequency) in agreement with the effect on the absorption of ketones.[15]

The infrared spectrum of 1-benzenesulfonylimino-pyridinium ylide (21) shows two strong bands for the SO_2 group in the 1285 and 1130-1140 cm^{-1} regions whereas



(21)

the corresponding methanesulfonylimino ylide exhibits bands at 1270 and 1115 cm^{-1}. N-sulfonyliminopyridinium ylides absorb at lower frequencies than sulfonamides, which absorb characteristically at 1300-1350 and 1140-1180 cm^{-1}, suggesting delocalization of the electron pair of the imino nitrogen on to the sulfonyl group (22-23).[15]



(22) (23)

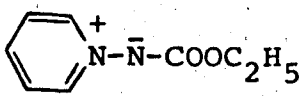
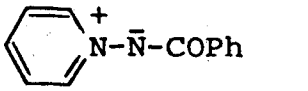
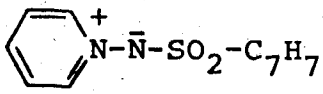
R = alkyl, phenyl

1.2.3.0.0. Ultraviolet spectra

The ultraviolet (uv) absorption of few N-imino-pyridinium ylides have been studied. The absorption

TABLE 1

uv Spectra of Some N-iminopyridinium ylides[15]

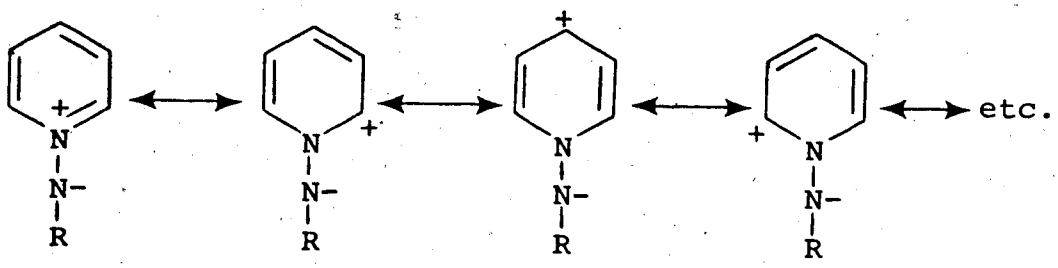
compound	λmax, nm(ε) (CH_3OH)	
	228 (6600)	315 (5530)
	233 (13,530)	317 (4850)
	240 (14,000)	317 (2180)

observed most frequently is a strong band near 230 nm which is strongly dependent on the solvent used.[7,15] Although the origin of this band is not certain it is

thought to be a $\pi \rightarrow \pi^*$ transition of the unbonded electron pair on the imino nitrogen. The acyl and sulfonyl N-imino pyridinium ylides, in addition to the absorption near 230 nm, also show a strong band in the 305-320 nm[15,24] as shown in Table 1.

1.2.4.0.0. Nuclear magnetic resonance

The canonical structures 24-27 for N-iminopyridinium ylides demonstrate the electron density distribution at various positions of the pyridine ring.[7] Consequently,



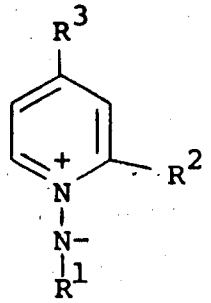
(24) (25) (26) (27)

R = aryl, acyl, sulphonyl

the nmr absorptions due to protons at the 2,4- and 6-positions of the pyridinium ring will be at a lower field than protons at the 3- or 5-positions. However, all chemical shifts may be influenced by substituents on the pyridinium ring or on the imino nitrogen[7,24,25] as shown in Table 2.

TABLE 2

Nmr Spectra of Some N-iminopyridinium ylides[a,b]



R^1	R^2	R^3	$H_{2,6}$	$H_{3,4,5}$	Ref.
-COOEt	H	H	8.66(6)	7.86-7.41	24
$-COOCH(CH_3)_2$	H	H	8.86(2 and 7)	7.66(2 and 7)	7
-COPh	H	H	8.93(7)	8.23-7.33	24
$-SO_2C_7H_7$	H	H	8.60(7)	8.08-7.55	24
-COOEt	H	Me	8.46(7)	7.40(6)	24
-COOEt	Me	H	8.62	7.98-7.39	24
-COOEt	H	Ph	8.72(7 and 5)	7.64(7 and 5)	7

[a] Measured in $CDCl_3$; δ scale.

[b] Coupling constants in hertz are given in parentheses.

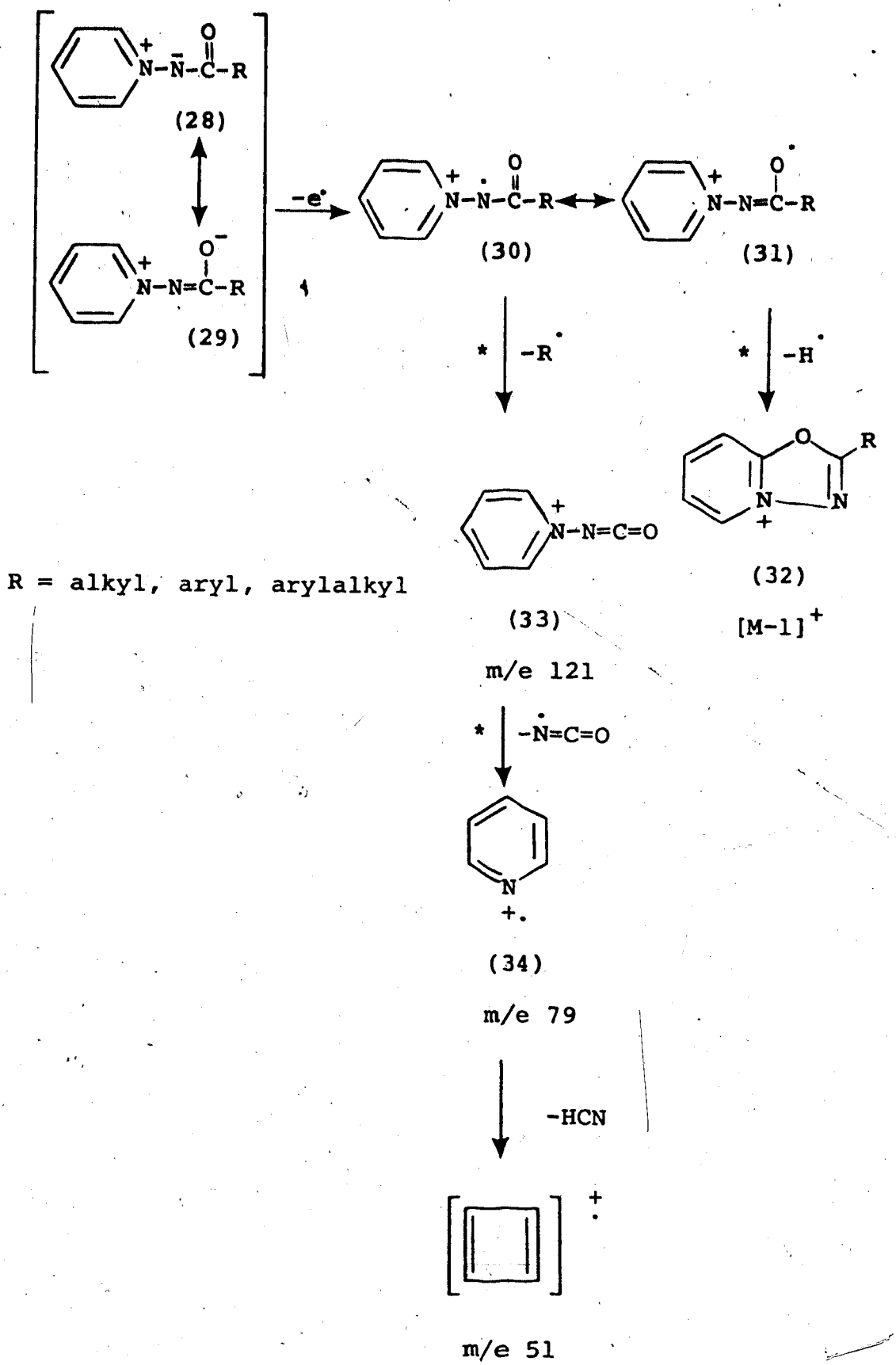
The isoelectronic character of N-iminopyridinium ylides with N-oxides is further demonstrated by the observation that the nmr spectrum of the parent N-imine in deuterium oxide is identical with the nmr of the pyridine-N-oxide.[11]

1.2.5.0.0. Mass Spectrometry

The mass spectral fragmentation patterns of few acyl and sulfonyl N-iminopyridinium ylides have been reported.[15,26,27]

Examination of canonical structures 28 and 29 indicates that an electron can be lost either from the imino nitrogen to give a molecular ion 30 or from oxygen to give a molecular ion 31. Acyl pyridinium ylides usually exhibit a $[M-1]^+$ ion as well as intense molecular ion except when R is ethyl.[26] In most cases, the intensity of the $[M-1]^+$ ion exceeds that of the molecular ion. This fragmentation was accompanied by a large metastable peak in all spectra that exhibited $[M-1]^+$ ion. Deuterium labeling studies provided evidence that the hydrogen expelled originated from the α-position of the pyridinium ring most probably by a mechanism that involves cyclization by an oxygen radical of the molecular ion 31. The resulting fragmentation is represented by the stable aromatic structure 32.

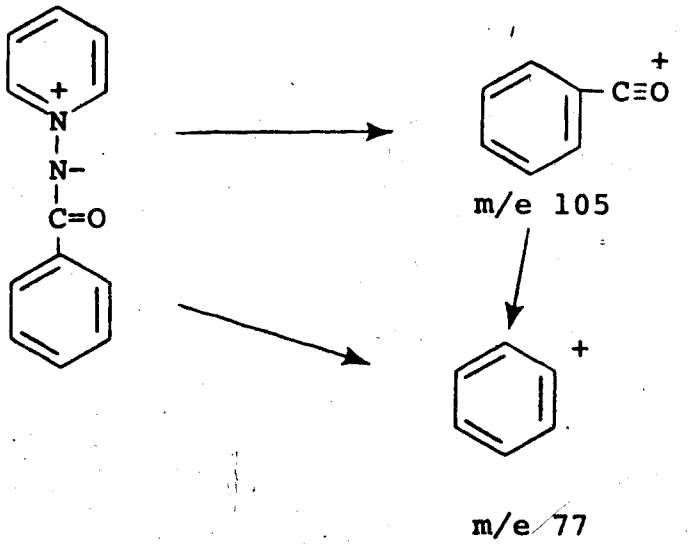
The most important primary fragmentation process of N-acyliminopyridinium ylides is α-cleavage of the molecular ion bearing the charge on the pyridinium nitrogen. Loss of the R radical affords a peak at m/e 121 attributed to 33 which is sometimes supported by a metastable peak. The α-cleavage ion 33 fragments further by elimination of -N=C=O to furnish a pyridine ion (34) at m/e 79 which



R = alkyl, aryl, arylalkyl

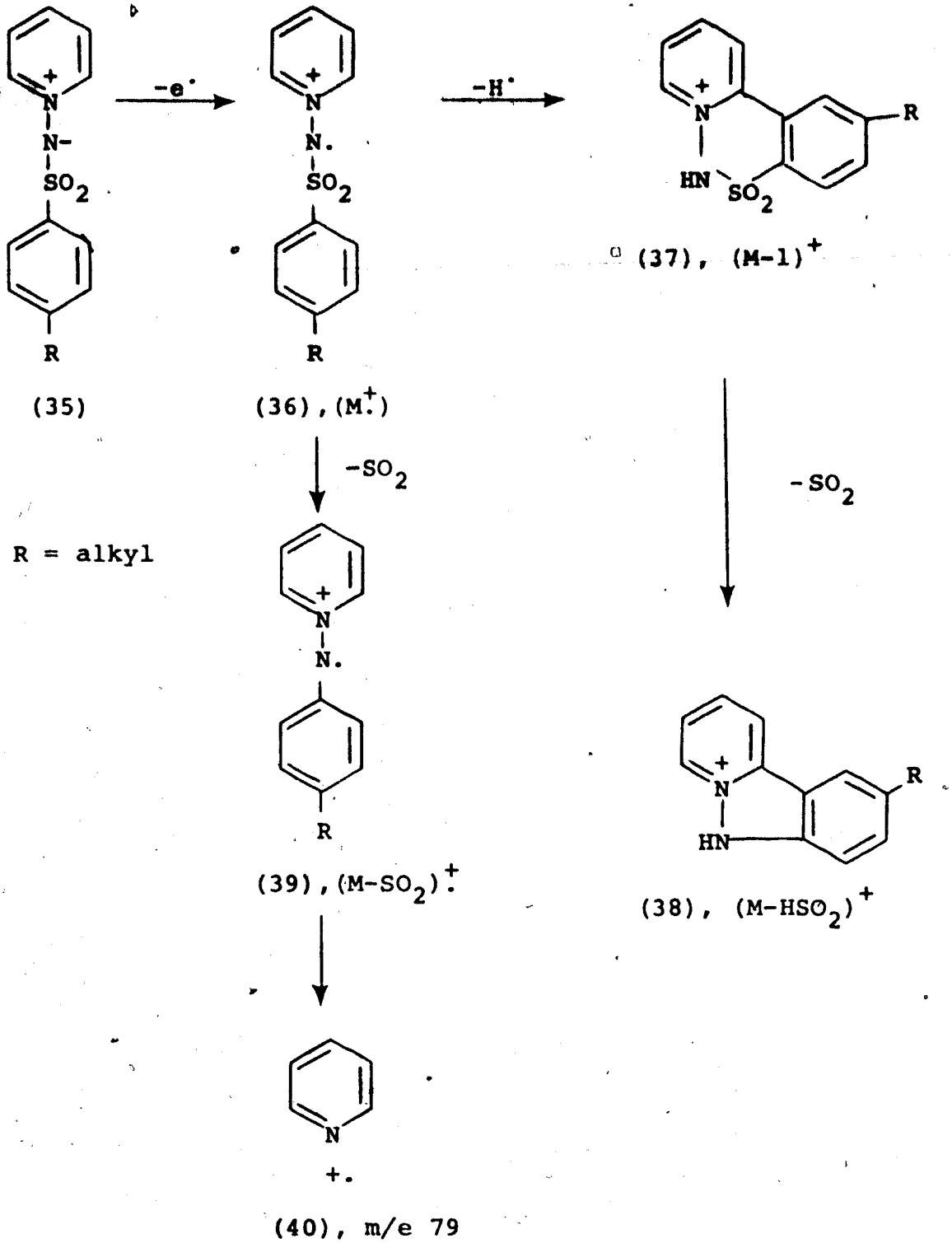
is often supported by an appropriate metastable peak. Ion 34 could then expel hydrogen cyanide to give a peak at m/e 51, $[C_4H_3]^+$, which is always observed in higher relative abundance.[26]

The major fragmentations described previously were rationalized by assuming that charge localization occurred on the pyridinium nitrogen. On the other hand, charge retention on the acyl moiety must occur to some extent since less intense peaks appear at m/e 105 and m/e 77 when R is a phenyl group as established by an accurate mass measurement.[26]



Mass spectral studies of some N-sulfonyliminopyridinium ylides have also been reported.[27] The fragmentation pathways are more complex than those of N-acyliminopyridinium ylides. The major fragmentations observed result in ions at (M^+), $(M-1)^+$, $(M-SO_2)^+$,

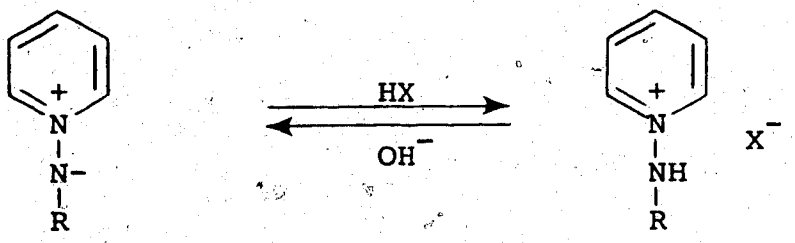
$(M-HSO_2)^+$ and pyridine ions as shown in structures (35-40).



1.3.0.0.0. Chemical properties of N-iminopyridinium ylides

1.3.1.00 Basicity

N-iminopyridinium ylides are bases and react with organic and inorganic acids at room temperature to form N-aminopyridinium salts 41.[7,15]



(1) (41)

R = alkyl, aryl, acyl, sulfonyl, arylalkyl

The pKa values of few N-iminopyridinium ylides have been determined as shown in Table 3.

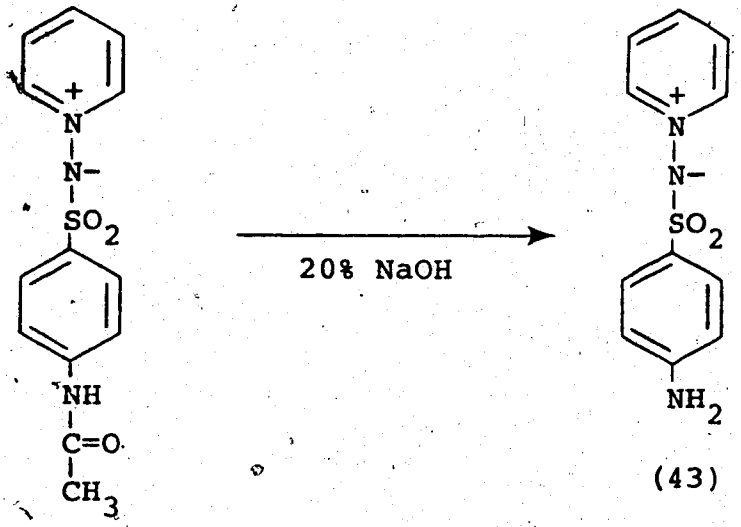
TABLE 3

pKa values of some N-iminopyridinium ylides[a]

R	pKa value	Ref
$CH_3-\overset{O}{\overset{\|}{C}}-$	3.6	12,11
$Ph-\overset{O}{\overset{\|}{C}}-$	3.2	11
NO_2-	-4.6	11
CH_3-	12-13	12

[a] Determined in water.

The pyridinium hydrogens at the 2-, 4- and 6-positions of 1 are active hydrogens since they undergo exchange with deuterium using 0.2 N sodium deuteroxide within the time interval the nmr spectra could be measured.[11] However, the N-iminopyridinium ylides are inert to strong alkali solutions. For example, 1-*p*-acetamidobenzenesulfonyliminopyridinium ylide (42) undergoes selective



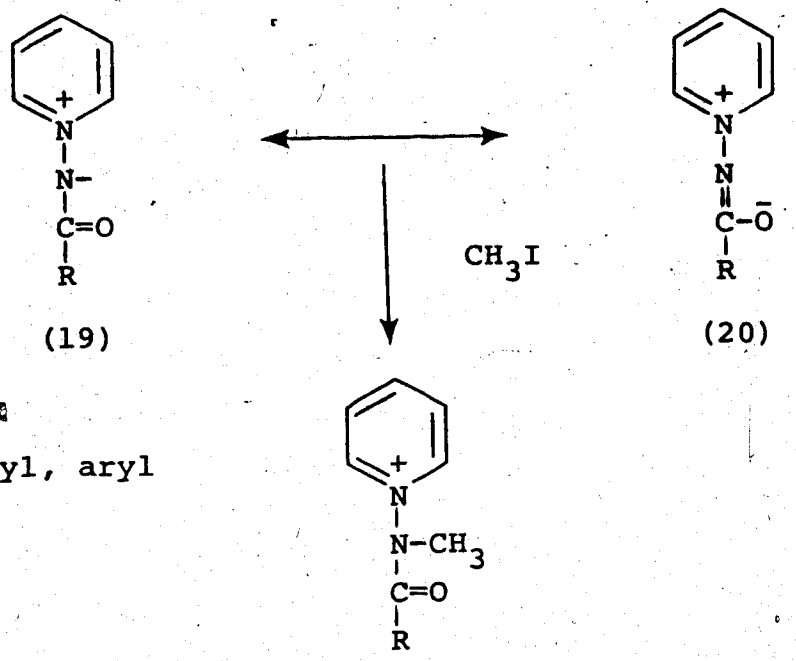
(42) (43)

hydrolysis to 1-*p*-aminobenzenesulfonyliminopyridinium ylide (43) when refluxed with 20% sodium hydroxide solution for 3 hours.[28]

1.3.2.0.0. Reaction of the imino moiety

The imino group of the N-iminopyridinium ylides undergoes protonation, alkylation and acylation because of its basicity and nucleophilicity.[7]

Two resonating forms, structures 19-20 can be drawn for N-acyliminopyridinium ylides indicating that

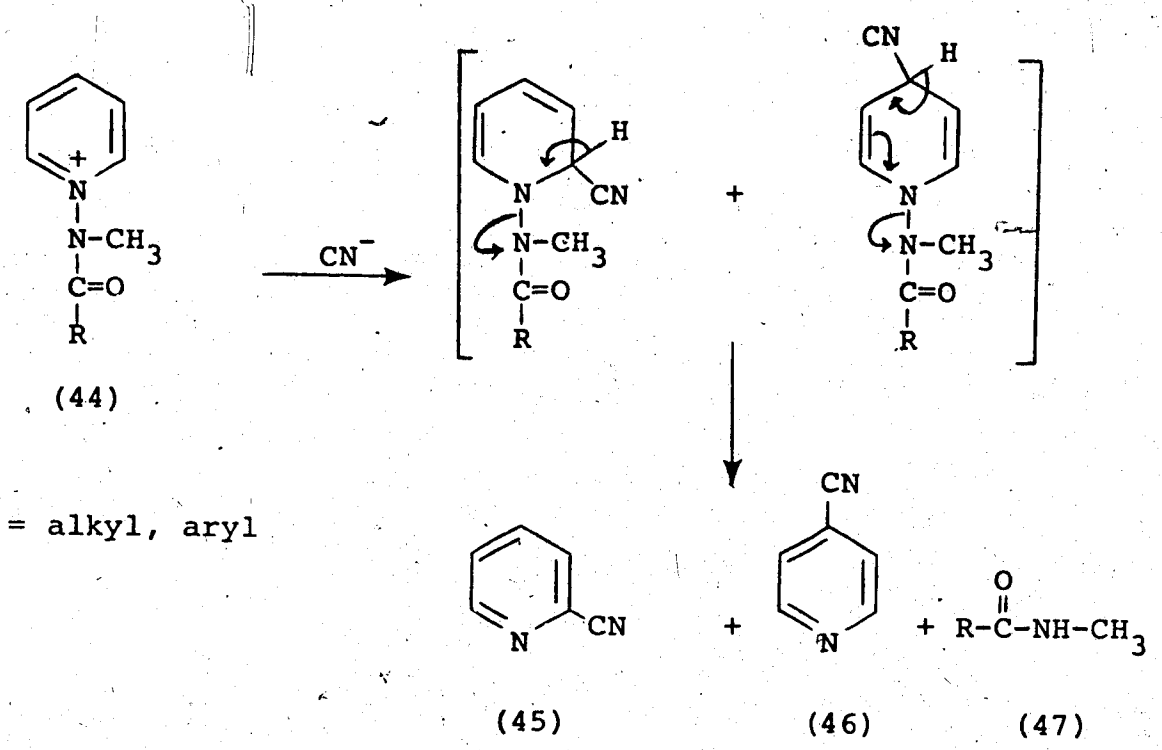


(19) (20)

(44)

either N-alkylation or O-alkylation is possible.[15] However, unlike the aliphatic N-imino derivatives the pyridinium N-imino ylides studied give predominantly the N-alkylation product 44. Alkylations were conducted using methyl iodide, dimethyl sulfate, allyl bromide and ethyl bromoacetate.[15,29,30]

The structure assigned to 44 was based on the observation that reaction with potassium cyanide gave 2-cyano and 4-cyano pyridines (45-46) along with the N-methyl amide 47. Acylation reactions with acid chlorides also afford N-substituted products.[31]



(44)

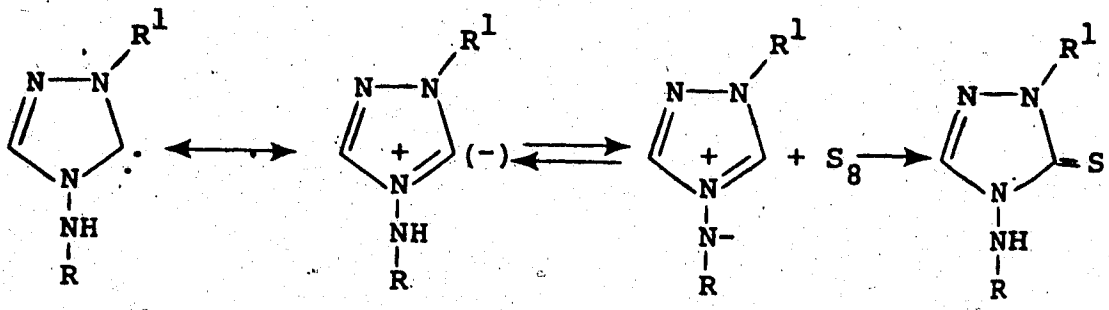
R = alkyl, aryl

(45) (46) (47)

N-acylimino and N-sulfonyliminopyridinium ylides undergo nitration using mild conditions at the imino nitrogen.[11]

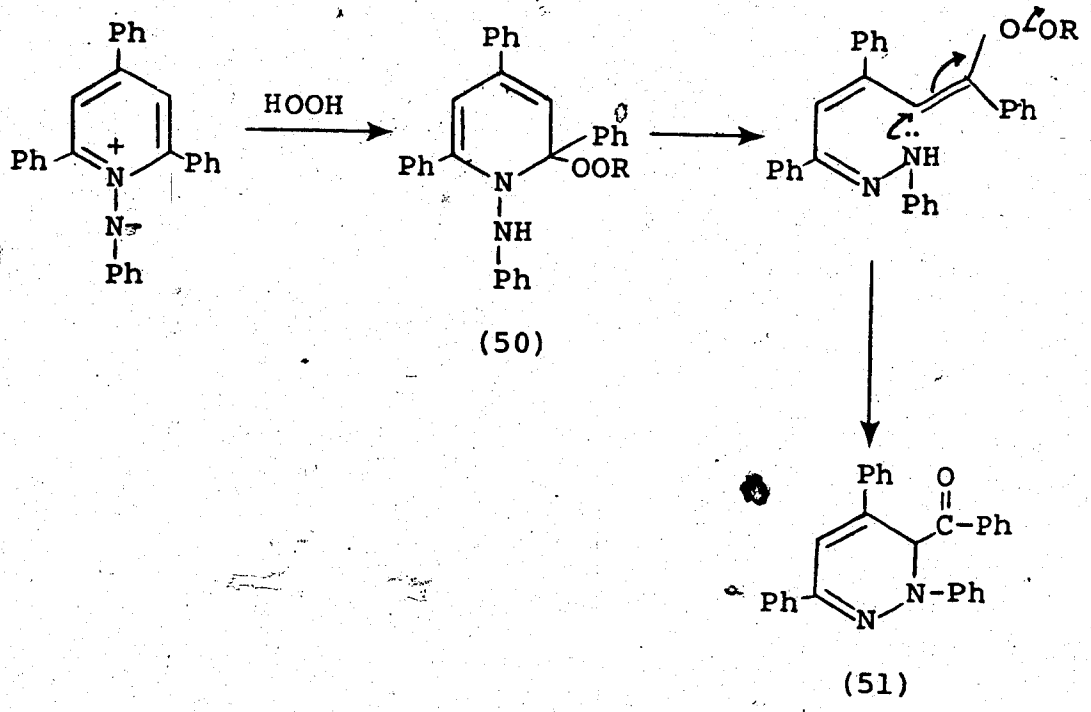
1.3.3.0.0. Reaction of a ring carbon as an electrophile or nucleophile

Although the reaction of elemental sulfur with N-imino pyridinium ylides has not been reported, it is known that sulfur reacts with N^4-imino-1,2,4-triazolium ylides 48 to yield the substituted product 49. The success of the latter reaction has been attributed to the acidity of the hydrogens adjacent to the quaternary nitrogen.[7]



(48) (49)

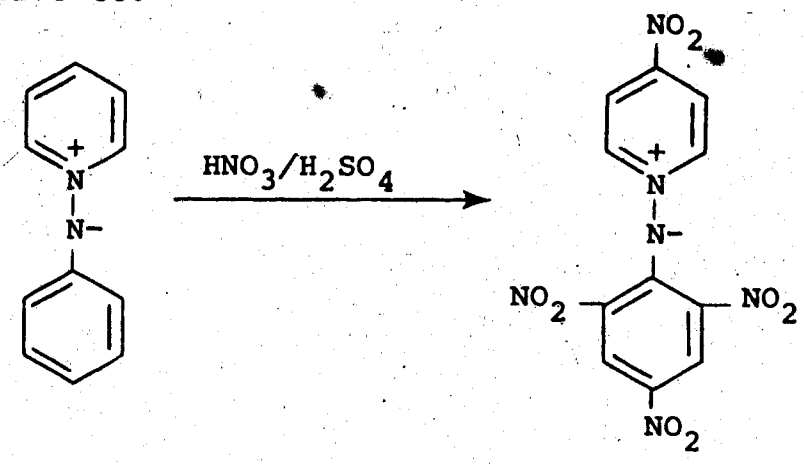
Hydroperoxides add to the 2- or 6-position of N-iminopyridinium ylides. The primary addition product 50 undergoes ring opening followed by rearrangment and ring closure to yield the 1,6-dihydropyridazine derivative 51.[32]



(50) (51)

Nitration of N-iminopyridinium ylides, excluding acyl and sulfonylimino ylides, provides the only example of a ring carbon which due to its nucleophilicity

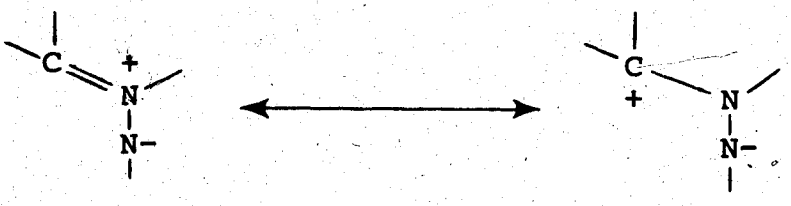
is attacked by an electrophile. Benzeneiminopyridinium ylide (52) undergoes nitration to the trinitrophenyl derivative 53.[7]



(52) (53)

1.3.4.0.0. 1,3-Dipolar cycloaddition reactions

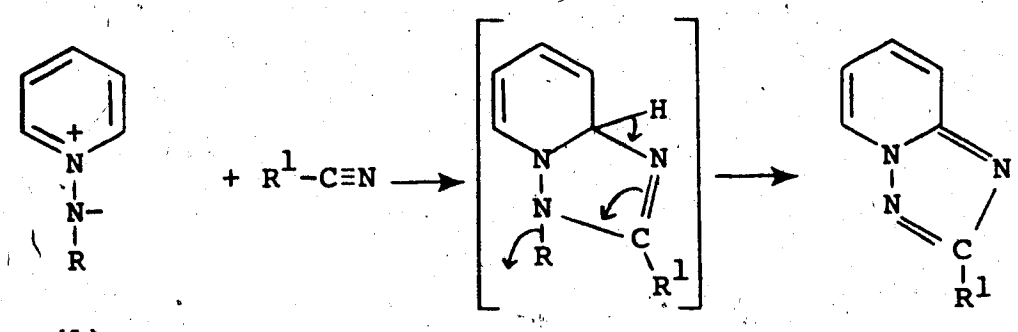
N-iminopyridinium ylides can be envisaged as derivatives of the structural moeity, azomethine imine (54), which is a 1,3-dipole. A typical reaction of this class



(54)

of compounds is the 1,3-dipolar cycloaddition reaction. 1,3-Dipolarcycloaddition reactions employing N-iminopyridinium ylides are often difficult since the reaction involves loss of the aromaticity of the pyridinium ring. However, in many reactions oxidation to another aromatic

product subsequent to the addition step exerts an essential influence on the stability of the adduct as seen for compound 55.



(1) (55)

R = EtCO

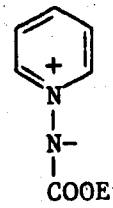
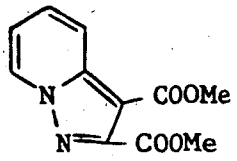
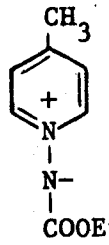
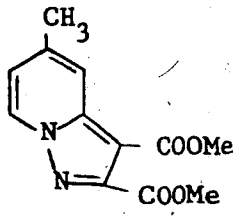
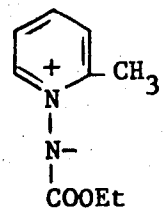
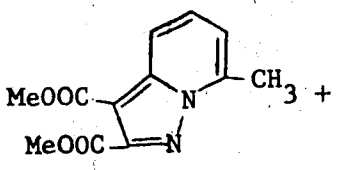
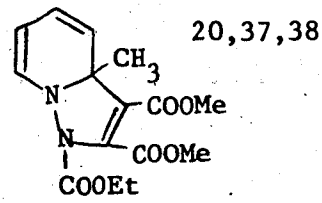
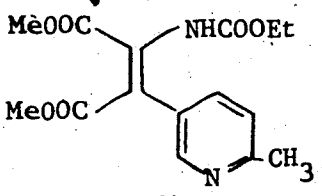
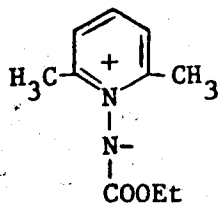
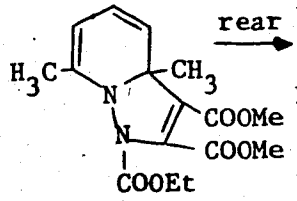
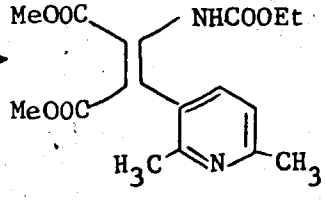
R^1 = alkyl

In this way, 1,3-dipolar cycloaddition reactions of N-iminopyridinium ylides with dipolarophiles such as nitriles,[10,12,30] acetylene dicarboxylic esters,[33,34] propiolonitriles[35] and carbon disulfide[36] have been successfully effected.

