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SOME STUDIES ON N-(CARBONYLAMINO)-1,2,3,6-TETRAHYDROPYRIDINES

by

JUPITA M. YEUNG

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

IN PHARMACEUTICAL SCIENCES

(MEDICINAL CHEMISTRY)

FACULTY OF PHARMACY AND PHARMACEUTICAL SCIENCES

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled "Some studies on N-(carbonylamino)-1,2,3,6-tetrahyro-pyridines", submitted by Jupita M. Yeung, in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Pharmaceutical Sciences (Medicinal Chemistry).

E. E. Knaus
(Supervisor)

Date: November 24, 1983

DEDICATED TO

MY FAMILY.

ABSTRACT

N-Iminopyridinium ylides are useful precursors for the synthesis of reduced 1,2,3,6-tetrahydropyridyl heterocycles possessing analgesic and hyperglycemic activities. The facile sodium borohydride reduction of pyridinium ylides afforded the target 1,2,3,6-tetrahydropyridines as the sole product. The potential pharmacological use of hyperglycemic agents anorexiants and the mechanism of the sodium borohydride reduction are discussed.

The N-carbonyliminopyridinium ylides (126-145, 185-196, 229-243) were prepared via the Zincke salt method or by direct N-amination of pyridines with hydroxylamine-O-sulfonic acid or O-mesitylenesulfonyl-hydroxylamine followed by the benzoylation of the N-aminopyridinium salt. A plausible mechanism for the formation of the ylides via the Zincke salt method is discussed.

Four modifications of the lead compound N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125) were investigated to determine (1) the effect of aromatic substitution on the phenyl ring, (2) the effect of replacing the phenyl ring by other ring systems and substituents, (3) the significance of the carbonylamino moiety and 1,2,3,6-tetrahydropyridine ring, and (4) the influence which substituents on the 1,2,3,6-tetrahydropyridine ring have on analgesic and hyperglycemic activities. Thus, four series of compounds, viz N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177), N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-208), structurally related N-(phenylcarbonylamino)-1,2,3,6-

tetrahydropyridines (210-219, 221-226) and N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252-275) were synthesized and tested as analgesic and hyperglycemic agents.

The analgesic activities were measured using the phenylquinone writhing test. Some of these compounds were also tested using the hot plate test. Pretreatment with naloxone hydrochloride, a μ-narcotic antagonist, did not alter the analgesic activities of compounds 172, 205, 222 and 253 indicating that these compounds do not act at the μ-opiate receptor. The hyperglycemic activities of the 1,2,3,6-tetrahydropyridine analogues were determined by the procedure developed by Barthelmai and Czok.[215] The partition coefficients P were measured using the method of Fujita[225] to determine whether there was a correlation between P and pharmacological activity.

The pharmacological test results indicated that the N-(carbonylamino)-1,2,3,6-tetrahyropyridine moiety is the most important structural requirement for potent analgesic and hyperglycemic activity. No correlation between the partition coefficient P and analgesic or hyperglycemic activity was evident. The structure-activity relationships for analgesic and hyperglycemic activity have been discussed in detail.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Edward E. Knaus for his advice and guidance throughout the course of my studies and in the preparation of this thesis.

I wish also to express my appreciation to the Alberta Heritage Foundation for Medical Research for a Studentship for financial support during the course of my post-graduate studies.

Finally, my thanks to friends and colleagues for their advice and encouragement.

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LIST OF ABBREVIATIONS

bp	-	boiling point
cm	-	centimeter
°C	-	degrees Celsius
$CDCl_3$	-	deuterochloroform
DMSO-d_6	-	hexadeuterodimethyl sulfoxide
ED_{50}	-	exact 50% effective dose
g	-	gram
h	-	hour
HPLC	-	high pressure liquid chromatography
^1H nmr	-	proton magnetic resonance
ip	-	intraperitoneal
ms	-	mass spectrum
mp	-	melting point
mg	-	milligram
mL	-	millilitre
mmol	-	millimole
ptc	-	phase transfer catalyst
psi	-	pounds per square inch
sec	-	second
sc	-	subcutaneous
tlc	-	thin layer chromatography
TMS	-	tetramethylsilane
Cmr	-	carbon magnetic resonance

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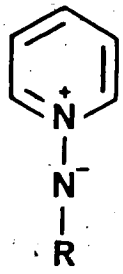
1.0.0.0.0 INTRODUCTION

It has become increasingly apparent that N-iminopyridinium ylides (1) and the protonated N-aminopyridinium salts (2) are useful precursors in heterocyclic chemistry, particularly for the synthesis of pyridine heterocycles.



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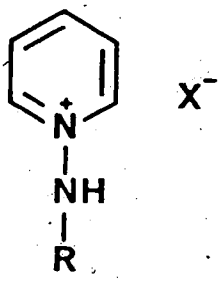

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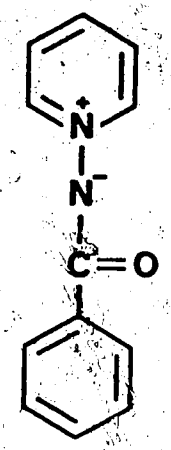
Efficient synthetic methods for the preparation of (1) have been developed. The nucleophilicity of the imino nitrogen, the electrophilicity of the pyridinium ring and the dipolar character permit a variety of reactions depending upon the nature of the substituents, the reagent and the reaction conditions.

The chemistry of the heteroaromatic N-imines has been reviewed.[1-4] Several nomenclatures have been used in the literature to describe N-iminopyridinium ylides. For example $C_5H_5\overset{+}{N}\text{-}\overset{-}{N}\text{-COPh}$ (3) has been named pyridine N-(or 1-)benzoylimine, pyridine N-(or 1-)benzoylimide, N-(or 1-)benzoyliminopyridinium ylide (or betaine), 1-benzoylamino-



(3)

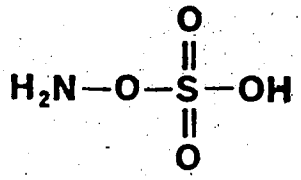
pyridinium hydroxide inner salt (Chemical Abstracts), or N-pyridiniobenzamidate (IUPAC). The N-iminopyridinium ylide nomenclature will be used in this thesis. The advantage of this name is that the iminopyridinium ylide nomenclature is in general use and it also expresses the isoelectronic relationship to pyridine-1-oxide.[5]

1.1.0.0.0 Synthesis of N-iminopyridinium ylides

The most useful synthetic methods can be classified in three categories: (i) direct N-amination, (ii) cyclization of hydrazone derivatives and (iii) miscellaneous methods.

1.1.1.0.0 Direct N-amination by hydroxylamine derivatives

The hydroxylamine derivatives used most extensively include hydroxylamine-O-sulfonic acid (HOSA) (4)[6-8] and O-mesitylenesulfonylhydroxylamine (MSH) (5)[9-11]. Recently, the new hybrid O-diphenylphosphinylhydroxylamine (DPH) (6) has been reported.[12]



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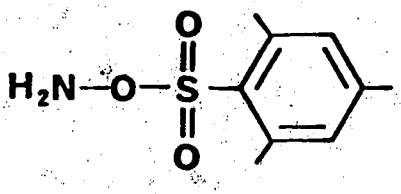

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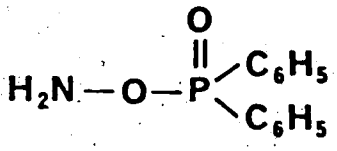

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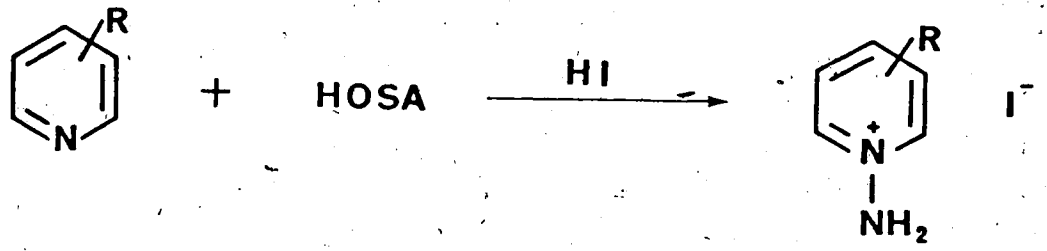
N-Aminopyridinium iodides (7) can be synthesized in satisfactory yield by reaction of an aqueous solution of the pyridine with HOSA (4) at elevated temperature.

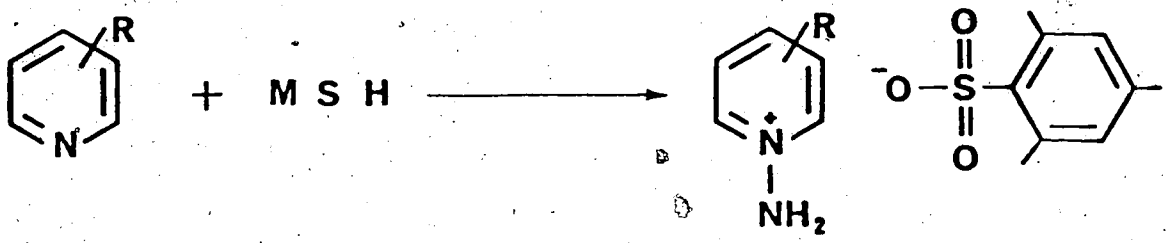


(4) (7)

The N-amination of pyridines bearing electron-withdrawing substituents (e.g. COEt, CN, NO_2)[13,14] with HOSA does not occur but it is widely used for the synthesis of many other heteroaromatic

N-aminoazonium salts.[8,14-22]

N-Amination with MSH[11] is one of the most efficient methods for the preparation of N-aminoazonium salts (8). Pyridines,[11,23-26] quinolines,[27-29] naphthyridines,[30] fused pyridines,[39] phenanthridines,[31,32] acridines,[33] diazines,[29] pyrazoles,[34,35] indazoles,[34] fused indazoles[36,37] and fused triazoles[37] have been N-aminated with MSH.



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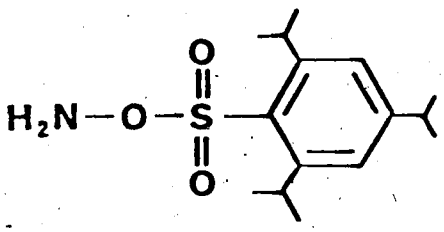
The less reactive O-2,4,6-triisopropylbenzenesulfonylhydroxylamine (9)[10] and the less stable p-toluenesulfonylhydroxylamine (10)[37-40] have also been used to N-aminate pyridines. Chloramine (NH_2Cl) is not sufficiently reactive for this purpose.[41]



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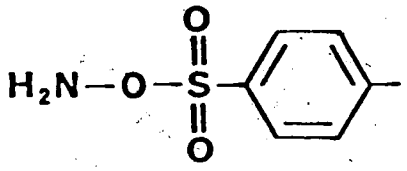

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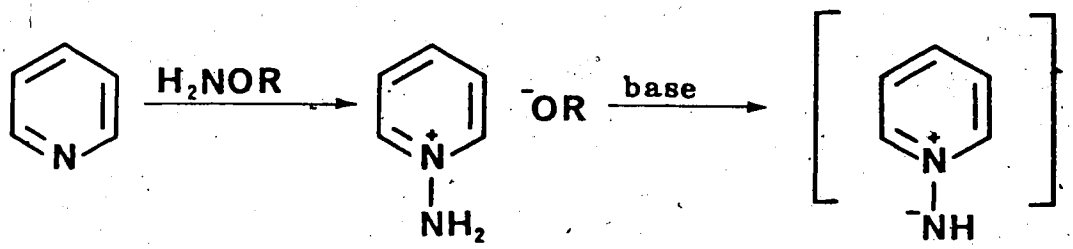
1.1.1.1.0 N-1 Unsubstituted iminopyridinium ylides

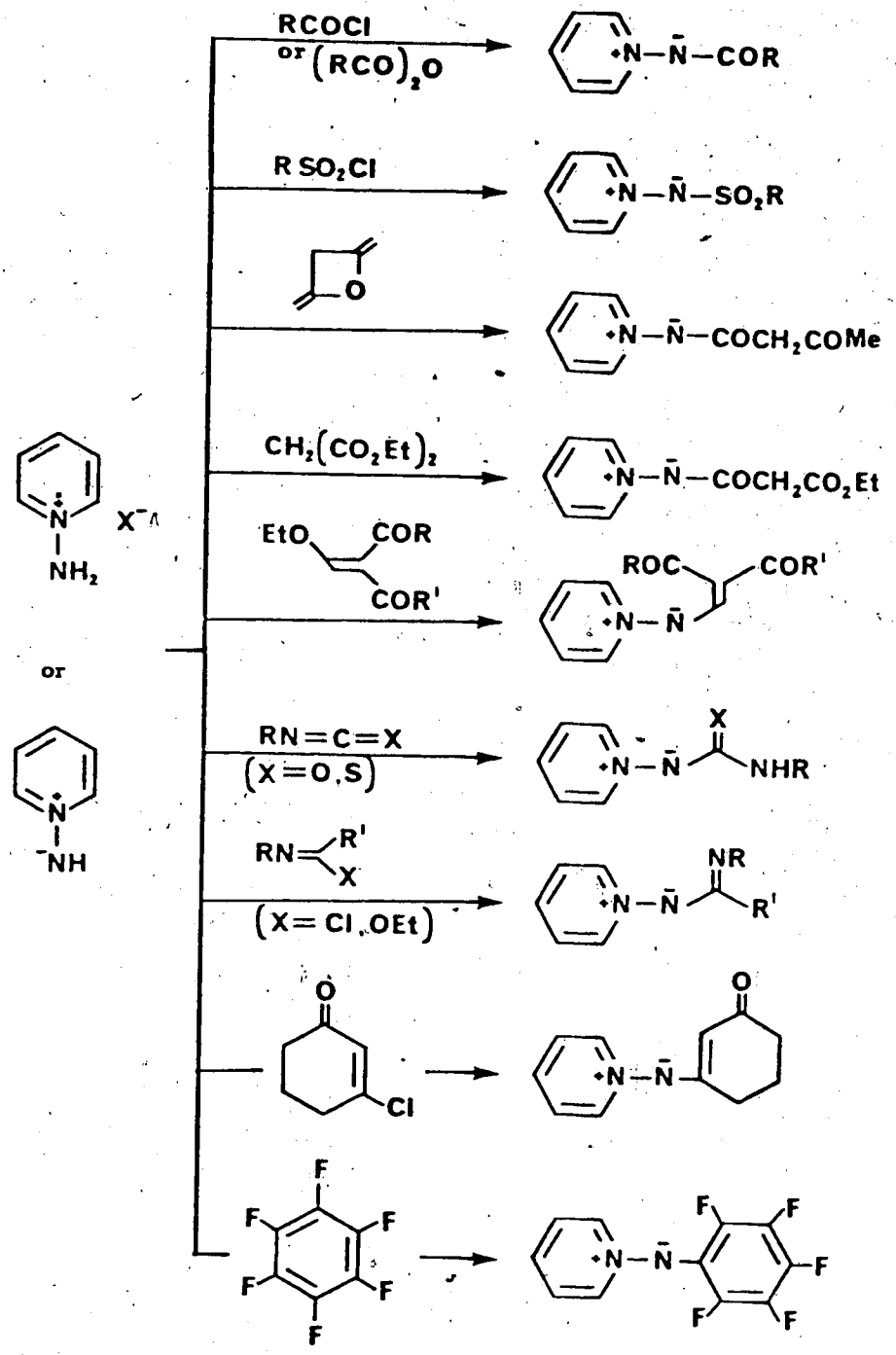
The N-1 unsubstituted iminopyridinium ylides are generally generated in situ by treatment of the N-aminopyridinium salt with base and are used without isolation for subsequent reactions due to their instability. The N-1 unsubstituted iminopyridinium ylide (11) has not been isolated to date.



(11)

1.1.1.2.0 N-1 Substituted iminopyridinium ylides

The N-1 substituted iminopyridinium ylides can be prepared by the reaction of N-aminopyridinium salts, in the presence or absence of base, with anhydrides or acyl halides,[14,16,17,20,21,42,43] diketene,[44] diethyl malonate,[45] sulfonyl chlorides,[14,46,47] α-halovinyl ketones and esters,[48-51] diethyl ethoxymethylenemalonate and related compounds,[50,52-54] isocyanates,[17,55] thioisocyanates [17,55] imidoyl chlorides and imidates,[56,57] nitro acetates, [14,58] and active halobenzenes.[59-61] Some representative N-imino pyridinium ylides prepared in this way are summarized by Scheme 1.



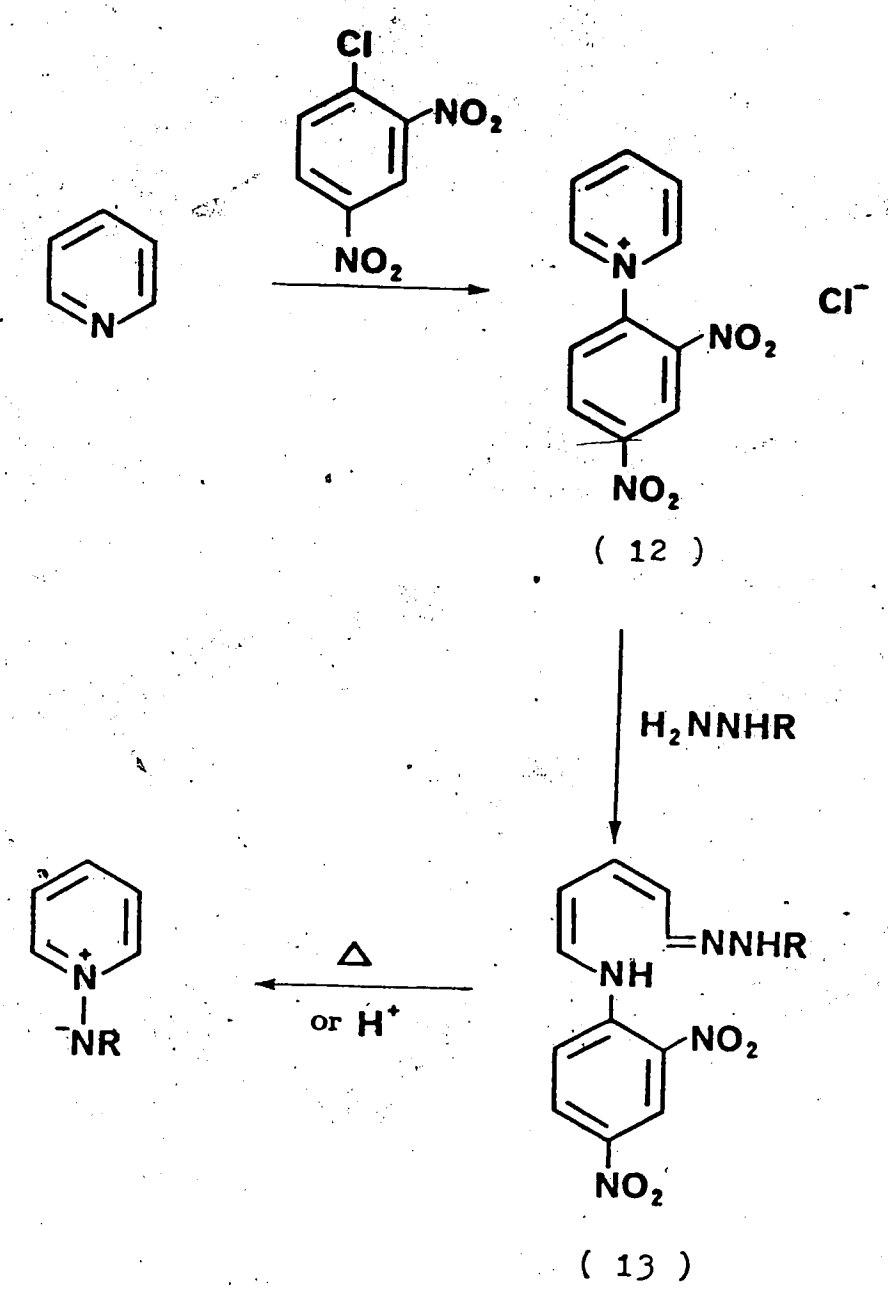
Scheme 1. Some representative N-iminopyridinium ylides prepared using N-aminopyridinium salts as precursors

1.1.2.0.0 Cyclization of hydrazone derivatives

The synthesis of N-iminoazonium ylides, formed by the ring opening of N-(2,4-dinitrophenyl)pyridinium chlorides or pyrylium salts upon reaction with hydrazine derivatives followed by recyclization, has been known for many years. In particular, the latter procedure was the first method reported for the synthesis of N-iminopyridinium ylides.[62]

1.1.2.1.0 Preparation from N-(2,4-dinitrophenyl)pyridinium chlorides and hydrazine derivatives

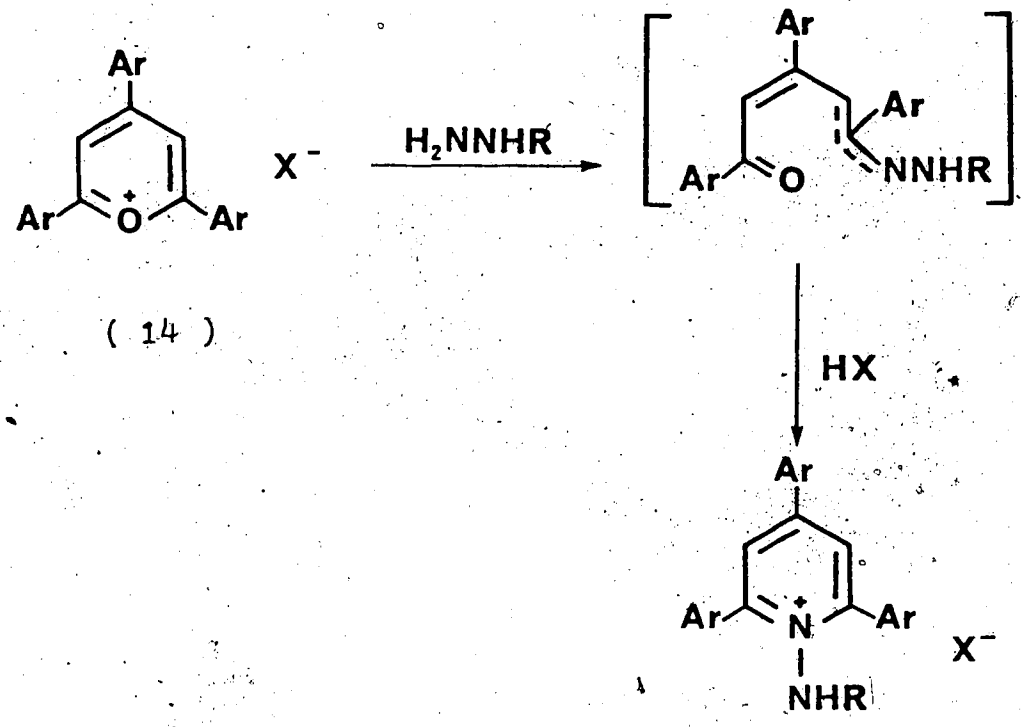
N-(2,4-Dinitrophenyl)pyridinium chlorides ("Zincke salts") (12), prepared from the reaction of pyridines with 2,4-dinitrochlorobenzene, react with hydrazine or monosubstituted hydrazine derivatives to give 5-(2,4-dinitroanilino)-2,4-pentadienal monohydrazones (13). The hydrazones recyclize upon heating at reflux in dioxane-water (4:1) or treatment with acid to give the corresponding N-iminopyridinium ylides. This method can be applied to pyridine,[63-67] 3-substituted (except those having an electron-withdrawing substituent) pyridines,[14,68,69] and 4-alkylpyridines.[68,69] The reaction fails for α-substituted pyridines.[69]



1.1.2.2.0 Preparation from pyrylium salts and hydrazine derivatives

Pyrylium salts (14) also react with hydrazine and hydrazine derivatives to give N-iminopyridinium ylides.[47,62,70-76] The reaction

involves the formation of intermediate hydrazones due to nucleophilic attack at the α-position of the pyrylium ring. The hydrazones undergo ring closure followed by dehydration. This method is only applicable to polysubstituted N-iminopyridinium ylides.



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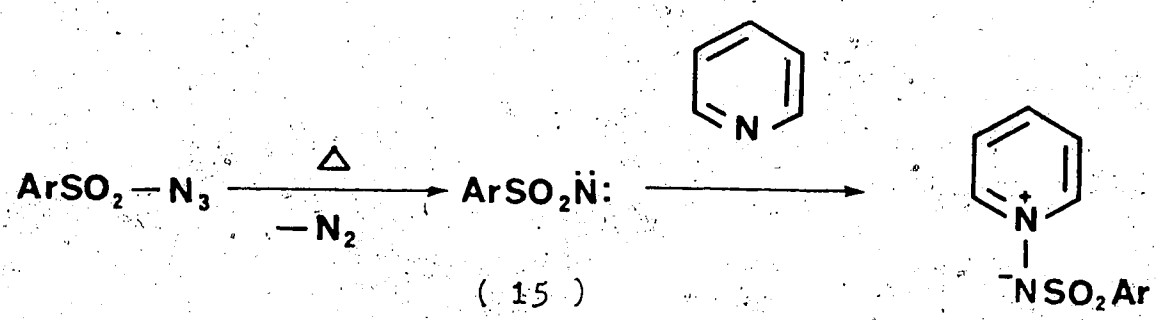
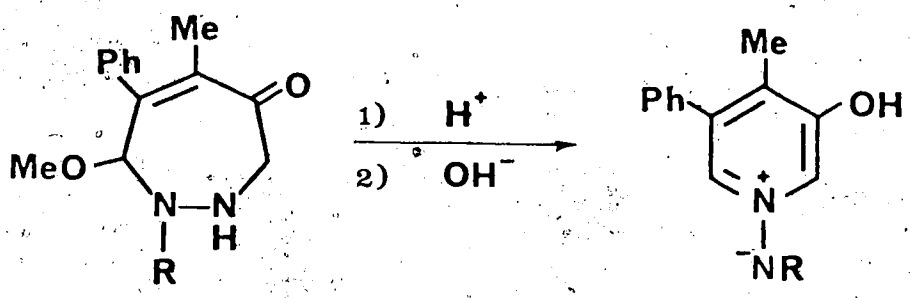
1.1.3.0.0 Miscellaneous methods

Nitrenes (15), generated photochemically or thermally from sulfonylazides or carbonylazides, add to the pyridine nitrogen to afford the N-iminopyridinium ylides as the major products.[20,21,47,77-81] However the yields are usually low and the scope is severely limited.



(15)

The formation of N-iminopyridinium ylides by acid catalysed rearrangement of some diazepinones (16)[82] and thermal reversion of 1,2(1H)-diazepines (17)[83] have also been extensively investigated.



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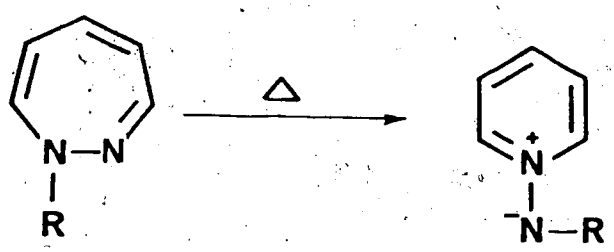

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1.2.0.0.0 Physical properties of N-iminopyridinium ylides

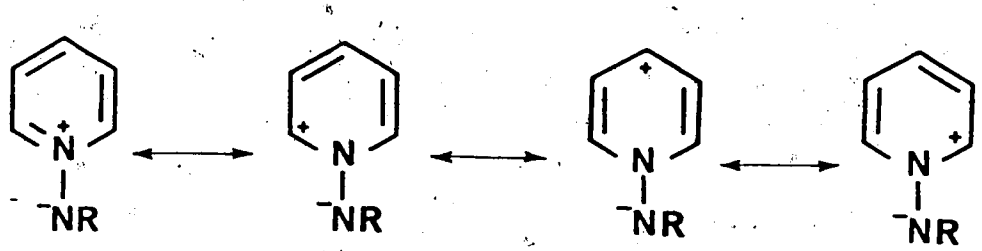
A systematic investigation of the physical properties of N-iminopyridinium ylides has not been reported. The data which is available is reported primarily in the experimental sections of publications.

1.2.1.0.0 Solubility

N-Iminopyridinium ylides are usually crystalline solids which are water soluble. The resulting solutions are neutral (pH 6.9 - 7.2)and exhibit low conductivity.[3,84] Most N-iminopyridinium ylides are soluble in polar solvents such as methanol, ethanol, chloroform and dichloromethane but are only very sparingly soluble in ether, benzene and other non-polar solvents.

1.2.2.0.0 Photoelectron spectra

The X-ray photoelectron spectra of N-acyliminopyridinium and N-arenesulfonyliminopyridinium ylides have been measured.[85] The binding energies of the 1s electrons of their nitrogen atoms indicate that the negative charge remains, to a large extent, on the imino nitrogen atom, whereas the positive charge on the ring nitrogen is delocalized on the pyridine ring with a high positive charge density at the 2- and 6-positions. This observation is in accord with the fact that N-iminopyridinium ylides can serve as 1,3-dipoles (azomethine imine). The following canonical structures (18 - 23) depict the possible charge delocalization.



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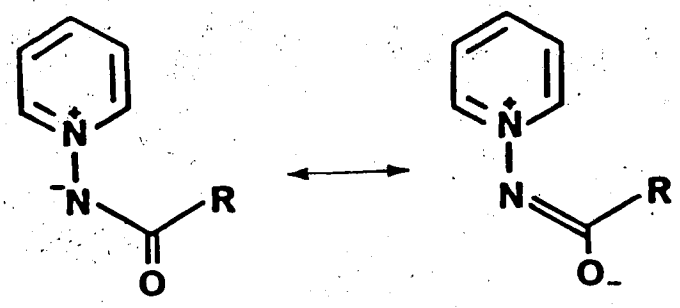

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1.2.3.0.0 Infrared spectra

The infrared (ir) spectral characteristics of acyliminopyridinium ylides have been reviewed.[1-3] The stretching frequencies of the resonating carbonyl group (22 - 23) for acyliminoazonium ylides are always present in the 1550 - 1650 cm^{-1} region.[3,20,21,26,42,65-67,86] These frequencies are generally about 100 cm^{-1} lower than those of the corresponding carbonyl portion of the amides, thus providing evidence for delocalization of the negative charge. The canonical form (23) indicates that the double bond character of the carbonyl portion of the imide is decreased. Consequently, the force constants of such bonds are also decreased, causing a frequency shift to a lower wavenumber.[87]

1.2.4.0.0 Ultraviolet spectra

The ultraviolet (uv) absorption spectra of N-iminopyridinium ylides are dependent upon many factors such as substituents attached to the imino nitrogen or to the pyridine ring and the solvent used. N-Acyliminopyridinium ylides usually show two intense absorption maxima at 230 - 235 and 330 - 360 nm in aprotic solvents such as chloroform or

dioxane.[20,21,68,69] In protic solvents such as methanol or water a hypsochromic effect for the long-wavelength absorption is observed. For example, N-iminopyridinium ylide displays a maximum at 352 nm in dioxane but at 313 nm in ethanol.[21] This long-wavelength absorption has been ascribed to a $n - \pi^*$ transition of the lone-pair electrons of the imino nitrogen.[88]

1.2.5.0.0 Nuclear magnetic resonance spectra

A complete analysis of the ^1H nmr spectra of a series of substituted N-iminopyridinium ylides has been reported.[89] The chemical shift positions (δ) for the pyridinium ring protons decrease in the following order where H-2(H-6) > H-4 > H-3 (H-5), as demonstrated by the canonical structures (18 - 21). The H-2 and H-6 absorptions are generally present at about 8-9 while H-3, H-4 and H-5 appear between 7.5 - 8.5. The chemical shifts may be influenced by substituent effects.[42,47,65-76,86,89] Although the exact position of H-4 cannot be obtained directly from the ^1H nmr spectrum, the Cmr spectrum of N-benzoyliminopyridinium ylide clearly indicates the significant downfield shifts of C-2 (143.1 ppm) and C-4 (137.8 ppm) relative to C-3 (129.4 ppm) which reflects the electron density of these positions.[90]

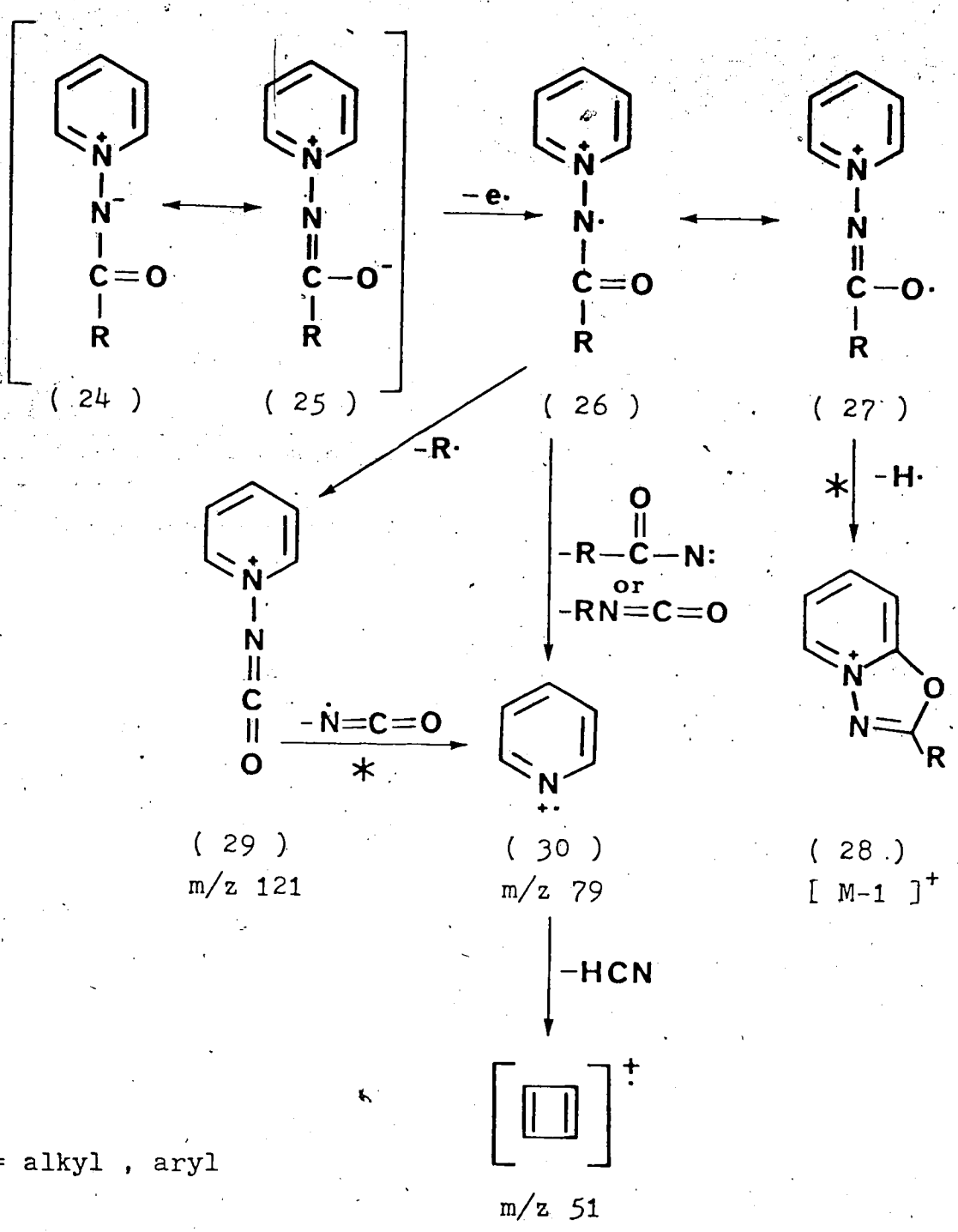
1.2.6.0.0 Mass spectra

The mass spectra of N-1 unsubstituted pyridine N-imines generated within the ion source by pyrolysis of the corresponding

hydrochlorides have been determined.[91] The mass spectrum exhibits peaks attributed to the loss of 15 (NH) and 16 (NH_2) mass units from the molecular ion.

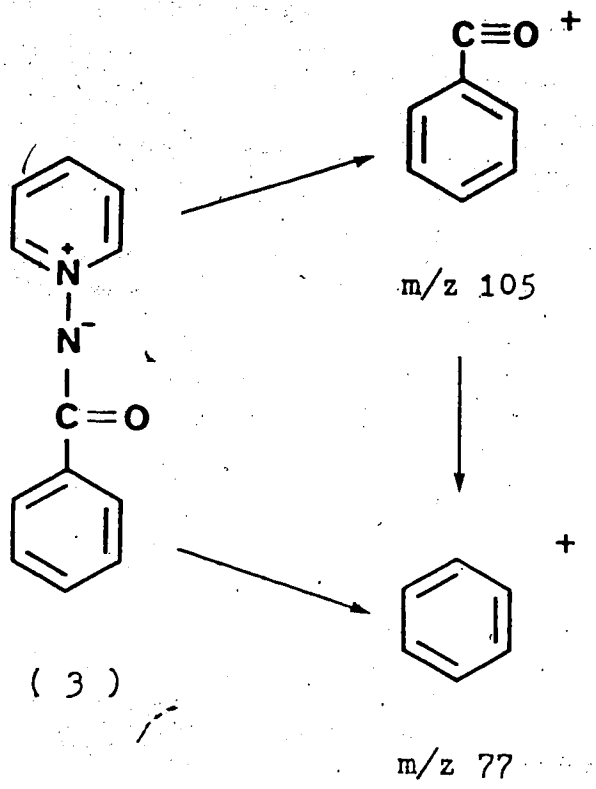
The major fragmentation of N-acyliminopyridinium ylides can be rationalized in terms of a charge localization on the pyridine nitrogen.[92] Examination of the canonical structures (24) and (25) indicates that an electron can be expelled either from the imino nitrogen to give the molecular ion (26), or from the oxygen to give the molecular ion (27). N-Acyliminopyridinium ylides normally exhibit a $[M-1]^+$ ion as well as an intense molecular ion except when R is ethoxy (24).[92] This fragmentation was accompanied by a large metastable peak in all spectra that exhibit a $[M-1]^+$ ion. The α-hydrogen that is lost has been established by deuterium labelling experiments.[92] The resulting fragment ion is best represented by a fully aromatized structure (28).

The most important primary fragmentation process for N-acyliminopyridinium ylides is α-cleavage of the molecular ion as indicated by Scheme 2. Loss of the R· radical affords a peak at m/z 121 attributed to (29) which is sometimes supported by a metastable peak. This ion fragments further by elimination of N=C=O to furnish a pyridine ion (30) at m/z 79 which is often supported by an appropriate metastable peak. Ion (30) can then expel hydrogen cyanide to give a peak at m/z 51, $[C_4H_3]^+$ which is always present in higher relative abundance than



R = alkyl , aryl

Scheme-2 Major fragmentation pathways for N-acylimino-pyridinium ylides



(3)

the fragment at m/z 79. On the other hand, charge retention on the acyl moiety also occurs to some extent since less intense peaks appear at m/z 105 and m/z 77 when R is a phenyl group (24).[92]

1.2.7.0.0. Acid-base properties

The basicity of N-iminopyridinium ylides is dependent upon the nature of the substituents attached to the imino nitrogen. Thus, N-1 unsubstituted iminopyridinium ylide (pka 13.6[14]) and N-methyl-iminopyridinium ylide (pka 12-13[93]) are very strong bases. Whereas N-acyliminopyridinium ylides (pka 3.2 for N-benzoylimine[14] and 3.6 for N-acetylimine[93]) and N-nitroiminopyridinium ylide (pka 4.6[14]) are weak bases.

N-Acyliminopyridinium ylides undergo hydrogen-deuterium exchange at the 2- and 6-positions upon treatment with deuterium oxide.[94] On the other hand, N-acyliminopyridinium ylides undergo exchange at the 2-, 4-, and 6-positions only in the presence of base.[14]

1.3.0.0.0. Chemical properties of N-iminopyridinium ylides

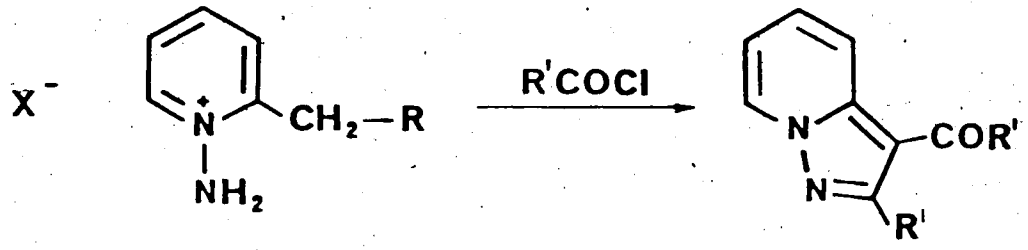
N-Iminopyridinium ylides possess a variety of reactivities depending on the nature of the substituents attached to the pyridinium ring and to the imino nitrogen. The most important types of reactions N-iminopyridinium ylides undergo are (i) reaction with electrophiles at the imino nitrogen, (ii) nucleophilic attack upon the pyridinium ring, (iii) 1,3-dipolar cycloaddition reactions, (iv) photochemical reactions, (v) thermal reactions, and (vi) reduction reactions.

1.3.1.0.0. Reactions with electrophiles

Reaction of N-aminopyridinium salts with acylating agents, imidoyl chlorides and active halobenzenes provides a general method for the preparation of N-1 substituted iminopyridinium derivatives (see section 1.1.1.2.0).

