Chemical Reviews

Volume 72, Number 1 February 1972

THE CHEMISTRY OF DIHYDROPYRIDINES

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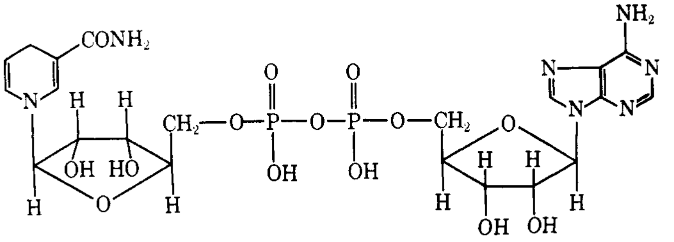
Received June 15, 1971

Contents

I. Introduction

Dihydropyridine chemistry began in 1882 when Hantzsch[1] published the synthesis which now bears his name. In the subsequent 50 years modifications of the original synthesis were developed and some reactions of dihydropyridines were studied. In the 1930's the discovery that a "hydrogen-transferring coenzyme" was a reduced nicotinamide derivative stimulated work on model dihydropyridines, generally N-substituted dihydronicotinamides. While the gross structure of the coenzyme NADH (reduced nicotinamide adenine dinucleotide; the oxidized pyridinium form is known as NAD) was established relatively early, the fine structure did not become recognized until the late 1950's. Early workers believed that NADH was a 1,2-dihydronicotinamide derivative and considerable confusion ensued as a result. Eventually it was proved unambiguously that NADH was the 1,4-dihydronicotinamide **1**.



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Model dihydropyridines have been used extensively to elucidate the mode of action of the coenzyme and, although considerable progress has been made, the exact mechanism of hydrogen transfer by NADH is still not completely understood. A number of excellent reviews on the structure, synthesis, stereochemistry, and hydrogen-transfer reactions of the pyridine nucleotides are available,[2–7] and this material will not be repeated here except where relevant.

Dihydropyridines, which are readily convertible to pyridines, are important intermediates in the synthesis of the latter. A detailed survey of synthetic reactions covering the literature up to 1957 exists,[8] but since it was written from the point

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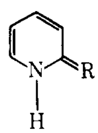
of view of pyridine synthesis rather than as an account of dihydropyridines the pertinent material is scattered and difficult to follow.

Dihydropyridines also play a role as intermediates in the reactions of pyridines, *e.g.*, in nucleophilic substitutions[9] and reductions,[10] as well as acylations in the presence of pyridine.[11]

Finally, dihydropyridines are of the utmost importance in biological systems, particularly NADH which is involved in biological oxidation–reduction. The physiological properties of dihydropyridines include antitumor activity,[12,13] porphyria-inducing activity,[14] and various others.[15–24] NADH has protecting action against ionizing radiation.[25] It has been postulated that dihydropyridines are involved in the cross-linking of elastin[26] and in the biosynthesis of indole alkaloids.[27,28]

II. Scope and Limitations

This review is confined to isolable or spectroscopically identifiable dihydropyridines. Specifically excluded are pyridine methenes **2a** and **3a**; ketodihydropyridines (dihydropyridones) **2b** and **3b**; pyridoneimines **2c** and **3c**; benzodihydropyridines (*e.g.*, dihydroquinolines and -isoquinolines) and quinolizidines. Biochemical aspects of NADH are not covered.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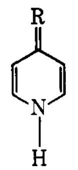
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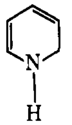
a, R = CH$_2$; b, R = O; c, R = NR$''$

The older literature surveys[29–31] on dihydropyridines deal with specialized aspects and contain much material which has since been shown to be incorrect. The latter will be discussed under the relevant headings.

III. Structure

A. CONSTITUTION AND STABILITY

In theory, five isomeric dihydropyridines **4–8** are capable of existence, but in fact most of the known dihydropyridines have either the 1,2-dihydro structure **4** or the 1,4-dihydro structure **5**. The reason why **4** and **5** are more common than **7** and **8** is presumably the involvement of the nitrogen lone pair in the π electron system of the former. The isomers **4** and **5** have the highest number of sp^2-hybridized centers.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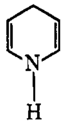
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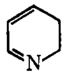
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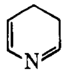
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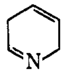
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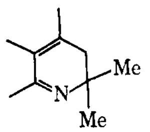
The only authenticated 2,3-dihydropyridines have partial structures **9**[32–34] or **10**[35] in which dehydrogenation to the corresponding pyridines is precluded. The formation of an unstable 2,5-dihydropyridine has been reported.[34] The structures of other alleged 2,3-dihydropyridines[36–41] have not been substantiated, and reinvestigation by modern techniques would be appropriate.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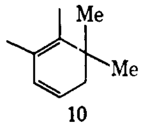
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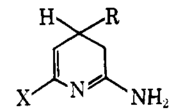
11, X = Cl, Br, I; R = H, Ph

The 3,4-dihydropyridines **11**[42] are stabilized by the amidine grouping as is the analogous 2-ethoxycarbonylamino-3,4-dihydropyridine which is regarded as a tautomeric mixture.[43] Again some earlier alleged 3,4-dihydropyridine structures[44–46] might be revised using modern techniques.

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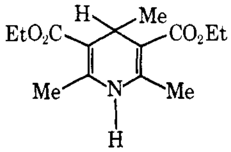
Hantzsch[1] assumed the product from the reaction of ethyl acetoacetate, acetaldehyde, and ammonia, now known to be



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12, to be a 2,3-dihydropyridine, but it was soon recognized[47–50] to be the 1,4 isomer. However, rigorous proof was presented only much later.[51,52] In the intervening years there was much confusion concerning the structures of dihydropyridines, particularly with regard to the distinction between the 1,2 and 1,4 isomers. A number of tests, held to be diagnostic for their differentiation,[37,53] were not reliable and led to the assignment of incorrect structures.[31,54] This was particularly serious in the case of the coenzyme NADH, **1**, which was erroneously regarded[31] as a 1,2-dihydropyridine until its structure was unambiguously established[55,56] by deuterium labeling.

The advent of spectroscopic techniques enormously facilitated structure determination and made possible unambiguous assignments,[57–63] often in conjunction with chemical evidence.[64–66] Several alleged[67–70] 1,2-dihydropyridines were later[26,71] shown to be the corresponding 1,4 isomers or *vice versa,* and one report[72] of a dihydropyridine structure was shown[73] to be erroneous.

No thermodynamic data have been reported for dihydropyridines to date. Studies on hydrogen-transfer reactions[74] and equilibration[75] indicate that the 1,4-dihydropyridines are thermodynamically more stable than the corresponding 1,2 isomers.

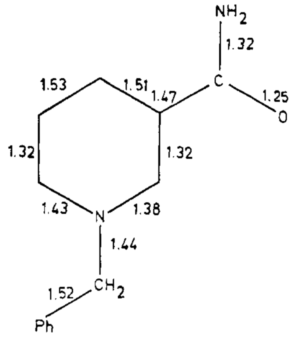

Figure 1. Bond lengths for 1-benzyl-1,4-dihydronicotinamide.[90]

Little systematic work has been carried out[76] on the correlation of reactivity with the nature and position of substituents. The parent 1,4-dihydropyridine **5** is described[77] as a very reactive substance in air; the corresponding 1,2 isomer **4** has not been isolated. Electron-attracting substituents capable of resonance interaction (COR, CO_2R, CN, NO_2) in the 3 and 5 positions stabilize dihydropyridines by extending the conjugation (see section III.C). Substituents in the 3,5 positions which donate electrons by resonance (SC_6H_5, OC_6H_5)[78,79] have a destabilizing effect. Alkyl substitution on nitrogen appears to have the same effect,[80] but a glucosyl substituent on the nitrogen[20,76,81–86] appears to have a remarkable stabilizing influence. Polycyclic[87–89] or otherwise highly substituted dihydropyridines seem to be less reactive; this may be due to steric factors.

B. CONFORMATION

The geometry of the dihydropyridines **13a** and **13b** has been determined by X-ray crystallography[90–92] which has shown the ring to be planar. The bond distances and conformation of the amide group of **13a** are shown in Figure 1. The single and

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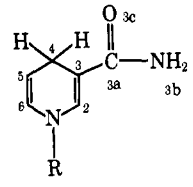
double carbon–carbon bonds have the expected bond lengths and the C_3–C_4–C_5 bond angle is essentially tetrahedral. The amide group is within 4° of the plane of the ring in **13a** and 22° in **13b**.



13a, R = $C_6H_5CH_2$
b, R = Pr

Little is known about the conformation of dihydropyridines in solution. Some authors have speculated[93–96] that the dihydronicotinamides **13** react in a boat-like conformation. However, the 60-MHz spectrum of **13b** indicates[97] that the methylene protons at C-4 are equivalent, implying either a rigid planar structure of the ring or else rapid interconversion of two or more nonplanar conformations. A recent 220-MHz study of reduced pyridine nucleotides[98] has shown that in these compounds the protons in the 4 position of the dihydronicotinamide ring are nonequivalent due to the differential shielding by the adenine group. A careful nmr study[99] has elucidated the conformation of pyridine nucleotides.

The low-temperature nmr spectrum of 1-ethoxycarbonyl-2,4-di-*tert*-butyl-1,2-dihydropyridine shows[63] the presence of two rotational isomers.

C. ELECTRONIC STRUCTURE[99a]

Semiempirical LCAO-MO calculations on the dihydropyridines **14b–f** and **15c–f** using the HMO or SCF methods[100–106] have shown that the π electron distributions are consistent with the assignment of localized double bonds. Theoretical calculations of electronic transitions of **14b,c** and of **15a–c** have been published.[102,107,108]

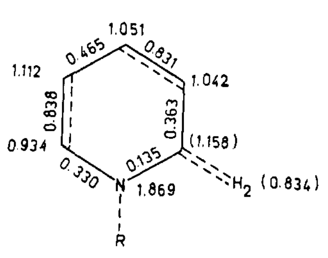


Figure 2. HMO molecular diagram[109] of 1,2-dihydropyridine (**14a**).

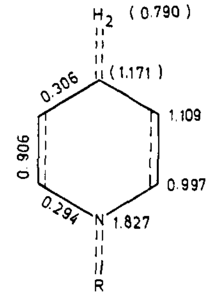
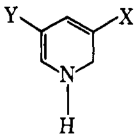
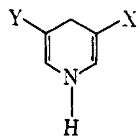


Figure 3. HMO molecular diagram[109] of 1,4-dihydropyridine (**15a**).





14a, X = Y = H
b, X = $CONH_2$; Y = H
c, X = H; Y = $CONH_2$
d, X = Y = COR
e, X = Y = CO_2R
f, X = Y = CN

15a, X = Y = H
b, X = COMe; Y = H
c, X = $CONH_2$; Y = H
d, X = Y = COR
e, X = Y = CO_2R
f, X = Y = CN

Figures 2 and 3 show molecular diagrams (π electron densities and π bond orders) for **14a** and **15a** calculated[109] using simple HMO treatment and including, in part, the hyperconjugation of the methylene groups. From the HMO calculations each model apparently has two localized double bonds (bond orders 0.831 and 0.906), and the lone electron pair on the nitrogen is only slightly delocalized (bond orders 0.135 and 0.335, nitrogen π electron densities 1.827 and 1.863, respectively). Analogous HMO molecular diagrams[103,105] show that in the 3,5-disubstituted dihydropyridines **14d–f** and **15d–f** π electrons are transferred to the substituents X and Y. The lone electron pair on the nitrogen is delocalized, resulting in decreased basicity of these compounds. Nevertheless, the double bond character of the bonds in **14** and **15** remains substantially unchanged.

The above-mentioned HMO calculations[109] show that the energy of the highest occupied molecular orbitals is high, and therefore the binding energy is low (0.011 β and 0.023 β for **14a** and **15a**, respectively, similar to the values calculated[100,101] for **14b,c** and **15c**). These results indicate that **14a** and **15a** might be expected to be strong electron donors, in agreement with the observed fact of their ready oxidation (see section VI.A) and the formation of stable π complexes with chromium.[110] The relatively high values[109] for the free valences in certain positions in **14a** and **15a** (0.52–0.56) predict considerable reactivity toward radical reagents. This is in accordance with their sensitivity to atmospheric oxygen. Substitution in the 3 and 5 positions with conjugating groups results[100,101,103,105] in lowered energies of the highest occupied molecular orbitals and transfer of the electronic charge to the substituents with a resulting decrease in reactivity.

Available information on the relative reliability of different π electron approximations is limited. An SCF calculation of the π electron structure of **15c** gives[102] π electron densities which are substantially in agreement with those obtained[101]

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from HMO treatment. However, there is a discrepancy in the π electron densities in the C5–C6 double bond (see Table I).

Table I

Calculated π Electron Densities in 13

Position	*HMO method*[101]	*SCF method*[102]
1	1.653	1.623
2	0.902	1.071
3	1.201	1.105
3a	0.766	0.753
3b	1.865	1.775
3c	1.424	1.506
5	1.181	1.068
6	0.942	1.084

The effect of σ–π interactions in dihydropyridines has not been investigated thus far. Calculations using the extended Hückel method or the more sophisticated CNDO or MINDO methods might be used to this end.

IV. Synthesis

A. PREPARATION FROM PYRIDINE DERIVATIVES

1. Reaction with Nucleophiles

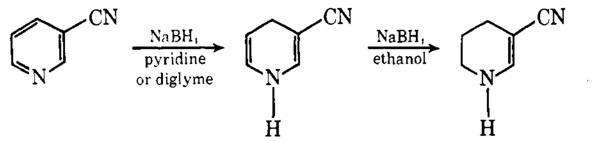
Some of the earlier work on nucleophilic addition to pyridinium salts has been described in ref 111 and 112.

a. Reduction with Complex Hydrides

A number of dihydropyridine derivatives have been prepared by reduction of the corresponding pyridines or pyridinium salts with complex metal hydrides. A review of the literature up to 1966 has been published.[10]

Reduction of pyridine with lithium aluminum hydride gave[113] an unstable product with reducing properties which could not be characterized. The structure of a complex formed from lithium aluminum hydride and pyridine has been elucidated (see **183**).

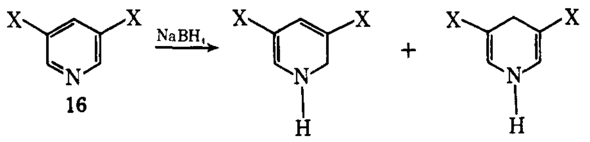
Sodium borohydride reduces pyridines with electron-withdrawing substituents in the 3 position, or, better, in the 3 and 5 positions, to dihydropyridines.[114–116] Thus 3-cyanopyridine was reduced[116] to the corresponding 1,4-dihydropyridine in aprotic solvents but to the tetrahydropyridine in ethanol according to eq 1.



(1)

Under the same conditions reduction of the nitrile groups takes place[116] in the isomeric 2- and 4-cyanopyridines. This is in accordance with the reactivity of cyanopyridines toward nucleophiles as predicted by quantum mechanical calculations based on simple Hückel approximation.[117]

The dinitriles **16a** and the diesters **16b,c** can be converted into the dihydropyridines **17** and **18** even in protic solvents[68,115,118] according to eq 2. The ratio of the 1,2 isomers **17** to the 1,4 isomers **18** is highly solvent dependent,[119] ranging from 13:87 in pyridine to 63:37 in acetonitrile for the diesters **17c** and **18c**.

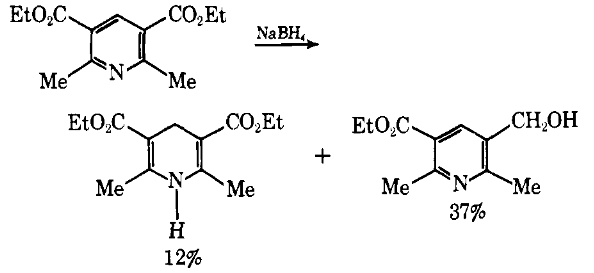


16 **17** **18** (2)

a, X = CN; **b**, X = CO_2Me; **c**, X = CO_2Et; **d**, X = COMe; **e**, X = CO_2H

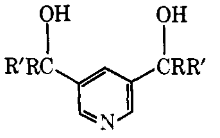
Sodium cyanoborohydride in acetic acid yields[119] the pure 1,4 isomers **18b–d**.

Treatment of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate with borohydride, surprisingly, results in reduction of one of the ester groups; the 1,4-dihydropyridine is also formed[120] in low yield as shown in eq 3.



(3)

Reduction of 3,5-diacetylpyridine with sodium borohydride yields[121,122] the diol **19a** together with small amounts of the isomeric 3,5-diacetyldihydropyridines **17d** and **18d**.[122] The tricyclic diketone **20**, on the other hand, afforded exclusively the corresponding 1,4-dihydro derivative.[114]



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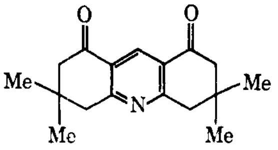

20

a, R = Me; R′ = H
b, R = R′ = H
c, R = R′ = Me

The effect of alkyl substituents on the nature of the reduction products of 3,5-dicyanopyridines has been studied systematically.[115,123] The results can be interpreted[104,124] using HMO calculations, taking into account π overlap between the σ-alkyl orbitals and the π electron system of the ring.

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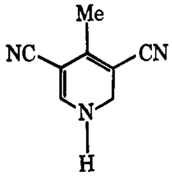
In some cases only one of the possible isomers is formed. Thus borohydride reduction of 3,5-dicyano-4-methylpyridine[115] and of 3,5-dicyano-2,6-dimethylpyridine[115,120] affords the dihydropyridines **21** and **22**, respectively. This specificity might be due to a combination of steric and electronic factors.



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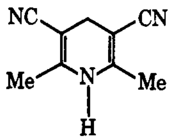

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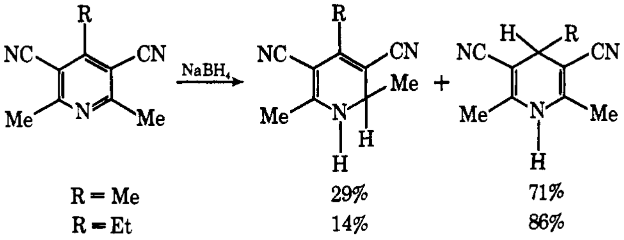
Electronic factors, including hyperconjugation, *i.e.*, the greater deactivating effect of methyl compared to ethyl, seem[115] to outweigh steric effects in eq 4 (see also ref 123 and 125).



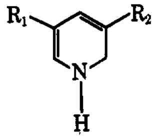
(4)

Lithium aluminum hydride reacts more vigorously and hence less selectively. The only preparatively useful reaction is that of 3,5-dicyanopyridine in which the ring is reduced more readily than the nitrile groups.[115,125,126] The effect of alkyl substituents is similar to that found for borohydride reductions, but the yield of 1,2 isomer is slightly higher.[115,125] The structure of the complex aluminum hydride does not appear to affect the isomer ratio obtained on reduction of **16a** except for the reagent $NaAlH_2(OCH_2CH_2OMe)_2$ which yields[125] essentially pure 1,4 isomer **18a**.

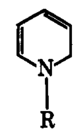
Appreciable quantities of the diol **19b** accompanied[118] the dihydropyridines **17b,c** and **18b,c** on reduction of the pyridines **16b,c** with lithium aluminum hydride (see also ref 126). The substitution of a methyl group in the 2 position of **16b** lowered the yield[126] of the corresponding 1,4-dihydropyridine. In other cases only the ester groups were reduced.[126–128] The alleged formation of a product in which both the ring and the ester groups have been reduced[129] should be reinvestigated.

3,5-Dibromopyridine was said[126] to afford a very unstable dihydro product. Reduction of an *N*-aryl-2-pyridone to the corresponding 1,2-dihydropyridine[130] has been reported without conclusive evidence.

Borohydride reduction of pyridinium salts or their alkyl derivatives yields unstable dihydropyridines which have been detected spectroscopically.[131,132] These dihydropyridines are usually reduced further to tetrahydropyridines[10,133–135] (see section VI.B.2) unless the hydrogen ion concentration is reduced by the addition of alkali[30,133] or cyanide.[136] In that case a mixture of 1,2- and 1,6-dihydropyridines, *e.g.*, **23a,b** results.[133]



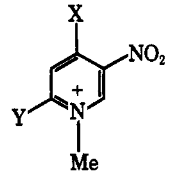
23a, R_1 = H; R_2 = Me
b, R_1 = Me; R_2 = H



24a, R = C_6H_5
b, R = $C(C_6H_5)_3$

1-Phenylpyridinium chloride afforded[71] the 1,2-dihydropyridine **24a** in good yield accompanied by the 1,4 isomer (~20%), while 1-triphenylmethylpyridinium fluoroborate gave[137] **24b** (77%) together with the corresponding 1,4 isomer (23%). Quaternary salts of pyridine or picoline with acetobromoglucose were erroneously reported[83,86] to give the corresponding 1,4-dihydropyridines, *i.e.*, the same product which is obtained on dithionite reduction (see section IV.A.1.c). However, recent spectroscopic evidence[138] shows these to be the expected 1,2 isomers.

Borohydride reduction of the 3-nitropyridinium salts **25** is remarkably regiospecific.[139,140] Thus **25a** affords the corresponding 1,4-dihydropyridine, **25b** the 1,2 isomer, and **25c** the 1,6-dihydro derivative.



25a, X = Y = H
b, X = H; Y = Me
c, X = OMe; Y = H

The 3-cyanopyridinium salt **26a** is reduced to a mixture of the corresponding di- and tetrahydropyridines **28a** and **29a** in methanol.[133] In the presence of alkali the isomeric 1,2- and 1,6-dihydropyridines **27a** and **28a** were isolated.[64,133] The reduction of dihydropyridines to tetrahydropyridines is discussed in section VI.B.2. The salt **26b**, which has a bulky substituent on the nitrogen, was reduced to a mixture of the isomeric dihydropyridines **27b** and **28b** in methanol; the 1,6 isomer **28b** was isolated from it by crystallization.[141]

The presence of a methyl substituent in the 4 position of **26b** did not affect the course of the reduction and again af-

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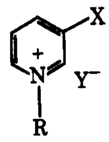
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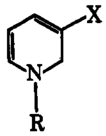
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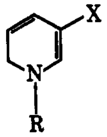
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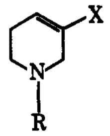
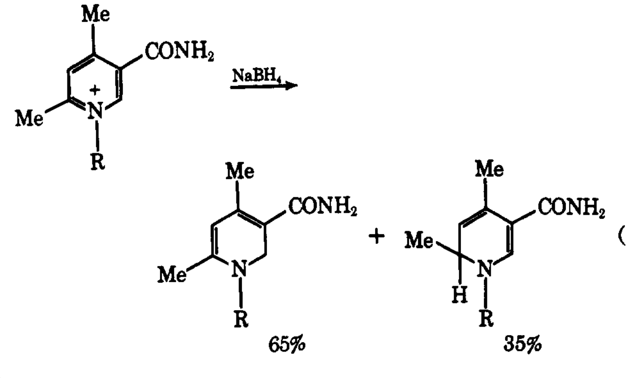

29

a, X = CN; Y = I; R = Me
b, X = CN; Y = Br; R = 2,6-$Cl_2C_6H_3CH_2$
c, X = CO_2Me; Y = I; R = Me
d, X = CO_2Me; Y = Br; R = 2,6-$Cl_2C_6H_3CH_2$
e, X = $CONH_2$; Y = $MeOSO_3$; R = Me
f, X = $CONH_2$; Y = I; R = *n*-Pr
g, X = $CONH_2$; Y = Br; R = $Cl_2C_6H_3CH_2$
h, X = $CONH_2$; Y = Cl, Br; R = $C_6H_5CH_2$
i, X = $CONH_2$; Y = Cl; R = R′ = $PrOCH_2$
j, X = $CONH_2$; Y = Cl; R = tetraacetylglucopyranosyl

forded[142] a mixture of the corresponding 1,2- and 1,6-dihydropyridines. However, the 4,6-dimethyl derivative of **26b** yielded only the corresponding 1,2-dihydropyridine owing to a combination of steric and electronic effects.[142]

Borohydride reduction of the ester **26c** similarly afforded[143,144] a mixture of the unstable 1,6-dihydropyridine **28c** and the tetrahydropyridine **29c**. In alkaline solution the 1,2-dihydropyridine **27c** together with the tetrahydro derivative **29c** were formed. 2-Methoxycarbonyl-1-methylpyridinium iodide similarly afforded a mixture of the corresponding 1,6-dihydro- and 1,2,5,6-tetrahydropyridines while in alkaline solution the 1,2-dihydro derivative was obtained.[145] Similar results were reported for 4-methoxycarbonyl-1-methylpyridinium iodide.[143] Borohydride reduction of **26d** gave[65] the crystalline 1,6-dihydropyridine **28d**. The presence of a 2-methyl group in **26d** (ethyl ester) and the replacement of the ester grouping by $-CH{=}NNHC_6H_5$ did not affect the nature of the reduction product.[65]

It has been shown[65,146,147] that the main products of the borohydride reduction of the nicotinamide derivatives **26e–h** are the corresponding 1,6-dihydropyridines **28e–h**. It has been variously claimed that the 1,4 isomer[148] or the 1,2 isomer[149] was formed along with the 1,6-dihydropyridine. Recent studies employing spectroscopic techniques[62] have shown that the 1,6-dihydro derivatives **28h–j** are formed on borohydride reduction of the corresponding pyridinium salts and that the introduction of a 4-methyl group into **26h–j** does not affect the course of the reaction.[62,142] Substitution of the amide hydrogens in **26h** by alkyl or aryl groups gave analogous products.[65] However, the nature of the anion Y in the pyridinium salt appears to have some effect.[52] Introduction of methyl groups into the 2 and 4 positions of **26g** gave[142] a mixture of the corresponding 1,2- and 1,6-dihydropyridines as shown in eq 5, in contrast with earlier findings.[150]



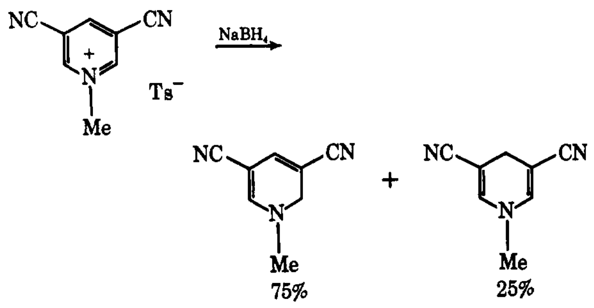
R = $Cl_2C_6H_3CH_2$

(5)

In the light of the above more recent results some older formulations[52,83,151–154] might be revised.

The borohydride reduction of NAD was shown[155] to give a product which had only 50% of the activity of NADH. More recent work[7,156] has shown that a mixture of the 1,2, 1,4, and 1,6 isomers of NADH was formed in this reaction.

3,5-Disubstituted pyridinium salts have a greater tendency to form dihydropyridines on borohydride reduction than do 3-substituted pyridinium salts. The products from the reduction of the symmetrically substituted dinitriles and diesters are generally mixtures of 1,2- and 1,4-dihydropyridines with the former predominating, *e.g.*,[157] eq 6.



(6)

3,5-Dicyano-1,2,4,6-tetramethylpyridinium tosylate could not be reduced with borohydride in alkaline solution since proton abstraction took place instead; at pH 5.5–6.5 the corresponding 1,2-dihydropyridine was formed.[158]

Some authors have claimed[52,65] that only the 1,2 isomers were formed; in the case of **30a** it was alleged[150] that the corresponding 1,2-[52] or 1,4-[65] dihydropyridine was formed exclusively depending on the reaction conditions.

Borohydride reduction of the unsymmetrically substituted pyridinium salts **31a,b** gave a mixture of the corresponding 1,2-, 1,4- and 1,6-dihydropyridines as shown[157] by nmr.

