THE PREPARATION AND PROPERTIES OF ANNELATED PYRIDINES AND RELATED HETEROCYCLIC SYSTEMS

A Dissertation

Presented to

The Faculty of the Department of Chemistry

College of Natural Sciences and Mathematics

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

by

Dalip Kumar Kohli

August 1978

To my parents

ACKNOWLEDGEMENT

I would like to acknowledge in deep appreciation the unfailing help, and guidance Dr. Randolph Thummel has provided during the last four years.

I would like to thank each member of our research group as well as the members of the faculty and staff, especially Dr. Harold Kohn, for their help.

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ABSTRACT

A series of monoannelated pyridines has been prepared in which a four, five or six-membered ring is fused at either the 2,3- or 3,4-position of the pyridine ring. The partial hydrogenation of isoxazole and substituted isoxazoles provides a convenient source of β-amino-α,β-unsaturated carbonyl compounds. The β-amino-α,β-unsaturated aldehydes react with five or six-membered cyclic ketones in a normal Friedlander type of reaction leading to the formation of 2,3-mono-annelated pyridines whereas β-amino-α,β-unsaturated ketones are found to yield rearranged 2,3-mono-annelated pyridines.

Condensation reactions were employed to prepare a similar series of bis-annelated pyridines in which all possible combinations of five and six-membered rings are fused to the pyridine nucleus. The reaction between β-aminomethylenecycloalkanones and cyclic ketones leads to the formation of [2,3:5,6]-bisannelated pyridines rather than expected [2,3:4,5]-bisannelated pyridines. The [2,3:4,5]bisannelated pyridines have been prepared by condensation between cyclic ketones, formaldehyde and ammonium acetate.

Utilizing the Friedlander condensation between 2-aminonicotinaldehyde and cyclic ketones a series of 2,3-fused 1,8-napthyridines have also been prepared.

Cyclobutapyridines are found to undergo catalytic hydrogenation at room temperature and one atmosphere of hydrogen to the corresponding azabicyclo[4.2.0]octanes.

The ^{1}H and ^{13}C NMR spectra of annelated pyridines have been determined. As the size of the ring fused to pyridine is decreased, the chemical shifts of bridgehead carbons increase, while the chemical shift of the carbon ortho to the fused ring decreases. The proton attached to this ortho carbon moves downfield except in the case of cyclobutapyridines.

The basicities of annelated pyridines and of 2,3-fused,-1,8-napthyridines have been determined as half neutralization potentials by titration in acetic anhydride using 0.1 N perchloric acid in acetic acid as titrant. Decreasing the size of the ring fused at the 2,3-position of pyridine decreases the basicity of the molecule, whereas ring fusion at the 3,4-position of pyridine has only a minor and apparently inconsistent influence on the basicity. For 1,8-napthyridines, decreasing the size of the fused ring also results in a decrease in the basicity, but due to the presence of two nitrogen atoms, the overall basicity of the molecule is not affected dramatically.

The gas phase basicities and photoelectron spectra of monoannelated pyridines has been determined in collaboration with Dr. Donald Aue of the University of California at Santa Barbara.

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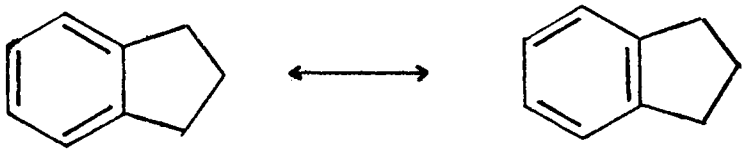
INTRODUCTION

INTRODUCTION

The concept of strain as applied to organic molecules involves the steric distortion of covalent bonds. This distortion may be realized by the bending, twisting, stretching or compressing of a bond from the minimum energy configuration predicted by conformational analysis and valence bond theory. Such conformational constraints are usually dictated by the geometry of the molecule in question and are most frequently evidenced in small ring compounds. Atoms to which strain has been applied accommodate this phenomenom in a manner which is evidenced by changes in physical as well as chemical properties. Strained bonds show diminished overlap of atomic orbitals, are therefore of higher energy, and hence are weaker and more reactive.

In 1930 Mills and Nixon proposed that the five-membered ring of indan may sufficiently distort the geometry of the benzene portion of this molecule so that Kekulé resonance form 1a would be preferred over 1b and thus partial bond fixation might result.[1]

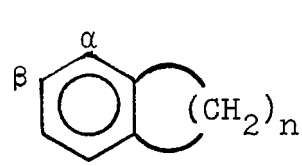


1a 1b

Since that time these predictions have been shown to be ambiguous.[2] Nevertheless, more recent calculations by Mannatt[3] using the CNDO/2 technique as well as an extended Huckel treatment by Halton[4] both support a preferred structure in which the bridging bond is lengthened for strained benzocycloalkenes. Since the middle of this century, advanced synthetic techniques have led to the preparation of a large number of other small ring fused aromatics which have renewed an interest in the question of aromatic bond localization.

The incorporation of ring strain into an aromatic molecule as a probe of bond localization offers the advantage of perturbing the σ-framework of the molecule much more significantly than the cyclic π-system. Various structural and spectroscopic studies on benzocyclopropene[4] and benzocyclobutene systems have sought to delineate any bond fixation.

Efforts to understand the effects of fusing a small ring onto the benzene nucleus have led to the presentation of a good deal of chemical, physical and theoretical data. Vaughn has reported on the behavior of benzocycloalkenes towards electrophilic reagents.[5] When a four-or five-membered ring is fused to benzene, reactivity at the β-position is found to be substantially greater than that at



n=2,3

α-carbon adjacent to the strained ring. Vaughn explains this difference by considering the bond order of the carbonium ion intermediates involved in the substitution reactions. Streitweiser points out the increased acidity of benzene protons ortho to a small fused ring.[6] He explains this observation as well as the difference in electrophilic reactivity by invoking substantial changes in the hybridization of the bridgehead carbons.

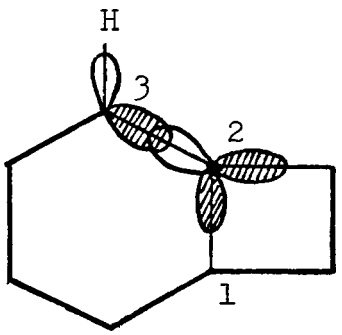


Figure 1. Benzocyclobutene. Shaded orbitals have increased p character: hence, unshaded orbitals have increased s character.

From Figure 1 it may be seen that the atomic orbitals of the bridgehead carbon used to construct the strained ring have higher p character. Hence, the remaining orbital has higher s character. The ortho carbon is thus bound to an orbital of higher electronegativity. Thus in forming the sigma bond with the bridgehead carbon C-2, the ortho carbon C-3 uses an orbital of higher p character in order to

maintain the carbon-carbon bond order. This rehybridization then leaves an orbital of higher s character on the ortho carbon, which in forming the sigma bond with the hydrogen atom causes the polarization of C-H bond toward carbon. This polarization of C-H bond might explain the increased acidity of proton attached to the ortho carbon.

A determination of ionization potentials, ultraviolet spectra, and charge-transfer spectra for a series of cyclo-alkenobenzenes, bis-cycloalkenobenzenes, and tris-cyclo-alkenobenzenes has aided in the investigation of the effects of strain on the π-electron sextet in the ground state as well as higher energy states.[7]

By comparison with the extensive studies of the effects of ring fusion on the benzene nucleus, similar pyridine systems have been given only sparse consideration. There are several features of the pyridine nucleus which make it attractive for studies related to aromaticity. First, the nitrogen atom introduces an element of assymmetry which allows for comparison between positionally isomeric molecules (i. e., 2,3- vs. 3,4-annelated pyridines). Secondly, the heteroatom provides a convenient means for directly probing the aromatic nucleus via basicity studies or the formation of derivatives such as pyridinium salts or N-oxides. Thirdly, the resonance energy of pyridine has been calculated to be about 21 Kcal/mol based on heats of atomization estimated from thermochemical data.[8] This value is substantially

less than the value of 36 Kcal/mol calculated for benzene. Thus, one might expect that it should be easier to perturb the aromaticity of pyridine than it would be to perturb it for benzene.

With a view to explore the effects of ring fusion on the physical and chemical properties of pyridine, we have prepared a series of monoannelated pyridines, in which a four-, five- or six-membered ring is fused at either the 2,3- or 3,4- position. Also a series of bis-annelated pyridines in which all possible combinations of five- and six-membered rings are fused to the pyridine nucleus have been synthesized.

The purpose of the following literature survey is to bring up to date the important developments in the area of annelated pyridines and related systems.

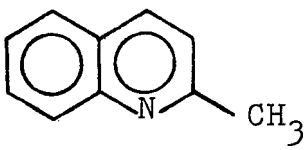
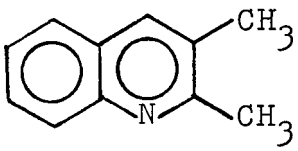
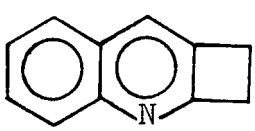
Prior to this work, the only systems on which the effects of small ring fusion have been investigated were 2,3-annelated quinolines. Wilk and coworkers[9] prepared a series of 2,3-annelated quinolines in which a four-, five- or six- membered ring is fused at the 2,3-position of the pyridine portion of the molecule. They examined the ultraviolet and fluorescence spectra of these molecules and found that as the size of the fused ring was decreased from five carbons to four carbons the UV absorption shifted to shorter wavelength and became less intense.

Markgraf[10] prepared cyclobuta[b] quinoline 2

utilizing a Friedlander reaction. He examined the basicity and NMR spectrum of this molecule and found well-defined systematic variations, when compared to model compounds. He observed that $^{13}C_4$-H coupling constant increases along the series of 2-methyl, 2,3-dimethyl, and cyclobuta[b]-quinoline (Table I).

TABLE I

$^{13}C_4$-H COUPLING CONSTANTS FOR SUBSTITUTED QUINOLINES

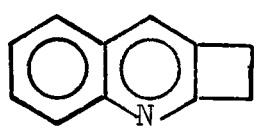
Compound	$J(^{13}C\text{-}H)^a$ Hz	C-H bond s character,[b] %
	126 ± 0.5	25.2
	130 ± 1	26.0
	139 ± 1	27.8

2

[a] In $CDCl_3$. [b] Defined as 0.20 $J(^{13}C\text{-}H)$: N. Müller and D. E. Pritchard, J. Chem. Phy., 31, 1471 (1959).

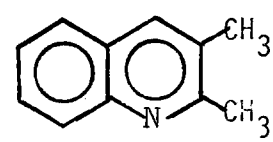
This data parallels the analogous data reported for the benzylic protons of toluene (122 Hz)[11], o-xylene (128)[11] and benzocyclobutene (138 Hz).[12] Such changes in $J(^{13}C\text{-}H)$ reflect the increase in strain going from adjacent methyl groups to the fused cyclobutene moiety. The ^{13}C-H coupling constants can also be expressed as percent s character of the benzylic type C-H bonds.

On examining the basicity of 2, Markgraf found a profound effect exerted by the fusion of the four-membered ring.[13] It was found that 2 was at least ten times less basic than comparable compounds such as 2,3-dimethylquinoline.



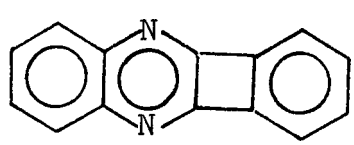
2

$pK_a = 4.55$

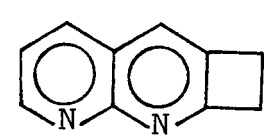


$pK_a = 5.99$

However, in a system such as benzo[3,4]cyclobuta-[1,2-b]-quinoxaline (3), the effect of four-membered ring fusion on the basicity of this molecule is found to be relatively small.



3

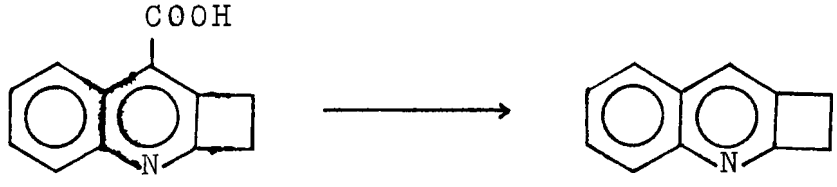


4a

A similarly small effect is observed in the case of cyclobuta[b]-1,8-napthyridine (4a).[14] The smaller effect observed in these cases can be attributed to the presence of

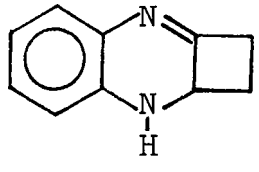
two nitrogen atoms, due to which the overall basicity of the molecule is not affected dramatically.

The effect of small ring fusion on the chemical properties of 2,3-annelated-quinolines has been investigated in some cases. Markgraf and coworkers[10b] prepared cyclobuta[b]quinoline-4-carboxylic acid (5) by the Pfitzinger reaction of isatin with cyclobutanone. Repeated efforts to effect the decarboxylation of 5 to 2 were without success.



5 2

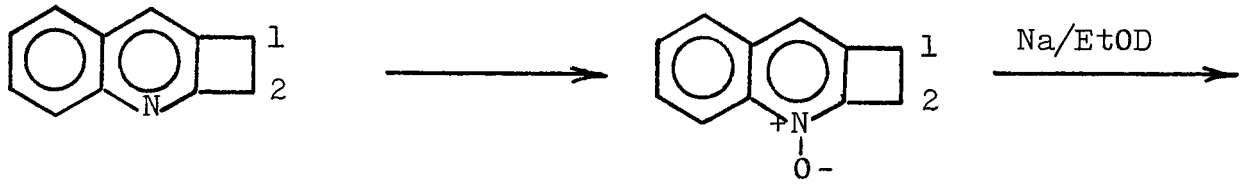
This result was unexpected since the facile decarboxylation of anologous 2,3-annelated-quinoline-4-carboxylic acids containing 5-19 membered rings have been reported.[15] Thus the fusion of a four-membered ring may be responsible for the alteration of chemical reactivity. Another example of such an influence was observed in the inability to achieve aromatization of 1,2,2a,3-tetrahydrocyclobuta[b]quinoxaline(6).[16] In this case it is clear that the resonance energy which



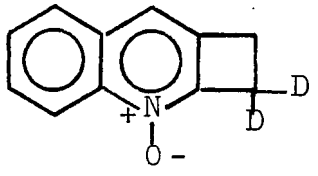
6

would be gained after aromatization of 6 is not enough to compensate for the ring strain introduced in the molecule due to the fusion of a four-membered ring to the aromatic nucleus.

The conversion of 2 into its N-oxide 7 sufficiently altered the acidity of the hydrogens at C-2 to permit deuterium exchange, whereas no exchange occured at C-1.[10b]



2 7



8

The structural assignment of the product thus obtained, cyclobuta[b]quinoline-2d$_2$-3-oxide (8), was based on its NMR spectrum which contained a two proton singlet at δ 3.22 in the aliphatic region. Both the number and location of deuterium atoms were thus determined by the absence of a peak at δ 3.60, the absence of splitting the C-1 methylene signal. That no exchange occured at C-1 was consistent with the relative rates of exchange of 2-methyl- and 3-methylquinoline N-oxide.[17] The facile exchange of 7 is in accord with the known influence of N-oxides[18] and may be attributed principally to changes in the inductive effect of the heteroatom.[19]

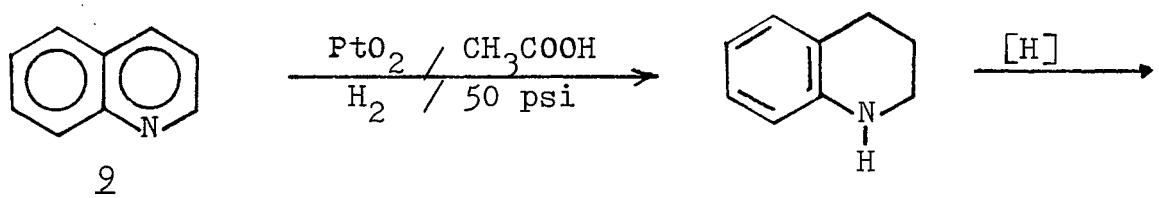
Although several mono- and bis-annelated pyridines have been known for some time, there are few reports on the physical or chemical properties of these molecules. In 1945, Prelog[20] reported the preparation of cycloalkenopyridines containing a five-, six- or a seven-membered ring fused at 2,3-position. He studied the ultraviolet spectra of these molecules and found that as the size of the fused ring was decreased, the absorption maxima moved to longer wavelength and the extinction coefficient increased. He also observed that the reduction of cycloalkenopyridines with sodium in alcohol yielded the corresponding cycloalkenopiperidines, which predominately had a trans configuration, when the number of carbon atoms in the fused ring was six or greater.

There are four general classes of reactions which have been utilized for the preparation of annelated pyridines.

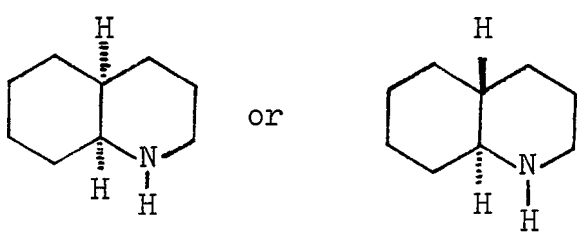
1. Hydrogenation of suitably substituted quinolines and isoquinolines:

It is well documented[21] that catalytic hydrogenation of pyridines bearing phenyl substituents, and of quinolines and isoquinolines and their homologs occurs preferentially in the pyridine ring. Hydrogenation of quinoline or isoquinoline over platinum oxide in acetic acid at room temperature and 50 psi initially gives the 1,2,3,4-tetrahydro products in high yields.[22-24] Further reduction to the decahydro stage appears to be facilitated by the addition of

mineral acid,[24] under which conditions the major product is the cis ring-fused isomer, whereas in the absence of mineral acid the trans ring-fused isomer of decahydroquinoline is reported to predominate.[24,25]

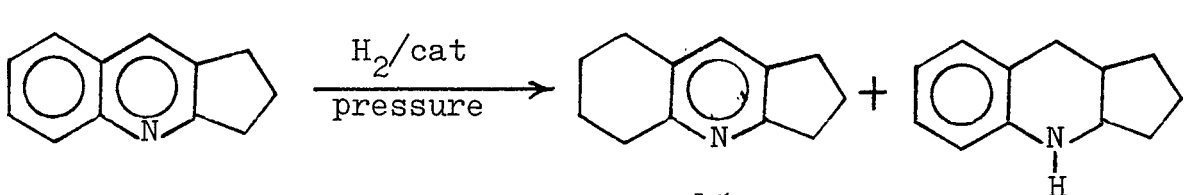


9 10

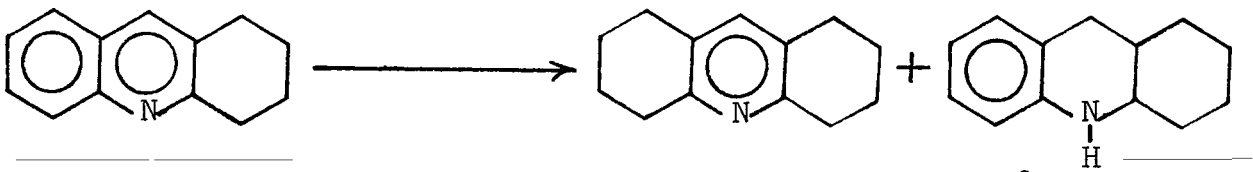


11 12

The introduction of the substituents in the 2-, and 3- position sterically inhibits the hydrogenation of the pyridine moeity and results in a mixture of 5,6,7,8- and 1,2,3,4-tetrahydroquinolines. Braun and coworkers[26] have reported the hydrogenation of 2,3-trimethylenequinoline (13) and 2,3-tetramethylenequinoline (14) resulting in the formation of tetrahydrogenated products (15-18). Compounds 15 and 17 were obtained in 49% and 48% yields respectively.



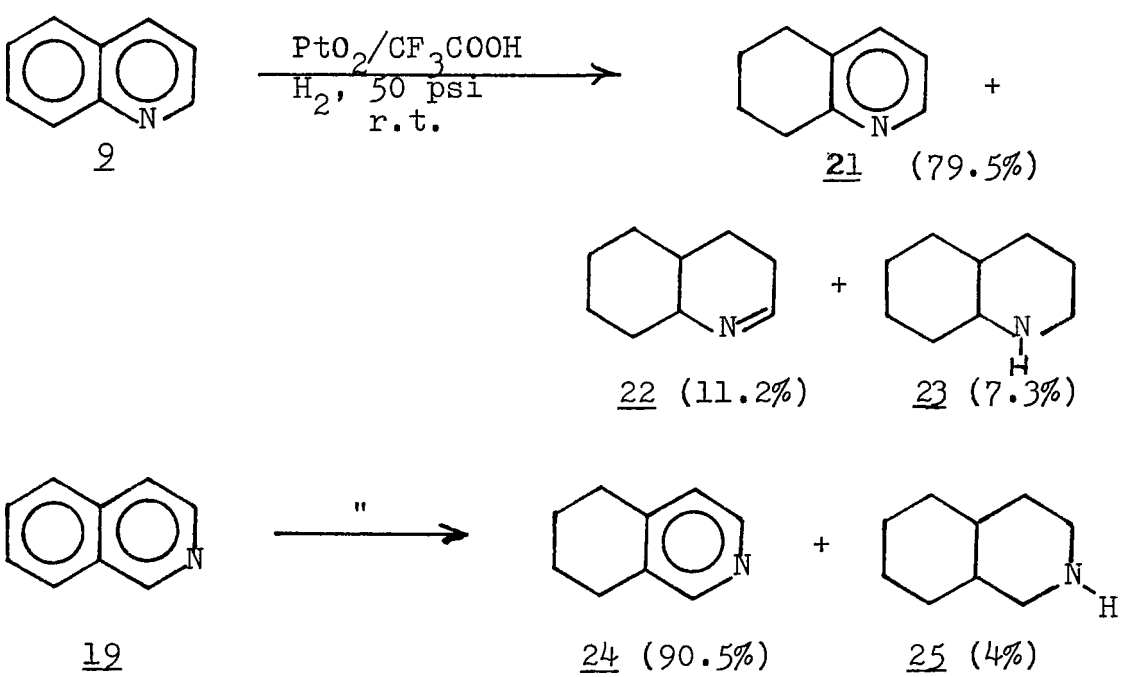
13 15 16



14 17 18

Booth and Bostock[27] recently hydrogenated quinoline to cis-decahydroquinoline with platinum in 12N hydrochloric acid. Interruption of this very slow reduction when 2 mol of hydrogen had been absorbed revealed that the major product (70%) at this stage was 5,6,7,8-tetrahydroquinoline.

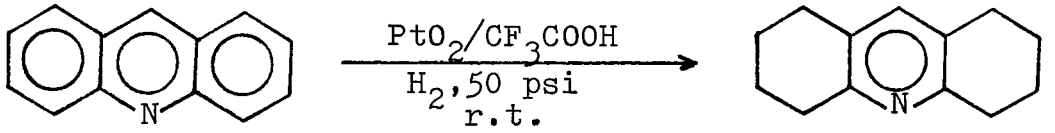
Eliel[28] has recently shown that quinoline (9), isoquinoline (19), and acridine (20) are predominately hydrogenated in the benzenoid portion of the molecule when the reduction is carried out in strong acid media such as trifluoroacetic acid.



9 21 (79.5%)

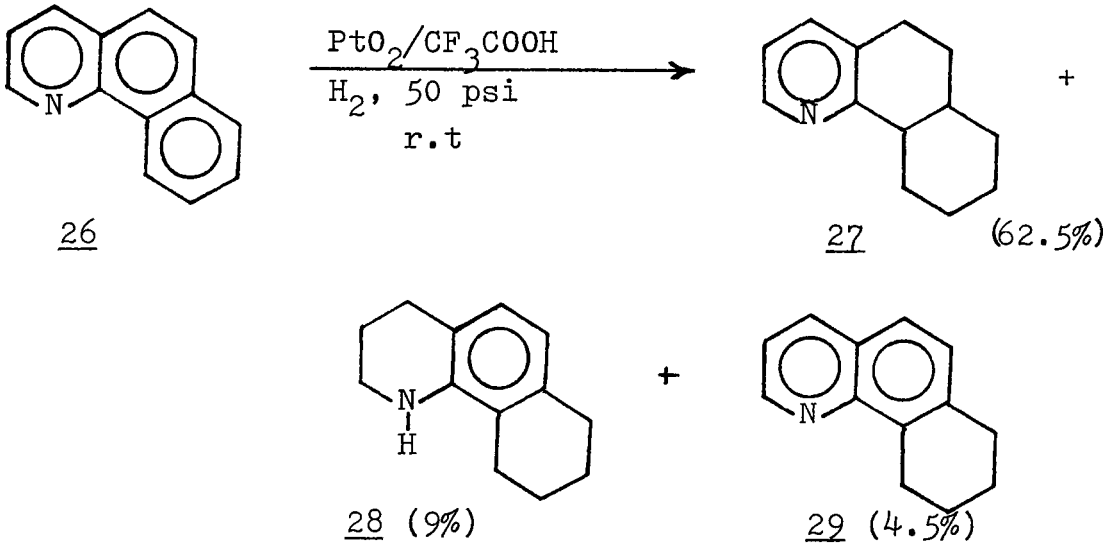
22 (11.2%) 23 (7.3%)

19 24 (90.5%) 25 (4%)



20 17 (~100%)

He also found that the highest yields of 5,6,7,8-tetrahydroquinolines result when there is a methyl substituent in the pyridine ring, or a second fused benzene ring (as in 20); lesser yields with no substituents; and the lowest yields when there is an alkyl substituent in the benzene ring, or a second benzene ring fused to it, as in benzo[h]quinoline (26).



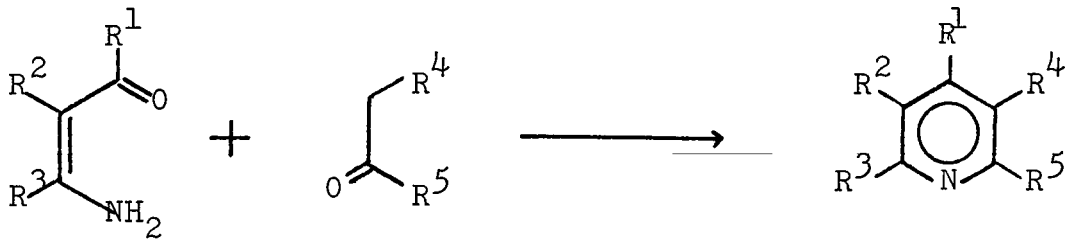
26 27 (62.5%)

28 (9%) 29 (4.5%)

2. Friedlander Reactions:

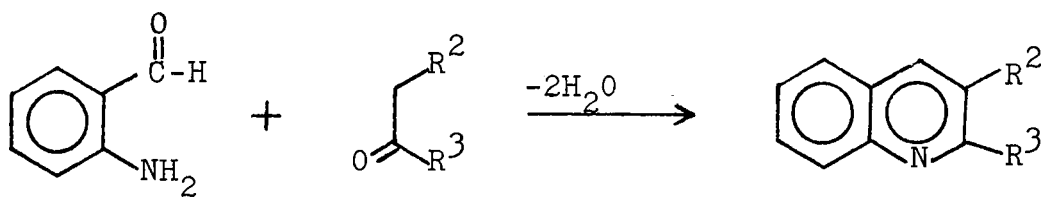
The Friedlander reaction[29] involves the reaction of a suitably substituted β-amino-α, β-unsaturated carbonyl compound[30] with a carbonyl compound containing a methylene group adjacent to the carbonyl group resulting in the formation of

substituted pyridines 31.



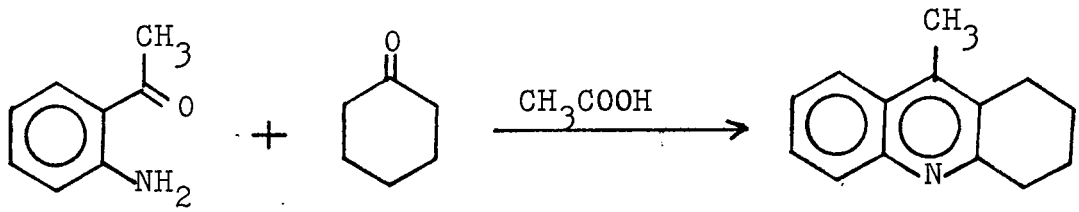
30 31

The Friedlander synthesis of substituted quinolines 33 involves the reaction of o-amino-benzaldehyde (32) with an aldehyde, ketone or a polyfunctional carbonyl compound having the grouping $-CH_2-CO-$.



32 33

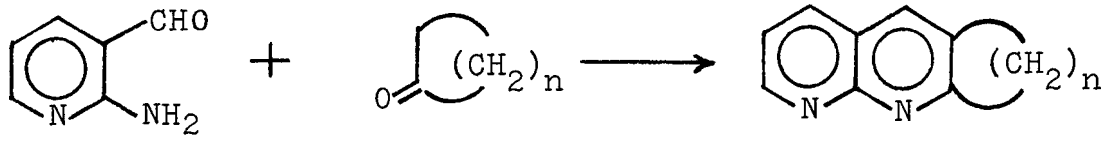
Kempter[30] and Fehnel[31] have reported the preparation of 2,3-annelated quinolines 35 from the reaction of o-amino-acetophenone (34) with five- and six-membered cyclic ketones under acidic conditions.



34 35

Friedlander condensations are usually carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base or by heating a mixture of reactants at temperatures ranging from 150-200°C in the absence of solvent and catalyst.

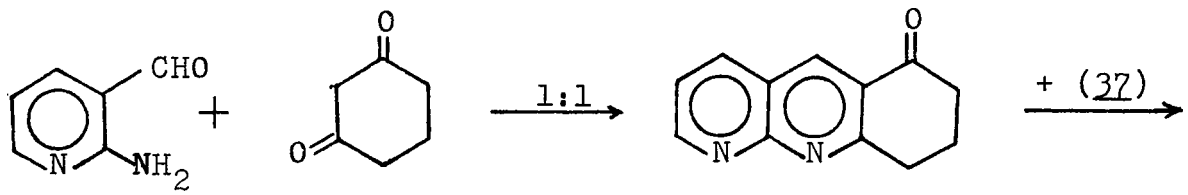
Utilizing the acid catalyzed condensation, we have prepared a series of 2,3-annelated-1,8-napthyridines (4) from the reaction of 2-aminonicotinaldehyde (37)[32] with cyclic ketones.[33]



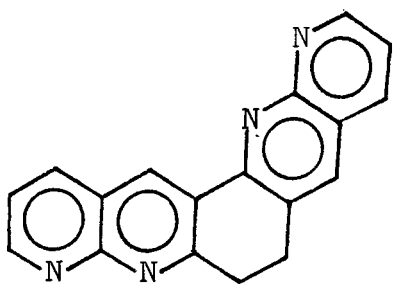
37 n=2,3,4 4a; n=2 4b; n=3 4c; n=4

In the preparation of cyclobuta[b]-quinoline (2) and cyclobuta[b]-1,8-napthyridine (38, n=2), higher yields are obtained when the reaction is carried out under basic conditions in an alcoholic solution.[10,33]

Caluwe and coworkers[34] have prepared pentacyclic systems such as 39 containing two 1,8-napthyridine units, by the reaction of 2-aminonicotinaldehyde (37) with 1,3-cyclohexanedione (36) under basic conditions. It seems that Friedlander reaction of o-amino-aldehydes is the most promising synthetic method for construction of systems such as (39).

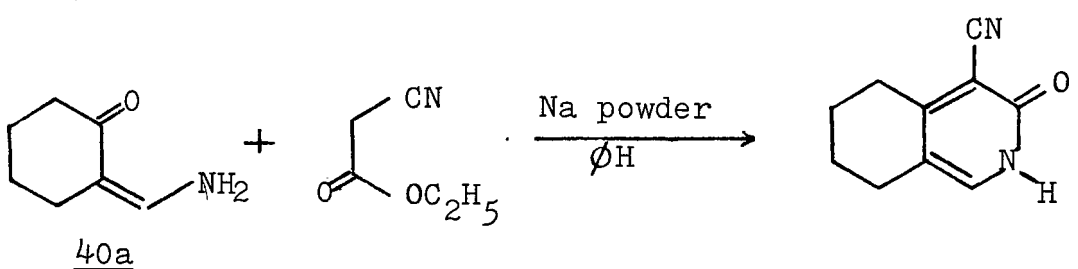


37 36 38

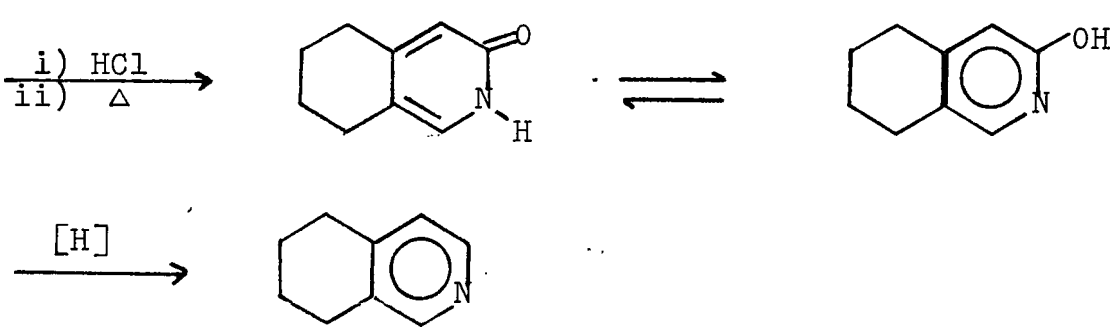


39

Extending the use of the Friedlander reaction to the preparation of annelated pyridines, Basu and Bannerjee[35] reported the preparation of 5,6,7,8-tetrahydroquinoline (24) from the reaction of β-aminomethylene cyclohexanone (40a) with cyano-acetic ester.

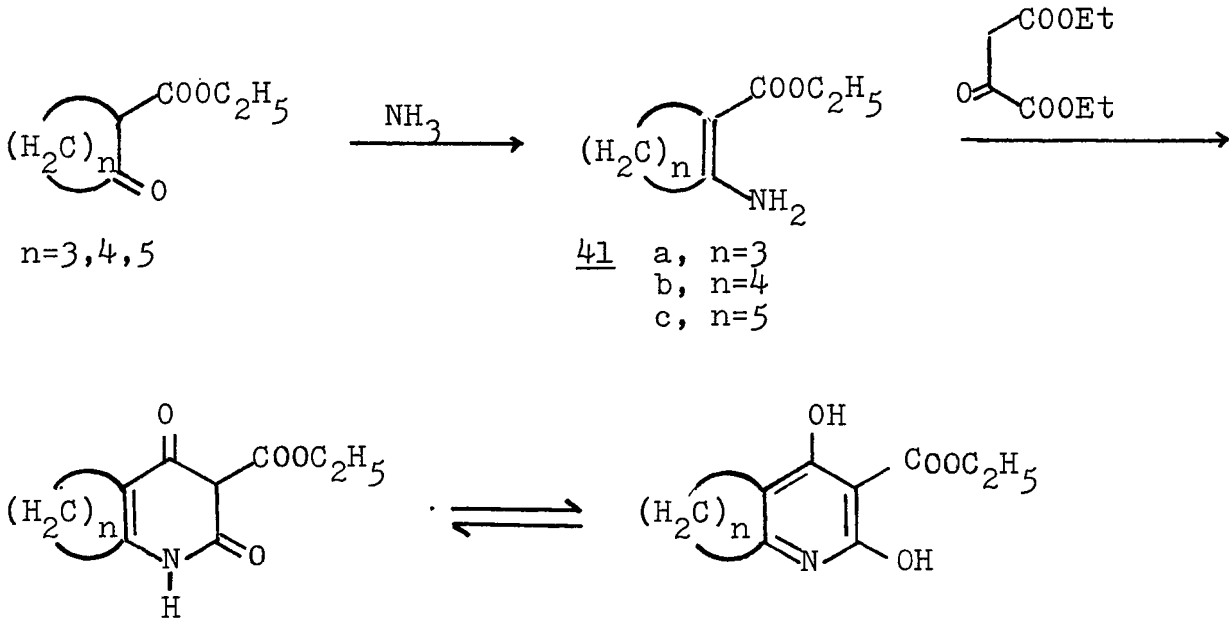


40a

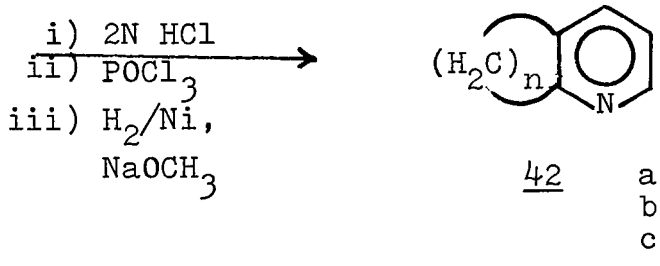


24

In 1945 Prelog[20] reported the reaction between ethyl-2-amino-1-cycloalkene-1-carboxylate (41) and malonic ester, leading to the formation of 2,3-annelated pyridines (42).



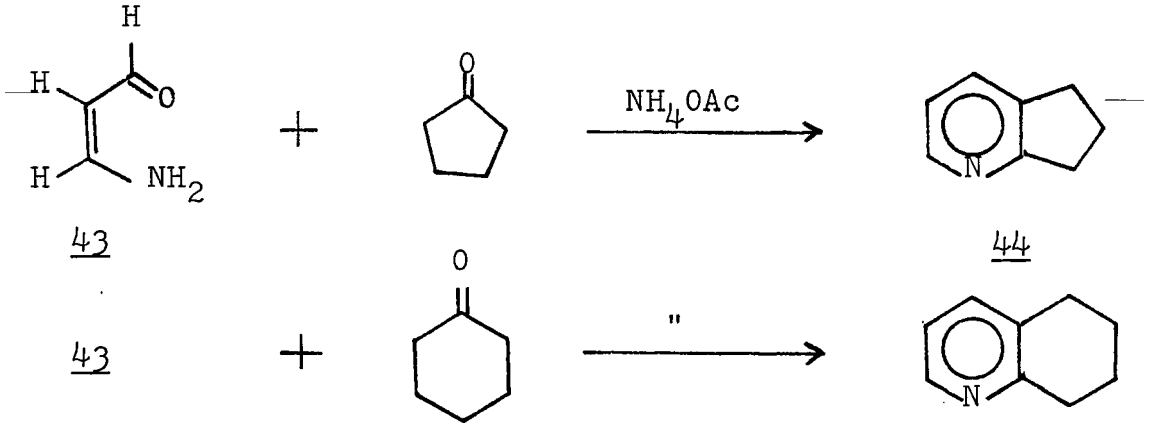
41 a, n=3
b, n=4
c, n=5



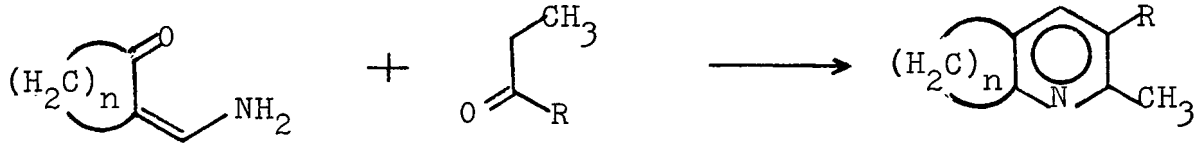
42 a, n=3
b, n=4
c, n=5

In 1969 Breitmaier and Bayer[36] reported a one step preparation of 2,3-trimethylene and 2,3-tetramethylene-pyridine (44) and (21) by the reaction of β-aminoacrolein (43) with cyclopentanone and cyclohexanone respectively. This Friedlander reaction of 43 with cyclic ketones provides

the most convenient route to these mono-annelated pyridines.



Continuing his studies on the preparation of annelated pyridines, Breitmaier[37] found that the reaction of 2-(aminomethylene)cycloalkanones (45) with 1,3-dicarbonyl compounds (46-47) results in the formation of cycloalkeno[b]pyridines (48-49).



45

	n
a	3
b	4
c	5
d	6
e	10

46, R= $COCH_3$

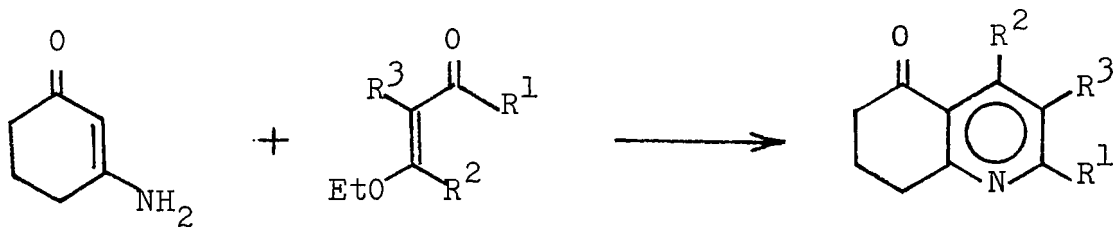
47, R= $COOC_2H_5$

48: R=$COCH_3$

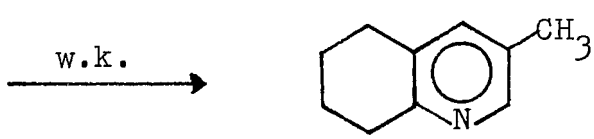
49: R=$COOCH_3$

	n
a	3
b	4
c	5
d	6
e	10

Extending the Breitmaier approach, Curran[38] prepared substituted 7,8-dihydroquinoline-5(6H)-ones (52), which could be readily reduced to 5,6,7,8-tetrahydroquinolines (53). The reaction of 3-amino-2-cyclohexanone (50) with 3-ethoxy-2-methylacryl aldehyde (51a) gave 52a in 50% yield.



50 51 52

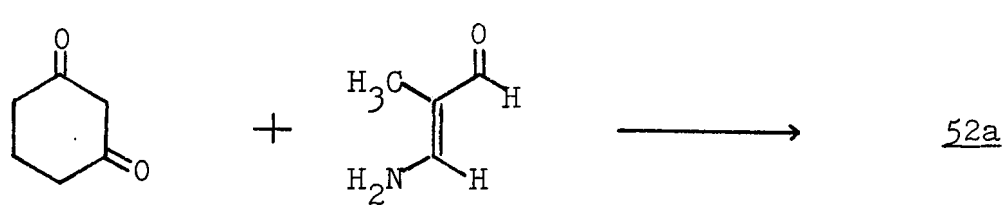


53

a; $R^1=R^2=H$, $R^3=CH_3$

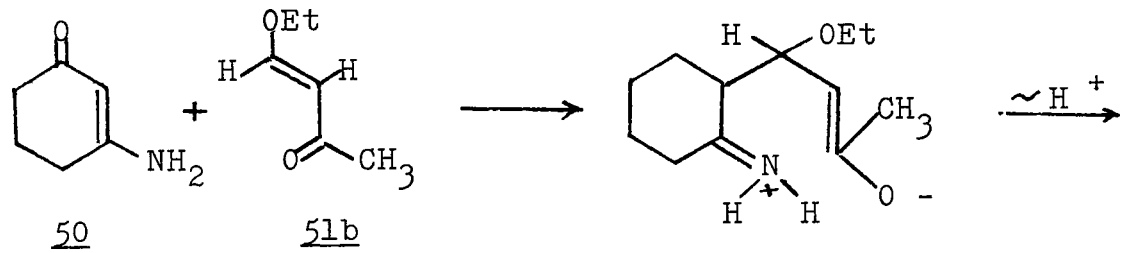
b; $R^1=CH_3$, $R^2=R^3=H$

The same 7,8-dihydroquinoline-5(6H)-one (52a) was obtained when cyclohexane-1,3-dione reacted with 3-amino-2-methylacryl aldehyde (54).

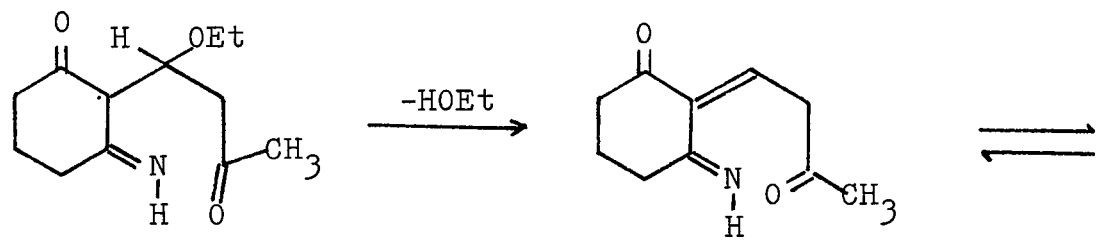


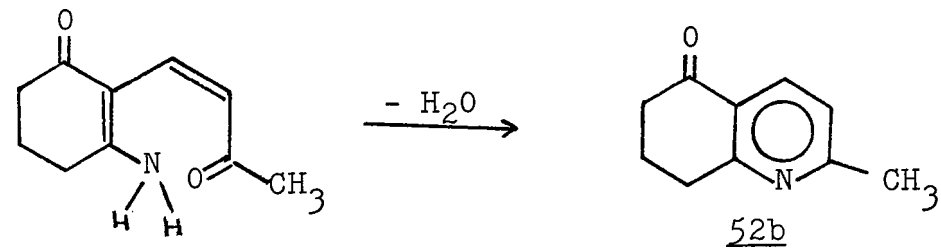
54 52a

Curran has proposed the following mechanism to account for the formation of 52b from 50 and 51b.