In general, alkylation of N-acyliminoazonium ylides take place at the imino-nitrogen even though both N-alkylation and O-alkylation of the imino group (22 and 23) are possible.[16,45,95,96] In contrast, alkylation of the N-phenylcarbonyliminopyridinium ylide (3) afforded only the O-alkylated product.[97]

Treatment of 2-alkyl or 2-hydroxymethyl-1-aminopyridinium salts (31) with acyl or aroyl chlorides in the presence of base afforded the bicyclic pyrazolo[1,5-a]pyridine derivatives (32). If the 3-position is not substituted cyclization also occurs at this position.[18,98]

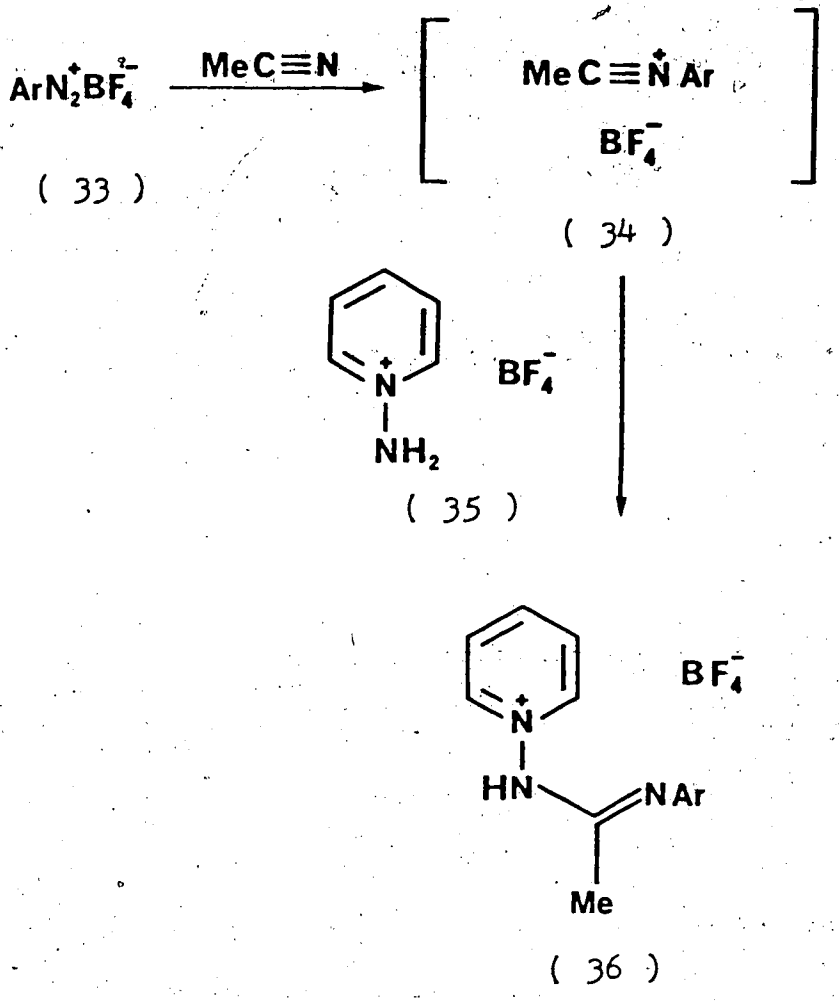


(31)

R = H , OH

(32)

Reaction of N-aminopyridinium chloride and pyridine N-imine with aryl diazonium salts gave aryl azides in high yields.[99] However reaction of N-aminopyridinium tetrafluoroborate (35) with aryl diazonium tetrafluoroborates (bearing the electron-withdrawing groups in the aryl group) (33) in acetonitrile gave N-(arylacetimidoyl)aminopyridinium salts (36). It has been suggested that the nitrilium ion (34) resulting from N-arylation of the solvent acetonitrile is attacked by the N-amino-pyridinium salt to give (36).[99]



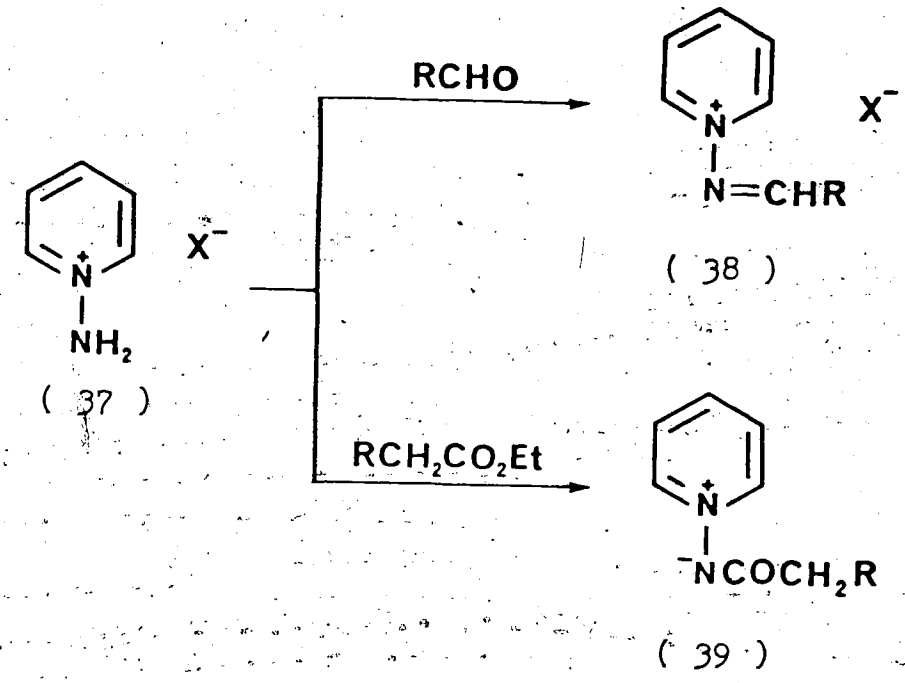
(33)

(34)

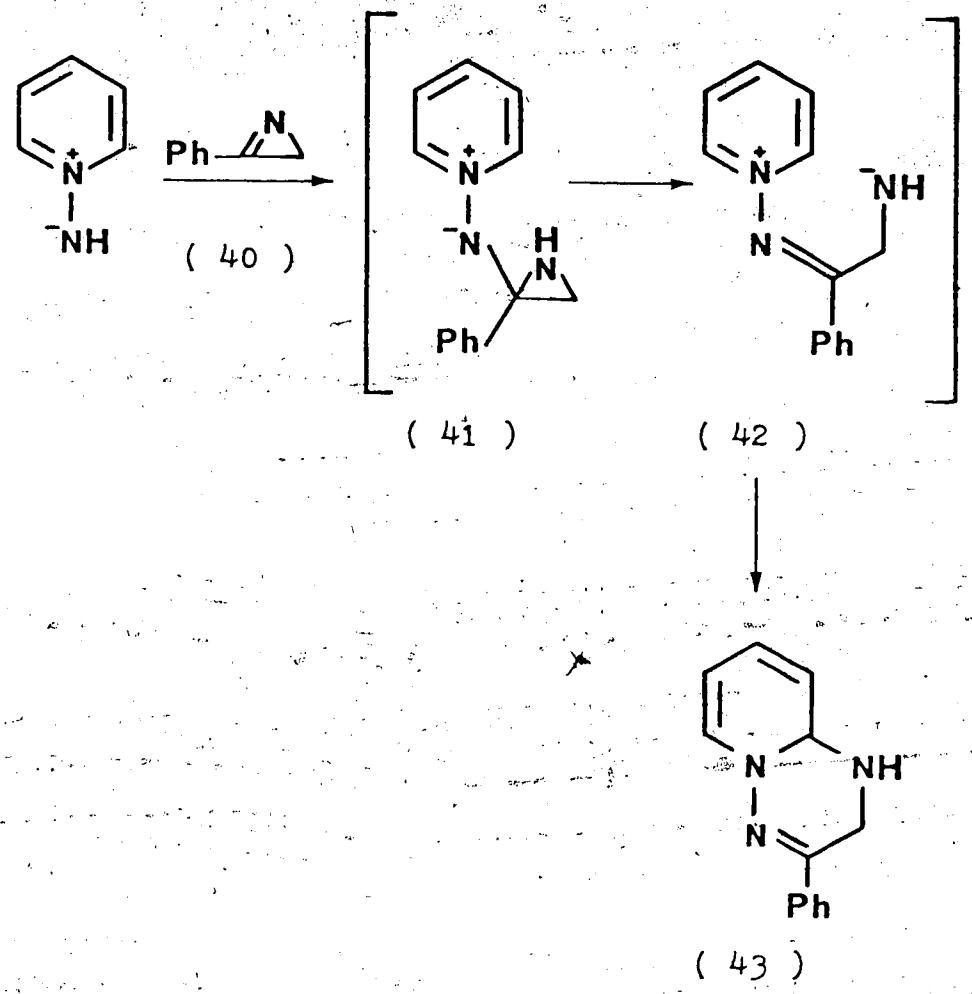
(35)

(36)

The reaction of N-aminoazonium salts (37) with aliphatic and aromatic aldehydes in the absence of base yielded the Schiff bases (38) in high yields.[99-102] Some esters such as diethyl malonate and ethyl cyanoacetate react with (37) in the presence of base to give the corresponding N-acyliminopyridinium ylides (39).[45]



Reaction of pyridine N-imines with the 2H-azirine (40) gave pyrido[1,2-b]triazine derivatives (43).[103-104] Although two modes of cycloaddition are possible for 3-substituted pyridine N-imines reaction of the 3-methyl derivative involved cycloaddition to the more hindered side. On the other hand, pyridine N-imines possessing electron-withdrawing substituents at the 3-position gave exclusively the cycloadduct resulting from addition to the less hindered side. This reaction probably involves nucleophilic addition of the N-imine to the 2H-azirine (40) to form (41) which may then undergo ring opening followed by cyclization of the 1,6-dipole (42) to give (43).



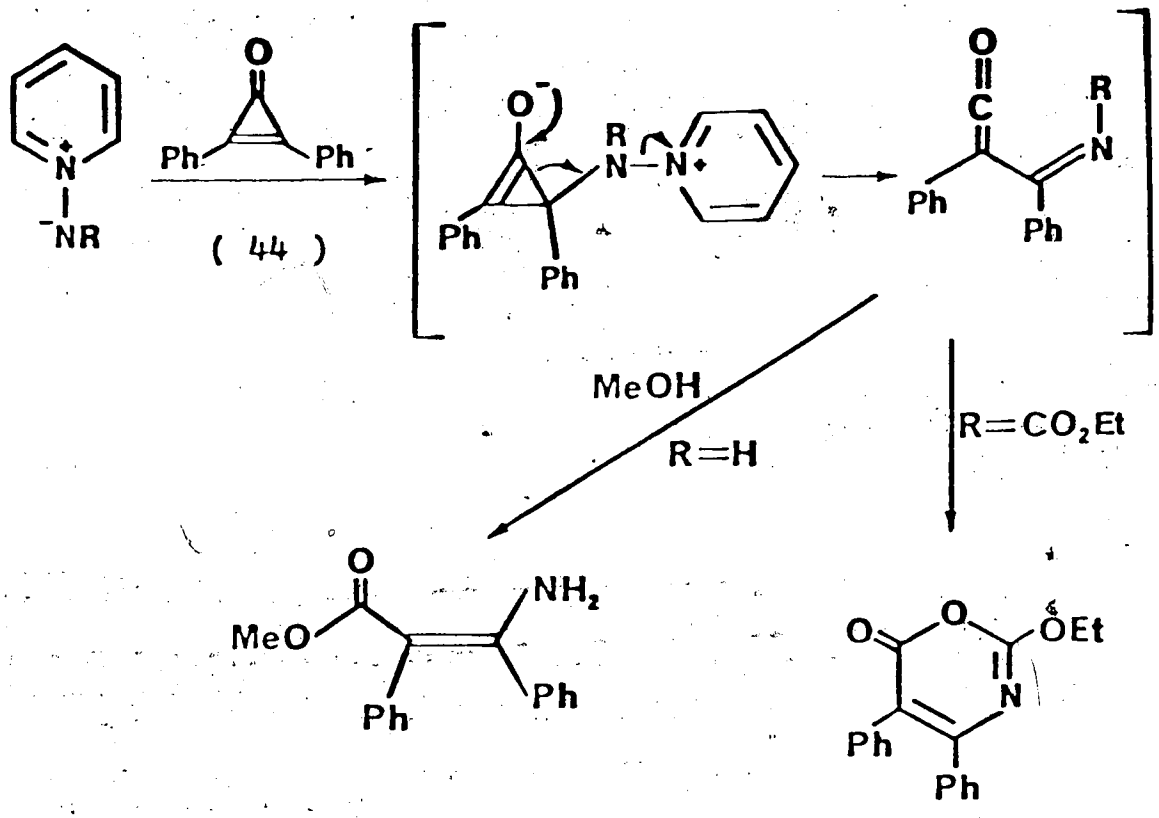
(40)

(41)

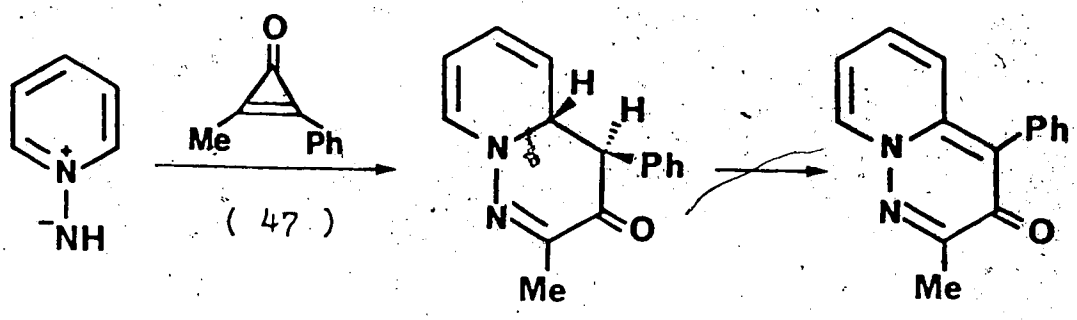
(42)

(43)

Diphenylcyclopropenone (44) is a highly reactive electrophilic carbonyl compound, which reacts with N-acyliminopyridinium ylides to give the 1,3-oxazin-6-one (45).[43,105] The reaction of pyridine N-imine with the cyclopropenone (44) in methanol afforded methyl 3-aminoacrylate (46).[106] It was proposed that these reactions involved ketene intermediates which are intercepted either by internal nucleophiles or by the solvent.



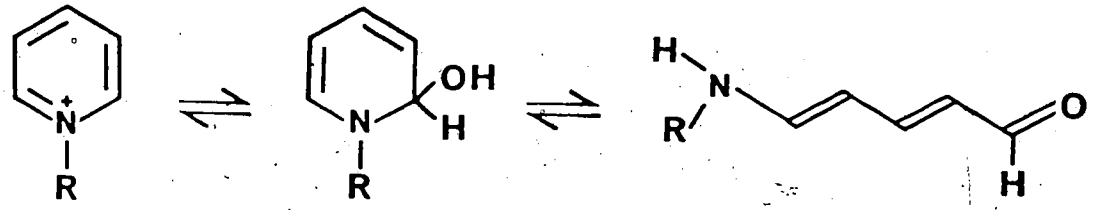
Another interesting difference in reactivity has also been observed. When pyridine N-imine was allowed to react with methylphenylcyclopropenone (47) in methanol, 3H-pyrido[1,2-b]pyridazin-3-one (49) was obtained in addition to a methyl 3-aminoacrylate.[107,108]



(48) (49)

1.3.2.0.0 Reaction with nucleophiles

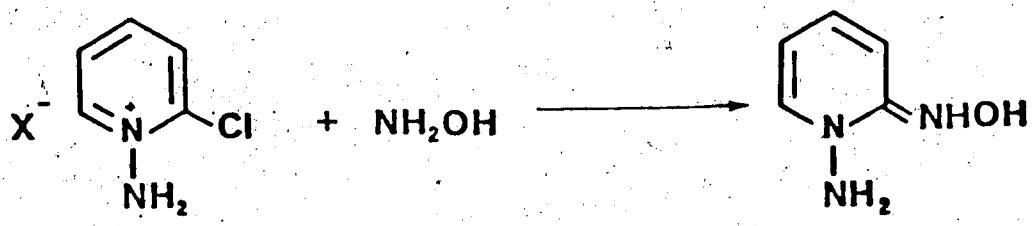
Nucleophilic attack by hydroxide ion at the C-2 position of pyridinium salts leading to the formation of pseudobases (50) is well known.[109-111] In many cases this is followed by a ring opening reaction and the formation of glutaconaldehyde derivatives (51). However, N-acyliminoazonium ylides are relatively stable to alkali.[112]



(50) (51)

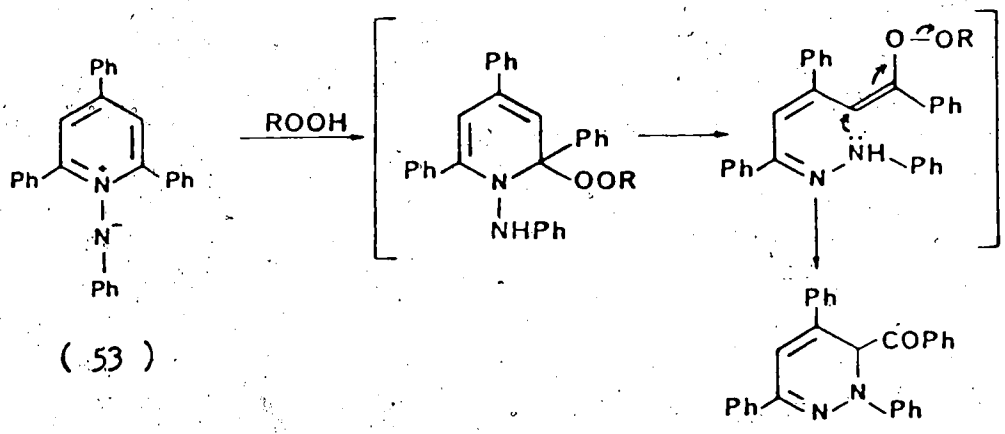
R = alkyl , aryl , substituted heteroatom

It has recently been reported that reaction of N-amino-2-chloropyridinium salts with hydroxylamine gave 1-amino-2-hydroxyimino-1,2-dihydropyridine (52).[113]



(52)

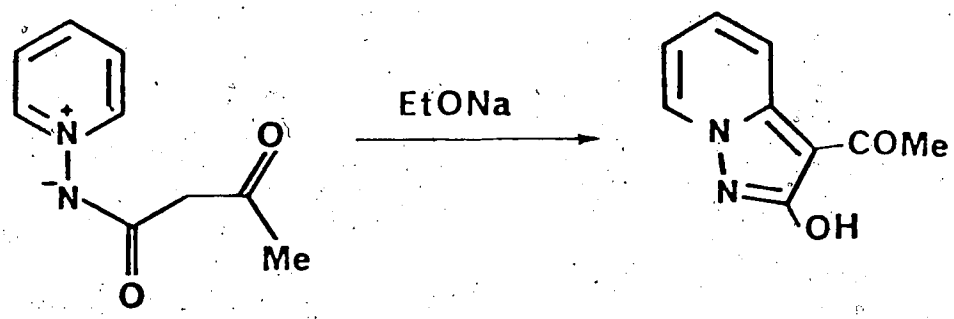
The N-phenyliminopyridinium ylide (53) has been reported to react with hydroperoxides (R = t-Bu, H) to give 1,6-dihydropyridazines (54).[114] This reaction may involve nucleophilic attack by the hydroperoxide ion at the 2-position of the pyridinium ring followed by ring opening and recyclization to yield (54).



(53)

(54)

The intramolecular cyclization of N-acetoacetyliminopyridinium ylide (55) upon treatment with sodium ethoxide yielded pyrazolo[1,5-a]-pyridine (56).[44]

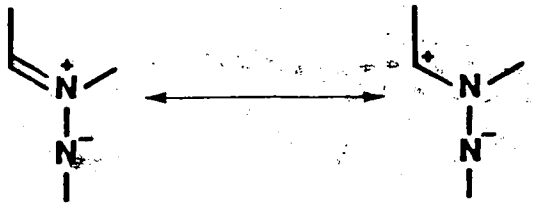


(55)

(56)

1.3.3.0.0 1,3-Dipolar cycloadditions

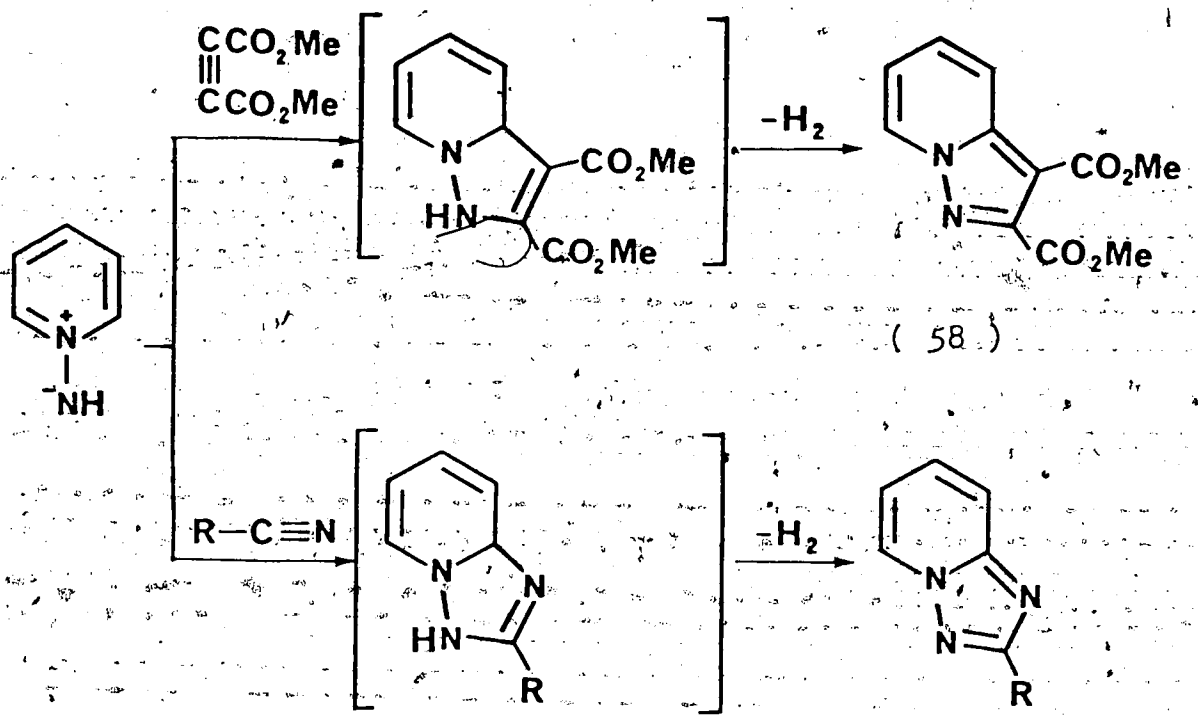
The 1,3-dipolar cycloaddition reaction of N-iminoazonium ylides have been studied extensively following the observation by Huisgen et al that they possess 1,3-dipolar character.[115] The 1,3-dipolar character of azomethine imine (57) is illustrated below.[116] The 1,3-dipolar cycloaddition reaction of a variety of activated alkynes and alkenes with N-iminopyridinium ylides afforded bicyclic dihydropyrazoles and tetrahydropyrazoles respectively.[116] The aromaticity of the heteroaromatic ring is destroyed after the initial reaction. Consequently



(57)

the primary cycloadducts usually undergo further reaction to achieve stabilization by aromatization, hydrogen transfer, rearomatization by rearrangement or N-N bond cleavage. These secondary reactions are highly dependent upon the nature of the heteroaromatic ring and the substituents present, particularly those attached to the imino nitrogen.

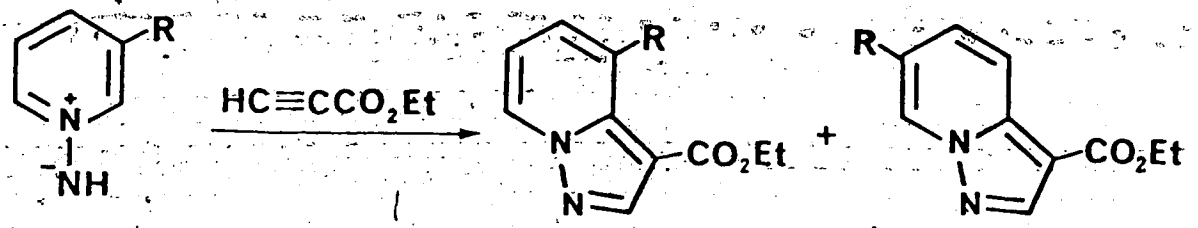
The 1,3-dipolar cycloaddition reaction of pyridine N-imine with activated dipolarophiles such as acetylenic esters,[55,115,117,118] ketones,[119] nitriles,[93,120] ethyl acetoacetate,[101] acetylacetone,[101] and β-haloacrylates[51] provided a facile synthesis of many pyrazolo[1,5-a]pyridines (58) and triazolo[1,5-a]pyridines (59).



(58)

(59)

Substituted N-iminopyridinium ylides also undergo the 1,3-dipolar cycloaddition reaction. The effect of substituents upon the side of attack in the reaction between ylides and ethyl propiolate has been investigated.[121] The results indicated that unless a large substituent is present at the 3-position, the cycloaddition reaction occurred preferentially at C-2 of the pyridinium ring, regardless of the electron-donating or electron-withdrawing character of the substituent. When the C-3 substituent is hydroxy, amino or acetamido exclusive addition at C-2 was observed.

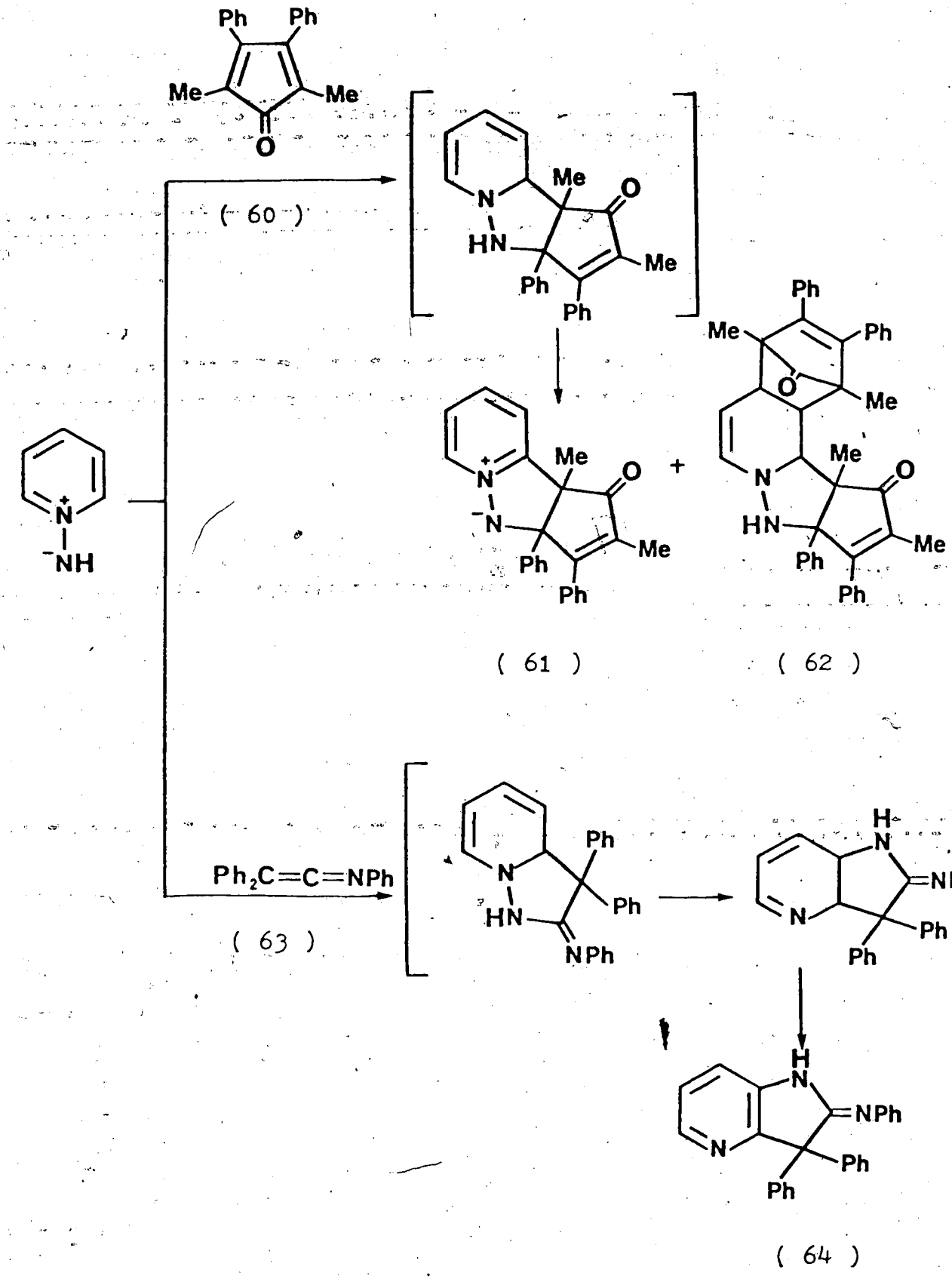


It has been reported that pyridine N-imine reacted with the cyclopentadienone (60) to give the previously unreported ylides (61) and the 1:2 adduct (62).[122] Pyridine N-imine also reacted with triarylketeneimines (63) to give (64).[123] A number of similar reactions have been reported recently.[124-126]

N-Acyliminopyridinium ylides also undergo the 1,3-dipolar cycloaddition reaction with various dipolarophiles. The order of reactivity as 1,3-dipoles is N-alkoxycarbonyl>N-acetyl> N-benzoyl.[80, 127] The differences in reactivity are due to variations in the electron density at the imino nitrogen which is greater for the N-alkoxycarbonyl than for N-benzoyl analogues.

1.3.4.0.0 Thermal Reactions

The most important thermal reactions that occur for substituted N-iminopyridinium ylides are intramolecular 1,5-cyclization and N-N bond fission. The reactions are highly dependent upon the nature of the substituent attached to the imino nitrogen. Thus, when the cyclic α-ketovinyliminopyridinium ylide (65) is heated at reflux in toluene, the fully aromatized pyrazolo[1,5-a]pyridine (66) is obtained.[48,49]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Ph
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Me
O
(60)
Me
O
N
HN
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Ph
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Ph
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O
Me
N
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(62)
Ph2C=C=NPh
(63)
Ph
N
HN
Ph
NPh
H
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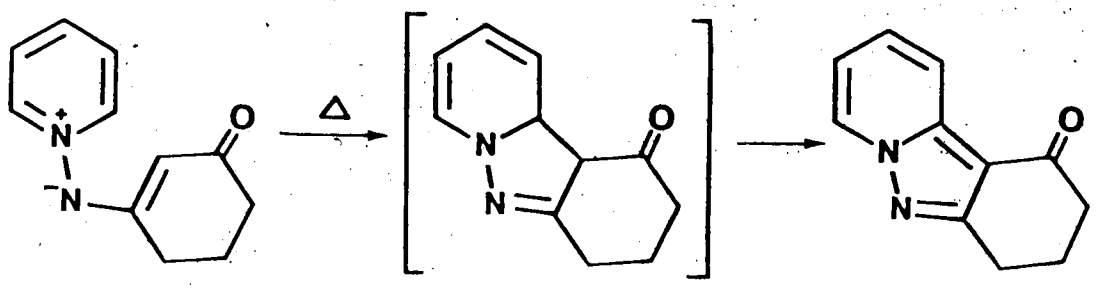
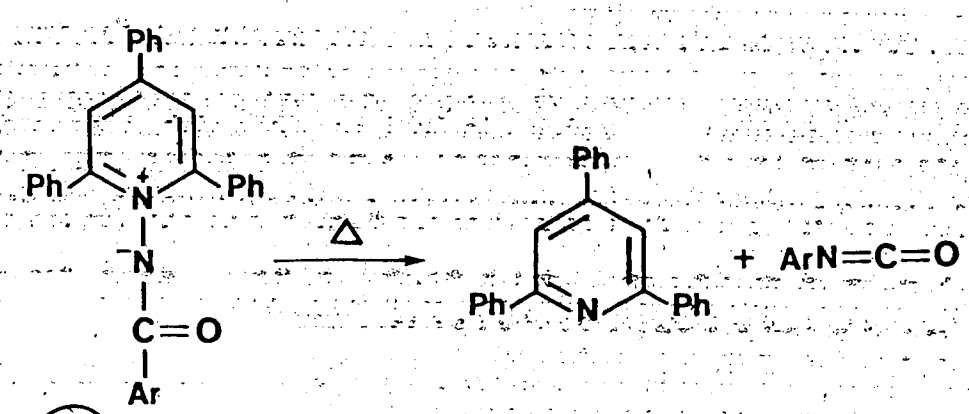
(64)

Additional examples involving thermal reactions have been reported subsequently.[50,52,54,128]



(65) (66)

Although N-acyliminopyridinium ylides exhibit 1,5-dipolar character, no intramolecular cyclization reaction has been reported to date. The predominant reaction is nitrogen-nitrogen bond cleavage. When N-benzoyliminopyridinium ylide is heated above its melting point (about 190 - 200°C), N-N bond fission occurred followed by a Curtis rearrangement to give pyridine and phenyl isocyanate which was isolated as diphenylurea.[129] It has been reported that the decomposition occurred at temperatures which were about 100°C less in the presence of copper (II) chloride.[130] The thermolysis of N-benzoylimino-2,4,6-triphenyl-pyridinium ylides (67) at 220°C afforded phenylisocyanate (68) in high yield. The reaction represents a new general method for the preparation of aryl isocyanate.[73,74]



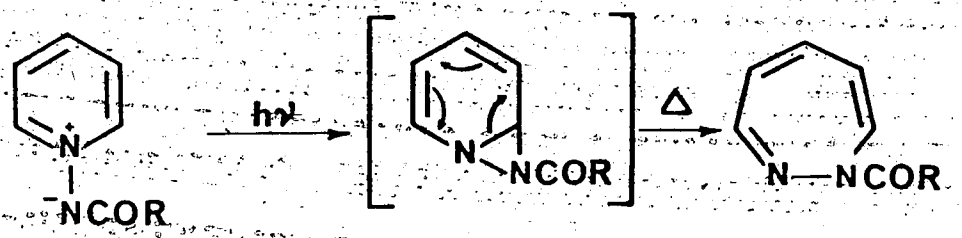
(67) (68)

1.3.5.0.0 Photochemical reactions

To date, several types of photochemical reactions involving N-iminopyridinium ylides have been reported. The most common photochemical reactions involve ring enlargement to 1,2-diazepines, 1,2-migration of the imino nitrogen and N-N bond scission. The photochemical reaction which occurs is highly dependent upon the nature of the substituent attached to the pyridinium ring or the imino nitrogen. An extensive review has been published.[131]

The photochemical synthesis of 1,2-diazepines from N-acyliminopyridinium ylides are now accepted procedures. Thus N-benzoylimino-,[21,25,26,132,133] N-acetylimino-,[25,81,132,134] and N-alkoxycarbonyliminopyridinium[20,21,81,135-137] ylides can be transformed into the corresponding 1,2-diazepines in high yields. This photorearrangement has been postulated to proceed via a 1,7-diazanorcaradiene intermediate (69). The intermediate (69) could be formed by a photo-

induced electrocyclic reaction of the 1,3-dipole followed by a thermally allowed disrotatory ring opening reaction which would give rise to the 1,2-diazepine (70).[138,139]



(69) (70)

The effect which ring substituents have upon the photochemical rearrangement of N-acyliminopyridinium ylides has been investigated.[131-133] The results can be briefly summarized as follows:

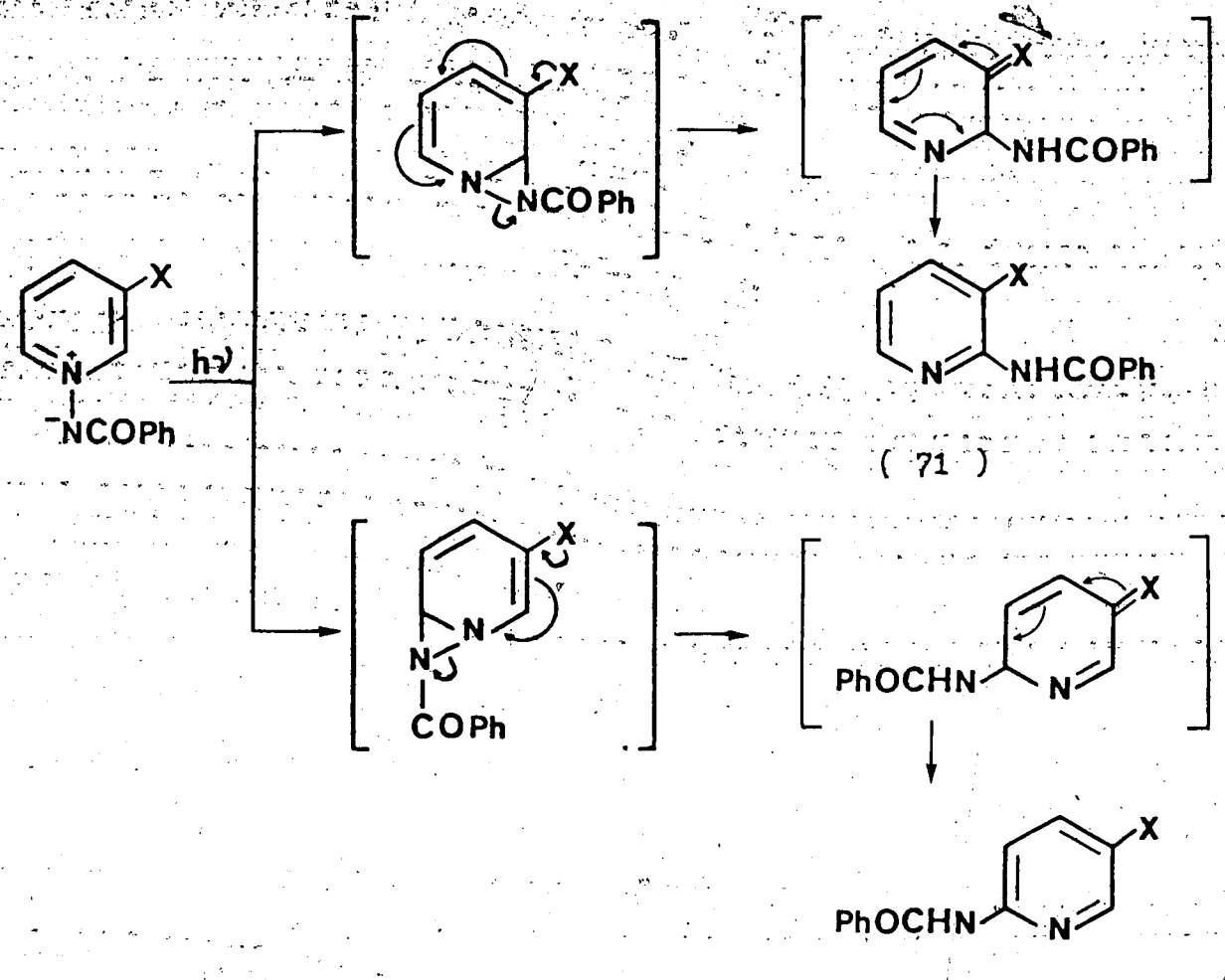
(1) Electron-donating substituents at the 4-position facilitate ring expansion to 1,2-diazepines whereas strong electron-withdrawing substituents prohibit this reaction.

(2) Substituents at the 2-position facilitate a regiospecific ring enlargement to the corresponding 3-substituted 1,2-diazepines presumably because of a steric effect which would prevent ring closure by the imino nitrogen at the C-2 position.

(3) Electron-withdrawing substituents attached to the 3-position exert a strong directing effect to give 4-substituted-1,2-diazepines, while electron donating groups exert little or no orientation effects since a mixture of 4- and 6-substituted-1,2-diazepines are obtained.

(4) Electron-donating substituents bearing an acidic hydrogen (OH,

NH_2 and NHCOPh) do not yield 1,2-diazepines, but afford a mixture of two isomeric 2-aminopyridines (71 and 72).

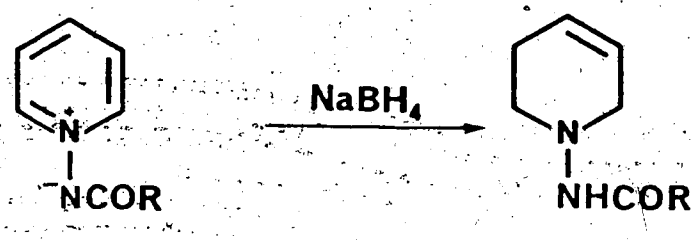


(71)

(72)

1.3.6.0.0 Reduction reactions

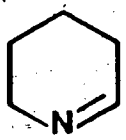
A variety of methods have been reported for the reductive N-N bond cleavage of N-iminopyridinium ylides, viz., zinc-acetic acid,[140] stannous chloride in hydrochloric acid,[141] tri-n-butyltin hydride,[142] and electrochemical reduction.[143] However, sodium borohydride reduction of N-acyliminopyridinium ylides afforded the corresponding 1,2,3,6-tetrahydropyridines (73).[42,65-67,144,145]



(73)

1.4.0.0.0 1,2,3,6-Tetrahydropyridines

The three possible tetrahydropyridines, namely 2,3,4,5-tetrahydropyridine (1-piperideine) (74), 1,2,3,4-tetrahydropyridine (2-piperideine) (75) and 1,2,3,6-tetrahydropyridine (3-piperideine) (76) are all known. Most studies have been carried out with substituted tetrahydropyridines. 1,2,3,6-Tetrahydropyridine (76) is the only one that exists as a stable free base.



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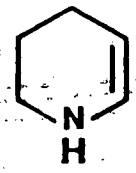

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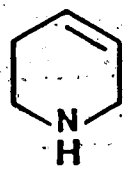


(76)

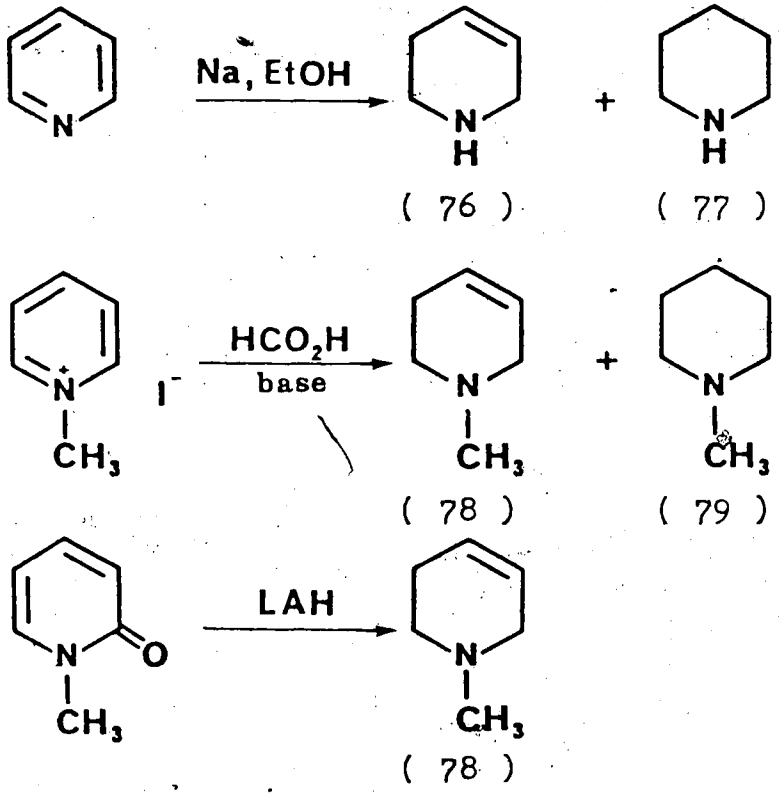
The chemistry and pharmacology of 1,2,3,6-tetrahydropyridines have been the subject of several reviews.[146-149] Although many piperidines have been examined pharmacologically, relatively few tetrahydropyridines have been studied. Those which have received the greatest attention are derivatives of 1,2,3,6-tetrahydropyridine. Many 1,2,3,6-tetrahydropyridines exhibit potent hypotensive and analgesic activities.[148,149]

1.4.1.0.0 Synthesis of 1,2,3,6-tetrahydropyridines

1,2,3,6-Tetrahydropyridines can be synthesized readily by partial reduction of pyridines, elimination reactions involving substituted piperidines or Diels-Alder cycloadditions using iminodienophiles.