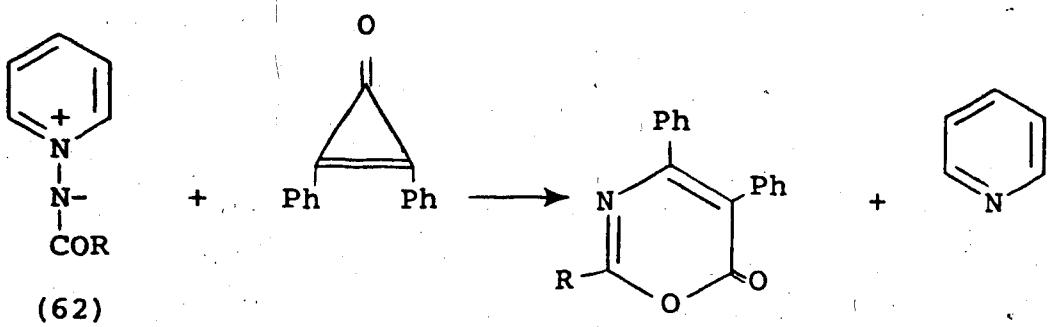
Table 4 depicts the reaction of dimethylacetylenedicarboxylate (DAC) with substituted N-alkylcarbonyliminopyridinium ylides. When the 2- and 6-positions of the pyridinium ring are unsubstituted pyrazolopyridines 56-57 are obtained. On the other hand, when the initial adduct has methyl substituents at the 2- and/or 6-positions oxidation to the pyrazole derivative does not occur; rather the relatively unstable dihydropyrazole compounds 58 and 60 rearrange to vinylpyridines 59 and 61, respectively.[20,37,38]

TABLE 4

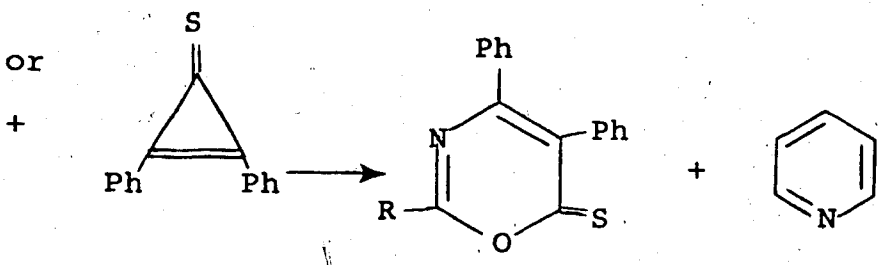
1,3-Dipolar Cycloaddition reactions of N-iminopyridinium ylides.

Ylide (1,3-dipole)	Dipolarophile	Adduct	Ref
	DAC	 (56)	37,38
	DAC	 (57)	37,38
	DAC  +  (58) → rear  (59)		20,37,38
	DAC  (60) → rear  (61)		20,37,38

N-Alkoxycarbonyliminopyridinium ylides and N-benzoyliminopyridinium ylides 62 react with diphenylcyclopropenone (DPP)[39] or diphenylcyclopropenethione[40] in benzene at room temperature or under reflux to yield 1,3-oxazines 63 and 1,3-oxazinethiones, 64, respectively, in good yields.



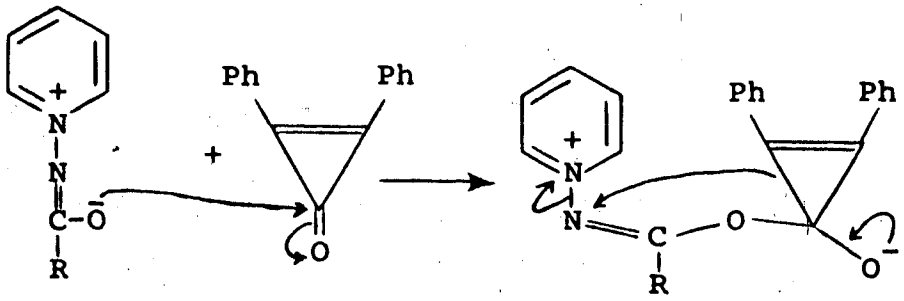
(62) (63)



(64)

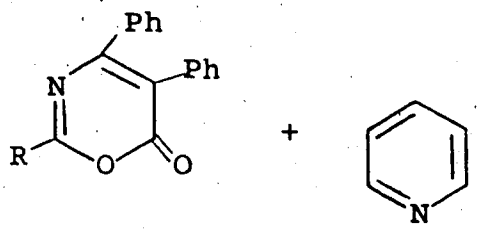
R = -OMe, -OEt, -Ph.

The mechanism[40] of the reaction has been postulated to proceed *via* nucleophilic attack by the ylide oxygen at the carbonyl carbon of DPP to yield the adduct 65 which undegoes subsequent cyclization to 63.



(65)

R = OMe, OEt, -Ph



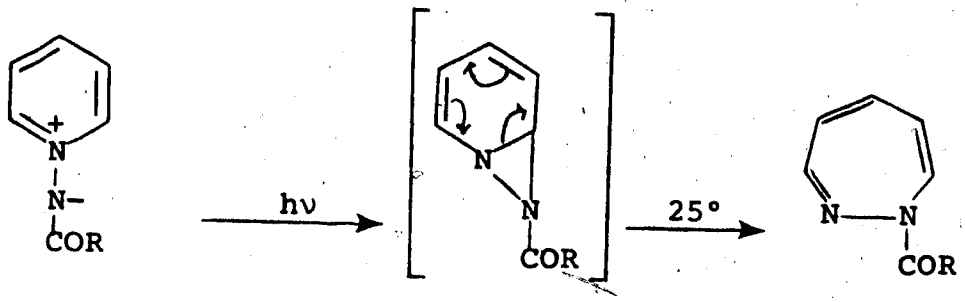
(63)

1.3.5.0.0. Photochemical reactions

N-Iminopyridinium ylides are photochemically active compounds which upon irradiation may give products resulting from N-N bond cleavage, ring enlargement and rarely rearrangement reactions. It is difficult to choose conditions for selective photochemical reactions due to the lack of data available. However, the solvent and nature of the substituent on the pyridinium ring play important roles.[7]

Irradiation of N-alkoxycarbonylimino and benzoylimino pyridinium ylides in methylene chloride, benzene or methanol give rise to 1-substituted-1,2-diazepines

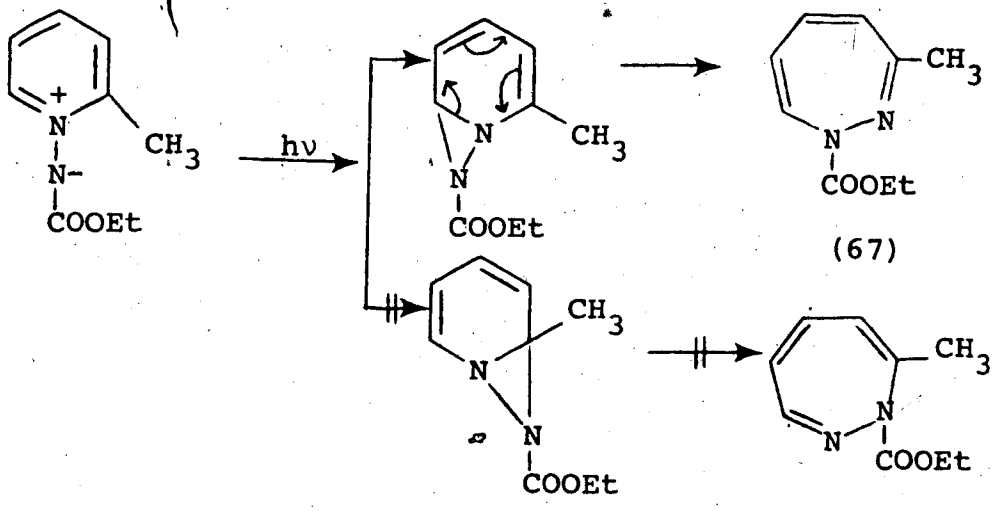
66 in good yields.[19,24] This reaction constitutes a



(66)

R = phenyl, alkoxy

convenient method of preparing 1,2-diazepines. Although no direct proof is available, the seven membered diazepine ring is believed to arise from an intermediate diaziridine which undergoes subsequent isomerization. N-Iminopyridinium ylides with a 2- or 3-substituent on the pyridinium ring undergo intramolecular 1,3-dipolar cyclization on the less hindered α-carbon to give compounds such as 67 and 68.[19]



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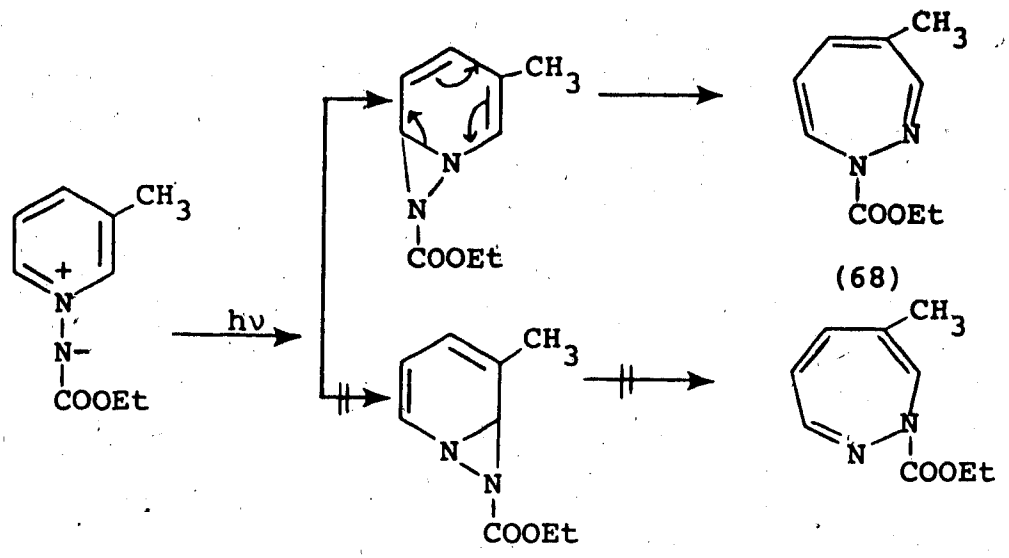
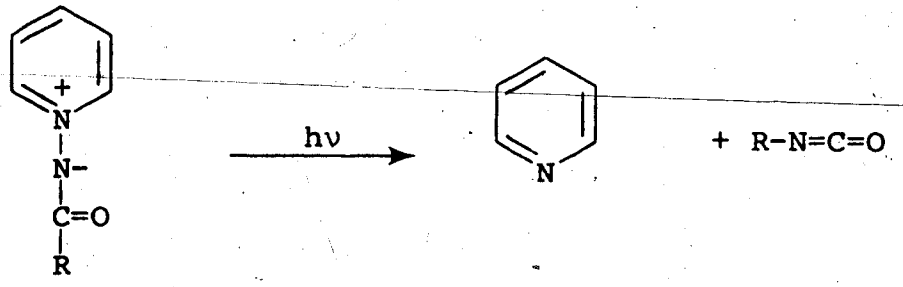


The most prominent side reaction which occurs during the photochemical synthesis of 1,2-diazepines from N-iminopyridinium ylides involves N-N bond cleavage resulting in the formation of pyridine and a nitrene species. N-Acetyliminopyridinium ylide (69) and isopropylcarbonylimino pyridinium ylide (70) in methylene chloride give substantial amounts of pyridine and isocyanates as a result of N-N bond cleavage.[7]

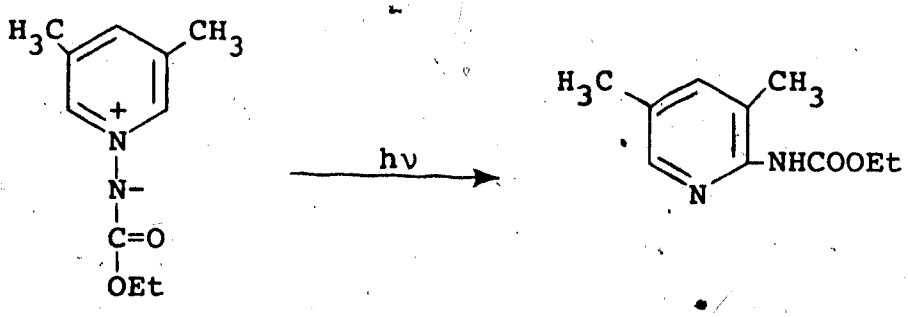


(69), R = $-CH_3$

(70), R = $-CH(CH_3)_2$

On the other hand, irradiation of N-ethoxycarbonylimino-3,5-dimethylpyridinium ylide (71) in methylene

chloride gives an aminopyridine derivative 72 in addition to the expected 1,2-diazepine.[7] Compound 72 is believed



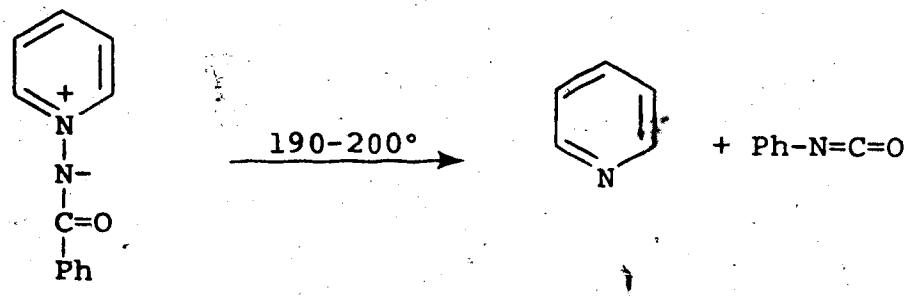
(71) (72)

to arise photochemically via a diaziridine intermediate.

1.3.6.0.0. Thermolysis reactions

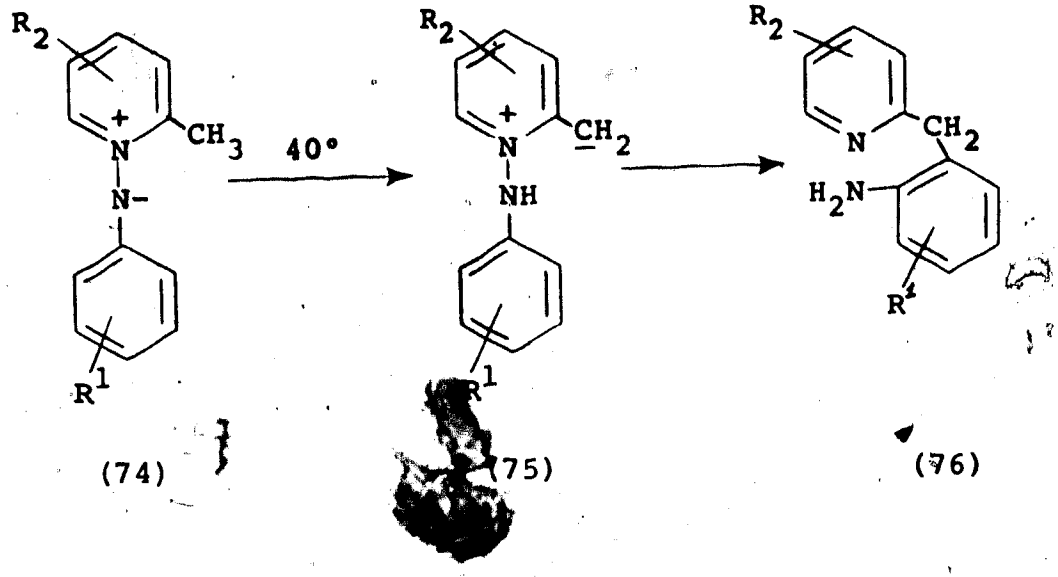
N-Iminopyridinium ylides are generally stable compounds but upon heating above their melting points undergo N-N bond cleavage and rearrangement reactions. The course of the reaction, as during photolysis, is dependent upon the substituents present on the pyridinium ring, the imino nitrogen and the nature of the solvent.[15]

N-Benzoyliminopyridinium ylide (73) upon heating at 190-200° gave pyridine and phenylisocyanate.[15]



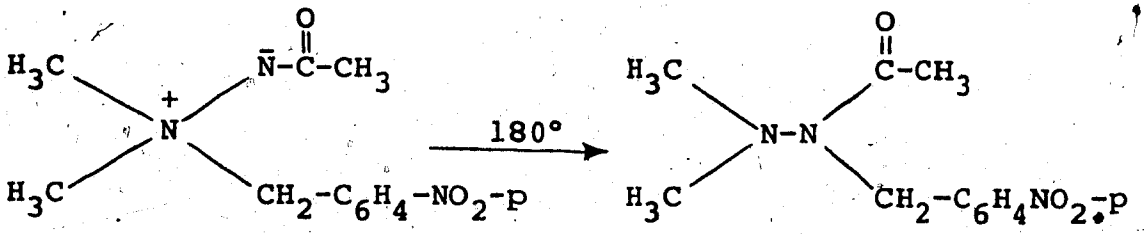
(73)

Rearrangement of N-imino-2-methylpyridinium ylides 74 to 2-benzylpyridine 76 has been reported.[5] The dark blue ylides 74 were transformed into the colourless



2-benzylpyridines 76 by warming to 40° in ethanol. It was observed that electron donating R^1-substitutents and electron withdrawing R^2-substitutents, especially at the 4- and 6-positions of the pyridinium ring accelerate the reaction. The initial step is believed to involve a prototropic shift from carbon to nitrogen, subsequent attack by methyl ylide 75 at the ortho position of the aniline ring and N-N bond cleavage would give rise to 76.

It is of interest to note that N-acetylimino-p-nitrobenzyldimethylammonium ylide (77) undergoes a thermal rearrangement at 180° in a manner similar to the Steven's rearrangement.[22,41]


H3C
N
N-C-CH3
O
H3C
CH2-C6H4-NO2-p
180°
H3C
N-N
C-CH3
O
H3C
CH2-C6H4NO2-p

(77)

1.4.0.0.0. Tetrahydropyridines

Tetrahydropyridines, sometimes referred to as piperidienes, have recently been the subject of several chemical and pharmacological studies.[42,43,44] Although many piperidines have been examined pharmacologically, relatively few tetrahydropyridines have been studied. Those which have received the greatest attention are derivatives of 1,2,5,6-tetrahydropyridine. Many 1,2,5,6-tetrahydropyridines exhibit potent hypotensive activities and some are analgesic agents.[43,44]

1.4.1.0.0. Methods of syntheses

There was no efficient method of synthesis until early 1950 when it was discovered that reduction of N-methylpyridinium iodide derivatives with potassium borohydride produced mainly N-methyl-1,2,5,6-tetrahydropyridine derivatives.[44] Several methods are now available for the synthesis of 1,2,5,6-tetrahydropyridines.

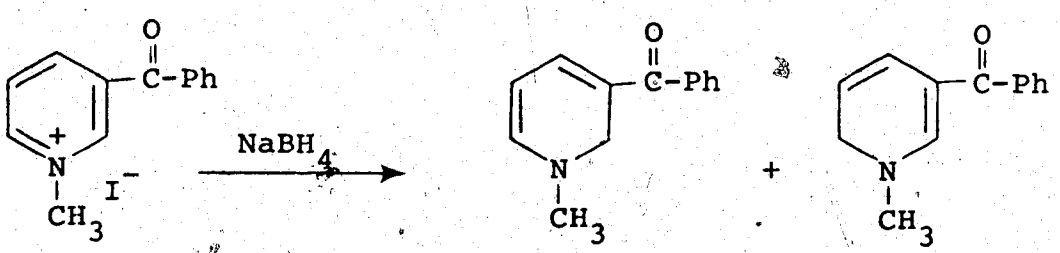
1.4.1.1.0. Preparation by sodium borohydride reduction

Reduction of quaternary pyridinium salts with sodium borohydride in methanol is an efficient synthetic reaction for preparation of 1,2,5,6-tetrahydropyridines.[45] Pyridinium salts have electrophilic centers at the 2-, 4- and 6-positions. Of these the 2- and 6-positions should be the most positive due to their proximity to

the quaternary nitrogen. Thus it was demonstrated that attack by hydride ion, from sodium borohydride or other metal hydrides, occurs predominantly at these two positions.[42]

Extensive studies on the reduction of the pyridinium salts and amines indicate that lithium aluminium hydride is effective for amines and sodium borohydride for amine salts. The former reaction most often affords 1,2- or 1,4-dihydropyridines whereas the latter reaction gives predominantly 1,2,5,6-tetrahydropyridines.[42]

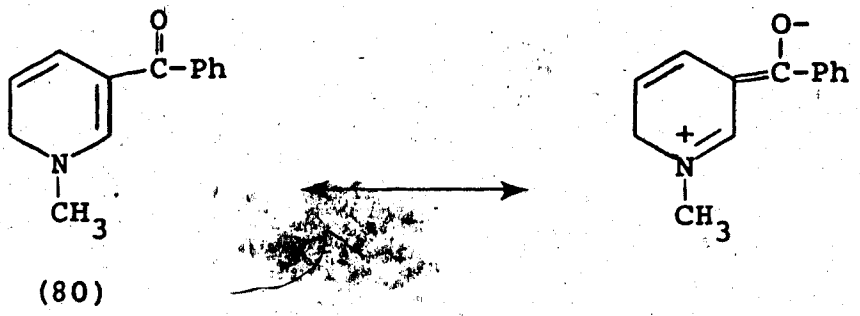
Dihydropyridines 79 and 80, prepared by sodium borohydride reduction of a 1,3-disubstituted pyridinium salt 78, appear to be stable towards further reduction because a number of such compounds have been isolated from reactions containing sufficient borohydride to complete the reduction to the tetrahydro state.[46] Since 1,4-dihydropyridines having 3-substituents which are



(78) (79) (80)

electron withdrawing have also been shown to be stable to borohydride reduction, the intermediate dihydropyridines in the formation of the 1,2,5,6-tetrahydropyridines are evidently dihydropyridines such as 79 and 80.[46]

1,2-Dihydropyridines possessing 3-substituents such as -C-Ph and C≡N are stable toward further reduction since the enamine system is stabilized due to extended conjugation.



(80)

The attack of an electrophile on the dienamine system of the 1,2-dihydropyridines 79 or 80 leads to the formation of an immonium species which on subsequent reduction furnishes the final 1,2,5,6-tetrahydropyridine product. The electrophile which attacks the dienamine system could be a proton from the solvent or borane formed from the sodium borohydride.[42,47] Anderson and Lyle[48] reported that attack by the electrophile (protonation) on the 1,2-dihydropyridine intermediate occurred at the 5-position. It is interesting to note that many 1,2-dihydropyridines have been reported to be stable in non-protic solvents such as diglyme and dimethylformamide until a proton source is added.[46]

The following correlations can be generalized for the sodium borohydride reductions of pyridinium salts.

a) Initial attack by hydride ion will occur

primarily at the 2- or 6-position in the absence of steric effects.

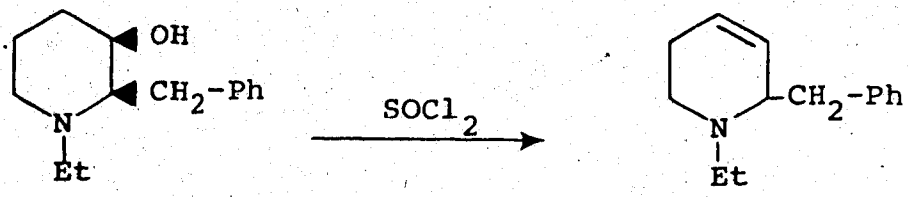
b) The dienamine system thus formed will normally undergo attack by a proton from the solvent at the 5-position.

c) Attack by borohydride ion or a proton are sensitive to steric interactions. If attack at a substituted position does occur it is at a greatly reduced rate.

d) Electron withdrawing substituents at the 3-position tend to stabilize the 1,2-dihydropyridine intermediate. Similarly, reductions effected using a non-protic solvent or a strong base as solvent prevent protonation, allowing one to obtain stable 1,2-dihydropyridines.

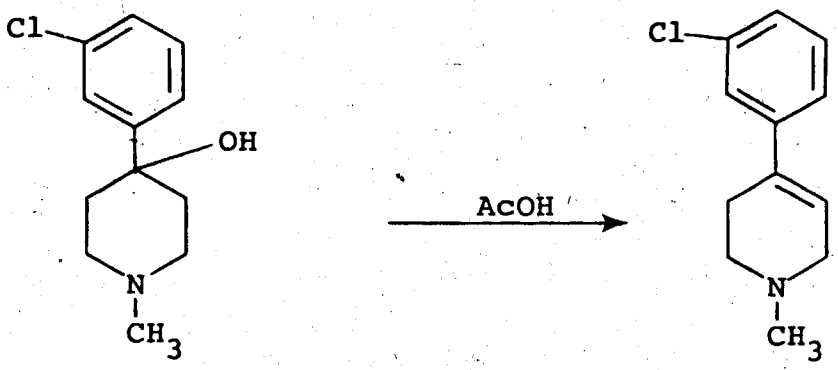
1.4.1.2.0 Preparation from piperidinols

Treatment of *cis*-2-benzyl-1-ethyl-3-piperidinol (81) with thionyl chloride in chloroform gives 2-benzyl-1-ethyl-1,2,5,6-tetrahydropyridine (82) in good yield.[44]



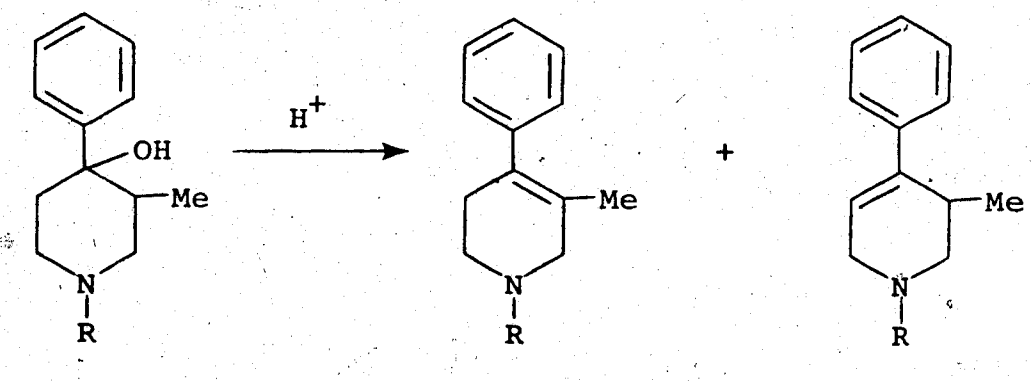
(81) (82)

An alternative method for the preparation of 1,2,5,6-tetrahydropyridines from piperidinols involves treating the latter with acetic acid as shown in the preparation of 4-(*m*-chlorophenyl)-1-methyl-1,2,5,6-tetrahydropyridine (83).[44]



(83)

Casy and his coworkers[49,50] have reported similar studies of the acid catalysed dehydration of 4-aryl-3-methyl-4-piperidinols 84 to the corresponding 1,2,5,6-tetrahydropyridines 85 and 86.



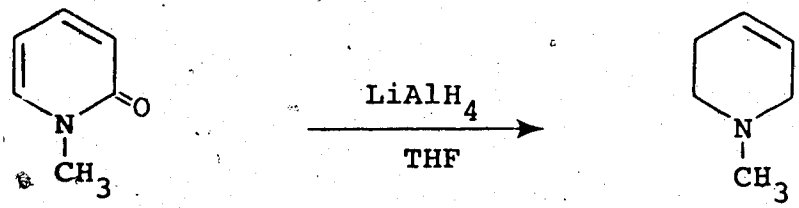
(84) (85) (86)

R = alkyl, phenyl

1.4.1.3.0. Preparation by aluminium hydride or lithium aluminium hydride reduction

In the early 1960's Ferles and his associates[44] reported that reaction of pyridine or methyl pyridines with two moles of aluminium hydride yielded 1,2,5,6-tetrahydropyridines, a reaction which has little practical application. Reduction of quaternary salts of pyridine using aluminium hydride in boiling ether afford similar products.[44]

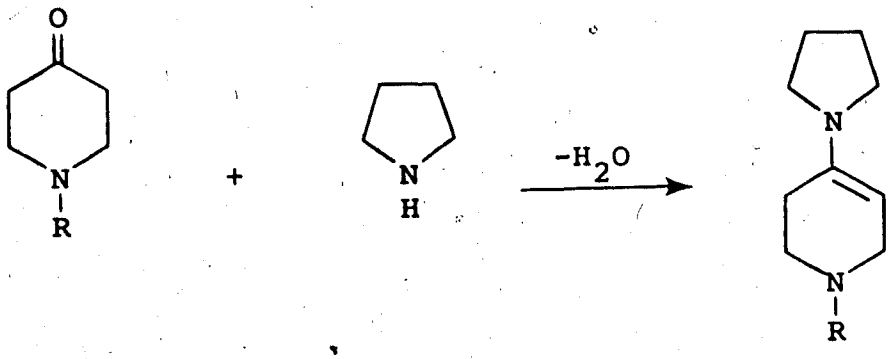
N-methyl-1,2,5,6-tetrahydropyridine (88) was obtained from 1-methyl-2-pyridone (87) using lithium aluminium hydride in tetrahydrofuran.[44]



(87) (88)

1.4.1.4.0. Preparation by amine-ketone condensation

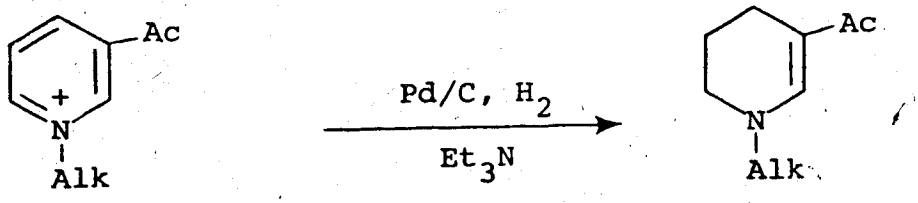
Another synthetic approach employs the reaction of N-substituted-4-piperdones with pyrolidine which gives rise to 1,2,5,6-tetrahydropyridines 89 after loss of a molecule of water.[43,44]



R = alkyl, phenyl (89)

1.4.1.5.0. Preparation by catalytic hydrogenation

A suitable method for the preparation of 1,4,5,6-tetrahydropyridines involves partial catalytic hydrogenation of quaternary pyridinium salts.[44,51] A number of 1-alkyl-3-acyl (3-cyano) pyridinium salts 90 were hydrogenated to 1-alkyl-3-acyl-1,4,5,6-tetrahydropyridines 91 in good yields using palladium on charcoal and hydrogen in the presence of triethylamine.