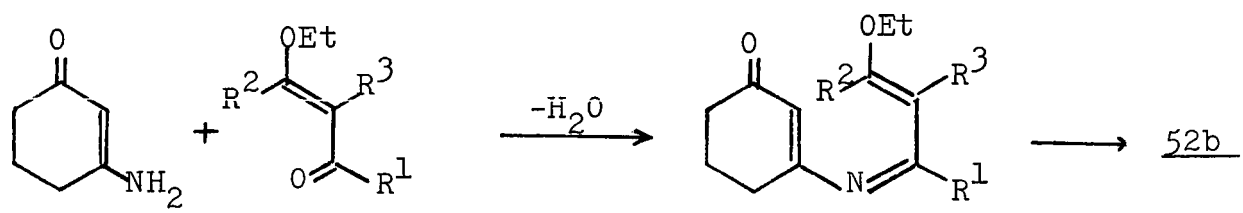
50 51b





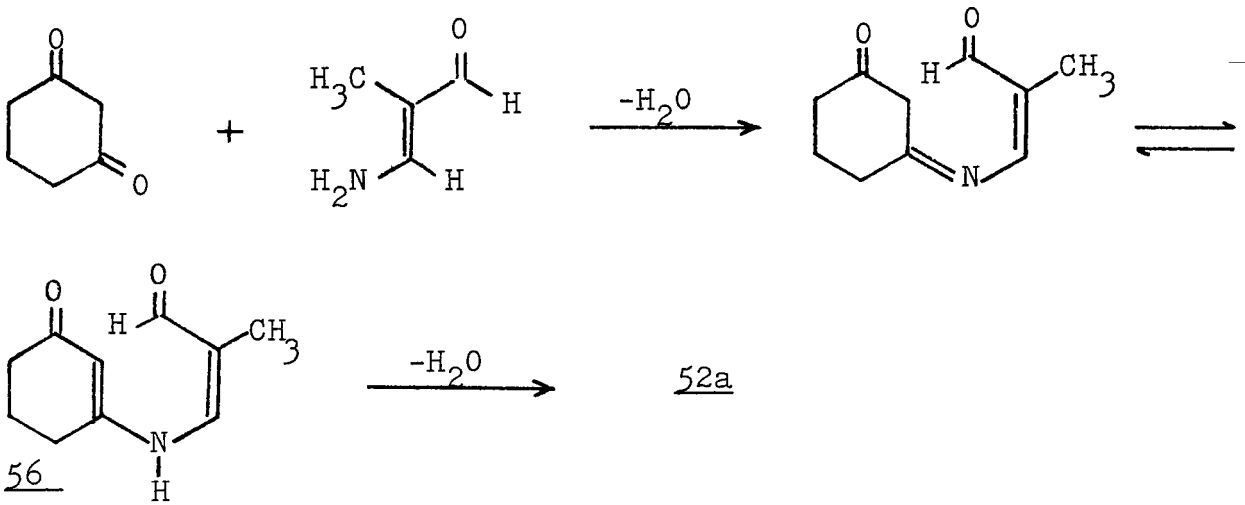
52b

However the formation of 52 could also be explained by initial formation of enamine 55 followed by cyclization.



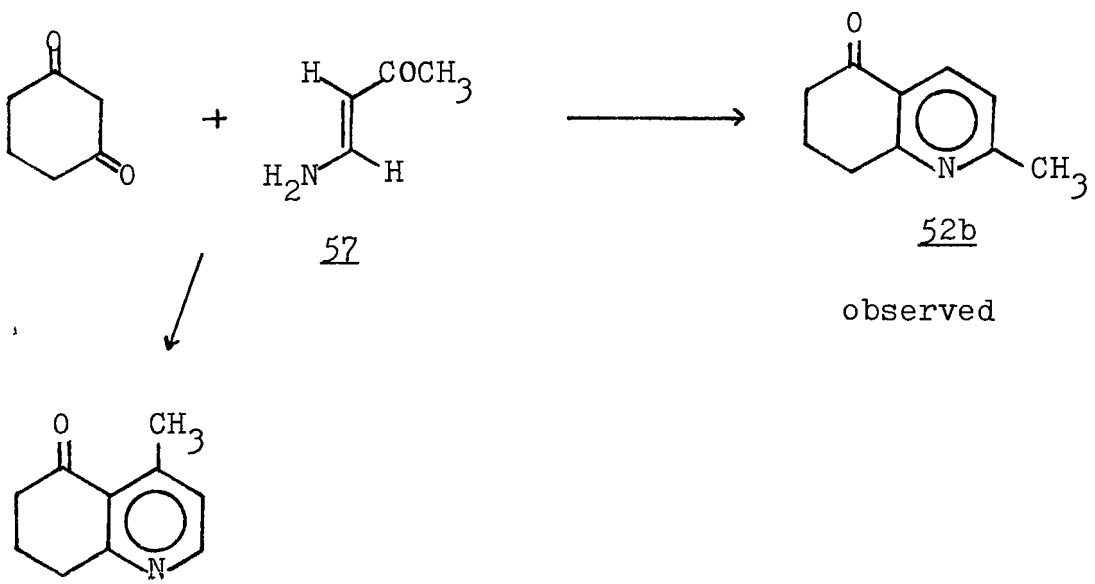
50 51b 55 52b

The formation of 52a from 1,3-cyclohexanedione and 54 could also possibly arise from an intermediate such as 56.



56

However when the reaction was carried out with 4-amino-3-butene-2-one (57) and cyclohexane-1,3-dione, 52b was obtained rather than 4-methyl isomer, which would be expected if the reaction proceeded through a normal Friedlander condensation.



57

52b

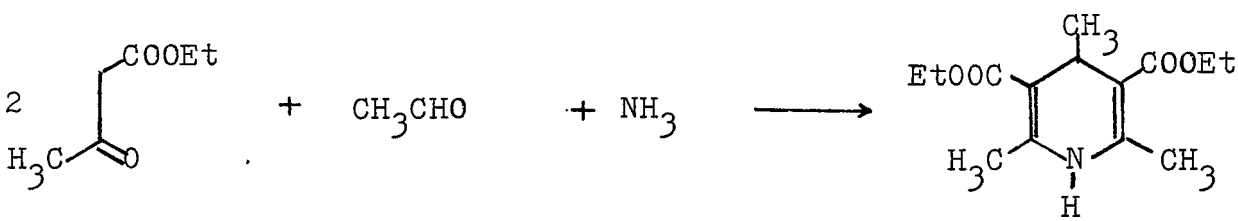
observed

expected

We have observed similar reactions in which β-amino-α, β-unsaturated aldehydes (54) react with cyclic ketones in a normal Friedlander reaction whereas β-amino-α, β-unsaturated ketones such as 57 give rearranged products. The above reaction as well as our observations will be discussed in greater detail in a later section.

3. Other condensation reactions:

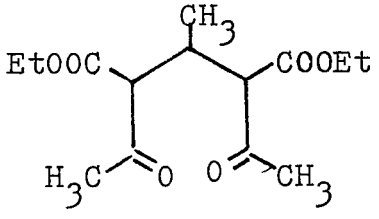
In 1882 Hantzsch[39] prepared 2,4,6-trimethyl-3,5-dihydropyridine diethyl dicarboxylate (58) by a condensation reaction involving two molecules of acetoacetic ester and one molecule each of acetaldehyde and ammonia.



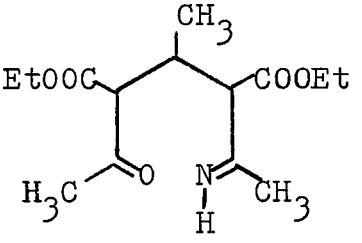
58

Bayer,[40] while investigating the mechanism of Hantzsch's pyridine synthesis, proposed the intermediacy of the 1,5-diketone (59) or its imine (60) in the formation of 58 .

In 1887, Paal[41] reported the preparation of 1,4-dihydropyridines from the reaction of 1,5-diketones and ammonia. Extending the approach of Paal, Tchelitchef and Paul[42] prepared a number of 3-substituted pyridines by the reaction of 1,5-dialdehydes or 1,5-keto-aldehydes or their dioximes

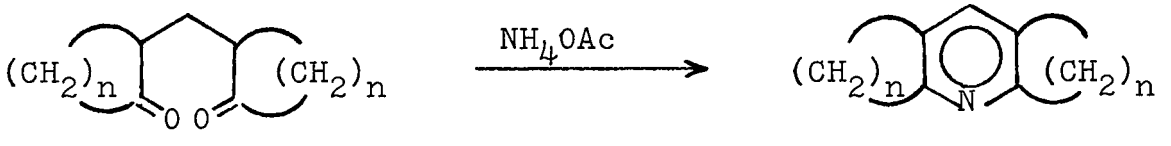


59



60

with hydroxylamine. Utilizing the reaction of 1,5-dicarbonyl compounds with ammonia to yield pyridines, Colonge[43] extended this approach to the preparation of [2,3:5,6]-bisannelated pyridines (62). The reaction of



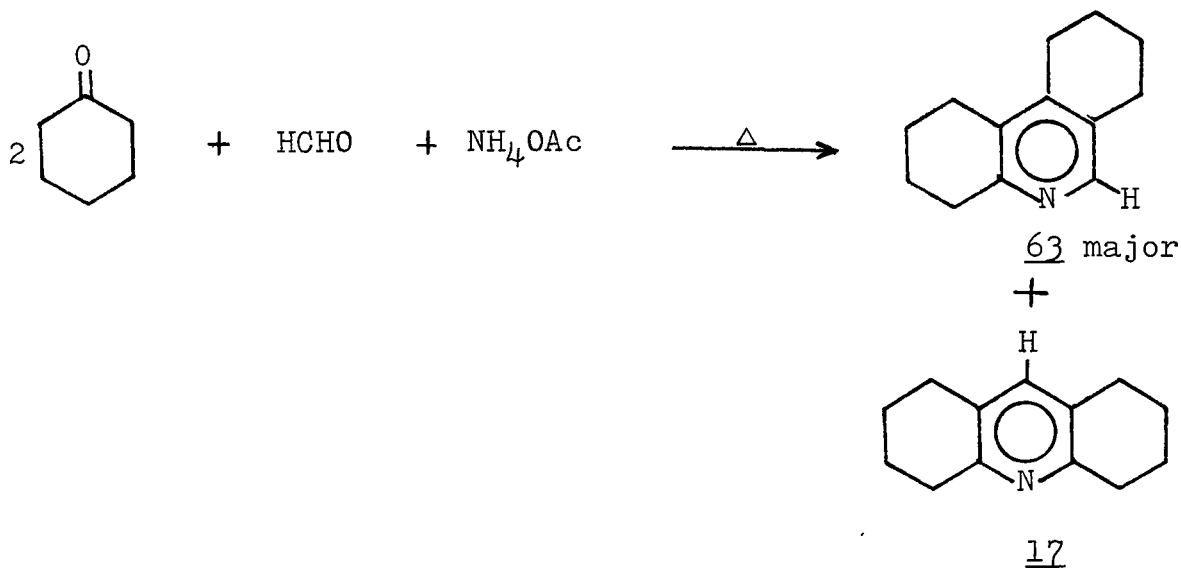
61 a; n = 3
b; n = 4
c; n = 5

62 a; n = 3
b; n = 4
c; n = 5

methylene-bis-2,2'-cycloalkanones[44] with ammonium acetate provided the bisannelated pyridines in 60-75% yield. This has proven to be the most convenient method for the preparation of bisannelated pyridines of the type 62 .

In 1939 Chichibabin[45] found that a condensation reaction involving an aliphatic aldehyde, a cyclic ketone and ammonia results in the formation of a mixture of [2,3:4,5]- and [2,3:5,6]-bisannelated pyridines in which

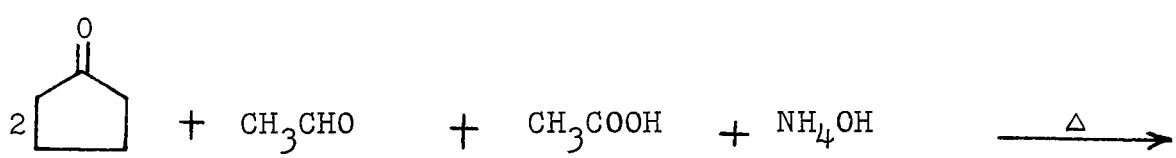
the former predominates.

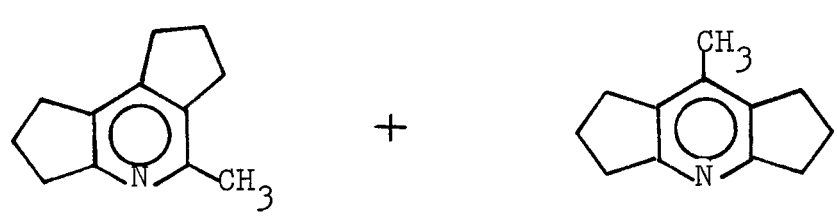


63 major

+

17



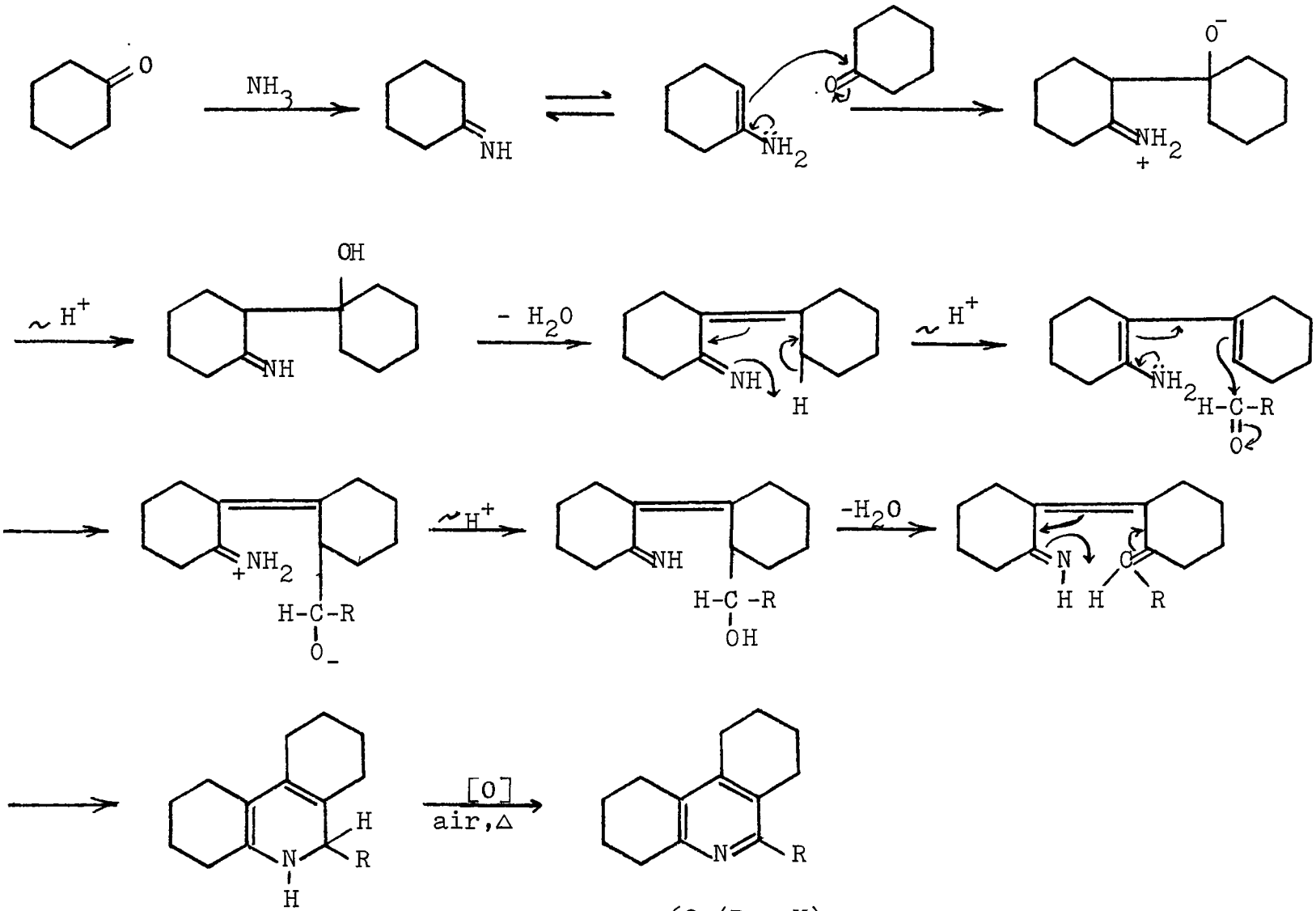


64 + 65

Given below is one of the several possible mechanisms which might explain the formation of [2,3;4,5]-bisannelated pyridines i.e. 63, Scheme 1.

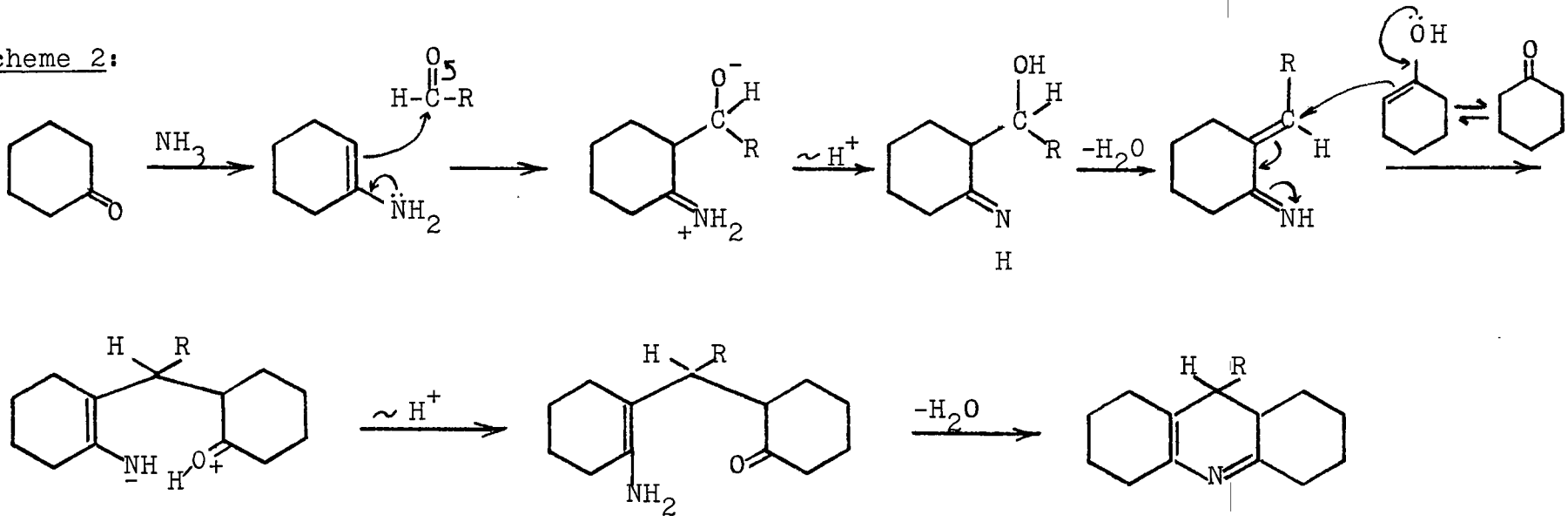
The formation of [2,3;5,6]-bisannelated pyridines can be explained by the mechanism shown in the Scheme 2.

Scheme 1:



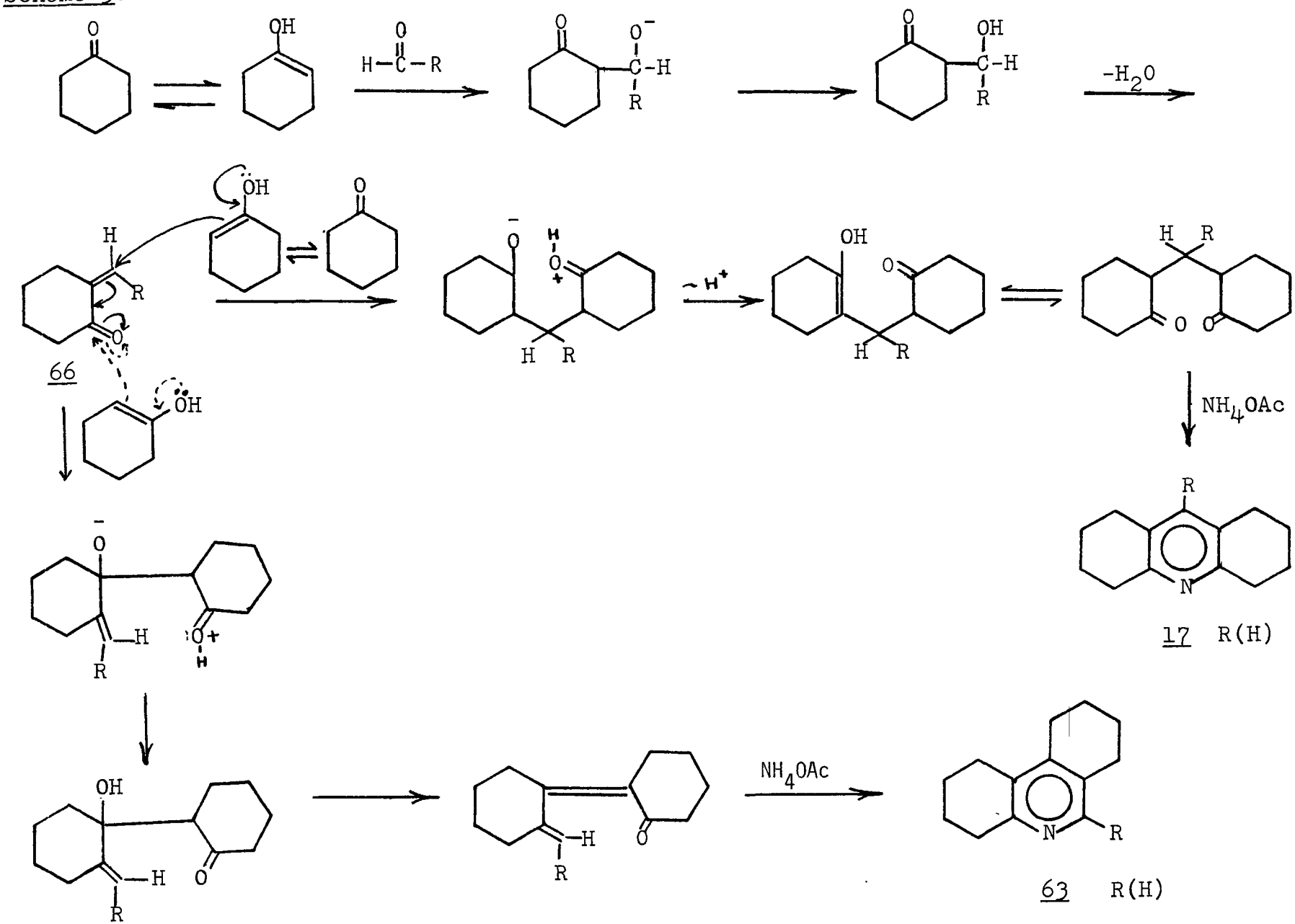
63 (R = H)

Scheme 2:

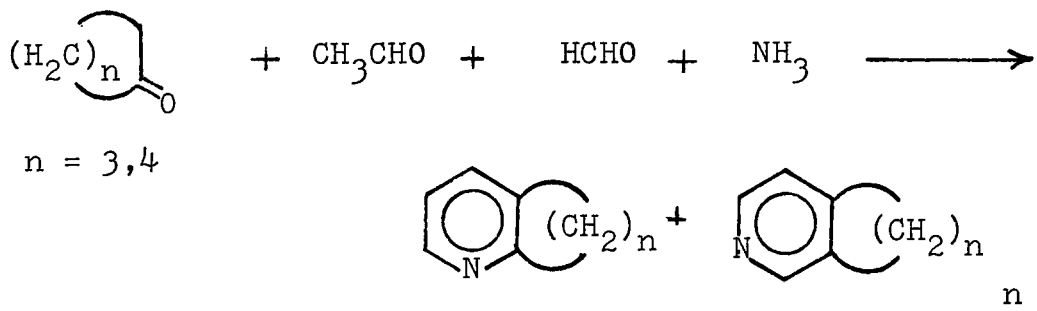


17 (R = H)

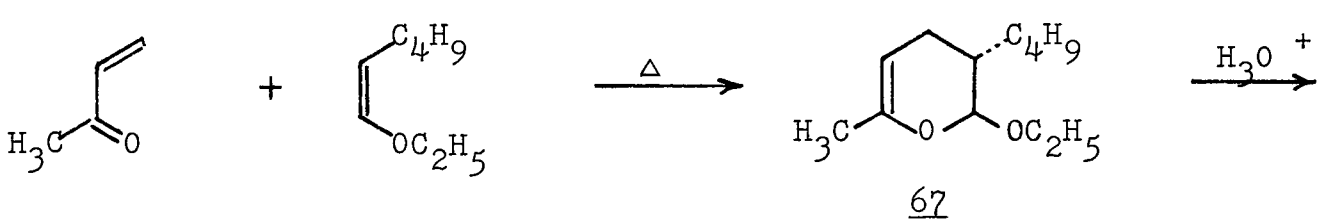
Scheme 3:



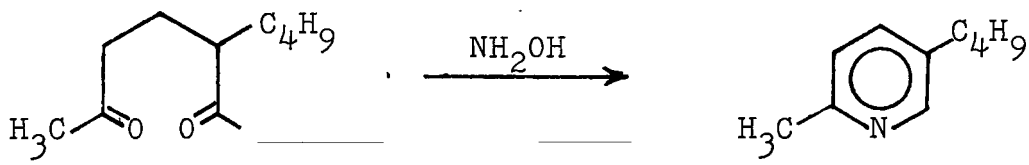
However the above mechanisms do not explain the predominant formation of one isomer over the other. Another possible mechanism which has a common intermediate (66) leading to to the formation of isomeric bisannelated pyridines is shown in Scheme 3. A similar condensation reaction could be applied to the preparation of 2,3- and 3,4-monoannelated pyridines. However no such results have been reported.



Another reaction which may be used for the preparation of annelated pyridines, is based on the cycloaddition of α,β-unsaturated aldehydes or ketones with vinyl ethers. The substituted 2-alkoxy-3,4-dihydro-1,2-pyrans (67) thus obtained are readily hydrolyzed to 1,5-dicarbonyl compounds, 68, which can react with hydroxylamine to yield substituted pyridines (69).[46] For example:

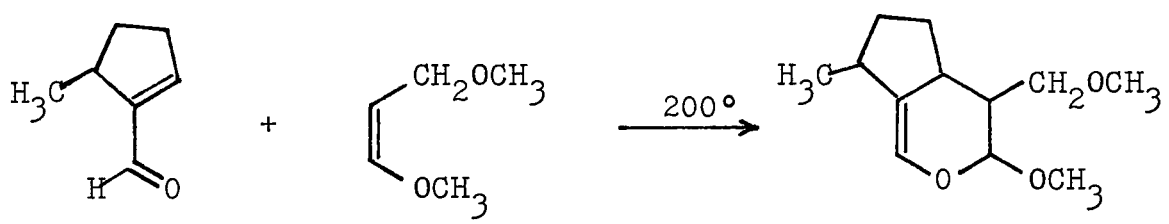


67

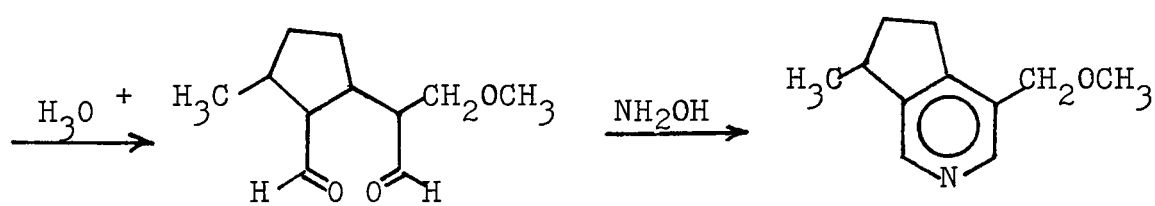


68 69

Utilizing the above approach, Huper[47] has reported the synthesis of the monoterpene alkaloid, Valerianin (74). The reaction of 5-methyl-1-cyclopentene carboxaldehyde (70) with 1,3-dimethoxy propene (71) at 200°C affords a 47% yield of dihydropyranyl ether 72, which could be hydrolyzed to 9-methoxy iridiidial (73), which, without isolation, is condensed with hydroxylamine to give 74 in 20% yield.



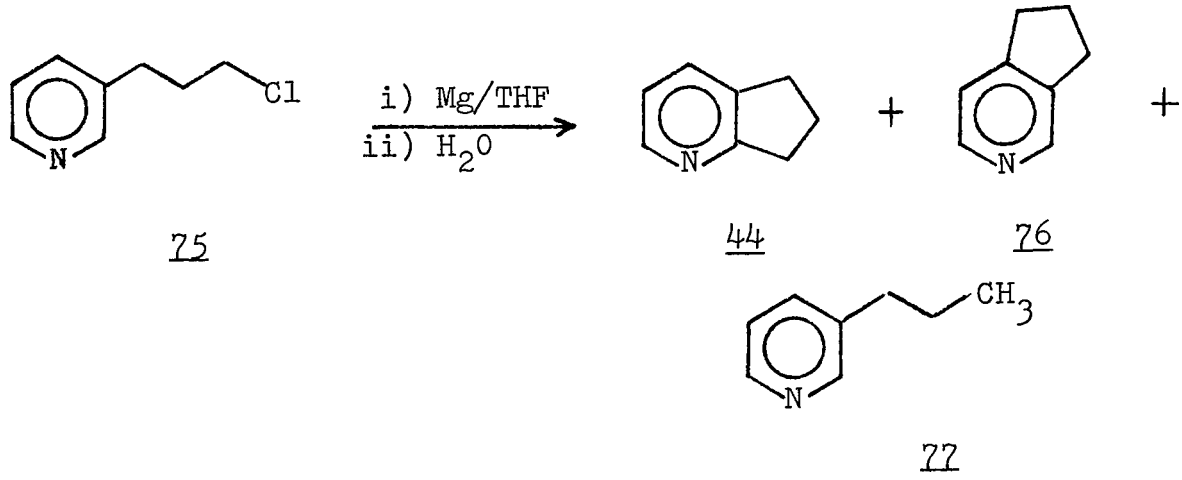
70 71 72



73 74

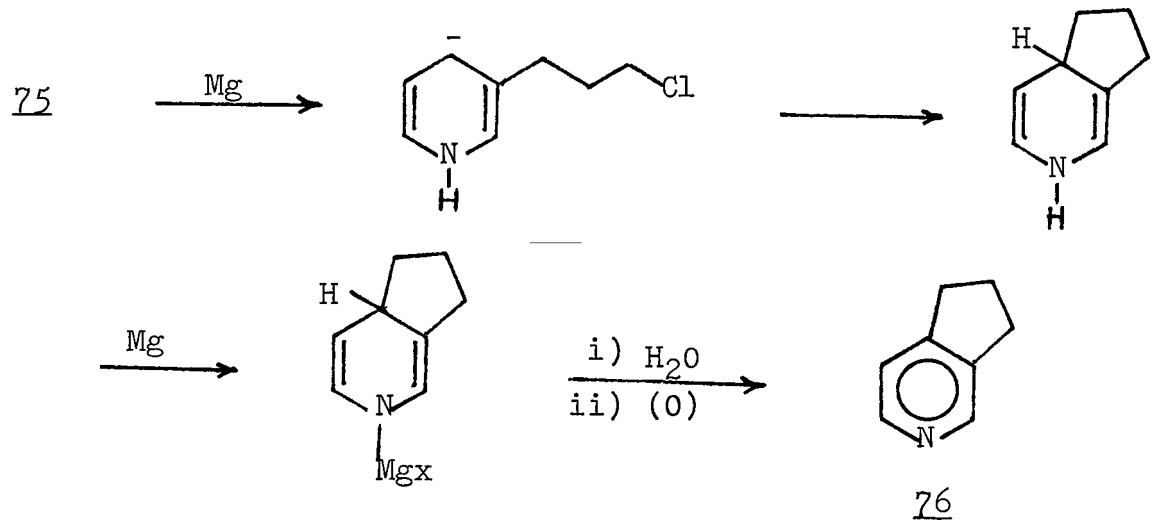
4. Intramolecular cyclizations:

In 1968, Eisch[48] reported the intramolecular cyclization of γ-(3-pyridyl)-propyl magnesium chloride (75) leading to the formation of 2,3- and 3,4- trimethylene pyridines 44 and 76. The complete consumption of 75 with excess magnesium at 25°C led to a product ratio for 76:44:77 of 20:10:70. However, removal of excess magnesium, dilution of the



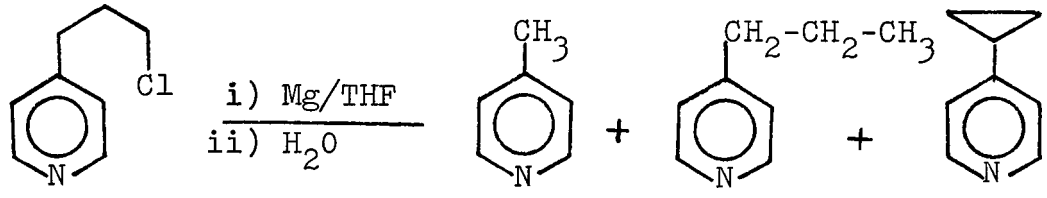
75 44 76 77

Grignard solution and heating changed this ratio to 20:50:30. The formation of 44 can be explained by the cyclization of γ-(3-pyridyl)-propyl Grignard reagent, whereas 76 is believed to be arising from the reaction of chloride 75 with magnesium metal as shown below. Intramolecular cyclization occurs only with 3-alkenylpyridines, as the anion formed at the γ-position of the alkyl group can then attack the electron deficient 2- and 4-positions of the pyridine ring. Whereas 4-alkenylpyridines lead to products arising from carbon-carbon bond fragmentation and



76

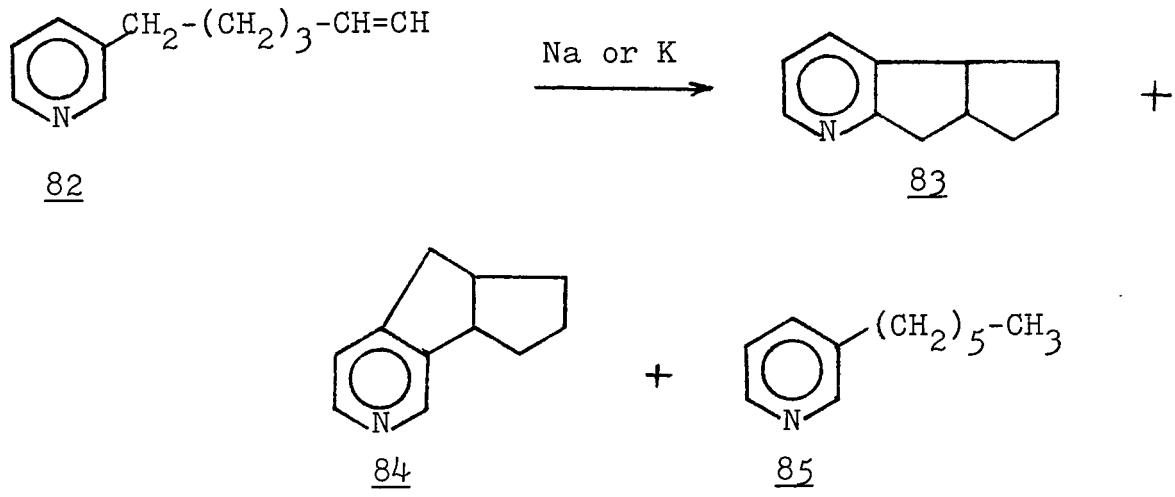
no cyclized materials are obtained, since the anion formed at the γ-position of the 4-alkyl group will not attack the relatively electron rich 3-position of the pyridine nucleus. Thus from the reaction of γ-(4-pyridyl)-propyl chloride (78) with magnesium in THF, the products 79-81 are obtained.



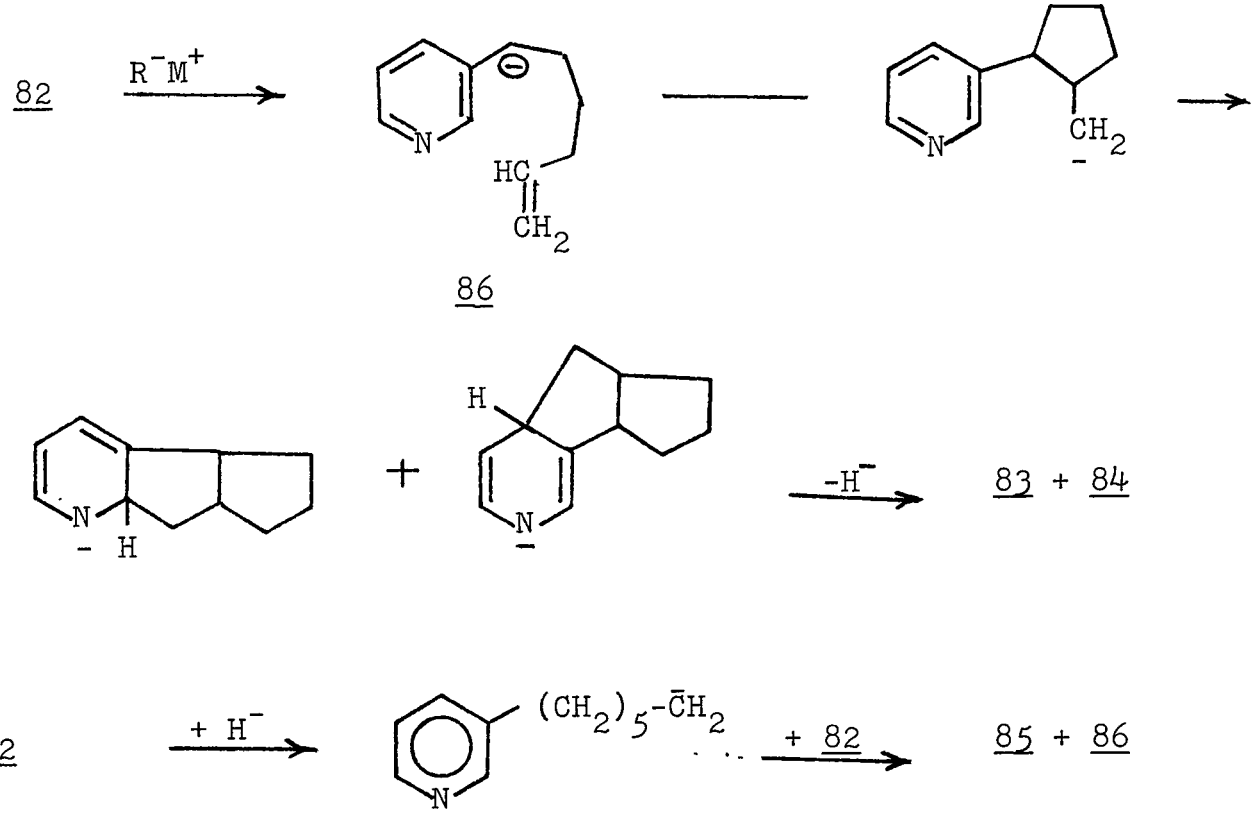
78 79 80 81

18% 50% 32%

A novel intramolecular cyclization of ω-pyridyl-1-alkenes leading to the formation of tricyclic products has been reported by Pines and coworkers.[49] Thus the reaction of 6-(3-pyridyl)-1-hexene (82) with sodium or potassium in o-chlorotoluene and an inert solvent such as sec-butyl-cyclohexane leads to the formation of 83 and 84 in 33% yield.



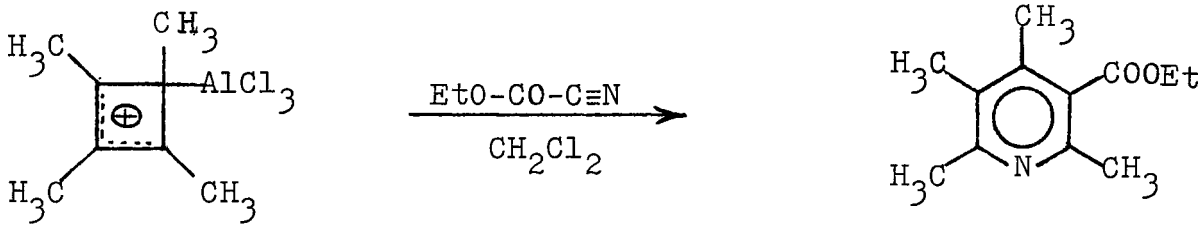
The following mechanism has been proposed to account for the formation of (83) and (84).



Miscellaneous Reactions:

Another route to the synthesis of some pyridine derivatives has been reported by a group from the Netherlands.[50] This route utilizes the unique properties of the $AlCl_3$-σ-complexes of cyclobutadienes(cyclobutyl cations).[51-53] Reaction at 0-20°C for 0.5-2 hours of 0.6 molar solution of the $AlCl_3$-σ-complexes 87,[51] 88[52] and 89-91[53] in methylene chloride with two equivalents of ethyl cyanoformate (92), yielded the $AlCl_3$-complexed pyridines, which after appropriate workup[50] gave the free pyridines in 60% (93), 53% (94), 41% (95), 40% (96) and 43% (97) isolated yield, scheme 4 and 5.

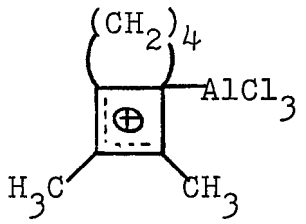
Scheme 4:



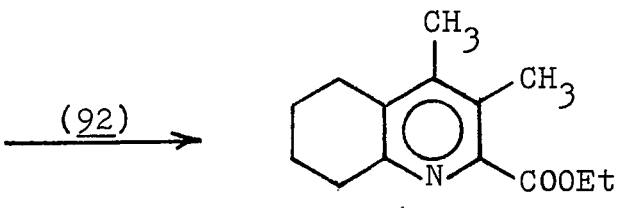
87 93

A possible mechanism has been suggested for the formation of substituted pyridines as shown below. It is believed that cyanoformate first acts as a base which liberates $AlCl_3$ from the complex. A subsequent Diels-Alder reaction of the resulting cyclobutadiene with cyanoformate yields an $AlCl_3$-complexed Dewar pyridine (98). Removal of the $AlCl_3$

Scheme 5

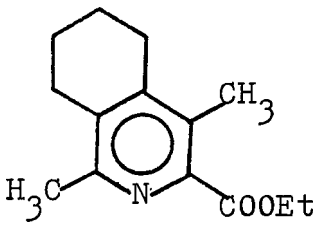


88

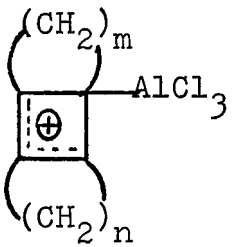


94a

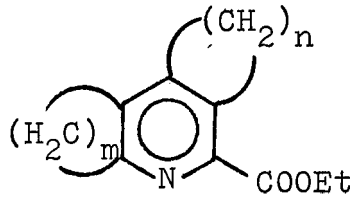
94b



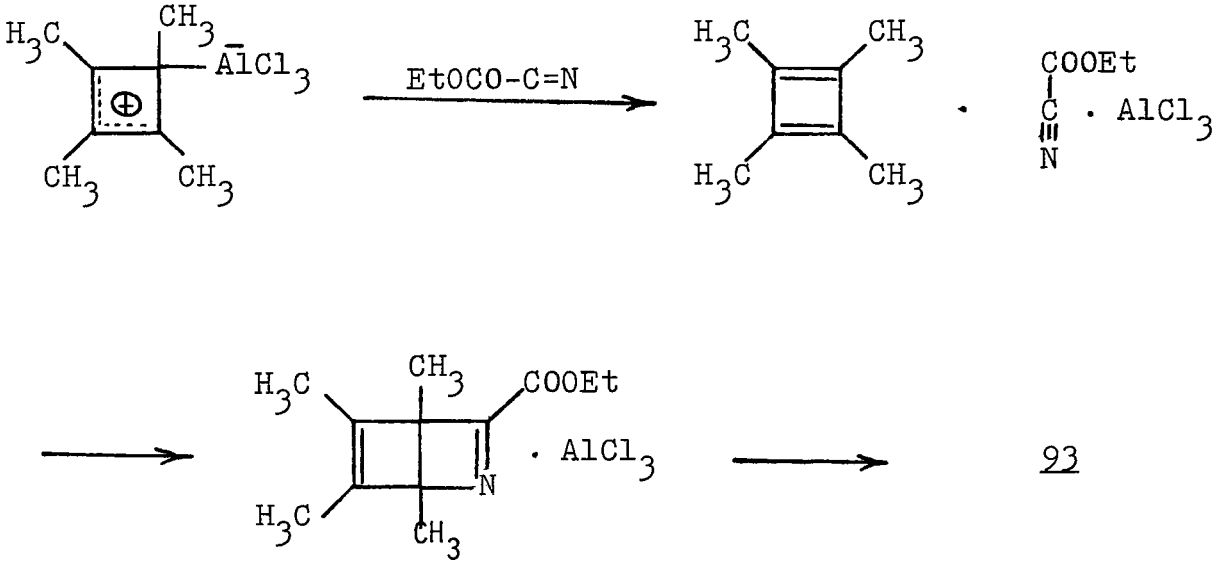
94c



89; (m = n = 4)
90; (m = n = 5)
91; (m = 4, n = 5)



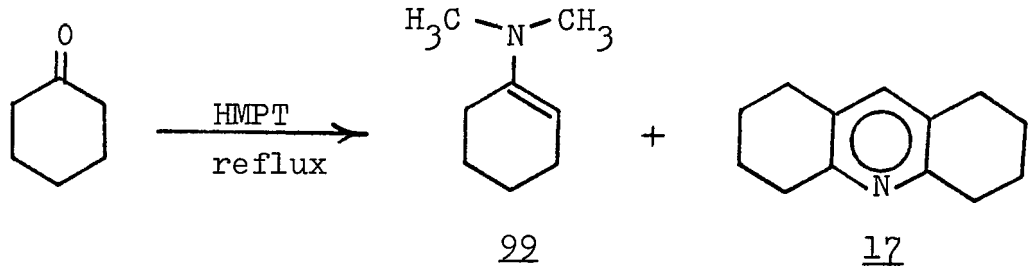
95; (m = n = 4)
96; (m = n = 5)
97; (m = 4, n = 5)



98

with base followed by cyclobutene ring opening then leads to the final product.

