Recent Advances in the Chemistry of Dihydropyridines

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Contents

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Albert I. Meyers was born in New York City where he received his bachelor's (1954) and doctorate (1957), training at New York University. After a year (1958) at Citgo Oil Co., he joined the faculty at Louisiana State University and rose to Boyd Professor of Chemistry in 1968. He joined the faculty at Wayne State University in 1970 and then moved in 1972 to his current position at Colorado State University. In 1965–1966 he was an NIH Special Fellow at Harvard. He is currently Associate Editor for the *Journal of the Americal Chemical Society* and Chairman of the Organic Division of the ACS. His research interests have been heterocyclic chemistry, new synthetic methods, total synthesis of natural products, and asymmetric syntheses.

I. Introduction

The chemistry of dihydropyridines was last reviewed in 1972 by Eisner and Kuthan.[1] In the intervening 9 years, nearly 200 research papers and 2 esoteric reviews,[2,3] not to mention several patents, have appeared on the subject. The recent interest in dihydropyridines can be traced to the coenzyme reduced nicotinamide adenine dinucleotide (NADH, 1) and the unique ability of this compound in biological systems to reduce unsaturated functionalities (carbonyls, conjugated olefins, etc.). Thus, a considerable portion of today's efforts in

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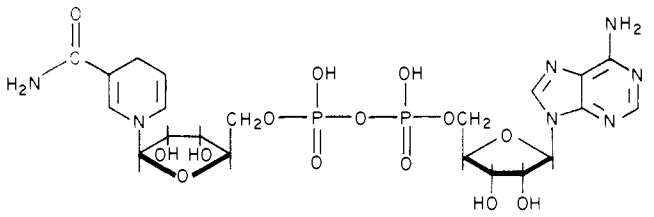

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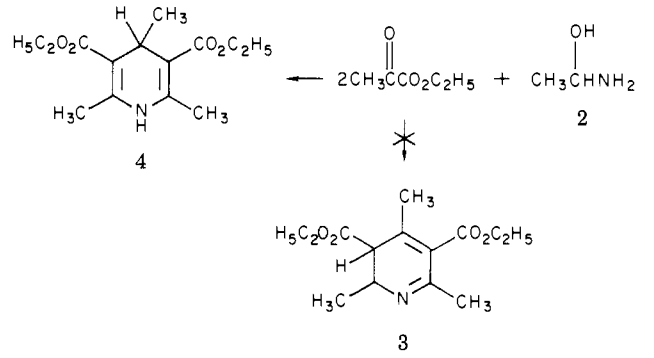
dihydropyridine chemistry is expended in synthesizing NADH mimics, exploring the reactions and mechanisms of these compounds, and utilizing these compounds in a variety of synthetic reactions. This review, then, is an attempt to cover the literature in these areas from 1972 to mid-1980. Our concern is almost exclusively with 1,2- and 1,4-dihydropyridines. For historical and background information the reader is encouraged to see Eisner and Kuthan's review.[1]

II. Synthesis of Dihydropyridines

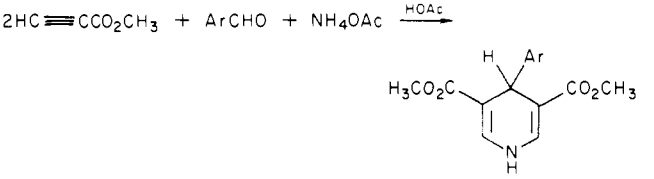
A. Hantzsch Ester Syntheses

The first synthesis of a dihydropyridine is attributed to Arthur Hantzsch for work done a century ago.[4] Interestingly, the product from the condensation of 2 mol of ethyl acetoacetate and 1 mol of "aldehydammoniak" (2) was assigned the 2,3-dihydropyridine structure 3 by Hantzsch. We now know that the product has the



1,4-dihydropyridine structure 4. In deference to Hantzsch these types of compounds have been known as Hantzsch esters, and because of the versatility and the general stability of the products, the Hantzsch ester synthesis has remained the most common method for the preparation of 1,4-dihydropyridines. Additionally, these dihydropyridines have found the widest usage over all other types of dihydropyridines.

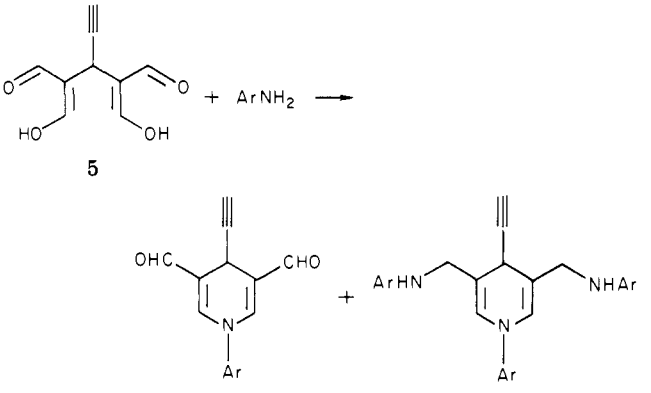
Recent interest in the Hantzsch esters has focused on substituents in the 2-, 4-, and 6-positions of the ring and on condensations involving compounds other than β-keto esters. The first report of a Hantzsch ester unsubstituted at the 1-, 2-, and 6-positions involved the reaction of methyl propiolate with an aromatic aldehyde and ammonium acetate in acetic acid.[5] The method



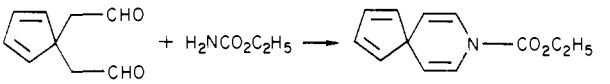
gave low or no yields when other substituted acetylenes were used and no dihydropyridines were obtained with alkyl or nitroaromatic aldehydes.

A mixture of 1,5,6- and 1,4,6-unsubstituted 1,4-dihydropyridines was obtained when (dialkylamino)alkadienes were condensed with β-amino-α,β-unsaturated ketones and esters.[6] The authors proposed two possible mechanisms for the 1,5,6-unsubstituted products. The first involves displacement of the dialkylamino functionality by the amine of the amino ketone (route A) and attack by the enamine results in the dihydropyridine (see Scheme I). Alternatively, attack by the α-carbon of the amino ketone on the 3-position of the aminoalkadiene (route B) (presumably via the enamine to imine which equilibrates to an enamine) followed by displacement of the dialkylamino group would also afford the dihydropyridine. The 1,4,6-unsubstituted product arises by the reverse of route B, namely, enamine attack at C-1 of the aminoalkadiene (route C) and amine condensation with the resulting olefin followed by loss of dialkylamine.

The condensation of 3-ethynyl-2,4-diformylpentanedial (5) with anilines gives rise to Hantzsch-type compounds unsubstituted in the 2- and 6-positions. Generally, the reaction produces a mixture of the dihydropyridinedicarboxaldehde (6) and the diamine (7).[7]



(Ar = phenyl substituted at various positions with NO_2, OCH_3, $N(CH_3)_2$ CO_2CH_3)



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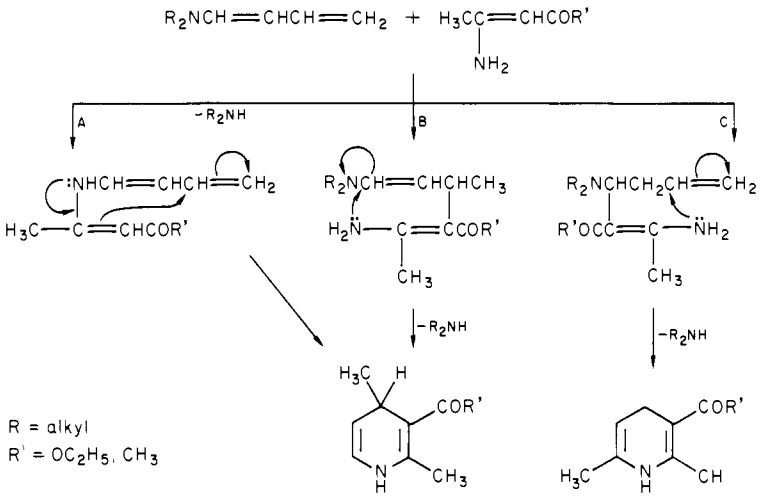
The use of spirodialdehydes also gives rise to spirodihydropyridines (8).[8]

Elaboration by the Bayer group of their work that gave the important new drug nifedipine (9) led to novel bicyclic dihydropyridines (10) and 2-aminodihydropyridines (11) by Michael addition of enaminocarbonyl compounds (12) or amidinoacetic esters (13), respectively, to alkylideneacetoacetic esters (14),[9] (see Scheme II). Substitution of aromatic aldehydes and 1,3-cyclohexanedione for esters 14 resulted in the bridged 5-ketodihydropyridines 15 and16 (see Scheme III). However, the authors found that when 3-alkoxy-3-aminoacrylic esters 17 were condensed with aldehydes in the normal Hantzsch manner, the products were not the expected and more stable 2-amino-1,4-dihydropyridines 18 but, rather, 2-amino-4,5-dihydropyridines 19. The product is especially intriguing in light of the fact that the reaction of an aldehyde with 3-aminocrotonic ester 20 results in the expected Hantzsch es-

SCHEME I



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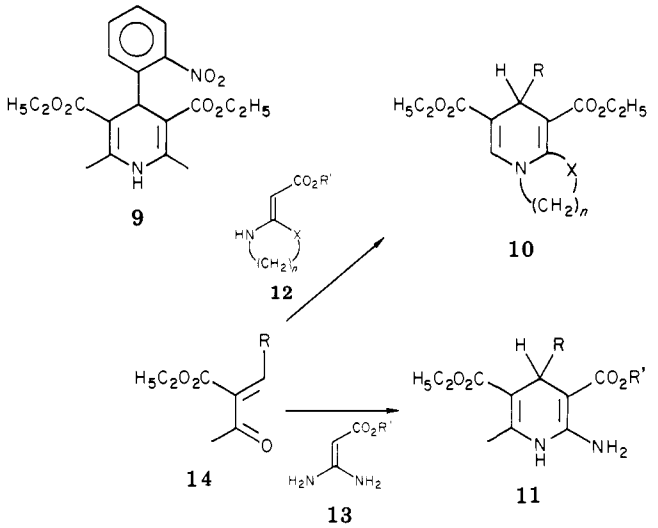
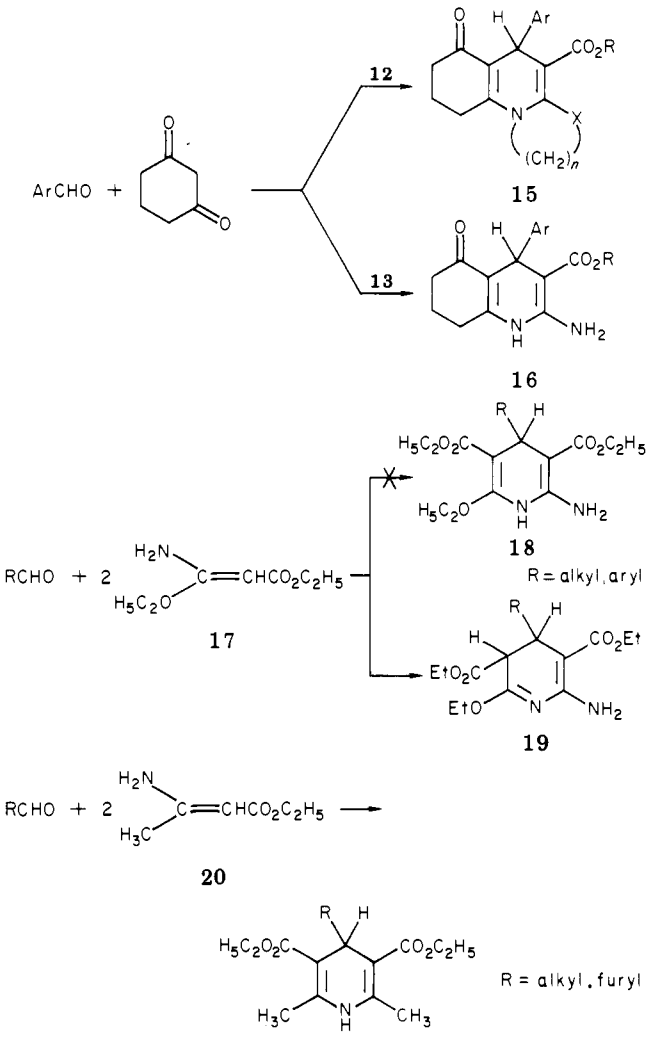


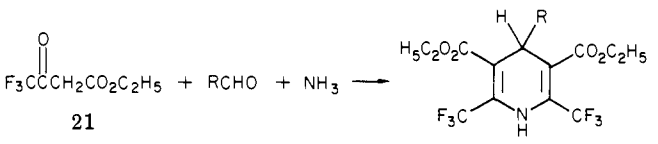
R = aryl; R' = alkyl; X = CH_2, n = 2–4; X = O, S, NH, n = 2

SCHEME III



ter.[10a,b] The authors speculate that relief of the steric interaction between the 6-alkoxy group and the 5-carboxylate function in **19** compensates for the lower stability of the product relative to **18**.[10a]

Another example of Hantzsch esters modified in the 2-, 4- and 6-positions is the introduction of trifluoromethyl groups in the 2- and 6-positions using ethyl 4,4,4-trifluoroacetoacetate (**21**), ammonia, and aldehyde.[11] Again, the goal was nifedipine-type products

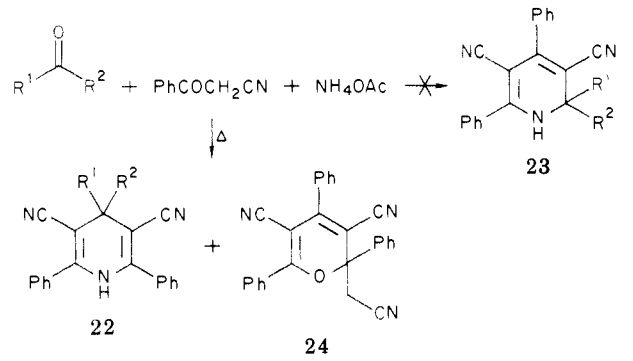


with R being 2- and 4-nitrophenyl, 2-, 3-, and 4-pyridyl, and 2-furanyl. The pyridyl compounds exhibited significant cytotoxic activity.