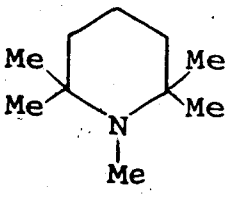
(90) (91)

1.4.2.0.0. Pharmacological activities of tetrahydropyridines

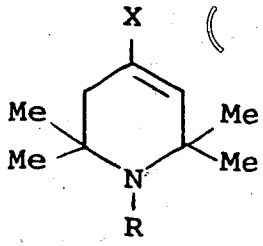
A great number of 1,2,5,6-tetrahydropyridine derivatives exhibit pharmacological activity. Many of these are tetrahydropyridine counterparts of piperidines known to exhibit a pharmacological effect. Although 1,2,5,6-tetrahydropyridines have a broad spectrum of activities their hypotensive and analgesic effects are most prominent. Other activities include muscle relaxant, sedative, antiinflammatory, antipyretic, antitussive, choleretic, diuretic, mydriatic and anthelmintic effects.[43,44]

1.4.2.1.0. Hypotensive agents

Pempidine (1,2,2,6,6-pentamethyl piperidine) (92) is an efficient ganglionic blocking agent and is therefore used to reduce blood pressure.[43] Many derivatives of 1,2,5,6-tetrahydropyridine 93 were evaluated as



(92)



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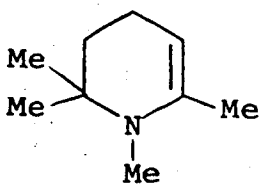


(94)

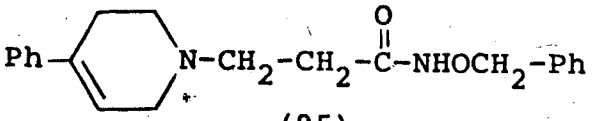
X = H, Me, Et, $-C\equiv CH$, $-(CH_2)_3-N(Me)_2$

R = H, Me, NHMe, NH_2

ganglionic blocking agents. These compounds exhibited

a wide range of activity, some of which were greater than pempidine itself.[43] 1,2,2,6-Tetramethyl-1,2,3,4-tetrahydropyridine (94) is reported to be a short acting ganglionic blocking agent.[43]

Compounds structurally related to 4-phenyl-1,2,5,6-tetrahydropyridinoalkanoic acids 95 are useful in the



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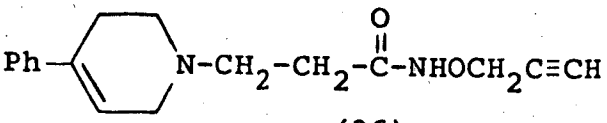
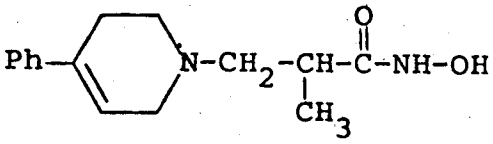


(96)

treatment of hypertention and peripheral vascular diseases.[43,53] The chemically related acetylene derivative 96, however, shows only analgesic activity.[43]

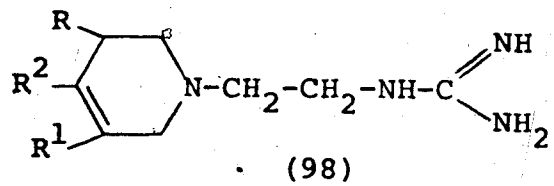
The hydroxamic acid derivative 97 has been studied extensively and was found to exhibit a potent hypotensive effect which is due to its α-adrenergic rather than



(97)

ganglionic blocking action.[43,44]

N-(2-Guanidinoethyl)-1,2,5,6-tetrahydropyridines 98 are described as long acting hypotensive agents and

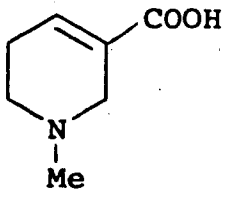


(98)

R, R^1, R^2 = H, lower alkyl

exhibit relatively lower toxicity as compared to their piperidino counterparts.[54,55]

Arecaidine (99) and arecoline (100) are two of the pharmacologically important alkaloidal constituents of the dried ripe seeds of the palm tree *Areca catecha* that have been characterized.[43,44] Arecoline (100) is used



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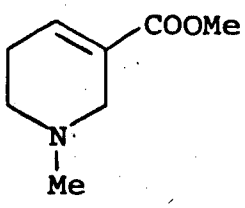


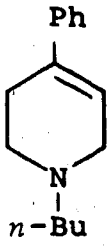
(100)

extensively as an anthelmintic and cathartic in veterinary medicine because of the peristalsis which it induces. It is also reported to exhibit a weak hypotensive effect in cats, and is known to exert parasympathetic activities similar to those of acetylcholine such as tremor, salivation and inhibition of spontaneous activity.[43]

The areca nut has been used for centuries as a constituent of betel which is chewed by the natives in East Africa. Betel has an exciting and intoxicating action which is habit forming. The component of betel responsible for its activity is arecaidine (99).[44]

1.4.2.2.0. Analgesics

1-Butyl-4-phenyl-1,2,5,6-tetrahydropyridine (101) is reported to be a mild analgesic whereas the related



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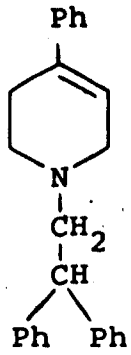
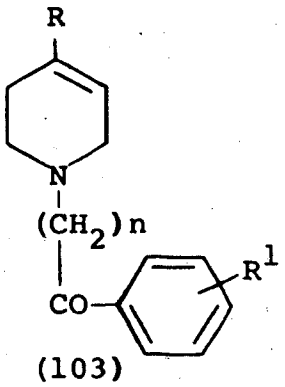


(102)

2,2-diphenyl ethyl derivative 102 exhibits a strong analgesic activity.[43] Many derivatives of 1-aroylalkyl-4-alkyl-1,2,5,6-tetrahydropyridines 103 are useful



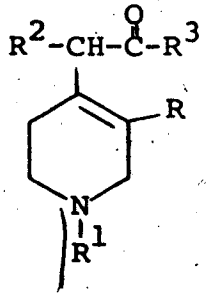
(103)

n = 1-3

R, R^1 = alkyl

analgesics, mydriatics, hypnotics and barbiturate potentiators.[43,56]

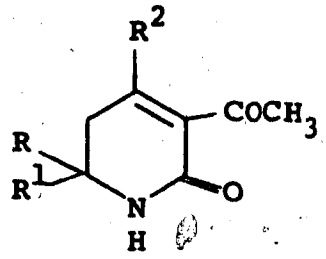
A number of compounds which include amides, ketones and alcohols of the general structure 104 have been shown



(104)

to possess analgesic and cough suppressant activity.[57]

Derivatives of hydrogenated pyridones 105 have been



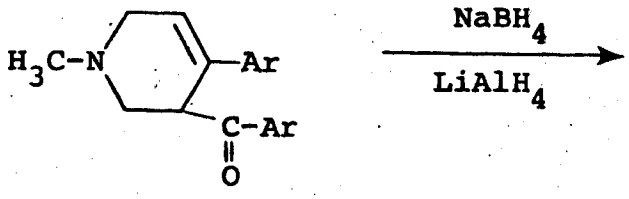
(105)

R, R^1, R^2 = H, lower alkyl, phenyl

reported to possess analgesic and antipyretic activity.[58]

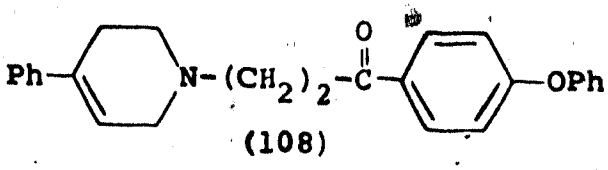
1.4.2.3.0. Miscellaneous activities

Derivatives of 5-benzoyl-1-methyl-4-aryl-1,2,5,6-tetrahydropyridine 106 and their alcohol reduction



(106) (107)

products 107 have been evaluated pharmacologically. The ketones were found to be useful antipyretics and anti-inflammatory agents whereas the alcohols possessed diuretic properties.[59,60] Compounds chemically related to 1-[2-(*p*-phenoxybenzoyl)ethyl]-4-phenyl-1,2,5,6-tetrahydropyridine (108) are claimed to be good muscle relaxants.[44]



(108)

Several 1,2,5,6-tetrahydropyridine derivatives with diversified chemical structures have been found to exhibit choleretic and sedative properties.[43,44]

2.0.0.0.0. OBJECTS OF RESEARCH

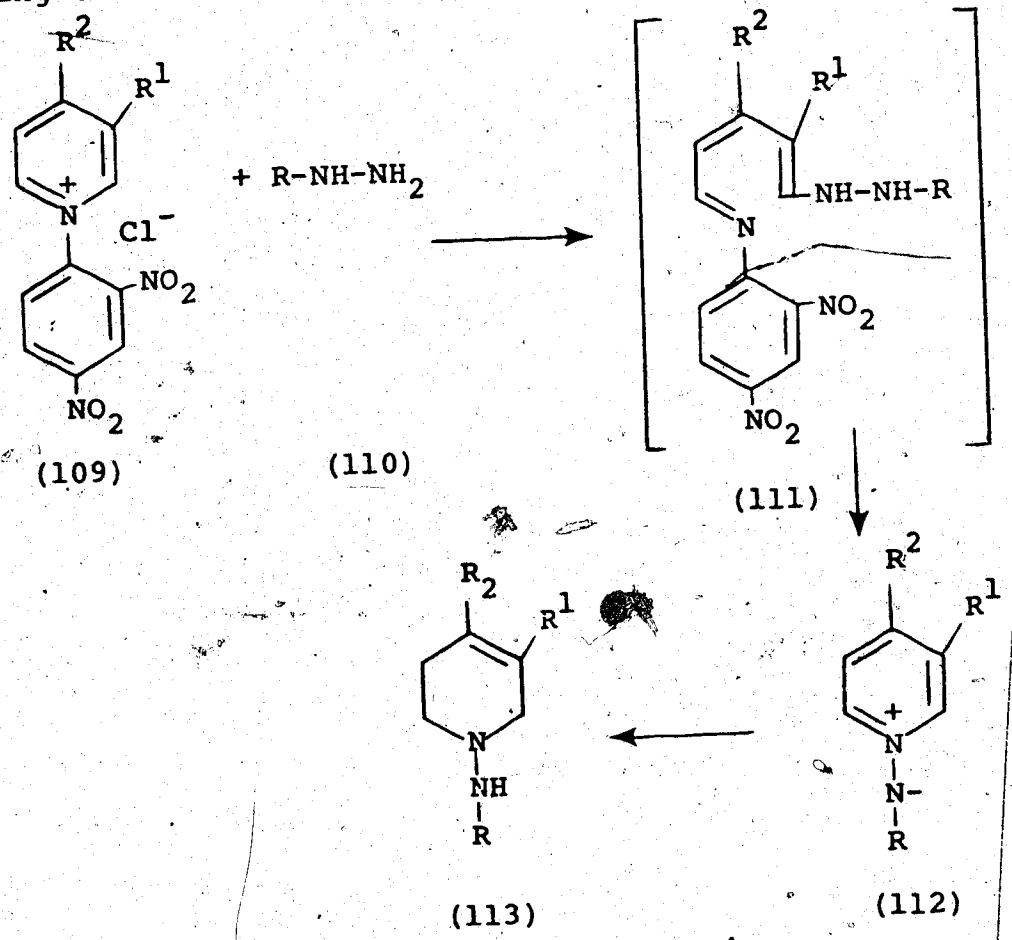
It is well documented that sodium borohydride reduction of quaternary pyridinium salts affords 1,2-(1,4-)dihydropyridine or 1,2,5,6-tetrahydropyridine derivatives.[42] It was of interest therefore, to prepare N-iminopyridinium ylides and to examine their use as precursors for the synthesis of novel N-amino-1,2-(1,4-)dihydropyridyl, 1,2,5,6-tetrahydropyridyl and piperidyl derivatives. Although many piperidines have been evaluated pharmacologically relatively few dihydropyridines and tetrahydropyridines have been examined.[43,44] Those which have received the greatest attention were derivatives of N-alkyl-1,2,5,6-tetrahydropyridines and were found to exhibit analgesic, hypotensive, antiinflammatory and many other activities.[43,59,60] However, the preparation and pharmacological evaluation of N-amino-1,2-(1,4-)-dihydropyridines or their 1,2,5,6-tetrahydropyridine analogs has not been reported. It was therefore of interest to examine the chemistry and pharmacology of this potentially new class of compounds in which the terminal nitrogen of the hydrazine moeity is part of a dihydropyridine, tetrahydropyridine or piperidine ring. The design, synthesis and pharmacological evaluation of a series of structurally related compounds would then allow development of an extensive structure-activity relationship (SAR) study.

There has been a considerable interest in recent years regarding the syntheses and properties of 1,2-(1,4-)-dihydropyridines.[77] This interest stems mainly from the synthetic utility of these systems for the preparation of interesting heterocyclic compounds.[78,79] Although the preparation and the antibacterial activity of N-sulfonylpiperidine derivatives have been studied,[81] the preparation of N-sulfonyl-1,2-dihydropyridines has not been reported. The synthesis of N-benzene (methane) sulfonyl-1,4-dihydropyridine from cyclopentadiene was recently described.[82] Many of the benzenesulfonamides already prepared and tested as antibacterial agents possess five and six-membered heteroaromatic rings as N^1-substituents.[81] It would be of interest, therefore, to develop a one step synthesis of benzenesulfonamides in which the N^1-sulfonamide nitrogen is part of a 1,2-(1,4-)dihydropyridyl ring system.

3.0.0.0.0. DISCUSSION

3.1.0.0.0. Preparation and sodium borohydride reduction of N-iminopyridinium ylides

Novel N-iminopyridinium ylides 112 were prepared by treatment of N-(2,4-dinitrophenyl)pyridinium chlorides 109[12,13,61] with aryl (alkyl) sulfonyl, pyridyl carbonyl, alkyl (phenyl) carbonyl and arylalkyl hydrazines 110 using the method



(109) (110) (111) (113) (112)

reported by Tamura.[13] The sodium borohydride reduction of ylides 112 now provides a convenient route to

TABLE 5

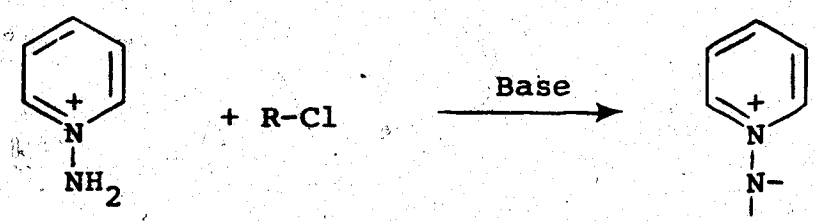
The synthesis of N-iminopyridinium ylides 112 and their reduction to N-amino-1,2,5,6-tetrahydropyridines 113.

R	R^1	R^2	% yield 112	% yield 113
a, $C_6H_5SO_2$-	H	H	85.6	38.9
b, CH_3SO_2-	H	H	3.5	65.0
c, C_6H_5CO-	H	H	45.7	85.5
d, CH_3CO-	H	H	34.4	38.4
e, 4-pyridylcarbonyl-	H	H	50.0	83.6
f, 3-pyridylcarbonyl-	H	H	46.2	80.0
g, 2-pyridylcarbonyl-	H	H	54.7	78.2
h, $C_6H_5CH_2CH_2$-	H	H	35.3	48.7
i, C_6H_5CO-	$-(CH_2)_3-OH$	H	70.0	52.6
j, 4-pyridylcarbonyl	$-(CH_2)_3-OH$	H	48.3	74.9
k, 4-pyridylcarbonyl	H	$-(CH_2)_3-OH$	44.8	66.7
ℓ. 2-pyridylcarbonyl-1-oxide	H	H	21.2	82.6

N-amino-1,2,5,6-tetrahydropyridines 113 as shown in Table 5.[62]

A typical procedure involves the reaction of N-(2,4-dinitrophenyl)pyridinium chloride (109e) with isonicotinic acid hydrazide (110e) in the presence of triethylamine at room temperature for 12 hr to afford the 2,4-dinitroanilino derivative 111 which on heating at reflux in

water-dioxane (1:4 v/v) for 12 hr gives rise to N-(4-pyridylcarbonylimino)pyridinium ylide (112e, 50.0%). Reduction of 112e using sodium borohydride in 95% ethanol at ice-bath temperature for 4 hr furnished N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e, 83.6%). The pyridinium ylides 112a,c,e-ℓ and tetrahydropyridine derivatives 113a,c,e-ℓ were prepared using similar procedures. N-methanesulfonyliminopyridinium ylide (112b) and N-acetyliminopyridinium ylide (112d) were prepared by a modified procedure employing the Schotten-Baumann reaction.[13,30] Thus reaction of N-amino pyridinium iodide[96] with methanesulfonyl and acetyl chloride (or acetic anhydride) afforded 112b and 112d, respectively.

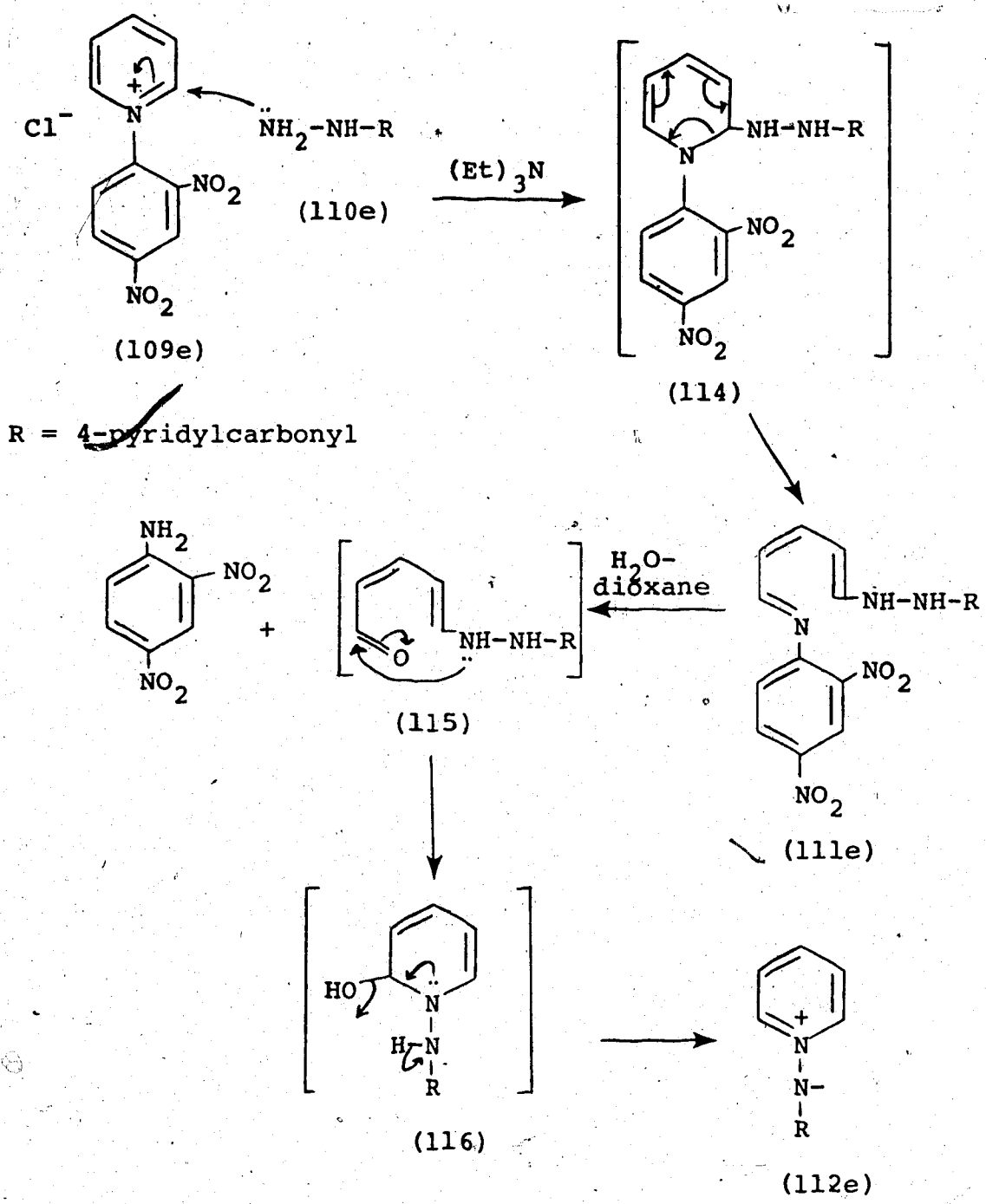


(112)

112b, R = CH_3SO_2-

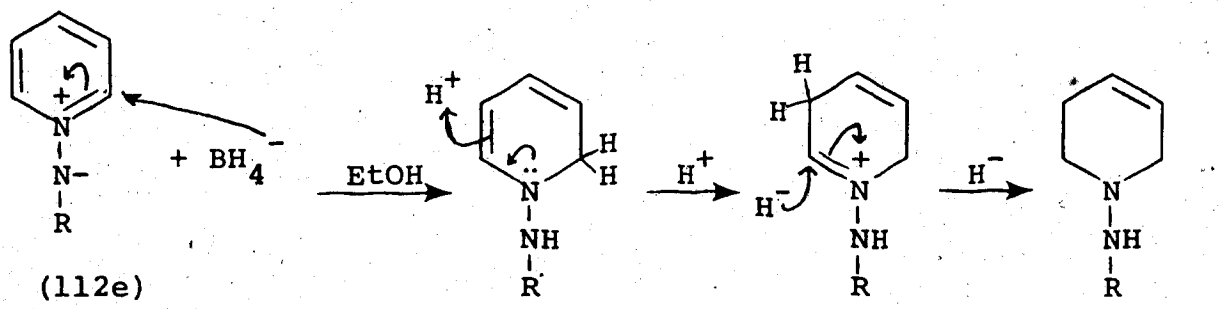
112d, R = CH_3CO-

The mechanism for the formation of N-(pyridylcarbonylimino)pyridinium ylide (112e) is expected to be similar to that reported for the formation of the isoelectronic N-oxides.[4,63] Nucleophilic attack by the free electron


Cl⁻
NH2-NH-R
(110e)
(Et)3N
NO2
NO2
(109e)
R = 4-pyridylcarbonyl
NH-NH-R
(114)
NH2
NO2
NO2
+
H2O-
dioxane
NH-NH-R
O
(115)
NH-NH-R
NO2
NO2
(111e)
HO
N
H
N
R
(116)
N
N-
R
(112e)

pair on the terminal nitrogen of the hydrazine 110e at the 2-position of the Zincke salt 109e would afford the dienamine 114 which can undergo immediate ring opening to the isolable 2,4-dinitro anilino derivative 111. Hydrolysis of the aldimine moiety of 111 using water-dioxane (1:4 v/v) affords the aldehyde derivative 115 and 2,4-dinitroaniline. Cyclization of 115 to the unstable dienamine derivative 116 and elimination of a molecule of water would give rise to the stable N-imino-pyridinium ylide 112e.

The mechanism for the reduction of pyridinium ylide 112e has not been investigated but it is expected to be



(112e) (117) (118) (113e)

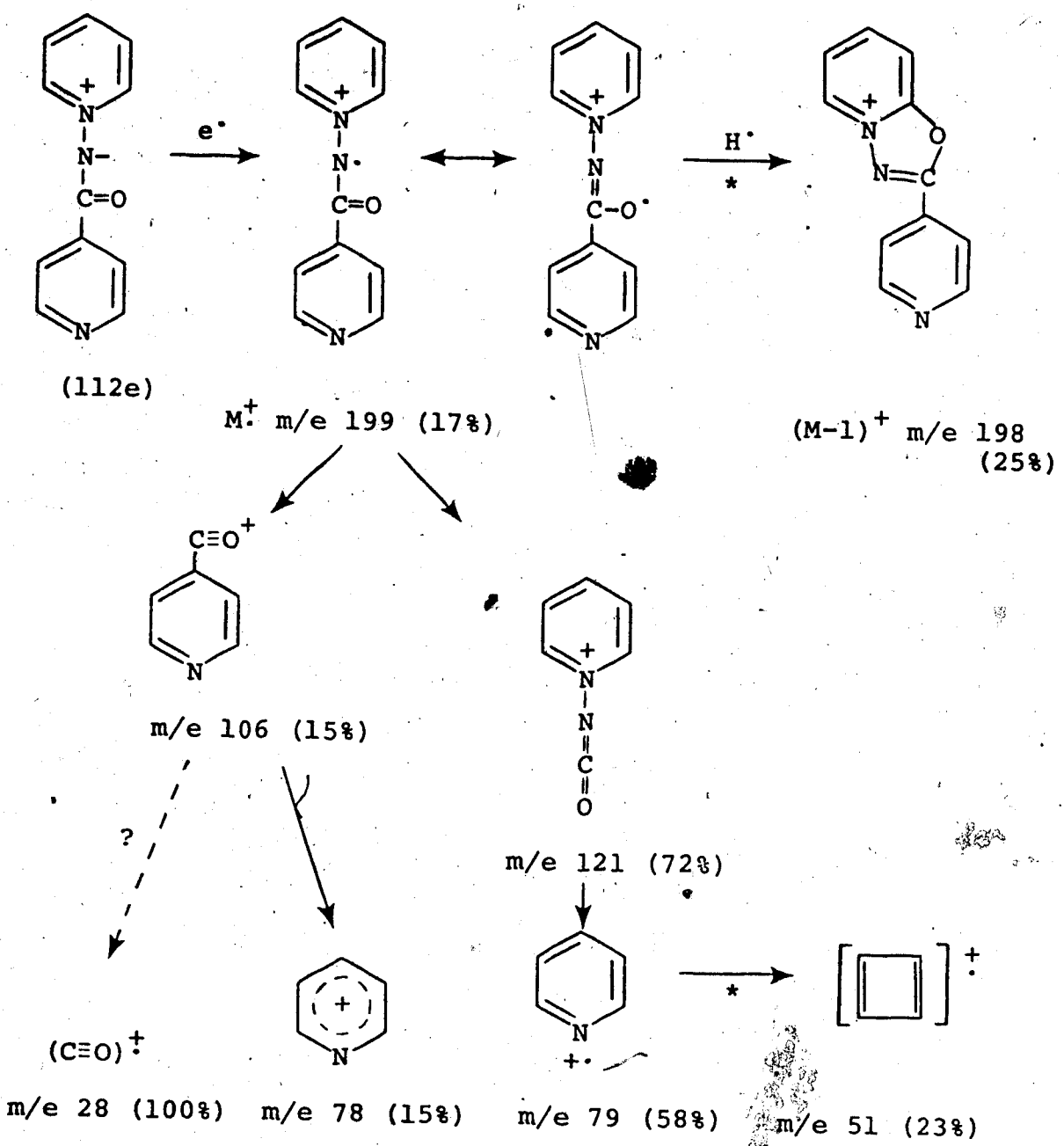
R = 4-pyridylcarbonyl

analogous to that reported for pyridinium salts.[42] Attack by hydride anion at the 2-position of the pyridinium ylide 112e would yield the dienamine 117 which on protonation and subsequent reduction of the imminium species 118 would afford the 1,2,5,6-tetrahydropyridine 113e.

The structure assigned to N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) is consistent with its ir, nmr and mass spectra. The ir spectrum shows the presence of a CO group (1570-1580 cm^{-1}).[15] The nmr spectrum in deuterium oxide exhibited a 4H multiplet at δ 8.83-8.33 due to C_2-H, C_6-H of the pyridinium ring and C_2-H, C_6-H of the pyridine ring, a 5H multiplet at δ 8.33-7.71 assigned to C_3-H, C_4-H, C_5-H of the pyridinium ring and C_3-H, C_5-H of the pyridine ring. The mass spectrum of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) gave a molecular ion (17%) at m/e 199 $(C_{11}H_9N_3O)^{\ddagger}$. The $(M-1)^+$ ion is observed at a slightly higher intensity than the molecular ion and is confirmed by the appearance of a corresponding metastable peak at m/e 197.0.[26] The remainder of the mass spectrum can be explained as illustrated in Scheme I. α-Fragmentation of the molecular ion at m/e 199 affords a fragment ion at m/e 121 $(C_6H_5N_2O)^+$ by loss of a pyridyl radical. The α-cleavage ion (m/e 121) fragments further by elimination of N=C=O to furnish a pyridine ion at m/e 79 $(C_5H_5N)^{\ddagger}$ which on expulsion of hydrogen cyanide would afford a peak at m/e 51 $(C_4H_3)^{\ddagger}$. The loss of hydrogen cyanide is supported by the presence of a metastable peak at m/e 32.9. The major fragmentations described were rationalized by assuming that charge localization occurred on the pyridinium nitrogen. On the other hand, charge retention on the acyl moeity gives

SCHEME I

Mass-spectral fragmentation pattern of N-(4-pyridylcarbonyl-imino)pyridinium ylide (112e)

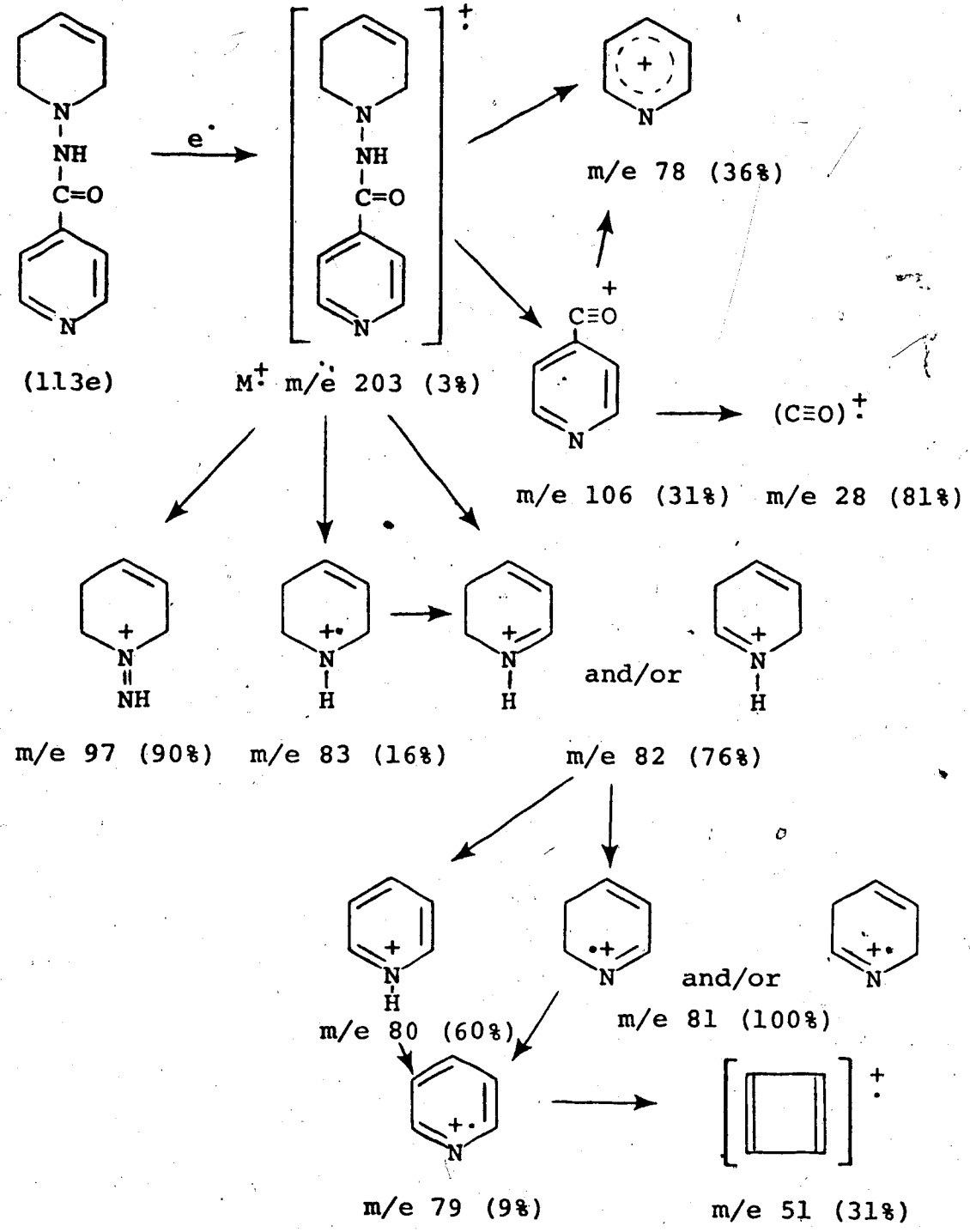


a less intense fragment ion at m/e 106 $(C_6H_4NO)^+$ which fragments further to the base peak at m/e 28 $(CO)^+$ by loss of the pyridyl radical and the pyridyl ion at m/e 78 $(C_5H_4N)^+$ by eliminating CO.[26]

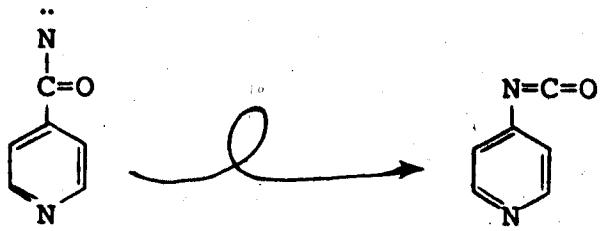
The structure of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) was consistent with its ir, nmr and mass spectra. The ir spectrum revealed the presence of an -NH- at 3240 and a CO group at 1650 cm^{-1}. The nmr spectrum in deuterochloroform exhibited a 1H singlet at δ 8.93 due to the -NH- (disappears after the addition of deuterium oxide), a 2H multiplet at δ 8.66 assigned to the C_2-H, C_6-H of the pyridine ring, a 2H multiplet at δ 7.67 due to the C_3-H, C_5-H of the pyridine ring, a 2H multiplet at δ 5.62 attributed to the C_3-H, C_4-H of the tetrahydropyridine ring, a 2H multiplet at δ 3.65-3.22 due to the C_2-H of the tetrahydropyridine ring, a 2H triplet ($J_{5,6}$ = 5.5 Hz) at δ 3.07 assigned to the C_6-H of the tetrahydropyridine ring and a 2H multiplet at δ 2.48-2.0 due to the C_5-H of the tetrahydropyridine ring. The mass spectrum exhibited a molecular ion at m/e 203 $(C_{11}H_{13}N_3O)^+$. The major fragmentation ions are shown in Scheme II. If the charge is localized on the tetrahydropyridyl ring of the molecular ion m/e 203, a fragment ion with high relative abundance appears at m/e 97 $(C_5H_9N_2)^+$ by loss of 4-pyridylcarbonyl radical. The ion at m/e 83 $(C_5H_9N)^+$ also arises probably

SCHEME II

Mass-spectral fragmentation pattern of N-(4-pyridylcarbonyl-amino)-1,2,5,6-tetrahydropyridine (113e)



from N-N bond cleavage accompanied by hydrogen transfer from the N-amino group to the tetrahydropyridine nitrogen. The species that is expelled could be envisaged as

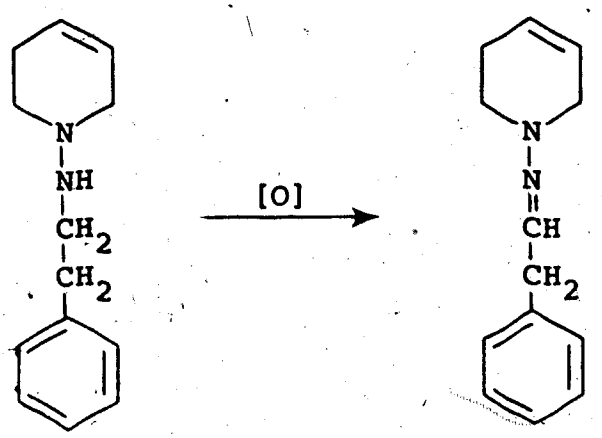


(119) (120)

structure 119 or 120.[26,64] The m/e 83 ion can easily lose a hydrogen atom from the 2- or 6-position to afford a fragment ion at m/e 82 $(C_5H_8N)^+$. Alternatively, ion m/e 82 could also arise directly from the molecular ion by loss of a 4-pyridylcarbonylamino radical followed by simultaneous hydrogen transfer from the 2- or 6-position to nitrogen in the tetrahydropyridine ring.[64] The ion at m/e 82 could then lose a molecule of hydrogen to give a fragment at m/e 80 $(C_5H_6N)^+$ or expel a hydrogen atom to give the most abundant ion m/e 81 $(C_5H_7N)^+$. The pyridine ion at m/e 79 $(C_5H_5N)^+$ which eliminates hydrogen cyanide to furnish ion m/e 51 $(C_4H_3)^+$ can arise either from the fragment at m/e 80 by loss of a hydrogen atom or from m/e 81 by loss of a hydrogen molecule. If the initial charge is localized at the carbonyl or pyridyl moeities of the molecular ion (m/e 203) α-fragmentation furnishes fragment ions at m/e 106 $(C_6H_4NO)^+$ and m/e 78

$(C_5H_4N)^+$. The 4-pyridylcarbonyl ion at m/e 106 further fragments to give an ion at m/e 28 $(CO)^{\cdot+}$ by loss of a pyridyl radical or gives rise to a pyridyl ion at m/e 78 $(C_5H_4N)^+$ by expelling CO.