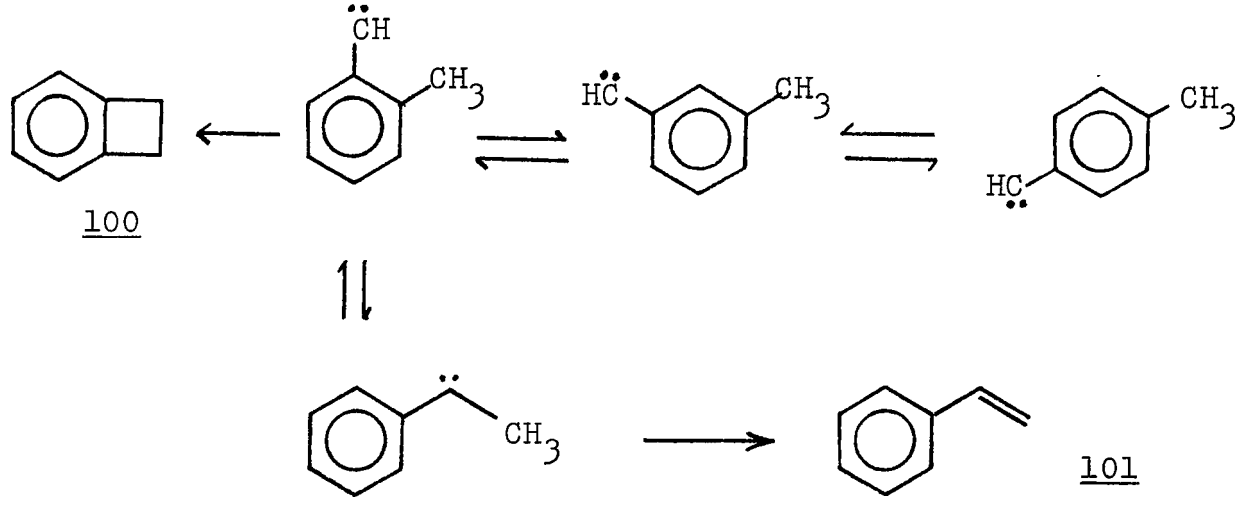
An unusual route to 1,2,3,4,5,6,7,8-octahydroacridines has been reported by Monson and coworkers,[54] who observed that when cyclohexanone is refluxed in hexamethylphosphoric triamide (HMPT) for forty minutes, there is substantial conversion to 1-dimethylaminocyclohexene (99). In addition to 99 there is obtained, upon distillation of the reaction mixture, a 15.2% yield of a mixture of oil and crystals from which recrystallization afforded a 4.8% yield of 1,2,3,4,5,6,7,8-octahydroacridine (17).



99 17

The authors have proposed the following mechanism for this unusual reaction, Scheme 6.

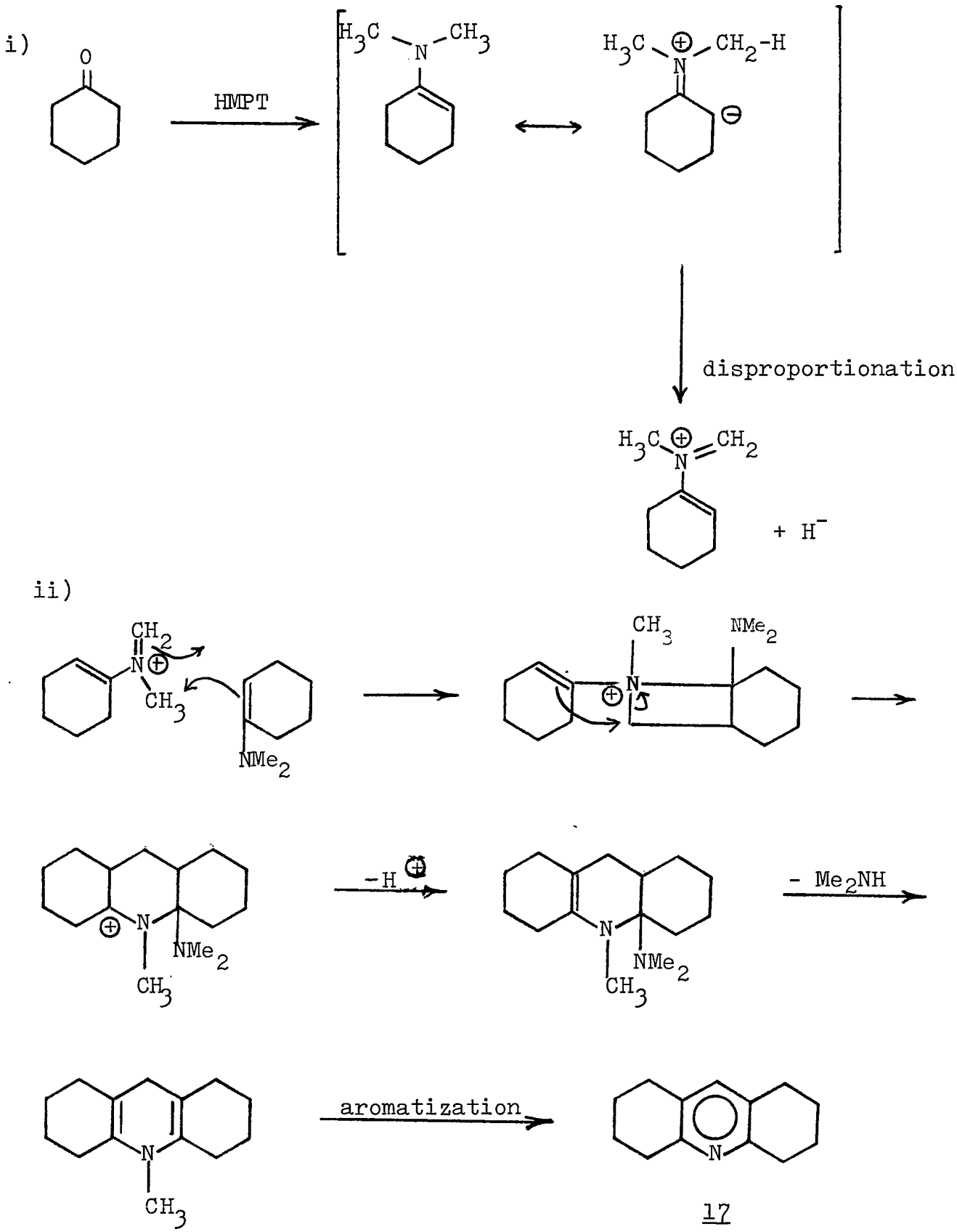
In 1975 Crow and coworkers[55] reported the first synthesis of cyclobutapyridines 104 and 105 by a carbene insertion reaction. This approach is based on earlier work,[56] in which it has been shown that in the case of α-methylphenyl carbenes, the intramolecular insertion of the carbene into an adjacent methyl C-H bond competes with its insertion into the adjacent ring double bond.



100 101

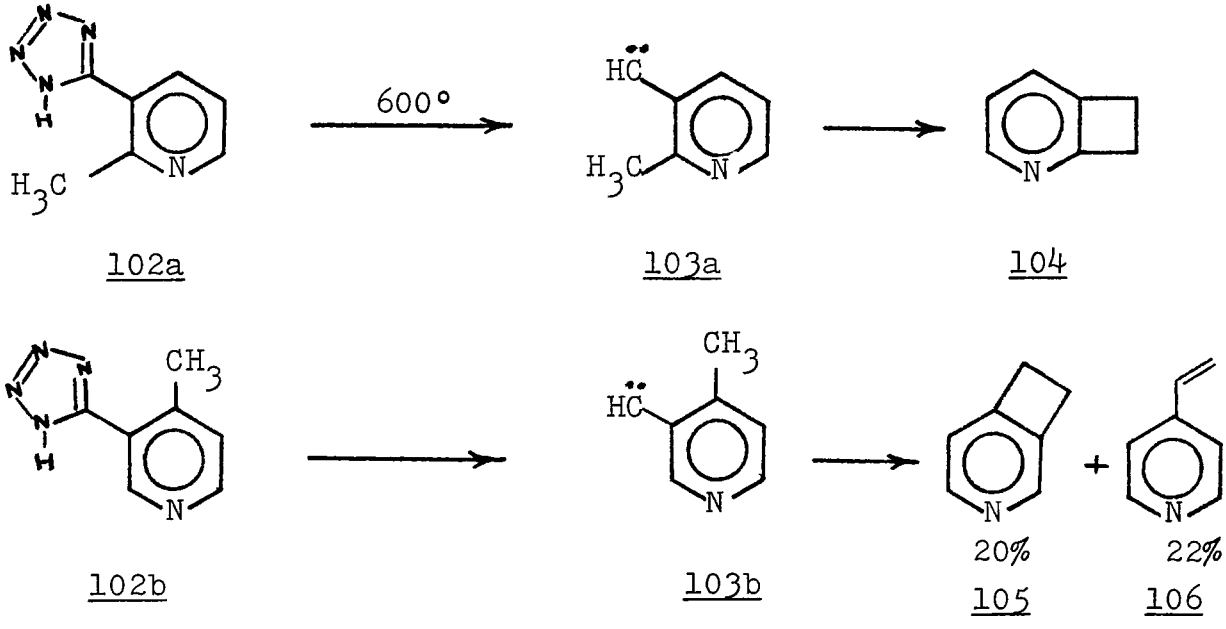
Regardless of the position of the ring methyl substituent with respect to the carbene -CH, the ultimate products are benzocyclobutene (100) and styrene (101). Since the ring

Scheme 6



17

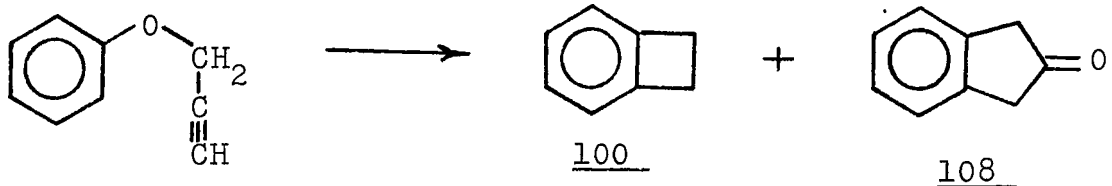
methyl group acts as a carbene trap in methylarylcarbenes leading to the formation of benzocyclobutene, Crow examined the behavior of picolyl carbenes (103). The picolyl carbenes (103) were generated from the pyrolysis of 5-picolyl tetrazoles (102) at 600°C and 0.01 mm pressure. The reaction scheme in terms of products observed is summarized below. The 3-pyridyl carbenes (103) are found to undergo



three distinct processes, i) the trapping by (2- or 4-) methyl groups, ii) insertion into the 2,3-bond, and iii) isomerization to the 2-carbene.

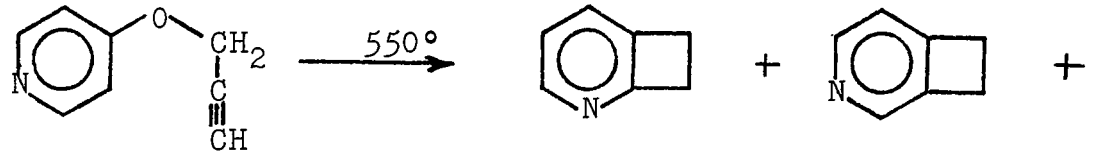
Another reaction in which pyridine behaves in a fashion similar to that of benzene is the pyrolysis of aryl propargyl ethers (107). The flash vacuum pyrolysis of aryl propargyl ether (107) provides a convenient route

to benzocyclobutene (100).[57] Trahanovsky,[58] extending

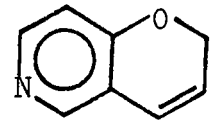


107 100 108

this approach to propargyl 4-pyridyl ether (109), obtained cyclobutapyridines (104) and (105) in 50% yield.



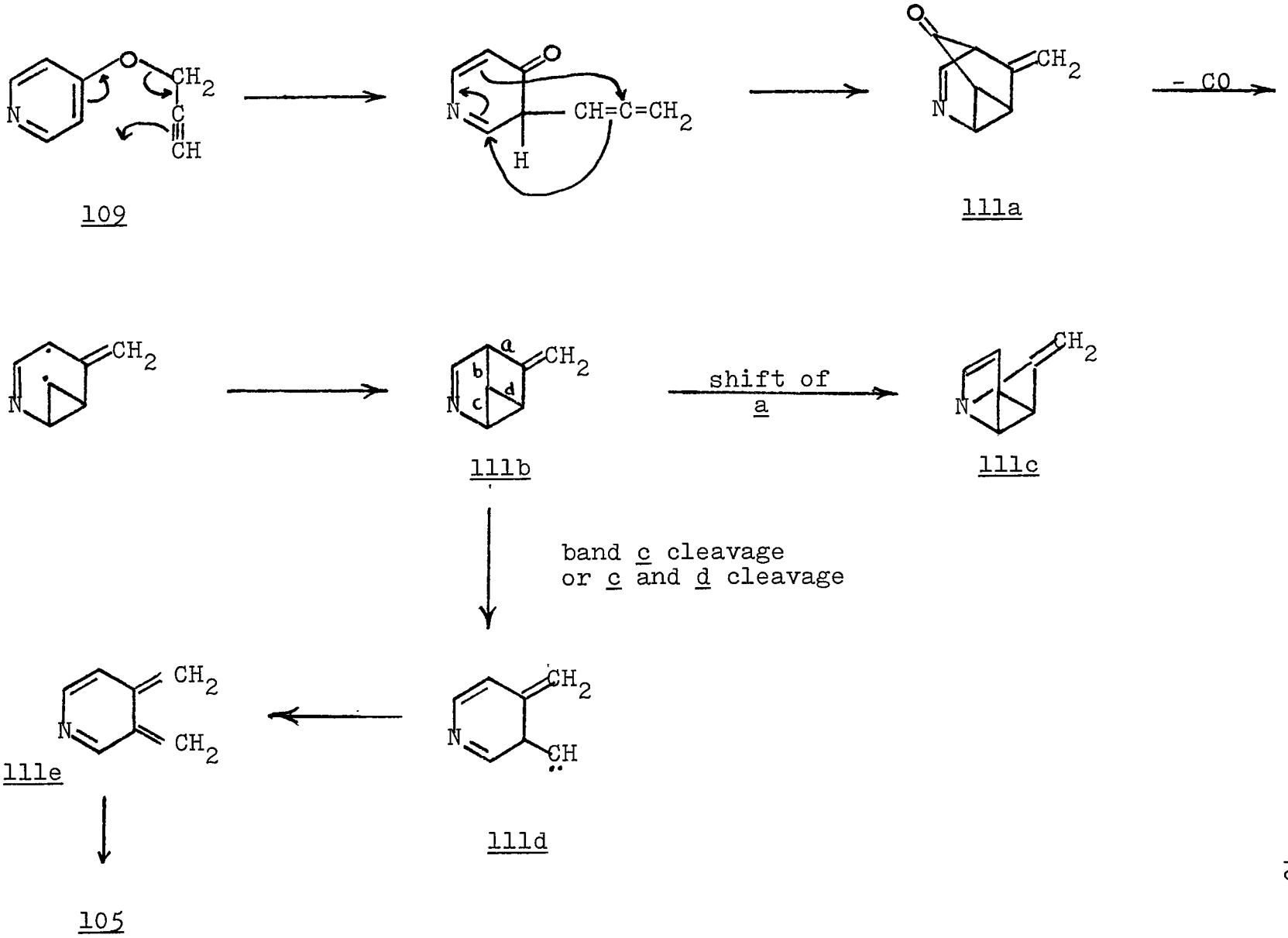
109 104 (35%) 105 (17%)



110 (4.7%)

Trahanovsky has proposed the following mechanism to account for the formation of 104 and 105 , Scheme 7 . The corresponding bond cleavages of (111c) would lead to a similar sequence resulting in the formation of (104).

Scheme 7


109
111a
- CO
111b
shift of a
111c
band c cleavage
or c and d cleavage
111d
111e
105

RESULTS AND DISCUSSION

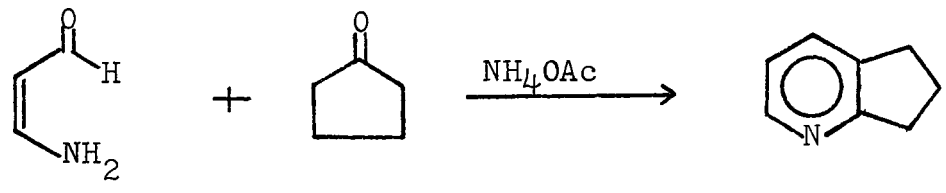
RESULTS AND DISCUSSION

Part I: Synthesis

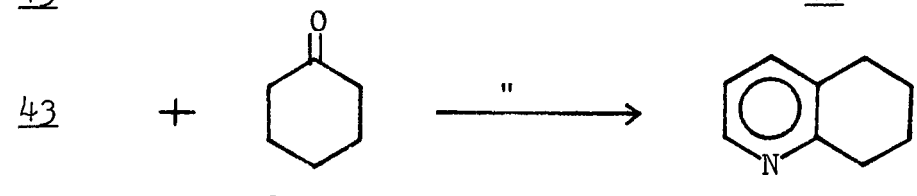
a) Synthesis of monoannelated pyridines and related compounds:

Annelated pyridines are most easily prepared by the condensation of cyclic ketones with an appropriate nitrogen-containing species to build up the pyridine ring. The general strategy of this approach involves starting with the ring (or rings) to be fused to pyridine already intact and using these cyclic precursors to build up the aromatic portion of the molecule, thus taking advantage of the driving force of resonance stabilization.

The preparation of 2,3-monoannelated pyridines is most easily carried out by the reaction of β-aminocrolein (43) with the cyclic ketones in the presence of a suitable catalyst.[36] Thus the reaction of 43 with cyclopentanone and cyclohexanone provided 2,3-trimethylenepyridine (44) and 5,6,7,8-tetrahydroisoquinoline (21) in 16% and 21% yields respectively.



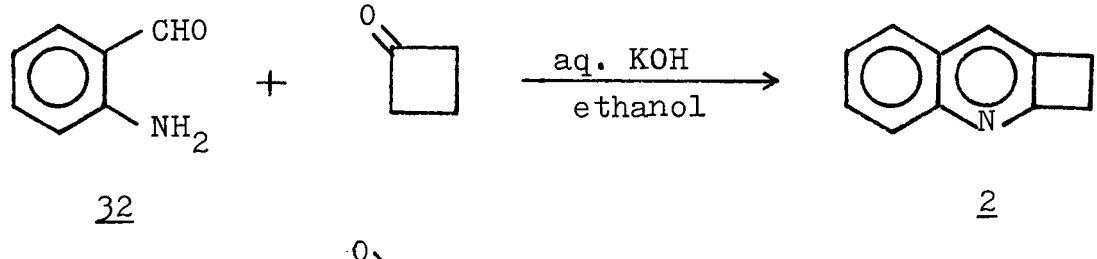
43 44



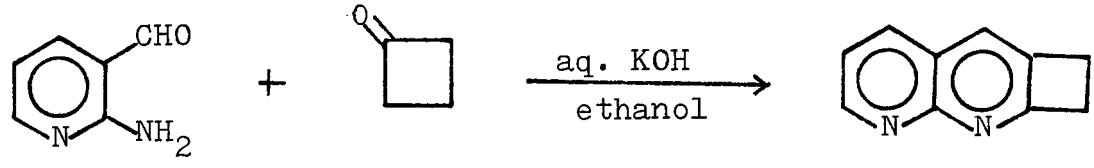
21

104

The treatment of β-aminoacrolein (43) with cyclobutanone, however, did not lead to the formation of cyclobuta[b]pyridine (104). The failure of this reaction was surprising since cyclobutanone undergoes a smooth condensation with o-aminobenzaldehyde (32) and 2-aminonicotinaldehyde (37) to provide 2 and 4a in good yield.[10,14] The treatment of β-aminoacrolein (43)



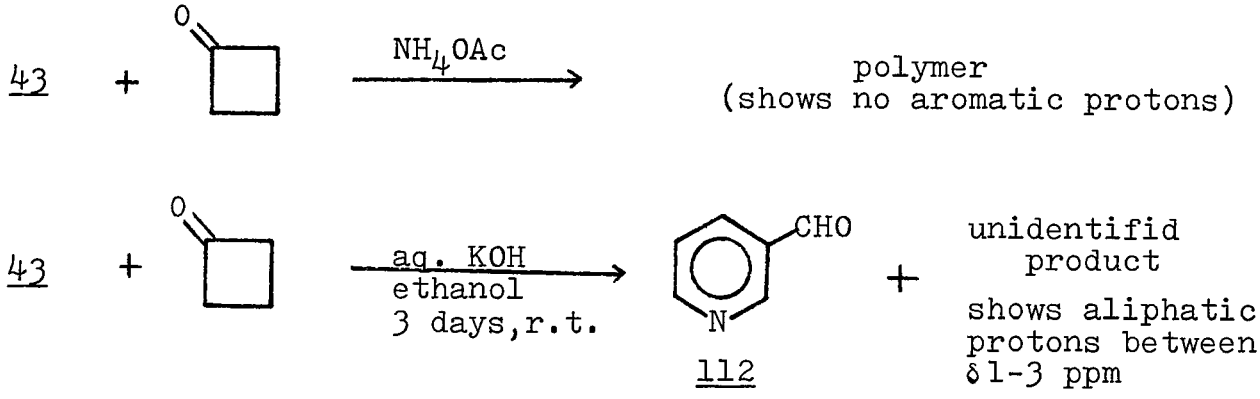
32 2



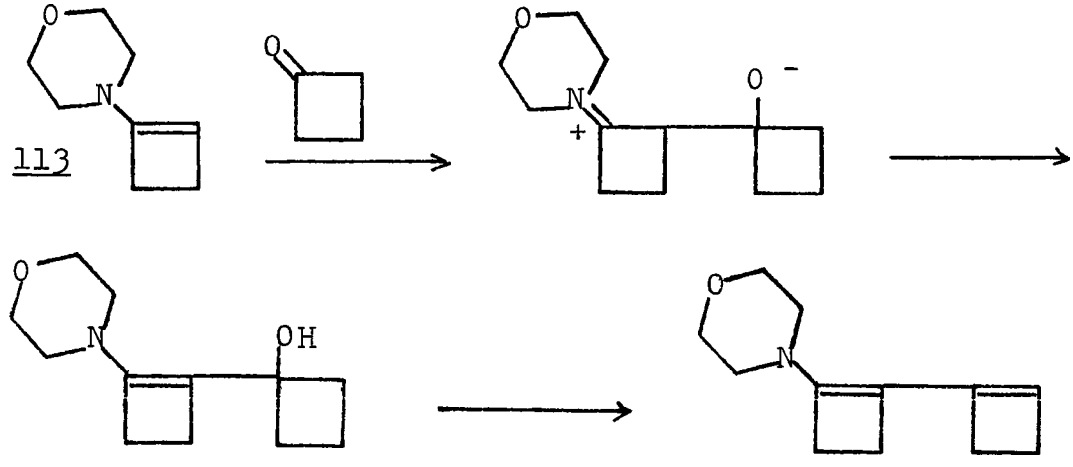
37 4a

with cyclobutanone was carried out under a variety of catalytic conditions. When the reaction was carried out in the presence of ammonium acetate as catalyst, a resinous material was obtained whose NMR spectrum indicated the absence of aromatic protons attributable to a pyridine ring. In the presence of aqueous

potassium hydroxide, the attempted condensation between 43 and cyclobutanone led to the formation of two products which could be isolated by preparative gas chromatography. One of the two products was identified as nicotinaldehyde (112) by NMR and IR, whereas the NMR spectrum of the other did not show any aromatic protons and from the spectral data alone, it could not be identified. The inability of cyclobutanone

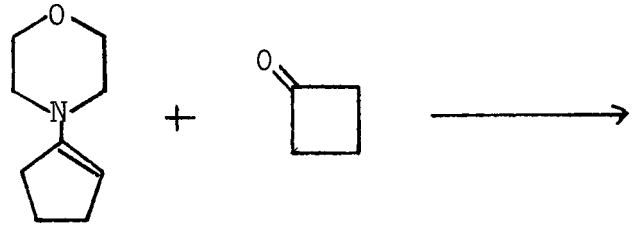


to undergo a condensation reaction with 43 can be explained by the high reactivity of the cyclobutanone-enamine type intermediates involved. In 1966 Musa and Bond[59] reported that the morpholine enamine of cyclobutanone (113) undergoes further condensation to give the di-enamine 114.

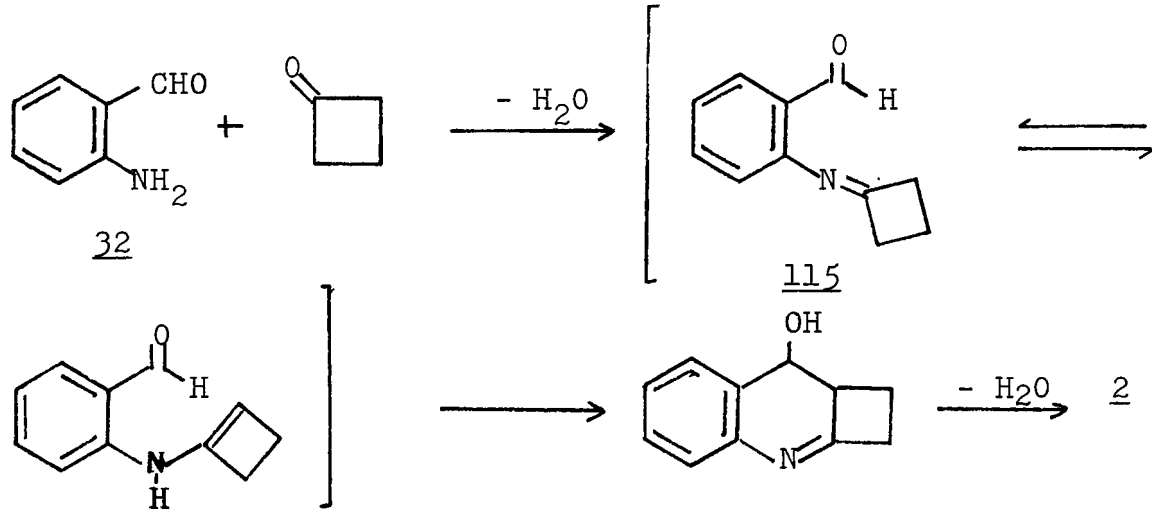


114

Under similar conditions the cyclopentanone enamine failed to react with cyclobutanone. In the reaction between o-amino-

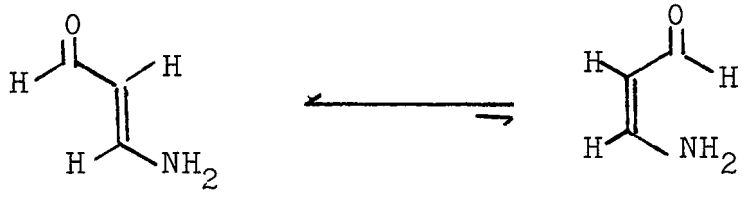


benzaldehyde (32) or 2-aminonicotinaldehyde (37) and cyclobutanone, a cyclobutanone enamine type of the intermediate 115 is formed, but due to the cis-configuration of the reacting β-amino-α, β-unsaturated carbonyl moeity, intramolecular cyclization is preferred over the reaction with another molecule of cyclobutanone as shown below.



32 115

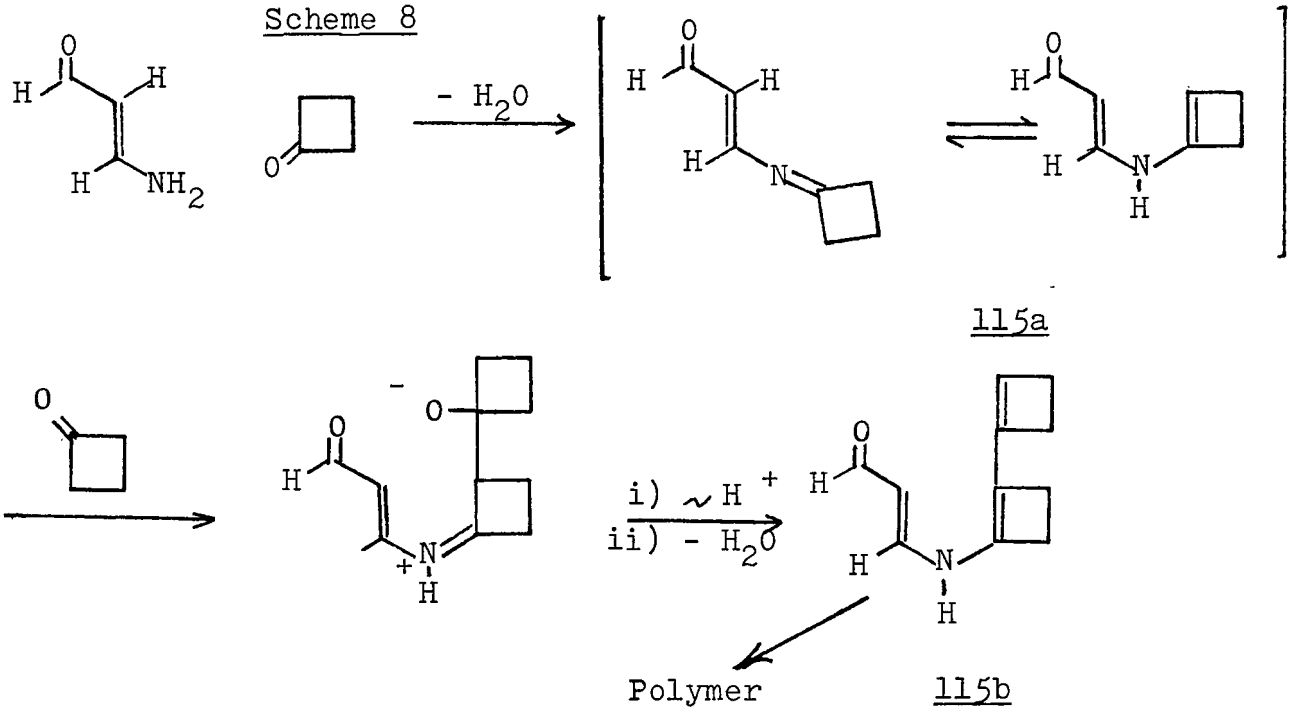
As compared to the cis-configuration of β-amino-α, β-unsaturated carbonyl moeity in the case of 33 and 37, β-aminoacrolein (43) exists predominately in the trans-configuration.[60]



43

Thus in the reaction between β-aminoacrolein and cyclobutanone, isomerization to the cis-configuration in the cyclobutanone enamine intermediate 115a is much slower than its reaction with another molecule of cyclobutanone to give dienamine 115b, which might rapidly polymerize. The polymerization of 115b is in accord with the known behavior of 1,1'-dicyclobutenyl type compounds,[61] scheme 8.

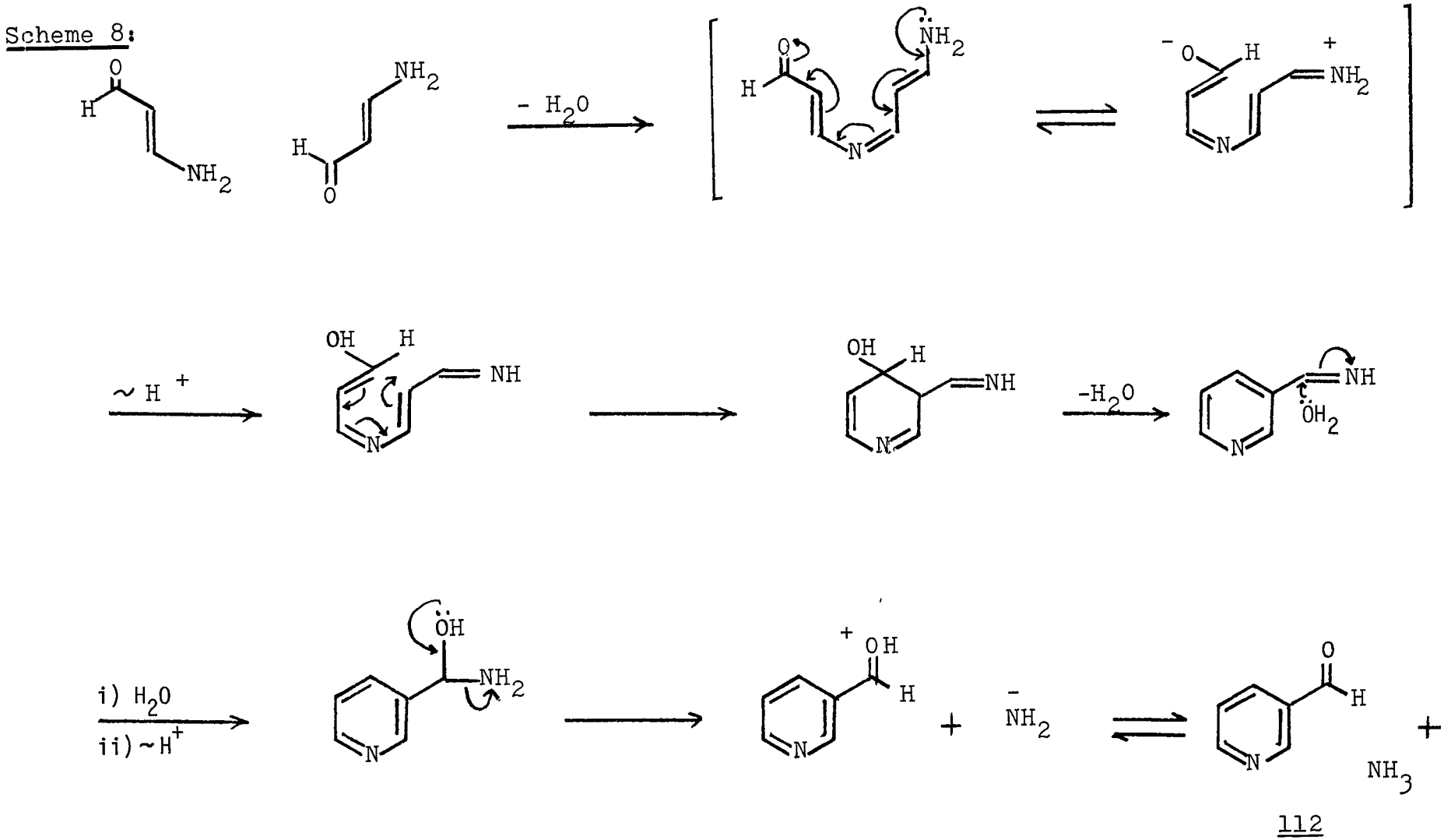
Scheme 8



A similar process does not occur in the reaction between β-aminoacrolein (43) and cyclopentanone or cyclohexanone due to the lower reactivity of the enamine intermediate.

The formation of nicotinaldehyde (112) in the reaction between 43 and cyclobutanone in presence of aqueous base can

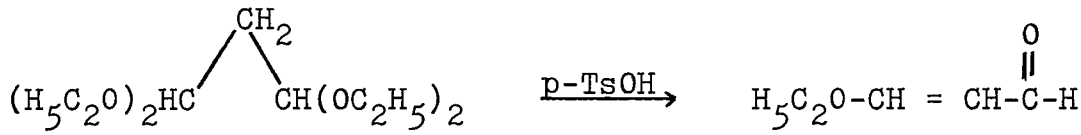
Scheme 8:



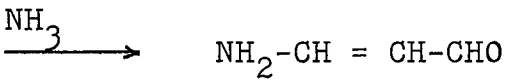
112

be explained by the self condensation between two molecules of β-aminoacrolein as shown in scheme 8.

The preparation of β-aminoacrolein (43) was initially attempted according to the procedure of Skoldinov.[62] This method involves the reaction of 1,1,3,3-tetraethoxypropane 116 with p-toluenesulfonic acid[63] followed by ammonolysis of the resulting 3-ethoxyacrolein 116a. The reaction of 1,1,3,3-

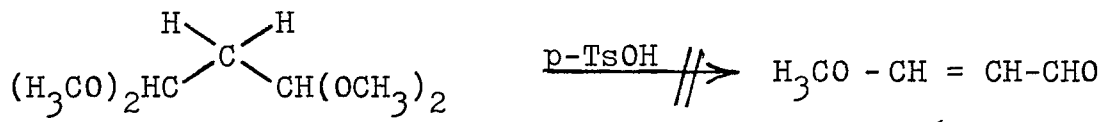


116 116a



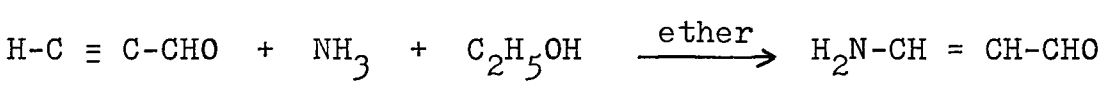
43

tetramethoxypropane (117) with p-toluenesulfonic acid under the conditions described by these authors afforded only starting material and a polymeric substance.



117 116b

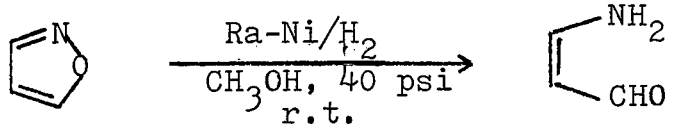
The method of Terpinski[64] involves the reaction between propargylaldehyde (118) and ammonia in the presence of ethanol in a sealed tube. This reaction presumably involves the



118 43

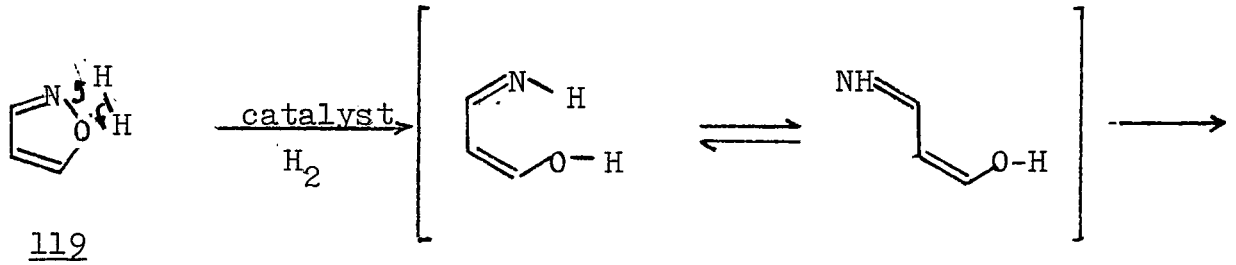
addition of ethanol to the triple bond to give 3-ethoxy acrolein (116a) followed by the ammonolysis to give 43. From the above reaction, 43 was obtained in about 15% yield and the purification of the crude material was carried out by sublimation.

A much improved method for the preparation of β-amino-acrolein is by the hydrogenolysis of isoxazole (119). The

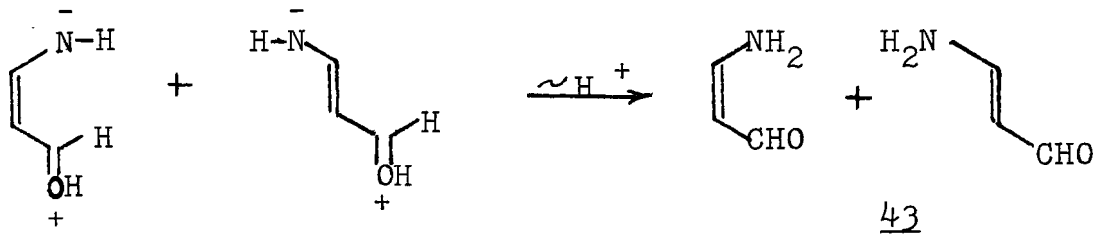


119 43

partial hydrogenation of isoxazole over Raney-nickel at 40 psi and room temperature provided 43 in greater than 80% yield. When the hydrogenation was carried out with freshly prepared Raney-nickel at 40 psi, 43 was obtained along with the further reduced product as indicated by the presence of aliphatic protons between δ 1-3 ppm by NMR. Lowering the hydrogenation pressure to 20 psi resulted in the formation of 43 as the only product. The hydrogenolysis of isoxazole occurs by breaking of nitrogen-oxygen bond with a simultaneous addition of one molecule of hydrogen followed by tautomerization as shown below.

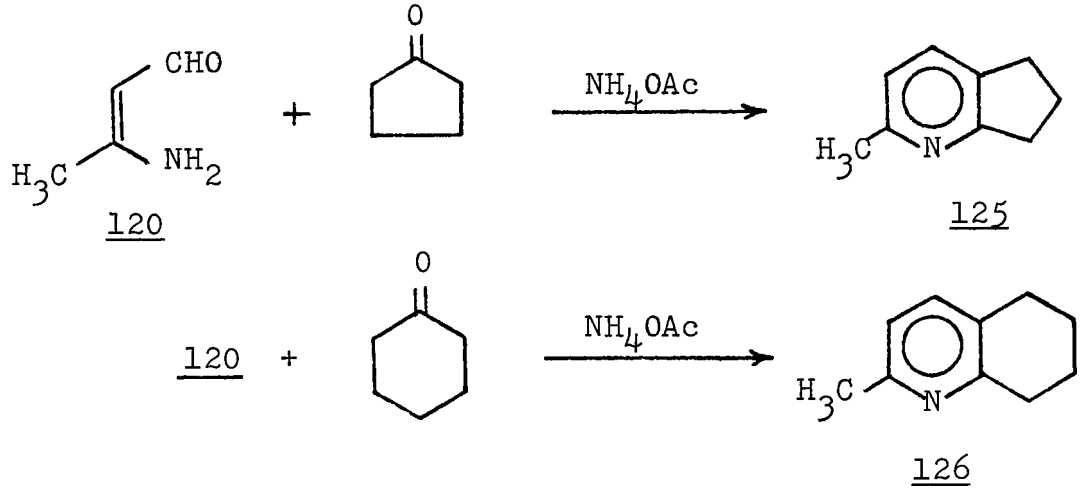


119



43

The Table II summarizes the different β-amino-α, β-unsaturated carbonyl compounds obtained from the hydrogenolysis of the corresponding isoxazoles. The reaction of these β-amino-α, β-unsaturated carbonyl compounds (120-124) with cyclic ketones was also studied. The reaction between 3-methyl-3-aminoacrolein (120) and cyclopentanone or cyclohexanone provided the expected annelated pyridines 125 and 126. The reaction be-



120

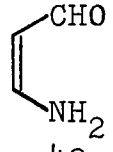
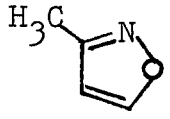
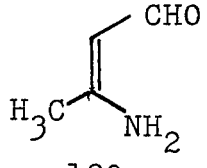
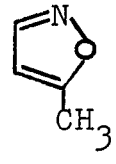
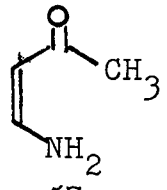
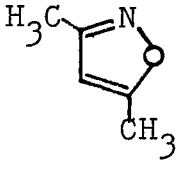
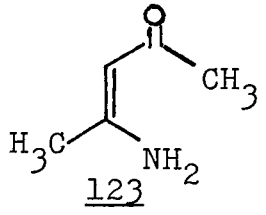
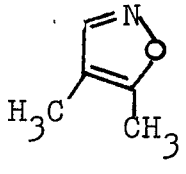
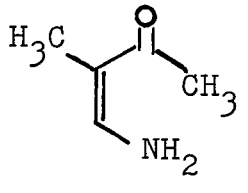
125

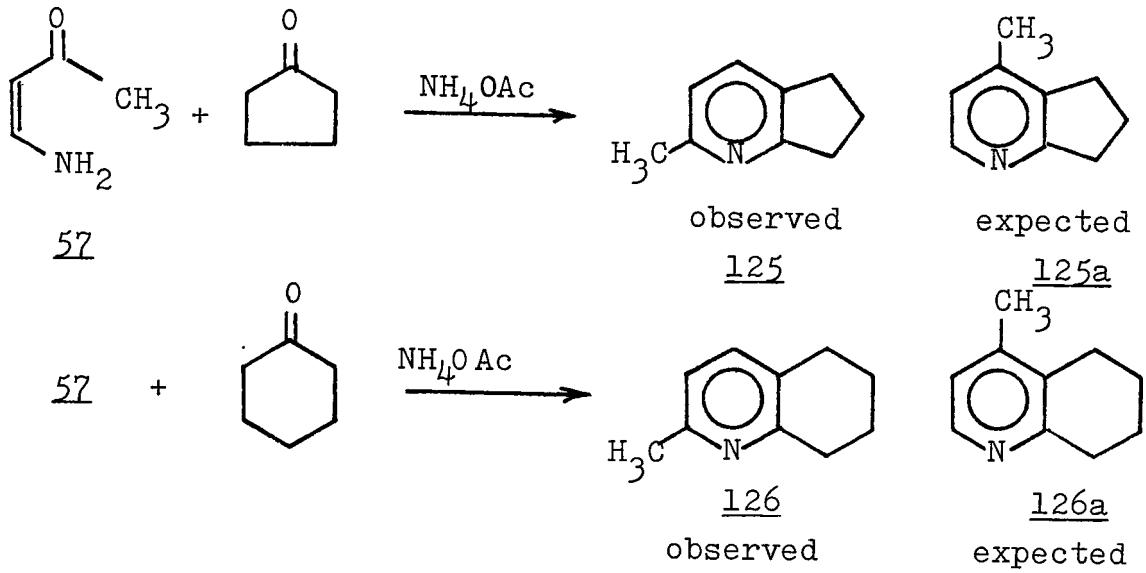
126

tween 4-amino-3-butene-2-one (57) and cyclopentanone or cyclohexanone led to the formation of the 2-methyl isomer instead of the expected 4-methyl isomer.