A reexamination of the condensation of acetone, cyclopentanone, or cyclohexanone with ammonium acetate and benzoylacetonitrile led to the conclusion that the products were 1,4-dihydropyridines **22**[12] and not 1,2-dihydropyridines **23**, as previously reported,[13] accompanied by a small amount of pyran **24** from the self-condensation of benzoylacetonitrile.

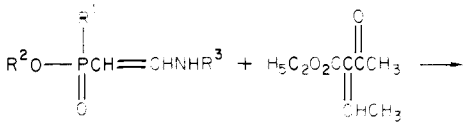
A phosphorylated Hantzsch ester (**27**) was prepared by the condensation of the enaminophosphate **25** with keto ester **26**.[14]

Finally, the first synthesis of a crown ether with a dihydropyridine integrated within the macrocycle (**28**) was reported by Kellogg's group[15] for the purpose of mimicking the reduction of carbonyls by the natural coenzyme, NADH (**1**).[16] This was followed by the

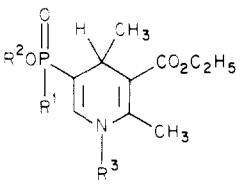


22 24

$R^1 = R^2 = CH_3$; $R^1R^2 = (CH_2)_4$, $(CH_2)_5$



25 26



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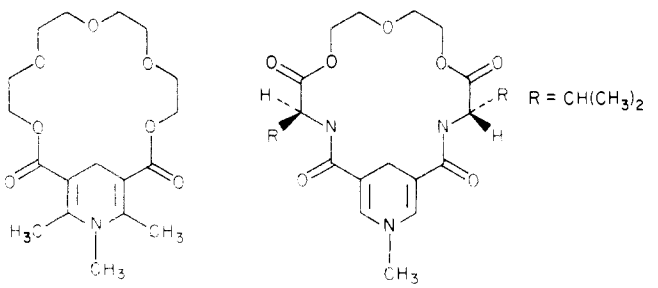
preparation of a chiral 1,4-dihydropyridine crown ether (**29**) that was used for asymmetric reductions of carbonyls.[17]

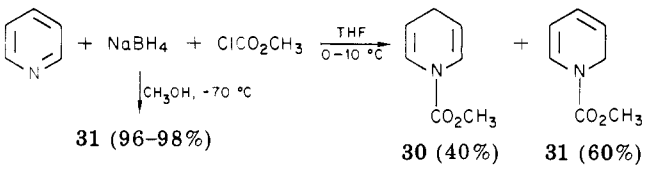


28 29

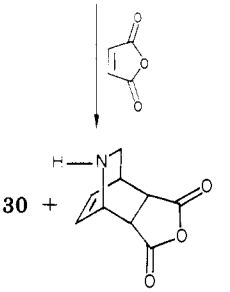
B. Syntheses by Hydride Reduction of Pyridines and Pyridinium Salts

The formation of dihydropyridines by the reduction of pyridines and pyridinium salts is complicated by the fact that mixtures of 1,2- and 1,4-dihydropyridines result. For example, when pyridine is treated with sodium borohydride in the presence of methyl chloroformate in tetrahydrofuran below 10 °C, a mixture containing ca. 40% of the 1,4-isomer **30** results.[18] The 1,2-isomer **31** can be removed by treating the mixture with maleic anhydride and washing with 15% sodium hydroxide, which removes the Diels–Alder adduct **32**. The 1,4 isomer can be virtually eliminated by performing the reaction in methanol at −70 °C.

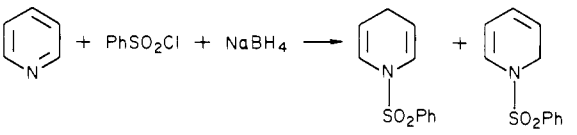
The temperature dependence of the ratio of products appears to be general. Knaus[19] found that the reaction of benzenesulfonyl chloride with pyridine (as both solvent and reactant) in the presence of sodium borohydride at 25 °C afforded a 5:4 ratio of 1,4 (**33**) to 1,2 isomer (**34**), respectively.



31 (96–98%) 30 (40%) 31 (60%)



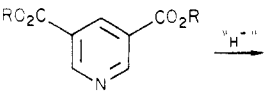
30 + 32



33 34

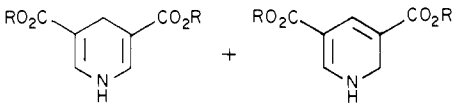
at 25 °C	5	:	4
at −65 °C	1	:	8

The product ratio can also be altered by changing the borohydride reducing agent. Pyridine-3,5-dicarboxylates (**35**), when reduced with sodium cyanoborohydride, resulted in high yields of 1,4-dihydropyridines **36** with only a trace of the 1,2-isomer **37**.[20] The use of diborane as the reducing agent afforded a greater amount of the 1,2-isomer **37**.



35

$R = C_2H_5$, CH_3

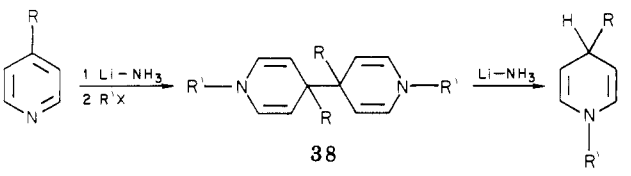


36 37

"H⁻" = $NaCNBH_3$	77%	23%
"H⁻" = B_2H_6	21%	79%

C. Other Reductions

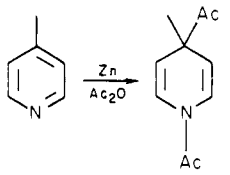
Reagents other than diborane also reduce pyridines to dihydropyridines. Lithium in liquid ammonia followed by an electrophile reduces alkylpyridines **38** to dimers, which can further react to afford monomers **39**.[21] Similarly, zinc in acetic anhydride reduces 4-



38 39

R = H, CH_3; R′ = H, CH_3, $CH_2CH_2CH_3$, CO_2CH_3

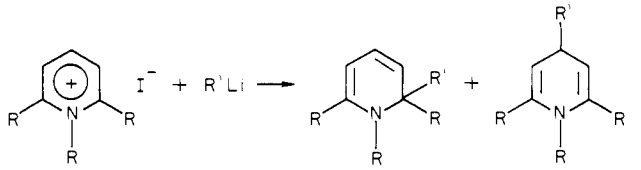
substituted pyridines to the corresponding 1,4-diacyl-4-alkyldihydropyridines **40**.[22]



40

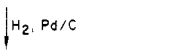
D. Nucleophilic Additions to Pyridines and Pyridinium Salts

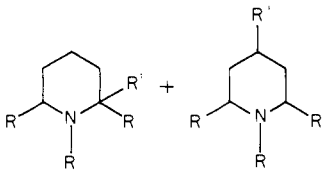
As with the borohydride reduction of pyridines and pyridinium salts, nucleophilic additions to these heterocycles frequently afford mixtures of 1,2- and 1,4-dihydropyridines. Alkyllithium reagents react with pyridinium salts to give low yields of the highly reactive alkyldihydropyridines **41**, which are characterized as the piperidines **42**. Phenyllithium and *tert*-butyllithium,



R = CH_3, H

41a 41b





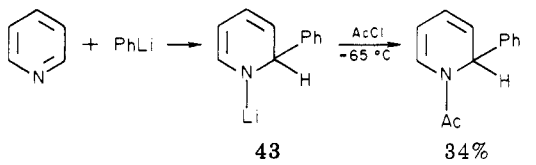
42a 42b

	41a	41b
for R' = Ph, $C(CH_3)_3$	41–80%	0%
	42a	**42b**
for R' = C_3H_7, C_4H_9	23–32%	7–8%

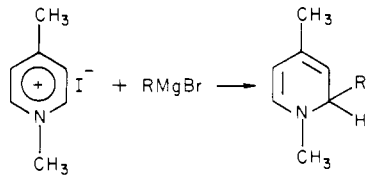
however, gave exclusively the 1,2-isomer (**41a**) in fair to good yields, (isolated as the dihydropyridines).[23,24]

In like manner, phenyllithium adds to pyridine exclusively in the 2-position, forming the reactive lithiopyridine **43** that can be readily acylated with acetyl chloride, providing a convenient route to N-substituted 2-phenyl-1,2-dihydropyridines.[25]

As with phenyllithium, the phenyl-Grignard also affords the 1,2 isomer exclusively. Unlike the alkyllithiums, however, ethylmagnesium bromide reacts with pyridinium salt **44** only at the 2-position to give the air-sensitive 1,2-dihydropyridine **45**, isolated in ca. 70% yield under rigorously oxygen-free conditions.[26]

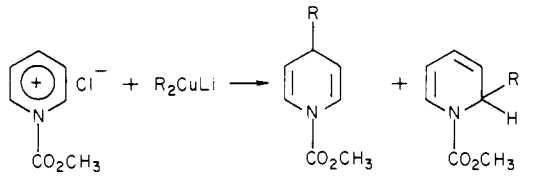


43 34%



R = Ph, C_2H_5

Lithium organocuprates, which have proven to be effective in 1,4 additions to α,β-unsaturated carbonyls, have also been shown to add predominately in the 4-position of pyridinium salts; this results in high yields of 1,4-dihydropyridines accompanied by small amounts of the 1,2 isomers.[27]

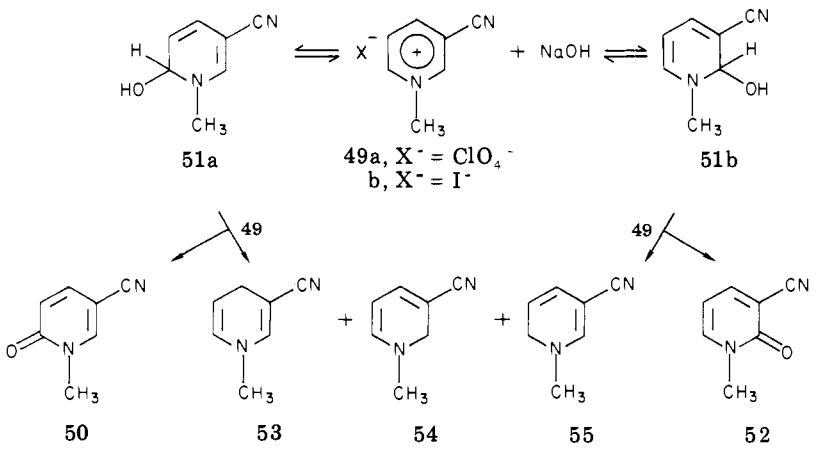


56–86% 2–8%

R = alkyl, aryl

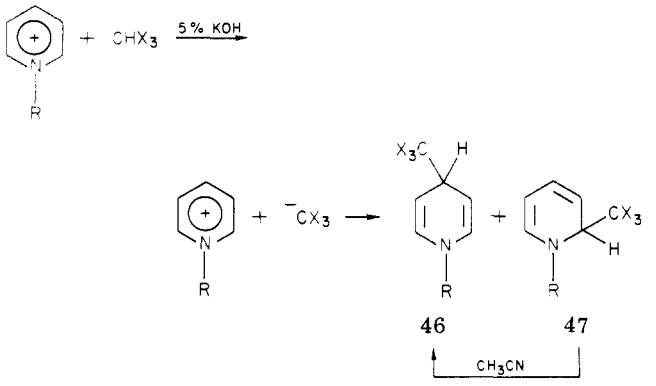
Haloformate anions can add to pyridinium salts to yield (trihalomethyl)dihydropyridines. The bulky tribromomethyl and triiodomethyl anions afford exclusively the 1,4-dihydropyridines **46** while the trichloromethylide gives only the 1,2-isomers **47**.[28] Interestingly, stirring the 1,2-dihydropyridine **47** in a polar aprotic solvent such as acetonitrile rearranged the compound to the more stable 1,4 isomer.

SCHEME IV



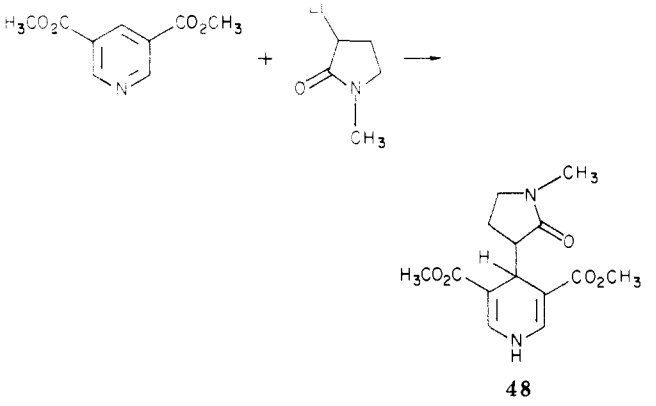
51a 49a, $X^- = ClO_4^-$ b, $X^- = I^-$ 51b

50 53 54 55 52



R = Et; 2,6-dichlorobenzyl; X = Cl, Br, I

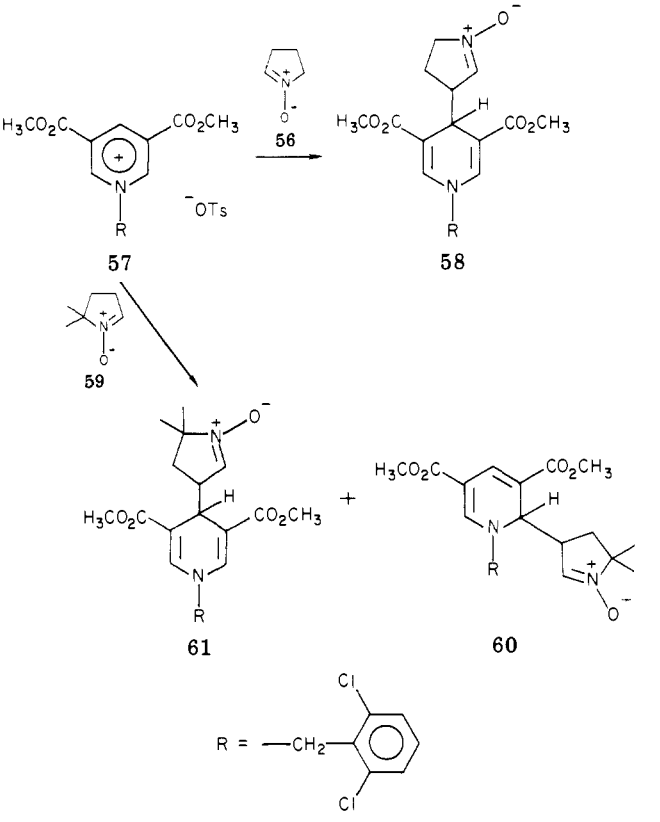
The carbanion of 1-methyl-2-pyrrolidinone has been shown to add to the 4-position of 3,5-bis(carbomethoxy)pyridine, affording the dihydropyridine 48.[29]



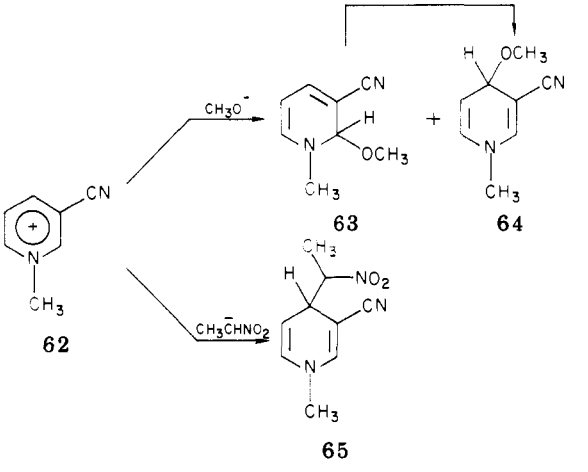
Pyridinium salts are sufficiently electrophilic to react with hydroxide ions.[30] An initial report on the reaction of 3-cyano-1-methylpyridinium perchlorate (**49a**) in aqueous potassium hydroxide concluded that 5-cyano-1-methyl-2-pyridone (**50**) was the primary product.[31] A subsequent investigation with iodide **49b** and sodium hydroxide resulted in the identification of a more complex mixture of products.[32] It was postulated that the 2-hydroxydihydropyridines **51** were intermediates that undergo a redox reaction with the pyridinium cation, resulting in the formation and isolation of pyridones **50** and **52** and dihydropyridines **53**, **54**, and **55** (Scheme IV).