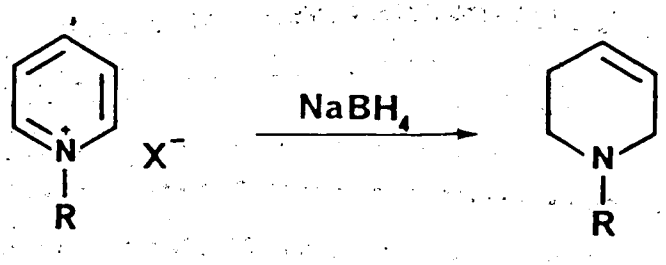
1.4.1.1.0 Reduction reactions

The synthesis of 1,2,3,6-tetrahydropyridines by reduction of pyridines and their salts with metal hydrides or other reducing agents have been extensively reviewed.[146,152] Thus, reduction of various pyridines with sodium and ethanol gave a mixture of 1,2,3,6-tetrahydropyridine (76) and piperidine (77).[150] Similarly, the reaction of a pyridinium salt with formic acid, in the presence of base, afforded 1-substituted-1,2,3,6-tetrahydropyridines (78) and piperidines (79),[151] although the yields were generally lower. The reduction of 1-methyl-2-pyridone with lithium aluminum hydride (LAH) also afforded the 1,2,3,6-tetrahydropyridine (78) in low yield.[151]

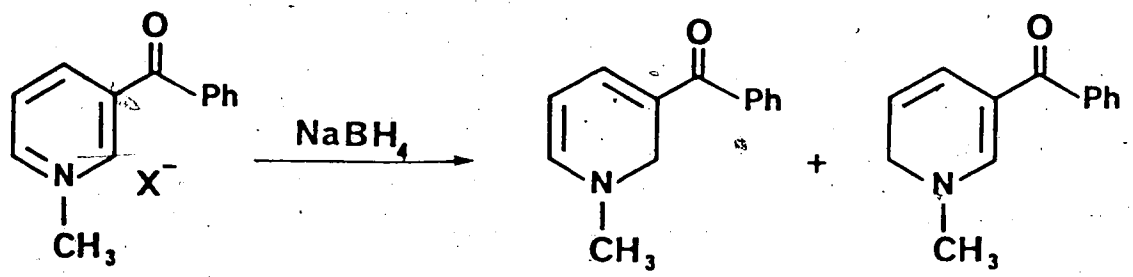


(76) (77) (78) (79) (78)

The reduction of pyridinium salts with sodium borohydride generally afforded 1,2,3,6-tetrahydropyridines (80) as the sole product.[152] However, when pyridinium salts bearing an electron-withdrawing substituent such as benzoyl or cyano at the 3-position are reduced, 1,2- and 1,6-dihydropyridine (81 and 82) were obtained.[153]



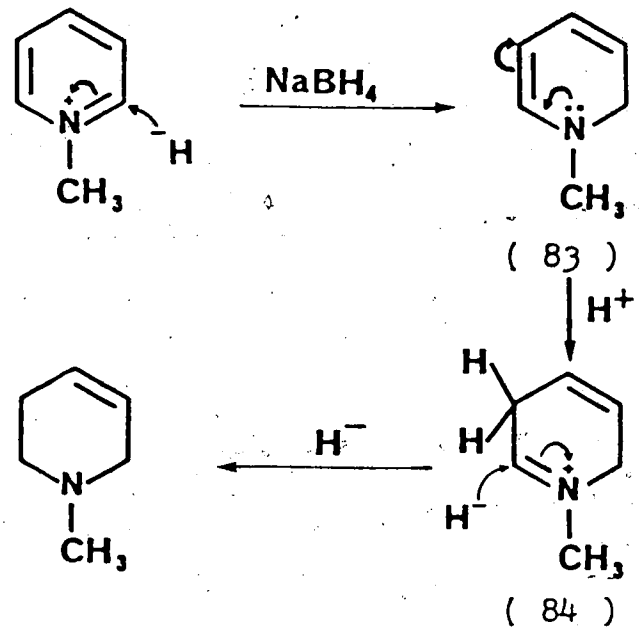
(80)

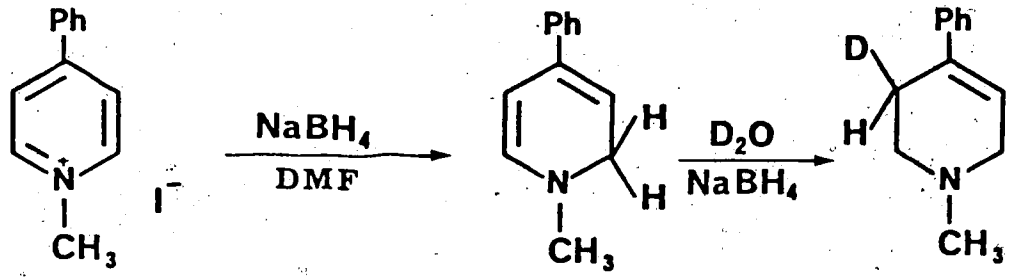


(81) (82)

Sodium cyanoborohydride has also been utilized recently to effect similar reductions of pyridinium salts.[154] The sodium borohydride reduction of pyridinium salts is still the most efficient synthetic reaction for the preparation of N-substituted 1,2,3,6-tetrahydropyridines. The mechanism for the reduction of pyridinium salts using

sodium borohydride has been investigated extensively. It has been demonstrated[152,155] that attack by hydride anion occurred at carbon adjacent to the quarternary nitrogen to give the 1,2-dihydropyridine intermediate (83), which on protonation and subsequent reduction of the iminium species (84) yielded 1-methyl-1,2,3,6-tetrahydropyridine. This mechanism is further supported by deuterium labelling experiments.[156, 157] The reduction of 1-methyl-4-phenylpyridinium iodide (85) with sodium borohydride in dimethylformamide and deuterium oxide afforded 1-methyl-3-deutero-4-phenyl-1,2,3,6-tetrahydropyridine (86). Nuclear magnetic resonance and mass spectral analysis indicated approximately one deuterium atom was incorporated at the 3-position.[157]





(85) (86)

The following correlations can be generalized for the sodium borohydride reduction of pyridinium salts:

(1) The initial attack by hydride ion will occur primarily at the 2- or 6-positions in the absence of steric effects.

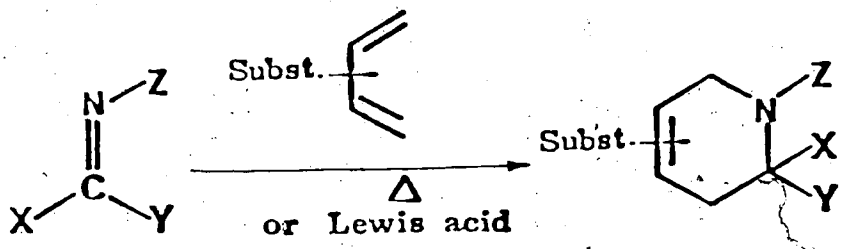
(2) The dienamine system thus formed will normally undergo protonation by a proton from the solvent at the 5-position.

(3) Attack by borohydride ion is sensitive to steric interactions. When attack at a substituted position does occur it is at a greatly reduced rate.

(4) Electron-withdrawing substituents at the 3-position tend to resonance stabilize the 1,2-dihydropyridine ring system. Similarly, reductions effected in non-protic solvent or a strong base as solvent yield 1,2-dihydropyridines since protonation of the dienamine does not occur.

(5) The 1,2,3,6-tetrahydropyridines obtained from the reduction of disubstituted or polysubstituted pyridinium salts always carry the maximum number of substituents on the double bond presumably due to hyperconjugation.

reactions utilizing imines where substituents X or Y are usually hydrogen, aryl, trichloromethyl and/or carboxyl groups have been reported.[168,169] These highly electrophilic imines are often unstable and in most cases have been generated in situ from a more stable precursor.

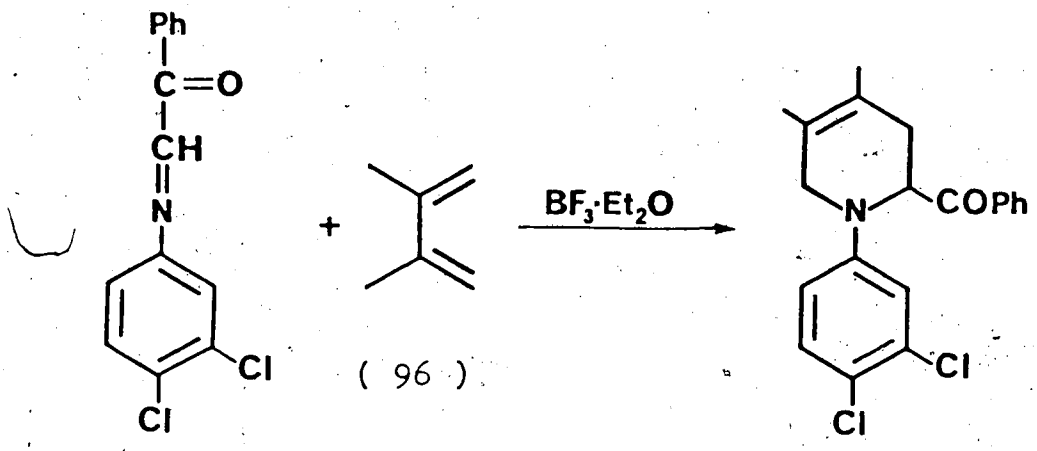


Z = SO_2Ar , COR

X,Y = H , CO_2R , Ar , CCl_3

Scheme 3 Diels-Alder cycloaddition reactions with iminodienophiles

A few examples of cycloaddition reactions where N-aryl imines have been used are known.[170] It appears that a second electron-withdrawing group must be present to provide sufficient reactivity. Thus, reaction of the imine (95) with the activated diene (96) in the presence of boron trifloride etherate afforded the Diels-Alder adduct (97) in good yield.[170]



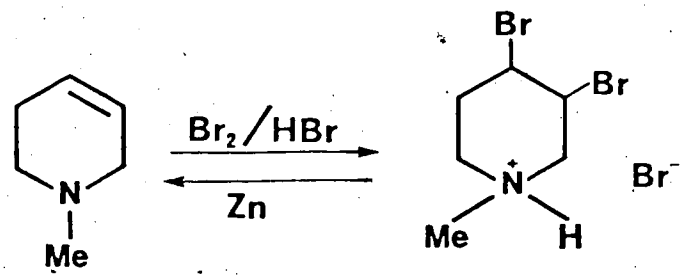
(95) (96) (97)

1.5.0.0.0 Chemical properties of 1,2,3,6-tetrahydropyridines

The reactions which 1,2,3,6-tetrahydropyridines undergo are as expected for an isolated double bond and a secondary or tertiary amine. A few specific reactions are discussed to illustrate this reactivity.

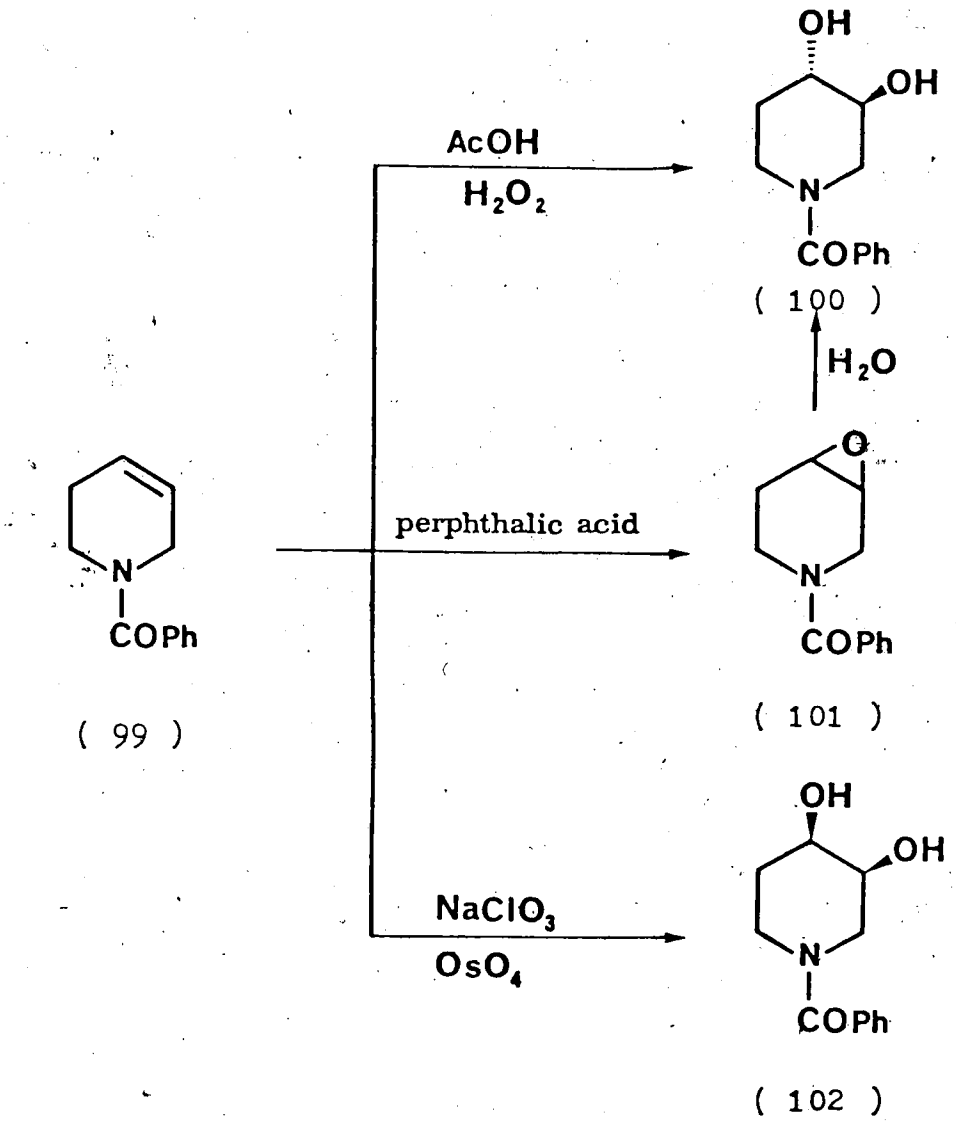
1.5.1.0.0 Addition to the olefinic bond

Catalytic hydrogenation of the olefinic bond of the 1,2,3,6-tetrahydropyridines afforded the corresponding piperidines.[97] Reaction of 1-methyl-1,2,3,6-tetrahydropyridine with bromine in hydrobromic acid afforded 1-methyl-3,4-dibromopiperidine hydrobromide (98), from which the parent compound could be recovered by reaction with zinc.[171]

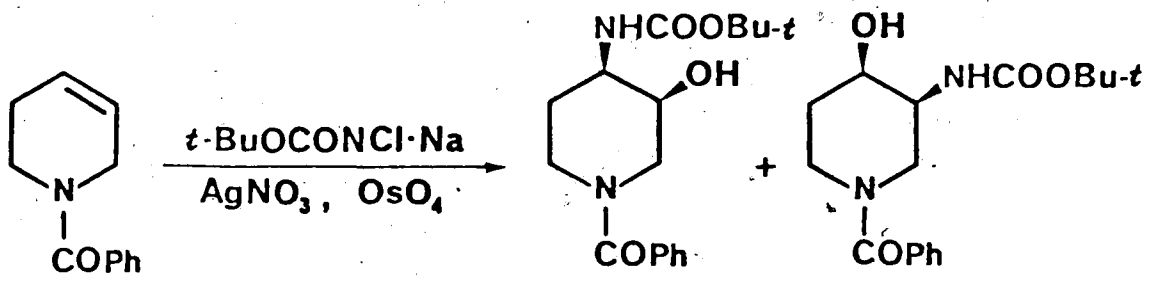


(98)

The trans-dihydroxylation of 1-benzoyl-1,2,3,6-tetrahydropyridine (99) with peracetic acid yielded trans-1-benzoylpiperidine-3,4-diol (100).[172] Reaction of (99) with perphthalic acid gave 1-benzoyl-3,4-epoxypiperidine (101), which on hydroxylation yielded the trans-diol (100).[172] The cis-dihydroxylation of (99) which yielded cis-1-benzoylpiperidine-3,4-diol (102) was readily accomplished with aqueous sodium chlorate-osmium tetroxide.[172]



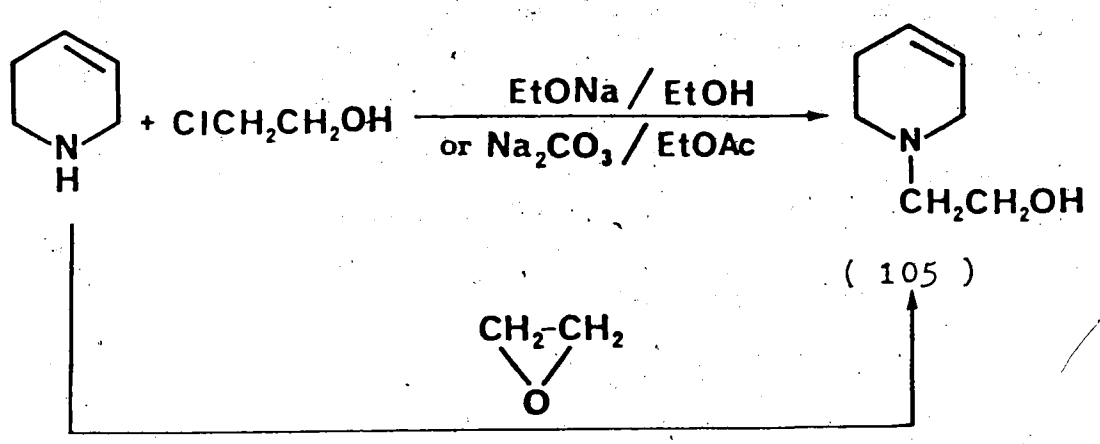
The viscinal oxyamination of (99) with t-BuOCONCl Na and $AgNO_3$ in the presence of a catalytic amount of OsO_4 afforded a 1:1 mixture of the regioisomers cis-1-benzoyl-3-hydroxy-4-tert-butoxycarbonyl-aminopiperidine (103) and cis-1-benzoyl-3-tert-butoxycarbonylamino-4-hydroxypiperidine (104).[173]



(99) (103) (104)

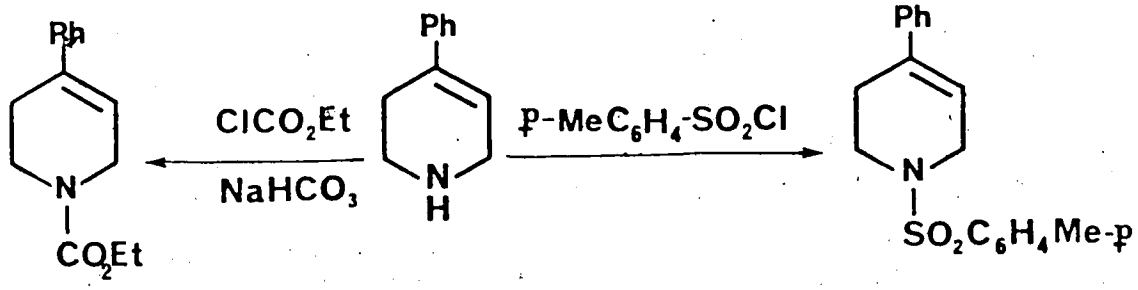
1.5.2.0.0 Reactions involving the ring nitrogen

Acylation of the 1,2,3,6-tetrahydropyridine ring nitrogen is usually performed by the reaction of an alkyl halide with the sodio derivative of the tetrahydropyridine. Thus, 1-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridine (105) was obtained from the reaction of ethylene chlorohydrin and 1,2,3,6-tetrahydropyridine pretreated with sodium ethoxide in ethanol,[174] or with sodium carbonate in ethyl acetate.[175] Compound (105) was also obtained upon reaction with ethylene oxide.[172]



(105)

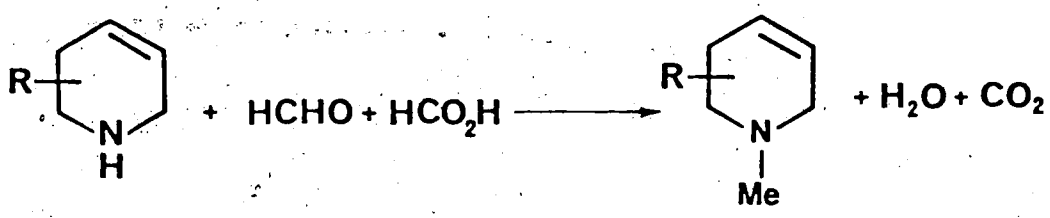
The related acylation of 1,2,3,6-tetrahydropyridines has been reported as illustrated for the preparation of 1-ethoxycarbonyl-4-phenyl-1,2,3,6-tetrahydropyridine (106) and 1-p-toluenesulfonyl-4-phenyl-1,2,3,6-tetrahydropyridine (107).[172,175,176]



(106) (107)

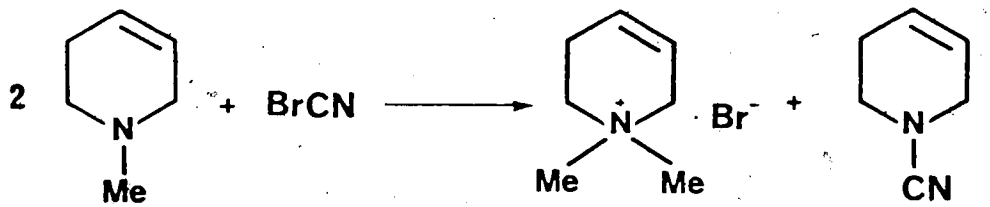
Methylation of 1,2,3,6-tetrahydropyridines with formaldehyde and an excess of formic acid (Eschweiler-Clark reaction) yielded the

N-methylated product (108).[177]

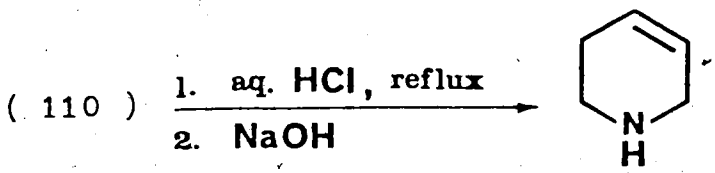


(108)

N-Demethylation of 1-methyl-1,2,3,6-tetrahydropyridine has been accomplished using the von Braun cyanogen bromide procedure.[178] One drawback of this method is that half of the tertiary amine is lost with the formation of the quaternary salt (109) in addition to the required 1-cyano derivative (110). Compound (110) was then converted to the required secondary amine.[178]



(109) (110)

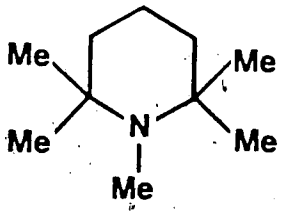


1.6.0.0.0 Pharmacological activities of 1,2,3,6-tetrahydropyridines

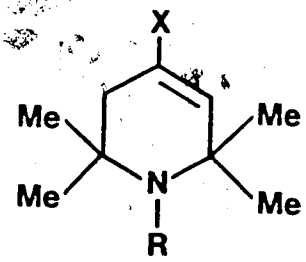
A large number of pharmacologically active 1,2,3,6-tetrahydropyridine derivatives have been reported in the literature. Many of these are tetrahydropyridine analogues of piperidines known to exhibit a pharmacological effect. Although 1,2,3,6-tetrahydropyridines exhibit a broad spectrum of activities, their hypotensive and analgesic effects are more prominent. Other activities include muscle relaxant, sedative, anti-inflammatory, antipyretic, antitussive, choleretic, diuretic, mydriatic and anthelmintic effects.[148,149]

1.6.1.0.0 Hypotensive agents

The pempidine (1,2,2,6,6-pentamethylpiperidine) (111) exhibited potent ganglionic blocking activity and was used to reduce blood pressure.[179,180] Many derivatives of 1,2,3,6-tetrahydropyridine (112) were subsequently evaluated as ganglionic blocking agents. These compounds exhibited a wide range of hypotensive potencies. Some of them were more potent than pempidine itself.[181]



(111)



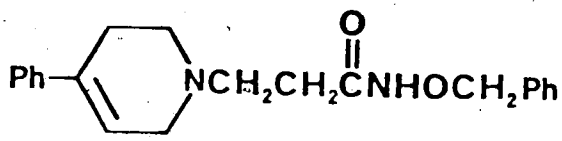
$X = H, Me, Et, C\equiv C, (CH_2)_3NMe_2$

$R = H, Me, NH_2, NHMe$

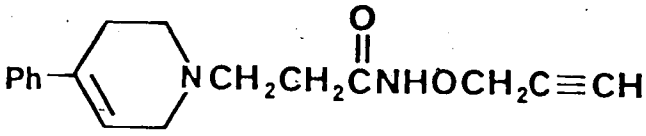
(112)

Compounds structurally related to 4-phenyl-1,2,3,6-tetrahydropyridinoalkanoic acid (113) were useful in the treatment of hypertension

and peripheral vascular diseases.[148,182] The structurally related acetylene derivative (114) exhibited only analgesic activity.[148,183]

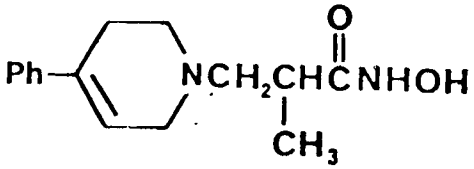


(113)



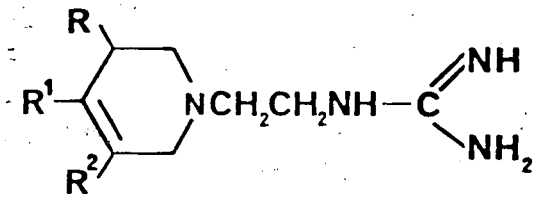
(114)

The hydroxamic acid derivative (115) has been studied extensively and was found to exhibit a hypotensive effect which was due to its α-adrenergic rather than ganglionic blocking action.[148]



(115)

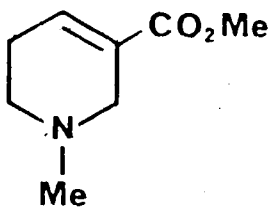
It has been reported that N-(2-guanidinoethyl)-1,2,3,6-tetrahydropyridines (116) are longer acting and less toxic hypotensive agents than their piperidino counterparts.[184,185]



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

(116)

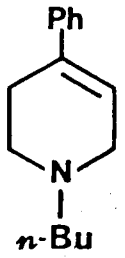
Arecoline (117) is one of the pharmacologically active alkaloids isolated from the dried ripe seeds of the palm tree Areca catecha that haye been characterized.[148,149] Arecoline (117) is used extensively as an anthelmintic and cathartic in veterinary medicine due to its peristalic action. It was also reported that (117) exhibited a weak hypotensive effect in cats and was known to exert parasympathetic activities similar to those of acetylcholine such as tremor, salivation and inhibition of spontaneous activity.[148]



(117)

1.6.2.0.0 Analgesic Agents

1-Butyl-4-phenyl-1,2,3,6-tetrahydropyridine (118) was reported to exhibit mild analgesic activity,[186] whereas the 2,2-diphenylethyl derivative (119) exhibited a potent analgesic activity.[187] Many derivatives of 1-aroylalkyl-4-alkyl-1,2,3,6-tetrahydropyridines (120) were useful analgesics, mydriatics, hypnotics and barbiturate potentiators.[148,188] A number of compounds which include amide, ketone and alcohol derivatives of the general structure (121) have been reported to possess analgesic and antitussive activities.[148]



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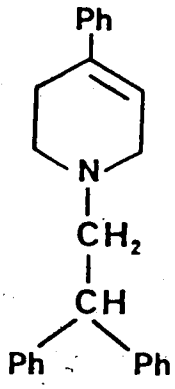

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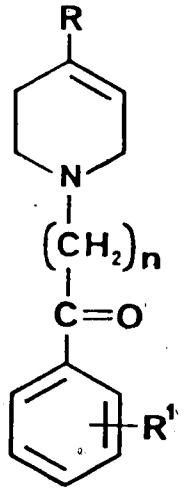
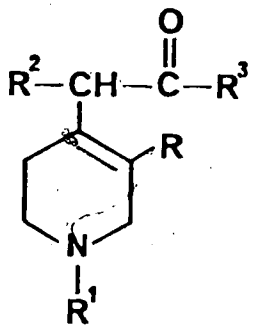


n= 1 — 3

R, R^1 = alkyl

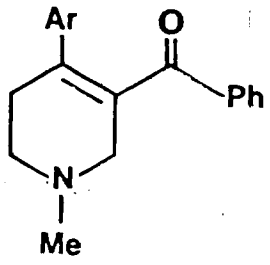
(120)



(121)

1.6.3.0.0 Miscellaneous Activities

Some derivatives of 5-benzoyl-1-methyl-4-aryl-1,2,3,6-tetrahydropyridine (122) and their alcohol reduction products (123) have been evaluated pharmacologically. The ketones (122) were found to be useful antipyretics and anti-inflammatory agents whereas the alcohols (123) possessed diuretic properties.[189,190] Compounds chemically related to 1-[2-(p-phenoxybenzoyl)ethyl]-4-phenyl-1,2,3,6-tetrahydropyridine (124) were claimed to be good muscle relaxants.[191] Several 1,2,3,6-tetrahydropyridine derivatives with diverse chemical structures have been found to exhibit choleretic and sedative properties.[149,149]



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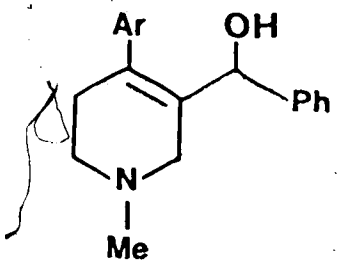

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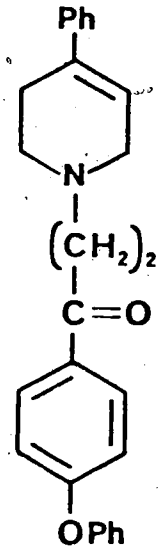


(124)

2.0.0.0.0. Objectives of research

The facile sodium borohydride reduction of N-(carbonyl-imino)pyridinium ylides to N-(carbonylamino)-1,2,3,6-tetrahydro-pyridines has been clearly established.[42,65-67] To date, the majority of pharmacologically active compounds having a 1,2,3,6-tetrahydropyridine ring possess N-alkyl substituents and were found to exhibit analgesic and anti-inflammatory activity in addition to a variety of other activities.[148,149] A broad spectrum pharmacological screen indicated that the "lead" compound, N-(phenyl-carbonylamino)-1,2,3,6-tetrahydropyridine , exhibited analgesic, anti-inflammatory and hyperglycemic activities.[192,193]

In view of these significant pharmacological test results it was therefore of interest to optimize the potency of this non-acidic lead compound. It was deemed important since aspirin and arylacetic acids (non-steroidal anti-inflammatory drugs) which are currently used as a first-line treatment for pain of inflammatory origin, all cause ulcerogenic side effects.[194-196] It was expected that non-acidic anti-inflammatory analgesic agents would be less irritating to the gastrointestinal tract.[197,198] On the other hand, N-(phenyl-carbonylamino)-1,2,3,6-tetrahydropyridine may represent a new class of anorexiants since the elevated glucose level may arise from endogenous energy substrates.

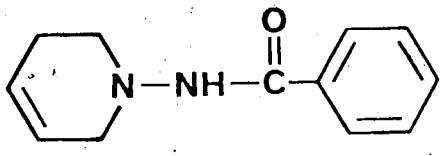
Therefore, it was of interest to determine the physico-chemical properties and structural requirements required for optimum analgesic and hyperglycemic activities. It was also of interest to investigate (1) the effect of aromatic substitution on the phenyl ring,

(2) the effect of replacing the phenyl ring by other ring systems and substituents, (3) the significance of the carbonylamino group spacer and the 1,2,3,6-tetrahydropyridine ring, and (4) the effect which substituents on the 1,2,3,6-tetrahydropyridine ring have on analgesic and hyperglycemic activities. The design, synthesis and pharmacological evaluation of these four classes of structurally related compounds would provide an extensive investigation of the structure-activity relationships (SAR).

3.0.0.0.0 Discussion

3.1.0.0.0 Strategies for drug design

The pharmacological activities of some N-(carbonylamino)-1,2,3,6-tetrahydropyridines were recently reported.[192,193] These two patents described their analgesic, anti-inflammatory and hyperglycemic activities. In view of their interesting pharmacological activities, N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125) was selected as a "lead" compound to determine the structural requirements for optimum analgesic and hyperglycemic activities.



(125)

Research directed toward the development of new and improved analgesics has advanced significantly for several classes of compounds. The non-steroidal anti-inflammatory drugs (NSAIDs) are now accepted as effective analgesics and are used extensively.[194,199,200] The consistent demand for new NSAIDs is obvious. The etiology of most inflammatory disorders remains unclear and thus non-specific NSAIDs continue to be the treatment of choice.[194, 199-203] There is also evidence that sub-groups of responders to different NSAIDs exist.[204] This individual variation in response ensures any new

NSAID will always be effective for a small group of patients.[205] The acidic nature of NSAIDs is intimately related to their ulcerogenic side effects.[194-196] It is generally believed that non-acidic anti-inflammatory analgesics are less irritating to the gastrointestinal tract.[197,198]

Hyperglycemic agents, as a class of drugs, have not been reviewed to any significant extent in pharmacology textbooks. It is tempting to postulate that one potential medical application of hyperglycemic drugs would be as anorexiants since blood glucose must arise from precursors in diet or from endogenous components. Anti-obesity therapy can be achieved either by decreasing the availability of exogenous energy substrates, thereby accelerating the utilization of the endogenous substrates or by metabolic regulation, defined here as intervention in the biosynthesis, storage or utilization of energy substrates.[206] On this basis, it would appear that hyperglycemic drugs may be valuable in weight control or weight reduction. Obesity continues to be a major health hazard and the long-term effectiveness of current anorexiants remains unsatisfactory.

The goal of this research program was to ultimately design compounds which exhibited optimum analgesic and anorectic (hyperglycemic) activities via structure-activity relationship (SAR) studies.

To persue this goal, four basic projects (see section 2.0.0.0.0) were planned for optimization of potency. A literature survey has indicated that some 40% of all compounds reported contain an unfused phenyl ring.[207] More than 50% of drug-oriented patents describe compounds having substituted phenyl rings.[208] Efficient strategies to optimize substituent selection are therefore of great value. The Topliss manual technique[209] was most applicable to our study.

The manual technique is a stepwise procedure, not involving statistical methodology, by which a small group of compounds representing different types of substitution on a phenyl ring can be selected and synthesized at one time. It is viewed as a manual method for applying the Hansch approach to drug design.[210,211]

The pharmacological results of a study of this type would then indicate if further elaboration of other functionalities such as the carbonylamino or 1,2,3,6-tetrahydropyridine ring were deemed necessary.

The use of N-iminopyridinium ylides as precursors provides an attractive synthetic route to these reduced pyridine heterocycles. The sodium borohydride reduction of N-iminopyridinium ylides afforded the target compounds viz, N-(carbonylamino)-1,2,3,6-tetrahydropyridines as the sole reduction products.[65,67] The precursors can be prepared either by the Zincke salt method[63-69] or direct

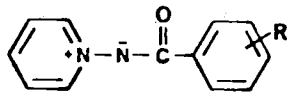
N-amination of the pyridine by hydroxylamine-O-sulfonic acid (HOSA)[6-8] or O-mesitylenesulfonylhydroxylamine (MSH)[9-11] followed by benzoylation.

Finally, the design of a drug requires an appropriate testing program. All analogues were tested for analgesic activity using the simple and economical phenyl-p-benzoquinone writhing test[212] which is used extensively for testing compounds exhibiting analgesic-anti-inflammatory activity. Some selected compounds in each of the four series were also subjected to the hot-plate test[213,214] to ensure that the analgesic effect observed in the phenyl-p-benzoquinone writhing test was not a false positive result. The blood glucose determinations were measured using the procedure developed by Barthelmai and Czok.[215]

3.2.0.0.0 Preparation of N-[(substituted-phenyl)carbonylimino]-pyridinium ylides (126-144)

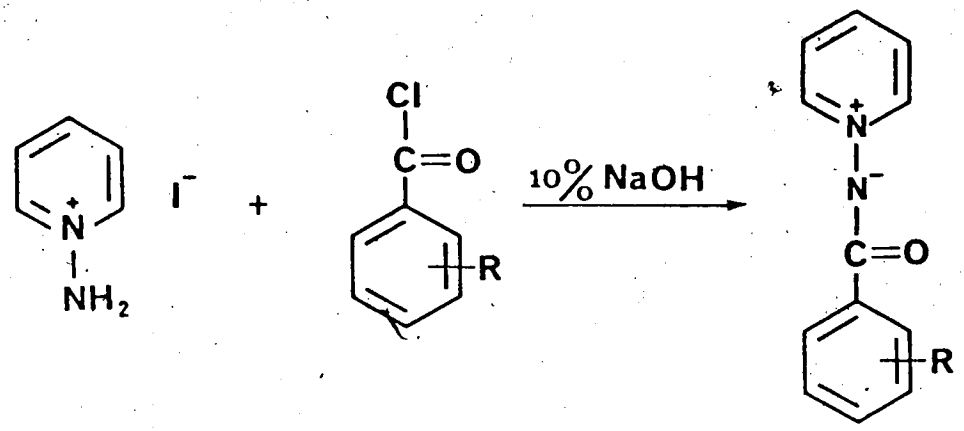
The required N-[(substituted-phenyl)carbonylimino]-pyridinium ylides were prepared by the Schotten-Baumann reaction.[16,65,216] Thus, reaction of N-aminopyridinium iodide[6,7] with substituted benzoyl chlorides in the presence of 10% aqueous sodium hydroxide afforded the corresponding ylides (126-144) in good to excellent yields as shown in Table 1.[42]

Table 1 Some physical data of N-[(substituted-phenyl)carbonylimino]pyridinium ylides (126-145)



Compound	R	Yield, %	m.p., °C	Formula	exact mass calcd	exact mass found
126	2-Me	99.9	111-112	$C_{13}H_{12}N_2O$	212.0950	212.0953
127	3-Me	98.2	95-96.5	$C_{13}H_{12}N_2O$	212.0950	212.0944
128	4-Me	60	171-173	$C_{13}H_{12}N_2O$	212.0950	212.0942
129	4-$(Me)_3C$	97.1	167.5-168.5	$C_{16}H_{18}N_2O$	254.1419	254.1400
130	3,4-Me_2	50	154-155	$C_{14}H_{14}N_2O$	226.1106	226.1101
131	2-MeO	99.2	103-105	$C_{13}H_{12}N_2O_2$	228.0898	228.0895
132	3-MeO	94.6	88-90	$C_{13}H_{12}N_2O_2$	228.0898	228.0882
133	4-MeO	34.2	149-151	$C_{13}H_{12}N_2O_2$	228.0898	228.0889
134	2-Cl	98.7	119-120	$C_{12}H_9N_2OCl$	232.0403	232.0400
135	4-Cl	35.7	184-186	$C_{12}H_9N_2OCl$	232.0403	232.0396
136	2,4-Cl_2	94.1	153-154	$C_{12}H_8N_2OCl_2$	267.9984	267.9968
137	3,5-Cl_2	68.1	129.5-131	$C_{12}H_8N_2OCl_2$	267.9984	267.9957
138	3,4-Cl_2	44	177-179	$C_{12}H_8N_2OCl_2$	267.9984	267.9957
139	2-F	97.8	125-126.5	$C_{12}H_9N_2OF$	216.0699	216.0687
140	3-F	93	119-120	$C_{12}H_9N_2OF$	216.0699	216.0686
141	4-F	100	204-204.5	$C_{12}H_9N_2OF$	216.0699	216.0687
142	2-CF_3	99	134-135	$C_{13}H_9N_2OF_3$	266.0667	266.0664
143	3-CF_3	70	138-139	$C_{13}H_9N_2OF_3$	266.0667	266.0660
144	4-CF_3	71.5	183.5-185	$C_{13}H_9N_2OF_3$	266.0667	266.0652
145	4-NO_2	NI[a]				

[a] NI = not isolated

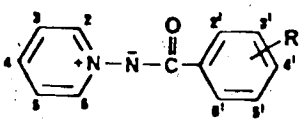


N-Aminopyridinium iodide was prepared according to the procedure of Gösl and Meuwsen[6,7] by amination of pyridine using freshly prepared HOSA.[217] When commercial HOSA was employed, the yields were low and variable.