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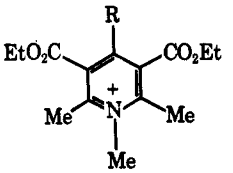
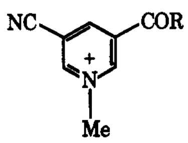


30a, R = H
b, R = C_6H_5
c, R = Me



31a, R = OEt
b, R = NH_2

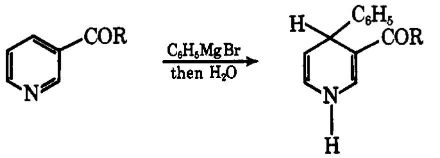
Lithium aluminum hydride reduction of **30b** is reported[51] to lead to the 1,2-dihydropyridine. Similar results were also obtained for alkylpyridinium salts.[26,65]

b. Addition of Organometallic Reagents

Dihydropyridines have been prepared by the action of organometallic reagents on pyridines, pyridine oxides, or pyridinium salts.

Pyridine and alkylpyridines react with lithium alkyls or aryls to give 2-substituted 1-lithio-1,2-dihydropyridines[159–161] which have been isolated as crystalline solids in some cases.[162] These have been converted into the unstable 1,2-dihydropyridines by hydrolysis, and into the corresponding pyridines by loss of lithium hydride on heating[163,164] or on treatment with oxygen.[162]

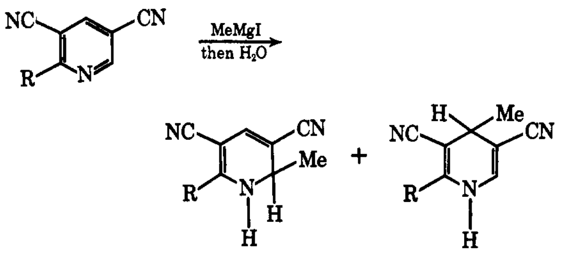
Reaction of the pyridyl ketones **32a–c** with Grignard reagents affords 1,4-dihydropyridines[165,166] as shown in eq 7. Attack of the reagent on the carbonyl group takes place[165,166] only with **32a**.



(7)

32a, R = C_6H_5 45%
b, R = mesityl 63%
c, R = duryl 88%

The action of Grignard reagents on substituted 3,5-dicyanopyridines has been developed as a useful synthetic method.[167–169] Unlike the attack of complex hydrides (section IV.A.1.a) reaction takes place only at the unsubstituted positions. Thus in the case of a pyridine with two nonequivalent positions a mixture of 1,2- and 1,4-dihydropyridines is formed according to eq 8; these may be separated by chromatography.[170]

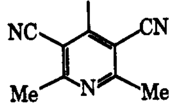


R = H or Me

(8)

On the other hand, if only one unsubstituted position is available, a single product results,[168,170,171] as in the case of 3,5-dicyano-2,4-dimethylpyridine which with methylmagnesium iodide affords[168,170] 3,5-dicyano-2,4,6-trimethyl-1,2-dihydropyridine.

Predictably, reaction of **33a** with Grignard reagents led to the expected 1,4-dihydropyridine, but some attack on the cyano group was also observed[168,172] (see also ref 173). No dihydropyridine was formed by the action of methylmagnesium iodide on **33b**[169] or on **33c**.[173,174]

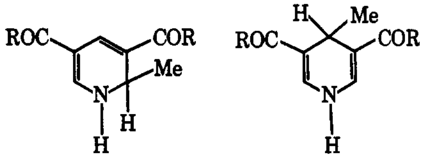


33a, R = H
b, R = Me
c, R = CO_2Et

Essentially the same results were obtained when lithium alkyls were used[171,172] instead of Grignard reagents except for a greater tendency for attack at the cyano groups.

The adducts of methylmagnesium iodide with 3,5-dicyanopyridines have been isolated and shown[106] to be 1-magnesiodihydropyridines of variable composition.

The dimethyl and diethyl esters of pyridine-3,5-dicarboxylic acid **16b,c** react with methylmagnesium iodide to give[80,118] mixtures of the dihydropyridines **34a**, **35a** and **34b**, **35b** together with some diol **19c** formed by reaction of the ester groups[118] (see also ref 175). 3,5-Diacetylpyridine gives **34c**, **35c** in low yield, the main product again being the diol **19c**, formed by attack of the reagent on the carbonyl groups.[122]



34 **35**

a, R = OMe
b, R = OEt
c, R = Me

The reactivity of the various positions in substituted 3,5-dicyanopyridines has been interpreted by means of simple HMO treatment.[104,118,124]

Pyridine 1-oxide reacts[176] with phenylmagnesium bromide to give a compound formulated as **36a** which has recently[176a] been shown to be acyclic.

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(159) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).
(160) R. Foster and C. A. Fyfe, *Tetrahedron*, **25**, 1489 (1969).
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(163) K. Ziegler and H. Zeiser, *Ber.*, **63**, 2111 (1930).
(164) G. S. Giam and J. L. Stout, *Chem. Commun.*, 478 (1970).
(165) R. C. Fuson and J. J. Miller, *J. Amer. Chem. Soc.*, **79**, 3477 (1957).
(166) R. E. Lyle and D. A. Nelson, *J. Org. Chem.*, **28**, 169 (1963).
(167) R. Lukeš and J. Kuthan, *Angew. Chem.*, **72**, 919 (1960).
(168) R. Lukeš and J. Kuthan, *Collect. Czech. Chem. Commun.*, **26**, 1422 (1961).
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(170) J. Kuthan, E. Janečková, and M. Havel, *ibid.*, **29**, 143 (1964).
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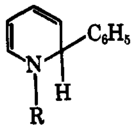
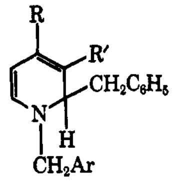
(173) J. F. Biellmann, H. J. Callot, and M. P. Goeldner, *Tetrahedron*, **26**, 4655 (1970).
(174) J. F. Biellmann, private communication.
(175) J. F. Biellmann and H. J. Callot, *Tetrahedron*, **26**, 4799 (1970).
(176) T. Kato and H. Yamanaka, *J. Org. Chem.*, **30**, 910 (1965).
(176a) T. J. Van Bergen and R. M. Kellogg, *ibid.*, **36**, 1705 (1971).



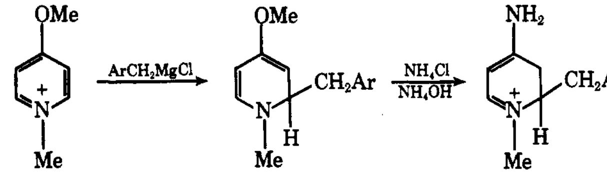
36a, R = OH
b, R = Me



37a, R = R′ = Me
b, R, R′ = $(CH_2)_4$

Initial attempts to isolate a dihydropyridine from the reaction of 1-methylpyridinium iodide with a Grignard reagent failed,[177] presumably because of the instability of the product. However, more recently **36b** was synthesized[178] using phenyllithium. The dihydropyridines **37a,b** were prepared[179–181] by the action of Grignard reagents on pyridinium salts and used in further reactions without purification owing to their instability. A related reaction is reported[182] in the patent literature. The structure of the product from nicotine methiodide with methylmagnesium iodide[15] has not been established with certainty. Reaction of 3,5-diethyl-1-phenyl-2-propylpyridinium iodide with methylmagnesium iodide gave a product which was originally[69] believed to be a 1,4-dihydropyridine but is now[26] shown to be the 1,6 isomer. 1-Methyl-2,4,6-triphenylpyridinium perchlorate with benzylmagnesium chloride afforded[183] 4-benzyl-1-methyl-2,4,6-triphenyl-1,4-dihydropyridine.

4-Methoxy-1-methylpyridinium iodide reacted with Grignard reagents (see ref 513) to give unstable 1,2-dihydropyridines which were converted into the more stable salts as shown in eq 9.



(9)

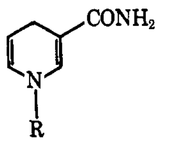
Recently a method has been described[63] in which a mixture of a 4-alkylpyridine and ethyl chloroformate (which react *in situ* to give the 1-ethoxycarbonylpyridinium salt) is treated with Grignard reagent to afford 1-ethoxycarbonyl-2,4-dialkyl-1,2-dihydropyridines.

Quaternary salts of nicotinic esters or nitriles react with Grignard reagents or with cadmium alkyls to give[184,185] the corresponding 1,6-dihydropyridines as the main product, accompanied by some 1,2 isomer. Cadmium alkyls may be used to alkylate the ring of nicotinic esters.[185] Salts of 1,4,6-trimethylnicotinic esters afford only the 1,2-dihydropyridine with cadmium alkyls; the presence of a methyl group in the 5 position does not affect the course of the reaction.

c. Dithionite Reduction

The observation that NAD could be converted into NADH by sodium dithionite[186] led to the preparation of numerous model compounds by this method. Reduction of 3-substituted or 3,5-disubstituted pyridinium salts with sodium dithionite in mildly basic solution affords the corresponding 1,4-dihydropyridines. The 1,2 or 1,6 isomers are formed only in exceptional cases. Sodium hydroxymethylsulfoxylate can replace[157] sodium dithionite but no dihydropyridines are obtained with zinc dithionite.[187]

1-Tetraacetylglucopyranosylpyridinium bromide was reduced to a product originally[20,81,83] formulated as a 1,2-dihydropyridine which has recently[138] been shown to be the 1,4 isomer. Numerous 1,4-dihydronicotinamides **13** have been prepared where R is alkyl,[52,54,152,154,188–191] benzyl or 2,6-dichlorobenzyl,[62,65,146,147,187,192–195] alkoxymethyl,[62,84] 2-chloro- or 2-hydroxyethyl,[196] or a sugar residue.[20,62,81,197]



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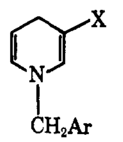

38

Similarly a number of 1-alkyl-3-cyano-1,4-dihydropyridines have been synthesized.[64,198,199] Some of the products had earlier been formulated as 1,2- or 1,6-dihydropyridines,[54,81,151,188–191,200] but these assignments are probably incorrect.

The 1,4-dihydropyridines **38** with various substituents in the 3 position have been prepared with X = $CH{=}NNHC_6H_5$, COMe, CO_2H, CO_2R, $CONMe_2$, $CONHC_6H_5$, 4-methyl-2-thiazolyl, benzoyl, and 2-benzthiazolyl.[65,84,193,195,198] A spectroscopic study of a series of dihydropyridines **38** has been carried out.[62] Dithionite reduction of some pyridinium 3-sulfonamides afforded products which were assigned the 1,2-dihydropyridine structure[201] although this assignment is probably not correct. No dihydropyridines could be isolated[65] from the pyridinium salts **26** when X was hydrogen or alkyl.

Introduction of a methyl group into the 2, 4, or 6 position of a pyridinium salt with an electron-withdrawing substituent

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(177) M. Freund and G. Bode, *Ber.*, **42**, 1746 (1909).

(178) R. Grashey and R. Huisgen, *Chem. Ber.*, **92**, 2641 (1959).

(179) R. Grewe and A. Mondon, *ibid.*, **81**, 279 (1948).

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(181) E. L. May and E. M. Fry, *J. Org. Chem.*, **22**, 1366 (1957).

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(183) K. Dimroth, K. Wolf, and H. Kroke, *Justus Liebigs Ann. Chem.*, **678**, 183 (1964).

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(186) O. Warburg, W. Christian, and A. Griese, *Biochem. Z.*, **282**, 157 (1935).

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(188) P. Karrer and F. Benz, *Helv. Chim. Acta*, **19**, 1028 (1936).

(189) P. Karrer and F. J. Stare, *ibid.*, **20**, 418 (1937).

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(193) D. C. Dittmer and R. A. Fouty, *J. Amer. Chem. Soc.*, **86**, 91 (1964).

(194) W. S. Caughey and K. A. Schellenberg, *J. Org. Chem.*, **31**, 1978 (1966).

(195) J. F. Biellmann and H. J. Callot, *Bull. Soc. Chim. Fr.*, 1154 (1968).

(196) O. M. Friedman, K. Pollak, and E. Khedouri, *J. Med. Chem.*, **6**, 462 (1963).

(197) P. Karrer and B. H. Ringier, *Helv. Chim. Acta*, **20**, 622 (1937).

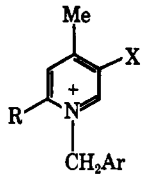
(198) J. H. Supple, D. A. Nelson, and R. E. Lyle, *Tetrahedron Lett.*, 1645 (1963).

(199) B. J. S. Wang and E. R. Thornton, *J. Amer. Chem. Soc.*, **90**, 1216 (1968).

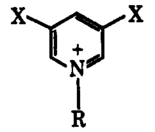
(200) P. Karrer, *Justus Liebigs Ann. Chem.*, **539**, 297 (1939).

(201) P. Karrer and W. Manz, *Helv. Chim. Acta*, **29**, 1152 (1946).

in the 3 position again gives the expected 1,4-dihydropyridine.[62,65,184,202] However, in the case of **39a** the 1,6-dihydropyridine (20%) accompanies the 1,4 isomer.[142] The 4,6-dimethyl derivative **39b** affords only the 1,4-dihydropyridine contrary to earlier[150] work, while **39c** forms a mixture of 1,2- and 1,6-dihydropyridines (2:3) and **39d** yields the 1,2-derivative exclusively.[142] The reasons for this unusual behavior are not properly understood.



39a, X = CONH$_2$; R = H
b, X = CONH$_2$; R = Me
c, X = CN; R = H
d, X = CN; R = Me



40a, X = CN
b, X = CONH$_2$
c, X = CO$_2$R

Treatment of 3,5-dicyano-1,2,4,6-tetramethylpyridinium tosylate with sodium hydroxymethylsulfoxylate proceeded slowly and yielded[158] the corresponding 1,4-dihydropyridine accompanied by 15–20% of the 1,2 isomer.

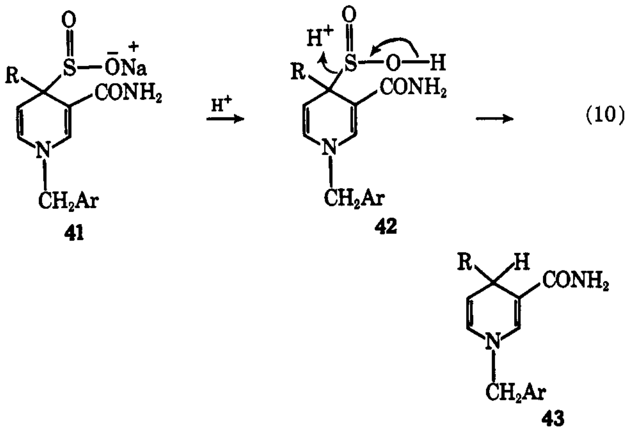
Isolation of a dihydropyridine from the dithionite reduction of 3-benzoyl-1-methyl-4-phenylpyridinium iodide failed.[166]

Dithionite reduction of pyridinium salts with electron-withdrawing substituents in the 3 and 5 positions affords exclusively the corresponding 1,4-dihydropyridines. In this way the pyridinium salts **30a–c**,[37,52,65,203,204] **31a,b**,[157] **40a**,[157] **40b**,[65,192,205] and **40c**[65] were converted into the corresponding 1,4-dihydropyridines. 3,5-Diacetyl-1,4-diphenyl-1,4-dihydropyridine[206] was prepared analogously. Diethyl 1,2,6-trimethyl-1,4-dihydropyridine-3,4-dicarboxylate was alleged[37] to be the product obtained by dithionite reduction of the corresponding pyridinium salt, but adequate structure proof is lacking.

The mechanism of dithionite reduction has been elucidated.[194,195,207] The reaction proceeds *via* an intermediate sodium sulfinate, *e.g.*, **41a**, which is stable in alkaline solution and which has been isolated. In neutral or acid solution the salt **41** is converted into the unstable acid **42** which decomposes as shown in eq 10. Earlier work[192,205] which formulated the intermediate sulfinates as 1,2-dihydropyridines is probably incorrect as is the formation of a charge-transfer complex.[208]

It has not been unequivocally established that the salt **41** is the primary addition product and a one-electron process has not been rigorously excluded; radical ions have been detected in certain analogous reactions.[209,210]

When dithionite reduction was carried out in deuterium oxide the monodeuterated dihydropyridine **43b** was formed.[194] Repeated oxidation to the pyridinium salt followed by dithionite reduction in D$_2$O yields the 4,4-dideuterio derivative,[194] and several deuterated dihydropyridines have been prepared in this way.[193,194,199]



41 **42** **43** (10)

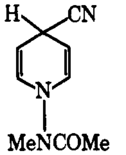
a, R = H; **b,** R = D

d. Addition of Cyanide Ion

The cyanide ion, which has a lower nucleophilicity than the reagents discussed in sections IV.A.1.a–c, reacts only with the more electron-deficient pyridinium salts.

The reaction of 1-methylpyridinium iodide with cyanide ion has been investigated[160] by nmr. The unstable adduct **44**, obtained by the action of cyanide on the corresponding pyridinium salt, has been isolated.[211] Similarly, the reaction of cyanide ion with pyridinium salts having electron-withdrawing substituents in the 3 position[75,111,160,212–217] and the 3,5 positions[75,111,160] have been studied spectroscopically. Formation of 1,4-dihydro adduct is usually reversible,[214] and rate and equilibrium constants have been measured.[214–218] Substituent and solvent effects have also been examined.[212,214,215]

Some cyano dihydro derivatives have been isolated, *e.g.*, **45b**,[148,219] **45c,d**,[215,220] and **45e**[199,215] (for further examples of **45** and the corresponding 4-methyl derivatives see ref 216 and 217). The ketone **45a** was described[166] as an unstable



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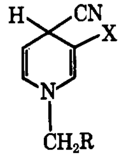
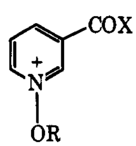


45a, R = H; X = COC$_6$H$_5$
b, R = Ar; X = COMe
c, R = H; X = CONH$_2$
d, R = Ar; X = CONH$_2$
e, R = H; X = CN



46a, R = Me; X = OEt
b, R = Me; X = NH$_2$
c, R = Et; X = NH$_2$
d, R = Bu; X = NH$_2$

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(202) A. Stock and F. Ötting, *Tetrahedron Lett.*, 4017 (1968).

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(215) R. N. Lindquist and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 1269 (1968).

(216) A. C. Lovesay, *J. Med. Chem.*, **12**, 1018 (1969).

(217) A. C. Lovesay, *ibid.*, **13**, 693 (1970).

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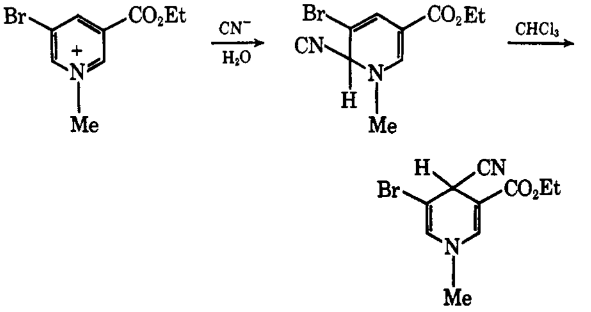
(220) M. Marti, M. Viscontini, and P. Karrer, *Helv. Chim. Acta*, **39**, 1451 (1956).

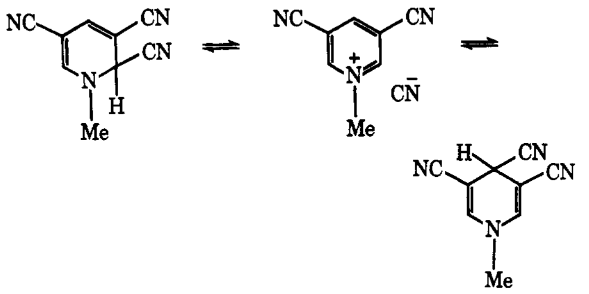
solid. Cyanide adducts of **46**, which may be detected spectroscopically, readily eliminate ROH to form cyanopyridines.[213,221]

It has been shown[75] that cyanide attack takes place initially in the 6 position to give the product of kinetic control. On standing this is converted into the thermodynamically more stable 1,4 derivative as shown in eq 11. The generality of this pathway has been questioned.[160,215]



(11)

Another well-documented case is cyanide addition to 3,5-dicyano-1-methylpyridinium tosylate.[222,223] The initially formed 1,2-dihydropyridine on heating is converted into the 1,4 isomer. It was suggested[223] that the rearrangement proceeds *via* an intermediate pyridinium salt as shown in eq 12. Cyanide addition to 1-methyl-3,4,5-tricyanopyridinium salts again takes place in the 2 position affording 1-methyl-2,3,4,5-tetracyano-1,2-dihydropyridine.[222,223] These results were explained by the mesomeric and inductive effects of the cyano groups which stabilize the dihydropyridines.



(12)

Cyanide addition to the fully substituted 3,5-dicyano-1,2,-4,6-tetramethylpyridinium tosylate afforded[158] the 1,4-dihydropyridine in 43% yield, the other products being the isomeric pyridine methenes (analogous to **2a** and **3a**) resulting by proton abstraction from the 2- and 4-methyl groups, respectively.

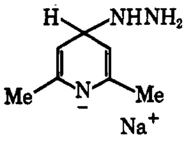
The structures of some cyanide adducts have not been rigorously established, 1,4-dihydro[224,225] and 1,2-dihydro[50,206] structures having been somewhat arbitrarily assigned to the products.

The recent findings[209,226] of intermediate radical ions in cyanide addition imply that a one-electron step may be significant in these reactions.

e. Reaction with Other Nucleophiles

In principle it is possible to prepare dihydropyridines by addition of various nucleophiles to pyridines or pyridinium salts. Whether such a reaction is a useful preparative method depends on the reactivity of the pyridine or pyridinium salt, the nucleophilicity of the reagent, and the stability of the dihydropyridine.

Pyridines react only with powerful nucleophiles. Thus the action of sodium hydrazide on 2,6-lutidine was reported[227] to give the adduct **47** which was stable in boiling benzene.



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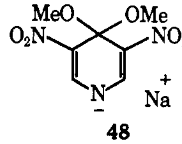
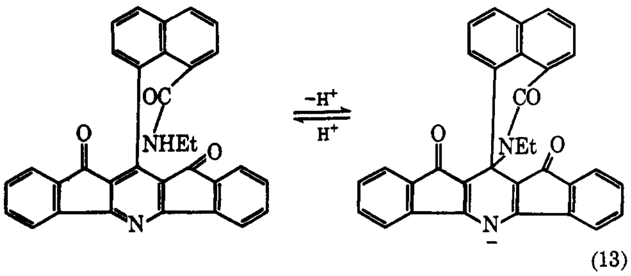


48

The Meisenheimer complexes **48** were prepared[228,229] by the action of sodium methoxide on 4-methoxy- or 4-chloro-3,5-dinitropyridine. Analogous products or their 1,2 isomers, obtained from other substituted 3,5-dinitropyridines,[230–234] were observed spectroscopically; they readily aromatized to pyridines.

Certain polyclic pyridines are converted into their dihydro derivatives by intramolecular nucleophilic attack,[235–237] *e.g.*,[238] eq 13. These dihydropyridine anions have found application in a color test for primary amines.



(13)

Bisulfite reduction converts a polycyclic pyridine, *e.g.*, **20**, into the corresponding dihydropyridine.[239] However, simple pyridinium salts give complex products since the resulting dihydropyridines are themselves able to react with bisulfite (see section VI.C.1).

Pyridinium salts, being more electrophilic than pyridines, react with a variety of nucleophiles. Thus, pyridinium salts

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(221) K. Wallenfels and H. Schüly, *Angew. Chem.*, **70**, 471 (1958).

(222) K. Wallenfels and W. Hanstein, *Angew. Chem. Intern Ed. Engl.*, **4**, 869 (1965); *Angew. Chem.*, **77**, 861 (1965).

(223) K. Wallenfels and W. Hanstein, *Justus Liebigs Ann. Chem.*, **709**, 151 (1967).

(224) O. Mumm and G. Hingst, *Ber.*, **56**, 2301 (1923).

(225) K. Wallenfels and H. Schüly, *Justus Liebigs Ann. Chem.*, **621**, 86 (1959).

(226) L. J. Winters, N. G. Smith, and M. I. Cohen, *Chem. Commun.*, 642 (1970).

(227) T. Kauffmann and H. Hacker, *Chem. Ber.*, **95**, 2485 (1962).

(228) J. E. Dickenson, L. K. Dyall, and V. A. Pickles, *Aust. J. Chem.*, **21**, 1267 (1968).

(229) P. Bemporad, G. Illuminati, and F. Stegel, *J. Amer. Chem. Soc.*, **91**, 6742 (1969).

(230) C. A. Fyfe, *Tetrahedron Lett.*, 659 (1968).

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(232) C. Abbolito, C. Iavarone, G. Illuminati, F. Stegel, and A. Vazzoler, *J. Amer. Chem. Soc.*, **91**, 6746 (1969).

(233) R. Schaah, F. Terrier, J. C. Halle, and A. P. Chartrousse, *Tetrahedron Lett.*, 1393 (1970).

(234) A. Chartrousse, F. Terrier, and R. Schaah, *C. R. Acad. Sci., Ser. C*, **271**, 1477 (1970).

(235) G. Vanags and E. I. Stankevich, *Zh. Obshch. Khim.*, **30**, 3287 (1960); *Chem. Abstr.*, **55**, 21119 (1961).

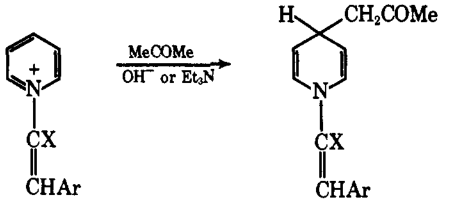
(236) L. Leitis, G. Duburs, M. Simanska, and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 41 (1963); *Chem. Abstr.*, **59**, 12182 (1963).

(237) L. Geita and G. Vanags, *Zh. Obshch. Khim.*, 93 (1960); *Chem. Abstr.*, **55**, 507 (1961).

(238) G. Duburs and G. Vanags, *Dokl. Akad. Nauk SSSR*, **134**, 1356 (1960); *Chem. Abstr.*, **55**, 10438 (1961).

(239) E. I. Stankevich and G. Vanags, *Dokl. Akad. Nauk SSSR*, **140**, 607 (1961); *Chem. Abstr.*, **56**, 4728 (1962).

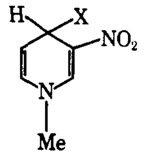
with bulky substituents on the nitrogen react with a number of carbanions derived from ketones, diethyl malonate, or nitromethane[61,240,241] as shown in eq 14. The structure of the resulting unstable 1,4-dihydropyridines was established spectroscopically.[61]



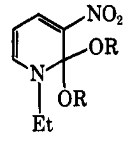
(14)

X = H or Ar′

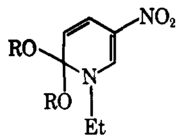
1-Methyl-3-nitropyridinium iodide reacted[139] with carbanions derived from malononitrile, cyanoacetic and malonic esters, phenacyl cyanide, and indanone, and with piperidine, to give the 1,4-dihydropyridines **49a–f** while treatment of the 2- or 6-chloro-3-nitropyridinium salts with sodium methoxide yielded[140] the dihydropyridines **50** and **51**, respectively.



49a, $X = CH(CN)_2$
b, $X = CH(CN)CO_2Et$
c, $X = CH(CO_2Et)_2$
d, $X = CH(CN)COC_6H_5$
e, $X = C_9H_7O$
f, $X = NC_5H_{10}$

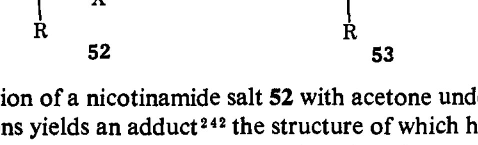


50, R = Me or $(CH_2)_2$



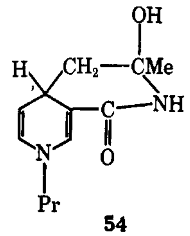
51

A series of 4-substituted dihydronicotinamides **53** was prepared from the corresponding pyridinium salts **52** with which they are in equilibrium.[225] Thus adducts, assumed to have structures **53**, were obtained with nitromethane and with sodium sulfide; the latter product may be oxidized to the corresponding disulfide.[225]

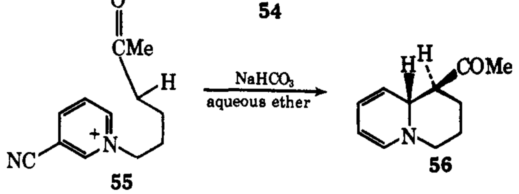


52 **53**

Reaction of a nicotinamide salt **52** with acetone under basic conditions yields an adduct[242] the structure of which has been confirmed[60] as **54**. In a related reaction ring closure of **55** to **56** takes place under unusually mild conditions.[244] An intramolecular cyclization has been proposed for a 2-pyridone derivative,[245] but no structural evidence has been presented.