The addition of cyclic nitrones to pyridinium salts affords stable dihydropyridines and represents a novel route to carbon–carbon bond formation.[33] The dihydropyridines formed depended upon the nitrone used in the reaction. Thus, 1-pyrroline 1-oxide (**56**) reacted with pyridinium salt **57** to give only the 1,4-dihydropyridine **58**, whereas 5,5-dimethyl-1-pyrroline 1-oxide (**59**) yielded a mixture of 1,2-dihydropyridine **60** (minor) and 1,4-isomer **61** (major).

The position of attack by nucleophiles on pyridinium salts to yield either 1,2- or 1,4-dihydropyridines has been explained by the possible intermediacy of a "charge transfer" complex prior to attack[34] or by the "hardness" or "softness" of the nucleophile.[35] An NMR investigation of the attack of methoxide ion on pyridinium salts **62** concluded that stable σ complexes were formed, leading to the formation of a mixture of 1,2 (**63**) and 1,4 isomers (**64**) under kinetic control followed by equilibration to the thermodynamically more stable 1,4

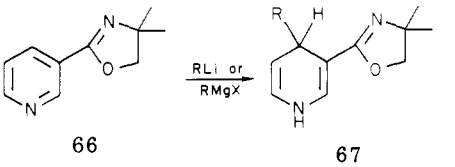


isomer.[36] When a carbanion, nitroethane anion, was



used the reaction produced only the 1,4-adduct **65**.[37] The authors concluded that either the reaction underwent a rapid isomerization to a highly stable 1,4-dihydropyridine or the 1,4 isomer was the only kinetic product.

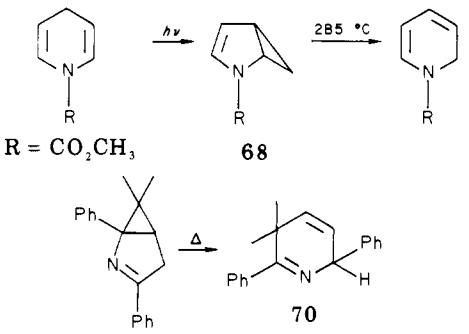
The activating ability of the oxazoline group is demonstrated by the ability of the heterocycle in the 3-position (**66**) of pyridine to direct organolithiums or Grignard reagents to the 4-position, affording exclusively 1,4-dihydropyridines **67**.[38,39] This contrasts with



the reaction of phenyllithium with pyridine that yields only the 1,2 isomer.[25]

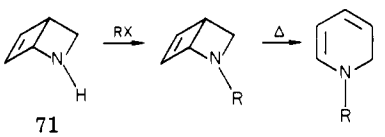
E. Syntheses via Rearrangements, Fragmentations, and Cycloadditions

Perhaps some of the most intriguing syntheses of dihydropyridines have come by intramolecular rearrangements and fragmentations and by intermolecular cyclizations. 2-Azabicyclo[3.1.0]hex-2-ene systems (**68**) rearrange when heated in the gas phase to 1,2-dihydropyridines.[40] Theoretically, this constitutes a

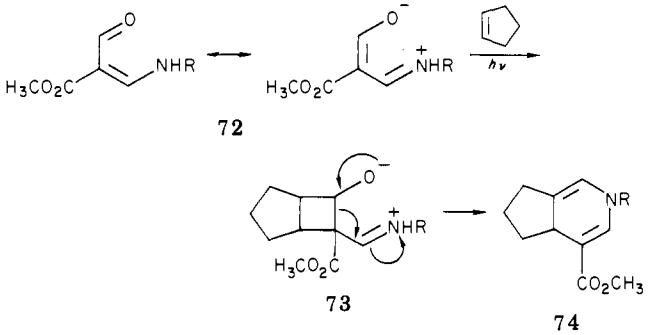


possible conversion of 1,4-dihydropyridines to 1,2-dihydropyridines since an azabicyclo[3.1.0]hexene would be the di-π-methane product from the photolysis of 1,4-dihydropyridines. Initial experiments, however, failed to afford such products.[41] Similarly, 2-azabicyclo[3.1.0]hex-3-ene **69** thermally rearranges to 2,3-dihydropyridine **70**.[42]

Though 1,2-dihydropyridine is unstable, the rearrangement of azabicyclo[2.2.0]hexenes to 1,2-dihydropyridines has allowed the use of 2-azabicyclo[2.2.0]-hex-5-ene (**71**) as a masked 1,2-dihydropyridine for the synthesis of N-substituted 1,2-dihydropyridines.[43]

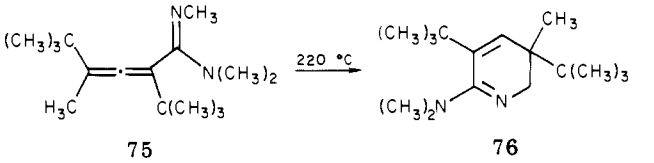


Photolysis has been used in the preparation of 1,4-dihydropyridines. Irradiation of the vinylogous formamide **72** with cyclopentene afforded the bicyclic 1,4-dihydropyridine **74**, presumably via the cyclobutane

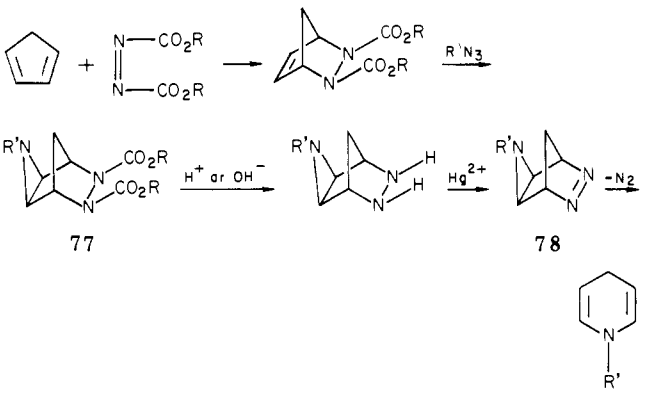


derivative **73**, which cleaves by a hetero-retroaldol reaction followed by recyclization to **74**.[44]

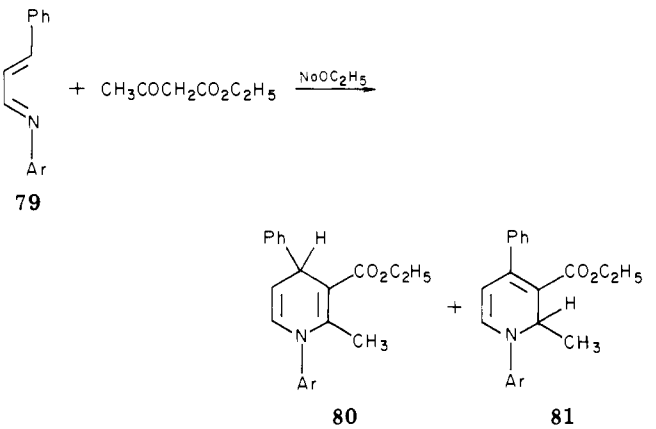
The thermal cyclization of allene amidines **75** has been shown to give 2,3-dihydropyridines **76**.[45]



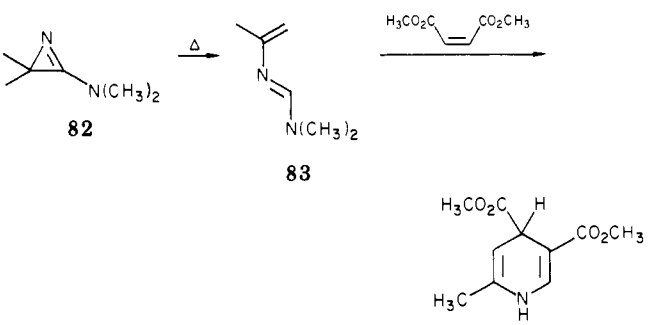
The only unequivocal synthesis of N-substituted 1,4-dihydropyridines involves a formal insertion of a substituted nitrogen into cyclopentadiene. In practice the cyclopentadiene is elaborated to an aziridino-2,3-diazabicyclo[2.2.1]heptane (**77**) followed by hydrolysis and oxidation to the azo compound **78** and then fragmentation to the dihydropyridines.[46,47]



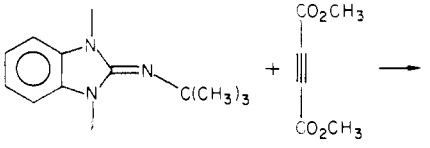
The Michael condensation of ethyl acetoacetate with cinnamylideneanilines **79** affords 1,4-dihydropyridines **80** and the 1,2-isomers **81**.[48] 1-Amino-2-azadienes (**83**),



products from the thermolysis of 2-amino-1-azirines (**82**), readily undergo cycloadditions with electrophilic olefins to yield 1,4-dihydropyridines.[49]



A related system involving heterocyclic imines **84** and acetylenedicarboxylate results in the insertion of the carbon system, presumably by way of an azadiene **85**, affording spirodihydropyridines **86**.[50]



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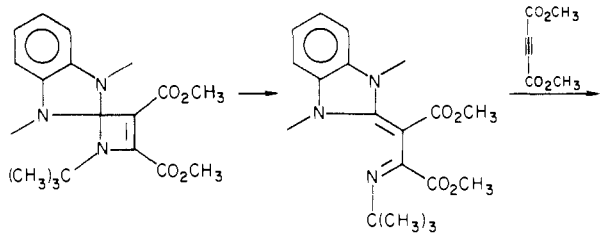

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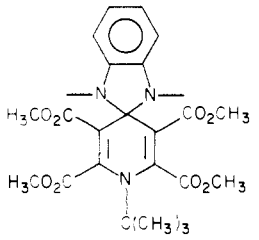
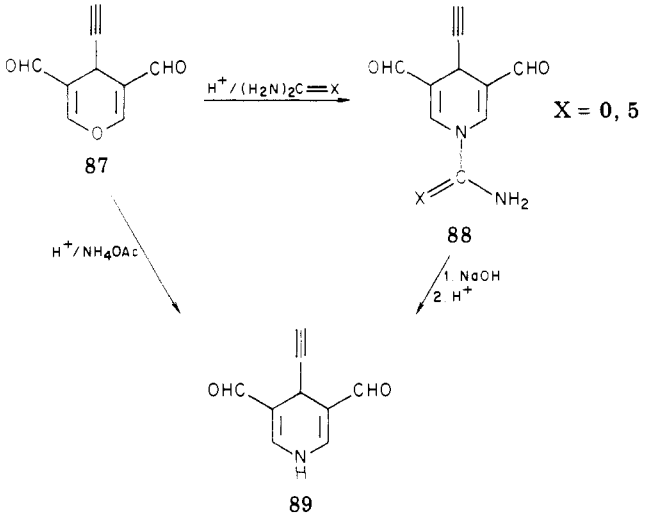


86

F. Insertion Reactions

4*H*-Pyrans **87** react with ammonium acetate, urea, thiourea, or cyanamide, yielding 1,4-dihydropyridines **88** and **89**, thus obviating the problem of amine condensation products (**7**) encountered with the 2,4-diformylpentanedial **5**.[7] The urea or thiourea in **88** is readily converted to the N–H product **89** by treatment with sodium hydroxide and then acid.[51]



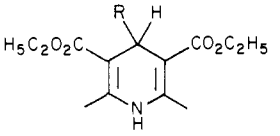
87 88 89

X = O, S

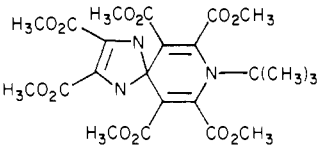
III. Physical and Chemical Properties

A. X-ray Structural Studies

The ability of the ring in 1,4-dihydropyridines to adopt a planar conformation depends upon whether there is substitution in the 4-position. The unsubstituted Hantzsch ester **90a** is planar[52] while the corresponding compound with a 4-phenyl[53] (**90b**) or a 4-(β-pyridyl)[54] (**90c**) group has a dihydropyridine ring that adopts what the authors term a flat boat conformation. The spirodihydropyridine **91** was also found to have a nonplanar conformation.[55] The only reported case of



90a, R = H
b, R = Ph
c, R = 2-pyridyl



91

a 4-unsubstituted 1,4-dihydropyridine ring being nonplanar was for the crown ether **28** when complexed with Na^+, in which the dihydropyridine ring assumed a pronounced boat conformation.[56]