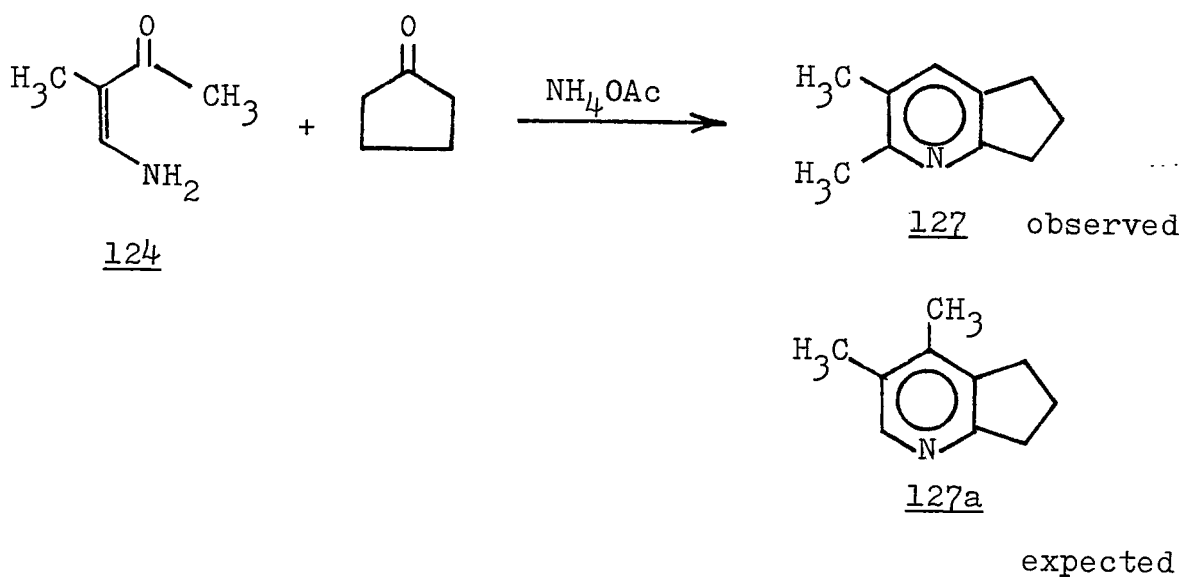
TABLE II

Preparation of β-Amino-α, β-Unsaturated Carbonyl Compounds from Hydrogenolysis of Isoxazoles

Isoxazole	Product	Yield %	m.p. °C	b.p. °C
 119	 43	82	104-5°C	
 119a	 120	50		48-49°C (0.1 mm)
 119b	 57	90		125-7°C (0.6 mm)
 119c	 123	83	43-44°	
 119d	 124	80	110-111°	

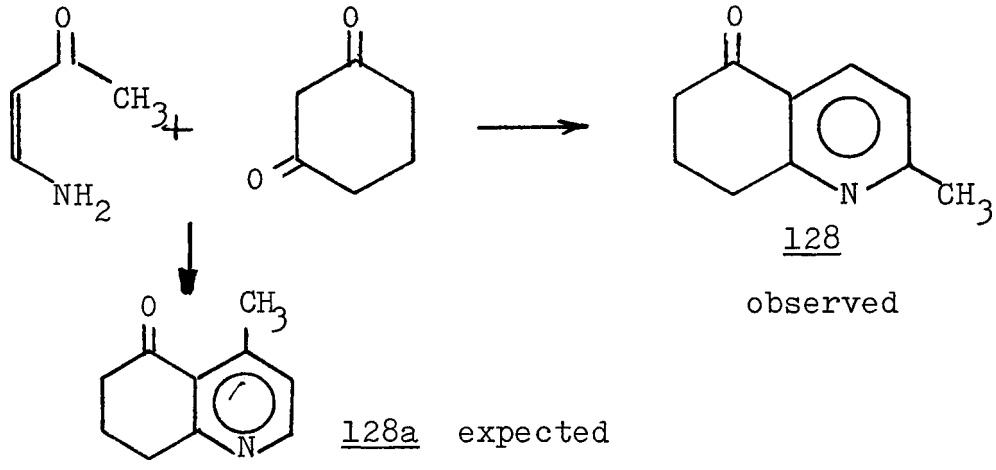


A similar rearrangement was observed in the reaction between 4-amino-3-methyl-3-butene-2-one (124) and cyclopentanone in the presence of ammonium acetate as catalyst leading to the formation of annelated pyridine 127 instead of the expected 127a.



124

Curran[38] has observed the same type of rearrangement in the reaction between 4-amino-3-butene-2-one (57) and 1,3-cyclohexanedione which led to the formation of the 2-methyl isomer 128 rather than the expected 4-methyl isomer 128a.

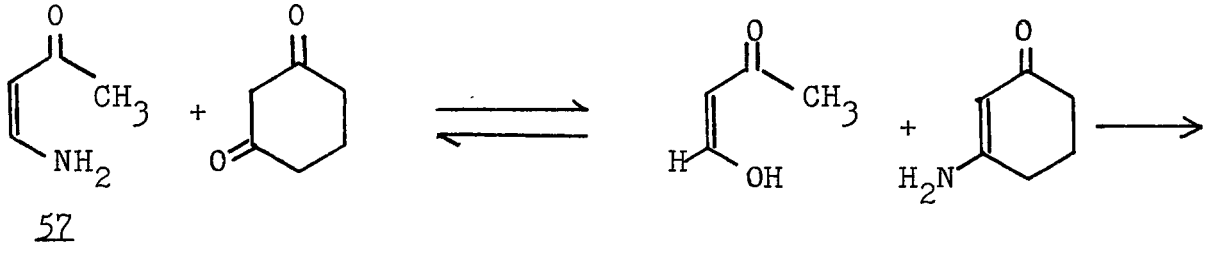


128 observed

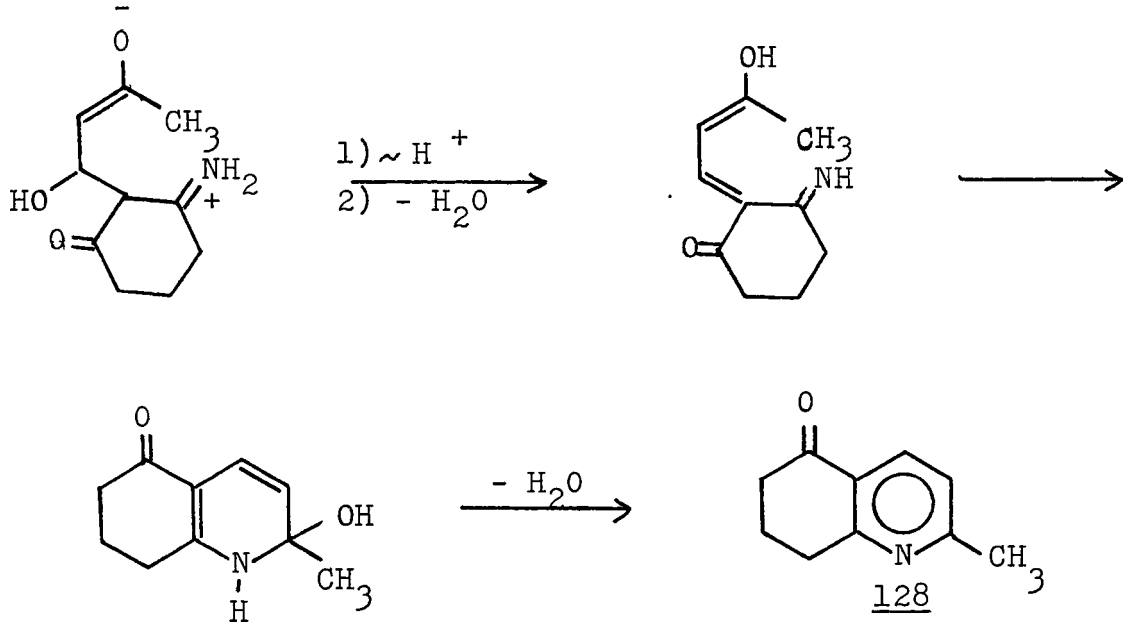
128a expected

Curran also observed that 128 was formed, irrespective of whether the reaction was carried out under basic or acidic conditions, indicating that a similar pathway may be followed in both mediums. He explains the formation of the rearranged product by invoking a prior equilibrium between the reacting partners under the conditions of the reaction, which after equilibrium react in a normal fashion leading to the formation of the observed product as shown in scheme 9.

Scheme 9:



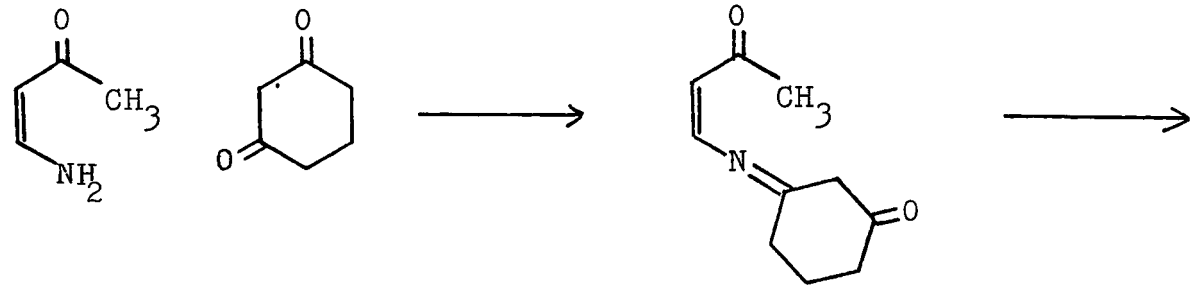
57

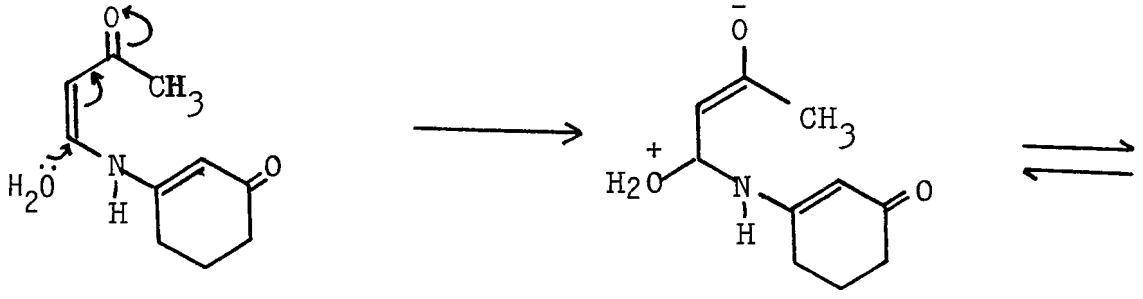


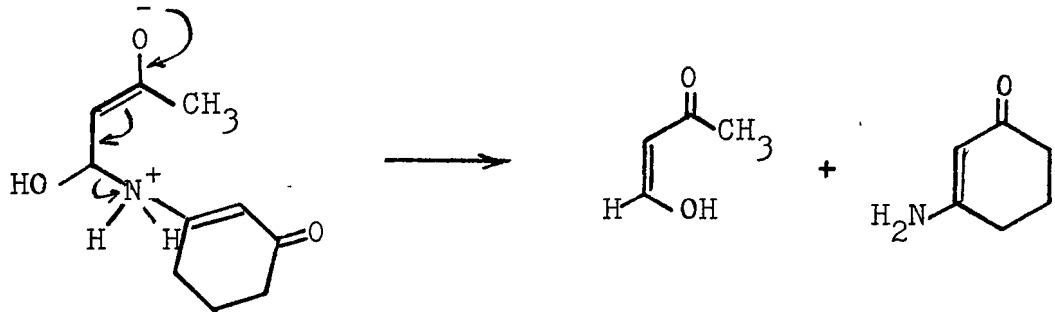
128

However, Curran does not explain how the prior equilibrium between the reacting partners is established. One can propose the following mechanism to account for this equilibrium between 57 and 1,3-cyclohexanedione, scheme 10.

Scheme 10:

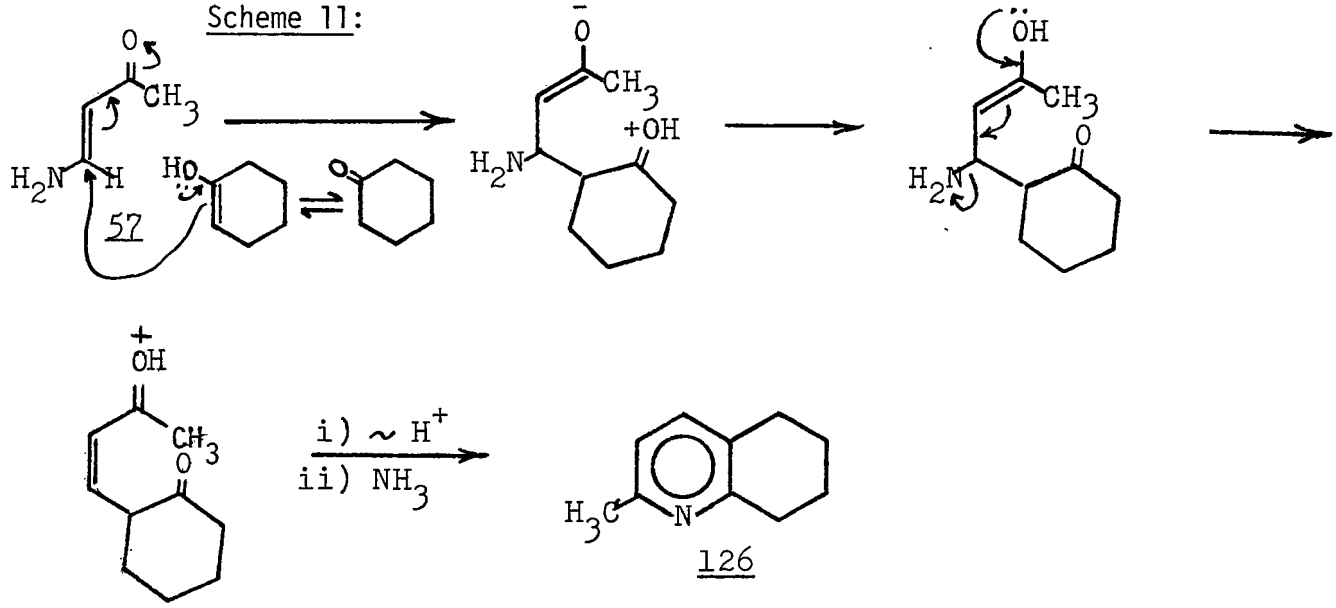






However the following mechanism would also account for the formation of the rearranged product in the reaction between 57 and cyclohexanone, scheme 11.

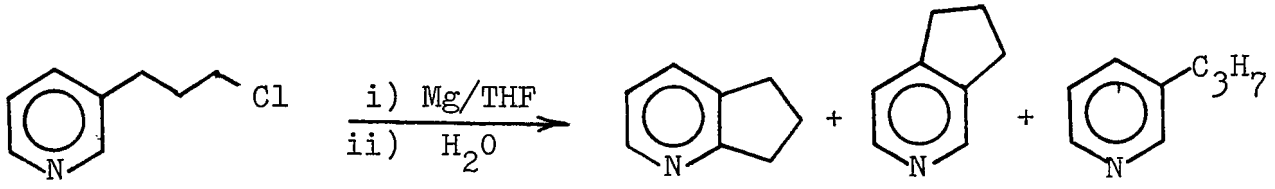
Scheme 11:



Curran's mechanism does explain the formation of the observed product, but it does not explain why an equilibrium between the reacting partners is established before the reaction.

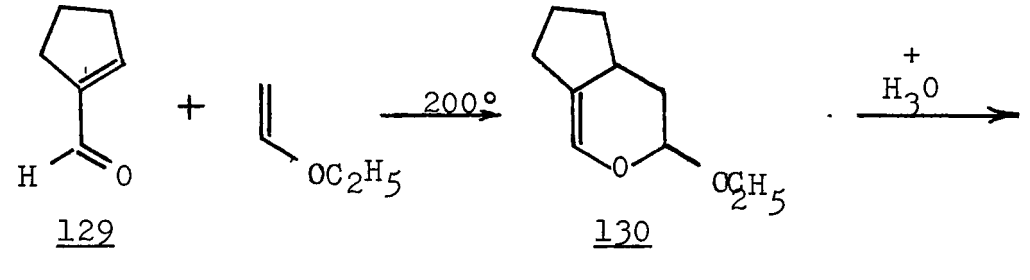
The preparation of 3,4-trimethylenepyridine (76) was carried out by two different methods. The first method involved the reaction of γ-(3-pyridyl)propyl chloride (75) with magnesium in THF followed by hydrolysis according to the procedure of Eisch.[48] From the mixture of products thus obtained,

76 was separated by distillation and preparative gas chromatography.

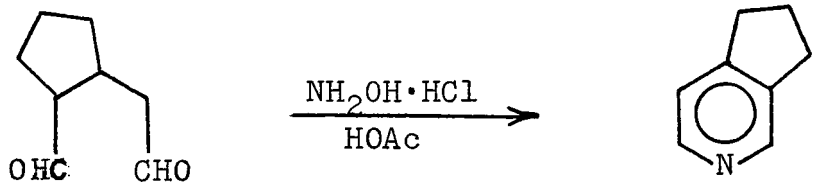


75 44 76 77

The second method utilized for the preparation of 76 is based on the reaction between 1,5-dialdehydes obtained from dihydropyranyl ethers and hydroxylamine to yield pyridines. Thus the reaction between 1-cyclopentenecarboxaldehyde[65] (129) and ethyl vinyl ether provided the dihydropyranyl ether 130 in 50% yield. The hydrolysis of 130 afforded the dialdehyde 131 in 95% yield, which without any further purification, was condensed with hydroxylamine to yield 2,3-trimethylene-pyridine (76) in 25% yield.

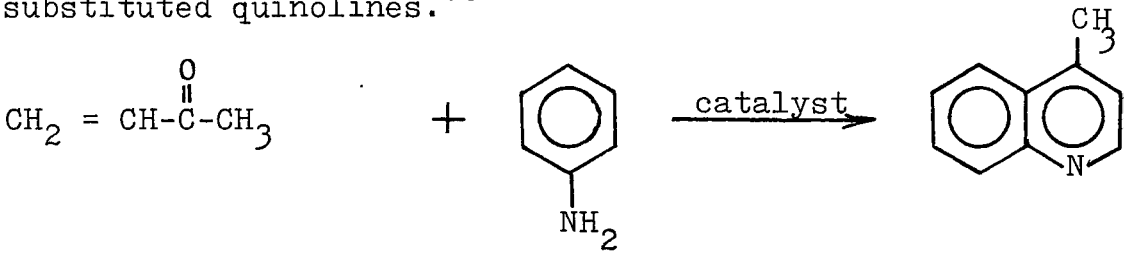


129 130

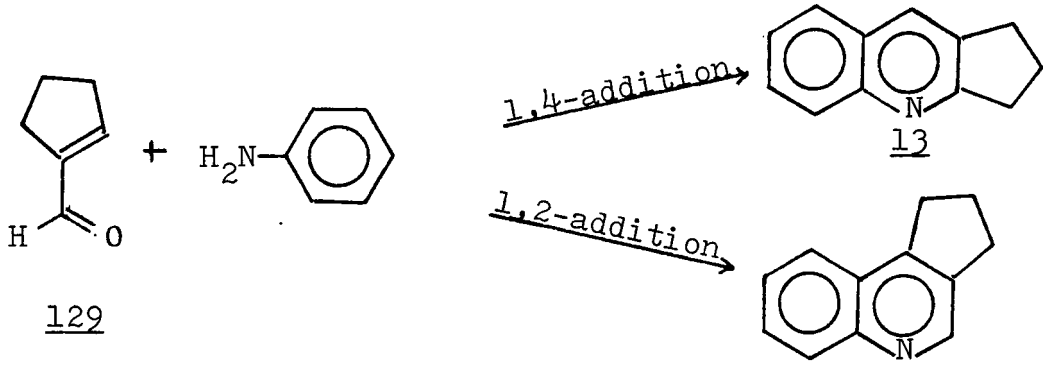


131 76

Due to the ready accessability of 1-cyclopentenecarboxaldehyde (129), we decided to explore its possible reaction with aniline. It is known that aniline reacts with α,β-unsaturated carbonyl compounds leading to the formation of substituted quinolines.[66]



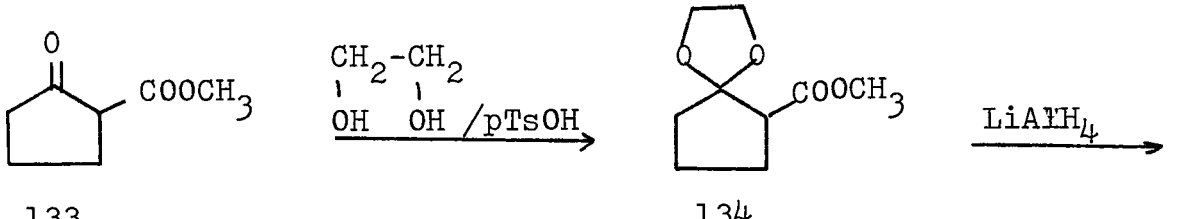
Due to the high reactivity of 129, it was speculated that reaction with aniline might lead to the formation of a mixture of 13 and 132.



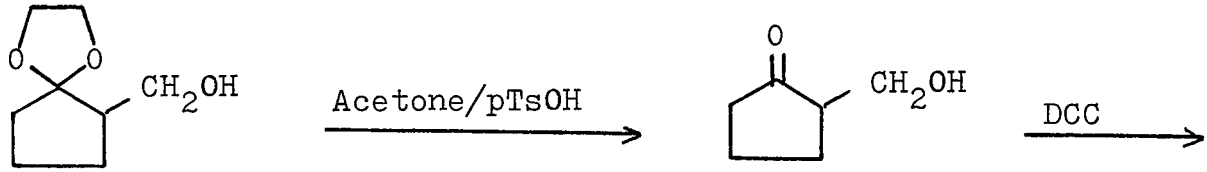
129 13 132

The reaction between 129 and aniline was found to be very exothermic. The analysis of the reaction mixture after twelve hours showed the formation of 13 as the only detectable product. The structure of 13 was confirmed by spectral data and comparison with an authentic sample.[67] Since the reaction between 129 and aniline failed to provide any 3,4-trimethylenequinoline (132), we decided to try a similar reaction between

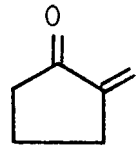
aniline and 2-methylenecyclopentanone (137).[68] The preparation of 137 was carried out as shown in the following scheme.



133 134

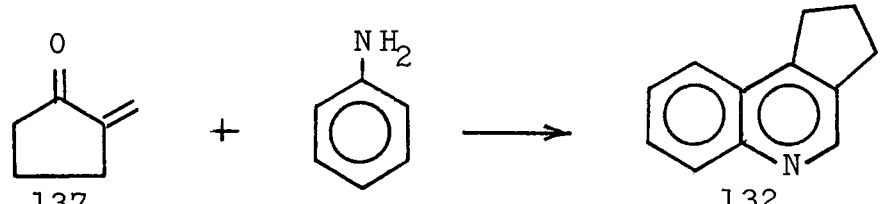


135 136



137

Treatment of aniline with 137 was expected to provide 132 via a Michael addition.

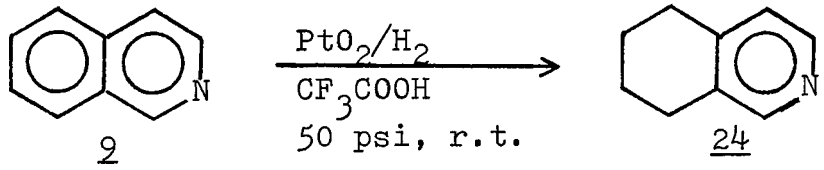


137 132

The reaction between aniline and 137 was found to be very slow at room temperature (no heat evolution). Analysis after twelve hours at 80°C showed the presence of only starting materials and no fused quinoline could be detected.

The presence of a catalyst such as copper chloride and longer reaction time might eventually lead to the success of this reaction.

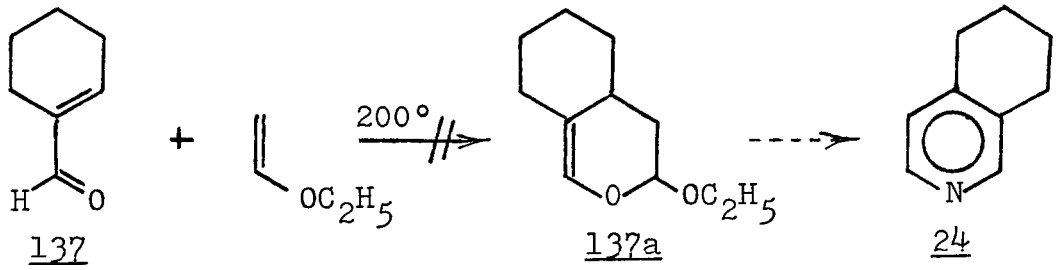
The preparation of 5,6,7,8-tetrahydroisoquinoline (24) was initially carried out by the hydrogenation of isoquinoline (9) over platinum oxide in trifluoroacetic acid according to the procedure of Eliel.[28] The isoquinoline was purified by



9 24

refluxing over Raney-nickel in ethanol to remove any sulfur compound which would otherwise poison the catalyst. Even after the required purification of isoquinoline, the hydrogenation of 9 under the above condition could not be repeated and it resulted only in the recovery of starting material.

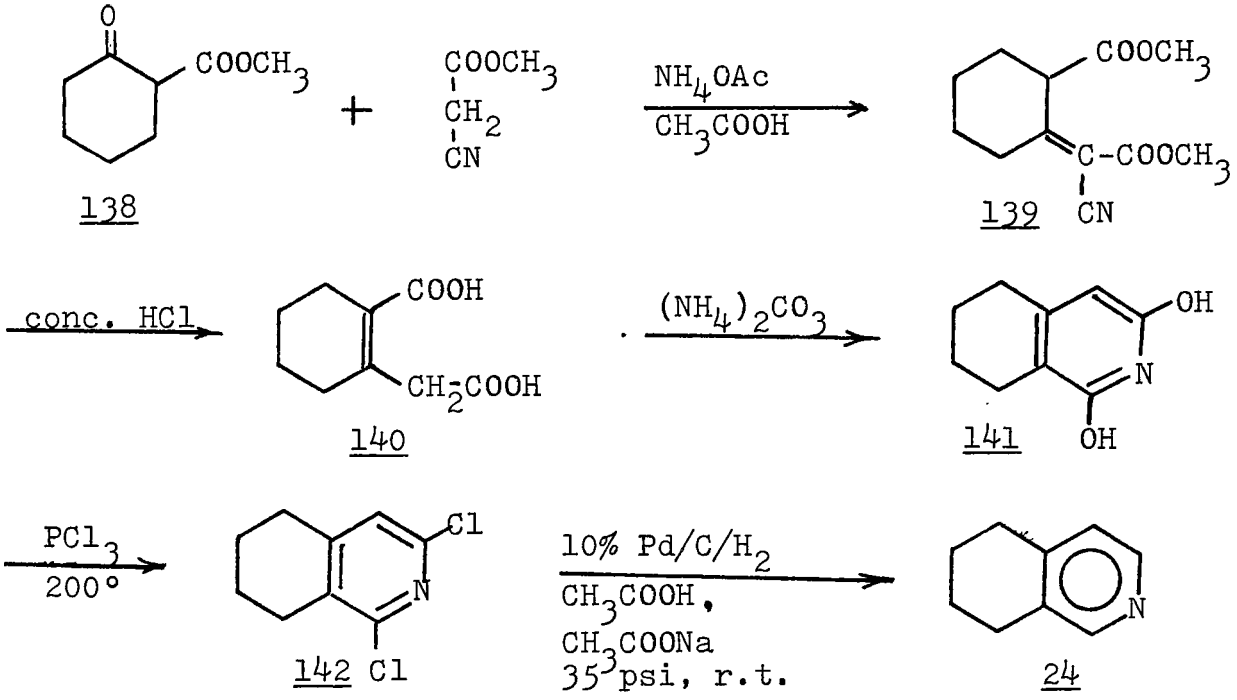
The preparation of 24 was also attempted by diene condensation. The reaction of 1-cyclohexene-1-carboxaldehyde (137)[69] with ethyl vinyl ether was expected to give the dihydropyranyl ether 137a. However this reaction resulted in the formation



137 137a 24

of a complex mixture in which 137a could not be detected.

The preparation of 24 was finally carried out by a multiple step synthetic scheme as shown below.[70]



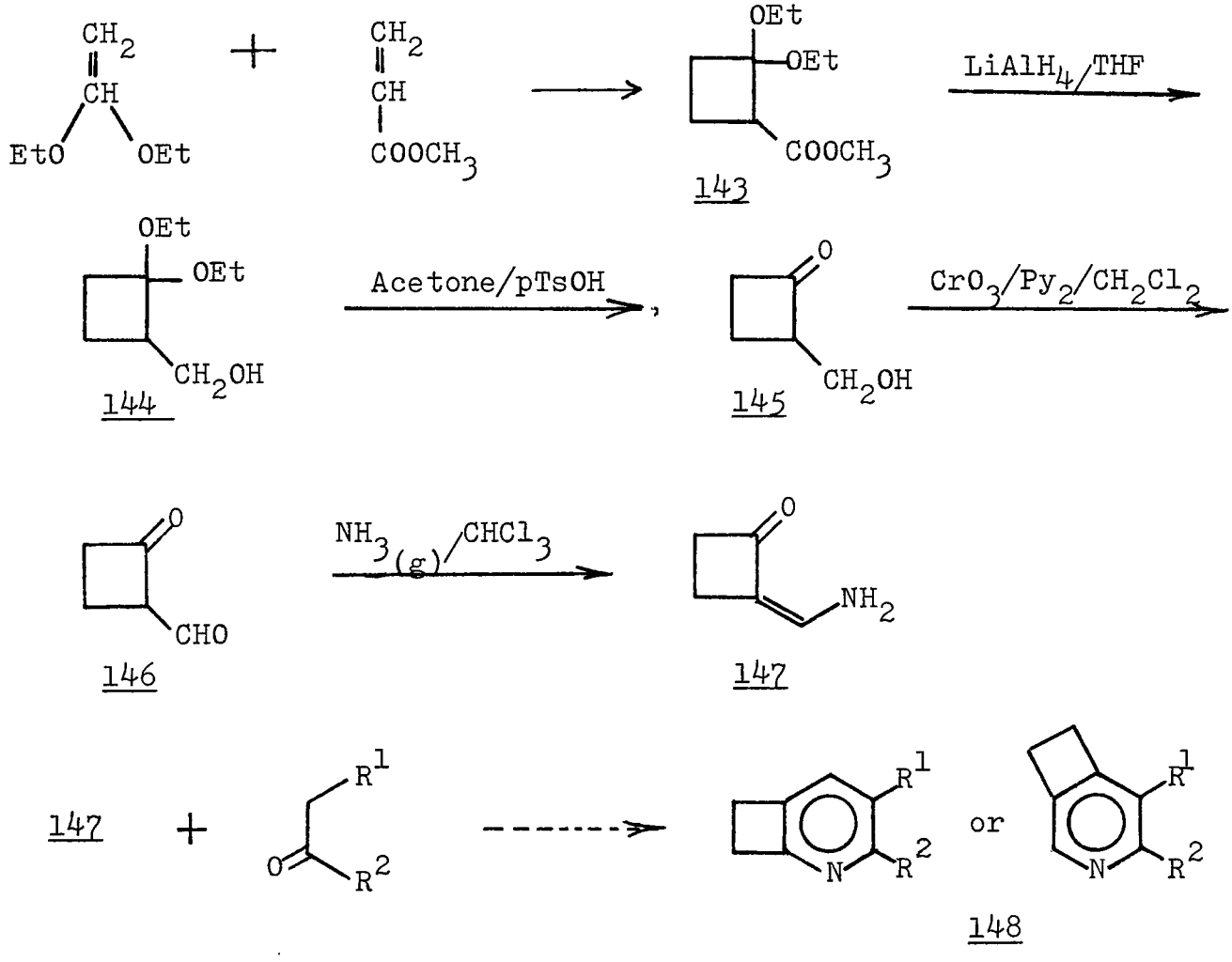
The reaction between commercially available ethyl-2-oxocyclohexane carboxylate (138) and cyanoacetic ester in the presence of ammonium acetate provided 139 in 55% yield. The hydrolysis of 139 with concentrated hydrochloric acid afforded 140 in 54% yield, which was converted to 141 in 87% yield by heating with ammonium carbonate at 230°C. The reaction of 141 with phosphorus trichloride at 200°C in a steel bomb gave 142 in 82% yield. The dehalogenation of 142 over palladium on charcoal in acetic acid and sodium acetate provided 24 in 93% yield.

Preparation of Cyclobutapyridines:

For the preparation of cyclobutapyridines three different synthetic approaches were considered. All of these approaches involve small ring cyclic precursors.

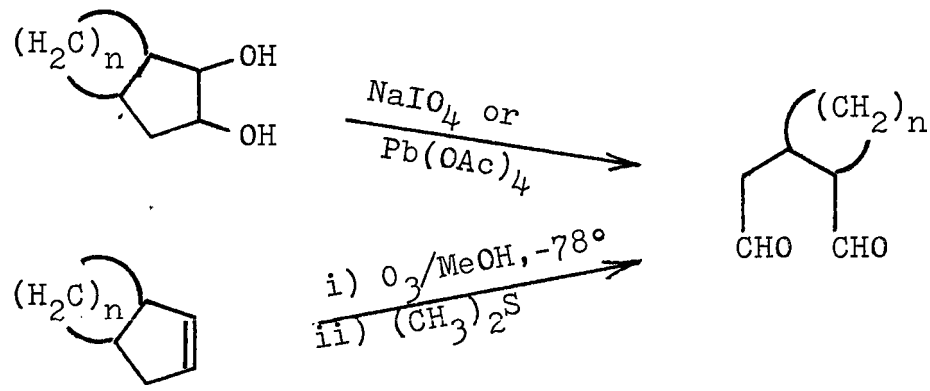
The first approach requires the preparation of 2-formylcyclobutanone (146), its reaction with ammonia to give the corresponding β-amino-α, β-unsaturated compound 147, followed by the reaction of 147 with a suitable carbonyl compound leading to the formation of annelated pyridines 148. The following scheme summarizes the approach. Scheme 12.

Scheme 12:



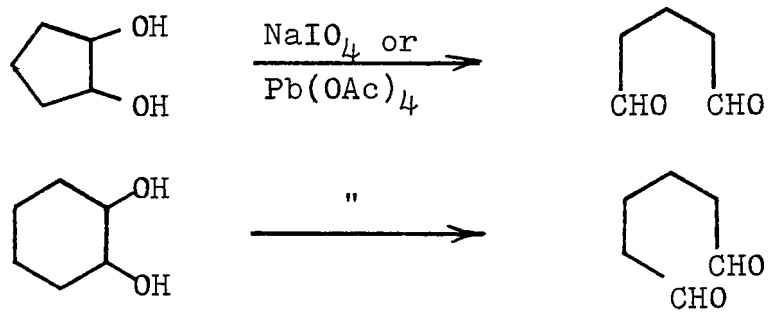
The reaction of 146 with ammonia leading to the formation of 147 is based on our earlier work in which 2-formyl cycloalkanones on reaction with ammonia lead to the formation of β-amino-α, β-unsaturated carbonyl compounds of the type 147. Compound 143 was prepared from ketene diethyl acetal[71] and methyl acrylate according to the procedure of Brannock.[72] The lithium aluminum hydride reduction of 143 provided 144 in 75% yield. The hydrolysis of 144 was carried out by refluxing with acetone/pTsOH to provide 145 in 98% yield. The Collins oxidation of 145 provided 146 in 59% yield. However, the reaction of 146 with ammonia gas in chloroform led to the formation of 147 in very low yield. Due to the shortage of 2-formyl cyclobutanone (146), this reaction could not be pursued further.

Since 1,5-dialdehydes serve as the precursors to pyridines, we directed our attention toward the generation of suitably substituted 1,5-dialdehydes. Two of the simplest routes for the generation of 1,5-dialdehydes would be the cleavage of cyclopentane-1,2-diol systems or the ozonolysis of suitably substituted cyclopentenes.



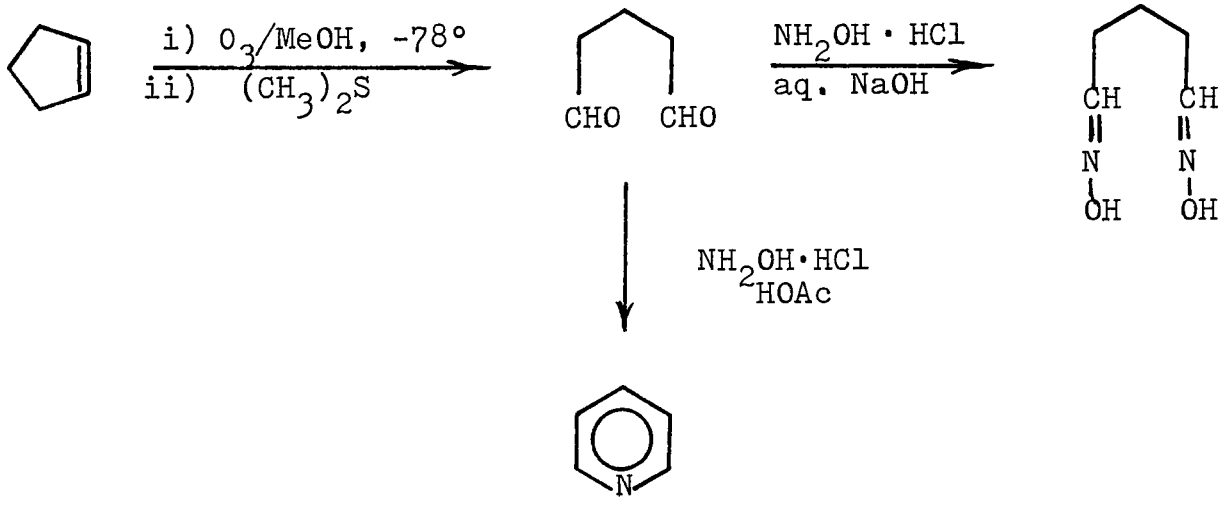
n = 1,2

Cyclopentane 1,2-diol was chosen as the model compound for cyclopentane 1,2-diol systems. The oxidation of cyclopentane 1,2-diol with lead tetraacetate or sodium periodate provided glutaraldehyde in less than 10% yield.



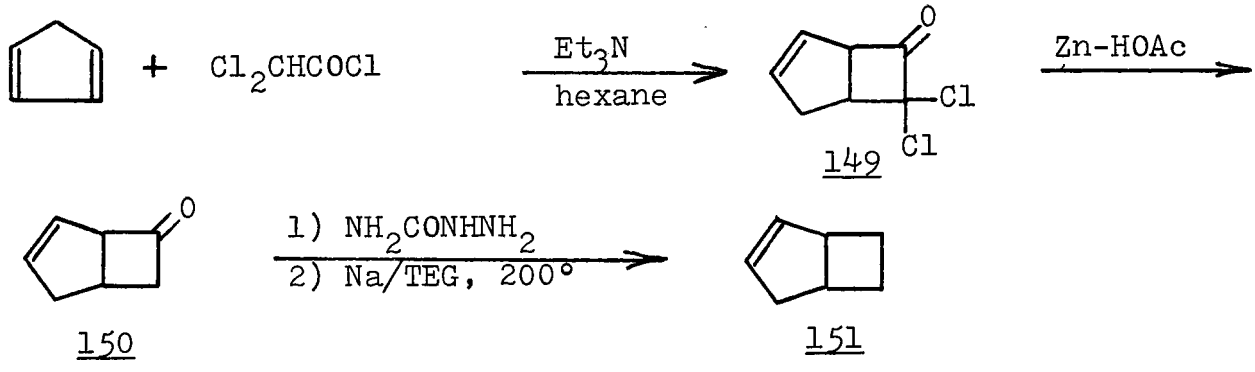
Under the similar conditions of oxidation, the oxidation of cyclohexane-1,2-diol provided adipaldehyde in greater than 60% yield. Since the oxidation of cyclopentane-1,2-diol to glutaraldehyde proceeded in such a low yield, this reaction was not pursued further.

Cyclopentene was chosen as the model compound for the substituted cyclopentene systems. The ozonolysis of cyclopentene led to the formation of glutaraldehyde which could be isolated as its dioxime in 26% yield.



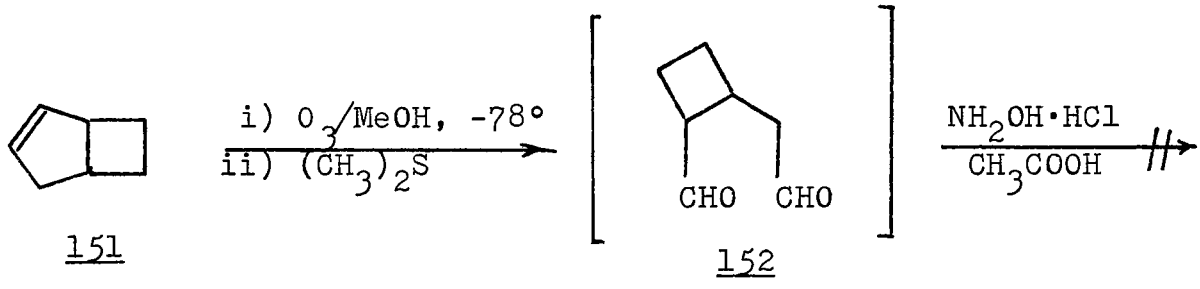
The glutaraldehyde formed from the ozonolysis of cyclopentene could also be converted into pyridine by the action of hydroxylamine in glacial acetic acid in about 20% yield.

A suitably substituted cyclopentene, which after ozonolysis could be condensed to cyclobuta[c]pyridine (105), is bicyclo[3,2,0]hept-2-ene (151). The preparation of 151 was carried out in three steps as shown in the following scheme.

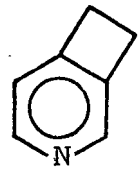


The reaction of freshly distilled cyclopentadiene with dichloroketene generated from dichloroacetyl chloride and triethylamine in hexane afforded 149 in 85% yield. The reduction of 149 with zinc in acetic acid provided 150 in 82% yield.[73] The bicyclic ketone 150 was then converted into its semicarbazone, which on reduction with sodium in triethylene glycol gave bicyclo[3,2,0]hept-2-ene (151) in 65% yield.

The ozonolysis of 151 was carried out in methanol at -78°C and after reductive workup with dimethyl sulfide, the dialdehyde formed was, without isolation, treated with hydroxylamine hydrochloride in acetic acid.



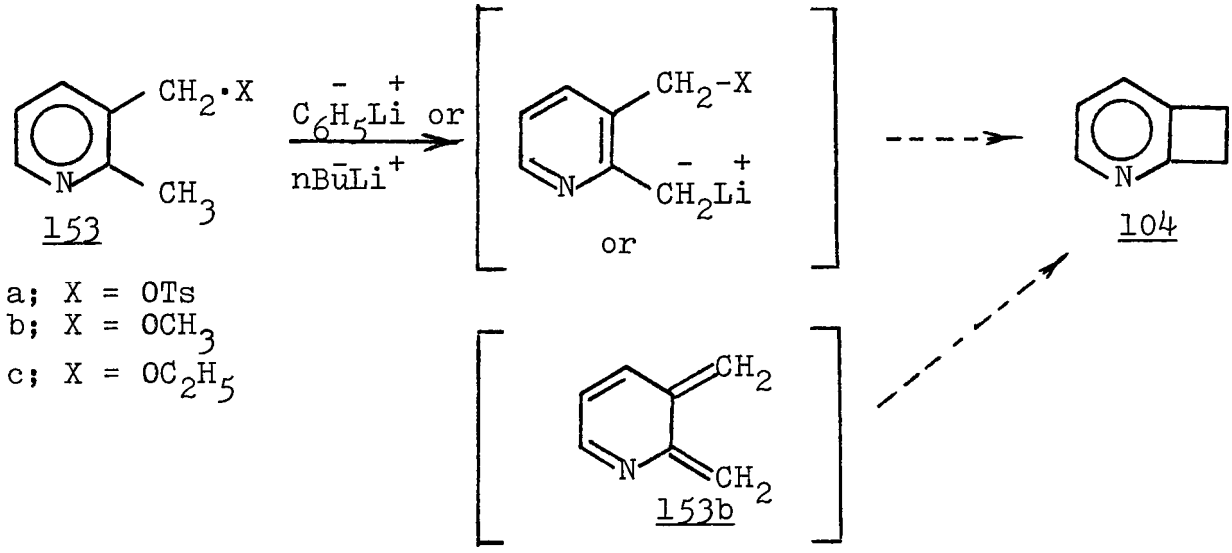
151 152



105

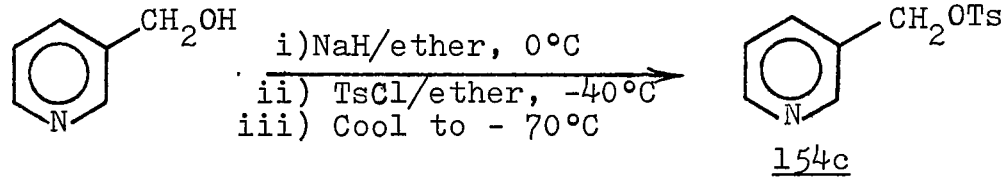
Analysis of the reaction mixture, after usual workup, was done by thin layer chromatography and VPC followed by preparative thin layer chromatography. None of the fractions examined showed the presence of aromatic protons by NMR. However when the reductive workup after ozonolysis was carried out with zinc in acetic acid and the dialdehyde thus obtained treated with hydroxylamine, the NMR of the crude reaction product indicated the presence of a 3,4-disubstituted pyridine. Analysis by TLC followed by preparative TLC failed to provide 105. This reaction is still under consideration.

The third approach considered involved the preparation of compounds of the type 153 followed by their reaction with a strong base leading to the formation of cyclobuta[b]-pyridine (104). The preparation of the tosylate (154) of 3-hydroxymethyl pyridine served as the model reaction for the preparation of 153a.