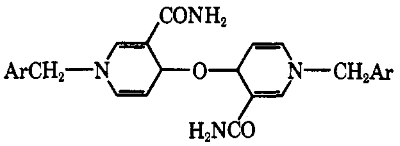


54



55 **56**

The action of hydroxide ion on pyridinium salts was first reported in 1881[246] and is further discussed in section VI.A.3. Treatment of 3-substituted pyridinium salts with hydroxide ion has been described by several workers.[59,219,225,247] The products were too unstable for isolation and tentative structure assignments were made on the basis of uv spectra.[219,225] The action of aqueous sodium hydroxide on the nicotinamide salt **52** gave a product formulated[59] as **57** (for another dimer of similar structure see ref 219). On treatment of **57** with ethanol a cyclic trimer was formed.[59]



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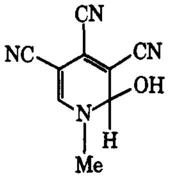

58

The pseudo base **58**, prepared from the corresponding pyridinium salt, could be isolated.[222,223] The structure of an analogous compound derived from a 3,5-diacetyl-1,4-diphenylpyridinium salt has not been established with certainty.[206]

Treatment of a 1-*tert*-butoxypyridinium salt with methoxide ion yielded 1-*tert*-butoxy-2-methoxy-1,2-dihydropyridine, the structure of which was confirmed[248] by nmr.

The reversible addition of sulfite ion to pyridinium salts **52** ($X = SO_3^-$) has been investigated by spectroscopy, and the equilibrium constants have been determined[249] under various conditions and with other pyridinium substrates. The product was assumed to be the 1,4-dihydropyridine **53**. Similarly, arylsulfinate ion reacted with **52** to give a charge-transfer complex whereas 1-benzyl-3-bromopyridinium bromide gave a stable dihydropyridine under these conditions.[250]

The action of alkaline hydrogen peroxide on the nicotinamide salts **52** led[251] to the isolation of secondary products formed from an intermediate dihydropyridine hydroperoxide.

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(240) F. Kröhnke, K. Ellegast, and E. Bertram, *Justus Liebigs Ann. Chem.*, **600**, 176 (1956).

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(242) J. W. Huff, *J. Biol. Chem.*, **167**, 151 (1947).

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(246) A. W. Hofmann, *Ber.*, **14**, 1497 (1881).

(247) R. M. Burton and N. O. Kaplan, *Arch. Biochem. Biophys.*, **101**, 139 (1963).

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(249) G. Pfleiderer, E. Sann, and A. Stock, *Chem. Ber.*, **93**, 3083 (1960).

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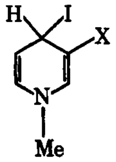
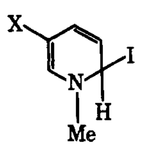
(251) D. W. Bristol and D. C. Dittmer, *J. Org. Chem.*, **35**, 2487 (1970).

The nature of pyridinium halides is still an open question. In 1932 Hantzsch[252] suggested covalent structures, *e.g.*, **59a** or **60a**, for the yellow modification of 1-methylpyridinium iodide, on the basis of conductivity measurements. Later[253] an equilibrium between **60** and the ionic pyridinium salt was put forward as a result of uv spectroscopic studies. Such an equilibrium was invoked[225] to explain the solvent effects on the uv spectra of dihydronicotinamides such as **60b**. On the other hand, it has been suggested[254] that pyridinium halides are in equilibrium not with dihydropyridines such as **59** or **60** but with charge-transfer complexes. Further uv studies led to a more general theory[255] which stated that if a pyridinium salt formed a charge-transfer complex with an anion, attack would take place in the 4 position; if not, attack would take place in the 2 or 6 positions. An alternative view was advanced[256] correlating attack at the 2 and 4 positions in pyridines with the hardness and softness, respectively, of the nucleophile.



59

a, X = H
b, X = $CONH_2$



60

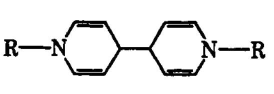
a, R = H
b, R = $CONH_2$

2. *One-Electron Reduction*

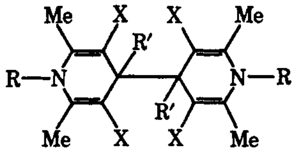
a. Reduction with Metals

Treatment of pyridines or pyridinium salts with metals can result in transfer of one electron into the lowest unoccupied molecular orbital with the formation of a radical intermediate which either dimerizes or else undergoes further reduction. Dimerization tends to take place in solvents of low polarity, but protic solvents are required for formation of monomeric pyridines. Metals such as sodium, sodium amalgam, zinc, or activated aluminum have been commonly used; occasionally magnesium, copper–zinc couple, or chromous salts have been employed.

The reaction of pyridine with sodium in aprotic solvents followed by treatment with moist ether yields[257] an unstable compound, presumably the tetrahydrobipyridyl **61a**, which could be dehydrogenated to 4,4′-bipyridyl.[258] Alkylation of the pyridine–sodium adduct gives a mixture of **61b** or **61c** together with the corresponding alkylpyridinium salt. The alkyl derivatives **61b,c** are obtained more conveniently by reduction of the corresponding alkylpyridinium salts with sodium amalgam[43,258–260] or with vanadous chloride.[261] Analogous tetrahydrobipyridyls **62a–d** have been prepared by reduction of suitable pyridinium salts[262–265] but rigorous structure proof is lacking. A compound resulting from the reduction of a pyridinium salt with amalgamated aluminum was formulated as **62d**,[44] but later it was regarded[37] as a 2,2′-tetrahydrobipyridyl. Reinvestigation of this and other[37,44,265] reduction products might clarify some contradictory findings. Reduction of 1-phenylpyridinium chloride with sodium amalgam yields largely 1-phenyl-1,4-dihydropyridine[43,67,68,71] with only small quantities of **61d**.[43,67]

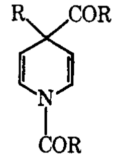


61a, R = H
b, R = Et
c, R = $C_6H_5CH_2$
d, R = C_6H_5
e, R = COMe
f, R = C_6H_5CO
g, R = CO_2Et
h, R = CO_2Na
i, R = SO_2Na

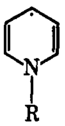


62a, R = R′ = Me; X = H
b, R = $C_6H_5CH_2$; R′ = X = H
c, R = Me; R′ = *i*-Bu; X = CO_2Et
d, R = R′ = Me; X = CO_2Et
e, R = H; R′ = Me; X = CO_2Et

The acylated tetrahydrobipyridyls **61e–g** are best prepared by the action of zinc on pyridine in acetic anhydride[72,266–268] or acid chlorides.[259,269–271] 4-Alkylpyridines, on the other hand, under these conditions formed[272] not the tetrahydrobipyridyls **61**[72,266] but the monomeric dihydropyridines **63**. More recently this reaction has been extended[273] to several 4-substituted pyridines which on treatment with zinc and methyl chloroformate yield a variety of products including 1-methoxycarbonyl- and 1,4-dimethoxycarbonyl-1,4-dihydropyridines and 2,2′-tetrahydrobipyridyls. Similarly, 4-triphenylsilyl-1,4-dihydropyridine is formed when pyridine is treated with lithium and hexaphenyltrisilane.[273a]



63, R = Me, Et, Pr



64, R = $C_6H_5CH_2$, C_6H_5CO, MeCO

Treatment of the sodium–pyridine adduct with carbon dioxide[274] or sulfur dioxide[21] has been claimed to give the tetrahydrobipyridyls **61h,i**, but no structure proof was given.

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(252) A. Hantzsch and A. Burawoy, *Ber.*, **65**, 1059 (1932).
(253) E. M. Kosower, *J. Amer. Chem. Soc.*, **77**, 3883 (1955).
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(259) E. Weitz, A. Roth, and A. Nelken, *Justus Liebigs Ann. Chem.*, **425**, 161, 187 (1921).
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(262) B. Emmert and O. Varenkamp, *Ber.*, **56**, 491 (1923).
(263) B. Emmert and O. Werb, *ibid.*, **55**, 1352 (1922).
(264) O. Mumm, O. Roder, and H. Ludwig, *ibid.*, **57**, 865 (1924).
(265) O. Mumm and H. Ludwig, *ibid.*, **59**, 1605 (1926).
(266) O. Dimroth and R. Heene, *ibid.*, **54**, 2934 (1921).
(267) O. Dimroth and F. Frister, *ibid.*, **55**, 1223 (1922).
(268) A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *J. Org. Chem.*, **29**, 2175 (1964).
(269) A. E. Arbuzov, *Bull. Acad. Sci. USSR, Classe Sci. Chim.*, 451 (1945); *Chem. Abstr.*, **42**, 5912 (1948).
(270) D. A. van Dorp and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **66**, 189 (1947).
(271) J. E. Colchester (Imperial Chemical Industries), British Patent 1,189,084 (1970); *Chem. Abstr.*, **73**, 25315b (1970).
(272) P. M. Atlani and J. F. Biellmann, *Tetrahedron Lett.*, 4829 (1969).
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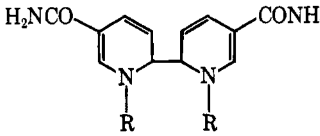
(273a) D. Wittenberg and H. Gilman, *Chem. Ind.* (*London*), 390 (1958).
(274) W. E. Kramer, L. A. Joo, and R. M. Haines, U. S. Patent, 3,147,-262 (1964); *Chem. Abstr.*, **61**, 13291 (1964).

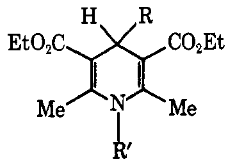
The formation of dimers such as **61** or **62** is supported by molecular orbital calculations[275] which show that **64** is a true representation of the π electron distribution in the intermediate radical; dimerization of two radicals **64** then leads to **61**.

A long-standing debate concerning the reversible dissociation of **61** to the radicals **64**[72,259,266,267,276–278] has been settled.[268] Modern techniques have established the absence of free radicals. The color of the "yellow form" obtained from **61e** on heating has been shown[268] to be due to small amounts of the colored 4,4′-dihydrobipyridyl. The thermolysis of tetrahydrobipyridyls is discussed in section IV.C.4.

Reduction of nicotinamide salts **52** *with zinc-copper couple or magnesium or chromous salts* yielded[279] a dimer which was formulated as the 6,6′-tetrahydrobipyridyl **65**. Recent nmr data do not entirely rule out the 4,4′-tetrahydrobipyridyl structure.[148]



65a, R = Pr
b, R = ArCH$_2$
c, R = Me



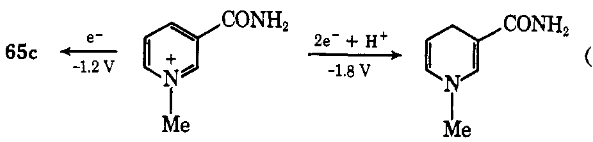
66a, R = Me; R′ = H
b, R = C$_6$H$_5$; R′ = H
c, R = C$_6$H$_5$; R′ = Me

In other instances reduction with metals yields monocyclic dihydropyridines. Treatment of pyridine with sodium in alcohol followed by hydroxylamine led[280] to the isolation of glutaraldehyde oxime; alkylpyridines behaved similarly[281] (see section VI.E). Reduction of certain Hantzsch pyridines with sodium amalgam[265] or amalgamated aluminum[44] yielded the monocyclic dihydropyridines **66a,b**; **66c** was similarly obtained from the corresponding pyridinium salt.[37] Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate was likewise obtained by reduction with amalgamated aluminum.[37,44] The reduction with sodium amalgam of 1-phenylpyridinium chloride[43,67,68,71] has been discussed above; similar results were obtained with 1-*p*-methoxyphenylpyridinium[68] and 1-methyl-4-phenylpyridinium[282] salts although the structures of the resulting 1,4-dihydropyridines have not been established with certainty.

Reduction of pyridinium salts with chromous ion is abnormal[283] since their half-wave potentials lie above that of the reducing agent. No explanation for this behavior has been advanced.

b. Electrolytic Reduction

Electrolytic reduction of 1-ethyl- and 1-benzylpyridinium salts at a platinum electrode gave[284] the dimers **61b** and **61c**, respectively, and several electrochemical preparations of dihydronicotinamides have been described.[152,154,285] Electrolysis of the salt of 1-methylnicotinamide at controlled potentials permitted the isolation of either 1-methyl-1,4-dihydronicotinamide or the 6,6′-tetrahydrobipyridyl **65c** according to eq 15. The corresponding 1-propyl derivative is said[286] to give the 4,4′-tetrahydrobipyridyl. However, this work conflicts with earlier[154] results and characterization of the products leaves something to be desired.

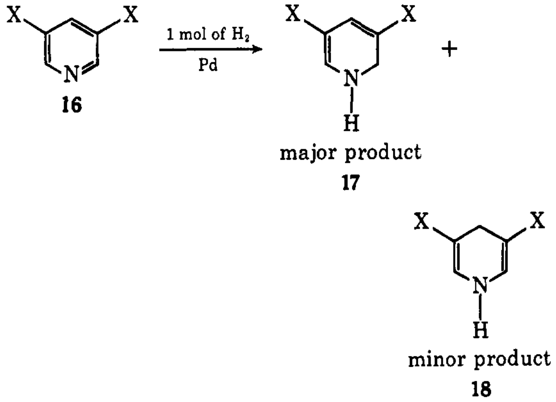


(15)

c. Catalytic Hydrogenation

This method is somewhat limited and has so far been used only for the preparation of some 3,5-disubstituted 1,2-dihydropyridines which are not accessible by other means. Hydrogenation must be carried out under controlled[37,287,288] conditions since the resulting dihydropyridines can undergo reduction (see section VI.B.1) or disproportionation[287–289] (see section VI.A.3).

Hydrogenation of the disubstituted pyridines **16a–d** yields products which consist mainly of the 1,2-dihydropyridines **17a–d** with only small amounts of the 1,4-dihydro isomers **18a–d** as shown in eq 16.



(16)

a, X = CN; **b**, X = CO$_2$Me; **c**, X = CO$_2$Et; **d**, X = COMe

Substitution of methyl groups, particularly in the 2,6 positions of **16**, reduces the rate of hydrogen uptake, and disproportionation and other reactions become competitive so that complex mixtures result.[288,290] Pentasubstituted pyridines do not take up hydrogen under these conditions.

Reduction of a substituent can compete with hydrogenation of the ring as shown[288] in eq 17.

Hydrogenation of the polycyclic compounds **67a,b** takes place[291] with formation of the corresponding 1,4-dihydro-

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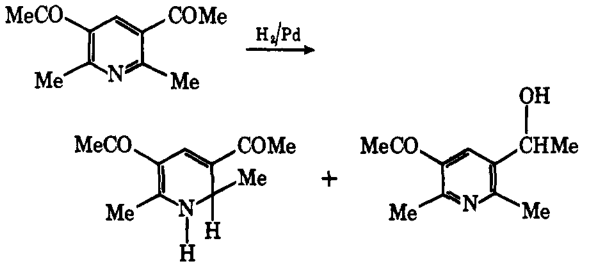
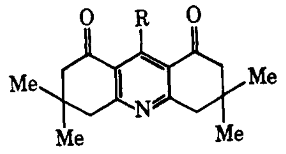
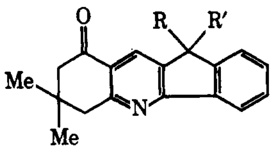


(17)

pyridine while under the same conditions **68a** is converted[292] into **68b**.

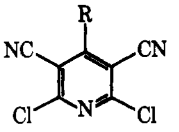


67a, R = H
b, R = C_6H_5

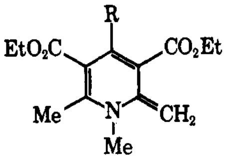


68a, R, R′ = O
b, R = H; R′ = OH

Hydrogenation of the dichloropyridines **69** yields the corresponding 4-alkyl-3,5-dicyano-1,2-dihydropyridines;[293] hydrogenolysis of the chlorine takes place prior to reduction of the ring.



69, R = Me or Et



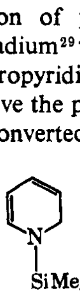
70a, R = H
b, R = Ar
c, R = alkyl

Hydrogenation of the pyridinemethenes **70** has been used[50,52,65,224] for the preparation of the corresponding 1,2-dihydropyridines. However, Karrer[52] has shown that the products were mixtures containing both 1,2- and 1,4-dihydropyridines. Some of the early work[265] might be usefully reinvestigated.

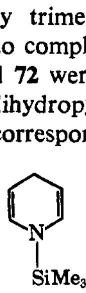
Pyridinium salts are reduced to tetrahydropyridines *via* 1,2- or 1,4-dihydropyridines which have been detected spectroscopically.[184]

d. Silylation

Trimethylsilylation of pyridine by trimethylsilane in the presence of palladium[294,295] leads to complex mixtures from which the dihydropyridines **71** and **72** were isolated. Methanolysis of **72** gave the parent 1,4-dihydropyridine. The picolines were also converted into the corresponding 1-trimethylsilyl dihydro derivatives, the reactivity being in the order 3-picoline > 4-picoline > 2-picoline.[295] A free-radical mechanism was suggested for trimethylsilylation. Hexachlorodisilane adds to pyridine in a similar manner.[295a]



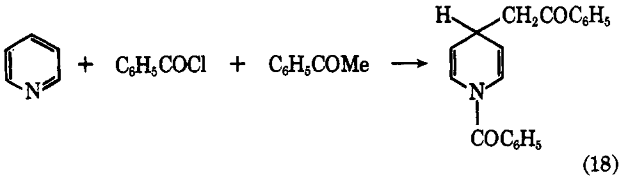
71



72

e. Miscellaneous

In the presence of acid chlorides pyridine reacts with acenaphthenone,[296] acetophenone,[11] homophthalic anhydride,[297] indoles,[298–301a] *N*-formylalanine,[302] and 5-acyloxyoxazoles[303] to yield 1,4-disubstituted 1,4-dihydropyridines as exemplified[11] in eq 18.



(18)

The action of dimethylaniline and benzoyl chloride gave[304] 4-(*p*-dimethylaminophenyl)pyridine; the intermediate dihydropyridine could not be isolated. On treatment with benzoyl chloride in dimethylformamide 4-picoline afforded[305] 1-benzoyl-4-methyl-1,4-dihydropyridine, whereas addition of 4-acyloxyoxazoles to 4-substituted pyridines resulted[303] in the formation of a 1,2-dihydropyridine. In a related reaction pyridine and acetic anhydride in the presence of niacytin or oxidized pyrrole degradation products yielded[306] the unstable 1-acetyl-1,2-dihydropyridine-2-acetic acid.

An ionic mechanism was proposed for this type of reaction,[297,303,307] but more recently a mechanism involving radicals has been suggested[275] based on semiempirical LCAO–MO methods (see also ref 272). Mechanistic studies of this kind of reaction seem desirable.

Dihydropyridines have been postulated[308,309] as intermediates in the transformation of pyridinyl radicals.

Pyridine reacts with silver phenylacetylide in the presence of benzoyl chloride to afford[310] the acetylenic 1,2-dihydropyridine **73a** and with methyl propiolate to give[311] **73b**. Hydrogen

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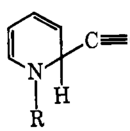
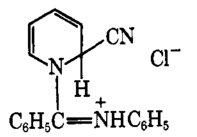
cyanide and the chloroimidate $C_6H_5CCl{=}NC_6H_5$ react[312] with pyridine with the formation of **74**.



73a, $R = COC_6H_5$; $R' = C_6H_5$
b, $R = CH{=}CHCO_2Me$; $R' = CO_2Me$

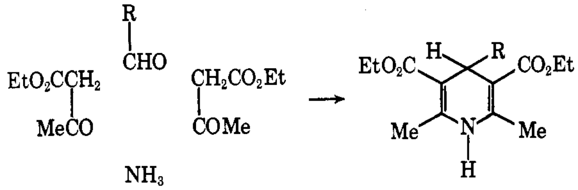


74

B. HANTZSCH SYNTHESIS AND RELATED CONDENSATIONS

1. Hantzsch Synthesis

The original Hantzsch dihydropyridine synthesis[1] consisted of the reaction of ethyl acetoacetate with aldehyde–ammonia which affords **75a** as shown in eq 19. This method has been widely used for the preparation of the dihydropyridines **75** where R is an aliphatic,[80,313–324] aromatic,[16,19,324–338] or heterocyclic[16–19,325,339–342] residue. α,β-Unsaturated aldehydes[48,324] and glyoxylic acid[175,343,344] have also been used in place of acetaldehyde.



(19)

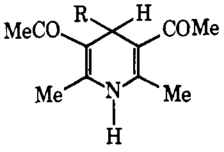
75a, R = Me
b, $R = C_6H_4NO_2$
c, R = H
d, $R = C_6H_5$
e, $R = CH_2CN$

1,3-Diketones have occasionally been used[57,336,345,346] instead of ethyl acetoacetate to give 3,5-diacyl-1,4-dihydropyridines **76**.

The Hantzsch synthesis is here defined as the reaction of an aldehyde with an active methylene compound and ammonia (or a primary amine). The reaction is usually carried out by warming the reagents in alcohol, and yields are good to excellent. For a summary of work up to 1957 see ref 8, pp 500 and 510; included are tables listing reagents, products, conditions, yields, and references.

2. Use of Enamines

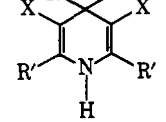
It was soon found[347] that ethyl 3-aminocrotonate (**77a**) could replace ethyl acetoacetate, and this modification has been used, for example, to prepare a series of dihydropyridines **78a** of medicinal interest.[17–19] Application of this method to the preparation of **75b** resulted in improved yields.[16] Reaction of terephthalaldehyde with **77a** gave the corresponding bisdihydropyridine.[348] In some instances an aldehyde has been treated with a 1:1 mixture of ethyl acetoacetate and **77a**,[17,19,327,349–351] although this method does not appear to have any significant advantages. Details on the above reactions are given in ref 8, pp 522 and 523.



76

$H_2NCR'{=}CHX$

77a, R′ = Me; $X = CO_2Et$
b, R′ = Me; X = CN
c, R′ = Ar; X = CN
d, $R' = p\text{-}MeC_6H_4$; X = CN



78a, R = quinolyl or aryl; $X = CO_2$ (alkyl), R′ = alkyl
b, X = CN; R′ = Me
c, X = CN; R′ = Ar

The use of 3-aminocrotononitrile (**77b**) leads to 3,5-dicyano-1,4-dihydropyridines **78b**.[352–357] An improved method has

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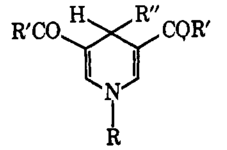
been described.[358,359] Similarly, 3-aryl-3-aminocrotononitriles (**77c**) afforded the related 2,6-diaryldihydropyridines.[356,360–362] Interestingly, reaction of salicylaldehyde with 3-aminocrotononitrile (**77b**) gave a product $C_{18}H_{14}N_2O_2$ (*i.e.*, $2C_7H_6O_2 + C_4H_6N_2 - 2H_2O$) instead of the expected dihydropyridine; however, the aryl derivative **77d** reacted normally.[356] Ketones,[360] chloromethyl ketones,[363] and glyoxylic acid[175,344,364] have been used instead of aldehydes; condensation is carried out in the presence of mineral acid. For summaries see ref 8, pp 523 and 527.

More recently, 3,5-diacyldihydropyridines lacking substituents in the 2,6 positions, **80**, have been prepared from β-amino-α,β-unsaturated ketones **79** in the presence of piperidine or acetic acid.[85,121,365–368] An alternative preparation of **80a** involved the sodium salt of acetoacetaldehyde, ammonium chloride, and hydrochloric acid.[369,370]

RNHCH=CHCOR′

79

a, R = H, R′ = Me



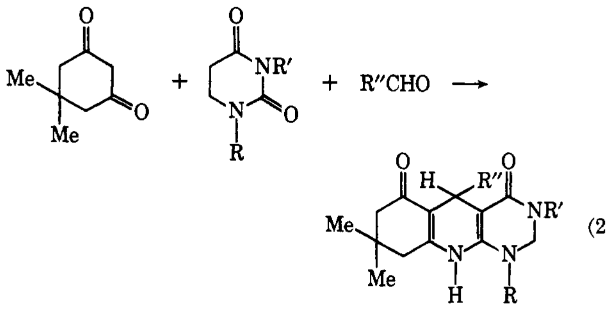
80

a, R = R″ = H; R′ = Me

Substituted 3-aminocyclohex-2-enones have been condensed[371] with aldehydes in acetic acid to give polycyclic dihydropyridines.

The use of two different enamines permits isolation of unsymmetrical dihydropyridines[349,350,372,373] (see ref 8, p 523). In one case[361] the symmetrical 3,5-dicyanodihydropyridine **78a** was obtained as a by-product.

Another method for preparing unsymmetrical 1,4-dihydropyridines consists of the condensation of aldehydes with cyclic 1,3-diketones such as cyclohexane-1,3-dione,[374] dimedone,[375,376] or indan-1,3-dione[377,378] and the enamines **77a**, **77b**, or **79**. 4-Aminouracil derivatives have similarly been condensed with an aldehyde and dimedone[379] as shown in eq 20. No symmetrical dihydropyridines have been found in any of these reactions.



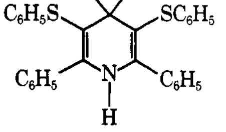
(20)

3. *Use of Ammonium Acetate–Acetic Acid*

This method sometimes works with active methylene compounds which do not react under the conditions of the Hantzsch synthesis. Thus **81** was converted[79] into the dihydropyridine **82**, and ω-cyanoacetophenone (**83**) reacted with aldehydes to give **84**. Surprisingly acetone, cyclopentanone, or cyclohexanone reacted[380] with **83** in the presence of ammonium acetate to give the 1,2-dihydropyridines **85a–c**. Analogously, acetone reacted with the sodium salt of acetoacetaldehyde and ammonium chloride to give 3,5-diacetyl-2,2-dimethyl-1,2-dihydropyridine; with aldehydes instead of acetone the 1,4-dihydropyridines **80** were formed.[370] These are the only authenticated instances of the formation of a 1,2-dihydropyridine in a Hantzsch-type synthesis (but see ref 333).

$$2C_6H_5SCH_2COC_6H_5 + C_6H_5CHO \xrightarrow[HOAc]{NH_4OAc}$$

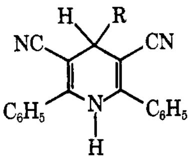
81



82

$C_6H_5COCH_2CN$

83



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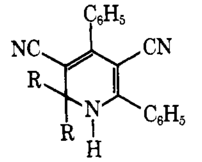

85a, R = Me

b, R, R = $-(CH_2)_4-$

c, R, R = $-(CH_2)_5-$

Cyclohexane-1,3-dione[374] and dimedone[381] afforded polycyclic 1,4-dihydropyridines with aldehydes and ammonium acetate–acetic acid.

4. *Use of 1,5-Diketones*

Since many active methylene compounds react with aldehydes to give 1,5-diketones, this behavior was exploited in another

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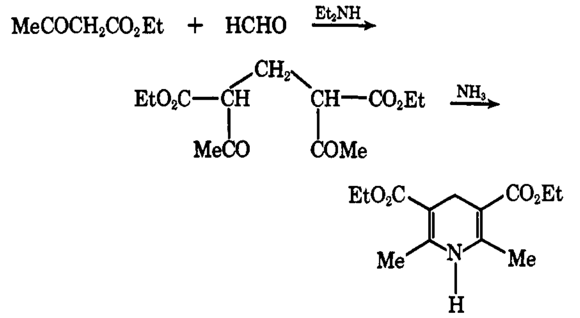
(378) G. Duburs and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 311 (1962); *Chem. Abstr.*, **59**, 6356 (1963).