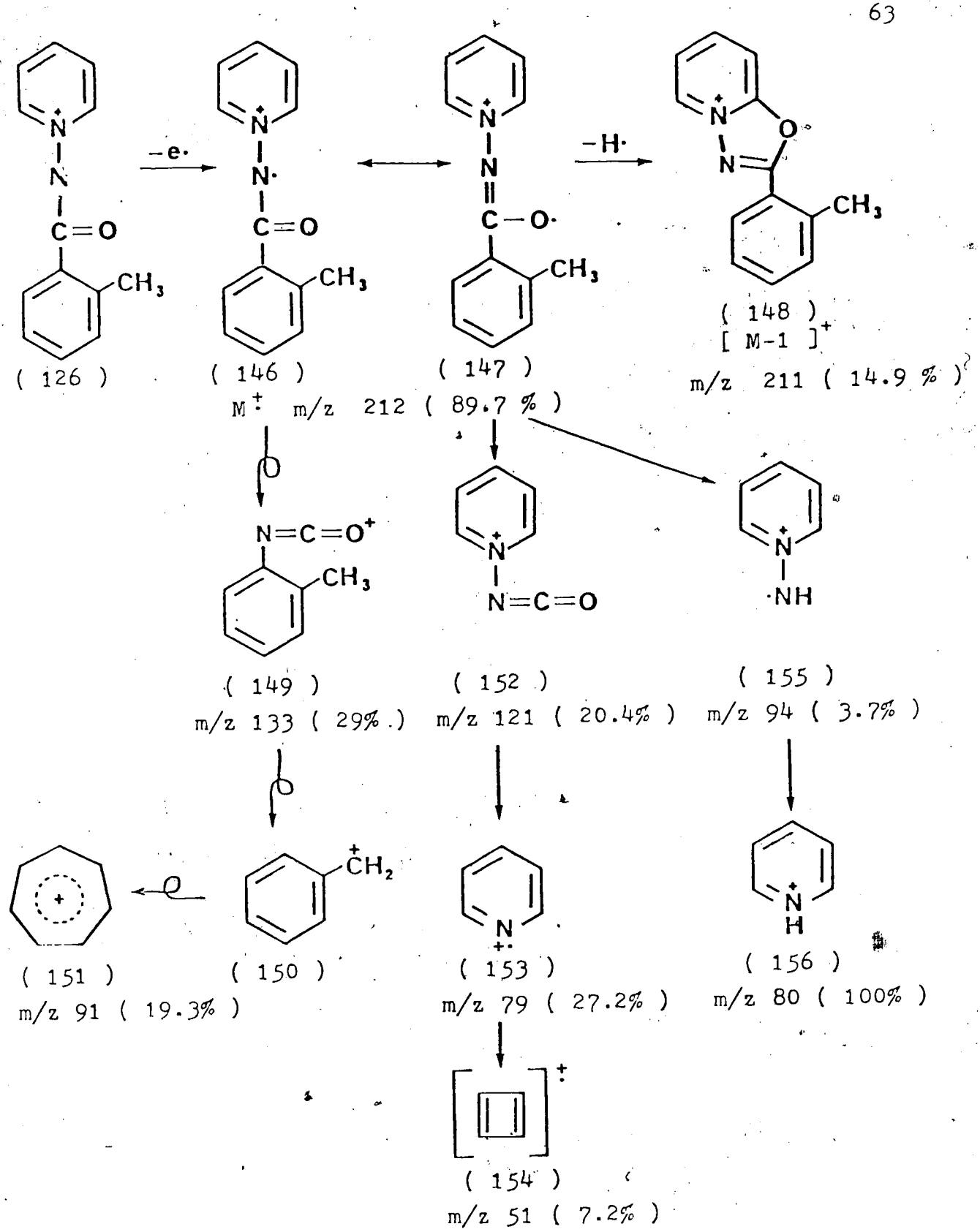
A typical procedure for preparation of the ylide involved the reaction of N-aminopyridinium iodide (8 mmol) in 25 mL of 10% sodium hydroxide with 2-methylbenzoyl chloride (12 mmol) which was added dropwise. After stirring for 24 h at 25°C water was added. Extraction with chloroform followed by neutral alumina column chromatography using ether-methanol (9:1 v/v) as eluant yielded N-[(2-methylphenyl)carbonylimino]pyridinium ylide (126) in quantitative yield.[42] The ir and ^1H nmr data for compounds (126-144) are summarized in Table 2.

The structure assigned to (126) is consistent with its ir, ^1H nmr and ms. The ir spectrum showed the presence of a CO absorption at 1570 cm^{-1}.[3,65] The frequency for the resonating carbonyl imide is generally about 100 cm^{-1} lower than

Table. 2 Infrared (ir) and proton magnetic resonance (^{1}H nmr) data of N-[(substituted-phenyl)carbonylimino]pyridinium ylides (126-145)

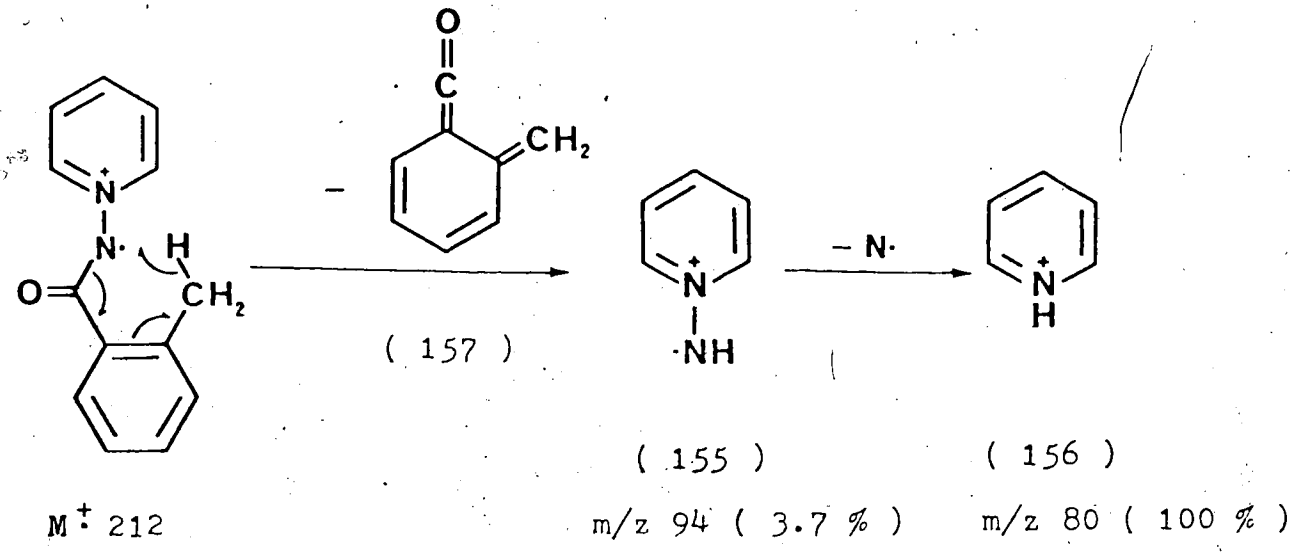


Compd	R	ir, cm^{-1} (KBr) for CO	^{1}H nmr, δ[a], ($CDCl_3$)
126	2-Me	1570	2.58 (s, 3H, Me), 7.11-7.38 (m, 3H, H_3^1, H_4^1, H_5^1), 7.38-8.01 (m, 4H, H_6^1, H_3, H_4, H_5), 8.85 (d, 2H, H_2, H_6)[c]
127	3-Me	1570	2.43 (s, 3H, Me), 7.24-8.13 (m, 7H, H_3, H_4, H_5, H_2^1, H_4^1, H_5^1, H_6^1), 8.87 (d, 2H, H_2, H_6)[c]
128	4-Me	1570	2.4 (s, 3H, Me), 7.25 (d, 2H, H_3^1, H_5^1)[b], 7.46-8.0 (m, 3H, H_3, H_4, H_5), 8.18 (d, 2H, H_2^1, H_6^1)[b], 8.92 (d, 2H, H_2, H_6)[c]
129	4-Me_3C	1580	1.35 (s, 9H, Me) 7.46 (d, H_3^1, H_5^1)[b], 7.55-8.01 (m, 3H, H_3, H_4, H_5), 8.15 (d, 2H, H_2^1, H_6^1)[b], 8.88 (d, 2H, H_2, H_6)[c]
130	3,4-Me_2	1560	2.29 (s, 6H, Me), 7.16 (d, $J_{5^1,6^1}$ = 8 Hz, 1H, H_5^1), 7.4-8.06 (m, 5H, H_3, H_4, H_5, H_2^1, H_6^1), 8.81 (d, 2H, H_2, H_6)[c]
131	2-MeO	1570	3.9 (s, 3H, OMe), 6.78-8.07 (m, 7H, H_3, H_5^1, H_4, H_5, H_3^1, H_4^1, H_6^1), 8.89 (d, 2H, H_2, H_6)[c]
132	3-MeO	1575	3.93 (s, 3H, OMe), 6.89-7.99 (m, 7H, H_3, H_4, H_5, H_2^1, H_4^1, H_5^1, H_6^1), 8.86 (d, 2H, H_2, H_6)[c]
133	4-MeO	1570	3.92 (s, 3H, OMe), 7.0 (d, 2H, H_3^1, H_5^1)[b], 7.52-8.05 (m, 3H, H_3, H_4, H_5), 8.22 (d, 2H, H_2^1, H_6^1)[b], 8.92 (d, 2H, H_2, H_6)[c]
134	2-Cl	1570	7.2-8.19 (m, 7H, H_3, H_4, H_5, H_3^1, H_4^1, H_5^1, H_6^1), 8.87 (d, 2H, H_2, H_6)[c]
135	4-Cl	1575	7.42 (d, 2H, H_3^1, H_5^1)[b], 7.58-8.1 (m, 3H, H_3, H_4, H_5), 8.2 (d, 2H, H_2^1, H_6^1)[b], 8.92 (d, 2H, H_2, H_6)[c]



Scheme 4 Major fragmentation pathways of N-[(2-methylphenyl)-carbonylimino]pyridinium ylide (126)

The origin of the base peak at m/z 80 deserves some comment. Loss of the ketene C_8H_6O (157) gave a fragment ion (155) at m/z 94 (3.7%) which on expulsion of a nitrogen radical could give rise to the base peak (156) at m/z 80 (100%). This pathway is absent in the 3-methyl,

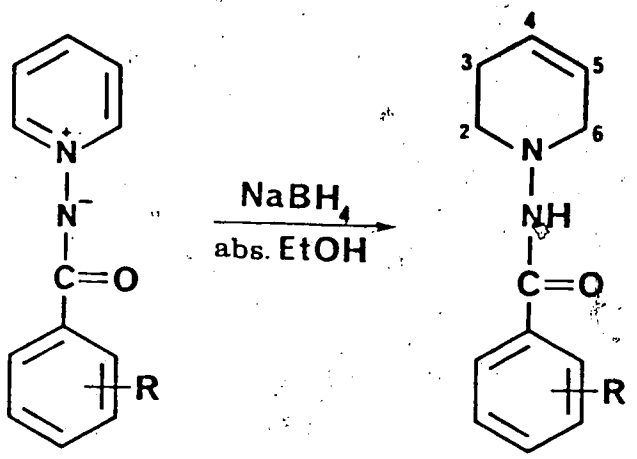


4-methyl and 3,4-dimethyl analogues (127, 128, 129). It is therefore suggested that this pathway is due to an ortho-effect. All the fragment ions were characterized by the exact mass measurements.

3.3.0.0.0 Preparation of N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177)

The sodium borohydride reduction of N-(carbonylimino)-pyridinium ylides provides an attractive route for the synthesis of 1,2,3,6-tetrahydropyridines.[65] Thus reduction of N-[(substituted-phenyl)carbonylimino]pyridinium ylides (126-145) using sodium

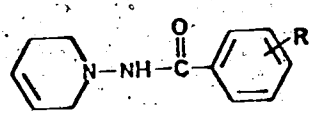
borohydride in absolute ethanol at ice-bath temperature gave the corresponding N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177) in excellent yields as shown in Table 3.[42]



A typical reduction involved the dropwise addition of a solution of N-[(2-methylphenyl)carbonylimino]pyridinium ylide (126) (5 mmol) in absolute ethanol to a solution of sodium borohydride (50 mmol) in absolute ethanol precooled to 0°C. The reduction was complete after 5 h at 0°C and water was added. Extraction with chloroform afforded the pure N-[(2-methylphenyl)carbonylamino]-1,2,3,6-tetrahydropyridine (158) in quantitative yield. In most cases, the products were isolated pure. However, some required purification by either decolorization, or column chromatography. The ir and ^1H nmr spectral data for compounds (158-177) are summarized in Table 4.

The structure assigned to (158) was consistent with the ir, ^1H nmr and mass spectral data obtained. The ir spectrum revealed the presence of NH at 3200 cm^{-1} and a CO group at 1620 cm^{-1}. The ^1H nmr (δ) spectrum in deuterochloroform exhibited a 5H multiplet at

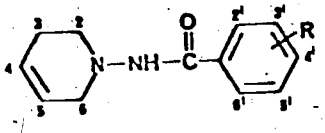
Table 3 Some physical data of N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177)



No.	R	Yield,%	m.p., °C	formula[a]	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
158	2-Me	99	162-163	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.34	7.51	12.96
159	3-Me	72.2	138-139	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.11	7.52	12.86
160	4-Me	98	137-139	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.09	7.60	12.96
161	4-$(Me)_3C$	100	147-148	$C_{16}H_{22}N_2O$	74.38	8.58	10.84	74.33	8.66	10.85
162	3,4-Me_2	93	139-140.5	$C_{14}H_{18}N_2O$	73.01	7.90	12.16	72.80	7.87	12.07
163	2-MeO	98.5	83.5-84.5	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	66.97	7.01	11.99
164	3-MeO	97.8	146.5-148	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	66.85	6.71	12.30
165	4-MeO	79.4	148-150	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.32	7.08	12.03
166	2-Cl	98.5	180-181	$C_{12}H_{13}N_2OCl$	60.89	5.50	11.84	60.87	5.54	11.80
167	4-Cl	95	160-162	$C_{12}H_{13}N_2OCl$	60.89	5.50	11.84	60.80	5.68	12.00
168	2,4-Cl_2	92	161-162	$C_{12}H_{12}N_2OCl_2$	53.16	4.46	10.33	53.19	4.57	10.34
169	3,5-Cl_2	99.8	181-182	$C_{12}H_{12}N_2OCl_2$	53.16	4.46	10.33	52.87	4.48	10.16
170	3,4-Cl_2	93	157-159	$C_{12}H_{12}N_2OCl_2$	53.16	4.46	10.33	53.36	4.62	10.48
171	2-F	97.7	132-133	$C_{12}H_{13}N_2OF$	65.44	5.95	12.72	65.13	5.93	13.09
172	3-F	94.6	145-146	$C_{12}H_{13}N_2OF$	65.44	5.95	12.72	65.07	6.05	12.64
173	4-F	99.3	153-154	$C_{12}H_{13}N_2OF$	65.44	5.95	12.72	65.05	6.06	12.45
174	2-CF_3	100	137-138	$C_{13}H_{13}N_2OF_3$	57.78	4.85	10.37	57.72	4.87	10.31
175	3-CF_3	99.2	169-170.5	$C_{13}H_{13}N_2OF_3$	57.78	4.85	10.37	57.86	4.85	10.18
176	4-CF_3	98.9	173-174	$C_{13}H_{13}N_2OF_3$	57.78	4.85	10.37	57.86	4.90	10.33
177	4-NO_2	48.7	202-203	$C_{12}H_{13}N_3O_3$	58.29	5.30	17.00	58.12	5.34	16.85

[a] All compounds gave analysis for C, H and N within ± 0.3% of theoretical value and are tabulated in the table.

Table 4 Infrared (ir) and proton magnetic resonance (^{1}H nmr) spectral data of N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177)



Compd	R	ir cm^{-1} (KBr) NH	CO	^{1}H nmr, δ [a], ($CDCl_3$)
158	2-Me	3200	1620	2.08-2.53 (m, 5H, Me, H_3), 3.11 (t, 2H, H_2)[b], 3.52 (m, 2H, H_6), 5.73 (m, 2H, H_4, H_5), 6.87-7.42 (m, 5H, H_3', H_4', H_5', H_6', NH)[d]
159	3-Me	3220	1650	2.11-2.37 (m, 2H, H_3), 2.38 (s, 3H, Me), 3.06 (t, 2H, H_2)[b], 3.33-3.55 (m, 2H, H_6), 5.73 (m, 2H, H_4, H_5), 7.23-7.81 (m, 4H, H_2', H_4', H_5', H_6'), 9.54 (s, 1H, NH)[d,e]
160	4-Me	3265	1650	2.42 (s, 3H, Me), 2.18-2.56 (m, 2H, H_3), 3.18 (t, 2H, H_2)[b], 3.55 (m, 2H, H_6), 5.77 (m, 2H, H_4, H_5), 7.3 (d, 2H, H_3', H_5')[c], 7.5 (s, 1H, NH)[d], 7.78 (d, 2H, H_2', H_6')[c]
161	4-Me_3C	3200	1630	1.34 (s, 9H, Me), 2.21-2.57 (m, 2H, H_3), 3.29 (t, 2H, H_2)[b], 3.57 (m, 2H, H_6), 5.75 (m, 2H, H_4, H_5), 7.18 (s, 1H, NH)[d], 7.48 (d, 2H, H_3', H_5')[c], 7.77 (d, 2H, H_2', H_6')[c]
162	3,4-Me_2	3220	1645	2.25-2.48 (s, 8H, Me, H_3), 3.11 (s, 2H, H_2)[b] 3.49 (m, 2H, H_6), 5.5 (m, 2H, H_4, H_5), 7.15 (d, $J_{5',6'}$ = 8 Hz, 2H, H_5', NH)[d], 7.46 (d, $J_{5',6'}$ = 8 Hz, 1H, H_6'), 7.52 (s, 1H, H_2')
163	2-MeO	3200	1650	2.15-2.58 (m, 2H, H_3), 3.25 (t, 2H, H_2)[b], 3.67 (m, 2H, H_6), 4.04 (s, 3H, Me), 5.8 (m, 2H, H_4, H_5), 6.95-7.33 (m, 2H, H_3', H_4'), 7.55 (t, $J_{5',6'}$ = 8 Hz of d, $J_{3',5'}$ = 2 Hz, 1H, H_5'), 8.32 (d, $J_{5',6'}$ = $J_{4',5'}$ = 8 Hz of d, $J_{4',6'}$ = 2.5 Hz, 1H, H_6'), 9.02 (s, 1H, NH)[d]

Table 4 continued

164	3-MeO	3220	1655	2.03-2.5 (m, 2H, H_3), 3.05 (t, 2H, H_2)[b], 3.47 (m, 2H, H_6), 3.8 (s, 3H, Me), 5.63 (m, 2H, H_4, H_5), 6.75-7.5 (m, 4H, H_2^1, H_4^1, H_5^1, H_6^1), 7.58 (s, 1H, NH)[d]
165	4-MeO	3240	1640	2.18-2.5 (m, 2H, H_3), 3.16 (t, 2H, H_2)[b], 3.54 (m, 2H, H_6), 3.9 (s, 3H, OMe), 5.76 (m, 2H, H_4, H_5), 7.0 (d, 2H, H_3^1, H_5^1)[c], 7.85 (d, 2H, H_2^1, H_6^1)[c], 8.04 (s, 1H, NH)[d]
166	2-Cl	3200	1655	2.26 (m, 2H, H_3), 3.24 (t, 2H, H_2)[b], 3.61 (m, 2H, H_6), 5.52-6.07 (m, 2H, H_4, H_5), 6.92-7.79 (m, 5H, H_3^1, H_4^1, H_5^1, H_6^1, NH)[d]
167	4-Cl	3220	1645	2.2-2.56 (m, 2H, H_3), 3.2 (t, 2H, H_2)[b], 3.54 (m, 2H, H_6), 5.76 (m, 2H, H_4, H_5), 7.1 (broad s, 1H, NH)[d], 7.48 (d, 2H, H_3^1, H_5^1)[c], 7.48 (d, 2H, H_2^1, H_6^1)[c]
168	2,4-Cl_2	3180	1640	1.9-2.55 (m, 2H, H_3), 3.14 (t, 2H, H_2)[b], 3.5 (m, 2H, H_6), 5.44-5.96 (m, 2H, H_4, H_5), 7.04-7.74 (m, H_3^1, H_5^1, H_6^1, NH)[d]
169	3,5-Cl_2	3160	1640	2.09-2.46 (m, 2H, H_3), 3.11 (t, 2H, H_2)[b], 3.48 (m, 2H, H_6), 5.72 (m, 2H, H_4, H_5), 7.65 (t, $J_{2^1,4^1} = J_{4^1,6^1} = 2$Hz, 1H, H_4^1), 7.85 (t, $J_{2^1,4} = J_{4,6^1} = 2$ Hz, 2H, H_2^1, H_6^1), 9.75 (s, 1H, NH)[d,e]
170	3,4-Cl_2	3220	1645	2.2-2.6 (m, 2H, H_3), 3.2 (t, 2H, H_2)[b], 3.6 (m, 2H, H_6), 5.82 (m, 2H, H_4, H_5), 7.46 (d, 1H, H_5^1)[c], 7.7 (d, $J_{5^1,6^1} = 8$ Hz of d, $J_{2^1,6^1} = 2.5$ Hz, 1H, H_6^1), 7.82 (s, 1H, NH)[d], 8.02 (d, $J_{2^1,6^1} = 2.5$ Hz, 1H, H_2^1)

Table 4 continued

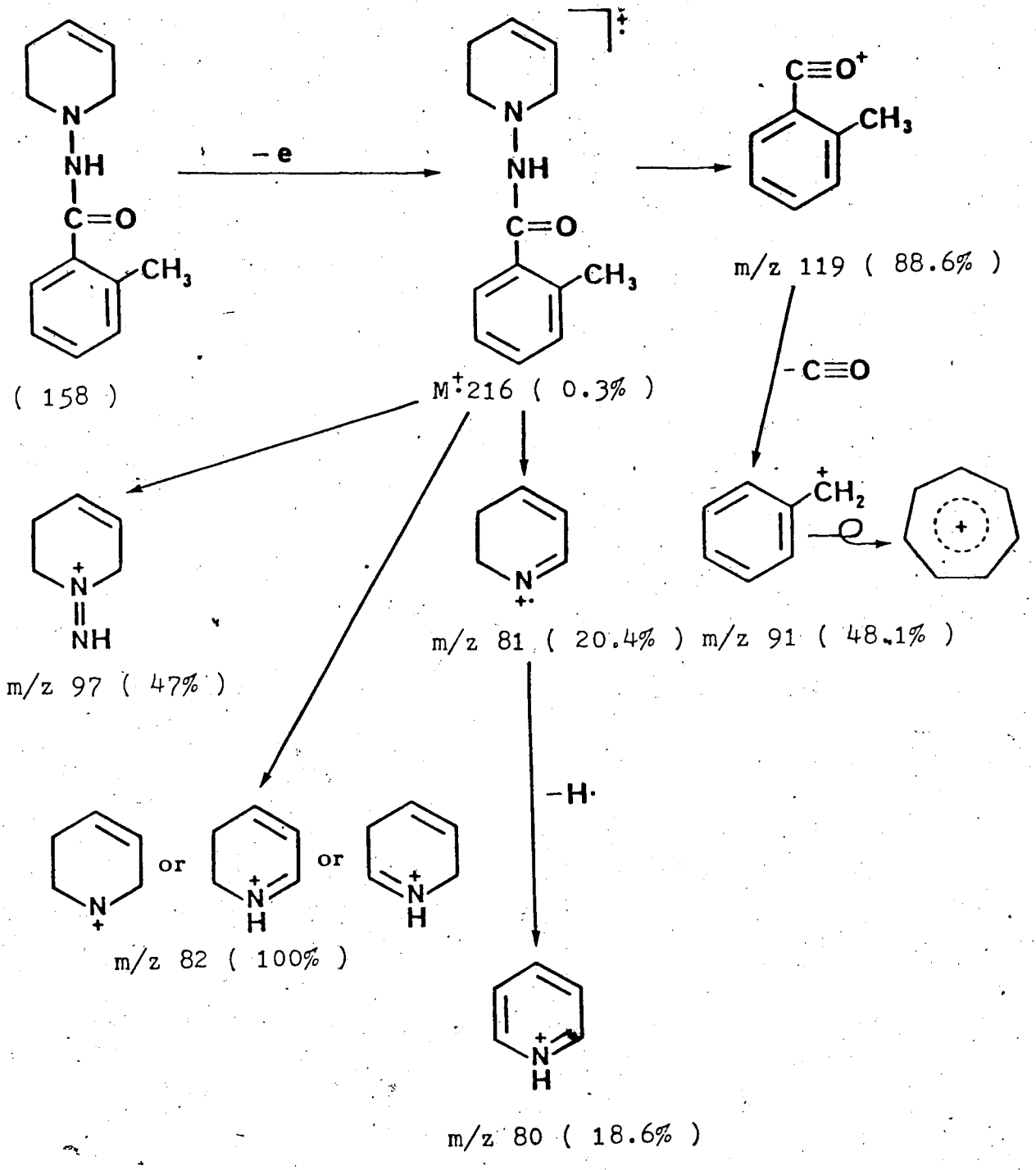
171	2-F	3225	1655	2.02-2.52 (m, 2H, H_3), 3.16 (t, 2H, H_2)[b], 3.54 (m, 2H, H_6), 5.7 (m, 2H, H_4, H_5), 6.88-8.26 (complex m, 5H, H_3^1, H_4^1, H_5^1, H_6^1, NH)[d]
172	3-F	3220	1650	2.13-2.5 (m, 2H, H_3), 3.15 (t, 2H, H_2)[b], 3.56 (m, 2H, H_6), 5.75 (m, 2H, H_4, H_5), 7.02-7.9 (complex m, 5H, H_2^1, H_4^1, H_5^1, H_6^1, NH)[d]
173	4-F	3220	1650	2.12-2.55 (m, 2H, H_3), 3.16 (t, 2H, H_2)[b], 3.55 (m, 2H, H_6), 5.7 (m, 2H, H_4, H_5), 7.09 (d, $J_{2',3'} = J_{5',6'} = 8$ Hz of d, $J_{3'F} = 8$ Hz of d, $J_{3',5'} = 2$ Hz, 2H, H_3^1, H_5^1), 7.69-7.88 (m, 2H, H_2^1, H_6^1), 7.58 (broad s, 1H, NH)[d]
174	2-CF_3	3205	1660	1.78-2.42 (m, 2H, H_3), 3.03 (t, 2H, H_2)[b], 3.41 (m, 2H, H_6), 5.44-5.96 (m, 2H, H_4, H_5), 7.28-7.98 (m, 4H, H_3^1, H_4^1, H_5^1, H_6^1), 9.59 (s, 1H, NH)[d]
175	3-CF_3	3190	1640	2.08-2.47 (m, 2H, H_3), 3.09 (t, 2H, H_2)[b], 3.49 (m, 2H, H_6), 5.69 (m, 2H, H_4, H_5), 7.42-7.98 (m, 2H, H_4^1, H_5^1), 7.99-8.27 (m, 2H, H_2^1, H_6^1), 9.73 (s, 1H, NH)[d,e]
176	4-CF_3	3220	1640	2.15-2.6 (m, 2H, H_3), 3.2 (t, 2H, H_2)[b], 3.59 (m, 2H, H_6), 5.78 (m, 2H, H_4, H_5), 7.72 (d, $J_{2',3'} = J_{5',6'} = 8$ Hz, 2H, H_3^1, H_5^1)[c], 7.98 (d, $J_{2',3'} = J_{5',6'} = 8$ Hz, 2H, H_2^1, H_6^1), 7.5-8.1 (broad s, 1H, NH)[d]
177	4-NO_2	3220	1656	2.11-2.45 (m, 2H, H_3), 3.08 (t, 2H, H_2)[b], 3.48 (m, 2H, H_6), 5.69 (m, 2H, H_4, H_5), 8.05 (d, 2H, H_3^1, H_5^1)[c], 8.29 (d, 2H, H_2^1, H_6^1)[c], 9.77 (s, 1H, NH)[d,e]

[a] Primes (H_2^1 ... H_6^1) signify phenyl hydrogens. [b] These peaks were t ($J_{2,3}$ = 7 Hz). [c] These peaks were d ($J_{2',3'} = J_{5',6'}$ = 8 Hz). [d] Exchanges with deuterium oxide. [e] Me_2SO-d_6 as solvent.

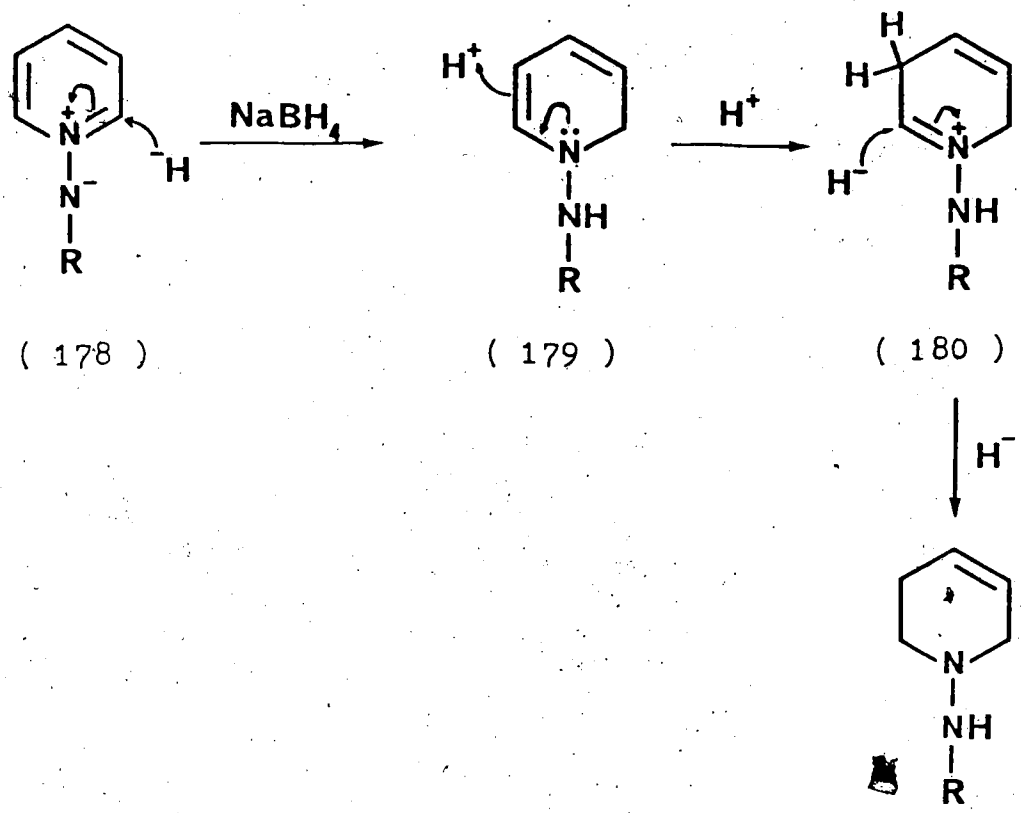
2.08 - 2.53 assigned to the methyl group and the C_3-H atoms of the tetrahydropyridine ring. A 2H triplet ($J_{2,3}$ = 7 Hz) at 2.31 was due to the C_2-H of the tetrahydropyridine ring. A 2H multiplet at 3.52 was assigned to the C_6-H of the tetrahydropyridine ring and a multiplet at 5.73 was attributed to the C_4-H and C_5-H of the tetrahydropyridine ring. The 5H multiplet at 6.87 to 7.42 was assigned to the phenyl hydrogens and the NH (exchanges with deuterium oxide). The microanalytical data found for $C_{13}H_{16}N_2O$ (158) for C, H and N was; calc'd C, 72.19; H, 7.46; N, 12.95; found, C, 72.34; H, 7.51; N, 12.96.

The mass spectrum exhibited a molecular ion at m/z 216 (0.3%). The major fragment ions are shown in Scheme 5. If the charge was localized on the carbonyl oxygen, α-cleavage with the loss of an N-aminotetrahydropyridine radical afforded an ion at m/z 119 (88.6%) which fragmented further to the benzylium ion which could rearrange to the tropylium ion at m/z 91 (48.1%). However, if the charge was localized on the tetrahydropyridine nitrogen, α-cleavage would yield an ion at m/z 97 (47%). The expulsion of a benzamide molecule from the molecular ion would furnish a fragment ion at m/z 81 (20.4%). The ion at m/z 81 could then expel a hydrogen radical to give a m/z 80 (18.6%) ion. The base peak at m/z 82 (100%) could be easily obtained from the direct N-N bond cleavage. Alternatively, it might be derived from N-N bond cleavage accompanied by hydrogen transfer from C_2-H or C_6H. All fragmentation ions were characterized by exact mass measurements.

The mechanism of sodium borohydride reduction of the N-iminopyridinium ylide (178) has not been investigated, but it is



Scheme 5 Major fragmentation pathways for N-[(2-methylphenyl)carbonylamino]-1,2,3,6-tetrahydropyridine (158)



(178) (179) (180)

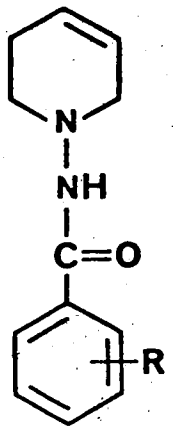
(181)

expected to be analogous to that of pyridinium salts.[152,155-157] Attack by hydride at the carbon adjacent to the quarternary pyridinium nitrogen (178) would yield the dienamine (179) which on protonation and subsequent reduction of the iminium species (180) would afford the 1,2,3,6-tetrahydropyridine (181).

3.3.1.0.0 Substituent selections for the N-[(substituted-phenyl)-carbonylamino]-1,2,3,6-tetrahydropyridines

The phenyl substituents selected to optimize the activities of the "lead" compound (125, R = H) were based on the guidelines which constitute the Topliss manual technique[209] presently used in drug

design. The substituents initially selected would provide maximum differences in physicochemical parameters such as hydrophobic (π), electronic (σ) and steric (E_S) effects.[218,219]



125, R= H

The initial analogues synthesized and tested were comprised of five compounds, viz., R = H, 4-Cl, 3,4-Cl_2, 4-CH_3 and 4-OCH_3. This set of five compounds contains the original group of compounds to be evaluated using the manual technique.[209] A comparison of the experimentally determined pharmacological potency rank order with the projected potency rank orders for the various physicochemical parameters of the manual technique should allow one to identify the probable operative physicochemical parameters. Identification of the operative physicochemical parameters provides the basis for further substituent selection.

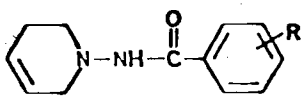
Analyses of the experimental rank order potency for analgesic activities (see Table 5) indicates that there may be a steric effect at the 4-position since the most active compound was the unsubstituted derivative.

Table 5 Hydrophobic (π), electronic (σ) and rank orders of initial substituent selections[209]

R	π	σ	Rank order: Observed analgesic	Observed hypergly.	Calc'd E_s
3,4-Cl_2	1.25	0.52	5	5	2-5
4-Cl	0.71	0.23	2	1	2-5
4-Me	0.56	-0.17	4	3	2-5
4-OMe	-0.02	-0.27	3	4	2-5
H	0	0	1	2	1

The experimentally observed rank order potency for the hyperglycemic activity did not correspond to any projected potency order for π , σ or E_s parameter dependencies. It was therefore concluded that special factors were operative which were not part of the assumptions used in the manual technique. Subsequently, four complete series of 2-, 3- and 4-monosubstituted methyl, methoxy, fluoro and trifluoromethyl substituents were synthesized to investigate the effect of substituent position and physicochemical effects such as electronic (σ), lipophilic (π), and steric (E_s) effects on analgesic and hyperglycemic activities. It was expected that these monosubstituted phenyl analogues would cover the entire spectrum of probable operable parameters.

Table 6 Some hyperglycemic and partition coefficient data of N-[(substituted-phenyl)carbonylamino]-1,2,3,6-tetrahydropyridines (158-177)

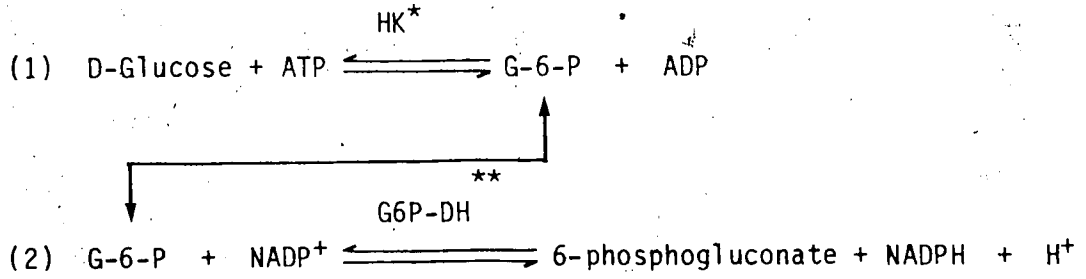


Compd	R	P[a]	dose mg/kg po	hypoglycemic-hyperglycemic act.[b] % change in blood glucose concns posttreatment 2h	4h
158	2-Me	28.8	100	-2.8 ± 6.8	-6.3 ± 5.6
159	3-Me	58.8	100	+117.2 ± 11.0	+108.5 ± 4.9
			30	+50 ± 11.6	
			34		+50 ± 1.7
160	4-Me	33.3	100	+73	+41
161	4-$(Me)_3C$	280	100	+1.8 ± 7.8	+4.7 ± 6.8
162	3,4-Me_2	71.3	100	+92.3 ± 27.4	+62.8 ± 27.0
163	2-MeO	5.5	100	+5.8 ± 5.9	+6.3 ± 1.2
164	3-MeO	10.5	100	+113.3 ± 29.1	+72.8 ± 23.3
165	4-MeO	34.1	100	+69	+26
166	2-Cl	34.2	100	+16.9 ± 9.0	+21.4 ± 5.8
167	4-Cl	19.1	100	+109	+26
168	2,4-Cl_2	30.6	100	-6.5 ± 6.4	+1.3 ± 8.8
169	3,5-Cl_2	16.4	100	+3.8 ± 8.5	+18.5 ± 13.4
170	3,4-Cl_2	26.4	100	+50	+59
171	2-F	7.5	100	+213 ± 40.1	+127 ± 36.9
			30	+50 ± 10.1	
172	3-F	44.4	100	+167.3 ± 46.3	+137.8 ± 59.2
173	4-F	83.9	100	+124 ± 58.5	+154 ± 91.0
174	2-CF_3	5.4	100	+1.2 ± 41.5	+19.6 ± 35.3
175	3-CF_3	26.6	100	+114.8 ± 6.2	+102 ± 4.6
176	4-CF_3	138.3	100	+43.3 ± 14.2	+37.3 ± 4.5
177	4-NO_2	103.3	100	+92.6 ± 31.3	+140.6 ± 70.3
125	4-H		100	+78	+50
chlorpropamide			100	-47 ± 12.1	-38 ± 9.3

[a] Partition coefficient. P = concentration in octanol/concentration in water. [b] The result is the mean value, or the mean value ± SEM, of four animals. Hyperglycemic activity is indicated by a plus number and hypoglycemic activity is indicated by a negative number.

3.3.2.0.0 Pharmacological evaluation of hyperglycemic activity

The hyperglycemic activity of N-(carbonylamino)-1,2,3,6-tetrahydropyridines and structurally related analogues was determined by the procedure developed by Barthelmai and Czok.[215] The detailed procedure is given in the experimental section. Briefly, the test compound is administered to a set of four overnight fasted rats, via a stomach tube, in dosages of 100 mg/kg initially. Blood samples are taken from the tail at 0, 2 and 4 hours post-treatment. The sera derived from the blood samples were analyzed for glucose by measurement of enzymatically produced NADPH[220] using an Abott ABA automated analyser. The principle of this determination is summarized below.[220]



* Hexokinase

** Glucose-6-phosphate dehydrogenase

The formation of the NADPH, as measured by the change in extinction at 340 nm, is proportional to the amount of glucose present. The test results obtained are summarized in Table 6. Chlorpropamide, a hypoglycemic agent, was included in the test for comparison.[221]

In the preliminary SAR studies the influence which substituents attached to the phenyl ring have upon blood glucose concentration was investigated. These results were compared to that of the unsubstituted "lead" compound (125) which elevated blood glucose 78 and 50% at 2 and 4 h respectively, after a 100 mg/kg po dose (see Table 6). Examination of the hyperglycemic activities of 2-, 3- and 4-methyl (158-160), methoxy (163-165), fluoro (171-173) and trifluoromethyl (174-176) derivatives indicate that the 3-substituted compounds are more potent than the corresponding 4-substituted analogues. All of the 2-substituted compounds were inactive, except the 2-fluoro (171) compound, which was more potent than the 3-fluoro (172) and 4-fluoro (173) compounds. The low activity of 2-methyl (158), 2-methoxy (163), 2-chloro (166) and 2-trifluoromethyl (174) compounds may be due to an ortho effect. If this is true, one would expect the 2-fluoro (171) compound to exhibit an activity similar to (125) which has a 2-hydrogen atom since fluorine, compared to methyl, chloro and trifluoromethyl, is most similar in size to hydrogen. The Van der Waals radii of fluorine and hydrogen are 1.35 Å and 1.2 Å respectively.[222]

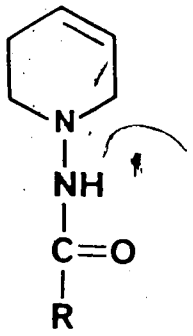
The partition coefficients P for compounds (158-177) were measured to determine whether there was a correlation between P and hyperglycemic activity.[223,224] The partition coefficient is defined as P = Conc.octanol/Conc.H_2O and was determined using the method of Fujita.[225] A correlation between P and hyperglycemic activities is not evident from the results obtained, since a large variation in P values was observed for compounds exhibiting weak or strong hyperglycemic activity. The mechanism by which this class of

compounds elevate blood glucose concentration is not understood.

3.3.2.1.0. Pharmacology of anoretic agents

Pharmacological therapy for the obese patient is currently focused on reducing food intake. Anoretic agents continue to be useful as short-term adjuncts to the weight reduction program.[226-229]

The assumption (see section 3.1.0.0.0) that the hyperglycemic effect constitutes the basis for the anoretic properties exhibited by N-(carbonylamino)-1,2,3,6-tetrahydropyridines was investigated elsewhere. Four of the compounds (125, 182-184) were



125, R= phenyl
182, R= 2-pyridyl
183, R= 3-pyridyl
184, R= 4-pyridyl

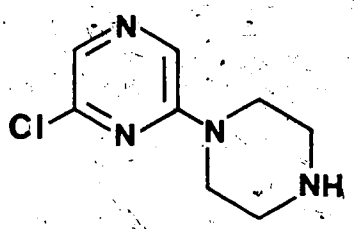
selected as model compounds for developmental work which was carried out at the University of Toronto by Dr. G.H. Anderson. Preliminary studies indicated that compounds 125, 182-184 selectively reduce caloric energy intake while proportionately protecting the level of protein intake in rats. A significant reduction in weight gain relative to the controls was observed. Plasma insulin, blood glucose, liver weight and plasma amino acid levels were all normal after sub-chronic (14 days) animal feeding experiments. However, tyrosine, tryptophan, serotonin and 5-hydroxyindoleacetic acid levels in the brain were significantly elevated.[230]

A large and fairly consistent body of evidence has been collected, showing that food intake is controlled in mammals by a delicate balance between several brain neuronal circuits involving different monoamines, amino acids and peptide neurotransmitters. Nor-adrenaline (NA), dopamine (DA), 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), glucose, endogenous opiates, cholecystokinin and several peptides have been shown to play a role in determining whether or not the individual needs to eat.[231-233]

Despite the large number of neuronal systems which influence food intake only dopaminergic and serotoninergic mechanisms serve as basis for mediating the activity of clinically useful anoretic drugs. Thus, amphetamine, phentermine, diethylpropion and mazindol represent part of a class of drugs which depend on a catecholaminergic mechanism for achieving a reduction in food intake. On the other hand, fenfluramine is representative of the other class that involves an intact serotoninergic mechanism.[234-236] In experimental animals, these anoretic drugs influence food intake by modifying either the release, concentration or reuptake of the biogenic amines involved in appetite regulation.[234-236] For example, anoretic doses of amphetamine and mazindol increase the brain DA turnover rate[237-240] while fenfluramine activates 5-HT function.[241]

The anoretic effects of amphetamine and mazindol can be antagonized by DA receptor blocking agents, and inhibition of catecholamine synthesis using α-methyl-p-tyrosine or by selective destruction of DA neurons using 6-hydroxydopamine plus desmethyl-imipramine.[232,242,243] On the other hand, manipulation of 5-HT

function with 5-HT receptor blockers, inhibitors of 5-HT synthesis or lesions of the mesencephalic raphe nuclei all effectively counteract fenfluramine-induced anorexia.[234] Much of the recent research interest in this area has focused on the anoretic properties of other 5-HT agonist drugs such as quipazine, m-chlorophenylpiperazine and MK-212. These agents have been reported to induce protein-sparing anorexia through direct activation of 5-HT receptor sites in the brain.[244-246] It is not known whether this novel class of N-(carbonyl-amino)-1,2,3,6-tetrahydropyridines act on dopaminergic or serotoninergic receptors or other yet unknown mechanisms.