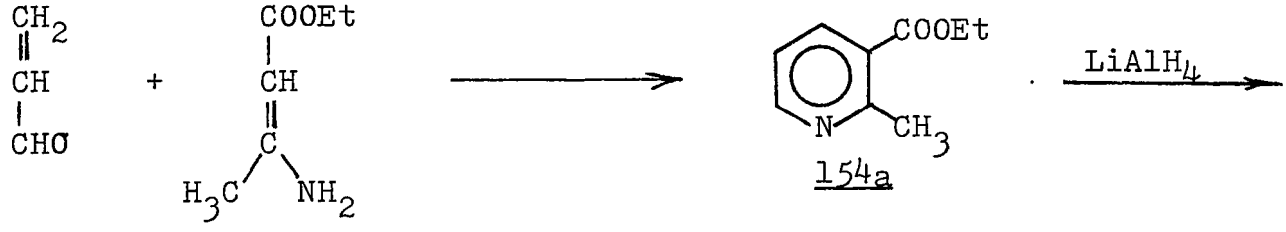


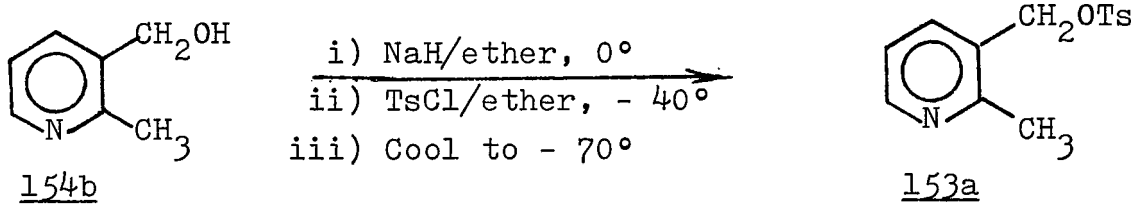
a; X = OTs
b; X = OCH_3
c; X = OC_2H_5

The tosylate 154c was obtained in 20% yield as a white crystalline solid.

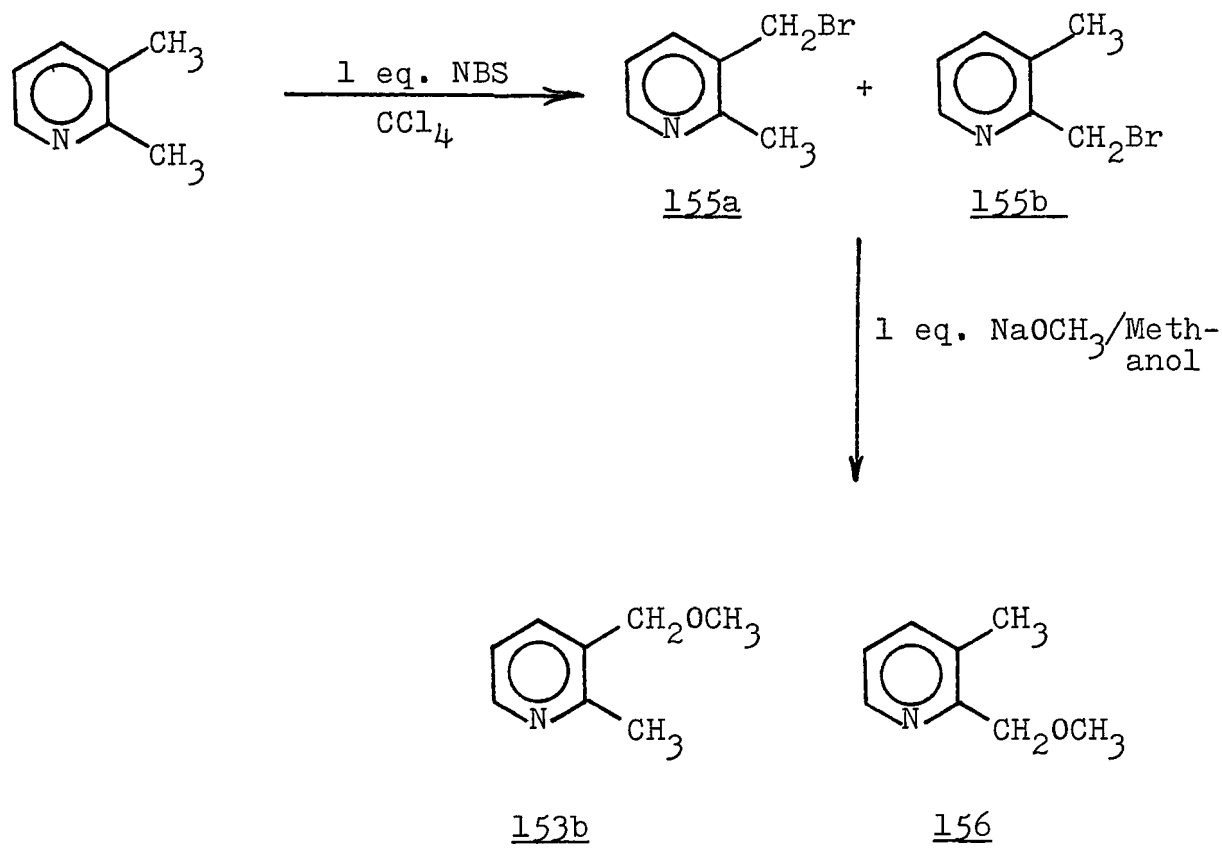


On the other hand, the preparation of the tosylate 153a could only be carried out in less than 5% yield and the reaction could not be repeated consistently.

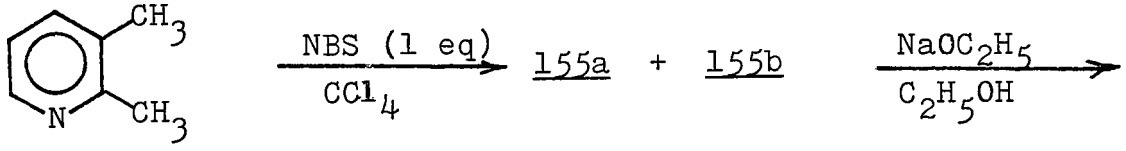


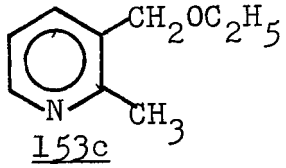


The methyl ether 153b was prepared according to the following scheme.

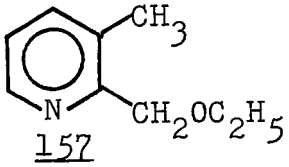


The reaction of 2,3-lutidine with N-bromosuccenimide in carbontetrachloride provided the mixture of 155a and 155b, which without isolation was treated with one equivalent of sodium methoxide in methanol to provide the mixture of ethers 153b and 156 in a 2:1 ratio. The separation of 153 and 156 was carried out by preparative gas chromatography. Similarly were prepared the corresponding ethyl ethers 153c and 157.



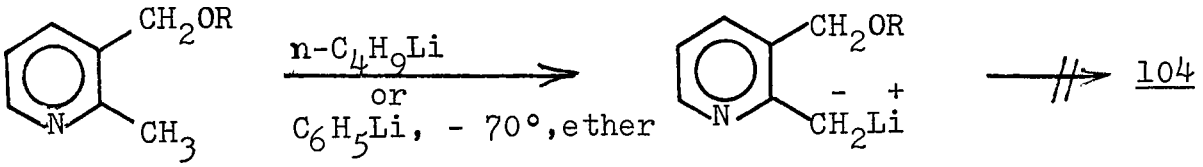


153c



157

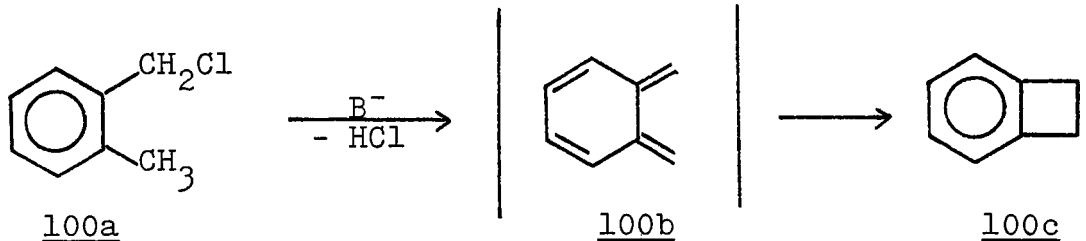
The reaction of 153b and 153c with n-butyl lithium or phenyl lithium after hydrolysis resulted only in the recovery of starting material. Presumably the reaction leads to the formation of carbanion 158 from which no elimination of ethoxide or methoxide occurs.



153b, R = OCH_3
153c, R = OC_2H_5

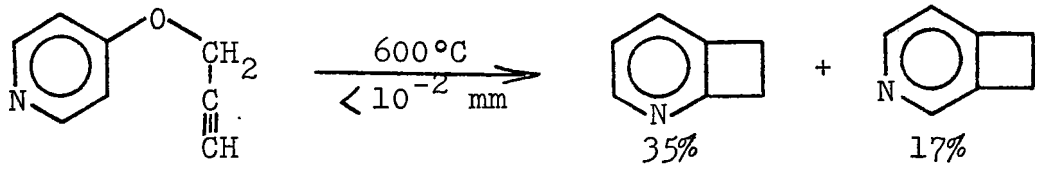
158a, R = OCH_3
158b, R = OC_2H_5

The preparation of benzocyclobutene (100c) by a similar elimination route has recently been reported by Boekelheide.[74] This elimination, however, is believed to involve the intermediate 100b.



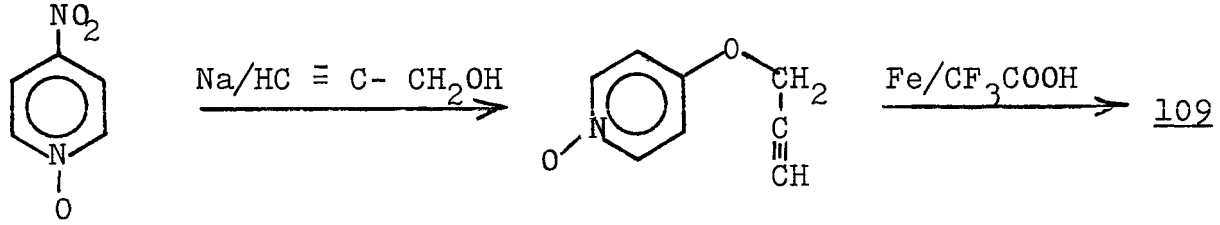
100a 100b 100c

The preparation of cyclobutapyridines 104 and 105 was eventually carried out according to a procedure recently reported by Trahanovsky.[58] The pyrolysis of propargyl-4-pyridyl ether (109) provided a mixture of 104 and 105 in 50% yield.[58]



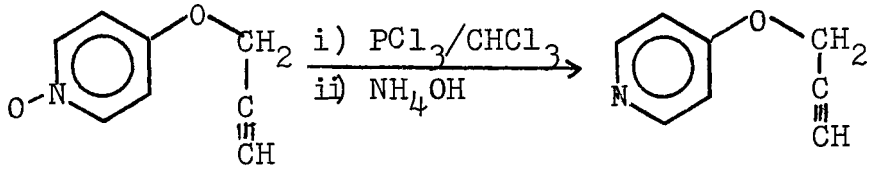
109 35% 104 17% 105

The pyrolysis of 109 was carried out at 600°-630°C and 10^{-2}-10^{-4} mm pressure. The pyrolysate obtained was first purified by a Kugelrohr distillation and the mixture of cyclobutapyridines was separated by preparative gas chromatography. The preparation of 109 was carried out from 4-nitropyridine-N-oxide according to the general procedure of Lietz[75] and Combes.[76]



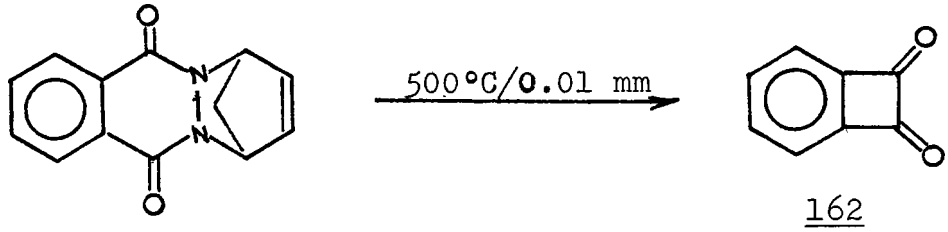
159 160 109

The reaction of commercially avaiable 4-nitropyridine-N-oxide (159) with sodium in propargyl alcohol afforded N-oxide 160 in greater than 90% yield. The reduction of 160 was initially carried out with iron in acetic acid according to the procedure of Combes.[76] This reaction provided 109 in less than 15% yield, since during the workup an emulsion was formed from which the product could not be separated. The reduction of N-oxide 160 with phosphorus trichloride according to the procedure of Brown[77] gave propargyl ether 109 in 74% yield.



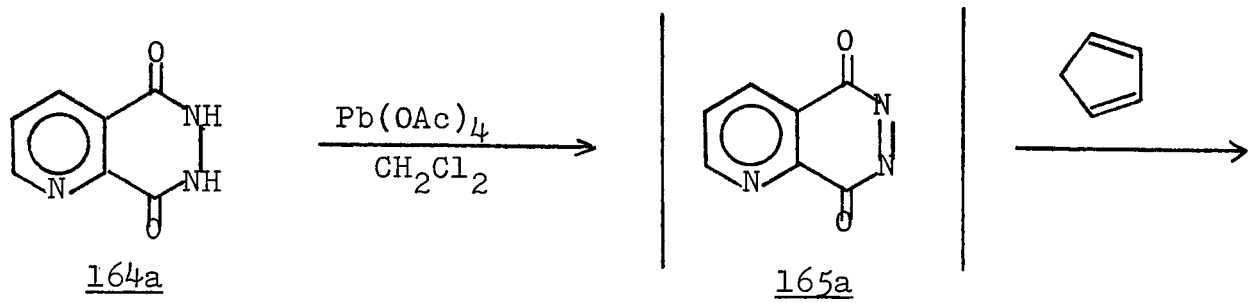
160 109

In continuation of our efforts toward the preparation of small ring fused pyridines, the preparation of pyridinecyclobutenediones 167a and 167b was attempted from a reaction similar to the one reported for the preparation of benzocyclobutenedione 162. The preparation of 162 was carried out by the pyrolysis of the cyclopentadiene adduct 161.[78]

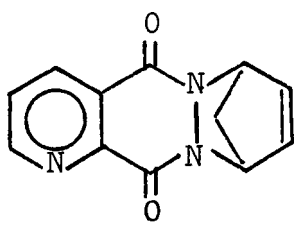


161 162 88%

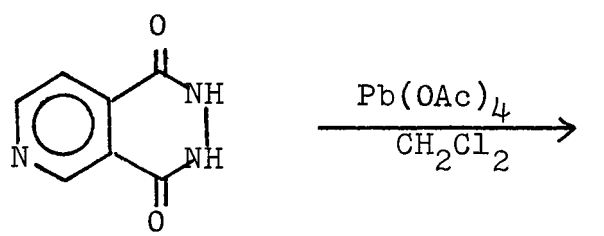
The cyclopentadiene adducts 166a and 166b were synthesized according to the procedure of Jones.[79] The oxidation of



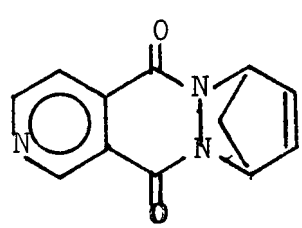
164a



166a



164b

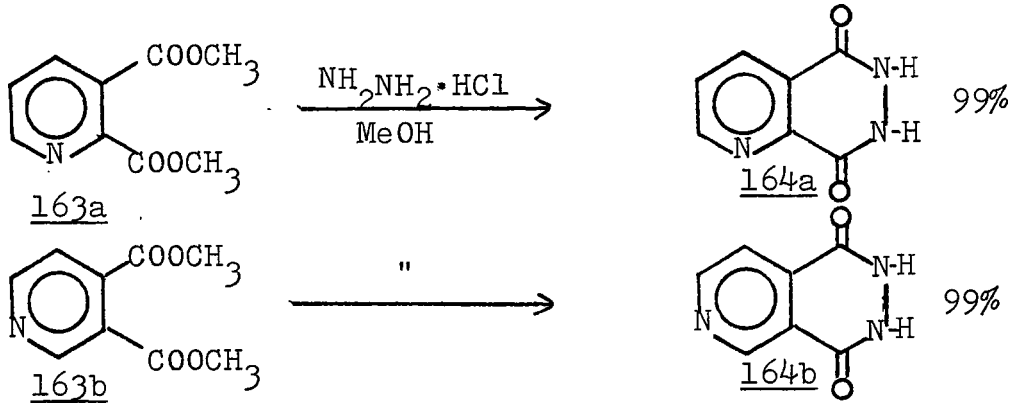


166b

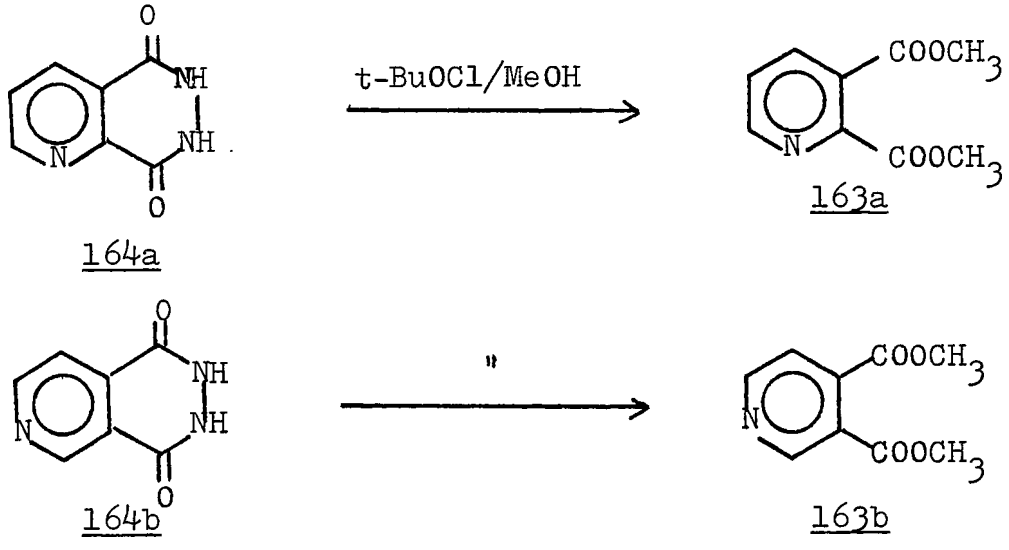
164a and 164b with lead tetraacetate in methylenechloride followed by reaction with cyclopentadiene gave the adducts 166a and 166b in 43% and 48% yields respectively.

The compounds 164a and 164b could be prepared from the reaction of diester 163a and 163b with hydrazinehydrate in

methanol in 94% and 99% yields respectively. When the oxidation of 164a and 164b was carried out with t-butylhypochlorite in methanol in the absence of cyclopentadiene or any other trapping reagent, the corresponding diesters 163a and 163b were isolated as the only products in about 50% yield.



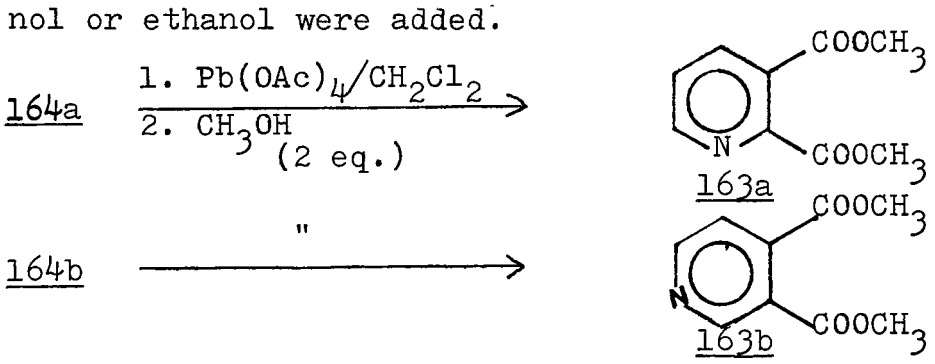
The corresponding diethyl esters were obtained when the oxidation was carried out in ethanol as the solvent.



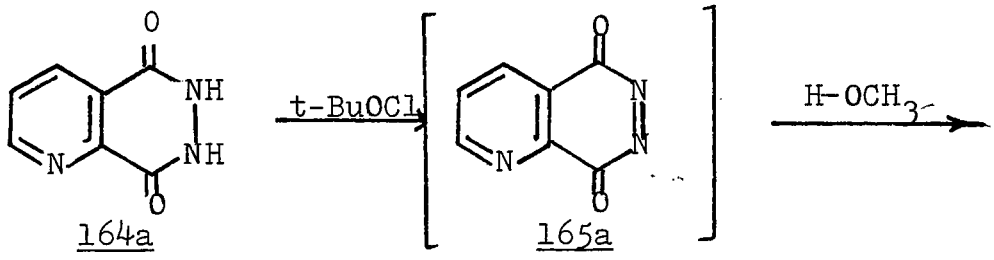
In a control experiment, the reaction of 164a and 164b with methanol·HCl in the absence of the oxidizing agent resulted

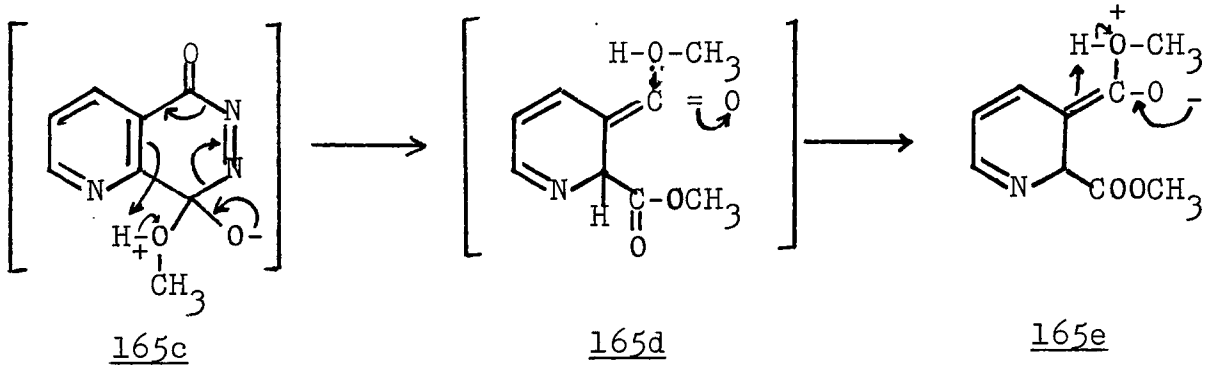
in the recovery of starting materials only.

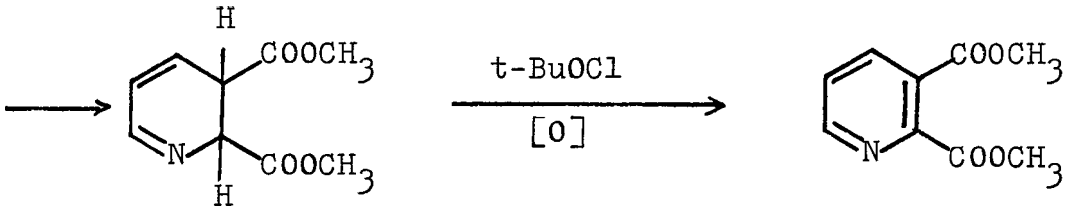
The same diesters were obtained when the oxidation of 164a or 164b was first carried out with lead tetraacetate in methylene chloride at -70°C and then two equivalents of methanol or ethanol were added.



The formation of diesters 163 from the oxidation of 164 with t-butyl hypochlorite or lead tetraacetate in the presence of methanol or ethanol can be explained by the following mechanism. Scheme 13.

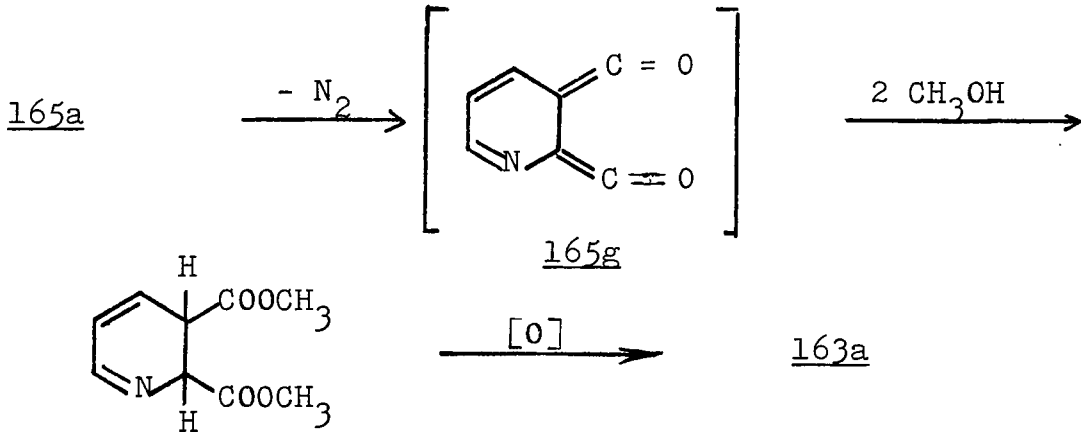






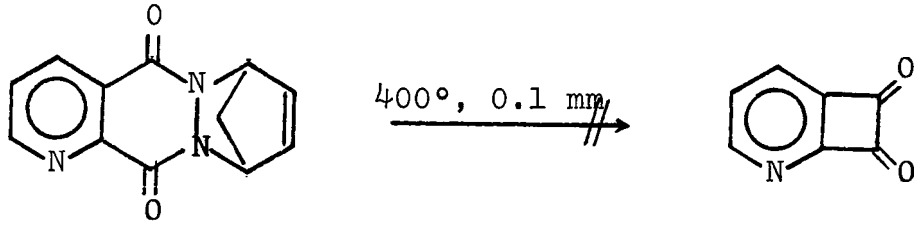
165f 163a

If the intermediate 165a loses nitrogen before the attack of methanol, a diketene intermediate 165g may be involved.

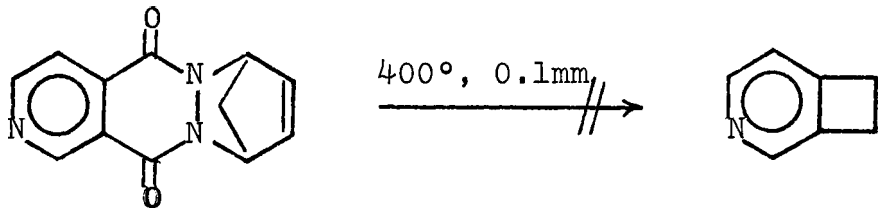


Our inability to isolate an intermediate such as 165f may be attributed to its rapid oxidation with t-butylhypochlorite or lead tetraacetate to 163a.

The pyrolysis of cyclopentadiene adducts 166a and 166b was carried out at 400°-500°C at 0.1 mm, which however resulted in the recovery of starting material only.



166a 167a



166b 167b

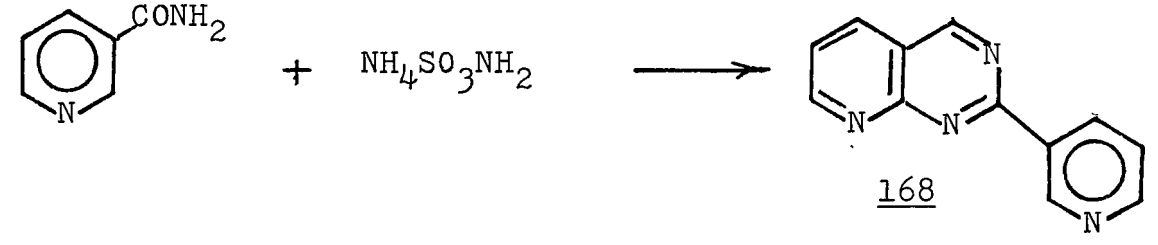
Synthesis of 2,3-annelated 1,8-napthyridines:

The Friedlander condensation of 2-aminonicotinaldehyde (37) with cyclic ketones provided 2,3-fused 1,8-napthyridines 4 a-c in good yield.

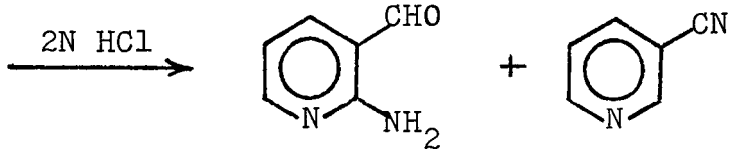
37 n = 2,3,4

4a; n = 2
4b; n = 3
4c; n = 4

The preparation of 2-aminonicotinaldehyde (37) was carried out according to the procedure of Caluwe.[32] The condensation between nicotinamide and ammonium sulfamate resulted in the formation of 2-(3'-pyridyl)pyrido[2,3-d]-pyrimidine (168), which on hydrolysis provided 37 in 40% yield.

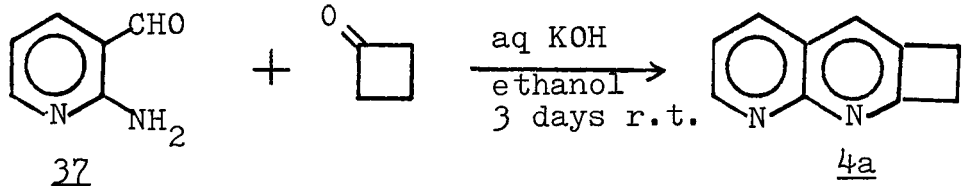


168



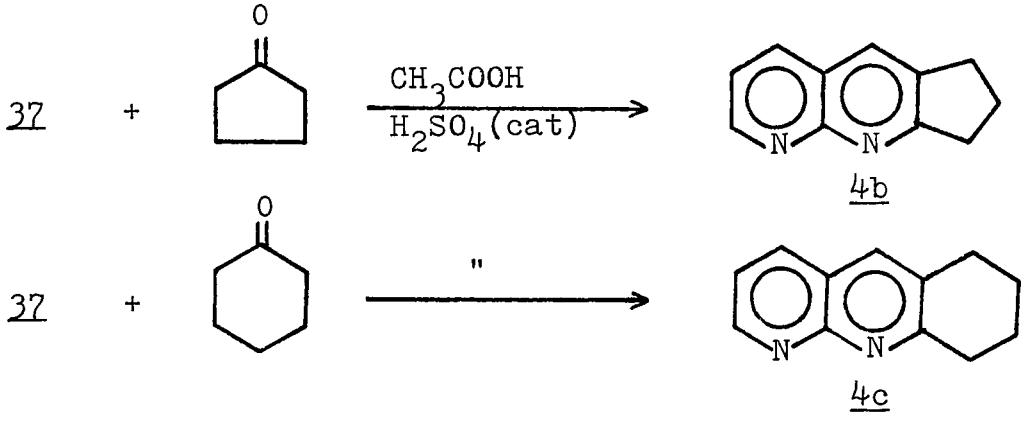
37

Cyclobuta[b]-1,8-napthyridine (4a) could be readily prepared from the reaction between 2-aminonicotinaldehyde (37) and cyclobutanone in presence of aqueous potassium hydroxide and ethanol in 39% yield.



37 4a

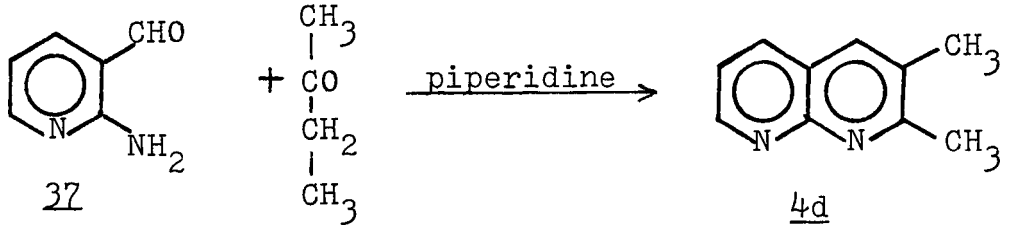
Friedlander reaction of 37 with cyclopentanone and cyclohexanone under acidic conditions led to the formation of 4b and 4c in 90% and 70% yields respectively.



4b

4c

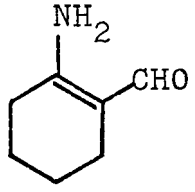
The condensation between 2-aminonicotinaldehyde and 2-butanone in the presence of piperidine as catalyst led to the formation of 2,3-dimethyl-1,8-napthyridine (4d). The crude product thus obtained was chromatographed on silica gel eluting with ether to yield 4d as a yellow solid in 34% yield.



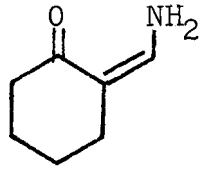
37 4d

Preparation of Bis-annelated Pyridines:

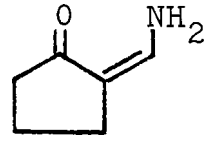
Hoping to extend the generality of the reaction of β-amino-α, B-unsaturated carbonyl compounds with cyclic ketones to the preparation of bis-annelated pyridines, we decided to prepare compounds 168, 40a, 40b and 147.



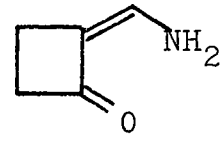
168



40a

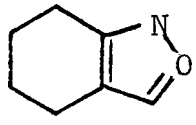


40b

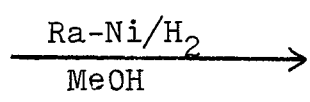


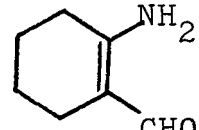
147

In the compound 168 it may be seen that ring fusion would force a cis-configuration on the reacting β-amino-α, β-unsaturated carbonyl moeity which might be more favorable to cyclo-condensation reactions as compared to β-aminoacrolein. One possible route to the preparation of 168 and 40a can be visualized from the hydrogenolysis of isoxazoles 167 and 169.

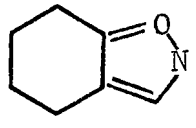


167

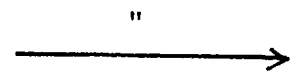


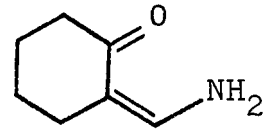


168



169

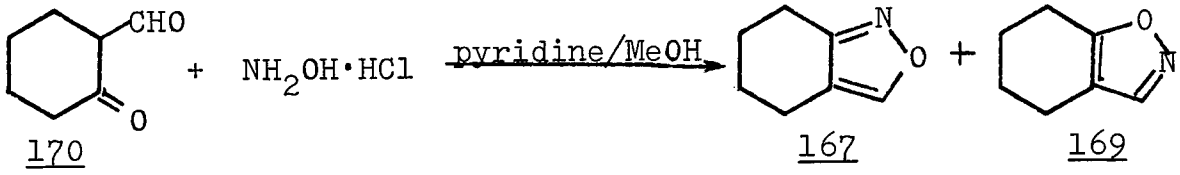




40a

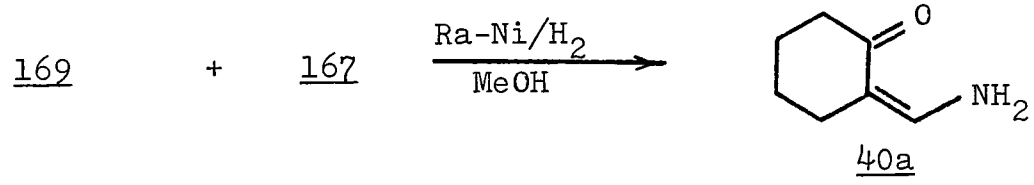
The reaction of 2-formylcyclohexanone (170) with hydroxylamine under the basic conditions according to the procedure

of Valentin[80] is reported to give the mixture of isoxazoles 167 and 169 in the ratio of 4:1. The aromatic proton in 167



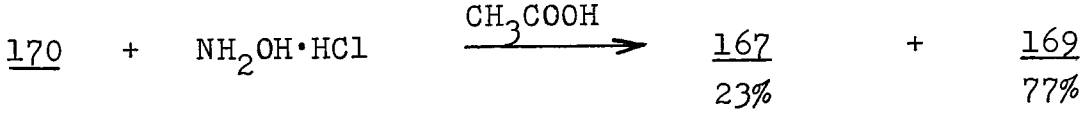
170 167 169

is found to resonate at δ 8.05 ppm and in 169 at δ 7.92 ppm.[82] When the above reaction was carried out, examination of the NMR spectrum of the mixture of isoxazoles 167 and 169 obtained revealed that the isoxazole 169 was formed predominately rather than 167 as reported by Valentin. Also the hydrogenolysis of the mixture of isoxazoles 167 and 169 over Raney-nickel provided 2-aminomethylenecyclohexanone (40a) as the only isolated product and no hydrogenated material from the minor isomer 167 could be isolated.



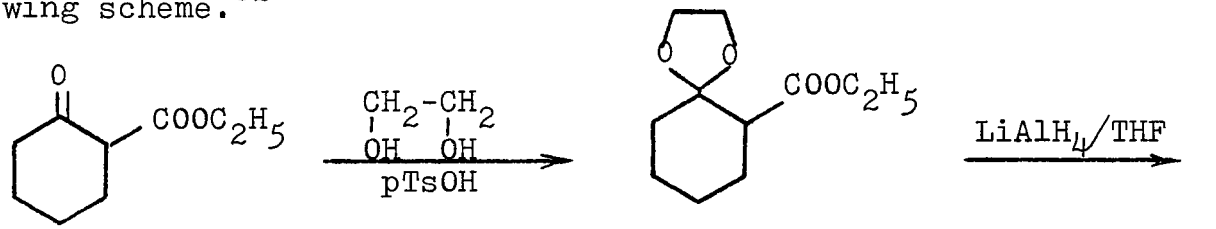
40a

The reaction of 170 with hydroxylamine hydrochloride in acetic acid according to the procedure of Johnson[81] gave the mixture of isoxazoles 167 and 169 in the ratio of 1:3.25 as shown by NMR.

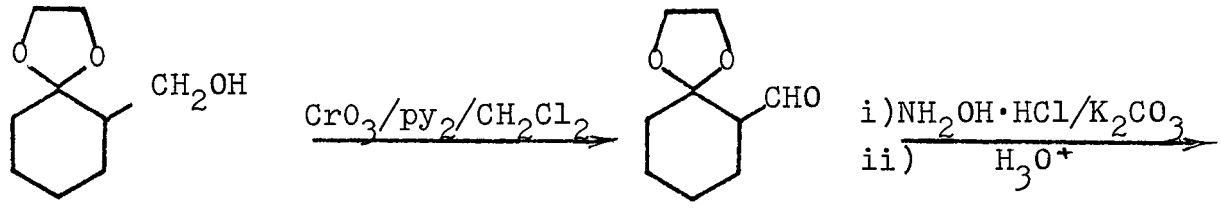


The hydrogenolysis of mixture of isoxazoles obtained from the above reaction also provided 40a as the only isolated

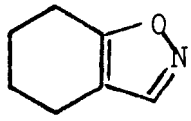
product and again no hydrogenated material from 167 was obtained. In order to confirm the structure of isoxazole 169, an unambiguous synthesis was carried out as shown in the following scheme.[82]



138



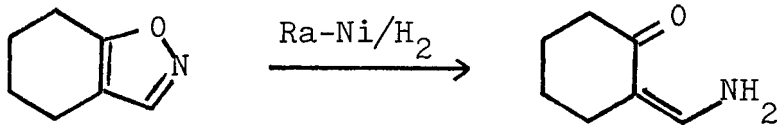
172 173



169a

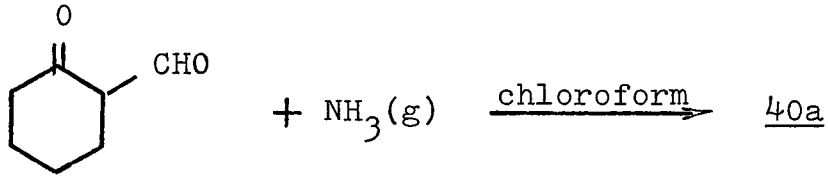
The reaction of commercially available ethyl-2-oxocyclohexane carboxylate (138) with ethylene glycol and a catalytic amount of toluenesulfonic acid afforded ketal 171 in 64% yield. The lithium aluminum hydride reduction of 171 gave 172 in 88% yield. The Collins oxidation of 172 provided 173 in 78% yield. The reaction of 173 first with hydroxylamine hydrochloride and potassium carbonate followed by treatment with 2N hydrochloric acid afforded 4,5,6,7-tetrahydrobenzisoxazole 169a in 67% yield. The chemical shift of the aromatic proton in 169a obtained from

the above synthetic scheme was found to be identical with the chemical shift of the aromatic proton in the major isomer obtained from the procedure of Valentin and Johnson. Also hydrogenolysis of 169a gave 40a, which was found to be identical to the reduction product obtained from the mixture of isoxazoles 167 and 169.



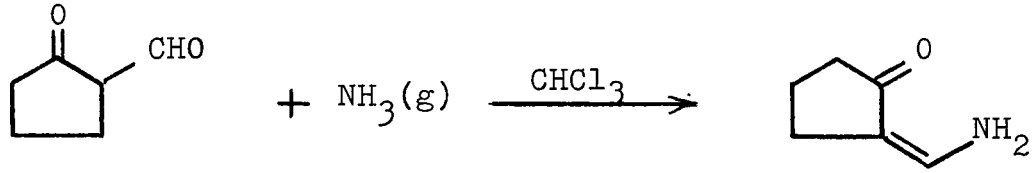
169a 40a

The structure of 40a was also confirmed by its independent synthesis from the reaction of 2-formylcyclohexanone and ammonia gas in chloroform.[35]



170

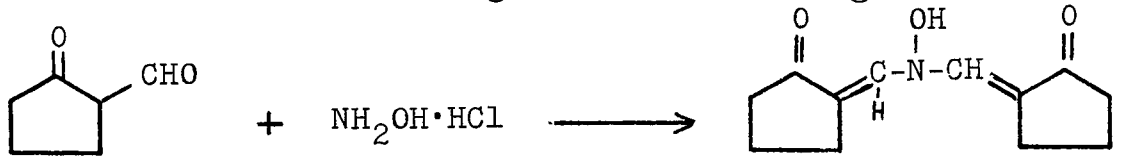
Similarly 2-aminomethylenecyclopentanone (40b) could be prepared by the action of ammonia gas on 2-formylcyclopentanone (174). The preparation of 174 was carried out according to



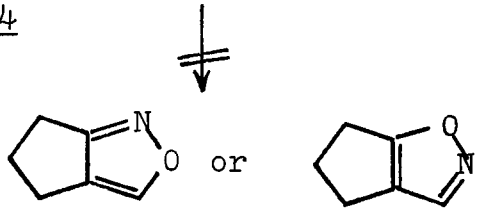
174 40b

the modified procedure of Johnson.[81] The compound 40b could not be obtained from the hydrogenolysis of the corresponding

isoxazole 176, since the reaction of 2-formylcyclopentanone (174) with hydroxylamine leads to the formation of the dimer 175 and no trimethylene isoxazole 176 is obtained. The failure to form 176 may be attributed to the ring strain introduced in the molecule on closing the isoxazole ring.[81]

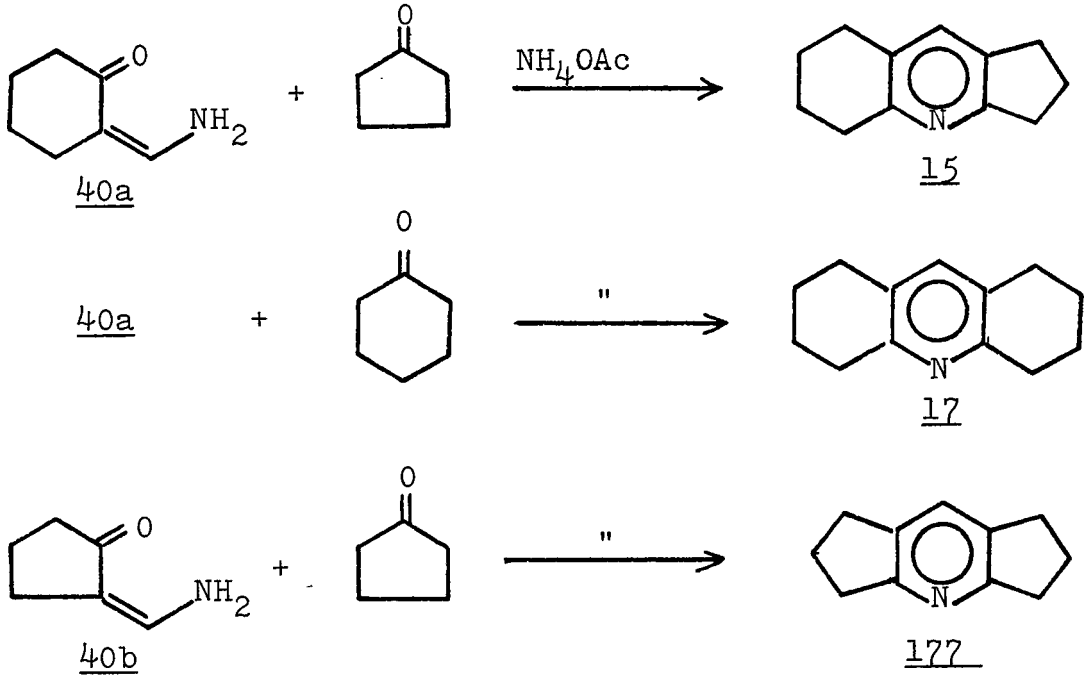


174 175

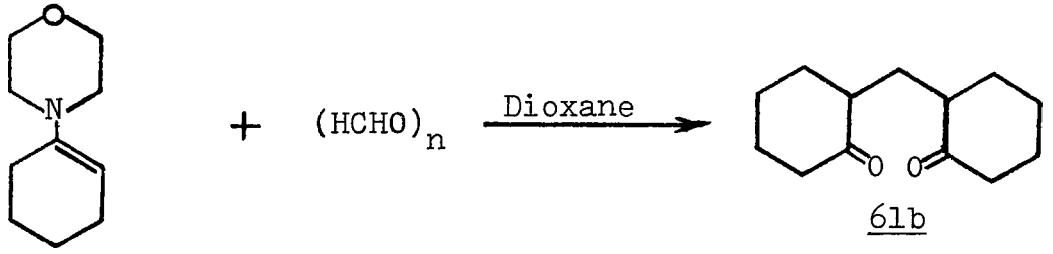


176

The reaction of β-amino-α, β-unsaturated ketones 40a and 40b with cyclic ketones was expected to give [2,3:4,5]-bisannelated pyridines. The major product observed upon the condensation of 40a and 40b were the rearranged [2,3:5,6]-bisannelated pyridines 15, 17 and 177.