(379) E. E. Grinshtein, E. I. Stankevich, and G. Duburs, *Khim. Geterotsikl. Soedin.*, 395 (1967); *Chem. Abstr.*, **70**, 87768 (1969).

(380) A. Sakurai and H. Midorikawa, *Bull. Chem. Soc. Jap.*, **42**, 220 (1969).

(381) G. Vanags and E. I. Stankevich, *Zh. Obshch. Khim.*, **30**, 3287 (1960); *Chem. Abstr.*, **55**, 21119 (1961).

variation on the Hantzsch synthesis[345,382–390] (see ref 8, p 302). A typical example is given[318,391] in eq 21; the diketone is

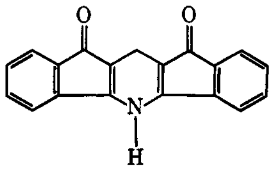

(21)

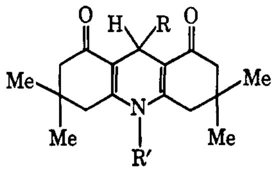
used here without isolation. 3,3-Dimethylglutaraldehyde has been used in a similar cyclization.[392]

The early literature is full of contradictions with regard to this reaction. Some 1,5-diketones were said to give dihydropyridines with ammonia while others did not.[385,387,393] This confusion was cleared up only recently when it was shown[394] that many so-called 1,5-diketones were in fact 3-hydroxycyclohexanones, *i.e.*, products of a subsequent intramolecular aldol condensation. The action of ammonia on the diketone **86** gave the isolable intermediate **87** which cyclized with concomitant dehydrogenation to 2,4,6-triphenylpyridine rather than to the expected dihydropyridine.[387]

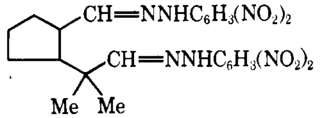
$C_6H_5COCH_2CH(C_6H_5)CH_2COC_6H_5$
86
$C_6H_5COCH_2CH(C_6H_5)CH_2C(C_6H_5){=}NH$
87

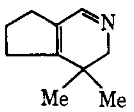
Ammonium acetate–acetic acid serves as an excellent reagent for the ring closure of 1,5-diketones.[78,79,335,395,396] Representative of a number polycyclic 1,4-dihydropyridines which have been prepared under these conditions are **88** and **89**. These arise from the condensation products of aldehydes with indan-1,3-dione[46,88,89,378,397–401] and dimedone,[239] respectively.


88


89

Acid treatment of the 2,4-dinitrophenylhydrazone **90** has been reported[35] to afford the 2,3-dihydropyridine **91** in low yield; presumably 2,4-dinitroaniline is eliminated in this reaction. In the absence of a quaternary carbon in the dialdehyde derivative, the pyridine is formed.


90


91

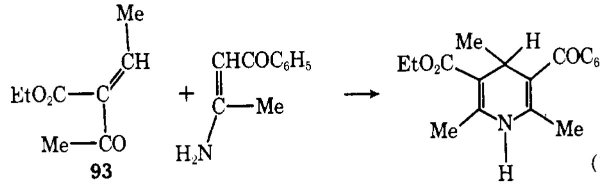
3-Aminocrotononitrile, (**77b**) reacted[402] with aromatic aldehydes to give the bis-enamines **92** which cyclized to the dihydropyridines **78b** in acid medium (see ref 8, p 309).

$$\mathbf{77b} + \mathrm{ArCHO} \longrightarrow$$

$$\underset{\mathbf{92}}{H_2NCMe{=}C(CN)CHArC(CN){=}CMeNH_2} \xrightarrow{H^+} \mathbf{78b}$$

5. *Use of α,β-Unsaturated Ketones*

Aldehydes may be condensed with active methylene compounds to give α,β-unsaturated ketones such as **93**. These can react with an enamine, or a ketone and ammonia, to give an unsymmetrical 1,4-dihydropyridine; *e.g.*,[403] see eq 22.


93
(22)

There are many examples of this reaction which are known,[57,336,358,359,404–409] and the older results are summarized in ref 8, p 449. Sometimes this method gives good results when the usual Hantzsch synthesis fails, as in the case of an ortho-substituted aromatic aldehyde.[358] Arylidene derivatives of indan-1,3-dione[371,378,410] and of barbituric acid[379] have been treated with enamines to give polycyclic 1,4-dihydropyridines such as **94** and **95**, respectively.

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(382) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, **281**, 94 (1894).
(383) E. Scholtz, *Ber.*, **30**, 2295 (1897).
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(389) A. Rieche and C. Bischoff, *Chem. Ber.*, **96**, 2607 (1963).
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(394) D. Wilson, *J. Org. Chem.*, **28**, 314 (1963).
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(396) R. Rehberg and F. Kröhnke, *Justus Liebigs Ann. Chem.*, **717**, 91 (1968).
(397) L. Geita and G. Vanags, *J. Gen. Chem. USSR*, **27**, 1058 (1957); *Chem. Abstr.*, **53**, 4232 (1959).
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(399) G. Duburs and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 287 (1962); *Chem. Abstr.*, **59**, 6356 (1963).
(400) L. Geita and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 235 (1962); *Chem. Abstr.*, **59**, 6355 (1963).
(401) G. Vanags and E. J. Ozola, *Zh. Obshch. Khim.*, **32**, 1151 (1962); *Chem. Abstr.*, **58**, 2430 (1963).
(402) E. Mohr, *J. Prakt. Chem.*, **56**, 124 (1897).
(403) C. Beyer, *Ber.*, **24**, 1662 (1891).
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(407) N. Palit and J. N. Chatterjea, *J. Indian Chem. Soc.*, **27**, 667 (1950); *Chem. Abstr.*, **46**, 3050 (1952).
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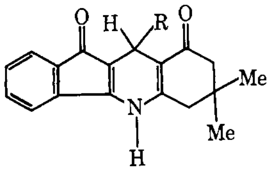
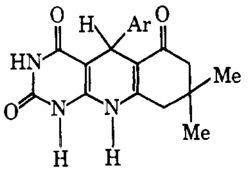
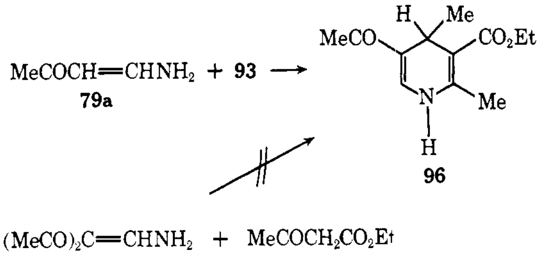


94

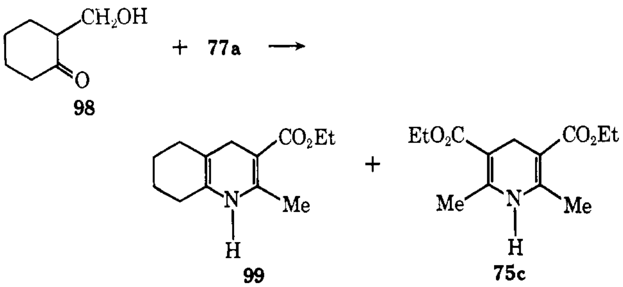


95

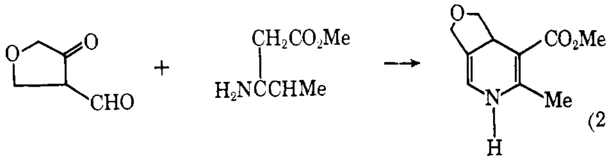
Ketones[412] or 1,3-diketones[411] and ammonia can be used instead of an enamine. The reaction of **93** with 4-aminobuten-2-one (**79a**) gives the dihydropyridine **96**, whereas ethyl acetoacetate and the enamine **97**, which should give the same dihydropyridine, instead afford a mixture of pyridines.[413]



Somewhat related is the reaction of 2-hydroxymethylcyclohexanone (**98**) with ethyl 3-aminocrotonate (**77a**) which yields[414] a mixture of **99** and **75c**, the latter presumably arising from **77a** and formaldehyde (formed on hydrolysis of **98**).

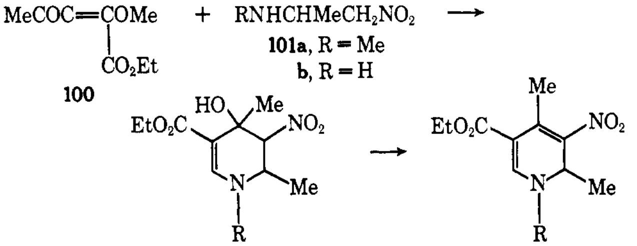


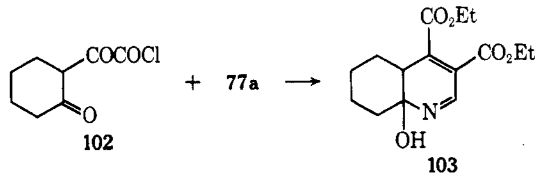
The following two reactions are somewhat remote from the Hantzsch synthesis but are included at this point because they involve the condensation of amines with ketones. They are the reaction (eq 23) of a β-ketoaldehyde with a β-amino ester,[415] which was formulated by the authors as a 1,4-dihydropyridine, and the condensation[416] of the enol ether **100** with **101a**. With **101b** only an acyclic product is formed.



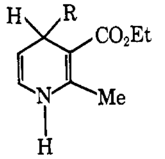
(23)

The structure of the putative hydroxydihydropyridine **103**, formed from **102** and ethyl 3-aminocrotonate (**77a**), is not in accord with its reported properties[40] and should probably be revised.





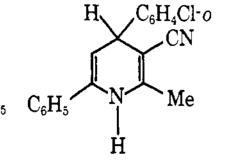
Whereas α-carbonyl-α,β-unsaturated ketones, *e.g.*, **93**, give dihydropyridines with ketones and ammonia, simple α,β-unsaturated ketones give pyridines.[354,417] The initially formed dihydropyridine either undergoes disproportionation or it is dehydrogenated by the unsaturated ketone; evidence for both pathways exists (see ref 8, p 436). There are a few exceptions, however. Thus acrolein or crotonaldehyde condense[418] with ethyl 3-aminocrotonate (**77a**) in the presence of piperidine to give the dihydropyridines **104a** and **104b**, respectively. Acrolein similarly reacts[419] with 3-aminocrotononitrile (**77b**). The latter compound condenses with chalcone to yield 3-cyano-4,6-diphenyl-2-methyl-1,4-dihydropyridine[408] and with the chalcone derivative **105** to give **106**. The meta and para isomers of **105** give pyridines under the same conditions.[417]



104a, R = H
b, R = Me

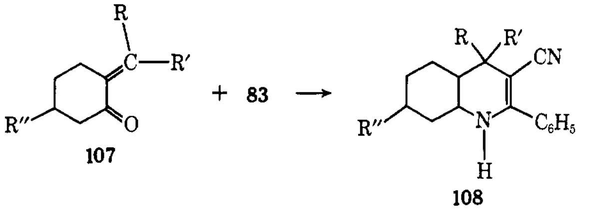
$o\text{-ClC}_6\text{H}_4\text{CH=CHCOC}_6\text{H}_5$

105



106

Chalcone and ω-cyanoacetophenone (**83**) gave a mixture of 3-cyano-2,4,6-triphenyl-1,4-dihydropyridine and the corresponding pyridine.[79] The cyclohexanone derivatives **107a** and **107b** afforded the dihydropyridines **108a** and **108b**, respectively, on treatment with **83**, but **107c** yielded the corresponding pyridine.[380] 4-Methylcyclohexanone reacted with **83** to give **108d**, presumably[380] *via* **107d**.



a, R = C_6H_5; R′ = R″ = H
b, R = R′ = R″ = Me
c, R = Me; R′ = R″ = H
d, R, R′ = $CH_2CH_2CHMeCH_2CH_2$; R″ = Me

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(411) E. I. Stankevich and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 283 (1962); *Chem. Abstr.*, **59**, 6356 (1963).

(412) E. Knoevenagel, *Justus Liebigs Ann. Chem.*, **281**, 25 (1894).

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(418) K. Tsuda, Y. Satch, N. Ikekawa, and H. Mishima, *J. Org. Chem.*, **21**, 800 (1956).

(419) Y. Sato and T. Nashimura, *Takamine Kenkyusho Nempo*, **10**, 27 (1958); *Chem. Abstr.*, **55**, 2634 (1961).

Simple aldehydes or ketones and ammonia generally give pyridines (ref 8, p 474). However, with primary amines or imines dihydropyridines are sometimes obtained. Thus propionaldehyde reacts with aniline,[69] *n*-butylamine,[420] or *n*-butylidenebenzylamine[70,421] to give a compound which was variously described as 3,5-diethyl-2-propyl-1,2-[70] or 1,4-[69] dihydropyridine. Recent work[26,421a] has unequivocally established the former to be correct.

Acetone reacts with ammonia to give a compound believed to be 2,2,4,6-tetramethyl-1,2-dihydropyridine,[422–425] although its structure has not been rigorously proved. Other ketones give mixtures of dihydropyridines with ammonia.[423,424]

Propionaldehyde and ammonium acetate react[423a] to give 3,5-diethyl-2-propylpyridine *via* a 2,3-dihydropyridine.

6. Source of Nitrogen

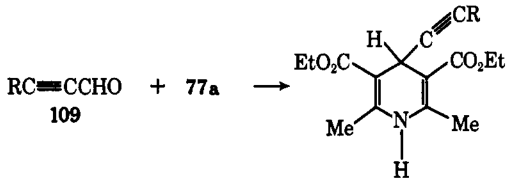
The source of nitrogen in the Hantzsch and related syntheses is usually ammonia or ammonium acetate although formamide has also been used.[345] Occasionally aldehyde–ammonia adducts, *e.g.*, hexamethylenetetramine[426,427] or aldehyde–ammonia,[1,428] have been employed.

The use of primary amines instead of ammonia in the Hantzsch synthesis is rare;[338] yields are reported to be low[47] or the reaction fails completely.[52,429] Better results are obtained by first forming the substituted enamines RNHCH=CHX, where X = CO_2Et,[430–433] CN,[363] or COMe.[85,365,366] Benzalaniline, which supplied both benzaldehyde and aniline, gave a dihydropyridine with ethyl acetoacetate.[329,431] 1,5-Diketones are cyclized by primary amines,[239,387,392,411,433] including hydrazine.[386,387] The action of hydroxylamine on 1,5-diketones affords pyridines (ref 8, p 307).

The dianils $CH_2(MeCOC{=}CHNHAr)_2$ are converted into N-substituted 1,4-dihydropyridines by hydrochloric acid.[368] Ethyl 3-methylaminocrotonate and ethyl ethylideneacetoacetate (**93**) failed to give a dihydropyridine.[434]

7. The Aldehyde Component

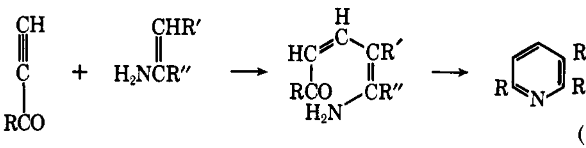
Aldehydes are sometimes used in combination with amines as mentioned above. 1,2-Dichloroethyl ethyl ether has been used as a source of chloroacetaldehyde[432,435,436] and certain geminal dihalides can take the place of formaldehyde or acetaldehyde.[437] Ketones[360] and chloromethyl ketones[363] react with 3-aminocrotononitrile (**77b**) in the presence of mineral acid. Acetylenic aldehydes **109a** and **109b** reacted with ethyl 3-aminocrotonate, (**77a**) to give the dihydropyridines **110a** and **110b**, respectively.[438]



110

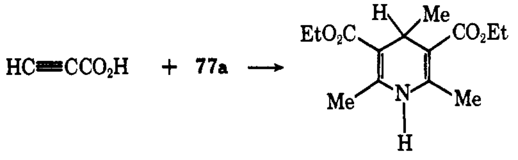
a, R = Me; **b**, R = C_6H_5

Propargylaldehyde and ethinyl ketones underwent a totally different reaction[438] (eq 24). Propiolic acid, on the other hand,



(24)

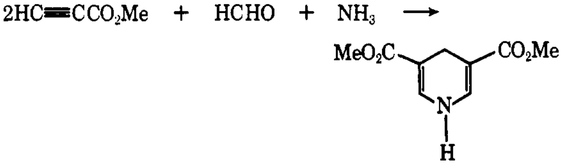
does not give a pyridone in an analogous reaction, but instead gives a 4-methyl-1,4-dihydropyridine[439] as shown in eq 25. A mechanism for this reaction has been proposed by the authors.



(25)

75a

In contrast, methyl propiolate[138] reacted with hexamethylenetetramine to give dimethyl 1,4-dihydropyridine-3,5-dicarboxylate according to eq 26.



(26)

8. By-Products

Dihydropyridines have occasionally been formed as unexpected by-products in various reactions.[440–442] On the other hand, by-products in dihydropyridine syntheses are rare. Ethyl 3-anilinocrotonate (**111**) reacted[433] with benzaldehyde to give **112** as well as the expected dihydropyridine **113**. Presumably **112** is formed by C-alkylation of the enamine **111** with benzaldehyde or benzalaniline, followed by reaction with a molecule of benzalaniline or benzaldehyde, and cyclization.

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(429) C. Paal and C. Strasser, *ibid.*, **20**, 2756 (1887).

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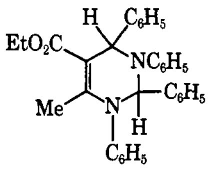
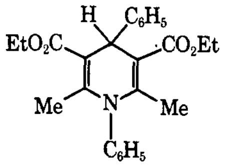
(442) N. Palit, *J. Indian Chem. Soc.*, **14**, 219 (1937).

$C_6H_5NHCMe{=}CHCO_2Et$

111



112

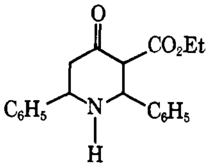


113

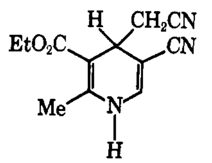
A compound, formed from benzaldehyde, ethyl acetoacetate, and ammonia, which was assigned[431] the structure C_6H_5-$CH{=}NCH(C_6H_5)NHCMe{=}CHCO_2Et$, is more likely to be a tetrahydropyrimidine analogous to **112**.

Ethyl acetoacetate, benzaldehyde, and ammonium acetate in acetic acid afforded[322] the piperidone **114** and not the expected dihydropyridine **75d**; with aliphatic aldehydes the dihydropyridines **75** were obtained under these conditions.

Cyanoacetaldehyde reacted[323] with ethyl 3-aminocrotonate (**77a**) to give not only the expected dihydropyridine **75e** but also **115**, resulting from the condensation of 2 mol of the aldehyde with one of **77a**.



114



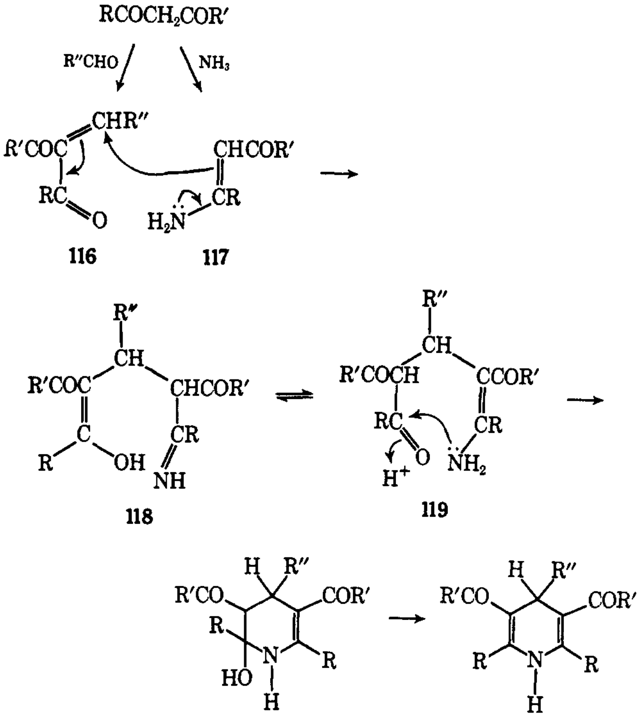
115

9. *Reaction Conditions and Mechanism*

Conditions for dihydropyridine synthesis vary widely and range from basic media, as used in the original Hantzsch method, to strong acid solution required for the reaction of 3-aminocrotononitrile with ketones. An early investigation[443] showed that ethyl acetoacetate, formaldehyde, and ammonia formed a dihydropyridine both in acid and in basic solution. In a more systematic study[346] it was established that acetylacetone, acetaldehyde, and ammonia reacted in aqueous solution at pH 5.5–9.3 with an optimum yield at pH 6.6–8.5, and ethyl acetoacetate, acetaldehyde, and ammonia yielded the dihydropyridine **75a** at pH 6–10 with an optimum yield at pH 8.5. Similar results using aromatic aldehydes were reported.[324] Another study[444] contradicts this work with the observation that good yields of **75a** could be obtained at pH 3.25–5.0.

A series of substituted benzaldehydes has been allowed to react with ethyl acetoacetate under a set of standardized conditions, and the effect of the substituents on the isolated yield of dihydropyridines has been determined.[327,328,331,333,334] In general, the yields could be directly correlated with the electron-withdrawing capacity of the substituent. Yields are lowered with ortho-substituted benzaldehydes because of steric effects (for examples of failure of reactions with ortho-substituted benzaldehydes see ref 356 and 409). Meta-substituted benzaldehydes give slightly higher yields than the corresponding para-substituted derivatives. Similar yield *vs.* substituent correlations have also been reported for aliphatic aldehydes.[320] It is doubtful that such experiments are very meaningful, but no kinetic or other mechanistic studies have been carried out on this reaction.

Scheme I



The mechanism of the Hantzsch reaction was proposed very early[393,403,445] and has changed little.[346,446] It may be depicted as shown in Scheme I.

The active methylene compound reacts with an aldehyde to give **116** and with ammonia to give **117**. Michael addition of these results in the tautomeric system **118** which undergoes cyclization to the hydroxytetrahydropyridine **119** followed by loss of water.

The available evidence is based largely on isolated intermediates. Thus it is well established that the unsaturated ketones **116**, the enamines **117**, and 1,5-diketones, the precursors of **118**, are all effective starting materials for the preparation of dihydropyridines. It has been shown[444] that ethyl acetoacetate with acetaldehyde and ammonia give intermediates corresponding to **116** and **117**. The isolation of an imine **118** has been claimed although no structure proof was given.[410] An intermediate corresponding to **119** has been isolated and its structure established unequivocally.[446] Another, less fully authenticated example was reported earlier.[408] An alternative mechanism, involving condensation of **116** and **117** in the opposite sense, has been disproved.[57]

C. MISCELLANEOUS SYNTHESES

1. *Cyclization of Nitriles and Amides*

The action of hydrogen bromide on the cyano ketone **120** is said to give the 3,4-dihydropyridine **121** which is in equilib-

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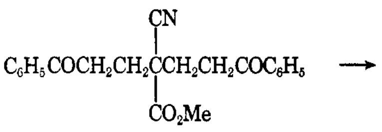
(443) R. Schiff and P. Prosio, *Gazz. Chim. Ital.*, **25**, 65 (1895); *Chem. Zentr.*, II, 894 (1895).

(444) A. Ehsan and Karimullah, *Pakistan J. Sci. Ind. Res.*, **11**, 5 (1968); *Chem. Abstr.*, **69**, 96403 (1968).

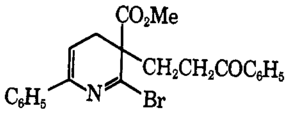
(445) E. Knoevenagel, *Ber.*, **31**, 739 (1898).

(446) K. L. Marsi and K. Torre, *J. Org. Chem.*, **29**, 3102 (1964).



$C_6H_5COCH_2CH_2\overset{CN}{\underset{CO_2Me}{C}}CH_2CH_2COC_6H_5 \longrightarrow$

120

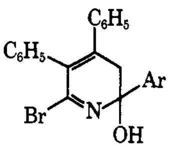


121

rium with the open-chain bromo imine.[45] Similarly treatment of **122** with bromine is claimed[36,447] to result in **123**. Reinvestigation of the structure of **121** and **123** is clearly desirable.

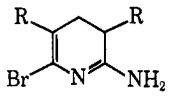
$CNCH(C_6H_5)CH_2COR$

122

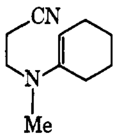


123

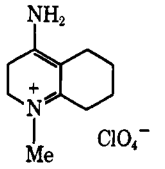
Cyclization of glutaronitrile or its 2,4-diphenyl derivative with hydrogen bromide afforded dihydropyridinium salts which were converted into **124a** or **124b** with mild base.[42] Ring closure of the unsaturated enaminonitrile **125**, using magnesium perchlorate as condensing agent, yielded[448,449] the dihydropyridinium salt **126**.



124a, R = H
b, R = Ph

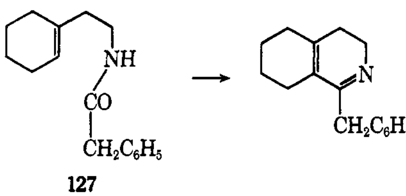


125



126

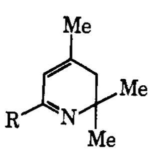
In a similar cyclization, analogous to the Bischler–Napieralski reaction, unsaturated amides such as **127** gave dihydropyridines[38,39,41] with phosphorus pentoxide or oxychloride.



127

The use of diols or of unsaturated alcohols in the Ritter reaction has yielded dihydropyridines,[32–34] *e.g.*, eq 27.

$Me_2C(OH)CH_2C(OH)Me_2 + RCN + H_2SO_4 \longrightarrow$

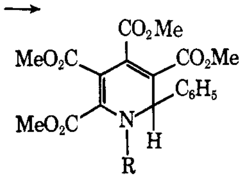


(27)

2. Cycloaddition Reactions

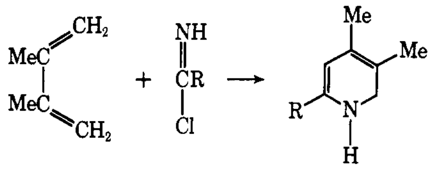
The reaction of pyridines, quinolines, etc., with dimethyl acetylenedicarboxylate, which gives quinolizines, is beyond the scope of this review; a recent account[450] deals with this subject. In only one case,[451] the reaction of dimethyl acetylenedicarboxylate with Schiff bases, has this method been applied to the preparation of simple dihydropyridines **128**. 3,4-Dihydroisoquinoline reacts analogously.

$MeO_2CC{\equiv}CCO_2Me + C_6H_5CH{=}NR \longrightarrow$



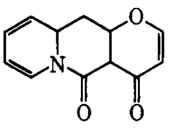
128

Imino chlorides have been subjected[452] to cycloaddition with dienes according to eq 28. However, the vigorous reaction conditions used make the proposed structures somewhat suspect, and reinvestigation by modern techniques would be desirable.

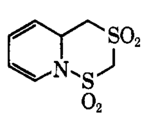


(28)

Ketene forms an adduct with pyridine,[453–455] the structure of which has been established as **129** only recently[66] (see also ref 455a). Sulfene also forms an adduct **130** with pyridine.[456]



129



130

3. From Pyridones and Reduced Pyridones

N-Substituted 2-pyridones on treatment with oxalyl chloride are reported to give the corresponding 2,2-dichloro-1,2-dihydropyridines.[457–459] There is a report[130] of the lithium aluminum hydride reduction of an *N*-aryl-2-pyridone to the corresponding 1,2-dihydropyridine although the structure of the latter is in doubt.