MK - 212

3.3.3.0.0 Pharmacology of nonnarcotic analgesic agents

The clinical effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain is well accepted. Clinical studies supporting their effectiveness have been published.[202,203] There have also been reports of other NSAIDs under clinical evaluation as oral analgesics.[247]

Extensive investigations have been carried out to examine the analgesic effect of NSAIDs in conventional animal models and to delineate their mechanism of action.[248-252] The tail flick and hot plate tests are two simple animal tests commonly used to determine analgesic activity. These two tests are viewed as simple threshold tests since the animal responds as soon as it receives the appropriate stimulus information. Thermal pain is thought to be communicated by small C-fibre systems.[253] Upon activation of these systems, the animal performs either a reflex (tail flick) or operant (vocalization, licking of the hind paws) escape response. Thus, the duration of the exposure to the noxious stimulus is limited by the time required for transmission over the appropriate spinal and brain stem reflex arcs. As a rule, tests involving brief noxious stimuli resulting in neural activation are generally not very sensitive to NSAIDs. This has been verified clinically in human experimental pain models.[254]

In contrast to the thermal and electrical threshold tests, the inflamed paw pressure and writhing analgesic tests that are most sensitive to the effects of NSAIDs provide clues to the mechanism of action of these agents.[248,250,254] Two characteristics of these tests are that the stimulus is associated with tissue damage or inflammation and that the stimulus is chemical.

Internal pressure applied to the rat's paw will produce a stimulus dependent effort to escape. Randall and Sallito[255] have demonstrated that injection of a small amount of normal saline into the foot pad has very little effect on the pressure threshold. In this pressure test, morphine increases the amount of pressure the animal is

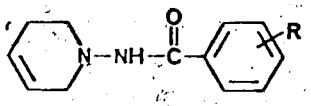
willing to accept whereas NSAIDs have no effect. The intraplantar injection of an irritant such as carrageenan[256] induces inflammation of the paw. The inflamed paw becomes hypersensitive to stimuli and an escape response (pain) is observed for compounds which previously did not exhibit a response. The NSAIDs show a distinct ability to elevate the pain threshold in the inflamed paw but exhibit no effect in normal animals. A higher dose of the NSAID does not completely block the response. These agents generally reverse only the hyperalgesic component which is analogous to the clinical situation in chronic somatic pain such as arthritis or inflammation. NSAIDs exhibit a similar analgesic effect for the writhing response evoked by the intraperitoneal (ip) injection of an irritant such as phenylbenzoquinone to mice.[257]

Therefore, it was considered appropriate to choose the most sensitive and economical analgesic tests commonly used to evaluate NSAIDs for screening purposes. The phenylquinone writhing test[212] was used to determine the analgesic activities of the N-(carbonylamino)-1,2,3,6-tetrahydropyridines prepared. Briefly, the test compound was injected subcutaneously to five mice at a dose of 0.004 mg/kg. After 30 min the pain inducing agent, 0.03% phenylbenzoquinone at a dose of 0.1 ml/10 g body weight, is administered ip. Ten min later, the mice are observed for a ten min period during which time the number of writhing responses is counted for each mouse. The average number of writhes is compared to the number of writhes observed for a control that received only the vehicle and phenylbenzoquinone. The analgesic test results and the partition coefficients for compounds (158-177) are

listed in Table 7. Aspirin, an anti-inflammatory analgesic, dextropropoxyphene, a weak narcotic analgesic and morphine sulfate, a strong narcotic analgesic were included in the study as reference compounds.

The analgesic test results (Table 7) indicated that compounds (158-177) all exhibited potent analgesic activity. The ED_{50} values for compounds (159) and (173) were determined. The dose-response curves were quite flat. The 3-methyl (159) and 4-fluoro (173) analogues exhibited ED_{50} values of 0.0004 mg/kg and 0.00036 mg/kg respectively in the phenylquinone writhing tests. It was interesting to note that mice administered a dose equal to or greater than 3 mg/kg sc showed locomotor retardation or sedation. It is possible that these compounds may exert other unknown pharmacological actions unrelated to their analgesic and hyperglycemic activities. We were aware of the fact that the phenylquinone writhing test does give a false positive result for some compounds not normally considered to be analgesics, such as amphetamine, cocaine, imipramine, chlorpromazine, and atropine.[258-260] This prompted us to determine analgesic activity using an alternative test which has a different site and mode of noxious stimulation. The analgesic activity exhibited by compounds (159) and (173) was also measured using the hot-plate test.[213-214] The mice were individually placed on a hot-plate at 55 $\pm$ 0.5°C. The reaction time (thumping of the rear leg or jumping) was observed before and 30 min after the sc administration of the test compound. The compounds (159) and (173) were found to exhibit ED_{50} values of 17 and 30 mg/kg sc respectively, relative to an ED_{50} of 3.09 mg/kg

Table 7 Partition coefficient and analgesic data of N-[(substituted-phenyl)-carbonylamino]-1,2,3,6-tetrahydropyridines (158-177)



Compd	R	P[a]	analgesic act., inhib act. on phenylquinone writhing[b] dose, mg/kg sc	% inhibition
158	2-Me	28.8	0.004	72.0 ± 2.0
159	3-Me	58.8	0.004	56 ± 0.1
			0.0004	50 ± 0.80
			17	50 ± 2.5[d]
160	4-Me	33.3	0.004	48 ± 0.9
161	4-$(Me)_3$C	280	0.004	48.8 ± 2.2
162	3,4-Me_2	71.3	0.004	50.8 ± 2.4
163	2-MeO	5.5	0.004	69.6 ± 1.7
164	3-MeO	10.5	0.004	68.8 ± 1.0
165	4-MeO	34.1	0.004	57.6 ± 2.23
166	2-Cl	34.2	0.004	52 ± 2.1
167	4-Cl	19.1	0.004	61.6 ± 1.3
168	2,4-Cl_2	30.6	0.004	57.2 ± 3.8
169	3,5-Cl_2	16.4	0.004	69.6 ± 1.8
170	3,4-Cl_2	26.4	0.004	48.8 ± 1.4
171	2-F	7.5	0.004	64.8 ± 2.1
172	3-F	44.4	0.004	65.6 ± 1.5
173	4-F	83.9	0.004	55.2 ± 1.0
			5	69 ± 1.55
			5	71 ± 1.39[e]
			0.00036	50 ± 1.02
			30	50 ± 3.0[d]
174	2-CF_3	5.4	0.004	64 ± 2.2
175	3-CF_3	26.6	0.004	54.4 ± 0.8
176	4-CF_3	138.3	0.004	46.4 ± 1.5
177	4-NO_2	103.3	0.004	51 ± 1.9
125	4-H		0.004	73.6 ± 0.6
aspirin			50	50
dextropropoxyphene			56	50
morphine sulfate			0.038	50 ± 1.61
			3.1	50 ± 2.8[d]

[a] Partition coefficient. P = concentration in octanol/concentration in water. [b] The result is the mean value, or the mean value ± SEM, of five animals. [d] Determined using the hot-plate test 30 min after a subcutaneous dose. [e] Naloxone hydrochloride (1 mg/kg sc) was administered 15 min prior to injection of 173.

for morphine sulfate. However, the dose-response curves obtained from the hot-plate test were relatively steep relative to those obtained in the phenylquinone writhing test.

It is not possible to make a meaningful quantitative comparison of the analgesic activities for compounds (158-177) since there are only small differences in activities. On the other hand, the dose-response curves for hyperglycemic activity were steep and there were clear potency differences. It is expected that this class of compounds should exert a singular analgesic effect at an effective analgesic dose, since (159) has no effect on blood glucose concentration at doses equal to or lower than 17 mg/kg po.

The preliminary structure-activity data shown in Table 7 suggests that the N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine moiety is the important structural feature, since analgesic potency is quite independent of the position and physicochemical properties of the aromatic substituent. For example, there was not a significant difference in activity between compounds having electron-donating substituents such as methoxyl and methyl, compared to those having electron-withdrawing substituents, such as fluoro, trifluoromethyl and nitro. The partition coefficient P does not appear to have a significant influence on analgesic activity. Compounds having lipophilic substituents, such as chloro, methyl, and trifluoromethyl, exhibit similar activity to those having substituents with low values such as methoxy and nitro.

The precise mechanism by which N-[(substituted-phenyl)-carbonylamino]-1,2,3,6-tetrahydropyridines exert their analgesic

activity has not been elucidated. The pure narcotic μ-antagonist naloxone was used to determine whether this novel class of compounds act at a μ-opiate receptor. Pretreatment of a mouse with naloxone would block the antinociceptive properties of analgesics which act specifically at the μ-opiate receptor. Alternatively, the activity of analgesics whose action is independent of the μ-opiate receptor would not be altered by naloxone pretreatment. This simple and rapid test was therefore used in an attempt to elucidate the mechanism of action of this class of compounds. Pretreatment of the mice using a 1 mg/kg sc dose of naloxone hydrochloride followed by injection of the test compound (173) at 5 mg/kg sc did not alter the writhing response observed in the phenylquinone writhing test. This blocking experiment suggests it is unlikely that N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridines produce analgesia via interaction with an opiate receptor. Moreover, none of the narcotic analgesics known show anti-inflammatory activity. It is not known whether these compounds act as prostaglandin synthetase inhibitors.

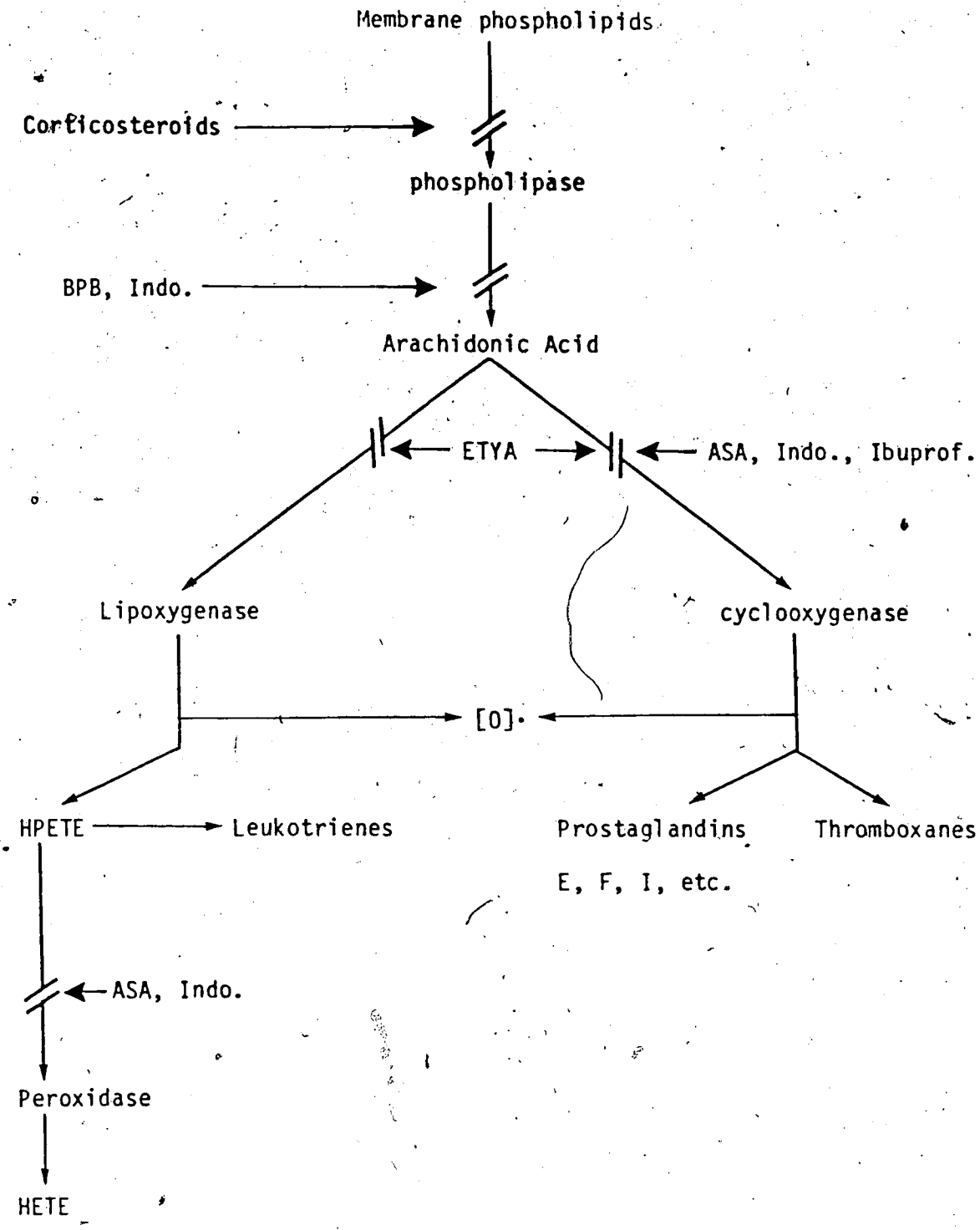
Vane was the first to report that NSAIDs, especially ASA and indomethacin, inhibit the transformation of arachidonic acid to stable prostaglandins.[261] This observation provided the first evidence that NSAIDs exert their major locus of action on this mediator system. These results suggested that some mediator derived from the arachidonic acid cascade may play a role in the transmission of nociceptive information.

All of the known clinically useful NSAIDs are capable of inhibiting prostaglandin (PG) biosynthesis. The mechanism by which a

number of inhibitors interact with products of the arachidonic acid cascade is illustrated by Scheme 6. Corticosteroids block formation of all the products arising from membrane lipids. Inhibitors of phospholipase (indomethacin, or p-bromophenyl bromide) will also block generation of arachidonate and its metabolites.[259] The classical NSAIDS (ASA, indomethacin, ibuprofen, etc) will selectively block formation of products from the cyclooxygenase pathway. 5,8,11,14-Eicosatetraynoic acid (ETYA) inhibits both the lipoxygenase and cyclooxygenase pathways.[262] Finally, Siegel et al reported that many NSAIDS,[263] but not acetaminophen,[264] inhibited the peroxidase that transformed (12S)-12-hydroperoxy-5,8,10,14-eicosatetraenoic acid (12-HPETE) to (12S)-12-hydroxy-5,8,10,14-eicosatetraenoic acid (12-HETE). This finding supports the proposal that inhibition of the production of 12-HETE contributes to the anti-inflammatory action of NSAIDS.[250] If the N-(phenylcarbonyl-amino)-1,2,3,6-tetrahydropyridines act as prostaglandin synthetase inhibitors, they should act on one or more of the previously described arachidonic cascade pathways. Further pharmacological evaluations are warranted to substantiate this lead.

3.4.0.0.0 Preparation of N-(carbonylamino)-1,2,3,6-tetrahydro-pyridines (197 - 208)

The preliminary SAR studies previously described (Section 3.3.2.0.0 and 3.3.3.0.0) indicated that analgesic and hyperglycemic activity were quite independent of the physicochemical properties of the aromatic substituents. It was therefore desirable to determine



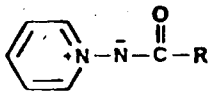
Scheme 6 Inhibition of the arachidonic acid cascade

what effect attachment of other ring systems and functionalities to the carbonylamino moiety would have on analgesic and hyperglycemic activity.

Reaction of N-aminopyridinium iodide with various acid chlorides afforded the N-(carbonylimino)pyridinium ylides (185-196). Some physical and spectral data are summarized in Tables 8 and 9 respectively. The synthesis of the 1-adamantyl (190) and 1-naphthoxymethyl (192) derivatives required the presence of a phase transfer catalyst (ptc) such as cetyltrimethylammonium bromide. These reactions did not proceed in the absence of the ptc. This was likely due to the low solubility of adamantyl and naphthoxymethyl acid chlorides in 10% aqueous sodium hydroxide.

The use of phase transfer catalysts is a well established synthetic technique.[266-269] The character of these reactions is reasonably well understood and a number of reviews[270,271] and monographs[272-274] describe their application. The ptc cycle, first suggested by Starks,[266,267] involves the use of a two phase system, viz., a lipophilic organic phase containing the substrate and an aqueous phase containing the nucleophilic salt. The two phases are generally immiscible so the nucleophile and substrate do not come into contact with each other precluding reaction. The ptc facilitates the transfer of the nucleophile into the organic phase. Once in the organic phase, the anionic nucleophile, which is not well-solvated or hydrogen bonded, reacts readily with the organic substrate. The ptc may initiate the entire sequence once again after displacement occurs as illustrated by Scheme 7.

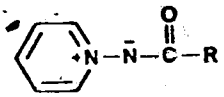
Table 8 Some physical data of N-(carbonylimino)pyridinium ylides (185-196)



Compd	R	yield, %	m p, °C	formula	exact mass calcd	exact mass found
185	methyl	88.8	167-168[a]	$C_7H_8N_2O$		ND[b]
186	tert-butyl	99.9	65-67	$C_{10}H_{14}N_2O$	178.1106	178.1107
187	cyclopropyl	30	151-153	$C_9H_{10}N_2O$	162.0793	162.0792
188	cyclopentyl	85.6	64-66	$C_{11}H_{14}N_2O$	190.1106	190.1107
189	cycloheptyl	99.5	92-93	$C_{13}H_{18}N_2O$	218.1419	218.1421
190	1-adamantyl	94	124-126	$C_{16}H_{21}N_2O$	257.1613	257.1608
191	ethoxy	82.4	106	$C_8H_{10}N_2O_2$	166.0743	166.0741
192	1-naphthoxymethyl	65.1	118-119	$C_{17}H_{14}N_2O_2$	278.1056	278.1056
193	3-furanyl	86.2	227-228	$C_{10}H_8N_2O_2$	188.0585	188.0586
194	2-thienyl	99.5	224-226	$C_{10}H_8N_2OS$	204.0357	204.0359
195	1-methyl-2-pyrrolyl	86	152-154	$C_{11}H_{11}N_3O$	201.0904	201.0902
196	2-[[1-(1,2,3,6-tetrahydro-pyridinyl)amino]-carbonyl]-6-pyridinyl[c]					

[a] Literature m p 168°C. [b] ND = not determined. [c] Not isolated.

Table 9 The ir and ^1H nmr spectral data of N-(carbonylimino)pyridinium ylides (185-196)

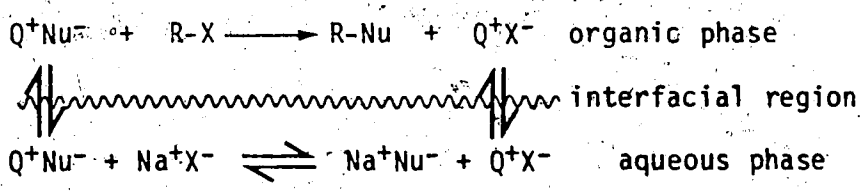


Compd	R	ir cm^{-1} (KBr) for CO	^1H nmr, δ, ($CDCl_3$)
185	methyl	1580	1.82 (s, 3H, Me), 7.73-8.36 (m, 3H, H_3, H_4, H_5)[a], 8.69 (d, 2H, H_2, H_6)[a,b]
186	t-butyl	1570	1.31 (s, 9H, t-butyl hydrogens), 7.57-8.19 (m, 3H, H_3, H_4, H_5)[a], 8.72 (d, 2H, H_2, H_6)[a,b]
187	cyclo-propyl	1580	0.54-1.29 (complex m, 4H, cyclopropyl H_2, H_3), 1.48-1.97 (complex m, 1H, cyclopropyl H_1), 7.52-8.12 (m, 3H, H_3, H_4, H_5)[a], 8.79 (d, 2H, H_2, H_6)[a,b]
188	cyclo-pentyl	1590	1.41-2.29 (complex m, 8H, cyclopentyl H_2, H_3, H_4, H_5), 2.53-3.11 (m, 1H, cyclopentyl H_1), 7.48-8.13 (m, 3H, H_3, H_4, H_5)[a], 8.72 (d, 2H, H_2, H_6)[a,b]
189	cyclo-heptyl	1580	1.22-2.22 (m, 12H, cycloheptyl H_{2-7}), 2.22-2.81 (m, 1H, cycloheptyl H_1), 7.45-8.14 (m, 3H, H_3, H_4, H_5)[a], 8.74 (d, 2H, H_2, H_6)[a,b]
190	1-ada-mantyl	1550	1.56-2.21 (m, 16H, adamantyl hydrogens), 7.43-8.1 (m, 3H, H_3, H_4, H_5)[a], 8.6 (d, 2H, H_2, H_6)[a,b]
191	ethoxy	1640	1.32 (t, J = 7 Hz, 3H, CH_3), 4.22 (q, J = 7 Hz, 2H, CH_2), 7.43-8.07 (m, 3H, H_3, H_4, H_5)[a], 8.91 (d, 2H, H_2, H_6)[a,b]
192	1-naph-thoxy-methyl	1590	4.94 (s, 2H, CH_2), 6.95-8.66 (m, 9H, pyridinium H_3, H_4, H_5, six naphthyl hydrogens), 8.42-8.88 (d, 3H, pyridinium H_2, H_6, one naphthyl hydrogen)[b]

Table 9 continued

193	2-furanyl	1572	6.56 (d, $J_{3,4}$ = 3.4 Hz of d, $J_{4,5}$ = 1.6 Hz, 1H, furanyl H_4), 7.18 (d, $J_{3,4}$ = 3.4 Hz, 1H, furanyl H_3), 7.56-7.68 (m, 1H, furanyl H_5), 7.75-8.12 (m, 3H, H_3, H_4, H_5)[a], 8.97 (d, 2H, H_2, H_6)[a,b]
194	2-thienyl	1570	7.09 (d, $J_{4,5}$ = 5 Hz of d, $J_{3,4}$ = 4 Hz, 1H, thienyl H_4), 7.51 (d, $J_{4,5}$ = 5 Hz of d, $J_{3,5}$ = 1.5 Hz, 1H, thienyl H_5), 7.63 (d, $J_{3,4}$ = 4 Hz, of d, $J_{3,5}$ = 1.5 Hz, 1H, thienyl H_3), 7.73-8.24 (m, 3H, H_3, H_4, H_5)[a], 8.97 (d, 2H, H_2, H_6)[a,b,c]
195	1-methyl-2-pyrrolyl	1580	4.02 (s, 3H, Me), 6.18 (d, $J_{3,4}$ = 4 Hz of d, $J_{4,5}$ = 3 Hz, 1H, pyrrolyl H_4), 6.72 (d, $J_{4,5}$ = 3 Hz of d, $J_{3,5}$ = 1.5 Hz, 1H, pyrrolyl H_5), 6.93 (d, $J_{3,4}$ = 4 Hz of d, $J_{3,5}$ = 1.5 Hz, 1H, pyrrolyl H_3), 7.41-8.05 (m, 3H, H_3, H_4, H_5)[a], 8.84 (d, 2H, H_2, H_6)[a,b]
196	2-[[1-(1,2,3,6-tetrahydopyridinyl)amino]-carbonyl]-6-pyridyl		ni[d]

[a] Signify pyridinium hydrogens. [b] These peaks were d ($J_{2,3}$ = $J_{5,6}$ = 6 Hz) of d ($J_{2,4}$ = $J_{4,6}$ = 2 Hz). [c] Me_2SO-d_6 was used as solvent. [d] ni, not isolated.



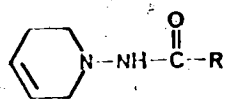
Scheme 7 Phase transfer catalytic cycle

Thus, a solution of 1-adamantyl carboxylic acid chloride (6.2 mmol) in petroleum ether (bp 90 - 110°C) was added to a solution of N-aminopyridinium iodide (4.2 mmol) in 10% aqueous sodium hydroxide in the presence of cetyltrimethylammonium bromide. The reaction was stirred vigorously at 50°C for 48 h. Addition of water and completion of the isolation procedure in the usual way afforded N-(1-adamantylcarbonylimino)pyridinium ylide (190) in 94% yield. The spectral data obtained was consistent with the structure assigned (see Table 9).

The sodium borohydride reduction of ylides (185-196) afforded the corresponding N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-208) in excellent yield. The physical, spectral and pharmacological data have been summarized in Tables 10 - 12 respectively.

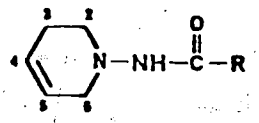
The analgesic test results suggested that the N-(carbonylamino)-1,2,3,6-tetrahydropyridine moiety is the most important structural feature since analgesic potency is independent of the steric and physicochemical properties of the R substituents. For example, compounds having aromatic heterocyclic rings (205-207), alkoxy (203), alkyl (197, 198) and cycloalkyl (199-202) R substituents all exhibited significant analgesic activities relative to aspirin and morphine.

Table 10 Some physical data of N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-208)



Compd	R	Yield, %	mp, °C	Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
197	Methyl	100	102-103	$C_7H_{12}N_2O$	59.98	8.63	19.98	59.75	8.57	19.63
198	tert-butyl	99.7	133-134	$C_{10}H_{18}N_2O$	65.90	9.95	15.37	65.51	9.83	15.65
199	cyclopropyl	88.5	124-125	$C_9H_{14}N_2O$	65.03	8.49	16.85	64.63	8.52	16.84
200	cyclopentyl	92.3	145-146	$C_{11}H_{18}N_2O$	68.01	9.34	14.42	67.73	9.30	14.28
201	cycloheptyl	95.2	152-153	$C_{13}H_{22}N_2O$	70.23	9.97	12.68	70.41	10.03	12.50
202	1-adamantyl	95	194-196	$C_{16}H_{24}N_2O$	73.81	9.29	10.76	73.70	9.37	10.41
203	ethoxy	98.2	67-68	$C_8H_{14}N_2O_2$	56.45	8.29	16.46	56.34	8.39	16.67
204	1-naphthoxymethyl	62.8	125-126	$C_{17}H_{18}N_2O_2$	72.33	6.42	9.92	72.31	6.45	9.99
205	2-furanyl	100	101-102	$C_{10}H_{12}N_2O_2$	62.50	6.25	14.58	62.14	6.29	14.76
206	2-thienyl	89.9	124-125	$C_{16}H_{12}N_2OS$	57.67	5.81	13.45	57.59	5.81	13.45
207	1-methyl-2-pyrrolyl	86.4	127-128	$C_{11}H_{15}N_3O$	64.39	7.32	20.49	64.24	7.44	20.09
208	2-[[1-(1,2,3,6-tetrahydropyridinyl)amino]-carbonyl]-6-pyridinyl	9	225-226	$C_{17}H_{21}N_5O_2$	62.37	6.47	21.39	62.15	6.23	21.50

Table 11 The ir and ^{1}H nmr spectral data of N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-208)



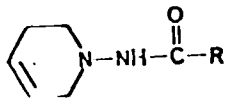
Comp'd	R	ir, cm^{-1} (KBr) NH	CO	^{1}H nmr, δ, ($CDCl_3$)
197	methyl	3200	1700	2.13 (s, 3H, CH_3), 2.11-2.55 (m, 2H, H_3)[a] 2.93 (t, 2H, H_2)[a,b], 3.19-3.56 (m, 2H, H_6)[a], 5.68 (m, 2H, H_4, H_5)[a], 7.24 (s, 1H, NH)[c]
198	t-butyl	3280	1660	1.51 (s, 9H, t-butyl hydrogens), 2.28-2.53 (m, 2H, H_3)[a], 3.1 (t, 2H, H_2)[a,b], 3.37-3.62 (m, 2H, H_6)[a], 5.76 (m, 2H, H_4, H_5)[a], 6.83 (s, 1H, NH)[c]
199	cyclopropyl	3210	1665	0.52-1.2 (m, 4H, cyclopropyl H_2, H_3), 2.12-2.66 (m, 3H, H_3, cyclopropyl H_1,)[a], 3.03 (t, 2H, H_2)[a,b], 3.24-3.62 (m, 2H, H_6)[a], 5.73 (m, 2H, H_4, H_5)[a], 7.0 (s, 1H, NH)[c]
200	cyclopentyl	3215	1660	1.45-2.23 (m, 8H, cyclopentyl H_{2-5}), 2.22-2.64 (m, 2H, H_3)[a], 3.15 (t, 2H, H_2)[a,b], 2.81-3.71 (m, 5H, H_2, H_6, cyclopentyl H_1)[a], 5.77 (m, 2H, H_4, H_5)[a], 6.7 (s, 1H, NH)[c]
201	cycloheptyl	3260	1670	1.33-2.12 (m, 12H, cycloheptyl H_{2-7}), 2.12-2.58 (m, 2H, H_3)[a], 2.72-3.37 (m, 2H, H_2, cycloheptyl H_1)[a], 3.36-3.63 (m, 2H, H_6)[a], 5.76 (m, 2H, H_4, H_5)[a], 6.99 (s, 1H, NH)[c]
202	1-adamantyl	3260	1650	1.62-2.21 (m, 16H, adamantyl hydrogens), 2.21-2.48 (m, 2H, H_3)[a], 3.01 (t, 2H, H_2)[a,b], 3.3-3.54 (m, 2H, H_6)[a], 5.72 (m, 2H, H_4, H_5)[a], 6.72 (s, 1H, NH)[c]
203	ethoxy	3220	1710	1.32 (t, J = 7Hz, 3H, CH_3), 2.19-2.54 (m, 2H, H_3)[a], 3.05 (t, 2H, H_2)[a,b], 3.32-3.57 (m, 2H, H_6)[a], 4.22 (q, J = 7Hz, CH_2), 5.71 (m, 2H, H_4, H_5)[a], 6.18 (s, 1H, NH)[c]

Table 11 (cont'd)

204	1-naphthoxy-methyl	3205	1670	2.14-2.48 (m, 2H, H_3)[a], 3.08 (t, 2H, H_2)[a,b], 3.39-3.61 (m, 2H, H_6)[a], 3.74 (s, 2H, CH_2), 5.43-6.04 (m, 2H, H_4, H_5)[a], 6.71-8.44 (m, 8H, naphthyl hydrogens, NH)[c]
205	2-furanyl	3220	1670	2.17-2.63 (m, 2H, H_3)[a], 3.16 (t, 2H, H_2)[a,b], 3.43-3.74 (m, 2H, H_6)[a], 5.81 (m, 2H, H_4, H_5)[a], 6.56 (d, $J_{3,4}$ = 3.4 Hz of d, $J_{4,5}$ = 1.6 Hz, 1H, furanyl H_4), 7.26 (d, $J_{3,4}$ = 3.4 Hz, 1H, furanyl H_3), 7.4 (s, 1H, NH)[c], 7.29-7.43 (m, 1H, furanyl H_5)
206	2-thienyl	3175	1655	2.13-3.71 (m, 6H, H_2, H_3, H_6)[a], 5.52-6.08 (m, 2H, H_4, H_5)[a], 7.14 (d, $J_{4,5}$ = 5 Hz of d, $J_{3,4}$ = 4 Hz, 1H, thienyl H_4), 7.56 (d, $J_{4,5}$ = 5 Hz, 1H, thienyl H_5), 7.88 (s, 1H, NH)[c], 8.16 (d, $J_{3,4}$ = 4 Hz, thienyl H_3)
207	1-methyl-2-pyrrolyl	3215	1645	2.12-2.53 (m, 2H, H_3)[a], 3.11 (t, 2H, H_2)[a,b], 3.36-3.75 (m, 2H, H_6)[a], 3.97 (s, 3H, CH_3), 5.72 (m, 2H, H_4, H_5)[a], 6.1 (d, $J_{3,4}$ = 4 Hz of d, $J_{4,5}$ = 3 Hz, 1H, pyrrolyl H_4), 6.61-6.81 (m, 2H, pyrrolyl H_3, H_5), 7.11 (s, 1H, NH)[c]
208	2-[[1-(1,2,3,6-tetrahydro-pyridinyl)-amino]carbonyl]-6-pyridinyl	3165	1650	2.19-2.62 (m, 4H, H_3)[a], 3.25 (t, 4H, H_2)[a,b], 3.66-3.85 (m, 4H, H_6)[a], 5.78 (m, 4H, H_4, H_5)[a], 7.92-8.56 (m, 3H, pyridine H_3, H_4, H_5), 9.09 (s, 2H, NH)[c]

[a] Signify 1,2,3,6-tetrahydropyridine hydrogens unless otherwise specified. [b] These peaks were t ($J_{2,3}$ = 7 Hz). [c] Exchanges with deuterium oxide.

Table 12 Some analgesic, hyperglycemic and partition coefficient data of N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-208)



Comp'd	R	p[a]	analgesic act., inhib act. on phenylquinone writhing[b] dose mg/kg sc	% inhibition	dose mg/kg po	hypoglycemic-hyperglycemic act.[c] % change in blood glucose concn posttreatment 2 h	4 h
197	methyl	3.3	30	99 ± 0.20	100	+35 ± 10.77	+36 ± 7.66
198	t-butyl	10.6	30	100 ± 0.00	100	+70 ± 36.73	+101 ± 73.64
199	cyclopropyl	13.3	30	100 ± 0.00	100	+66 ± 28.03	+111 ± 35.89
200	cyclopentyl	84.0	30	98 ± 0.24	100	+54 ± 12.54	+22 ± 2.33
201	cycloheptyl	31.7	30	98 ± 0.60	100	+100 ± 28.02	+82 ± 36.2
			0.00075	50 ± 0.87	50	+50 ± 17.37	
					60		+50 ± 7.42
202	1-adamantyl	28.3	30	86 ± 0.93	100	+33 ± 8.20	+22 ± 6.89
203	ethoxy	12.4	30	99 ± 0.20	100	+27 ± 6.92	+91 ± 60.50
			3	85.6 ± 0.68			
			3	86 ± 0.32[d]			
			0.00046	50 ± 0.37			
			19.5	50 ± 0.91[e]			
204	1-naphthoxymethyl	91.4	30	76 ± 1.55	100	+9 ± 7.60	+14 ± 6.17
205	2-furanyl	6.4	30	99 ± 1.20	100	+181 ± 45.51	+182 ± 71.54
			10	98.4 ± 0.24	17	+50 ± 32.94	
			10	99.2 ± 0.20[f]	30		+50 ± 33.93
			0.0075	50 ± 2.27			
206	2-thienyl	76.2	30	77 ± 0.73	100	+116 ± 45.38	+64 ± 17.48

Table 12 (cont'd)

207	1-methyl-2-pyrrolyl	20.0	30	90 + 0.98	100	+35	+	17.30	+25 + 12.14
208	2-[[1-(1,2,3,6-tetrahydropyridinyl)-amino]-carbonyl]-6-pyridinyl	0.3	30	60 + 1.14	100	+8	+	4.60	+10 + 5.81
Aspirin			50	50					
Dextropropoxyphene			56	50					
morphine sulfate			0.038	50 + 1.61.					
			3.1	50 + 2.8[e]					

[a] Partition coefficient, P = concentration in octanol/concentration in water. [b] The result is the mean value, or the mean value ± SEM, of five mice. [c] The result is the mean value, or the mean value ± SEM, of four rats. [d] Naloxone hydrochloride (0.6 mg/kg sc) was administered 15 min prior to injection of compound (203). [e] The result is the mean value, or the mean value + SEM, of five mice in the hot-plate test at 55 + 0.5°C at 30 min after dosing. [f] Naloxone hydrochloride (2 mg/kg sc) was administered 15 min prior to injection of compound (205).

The partition coefficient did not appear to have a significant influence on analgesic activity since compounds of both high and low polarity are equiactive. Pretreatment with naloxone hydrochloride did not alter the analgesic activity of compounds (203) and (205).

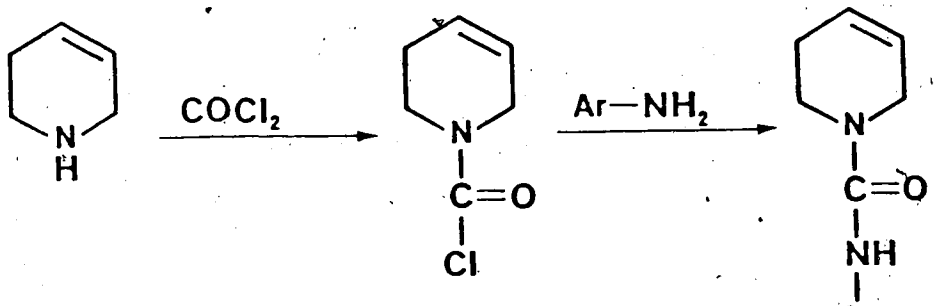
The influence that the R substituent has upon blood glucose concentration was also investigated. N-(Carbonylamino)-1,2,3,6-tetrahydropyridines (197-208) do not require an aromatic R substituent since alkyl (197, 198), cycloalkyl (199-202) and alkoxy (203) analogues all exhibited hyperglycemic effects. The five-membered aromatic heterocycles (205-207) were also prepared to examine the effect of ring size and various heteroatoms on hyperglycemic activity. The 2-furanyl derivative (205) was more potent than the 2-thienyl compound (206) which in turn was more potent than the 2-pyrrolyl (207) analogue. These results suggest that the N-(carbonylamino)-1,2,3,6-tetrahydropyridine moiety is likely the most important structural component since hyperglycemic activity is relatively independent of the nature of the R substituent. A correlation between the partition coefficient P and hyperglycemic activity was not evident from the results obtained.

3.5.0.0.0 Elaboration of the carbonylamino and 1,2,3,6-tetrahydropyridyl ring moieties of the structurally related N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine analogues (210 - 219, 221 - 226)

The SAR studies previously described suggested that the N-(carbonylamino)-1,2,3,6-tetrahydropyridine moiety is an important structural requirement for analgesic and hyperglycemic activity. It

was therefore of interest to determine what effect replacement of the 1,2,3,6-tetrahydropyridyl ring by other ring systems (substituents) and modification of the carbonylamino moiety would have upon analgesic and hyperglycemic activity.

The N-(aminocarbonyl)-1,2,3,6-tetrahydropyridines (210 - 212) were synthesized by reaction of 1-chlorocarbonyl-1,2,3,6-tetrahydropyridine (209), obtained from reaction of 1,2,3,6-tetrahydropyridine with phosgene, with aromatic amines. Thus, treatment of (209)



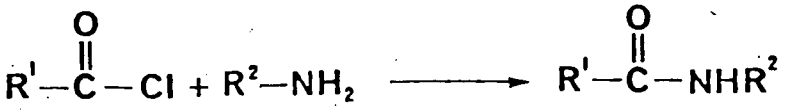
(209)

210, Ar= phenyl
211, Ar= 3-trifluoromethylphenyl
212, Ar= 4-pyridyl

with aniline and 3-trifluoromethylaniline yielded (210) and (211) respectively in excellent yield. On the other hand, synthesis of the 4-pyridylaminocarbonyl analogue (212) required an equimolar quantity of 4-dimethylaminopyridine. Low yields of (212) were obtained when a catalytic quantity of 4-dimethylaminopyridine was used. The reaction did not proceed in the absence of a catalyst. This was likely due to

the low reactivity of 4-aminopyridine.

The N-alkyl(cycloalkyl)amides (213-219) were prepared via two similar synthetic procedures. Reaction of 4-pyridinecarboxylic acid chloride hydrochloride with the amine in dry aprotic solvent in the presence of triethylamine afforded N-alkyl(cycloalkyl)isonicotinamides (213 - 215) in high yield. The related N-alkyl(cycloalkyl)-benzamides (216 - 219) were obtained from the reaction of benzoyl chloride with the amine in 10% sodium hydroxide.