The structures of 1,2-dihydropyridines have been examined by using X-ray crystallography as the chromium(0) tricarbonyl complexes. In these complexes the nitrogen-dienamine system is planar and bonded to the metal atom while the methylene group in the dihydropyridine ring is bent out of the plane.[57,58]

B. Mass Spectral Fragmentation

The mass spectral fragmentation patterns of 1,4-dihydropyridines have been examined, but no literature exists on any of the other dihydropyridine isomers. The initial product of molecular fragmentation of 1,4-dihydropyridines is the loss of a substituent in the 4-position, affording a pyridinium cation, though a thermolysis prior to fragmentation has been reported for 3-substituted 4-cyano-*N*-alkyl-1,4-dihydropyridines.[59] Fragmentations subsequent to the formation of the pyridinium cation are dependent upon the structure of the dihydropyridine.[60–64]

C. NMR and UV Spectra

Though a considerable body of NMR data exists in the literature of dihydropyridine chemistry, little has been done in a systematic way to correlate substituent effects with NMR spectra. As with mass spectral studies, the NMR investigations that do exist have been limited to 1,4-dihydropyridines. The chemical shifts, both ^1H and ^{13}C, of 4-aryl Hantzsch esters have a nearly linear relationship with the Hammett σ^+ constants.[65,66] NMR and UV studies have shown that when one of the substituents in the 4-position of 1,4-dihydropyridines is hydrogen, steric interactions are absent;[67] however, they become significant when the 4-position bears a dimethyl substitution.[68] The activation enthalpies for the transition from boat to planar conformation of N-substituted Hantzsch esters were found by NMR to be between 3 and 5 kcal/mol while those for N–H Hantzsch esters were negligible.[69] Ultraviolet spectra have also been used to investigate electronic transitions in dihydropyridine rings, and these assignments have been correlated with quantum chemical calculations.[70]

D. Miscellaneous Properties

The relative stabilities of 1,2- and 1,4-dihydropyridines have been examined by Fowler.[71] Equilibration of either *N*-methyl-1,2-dihydropyridine or *N*-methyl-1,4-dihydropyridine with potassium *tert*-butoxide afforded a 92:8 mixture of 1,4- to 1,2-dihydropyridines, respectively, in both cases. The enhanced stability of the 1,4 isomer was attributed to a favorable electronic interaction via either homoaromaticity or

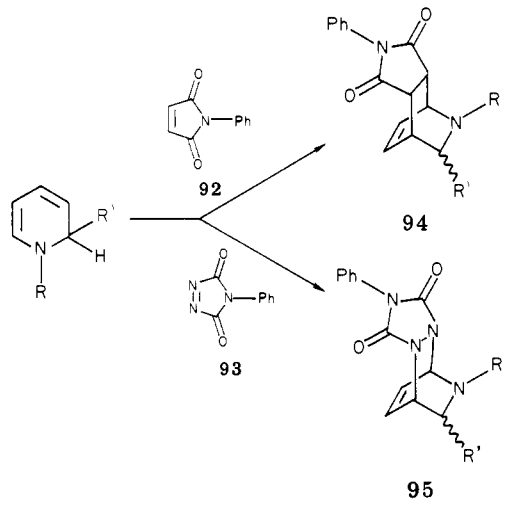
hyperconjugation. Quantum chemical calculations support these findings.[72] A photoelectron spectroscopic study of 1,4-dihydropyridines found that there is little difference electronically between these dihydropyridines and 1,4-cyclohexadiene, suggesting that the nitrogen has virtually no inductive effect or that the inductive and resonance effects cancel each other.[73]

1,4-Dihydronicotinamides bearing electron-donating groups in the 1- and 3-positions are unstable in aqueous acid, undergoing hydration of the 5,6 double bond. Interestingly, though the corresponding pyridinium salts containing electron-withdrawing groups are base labile, the coenzyme NADH (1) has substituents in the 1- and 3-positions for which the 1,4-dihydropyridine and pyridinium salt are relatively stable near neutral pH.[74]

IV. Reactions of the Dihydropyridine Ring

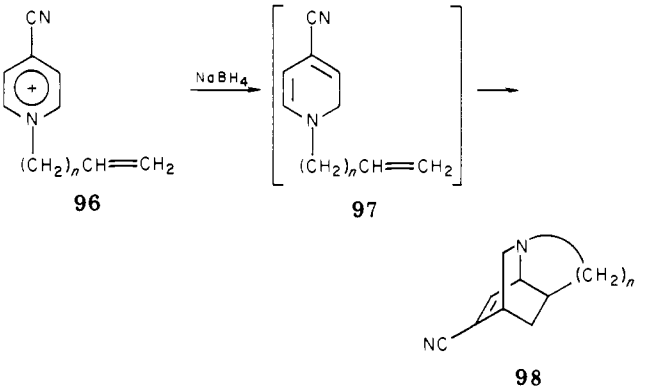
A. [2 + 2] and [4 + 2] Cycloaddition Reactions

Depending upon the acceptor molecule employed, 1,2-dihydropyridines typically undergo [4 + 2] cycloaddition reactions while 1,4-dihydropyridines act as enamines and add in a [2 + 2] fashion. Knaus has shown that N-substituted 1,2-dihydropyridines react with dienophiles such as maleimides **92** and 1,2,4-triazoline-3,4-diones **93** to afford the Diels–Alder–adducts **94** and **95**.[75,76] *N*-Alkenylpyridinium salts **96**, when

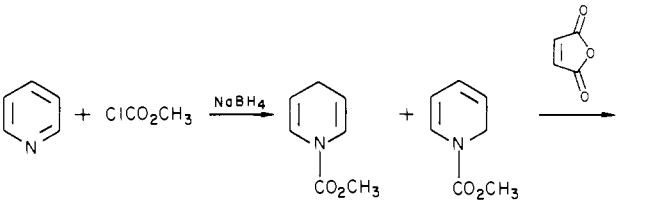


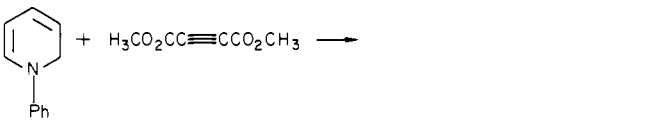
R = $CO_2C_2H_5$, SO_2Ph, etc.; R' = H, Ph

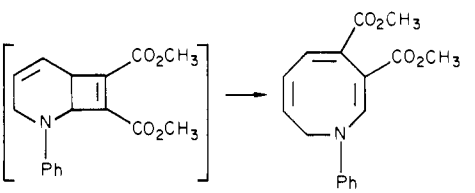
reduced with sodium borohydride, lead to the intramolecular Diels–Alder reaction of the intermediate 1,2-dihydropyridine **97**, yielding the tricyclic amine **98**.[7] The propensity for 1,2-dihydropyridines to undergo [4 + 2] additions was exploited by Fowler[18] in the separation of a mixture of 1,2- and 1,4-dihydropyridines obtained from the reduction of pyridine and methyl chloroformate. Addition of maleic anhydride yielded the adduct **99** from the 1,2-dihydropyridine while the 1,4 isomer did not react. 1,2-Dihydropyridines can react in a [2 + 2] manner. Acheson[77] has shown that dimethyl acetylenedicarboxylate will react with 1,2-dihydropyridines to afford 1,2-dihydroazocines **101**, presumably via the [2 + 2] adduct cyclobutapyridines **100**.



n = 1–3

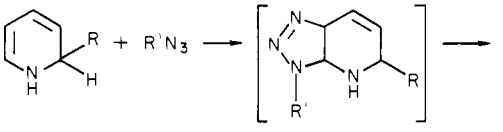


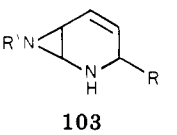




An examination of the [2 + 2] and [4 + 2] cycloreactive character, or enamine vs. diene character, of 1,2-dihydropyridines resulted in the conclusion that the two double bonds of *N*-methyl-1,2-dihydropyridine were not in the same plane.[78]

1,2-Dihydropyridines also behave as enamines toward azides, undergoing a 1,3-cycloaddition reaction to yield the bicyclic intermediates **102** that extrude nitrogen, affording the diazabicycloheptenes **103**.[79]

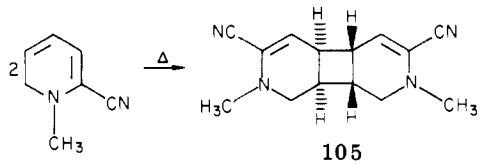




R = $(CH_2)_3CH_3$, Ph
R' = CN, $PhSO_2$, etc.

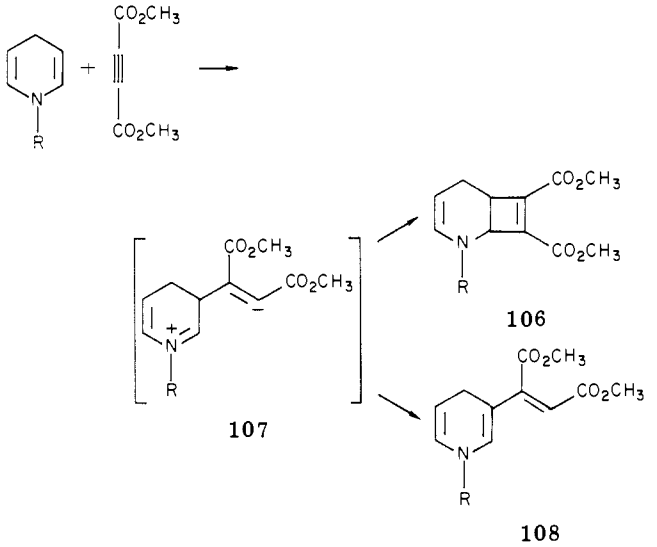
Upon heating, 1,2-dihydropyridine **104** (strictly a 1,6-dihydropyridine) dimerizes in a head-to-head [2 +

2] cycloaddition to give the adduct **105**.[80]



104 105

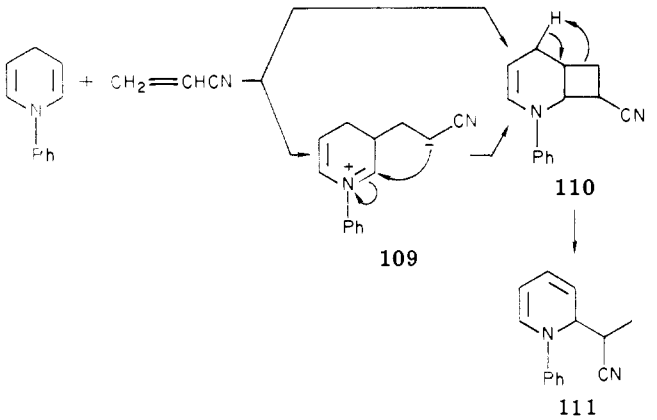
The reaction of dimethyl acetylenedicarboxylate with 1,4-dihydropyridines results in the formation of cyclobutapyridines **106**; however, in contrast to the isomeric products (**100**) from 1,2-dihydropyridines, the 1,4 adducts do not ring open.[81] The reaction is not a concerted process, but involves a zwitterionic intermediate **107** which either cyclizes to **106** or accepts a proton, yielding the vinylic 1,4-dihydropyridine **108**.[81c,d] A



107 106 108

R = alkyl, aryl

similar reaction of a 1,4-dihydropyridine with acrylonitrile leads to a substantially different product, the 2-substituted 1,2-dihydropyridine **111**.[82] The product

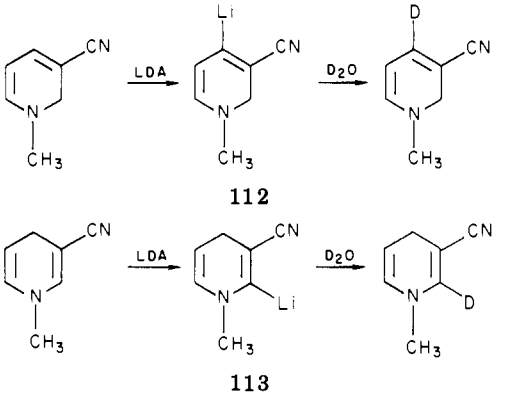


109 110 111

could arise from a concerted [2 + 2] addition, affording the cyclobutapyridine **110** that ring opens, or, analogous to the reaction with dimethyl acetylenedicarboxylate, a zwitterion (**109**) is formed that cyclizes to **110** and ring opens with proton abstraction to give 1,2-dihydropyridine **111**.

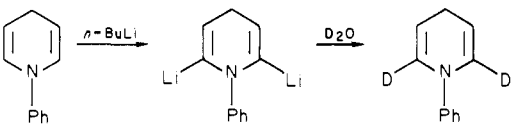
B. Electrophilic Additions to the Ring Carbons

Dihydropyridines react with strong metalating agents, in most cases forming vinyl carbanions that readily react with electrophiles. 3-Cyano-1,2- and 1,4-dihydropyridines react with lithium diisopropylamide (LDA), affording 4-lithio- and 2-lithiodihydropyridines (**112** and **113**), respectively, which when quenched with deuterium oxide, yield the deuterated dihydropyridines.[83] 1-Phenyl-1,4-dihydropyridine, when



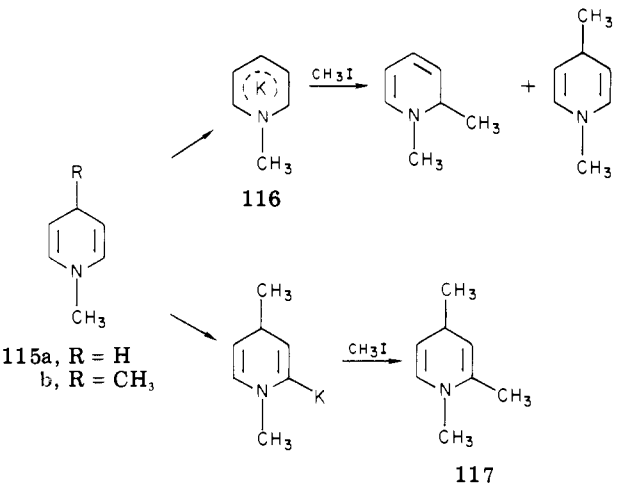
112 113

treated with excess *n*-butyllithium followed by quenching with deuterium oxide, affords a product having a proton NMR spectrum integrating for less than one proton in the 2-positions, indicating the intermediacy of a dilithiated species (**114**).[47] The in-



114

triguing challenge of abstracting a methylene proton from a dihydropyridine, thus giving an 8π system (antiaromatic), was met by Schlosser[84] on reacting *N*-methyl-1,4-dihydropyridine (**115a**) with [(trimethylsilyl)methyl]potassium. The intermediate (*N*-methyldihydropyridyl)potassium **116**, when treated with methyl iodide, afforded a mixture of 1,2- and 1,4-dihydropyridines. The use of the same reagent on 1,4-dimethyl-1,4-dihydropyridine (**115b**) followed by methyl iodide gave only the 2-methyl-1,4-dihydropyridine **117**.