Phenylethylamino-1,2,5,6-tetrahydropyridine (113h) was found to undergo oxidation readily during purification and on storage to a compound which exhibits spectral data consistent with structure 121. The high resolution

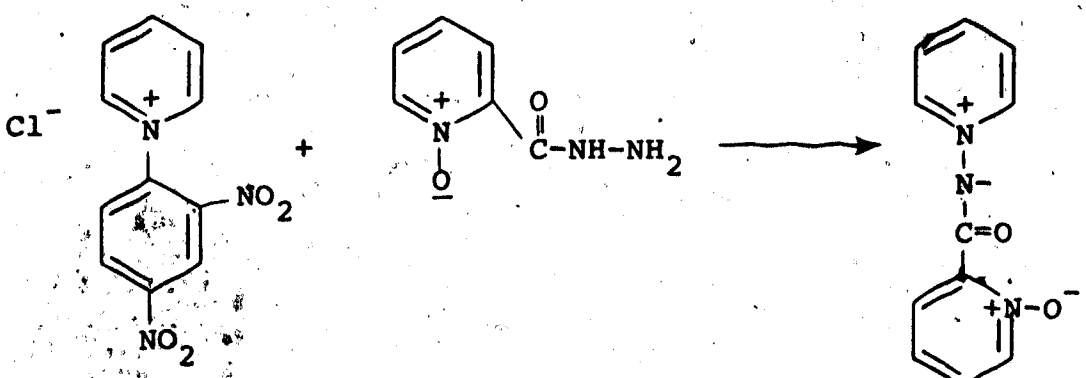


(113h) (121)

mass spectrum exhibited a molecular ion at m/e 200.1316 $(C_{13}H_{16}N_2)^{\cdot+}$; Mass Calcd. for $C_{13}H_{16}N_2$: 200.1314. The nmr spectrum in deuterochloroform showed a 5H multiplet at δ 7.15 due to the phenyl hydrogens, a 1H triplet ($J = CH-CH_2 = 6$ Hz) at δ 6.82 due to -N=CH-, a 2H multiplet at δ 5.68 attributed to C_3-H, C_4-H, a 2H doublet ($J = CH-CH_2 = 6$ Hz) at δ 3.53 due to $-CH_2-$, a 2H multiplet at δ 3.38 assigned to C_2-H, a 2H triplet ($J_{5,6} = 5.5$ Hz) at δ 3.2 due to C_6-H and a 2H multiplet at δ 2.26

attributed to C_5-H. No change on addition of deuterium oxide was observed.

N-(2-Pyridylcarbonylimino-1-oxide)pyridinium ylide (112ℓ) was prepared by treatment of picolinic acid hydrazide-1-oxide (122) with N-(2,4-dinitrophenyl)pyridinium chloride (109ℓ). The hydrazide 122 was obtained from the



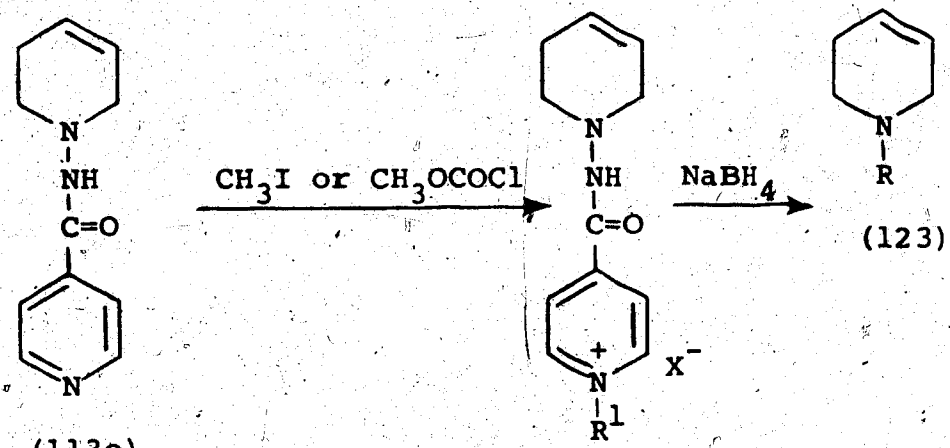
(109ℓ) (122) (112ℓ)

reaction of hydrazine hydrate and methylpicolinate-1-oxide.[65] The structure was consistent with its ir, nmr and mass spectra. The ir spectrum showed the presence of the $\overset{+}{N}\text{-}\overset{-}{O}$ (1250 cm^{-1})[66] and CO (1590 cm^{-1}) groups. The nmr spectrum in deuterated dimethyl sulfoxide exhibited a 1H singlet at δ 12.12 due to the -NH- (disappears after the addition of deuterium oxide), a 2H multiplet at δ 8.7-8.13 assigned to C_4-H, C_6-H, a 2H multiplet at δ 7.86-7.43 due to C_3-H, C_5-H and a 2H singlet at δ 5.0 attributed to the $-NH_2$ (disappears after the addition of deuterium oxide). The high resolution mass spectrum displayed an intense molecular ion at m/e 153.0535

$(C_6H_7N_3O_2)^{+\cdot}$; Mass Calcd. for $C_6H_7N_3O_2$: 153.0538. Aromatic N-oxides can be readily recognized by mass spectrometry since they form abundant fragments arising from the loss of an oxygen atom.[67] The molecular ion at m/e 153 loses an oxygen atom to give $(M-16)^+$ ion at m/e 137 $(C_6H_7N_3O)^{+\cdot}$.

3.1.1.0.0. Quaternization and sodium borohydride reduction of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e)

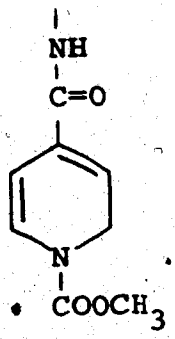
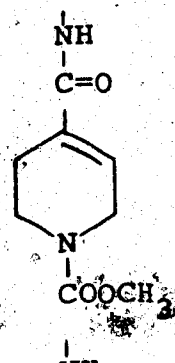
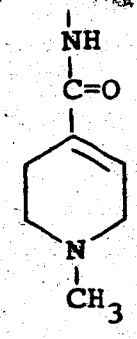
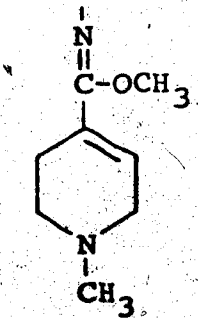
To readily reduce the pyridyl ring of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) it was



necessary to convert 113e to a pyridinium salt derivative. This was achieved by first reacting 113e with methyliodide or methylchloroformate for 30 minutes at -65° followed by the addition of sodium borohydride and allowing the reaction to proceed for an additional 3 hr.[68] Reaction of methylchloroformate with 113e in methanol at

TABLE 6

Sodium borohydride reduction of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) quaternary salts

	R	Solvent	Reaction temp.°C	% Yield 123
a		methanol	-65	70.5
b		ethanol 95%	0	52.7
c		methanol	-65	23.7
d		methanol	-65	17.1

-65° under the specified conditions afforded N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)-carbonylamino]-1,2,5,6-tetrahydropyridine (123a, 70.5%) whereas reaction in ethanol 95% at ice-bath temperature gave N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b, 52.7%).

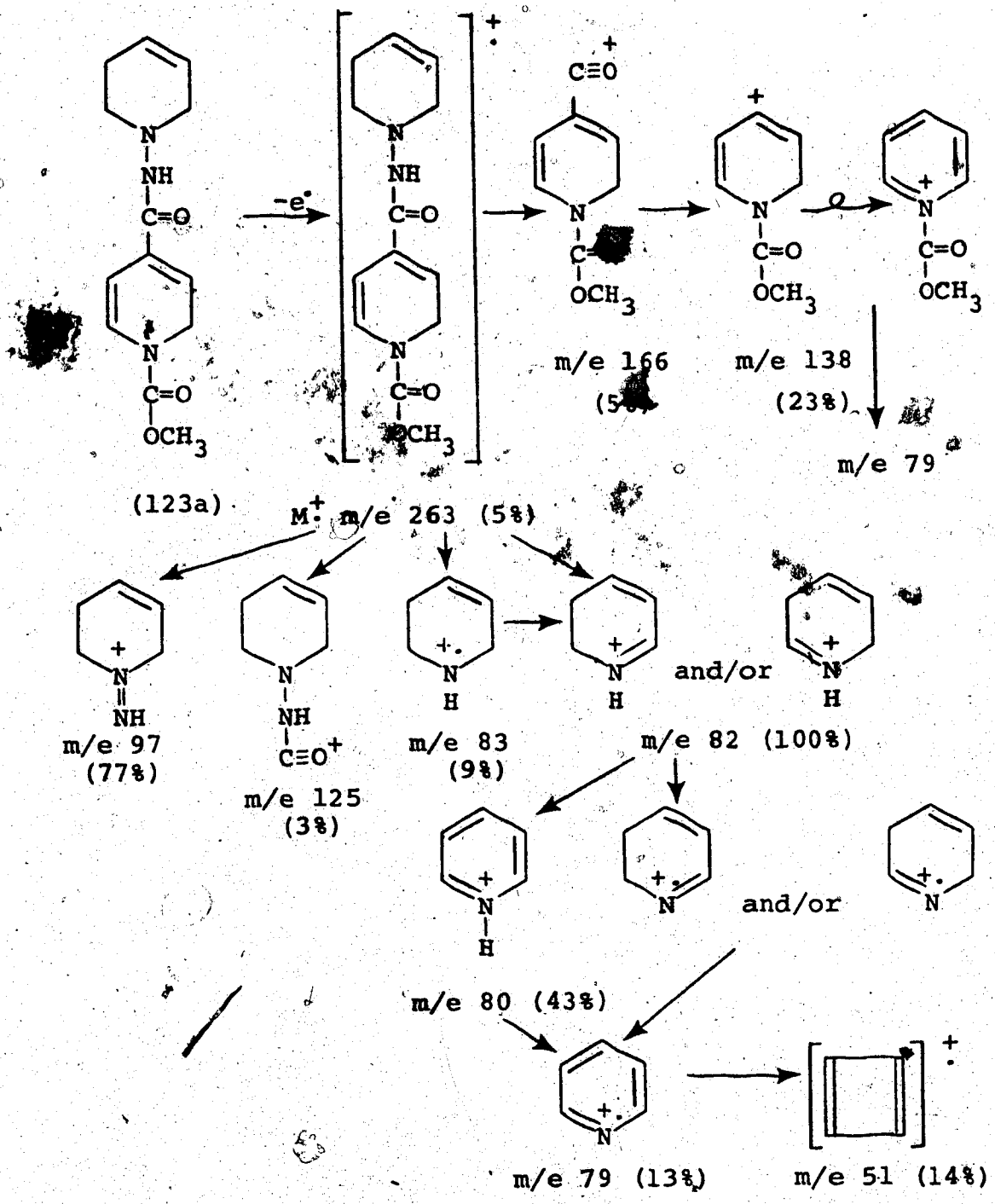
Treatment of 113e with methyl iodide followed by sodium borohydride reduction in methanol at -65° furnished N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123c, 23.7%) and N-[1-(1,2,5,6-tetrahydropyridyl)]-C-methoxy-C-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)]azomethine (123d, 17.1%). The isolation of both 123c and 123d indicates that reaction of 113e with excess methyl iodide must involve methylation at both the pyridine nitrogen and the carbonyl oxygen.

The structures of 123 were assigned on the basis of their ir, nmr and mass spectra. For example, the ir spectrum of N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)-carbonylamino]-1,2,5,6-tetrahydropyridine (123a) revealed the presence of -NH- (3200 cm^{-1}), CO (1710, 1670 cm^{-1}) and $-CH_3$ (1390 cm^{-1}).[66] The nmr spectrum in deuterochloroform exhibited a 1H singlet at δ 7.18 due to the -NH- (disappears after the addition of deuterium oxide), a 1H doublet ($J_{5,6}$ = 8 Hz) at δ 6.84 assigned to the C_6-H of the dihydropyridine ring, a 1H octet ($J_{2,3}$ = 5 Hz; $J_{2',3}$ = 5 Hz; $J_{3,5}$ = 2 Hz) at δ 6.20 due to the C_3-H

of the dihydropyridine ring, a 2H multiplet at δ 6.0-5.61 attributed to the C_3-H, C_4-H of the tetrahydropyridine ring, a 1H quartet ($J_{5,6}$ = 8 Hz; $J_{3,5}$ = 2 Hz) at δ 5.45 due to the C_5-H of the dihydropyridine ring, a 2H doublet ($J_{2,3}$ = 5 Hz) at δ 4.51 assigned to the C_2-H of the dihydropyridine ring, a 3H singlet at δ 3.80 attributed to the $-CH_3$, a 2H multiplet at δ 3.58-3.32 due to the C_2-H of the tetrahydropyridine ring, a 2H triplet ($J_{5,6}$ = 6 Hz) at δ 3.08 due to the C_6-H of the tetrahydropyridine ring and a 2H multiplet at δ 2.52-2.08 assigned to the C_5-H of the tetrahydropyridine ring. The mass spectrum exhibited a molecular ion at m/e 263 $(C_{13}H_{17}N_3O_3)^{+\cdot}$. The major fragment ion species are summarized in Scheme III. The mass of all fragment ions were confirmed by high resolution mass measurements. If the charge is localized on the tetrahydropyridine ring of the molecular ion at m/e 263, a fragment ion at m/e 97 $(C_5H_9N_2)^+$ appears after elimination of a 1-methoxycarbonyl-1,2-dihydropyridyl-4-carbonyl radical. Alternatively, if the initial charge is localized at the 1-methoxycarbonyl-1,2,-dihydropyridyl-4-carbonyl moeity of the molecular ion at m/e 263, α-fragmentation affords two fragment ions at m/e 125 $(C_6H_9N_2O)^+$ and m/e 166 $(C_8H_8NO_3)^+$ by loss of 1-methoxy-1,2-dihydropyridyl radical and N-amino-1,2,5,6-tetrahydropyridyl radical, respectively. The ion at m/e 166 can expel CO to give rise to the stabilized ion

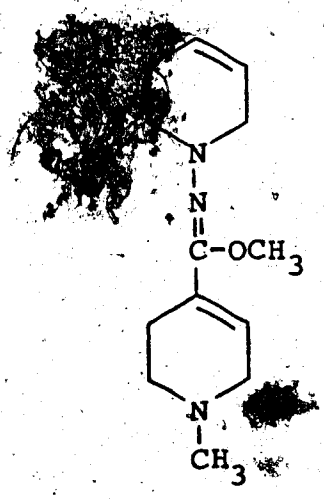
SCHEME III

Mass spectral fragmentation pattern of N-[4-(1-methoxy-carbonyl-1,2-dihydropyridyl)carbonylamino]-1,2,5,6-tetra-hydropyridine (123a)



at m/e 138 $(C_7H_8NO_2)^+$ which may itself lose a methoxycarbonyl radical to furnish a pyridine ion at m/e 79 $(C_5H_5N)^+$. The ion at m/e 83 $(C_5H_9N)^+$ probably arises from N-N bond cleavage of the molecular ion at m/e 263 accompanied by hydrogen transfer from the N-amino group to the tetrahydropyridine ring nitrogen.[26,64] The fragmentation patterns of the ions at m/e 82 $(C_5H_8N)^+$, m/e 81 $(C_5H_7N)^+$, m/e 80 $(C_5H_6N)^+$, m/e 79 $(C_5H_5N)^+$ and m/e 51 $(C_4H_3)^+$ are described in Scheme II.

The structure of 123d was consistent with its ir,

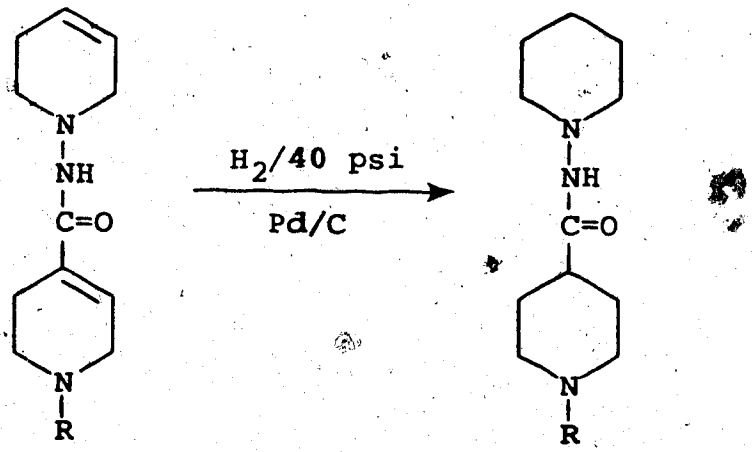


(123d)

nmr and mass spectra. The ir spectrum showed the presence of $-CH_3$ (1390 cm^{-1}) and -N=C (1655 cm^{-1}).[66] The nmr spectrum in deuterochloroform exhibited a 1H multiplet at δ 6.55 due to the C_3-H of the N-methyltetrahydropyridine, a 2H multiplet at δ 6.2-5.5 assigned to the C_3-H, C_4-H of the N-iminotetrahydropyridine, a 2H multiplet at δ 4.5-4.1 due to the C_2-H of the N-iminotetrahydropyridine, a 2H multiplet at δ 4.10-3.65 attributed to the C_2-H of the

N-methyltetrahydropyridine, a 3H singlet at δ 3.52 due to the $-OC\underline{H}_3$, a 2H triplet ($J_{5,6}$ = 5 Hz) at δ 3.11 due to the C_6-H of the N-iminotetrahydropyridine, a 6H multiplet at δ 2.78-2.28 attributed to the C_5-H of the N-iminotetrahydropyridine, C_5-H, C_6-H of the N-methyltetrahydropyridine, a 3H singlet at δ 2.39 due to the $-N-C\underline{H}_3$. The high resolution mass spectrum exhibited a molecular ion at m/e 235.1685 $(C_{13}H_{21}N_3O)^+$.; Mass Calcd. for $C_{13}H_{21}N_3O$: 235.1684.

Catalytic hydrogenation of N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b) and N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123c) in methanol for 12 hr afforded N-(1-methoxycarbonyl-piperidyl-4-carbonylamino)piperidine (124, 98%) and



123b, 124 R = $-COOCH_3$

123c, 125 R = $-CH_3$

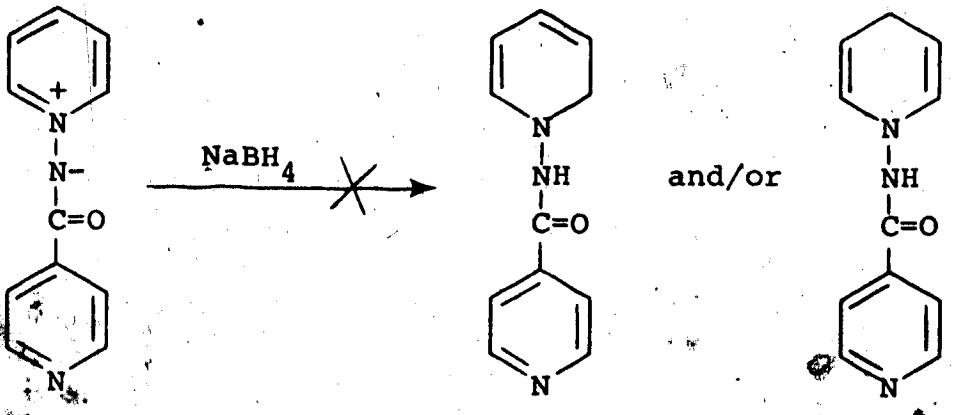
N-(1-methylpiperidyl-4-carbonylamino)piperidine (125, 97.6%), respectively. The ir, nmr, and mass spectra of 124 and 125 were consistent with the assigned structures.

3.1.2.0.0. Attempted reduction of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) to the 1,2-(1,4-)-dihydropyridine derivatives

Several attempts to reduce N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) to the desired 1,2-(1,4-)dihydropyridine analogs in various solvent systems were not successful. Similarly, reduction with tetrabutylammonium borohydride[69,70] in non-protic solvents was also unsuccessful. In those reactions where reduction did occur 1,2,5,6-tetrahydropyridine derivatives were isolated.

3.1.2.1.0. Reduction of N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) using sodium borohydride

The sodium borohydride reduction of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) employing the two phase solvent systems reported by Kutney and his coworkers[69b] at ice-bath temperature for three hours failed to give the expected 1,2-(1,4-)dihydropyridine derivatives 126 and/or 127 since the starting material 112e was recovered. The use of a two phase solvent system such as 10 ml of distilled water, 10 ml of methanol, 20 ml of 5% sodium hydroxide solution and 20 ml of ether was conceived



(112e) (126) (127)

to provide an organic solvent for the soluble 1,2-(1,4-)-dihydropyridines as soon as they are formed leaving behind the unreacted water soluble ylide 112e in the aqueous phase. The sodium hydroxide solution was used to prevent the protonation of the dihydropyridine system. The different solvent systems examined and the results obtained are summarized in Table 7. The starting material was recovered in all reactions except 1,2,5,6-tetrahydropyridine derivative 113e (20%) was obtained when 80 ml of 95% ethanol with 20 ml of 40% sodium borohydride solution was used as the solvent.

TABLE 7

Sodium borohydride reduction of N-(4-pyridylcarbonylimino)-pyrdinium ylide (112e) in various solvent systems

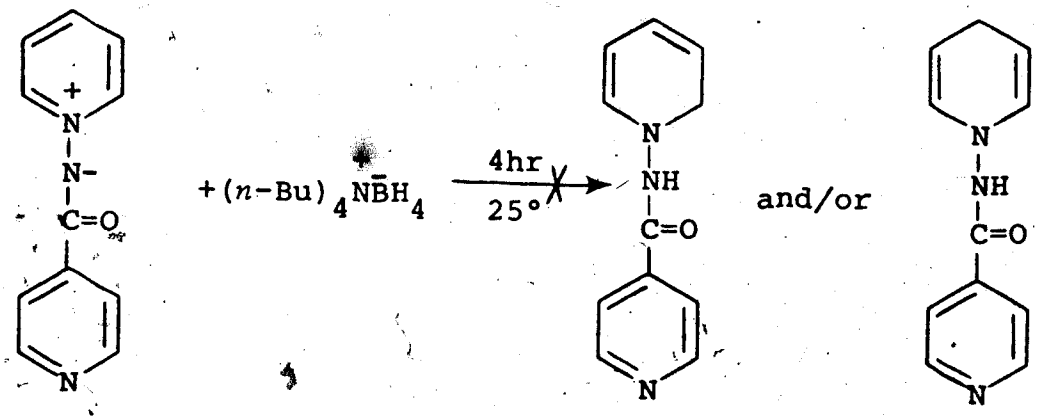
Reaction conditions and products	Reactions 1	2	3	4	5	6	7	8
Water (ml)	10	10	10	20	10	-	-	-
Methanol (ml)	10	-	-	-	10	-	-	-
Ethanol 95% (ml)	-	-	-	-	-	-	80	-
Ether (ml)	20	20	-	-	40	-	-	-
Chloroform (ml)	-	-	40	-	-	-	-	-
Sodium hydroxide sol'n (ml)	20,5%	20,5%	20,5%	-	20,10%	80,10%	20,40%	-
Sodium bicarbonate sol'n (ml)	-	-	-	20, Saturated	-	-	-	-
Dry tetrahydrofuran (ml)	-	-	-	-	-	-	-	60
Reaction temperature °C	0	0	0-25	0	0	25	0	0
Reaction time (hr)	3	3	3	4	1	2	3	3
Product(s)	a	a	a	a	a	a	b	a

[a] No reaction took place, the starting material 112e was isolated.

[b] 1,2,5,6-tetrahydropyridine derivative 113e was obtained (20%).

3.1.2.2.0. Reduction of N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) using tetrabutylammonium borohydride (128)

Tetrabutylammonium borohydride (128) has been reported as a versatile reducing agent in aprotic solvents such as benzene, hexane and ether where the use of sodium borohydride is limited because of its low solubility.[69,70] Tetrabutylammonium borohydride (128) has been used as a mild and selective reagent for the reduction of aldehydes, ketones, alkylhalides and acylhalides.[70,71,72] It is prepared by the reaction of sodium borohydride and tetrabutylammonium chloride.[71] Reduction of N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) using tetrabutylammonium borohydride (128) in aprotic solvents for 4 hr at room temperature was investigated with the expectation of preparing N-amino-1,2-(1,4-)dihydropyridine derivatives 126 and 127. For example, reaction under these conditions using dry



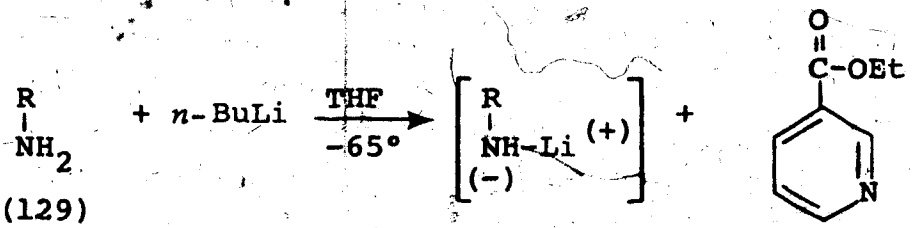
(112e) (128) (126) (127)

pyridine as solvent afforded N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e, 2%) and the unreacted ylide 112e (80%). The formation of the tetrahydropyridine 113e could be due to the presence of small amounts of moisture which would act as a proton source. When dry pyridine or dry tetrahydrofuran containing one equivalent of water was employed as solvent, the same results were obtained. Similarly, use of dry tetrahydrofuran or dry dimethylformamide as solvent resulted in high recovery (85%) of the starting material and traces of the tetrahydropyridine 113e whereas reaction in dry methylene chloride led to the recovery of only the starting material.

On the other hand, the use of ethanol 95% as a reaction solvent resulted in complete reduction of 112e to N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e, 68%). Since the formation of 1,2,5,6-tetrahydropyridines proceed *via* the intermediate formation of the corresponding 1,2-dihydropyridines,[42] these findings suggest that the 1,2-dihydropyridine intermediate 126 could be a very unstable species which either reverts back to the ylide or undergoes protonation and reduction to the 1,2,5,6-tetrahydropyridine analog.

3.2.0.0.0. Reduction of alkyl(aryl)hydrazine derivatives with alkyl nicotinates and acyl chlorides

The reaction of hydrazines with alkyl esters was investigated as a method of synthesizing a series of compounds structurally related to the N-amino-1,2,5,6-tetrahydropyridines 113. No reaction occurred when N-aminopiperidine (129a) and ethyl nicotinate (130) were refluxed for 12 hr in methylene chloride or absolute ethanol. However, when the nucleophilicity of 129a was increased by base catalysed proton abstraction[73,74,75] from the N-amino group to generate the nitrogen anion, the reaction proceeded readily at room temperature. Thus treatment of 129a with *n*-butyllithium in tetrahydrofuran at -65°C under an atmosphere of nitrogen followed



(129) (130) (131)

a, R = piperidyl-

b, R = morpholinyl-

c, R = homopiperidyl-

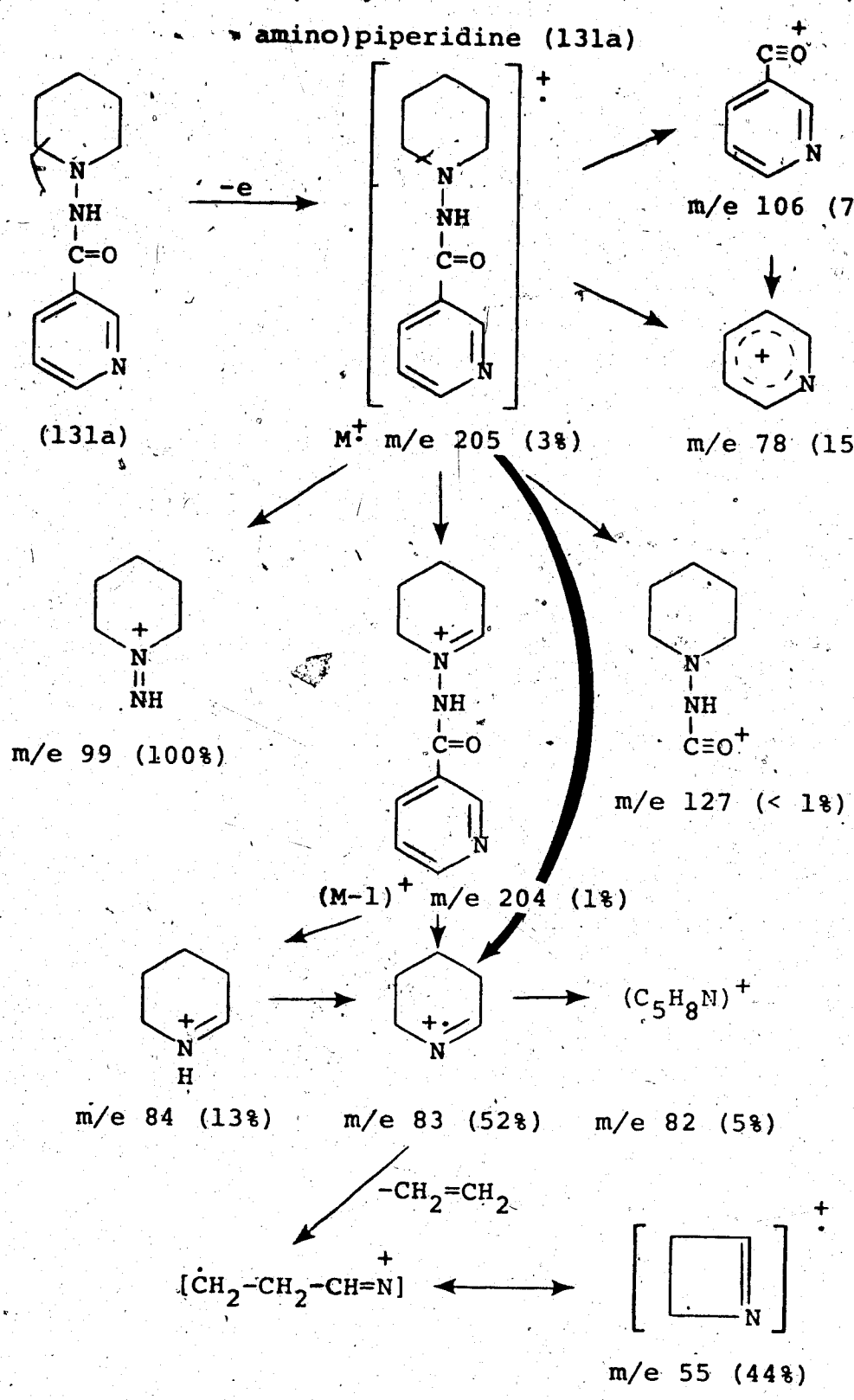
d, R = dimethylamino-

by addition of dry ethylnicotinate (130) afforded N-(3-pyridylcarbonylamino)piperidine (131a, 40.3%). The structurally related compounds 131b-131d were synthesized employing similar procedures.