213, R^1= 4-pyridyl, R^2= cyclopentyl

214, R^1= 4-pyridyl, R^2= cyclohexyl

215, R^1= 4-pyridyl, R^2= 2-furanylmethyl

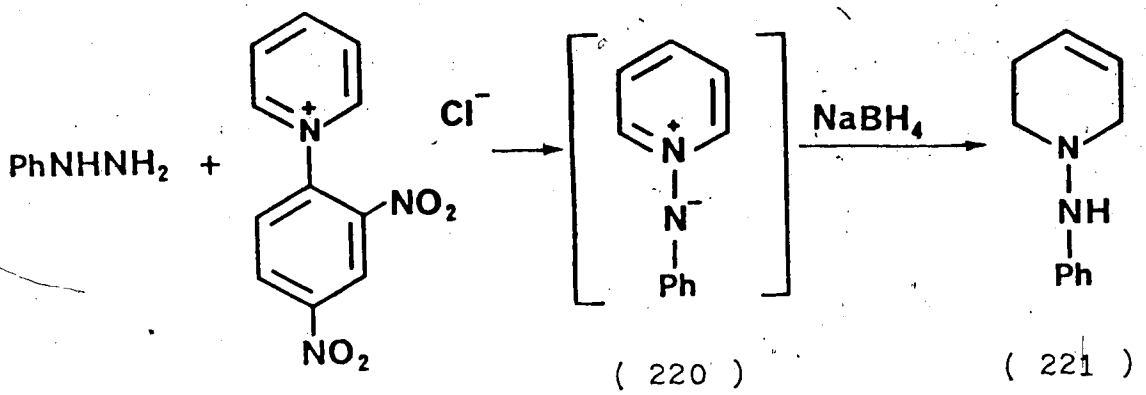
216, R^1= phenyl, R^2= cyclopropyl

217, R^1= phenyl, R^2= cyclopentyl

218, R^1= phenyl, R^2= cyclohexyl

219, R^1= phenyl, R^2= 2-furanylmethyl

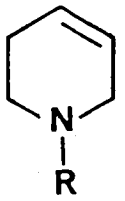
Reaction of phenylhydrazine with 2,4-dinitrophenylpyridinium chloride afforded the unstable N-(phenylimino)pyridinium ylide (220) which was immediately reduced with sodium borohydride to give N-(phenylamino)-1,2,3,6-tetrahydropyridine (221) in 6.5% yield. The pentafluorophenyl analogue of the ylide (220) has been synthesized in high yield by the reaction of N-aminopyridinium iodide with hexafluorobenzene under alkaline condition.[60] An alternative synthesis of the ylide (220)



(220) (221)

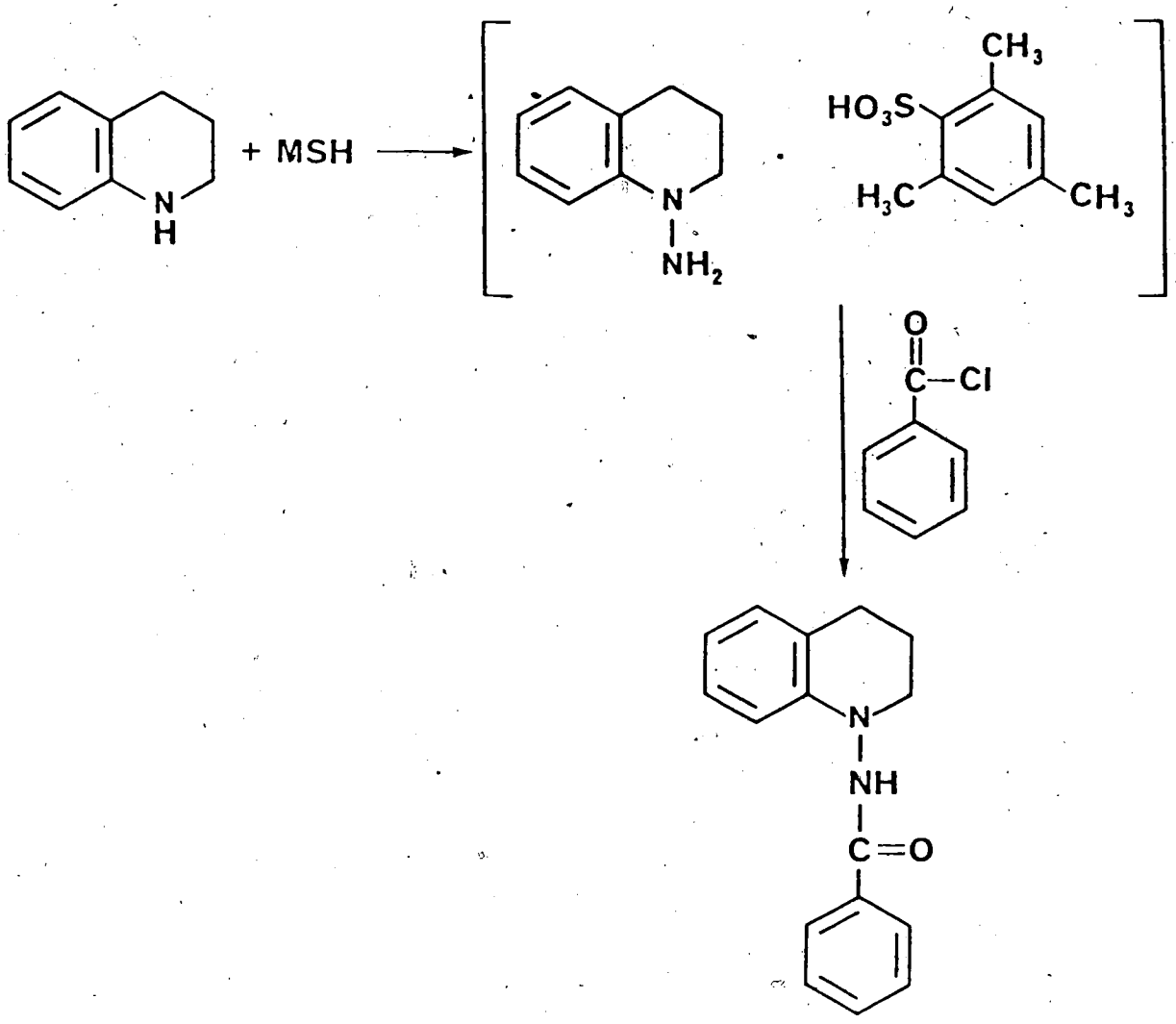
employing iodobenzene in the place of hexafluorobenzene was unsuccessful even at elevated temperature. Activation of the phenyl ring appears to be necessary for ylide formation.

N-(Phenylcarbonyl)-1,2,3,6-tetrahydropyridine (222)[275] was prepared by reaction of 1,2,3,6-tetrahydropyridine with benzoyl chloride in 10% aqueous sodium hydroxide. Condensation of 1,2,3,6-tetrahydropyridine with 1-chloro-4-nitrobenzene yielded N-(4-nitrophenyl)- 1,2,3,6-tetrahydropyridine (223) in 70% yield.



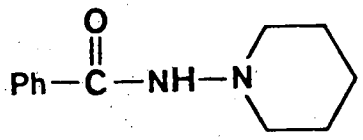
222, R= benzoyl
223, R= 4-nitrophenyl

N-(Phenylcarbonylamino)-1,2,3,4-tetrahydroquinoline (224) was prepared in 48% yield from the reaction of N-amino-1,2,3,4-tetrahydroquinoline mesitylenesulfonate, obtained by amination of 1,2,3,4-tetrahydroquinoline with mesitylenesulfonylhydroxylamine (MSH), with benzoyl chloride in 10% aqueous sodium hydroxide. Reduction of the lead

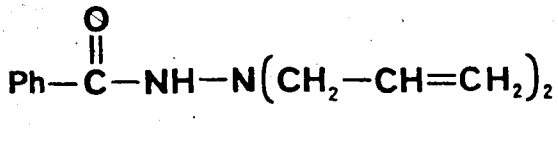


(224)

compound N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125) using palladium-on-charcoal and hydrogen gas yielded N-(phenylcarbonylamino)-piperidine (225) in 84% yield while reaction of benzoylhydrazine with allylbromide afforded N,N-diallylbenzoylhydrazine (226) in 62% yield. The physical, spectral and pharmacological data of these structurally related N-(carbonylamino)-1,2,3,6-tetrahydropyridine analogues (210-219, 221-226) are summarized in Tables 13 - 15 respectively.



(225)



(226)

N-(Phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125) was also structurally modified to investigate the effect which elaboration of the carbonylamino moiety and replacement of the 1,2,3,6-tetrahydropyridyl ring systems by other ring systems or substituents has upon analgesic and hyperglycemic activity. Reversal of the carbonylamino moiety of (125) to an aminocarbonyl moiety as in (210) resulted in a moderate reduction in analgesic activity (74% to 38% inhibition for a 0.004 mg/kg sc dose, Table 15). The 4-pyridyl compound (212) was less active than the corresponding phenyl (210) and 3-trifluoromethylphenyl (211) analogues. Replacement of the carbonylamino group of (125) by an amino group as for (221) or a carbonyl group as for (222) reduced analgesic activity slightly relative to (125). Complete removal of the carbonylamino moiety as for (223) reduced analgesic activity to a 30%

Table 13 Some physical data of structurally related N-(carbonylamino)-1,2,3,6-tetrahydropyridine analogues (210-219, 221-226)

Compd	Yield, %	mp, °C	Formula[a]	Calculated			Found		
				C	H	N	C	H	N
210	94	145-146	$C_{12}H_{14}N_2O$	71.26	6.98	13.85	71.36	7.09	13.82
211	88	73-75	$C_{13}H_{13}N_2OF_3$	57.78	4.85	10.37	57.84	4.85	10.28
212	56	143-144	$C_{11}H_{13}N_3O$	65.01	6.45	20.68	64.72	6.53	20.77
213	85	139-139.5	$C_{14}H_{14}N_2O$	69.45	7.42	14.73	69.42	7.43	14.55
214	87	139-140	$C_{12}H_{16}N_2O$	70.56	7.90	13.71	70.61	7.92	13.64
215	97	80-81	$C_{11}H_{10}N_2O_2$	65.34	4.98	13.85	65.06	5.03	13.90
216	57	94-95	$C_{10}H_{11}NO$	74.51	6.88	8.69	74.84	6.96	8.70
217	95	158-159.5	$C_{12}H_{15}NO$	76.16	7.99	7.40	76.20	7.95	7.32
218	100	148-149.5	$C_{13}H_{17}NO$	76.81	8.43	6.89	76.79	8.46	6.79
219	100	99-100	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	71.46	5.57	6.84
221	6.5	oil	$C_{11}H_{14}N_2$[b]	75.88	8.10	16.09	74.32	6.04	16.14
222	90	60-62	$C_{12}H_{13}NO$	76.98	7.00	7.48	76.79	6.96	7.27
223	70	113-114	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.68	5.91	13.74
224	48	195-196	$C_{16}H_{16}N_2O$	76.15	6.40	11.11	76.03	6.38	11.15
225	84	198-199	$C_{12}H_{16}N_2O$	70.54	7.90	13.72	70.40	7.92	13.62
226	62	113-115	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.43	7.54	13.05

[a] All compounds gave analyses for C, H, and N within ± 0.4 % of theoretical value except where specifically noted.

[b] C: calcd, 75.88; found, 74.32; H: calcd, 8.10; found, 6.04; exact mass for $C_{11}H_{14}N_2$: calcd, 174.1158; found (high resolution ms), 174.1158.

Table 14 The ir and ^{1}H nmr spectral data of structurally related N-(carbonylamino)-1,2,3,6-tetrahydropyridine analogues (210-219, 221-226)

Comp'd	ir, cm^{-1} (KBr) NH	CO	^{1}H nmr, , ($CDCl_3$)
210	3320	1638	1.98-2.36 (m, 2H, H_3)[a], 3.6 (t, 2H, H_2)[a,b], 3.88-4.13 (m, 2H, H_6)[a], 5.47-6.13 (m, 2H, H_4, H_5)[a], 6.92-7.6 (m, 5H, phenyl hydrogens), 8.1 (s, 1H, NH)[c]
211	3320	1650	1.92-2.38 (m, 2H, H_3)[a], 3.58 (t, 2H, H_2)[a,b], 3.83-4.14 (m, 2H, H_6)[a], 5.38-6.1 (m, 2H, H_4, H_5)[a], 7.1-7.86 (m, 4H, phenyl hydrogens), 8.58 (s, 1H, NH)[c]
212	3250	1690	1.9-2.5 (m, 2H, H_3)[a], 3.62 (t,2H,H_4,H_2)[a,b], 3.9-4.1 (m, 2H, H_6)[a], 5.45-6.05 (m, 2H, H_5)[a], 7.43 (d, 2H, H_3^1, H_5^1)[d,e], 8.33 (d, 2H, H_2^1, H_6^1)[d,e], 8.54 (s, 1H, NH)[c]
213	3320	1645	1.22-2.33 (m, 8H, cyclopentyl H_{2-5}), 4.14-4.66 (m, 1H, cyclopentyl H_1), 6.94-7.37 (broad s, 1H, NH)[c], 7.65 (d, 2H, H_3^1, H_5^1)[d,e], 8.65 (d, 2H, H_2^1, H_6^1)[d,e]
214	3200	1650	0.95-2.33 (m, 10H, cyclohexyl H_{2-6}), 3.72-4.4 (m, 1H, cyclohexyl H_1), 6.66-7.04 (broad s, 1H, NH)[c], 7.75 (d, 2H, H_3^1, H_5^1)[d,e], 8.77 (d, 2H, H_2^1, H_6^1)[d,e]
215	3360	1650	4.63 (d, J_{CH_2-NH} = 5.5 Hz, 2H, CH_2), 6.18-6.43 (m, 2H, furanyl H_3, H_4), 7.29-7.43 (m, 1H, furanyl H_5), 7.64-7.84 (d, 2H, H_3^1, H_5^1)[d,e], 8.5 (s, 1H, NH)[c], 8.64 (d, 2H, H_2^1, H_6^1)[d,e]
216	3205	1610	0.57-1.05 (m, 4H, cyclopropyl H_2, H_3), 2.73-3.16 (m, 1H, cyclopropyl H_1), 6.81-7.96 (m, 6H, phenyl hydrogens, NH)[c]
217	3320	1680	1.24-2.35 (m, 8H, cyclopentyl H_{2-5}), 4.15-4.66 (m, 1H, cyclopentyl H_1), 6.3 (broad s, 1H, NH)[c] 7.26-7.95 (m, 5H, phenyl hydrogens)
218	3260	1635	0.87-2.53 (m, 10H, cyclohexyl H_{2-6}), 3.68-4.35 (m, 1H, cyclohexyl H_1), 6.28 (braod s, 1H, NH)[c], 7.3-7.97 (m, 5H, phenyl hydrogens)

Table 14 (cont'd)

219	3320	1650	4.6 (d, $J_{CH_2, NH}$ = 5.5 Hz, 2H, CH_2), 6.17-6.37 (m, 2H, furanyl H_3, H_4), 6.8 (broad s, 1H, NH)[c], 7.3-7.96 (m, 6H, furanyl H_5, phenyl hydrogens)
221	3260 (film)	--	2.13-2.47 (m, 2H, H_3)[a], 2.82 (t, 2H, H_2)[a,b], 3.18-3.38 (m, 2H, H_6)[a], 4.5 (s, 1H, NH)[c], 5.47-5.97 (m, 2H, H_4, H_5)[a], 6.62-7.4 (m, 5H, phenyl hydrogens)
222	--	1630	1.98-2.5 (m, 2H, H_3)[a], 3.18-4.43 (m, 4H, H_2, H_6)[a], 5.5-6.14 (m, 2H, H_4, H_5)[a], 7.35-7.64 (m, 5H, phenyl hydrogens)
223	--	--	2.18-2.6 (m, 2H, H_3)[a], 3.65 (t, 2H, H_2)[a,b], 3.82-4.14 (m, 2H, H_6)[a], 5.67-6.27 (m, 2H, H_4, H_5)[a], 6.27-7.06 (m, 2H, phenyl H_2, H_6), 8.05-8.42 (m, 2H, phenyl H_3, H_5)
224	3240	1652	2.15 (quin. $J_{2,3} = J_{3,4}$ = 6 Hz, 2H, tetrahydroquinolinyl H_3), 2.81 (t, $J_{3,4}$ = 6 Hz, 2H, tetrahydroquinolinyl H_4), 3.63 (t, $J_{2,3}$ = 6 Hz, tetrahydroquinolinyl H_2), 6.58-7.28 (m, 4H, tetrahydroquinolinyl H_{5-8}), 7.35-8.22(m, 5H, phenyl hydrogens), 10.38 (s, 1H, NH)[c,f]
225	3200	1645	1.22-1.97 (m, 6H, piperidyl H_{3-5}), 2.7-3.16 (m, 4H, piperidyl H_2, H_6), 7.36-8.04 (m, 5H, phenyl hydrogens), 9.43 (s, 1H, NH)[c,f]
226	3220	1650	3.57 (d, $J_{1,2}$ = 6 Hz, 4H, allyl H_1), 4.95-5.46 (m, 4H, allyl H_3), 5.55-6.46 (m, 2H, allyl H_2), 7.13-7.94 (m, 6H, phenyl hydrogens, NH)[c]

[a] Signify 1,2,3,6-tetrahydropyridine hydrogens. [b] These peaks were t ($J_{2,3}$ = 6 Hz).
[c] Exchanged with deuterium oxide. [d] H_2^1, H_3^1, H_5^1, H_6^1 signifying pyridyl hydrogens.
[e] These peaks were d ($J_{2^1,3^1} = J_{4^1,5^1}$ = 5 Hz). [f] Me_2SO-d_6 was used as solvent.

Table 15 Some pharmacological data of N-(carbonylamino)-1,2,3,6-tetrahydropyridine analogues (210–219, 221–226)

	analgesic act., inhib act. on phenylquinone writhing[a]		hypoglycemic-hyperglycemic act.[b] % change in blood glucose concns posttreatment	
compd	dose, mg/kg sc	% inhibn	dose, mg/kg po	2h / 4h
210	0.004	38 ± 1.9	100	+6.8 ± 0.3 / +12.3 ± 0.4
211	0.004	36 ± 0.9	100	-0.5 ± 0.2 / +16.3 ± 0.1
212	0.004	16 ± 0.8	100	+36.5 ± 1.1 / +45.7 ± 2.2
213	0.004	42 ± 0.8	100	-9.3 ± 3.9 / -2.3 ± 5.3
214	0.004	53 ± 1.0	100	-15 ± 5.9 / -11.2 ± 4.7
215	0.004	56 ± 1.2	100	+34.5 ± 23.3 / +42.8 ± 35.
216	0.004	38 ± 1.3	100	-3.5 ± 3.1 / +4.8 ± 3.3
217	0.004	32 ± 0.6	100	+3.0 ± 4.4 / +0.3 ± 4.1
218	0.004	43 ± 0.6	100	-11.5 ± 3.8 / 0 ± 6.3
219	0.004	30 ± 0.8	100	+24 ± 20.8 / +14.8 ± 16.
221	0.004	59 ± 1.1	100	+79.8 ± 42.9 / +101.5 ± 53.
222	0.004	80 ± 0.7	100	+76 ± 37.7 / +54.5 ± 21.
	5	98 ± 0.4	80	+13 ± 0.4 / +4 ± 0.1
	5	95 ± 0.6[c]	50	-5.3 ± 0.0 / -3 ± 0.2
	0.0012	50 ± 1.21		
	35	50 ± 0.5[d]		
223	0.004	30 ± 0.8	100	+5.8 ± 0.3 / -4.8 ± 0.3
224	0.004	36 ± 2.2	100	-2.8 ± 0.2 / +11.5 ± 0.3
225	0.004	34 ± 1.2	100	+6.8 ± 0.4 / +11.5 ± 0.2
226	0.004	32 ± 1.0	100	+43.5 ± 1.0 / +33 ± 0.5
125	0.004	73.6 ± 0.6	100	+78 / +50
aspirin	50	50		
dextropropoxyphene	56	50		
morphine sulfate	0.038	50 ± 1.61		
	3.1	50 ± 2.8[d]		
chlorpropamide			100	-42 ± 12.1 / -38 ± 9.3

[a] The result is the mean value, or the mean value ± SEM, of five animals. [b] The result is the mean value, or the mean value ± SEM, of four animals. Hyperglycemic activity is indicated by a plus number and hypoglycemic is indicated by a negative number. [c] Naloxone hydrochloride (1 mg/kg sc) was administered 15 min prior to injection of 222. [d] Determined using the hot-plate test 30 min after a subcutaneous dose.

inhibition for a 0.004 mg/kg sc dose. Replacement of the 1,2,3,6-tetrahydropyridine ring of (125) by a cyclopropyl (216), cyclopentyl (217), cyclohexyl (218) or 2-furanylmethyl (219) ring resulted in a moderate reduction of analgesic activity. The 4-pyridyl analogues (213 - 215) were more potent than the corresponding phenyl analogues (217 - 219) having the same R^2-substituents. Similarly, replacement of the 1,2,3,6-tetrahydropyridyl ring of (125) by a 1-(1,2,3,4-tetrahydroquinolyl) (224), 1-piperidyl (225) or a diallylamino (226) moiety provided compounds exhibiting 32 - 36% inhibition in the phenylquinone writhing test for a 0.004 mg/kg sc dose. The most active analgesic in this group of compounds was N-(phenylcarbonyl)-1,2,3,6-tetrahydropyridine (222). The analgesic activity of (222) was also determined using the hot-plate test. In this test it exhibited an ED_{50} of 35 mg/kg sc relative to an ED_{50} of 3.09 mg/kg sc for morphine sulfate. N-(Phenylcarbonyl)-1,2,3,6-tetrahydropyridine (222) does not act at an opiate μ-receptor since pretreatment with naloxone hydrochloride did not alter the activity of (222).

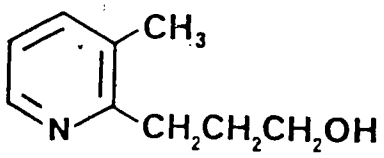
The influence which various structural components of the carbonylamino-1,2,3,6-tetrahydropyridyl moiety of (125) have upon blood glucose concentration was also investigated. The reverse aminocarbonyl (NHCO) derivatives (210 - 212) were less potent hyperglycemic agents than (125) which elevated blood glucose 78 and 50% respectively at 2 and 4 h post-treatment for a 100 mg/kg po dose. The 4-pyridyl analogue (212) increased blood glucose 37 and 46% respectively at 2 and 4 h, while the phenyl (210) and 3-trifluoromethylphenyl analogues (211) were mild hyperglycemic agents. Replacement of the carbonylamino group of (125)

by an amino group (221) enhanced the hyperglycemic effect elevating blood glucose 102% at 4 h whereas replacement by a carbonyl group (222) gave a compound with a potency similar to compound (125). Replacement of the phenylcarbonylamino moiety of (125) by a 4-nitrophenyl substituent (223) abolished hyperglycemic activity. On the other hand, replacement of the 1,2,3,6-tetrahydropyridyl ring of (125) by a cyclopropyl (216), cyclopentyl (217) or cyclohexyl (218) abolished hyperglycemic activity. A similar replacement of the 1,2,3,6-tetrahydropyridyl ring of (125) by 1,2,3,4-tetrahydroquinolyl (224), 1-piperidyl (225) or diallyl (226) moiety reduced but did not abolish hyperglycemic activity (see Table 15). These results indicated that the N-(carbonylamino)-1,2,3,6-tetrahydropyridine of (125) is an important structural moiety for potent hyperglycemic activity although phenylamino (221) and phenylcarbonyl (222) still exhibited a potent hyperglycemic effect.

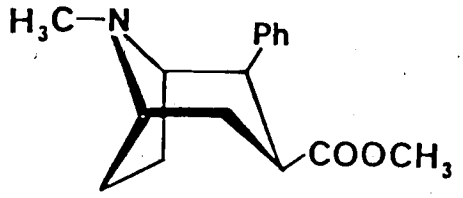
3.6.0.0.0 Preparation of N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252 - 275)

The SAR obtained thus far indicated that analgesic activity was quite independent of the nature of the substituents attached to the carbonylamino group. However, replacement of the 1,2,3,6-tetrahydropyridine by other ring systems or modification of the carbonylamino moiety reduced analgesic activity. These correlations suggested that the analgesic activity may be more dependent upon the position and physicochemical properties of substituents attached to the 1,2,3,6-tetrahydropyridyl ring.

On the other hand, changes in blood glucose concentration were sensitive to modification of the carbonylamino moiety. Replacement of the 1,2,3,6-tetrahydropyridine by other ring systems or functionality either reduced or abolished hyperglycemic activity. Blank et al[276] recently reported a series of 3-(3-methyl-2-pyridyl)propan-1-ols (227) and structurally related compounds which exhibited hypoglycemic and



(227)



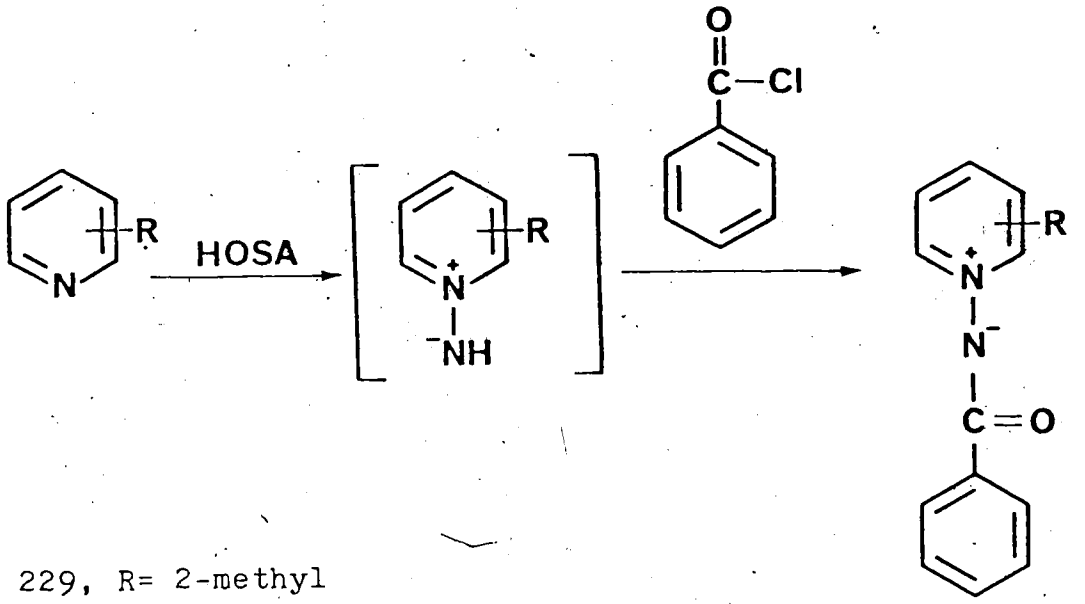
(228)

hyperglycemic activities within the same series of compounds. The position and physicochemical properties of substituents can exert a significant effect on blood glucose levels for a given class of compounds since Clark et al[277] also observed both hypo- and hyperglycemic activities for a series of 2-aryltropane-3-carboxylic acid esters (228).

Some analogues of N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125), having substituents attached to the 1,2,3,6-tetrahydropyridine ring, were therefore prepared to investigate the effect of substituent chain length, substituent position and physicochemical properties of substituents upon analgesic, hypo- and hyperglycemic activities. The substituents selected included fluoro, methyl, methoxy,

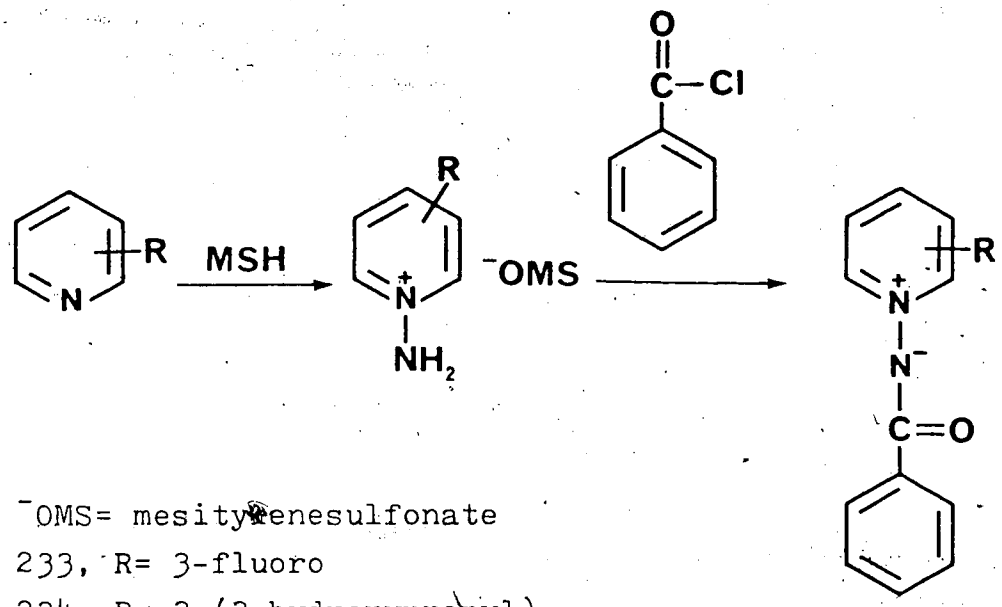
acetyl, hydroxymethyl, hydroxyethyl, hydroxypropyl, methoxypropyl, acetoxypropyl, carboxyethyl and methoxycarbonylethyl located at various positions of the 1,2,3,6-tetrahydropyridyl ring which were synthetically accessible.

Thus amination of alkyl substituted pyridines with HOSA in the presence of base generated the nonisolable pyridine N-imines which were subsequently benzoylated to afford the corresponding ylides (229 - 232). The latter were employed as precursors for the synthesis of the required alkyl substituted 1,2,3,6-tetrahydropyridine derivatives (255 - 258).



229, R= 2-methyl
230, R= 3-methyl
231, R= 4-methyl
232, R= 3,4-dimethyl

On the other hand, compounds (233 - 238) were prepared more efficiently by amination of the substituted pyridines with MSH followed by benzoylation to yield the ylide.



$^-$OMS= mesitylenesulfonate

233, R= 3-fluoro

234, R= 3-(3-hydroxypropyl)

235, R= 4-acetoxymethyl

236, R= 3-acetoxymethyl

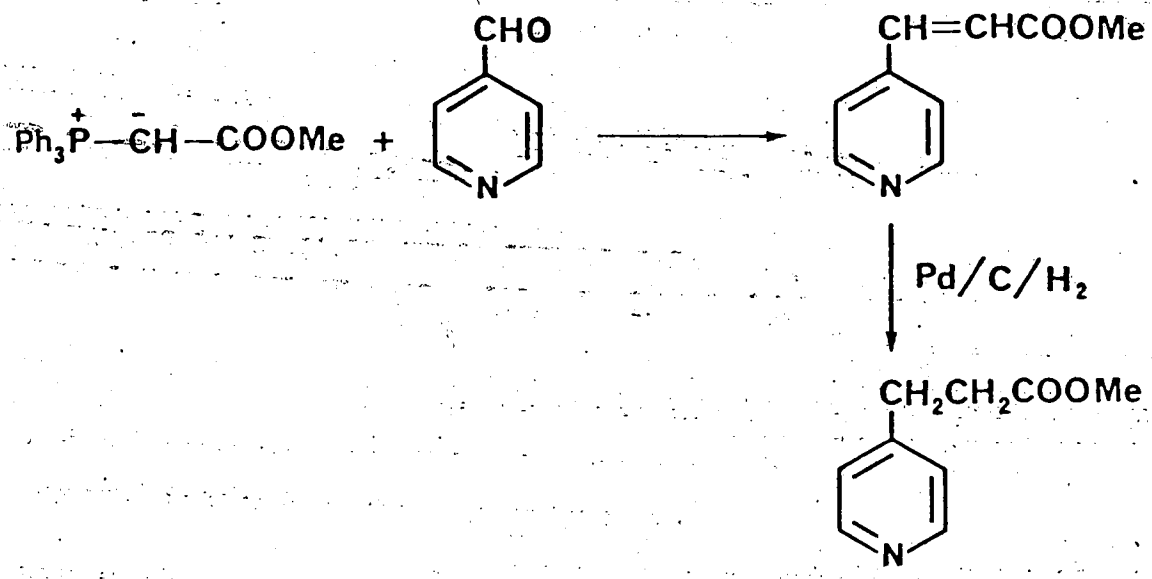
237, R= 3-(2-methoxycarbonylethyl)

238, R= 4-(2-methoxycarbonylethyl)

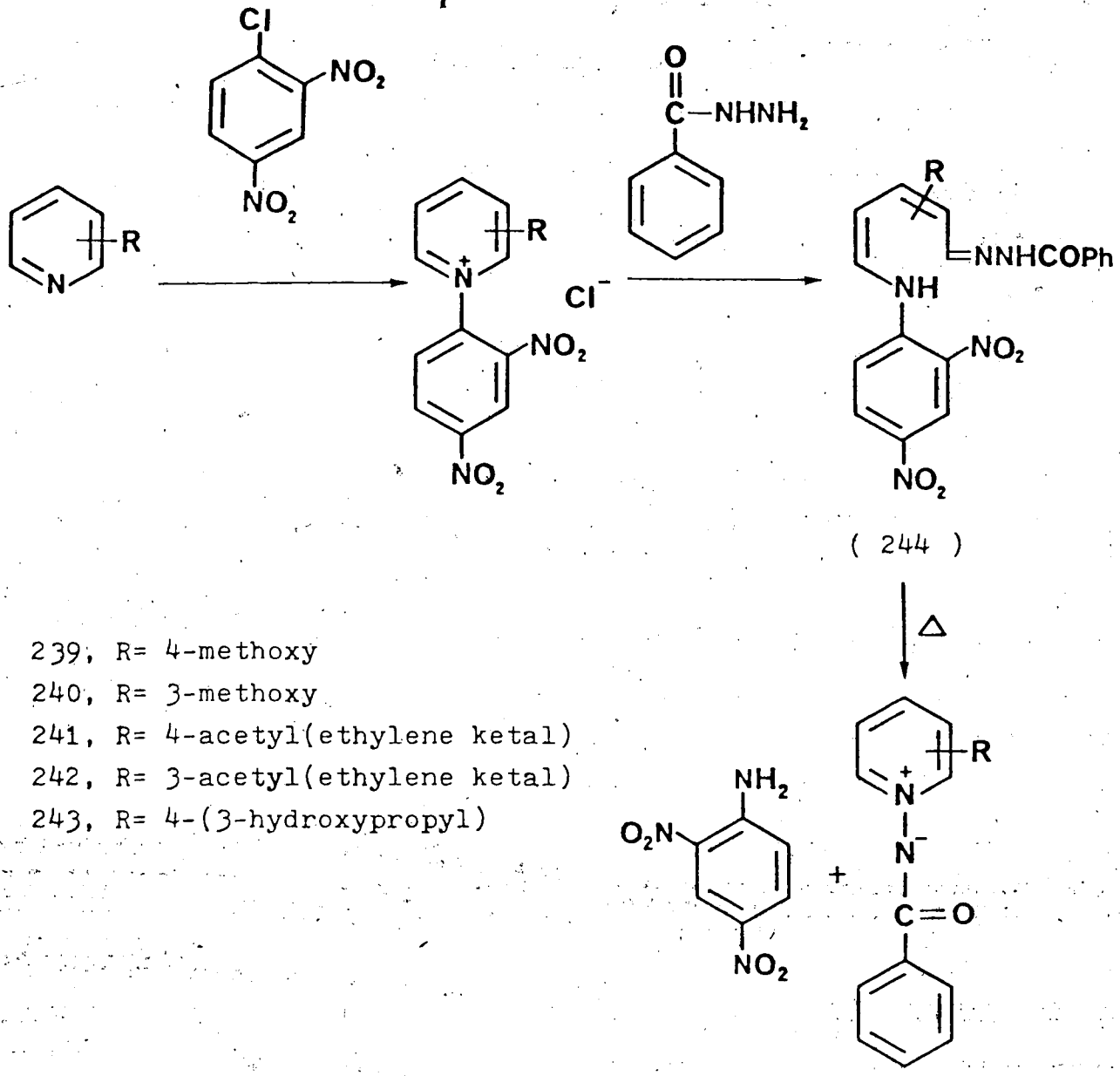
Although MSH is a more efficient aminating reagent than HOSA,[11,23-26] it is unstable[278] and potentially explosive.[279] Caution in preparing and storing MSH is advisable.

3-(2-Methoxycarbonylethyl)pyridine was prepared by hydrogenation, in the presence of palladium-on-charcoal, of methyl 3-pyridylacrylate, obtained by esterification of 3-pyridylacrylic acid with thionyl chloride in refluxing benzene followed by addition of methanol. On the other hand, 4-(2-methoxycarbonylethyl)pyridine was

prepared by catalytic hydrogenation of methyl 4-pyridylacrylate, obtained via the Wittig reaction of methoxycarbonylmethylene-triphenylphosphorane[280] with 4-pyridinecarboxaldehyde.[281,282]



Reaction of the required N-(2,4-dinitrophenyl)pyridinium chlorides (Zincke salts),[284] prepared from the reaction of the selected pyridine with 2,4-dinitrochlorobenzene, with benzoyl hydrazine gave 5-(2,4-dinitroanilino)-2,4-pentadienal hydrazones (244). Upon heating at reflux in dioxane-water (4:1 v/v), the hydrazones recyclized to yield the corresponding ylides (239 - 243).[284]



239, R= 4-methoxy
240, R= 3-methoxy
241, R= 4-acetyl(ethylene ketal)
242, R= 3-acetyl(ethylene ketal)
243, R= 4-(3-hydroxypropyl)

3-Methoxypyridine was prepared by methylation of 3-hydroxypyridine[283] and 4-methoxypyridine was prepared by catalytic N-deoxygenation of 4-methoxypyridine-1-oxide. Although it has been

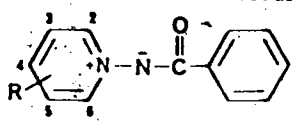
reported that the 4-methoxy ylide (239) cannot be prepared via the Zincke salt method[69] or the HOSA procedure,[14] a low yield (7.6%) of (239) was obtained, via the Zincke salt procedure. Several attempts to aminate 4-methoxypyridine with MSH were unsuccessful.

The keto groups of 3- and 4-acetylpyridine were protected as the ethylene ketals. The ketals were prepared by reaction of the ketone with ethylene glycol and pyridinium tosylate (pyridinium p-toluenesulfonate) in refluxing benzene[285] before generation of the Zincke salts. The yield of ylide (242) prepared in this way was only 20%. However amination of the ethylene ketal of 3-acetylpyridine with MSH and benzoylation with benzoyl chloride gave (242) in 77% yield. The physical and spectral data for N-(phenylcarbonylamino)-substituted-pyridinium ylides (229 - 243) are summarized in Tables 16 and 17.

A plausible mechanism for the formation of N-(phenylcarbonylimino)pyridinium ylides prepared via the Zincke salt procedure is illustrated by Scheme 8. Nucleophilic attack by the hydrazine at the 2-position of the Zincke salt (245) followed by electrocyclic ring opening of the dihydropyridine ring (246) could give rise to the intermediate (247).[109,286,287] The subsequent isomerization of (247) could yield the isolable 2,4-pentadienal derivative (248).[109] Upon heating, compound (248) could afford the electrocyclic ring closure intermediate (249) which could then undergo aromatization to give the N-iminopyridinium ylide (251) and 2,4-dinitroaniline (250).[288]

The sodium borohydride reduction of the ylides (229 - 243) afforded the corresponding N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252, 255-262, 266, 267, 274, 275),

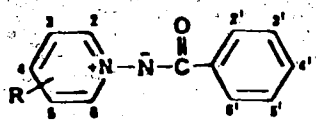
Table 16 Some physical data of N-(phenylcarbonylimino)-substituted-pyridinium ylides (229-243)



Comp'd	R	Yield,	mp, °C	formula	exact mass calc'd	exact mass found
229	2-methyl	37.4	118-119	$C_{13}H_{12}N_2O$	212.0949	212.0941
230	3-methyl	39	215-217	$C_{13}H_{12}N_2O$	212.0950	212.0935
231	4-methyl	18	oil	$C_{13}H_{12}N_2O$	212.0950	212.0939
232	3,4-dimethyl	59.5	104-106	$C_{14}H_{14}N_2O$	226.1106	226.1088
233	3-fluoro	99.2	179-181[a]	$C_{12}H_9N_2OF$		N.D.[b]
234	3-(3-hydroxypropyl)	97	oil	$C_{12}H_{16}N_2O_2$	256.1212	256.1217
235	4-acetoxymethyl	64	154-155	$C_{15}H_{14}N_2O_3$	270.1004	270.0991
236	3-acetoxymethyl	97.5	oil	$C_{15}H_{14}N_2O_3$	270.1005	270.0992
237	3-(2-methoxycarbonylethyl)	87	oil	$C_{16}H_{16}N_2O_3$	284.1161	284.1140
238	4-(2-methoxycarbonylethyl)	54	136-138	$C_{16}H_{16}N_2O_3$	284.1161	284.1141
239	4-methoxy	7.6	190-191	$C_{13}H_{12}N_2O_2$	228.0898	228.0883
240	3-methoxy	38.6	136-138[c]	$C_{13}H_{12}N_2O_2$		N.D.[b]
241	4-acetyl(ethylene ketal)	43	194-195	$C_{16}H_{16}N_2O_3$	284.1161	284.1148
242	3-acetyl(ethylene ketal)	20	123-125	$C_{16}H_{16}N_2O_3$	284.1161	284.1145
243	4-(3-hydroxypropyl)	33	163-165	$C_{15}H_{16}N_2O$	256.1212	256.1187

[a] Literature[26] mp 181-182°C. [b] ND = not determined. [c] Literature[26] mp 137-138°C.