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(447) E. P. Kohler and F. A. Allen, *J. Amer. Chem. Soc.*, **46**, 1522 (1924).

(448) A. I. Meyers, J. C. Sircar, and S. Singh, *J. Heterocycl. Chem.*, **4**, 461 (1967).

(449) A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, **32**, 1250 (1967).

(450) R. M. Acheson, *Advan. Heterocycl. Chem.*, **1**, 125 (1963).

(451) R. Huisgen and K. Herbig, *Justus Liebigs Ann. Chem.*, **688**, 98 (1965).

(452) M. Lora-Tamayo, G. G. Munoz, and R. Madronera, *Bull. Soc. Chim. Fr.*, 1331 (1958).

(453) H. Staudinger, H. W. Klever, and P. Kober, *Justus Liebigs Ann. Chem.*, **374**, 1 (1910).

(454) O. Wollenberg, *Ber.*, **67**, 1675 (1934).

(455) J. A. Berson and W. M. Jones, *J. Amer. Chem. Soc.*, **78**, 1625 (1956).

(455a) R. N. Pratt, D. P. Stokes, G. A. Taylor, and S. A. Procter, *J. Chem. Soc. C*, 1472 (1971).

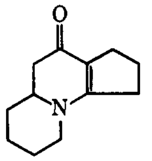
(456) J. S. Grossert, *Chem. Commun.*, 305 (1970).

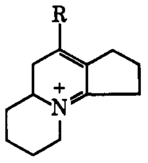
(457) M. M. Shemyakin and E. I. El'kina, *J. Gen. Chem. USSR*, **11**, 349 (1941); *Chem. Abstr.*, **35**, 5893 (1941).

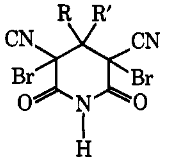
(458) E. I. El'kina and M. M. Shemyakin, *J. Gen. Chem. USSR*, **13**, 301 (1943); *Chem. Abstr.*, **38**, 1504 (1944).

(459) Ya. L. Danyushevskii and Ya. L. Gol'dfarb, *Dokl. Akad. Nauk SSSR*, **72**, 899 (1950); *Chem. Abstr.*, **44**, 9446 (1950).

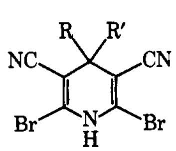
O-Alkylation (see ref 512) of the dihydropyridone **131** yields the corresponding enol ether salt **132a**, while reaction of **131** and other dihydropyridones with Grignard reagents, followed by perchloric acid, gives[460] the salts **132b–d**. The


131


132a, R = OMe
b, R = Me
c, R = Bu-*tert*
d, R = C_6H_5

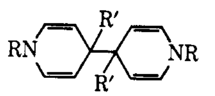

133

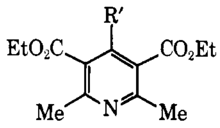
action of triphenyl phosphite on the glutarimide **133** yields[461] 4,4-disubstituted 2,6-dibromo-3,5-dicyano-1,4-dihydropyridines (**134**).

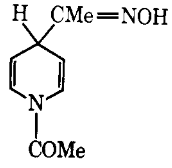

134

4. *From Tetrahydrobipyridyls*

One-electron reduction of pyridines or pyridinium salts leads to the tetrahydrobipyridyls **135** (see section IV.A.2.a). On heating these break down to a 1:1 mixture of the corresponding pyridine and 1,4-dihydropyridine.[37,44,72,73,264,265,270,273]


135a, R = COMe; R′ = H

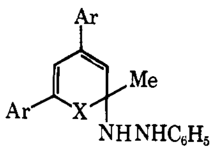

136a, R′ = H
b, R′ = Me

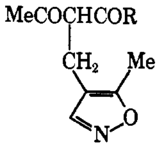

137

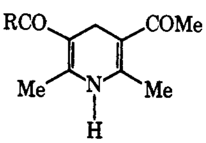
The tetrahydrobipyridyls are generally formulated as the 1,4 isomers as shown; however, in the case of the pyridine **136a**, an unstable primary reduction product was obtained which isomerized to a stable tetrahydrobipyridyl on heating. Both isomers gave the 1,4-dihydropyridine on pyrolysis.[37,44] A series of tetrahydrobipyridyls derived from the pyridines **136** was prepared;[265] the ease of dissociation increased in the order R′ = H < Me < Et < *i*-Bu. Although it was earlier believed that on heating **135a** gave 1,4-diacetyl-1,4-dihydropyridine[72] it was subsequently shown that this was incorrect.[73] However, it was confirmed[73] that action of hydroxylamine on **135a** afforded[462] the dihydropyridine **137**.

5. *From Other Heterocycles*

Very few conversions of pyrans into dihydropyridines are known although the formation of pyridines from pyrylium salts is a well-known reaction (ref 8, p 210). It has been claimed,[463] without any evidence, that 2-methyl-4,6-ditolylpyrylium perchlorate with phenylhydrazine gives first **138a** and then **138b**. Certain complex polycyclic pyran derivatives have been converted into the corresponding dihydropyridines, *e.g.*, **88**, by heating with ammonia or primary amines.[87,88,464,465]

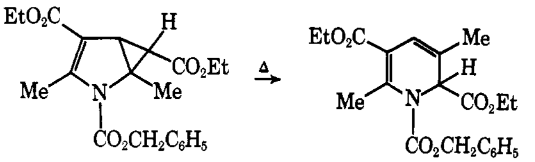

138a, X = O
b, X = $NNHC_6H_5$

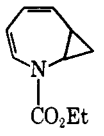

139a, R = Me
b, R = OEt

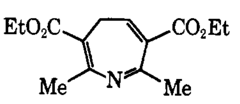

140

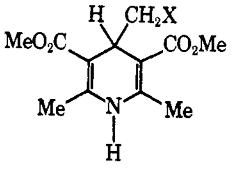
The isoxazoles **139a** and **139b** on catalytic hydrogenation are converted into the 1,4-dihydropyridines **140** by hydrogenolysis of the N–O bond, recyclization, and loss of water.[466,466a]

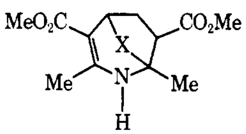
Pyrolysis of the homoazepine **141** afforded 1-ethoxycarbonyl-2-vinyl-1,2-dihydropyridine,[467] while the homopyrrole, diethyl 2-azo-2-benzyloxycarbonyl-1,3-dimethylbicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate (**140a**), yielded[468] the isomeric diethyl 1-benzyloxycarbonyl-3,6-dimethyl-1,2-dihydropyridine-2,5-dicarboxylate (**140b**) (see also ref 468a).


140a **140b**


141


142


143a, X = Cl
b, X = Br
c, X = I


144a, X = O
b, X = S

The action of hydrogen chloride or bromide on the 4*H*-azepine **142** produced the dihydropyridines **143a** and **143b**,

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(460) A. I. Meyers and S. Singh, *Tetrahedron*, **25**, 4161 (1969).

(461) M. Leduc, M. F. Chasle, and A. Foucaud, *Tetrahedron Lett.*, 1513 (1970).

(462) B. Emmert and A. Wolpert, *Ber.*, **74**, 1015 (1941).

(463) O. Diels and K. Alder, *ibid.*, **60**, 716 (1927).

(464) L. Geita and G. Vanags, *Latv. PSR Zinat. Akad. Vestis*, 127 (1958); *Chem. Abstr.*, **53**, 11371 (1959).

(465) L. Geita and G. Vanags, *Zh. Obshch. Khim.*, **28**, 2801 (1958); *Chem. Abstr.*, **53**, 9165 (1959).

(466) M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *J. Amer. Chem. Soc.*, **89**, 5460 (1967).

(466a) G. Stork, M. Ohashi, H. Kamachi and K. Kakisawa, *J. Org. Chem.*, **36**, 2784 (1971).

(467) W. H. Okamura, *Tetrahedron Lett.*, 4717 (1969).

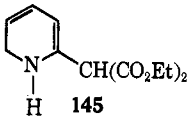
(468) J. F. Biellmann and M. P. Goeldner, *Tetrahedron*, **27**, 2957 (1971)

(468a) F. W. Fowler, *Angew. Chem., Intern. Ed. Engl.*, **10**, 135 (1971); *Angew. Chem.*, **83**, 148 (1971).

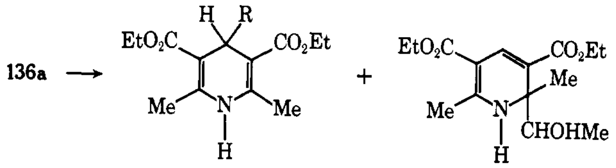
respectively; bromine reacted analogously.[469] Similarly, **143a** was obtained when hydrochloric acid reacted with a compound formulated as a 2-hydroxy-2,3-dihydro-4*H*-azepine;[470] the reported properties of the latter, however, are in better accord with the structure **144a**. The sulfide **144b** with methyl iodide underwent a series of complex rearrangements[471,472] to give **143c**.

6. *Miscellaneous*

After catalytic hydrogenation and distillation the amino ketone $C_6H_5CH_2OCONHCH_2CH_2CH(OMe)CH_2COCH(CO_2Et)_2$ afforded[473] the dihydropyridine **145**.


145

Irradiation of the pyridine **136a** or **136b** in alcohols resulted in photoaddition of the solvent and photoreduction, with the formation of 1,2- and 1,4-dihydropyridines,[474] *e.g.*



R = H or CHOHMe

V. Physical Properties

A. ELECTRONIC SPECTRA

1. *Dihydropyridines*

Until the advent of nmr spectroscopy ultraviolet and visible spectroscopy was the most useful technique for the identification of dihydropyridines and even now it is still an invaluable diagnostic tool.

Among the many applications are structure determination (ref 26, 59, 62, 126, 141, 143, 279), kinetic measurements (ref 76, 215, 218, 233, 363, 475–486), determination of equilibrium constants (ref 216, 217, 487, 488), mechanistic studies (ref 65, 75, 111, 131, 152, 157, 184, 205, 213, 225, 247, 286), and analysis of isomer mixtures (ref 119, 489).

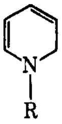
As a result of their conjugated structures dihydropyridines absorb light above 240 nm. Transparency in that region has been used[490] to identify some unconjugated 2,5-dihydropyridinium salts. Dihydropyridines usually have two absorption maxima, band I in the region of 200–240 nm, and band III at 300–400 nm. The former band is often not reported, possibly because of inadequate instrumentation or inappropriate solvents. A third band, II, at 250–300 nm is frequently present in cross-conjugated 1,2- or 1,6-dihydropyridines and has been used to distinguish this type from the 1,4 isomers which normally display a two-banded spectrum.[52,58,65,142,150,168]

Molecular extinction coefficients range from 3000 to 5000 for simple alkyl-substituted dihydropyridines to 5000–25,000 for dihydropyridines with conjugating substituents. Band I is generally more intense than band III, and band II is of variable intensity.

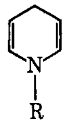
Table II summarizes the uv and visible spectra of the most characteristic dihydropyridine types **146–157**. The data are for the simplest known representative of a given type, and references to analogous compounds are listed. Unless otherwise stated the spectra were determined in ethanol or methanol.

Table II is not intended to be exhaustive. Among others, certain polycyclic[236,238,362,399,401,488,491–493] or otherwise complex[61,84,141,178,183,198] dihydropyridines have been excluded.

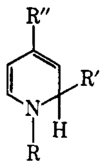
The following dihydropyridines are illustrative of the most common type of chromophore.



146a, R = Me
b, R = $SiMe_3$
c, R = C_6H_5



147a, R = H
b, R = $SiMe_3$
c, R = C_6H_5



148a, R = COMe; R′ = CH_2CO_2H; R″ = H
b, R = CO_2Et; R′ = R″ = Bu-*tert*
c, R = OH; R′ = C_6H_5; R″ = H
d, R = tetraacetylglucosyl; R′ = R″ = H
e, R, R′ = $SO_2CH_2SO_2CH_2$; R″ = H, 3,5-Me_2 (*cf.* **130**)

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(469) M. Anderson and A. W. Johnson, *J. Chem. Soc.*, 2411 (1965).
(470) M. Anderson and A. W. Johnson, *ibid.*, *C*, 1075 (1966).
(471) J. Ashby and U. Eisner, *ibid.*, *C*, 1706 (1966).
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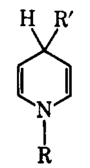
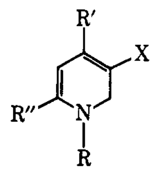
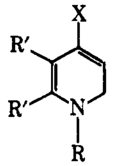


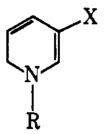
149a, R = COMe; R′ = CMe═NOH
b, R = CO$_2$Et; R′ = H
c, R = tetraacetylglucosyl; R′ = H
d, R = NMeCOMe; R′ = CN



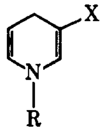
150a, R = CH$_2$C$_6$H$_3$Cl$_2$; X = CN; R′, R″ = H
b, R = CH$_2$C$_6$H$_3$Cl$_2$; X = CONH$_2$; R′ = R″ = Me
c, R = Me; X = CO$_2$Me; R′ = R″ = H
d, R = Me; X = NO$_2$; R′ = Me; R″ = H



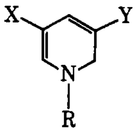
151a, R = Me; X = CO$_2$Me; R′ = H
b, R = Me; X = C$_6$H$_5$; R′, R″ = (CH$_2$)$_4$



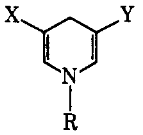
152a, R = Me; X = CN
b, R = CH$_2$C$_6$H$_5$; X = CONH$_2$
c, R = Me; X = CO$_2$Me



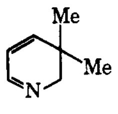
153a, R = Me; X = SO$_2$NH$_2$
b, R = H; X = CN
c, R = CH$_2$C$_6$H$_5$; X = CONH$_2$
d, R = Me; X = CO$_2$Me
e, R = CH$_2$C$_6$H$_5$; X = COMe
f, R = Me; X = NO$_2$



154a, R = H, X = Y = CN
b, R = Me; X = Y = CN, 2,4-(CN)$_2$
c, R = Me; X = CN; Y = CONH$_2$
d, R = CH$_2$C$_6$H$_3$Cl$_2$; X = Y = CONH$_2$
e, R = H; X = Y = CO$_2$Me
f, R = (CH$_2$)$_2$C$_6$H$_5$; X = Y = CO$_2$Me, 2-C$_6$H$_5$-4,6-(CO$_2$Me)$_2$, (*cf.* **128**)
g, R = H; X = Y = COMe
h, R = Me; X = Y = C$_6$H$_5$



155a, R = H; X = Y = CN
b, R = H; X = Y = CN, 2,6-(C$_6$H$_5$)$_2$ (*cf.* **78e**)
c, R = Me; X = CN; Y = CONH$_2$
d, R = Me; X = CN; Y = CO$_2$Me
e, R = CH$_2$C$_6$H$_3$Cl$_2$; X = Y = CONH$_2$
f, R = H; X = Y = CO$_2$Me
g, R = H; X = CO$_2$Et; Y = COMe, 2,6-Me$_2$
h, R = H; X = Y = COMe
i, R = Me; X = Y = COMe



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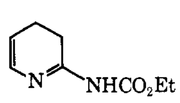

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Little systematic work has been done on the correlation of the nature and position of dihydropyridine substituents with their uv spectra.[80] Since band III was found[80] to be most sensitive to substituent effects, these will be discussed only with respect to this band.

Table II shows that 1,2-dihydropyridines absorb at longer wavelengths than the corresponding 1,4 isomers (or the cross-conjugated 1,6 isomers, *e.g.*, **152**). Decreases in the wavelengths of the absorption maxima are in the order NO$_2$ > COR, C$_6$H$_5$ > CO$_2$R, CONH$_2$ > CN > SO$_2$NH$_2$ for substituents in the 3 and/or 5 positions (see also ref 65, 80, and 500).

Substituent effects are particularly apparent at the 1 position. The absorption maxima of a series of 1-(para-substituted phenyl)-4,4-dimethyl-1,4-dihydropyridines[392] show striking differences, ranging from 413 nm for *p*-nitrophenyl to 278 nm for *p*-methoxyphenyl. The electron-releasing trimethylsilyl group, on the other hand, produces a bathochromic shift (*cf.* **147a,b**). Introduction of 1-alkyl substituents into dihydropyridines with conjugating substituents in the 3 and/or 5 positions results in a substantial red shift[80] (*cf.* ref 288 and 504; 503 and 157).

Electron-withdrawing groups in the 1 position produce a hypsochromic shift (*cf.* **148** and **149** with **146** and **147**). The shifts in NADH model compounds which have a sugar residue at nitrogen are well documented.[62,81,85,138,189,197,216,487,496] For other 1-substituted derivatives, see ref 84, 85, and 196.

Substitution of alkyl groups at other positions in the ring results in hypsochromic shifts. In the absence of steric effects (see below), small but definite blue shifts result from introduction of alkyl groups at unsaturated centers in the ring.[35,142,295,494]

Substituents in the 4 position of 1,4-dihydropyridines[52,57,58,62,80,118,142,168,170,195,216,323,357,363,503] or the 2 position in 1,2-dihydropyridines[68,118,142,168,170] in general cause a substantial blue shift, the magnitude of which is dependent on the substitution pattern of the molecule. It is believed[52,80,357] to be steric in origin, as a result of nonbonded repulsion between it and an adjacent chromophore in the 3 and/or 5 position.

In the absence of an adjacent substituent there is no spectral change, *e.g.*, on going from 1-benzyl-4-methyl-1,6-dihydronicotinamide to the corresponding 4,6-dimethyl derivative,[142] or from 1-phenyl-1,4-dihydropyridine[71] to the 4,4-dimethyl analog.[392]

Alternative explanations attribute the operation of this effect to the ground[509] or excited[357] state. However, the

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Table II

Ultraviolet Spectra of Dihydropyridines[a]

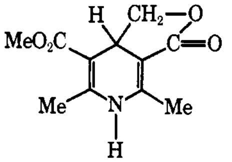
Compd	*R*	*X*	*Y*	*Other*	λ_{max}, *nm* *Band* *I*	*II*	*III*	*Ref*	*Analog references*
146a	Me						325	494	26, 69, 71, 131, 490
146b[b]	$SiMe_3$				220		320	295	
147a	H						278	294	
147b[c]	$SiMe_3$						288	295	43, 59, 68, 146, 392
148a	COMe			$2\text{-}CH_2CO_2H$			298	306	66, 273, 303, 310, 455
148b	CO_2Et			$2,4\text{-}Bu^t_2$			292	63	
148c	OH			$2\text{-}C_6H_5$		237	313	176	
148d	TAG[c]						310	138	86[d]
148e	SO_2CH_2			$2\text{-}CH_2SO_2$, $3,5\text{-}Me_2$			287	456	
149a	COMe			4-CMe=NOH			252	73	268, 272, 297, 302, 303, 305
149b[b]	CO_2Et						230	273	
149c	TAG[c]						275	138	
149d	NMeCOMe			4-CN			275	211	
150a	DCB[e]	CN		4-Me			390	142	133
150b	DCB[e]	$CONH_2$		$4,6\text{-}Me_2$			392	142	150
150c	Me	CO_2Me					432	143	144
150d	Me	NO_2		4-Me	255		520	139	
151a	Me	CO_2Me				260	320	143	
151b	Me	C_6H_5		$5,6\text{-}(CH_2)_4$			312	460	
152a	Me	CN				240	349	64	65, 142, 244
152b	$CH_2C_6H_5$	$CONH_2$				267	358	62	52, 65, 142, 150, 216, 225, 279
152c	Me	CO_2Me				263	362	143	65, 131, 144, 150
153a[f]	Me	SO_2NH_2					317	201	
153b	H	CN					330	116	64, 65, 133, 195, 198
153c	$CH_2C_6H_5$	$CONH_2$					352	62	43, 52, 60, 65, 81, 84, 131, 142, 152–154, 189, 191, 194–196, 216, 496–502
153d	Me	CO_2Me					363	143	65, 131, 150, 418, 497, 500
153e	$CH_2C_6H_5$	COMe					371	500	65, 166, 195, 198
153f	Me	NO_2					400	139	
154a	H	CN	CN		213	254	382	503	58, 123, 157, 158, 168, 170, 171, 222, 223, 293, 489
154b	Me	CN	CN	$2,4\text{-}(CN)_2$		263	418	223	
154c	Me	CN	$CONH_2$				396	157	
154d	DCB[e]	$CONH_2$	$CONH_2$			286	391	65	
154e	H	CO_2Me	CO_2Me		213	281	386	118	52, 65, 150
154f	$(CH_2)_2C_6H_5$	CO_2Me	CO_2Me	$2\text{-}C_6H_5\text{-}4,6\text{-}(CO_2Me)_2$	206, 233	281	388	451	
154g	H	COMe	COMe		217	281	386	288	370, 504, 505
154h	Me	C_6H_5	C_6H_5			320	415	131	
155a	H	CN	CN		206		352	503	58, 80, 126, 157, 158, 168, 170, 173, 222, 223, 323, 357, 363, 489
155b	H	CN	CN	$2,6\text{-}(C_6H_5)_2$	206	242, 263	365	362	
155c	Me	CN	$CONH_2$				377	157	
155d	Me	CN	CO_2Me				379	157	323
155e	DCB[e]	$CONH_2$	$CONH_2$				381	65	
155f	H	CO_2Me	CO_2Me		213	242[i]	374	118	52, 57, 65, 80, 126, 195, 225, 323, 344, 357, 446, 469–472, 503, 506–508
155g	H	CO_2Et	COMe	$2,6\text{-}Me_2$	244	265	392	466	57, 375
155h	H	COMe	COMe		232	265	395	80	57, 85, 344, 370, 371, 376, 492
156[g]						240		35	33, 34, 460
157[h]						286		43	

[a] In ethanol or methanol unless otherwise specified. [b] Cyclohexane. [c] Tetraacetyl-β-D-glucopyranosidyl. [d] Erroneously described as 1,4-dihydropyridines. [e] 2,6-Dichlorobenzyl. [f] Erroneously described as the 1,2-dihydropyridine. [g] Water. [h] Tautomeric mixture. [i] Inflection.

situation becomes more complex when other substituents are present and has been systematically investigated[80] for 1,4-dihydropyridines **155**. With further substitution in the 2,6 and the 1,2,6 positions, a "buttressing" effect comes into play where neighboring groups appear to bend the 3,5 substituents out of the plane of the ring. When "saturation" is reached, additional substitution does not produce further shifts (see also ref 158). Steric, electronic, and conformational factors are delicately balanced and interpretation of the spectral shifts is difficult.

Steric effects have also been shown[26] to affect the spectra of alkyl dihydropyridines. Steric interaction between substituents in the 1 and 2 position is more severe in 1,6- than in 1,2-dihydropyridines which accounts[26] for the former absorbing at shorter wavelengths than the latter.

Conformational effects have scarcely been investigated and such a study is likely to yield interesting results. For example, 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine (**76**, R = H) has λ_{max} 404 nm and appears to be abnormal when compared to a series of other 1,4-dihydropyridines,[80] while the polycyclic dihydropyridine **89** (R = R′ = H),[468] in which the conformation of the carbonyl groups is fixed, has an absorption maximum (388 nm) in line with that of the above-mentioned dihydropyridines. Another illustration is the difference in the absorption of the 1,4-dihydropyridine ester **75a** (λ_{max} 349 nm)[80] with that of the lactone **158** (λ_{max} 360 nm).[472] Comparison of the 2,3-dihydropyridine **159a** (λ_{max} 263 nm)[33] with the six-membered analog **159b** (λ_{max} 255 nm)[34] shows the effect of ring size in bicyclic systems.



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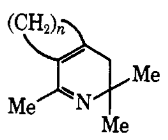


159a, $n = 3$
b, $n = 4$

Substituents in the 4 position of 1,4-dihydropyridines and the 2 position in 1,2-dihydropyridines sometimes exert what appears to be an electronic effect, particularly when steric effects are small, although the evidence is somewhat conflicting. The relatively small-sized electron-withdrawing cyano group produces a blue shift when introduced into the 4 position of a 1,4-dihydropyridine[200,212,214,216,510] or the 2 position of a 1,2-dihydropyridine.[157,223] However, in some tetraacetylglucosyl-1,4-dihydronicotinamides a red shift is actually observed.[62,216] Introduction of a cyano substituent into the 4 position of the highly substituted 3,5-dicyano-1,-2,4,6-tetramethyl-1,4-dihydropyridine does not change the spectrum.[158]

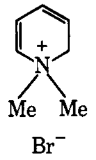
The effect of the electron-releasing SO_2^- group appears to be in the opposite direction,[194,195] but this may be partly due to solvent effects since spectral measurements of the dithionite adducts **41** were not carried out under the same conditions as those on the corresponding dihydronicotinamides **43**.

There are conflicting reports on the effect of a carboxylate group in the 4 position of a 1,4-dihydropyridine. In the case of the Hantzsch ester **75c** introduction of a 4-carboxyl group results in an appreciable hypsochromic shift;[195] similar shifts have been observed for related compounds.[173,511] Esters of the above acid[175] expectedly are shifted to shorter wavelengths, presumably because of their greater bulk. Addition of alkali to the above acid does not change the spectrum. On the other hand, treatment of carboxylic acids derived from polycyclic dihydropyridines, *e.g.*, **89** (R = CO_2H, R′ = H) with base results[344,468] in a bathochromic shift. It is possible that electronic effects in this case predominate over steric factors, whereas the reverse may hold for **75**. Enolization of the carbonyl groups in **89** is also possible. Electron-withdrawing substituents such as $CH(CN)_2$ in the 4 position of **153f** cause a hypsochromic shift of 55 nm relative to **153a**, whereas the electron-releasing piperidino group produces a shift of only 35 nm.[139] Some data on para-substituted phenyl groups in the 4 position of 1,4-dihydropyridines have been recorded.[57]

Solvent effects on the spectra of dihydropyridines have been found[150,157,357,392,499] to be relatively small, suggesting that excited states are only slightly more polar than ground states.

2. *Dihydropyridinium Cations*

Although a number of dihydropyridine spectra have been measured in acid solution,[51,52,64,65,154,166,392,452,478,501] it cannot be presumed, *a priori*, that these represent protonated species. Dihydropyridines undergo acid-catalyzed reactions in nucleophilic solvents (see section VI.C.1), and, unless protonation is demonstrably reversible, results should be treated with caution. Table III summarizes the known data on the dihydropyridinium cations **160–162** (see also section VI.D). The cations absorb at shorter wavelengths than the neutral dihydropyridines.