The structures of 131 were consistent with their ir, nmr and mass spectra. For example, the ir spectrum of N-(3-pyridylcarbonylamino)piperidine (131a) revealed the presence of -NH- (3200 cm^{-1}) and CO (1660-1640 cm^{-1}). The nmr spectrum in deuterated dimethylsulfoxide showed a 1H singlet at δ 9.53 due to the -NH- (disappears after the addition of deuterium oxide), a 1H doublet ($J_{2,4}$ = 2 Hz) at δ 8.93 assigned to the C_2-H of the pyridine ring, a 1H quartet ($J_{5,6}$ = 5 Hz; $J_{4,6}$ = 2 Hz) at δ 8.68 due to the C_6-H of the pyridine ring, a 1H quartet ($J_{4,5}$ = 8 Hz; $J_{4,6}$ = 2 Hz) at δ 8.13 attributed to the C_4-H of the pyridine ring, a 1H quartet ($J_{4,5}$ = 8 Hz; $J_{5,6}$ = 5 Hz) at δ 7.48 due to the C_5-H of the pyridine ring, a 4H multiplet at δ 3.06-2.68 assigned to the C_2-H, C_6-H of the piperidine ring, a 6H multiplet at δ 1.85-1.18 due to the C_3-H, C_4-H, C_5-H of the piperidine ring. The mass spectrum exhibited a molecular ion at m/e 205 $(C_{11}H_{15}N_3O)^{+\cdot}$. The other major fragment ions are shown in Scheme IV. If the initial charge is localized on the piperidyl nitrogen of the molecular ion at m/e 205 α-fragmentation would give an abundant fragment ion at m/e 99 $(C_5H_{11}N_2)^+$ by loss of a 3-pyridylcarbonyl radical. A less intense peak would appear at

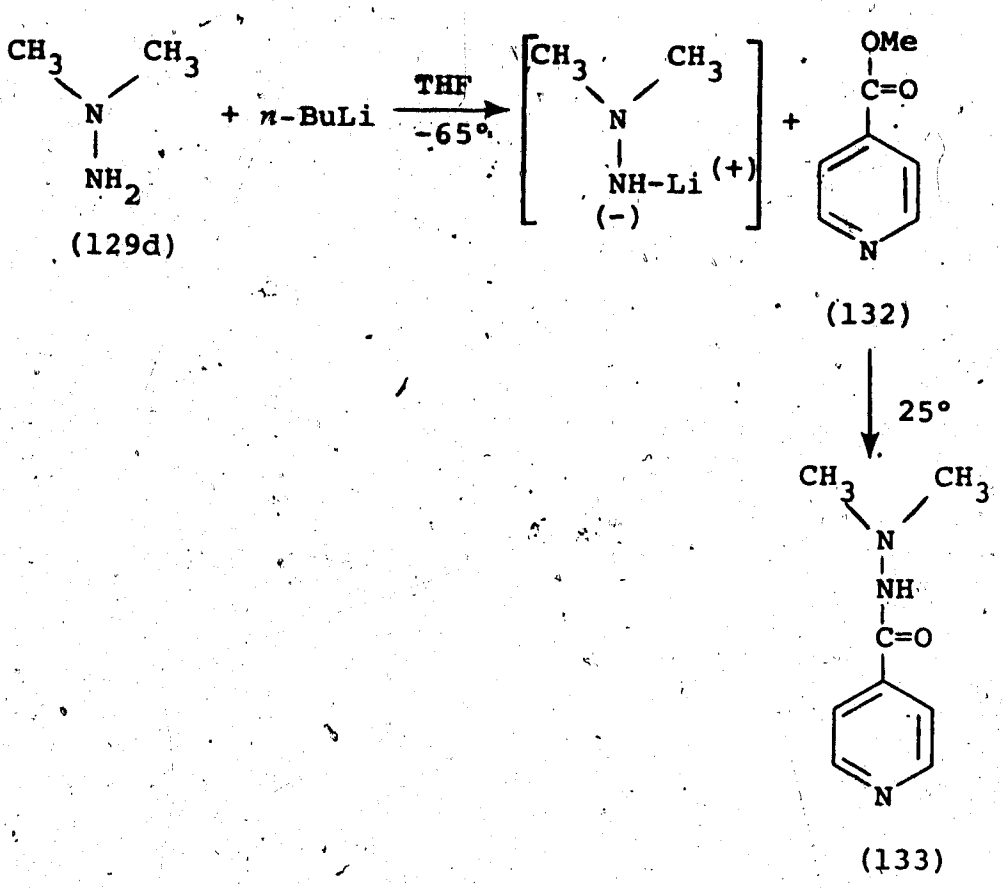
SCHEME IV

Mass spectral fragmentation pattern of N-(3-pyridylcarbonyl-amino)piperidine (131a)



m/e 106 $(C_6H_4NO)^+$ if the initial charge is localized at the 3-pyridylcarbonyl moeity of the molecular ion m/e 205 which could expel CO to afford another fragment ion at m/e 78 $(C_5H_4NO)^+$. The ion at m/e 78 can also arise directly from the molecular ion at m/e 205 by expelling a N-carbonylaminopiperidyl radical. The $(M-1)^+$ ion at m/e 204 $(C_{11}H_{14}N_3O)^+$ which appears at a very low intensity can give rise to an ion at m/e 84 $(C_4H_{10}N)^+$ as a result of N-N bond cleavage accompanied by hydrogen transfer from the N-amino group to the piperidine nitrogen.[26,64] It is also conceivable that the fragment ion at m/e 84 can also arise from the molecular ion at m/e 205 by simultaneous expulsion of 3-pyridylcarbonylamino radical and hydrogen transfer from the 2-position to the nitrogen of the piperidine ring.[64] The fragment ion at m/e 83 $(C_5H_9N)^+$ could arise either from the $(M-1)^+$ ion by loss of 3-pyridylcarbonylamino radical or from the ion at m/e 84 by expulsion of hydrogen. The ion at m/e 83 could lose hydrogen to give an ion at m/e 82 $(C_5H_8N)^+$, or may eliminate ethylene to afford an abundant ion at m/e 55 $(C_3H_5N)^+$. The expected fragment ion at m/e 127 $(C_6H_9N_2O)^+$ appears in low relative abundance (< 1%).

Similarly, reaction of 1,1-dimethylhydrazine (129d) with *n*-butyllithium in tetrahydrofuran at -65°C followed by the addition of methylisonicotinate (132) affords N-N-dimethylisonicotinic acid hydrazide (133, 6%).

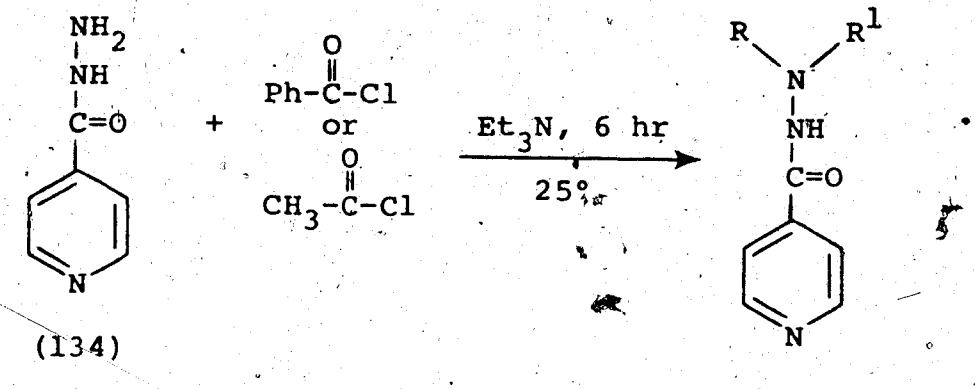


(129d)

(132)

(133)

In a related one step synthetic reaction employing the Schotten-Baumann reaction,[1,13] reaction of isonicotinic



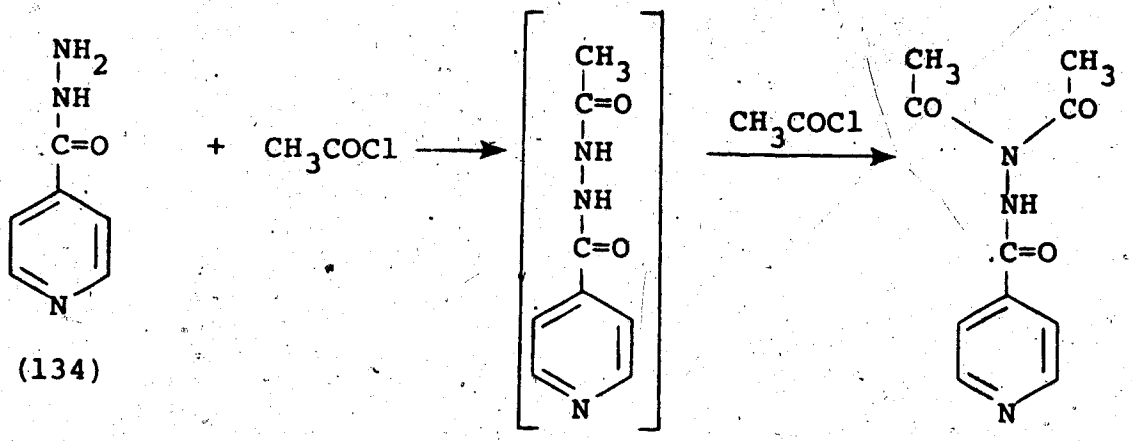
(134)

(135)

a, R = PhCO-; R^1 = H

b, R = R^1 = CH_3CO-

acid hydrazide (134) with benzoyl chloride or acetyl-chloride in dry tetrahydrofuran gives rise to 1-benzoyl-2-(4-pyridylcarbonyl)hydrazine (135a, 6.5%) or 1,1-diacetyl-2-(4-pyridylcarbonyl)hydrazine (135b, 9.3%), respectively. The nucleophilic displacement of the chloride ion from acetyl chloride by the hydrazine 134 does not stop at the monoacetyl derivative 136 but



(134) (136) (135b)

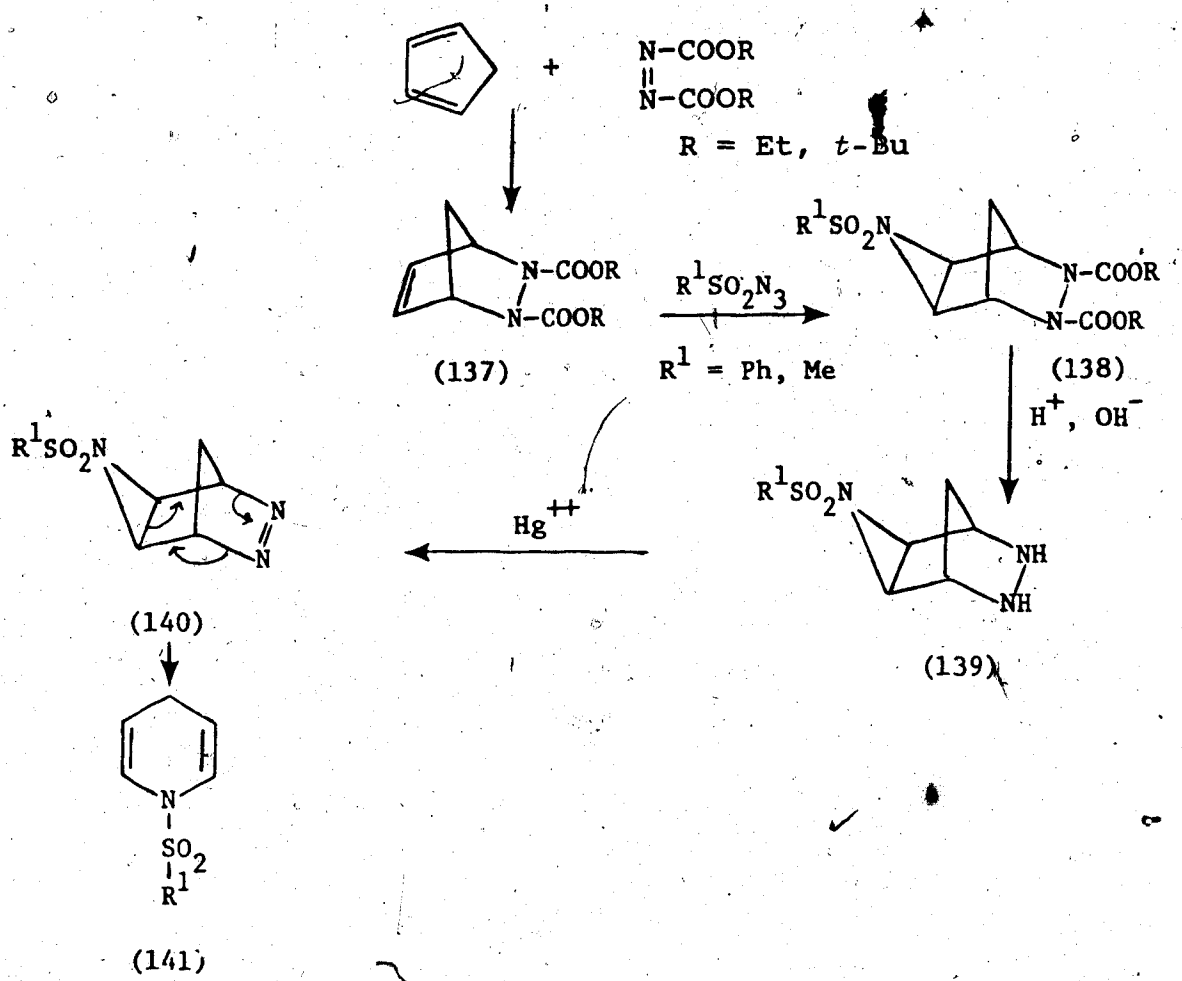
reacts further to give the diacetyl derivative 135b. The structures assigned to 135 were consistent with their ir, nmr and mass spectra.

3.3.0.0.0. The sodium borohydride reduction of N-sulfonyl-pyridinium salts. Synthesis of N-sulfonyl-1,2-(1,4-)dihydropyridines.[76]

There has been a considerable interest in recent years regarding the synthesis and properties of 1,2-(1,4-)-dihydropyridines.[77] This interest was due to the synthetic utility of these systems in preparing various heterocyclic

compounds.[78,79] In addition, the 1,4-dihydropyridine ring system is of biological importance since it is present in the reduced forms of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH).[77,80]

Although the preparation and antibacterial activity of some N-sulfonylpiperidine derivatives have been studied,[81] the preparation of N-sulfonyl-1,2-dihydropyridines has not been reported. The synthesis of N-benzene (methane) sulfonyl-1,4-dihydropyridine from cyclopentadiene was recently described.[82] This procedure involves the cycloaddition reaction of alkyl or phenyl



sulfonyl azides to 2,3-diazabicycloheptenes 137 which affords the aziridino adduct 138. Acid or base hydrolysis of 138 followed by oxidation of the hydrazino derivative 139 produces the tricyclic azo compound 140 which spontaneously fragments in a retro Diels-Alder reaction to give N-benzene (methane) sulfonyl-1,4-dihydropyridine.[82,83]

Many of the benzenesulfonamides already prepared and tested as antibacterial agents possess five and six-membered heteroaromatic rings as N^1-substituents.[81] It would be of interest, therefore, to develop a one step synthesis of benzenesulfonamides in which the N^1-sulfonamide nitrogen is part of a 1,2-(1,4-)dihydropyridyl ring system. The sulfonyl group stabilizes the dihydropyridine structure making them more resistant to air oxidation than simple N-alkyl derivatives. Because of the resonance interaction of the lone pair of electrons on nitrogen with the sulfonyl group, the carbon-carbon double bond of these dihydropyridines have little enamine character.[68]

Treatment of a mixture of pyridine and sodium borohydride with alkyl (aryl) sulfonyl chlorides or sulfonic acid anhydrides, using a modification of the procedure reported by Fowler[68] for the preparation of N-methoxycarbonyl-1,2-dihydropyridine, now provides a convenient route to N-sulfonyl-1,4-dihydropyridines 141 and

N-sulfonyl-1,2-dihydropyridine 142.

(141) (142)

a, R = Me-

b, R = Ph-

c, R = *p*-Me-C_6H_4-

d, R = *p*-MeCONH-C_6H_4-

Reaction of pyridine with methanesulfonyl chloride in methanol at -65°C in the presence of sodium borohydride afforded N-methanesulfonyl-1,2-dihydropyridine (142a, 32.1%) as the sole product. A similar reaction employing methanesulfonic anhydride[84] gave 142a (37.2%). On the other hand, reaction with benzene sulfonyl chloride using the same conditions, gave rise to an isomeric mixture of 141b and 142b in a ratio of 1:8 as determined from the integrals of the H-4 and H-2 absorptions at δ 2.68 and 4.16 for the respective compounds. This ratio was determined for the unpurified reaction product since 1,2-dihydropyridines 142 undergo considerable decomposition upon purification. The reaction of benzenesulfonyl chloride with pyridine (both solvent and reactant) in the presence of sodium borohydride at 25°C

was investigated to determine if the isomeric product ratio 141:142 was dependent upon solvent and temperature. Reaction under these conditions gave rise to an isomeric mixture of 141b and 142b in a ratio of 5:4. The results of similar reactions employing benzene sulfonic anhydride are shown in Table 8. The reaction of *p*-toluenesulfonyl chloride with pyridine (both solvent and reactant) at 25°C in the presence of sodium borohydride yielded an isomeric mixture of 141c and 142c in a ratio of 1:1.

Structure-activity studies of benzenesulfonamides have shown that a N^4-amino group or a group such as N^4-acetamido group which can undergo metabolic biotransformation to a N^4-amino group *in vivo* is required for antibacterial activity.[85] It was, therefore, of interest to investigate this reaction employing N-acetylsulfanilyl chloride. Reaction with pyridine using methanol as solvent at -65°C did not occur probably due to the low solubility of N-acetylsulfanilyl chloride. When the reaction was carried out using pyridine as solvent at 25°C an isomeric mixture of 141d and 142d in a ratio of 2:1 was obtained. The presence of both 141d and 142d was substantiated further since catalytic reduction with palladium-charcoal and hydrogen gave N-(*p*-acetamidobenzenesulfonyl)piperidine (143) as a single product which was identical with the product obtained from the reaction of piperidine and N-acetylsulfanilyl chloride.[86]

TABLE 8

Isomeric product ratios of 1,4- and 1,2-dihydropyridines

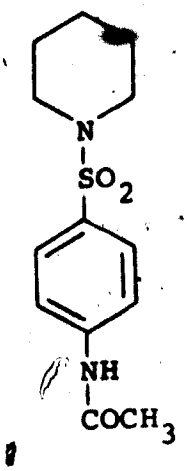
Product Mixture	Reactant	Solvent	Reaction temp.(C°)	Reaction time(h)	Ratio 141:142[a]	Ratio 141:142	Yield 141(%)	Yield 142(%)
141b and 142b	$PhSO_2Cl$	MeOH	-65	1.5	1:8	1.8:5.8[b]	1.8[b,d]	5.8[b,d]
141b and 142b	$PhSO_2Cl$	C_5H_5N	25	15	5:4	12:5[c]	17[c,d]	7.1[c,d]
141b and 142b	$(PhSO_2)_2O$	MeOH	-65	1.5	4:29	1:5[c]	6.7[c,d]	33.6[c,d]
141b and 142b	$(PhSO_2)_2O$	C_5H_5N	25	15	7.5:4	3.4:1[c]	23.7[c,d]	7.0[c,d]
141c and 142c	*p*-Me-C_6H_4-SO_2Cl	C_5H_5N	25	15	1:1	7:5[b]	7.7[b]	6.3[b]
141d and 142d	*p*-MeCONH-$C_6H_4SO_2Cl$	C_5H_5N	25	15	2:1	4:1[c]	16.7[c]	4.2[c]

[a] Determined from the integrals of the C_4-H and C_2-H of 141 and 142, respectively, for the unpurified reaction mixture.

[b] Determined from percentage yields of purified isolated products 141 and 142.,

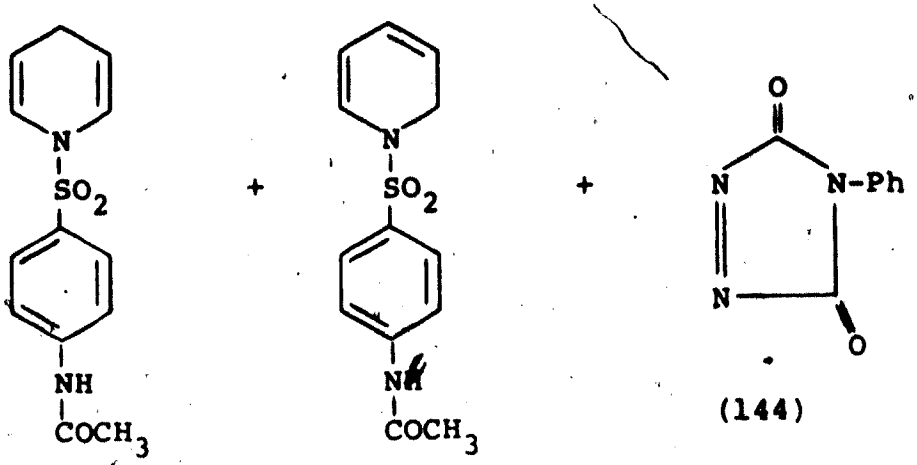
[c] Determined from the integrals of the C_4-H and C_2-H for a purified mixture of 141 and 142, respectively, eluted from a neutral alumina column.

[d] There is a considerable loss of both 141 and 142 during column purification since only 40-60% of 141 and 25-40% of 142 is recovered.

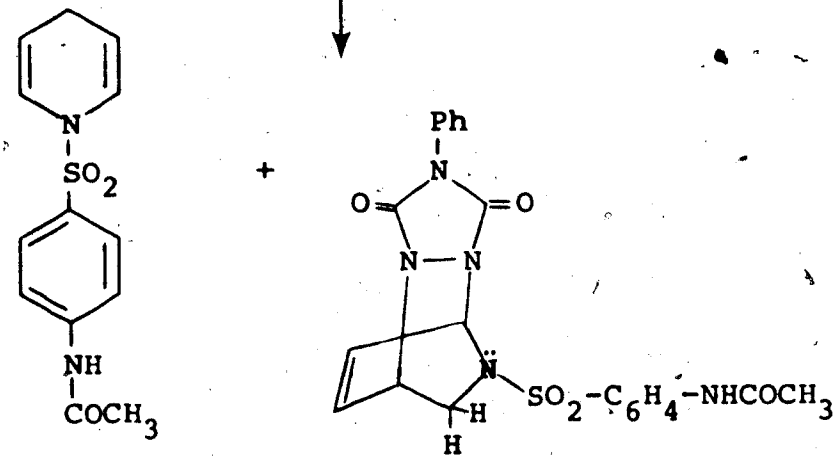


(143)

A successful separation of 141d and 142d could not be achieved using column or thin layer chromatography. However, pure 141d could be obtained by treating a mixture of 141d and 142d with 4-phenyl-1,2,4-triazoline-3,5-dione (144).[87] The 1,2-dihydro isomer 142d reacts readily *via* a($\pi^2 + \pi^4$) cycloaddition reaction with 144 to give 5-*endo*-*p*-acetylsulfanilyl-2,3,5-triazabicyclo-[2.2.2.]oct-7-ene-2,3-*endo*-dicarboxylic acid N-phenyl-imide (145) which is consistent with the reported reaction of 142b with 144.[88] Compounds 141d and 145 are readily separated by preparative thin layer chromatography. Both acidic and alkaline hydrolysis of the N^4-acetamido group of 141d to liberate the free amine gave rise to intractable tar even though acidic hydrolysis of the N^4-acetamido group of 143 proceeds smoothly.[89]



(141d) (142d) (144)



(141d) (145)

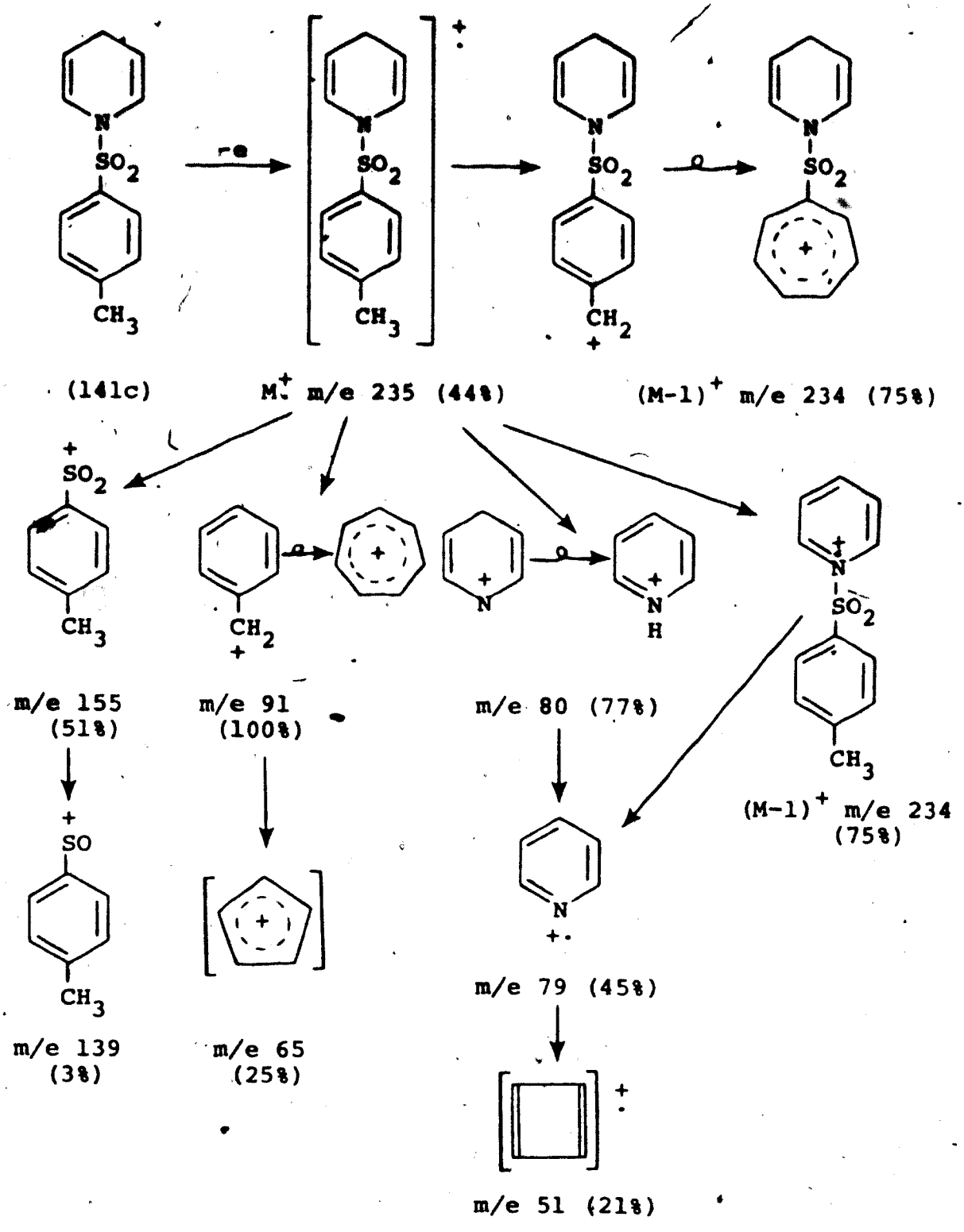
The reduction of N-sulfonylpyridinium salts appears to be dependent upon solvent and temperature. Attack by a hydride anion occurs predominantly or exclusively at the 2-position to give N-sulfonyl-1,2-dihydropyridines 142 using methanol as solvent at -65°C whereas attack at the 4-position is usually favoured slightly when pyridine is employed as solvent at 25°C as shown in

Table 8.

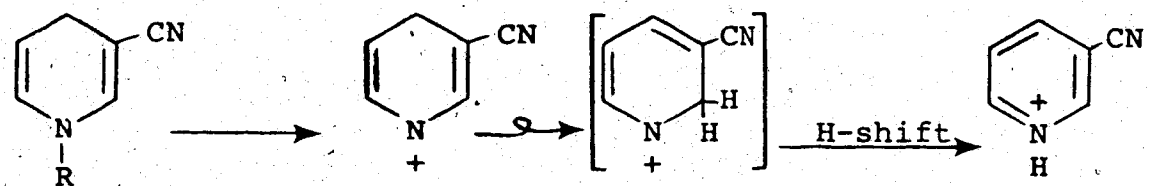
The structures of 1,2-(1,4-)dihydropyridine derivatives 141 and 142 were consistent with their ir, nmr and mass spectra. The ir spectrum of N-(*p*-toluenesulfonyl)-1,4-dihydropyridine (141c) revealed the presence of a $-SO_2-$ group (1345, 1170 cm^{-1}). The nmr spectrum in deuterochloroform showed a 2H doublet (J = 8 Hz) at δ 7.68 due to the *ortho*-phenylhydrogens, a 2H doublet (J = 8 Hz) at δ 7.38 due to the *meta*-phenylhydrogens, a 2H quartet ($J_{2,3} = J_{5,6} = 8.5$ Hz; $J_{2,4} = J_{4,6} = 1.5$ Hz) at δ 6.44 assigned to the C_2-H, C_6-H, a 2H multiplet ($J_{2,3} = J_{5,6} = 8.5$ Hz) at δ 4.86 due to the C_3-H, C_5-H, a 2H multiplet at δ 2.7 attributed to the C_4-H and a 3H singlet at δ 2.42 due to the $-CH_3$. Most N-alkyl or N-aryl 1,2-(1,4-)dihydropyridines exhibit well defined fragmentation processes in the mass spectrometer and these transformations can be rationalized on the basis of well established principles.[90,91,92] However, the fragmentation of N-sulfonyl-1,2-(1,4-)dihydropyridines has not been reported. The mass spectrum of N-(*p*-toluenesulfonyl)-1,4-dihydropyridine (141c) gave an abundant molecular ion at m/e 235 $(C_{12}H_{13}NO_2S)^{+\cdot}$ and an even more abundant $(M-1)^+$ ion at m/e 234 $(C_{12}H_{12}NO_2S)^+$ which may be due to the formation of both the benzylium ion derivative[64] and the N-(*p*-toluenesulfonyl)pyridinium ion.[90] The fragmentation pattern of 141c is shown in Scheme V. The base peak was the tropilium ion at m/e 91

SCHEME V

Mass spectral fragmentation pattern of N-(*p*-toluenesulfonyl)-1,4-dihydropyridine (141c)



$(C_7H_7)^+$ which can easily arise from the molecular ion at m/e 235 by loss of a 1-sulfonyldihydropyridyl radical.[90] The benzylium ion at m/e 91 expels acetylene[64] to give a fragment ion at m/e 65 $(C_5H_5)^+$. The molecular ion at m/e 235 loses a 1,4-dihydropyridyl radical to give the fragment ion at m/e 155 $(C_7H_7O_2S)^+$ which in turn eliminates an oxygen atom to furnish the fragment ion at m/e 139 $(C_7H_7OS)^+$. On the other hand, the molecular ion at m/e 235 gives rise to the fragment ion at m/e 80 $(C_5H_6N)^+$ by expelling a *p*-toluenesulfonyl radical. Wang and Thornton[91] reported the possible formation of ion 146 from fragmentation of N-alkyl-1,4-dihydropyridine



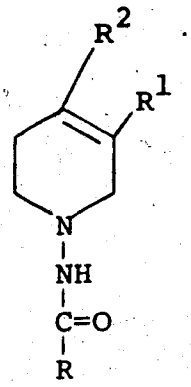
(147) (146) (148)

R = alkyl > Me

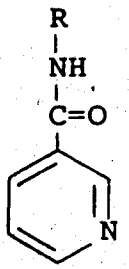
derivatives 147 which may rearrange by a H-shift to form the stable 3-cyano pyridinium ion (148). The ion at m/e 80 could arise in a similar manner. The pyridine ion at m/e 79 $(C_5H_5N)^+$ which affords the ion at m/e 51 $(C_4H_3)^+$ can arise either from the ion at m/e 80 by loss of a hydrogen or from the ion at m/e 234 by expelling a *p*-toluenesulfonyl radical. The mass of all fragment ions was consistent with their accurate mass measurements.

4.0.0.0.0. SOME *in vivo* PHARMACOLOGICAL TESTING RESULTS

A series of selected N-carbonylamino-1,2,5,6-tetrahydropyridines 113 and the structurally related 3-pyridyl carbonylhydrazine derivatives 131 were subjected to broad spectrum pharmacological screening which was carried



(113)



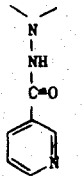
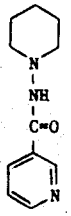
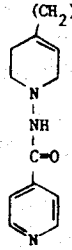
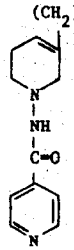
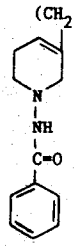
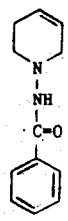
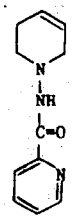
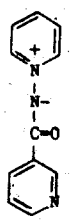
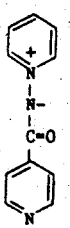
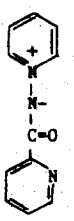
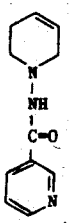
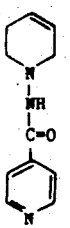
(131)

out under a "Screening Program for New Drug Type Discoveries" under an agreement between Canadian Patents and Development Limited (CPDL) and Bio-Research Laboratories Limited. A schedule describing the complete details of the primary screening program is included as an appendix at the end of the chapters. The pharmacological test results obtained are shown in Table 9.