Table 17 The ir and ^{1}H nmr spectral data of N-(phenylcarbonylimino)-substituted-pyridinium ylides (229-243)

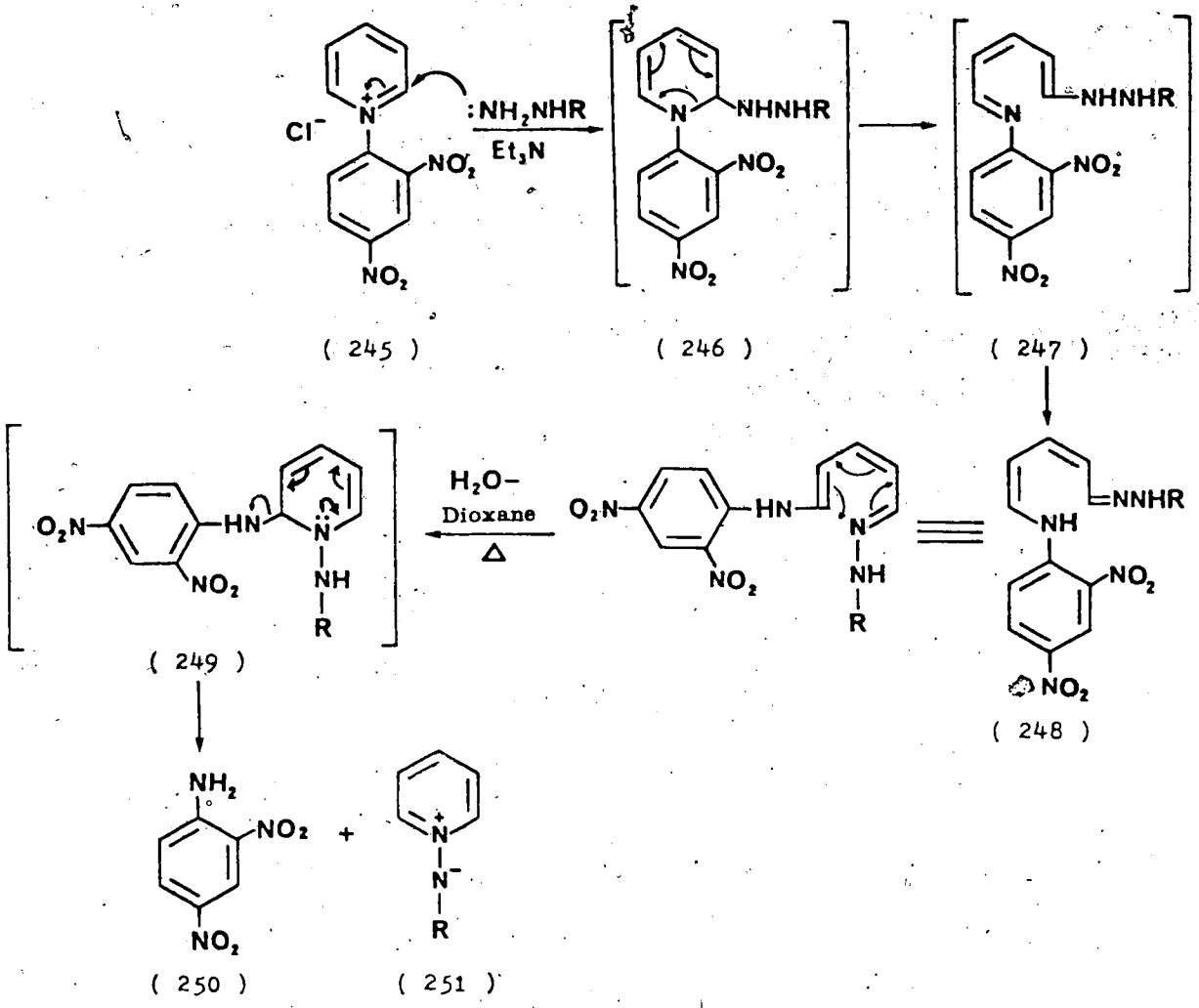


Comp'd	R	ir cm^{-1} for CO, (KBr)	^{1}H nmr, δ, ($CDCl_3$)
229	2-methyl	1560	2.6 (s, 3H, Me), 7.35-8.32 (m, 8H, H_3, H_4, H_5, $H_{2'-6'}$)[a,c], 8.74 (d, 1H, H_6)[a,b,d]
230	3-methyl	1560	2.53 (s, 3H, Me), 7.28-8.36 (m, 7H, H_4, H_5, $H_{2'-6'}$)[a,c], 8.64-8.9 (m, 2H, H_2, H_6)[a,b,d]
231	4-methyl	1530	2.6 (s, 3H, Me), 7.38-8.32 (m, 7H, H_3, H_5, $H_{2'-6'}$)[a,c], 8.79 (d, 2H, H_2, H_6)[a,b,d]
232	3,4-dimethyl	1540	2.37 (s, 3H, 3-Me), 2.45 (s, 3H, 4-Me), 7.33-8.29 (m, 6H, H_5, $H_{2'-6'}$)[a,b], 8.51-8.77 (m, 2H, H_2, H_6)[a]
233	3-fluoro	1560	7.19-8.24 (m, 7H, H_4, H_5, $H_{2'-6'}$)[a,c], 8.73-8.97 (m, 1H, H_6)[a], 9.31-9.52 (m, 1H, H_2)[a,d]
234	3-(3-hydroxypropyl)	1560 (film) 3400 (OH)	1.6-2.18 (m, 2H, $-CH_2-CH_2-OH$), 2.88 (t, J = 7 Hz, 2H, $-CH_2-CH_2CH_2OH$), 3.53 (t, J = 7 Hz, $-CH_2CH_2-CH_2-OH$), 4.56 (s, 1H, OH)[e], 7.21-8.81 (m, 9H, H_2, H_{4-6}, $H_{2'-6'}$)[a,c]
235	4-acetoxymethyl	1560 1750 (COOMe)	2.2 (s, 3H, Me), 5.3 (s, 2H, CH_2), 7.39-7.79 (m, 5H, H_3, H_5, $H_{3'-5'}$)[a,c], 8.14-8.47 (m, 2H, H_2, H_6)[c], 8.96 (d, 2H, H_2, H_6)[a,b]
236	3-acetoxymethyl	1560 (film) 1750 (COOMe)	2.11 (s, 3H, Me), 5.16 (s, 2H, CH_2), 7.35-8.47 (m, 7H, H_4, H_5, $H_{2'-6'}$)[a,c], 8.79-9.02 (m, 2H, H_2, H_6)[a]
237	3-(2-methoxycarbonyl-ethyl)	1560 (film) 1740 (COOMe)	2.53-3.27 (m, 4H, $-CH_2CH_2COOMe$), 3.6 (s, 3H, CH_3), 7.28-7.9 (m, 5H, H_4, H_5, $H_{3'-5'}$)[a,c], 8.04-8.31 (m, 2H, H_2, H_6)[c], 8.65-8.8 (m, 2H, H_2, H_6)[a]

Table 17 (cont'd)

238	4-(2-methoxycarbonyl-ethyl)	1555 1740 (COOMe)	2.54-3.28 (m, 4H, $-CH_2CH_2COOMe$), 3.73 (s, 3H, CH_3), 7.31-7.68 (m, 5H, H_3, H_5, H_3^1-5^1)[a,c], 8.05-8.44 (m, 2H, H_2^1, H_6^1)[c], 8.78 (d, 2H, H_2, H_6)[a,b]
239	4-methoxy	1560	3.98 (s, 3H, CH_3), 7.09 (d, 2H, H_3, H_5)[a,b], 7.31-7.55 (m, 3H, H_3^1-5^1)[c], 8.06-8.3 (m, 2H, H_2^1, H_6^1)[c], 8.57 (d, 2H, H_2, H_6)[a,b]
240	3-methoxy	1555	3.9 (s, 3H, CH_3), 7.3-7.7 (m, 5H, H_4, H_5, H_3^1-5^1)[a,c], 8.07-8.77 (m, 4H, H_2, H_6, H_2^1, H_6^1)[a,c]
241	4-acetyl(ethylene ketal)	1570	1.7 (s, 3H, CH_3), 3.69-4.23 (m, 4H, $-OCH_2CH_2O-$), 7.33-7.66 (m, 3H, H_3^1-5^1)[c], 7.81 (d, 2H, H_3, H_5)[a,b], 8.1-8.45 (m, 2H, H_2^1, H_6^1)[c], 8.9 (d, 2H, H_2, H_6)[a,b]
242	3-acetyl(ethylene ketal)	1560	1.79 (s, 3H, CH_3), 3.74-4.38 (m, 4H, $-OCH_2CH_2O-$), 7.33-8.47 (m, 7H, H_4, H_5, H_2^1-6^1)[a,c], 8.82-9.09 (m, 2H, H_2, H_6)[a,b]
243	4-(3-hydroxypropyl)	1554	1.67-2.21 (m, 2H, $-CH_2-CH_2-CH_2OH$), 2.93 (t, J = 7 Hz, 2H, $-CH_2-CH_2CH_2OH$), 3.55 (s, 1H, OH)[e], 3.67 (t, J = 7 Hz, 2H, $-CH_2CH_2-CH_2-OH$), 7.31-7.83 (m, 5H, H_3, H_5, H_3^1-5^1)[a,c], 8.02-8.34 (m, 2H, H_2^1, H_6^1)[c], 8.72 (d, 2H, H_2, H_6)[a,b,d]

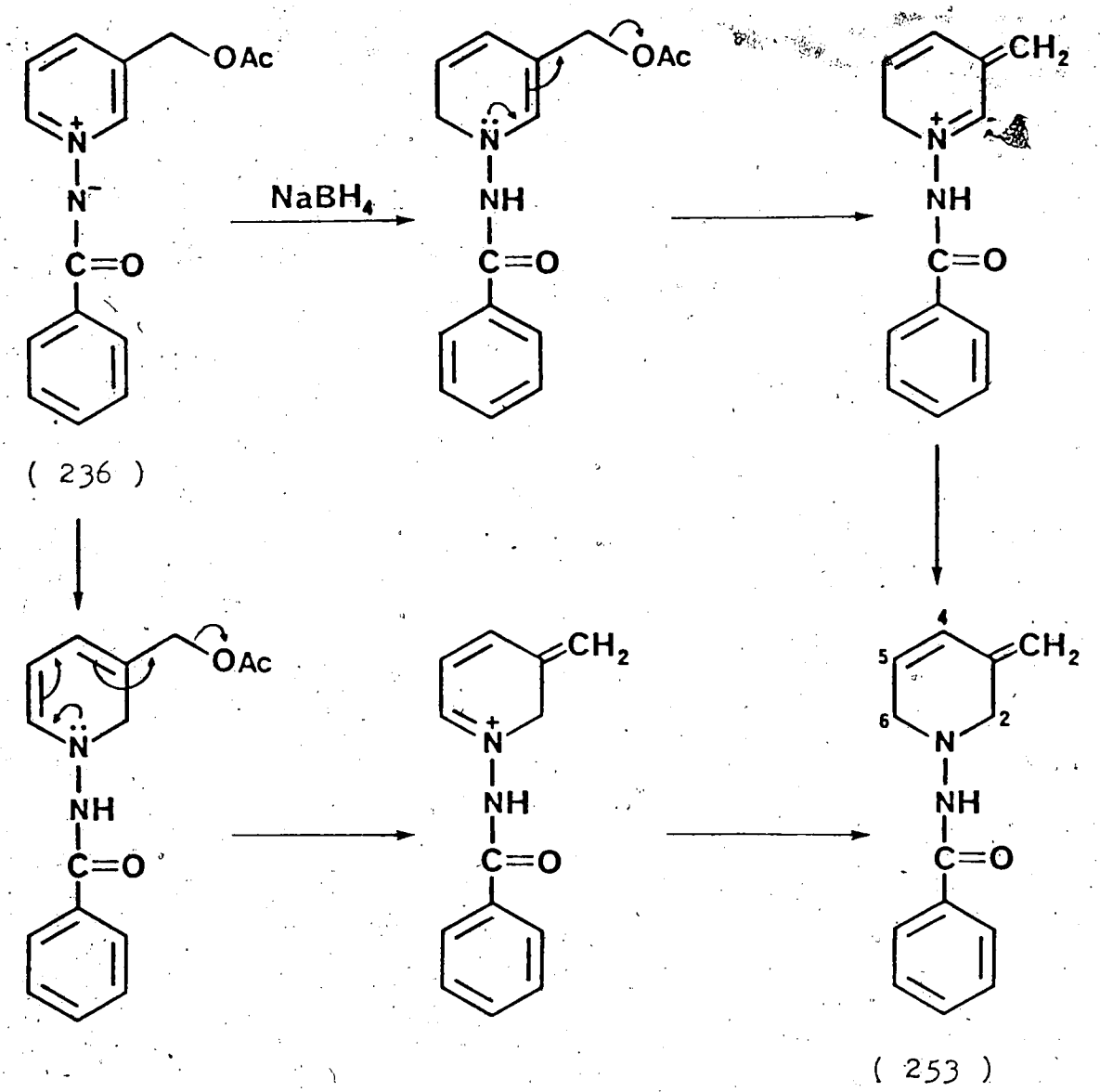
[a] H_2...H_6 signify pyridinium hydrogens. [b] These peaks were d ($J_{2,3}$ = $J_{5,6}$ = 7 Hz). [c] H_2^1...H_6^1 signify phenyl hydrogens. [d] Me_2SO-d_6 was used as solvent. [e] Exchanges with deuterium oxide.



Scheme 8 Plausible mechanism for the formation of N-iminopyridinium ylides prepared via the Zincke salt procedure

although formation of the 3-methylene (253) and 4-hydroxymethyl (265) analogues were not expected.

The formation of the 3-methylene derivative (253) from the 3-acetoxymethyl compound (236) is not unique.[289] It appears that

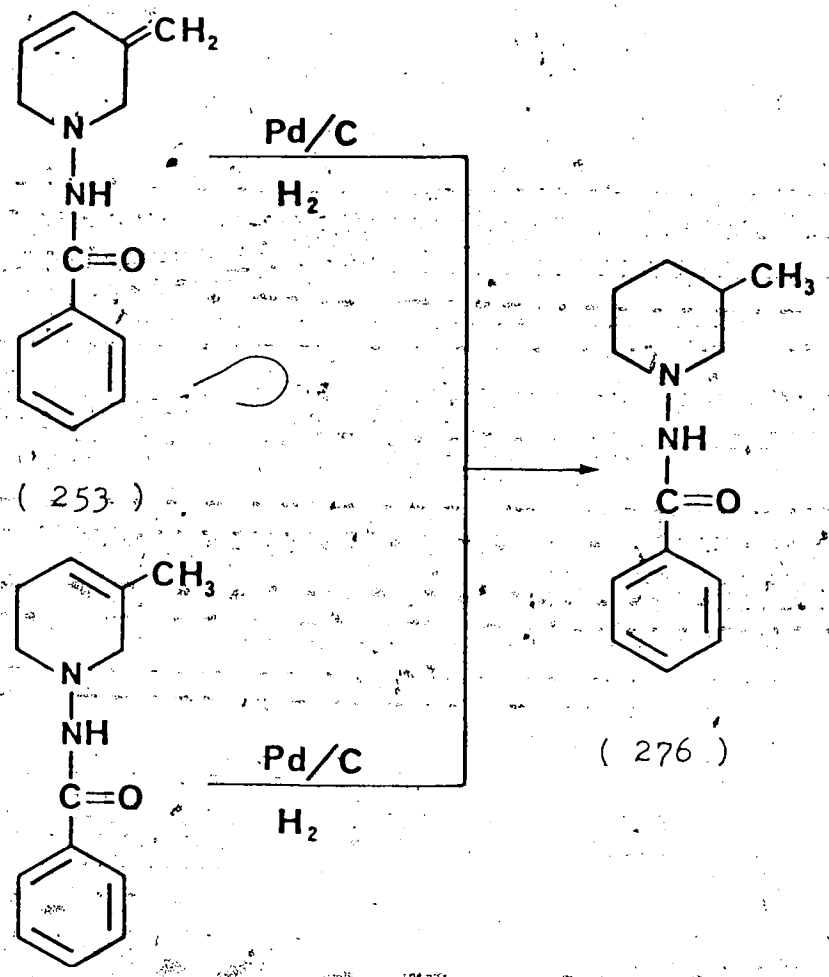


the reductive elimination was a preferred mode of reaction since the pyridinium ylide (236) contains an effective leaving group.

The structure assigned to (253) was consistent with the spectral data observed (see Table 19). The ir spectrum revealed the presence of NH peak at 3200 and CO at 1650 cm^{-1}. The 200 MHz ^1H nmr (δ) spectrum in (methylsulfoxide)-d_6 exhibited a 2H multiplet at 3.63 assigned to C_6-H. A 2H singlet at 3.64 was due to C_2-H. Two 1H singlets at 4.89 and 4.93 were attributed to the exocyclic methylene.[290] A 1H doublet ($J_{4,5}$ = 10 Hz) of doublet ($J_{5,6}$ = 3.5 Hz) of doublet ($J_{5,6}$ = 3.5 Hz) at 5.91 was assigned to C_5-H and a 1H doublet ($J_{4,5}$ = 10 Hz) at 6.22 was attributed to the C_4-H. A 3H multiplet at 7.4 - 7.6 was due to the meta- and para-phenyl hydrogens while a 2H doublet (J = 8 Hz) at 7.8 was assigned to the ortho-phenyl hydrogens. A 1H singlet at 9.6, which exchanges with deuterium oxide, was attributed to the NH hydrogen. These assignments were confirmed by double resonance studies. Irradiation at 4.89 and 4.93 δ did not alter the remainder of the spectrum. However, irradiation at 3.63 collapsed the doublet of doublet of doublet at 5.91 to a doublet due to loss of $J_{5,6}$ coupling.

The high resolution ms of (253) exhibited a molecular ion ($C_{13}H_{14}N_2O^{+\cdot}$) at m/z 214 (exact mass calc'd: 214.1106; found: 214.1084). The microanalytical data was in agreement with the formula $C_{13}H_{14}N_2O$ (Table 18).

The assigned structure (253) was further confirmed by unambiguous chemical methods. Catalytic hydrogenation of the 3-methylene (253) and 5-methyl (256) derivatives afforded N-(phenylcarbonylamino)-3-methylpiperidine (276).

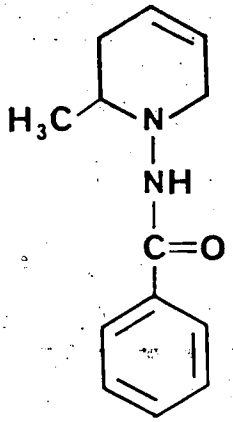


The product (276) obtained in these two reductions exhibited identical mp (163 - 164°C), ir and ^1H nmr spectra. The ir spectrum of (276) revealed the presence of a NH peak at 3200 and CO at 1650 cm^{-1}. The ^1H nmr (δ) in deuterochloroform exhibited a 3H doublet (J = 6 Hz) at 0:89 assigned to the methyl group. A 9H complex multiplet at 1.4 - 3.45 was due to the piperidyl hydrogens, while a 6H complex multiplet at 7.1 - 7.98 was attributed to the phenyl hydrogens and NH, exchanges with deuterium oxide. The microanalytical data

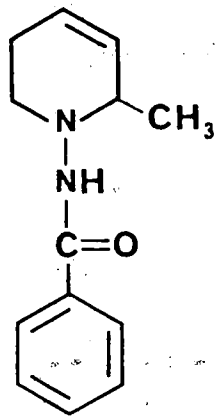
obtained for (276) was in agreement with the formula $C_{13}H_{18}N_2O$.

The sodium borohydride reduction of the 4-acetoxymethyl ylide (235) afforded N-(phenylcarbonylamino)-4-hydroxymethyl-1,2,3,6-tetrahydropyridine (265). The 4-acetoxymethyl substituent was also converted to the hydroxymethyl group.[291]

The product obtained from the reduction of N-(phenylcarbonylimino)-2-methylpyridinium ylide (229) was assigned structure (258) rather than (277) based on ^1H nmr spectral data (see Table 19).



(258)



(277)

The chemical shift positions for the 1,2,3,6-tetrahydropyridyl hydrogens are well known.[42,65-67] The chemical shift positions for the C_2-H and C_6-H of (258) and (277) are expected to be quite similar but their multiplicity and integration should differ significantly. The degree of shielding for a proton on carbon depends on the inductive effects of the groups attached to that carbon atom. Therefore, the

C_6-H always appears at lower field than the C_2-H since C_6-H is flanked by the electronegative ring nitrogen and C_4-C_5 olefinic group. The C_2-H which is only adjacent to the ring nitrogen therefore appears at higher field. The 2H multiplet at 3.58 - 3.83 δ was assigned to the C_6-H. A 1H multiplet, or a complex quartet, at 3.15 - 3.58 is attributed to C_2-H. This assignment is consistent only with structure (258). If the product had structure (277) the C_6-H multiplet at 3.58 - 3.83 should have integrated for one hydrogen, while the C_2-H complex quartet at 3.15 - 3.58 should have integrated for two hydrogens and appeared as a triplet ($J_{2,3}$ = 6 - 7 Hz). The C_2-H of unsubstituted 1,2,3,6- tetrahydropyridines always appear as a triplet.

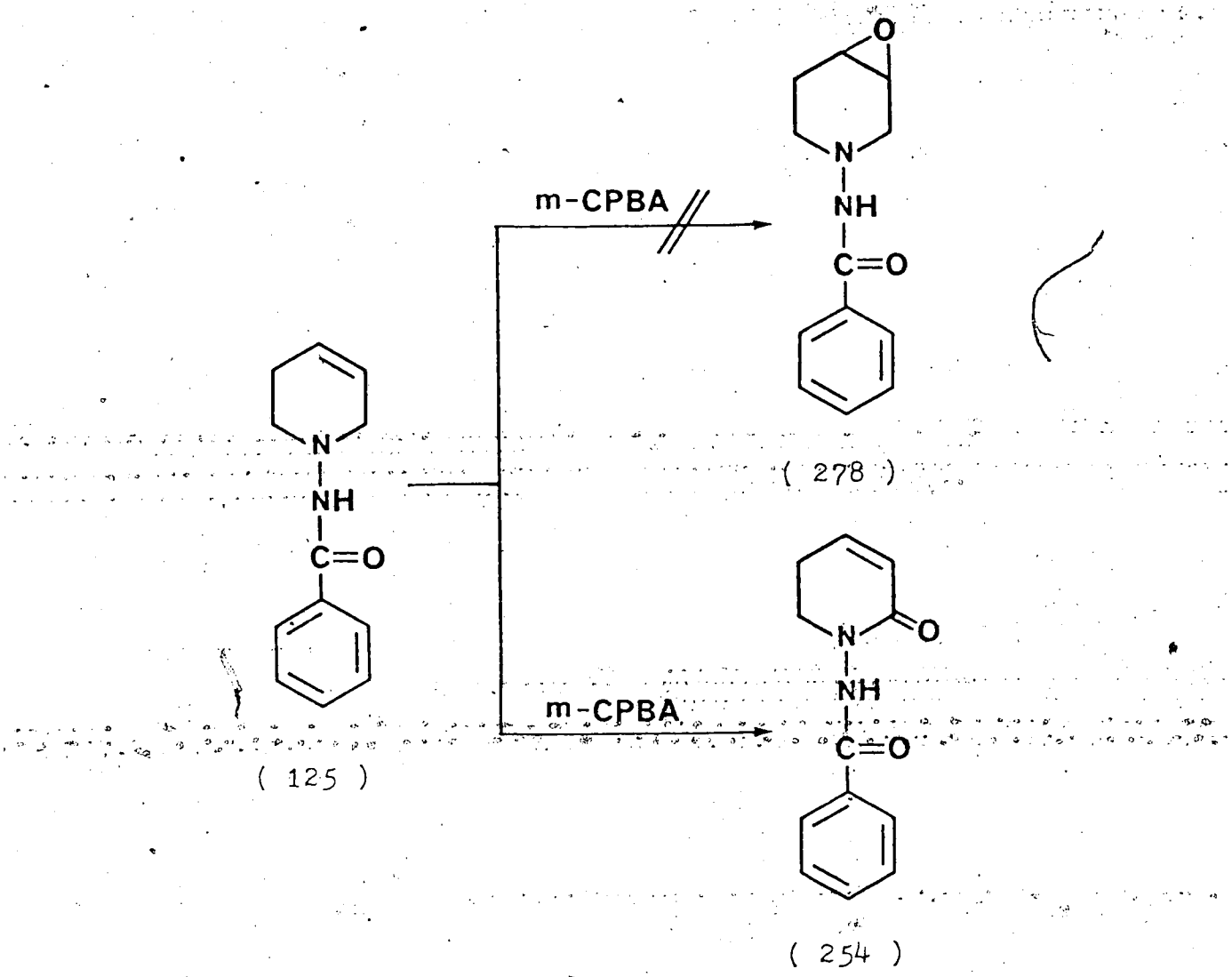
The 3-methoxypropyl compounds (268, 269) were synthesized by converting the 3-hydroxypropyl analogues (266, 267) to the mesylates and then displacement of the mesylate using sodium methoxide. The 3-acetoxypropyl derivatives (270, 271) were prepared by acetylation of (266) and (267) using acetic anhydride.

Hydrolysis of 2-methoxycarbonylethyl derivatives (274, 275), with sodium hydroxide yielded the 2-carboxyethyl compounds (272, 273).

The sodium borohydride reduction of the acetyl(ethylene ketal) ylides (241, 242) afforded the corresponding ethylene ketals of the acetyl-1,2,3,6-tetrahydropyridines which were subsequently converted to the acetyl-1,2,3,6-tetrahydropyridines (261, 262) using aqueous acetone and pyridinium tosylate.[285] The 1-hydroxyethyl compounds (263, 264) were prepared by sodium borohydride reduction of the acetyl derivatives (261, 262).

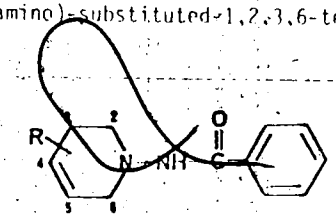
The meta-chloroperbenzoic acid (m-CPBA) oxidation of

compound (125) afforded the 6-oxo derivative (254) as the sole product.[292,293] Epoxidation of the olefinic bond was not observed.[275]



The influence which substituents R attached to the 1,2,3,6-tetrahydropyridyl ring had on activity was investigated (see Table 20). The analgesic test results indicated that the analgesic potency is quite independent of the physicochemical properties, position of attachment and chain length of the R substituents. Compounds 252 - 263, 265 - 275

Table 18 Some physical data of N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252-275)

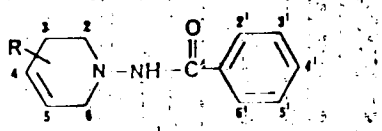


Comp'd	R	Yield	mp, °C	formula	calculated C	H	N	found C	H	N
252	5-fluoro	100	151.5-153	$C_{12}H_{13}N_2OF$	65.44	5.95	12.72	65.37	6.03	12.57
253	3-methylene	80	157-158	$C_{13}H_{14}N_2O$	72.86	6.59	13.08	72.71	6.74	13.11
254	6-oxo	20	159-160	$C_{12}H_{12}N_2O_2$	66.65	5.59	12.96	66.27	5.71	12.95
255	4-methyl	61	181-182	$C_{13}H_{16}N_2O$	72.19	7.46	12.96	72.17	7.36	13.10
256	5-methyl	45	156-157	$C_{13}H_{16}N_2O$	72.19	7.46	12.96	72.14	7.46	12.79
257	4,5-dimethyl	24	191-192	$C_{14}H_{18}N_2O$	73.01	7.88	12.16	72.90	7.88	12.02
258	2-methyl	45	147-150	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.02	7.70	12.82
259	4-methoxy	93	167-168	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.14	7.07	11.99
260	5-methoxy	73	162-163	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.11	7.08	12.33
261	4-acetyl	75	203-204	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.64	6.79	11.15
262	5-acetyl	30	179-180	$C_{14}H_{16}N_2O_2$	68.83	6.60	11.47	68.97	6.28	11.32
263	4-(1-hydroxyethyl)	92	156-157	$C_{14}H_{18}N_2O_2$	68.27	7.36	11.37	68.01	7.43	11.32
264	5-(1-hydroxyethyl)	91	181-183	$C_{14}H_{18}N_2O_2$	68.27	7.36	11.37	68.08	7.40	11.33
265	4-hydroxymethyl	87	173-174	$C_{13}H_{16}N_2O_2$	67.22	6.94	12.06	67.60	7.28	11.76
266	4-(1-hydroxypropyl)	47	157-158	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	68.92	7.60	10.66
267	5-(1-hydroxypropyl)	30	167-168	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	69.08	7.67	10.65

Table 18 (cont'd)

268	4-(3-methoxypropyl)	90	133-134	$C_{16}H_{22}N_2O_2$	70.03	8.09	10.21	69.99	8.05	10.22
269	5-(3-methoxypropyl)	83	103-105	$C_{16}H_{22}N_2O_2$	70.03	8.09	10.21	69.84	8.13	10.21
270	4-(3-acetoxypropyl)	97	140-142	$C_{17}H_{22}N_2O_3$	67.51	7.34	9.27	67.39	7.30	9.20
271	5-(3-acetoxypropyl)	55	163-165	$C_{17}H_{22}N_2O_3$	67.51	7.34	9.27	67.47	7.39	9.27
272	4-(2-carboxyethyl)	94	160-161	$C_{15}H_{18}N_2O_3$	65.68	6.61	10.21	65.77	6.78	9.99
273	5-(2-carboxyethyl)	87	193-195	$C_{15}H_{18}N_2O_3$	65.68	6.61	10.21	65.91	6.74	10.21
274	4-(2-methoxycarbonylethyl)	73	147-148	$C_{16}H_{20}N_2O_3$	66.65	6.99	9.72	66.39	7.06	9.62
275	5-(2-methoxycarbonylethyl)	30	140-142	$C_{16}H_{20}N_2O_3$	66.65	6.99	9.72	66.40	7.09	9.82

Table 19 The ir and ^{1}H nmr spectral data of N-(phenylcarbnylamino)-substituted-1,2,3,6-tetrahydropyridines (252-275)



Comp'd	R	ir, cm^{-1} (KBr) NH	CO	others	^{1}H nmr, δ, ($CDCl_3$)
252	5-fluoro	3200	1650		2.03-2.5 (m, 2H, H_3)[a], 3.1 (t, 2H, H_2)[a,b], 3.5-3.75 (m, 2H, H_6), 5.1-5.58 (m, 1H, H_4)[a], 7.26-8.28 (m, 6H, $H_2{}^1$-$_6{}^1$, NH)[c,d]
253	3-methylene	3220	1650		3.63 (m, 2H, H_6)[a], 3.64 (s, 2H, H_2)[a], 4.89 (s, 1H, one = CH_2 hydrogen)[a], 4.93 (s, 1H, one = CH_2 hydrogen)[a], 5.91 (d of d of d $J_{4,5}$ = 10 Hz, $J_{6,6}$ = 3.5 Hz, 1H, H_5)[a], 6.22 (d, $J_{4,5}$ = 10 Hz, 1H, H_4)[a], 7.4-7.6 (m, 3H, $H_3{}^1$-$_5{}^1$)[c], 7.8 (d, $J_{2',3'}$ = $J_{5',6'}$ = 8 Hz, 2H, $H_2{}^1$, $H_6{}^1$)[c], 9.6 (s, 1H, NH)[d,e]
254	6-oxo	3300	1670	1690 (C_6 = O)	2.32-2.74 (m, 2H, H_3)[a], 3.78 (t, 2H, H_2)[a,b], 5.94 (d, $J_{4,5}$ = 10 Hz, 1H, H_5)[a], 6.63 (d of t, $J_{4,5}$ = 10 Hz, $J_{3,4}$ = 7 Hz, 1H, H_4)[a], 7.03-7.9 (m, 5H, $H_2{}^1$-$_6{}^1$)[c], 10.48 (s, 1H, NH)[d]
255	4-methyl	3200	1645		1.63 (s, 3H, CH_3), 2.05-2.52 (m, 2H, H_3)[a], 3.04 (t, 2H, H_2)[a,b], 3.27-3.53 (m, 2H, H_6)[a], 5.35-5.63 (m, 1H, H_5)[a], 7.31-7.98 (m, 6H, $H_2{}^1$-$_6{}^1$, NH)[c,d]
256	5-methyl	3200	1650		1.68 (s, 3H, CH_3), 2.03-2.56 (m, 2H, H_3)[a], 3.05 (t, 2H, H_2)[a,b], 3.31-3.59 (m, 2H, H_6)[a], 5.38-5.71 (m, 1H, H_4)[a], 7.26-8.07 (m, 5H, $H_2{}^1$-$_6{}^1$)[c], 8.67 (s, 1H, NH)[d,e]
257	4,5-dimethyl	3200	1650		1.62 (s, 6H, CH_3), 1.95-2.45 (m, 2H, H_3)[a], 3.05 (t, 2H, H_2)[a,b], 3.21-3.52 (m, 2H, H_6)[a], 7.28-8.07 (m, 5H, $H_2{}^1$-$_6{}^1$)[c], 9.42 (s, 1H, NH)[d,e]
258	2-methyl	3230	1655		1.25 (d, J = 7 Hz, 3H, CH_3), 2.02-2.42 (m, 2H, H_3)[a], 3.15-3.58 (m, 1H, H_2)[a], 3.58-3.83 (m, 2H, H_6)[a], 5.51-6.04 (m, 2H, H_4, H_5)[a], 7.03-7.98 (m, 6H, $H_2{}^1$-$_6{}^1$, NH)[c,d]

Table 19 (cont'd)

259	4-methoxy	3250	1650		2.23-2.58 (m, 2H, H_3)[a], 3.21 (t, 2H, H_2)[a,b], 3.52-3.73 (m, 5H, H_6, OCH_3)[a], 4.55 (t, $J_{5,6}$ = 4 Hz, 1H, H_5)[a], 7.29-7.91 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
260	5-methoxy	3250	1650		2.06-2.59 (m, 2H, H_3)[a], 3.16 (t, 2H, H_2)[a,b], 3.4-3.6 (m, 5H, H_6, OCH_3)[a], 4.73 (t, $J_{3,4}$ = 4 Hz, 1H, H_4)[a], 7.29-7.94 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
261	4-acetyl	3260	1650	1675 ($COCH_3$)	2.32 (s, 3H, CH_3), 2.48-2.84 (m, 2H, H_3)[a], 3.25 (t, 2H, H_2)[a,b], 3.72-4.03 (m, 2H, H_6)[a], 6.7-6.98 (m, 1H, H_5)[a], 7.27-8.02 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
262	5-acetyl	3220	1650	1670 ($COCH_3$)	2.28 (s, 3H, CH_3), 2.4-2.81 (m, 2H, H_3)[a], 3.12 (t, 2H, H_2)[a,b], 3.64-3.87 (m, 2H, H_6)[a], 6.78-7.08 (m, 1H, H_4)[a], 7.32-7.97 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
263	4-(1-hydroxyethyl)	3240	1650	3410 (OH)	1.24 (d, J = 6 Hz, 3H, $-CH(OH)CH_3$), 2.32 (m, 2H, H_3)[a], 3.11 (t, 2H, H_2)[a,b], 3.35-3.67 (m, 2H, H_6)[a], 4.15 (q, J = 6 Hz, 1H, $-CH(OH)CH_3$), 4.47 (s, 1H, OH)[d], 5.46-5.72 (m, 1H, H_5)[a], 7.28-8.04 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 9.26 (s, 1H, NH)[d,e]
264	5-(1-hydroxyethyl)	3220	1655	3400 (OH)	1.22 (d, J = 6 Hz, 3H, $-CH(OH)CH_3$), 2.06-2.48 (m, 2H, H_3)[a], 3.07 (t, 2H, H_2)[a,b], 3.39-3.68 (m, 2H, H_6)[a], 4.19 (q, J = 6 Hz, 1H, $-CH(OH)CH_3$), 5.55-5.82 (m, 1H, H_4)[a], 7.39-8.06 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 9.49 (s, 1H, NH)[d,e]
265	4-hydroxymethyl	3260	1655	3410 (OH)	2.14-2.55 (m, 2H, H_3)[a], 3.18 (t, 2H, H_2)[a,b], 3.4-3.63 (m, 2H, H_6)[a], 3.86-4.16 (m, 2H, CH_2OH), 4.67 (s, 1H, OH)[d], 5.55-5.80 (m, 1H, H_5)[a], 7.33-8.12 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 9.4 (s, 1H, NH)[d,e]
266	4-(3-hydroxypropyl)	3280	1650	3450 (OH)	1.41-3.80 (complex m, 13H, H_2, H_3, H_6, $-CH_2CH_2CH_2OH$)[a,d], 5.24-5.52 (m, 1H, H_5)[a], 7.26-7.97 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 8.73 (s, 1H, NH)[d,e]
267	5-(3-hydroxypropyl)	3200	1650	3360 (OH)	1.16-2.53 (m, 6H, H_3, $-CH_2CH_2CH_2OH$)[a], 3.08 (t, 2H, H_2)[a,b], 3.29-3.8 (m, 4H, H_6, $-CH_2CH_2CH_2OH$)[a], 4.39 (s, 1H, OH)[d], 5.35-5.68 (m, 1H, H_4)[a], 7.41-8.09 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 9.52 (s, 1H, NH)[d,e]
268	4-(3-methoxypropyl)	3250	1650		1.61-2.56 (m, 6H, H_3, $CH_2CH_2CH_2OCH_3$)[a], 3.03-3.94 (m, 9H, H_2, H_6, $-CH_2CH_2CH_2OCH_3$)[a], 5.42-5.63 (m, 1H, H_5)[a], 7.28-8.12 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]

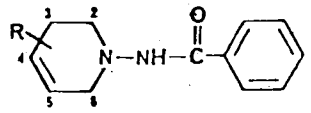
Table 19 (cont'd)

269	5-(3-methoxypropyl)	3220	1650		1.65-2.63 (m, 6H, H_3, $-CH_2\underline{CH_2}CH_2OCH_3$)[a], 3.21 (t, 2H, H_2)[a,b], 3.4-3.68 (m, 7H, H_6, $-CH_2CH_2\underline{CH_2}OCH_3$)[a], 5.52-5.77 (m, 1H, H_4)[a], 7.36-8.13 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
270	4-(3-acetoxypropyl)	3250	1650	1740 ($OCOCH_3$)	1.61-2.56 (m, 9H, H_3, $-CH_2\underline{CH_2}CH_2OCOCH_3$)[a], 3.21 (t, 2H, H_2)[a,b], 3.41-3.74 (m, 2H, H_6)[a], 4.14 (t, J = 7 Hz, 2H, $-CH_2CH_2\underline{CH_2}OCOCH_3$), 5.32-5.61 (m, 1H, H_5)[a], 7.35-8.04 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
271	5-(3-acetoxypropyl)	3250	1650	1735 ($OCOCH_3$)	1.44-2.43 (m, 9H, H_3, $-CH_2\underline{CH_2}CH_2OCOCH_3$)[a], 2.98 (t, 2H, H_2)[a,b], 3.25-2.53 (m, 2H, H_6)[a], 4.01 (t, J = 7 Hz, 2H, $-CH_2CH_2\underline{CH_2}OCOCH_3$), 5.34-5.65 (m, 1H, H_4)[a], 7.3-7.9 (m, 5H, $H_2{}^1{}_{-6}{}^1$)[c], 8.02 (s, 1H, NH)[d]
272	4-(2-carboxyethyl)	3240	1650	1710 (COOH)	2.2-2.63 (m, 6H, H_3, $-CH_2\underline{CH_2}COOH$)[a], 3.13 (t, 2H, H_2)[a], 3.37-3.64 (m, 2H, H_6)[a], 5.33-5.61 (m, 1H, H_5)[a], 7.31-7.99 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d], 8.66-9.44 (broad s, 1H, COOH)[d,e]
273	5-(2-carboxyethyl)	3260	1645	1730 (COOH)	2.05-2.56 (m, 6H, H_3, $-CH_2\underline{CH_2}COOH$)[a], 3.02 (t, 2H, H_2)[a,b], 3.38-3.65 (m, 2H, H_6)[a], 5.34-5.61 (m, 1H, H_4)[a], 7.4-8.3 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d], 9.5 (s, 1H, COOH)[d,e]
274	4-(2-methoxycarbonyl-ethyl)	3220	1650	1740 ($COOCH_3$)	2.11-2.63 (m, 6H, H_3, $-CH_2\underline{CH_2}COOCH_3$)[a], 3.5 (t, 2H, H_2)[a,b], 3.33-3.65 (m, 2H, H_6)[a], 3.7 (s, 3H, $COOCH_3$), 5.58 (m, 1H, H_5)[a], 7.27-8.05 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]
275	5-(2-methoxycarbonyl-ethyl)	3230	1650	1740 ($COOCH_3$)	2.12-2.65 (m, 6H, H_3, $-CH_2\underline{CH_2}COOCH_3$)[a], 3.13 (t, 2H, H_2)[a,b], 3.34-3.67 (m, 2H, H_6)[a], 3.65 (s, 3H, $COOCH_3$), 5.6 (m, 1H, H_4)[a], 7.31-8.02 (m, 6H, $H_2{}^1{}_{-6}{}^1$, NH)[c,d]

[a] $H_{2\ldots6}$ signify 1,2,3,6-tetrahydropyridyl hydrogens. [b] These peaks appeared as a t ($J_{2,3}$ = 7 Hz). [c] $H_2{}^1{}_{\ldots6}{}^1$ signify phenyl hydrogens.

[d] Exchanges with deuterium oxide. [e] Me_2SO-d_6 as solvent.

Table 20 Some analgesic, hyper- or hypoglycemic and partition coefficient data of N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252-276)



Comp'd	R	p[a]	analgesic act., inhib act. on phenylquinone writhing[b] dose mg/kg sc	inhibition	dose mg/kg po	hyper- or hypoglycemic act.[c] change in blood glucose concns posttreatment 2 h	4 h
252	5-fluoro	18.5	0.004	31 ± 1.1	100	+64 ± 1.3	+42 ± 1.0
					90	+50 ± 0.5	
253	3-methylene	23.5	0.004	79 ± 0.5	100	+5 ± 0.1	+4 ± 0.2
			0.0004	50 ± 1.2			
			4.2	50 ± 2.2[d]			
			5	93 ± 0.7			
			5	91 ± 0.4[e]			
254	6-oxo	14.9	0.004	54 ± 2.1	100	+1 ± 4.2	+4 ± 0.5
255	4-methyl	15.7	0.004	67 ± 1.6	100	+48 ± 23	+43 ± 23
256	5-methyl	23.6	0.004	53 ± 1.8	100	+124 ± 43	+116 ± 44
257	4,5-dimethyl	22.3	0.004	52 ± 1.7	100	+27 ± 13	+20 ± 6.9
258	2-methyl	5.0	0.004	69 ± 0.9	100	+12 ± 4.2	+16 ± 2.4
259	4-methoxy	14.4	0.004	21 ± 1.6	100	+5 ± 0.1	+7 ± 0.3
260	5-methoxy	41.4	0.004	20 ± 0.7	100	-7 ± 0.6	-9 ± 0.5
261	4-acetyl	2.4	0.004	23 ± 0.6	100	-12 ± 0.1	-19 ± 0.4
262	5-acetyl	0.8	0.004	53 ± 1.0	100	-5 ± 0.2	-17 ± 0.3
263	4-(β-hydroxyethyl)	1.1	0.004	19 ± 1.4	100	-10 ± 0.2	-5 ± 0.1
264	5-(1-hydroxyethyl)	2.8	0.004	0 ± 2.7	100	-8 ± 0.2	-16 ± 0.1
265	4-hydroxymethyl	4.4	0.004	53 ± 1.1	100	-10 ± 0.3	-14 ± 0.2
266	4-(3-hydroxypropyl)	16.7	0.004	66 ± 1.4	100	+4 ± 0.2	-6 ± 0.3

Table 20 (cont'd)

267	5-(3-hydroxypropyl)	13.2	0.004	48 + 2.2	100	-2 + 1.3	-6 + 1.4
268	4-(3-methoxypropyl)	30.6	0.004	35 + 1.6	100	+1 + 0.3	-9 + 0.3
269	5-(3-methoxypropyl)	8.1	0.004	72 + 0.9	100	-10 + 0.4	-11 + 0.4
270	4-(3-acetoxypropyl)	33.4	0.004	58 + 1.3	100	+2 + 0.6	+3 + 0.4
271	5-(3-acetoxypropyl)	31.1	0.004	67 + 1.7	100	-8 + 0.2	+7 + 0.2
272	4-(2-carboxyethyl)	10.0	0.004	35 + 3.0	100	-4 + 0.3	+7 + 0.4
273	5-(2-carboxyethyl)	15.3	0.004	51 + 0.9	100	-14 + 0.3	-4 + 0.3
274	4-(2-methoxy-carbonylethyl)	8.9	0.004	70 + 1.3	100	-9 + 0.2	-9 + 0.3
275	5-(2-methoxy-carbonylethyl)	5.5	0.004	34 + 2.2	100	-2 + 0.3	+6 + 0.2
125	hydrogen		0.004	73 + 0.6	100	+78	+50
aspirin			50	50			
dextropropoxyphene			56	50			
morphine sulfate			0.038	50 + 1.61			
			3.1	50[d]			
chlorpropamide					100	-42 + 12.1	-38 + 9.3

[a] P = partition coefficient. [b] The result is the mean value, or the mean value + SEM, of five mice. [c] The result is the mean value, or the mean value + SEM, of four rats. An increase in blood glucose concentration is indicated by a plus number and a decrease in blood glucose concentration is indicated by a negative number. [d] Determined using the hot-plate test 30 min after a subcutaneous dose. [e] Naloxone hydrochloride (1 mg/kg sc) was administered 15 min prior to injection of the test compound.

all exhibited reduced analgesic activities relative to the lead compound (125). The 5-(1-hydroxyethyl) compound (264) was devoid of analgesic activity, while the 3-methylene (253), 5-(3-methoxypropyl) (269) and 4-(2-methoxycarbonylethyl) (274) compounds still retained comparable analgesic activities relative to (125). The most active analgesic derivative in this class was the 3-methylene compound (253) which exhibited an ED_{50} of 0.0004 mg/kg sc in the phenylquinone writhing test and 4.2 mg/kg sc in the hot-plate test. Pretreatment with naloxone hydrochloride did not alter the analgesic activity of (253). A correlation between the partition coefficient P and analgesic activity was not evident.