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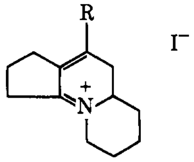
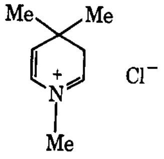


161a, R = Me
b, R = C_6H_5
c, R = OMe
d, R = NH_2



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Although data are scant it may be seen from Table III that, in accordance with expectation, electron-releasing substituents at the end of the conjugated immonium salt **161** cause a bathochromic shift.[512]

Table III

Dihydropyridinium Cations

Compd	*Solvent*	*R*	λ_{max}, *nm*	*Ref*	*Analog references*
160	EtOH		247	243	
161a	$CHCl_3$	Me	304	460	448, 449, 490, 494
161b	$CHCl_3$	C_6H_5	332	460	
161c	EtOH	OMe	334	512	
161d	EtOH	NH_2	348	512	513
162	MeCN		278	392	

3. *Dihydropyridine Anions*

Dihydropyridines are weakly acidic and the action of strong bases affords the corresponding anions, the spectra of which are shown in Table IV. Appreciable red shifts occur on con-

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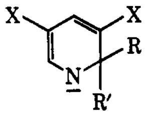
Table V

Calculated and Observed Uv Spectra of Some Dihydropyridines[102]

Compd	Calculated spectra				Observed spectra		Ref
	E_{max}, eV[a,c]	f[c]	E_{max}, eV[b,c]	f[c]	E_{max}, eV	f	
146	3.82	0.27	4.33	0.28	3.8	~0.1	490
	5.72	0.0022	4.43	0.04	4.5	~0.1	494
147	4.30	0.09	4.63	0.095	4.6	0.07	
	5.61	0.13	5.24	0.017	5.4	0.17	392
153e	3.44	0.25	4.23	0.20	3.2–3.3	0.2	102, 500
	5.36	0.12	5.15	0.006	5.2		
153c	3.47	0.23			3.5	0.2	102
	5.05	0.11					
	5.53	0.22			5.8	0.2	
	6.29	0.92					

[a] Using singly excited configurations. [b] Using singly and doubly excited configurations. [c] E_{max} = transition energy, f = oscillator strength.

version of a dihydropyridine into its anion. Some polycyclic dihydropyridines are strong enough acids to form anions with weaker bases in protic solvents.[238, 371, 399, 401, 488, 491]



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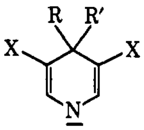

164a, X = CN; R = R′ = H
b, X = CO_2Et; R = Me; R′ = H
c, X = NO_2; R = R′ = OMe

Although data are scarce, the same trends that are found in neutral dihydropyridines are evident; *i.e.*, 1,2 isomers absorb at longer wavelengths than 1,4-dihydropyridines and λ_{max} decreases in the order NO_2 > CO_2Et > CN. The effect of additional alkyl substituents is also similar.[80]

Table IV

Dihydropyridine Anions

Compd	Solvent	X	R	R′	λ_{max}, nm	Ref	Analog ref
163	DMSO	NO_2	OMe	H	487	230	229, 234
164a	DMSO	CN	H	H	426	80	
164b	DMSO	CO_2Et	Me	H	452	80	
164c	MeOH	NO_2	OMe	OMe	455	232	230, 234

4. Theoretical Considerations

The uv absorption characteristics of the dihydropyridines **150, 152, 153, 154,** and **155** were originally discussed in terms of valence bond canonical structures,[65, 157] or of independent excitations of different parts of the conjugated system.[157, 499] The relative positions of band III in isomeric 1,2-, 1,4-, and 1,6-dihydronicotinamides and in some derivatives of **154** and **155** have been correctly predicted by simple Hückel LCAO–MO treatment.[101, 103, 105, 107] Application[102, 108] of LCAO–SCF–MO calculations to electronic transitions in the dihydropyridines **146, 147, 150, 152,** and **153**, using the method of limited configuration interaction, has been relatively successful. In particular, the low intensity of absorption of **147** compared to that of **153** has been satisfactorily interpreted[102] on the basis of computed transition moments. The computational significance of doubly excited configurations has been postulated.[102, 108] Calculations are shown in Table V.

B. FLUORESCENCE

Although the characteristic fluorescence of numerous dihydropyridines has been known for a long time only a few fluorescence spectra have been measured. The emission maxima for 1,6- and 1,4-dihydronicotinamide derivatives were found[59, 60, 154] to be at 443–505 nm and 395–480 nm, respectively; no quantum yields were reported. The activation maxima are at 310–470 nm.[59, 60]

In earlier days fluorescence characteristics were used[53, 496] to distinguish 1,2- (1,6-) from 1,4-dihydropyridines. The latter, *e.g.*, **153** and **155,** usually fluoresce in the solid state as well as in solution on exposure to ultraviolet light; a strong blue[37, 53, 65, 85, 146, 170, 206, 362, 439, 496] or yellow[118, 146, 362] fluorescence is observed. The presence of 1-alkyl substituents reduces or eliminates this fluorescence.[52, 319] Under the same conditions the 1,2- or 1,6-dihydropyridines **151, 152, 154** display either a weak yellow or blue-green fluorescence, or no fluorescence at all.[65, 170, 206] However, these criteria are far from general or reliable and may be seriously misleading; their use is not recommended. Certain secondary reaction products of 1,4-dihydropyridines also fluoresce strongly.[60, 242]

Fluorescence of dihydropyridines may be used for their detection on thin-layer chromatograms[118, 123, 125, 170, 362, 503] or for following certain biochemical reactions.[497, 510, 514]

A qualitative hypothesis correlating fluorescence characteristics with dihydropyridine structure has been proposed,[53] but this should be explored using modern theory. Fluorescence may be considered to support the concept of a rigid planar structure for the dihydropyridine ring.

C. INFRARED SPECTRA

Correlations of dihydropyridine structure with absorption maxima in the ir region has not been developed to any extent. However, dihydropyridines give rise to characteristic bands in the following regions.

1. All dihydropyridines show absorption in the 1500–1700-cm^{-1} region which is assigned to the C=C or C=N stretching modes.[64] In the presence of a conjugating substituent (*e.g.*, C=O), which absorbs in or near the same region, only the

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(514) N. O. Kaplan, S. P. Colowick, and C. C. Barnes, *J. Biol. Chem.*, **191**, 461 (1951).

skeletal vibrations of the whole conjugated system are observed.[59,379,491,515,516] In the light of this fact, some earlier assignments might be revised.[59,85,166,206,517] It is possible that in the case of some N-unsubstituted dihydropyridines absorption due to NH bending is also present.[362,491,515]

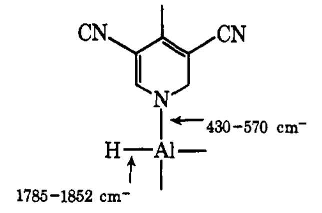
2. Substituents on a dihydropyridine ring absorb at 1700–3100 cm^{-1}. Characteristic stretching modes of the C=O or C≡N groups are shifted to lower frequencies[58,64,169,206,491] than those in the corresponding pyridine derivative, indicating a higher degree of conjugation with the dihydropyridine ring. The bands at 1564–1575 cm^{-1} are reported[515] to be characteristic of 1-alkyl-1,4-dihydropyridines **155** (see also ref 363 and 518).

3. All N-unsubstituted dihydropyridines absorb in the 3100–3500-cm^{-1} region and show the characteristic stretching frequencies for bonded and nonbonded NH groups.[57,58,323,461,516] The number and position of these depend on structural factors and on the conditions of measurement. Absorption in this region has been used for structure determination.[58,165,362,367,516,519] Isomeric 3,5-dicyanodihydropyridines, *e.g.*, **154a** and **155a**, could be distinguished[58] by the differences in this and in the 1500–1700-cm^{-1} regions.

Some correlations between C=C, C=O, and C≡N stretching vibrations and π bond orders in **155** have been made[106,520] by means of simple Hückel LCAO–MO treatment.

Table VI lists a number of typical dihydropyridines with their characteristic ir frequencies. Since no structure–frequency correlations have been made, a range of frequencies rather than individual frequencies are listed in some cases. The table is not intended to be exhaustive and a number of published spectra have been omitted (see ref 42, 43, 52, 61, 103, 141, 198, 229, 241, 302, 310, 379, 399, 456, 490, 493, 516, 521).

Absorption at 300–600 cm^{-1} and the characteristic Al–H stretching frequencies have been used[106] to elucidate the structures of some 3,5-dicyanopyridine adducts **165** and **166** with Grignard reagents and with complex hydrides, respectively.



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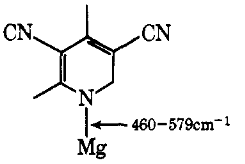

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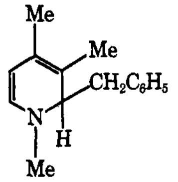

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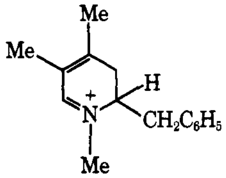

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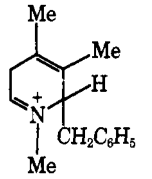

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The Raman spectra of some dihydropyridines have been determined.[517]

D. NUCLEAR MAGNETIC RESONANCE

Nuclear magnetic resonance has been found to be an invaluable tool for the investigation of dihydropyridine chemistry. Up to now only proton magnetic resonance spectra have been determined, but no doubt eventually the spectra of other nuclei (^{13}C, ^{15}N) will be studied.

The most useful application of nmr has been to structure determination,[521a] specifically of simple 1,2-dihydropyridines,[26,71,148,159,243,295,306,467] 2,3-dihydropyridines,[34,513] 1,4-dihydropyridines,[61,71,148,272,294,295,392] 1,4-dihydronicotinamides,[43,52,60,62,97,142,148,193–195,216,501,522] other 3-substituted 1,4-dihydropyridines[116,139,148,193,195,204,217,244,480,495] and related 1,2 and 1,6 isomers,[62,139,140,142,148] Hantzsch-type 1,4-dihydropyridines [80,157,158,173,175,204,324,353,466,468–470,472,518,523,524] and some of their 1,2 isomers,[158,288,370,380,504] 2-amino-3,4-dihydropyridine derivatives,[42,43] NADH and related compounds,[98,525] anions from 3,5-dinitropyridines,[229–232,234] and other, more complex structures.[141,198,244,302,456,493,516]

Specifically deuterated dihydropyridines have been found particularly useful in nmr investigations.[139,160,193,194,501,522]

Another important use of nmr spectroscopy has been the detection and identification of dihydropyridine intermediates which may or may not have been isolated as, for example, in the reaction of pyridines or pyridinium salts with complex hydrides,[74] organometallic reagents,[159,160,162] sodium dithionite,[194,195,207,526] alkoxides,[229,230,232,234,248] and cyanide ion.[148,160,215–217]

Reaction kinetics[218,522] and tautomeric equilibria[43] have been followed by nmr techniques.

Table VII summarizes some typical dihydropyridine spectra. The chemical shifts of the ring protons at unsaturated centers range from τ 2.4 to 5.6; as might be expected, proximity of an electron-withdrawing substituent or of the ring nitrogen results in shifts to lower field. The ring protons at saturated centers produce signals at τ 5.5–7.0, but an unusually low-field shift at τ 4.46 has been noted[306] for the proton in the 2 position of 1-acetyl-1,2-dihydropyridine-2-acetic acid (**148a**).

Vicinal coupling constants across a double bond (CH=CH) are generally larger than those across a single bond (=CH—CH=). The NH proton is frequently coupled to the adjacent 2 and/or 6 proton (*e.g.*, ref 288), but whether or not this occurs may depend on the solvent.[80] The ring methylene protons are equivalent[71,80,97,141,148,194] indicating a planar or rapidly inverting conformation of the ring (see section III.B). Long-range coupling across the ring is frequently observed (see Table VII).

The anomeric configuration of the sugar residue in NADH was established by nmr method.[526a]

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(515) E. I. Stankevich and G. Vanags, *Zh. Org. Khim.*, **1**, 809 (1965); *Chem. Abstr.*, **63**, 6817 (1965).

(516) E. I. Stankevich and G. Vanags, *Zh. Org. Khim.*, **1**, 815 (1965); *Chem. Abstr.*, **63**, 6817 (1965).

(517) G. B. Bonino, R. Manzoni-Ansidei, and G. Lemerte, *Ric. Sci.*, (2) 7, I, 132 (1936); *Chem. Abstr.*, **31**, 3388 (1937).

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(521) Yu. E. Pelcere, E. E. Grinstein, E. I. Stankevich, and G. Vanags, *Khim. Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly*, 406 (1967); *Chem. Abstr.*, **70**, 87742 (1969).

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(526) J. F. Biellmann and H. J. Callot, *Tetrahedron Lett.*, 3991 (1966).

(526a) R. U. Lemieux and J. W. Lown, *Can. J. Chem.*, **41**, 889 (1963).

Table VI

Infrared Spectra of Dihydropyridines

Compound	ν_{max}, cm^{-1} Region 1	Region 2	Region 3	Ref	Analog references
167	1582,[a] 1605, 1653			490	494
146b	1552, 1625			295	
147a	1680		3450	294	
148e	1610			456	
149a	1630, 1660	1700		73	300
151a	1633, 1643, 1667	1725		143	
152	1580–1600, 1640–1653	2188	3190, 3400[b]	59	64
153	1605–1650, 1670–1690	2180–2200	3000–3440[b]	59	43, 64, 165, 166, 418, 495
154a	1505, 1540, 1560, 1642	2192	3300	503	58, 123, 170, 171
154e	1522, 1649	1690	3140, 3340	118	
154f	1688–1693	1708–1740[c]		451	
154g	1642	1682	3420	288	
155a	1500, 1620, 1685	2192	3325, 3380	503	58, 123, 168, 170, 172, 173, 323, 363
155b	1583, 1658	2212	3290, 3431	362	
115	1610, 1675	2220	3300, 3420	323	
155f	1510,[e] 1618	1720	3350, 3472	118	52, 323, 324, 446, 469–472, 479, 515
155g	1650	1700	. . .[d]	466	375, 446
155h	1600, 1660	2970, 2880		80	85, 165, 172, 206, 367, 376, 381, 468
89	1480–1596,[c] 1600–1608		3007, 3090 3120, 3215[c]	239	371, 515
157	1667	1695, 1727	3145	43	
159a	1600, 1667			33	34
161a	1626, 1681			460	
161c	1563, 1681			512	
161d	1536, 1656		3165, 3356	512	513
168	1597,[a] 1678			490	494
169	1600, 1678, 1706			490	494

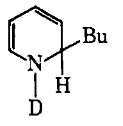
[a] Band due to phenyl group. [b] Only when NH_2 or $CONH_2$ substituents present. [c] One or two maxima. [d] Not reported. [e] Inflection at this value.

Table VII

Nuclear Magnetic Resonance Spectra of Dihydropyridines[a]

Compound	Chemical shifts, τ 2H	3H	4H	5H	6H	Coupling constants, Hz $J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{2,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,6}$	$J_{2,6}$	Ref
170	6.16	5.23	4.39	5.65	4.06	4.2	9.8	5.4	7.1	1.1	1.3	0.9	1.4		159
147a	4.27	5.23	6.85	5.58	4.27[b]										294
146c	5.74	4.79	4.20	5.06	3.59	3.6	7.7	4.5	6.9	1.5	0.9	0.9	0.9		71
147c	3.73	5.47	7.02	5.47	3.73	9.0	3.9			1.6					71
152b	2.90		4.34	5.33	6.12			9.4	3.9	1.5				1.0	62
153c	2.81		6.82	5.24	4.25			3.4	8.2	0.5			1.7	1.5	62
153b	3.41		6.90	5.40	4.20[b]										116
154e	4.36		7.49		7.61					0.75			1.5[c]		288
155e[d]	3.26		6.40		3.26										80

[a] In $CDCl_3$ unless otherwise stated. [b] Coupling constants not reported. [c] $J_{1,6}$ = 7.0 Hz; $J_{1,2}$ = 1.7 Hz. [d] Diethyl ester in C_6D_6; $J_{1,2}$ = 5.0 Hz.



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E. MASS SPECTROMETRY

In recent years mass spectrometry has occasionally been used in structure determination of dihydropyridines.[173,215,306,456] Detailed investigations of mass spectral fragmentations have been reported,[199,439,527,528] and no doubt this method will acquire increasing importance in structure determination.

The most important fragmentation process is the formation of the aromatic pyridinium ion. This may take place either by loss of a hydrogen radical[199,439] as shown in eq 29 or by loss of a radical R· from the 4 position of a substituted 1,4-dihydro-

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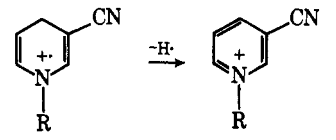
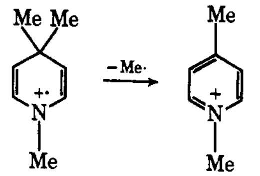
(527) R. E. Lyle and E. White, *Tetrahedron Lett.*, 1871 (1970).

(528) R. E. Lyle and E. White, *J. Org. Chem.*, **36**, 772 (1971).



(29)

pyridine as shown[199,439] in eq 30 and 31. Similarly, substituted 2-aryl-1,2-dihydropyridines preferentially lose[527,528] an aryl radical to give a pyridinium ion as shown in eq 32.



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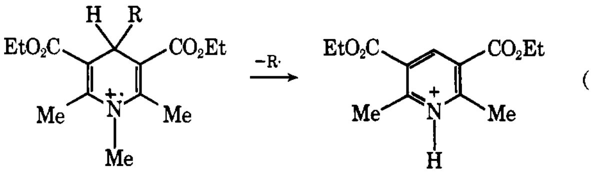
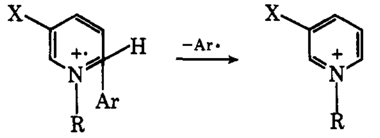


(31)



(32)

X = CN or $CONH_2$

Other, less important fragmentations are the loss of *N*-alkyl substituents,[199,527,528] cleavage of 3 and/or 5 substituents,[439] and opening of the heterocyclic ring. The kinetic isotope effect k_H/k_D for a 4H (4D) substituent was found[199] to be inversely related to the ionizing voltage.

F. MISCELLANEOUS

The measured[499] dipole moment (3.89 D) of 1-benzyl-1,4-dihydronicotinamide was found to be much smaller than that calculated[102] (5.9 D) by the Pople LCAO–SCF method.

Molecular exaltations were shown[529] to distinguish between certain isomeric dihydropyridines.

Very few pK_a values have been determined.[392,530] Optical rotations of dihydropyridines with sugar residues in the 1[138] or 4[388] positions have been reported.

2,4,4,6-Tetraphenyl-1,4-dihydropyridine has photochromic properties.[395,531]

VI. Chemical Properties

According to one author (ref 8, p 81) "the most important reaction of dihydropyridines is their oxidation to the corresponding pyridine." While this is clearly a matter of opinion, there is no doubt that a vast volume of the work on dihydropyridines has been concerned with this aspect. This is understandable in view of the important role of NADH in hydrogen transfer in biological systems. A number of reviews on this subject exist,[4-7] and it is not intended here to deal with the biochemical aspects.

A. OXIDATION

While a classification of dihydropyridine oxidations into dehydrogenation, hydrogen transfer, and disproportionation might seem somewhat arbitrary, it is adopted here for the sake of clarity. Under the heading "dehydrogenation" are listed reactions, the principal aim of which is the preparation of a pyridine. "Hydrogen transfer," on the other hand, includes studies designed to investigate the mode of action of NADH, and the nature of the reduced product is of greater importance than the pyridine. Finally, the term "disproportionation" is confined to those reactions in which the dihydropyridine is both the donor and the acceptor of hydrogen.

1. Dehydrogenation

Nitrous or dilute nitric acids are among the oldest and still most commonly used reagents.[1,318,338,381,391] The former is used either in the form of dinitrogen tetroxide or else it is generated from sodium nitrite–acetic acid. Chromic acid is another popular reagent.[49,58,206,358] Sulfur is particularly useful since it is often the only reagent which dehydrogenates without any side reactions (see below).[320,321,323,327] A number of dihydropyridines have been dehydrogenated[335,418,532] by heat alone although it is not entirely clear whether this is due to aerial oxidation or disproportionation. A series of Hantzsch esters has been dehydrogenated by palladium in a hydrocarbon solvent containing a catalytic amount of acetic acid;[533] potassium permanganate in acetic acid could also be used.[533] Some dihydropyridines have been dehydrogenated in moderate yield by heating with palladium on carbon.[43,58,170,534] High-potential quinones such as chloranil[165] or dichlorodicyanoquinone[42] have found application. Other reagents include *p*-nitrosodimethylaniline,[61,241] hydrogen peroxide,[235,415] diisoamyl disulfide,[32] silver nitrate,[196] platinum in acetic acid,[69] mercuric acetate,[361] iodine,[71] and iron or nickel carbonyls.[110] In one case treatment of an alleged bis(hydroxymethyl)dihydropyridine derivative with thionyl chloride gave[129] the corresponding bis(chloromethyl)pyridine; presumably the reaction was carried out in the presence of air which caused the dehydrogenation. The formation of 4-(1-acetyl-3-indolyl)pyridinium chloride instead of the expected 4-(1-acetyl-3-indolyl)-1,4-dihydropyridine was traced[300] to the presence of excess 1-acetylpyridinium chloride which acted as a hydrogen acceptor. Oxygen or air have been used in a number of instances,[26,37,269,298,460] and a mechanism for this reaction has been proposed.[37] Quantitative estimation of dihydropyridines by titration with iodine or potassium ferricyanide has been reported.[26,65,197,279,496] The older work is summarized in ref 8, p 236.

Oxidation of the tetrahydrobipyridyls **171** may give different products according to conditions. With air, manganese dioxide, lead dioxide, or dinitrogen tetroxide the corresponding bipyridyls **172** are obtained.[266] The reaction with air or oxygen has been shown[268-270] to proceed *via* the dihydrobipyridyl **173**.

Occasionally dehydrogenation of a dihydropyridine proceeds abnormally. One such reaction commonly encountered is the loss of a substituent, usually, but not always, from the 4

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(529) K. Auwers, *Ber.*, **63**, 2111 (1930).

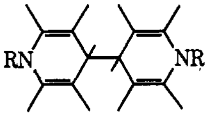
(530) E. I. Stankevich, J. Popelis, E. Grinshtein, A. Ozola, and G. Duburs, *Khim. Geterotsikl. Soedin.*, 122 (1970); *Chem. Abstr.*, **72**, 89602 (1970).

(531) A. Peres de Carvalho, *C. R. Acad. Sci.*, **200**, 60 (1935).

(532) I. Guareschi and E. Grande, *Atti Reale Accad. Sci. Torino*, **34**, 18/6 (1899); *Chem. Zentr.*, II, 440 (1899).

(533) A. Kamal, M. Ahmad, N. Mohd, and A. M. Hamid, *Bull. Soc. Chem. Jap.*, **37**, 610 (1964).

(534) R. E. Misner, *Diss. Abstr.*, **29B**, 2817 (1969).



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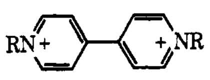

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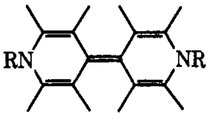

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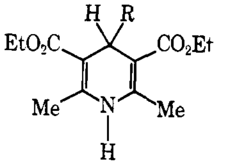
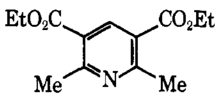
position. Thus dehydrogenation of the Hantzsch esters **75** gave the dealkylated pyridines **174** when R = isopropyl[313] (but not *n*-propyl[314]), benzyl,[316, 335] *p*-dimethylaminophenyl,[328] carboxyl,[175] or cyanomethyl.[323] In the case of the nitrile **175** a benzyl group was lost from the 2 position.[171, 535] Dehydrogenation with the loss of a substituent took place with nitrous acid, or, in one case, chloranil,[323] but when sulfur was used the expected pyridine was obtained.[320, 321, 323, 327] In a systematic study of this reaction it was found[536] that loss of a substituent occurred if a stable carbonium ion could be formed (*e.g.*, isopropyl, *tert*-butyl, benzyl). Steric factors were also involved since the isopropyl group was lost from **75g**, but not from the corresponding dinitrile (**75g**, CN instead of CO_2Et). Benzyl alcohol, benzyl acetate, and benzaldehyde were isolated when **75h** was subjected to oxidative dealkylation, and a mechanism for the reaction was proposed.[536] A slightly different mechanism was put forward[535] for loss of the 2-benzyl group from **175**. In certain cases substituents in the 4 position were lost on heating.[532]



75a, R = Me
b, R = $C_6H_4NO_2$
c, R = H
d, R = C_6H_5
e, R = CH_2CN
f, R = D
g, R = Pr-*i*
h, R = $CH_2C_6H_5$
i, R = CH_2Cl
j, R = $CH{=}CHC_6H_5$



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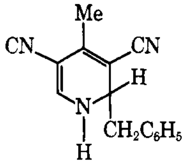

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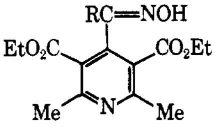
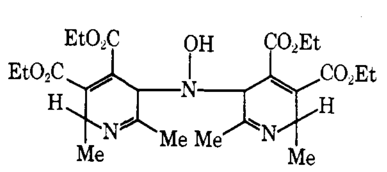


176a, R = H
b, R = CN

Other abnormal dehydrogenations include reaction of nitrous acid with a substituent. Thus dehydrogenation of **175i** or **175e** gave the pyridines **176a** and **176b**, respectively.[323, 436] Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,4-dicarboxylate under similar conditions was claimed[87] to give the unlikely product **177**, formulated as a 2,5-dihydropyridine. 1-Methyl-3,4,5-tricyano-1,4-dihydropyridine afforded the stable hydroxy-1,2-dihydropyridine **58**. With dinitrogen tetroxide **58** could be further oxidized to the corresponding pyridone.[222, 223] Loss of an *N*-acyl substituent usually occurs on dehydrogenation; thus, 1-benzoyl-4-phenacyl-1,4-dihydropyridine was converted[11] into 4-phenacylpyridine with oxygen, although iodine converted it into the enol ether **178**. On heating with nitrobenzene the dihydropyridine **74** gave picolinamide.[312]



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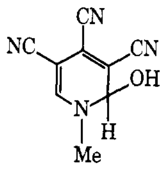

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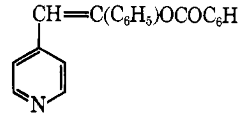

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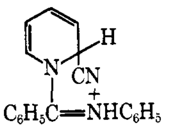

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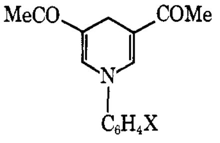

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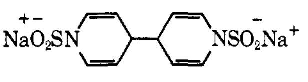

61i

Little work has been reported on the correlation of structure with ease of oxidation and more information is clearly desirable. Some quantitative data[76] are shown in Table VIII.

Table VIII

Rates of Dehydrogenation of Dihydropyridines

Isomer	R_1	R_3	R_5[a]	*Oxidizing agent*	K[b]	E_A, *kcal*
1, 4	DCB[c]	$CONH_2$	H	BQ[d]	800	
				DPP[e]	220	3.8
1, 2	DCB[c]	$CONH_2$	H	BQ	540	
				DPP	190	3.1
1, 4	DCB[c]	COMe	H	BQ	45	
				DPP	35	
1, 4	DCB[c]	CO_2Et	H	DPP	420	
1, 4	$C_6H_5CH_2$	$CONH_2$	H	DPP	420	
1, 4	$C_6H_5OCH_2$	$CONH_2$	H	DPP	16.5	
1, 4	TAG[f]	$CONH_2$	H	DPP	2.7	7.2
1, 4	DCB	$CONH_2$	$CONH_2$	DPP	2.6	
1, 2	DCB	$CONH_2$	$CONH_2$	DPP	1.5	
1, 4	DCB	CO_2Me	CO_2Me	DPP	3.0	
1, 2	DCB	CO_2Me	CO_2Me	DPP	<0.05	

[a] Substituents in the 1, 3, and 5 position, respectively. [b] Second-order rate constant. [c] 2,6-Dichlorobenzyl. [d] Benzoquinone. [e] Dichlorophenol indophenol. [f] Tetraacetylglucopyranosidyl.

The above dehydrogenations were hydride-transfer reactions as shown by their second-order kinetics and low activation energies.

Surprisingly, the 1,2-dihydropyridines were dehydrogenated less readily than the corresponding 1,4 isomers. The relative rates of dehydrogenation decrease with the substituents in the 3 position in the order $CONH_2$ > CO_2Et > COMe, and with the substituents on the nitrogen in the order $C_6H_5CH_2$ >

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(535) J. Kuthan and R. Bartoníčková, *Z. Chem.*, **4**, 271 (1964).
(536) B. Loev and K. M. Snader, *J. Org. Chem.*, **30**, 1914 (1965).

$Cl_2C_6H_3CH_2 > C_6H_5OCH_2 >$ TAG, in agreement with other work.[537]

This work has recently been repeated and extended.[216] It was found that 1-alkyl-1,6-dihydro-4-methylnicotinamides were dehydrogenated at a faster rate than the corresponding 4-unsubstituted derivatives. The presence of a methyl substituent in the 4 position of a 1,4-dihydronicotinamide did not appreciably affect the rate.

The rates of dehydrogenation in a series of 1-substituted 3,5-diacetyl-1,4-dihydropyridines **179** were shown[368] to decrease in the order $p\text{-}HOC_6H_4 > C_6H_5CH_2 > C_6H_5$.