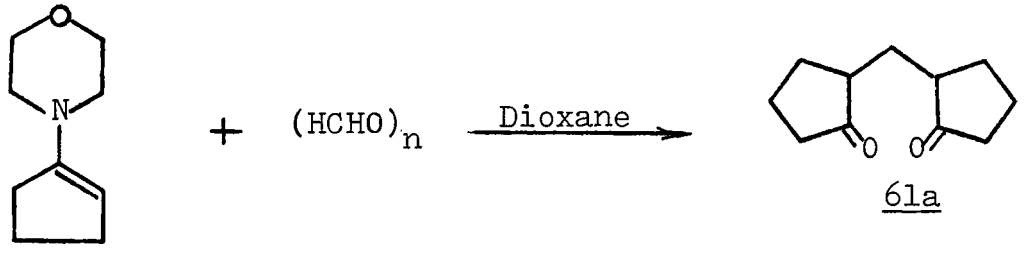


The identity of these materials was confirmed by their characteristic aromatic proton resonance at 7.02-7.30 ppm as well as the independent synthesis of 17 and 177. This independent synthesis was carried out according to the method of Colonge.[43] The condensation of the morpholino enamine of cyclohexanone with paraformaldehyde in dioxane gave dioxo-2,2'-di(cyclohexyl)methane[44] (61b) in 16% yield.



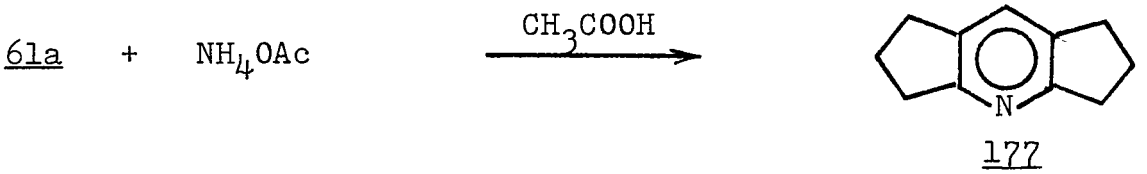
61b

A similar reaction with the enamine of cyclopentanone afforded 61a in 14% yield.[44]

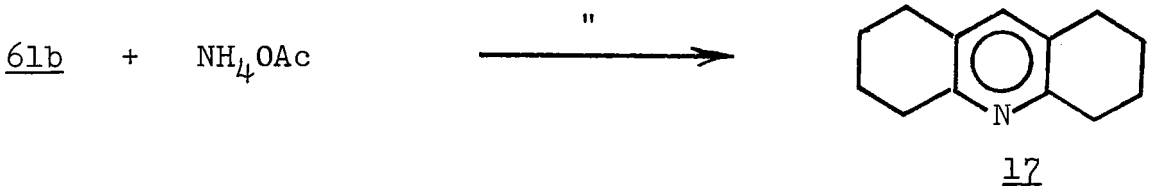


61a

The treatment of diketones 61a and 61b with ammonium acetate in acetic acid provided bisannelated pyridines 177 and 17 in 83% and 97% yields respectively.[43]



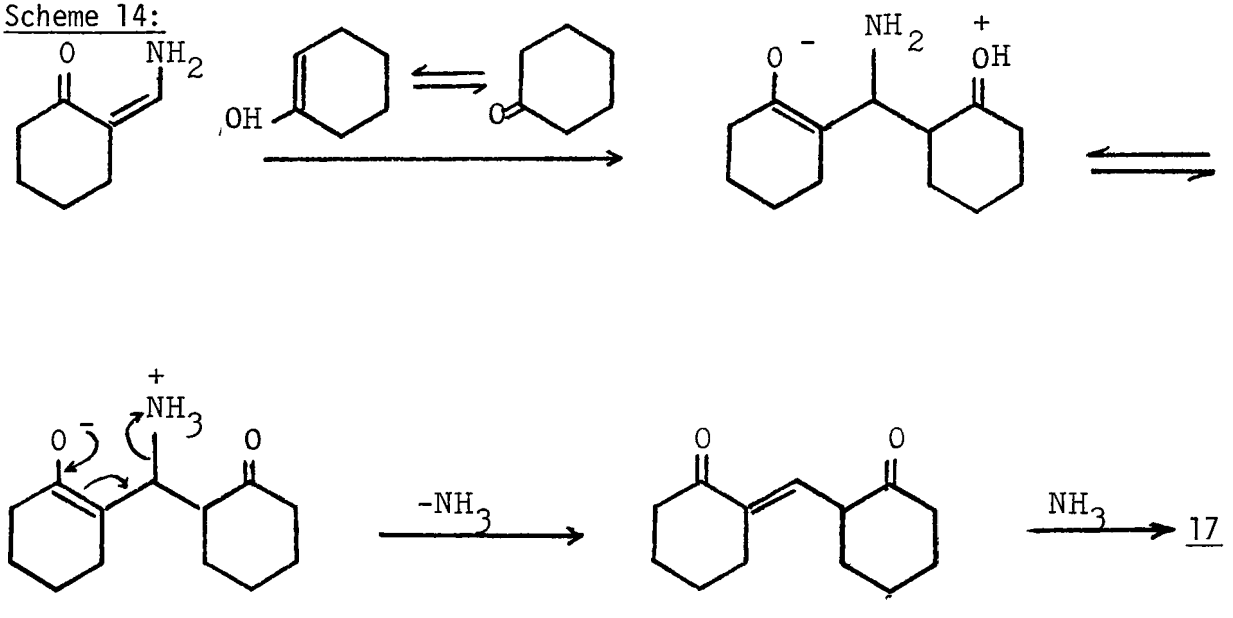
177



17

The reaction of β-amino-α, β-unsaturated ketones 40a and 40b with cyclic ketones leading to the formation of rearranged pyridines is similar to the reaction observed in the case of acyclic β-amino-α, β-unsaturated ketones. Thus this rearrangement appears to be general for the condensation of β-amino-α, β-unsaturated ketones with cyclic ketones. A mechanism similar to the one proposed for acyclic β-amino-α, β-unsaturated ketones would also account for the formation of [2,3:5,6]-bis-annelated pyridines as shown in the scheme 14.

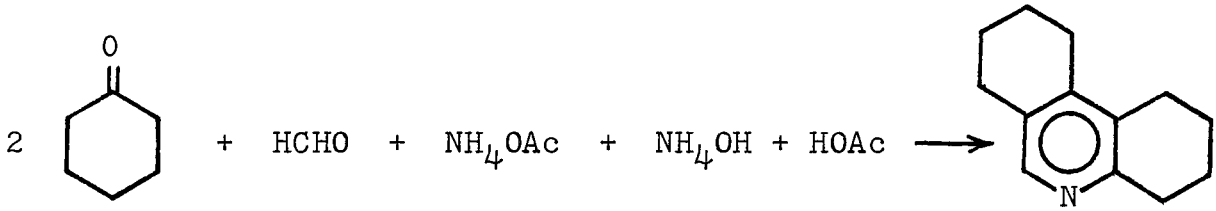
Scheme 14:



In the reaction between 40a and cyclohexanone in the presence of ammonium acetate as catalyst, none of the intermediates proposed in the above mechanism (scheme 14) could be isolated. Furthermore, when the reaction was carried out in acetic acid as a solvent and catalyst, VPC analysis after workup indicated

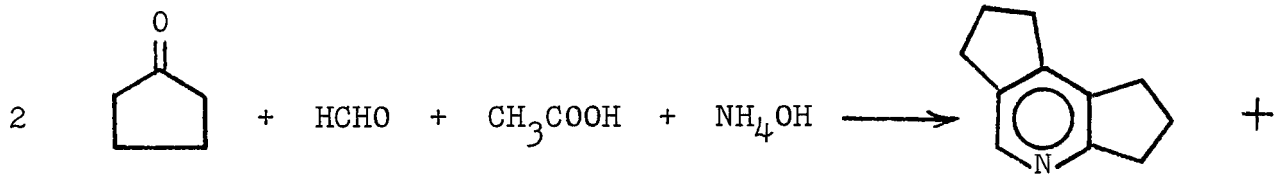
that no annelated pyridine was formed. This analysis did show the presence of a major peak with much shorter retention time than that of 17 and it was collected by preparative VPC. The analysis by NMR showed the presence of two downfield singlets at δ 8.7 ppm and 8.2 ppm each integrating to one proton and two multiplets at δ 2.87 ppm and 1.88 ppm each integrating to four protons. Analysis by IR showed the presence of a carbonyl group at 1730 cm^{-1} and a weak absorption for -OH. This same material was also obtained along with 17, when the reaction between 40a and cyclohexanone was carried out in the presence of triethylamine and piperidinium acetate as catalyst. Possibly this substance is the intermediate in this reaction. But on the basis of the spectral data alone, no definitive structure could be assigned to this material.

The synthesis of [2,3:5,6]-bis-annelated pyridines was accomplished by a condensation reaction first reported by Chichibabin.[45] The reaction of two equivalents of cyclohexanone with formaldehyde in the presence of ammonium acetate provided 1,2,3,4,5,6,7,8-octahydrophenanthridine (63) in 54% yield.

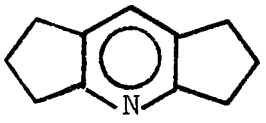


63

A similar reaction with cyclopentanone provided a mixture of isomeric bis-annelated pyridines 177 and 178 in which 178 was found to be the major isomer.



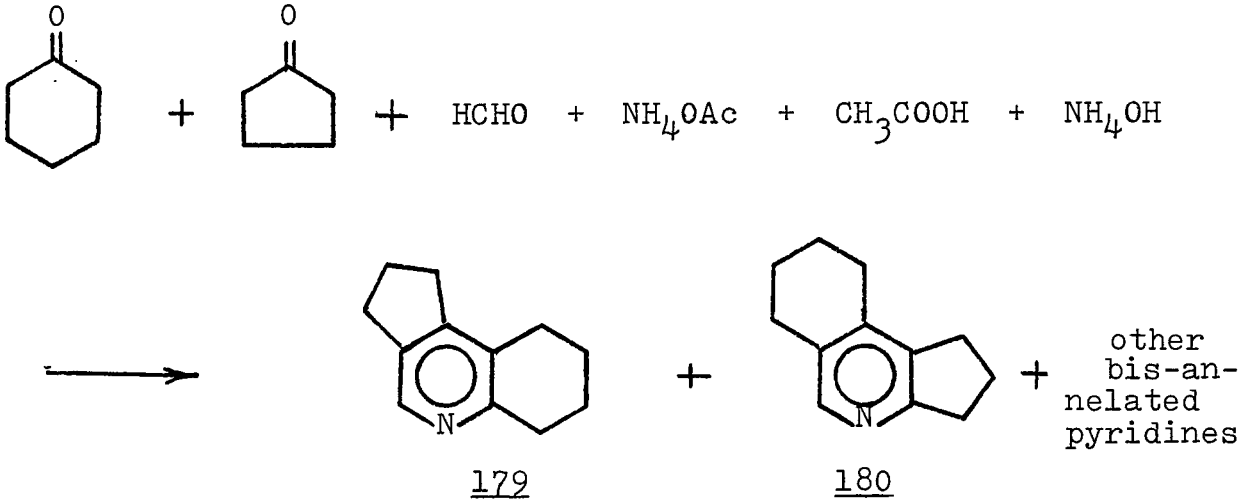
177 90%



178 10%

The separation of 177 and 178 was achieved by column chromatography on silica gel eluting with ether-hexane (2:3). The para-fused isomer, 177, was found to have a lower R_f value as well as a shorter retention time as compared to the meta-fused isomer, 178.

When an equimolar mixture of cyclohexanone and cyclopentanone was heated with formaldehyde and ammonium acetate, it provided a complex mixture of which 179 and 180 were major components which could be isolated pure by preparative gas chromatography.

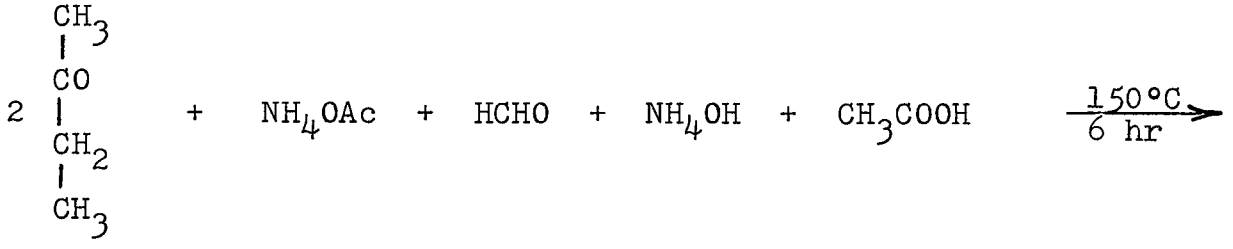


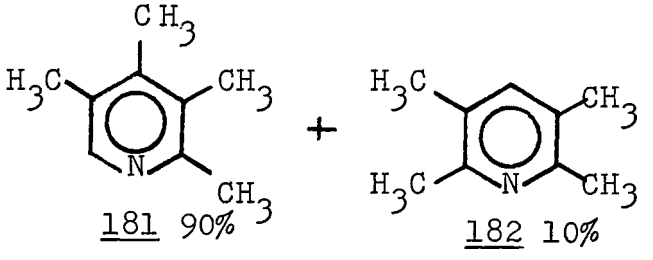
179 180

The assignment of the structures of 179 and 180 was done by ^{1}H and ^{13}C analysis and by analogy with comparable systems such as 63 and 178.

Tetramethylpyridines:

The preparation of [2,3:4,5]-tetramethylpyridine (181) was carried out by a condensation reaction similar to the one used for the preparation of [2,3:4,5]-bis-annelated pyridines. The reaction of 2-butanone with formaldehyde and ammonium acetate at 150° C for 6 hours provided a mixture of [2,3:4,5]-tetramethylpyridine (181) and [2,3:5,6]-tetramethylpyridine (182) in a 9:1 ratio.



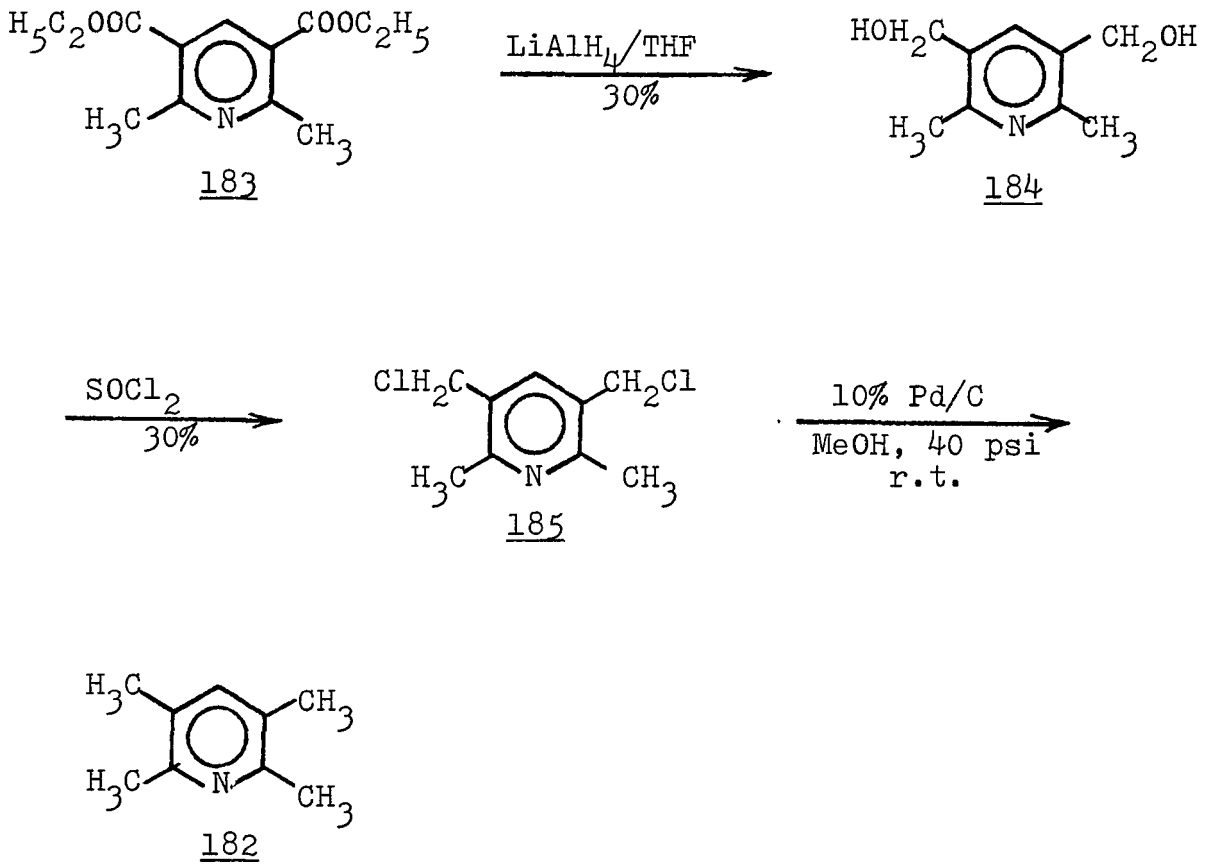


181 90%

182 10%

The separation of 181 and 182 was carried out by chromatography on silica gel eluting with ether-hexane (2:3). The preparation of 182 was accomplished according to the procedure of Tsuda.[83] The lithium aluminum hydride reduction of 183[84] gave 184 in 30% yield. The reaction of 184 with thionyl chloride afforded 185, which could be readily dehalogenated

by paladium on charcoal in 82% yield.



Part II: Physical Properties Data

Carbon-13 and Proton NMR Spectral Data:

Pyridine NMR chemical shift assignments are greatly facilitated by the electronic influence which the nitrogen atom exerts on the other ring positions. Thus, the two-and six-positions are the most deshielded due to the proximity of this electronegative heteroatom. The four-position possesses significant positive character by resonance and is next most deshielded. Atoms at positions three- and five are found at highest field.

In Table III are recorded the proton and carbon-13 chemical shifts which we have determined for mono-annelated pyridines as well as dimethyl substituted analogs. The carbon-13 chemical shifts for bis-annelated pyridines are recorded in Table VI. The changes in carbon-13 chemical shifts are tabulated in Table IV.

Carbon-13 Assignments:

The ^{13}C chemical shift assignments for the aromatic ring carbons in annelated pyridines were made by use of substituent chemical shift effects for pyridine and benzene derivatives.[85,86] The chemical shift values for 2,3-dimethyl and 3,4-dimethylpyridines calculated from the additivity relationship (1) and

$$\delta_c(k) = C_k + \sum_i A_{ik} (R_i) \quad \text{——} \quad 1$$

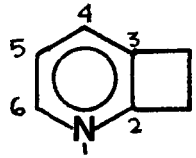
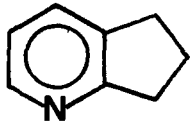
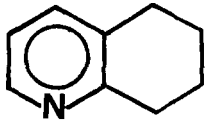
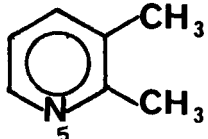
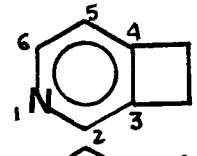
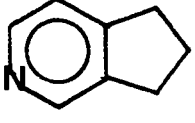
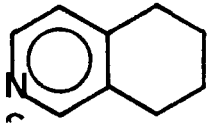
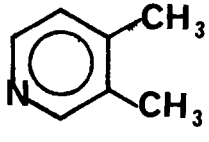
C_k is constant term for nucleus k (= chemical shift of carbon k in pyridine), and A_{ik} is shift increment predicted for carbon k upon introduction of substituent R_i at carbon i

the additivity parameters[85] were used as a standard for assigning the experimentally observed values.

For 2,3-monoannelated pyridines, the bridgehead carbons (C-2 and C-3) were assigned to lower field than C-6 and C-5 respectively, consistent with the alkyl substituent effect which tends to deshield the substituted carbon. For 3,4-mono-annelated pyridines, C-2 was assigned to a lower field than C-6, consistent with a para alkyl effect which tends to shield the para carbon by 2.5 ppm and also by comparison with the assigned values for 3,4-dimethylpyridine. Again substituted carbon C-3 was assigned to a lower field than C-5 due to the alkyl substituent effect.

The symmetrically substituted [2,3:4,5] bis-annelated pyridines 17 and 177 could be readily assigned since, due to symmetry, the pairs C-2, C-6 and C-3, C-5 have identical

Table III: Proton and Carbon-13 Chemical Shifts[a] for the Aromatic Ring of Mono-Annelated Pyridines

	H_2	H_3	H_4	H_5	H_6	C_2	C_3	C_4	C_5	C_6
 104			7.32	7.10	8.39	164.2	140.2	129.6	122.9	148.6
 44			7.47	7.00	8.31	165.3	136.8	132.0	120.8	147.0
 21			7.31	6.98	8.31	157.1	132.1	136.7	120.7	146.4
			7.37	7.00	8.29	156.7	131.0	136.6	120.8	146.1
 105	8.16			6.92	8.39	147.8	142.4	155.3	118.2	142.7
 76	8.44			7.14	8.33	147.1	139.9	153.3	119.7	145.7
 24	8.27			6.94	8.24	150.3	132.8	145.9	123.7	146.3
	8.28			6.99	8.26	149.6	131.6	145.0	124.1	146.9

[a] $CDCl_3$ solutions, reported in ppm relative to internal TMS.

chemical shifts. Carbon C-4 was always observed to split into a doublet in the proton coupled spectrum and thus could be easily assigned. For the unsymmetrical bis-annelated pyridine 15, C-2 and C-3 were assigned by comparison with the symmetrical analog 177 and C-5 and C-6 by comparison with 17.

In the case of [2,3:4,5]-bis-annelated pyridines 181, 63, 180, 179 and 178, C-6 carbon resonance was easily assigned since it appeared as a doublet in the proton coupled spectra. Again C-2 was assigned to a lower field than C-6 due to alkyl substituent effect. The next most deshielded carbon was then assigned as C-4 by comparison with 3,4-dimethylpyridines. In compounds 63 and 181 only four resonances were observed for aromatic carbons. The carbons C-2, C-6 and C-4 were assigned as shown above. The remaining resonance was then assigned to C-3 and C-5 in 63 and 181. The assignments for C-3 and C-5 in 178-180 were carried out as follows. In going from 63 to 180, C-5 in both of these compounds is expected to have about the same chemical shift since it is a part of a six-membered ring in both of these compounds having same alkyl substitution pattern. Since C-5 in 63 has a chemical shift of 129.6 ppm, the chemical shift at 129.8 ppm in 180 was assigned to C-5. The remaining chemical shift was then assigned to C-3 in 180. In compound 179, C-3 was assigned at 128.1 ppm analogous to C-3 in 63. The chemical shift at 136.8 ppm then could be assigned to C-5 in 179. Finally C-5 in 178 was assigned by comparison with C-5 in 179 and the remaining chemical shift was then assigned to C-3 in 178. The C-3 and C-5 chemical shifts in [2,3:4,5] bis-annelated pyridines have been assigned by analogy and thus are unambiguous

TABLE IV

Changes in Carbon-13 Chemical Shifts Upon Decreasing Annelated Ring Size

Compound	Altered Ring-Fusion	ΔC_2	ΔC_3	ΔC_4	ΔC_5	ΔC_6
44 → 104	2,3	+1.1	-3.4	+2.4	+2.1	+1.6
21 → 44	2,3	-8.2	-4.7	+4.7	-0.1	-0.6
17 → 15	2,3	-8.5	-4.8	+4.5	+0.1	-0.7
15 → 177	5,6(2,3)[a]	-8.6	-5.1	+4.4	-0.2	-0.8
63 → 180	2,3	-8.2	-5.4	+2.0	-0.2	-1.2
17 → 177	2,3 & 5,6	-9.3	-5.0	+8.9	-5.0	-9.3
76 → 105	3,4	-0.7	-2.5	-2.0	+1.5	+3.0
24 → 76	3,4	+3.2	-7.1	-7.4	+4.0	+0.6
63 → 179	4,5(3,4)[a]	+4.7	-7.2	-8.3	+1.5	-0.7
180 → 178	4,5(3,4)[a]	+5.2	-7.5	-7.2	+2.5	-1.2
63 → 178	2,3 & 4,5	-9.4	-2.9	-5.2	-7.7	+4.0

[a]Numbering patterns (C_2 and C_6, C_3 and C_5) in these molecules are reversed to preserve consistency throughout the table.

Table V: NMR Spectral Data for Annelated Benzenes[84]

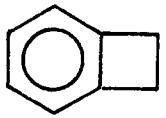
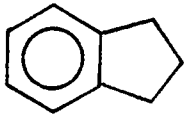
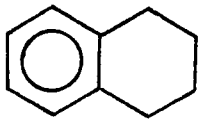
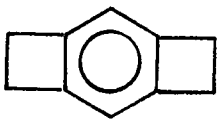
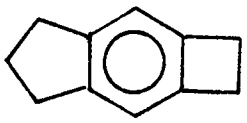
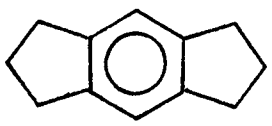
Compound		H_2	H_3	H_4	H_5	H_6	C_2	C_3	C_4	C_5	C_6
	100c		6.90	6.76			145.6	122.1	126.6		
	100d		7.07	6.99			144.0	124.4	126.2		
	100e		7.07	7.07			137.0	129.2	125.2		
	100f		6.64								
	100g		6.91								
	100h		7.08								

TABLE VI

Proton and Carbon-13 Chemical Shifts for the Aromatic Ring of Bis-Annelated Pyridines

	Chemical Shifts (ppm)						
	HA_γ						$J_{C_A-H_\gamma}$
177	7.30	163.2	134.1	128.4	134.1	163.2	159.8 Hz
15	7.15	162.4	133.9	132.8	129.0	154.6	155.2
17	7.02	153.9	129.1	137.3	129.1	153.9	152.2
182	7.10	153.1	128.1	138.5	128.1	153.1	152.6
178	8.18	162.8	132.5	149.2	137.2	142.9	174.9
179	8.22	154.1	128.1	152.3	136.8	142.2	174.0

TABLE VI (continued)

Proton and Carbon-13 Chemical Shifts for the Aromatic Ring of Bis-Annelated Pyridines

		Chemical Shifts (ppm)						
		HA_γ	C_2	C_3	C_4	C_5	C_6	$J_{C_A-_\gamma H}$
	180	8.06	161.6	135.0	142.0	129.8	148.1	173.7
	63	8.06	153.4	129.6	144.0	129.6	146.9	172.2
	181	8.04	153.9	129.1	143.6	129.1	146.3	172.2

only to the extent that such analogies are valid.

Chemical Shift Trends:

For mono-annelated pyridines as the size of the fused ring is decreased from six to five carbons, a very consistent variation in pyridine chemical shifts is observed. Decreasing the size of the fused ring from five to four carbons results in a smaller but consistent variation in chemical shifts with the exception of C-2 for both cyclobutapyridines. For a ring fused at the 2,3-position, both bridgehead carbon atoms are observed to shift downfield with C-2 shifting 8.2 ppm and C-3 shifting 3.4 to 4.7 ppm. For 3,4-fused systems, the shift is also downfield with C-3 shifting 7.1 ppm in going from 24 to 76 and 2.5 ppm in going from 76 to 105 while C-4 shifts 7.4 ppm in going from 24 to 76 and 2.0 ppm for 76 to 105. At the pyridine ring positions ortho to the bridgehead carbons, the change is in the opposite direction, shifting upfield 4.7 ppm for 21 to 44 and 2.4 ppm in going from 44 to 104. A similar upfield shift of 1.5-4.0 ppm is observed for C-5 in the case of 3,4-fused systems. The chemical shift of the hydrogen bonded to the carbon ortho to the bridgehead is found to move downfield as the size of the fused ring is decreased from six carbons to five whereas decreasing the ring size from five to four carbons results in an upfield shift of this proton. A similar upfield shift is observed for the proton attached to the ortho carbon atom in the case of benzocyclobutene (100c) when compared to its higher homologs 100d and 100e (Table V). The carbon-13

chemical shifts for mono-annelated benzenes show a consistent variation similar to what is observed for mono-annelated pyridines but again, the changes observed are much smaller when the size of the fused ring is decreased from five to four carbons as compared to decreasing the fused ring size from six to five carbons (Table V).

For mono-annelated pyridines, the changes in proton and carbon chemical shifts at positions meta and para to the bridgehead vary only slightly when the altered ring size is decreased from six to five carbons, indicating that the influence of the fused ring is localized around the bridgehead and does not significantly affect the molecule as a whole. But when the size of the fused ring is decreased from five to four carbons, all the carbon atoms in the pyridine ring are seen to be equally affected, indicating that the effect of the small ring fusion is not as much localized around the bridgehead carbons, but affects the molecule as a whole.

In Table VI are recorded the proton and carbon-13 chemical shifts for bis-annelated pyridines. The changes in carbon-13 chemical shifts are tabulated in Table IV. The changes in chemical shifts observed for bis-annelated pyridines are much more impressive than observed for mono-annelated pyridines. For a ring fused at the 2,3-position, both bridgehead carbon atoms are observed to shift downfield with C-2 shifting 8.2-8.7 ppm and C-3 shifting 4.4-5.4 ppm as the size of the fused ring is decreased from six carbons to five. For

3,4-fused systems, the shift is also downfield with C-3 shifting 7.1-7.5 ppm and C-4 shifting 7.2-8.3 ppm. The chemical shift of the carbon ortho to the bridgehead is observed to move upfield shifting 1.5-3.1 ppm when the ortho carbon is bound to a methylene and 3.2-5.2 ppm when it is bonded to a hydrogen. The chemical shift of the hydrogen bonded to this ortho carbon is found to move downfield as the size of the fused ring is decreased from six carbons to five. In Table VI are also recorded $J_{C_{Ar}H}$ coupling constants for bis-annelated pyridines. The coupling constant between the ortho carbon and hydrogen increases regularly along the series 17, 15, 177 as well as along the series 63, 180, 179 and 178.

Also in the case of bis-annelated pyridines the chemical shift effects appear to be additive.[85] In going from 17 to 177, C-4 is ortho to two rings both of which decrease by one carbon. The chemical shift of this carbon moves upfield by 8.9 ppm about twice the value observed when only one ring is altered as in going from 21 to 44. Furthermore, the effect of decreasing two rings in going from 63 to 178 can be reasonably well approximated by summation of changes observed in going from 63 to 180 and in going from 63 to 179. We calculate ΔC-2 = -8.9, ΔC-3 = -3.9, ΔC-4 = -6.3, ΔC-5 = -7.4 and ΔC-6 = + 3.5 ppm. The observed values in going from 63 to 178 are ΔC-2 = -9.4, ΔC-3 = -2.9, ΔC-4 = -5.2, ΔC-5 = -7.7 and ΔC-6 = +4.0.

Pyridine Basicities:

The basicities of annelated pyridines were determined as half neutralization potentials (HNP) by titration at 25°C with 0.1 N perchloric acid in acetic acid using acetic anhydride as the solvent. The HNP's were determined for a series which includes pyridine and seven methyl substituted derivatives of known basicity.[87a] A plot of HNP vs. pK_a for these compounds resulted in a straight line from which the pK_a's of the annelated pyridines could be determined,[87b,88] figure 2.

The basicity data for mono-annelated and bis-annelated pyridines is reported in tables VII and VIII, respectively.

The most dramatic effect is observed where the size of the ring fused to the 2,3-(or 5,6-) position is decreased. Thus the basicity of cyclobuta[b]pyridine (104) (pK_a = 4.85) is found to be significantly less than that of its next higher homolog 44 (pK_a 5.95), which in turn is found to be less basic than its next higher homolog 21 (pK_a 6.65). The decrease in basicity of cyclobutapyridine 104 is so dramatic that it is in fact less basic than pyridine (pK_a 5.30). Also there is comparable difference of almost 2 pK_a units between the positionally isomeric cyclobutapyridines with the 3,4-fused isomer (pK_a 6.75) being decidedly more basic. This difference in basicity between the positionally isomeric annelated pyridines becomes much less significant as the size of the fused ring is increased, such that six-membered 2,3-fused isomer 21 is almost as basic (pK_a 6.65) as the 3,4-fused isomer 24 (pK_a 6.83). The fusion of a

Figure 2:

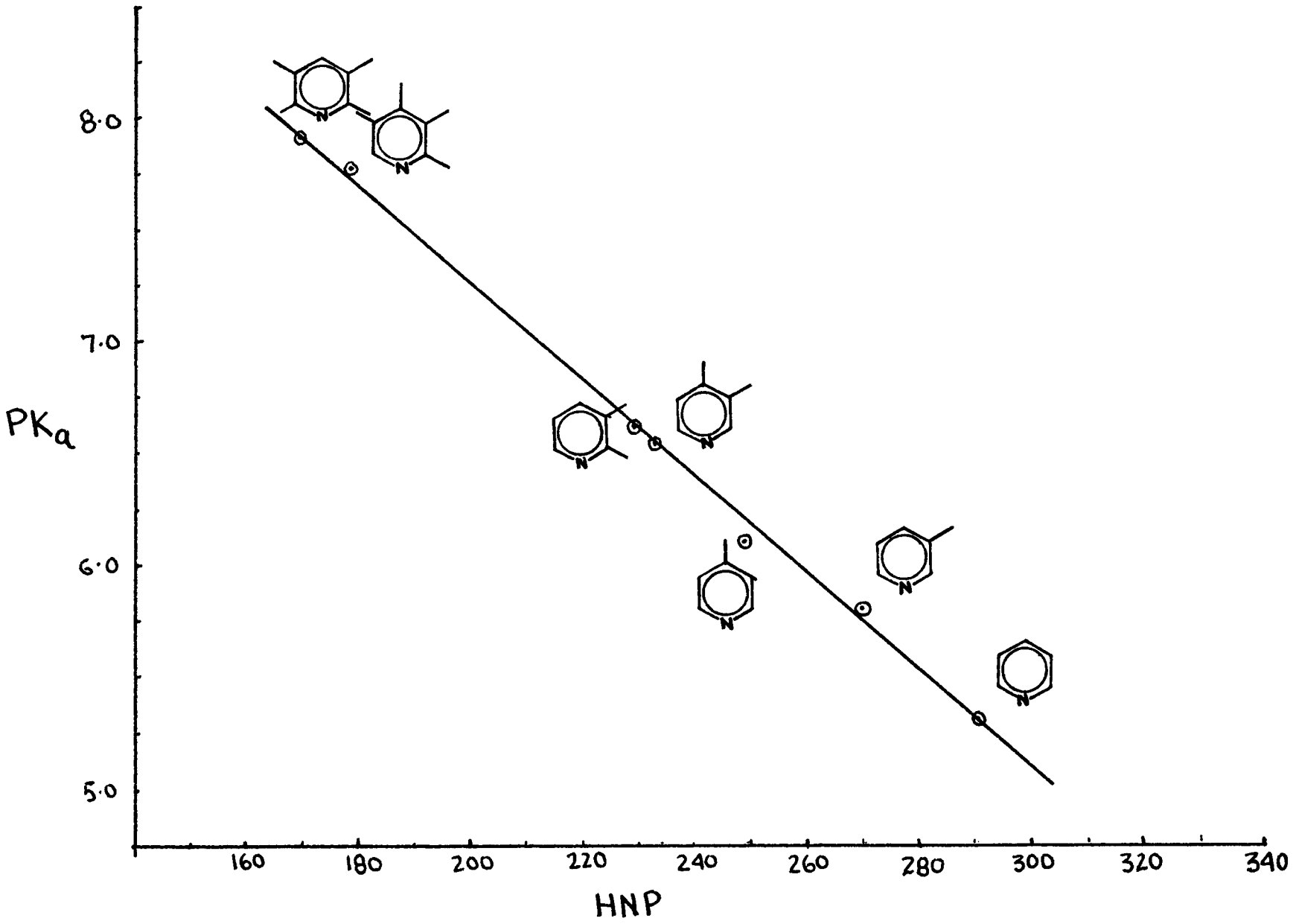


TABLE VII

Basicities of Methyl-Substituted and Mono-Annelated Pyridines

Methyl-Substituted Pyridines	HNP[a]	pK_a[c]
Pyridine	289	5.30[b]
3-Methylpyridine	269	5.85[b]
4-Methylpyridine	248	6.10[b]
2,3-Dimethylpyridine	234	6.56[b]
3,4-Dimethylpyridine	231	6.61[b]
2,4,6-Trimethylpyridine	186	7.63[b]
2,3,5,6-Tetramethylpyridine (182)	169	7.91[b]
2,3,4,5-Tetramethylpyridine (181)	180	7.78[b]
Mono-Annelated Pyridines		
1. Cyclobuta[b]pyridine (104)		4.85
2. 2,3-Trimethlenepyridine (44)	260	5.95
3. 5,6,7,8-Tetrahydroquinoline (21)	229	6.65
4. Cyclobuta[c]pyridine (105)		6.75
5. 3,4-Trimethylenepyridine (76)	215	6.96
6. 5,6,7,8-Tetrahydroisoquinoline (24)	221	6.83

[a] Duplicate runs, ± 2 mv, at 25°C

[b] Reference 87a

[c] pK_a refers to the pK_a of the protonated amine.

Table VIII: Basicities of Bis-Annelated Pyridines

	HNP[a]	pK_a[c]
(2,3:5,6)-Di(trimethylene)pyridine (177)	239	6.42
2,3-Trimethylene-5,6,7,8-tetrahydroquinoline (15)	200	7.30
1,2,3,4,5,6,7,8-Octahydroacridine (17)	165	8.09
(2,3:4,5)-Di-(trimethylene)pyridine (178)	196	7.39
3,4-Trimethylene-5,6,7,8-tetrahydroquinoline (179)	167	8.05
2,3-Trimethylene-5,6,7,8-tetrahydroisoquinoline (180)	198	7.35
1,2,3,4,7,8,9,10-Octahydrophenanthridine (63)	180	7.75

[a] Duplicate runs, ± 2 mv, at 25°C

[c] pK_a refers to the pK_a of the protonated amine.

five-membered ring in the 3,4-position results in an increase in basicity such that 76 (pK_a 6.96) is more basic tha 24 (pK_a 6.83). Whereas the basicity of four-membered fused 3,4-isomer (pK_a 6.75) falls in between that of 76 and 24. It seems that the size of the ring fused at 3,4-position has only a minor and apparently inconsistent influence on the basicity of the molecule.

The basicities of bis-annelated pyridines are recorded in Table X. With two rings fused to the pyridine nucleus, the effects are even more impressive with the para-bis-annelated series 17, 15, 177 spanning 1.67 units. The observed basicities for meta-bisannelated pyridines are consistent with the observations made for mono-annelated pyridines. With a 2,3-fused six-membered ring and a 3,4-fused five-membered ring, 3,4-trimethylene-5,6,7,8-tetrahydroquinoline (179) is the most basic (pK_a 8.05) while 2,3-trimethylene-5,6,7,8-tetrahydroisoquinoline (180) with the opposite orientation is the least basic (pK_a 7.35). Pyridines 63 and 178 fall in between.

Ultraviolet Spectral Data for Annelated Pyridines:

The ultraviolet spectral data for mono- and bis-annelated pyridines is recorded in Tables IX and X.

In the mono-annelated pyridines the absorptions for cyclobutapyridines occur at about the same energies as observed for next higher homologs 44 and 76. While the extinction co-efficients for 105 are nearly identical to those observed for the other 3,4-fused systems 76 and 24, a regular trend of increasing

Table IX: Ultraviolet Spectral Data for Mono-Annelated Pyridines

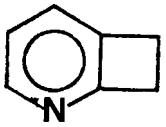
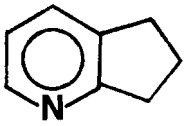
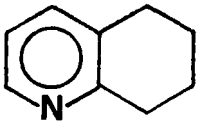
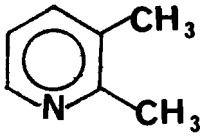
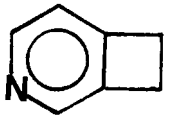
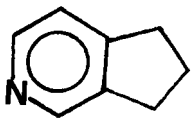
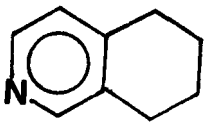
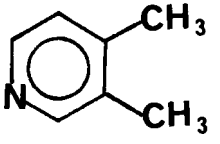
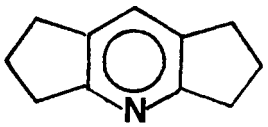
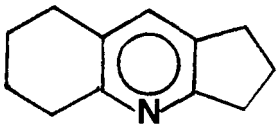
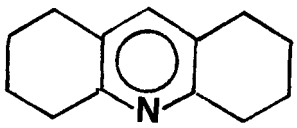
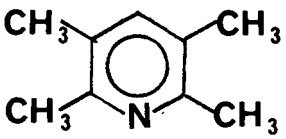
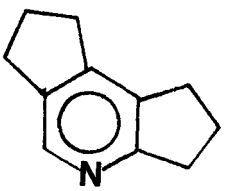
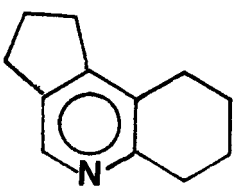
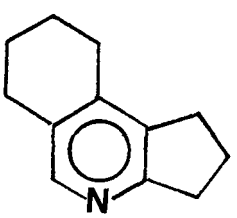
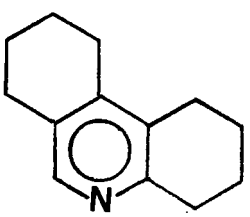
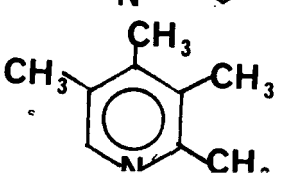
	λmax (95% EtOH) (ε)			
	278(3424)	272 (4800)	269(4767)	
	278(2768)	274(3580)	270(3873)	265(3421)
	276(2180)	271(2556)	268(2851)	264(2491)
	271(2417)	265(3182)	259(2767)	
	263(1621)	258(1951)	253(1736)	
	267(1758)	259(2027)	254(1646)	
	269(1771)	261(2169)	254(1708)	
	267(1842)	259(2248)	255(1947)	

TABLE X

Ultraviolet Spectral Data for Bis—Annelated Pyridines

λmax (95% EtOH) (ε)

	177	297(4875)	292(7200)	287(7925)	282(6800)
	15	295(4805)	289(6603)	285(7000)	281(6217)
	17	291(3980)	286(5073)	281(5520)	277(4625)
	182	281(3388)	275(4518)	272(4556)	267(3743)
	178	278(2804)	274(2942)	270(2927)	
	179	276(2840)	272(2985)	268(3205)	
	180	276(4300)	272(4470)		
	63	279(3064)	276(3321)	271(3423)	267(3013)
	181	275(2552)	271(2958)	267(4000)	263(2682)

extinction co-efficients is observed for the series 21, 44, and 104.

For bis-annelated pyridines, a longer wavelength (lower energy) absorption is found for [2,3:5,6]- vs.[2,3:4,5] bis-annelated pyridines including the tetramethyl pyridines. The maxima observed for [2,3;5,6]-bis-annelated pyridines move to longer wavelength and the extinction co-efficients are seen to increase as the size of the fused ring is decreased.

Photoelectron Spectra and Gas Phase Basicities:[105]

In collaboration with Dr. Donald Aue of the University of California at Santa Barbara, the photoelectron spectra and gas phase basicities of a series of mono-annelated pyridines have been determined and the data tabulated in tables XI and XII. The correlation between ionization potentials is shown in Figure 3.