115a, R = H
b, R = CH_3

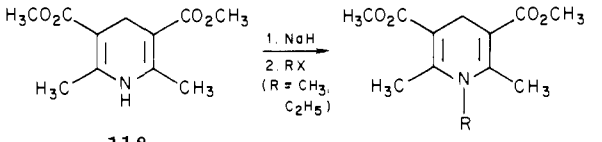
116 117

Apparently, the methyl group in the 4-position sufficiently hinders the doubly allylic proton such that the vinyl protons are more acidic.[84]

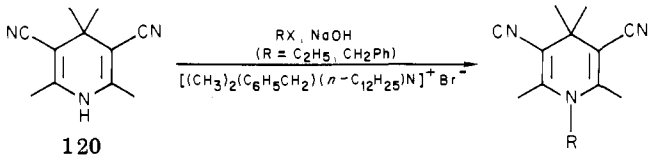
C. N-Alkylations

Dihydropyridines not substituted on nitrogen are sufficiently acidic for the removal of the proton by strong base, such as sodium hydride or organometallics.

N-Alkyldihydropyridines result when the metal amides are treated with alkyl halides (e.g., **118** and **119**).[85-88]



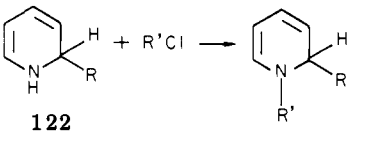
118 **119**



120 **121**

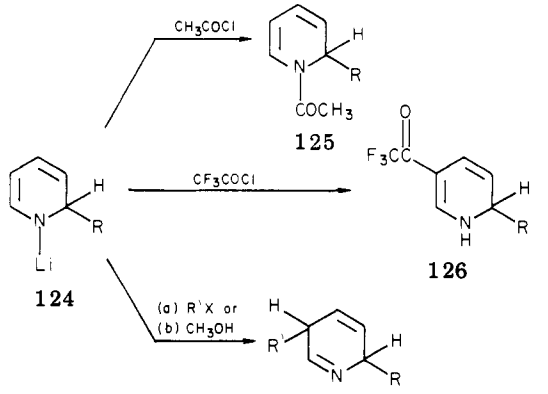
Phase transfer catalysis has similarly been used to generate *N*-alkyl-1,4-dihydropyridines (**120–121**).[89]

The nitrogen-unsubstituted 1,2-dihydropyridines **122** are sufficiently nucleophilic to react with acyl and sulfonyl chlorides to yield, among other products, *N*-acyl and *N*-sulfonyl adducts **123**.[90] *N*-Lithio-1,2-dihydropyridines **124**[91] can react at either carbon or nitrogen depending upon the electrophile. Acetyl chloride adds primarily to the nitrogen, affording the *N*-acetyl-1,2-dihydropyridine **125**, whereas trifluoroacetyl chloride yields the 5-trifluoroacetyl-1,2-dihydropyridine **126**.[92] Alkyl isocyanates also add to the nitrogen.[93] Alkyl halides and methanol add to **124** to give 2,5-dihydropyridines **127**.[94]



122 **123**

R = Ph, $(CH_2)_3CH_3$; R′ = CH_3CO, CH_3SO_2

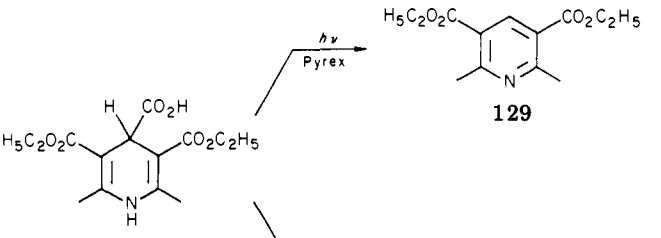


125 **126** **124** **127a**, R′ = alkyl; **b**, R′ = H

R = Ph, $(CH_2)_3CH_3$

D. Photochemical Reactions

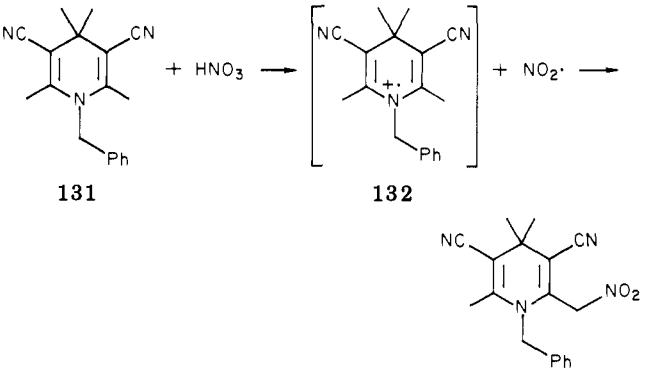
Only a few examples exist of systematic examinations of photolyses of dihydropyridines, and they deal exclusively with the 1,4 isomers. Mitsunobu and coworkers[95] demonstrated that Hantzsch esters were photooxidized to the corresponding pyridines in the presence of oxygen. Dihydropyridine **128** also gave a pyridine (**129**) when photolyzed through Pyrex in the absence of oxygen, apparently via decarboxylation. When **128** was photolyzed through quartz, an isomerization and decarboxylation occurred, affording the 1,2-dihydropyridine **130**.[96]



128 **129** **130**

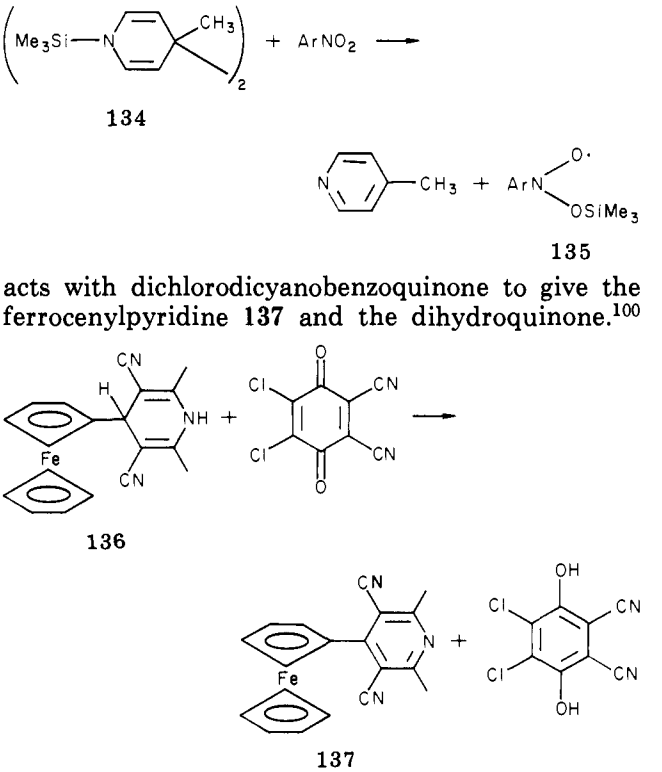
E. Miscellaneous Reactions

Hantzsch esters such as **131** react with nitric acid to yield the 2-nitromethyl derivative **133**,[97] with the radical-cation **132** being implicated as an intermediate.[98]



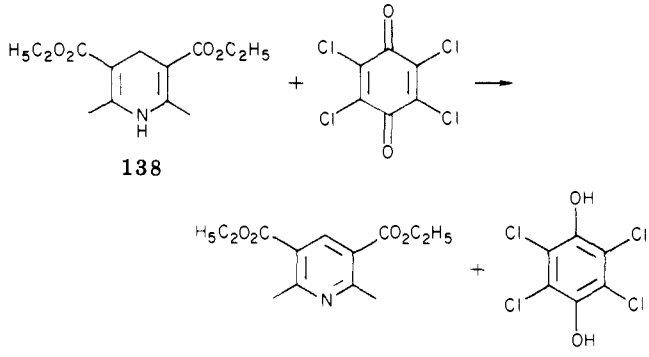
131 **132** **133**

In the presence of aromatic nitro compounds the *N*-(trimethylsilyl)dihydropyridine dimer **134** affords 4-picoline and the nitroxide radical **135** via a radical mechanism.[99] The ferrocenyldihydropyridine **136** reacts with dichlorodicyanobenzoquinone to give the ferrocenylpyridine **137** and the dihydroquinone.[100]



134 **135** **136** **137**

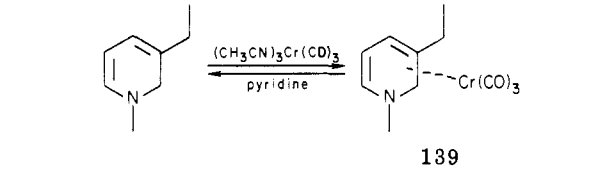
Though the reaction proceeds by a radical mechanism, the ferrocene and not the dihydropyridine is the source of the radical. A similar reaction with simple Hantzsch ester **138** and chloranil in a CsI pellet apparently takes place by way of a hydride ion shift.[101] Dihydro-



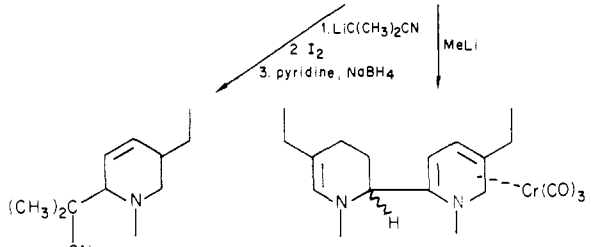
138

pyridines are oxidized by peroxides in a free radical mechanism to the corresponding pyridines.[102]

Though most non-Hantzsch-type dihydropyridines are unstable in air, 1,2-dihydropyridines can form very stable chromium tricarbonyl complexes (**139**).[103] Upon



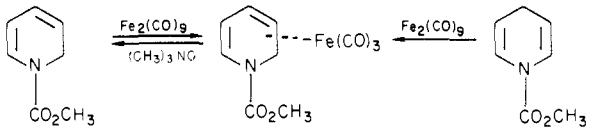
139



141 140

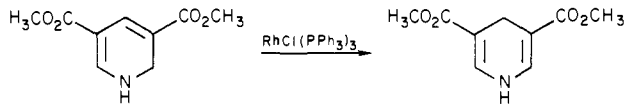
treatment with pyridine, the dihydropyridine is regenerated, providing a convenient method for handling these unstable dihydropyridines.[104] The chromium tricarbonyl complexes are capable of reacting with alkyllithium reagents. With methyllithium, the dimer **140** is formed,[105] while lithium dimethylacetonitrile gave, after oxidation with iodine, treatment with pyridine, and reduction with sodium borohydride, tetrahydropyridine **141**.[106]

Iron tricarbonyl complexes of dihydropyridine can similarly be formed. Both 1,2- and 1,4-dihydropyridines react with $Fe_2(CO)_9$ to give the (1,2-dihydropyridine)-iron tricarbonyl **142**, which, on treatment with trimethylamine oxide, regenerates only the 1,2-dihydropyridine.[107]



142

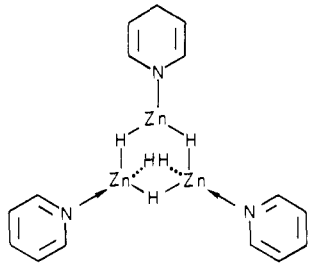
The reverse isomerization occurs with catalytic amounts of rhodium complexes. Thus 1,2-dihydropyridine **143** is isomerized to the 1,4 isomer with $RhCl(PPh_3)_3$ in benzene at 100 °C.[108] Dihydropyridines



143

are also easily dehydrogenated to the corresponding pyridines by using catalytic amounts of transition metals such a palladium.[109]

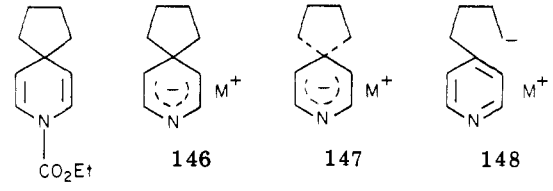
Pyridine reacts with zinc hydride to form a complex of (1,4-dihydro-1-pyridyl)zinc hydride, zinc hydride, and pyridine (**144**).[110] Hydrolysis of the complex affords



144

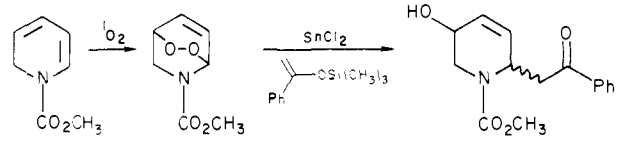
a mixture of 1,4-dihydropyridine and pyridine. The complex is also a selective reducing agent for carbonyl compounds.

4,4-Spiroalkyl-*N*-carbethoxy-1,4-dihydropyridines **145** react readily with organometallic reagents, generating the relatively stable salts of the spirodihydropyridines **146**. There was no interaction between the pyridyl ring and the σ electrons of the other ring in a "nonclassical" species (**147**), nor did any ring cleavage products (**148**) exist.[111]



145 146 147 148

1,2-Dihydropyridines readily react with singlet oxygen to give endoperoxides **149**, which in the presence of tin chloride, react with various electron rich olefins (enamines, vinyl ethers, etc) to form carbon–carbon bonds.