MO calculations predict[103,105] that 1,2-dihydropyridines with electron-withdrawing groups in the 3 and 5 positions should be more readily oxidized than their 1,4 isomers. This may be true for free radical dehydrogenations (see below), but it has not been verified experimentally so far. Silver oxide selectively dehydrogenates[503] 3,5-dicyano-1,2-dihydropyridine in the presence of the corresponding 1,4 isomer.

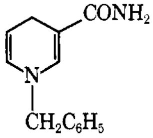
Reports exist[16,460] on dihydropyridines which resist dehydrogenation. One tricyclic 1,4-dihydropyridine on attempted dehydrogenation with nitrous acid afforded[88] the corresponding *N*-nitroso derivative. It has been claimed[21] that hydrogen peroxide oxidizes **61i** to the corresponding disulfonate. Ozonolysis of **75a** or **75d** gave[52] acetic and benzoic acid, respectively, indicating that addition of ozone to the double bonds competes favorably with dehydrogenation.

In reactions somewhat analogous to dehydrogenations, dihydropyridines have been converted into pyridines by elimination of lithium hydride,[162,163] benzoic acid,[310] trimethylsilane,[295] phenol,[78,79] water,[176] carbon dioxide,[175] or *N*-methylacetamide.[211]

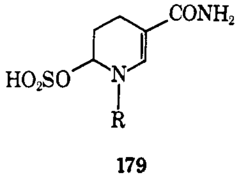
2. Hydrogen Transfer

Most of the experiments on the hydrogen transfer of dihydropyridines have been designed to elucidate the mode of action of NADH. Although many details, including stereochemistry,[4,538,539] of hydrogen transfer in enzymatic systems have been clarified, one unresolved question is whether it is a one-electron or a two-electron reduction. Examples of both types of mechanism have been encountered in model systems: the older work has been extensively reviewed[4-6] and will only be briefly mentioned here.

Early work showed that 1-benzyl-1,4-dihydronicotinamide (**13a**) could reduce malachite green, diphenylpicrylhydrazyl, and various quinones.[54,495,498] Other reducible compounds include hexachloroacetone,[495,540] pyruvic acid,[96,498] aromatic nitro compounds and their reduction products,[541] the alkyl sulfite[542] **179**, thiobenzophenone,[519] and tropylium ion.[480] The Hantzsch ester **75c** has been used to reduce pyruvic acid,[543] chloranil,[506,544] maleic acid and its derivatives,[545] various olefins,[545] azo compounds,[545] quinoline and isoquinoline,[546] indolenines,[547-550] certain α,β-unsaturated ketones,[508,544,545] and dipyridyl *N*-oxides.[550a]



13a



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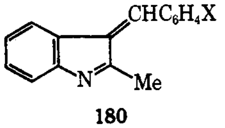
a, $R = CH_2C_6H_3Cl_2$



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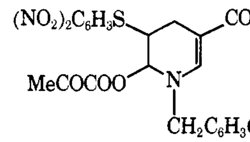
Evidence for direct hydride transfer was obtained for deuterium-labeled NAD[538] and for the reduction of pyruvic acid in deuterium oxide, which gave unlabeled lactic acid.[543] Deuterium transfer was shown to take place from **75f** to 1-phenyl-4-trifluorobut-2-en-1-one,[508] 3-benzoylacrylic acid,[508] and thiobenzophenone.[519] Kinetic results were used to establish hydride transfer for the reduction of quinones,[76] tropylium ion,[480,481] dichlorophenol indophenol,[76] riboflavine,[537] and thiobenzophenone.[519] The rates of reduction for the indolenines **180** decreased in the order $X = p\text{-}NO_2 > o\text{-}Cl > p\text{-}MeO$, and a Hammett ρ value of $+0.6$ was found[547] for the reaction (see also ref 548 and 549). Reduction of hexachloroacetone with **13a** in formamide gave hexachloro-2-propanol in high yield by direct hydrogen transfer;[193,495] in cyclohexane tetra- and pentachloroacetone were produced by a free-radical reaction.[193] Reduction of hexachloroacetone to the corresponding alcohol also took place in aqueous solution where the yield was dependent upon pH.[202] Pyruvic acid on treatment with 1-(2′,6′-dichlorobenzyl)-5-(2′,4′-dinitrophenylthio)-1,4-dihydronicotinamide gave the adduct **181** which decomposed to lactic acid and the pyridinium salt.[96]

Intramolecular hydrogen bonding in aromatic aldehydes is important; thus, substituted salicylaldehydes dehydrogenate **75c** under conditions where substituted benzaldehydes do not.[551]



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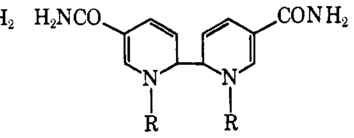

65

Few examples of free-radical hydrogen-transfer reactions are known. The dihydropyridine **75c** was dehydrogenated photolytically by bromotrichloromethane,[475] and by 2-sulfhydrylbenzophenone.[552] Since there was no deuterium transfer in the latter reaction, it was implied[552] that enzymatic reactions proceed by hydride transfer. Benzophenone, benzaldehyde, and cinnamaldehyde were reduced by dihydro-

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pyridines in the presence of sodium or lithium metal,[553] presumably *via* the metal ketyls. The dimer **65** appears to be oxidized by a free-radical process.[279] Interaction of **13a** with *p*-benzoquinone or 1,4-naphthoquinone, but not chloranil or 2,6-di-*tert*-butylbenzoquinone, was shown to give esr signals.[554] The formation of a charge-transfer complex in the oxidation of NADH by ferric ion points to a one-electron process; with a large excess of ferric ion the NADH becomes a two-electron donor.[555]

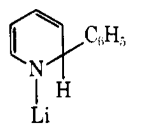
The kinetics and mechanism of the dehydrogenation of the 1,4-dihydropyridines **13a** and **75c** with triphenylverdazyl radical and triphenylverdazyl cation have been studied.[485,556–558] The cation reacts 10^6 times faster than the radical.[485] Solvent effects on the rates have been investigated, and the rate-determining step is believed to be hydrogen transfer from the radical–dihydropyridine charge-transfer complex rather than a one-electron transfer.[558]

A somewhat similar complex between a dihydropyridine cation radical and tetramethylthiocarbamate anion is believed[559] to be an intermediate in the cleavage of the S–S bond in tetramethylthiuram disulfide by the dihydronicotinamide **13a**.

Electrochemical oxidation of dihydronicotinamide derivatives to the corresponding pyridinium salts has been shown[560] to proceed *via* a one-electron process giving an intermediate radical ion. The fate of the latter depends on conditions: in the presence of base it undergoes proton transfer, in the presence of oxygen hydrogen peroxide is formed, and in buffered solution disproportionation takes place with the formation of complex products.

A number of catalyzed hydrogen-transfer reactions have been discovered. For example, the rate of aerial oxidation of **13a** is enhanced by quinones,[476,561] and a mechanism has been proposed.[561] Flavines and related compounds catalyze the aerial oxidation of various dihydropyridines *via* radical intermediates.[562] A general mechanism to account for the hydrogen transfer from reduced nicotinamides to flavines has been postulated.[486] Phenazine, alone or, better, in the presence of cupric ion, catalyzes the oxidation of **13a**, and two possible mechanisms have been proposed.[483,484,556,557,563] One of these involved the intermediacy of the hydroperoxide of **13a**. The same intermediate was postulated[564] in the oxidation of cyclobutanone to butyrolactone and butyric acid by oxygen in the presence of **13a**. Fluorenone reacts with **75c** in the presence of catalytic amounts of various aldehydes or ketones; a free-radical mechanism has been put forward.[565]

Dihydropyridine–metal complexes are able to reduce carbonyl compounds. Thus, pyridine solutions of phenyllithium[566] and lithium aluminum hydride[74] which contain the complexes **182** and **183**, respectively, selectively reduce aromatic ketones. A solution of *n*-butyllithium in pyridine in the presence of tetramethylethylenediamine similarly reduced benzophenone.[567] The rates of hydrogen transfer from the 1,2- and 1,4-dihydropyridine units in **183** are about equal.[568]



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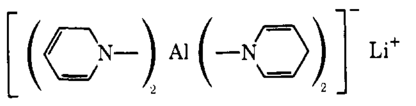

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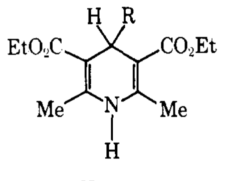
3. Disproportionation

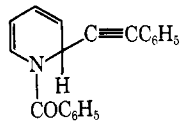
The earliest reported[246] dihydropyridines allegedly resulted from action of sodium hydroxide on quaternary pyridinium salts. The products were unstable reducing substances, and their structures were never established. It was later[569] suggested that, by analogy with the behavior of quinolines, the initially formed 1-substituted 2-hydroxy-1,2-dihydropyridines disproportionated into 2-pyridones and presumably 2-hydroxytetrahydropyridines.

Disproportionation of dihydropyridines has been carried out by means of concentrated hydrochloric acid,[1,69,443] or by heat.[429,532] However, the mildest and most useful method is probably the action of palladium. Early workers[289,570] found that on heating the dihydropyridine **75c** with palladium the corresponding pyridine together with a compound believed to be a hexahydropyridine resulted. This was subsequently[287] shown to be the 1,4,5,6-tetrahydropyridine. Similar results were obtained with other dihydropyridines[418,455] at room temperature. Diethyl 1,2-dihydropyridine-3,5-dicarboxylate disproportionated about 25 times faster than its 1,4 isomer.[288]

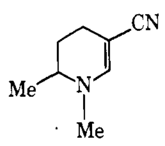
Intramolecular disproportionation took place on heating **75j**, affording the corresponding pyridine having a phenethyl substituent in the 4 position.[335] The dihydropyridine **73a** on treatment with alkali gave 2-styrylpyridine.[310]



75c, R = H
f, R = D
j, R = CH=CHC6H5



73a



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The "disproportionation" of tetrahydrobipyridyls has been discussed earlier (section IV.C.4).

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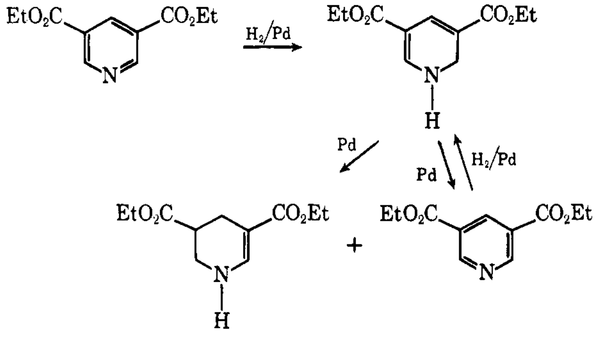
B. REDUCTION

1. Catalytic Hydrogenation

Catalytic hydrogenation of dihydropyridines can yield the corresponding tetrahydro[37,64,166,181,270,302,425,571] or hexahydro[11,66,70,144,176,189,295,310,392,421,425,571] derivative. Tetrahydrobipyridyls appear to give bipiperidyls on hydrogenation[268,462] although piperidines have also been obtained.[37,279] It has been reported[37,52,224,264] that 1,2- and 1,4-dihydropyridines (at least of the Hantzsch-type **75**) may be distinguished by hydrogenation. The former take up 1 mol of hydrogen to give tetrahydropyridines, whereas the latter are slowly reduced to piperidines. A series of pyridinium salts was shown to give tetrahydropyridines on hydrogenation, whereas the corresponding pyridine gave the piperidine.[287] The former reaction presumably proceeds *via* a 1,2-dihydropyridine, the latter *via* the 1,4 isomer. Later work[184] gave essentially similar results but showed that *N*-benzyldinicotinamide (**155e**) was reduced to the debenzylated tetrahydro derivative *via* a relatively stable 1,2-dihydropyridine. N-Substituted 3-cyano-1,4- and 1,6-dihydropyridines both gave the corresponding tetrahydro compound[184] in contrast with the Hantzsch esters **75** (see above). 3-Cyano-1,6-dimethyl-1,2- and -1,6-dihydropyridines each gave 3-cyano-1,6-dimethyl-1,4,5,6-tetrahydropyridine on hydrogenation, which was explained by isomerization on the catalyst surface.[184] It has been proposed[288] that hydrogenation of diethyl pyridine-3,5-dicarboxylate to the corresponding 1,4,5,6-tetrahydropyridine does not proceed by hydrogenation of the intermediate 1,2-dihydropyridine (which can be isolated) but by its disproportionation according to eq 33.



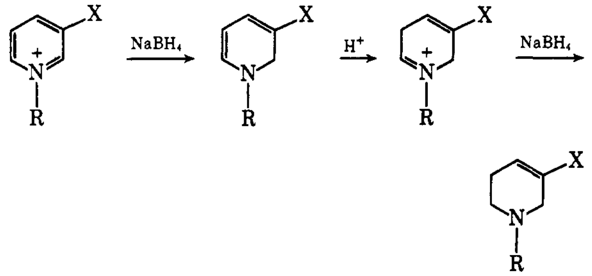
(33)

Bulky substituents in the 4 position of 1,4-dihydropyridines inhibit hydrogenation.[19,297,324] Bicyclic 2,3-dihydropyridines or their salts are reduced to the corresponding 1,2,3,6-tetrahydropyridines.[38,39] Hydrogenation of 4-cyano-1-methyl-1,4-dihydronicotinamide gave a mixture of 1-methyltetra- and -hexahydronicotinamides;[220] cyanide ion is presumably eliminated first, followed by reduction of the resulting quaternary pyridinium salt.

2. Hydride and Other Types of Reduction

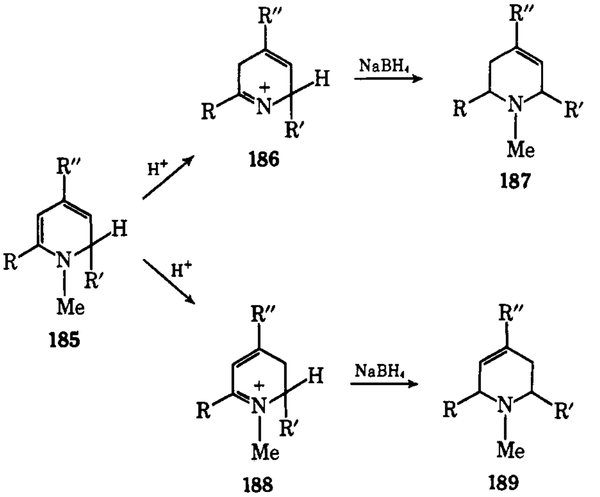
The sodium borohydride reduction of pyridinium salts proceeds *via* 1,2-dihydropyridines which are further reduced to 1,2,5,6-tetrahydropyridines[131–133,144,145,572] (see section IV. A.1.a).

The 1,4- and 1,6-dihydropyridines are more resistant to borohydride reduction[131,573,574] and can sometimes be isolated. The mechanism of the reduction of 3-substituted 1,2-dihydropyridines with borohydride in aqueous solvents is postulated to proceed by protonation at C-5 followed by reduction of the C=N bond[131,132] according to eq 34. The proton was believed to be derived from the solvent,[131,132] but more recent work[574] has shown that diborane or one of its hydrolysis products is essential for the reduction and the protonating species is claimed to be a borane–water complex $R_3B\cdots OH_2$.



(34)

4-Substituted 1,2-dihydropyridines behave somewhat differently in that protonation ocurs at C-3 and/or C-5. Thus, the dihydropyridines **185a** gave[132] **187a** *via* the 3-protonated intermediate **186a**, whereas **185d** afforded[513] **189d** *via* the 5-protonated intermediate **188d**. The alkyl-substituted dihydropyridine **185b** yielded mixtures of **187b** and **189b**; **185c** behaved similarly.[575]



a, R = C_6H_5; R′ = H; R″ = Me
b, R = H; R′ = $CH_2C_6H_4OMe$; R″ = Me
c, R = H; R′ = $CH_2C_6H_4OMe$; R″ = Et
d, R = H; R′ = $CH_2C_6H_5$; R″ = OMe

An alternative, but less plausible mechanism for the borohydride reduction *via* a 1,4-dihydropyridine, which is in equilibrium with the corresponding 3,4-dihydropyridine, has been postulated.[135]

In dihydropyridinium salts[490,576] such as **186** and **188**, and in 2,3-dihydropyridines,[34] only the C=N bond is reduced with

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(571) D. Craig, U. S. Patent 2,479,815 (1949); *Chem. Abstr.*, **44**, 4044 (1950).

(572) K. Wallenfels, D. Hofmann, and H. Schüly, *Justus Liebigs Ann. Chem.*, **621**, 188 (1959).

(573) N. Kinoshita and T. Kawasaki, *Yakugaku Zasshi*, **83**, 120 (1963); *Chem. Abstr.*, **59**, 5126 (1963).

(574) F. Liberatore, V. Carelli, and M. Cardellini, *Tetrahedron Lett.*, 4735 (1968).

(575) M. Takeda, A. E. Jacobson, K. Kanematsu, and E. L. May, *J. Org. Chem.*, **34**, 4161 (1969).

(576) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **7**, 409 (1964); *Chem. Abstr.*, **61**, 4304 (1964).

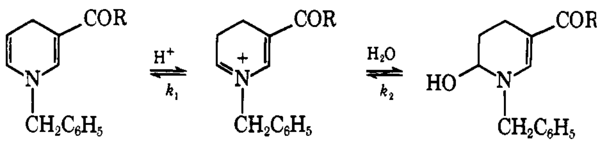
sodium borohydride. In the latter case hydrogenation gave the 1,2,3,4-tetrahydropyridine, presumably by 1,4 addition, and borohydride the expected 1,2,3,6 isomer.[33] Dihydropyridines have also been reduced with sodium-alcohol[422] or formic acid.[422] The electrochemical reduction of a putative 2,2′-tetrahydrobipyridyl was said to give a hexahydro derivative.[286]

C. REACTIONS

1. Nucleophilic Addition to Protonated Dihydropyridines

One of the most extensively investigated reactions of dihydropyridines is the addition of the elements of water to give hydroxytetrahydro derivatives. Interest in such compounds was stimulated by their relationship to NADH–X, an enzyme–NADH adduct.

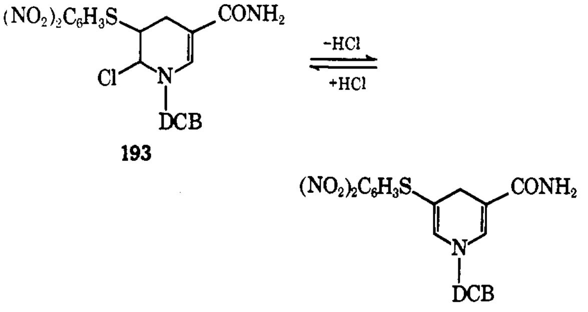
In a pioneering study[500] it was shown that mild acid treatment of the dihydropyridines **190a** gave a mixture of the tetrahydropyridine **192a** and a dimeric compound (see below). Kinetic measurements suggested a mechanism involving rapid reversible protonation of **190** to give **191** followed by addition of the nucleophile in a rate-determining step. The structure of **192** has been confirmed by nmr and by X-ray crystallography.[502] It has also been shown that the formation of **192** was reversible.[502] More sophisticated mechanistic studies[477,478,502,522] with related systems have shown that the original mechanism is generally correct, but that the relative magnitudes of the rate constants K_1 and K_2 can be reversed by changes of solvent and pH. A claim[147] that isomeric 1,4- and 1,6-dihydropyridines gave the same adduct was found to be erroneous since it was later shown[148] that the dihydropyridines used in these experiments were mixtures; the kinetic results obtained with these mixtures[147] are therefore also of little value.



190 **191** **192**

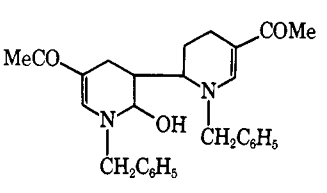
a, R = Me
b, R = NH$_2$

Other nucleophiles add to the protonated dihydropyridines in a similar fashion, and adducts of general structure **192** (OCOR instead of OH) have been obtained from pyruvic[96] and maleic[577] acids. Adducts **192** (Cl, OMe, OPO_3H_2, and SC_6H_5 instead of OH) have been obtained from hydrogen chloride,[166] methanol,[502] phosphoric acid,[522] and thiophenol,[572] respectively. Similarly, 2,4-dinitrophenylsulfenyl chloride added to **190b** (2,6-dichlorobenzyl instead of benzyl) to give a compound, of probable structure **193**, which loses HCl reversibly to give the dihydropyridine **194** as shown in eq 35. An isomeric adduct is obtained from the corresponding 1,6-dihydronicotinamide derivative.[572] The adduct **192b** was obtained as a by-product during the dehydrogenation of **190b** with tropylium ion; it was believed to be formed by reaction of **191** with ditropyl ether followed by protolysis of the cycloheptatrienyloxy analog **192b** (C_7H_7O instead of OH).[481]



193 **194** (35)

Dihydropyridines are sufficiently nucleophilic to add to the protonated species **191**. Thus, in the reaction of **190a** with acid[500] a dimeric by-product **195** was obtained along with **192a**. The structure **196** of a cage-like dimer obtained by the action of acid on 1-methyl-1,4-dihydronicotinamide[54] was determined by X-ray methods.[578] Treatment of the HCl adduct of 3-benzoyl-4-phenyl-1,4-dihydropyridine with water gave[166] **197**. On heating a mixture of 1-dichlorobenzyl-3-cyano-1,2- and -1,6-dihydropyridines in chloroform the dimer **198** was formed.[141] Reaction of the above 1,2-dihydropyridine with the corresponding pyridinium salt gave a product analogous to **198** with an additional double bond in the 5′,6′ position. These dimeric products are formed by a common mechanism involving the attack of an enamine on the protonated species.



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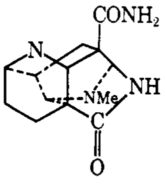

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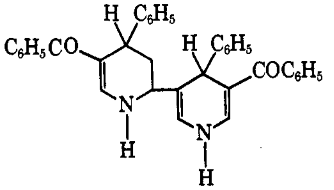

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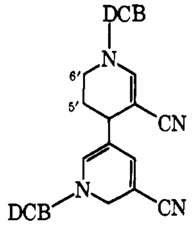
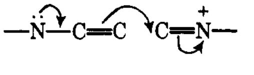


198

DCB = 2,6-dichlorobenzyl



A mechanistically similar reaction is the acid-catalyzed cyclization of **199a** and **199b** to **201a** and **201b**, respectively, which may be of biological significance.[198] Presumably the spiroindolenine **200** is an intermediate by analogy with other reactions of indoles.

Addition of sulfurous acid to dihydronicotinamides led to confusing[187,542,572,579] results. Eventually it was shown[580] that

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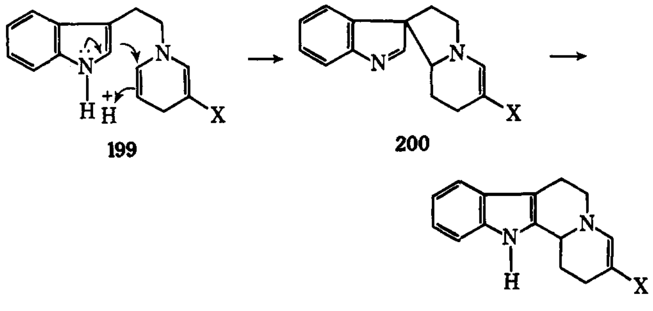
(577) A. S. Astakhova and M. L. Khidekel, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1322 (1964); *Chem. Abstr.*, **61**, 11966 (1964).

(578) H. L. Ammon and L. H. Jensen, *J. Amer. Chem. Soc.*, **88**, 613 (1966).

(579) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 2571 (1959).

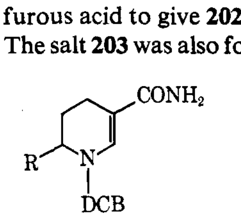
(580) H. Diekmann, D. Hofmann, and K. Wallenfels, *Justus Liebigs Ann. Chem.*, **674**, 79 (1964).

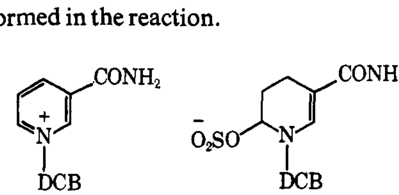


199 200 201

a, X = CN
b, X = COC$_6$H$_5$

1-dichlorobenzyl-1,4-dihydronicotinamide reacted with sulfurous acid to give **202a** which with alkali rearranged to **202b**. The salt **203** was also formed in the reaction.





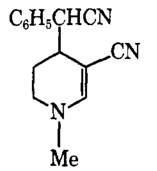
202a, R = OSO$_2$H
b, R = SO$_3$H

203

DCB = 2,6-dichlorobenzyl

2. Nucleophilic Addition Reactions

The addition of nucleophiles to the double bond of dihydropyridines has also been achieved. Thus, phenylacetonitrile reacted with 3-cyano-1-methyl-1,6-dihydropyridine in the presence of triton B to give[579] **204**. Alkyl-substituted 1,6-dihydropyridines or their salts[136,490,494,576] add cyanide ion reversibly to give adducts such as **205**; this reaction may be used for protecting these dihydropyridines. The ready formation of a bridged lactone from a 1,4-dihydropyridine-4-carboxylic acid[524] is a further example.



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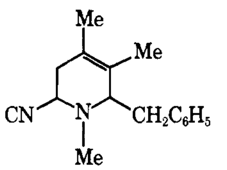

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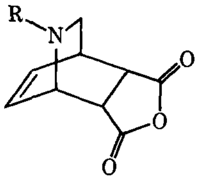
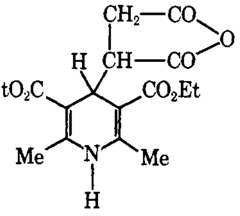


206

3. Cycloadditions

There are many reports on the reaction of maleic anhydride with dihydropyridines, but structures have not always been assigned.[37,69] Diels–Alder adducts such as **206** have been obtained from a number of 1,2- or 1,6-dihydropyridines;[310,581] their stereochemistry, however, was assumed. One such adduct was reported[582] for a 1,4-dihydropyridine; the structure of the latter was later[26,421a] shown to be the 1,2-dihydropyridine. Other dienophiles which have been reacted with dihydropyridines include *N*-phenylmaleimide,[71] methyl vinyl ketone,[149] and acrylonitrile.[583] The reaction of the latter with 3-cyano-1-methyl-1,6-dihydropyridine was shown[583] to proceed by a two-step ionic mechanism and not by a concerted process. There is only one report[577] of the reaction of a 1,4-dihydropyridine with maleic anhydride. Two 1:1 adducts were formed but their proposed structures cannot be regarded as proven. The Hantzsch ester **75c** with maleic anhydride gave[204] the adduct **207**; this reaction is analogous to the reaction[584] of 1-phenyl-1,2-dihydropyridine with dimethyl acetylenedicarboxylate which yields **208**. Both reactions are presumably initiated by hydride transfer followed by combination of the resulting ions; in the case of **208** there is a subsequent sigmatropic 1,5-hydrogen shift. Interaction, possibly of a charge-transfer type, has been observed[392] between a 1-aryl-4,4-dimethyl-1,4-dihydropyridine and maleic anhydride. A 1,2-dihydropyridine was shown to add to itself.[584a]



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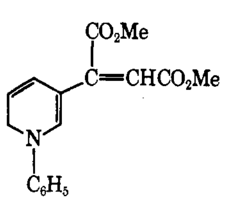
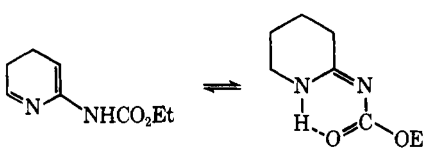


208

Two reactions which presumably proceed *via* cycloaddition are the formation of **209** and **210** from 1-trimethylsilyl-1,4-dihydropyridine and ethyl azidoformate and *p*-toluenesulfonyl isocyanate, respectively. The amidine **209**, obtained after methanolysis of the trimethylsilyl derivative, is a tautomeric mixture.[43]



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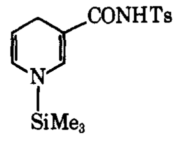

210

4. Miscellaneous Addition Reactions

Chlorine,[1] bromine,[1,435] and thiocyanogen[585] have been allowed to react with 1,4-dihydropyridines to give heptachloro, tetrabromo, and dithiocyano adducts, respectively. The structures of these have not been established.