Compounds 113e, 113f, 113g, 113c and 131a were found to be active analgesics while 131d exhibits slight analgesic and antidepressant activity. Compounds 113e, 113f, 113g, 113c and 113k all exhibit antiinflammatory

TABLE 9

Pharmacological test results for N-amino-1,2,5,6-tetrahydropyridines and related compounds

Compound Number		131d	131a	113k	113j	113i	113c	113g	112f	112e	112g	113f	113a
TEST	Dose (mg/Kg)												
Neuropharmacological Profile	128 Normal								Quiet	Normal	Normal	Quiet	Very depressed
Analgesic	128	-45%*	-78.4%**	-11%	-43%*	-20%	-84%**	-57%**	-	-	-	47mg/Kg**	53mg/Kg**
Anti-depressant	128	30 min: -38%*; 60 min: -21%	0%	120 min: -12%; 180 min: -8.7%	120 min: -31%; 180 min: 0%	120 min: -23%; 180 min: 0%	120 min: -32%; 180 min: -4.2%	120 min: -4.5%; 180 min: 0%	-	-	-	-	-
Antiinflammatory	64	0%	0%	3 hr: -25%; 5hr: -75%**	3 hr: 0%; 5 hr: -25%	3 hr: -25%; 5 hr: -25%	3 hr: -25%; 5 hr: -75%**	3 hr: -25%; 5 hr: -75%**	-	-	-	**	**
Hypoglycemic	100	20%	≤20%	≤20%	<20%	<40%*	+78%***	+50%***	*	-	-	200 mg/Kg +60%***	+80%***
Anti-histaminic	0.1 mg/ml	0%	-10.5%	-4.9%	+1.6%	-3.6%	-4.9%	-20%*	-	-	-	-	-
Anaphylactic	100 mg	0%	28.9%	17%	20%	-6.7%	-6,7%	20%	-	-	-	-	-
Cardiovascular	20	-	-	-	-	-	-	-	-	-	-	-	-

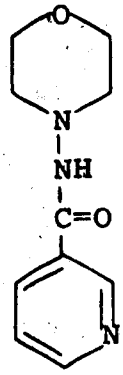
Activity Code : - = Inactive; * = Slightly active; ** = Active; *** = Hyperglycemic.

activity. It is interesting to note that those compounds which are active antiinflammatory agents all possess an aromatic ring (pyridine or phenyl), and a N-carbonylamino-1,2,5,6-tetrahydropyridyl moiety. In contrast, 131a and 131d both of which have a 3-pyridyl ring but possess a N-carbonylaminopiperidyl or N-N-dimethyl hydrazine moeity lack antiinflammatory activity. This observation is significant since one can selectively synthesize compounds which exhibit only analgesic activity (131a and 131d) or those exhibiting both analgesic and anti-inflammatory activity (113e, 113f, 113g and 113c). Similarly, it suggests that the tetrahydropyridine structure may be an essential requirement for the anti-inflammatory activity of these compounds.

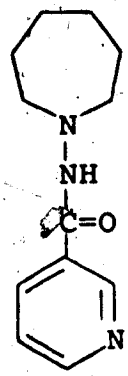
A very unique pharmacological property is the potent hyperglycemic effect exhibited by 113e, 113f, 113g and 113c, all of which contain an aromatic ring (pyridyl or phenyl) and an unsubstituted N-carbonylamino-1,2,5,6-tetrahydropyridyl moiety. The hyperglycemic activity of these compounds is especially important since it may be exploited for the development of anorectic agents useful in weight control and/or weight loss in addition to its possible use in the treatment of insulin induced hypoglycemia. The observation that 113c exhibits a potent hyperglycemic effect while 113i is a slightly active hypoglycemic effect is interesting. This observation could indicate that the N-carbonylamino-1,2,5,6-

tetrahydropyridine ring must be unsubstituted for hyperglycemic activity (compare also with 113j and 113k) or that the reversal in activity is in fact due to the hydroxypropyl substituent present in 113i. The parent pyridinium ylides 112e, 112f and 112g were devoid of activity except for a mild hypoglycemic effect exhibited by 112f. This lack of activity is likely due to their rapid rate of excretion because of their high water solubility.

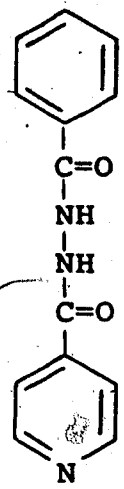
In addition to the compounds described in Table 9, other related compounds have been prepared and submitted for broad spectrum screening. Compounds 135a and 135b were synthesized to determine the pharmacological effect resulting from acyl substitution on the terminal hydrazine nitrogen of isonicotinic acid hydrazide. It was of interest to compare the activity of 135a and 135b to the structurally related monoamine oxidase inhibitor, iproniazide (149),[85] which acts as a central nervous system stimulant. Compounds 131b and 131c were prepared so that their activity could be compared to that of the piperidine analog 131a. It is reported that the ratio of analgesic activity of the drugs phenadoxone (151) and diapanone (150) is 7/4.[85] Similarly, the drug ethoheptazine (152) is reported to be as active an analgesic as meperidine (153) but has the advantage of being free of addiction liability and having a low



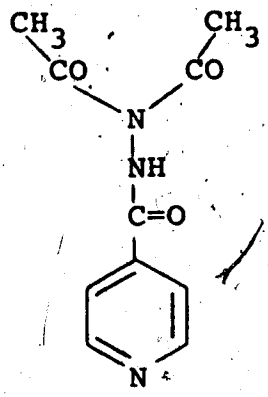
(131b)



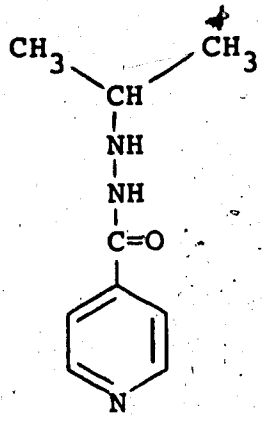
(131c)



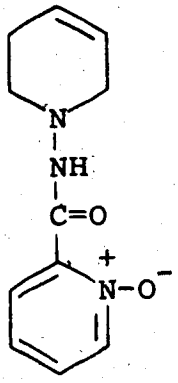
(135a)



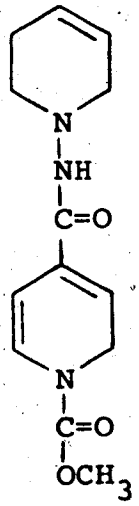
(135b)



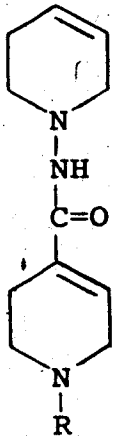
(149)

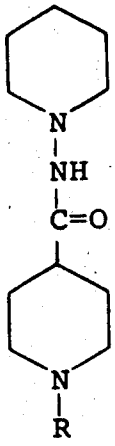


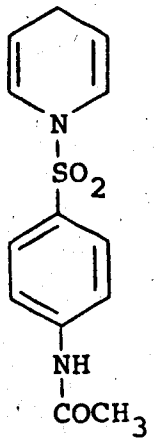
(113ℓ)



(123a)



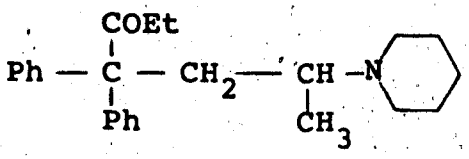




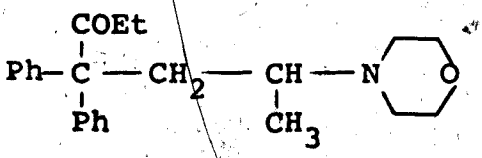
(141d)

123b, R = $-COOCH_3$ 124, R = $-COOCH_3$

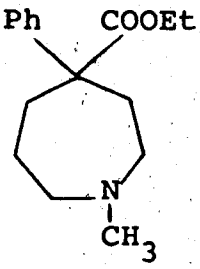
123c, R = $-CH_3$ 125, R = $-CH_3$



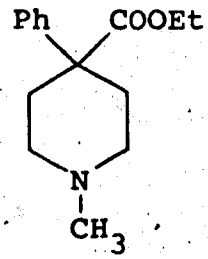
(150)



(151)



(152)



(153)

incidence of side effects.[85,93,94] Thus testing of 131b and 131c should indicate whether the morpholine ring or the homopiperidyl ring is isosteric with the piperidyl ring of 131a.

The test results for 113ℓ (the N-oxide derivative of 113g) may indicate whether an increase in water solubility affects the analgesic, antiinflammatory and hyperglycemic activity of 113g. Compounds 123a, 123b, 123c, 124 and 125 in which the pyridyl group of tetrahydropyridines 113 has been reduced to a dihydropyridine, tetrahydropyridine or piperidyl moeity, were designed to determine if the aromatic group of 113 is essential for the pharmacological activities observed. The

preliminary pharmacological test results of the novel compound 141d in which the N^1-sulfonamide nitrogen is part of a 1,4-dihydropyridine ring system will allow comparison with the known N^1-substituted derivatives already reported in the literature.

The design, synthesis and pharmacological evaluation of N-carbonylamino-1,2,5,6-tetrahydropyridines and the related compounds described provide the groundwork for an extensive structure-activity study to determine the structural requirements for optimum analgesic, antiinflammatory, hyperglycemic, and hypoglycemic activities.

5.0.0.0.0. EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were determined using tetramethylsilane (TMS) as an internal standard with a Varian A-60, EM-360A or HA-100 spectrometer. Infrared (ir) spectra were recorded on a Unicam SP-1000 spectrometer. Mass spectra were measured with an AEI-MS-9 or MS-50 mass spectrometer and these exact mass measurements are often used in lieu of elemental analysis. The following abbreviations will be used throughout this section: br, broad; d, doublet; m, multiplet; s, singlet; t, triplet; Lit, literature.

5.1.0.0.0. Preparation of N-iminopyridinium ylides and their 1,2,5,6-tetrahydropyridine reduction products

5.1.1.0.0. Preparation of N-(2,4-dinitrophenyl)pyridinium chloride (109a)

General procedure A

A mixture of freshly distilled pyridine (7.5 g, 95 mmol) and 1-chloro-2,4-dinitrobenzene (15 g, 74.2 mmol) in 100 ml dry acetone was allowed to reflux for 15 hr. Removal of the solvent *in vacuo* afforded a residue which was washed with 100 ml ether. Recrystallization from

absolute ethanol gave N-(2,4-dinitrophenyl)pyridinium chloride (109a) (18.93 g, 90.8%) as a yellowish white crystalline solid mp 191.5-193° (Lit mp 190-191°).[61]

5.1.2.0.0. Preparation of N-benzenesulfonyliminopyridinium ylide (112a) from N-(2,4-dinitrophenyl)pyridinium Chloride (109a) and benzenesulfonyl hydrazine

General procedure B

To an ice-cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109a) (3.26 g, 11.6 mmol) in methanol (30 ml) was added dropwise benzenesulfonylhydrazine (3.92 g, 22.8 mmol) in methanol (40 ml) and then triethylamine (0.9 ml). The reaction mixture was allowed to stand at room temperature overnight. The solid which precipitated was filtered off and washed in succession with 60 ml each of methanol, water, methanol and ether. A suspension of the solid obtained above in dioxane-water (4:1 v/v) (200 ml) was heated under reflux for 12 hr to afford a clear solution. The solution was removed *in vacuo* below 55°, water was added to the residue and the insoluble material removed by filtration. The filtrate was concentrated under reduced pressure to yield N-benzenesulfonyliminopyridinium ylide (112a). Chromatography on a neutral alumina column 2.5 x 26 cm using ether-methanol (1:1 v/v) (400 ml) as eluant afforded

pure N-benzenesulfonyliminopyridinium ylide (112a) (2.32 g, 85.6%), mp 150-152° (Lit mp 150-152°).[95]

5.1.2.1.0. Sodium borohydride reduction of N-benzenesulfonyliminopyridinium ylide (112a) to N-benzenesulfonylamino-1,2,5,6-tetrahydropyridine (113a)

General procedure C

Sodium borohydride (100 mg) was added to a solution of 95% ethanol (40 ml) pre-cooled to 0°. A solution of N-benzenesulfonyliminopyridinium ylide (112a) (0.31 g, 1.32 mmol) in 95% ethanol (40 ml) was added dropwise during 20 min. After stirring for 4 hr at 0° the reaction mixture was poured onto crushed ice (150 ml) and allowed to come to room temperature. Extraction with chloroform (4 x 75 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* gave a yellow semi-solid which was subjected to preparative tlc on four 20 x 20 cm silica gel GFP 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as the development solvent. Extraction with warm methanol (50 ml) of the fraction with R_f of 0.78 gave N-benzenesulfonylamino-1,2,5,6-tetrahydropyridine (113a) (0.123 g, 38.9%); ir (neat): 1330 and 1165 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 8.13-7.42 (m, 5, Ph), 6.23 (S, 1, NH, exchanges with deuterium oxide), 5.82-5.22 (m, 2, C_3-H, C_4-H), 3.32-2.95 (m, 2, C_2-H),

2.70 [t($J_{5,6}$ = 5.5 Hz), 2, C_6-H], 2.23-1.82 (m, 2, C_5-H); Anal. Calcd. for $C_{11}H_{14}N_2O_2S$: C, 55.44; H, 5.92; N, 11.75. Found: C, 55.44; H, 6.16; N, 11.81.

5.1.3.0.0. Preparation of N-methanesulfonyliminopyridinium ylide (112b) from the reaction of methanesulfonyl chloride, hydroxylamine-O-sulfonic acid and pyridine

A solution of hydroxylamine-O-sulfonic acid (11.4 g, 101 mmol) in water (100 ml) was neutralized with a solution of potassium hydroxide (5.6 g) in water (20 ml) at 5°. This solution was added dropwise to pyridine (40.0 g, 506 mmol) at 70-80°. The solution was maintained at this temperature for another 30 min and potassium carbonate (14.0 g) was added with cooling. The solvent was removed *in vacuo* below 40°, the residue dissolved in 95% ethanol (300 ml) and the insoluble inorganic salts filtered off. Potassium carbonate (20.0 g) was added to the filtrate. After one hr methanesulfonyl chloride (11.6 g, 101 mmol) was added and the solution stirred at 25° for 12 hr. Filtration and then removal of the solvent from the filtrate *in vacuo* afforded a residue which was chromatographed on a 2.5 x 26 cm neutral alumina column. Elution with chloroform (1750 ml) gave N-methanesulfonyliminopyridinium ylide (112b) which on recrystallization from absolute ethanol-ethyl acetate

(1:1 v/v) yielded (0.598 g, 3.5%), mp 171-173° (Lit mp 177-178°).[25]

5.1.3.1.0. Sodium borohydride reduction of N-methanesulfonyliminopyridinium ylide (112b) to N-methanesulfonylamino-1,2,5,6-tetrahydropyridine (113b)

A solution of N-methanesulfonyliminopyridinium ylide (112b) (0.21 g, 1.22 mmol) in 95% ethanol (30 ml) was added to a pre-cooled solution of sodium borohydride (0.2 g) in 95% ethanol (40 ml) and the reaction was completed as described under procedure C. The reaction product was subjected to preparative tlc on four 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as development solvent. Extraction with warm methanol (50 ml) of the fraction having R_f of 0.59 afforded N-methanesulfonylamino-1,2,5,6-tetrahydropyridine (113b) (0.141 g, 65.0%), mp 68-70°; ir (chloroform): 1330, 1165 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 6.0 (S, 1, NH, exchanges with deuterium oxide), 5.61 (m, 2, C_3-H, C_4-H), 3.52-3.25 (m, 2, C_2-H), 3.0 [t($J_{5,6}$ = 6.0 Hz), 2, C_6-H], 3.0 (S, 3, $-CH_3$), 2.47-2.02 (m, 2, C_5-H); Mass Calcd. for $C_6H_{12}N_2O_2{}^{32}S$: 176.0620. Found 176.0621.

5.1.4.0.0. **Preparation of N-benzenecarbonyliminopyridinium ylide (112c) from N-(2,4-dinitrophenyl)pyridinium chloride (109c) and benzoylhydrazine**

To an ice-cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109c) (6.52 g, 23.16 mmol) in methanol (60 ml) was added dropwise benzoylhydrazine (6.20 g, 45.6 mmol) in methanol (40 ml) and then triethylamine (1.8 ml). The reaction was completed as described under procedure B. The reaction product was purified on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) (400 ml) gave N-benzenecarbonylimino-pyridinium ylide (112c) (2.097 g, 45.7%) as a yellowish crystalline solid, mp 176-178°. (Lit mp 177-180°).[13]

5.1.4.1.0. **Sodium borohydride reduction of N-benzene-carbonyliminopyridinium ylide (112c) to N-benzenecarbonylamino-1,2,5,6-tetrahydro-pyridine (113c)**

A solution of N-benzenecarbonyliminopyridinium ylide (112c) (1.43 g, 7.23 mmol) in 95% ethanol (80 ml) was added to a solution of sodium borohydride (0.4 g) in 95% ethanol (40 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was purified on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (5:1 v/v)

(250 ml) afforded N-benzenecarbonylamino-1,2,5,6-tetrahydropyridine (113c) (1.25 g, 85.5%), mp 137-139°; ir (chloroform): 3440, 3350 (NH) and 1675 cm^{-1} (CO); nmr ($CDCl_3$): δ 9.93 (S, 1, NH, exchanges with deuterium oxide), 7.9-7.0 (m, 5, Ph), 5.87-5.32 (m, 2, C_3-H, C_4-H), 3.62-3.25 (m, 2, C_2-H), 2.99 [t ($J_{5,6}$ = 6 Hz), 2, C_6-H], 2.39-2.0 (m, 2, C_5-H); Mass Calcd. for $C_{12}H_{14}N_2O$: 202.1106. Found: 202.1095

5.1.5.0.0. Preparation of N-methanecarbonyliminopyridinium ylide (112d) from N-aminopyridinium iodide and acetic anhydride

A solution of 0.74 g of N-aminopyridinium iodide[96] in acetic anhydride (20 ml) was allowed to stand at room temperature for 48 hr after which it was poured into distilled water (20 ml) in a separatory funnel. The solution was made alkaline with sodium hydroxide (20%), extracted with chloroform (200 ml) and dried (sodium sulfate). Removal of the solvent *in vacuo* afforded pure N-methanecarbonyliminopyridinium ylide (112d) (0.156 g, 34.4%), mp 167-169°. (Lit mp 168°).[30,97]

5.1.5.1.0. Sodium borohydride reduction of N-methanecarbonyliminopyridinium ylide (112d) to N-methanecarbonylamino-1,2,5,6-tetrahydropyridine (113d)

A solution of N-methanecarbonyliminopyridinium ylide (112d) (0.144 g, 1.06 mmol) in 95% ethanol (30 ml) was

added to a solution of sodium borohydride (0.1 g) in 95% ethanol (40 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was subjected to preparative tlc on four 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, using ether as the development solvent. Extraction with warm methanol (50 ml) of the fraction having R_f of 0.29 afforded N-methanecarbonylamino-1,2,5,6-tetrahydropyridine (113d) (0.057 g, 38.4%), mp 86-88°; ir (chloroform): 3430-3300 (-NH-) and 1665 cm^{-1} (CO); nmr ($CDCl_3$): δ 7.28 (S, 1, NH, exchanges with deuterium oxide), 5.65 (m, 2, C_3-H, C_4-H), 3.5-3.1 (m, 2, C_2-H), 2.98 [t($J_{5,6}$ = 5.5 Hz), 2, C_6-H], 2.5-1.83 (m, 2, C_5-H), 2.11 (S, 3, CH_3); Mass Calcd. for $C_7H_{12}N_2O$: 140.0948. Found: 140.0950.

5.1.6.0.0. Preparation of N-(4-pyridylcarbonylimino)-pyridinium ylide (112e) from N-(2,4-dinitrophenyl)pyridinium chloride (109e) and isonicotinic acid hydrazide

To an ice cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109e) (6.52 g, 23.16 mmol) in methanol (20 ml) was added a suspension of isonicotinic acid hydrazide (6.2 g, 45.26 mmol) in methanol (60 ml) in five aliquots with stirring. Triethylamine (1.8 ml) was then added and the reaction was completed with

continuous stirring as described under procedure B. The reaction product was purified on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) (625 ml) gave N-(4-pyridylcarbonylimino)pyridinium ylide (112e) (2.3 g, 50.0%), mp 219-221°; ir (KBr): 1580-1570 cm^{-1} (CO); nmr (deuterium oxide): δ 8.83-8.33 [m, 4, C_2-H, C_6-H (pyridine), C_2-H, C_6-H (pyridinium)], 8.33-7.71 [m, 5, C_3-H, C_5-H (pyridine), C_3-H, C_4-H, C_5-H (pyridinium)]; Mass Calcd. for $C_{11}H_9N_3O$: 199.0746. Found: 199.0747.

5.1.6.1.0. Sodium borohydride reduction of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) to N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e)

A solution of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) (2.14 g, 10.7 mmol) in 95% ethanol (30 ml) was added dropwise to a solution of sodium borohydride (0.7 g) in 95% ethanol (60 ml) pre-cooled to 0° and the reaction completed as described under procedure C. The reaction product was then purified on a 2.5 x 25 cm neutral alumina column. Elution with ether-methanol (5:1 v/v) (500 ml) gave N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) (2.0 g, 83.6%), mp 141-144°; ir (KBr): 3240 (-NH-) and 1650 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.93 (S, 1, NH, exchanges with deuterium oxide), 8.66 [m, 2, C_2-H, C_6-H (pyridine)], 7.67 [m, 2, C_3-H, C_5-H

(pyridine)], 5.62 [m, 2, C_3-H, C_4-H (tetrahydropyridine)], 3.65-3.22 [m, 2, C_2-H (tetrahydropyridine)], 3.07 [t($J_{5,6}$ = 5.5 Hz), 2, C_6-H (tetrahydropyridine)], 2.48-2.0 [m, 2, C_5-H (tetrahydropyridine)]; Mass Calc. for $C_{11}H_{13}N_3O$: 203.1059. Found: 203.1056.

5.1.7.0.0. Preparation of N-(3-pyridylcarbonylimino)-pyridinium ylide (112f) from N-(2,4-dinitrophenyl)pyridinium chloride (109f) and nicotinic acid hydrazide

To an ice-cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109f) (3.26 g, 11.58 mmol) in methanol (20 ml) was added a suspension of nicotinic acid hydrazide (3.1 g, 22.63 mmol) in methanol (60 ml) in five aliquots with stirring. Triethylamine (0.9 ml) was then added and the reaction completed with continuous stirring as described under procedure B. The reaction product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (6:1 v/v) (250 ml) to afford N-(3-pyridylcarbonylimino)pyridinium ylide (112f) (1.06 g, 46.2%), mp 167-169°; ir (chloroform): 1600-1560 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.90 [d($J_{2,4}$ = 2 Hz) of d ($J_{2,6}$ = 1 Hz), 1, C_2-H (pyridine)], 9.02-8.18 [m, 4, C_4-H, C_6-H (pyridine), C_2-H, C_6-H (pyridinium)], 8.18-7.0 [m, 4, C_5-H (pyridine), C_3-H, C_4-H, C_5-H (pyridinium)]; Mass Calcd. for $C_{11}H_9N_3O$: 199.0746. Found: 199.0750.

5.1.7.1.0. Sodium borohydride reduction of N-(3-pyridylcarbonylimino)pyridinium ylide (112f) to N-(3-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113f)

A solution of N-(3-pyridylcarbonylimino)pyridinium ylide (112f) (1.75 g, 8.8. mmol) in 95% ethanol (30 ml) was added dropwise to a solution of sodium borohydride (0.6 g) in 95% ethanol (40 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (6:1 v/v) (300 ml) to give N-(3-pyridylcarbonylamino-1,2,5,6-tetrahydropyridine (113f) (1.43 g, 80.0%), mp 119-121°; ir (chloroform): 3480, 3440, 3345, 3290 (-NH-) and 1680, 1660 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.99 [d($J_{2,4}$ = 2 Hz), 1, C_2-H (pyridine)], 8.87 (S, 1, NH, exchanges with deuterium oxide), 8.6 [d($J_{5,6}$ = 5 Hz) of d ($J_{4,6}$ = 2 Hz), 1, C_6-H (pyridine)], 8.14 [d($J_{4,5}$ = 8 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_4-H (pyridine)], 7.28 [d($J_{4,5}$ = 8Hz) of d($J_{5,6}$ = 5Hz), 1, C_5-H (pyridine)], 5.6 [m, 2, C_3-H, C_4-H (tetrahydropyridine)], 3.63-3.28 [m, 2, C_2-H (tetrahydropyridine)], 3.07 [t($J_{5,6}$ = 5 Hz), C_6-H (tetrahydropyridine)], 2.41-2.0 [m, 2, C_5-H (tetrahydropyridine)]; Mass Calcd. for $C_{11}H_{13}N_3O$: 203.1059. Found: 203.1062.

5.1.8.0.0. Preparation of N-(2-pyridylcarbonylimino)-pyridinium ylide (112g) from N-(2,4-dinitrophenyl)pyridinium chloride (109g) and picolinic acid hydrazide

To an ice cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109g) (5.43 g, 19.29 mmol) in methanol (30 ml) was added a suspension of picolinic acid hydrazide (5.68 g, 41.4 mmol) in methanol (60 ml) in five aliquots with stirring. Triethylamine (1.8 ml) was then added and the reaction completed with continuous stirring as described under procedure B. The product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (5:1 v/v) (600 ml) to afford N-(2-pyridylcarbonylimino)pyridinium ylide (112g) (2.1 g, 54.7%), mp 178-181°; ir (chloroform): 1583, 1562 cm^{-1} (CO); nmr ($CDCl_3$): δ 9.03-8.37 [m, 3, C_6-H (pyridine), C_2-H, C_6-H (pyridinium)], 8.33-7.13 [m, 6, C_3-H, C_4-H, C_5-H (pyridine), C_3-H, C_4-H, C_5-H (pyridinium)]; Mass Calcd. for $C_{11}H_9N_3O$: 199.0746. Found: 199.0747.

5.1.8.1.0. Sodium borohydride reduction of N-(2-pyridylcarbonylimino)pyridinium ylide (112g) to N-(2-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113g)

A solution of N-(2-pyridylcarbonylimino)pyridinium ylide (112g) (0.21 g, 1.04 mmol) in 95% ethanol (30 ml)

was added dropwise to a solution of sodium borohydride (0.3 g) in 95% ethanol (30 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was then subjected to preparative tlc using four 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, with benzene-ether (1:4 v/v) as development solvent. Extraction with warm methanol (50 ml) of the fraction having R_f 0.65 afforded N-(2-pyridylcarbonylamino)1,2,5,6-tetrahydropyridine (113g) (0.166 g, 78.2%), mp 82-83°; ir (chloroform): 3440, 3400, 3320 (-NH-) and 1680, 1675 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.9 (S, 1, NH, exchanges with deuterium oxide), 8.45 [d($J_{5,6}$ = 5 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_6-H (pyridine)], 8.15 [d($J_{3,4}$ = 7.5 Hz) of d($J_{3,5}$ = 1 Hz), 1, C_3-H (pyridine)], 7.78 [d($J_{3,4}$ = $J_{4,5}$ = 7.5 Hz) of d($J_{4,6}$ = 2Hz), 1, C_4-H (pyridine)], 7.36 [d($J_{4,5}$ = 7.5 Hz) of d($J_{5,6}$ = 5Hz) of d($J_{3,5}$ = 1 Hz), 1, C_5-H (pyridine)], 5.7 [m, 2, C_3-H, C_4-H (tetrahydropyridine)], 3.7-3.3 [m, 2, C_2-H (tetrahydropyridine)], 3.11 [t($J_{5,6}$ = 5.5 Hz), 2, C_6-H (tetrahydropyridine)], 2.52-2.02 [m, 2, C_5-H (tetrahydropyridine)]; Mass Calcd. for $C_{11}H_{13}N_3O$: 203.1059. Found: 203.1056

5.1.9.0.0. Preparation of N-(phenylethylimino)pyridinium ylide (112h) from N-(2,4-dinitrophenyl)-pyridinium chloride (109h) and phenylethyl-hydrazine

To an ice-cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109h) (3.26 g, 11.58 mmol) in methanol (20 ml) was added a solution of phenylethyl-hydrazine (3.1 g, 22.79 mmol) in methanol (100 ml) with stirring. Triethylamine (0.9 ml) was then added and the reaction completed with continuous stirring as described under procedure B. The reaction product was then purified by elution from a 2.5 x 25 cm neutral alumina column using ether-methanol (1:1 v/v) (325 ml) to give N-(phenylethylimino)pyridinium ylide (112h) (0.81 g, 35.3%) as a reddish oil; nmr ($CDCl_3$): δ 922 [d($J_{2,3}$ = $J_{5,6}$ = 6 Hz) of d($J_{2,4}$ = $J_{4,6}$ = 1.5 Hz), 2, C_2-H, C_6-H (pyridinium)], 8.3-7.7 [m, 3, C_3-H, C_4-H, C_5-H (pyridinium)], 7.11 (m, 5, Ph), 3.55 (m, 2, -N-C$\underline{H}_2$), 3.04 (m, 2, Ph-C$\underline{H}_2$); Mass Calcd. for $C_{13}H_{14}N_2$: 198.1167. Found: 198.1156.

5.1.9.1.0. Sodium borohydride reduction of N-(phenylethyl-imino)pyridinium ylide (112h) to N-(phenylethyl amino)-1,2,5,6-tetrahydropyridine (113h)

A solution of N-(phenylethylimino)pyridinium ylide (112h) (0.16 g, 0.81 mmol) in 95% ethanol (30 ml) was added to a solution of sodium borohydride (0.06 g) in 95%

ethanol (30 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was then subjected to preparative tlc on four 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, using benzene-ether (2:3 v/v) as development solvent. Extraction with warm methanol (50 ml) of the fraction having R_f of 0.51 afforded N-(phenylethylimino)-1,2,5,6-tetrahydropyridine (113h) (0.081 g, 48.7%) as a very low melting solid; ir (neat): 3350 cm^{-1} ($-NH_7$); nmr ($CDCl_3$): δ 7.16 (m, 5, Ph), 5.6 (m, 2, C_3-H, C_4-H), 3.28-2.50 (complex m, 8, $-CH_2-CH_2-$, C_2-H, C_6-H), 2.2 (m, 2, C_5-H).

5.1.10.0.0. Preparation of N-benzenecarbonylimino-3(3^1-hydroxypropyl)pyridinium ylide (112i) from N-(2,4-dinitrophenyl)-3-(3^1-hydroxypropyl)-pyridinium chloride (109i)[61] and Benzoyl-hydrazine

To an ice cooled solution of N-(2,4-dinitrophenyl)-3-(-3^1-hydroxypropyl)pyridinium chloride (109i)[61] (4.5 g, 13.25 mmol) in methanol (30 ml) was added dropwise benzoylhydrazine (3.55 g, 26.1 mmol) in methanol (60 ml) with stirring. Triethylamine (1.8 ml) was then added and the reaction was completed with continuous stirring as described under procedure B. The reaction product was then purified on a 2.5 x 22 cm neutral alumina

column. Elution with ether-methanol (5:1 v/v) (550 ml) yielded N-benzenecarbonylimino-3-(3^1-hydroxypropyl)-pyridinium ylide (112i) (2.69 g, 70.0%); ir (neat): 3280-3320 (OH), 1595 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.57-8.30 [m, 2, C_2-H, C_6-H (pyridinium)], 8.27-7.87 [m, 2, *ortho*-phenylhydrogens)], 7.74-7.18 [complex m, 5, C_4-H, C_5-H (pyridinium), *meta* and *para*-phenyl hydrogens], 4.32 (S, 1, OH, exchanges with deuterium oxide), 3.46 [t(J = 6Hz), 2, $-CH_2-CH_2-\underline{CH_2}-OH$], 2.72 [t(J = 7.5 Hz), 2, $-\underline{CH_2}-CH_2-CH_2-OH$], 2.0-1.43 (m, 2, $-CH_2-\underline{CH_2}-CH_2-OH$); Mass Calcd. for $C_{15}H_{16}N_2O_2$: 256.1212. Found: 256.1217.

5.1.10.1.0. Sodium borohydride reduction of N-benzenecarbonylimino-3-(3^1-hydroxypropyl)pyridinium ylide (112i) to N-benzenecarbonylamino-3-(3^1-hydroxypropyl)-1,2,5,6-tetrahydropyridine (113i)

A solution of N-benzenecarbonylimino-3-(3^1-hydroxypropyl)pyridinium ylide (112i) (0.275 g, 1.07 mmol) in 95% ethanol (30 ml) was added dropwise to a solution of sodium borohydride (0.8 g) in 95% ethanol (40 ml) pre-cooled to 0°. The reaction was allowed to proceed for 10 hr and completed as described under procedure C. The reaction product was then purified by elution from a 2.5 x 22 cm neutral alumina column using ether-methanol (6:1 v/v) (125 ml) to give N-benzenecarbonylamino-3-(3^1-hydroxypropyl)-1,2,5,6-tetrahydropyridine (113i) (0.147 g,

52.6%), mp 156-159°; ir (KBr): 3360-3280 (OH), 3200 (-NH-), 1655-1640 cm^{-1} (CO); nmr (DMSO-d_6): δ 9.6 (S, 1, NH, exchanges with deuterium oxide), 8.08-7.70 (m, 2, *ortho*-phenyl hydrogens), 7.70-7.39 (m, 3, *meta* and *para*-phenyl hydrogens), 5.73-5.30 [m, 1, C_4-H (tetrahydropyridine)], 4.48 (S, 1, OH, exchanges with deuterium oxide), 3.66-3.21 [complex m, 4, C_2-H (tetrahydropyridine), $-CH_2-CH_2-\underline{CH}_2-OH$], 3.0 [t($J_{5,6}$ = 6 Hz), 2, C_6-H (tetrahydropyridine)], 2.45-1.67 [complex m, 4, C_5-H (tetrahydropyridine), $-\underline{CH}_2-CH_2-CH_2-OH$], 1.67-1.20 (m, 2, $-CH_2-\underline{CH}_2-CH_2-OH$); Mass Calcd. for $C_{15}H_{20}N_2O_2$: 260.1525. Found: 260.1530.