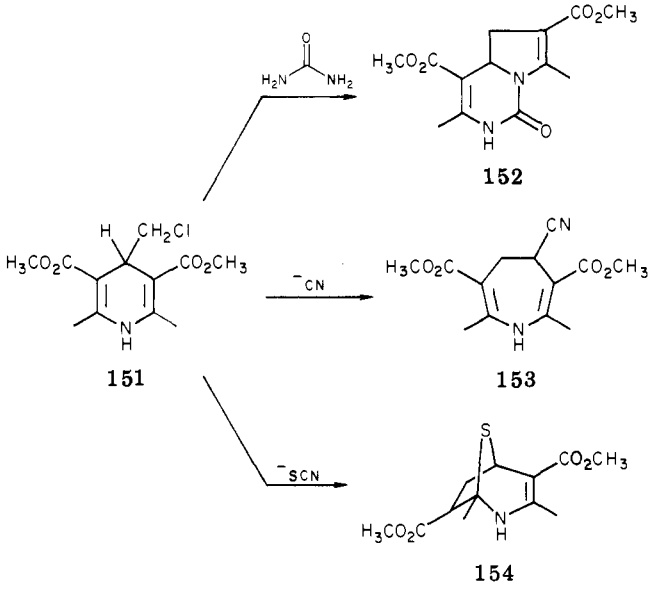


149 150

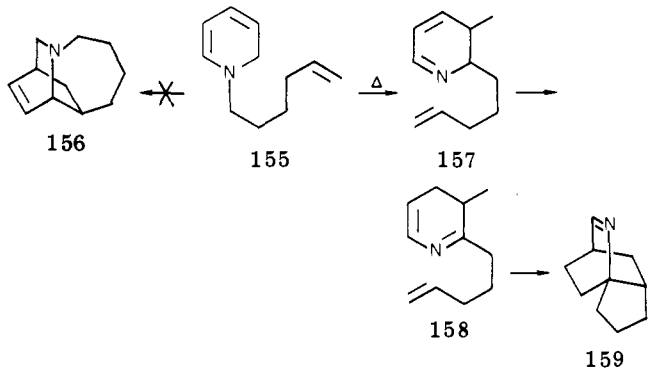
The result is the formation of an elaborated tetrahydropyridine (**150**) without the use of carbanions.[112]

A variety of interesting products are obtained from the reaction of the 4-chloromethyl-1,4-dihydropyridine **151** with nucleophilic reagents. The reaction with urea afforded pyrrolo[1,2-*c*]pyrimidines **152**, while cyanide gave the 4,5-dihydroazepine **153** and thiocyanate generated the bicyclic product **154**.[113]

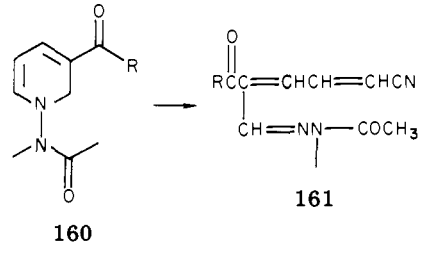
1,2-Dihydropyridines have been implicated in the biosynthesis of indole alkaloids.[114] Thus, the thermolysis of *N*-(5-hexenyl)-1,2-dihydropyridine (**155**) was



studied as a model for the biosynthetic Diels–Alder reactions. Dihydropyridine **155** failed, however, to give the expected tricyclic amine **156**; rather, it isomerized to the 2,3-dihydropyridine **157** and then to the 3,4-dihydropyridine **158** that underwent a Diels–Alder reaction, affording the final product **159**.[115] This is in

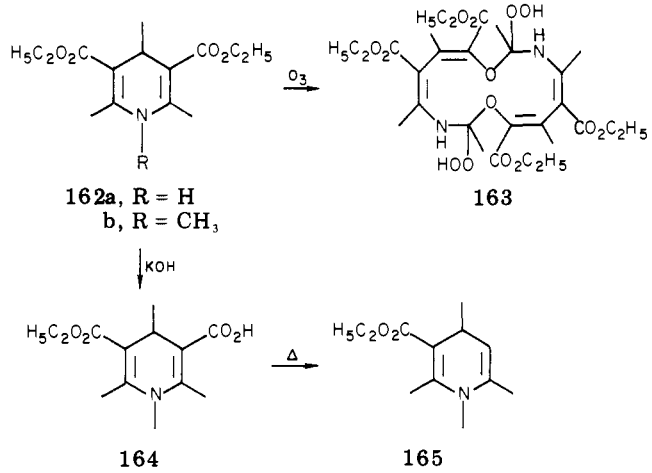


marked contrast to Fowler's[71] observations with the 4-cyano-1,2-dihydropyridines (**97**). Another rearrangement of 1,2-dihydropyridines involves a reverse Cope-type reaction whereby 2-cyano-1,2-dihydropyridine **160** affords the ring-opened product **161**.[116]



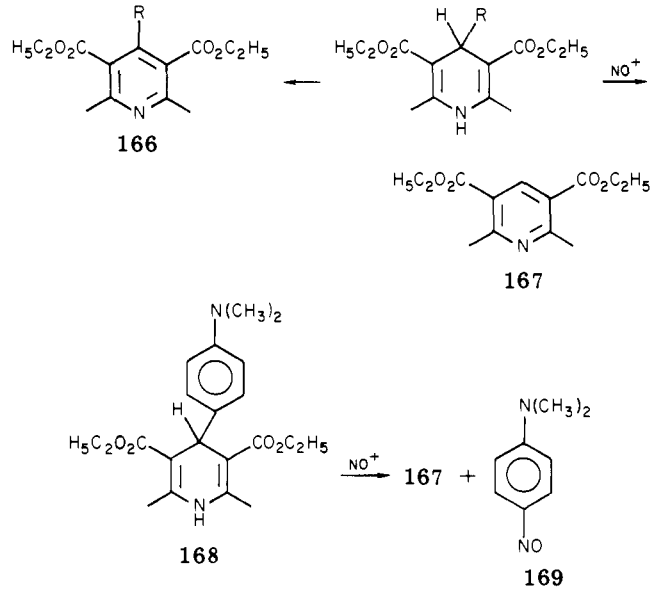
R = 3-indolyl

The ozonolysis of Hantzsch ester **162a** generates the macrocyclic hydroperoxide **163**.[117] Treatment of **162a** with primary alcohols in the presence of a basic catalyst results in transesterification; however, secondary or tertiary alcohols fail to react.[118] One equivalent of alcoholic potassium hydroxide causes the saponification of one of the ester groups, yielding acid **164** which upon heating decarboxylates to **165**.[119] Hantzsch esters such as **138** are aromatized to the corresponding pyridines when reacted with pyridine *N*-oxide.[120] Hexafluoro-



acetone is readily reduced to the alcohol by *N*-benzyl-1,4-dihydropyridine. Whether a charge transfer complex or a one-electron transfer is involved is unclear.[121]

The ability of 1,4-dihydropyridines to undergo oxidation or reduction is influenced by substitution in the 3-, 4- and 5-positions more than in the 1-position.[122-124] The course of the oxidation can be substantially altered by a change in the oxidant or by changing the electronic character of the substituent in the 4-position. The typical product of the oxidation of 4-substituted 1,4-dihydropyridines is the 4-pyridyl compound **166**.

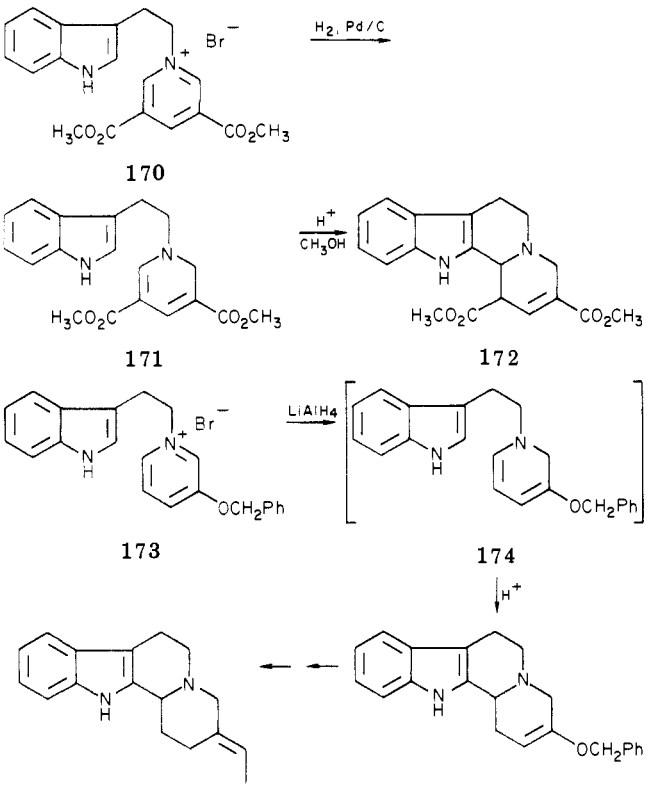


However, 4-alkyl-1,4-dihydropyridines in the presence of nitrous acid lose the alkyl group to give pyridines unsubstituted in the 4-position (**167**).[125] Similarly, 4-[*p*-(dimethylamino)phenyl]-1,4-dihydropyridine **168** reacts with electrophiles such as nitrite to give products of electrophilic aromatic substitution **169** and the pyridine.[125]

V. Utility (Use of Dihydropyridines as Starting Materials or Intermediates in Synthesis)

A. Natural Product Synthesis

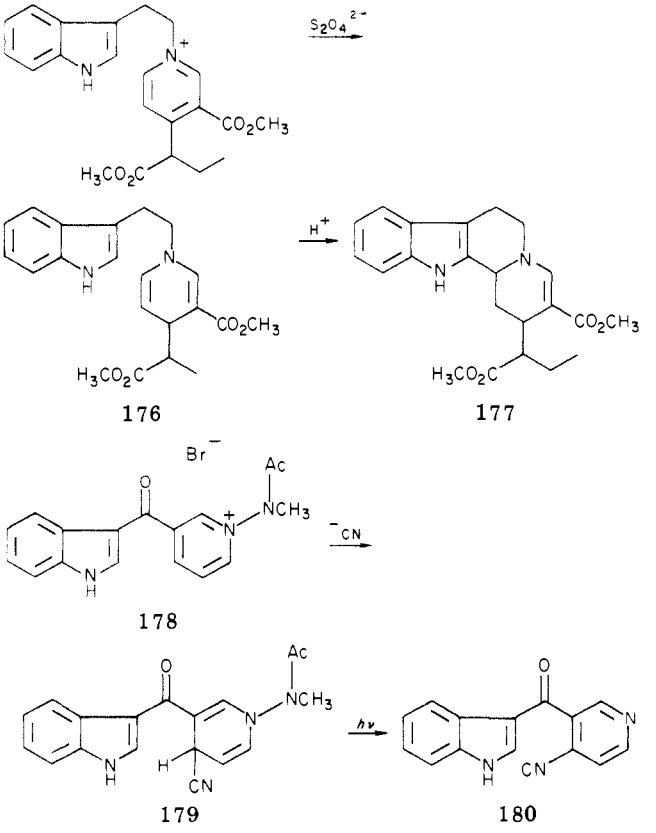
In natural product syntheses dihydropyridines have found their widest applicability in the preparation of alkaloids. The indoloquinolizidine **172** was prepared by the partial catalytic hydrogenation of indole pyridinium salt **170** to the indole dihydropyridine **171** fol-



170 171 172 173 174 175

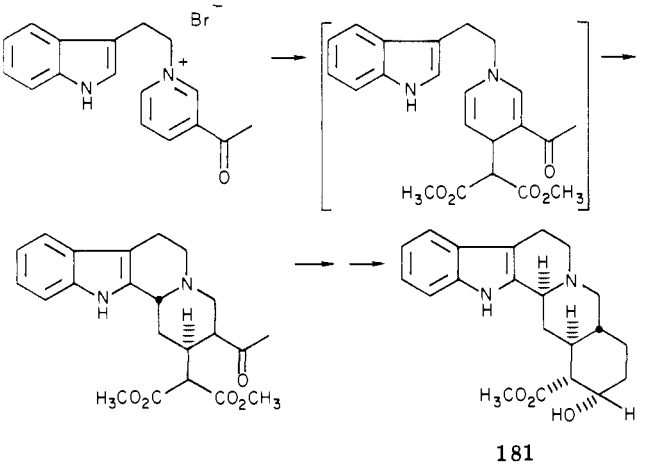
lowed by acid-induced cyclization.[126] A similar sequence in which the dihydropyridine was generated by lithium aluminum hydride reduction of **173** and immediate acid catalyzed cyclization of the intermediate dihydropyridine **174** led eventually to the alkaloid deplanceine (**175**).[127]

Dithionite reduction of indole pyridinium salts results in the corresponding 1,4-isomer **176** that has been cyclized with acid to yield the indole alkaloid **177**.[128]



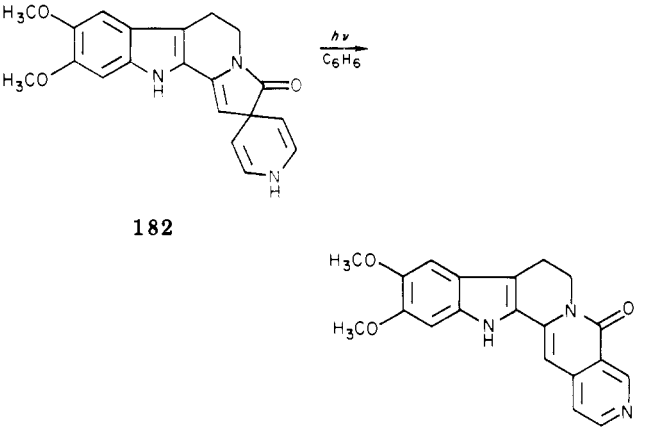
176 177 178 179 180

Cyanide ion addition to indole pyridinium salt (**178**) also produces a 1,4-dihydropyridine (**179**). When pyhotolyzed, the product is a 4-cyanopyridine (**180**).[129a] Similarly, Wenkert has used 1,4-dihydropyridines in the synthesis of yohimbine (**181**).[129b,c] Photolysis of spi-



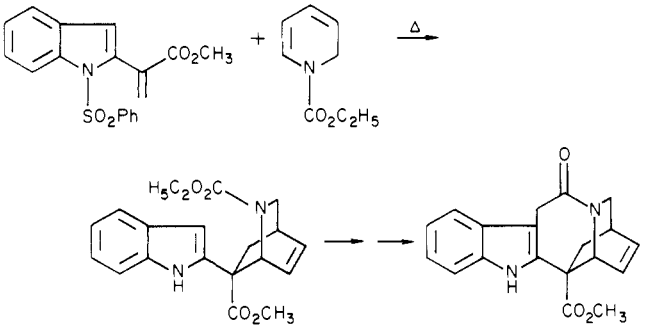
181

rodihydropyridine **182** results in a rearrangement to the indole alkaloid nauclefine (**183**).[130]