Spectral Data for 2,3-fused-1,8-napthyridines:

The ^{1}H NMR spectral data for 2,3-fused-1,8-napthyridines 4a-d is recorded in table XIII. The ultraviolet spectral data is recorded in table XIV. In table XV are recorded the half neutralization potentials (HNP) for 4a-d as determined by titration at 25°C in acetic anhydride with 0.10 N perchloric acid in acetic acid as the titrant. Also recorded are the pK_a's as determined by titration with 0.0908 N hydrochloric acid at 25°C in 4% ethanol-water. A plot of HNP vs. pK_a affords the expected straight line relationship.[87,88]

Table XI : Photoelectron Spectra of Mono-Annelated Pyridines

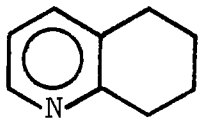
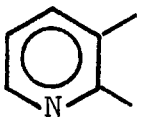
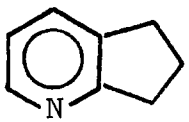
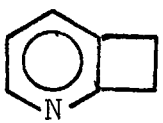
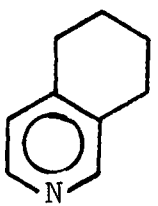
	(V) IP eV	(V) IP K·cal	(a) IP eV	(a) IP K·cal	π_A eV	n eV	π_S eV	Fourth band eV
	9.13	210.54	8.68	223.23	9.13	9.13	9.95	11.16
	9.13	210.54	8.84	203.86	9.13	9.13	10.07	12.0
	9.16	211.24	8.68	200.17	9.16	9.16	10.07	11.73
	9.25	213.31	8.77	202.24	9.25	9.25	9.76	12.0
	9.20	212.16	8.77	202.24	9.20	9.20	9.70	11.31

Table XI : (cont'd)

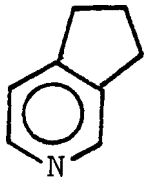
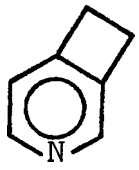
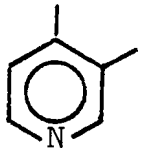
	(V) IP eV	(V) IP K·cal	(a) IP eV	(a) IP K·cal	π_A eV	n eV	π_S eV	Fourth band eV
	9.18	211.70	8.72	201.09	9.18	9.18	9.73	11.73
	9.38	216.31	8.77	202.24	9.38	9.38	10.02	11.41
	9.33	215.16	8.79	202.71	9.33	9.33	9.80	12.05

Table XII: The Gas Phase Basicity of Mono-Annelated Pyridines

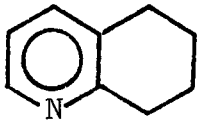
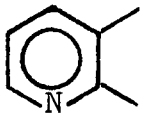
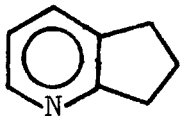
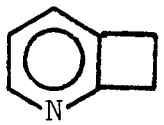
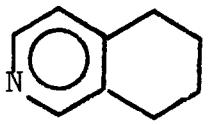
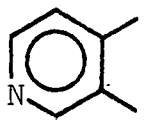
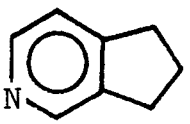
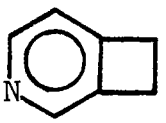
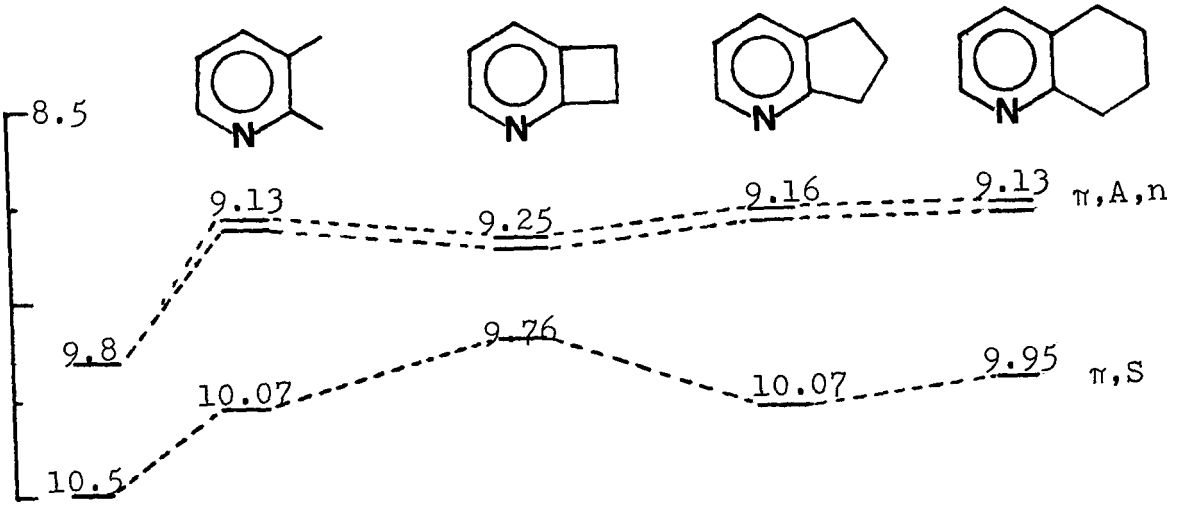
	GB	IP (V)	IP (a)
	216.9	9.13	8.68
	215.4	9.13	8.84
	215.0	9.16	8.68
	212.6	9.25	8.77
	216.9	9.20	8.77
	215.4	9.33	8.79
	216.0	9.18	8.72
	215.0	9.38	8.77

Figure 3


8.5
9.13
9.25
9.16
9.13
π,A,n
9.8
9.76
10.07
10.07
9.95
π,S
10.5

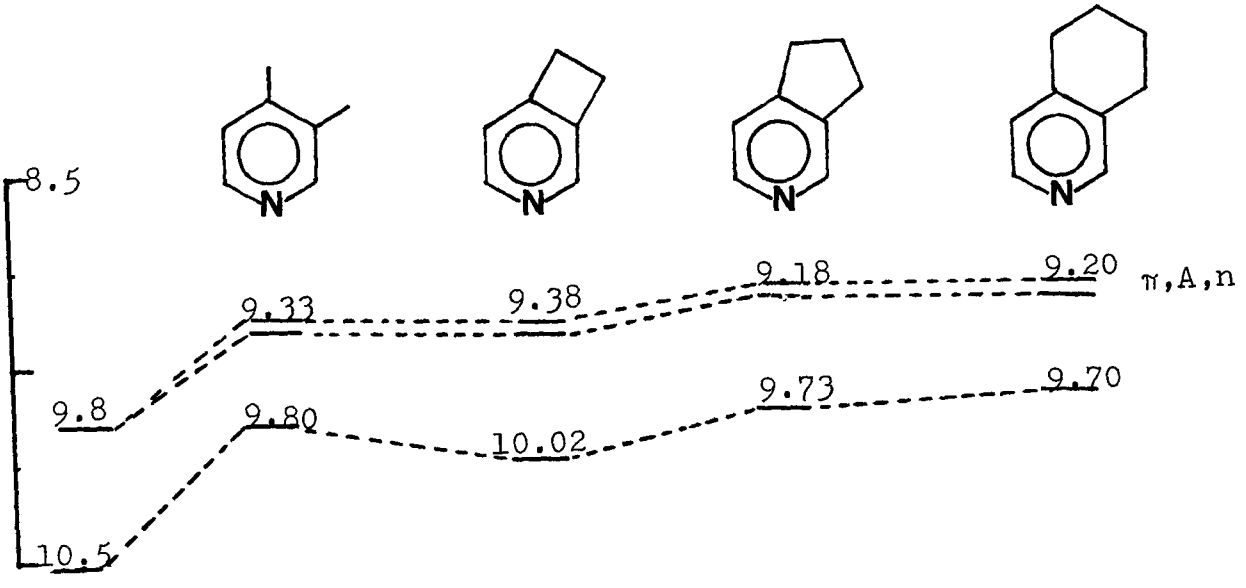

8.5
9.33
9.38
9.18
9.20
π,A,n
9.8
9.80
10.02
9.73
9.70
10.5

Table XIII: Chemical Shifts for the Aromatic Ring Protons in 2,3-Fused 1,8-Napthyridines

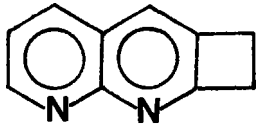
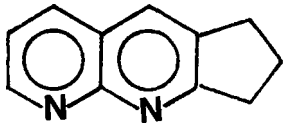
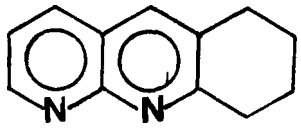
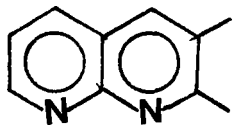
		Chemical Shifts (ppm)			
		H_4	H_5	H_6	H_7
	4a	7.63	8.10	7.37	8.96
	4b	7.80	8.04	7.33	8.96
	4c	7.78	8.14	7.37	9.01
	4d	7.85	8.08	7.39	9.00

Table XIV: Ultraviolet Spectral Data for 2,3-Fused 1,8-Napthyridines

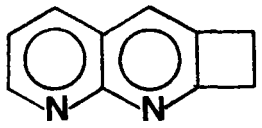
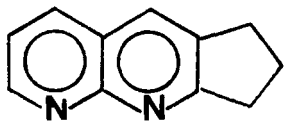
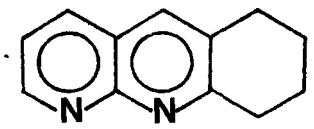
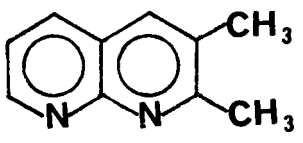
		λmax (95% Ethanol) (ε)			
	4a	260(5,300)	302(9,500)	307(10,200)	315(10,700)
	4b	260(4,540)	305(10,500)	310(10,600)	318(12,500)
	4c	265(3,800)	307(8,500)	313(8,700)	320(9,900)
	4d		303(6,710)	308(6,850)	316(7,760)

Table XV

Basicities of 1,8-Napthyridines

Compound		HNP	pK_b[a]
Cyclobuta[b]-1,8-napthyridine	(4a)	312 mv	4.37
Cyclopenta[b]-1,8-napthyridine	(4b)	296	4.49
Cyclohexa[b]-1,8-napthyridine	(4c)	275	4.82
2,3-Dimethyl-1,8-napthyridine	(4d)	288	4.74

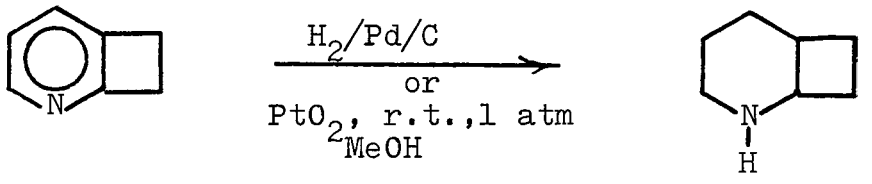
[a] Determined by titration at 25°C in 4% ethanol-water with 0.0980 N hydrochloric acid.

Chemical Properties

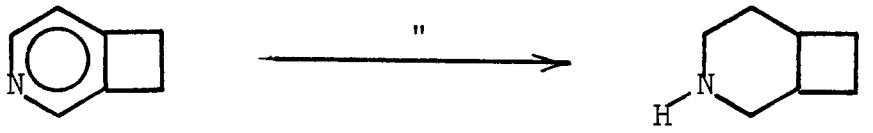
Hydrogenation:

Both cyclobutapyridines 104 and 105 were observed to undergo catalytic hydrogenation at room temperature and one atmosphere of hydrogen utilizing either palladium on charcoal or platinum oxide as the catalyst. When a mixture of 104 and 105 was hydrogenated, the 2,3-isomer 104 was seen to reduce just slightly faster than the 3,4-isomer 105. The resulting azabicyclo[4.2.0]octanes 191 and 192 were purified by preparative VPC and identified by their spectral properties. These two isomers represent the last two unreported

azabicyclooctanes.[89] Under identical reduction conditions,



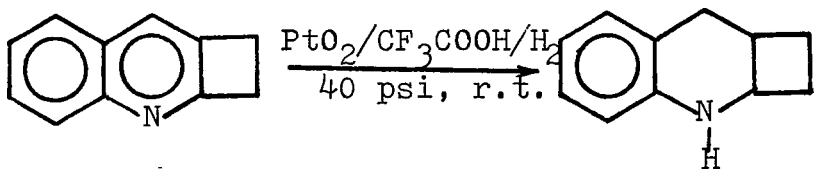
104 191



105 192

a mixture of 2,3- and 3,4-lutidine was totally unreactive.

When cyclobuta[b]quinoline (2) was hydrogenated at 40 psi in trifluoroacetic acid utilizing platinum oxide as the catalyst, 193 was found to be the major product. Although these reaction conditions have been reported to promote preferential reduction of the benzene portion of quinoline,[28] just the opposite is observed in this case.



2 193

Clearly in the above case relief of ring strain inherent in 2 is responsible for predominate reduction of the pyridine portion of the molecule as compared to the benzene portion.

EXPERIMENTAL

EXPERIMENTAL

Proton nuclear magnetic resonance spectra of 2,3-fused 1,8-napthyridines were obtained on a Varian Associates EM 390 NMR spectrometer. Proton and carbon magnetic resonance spectra of annelated pyridines were recorded on a Varian Associates XL-100 spectrometer. All chemical shifts are reported in ppm downfield from TMS. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Ultraviolet spectra were obtained on a Cary 14 spectrometer. All melting points are uncorrected. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona.

Cyclobuta[b]-1,8-napthyridine: (4a) (DK-62)

A solution of 0.5 g (4mmol) of 2-aminonicotinaldehyde (37) and 0.24 g (3.4mmol) of cyclobutanone in 10 ml of 95% ethanol containing 2 ml of 33% aqueous potassium hydroxide was allowed to stand at room temperature for three days, brought rapidly to reflux, diluted with 20 ml of water, treated with charcoal, and filtered. The filtrate was then extracted with four 20 ml portions of dichloromethane. The extracts were dried over potassium carbonate and evaporated to yield 0.25 g of a yellow solid. This material was purified in a thermal gradient sublimer (100°C/0.005 mm) to give 0.20 g (39%) of white crystals, m.p. 147-148°C; NMR (deuteriochloroform): δ 8.96 (H_7, d of d, $J_{7,6}$= 4.4 Hz, $J_{7,5}$= 2.1 Hz), 8.10 (H_5, d of d, $J_{5,6}$= 8.3 Hz, $J_{5,7}$= 2.1 Hz), 7.63 (H_4, t,

J= 1.2 Hz), 7.37 (H_6, d of d, $J_{6,7}$= 4.4 Hz, $J_{6,5}$= 8.3 Hz), 3.63 (m, 2H), and 3.30 ppm (m, 2H); IR (potassium bromide): 3060, 2960, 1620, 1595, 1410, 1370, 800 and 750 cm^{-1}; UV λ max (95% ethanol): 315 (10,700), 307 (10,200), 302 (9,500), and 260 mμ (5,300); mass spectrum: m/e (relative intensity) 156 (100), 155 (72), 149 (27), 144 (23) and 89 (31).

Anal. Calcd. for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 77.04; H, 5.31; N, 17.66.

Cyclopenta[b]-1,8-napthyridine: (4b) (DK-63)

To a mixture of 0.61 g (5mmol) of 2-aminonicotinaldehyde (37) and 0.38 g (4.5mmol) of cyclopentanone was added 5 ml of glacial acetic acid and two drops of concentrated sulfuric acid. The mixture was refluxed for six hours, cooled, and poured into 8 ml of ammonium hydroxide and 20 g of ice. A yellow precipitate was obtained which turned into a gummy solid upon standing. The whole mixture was extracted four times with dichloromethane. The extracts were dried over potassium carbonate and evaporated to give 0.79 g of 4b, m.p. 125°C. The crude product could be purified by sublimation to give crystals, m.p. 140-141°C; NMR (deuteriochloroform): δ 8.96 (H_7, d of d, $J_{7,6}$= 4.2 Hz, $J_{7,5}$= 1.9 Hz), 8.04 (H_5, d of d, $J_{5,6}$= 8.0 Hz, $J_{5,7}$= 1.9 Hz), 7.80 (H_4, t, J=1.4 Hz), 7.33 (H_6, d of d, $J_{6,7}$= 4.2 Hz, $J_{6,5}$= 8.0 Hz), 3.20 (t, 2H, J=7.5 Hz), 3.07 (t, 2H, J=7.5 Hz), and 2.18 ppm (quintet, 2H, J = 7.5 Hz): IR (potassium bromide): 3020, 2990, 1620, 1595, 1560, 1408, 790, and 735 cm^{-1}; UV λ max (95% ethanol): 318 (12,500), 310(10,600)

305 (10,500), and 260 mμ (4540); mass spectrum; m/e (relative intensity) 170 (91), 169 (100), 158 (55), 149 (14) 142 (28), 115 (27), and 91 (24).

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.34; H, 5.88; N, 16.89.

Cyclohexa[b]-1,8-napthyridine: (4c) (DK-64)

A mixture of 0.5 g (4.1mmol) of 2-aminonicotinaldehyde (37) and 0.30 g (3.4mmol) of cyclohexanone in 5 ml of glacial acetic acid containing two drops of concentrated sulfuric acid was refluxed for eight hours and then worked up in the same manner as described above to yield 0.71 g of a brown solid, m.p. 103-104°C. Purification by sublimation gave 0.44 g (70%) of white crystals of 4c, m.p. 110-111°C; NMR (deuteriochloroform): δ 9.01 (H_7, d of d, $J_{7,6}$= 4.2 Hz, $J_{7,5}$= 2.0 Hz), 8.14 (H_5, d of d, $J_{5,6}$= 8.1 Hz, $J_{5,7}$= 2.0 Hz), 7.78 (H_4, broad s), 7.37 (H_6, d of d, $J_{6,7}$= 4.2 Hz, $J_{6,5}$= 8.1 Hz), 3.22 (t, 2H, J = 6 Hz), 2.98 (t, 2H, J = 6 Hz) and 1.96 ppm (m, 4H); IR (potassium bromide): 3020, 2920, 1550, 1474, 1446, 1410, and 800 cm^{-1}; UV λ max (95% ethanol): 320 (9,900), 313 (8,700), 307 (8,500), and 265 mμ (3,800).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.20. Found: C, 78.29; H, 6.62; N, 15.26.

2,3-Dimethyl-1,8-napthyridine: (4d)

A mixture of 0.61 g (5mmol) of 2-aminonicotinaldehyde (37), 5 ml of 2-butanone and 0.12 g of piperidine was refluxed

for 20 hours. The unreacted 2-butanone was removed under vacuum and the resulting yellow solid (0.63 g) was chromatographed on silica gel, eluting with ether to yield 0.27 g (34%) of yellow crystalline solid (4d), m.p. 135-136°C; NMR (deuteriochloroform): δ 9.00 (H_7, d of d, $J_{7,6}$= 4.2 Hz, $J_{7,5}$= 2.0 Hz), 8.08 (H_5, d of d, $J_{5,6}$= 8.0 Hz, $J_{5,7}$= 2.0 Hz), 7.85 (H_4, broad s), 7.39 (H_6, d of d, $J_{6,7}$= 4.2 Hz, $J_{6,5}$= 8.0 Hz), 2.76 (s, 3H, 2-methyl) and 2.48 ppm (s, 3H, 3-methyl); IR (potassium bromide): 3010, 1638, 1603, 1560, 1448, 1423, 1378, 1000, and 795 cm^{-1}; UV λ max (95% ethanol): 316 (7,760), 308 (6,850), and 303 mμ (6,710).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6,37; N, 17.71. Found: C, 76.23; H, 6.52; N, 17.72.

Generalized Procedure for the Hydrogenolysis of Isoxazoles:

A solution of 0.05 mol of isoxazole in 50 ml of absolute methanol was hydrogenolyzed in the presence of Raney-nickel catalyst at 40 psi and room temperature in a 500 ml pressure bottle with stirring. The reaction was stopped when one equivalent of hydrogen was taken up and the catalyst was then removed by filtration. Evaporation of methanol yielded a crude β-amino-α,B-unsaturated carbonyl compound which was purified by recrystallization from a suitable solvent or by sublimation in a thermal gradient sublimer at 0.05 mm.

β-Aminoacrolein: (43) (DK-72)

It was prepared in 82% yield by the hydrogenolysis of

isoxazole according to the above procedure; m.p. 104-105°C, lit.[63] m.p. 105-106°C; NMR (D_2O) δ 5.41 (d,d, J = 9 Hz, 1H), 7.50 (d, J = 12 Hz, 1H), 8.70 (d, J = 9 Hz, H); IR (KBr): 3200, 3100, 2730, 1580, 1400, 1350, 1300, 1200, and 1030 cm^{-1}.

4-Amino-3-butene-2-one: (57) (DK-86)

Hydrogenolysis of 5-methylisoxazole afforded 4-amino-3-butene-2-one in 90% yield, b.p. 125-127°C (0.6mm); lit.[99] b.p. 97-100°C, (0.15 mm); NMR ($CDCl_3$) δ 2.05 (s, 3H, $-CH_3$), 3.42 (s, NH_2), 5.02 (d, 1H, olefinic) and 6.7 ppm (m, 1H, olefinic).

4-Amino-3-methyl-3-butene-2-one: (124) (DK-71)

Hydrogenolysis of 4,5-dimethyl isoxazole provided 124 in 80% yield; m.p. 110-111°C; lit.[100] m.p. 108°C; NMR (D_2O) δ 1.83 (s, 3H, $-\overset{O}{\overset{\|}{C}}-\underline{CH}_3$), 2.40 (s, 3H, $-\overset{CH_3}{\overset{|}{C}} = CH-NH_2$) and 7.99 ppm (s, 1H, olefinic H).

3-Amino-3-methyl-acrolein: (120) (DK-86)

Hydrogenolysis of 3-methyl isoxazole provided 3-amino-3-methylacrolein in 50% yield; b.p. 48-49°C (0.1 mm); NMR ($CDCl_3$) δ 1.98 (s, 3H, $-CH_3$), 4.98 (d, J = 3 Hz, olefinic H) and 9.97ppm (d,J =3Hz) - $\overset{O}{\overset{\|}{C}}-H$.

4-Amino-4-methyl-3-butene-2-one: (123) (DK-167)

Hydrogenolysis of 3,5-dimethyl isoxazole provided 123 in 83% yield, m.p. 43-44°C, lit.[101] m.p. 43°C; NMR ($CDCl_3$) δ 1.95 (broad s, 6H, $-(CH_3)_2$), 4.92 (s, 1H, olefinic H) and 6.20 ppm (broad , NH_2).

2-Aminomethylenecyclohexanone: (40a) (DK-100)

A solution of 2 g (0.016 mol) of 4,5,6,7-tetrahydro-1,2-benzisoxazole (169) in 30 ml of absolute methanol was hydrogenolyzed in the presence of Raney-nickel at 40 psi and room temperature. The reaction was stopped when one equivalent of hydrogen had been absorbed. The catalyst was removed by filtration and the methanol was evaporated to provide 1.45 g (72%) of a yellow solid, m.p. 94-95°C, which was recrystallized from acetone to give light yellow crystals, m.p. 108-109°C, lit.[35] m.p. 110-111°C; NMR ($CDCl_3$) δ 1.65 (m, 4H, $-(CH_2)_2-$), 2.25 (m, 4H, $-(CH_2)_2-$) and 6.65 (t, = CH (trans), J = 10 Hz) and 7.6 ppm (t, = CH (cis), J = 10 Hz); IR (KBr) 3360, 3180, 2930, 2860, 1660, 1620, 1450, 1390, 1300, 1160, 1020, 910, 895 and 825 cm^{-1}.

2-Oxocyclopentanecarboxaldehyde:[81] (174) (DK-114)

The modified procedure of Johnson[81] was followed. In a one liter, three necked flask fitted with a mechanical stirrer, a nitrogen inlet and a dropping funnel was placed 28 g (0.5 mol) of sodium ethoxide in 50 ml of dry benzene. The reaction flask was flushed with nitrogen and a solution of 36.5 g (~0.5 mol) of ethylformate in 50 ml of benzene was added. The reaction flask was cooled with chilled water and a solution of 41.5 g (~0.5 mol) of cyclopentanone in 100 ml of dry benzene was added with rapid stirring. The stirring was continued for 8 hours at slightly below room temperature and then 100 ml of cold water was added dropwise and the stirring continued for fifteen more minutes. The aqueous layer

was separated and the benzene layer was washed with water and then dilute sodium hydroxide solution. The combined aqueous layers were acidified with 6N HCl and then extracted with ether. The combined ether layers were washed with a dilute solution of sodium bicarbonate followed by water. The ether extract was dried over sodium sulfate and the ether removed to give a brown oil, which was cooled and the crystalline 2,4-dihydroxymethylene cyclopentanone[94], 0.7 g, (m.p. 114°C) was separated and the remaining oil was distilled rapidly at 0.5-1.5 mm giving a pale yellow solid. Recrystallization from petroleum ether afforded 3.24 g (57%) of a colorless solid m.p. 77-78°C, lit.[94] m.p. 76-77°C.

2-Aminomethylenecyclopentanone: (40b) (DK-119)

Into a solution of 1.0 g (8mmol) of 2-oxocyclopentane carboxaldehyde[81] in 10 ml of chloroform was passed a slow stream of ammonia gas for 20 minutes such that the temperature of the solution did not rise appreciably. The reaction mixture was allowed to stand overnight, then dried over $MgSO_4$, filtered, and the solvent removed under vacuum to give 0.96 g of a dark yellow solid which was recrystallized from chloroform-petroleum ether (1:1) to give light yellow crystals, m.p. 109-110°C, which darkened upon standing. NMR ($CDCl_3$) δ 7.32 (t, =C<u>H</u> (cis), J = 10 Hz), 6.72 (t, =C<u>H</u> (trans), J = 10 Hz), 4.9 (broad s, N<u>H</u>$_2$), 2.6-1.8 ppm (m, 6H). Upon addition of D_2O, the two triplets collapse to singlets and the signal at 4.9 disappears. IR (KBr) 3400-2900 (b), 2400, 1680

(b), 1120, 915, 875, and 635 cm^{-1}.

2-Aminomethylenecyclohexanone: (40a) (DK-115)

Treatment of 5.0 g (.04 mol) of 2-oxocyclohexane carboxaldehyde[92] in 25 ml of chloroform as described above led to the isolation of 2.5 g (50%) of 40a after recrystallization from acetone, m.p. 104-105°C; lit.[35] m.p. 110-111°C.

Friedländer Condensations:

To an equimolar mixture of the β-amino-α,β-unsaturated carbonyl compound and the appropriate ketone was added 10-30 mg of ammonium acetate and the mixture was heated to 120°C for 12-20 hours. After cooling the mixture was triturated with ether and the ether soluble portion dried over $MgSO_4$, filtered, and the solvent removed under vacuum. The dark crude oil obtained was first purified by vacuum distillation and then by chromatography on silica gel, eluting with ether-petroleum ether (2:5).

2,3-Trimethylenepyridine: (44) (DK-136)

Reaction of 3.0 g of β-aminoacrolein with 3.53 g of cyclopentanone provided 0.80 g (16%) of 44, b.p. 38-40°C (.2 mm), lit.[36] b.p. 87-88°C (11 mm): NMR ($CDCl_3$) δ 8.31 (d, H_6, $J_{6,5}$= 5.0 Hz), 7.47 (d, H_4, $J_{4,5}$= 7.5 Hz), 7.00 (d of d, H_5, $J_{5,4}$= 7.5 Hz, $J_{5,6}$= 5.0 Hz), 2.96 (2 overlapping t, 4H) and 2.10 ppm (m, 2H); IR (thin film) 3050, 2963, 2853, 1720, 1597, 1586, 1430, 1267, 790 and 725 cm^{-1}.

5,6,7,8-Tetrahydroquinoline: (21) (DK-137)

Reaction of 3.0 g of β-aminoacrolein with 4.03 g of cyclohexanone provided 1.15 g (21%) of 21, b.p. 45-47°C (.25 mm), lit.[36] b.p. 98-99°C (12 mm): NMR ($CDCl_3$): δ 8.31 (d, H_6, $J_{6,5}$= 4.8 Hz), 7.31 (d, H_4, $J_{4,5}$= 7.5 Hz), 6.98 (d of d, H_5, $J_{5,4}$= 7.5 Hz, $J_{5,6}$= 4.8 Hz), 2.89 (t, 2H), 2.73 (t, 2H) and 1.80 ppm (m, 4H); IR (thin film) 3064, 2945, 2872, 1720, 1590, 1455, 1430, 1265, 785 and 730 cm^{-1}.

2,3:5,6-Di(trimethylene)pyridine: (177) (DK-120)

Reaction of 0.5 g (4.5mmol) of 40b with 0.38 g (4.5 mol) of cyclopentanone in the presence of 10 mg of ammonium acetate provided 0.63 g of material which after distillation showed a major peak at 21 minutes retention time by VPC (10 ft x 1/8 in 10% Carbowax 20 M on Chromsorb W 60/80 at 150°C and 30 ml/min). Isolation of this peak provided a white crystalline material, m.p. 86-87°C, which was found to be identical with authentic 177 prepared by the method of Colonge and coworkers[43] (m.p. 87°C): NMR ($CDCl_3$) δ 7.30 (s, Ar-H), 2.95 (t, 4H), 2.87 (t, 4H) and 2.10 ppm (quintet, 4H); IR (thin film) 2950, 2850, 1605, 1570, 1442, 1415, 1305, 1230, 1215 and 730 cm^{-1}.

1,2,3,4,5,6,7,8-Octahydroacridine: (17) (DK-108)

Reaction of 2.0 g (16mmol) of 40a with 1.57 g (16mmol) of cyclohexanone in the presence of 20 mg of ammonium acetate provided 3.14 g of a brown oil which was distilled, b.p. 95-98°C (0.4 mm), to yield 0.79 g (26%) of a crystalline

material, m.p. 69-70°C, which was found to be identical with authentic 17 prepared by the method of Colonge and coworkers[43] (m.p. 69°C): NMR ($CDCl_3$) δ 7.02 (s, Ar-H), 2.85 (t, 4H), 2.70 (t, 4H) and 1.85 ppm (m, 8H); IR (thin film), 2930, 2860, 1660, 1640, 1607, 1450, 1250, 985, 936, 820, and 710 cm^{-1}.

2,3-Trimethylene-5,6,7,8-tetrahydroquinoline: (15) (DK-129)

Reaction of 3.2 g (.026 mol) of 40a with 2.2 g (.026 mol) of cyclopentanone in the presence of 30 mg of ammonium acetate provided 4.40 g of a brown oil which was distilled to yield 0.96 g of crude product, b.p. 84°C (0.5 mm); lit.[26] b.p. 169-197°C (18 mm). This material was purified by column chromatography to provide 0.35 g (8%) of a colorless oil which was identified as 15; NMR ($CDCl_3$) δ 7.15 (s, Ar-H), 3.0-2.7 (overlapping triplets, 8H), 2.06 (quintet, 2H), and 1.84 ppm (m, 4H); IR (thin film) 2935, 2860, 1610, 1575, 1450, 1420, 1227, 920 and 750 cm^{-1}.

2,3-Trimethylene-6-methylpyridine: (125) (DK-93)

Reaction of 0.42 g (0.005 mol) of 120 with 0.42 g (0.005 mol) of cyclopentanone in the presence of 15 mg of ammonium acetate provided 0.55 g of a brown oil. Analyses by VPC (10 ft x 1/8 in 10% Carbowax 20 M + 5% KOH on Chromsorb W 60/80 at 150°C and 30 ml/min) showed a major peak with 6 min retention time. Isolation of this peak by preparative gas chromatography provided 125 as a colorless oil, identified by NMR. NMR ($CDCl_3$) δ 2.13 (quintet, J = 7 Hz, 2H), 2.50 (s,

3H, -$\underline{CH}_3$), 2.90 (q, J=7 Hz, 4H), 6.80 (d, $J_{5,4}$= 7Hz, H_5) and 7.32 ppm (d, $J_{4,5}$= 7 Hz, H_4).

2-Methyl-5,6,7,8-tetrahydroquinoline: (126) (DK-92)

Reaction of 0.42 g (0.005 mol) of 120 with 0.49 g (0.005 mol) of cyclohexanone in the presence of 15 mg of ammonium acetate provided 0.6 g of a brown oil. Analysis by VPC (10 ft x 1/8 in 10% Carbowax 20 M + 5% KOH on Chromsorb W 60/80 at 150°C and 30ml/min showed the presence of a major peak at 9 min retention time. Isolation of this peak by preparative gas chromatography provided 126 as a colorless oil, identified by NMR. NMR ($CDCl_3$) δ 1.82 (m, 4H), 2.5 (s, 3H, -$\underline{CH}_3$), 2.78 (m, 4H), 6.90 (d, $J_{5,4}$= 8 Hz, H_5) and 7.25 ppm (d, $J_{4,5}$= 8Hz, H_4).

2,3-Trimethylene-5,6-dimethylpyridine: (127) (DK-95)

Reaction of 0.5 g (0.005 mol) of 124 with 0.42 g (0.005 mol) of cyclopentanone in the presence of 20 mg of ammonium acetate provided 0.67 g of a dark brown oil, which showed a major peak at 9 min retention time by VPC (10 ft x 1/8 in 10% Carbowax 20 M + 5% KOH on Chromsorb W 60/80 at 150°C and 30ml/min). Isolation of this peak by preparative gas chromatography gave 127 as a colorless oil, identified by NMR. NMR ($CDCl_3$) δ 2.10 (m, 2H), 2.12 (s, 3H, 3-$\underline{CH}_3$), 2.32 (s, 3H, 2-$\underline{CH}_3$), 2.9 (m, 4H), 7.02 ppm (s, ArH_4).

3,4-Trimethylenepyridine: (76) (DK-154)

The procedure of Eisch and Russo[48a] was followed. To a mixture of 1.34 g (.005 mol) of magnesium metal in 25 ml of

dry THF was added over one hour a solution of 7.80 g (.05 mol) of γ-(3-pyridyl)propyl chloride[48b] in 60 ml of dry THF. The reaction mixture was stirred vigorously and heated with a heat gun at five minute intervals during addition. After stirring for 20 hours at 25°C, hydrolysis was carried out by the addition of 7.8 ml of saturated ammonium chloride solution with vigorous stirring. The mixture was suction filtered and the salts washed well with THF. The filtrate was dried over K_2CO_3, filtered again, and the solvent evaporated to yield 4.0 g of liquid which showed three peaks in the ratio of 7:1:2 by VPC (10 ft x 1/8 in 10% Carbowax 20 M + 10% KOH on Chromsorb W 60/80 at 150°C and 30 ml/min). This material was distilled into four fractions, b.p. 40-90°C (8 mm). The fourth fraction weighed 0.80 g and contained 50% of the longest retention time peak. This peak was isolated by preparative gas chromatography and shown to be 3,4-trimethylenepyridine: NMR ($CDCl_3$) δ 8.44 (s, H_2), 8.33 (d, H_6, $J_{6,5}$= 4.9 Hz), 7.14 (d, H_5, $J_{5,6}$= 4.9 Hz), 2.91 (two overlapping triplets, 4H), and 2.10 ppm (quintet, 2H); IR (thin film) 3040, 2960, 2855, 1605, 1577, 1491, 1430, 1180, 827 and 721 cm^{-1}.

5,6,7,8-Tetrahydroiosquinoline: (24) (DK-159)

The procedure of Vierhapper and Eliel[28] was followed. To a solution of 2.15 g (16.6mmol) of iosquinoline (refluxed over Raney-nickel, filtered, and distilled) dissolved in 15 ml of ice cold trifluoroacetic acid was added 250 mg of platinum oxide and the mixture was hydrogenated at 50 psi. After two

equivalents of hydrogen had been absorbed the solution was filtered, diluted with 20 ml of water, and carefully made basic with 50% NaOH. The basic solution was extracted with ether, the ether extracts dried over KOH, and the solvent evaporated to yield 1.50 g (68%) of a colorless liquid, b.p. 68-71°C (1.5 mm). VPC analysis (10 ft x 1/8 in 10% Carbowax 20 M and 10% KOH on Chromsorb W 60/80 at 145°C and 30ml/min) showed the presence of 10% unreduced quinoline. Final purification could be effected only by preparative VPC: NMR ($CDCl_3$) δ 8.31 (d, H_2, $J_{2,3}$= 4.8 Hz), 7.31 (d,H_4, $J_{4,3}$= 7.5 Hz), 6.98 (d of d, H_3, $J_{3,4}$= 7.5 Hz, $J_{3,2}$= 4.8 Hz), 2.89 (t, 2H, H_8), 2.73 (t, 2H, H_5) and 1.8 ppm (m, 4H); IR (thin film) 3028, 2940, 2868, 1608, 1570, 1440, 1420, 1295, 830 and 720 cm^{-1}.

Meta-Bis-Annelated Pyridines were prepared by the method of Chichibabin[45]. A mixture of the ketone (or ketones), ammonium acetate, 38% aqueous formaldehyde, and 28% ammonium hydroxide was heated at 150-200°C for 8-15 hours. The reaction mixture was cooled and extracted four times with ether. The combined ether extracts were then extracted four times with 10% HCl. The acidic solution was cooled in ice, made basic with sodium hydroxide pellets, and extracted four times with ether. The ether extracts were dried over sodium sulfate, filtered, and the solvent evaporated to provide a dark oil which was fractionally distilled. Further purification was effected by column chromatography or preparative VPC.

1,2,3,4,7,8,9,10-Octahydrophenanthridine: (63) (DK-126)

A mixture of 49 g (.5 mol) of cyclohexanone, 75 g ammonium acetate, 40 g 38% aqueous formaldehyde, and 13 ml 28% ammonium hydroxide was heated at 180-200°C overnight and worked up in the manner described above. Distillation provided 25 g (54%) of 63 b.p. 110°C (0.5 mm). VPC analysis (10 ft x 1/8 in 10% Carbowax 20 M and 10% KOH on Chromsorb W 60/80 mesh at 150°C and 30ml/min) showed this material to be 98% of a single component: NMR ($CDCl_3$) δ 8.06 (s, Ar-H), 2.85-2.50 (four overlapping triplets, 8H) and 1.79 ppm (m, 8H); IR (thin film) 2940, 2870, 1592, 1470, 1415, 1325, 1250, 932, 830 and 730 cm^{-1}.

2,3:4,5-Di(trimethylene)pyridine: (178) (DK-128)

A mixture of 50 g (.595 mol) of cyclopentanone, 60 g of glacial acetic acid (in place of ammonium acetate), 22g of 38% aqueous formaldehyde and 55 g of 28% ammonium hydroxide was heated at 180-200°C overnight and worked up in the manner described above. Fractional distillation provided a small amount of material, b.p. 93-94°C (.3 mm), which VPC analysis (10 ft x 1/8 in 10% Carbowax 20 M on Chromsorb W 60/80 at 150°C and 30ml/min) showed to be contaminated by the symmetrical isomer 177. Chromatography on silica gel, eluting with ether-petroleum ether (2:3), provided 20 mg of pure 177 (m.p. 84-85°C) and 0.66 g of 178 as a colorless oil (pure by VPC). NMR ($CDCl_3$) δ 8.18 (s, ArH), 2.95-2.70 (four overlapping triplets, 8H), 2.08 (quintet, 2H) and 2.05 ppm

(quintet, 2H); IR (thin film) 2950, 2850, 1617, 1580, 1470, 1440, 1395 and 750 cm^{-1}.

3,4-Trimethylene-5,6,7,8-Tetrahydroquinoline: (179) and 3,4-Trimethylene-5,6,7,8-Tetrahydroisoquinoline: (180) (DK-162)

A mixture of 49 g (0.5 mol) of cyclohexanone, 42 g (0.5 mol) of cyclopentanone, 75 g of ammonium acetate, 40 g of 38% aqueous formaldehyde, and 11.5 g of 28% ammonium hydroxide was heated overnight at 200°C and worked up in the manner described above. Simple distillation provided 15 g of material which was carefully fractionated to provide 2.37 g of a mixture of bis-annelated pyridines, b.p. 108-110°C (0.4 mm). This fraction was chromatographed on silica gel, eluting with ether-petroleum ether (2:3), to provide 1.33 g of material which showed only two peaks in the ratio 74:26 by VPC (10 ft x 1/8 in in 10% Carbowax 20 M and 10% KOH on Chromsorb W 60/80 at 150°C and 30ml/min). Both peaks were isolated pure by preparative VPC and structural assignments were made based on ^{1}H and ^{13}C NMR as described in the text. The major peak was assigned as 179: NMR ($CDCl_3$) δ 8.22 (s, Ar-H), 3.0-2.5 (four overlapping triplets, 8H, Ar-CH_2-) 2.07 (quintet, 2H), and 1.83 ppm (m, 4H); IR (thin film) 2940, 2870, 1604, 1581, 1470, 1412, 1199, 925, 887, and 830 cm^{-1}. The minor peak was assigned as 180: NMR ($CDCl_3$) δ 8.06 (s, Ar-H), 3.0-2.6 (four overlapping triplets, 8H, Ar-CH_2-), 2.09 (quintet, 2H), and 1.80 ppm (m, 4H); IR (thin film) 2870, 2830, 1600, 1573, 1481, 1440, 1402, 928 and 820 cm^{-1}.

2,3,4,5-Tetramethylpyridine: (181) (DK-156)

A mixture of 36 g (0.5 mol) of 2-butanone, 20 g of 38% aqueous formaldehyde, 37.5 g of ammonium acetate and 6 ml of 28% ammonium hydroxide was heated at 150°C overnight and worked up in the manner described above. Fractional distillation provided 3.5 g of material, b.p. 70-76°C (5 mm) which showed one major peak by VPC (10 ft x 1/8 in 10% Carbowax 20 M and 10% KOH on Chromsorb W 60/80 at 148°C and 30ml/min). Further purification by chromatography on silica gel, eluting with ether (2:3), provided pure 181 as a colorless liquid. NMR ($CDCl_3$) δ 8.04 (s, Ar-H), 2.45 (s, 3H) and 2.15 ppm (broad s, 9H); IR (thin film) 2988, 2940, 2920, 1590, 1450, 1395, 1210, 1005, 750 and 730 cm^{-1}.

2,3,5,6-Tetramethylpyridine: (182) (DK-158)

The procedure of Tsuda and coworkers[83] was followed. Reduction of 2,6-dimethyl-3,5-dicarbethoxypyridine[29] with lithium aluminum hydride provided the corresponding diol which was converted to the dichloride with thionyl chloride. Catalytic hydrogenation of the dichloride provided 16, m.p. 76-77°C, lit.[83] m.p. 76°C. NMR ($CDCl_3$) δ 7.10 (s, Ar-H), 2.41 (s, 6H) and 2.18 ppm (s, 6H); IR (KBr) 2930, 2865, 1610, 1440, 1260, 1022, 800 and 733 cm^{-1}.

Dioxo-2,2'-di(cyclopentyl)-methane[44] (61a) (DK-116)

A mixture of 38.25 g (0.25 mol) the morpholine enamine of cyclopentanone, 3.8 g (0.12 mol) of paraformaldehyde and

5 ml of dioxane was heated under nitrogen at 155°C for 8 hours. The reaction mixture was cooled and acidified with 5N HCl. The aqueous layer was extracted four times with benzene and the combined benzene extracts were washed with dilute sodium bicarbonate solution and then with water. The benzene layer was dried over sodium sulfate and concentrated *in vacuo* to a yellow oil, which was fractionally distilled under vacuum to provide 3.51 g (17%) of a light yellow semisolid, b.p. 110-112°C (0.7 mm); lit.[44] b.p. 160°C (11 mm).

Dioxo-2,2'-di(cyclohexyl)-methane:[44] (61b) (DK-121)

Following the above procedure, (61b) was prepared in 14% yield from the morpholine enamine of cyclohexanone and paraformaldehyde: b.p. 125-130°C (0.5 mm); lit.[44] b.p. 186°C (11mm).

2,3,5,6-Di(trimethylene)pyridine:[43] (177) (DK-117)

A mixture of 2.5 g (0.014 mol) of Dioxo-2,2'-di(cyclopentyl)methane[44] 61a and 2.5 g of ammonium acetate in 10 ml of glacial acetic acid was refluxed for .75 hour. The solution was cooled and then made basic with 50% sodium hydroxide. The basic solution was extracted four times with 30 ml portions of ether and the combined ether extracts were dried over sodium sulfate. The removal of ether provided 1.83 g (83%) of a crystalline solid, which was identified as 177, m.p. 86-87°C, lit.[43] m.p. 87°C; NMR ($CDCl_3$) δ 2.10 (quintet, 4H), 2.87 (t, 4H), 2.95 (t, 4H) and 7.30 ppm (s, ArH); IR (thin film) 2950, 2850, 1605, 1570, 1442, 1415, 1305, 1230, 1215 and 730 cm^{-1}.

1,2,3,4,5,6,7,8-Octahydro acridine:[43] (17) (DK-122)

A mixture of 2.5 g (0.011 mol) of Dioxo-2,2'-di(cyclohexyl)-methane[44] (61b) and 2.5 g of ammonium acetate in 10 ml of glacial acetic acid was refluxed for 1.5 hours. The reaction mixture was cooled, made basic with 50% sodium hydroxide solution and extracted four times with ether. The combined ether extracts were dried over magnesium sulfate. The removal of ether gave a brown oil, which was distilled under reduced pressure to yield 2.05 g of a light yellow solid, b.p. 98-99°C (0.5 mm). Recrystallization from petroleum ether provided 2.0 g (97%) of a light yellow solid, m.p. 69-70°C, which was identified as 17, lit.[43] m.p. 72.5°C; NMR ($CDCl_3$) δ 1.85 (m, 8H), 2.70 (t, 4H), 2.85 (t, 4H) and 7.02 ppm (s, ArH); IR (thin film) 2930, 2860, 1660, 1640, 1607, 1450, 1250, 985, 936, 820 and 710 cm^{-1}; UV (95% EtOH) 290.5 (ε 3979), 285.5 (ε 5073), 281 (ε 5521) and 276 nm (ε 4625).

1-Cyclopentenecarboxaldehyde: (129) (DK-203)

1-cyclopentenecarboxaldehyde was prepared by either one of these procedures.

Procedure I:[65a] A mixture of 25 g of anhydrous potassium carbonate, 10.6 g (0.09 mol) of 1,2-cyclohexanediol in 125 ml of dry benzene was vigorously stirred. To this stirring mixture, 38 g (0.085 mol) of lead tetraacetate was added over a period of one hour. A nitrogen atmosphere was maintained during the addition. After stirring for another hour, the salts were removed by filtration and thoroughly extracted

with benzene. The combined filtrates were dried over sodium sulfate and the benzene removed on a rotary evaporator. Distillation of the residue afforded 6.3 g (64%) of colorless adipic aldehyde b.p. 70-71°C (3 mm); lit.[65a] b.p. 68-70°C (3 mm); NMR ($CDCl_3$) δ 1.65 (m, 4H), 2.5 (m, 4H) and 9.95 ppm (s, $-\overset{O}{\overset{\|}{C}}-\underline{H}$).

Five grams of freshly distilled adipic aldehyde was heated with 35 ml of water at 110°C in a sealed tube for five hours. After cooling, the reaction mixture was extracted five times with ether and the product isolated by distillation affording 1.5 g (38%) of 1-cyclopentenecarboxaldehyde, b.p. 57-59°C;(23 mm) lit.[65a] b.p. 57-59°C (23 mm); NMR ($CDCl_3$) δ 2.02 (q, J = 7Hz, 2H), 2.46 (m, 4H), 6.9 (broad s, olefinic H) and 9.72 (s, $-\overset{O}{\overset{\|}{C}}-\underline{H}$); IR (thin film) 1680 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-$).

Procedure II:[65b]

To a stirring solution of 20 g of potassium periodate and 4 ml of concentrated nitric acid in 180 ml of water, 50% sodium hydroxide was added dropwise until a pH of 4 was attained. To this solution, 10 g (0.09 mol) of 1,2-cyclohexanediol was added in one portion. After stirring for 25 min, 25 ml of ether and 21 ml of aqueous potassium hydroxide was added and the mixture stirred for another 30 minutes. The layers were separated and the aqueous layer was extracted five times with ether. The combined ether extracts were dried over sodium sulfate. Removal of the solvent, followed by distillation, afforded 4.5 g (58%) of 1-cyclopentenecarboxaldehyde, b.p. 57-60°C (23 mm); lit.[65a] b.p. 57-60°C (23 mm).