5.1.11.0.0. <u>Preparation of N-(4-pyridylcarbonylimino)-3-(3[1]-hydroxypropyl)pyridinium ylide (112j) from N-(2,4-dinitrophenyl)-3-(3[1]-hydroxypropyl)pyridinium chloride (109j)[61] and isonicotinic acid hydrazide</u>

To an ice cooled solution of N-(2,4-dinitrophenyl)-3-(3[1]-hydroxypropyl)pyridinium chloride (109j)[61] (5.22 g, 15.36 mmol) in methanol (40 ml) was added a suspension of isonicotinic acid hydrazide (4.21 g, 30.0 mmol) in methanol (60 ml) in five aliquots with stirring. Triethylamine (1.8 ml) was then added and the reaction completed as described under procedure B. The reaction product was then purified by elution from a 2.5 x 21 cm

neutral alumina column using ether-methanol (5:1 v/v) (500 ml) to give N-(4-pyridylcarbonylimino)-3-(3^1-hydroxypropyl)pyridinium ylide (112j) (1.91 g, 48.3%), mp 111-113°; ir (KBr): 3260-3240 (OH) and 1590 cm^{-1} (CO); nmr (DMSO-d_6): δ 8.98-8.52 [complex m, 4, C_2-H, C_6-H (pyridinium), C_2-H, C_6-H (pyridine)], 8.30-7.71 [complex m, 4, C_4-H, C_5-H (pyridinium), C_3-H, C_5-H (pyridine)], 4.69 (S, 1, -OH, exchanges with deuterium oxide), 3.52 [t(J = 7 Hz), 2, $-CH_2-CH_2-\underline{CH_2}-OH$], 2.88 [t(J = 7 Hz), 2, $-\underline{CH_2}-CH_2-CH_2-OH$], 2.18-1.50 (m, 2, $-CH_2-\underline{CH_2}-CH_2-OH$); Mass Calcd. for $C_{14}H_{15}N_3O_2$: 257.1164. Found: 257.1169.

5.1.11.1.0. Sodium borohydride reduction of N-(4-pyridylcarbonylimino)-3-(3^1-hydroxypropyl)pyridinium ylide (112j) to N-(4-pyridylcarbonylamino)-3-(3^1-hydroxypropyl)-1,2,5,6-tetrahydropyridine (113j)

A solution of N-(4-pyridylcarbonylimino)-3-(3^1-hydroxypropyl)pyridinium ylide (112j) (1.72 g, 6.68 mmol) in 95% ethanol (40 ml) was added dropwise to a solution of sodium borohydride (0.5 g) in 95% ethanol (60 ml) pre-cooled to 0° and the reaction was completed as described under procedure C. The reaction product was then purified by elution from a 2.5 x 20 cm neutral alumina column using ether-methanol (5:1 v/v) (450 ml) to afford N-(4-pyridylcarbonylamino)-3-(3^1-hydroxypropyl)-

1,2,5,6-tetrahydropyridine (113j) (1.31 g, 74.9%), mp 142-144°; ir (KBr): 3300-3260 (-OH), 3220 (-NH-), 1660, 1640 cm^{-1} (CO); nmr (DMSO-d_6): δ 9.90 (S, 1, NH, exchanges with deuterium oxide), 8.80 [d($J_{2,3} = J_{5,6}$ = 5 Hz), 2, C_2-H, C_6-H (pyridine)], 7.80 [d($J_{2,3} = J_{5,6}$ = 5 Hz) of d($J_{3,5} = J_{2,6}$ = 1.5 Hz), 2, C_3-H, C_5-H (pyridine)], 5.88-5.28 [m, 1, C_4-H (tetrahydropyridine)], 4.48 (S, 1, OH, exchanges with deuterium oxide), 3.72-3.21 [complex m, 4, C_2-H (tetrahydropyridine), $-CH_2-CH_2-\underline{CH_2}-OH$], 3.0 [t($J_{5,6}$ = 6 Hz), 2, C_6-H (tetrahydropyridine)], 2.46-1.70 [complex m, 4, C_5-H (tetrahydropyridine), $-\underline{CH_2}-CH_2-CH_2-OH$], 1.70-1.22 [m, 2, $-CH_2-\underline{CH_2}-CH_2-OH$]; Mass Calcd. for $C_{14}H_{19}N_3O_2$: 261.1477. Found: 261.1483.

5.1.12.0.0. Preparation of N-(4-pyridylcarbonylimino)-4-(3^1-hydroxypropyl)pyridinium ylide (112k) from N-(2,4-dinitrophenyl)-4-(3^1-hydroxypropyl)-pyridinium chloride (109k)[61] and isonicotinic acid hydrazide

To an ice-cooled solution of N-(2,4-dinitrophenyl)-4-(3^1-hydroxypropyl)pyridinium chloride (109k)[61] (5.0 g, 14.73 mmol) in methanol (40 ml) was added a suspension of isonicotinic acid hydrazide (4.04 g, 29.41 mmol) in methanol (60 ml) in five aliquots with stirring. Triethylamine (1.8 ml) was then added and the reaction completed with continuous stirring as described under

procedure B. The reaction product was then purified by elution from a 2.5 x 20 cm neutral alumina column using ether-methanol (5:1 v/v) (500 ml) to give N-(4-pyridylcarbonylimino)-4-(3^1-hydroxypropyl)pyridinium ylide (112k) (1.70 g, 44.8%), mp 160-162°; ir (KBr): 3240-3220 (-OH), 1630 cm^{-1} (CO); nmr (DMSO-d_6): δ 8.90-8.60 [complex m, 4, C_2-H, C_6-H (pyridinium), C_2-H, C_6-H (pyridine)], 8.10-7.73 [complex m, 4, C_3-H, C_5-H (pyridinium), C_3-H, C_5-H (pyridine)], 4.73 (S, 1, -OH, exchanges with deuterium oxide), 3.50 [t(J = 7 Hz), 2, $-CH_2-CH_2-\underline{C}H_2-OH$], 2.92 [t(J = 7 Hz), 2, $-\underline{C}H_2-CH_2-CH_2-OH$], 2.16-1.55 (m, 2, $-CH_2-\underline{C}H_2-CH_2-OH$); Mass Calcd. for $C_{14}H_{15}N_3O_2$: 257.1164. Found: 257.1161.

5.1.12.1.0. Sodium borohydride reduction of N-(4-pyridylcarbonylimino)-4-(3^1-hydroxypropyl)pyridinium ylide (112k) to N-(4-pyridylcarbonylamino)-4-(3^1-hydroxypropyl)-1,2,5,6-tetrahydropyridine (113k)

A solution of N-(4-pyridylcarbonylimino)-4-(3^1-hydroxypropyl)pyridinium ylide (112k) (0.65 g, 2.53 mmol) in 95% ethanol (30 ml) was added dropwise to a solution of sodium borohydride (0.2 g) in 95% ethanol (40 ml) pre-cooled to 0° and the reaction completed as described under procedure C. The reaction product was purified by elution from a 2.5 x 21 cm neutral alumina column

using ether-methanol (5:1 v/v) (375 ml) to afford N-(4-pyridylcarbonylamino)-4-(3[1]-hydroxypropyl)-1,2,5,6-tetrahydropyridine (113k) (0.449, 66.7%), mp 167-169°; ir (KBr): 3290-3270 (-OH), 3200 (-NH-), 1660, 1640 cm^{-1} (CO); nmr (DMSO-d_6): 9.93 (S, 1, NH, exchange with deuterium oxide), 8.78 [d($J_{2,3} = J_{5,6}$ = 6 Hz), 2, C_2-H, C_6-H (pyridine)], 7.74 [d($J_{2,3} = J_{5,6}$ = 6 Hz), of d ($J_{2,6} = J_{3,5}$ = 1.5 Hz), 2, C_3-H, C_5-H (pyridine)], 5.36 [m, 1, C_3-H (tetrahydropyridine)], 4.44 [t(J = 5Hz), 1, -OH, exchanges with deuterium oxide], 3.64-3.17 [complex m, 4, C_2-H (tetrahydropyridine), $-CH_2-CH_2-\underline{CH_2}-OH$], 3.0 [t($J_{5,6}$ = 6 Hz), 2, C_6-H (tetrahydropyridine)], 2.32-1.76 [complex m, 4, C_5-H (tetrahydropyridine), $-\underline{CH_2}-CH_2-CH_2-OH$], 1.76-1.20 (m, 2, $-CH_2-\underline{CH_2}-CH_2-OH$); Mass Calcd. for $C_{14}H_{19}N_3O_2$: 261.1477. Found: 261.1468.

5.1.13.0.0. Preparation of picolinic acid hydrazide-1-oxide (122) from 2-methoxycarbonylpyridine-1-oxide[65] and hydrazine hydrate

To 2-methoxycarbonylpyridine-1-oxide[65] (2.10 g, 13.74 mmol) in methanol (40 ml) was added dropwise a solution of hydrazine monohydrate (0.687 g, 13.74 mmol) in methanol (30 ml). The reaction was maintained at 60° for 1.5 hr with stirring. Removal of the solvent *in vacuo* and recrystallization of the residue from absolute ethanol afforded picolinic acid hydrazide-1-oxide

(122) as a white solid, (2.002 g, 95.2%), mp 146-148°; ir (KBr): 3320 (-NH-), 3180, 3160 ($-NH_2$), 1660 (CO), 1250 cm^{-1} ($\overset{+}{N}-\bar{O}$); nmr (DMSO-d_6): δ 12.12 (S, 1, NH, exchanges with deuterium oxide), 8.7-8.13 (m, 2, C_6-H, C_4-H), 7.86-7.43 (m, 2, C_3-H, C_5-H), 5.0 (S, 2, $-NH_2$, exchange with deuterium oxide); Mass Calcd. for $C_6H_7N_3O_2$: 153.0538. Found: 153.0535.

5.1.13.1.0. Preparation of N-(2-pyridylcarbonylimino-1-oxide)pyridinium ylide (112ℓ) from N-(2,4-dinitrophenyl)pyridinium chloride (109ℓ) and picolinic acid hydrazide-1-oxide (122)[65]

To an ice-cooled solution of N-(2,4-dinitrophenyl)-pyridinium chloride (109ℓ) (1.82 g, 6.48 mmol) in methanol (30 ml) was added a suspension of picolinic acid hydrazide-1-oxide (122)[65] (1.98 g, 12.95 mmol) in methanol (40 ml) in five aliquots with stirring. Triethylamine (0.9 ml) was then added and the reaction completed with continuous stirring as described under procedure B. The reaction product was purified by elution from a 2.5 x 21 cm neutral alumina column using ether-methanol (1:4 v/v) (250 ml) to yield a brownish solid which on recrystallization from acetone afforded N-(2-pyridylcarbonylimino-1-oxide)pyridinium ylide (112ℓ) (0.295 g, 21.2%), mp 201-204°; ir (KBr): 1590, 1570 (CO) and 1250 cm^{-1} ($\overset{+}{N}-\bar{O}$); nmr (DMSO-d_6): 8.90 [d($J_{2,3} = J_{5,6}$ = 7 Hz) of

d($J_{2,4} = J_{4,6}$ = 2 Hz), 2, C_2-H, C_6-H (pyridinium imine)], 8.35 [m, 1, C_6-H (pyridinium oxide), 8.28-7.85 [complex m, 3, C_3-H, C_4-H (pyridinium oxide), C_4-H (pyridinium imine)], 7.70-7.30 [complex m, 3, C_5-H (pyridinium oxide), C_3-H, C_5-H (pyridinium imine)]; Mass Calcd. for $C_{11}H_9N_3O_2$: 215.0695. Found: 215.0697.

5.1.13.1.1. Sodium borohydride reduction of N-(2-pyridylcarbonylimino-1-oxide)pyridinium ylide (112ℓ) to N-(2-pyridylcarbonylamino-1-oxide)-1,2,5,6-tetrahydropyridine (113ℓ)

A solution of N-(2-pyridylcarbonylimino-1-oxide)-pyridinium ylide (112ℓ) (0.101 g, 0.47 mmol) in 95% ethanol (30 ml) was added to a solution of sodium borohydride (0.050 g) in 95% ethanol (10 ml) pre-cooled to 0° and the reaction was completed as described under procedure C to give N-(2-pyridylcarbonylamino-1-oxide)-1,2,5,6-tetrahydropyridine (113ℓ) (0.085 g, 82.6%), mp 91-93°; ir (chloroform): 3440 (-NH-), 1680 (CO), 1260 cm^{-1} ($\overset{+}{N}-\bar{O}$); nmr ($CDCl_3$): 12.39 (S, 1, NH, exchanges with deuterium oxide), 8.68-8.08 [complex m, 2, C_6-H, C_4-H (pyridinium oxide)], 7.70-7.20 [complex m, 2, C_3-H, C_5-H (pyridinium oxide)], 5.[redacted] [m, 2, C_3-H, C_4-H (tetrahydropyridine)], 3.75-3.35 [m, 2, C_2-H (tetrahydropyridine)], 3.19 [t($J_{5,6}$ = 6 Hz), 2, C_6-H (tetrahydropyridine)], 2.60-2.08 [m, 2, C_5-H (tetrahydropyridine)]; Mass Calcd. for $C_{11}H_{13}N_3O_2$: 219.1008. Found: 219.1009.

5.2.0.0.0. Quaternization and sodium borohydride reduction of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e)

5.2.1.1.0. Reduction to N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123a)

General procedure D

A solution of methylchloroformate (0.202 g, 2.15 mmol) in methanol (20 ml) was added dropwise with stirring to a solution of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) (0.218 g, 1.07 mmol) in methanol (20 ml) pre-cooled to -65°. The reaction was allowed to proceed for 30 min at -65° with stirring. Sodium borohydride (0.8 g) was added and the reaction was allowed to proceed for an additional 3hr [redacted] 65°. The reaction mixture was then poured onto crushed ice (125 ml) followed by gradual warming to room temperature. Extraction with chloroform (200 ml), drying (sodium sulfate) and removal of solvent *in vacuo* gave a white solid which was purified by elution from a 2.5 x 20 cm silica gel column using ether (400 ml) to afford N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)-carbonyl-amino]-1,2,5,6-tetrahydropyridine (123a) (0.199 g, 70.5%), mp 132-134°; ir (KBr): 3200 (-NH-), 1710, 1670 (CO) 1390 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): δ 7.18 (S, 1, NH,

exchanges with deuterium oxide), 6.84 [d($J_{5,6}$ = 8 Hz), 1, C_6-H (dihydropyridine)], 6.20 [d($J_{2,3}$ = 5 Hz) of d ($J_{2',3}$ = 5 Hz) of d($J_{3,5}$ = 2 Hz), 1, C_3-H (dihydropyridine)], 6.00-5.61 [m, 2, C_3-H, C_4-H (tetrahydropyridine)], 5.45 [d($J_{5,6}$ = 8 Hz) of d($J_{3,5}$ = 2 Hz), 1, C_5-H (dihydropyridine)], 4.51 [d($J_{2,3}$ = 5 Hz), 2, C_2-H (dihydropyridine)], 3.80 (S, 3, $-CH_3$), 3.58-3.32 (m, 2, C_2-H (tetrahydropyridine)], 3.08 [t($J_{5,6}$ = 6 Hz), 2, C_6-H (tetrahydropyridine)], 2.52-2.08 [m, 2, C_5-H (tetrahydropyridine)]; Mass Calcd. for $C_{13}H_{17}N_3O_3$: 263.1270. Found 263.1267.

5.2.1.2.0. Reduction to N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b)

Method A

A solution of methylchloroformate (0.38 g, 4.02 mmol) was added dropwise to a solution of N-(4-pyridylcarbonylimino)pyridinium ylide (112e) (0.40 g, 2.01 mmol) in 95% ethanol (40 ml) pre-cooled to -65° and the reaction was allowed to proceed for 30 min at -65° with stirring. Sodium borohydride (0.25 g) was added at once and the reaction allowed to proceed for 4 hr at 0° prior to completion as described under procedure D. The reaction product was then purified by elution from a 2.5 x 17 cm neutral alumina column with ethyl acetate (400 ml) to give N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)-carbonylamino]-1,2,5,6-tetrahydropyridine (123b) (0.281 g,

52.7%), mp 153-155°; ir (KBr): 3180 (-NH-), 1715, 1675 (CO), 1375 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): δ 7.3-6.88 [m, 1, C_3-H (N-tetrahydropyridylcarbonyl)], 6.72 (S, 1, NH, exchanges with deuterium oxide), 6.0-5.48 [m, 2, C_3-H, C_4-H (N-aminotetrahydropyridine)], 3.80 (S, 3, $-CH_3$), 3.80-3.32 [complex m, 4, C_2-H (N-tetrahydropyridylcarbonyl), C_2-H (N-aminotetrahydropyridine)], 3.07 [t($J_{5,6}$ = 6 Hz), 4, C_6-H (N-tetrahydropyridylcarbonyl), C_6-H (N-aminotetrahydropyridine)], 2.50-1.70 [complex m, 4, C_5-H (N-tetrahydropyridylcarbonyl), C_5-H (N-aminotetrahydropyridine)]; Mass Calcd. for $C_{13}H_{19}N_3O_3$: 265.1426. Found: 265.1429. Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.63; H, 7.27; N, 15.75.

Method B

To a solution of N-[4-(1-methoxycarbonyl-1,2-dihydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123a) (1.172 g, 4.46 mmol) in 95% ethanol (120 ml) pre-cooled to 0° was added sodium borohydride (0.35 g). The reaction was allowed to proceed for 5 hr at 0° with continuous stirring and then completed as described under procedure D. The reaction product was purified by elution from a 2.5 x 18 cm neutral alumina column using ethyl acetate (700 ml) to give N-(4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b) (0.69 g, 58.4%), mp 153-156°; identical ir to the product prepared under method A.

5.2.2.0.0. Reduction to N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123c) and N-[1-(1,2,5,6-tetrahydropyridyl)]-C-methoxy-C-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)]azomethine (123d)

Methyl iodide (10 ml) was added to a solution of N-(4-pyridylcarbonylamino)-1,2,5,6-tetrahydropyridine (113e) (5.0 g, 24.6 mmol) in dry methylene chloride (120 ml). The reaction was allowed to proceed for 4 hr with stirring at 25° prior to refluxing for an additional 4 hr. Removal of the solvent *in vacuo* afforded a hygroscopic intense yellow solid which was dissolved in methanol (120 ml) and the solution cooled to -65°. Sodium borohydride (1.8 g) was added in one aliquot and the reaction was allowed to proceed for 4 hr at -65° prior to completion as described under procedure D. The reaction mixture was chromatographed using a 2.5 x 18 cm neutral alumina column. Elution with ether-methanol (10:1 v/v) (400 ml) gave N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123c) (1.289 g, 23.7%), mp 119-122°; ir (KBr): 3200 (-NH-), 1665, (CO), 1375 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): δ 6.94 (S, 1, NH, exchanges with deuterium oxide), 6.52 [m, 1, C_3-H (N-methyltetrahydropyridine)], 6.00-5.44 [m, 2, C_3-H, C_4-H (N-aminotetrahydropyridine)], 3.72-3.33 [m, 2, C_2-H (N-aminotetrahydropyridine)], 3.07

[t($J_{5,6}$ = 6 Hz), 4, C_6-H (N-aminotetrahydropyridine), C_2-H (N-methyltetrahydropyridine)], 2.63-2.08 [complex m, 6, C_5-H (N-aminotetrahydropyridine), C_5-H, C_6-H (N-methyltetrahydropyridine)], 2.38 (S, 3, $-CH_3$); Mass Calcd. for $C_{12}H_{19}N_3O$: 221.1529. Found: 221.1529.

Further elution with ether-methanol (5:1 v/v)(500 ml) gave a solid which was further purified by preparative tlc using twenty four 20 x 20 cm silica gel GF 254 plates, 0.75 mm in thickness, with ethyl acetate-methanol (1:1 v/v) as development solvent. Extraction with warm methanol (200 ml) of the fraction having R_f 0.30 afforded N-[1-(1,2,5,6-tetrahydropyridyl)]-C-methoxy-C-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)]azomethine (123d) (0.987 g, 17.1%), mp 133-136°; ir (KBr): 1655 (C=N),[66] 1390 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): 6.55 [m, 1, C_3-H (N-methyltetrahydropyridine)], 6.2-5.5 [m, 2, C_3-H, C_4-H (N-aminotetrahydropyridine)], 4.5-4.1 [m, 2, C_2-H (N-aminotetrahydropyridine)], 4.10-3.65 [m, 2, C_2-H (N-methyltetrahydropyridine)], 3.52 (S, 3, $-OCH_3$), 3.11 [t($J_{5,6}$ = 5 Hz), 2, C_6-H (N-aminotetrahydropyridine)], 2.78-2.28 [complex m, 6, C_5-H (N-aminotetrahydropyridine), C_5-H, C_6-H (N-methyltetrahydropyridine)], 2.39 (S, 3, $-N-CH_3$); Mass Calcd. for $C_{13}H_{21}N_3O$: 235.1684. Found: 235.1685.

5.3.0.0.0. Catalytic hydrogenation of N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b) and N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)-carbonylamino]-1,2,5,6-tetrahydropyridine (123c)

5.3.1.0.0. Reduction to N-(1-methoxycarbonyl-4-piperidyl-carbonylamino)piperidine (124)

Catalytic hydrogenation of N-[4-(1-methoxycarbonyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydropyridine (123b) (1.572 g, 5.93 mmol) in methanol (120 ml) was effected using palladium-on-charcoal (200 mg) and hydrogen gas at 40 psi for 12 hr. The charcoal was removed by filtration and the recovered charcoal washed with methanol (30 ml). Removal of the solvent *in vacuo* gave a product which was purified by elution from a 2.5 x 20 cm neutral alumina column using ether-methanol (10:1 v/v) (600 ml) to afford N-(1-methoxycarbonyl-4-piperdyl-carbonylamino)piperdine (124) (1.321 g, 82.8%), mp 160-162°; ir (KBr): 3220 (-NH-), 1695, 1655 (CO), 1380 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): δ 6.6 (S, 1, NH, exchanges with deuterium oxide), 4.48-4.0 [m, 1, C_4-H (N-piperidyl-carbonyl)], 3.75 (S, 3, $-OCH_3$), 3.35-2.0 [complex m, 8, C_2-H, C_6-H (N-piperdylcarbonyl), C_2-H, C_6-H (N-amino-piperidine)], 2.0-1.22 [complex m, 10, C_3-H, C_5-H (N-piperidylcarbonyl), C_3-H, C_4-H, C_5-H (N-aminopiperidine)];

Mass Calcd. for $C_{13}H_{23}N_3O_3$: 269.1740. Found: 269.1744.

5.3.2.0.0. Reduction to N-(1-methyl-4-piperidylcarbonylamino)piperdine (125)

Catalytic hydrogenation of N-[4-(1-methyl-1,2,5,6-tetrahydropyridyl)carbonylamino]-1,2,5,6-tetrahydro pyridine (123c) (0.163 g, 0.738 mmol) in methanol (60 ml) was carried out in the presence of palladium-on-charcoal (40 mg) and hydrogen gas at 40 psi for 12 hr. The charcoal was removed by filtration and the recovered charcoal washed with methanol (30 ml). Removal of the solvent *in vacuo* afforded N-(1-methyl-4-piperidylcarbonylamino)piperidine (125) (0.162 g, 97.6%), mp 171-174°; ir (KBr): 3215 (-NH-), 1655 (CO), 1380 cm^{-1} ($-CH_3$);[66] nmr ($CDCl_3$): 6.48 (S, 1, NH, exchanges with deuterium oxide), 3.70 [S, 1, C_4-H (N-methylpiperidine)], 3.30-2.37 [complex m, 8, C_2-H, C_6-H (N-methylpiperidine), C_2-H, C_6-H (N-aminopiperidine)], 2.27 (S, 3, $-N-CH_3$), 2.10-1.15 (complex m, 10, C_3-H, C_5-H (N-methylpiperidine), C_3-H, C_4-H, C_5-H (N-aminopiperidine)]; Mass Calcd. for $C_{12}H_{23}N_3O$: 225.1840. Found: 225.1840.

5.4.0.0.0. *n*-Butyllithium catalysed condensation reactions to give some pyridylcarbonylhydrazine derivatives

5.4.1.0.0. Preparation of N-(3-pyridylcarbonylamino)piperdine (131a) from N-aminopiperidine and ethyl nicotinate

General procedure E

A solution of *n*-butyllithium (13.43 ml of 2.0 M hexane solution, 26.86 mmol) in anhydrous tetrahydrofuran (40 ml), under a nitrogen atmosphere, was pre-cooled to -65°. To this a solution of N-aminopiperidine (2.686 g, 26.86 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction was allowed to proceed for 30 min with continuous stirring. A solution of ethyl nicotinate (4.06 g, 26.86 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction was allowed to proceed for 3 hr during which the temperature was gradually raised to 25°. Distilled water (20 ml) was added slowly. Extraction with chloroform (4 x 100 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* afforded a yellowish solid which was recrystallized from acetone to give N-(3-pyridylcarbonylamino)piperidine (131a) (2.22 g, 40.3%), mp 151-153°; ir (KBr): 3200 (-NH-), 1660-1640 cm^{-1} (CO); nmr (DMSO-d_6): δ 9.53 (S, 1, NH, exchanges with deuterium oxide), 8.93 [d($J_{2,4}$ = 2 Hz), 1, C_2-H (pyridine)], 8.68 [d($J_{5,6}$ = 5 Hz)

of d($J_{4,6}$ = 2 Hz), 1, C_6-H (pyridine)], 8.13 [d($J_{4,5}$ = 8 Hz) of d ($J_{4,6}$ = 2 Hz), 1, C_4-H (pyridine)], 7.48 [d($J_{4,5}$ = 8 Hz) of d ($J_{5,6}$ = 5 Hz), 1, C_5-H (pyridine)], 3.06-2.68 [m, 4, C_2-H, C_6-H (piperidine), 1.85-1.18 [m, 6, C_3-H, C_4-H, C_5-H (piperidine); Mass Calcd. for $C_{11}H_{15}N_3O$: 205.1215. Found: 205.1220.

5.4.2.0.0. Preparation of N-(3-pyridylcarbonylamino)-morpholine (131b) from N-aminomorpholine and ethyl nicotinate

A solution of *n*-butyllithium (11.34 ml of 2.0 M hexane solution, 22.7 mmol) in anhydrous tetrahydrofuran (40 ml), under a nitrogen atmosphere, was pre-cooled to -65°. To this a solution of N-aminomorpholine (2.314 g, 22.7 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise. The reaction was allowed to proceed for 30 min with continuous stirring. A solution of ethyl nicotinate (3.428 g, 22.7 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction completed as described under procedure E. The reaction product was then purified by elution from a 2.5 x 21 cm neutral alumina column using ether-methanol (10:1 v/v) (375 ml) to give a solid which on recrystallization from acetone gave N-(3-pyridylcarbonylamino)morpholine (131b) (0.28 g, 6%), mp 179-181°; ir (chloroform): 3340 (-NH-), 1680 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.92 [m, 1, C_2-H (pyridine)],

8.63 [d($J_{5,6}$ = 5.5 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_6-H (pyridine)], 8.07 [d($J_{4,5}$ = 8 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_4-H (pyridine)], 7.54 (br, S, 1, NH, exchanges with deuterium oxide), 7.28 [d($J_{4,5}$ = 8 Hz) of d($J_{5,6}$ = 5.5 Hz), 1, C_5-H (pyridine)], 3.79 [t($J_{2,3}$ = $J_{5,6}$ = 4.5 Hz), 4, C_3-H, C_5-H (morpholine)], 2.93 [t($J_{2,3}$ = $J_{5,6}$ = 4.5 Hz), 4, C_2-H, C_6-H (morpholine)]; Mass Calcd. for $C_{10}H_{13}N_3O_2$: 207.1008. Found: 207.1012.

5.4.3.0.0. Preparation of N-(3-pyridylcarbonylamino)-homopiperidine (131c) from N-aminohomopiperdine and ethyl nicotinate

A solution of *n*-butyllithium (6.05 ml of 2.0 M hexane solution, 12.1 mmol) in anhydrous tetrahydrofuran (40 ml), under a nitrogen atmosphere, was pre-cooled to -65°. To this a solution of N-aminohomopiperidine (1.38 g, 12.1 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise. The reaction was maintained at -65° for 30 min with continuous stirring. A solution of ethyl nicotinate (1.83 g, 12.1 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction was completed as described under procedure E. The reaction product was purified by elution from a 2.5 x 20 cm neutral alumina column using ether-methanol (10:1 v/v) (300 ml) to give N-(3-pyridylcarbonylamino)homopiperidine (131c) (1.13 g, 42.7%), mp 107-110°; ir (KBr): 3200

(-NH-), 1665, 1640 cm^{-1} (CO); nmr ($CDCl_3$): δ 9.06 [m, 1, C_2-H (pyridine)], 8.90-8.60 [m, 1, C_6-H (pyridine)], 8.15 [d($J_{4,5}$ = 8 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_4-H (pyridine)], 7.40 [d($J_{4,5}$ = 8 Hz) of d($J_{5,6}$ = 5 Hz), 1, C_5-H (pyridine)], 3.43-2.76 [m, 4, C_2-H (homopiperidine)], 2.07-1.33 [m, 8, C_3-H, C_4-H, C_5-H, C_6-H, (homopiperidine)]; Mass Calcd. for $C_{12}H_{17}N_3O$: 219.1372. Found: 219.1377.

5.4.4.0.0. Preparation of N,N-dimethylnicotinic acid hydrazide (131d) from 1,1-dimethylhydrazine and ethyl nicotinate

A solution of *n*-butyllithium (13.18 ml of 2.0 M hexane solution, 26.37 mmol) in anhydrous tetrahydrofuran (40 ml), under a nitrogen atmosphere, was precooled to -65°. To this a solution of 1,1-dimethylhydrazine (1.582 g, 26.37 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction was allowed to proceed 30 min at -65° with continuous stirring. A solution of ethyl nicotinate (3.98 g, 26.37 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction completed as described under procedure E. The reaction product was then purified by elution from a 2.5 x 20 cm neutral alumina column using ether-methanol (1:1 v/v) (500 ml) to give N,N-dimethylnicotinic acid hydrazide (131d) (1.49 g, 34.2%), mp 78-80°; ir (chloroform): 3240 (-NH-) and 1665 cm^{-1} (CO);

nmr ($CDCl_3$): δ 9.0 [d($J_{2,4}$ = 2 Hz) of d($J_{2,5}$ = 1 Hz), 1, C_2-H], 8.61 [d($J_{5,6}$ = 5 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_6-H], 8.18 [d($J_{4,5}$ = 8 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_4-H], 7.28 [d($J_{4,5}$ = 8 Hz) of d($J_{5,6}$ = 5 Hz) of d($J_{2,5}$ = 1 Hz), 1, C_5-H], 2.70 (S, 6, $-N(CH_3)_2$); Mass Calcd. for $C_8H_{11}N_3O$: 165.0902. Found: 165.0902.

5.4.5.0.0. Preparation of N,N-dimethylisonicotinic acid hydrazide (133) from 1,1-dimethylhydrazine and methyl isonicotinate

A solution of *n*-butyllithium (13.18 ml of 2.0 M hexane solution, 26.37 mmol) in anhydrous tetrahydrofuran (40 ml), under a nitrogen atmosphere, was pre-cooled to -65°. To this a solution of 1,1-dimethylhydrazine (1.582 g, 26.37 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction was allowed to proceed for 30 min at -65° with continuous stirring. A solution of methyl isonicotinate (3.612 g, 26.37 mmol) in anhydrous tetrahydrofuran (30 ml) was added dropwise and the reaction completed as described under procedure E. The reaction product was then purified by elution from a 2.5 x 22 cm neutral alumina column using ether-methanol (1:3 v/v)(250 ml) to yield N,N-dimethylisonicotinic acid hydrazide (133) (0.26 g, 6.0%) as a yellow oil; ir (chloroform): 3340 (-NH-), 1680 cm^{-1} (CO); nmr ($CDCl_3$): δ 8.62 [d($J_{2,3}$ = $J_{5,6}$ = 5 Hz) of d($J_{2,5}$ = $J_{3,6}$ = 2 Hz), 2, C_2-H, C_6-H], 7.62 [d($J_{2,3}$ = $J_{5,6}$ = 5 Hz)

of d($J_{2,5}$ = $J_{3,6}$ = 2 Hz), 2, C_3-H, C_5-H], 2.68 (S, 6, -N-$(CH_3)_2$; Mass Calcd. for $C_8H_{11}N_3O$: 165.0902. Found: 165.0903.