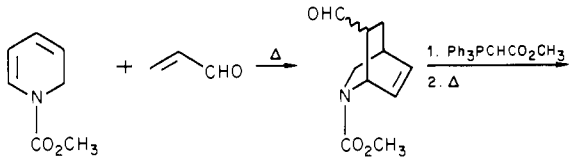
182 183

The ability of 1,2-dihydropyridines to undergo Diels–Alder reactions has been utilized in the synthesis of alkaloids. Sundberg demonstrated that heating a mixture of an indoleacrylate and a 1,2-dihydropyridine yielded an adduct **184** that was eventually converted to the catharanthine-like alkaloid **185**.[131] Wender has



184 185

used the Diels–Alder reaction between acrolein and *N*-carbomethoxy-1,2-dihydropyridine to form *cis*-hydroisoquinolines **187** via the bicyclic adducts **186**.[132] The tetrahydropyridine baikiain (**188**) has been used with sodium hypochlorite to produce 2,5-dihydro-



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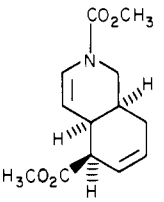
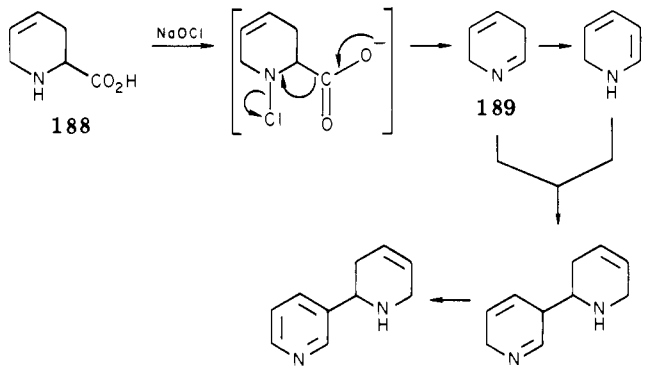


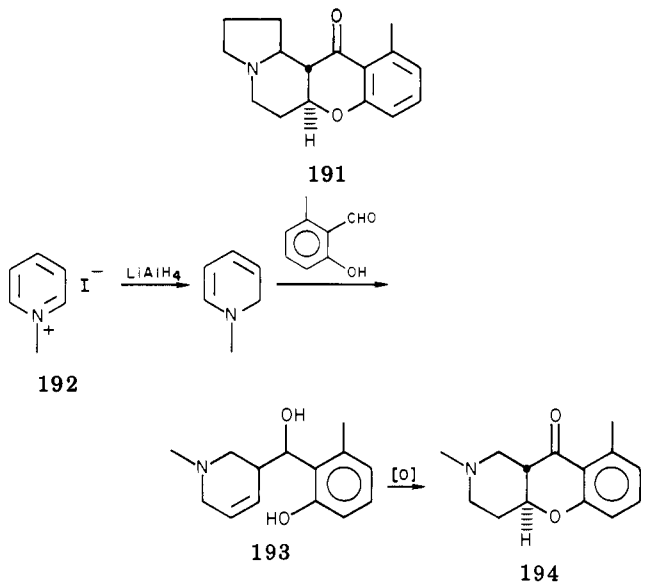
187

pyridine **189** that isomerizes to 1,2-dihydropyridine. The two isomeric dihydropyridines then combine to afford the natural product anatabine (**190**).[133] A model



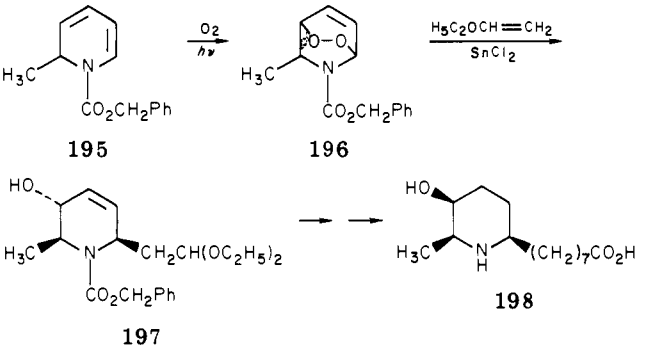
188 189 190

reaction utilizing a dihydropyridine was used to develop the synthetic strategy for preparing the alkaloid elaeocarpine (**191**) in two steps. Thus, lithium alu-



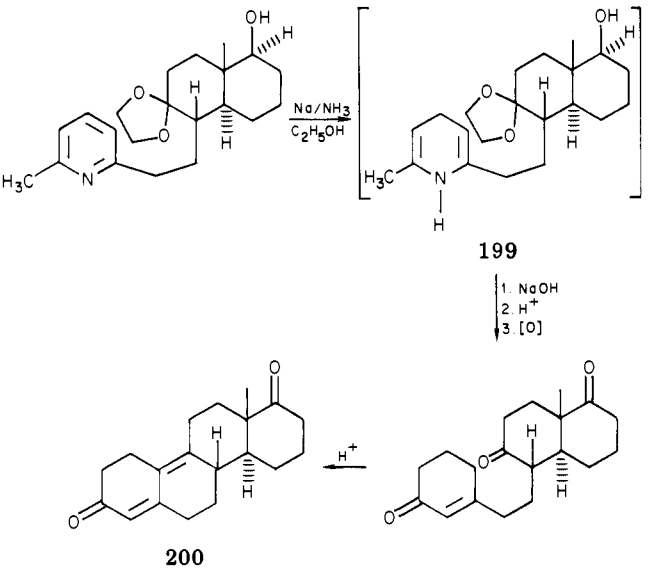
191 192 193 194

minum hydride reduction of *N*-methylpyridinium iodide (**192**) followed by the addition of 6-methylsalicylaldehyde furnished condensation product **193**. Oxidation and chromanone cyclization yielded chromanopiperidine derivative **194**. When the sequence was repeated with a dihydroindolizinium salt, elaeocarpine resulted.[134] Carpamic acid (**198**) was synthesized by the photooxygenation of dihydropyridine **195** to the bicyclic peroxide **196**, that, when reacted with ethyl vinyl ether in the presence of tin chloride, stereoselectively gave the tetrahydropyridinol **197**. Six more steps gave carpamic acid.[135]



195 196 197 198

In an elegant synthesis of homoestrone (**200**), Danishefsky[136] employed a 1,4-dihydropyridine (**199**) as an



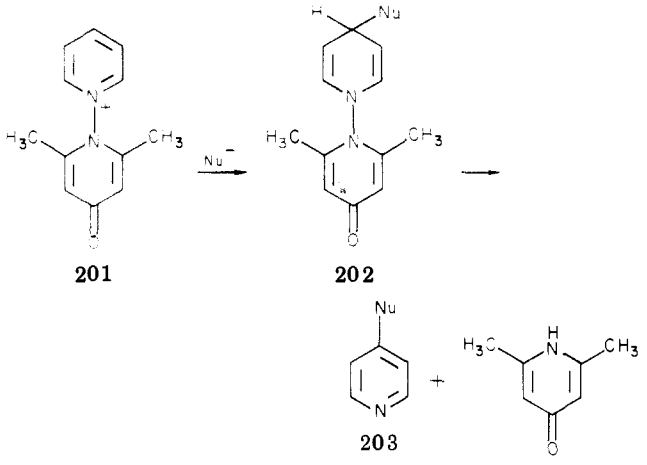
199 200

intermediate in a bis annelation sequence leading to the homosteroid ring system. The vinylpyridine nucleus thus served as a synthetic equivalent to vinylcyclohexenones, which are traditionally used in steroid total syntheses.

B. Pyridine Synthesis

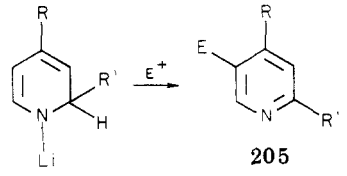
Unactivated pyridine rings are generally unreactive toward nucleophiles. Though *N*-oxide formation or quaternization enhances the reactivity of the pyridine ring, nucleophilic attack frequently occurs at both the 2- and the 4-positions. Katritzky[137] found that the 1-(4-oxopyridyl)pyridinium cation **201** was susceptible to nucleophilic attack at the 4-position of the pyridine ring from a wide variety of reagents (Grignards, lithium enolates, sodium salts of nitroalkanes, nitriles, thiolates) while blocking attack at the 2-positions. The intermediate 1,4-dihydropyridine **202** readily decomposed on heating to the 4-substituted pyridine **203**. Anions of benzimidazole and benzotriazole also afforded dihydropyridines **202**; however, the pyridines were formed by photolytic decomposition of the dihydropyridine in the presence of benzoyl peroxide.

Substitution in the 3-position of the pyridine ring has posed a problem as well. Giam and co-workers[138] found



201 202 203

that *N*-lithio-2- and -4-substituted-dihydropyridines **204** react with a number of electrophiles (epoxides, alkyl halides, haloamines, etc.), affording the 3-substituted pyridines **205** (strictly, 2,5-disubstituted pyridines).

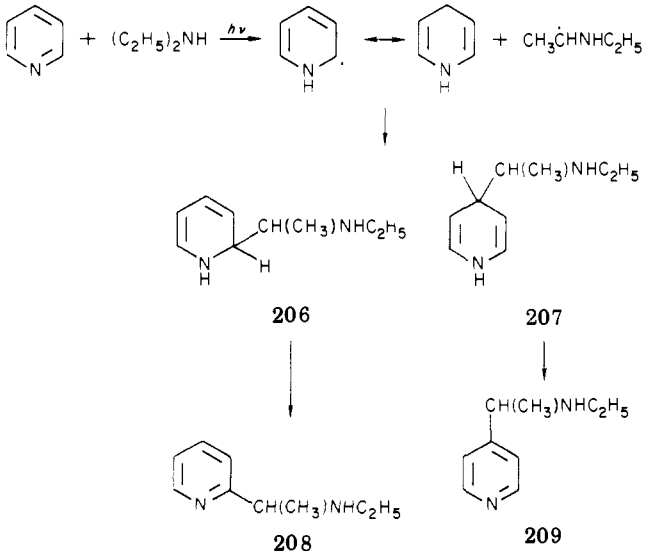


204 **205**

R = H, $CH(CH_3)_2$; R' = $(CH_2)_3CH_3$, Ph

This procedure has also been used with disulfides to form 2-substituted-5-thiopyridines.[139]

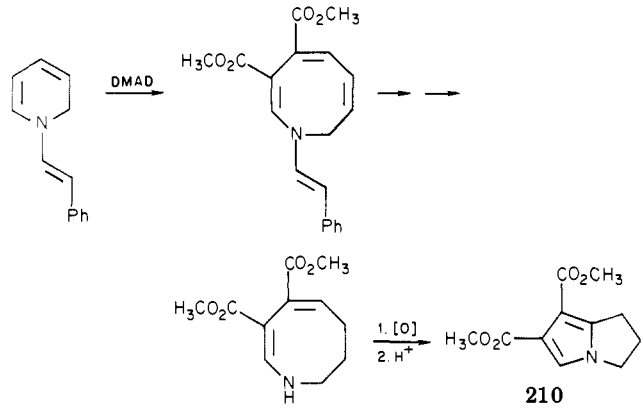
Dihydropyridines **206** and **207** have been implicated as intermediates in the photoreactions of pyridine with alkylamines that lead to 2- and 4-substituted pyridines **208** and **209**.[140]



206 **207** **208** **209**

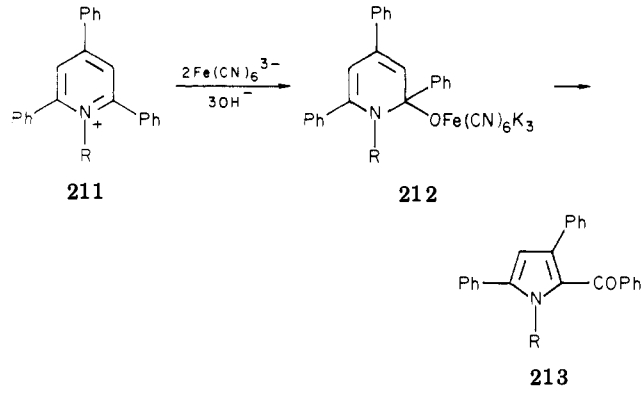
C. Ring Expansion and Contraction

As shown earlier,[77] 1,2-dihydropyridines react readily with dimethyl acetylenedicarboxylate (DMAD) to provide a 1,2-dihydroazocine (**101**). Mariano and coworkers[141] have used this sequence to prepare pyrrolizidines **210**.