6-Ethoxy-3,4-trimethylene-5,6-dihydropyran: (130) (DK-214)

A mixture of 1 g (0.01 mol) of 1-cyclopentenecarboxaldehyde,[14,15] 3 ml of ethyl vinyl ether and a catalytic amount of hydroquinone was heated in a steel bomb at 220°C for 18 hours. After cooling, the dark brown liquid was distilled to afford 0.85 g (50%) of a colorless oil, b.p. 40-41°C (9 mm): NMR ($CDCl_3$) δ 1.13 (t, 3H), 1.70 (t, 2H), 2.20 (m, 2H), 3.63 (m, 4H), 5.0 (s, 1H) and 6.05 ppm (broad s, 1H).

2,3-Trimethyleneglutaraldehyde: (131) (DK-218)

A mixture of 10 ml of water, 0.8 ml of concentrated hydrochloric acid and 0.5 g (0.003 mol) of 6-ethoxy-3,4-trimethylene-5,6-dihydropyran (130) was stirred for one hour. The solution was neutralized with aqueous sodium bicarbonate, saturated with sodium chloride, and extracted twice with ether. Removal of ether from the dried extract afforded 0.4 g (95%) of an oil. IR (thin film) 1690 and 1730 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-H$).

3,4-Trimethylenepyridine from 2,3-trimethyleneglutaraldehyde: (76) (DK-219)

To a stirring suspension of 1 g of hydroxylamine hydrochloride in 5 ml of glacial acetic acid, 0.4 g (0.0029 mol) of 2,3-trimethyleneglutaraldehyde (131) was added in one portion. After heating at 100°C for four hours, the reaction mixture was cooled and made basic with aqueous sodium hydroxide. The basic mixture was extracted four times with 30 ml portions of ether. The combined extracts were dried over

sodium sulfate and filtered. The removal of ether provided 0.16 g of an oil, which was analyzed by VPC (10 ft x 1/8 in 10% Carbowax 20 M + 5% KOH on Chromsorb W at 150°C and 30ml/min) and the major peak (50%) was collected by preparative gas chromatography and shown to be 3,4-trimethylenepyridine: NMR ($CDCl_3$) δ 2.10 (quintet, 2H), 2.91 (two overlapping triplets, 4H), 7.14 (d, H_5, $J_{5,6}$= 4.9 Hz), 8.33 (d, H_6, $J_{6,5}$= 4.9 Hz) and 8.44 ppm (s, H_2).

Methyl-1,4-Dioxaspiro[4,4]-nonane-6-carboxylate: (134) (DK-205)

A mixture of 14.2 g (0.1 mol) of 2-oxocyclopentanecarboxylate (133), 6.2 g (0.1 mol) of ethylene glycol and 0.5 g of p-toluenesulfonic acid in 250 ml of dry benzene was refluxed until 0.1 mol of water was collected in Dean-Stark trap. The benzene was removed under vacuum and the residue taken up in ether. The ether solution was washed with 15% aqueous sodium hydroxide and then with brine. The ether solution was dried over magnesium sulfate and the ether removed on a rotary evaporator. Distillation of the residue afforded 9.75g (52%) of a colorless oil, b.p. 60-61°C (0.2 mm); NMR ($CDCl_3$) δ 1.85 (m, 6H), 2.90 (t, J= 7Hz, tert H), 3.64 (s, 3H, $\overset{O}{\overset{\|}{C}}-O\,\underline{CH_3}$) and 3.92 ppm (t, J = 3 Hz, 4H); IR (thin film) 1742 cm^{-1} ($-\overset{O}{\overset{\|}{C}}-O-$).

6-Hydroxymethyl-1,4-dioxaspiro[4,4]-nonane: (135) (DK-206)

To a rapidly stirring suspension of 1.52 g (0.04 mol) of lithium aluminum hydride in 200 ml of THF, 9.3 g (0.05 mol)

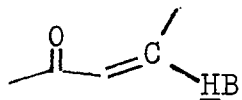
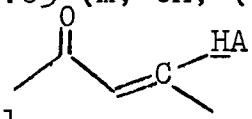
of 134 was added dropwise at room temperature. The mixture was then heated to reflux for six hours and then allowed to stir overnight at room temperature. Water, 1.50 ml, was added dropwise, followed by the addition of 1.50 ml of 15% sodium hydroxide and 4.5 ml of water respectively. The mixture was stirred for an additional hour, and then filtered. The solids were washed with 100 ml of THF and the combined filtrates concentrated *in vacuo* to give an oil which was distilled to give 6.4 g (81%) of a colorless oil; IR (thin film) 3420 cm^{-1} (-OH) and the region 1600-1800 cm^{-1} showed no absorptions.

2-Hydroxymethylcyclopentanone: (136) (DK-207)

A solution of 3 g (0.019 mol) of 135 in 50 ml of acetone containing 0.20 g of p-toluenesulfonic acid was refluxed overnight. The acetone was removed on a rotary evaporator and the residue was distilled to provide 1.15 g (53%) of a colorless oil, b.p. 75-76°C (0.6 mm); lit.[98] b.p. 100-120°C (8 mm).

2-Methylenecyclopentanone: (137) (DK-209)

A mixture of 1 g (0.009 mol) of 136, 1.8 g of dicyclohexylcarbodiimide (DCC) and 10 mg of cuprous chloride in 50 ml of ether was refluxed for three hours. The precipitate was removed by filtration and the filtrate concentrated to an oil, which was distilled to give 0.25 g (33%) of a colorless oil, b.p. 25-30°C (0.2 mm); lit.[68] b.p. 25-30°C (0.2mm); NMR (CCl_4)

δ 1.75-2.65 (m, 6H, $(CH_2)_2$, 5.15 (s, ) and 5.73 ppm (s, ); IR (thin film) 1735 (s, -C-) and 1620 cm^{-1} (m, C = C).

Condensation of Ethyl-2-oxo-cyclohexane carboxylate with cyano acetic ester:[70] (139) (DK-254)

A mixture of 25.5 g (0.15 mol) of ethyl-2-oxo-cyclohexane carboxylate (138), 17 g (0.15 mol) of cyano acetic ester, 2.3 g of ammonium acetate and 7.2 g of glacial acetic acid in 300 ml of benzene was refluxed at 160°C until one equivalent (2.7 ml) of water was collected in a Dean-Stark trap. The reaction mixture was refluxed for an additional hour, cooled,and the benzene was evaporated on a rotary evaporator. The residue was taken up in 150 ml of ether and washed first with a saturated solution of sodium carbonate and then with water. The ether solution was dried over magnesium sulfate, filtered and the ether evaporated. Distillation of the residue provided 22 g (55%) of a liquid, b.p. 150-152°C (0.3 mm), lit.[70] b.p. 160-170°C (1 mm), identified as 139 by NMR; NMR ($CDCl_3$) δ 4.26 (overlapping q, 4H, $-\overset{O}{\overset{\|}{C}}O-CH_2$, J = 8Hz), 2.45 (m, 4H), 1.65 (m, 4H) and 1.32 ppm (overlapping t, 6H, J = 5 Hz).

2-Carboxy-cyclohexene-1-acetic acid:[70] (140) (DK-255)

A solution of 22 g (0.08 mol) of 139[30] in 100 ml of concentrated hydrochloric acid was refluxed with stirring for six hours, after which 25 ml of concentrated hydrochloric acid was added and the refluxing continued for another two

hours. The reaction mixture was cooled and then filtered. The crystalline solid was washed with water and then dried under vacuum to yield 10 g (54%) of a white crystalline solid m.p. 170°C, lit.[70] m.p. 165°C.

1,3-Dihydroxy-5,6,7,8-tetrahydro-isoquinoline:[70] (141) (DK-256)

In a 100 ml round bottomed flask, 9 g (0.048 mol) of 140 and 16 g of ammonium carbonate were thoroughly mixed. A distillation stillhead was attached to the reaction flask, which was immersed in an oil bath up to the neck. The reaction mixture was slowly heated to 230°C. Above 140°C, a blue liquid distilled along with the sublimation of a small amount of ammonium carbonate. Above 180°C, the reaction mixture melted with the vigorous evolution of ammonia gas. The heating was stopped when no more ammonia was evolved. The reaction mixture was cooled and the crude reaction product was recrystallized from 70% acetic acid , m.p. 204-205°C, lit.[70] m.p. 205°C; yield 7 g (87%).

1,3-Dichloro-5,6,7,8-tetrahydro-isoquinoline:[30] (142) (DK-257)

A mixture of 3 g (0.018 mol) of Dihydroxy compound 141 and 6 g of phosphorus trichloride was heated in a steel bomb (with a glass liner) at 200°C for three hours. After cooling, the reaction mixture was poured onto ice and the light brown solid was collected by filtration. Recrystallization from ethanol afforded 3 g (82%) of a light brown solid, m.p. 86-87°C, lit.[70] m.p. 87°C, NMR ($CDCl_3$) δ 1.84 (m, 4H, $-CH_2-CH_2$),

2.7 (m, 4H, benzylic-CH_2-) and 6.95 ppm (s, ArH).

5,6,7,8-Tetrahydro isoquinoline: (24) (DK-259)

In a 50 ml erlenemeyer flask were placed 1 g (0.005 mol) of 142, 0.82 g (0.01 mol) of powdered anhydrous sodium acetate and 20 ml of glacial acetic acid. The mixture was heated to about 70°C and shaken until solution was complete. The solution was transferred to a pressure bottle and 0.28 g of 5% Palladium on charcoal added to it. The mixture was hydrogenated at 30 psi and 50°C. Hydrogen absorption was rapid during the first 15 minutes and then gradually slackened; the theoretical amount was absorbed in two hours. The warm acid solution was separated from the catalyst by filtration through a 1-to 2- mm layer of Norit on a Buchner funnel. The acetic acid was removed on a rotary evaporator and the residue dissolved in 20 ml of water. The aqueous solution was made basic with 50% sodium hydroxide and extracted with three 50 ml portions of ether. The combined ether extracts were dried over potassium carbonate and the ether was removed. Distillation of the residue afforded 0.62 g (93%) of a colorless oil, b.p. 68-70°C (1.5 mm), identified as 24 by NMR ($CDCl_3$) δ 1.8 (m, 4H), 2.73 (t, 2H, H_5), 2.89 (t, 2H, H_8), 6.98 (d of d, H_3, $J_{3,4}$= 7.5 Hz, $J_{3,2}$= 4.8 Hz), 7.31 (d, H_4, $J_{4,3}$= 7.5 Hz) and 8.3 ppm (d, H_2, $J_{2,3}$ = 4.8 Hz).

Methyl-2,2-diethoxy-cyclobutane-1-carboxylate: (143) (DK-174)

It was prepared in 60% yield by the procedure of

Brannock[72] from 2,2-diethoxyethylene[71] and methyl acrylate, b.p. 55°C (0.3 mm); lit.[72] b.p. 52-53°C (0.8-1 mm).

2.2-Diethoxy-1-hydroxymethyl cyclobutane: (144) (DK-175)

To a rapidly stirring suspension of 1.14 g (0.03 mol) lithium aluminum hydride in 100 ml of dry tetrahydrofuran under nitrogen, 6.1 g (0.031 mol) of methyl-2,2-diethoxy-cyclobutane-1-carboxylate[72] (143) was added dropwise. The mixture was refluxed for 8 hours and then allowed to stir at room temperature overnight. The salts were hydrolyzed by the addition of 1.14 ml of water, 1.14 ml of 15% aqueous sodium hydroxide and 3.5 ml of water respectively. The reaction mixture was stirred for another hour, followed by filtration to remove salts. The filtrate was dried over magnesium sulfate, followed by the removal of the solvent. Distillation of the residue afforded 3.9 g (75%) of a colorless liquid, b.p. 49-50°C (0.1 mm); lit.[95] b.p. 61°C (0.8 mm); NMR (CCl_4) δ 1.19 (overlapping t, J=7.5 Hz, 6H), 1.65-2.35 (m, 4H, ring-CH_2), 3.1 (s, OH), 3.50 (overlapping q, J = 7.5 Hz) and 3.62 ppm (broad, 2H, -CH_2); IR (thin film) 3460 (OH), 3010-2880 (C-H), 1449, 1395, 1320, 1270-950 (C-O-C), 908 and 852 cm^{-1}.

2-Hydroxymethyl cyclobutanone:[96] (145) (DK-181)

A solution of 5 g (0.029 mol) of 2,2-Diethoxy-1-hydroxy-methyl cyclobutane (144) in 150 ml of dry acetone containing a catalytic amount of p-toluenesulfonic acid was refluxed for 24 hours. The acetone was removed on a rotary evaporator and

the residue was taken up in ether. The ether solution was washed with 5% aqueous sodium bicarbonate solution and then with brine. The ether solution was dried over magnesium sulfate and concentrated in vacuo to an oil, which was distilled to provide 2.90 g (98%) of a colorless oil; b.p. 114-115°C (15 mm); IR (thin film) 3430 (s, -OH), 2950-2880 (C-H) and 1775 cm^{-1} (s, $-\overset{O}{\overset{\|}{C}}-$); NMR ($CCl_4$) δ 2.0 (m, 4H, ring $-CH_2$), 2.92 (t, 2H, -OH and tert ring H) and 3.5 ppm (m, $-CH_2OH$).

2-Formylcyclobutanone: (146) (DK-182)

Chromium trioxide, 7 g (70mmol), was added to a magnetically stirred solution of 11.7 g (40mmol) of pyridine in 150 ml of dry methylene chloride. The deep burgandy solution was stirred for 15 minutes under an atmosphere of nitrogen. A solution of 0.7 g (7mmol) of 2-hydroxymethyl cyclobutanone (145) in 15 ml of methylene chloride was added in one portion. A tarry black precipitate separated immediately. After stirring for 15 minutes at room temperature, the solution was decanted from the solids, which were washed with 200 ml of ether. The combined organic solutions were washed successively with 100 ml portions of 5% aqueous sodium hydroxide, 5% aqueous hydrochloric acid, 5% aqueous sodium bicarbonate solution and saturated sodium chloride solution. The organic solution was dried over magnesium sulfate and the solvent removed on a rotary evaporator to provide 0.40 g (59%) of a light yellow oil, IR (thin film) 2860-2940 (-C-H), 1775 (s, $-\overset{O}{\overset{\|}{C}}-$) and 1745 (s, $-\overset{O}{\overset{\|}{C}}-H$) cm^{-1}. The -OH region showed no absorption.

7,7-Dichlorobicyclo-[3,2,0]-hept-2-ene-6-one: (149) (DK-191)

Was prepared in 85% yield by the procedure of Grieco[73] from cyclopentadiene, dichloroacetyl chloride and triethylamine; b.p. 49-50°C (3 mm); lit.[73] b.p. 49-50°C (3 mm); NMR (CCl_4) δ 2.70 (m, 2H, $-CH_2-$), 4.10 (m, 2H, bridgehead), 5.90 (m, 2H, CH=CH); IR (thin film) 1805 (>C=O) and 1608 cm^{-1} (C=C).

Bicyclo-[3,2,0]-hept-2-ene-6-one:[73] (150) (DK-192)

To a vigorously stirred suspension of 11 g of zinc dust in 15 ml of glacial acetic acid at room temperature was added dropwise 5 g (0.028 mol) of 7,7-dichlorobicyclo-[3,2,0]-hept-2-ene-6-one (149) in 5 ml of glacial acetic acid. After the addition was complete the temperature of the reaction mixture was raised to 70°C and maintained for forty minutes. The reaction mixture was cooled, diluted with 150 ml of ether and then filtered. The filtrate was washed with saturated sodium bicarbonate solution to remove acetic acid and then with brine. The ether solution was dried over magnesium sulfate. Removal of the ether followed by distillation afforded 2.5 g (82%) of a colorless oil, b.p. 65-66°C (16 mm); lit.[73] b.p. 60°C (~15 mm); NMR (CCl_4) δ 2.4-2.9 (3H, m), 3.0-3.6 (m, 2H), 3.6-4.0 (m, 1H) and 5.80 ppm (broad s, 1H); IR (thin film) 1778 cm^{-1} (>C=O).

Bicyclo-[3,2,0]-hept-2-ene: (151) (DK-229)

A solution of 3.6 g (0.162 mol) of sodium in 50 ml of triethylene glycol was heated under a nitrogen atmosphere.

When the temperature reached 130°C, 9 g (0.054 mol) of the semicarbazone of bicyclo-[3,2,0]-hept-2-ene-6-one (150) was added in one portion and the temperature raised to 200°C at which point a distillation stillhead was attached at the top of the condenser. A slow stream of nitrogen was passed through the reaction mixture and volatile materials collected in a dry-ice cooled receiver during a period of two hours. The crude product thus obtained was distilled through a small vigreux column to provide 3.3 g (65%) of a colorless oil, b.p. 72-90°C (760 mm); NMR ($CDCl_3$) δ 1.65-3.15 (8H) and 5.72 ppm (s, 2H, olefinic protons); IR (thin film) 3050, 2970-2910, 2840, 1480 (w), 1350, 1050, 925 and 720 cm^{-1}.

2-Methyl-3-ethylnicotinate: (154a) (DK-241)

Was prepared in 50% yield by the procedure of Tsuda[102] from ethyl-3-amino crotonate and acrolein: b.p. 65-70°C (1 mm); lit.[102] b.p. 107°C (13 mm).

2-Methyl-3-hydroxymethylpyridine:[103] (154b) (DK-242)

To a stirring suspension of 2.5 g (0.066 mol) of lithium aluminum hydride in 100 ml of ether, 10 g (0.06 mol) of 2-methyl-3-ethylnicotinate (153a) was added under nitrogen at ice bath temperature. After the addition was complete, the mixture was refluxed for 3 hours, cooled, and hydrolyzed by the addition of 7.5 ml of water. The salts were removed by filtration and washed with ether. The combined filtrates were dried over magnesium sulfate and the ether was removed

on a rotary evaporator to yield a light yellow oil, which was distilled to provide 3.85 g (46%) of a colorless oil, b.p. 95-96°C (0.6 mm); lit.[103] b.p. 138-140°C (9 mm); NMR ($CDCl_3$) δ 2.41 (s, 3H), 4.62 (s, 2H, $-C\underline{H}_2-OH$), 6.14 (broad s, OH), 7.01 (dd, $J_{5,6}$= 5 Hz, $J_{4,5}$= 3 Hz, H_5), 7.7 (d, J = 8 Hz, H_4) and 8.15 ppm (d, J = 5 Hz, H_6).

Tosylate of 3-Hydroxymethylpyridine: (154c) (DK-243)

A mixture of 1.2 g (0.025 mol) of sodium hydride and 2.75 g (0.025 mol) of 3-hydroxymethylpyridine in 30 ml of ether was stirred at 0°C for 2 hours. The reaction mixture was cooled to -40°C and a solution of 4.75 g (0.025 mol) of recrystallized p-toluenesulfonyl chloride in 25 ml of ether was added dropwise. The temperature of the reaction mixture was maintained at -40°C for five more hours, it was then filtered and the filtrate was cooled to -70°C and kept at this temperature for two hours. A white crystalline solid separated which was removed by filtration to provide 1.30 g (20%) of 154c, m.p. 45-46°C; NMR ($CDCl_3$) δ 2.40 (s, 3H, $-CH_3$), 5.02 (s, 2H, $-CH_2-$) 7.25-8.50 (8H, aromatic protons).

Tosylate of 2-methyl-3-hydroxymethylpyridine: (153a) (DK-244)

Following the above procedure 153a was prepared in 5% yield from 2-methyl-3-hydroxymethylpyridine (154b), m.p. 93-94°C; NMR ($CDCl_3$) δ 2.42 (s, 6H, two-CH_3 gps), 5.06 (s, 2H, $-CH_2-$) and 7.3-8.45 ppm (7H, aromatic protons).

3-Methyl-2-methoxymethylpyridine (156) and 2-Methyl-3-methoxymethylpyridine:(153b) (DK-50)

In a dry 250 ml round bottomed flask was placed 2.5 g (0.023 mol) of 2,3-lutidine and 4.2 g (0.028 mol) of N-bromosuccinimide in 100 ml of carbon tetrachloride. The mixture was refluxed for four hours and then filtered hot. The filtrate was cooled and filtered again to remove precipitated succinimide. The solvent was removed until about 10 ml of the solution was left. This solution of brominated products was used without any further purification.

To a stirring solution of 2 g (~0.03 mol) of sodium-ethoxide in 20 ml of absolute ethanol, the above solution of brominated lutidine was added dropwise. The mixture was stirred for thirty minutes, hydrolyzed with water and then extracted four times with 30 ml portions of ether. The combined ether extracts were dried over potassium carbonate and filtered. Evaporation of ether provided an oil which was distilled under vacuum to provide 1.75 g of a colorless oil, the analysis by VPC on a 1/8" x 15' 10% Carbowax 20 M on Chromsorb W at 110°C, showed the presence of two peaks in the ratio (2:3) with retention times of 6.0 and 8.0 minutes respectively. These two peaks were collected by preparative gas chromatography on a 1/4" x 10' 10% Carbowax 20 M at 110°C. The shorter retention time peak was identified as 3-methyl-2-methoxymethylpyridine (156); NMR (CCl_4) δ 2.36 (s, 3H, 3-methyl), 3.28 (s, 3H, -O-CH_3), 4.53 (s, 2H, -CH_2-), 7.0 (d of

d, H_5), 7.37 (d, H_4) and 8.26 ppm (d, H_6). The longer retention time peak was identified as 2-methyl-3-methoxymethylpyridine (153b); NMR (CCl_4) δ 2.5 (s, 3H, 2-methyl), 3.40 (s, 3H, O-$\underline{CH_3}$), 4.43 (s, 2H, -CH_2-), 7.06 (d of d, H_5), 7.63 (d, H_4) and 8.43 ppm (d, H_6).

2-Methyl-3-ethoxylmethylpyridine (153c) and 3-Methyl-2-ethoxymethylpyridine: (157) (DK-54)

Following the above procedure, the ethyl esters 153c and 157 could be obtained as a mixture in 60 % yield. The separation of the isomers was carried out by preparative VPC on a 1/4" x 10' 10% Carbowax 20 M at 110°C and the structures were confirmed by NMR. Again, shorter retention time isomer was characterized as (157); NMR (CCl_4) δ 1.2 (m, 3H, -$CH_2\underline{CH_3}$), 2.42 (d, J = 4 Hz, -CH_3), 3.50 (m, 2H, O-$\underline{CH_2}CH_3$), 4.57 (s, 2H, -CH_2-), 7.02 (d of d, H_5), 7.39 (d, H_4) and 8.30 ppm (d, H_6). The longer retention time isomer was characterized as 153c; NMR (CCl_4) δ 1.20 (t, J = 7 Hz, 3H), 2.42 (s, 3H, -CH_3), 3.50 (q, 2H , J = 7.5 Hz, $\underline{CH_2}$-CH_3), 4.42 (s, 2H, -CH_2), 6.98 (dd, $J_{5,6}$ = 5 Hz, $J_{4,5}$ = 3 Hz, H_5), 7.32 (d, H_4) and 8.32 ppm (broad, H_6).

Propargyl-4-pyridyl ether-N-oxide: (160) (DK-245)

To 50 ml of propargyl alcohol, cooled with an ice bath and under nitrogen, is added 1.35 g (0.06 mol) of sodium cut into small pieces. When the sodium had dissolved, 7.0 g (0.05 mol) of 4-nitropyridine-N-oxide was added in one portion

and the mixture was refluxed for three hours. The unreacted propargyl alcohol was removed by distillation at 50°C under reduced pressure and the residue was dissolved with conc HCl. The water was removed on the rotary evaporator and the residue was dried under vacuum and digested with two 100 ml portions of chloroform. Evaporation of the chloroform afforded 7.0 g of a yellow solid. This crude material gave a satisfactory NMR; NMR ($CDCl_3$) δ 8.11 (d, 2H, J = 7.5 Hz, H_2 and H_6), 6.87 (d, 2H, J = 7.5 Hz, H_3 and H_5), 4.70 (d, 2H, J = 2.5 Hz, $-CH_2-$) and 2.60 ppm (d, 2H, J = 2.5 Hz, -C≡C-H). The N-oxide proved to be very hygroscopic and thus was used in the next step without further purification.

Propargyl-4-pyridyl ether: (109)

To a mixture of 10 g (0.074 mol) of propargyl-4-pyridyl ether-N-oxide in 125 ml of chloroform at 0°C was added dropwise 20 ml of phosphorous trichloride. After addition was complete, the reaction mixture was allowed to come to room temperature and refluxed for one hour. The mixture was then cooled, poured onto ice, and made basic with concentrated ammonium hydroxide. This solution was extracted with chloroform and the combined extracts dried over potassium carbonate. Evaporation of the solvent yielded a material which was recrystallized from 1:1 chloroform-hexane to give 6.5 g (74%) of propargyl-4-pyridyl ether, m.p. 77-78°C; (lit.[58] m.p. 77-77.5°C).

Cyclobutapyridines: (104, 105) (DK-252)

Vacuum pyrolysis (600°C/ 10^{-2}-10^{-4} mm) of 1-2 g portions of propargyl-4-pyridyl ether according to the method of Trahanovsky afforded ~50% yield of a mixture of 104 and 105. The crude pyrolysis product was first purified by Kugelrohr distillation at 40°C (4-5 mm) after which the two isomers were separated by preparative gas chromatography on a 3/8 in x 15 ft column of Carbowax 20 M and 10% KOH on Chromsorb W 60/80 mesh at 95°C and 100ml/min. The retention times of 104 and 105 were 30 minutes and 34 minutes respectively. The structure of 104 was confirmed by NMR; NMR ($CDCl_3$) δ 3.09 (dd, J 6.3; $-CH_2$), 3.39 (dd, J 6.3; 2-CH_2), 7.10 (dd, J 4,4; H_5), 7.32 (d, J 4; H_4) and 8.39 ppm (d, J 4, H_6). The structure of 105 was also confirmed by NMR; NMR ($CDCl_3$) δ 3.22 (broad, overlapping multiplets, 4H, 3- and 4-CH_2), 6.92 (dd, J = 5 Hz, H_5), 8.16 (s, H_2), and 8.39 ppm (d, J = 5 Hz, H_6).

Pyridine-2,3-dicarboxylic acid dimethyl ester: (163a) (DK-23)

The reaction of pyridine-2,3-dicarboxylic acid with methanol in the presence of concentrated sulfuric acid according to the method of Armarego[91] provided 163a in 86% yield, m.p. 52-53°C, lit.[91] m.p. 57.5°C; NMR ($CDCl_3$) δ 3.9 (s, 3H), 4.0 (s, 3H), 7.5 (dd, $J_{5,6}$= 5 Hz, $J_{5,4}$= 3,5 Hz, H_5), 8.5 (dd, $J_{4,5}$= 8 Hz, $J_{4,6}$= 2 Hz, H_4) and 8.8 ppm (dd, $J_{6,5}$= 5 Hz, $J_{6,4}$= 2 Hz, H_6). IR (KBr) 1772 cm^{-1} (-$\overset{O}{\overset{\|}{C}}$-).

6,7-Dihydropyrido [2,3-d] pyridazine-5,8-dione[90] (164a) (DK-24)

To a solution of 10 g (0.05 mol) of 163a in 50 ml of

methanol, was added 3 g (0.06 mol) of hydrazinehydrate and the reaction mixture was refluxed for one hour. The reaction mixture was cooled and the precipitated yellow solid was collected by filtration. Recrystallization from methanol provided 8.5 g of a yellow solid, m.p. 260 (decomp.) Further purification was realized by sublimation in a thermal gradient sublimer yielding a white crystalline solid m.p. 316-317°C, which was identified as 164a by NMR (DMSO-d_6) δ 7.8 (dd, $J_{5,6}$= 5 Hz, $J_{5,4}$= 3.5 Hz, H_5), 8.5 (dd, $J_{4,5}$= 8 Hz, $J_{4,6}$= 2 Hz, H_4) and 8.9 ppm (dd, $J_{6,5}$= 5 Hz, $J_{6,4}$= 2 Hz, H_6).

6,7-Dihydropyrido [3,4-d] pyridazine-4,7-dione[90] (164b) (DK-36)

Following the above procedure 164b was prepared in 99% yield from dimethyl-3,4-pyridine-dicarboxylate 163b, and hydrazinehydrate, m.p. 364-365°C; NMR (D_2O) δ 7.8 (d, $J_{5,6}$= 5 Hz, H_5), 8.9 (d, $J_{6,5}$ = 5 Hz), and 9.3 ppm (s, H_2).

Pyridine-3,4-dicarboxylic acid dimethyl ester:[91](163b) (DK-35)

This compound was prepared in 100% yield from the reaction of cinchomeronic acid anhydride and methanol in the presence of concentrated sulfuric acid, b.p. 104-105°C (0.8 mm), lit.[91] b.p. 104-105°C (0.8 mm); NMR ($CDCl_3$) δ 3.95 (s, 6H, methyl), 7.6 (d, $J_{5,6}$= 5 Hz, H_5), 8.9 (d, $J_{6,5}$= 5 Hz, H_6) and 9.2 ppm (s, H_2).

Oxidation of 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione with t-butyl hypochlorite in methanol:(163a) (DK-25,33)

To a solution of 0.4 g (2.4mmol) of 164a in 200 ml of

methanol at 0°C, 0.45 g (4.1mmol) of t-butylhypochlorite was added dropwise. After the addition was complete, the reaction mixture was stirred at room temperature for one hour. The solvent was removed and the residue was dissolved in a minimum amount of water. This aqueous solution was made basic with 15% sodium hydroxide solution and extracted three times with 20 ml portions of chloroform. The removal of chloroform from dried extract yielded 0.32 g (67%) of a solid, m.p. 56-57°C, identified as 163a, lit.[92] m.p. 57.5°C; NMR ($CDCl_3$) δ 3.9 (s, 3H), 4.0 (s, 3H), 7.5 (dd, $J_{5,6}$= 5 Hz, $J_{5,4}$= 3.5 Hz, H_5), 8.5 (dd, $J_{4,5}$= 8 Hz, $J_{4,6}$= 2Hz, H_4) and 8.8 ppm (dd, $J_{6,5}$= 5 Hz, $J_{6,4}$= 2 Hz, H_6).

Oxidation of 6,7-Dihydropyrido[3,4-d]pyridine-4,7-dione with t-butylhypochlorite in methanol: (163b) (DK-38)

The oxidation of 6,7-dihydropyrido[3,4-d]pyridazine-4,7-dione[90] with t-butylhypochlorite in methanol was carried out similar to the above procedure yielding pyridine-3,4-dicarboxylic acid dimethyl ester in 49% yield identified by NMR; NMR ($CDCl_3$) δ 3.95 (s, 6H, $-CH_3$), 7.6 (d, J = 5.5 Hz, H_5), 8.9 (d, J = 5 Hz, H_6) and 9.2 ppm (s, H_2); b.p. 104-105°C (0.8 mm), lit.[91] b.p. 104-105°C (0.8 mm).

Oxidation of 6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione with lead tetraacetate in the presence of methanol: (163a) (DK-41)

To a suspension of 0.40 g (2.4mmol) of 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione[90] in 50 ml of methylene

chloride at 0°C, 1.45 g (3.3mmol) of lead tetraacetate was added in one portion, followed by the addition of 0.23 g (0.005 mol) of methanol. The reaction mixture was allowed to stir at room temperature for 2 hours and filtered. The filtrate was made slightly basic with a saturated solution of sodium carbonate, and the basic solution was extracted with three 30 ml portions of chloroform. The combined extracts were dried over magnesium sulfate and the chloroform was removed on a rotary evaporator. The resulting residue 0.34 g (55%) was identified as dimethylpyridine-2,3-dicarboxylate; m.p. 54-55°C, lit.[91] m.p. 56-57°C; IR (KBr) 1772 cm^{-1}(-C-).

7,10-Dihydro-7,10-methanopyridazo[1,2-a]pyrido[2,3-d]pyridazine-5,12-dione:[79] (166a) (DK-37)

It was prepared in 43% yield by the method of Jones,[79] from 6,7-dihydropyrido[2,3-d]pyridazine-5,8-dione lead tetraacetate, and cyclopentadiene, m. p. 226-227°C, lit.[79] m.p. 220°C (decomp.)

7,10-Dihydro-7,10-methanopyridazino[1,2-a]pyrido[3,4-d]-pyridazine-5,12-dione:[79] (166b) (DK-42)

It was prepared according to the procedure of Jones[79] from 6,7-dihydropyrido[3,4-d]pyridazine-5,8-dione in 50% yield, m.p. 227-228°C, lit.[79] m.p. 227 (decomp.).

2-Oxo-cyclohexanecarboxaldehyde: (170) (DK-97)

It was prepared by the procedure of Ainsworth[92] in 70% yield from cyclohexanone and ethyl formate, b.p. 50-51°C, (1.5mm),

lit.[92] b.p. 70-72°C (5 mm); NMR (CCl_4) δ 1.7 (m, 4H), 2.3 (m, 4H) and 8.8 ppm (s, 1H).

4,5,6,7-Tetrahydro-1,2-benzisoxazole: (169) (DK-109)

The general procedure of Johnson[81] was followed. A mixture of 5 g (0.039 mol) of 2-oxo-cyclohexanecarboxaldehyde[92] (170), 6 g (0.086 mol) of powdered hydroxylamine hydrochloride in 52 ml of glacial acetic acid was refluxed at 140°C for 1 hour. The acetic acid was mostly removed under reduced pressure (at 40-50°C), and the residue was diluted with water and extracted with ether. The ether solution was washed with dilute sodium bicarbonate solution to remove acetic acid and any unreacted hydroxymethylene cyclohexanone, and then with water followed by saturated salt solution. Evaporation of dried (over magnesium sulfate) solution afforded 6.3 g of a reddish oil which was distilled to give 3.17 g (64%) of a colorless liquid, b.p. 44-45°C (5 mm) shown to be a mixture of 4,5,6,7-Tetrahydro-1,2-benzisoxazole (169) (77%) and 3,4,5,6-Tetrahydro-1,2-benzisoxazole (167), (23%) by NMR. NMR (CCl_4) δ 1.76 (m, 4H, $(CH_2)_2$). 2.51 (m, 4H, $(CH_2)_2$), 7.92 (s, aromatic H) and 8.06 (s, aromatic H). The signal at 7.92 was assigned to the aromatic proton of 4,5,6,7-Tetrahydro-1,2-benzisoxazole 169, while the one at δ 8.05 was assigned to the aromatic proton in the minor isomer 167.

Ethyl 1,4-Dioxaspiro[4,5]decane-6-carboxylate:[82] (171) (DK-124)

To 5 g (0.03 mol) of ethyl-2-oxo-cyclohexanecarboxylate

(138) dissolved in 100 ml of dry benzene was added 2.5 g (~0.04 mol) of ethylene glycol and 0.20 g of p-toluenesulfonic acid. This mixture was heated to reflux until 0.03 mol of water was collected in a Dean-Stark trap. The benzene was removed on a rotary evaporator and to the residue was added 25 ml of 10% aqueous sodium hydroxide. This mixture was extracted three times with ether, and the combined ether phases were washed with water and then brine. The ether extract was dried over magnesium sulfate and concentrated *in vacuo* to an oil. The oil was distilled to provide 4.07 g (64%) of 171 b.p. 85-86°C (0.1 mm); lit.[82] b.p. 140-142°C (19 mm); NMR (neat) δ 1.2 (t, J = 7 Hz, 3H), 1.65 (m, 8H, $(CH_2)_4$), 2.75 (m, 1H, -CH-COOEt), 3.85 (s, 4H, Ketal) and 4.05 ppm (q, J = 7 Hz, 2H); IR (thin film) gives no evidence for starting material.

6-Hydroxymethyl-1,4-dioxaspiro[4,5]decane:[82] (172) (DK-125,132)

To a rapidly stirring suspension of 4.56 g (0.12 mol) of lithium aluminum hydride in 300 ml of dry tetrahydrofuran was added dropwise 20 g (0.09 mol) of ethyl-1,4-dioxaspiro-[4,5]decane-6-carboxylate at room temperature. The mixture was then heated to reflux for six hours and then allowed to stir overnight at room temperature. Water, 4.5 ml, was added dropwise followed by the addition of 4.5 ml of 15% aqueous sodium hydroxide and 13.5 ml of water. The mixture was stirred for an additional one hour. The solids were filtered and washed with THF and the filtrate was concentrated *in vacuo*

to a colorless oil, which was distilled to give 13.6 g (88%) of a colorless oil, b.p. 74-75°C (0.2 mm); IR (thin film) 3460 cm^{-1} (s, OH) and the carbonyl region (1760-1620 cm^{-1} -C-) showed no absorption.

1,4-Dioxaspiro[4,5]decane-6-carboxaldehyde:[82] (173) (DK-138)

The general oxidation procedure of Ratcliffe and Rodehorst was followed.

Chromium trioxide 15 g (0.15 mol) was added to a mechanically stirred solution of 23.70 g (0.30 mol) of pyridine in 300 ml of dry methylene chloride. The deep burgandy solution was stirred for 15 minutes at room temperature. At the and of this period a solution of 172 in 20 ml of methylene chloride was added in one portion. A tarry black deposit separated immediately. After stirring an additional 15 minutes at room temperature, the solution was decanted from the black solids, which were washed with 200 ml of ether. The combined organic solutions were passed through a short (silica gel-celite) column to remove tars. The clear filtrate was washed with dilute sodium hydroxide, followed by water and then brine. The organic solution was dried over sodium sulfate and concentrated in vacuo to give an oil which was distilled to provide 3.10 g (78%) of a colorless oil, b.p. 56-57°C (0.1 mm), NMR (CCl_4) δ 1.53 [m, 8H, $(CH_2)_4$], 2.33 (m, -CH-CHO), 3.90 (s, 4H, Ketal) and 9.06 ppm (d, J = 1.5 Hz, -C-H); IR (thin film) 2780 (w, -C-H) and 1720 cm^{-1} (O=C-H).

4,5,6,7-Tetrahydro-1,2-benzisoxazole: (169a) (DK-140)

To 34 ml of (1:1) aqueous ethanol was added 1.18 g (0.017 mol) of hydroxylamine hydrochloride, 0.017 g of potassium carbonate, and 2.9 g (0.017 mol) of 1,4-dioxaspiro[4,5]decane-6-carboxaldehyde (173) and the solution was stirred for 6 hours. The solution was acidified with 1N HCl and then heated on a steam bath for 1.5 hours. The solution was then cooled and extracted four times with ether and the combined ether layers were washed once with a small amount of water and then brine. The ether extract was dried over magnesium sulfate and concentrated in vacuo to an oil. The oil was distilled and the fraction of boiling point 71-72°C (4 mm) was retained to afford 1.40 g (67%) of a colorless oil; NMR (CCl_4) δ 7.92 (s, aromatic H), 2.51 (m, $(CH_2)_2$, 4H) and 1.76 ppm (m, $(CH_2)_2$, 4H).

2,3-trimethylenequinoline: (13) (DK-197)

1-cyclopentenecarboxaldehyde (129) 0.5 g (0.005 mol) and 0.6 g (0.006 mol) of aniline were mixed at room temperature in a glass tube. A very exothermic reaction occured and the mixture turned dark brown. The tube was cooled, sealed and kept at 80°C overnight. The tube was cooled again and the reaction mixture thoroughly extracted with ether. The ether solution was dried over sodium carbonate and the ether removed on a rotary evaporator yielding 0.45 g of a brown oil, which was analyzed by VPC (10 ft x 1/8 in 10% Carbowax + 5% KOH on Chromsorb W at 150°C) and the major peak (70%) was collected by preparative gas chromatography and was shown to

be 2,3-trimethylenequinoline by NMR and comparison with an authentic sample[97]; NMR ($CDCl_3$) δ 2.2 (quintet, 2H), 3.15 (q, 4H, benzylic H) and 7.23-8.10 ppm (5H, aromatic protons).

Isoxazole:[104] (119) (DK-87)

A mixture of 82 g (0.05 mol) of 1,1,3,3-tetramethoxy propane, 38 g of hydroxylamine hydrochloride, and 250 ml of water was stirred and warmed (~50°C) until a single phase was formed. The solution was refluxed for 0.5 hour and then distilled until a drop of the distillate gave no precipitate with a saturated cadmium chloride solution. A further purification was realized by treating the distillate with 120 g of cadmium chloride in 75 ml of water, leaving 2 hours in the refrigerator, filtering, washing the precipitate with saturated aqueous cadmium chloride solution, mixing the precipitate with 250 ml of water and then distilling. The fraction boiling from 80-98°C was collected, ammonium sulfate was then added to the isoxazole-H_2O (distillate) layer and the whole redistilled to yield 18 g of colorless liquid, b.p. 90-95°C, lit.[104] b.p. 93-95°C.

1,2,3,4-Tetrahydro-2,3-cyclobutenoquinoline: (193) (DK-187)

A solution of 1.25 g (0.008 mol) of 2,3-cyclobutenoquinoline[19] in 10 ml of cold trifluoroacetic acid was hydrogenated in the presence of platinum oxide (0.12 g) at 40 psi and room temperature. After fifteen minutes, three equivalents of hydrogen was absorbed, and the reaction was stopped. The

catalyst was removed by filtration and the filtrate was diluted with 20 ml of water. The aqueous solution was made basic with 50% sodium hydroxide and extracted four times with ether. The combined ether extracts were dried over sodium sulfate and the removal of the ether afforded 1.10 g of an oil, which was analyzed by TLC. Further purification was realized by column chromatography on a 30 g silica gel column, eluting with (2:3) ether-hexane, resulting in 0.20 g (15%) of a colorless oil, identified as 193 by NMR and mass spectra; NMR ($CDCl_3$) δ 1.45-1.80 (m, 2H, ring-CH_2), 1.92-2.05 (m, 2H, ring-CH_2), 2.45-2.82 (m, 3H, benzylic protons and C-3 bridgehead H), 3.91 (m, 2H, C-2 bridgehead H and N-H), 6.37-6.96 ppm (m, 4H, aromatic H).

2-Azabicyclo[4·2·0]Octane and 3-Azabicyclo[4·2·0]Octane: 191 and 192

To a solution of 0.40 g (3.8 mmol) of a 2:1 mixture of 104 and 105 respectively in 30 ml of methanol was added 20 mg of 10% palladium on charcoal. The mixture was hydrogenated at room temperature and atmospheric pressure for 16 hours after which time VPC analysis (1/8 in x 15 ft 10% Carbowax 20 M + 5% KOH on Chromsorb W 80/100 mesh at 130°C and 30 ml/min) showed the disappearance of peaks at 6.5 and 7.5 min corresponding to 104 and 105 and appearance of two new peaks at 2.3 and 2.6 min. The catalyst was removed by filtration and the methanol was evaporated to yield 0.35 g of an oil from which the two new peaks were isolated pure by preparative VPC. The shorter

retention time peak was identified as 2-azabicyclo[4·2·0]octane (191) by spectral data. NMR (C_6D_6) δ 4.4 (q, J = 7 Hz, bridgehead H at C-2), 2.50-2.96 (m, 2H), 1.86-2.32 (m, 3H), 1.70-1.86 (m, 4H , cyclobutane ring CH_2), 1.25-1.68 (m, 2H), and 1.18 ppm (s, N-H). IR (thin film) 3290, 2940, 2870, 1500, 1320, 1335 cm^{-1}; UV λ_{max} (95% EtOH) 269 (4767), 272 (4800), and 278 mμ (3424). The longer retention time peak was identified as 3-azabicyclo-[4·2·0]octane 192 by spectral data. NMR (C_6D_6) δ 2.5-3.0 (m, 4H, protons at C-2 and C-6), 2.14-2.48 (m, 2H), 1.78-2.06 (m, 4H, cyclobutane ring $C\underline{H}_2$), 1.26-1.76 (m, 2H) and 0.98 ppm (s, N-H); IR (thin film) 3295, 2930, 1465, 1312 cm^{-1}; UV λ_{max} (95% EtOH) 253 (1736), 258 (1951) and 263 mμ (1621).

3-Azabicyclo[4·2·0]Octane: 192

A solution of 30 mg of 105 in 3 ml of methanol was hydrogenated in the presence of 10 mg of 10% palladium on charcoal at room temperature and one atmosphere of hydrogen. The reaction was followed by VPC (1/8 in x 15 ft 10% Carbowax 20 M + 5% KOH on Chromsorb W 80/100 mesh at 130°C and 30ml/min) and stopped when the peak at 7.5 min retention time corresponding to 105 had disappeared. The catalyst was removed by filteration and methanol evaporated to yield 25 mg of a light yellow oil which on analysis by VPC showed a single peak with a retention time of 2.6 min. The infrared spectrum of the material obtained was identical to that of 3-azabicyclo[4·2·0]octane 192.

Basicity Measurements:

Basicities were determined according to the method of

Markgraf and Katt[10b] by potentiometric titration with a Radiometer RTS622 recording titration system fitted with a glass indicator electrode and a saturated calomel reference electrode, previously equilibrated with acetic anhydride for 48 h. Titrations were carried out at 25.00 ± 0.05°C under a nitrogen atmosphere in a water-jacketed cell connected to a constant-temperature bath and fitted with a neoprene cover drilled to accommodate two electrodes, buret, thermometer, and nitrogen inlet tube. In a typical run, an accurately weighed amount of the pyridine derivative (ca. 5 x 10^{-2} mol) was dissolved in acetic anhydride in a nitrogen-swept 25-mL volumetric flask; a 10-mL aliquot was transferred to the titration cell, diluted with 60 mL of acetic anhydride, and with magnetic stirring titrated with 0.10 N perchloric acid in acetic acid (Fisher No. SOP-339, ca. 3.5 mL). The end point and half-neutralization potential were determined graphically. All runs were carried out in duplicate, with a precision of ± 2 mV. The same procedure was followed for 2,3-fused 1,8-napthyridines.

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$$AH^+ + B \longrightarrow BH^+ + A$$

$$\Delta G^\circ = GB(A) - GB(B)$$

$$\Delta H^\circ = PA(A) - PA(B)$$

where GB(A) is the gas phase basicity of A and PA(A) is the proton affinity of A.