5.5.0.0.0. Preparation of 4-pyridylcarbonylhydrazine derivatives employing the Schotten-Bauman reaction

5.5.1.0.0. Preparation of 1-benzoyl-2-(4-pyridylcarbonyl)-hydrazine (135a) from isonicotinic acid hydrazide and benzoyl chloride

General procedure F

To an ice-cooled solution of isonicotinic acid hydrazide (0.50 g, 3.65 mmol) and dry triethylamine (1 ml) in dry tetrahydrofuran (60 ml) was added dropwise a solution of benzoyl chloride (0.513 g, 3.65 mmol) in tetrahydrofuran (15 ml). The reaction was allowed to proceed for 6 hr at 25° with stirring. Extraction with chloroform (4 x 75 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* afforded a residue which was purified by elution from a 2.5 x 22 cm neutral alumina column using ether-methanol (1:2 v/v) (300 ml) to give 1-benzoyl-2-(4-pyridylcarbonyl)hydrazine (135a) (0.057 g, 6.5%), mp 215-217°; ir (KBr): 3200 (-NH-), 1670, 1650 cm^{-1} (CO); nmr (DMSO-d_6): δ 10.68 (br, S, 2, -NH-NH-, exchange with deuterium oxide), 8.75 [d($J_{2,3}$ = $J_{5,6}$ = 6 Hz), 2, C_2-H, C_6-H (pyridine)], 8.05-7.7 [complex m, 4, C_3-H,

C_5-H (pyridine), *ortho*-phenyl hydrogens], 7.6-7.33 (m, 3, *meta* and *para*-phenyl hydrogens); Mass Calcd. for $C_{13}H_{12}N_3O_2$: 241.0852. Found: 241.0857.

5.5.2.0.0. Preparation of 1,1-diacetyl-2-(4-pyridylcarbonyl)hydrazine (135b) from isonicotinic acid hydrazide and acetylchloride

A solution of acetylchloride (1.146 g, 14.6 mmol) in dry tetrahydrofuran (30 ml) was added dropwise to an ice-cooled solution of isonicotinic acid hydrazide (1.0 g, 7.3 mmol) and dry triethylamine (30 ml) in tetrahydrofuran (60 ml). The reaction was completed as described under procedure F. The reaction product was recrystallized from absolute ethanol to yield 1,1-diacetyl-2-(4-pyridylcarbonyl)hydrazine (135b) (0.15 g, 9.3%), mp 158-160°; ir (KBr): 3250 (-NH-), 1735, 1705, 1675 (CO), 1380 cm^{-1} ($-CH_3$);[66] nmr (DMSO-d_6): 11.13 (br, S, 1, NH, exchanges with deuterium oxide), 8.70 [d($J_{2,3} = J_{5,6}$ = 6 Hz) of d($J_{2,5} = J_{3,6}$ = 1.8 Hz), 2, C_2-H, C_6-H], 7.78 [d($J_{2,3} = J_{5,6}$ = 6 Hz) of d($J_{3,5}$ = 2 Hz), 2, C_3-H, C_5-H], 2.37 (S, 6, $-(COCH_3)_2$; Mass Calcd. for $C_{10}H_{11}N_3O_3$: 221.0801. Found: 221.0802.

5.6.0.0.0. Preparation of N-sulfonyl-1,2-(1,4)-dihydropyridines

5.6.1.0.0. Preparation of N-methanesulfonyl-1,2-dihydropyridine (142a) from reaction of pyridine, methanesulfonyl chloride (methanesulfonic anhydride)[84] and sodium borohydride in methanol

General procedure G

Sodium borohydride (0.8 g) was added to a solution of pyridine (1.58 g, 20.0 mmol) in methanol (7.5 ml) pre-cooled to -65°. A solution of methanesulfonyl chloride (2.29 g, 20.0 mmol) in dry ether (5 ml) was added dropwise during 15 min. After stirring for 1.5 hr at -65° the reaction mixture was poured onto crushed ice (75 ml) and allowed to come to room temperature. Extraction with chloroform (3 x 30 ml), drying (sodium sulfate), and removal of the solvent *in vacuo* gave a yellow oil which was chromatographed on a 2.5 x 15 cm neutral alumina column. Elution with 300 ml chloroform gave N-methanesulfonyl-1,2-dihydropyridine (142a) (1.02 g, 32.1%) as a yellow oil; ir (neat): 1350, 1160 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 6.62-6.24 (m, 1, C_6-H), 6.18-5.8 (m, 1, C_4-H), 5.73-5.3 (m, 2, C_3-H, C_5-H), 4.25 [d($J_{2,3}$ = 4 Hz) of d($J_{2,4}$ = 1.5 Hz), 2, C_2-H], 2.92 (S, 3, $-CH_3$); Mass Calcd. for $C_6H_9NO_2{}^{32}S$: 159.0354. Found: 159.0355.

When the reaction was carried out as described

above using methanesulfonic anhydride[84] (3.48 g, 20.0 mmol) 1.18 g (37.1%) of N-methanesulfonyl-1,2-dihydropyridine (142a) was obtained.

5.6.2.1.0. Preparation of N-benzenesulfonyl-1,4-dihydropyridine (141b) and N-benzenesulfonyl-1,2-dihydropyridine (142b) from reaction of pyridine, benzenesulfonyl chloride (benzenesulfonic anhydride) and sodium borohydride in methanol

Sodium borohydride (0.8 g) was added to a solution of pyridine (1.58 g, 20.0 mmol) in methanol (20 ml) pre-cooled to -65°. A solution of benzenesulfonyl chloride (3.52 g, 20.0 mmol) in dry ether (10 ml) was added dropwise during 15 min and the reaction was completed as described under procedure G. The reaction product was then chromatographed on a 2.5 x 15 cm neutral alumina column. Elution with benzene (400 ml) gave 0.591 g (13.37%) of an isomeric mixture of N-benzenesulfonyl-1,4-dihydropyridine (141b) and N-benzenesulfonyl-1,2-dihydropyridine (142b) which was purified further by tlc using five 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, with benzene as development solvent. Extraction of the fraction having an R_f of 0.55-0.6 gave N-benzenesulfonyl-1,4-dihydropyridine (141b) (0.078 g, 1.8%), mp 83-85° (Lit mp 86-89°);[82] ir (KBr): 1352, 1175 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 7.58 (m, 5, Ph), 6.47

[d($J_{2,3} = J_{5,6}$ = 8.5 Hz) of d($J_{2,4} = J_{4,6}$ = 1.5 Hz), 2, C_2-H, C_6-H], 4.88 [m($J_{2,3} = J_{5,6}$ = 8.5 Hz), 2, C_3-H, C_5-H], 2.68 (m, 2, C_4-H); Mass Calcd. for $C_{11}H_{11}NO_2{}^{32}S$: 221.0511. Found: 221.0506.

Extraction of the fraction having an R_f of 0.3-0.5 gave N-benzenesulfonyl-1,2-dihydropyridine (142b) (0.257 g, 5.8%), mp 68-69°; ir (KBr): 1360, 1340, 1175 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 7.62 (m, 5, Ph), 6.63 [d($J_{5,6}$ = 7.75 Hz) of d($J_{4,6}$ = 0.8 Hz), 1, C_6-H], 5.8 (m, 1, C_4-H), 5.34 (m, 2, C_3-H, C_5-H), 4.16 [d($J_{2,3}$ = 4 Hz) of d($J_{2,4}$ = 1.5 Hz), 2, C_2-H]; Mass Calcd. for $C_{11}H_{11}NO_2{}^{32}S$: 221.0511. Found: 221.0506.

Reaction of benzenesulfonic anhydride[84] (5.86 g, 20.0 mmol) with pyridine (1.58 g, 20.0 mmol) in the presence of sodium borohydride (0.8 g) as described under procedure G and purification of the reaction mixture as described above afforded 1.78 g of an isomeric mixture consisting of N-benzenesulfonyl-1,4-dihydropyridine (141 b) (0.3 g, 6.7%) and N-benzenesulfonyl-1,2-dihydropyridine (142b) (1.49 g, 33.6%) as determined by the integrals of the C_4-H and C_2-H of 141b and 142b, respectively.

5.6.2.2.0. Preparation of N-benzenesulfonyl-1,4-dihydropyridine (141b) and N-benzenesulfonyl-1,2-dihydropyridine (142b) from reaction of pyridine, benzenesulfonyl chloride (benzenesulfonic anhydride) and sodium borohydride in pyridine

Procedure H

Sodium borohydride (0.8 g) was added to a mixture of pyridine (10 ml) and benzenesulfonyl chloride (3.53 g, 20.0 mmol) pre-cooled to 0° with stirring. The reaction was allowed to proceed for 15 hr at 25° after which it was poured onto crushed ice (100 ml). Extraction with chloroform (4 x 100 ml), drying (sodium sulfate), and evaporation of the solvent *in vacuo* afforded a brown oil which was subjected to chromatography on a 2.5 x 25 cm neutral alumina column. Elution with benzene (700 ml) gave 1.06 g of an isomeric mixture composed of N-benzenesulfonyl-1,4-dihydropyridine (141b) (0.75 g, 17%) and N-benzenesulfonyl-1,2-dihydropyridine (142b) (0.312 g, 7.1%) as determined by the integrals of the C_4-H and C_2-H of 141b and 142b, respectively.

Reaction of benzenesulfonic anhydride[84] (5.86 g, 20.0 mmol) with pyridine (10 ml) in the presence of sodium borohydride (0.8 g) as described under procedure H and then elution from a neutral alumina column as described above gave 1.36 g of an isomeric mixture composed of N-benzenesulfonyl-1,4-dihydropyridine (141b)

(1.05 g, 23.7%) and N-benzenesulfonyl-1,2-dihydropyridine (142b) (0.31 g, 6.95%) as determined by the integrals of the C_4-H and C_2-H of 141b and 142b, respectively.

5.6.3.0.0. Preparation of N-*p*-toluenesulfonyl-1,4-dihydropyridine (141c) and N-*p*-toluenesulfonyl-1,2-dihydropyridine (142c) from reaction of pyridine, *p*-toluenesulfonyl chloride and sodium borohydride in pyridine

Sodium borohydride (0.8 g) was added to a mixture of pyridine (10 ml) and *p*-toluenesulfonyl chloride (3.81 g, 20.0 mmol) pre-cooled to 0° with stirring. The reaction was completed as described under procedure H to give a brown semi-solid which was subjected to chromatography on a 2.5 x 26 cm neutral alumina column. Elution with benzene (250 ml) gave N-*p*-toluenesulfonyl-1,4-dihydropyridine (141c) (0.36 g, 7.7%), mp 93-95°; ir (KBr): 1370, 1345, 1170 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 7.68 [d(J = 8 Hz), 2, *ortho*-phenyl hydrogens], 7.38 [d(J = 8 Hz), 2, *meta*-phenyl hydrogens], 6.44 [d($J_{2,3} = J_{5,6}$ = 8.5 Hz) of d($J_{2,4} = J_{4,6}$ = 1.5 Hz), 2, C_2-H, C_6-H], 4.86 [m, ($J_{2,3} = J_{5,6}$ = 8.5 Hz), 2, C_3-H, C_5-H], 2.7 (m, 2, C_4-H), 2.42 (S, 3, $-CH_3$), Mass Calcd. for $C_{12}H_{13}NO_2{}^{32}S$: 235.0667. Found: 235.0659.

Further elution with benzene-ether (4:1 v/v) (250 ml) gave N-*p*-toluenesulfonyl-1,2-dihydropyridine (142c)

(0.297 g, 6.32%), mp 59-61°; ir (KBr): 1350, 1170 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 7.67 [d(J = 8 Hz), 2, *ortho*-phenyl hydrogens], 7.38 [d(J = 8 Hz), 2, *meta*-phenyl hydrogens], 6.58 [d($J_{5,6}$ = 7.75 Hz) of d($J_{4,6}$ = 0.8 Hz), 1, C_6-H], 5.8 [d($J_{3,4}$ = 8 Hz) of d($J_{4,5}$ = 4.5 Hz) of d($J_{2,4}$ = 1.5 Hz), 1, C_4-H], 5.36 (m, 2, C_3-H, C_5-H), 4.12 [d($J_{2,3}$ = 4 Hz) of d($J_{2,4}$ = 1.5 Hz), 2, C_2-H], 2.42 (S, 3, $-CH_3$); Mass Calcd. for $C_{12}H_{13}NO_2{}^{32}S$: 235.0667. Found: 235.0659.

5.6.4.0.0. Preparation of N-*p*-acetylsulfanilyl-1,4-dihydropyridine (141d), N-*p*-acetylsulfanilyl-1,2-dihydropyridine (142d) and 5-endo-*p*-acetylsulfanilyl-2,3,5-triazabicyclo[2.2.2.]-oct-7-ene-2,3-endo-dicarboxylic acid N-phenyl-imide (145)

Sodium borohydride (0.8 g) was added to a mixture of pyridine (10 ml) and *p*-acetylsulfanilyl chloride (4.67 g, 20.0 mmol) pre-cooled to 0° with stirring. The reaction was completed as described under procedure H to give a reddish semi-solid which was chromatographed on a 2.5 x 26 cm neutral alumina column. Elution with ether-methanol (6:1 v/v) (300 ml) gave 1.198 g of an isomeric mixture consisting of N-*p*-acetylsulfanilyl-1,4-dihydropyridine (141d) (0.96 g, 16.7%) and N-*p*-acetyl-sulfanilyl-1,2-dihydropyridine (142d) (0.24 g, 4.2%) as

determined from the integrals of the C_4-H and C_2-H of 141d and 142d, respectively. 4-Phenyl-1,2,4-triazoline-3,5-dione (144) (0.069 g, 0.392 mmol) in dry methylene chloride (10 ml) was added dropwise with stirring to a solution of 0.543 g of the above mixture of 141d and 142d (containing 0.109 g, 0.392 mmol of 142d) in methylene chloride (20 ml) pre-cooled to 0°. The reaction was allowed to proceed for 1 hr, after which the solvent was removed *in vacuo* to give a white solid. Preparative tlc on four 20 x 20 cm silica gel GF 254 plates, 0.5 mm in thickness, with ethyl acetate as a development solvent afforded N-*p*-acetylsulfanilyl-1,4-dihydropyridine (141d) (0.094 g) having an R_f of 0.86, mp 138°-140°; ir (KBr): 1705, 1690 (CO), 1350, 1168 cm^{-1} (SO_2); nmr ($CDCl_3$): δ 9.78 (S, 1, -NH-, exchanges with deuterium oxide), 7.81 (m, 2, *ortho*-phenyl hydrogens), 7.58 (m, 2, *meta*-phenyl hydrogens), 6.38 [d($J_{2,3} = J_{5,6}$ = 8.5 Hz) of d($J_{2,4} = J_{4,6}$ = 1.5 Hz), 2, C_2-H, C_6-H], 4.86 [m($J_{2,3} = J_{5,6}$ = 8.5 Hz), 2, C_3-H, C_5-H], 2.67 (m, 2, C_4-H), 2.16 (S, 3, $-CH_3$); Mass Calcd. for $C_{13}H_{14}N_2O_3{}^{32}S$: 278.0725. Found: 278.0721.

Extraction of the fraction having an R_f 0.27 gave 5-endo-*p*-acetylsulfanilyl-2,3,5-triazabicyclo[2.2.2.]-oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (145) (0.060 g), mp 200-204°; ir (KBr): 1700 (CO), 1372, 1160 cm^{-1} (SO_2); nmr (DMSO-d_6): δ 10.5 (S, 1, -NH-,

exchanges with deuterium oxide), 8.0-7.25 (m, 9, phenyl hydrogens), 6.68-5.3 (m, 3, C_4-H, C_7-H, C_8-H), 4.96 (m, 1, C_1-H), 4.5 (m, 2, C_6-H), 3.15 (S, 3, $-CH_3$). Anal. Calcd. for $C_{21}H_{19}N_5O_5S$: C, 55.63; H, 4.19; N, 15.45. Found: C, 55.66; H, 4.21; N, 15.62.

5.6.4.1.0. Catalytic hydrogenation of N-*p*-acetylsulfanilyl-1,4-dihydropyridine (141d) and N-*p*-acetylsulfanilyl-1,2-dihydropyridine (142d) to N-*p*-acetylsulfanilylpiperidine (143)

Catalytic hydrogenation of a 4:1 mixture of N-*p*-acetylsulfanilyl-1,4-dihydropyridine (141d) and N-*p*-acetylsulfanilyl-1,2-dihydropyridine (142d) (95 mg) in methanol (30 ml) was carried out in the presence of palladium-on-charcoal (30 mg) and hydgrogen gas at 50 psi for 72 hr. Removal of the charcoal by filtration and evaporation of the solvent *in vacuo* afforded N-*p*-acetylsulfanilylpiperidine (143) as a white solid, mp 156° (Lit mp 156°),[86] identical ir and nmr with the authentic sample.

6.0.0.0.0. BIBLIOGRAPHY

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APPENDIX

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NEUROPHARMACOLOGICAL PROFILE

METHOD: Observation of behaviour.

PROCEDURE: The test compound at an initial dose of 128 mg/kg body weight, is injected intraperitoneally to four Swiss Albino Mice, equally divided as to sex. The body weight of the animals is in the range of 18-22 g. Immediately after injection the animals are placed together in a clear plastic cage (29 x 18 x 15 cm) and continuously observed over a period of 60 minutes. The observation is followed up in hourly intervals for another 5 hours.

Each animal is examined and a joint score entered in each of the categories described on the evaluation sheet (see example). If the compound causes lethality at this dose level, the dose is lowered until a non-lethal level is reached.

RESULTS: In each of the categories described on the evaluation sheet, the effect of the test compound on the behaviour of the treated animals is scored with respect to the behaviour of a vehicle treated control group and various known standard compounds. The results are given in the form of a summary for each group.

REFERENCES: Vane, J.R. (196[redacted] in Evaluation of Drug Activities: Pharmacokinetics
Editors, Laurence, D.R. and Bacharach, A.L.
Academic Press.

Irwin, S. (1964) in Pharmacological Techniques in Drug Evaluation by Nodine, J.H. and Siegler, P.E.
Year Book Med. Publishers Inc.

NEUROPHARMACOLOGICAL PROFILE

CMPD NO. _____ PROJ: _____
VEHICLE _____ DATE: _____
SPECIES _____ SIGN: _____
ROUTE _____

	AWARENESS / MOOD						M.A.		C.N.S.				P	MOTOR INCO.			MUSCLE TONE			REFLEXES					AUTONOMIC SYSTEM										
TIME AFTER DRUG ADM.	ALERTNESS	PASSIVITY	GROOMING	RESTLESSNESS	IRRITABILITY	FEARFULLNESS	SPONT.ACTIVITY	RESPONSE S.T.P.	STARTLE RESP.	TAIL LASHING	TREMORS	CONVULSIONS	POSTURE	ABNORMAL GAIT	ATAXIA	ROTO ROAD*	GRIP STRENGTH	LIMB TONE	ABDOMIN.TONE	PINNAL R.	CORNEAL R.	ESCAPE R.	PLACING R.	RIGHTING R.	WRITHING	URINATION	DIARRHEA	SALIVATION	RETCHING	PILOERECTION	SKIN COLOR	TEMPERATURE	RESPIRATION	PUPIL SIZE	EYELID TONE	EXOPTHALAMOS	LACRIMATION
SCORE	↓↑	↑	±	↑	↑	↑	↓↑	↓↑	↓↑	↑	↑				±		↓↑	↓↑	↓↑	±	±	±	±	±	±	±	±	±	±	±		↓↑		↓↑	↓	±	↑
Minutes 0 - 1																																					
1 - 5																																					
5 - 10																																					
10 - 15																																					
15 - 20																																					
20 - 30																																					
30 - 60																																					
>60																																					

ONSET OF DRUG ACTION: _____
DURATION OF DRUG ACTION: _____
TOXICITY: _____

ANALGESIC

METHOD: Phenylquinone writhing test.

PROCEDURE: Five male Swiss Albino Mice, 18-22 g of body weight, are injected subcutaneously with the test compound at a dose of 128 mg/kg/10 ml (or at a lower non-toxic dose, established during the neuropharmacological profile evaluation). 30 minutes later, 0.03% phenyl-*p*-benzoquinone is injected in a volume of 0.1 ml/10 g body weight.

After 10 minutes the animals are placed in glass jars for observation.

Phenylquinone produces a characteristic muscular activity called a "writhe". The total number of writhes exhibited by each animal is recorded. 5 animals are observed at the same time. The total number of writhes of the treated group is compared to that of a vehicle treated control group.

RESULTS: Percent change is calculated as follows:

$$\% \text{ change} = \frac{\text{no. of writhes in treated group}}{\text{no. of writhes in control group}} \times 100 - 100$$

REFERENCE: Collier, H.O., Dinneen, L.C., Johnson, C.A. and Schneider, C. (1968) Br. J. Pharmac. Chemother. 32: 295-310.

ANTI-DEPRESSANT

METHOD: Antagonism of Tetrabenazine induced ptosis in the mouse.

PROCEDURE: Six male Swiss Albino Mice are injected subcutaneously with 128 mg/kg/10 ml of the test compound (or with a lower, non-toxic dose established during the N.P.P. evaluation).

15 minutes later the animals are treated with 60 mg/kg/10 ml Tetrabenazine, administered intraperitoneally.

At 30 minutes and 60 minutes after administration of Tetrabenazine, the degree of ptosis exhibited by each animal is evaluated and recorded. The ptosis score is as follows:

0 for totally open eyes

1 for 1/4 closed eyes

2 for 1/2 closed eyes

3 for 3/4 closed eyes

4 for totally closed eyes

RESULTS: Each animal is scored. The total number of scores of the treated group is compared to the total score of a vehicle treated control group.

The % protection is calculated as follows:

$$100 - \left(\frac{\text{total score of treated group}}{\text{total score of control group}} \times 100\right) = \% \text{ protection}$$

REFERENCES: Rubin, B., Malone, H.H., Waugh, M.H. and Burke, J.C. (1957) J. Pharmacol. Exp. Therap. 120: 125.

Barnett, A. and Taber, R.T. in Screening Methods in Pharmacology Volume II (1971) edit. Turner, P.A. and Hebborn, P. Academic Press, New York and London.

CARDIOVASCULAR

METHOD: Direct measurements of arterial blood pressure in anesthetized rats.

PROCEDURE: Sprague-Dawley rats of either sex weighing 250-400 g are used. The anesthesia is induced by the intraperitoneal injection of 1.9 g/kg body weight Urethane.

The femoral vein is cannulated for drug administration. The blood pressure is monitored via a Statham pressure transducer connected to a cannula in the left carotid. A Grass polygraph is used to obtain a continuous record of the arterial blood pressure and the heart rate. After the preparation is stabilized, the test compound is administered at various doses at a volume of 0.01-0.05 ml/rat. Additionally the response to α and β sympathomimetics before and after administration of the test compound is established.

RESULTS: The drug induced changes in BP and HR are expressed as % difference from the pre-drug values for each individual preparation.

ANTI-INFLAMMATORY

METHOD: Antagonism of carrageenan induced rat paw edema.

PROCEDURE: Six female Sprague-Dawley rats, weighing 120-160 g, are injected subcutaneously with a nontoxic dose of the test compound (maximal dose 64 mg/kg).

At the same time, 0.1 ml of a 1% solution of carrageenan in physiological saline is injected under the plantar skin of the left hind paw. Then the volume of the injected paw is measured by a mercury displacement technique.

The injected paw is dipped into a glass cylinder containing mercury. The open end of the cylinder is connected to a Statham pressure transducer and a Grass polygraph is used to record the changes in pressure, caused by the displacement of mercury.

The volume is measured immediately after and at three hours and five hours after the injection.

RESULTS: The edema volume is calculated as follows:

V_o = volume of paw measured immediately after carrageenan injection

V_x = volume of paw measured at time x after injection

$V_e = V_x - V_o$ = edema volume at time x

A test statistic of the mean edema volume ±2 S.D. is calculated from the control group. The individual edema volumes of the treated animals are compared to this test statistic. The group score is expressed as percentage of animals showing edema volume < or > the test statistic.

REFERENCE: Winter, C.A. (1965) in International Symposium on Non-Steroidal Anti-Inflammatory Drugs, ed. Garattini, S. and Dukes, M.N.G., pp. 190-202, Excerpta Medica Foundation, Amsterdam.

HYPOGLYCEMIC

METHOD: Measurement of blood glucose concentration in the rat.

PROCEDURE: 100 mg/kg of the test compound is administered orally to four Sprague-Dawley rats. Just before, and two and four hours after treatment blood samples are taken from the animals' tails. The concentration of glucose in the blood is determined with Eskalab reagent tablets.

RESULTS: The concentration of glucose in the post-treatment blood samples is compared with that of the pretreatment sample and the activity of the compound is expressed as follows:

Concentration with respect to control	Score
increase	-
no effect	0
5 - 10% decrease	+
10 - 20% decrease	++
20 - 30% decrease	+++
30 - 40% decrease	+++

REFERENCE: Holland, G.F., Jaeger, D.A., Wagner, R.L., Laubach, G.D., McLamore, W.M. and P'an, S.Y., (1961). J. Med. Pharm. Chem., 3: 99-109.

ANTI-HISTAMINIC

METHOD: Antagonism of histamine in the isolated Guinea pig ileum preparation.

PROCEDURE: 2-4 cm of ileum is removed from a male albino Guinea pig and mounted in a muscle bath filled with Tyrode's solution. One end is attached to a force displacement transducer and the force of contraction of the intestinal muscle is recorded on a Grass polygraph. The tissue is then challenged with 0.05 µg/ml bath of histamine, repeatedly, at five minute intervals until a constant level of response is established. 0.1 mg/ml bath of the test compound is then added to the bath, allowed to equilibrate with the tissue for one minute, and washed out. Four minutes later, the muscle is again challenged with 0.05 µg/ml bath of histamine. Responses to histamine are obtained every five minutes for a further one half hour.

RESULTS: Compounds which produce an essentially complete blockade of the response to histamine are considered active.

REFERENCE: Perry, W.L.M., (1968) Pharmacological Experiments on Isolated Preparations. Livingstone, Edinburgh, pp. 58-68.

ANTI-ANAPHYLACTIC

METHOD: Inhibition of passive cutaneous anaphylaxis in the rat.

PROCEDURE: Several Sprague-Dawley rats are treated with the following:

Agent	Volume	Route
0.5% solution egg albumin	0.2 ml	I.M.
0.5% bovine serum albumin	0.2	I.M.
Bordetella pertussis vaccine	1.0	I.P.

The animals are sacrificed after 11-13 days, and the serum obtained from their blood is pooled and frozen. The serum contains antibodies to the substances with which the animals were treated and will be referred to as "anti-serum".

Each of four Sprague-Dawley rats are injected intradermally with two 0.1 ml volumes of anti-serum on either side of their backs. 24 hours later 100 mg/kg of the test compound is injected intravenously and the animals are immediately challenged with egg albumin. This "antigen" is also administered intravenously together with Evan's blue dye. Half an hour after the challenge, the animals are sacrificed and the skin of their backs is removed. The anaphylactic reaction at the site of the intradermal

injection of anti-serum results in the formation of a swelling or "wheal". The size of this wheal is proportional to the intensity of the reaction. The concentration of anti-serum injected is adjusted to produce a wheal at least 20 mm diameter.

RESULTS: The test compound is considered active if it inhibits "wheal" formation by > 50%.

REFERENCE: Goose, J. and Blair, A.M.J.N., (1969) Immunology, 16: 749-7[redacted].

ANTI-MICROBIAL

METHOD: Agar-dilution technique.

PROCEDURE: The compounds under study were examined for their effectiveness against the following bacteria, fungi and yeasts:

Test Organism	Growth Medium	
Escherichia coli	ATCC 8739	)
Pseudomonas aeruginosa	ATCC 10145	)
Klebsiella pneumoniae	ATCC 4352	)
Staphylococcus aureus	ATCC 6538	)Trypticase Soy
Streptococcus faecalis	ATCC 8030	) Agar
Bacillus subtilis	ATCC 6633	)
Salmonella typhimurium	ATCC 13311	)
Haemophilus influenzae	C 19418	)Trypticase Soy
Streptococcus pyogenes	spital isolate)	Agar plus 5%
Streptococcus penumonia	C 6303	)defibrinated
		rabbit blood
Aspergillus niger	TCC 10535	)
Trichophyton mentagrophytes	ATCC 9533	)Sabouraud Agar
Microsporum gypseum	ATCC 14683	) (modified)
Candida albicans	ATCC 10231	)
Sassaromyces carlsbergensis	ATCC 9080	)

Compounds, unless soluble in water, were dissolved in DMSO and diluted serially to various concentrations. The concentrations of stock were prepared in such a way that when 0.5 ml was added to 15 ml of agar media the desired final concentrations were obtained. The test organisms were previously grown for 2 days at 35°C for bacteria and yeasts and 1 week for fungi at 24°C on slants of the same media mentioned above. The agar plates were

streaked with a loopful of cell suspension which had been washed off from the slants and diluted to approximately 10^5 organisms/ml. The plates were incubated for 2 to 14 days for fungi at 24°C and at 35°C for bacteria.

RESULT: The result is expressed as minimal inhibitory concentration which was defined as the lowest concentration of each compound that prevented visible growth on the media.

ANTI-PROTOZOAL

METHOD: Tube dilution technique as described in Ref. (1).

PROCEDURE: The test organisms used were:

1) Trichomonas foetus ATCC 30003 growing in modified TYM basal medium.
2) Entamoeba histolitica ATCC 30015 growing in TP-S-1 monophasic medium as devised by Diamond (2).

Each test compound was added to the liquid medium of 10 µg/ml final concentration for the amoebae and at 50 µg/ml for Trichomonas. Each tube was then innoculated with a known number of trophozoites (1×10^5/ml) grown in the same medium for 48 hrs. The inoculated media were incubated for 24 and 48 hours at 35°C.

To enumerate the total population of parasites an aliquot of each test culture was diluted in saline containing formaldehyde (1%). Cell counting was performed with the aid of a Speirs-Levy eosinophil counting chamber.

RESULT: The result is expressed as minimal inhibitory concentration which was taken as the lowest concentration of each compound that inhibited 90% of growth.

REFERENCES: (1) Diamond, L.S. and Burtgis, I.L., (1971). Arch. Invest. Medica., Vol. 2. Supp.

(2) Diamond, L.S., (1968). J. Parisitol., 54: 1047.

BIOLOGICAL SCREENING PROGRAM

STANDARD COMPOUNDS

TEST CLASS (specific test)	Test Animal	Standard Compound Dose (mg/kg)/Route	Effect	Criterion
ANALGESIC (phenylquinone induced writhing)	Mouse	Aspirin 50 mg/kg s.c.	-50%	-30-50% sl. active >50% active
		Dextropropoxyphene 56 mg/kg s.c.	-50%	
ANTI-DEPRESSANT (Antagonism of tetrabenazine induced ptosis)	Mouse	Amitriptyline 8 mg/kg s.c.	-90%(30 min) -49%(60 min)	-30%) -10%) active
ANTI-INFLAMMATORY (Antagonism of carageenanedema)	Rat	Indomethacine 32 mg/kg s.c.	-17% (3 hrs) -83% (5 hrs)	>-30% active
HYPOGLYCEMIC (Measurement of blood glucose concentration)	Rat	Chlorpropamide 100 mg/kg p.o.	>40% reduction	>20% reduction active
ANTI-HISTAMINIC (Antagonism of histamine in the isolated guinea-pig ileum preparation)	Guinea Pig	Diphenhydramine 0.01 mg/ml$_B$ invitro	-100%	-50% active
ANTI-ANAPHYLACTIC (Inhibition of Passive Cutaneous Anaphylaxis)	Rat	Disodium chromoglycate 100 mg/kg i.v.	-91%	-50% active

BIOLOGICAL SCREENING PROGRAM

Compound: Name:

Originator: Structure:

Amount rec'd.: _____

Date rec'd.: _____

Test started: _____ M.W.: _____ M.P. °C: _____ Solub. _____

Literature ref:

SUMMARY:

Test	Route	Dose (mg/kg)	RESPONSE		Activity Score
Toxicity (Min. tox. dose)	i.p. i.v. p.o. s.c.				
Neuropharmacol. profile	i.p.				
Analgesic	s.c.				
Anti-depressant	s.c.		30 min	60 min	
Cardiovascular	i.v.		BP	HR	
Anti-inflammatory	s.c.		3 hrs	5 hrs	
Hypoglycemic	p.o.				
Anti-histaminic	in vitro	mg/ml			
Anaphylactic	i.v.				
Anti-microbial bacteria / fungi	in vitro	MIC µg/ml			
Anti-protozoal trichomonas / entamoeba	in vitro	MIC µg/ml			

- inactive * slightly active ** active

VITA

NAME: Kinfe Redda

PLACE OF BIRTH: Senafe, Eritrea

YEAR OF BIRTH: 1946

POST-SECONDARY EDUCATION AND DEGREES:

Haile Selassie I University (National University)
Addis Ababa, Ethiopia
1964-1970 B. Pharm.

HONORS AND AWARDS:

Canadian International Development Agency (CIDA) scholarship
University of Alberta, Edmonton, Alberta, Canada.
1973-1977

RELATED WORK EXPERIENCE:

Hospital pharmacist
Iteghe Menen Hospital
Asmara, Eritrea
1970-1971

Teaching Assistant
Haile Selassie I University (National University)
1971-1973

Teaching Assistant

University of Alberta

1974-1977

PUBLICATIONS:

(1) E.E. Knaus and K. Redda, J. Heterocycl. Chem., 13, 1237 (1976).

(2) E.E. Knaus and K. Redda, Can. J. Chem., 55, 1788 (1977).