210

A ring contraction of pyridinium salts **211** to pyrroles **213** by oxidation with potassium hexacyanoferrate(III) is believed to occur via the dihydropyridine **212**.[142]

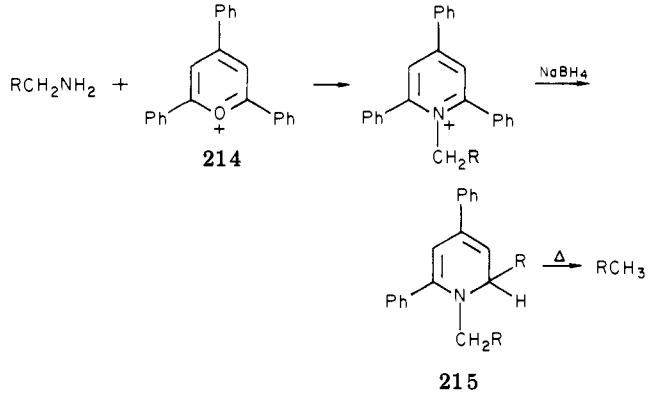


211 **212** **213**

R = alkyl, aryl

D. Miscellaneous

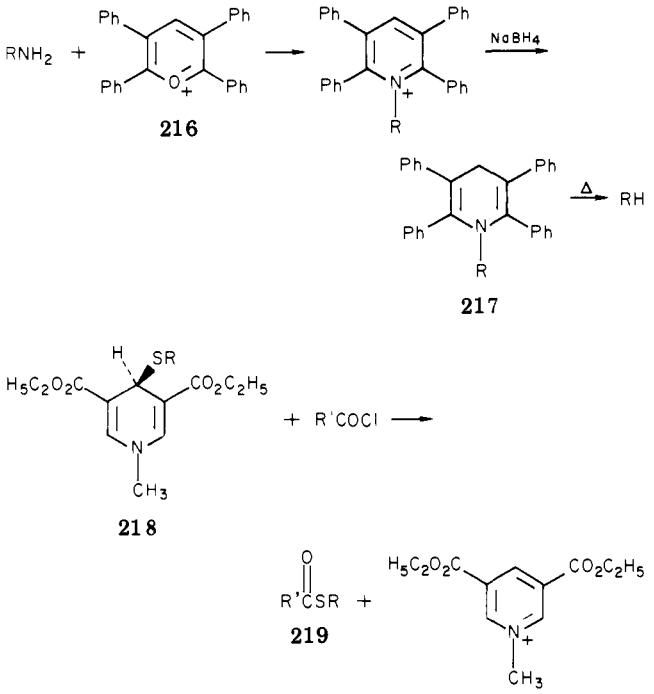
Katritzky[143] has used pyrylium salts **214** that lead to 1,2-dihydropyridine intermediates **215** for the conversion RNH_2 to RH, a transformation that can be readily accomplished with arylamines via diazotization but one that is done with difficulty with aliphatic amines. The



214 **215**

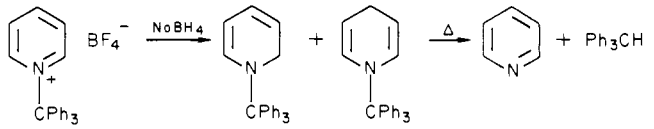
conversion worked well for benzylic and allylic amines but failed in other cases. The use of pyrylium salt **216** and the resultant 1,4-dihydropyridine **217** increased the scope of the reaction to aliphatic and aromatic amines.[144,145]

Thiolate transfer has been effected with 1,4-dihydropyridines. Thus, thiodihydropyridine **218** readily reacts with a variety of acid chlorides to give high yields of thio esters **219**.[146]

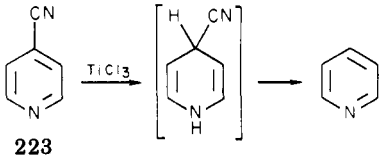


R = benzyl, phenyl, alkyl; R' = phenyl, alkyl

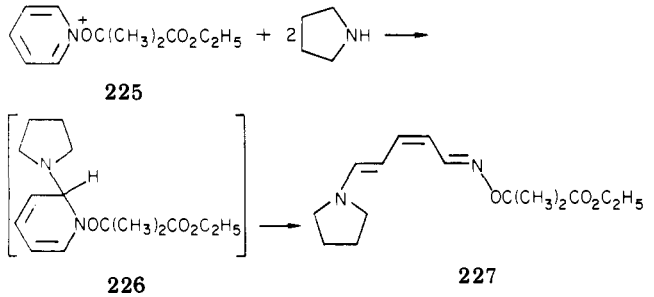
Dihydropyridines can also act as masked pyridines during hydride reactions.[146] 1-(Triphenylmethyl)-pyridinium fluoroborate (**220**) is reduced by sodium borohydride to a mixture of 1,2- and 1,4-dihydropyridines **221** and **222**. Upon heating, pyridine is generated. The reaction apparently does not work for



substituted pyridines. 1,4-Dihydropyridines (**224**) are also involved in the reductive decyanation of pyridinecarbonitriles (**223**) to pyridine using titanium trichloride.[147]



The reaction of pyrrolidine with the *N*-(acyloxy)-pyridinium salt **225** results in the formation of 1,2-dihydropyridine **226**. Disrotatory opening of the dihydropyridine gives the unique pyrrolidine **227**.[148]



Finally, dihydropyridines are believed to be intermediates in the biosynthesis of the biopolymer elastin.[149]

VI. NADH Mimics

A. Reduction of Unsaturated Systems

The distinction between the synthetic utility of a dihydropyridine and simply referring to a reaction as that of an NADH mimic may arise more from the prejudices of the authors of papers and the reviewers than objectivity would dictate. Nonetheless, the reductions presented in this section are patterned after those found in living systems.

Though 1,4-dihydropyridines can reduce ketones and aldehydes to alcohols, the reaction rate is enhanced by the presence of divalent metal ions. Thus, Hantzsch esters have reduced pyridoxyl phosphate in the presence of metal ions (Ni^{2+}, Co^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}),[150] nicotinamides have reduced α-keto esters,[151] α-diketones, α-hydroxy ketones,[152] 2-acylpyridines,[153] α,-α,α-trifluoroacetophenone,[154] benzaldehydes, acetophenone,[155] and cinnamoylpyridines[156] in the presence of Mg^{2+} or Zn^{2+}, and nicotinamide-4-sulfinates have reduced α-diketones and α-keto esters in the presence of Mg^{2+}.[157] Similarly, the reduction of imines to amines has been carried out with α-imino esters,[158] α-imino acids,[159] and α,β-unsaturated iminium salts,[160] in reductive aminations[161] and photolytically.[162] In addition to the reduction of carbonyls and imines with 1,4-dihydropyridines, reductions of thiol esters,[163] thioketones,[164] cyano olefins,[165] and the aromatic ring in 1,3,5-trinitrobenzene[166] have been accomplished.

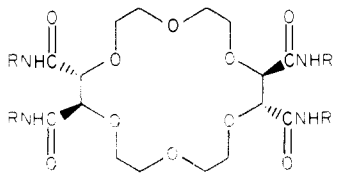
Since the reduction of carbonyls with dihydropyridines is an equilibrium reaction with the product alcohols and pyridinium salts, it is interesting that the oxidation of alcohols with pyridinium salts in the presence of alkoxide ions to aldehydes and dihydropyridines has been reported.[167] Dihydropyridines have also been used with catalytic amounts of nicotinamide coenzyme in reductions in order to regenerate NADH from NAD^+.[168]

B. Asymmetric Reductions

Perhaps the greatest potential for NADH mimics is in their ability to induce asymmetry in organic molecules. Achiral dihydronicotinamides have been used with chiral micelles and polypeptides in the reduction of aryl trifluoromethyl ketones to chiral alcohols,[169] and achiral Hantzsch esters have reduced α-ketomenthyl esters to give enantiomerically enriched α-hydroxy esters.[170] Hantzsch esters bearing menthyl esters have also been used to asymmetrically reduce α-keto esters[170] and iminium salts.[171] Dihydronicotinamides with amino acids,[172,145] chiral diols,[173,170] and chiral benzyl groups[174,153] have also been used in asymmetric reductions. In addition, crown ether **29**[17] reduces carbonyls.

C. Crown Ethers and Micelles

Dihydropyridine crown ethers have been prepared with the polyether attached to the dihydropyridine ring at the 3- and 5-positions (**28**)[15] and via N-substitution (**228**),[175] and an attempt was made at substitution in the 2- and 6-position (**229**).[176] These crown ethers are



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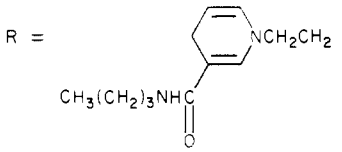

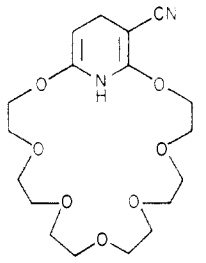

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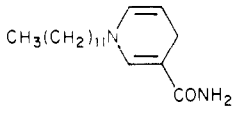
capable of complexing salts and reducing them as well,[177] essentially combining the features of an enzyme and NADH in one molecule.

The micelle-bound dihydropyridine **230** was found to



230

have a dramatic variation in the rate of hydration of the dihydronicotinamide moiety depending upon the cation present in an acid solution. This behavior is apparently similar to that found in enzyme–NADH complexes.[178]

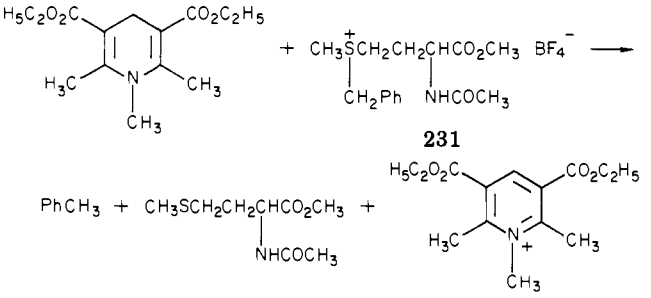
D. Mechanism of NADH Reductions

The mechanism by which NADH transfers hydrogen in redox reactions has been extensively examined in model systems. Still, there remains no concensus on whether the process occurs by a one-step hydride transfer[179] or by multistep mechanisms involving the transfer of electrons, free radicals, or charge-transfer complexes.[98,180] Indeed, each mechanism may be involved in the particular model reaction studied, but whether these reactions are good models[181] for NADH reductions remains unclear. For example, Kellogg[182] found that a mixture of 3,5-bis(alkoxycarbonyl)-1,4-dihydropyridines and pyridinium salts under equilibrating conditions resulted in an isomerization to 1,2-dihydropyridines. Whether this isomerization occurs with NADH is not known. A pyridinium salt attached to a micelle formed a charge-transfer complex with dihydronicotinamides,[183] much like the known interaction between pyridine and the aromatic rings of adenine.[184] It is speculated that this may happen between NADH, its substrate, and the enzyme.

Though models for enzyme–coenzyme–substrate reactions may provide us with a diverse array of synthetic routes which can be utilized in a variety of ways, the precise mechanism for the NADH system will probably require a clearer understanding of the enzymes involved in these redox reactions.

E. Miscellaneous

Polymer-bound dihydropyridines have been found to reduce dyes and the central iron of ferriporphorins.[185] Dihydropyridines have also been used for the nucleophilic displacement of sulfonium salts (**231**) from sp^3-hybridized carbon by a (formal) hydride.[186] Nitro



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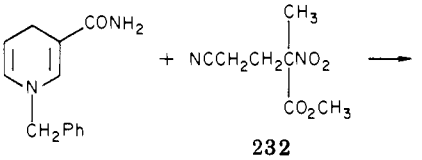
groups have similarly been displaced from nitroalkanes (**232**).[187]



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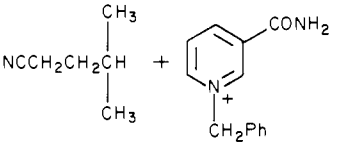
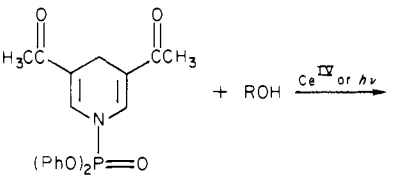


As a mimic of phosphorylations in nature, phosphoryl dihydropyridine **233** was found to react with alcohols either in the presence of ceric ion or photolytically, yielding phosphates.[188]



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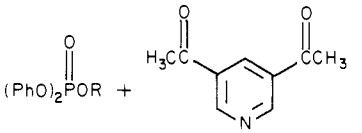
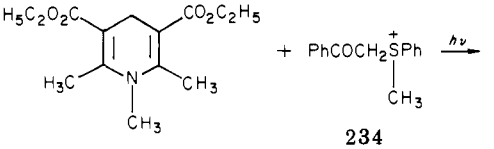


R = alkyl

Hantzsch esters were found to displace phenacyl onium salts **234** photolytically.[189]



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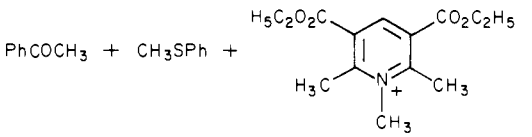
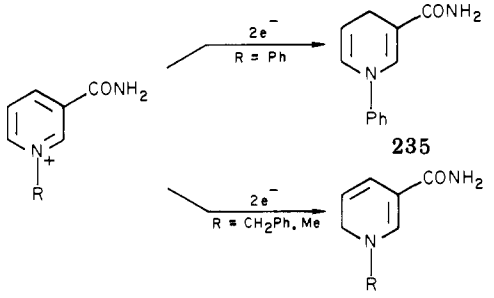


As a model for the reduction of NAD^+, the electrochemical 2e- reduction of 1-phenyl- and 1-alkylnicotinamides was examined. The 1-phenyl compound gave exclusively the 1,4-dihydronicotinamide **235** while

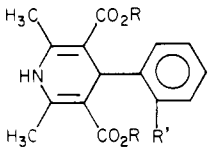
the 1-alkyl compounds gave only the 1,6-isomers **236**.[190]



In the presence of pyridinium salts, 1,4-dihydropyridines irreversibly isomerize to 1,2-dihydropyridines.[191] In view of these findings, a 1,2-dihydropyridine must not be involved in NADH equilibria since NADH is regenerated when NAD^+ is allowed to equilibrate with simple 1,4-dihydronicotinamides.[192]

VII. Pharmacology

Dihydropyridines have had a unique evolutionary history over this past century. First synthesized in the laboratory by Hantzsch,[4] dihydropyridines were later discovered to be the active part of NADH, the essential reducing coenzyme in animals. Over 30 years after that discovery, during which extensive research into the reaction mechanisms and utility of dihydropyridines was carried out, a biologically active dihydropyridine was synthesized. Having no relationship to NADH, the compound (**237a**) was a derivative of those synthesized by Hantzsch. Since the publication by Loev and co-



237a, R = C_2H_5; R′ = CF_3
b, R = CH_3; R′ = NO_2

workers[193] of their work in this area, a veritable flood of papers and patents has appeared on the chemistry and pharmacology of these unique "calcium antagonist" vasodilators. This has culminated in the marketing of a new drug, nifedipine (**237b**).[194]

Other pharmacological properties of dihydropyridines have been found; however, that is beyond the scope of this review. Suffice it to say that dihydropyridines offer a rich source of compounds possessing biological activity, and in all probability we will be hearing a great deal about dihydropyridines in the years to come.

Acknowledgments. The majority of the references in this review were obtained by an on-line computer search of *Chemical Abstracts*. We thank Ms. Joan Fortune, manager of Information Services of American Critical Care, and her staff for these references. Appreciation is also expressed to Ms. Diane Lulofs for preparing the manuscript.

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