Hydroxylation of *N*-benzyl-1,4-dihydronicotinamide to 1-benzyl-5,6-dihydroxy-1,4,5,6-tetrahydronicotinamide has been achieved[484,583,586,587] by treatment with air in the presence of cupric salts.

Free-radical addition of trimethylsilane to 1-trimethylsilyl-1,2-dihydropyridine has been postulated[295] to account for the formation of 1,5-bis(trimethylsilyl)-1,2-dihydropyridine.

5. Substitution Reactions

Displacement of substituents on the dihydropyridine ring sometimes takes place. Thus the intermediate **211a**, formed on

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(581) K. Wallenfels and M. Gellrich, *Justus Liebigs Ann. Chem.*, **621**, 198 (1959).

(582) D. Craig, A. K. Kuder, and J. Efroymson, *J. Amer. Chem. Soc.*, **72**, 5236 (1950).

(583) K. Schenker and J. Druey, *Helv. Chim. Acta*, **45**, 1344 (1962).

(584) R. M. Acheson and P. A. Tasker, unpublished results.

(584a) T. Liberatore, A. Casini, V. Cardelli, A. Arnone, and R. Mondelli, *Tetrahedron Lett.*, 2381 (1971).

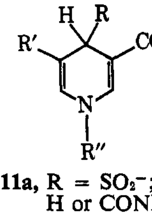
(585) H. P. Kaufmann and J. Liepe, *Ber.*, **56**, 2514 (1923).

(586) L. A. Negievich, O. M. Grishin, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **34**, 684 (1968); *Chem. Abstr.*, **70**, 115130 (1969).

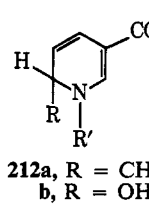
(587) L. A. Negievich, O. M. Grishin, and A. A. Yasnikov, *Ukr. Khim. Zh.*, **34**, 802 (1968); *Chem. Abstr.*, **70**, 28776 (1969).

dithionite reduction of the corresponding pyridinium salt, is converted into **211b** in acid solution by direct displacement for which a mechanism has been proposed[192,195,205] (see section IV.A.1.b).

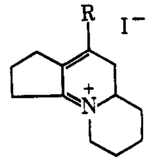
Replacement of nitromethyl and hydroxyl substituents by hydrogen in compounds the structures of which have not been established, but which are probably **211c** or **212a**, and **212b**, have been achieved[225] using dithionite or borohydride. Since the 1,4-dihydropyridine **211b** was obtained with the former reagent and the 1,6 isomer **212c** with the latter, it is likely that these displacements take place *via* elimination–addition.



211a, R = SO_2^-; R′ = H or $CONH_2$
b, R = H; R′ = H or $CONH_2$
c, R = CH_2NO_2; R′ = H



212a, R = CH_2NO_2
b, R = OH
c, R = H

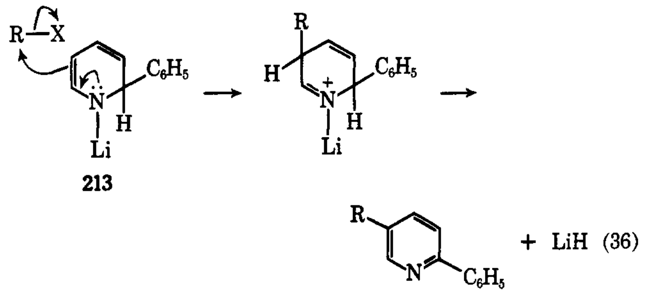


161c, R = NH_2
d, R = OH

Amino and methoxy substituents in the 2,3-dihydropyridinium salts **161a** and **161b** may be displaced by nucleophiles.[448,449,513]

6. *Miscellaneous*

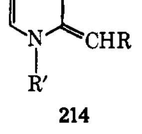
Treatment of the lithium complexes **213** with alkyl or aryl halides affords the corresponding 2-phenyl-5-substituted pyridines;[164] bromine gives 5-bromo-2-phenylpyridine. The reaction presumably proceeds by alkylation followed by loss of lithium hydride as shown in eq 36. A similar reaction is believed[567] to account for the formation of 2-butyl-5-diphenylhydroxymethylpyridine from pyridine, butyllithium, and benzophenone (see also ref 588).



213

+ LiH (36)

There are a number of reports[37,83,589–591] that the condensation of aldehydes with dihydropyridines gives products formulated as **214** or their isomers. However, no structure proofs have been presented and reinvestigation of this reaction is desirable.



214

D. ACID–BASE PROPERTIES

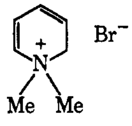
Almost no work has been reported on the acid–base properties of 1,2- and 1,4-dihydropyridines. They are both weakly acidic and weakly basic. One of the few quantitative values reported[592] in the literature (see section V.F) is the basicity of 1,4,4-trimethyl-1,4-dihydropyridine which has a pK_a value of 7.4.

Dihydropyridines are insufficiently basic for direct N-alkylation but the corresponding anion, prepared by the action of strong base, is a powerful nucleophile and reacts readily with alkyl halides. Thus, the Hantzsch ester **75c** was treated with phenyllithium followed by methyl iodide; the *N*-methyl derivative, incorrectly formulated as the 1,2 isomer, was obtained in only 3% yield.[203] However, high yields of 1-methyl-1,4-dihydropyridines were produced when the parent compounds were treated with sodium hydride in dimethoxyethane followed by methyl iodide or dimethyl sulfate.[80,119,175] Methyl iodide and an unspecified base were used[461] to methylate a dibromodicyano-1,4-dihydropyridine. The sodium salt of 3,5-dicyano-2,4,4,6-tetramethyl-1,4-dihydropyridine has been isolated.[106] Other metal complexes, prepared by the action of phenyllithium,[162,566] lithium aluminum hydride,[74,106] and Grignard reagents[106] on various pyridines are not salts but have covalent metal–nitrogen bonds. For further dihydropyridine–metal complexes, see section IV.A.1.e.

2,3-Dihydropyridines, which are imines rather than enamines, are more basic and are readily methylated with methyl iodide.[38,39] Attempts to convert N-substituted 1,2- and 1,4-dihydropyridines into the corresponding quaternary salts with methyl iodide failed.[71,392] The only known dihydropyridinium quaternary salt is **160**; it was prepared from the corresponding tetrahydropyridinium salt.[243]

N-Acylation of 1,4-dihydropyridines has been carried out using methylmagnesium iodide followed by acetyl chloride,[37] acetyl chloride–aluminum chloride,[37] and acetic anhydride alone[121] or with pyridine[121,166] and by acylation of their anions.[119] The alleged[592] *N*-arylsulfonyldihydropyridine structure of the product obtained from **75a** and a sulfonyl chloride is probably incorrect.

Protonation of 1,2- and 1,4-dihydropyridines having an electron-withdrawing group in the 3 position takes place at C-5 and gives the salts **215** and **216** respectively. Evidence for these structures is derived from uv data[64,166,500,572,579] and from addition reactions in acid solution (see above).



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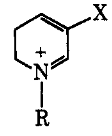

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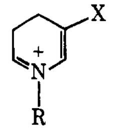

216

X = $CONH_2$, CN, COR

Salts of type **217** have been isolated in a number of cases.[448,460,490,512,575] Alkyl-substituted 1,2-dihydropyridines not possessing electron-withdrawing groups form salts of type **218**; these are readily isomerized to **217**.[490,494,576] Nothing is known of the site of protonation of Hantzsch-type dihydropyridines, *i.e.*, those having electron-with-

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[588] C. Giam and S. D. Abbott, *J. Amer. Chem. Soc.*, **93**, 1294 (1971).

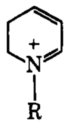
[589] A. N. Ginsburg and A. D. Gavrikova, *Biokhimiya*, **12**, 406 (1947); *Chem. Abstr.*, **43**, 705 (1949).

[590] C. Sannié and J. J. Panouse, *Bull. Soc. Chim. Biol.*, **36**, 237 (1954); *Chem. Abstr.*, **49**, 8273 (1955).

[591] C. Sannié and J. J. Panouse, *Bull. Soc. Chim. Biol.*, **36**, 247 (1954); *Chem. Abstr.*, **49**, 8273 (1955).

[592] B. C. Jain, B. H. Iyer, and P. C. Guha, *J. Indian Chem. Soc.*, **24**, 173 (1947); *Chem. Abstr.*, **43**, 2597 (1949).

drawing substituents in both the 3 and 5 positions: protonation at oxygen rather than at carbon might be expected. Exploratory experiments[593] for such compounds showed that the nature of the protonated species depended upon both the solvent and the acid strength.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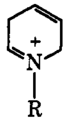
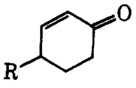

218

E. RING-OPENING REACTIONS

Early workers found that dihydropyridines could be degraded by the action of concentrated acid or alkali.[1,47,404,594] The Hantzsch esters on treatment with alkali gave the cyclohexenones 219 by ring-opening to 1,5-diketones followed by intramolecular aldol condensation[47,404,443,594,595] (see also ref 596).


219

Hydroxylamine opens the dihydropyridine ring in a number of instances[49,280,401,422,442] with the formation, usually, of the dioxime derived from the resulting 1,5-diketone.

Much confusion attended the reaction of dihydropyridines with 2,4-dinitrophenylhydrazine. At one time it was regarded as a diagnostic test for distinguishing the 1,2 and 1,4 isomers; only the former were said to react.[51,203] Later[52] it was shown that only N-substituted 1,4-dihydropyridines gave 2,4-dinitrophenylhydrazones, formulated as derivatives of the corresponding 1,5-diketones. 1,2-Dihydropyridines and N-unsubstituted 1,4-dihydropyridines do not react. 4-Substituted 3,5-diacetyl-1,4-dihydropyridines are said to form normal 2,4-dinitrophenylhydrazones[121] derived from the two carbonyl groups with the ring intact. The only evidence for the structure of these and other[147] derivatives is their chemical composition.

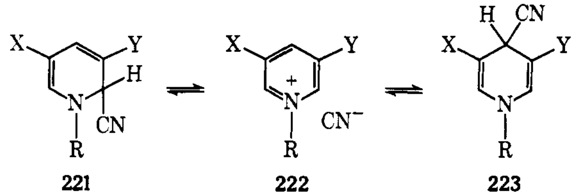
Among other ring-opening reactions which have appeared in the literature is the action of impure maleic anhydride, presumably containing the acid, which converted the *N*-methyl derivative of **75c** into the corresponding 1,5-diketone.[204] Oxidative ring-opening of 3,5-dicyano-2,6-diphenyl-4-*m*-hydroxyphenyl-1,4-dihydropyridine has been observed.[356] On strong heating with sodium in ethylene glycol 4-benzyl-1-methyl-2,4,6-triphenyl-1,4-dihydropyridine (**220**) was converted into 1,2,3,5-tetraphenylbenzene.[183]

The ring opening of some pyridine betaines on treatment with ketones, *e.g.*, acetone or acetophenone, under mild basic conditions is believed[597] to proceed *via* a 1,2-dihydropyridine. Recent work[597a] on ring-opening reactions of an alleged dihydropyridine is in error since the starting "dihydropyridine" has been shown[176a] to have an acyclic structure.

F. ISOMERIZATION

Surprisingly, very few examples of the isomerization of dihydropyridines are known and no systematic work has been done on this topic.

Two examples have been recorded involving isomerization *via* elimination–addition of cyanide ion. On heating alone or in dimethylformamide **221a** is converted into **223a** presumably *via* the ion pair **222a** according to eq 37 (see also eq 11 and 12), although an alternative mechanism has been suggested.[222,223] Spectroscopic evidence indicates[75] that addition of cyanide ion to the pyridinium salts **222** proceeds in a kinetically controlled reaction *via* the unstable 1,2 isomer **221**, which then rearranges to the more stable product **223**. In one case the 1,2 isomer **221b** was isolated and was shown to rearrange to **223b** in chloroform. These observations have been confirmed[160,215] although some of the conclusions have been questioned. More work is clearly needed to establish the exact course of this reaction.



(37)

a, X = Y = CN, R = Me
b, X = CO$_2$Et, Y = Br, R = Me

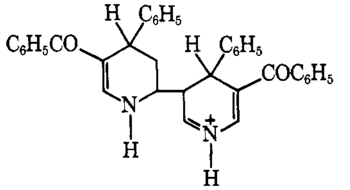
Methoxide ion addition to 2,6-dimethoxy-3,5-dinitropyridine appears[234] to take place in the 4 position followed by rapid isomerization to the more stable 1,2-dihydropyridine.

Similarly, addition of acyloxyoxazoles to acylpyridinium salts seems[303] to involve transient formation of an unstable 1,2-dihydropyridine; the 1,4-dihydropyridine is isolated as the reaction product.

There is very tenuous evidence that isomerization of 3-nitro-1,2- and -1,4-dihydropyridines can take place;[139] the corresponding dihydroquinolines are known to isomerize.[598]

Isomerization *via* an oxidation–reduction process has been invoked to account for the fact that the same addition product **203** is obtained[580] from both 1,4- and 1,6-dihydronicotinamides and sulfurous acid.

The protonated dihydropyridines **218** have been shown to isomerize.[490,494] Similarly the protonated species **224** could be converted into either the corresponding 1,4-dihydropyridine or into an alleged 3,4-dihydropyridine.[166] Acid converted the dihydropyridine **225** into the conjugated isomer.[34]



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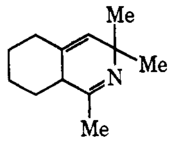

225

Metals are capable of isomerizing dihydropyridines. Thus 1-trimethylsilyl-1,2-dihydropyridine is converted into the 1,4 isomer by palladium or rhodium catalysts.[295] Evidence

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(593) P. J. Brignell, Ph.D. Thesis, London, 1964.

(594) O. Cohnheim, *Ber.*, **31**, 1033 (1898).

(595) A. J. Birch, *J. Chem. Soc.*, 1270 (1947).

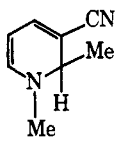
(596) S. Danishefsky and R. Cavanaugh, *J. Amer. Chem. Soc.*, **90**, 520 (1968).

(597) F. Kröhnke, M. Meyer-Delius, and I. Vogt, *Justus Liebigs Ann. Chem.*, **597**, 87 (1955).

(597a) T. Kato, H. Yamanaka, T. Adachi, and H. Hiranuma, *J. Org. Chem.*, **32**, 3788 (1967).

(598) T. Severin, D. Bätz, and H. Lerche, *Chem. Ber.*, **101**, 2731 (1968).

for isomerization on a catalyst surface is provided by the observation[184] that on hydrogenation **226** afforded **227**. Treatment of 1,3,4-trimethyl-1,2-dihydropyridine with chromium hexacarbonyl gives a mixture of **228** and the complex derived from the 1,6 isomer.[110] The same reagent isomerizes 1,4-dihydropyridines to give complexes such as **228**. The pure complexes give a mixture of isomers on heating.



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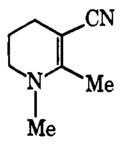

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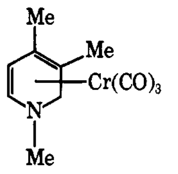


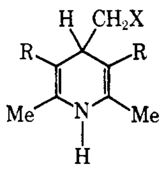
228

No base-catalyzed isomerization of the quaternary salt **160** could be achieved under conditions more vigorous than required for ring-hydrogen exchange; however, the presence of minute equilibrium concentrations of the 1,4 isomer of **160** was postulated to account for exchange in the 4 position.[243] No isomerization of N-substituted 3-cyano-1,4-dihydropyridines could be detected in the mass spectrometer.[199] The photochemical isomerization of 1,2- to 1,4-dihydropyridines is described below (section VI.H).

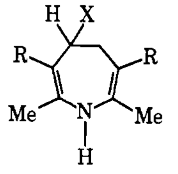
The 1,2 and 1,6 isomers of NADH have been prepared and their isomerization has been described.[7,156]

G. REARRANGEMENT

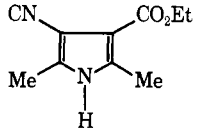
Early work[599] on the rearrangement of the dihydropyridine **229a** to a pyrrole has been reinvestigated.[323] It was found that with cyanide ion **229a** was converted into the dihydroazepine **230a** which in turn was transformed into the pyrrole **231**. The mechanism of the conversion of **229a** into **230a** involves[479] formation of the conjugate base of **229a** in a rate-determining step followed by rapid rearrangement to the azepine **232a** and nucleophilic addition of cyanide ion. The azepines **232a** and **232b** could be prepared[469] by the action of strong base on **229a** and **229b**, respectively; under slightly different conditions, the corresponding 3*H*-azepine was formed. Other nucleophiles were able to bring about ring expansion of **229b**. Thus with sodium borohydride the dihydroazepine **230b** was formed.[471] The bridged tetrahydroazepines **144b–e** were obtained[471,472] by the action of hydrosulfide, hydroselenide, methylamine, and benzylamine, respectively, on **229b**. The action on **229b** of sodium iodide in acetonitrile[479] and of methanol–hydrochloric acid[470] furnished the dihydropyridines **229c** and **229d**, respectively. It is unlikely, however, that these were formed by a direct displacement of chloride; a ring expansion–ring contraction sequence is probably involved. A similar ring expansion has recently been described[600] for a 1,2-dihydropyridine.



229a, R = CO_2Et; X = Cl
b, R = CO_2Me; X = Cl
c, R = CO_2Me; X = I
d, R = CO_2Me; X = OMe
e, R = COMe; X = Cl
f, R = COMe;X = $CH(COMe)_2$



230a, R = CO_2Et; X = CN
b, R = CO_2Me; X = H



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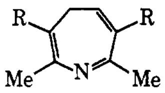
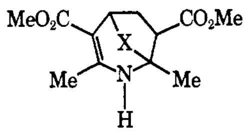
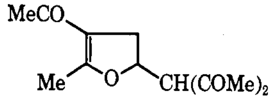


232a, R = CO_2Et
b, R = CO_2Me



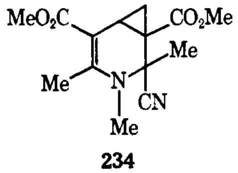
144a, X = O
b, X = S
c, X = Se
d, X = NMe
e, X = $NCH_2C_6H_5$



233

The diacetyldihydropyridine **229e** behaved quite differently.[601,602] On brief treatment with water it rearranged to a mixture of the dihydrofuran **233** and the dihydropyridine **229f**. Again, the latter compound is probably not formed by direct displacement.

A substituent on the nitrogen profoundly affects the nature of dihydropyridine rearrangements. Thus the *N*-methyl derivative of **229b** with cyanide ion gave **234** together with other products,[518] with base the 1*H*-azepine **235**,[518] and with barium carbonate in boiling mesitylene[603] the fulvene **239**.



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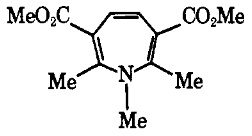

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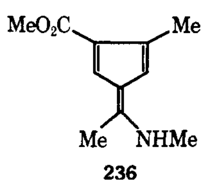

236

Attempts have been made to elucidate the mechanism of these conversions.[363,603a]

A remarkable series of pyrolytic rearrangements has been described. On heating alone or in various solvents the dihydropyridine **237a** gave[343,524] a mixture of products including

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(599) E. Benary, *Ber.*, 53, 2218 (1920).

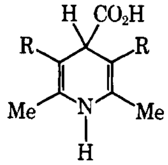
(600) T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.*, 36, 978 (1971).

(601) R. C. Allgrove and U. Eisner, *Tetrahedron Lett.*, 499 (1967).

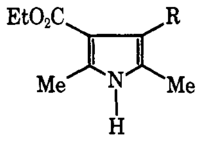
(602) R. C. Allgrove, L. A. Cort, U. Eisner, and J. A. Elvidge, *J. Chem. Soc. C*, 434 (1971).

(603) R. F. Childs, R. Grigg, and A. W. Johnson, *ibid.*, *C*, 201 (1967).

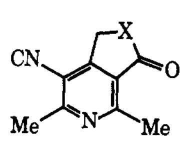
(603a) M. Mahendran and A. W. Johnson, *ibid.*, *C*, 1237 (1971).



237a, R = CO$_2$Et
b, R = CN
c, R = COMe



238a, R = H
b, R = CH$_2$CO$_2$Et



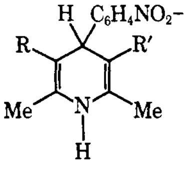
239a, X = O
b, X = NH

diethyl 2,6-dimethylpyridine-3,5-dicarboxylate and the pyrroles **238a** and **238b**. The 1-methyl and 4-methyl derivatives of **237a** were also investigated.[524] The related **237b** did not give pyrroles but instead was converted[173,364] into a mixture of pyridines including **239a** and **239b**. Similar rearrangements have been carried out with the diketone **237c** and a related tricyclic diketone.[511,604] Mechanisms for these rearrangements have been proposed.[173,511,524]

H. PHOTOCHEMISTRY

Very little work has been reported on the photochemistry of dihydropyridines, a field which should yield interesting results.

Irradiation of the *o*-nitrophenyldihydropyridines **240a–c** resulted[605] in disproportionation and loss of water to afford the *o*-nitrosophenylpyridines **241a–c**. When circularly polarized light was used for irradiation of **240c** the resulting pyridine **241c** was found to be very slightly optically active,[409] chirality being due to restricted rotation.



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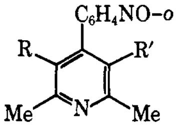

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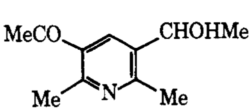


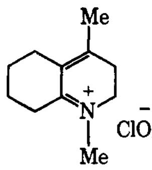
242

a, R = R′ = CO$_2$Et
b, R = R′ = COMe
c, R = COMe; R′ = CO$_2$Et

A similar reaction was reported for 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine. This on irradiation gave the pyridine **242** in which one of the original carbonyl groups has been reduced.[504] A preliminary report[606] describes an analogous reaction using 3-benzoyl-4-phenyl-1,4-dihydropyridine.

Dihydropyridines lacking substituents in the 2 and 6 positions behave differently on photolysis.[504] Diethyl 1,4-dihydropyridine-3,5-dicarboxylate is partly isomerized to the corresponding 1,2-dihydropyridine; the main product of the reaction is the photodimer **243**. This closes to a cage dimer on further irradiation. In the solid state the anti dimer corresponding to **243** is formed. The diketone, 3,5-diacetyl-1-methyl-1,4-dihydropyridine, behaves analogously. In acetone photooxidation of the above diester to the corresponding pyridine takes place.[607]

4-Chloromethyl-3,5-dicyano-2,6-dimethyl-1,4-dihydropyridine on irradiation is converted into 3,5-dicyano-2,4,6-trimethylpyridine.[607]



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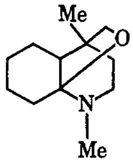
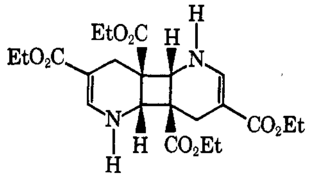


243a



243b

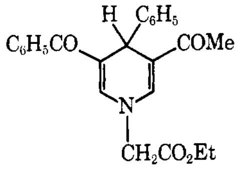
Irradiation of diethyl 1-benzyloxycarbonyl-3,6-dimethyl-1,2-dihydropyridine-2,5-dicarboxylate **140b** yields[468] the isomeric diethyl 2-aza-2-benzyloxycarbonyl-1,3-dimethylbicyclo[3.1.0]hex-3-ene-4,6-dicarboxylate **140a**.

Photoaddition of methanol in the presence of chloride ions to the salt **243a** yielded[608] **243b**.

I. MISCELLANEOUS

Deuterium exchange takes place in the 2 position[310] of **73a**, the 2,2,4,6 positions[243] of the salt **160**, and the 4 position of 1-substituted 4-cyano-1,4-dihydronicotinamides.[216] The hydrogen in the 2 position of the 1,4-dihydropyridine **211a** exchanges under conditions where **211b** is unaffected.[195,526] The methyl hydrogens in the 2 and 6 (but not the 4) positions in 3,5-dicyano-1-phenyl-2,4,4,6-tetramethyl-1,4-dihydropyridine are exchangeable.[363] NADH and model compounds such as 1-propyl-1,4-dihydronicotinamide undergo exchange of the 4 proton with the corresponding oxidized form (pyridinium salt); a 1:1 complex is believed to be involved.[609,610]

Substituents on the dihydropyridine ring are very stable. Thus ester groups in the 3 and 5 positions of **75** could not be hydrolyzed[1,19,324] without decomposition of the molecule, although it has been claimed[1,404,594] that unstable monoesters were obtained from **75** by hydrolysis and decarboxylation. On the other hand, the ester group in **244** has been hydrolyzed[367] to the corresponding acid. The carboxyl group in **237a** has been functionalized[175] and the corresponding mixed anhydride, amide, and benzyl ester have been prepared; hydrogenolysis of the latter regenerates the carboxyl function.



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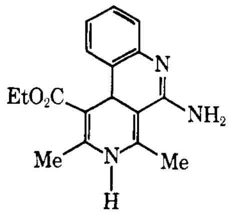

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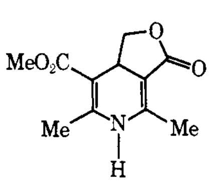

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(604) J. F. Biellmann, R. J. Highet, and M. P. Goeldner, *Chem. Commun.*, 295 (1970).

(605) J. A. Berson and E. Brown, *J. Amer. Chem. Soc.*, 77, 447 (1955).

(606) D. A. Nelson and J. F. McKay, Abstracts, 154th National Meeting of the Americal Chemical Society, Chicago, Ill., Sept 1967, No. S 23.

(607) U. Eisner and D. Pashayan, unpublished results.

(608) R. Gault and A. I. Meyers, *Chem. Commun.*, 778 (1971).

(609) J. Ludowieg and A. Levy, *Biochemistry*, 3, 373 (1964).

(610) R. Unzelman, J. Ludowieg, and L. Strait, *Experientia*, 20, 506 (1964).

The ester function in the methyl ester corresponding to **237b** has been selectively reduced with lithium borohydride.[173]

The carbonyl group in 3-benzoyl-4-phenyl-1,4-dihydropyridine was inert toward complex metal hydrides and metalloorganic reagents.[166] In contrast the carbonyl groups in the 3 and 5 positions of a tricyclic dihydropyridine could be reduced with zinc and acetic acid.[46]

Involvement of substituents in intramolecular cyclization has been observed. Thus **245** was formed from the corresponding 3-cyano-4-*o*-nitrophenyl-1,4-dihydropyridine[372] on reduction, and dimethyl 4-acetoxymethyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate gave **158** with ammonia.[472]

N-Acetyl substituents are readily removed either reductively[166] or on thermolysis.[11,296] On heating with dibenzylamine and palladium, 1-benzoyl-4-(3-indolyl)-1,4-dihydropyridine gave hydrogen, benzaldehyde, *N*,*N*′-dibenzylbenzamide, and 4-(3-indolyl)pyridine.[611] An *N*-ethoxycarbonyl substituent in a 1,2-dihydropyridine was displaced by lithium on treatment with butyllithium.[63]

Simple 1-substituted 1,2-dihydropyridines form stable π complexes such as **228** with chromium carbonyls.[110]

Acknowledgments. One of us (U. E.) wishes to thank Dr. T. Spande, NIAMD, National Institutes of Health, for valuable suggestions, Dr. M. A. Ali, Howard University, for helpful discussions, Dr. D. Pashayan, Howard University, for help with proofreading, and the National Science Foundation for Grants GP 8353 and 20008.

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(611) D. Beck and K. Schenker, *Helv. Chim. Acta*, **51**, 260 (1968).