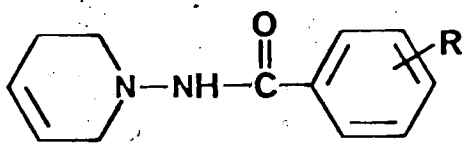
The hyperglycemic test results (Table 20) showed that the methyl derivatives (255 - 258) exhibited significant hyperglycemic activities. However, when the chain length of the R substituent was more than one carbon, irrespective of their physicochemical properties and position of attachment, the hyperglycemic activity was abolished (260 - 275). This indicated that the methyl group may play a role in retaining hyperglycemic activities. The partition coefficient P does not appear to have a significant influence on hyperglycemic activity since a large variation in P values was observed for compounds with or without hyperglycemic activity.

3:7.0.0.0 Overall structure-activity relationships for N-(carbonylamino)-1,2,3,6-tetrahydropyridines

Some structure-activity correlations describing the analgesic activity of N-(carbonylamino)-1,2,3,6-tetrahydropyridines and

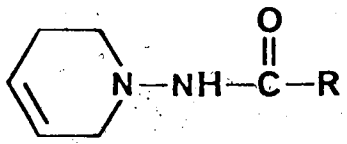
structurally related compounds are summarized below:

1. The analgesic test results indicate that the N-(phenylcarbonyl-amino)-1,2,3,6-tetrahydropyridine moiety is an important structural feature since the analgesic potency is independent of the position and physicochemical properties of the aromatic substituents (279).



(279)

2. The analgesic test results further suggest that the N-(carbonyl-amino)-1,2,3,6-tetrahydropyridine moiety is an important structural requirement since analgesic potency is quite independent of the steric and physicochemical properties for the R substituents of compounds (280). For example, compounds having aryl, arylalkyl, alkoxy, alkyl, cycloalkyl and 5-membered aromatic heterocyclic ring R substituents all exhibited significant activities relative to morphine sulfate.

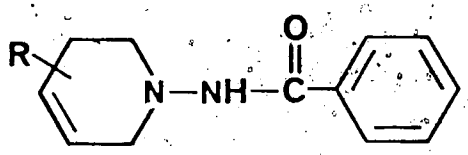


(280)

3. Replacement of the 1,2,3,6-tetrahydropyridyl ring by other ring systems or functionalities such as cycloalkyl, 1-piperidyl, 1-quinolyl or diallyl substituents reduced analgesic activity. Similarly, replacement of the carbonylamino moiety by an amino,

carbonyl, aminocarbonyl or removal of the carbonylamino moiety also reduced analgesic activity with carbonylamino > carbonyl > amino > removal of carbonylamino > aminocarbonyl.

4. Introduction of a R-substituent onto the 1,2,3,6-tetrahydropyridine (281) reduced analgesic activity significantly, except for the 3-methylene derivative. For example, compounds having fluoro, methyl, hydroxyethyl, hydroxypropyl or carboxyethyl substituents and their derivatives exhibited reduced analgesic activities relative to the lead compound.



(281)

5. The partition coefficient P does not appear to correlate with analgesic activity.
6. The N-(carbonylamino)-1,2,3,6-tetrahydropyridines described above do not act at an μ-opiate receptor since pretreatment with naloxone hydrochloride did not alter analgesic activity.

Some structure-activity correlations for hyperglycemic activity are summarized below:

1. Substitution on the phenyl ring of (279) indicated that the 3-substituted analogues are more potent than the corresponding 4-substituted analogues. All the 2-substituted analogues are relatively inactive except for the 2-fluoro compound (171).

2. An aromatic R substituent attached to the carbonylamino-1,2,3,6-tetrahydropyridine moiety is not required since compounds (280) having alkyl, cycloalkyl and alkoxy substituents exhibited a potent hyperglycemic effect.

3. Replacement of the carbonylamino moiety of (125) by a carbonyl group reduced and by an amino enhanced hyperglycemic activity. Replacement of the phenylcarbonylamino moiety by a 4-nitrophenyl substituent abolished hyperglycemic activity.

4. Replacement of the 1,2,3,6-tetrahydropyridyl ring by cycloalkyl rings destroyed hyperglycemic activity whereas replacement of the 1,2,3,6-tetrahydropyridyl ring by a 1-(1,2,3,4-tetrahydroquinolyl), 1-piperidyl or diallyl moiety reduced hyperglycemic activity.

5. Incorporation of methyl substituents onto the 1,2,3,6-tetrahydropyridine (281) reduced hyperglycemic activity, except for the 5-methyl derivative (256). On the other hand, introduction of substituents of more than one carbon atom in chain length such as hydroxyethyl, hydroxypropyl, carboxyethyl and their derivatives abolished hyperglycemic activity.

6. A correlation between the partition coefficient P and hyperglycemic activity was not evident from the results obtained to date.

4.0.0.0.0. Experimental

Melting points were determined with a Büchi capillary apparatus and are uncorrected. Infrared spectra (potassium bromide discs unless otherwise specified) were taken on a Unicam SP 1000 or Perkin Elmer 267 spectrophotometer. Nuclear magnetic resonance spectra were recorded for solutions of deuterochloroform with TMS as internal standard unless otherwise noted. The ^1H nmr spectra were recorded on a Varian EM-360A or Bruker WH-200 spectrometer. Mass spectra were measured with an AEI-MS-9 or Hewlett Packard 5995A mass spectrometer. All of the products described gave rise to a single spot on tlc using three different solvent systems of low, medium and high polarity. Microanalyses were within 0.4% of theoretical values when indicated by symbols of the elements. All preparative tlc plates were 20 x 20 cm and the Kieselgel silica gel DF-5 (Camag) was 0.75 mm in thickness.

4.1.0.0.0 Reagents and Solvents

N-Aminopyridinium iodide was prepared according to the procedure of Gösl and Meuwsen[7] by amination of pyridine using freshly prepared hydroxylamine-O-sulfonic acid (HOSA).[217] O-Mesitylene-sulfonylhydroxylamine (MSH) was prepared according to the procedure of Tamura.[10]

All acid chlorides were prepared by heating the carboxylic acid (1 mmol) with thionyl chloride (2 mmol) in dry benzene for 4 h at reflux. Excess thionyl chloride and benzene were removed in vacuo and the products were collected by fractional distillation at reduced pressure at water aspirator pressure.

Benzene, toluene, acetone and acetonitrile were dried by heating for 4 h in the presence of calcium hydride at reflux prior to distillation. The solvents were stored under an atmosphere of nitrogen prior to use.

Dry ether and tetrahydrofuran were distilled from sodium and benzophenone under a nitrogen atmosphere immediately prior to use.

Pyridine was dried by heating at reflux in the presence of potassium hydroxide pellets prior to distillation and storage over potassium hydroxide pellets.

4.2.0.0.0 Preparation of N-(phenylcarbonylimino)pyridinium ylides (126-144)

General procedure A

The acid chloride (12 mmol) was added dropwise to a solution of N-aminopyridinium iodide (8 mmol) in 25 mL of 10% aqueous sodium hydroxide with stirring. The reaction was allowed to proceed for 24 h at 25°C with stirring and then water (75 mL) was added. Extraction with chloroform (4 x 75 mL), decolorization using activated charcoal, drying (Na_2SO_4) and removal of solvent in vacuo gave the crude product which was purified by elution from a neutral alumina column. The initial 100 mL ether eluate was discarded. Further elution with 300 mL of ether-methanol (9:1 v/v) afforded ylides (126-144).

The following modifications for the purification of ylides (126-144), which did not require column chromatography were employed in the specific instances listed below. The 2-methyl (126), 3-methoxy (132), 2-chloro (134) and 2-trifluoromethyl (142) derivatives were

obtained as pure products. The 4-tert-butyl analogue (129) was washed with 10 mL cold ether to obtain a pure sample. The 2-fluoro (139) compound was purified by recrystallization from methylene chloride and the 3-fluoro compound (140) was recrystallized from ether.

4.2.1.0.0 Preparation of N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridines (158-177)

General procedure B

A solution of the ylide (126-145) (5 mmol) in 20 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (25 mmol) in 20 mL of absolute ethanol precooled to 0°C. The reduction was allowed to proceed for 5 h at 0°C with stirring. Water (80 mL) was added, and the mixture was allowed to return to 25°C. Extraction with chloroform (4 x 75 mL), drying (Na_2SO_4) and removal of the solvent in vacuo gave compounds (158-177). In most reactions the products (158-177) were isolated pure.

Those products (158-177) requiring purification were purified as outlined in the specific instances listed below. The 3-methyl analogue (159) was purified by elution from a neutral alumina column using ether-methanol (9:1 v/v) as eluant. The 4-methoxy (165) and 4-trifluoromethyl (176) compounds were purified by recrystallization from ether and the 4-chloro compound (167) was recrystallized from chloroform-ether. The 2-fluoro derivative (171) was decolorized using activated charcoal. The 4-nitro compound (177) was purified by preparative silica gel tlc using chloroform-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.5 with hot

absolute ethanol afforded (177).

4.3.0.0.0 Preparation of N-(carbonylimino)pyridinium ylides (185-189, 191, 193-196)

The ylides (185-189, 191, 193-196) were prepared according to general procedure A. The following modifications for purification of ylides (185-189, 191, 193-196), which did not require column chromatography, were followed in the specific instances listed below. The ylides (185, 186, 188-193) were isolated pure, whereas compound (196) was washed with 10 mL cold chloroform to afford the pure product.

4.3.1.0.0 Preparation of N-(carbonylimino)pyridinium ylides (190, 192) using phase transfer reaction catalysis

A solution of the carboxylic acid chloride (6 mmol) in petroleum ether (bp 90 - 110°C) (30 mL), was added dropwise to a solution of N-aminopyridinium iodide (4 mmol) in 10% aqueous sodium hydroxide (10 mL). A catalytic quantity of cetyltrimethylammonium bromide (0.04 mmol) was added with vigorous stirring and the reaction was allowed to proceed for 48 h. Water (75 mL) was added and the reaction was completed according to general procedure A to give (190 and 192).

4.3.2.0.0. Preparation of N-(carbonylamino)-1,2,3,6-tetrahydropyridines (197-207)

The sodium borohydride reductions of ylides (185-195) afforded the corresponding 1,2,3,6-tetrahydropyridines (197-207) as

described by general procedure B.

The compounds which required purification are listed below. Compounds (199, 200, 202, 206 and 207) were purified by elution from a neutral alumina column using ether-methanol (9:1 v/v) as eluant while (204) was purified by preparative silica gel tlc using chloroform-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.65 using absolute ethanol afforded (204).

4.3.3.0.0 Preparation of N-[[[2-[1-(1,2,3,6-tetrahydropyridinyl)-amino]-carbonyl]-6-pyridinyl]carbonyl]amino]-1,2,3,6-tetra-hydro-pyridine (208)

A solution of 2,6-pyridinedicarboxylic acid chloride (5 g, 30 mmol) in 10 mL dry dimethylformamide (DMF) was added dropwise to a solution of N-aminopyridinium iodide (14.4 g, 60 mmol) in 50 mL of dry DMF at 0°C with stirring during 30 min. Triethylamine (18.2 g, 180 mmol) was added in three aliquots, and the reaction was allowed to proceed for 48 h at 25°C prior to the addition of water (100 mL). Extraction with chloroform (4 x 150 mL), drying (Na_2SO_4) and removal of the solvent in vacuo afforded a dark residue. This residue was dissolved in 15 mL methanol and the purple solid that precipitated from the solution upon addition of 200 mL ether was filtered. A solution of the purple solid in 10 mL of absolute ethanol was added dropwise to a solution of sodium borohydride (2.6 g, 68 mmol) in 30 mL of absolute ethanol precooled to 0°C. The reaction was completed according to general procedure B to give a brown solid which was purified on 20 preparative silica gel tlc plates using chloroform-methanol (9:1 v/v) as

the development solvent. Extraction of the band having R_f 0.45 using hot absolute ethanol gave a reddish oil from which (208) was precipitated as a tan solid upon trituration with ether.

4.4.0.0.0 Preparation of 1-chlorocarbonyl-1,2,3,6-tetrahydropyridine (209)

A mixture of 1,2,3,6-tetrahydropyridine (18.5 mL, 20.2 mmol) and dry pyridine (16.3 mL, 20.2 mmol) was added dropwise during 30 min to a solution of phosgene (20 g, 20.2 mmol) in dry toluene (500 mL) precooled to 0°C under a nitrogen atmosphere with stirring. The reaction was allowed to proceed for 1 h at ice-bath temperature and the precipitate was filtered off. Removal of the solvent in vacuo gave a yellow oil which was fractionally distilled to yield 1-chlorocarbonyl-1,2,3,6-tetrahydropyridine (50%, bp 140°/40 mm Hg) as a pale yellow oil; ir (KBr) 1750 (CO) cm^{-1}; ^1H nmr (δ) 2.06 - 2.54 (m, 2H, H_3), 3.62 - 4.02 (m, 2H, H_2), 4.02 - 4.37 (m, 2H, H_6), 5.53 - 6.13 (m, 2H, H_4, H_5). Exact mass calcd. for C_6H_8NOCl: 145.0294; found (high resolution ms), 145.0293.

4.4.1.0.0 Preparation of N-(aminocarbonyl)-1,2,3,6-tetrahydropyridines (210, 211)

The aromatic amine (7 mmol) was added dropwise during 10 min to a solution of 1-chlorocarbonyl-1,2,3,6-tetrahydropyridine (7 mmol) in dry THF (50 mL) containing dry potassium carbonate (1 g) at 0°C with stirring under a nitrogen atmosphere. The reaction was allowed to proceed at 25°C for 24 h, ether (100 mL) was added and the precipitate

was filtered off. The filtrate was washed with water (10 mL), dried (Na_2SO_4), decolorized (activated charcoal), filtered and the solvent removed in vacuo to yield an orange solid. Purification by elution from a silica gel column using 200 mL ether-methanol (9:1, v/v) as eluant gave a white solid which was washed with cold ether to give the N-(phenylaminocarbonyl) derivative (210). The N-[3-(trifluoromethylphenylaminocarbonyl)] (211) compound was purified by elution from a silica gel column using 300 mL benzene prior to recrystallization from ether.

4.4.2.0.0 Preparation of N-(4-pyridylaminocarbonyl)-1,2,3,6-tetrahydropyridine (212)

A solution of 1-chlorocarbonylamino-1,2,3,6-tetrahydropyridine (2 g, 13.8 mmol) and 4-dimethylaminopyridine (1.68 g, 13.8 mmol) in methylene chloride (100 mL) was heated under reflux for 24 h. 4-Aminopyridine (1.3 g, 13.8 mmol) was added to the reaction mixture which was heated at reflux for a further 24 h. The pH of the reaction mixture was adjusted to 10 using saturated potassium carbonate. The organic phase was separated. Removal of the solvent in vacuo gave a white solid which was washed with ether to remove 4-dimethylaminopyridine. The product was purified by elution from a 2.5 x 20 cm silica gel column using 300 mL ether-methanol (9:1 v/v) as eluant prior to preparative silica gel tlc using ethyl acetate-methanol (7:3 v/v) as development solvent. Extraction of the fraction having R_f 0.5, followed by recrystallization from ether, gave (212).

4.4.3.0.0 Preparation of N-cycloalkyl(alkyl)isonicotinamides (213-215)

General procedure C

A mixture of the cycloalkyl(alkyl)amine (10 mmol) and triethylamine was added dropwise during 30 min to a suspension of 4-pyridyl acid chloride hydrochloride (10 mmol) in dry methylene chloride (30 mL) precooled to -78°C with stirring. The reaction was allowed to proceed for 3 h at 25°C prior to the addition of water (50 mL). Extraction with chloroform (4 x 50 mL), washing with brine (10 mL), drying (Na_2SO_4), decolorization (activated charcoal), filtration and removal of the solvent in vacuo afforded compounds (213-215).

Cyclohexylamine was added to 4-pyridyl acid chloride hydrochloride at 0°C and the reaction was allowed to proceed for 18 h to yield compound (214) according to general procedure C. 2-Furanylmethylamine was added to 4-pyridyl acid chloride hydrochloride at 0°C and the reaction was allowed to proceed for 1 h at 25°C. The product was washed with 10 mL cold ether to afford compound (215).

4.4.4.0.0 Preparation of N-cycloalkyl(alkyl)benzamides (216-219) and N-(phenylcarbonyl)-1,2,3,6-tetrahydropyridine (222)

General procedure D

Benzoyl chloride (12 mmol) was added dropwise to a precooled solution of the cycloalkyl(alkyl)amine (8 mmol) in 20 mL 10% aqueous sodium hydroxide with stirring. The reaction was allowed to proceed at 25°C for 1 h and then water (50 mL) was added. Extraction with chloroform (4 x 50 ml), drying (Na_2SO_4) and removal of the solvent in vacuo afforded compounds (216-219 and 222).

Cyclopropylbenzamide (216) was recrystallized from ethanol. Cyclopentyl- and cyclohexylbenzamides (217, 218) were washed with water and then cold ether. 2-Furanylmethylbenzamide (219) was obtained by evaporating the reaction mixture to dryness. The solid obtained was washed with water and then ether. N-(Phenylcarbonyl)-1,2,3,6-tetrahydropyridine (222) was purified by elution from a neutral alumina column using ether-methanol (9:1 v/v) as eluant.

4.4.5.0.0 Preparation of N-(phenylamino)-1,2,3,6-tetrahydropyridine (221)

Phenylhydrazine (4.8 mL, 85 mmol) was added dropwise to an ice-cooled solution of 2,4-dinitrophenylpyridinium chloride[284] (20 g, 71 mmol). The reaction was allowed to proceed for 24 h at 25°C with stirring. The solid which precipitated was filtered and washed in succession with 50 mL each of methanol, water, methanol and ether. A suspension of the solid obtained above in dioxane-water (4:1 v/v) was heated at reflux for 12 h to afford a clear solution. The solvent was removed in vacuo at 30°C and the unstable ylide was extracted with ethanol (200 mL) which was immediately cooled in an ice-bath and a solution of sodium borohydride (13.4 g, 355 mmol) in 40 mL absolute ethanol pre-cooled to 0°C was added in three aliquots. The reduction was allowed to proceed at ice-bath temperature for 4 h and then water (200 mL) was added. Extraction with ether (4 x 50 mL), washing the ether extract with water (10 mL), drying the ether extract (Na_2SO_4) and removal of the solvent in vacuo at 30°C gave (221) which was immediately chromatographed on a 2.5 x 10 cm silica gel column using

ether as eluant. The product was further purified by preparative HPLC (Prep. Pak-500 silica cartridge) using petroleum ether-ether (8:2 v/v) as eluant at a flow rate of 250 mL/min. Collection of the 1500 mL - 4500 mL fraction gave (221) as an unstable red oil.

4.4.6.0.0 Preparation of N-(4-nitrophenyl)-1,2,3,6-tetrahydropyridine (223)

A mixture of 1-chloro-4-nitrobenzene (2 g, 12.7 mmol) and 1,2,3,6-tetrahydropyridine (20 mL) was heated at reflux for 5 days. Ether (100 mL) was then added to the cooled reaction mixture and the precipitate was filtered off. Removal of the solvent from the filtrate in vacuo afforded an orange solid which on elution from a silica gel column using 200 mL hexane yielded (223) as a yellow solid.

4.4.7.0.0 Preparation of N-(phenylcarbonylamino)-1,2,3,4-tetrahydroquinoline (224)

A solution of O-mesitylenesulfonylhydroxylamine[10] (1.71 g, 7.97 mmol) in 2 mL methylene chloride was added dropwise during 10 min to a solution of 1,2,3,4-tetrahydroquinoline (1 mL, 7.97 mmol) in 2 mL methylene chloride pre-cooled to 0°C with stirring. The reaction was allowed to proceed at 25°C for 1 h. Triethylamine (4.4 mL, 31.8 mmol) was added in three aliquots and then benzoyl chloride (1.39 mL, 11.95 mmol) was added dropwise. The reaction was allowed to proceed at 25°C for 24 h and the precipitate was filtered off and washed with methylene chloride (2 x 10 mL). The filtrate was then washed with water (2 x 10 mL) and brine (10 mL). The organic fraction was treated with norite,

filtered and dried (Na_2SO_4). Removal of the solvent in vacuo gave impure (224) which was purified by elution from a 2.5 x 20 cm silica gel column using 300 mL ether to yield (224). The product (224) sublimes (163°/0.04 mm Hg) to give a white crystalline solid.

4.4.8.0.0 Preparation of N-(phenylcarbonylamino)piperidine (225)

General procedure E

Hydrogenation of N-(phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125)[65] (0.5 g, 2.48 mmol) in 20 mL methanol and hydrogen gas at 40 psi in the presence of 10% palladium-on-charcoal (50 mg) for 4 h, filtration and removal of the solvent in vacuo afforded (225) as an off-white solid. Recrystallization from ethyl acetate gave (225) as a white crystalline solid.

4.4.9.0.0 Preparation of N,N-diallylbenzoylhydrazine (226)

Allyl bromide (1.33 mL, 14.7 mmol) was added to a solution of benzoylhydrazine (2 g, 14.7 mmol) in 20 mL 10% sodium hydroxide with stirring. The reaction was allowed to proceed for 24 h at 25°C and water (50 mL) was added. Extraction with chloroform (4 x 75 mL), drying (Na_2SO_4) and removal of the solvent in vacuo gave impure (226). The product was partially purified by elution from a 2.5 x 20 cm neutral alumina column. The initial 100 mL ether eluate was discarded. The subsequent 300 mL ether-methanol (9:1 v/v) eluate was collected and further purified by preparative silica gel tlc with chloroform-methanol (30:1 v/v) as development solvent. Extraction of the band having

R_f 0.5 with hot absolute ethanol afforded (226) as a white solid.

4.5.0.0.0 Preparation of N-(phenylcarbonylimino)-methylpyridinium ylides (229-232)

General procedure F

To a freshly prepared solution of hydroxylamine-O-sulfonic acid (0.2 mmol) in cold water (100 mL) was added the methylpyridine (0.4 mmol). The mixture was heated to 90°C for 20 min. It was then cooled to 25°C with stirring and potassium carbonate (0.2 mmol) was added slowly. The water and excess of methylpyridine were removed in vacuo. The residue was treated with 95% ethanol (200 mL) and the precipitate of potassium sulfate was removed by filtration. The filtrate was concentrated at 40°C followed by dissolution in 10% aqueous sodium hydroxide (20 mL). Benzoyl chloride (40.5 mmol) was then added dropwise to the reaction mixture. The reaction was allowed to proceed for 12 h at 25°C. The precipitated crystals were collected and recrystallized from methanol to yield the methylpyridinium ylides (229 - 232).

4.5.1.0.0 Preparation of N-aminopyridinium mesitylenesulfonates

General procedure G

A solution of O-mesitylenesulfonylhydroxylamine(8 mmol) in 2 mL methylene chloride was added dropwise during 10 min to a solution of the pyridine (8 mmol) in 2 mL methylene chloride pre-cooled to 0°C with stirring. The reaction was allowed to proceed at 25°C for 1 h with stirring. The precipitate was collected after addition of ether

(100 mL) and recrystallized from ethyl acetate-methanol to yield the respective N-aminopyridinium mesitylenesulfonate.

The 2-fluoro (91.4%, mp 147-148°C), 3-(3-acetoxypropyl) (37%, mp 46-48°C), 3-acetoxymethyl (73%, mp 116-117°C), 3-(2-methoxycarbonylethyl) (72%, mp 89-90°C) and 4-(2-methoxycarbonylethyl) (76%, mp 79-80°C) pyridinium mesitylenesulfonates were prepared by a similar procedure.

4.5.1.1.0 Acetylation of pyridinecarbinols

A mixture of the pyridinecarbinol (5 g, 92 mmol) in acetic anhydride (10 mL) and pyridine (10 mL) was stirred at 25°C for 12 h followed by addition of saturated sodium bicarbonate (40 mL). Extraction with chloroform (4 x 50 mL), drying (Na_2SO_4) and removal of the solvent in vacuo afforded the 4-acetoxy- (96%, oil) and the 3-acetoxymethylpyridines (99%, oil).

4.5.1.2.0. Preparation of 3-(2-methoxycarbonylethyl)pyridine

Thionyl chloride (4.8 mL, 67.1 mmol) was added dropwise to a solution of 3-pyridineacrylic acid (5 g, 33.6 mmol) in dry benzene (150 mL). The reaction was heated at reflux for 4 h and then freshly distilled methanol (10 mL) was added dropwise during 20 min to the hot solution. The reaction mixture was heated at reflux for an additional 4 h and basified to pH 8 using aqueous sodium bicarbonate (50 mL). The organic phase was separated and the aqueous phase was extracted with chloroform (4 x 50 mL). The combined organic phases were washed with brine (10 mL) and the solvent was removed to yield methyl 3-pyridine-

acrylate (10.94 g, 100% , oil). The product was hydrogenated according to general procedure E to afford pure 3-(2-methoxycarbonylethyl)pyridine (11.05 g, 100%, oil).

4.5.1.3.0 Preparation of 4-(2-methoxycarbonylethyl)pyridine

To a solution of methoxycarbonylmethylene triphenylphosphorane[280] (7 g, 21 mmol) in methylene chloride (50 mL) 4-pyridylcarboxaldehyde (2 mL, 21 mmol) in methylene chloride (10 mL) was added dropwise during a period of 10 min. The reaction was allowed to proceed at 25°C for 24 h and subsequently quenched with water (50 mL). Extraction with methylene chloride (4 x 50 mL), washing with brine (10 mL), drying (Na_2SO_4) and removal of the solvent in vacuo gave the crude methyl 4-pyridylacrylate, which was purified by neutral alumina column chromatography with 300 mL hexane-ether (1:1 v/v) (3.04 g, 89%) as eluant. Hydrogenation of methyl 4-pyridylacrylate (3 g, 18.4 mmol) for 24 h according to general procedure E afforded 4-(2-methoxycarbonylethyl)pyridine (2.982 g, 99%, oil).

4.5.2.0.0 Preparation of N-(phenylcarbonylimino)-fluoro(alkyl)-pyridinium ylides (233, 234)

Reaction of N-amino-3-fluoro(3-acetoxypropyl)pyridinium mesitylenesulfonate (10 mmol) and benzoyl chloride (15 mmol) in 10% aqueous sodium hydroxide according to general procedure A yielded the 3-fluoro (233) and 3-(3-hydroxypropyl) (234) ylides.

4.5.2.1.0 Preparation of N-(phenylcarbonylimino)-4-acetoxymethyl-pyridinium ylide (235)

To an ice-cooled solution of 4-acetoxymethylpyridine (0.7 g, 4.7 mmol) in methylene chloride (5 mL) was added dropwise a solution of MSH (1 g, 4.7 mmol) in methylene chloride (5 mL). The reaction was allowed to proceed for 1 h at 25°C to give a viscous oil which was dissolved in acetonitrile (50 mL). Benzoyl chloride (0.8 mL, 7 mmol) and triethylamine (1.6 mL, 11.6 mmol) was added dropwise in succession to the reaction mixture. The reaction was completed according to general procedure A to afford the 4-acetoxymethyl ylide (235).

4.5.2.2.0 Preparation of N-(phenylcarbonylimino)-alkylpyridinium ylides (236-238)

General procedure H

The N-amino-alkylpyridinium mesitylenesulfonate (14 mmol) was dissolved in benzoyl chloride (5 mL) and was heated at 70°C for 24 h. The precipitate was collected and washed with acetone prior to dissolution in saturated aqueous sodium bicarbonate (50 mL). Extraction with chloroform (4 x 50 mL), washing with brine (10 mL) and removal of the solvent in vacuo gave the product which was purified by neutral alumina column chromatography with ether as eluant to afford ylides (236 and 237). The ylide (238) was obtained in pure form and did not require purification.

4.5.2.3.0 Preparation of N-(phenylcarbonylimino)pyridinium ylides (239-243)

General procedure I

A mixture of the pyridine (35 mmol) and 1-chloro-2,4-dinitrobenzene (52.6 mmol) in dry acetone (100 mL) was heated at reflux for 15 h. The precipitate was collected after addition of ether (200 mL), and washed with an additional 100 mL ether to afford the N-(2,4-dinitrophenyl)pyridinium chloride. To an ice-cooled solution of the N-(2,4-dinitrophenyl)pyridinium chloride (24 mmol) in methanol (50 mL) was added benzoyl hydrazine (24 mmol) in methanol (50 mL) in five aliquots with stirring. Triethylamine (48 mmol) was then added. The reaction mixture was allowed to stand at room temperature overnight. The solid that precipitated was filtered and washed in succession with 60 mL each of methanol, water, methanol and ether. The solid obtained was suspended in dioxane-water (4:1 v/v) (200 mL) and was heated at reflux for 12 h to afford a clear solution. The solvent was removed in vacuo below 45°C. Water (200 mL) was added to the residue and the insoluble material was removed by filtration. The filtrate was concentrated in vacuo to give a residue which was purified by elution from a neutral alumina column using chloroform-methanol (9:1 v/v) as eluant to afford ylides (239-243).

The following modification for the preparation of ylides (239-243) were followed in the specific instances listed below. The 3-methoxy ylide (240) was purified by neutral alumina column chromatography using 300 mL chloroform-methanol (8:2 v/v) as eluant and the 4-(3-hydroxypropyl) ylide (243) was purified by neutral alumina

column chromatography using 300 mL ether-methanol (7:3 v/v) as eluant. The 4-acetyl(ethylene ketal) ylide (241) was purified by preparative silica gel tlc using chloroform-ether (7:3 v/v) as development solvent. Extraction of the band having R_f 0.2 with hot absolute ethanol yielded (241). The 3-acetyl(ethylene ketal) ylide (242) was purified by preparative silica gel tlc using chloroform-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.6 with hot absolute ethanol afforded (242).

4.5.2.3.1 Preparation of 3- and 4-methoxypyridine

Hydrogenation of 4-methoxypyridine-1-oxide using general procedure E yielded pure 4-methoxypyridine (89%, oil). 3-Methoxypyridine was prepared by methylation of 3-hydroxypyridine[283] Thus, a solution of 3-hydroxypyridine (4.5 g, 47.4 mmol) in 60 mL tert-butanol-tetrahydrofuran (2:1 v/v) was added dropwise during 30 min to a solution of diazomethane (2 g, 47.4 mmol) in ether (generated from 14.4 g of Diazald) at -15°C with stirring. The reaction was allowed to proceed for 4 h at 25°C. The reaction mixture was filtered. The filtrate was concentrated in vacuo at 40°C to give a viscous oil which was purified by neutral alumina column chromatography using 200 mL ether as eluant to afford 3-methoxypyridine (3.2 g, 62%).

4.5.2.3.2 Preparation of acetylpyridines(ethylene ketals)[285]

To a solution of the acetylpyridine (2 mL, 17.5 mmol) in benzene (100 mL), ethylene glycol (5 mL, 90 mmol) and pyridinium tosylate (1 g, 4 mmol) were added. The reaction mixture was brought to

reflux temperature and water was removed using a Dean-Stark trap. The mixture was heated at reflux until the volume of water in the trap remained at constant volume (48 h). Excess solvent was removed in vacuo. Ether (100 mL) was added and the mixture was washed with saturated sodium bicarbonate (30 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed in vacuo to yield pure 4- and 3-acetylpyridine(ethylene ketals) (2.467 g, 100%, oil).

4.5.3.0.0 Preparation of N-(phenylcarbonylamino)-substituted-1,2,3,6-tetrahydropyridines (252, 253, 255-262, 265-267, 274 and 275)

The sodium borohydride reduction of ylides (229-243) according to general procedure B afforded the corresponding 1,2,3,6-tetrahydropyridines (252, 253, 255-262, 265-267, 274 and 275).

Some modifications for the reduction (reaction) time and method of purification are outlined below. The 5-fluoro compound (252) was purified by decolorization using activated charcoal. The 4-methyl (255) and 5-methyl (256) derivatives were purified by neutral alumina column chromatography using 300 mL ether-methanol (4:1 v/v) as eluant. The 4,5-dimethyl compound (257) was purified by preparative silica gel tlc using ether-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.35 using hot absolute ethanol afforded (257). The 2-methyl compound (258) was purified by preparative silica gel tlc using chloroform-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.75 yielded an off-white solid which was sublimed at 125°/0.04 mm Hg to give (258). The 4-methoxy compound (259)

was subjected to reduction for 30 h and was purified by decolorization using activated charcoal. Reduction of the 5-methoxy compound (260) was allowed to proceed for 6 h and the product was purified by neutral alumina column chromatography using chloroform-methanol (9:1 v/v) as eluant followed by recrystallization (methanol-ether). The 4-hydroxymethyl compound (265) was obtained by reduction of the 4-acetoxymethyl ylide (235) for 8 h as described by procedure B and was purified by neutral alumina column chromatography using ether-methanol (9:1 v/v) as eluant. The 3-methylene (253) was obtained from reduction of the 3-acetoxymethyl ylide (236) for 12 h and was purified by preparative silica gel tlc using chloroform-methanol (19:1 v/v) as development solvent. Extraction of the band having R_f 0.5 using warm ethanol afforded (253). The 4-(3-hydroxypropyl) compound (266) was reduced for 8 h and was purified by neutral alumina column chromatography using ether-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.5 using warm ethanol afforded (266). The 5-(3-hydroxypropyl) compound (267) was reduced for 10 h and was purified by preparative silica gel tlc using acetone-ethyl acetate (3:1 v/v) as development solvent. Extraction of the band having R_f 0.5 using warm ethanol afforded (267). The 4-(2-methoxycarbonylethyl) compound (274) was reduced for 10 h and was purified by neutral alumina column chromatography using chloroform as eluant. The 5-(2-methoxycarbonylethyl) compound (275) was reduced for 7 h and was purified by neutral alumina column chromatography using chloroform as eluant. The 4-acetyl compound (261) was obtained from reduction of 4-acetyl(ethylene ketal) ylide (241) for 8 h and was purified by decolorization using activated

charcoal followed by deprotection (see 4.5.3.1.0) of the keto group. The 5-acetyl compound (262) was obtained by reduction of the 3-acetyl-(ethylene ketal) ylide (242) for 9 h and was purified by silica gel column chromatography using ether-methanol (9:1 v/v) as eluant followed by preparative silica gel tlc using ethyl acetate as development solvent. Extraction of the band having R_f 0.5 using warm ethanol followed by deprotection (see section 4.5.3.1.0) of the keto group afforded (262).

4.5.3.1.0 The conversion of N-(phenylcarbonylamino)-4- and 5-acetyl-(ethylene ketal)-1,2,3,6-tetrahydropyridine to N-(phenyl-carbonylamino)-4- and 5-acetyl-1,2,3,6-tetrahydropyridine (261, 262)

The 4- and 5-acetyl(ethylene ketals) (0.84 mmol) were deprotected[285] by dissolution in moist acetone (1 mL water in 15 mL acetone) containing pyridinium tosylate (0.25 mmol) and heating at reflux for 3 h. Excess solvent was removed and chloroform (50 mL) was added. The mixture was washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic phase was separated and dried (Na_2SO_4) and the solvent removed in vacuo to give a solid which was further washed with cold ether (10 mL) to yield the corresponding 4- and 5-acetyl compounds (261, 262).

4.5.4.0.0 Preparation of N-(phenylcarbonylamino)-6-oxo-1,2,3,6-tetra-hydropyridine (254)[275]

N-(Phenylcarbonylamino)-1,2,3,6-tetrahydropyridine (125) (0.5 g, 2.48 mmol) was added to a mixture of sodium dihydrogen

phosphate monohydrate (0.41 g) and disodium hydrogen phosphate heptahydrate (0.8 g) in 15 mL water and meta-chloroperbenzoic acid (m-CPBA) (0.47 g, 2.72 mmol) in methylene chloride (15 mL). The reaction mixture was stirred at 25°C for 3 h prior to the addition of additional m-CPBA (0.47 g, 2.72 mmol). The reaction was allowed to proceed for a further 48 h. The organic phase was separated and the aqueous phase was extracted with methylene chloride (3 x 40 mL). The combined organic extracts were washed successively with 15% aqueous sodium thiosulfate (2 x 30 mL), 10% aqueous sodium carbonate (2 x 30 mL) and then with brine (2 x 30 mL). The methylene chloride extract was dried (Na_2SO_4). Removal of the solvent in vacuo gave the crude product which was initially purified by elution from a 2.5 x 20 cm neutral alumina column using 200 mL ether-methanol (9:1 v/v) as eluant. The eluate was concentrated and further purified by preparative silica gel tlc using ether-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.4 with hot absolute ethanol afforded (254) as a white crystalline solid.

4.5.5.0.0 Preparation of N-(phenylcarbonylamino)-4- and 5-(1-hydroxyethyl)-1,2,3,6-tetrahydropyridines (263, 264)

Reduction of N-(phenylcarbonylamino)-4- and 5-acetyl-1,2,3,6-tetrahydropyridines (261, 262) with sodium borohydride as outlined by general procedure B afforded the corresponding 4- and 5-(1-hydroxyethyl) compounds (263, 264).

4.5.6.0.0 Preparation of N-(phenylcarbonylamino)-4- and 5-(3-methoxypropyl)-1,2,3,6-tetrahydropyridines (268, 269)

To a pre-cooled solution of the N-(phenylcarbonylamino)-hydroxypropyl-1,2,3,6-tetrahydropyridine (266, 267) (0.5 g, 1.9 mmol) and triethylamine (0.8 mL, 5.8 mmol) in methylene chloride (10 mL) methanesulfonyl chloride (0.3 mL, 3.8 mmol) was added dropwise with stirring. After stirring at 0°C for 30 min, excess sodium methoxide (0.54 g, 10 mmol) in methanol (20 mL) was added to the reaction mixture in three aliquots. The reaction was allowed to proceed for 24 h at reflux temperature. Extraction with methylene chloride (4 x 50 mL), washing with brine (20 mL), drying (Na_2SO_4) and removal of the solvent in vacuo afforded N-(phenylcarbonylamino)-4-(3-methoxypropyl)-1,2,3,6-tetrahydropyridine (268).

The 5-(3-methoxypropyl) compound (269) was purified by preparative silica gel tlc using chloroform-methanol (9:1 v/v) as development solvent. Extraction of the band having R_f 0.4 with hot absolute ethanol afforded (269).

4.5.7.0.0 Preparation of N-(phenylcarbonylamino)-4- and 5-(3-acetoxypropyl)-1,2,3,6-tetrahydropyridines (270, 271)

To a solution of the N-(phenylcarbonylamino)-hydroxypropyl-1,2,3,6-tetrahydropyridine (266, 267) (0.5 g, 1.9 mmol) in ethyl acetate (20 mL) was added acetic anhydride (0.9 mL, 9.6 mmol). The reaction was allowed to proceed at 50°C for 4 h. The solvent was removed in vacuo and the solid obtained was purified by neutral alumina column chromatography by elution with ether-methanol (9:1 v/v) which afforded compounds (270 and 271).

4.5.8.0.0 Preparation of N-(phenylcarbonylamino)-4- and 5-(2-carboxyethyl)-1,2,3,6-tetrahydropyridines (272, 273)

To a solution of sodium hydroxide (0.023 g, 5.7 mmol) in methanol (30 mL) was added a solution of N-(phenylcarbonylamino)-4- or 5-(2-methoxycarbonylethyl)-1,2,3,6-tetrahydropyridine (274, 275) in methanol (5 mL). The reaction mixture was allowed to reflux for 3 h after which the pH was adjusted to 4 using 0.1N hydrochloric acid. Removal of the solvent gave a solid which was washed with water (20 mL) and cold ether (10 mL) to afford compounds (272, 273).

4.5.9.0.0 Preparation of N-(phenylcarbonylamino)-3-methylpiperidine (276)

Hydrogenation of N-(phenylcarbonylamino)-3-methylene-1,2,3,6-tetrahydropyridine (253) or N-(phenylcarbonylamino)-5-methyl-1,2,3,6-tetrahydropyridine (256) according to the general procedure E afforded N-(phenylcarbonylamino)-3-methylpiperidine (276) (95%, mp 163-164°C). Anal. calc'd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83; found: C, 71.33; H, 8.31; N, 12.66.

4.6.0.0.0 Analgesic testing

A. Phenylquinone writhing test[212]

Five male ICR mice (20 - 25 g) were confined to their own glass jars and were denied food and water for the duration of the experiment. The test compound, suspended using ultrasonic mixing in a solution of physiological saline and Tween 80 surfactant, was

administered subcutaneously to each mouse at a volume of 0.1 mL/10 g body weight. Thirty min later each mouse received a 0.1 mL/10 g body weight intraperitoneal injection of 0.03% phenyl-p-benzoquinone in 5% ethanol. Ten min later, each mouse was observed to determine the number of writhing abdominal constriction responses over a ten min period. The average number of writhes for the five mice were compared to the vehicle and phenyl-p-benzoquinone treated control group. The percent change is calculated according to the following equation:

% change = 100 - (no. of writhes in treated group/no. of writhes in control group) x 100

No. of writhes in control group = 24.9

B. Hot plate test[213,214]

Five male ICR mice (20 - 25 g) were individually placed on a copper hot plate maintained at a temperature of 54.5 ± 0.5°C (boiling acetone). Each mouse was timed from the moment it was put on the hot plate until the time it showed discomfort (thumping of the rear leg or jumping off the hot plate surface). The mice were then administered a subcutaneous dose of the test compound in a volume of 0.1 mL/10 g body weight and 30 min later, the hot plate assay was repeated. The average time of contact with the hot plate was compared before and after the dosing of the test compound. No mouse was allowed to stay on the hot plate for more than 30 sec. The percent of analgesia was calculated using the following equation:

$$\% \text{ analgesia} = \frac{T_t - T_o}{T_{max} - T_o} \times 100$$

T_o = control time; T_t = latency time at 30 min;

T_{max} = 30 sec.

4.7.0.0.0 Hyperglycemic test[215]

Four male Wistar rats weighing 230 - 260 g were used in each group. The test compound, suspended in 1% tragacanth in distilled water, was administered orally in a volume of 1 mL/100 g body weight to overnight fasted rats. Blood samples were obtained from the tail at 0, 2 and 4 h post-treatment. The sera derived from the blood samples were analyzed for glucose by spectrophotometric determination of enzymatically produced NADPH, using an Abott ABA-100 Analyzer.

4.8.0.0.0 Partition coefficient[225]

An accurately weighed sample (3-4 mg range) was allowed to equilibrate between 3 mL each of 1-octanol and water for 5 min on a rocking mixer. The equilibrium concentration of the test compound was determined by quantitative uv analysis of the water phase using a Pye Unicam SP 1800 uv spectrophotometer. The concentration of the test compound in the 1-octanol phase was determined by difference. A standard concentration-absorbance plot prepared for each compound having a known amount (1-2 mg) of sample in 100 mL water. The partition coefficient P was calculated from the equation shown below.

P = conc. octanol/conc. water.

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